Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Health Technology Assessment of C-reactive protein point-of-care testing to guide antibiotic prescribing for acute respiratory tract infections in primary care settings

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About the Health Information and Quality Authority (HIQA)

The Health Information and Quality Authority (HIQA) is an independent statutory authority established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children and Youth Affairs, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.

- **Regulating social care services** — The Office of the Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.

- **Regulating health services —** Regulating medical exposure to ionising radiation.

- **Monitoring services** — Monitoring the safety and quality of health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these services.

- **Health technology assessment** — Evaluating the clinical and cost-effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.

- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.

- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health services, in conjunction with the Department of Health and the HSE.

Foreword

Antimicrobial resistance occurs when bacteria adapt in response to the use of medicines. When bacteria become antibiotic resistant, infections become more difficult to manage and treat. Antimicrobial resistance is a significant threat to public health, and widely acknowledged to be associated with the excessive and inappropriate consumption of antibiotics. Most antibiotics are prescribed in primary care settings and frequently to treat respiratory tract infections, which account for approximately one quarter of primary care attendances.

The objective of C-reactive protein point-of-care testing (CRP POCT) is to assist the clinician in ruling out serious bacterial infection, thereby supporting a decision not to prescribe an antibiotic to those who are unlikely to benefit from treatment. HIQA's health technology assessment reviews the clinical and cost-effectiveness of CRP POCT. The assessment will inform a decision as to whether CRP POCT should be used to support antibiotic prescribing in primary care for patients presenting with symptoms of acute respiratory tract infection. The assessment also considers the organisational implications associated with introducing CRP POCT in primary care.

Work on the assessment was undertaken by an Evaluation Team from the HTA Directorate in HIQA. A multidisciplinary Expert Advisory Group was convened to advise HIQA during the course of the assessment. HIQA would like to thank its Evaluation Team, the members of the Expert Advisory Group and all who contributed to the preparation of this report.

Dr Máirín Ryan

Deputy Chief Executive and Director of Health Technology Assessment

Advice to the Minister for Health

The purpose of this health technology assessment (HTA) is to provide advice to the Minister for Health, the Department of Health and the Health Service Executive (HSE) on the implementation of near-patient testing to guide antimicrobial prescribing for acute respiratory tract infections in primary care settings. The Health Information and Quality Authority (HIQA) agreed to undertake the HTA following a formal request from the Department of Health. Following a scoping review, C-reactive protein (CRP) point-of-care testing (POCT) was identified as the only point-of-care test with evidence for patients with symptoms of acute respiratory tract infection applicable to the primary care setting. The HTA aimed to establish the clinical and cost-effectiveness of CRP POCT. The HTA also examined the organisational implications of the potential introduction of the technology in primary care.

The key findings of this HTA, which informed HIQA's advice, are:

- Respiratory tract infections (RTIs) are the most frequent infections encountered in primary care, accounting for approximately 23% of general practice consultations in Ireland. RTIs are seasonal in nature, with the peak occurring in the winter months. Most RTIs are viral and self-limiting, but a small number are caused by bacteria and respond to antibiotic treatment. In the majority of cases, a strategy of no antibiotic or delayed antibiotic prescribing is generally recommended. Use of antibiotics is recommended in patients with a diagnosis of pneumonia and in those with lower RTI with risk factors for complications, but not for those with acute bronchitis.

- Overprescribing of antibiotics for RTIs in primary care is common in most industrialised countries, with high levels of inappropriate prescribing documented. Antibiotic treatment of RTIs can expose patients to an increased risk of an adverse event, with one out of five patients experiencing mostly minor and self-limiting adverse events. Antimicrobial resistance (AMR) is a growing and significant threat to public health, and it is widely recognised that antibiotic resistance is driven by excessive and inappropriate antibiotic prescribing. Increased antibiotic consumption correlates with increased antibiotic resistance, with countries that have moderate to high consumption of antibiotics also having high AMR. Ireland has a high rate of antibiotic prescribing relative to some European countries.

- In cases with uncertainty following clinical examination, CRP POCT is intended to assist GPs rule out serious bacterial infections, thereby supporting a decision not to provide an antibiotic to those who are unlikely to benefit from treatment.

- Based on a systematic review, the use of CRP POCT to inform antibiotic prescribing in primary care for acute RTIs leads to a 24% reduction in antibiotic prescribing (risk ratio: 0.76, 95% CI: 0.67 to 0.86). Similar levels of reduction in antibiotic prescribing were seen in patients with upper and lower RTIs. There was substantial heterogeneity across trials in the estimated treatment effect.

- Due to limited data, it is unclear what impact CRP POCT testing has on antibiotic prescribing in children. There were no studies that met our inclusion criteria that provided data specifically on patients from long-term care facilities or out-of-hours clinics. As trials were based on short term follow-up data at three months, it is unclear whether clinicians continue to use CRP POCT as a decision support tool over the longer term.

- The use of CRP POCT does not lead to an increase in adverse effects such as mortality, hospitalisations, or reconsultations. There was limited evidence regarding other outcomes of clinical effectiveness and safety.

- CRP POCT devices generally demonstrate acceptable analytical performance in a laboratory setting. When used at the point of care, however, the accuracy and precision of the devices was more variable. The overall time taken for the test to be completed ranges from just over 3 minutes to over 13 minutes. Participating in an external quality assurance scheme more than once, performing internal quality control at least weekly, the type of instrument used, having laboratory-qualified personnel performing the tests and performing more than ten CRP tests per week were all associated with good test performance.

- In previous studies, CRP POCT was found to be a cost-effective adjunct to clinical judgment alone. An economic model was developed to evaluate the impact of introducing a national programme of CRP POCT in Ireland with and without additional enhanced communication training for GPs. Both POCT strategies were more costly than usual care, but both resulted in reduced antibiotic prescribing in the community.

- An estimated 1.3 million CRP POC tests (95% CI: 1.1 to 1.5 million) would be carried out each year in primary care if CRP POCT was made available across all GP practices. It was estimated that the annual number of antibiotic prescriptions issued for RTIs in primary care would decrease from 2.4 million to 1.8 million per annum if GP use of CRP POCT without communication skills training is implemented, and to 1.2 million prescriptions per annum when combined with enhanced communication training. GP use of CRP POCT with communication training may be more cost-effective than GP use of CRP POCT without communication training, although there is little to differentiate the two interventions in terms of cost-effectiveness based on three month follow-up data.

- Assuming that the HSE would finance a CRP testing device per practice and provide the associated consumables and the cost of communication training, GP use of CRP POCT with communication training would save an estimated €1 million over five years relative to usual care. However, the intervention would cost an additional €4.5 million more than usual care if one device per GP is purchased. The findings are subject to the assumption of the ongoing use of CRP POCT by GPs once introduced into practice. Due to the limited evidence available, there is substantial uncertainty regarding this assumption. If GPs are reimbursed based on a fee per test, based on the range of reimbursement fees applied in Europe, the five year budget impact increases by between €8.2 million and €54.3 million.

- The introduction of CRP POCT is likely to displace clinical activity through increased consultation times, although that may be moderated through other effects such as future reductions in consultations for RTIs. Displacement of activity may adversely affect the continued effective use of CRP POCT in general practice.

- The implementation of CRP POCT would require changes to working processes and patient flow within the general practice. Individual practices and practitioners will need to consider how to integrate CRP POCT into their practice when establishing a testing service. The economic evaluation assumed financial support from the HSE to procure the devices in order to ensure the systematic adoption and use of CRP POCT technology by GP contractors in primary care. The use of non-financial incentives should also be considered to promote adoption and ongoing use of the technology.

- Consideration may be given to introducing clinical guidelines to support the use of CRP POCT to inform antibiotic prescribing decisions for acute RTIs with associated clinical uncertainty. Guidelines may help to ensure a standard approach to using CRP POCT to guide prescribing and potentially reducing the possibility of indication creep. Healthcare professionals performing the CRP POCT will require training on how to use the analysers, how and where to record the results, how and why internal and external quality control is performed, and what to do if an analyser does not work properly. A CRP POCT programme should leverage off the expertise and knowledge of the hospital laboratory network to support the development of a quality-assured service. Enhanced communication training may also be suggested for GPs to support patient cooperation and satisfaction in situations of non-prescribing of antibiotics for acute RTIs. The acceptance of the CRP POCT programme among the general public may be improved by an antibiotic prescribing awareness campaign for patients.

- Introduction of CRP POCT should be considered in the context of a potential national quality management system for point-of-care testing in primary care. Such a system would support the quality assurance, governance, and training required to deliver a safe and effective service.

Arising from the findings above, HIQA's advice to the Minister for Health, the Department of Health and the HSE is as follows:

- Ireland has a high rate of antibiotic prescribing in patients presenting to primary care with acute respiratory tract infections, even though only a small number are caused by bacteria and respond to antibiotic treatment. Inappropriate antibiotic consumption correlates with increased antimicrobial resistance, giving rise to increased morbidity and mortality from bacterial infections as well as increased economic burden on the healthcare sector.

- Based on limited data, the use of CRP POCT in primary care settings to inform antibiotic prescribing for acute RTIs may lead to a significant reduction in antibiotic prescribing without compromising patient safety. The estimated economic impact is subject to substantial uncertainty due to the lack of longer-term follow-up data and the challenges in encompassing all costs associated with quality assurance and governance. If uptake and use of CRP POCT is sustained, the five year budget impact is approximately €1 million if combined with enhanced communication skills training, or €5 million if introduced without

the training. The budget impact will increase by between €8 million and €54 million if fee-per-item reimbursement applies.

- The adoption of CRP POCT will also have organisational implications for general practices in terms of impact on patient flow, the need for quality assurance, and potential displacement of activity through longer consultation times for patients who undergo the test.
- The introduction of CRP POCT in primary care should be within the context of a supporting national quality management system for POCT to ensure a safe and effective service.
- CRP POCT must be considered within the context of a suite of initiatives to improve antimicrobial stewardship. In light of considerable uncertainty regarding the longer-term sustainability and effectiveness gains from CRP POCT over time, a carefully managed and monitored pilot programme or partial roll-out of CRP POCT may offer the best prospect to evaluate a CRP POCT programme and establish whether a national roll-out of the technology is advisable.

Executive summary

Background

In the context of the National Action Plan on Antimicrobial Resistance (iNAP) 2017-2020, HIQA was requested to undertake a health technology assessment (HTA) of near-patient testing to guide antimicrobial prescribing. Following a scoping review, the request was focused on biomarker point-of-care testing for respiratory tract infections. C-reactive protein (CRP) point-of-care testing (POCT) was identified as the only point-of-care test with evidence for patients with symptoms of acute respiratory tract infection applicable to the primary care setting. The assessment is intended to inform a decision as to whether CRP POCT should be used to support antibiotic prescribing in primary care for patients presenting with symptoms of acute respiratory tract infections (RTI) for whom there is clinical uncertainty regarding the need for an antibiotic.

The Terms of Reference agreed between HIQA and the Department of Health were to:

- describe the epidemiology of respiratory tract infections in primary care
- describe current antibiotic prescribing patterns in Ireland and the associated burden of antimicrobial resistance
- describe the available CE marked point-of-care tests suitable for use in the primary care setting
- undertake a systematic review of the safety and efficacy of point-of-care testing (POCT) to guide antibiotic prescribing for patients presenting with symptoms of acute respiratory tract infection in primary care
- undertake a systematic review of the analytical performance and diagnostic test accuracy of the commercially available CE marked point-of-care tests
- undertake a systematic review of the literature on the cost-effectiveness of POCT for this indication
- undertake an economic evaluation and budget impact analysis of the introduction of POCT in primary care in Ireland for this indication
- consider any wider organisational, ethical or societal implications that POCT may have for patients, the general public or the healthcare system.

Methods

This research was carried out in accordance with HIQA's guidelines for the conduct of HTAs. In summary, the following took place:

- The Terms of Reference of the HTA were agreed between HIQA and the Department of Health.
- An Expert Advisory Group was convened, with representation from health policy decision-makers, clinicians, professional bodies, patient representatives, experts in the fields of point-of-care testing, healthcare acquired infection and antimicrobial stewardship, economic evaluation and ethics. An Evaluation Team was appointed comprising HIQA staff.
- A EUnetHTA relative effectiveness assessment (REA) of CRP POCT was conducted in parallel with the HTA.
- The epidemiology of RTIs, the burden of antimicrobial resistance and current antibiotic prescribing patterns in Irish primary care were assessed.
- The available CE marked CRP POC tests suitable for use in the primary care setting were identified.
- A systematic review of the clinical effectiveness and safety of CRP POCT was carried out to identify studies investigating the impact of CRP POCT on antibiotic prescribing for acute RTIs, health service utilisation and mortality in the primary care setting.
- A systematic review of diagnostic test accuracy was carried out to identify studies reporting the ability of CRP POCT to accurately rule in or rule out the diagnosis of specific RTIs.
- A systematic review of analytical performance was carried out to identify studies comparing the accuracy, precision and ease of use of CRP POC tests with each other and/or laboratory standard tests.
- A systematic review was undertaken to summarise the available cost-effectiveness evidence of CRP POCT in guiding antibiotic prescribing for acute RTIs in the primary care setting.
- An economic model was adapted to the Irish setting to estimate the cost-effectiveness of CRP POCT in Irish primary care.
- A budget impact analysis reporting the incremental costs associated with the potential implementation of CRP POCT over a five-year time period was performed from the perspective of the public health and social care system.
- An analysis of the organisational implications was undertaken with a view to identifying broader considerations that may influence decision-making.

- The complete draft report was reviewed by the Expert Advisory Group, before being made available for public consultation, to give interested parties an opportunity to comment on the draft before it was finalised.
- A final draft of the report, including a report on the results of the public consultation, will be submitted to the Board of HIQA for approval.
- Subject to its approval, the completed assessment will be submitted to the HSE, the Department of Health and the Minister for Health as advice, and published on the HIQA website.

Description of technology

CRP POCT is used to measure the level of C-reactive protein in a person's blood. While raised concentrations of serum CRP often occur in bacterial infections, typically only minor elevations are observed in viral infections. The objective of CRP POCT is to rule out serious bacterial infections, thereby supporting a decision not to provide an antibiotic to those who are unlikely to benefit from treatment. It may also help to identify those patients who are most likely to benefit from an antibiotic.

Fifteen CRP POCT devices were identified that were suitable for use in a primary care setting. These can broadly be divided into two categories: quantitative devices and semi-quantitative devices. The first fully quantitative CRP POCT system was launched in 1993. The first semi-quantitative CRP POCT system was launched in 2014. Most quantitative tests require whole blood, plasma or serum, whereas semi-quantitative test methods require a capillary blood sample.

The use of CRP POCT in patients with suspected lower RTIs has been included in clinical guidelines in the UK, Norway, Sweden, the Netherlands, Germany, Switzerland, Czech Republic and Estonia to guide antibiotic prescribing.

Burden of disease

RTIs are the most frequent infections encountered in primary care, accounting for approximately 23% of general practice consultations in Ireland. Most are viral, but a small number are caused by bacteria and may respond to antibiotics. Patient groups generally considered at highest risk of acute RTIs and their sequelae include: paediatric (<5 years) and geriatric (>70 years) patients, those with a pre-existing lung condition (such as chronic obstructive pulmonary disease [COPD] or asthma), immuno-compromised patients, and patients resident in long-term care (LTC) facilities such as nursing homes. RTIs are seasonal in nature, with incidence peaking in the winter months.

RTIs may be classified as upper (pharyngitis, tonsillitis, laryngitis, rhinosinusitis, otitis media and the common cold) or lower (pneumonia, bronchitis, tracheitis and acute infective exacerbations of COPD). Influenza may affect both the upper and lower respiratory tract. Most RTIs are self-limiting. The natural course of upper RTIs (URTIs) typically ranges from four days to 2.5 weeks, while lower RTIs (LRTIs) typically range from three weeks to six months for resolution of all symptoms, depending on the type of infection.

In uncomplicated cases of URTIs that do not exceed the expected duration of illness, a strategy of no antibiotic prescribing or delayed antibiotic prescribing is generally recommended. Use of antibiotics is recommended in patients with a diagnosis of pneumonia and in those with LRTI with risk factors for complications, but not for those with acute bronchitis. Overprescribing of antibiotics for RTIs in primary care is common, with high levels of inappropriate prescribing documented in observational studies benchmarking antibiotic prescribing versus clinical guidelines. Antibiotic treatment of RTIs can expose patients to an increased risk of an adverse event, with adverse events occurring in one out of every five patients.

Antimicrobial resistance (AMR) is a growing and significant threat to public health, and it is widely recognised that antibiotic resistance is driven by excessive and inappropriate antibiotic prescribing. Increased antibiotic consumption correlates with increased antibiotic resistance, with countries that have moderate to high consumption of antibiotics also having high antimicrobial resistance. At the patient level, there is a clear link between antibiotic dose and duration and the emergence of antibiotic resistance, and there is also evidence that patients who have been treated frequently with antibiotics are at greater risk of antibiotic resistance.

AMR results in increased morbidity and mortality from bacterial infections as well as increased economic burden on the healthcare sector in the treatment and care of patients infected with multidrug-resistant strains as well as a loss of productivity. AMR results in the death of approximately 50,000 people per year in the US and Europe, and in the region of 700,000 people globally. Rates of AMR in Ireland are high relative to a number of other European countries.

Clinical effectiveness and safety

A systematic review was carried out to identify studies investigating the impact of CRP POCT on antibiotic prescribing for acute RTIs, health service utilisation and mortality. Eleven studies were included in analysis, of which nine were conducted in Europe. The studies included both randomised and non-randomised trials. Study

participant groups included URTI only, LRTI only, and a combination of LRTI and URTI. Eight of the studies included only adult patients.

The pooled estimates across studies showed a statistically significant reduction in antibiotic prescribing in the CRP test group, compared with usual care (RR: 0.82 (95% CI: 0.67 to 1.00) for randomised controlled trials (RCTs); 0.68 (95% CI: 0.61 to 0.75) for cluster RCTs; 0.61 (95% CI: 0.54 to 0.69) for observational studies). There was substantial heterogeneity across trials in the estimated treatment effect. In patients where there is clinical uncertainty as to whether an antibiotic is needed, five patients would need to undergo CRP POCT to prevent one antibiotic prescription (95% CI: 4-8). Based on randomised trial evidence alone, the number needed to test was seven (95% CI: 5-14). Similar levels of reduction in antibiotic prescribing were seen in patients with URTI and LRTI. There was limited evidence regarding other outcomes of clinical effectiveness.

No significant difference was found between those receiving the CRP POCT and those who did not in terms of proportion of patients recovered at seven days and the time taken for the resolution of symptoms. The use of CRP POCT does not lead to an increase in adverse effects such as mortality, hospitalisations or reconsultations. In the studies that reported on patient satisfaction, patients were mostly satisfied and there was no difference in satisfaction between the CRP POCT group and the usual care group, suggesting that the provision of CRP POCT neither improves nor disimproves patients' consultation experience. There was a lack of longer-term follow-up data to determine whether the impact of CRP POCT on antibiotic prescribing is sustained. Despite finding an effect at three months, one study showed no statistically significant effect on prescribing at 12 months associated with limited use of CRP POCT, suggesting that long term sustainability may be an issue.

The use of CRP POCT to inform antibiotic prescribing in primary care for acute RTIs leads to a significant reduction in antibiotic prescribing without compromising patient safety. Due to the limited data on children, it is unclear what the impact of CRP POCT is on antibiotic prescribing in children with RTIs. There were no studies that met our inclusion criteria that provided data specifically on patients from long-term care facilities or out-of-hours clinics, both of whom are potentially important populations with respect to CRP POCT.

Diagnostic test accuracy of CRP POCT

A systematic review of diagnostic test accuracy identified 15 studies that evaluated the diagnostic test accuracy of CRP POCT in the diagnosis of RTI in primary care, of

which 14 were European studies. The evidence base is characterised by a high level of heterogeneity in patient populations, diagnostic criteria, CRP cut-points, how the performance of the test was reported and the absence of a universal reference standard for the diagnosis of RTIs requiring antibiotic treatment.

Two studies reporting the usefulness of CRP testing in diagnosing acute sinusitis provided limited evidence of benefit. Both studies identified a low threshold (10 and 17 mg/L) that may be useful to rule out sinusitis, however, as most clinical guidelines for the diagnosis and management of acute sinusitis (of less than 10 days' duration) do not generally recommend the use of antibiotics, the utility of CRP POCT in sinusitis is unclear.

CRP testing is better at ruling in than ruling out bacterial pharyngitis at a threshold of 35 mg/L and one study suggests it may be useful when used in combination with other signs and symptoms. The utility of CRP testing for the detection of bacterial pharyngitis is sensitive to the cut-point used.

For LRTI and pneumonia, there was mixed evidence regarding the diagnostic test accuracy of CRP testing. CRP testing may be useful at ruling in a diagnosis of pneumonia at a cut-point of 100 mg/L, but is not reliable at ruling out pneumonia at a cut-point of 20 mg/L. The use of CRP POCT may be more useful when used in combination with a prediction rule that incorporates specific signs and symptoms and may increase the specificity of clinical judgment.

Analytical performance of CRP POCT devices

A systematic review of analytical performance identified 18 studies. The included studies were generally found to be at high risk of bias in a number of domains.

Two studies evaluated two of the CE marked semi-quantitative devices (Actim® and Cleartest®). The agreement between the reference test and the POCT was found to be moderate to good, although the accuracy of the test was shown to decrease after the optimal 5 minute read time. As the included semi-quantitative devices have an upper limit of 80mg/L, they may be of limited use in terms of current guidelines for antibiotic prescribing that use a cut-point of ≥100 mg/L for antibiotic prescribing.

The majority of the evidence suggested acceptable performance for all 11 quantitative devices in the laboratory setting. Most of the devices had a mean difference of <10 mg/L or <10% bias except at concentrations above 100 mg/L. Precision was also acceptable in the laboratory for six of the devices, suggesting that under idealised circumstances in the laboratory most of the devices are accurate and

precise. When used in primary care, the results for the accuracy and precision of the devices were more variable, with very little precision data available in this setting.

Of the devices assessed in both the laboratory setting and the primary care setting, all had acceptable accuracy and precision in the laboratory while only one had reliably acceptable performance at the point of care. Accuracy and precision appear to be negatively impacted when the device is used at the point of care by healthcare professionals, suggesting that appropriate training and use of robust standardised operating procedures may be required to moderate these sources of error.

Devices that are easier to use tend to have less pre-analytical handling and are designed in a way that they are less susceptible to human error. The overall time taken for the test to be performed was an important factor in ease of use, with times ranging from just over 3 minutes to over 13 minutes. Participating in an external quality assurance scheme more than once, performing internal quality control at least weekly, the type of instrument used, having laboratory-qualified personnel performing the tests and performing more than 10 CRP tests per week were all associated with good test performance.

Systematic review of economic evaluations

A systematic review identified five studies estimating the cost-effectiveness of CRP POCT in a primary care setting: four cost-utility analyses and three cost-effectiveness analyses (two studies reported both cost-utility and cost-effectiveness analyses). All five studies included an intervention of usual care based on clinical judgment and clinical judgment supported by CRP POCT. Three included an intervention combining CRP POCT with enhanced communication skills training for GPs.

In terms of cost-utility, CRP POCT was found to be a cost-effective alternative to clinical judgment alone.

Overall, the studies were well designed with similarly well-defined patient populations, although reporting was often poor and little consideration was given to the extent of the uncertainty in costs and quality-adjusted life years (QALYs) – the measure of health outcome used in cost-utility analyses. The applicability of the identified studies to Ireland was limited due to a number of factors, including the generalisability of data on the frequency of antibiotic prescribing; unclear validity of including utility data; uncertainty around the appropriate time horizon; and the discount rate used.

Economic evaluation

A decision tree model was developed to simulate the impact of introducing a national programme of CRP POCT with and without additional enhanced communication training for GPs.

An estimated 2.4 million prescriptions are currently issued for RTIs in Ireland annually. If CRP POCT is available across all GP practices, an estimated 1.3 million CRP tests (95% CI: 1.1 to 1.5 million) would be carried out each year in primary care, assuming that a high short term uptake is repeated in subsequent winter seasons. Implementation of CRP POCT in primary care is predicted to result in a substantial reduction in antibiotic prescribing for RTIs. The annual number of antibiotic prescriptions would reduce to an estimated 1.8 million per annum for CRP POCT alone, and 1.2 million per annum for CRP POCT when combined with enhanced communication training for GPs.

Assuming ongoing uptake of CRP POCT, both POCT strategies were more costly than usual care, but both resulted in reduced antibiotic prescribing in the community. The incremental cost per prescription avoided associated with the POCT strategies was €111 (95% CI: €45 to €243) for combined CRP POCT and communication training, while GP use of CRP POCT without communication training was dominated (less effective and more costly). GP use of CRP POCT with communication training may be more cost-effective than GP use of CRP POCT without communication training, although there was little to differentiate the two in terms of cost-effectiveness.

GP use of CRP POCT with communication training was estimated to save €1 million over five years relative to usual care if one device is purchased for each of the estimated 1,734 practices in Ireland. However, it would cost an additional €4.5 million more than usual care if one device per GP is purchased. GP use of CRP POCT without communication training has an estimated five-year budget impact of between €18.1 million (one device per practice) and €23.9 million (one device per GP). Based on typical reimbursement fees applied in Europe, inclusion of a fee per test increases the five year budget impact by between €8.2 million and €54.3 million.

The budget impact estimates were subject to considerable uncertainty influenced by the baseline prescribing rate, the cost of antibiotics, the cost of the consumables for the CRP test, and the proportion of acute RTI episodes that would be considered eligible for CRP POCT.

As part of the base case model, it was assumed that the HSE would finance the CRP POCT devices and associated consumables as well as the cost of enhanced

communication training. While the introduction of CRP POCT is likely to displace some clinical activity due to increased consultation times for patients undergoing a CRP test, this may be moderated through other effects such as future reductions in consultations for RTIs. While GP time was included in the cost-effectiveness model as an opportunity cost, it was not included in the budget impact as it is not a direct cost to the HSE, although it was included in a scenario analysis in the form of a fee-per-item. However, it is important that the opportunity cost of CRP POCT to GP practice is recognised and it may be necessary to explore approaches to providing practice support to minimise disruption to primary care capacity and ensure the continued use of the technology to inform decision-making.

Organisational issues

The implementation of CRP POCT would require changes to working processes and patient flow within general practices. Individual practices and practitioners would need to consider their own staffing, infrastructure and culture when establishing a testing service. Following clinical assessment by the GP, if considered necessary to inform decision-making, the CRP POC test could be undertaken by the GP, practice nurse and/or a healthcare assistant depending on the diagnostic protocol adopted by the practice.

Practice resources would be impacted if adoption of the CRP POCT was to be self-funded by doctors, in which case rapid uptake of CRP POCT in primary care is unlikely. Funding would therefore be required from the HSE to ensure the systematic adoption and use of CRP POCT technology by GP contractors in primary care. Non-financial incentives should also be considered to encourage the adoption of the technology. Consideration should be given to the introduction of clinical guidelines that incorporate advice on the appropriate use of CRP POCT in inform prescribing for acute RTIs for which there is uncertainty regarding the need for an antibiotic following clinical examination. Guidelines may help to ensure a standardised approach to using CRP POCT to guide prescribing decisions for patients presenting with acute RTIs, and may also potentially reduce the possibility of indication creep.

Procurement options for the CRP POCT devices include: direct purchase by the primary care practice; purchase by a community health organisation (CHO) to cover practices in their region; block purchase or tender proposal by HSE procurement on a national level; purchase and ownership of devices by central or supporting hospital laboratory services, loaned or leased back to primary care practices; loan or lease agreements facilitated by industry.

All healthcare professionals performing CRP POCT would require training on how to use the analysers, how and where to record the results, how and why internal and external quality control is performed, and what to do if an analyser does not work properly. Communication training relating to the role and potential value of CRP POCT could also be suggested for GPs to support and facilitate conversations with the patient regarding the requirement, if any, for an antibiotic. A CRP POCT programme should leverage off the expertise and knowledge of the hospital laboratory network to support and provide oversight in the development of a quality-assured service.

To ensure the accuracy and reliability of testing, all testing should be ISO-accreditable, including meeting requirements in relation to internal quality control, quality assurance and the recording of training and test results. Participation in external quality assurance schemes is an important component of this process. A WHO manual provides recommendations on how to establish an external quality assurance (EQA) scheme for POCT while international examples of EQA for CRP POCT are available from Wales, Denmark and Norway. The introduction of CRP POCT should be considered in the context of a potential national quality management system applicable across point-of-care testing in primary care. Such a system would support the quality assurance, governance, and training required to deliver a safe and effective service. A centralised service would also facilitate the IT structures necessary to provide connectivity and traceability.

The acceptance of the CRP POCT programme among the general public may be enhanced by an antibiotic prescribing awareness campaign for patients. This may take the form of advertising campaigns and patient education leaflets.

Conclusions

Ireland has a high rate of antibiotic prescribing in patients presenting to primary care with acute respiratory tract infections, even though only a small number are caused by bacteria and respond to antibiotic treatment. Increased and inappropriate antibiotic consumption correlates with increased antimicrobial resistance (AMR). AMR gives rise to increased morbidity and mortality from bacterial infections as well as increased economic burden on the healthcare sector. Increased antibiotic prescribing also leads to greater harms through exposing patients to adverse events.

CRP POCT is used to measure the level of C-reactive protein in a person's blood, which can be used as an indicator of bacterial infection. Clinical trials have demonstrated that the use of CRP POCT in primary care settings to inform antibiotic prescribing for acute RTIs leads to a significant reduction in antibiotic prescribing

without compromising patient safety. The diagnostic test accuracy of CRP alone to identify bacterial RTIs is equivocal, although the accuracy improves relative to symptoms and signs when used as part of a clinical prediction rule or algorithm. Most devices have acceptable performance in a laboratory setting. There was limited evidence regarding analytical performance of the devices in the primary care setting, with studies suggesting that adequate test performance in a primary care setting may be achieved through training. There was evidence from a large Norwegian study that participation in quality assurance processes improves test performance.

The interpretation of the cost-effectiveness of CRP POCT is unclear as there is no reference willingness-to-pay threshold for cost per prescription avoided. The budget impact may be close to budget neutral if combined with enhanced communication skills training, or high if introduced without the training. However, including reimbursement as a fee-per-item will result in a substantially increased budget impact. The estimated economic impact is subject to substantial uncertainty due to the lack of longer-term follow-up data. The adoption of CRP POCT will also have organisational implications for general practices in terms of impact on patient flow, the need for quality assurance, and potential displacement of activity through longer consultation times for patients who undergo the test. Ongoing training requirements and participation in quality assurance will also place a burden on GP practices.

CRP POCT must be considered within the context of a suite of initiatives to improve antimicrobial stewardship. In light of the uncertainty regarding longer-term sustainability and effectiveness gains over time, a carefully managed and monitored pilot programme or partial roll-out of CRP POCT may offer the best prospect to evaluate a CRP POCT programme and whether a national roll-out is advisable.

Plain English summary

The Health Information and Quality Authority (HIQA) has carried out an assessment on whether C-reactive protein (CRP) point-of-care testing (POCT) should be used in primary care to guide antibiotic prescribing for acute respiratory tract infections. At the moment, a general practice doctor (GP) uses their own clinical judgment (without a point-of-care test) to decide if a patient needs an antibiotic for these infections.

Respiratory tract infections include pneumonia, bronchitis, tonsillitis, and the common cold. Respiratory tract infections are the most common infections seen in primary care, causing about one quarter of visits to GPs in Ireland. Most are caused by viruses, which do not respond to antibiotics. Others are self-limiting, that is, the patient will get better without treatment. Ireland has a high rate of antibiotic prescribing in patients with these infections. The benefits of antibiotics must be weighted against the possible harms. Antibiotics commonly cause unwanted effects such as diarrhoea, vomiting and rash. Antibiotics are directly associated with antbiotic resistance in common bacteria in the community. This means that even when antibiotics are taken, they may fail to cure an infection if resistant bacteria are present. This can lead to increased levels of illness and death from bacterial infections, as well as higher healthcare costs.

C-reactive protein (CRP) is a protein produced in the liver. The levels of CRP rise in the bloodstream when the body responds to infections and inflammatory triggers. Raised levels of CRP in the bloodstream often occur in bacterial infections; while usually only minor increases are observed in viral infections.

Rapid tests have been developed that can detect the level of CRP in the blood. When used in combination with a GP's clinical judgment, the test can help the doctor to identify people with infections that are most likely to respond to an antibiotic.

Clinical trials have shown that using CRP POCT in primary care to guide antibiotic prescribing for acute respiratory tract infections leads to a significant reduction in antibiotic prescribing. There were no deaths in the studies. Despite fewer antibiotics being prescribed, there was no evidence that patients took longer to recover, had to be admitted to hospital, or go back to their doctor more frequently, or that they were less satisfied with their care. It is not clear if CRP POCT is useful to guide antibiotic prescribing decisions in children with acute respiratory tract infections due to the low number of studies in this group. As the clinical studies were usually short, it is not known if CRP POCT as a tool to aid decision-making to reduce antibiotic prescribing is effective over time. One study that followed-up with the study

participants in the longer term found that improvements in antibiotic prescribing observed after three months were greatly reduced at one year.

Most devices have acceptable performance in laboratories. There was evidence from studies suggesting that adequate test performance in a primary care setting may be achieved through training, and that participating in quality-assurance processes improves test performance.

HIQA also assessed the costs and benefits of introducing CRP POCT in primary care. There may be no additional cost of providing CRP POCT if it is combined with enhanced communication skills training. However, the cost would be high if it were to be introduced without the additional training. There is a lot of uncertainty around these estimates due to the lack of research with longer-term follow-up.

Introducing CRP POCT will also have an impact on the organisation of general practices in terms of impact on patient flow, the need for quality assurance of the testing, and potentially longer consultation times for patients who undergo the test.

Following this research, HIQA has recommended that the Minister for Health should consider a carefully managed and monitored pilot programme (or partial introduction) of CRP POCT to see if it is a useful test for both GPs and patients, considering that it would be a significant investment by the health service. If this is considered a success, a national roll-out of the technology would be advised. HIQA has also recommended that the Minister should consider introducing CRP POCT only as part of wider set of initiatives to improve the use of antibiotics in Irish primary care.

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Conflicts of Interest

There were no reported conflicts of interest for the Expert Advisory Group or Evaluation Team.

List of abbreviations

AMR	Antimicrobial Resistance
BIA	Budget Impact Analysis
CAP	Community-Acquired Pneumonia
CE	Conformité Européenne
CEA	Cost-Effectiveness Analysis
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-Reactive Protein
DDD	Defined Daily Dose
DID	Defined daily doses per 1,000 Inhabitants per Day
ECDC	European Centre for Disease Control
EQA	External Quality Assurance
EUnetHTA	European Network for Health Technology Assessment
FDA	Food And Drugs Authority
GAS	Group A Streptococci
GMS	General Medical Services
GP	General Practitioner
HCAI	Healthcare Associated Infection
HCW	Health Care Worker
HPSC	Health Protection Surveillance Centre
ICER	Incremental Cost-Effectiveness Ratio
IEQAS	Irish External Quality Assessment Scheme
IQC	Internal Quality Control
iNAP	Ireland's National Action Plan on Antimicrobial Resistance
LRTI	Lower Respiratory Tract Infection
NNH	Number Needed to Harm
NNT	Number Needed to Treat
NVRL	National Virus Reference Laboratory
OOH	Out-Of-Hours
OR	Odds Ratio
PCRS	Primary Care Reimbursement Service
PICOS	Population, Intervention, Comparator, Outcomes, Study Design
POCT	Point-Of-Care Testing
QA	Quality Assurance
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
RR	Relative Risk
RTI	Respiratory Tract Infection
SOP	Standard Operating Procedure
URTI	Upper Respiratory Tract Infection

1 Introduction

1.1 Background to the request

In February 2018, the Health Information and Quality Authority (HIQA) commenced work on a health technology assessment (HTA) in relation to point-of-care testing (POCT). HIQA agreed to undertake the HTA following a formal request from the Lead of the Primary Care Clinical Programme in the Health Services Executive (HSE). The aim of the HTA is to establish the clinical and economic impact of providing point-of-care testing to inform prescribing of antibiotics for patients presenting with symptoms of acute respiratory tract infections (RTIs) in primary care.

This request was subsequently endorsed by the Department of Health and was prioritised for inclusion in the 2018 HIQA HTA work plan. Completion of this work is consistent with two of the strategic objectives (2.3.2 and 5.2.3) of Ireland's National Action Plan on Antimicrobial Resistance (iNAP) 2017-2020. The assessment will inform a decision as to whether point-of-care testing (POCT) should be used to inform antibiotic prescribing in primary care for patients presenting with symptoms of acute RTIs for whom there is clinical uncertainty regarding the presence of a bacterial infection. It will examine the clinical effectiveness of POCT for this indication and will include an economic evaluation and assessment of the budget impact, organisational and other implications associated with its introduction in primary care.

Antimicrobial resistance is a growing and significant threat to public health, and it is widely recognised that antibiotic resistance is driven by excessive and inappropriate antibiotic prescribing.[1, 2] Studies have shown that increased antibiotic consumption correlates with increased antibiotic resistance, with countries that have moderate to high consumption of antibiotics also having high levels of antimicrobial resistance. At the patient level, there is a clear link between antibiotic dose and duration and the emergence of antibiotic resistance. There is also evidence that patients who have been treated frequently with antibiotics are at greater risk of antibiotic resistance.[2, 3] The consequence of antimicrobial resistance is increased mortality and morbidity from bacterial infections as well as an increased burden on the healthcare sector in the treatment and care of patients infected with multidrug-resistant strains.[4] In 2007 it was estimated that the societal costs in Europe of selected antibiotic-resistant bacteria was about €1.5 billion.[5]

Although the scale of a reduction in use that would be required to have a beneficial effect on resistance is as yet unclear, the clear link between antibiotic prescribing

and antimicrobial resistance has led to strategies promoting the rational use of antibiotics with the ultimate goal of decreasing antibiotic consumption without increasing morbidity or mortality. Currently, most antibiotics are prescribed in primary care, with international data suggesting that RTIs account for approximately 60% of prescriptions for antibiotics issued in that setting. While most RTIs are viral, a small number are caused by bacteria and may respond to antibiotic therapy.[6, 7] It is not possible to determine if a respiratory infection is bacterial or viral based solely on presenting symptoms.[8, 9] Where there is clinical uncertainty regarding the need for an antibiotic, the use of a biomarker, such as C-reactive protein, may be helpful in differentiating between bacterial and viral infections. The objective of C-reactive protein POCT is to rule out serious bacterial infections, thereby helping identify those patients who are most likely to benefit from an antibiotic and supporting a decision not to provide an antibiotic to those who are unlikely to benefit from treatment.

HIQA is a national representative body for the European Network for Health Technology Assessment (EUnetHTA), work by which is funded by a grant from the European Commission. Its mission is to support collaboration between European HTA organisations and bring added value to healthcare systems at the European, national and regional levels. It is intended that work undertaken by, and output from, EUnetHTA will be applicable at local (regional and national) level across Europe and will therefore limit unnecessary duplication and improve efficiency in the assessment of new medical technologies. In 2017, HIQA agreed to act as lead author for a rapid relative effectiveness assessment of an emerging medical technology as part of its commitment to EUnetHTA. To facilitate timely production of the HTA on POCT, work on one of the biomarkers relevant to this assessment, C-reactive protein (CRP), was undertaken as a rapid assessment through our work with EUnetHTA. The pilot assessment, co-authored by colleagues from Austria, was published by EUnetHTA in February 2019.

1.2 Terms of reference

This HTA is being carried out to assess the impact of providing point-of-care testing to inform antibiotic prescribing for patients presenting with symptoms of RTI in primary care. The economic impact and resource implications of differing reimbursement mechanisms for POCT in primary care as well as organisational issues associated with the delivery of a POCT service will also be considered.

Based on this HTA, the Department of Health will decide whether point-of-care testing to inform antibiotic prescribing for acute RTIs should be made available in primary care. In consultation with the Department of Health, HIQA's Evaluation

Team developed questions in relation to the critical information required to inform such a decision.

The Terms of Reference for this HTA are to:

- describe the epidemiology of respiratory tract infections in primary care
- describe current antibiotic prescribing patterns in Ireland and the associated burden of antimicrobial resistance
- describe the available CE marked point-of-care tests suitable for use in the primary care setting
- undertake a systematic review of the safety and efficacy of point-of-care testing (POCT) to guide antibiotic prescribing for patients presenting with symptoms of acute respiratory tract infection in primary care
- undertake a systematic review of the analytical performance and diagnostic test accuracy of the commercially available CE marked point-of-care tests
- undertake a systematic review of the literature on the cost-effectiveness of POCT for this indication
- undertake an economic evaluation and budget impact analysis of the introduction of POCT in primary care in Ireland for this indication
- consider any wider organisational, ethical or societal implications that POCT may have for patients, the general public or the healthcare system.

The population of interest for this HTA is represented by patients of all ages who present with symptoms of acute RTI in the primary care setting and for whom there is clinical uncertainty regarding the presence of a serious bacterial infection. However, the size of the target population for this intervention is difficult to estimate. Subgroups of particular interest include:

- upper versus lower RTI
- children
- older adults (≥65 years of age)
- patients attending out-of-hours (OOH) services and
- patients resident in long-term care (LTC) facilities.

1.3 Overall approach

Following an initial scoping of the technology, the Terms of Reference of this assessment were agreed between HIQA and the Department of Health.

HIQA has convened an Expert Advisory Group comprising representation from relevant stakeholders including the Department of Health; the National Clinical Programmes for Healthcare Associated Infection (HCAI) and Antimicrobial Resistance, Pathology and Primary Care in the Health Service Executive (HSE); the Health Products Regulatory Authority (HPRA); health care practitioners with specialist expertise in pathology, laboratory medicine and primary care; an international expert in implementation of quality improvement initiatives to reduce HCAI and antimicrobial resistance; and public representation. The role of the Expert Advisory Group is to inform and guide the process, provide expert advice and information, and to provide access to data where appropriate. A full list of the membership of the Expert Advisory Group will be made available in the acknowledgements section of this report.

The Terms of Reference of the Expert Advisory Group are to:

- contribute to the provision of high-quality and considered advice by HIQA to the Minister for Health
- contribute fully to the work, debate and decision-making processes of the group by providing expert guidance, as appropriate
- provide expert advice on relevant issues outside of group meetings, as requested
- provide advice to HIQA regarding the scope of the analysis
- support the Evaluation Team led by HIQA during the assessment process by providing access to pertinent data, as appropriate
- review the project plan outline and advise on priorities, as required
- review the draft report from the Evaluation Team and recommend amendments, as appropriate
- contribute to HIQA's development of its approach to HTA by participating in an evaluation of the process on the conclusion of the assessment.

HIQA has appointed an Evaluation Team comprising staff from the HTA Directorate to carry out the assessment.

The Terms of Reference of the HTA were reviewed by the Expert Advisory Group at its first meeting. Draft findings on the technologies indicated for point-of-care testing to inform antibiotic prescribing in primary care, and findings from three different systematic reviews of the literature (clinical effectiveness and safety of CRP POCT; diagnostic test accuracy of CRP POCT for respiratory tract infections; and analytical test performance of relevant CRP point-of-care devices) were discussed at that meeting. Considerations regarding the cost-effectiveness, budget impact,

organisational, social and ethical implications of providing CRP POCT to inform antibiotic prescribing for RTI were discussed at subsequent meetings. Draft versions of this report were circulated for review by the Expert Advisory Group before a final draft report was prepared for public consultation. After the public consultation was completed, a final version of this report was circulated for review by the Expert Advisory Group before being submitted to the Board of HIQA for approval. The completed assessment has been submitted to the Minister for Health and the Health Service Executive as advice and published on the HIQA website.

2 Description of technology

The purpose of this chapter is to provide a brief description of C-reactive protein point-of-care testing in relation to the clinical treatment of acute respiratory tract infections. Reimbursement of CRP POCT in Europe is also discussed.

2.1 C-reactive protein (CRP) point-of-care testing (POCT)

Pathology test results inform diagnostic and treatment decisions that affect health outcomes. These tests have traditionally been performed in laboratories which have systems in place to ensure that the results obtained are comparable between different laboratories and of a consistent quality. Technological development has allowed some pathology testing to be performed near or at the site of the patient at the time of the consultation or encounter with the result leading to possible changes in the care of the patient. This testing is usually performed outside a laboratory environment by health professionals including nursing and medical staff. Referred to as 'near patient testing' under Regulation (EU) 2017/746 on in vitro diagnostic medical devices (the IVDR),[10] or more commonly as 'point-of-care testing' (POCT), it is intended to provide more rapid and accessible test results than can be achieved from laboratory settings. For consistency, the term POCT will be used in this HTA.

This HTA is limited to the use of CRP POCT in patients who present with symptoms of acute respiratory tract infections (RTI) in the primary care setting. In the case of CRP POCT, the purpose of the test is to assist the clinician in assessing the likelihood of a serious bacterial infection as opposed to a less serious bacterial infection or viral infection, thereby supporting a decision on whether or not to provide an antibiotic. CRP is one of the cytokine-induced acute-phase proteins produced by the liver, the levels of which rise during a general, non-specific response to various infectious and inflammatory triggers.[11-15] CRP combines with bacterial polysaccharides or phospholipids released from damaged tissue to become an activator of the complement pathway. In healthy people, the serum or plasma CRP levels are below 5 mg/L.[16-18] A rapid increase in CRP can occur about six hours after an acute inflammatory stimulus, with CRP values peaking at approximately 20 to 500 mg/L after 48 hours.[19, 20] As elevated CRP levels may be associated with pathological changes, the CRP assay provides information for the diagnosis, therapy, and monitoring of infectious and inflammatory diseases.[11, 15, 19, 20] Raised concentrations of serum CRP often occur in bacterial infections; however, typically only minor elevations are observed in viral infections.[21] Therefore, when used in combination with clinical judgment, CRP testing may aid the medical practitioner to differentiate between mild and severe respiratory tract infections, and to distinguish between

serious bacterial or self-limiting viral infections.

Fifteen CRP POCT devices were identified for inclusion in this HTA during the scoping phase of this assessment. These can broadly be divided into two categories:

1. Quantitative devices, that is, devices comprising a test kit and analyser
2. Semi-quantitative devices, that is, devices comprising strips, dipsticks or single-use disposable tests.

Table 2.1 provides an overview of the two different categories of CRP POCT devices, including their mechanism of action, similarities and differences.

Quantitative tests require a small amount of whole blood, plasma or serum. The results are expressed in mg/litre (mg/L) with clinical guidelines typically recommending treatment with antibiotics when the CRP result is above a certain level. Certain analysers are suitable for use with other assays in addition to CRP; for example, immunochemical faecal occult blood tests, urine albumin, glycated haemoglobin, urine albumin/creatinine ratio, D-dimer levels, lipoprotein A, total leucocytes, white blood cells, haematocrit and haemoglobin.

Semi-quantitative test methods do not require an analyser. A small amount of capillary blood is applied directly to the test strip, or mixed with dilution buffer for a dipstick test, which then provides an indication of whether the patient has a low, medium or high CRP level. For one particular device, the CRP test is used in combination with a viral biomarker (that is, Myxovirus resistance protein A (MxA) in the FebriDx® test) to provide additional information regarding the likely aetiology (bacterial or viral) of the infection.[14]

Appendix A provides the features of the 15 marketed CRP POCT devices in Europe relevant to this assessment. Data to inform this table were collected from the manufacturers and the literature review in the assessment process. Additional data were obtained from medtech innovation briefings on three of the CRP POCT devices — Alere Afinion™ CRP, QuikRead go® and FebriDx® undertaken by NICE in the UK.[12-14]

It should be noted that Roche Diagnostics Limited launched a CRP test disk for the Roche cobas b101 instrument in March 2018; however, devices were included in this section based on a scoping exercise, evidence from systematic reviews and manufacturer feedback at a point of time in the assessment (February 2018), which preceded the launch date.

Table 2.1 Overview of commercially available quantitative and semi-quantitative CRP POCT devices

Device type	Mechanism of action	Similarities	Differences
Quantitative assay kit and analyser instrument	Analysis using: ▪ Immunoturbidimetric measurement using fingerstick blood samples, whole blood, serum or plasma (n=6). ▪ Solid-phase immuno-chemical (or immuno-metric) assays (n=2). ▪ Fluorescence immunoassays (n=2). ▪ Solid-phase sandwich immunoassay (n=1). ▪ Multi-method immunoassay with haematology and clinical chemistry targets (n=1).	All tests: ▪ are CE marked ▪ can detect whether CRP levels are low or high in a blood sample ▪ use relatively small volumes (2.5 to 20 µL of capillary blood ▪ time to result does not exceed 15 mins for any technology.	All 12 tests require an analyser. Quantitative CRP result. Time to result ranges from 4 to 13.5 mins across 12 analysers. Analytical range: 0.5 mg/L to 400 mg/L with all technologies covering 8 to 160 mg/L. Additional POCT assays are possible with all analysers.
Semi-quantitative test strips or single-use disposable test (SUDT)	Immunochromatographic assay test strip for CRP (n=2). Lateral flow immunoassay using direct sampling micro-filtration technology (n=1).		Tests do not require an analyser. Semi-quantitative result – categorised as low, medium or high for strips and low or high for single-use disposable device. Time to result ranges from 7.5 to 15 mins across 3 tests. Analytical range for CRP in bands for semi-quantitative tests: 0 – >80 mg/L for strips and high of ≥20 mg/L for single-use disposable device. One device co-tests for the viral biomarker MxA.

Abbreviations: n = number of tests with the specified mechanism of action

Local, national and international clinical guidelines describe how CRP POCT may be used to inform prescribing decisions in primary care. For example in the UK, NICE guidelines for the diagnosis and management of pneumonia in adults[22] recommend the use of CRP POCT when it is not clear if antibiotics should be prescribed based on clinical assessment and to use the following algorithm to guide prescribing in these patients:

- not routinely offering antibiotic therapy if the CRP concentration is less than 20mg/L
- considering a delayed antibiotic prescription (a prescription for use at a later date if the symptoms worsen) if the CRP concentration is between 20mg/L and 100mg/L
- offering antibiotic therapy if the CRP concentration is greater than 100mg/L.

It should be noted that semi-quantitative devices will narrow the CRP threshold choices available for clinical guidance on higher CRP cut-points. The CRP POCT can be used in combination with communication training, an education component and/or tests for other biomarkers in addition to standard care to assist the treating clinician in differentiating between bacterial and viral aetiology, and thereby guide antibiotic prescribing. In order for the administration of CRP POCT to be most beneficial in the primary care setting, it must provide timely and quality-assured results to the medical practitioner, ideally during the consultation, that is, within a number of minutes.

2.2 Indications

Orion Diagnostica was the first to launch a fully quantitative CRP POCT system (QuikRead®) in 1993. The CRP system is indicated for use in patients when it is not clear if antibiotics should be prescribed based on clinical assessment alone. This original device has been followed by newer generation quantitative devices from the originator and competing manufacturers in the in vitro diagnostic medical device (IVD) market. The test is indicated for the quantitative determination of CRP in human whole blood and in human serum and plasma. The measurement of CRP provides information for the detection and evaluation of infection, tissue injury, inflammatory disorders and associated diseases. These tests are CE marked in accordance with the IVD Directive (98/79/EC) and are classified as general category IVDs.[10] The CE marking process for this class of IVDs involves the manufacturer self-declaring that the device is in conformity with the IVD Directive. Semi-quantitative CRP test strips Actim® and Cleartest® are also CE marked in accordance with the IVD directive. All these IVDs are intended for use by a

healthcare professional.

FebriDx® is a CE marked rapid immunoassay for the visual, qualitative, in vitro detection of elevated levels of both MxA and CRP directly from peripheral whole blood. Since its initial launch, an updated version of the device that includes the all-in-one built-in safety lancet, calibrated blood collection and transfer system, and integrated push-button buffer delivery mechanism to help prevent user-related errors and improve test performance has been developed.

CRP POCT devices are subject to EU Regulation 2017/746 on In Vitro Diagnostic Devices (the IVDR) which came into force at the end of May 2017. The Regulation has a staggered transitional period, with full application after five years. The regulation replaces the existing IVD directive (98/79/EC) and is intended to strengthen the current regulatory system by providing:

- clearer requirements regarding clinical data for IVDs, and their assessment
- more specific product requirements, such as unique identifiers for IVDs
- improved pre-market assessment and post-market surveillance of all high-risk devices
- increased control and monitoring of Notified Bodies by the National Competent Authorities and the Commission
- more stringent requirements for POCT (near-patient tests)
- enhanced traceability for IVDs.

One of the key changes under the IVDR relates to the conformity assessment procedures required of manufacturers prior to an IVD being placed on the market. Requirements vary based on the risk classification of the device, that is, for low risk (Class A) up to high risk (Class D). Assessment and certification by a notified body will be required for those IVDs in Classes B, C and D. Class A devices placed on the market in a sterile condition shall also require notified body involvement, limited to the sterile aspects of the product. Devices for POCT (near patient testing) are classified in their own right under Rule 4(b) of Annex VIII of the IVDR. Depending on the intended purpose specified by the manufacturer, CRP POCT devices will likely be in Class C (under Rule 3) or Class B (under Rule 6). This represents a significant change to the existing regulatory system, where the majority of IVDs are self-declared by the manufacturer rather than being assessed by a notified body. Detailed requirements for the performance evaluation of IVDs are outlined in the IVDR. The performance evaluation will comprise data on the scientific validity, analytical performance and clinical performance of the device. Under the IVDR, IVDs for POCT must perform appropriately for their intended purpose taking into account

the skills of the intended user and the potential variation in the user's technique and environment, with sufficient information provided in order for the user to be able to correctly interpret the result provided. It is recognised that the enhanced regulatory burden arising from implementation of the IVDR may impact the number and range of IVDs on the market.

The Health Products Regulatory Authority (HPRA) is designated as the Competent Authority for medical devices in Ireland. Its role is to ensure that all medical devices sold into the Irish market comply with the relevant legislation. This means that a medical device must achieve the performance criteria specified by the manufacturer and in doing so must not compromise the health and safety of patients, service providers and any other persons. In its role as the Competent Authority, the HPRA operates a vigilance system for medical devices. Vigilance issues include adverse incidents and field safety corrective actions (FSCAs).

An adverse incident is an event during use of the device which might lead to or might have led to the death of a patient, user or other persons, or to a serious deterioration in their state of health. The HPRA strongly encourages those who have experienced a safety issue with a medical device to report that issue to them. The HPRA currently operates a voluntary reporting system for users of medical devices, healthcare professionals or any other person who identifies a medical device safety issue. There is a mandatory requirement for manufacturers to report vigilance issues to the appropriate national Competent Authority. The European guidelines for a medical devices vigilance system are outlined in MEDDEV 2.12/1.[23]

A field safety corrective action (FSCA) is an action taken by a manufacturer to reduce a risk of death or serious deterioration in the state of health associated with the use of a medical device that is already placed on the market. Such actions, whether associated with direct or indirect harm, should be reported and should be notified via a field safety notice (FSN). The FSCA may include, for example:

- the return of a medical device to the supplier
- device modification
- advice given by manufacturer regarding the use of the device and/or the follow up of patients, users or others.

It is very important that providers of CRP POCT have adequate traceability systems in place in the event of a field safety corrective action necessitating, for example, a review of results or the recall of patients for repeat testing.

2.3 Potential benefits and harms of the technology

The aim of CRP POCT is to provide quality-assured CRP test results, which allow physicians to differentiate between mild and severe respiratory tract infections, and to rule out potentially serious bacterial infections, when it is not clear if antibiotics should be prescribed based on clinical assessment alone. The physician follows diagnostic and treatment guidelines, basing antibiotic treatment decision(s) for the patient (of no antibiotic therapy, delayed antibiotic prescription or offering antibiotic therapy) on whether CRP results fall below or above explicit thresholds as outlined earlier.

The technology should therefore have a moderating influence on the need for the physician to issue an immediate prescription for antibiotics to patients with low, medium or high CRP levels. The test result should be available in minutes during patient consultation to support an immediate treatment decision in primary healthcare settings, thus eliminating the delay in receipt of laboratory results (which may often take hours or even days to arrive) and speeding up patient referral to secondary care if required. By assisting physicians to make immediate treatment decisions, the technology is intended to enhance patient safety and compliance with clinical guidelines for the management of RTI, as well as physician and patient satisfaction. A CRP test measured during the patient visit has been found to increase patient satisfaction and understanding of when antibiotics are needed or not needed.[24]

Commercially available CRP POCT analysers intended for use in primary care range in size and weight (from 1kg to 35kg) with some considered to be portable instruments that can be easily moved to the point of need (for example if a general practitioner (GP) is providing care in a number of settings including out-of-hours clinics or long-term care facilities).

Debate over the accuracy of point-of-care tests and their effect on antibiotic prescribing is ongoing. Some studies have found the analytical performance of POCT comparable to laboratory testing, while others have reported that certain pieces of equipment are more accurate and precise than others.[25, 26] The ability of CRP POCT to aid in the diagnosis of serious bacterial RTIs is unclear, with some studies finding it useful in primary care, [27] while others have reported it to have limited utility.[28] The subsequent effect of CRP POCT on the prescription of antibiotics has shown conflicting results, with some studies finding it significantly reduces antibiotic prescribing,[29, 30] while others have found it has little effect[27, 31]

or may even lead to an increase in antibiotic use[32] and hospitalisation rates.[29] However, the CRP POCT can produce false positive as well as false negative results, leading to the possibility of over- or under-treatment of RTIs.[29] Some commonly prescribed medications (such as lipid-lowering agents, ACE inhibitors, ARBs, anti-diabetic agents, anti-inflammatory and anti-platelet agents, and beta-adrenoreceptor antagonists) are known to lower CRP levels, and this should be taken into account during the patient consultation, as a low CRP test result may carry a risk of inappropriate treatment choices by the clinician.[33] Over-treatment can lead to avoidable adverse reactions to antibiotics and contribute to antimicrobial resistance; while in those who are under-treated, there is the potential to increase morbidity or mortality.

The safety and effectiveness and diagnostic test accuracy of CRP POCT in patients presenting with acute RTI as well as the analytical performance of the commercially available CE marked tests is assessed in detail in the safety and effectiveness domains of this report.

2.4 Implementation of CRP POCT in other European countries

The first fully quantitative CRP POCT system (QuikRead®) was launched in 1993. This original device has been followed by newer generation quantitative devices from the originator and competing manufacturers in the IVD market. The first semi-quantitative CRP and viral biomarker co-test (FebriDx®) was CE marked in September 2014.

The use of POCT for CRP in patients with suspected lower RTI has been included in guidelines in the UK, Norway, Sweden, the Netherlands, Germany, Switzerland, Czech Republic and Estonia to determine severity of infection and to guide antibiotic prescribing.[22, 34] Leading adopters of the technology include the Netherlands and the Scandinavian countries.[25] The UK NICE guidelines for the diagnosis and management of pneumonia in adults have issued a non-mandatory recommendation that point-of-care CRP testing should be considered for people with symptoms of lower respiratory tract infection in primary care if a diagnosis is unclear after clinical assessment, and that antibiotics should be prescribed based on the result.

In many European countries, healthcare is budget-driven, not reimbursement-driven. These countries appear not to provide direct reimbursement for use of CRP POCT in primary care. The reimbursement estimate per test was estimated from data provided by one of the five manufacturer(s) who engaged in the assessment, and from data shared by the HTA agency from the relevant country (Table 2.3).

Table 2.3 Tracker of CRP POCT implementation and summary of reimbursement recommendations for CRP POCT in European countries

Country	Implementation of CRP POCT	Status of recommendation (positive / negative / ongoing / not-assessed / no detail available)	If positive, level of reimbursement*
Belgium	Yes[24]	No details available	No details available
Czech Republic [b]	Yes[34]	No details available	No details available
Denmark [b]	Yes[35, 36]	Positive	about DKK 65-77 per test [b]
Estonia	Yes[34]	No details available	No details available
Finland	Yes[37]	No details available	No details available
Germany [a b]	Yes[34] (ambulatory care setting only) [a]	Positive, also under assessment (appears to be ambulatory care setting only) [a]	€1.15 per test in general laboratory, €4.90 in special laboratory [a]
Hungary [a b]	Yes	Positive (reimbursed regardless of test product) [a]	No price available
Ireland	No	Not assessed	Not relevant
Italy [a]	Yes	Positive (tests are performed and reimbursed in NHS)	No details available
Lithuania [a]	Yes (inpatient & outpatient settings only) [a]	Positive (inpatient and outpatient only)	No price available
Netherlands [a b]	Yes[34]	Positive (depending on the indication (e.g. pneumonia)) [a]	about €3.90/test [b]
Norway [a b]	Yes[34]	Positive (CRP tests are reimbursed; CRP POCT are the most widely used)	NOK 42/test [b]

Footnotes: a. Feedback from WP4 partners; b. Dossier submission from Orion on availability of QuikRead® (and price if available) in European countries.

Key: CHF – Swiss Franc; DKK – Danish Krone; NHS – National Health Service; NOK – Norwegian Krone.

Table 2.3 continued

Country	Implementation of CRP POCT	Status of recommendation (positive / negative / ongoing / not-assessed / no detail available)	If positive, level of reimbursement*
Poland [a b]	Yes (primary care, ambulatory & hospital setting)[a]	Positive	No price available
Slovakia [b]	Yes	No details available	No details available
Slovenia [a]	Yes (emergency and primary care settings)	Positive (higher costs for CRP POCT than lab test) [a]	No details available
Spain [a]	Yes[24] (primary care, ambulatory & hospital setting) [a]	Positive (included in common services portfolio of NHS)	No details available
Sweden	Yes[34]	No details available	No details available
Switzerland [a b]	Yes[34]	Positive (regardless of setting; fixed price per test) [a]	CHF 10 [b]
United Kingdom [a]	Yes[22, 24]	Negative (non-mandatory recommendation in guideline)	No price available

Footnotes: a. Feedback from WP4 partners; b. Dossier submission from Orion on availability of QuikRead (and price if available) in European countries.

Key: CHF – Swiss Franc; DKK – Danish Krone; NHS – National Health Service; NOK – Norwegian Krone.

2.5 CRP POCT in the primary care setting

The identified CRP POCT devices are intended for use by healthcare professionals and are suitable for use in primary care. Depending on the clinical guideline or care pathway developed, the test may be administered by a general medical practitioner (GP), practice nurse, healthcare assistant or pharmacist.[38] Primary care settings may include GP practices, out-of-hours clinics, long-term care facilities and community pharmacies. As noted, the suggested use of CRP POCT is in patients presenting with symptoms of acute RTI where the clinical assessment of the infection type (bacterial or viral) is inconclusive, and it is unclear if antibiotics should be prescribed.

The type of equipment required for implementing CRP POCT in primary care depends on whether the technology adopted is a quantitative test (that is, assay with analyser) or semi-quantitative test (that is, strip or single-use disposable device). As previously noted, the features of the commercially available CE marked technologies identified in this assessment are listed in Appendix A. For certain brands of CRP POCT analyser and assay vial system, scanners and barcode label printers may be required to facilitate information transfer of the batch and lot number of the assay vial to the electronic health record of the patient. The facility to either scan or directly upload results into the clinical record and laboratory information management system would be beneficial when considering any potential future wide-scale procurement of CRP POCT analysers.[38] It would fall within the remit of the national POCT steering committee to set the technical specification requirements for the CRP POCT device that would then be shortlisted for procurement and implementation in primary care.

Lancets and capillary sticks are needed for the capillary blood sample for all tests, with the exception of the FebriDx®, which has an integrated lancet and capillary in the single-use disposable device.

When providing POCT, suitable facilities are required for sample collection, execution of the point-of-care tests, storage of instrumentation (if any), safe disposal of sharps and clinical waste, and to ensure that consumables such as test kits and reagents are stored under the appropriate conditions as defined by the manufacturer. Relevant regulations include the European Union (Prevention of Sharps injuries in the Healthcare Sector) Regulations 2014.[39]

Refrigeration of test kits at 2-8°C is required for a number of the assay tests identified, with a specification that the kits be brought to room temperature prior to use. The unique storage details specific to each device are listed in Appendix A.

Given the requirement for a blood, serum or plasma sample, usual local and national infection prevention and control guidelines will apply to minimise the risk of the patient acquiring a preventable healthcare-associated infection and also to protect staff from acquiring an infection in the workplace. Disposable gloves should be worn for all activities that carry a risk of exposure to blood or body fluids.

The disposal of all samples and other test materials should follow usual official regulations. Consumables such as lancets, disposable strips, cartridges, patient samples, and any used cuvettes, capillaries and plungers if required for the analyser type, should be handled and disposed of as appropriate for potentially

infectious (bio-hazardous) waste. Waste receptacles must be of sufficient size and volume to accommodate the waste generated, including sharps bins where relevant. When used in accordance with Good Laboratory Practice, good occupational hygiene and the instructions for use, the reagents supplied with these tests should not present a hazard to health. Some of the assays minimise the exposure to test reagents as they use all-in-one test cartridges (with the reagent included), while one analyser uses a closed-sample system for reagent mixing (that is, AQT90 FLEX®).

Training of healthcare professionals is required to use CRP POCT in primary care. The level of training involved will depend on whether the technology adopted is a quantitative test (that is, assay with analyser) or semi-quantitative test (that is, test strip, dipstick or single-use disposable device). Training in pre-analytic handling including machine calibration is required for quantitative tests; training in the interpretation of the tests is required for both quantitative and semi-quantitative tests. The practical aspects of using the available tests and the level of training support available from manufacturers (where provided) are detailed in Appendix A. In addition, support may be needed from hospital laboratories to provide advice on quality assurance, external quality control and training in tandem with that provided by the manufacturers. It would be appropriate for the POCT national steering committee to make recommendations on the potential role for medical scientists, as community POCT teams, in delivering the training programme and governance structures for CRP POCT in primary care.

In some countries, national guidelines for the implementation of POCT in primary care are available that detail the requirements for staff training in the use of POCT. For example, the Guidelines for Safe and Effective Management and Use of Point of Care Testing in Primary and Community Care in Ireland (2009)[40] state that:

> It is imperative that all staff performing POCT are trained and competent in the use of the test. This training may be conducted by the manufacturer or authorised representative. Relevant professional organisations may also provide training on certain tests. It is important to agree the detail and level of training to be provided by the manufacturer or his representative at the time of purchase of the POC test and to ensure that this training is completed and recorded prior to implementation of the POCT service. Training records should be kept in each testing location. Where appropriate, trainers should be designated and such individuals should receive extra training. The competency of the individual performing POCT should be assessed on an ongoing basis and supplementary training provided if required.

A training programme should be put in place and should include the following elements:

- Instructions on safe working practices
- Principles of operation of the device
- Review of the manufacturer's instructions for use (IFU), limitations of the device, interferences
- Review and understanding of error messages, interpretation, and appropriate responses
- Calibration and quality control requirements, including acceptable limits, appropriate record keeping and required actions for failed results
- Patient preparation, sample collection and handling according to the manufacturer's stated requirements and health and safety regulations
- Interpretation and recording of patient results and appropriate patient referral and follow-up
- Training of new recruits and periodic refresher training for service providers.

There may also be a healthcare policy requirement to include communication training and/or an education piece for physicians and patients around the link between antibiotic prescribing and anti-microbial resistance.

The workflow at the testing site may need to be reconsidered if POCT has not previously been used in the primary care setting (that is, who will perform the test and report the result to the patient). For quantitative tests, the number of analysers required will depend on the number of practitioners performing the test and the layout of the practice setting.

Independent accreditation is an important and often mandatory requirement for pathology laboratories as part of their quality assurance processes. International standards for POCT have been developed by the International Standards Organization (ISO) in the form of ISO 22870: 2016.[41] This document gives specific requirements applicable to POCT and is intended to be used as a companion to ISO 15189: 2012 *Medical Laboratories – Requirements for Quality and Competence*

Standard.[42] The ISO 22870: 2016 standard specifies requirements for competence and quality in POCT performed in hospitals, clinics and healthcare organisations providing ambulatory care; it excludes patient self-testing in a home or community setting. National guidelines in some countries recommend that any POCT service in primary care be ISO accreditable.[40, 43] These guidelines may recommend any site providing a POCT service to undergo a relevant accreditation procedure in order to provide assurance of the validity of the point-of-care results taking into account clinical context and patient safety.[43] Examples of organisations that provide external quality assurance include SKUP, a Scandinavian cooperation between agencies in Denmark, Norway and Sweden for evaluation of near-patient laboratory equipment which publishes independent evaluations of the analytical performance of CRP POCT equipment, and WEQAS in Wales, which is supporting roll-out of CRP POCT to inform antibiotic prescribing in Wales.

2.6 Discussion

CRP devices are indicated for the quantitative determination of CRP in human whole blood and in human serum and plasma. The measurement of CRP provides information for the detection and evaluation of infection, tissue injury, inflammatory disorders and associated diseases.

The aim of the CRP POCT technology is to provide quality-assured test results, which allow physicians to differentiate between mild and severe respiratory tract infections, and to distinguish between serious bacterial or self-limiting viral infections, when it is not clear if antibiotics should be prescribed based on clinical assessment alone. Clinical guidelines have been developed for use by clinicians, basing antibiotic treatment decision(s) for the patient (of no antibiotic therapy, delayed antibiotic prescription or offering antibiotic therapy) depending on whether CRP results fall below or above explicit thresholds.

Fifteen CE marked CRP POCT systems were identified for inclusion in this HTA, the majority of which are CE marked, meaning they are declared to be in conformity with the IVD Directive. The systems evaluated may be broadly classified into one of two categories: quantitative methods (that is, analysers using either capillary or venous blood) and semi-quantitative methods (that is, strips, dipsticks or single-use disposable tests using capillary blood). All tests share the following similarities: each test can detect whether levels are low or high in a blood sample; all use relatively small volumes, such as 2.5 to 20 µL of capillary blood (with the exception of AQT90 FLEX® CRP assay which uses 2mL of venous blood); and the time to result does not exceed 15 minutes for any technology. Aside from the differences between quantitative and semi-quantitative technologies in terms of the

requirement for an analyser, the former also differ in the size and portability of the analyser devices; the requirement for calibration and the extent to which pre-analytical handling is required; analyser warm-up and performance times; and the degree to which test data can be stored on the device, printed and/or transferred to electronic patient files. These differences may contribute to differences in the acceptability and performance of the tests by the intended user, that is, healthcare staff who are not laboratory specialists working in the primary care setting.

CRP POCT can be used in combination with communication training, an education component and/or tests for other biomarkers in addition to standard care to assist the treating clinician in differentiating between bacterial and viral aetiology, and thereby guide antibiotic prescribing.

The proposed benefits of the technology are that it should have a moderating influence on the need for the physician to issue an immediate prescription for antibiotics to patients whose CRP levels fall below a stated threshold; it supports an immediate treatment decision in primary healthcare settings, thus eliminating the delay in receipt of laboratory results and speeding up patient referral to secondary care, if required; and it is proposed that use of CRP POCT enhances patient safety and compliance with clinical guidelines, as well as physician and patient satisfaction. There is a risk that CRP POCT can produce false positive as well as false negative results leading to the possibility of over- or under-treatment of RTIs. Over-treatment can lead to avoidable adverse reactions to antibiotics and contributes to antimicrobial resistance; while in those who are under-treated, there is the potential risk of increased rates of morbidity or mortality.

Use of CRP POCT in the management of patients with suspected lower RTI has been included in guidelines in the UK, Norway, Sweden, the Netherlands, Germany, Switzerland, Czech Republic and Estonia, with the Netherlands and Scandinavian countries being leading adopters of the technology in primary care. At least 18 European countries have CRP POCT technology available to medical practitioners for use in patients in primary, outpatient and/or ambulatory care settings. Reimbursement status and policy differs between countries. CRP POCT may be performed on patients, if viewed as necessary by a medical practitioner, and is reimbursed on the NHS (Spain and Italy). CRP POCT is reimbursed regardless of setting, and there is a fixed price paid per test used (Switzerland). Some countries operate an indication-specific reimbursement model for CRP POCT (such as for the diagnosis of pneumonia in the Netherlands); while other healthcare systems reimburse the test regardless of which system is used by the medical practitioner (Hungary). Pricing of the CRP POCT appears to vary by test type, manufacturer,

healthcare setting and country.

2.7 Key messages

- CRP point-of-care testing is used to measure the level of C-reactive protein in a person's blood. Typically, raised concentrations of serum CRP occur in bacterial infections while lower elevations are observed in viral infections.
- The purpose of the test is to assist the clinician assess the likelihood of a serious bacterial infection as opposed to a less serious bacterial infection or viral infection, thereby supporting a decision on whether or not to provide an antibiotic.
- Fifteen CRP POCT devices were identified that were suitable for use in a primary care setting. These can broadly be divided into two categories: quantitative devices and semi-quantitative devices.
- The majority of quantitative tests require whole blood, plasma or serum. Semi-quantitative test methods require capillary blood.
- The first fully quantitative CRP POCT system was launched in 1993. The first semi-quantitative CRP was launched in 2014.
- The use of POCT for CRP in patients with suspected lower RTI has been included in guidelines in the UK, Norway, Sweden, the Netherlands, Germany, Switzerland, Czech Republic and Estonia to determine severity of infection and to guide antibiotic prescribing.

3 Burden of disease

This assessment is concerned with the use of C-reactive protein (CRP) point-of-care testing (POCT) in the diagnosis and treatment of acute respiratory tract infections (RTIs). The purpose of this chapter is to outline the epidemiology of acute RTIs.

3.1 Description of respiratory tract infections (RTIs)

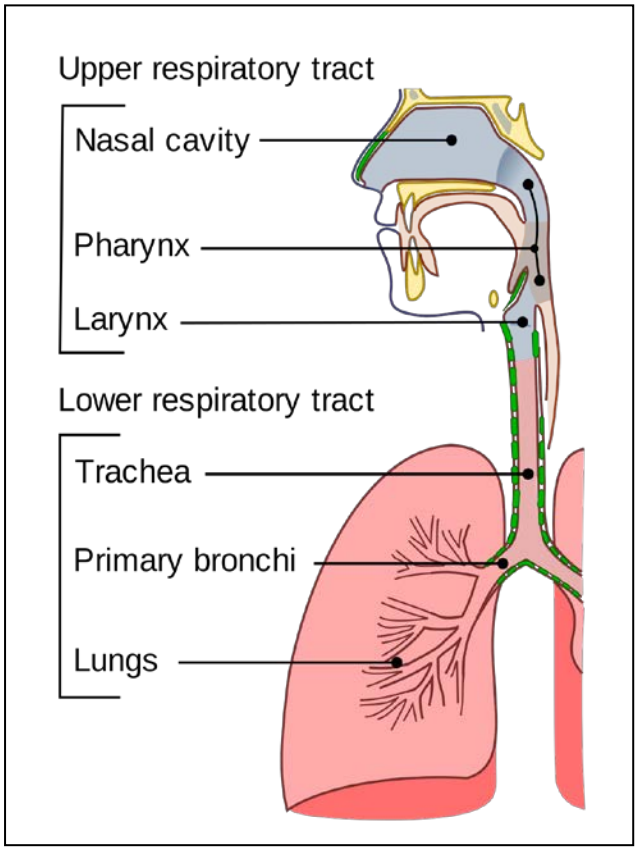
Respiratory tract infections (RTIs) are the most frequent infections encountered in primary care; most are viral, but a small number are caused by bacteria and may respond to antibiotics. Symptoms of RTI include cough, discoloured and/or increased sputum production, fever, runny nose, respiratory distress, feeling unwell, or combinations of focal and systemic symptoms. RTIs may be classified as upper or lower respiratory tract infections, the boundary of which is typically the larynx. Upper respiratory tract infections (URTIs) include pharyngitis, tonsillitis, laryngitis, rhinosinusitis, otitis media and the common cold.[29] Lower RTIs (LRTIs) include pneumonia, bronchitis, tracheitis and acute infective exacerbations of COPD. Influenza may affect both the upper and lower respiratory tract. The pragmatic definition of a LRTI adopted in the 2011 guidelines produced by the European Respiratory Society (ERS) in collaboration with the European Society for Clinical Microbiology and Infectious Disease (ESCMID) is as follows: *'an acute illness (present for 21 days or less), usually with cough as the main symptom, with at least one other lower respiratory tract symptom (sputum production, dyspnoea, wheeze or chest discomfort/pain) and no alternative explanation (for example, asthma*).'[44]

The distinction between the upper and lower respiratory tract is illustrated in Figure 3.1. The definition of the different types of acute RTIs, their associated symptoms and burden of disease, along with the natural course of the illnesses at an individual patient level are detailed in Appendix B.

In the majority of cases of RTI, no pathogen is identified, primarily because the organism is missed, or as in the case of patients presenting in primary care, testing is not performed because of challenges obtaining samples, limited access to diagnostics, and the limited clinical utility in obtaining results subsequent to the requirement for an empirical treatment decision to be made. A potential pathogen was identified in 59% of adults presenting to primary care with LRTI in a large EU-funded prospective case-control diagnostic study (n=3,104) undertaken in 11 European countries by the GRACE (Genomics to combat Resistance against Antibiotics for Community acquired lower respiratory tract infection (LRTI) in

Europe) consortium. Overall, a bacterial pathogen was identified in 21% of patients, with a viral pathogen identified in 48%; both bacterial and viral pathogens were identified in 10% of cases.[45] The most common bacterial pathogens isolated were *Streptococcus pneumoniae* (5.5%) and *Haemophilus influenzae* (5.4%), while the most common viral pathogens isolated were human rhinovirus (20.1%), influenza virus (9.9%) and human coronavirus (7.4%). This evidence is consistent with the literature reported in the 2011 European Respiratory Society (ERS)/European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guidelines, which noted that viruses are involved in up to 60% of community-acquired LRTIs. The most common bacterial pathogens isolated are *Streptococcus pneumoniae* and *Haemophilus influenza*, although published estimates vary, ranging from 3% to 30% and from 3% to 14%, respectively, of community-acquired LRTI cases.[44]

Figure 3.1 Anatomy of the respiratory tract



The aetiology of a subset of LRTI, specifically community-acquired pneumonia (CAP) in adults presenting to primary care, was also reported in the prospective study by the GRACE consortium. CAP was diagnosed in 4.5% of adults (6.4% of those > 65 years) presenting with LRTI in primary care. Potential bacterial pathogens were significantly more likely to be identified in those with CAP, with a bacterial pathogen

identified in 30% of cases. Viral pathogens were identified in 37% of cases, while both bacterial and viral pathogens were identified in 7% of cases. No pathogen was identified in 40% of CAP cases. Again, the most common bacterial pathogens isolated were *Streptococcus pneumoniae* (9.2%) and *Haemophilus influenzae* (14.2%).[45] This evidence is also consistent with other literature including that reported in the 2011 ERS/ESCMID guidelines which noted that viruses are involved in up to 30% of CAP, again with *Streptococcus pneumoniae* and *Haemophilus influenzae* being the most common bacterial pathogens.[44, 46, 47]

3.2 Natural course of RTIs

RTIs comprise a collection of specific diagnoses which can be broadly classified as upper and lower RTIs, the boundary of which is typically the larynx. Upper respiratory tract infections (URTIs) include pharyngitis, tonsillitis, laryngitis, rhinosinusitis, otitis media and the common cold.[29] Lower RTIs (LRTIs) include pneumonia, bronchitis, tracheitis and acute infective exacerbations of COPD. Influenza may affect both the upper and lower respiratory tract. The definition and symptoms of each of these conditions, described along with the burden of the disease and the natural course of the illness in the individual patient, are detailed in Appendix B. The natural course of URTIs is typically shorter (ranging from four days for acute otitis media to 2.5 weeks for acute rhinosinusitis) than for LRTI (ranging from three weeks for acute bronchitis/cough to three to six months (to complete recovery) for community-acquired pneumonia [CAP]).

LRTIs with a bacterial aetiology are often assumed to result in a different illness course than non-bacterial causes, but evidence of actual difference is lacking. The illness course of a bacterial LRTI in a large study population (n=1,021) of adult patients presenting to primary care with symptoms of acute cough for whom pneumonia was not clinically suspected was evaluated as part of a secondary analysis of a multicentre European trial by the GRACE consortium. While a slightly worse course of disease was observed in those for whom a bacterial origin was identified, the relevance of this difference was not found to be clinically meaningful. The authors concluded that, similar to non-bacterial LRTI, the illness course of bacterial LRTI is generally mild and self-limiting.[48]

3.3 Risk factors associated with acute RTIs

The respiratory tract is vulnerable to infection from bacteria or viruses. RTIs are seasonal and tend to be more common during the winter. Children tend to acquire more URTIs than adults. This is due to the lack of immunity to the multiple viruses that can cause colds. Most RTIs are self-limiting. However, extra care and additional treatment may be required for people who are more vulnerable to the

effects of opportunistic infection. The following patient groups with the disease states or environmental factors listed are at most risk:[49, 50]

- Paediatric < five years
- Geriatric > 70 years
- Pre-existing lung condition (such as COPD or asthma)
- Immuno-compromised (such as HIV positive patients)
- Immuno-suppression medication regimen (such as tacrolimus)
- Smokers
- Long-term care residents of nursing homes
- Under-nutrition in children
- Indoor and ambient air pollution.

The risk factors for complicated influenza should also be noted for selected populations:[51]

- Neurological, hepatic, renal, pulmonary and chronic cardiac disease
- Diabetes mellitus
- Severe immunosuppression
- Age over 65 years
- Pregnancy (including up to two weeks post-partum)
- Children under six months of age
- Morbid obesity (BMI ≥40).

The 2015 Global Burden of Disease Study of LRTIs detected a relationship between incidence and mortality from LRTIs and the Social Demographic Index (SDI).[52] Mortality from LRTIs decreased rapidly when transitioning from low to middle SDI countries. This association with socio-demographic issues is particularly evident for children aged less than five years where the burden of LRTI remains high, particularly in countries with low socio-demographic development. This may have implications for subsets of socially deprived populations within European countries.

The risk of complications in a primary care patient with LRTI was also assessed by the Joint Task Force of the European Respiratory Society (ERS) and European Society for Clinical Microbiology and Infectious Diseases (ESCMID).[44] They recommend that patients with an elevated risk of complications should be monitored carefully and referral should be considered. In patients aged 65 years of age and older, the following characteristics are associated with a complicated course:[44]

- presence of chronic obstructive pulmonary disease (COPD), diabetes or heart failure
- previous hospitalisation in the past year
- taking oral corticosteroids
- antibiotic use in the previous month
- general malaise
- absence of upper respiratory symptoms
- confusion/diminished consciousness
- pulse >100, temperature >38, respiratory rate >30, blood pressure <90/60
- when the primary care physician diagnoses pneumonia.

In patients aged less than 65 years, the task force reported that diabetes, a diagnosis of pneumonia and possibly also asthma are risk factors for complications. For all age groups, serious conditions such as active malignant disease, liver and renal disease and other disorders that are relatively rare in primary care but which affect immunocompetence also increase the risk of complications.

3.4 Epidemiology of RTIs across the European Union in primary care settings

No international studies were identified that reported European-level data for patients presenting with RTI in primary care. As noted previously, the Global Burden of Disease study reports international data for RTIs, but these data do not include incidence data from primary care.

In the absence of similar epidemiological data limited to patients presenting to primary care, the data reported in this section relies heavily on published studies and surveillance data from a limited number of European countries, and in particular the Netherlands and the United Kingdom for which large-scale studies based on primary care data were identified.

Estimates from the Second Dutch National Survey of General Practice (2000-2002)[53] report that 15% of all episodes in general practice related to RTI illness. In total, 4.2% of those presenting to primary care were diagnosed with a RTI with an incidence rate of 144 per 1,000 person-years. On average, URTI and LRTI accounted for 100 and 44 GP consultations per 1,000 person-years, respectively. If signs and symptoms were added to the total incidence figures, the incidence of GP consultations for RTI was 215 per 1,000 person-years. The median age of patients presenting to the GP with at least one episode of RTI was 31 years (range 0 to 105) and 44% were male. A subset of patients had at least three episodes of GP-diagnosed RTI in one year (42 per 1,000 total patient population). The incidence

of URTI was significantly higher in children aged less than five years than in other year-cohorts (392 per 1,000 child-years; relative risk (RR) 4.9 (95% CI: 4.8-5.0)), and with the exception of acute otitis media (15 vs 16/1,000; RR 0.9, (95% CI: 0.85-0.95)), incidences were higher for females that for males (103 vs. 74 per 1,000; RR 1.4 (95% CI: 1.35-1.45)). Among patients presenting to primary care, the four most common URTI diagnosed were rhinitis, acute sinusitis, acute otitis media and acute tonsillitis, with incidence rates of 51.0, 22.7, 15.6 and 10.2 per 1,000 person-years, respectively. A U-shape association was observed between age and LRTI, with a higher incidence observed in children aged 0 to 4 years (78 per 1000) and adults aged 75 years and older (70 per 1,000) compared with the other age categories (23 per 1,000). This U-shape association was also evident when restricted to diagnoses of pneumonia with incidence rates of 16.6 and 21.6/1,000 person years in those aged 0-4 years and adults aged 74 years and older, respectively. The incidence of both upper and lower RTI was significantly higher in patients with chronic lung disease (209/1,000 [RR: 1.5] and 156/1000 person years [RR 5.2], respectively) compared with the total patient population. LRTI were also noted to be significantly more common in patients with diabetes mellitus (RR: 2.2) and cardiovascular disease (RR: 2.2).[53]

Using data from the UK General Practice Research Database which has been widely used for pharmacoepidemiological research, Millett et al. estimated the incidence of community-acquired LRTI and pneumonia among older adults (aged 65 years and older) over a 14-year study period (1997-2011). The crude overall LRTI incidence was 122.9 episodes/1,000 person years. Incidence increased with increasing age from 92.2 episodes/1,000 person-years (65-69 years) to 187.9 episodes/1,000 person-years (85-89 years), and was noted to be higher in males than females. Incidence was also noted to be higher in patients with a history of COPD. The overall incidence of CAP was 8.0/1,000 person years, was higher in males than females, and was noted to increase significantly with increasing age (from 2.8 to 21.8 episodes/1,000 person-years in those aged 65-69 years and 85-89 years, respectively).[54] The substantial burden associated RTIs was also confirmed in a more recent study of respiratory and communicable disease incidence from a primary care sentinel network in England. The 2014-2015 mean weekly incidences of the common cold, acute otitis media (AOM), pneumonia and influenza-like illness were 105.1, 26.0, 2.5, and 9.8 cases per 100,000 population, respectively; there was evidence of seasonal variation for all four conditions. A U-shape association was again observed for pneumonia: after controlling for other factors; multivariate logistic regression analysis showed that compared with those aged 0-4 years, the odds of a pneumonia were significantly lower for those aged 5-24 years (OR 0.33) and those aged 25-49 years (OR 0.57) and highest for those

aged 75 years and older (OR 6.37).[55]

A proportion of RTIs are vaccine-preventable, with variation in vaccination policy, and access to and uptake of vaccine, contributing to differences in disease burden. For example, seasonal influenza is a vaccine-preventable disease and annual influenza vaccination remains the most effective preventive strategy for severe influenza. The substantial burden associated with influenza in primary care is evident in a study using data from the UK Clinical Practice Research Datalink (CPRD) and surveillance data that tracked GP episodes for respiratory illness, otitis media and antibiotic prescriptions attributable to influenza during 14 seasons (1995-2009). Seasonal mean estimates of influenza-attributable GP episodes were 857,996 corresponding to 1.5% of the total population, with a wide inter-seasonal variability. In an average season, 2.4% of children aged less than five years and 1.3% of those aged 75 years and older had a GP episode for respiratory illness attributed to influenza A while 0.5% and 0.1%, respectively, had episodes related to influenza B. Of note, two-thirds of influenza-attributable GP episodes were estimated to result in a prescription of antibiotics.[56] While the ECDC recommends the vaccine for all Europeans, it is noted to be especially important for those at higher risk of serious influenza complications: individuals with specific chronic medical conditions, pregnant women and children aged 6-59 months, the elderly and healthcare workers.[57] The HSE advocates that all those aged over 65 years, health care workers, pregnant women, and all those aged six months to 65 years with underlying medical conditions should be vaccinated against seasonal influenza.

In Ireland, influenza vaccination coverage is moderate among those aged 65 years and over. The vaccine uptake rate was estimated at 54.4% in 2016/17 versus the EU target of 75%.[58] Provisional data for 2017/2018 indicate an uptake rate of 54%.[59] The trend for influenza vaccine coverage among this cohort of patients has been fluctuating since 2004/5 with 61.4% coverage followed by uptake peaks of 70.1% in 2008/9 and 63.8% in 2010/11. There is also evidence of wide variation in coverage rates in those patients over 65 years old by CHO area. Influenza vaccination coverage has remained low (~30%) in other vaccine-targeted population groups, such as health care workers (HCWs) and clinical risk groups (for example, patients between 18 and 65 years of age with medical conditions and pregnant women).

HCWs have reported influenza vaccination coverage of 30.8% among hospital staff and 27.1% among long-term care facility (LTCF) staff for 2016/17.[58] While these rates among HCWs represent the best coverage rates over a six-year period, they remain low when compared with reported influenza vaccine coverage rates for

2014/15 among HCWs in England (~55%) and the Netherlands (~75% in primary care/outpatients).[58]

No large-scale international studies were identified that reported European-level data for patients presenting with RTI in primary care. However, one retrospective observational study of primary care databases from Belgium, the Netherlands and Sweden reported on the incidence of consultations for seven acute infections (URTI, sinusitis, tonsillitis, otitis media, bronchitis, pneumonia and cystitis) in 2012 and the antibiotic prescriptions corresponding with these diagnoses. For the six RTI diagnoses under study, consultation incidences were 162, 173 and 296 per 1,000 registered patients per year for Sweden, the Netherlands and Belgium, respectively. Consultation incidence for the diagnoses of URTI and bronchitis in Belgium were twice as high as those observed in the Netherlands and Sweden. In the Netherlands, the consultation incidence for sinusitis was higher than in the other countries, while the consultation incidence for tonsillitis in Sweden was twice that of the Netherlands. High consultation incidences were associated with high antibiotic prescription rates, with GPs in the Netherlands and Sweden noted as prescribing fewer antibiotics for RTIs than those in Belgium. [60]

While data have been collected on GP visits for influenza-like illness in different countries, given the wide rates of national case definitions, differences in consultation behaviour, vaccination coverage and obligatory doctor visits for absence from school or work, the estimated consultation rates differ between countries. A large community study on influenza in the UK, the Flu Watch cohort study, reported age-group specific and overall estimates of the rates of influenza symptomatic disease. Seasonal and pandemic influenza over five successive cohorts (England 2006-2011) were tracked. The proportion of illnesses resulting in at least one GP consultation was 11.6%, 15.3% and 21% for those with any respiratory illness, influenza like illness with, and without confirmed fever, respectively.[61]

3.5 Diagnosis and medical management of RTIs

3.5.1 European guidelines

A summary of European and national guidelines for the diagnosis and management of acute respiratory tract infections is summarised in Appendix C.

There are commonalities in the care pathways for the diagnosis and management of acute RTIs across Europe. URTIs — common cold, acute sore throat/acute pharyngitis/acute tonsillitis, acute otitis media (AOM) and acute rhinosinusitis are characterised as self-limiting, and often viral in aetiology. For these URTIs, the guidelines recommend that a clinical assessment should include a history

(presenting symptoms, use of over-the-counter or self-medication, previous medical history, relevant risk factors, relevant comorbidities) and a physical examination to identify relevant clinical signs.[62] For acute sore throat, pharyngitis and tonsillitis, there is a preference for using clinical prediction rules (such as the FeverPAIN, McIsaac or Centor scores) to identify those patients likely to benefit from antibiotics, rather than routinely conducting a pharyngeal swab for group A streptococci (GAS).[62-66] A diagnosis of AOM in patients is generally made on the basis of conventional otoscopy, and there is little evidence that antibiotics reduce complications from AOM. For acute sinusitis, patients present with symptomatic inflammation of the mucosal lining of the nasal cavity and paranasal sinuses (less than four weeks' duration). Unilateral symptoms and purulence make bacterial aetiology more likely. In uncomplicated cases of URTIs that do not exceed the expected durations of illness, a no-antibiotic prescribing strategy or a delayed antibiotic prescribing strategy is generally recommended for patients.[62, 67] The guidelines suggest advice should be given to patients about the typical duration of illness and how to manage symptoms, including using analgesics for pain and antipyretics for fever. Antibiotics are generally only recommended for patients who are systemically very unwell, for patients with signs or symptoms of a more serious illness and/or complications, and for patients who are at high risk of complications due to a pre-existing comorbidity. Select patient groups (such as those immunocompromised or with severe comorbidities) may also require immediate antibiotic treatment.

Guidelines for the management of LRTI and specifically community-acquired pneumonia in adults have been published by a number of European countries in addition to consensus guidelines published by a joint taskforce of the European Respiratory Society (ERS) and the European Society for Clinical Microbiology and Infectious Disease (ESCMID).[44] The guidelines distinguish between cough (or acute bronchitis) and pneumonia. The use of CRP measurement is recommended if, after clinical assessment, a diagnosis of pneumonia has not been made and it is unclear if antibiotics should be prescribed. Use of antibiotics is recommended in patients with a diagnosis of pneumonia and in those with LRTI with other risk factors for complications due to comorbidities, but not in other patients who are less unwell, including those with acute bronchitis.[22, 40, 62, 68]

The Community Antimicrobial Stewardship subcommittee of the SARI National Committee developed antimicrobial prescribing guidelines for primary care in Ireland from 2009-2011 as a printed resource for GPs.[69] Since 2011, the antibiotic prescribing guidelines have been overseen by the RCPI/HSE Clinical Advisory Group on Healthcare-Associated Infection and Antimicrobial Resistance (HCAI/AMR) and are published on the HSE website.

3.5.2 Diagnosis and medical management of RTIs in practice

RTIs are commonly encountered in primary care with data suggesting that they account for around 60% of antibiotic prescriptions issued within primary care.[62] Irish data reported by Murphy et al. (2011) on 16,899 consultations from 171 GPs confirmed 68% of antibiotic prescriptions were for respiratory symptoms for private patients, and 62% for GMS patients.[70] However, as previously noted, acute RTIs are often viral, are self-limiting and do not require an antibiotic.[62, 71, 72] The percentage of Irish respondents to a Eurobarometer survey who reported using at least one antibiotic in 2016 (44%) was fractionally higher compared to 2013 (43%).[73] However, 39% of respondents to the Healthy Ireland survey (2017) reported that they were prescribed an antibiotic in the previous 12 months.[74]

Acute LRTI is a broad description of a group of disease entities, encompassing acute bronchitis, pneumonia and exacerbations of chronic lung disease. In primary care, it can be difficult to differentiate between those different conditions without doing extensive additional diagnostic tests due to the substantial overlap in presenting symptoms. As noted, patients can present with cough, sputum production, dyspnoea, tachypnoea, fever, chest discomfort/pain, wheezing and auscultatory abnormalities.[44] Reports indicate that around 5-12% of patients presenting in primary care with symptoms of a LRTI are diagnosed with community-acquired pneumonia (CAP)[75, 76] and 22-42% of these patients are admitted to hospital.[22]

CAP causes considerable morbidity and mortality across Europe and the pathogen is most commonly bacterial in origin.[77] A patient is suspected of having pneumonia when one or more of the following signs and symptoms are present: new focal chest signs, dyspnoea, tachypnoea, pulse rate >100, fever >4 days.[44] Once a clinical diagnosis of CAP is made, antibiotic therapy is initiated and CRP POCT is not indicated. However, in patients presenting with symptoms that may be indicative of suspected pneumonia in primary care, but clinical uncertainty remains for the physician, European guidelines recommend that a test for serum-levels of C-reactive protein (CRP) can be done.[44] A CRP level of <20 mg/L at presentation, with symptoms for longer than 24 hours, makes the presence of pneumonia highly unlikely; a level of >100 mg/L makes pneumonia likely. In the case of persisting doubt after C-reactive protein testing, the guidelines recommend a chest X-ray should be considered to confirm or reject the diagnosis. On the other hand, the NICE clinical guideline on the diagnosis and management of adult pneumonia (2014) offers advice on the use of C-reactive protein thresholds to inform antibiotic prescribing in patients presenting with LRTI, if after clinical

assessment a diagnosis of pneumonia has not been made and it is not clear whether antibiotics should be prescribed.

The Dutch College of General Practitioners (NHG) guidelines provide recommendations regarding the use of CRP levels to help inform antibiotic prescribing in patients who present with signs and symptoms of pneumonia and in those patients with acute cough who have other risk factors for complications due to their age (younger than 3 months or older than 75 years) or relevant comorbidities. A prospective observational study evaluated the use of CRP POCT with these guidelines, and found that differences in antibiotic prescription rate were most obvious in patients who presented with CRP values between 20 and 100 mg/L. Most GPs followed the NHG guidelines and low CRP values supported their decision not to prescribe antibiotics.[68]

Interestingly, in cases of acute cough studied in 13 countries in Europe, the variation in clinical presentation of patients does not explain the considerable variation in antibiotic prescribing; with such variation not being associated with clinically important differences in recovery.[78] Without access to CRP POCT, there may be 'defensive prescribing of antibiotics' by doctors for patients presenting with symptoms of LRTI, especially where the clinical assessment is inconclusive and the need for antibiotics is unclear. A 2015 observational study from the Netherlands of the (antibiotic) management of patients with RTIs, whose care was benchmarked to the prescribing guidelines for acute otitis media (AOM), acute sore throat, rhinosinusitis or acute cough, reported an overall antibiotic prescription rate of 38%. Of these prescriptions, 46% were not indicated by the guidelines. Relative overprescribing was highest for throat (including tonsillitis) and lowest for ear consultations (including AOM). Absolute overprescribing was highest for LRTIs (including bronchitis). Overprescribing was highest for patients between 18 and 65 years of age, when GPs felt patients' pressure for an antibiotic treatment, for patients presenting with fever and with complaints longer than one week.[79]

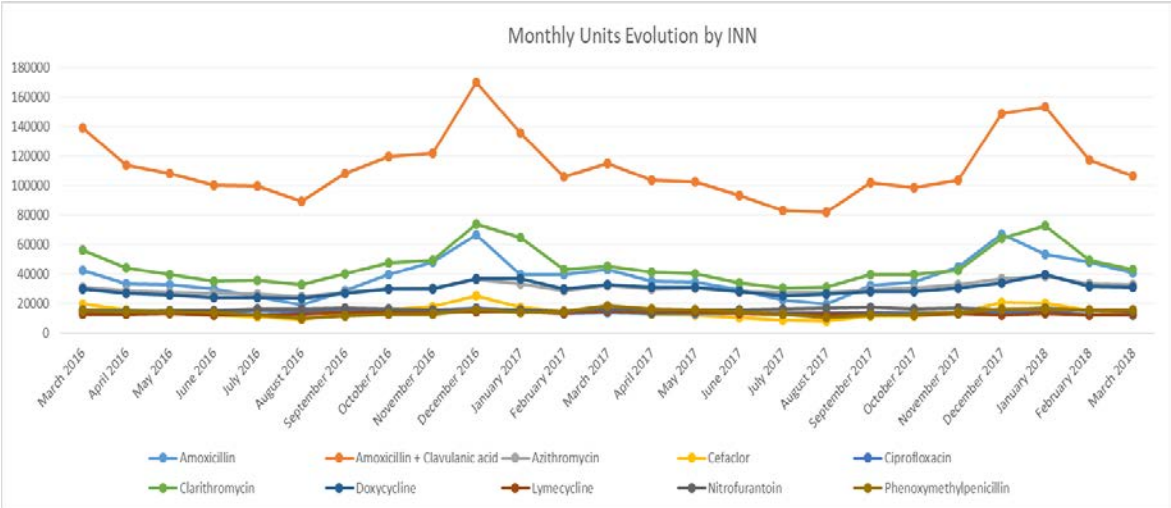
A 2018 US retrospective study, examining the adherence to guidelines from the Infectious Disease Society of America (IDSA) for the testing and treatment of children with pharyngitis, found that 28% of the antibiotics prescribed for pharyngitis in the cohort were not indicated for the specified condition.[80]

In a 12-country randomised placebo-controlled trial by the GRACE consortium (n=2,061), no clear evidence of benefit was seen with amoxicillin therapy in adults presenting with acute LRTI in whom pneumonia was not suspected clinically. Compared with placebo, use of amoxicillin was not associated with a difference in symptom severity or the duration of symptoms rated 'moderately bad' or worse in

the first few days of infection (HR 1.06 [95% CI: 0.96-1.18]), neither overall nor when limited to patients aged 60 years or older. While new or worsening symptoms were significantly less common in the amoxicillin group (15.9% vs. 9.3%, p=0.043), the number needed to treat (NNT) was high (NNT=30) and was matched by a similarly sized number needed to harm for side effects (NNH=21).[71] Similar estimates were reported by a 2017 updated Cochrane review examining the efficacy of antibiotics in the treatment of acute bronchitis.[72] In many cases, the use of antibiotics will not be beneficial to the patient's recovery and will expose them to potential side effects.

Antibiotic utilisation on the GMS scheme in Ireland between 2012 and 2015 decreased from 2,874,228 to 2,629,379 items, which was a reduction in the rate of items/1000 GMS population from 1,550 to 1,487.[81] Antibiotic utilisation based on total defined daily doses per 1,000 inhabitants per day (DID) showed a slight increase over the four-year analysis period; the increase was most prominent in the older age category (65 years and over) where DID significantly increased from 50.20 to 56.94 compared to younger populations (less than 16 years) which decreased from 20.99 to 20.75 DID.[81] Expenditure in the same period decreased from €17.93 million to €16.19 million. Figure 3.2 displays the total pharmacy prescription data (private and GMS) evolution from 2016 to 2018 by monthly units.

Figure 3.2 Pattern of antibiotic prescribing in Ireland, March 2016 to March 2018



Source: ICGP (produced by hMR)

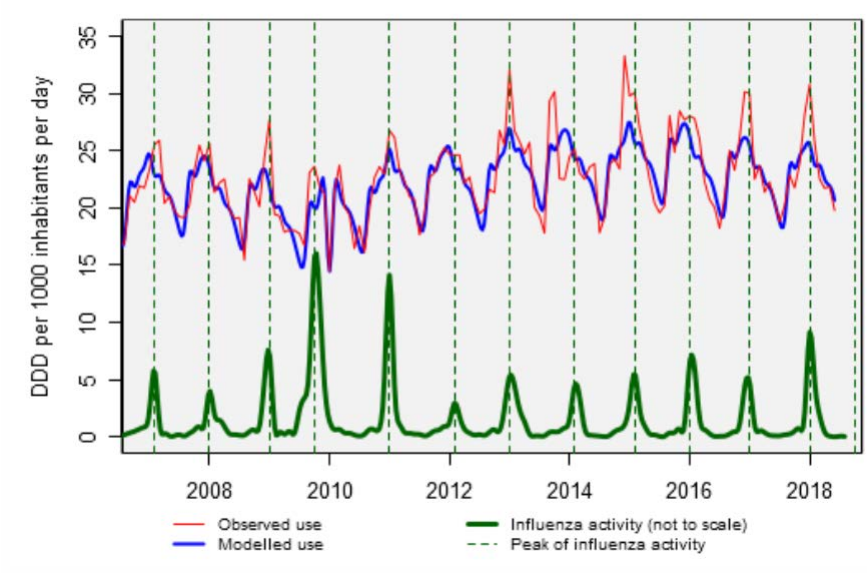
The data indicate that amoxicillin plus clavulanic acid (co-amoxiclav) and clarithromycin were the most commonly prescribed antibiotics despite not being recommended by the HSE as first-line treatments in primary care. In Ireland,

antibiotics prescribed to those aged over 65 is increasing while figures for children and younger adults are decreasing.[82]

The evidence shown of repetitive seasonal overuse of antibiotics in Irish primary care is of particular concern with emergent antimicrobial resistance. Influenza-like illness (ILI) is predominantly of viral aetiology. The clinical features of ILI may not be sufficiently specific to confirm or exclude influenza, as there may be other primary viral sources or co-infections causing the illness (such as adenovirus, parainfluenza virus, picornavirus and/or respiratory syncytial virus (RSV)). Whilst there may also be an excess of influenza-associated bacterial infections, a population-based study of the clinical complications with influenza in the UK reported that the great majority of these infections tend to be URTIs and acute bronchitis (incidence of 5.51% and 1.48%, respectively), followed by otitis media (1.05%) and pneumonia (0.38%).[83] Overall, ILI has been shown to be a good predictor of inappropriate antibiotic prescribing for RTIs in primary care.

The Health Protection Surveillance Centre (HPSC) publishes weekly influenza surveillance reports on sentinel GP ILI consultation rates and influenza detection rates from the National Virus Reference Laboratory (NVRL) documenting influenza activity in Ireland. The annual cumulative influenza activity data has been compared with the antibiotic consumption in primary care by the HPSC. Figure 3.3 compares the trend of monthly rates of antibiotic consumption (observed and modelled) versus influenza-like illness activity (not to scale) between 2007 and 2018.

Figure 3.3 Trend of antibiotic consumption (observed and modelled) versus influenza-like illness activity in Ireland (2007 to 2018)

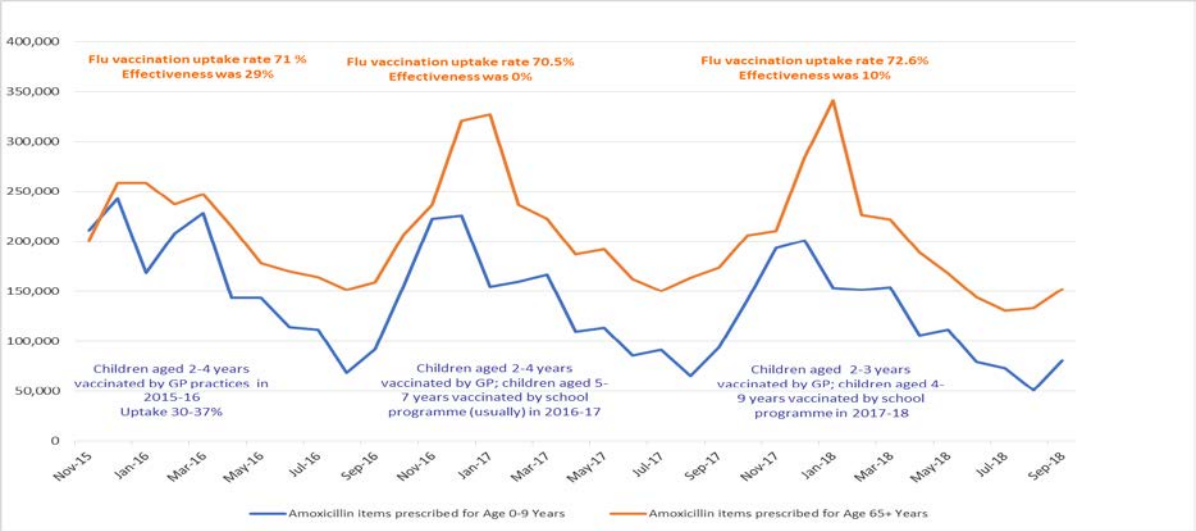


Source: HPSC Primary Care Antimicrobial Consumption Results Report (Q2 2018)

The data illustrate the annual seasonal fluctuation with high winter peaks of influenza-like illness, which appear to be associated with peaks in antibiotic consumption in Ireland.[84] This association is not unique to Ireland, and has been reported in the USA.[85] Using a time-series regression model on monthly sales of fluoroquinolone antibiotics and outpatient surveillance data on influenza activity between 2000 and 2007, respiratory fluoroquinolone usage was shown to be extremely seasonal; the cross-correlation function computed for the two data sets showed that respiratory fluoroquinolone usage was strongly associated with influenza activity. The authors predict that there may be similar findings for future studies investigating an association of influenza activity with the use of other antimicrobials used to treat respiratory infections, which is also suggested from the data presented in Figure 3.3. An ecological study in Canada (2009) showed that in the province of Ontario, offering universal influenza immunization to the entire population was associated with reduced influenza-associated antibiotic prescriptions.[86]

Figure 3.4 shows data from NHS Improvement from 2015 to 2018 illustrating the impact of the childhood influenza vaccination programme on amoxicillin prescribing for children aged 0-9 years.

Figure 3.4 Impact of influenza vaccination uptake rate and effectiveness on primary care amoxicillin prescribing in children and older people in England (2015-2018)



Source: NHS Improvement, 2019

The cumulative influenza vaccination uptake rate in the UK in children aged four to nine years was 59.5% in 2017-18.[87] These data from NHS Improvement also show the association between influenza vaccination effectiveness and amoxicillin prescribing in people aged 65 years and over. It can be seen during the winter months of 2016/17 and 2017/18, when flu vaccination effectiveness was known to be reduced in older people, amoxicillin prescribing increased.

In a study by Murphy et al. (2012) of 171 GPs participating in the continuing medical education (CME) network run by the Irish College of General Practitioners (ICGP), data were collected from 16,899 patient consultations.[88] Participating GPs gathered data on 100 consecutive consultations using a predefined piloted data collection pro forma. Out-of-hours consultations were not recorded, and no data were collected during the summer months. Anonymised patient information was recorded including the age, gender and patient payment status. GPs recorded the reason for the consultation, or the diagnosis if it was reached. These were classified by the associated body system, such as respiratory, urinary tract and skin disorders. All consultations associated with the respiratory system were further categorised into clinical entities, and classified as symptoms or as diagnoses. When an antibiotic was prescribed during the consultation, details of the prescription and directions for use were recorded on the data collection pro forma provided. GPs were also asked to record in the pro forma if they felt the antibiotic was necessary, not necessary or unsure. It was also recorded if the patient had received an antibiotic for the same

condition in the previous two weeks. Each antibiotic prescribed and the reason for the consultation was then compared to the HSE guidelines on community prescribing of antibiotics in Ireland. The authors reported that symptoms/diagnoses associated with the respiratory system accounted for the majority of antibiotic prescriptions (65%, 2,205).[88] Almost 23% (3,824) of consultations recorded either a diagnosis or symptom(s) of the respiratory system.[89] In the UK, a quarter of the population will visit their GP with a RTI each year which accounts for 60% of all antibiotic prescriptions.[62] The majority of these consultations from the Irish study received an antibiotic prescription (58%, 2,205).[88] Looking at subgroups, children (aged 1-14 years) had the highest consultation rate where a respiratory symptom/diagnosis was recorded (34%, 1,298); this group of patients were twice as likely as older patients (over 65 years old) to consult with respiratory symptoms or diagnoses. Children (aged 0-14 years) had the lowest percentage rate of antibiotic prescribing when presenting with respiratory symptoms (52%, 767); while the highest percentage was seen for patients aged 15-64 years (62%, 1,104). Of interest, there was considerable antibiotic prescribing for conditions, such as URTI (33%), cough (36%), bronchitis (85%), otitis media (93%), sinusitis (90%), tonsillitis (95%) and sore throat (53%), that are generally not considered appropriate for antibiotic prescribing in the antimicrobial guidelines for GPs, as a no or delayed antibiotic strategy is advocated if clinically appropriate for the patient. However, it should be noted that severe cases of sinusitis, with symptoms longer than 10 days, and tonsillitis, with FeverPAIN scores of 4 or 5, may require immediate antibiotic treatment.[90] In total, there were 440 (13.80%) delayed prescriptions for antibiotics from those categorised as private or GMS patients. Private patients were more likely to receive a delayed prescription (OR 1.36). The majority of antibiotics prescribed for both groups were for symptoms of a respiratory-related illness. Private patients were more likely than GMS patients to receive an antibiotic when consulting with a respiratory illness (OR 1.47).[70]

Focusing on the younger patient cohorts, a study by Keogh et al. (2012) compared overall antibiotic prescribing prevalence rates per 1,000 Irish GMS children (in 2009) to European prescribing rates per 1000 children (in different time periods).[91] From an Irish perspective, the population with GMS coverage have a lower socioeconomic status, on average, than the general population in Ireland, therefore the results of the study are subject to bias as those in lower socioeconomic groups have higher morbidity rates in general. Ireland (621/1,000 population) reported the highest prevalence of antibiotic prescribing compared with Italy (512/1,000 population), Denmark (328/1,000 population), the Netherlands (193/1,000 population) and Scotland (142/1,000 population) when examining children (all groups inclusive of 0-15 year olds). Ireland (835/1,000

population) also reported higher rates than Germany (429/1,000 population) for younger children (all groups inclusive of 0-4 year olds).[91] However, it should be noted that there is high heterogeneity across the different study groups, in terms of ages, sample size, and year the data are assessed.

The influence of free GP care for patients under six years of age since July 2015 on antibiotic prescribing for childhood URTIs in Irish general practice was captured in a cross-sectional study using two weeks of consultation data in January for three successive years (2015 to 2017).[92] This study reported on consultations for under-sixes with URTI symptoms from four daytime practices and two out-of-hours centres. Compared with antibiotic prescription rates for URTIs of 69.6% in daytime practices in 2015, patients were 34% and 29% less likely to receive an antibiotic prescription in 2016 (46.2%) and 2017 (49.5%).[92]

As is the case in Ireland, the highest level of antibiotic prescribing was in the GP setting in England (74% in 2016).[93] Consumption of antibiotics decreased from 17.3 to 15.9 DDD per 1,000 inhabitants per day (-8.1%) from 2012 to 2016, with a 2.1% decline being observed between 2015 and 2016.[93] The 'other community setting', which includes out-of-hours clinics, contributes 3.4% of total antibiotic use and the decreases in prescribing in the GP setting were not substantively offset by increases by other community prescribers.[93] GP prescribing accounted for 86.3% of all antibiotic items in the community in England in 2016, which is similar to levels that have been observed in recent years. The total amount of antibiotic items prescribed continued to decrease between 2012 and 2016 from 2.17 to 1.88 (a reduction of 13.4%) antibiotic items prescribed per 1,000 inhabitants per day; there was a greater decline in items prescribed compared to DDD, suggesting longer duration prescriptions (potentially as prophylaxis), higher doses of antibiotics per prescription or switches to antibiotics with higher DDD per daily use.[93] In 2016, there was a reduction of 2.2% in the rate of items prescribed compared with 2015. This decline observed over the five-year period primarily reflected changes in primary care prescribing in GP and dental practice settings. 'Other community settings', while broadly similar to 2012, had an increasing trend in consumption since 2013, though this setting accounted for only 5.3% of prescribing in 2016.[93]

There are no Irish data available that identify ideal prescribing proportions for acute RTIs. However, two studies by Smith et al. (2018)[52] and Adraienssens et al. (2011)[94] quantified the ideal antibiotic prescribing proportions in acute RTIs for which antibiotic therapy is sometimes but not always indicated. The study by Smith et al. elicited the expert opinions of 14 academic experts from the UK, and also validated the estimates by achieving consistent results from an online survey of 43

practising prescribers in English primary care.[52] The study by Adraienssens et al. (on behalf of the ESAC project group) elicited expert opinions from 40 experts from 25 countries (all European except Israel and included two experts from Ireland) across seven dimensions on three quality indicators for the main indications for antibiotic prescribing – namely the percentage prescribed 1) antibiotics, 2) recommended antibiotics and 3) quinolones.[94] The ideal prescribing proportions are presented in Table 3.1.

Table 3.1 Ideal prescribing proportions – the proportions of patients that should receive oral antibiotics when presenting to primary care with different conditions

Condition		Ideal prescribing proportions (%)	
		Smith et al. 2018[52] (IQR)	ESAC study[94] (acceptable range)
Acute URTI	Aged >1yo		0-20
Acute sore throat	No relevant comorbidities	13 (7-22)	
	Aged >1yo (tonsillitis)		0-20
Acute rhinosinusitis	No relevant comorbidities	11 (5-18)	
	Aged >18yo (acute/chronic sinusitis)		0-20
Acute otitis media	Aged 6mo-2yo	19 (9-33)	
	Aged 2-18yo	17 (8-30)	
	Aged >2yo with AOM/myringitis		0-20
Acute cough	No relevant comorbidities	10 (6-16)	
Acute bronchitis/bronciolitis	No relevant comorbidities	13 (6-22)	
	Aged 18-75yo		0-30
AECOPD	All patients	54 (31-78)	
Pneumonia	Aged 18-65yo		90-100

The reported proportions from Smith et al. have been used to help quantify inappropriate antibiotic prescribing in England.[95, 96] A cross-sectional study extracted English data (2013-15) relating to antibiotic prescriptions and consultation diagnoses at primary care level from The Health Improvement Network (THIN) database in the UK, and compared the results with ideal

prescribing.[95] For most conditions, substantially higher proportions of consultations resulted in an antibiotic prescription than was deemed appropriate according to expert opinion. An antibiotic was prescribed in 41% of all acute cough consultations when experts advocated 10%. For other conditions the proportions were: bronchitis (actual 82% versus ideal 13%); sore throat (actual 59% versus ideal 13%); rhinosinusitis (actual 88% versus ideal 11%); and acute otitis media in 2- to 18-year-olds (actual 92% versus ideal 17%).[95] Substantial variation between GP practices was reported. The actual proportion of consultations followed by a same-day systemic antibiotic prescription is compared with those who received a systemic antibiotic within 30 days in Table 3.2.

Table 3.2 Actual prescribing proportions 1) on same day as consultation and 2) within 30 days of consultation among patients without comorbidities presenting to primary care with different conditions

Condition		Percentage of consultations	
		Same-day systemic antibiotic prescription[52] (IQR)	Systemic antibiotic prescription within 30 days [52] (IQR)
Acute URTI	No relevant comorbidities	25 (25-25)	34 (34-34)
Acute LRTI	No relevant comorbidities	87 (87-88)	89 (89-90)
Acute sore throat	No relevant comorbidities	59 (58-59)	63 (63-64)
Acute rhinosinusitis	No relevant comorbidities	88 (88-88)	90 (89-90)
Acute otitis media	Aged 6mo-2yo	92 (91-92)	93 (93-94)
	Aged 2-18yo	88 (88-89)	90 (89-90)
Acute cough	No relevant comorbidities	41 (41-41)	48 (48-48)
Acute bronchitis/bronciolitis	No relevant comorbidities	82 (82-82)	89 (89-90)
AECOPD	All patients	73 (72-74)	Not reported
Influenza-like illness	No relevant comorbidities	18 (18-19)	29 (28-29)

A related study identified inappropriate prescribing in English primary care ranging from 8.8% to 23.0% of all systemic antibiotic prescriptions (most to least conservative scenario).[96] However, one-third of all antibiotic prescriptions lacked an informative diagnostic code. Inappropriate prescribing was identified in all

included practices, ranging from 3.6% of a practice's prescriptions (minimum of most conservative scenario) to 52.9% (maximum of least conservative scenario). The four conditions that contributed most to identified inappropriate prescribing were sore throat (23.0%), cough (22.2%), sinusitis (7.6%) and acute otitis media (5.7%).[96]

Studies on the antibiotic prescribing patterns of Irish general practitioners (GPs) for acute RTIs in out-of-hours compared to daytime settings are lacking. One Irish study of the antibiotic prescribing for URTIs in the under-six age group discussed earlier, demonstrated that the out-of-hours setting was associated with a 42% increased likelihood of receiving an antibiotic prescription for URTIs, and a 47% decreased likelihood of receiving a deferred antibiotic.[92] However, it has been demonstrated that Irish GPs are more likely to prescribe an antibiotic for urinary tract infections approaching and during the weekend.[97] Prescribing of antimicrobials per total number of prescriptions was compared between weekdays (Monday to Thursday) and the weekend (Friday to Sunday). The antimicrobial prescribing rate was greater by 9.2 % on Friday compared to average prescribing on other weekdays (21.4 vs. 19.6 %). The chance of an antimicrobial prescription was 1.07 (95% CI: 1.04-1.10) higher on weekend days compared to weekdays.[97] A German cross-sectional study of daytime general practice also found the prescribing rate of antibiotics on Fridays was 23.3% higher than the average of the other days of the working week.[98] Analyses of total antibiotic prescribing patterns in out-of-hours primary care in Denmark has reported that the prescription proportion was higher for weekends (17.6%) than for weekdays (10.6%).[99] A Dutch study has also shown that children were more than twice as likely to receive an antibiotic prescription during out-of-hours consultation as compared to a daytime consultation.[100] However, another Dutch study examined the extent to which patients with a URTI who consulted their GP and did not get an antibiotic prescription contacted the out-of-hours services afterwards, within the same disease episode.[101] Preliminary analyses showed that 3.4% of the 0-12 year olds who consulted their GP during office hours also contacted an out-of-hours within the same disease episode. Whether or not the GP prescribed antibiotics did not make a significant difference to reconsultation levels (4.3% vs. 3.1%). Almost 1% of URTI patients over 12 years old contacted the out-of-hours after consulting a GP during day care. Again, there was no real difference between patients reconsultation levels based on whether or not they were prescribed antibiotics during office hours (0.9% vs. 0.8%).[101] The results from this study suggest that a practice of restrictive antibiotic prescribing during office hours does not invoke additional consultations after hours.

The out-of-hours antibiotic stewardship improvement project was first piloted by

DDoc (North Dublin) and Southdoc (Cork) from November 2016 to April 2017. The Southdoc project continued with the aim to reduce the percentage of antibiotics prescribed from the red category* as a percentage of total antibiotics prescribed by 50%, from 45% to 22.5%, by the end of May 2018. By March 2018, Southdoc had maintained the huge reduction in percentage of total antibiotics prescribed that were red category from 45% to 16% on average over four months, and co-amoxiclav had reduced from 34% to an average of 10% of total antibiotics prescribed. These achievements led to a revised aim of reduce the percentage of antibiotics prescribed from the red category to 11.5% by June 2018.

Patients in Irish nursing homes are prescribed more than twice the number of antibiotics than other European long-term care facility (LTCF) resident (Ireland 1/10 vs. Scotland 1/15).[102] Ireland is a participant in an EU-funded survey examining the point prevalence of healthcare associated infections and antimicrobial use in European LTCFs (HALT). Data on the organisation of healthcare in participating Irish sites (224 sites, n=10,044 residents) from the 2016 survey have been published. This reported the national crude antimicrobial use prevalence was 9.8%, with a median antimicrobial use prevalence of 8.3%.[102] The median prevalence was higher in LTCF <12m (12.1%) and rehabilitation LTCF (10.9%). At 30.8%, the prevalence in palliative care LTCF was more similar to that reported in acute hospitals. The majority of antimicrobials for long-term care patients were prescribed within the LTCF (83%). Overall, 59% of antimicrobials were prescribed to treat infection. Over one-third (36%) of therapeutic antimicrobials were prescribed for RTI in the LTCF.[102]

3.5.3 Individual-level harms associated with consumption of antibiotics

Antibiotic treatment of RTIs can expose patients to an increased risk of an adverse event or an episode of drug-associated toxicity. Common side effects of antibiotics are gastrointestinal symptoms, skin rashes, and thrush; specific effects with particular antibiotic classes include nephrotoxicity associated with aminoglycosides and teeth staining attributable to tetracyclines.[103] Adverse drug events from antibiotic exposure may occur in one out of every five patients. From a review of 6,614 cases between 2004 and 2006, a community study measured emergency department visits for any drug-related adverse events, and antibiotics were implicated in 19.3% of all visits.[104] A hospital study documented 1,488 patients

* The list of preferred antibiotics in primary care (Green) and the antibiotics to be avoided first line in primary care (Red) are produced by the HSE Quality Improvement Division in collaboration with the HSE MMP and the ICGP (https://www.hse.ie/eng/services/list/2/gp/antibiotic-prescribing/antibicrobial-stewardship-audit-tools/campaign-materials/antibioticgpbooklet.pdf). A copy of the list is provided in Appendix 4.

receiving antibiotics, with 298 of those patients (20%) having experienced at least one antibiotic-associated adverse drug reaction.[105]

The most important adverse reactions associated with the use of penicillin antibiotics are hypersensitivity reactions. However, true penicillin allergy is rare, with the estimated frequency of anaphylaxis at 1-5 per 10,000 cases of penicillin therapy.[106] Hypersensitivity reactions may result in pruritus, urticaria, wheezing, nausea, vomiting, and in severe cases laryngeal oedema and ultimately, cardiovascular collapse.[106] The identification of patients who are misclassified as ß-lactam allergic may lead to the improved utilisation of antibiotics and may slow the emergence of drug-resistant bacteria.[106] The widely cited rate of 10% cross-sensitivity to cephalosporins among penicillin allergic patients appears to be based on data collected and reviewed in the 1960s and 1970s and results of in-vitro (immunological) tests that were not supported by clinical skin tests in penicillin-sensitive patients.[107] The information contained in the 56th and subsequent editions of the BNF now states that the hypersensitivity rate between penicillins and cephalosporins is 0.5%-6.5%.[107]

The relative merit of the benefits and harms of antibiotic treatment can be considered in the context of the numbers needed to treat and to harm. For example, in the case of acute bronchitis the numbers needed to treat (NNT) to benefit is 6 based on the outcome of abnormal lung exam, and 11 based on the outcome of clinician's global assessment.[72] For the same indication, the number needed to harm (NNH) is 24. That is, 24 patients need to be treated for one to experience a harm. By contrast, for acute otitis media the NNT is 24 and the NNH is 13.[108] For acute sinutsitis, the NNT ranges from seven to 20 depending on the outcome measure, and the NNH is 10.[109] It is clear that harm may be a more likely outcome than benefit, depending on the choice of outcome. It should be borne in mind that the benefits and harms may not be considered of equal importance. The key point is that harms from antibiotic consumption are common in patients with acute RTIs.

The EMA Committee for Human Medicinal Products (CHMP) endorsed recommendations put forth in October 2018 by the agency's Pharmacovigilance Risk Assessment Committee (PRAC). The committee concluded that marketing authorisation for medicines containing cinoxacin, flumequine, nalidixic acid, and pipemidic acid should be suspended. The CHMP also confirmed that the use of the remaining fluoroquinolone antibiotics should be restricted. The PRAC began its review in 2017. Updated prescribing information for healthcare professionals and information for patients will describe the disabling and potentially permanent adverse effects and will advise patients to stop treatment with a fluoroquinolone

antibiotic at the first sign of an adverse effect involving muscles, tendons or joints, and the nervous system.

The new restrictions on the use of fluoroquinolone antibiotics advise against their use for the following:

- To treat infections that might get better without treatment or are not severe (such as throat infections).
- To treat nonbacterial infections, e.g. nonbacterial (chronic) prostatitis.
- For preventing traveller's diarrhoea or recurring lower urinary tract infections (urinary infections that do not extend beyond the bladder).
- To treat mild or moderate bacterial infections unless other antibacterial medicines commonly recommended for these infections cannot be used.

Fluoroquinolones should generally be avoided in patients who have previously had serious side effects with a fluoroquinolone or quinolone antibiotic. Fluoroquinolones should be used with special caution in the elderly, patients with kidney disease and those who have had an organ transplantation because these patients are at a higher risk of tendon injury. Since the use of a corticosteroid with a fluoroquinolone also increases this risk, combined use of these medicines should be avoided.

On the basis of available evidence, the EMA concluded that fluoroquinolones are associated with prolonged (up to months or years), serious, disabling, and potentially irreversible drug reactions affecting more than one and sometimes multiple systems, organ classes, and senses. The adverse effects include tendonitis, tendon rupture, arthralgia, pain in the extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impaired hearing, vision, taste, and smell.

The CHMP opinion was forwarded to the European Commission, which issued a final legally binding decision on 14 February 2019 for Quinsair and on 11 March 2019 for other quinolone and fluoroquinolone antibiotics given by mouth and by injection, which is applicable in all EU countries. National authorities will enforce this decision for the fluoroquinolone and quinolone medicines authorised in their countries and they will also take other appropriate measures to promote the correct use of these antibiotics.[(110)]

The safety of reducing antibiotic prescribing for self-limiting respiratory tract infections in primary care was examined in a cohort study of registered patients with 45.5 million person years of follow-up data between 2005 and 2014 from 610 UK general practices.[(111)] It was reported that general practices prescribing antibiotics less often for RTIs had slightly higher rates of pneumonia and peritonsillar abscess

than higher prescribing practices. This rate applied to a general practice with an average list size of 7,000 patients that reduced the proportion of RTI consultations with antibiotics prescribed by 10%, may translate to it encountering about one additional case of pneumonia each year and one additional case of peritonsillar abscess each decade.[111] It also reported that complications may be fewer than expected if general practitioners are able effectively to stratify antibiotic prescribing according to the level of risk. There was no evidence found that mastoiditis, empyema, meningitis, intracranial abscess, or Lemierre's syndrome were more frequent in the low prescribing practices. Such reductions in antibiotic prescribing would be expected to reduce the risks of antibiotic resistance, the side effects of antibiotics, and the medicalisation of largely self-limiting illnesses.[111]

3.6 Consequences of RTIs for society

The Global Burden of Disease study of LRTIs focused on the burden associated with pneumonia and bronchitis in 195 countries during 2015.[49] It estimated that LRTIs were the fifth leading cause of death (of 249 causes) and the leading infectious cause of death worldwide. LRTIs were the second-leading cause of disability-adjusted life years (DALYs) globally in 2015 after ischaemic heart disease. Globally, pneumonia remains the most common cause of death in children younger than five years of age, causing 1.6 million deaths annually. While the pneumococcal vaccine is recommended for children by the World Health Organization (WHO), global coverage was estimated at only 25% in 2013, with estimates that pneumococcal disease is responsible for over 30% of deaths from vaccine-preventable diseases in children.[112] The Global Burden of Disease study also highlights the burden of LRTIs in the elderly population, with nearly 700,000 deaths in patients aged older than 70 years due to pneumococcal pneumonia worldwide.[49] Among high-income countries (21 of the 34 of which are European), LRTIs were responsible for 486,408 deaths (that is, 45.5 per 100,000) and 5.1 million DALYs in 2015; a 21.6% increase in deaths and 9% increase in DALYs was noted between 2005 and 2015.

The number of deaths due to LRTIs in children aged younger than five years in the high income countries was estimated at 3.4 per 100,000 in 2015; this represented a decrease of 34.9% between 2005 and 2015.[49] Data from 14 hospital-based studies estimate the incidence of admissions for severe acute LRTI in Europe in 2010 was approximately 14 episodes per 1,000 children per year in children aged 0-11 months, and approximately seven episodes per 1,000 children per year in those aged 0-59 months. This translates to approximately 553,000 episodes per annum in children aged younger than five years in Europe.[113]

The global burden of disease data are limited to LRTIs and are primarily based on data from hospital in-patient databases. No European-equivalent database was identified relevant to the burden of RTIs in primary care. The General Practice Research Database (now part of the Clinical Practice Research Datalink, a publicly funded research data service) in the UK has been widely used for pharmacoepidemiological research. It comprises anonymised electronic data submitted by general practitioners covering approximately 5% of the total UK population. Using these data, a 2007 study looking at the health burden of influenza in England and Wales estimated that 779,000 to 1,164,000 general practice consultations, 19,000 to 31,200 hospital admissions and 18,500 to 24,800 deaths annually are attributable to influenza infections.[114] These data on GP consultations tally with the seasonal mean estimate of 789,219 influenza-attributable GP episodes between 1995 and 2009 in the UK.[56] In an average season during this time period, 2.4% (and 0.5%) of children aged less than five years and 1.3% (and 0.1%) of elderly patients aged over 74 years had a GP episode for respiratory illness attributed to influenza A (and B). The study noted that while the bulk of the burden in primary care falls on those aged less than 45 years, elderly patients are more likely to be hospitalised and to die.[114] Annual influenza epidemics are estimated to cause between 12,000 and 13,800 deaths in the UK.[51] Research by the HSE Health Protection Surveillance Centre, as part of a wider European study, estimates that between 200 and 500 people in Ireland die each year from influenza-related illness and up to 1,000 people could die in a particularly severe flu season.[115]

The British Lung Foundation provides detailed mortality rates and incidence statistics by lung condition.[116, 117] The research project team used The Health Improvement Network (THIN) database records of 12.6 million patient records from 591 GP surgeries for 2004-13 to estimate prevalence and incidence data. Mortality data were obtained from the Office for National Statistics for England and Wales, the General Register Office for Scotland and the Northern Ireland Statistics and Research Agency. In 2012, 1,589 people in the UK died from acute LRTI – which represents 0.3% of all deaths and 1.4% of deaths from lung disease.[116] In the period 2001-10, approximately 13 people per million died from acute LRTI each year in the UK. This age-standardised mortality rate per million can be compared with 26 deaths per million in Ireland. The age-standardised mortality ratios by region report that in Northern Ireland death rates were higher among males (1.33) but similar to UK rates generally among females (1.06).[116] In 2012, 345 people for every 100,000 had one or more episodes of pneumonia, down from 307 per 100,000 in 2004.[117] For 2012, this compares with 272 people in Northern Ireland. Overall, this pattern for episodes of pneumonia was seen to

be fairly constant in the years 2004 to 2012. In the period 2001-10, 214 people for every million died from pneumonia in the UK. This age-standardised mortality rate per million can be compared with 166 deaths per million in Ireland. The age-standardised mortality ratios by region report that in Northern Ireland death rates were higher than in the UK generally from 2008 to 2012.[117]

From the 4.9 million deaths in 2014 reported in the European Union, 118,300 were due to pneumonia.[118] Adult females (59,900 deaths) and males (58,400 deaths) were almost equally affected. Ninety percent of these deaths concerned people aged over 65. In absolute terms, the United Kingdom (28,200 deaths, or 24% of the EU total) was the Member State that recorded the most deaths from pneumonia in 2014, followed by Germany (16,700, 14%), Poland (12,300, 10%), France (11,100, 9%), Italy (9,100, 8%) and Spain (8,400, 7%). However, for a relevant inter-country comparison, these absolute numbers need to be adjusted to the size and structure of the population. At EU level, the average rate of deaths was estimated at 25 deaths from pneumonia per 100,000 inhabitants in 2014. Among EU Member State data, Ireland registered 37 deaths from pneumonia per 100,000 inhabitants in 2014. These figures are not age-standardised mortality rates. However, there has also been gender mortality differences reported in a 2018 study of trends in mortality from pneumonia across 19 countries (excluding Ireland) in the European Union.[119] This temporal analysis of the European detailed mortality database between 2001 and 2014 reported median pneumonia mortality across the EU for the last recorded observation was 19.8 per 100,000 for males and 6.9 per 100,000 for females. Mortality rates were higher in males across all the EU countries included in the study.

In total, it is estimated that there are 5.5 million consultations each year for acute respiratory illness in England and Wales.[114] However, the majority of such consults will often relate to other RTI including specifically acute cough or bronchitis and URTIs, such as acute otitis media (AOM), cough, sore throat/ pharyngitis/ tonsillitis, rhinosinusitis and the common cold, which are largely self-limiting and complications are likely to be rare if antibiotics are withheld.[62]

Patients with COPD are at increased risk of acute RTIs and their sequelae. UK estimates of inpatient mortality attributable to exacerbations of COPD range from 4% to 30%.[120] The wide variation in these estimates results from the fact that studies investigated different subgroups of patients. The factors contributing to frequent exacerbations remain unclear, but viral infections appear to be a major cause of exacerbations. The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort study identified a distinct 'frequent exacerbator' group, who were more susceptible to exacerbations of COPD

irrespective of their disease severity.[121] These patients could be identified by a previous history of two or more exacerbations per year. Patient mortality has been shown to be significantly related to the frequency of these severe exacerbations requiring hospital care.[122] There are also data on mortality following discharge from hospital after treatment for an acute exacerbation of COPD. In the UK it has been reported that death occurred in 14% of cases (184/1,342) within three months of admission.[123] COPD exacerbations were responsible for more than 0.9% of all 11.7 million hospital admissions and 2.4% of the 4.2 million acute medical admissions in England for 2003/2004. Most of these admissions are on an emergency basis, with the mean length of stay remaining almost unchanged at about 10 days.[120]

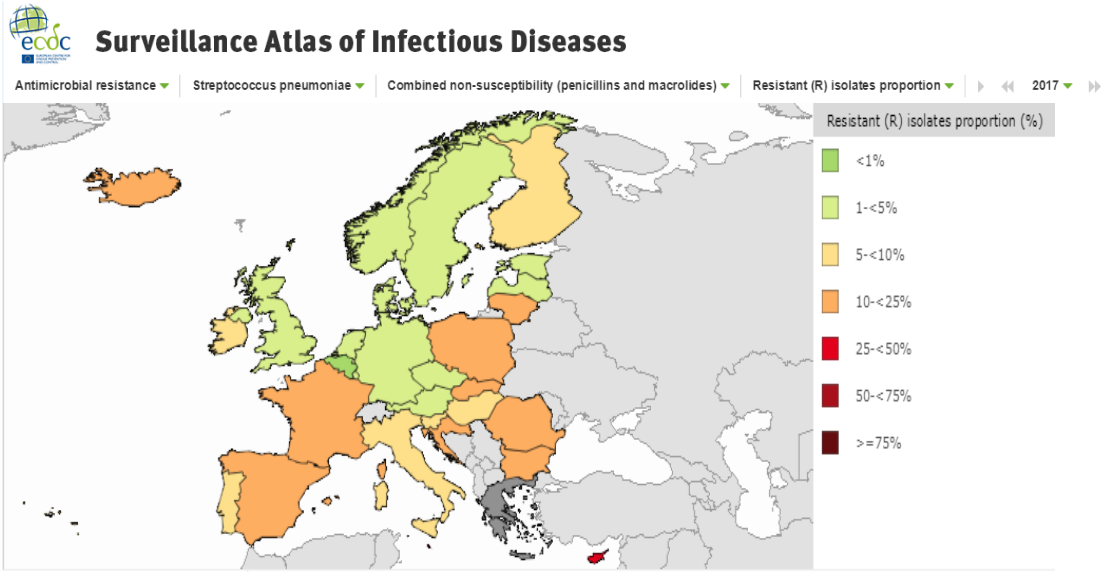
3.7 Antimicrobial resistance

Antimicrobial-resistant organisms are found in people, food, animals, plants and the environment (in water, soil and air) and they can move between ecosystems.[124] Antimicrobial resistance (AMR) occurs naturally and over time when microorganisms (such as bacteria, fungi, viruses and parasites) are exposed to antimicrobial substances.[124] As a result, treatments become ineffective and infections persist in the body, increasing the risk of spread to others.[124] However, new AMR mechanisms are emerging and spreading globally, threatening our ability to treat infectious diseases, resulting in prolonged illness, disability and death, and increasing the cost of health care. Although the emergence of AMR is a natural phenomenon, the misuse and overuse of antimicrobials is accelerating this process.[125]

3.7.1 Antimicrobial resistance in Europe

The European Antimicrobial Resistance Surveillance Network (EARS-Net) has documented the changing epidemiology of bacteraemias in Europe, highlighting the emergence and spread of totally or almost totally resistant bacteria in European hospitals.[126] The primary care setting accounts for 80% to 90% of all antibiotic prescriptions.[127] In 2017, the European Centre for Disease Control (ECDC) Surveillance Atlas of Infectious Disease reported high levels of *Streptococcus pneumoniae* with combined non-susceptibly to penicillins and macrolides in Bulgaria, Cyprus, Croatia, France, Iceland, Lithuania, Poland, Romania, Slovakia and Spain (Figure 3.1).

Figure 3.1 Antimicrobial resistance (combined non-susceptibility for penicillins and macrolides) versus Streptococcus pneumoniae in EU/EEA countries, 2017



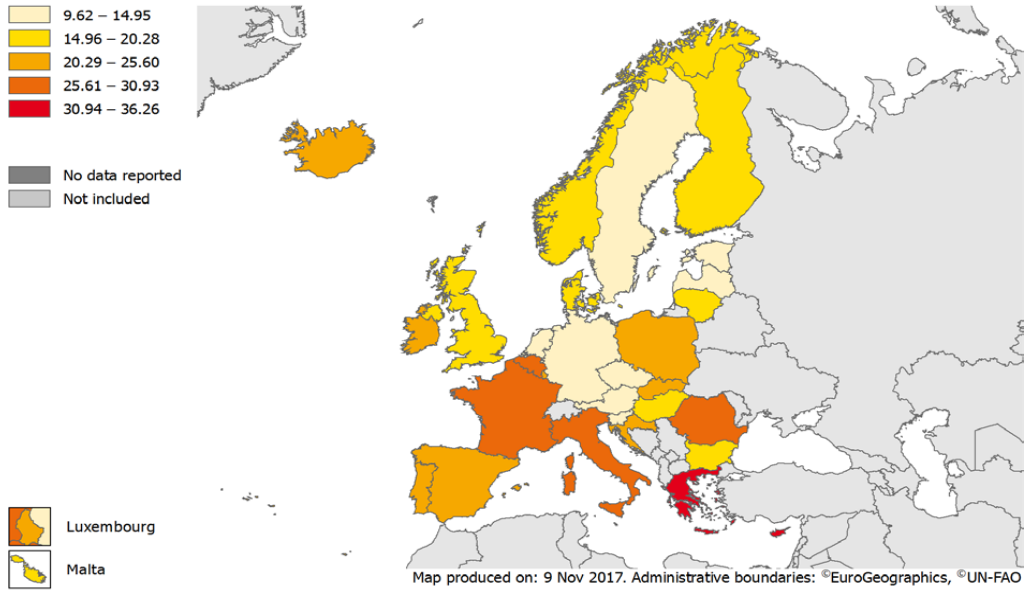
Source: ECDC Surveillance Atlas of Infectious Diseases (https://atlas.ecdc.europa.eu/public/index.aspx)

During the same time period, high levels carbapenem-resistant *Klebsiella pneumoniae* were reported in Bulgaria, Cyprus, Greece, Italy and Romania. This trend indicates higher rates of antimicrobial resistance in southern and eastern European countries.

The European Surveillance of Antimicrobial Consumption Network (ESAC-Net) collates data for the EU and EEA countries on community-level antibiotic consumption for systemic use. Data for 2016 indicate an EU/EEA population-weighted mean consumption of 21.9 DID. Although consumption was noted to be lower than in previous years, overall antibiotic consumption in the community showed no significant decreasing trend for the period 2012-2016.[128] There is substantial inter-country variation with consumption ranging from 10.4 (the Netherlands) to 36.3 DID (Greece) (Figure 3.2). A number of countries, specifically Finland, Luxembourg, Norway and Sweden (Northern Europe), showed a decreasing trend in consumption during the 2012-2016 period, whereas increases were noted in Greece and Spain (Southern Europe).[128] Despite broad consistency between national guidelines on the diagnosis and treatment of RTIs, given that the majority of community prescribing is for RTIs, it is likely that some of this variation is driven by differences in actual antibiotic prescribing practices for these conditions in primary care. DID are adjusted for population size, and provide an accurate measure of overall antimicrobial consumption at national level. However, DID are not a measure of antimicrobial prescriptions and are not adjusted for age, sex, and other

demographic factors. Thus, they may not accurately reflect demographic variations or some changes in prescribing practice.

Figure 3.2 Consumption of antibiotics for systemic use in the community, EU/EEA countries, 2016 (expressed as DDD per 1,000 inhabitants per day)



Source: The European Centre for Disease Control (ECDC) Summary of the latest data on antibiotic consumption in the EU (November 2017).[129]

The rate of antimicrobial consumption in the primary care setting in Ireland for 2017 was 23.1 DID, a decrease on the rate for the previous year (24.1 DID).[130] This overall rate is mid-range in comparison with other European countries. There is considerable regional variation in antibiotic consumption across the community healthcare organisations (CHOs) in Ireland, with values ranging from 22.7 to 31.07 DID in Q1 2018 (HPSC).[131] The consumption data of antimicrobials in Ireland for 2016 is presented by antibiotic class distribution for the primary care setting in Appendix D. The trend of consumption of antimicrobials by antibiotic class (ATC JA01) is also illustrated (1998 to 2016) in Appendix D.

This observation of increased antibiotic consumption (which can be interpreted as a proxy for antibiotic prescribing patterns) correlating with increased antibiotic resistance, has been shown in a number of ecological studies. These studies identified countries in the south and east of Europe that have moderate to high consumption of antibiotics and corresponding high rates of antimicrobial resistance.[2] Quality appraisal of antibiotic use is also undertaken by ESAC using 12 different quality indicators based on the type of antibiotic consumed (n=5), the

relative proportions of these types (n=4), use of broad versus narrow spectrum antibiotics (n=1) and seasonal variation in consumption (n=2). The 2012 ESAC quality appraisal of antibiotic use in an outpatient setting between 2004 and 2009 also showed an important north-south divide when the quality of antibiotic use is considered.[132]

A systematic review and meta-analysis of a large set of studies (n=243) found that antibiotic consumption is associated with the development of antibiotic resistance at both the individual and community level.[133] This link was reported to be particularly strong for countries in Southern Europe.

While antibiotic use is widely associated with antibiotic resistance, demonstrating causality is difficult because of population-based confounders and because there is wide variation in the effects of antibiotics that are within the same class on the selection of resistant organisms.[134] However, several case reports of fluoroquinolone-associated Clostridium difficile diarrhoea have been published.[135] At the patient level, there is a clear link between antibiotic dose and duration and the emergence of antibiotic resistance, and there is also evidence that patients who have been treated frequently with antibiotics are at greater risk of antibiotic resistance.[2, 136] As mentioned previously, the EARS-Net has noted the emergence and spread of totally or almost totally resistant bacteria in European hospitals.[126] Notably, however, the primary care setting accounts for 80% to 90% of all antibiotic prescriptions.[127] However, it is noted that due to difference in molecular mechanisms of resistance and associated fitness costs, the persistence of resistance differs between antibiotics. For example, compared with the newer macrolides azithromycin and clarithromycin, persistence of resistance selection following amoxicillin therapy in patients with community-acquired LRTI is significantly shorter.[134]

3.7.2 Factors associated with increased prevalence of antimicrobial resistance in the population

The major drivers behind the occurrence and spread of antimicrobial resistance (AMR) are the use of antimicrobial agents and the transmission of antimicrobial-resistant microorganisms between humans, between animals, and between humans, animals and the environment. While antimicrobial use exerts ecological pressure on bacteria and contributes to the emergence and selection of AMR, poor infection prevention and control practices and inadequate sanitary conditions favour the further spread of these bacteria.[137] Globalisation, the rapid and frequent travelling and the increasing international market exchange of foods and feeds, and modern health care will increase the spread and selection of resistant

bacteria favouring the persistence of multi-resistant bacteria.[138]

Other important factors that may affect the development of AMR in patients include the dose, duration of treatment and class of antibiotic (selective pressure), disease transmission and exposure rates, host susceptibility (such as vaccination status), and transmissibility (fitness cost) of the pathogen.[139] Currently, approximately 40% of Streptococcus pneumoniae isolates are penicillin-resistant in several countries that lack significant conjugate vaccine coverage.[140]

Recent antibiotic use has been identified as the foremost risk factor for the development of resistance among invasive pneumococcal disease cases, but other risk factors include age (particularly children aged less than five years of age), female gender, hospitalisation, living in an urban area, attending day care, paediatric serotypes (that is, serotypes found commonly in children), HIV infection, and immunosuppression. Studies have found that previous use of beta-lactam antibiotics, extremes of age (for example, children aged less than five years and the elderly), and child care attendance were associated with penicillin-non-susceptible pneumococcal infections.[140]

The rapid seasonal decrease in resistance associated with markedly reduced antibiotic use suggests that drug-resistant pneumococci may pay a fitness cost.[141] The observed fitness cost of resistance genes/mutations is a prerequisite for reversibility of antibiotic resistance by reduced antibiotic use.[138] However, so far the clinical evidence for reversibility is limited.[142, 143] The potential of reversing antibiotic resistance through the reduction of antibiotic use will be dependent on the fitness cost of the resistance mechanism, the epidemic potential of the bacteria/strain, and the transmission route of the species.[138]

The English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) report of 2018 also provides data that shows the proportion of isolates of *Klebsiella pneumoniae*, *Klebsiella oxytoca* and *Pseudomonas spp*. resistant to key antibiotics remained broadly stable between 2013 and 2017.[144] However, the proportion of isolates of *Escherichia coli* (*E. coli*) resistant to co-amoxiclav was reported as increasing from approximately 20% (2013) to around 30% (2017).[144] Non-susceptibility to co-amoxiclav in *E. coli* appeared to increase slightly between 2016 and 2017.[144] However, ongoing work by Public Health England has raised doubt as to the robustness of this finding, as some data, particularly that reported from laboratories using specific automated antibiotic susceptibility testing devices, may be overestimating resistance levels, particularly intermediate resistance.[144]

An electronic database study in Oxfordshire (1999-2011) demonstrated a link between increased usage of co-amoxiclav with an increased incidence of *E. coli* bacteraemia attributable to co-amoxiclav-resistant isolates.[145] The study reported that *E. coli* bacteraemia incidence increased from 3.4/10,000 bedstays in 1999, to 5.7/10,000 bedstays in 2011. The increase was fastest around 2006, and was essentially confined to organisms resistant to ciprofloxacin, co-amoxiclav, cefotaxime and/or aminoglycosides. Bacteraemia isolates resistant to co-amoxiclav comprised about 70% of all resistant cases. It was notable that from 2006 onwards, there was a rapid rise in co-amoxiclav resistant *E. coli* incidence per 10,000 bed stays. The proportion of co-amoxiclav-resistant *E. coli* bloodstream infections (BSI) doubled in many of the subsequent years and trebled in mid-2010. This dramatic change in proportions of co-amoxiclav resistant isolates was preceded by an antibiotic switching policy from second- and third-generation cephalosporins towards co-amoxiclav with gentamicin as the empirical treatment for sepsis in October 2006, in response to rising *Clostridium difficile* infection rates.[145] Given the predominance of co-amoxiclav prescribing in Irish primary care, there is an awareness among health authorities about the trend of increasing proportions of patients with extended-spectrum β-lactamases (ESBL) producing *E. coli* BSI (as a percentage of total *E. coli* BSI) from 7.5% in 2011 to 11.3% in 2017.[146]

3.7.3 Consequences of antimicrobial resistance for society

The consequence of antimicrobial resistance is increased mortality and morbidity from bacterial infections as well as an increased economic burden on the healthcare sector in the treatment and care of patients infected with multidrug-resistant strains as well as a loss of productivity.[4, 147]

The attributable deaths and DALYs caused by infections with antibiotic-resistant bacteria in countries of the EU and European Economic Area (EEA) in 2015 was reported by Cassini et al. (2018).[148] From European Antimicrobial Resistance Surveillance Network (EARS-Net) data, there were 671,689 (95% uncertainty interval [UI] 583,148-763,966) infections with antibiotic-resistant bacteria; of which 63.5% (426,277 of 671,689) were associated with healthcare. These infections accounted for an estimated 33,110 (28,480-38,430) attributable deaths and 874,541 (768,837-989,068) DALYs. The burden was highest in infants (aged <1 year old) and people aged 65 years or older; this had increased since 2007, and was highest in Italy and Greece. These estimates corresponded to an incidence of 131 (113-149) infections per 100,000 population, and an attributable mortality of 6.44 (5.54-7.48) deaths per 100,000 population, causing 170 (150-192) DALYs per 100,000 population. 67.9% (115 of 170) of the total DALYs per 100,000 were caused by infections with four antibiotic-resistant bacteria with the

largest effect on health in the study: third-generation cephalosporin-resistant *E. coli*, MRSA, carbapenem-resistant *Pseudomonas aeruginosa*, and third-generation cephalosporin-resistant *K. pneumonia*. Despite its relatively low incidence, carbapenem-resistant *K. pneumoniae* had a high burden of disease because of its high attributable mortality.[148]

Italy and Greece had a substantially higher estimated burden of antibiotic-resistant bacteria than other EU and EEA countries.[148] The burden of infections with antibiotic-resistant bacteria was focused in the southern and eastern parts of the EU and EEA. A substantial proportion of the burden of infections with antibiotic-resistant bacteria in the EU and EEA in 2015 was estimated to have been due to community-associated infections. Between 2007 and 2015, the burden increased for all antibiotic-resistant bacteria. The proportion of the DALYs due to all carbapenem-resistant bacteria combined increased from 18% (56,150 of 311,715) in 2007 to 28% (185,421 of 678,845) in 2015, and the proportion of the DALYs due to carbapenem-resistant *K. pneumoniae* and carbapenem-resistant *E. coli* combined doubled from 4.3% (13,515 of 311,715) in 2007 to 8.79% (57,536 of 678,845) in 2015, reflecting the emergence and rapid increase of carbapenem-resistant *K. pneumoniae* infections in the EU and EEA during this period.[148]

The societal costs in Europe of selected antibiotic-resistant bacteria were estimated to be about €1.5 billion a year in 2007.[149] Antimicrobial resistance kills around 50,000 people a year in the US and Europe, and is estimated to kill more than 700,000 people globally.[125] Predictive macroeconomic models, which found that if resistance is not addressed, the world will produce around $8 trillion USD less per year by 2050, and a cumulative $100 trillion USD would be wiped off the world's production over the next 35 years.[125] However, this review on antimicrobial resistance only estimates lost economic output, and does not take into account any increased associated healthcare costs. The OECD 'Stemming the Superbug Tide' report (2018) reports that average antimicrobial resistance growth seems to be slowing down across OECD countries, but serious causes for concern remain.[150] It predicts that across OECD and G20 countries, resistance to second- and third-line antibiotics – which represent the back-up line of defence to treat infections – is expected to be 70% higher in 2030 compared to 2005 figures. Across EU countries, resistance to third-line treatments will double in the same time period. The report projects a trend for AMR rates that are estimated to contribute to approximately 2.4 million individuals dying in Europe, North America and Australia between 2015 and 2050. Italy and Greece are forecast to top the list, with an average mortality rate of, respectively, 18 and 15 deaths per 100,000 persons per year between 2015 and 2050. Under this scenario, it is estimated that up to $3.5 billion USD is expected to be spent yearly between 2015 and 2050 on

AMR-related complications across 33 OECD and EU countries. This corresponds to 10% of healthcare costs caused by communicable diseases, or to about $2.40 USD per capita per year on average, with around $6.20-6.60 USD per capita in Italy, Malta and the United States. Each year, AMR will result in 568 million extra hospital days across all the European countries included in this OECD model.[150]

Antimicrobial resistance increases the cost of healthcare with lengthier stays in hospitals and a requirement for more intensive care.[124] It complicates treatment and can result in additional antibiotic courses and outpatient visits, excess hospitalisations and work loss.[140] Specific to antibiotic-resistant pneumococcal pneumonia, a 2014 study by Reynolds et al. found that resistance led to 32,398 additional outpatient visits and 19,336 additional hospitalisations, accounting for $91 million USD (4%) in direct medical costs and $233 million USD (5%) in total costs, including work and productivity losses.[151] In adults, increased costs due to penicillin non-susceptible pneumonia and bacteraemia were due to prolonged hospitalisations and the use of more expensive antibiotics.[140] Data from the US estimated that 55% of all antibiotics prescribed for acute RTIs in outpatients are probably not needed, leading to a waste of $732 million (1999 USD values) of $1.32 billion USD spent.[139]

If resistance to currently available antibiotics becomes widespread, this will adversely impact on the delivery of effective medical care in a wide range of clinical settings. A risk assessment study of antibiotic pan-drug-resistance in the UK indicated that there is an approximately 20% chance of such a situation arising in the UK over a five-year time frame. The impact of such an event, were it to occur, would be very significant in clinical and public health terms, with marked increases in morbidity and mortality.[147]

3.8 Use of C-reactive protein POCT currently used in Europe to guide antibiotic prescribing

C-reactive protein POCT for patients with suspected LRTI has been included in guidelines in Norway, Sweden, Netherlands, Germany, Switzerland, Czech Republic, Estonia and the United Kingdom.[22, 34] The Scandinavian countries in particular have been leading adopters of the technology.[25] An international cross-sectional survey reported on the use of POC tests by primary care clinicians in Australia, the USA and Europe (Belgium, the Netherlands and the UK) .[152] C-reactive protein POCT was carried out by 48% of the Dutch primary care clinicians, which contrasted with a usage of 3% reported for Belgium and 15% for the UK. In the survey, clinicians from Belgium and the UK expressed a desire to use C-reactive protein POCT (75% and 61%, respectively) that was higher than

their current use of the tests; this latent demand for access to C-reactive protein POCT is suggestive of an unmet clinical need in primary care to assist prescribing decisions for patients presenting with RTIs.

As outlined in the description of the technology chapter, the CRP POCT technology is being used in the following countries: Belgium, Czech Republic, Denmark, Estonia, Finland, Germany, Hungary, Italy, Lithuania, the Netherlands, Norway, Poland, Slovakia, Slovenia, Spain, Sweden, Switzerland and the United Kingdom. Many European countries appear not to provide direct reimbursement of the technology in the primary care setting; with only confirmation of reimbursement in primary care from Denmark, Hungary, Italy, Lithuania, the Netherlands, Norway, Poland, Slovenia, Spain and Switzerland. Although recommended and available for use in many European countries, there are no reliable data on the current and/or expected annual usage of CRP POC tests in the respective European countries.

The use of CRP POCT is not currently included in clinical guidelines for guiding antibiotic prescribing for acute RTIs in primary care in Ireland.

3.9 Discussion

Respiratory tract infections (RTIs) are the most frequent infections encountered in primary care. No international studies were identified that reported European-level data on the burden of RTIs in this setting, therefore estimates used in this report rely heavily on published studies and surveillance data from a limited number of European countries for which large-scale studies based on primary care data were identified. These confirmed the substantial burden of RTIs with estimates that 15% of all episodes in primary care relate to RTIs, with consultations for URTI-related illness more than twice as common as those for LRTI. Given differences in consultation behaviour, vaccination coverage and obligatory doctor visits for absences for school or work, consultation rates for RTIs are likely to differ between countries. While consultation rates may vary, there is broad consistency in clinical guidelines in the care pathways for diagnosis and management of acute RTIs. URTIs are characterised as self-limiting and often viral in aetiology with a no antibiotic or delayed antibiotic prescribing strategy generally recommended in uncomplicated URTIs that do not exceed the expected durations of illness. Immediate antibiotic therapy is typically only recommended for URTIs in patients who are systemically very unwell and for those patients who have a high risk of complications due to a pre-existing comorbidity. In respect of LRTI, there is also broad consistency in guidelines for the diagnosis and management of LRTI and specifically community-acquired pneumonia. Studies suggest that around 5% to 12% of patients presenting in primary care with symptoms of a LRTI are

diagnosed with community-acquired pneumonia (CAP). Given the substantial morbidity and mortality associated with CAP and the higher probability of a bacterial aetiology, antibiotics are recommended in all patients with a clinical diagnosis of pneumonia and in those with LRTIs with risk factors for complications (such as comorbidities). Antibiotics are not recommended in those patients who are less unwell including those with acute bronchitis, with European guidelines recommending use of CRP measurement if after clinical assessment a diagnosis of pneumonia has not been made and it is unclear if antibiotics should be prescribed.

European surveillance data indicate a greater than threefold variation between countries in the consumption of antibiotics for systemic use in the community, with a trend towards higher antibiotic consumption in southern and eastern European countries. Given the substantial burden of acute RTIs in primary care and despite the broad consistency between national guidelines for RTIs, much of this variation may relate to variation in actual antibiotic prescribing practices for these conditions in primary care. Overprescribing of antibiotics is common in this setting, with high levels of inappropriate prescribing documented in observational studies benchmarking antibiotic prescribing versus clinical guidelines. Prescribing an unnecessary antibiotic will potentially expose the patient to needless adverse effects without aiding recovery. Furthermore, there is the major societal concern about the increasing emergence of antimicrobial resistance (AMR), a major driver for which is the misuse and overuse of antibiotics. European surveillance data has documented substantial inter-country variation in the prevalence of antimicrobial-resistant strains including penicillin-resistant Streptococcus pneumoniae, with a trend towards higher rates of antimicrobial resistance in southern and eastern European countries.

While antibiotic use is widely associated with antibiotic resistance, demonstrating causality is difficult because of population-based confounders and wide variation in the effects of antibiotics that are within the same class on the selection of resistant organisms. There is very limited evidence that a reduction in the overall rates of antibiotic prescribing leads to reversal or an overall reduction in AMR. At a patient level, however, there is a clear link between antibiotic dose and duration and the emergence of antibiotic resistance with further evidence that patients who have been frequently treated with antibiotics are at greater risk of AMR.

The use of CRP POCT to inform prescribing for patients with suspected LRTI in primary care has been included in national guidelines in several European countries. A survey of EUnetHTA partners suggests that CRP POCT is available for use in at least 17 European countries with confirmation that the technology is reimbursed when used in primary care for this indication in Denmark, Hungary,

Netherlands, Norway, Poland, Slovenia and Switzerland.

3.10 Key messages

- Respiratory tract infections (RTIs) are the most frequent infections encountered in primary care, accounting for an estimated 23% of general practice consultations in Ireland. Most are viral, but a small number are caused by bacteria and may respond to antibiotics.
- Depending on the site of infection, RTIs may be classified as upper (pharyngitis, tonsillitis, laryngitis, rhinosinusitis, otitis media and the common cold) or lower (pneumonia, bronchitis, tracheitis and acute infective exacerbations of chronic obstructive pulmonary disease [COPD]). Influenza may affect both the upper and lower respiratory tract.
- Most RTIs are self-limiting. The natural course of upper RTIs (URTIs) is typically shorter (ranging from four days for acute otitis media to 2.5 weeks for acute rhinosinusitis) than for lower RTIs (LRTIs) (range three weeks for acute bronchitis/cough to three to six months (to complete recovery) for community-acquired pneumonia [CAP]).
- Patient groups generally considered to be at highest risk of acute RTI and their sequelae include: paediatric (<5 years) and geriatric (>70 years) patients, those with a pre-existing lung condition (such as COPD or asthma), immuno-compromised patients, and long-term care (LTC) residents of nursing homes.
- For URTI, international clinical guidelines recommend clinical assessment should include a detailed clinical history and physical examination of the patient. Clinical prediction rules are used for some types of URTI to identify those patients most likely to benefit from antibiotic treatment. In uncomplicated cases of URTI that do not exceed the expected durations of illness, a strategy of no antibiotic or delayed antibiotic prescribing is generally recommended.
- For the management of LRTI and specifically CAP, a number of national clinical guidelines recommend CRP measurement if after clinical assessment a diagnosis of pneumonia has not been made and there is uncertainty regarding whether or not antibiotics should be prescribed. Use of antibiotics is recommended in patients with a diagnosis of pneumonia and in those with LRTI with risk factors for complications, but not for those with acute bronchitis.
- Overprescribing of antibiotics for RTIs in primary care is common, with high levels of inappropriate prescribing documented in observational studies benchmarking antibiotic prescribing versus clinical guidelines.

- Adverse drug events from antibiotic exposure may occur in one out of every five patients. Common side effects of antibiotics are gastrointestinal symptoms, skin rashes, and thrush.
- Antimicrobial resistance (AMR) is a growing and significant threat to public health, and it is widely recognised that antibiotic resistance is driven by excessive and inappropriate antibiotic prescribing. Increased antibiotic consumption correlates with increased antibiotic resistance, with countries that have moderate to high consumption of antibiotics also having high AMR. A causal link between antibiotic consumption and resistance is difficult to establish.
- At the patient level, there is a clear link between antibiotic dose and duration and the emergence of antibiotic resistance, and there is also evidence that patients who have been treated frequently with antibiotics are at greater risk of antibiotic resistance.
- AMR results in increased morbidity and mortality from bacterial infections as well as increased economic burden on the healthcare sector in the treatment and care of patients infected with multidrug-resistant strains as well as a loss of productivity. AMR results in the death of approximately 50,000 people per year in the US and Europe, and in the region of 700,000 people globally.

4 Clinical effectiveness and safety

In the context of this HTA, CRP POCT is used to determine whether antibiotic prescribing is appropriate for a patient presenting in primary care with a respiratory tract infection. In line with the agreed scope of the HTA, this chapter will examine the current evidence of efficacy and safety for CRP POCT in a primary care setting. The primary focus is to determine whether the use of CRP POCT in primary care leads to a significant reduction in antibiotic prescribing without compromising patient safety.

4.1 Search strategy

A full systematic review approach was used to search for evidence of clinical effectiveness and safety.

4.1.1 PICOS

The PICOS (Population, Intervention, Comparator, Outcomes, Study design) analysis used to formulate the search is presented in Table 4.1 below. Detailed PICOS are provided in Appendix F.

4.1.2 Bibliographic search

To identify relevant studies, systematic searches were carried out on the following databases:

- MEDLINE (OVID, Pubmed)
- Embase
- CINAHL (via EBSCOHost)
- The Cochrane Library

Hand searching of the literature was also undertaken including a cross-check of the reference list of included studies and relevant systematic reviews as well as citation tracking. Ad hoc internet searches were undertaken to identify other relevant grey literature. Finally, lists of relevant studies provided by manufacturers in their submission files were searched for additional studies. Submission files were submitted by three companies: Abbott (Alere), Orion Diagnostica Oy, and RPS Diagnostics. These files were used along with material from other company websites to inform the technology description domain. The following clinical trial registries were searched for registered ongoing clinical trials and observational studies: ClinicalTrials.gov and International Clinical Trials Registry Platform (ICTRP).

Table 4.1 Scope for search for studies of clinical effectiveness

Description	Project scope
Population	The population of interest is represented by patients of all ages who present with symptoms of acute respiratory tract infection (RTI – see Appendix B) in primary care (health care provided in the community through a general practice). Subgroups of particular interest include: children, older adults (≥65 years of age), patients attending out-of-hours (OOH) services and those in long-term care (LTC) facilities.
Intervention	CRP point-of-care test for use in primary care setting (+/- communication training, +/- education component, +/- other biomarkers) in addition to standard care. Testing for CRP may assist the clinician in differentiating between bacterial and viral aetiology and therefore guide antibiotic prescribing. Point of care tests allow the test to be done at the time of consultation with results available within minutes. The full list of included devices is provided in Appendix F.
Comparison	Standard care alone
Outcomes	**Primary outcomes:** ▪ Number of patients given antibiotic prescriptions (delayed +immediate) for acute RTI (at index consultation and at 28-days follow-up) ▪ Number of patients with substantial improvement or complete recovery at seven and 28-days follow-up ▪ Patient mortality at 28-days follow-up **Secondary outcomes:** • Number of patients given an antibiotic prescription for immediate use versus delayed use • Number of patients who redeemed a prescription for an antibiotic • Time to resolution of acute respiratory infection symptoms • ADR, including number of patients reconsulting or hospitalised due to ADR • Number of patients with RTI complications resulting in reconsultation • Number of patients with RTI complications in need of hospitalisation • HRQOL • Patient satisfaction • Physician satisfaction
Study design	RCTs, cluster RCTs, non-randomised studies, observational studies

The full set of search terms can be found in Appendix G. A separate search for clinical guidelines (G-I-N, National Guidelines Clearinghouse, hand searches) was also undertaken.

At the time of the systematic literature searches, no limitations were applied with regard to study design or language. No limits were applied for the year of publication for the first two systematic reviews (clinical effectiveness and diagnostic test accuracy). The search for the third systematic review (analytical performance) was limited to publications from 1990 onwards as performance data from older studies were considered unlikely to be relevant to the current commercially available point-of-care tests.

Two authors independently reviewed titles and abstracts. The full text of potentially eligible articles was reviewed by the two authors independently and the study included or excluded based on predefined criteria. Studies that did not provide data on the relevant outcomes were excluded. Studies that reported on duplicate data were identified and excluded if no additional data were available in the secondary publication. Abstracts from conferences were also excluded. Any disagreement in study selection was resolved through discussion. Studies excluded at full-text review are listed in Appendix G.

4.1.3 Data extraction and analysis

Two review authors independently extracted data using prepared data extraction forms. The authors resolved any discrepancy through discussion or with a third author.

Measures of treatment effect are reported as a risk ratio with 95% confidence intervals for each dichotomised outcome. When results could not be pooled, they were presented qualitatively. Where it was appropriate to pool data, Review Manager 5 software was used to perform meta-analysis. Heterogeneity was investigated using the I^2 statistic. The choice between fixed and random effects meta-analysis was based on an assessment of the statistical and clinical heterogeneity across studies. Where substantial statistical heterogeneity was observed and sufficient studies were available, a meta-regression was considered to explore study characteristics that may be potential sources of heterogeneity. The following subgroup analyses were planned, by:

- Study type, RCT versus cluster RCT versus observational studies
- Age group, children versus adults, younger adults (<65 years) versus older adults (≥65 years)

- Presenting symptoms, upper versus lower respiratory tract infections
- Setting, out of hours and those in long-term care.

The sample size of cluster randomised controlled trials were modified as recommended in the Cochrane Handbook.[153] Design effect = 1 + (M-1) ICC, where M is the mean cluster size (that is, the average number of people in each cluster) and the ICC is the inter-cluster correlation. For studies where the ICC was reported, the ICC was taken from the study. When it was not reported, the ICC was taken from the literature as recommended in the Cochrane handbook.

4.1.4 Quality appraisal

Two reviewers independently assessed the quality or risk of bias of full-text articles included in the review using standardised critical appraisal instruments, with any disagreements resolved through discussion. As both randomised controlled trials and non-randomised studies were included, two separate methods were used to assess the risk of bias of included studies. The Cochrane risk of bias tool was used to assess RCTs and cluster RCTs.[154] This tool is used to assess the included studies for selection bias (random sequence generation and allocation concealment, performance bias, detection bias, attrition bias, reporting bias and any other sources of bias.[154] For non-randomised controlled trials and observational studies, the Newcastle Ottawa quality assessment scale was used. With this tool, the studies are assessed for selection bias, comparability and outcomes.[155]

The quality of the body of evidence was assessed for each outcome using GRADE (Grading of Recommendations, Assessment, Development and Evaluation).[156] External experts, members of the authoring, co-authoring and reviewing teams were involved in grading the importance of each of the outcomes identified. Feedback from the patient representative was included as part of the authors' review. The main findings of the review were presented in the 'Summary of findings' (SoF) table, created using the GRADE PRO tool (https://gradepro.org/). Primary review outcomes were listed with estimates of relative effects along with the number of participants and studies contributing data for each outcome. For each individual outcome, the quality of the evidence was assessed using the GRADE approach, which involves considering within study risk of bias (limitations in design, inconsistency, indirectness, imprecision and publication bias). Magnitude of the effect, dose-response effect and other plausible confounders were considered in relation to observational studies. Results are expressed as one of four levels of quality (high, moderate, low or very low) (see Table 4.2). The summary of findings table is reported in Appendix J.

Table 4.2 Definition of quality of evidence (GRADE)

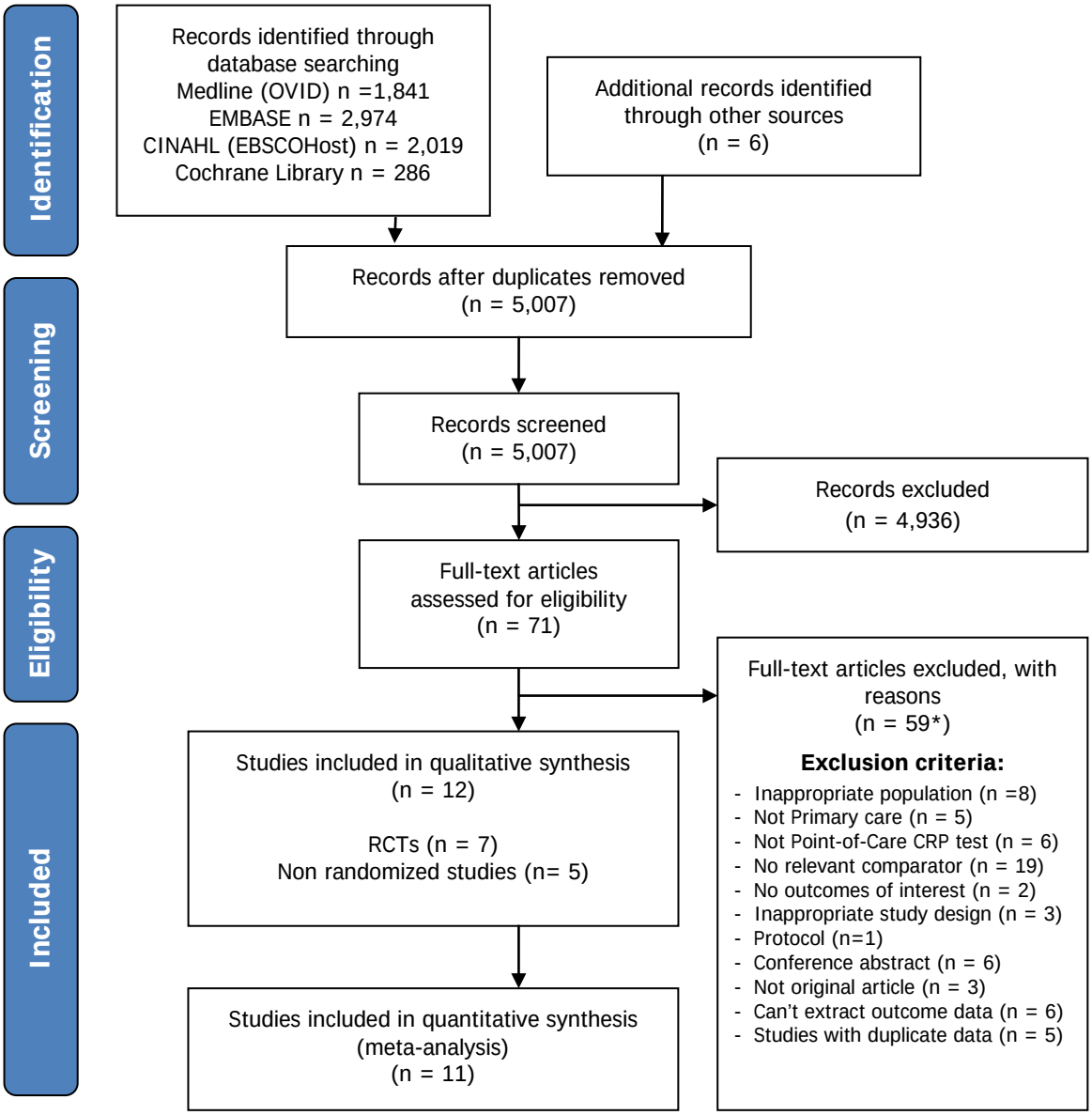
Quality rating	Definition
High	We are very confident that the true effect lies close to the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.

Source: GRADEpro handbook

4.2 Study selection

In April 2018, a total of 5,007 articles were identified through database searching and manufacturers' submissions. After title and abstract screening, 71 articles were identified as being potentially relevant. Of these, 59 articles were subsequently excluded due to the reasons listed in Figure 4.1. The most common reason for exclusion was the lack of a suitable comparator group. The majority of these studies were observational studies that reported on CRP POCT versus no CRP POCT, but upon reading the full text of the article it was clear that all physicians had access to CRP POCT, but that some chose not to use it. These studies were excluded as it was unclear if the non-use of CRP POCT was because these physicians never used it in their practice to inform a decision or because following clinical examination of the individual patients they felt it was unnecessary. Five studies were identified that presented duplicate data of studies that were already included.[157-161] This left 12 studies for inclusion in the systematic review,[35, 36, 162-171] of which 11 studies were included in the meta-analysis.[36, 162-171] The twelfth study met our inclusion criteria, but did not present enough information in the paper to allow data to be extracted for meta-analysis; attempts to contact the author were unsuccessful.[35] This study (Bjerrum et al. 2004) only reported on the primary outcome (the number of patients given an antibiotic prescription at the index consultation) and the results from this study have been included in the narrative for this outcome.

Figure 4.1 Flow chart: systematic review of clinical effectiveness and safety



* Some studies were excluded for more than one reason and therefore 64 reasons were given for full-text exclusion for 59 studies.

The search also identified seven relevant systematic reviews.[29-31, 172-175] These studies were checked for additional references. One systematic review[30] included four additional studies, two of which had been excluded in this study as they were duplicate studies,[159] and two studies had been excluded as the testing was undertaken in an emergency department and therefore did not meet our inclusion criteria.[176, 177] In the scoping phase of this assessment, we identified a relevant Cochrane review by Aabenhaus et al. from 2014.[29] A decision was made at that time not to directly update this review as our review included additional outcomes of interest and it included more study types (observational studies in addition to RCTs); however, we did base our review on the Aabenhaus review. The references of included studies were also searched for additional relevant articles, but none were identified. Manufacturers' submissions were also checked for additional studies; six were identified that appeared to be relevant, but on full text review all were excluded.

The systematic search of databases was updated in March 2019. A total of 1,175 additional articles were identified, and after title and abstract screening, six articles were identified as being potentially relevant. Following full-text review, one pragmatic RCT study by Schot et al (2018) was identified for inclusion in the systematic review.[178]

4.3 Results: clinical effectiveness

4.3.1 Included studies

The systematic review retrieved 13 studies that assessed the clinical effectiveness and/or safety of using CRP POCT to guide antibiotic prescribing in patients presenting to primary care with acute RTIs (Table 4.3). Four studies were individually randomised RCTs (n=3,345),[36, 164, 165, 171] three were cluster RCTs (n=4,874, modified n=1975),[162, 163, 168] one was a pragmatic RCT (a combination of cluster and individual randomisation, n=309), and five were non-randomised studies (n=8,998 for four studies included in meta-analysis).[35, 166, 167, 169, 170] A detailed description of the 13 studies is found in Appendix H.

Eleven of the studies were carried out in Europe, one in Russia,[162] and one in Vietnam.[165] The length of follow-up varied from no follow-up to 90 days. All included studies reported on at least the primary outcome, antibiotic prescribing at the index consultation comparing those who had access to CRP POCT to those who were treated with usual care. Presenting symptoms and inclusion criteria differed between studies with some studies including only patients with LRTIs,[162, 170, 171, 178] others patients with URTI only (in particular sinusitis),[35, 167, 169] while others included both URTI and LRTI.[36, 163-166, 168] Some studies included patients with

exacerbations of chronic obstructive pulmonary disease (COPD), while others excluded patients with chronic disease. Most studies only included adults, while three included adults and children.[35, 36, 165] One study included only children.[178] The studies tended to include more woman than men (RCT range 57-72% female). Four studies received funding from the manufacturers of the CRP POCT devices.[164, 167, 171, 178] The identified studies included in this HTA related to only three of the 15 CE marked devices (QuikRead® CRP kit/QuikRead® 101, Alere Afinion™ CRP, and NycoCard™ CRP for use with NycoCard™ II Readers). All three of these devices are quantitative devices.

The non-randomised studies differed substantially from the RCTs in a number of ways and as a result have been analysed separately. Not only did they differ in terms of study design, but they also differed in terms of access to the intervention. In the RCTs, all patients in the intervention group received the intervention, while no patients in the control group received it. In the non-randomised studies, the intervention group had access to CRP POCT, but the clinicians may or may not have used it, while the control group had no access to CRP POCT.

As there was clinical heterogeneity due to the spectrum of RTIs included in each study, a random effects model was used for meta-analysis unless otherwise stated. The pragmatic RCT study by Schot et al. is not included in the meta-analysis, because it is the only study where children are the exclusive target population.

Table 4.3 Main characteristics of included studies

Author and year or study name	Study type	Number of patients	Intervention (s)	Main endpoints	Included in clinical effectiveness and/ or safety domain
Andreeva 2014	Cluster RCT	179	CRP POCT Afinion™ test system	Antibiotic Rx at index consultation, Antibiotic Rx at 28 days F/U, Mortality	Effectiveness Safety
Bjerrum 2004	Observational study	367 GPs	CRP POCT	Antibiotic Rx at index consultation	Effectiveness
Cals 2009	Cluster RCT	431	CRP POCT NycoCard™ II reader	Antibiotic Rx at index consultation, Antibiotic Rx at 28 days F/U, Substantial improvement/complete recovery at 7 and 28 days, Mortality, Time to resolution of RTI symptoms, Reconsultations, Patient satisfaction	Effectiveness Safety

Author and year or study name	Study type	Number of patients	Intervention (s)	Main endpoints	Included in clinical effectiveness and/ or safety domain
Cals 2010	RCT	258	CRP POCT QuikRead® CRP	Antibiotic Rx at index consultation, Antibiotic Rx at 28 days F/U, Substantial improvement/complete recovery at 7 and 28 days, Mortality, Antibiotic Rx for delayed used, Time to resolution of RTI symptoms, Reconsultations, Patient satisfaction	Effectiveness Safety
Diederichsen 2000	RCT	812	CRP POCT NycoCard™ reader	Antibiotic Rx at index consultation, Substantial improvement/complete recovery at 7 and 28 days	Effectiveness Safety
Do 2016	RCT	2,037	CRP POCT NycoCard™ analyser with NycoCard™ II reader	Antibiotic Rx at index consultation, Antibiotic Rx at 28 days F/U, Mortality, Time to resolution of RTI symptoms, Reconsultations, Hospitalistions, Patient satisfaction	Effectiveness Safety
Jakobsen 2010	Observational	803	CRP POCT NycoCard™ CRP QuikRead® CRP	Antibiotic Rx at index consultation	Effectiveness
Kavanagh 2011	Pilot cross-sectional study	120	CRP POCT QuikRead® CRP	Antibiotic Rx at index consultation, Antibiotic Rx for delayed used, Reconsultations, Patient satisfaction	Effectiveness Safety
Little 2013	Cluster RCT	4,264	CRP POCT QuikRead® CRP	Antibiotic Rx at index consultation, Mortality, Time to resolution of RTI symptoms, Reconsultations, Hospitalisation	Effectiveness Safety
Llor (a) 2012	Non-randomised before-after study	3,356	CRP POCT NycoCard™ CRP	Antibiotic Rx at index consultation	Effectiveness
Llor (b) 2012	Non-randomised before-after study	560	CRP POCT NycoCard™ CRP	Antibiotic Rx at index consultation	Effectiveness
Melbye 1995	RCT	239	CRP POCT NycoCard™ Reader	Antibiotic Rx at index consultation, Antibiotic Rx at 28 days F/U, Substantial improvement/complete recovery at 7 and 28 days	Effectiveness Safety

Author and year or study name	Study type	Number of patients	Intervention (s)	Main endpoints	Included in clinical effectiveness and/ or safety domain
Schot 2018	Pragmatic RCT (Cluster randomisation for daytime general practice and individual randomisation for OOH setting)	309	CRP POCT Afinion™ test system	Antibiotic Rx at index consultation, reconsultation and antibiotic prescribing during the same illness episode, consultation for a new episode of RTI within 3 months of the index consultation, and antibiotic prescriptions at these consultations.	Effectiveness Safety

Key: CAP – community acquired pneumonia; CRP – C-reactive protein; DTA – diagnostic test accuracy; F/U – follow-up; LRTI – lower respiratory tract infection; OOH – out-of-hours; POCT – point-of-care testing; RCT – randomised controlled trial; Rx – prescription.

The study populations and included indications are listed in Table 4.4 below.

Table 4.4 Study populations and indications in included studies

Study (year)	Study country & population	Indications
Andreeva (2014)	Russia; adult patients (aged 18 years and over).	Acute cough and LRTI (including acute bronchitis, pneumonia, and infectious exacerbations of COPD or asthma).
Bjerrum (2004)	Denmark; patients of all ages.	Acute sinusitis, acute tonsillitis, or acute otitis.
Cals (2009)	Netherlands; adult patients.	Suspected LRTI with a cough lasting less than four weeks together with one focal and one systemic symptom.
Cals (2010)	Netherlands; adult patients (aged 18 years and over).	LRTI (cough duration < four weeks with at least one focal sign and one systemic sign or symptom) or rhinosinusitis (duration < four weeks with at least two symptoms or signs).
Diederichsen (2000)	Denmark; patients of all ages.	Respiratory infections.
Do (2016)	Vietnam; patients aged one to 65 years.	Non-severe acute respiratory tract infection with at least one focal and one systemic symptom lasting less than two weeks.

Study (year)	Study country & population	Indications
Jakobsen (2010)	Norway, Sweden and Wales; adult patients (aged 18 years and over).	Acute cough (duration less than four weeks).
Kavanagh (2011)	Ireland; adult patients (aged 18 years and over).	Acute cough and/or sore throat (duration less than four weeks).
Little (2013)	Belgium, Spain, Poland, UK, Netherlands; adult patients (aged 18 years and over).	Diagnosis of respiratory tract infection.
Llor (a) (2012)	Spain; age restrictions not reported.	LRTI (acute bronchitis, acute exacerbation of chronic bronchitis or chronic obstructive pulmonary disease (COPD), pneumonia)
Llor (b) (2012)	Spain; age restrictions not reported.	Acute rhinosinusitis.
Melbye (1995)	Norway; adult patients (aged 18 years and over).	Suspected pneumonia, bronchitis or asthma; symptoms of cough or shortness of breath, chest pain on deep inspiration or cough.
Schot (2018)	Netherlands; children (aged 3 months to 12 years old)	Suspected non-serious LRTI, including presence of acute cough (<21 days) and reported fever (>38 °C, < 5 days).

Key: LRTI – lower respiratory tract infection; COPD, chronic obstructive pulmonary disease.

4.3.2 Impact on clinical management

Number of patients given an antibiotic prescription at the index consultation

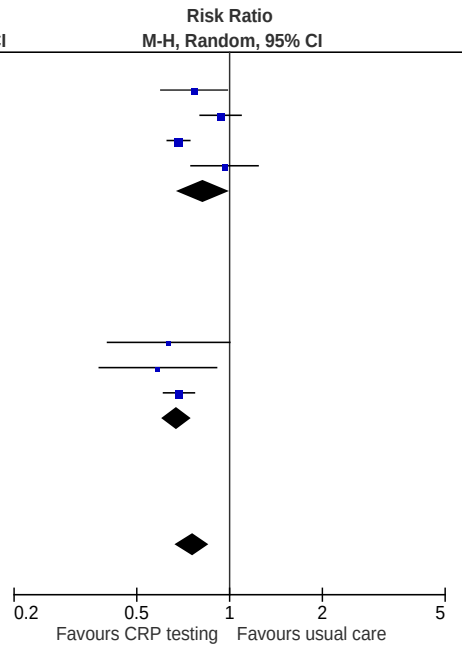
All 11 studies included in the meta-analysis (randomised n=7; observational n=4) reported on this outcome.[36, 162-171] The seven RCTs (individually randomised studies n=3,345, cluster randomised trials with modified sample size n=1,975) and four non-randomised studies (n=4,839) all showed point estimates in favour of CRP POCT to reduce antibiotic prescribing; however, in four studies the difference was not statistically significant.[36, 162, 167, 171]

The pooled estimate for the RCTs showed a statistically significant reduction in antibiotic prescribing in the CRP test group, compared with usual care (RR 0.76, 95% CI: 0.67-0.86, I^2 = 70%) (Figure 4.2). There was substantial heterogeneity in this pooled estimate (70%). This could not be attributed to differences in trial type, as even in our planned subgroup analysis, grouping the trials based on type of randomisation used (individual or cluster), there was substantial heterogeneity in the

individually randomised group (I^2 = 82%, n=4), but not in the cluster randomised group (I^2 = 0%, n=3). When performing a sensitivity analysis, much of the heterogeneity observed in the individually randomised subgroup was due to the 2016 study by Do et al. (I^2 decreases from 82% to 5% when this study is removed).[165] The study by Do et al. differs from the other studies as it was carried out in Vietnam, while the other studies were carried out in Europe or Russia. It also reported a high level of antibiotic prescribing in the usual care arm, even though they excluded patients with severe RTI. Inclusion of the study by Do et al. in the meta-analysis of individually randomised trials produced a pooled effect of CRP POCT on antibiotic prescribing of RR 0.82 (95% CI: 0.67, 1.00, I^2 = 82%, n=4) while removing this trial produces an RR of 0.90 (95% CI: 0.80, 1.02, I^2 = 5%, n=3). Removal of this study from the pooled analysis makes only a small difference to the overall pooled effect estimate (RR 0.78 95% CI: 0.66, 0.92, I^2 = 68%, n=6). In the cluster randomised trials, there was a statistically significant reduction in antibiotic prescribing in the CRP POCT group compared with usual care (RR 0.68 95% CI: 0.61, 0.75, I^2 = 0%). However, it should be noted that two of these three studies (Cals 2009 [163] and Little 2013 [168]), used a factorial design and included a communication component which was shown by the authors to have a significant effect on lowering antibiotic prescriptions at the index consultation both on its own and when used in combination with CRP POCT. Removal of these studies from the meta-analysis had only a small effect on the pooled estimate (RR 0.80, 95% CI: 0.67, 0.96, I2 =77%).

Figure 4.2 Forest plot: Antibiotic prescribing at index consultation (RCTs and Cluster RCTs)

Study or Subgroup	CRP testing Events	CRP testing Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Individually randomised trials						
Cals 2010	56	129	73	129	12.9%	0.77 [0.60, 0.98]
Diederichsen 2000	179	414	184	398	18.5%	0.94 [0.80, 1.09]
Do 2016	441	1017	647	1019	22.5%	0.68 [0.63, 0.74]
Melbye 1995	54	108	68	131	12.8%	0.96 [0.75, 1.24]
Subtotal (95% CI)		**1668**		**1677**	**66.8%**	**0.82 [0.67, 1.00]**
Total events	730		972			
Heterogeneity: Tau² = 0.03; Chi² = 16.62, df = 3 (P = 0.0008); I² = 82%						
Test for overall effect: Z = 1.97 (P = 0.05)						
1.1.2 Cluster randomised trials						
Andreeva 2014	18	49	22	38	6.0%	0.63 [0.40, 1.00]
Cals 2009	20	65	31	59	6.4%	0.59 [0.38, 0.91]
Little 2013	304	920	407	844	20.8%	0.69 [0.61, 0.77]
Subtotal (95% CI)		**1034**		**941**	**33.2%**	**0.68 [0.61, 0.75]**
Total events	342		460			
Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 2 (P = 0.76); I² = 0%						
Test for overall effect: Z = 7.08 (P < 0.00001)						
Total (95% CI)		**2702**		**2618**	**100.0%**	**0.76 [0.67, 0.86]**
Total events	1072		1432			
Heterogeneity: Tau² = 0.02; Chi² = 19.82, df = 6 (P = 0.003); I² = 70%						
Test for overall effect: Z = 4.23 (P < 0.0001)						
Test for subgroup differences: Chi² = 2.83, df = 1 (P = 0.09), I² = 64.7%						



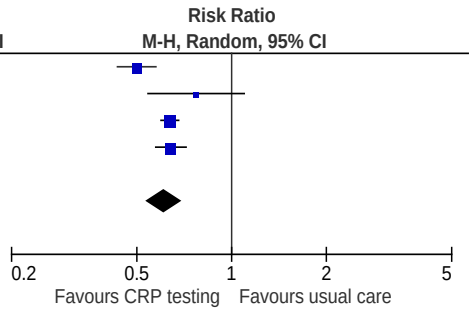
The observational studies show a similar effect of CRP POCT on antibiotic prescribing with a pooled RR of 0.61 (95% CI: 0.54-0.69) (Figure 4.3). There was substantial heterogeneity in the pooled estimate with an I^2 = 74%. In a sensitivity analysis, it was identified that the 2010 study by Jakobsen et al. was the source of the heterogeneity. When this trial was removed from the meta-analysis, the effect of CRP POCT on antibiotic prescribing remained, but the heterogeneity decreased (RR 0.64, 95% CI: 0.61-0.68, I^2 = 0%, n=3). The study by Jakobsen et al. compared antibiotic prescribing in Norway and Sweden, where CRP POCT is often used in routine consultation, to Wales in the UK where it is not available to GPs. As Sweden and Norway and the UK have different health systems and patients may have different expectations about receiving an antibiotic, this control group may not have been a suitable comparator.[166] The 2004 study by Bjerrum et al. also reported a significant difference in prescribing between their CRP POCT group and the usual care group, but the data were not available in a format where it could be extracted for meta-analysis (OR 0.43, 95% CI: 0.33-0.58).[35]

There was an absolute risk reduction of 10.0% and an NNT (number needed to test) of 10 (95% CI: 5-152) to save one antibiotic prescription at the index consultation based on individually randomised RCTs and an absolute risk reduction of 15.9% and an NNT of 6 (95% CI: 5-9) for cluster randomised RCTs. The observational studies showed an absolute risk reduction in receiving an antibiotic of 28.4% and an NNT of 4 (95% CI: 3-5). Across all studies, five patients would need to be tested for CRP using a POC test to prevent one antibiotic prescription (95% CI: 4-8).

Figure 4.3 Forest plot: Antibiotic prescribing at index consultation (Non-randomised studies)

Study or Subgroup	CRP testing Events	CRP testing Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
Jakobsen 2010	175	503	209	300	26.0%	0.50 [0.43, 0.58]
Kavanagh 2011	27	60	35	60	9.7%	0.77 [0.54, 1.10]
Llor 2012	653	1488	1288	1868	34.8%	0.64 [0.60, 0.68]
Llor 2012b	156	275	252	285	29.5%	0.64 [0.57, 0.72]
Total (95% CI)		**2326**		**2513**	**100.0%**	**0.61 [0.54, 0.69]**
Total events	1011		1784			

Heterogeneity: Tau² = 0.01; Chi² = 11.51, df = 3 (P = 0.009); I² = 74%
Test for overall effect: Z = 7.63 (P < 0.00001)



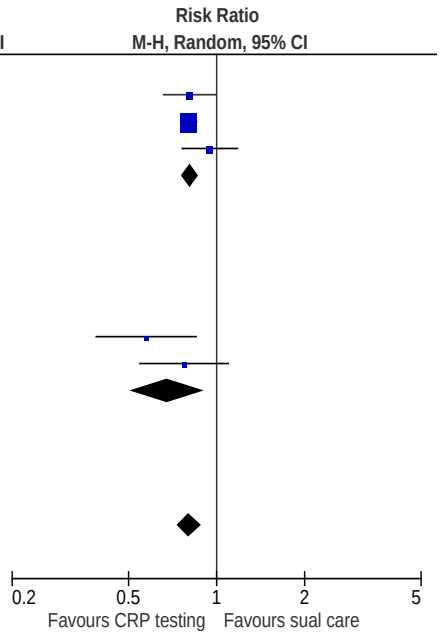
Schot et al. reported in their study that GPs in the CRP POCT group prescribed antibiotics to 30.9% of the children compared to 39.4% in the control group at the index consultation (OR 0.6; 95% CI = 0.30 to 1.24).[178] The observed reduction was not statistically significant.

Number of patients given an antibiotic prescription within 28 days follow-up

Five RCT studies reported on this outcome (Figure 4.4),[162-165, 171] of which three were individually randomised studies (n=2,533) and two cluster randomised studies (modified sample size n=211). No observational studies reported on prescribing beyond the index consultation. All included studies showed point estimates in favour of CRP POCT to reduce antibiotic prescribing within 28 days (RR 0.81, 95% CI: 0.74-0.88, I^2 = 21%); however, in three of the studies the difference was not significant. Not all of the studies had a follow-up period of 28 days: the study by Melbye et al. had a 21-day follow-up period [171], while the studies by Do et al. and Andreeva et al. had a 14-day follow-up period.[162, 165] There was no indication that more patients subsequently received an antibiotic during the follow-up period in the CRP POCT group compared with usual care. Schot et al. reported that children in both the CRP POCT and control groups had similar rates of reconsultations within the same episode of illness (33% versus 34%; OR 0.95; 95% CI = 0.46 to 1.99).[178]

Figure 4.4 Forest plot: Antibiotic prescribing within 28 days (RCTs and Cluster RCTs)

Study or Subgroup	CRP testing Events	CRP testing Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Individually randomised trials						
Cals 2010	68	129	84	129	15.8%	0.81 [0.66, 1.00]
Do 2016	598	1017	747	1019	58.2%	0.80 [0.75, 0.85]
Melbye 1995	61	108	78	131	14.5%	0.95 [0.76, 1.18]
Subtotal (95% CI)		**1254**		**1279**	**88.6%**	**0.82 [0.76, 0.87]**
Total events	727		909			
Heterogeneity: Tau² = 0.00; Chi² = 2.11, df = 2 (P = 0.35); I² = 5%						
Test for overall effect: Z = 6.04 (P < 0.00001)						
1.2.2 Cluster randomised trials						
Andreeva 2014	20	49	27	38	5.1%	0.57 [0.39, 0.85]
Cals 2009	29	65	34	59	6.4%	0.77 [0.55, 1.10]
Subtotal (95% CI)		**114**		**97**	**11.4%**	**0.68 [0.51, 0.91]**
Total events	49		61			
Heterogeneity: Tau² = 0.01; Chi² = 1.24, df = 1 (P = 0.27); I² = 19%						
Test for overall effect: Z = 2.63 (P = 0.009)						
Total (95% CI)		**1368**		**1376**	**100.0%**	**0.81 [0.74, 0.88]**
Total events	776		970			
Heterogeneity: Tau² = 0.00; Chi² = 5.07, df = 4 (P = 0.28); I² = 21%						
Test for overall effect: Z = 4.58 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.49, df = 1 (P = 0.22), I² = 32.9%						



Planned subgroup analysis

Subgroup analysis was performed for upper (sinusitis, sore throat etc.) versus lower RTIs (bronchitis, acute exacerbations of COPD, pneumonia, cough) for the outcome of antibiotic prescribing at the index consultation. Eight studies (three RCTs [164, 168,

171)], one cluster RCT [162] and four non-randomised studies [166, 167, 169, 170]) provided data on either LRTI or URTI or both (Figures 4.5 and 4.6).

Figure 4.5 Antibiotic prescribing at index consultation (RCTs and Cluster RCTs)

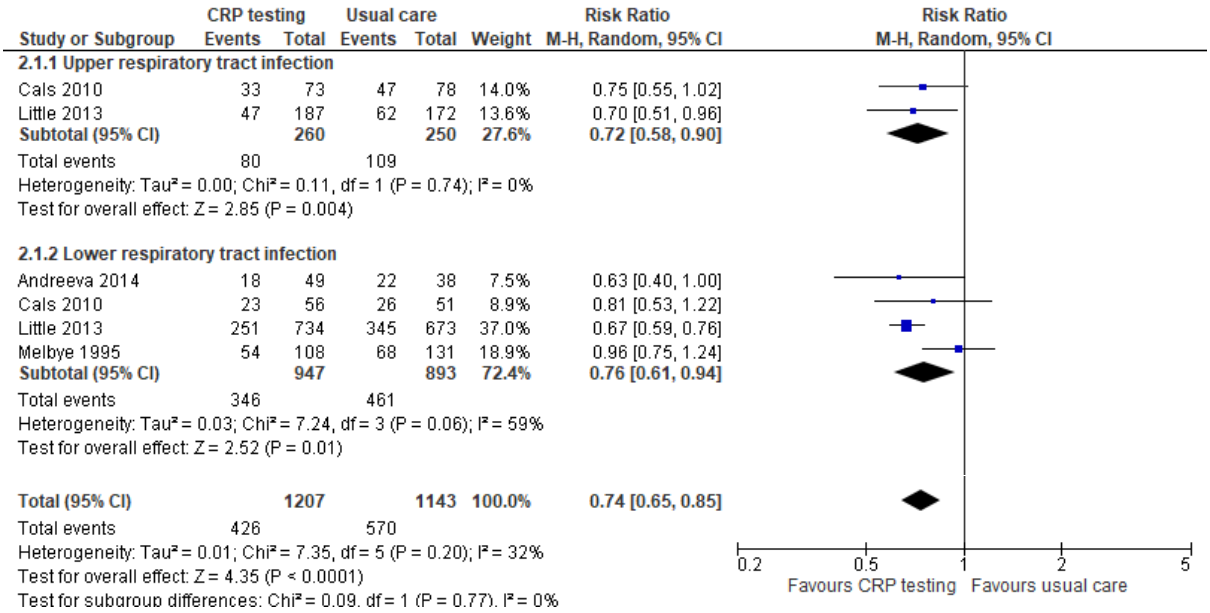
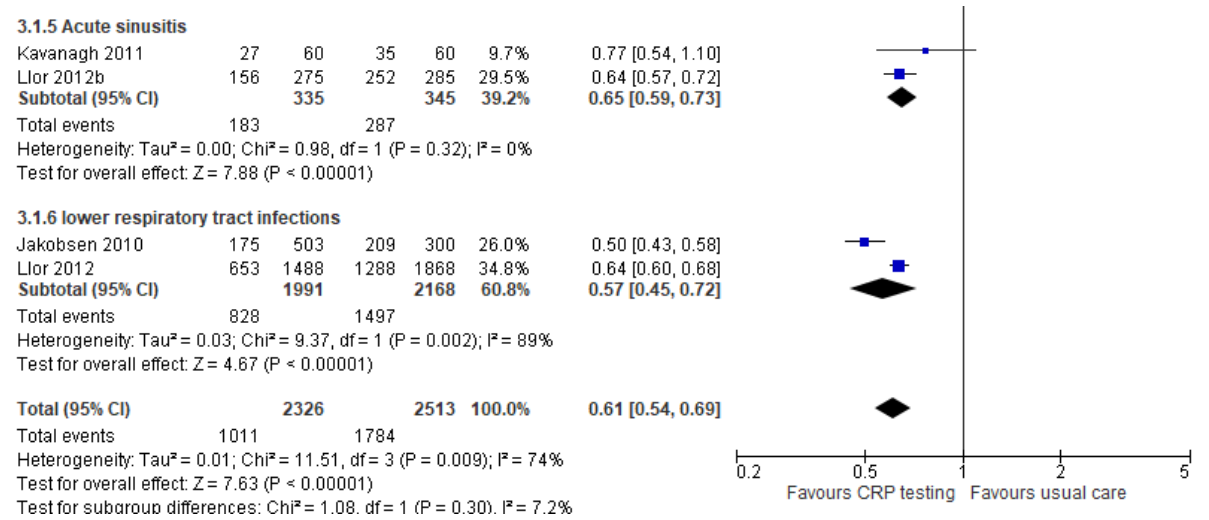


Figure 4.6 Forest plot of comparison: Antibiotic prescribing at index consultation (non-randomised studies)



Two RCTs provided data on URTI.[164, 168] The study by Cals et al. 2010 shows a non-significant reduction in antibiotic prescribing, while the study by Little et al. shows

the reduction to be significant; the pooled data suggest a significant reduction in antibiotic prescribing (RR 0.72, 95% CI: 0.58-0.90, I^2 = 0%). The non-randomised studies show a similar finding: both studies have a point estimate favouring CRP POCT, but the difference is not statistically significant in the Kavanagh et al. study but is significant in the Llor 2012 study. Overall, the pooled estimate shows a significant reduction in antibiotic prescribing between the CRP POCT group and the usual care group (RR 0.65, 95% CI: 0.59-0.73, I^2 = 0%).

Four RCTs provided data on LRTI.[162, 164, 168, 171] Three of the studies had a non-significant reduction in antibiotic prescribing in the CRP POCT group compared with the usual care group,[162, 164, 171] while one study showed significant difference.[168] The pooled RR suggests CRP POCT does lower antibiotic prescribing in patients with LRTI (RR 0.76, 95% CI: 0.61-0.94), however there is substantial heterogeneity (I^2 = 59%). This finding is backed up by two non-randomised studies (Llor 2012 and Jakobsen) with a pooled estimate of RR 0.57 (95% CI: 0.45-0.72, I^2 = 89%).

Two RCTs included adults and children.[36, 165] The study by Do et al. found a similar and significant effect of using CRP POCT on antibiotic prescribing with children and adults (children n=1,028, RR 0.69, 95% CI: 0.62-0.78, adults n=1,008, RR 0.67, 95% CI: 0.60-0.76; combined cohort n=2,036, RR 0.68, RR: 0.63-0.74). The study by Diederichsen et al. also included adults and children in their study. While they did not report the antibiotic prescribing separately for adults and children, the Cochrane review by Aabenhaus et al. used unpublished data to calculate the effect of CRP POCT in children and adults separately for this study and reported that CRP POCT did not have a significant effect on the prescribing of antibiotics in either group (children n=139, RR 1.09, 95% CI: 0.70-1.71; adults n=673, RR 0.91, 95% CI: 0.78–1.07). As noted previously, however, the effect of CRP POCT on antibiotic prescribing in the combined cohort in this study was not significant (children and adults n=812, RR 0.94, 95% CI: 0.80-1.09).

Although it was not possible to do a subgroup analysis based on CRP cut-points, there was an option to undertake a subgroup analysis of studies where there was a clear recommendation to the GP on the basis of specified CRP levels, specifically if CRP <20 mg/L not to prescribe antibiotics, to prescribe antibiotics when CRP >100 mg/L and to use clinical judgment when CRP between 20 and 99 mg/L as per NICE guidelines for pneumonia. Four studies fit these criteria (see Appendix I for description of algorithm used in each study): two individually randomised RCTs [164, 165], one cluster RCT [168] and one non randomised study [170]. Combining the RCTs (using modified sample size for cluster RCT) produces a pooled estimate of RR 0.69 ([95% CI: 0.65, 0.74], I^2 = 0%). The non-randomised study by Llor et al. agreed with the pooled estimate (0.64 [0.60, 0.68]) suggesting that providing GPs with clear

cut-points based on clinical guidelines may enhance the effect of CRP POCT on antibiotic prescribing.

Number of patients given an antibiotic prescription for immediate use versus delayed use and redemption of prescriptions

One RCT [164] and one non-randomised study [167] included information on whether the prescribed antibiotic was delayed or for immediate use. These studies by Cals et al. 2010 and Kavanagh et al. 2011, showed no difference in the number of patients provided a 'delayed' prescription between the CRP group and the usual care groups (RR 0.84, 95% CI: 0.53-1.33 and RR 1.30, 95% CI: 0.63-2.66, respectively). However, the study by Cals et al. 2010 also looked at how many patients redeemed their delayed prescription, and found significantly more redeemed prescriptions in the usual care group compared with the CRP POCT group (72% vs. 23%). As the study by Cals et al. 2010 showed no significant difference in recovery at seven days between the CRP POCT group and the usual care group ([D0005], [C0008]), this might suggest that patients were more reassured that they did not need an antibiotic when the findings from the clinical examination were supported by their CRP test result. Further qualitative studies would need to be done to explore the reasons for redemption of delayed prescriptions. Other than the study by Cals et al. 2010, no study provided information on the number of patients who redeemed a prescription for antibiotics.

Number of patients with substantial improvement or complete recovery at seven days and 28 days

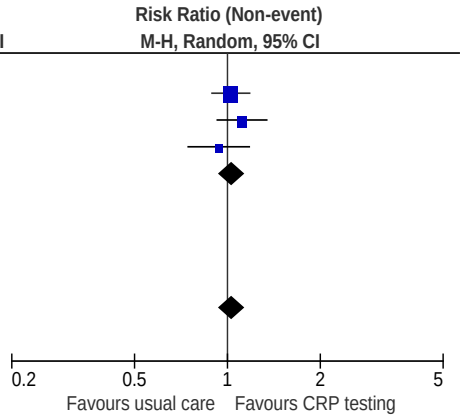
Three studies (n=1264 patients) reported on the number of patients that made a substantial or complete recovery by day seven (Figure 4.7).[36, 164, 171] The study by Diederichsen et al. did not include this information in their paper, but the author had provided this information for the Cochrane review by Aabenhaus et al. and this data was extracted directly from the Aabenhaus review.[29] There was no difference in the number of patients making a substantial or compete recovery between the CRP POCT group and the usual care group at seven days (RR 1.03, 95% CI: 0.93-1.14, I^2 = 0%). Of note, the study by Cals et al. 2009 (n = 388 patients) also reported that there was no significant difference in clinical recovery between the groups at seven days, but the data was not extractable for meta-analysis [163].

Three studies (one individually randomised RCT[171] and two cluster RCTs[162, 163]) reported on recovery beyond seven days: Andreeva et al., Melbye et al. and Cals et al. reported on clinical recovery at 14 days, 21 days and 28 days, respectively. Cals 2009 data was extracted directly from the Aabenhaus et al. review as this data was

not available in the study paper. In all three studies, there was no difference in recovery beyond seven days between the CRP POCT group and the usual care group (n=527, with modified sample sizes for cluster RCTs. RR 0.94 [95% CI: 0.68-1.28], I^2 = 0%]).

Figure 4.7 Forest plot: Recovery by day 7 (RCTs and Cluster RCTs)

Study or Subgroup	CRP testing Events	CRP testing Total	Usual care Events	Usual care Total	Weight	Risk Ratio (Non-event) M-H, Random, 95% CI
1.3.1 Individually randomised trials						
Cals 2010	27	118	31	125	51.1%	1.03 [0.89, 1.18]
Diederichsen 2000	251	407	252	384	29.5%	1.12 [0.93, 1.34]
Melbye 1995	46	102	53	128	19.4%	0.94 [0.75, 1.18]
Subtotal (95% CI)		**627**		**637**	**100.0%**	**1.03 [0.93, 1.14]**
Total events	324		336			
Heterogeneity: Tau² = 0.00; Chi² = 1.43, df = 2 (P = 0.49); I² = 0%						
Test for overall effect: Z = 0.63 (P = 0.53)						
Total (95% CI)		**627**		**637**	**100.0%**	**1.03 [0.93, 1.14]**
Total events	324		336			
Heterogeneity: Tau² = 0.00; Chi² = 1.43, df = 2 (P = 0.49); I² = 0%						
Test for overall effect: Z = 0.63 (P = 0.53)						
Test for subgroup differences: Not applicable						



Time to resolution of acute respiratory infection symptoms

Four studies reported on the time to resolution of symptoms (Table 4.5).[163-165, 168] All four studies reported the median time to resolution of symptoms; however, no attempt was made to pool these data as the definition of resolution of symptoms differed between studies. All of the studies reported no significant difference in the time to resolution of symptoms between the CRP POCT and usual care groups, even when one group had received more antibiotics than the other group.

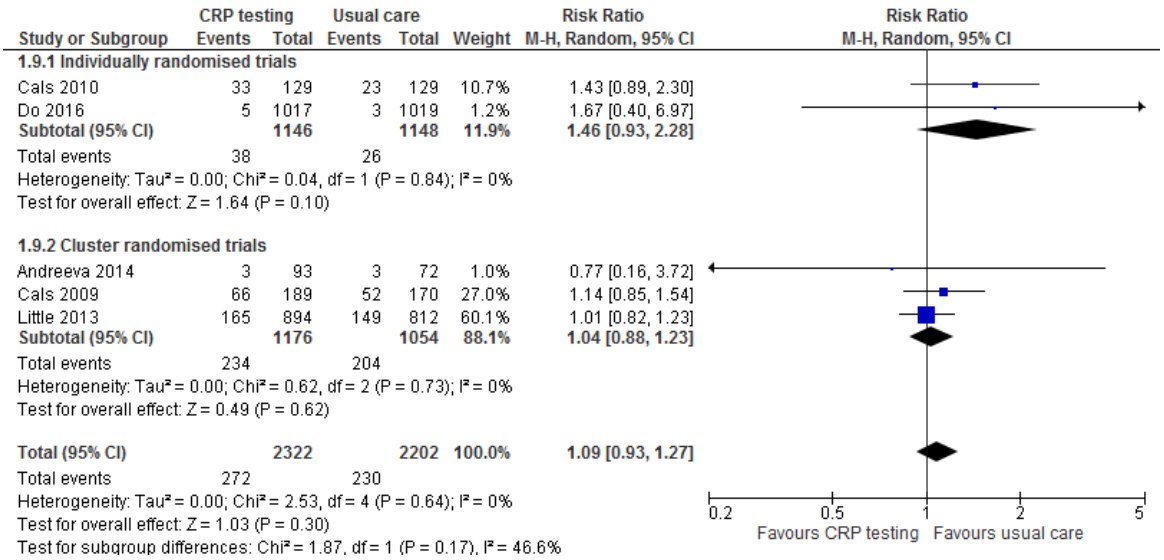
Table 4.5 Median time to resolution of symptoms

Author (year)	Patients	Median time to symptom resolution in CRP group (days)	IQR (days)	Median time to symptom resolution in usual care group (days)	IQR (days)
Do (2016)	All patients	5	4 to 7	5	4 to 7
	Children	5	3 to 7	5	4 to 7
	Adults	6	4 to 10	5	4 to 8
Cals (2010)	Rhinosinusitus	14	10 to 28	14	7 to >28
	LRTI	15.5	9.5 to 28	20	13.3 to >28
Cals (2009)	All patients	22	14 to 28	22	14 to 28
Little (2013)	All patients	5	3 to 9	5	3 to 9
	URTI	5	3 to 7	4	3 to 8
	LRTI	6	3 to 9	5	3 to 9

Number of patients reconsulting

Six studies reported on reconsultations – five RCTs (of which two were individually randomised and three were cluster randomised trials) and one non-randomised study (Figure 4.8) [162-165, 167, 168]. While the point estimates for reconsultation exceeded that of usual group in all but one study, this difference was not statistically significant in any study. The difference in reconsultation rates between the CRP POCT group and the usual care group was not statistically significant in the pooled meta-analysis (RCTs n=4,524, RR 1.09, 95% CI: 0.93-1.27 I^2= 0% and non-randomised study n=120, RR 1.56, 95% CI: 0.73-3.32).

Figure 4.8 Forest plot: Reconsultations (RCTs and Cluster RCTs)



Schot et al. reported that children in both the CRP POCT and control groups had similar rates of reconsultations within the same episode of illness (33% versus 34%; OR 0.95; 95% CI: 0.46-1.99).[178]

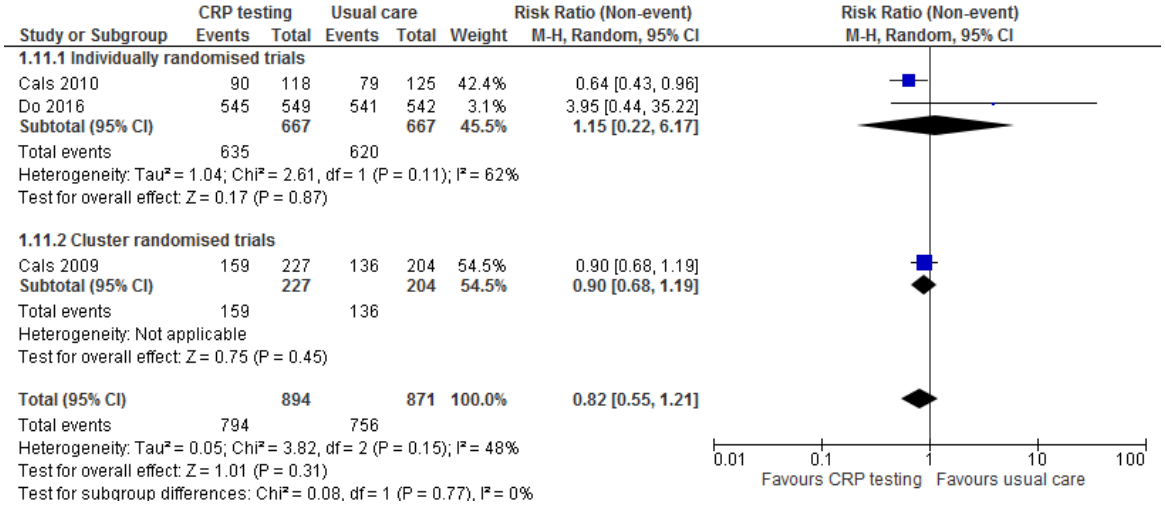
Health-related quality of life

There were no studies that reported on health-related quality of life (HRQoL).

Patient and physician satisfaction

None of the included studies reported on physician satisfaction with CRP POCT. Four studies in total reported on patient satisfaction (n=1,885). In three of these studies satisfaction with their clinician visit was measured using a Likert scale: one individually randomised study,[164] one cluster randomised study [163] and one non-randomised study.[167] The fourth study was an RCT and the authors used a scale of 1 to 10 to measure patient satisfaction regarding participation in the trial.[165] The patients were generally satisfied with the care received as part of the clinician visit and there was no significant difference between the CRP POCT group and the control group (RCTs RR 0.82 [95% CI: 0.55, 1.21], I^2 = 48%; non-randomised study by Kavanagh et al. RR 1.00 [95% CI: 0.86-1.16]). Although in one study, Cals et al. 2010, patients were more often satisfied in the CRP POCT group than in the usual care group (Figure 4.9).

Figure 4.9 Forest plot: Patient satisfaction, satisfied (RCTs and Cluster RCTs)



4.4 Results: safety

For the assessment of safety, all 13 studies identified for inclusion in the systematic review of clinical effectiveness were considered.

Does the use of CRP POCT to guide antibiotic prescribing impact mortality in those presenting with symptoms of an acute RTI compared with standard care?

None of the included RCTs or observational studies reported the death of a patient. Five of the included RCTs specifically stated that there were no deaths during the study period (n=7,165 patients, CRP test group n=3,696, usual care group n= 2,469).[162-165, 168] It is therefore unlikely that the use of CRP POCT will have any beneficial or detrimental effect on mortality.

Adverse drug reactions (ADR), including number of patients reconsulting or hospitalised due to ADR

There were no studies that reported specifically on reconsultations or hospitalisations due to an antibiotic-related ADR. Most papers that did report on hospitalisations or reconsultations did not state the reason for the hospitalisation. It is therefore conceivable that a number of the hospitalisations and reconsultations presented in the next section could have been due to ADRs, although it is noted that with the exception of anaphylactic reactions, antibiotics are generally not associated with serious ADRs

Number of patients in need of hospitalisation

In the RCTs, six studies reported on hospitalisations during the follow-up period.[162-165, 168] Three of these studies reported either no serious adverse events (defined as death or hospitalisation) [162-164] or patient recovery to some extent during the two-week follow-up period.[162] Two studies by Do et al.[165] and Little et al.[168] reported 14/1,775 and 30/4,264 hospitalisations, respectively. In the study by Do et al. there was no significant difference between the CRP POCT group and the control group (RR 0.73, 95% CI: 0.25-2.09), but in the case of the study by Little et al. there were significantly more hospitalisations in the CRP POCT group than the control group (RR 2.52, 95% CI: 1.13-5.65). However, the authors state that after controlling for all potential confounders this difference was no longer significant (OR 2.91, 95% CI: 0.96-8.85, p=0.060). The reasons for hospitalisation were available for 15/30 patients and included cardiac problems (n=2), respiratory problems (n=8), generally unwell or pyrexia (n=2), gastrointestinal symptoms (n=2) and sinusitis (n=1). It is unclear whether these reasons are directly related to the RTI the patients presented with and the prescribing or non-prescribing of an antibiotic, or if the hospitalisations were due to unrelated problems. The pragmatic RCT in children by Schot et al. reported 3/81 non-urgent referrals to secondary care for baseline epsides of LRTIs in the CRP POCT group. In the study there was no significant difference between the CRP POCT group and the control group (RR 0.73, 95% CI: 0.18-2.98).

4.5 Discussion

Overall, our results suggest that C-reactive protein POCT, when used to guide management of patients who present with symptoms of acute RTI, leads to reduced antibiotic prescribing both at index consultation and up to 28 days follow-up. All studies showed a point estimate that favours the use of C-reactive protein testing in reducing antibiotic prescribing, but in some studies this difference was not significantly different to usual care. There was substantial heterogeneity in the pooled results for the individually randomised RCTs and the non-randomised studies. A sensitivity analysis showed that most of the heterogeneity in the individually randomised RCTs was due to one study by Do et al., which was carried out in Vietnam [165]. The study had a high level of prescribing in the usual care arm (63.5%), even though they excluded anyone presenting with severe acute RTIs and therefore may have been different to the other studies. Removal of this study from the RCT analysis results in a non-significant reduction in antibiotic prescribing in the C-reactive protein POCT group with much lower heterogeneity (I^2 = 5%). In the non-randomised studies, the effect of C-reactive protein POCT on reducing antibiotic prescribing remains, but the heterogeneity is reduced (I^2 = 0%) with the removal of one study that used a control group from a different country to the intervention

group [166]. This reduction in antibiotic prescribing in the C-reactive protein POCT group does not appear to lead to a significant difference in clinical recovery or reconsultation rates. Due to the limited number of studies available, it was not possible to carry out a meta-regression to determine if the heterogeneity could be explained by study-level characteristics. Treatment effects in the early trials (Melbye 1995 and Diederichsen 2000) were much smaller than the later trials, but this apparent trend could also be associated with changes to the CRP testing equipment or the patient populations.

Delayed prescribing is a method whereby a prescription is issued to the patient for use at a later date, if their symptoms do not improve. Only two studies reported on the use of delayed prescriptions [164, 167] and there appears to be no significant difference in the use of delayed prescriptions between the C-reactive protein POCT group and the usual care group. The use of delayed prescriptions has been shown to be a very effective method of reducing antibiotic prescription redemption.[179] In both of these studies, the algorithm given to the GPs in the C-reactive protein POCT group suggested the use of a delayed prescription if the CRP levels were intermediate. As a result one might expect more delayed prescribing in the group receiving the C-reactive protein POCT; however, in both of these studies it appeared that GPs were already using delayed prescribing in their usual care. Of note, Cals et al. also looked at redemption rates for the delayed prescriptions and found it to be significantly lower in the C-reactive protein POCT group. While it is not possible to draw a conclusion based on a single paper, this could suggest that knowing their C-reactive protein POCT result provides patients with greater reassurance that an antibiotic is not warranted.

In the studies that reported on patient satisfaction,[163-165, 167] the patients were mostly satisfied and there was no difference in satisfaction between the C-reactive protein POCT group and the usual care group, suggesting that the provision of C-reactive protein POCT neither improves nor disimproves their consultation experience.

In addition to the outcomes we had identified as important, one study [162] reported on referral to radiography and found there was a significantly lower rate of referral in the C-reactive protein POCT test group compared with the usual care group (55.5% vs. 96% p=0.004). Although no conclusions can be drawn from this, if C-reactive protein POCT leads to a reduction in referrals for further testing it could lead to substantial savings for the healthcare system without negatively impacting on patient safety.

A number of the studies[163, 168-170] included an educational or communication component in their intervention with C-reactive protein POCT. This may have enhanced the effect of C-reactive protein POCT on antibiotic prescribing, but the removal of Little 2013 and Cals 2009 from the RCT meta analysis only changes the pooled risk ratio a small amount and still leads to the conclusion that C-reactive protein POCT leads to a significant reduction in antibiotic prescribing (RR 0.80, 95% CI: 0.67-0.96).

Due to a lack of studies we were unable to carry out all of our pre-planned subgroup analysis. From the 2014 Cochrane review by Aabenhaus et al.[29] we expected heterogeneity by study type. Therefore we planned subgroup analysis for individually randomised and cluster randomised trials; non-randomised (observational) studies were analysed separately due to the difference in quality of this study type. There were sufficient studies to analyse URTI separately to LRTI and in all study types antibiotic prescribing was significantly lower in the C-reactive protein POCT group (Figure 5.6), suggesting that C-reactive protein POCT is useful for both upper and lower respiratory tract infections. However, there was substantial heterogeneity, particularly in the non-randomised studies. Although most studies included adults of all ages, there was no separation of results for younger adults (<65 years) versus older adults. More studies involving C-reactive protein POCT would be useful in older adults as often older adults have comorbidities and may be on multiple medications, and it is currently unclear what effect this may have on C-reactive protein POCT and on GP prescribing. There were no studies that met our inclusion criteria that included patients from long-term care facilities or out-of-hours clinics, so it was not possible to look at these populations separately. Only three RCTs included children, two of which reported results for both children and adults. In both of these trials the effect of C-reactive protein POCT on prescribing antibiotics was similar in adults and children, although one study found a significant effect while the other reported no effect.[160, 165] The study on children alone found a reduction in antibiotic prescriptions from the use of CRP POCT, although the difference was not statistically significant.[178] The study had difficulties in recruiting patients and the rate of prescribing in the control arm was much lower than expected, suggesting the study may have been underpowered. It was unclear why the trial experienced challenges in patient recruitment, although it may be indicative of a lack of clinical acceptability for doctors and or patients. In light of the limited data including children and the lack of consistency in results, it is not possible to state from this review what the impact of CRP POCT testing is on antibiotic prescribing in children with RTIs.

The reduction in antibiotic prescribing arising from the use of CRP POCT to inform antibiotic prescribing does not lead to an increase in mortality. For the majority of studies (5 out of 7) there were no hospitalisations reported; two studies reported

hospitalisations within the study period, but it was unclear if the events were directly related to the RTI or not. In the study by Do et al. there were a similar number of hospitalisations in both the CRP POCT group and in the usual care group, suggesting that CRP POCT had no influence on hospitalisations. The study by Little et al., on the other hand, had significantly more hospitalisations in the CRP POCT group than in the usual care arm. The authors investigated this finding further and state that after controlling for confounders the difference is no longer significant, but more studies are needed that specifically look at the effect of using CRP POCT on hospitalisation rates and to determine the main reasons for hospitalisation. A counterbalance to the safety of CRP is to consider the side effects of antibiotics. Common side effects include gastrointestinal effects and fever, while there can be more severe adverse effects including major allergic reactions and anaphylaxis. Ordinarily the benefit-harm balance is considered for a treatment in the context of that treatment being likely to have a beneficial treatment effect. In the case of antibiotics being prescribed for a viral infection, the patient does not have the potential to benefit but does take on the risk of harm.

The studies included in the systematic review were all characterised by patient follow-up periods of no more than four weeks. One study has subsequently published data with 3.5 years follow-up that gives some evidence in relation to the sustained impact of CRP POCT for RTIs.[159] These limited data suggests that the initial introduction of CRP POCT might be associated with behavioural change that leads to reduced consultation by patients for subsequent episodes of RTI.

A key question is whether the availability of CRP POCT within a general practice continues to impact on antibiotic prescribing over the longer term. That impact could be initiated through raised awareness among both patients and clinicians, and that the associated behavioural change might be sustained. Whether those behavioural changes require ongoing access to CRP POCT is not known, and it is possible that behaviours could revert to those in place before the introduction of CRP POCT. While individual patient follow-up was short, some trials had longer data collection periods ranging from 2 to 16 months (average 6.5 months). It is unclear whether or not individual practices collected data over entire study timeframes. None of the included studies reported time trends in effectiveness or test usage. A more recent study has included outcomes at three months and an audit carried out at 12 months.[180] The effect of CRP POCT was reduced at 12 months and no longer statistically significant. The trial was not powered to detect the treatment effect observed, and a key finding was that the CRP POC test was rarely used at 12 months. Reduced use of the tests will have knock-on effects for reduced effectiveness, but also will incur fewer costs. It is probable that there is a correlation between test usage and the reduction in antibiotic prescribing. Ongoing use of CRP

testing in primary care will be influenced by a variety of factors, including the disease spectrum of patients presenting and on the types of incentives or disincentives in place to use the test. Sustained use of CRP POCT also implies ongoing training and participation in quality assurance. It is possible that there may be an initial enthusiasm for using CRP POC tests, but that over time there is a perception that the clinical gain is not commensurate with the effort involved in maintaining a quality assured testing service. Consultations for RTIs peak in the winter months, and the inevitable reduction in CRP POC testing during the summer months may not recover during the subsequent winter. It is clear that understanding how to ensure ongoing use of CRP POCT is essential to maintaining effectiveness over the longer term.

Another potential behavioural impact of CRP POCT is test creep whereby some clinicians become reliant on test results to support clinical decision-making. The risk is that some clinicians may allow the test to overrule their own clinical judgment. The CRP POCT test is only intended to support decision-making in the context of clinical uncertainty. The application or use of prescribing rules attached to CRP cut-points may also facilitate conditions for overruling clinical judgment, particularly where test results are just above a cut-point. The test result should not be viewed in isolation but in conjunction with the patient's symptoms, history, and all of the other factors that feed into clinical judgment.

Our study shows similar results to other published systematic reviews in the area,[29, 30, 172, 175] with the conclusion that although some studies show no significant difference between CRP POCT and usual care in terms of antibiotic prescribing, when combined, the pooled estimates suggest CRP POCT does have a significant effect on prescribing. We included both RCTs and observational studies in our review to ensure the review reflected the findings from a range of study types and not just clinical trials where GPs might be more motivated to follow the suggested algorithms and limit their antibiotic prescribing. Our study is in agreement with other published systematic reviews in the area in terms of safety,[29, 30, 172, 175] which concluded that use of CRP POCT to inform antibiotic prescribing in primary care for acute RTIs leads to a significant reduction in antibiotic prescribing without compromising patient safety.

4.6 Key messages

- A systematic review was carried out to identify studies investigating the impact of CRP POCT on antibiotic prescribing for acute RTIs, health service utilisation and mortality. Eleven studies were included in analysis, of which nine were conducted in Europe. The studies were a mixture of randomised and non-randomised trials.

- The studies included a mixture of populations including URTI only, LRTI only, and a combination of LRTI and URTI. Eight of the studies included only adult patients.
- The pooled estimate for the RCTs showed a statistically significant reduction in antibiotic prescribing in the CRP POCT group, compared with usual care (RR: 0.76). In the cluster randomised trials, there was a statistically significant reduction in antibiotic prescribing in the CRP POCT group compared with usual care (RR: 0.68). The observational studies show a similar effect of CRP POCT on antibiotic prescribing with a pooled RR of 0.61. There was substantial heterogeneity across trials in the estimated treatment effect.
- Five patients would need to be tested for CRP POCT to prevent one antibiotic prescription (95% CI: 4-8), although based on randomised trial evidence alone the number needed to treat was seven (95% CI: 5-14).
- Similar levels of reduction in antibiotic prescribing were seen in patients with URTI and LRTI.
- There was substantial heterogeneity in the pooled results for the individually randomised RCTs and the non-randomised studies.
- There was limited evidence regarding other outcomes of clinical effectiveness.
- No significant difference was found between those receiving the CRP POCT and those who did not in terms of proportion of patients recovered at seven days and the time taken for the resolution of symptoms.
- The use of CRP POCT does not lead to an increase in adverse events such as mortality, hospitalisations, or reconsultations.
- In the studies that reported on patient satisfaction, the patients were mostly satisfied and there was no difference in satisfaction between the CRP POCT group and the usual care group, suggesting that the provision of CRP POCT neither improves nor disimproves their consultation experience.
- The use of CRP POCT to inform antibiotic prescribing in primary care for acute RTIs leads to a significant short-term reduction in antibiotic prescribing without compromising patient safety. The sustainability of the effect of CRP POCT is unclear due to a lack of longer-term follow-up data.
- Due to the limited data on children, it is unclear what the impact of CRP POCT testing is on antibiotic prescribing in children with RTIs.
- There were no studies that met our inclusion criteria that provided separate data on patients from long-term care facilities or out-of-hours clinics.

5 Diagnostic test accuracy of CRP point-of-care testing

The systematic review of clinical effectiveness and safety addressed the question of whether the use of CRP POCT in primary care lead to a significant reduction in antibiotic prescribing without compromising patient safety. Separate from clinical effectiveness is the question of the diagnostic test accuracy of CRP POCT in relation to acute RTIs. The sensitivity and specificity of a test have important implications for the rate of false positives and false negatives – that is, cases that are misdiagnosed on the basis of the test result. This chapter addresses the issue of diagnostic test accuracy.

5.1 Search strategy

A full systematic review approach was used to search for evidence of diagnostic test accuracy. The review approach replicated the search used for clinical effectiveness and safety (Chapter 4) with modifications for the outcomes and study design.

5.1.1 PICOS

The PICOS (Population, Intervention, Comparator, Outcomes, Study design) analysis used to formulate the search is presented in Table 5.1 (detailed PICOS are provided in Appendix K).

Table 5.1 Scope for search for studies of diagnostic test accuracy

Description	Project scope
Population	The population of interest is represented by patients of all ages who present with symptoms of acute respiratory tract infection in primary care. Subgroups of particular interest include: children, older adults (≥65 years of age), patients attending out-of-hours (OOH) services and those in long-term care (LTC) facilities.
Intervention	CRP POCT for use in primary care setting (+/- other biomarkers). Testing for CRP may assist the clinician in differentiating between bacterial and viral aetiology and therefore guide the prescription of antibiotics. Point of care tests allow the test to be done at the time of consultation with results available within minutes.
Comparison	For the diagnostic test accuracy review, the diagnostic standard used for comparison will be dependent on the acute RTI of interest (microbiological/laboratory/radiological confirmation). Each disease group will be analysed separately.

Description	Project scope
Outcomes	Primary outcomes: ▪ Sensitivity and specificity, ▪ PPV and NPV ▪ Likelihood ratio ▪ Area under the ROC curve (AUC) ▪ DOR
Study design	Diagnostic test accuracy studies

Key: AUC – Area under curve; CRP – C-reactive protein; DOR – Diagnostic odds ratio; DTA – Diagnostic test accuracy; LTC - Long term care; MeSH – Medical Subject Heading; OOH – Out-of-hours; NPV – negative predictive value; PPV – positive predictive value; RTI – respiratory tract infection; ROC – Receiver operating characteristic.

5.1.2 Bibliographic search

To identify relevant studies, systematic searches were carried out on the following databases:

- MEDLINE (OVID, Pubmed)
- Embase
- CINAHL (via EBSCOHost)
- The Cochrane Library

Hand searching of the literature was also undertaken including a cross-check of the reference list of included studies and relevant systematic reviews as well as citation tracking. Ad hoc internet searches were undertaken to identify other relevant grey literature. Finally, lists of relevant studies provided by manufacturers in their submission files were searched for additional studies. Submission files were submitted by three companies: Abbott (Alere), Orion Diagnostica Oy, and RPS Diagnostics. These files were used along with material from other company websites to inform the technology description domain. The following clinical trial registries were searched for registered ongoing clinical trials and observational studies: ClinicalTrials.gov and International Clinical Trials Registry Platform (ICTRP).

The full set of search terms can be found in Appendix L. A separate search for clinical guidelines (G-I-N, National Guidelines Clearinghouse, hand searches) was also undertaken.

At the time of the systematic literature searches, no limitations were applied with regard to study design or language. No limits were applied for the year of publication for the first two systematic reviews (clinical effectiveness and diagnostic test accuracy). The search for the third systematic review (analytical performance)

was limited to publications from 1990 onwards as performance data from older studies were considered unlikely to be relevant to the current commercially available point-of-care tests.

Two authors independently reviewed titles and abstracts. The full text of potentially eligible articles was reviewed by the two authors independently and the study included or excluded based on predefined criteria. Studies that did not provide data on the relevant outcomes were excluded. Studies that reported on duplicate data were identified and excluded if no additional data were available in the secondary publication. Abstracts from conferences were also excluded. Any disagreement in study selection was resolved through discussion. Studies excluded at full text review are listed in Appendix L.

5.1.3 Data extraction and analysis

Two review authors independently extracted data using prepared data extraction forms. The authors resolved any discrepancy through discussion or with a third author.

5.1.4 Quality appraisal

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was applied to assess the quality of all studies identified in systematic review 2. This tool is designed for use in systematic reviews to evaluate the risk of bias across four domains (patient selection, index test, reference standard and flow of participants) and applicability across three domains (patient selection, index test and reference standard) and is guided by prompt questions. Two authors from HIQA independently assessed the quality of included studies. Disagreements with regard to judgments of study quality were resolved through discussion. The GRADE summary of findings table is provided in Appendix O.

5.2 Study selection

A total of 4,846 studies were identified through searches of the selected databases and the grey literature. Following screening, 49 articles were identified as being potentially relevant. Of these, 35 studies were later excluded (Figure 5.1). The most common reason for exclusion was inappropriate setting, that is, the study was not limited to patients presenting to a primary care setting. Following an eligibility assessment, 15 studies were included in the analysis. The search also identified three relevant systematic reviews[28, 181, 182] and one meta-analysis.[183] A cross-check of the references included in these papers resulted in one potentially relevant paper being identified.[184] The paper was excluded following contact with the author as

data relating to primary care patients excluding those presenting to outpatient clinics were not available.

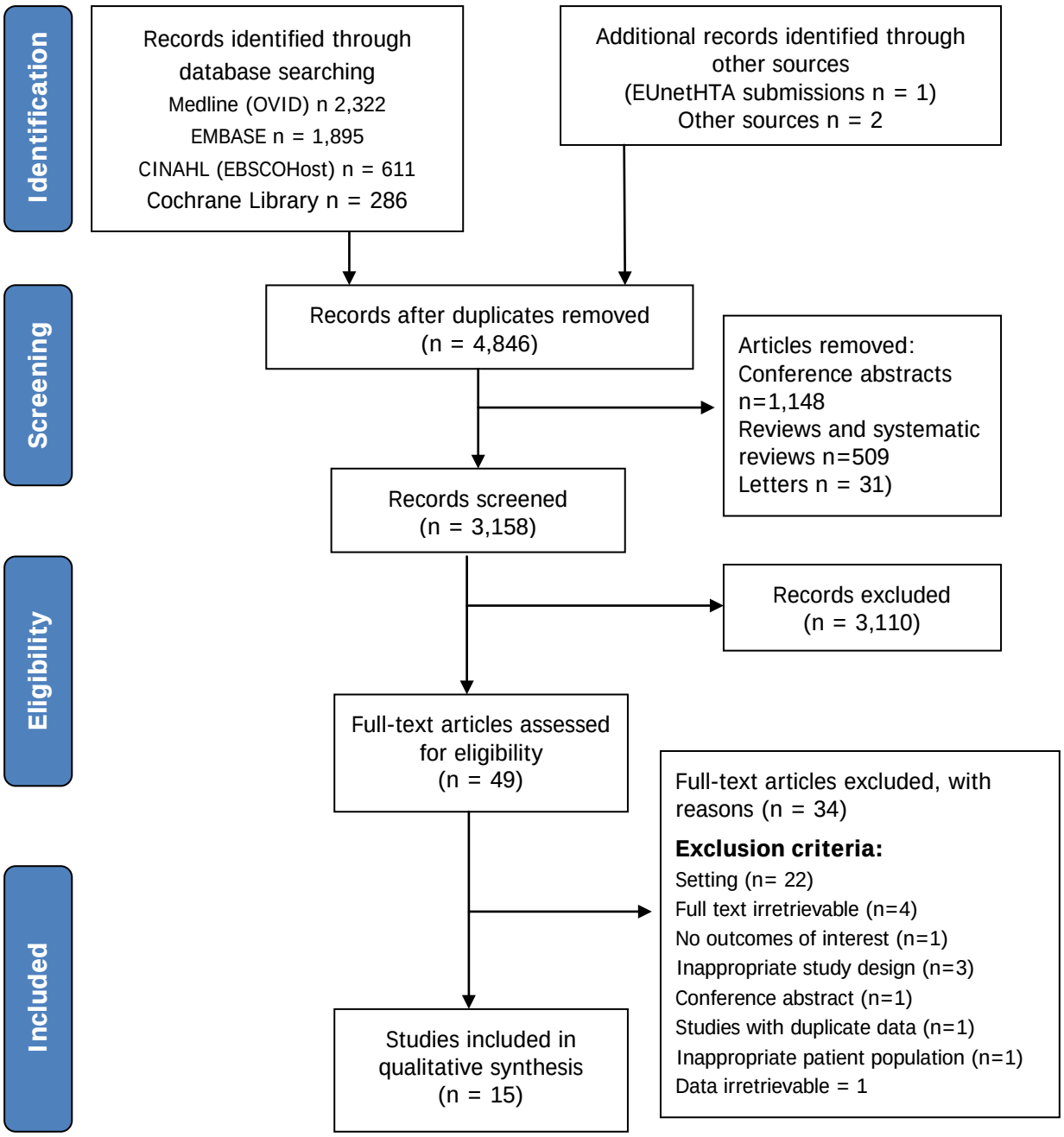
5.3 Results

The search of the literature retrieved 15 diagnostic test studies that evaluated the diagnostic test accuracy of CRP point-of-care tests in the diagnosis of RTI in primary care (Table 5.2).

All fifteen studies were carried out in Europe.[185-199] The studies evaluated the utility of CRP POCT across a range of RTIs including pharyngitis, acute tonsillitis, sinusitis and lower respiratory tract infection (LRTI) including pneumonia. The majority of included studies enrolled patients aged 15 years and older.[186-190, 192-199] One study recruited children aged between three months and 15 years of age only.[191] The utility of CRP levels in the evaluation of patients presenting with signs and symptoms of RTI was assessed using cut-points ranging from 6 to 100 mg/L. CRP levels were measured using commercially available POCT devices suitable for use in primary care in four of the 15 studies.[188-190, 199] Two studies used a CRP POC test; however, the analysis was carried out by a laboratory technician.[195, 197] The remaining studies used standardised laboratory testing for CRP.[186, 187, 191-194, 196, 198] Two studies received research funding from manufacturers of CRP POCT devices.[197, 198] A detailed description of the 15 studies is found in Appendix M.

In terms of risk of bias, a number of included studies were judged to be of unclear or high risk of bias in terms of the index test. One study was at high risk of bias in relation to patient selection (Melbye 1988), and another was at high risk of bias regarding the reference standard (Gulich 1999). Full details of the risk of bias assessment are provided in Appendix O.

Figure 5.1 Flow chart: systematic review of clinical effectiveness and safety



Diagnostic test accuracy may vary between patient subgroups, and by testing methodology and equipment. For the purposes of analysis, studies have been grouped according to the type of RTI identified in the systematic review. There was a high level of heterogeneity across studies reflecting differences between studies in the criterion used to define test positivity, diagnostic criteria, patient populations and the absence of a universal reference standard for the diagnosis of RTIs requiring antibiotics. For this reason, meta-analysis of the data was not appropriate. Due to the inconsistency of effect measures and positivity thresholds reported by individual studies, a narrative summary of the reported diagnostic test accuracy outcome measures is provided. As noted, details of study, population, intervention and comparator characteristics are presented in Appendix M. A number of identified studies reported mean CRP levels in the sample population. Although this is not a measure of diagnostic test accuracy, it is included in the analysis to provide context in relation to the clinical usefulness of CRP cut-points. Measurement of patient CRP levels is not intended to reflect the diagnostic test accuracy of CRP POC tests. In the majority of the included studies sensitivity and specificity data were reported and presented. To aid with the interpretation of these data, additional tables have been included in the appendix that report the likelihood ratios (LR) for studies for which it was possible to extract or calculate these values.

Evidence was identified for three RTI types– sinusitis, pharyngitis or tonsillitis and lower respiratory tract infections or pneumonia. As there is substantial overlap between the AEs, the evidence is presented sequentially for the three conditions to facilitate ease of reading.

Table 5.2 Main characteristics of included studies

Author and year or study name	Indication	Patient population	Number of patients	Intervention (s)	Main endpoints	Reference test*
Calvino 2014	Acute pharyngitis	Patients aged >18 years	148	CRP POCT QuikRead go®	Mean CRP level	Microbiologic culture
Christensen 2014	Acute tonsillitis	Patients aged 15 to 40 years	100	Standard CRP laboratory measurement	Mean CRP level, Sensitivity, Specificity, AUC	Laboratory culture
Ebell 2017	Acute rhinosinusitis	Patients aged 18 to 65 years	175	Standard CRP laboratory measurement	DOR	Abnormal CT + other
Gulich 2002	Acute pharyngitis	Patients aged ≥16 years	265	NycoCard™ CRP	Sensitivity, Specificity, PPV, NPV, AUC	Microbiologic culture
Gulich 1999	Acute pharyngitis	Patients aged 16 to 75 years	161	NycoCard™ CRP	Sensitivity, Specificity, PPV, NPV	Microbiologic culture
Hansen 1995	Acute rhinosinusitis	Patients aged 18 to 65 years	168	NycoCard™CRP	DOR, sensitivity, specificity, PPV, NPV	Abnormal CT + laboratory culture
Heiskansen-Kosma 2000	Acute pneumonia	Children aged ≤15 years	193	Standard CRP laboratory measurement	Mean CRP level	EIA and immune complex assays
Holm 2007	LRTI	Patients aged ≥18 years	364	Standard CRP laboratory measurement	Sensitivity, specificity, PPV, NPV, DOR	Chest radiography + laboratory culture
Hopstaken 2003	LRTI	Patients aged ≥18 years	243	Standard CRP laboratory measurement	AUC, DOR	Chest radiograph
Hopstaken 2009	LRTI	Adult patients	95	Standard CRP laboratory measurement	Sensitivity, specificity, PPV, NPV, AUC	Chest radiography + laboratory tests
Lagerström 2006	CAP	Patients aged ≥16 years	82	CRP POCT device (NycoCard™ reader) in laboratory	Median CRP levels	Chest radiography

Author and year or study name	Indication	Patient population	Number of patients	Intervention (s)	Main endpoints	Reference test*
Melbye 1988	CAP	Patients aged ≥15 years	69	Standard CRP laboratory measurement	Sensitivity, specificity, NPV, LR	Chest radiography
Minnaard 2015	Acute pneumonia	Adult patients	200	CRP POCT device (Afinion™, NycoCard™ reader II, Eurolyser Smart 700/340, QuikRead go®, QuikRead® 101) in laboratory	Sensitivity, specificity, PPV, NPV	Chest radiography + laboratory culture
Teepe 2016	Acute or deteriorating cough	Patients aged ≥18 years	3,104	Standard CRP laboratory measurement		Laboratory culture for bacterial LRTI. Chest radiography + laboratory culture for bacterial pneumonia.
Van Vugt 2013	Acute cough	Adult patients	2,820	Standard CRP laboratory measurement	Sensitivity, specificity, PPV, NPV, LR, AUC, DOR	Chest radiography

* Further details provided in Appendix M.

Key: CAP – community acquired pneumonia; CRP – C-reactive protein; DTA – diagnostic test accuracy; EIA, enzyme immunoassay; F/U – follow-up; LRTI – lower respiratory tract infection; POCT – point-of-care testing; RCT – randomised controlled trial; Rx – prescription; PPV – positive predictive value; NPV – negative predictive value; LR – likelihood ratio; AUC – area under the curve; DOR – diagnostic odds ratio.

5.3.1 Optimal test threshold and the ability to reliably rule in or rule out the need for antibiotic therapy

5.3.1.1 Sinusitis

Two studies were identified for inclusion. A 2017 paper by Ebell et al. reported the results of a univariate logistic regression analysis of the association between CRP levels and acute maxillary rhinosinusitis across a range of cut-points (10 mg/L, 15 mg/L and 20 mg/L). The authors reported that at a CRP threshold of >15 mg/L, the diagnostic odds ratio (DOR) of acute sinusitis was 4.75 (95% CI: 2.5-9.02), when using the presence of purulent or mucopurulent fluid from antral puncture as the reference standard (Table 5.3). A clinical decision rule incorporating signs, symptoms and CRP testing at a cut-point of ≥17 mg/L classified almost half of patients as low risk, allowing clinicians to rule out acute bacterial rhinosinusitis in these patients and to treat them symptomatically without prescribing antibiotics.[187]

A 1995 paper by Hansen et al. assessed the usefulness of CRP testing using the NycoCard™ CRP POCT device for the prediction of acute maxillary sinusitis across a range of CRP thresholds (<11 mg/L, 11-24 mg/L, 25-49 mg/L, >49 mg/L), using the presence of purulent or mucopurulent fluid from antral puncture as the reference standard.[190] A cut-point of 10 mg/L was found to be the most appropriate threshold above which most patients were likely to have acute maxillary sinusitis. Sensitivity and specificity were reported to be 0.73 and 0.6 respectively at this threshold, suggesting that at this cut-point CRP POCT may be most useful as a rule-out test to identify patients who do not require antibiotic therapy for resolution of symptoms (Table 5.3). The addition of erythrocyte sedimentation rate (ESR) increased the sensitivity of the test, but not its specificity (0.82 and 0.57 respectively).

Table 5.3 Diagnostic test accuracy of CRP for acute maxillary sinusitis

Author year	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	DOR (95% CI)
Ebell 2017 (n=175, sinusitis* 52%, bacterial sinusitis** 35%)					>10mg/L*: 4.29 (2.27-8.11) >15mg/L*: 4.75 (2.50-9.02) >20mg/L*: 3.92 (2.02-7.61) >10mg/L**: 2.56 (1.32 – 4.97) >15mg/L**: 2.75 (1.42-5.33) >17 mg/L**: 2.75 (1.42-5.33) >20mg/L**: 2.43 (1.28-4.6)
Hansen 1995 (n=174, sinusitis 53%)	10 mg/L: 0.73 25 mg/L: 0.52 50 mg/L: 0.33 CRP 10 mg/L + ESR: 0.82	10 mg/L: 0.6 25 mg/L: 0.78 50 mg/L: 0.9 CRP 10 mg/L + ESR: 0.57	CRP 10 mg/L + ESR: 0.68	CRP10 mg/L + ESR: 0.74	11-24 mg/L: 2.7 (1.2-6.1) 25-49 mg/L: 3.5 (1.4-8.6) >49 mg/L: 7.4 (3.1-18)

***Reference standard:** Antral puncture revealing purulent or mucopurulent fluid.

****Reference standard:** Positive bacterial culture of antral puncture fluid.

5.3.1.2 Pharyngitis and tonsillitis

Four studies published between 1999 and 2014 were identified. Calvino et al. investigated the use of CRP POCT to identify patients with GAS infection among those presenting to primary care with acute pharyngitis who met all four Centor criteria (clinical signs and symptoms that indicate a higher likelihood of isolating *Streptococcus*: absence of cough, tonsillar exudates, history of fever, tender anterior cervical adenopathy).[199] Using throat culture as the reference standard, the prevalence of bacterial pharyngitis and GAS were high (80.4% and 55.7%, respectively). There was no statistically significant difference in mean CRP concentrations between GAS infection (34.4 mg/L [95% CI: 25.6 to 43.3]) and non-GAS infection (29.9 mg/L [95% CI: 19.7 to 40.2]). Mean CRP levels were noted to be higher in patients with group C *Streptococcus* (n=13, mean 56.3 mg/L) compared with GAS infection. Mean CRP levels were comparable for patients with GAS infection and patients for which no bacterial cause of pharyngitis could be identified (n=29, 27.9 mg/L) (Table 5.4). On this basis, the authors concluded that CRP levels are not useful for distinguishing those patients who require antibiotic therapy.

Christensen et al. reported the mean CRP value in a group of patients (aged 15 to 40 years) presenting with signs of acute tonsillitis and meeting at least one of the

four Centor criteria.[186] In contrast to the finding of Calvino et al., mean CRP levels were found to be significantly higher in patients with GAS isolated compared to those without GAS (44 mg/L [95% CI: 38 to 60], 15 mg/L [95% CI: 10 to 19], respectively) (Table 5.4).

Table 5.4 CRP levels in patients with pharyngitis or tonsillitis

Author (year)	Prevalence	Mean CRP values (mg/L)
Calvino 2014 (n=149)	Bacterial pharyngitis: 80.4% GAS: 55.7%	**GAS (56.1%)**: 34.4 (95% CI: 25.6 - 43.3) **Non-GAS (43.9%)**: 29.9 (95% CI: 19.7-40.2) GBS (5.4%): 19.1 (95% CI: 0 –41.0) GCS (8.8%): 56.3 (95% CI: 25.7–86.9) GGS (3.4%): 31.6 (95% CI:0 –65.3) Other streptococcus (6.7%): 9.2 (95% CI:4.4 –14.0) No bacteria (19.5%): 27.9 (95% CI: 11.0 –44.9)
Christensen 2014 (n=100)	Bacterial pharyngitis: 52% GAS: 26%	**GAS (26%)**: 44 (95% CI: 38-60) **non-GAS (74%)**: 15 (95% CI:10-19)

Key: CRP – C-reactive protein; PPV - Positive predictive value; NPV – Negative predictive value; AUC – Area under the curve; CI – confidence interval; GAS - group A streptococcus; GBS - group B streptococcus; GCS - group C streptococcus; GGS - group G streptococcus.

A 1999 prospective observational study by Gulich et al. reported that CRP POCT can improve diagnostic accuracy in differentiating bacterial from non-bacterial pharyngitis in primary care.[189] The study population comprised patients presenting with symptoms of sore throat; the prevalence of bacterial pharyngitis was 23.6%.[189] An optimal threshold value of 35 mg/L was determined by ROC analysis to differentiate between bacterial and non-bacterial pharyngitis (AUC 0.85). At this cut-point, sensitivity and specificity were reported to be 0.78 (95% CI: 0.61-0.90) and 0.82 (95% CI: 0.73-0.88), respectively (Table 5.5). This was an improvement from clinical diagnosis only (sensitivity 0.61 [95% CI: 0.45-0.75], specificity 0.73, [95% CI: 0.65-0.81]). Using clinical assessment and CRP measurement, 81% of patients presenting with symptoms of sore throat (n=161) were correctly diagnosed compared with 70% of patients diagnosed without information on CRP measurement (n=179). The distinction between bacterial and non-bacterial pharyngitis may not be as useful in terms of current antibiotic prescribing guidelines where antibiotic treatment is only recommended in those with GAS pharyngitis.

Table 5.5 Diagnostic test accuracy of CRP in identifying patients with acute pharyngitis/tonsillitis in primary care settings who require antibiotic therapy

Author (number of patients, prevalence)	CRP Cut-Point (mg/L)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
Gulich 1999 *(N=161, bacterial pharyngitis: 23.6%)*	≥ 35ml/L*	0.78 (0.61–0.90)	0.82 (0.73–0.88)	0.57 (0.42–0.70)	0.92 (0.85–0.96)	0.85
Gulich 2002 *(Phase1: n=116, GAS:28.7% phase 2: n=265, GAS: 27.5%*	≥ 35ml/L*	**Derivation Streptoscore:** 0.88 (0.58-0.99) **Validation Strepto score:** 0.74 (0.53-0.89)	**Derivation Streptoscore:** 0.95(0.81-1.0) **Validation Strepto score**: 0.95 (0.88-1.00)	**Validation Strepto score**: 0.86 (0.65-0.95	**Validation Strepto score**: 0.91 (0.81-0.96)	
Christensen 2014 (*n=100, bacterial pharyngitis 52%, GAS 26%)*	6mg/L	**Centor score 1-4:** 0.90 **Centor score 2-4** 0.83	**Centor score 1-4:** 0.45 **Centor score 2-4** 0.70			**Centor score 1-4:** 0.77 (0.66-0.87) **Centor score 2-4:** 0.76 (0.65-0.88)

Key: CRP – C-reactive protein; PPV - Positive predictive value; NPV – Negative predictive value; AUC – Area under the curve; CI – confidence interval; GAS - group A streptococcus; GBS - group B streptococcus; GCS - group C streptococcus; GGS - group G streptococcus.

*The Centor criteria (tonsillar exudate, tender anterior cervical lymphadenopathy or lymphadenitis history of fever (over 38°C), and/or absence of cough) are an algorithm to estimate the probability of group A β haemolytic *Streptococcus* (GABHS) as the origin of sore throat. Each of the Centor criteria score 1 point (maximum score of 4).

**The clinical strepto-score (throat mucosa, uvula, tonsils, soft palate) was based on clinical examination. Each criterion was scored 0 to 2 points (total score 0 to 8 points).

5.3.1.3 LRTI and Pneumonia

Eight studies included in the analysis investigated the diagnostic value of CRP measurement in patients presenting with signs and symptoms of LRTI including pneumonia in primary care.

Two studies presented the mean CRP level in patients with radiologically confirmed pneumonia, one in a paediatric population and the other in an adult population.

Heiskanen-Kosma et al. studied the ability of CRP to distinguish bacterial from viral pneumonia in paediatric patients with radiologically confirmed pneumonia (n=82). Patients were divided into four groups according to the aetiology of infection (pneumococcal, mycoplasmal or chlamydial, viral or unknown aetiological groups) as determined by laboratory analysis of serological data. Measured CRP values were similar between the groups and there was no significant association with the aetiology of pneumonia (range 24.9 to 31.8 mg/L) (Table 5.6). Lagerstrom et al. analysed serum CRP concentrations using a laboratory based NycoCard™ reader in adult patients with radiologically confirmed CAP.[195] The median CRP was reported to be 65 (5-150) mg/L. CRP levels exceeded 5 mg/L, 20mg/L, 50mg/L and 100mg/L in 93%, 79%, 59% and 31% of patients, respectively, suggesting that at a cut-point of 100 mg/L only a third of pneumonia cases would be identified (Table 5.6). It was noted patients with CRP <20 mg/L had been ill for longer prior to CRP measurement (median 8.5 days [range 1-14] vs. 6 days [range 1-28] for all patients).

Three studies presented the difference in the mean CRP value in patients with pneumonia and those without pneumonia. Hopstaken et al. assessed the diagnostic test accuracy of CRP in patients presenting with signs and symptoms of LRTI. Median CRP levels were higher in the pneumonia (145 mg/L (36-213)) than the non-pneumonia group (17 mg/L (2-216)). Three studies from the GRACE consortium reported average CRP levels within a sample of patients presenting to primary care physicians with acute cough.[48, 197, 198] Standard laboratory measurement was used in two studies while the third used a number of CRP POCT in the laboratory. The results may have been drawn from the same study data and are very similar for the studies by Van Vugt 2013 and Minnaard 2015 (Table 5.6). Teepe 2016 differed from the other two studies as it identified a subset of patients with bacterial pneumonia. Overall, in adults, there was greater consistency in the mean CRP levels reported in patients without pneumonia than in those with pneumonia (Table 5.6).

Four studies evaluated the use of CRP testing alone in the diagnosis of pneumonia at a cut-point of >20 mg/L. Holm et al. studied CRP levels as a predictor of pneumonia in adults diagnosed with community-acquired pneumonia (CAP) by their GP.[192] A cut-point of 20 mg/l was chosen by the authors from the literature, on the basis that a relatively low value is required to achieve acceptable sensitivity in predicting pneumonia in primary care. They reported that at a cut-off of 20 mg/L, CRP was found to have better sensitivity than GP's clinical diagnosis alone in the identification of pneumonia patients (0.73 vs. 0.60) while other measures of diagnostic test accuracy (specificity, PPV, NPV) were comparable. However, the authors concluded that the sensitivity and specificity of CRP in predicting pneumonia was too low (Table 5.7).

Table 5.6 CRP levels in patients presenting with symptoms of LRTI in primary care

Author Year	Mean CRP values (mg/L)
Mean CRP levels in patients with radiologically confirmed CAP	
Heiskanen-Kosma 2000	Pneumococcal aetiology: 26.8 mg/L (20.1–33.5 mg/L) Mycoplasmal or chlamydial aetiology: 31.8 mg/L (20.5–33.1 mg/L) Viral aetiology: 26.1 mg/L (19.1–33.1 mg/L) Unknown aetiology: 24.9 mg/L (18.8–31.0 mg/L)
Lagerström 2006	65 (5-150)* CRP: > 100mg/L: 31% < 50mg/L: 41% < 20mg/L: 21% >5mg/L: 93%
Mean CRP levels in pneumonia and non-pneumonia patients	
Hopstaken 2009	Pneumonia : 145 mg/L (36-213)* No pneumonia: 17 mg/L(2-216)*
Minnaard 2015**	Pneumonia: 62 mg/L (SD 81) No pneumonia: 19 mg/L (SD 28)
Van Vugt 2013**	Pneumonia: 69 mg/L (SD 83) No Pneumonia: 19 mg/L (SD 35)
Teepe 2016**	LRTI bacterial infection: 34 mg/L (SD 53) Bacterial pneumonia: 97 mg/L (SD 98) All patients: (19 mg/L (SD 35)

Key: CRP – C-reactive protein; CAP – Community acquired pneumonia; SD – standard deviation.

*Data presented as median (range).

**These studies are presented together as they were both part of the GRACE study and it would appear that the study population used in the Minnaard study was a subset of the cohort used by Van Vugt and Teepe.

Lagerstrom et al. evaluated inflammatory parameters in patients with respiratory symptoms and clinically suspected CAP (n=177) recruited into a previous study. They reported the results at a threshold of 20 mg/L and 50 mg/L, but it was unclear why these thresholds were selected. At a cut-point of 20 mg/L, sensitivity and specificity were 0.79 and 0.65, respectively (Table 5.7). The improved specificity of the test at a cut-point of 50 mg/L (0.84) compromised test sensitivity (0.59). As

41% of pneumonia patients had CRP levels <50 mg/L and 21% had CRP levels <20 mg/L the authors concluded that CRP testing is not sufficiently sensitive to rule out pneumonia in primary care.

Minnard et al. aimed to compare the diagnostic test accuracy of CRP POCT devices versus laboratory standard CRP tests, and to determine if differences in test accuracy affect the ability of tests to predict pneumonia in adults. Cut-points of 20 mg/L and 100 mg/L were selected from the literature and guidelines as they were the most commonly used thresholds for distinguishing pneumonia from non-pneumonia. At a cut-off of 20 mg/L, sensitivity was low for a rule-out test and was comparable across all CRP tests, ranging from 48.0% to 61.4% (Table 5.8). At a cut-point of 100 mg/L specificity was high and ranged from 97.7 to 99.0% indicating that at this threshold the test was sufficiently specific to rule in pneumonia (Table 5.9).The authors concluded that all five POCT devices used in the study performed as well as the laboratory analyser in detecting pneumonia.[197]

Hopstaken et al. aimed to assess the diagnostic value of CRP for pneumonia in primary care patients with LRTI and constructed ROC curves summarising the diagnostic test accuracy of CRP in differentiating pneumonia from acute bronchitis across a range of CRP thresholds (10 mg/L, 20 mg/L and 100 mg/L).[194] In contrast to the studies by Holm et al, Lagerstrom et al. and Minnaard et al., at a cut-point of 20 mg/L the test demonstrated 100% sensitivity in identifying pneumonia patients which was therefore determined by the authors to be the optimal cut-off value to rule out pneumonia in a primary care setting (Table 5.7).

Unlike the other studies, Melbye et al. did not investigate CRP at a threshold of 20 mg/L, instead they investigated the diagnostic value of CRP at cut-points of >11 mg/L and >50 mg/L in differentiating pneumonia from non-pneumonia in patients aged 15 years and older treated with antibiotics by a GP for clinically suspected pneumonia.[196] The authors did not state their reasons for selecting these thresholds, but found at a threshold of 11 mg/L, sensitivity and specificity were 0.82 and 0.60, respectively (Table 5.7). Increasing the CRP threshold to 50 mg/L resulted in improved specificity (0.96), but at the expense of lower sensitivity (0.74). The authors concluded that further studies must be done to establish the most practical cut-off level in the diagnosis of pneumonia.

Table 5.7 Diagnostic test accuracy of CRP at pre-specified cut-points

Author year	Sensitivity	Specificity	PPV	NPV	Likelihood ratios	AUC	DOR (95% CI)
Holm 2007	CRP ≥20 mg/L: 0.73	CRP ≥20 mg/L: 0.65	CRP ≥20 mg/L: 0.24	CRP ≥20 mg/L: 0.94			CRP ≥20 mg/L: 5.02 (2.59 – 9.88)
Hopstaken 2009	CRP 10 mg/L: 100, CRP 20 mg/L: 100, CRP 100 mg/L: 81.8	CRP 10 mg/L: 36.1, CRP 20 mg/L: 50.6, CRP 100 mg/L: 84.3	CRP 10 mg/L: 17.2, CRP 20 mg/L: 21.2, CRP 100 mg/L: 40.9	CRP 10 mg/L: 100, CRP 20 mg/L: 100, CRP 100 mg/L: 97.2		AUC 0.90	
Lagerstrom 2006	CRP 20 mg/L: 0.79 CRP 50mg/L: 0.59	CRP 20 mg/L: 0.65 CRP 50 mg/L: 0.84	CRP 20 mg/L: 66.33% CRP 50 mg/L: 76.19	CRP 20 mg/L: 78.48% CRP 50 mg/L: 70.18	CRP 20 mg/L: LR+ = 2.28 LR- = 0.32 CRP 50 mg/L: LR+ = 3.71 LR- = 0.49		
Melbye 1988	CRP > 11 mg/L: 82%, CRP > 50 mg/L: 74%	CRP > 11 mg/L 60%, CRP > 50 mg/L: 96%		CRP > 11 mg/L: 0.28, CRP > 50 mg/L: 0.8	CRP > 11 mg/L: 2.1, CRP > 50 mg/L: 37		
Minnaard 2015	Tables 17/18	Tables 17/18	Tables 17/18	Tables 17/18			

Key: CRP – C-reactive protein; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio; DOR, diagnostic odds ratio; SD, standard deviation.

Table 5.8 Single test accuracy measures at CRP cut-point of 20 mg/L[197]

CRP test	Sensitivity (95% CI)	Specificity (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Laboratory analyser	61.4 (53.2 – 69.1)	76.0 (74.3 – 77.5)	11.8 (9.6 – 14.3)	97.4 (96.6 – 98.0)
Afinion™	55.0 (45.2 – 64.4)	73.0 (63.6 – 80.7)	9.6 (7.8 – 11.9)	96.9 (96.0 – 97.6)
NycoCard™ Reader II	54.0 (44.3 – 63.4)	75.0 (65.7 – 82.5)	10.1 (8.2 – 12.5)	96.9 (96.1 – 97.6)
Eurolyser Smart	48.0 (38.5 – 57.7)	79.0 (70.0 – 85.8)	10.7 (8.5 – 13.3)	96.7 (95.8 – 97.3)
QuikRead go®	52.0 (42.3 – 61.5)	72.0 (62.5 – 79.9)	8.8 (7.1 – 11.0)	96.6 (95.7 – 97.3)
QuikRead® 101	49.0 (39.4 – 58.7)	74.0 (64.6 – 81.6)	9.0 (7.1 – 11.2)	96.5 (95.6 – 97.2)

Table 5.9 Single test accuracy measures at CRP cut-point of 100 mg/L[197]

CRP test	Sensitivity (95% CI)	Specificity (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Laboratory analyser	24.3 (17.9 – 27.8)	97.7 (97.0 – 98.2)	35.4 (26.6 – 45.4)	96.1 (95.3 – 96.8)
Afinion™	20.0 (13.3 – 28.9)	99.0 (94.6 – 99.9)	51.1 (38.2 – 63.8)	95.9 (95.1 – 96.6)
NycoCard™ Reader II	20.0 (13.3 – 28.9)	98.0 (93.0 – 99.4)	34.3 (24.9 – 45.1)	95.9 (95.1 – 96.6)
Eurolyser Smart	19.0 (12.5 – 27.8)	99.0 (94.6 – 99.9)	49.8 (36.9 – 62.8)	95.9 (95.1 – 96.6)
QuikRead go®	20.0 (13.3 – 28.9)	99.0 (94.6 – 99.9)	51.1 (38.2 – 63.8)	95.9 (95.1 – 96.6)
QuikRead® 101	19.0 (12.5 – 27.8)	99.0 (94.6 – 99.9)	49.8 (36.9 – 62.8)	95.9 (95.1 – 96.6)

In daily practice the interpretation of a CRP value is made in addition to clinical judgment based on presenting signs and symptoms.

Holm et al. investigated the diagnostic test accuracy of CRP measurement in combination with a GP's diagnosis of pneumonia. Holm et al. found the combination of a GP's clinical diagnosis and CRP measurement at a threshold of ≥20 mg/L was less sensitive (0.49 vs. 0.60), but more specific (0.84 vs. 0.68) than a GP diagnosis alone (Table 5.10).

Three studies investigated the use of CRP testing in combination with a clinical prediction rule to differentiate between pneumonia and other LRTIs in general practice (Table 5.10). Hopstaken et al. described the diagnostic value of performing and recording extensive standardised medical history and clinical examination in combination with CRP measurement. ROC curves were constructed and the respective AUC were calculated to determine the overall diagnostic power of CRP at different cut-off values (10 mg/L, 20 mg/L, and 50 mg/L). In combination with signs and symptoms, CRP of 20 mg/L was selected as the optimal CRP threshold. The 'symptoms and signs + CRP cut-off value of 20' prediction model was significantly better at predicting the probability of pneumonia than the 'symptoms and signs' only model (P<0.001).[193] Use of the clinical decision rule allowed a group of patients at low risk of pneumonia to be identified. The combined predictive value of patients not having pneumonia was 97% (95% CI: 92-99%). If the prediction rule was applied to patients who received antibiotic treatment, 41% of prescriptions could have been avoided, with a 2.5% risk of patients with pneumonia being missed. The authors noted further validation of the prediction rule to identify low-risk patients was required.

Van Vugt et al. aimed to quantify the diagnostic accuracy of CRP in addition to signs and symptoms for the prediction of pneumonia.[198] Adults presenting with acute cough (n=2,820) were grouped into pneumonia (n=140) or no pneumonia based on chest radiographs (prevalence CAP = 5%).The diagnostic accuracy of CRP at clinically relevant thresholds (>20 mg/L, >30mg/L, >50mg/L, >100 mg/L) was investigated for the prediction of pneumonia in adults presenting with acute cough in addition to 14 preselected diagnostic criteria based on history taking and physical examination.[198] The optimal cut-off level was assessed using the AUC. A simplified diagnostic risk classification system using six different signs and symptoms was subsequently developed by rounding all regression coefficients in the model. Addition of CRP at the optimal cut-off of >30 mg/L significantly increased the AUC (from 0.70 (0.65-0.75) to 0.77 (0.73-0.81); p<0.05), and improved the diagnostic classification (net reclassification improvement 28% (95% CI: 17 to 30%); Table 5.10). The signs and symptoms model was useful in correctly identifying patients

with low (score of 0, probability <2.5%) or high (score ≥3, probability >20%) risk of pneumonia in 26% of the patients. In 74% of patients where doubt remained (estimated risk 2.5%-20%), measurement of CRP helped to correctly exclude pneumonia. Of the 1,987 patients without pneumonia who were classified as intermediate risk, the addition of CRP >30 mg/L meant 957 were reclassified correctly to low risk and 64 were incorrectly classified as high risk. Of the 105 patients with pneumonia classified as intermediate risk, addition of CRP reclassified 27 incorrectly to low risk and 22 to high risk. Thirty-nine percent (54/140) of all patients with radiographic pneumonia had a CRP <20 mg/L. These patients tended to be older (p=0.01), more often had positive signs and symptoms of the diagnostic model and more often used steroids (inhaled or oral). However, despite increased diagnostic accuracy with the addition of CRP measurement to clinical signs and symptoms, a substantial group of patients were classified as intermediate risk, for which clinical decision-making remains challenging.

Minnaard et al. applied the same symptoms and signs model as Van Vugt with and without CRP to their nested case control population. Minnaard's study population was also drawn from the GRACE study and may be a subset of the cohort used in the Van Vugt study (Table 5.10). As with the Van Vugt study, use of the signs and symptoms model without CRP testing had an AUC of 0.70 (95% CI: 0.65-0.75) and this increased to 0.79 following the addition of CRP testing. Each of the five POCT tests (Afinion™, NycoCard™ Reader II, Smart Eurolyser, QuikRead go® and QuikRead® 101) had a similar diagnostic accuracy to the laboratory CRP analyser (AUC 0.79 to 0.80 compared with 0.79 with laboratory CRP analyser).

Table 5.10 Diagnostic test accuracy of CRP in combination with signs and symptoms

Author Year	Sensitivity	Specificity	PPV	NPV	Likelihood ratios	AUC (95% CI)	DOR (95% CI)
Holm 2007	Clinical pneumonia + CRP ≥20 mg/L: 0.49	Clinical pneumonia + CRP ≥20 mg/L: 0.84	Clinical pneumonia + CRP ≥20 mg/L: 0.32	Clinical pneumonia + CRP ≥20 mg/L: 0.91			Clinical pneumonia + CRP ≥20 mg/L: 4.97 (2.60 – 9.52)
Hopstaken 2003						CRP 10 mg/L: 0.77 CRP 20 mg/L: 0.8, CRP 50 mg/L: 0.87	CRP 10 mg/L: 11.7 (1.55-88.61), CRP 20 mg/L: 8.48 (2.45–29.39), CRP 50 mg/L: 17.62 (5.77-53.85)
Teepe 2016*			For LRTI bacterial infection: Signs and Symptoms (discoloured sputum) + CRP >30 mg/L: 0.371 (95% CI: 0.312 – 0.433) For bacterial pneumonia: Signs and Symptoms (Comorbidity, temperature ≥ 38°C, crackles on lung auscultation) + CRP >30 mg/L: 0.25 (95% CI: 0.006 – 0.806)	For LRTI bacterial infection: Signs and Symptoms (discoloured sputum) + CRP >30 mg/L: 0.875 (95% CI: 0.854 – 0.893) For bacterial pneumonia: Signs and Symptoms (Comorbidity, temperature ≥ 38°C, crackles on lung auscultation) + CRP >30 mg/L: 0.997 (95% CI: 0.993 – 0.999)		For LRTI bacterial infection: Signs and Symptoms (discoloured sputum) + CRP >30 mg/L: 0.62(95% CI: 0.59 – 0.65 For bacterial pneumonia: Signs and Symptoms (Comorbidity, temperature ≥ 38oC, crackles on lung auscultation) + CRP >30 mg/L: 0.79 (95% CI: 0.71 – 0.87	

Author Year	Sensitivity	Specificity	PPV	NPV	Likelihood ratios	AUC (95% CI)	DOR (95% CI)
Van Vugt 2013*	Low risk: 22%, High risk: 29%	Low risk: 43% High risk: 97%	High risk: 31%	Low risk: 98%	Low risk**: Positive likelihood ratio 0.4, Negative likelihood ratio: 1.8 Intermediate risk**: Positive likelihood ratio 1.2 Negative likelihood ratio 0.9 High risk**: Positive likelihood ratio 8.6 Negative likelihood ratio 0.7	CRP >30 mg/L: 0.77 (0.73 to 0.81)	CRP >20 mg/L: 3.5(2.4-5) CRP >30 mg/L: 3.8(3.7-5.5) CRP >50 mg/L: 4.8(3.2-7.1) CRP >100 mg/L: 6.0 (3.6-10)
Minnaard 2015*						Signs and symptoms model: 0.70 (0.65-0.75) Signs and symptoms model + CRP: 0.79	

***** These studies are presented together as they were both part of the GRACE study and it would appear that the study population used in the Minnaard study was a subset of the cohort used by Van Vugt and Teepe.

** Probability of pneumonia based on signs and symptoms (breathlessness, absence of runny nose, diminished vesicular breathing, crackles, tachycardia, temperature (>37.8°C)) in addition to CRP measurement.

5.3.2 Reference standard for acute RTIs and likelihood of correct classification of the target condition

The reference standard varies depending on the clinical indication for which CRP testing is being used. RTIs comprise a collection of specific diagnoses which can be broadly classified as URTIs and LRTIs. The reference standards for these conditions differ. This section is limited to those RTIs for which studies were identified in this systematic review of diagnostic test accuracy.

5.3.2.1 Sinusitis

The identified reference standard for the diagnosis of acute maxillary sinusitis is computed tomography (CT) and/or sinus aspiration.[190] Practice guidelines generally do not recommend the use of imaging because: the accuracy of radiography is thought to be poor; ultrasound and radiography are not widely available in the primary care setting; and CT is expensive and results in potentially harmful radiation exposure. Although a CT scan is highly sensitive for the detection of fluid in the sinuses, this fluid may also be caused by a viral infection, so the test lacks specificity, and is therefore suboptimal as a reference standard.[182, 187] For example, in one study mucosal swelling or increased fluid in the maxillary sinuses was reported in 70% of patients on CT; however only 53% had purulence or mucopurulence on puncture, indicating that CT alone is not sufficient for the diagnosis of acute maxillary sinusitis.[190] Antral puncture can detect purulent secretions which are associated with bacterial infection. Bacterial culture of these secretions is the most specific test for the diagnosis of acute maxillary sinusitis. However, as bacteria may not grow in vitro, even if present in the sinus, the test cannot be considered 100% sensitive as a reference standard.[187] While antral puncture plus/minus bacterial culture is suggested as the preferred reference standard test, it is not widely used due to the discomfort associated with the test and the lack of expertise in performing antral puncture in the primary care setting.[182] ROC curves constructed for the three different reference standards for acute sinusitis, abnormal finding on a CT scan, the presence of purulent or mucopurulent fluid from an antral puncture of the maxillary sinus, and positive bacterial culture of antral fluid yielded AUC of 0.75, 0.77 and 0.72, respectively.[187]

5.3.2.2 Pharyngitis/Tonsillitis

Microbiological culture of throat swabs remains the gold standard to diagnose tonsillar bacterial infection. The accuracy of throat swab cultures was noted to be 90% by Gulich et al., as reported in a previous study.[189] Microbiological culture has several limitations which limit its routine use in primary care, most notably its relative expense and that it cannot inform therapeutic decisions during the first

consultation given a turn-around time of 48 to 72 hours.[186] The majority of clinical guidelines recommend limiting the use of antibiotics to pharyngitis/tonsillitis caused by streptococcal infections and/or GAS in particular. Microbiological culture of throat swabs may determine GAS carrier status; however, the cause of infection may be attributable to other pathogens. Furthermore, in vitro culture conditions may not facilitate growth of the bacterial sample, even if present in the respiratory tract.

5.3.2.3 LRTI including Pneumonia

No gold standard for LRTI requiring antibiotics exists. Community-acquired pneumonia is an anatomical diagnosis based on radiographic and clinical criteria. It includes infections due to bacterial, fungal and viral aetiologies with the severity of the condition varying depending on host and virulence factors. It is not considered necessary to distinguish between bacterial and viral pneumonia given that all relevent guidelines advocate identification of patients with pneumonia and treatment with antibiotics regardless of bacterial or viral aetiology.[198] Conventional radiography is the reference standard for defining pneumonia in international guidelines and medical literature. However, interpretation of chest radiographs is subject to inter-observer variation.[192, 196] It is noted that interpretation of minor pathological changes may not be reliable, [195, 196] with studies acknowledging that use of chest radiography as a reference standard has the potential to lead to misclassification.[197] A 2015 meta-analysis of the diagnostic test accuracy of different imaging options for community-acquired pneumonia reported a pooled sensitivity of 0.77 (0.73 to 0.80) and specificity of 0.91 (0.87 to 0.94) for chest X-ray using hospital discharge diagnosis as the reference standard.[200, 201]

Chest radiography is not recommended for routine use in primary care for economic and logistical reasons.[192, 194] In general practice, the decision to initiate antibiotic treatment therefore relies on clinical assessment, although its predictive value is noted to be poor. For example, the study by Holm et al. noted that the PPV of a GP's clinical diagnosis of radiographic pneumonia was only 0.23.[192] Accurate diagnostic markers are therefore needed to inform clinical decision-making during the first consultation.

5.3.3 Comparison to other optional tests in terms of accuracy measures

This systematic review of diagnostic accuracy is limited to CRP testing for the specified indications, and as such a comprehensive analysis of the performance of alternative tests was beyond the scope of this study. This section is therefore restricted to descriptions of test accuracy of alternate tests identified in clinical guidelines and in the studies included in this systematic review (Table 5.2).

5.3.3.1 Sinusitis

Hansen et al. evaluated the diagnostic value of erythrocyte sedimentation rate (ESR) for acute maxillary sinusitis. ESR and CRP concentration were found to be better diagnostic criteria than other symptoms and signs related to this condition, and both analyses can be performed in general practice. The combination of these two variables had a sensitivity of 0.82 and specificity of 0.57, and were said to be better than clinical examination only as a basis for deciding to give antibiotics, however the study did not seek to determine which of the two infection markers had greater diagnostic value. Ebell et al. found that CRP and ESR were the strongest individual predictors of acute bacterial rhinosinusitis compared to other signs and symptoms associated with the condition as determined by univariate logistic regression analysis. The OR for CRP was higher than for ESR, suggesting that CRP may have greater predictive value at determining which patients have acute sinusitis. However, this study did not set out to ascertain which of the infection markers was a better predictor; the aim was to develop a clinical decision rule.

A 2016 systematic review of imaging and laboratory tests used in the diagnosis of acute rhinosinusitis identified a single study that evaluated the accuracy of a test strip comparable to those ordinarily used in the diagnosis of urinary tract infection. The researchers found that leucocyte esterase and nitrite were highly specific, while pH and protein were highly sensitive. A score that assigned points (0 to 3) to each of these tests successfully identified patients at low (0%), moderate (33%) and high (100%) risk of acute rhinosinusitis. However, the study was considered to be at high risk of bias as it used imaging rather than antral puncture as the reference standard and the thresholds for classifying patients into risk groups were established post hoc.[182] Three studies identified in the systematic review evaluated the presence of leucocytes in nasal washings was, with LR+ ranging from 3.06 to 4.92, and LR- from 0.08 to 0.74. Rhinoscopy for pus in the nasal cavity or throat and white blood cell count both lacked sufficient accuracy for the diagnosis of acute rhinosinusitis.[182]

5.3.3.2 Pharyngitis

To enhance the appropriate prescribing of antibiotics, clinical prediction rules have been developed to distinguish streptococcal pharyngitis from pharyngitis by other causes. Rapid antigen detection tests (RADT), which use a pharyngeal swab and yield results in five to seven minutes, have also been developed to detect GAS.

Identified clinical practice guidelines for pharyngitis advocate the use of the four-point Centor score (oral temperature ≥38.3°C, tonsillar exudate, absence of cough, and swollen cervical lymph nodes), the McIsaac score or FeverPAIN score to stratify patients based on their probability of GAS. The guidelines recommend limiting

antibiotic treatment (deferred or immediate) or antibiotic treatment conditional on further testing (that is, a positive rapid antigen detection test [RADT]) to those with higher scores (Centor score 3-4; McIsaac score ≥2; FeverPAIN ≥2). [A0025] A combination of CRP measurement and clinical examination based on the Centor score was used in three out of four studies retrieved evaluating CRP testing in pharyngitis patients.[186, 188, 199] As a decision rule for considering antibiotic prescribing (score ≥3) in adults presenting to primary care with pharyngitis, the Centor score is reported to have a reasonable specificity (0.82, 95%CI: 0.72-0.88) and a post-test probability of 12% to 40% based on a prior prevalence of GAS of 5% to 20%.[202] In a systematic review of RADTs, the heterogeneity between studies was moderate but immunochromatographic RADTs were noted to be very sensitive (range 86% to 91%) and highly specific (range 93% to 97%) for the detection of GAS pharyngitis in adults, but the evidence was inconsistent in children. For enzyme-linked immunoassay RADTs, only a few studies were identified in the review; in adults the results were inconsistent, while they were shown to have high sensitivity and specificity in children (0.86 and 0.92). Specificity is decreased because of the poor capability of the test to differentiate between acute tonsillitis secondary to GAS and tonsillar infection of other origin in GAS carriers.[203] The clinical sensitivity of the RADT is noted to be influenced by the quality of the tonsillar swab, physician experience and the GAS inoculum.[186]

Use of other infection markers, such as procalcitonin, white blood cell count and absolute neutrophil count, to detect GAS acute tonsillitis has also been investigated. In addition to CRP POCT, the study by Christensen et al. aimed to determine if the addition of infection markers such as procalcitonin, white blood cell count, and the absolute neutrophil count could increase diagnostic accuracy when used alongside the Centor score and RADT. CRP testing was more sensitive (90%), but less specific (45%), than procalcitonin (sensitivity 72%; specificity 58%), white blood cell count (sensitivity 69%; specificity 73%), or absolute neutrophil count (sensitivity 66%; specificity 87%). However, the sensitivities and specificities were higher using the RADT than any of the infection markers. The authors concluded that CRP, procalcitonin, white blood cell count and absolute neutrophil count should not be performed in patients with acute tonsillitis, as they do not contribute significantly to an increase in the sensitivity or specificity of the RADT.

5.3.3.3 LRTI including pneumonia

Diagnosis of pneumonia in primary care is usually based on clinical findings, but may sometimes be supported by microbiological analysis of sputum samples. However, sputum culture may grow bacteria without any clinical relevance and therefore findings from microbiological analysis cannot be used as definitive evidence of the

causative agent of infection.[192] As it is not feasible to obtain chest radiographs in all patients with LRTI in primary care, clinicians typically rely on signs and symptoms and simple additional tests, when available. The diagnostic value of history and findings on clinical examination for pneumonia in primary care were evaluated in the study by Van Vugt et al. included in this systematic review. The AUC for previously published models of signs and symptoms for pneumonia varied between 0.55 (95% CI: 0.50-0.61) and 0.68 (95% CI: 0.66-0.76). All models showed poor calibration for pneumonia, with a Hosmer-Lemeshow of $p<0.001$, indicating poor fit. The authors developed a simplified diagnostic model based on symptoms and signs (absence of runny nose; presence of breathlessness, crackles and diminished breath sounds on auscultation; tachycardia [>100/min]; and fever [≥37.8C]) which had an AUC of 0.70 (95% CI: 0.65-0.75) and good calibration for pneumonia (Hosmer-Lemeshow of $p=0.50$). The diagnostic value of procalcitonin in addition to signs and symptoms was also evaluated but was found to provide limited additional value (increased AUC to 0.71 [0.67 to 0.76]) in this cohort of primary care patients presenting with LRTI.[198] Teepe et al. investigated the diagnostic utility of adding CRP or procalcitonin to a signs and symptoms diagnostic model for bacterial LRTI and separately for bacterial pneumonia.[48] Although they found that CRP added diagnostic value to their model, procalcitonin did not.

5.4 Discussion

The evidence base for the diagnostic test accuracy of CRP testing in primary care is characterised by a high level of heterogeneity in patient populations, diagnostic criteria, CRP cut-points, how the performance of the test was reported and the absence of a universal reference standard for the diagnosis of RTIs requiring antibiotic treatment. Meta-analysis of the data was therefore not appropriate and a narrative review is presented. Planned subgroup analysis (children, older adults [≥65 years of age], patients attending out-of-hours services and those in long-term care facilities) were not possible due to limited data. However, the results of this systematic review do provide important insights into the performance of CRP as a test to help identify patients who will benefit from antibiotic treatment and to aid decision-making for a number of conditions.

As outlined in the study PICOS, the study was limited to patients presenting to primary care with symptoms of acute RTI. This criterion was strictly applied, so studies that included patients presenting to other treatment settings such as hospital emergency departments, urgent care centres and outpatient clinics were excluded unless the data specific to primary care could be extracted. The applicability of data from these settings to primary care was considered limited due to differences in staffing, access to diagnostic services and the spectrum of presenting patients. This

restriction may not be relevant to all countries, where certain outpatient clinics and urgent care centres may be considered part of the primary care system. While some studies highlighted the similarity between patients presenting to primary care clinics and those who self-refer to urgent care clinics and emergency departments, these studies were still excluded as concerns remained around potential differences in staffing and access and diagnostics services. However, this meant that certain CRP POC devices such as FebriDx® were not included in this systematic review as the available studies did not meet our inclusion criteria for setting.[204, 205] FebriDx® combines CRP at a cut-point of 20 mg/L with a viral biomarker.

The diagnostic test accuracy of CRP in sinusitis

Two studies reporting the usefulness of CRP testing in diagnosing acute sinusitis provided limited evidence of benefit. Both studies examined a range of thresholds and chose a relatively low CRP threshold (10 and 17 mg/L) that was suitable for ruling out a diagnosis of acute bacterial sinusitis. A clinical decision rule incorporating signs, symptoms and CRP at a cut-point of ≥17 mg/L allowed half of patients to be identified as low risk for acute bacterial sinusitis, allowing clinicians treat them symptomatically without prescribing antibiotics, with the authors noting prospective validation of the tool through further research was required. However, considering many current clinical guidelines do not generally recommend the use of antibiotics in acute sinusitis, the utility of CRP testing on its own or as part of a clinical prediction rule is unclear. A 2016 systematic review of test accuracy in the diagnosis of acute rhinosinusitis in primary care identified four studies that assessed the performance of CRP testing.[182] While this review was not limited to a GP setting, it did include one of the studies reported here.[190] Pooled analysis of all four studies reported sensitivities of 73%, 39% and 22% at thresholds of 10mg/L, 20-25mg/L and 40-49mg/L. The corresponding specificity estimates were 60%, 87% and 91%, respectively. The review concluded that there was no clearly preferred single threshold for defining an abnormal (CRP) test, and suggested the use of two thresholds to define low (<10mg/L), medium (10-30mg/L) and high (>30mg/L) risk groups.

The diagnostic test accuracy of CRP in pharyngitis/tonsillitis

Among patients with acute pharyngitis, many clinical guidelines recommend that only those infections caused by streptococcal infections and particularly group A beta-haemolytic streptococcus (GAS) should be treated with antibiotics. Patients with other viral or bacterial infections generally do not benefit from antibiotics. GAS pharyngitis is usually self-limiting, but may rarely be associated with serious complications which can be prevented with antibiotic treatment. For this reason, the

majority of the evidence retrieved on the diagnostic test accuracy of CRP in identifying patients with acute pharyngitis/tonsillitis who require antibiotic therapy specifically relates to the identification of those patients with GAS pharyngitis. Two studies presented the mean levels of CRP in patients with acute pharyngitis or tonsillitis, with contrasting results.[186, 199] The inclusion criteria differs substantially between these studies, with patients in the Calvino study presenting with all four Centor criteria, while in the Christensen study none of the included patients had a Centor score of four. The studies also differed in the proportion of patients in the non-GAS group with no bacteria or other non-GAS bacteria. It is unclear if other types of bacterial infection would be expected to cause a similar rise in CRP levels; in the Calvino study, group C streptococcal infection caused the highest rise in CRP values (mean CRP 56.3mg/L group C versus 34.4 mg/L group A). In addition, as the reference standard was a throat swab, some of the patients who were positive for GAS may have been carriers who also had viral/other bacterial pharyngitis and this proportion may have differed between studies.

Two studies sought to determine the optimal threshold for CRP testing in patients presenting with sore throats.[186, 189] The cut-point chosen differed substantially (6 mg/L versus 35 mg/L). The studies differed in their aim in that the Guilich study sought to use CRP to distinguish between bacterial and non-bacterial pharyngitis, while Christensen and colleagues wanted to distinguish between GAS and non-GAS pharyngitis.

Guilich and colleagues reported that at a threshold of 35 mg/L, CRP is better at ruling in than ruling out bacterial pharyngitis and improves both the sensitivity and specificity of GP clinical diagnosis alone. They subsequently went on to use this threshold as part of a two-step clinical algorithm whereby about 30% of patients presenting with sore throat required a CRP measurement after clinical assessment. The specificity of the algorithm was higher than the sensitivity (Table 5.5). As not treating patients with GAS pharyngitis is generally not a major safety concern in most countries, the lower sensitivity but higher specificity may be an acceptable trade off. However, the score developed in this study needs validation. Christensen et al., at a threshold of 6 mg/L, reported that CRP in combination with the Centor score may be useful in ruling out GAS pharyngitis, but only if RADT is not available. Given the mean value for those with non-GAS infection was 15 mg/L (95% CI: 10-19) in this study, the cut-point of 6 mg/L may have been too low to adequately distinguish between patients with acute pharyngitis caused by GAS and non-GAS infection. The low specificity of this cut-point means that many false positives may be treated unnecessarily with antibiotics.

Overall, CRP at a cut-point of 6 mg/L CRP is unlikely to be useful in guiding antibiotic prescribing either on its own or in combination with the Centor score as it is better at ruling out GAS pharyngitis, but would lead to unnecessary antibiotic prescribing.

At a cut-point of 35 mg/L, it may be useful for determining bacterial pharyngitis and one study suggests it could be useful for determining GAS pharyngitis as part of a clinical prediction rule, but further validation studies would be required. Notably, patients with evidence of GAS infection according to microbiological analysis of pharyngotonsillar swabs had a mean CRP concentration of 34.4 mg/L in the study by Calvino et al., suggesting that at a threshold of 35 mg/L as proposed by Gulich et al. some patients presenting with GAS infection may not be identified. A lower threshold may be more suitable in order to avoid failure to detect GAS infections requiring antibiotic therapy.

The diagnostic test accuracy of CRP in LRTI/pneumonia

Current clinical guidelines recommend antibiotic treatment for pneumonia, but not for other lower respiratory tract infections as these are generally considered to be self-limiting with limited clinical benefit from antibiotic treatment.

There was limited data on the levels of CRP in paediatric patients. One study included in this review included paediatric patients with pneumonia and reported mean levels between 24 and 32 mg/L, they reported infants younger than 12 months had very low CRP levels (mean 14 mg/L, unmeasurable in 65% of infants older than 12 months) and therefore more studies are needed to establish the diagnostic accuracy of CRP in children presenting with LRTIs. In adults, there was greater consistency in CRP levels in those patients without pneumonia (mean CRP 17 to 19 mg/L), than those with those with pneumonia (mean CRP 62 to 145 mg/L). CRP concentration was shown to be low (<20 mg/L) in a proportion of adults with pneumonia (Van Vugt 39%, Lagerstrom 21%).[195, 198]

Five studies reported on the diagnostic accuracy of CRP at a specified threshold for diagnosing pneumonia. Four studies reported on a cut-point of 20 mg/L, three of which reported a sensitivity between 0.48 and 0.79, which was considered by the authors to be too low to reliably rule out pneumonia.[192, 195, 197] In contrast, the fourth study by Hopstaken reported a sensitivity of 100% at a cut-point of 20 mg/L. Melbye reported a sensitivity of 0.82 at a cut-point of 11 mg/L suggesting that 18% of pneumonia patients could be missed at this lower CRP level. At a threshold of 50 mg/L (n=2) and 100 mg/L (n=2) specificity was between 0.84 and 0.99, and may be suitable for ruling in a diagnosis of pneumonia.[194-197]

Four studies investigated the diagnostic accuracy of CRP in combination with signs and symptoms for determining pneumonia in patients presenting with LRTIs. One study, Holm et al., found the addition of CRP at a cut-point of 20 mg/L increased the specificity of clinical judgment, but reduced the sensitivity, suggesting it would have limited use in primary care unless the GP was trying to rule in a diagnosis of pneumonia. Two other studies used CRP in combination with a clinical prediction rule to classify patients into low, intermediate and high risk of pneumonia.[193, 198] In both studies, addition of CRP testing to the prediction rule increased its discriminative power. In Teepe the addition of CRP increased the diagnostic value of their prediction rule, but the authors concluded that it was insufficient to exclude a bacterial pneumonia. In the Hopstaken paper, use of the rule would have saved 41% of prescriptions for antibiotics with a 2.5% risk of missing a case of pneumonia. In the Van Vugt study, CRP was only useful in the intermediate risk category where there was clinical uncertainty, and allowed for the reclassification of around half of this group into high- or low-risk categories.

5.5 Key messages

- The search of the literature retrieved 15 diagnostic test studies (all of which were European studies) that evaluated the diagnostic test accuracy of CRP in the diagnosis of RTI in primary care.
- The evidence base is characterised by a high level of heterogeneity in patient populations, diagnostic criteria, CRP cut-points, how the performance of the test was reported and the absence of a universal reference standard for the diagnosis of RTIs requiring antibiotic treatment.
- Two studies reporting the usefulness of CRP testing in diagnosing acute sinusitis provided limited evidence of benefit. Both studies identified a low threshold (10 and 17 mg/L) that may be useful to rule out sinusitis, however, as most guidelines for acute sinusitis (of less than 10 days' duration) do not generally recommend the use of antibiotics, the utility of CRP POCT in sinusitis is unclear.
- CRP is better at ruling in than ruling out bacterial pharyngitis at a threshold of 35 mg/L and one study suggests it may be useful when used in combination with other signs and symptoms. The utility of CRP for the detection of bacterial pharyngitis is sensitive to the cut-point used.
- For LRTI and pneumonia, there was mixed evidence regarding the diagnostic test accuracy of CRP. CRP may be useful at ruling in a diagnosis of pneumonia at a cut-point of 100 mg/L, but is not reliable at ruling out pneumonia at a cut-point of 20 mg/L. When used in combination with specific signs and symptoms, CRP testing may increase the specificity of clinical judgment.

6 Analytical performance of CRP point-of-care test devices

This report examines CRP point-of-care tests that are suitable for use in a primary care setting, providing results within the time taken for a typical primary care consultation. This section considers whether the commercially available CE marked CRP point-of-care tests marketed for use in primary care have comparable analytical performance relative to standard laboratory CRP. The review of diagnostic test accuracy focused on the sensitivity and specificity of the test in distinguishing between viral and bacterial acute RTIs. This section takes a broader perspective on accuracy, precision and reliability of the devices in relation to measuring CRP levels, and also considers the usability of the devices.

6.1 Search strategy

A full systematic review approach was used to search for evidence of diagnostic test accuracy. The review approach replicated the search used for clinical effectiveness and safety (Chapter 4) with modifications for the outcomes and study design.

6.1.1 PICOS

The PICOS (Population, Intervention, Comparator, Outcomes, Study design) analysis used to formulate the search is presented in Table 6.1 (detailed PICOS are provided in Appendix P).

Table 6.1 Scope for search for studies of clinical effectiveness

Description	Project scope
Population	The population of interest is represented by patients of all ages who present to primary care.
Intervention	CRP point-of-care test for use in primary care setting (+/- other biomarkers). Twelve CE marked quantitative devices and three CE marked semi quantitative methods will be considered in this assessment.
Comparison	Standard laboratory CRP measurement or another CRP POCT instrument
Outcomes	**Primary outcomes:** • Measures of accuracy (level of agreement between the result of one measurement and the true value) and precision (degree of reproducibility of the result) will be extracted for each CRP POCT device. **Secondary outcomes** ▪ Where available, information on ease of use and suitability for primary care

Description	Project scope
	POCT will also be collected and summarised for each device.
Study design	Any study reporting on analytical performance.

Key: CRP – C-reactive protein; MeSH – Medical Subject Heading; POCT – Point-of-care testing.

6.1.2 Bibliographic search

To identify relevant studies systematic searches were carried out on the following databases:

- MEDLINE (OVID, Pubmed)
- Embase
- CINAHL (via EBSCOHost)
- The Cochrane Library

In addition, OpenGrey and Scopus were searched as studies investigating analytical performance are more likely to be found in the grey literature. Hand searching of the literature was also undertaken including a cross-check of the reference list of included studies and relevant systematic reviews as well as citation tracking. Ad hoc internet searches were undertaken to identify other relevant grey literature. Finally, lists of relevant studies provided by manufacturers in their submission files were searched for additional studies. Submission files were submitted by three companies: Abbott (Alere), Orion Diagnostica Oy, and RPS Diagnostics. These files were used along with material from other company websites to inform the technology description domain. The following clinical trial registries were searched for registered ongoing clinical trials and observational studies: ClinicalTrials.gov and International Clinical Trials Registry Platform (ICTRP).

6.1.3 Data extraction and analysis

Two review authors independently extracted data using prepared data extraction forms. The authors resolved any discrepancy through discussion or with a third author.

6.1.4 Quality appraisal

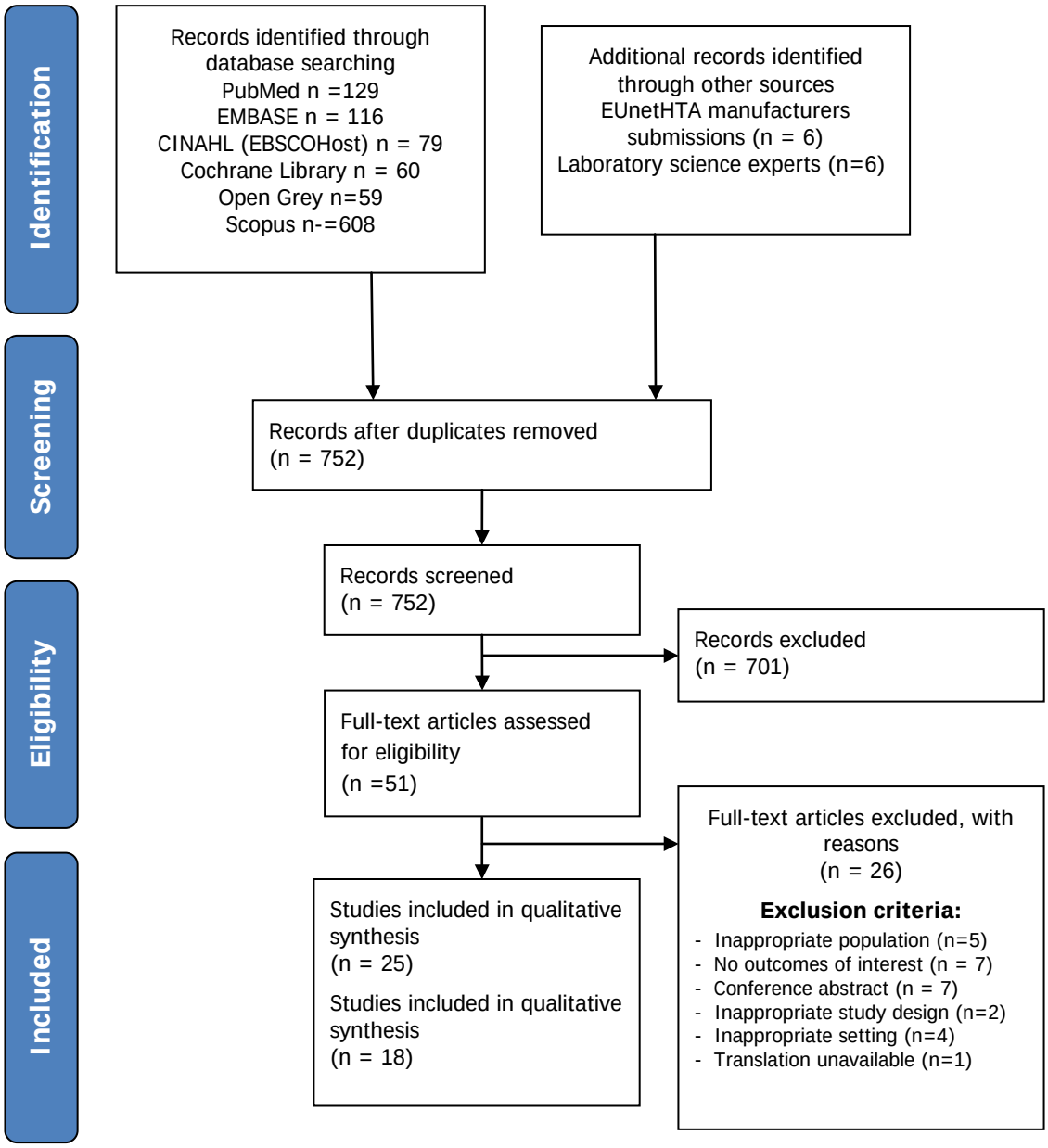
Standardised critical appraisal instruments to rate the quality of analytical performance studies are limited. As a result, a modified QUADAS-2 tool was used to assess the quality of studies in systematic review 3. All questions from QUADAS-2 were retained. These related to patient selection, index test, reference test, and flow of participants. An additional question was added relating to the operator of the index test. Two authors from HIQA independently assessed the quality of the

included studies. Disagreements in judgments were resolved through discussion. The GRADE summary of findings table is provided in Appendix S.

6.2 Study selection

A total of 746 studies were identified from database searching. Submission files received from manufacturers were also consulted to identify relevant studies for this review; six articles were identified as being potentially relevant; however, all six had already been identified through the systematic search. After consultation with laboratory experts, six additional studies were identified from the Scandinavian evaluation of laboratory equipment for point-of-care testing (SKUP)[206-211] resulting in 752 studies. After title and abstract screening, 51 potentially relevant articles were identified for full-text review. Following exclusion of 26 studies for reasons listed in (Figure 6.1), 25 studies remained that were relevant for inclusion in this review. At the full-text stage the most common reasons for exclusion were inappropriate population and no relevant outcomes. These studies often included a specific irrelevant disease group as the population of interest or did not report on accuracy, precision or ease of use of the device. Four studies were excluded as they were performed in the emergency department. One study was in Korean and no appropriate translation could be identified.[212] No relevant systematic review was retrieved from any database during the search.

Figure 6.1 Flow chart: systematic review of clinical effectiveness and safety



6.3 Included studies

The systematic review of analytical performance of CRP POCT devices retrieved a total of 25 studies.[25, 206, 207, 209, 211, 213-225] While five of these studies relating to the NycoCard™ device were identified as meeting the inclusion and exclusion criteria, on review it was evident that there had been substantive updates to the device (from a semi-quantitative to a quantitative device) since their publication, so that the results could not be considered relevant to the currently marketed version of the device. These studies were therefore excluded from this review.[226-230] In addition, of the six studies undertaken as part of an external validation assessment by the Scandinavian evaluation of laboratory equipment for point-of-care testing (SKUP), two studies were identified as being updates due to substantive changes in the POCT device, so the decision was taken not to include the two original studies in the review. This review is therefore limited to 18 studies.[25, 206, 207, 209, 211, 213-225] The literature was identified from eight countries with all but one study (n=1 Japan) conducted in Europe. Study details are summarised in Table 6.2 below. A detailed summary of the included studies is provided in Appendix R.

6.3.1 Methods of comparison

In all studies the analytical performance of CRP POCT was compared with standard CRP measurement by trained laboratory staff using laboratory-grade analyser equipment. Three approaches to how the comparison was undertaken were identified:

Approach A: Fresh whole capillary or whole blood samples were obtained as appropriate and tested at the point of care by those who would ordinarily use the device at the point of care with a second venous sample from the patient sent to the laboratory for standard testing. In most studies a healthcare professional performed the test at the point of care, but in some Scandinavian studies, biomedical scientists in the primary care centres performed the test at the point of care.

Approach B: Venous samples submitted from patients in primary care or hospital inpatients were tested in the hospital laboratory by a trained laboratory technician using both a POCT device and a laboratory analyser. The venous samples included fresh whole blood (with anticoagulant) or serum samples and frozen samples from laboratory library stores.

Approach C was taken by an external quality assurance (EQA) study in Norway. Blood samples of known CRP concentration were distributed to primary care centres. POCT was then undertaken by healthcare professionals and staff to assess the performance of the device when operated by the intended user.

Approach A only was adopted in two studies,[224, 225] approach B only in 10 studies [25, 213, 214, 216-221, 223] and approach C only in one study,[215] Both approaches A and B were adopted in four studies, thereby allowing different aspects of analytical performance to be assessed within the same study.[206, 207, 209, 211] Finally, in one study Approach A was used for one device and approach B was used to assess another device [222].

Blood samples used for CRP testing were obtained from patients attending primary care (n=5)[214, 221, 222, 224, 225] and samples submitted to the hospital laboratory (n=3).[213, 216, 223] In five studies [25, 217-220] CRP testing was undertaken on frozen samples from laboratory library stores. There were four external quality assessment studies by SKUP that used both hospital and primary care blood samples. Finally, the external quality assessment study by Bukve et al. used prepared laboratory and hospital samples.[215]

One study limited the inclusion criteria to patients presenting to primary care with symptoms of suspected RTI.[221] The remaining studies did not have specific inclusion criteria, but instead included patients with a range of medical conditions for which a CRP blood test was clinically indicated. Details of the patient population (presenting symptoms, age, gender) were not generally reported for those studies using laboratory library samples.

Length of time between testing samples at the point of care and transportation of a patient blood sample to the laboratory for standardised laboratory measurement was unclear across the literature. Furthermore, in most studies it was unclear for what length of time laboratory library samples had been stored before CRP levels were tested.

There were five studies that compared the performance of more than one CRP POCT device (range 2-8).[25, 214, 215, 217, 222] These studies were mostly conducted in a laboratory to eliminate or reduce the risk of operator bias. One study tested one device at the point of care and then transferred a venous sample to the laboratory to be tested on a different POCT device by laboratory technicians.[222] A total of two semi-quantitative (Actim®, Cleartest®)[214, 219] and 11 quantitative POCT devices were assessed. Results for the NycoCard™ and NycoCard™ Reader II device have been presented separately, as have results for the QuikRead® 101 and QuikRead go® devices.

Table 6.2 Main characteristics of included studies

Author and year or study name	Number of samples (setting tested)	Intervention (s)	Main endpoints
Bains (2017)	44 (Lab)	ichroma™	Accuracy (bias, correlation)
Brouwer (2015)	100 (Lab)	Actim®*; Cleartest®*, Afinion™, Eurolyser Smart, ichroma™, Microsemi™, AQT90 FLEX®	Accuracy (agreement, bias, correlation); Precision (CV), Ease of use
Bukve (2016)	3 (Lab) 22 (POC)	ABX Micros 200™, Afinion™, ichroma™, NycoCard™, QuikRead go®	Accuracy (bias)
Ciftci (2014)	96 (Lab)	ichroma™	Accuracy (bias
Clouth (2009)	200 (Lab)	NycoCard™, ABX Micros CRP™	Accuracy (agreement, bias); Precision (CV), Ease of use
De Graff (2016)	43 (Lab)	spinit®	Accuracy (correlation); Precision (CV)
Evrard (2005)	100 (Lab)	Actim®*	Accuracy (agreement) Ease of use
Ivaska (2015)	48 (Lab)	Afinion™	Accuracy (bias, correlation)
Matheeussen (2018)	2,922 (POC)	QuikRead® 101	Accuracy (agreement, bias, correlation); Precision (CV)
Minnaard (2013)	8 (Lab)	Afinion™, NycoCard™ Reader II, Eurolyser Smart, QuikRead go®, QuikRead® 101	Accuracy (bias) Precision (CV), Ease of use
Monteny (2006)	59 (Lab and POC)	NycoCard™, QuikRead®	Accuracy (agreement, bias, correlation)
Nomura (2014)	244 (Lab)	Microsemi™	Accuracy (correlation)
Seamark (2003)	234 (POC)	QuikRead®	Accuracy (bias, correlation), Precision (CV) Ease of use
SKUP (2001)	40 (Lab) 40 (POC)	QuikRead® 101	Accuracy (agreement, bias, correlation), Precision (CV), Ease of use

Author and year or study name	Number of samples (setting tested)	Intervention (s)	Main endpoints
SKUP (2002)	160 (Lab and POC)	ABX Micros CRP™	Accuracy (agreement, bias, correlation), Precision (CV), Ease of use
SKUP (2011)	114 (Lab) 80 (POC)	ichroma™	Accuracy (agreement, bias, correlation), Precision (CV), Ease of use
SKUP (2013)	100 (Lab) 86 (POC)	Smart Eurolyser	Accuracy (agreement, bias, correlation), Precision (CV), Ease of use
Verbakel (2013)	135 (POC)	Afinion™	Accuracy (agreement, bias) Ease of use

Notes: * Semi-quantitative tests. All other quantitative

Key: CV – co-efficient of variation; POC – point-of-care; Lab – laboratory.

6.3.1 Quality of studies

Details of the quality of the evidence included in this systematic review are included in Appendix S.

Overall, studies were of low or unclear risk of bias by QUADAS 2. However, there were three clear areas where bias was of concern. It was not clear if operators were blinded to the results of the POCT or had prior information regarding the CRP concentration of the sample being tested. This could introduce bias, particularly in the laboratory setting where the same individual could be performing both the POCT and laboratory reference test. Another potential source of bias related to the lack of clarity around the length of time the samples were stored prior to their use or the time interval between performance of the POCT and reference tests. The absence of a clear explanation of the experimental design of these studies limits the interpretation of the results. Finally, in several of the studies, the population samples were not specific to patients presenting to primary care with symptoms of RTI with samples also taken from hospital inpatient and outpatient settings in addition to stored laboratory samples for which little if any detail of the patient population from which they were derived provided. Therefore the spectrum of patients was often not the same as those who would receive the test in practice. In many studies, principally those where multiple devices were compared with each other, frozen or EDTA-treated venous samples were taken from laboratory stores. The advantage of

this approach is that the samples are of a known concentration, allowing a range of CRP concentrations to be analysed. This method also eliminates bias that could be introduced due to heterogeneity of the operator at the point of care, which is important when comparing devices with each other. The disadvantage of the approach is that laboratory venous blood samples that have been frozen or treated with EDTA or heparin are not the same as capillary blood samples tested at the point of care thereby introducing a potential source of bias. By controlling the sample and operator variables, these studies also create an artificial environment that does not reflect the intended use of these POCT devices, that is, in primary care by non-laboratory trained healthcare professionals.

An additional potential source of bias is the source of funding of the studies. One study was sponsored by the manufacturer [(224)] and in a further two studies, the equipment and training was funded by the manufacturer.[(218, 225)] Research in one of the studies was undertaken by company employees.[(223)] Four studies were recipients of educational grants.[(220-222, 225)]

6.4 Results: accuracy

Data in relation to three main indicators of accuracy were presented in the literature for quantitative CRP POCT devices: correlation, agreement and bias. These terms were used interchangeably in the literature. The following is a brief explanation of how these terms are used in this assessment.

Correlation: This was presented as a linear regression which quantifies the strength of the relationship.[(231)] Correlation was reported as a Spearman's, Pearson's or intra-class correlation coefficient with the r value indicating the strength of relationship (range: -1 to +1) and the r^2 value (range: 0-1) explaining the proportion of variance that the two variables have in common.[(231)]

Agreement: Regression analysis was used to indicate the level of agreement between the laboratory standard method and the POCT method. For quantitative devices, this was reported using a Passing-Bablok regression analysis (n=4 studies) [(214, 221, 222, 225)] or a Deming regression (n=1). The Passing-Bablok regression analysis overcomes some of the limits of correlation analysis related to data distribution and presents a constant or proportional difference between two methods. If the slope of the regression line includes 1.00, there is no proportional difference between the device and the laboratory reference method. For semi-quantitative devices, the agreement between the CRP POCT device and the reference test was reported as a Cohen's Kappa value (range 0-1), with values closer to 1 indicating high levels of agreement between the methods.

Bias: This was reported in five studies as a mean difference or percentage difference in CRP values calculated from a Bland-Altman plot.[25, 214, 221, 222] The Bland-Altman method describes the agreement between two quantitative measurements and establishes limits of agreement using the mean and standard deviation. Bland-Altman recommends that 95% of the data points for the mean difference between the two methods should lie within two standard deviations. It gives an indication of how much the POCT measurements deviate from the reference measurements and the direction of this bias. In other studies, a mean difference or percentage mean difference was presented but it was not clear if Bland-Altman methodology had been used.[206, 207, 209, 211, 213, 215, 216, 220, 224, 225]

6.4.1 Accuracy of semi-quantitative devices

The accuracy of two semi-quantitative devices compared with standard CRP laboratory measurement was reported in two studies, both of which were undertaken by trained laboratory staff in the laboratory (Table 6.3). In the study by Brouwer et al., two independent observers read the test-strip results and these values were compared with the CRP level as measured by standard laboratory testing using four CRP concentration categories (CRP 0-10 mg/L, 10-40 mg/L, 40-80 mg/L and >80 mg/L); results were reported as Cohen's Kappa values reflecting the level of agreement between the measurements. Both semi-quantitative devices performed poorly when read after 5 minutes (the optimal time as indicated by the manufacturer) with Kappa values ≤0.63 and ≤0.61 for Actim® and Cleartest®, respectively. The percentage discrepancy between CRP POCT and standard testing measurement ranged between 27% and 35% for the Actim® strips and 33% and 39% for Cleartest®. The tests were re-read at 15 minutes to evaluate if test accuracy varied according to the time at which they were read. The accuracy of both tests was found to decline, with Kappa values of ≤0.46 and ≤0.25 reported for the Actim® and Cleartest® devices, respectively. Separately, the accuracy of the Actim® device was also reported by Evrard et al., who reported an overall Kappa value of 0.93 when tested using samples from four CRP concentration categories(<10, 10-40, 40-80 and >80mg/L).

Table 6.3 Agreement of the semi-quantitative POCT tests with the reference standard

Device	Agreement (κ)	Discrepancy (%)	Agreement (κ)	Discrepancy (%)
	After 5 minutes		**After 15 minutes**	
Actim®(219)	0.93			
Actim®(214)				
Observer 1	0.53	35	0.46	39
Observer 2	0.63	27	0.39	44
Inter-observer agreement	0.81	14	0.83	12
	5 minutes vs. 15 minutes			
Intra-observer agreement	0.64			
Observer 1	0.60			
Observer 2				
Cleartest®(214)				
Observer 1	0.61	39	0.17	60
Observer 2	0.56	33	0.25	56
Inter-observer agreement	0.55	33	0.74	16
	5 minutes vs. 15 minutes			
Intra-observer agreement	0.40			
Observer 1	0.20			
Observer 2				

(κ) – Cohen's Kappa

6.4.2 Accuracy of quantitative devices

A summary of the accuracy results for the quantitative CRP POCT are presented in Table 6.4. Results obtained under idealised laboratory conditions and at the point of care (primary care setting) are presented separately. Seventeen studies evaluated quantitative devices, 12 of which evaluated the accuracy of 10 different POCT devices in the laboratory; eight studies evaluated the accuracy of seven POCT devices in the primary care setting. All studies compared the CRP result obtained on the POCT device with that obtained using standard CRP measurement by trained laboratory staff using laboratory-grade analyser equipment. The comparator equipment differed between studies (Appendix R). Three main indicators of accuracy were reported: correlation, agreement and bias; studies varied in the number of accuracy indicators they reported (range: 1 to 3).

In Table 6.4 the correlation coefficients (r or R) and the coefficient of determination (r^2 or R^2) all exceed 0.9, indicating excellent correlation between the devices and the reference laboratory measurement irrespective of whether the device was tested in the laboratory or at the point of care. No correlation data were available for the NycoCard™ Reader II.

Agreement with a laboratory reference standard was reported in four studies as the result of Passing-Bablok regression analysis for seven devices tested in the laboratory setting.[214, 217, 221, 222] In a comparative study of six quantitative devices, Brouwer et al. noted that the AQT90 FLEX® and Smart Eurolyser exhibited the best agreement (1.03 [95% CI: 1.00-1.06]; 1.00 [95% CI: 0.96-1.04] respectively). Values close to the reference standard were reported for the Afinion™, Microsemi™ and QuikRead go® devices, but their 95% CI did not include the value 1.00 (0.87, 95% CI: 0.84-0.91, 1.16, 95% CI: 1.14–1.18 and 0.85, 95% CI: 0.83–0.87 respectively), indicating that the devices systematically under- or overestimated the CRP level (Table 6.4). A lower level of agreement was noted for the ichroma™ device (0.79 [95% CI: 0.76–0.82]).[214] Results from studies by Matheeussen et al. and Monteny et al. reported a systematic underestimation of CRP levels by the QuikRead® 101 device (0.94 [95% CI: 0.93–0.95])[221], (0.83 [95% CI: 0.81–0.85]),[222] respectively).

Three studies assessed agreement with the reference standard when tested at the point-of-care using Passing-Bablok regression analysis (Table 6.4).[218, 222, 225] Good agreement was noted for the Afinion™ (1.02, 95% CI:1.01-1.08)[225] and NycoCard™ (0.95, 95% CI: 0.9-1.0) devices.[222, 225] Using Deming regression, the spinit® device was noted to overestimate CRP values by 12%.[218]

Thirteen studies reported the accuracy of CRP POCT devices compared with the laboratory standard on the basis of their bias calculated as a mean difference or percentage difference in CRP level. Six of these studies were set in the laboratory,[25, 211, 213, 214, 217, 220-222] seven were set in the POC [206, 207, 211, 215, 222, 224, 225] with two studies reporting bias from the laboratory and the POC (Table 6.4).[211, 222]

Two studies provided the majority of the data for the laboratory setting as they compared multiple devices.[25, 214] Minnaard et al. compared five quantitative CRP devices (Afinion™, NycoCard™ Reader II, Smart Eurolyser, QuikRead go® and QuikRead® 101).[25] The study took place under idealised laboratory conditions and compared the accuracy of the devices using low concentration (<20mg/L), intermediary (20-100mg/L) and high concentration (100mg/L) CRP samples, the results of which are summarised in Table 6.4. For all devices, the mean difference was less than 2mg/L at low concentrations (<20 mg/L), with QuikRead go®

(0.2mg/L, 95% CI: -1.2 to 1.5) and the NycoCard™ Reader II (0.3 mg/L, 95% CI: -4.4 to 5.0) the most accurate. At the intermediary concentration (20-100 mg/L) the Afinion™ was the most accurate device (-0.3mg/L, 95% CI: -6.4 to 5.8) with all the other devices reporting a mean difference between 2.3 mg/L (QuikRead go®) and 7.8 mg/L (Smart Eurolyser). The largest mean difference values were reported with the high concentration (>100 mg/L) CRP sample, ranging between 0.9mg/L (95% CI: -53.2 to 55.0) (Smart Eurolyser) and 14.7mg/L (95% CI: -21.1 to 50.5) (Afinion™). The authors concluded that the Afinion™, NycoCard™ Reader II, QuikRead® go and QuikRead® 101 showed better agreement than the Smart Eurolyser device and that for all of the POC devices tested the agreement between the POC test and the laboratory standard decreased at higher CRP concentrations, resulting in wider confidence intervals around the mean differences at CRP concentrations greater than 100 mg/L.

Brouwer et al. reported on six quantitative devices (QuikRead go®, Smart Eurolyser, Afinion™, ichroma™, Microsemi™ and AQT90 FLEX®), with all bar the ichroma™ (-12.3 mg/L) reporting a mean difference between ±3.7mg/L (Afinion™) and ±9.2 mg/L (QuikRead go®) (Table 6.4).[214] Additional studies for the Afinion™, NycoCard™ and QuikRead® 101 devices in the laboratory reported mean differences <±2.5 mg/L.[217, 220, 221] Additional studies for the ichroma™ device reported mean differences of -8.1mg/L [213] and -7 mg/L.[216] A SKUP analysis reported the bias for the ichroma™ device in the laboratory setting as 0.4%, however, the device over predicted at low concentrations by 6.6% and under predicted at high concentrations by 6.2%, clearly showing that presenting the bias at different concentrations of CRP provides a more useful overview of the devices performance.[209]

Table 6.4 Accuracy of the quantitative POCT tests compared with a reference standard when tested in the laboratory or at the point of care

	Laboratory				Point of Care			
Device	**Number of studies (n)**	**Agreement (Slope of Passing-Bablok Regression [95% CI])**	**Bias: Mean difference from Bland-Altman Plot (CI 95%) or % Bias**	**Correlation * (95% CI)**	**Number of studies (n)**	**Agreement: Slope of Passing-Bablok Regression (95% CI)**	**Bias: Mean difference from Bland-Altman Plot (CI 95%) or % Bias**	**Correlation * (95% CI)**
Afinion™	n=3 [25, 214, 220]	0.8 (0.84-0.91) [214]	**<20mg/L:** -1.1 mg/L (-3.2; 1.0) **20-100mg/L:** -0.3mg/L (-6.4;5.8) **>100mg/L:** 14.7mg/L (-21.1;50.5) [25] -3.7mg/L [214] to 2.3mg/L (-5.5;10.1) [220]	SCC r^2: 0.982 (0.973-0.988) [214] ICC: 0.994 (0.990 – 0.997) [220]	n=2[215, 225]	1.02 (1.01-1.08)[225]	1.3% (-15.4;12.8)[225] **25mg/L**: 1.7% (1.0;2.5) **63.9mg/L**: 2.0% (1.0;3.0)[215]	NR
NycoCard ™	n=1[217]	Equivalency of both tests shown by Passing-Bablok [217]	No systematic differences between tests shown with Bland-Altman [217]	SCC R: 0.9838[217]	n=2[215, 222]	0.95 (0.9 – 1.0)[222]	**0-70mg/**L:1.4mg/L (2SD:11) **>70mg/L**:-1.9mg/L (2SD:35.4) **Overall**: 0.6mg/L (2SD: 19.7)[222] **25.0mg/L**: 7.8% (3.0;13.0) **63.9mg/L**: 14.9% (10.1;20.0) [215]	PCC r: 0.99[222]
NycoCard ™ Reader II	n=1[25]	NR	**<20mg/L:** 0.3mg/L (-4.4;5.0) **20-100mg/L:** 3.0mg/L (-6.2;12.2) **>100mg/L: -**10.7mg/L (-30.4;9.1)[25]	NR	n=0	NR	NR	NR

	Laboratory				Point of Care			
Device	**Number of studies (n)**	**Agreement (Slope of Passing-Bablok Regression [95% CI])**	**Bias: Mean difference from Bland-Altman Plot (CI 95%) or % Bias**	**Correlation * (95% CI)**	**Number of studies (n)**	**Agreement: Slope of Passing-Bablok Regression (95% CI)**	**Bias: Mean difference from Bland-Altman Plot (CI 95%) or % Bias**	**Correlation * (95% CI)**
QuikRead go®	n=2[25, 214]	0.85 (0.83-0.87)[214]	**<20mg/L:** 0.2mg/L (-1.2;1.5) **20-100mg/L:** 2.3mg/L (-3.6;8.3) **>100mg/L:** -8.9mg/L(-21.4;3.5)[25] -9.2 mg/L [214]	SCC r^2: 0.996 (0.994-0.997)[214]	n=1[215]	NR	**25.0mg/L**: 8.0% (7.1;8.9) **63.9mg/L**: 12.0% (11.0;13.0)[215]	NR
QuikRead® 101	n=4[25, 206, 221, 222]	0.83 (0.81-0.85)[222] to 0.94 (0.93-0.95)[221] Regression slope: 0.98[206]	**<20mg/L:** -1.4mg/L (-3.2;0.4) **20-100mg/L:** -6.5mg/L (-15.6;2.7) **>100mg:** 3.2mg/L(-8.4;14.8)[25] **0-70mg/**L:-0.4mg/L (2SD:11.8) **>70mg/L**:-26.4mg/L (2SD: 44) **Overall**: -6.1mg/L (2SD 31.3)[222] 0.4mg/L (18.8;19.5)[221]	PCC r: 0.99[222] SCC r:0.976 (0.973-0.979)[221] R^2: 0.977[206]	n=3 [206, 215, 224]	NR	**25.0mg/L**: 1.7% (0.8;2.6) **63.9mg/L**: -0.6% (-1.6;0.5)[215] -1mg (+/-10mg/L)[224] **<75mg/L**: -10% **>75 mg/L**: -20% Stated as approximate results[206]	PCC r: 0.996[224]

	Laboratory				Point of Care			
Device	**Number of studies (n)**	**Agreement (Slope of Passing-Bablok Regression [95% CI])**	**Bias: Mean difference from Bland-Altman Plot (CI 95%) or % Bias**	**Correlation * (95% CI)**	**Number of studies (n)**	**Agreement: Slope of Passing-Bablok Regression (95% CI)**	**Bias: Mean difference from Bland-Altman Plot (CI 95%) or % Bias**	**Correlation * (95% CI)**
Smart Eurolyser	n=3 [25, 211, 214]	1.00 (0.96;1.04)[214]	**<20mg/L:** 1.9mg/L(-10.2;14.1) **20-80mg/L:** 7.8 mg/L (-27.7;43.3) **>100mg/L:** 0.9mg/L (-53.2;55.0)[25] **Low** (1.8-27,4 mg/L): -4.4% (-7.4;-1.4) **Medium** (27.5-41.1 mg/L) 5.5% (2.9;8.2) **High** (41,7-280 mg/L): 9.6% (5.6;13.5)[211] -3.9 mg/L [214]	SCC r^2: 0.970 (0.954-0.980)[214]	n=1 [211]	NR	Primary Health Centre 1: **Low** (0.3-13.5mg/L): -11.2% (-14.7;-7.8) **High** (14.3-148mg/L): -8.6%(-12.9;-4.3) **Overall:** -9.8% (-12.5;-6.9) Primary Health Centre 2: **Low** (**0.3-9.0mg/L): -**17.0% (-24.0;-9.6) **High** (**9.7-109mg/L):** -4.8% (-9.9;0.3) **Overall:** -10.3%(-15.1;-5.6)[211]	NR
ichroma™	n=4[209, 213, 214, 216]	0.79 (0.76;0.82)[214] Linear Regression = 0.74[213]	**Low** (0.0-13.5mg/L): 6.6% (2.8;10.4) **Medium** (13.5-56.4mg/L): 3.3% (1.0;7.6) **High** (56.6-264.6mg/L): -6.2% (-10.2;2.2) **Overall:** 0.4%(-2.2;2.9)[209] -8.1mg/L [213] -7mg/L (-139.1;125.1) [216] -12.3 mg/L [214]	r^2 = 0.905[213] SCC r^2: 0.967 (0.953-0.976)[214]	n=1[215]	NR	**25.0mg/**L:-9.7%(-11.6;-7.7) **63.9mg/L**:-9.1%(-8.18;-0.2)[215]	NR

	Laboratory				Point of Care			
Device	**Number of studies (n)**	**Agreement (Slope of Passing-Bablok Regression [95% CI])**	**Bias: Mean difference from Bland-Altman Plot (CI 95%) or % Bias**	**Correlation * (95% CI)**	**Number of studies (n)**	**Agreement: Slope of Passing-Bablok Regression (95% CI)**	**Bias: Mean difference from Bland-Altman Plot (CI 95%) or % Bias**	**Correlation * (95% CI)**
Microsemi ™	n=2[214, 223]	1.116 (1.14;1.18)[214]	5.1 mg/L [214]	r=0.989[223] SCC r^2: 0.997 (0.9969-0.998)[214]	n=0	NR	NR	NR
spinit®	n=0		NR	NR	n=1[218]	Deming regression value =1.12[218]	NR	R=0.98[218]
AQT90 FLEX®	n=1 [214]	1.03 (1.00;1.06)[214]	5.8 mg/L [214]	SCC r^2: 0.992 (0.995-0.998)[214]	n=0	NR	NR	NR
ABX Micros 200™	n=2[207, 217]	Regression slope 0.84 to 1.15 [207]	NR	SCC R:0.9934 R: 0.98 – 0.99[207]	n=2[207, 215]	NR	**25.0mg/L**: -6.2%(-10.0;-2.1) **63.9mg/**L: 0.0%(-1.0;1.0)[215] **Primary care centres (n=4): Overall: 40% Primary care centres involved initially and at 6 months (n=2): 10-135mg/L**: -27.6% After 6 months use this decreased to -14.7%.[207]	R^2: 0.81 to 0.98 for 4 practices[207]

- Correlation values reported included: Spearman (SCC) Pearson (PCC)* & Intra-class correlation coefficient (ICC)

One external quality assurance scheme (EQAS) for CRP POCT reported the accuracy of multiple devices (Afinion™, NycoCard™, QuikRead go®, QuikRead® 101, ichroma™ and ABX Micros™) in the primary care setting in Norway.[215] The EQAS scheme evaluated instrument performance at two different CRP concentration levels using certified reference material. Each participant received two EQA samples which comprised whole blood with human recombinant CRP added to a known concentration (25.0mg/L and 63.9mg/L). The Afinion™ and the QuikRead® 101 were found to have low bias (<±2%) at both concentrations (Table 6.4). Comparable results were found for the QuikRead go®, NycoCard™ and ichroma™ devices with estimates of bias at 25 mg/L between ±7% and ±10% and estimates of bias at 63.9 mg/L between ±9% and ±15%. The QuikRead go® (12.0%, 95% CI: 11.0; 13.0) and NycoCard™ (14.9%, 95%CI: 10.1; 20.0) performed particularly poorly when the higher concentration sample was tested. The ABX Micros™ had acceptable bias with evidence of lower bias at the higher concentration level (25.0 mg/L -6.2%, at 63.9 mg/L 0.0%). Consistent with the Bukve study, Verbakel et al. reported low levels of bias (≤2%) for the Afinion™ device when tested in the primary care setting.[215, 225] Inconsistent data were found for a number of these devices in other studies. In contrast to the Bukve study, the NycoCard™ device was found to have low levels of bias (<2%), even at high concentrations (> 70 mg/L).[222] A SKUP study from 2002, in contrast to the Bukve study, reported poor levels of accuracy for the ABX Micros™ device in four primary care centres.[207, 215] The SKUP study reported the POC results to be around 40% lower (n=4 primary care practices) than the hospital reference method. Testing was repeated in two of these practices after six months of use with improvements in accuracy seen (from approx. 28% lower to 14% lower than the reference method) in these centres suggesting that with practice operators made fewer mistakes.

In two of the SKUP reports and a study by Monteny et al., accuracy data is reported in the laboratory and at the point of care.[206, 211, 222] A 2001 SKUP study reported data on the QuikRead® device when tested at the point of care in three general practices using whole blood and in the laboratory setting using plasma. In the laboratory, the study found good consistency between the laboratory reference method and the QuikRead® device (Regression equation y=0.98x +0.32, Table 6.4). However, in the POC setting the device consistently underestimated the CRP levels compared with the hospital reference method; this underestimation was greater at higher CRP concentrations (<75 mg/L approx.-10%, >75 mg/L up to -20%). The authors suggested the discrepancy was due to the use of whole blood at the point of care with no correction for haematocrit. Subsequent to this feedback, the company responded that the device would be recalibrated (3% at the lower end of the concentration range and 13% at the higher end) to correct these systematic

differences. The data from this 2001 SKUP report are therefore less likely to be relevant.

In the SKUP analysis for the Smart Eurolyser, data was reported as a percentage bias at different concentrations (Table 6.4).[211] The bias in the laboratory ranged from -4.4% (-7.4; -1.4) to 9.6% (5.6; 13.5). When tested at two POC centres the bias was a maximum of -17.0% (-24.0;-9.6) at low CRP concentrations. The overall bias across the range of CRP concentrations at the two POC centres was -9.8% and -10.3%, respectively. This indicates a clear difference when using CRP POCT devices in the laboratory and at the point of care. SKUP pre-defines an acceptable level of bias as of +/- 1 mg/L or < 26% from the comparison method. In total, 98% of the results for the Smart Eurolyser fulfilled this goal for accuracy with venous EDTA samples in the hospital evaluation and with capillary samples at both primary healthcare centres.

Monteny et al. also reported the Bland-Altman mean difference based on CRP concentration in the laboratory and POC setting.[222] However, in this study different devices were used, with NycoCard™ being used at the POC and QuikRead® being used in the laboratory setting. The overall mean difference for the QuikRead® 101 was -6.1mg/L; at concentrations below 70mg/L the mean difference was -0.4mg/L, but this increased to -26.4mg/L at higher concentrations (>70mg/L). This is in contract with the Minnaard study that reported bias of 3.2 mg/L at concentrations over 100 mg/L. Monteny also reported on the NycoCard™ device at the POC and overall the NycoCard™ device was more accurate than the QuikRead® 101 device (overall mean difference of 0.6 mg/L; 1.4 mg/L at lower CRP concentrations and -1.9 mg/L at higher concentrations). The authors concluded that the NycoCard™ device was more suitable for use in primary care.

In addition to accuracy results reported in Table 6.4, Bukve et al. reported on an external quality assurance scheme (EQAS) for CRP POCT in Norway, which comprised 19 rounds of EQAS (twice a year for nine years), with a mean of 2,134 participating GP offices or nursing homes in each round.[215] Participants' performance was considered good if the reported CRP measurement from their POCT equipment was within +/- 8% of the target interval, poor if the result exceeded the target value by +/- 15% and acceptable for results between these limits. The percentage of participants exhibiting good performance in each survey varied from 78% to 81%; good performance increased over time with participation in further rounds of EQA. The authors also examined what factors were associated with good performance compared with acceptable/poor performance and found that participants were more likely to achieve a good performance if they had taken part in more than one EQAS round, had a trained laboratory scientist performing the test,

performing the test more than 10 times per week, and performing internal quality control at least once per week. The type of instrument used was also found to be an important factor when determining the quality of the analysis performed in the primary care setting: the authors reported QuikRead® 101 as the reference value in a logistic regression analysis and found QuikRead go® had an OR of 0.87 (95% CI: 0.76-0.98), Afinion™ OR 0.70 (95% CI: 0.65-0.77), ichroma™ OR 0.36 (95% CI: 0.31-0.42), ABX Micros CRP™ OR 0.34 (95% CI: 0.29-0.42) and NycoCard™ CRP/NycoCard™ CRP with Reader II OR 0.32 (95% CI: 0.31-0.42). This suggests that use of QuikRead® 101, QuikRead go® and Afinion™ contributed to good participant performance. However, the authors also noted that changing the instrument did not seem to have a significant effect on results. Overall, GP offices tended to perform better than nursing homes, emergency primary healthcare centres and occupational healthcare centres, but the authors noted this may be related to how often the test is performed in these settings.

6.5 Results: precision

The precision of 11 CRP POCT devices was evaluated in 10 studies (Table 6.5). Precision was most often expressed as the level of imprecision and reported as a coefficient of variation (CV). Imprecision was reported as within-day variation (whereby the same samples are tested multiple times on the same device on the same day) and a between-day variation (whereby the same sample was tested on the same device on multiple days). Studies also compared the precision of the devices at different CRP concentrations (low, medium, high). The number of samples used; the range of CRP concentrations defined as low, medium and high; and the number of measurements taken varied greatly between studies. A number of studies noted that there is no agreed international standard in relation to the maximum acceptable level of imprecision. The studies by SKUP and Minnaard stated a priori that the maximum acceptable imprecision they considered was a CV of ≤10%. Brouwer et al. considered a value of ≤15% sufficient.

Of the 10 studies reporting precision data for devices when tested under idealised laboratory conditions, two studies, by Brouwer et al. [214] and Minnaard et al.,[25] which compared the analytical performance of eight and five CRP POCT devices, respectively, provided the majority of the data. Brouwer et al. [214] tested within-day variation using two samples with CRP concentrations ranging from 57mg/L to 120mg/L. Minnaard et al. [25] used a low concentration sample (18-25mg/L) and high concentration sample (95-136mg/L) and tested both within-day and between-day precision.

Overall acceptable levels of precision (CV <10%) were reported for the Afinion™, QuikRead go®, QuikRead® 101, Microsemi™, AQT90 FLEX® and ABX Micros™ devices when tested in the laboratory setting. In studies that compared the precision of the devices at a number of CRP concentration ranges, precision was noted to be concentration-dependent, with greater levels of imprecision reported at the extremes of the concentration range (Table 6.5).

High levels of imprecision (CV >10%) were reported in studies for the ichroma™ and NycoCard™ II Reader devices. Inconsistent data were obtained for the Smart Eurolyser device with acceptable (within-day CV <10%) precision reported by Brouwer et al. and poor levels of precision (maximum CV = 19.4% [within-day] and 30.5% [between-day]) reported by Minnaard et al. (Table 6.5).

Fewer studies reported data in relation to the precision of the devices when tested at the point of care, with data available for only five quantitative devices (ABX Micros 200™, ichroma™, QuikRead® 101, Smart Eurolyser and spinit®). Six studies reported within-day precision of devices when tested at the point of care,[209, 211, 224] four of which were SKUP reports. Acceptable levels of precision (CV <10%) were reported for two (QuikRead® system and spinit®) of the five CRP POCT devices assessed. Inconsistent levels of precision were reported for the ichroma™, Smart Eurolyser and ABX Micros™ devices with CV values of greater than 10% reported in at least one primary care practice or at one of the specific concentration ranges assessed. High levels of imprecision were recorded with the ABX Micros™ device (CV ≥ 24.6%) at CRP concentrations under 25mg/L; however, at CRP concentrations over 25mg/L the CV value was less than 3.2% (Table 6.5).

Table 6.5 Summary range of the within-day and between-day imprecision values of the quantitative POCT devices

	Laboratory			Point-of--Care		
Device	**Studies (n)**	**Within-Day CV (%)**	**Between-Day CV (%)**	**Studies (n)**	**Within-Day CV (%)**	**Between-Day CV (%)**
Afinion™	2	2.6[b(214)] - 7.4[a(25)]	4.6[a] - 7.3[b(25)]	0	NR	NR
NycoCard™	1	1.876[(217)]	NR	0	NR	NR
NycoCard™ Reader II	1	9.8[b] to 13.3[a(25)]	6.0[b] to 16.9[a(25)]	0	NR	NR
QuikRead go®	2	1.1[b] to 2.6[a(25)]	4.0[b] to 8.3[a(25)]	0	NR	NR
QuikRead® 101	3	5.4[a] to 5.7[b(25)] **8-25mg/L**: 6.1 (5.0-7.8) **25-100mg/L**: 2.4 (2.1-2.9) **>100 mg/L**: 1.7 (1.4-2.3) **Overall**: 2.5 (2.1-2.8)[(206)] 3.4%[(221)]	6.3[b] - 9.3[a(25)]	2	Inter-assay: **21mg/L**: 8.7 **63mg/L**: 4.5 Intra-assay: **25mg/L:** 6.4 **70mg/L**:3.6[(224)] 3.4 - 6.0[(206)]	2.5 (1.9 - 3.6) - 2.6 (2.1 - 3.7) [(206)]
Smart Eurolyser	3	2.8[a(214)] to19.4[a(25)]	18.0[b] to 30.5[a(25)]	1	Overall CV: 8 (6.8-9.7) 7.4 - 12.1[(211)]	21.0 - 25.7 with control material[(211)]
ichroma™	2	3.3[(209)] - 18.7[a(214)]	NR	1	5.7 - 15.0[(209)]	16.1 - 24.1 with control material[(209)]
Microsemi™	1	1.3[b] - 3.0[a(214)]	NR	0	NR	NR
spinit®	0	NR	NR	1	6.9[(218)]	NR
AQT90 FLEX®	1	3.5[a] - 7.6[b(214)]	NR	0	NR	NR
ABX Micros™	2[(207, 217)]	0.9160[(217)] **<2mg/L**: 57.7 **2-25mg/L**: 3.9 **25-75mg/L**: 5.3 **75-100mg/L**: 1.4 [(207)]	NR	1	Initial Results: **<2mg/L**: 53.4-103.6 **2-25mg/L**: 24.6-38.4 **25-75mg/L**: 0.1-3.1 **>75mg/L**: 0.7 Six month results: 1.4 - 5.0[(207)]	NR

[a,b] Two studies reporting on precision measured imprecision at two different CRP concentrations. [a] represents the lower concentration range (16 -37 mg/L in Minnaard et al. and 57 to 82 mg/L in Brouwer et al.) and [b] represents the higher concentraion range (82 to 160 g/L in Minnaard et al. and 77 to 120 mg/L in Brouwer et al.).

6.6 Test performance

6.6.1 Intra- and inter-observer variation in test interpretation

Data on this outcome are limited to one study which evaluated two semi-quantitative tests (Actim® and Cleartest®).[214] As illustrated in Table 6.3, there was evidence of inter-observer variation for both devices. Inter-observer agreement values after 5 minutes were 0.81 and 0.55 for Actim® and Cleartest®, respectively. When tests were re-read at 15 minutes, the inter-observer agreement values were 0.83 and 0.74 for Actim® and Cleartest®, respectively.

In terms of intra-observer variation, as noted, tests were read at 5 minutes and re-read by the same two observers at 15 minutes. For the Actim® device, the intra-observer agreement for observers one and two were 0.64 and 0.60, respectively. For the Cleartest® device, these values were 0.40 and 0.20, respectively. Although the test was read twice by the same observer, the 10-minute time lapse between the readings may account for the low intra-observer agreement as the test is known to be time-critical, with 5 minutes being the optimal time to read the test.

6.6.2 Impact of setting on analytical performance

While data comparing the accuracy of the POCT versus a laboratory standard in laboratory and primary care settings are available for eight devices, due to differences in the choice of comparator, it is only appropriate to evaluate the impact of setting if the device was tested in both settings (laboratory by trained laboratory personnel and in primary care by the intended users) within the same study. Data to inform this question are derived from the external quality assurance reports by SKUP on the Smart Eurolyser, ichroma™, ABX Micros™ and QuikRead® 101 devices (Table 6.6).

Table 6.6 Accuracy and precision of the quantitative POCT tests compared with a reference standard when tested both in the laboratory and at the point of care

	Laboratory		Point-of-care	
Device	**Measures of accuracy**	**Measures of precision**	**Measures of accuracy**	**Measures of precision**
QuikRead® 101 [206]	Regression equation: 0.98x +0.32 R^2: 0.977	Within-day CV %: **8-25mg/L**: 6.1 (5.0-7.8) **25-100mg/L**: 2.4 (2.1-2.9) **>100 mg/L**: 1.7 (1.4-2.3) 20 **Overall**: 2.5 (2.1-2.8) Between-day CV %: **62.9 mg/L**: 3.4% (2.3-6.4)	**<75mg/L**: -10% **>75 mg/L**: -20% Stated as approximate results	Within-day CV %: Practice A: **8-25 mg/L**: 7.7 **25-100 mg/L**:1.3 **>100 mg/L:** 0.6 **Overall**:3.4 Practice B: **8-25 mg/L**: 5.9 **25-100 mg/L**:2.0 **>100 mg/L:** - **Overall**:2.8 Practice C: **8-25 mg/L**: 11.5 **25-100 mg/L**:8.3 **>100 mg/L:** 3.0 **Overall**:6.0 Between-day CV %: Practice A: **58.7 mg/L**: 2.5 (1.9-3.6) Practice B: **58.5 mg/L**: 2.6 (2.1-3.7)
Smart Eurolyser[211]	**Low** (1.8-27,4 mg/L): -4.4% (-7.4;-1.4) **Medium** (27.5-41.1 mg/L) 5.5% (2.9;8.2) **High** (41,7-280 mg/L): 9.6% (5.6;13.5)	Within-day CV%: **Low** (1.8-27.4): 6.7% (5.4-8.9) **Medium** (27.5-41.1): 4.1%(3.4-5.4) **High** (41.7-281): 3.3% (2.7-4.4) **Overall**: 4.9 (4.3-5.7). Between-day CV%: **Low** (9.7mg/L): 7.9% **High** (75.5mg/L): 3.7%	Primary Health Centre 1: **Low** (0.3-13.5mg/L): -11.2% (-14.7;-7.8) **High** (14.3-148mg/L): -8.6%(-12.9;-4.3) **Overall:** -9.8% (-12.5;-6.9) Primary Health Centre 2: **Low** (**0.3-9.0mg/L): -**17.0% (-24.0;-9.6) **High** (**9.7-109mg/L):** -4.8% (-9.9;0.3) **Overall:** -10.3%(-15.1;-5.6)	Within-day CV: Primary Health Centre 1: **Low** (0.3-13.5mg/L): 8.3% (6.1;12.8) **High** (14.3-148mg/L): 6.7% (6.0-9,6) **Overall**: -9.8% (-12.5;-6.9) Primary Health Centre 2: **Low** (0.3-9.0mg/L): 15.4% (11.3;24.3) **High** (9.7-109mg/L): 8.6% (6.5-12.9) **Overall**: -12.1% (9.7;16.2) **Overall**: 8.0% (6.8;9.7) Between-day CV%: Primary Care centre 1

				Low (9.7mg/L): 23.1% **High** (74.5mg/L): 25.7% Primary Care Centre 2: **Low** (11.3mg/L): 25.4% **High** (79.1mg/L): 21.0%
ichroma™[209]	**Low** (0.0-13.5mg/L): 6.6% (2.8;10.4) **Medium** (13.5-56.4mg/L): 3.3% (1.0;7.6) **High** (56.6-264.6mg/L): -6.2% (-10.2;2.2) **Overall:** 0.4%(-2.2;2.9)[209]	Capillary samples within-day CV%: **Low**: 4.5(3.5-6.6) **Medium**: 3.7 (3.0-4.8) **High**:4.9 (4.0-6.4) **All**: 4.3 (3.8-5.1) Venous samples within-day CV %: **Low**: 4.8 (3.7-4.8) **Medium**: 2.9 (2.4-3.9) **High:** 4.3 (3.6-5.7) **All**: 3.9 (3.5-4.7)	NR	Within-day CV %: 5.7 - 15.0 Between-day CV%: Primary care centre 1: 24.1% Primary care centre 2:16.1%
ABX Micros 200™ [207]	NR	Within-day CV %: **<2mg/L**: 57.7 **2-25mg/L**: 3.9 **25-75mg/L**: 5.3 **75-100mg/L**: 1.4	**10-135mg/L**: -27.6% After 6 months use this decreased to -14.7% R^2: 0.81 to 0.98 for 4 practices	Within-day CV %: Initial Results: **<2mg/L**: 53.4-103.6 **2-25mg/L**: 24.6-38.4 **25-75mg/L**: 0.1-3.1 **>75mg/L**: 0.7 Six month results: 1.4 - 5.0

In terms of accuracy, SKUP set an allowable level of bias of +/- 1 mg/L or <26% from the comparison method. A total of 98% of the results for the Smart Eurolyser fulfilled this goal for accuracy, with venous EDTA samples in the hospital evaluation and with capillary samples at two primary healthcare centres. In the laboratory setting, the Smart Eurolyser exhibited a negative bias at low concentrations <30 mg/L and a positive bias at higher concentrations (all <10%); while at the POC a negative bias was seen at low and high concentrations, however it was more pronounced at lower concentrations (at low concentration bias 11.2% and 17.0% in two primary care centres) (Table 6.6). In terms of precision, the Smart Eurolyser fulfilled the quality goals for imprecision in the laboratory setting and in primary care at CRP concentrations above 3.2 mg/L. However, the mean CV was higher in the primary care setting (8%, 95% CI: 6.8-9.7) compared with the laboratory setting (4.9%, 95% CI: 4.3-5.7). The internal control material was used to assess reproducibility and was measured each day of the evaluation. In the laboratory setting, an acceptable CV was reported (CV <10%), but at the point of care the CV was between 21% and 25.7% at different concentrations in the two centres, suggesting poor reproducibility with the control material in the primary care setting. It was unclear if this poor reproducibility was due to operator error or was to do with the control material. Overall, the Smart Eurolyser had acceptable performance (except for the control material) but the performance of the device was consistently better in the laboratory setting (Table 6.6).

The ichroma™ device was tested by SKUP in 2011. Accuracy was not accessed at the point of care as the blood taken for comparison to the laboratory method did not reach the laboratory within the day of sampling. Precision was reported in both settings with acceptable within day repeatability reported in the laboratory for both capillary and venous blood samples. The internal quality control material was measured each day of the evaluation and used to measure between day variation, this was also found to be acceptable in the laboratory setting (<10%). Precision measured in forty samples from two primary care health centres resulted in a CV of 5.7% in one centre and 15.0% in the other. The between day variation measured using the quality control material resulted in unacceptable imprecision of 16% and 20% in the two primary health care centres. It was suggested that the colourless control material may not be ideal for use in the primary care setting.

The QuikRead® device was analysed by SKUP in 2001 in the laboratory using plasma samples and in three general practices using whole blood. Although the agreement was acceptable in the laboratory setting, when used at the POC, the device consistently underestimated the CRP levels compared with the reference method (<75 mg/L approx. -10%, >75 mg/L up to -20%). The authors suggested the

discrepancy was due to the use of whole blood at the point of care with no correction for haematocrit. Subsequent to this feedback, the company responded that the device would be recalibrated (3% at the lower end of the concentration range and 13% at the higher end) to correct these systematic differences. The data therefore may not be relevant to the current QuikRead® technology. In terms of precision, overall precision was considered acceptable with CV <10% in the laboratory and in two out of three general practices. One practice had a higher variation of 3% to 12%. The highest CV was with samples with CRP concentration of <25 mg/L.[206]

SKUP reported that the ABX Micros™ had acceptable levels of bias in the laboratory setting (< ± 15%), but unacceptably high levels of bias when first measured in the primary care setting (around 28% lower than reference method). Accuracy improved after six months of use to -14%, suggesting that, with practice, operators made fewer mistakes. The device had acceptable precision in the laboratory setting at CRP concentrations above 2 mg/L and at concentrations above 25 mg/L in the primary care setting. The overall precision in the primary care setting improved after six months of practice, particularly in the CRP 2-25 mg/L concentration range category. Imprecision reduced from 24% to 5% in one primary care site and from 37.8% to 2.7% in the other.

6.7 Ease of use

The ease of use of the CRP POCT devices was presented in some form in ten[25, 206, 207, 209, 211, 214, 217, 219, 224, 225] of the 18 studies. Often this was a note in the discussion without reference to the use of a validated tool to objectively measure the ease of use. In a number of the studies the operator was a trained laboratory technician rather than a healthcare professional and therefore may have a different view on ease of use of equipment. Of the ten studies included in this section, only seven used a questionnaire or other tool to obtain the information.[25, 206, 207, 209, 211, 214, 225] The information presented below is summarised in Table 6.7.

Table 6.7 Summary of the ease of use evidence for CRP POCT devices

Analyser	Pre-analytical handling time and (total time)[214]	Pre-analytical handling time and (total time with warm up, without warm up)[25]	Overall handling time	Overall liability to flaws[25]	SKUP evaluation	Practical aspect of test[214]
Semi quantitative methods						
Actim® strips	2.5 min (7.5 min)					Relatively complex pre-analytical handling, cut off at 80 mg/L.
Cleartest® strips	2.5 min (7.5 min)					Relatively complex pre-analytical handling, cut of at 80 mg/L.
Quantitative methods						
QuikRead go®	2.5 min (4 min)	30 sec (4.83 min, 4 min)		Moderate		Relatively complex pre-analytical handling, issues with cap on cuvette.
Smart Eurolyser	45 sec (5.25 min)	50 sec (5.25 min, 5.17 min)		Small	Satisfactory in terms of the manual, time factors and the operation of the device. Unsatisfactory for the control materials.	No Ht correction, integrated capillary not always easy to fill with blood
Afinion™	30 sec (4.25 min)	35 sec (8.25 min, 4.25 min)		Small		Not portable when on. Relatively often error codes due to small sample volume and sample drying out.
ichroma™	2 min (5 min)				Better suited to users with laboratory experience as the preparation of the device and the number of steps involved rated as intermediate	Relatively complex pre-analytical handling. No Ht correction
Microsemi™	30 sec (4.5 min)					CRP measurement only possible in combination with haematology parameters. Size of analyser may be issue as large and heavy.

Analyser	Pre-analytical handling time and (total time)[214]	Pre-analytical handling time and (total time with warm up, without warm up)[25]	Overall handling time	Overall liability to flaws[25]	SKUP evaluation	Practical aspect of test[214]
AQT90 FLEX®	30 sec (13.5 min)					Need venous blood sampling. Size of analyser may be issue as large and heavy.
NycoCard™ Reader II		3.33 min (7.25 min, 6.83 min)		Large		
QuikRead® 101		1.83 min (3.83 min, 3.33 min)	6 to 8 minutes in primary care setting[224]	Moderate	Overall operation was satisfactory, but training was required. May be issue with cuvette lids. Biomedical scientists found timing acceptable but the GP thought it may be too long.	
ABX Micros™					Score 3.8/4. However, may be issues with pre-analytical handling.	

6.7.1 Ease of use recoded by laboratory personnel

Browner et al. compared six quantitative POCT devices (QuikRead go®, Smart Eurolyser, Afinion™, ichroma™, Microsemi™) and two semi-quantitative methods to measure CRP. The authors carried out a practical evaluation of all the POCT devices in the laboratory setting, evaluating: the minimum amount of material required, analytical range, pre-analytical handling of the of the samples and estimated pre-analytical time, if haematocrit (Ht) correction was required, size and weight of the analyser, and whether the device also measures other analytes.[214] Details on pre-analytical handling time can be found in Table 6.7, other details on size, weight and analytical range of the devices can be found in Appendix A. The authors concluded that the Afinion™ device required the least pre-analytical handling. The Afinion™ and the Smart Eurolyser required less than a minute pre-analytical handling, while the QuikRead go®, ichroma™, Actim® and Cleartest® semi-quantitative strips required 2-3 minutes of pre-analytical handling. These six devices all use capillary blood samples. AQT90 FLEX® required no additional pre-analytical handling, but required a venous blood sample which is a disadvantage given the intended use of the equipment in the primary care setting. It was reported that a clear disadvantage of the semi-quantitative strips was the requirement that it be read after 5 minutes and that the results were time-sensitive, which may be restrictive in a busy clinical environment. The upper CRP cut-point used by the strips was 80 mg/L; this is not consistent with the cut-point of 100 mg/L identified in a number of national and European guidelines. Brouwer et al. concluded that when combining analytical performance and practical evaluation, the Afinion™ and the Smart Eurolyser were the preferred analysers for CRP POCT.

The practicality of a requirement to read the Actim® strip at exactly 5 minutes was also questioned by Evrand et al., who assessed the performance of this device in the laboratory setting.

In the study by Clouth et al.,[217] the authors used two point-of-care devices: the NycoCard™ and the Micros CRP™. No questionnaire or survey was used; rather, the authors provided a narrative account that both tests were rapid and easy to perform and required no specialist training. They also noted that both are useful for use as POCT in a range of settings including general practice.

6.7.2 Ease of use recorded by primary care personnel

Minnaard et al. compared five quantitative devices (Afinion™, NycoCard™ Reader II, Smart Eurolyser, QuikRead go® and QuikRead® 101) using a standardised questionnaire published by Geersing et al. to assess user-friendliness.[25, 232] The questionnaire was completed by 20 GPs and GP assistants who were unfamiliar with

point-of-care testing. Two main items were reported for user-friendliness: the time required for analysis (including warm-up time of the device, pre-analytical handling, analysis time, blank measurement and time needed for calibration and/or internal quality control measurements) and susceptibility to flaws (blood application on test kit flaws, buffer application flaws, test kit placement in analyser flaws and loss of material flaws). Table 6.7 reports the pre-analytical handling time as reported by Minnaard et al. as well as the total time for assay with and without a warm-up period. For most devices, the warm-up period is less than a minute and therefore adds little to the overall time; however, for the Afinion™ device it adds an additional 4 minutes to the assay time, which brings the total time to 8 minutes and 15 seconds. The warm-up time would not be a factor in every consultation and if not taken into account the total time required varies between 3 minutes and 20 seconds (QuikRead® 101) and 6 minutes and 50 seconds (NycoCard™ Reader II). In terms of susceptibility to flaws, Minnaard reported that the Afinion™ and the Smart Eurolyser were the least susceptible to flaws based on the opinion of 20 GPs and GP assistants. The Afinion™ was least susceptible to flaws in blood application, buffer application, placement in analyser and loss of material. The NycoCard™ Reader II scored poorly in each category, while the QuikRead go® and QuikRead® 101 were moderate in overall suscepibility to flaws. The Afinion™ and the Smart Eurolyser required the fewest separate actions, minimising the chance of mistakes. The conclusion from this study was that four devices (not the Smart Eurolyser) showed adequate analytical performance and agreement and that Afinion™ and the Smart Eurolyser were the easiest to operate.[25]

Verbakel et al.[225] evaluated the ease of use of the Afinion™ device by asking 10 participating physicians who performed the CRP POCT to fill out a questionnaire, consisting of a five-point Likert scale to rate seven items (device start-up, handling of the capillary, filling of the capillary, placing the capillary in the cartridge, placing the test cartridge in the test device, duration of analysis and display of results). Median scores of 4 to 5 were obtained for each item evaluated, indicating that GPs found it very user-friendly.

Seamark et al.[224] evaluated the QuikRead® device. The study was funded by an educational grant by the supplier of the QuikRead® system. Although no formal questionnaire or instrument was used to evaluate ease of use, the authors state that the QuikRead® system was quick and simple to use in a routine phlebotomy clinic and that the capillary blood method was acceptable to patients. They also commented on the time taken for the assay as being 6 and 8 minutes in a real-life situation and that there were no device failures during the testing period.

6.7.3 SKUP (Scandinavian Evaluations of Laboratory Equipment for Primary Health Care) evaluations

SKUP carried out evaluations on four point-of-care devices (ichroma™, QuikRead® 101, Smart Eurolyser and ABX Micros™ systems).[206, 207, 209, 211] In each case, a questionnaire was used that asked the end user (either biomedical scientists or GPs) to evaluate the device based on a list of criteria within four domains: (i) the information provided by the user manual, (ii) the time factors in the measurement and preparation of the test, (iii) the rating for the performance of the internal and external quality control and (iv) the rating of the operation facilities and how easy the system was to handle. Each area was graded as satisfactory, intermediate or unsatisfactory.

The smart Eurolyser was evaluated in the primary care setting by two nurses and two biomedical scientists. The manual provided with the device, time factors and the operation of the device were rated as satisfactory by the four evaluators. However, all evaluators reported having difficulties with the control material, and although acceptable precision (CV <10%) was reported in the hospital laboratory evaluation, high levels of imprecision (CV >20%) were reported in the two primary care centres. There were also three technical errors with the device reported during the evaluation.

For the ichroma™, two evaluators rated the user-friendliness of the device. According to both of the evaluators, the instrument is best suited for users with laboratory experience. The preparation of the instrument and sample as well as the number of steps involved were rated as intermediate, suggesting that these steps were not as straightforward as they could be. No invalid tests were reported during the testing.

For the QuikRead® 101 device, three evaluators rated the device: one GP and two biomedical scientists in primary care centres. The overall assessment of the QuikRead® instrument was that it was relatively easy to operate, but requires training. Some of the evaluators commented that there may be problems with putting the lid on the cuvettes. The analysis time of 2-4 minutes was acceptable to biomedical scientists but the GP commented that it may be too long.

The ABX Micros™ system was assessed in primary care by a GP, a nurse and two biomedical scientists. The questionnaire for this assessment asked about the manufacturer's training, the manual, the instrument and user's ability to operate the instrument. The device received an above-average rating for connections, reagent storage, waste disposal and operation of the device. The device scored well overall,

scoring 3.8 out of 4.0. Maintenance of the device was set as 1-2 minutes per day and five to 10 minutes per week. The authors stated that the ABX™ required a very long training time as pre-analytical errors probably contributed to bias and uncertainty in their analysis.

6.8 Discussion

A total of 18 studies evaluated the analytical performance of two semi-quantitative POCT devices and 11 quantitative POCT devices. The literature regarding the analytical performance of quantitative and semi-quantitative POCT devices varied widely in terms of the study design, reported results and the quality of evidence presented. Analytical performance was presented as a measure of accuracy and/or precision. Ten studies also include information on the ease of use of the device. There were three methodologies used in the included studies, with methods differing in the origin of the blood sample, the operator performing the test or the setting for the test (laboratory or primary care). All studies compared the CRP levels obtained when using a POCT device with those obtained using a standard laboratory technique; the most common methods of reporting accuracy were agreement from a Passing-Bablok regression, correlation from a Pearson or Spearman correlation coefficient or a mean difference from Bland-Altman plots. The most common method of reporting precision was a coefficient of variation based on measuring samples a number of times in one day (within-day CV) or measuring samples a number of times over a number of days (between-day CV).

Analytical performance refers to the ability of a laboratory assay to conform to predefined technical specifications.[233] Studies noted that there are few international guidelines that specify analytical quality requirements for CRP POCT devices. Two of the studies identified in this systematic review reported on acceptable levels of accuracy from three Scandinavian quality improvement schemes.[211, 215] Accuracy criteria used by the Norwegian EQAS scheme were noted to be as follows: good if the CRP value was +/- 8% of the target value; poor if it exceeded +/- 15%; and adequate if it was between these two values.[215] The 2013 SKUP report [211] outlined the analytical performance requirements specified by a number of bodies including the National Danish Committee for General Practice Laboratory Testing. These criteria are based on consultation with GPs in Denmark who have highlighted that they want to be able to detect a CRP decrease from 40 mg/L to 20 mg/L and to be able to detect the difference between 35 mg/L and 50 mg/L. The Danish analytical quality goals for CRP POCT in primary care (CRP >15mg/L) are: bias ≤+/- 10% and imprecision (CV) ≤10%. In Sweden, the Equalis Expert group has recommended that a maximum deviation for a single result measured in whole blood should be within +/- 15% of hospital laboratory method (as measured by five agreeing

hospitals) for CRP POCT used in primary care centres. SKUP itself considers a deviation of +/- 1 mg/L or ≤+/-26% (depending on the concentration range) acceptable for bias and a CV <10% for precision. Other studies specified criteria for accuracy as (r^2 > 0.95 and 95% confidence interval (CI) of the slope and intercept including 1.0 and 0.0, respectively). Correlation by itself is not generally recommended as a method for assessing comparability between methods and good correlation does not necessarily mean good agreement between methods, particularly when two methods are being used to measure the same analyte.[231] These differences in the assessment of analytical performance, as well as differences in the study methodology, makes direct comparison of the study data difficult.

The relevance of accuracy and precision of these devices in clinical decision-making can be seen by using the NICE guidelines for pneumonia as an example. For pneumonia guidelines, GPs are most interested in whether patients have a CRP <20 mg/L where they can prescribe no antibiotics, greater than 100 mg/L where they should prescribe antibiotics and between 20 and 99 mg/L where they should consider a delayed antibiotic. These are broad concentration categories and it could be argued that we are only interested to know if the analytical performance using CRP POCT is sufficient to ensure that the categorisation of patient samples is consistent with that can be achieved with laboratory-grade testing. Therefore, while some of the devices have poorer performance in the lower (<2 mg/L) or upper (>100 mg/L) CRP concentrations, this may not be clinically relevant for the use of these devices for patients presenting with RTIs.

There were very few studies (n=2) that evaluated semi-quantitative devices, the agreement between the reference test and the POCT was found to be moderate to good with Kappa values of 0.53 to 0.93 for the Actim® test[214, 219] and moderate for the Cleartest® (Kappa values 0.56 to 0.61).[214] The inter-observer variation was lower for the Actim® test than the Cleartest® (Table 6.3). There was also evidence from one study that the test was time-dependant and that accuracy decreased between reading the results at the optimal five minutes compared to 15 minutes.[214] The time critical nature of these semi-quantitative tests may not be ideal in a busy clinic environment where it may be difficult to read a test at exactly 5 minutes. Both of the semi-quantitative tests were found to have complex pre-analytical handling and were difficult to interpret.[214] The main advantage of the strips was said to be the cost as no analyser was needed and the main disadvantages were the difficult pre-analytical handling, the accuracy, the time-critical nature of the strips and that the results are not automatically entered into the patient record. In addition, the semi-quantitative tests included here (Actim® and Cleartest®) have an upper limit of 80mg/L and are therefore of limited use in terms of a number of current guidelines

for managing LRTIs where a cut-point of 100 mg/L is recommended for antibiotic prescribing.

In the laboratory setting, the majority of the evidence suggested acceptable performance for all 11 quantitative devices. In comparison to a standard laboratory technique, the accuracy data showed that most devices had acceptable levels of accuracy except at the higher end of CRP concentration levels (CRP > 100 mg/L). Although precision was also acceptable for most devices, CV values greater than 10% were reported in the laboratory setting in at least one study for the Smart Eurolyser, the NycoCard™ Reader II and the ichroma™ devices. This suggests that under idealised circumstances most of the devices are accurate and precise.

When used at the point of care (that is, the primary care setting), the data available for accuracy and precision were far more variable. In terms of accuracy, the Afinion™ (n=2) and the ichroma™ (n=1) devices both reported levels of bias < 10%. Bias was variable or not available for the other devices. Very little data were available on precision in the primary care setting. Acceptable precision was reported for the QuikRead® 101 and the spinit® devices, while the Smart Eurolyser and the ichroma™ devices had inconsistent results. The lack of data at the point of care and the variable results makes it difficult to draw conclusions about the suitability of many of these devices for the primary care setting.

All data on the difference in analytical performance of the devices in the laboratory setting compared to the primary care setting came from four SKUP reports.[206, 207, 209, 211] Four devices were analysed. The Smart Eurolyser had acceptable accuracy and precision in the laboratory and at the POC, but it had better performance in the laboratory. The other devices (ABX Micros™, ichroma™ and QuikRead®) had acceptable levels of precision and accuracy in the laboratory but unacceptable levels of either precision or accuracy in at least one primary care centre. Based on the SKUP data, it appears that all four devices had acceptable analytical performance in the laboratory setting, but performance was more variable and poorer at the point of care. This may have been caused by the type of material used in the analysis (whole blood versus plasma), the method of blood extraction (capillary versus venous sample) or related to the skill, experience or training of the operator (non-laboratory trained personnel versus trained laboratory technician) or the level of training received by the operator. There was evidence that analytical performance varied between primary care sites and improved over time, suggesting that thorough and ongoing training is necessary when using CRP POCT devices in the primary care setting. The difference in analytical performance was larger for some devices than others.

Four of the studies provided a direct comparison of multiple devices either in the laboratory or point-of-care setting,[25, 214, 215, 222] Minnaard et al. and Brouwer et al. compared multiple devices in the laboratory setting. The Afinion™ device was consistently found to be a preferred device based on analytical performance and ease of use both in the laboratory [25, 214] and at the point of care.[215] Consistent evidence of acceptable analytical performance was also found for the QuikRead go® and QuikRead® 101 devices both in the laboratory [25, 214] and at the POC [215] and for the NycoCard™ device.[25, 222] Evidence for the Smart Eurolyser device were conflicted, with findings of unacceptably high imprecision[25] and that it was a preferred analyser.[214] The ichroma™ device was reported by Brouwer et al. to be the poorest in terms of accuracy and precision in the laboratory setting, while Bukve et al. reported the accuracy of the ichroma to be similar to the NycoCard™, but poorer than the Afinion™ or QuikRead® systems.[214, 215]

Devices with less pre-analytical handling and that are designed in a way that they are less susceptible to flaws tend to be easier to use. Complex pre-analytical handling might introduce variation if the test is not performed on a regular basis, can lead to spills of biological materials, test errors and the use of more than one set of consumables if the test fails.[214] The overall time taken for the test to be performed was an important factor, with times ranging from just over 3 minutes (QuikRead®) to over 13 mins (AQT90 FLEX®), but it is unclear from the literature what time period would be considered acceptable in the primary care setting. Two studies comparing multiple devices and reporting on ease of use found the Afinion™ and the Smart Eurolyser to be the easiest to use.[25, 214]

On the basis of these findings, it would appear that most of the devices could be used in the primary care setting, but training would need to be put in place to ensure healthcare personnel who are likely to use the device in practice are thoroughly trained. In addition, an external quality assurance scheme would need to be established to ensure adequate levels of accuracy and precision are being maintained over time. Bukve et al. presented the results of the Norwegian EQAS scheme from 2006 to 2015 and reported that: participating in the EQAS scheme more than once, performing internal quality control at least weekly, the type of instrument used, having laboratory-qualified personnel performing the tests and performing more than 10 C-reactive protein tests per week were associated with good test performance. Core to a quality assurance scheme is the use of predefined levels for accuracy and precision so that those using CRP POCT in primary care can be assured that test results have an acceptable level of analytical performance.

One of the limitations of any study of this type is selecting a suitable reference test. All included studies used an established laboratory method in a hospital setting as

their reference standard, and although some studies reported details of the accuracy and precision of the device used, many provided no information beyond the name of the instrument. SKUP reports used the average of more than one reference standard, which should provide a more reliable reference standard assuming the two methods are in agreement. In addition, the devices can be updated and improved and therefore some of the data included in this review may refer to the analytical performance of a device that has since been improved by the manufacturer on the basis of user feedback.

The risk of bias analysis raised certain concerns regarding the available evidence. Of particular importance were the potential for a lack of blinding, unclear time lag between sample collection and analysis, and the applicability of the patient population to the primary care setting, which is of interest here. It is not clear whether these potential sources of bias would make the analytical performance of the CRP POCT appear more or less favourable relative to its true performance. The potential for conflict of interest through industry funding was also noted, although only four of the 18 studies reported industry support. A substantial proportion of the evidence presented here was obtained from two studies, neither of which was industry supported.

6.9 Key messages

- Eighteen studies were identified that provided analytical performance information on 11 quantitative devices. The included studies were generally found to be at high risk of bias in a number of domains.
- Two studies evaluated semi-quantitative devices. The agreement between the reference test and the POC test was found to be moderate to good. The accuracy of the test was shown to decrease after the optimal five minutes. Due to the upper limit of 80mg/L, the semi-quantitative tests included may be of limited use in terms of current guidelines for antibiotic prescribing that use a cut-point of ≥100 mg/L for immediate antibiotic prescribing.
- The majority of the evidence suggested acceptable performance for all 11 quantitative devices in the laboratory setting. Most of devices had a mean difference of <10 mg/L or <10% bias except at concentrations above 100 mg/L. Precision was also acceptable in the laboratory for six of the devices, suggesting that under idealised circumstances in the laboratory most of the devices are accurate and precise.
- When used at the point of care, the results of accuracy and precision of the devices were more variable. Bias in accuracy was <5% for one device (Afinion™), <15% for three others (NycoCard™, the QuikRead go®, and the

ichroma™), and more variable for QuikRead® and the Smart Eurolyser. Very little data were available on precision at the point of care.

- Four studies compared multiple devices and provide a direct comparison of the devices. While most devices showed acceptable performance in the laboratory setting, only some were considered suitable for POC testing.
- Four studies examined analytical performance of the devices in the laboratory setting and the primary care setting. All four devices had acceptable accuracy and precision in the laboratory, while only one had reliably acceptable performance at the point of care. Accuracy and precision are negatively impacted when the device is used at the point of care by non-laboratory trained healthcare professionals.
- Devices that are easier to use tend to have less pre-analytical handling and are designed in a way that they are less susceptible to flaws. The overall time taken for the test to be performed was an important factor in ease of use, with times ranging from just over 3 minutes to over 13 minutes.
- Participating in an external quality assurance scheme more than once, performing internal quality control at least weekly, the type of instrument used, having laboratory-qualified personnel performing the tests and performing more than ten CRP tests per week were all associated with good test performance.

7 Systematic review of economic evaluations

This chapter reviews previously published cost-effectiveness analyses (CEAs) of the use of C-reactive protein (CRP) point-of-care testing (POCT) to guide antimicrobial prescribing in the community for acute respiratory tract infections (RTIs).

7.1 Search strategy

A systematic review was undertaken to summarise the available cost-effectiveness evidence of CRP POCT to guide antimicrobial prescribing, and to assess the applicability of the results to inform cost-effectiveness in an Irish health and social care setting.

Electronic searches of Medline, EMBASE, EBSCOhost, and the Cochrane Register of Controlled Trials were performed, with no restriction imposed on the date of publication. The search was restricted to published manuscripts and humans (search strings presented in Appendix T). A grey literature search was also conducted via Google Scholar, and national and HTA electronic sources (see Appendix T). Scopus was searched to identify any relevant papers that were not captured by the electronic and grey literature search. The review followed national guidelines for the retrieval and interpretation of economic literature.[234]

The PICOS criteria (Population, Intervention, Comparator, Outcomes, and Study design) used for the systematic review are shown in Table 7.1.

Table 7.1 Inclusion criteria for review of cost-effectiveness studies

Population	Patients of all ages presenting with symptoms suggestive of acute respiratory illness (RTI) in primary care settings for whom the aetiology (viral or bacterial) is uncertain. Specific subgroups of interest include: patients attending out-of-hours (OOH) services and those in long-term care (LTC) facilities.
Intervention	CRP POCT in primary care (+/- communication training, +/- other biomarkers).
Comparator	Usual care (that is, clinical judgment).
Outcomes	Any measure of costs and benefits (e.g., utilities, or relevant health outcome).
Study Designs	Economic evaluations (cost-effectiveness, cost-utility, cost-benefit, cost-minimisation), partial economic evaluations (cost analysis, cost-of-illness), and decision analysis studies.

All titles and abstracts retrieved by electronic searching were downloaded and stored

in EndNote reference manager (Version X7). Citations were independently screened by two reviewers, as per the inclusion/exclusion criteria. Any references obtained by hand searching were added to the database; duplicates were removed. Data extraction using standardised data extraction forms were performed independently by two people, with disagreements resolved by discussion.

The quality of the studies was assessed using the Consensus on Health Economic Criteria (CHEC) list[235] and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) questionnaire.[236] The CHEC list assesses the methodological quality of economic evaluations in a systematic review, and the ISPOR questionnaire assesses the relevance and credibility of modelling studies.

7.2 Results

Details of the search process are presented in Figure 7.1. Seven hundred and eighty-five records were obtained, after 46 duplicates were removed. Ten studies were assessed for eligibility, of which five relevant studies were identified and included in the systematic review.

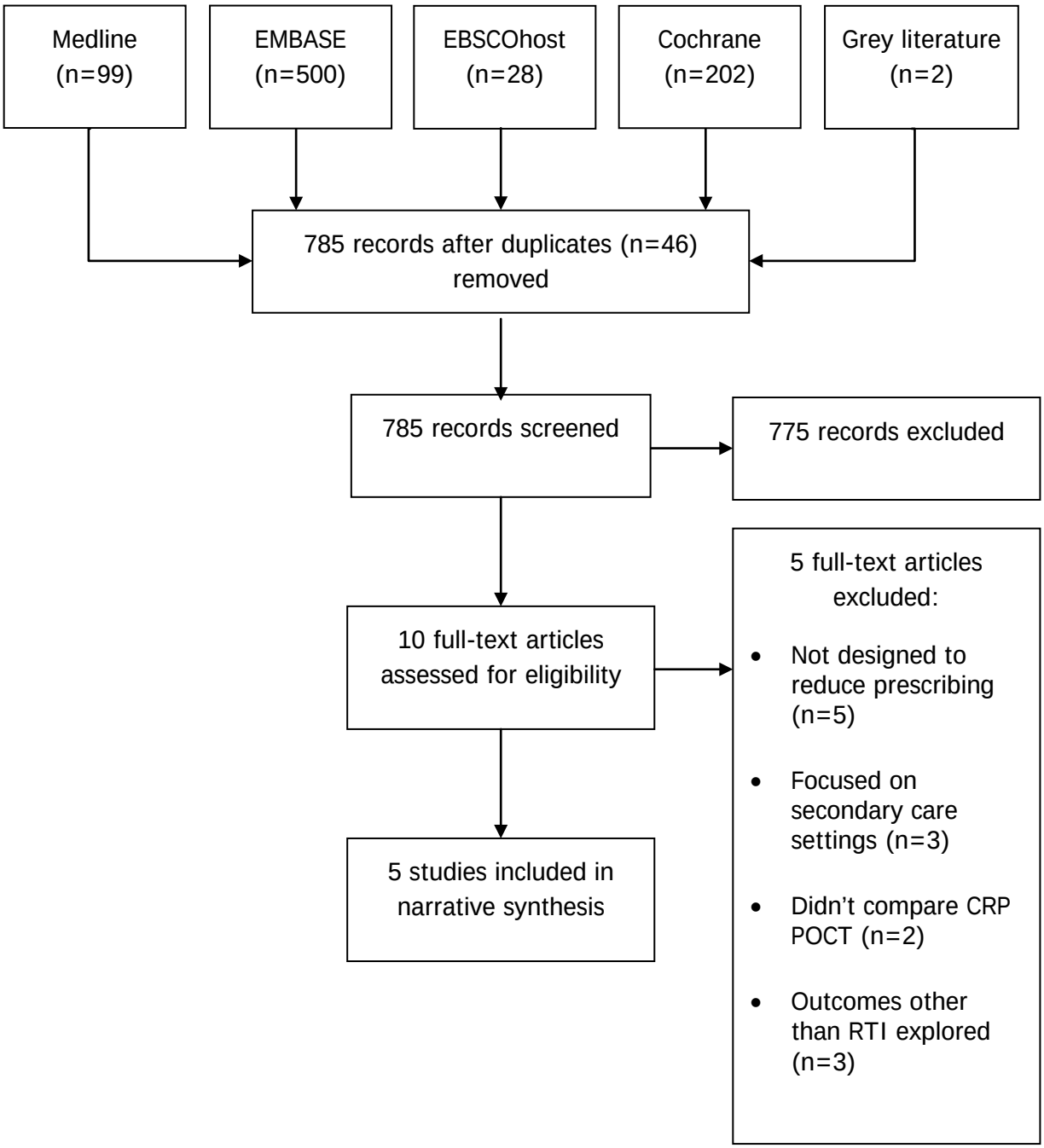
7.2.1 Overview of studies

The systematic review identified five relevant studies (Table 7.2).[237-241] Three of the studies were trial-based economic evaluations [237, 240, 241] and two were model-based.[238, 239] None of the studies considered the cost-effectiveness of CRP POCT in an Irish setting. A detailed description of each study is provided below. In each case, original costs are reported; Irish-equivalent 2018 prices, adjusted for inflation and purchasing power parity, are reported in parentheses. Further details of the studies can also be found in Appendix U.

A 2011 cost-effectiveness analysis by Cals et al.[237] in the Netherlands compared three interventions against usual care (clinical judgment) in adults aged 18 or older presenting to primary care with acute cough or assumed lower respiratory tract infection (LRTI):

- GP use of CRP POCT
- GP communication training
- GP use of CRP POCT plus communication training.

Figure 7.1 Flow chart: studies identified and included in the review of cost-effectiveness studies



The economic evaluation was conducted alongside a factorial, cluster, randomised trial and assumed a 28-day time horizon to model costs and consequences, from the perspective of the health system. Costs included direct healthcare costs and intervention costs. The CEA reported the incremental cost per percentage reduction in antibiotic prescribing at index consultation using incremental cost-effectiveness ratios (ICERs). The trial found antibiotic prescribing was lowest (23%) in the combined intervention arm (CRP POCT plus communication training); communication training only and CRP POCT only had higher prescribing at 33% and 39%, respectively, while usual care had the highest level of prescribing at 68%.

Table 7.2 Economic studies included in the systematic review

Study	Design	Population	Intervention(s)
Cals et al. (2011); Netherlands	CEA	Adults aged 18+ with acute cough/assumed LRTI	▪ GP plus CRP ▪ GP communication training ▪ GP plus CRP + GP communication training ▪ usual care (clinical judgment)
Oppong et al. (2013); Norway and Sweden	CEA and CUA	Adults aged 18+ with acute cough/assumed LRTI	▪ GP plus CRP POCT ▪ no CRP point-of-care test (clinical judgment)
NICE (2014); UK	CUA	Adults aged 18+ with LRTI	▪ GP plus CRP POCT ▪ no CRP point-of-care test (clinical judgment)
Hunter (2015); UK	CUA	Hypothetical cohort of 100 patients (aged 50, 62% female) with assumed RTI	▪ GP plus CRP ▪ nurse plus CRP ▪ GP plus CRP + communication training ▪ usual care (clinical judgment)
Oppong et al. (2018); Europe (Belgium, Netherlands, Poland, Spain, UK)	CEA and CUA	Patients with assumed RTI (age not specified)	▪ GP CRP ▪ GP communication training ▪ GP CRP + GP communication training ▪ usual care (clinical judgment)

Key: CEA – cost-effectiveness analysis; CRP POCT – C-reactive protein point-of-care testing; CUA – cost-utility analysis; LRTI – lower respiratory tract infection.

Communication training proved dominant due to lower average costs per patient and lower antibiotic prescribing compared with usual care. The additional cost associated with a CRP test meant CRP POCT was associated with an ICER of €5.79 (€7.76) per percentage reduction in antibiotic prescribing, while the combined intervention had

an ICER of €4.15 (€5.56). In an exploratory analysis, Cals et al. compared the intervention with the greatest effect (CRP POCT plus communication training) against the dominant intervention (communication training), and found the combined intervention cost €121.70 (€163.10) per percentage reduction in antibiotic prescribing. To more broadly consider the implementation costs associated with the introduction of CRP POCT, the authors doubled staff costs in the intervention arms in a scenario analysis and found similar results. Varying levels of adoption of CRP POCT by GPs were considered in other scenarios; here, the interventions were cost-effective if society was willing to pay up to €150 (€201) per percentage reduction in antibiotic prescribing.

In 2013, Oppong et al.[240] compared the cost-effectiveness of CRP POCT by GPs against no CRP POCT (clinical judgment) in adults aged 18 or older with acute cough or assumed lower respiratory tract infection (LRTI) in Norway and Sweden. The economic evaluation was conducted alongside a prospective observational study, which was developed by the Genomics to combat Resistance against Antibiotics in Community-acquired lower respiratory tract infections in Europe (GRACE) consortium. Both a cost-utility analysis (CUA) (using cost per quality-adjusted life year (QALY) gained) and CEA (using cost per prescription avoided) were undertaken from the perspective of the health system with a 28-day time horizon assumed. The observational study collected information on resource use, quality of life (using EQ-5D), and antibiotic prescribing. Although non-significant differences in costs, QALYs, and antibiotic prescribing were observed, Oppong et al. reported CRP POCT cost an additional €11.27 (€13.00) and generated 0.0012 more QALYs compared with no testing, and was associated with a 10% reduction in antibiotic prescribing. The ICER was €9,391 (€10,828) per QALY gained, and the cost per prescription avoided was €112.70 (€129.96). At €30,000 willingness-to-pay, CRP POCT had an incremental net monetary benefit (INMB) of €25.20 (€29.06) versus no testing and a 70% probability of being most cost-effective. Oppong et al. concluded CRP POCT was likely cost-effective, both in terms of reducing antibiotic prescribing and improving QALYs gained. No sensitivity or scenario analyses were undertaken.

In 2014, the National Institute for Health and Care Excellence (NICE) developed a guideline for the diagnosis and management of community-acquired pneumonia in the UK.[239] The guideline crudely compared the costs and consequences of CRP POCT by GPs against usual care (clinical judgment) in patients with suspected LRTI, from the perspective of the National Health Service (NHS) in the UK. Although not stated in the guideline, a 28-day time horizon was likely assumed. The model considered direct healthcare costs, intervention costs, and hospital admission costs and compared these against expected QALY gains. The guideline found CRP POCT cost £35.14 (€39.84) per patient, while usual care cost £16.14 (€18.40) per patient.

With an expected incremental cost of £18.92 (€21.44) and QALY gain of 0.0012, derived from Oppong et al.,[240] CRP POCT generated an ICER of £15,763 (€17,865) per QALY gained versus usual care. NICE concluded that CRP POCT was likely cost-effective as the ICER fell below the commonly accepted willingness-to-pay threshold of £20,000 per QALY gained in the UK. However, NICE acknowledged large-scale implementation would be expensive and could outweigh the benefits of reduced antibiotic prescribing. The guideline ultimately concluded that CRP POCT should be 'considered' in the UK. No sensitivity or scenario analyses were undertaken.

In 2015, Hunter[238] compared three CRP POCT strategies against usual care (clinical judgment) in the UK using a decision-analytic model and CUA:

- GP use of CRP POCT
- Nurse use of CRP POCT
- GP use of CRP POCT plus communication training.

Hunter used a decision tree and Markov model to model illness progression in a hypothetical cohort of 100 adults presenting to primary care with an assumed RTI. A UK NHS perspective was assumed and a three-year time horizon was adopted in the base case analysis. Future costs and consequences were discounted at 3.5% per annum, as per NICE guidance.[242] Hunter included direct healthcare costs, intervention costs, and hospital admission costs in the analysis. Health outcomes were measured using QALYs. Net monetary benefit (NMB) was used to rank the cost-effectiveness of the different strategies at the commonly used willingness-to-pay threshold of £20,000 per QALY gained in the UK. GP/nurse use of CRP POCT generated lower costs and higher QALY gains compared with usual care, although the differences were largely marginal. Across 100 patients, for example, GP use of CRP POCT saved £42 (€45.87) and generated 0.13 more QALYs than usual care. In terms of NMB, the differences were similarly marginal: the NMB of GP and nurse use of CRP POCT was £50,972 (€55,670) and £50,978 (€55,676), respectively, while the NMB of usual care was £50,945 (€55,640). GP use of CRP POCT plus communication training cost more and generated fewer QALYs compared with usual care. At £50,933 (€55,627), the strategy had the lowest NMB. Probabilistic sensitivity analysis and one-way sensitivity analyses were undertaken to assess parameter uncertainty. The results remained broadly unchanged in these analyses, with each strategy returning a positive NMB. Hunter also extended the time horizon in a structural sensitivity analysis, modelling costs and consequences over nine years, and found similar results. Hunter concluded that although differences in NMB were minimal, CRP POCT led to fewer antibiotic prescriptions and infections than usual care over three years.

A recent study by Oppong et al.[241] in 2018 considered the cost-effectiveness of similar CRP POCT interventions in patients with assumed RTI in five European countries (Belgium, the Netherlands, Poland, Spain and the UK). Versus usual care (clinical judgment), the study compared:

- GP use of CRP POCT
- GP communication training (internet-based)
- GP use of CRP POCT plus communication training (internet-based).

The economic evaluation was conducted alongside a multinational, cluster, randomised, factorial controlled trial (GRACE INTRO trial, which was developed by the GRACE consortium). Both a CUA (using cost per QALY gained) and CEA (using cost per percentage reduction in antibiotic prescribing) were undertaken from the perspective of the health system, with costs and consequences evaluated over a 28-day time horizon. Direct staff/service costs, including hospital admission costs, and medical investigation/intervention costs were considered, along with the cost of antibiotic resistance in the CUA. The cost of antibiotic resistance was excluded from the CEA as it assumed that it is indirectly captured via any difference in antibiotic costs due to changes in the spectrum of antibiotics prescribed. Although dominated by communication training, CRP POCT dominated usual care due to lower costs and higher QALY gains. The combined intervention was dominated by usual care due to higher costs and lower QALY gains. Some variation in findings was observed across countries. In Belgium, the UK and the Netherlands, communication training was most cost-effective; in Poland, CRP POCT was most cost-effective; and in Spain, usual care was most cost-effective. Considerable uncertainty in costs and QALYs was observed, however this was not discussed in the paper. When the cost of antibiotic resistance was excluded in a sensitivity analysis, Oppong et al. found usual care was cost-effective overall.

The CEA showed that usual care was the least costly, but also the least effective in reducing antibiotic prescribing. The comparator had the highest level of prescribing at 59.6%, while CRP POCT had the lowest level at 33.6%. The combined intervention and communication training had slightly higher prescribing at 34.1% and 40.9%, respectively. Versus usual care, communication training had an ICER of €68.80 per percentage reduction in antibiotic prescribing. Comparing CRP POCT with communication training, the ICER was €176.54 per percentage reduction in antibiotic prescribing, while the ICER for the combined CRP and communication training intervention compared with CRP POCT was €338.89. Versus usual care, the ICERs ranged from €68.80 for communication training to €126.21 for the combined intervention per percentage reduction in antibiotic prescribing. Country-specific estimates showed CRP POCT was most cost-effective in Belgium and the

Netherlands (if society was willing to pay up to €73 per percentage reduction in antibiotic prescribing). In Poland, Spain and the UK, communication training was most cost-effective.

7.2.2 Quality of included studies

A quality assessment of each study included in the review was undertaken using the CHEC list.[235] The list identifies a set of items against which the methodological quality of economic evaluations included in a systematic review is assessed. In particular, the items assess the research question, study design, patient population, perspective and time horizon, measurement and valuation of costs and outcomes, analysis and sensitivity analyses, reporting, and transparency. Overall, the studies were well designed with similarly well-defined patient populations. A health system perspective was commonly and appropriately assumed, however the time horizons were particularly short, limited to 28 days, with the exception of Hunter who modelled costs and consequences over three years. With the exception of the study by Cals et al.,[237] QALYs were used as a measure of health gain, despite the limited ability of a 28-day time horizon to allow for meaningful differences in quality of life to emerge. Across each study, reporting was generally good, but often no sensitivity or scenario analyses were undertaken. There were no obvious issues with transparency; Hunter[238] was funded by CRP device manufacturer Alere, but used published data on effectiveness to inform the analysis, suggesting there were no obvious conflicts of interest.

In addition to the CHEC list, the ISPOR questionnaire on relevance and credibility was used to assess the two model-based economic evaluations[238, 239] included in the systematic review.[236] Relevance was assessed on the grounds of the study population, characteristics of the intervention, outcomes measured and the overall study context. The credibility of the results was considered using criteria related to the design, validation and analysis methods, the quality of the data used, as well as how the results were reported and interpreted, and whether the authors had any conflicts of interest. The paper by Hunter[238] was broadly relevant to Ireland, but concerns about credibility were identified. With the exception of the nurse use of CRP POCT intervention, the comparators were relevant to an Irish setting. The decision-analytic model, which was based on a previous model developed by NICE,[62] was suitably constructed and sufficient analyses and sensitivity analyses were undertaken. However, reporting was often poor, and little consideration was given to the extent of the uncertainty in costs and QALYs, which was evident in the plotted cost-effectiveness plane. Hunter used NMB to rank the available options, but did not report credible or confidence intervals, despite undertaking a probabilistic sensitivity analysis. The conclusions drawn by Hunter were therefore likely overstated, as there was likely no significant difference in NMB across the different

strategies. Assessment of the analysis undertaken by NICE[239] was difficult, as it served only to provide a crude comparison of the expected costs and consequences of CRP POCT versus no testing (clinical judgment). Reporting was poor, and the analysis was limited to a direct incremental comparison of costs and QALYs (that is, no sensitivity or scenario analyses were undertaken).

7.2.3 Applicability of the evidence

The systematic review was undertaken with a view to assessing the available evidence on cost-effectiveness and its applicability to an Irish setting. A number of issues with respect to applicability emerged. These related to the:

- generalisability of data on the frequency of antibiotic prescribing
- use of CUA in the context of RTIs
- uncertainty around the appropriate time horizon
- relevance of the strategies to Ireland
- applied discount rate.

These issues are discussed separately below.

It is difficult to determine whether the prescribing patterns reported in the included studies are generalisable to Ireland. The parameter on antibiotic prescribing by clinical judgment alone (that is, usual care) is a key parameter in considering the cost-effectiveness of CRP POCT. The included studies in the review informed the parameter using information from an alongside clinical trial[237, 240, 241] or previously published clinical trials.[238, 239] As none of the clinical trials were conducted in Ireland, the findings have poor applicability to an Irish setting due to differences in rates of antibiotic prescribing. One study found 62% of respiratory visits to a GP in Ireland resulted in an antibiotic prescription being issued, with 54% issued at index consultation.[70] This is similar to the rate of antibiotic prescribing reported by NICE (53%), but smaller than the rate reported by Hunter (59%). It is also smaller than the rate reported by Cals et al. (67%). The rate of antibiotic prescribing at index consultation was not reported in the 2013 paper by Oppong et al.; the 2018 paper reported overall antibiotic prescribing was 59%, which was smaller than the overall rate reported in Ireland.

In addition to the potential differences in the rate of antibiotic prescribing at index consultation between these settings, the time lag from when the trials were conducted must also be considered. Whether the rate of prescribing observed in these trials, many of which were conducted before 2010, reflects current prescribing practices is unclear. Antibiotic prescribing and consumption patterns are changing in Europe, likely influenced by the increasing awareness of the threat posed by

antibiotic consumption on antimicrobial resistance. Between 2012 and 2016, significant downward trends in antibiotic consumption in the community were observed in Sweden and Norway.[243] Consumption was also trending downwards in the UK and Netherlands, while an overall upward trend was observed in Ireland.[243] It should be noted that total antibiotic use in the community in Ireland has followed a downward trend since a peak in 2015.[59] In considering the potential cost-effectiveness of CRP POCT in Ireland, it is important that up-to-date Irish data on prescribing practices are used, where possible.

A CUA was often used to determine cost-effectiveness. Measuring health outcomes using QALYs is problematic in the context of RTIs, which are transitory, whether an antibiotic is consumed or not. In addition, there is no evidence that the use of CRP POCT improves quality of life over usual care. Oppong et al.[240] reported a non-significant QALY gain of 0.0012 in favour of CRP POCT. The more recent 2018 paper by Oppong et al.[241] also reported QALYs and, although significance was not reported, found broadly comparable estimates, suggesting QALYs do not differ based on whether a CRP point-of-care test is used. The use of a CUA in this context is therefore limited. A CEA using cost per prescription avoided or cost per percentage reduction in antibiotic prescribing is more applicable.

The few studies that conducted a CEA may, however, have been limited by the length of follow-up assumed. Cals et al.[237] and Oppong et al.[240, 241] each conducted a CEA but assumed a 28-day time horizon, which may be insufficiently long to reflect antibiotic prescribing for subsequent RTI episodes. Cals et al.[159] reported follow-up data over 3.5 years and found antibiotic prescribing for subsequent RTI episodes varied by intervention, but not significantly. Variation in antibiotic prescribing by interventions at both index and subsequent consultations may be important in determining overall cost-effectiveness; however, there is limited evidence to suggest prescribing behavior differs by intervention over time. Hunter[238] assumed a three-year time horizon to incorporate these data, despite the lack of significant findings on follow-up prescribing.

The study undertaken by Hunter[238] is most relevant to this HTA. Consistent with the objective of this economic model, Hunter compared the costs and consequences of different CRP POCT strategies with usual care in patients presenting to primary care with an assumed RTI. Hunter developed a decision-analytic model, synthesised data, and assumed a health system perspective. However, Hunter conducted a CUA and used prescribing data which are poorly generalisable to an Irish setting. Additionally, Hunter considered a strategy in which a nurse conducts the CRP test and issues a prescription. This is problematic in Ireland as nurse prescribing is sparse; as of 2016, there were 894 nurses/midwives registered to prescribe.[244]

Whether any of these nurses are registered at a primary care practice is unknown. It is also unclear whether prescribing for RTIs by nurses is supported in Ireland. To consider this as a strategy in Ireland would involve training many practice nurses to become registered prescribers, which would be costly, time-consuming, and ultimately impractical given the time pressure to implement CRP POCT. Lastly, as the analysis was undertaken from a UK perspective, Hunter followed UK guidelines and discounted future costs and consequences at 3.5% per annum.[242] In Ireland, costs and consequences are discounted at 5%.[245] The results from Hunter would therefore be overstated in an Irish context.

Since conducting the systematic review, a further economic analysis of CRP POCT was published. In Wales, Holmes et al. performed a CUA and CEA of the use of CRP POCT to guide anitibiotic prescribing in patients presenting to primary care with symptoms of acute RTI.[246] The authors evaluated both the pragmatic use of CRP POCT compared to clinical judgement, using evidence from a general practice that installed a device over a three-month period, and the use of CRP POCT as outlined in clinical guidelines in Wales. In both scenarios, the incremental cost per QALY gained (CUA) and prescription avoided (CEA) was calculated using a decision-analytic model. Holmes et al. found that pragmatic use of CRP POCT cost £19,705 per QALY gained and £16.07 per antibiotic prescription avoided. However, if the device was used according to clinical guidelines, CRP POCT costs considerably less per QALY gained (£4,390) and prescription avoided (£9.32), as greater reductions in anitibiotic prescribing were outlined in the Welsh guidelines than were observed in practice. Although a CEA was undertaken, the economic analysis had similar applicability issues to Ireland as the other studies reviewed in this chapter. For instance, the model was conducted over a short time horizon (28 days) and it was difficult to generalise the prescribing data to Ireland. One further issue associated with the study, as with previous economic analyses, was that it did not evaluate the cost-effectiveness of implementing a CRP POCT programme, which was a primary aim of this HTA.

7.3 Discussion

Few studies have been conducted on the cost-effectiveness of CRP POCT to guide antimicrobial prescribing in the community for RTIs, none of which were conducted in Ireland. Although the studies were generally of good quality, they were not applicable to an Irish setting. Above all, the studies used data that were poorly generalisable to an Irish setting, particularly prescribing data. In considering the potential cost-effectiveness of CRP POCT in Ireland, it was important to include up-to-date Irish data, where possible. Many of the studies modelled outcomes using QALYs, despite the transient nature of an RTI and lack of evidence that QALYs differ

across interventions. A CEA rather than CUA may be more applicable. The available evidence was therefore insufficient in determining cost-effectiveness in Ireland.

7.4 Key messages

- A systematic review was undertaken to identify studies estimating the cost-effectiveness of CRP POCT in a primary care setting. Five studies were found: four cost-utility analyses and one cost-effectiveness analysis.
- All five studies included an intervention of usual care based on clinical judgment and clinical judgment supported by CRP POCT. Three included an intervention combining CRP POCT with intensive communication training for GPs.
- In terms of cost-utility, CRP POCT was found to be a cost-effective alternative to clinical judgment alone.
- Overall, the studies were well designed with similarly well-defined patient populations, although reporting was often poor and little consideration was given to the extent of the uncertainty in costs and QALYs.
- The applicability of the identified studies to Ireland was limited due to a number of factors, including: the generalisability of data on the frequency of antibiotic prescribing; relevance of the utility data; uncertainty around the appropriate time horizon; and the discount rate used.

8 Economic evaluation

This chapter sets out an economic evaluation of a national CRP POCT programme in primary care in Ireland. Details of the model structure and parameter inputs used to evaluate CRP POCT in Ireland are presented along with the results of a cost-effectiveness analysis specific to an Irish population. A detailed budget impact analysis that estimated the total cost of implementing CRP POCT in Ireland was also undertaken and is reported in this chapter.

8.1 Health-economic analysis

In the absence of applicable published cost-effectiveness evidence from another setting, an economic analysis specific to Ireland was undertaken. This section details the methods used to evaluate cost-effectiveness in an Irish setting and presents the findings from the research. A budget impact analysis was also undertaken, as detailed here.

8.1.1 Study objective

The purpose of this HTA, in particular the economic analysis, was to examine the cost-effectiveness of CRP POCT to guide antimicrobial prescribing in the community for acute RTIs in Ireland and investigate the total budget impact of implementing CRP POCT.

8.1.2 Type of economic evaluation

A cost-effectiveness analysis (CEA) was carried out to estimate the incremental cost per prescription avoided for a range of strategies compared with usual care (clinical judgment). A cost-utility analysis (CUA) was not undertaken given the transient nature of RTIs and limited evidence that QALYs differ across any of the strategies. A decision-analytic model was developed to model the probability that antibiotics would be prescribed and subsequently consumed, or redeemed.

8.1.3 Target population and setting

The model considered outcomes for the Irish population; specifically, patients presenting to general practice with an acute RTI. Restricting the use of CRP to consultations involving adults aged 15 years or older was considered in a sensitivity analysis.

8.1.4 Study perspective, time horizon and discount rate

In line with national guidelines,[245] the CEA was undertaken from the perspective of the publicly funded health and social care system. Hence, only direct medical costs

were considered in the analysis. Indirect costs, such as the cost of lost productivity owing to illness or out-of-pocket costs borne by the patient, for instance, were not considered as these costs are consistent with a broader perspective. The model assumed a five-year time horizon in the base case analysis to project future costs that could be modelled in the budget impact analysis.[159] A cycle length of one year was assumed, with the probability of prescribing modelled over 28 days to capture known outcomes arising from index consultation and associated healthcare costs. A discount rate of 5% was applied to future costs and benefits in the base case analysis, as per Irish guidelines.[245] Lower and higher discount rates were applied in sensitivity analyses.

8.1.5 Technology

Chapter 2 provides a detailed description of the intervention. Briefly, CRP is a biomarker of infection that activates during tissue injury or infection. Levels of CRP are typically low (<20 mg/L), but rise rapidly in response to tissue damage. CRP levels greater than 20 mg/L may be indicative of a bacterial infection, for which antibiotics are effective and may be prescribed. Devices have been manufactured to measure CRP levels and provide rapid diagnostic information on the presence of viral versus bacterial infection. The device is designed to be used at the point of care (that is, during consultation). By providing rapid diagnostic information on viral versus bacterial infection, the device has the potential to address, and ultimately reduce, inappropriate antimicrobial prescribing, particularly in the community where antibiotic prescribing is highest. The CRP POC test, as used in the community, is the focus of this HTA.

8.1.6 Choice of comparators

Consistent with the objectives of the HTA, the economic analysis compared two CRP POCT strategies against usual care:

1. GP use of CRP POCT (GP CRP)
2. GP use of CRP POCT plus enhanced communication skills training (GP CRP + comm)

Enhanced communication training here refers to a bespoke training module designed to support GPs in their communication with patients on the most appropriate use of antibiotics in patients with acute RTIs the community.[158]

8.1.7 Model structure

A de novo decision-analytic model was developed to investigate cost-effectiveness. The model comprised a decision tree that simulated the probability that antibiotics

would be prescribed and subsequently consumed, or redeemed. The model did not simulate the risk of subsequent RTIs as there was insufficient evidence to suggest that risk of further RTIs varied by initial treatment strategy.[159] Furthermore, there was insufficient evidence to suggest that prescribing for these episodes varied by initial treatment strategy.[159] The model therefore comprised a decision tree that simulated patient outcomes over 28 days following index consultation.

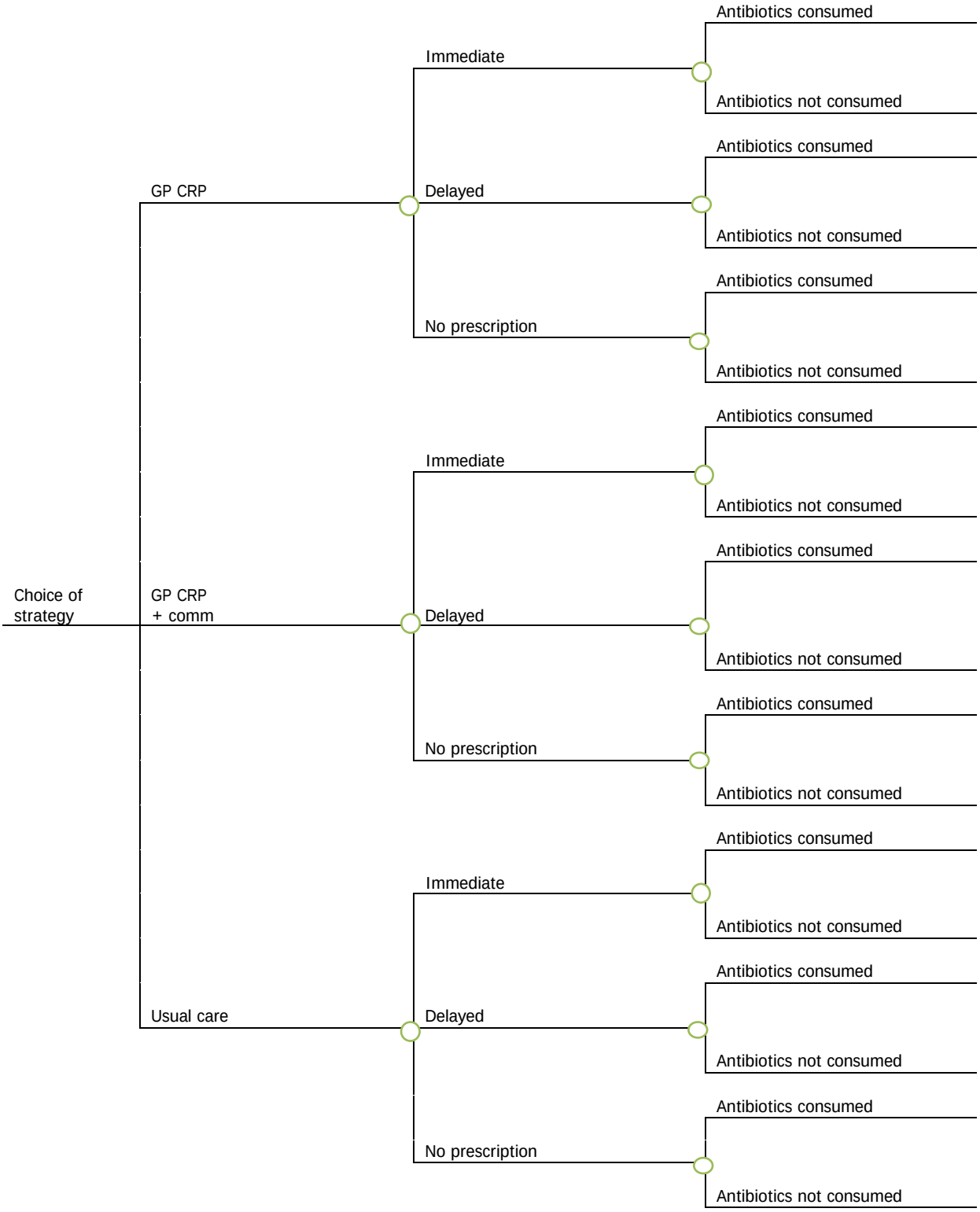
At baseline, patients entered the decision tree into one of the three strategies. At index consultation, patients could be prescribed an antibiotic immediately or issued a delayed, or deferred, prescription, or receive no prescription. The probability that an antibiotic would be prescribed was influenced by the strategy. The model further simulated the probability that antibiotics would be consumed, or redeemed, to reflect the associated cost of antibiotics. As per Spurling et al.,[179] not all patients consume antibiotics, and the rate of antibiotic consumption depends on whether patients receive an immediate, delayed or no prescription. A schematic of the decision tree is presented in Figure 8.1.

The model was replicated over five cycles (one cycle per year) in the base case analysis with all patients modelled simultaneously in each cycle.

8.1.8 Model assumptions

The model did not consider all-cause mortality. It was assumed that excluding all-cause mortality would have little to no impact on the results given the short time horizon assumed (five years).

Figure 8.1 Decision tree depicting patients' outcomes



8.1.9 Model outputs

The outputs of the model included the average number of antibiotics prescribed over the course of the time horizon and the average costs for each of the strategies modelled. Summary measures included the discounted incremental cost-effectiveness ratio (ICER), or cost per prescription avoided, and plots of the incremental cost-effectiveness plane. The discounted ICER presents the additional costs divided by the additional benefits of one intervention relative to another. The ICER is typically considered in the context of a willingness-to-pay threshold, which represents the maximum a decision-maker is willing to pay for a unit benefit, such as a life year gained (LYG) or a quality-adjusted life year (QALY) gained. However, there is no clear threshold on which to judge the incremental cost per prescription avoided, so the ICER is not compared to a predefined or notional threshold, but is used to provide summary estimates of the potential incremental costs and consequences of the interventions relative to usual care and the extent of the uncertainty in these estimates.

A probabilistic model of 10,000 iterations was used in the base case analysis that explicitly took into account the uncertainty in the model parameters, which were varied simultaneously within the model. All parameters were varied over the 10,000 simulations according to predefined probability distributions. Choice of probability distribution was informed by the nature and availability of the parameter. Where possible, published evidence was used and, where evidence was limited or unavailable, plausible distributions or ranges were derived with the support of the Expert Advisory Group.

8.1.10 Sensitivity analysis

A univariate sensitivity analysis shows how influential uncertainty in each parameter is by itself and how sensitive the results are to fluctuations in each parameter value. Given the uncertainty around the parameters themselves, it is important to understand how this translates into uncertainty about the results. Deterministic sensitivity analysis was used to examine this, where each parameter in turn was fixed at its upper and lower bounds, while all the other parameters were held constant at their ‘best estimate’ or baseline value. Sensitivity analyses involving changes in key parameters and model assumptions were also undertaken to assess the robustness of the results to these changes.

8.1.11 Budget impact analysis

The budget impact analysis was conducted from the perspective of the publicly funded health and social care system. The analysis reports the incremental annual

cost of the CRP POCT strategies versus usual care over five years. As with the CEA, indirect costs due to lost productivity associated with illness or absenteeism, for example, were not included. Costs used in the budget impact analysis were the same as those used in the CEA analysis. A budget impact analysis is inclusive of value-added tax (VAT), where applicable. The cost of a CRP device therefore includes VAT at 23%, which is also added to consumables (that is, materials and reagents).

8.2 Model parameters

The economic model required a range of input parameters that described national GP consultation rates; RTI-incidence; RTI-prescribing; risk reduction in RTI-prescribing; and associated healthcare costs. The purpose of this section is to provide details of the values used for the key parameters. As the model was probabilistic, parameters generally have a base-case value and an associated range or distribution of values. The overall costs and consequences of the different strategies were calculated by averaging the results of 10,000 model simulations. Summarising across simulations provides an estimate of overall average costs and consequences, as well as the uncertainty associated with these values.

8.2.1 Population data (epidemiological inputs)

The CEA modelled outcomes for adults presenting to primary care with a RTI in Ireland. The most recent available data on the proportion of patients presenting to primary care with a RTI derives from a 2012 paper by Murphy et al. (2012).[88] (At the time of writing, this was the only available data source identified that reported the proportion of patients presenting to primary care with a RTI in Ireland.) According to Murphy et al. (2012), 23% of consultations in Ireland were for a RTI (Table 8.1). The CEA also modelled outcomes for adults (aged 15 or older) in a sensitivity analysis. Using a combination of figures from the Murphy study and unpublished data, it was estimated that 18.9% of consultations were for RTIs.

Table 8.1 Proportion of patients presenting to primary care in Ireland with a RTI

	Consultations	RTI	Proportion	Source
All patients	16,899	3,889	23.0%	Murphy et al. (2012)
Adults	-	-	18.9%	Estimated using Murphy et al. (2012)

Key: RTI, respiratory tract infection

To calculate the total number of patients entering the decision-analytic model, the proportion derived from Murphy et al. (2012)[88] is applied to the total number of GP consultations, taken from the CSO (2018) and GP consultation data from Healthy

Ireland (2015). This suggests 3.9 million consultations annually are for RTIs, of which 2.9 million are by adults aged 15 or older (Table 8.2).

Table 8.2 Annual number of GP consultations

	Mean	SD	Source
All patients			
GMS	8,805,517	235,129	CSO (2018) and Healthy Ireland (2015)
Private	8,067,411	281,751	CSO (2018) and Healthy Ireland (2015)
Total	16,872,928		
RTI-visits	3,892,584		
Adults only			
GMS	8,086,751	224,082	CSO (2018) and Healthy Ireland (2015)
Private	7,159,251	257,383	CSO (2018) and Healthy Ireland (2015)
Total	15,246,002		
RTI-visits	2,881,494		

Key: GMS – general medical services; RTI – respiratory tract infection.

The majority of patients presenting to primary care with a RTI may be immediately diagnosed due to the presence of (or lack thereof) symptoms. For these patients, a CRP test is unnecessary. A subset of patients present with clinically unclear or uncertain symptoms and would benefit from a CRP test. Estimating the proportion of patients that are eligible for a CRP test is important in the context of cost-effectiveness and budget impact as not all patients require a CRP test. Two published sources provide evidence on the proportion of patients that would be eligible for a CRP test (Table 8.3).[35, 170] These sources are used to derive a pooled estimate on the proportion of patients eligible for a CRP test in Ireland. It is estimated that 34% (95% CI: 30-39%) of patients presenting to primary care have an unclear diagnosis and would benefit from a CRP test. That represents 1.3 million patients (or CRP tests) per annum. The same proportion being subject to clinical uncertainty (34%) is assumed for adults only.

Table 8.3 Proportion of patients eligible for a CRP test

Study	CRP	Total	Proportion	Patients
Llor et al. 2012	545	1488	0.37	LRTIs
Bjerrum et al. 2004	462	1,444	0.32	Sinusitis

Key: CRP – C-reactive protein; LRTI – lower respiratory tract infection

8.2.2 Prescribing

To model the effect of CRP POCT, two sources of evidence on prescribing are required:

1. Data on national prescribing without CRP POCT (that is, usual care)
2. The treatment effect of implementing CRP POCT relative to usual care.

These data sources are described separately below.

National prescribing rates (usual care)

There are limited data for Ireland on antibiotic prescribing at index consultation and within 28 days (that is, delayed/deferred prescribing). The data used here comes from the study by Murphy et al. (2012), who report that 54.0% of patients presenting to primary care with a RTI receive an immediate antibiotic prescription.[88] A further 7.7% of patients are given a deferred prescription. These data are used to inform usual care in the base case analysis. Among adults aged 15 or older, 57.3% received a prescription immediately, while 7.9% received a delayed prescription (Table 8.4).

To account for the change in antibiotic prescribing nationally since the time Murphy et al. collected their data, an adjustment factor was applied to the base case estimate in sensitivity analysis. Using data from the Health Protection Surveillance Centre (HPSC) on total outpatient antimicrobial use in Ireland from 2009 (when the majority of data was collected by Murphy et al.) to 2017, expressed in defined daily doses per 1,000 inhabitants per day (DID), an adjustment factor of 1.111 was applied to the base case estimate to reflect the increase in antibiotic use during this period (Table 8.5). This increased the rate of prescribing for an immediate and delayed prescription to 60.0% and 8.4%, respectively.

Table 8.4 Estimates of prescribing at index consultation and within 28 days (usual care)

	Estimate	Lower	Upper	Source
All patients				
Immediate prescribing	0.540	0.524	0.556	Murphy et al. (2012)
Delayed prescribing	0.077	0.068	0.087	Murphy et al. (2012)
Adults only				
Immediate prescribing	0.573	0.554	0.592	Murphy et al. (2012)
Delayed prescribing	0.079	0.069	0.090	Murphy et al. (2012)

Table 8.5 Total outpatient antimicrobial use in Ireland 2009-2017 by major antimicrobial class, expressed in DID

	2009	2017	Source
Total Consumption	20.8	23.1	HPSC (2018)

Key: DID – defined daily doses per 1,000 inhabitants per day

Treatment effect of CRP POCT

The systematic review (detailed in Chapter 4) provided evidence of the effectiveness of CRP POCT on antibiotic prescribing. These data were analysed using a network meta-analysis. As the data sources in the systematic review comprised RCTs and observational studies, two network meta-analyses were undertaken to separate the effect of CRP POCT on antibiotic prescribing according to study design. The risk reduction in prescribing, or treatment effect of CRP POCT, was largely comparable across both study designs; however, the estimates of risk reduction were greater and more uncertain using the observational evidence (Table 8.6).

Table 8.6 Relative risk of prescribing (network meta-analysis)

	Estimate	Lower	Upper	Source
Prescribing at index consultation (RCT evidence)				
GP CRP	0.73	0.59	0.91	Systematic review
GP CRP + comm	0.51	0.32	0.80	Systematic review
Prescribing at index consultation (observational evidence)				
GP CRP	0.65	0.30	1.42	Systematic review
GP CRP + comm	0.50	0.15	0.84	Systematic review

The RCT evidence was used in the base case analysis given the rigour of the study design, with the observational evidence applied in sensitivity analysis.

As the systematic review did not investigate the effect on prescribing of an enhanced communication component on its own, a communication intervention with no CRP POCT was not included.

8.2.3 Antibiotic consumption

Although antibiotics may be prescribed to patients, not all patients consume or redeem prescriptions. Whether patients are given an immediate or deferred prescription is also likely to influence consumption. According to Spurling et al. (2017),[179] the proportion of patients redeeming prescriptions is high among patients that receive an immediate prescription (96% [95% CI: 92 to 99%]) and low among patients that are given a deferred prescription (34% [95% CI: 28 to 40%])

(Table 8.7). Patients for whom no antibiotics are prescribed still consume antibiotics (14% [95% CI: 9 to 19%]), for example because they subsequently receive an antibiotic prescription for the same episode of RTI. It was assumed these patients redeemed old prescriptions or consumed antibiotics previously prescribed (and redeemed). These data were incorporated into the model to reflect the cost of antibiotic consumption, rather than antibiotic prescription, as not all prescriptions are redeemed.

Table 8.7 Proportion redeeming prescriptions (consumption)

	Estimate	Lower	Upper	Source
Immediate prescription	0.96	0.92	0.99	Spurling et al. (2017)
Delayed prescription	0.34	0.28	0.40	Spurling et al. (2017)
No prescription	0.14	0.09	0.19	Spurling et al. (2017)

8.2.4 Cost estimates

Table 8.8 presents the cost inputs used in the analysis. All cost estimates were valued at (or inflated to) 2018 prices and expressed in Euro (€) currency.

In the economic model, costs associated with CRP included the cost of the device; CRP test (that is, materials/reagents); depreciation of the device; and the opportunity cost of a GP's time in performing the test. It was assumed that all CRP tests were conducted by GPs, and not by other practice staff. It was assumed that while a CRP POC test can take up to 14 minutes to complete, carrying out the test would extend a consultation by an average of 3 minutes.[238] This is because the consultation can continue while the device is completing the test, and the GP may ask the patient to move to the practice waiting area to be called in when the results are known. A scenario analysis was used to explore the impact of increasing the effect on consultation times to 6 minutes.

The cost of a CRP device and its associated test cost were provided by a leading manufacturer of CRP devices in Ireland through personal communications. (The manufacturer is unnamed due to the commercial sensitivity of CRP pricing.) A single CRP test in terms of materials/reagents was estimated to cost €4.31 (95% CI: €3.54 to €5.24) (Table 8.8). Depreciation was estimated to cost €0.66 (95% CI: €0.53 to €0.78) per CRP test, as calculated by annuitising the cost of the CRP device over its expected seven-year lifespan (Table 8.9). The cost was applied to each CRP test and was not incorporated into the cost of the CRP device, which was applied separately for both CRP POCT strategies on the assumption that the HSE incurs the cost of purchasing one device per GP (N=2,954, as per Teljeur et al. (2013)).[247]

The cost of training GPs to use the CRP device is derived from Hunter (2015),[238] and estimated to cost €0.44 (95% CI: €0.36 to €0.53). It is assumed training was provided by the manufacturer, as in Hunter (2015). To account for the added cost of CRP test failures/errors, which reportedly occur in 6% of cases,[248] the cost of a CRP test was reapplied, or doubled, for 6% of patients. The cost of an external quality assurance scheme was incorporated into the model. The external quality assurance scheme was estimated to cost €406 per annum, according to an external quality assurance provider. The cost was applied on a per-device basis as all CRP POCT devices must be registered with an external quality assurance provider. Under the scheme, GPs must submit three CRP samples for laboratory assessment, five times per annum.

The cost of the enhanced communication training was added to the combined intervention in the first year, with refresher training provided in year 4 on the assumption that training will be required three years later – it was assumed the training module is already developed and available, so no cost of developing the module was incurred. It was assumed that training takes two hours, which was costed in terms of the opportunity cost of a GP's time at €629.71 (or €5.25 per minute). To train all GPs in Ireland, the cost was estimated to be €1.9 million. In addition to intervention costs, the cost of one GP consultation per RTI was modelled. The cost of a GP consultation was derived from a previous HIQA HTA on smoking cessation in Ireland.[249] The HTA estimated that a GP consultation costs €49.04 (95% CI: €47.10 to €51.07) for both public and private patients. The cost of antibiotics was also included and derived from the HSE reference list[250] and the Primary Care Reimbursement Service (PCRS) (2018). A weighted cost of antibiotics in terms of the total use of antibiotics in primary care, expressed in DID, was applied (Table 8.10).[251]

8.2.5 Discount rate

Discounting reflects a societal preference for benefits to be realised in the present and costs to be experienced in the future. Discounting facilitates comparison between costs and benefits that occur at different times. Costs and benefits were discounted at the rate of 5% as set out by the Department of Finance.[245] The discount rate was fixed in the main analyses and varied from 0% to 10% in a univariate sensitivity analysis to illustrate the impact of discounting.

Table 8.8 Estimates of cost inputs

	Estimate	Lower	Upper	Source
CRP test (materials/reagents)	€4.31	€3.54	€5.24	Manufacturer (2018)
Depreciation	€0.66	€0.53	€0.78	Manufacturer (2018)
Additional consultation time due to test (mins)	3.00	2.25	3.75	Hunter (2015)
GP cost per minute*	€5.32	€4.31	€6.38	PSSRU (2017)
Cost of GP training	€0.44	€0.36	€0.53	Hunter (2015)
External quality assurance scheme	€406	€333	€493	QA provider (2018)
GP comm. Training per GP, (in year 1 and year 4)	€630	€517	€766	Hunter (2015)
GP consultation	€49.04	€47.10	€51.07	HIQA (2017)
Antibiotic prescription	€11.77	€9.67	€14.32	HSE (2018)

* Assuming a consultation costs €49.04 and lasts 9.22 minutes.[252]

Table 8.9 Calculating per test unit cost of depreciation

		€
Device*	A	1,670.00
Lifespan	B	7 years
Discount rate	C	5%
Annuity factor	D	5.8
Annual cost	A/D	€288.61
Unit cost	(A/D)*proportion eligible for CRP test	€0.66

* Includes analyser (€1,400), printer (€125), scanner (€130), connectivity (€15).

Table 8.10 Calculating antibiotic costs using DID (HPSC 2017)

Case drug	Reimbursement price*	DID	Weighted cost	Source
Amoxicillin/Clavulanic Acid [penicillins]	€13.83	13.00	€8.21	HSE (2018)
Clarithromycin [macrolides]	€11.42	4.20	€2.19	HSE (2018)
Doxycycline [tetracyclines]	€7.47	2.80	€0.96	PCRS (2018)
Cefaclor [Cephalosporins]	€17.19	1.10	€0.86	PCRS 2018)
Ciprofloxacin [Quinolones]	€12.66	0.80	€0.46	PCRS 2018)
Total			€12.68	

* Includes €5.48 pharmacy fee, as per NCPE guidelines for inclusion of drug costs in economic evaluation (NCPE 2018).[253]

Note: Total cost is further adjusted for public vs. private patients (assuming €1.75 reduction for GMS patients).

Key: DID– defined daily doses per 1,000 inhabitants per day; HPSC – Health Protection Surveillance Centre.

8.2.6 Budget impact analysis

A budget impact analysis was undertaken to show the total cost of implementing the CRP POCT strategies in Ireland over the next five years. The cost of implementing the strategies was estimated as an additional cost, or incremental cost, relative to usual care. In the base case analysis, it was assumed that CRP devices were purchased by the HSE and CRP test costs were incurred by the HSE. In the base case analysis, two cost scenarios were presented: one in which the HSE purchased one CRP device per GP (N=2,954)[247] and another in which the HSE purchased one device per practice (N=1,734).[254] In a scenario analysis, the cost of a CRP test was excluded on the assumption that this is accounted for elsewhere in the system to assess the overall budget impact of excluding this cost. As in the base case analysis, two cost scenarios were presented to show the cost implications of purchasing one device per GP versus one device per practice.

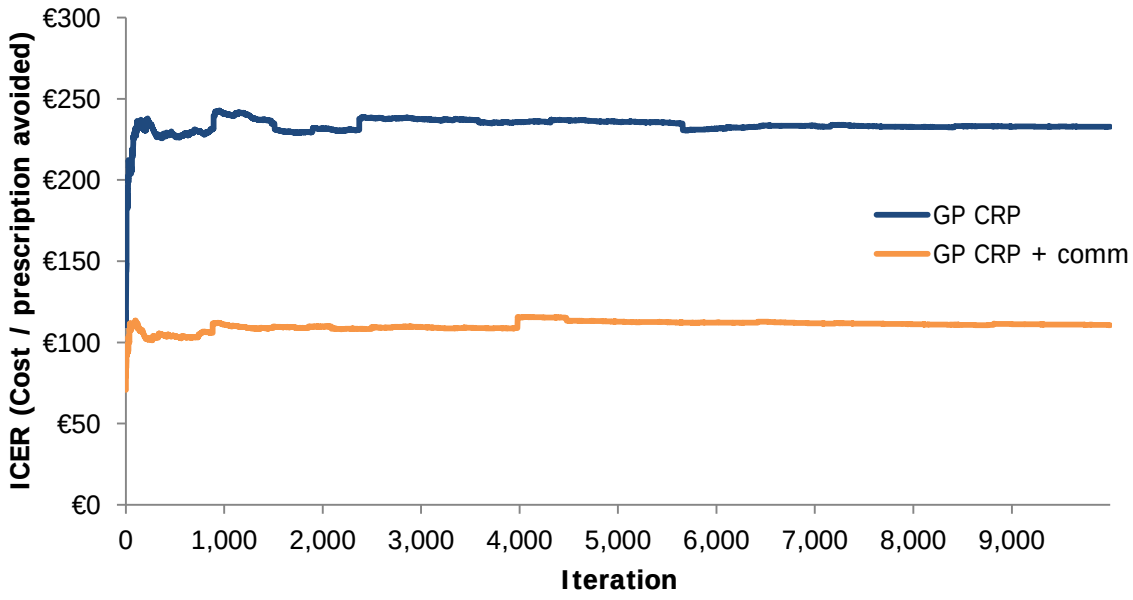
As discussed previously, the cost of VAT was included in the cost of the device as well as consumables in the budget impact analysis. However, the cost of a GP consultation was not included as GPs are paid for GMS consultations through a capitation fee. An increase in consultation length will not incur a cost to the HSE unless CRP POCT is funded on a fee-per-item basis. Hence an increase in GMS GP consultations that is not associated with fee-per-item care will not result in an increased budget impact for the HSE.

8.3 Results of the economic analysis

A Monte Carlo simulation was performed to derive estimates of the costs and consequences of each strategy in the economic model. The model was replicated over 10,000 simulations with parameters sampled from predefined probability distributions in each simulation. To determine if the model had converged on a result, the mean ICER was monitored across simulations (Figure 8.2). After 4,000 simulations, the estimated mean ICER was consistently within 1% of the estimated mean ICER after 10,000 simulations. The model took 3.5 hours to complete 10,000 simulations. Due to the computational burden of running the model, scenario analyses were based on 4,000 simulations.

The average cost per patient and average number of prescriptions issued per strategy (undiscounted) and per RTI consultation (discounted) were calculated for patients presenting to primary care with a RTI in Ireland. The average incremental cost per prescription avoided (per RTI consultation) for GP use of CRP (GP CRP) and GP use of CRP with communication training (GP CRP + comm) versus usual care was calculated, with results plotted on incremental cost-effectiveness planes. All analyses were carried out using Microsoft Excel software.

Figure 8.2 Cumulative mean ICER (cost per prescription avoided) by simulation



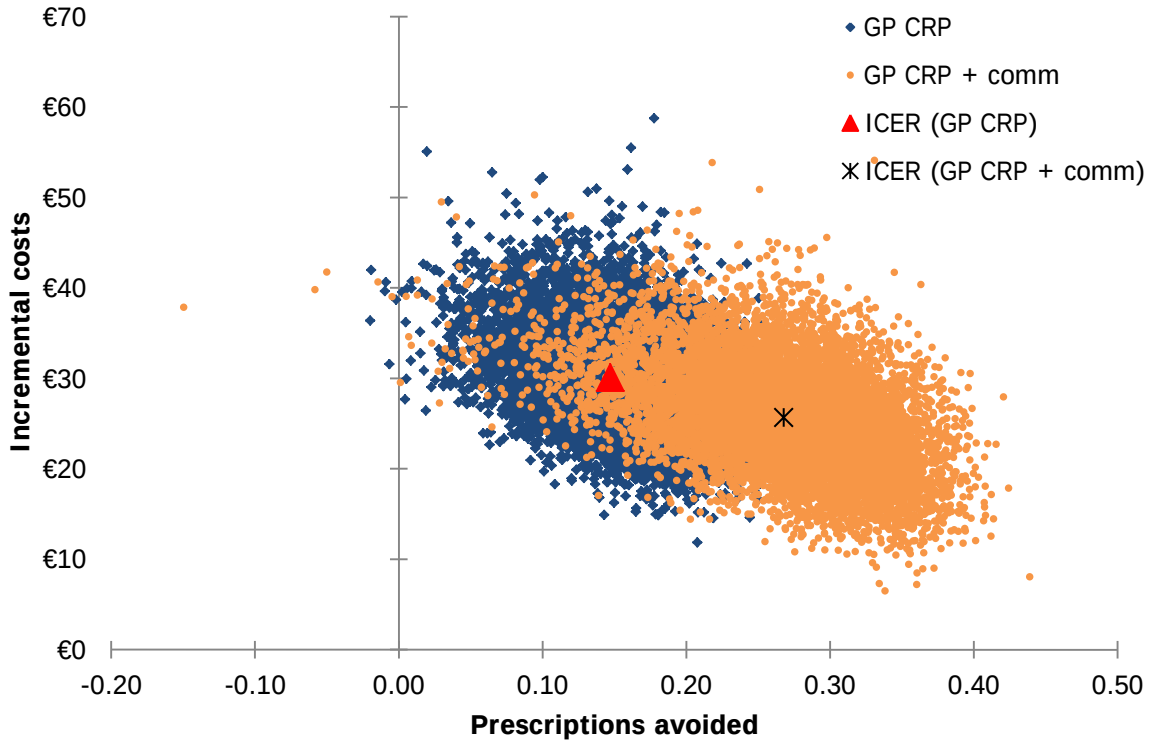
8.3.1 Base case analysis

Under the CRP interventions, an estimated 1.3 million CRP tests (95% CI: 1.1 to 1.5 million) would be carried out each year in primary care assuming that CRP POCT is available across all GP practices.

Table 8.11 presents the cost-effectiveness findings from the base case analysis. Over five years, usual care leads to 12.0 million (undiscounted) prescriptions (or 2.4 million prescriptions per annum). GP CRP leads to 8.8 million prescriptions, while GP CRP + comm leads to 6.3 million prescriptions. Over five years, that reflects a 26% and 48% reduction in antibiotics for GP CRP and GP CRP + comm, respectively. In terms of discounted incremental costs and number of prescriptions avoided per RTI consultation, the results suggest there is little difference between the two CRP POCT strategies. However, there is some evidence that GP CRP + comm is more cost-effective than GP CRP as it has fewer prescriptions per RTI consultation over five years and lower costs. Versus usual care, GP CRP + comm has an ICER (cost per prescription avoided) of €111 (95% CI: €41 to €278). As GP CRP is more costly and less effective than GP CRP + comm, the strategy is said to be dominated (a strategy dominates another if it is both more effective and less costly).

The results of the probabilistic analysis are plotted on an incremental cost-effectiveness plane (Figure 8.3). The point-estimates are plotted in the north-east quadrant, suggesting both strategies generate fewer prescriptions than usual care, but at additional costs. Although the point-estimates largely overlap, there is some evidence that GP CRP is dominated by the combined intervention.

Figure 8.3 Incremental cost-effectiveness plane for GP CRP and GP CRP + comm vs. usual care (base case analysis)



8.3.2 Cost-effectiveness sensitivity analyses

Sensitivity analyses involving changes in key parameters and model structure are undertaken to assess both parameter and structural uncertainty. First, the RCT evidence informing the risk reduction in prescribing is replaced with observational evidence to assess potential changes in cost-effectiveness findings. Second, a shorter time horizon of one year is assumed to investigate structural uncertainty in the model. Third, the proportion of patients eligible for a CRP test (that is, those for whom there is clinical uncertainty on the presence of viral versus bacterial infection) is varied to investigate potential changes in cost-effectiveness findings of low/high levels of uncertainty. Here, the proportion of patients eligible for a CRP test is varied between 20% and 50%. Fourth, the data provided by Murphy et al. (2012) on prescribing at index consultation via usual care are adjusted to reflect the 11.1% increase in prescribing observed between 2009 and 2017 in primary care in Ireland. Finally, the model considers outcomes for adults aged 15 or older only. In each probabilistic sensitivity analysis, 4,000 Monte Carlo simulations were performed, with results plotted on incremental cost-effectiveness planes.

Table 8.11 Estimated incremental cost-effectiveness ratios (€/prescription avoided) (base case analysis)

	Costs (95% CI)	Incremental costs (95% CI)	(Undiscounted) Prescriptions, millions	(Discounted) Prescriptions* (95% CI)	Prescriptions avoided* (95% CI)	ICER (€ / prescription avoided) (95% CI)
Usual care	€255 (€244 to €267)	-	12.0 (11.1 to 12.8)	0.56 (0.54 to 0.58)	-	-
GP CRP	€285 (€272 to €301)	€30 (€21 to €41)	8.8 (7.2 to 10.7)	0.41 (0.34 to 0.50)	0.15 (0.06 to 0.22)	Dominated
GP CRP + comm	€281 (€266 to €297)	€26 (€15 to €38)	6.2 (4.1 to 9.3)	0.29 (0.19 to 0.43)	0.27 (0.13 to 0.37)	€111 (€45 to €243)

* Per RTI consultation

Key: CI - confidence interval; ICER - incremental cost-effectiveness ratio.

Replacing the RCT evidence on the risk reduction in prescribing with observational evidence introduces some uncertainty in the cost-effectiveness findings. Table 8.12 shows the two CRP POCT strategies have uncertain ICERs versus usual care; GP CRP is dominated, while GP CRP + comm has an ICER of €580 (95% CI: €-481 to €831). The uncertainty is introduced via prescribing as the strategies sometimes lead to increased prescriptions versus usual care, as shown on the incremental cost-effectiveness plane presented in Figure 8.4.

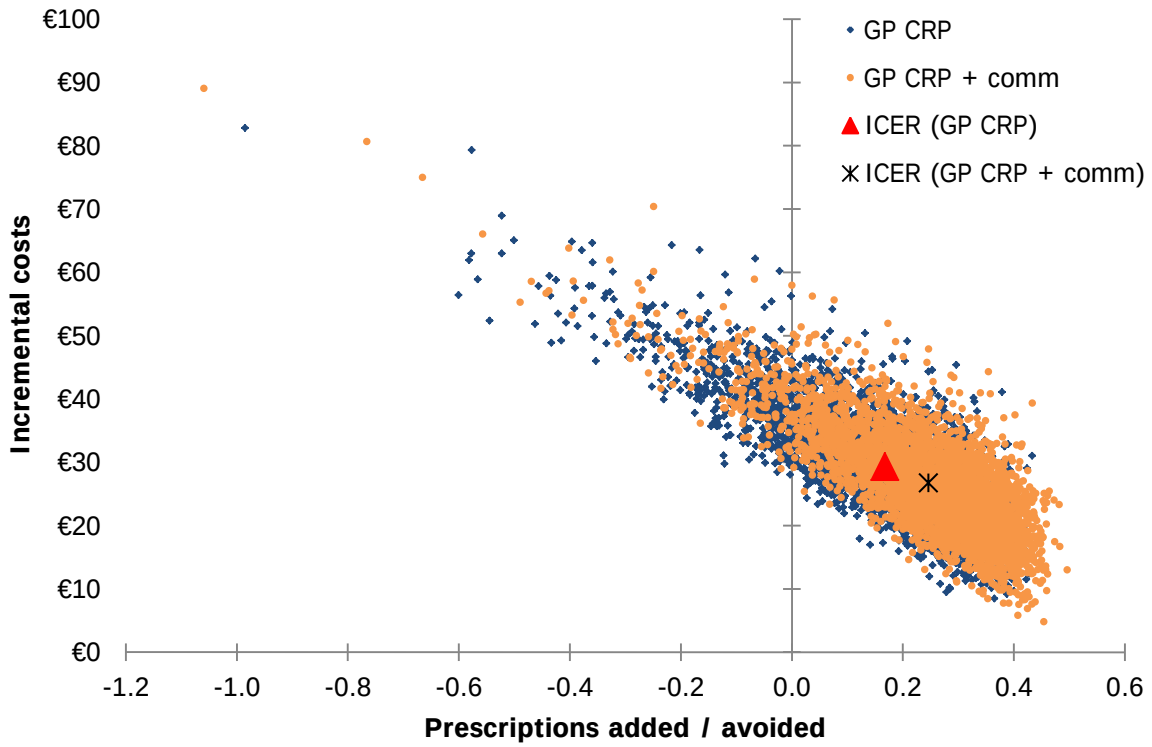
Table 8.12 Estimated incremental cost-effectiveness ratios (€/prescription avoided) (using observational evidence on the relative risk reduction in prescribing)

	Costs (95% CI)	Incremental costs (95% CI)	Prescriptions* (95% CI)	Prescriptions avoided* (95% CI)	ICER (€ / prescription avoided) (95% CI)
Usual care	€255 (€244 to €267)	-	0.56 (0.54 to 0.58)	-	-
GP CRP	€285 (€268 to €307)	€29 (€15 to €49)	0.39 (0.19 to 0.74)	0.17 (-0.19 to 0.38)	Dominated
GP CRP + comm	€282 (€265 to €303)	€27 (€13 to €46)	0.31 (0.14 to 0.65)	0.25 (-0.09 to 0.42)	€580 (€-481 to €831)

* Per RTI consultation

Key: CI – confidence interval; ICER – incremental cost-effectiveness ratio.

Figure 8.4 Incremental cost-effectiveness plane for GP CRP and GP CRP + comm vs. usual care (sensitivity analysis using observational evidence on the risk reduction in prescribing)



Shortening the time horizon to one year reduces average costs for each strategy. However, the cost-effectiveness of the interventions remains unchanged: both strategies generate fewer prescriptions than usual care at marginally higher costs (Table 8.13; Figure 8.5), and there is some evidence that GP CRP is dominated by the combined intervention as in the base case analysis.

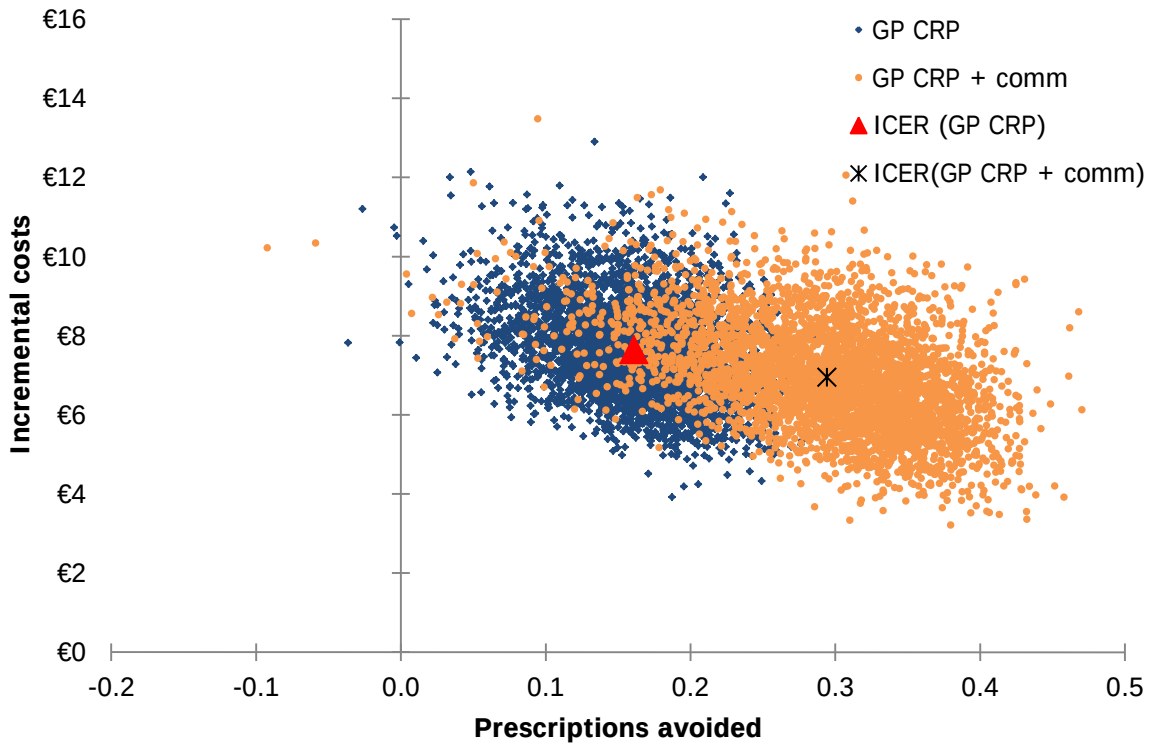
Table 8.13 Estimated incremental cost-effectiveness ratios (€/prescription avoided) (over one-year time horizon)

	Costs (95% CI)	Incremental costs (95% CI)	Prescriptions* (95% CI)	Prescriptions avoided* (95% CI)	ICER (€ / prescription avoided) (95% CI)
Usual care	€56 (€54 to €59)	-	0.62 (0.6 to 0.63)	-	-
GP CRP	€64 (€61 to €67)	€8 (€6 to €10)	0.45 (0.37 to 0.55)	0.16 (0.07 to 0.24)	Dominated
GP CRP + comm	€63 (€60 to €67)	€7 (€5 to €10)	0.32 (0.21 to 0.47)	0.29 (0.15 to 0.4)	€27 (€12 to €58)

* Per RTI consultation

Key: CI – confidence interval; ICER – incremental cost-effectiveness ratio.

Figure 8.5 Incremental cost-effectiveness plane for GP CRP and GP CRP + comm vs. usual care (sensitivity analysis with one-year time horizon)



A sensitivity analysis that compares different proportions of patients eligible for a CRP test is undertaken to assess the impact of low/high levels of clinical uncertainty on cost-effectiveness findings. In this analysis, the proportion of patients with clinical uncertainty is varied between 20% and 50% (the base case estimate is 34.3%). The results are presented in Figure 8.6, with the proportion of patients eligible for a CRP test depicted on the y-axis and cost per prescription avoided is presented on the x-axis. The results show that as clinical uncertainty increases, the cost of each strategy increases along with its associated ICER. Under each scenario, the combined intervention is said to dominate GP CRP.

The results remain broadly unchanged in other sensitivity analyses. Adjusting the level of prescribing for usual care to reflect the increase in prescribing in Ireland between 2008 and 2017 has little effect on the ICER of the two CRP POCT strategies, as shown in Table 8.14 and Figure 8.7. Similarly, limiting the analysis to adults aged 15 or older has little impact on the cost-effectiveness findings, as shown in Table 8.15 and Figure 8.8. In both scenarios, the CRP POCT strategies are more costly and more effective than usual care, and there is some evidence that GP CRP + comm is more cost-effective than GP CRP.

Figure 8.6 Sensitivity analysis on the proportion of patients eligible for CRP test

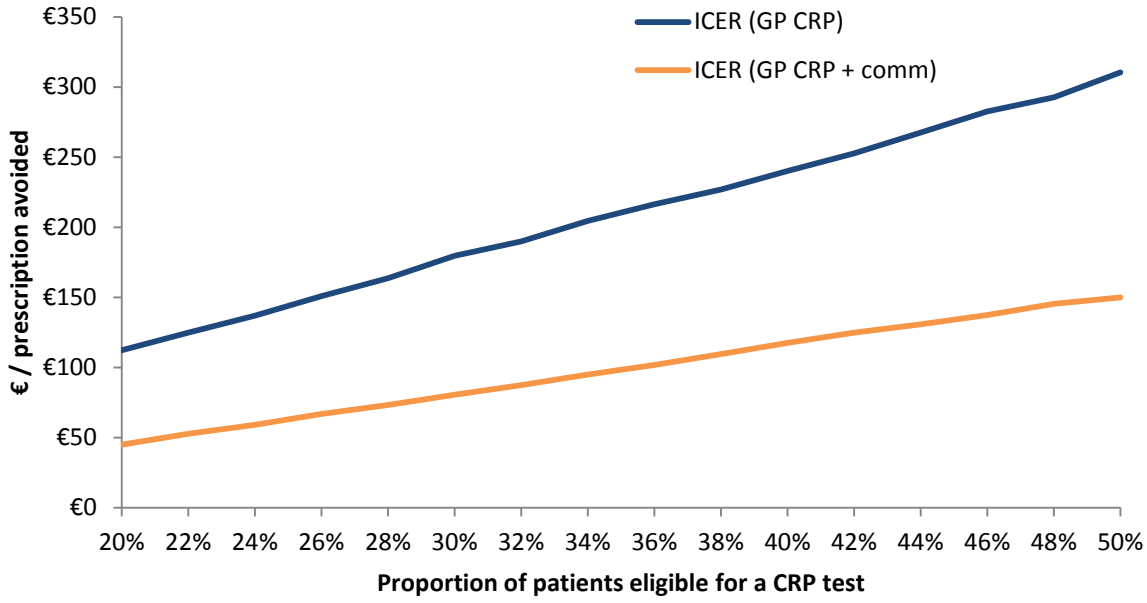


Table 8.14 Estimated incremental cost-effectiveness ratios (€/prescription avoided) (adjusted for prescribing change between 2009 and 2017)

	Costs (95% CI)	Incremental costs (95% CI)	Prescriptions* (95% CI)	Prescriptions avoided* (95% CI)	ICER (€ / prescription avoided) (95% CI)
Usual care	€258 (€247 to €270)	-	0.62 (0.61 to 0.64)	-	-
GP CRP	€288 (€273 to €303)	€30 (€20 to €41)	0.46 (0.38 to 0.55)	0.16 (0.07 to 0.24)	Dominated
GP CRP + comm	€283 (€268 to €299)	€24 (€13 to €37)	0.33 (0.22 to 0.48)	0.3 (0.15 to 0.41)	€87 (€36 to €219)

* Per RTI consultation

Key: CI – confidence interval; ICER – incremental cost-effectiveness ratio.

Figure 8.7 Incremental cost-effectiveness plane for GP CRP and GP CRP + comm vs. usual care (sensitivity analysis adjusted for prescribing change between 2009 and 2017)

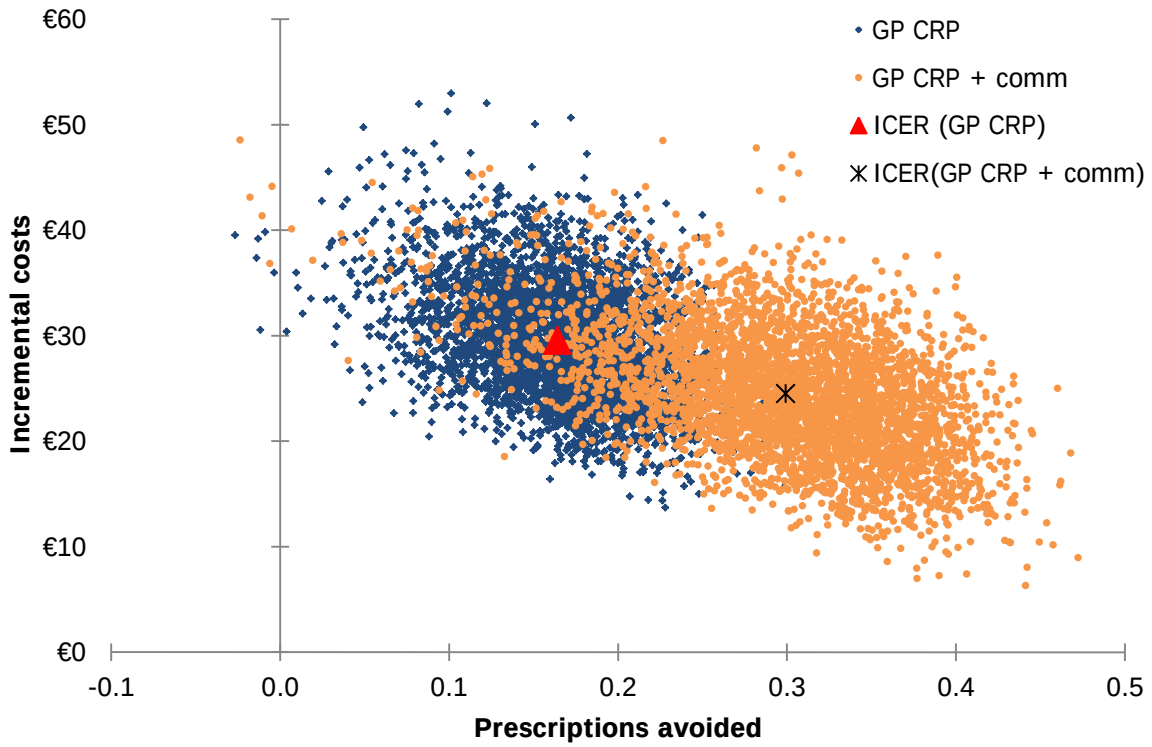


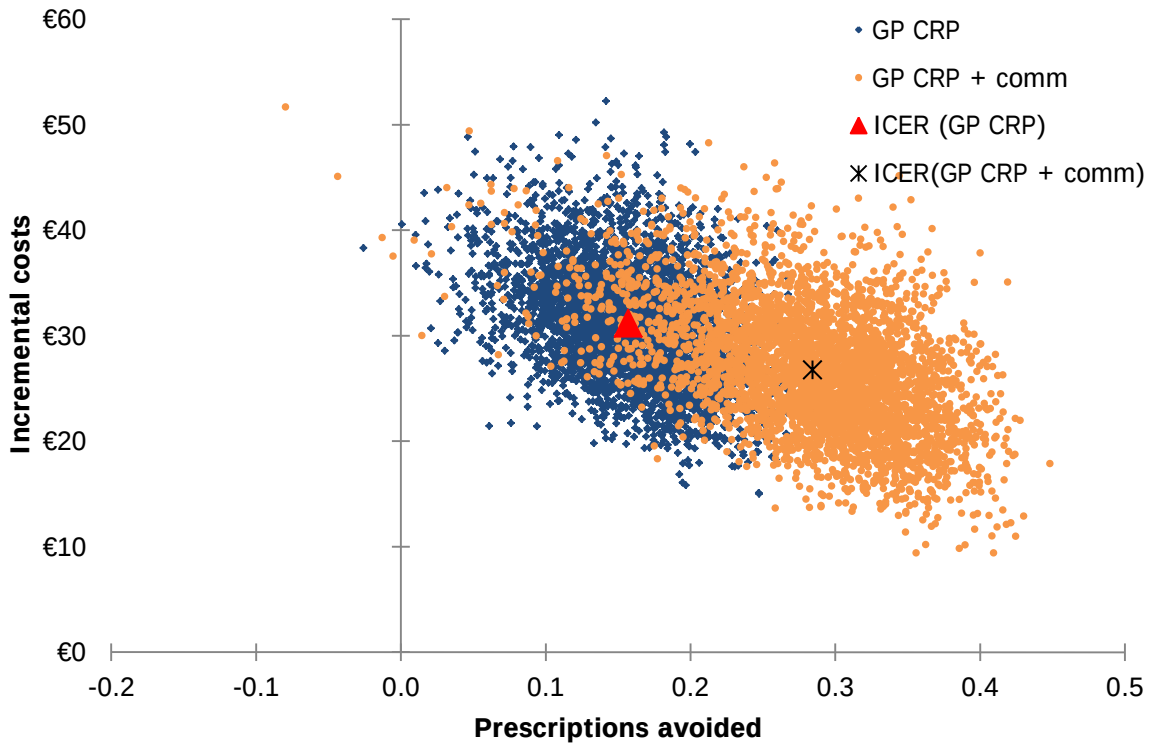
Table 8.15 Estimated incremental cost-effectiveness ratios (€/prescription avoided) (adults aged 15 or older)

	Costs (95% CI)	Incremental costs (95% CI)	Prescriptions* (95% CI)	Prescriptions avoided* (95% CI)	ICER (€ / prescription avoided) (95% CI)
Usual care	€257 (€246 to €269)	-	0.59 (0.57 to 0.61)	-	-
GP CRP	€288 (€273 to €303)	€31 (€21 to €42)	0.44 (0.36 to 0.53)	0.16 (0.06 to 0.24)	Dominated
GP CRP + comm	€284 (€269 to €300)	€27 (€16 to €40)	0.31 (0.2 to 0.46)	0.28 (0.14 to 0.39)	€104 (€45 to €243)

* Per RTI consultation

Key: CI – confidence interval; ICER – incremental cost-effectiveness ratio.

Figure 8.8 Incremental cost-effectiveness plane for GP CRP and GP CRP + comm vs. usual care (sensitivity analysis on adults aged 15 or older)



Univariate deterministic sensitivity analysis is carried out to identify how sensitive the results are to changes in input parameters. In this analysis, the model is run with a single parameter held at its upper/lower bound while all other parameters take on their average values, to assess the effect the univariate change has on the ICER for a given comparison. This is repeated for each parameter in the model, and the results are plotted using tornado plots, which rank the relative effects of each parameter on the ICER of the two interventions versus usual care.

Figure 8.9 shows the univariate sensitivity analysis for GP CRP versus usual care. The risk reduction in prescribing at index consultation has the greatest effect on the cost per prescription avoided. At the higher parameter estimate (RR 0.91), the cost per prescription avoided is increased to €542 (base case ICER is €200), whereas at the lower estimate, the ICER is reduced to €121. The duration of a CRP test, costed in terms of GPs' time, has the next greatest effect on the ICER for GP CRP. At the quicker time of 2.25 minutes, the ICER is reduced to €156; however, if the test takes an average of 3.75 minutes, the ICER is increased to €244. A similar effect on the ICER versus usual care is observed for the cost of a GP and the proportion of patients eligible for a CRP test. Few other inputs have an effect on the ICER.

The univariate sensitivity analysis for GP CRP + comm finds the same inputs have the greatest effect on the ICER versus usual care; however, the magnitude of the effect is smaller (Figure 8.10). As with GP CRP, the risk reduction in prescribing at index consultation has the greatest effect on the ICER, which is increased to €239 at the higher parameter estimate (RR 0.80; base case estimate is RR 0.51); at the lower estimate (RR 0.32), the ICER is reduced to €54. Both the duration of the test and the cost of a GP have the next greatest effect on the ICER for GP CRP + comm, but these effects are modest. The univariate sensitivity analysis generally demonstrates the robustness of the strategy to changes in key parameters.

Figure 8.9 Univariate sensitivity analysis of GP CRP vs. usual care

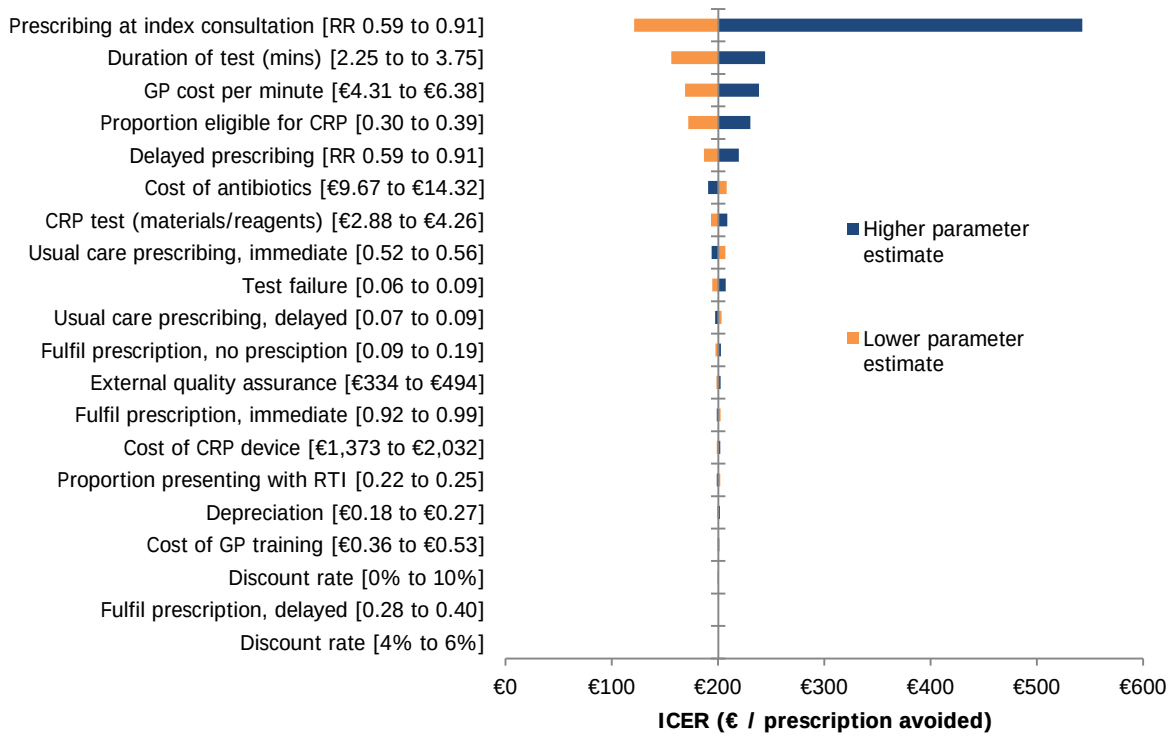
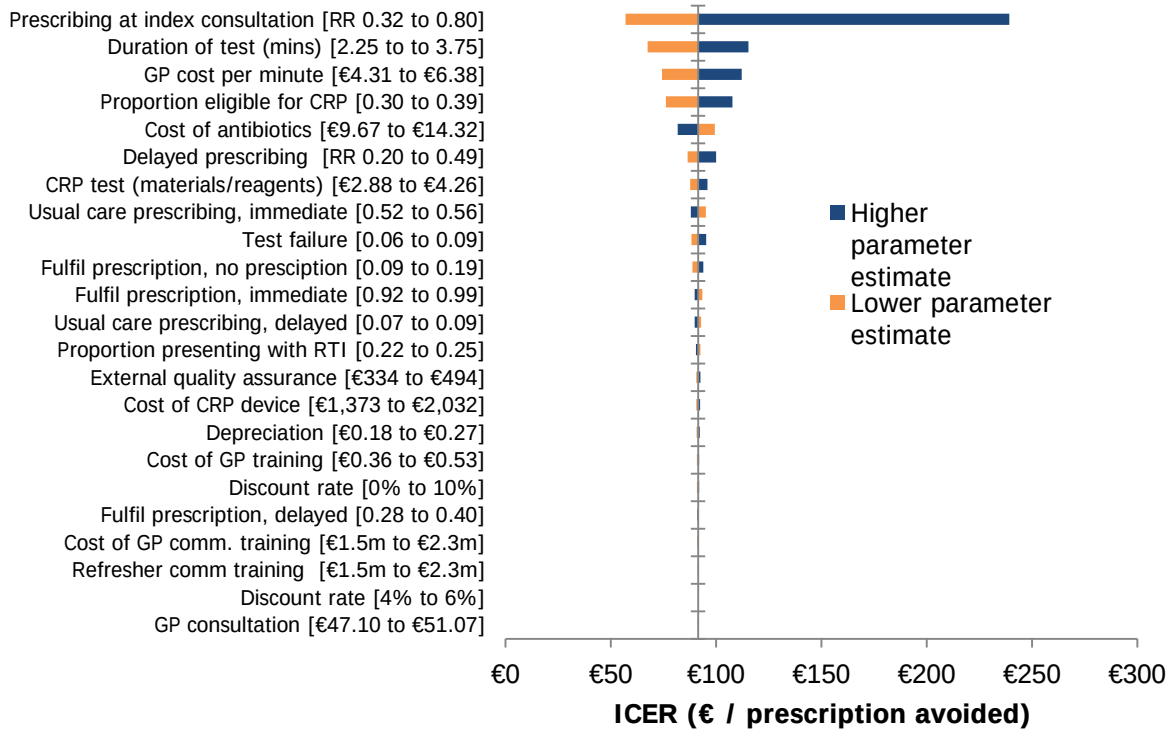


Figure 8.10 Univariate sensitivity analysis of GP CRP + comm vs. usual care



8.3.3 Budget impact analysis

A budget impact analysis is undertaken to show the total cost of implementing the CRP POCT strategies in Ireland over the next five years. The cost of implementing the strategies is estimated as an additional cost, or incremental cost, relative to usual care. In the base case analysis, the total five-year cost of implementing CRP POCT is calculated with all costs borne by the HSE; specifically, the cost of investing in CRP devices and test costs. With respect to CRP devices, two cost scenarios are considered: the first presents a breakdown of the budget impact should the HSE invest in one device per GP in Ireland, and the second considers the budget impact of investing in one device per GP practice.

In one scenario analysis, the cost of a CRP test was excluded from the HSE budget with the assumption that GPs would cover the cost through out-of-pocket fees to patients. The budget impact of investing in one device per GP in Ireland and one device per GP practice is similarly presented. In a separate scenario analysis, the cost of implementing an internal quality assurance scheme in which training in the use of CRP POCT devices is provided and organised by the government is modelled deterministically. Although training is included in the model, it assumes that training is provided by manufacturers at little cost to the HSE. Implementing CRP POCT with

an internally organised quality assurance scheme will add additional costs to the POCT strategies that need to be considered.

Table 8.16 presents the total (and disaggregated) five-year budget impact of implementing the CRP POCT strategies relative to usual care, with CRP test costs incurred by the HSE.

If the HSE purchases one CRP device per GP in Ireland, both CRP POCT strategies generate additional costs relative to usual care over five years. The budget impact of GP CRP is €23.9 million (95% CI: €5.1 to €43.8 million) over five years, while the budget impact for GP CRP + comm is €4.5 million (95% CI: €-22.8 to €34.8 million) over the same period. Both strategies generate a cost saving in terms of antibiotic costs each year; however, the additional cost of the device and its associated use (that is, CRP tests) and commitment to external quality assurance lead to increased costs overall. However, there is some evidence that the combined intervention may be budget-saving over five years. This is more pronounced if the HSE purchases one device per practice rather than one per GP, with potential savings of €1 million (95% CI: €-26.5 to €28.1 million) available for GP CRP + comm over five years. GP CRP remains more costly over five years despite the reduced cost of the device and external quality assurance, although some uncertainty is observed; the five-year budget impact of GP CRP is €18.1 million (95% CI: €-0.3 to €37.8 million).

The scenario analysis in which CRP test costs are excluded from the budget impact is presented in Table 8.17. With CRP test costs incurred elsewhere in the system, both strategies are largely budget-saving. Some uncertainty in GP CRP is observed if one device is purchased per GP in Ireland; however, potential savings of €14.2 million (95% CI: €-31.8 to €4.4 million) are available. In contrast, the combined intervention is associated with a budget saving of €33.4 million (95% CI: €-59.5 to €-5.2 million). If instead one device is purchased per practice, both strategies are budget-saving over five years, with the greatest savings arising from implementation of GP CRP + comm, which saves €39.1 million (95% CI: €-64.1 to €-11.4) over five years.

Table 8.16 Five-year budget impact with CRP test costs incurred by HSE: base case analysis (€ millions)

		CRP test costs incurred by HSE			
		One device per GP		One device per practice	
Year	Cost component	GP CRP	GP CRP + comm	GP CRP	GP CRP + comm
Year 1	CRP device	€6.1 (€5 to €7.3)	€6.1 (€5 to €7.3)	€3.6 (€2.9 to €4.3)	€3.6 (€2.9 to €4.3)
	Antibiotics	€-5.6 (€-8.9 to €-2)	€-10.2 (€-15.4 to €-4.4)	€-5.6 (€-9 to €-1.9)	€-10.2 (€-15.1 to €-4.4)
	CRP test costs	€7.6 (€6.2 to €9.4)	€7.6 (€6.2 to €9.4)	€7.6 (€6.2 to €9.4)	€7.6 (€6.2 to €9.4)
	GP comm training	-	€1.9 (€1.5 to €2.3)	-	€1.9 (€1.5 to €2.3)
	External QA	€1.5 (€1.2 to €1.8)	€1.5 (€1.2 to €1.8)	€0.9 (€0.7 to €1)	€0.9 (€0.7 to €1)
Total incremental cost (year 1)		€9.6 (€5.7 to €13.8)	€6.9 (€1.3 to €13)	€6.5 (€2.7 to €10.4)	€3.8 (€-1.4 to €9.6)
Year 2	Antibiotics	€-5.6 (€-8.9 to €-2)	€-10.2 (€-15.4 to €-4.4)	€-5.6 (€-9 to €-1.9)	€-10.2 (€-15.1 to €-4.4)
	CRP test costs	€7.6 (€6.2 to €9.4)	€7.6 (€6.2 to €9.4)	€7.6 (€6.2 to €9.4)	€7.6 (€6.2 to €9.4)
	External QA	€1.5 (€1.2 to €1.8)	€1.5 (€1.2 to €1.8)	€0.9 (€0.7 to €1)	€0.9 (€0.7 to €1)
Total incremental cost (year 2)		€3.6 (€-0.2 to €7.6)	€-1.1 (€-6.5 to €5)	€2.9 (€-0.8 to €6.8)	€-1.7 (€-6.8 to €4.2)
Year 3	Antibiotics	€-5.6 (€-8.9 to €-2)	€-10.2 (€-15.4 to €-4.4)	€-5.6 (€-9 to €-1.9)	€-10.2 (€-15.1 to €-4.4)
	CRP test costs	€7.6 (€6.2 to €9.4)	€7.6 (€6.2 to €9.4)	€7.6 (€6.2 to €9.4)	€7.6 (€6.2 to €9.4)
	External QA	€1.5 (€1.2 to €1.8)	€1.5 (€1.2 to €1.8)	€0.9 (€0.7 to €1)	€0.9 (€0.7 to €1)
Total incremental cost (year 3)		€3.6 (€-0.2 to €7.6)	€-1.1 (€-6.5 to €5)	€2.9 (€-0.8 to €6.8)	€-1.7 (€-6.8 to €4.2)
Year 4	Antibiotics	€-5.6 (€-8.9 to €-2)	€-10.2 (€-15.4 to €-4.4)	€-5.6 (€-9 to €-1.9)	€-10.2 (€-15.1 to €-4.4)
	CRP test costs	€7.6 (€6.2 to €9.4)	€7.6 (€6.2 to €9.4)	€7.6 (€6.2 to €9.4)	€7.6 (€6.2 to €9.4)
	GP refresher comm training	-	€1.9 (€1.5 to €2.3)	-	€1.9 (€1.5 to €2.3)
	External QA	€1.5 (€1.2 to €1.8)	€1.5 (€1.2 to €1.8)	€0.9 (€0.7 to €1)	€0.9 (€0.7 to €1)
Total incremental cost (year 4)		€3.6 (€-0.2 to €7.6)	€0.8 (€-4.6 to €6.8)	€2.9 (€-0.8 to €6.8)	€0.2 (€-4.9 to €6)
Year 5	Antibiotics	€-5.6 (€-8.9 to €-2)	€-10.2 (€-15.4 to €-4.4)	€-5.6 (€-9 to €-1.9)	€-10.2 (€-15.1 to €-4.4)
	CRP test costs	€7.6 (€6.2 to €9.4)	€7.6 (€6.2 to €9.4)	€7.6 (€6.2 to €9.4)	€7.6 (€6.2 to €9.4)
	External QA	€1.5 (€1.2 to €1.8)	€1.5 (€1.2 to €1.8)	€0.9 (€0.7 to €1)	€0.9 (€0.7 to €1)
Total incremental cost (year 5)		€3.6 (€-0.2 to €7.6)	€-1.1 (€-6.5 to €5)	€2.9 (€-0.8 to €6.8)	€-1.7 (€-6.8 to €4.2)
Total incremental budget impact		€23.9 (€5.1 to €43.8)	€4.5 (€-22.8 to €34.8)	€18.1 (€-0.3 to €37.8)	€-1 (€-26.5 to €28.1)

Key: QA – quality assurance; CRP – C-reactive protein; HSE – Health Service Executive.

Table 8.17 Five-year budget impact with CRP test costs not incurred by HSE: scenario analysis (€millions)

		CRP test costs not incurred by HSE			
		One device per GP		One device per practice	
Year	Cost component	GP CRP	GP CRP + comm	GP CRP	GP CRP + comm
Year 1	CRP device	€6.1 (€4.9 to €7.4)	€6.1 (€4.9 to €7.4)	€3.6 (€2.9 to €4.3)	€3.6 (€2.9 to €4.3)
	Antibiotics	€-5.5 (€-9 to €-1.8)	€-10.1 (€-15.3 to €-4.4)	€-5.6 (€-9.2 to €-2)	€-10.2 (€-15.1 to €-4.6)
	CRP test costs	-	-	-	-
	GP comm training	-	€1.9 (€1.5 to €2.3)	-	€1.9 (€1.5 to €2.3)
	External QA	€1.5 (€1.2 to €1.8)	€1.5 (€1.2 to €1.8)	€0.9 (€0.7 to €1)	€0.9 (€0.7 to €1)
Total incremental cost (year 1)		€2 (€-1.7 to €5.9)	€-0.7 (€-6 to €5)	€-1.2 (€-4.8 to €2.4)	€-3.8 (€-8.9 to €1.8)
Year 2	Antibiotics	€-5.5 (€-9 to €-1.8)	€-10.1 (€-15.3 to €-4.4)	€-5.6 (€-9.2 to €-2)	€-10.2 (€-15.1 to €-4.6)
	CRP test costs	-	-	-	-
	External QA	€1.5 (€1.2 to €1.8)	€1.5 (€1.2 to €1.8)	€0.9 (€0.7 to €1)	€0.9 (€0.7 to €1)
Total incremental cost (year 2)		€-4 (€-7.5 to €-0.3)	€-8.6 (€-13.8 to €-3)	€-4.7 (€-8.3 to €-1.2)	€-9.3 (€-14.2 to €-3.7)
Year 3	Antibiotics	€-5.5 (€-9 to €-1.8)	€-5.5 (€-9 to €-1.8)	€-5.6 (€-9.2 to €-2)	€-5.6 (€-9.2 to €-2)
	CRP test costs	-	-	-	-
	External QA	€1.5 (€1.2 to €1.8)	€1.5 (€1.2 to €1.8)	€0.9 (€0.7 to €1)	€0.9 (€0.7 to €1)
Total incremental cost (year 3)		€-4 (€-7.5 to €-0.3)	€-8.6 (€-13.8 to €-3)	€-4.7 (€-8.3 to €-1.2)	€-9.3 (€-14.2 to €-3.7)
Year 4	Antibiotics	€-5.5 (€-9 to €-1.8)	€-10.1 (€-15.3 to €-4.4)	€-5.6 (€-9.2 to €-2)	€-10.2 (€-15.1 to €-4.6)
	CRP test costs	-	-	-	-
	GP refresher comm training	-	€1.9 (€1.5 to €2.3)	-	€1.9 (€1.5 to €2.3)
	External QA	€1.5 (€1.2 to €1.8)	€1.5 (€1.2 to €1.8)	€0.9 (€0.7 to €1)	€0.9 (€0.7 to €1)
Total incremental cost (year 4)		€-4 (€-7.5 to €-0.3)	€-6.8 (€-12 to €-1.1)	€-4.7 (€-8.3 to €-1.2)	€-7.4 (€-12.4 to €-1.9)
Year 5	Antibiotics	€-5.5 (€-9 to €-1.8)	€-10.1 (€-15.3 to €-4.4)	€-5.6 (€-9.2 to €-2)	€-10.2 (€-15.1 to €-4.6)
	CRP test costs	-	-	-	-
	External QA	€1.5 (€1.2 to €1.8)	€1.5 (€1.2 to €1.8)	€0.9 (€0.7 to €1)	€0.9 (€0.7 to €1)
Total incremental cost (year 5)		€-4 (€-7.5 to €-0.3)	€-8.6 (€-13.8 to €-3)	€-4.7 (€-8.3 to €-1.2)	€-9.3 (€-14.2 to €-3.7)
Total incremental budget impact		€-14.2 (€-31.8 to €4.4)	€-33.4 (€-59.5 to €-5.2)	€-20.1 (€-38.2 to €-2.5)	€-39.1 (€-64.1 to €-11.4)

Key: QA – quality assurance; CRP – C-reactive protein; HSE – Health Service Executive.

A further scenario analysis was considered in which an internal quality assurance scheme was implemented alongside CRP POCT with training in the use of CRP POCT provided by the HSE. Table 8.18 presents the results from this analysis. Two cost considerations are presented: one in which training is provided to each GP practice in Ireland and one in which practices are grouped (n=500), with training provided to approximately three practices per group. Implementing an alongside internal quality assurance scheme increases the budget impact of both CRP POCT strategies versus usual care. In the base case analysis, GP CRP and GP CRP + comm were associated with a budget impact of €23.9 million and €4.5 million, respectively.

The added cost of training increases the total budget impact by almost €10 million: GP CRP and GP CRP + comm are increased to €32.6 million and €12.2 million, respectively, if training is delivered to all 1,734 GP practices. Grouping practices so that training is delivered to approximately three practices concurrently has little effect on reducing the incremental cost of implementing an alongside internal quality assurance scheme.

Table 8.18 Five-year budget impact of implementing alongside internal quality assurance scheme: scenario analysis (€ millions)

	By GP practice (n=1,734)		By grouped practices (n=500)	
	GP CRP	GP CRP + comm	GP CRP	GP CRP + comm
Year 1	€12.6	€9.6	€12.4	€9.4
Year 2	€5.0	€0.2	€4.9	€0.0
Year 3	€5.0	€0.2	€4.9	€0.0
Year 4	€5.0	€2.1	€4.9	€1.9
Year 5	€5.0	€0.2	€4.9	€0.0
Total	€32.6	€12.2	€31.9	€11.5

Univariate sensitivity analysis

Univariate deterministic sensitivity analysis is undertaken to identify how sensitive the budget impact is to changes in input parameters. Here, the analysis assumes CRP devices are purchased for each GP in Ireland and CRP test costs are incurred by the HSE (as in the base case analysis). Figure 8.11 shows the results for GP CRP versus usual care. The risk reduction in prescribing has the greatest effect on the budget impact for the intervention versus usual care. At the lower parameter estimate (RR 0.59), the budget impact of GP CRP is reduced to €8.5 million; at the higher estimate (RR 0.91), the budget impact is increased to €40.8 million. The cost of a CRP test and cost of antibiotics have the next greatest effect on the budget impact of GP CRP. At the higher CRP test cost of €5.24, the budget impact is increased to €29.5 million; at the lower cost of €3.54 per test, the budget impact is

reduced to €17.5 million. In terms of the cost of antibiotics, at the higher cost of €14.32, GP CRP is associated with a budget impact of €16.7 million due to the increased cost of usual care. At the lower threshold of €9.67, the budget impact increases to €28.0 million. Few other parameters have an effect on the budget impact of GP CRP. Importantly, none of the parameters generate budget savings when held at their low/high values.

Figure 8.12 presents the results for GP CRP + comm. The results are sensitive to changes in some parameters, with budget savings available when prescribing at index consultation (€16.1 million), the cost of a CRP test (€2.9 million), proportion eligible for a CRP test (€1.8 million), proportion consuming antibiotics without being issued a prescription (€0.6 million) are held at their lower value, and cost of antibiotics is held at its upper value (€8.9 million). Changes to the other parameters do not introduce budget savings. The budget impact of GP CRP + comm is increased to €31.8 million if prescribing at index consultation is held at its upper value (RR 0.80). As with GP CRP, the results are most sensitive to the cost of antibiotics and CRP tests.

Figure 8.11 Univariate sensitivity analysis of budget impact of GP CRP vs. usual care (with investment in CRP devices by GPs and CRP test costs incurred by the HSE)

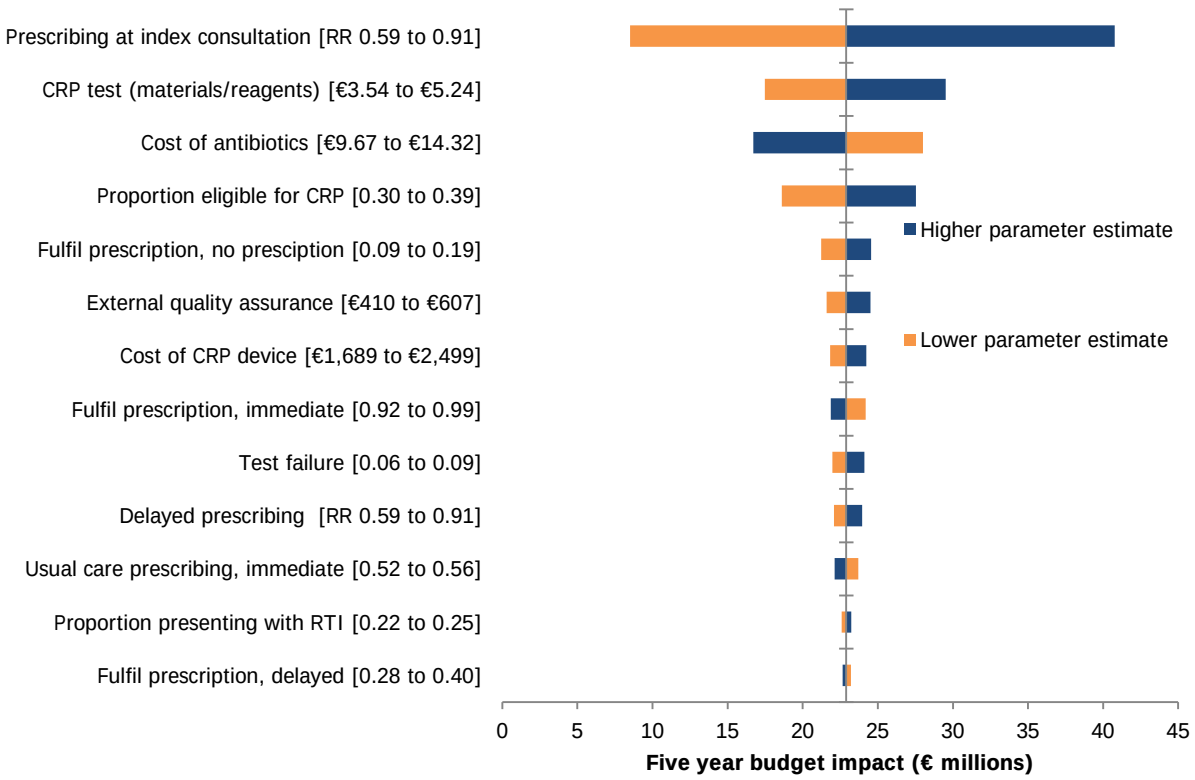
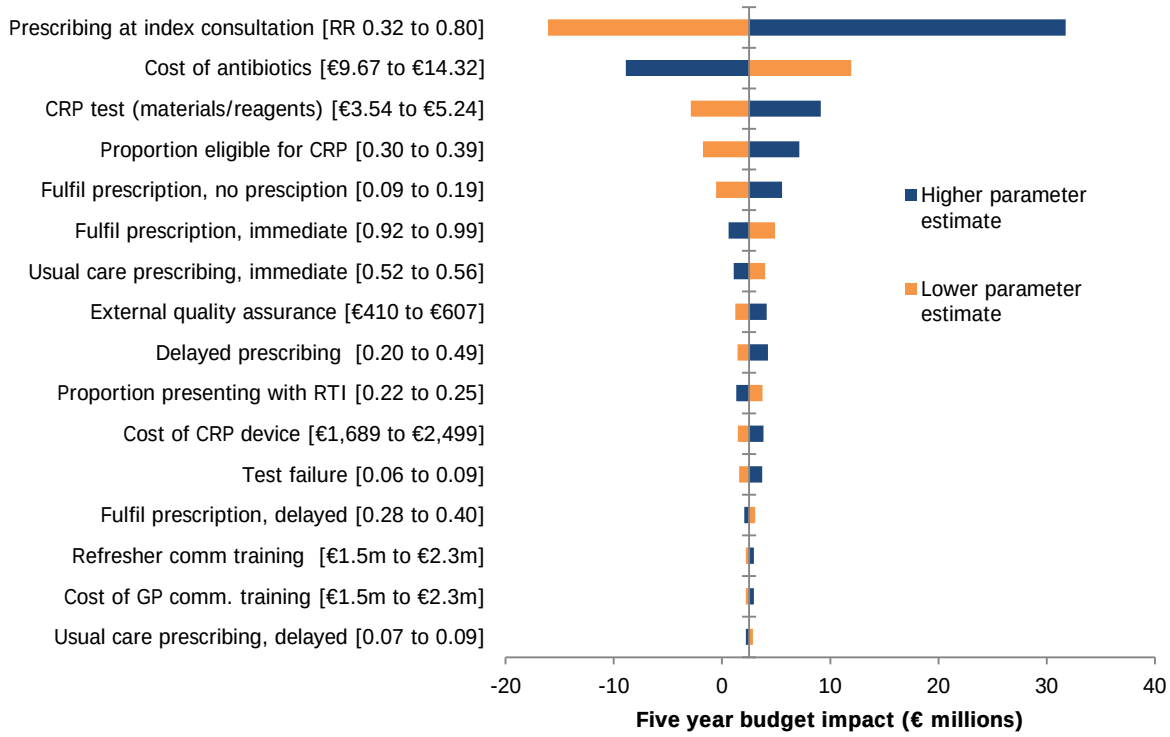


Figure 8.12 Univariate sensitivity analysis of budget impact of GP CRP + comm vs. usual care (with investment in CRP devices by GPs and CRP test costs incurred by the HSE)

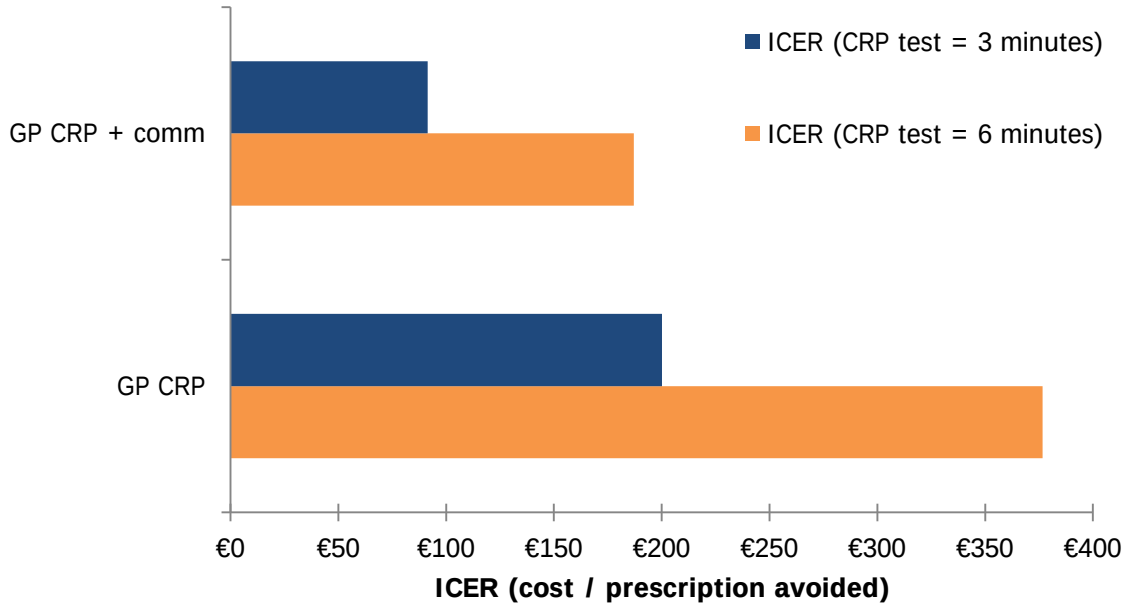


8.3.4 Sensitivity to assumptions about additional consultation time required to carry out CRP POCT

Uncertainty in relation to the amount of time added to a consultation due to the CRP test impacts on uncertainty in the cost-effectiveness. There are limited data available to support a parameter estimate, so the figure of 3 minutes used in the base case was derived from a previous economic evaluation.[238] Scenario analyses were used to further explore the impact of using different assumptions about the additional time.

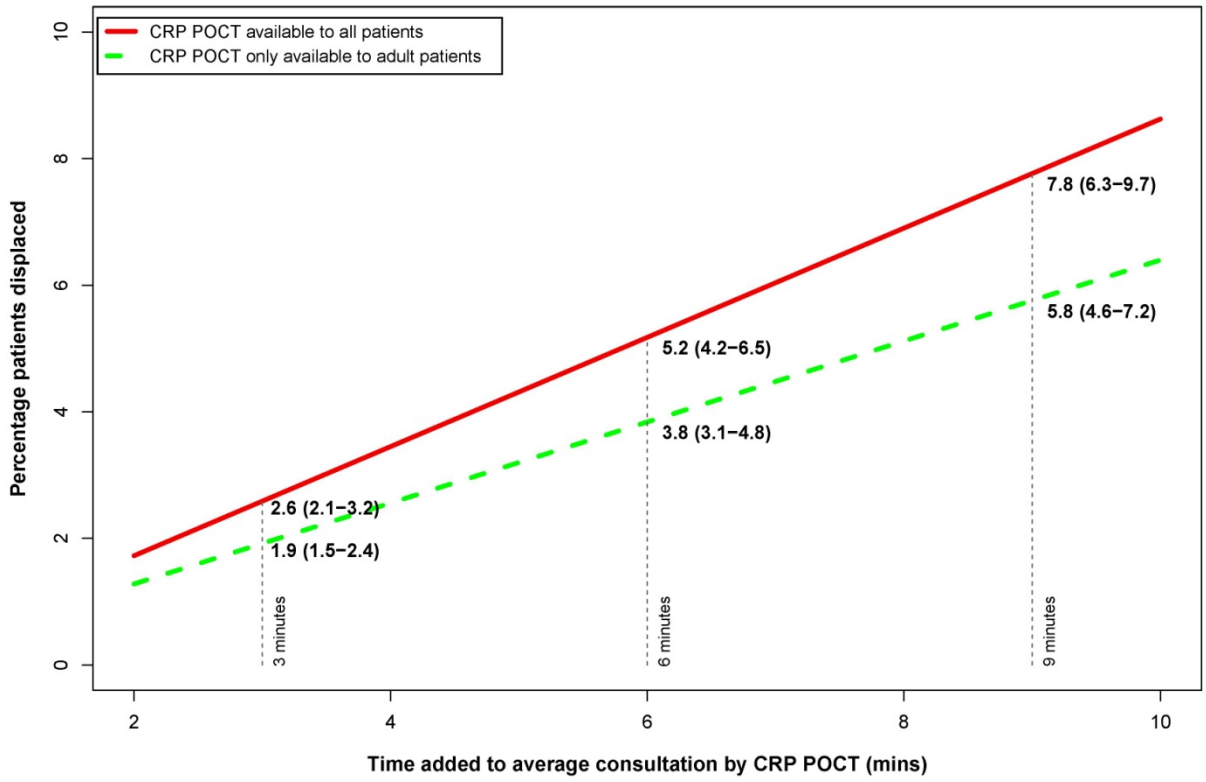
The first scenario analysis investigated the impact on the incremental cost-effectiveness ratio of increasing the additional consultation time to 6 minutes. As shown in Figure 8.13, the ICERs are highly sensitive to changes in the time required to complete the CRP test. At 6 minutes, the ICER for GP CRP and GP CRP + comm almost doubles to €376.61 (from €200.17 in the base case analysis) and €187.07 (from €91.38), respectively.

Figure 8.13 Estimated incremental cost-effectiveness ratios (€/prescription avoided) by different durations of time added to a consultation due to a CRP test



A second scenario analysis explored the opportunity cost in the form of displaced patient care. For example, given that the average consultation is assumed to take 9.2 minutes, if a CRP POC test added 4.6 minutes to a consultation then two CRP POC tests would displace one typical patient consultation. In the base case it was assumed that the CRP POC test adds 3 minutes to a consultation. In that case, if the CRP POC test can be used for both adults and children presenting with acute RTIs and for whom there is clinical uncertainty, 2.6% (95% CI: 2.1 to 3.2%) of activity will be displaced (Figure 8.14). If the test adds 9 minutes to a consultation, 7.8% (95% CI: 6.3 to 9.7%) of activity will be displaced. If only adults are eligible for CRP POCT, then the degree of displaced activity is reduced, although it is still substantial. Using the base case value of 3 minutes, 1.9% (95% CI: 1.5 to 2.4%) of activity will be displaced.

Figure 8.14 Percentage of activity displaced by CRP POCT



8.3.5 Scenario analysis of reimbursement for carrying out CRP POCT

Reimbursement for CRP POCT is provided in some European countries and ranges from €1.22 in Germany to €8.14 in Denmark per CRP test. A scenario analysis that considered reimbursement of GPs in Ireland for each CRP test performed was undertaken using these low/high thresholds. The additional cost of reimbursement of CRP tests considerably increases the budget impact of POCT over five years, even at the lower reimbursement fee of €1.22 per CRP test. At the lower estimate of reimbursement, CRP POCT alone could cost an additional €31.1 million over five years relative to usual care (Table 8.19). Combined with enhanced communication training, CRP POCT could add €10.7 million to the budget, which is approximately €8 million more than without the fee. At the higher reimbursement fee of €8.14, the budget impact of both strategies exceeds €50 million over five years.

Table 8.19 Five-year budget impact of different reimbursement of GPs per CRP test scenarios (€ millions, based on one device per practice)

	€1.22 / CRP test		€8.14 / CRP test	
	GP CRP	GP CRP + comm	GP CRP	GP CRP + comm
Year 1	€11.1	€8.1	€20.3	€17.4
Year 2	€5.0	€0.2	€14.2	€9.4
Year 3	€5.0	€0.2	€14.2	€9.4
Year 4	€5.0	€2.1	€14.2	€11.3
Year 5	€5.0	€0.2	€14.2	€9.4
Total	€31.1	€10.7	€77.2	€56.9

Based on reimbursement fees used in Europe, inclusion of a per test fee increases the five year budget impact by between €8.2 million and €54.3 million.

8.4 Discussion

The economic model presented in this chapter was used to estimate the cost-effectiveness and budget impact of CRP POCT for acute RTIs in the primary care setting. Three alternatives were included: current practice, and GP-delivered CRP POCT with and without the provision of additional communication training. The parameters used in the model were derived from a wide variety of sources based on Irish and international data. A decision tree model was developed that simulated the national population over five successive years to determine the impact of the three different strategies to guide antimicrobial prescribing in Ireland.

8.4.1 Main results

The economic analysis comprised a cost-effectiveness analysis and budget impact analysis, the results of which are detailed below. The analysis assumed that the uptake of CRP would remain high over the longer term. The annual number of CRP tests carried out in the primary care setting was estimated at 1.3 million (95% CI: 1.1 to 1.5 million). Under usual care there are an estimated 2.4 million antibiotic prescriptions each year associated with acute RTIs. With GP CRP that would fall to 1.8 million per annum, and with the combined GP CRP and communication training that would fall to an estimated 1.2 million per annum.

8.4.1.1 Summary of the cost-effectiveness findings

The cost-effectiveness analysis evaluated the costs and consequences of implementing CRP POCT relative to usual care in Ireland. Two POCT strategies were modelled: (1) GP use of CRP POCT and (2) GP use of CRP POCT with communication skills training, which is a training module designed to support GPs in their

communication with patients on the most appropriate use of antibiotics in the community. The model considered outcomes for the Irish population over a five-year time horizon. Costs specific to the HSE were modelled, with outcomes specified as the number of prescriptions avoided per RTI consultation. Relative to usual care, the model found both POCT strategies were more costly, largely due to the added cost of CRP tests, but both reduced antibiotic prescribing in the community. The combined intervention avoided 0.27 (95% CI: 0.13 to 0.37) prescriptions per RTI consultation, at an incremental cost of €26 (95% CI: €15 to €38), while GP CRP avoided 0.15 (95% CI: 0.06 to 0.22) prescriptions at an incremental cost of €30 (95% CI: €21 to €41). The ICER, or cost per prescription avoided, was €111 (95% CI: €45 to €243) for the combined intervention. As GP use of CRP was more costly and less effective than GP use of CRP with communication training, the strategy is said to be dominated (that is, not cost-effective versus GP CRP + comm).

The findings were generally robust to sensitivity analyses. However, some uncertainty in the cost-effectiveness of GP use of CRP POCT was introduced when the (RCT) evidence informing the risk reduction in prescribing was replaced with observational evidence. Using observational evidence, the two strategies sometimes generated additional prescriptions versus usual care. The univariate sensitivity analyses highlighted that prescribing at index consultation had the greatest effect on the ICER for both strategies, however the effect on GP CRP + comm was largely marginal. The higher parameter estimate (RR 0.80) for GP CRP + comm increased the ICER from €111 (in the base case) to €239. The results were somewhat sensitive to the univariate change in the duration of a CRP test. At the upper threshold of 3.75 minutes per test, the ICER increased to €115 for GP CRP + comm. The proportion of patients eligible for CRP (that is, patients for whom there is clear clinical uncertainty on the presence of viral versus bacterial infection) had a similar effect on the ICERs at the upper threshold of 39% eligibility. Few other parameters had an effect on the ICER for either strategy.

Although comparisons with previous economic analyses are challenging, the results of the economic model are broadly consistent with the literature. The only study that estimated a cost per prescription avoided reported results for GP use of CRP POCT versus usual care. Oppong et al. (2013)[240] found GP use of CRP POCT in Norway and Sweden was associated with a cost per prescription avoided of €112.70 (or €130 in 2018 Irish prices, adjusted for inflation and purchasing power parity) versus usual care, which is comparable with the combined intervention (GP CRP + comm) in this analysis (€111). The authors also reported outcomes using QALYs and concluded the strategy was likely cost-effective as the strategy produced a cost per QALY gained of €9,391 (€10,833). In the UK, the strategy was similarly deemed cost-effective by NICE (2014), who reported a cost per QALY gained of £15,763 (€17,866) versus

usual care. Hunter (2015)[238] also concluded that the strategy was likely cost-effective as it had a higher net monetary benefit than usual care, although this difference was marginal. Hunter also modelled outcomes for the combined intervention and found the strategy had a lower net monetary benefit than GP CRP due to higher costs and lower QALY gains. However, Hunter (2015)[238] did not report the range of costs and QALY gains, despite using probabilistic analysis, suggesting there may be no difference between the interventions. In contrast, Cals et al. (2011)[237] reported GP CRP + comm was more effective than GP CRP in reducing antibiotic prescribing in the Netherlands, and found that costs were similarly higher. Oppong et al. (2018)[241] also considered the combined intervention in their pan-European analysis and found the strategy was the most effective (in terms of reducing antibiotic prescribing), and also the most costly. Versus usual care, the authors reported GP CRP + comm had a cost per percentage reduction in prescribing of €126. In contrast, GP CRP had a lower cost per percentage reduction in prescribing of €95 due to lower intervention costs. The authors concluded, however, that the most cost-effective strategy was communication training on its own, which had a cost per percentage reduction in prescribing of €68. However, the basis for their conclusion was based on QALY gains rather than percentage reduction in prescribing; communication training had the same or highest QALY gains and lowest costs. Enhanced communication training as a distinct intervention was not modelled in this economic analysis as it fell outside the scope of the HTA.

8.4.1.2 Summary of the budget impact findings

This chapter also presented the total incremental five-year budget impact of implementing CRP POCT relative to usual care in Ireland. Due to the initial cost in the first year of implementing CRP POCT and subsequent cost of an external quality assurance scheme, along with the initial and subsequent cost of enhanced communication training, GP CRP + comm adds €4.5 million to the budget over five years relative to usual care if the HSE purchases one device per GP in Ireland. If one device per practice is purchased, savings of €1 million are available; however, some uncertainty in both scenarios is observed. If the cost of CRP tests is excluded from the budget impact, the cost savings arising from implementing GP CRP + comm are considerable, whether CRP devices are purchased for each GP in Ireland (€33.4 million) or each GP practice (€39.1 million). The cost-savings arise from the reduction in prescribing, which saves approximately €10 million each year (excluding year 1, and year 4 due to the initial cost of implementing CRP POCT and subsequent costs of refresher communication training.

There is some uncertainty in the budget impact of GP CRP on its own. Over five years, the strategy likely adds additional costs relative to usual care as the reduction

in prescribing is less advantageous than GP CRP + comm. However, there is some evidence that the strategy could be cost-saving; specifically, if the cost of a CRP test is excluded, the strategy becomes budget-saving, with potential savings of €14.2 million available if CRP devices are purchased for each GP in Ireland, and potential savings of €20.1 million if CRP devices are purchased for each GP practice. However, investment in internal quality assurance or the provision of a reimbursement fee associated with CRP POC tests substantially increases the budget impact.

8.4.2 Interpretation of the ICER

In this evaluation, the incremental cost-effectiveness ratio is presented as a cost per prescription avoided. While this outcome facilitates comparison across interventions that are intended to impact on prescribing rates, it does not support comparison of interventions intended to affect other outcomes. An alternative outcome measure is utility in the form of quality-adjusted life years (QALYs). A CUA is the preferred evaluation type for the reference case in Ireland, and it is considered the gold standard method for conducting economic evaluations. The QALY can be used to simultaneously incorporate changes in the quantity of life and in the quality of that life. In the case of CRP POCT, the intervention is intended to reduce antimicrobial prescribing without negatively impacting on patient outcomes. In this case, utility might be affected by a change to the disease course due to a changed treatment pathway, or through adverse effects of antibiotic treatment. To consider a cost-utility analysis there needs to be evidence of a minimally clinically important difference due to a change in patient management. For CRP POCT, the impact on quality of life is likely to be minimal and potentially not measurable for the majority of patients. The impact may be measurable for those who have an adverse reaction to antibiotic treatment, although that effect applies to a very small proportion of patients. In light of the lack of clear evidence regarding an effect on utilities, it was a pragmatic choice to carry out a cost-effectiveness analysis. Another issue for a cost-effectiveness analysis of cost per prescription avoided is that there is no accepted willingness-to-pay (WTP) threshold below which an intervention might be considered cost-effective. While it can be argued that there is no accepted WTP threshold for cost-utility analyses in Ireland, there are thresholds of €20,000 and €45,000/QALY that have been routinely used for reporting purposes. Although the cost-effectiveness analysis does not enable comparisons with other healthcare interventions or against a willingness-to-pay threshold, it does enable a comparison of the three interventions included.

Although it is difficult to place the findings of this analysis in the context of cost-utility values, it is reassuring that GP CRP had a comparable cost per prescription avoided as that reported by Oppong et al., who estimated that the intervention was

associated with a cost per QALY gained of €9,391 (or €10,833 in Irish-equivalent 2018 prices). It is possible that the strategy could be assumed to have a similar cost utility value, while the combined intervention, which had a lower cost per prescription avoided, could have a lower cost-utility value. However, these arguments are dubious, particularly in the context of the findings by Oppong et al., who reported no significant difference in QALY gains between the interventions.

8.4.3 Scenario and sensitivity analyses

Scenario and sensitivity analyses were used to explore the impact of different assumptions in the model, particularly in relation to uncertainty. Scenario analyses facilitate the incorporation of an alternative set of assumptions to determine the impact on the estimated cost-effectiveness. For example, a key assumption in this evaluation was the duration added to a GP consultation by carrying out a CRP POCT test. Although a wide range of values can be used in the model, the estimated 'average' duration will drive the summary estimate of cost-effectiveness. An important feature of scenario analysis is to consider whether the decision-maker has any control over the underlying assumption. For example, a decision-maker may be unable to influence the efficacy of a treatment, but they may be in a position to negotiate a lower price. As such, some scenario analyses illustrate the impact a different set of assumptions has on decision-making, while others may give practical guidance on the scope to affect the cost-effectiveness of an intervention. Uncertainty in specific parameters was found to have a strong influence on uncertainty in the estimated cost-effectiveness and budget impact of CRP POCT:

- Treatment effect of the intervention

  The relative risk of antibiotic prescribing in patients who received either intervention was the key parameter that defined the reduction in antibiotic prescribing. The data that underpinned this parameter were derived from a systematic review presented in Chapter 4. The treatment effect, particularly for GP CRP with enhanced communication training, was substantial. For GP CRP with no enhanced communication training, the rate of prescribing is expected to reduce by a quarter, on average. For GP CRP with enhanced communication training the reduction is of the order of 50% based on limited evidence. A key consideration is whether the trials are generalisable to the Irish primary care setting in terms of how patients are managed, baseline antibiotic prescribing, and the demographics of the RTI patient population. The trials may be considered broadly applicable, although it is unclear if such large treatment effects would be seen in practice. The observational studies showed an even greater treatment effect, suggesting that the reductions in

prescribing may indeed be realised in a national programme. It is worth highlighting that the relative risk parameters were subject to substantial uncertainty, and this was shown to be very influential on uncertainty in both the cost-effectiveness and budget impact analyses. In the event that CRP POCT is rolled out nationally, it will form one of a number of initiatives aimed at reducing antimicrobial prescribing. It is unclear how those initiatives may interact and whether their individual impacts would be reduced. It was assumed that the trials took place in settings where other strategies were also in place to reduce antimicrobial prescribing and that the findings are broadly applicable.

- Duration of test

The cost-effectiveness of CRP POCT interventions was sensitive to the amount of GP time needed to administer the test. In the model it was assumed it would add an average of 3 minutes (95% CI: 2.25 to 3.75 minutes) of GP time to a consultation. In the context of an average consultation being 10 minutes or less and 23% of consultations being for RTIs and an average 34% of RTI episodes potentially getting a CRP test, the intervention could add substantially to GP time. As the perspective of the HTA is the publicly funded healthcare system, GP time is considered as an opportunity cost. If a consultation takes an additional 3 minutes, the HSE does not pay financially for that time unless a fee per service agreement is entered into. However, if the use of the CRP POC test extends a consultation by 3 minutes, that will displace care for other patients. In the base case analysis, approximately three consultations involving a CRP POC test will displace one typical consultation, lasting approximately 9 minutes. Given the prevalence of acute RTIs and the large proportion potentially eligible for CRP tests, a very substantial number of consultations could be displaced through GPs administering CRP tests. Displacement of other activities will include those that are associated with fees or income, such as immunisations, ECGs, antenatal care and diabetes visits. A reduction in income may adversely impact on use of CRP POCT, as GPs might either not use it or might charge patients a fee on a test-by-test basis. The displacement of activity may be partly offset by potential reductions in consultations for subsequent episodes of self-limiting acute RTIs. An important consideration is whether other practice staff could administer the test, such as practice nurses, thereby potentially reducing the opportunity cost of CRP POCT.

- Cost of GP time

  It was assumed in the model that the additional consultation time incurred by carrying out a CRP test would be an opportunity cost of GP time. The majority or practices employ a practice nurse or healthcare assistant and some may be able to reorganise workflows so that staff other than the GP carry out some or all of the CRP tests. This could potentially reduce but not eliminate the opportunity cost associated with carrying out the test, and it is likely that practices would seek to manage CRP testing in a manner that minimises disruption to capacity. However, a conservative approach was adopted for the analysis which used the cost of GP time to calculate the value of the opportunity cost, and may therefore be an over-estimate for practices where testing is delegated to a practice nurse or healthcare assistant. It must be borne in mind that the perspective of the analysis is that of the HSE. Additional consultation time does not incur a direct cost to the HSE, although arguably displaced care can generate additional costs if patients experience poorer outcomes due to delayed consultations. It is important to bear in mind that the staff that carry out CRP testing should have received adequate training to ensure an acceptable standard of testing. Based on reimbursement fees observed in Europe, inclusion of a fee per test increases the five year budget impact by between €8.2 million and €54.3 million.

- Cost of antibiotics

  Uncertainty in the cost of antibiotics prescribed to treat acute RTIs impacted on uncertainty in both the cost-effectiveness and the budget impact. Depending on the extent to which the choice of antibiotics could be affected, it may be possible for the total cost of prescribing antibiotics for acute RTI to be reduced.

- Cost of CRP test

  The cost of the CRP test comprises the testing device and the consumables (that is, materials and reagents). Uncertainty in the cost of the consumables has a greater impact on uncertainty in the cost-effectiveness and budget impact than the cost of the device. On a per consultation basis, the consumables contribute a greater proportion to the cost of the CRP testing than the device itself. Should CRP POCT be rolled out, it would be prudent to determine the approach to procurement that delivers best value for money.

- Discount rate

  The estimated cost-effectiveness was affected by the discount rate used. The discount rate reflects time preferences, specifically a societal preference for benefits to be realised in the present and costs to be experienced in the future. With acute RTIs, as the disease course and treatment is so short, costs and benefits are largely incurred at the same time. The exception is the device: for cost-effectiveness, the cost of the device is a capital expenditure that must be annuitised over the device lifespan, in this case seven years. Most other European countries have discount rates in the region of 3% to 4%, and it is possible that the discount rate in Ireland may change to reflect the changing economic circumstances. However, the results should be considered in terms of the discount rate that currently applies.

8.4.4 Strengths and limitations

A key limitation of the analysis is that it is not possible to state whether the included interventions can be considered cost-effective either relative to other interventions or to a willingness-to-pay threshold. An economic evaluation typically seeks to address two questions: is an intervention an efficient use of resources (cost-effectiveness), and is it affordable (budget impact). Both are important considerations for decision-making. An intervention may be efficient but unaffordable, or may be affordable but an inefficient use of resources. In both cases the decision may be made not to invest in the intervention. In this case we cannot easily determine if CRP POCT is an efficient use of resources, hence the decision must be considered in terms of the budget impact and in the wider context of the policy goal regarding reducing antimicrobial resistance.

The treatment effect is marked, particularly for GP CRP with enhanced communication training. The data came from randomised controlled trials with observational data included as a scenario analysis. It is possible that the relative effect is applicable irrespective of the rate of prescribing in usual care. However, it is also possible that conditions in Ireland differ from other countries for a variety of reasons, and that due to those differences the treatment effects from the trials do not apply to the Irish setting. One study showed that CRP POCT usage diminished substantially over time, reducing the effectiveness of a CRP POCT programme.[180] The effectiveness of enhanced communications training was maintained, however. It is possible that the fall off in usage is affected by the seasonal nature of RTIs. While demand may be high in the first winter period that CRP POCT is available, the test may drop out of favour after the fall off in demand during the off-peak season.

Clinicians might find that the inconvenience of quality assurance, device maintenance, additional consultation time and the need for ongoing training may outweigh the perceived clinical benefits. However, the finding of decreased usage came from an audit exercise associated with a single study. It is possible that with the appropriate support clinicians may continue to use the test to guide prescribing decisions over the longer term.

The trials measuring the treatment effect of CRP POCT have short-term follow-up: the longest reported follow-up was 28 days. While this provides information in relation to the treatment of a specific episode of acute RTI, it does not provide information about impact on subsequent patient behaviour. One trial by Cals et al. published longer-term follow-up data collected 3.5 years after the start of the study.[159] They found that while visit rates for RTIs were lower in the CRP and communication skills groups than in the usual care groups, the difference was not statistically significant. However, it does provide some support for the hypothesis that CRP testing and the communication training may lead to reduced visit rates through increased awareness and patient self-management of future RTIs. These are potentially important considerations as they support the notion that the effect of CRP POCT on patient behaviour may be sustained over the longer term and may reduce GP attendance, which would be a counterbalance to the increased duration of consultations involving CRP testing. It is also possible that the rate of utilisation of the CRP test may decrease over time. If the test is seen as disruptive to workflow, then a GP may become more selective about when it is used by implicitly adopting a narrower definition of clinical uncertainty. Usage may also decrease if patients learn through experience that it is generally unlikely that an antibiotic is appropriate to treat a RTI. In the event that there is a rapid falling off of usage, the initial investment in devices will not be countered by sustained reduced antibiotic prescribing. The initial budget impact will stand without the benefit of ongoing reduced prescribing. Such an eventuality will also lead to an increased ICER.

A number of key parameters regarding the epidemiology of RTIs in primary care in Ireland were derived from three publications relating to a single study with data collected between 2008 and 2010.[70, 88, 89] The study included GPs involved in small-group continuing medical education. Data were not collected during the summer months and out-of-hours consultations were excluded. By comparing the characteristics of the GPs in the survey sample to those nationally,[255, 256] younger GPs and female GPs are over-represented, while single-handed practices are under-represented. RTIs were classified by the study team based on symptoms recorded, rather than on classification by the GP. Based on these issues, it is possible that the data from the Murphy study may be biased with respect to primary care-based RTI consultations in Ireland at present. The potential impact of that bias can be

considered through the univariate sensitivity analyses. The key parameters obtained from the Murphy study are the proportion of primary care attendances that are for RTIs and the proportion of those attendances that result in an antibiotic prescription. The uncertainty around those two proportions did not have a marked impact on the uncertainty in either the ICER or the budget impact. It must be stressed that due to the large sample of patients in the study (n=16,899), the estimates for the two proportions are very precise and the imprecision was increased to acknowledge the potentially biased sample. Another consideration is whether prescribing patterns have changed markedly since the study was conducted. A scenario analysis was used in which the relative change in defined daily doses between 2009 and 2018 was applied, which showed an increase in prescribing relative to the study period. In the absence of other Irish data sources, the Murphy study represents the only applicable local data. Data on the proportion of RTI patients receiving an antibiotic prescription was also adjusted in a scenario analysis to take into account that prescribing patterns may have changed since the Murphy study was carried out. That adjustment was based on the relative change in DID for total antibiotic use in the community in Ireland. It is acknowledged that this represents a crude adjustment, although it does provide an approximate indication of what the prescribing rate may be at present.

Data on the rate of primary care consultations by age and sex were derived from Irish survey data. The figures for children predate the introduction of the under-sixes GP visit card and hence may underestimate visit rates. Allowances were made by increasing the visit rates in under-sixes who were not eligible for a GMS card using the commonly found effect that acquisition of a medical card leads to an increase of one visit per annum on average.[257] In light of the lack of evidence regarding the effectiveness of CRP POCT in children with RTIs, it may be pragmatic to focus on results based on the adult population only.

The model was designed to include the entire national cohort of patients attending primary care with a respiratory tract infection. This choice was influenced by the available data and the need to model the budget impact of CRP POCT, which is based on the total population and not a notional cohort (of 1,000 patients, for example). The use of the national cohort has some important implications for the model. First, the model simulated GP consultations rather than patients with acute RTI episodes. The available Irish data on acute RTIs in primary care related to consultations rather than episodes, therefore the approach adopted was consistent with the Irish data. As the model simulates consultations, it is not possible to explore the impact of potentially reduced rates of subsequent RTI consultations for patients in the intervention groups relative to usual care. The model structure means that the number of acute RTI consultations is the same for each year modelled, not

decreasing in response to the intervention or changing due to a changing demographic profile. It was further assumed that the proportion of patients with acute RTI who are given the test will remain the same each year. Depending on how testing impacts on patient and GP behaviour, and on how disruptive the test is to practice workflow, the proportion patients tested might decrease quite substantially over time. A reduction in testing would likely result in a less marked impact on antibiotic prescribing.

The estimates of cost-effectiveness and budget impact are based on CRP POCT being rolled out to all GPs. In the base case analysis it was assumed that approximately 3,000 CRP POCT devices would be required to get full coverage. That is, it was assumed that all GPs would have direct access to a CRP POCT device in their practice. The number of devices needed is subject to uncertainty and may depend on the funding model used. Sensitivity analyses were used to explore the impact of having one device per GP or one device per practice as extremes. Another aspect is access to CRP POCT in long-term care facilities (LTCFs) for older persons. In many instances GPs visit LTCFs to provide consultations as residents may not be in a position to travel to their GP's practice. Given the portability of some of the CRP testing devices, it may be reasonable to assume that the GP will bring a device with them, rather than the LTCF investing in a device that is kept on site permanently. However, the most appropriate approach to ensuring access to CRP POCT devices in LTCFs would have to be determined as part of a policy decision.

The model incorporated costs associated with the CRP test, antibiotic prescribing, communication training, and the treatment of adverse reactions. The model did not include the cost of a public awareness campaign. Introducing CRP testing nationwide might benefit from a public awareness campaign to ensure patients understand the reason for it and the potential benefits at both an individual patient level and at a societal level. However, the nature of such an awareness campaign is that it must be linked into the wider context of initiatives to tackle antimicrobial resistance. As such, it would be very challenging to cost such a campaign in isolation.

The model did not include a cost for governance of the CRP POCT programme. While such a role might naturally sit within the hospital laboratory network, a clear structure and costing was not identified. Similarly, no costs were included for accreditation or for a centralised system for monitoring test results, batch numbers and other data. In both cases the costs would fall partly but not entirely on CRP POCT, as the structures would also apply to other POC tests carried out in the primary setting. In the event that the hospital laboratory network takes on the responsibility of governance, there would be logistical and resource implications that would have to be considered.

GP time was not included in the budget impact analysis as it is considered an opportunity cost for GMS patients and a potentially out-of-pocket expense for non-GMS patients. While opportunity costs are included in a cost-effectiveness analysis, they are excluded from the budget impact as they do not incur an immediate expense. However, although opportunity costs do not appear in the budget impact figures, where they have a potentially important bearing they should be considered as important contextual information when interpreting the budget impact. A scenario analysis was used to determine the change in budget impact if a reimbursement fee was provided for carrying out the CRP POCT.

The opportunity cost to a practice of an increased consultation time is complex to determine, and will depend on the mix of GMS and private patients in a given practice. Although GMS patients are associated with a capitation fee, displaced care can include consultations with linked fee-per-item activity such as immunisations. However, the opportunity cost must be weighed against the contribution of CRP POCT to efforts to ensure high quality prescribing practice. Reimbursement for CRP POCT is provided in some European countries, ranging from €1.22 in Germany to €8.14 in Denmark. Reimbursement may acknowledge the disruptive nature of the test, but can also create incentives that may distort use of the test. As was shown in a scenario analysis, the inclusion of reimbursement resulted in a substantially increased budget impact.

The cost of external quality assurance was incorporated on the basis of an annual cost of participation in an EQA process. The cost of initial and refresher training was also incorporated. However, practice costs for participation in EQA and internal quality assurance were not included. These costs would arise in the form of opportunity costs for time spent on quality assurance processes, such as testing samples with known CRP levels. The amount of time required and the value of the opportunity cost will depend on recommended frequency of quality assurance and the member(s) of staff involved in QA. In the event that reimbursement is provided on a fee-per-item basis, it is assumed that the fee would recompense for both carrying out the test and for correct maintenance of the test equipment.

8.5 Summary

The findings presented in this chapter suggest CRP POCT reduces antibiotic prescribing in primary care, irrespective of whether the strategy is implemented by GP use of CRP or GP use of CRP with enhanced communication skills training. However, the strategies introduce additional costs via CRP test costs, for example, which increase the cost of delivering care. Whether the strategies are cost-effective is somewhat unclear in terms of conventional criteria for decision-making. As cost-

effectiveness was specified using a cost per prescription avoided, as opposed to cost per QALY gained, it was not possible to compare the results against a predefined or notional cost-effectiveness threshold. It is likely that both strategies are cost-effective, and the results are consistent with the literature. The combined intervention (that is, GP CRP + comm) is likely more cost-effective as it is associated with a greater reduction in prescribing and is less costly than GP use of CRP POCT on its own. In terms of the budget impact, the evidence suggests that the combined intervention could generate considerable cost-savings over five years relative to usual care, with significant cost-savings available most years due to reduced antibiotic costs. GP CRP testing likely adds additional costs, although there is some evidence that the strategy could be budget-saving. The introduction of CRP POCT creates an opportunity cost by potentially displacing clinical activity through increased consultation times, although that may be moderated through other effects, such as future reductions in consultations for RTIs.

8.6 Key messages

- A decision tree model was developed to simulate the impact of introducing a national programme of C-reactive protein point-of-care testing with and without additional enhanced communication training for GPs.
- An estimated 1.3 million CRP POC tests (95% CI: 1.1 to 1.5 million) would be carried out each year in primary care if CRP POCT is available across all GP practices.
- An estimated 2.4 million prescriptions are currently issued for RTIs in Ireland annually. The annual number of antibiotic prescriptions would be an estimated 1.8 million per annum for GP use of CRP without communication skills training, and 1.2 million per annum with enhanced communication training.
- Both POCT strategies were more costly than usual care, but both resulted in reduced antibiotic prescribing in the community. The incremental cost per prescription avoided associated with the POCT strategies was €111 (95% CI: €45 to €243) for combined CRP POCT and communication training while GP use of CRP POCT without communication training was dominated (less effective and more costly). GP use of CRP POCT with communication training may be more cost-effective than GP use of CRP POCT without communication training, although there is little to differentiate the two interventions in terms of costs and prescriptions avoided.
- GP use of CRP POCT with communication training saves €1 million over five years relative to usual care if one device per practice is purchased, but costs an additional €4.5 million more than usual care if one device per GP is purchased. GP use of CRP without communication training has an estimated five-year budget

impact of between €18.1 million (one device per practice) and €23.9 million (one device per GP).

- In the event that GPs are reimbursed on a fee per test basis, based on reimbursement fees observed in Europe the five year budget impact by between €8.2 million and €54.3 million.
- The budget impact estimates were subject to considerable uncertainty influenced by the baseline prescribing rate, the cost of antibiotics, the cost of the CRP test, and the proportion of acute RTI episodes that would be considered eligible for CRP testing.
- As part of the base case model it was assumed that the HSE would finance the CRP testing devices and associated consumables, and the cost of communication training.
- The introduction of CRP POCT is likely to displace clinical activity through increased consultation times, although that may be moderated through other effects such as future reductions in consultations for RTIs.
- The results of the economic model were subject to substantial uncertainty, and rely on the assumption that use of CRP POCT will continue.

9 Organisational issues

This chapter reviews the potential implications of changes to the diagnosis and treatment of acute RTIs in the Irish primary care system if CRP POCT is adopted. The purpose of this review is to identify and discuss any broader issues relevant to the decision-making process, and to highlight potential changes to the organisation or delivery of services required to support the delivery of CRP POCT in primary care in Ireland. This chapter was developed broadly in line with the structure described in the EUnetHTA Core Model.[258] Where possible, evidence from international CRP POCT programmes, with particular focus on Wales, informs suggested changes to the organisation or delivery of services required to support the delivery of CRP POCT in primary care.

9.1 Primary care

General practices provide first-level contact with the healthcare system, which is fully accessible by self-referral. General practitioners (GPs) may also have responsibility for the care of persons living in residential care facilities. There has been a movement towards GP-led delivery of primary care in Ireland. Patients with a general medical services (GMS) card are entitled to free GP care, with GPs reimbursed for this care through the GMS scheme by the HSE. For each eligible GMS patient, GPs are paid an annual capitation payment (weighted by the age and sex of the patient); GPs may also claim for a range of other fees and allowances depending on the number and variety of services provided to patients.[259] The GP visit (GPV) card was introduced in 2005, and was extended regardless of income to patients under six years old and 70 years old and over in 2015. Those who do not hold a GMS or GPV card pay a consultation fee to visit the GP. Hereafter, the terms public and private patients are used to describe these two groupings. The fee paid by private patients can vary by individual practitioner. The average cost associated with a private GP visit was estimated to be €49.97 in 2017.[249] Additional fees are payable by private patients on a fee-for-service basis for services, such as phlebotomy tests, and any follow-up appointments with the doctor or nurse.

Using 2015 Healthy Ireland data on GP visits, 2018 PCRS data on GMS eligibility and 2018 population estimates from the CSO, there is an estimated 16.9 million GP consultations per annum. In 2016, 45.6% of the population had public (GMS plus GPV card holders) coverage.[249, 260] Consultation rates are noted to differ by patient status, with average annual consultation rates of 5.6 and 2.7 for public (GMS plus GPV card holders) and private patients, respectively in 2014.[261]

It is estimated that Ireland has 62.6 general practitioners per 100,000 population.[261] There are an estimated 2,954 GPs working in Ireland.[247] Based on 2016 data, there are an estimated 1,734 GP practices in Ireland (of which 201 do not have a GP operating with a GMS contract number).[254] There are 15 GP out-of-hours cooperatives with treatment centres located across 85 sites.[262] The total number of long-term care facilities (LTCFs) serving the needs of older persons in Ireland is estimated at 576, of which 121 (21%) are HSE-registered facilities, providing a total system maximum bed capacity of 30,682 beds.[263] In addition to LTCFs for older adults (general nursing homes), LTCFs comprise facilities caring for residents with intellectual disabilities and long-stay facilities for residents with psychiatric conditions. In recent years, there has been a systematic movement away from residential care in LTCFs for the latter groups towards decongregation to community-based care.

9.1.1 Practice resources

The logistics of offering the CRP POCT in primary care were described in detail in Chapter 2.5. On the basis of this information, consideration should be given to the following issues if CRP POCT is adopted.

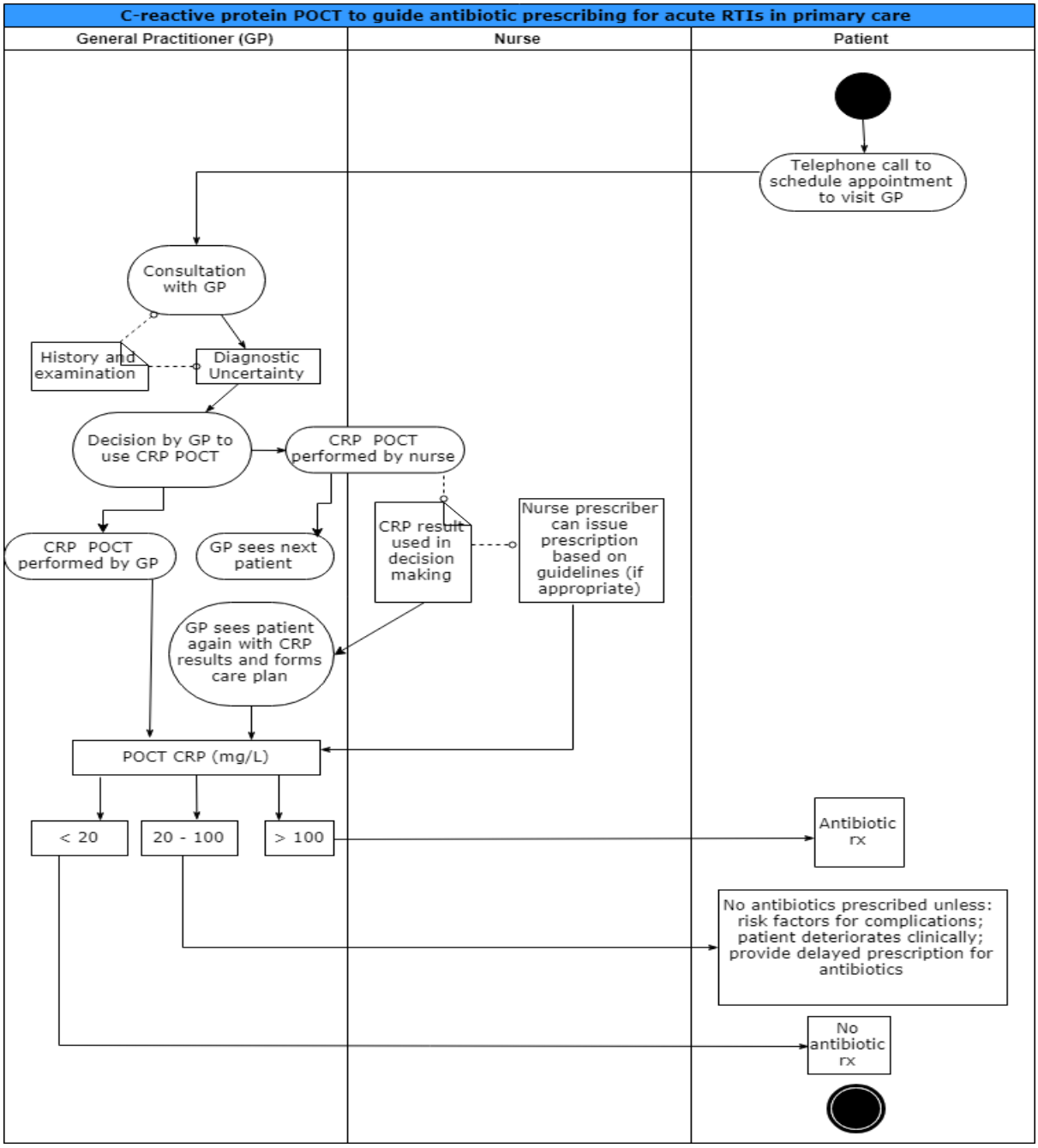
Identified CE marked POCT devices included semi-quantitative (n=3) and quantitative (n=12) devices, with the latter requiring the use of an analyser. The majority of these quantitative devices are compact desktop devices that could typically be accommodated within existing GP treatment rooms without a need to invest in or alter premises. For GPs who provide care in a number of primary care settings (including out-of-hours clinics and LTCFs), adoption of a compact portable analyser could potentially facilitate its use across these sites, eliminating the need for capital investment in multiple devices. While some of the equipment required to support CRP POCT (including lancets and capillaries for taking blood samples) are typically stock items in any surgery, certain brand consumables used with CRP POCT analysers may require refrigeration; as a result, additional refrigerator capacity may be required should CRP POCT be adopted.

CRP POCT can be undertaken by individuals trained in the use of the device. To date in Ireland, the current practice for POCT has been that such tests are carried out by the GP or the practice nurse. There are approximately 37.1 practice nurses per 100,000 population, equivalent to one practice nurse per 1.7 GPs.[247] The Irish Practice Nurses Association (IPNA) estimates that approximately 2,000 nurses are employed in either full-time, part-time or job sharing roles in primary care. Depending on who has the responsibility for carrying out the CRP POCT test (that is, the practice doctor or nurse), changes to how patient flow is managed in the

practice may be necessary with a potential impact on the length of patient consultation times. Figure 9.1 illustrates a possible treatment pathway for the use of CRP POCT. If the test is undertaken by the practice nurse, it may involve the patient having the initial consult with the doctor followed by the POCT with the nurse, and a subsequent reconsult with the GP to review the test results, a prescription (if necessary) and communication around the test result. For registered nurse prescribers, this latter step could be simplified with the prescription (if necessary) and communication around the test results delivered by the nurse. The IPNA estimates that over 50 nurse prescribers are currently working on the basis of collaborative prescribing agreements for patients with certain chronic conditions. The implementation of CRP POCT may require changes to working processes and patient flow within the general practice. Individual practices and practitioners may need to consider their own staffing, infrastructure and culture when establishing the workflow for a CRP testing service.[34]

Most GPs in Ireland practice from well-equipped premises, with about 10% already practicing from a purpose-built primary care centre.[255] Most practices are equipped with computers, clinical and diagnostic equipment, and employ management personnel to support the administration of the practice.[255] Eighty-two percent of practices employ a full- or part-time practice nurse. Practice nurses may have variable roles depending on the workflow arrangements of the GP practice. These roles may consist of: 1) triage of patients at presentation, 2) task-orientated work alongside the GP (for example, carrying out phlebotomy services, INR testing or blood glucose testing), and/or 3) autonomous workload with primary responsibility for chronic disease management (CDM) and childhood immunisation. Many practice nurses will provide services to patients on the basis of a prior scheduled appointment. This could potentially cause a barrier to the option of patients moving between the GP and the practice nurse to carry out the CRP POCT. Healthcare assistants (HCAs) and clinical support workers are FETAC level 5 trained. They have started to undertake advanced roles in primary care, such as venepuncture, urinalysis, oxygen therapy, safe administration of medication, wound dressings, vital sign and blood glucose monitoring. HCAs could be considered for a potential role in the delivery of CRP POCT in primary care.

Figure 9.1 Sample patient flow for use of CRP POC testing for acute RTIs in primary care



Evidence from Chapter 2 indicates that the turnaround time for a test varies according to the device, ranging from 4 to 15 minutes due to differences in the test type (quantitative or semi-quantitative), the extent to which pre-analytical handling is required, analyser warm-up time and performance time. This range was also reported in Chapter 6 on the systematic review of analytical performance with

results of 3.0 to 13 minutes. While the need for an analyser is eliminated with the semi-quantitative devices, as noted in Chapter 6, the accuracy of the tests decline after the optimal read time of 5 minutes, presenting potential challenges for their incorporation into busy practices. Choice of the CRP POCT device is therefore an important consideration for work practices. For the economic evaluation, it is assumed that carrying out a CRP POCT test will lengthen a GP consultation by an average of 3 minutes, potentially having a substantial impact on workload, patient flow and work practices. For the evaluation it was assumed that the additional 3 minutes would fall on the GP while in some practices it may be possible to transfer the additional workload to other members of staff, such as practice nurses or healthcare assistants. The test duration may have implications for what practice resources are allocated and how they are used for CRP POCT. Evidence from the systematic review of analytical performance (Chapter 6) indicates that participating in an external quality assurance scheme more than once, performing internal quality control at least weekly, the type of instrument used, having laboratory-qualified personnel performing the tests and performing more than 10 CRP tests per week were all associated with good test performance. This would suggest that user experience and familiarity with the device are an important consideration, so that there may be potential for synergies in larger primary care practices if testing were restricted to a smaller number of individuals.

Adoption of CRP POCT would result in additional clinical waste, the handling and disposal of which should be in accordance with the usual requirements for potentially biohazardous waste. Consistent with current practice, waste disposal costs are the responsibility of the GP practice.

Compliance with international standards for POCT (ISO 22870: 2016) would provide assurance of the validity and capture of the POCT results in the patient electronic health record. To facilitate ISO accreditation, connectivity with the CRP POCT analyser may require investment in barcode printers, scanners and/or middleware IT programmes to ensure integration across the wider practice ICT infrastructure.[264]

9.1.2 Training

Consistent with best practice, all healthcare professionals performing CRP POCT will require training on how to use the analysers, how and where to record the results, how and why internal and external quality control is performed, and what to do if an analyser does not work properly.[265] The level of training will depend on whether the technology adopted is semi-quantitative or quantitative. As outlined in section 2.5, the national guidelines for the implementation of POCT in primary care (2009) detail

the requirements for staff training on POCT including the core elements required for a POCT training programme.[40]

The logistics of diagnostic modalities in primary care were assessed by the National Institute of Health Research (UK) in 2016.[266] It assessed the evidence base for diagnostic services provided outside hospital settings, for example in the community or in general practice. A framework map and evidence synthesis reported a STEP-UP map for POCT. The report on staff training for the provision of a POCT service recommended that training occur prior to the introduction of CRP POCT, which included providing an understanding of the specific CRP POCT device used; the skills for setting up the device, performing the test, recording the results, using the quality assurance materials, and disposing of sharps; and an understanding of the relevant health and safety legislation.[266] These recommendations are consistent with current best practice for the provision of POCT in the Irish primary care setting.[40]

For further consistency with international best practice, training protocols should include standard operating procedures (SOPs) for the CRP POCT devices.[267] Examples of such SOPs are available from the pilot study of CRP POCT implementation in primary care in Wales, in which SOPs for the CRP POCT device, including internal quality control (IQC) procedures, monitoring, basic troubleshooting and competency documents, were prepared by the hospital laboratory POCT teams. Issues relating to clinical governance, risk management, user competence training, IQC and external quality assurance (EQA) as defined by ISO 22870: 2016 standards for POCT analysers were considered in the development of the master reference documents. During the introduction phase of implementation in Wales, the hospital laboratory POCT teams provided quality control assurance and troubleshooting support. A robust user competency assessment process, which was routinely audited and supported by the hospital laboratory POCT team, was found to be beneficial.[38] In the event of a decision to provide CRP POCT in Ireland, consideration could be given to the adoption or adaptation of such measures to facilitate consistent provision of a quality-assured service across all sites. There may be useful lessons from the transfer of INR testing services from the hospital setting to primary care, which has been facilitated by HSE staff providing the training on the use of INR POCT. In this case, the INR POCT device manufacturer provided support around training on the use of the device, troubleshooting and use of the companion computer software package for the device.

Although initial training on the use of the CRP POCT device can be provided by the device manufacturer, consideration should also be given to developing training programmes that are available nationally, potentially in conjunction with the hospital laboratories. A training programme and standard operating procedures provided to

ISO 22870: 2016 standards for POCT specific to all the requirements for quality and competence applicable to CRP POCT would help support the development of a quality-assured process. This ISO standard relates to hospitals, clinics and organisations providing ambulatory care, but excludes patient self-testing in home or community settings. This dedicated training would be provided in relation to the use of the CRP POCT device including advice on its operation, quality control and troubleshooting. Expert opinion has estimated a total of 3 hours of training in the first year (of which 2 hours are required for initial training) and approximately 1.5 hours in subsequent years. The follow-up training time to maintain the competency of the CRP POCT user may vary depending on the number of tests carried out by the user over the previous year. The training may need to be carried out after hours at the primary care site, so as not to disrupt patient care. There may be efficiencies in conducting training events for a group of CRP POCT users at a regional centre, as per the annual flu vaccination training programme for community pharmacists. For practice nurses, not all regions may have the same level of resources for training or support from Professional Development Co-ordinators in place to facilitate the roll-out of CRP POCT training.

As with other POC testing and phlebotomy services in primary care, it would be the responsibility of the primary care practice to ensure that appropriate occupational health advice is also provided to all staff performing CRP POCT. Irish-specific health and safety legislation for handling chemical reagents and assays would relate to the Safety, Health and Welfare at Work (Chemical Agents) Regulations 2001 and 2015.[(268)] To ensure provision of a safe and effective point-of-care service, a range of control measures have been suggested to limit the performance and interpretation of point-of-care tests to staff that have been trained in the use of the device and for whom competency has been documented. These include verification of competency prior to use of the device in practice, [(267)] restricting access to devices to trained users (for example through barcodes or passwords),[(267)] and maintaining a record of the staff trained in the conduct and interpretation of tests.[(40)] Web-based training has been identified as a valuable aid to delivering individual and continuous training modules to facilitate these requirements.[(267)]

As a clinical decision may run contrary to patient expectations, communication skills training may be useful in supporting clinicians in communicating potentially complex information to patients and caregivers regarding the significance and meaning of CRP POCT results, as well as providing additional supports to GPs in their communication of the benefits and risks of antibiotic prescribing. In the systematic review of the efficacy and safety of CRP POCT in Chapter 4, a number of studies included enhanced communication skills training in the intervention arm. The studies by Cals et al. consisted of a core two-hour training seminar that was built around the

'elicit-provide-elicit framework' for efficient information exchange.[159, 163, 237, 269] This was derived from behaviour-change counselling based on motivational interviewing.[270] This patient-centred strategy aims to achieve shared decision-making about the investigation and treatment of acute infections by focusing on providing information that meets the needs of patients..[269]

The clinical effectiveness of CRP POCT and enhanced communication skills was estimated where all participating GPs in the trials received the training in both areas. It is therefore assumed that for the efficacy of the combined intervention to be achieved in a general practice setting in Ireland, all GPs would have to attend enhanced communication skills training.

Staff using the devices would separately have to attend training on CRP POCT. In a practice there could be one or more staff members who are nominated to operate the CRP POCT device. They could be GPs, practice nurses, healthcare assistants or other staff. Given the mobility of GP staff in the out-of-hours setting, there may be challenges to ensuring the availability of competent-trained CRP POCT users at all times. It should be noted that not all out-of-hours clinics have nursing staff on site to support the GP. If a group of permanent nursing staff or HCAs are available in the out-of-hours setting, it may be pragmatic to focus CRP POCT training for these non-transient staff. In LTCFs, the portability of the CRP POCT device may lend itself to the appropriately trained treating physician conducting the CRP POCT on patients. CRP POCT education could be considered for inclusion in antimicrobial stewardship training for nursing home staff to enable the implementation of CRP POCT in LTCFs. The out-of-hours setting may create challenges for communication as it will be less likely that a patient's usual GP is on duty when they attend.

9.1.3 Acceptability

International data suggest that CRP POCT is generally well accepted and useful to guide antibiotic prescribing for acute RTIs in primary care. However, stakeholders differ in their perception of barriers and facilitators to its implementation.

None of the included studies in the systematic review of clinical effectiveness and safety (Chapter 4) reported on physician satisfaction with CRP POCT. Four studies reported on patient satisfaction (n=1,885) with their clinician visit: two individually randomised studies,[164, 165] one cluster randomised study[163] and one non-randomised study.[167] Patients were generally satisfied with the test, with no significant difference between the CRP POCT and control groups.

In a 2015 prospective study from Sweden, GPs considered CRP POCT essential to the further management of patients in 38% of cases.[271] However, it should be

noted that in 86% of visits the CRP test did not result in a change to the prescribing decision. Factors that potentially impacted this finding included a generally low antibiotic prescription rate and a high frequency of CRP POCT for RTIs in Sweden. It was reported that the strongest predictors for revised decisions on antibiotic treatment were the error estimates of CRP (between estimated and measured CRP levels), and the physician's opinion that CRP measurement was crucial. This seems to indicate a learning curve in CRP POCT and that less experienced GPs are more likely to use CRP POCT to inform decision-making.

GPs have also expressed generally positive attitudes to the use of CRP POCT to guide antibiotic prescribing for RTIs in studies from Ireland and the Netherlands.[164, 167] Potential advantages identified include the rapid availability of test results to support diagnostic and therapeutic processes for LRTI and other common infections, enhancing GP confidence in prescribing decisions, and empowering GPs to prescribe antibiotics less frequently without alienating their patients. However, issues that concerned GPs included the interpretation of unclear test results and the reimbursement of CRP POCT. These attitudes and observations mirrored the results of an online survey to gather feedback on the practical aspects of CRP POCT in Scotland (n=10 practices, n=15 GPs), and its perceived impact on GP decision-making and prescribing of antibiotics.[248] Several respondents commented that using the test improved patient engagement and provided additional support to decisions not to prescribe an antibiotic based on clinical assessment. Sixty percent of respondents found the test helpful in dealing with difficult patients who insisted on an antibiotic. Other potential benefits identified by some doctors were an increased use of delayed prescriptions for LRTI and a reduction in reconsultations.[248]

The main practical concern among GPs was the additional time that the test adds to a patient consultation. Within the context of a standard 10-minute allocation for a patient consultation, accommodating on average 3 or more additional minutes to complete CRP POCT along with the time to explain the test results to a patient could have a substantial impact on workload, patient flow and work practices.[248] However, the reduced number of patients seeking a second appointment for the same symptoms may help mitigate the increased time required for the primary consultation and CRP POCT. Doctors in the Scottish pilot study also identified that a portable instrument would be of interest for home visits and the care of residents in long-term care facilities.[248] Although point-of-care tests might enhance confidence and job satisfaction among users, some GPs expressed concern that an overreliance on tests could undermine clinical expertise.[272]

Identified prerequisites for the acceptability of CRP POCT technology to doctors include that the technology is reliable and acceptable to their patients, the CRP

result is correct, and the technology is practical and applicable in their own practice.[273] However, there is evidence that interventions aimed at more prudent antibiotic prescribing may need to be tailored to the needs of individual groups and local conditions.[274] Acceptability of interventions tend to increase if they are context-sensitive and take into account the varying roles and changing priorities of primary care practitioners.[274]

The active involvement of trained laboratory personnel through involvement of external quality assurance bodies (see Section 9.3.1) or the involvement of hospital laboratories and staff in the quality control, training and maintenance of CRP POCT devices in primary care, would ensure consistency with the future of laboratory services as outlined in the National Laboratory Handbook.[275]

9.2 Impact on patients

There is mixed awareness among the general public about the role of antibiotics in the treatment of acute RTIs, especially those infections with mild, self-limiting symptoms of viral aetiology. The Healthy Ireland Survey (2017) reports that 68% of respondents correctly agree that antibiotics can kill bacteria; 51% of respondents are correct in disagreeing that antibiotics can kill viruses; and 67% correctly disagree that antibiotics work on most coughs and colds.[74] However, these responses indicate that beliefs persist among the Irish public that antibiotics can kill viruses (~50%) and can work on most coughs and colds (33%).[74] These data highlight a need for a patient and caregiver education programme around the appropriate prescribing of antibiotics and the potential use of CRP POCT to inform GP decision-making.

9.2.1 Access to CRP

As demonstrated in Chapter 4, the use of CRP POCT is associated with a reduction in antibiotic prescribing. The benefit from using the technology in the context of a patient population attending a high-prescribing practice may be considerable, however this may be less so among patient populations where prescribing rates are already low.[276] There appears to be awareness of the link between antibiotic prescribing/consumption and antimicrobial resistance among the general public, with 90% of the respondents aware that if taken too frequently, antibiotics may not work in the future.[74] However, the acceptance of the CRP POCT programme among the general public may be enhanced by an antibiotic prescribing awareness campaign for patients, their caregivers and/or parents. This may take the shape of advertising campaigns and patient education leaflets for distribution at or prior to the patient consultation.

Consideration may be given by the Department of Health to allocate funding through the HSE in the context of iNAP and the wider policy objective of reducing anti-microbial resistance in the community. There is a public-private mix of patients in primary care, and private patients usually pay out of pocket for test services, such as phlebotomy. If the CRP POCT is only funded for public patients, this may create a barrier to access to the test for the private patients who may be unwilling to pay the additional charges for the test. The unintended consequence may be that there would be reduced acceptance of the technology among fee-paying patients.

9.2.2 Acceptability

From the results of the systematic review of clinical effectiveness and safety, it was found that patients were generally satisfied with the test, with no significant difference between the CRP POCT and the control groups in terms of acceptability.

Kavanagh et al. (2011) demonstrated that the use of CRP in the management of RTIs in a primary care setting in Ireland did not cause a reduction in patient satisfaction.[167] There were similar high levels of patient satisfaction in both study groups, with no measurable difference between public and private patients.[167] Patient experience of the CRP point-of-care test was positive as it provides reassurance when no antibiotic is required, especially for the 'worried well' patients.[248] Patients reported significantly greater levels of confidence in their doctor and a greater motivation to look after their own condition when POCT was used.[277]

However, it should be noted that some patients may dislike POCT (for example, due to lancet or needle phobia) or patients may experience anxiety resulting from intermediate results (for example, the uncertainty around a CRP reading of 20-100 mg/L and a delayed prescription).[272] This emphasises the importance of communicating the link between excessive antibiotic prescribing and antimicrobial resistance to the public as outlined in Section 9.5.1.

9.3 Quality assurance

There needs to be quality assurance and confidence in the results of CRP POCT for both the diagnosing physician and the patient.[278, 279] The quality assessment process is crucial to assuring the accuracy and reliability of a CRP POCT service. The ultimate responsibility for the quality control of the CRP POCT lies with the primary care service provider, but it could be complemented by outsourcing aspects of the process as part of an external quality assurance (EQA) scheme.[34] The internal quality control (IQC) is where a control sample is tested by the user, in accordance with the manufacturer's instructions, to ensure that the device is performing within certain defined specifications on a daily basis.[40] Performing IQC at least once a

week was noted to be associated with good test performance in the systematic review of analytical performance (Chapter 6).

Point-of-care test guidelines recommend that POCT providers in primary care should participate in an EQA scheme, where available.[40] The objective of an EQA scheme is to monitor and document analytical quality, identify poor performance, detect analytical errors and take corrective actions.[280] This process enables the POCT service providers to determine how their device is performing compared with similar analyser devices across other primary care sites. Evidence from the systematic review of analytical performance of CRP POCT devices (Chapter 6) highlighted the association between participation in an EQA scheme and good test performance. The EQA programme would provide clinically relevant challenges that mimic patient samples and have the effect of checking the entire examination process, including the pre- and post-examination procedures. The ideal EQA sample behaves as a native patient sample in all methods and has the same numeric relationship between measurement procedures as is observed for a panel of patient samples (that is, the sample is commutable), and has a target value established with a reference method.[280] As part of the EQA process, the frequency of tests per annum, acceptance limits of results, allowances for between-lot variation, and pre-and post-analytical procedures along with follow-up for handling unacceptable results, are specified for the different sample types.[280, 281]

The ISO standards also provide recommendations on how to develop, regulate and maintain POCT services. The relevant ISO standards for POCT in clinics and organisations providing care in the primary care setting (ISO 22870: 2016) detail the specific applicable requirements for quality and competence.[41]

The supervision of end users, regular quality control and proficiency testing are key to providing reliable results for CRP POCT in routine care. The development of a CRP POCT infrastructure connected to a POCT middleware hub to facilitate the management and governance of the CRP POCT programme may also be considered. The Irish guidelines for the safe and effective management and use of Point of Care Testing (2007) state that connectivity between disparate computer systems and POCT analysers is an essential component in the provision of an effective POCT service within an organisation.[282] Specific POCT guidelines for the safe and effective management of POCT in primary care were issued in 2009.[283] These guidelines do not highlight the same concerns around the connectivity of POCT devices. For a modern healthcare system, this management software may allow laboratory scientists to manage the quality control of the programme from a central resource. It would enable test performance comparison between CRP POCT providers. Troubleshooting of the CRP POCT devices may also be more easily facilitated

through such an open connectivity solution. The ability of the CRP POCT device to interface with the National Health Network (NHN) would allow data to be captured by the middleware system, enabling CRP POCT audit and feedback to users, and the potential to identify all affected CRP POCTs in the event of a test reagent batch recall. POCT middleware would provide an additional level of quality control and governance for a CRP POCT programme, that otherwise may be untraceable; it therefore has the potential to reduce the dependency on an EQA scheme. The cost of implementing a National POCT Middleware system has been estimated at €1.6 million with ongoing annual maintenance contract charges of approximately 20% thereafter. Given the size of the investment, it might not be an upfront consideration for a national CRP POCT programme, especially if the best option may be to carry out a pilot programme. The requirement for middleware may need to be an aspiration for the future governance of POCT nationally.

The Health Products Regulatory Authority (HPRA) is designated as Competent Authority (CA) for medical devices in Ireland, and monitors the safety of medical devices in Ireland after they are placed on the market. Any concerns relating to a medical device should be notified to the manufacturer and the HPRA (www.hpra.ie).

9.3.1 Experience in Norway, Denmark and Wales

EQA of laboratory medicine services, included POCT in primary care, is provided by a diverse group of organisations across Europe. This section reviews the experience of EQA in national schemes in Norway, Denmark and Wales.

9.3.1.1 Norwegian Quality Improvement of laboratory examinations (NOKLUS)

The Norwegian Quality Improvement of Primary Health Care Laboratories (NOKLUS) is a not-for-profit national organisation with headquarters in Bergen. It is governed by a management committee consisting of representatives from the Norwegian Government, the Norwegian Medical Association and the Norwegian Society of Medical Biochemistry and is ISO certified (NS-EN ISO 9001: 2015).

It offers services to all Norwegian GP surgeries, hospital laboratories, nursing homes and other healthcare institutions. All of the services offered to GP offices are funded by the Norwegian Medical Association through a quality improvement fund. NOKLUS laboratory consultants organise training courses and provide guidance and advice for scheme participants. These consultants are experienced biomedical engineers employed by local hospitals. The consultants work in partnership with the medical specialists employed by the same institution.

Services offered include guidance and tuition through site visits, telephone, email, consultations and courses to all participants outside of the hospital setting, along

with advice on the selection of control materials and testing methodologies. All NOKLUS participants are offered access to the external quality assessment (EQA) programmes. NOKLUS has introduced 'extended' EQA compared with other countries, as it also offers a laboratory consultancy that can help each GP office.[284] The primary target groups are the non-hospital laboratories; a 2012 report noted high levels of participation by GP offices (99.8%) and nursing homes (92%).

9.3.1.2 Danish Institute of External Quality Assurance for Laboratories in Health Care (DEKS)

DEKS is a Danish non-profit organisation whose objective is to support the quality development of clinical laboratories for the benefit of all patients. The institute assists with the quality assurance programmes for all hospital-based clinical laboratory specialities in addition to supporting GPs at primary care level. Organisation and advice is provided by medical scientists and laboratory specialists. It offers a variety of educational EQA schemes, calibration materials and reference materials, alone and in collaboration with other Nordic and English programmes. DEKS also provides training support to scheme participants.

9.3.1.3 Welsh External Quality Assessment Scheme (WEQAS)

WEQAS operates as an independent organisation, hosted by Cardiff and Vale University Local Health Board, supplying more than 35,000 sites per month. It is one of the largest EQA providers in the UK and is ISO accredited for laboratory and point-of-care services. Supported by a steering committee, it provides over 40 EQA programmes, which comprise external audit, performance analysis and an educational advisory service.[285] Specific EQA services to support POCT include provision of:

- ready-to-use commutable liquid clinical samples
- tailored programmes with managed service, including online support and a helpline for troubleshooting
- assist POCT sites with ISO 22870: 2016 compliance
- network performance reports
- education and training.

The CRP POCT guidance for Wales (2016) offers advice on the appropriate level of quality assurance at primary care level.[276] The test provider is advised to collaborate with the local hospital POCT department for advice and assistance on selecting the most appropriate device, developing operating protocols on how the test is used, and ensuring all users are trained and have documented competency.[276] This advice extends to ensuring that records of internal quality

control, EQA, clinical audit and storage of results in patient records are adequately maintained.[276] The Welsh Scientific Advisory Committee (WSAC) has published a detailed policy document outlining the requirements and processes for POCT (2016);[286] examples of local governance policies are also available for reference.[287]

9.3.2 Potential EQA structures in Ireland

The World Health Organization (WHO) has published a reference manual for countries establishing a national EQA programme for clinical laboratories and other testing services at all healthcare levels, which describes some of the strategic, managerial, financial, technical and scientific aspects to be considered.[288] The fundamental standard for the principles and requirements of running an EQA programme are described in detail in ISO 17043: 2010.[285] The WHO recommends that a national EQA organising centre is accredited to this standard.[288] However, it also observes that all other EQA activities at the hospital laboratory network level, including the internal quality control measures and other quality elements, are an integral part of the quality laboratory management and POCT processes as defined in both ISO 15189: 2012 and ISO 22870: 2016.[288] The WHO details:

Two main strategies that can be used to establish a national EQA programme depending on the local situation. In the first strategy, different non-governmental organisations provide EQA services that may be competitive or complementary to each other. In the second strategy, a relevant national agency, that may include a government ministry or other professional or academic institution with a long-standing interest or passion in supporting laboratory quality, is mandated by the government as an organizing centre to run the programme. These two strategies are not mutually exclusive since some countries combine not-for-profit providers with a government EQA programme.[288]

A hybrid strategy of these options may be an alternative to consider before deciding on the development of a national EQA programme for CRP POCT in primary care. Should a decision be made to introduce CRP POCT in primary care in Ireland, consideration would need to be given to a national EQA programme to support its delivery. There are a number of existing organisations (or collaborations between organisations) that could provide leadership in this regard.

9.3.2.1 Irish External Quality Assessment Scheme (IEQAS)

IEQAS was established in 1981, and is a not-for-profit national independent scheme for the objective assessment of analytical performance in laboratory medicine and primary care in Ireland. IEQAS is the sole distributor in Ireland for Labquality (Finland), who provide over 150 EQA schemes, including one for quantitative CRP

POCT in primary care. IEQAS monitors the quality of results reported, and offers professional advice and guidance as necessary. The EQA scheme provides a means of external audit that operates continuously, thus helping participants to achieve continuous quality improvement in the operation of the POCT. For example, the IEQAS POCT EQA scheme for HbA1c posts samples four times per year at regular intervals, and it recommends that all trained users of the POCT should participate in the EQA process. Reports are confidential. Safe handling and disposal of any surplus material is the responsibility of the primary care test site. IEQAS is overseen by a Steering Committee consisting of nominees from the major professional bodies involved in laboratory medicine in Ireland, including the Academy of Clinical Science and Laboratory Medicine, the Association of Clinical Biochemists in Ireland and the Faculty of Pathology of the Royal College of Physicians of Ireland.

9.3.2.2 Hospital laboratory network

The National Laboratory Handbook suggests a potential role for hospital laboratory staff in the quality control, training and maintenance of POCT devices in primary care.[275] This is also in accordance with the 2009 National Guidelines for Point of Care Testing, which highlight the potential for local laboratory services to provide specialist advice and expertise.[40] There are 42 hospital laboratory network sites in Ireland.[289] Following a 2007 HSE review of laboratory medicine services,[290] it was proposed that services would be reorganised as a 'hub and spoke model'. The proposal included the development of four regional hub laboratory medicine networks (two in Dublin, one in Cork and one in Galway), each with centralised routine testing at the regional hospital laboratories, and was signed-off by the HSE interim board in 2012. The regional hubs handle 'hot' laboratory work plus all 'cold' pathology blood tests from the primary care network. Remaining hospital laboratories continue to carry out their own 'hot' laboratory work.

9.3.2.3 Collaboration between IEQAS and the hospital laboratory network

If proficiency (EQA) tests were not to be commercially acquired, the strategy may be to source locally prepared samples. This decision would be guided by the availability of source biological materials, funding, human resources, the expertise required to prepare the items locally, and the number of participating CRP POCT sites.[288]

There are already ongoing collaborations between hospitals and IEQAS in the production and supply of local EQA test samples for other point-of-care tests in the primary care setting in Ireland. An example is the collaboration between Tallaght University Hospital and IEQAS on sourcing HbA1c EQA test samples. The samples from consenting patients are sourced at the diabetes outpatient clinic, and these blinded real samples for the external quality assurance of HbA1c POCTs are offered

pro bono to IEQAS, who are responsible for the logistics and distribution of the EQA samples to primary care sites. For the HbA1c POCT EQA scheme, two samples from fresh donor blood with HbA1c values covering the diabetes range are distributed quarterly. For other EQA tests of FBC or clinical chemistry, frequency can range from six to 12 times per year.

The frequency of supply of EQA samples may depend on the availability of donor samples and the number of participating hospital clinics. Consideration could also be given to the establishment of an expert quality assurance panel, separate to IEQAS, which would be involved in any initial EQA scheme set-up and the ongoing anonymous review of the results from participating primary care sites. Similar to the CRP POCT programme in Wales, the role of hospital laboratories may be in identifying and recommending the CRP POCT analyser(s) appropriate for the scheme, producing the training manuals and standard operating procedures for the programme, and providing support to the test sites at the implementation and ongoing maintenance phases.[38] Such collaboration may also include site visits to the general practice to monitor competencies and compliance with IQC monitoring. This may require the coordinated support of resources from the hospital laboratory network. All resources identified for the CRP POCT service could, for example, be incorporated into a service level agreement (SLA) with the local hospital laboratory.[276] The SLA could also define the level of service provided by the hospital laboratory, and the responsibilities of all parties including all additional costs incurred by participating in the CRP POCT programme.[276]

9.4 Implementation and management challenges

9.4.1 Evidence from pilot and implementation studies of CRP POCT in primary care (UK)

As part of a review of the approaches and stages of implementation of CRP POCT across the UK, some international examples of approaches to piloting or introducing the technology were identified. This is not intended to be a comprehensive overview, but rather to provide some illustrative examples.

9.4.1.1 Wales

In 2016, the Welsh Government set out a specific recommendation to implement CRP POCT at a national level in its Together for Health Delivery Plan on tackling antimicrobial resistance.[291] The delivery plan provides a framework for empowering and enabling NHS organisations across Wales to work with partner organisations, patients and the public in meeting Welsh Government expectations in tackling antimicrobial resistance (AMR) and its consequences. As part of the delivery theme

to improve infection prevention and control practices, the specific priorities for 2016 to 2018 included that:

> Public Health Wales will lead a multi-agency working group to roll out the use of C-Reactive Protein Point of Care Testing as a prognostic tool in primary care to aid clinical decisions about the appropriateness of prescribing antibiotics.[(291)]

In 2017, the Wales Antimicrobial Resistance Implementation Group published guidance on using CRP POCT to support clinical decisions in primary care. This was directed at all GP practices in Wales, GP cluster leads, local medical committees, pharmacy leads, directors of primary care, point-of-care testing leads, laboratory clinical leads and health board antimicrobial stewardship groups. This guidance is intended to help GPs to decide whether a patient needs antibiotics while they are present at the surgery.

Pilot Study: The Alere Afinion™ CRP POCT analyser was introduced into one GP practice in Anglesey (part of the Betsi Cadwaladr University Health Board (UHB) in North Wales), over a three-month period (November 2015 to January 2016), to determine whether CRP POCT would have an impact on antibiotic prescription rates.

Overall, 94 patients received CRP POCT; 71 patients for acute respiratory tract infections (RTIs) and 23 patients for other indications. These other indications were urinary tract infection (n=6), wound infection (n=7), abdominal pain (n= 3), rheumatoid arthritis flare-up (n=2), cellulitis (n=1), diarrhoea with rigors (n=1), diverticulitis (n=1), gout (n=1), and intrapatellar bursitis (n=1). This use of CRP POCT on clinical situations (n=9) may not lead to a reduction in antibiotic prescribing, and may need to be considered in terms of cost exacerbations that would not impact on reducing AMR. Of the 71 RTI patients, 53 (74.6%) did not receive an antibiotic. Compared with the same three-month period the previous year (November 2014 to January 2015), antibiotic prescriptions decreased by 21.39%. This was statistically significant (P=0.04) when compared with other practices in the health board, where antibiotic prescription rates fell by 10.6%. Patient and user feedback was mostly positive.

It should be noted that a minor transcription error rate of (2/94) occurred in the study, and high cartridge error rates were identified by the laboratory staff (as reported in the user survey). The observed high cartridge error rate seems to highlight the potential need for ongoing support of non-laboratory trained staff to run diagnostic tests.

Current situation: The funding for CRP POCT is not identified centrally; the GP clusters have been putting in individual bids for funding. It is not always known in advance which clusters have been successful and when the GPs start testing. The challenges have been to identify each practice before they start using the CRP POCT and to ensure that a governance process is put in place prior to POCT service provision. The POCT coordinators in each Health Board are fully engaged for CRP POCT device training and quality assurance. The CRP POCT usage practices identified are now being monitored for the impact on antibiotic prescribing rates. The 12-month outcome data gathered from the cluster of 11 GP practices in North Wales in Betsi Cadwalader University Health Board will be published in early 2019.

9.4.1.2 Scotland

In 2016, the Scottish Antimicrobial Prescribing Group (SAPG) developed a proposal to evaluate the feasibility and acceptability of CRP POCT in GP practices, which would help to inform wider roll-out of the test in the future.

Pilot Study: Operated in 10 GP practices across four NHS board areas between November 2015 and February 2016, the pilot study assessed both the practicalities of implementing CRP POCT as well as the perceived impact on antibiotic prescribing behaviour. The pilot used loaned Alere Afinion™ analysers, and was supported by training sessions to demonstrate how the test should be carried out, and it used the NICE-recommended testing ranges to inform the treatment options. The results were informed by data from 246 individual patient consultations and the results of an online questionnaire completed by 15 GPs. A variety of testing models were used, with four GPs carrying out the test independently, eight GPs having a practice nurse carry out the test and three GPs using a combination of both. (Note: for 15 patients (6%), there were problems with instrument error message, so no result was recorded.) Feedback demonstrated that:

- Twenty percent reported problems with user technique (for example, not using an adequate blood sample, or cartridge air bubbles). It was suggested that a training DVD to provide a refresher on user technique would be useful.
- The majority of respondents (~90%) felt that CRP POCT provided reassurance when not prescribing an antibiotic.
- Almost two-thirds (60%) of GPs thought that CRP POCT was a useful additional tool to support clinical practice, especially in dealing with patients who insisted on an antibiotic.
- Forty percent of GPs subjectively thought that CRP POCT reduced levels of patient re-attendance with the same symptoms.
- No prescription for antibiotics was issued in 64% of the cases when CRP POCT was used.

- Patient experience of the test appeared to be positive, especially for reassuring 'worried-well' patients. While the majority of GP respondents said they would like to see CRP testing used routinely, there were concerns around cost-effectiveness.
- The main practical concern among GPs was the additional time that CRP POCT may add to the consultation, with 3.5 minutes for the test plus the time to explain the test results within a 10-minute patient consultation. A patient management plan has to take place within the consultation regardless of the use of CRP POCTs.

Current situation: The SHTG advice statement to NHS Scotland of May 2018 recommended that 'additional piloting, with monitoring and evaluation, should be undertaken by the organisations in Scotland with responsibility for diagnostic testing, prior to any widespread implementation of CRP testing.'

9.4.1.3 England

The NICE guidelines for the diagnosis and treatment of pneumonia (2014) recommendation for the use of CRP POCT in non-pneumonia LRTI cases with clinical uncertainty was not mandatory, which has led to an uneven adoption of the technology. CRP POCT has been piloted across a broad range of commissioning areas across England. Where the test has been used, it has helped to support reduced levels of inappropriate antibiotic prescribing and strengthen local antimicrobial stewardship initiatives. However, CRP POCT has also been decommissioned in at least one large Clinical Commissioning Group (CCG) in England.

Pilot Study 1: Herts Valley CCG

A three-month pilot to introduce CRP POCT in a GP surgery in Hertfordshire (Attenborough GP Surgery, Bushey) received an NHS Innovation Challenge Prize (Acorn Award) for its contribution to local antimicrobial stewardship efforts. The pilot, which ran from November 2014 to early 2015, saw eligible patients presenting with acute cough symptoms offered a test to measure their CRP levels to help determine whether an antibiotic should be prescribed. Every patient receiving a definitive test advising against antibiotics was followed-up with a month later by checking their record or by telephone. The results reported that:

- the use of CRP POCT saw antibiotic prescribing fall by 23%
- the proportion of patients re-attending for the same complaint within 28 days halved.

This pilot study was followed by an implementation study from November 2016 to January 2017 to evaluate CRP POCT utilisation in five general practices across the clinical commissioning group (CCG), purposively sampled because they were medium to high antibiotic prescribers. These five intervention practices with a total list size of 63,743 patients recorded 682 eligible LRTI presentations during the study period, of which 176 (26%) involved a CRP test; they were compared with three control practices, which recorded 258 LRTI presentations (based on the same eligibility criteria) from 35,928 patients. Overall, fewer initial presentations to intervention practices resulted in antibiotic prescription (59% of initial presentations, as compared to 79%) and follow-up consultations (30% compared to 38%), although there was little difference to antibiotic prescribing at follow-up (both arms 68%). Furthermore, initial presentations associated with antibiotic prescription, which subsequently resulted in a follow-up consultation with an additional prescription, were more common amongst control practices (21% compared to 13%). The results of the implementation study are shown in Table 9.1.

Pilot Study 2: Swale CCG

As part of an AMR campaign with Swale CCG, CRP POCT was implemented as a pilot for a total of six months in 2017. A delayed antibiotic prescribing policy, Public Health England 'Treat Your Infection' leaflets, and two QuikRead go® analysers (Roche Diagnostics) were used across three outlier GP practices. Seventy-two percent of the CRP <20 mg/L subgroup were not prescribed an antibiotic. There was a 13% reduction in total antibiotics prescribed for the participating practices with CRP POCT from July to December 2017 versus the same period in 2016; whilst the other practices in Swale CCG only achieved a 5% reduction for the same comparison periods.

Table 9.1: Implementation study of CRP POCT from Herts Valley CCG (England)

	Intervention arm (n=682) [5 GP practices]		Control arm (n=258) [3 GP practices]		Adjusted Odds Ratio (95% CI)
	Outcome events	%	Outcome events	%	
CRP test at initial presentation	176	26	-	-	-
Antibiotic Rx at initial presentation	405	59	204	79	0.38 (0.27 – 0.53)
Follow up consultation after initial presentation	206	30	99	38	0.68 (0.51 – 0.92)
Antibiotic Rx at follow-up consultation	140	68	67	68	NR
Initial presentation with antibiotic Rx, then follow-up consultation with additional antibiotic Rx	92	13	55	21	NR

Pilot Study 3: Swindon CCG

In August 2016, a six-month pilot study was commenced in Swindon Urgent Care Centre (UCC) to determine whether POCT would reduce unnecessary antibiotic prescriptions in viral LRTIs, and to assess the cost impact and sustainability of CRP POCT. An Alere Afinion™ analyser was placed by the manufacturer for free in this out-of-hours setting for the duration of the six-month study. Criteria for patient management used the NICE guideline recommended testing ranges to inform the treatment options. The pilot champion developed the protocol, the patient flow chart and the audit sheet to be completed by the participating clinicians. Swindon CCG provided funding for the test cartridges. The trend was from 'prescribe' to either 'back-up' or 'don't prescribe'; however, there were nine patients where the decision changed from 'no antibiotics' to 'prescribe' antibiotics after testing. Antibiotics were sometimes prescribed despite a CRP of <5 mg/L. The reasons documented for this were duration of symptoms (typically longer than three weeks), sputum colour (yellow, green or brown) or existing comorbidity. Two hundred and eight CRP POC tests were used, but only 141 were included in the data set. It was reported that analyser errors occurred at times and clinicians not completing audits correctly rendering the data uninterpretable.

Current situation: There is no central funding for CRP POCT in primary care in England. There is anecdotal evidence of wide and varied approaches to the implementation of the technology depending on the setting and the CCG. CRP POCT analysers appear to have been offered free of charge by one manufacturer (Alere) to encourage uptake among those GPs and practices interested in early adoption. Overall, utilisation of CRP POCT for LRTIs has been quite limited in English primary care, with the technology costs and lack of funding suggested as important barriers.

There have been interesting recent developments in NHS Sunderland CCG, which was chosen as the winner of an Antibiotic Guardian Award (diagnostic category) in 2018. The six-month temporary placement of CRP POCT in practices appears to have changed prescriber behaviour, with early evidence of sustained prescribing changes after removal of the technology. The concept appears to build geographical communities of experience, while effecting sustained behavioural changes. There is also the benefit for the publicly funded healthcare system of reducing expenditure on devices and consumables, as the technology is removed after six months and moved on to the next practice.

The key points to consider from the UK pilot studies are as follows:

- Table 9.2 reports consistency in the percentage of LRTI patients reported with low, medium or high CRP levels in the pilot studies.
- There was also consistency in the no-antibiotic prescribing rates (both >80%) for Swale CCG and Betsi Cadwaladr University Health Board (UHB); while the other two studies (one of which was in an out-of-hours setting) were consistent at a lower rate of ~60%.
- The delayed antibiotic rates ranged from 3% to 15%, while the immediate antibiotic rates ranged from 13% to 23% across the four studies.
- Where reported, CRP POCT had influenced the prescribing decision in 57% to 74% of cases.
- The year-on-year reduction in antibiotic prescribing rates for LRTI was reported at 13% to 21.4%. This is consistent with the 23% reported in the Herts Valley CCG pilot.
- The implementation study carried out in Herts Valley CCG reported the odds of antibiotic prescribing after initial presentation were reduced by 62%, and the odds of follow-up consultation were reduced by 32% (Table 9.1).
- Concerns were noted in the studies around transcription errors, high cartridge error rates and training updates for healthcare practitioners.

Table 9.2: Summary comparison of the pilot studies of CRP POCT in the UK

Country	GP practices (GPs)	No. of LRTI patients with CRP*	CRP POCT results (% patients)			Antibiotic prescription (Rx) (% patients)			Influence of CRP on prescribing decision	Reduction in antibiotic prescriptions YoY (%)
			Low	Med	High	No Rx	Delayed Rx	Immediate Rx		
Scotland	SAPG study 10 (15)	231	72	24	4	64	14	22	74% (yes)	**NR**
Wales	Betsi Cadwaladr UHB 1 (1+5)[Ω]	71	77	23	0	80	3	17	**NR**	21.4%
England	Swale CCG 3 (1+2)[∞]	97	79	20	1	84	3	13	**NR**	13%
	Swindon CCG 1 (OOH)	141	**NR**	**NR**	**NR**	62	15	23	57% (yes)	**NR**

* (valid CRP results for patients with RTI)

[Ω] (1 GP + 4 nurses and 1 HCA for competency assessment)

[∞] (1 GP + 2 nurses designated users)

Key: NR – not reported; OOH – out-of-hours; YoY – Year-on-year comparison.

9.4.2 Potential management challenges

Potential management challenges to the adoption of CRP POCT can be categorised into logistical, quality control and governance concerns. The logistical challenges of introducing diagnostic modalities in primary care can be described using the STEP-UP framework assessment:[266]

- **S**kills – POCT users are healthcare practitioners (HCPs), not trained medical laboratory scientists. There needs to be the recognition of the competencies required to operate the CRP POCT device and to interpret the results with a potential need to incorporate verification of these competencies into a quality assurance system.
- **T**raining – could be provided by both the device manufacturer and the affiliated hospital laboratories. Training protocols would be required as part of the SOPs identified. Additional enhanced communication skills training may be necessary for GPs to communicate the results and their implications for antibiotic prescribing. Training renewals may be necessary on a six-monthly or annual basis. Online training resources could be used to facilitate adequate and continuous training for device users.
- **E**quipment – a CRP POCT analyser and accompanying test system (such as cartridge solution and test strips), control solution/cartridges for internal quality assurance, barcode scanner and printer and the lancets/sharps disposal bins will be required for the operation of a CRP POCT programme in primary care. Consideration could be given to the use of a range of minimum acceptable technical specifications and clinical functionalities for users that have been pre-specified by an expert CRP POCT quality assurance panel. For a CRP POCT device to be considered for use by the national CRP POCT programme, it would need to meet these minimum standards. Therefore, the selection of recommended CRP POCT devices should not solely focus on the most economically advantageous technology. If the strategy is to centrally acquire and block purchase the technology (for example, via tender), it must be noted that this can be expensive to manage, despite the obvious economies of scale.
- **P**remises – given the size of the majority of CRP POCT devices (Appendix A), it should be possible to accommodate these within existing GP treatment room infrastructures. Consideration must also be given to the use of the technology in out-of-hours clinics and long-term care facilities. For GPs that provide care in a number of settings, the use of a portable device may minimise the requirement for an individual analyser per treatment site.
- **U**ser perspective – the HCP user of the CRP POCT will be fundamentally concerned about the accuracy and reliability of the test results to aid clinical

decision-making on whether or not to prescribe antibiotics for acute RTIs. The importance of turnaround times for the test results, ease of use of the CRP POCT and the safe disposal of clinical waste/sharps were identified by the Expert Advisory Group.

- **P**rimary-secondary interface – ICT upgrades may be required to facilitate the communication of results between hospital labs' Medical Laboratory Information System (MedLIS) and GP surgeries. However, there may be an opportunity to use the existing Healthlink infrastructure as the communication link for EQA results.

The governance structures around implementation of a CRP POCT programme at a national and local level in Ireland may be informed by the experience in Wales. A national CRP POCT coordinator was nominated whose role is to monitor the introduction and impact of CRP POCT on clinical practice and antimicrobial prescribing. At a local level, it was recommended that the Health Board Antimicrobial Stewardship Group maintain oversight of the introduction and impact of CRP POCT in primary care. There was an explicit target of a 50% reduction in inappropriate antimicrobial prescribing set for 2020. However, it was expected that a primary care lead would be nominated for all AMR Stewardship Groups and Point of Care Groups for all Health Boards. It was also proposed that these individuals will work closely with the local POCT lead and provide assurance to the individual Health Board that prudent prescribing initiatives implemented locally are effective.[(276)]

The national guidelines for the safe and effective management and use of Point of Care Testing in primary and community care in Ireland (2009) set out criteria for the clinical and managerial governance of any POCT service including the designation of a person responsible and accountable for the service.[(283)] The development and use of standard operating procedures (SOPs) for all aspects of a POCT service is recommended, including SOPs for the performance of any test, record keeping, interpretation of results, patient referral criteria, quality assurance, patient and staff safety and health.[(40)] These SOPs may be developed by the hospital laboratory staff (with final approval by an expert quality assurance panel), who would provide the appropriate advice on how to manage an unexpected or misleading rise in CRP that does not correlate with the clinical findings.[(34)] The guidelines specify the use of CE marked devices and that adverse incidents arising from their use should be reported to the manufacturer, the HPRA and/or the appropriate professional regulatory body, as appropriate.[(40)]

As discussed in Section 9.3, the relevant ISO standards, ISO 15189: 2012 and ISO 22870: 2016, also provide recommendations on how to develop, regulate and maintain POCT services. By ensuring all test sites are operating in accordance with

such standards, it provides confidence for patients (and doctors) in the reliability and accuracy of the CRP test results.

The practical issues of restructuring clinic patient flow and the implications for doctor workload have been outlined in Section 9.1.1. There is a risk management concern associated with the collection of blood, serum or plasma samples, and the disposal of contaminated test materials and lancets. National HPSC infection control and prevention guidelines (2013) will apply to minimise the risk of the patient acquiring a preventable healthcare-associated infection, and also to protect staff from acquiring an infection in the workplace.[292] Current Irish legislation places the primary responsibility for waste and its disposal on the producer, that is, the GP.[293] Proper segregation, packaging, labelling, storage and transport of health care waste are outlined in The Segregation, Packaging and Storage Guidelines for Healthcare Risk Waste (2010).[294] Education and training of staff is essential to prevent injury.[292]

9.5 Other considerations

9.5.1 Communication

Following the strategy detailed in Ireland's National Action Plan (iNAP) on Antimicrobial Resistance (2017-2020),[295] the Department of Health and the HSE have a responsibility for communicating public health policy concerning antimicrobial resistance (AMR). Should a decision be made to introduce CRP POCT to guide antibiotic prescribing for RTIs in primary care, these bodies would also have a key role in its planning and introduction and in communicating with the relevant stakeholder groups – that is, all patients with acute RTIs who are seen by primary care general practitioners, relevant caregivers (whether that is parents or home helps), and the healthcare providers charged with providing the test. This may require a coordinated public awareness campaign by the Department of Health and the HSE to highlight that reduced antibiotic prescribing and improved antibiotic stewardship will contribute to a reduction in antimicrobial resistance. At a local level, this patient information campaign may take the form of education leaflets and posters in surgeries.

Doctors and nurses in primary care can build on the established trust that exists with their patients to communicate directly on the merits of the technology for patient education and managing patient expectations around antibiotics.[276] This does require an understanding of how to communicate potentially complex information to patients regarding antibiotic prescribing, and will help support the clinical practices of doctors and nurses. Although a clinical decision may run contrary to patient expectations, an understanding of how to communicate issues relating to antibiotics may be beneficial.[276] As described in Section 9.1.2, it will be necessary to provide

training resources for GPs and the opportunity to improve clinicians' communication skills in relation to antimicrobial prescribing for patients with an acute RTI.

CRP POCT may instigate improved dialogue between doctors and patient on the need for antibiotics, and promote increased confidence among doctors in their antibiotic prescribing decisions. For those patients who do not receive an antibiotic or do receive a delayed prescription, it is important that clear 'safety-netting' information and advice is given, to prompt patients on the appropriate next steps for either reconsultation or the need to fill the prescription at the pharmacy.

9.5.2 Eligibility

The use of CRP POCT may be considered by the treating doctor for patients presenting with symptoms of RTI in primary care if a diagnosis is unclear after clinical assessment. Treatment protocols or clinical guidelines have been developed in other countries to support the use of CRP POCT to guide antibiotic prescribing in RTIs (such as the 2014 NICE guidelines on the diagnosis and treatment of pneumonia).[22] The clinical algorithm applied follows explicit CRP-level cut-points, such as 20 mg/L and 100mg/L. If the CRP level in a patient with a LRTI is more than 100 mg/L, then the patient would generally be prescribed immediate antibiotics, and a clinical assessment of severity and the need for hospitalisation should be undertaken; in patients with a CRP level less than 20 mg/L, antibiotics would generally be avoided. However, in patients with a CRP level in the intermediate range (20-100 mg/L) the test results are more difficult to interpret, and current NICE guidelines suggest that a delayed prescription can be useful in these circumstances.[276] However, this decision is predicated on the severity of the symptoms of the presenting patient, the medical history of the patient, and the clinical judgment of the GP. Consideration may be given to the development of clinical guidelines to support the place of CRP POCT in the treatment pathway for acute RTIs in primary care. Guidelines can help to ensure that a standardised and evidence-based approach is adopted by clinicians when using CRP POCT to guide prescribing decisions. Clinical guidelines also provide a means to reduce the possibility of indication creep by clearly specifying appropriate use of the technology.

9.5.3 Impact on activity and other technologies

CRP POCT, and the associated communication strategy, may result in a change to patient consultation practices for RTIs. Improved awareness around the aetiology of RTI, achieved through education and training provided as part of a CRP POCT programme, may, for example, result in fewer consultations for these indications. Hence, future requirements for additional human resources during peak periods for RTIs (the winter season) could be mitigated over time, as patients gain knowledge

and experience of how various RTIs are managed and change their consultation patterns accordingly.

As noted in Chapter 6, staff members, such as laboratory technicians and administrative personnel, have also carried out CRP POCT in primary care studies. A CRP POCT pilot programme in a general practice in Wales involved the support of a multidisciplinary team – with professionals providing expertise from primary care (for pharmacy) and the health board (for additional pharmacy and blood sciences support as required).[38] However, as outlined in Section 9.1.1, in Ireland the current practice of POCT is confined to the doctor and the practice nurse.

Beyond the implications for practice workflow already discussed, CRP POCT in primary care also has the potential to reduce adverse events associated with antibiotics and to reduce the number of X-rays requested in suspected pneumonia cases. It is noted, however, that the latter was not assessed as an outcome in any of the studies included in the systematic review of the efficacy and safety of CRP POCT (Chapter 4).

Depending on the extent to which the hospital laboratory network is involved in the roll-out of CRP POCT in primary care, there may be requirements for additional resources within the hospital laboratory network for the operation, management and governance of the staff training and external quality assurance for the CRP POCT programme.

9.5.4 Funding

At least 18 European countries have CRP POCT technology available to medical practitioners for use in patients in primary, outpatient and/or ambulatory care settings. Reimbursement status and policy differs between countries. As outlined in Chapter 2 (Table 2.3), the reimbursement estimate per test in the primary care setting was estimated to range from €1.22 to €8.14 in Irish euro equivalent depending on the country. However, the evidence from other European countries suggests that the rapid uptake of CRP POCT in primary care is unlikely in the absence of a funded implementation programme.[248, 296]

Slow uptake and limited availability of CRP POCT in primary care would likely reduce its potential impact on antibiotic prescribing rates. Ultimately, in the context of the wider policy objective of reducing antimicrobial resistance in the community,[295] the Department of Health may consider that dedicated funding for a CRP POCT programme would be provided by the HSE. This funding may have to cover the procurement of the analyser device and also potentially the reimbursement/incentives for the use of the technology in primary care.

Potential procurement options for the CRP POCT analyser identified in a 2016 UK study[34] included:

- direct purchase by the primary care practice
- block purchase by regional organisations to cover practices in their region
- block purchase or tender proposal at a national level
- purchase and ownership of devices by the central or supporting hospital laboratory services, and loaned or leased to primary care practices (with the option of including service contracts to cover all consumables, quality assurance, maintenance and training)
- loan or lease agreements facilitated by industry (with the option of including service contracts to cover quality assurance, maintenance and training).

The cost of consumables (such as test reagents and internal quality control tests) used for the CRP POCT could potentially be paid for by either the GP practice, HSE procurement or the hospital laboratory network (through the SLA). However, potential operational and cost efficiencies may be achieved by partnering with the expertise and supply chain available through the hospital laboratory network for the provision of all consumables, POCT device maintenance, staff training and external quality assurance. An initial pilot programme may be required to estimate the extent to which this could be achieved within existing resources.

The partial or complete reimbursement for conducting the CRP POC test as part of the clinical examination could fall on the HSE Primary Care Reimbursement Service (PCRS), the patient or a combination of both, depending on the patient's GMS status. However, there may be equity of access issues if differential reimbursement models apply to public and private patients (for example, if the cost of the test were reimbursed for GMS and GPV card holders, but not for all other patients, who would have to pay out of pocket for the test). Depending on the reimbursement method chosen, potential influencers on the uptake of CRP POCT could be supplier-induced demand for the use of the technology or indication drift in the use of CRP POCT for non-RTI conditions (such as inflammatory disorders or urinary tract infections). Supplier-induced demand could potentially be monitored through audits. An indication shift could lead to improved clinical care for those indications, although that was outside the scope of this assessment. There have been instances in INR POCT programmes in primary care where the POCT device was funded by the practice and the consumables were provided by the HSE, and service charges were required from all patients. However, if this were to happen for CRP POCT, patients may object to the test.

Successful adoption models of CRP POCT in other European countries were characterised by having a slow and long early adoption phase, followed by policy changes that then triggered large-scale adoption.[34] Thus, a pilot CRP POCT programme in a selection of primary care centres, out-of-hours clinics or long-term care facilities in a community healthcare organization (CHO), which contains one of the four national hospital lab hubs, may be the most prudent approach to managing the challenges of adopting the technology. Successful wider implementation should address these issues around the capital funding and reimbursement for use of the technology along with consideration of the development of clinical guidelines to support the place of CRP POCT in the treatment pathway.[164]

9.5.5 Incentives

Financial incentives could be considered to encourage the use of CRP POCT for antimicrobial stewardship. Although financial incentives have been considered elsewhere for improving prescribing practices, a 2015 Cochrane review found limited evidence of their effectiveness in altering GP prescribing practices, with associated uncertainty in their effectiveness in improving quality of care and health outcomes.[297] However, it is noted that the introduction of a national financial incentive (the Quality Premium) in England coincided with a 3% drop in the rate of antibiotic prescribing (equating to 14.65 prescriptions per 1,000 RTI consultations).[298] This option may be considered for incentivising the use of CRP POCT for antimicrobial stewardship.

A more successful approach may be to focus on non-financial incentives, which may appeal to the intrinsic motivation of the doctors to alter their antibiotic prescribing behaviour. For example, a cluster randomised experiment tested the motivational effects of the introduction of a mandatory accreditation system for 1,146 GPs in general practice in Denmark.[299] The intervention covered 16 standards across four themes, which were: 1) quality and patient safety, 2) patient safety critical standards, 3) good patient continuity of care, and 4) management and organisation. It reported no evidence of the crowding out of motivation of doctors relating to the accreditation of general practice. The mandatory accreditation system was associated with increased intrinsic motivation of GP work.[299] The development of clinical guidelines or treatment algorithms that incorporate CRP POCT to guide decision-making may also help facilitate changes in antibiotic prescribing behaviour among doctors in primary care.

The choice of reimbursement model, such as a fee-per-test scheme, could, however, have the unintended consequence of creating the moral hazard of supplier-induced demand for the use of CRP POCT. That is, creating a financial incentive to perform CRP POCT in situations where it is unlikely to change decision-making, for example

in patients where there is high certainty based on clinical assessment regarding the need, or absence of the need for an antibiotic. An adverse consequence of a fee-per-test reimbursement scheme may also include private patients paying more in discretionary fees to access CRP POCT than public patients.

Table 9.3 lists the potential incentives and disincentives for CRP POCT adoption among the stakeholders in primary care. This approach is adapted to the Irish context from the paper by Huddy et al. (2016).[34]

The incentives around a CRP POCT programme need to support the professional aspirations of doctors. These include:

- improving health in the general population by helping to reduce the risk of AMR
- improving the diagnosis and treatment outcomes of their patients with RTIs by avoiding unnecessary antibiotics and reducing exposure to the risk of adverse effects whilst still maximising treatment outcomes and recovery times for patients with self-limiting RTIs. CRP POCT also supports the doctor in identifying those patients with uncertain symptom severity who actually do require immediate antibiotic treatment
- maintaining their practice income so that the creation of the reimbursement scheme for a CRP POCT test should not create a conflict of interest between the income of practices and the quality of care provided to patients.

It will be important that doctors get early and regular updates on the impact of the adoption of the CRP POCT technology on their antibiotic prescribing. This feedback may help to reinforce new prescribing behaviours among doctors. Although, it is to be expected that doctors with low antibiotic prescribing rates may not see the benefits to doctors with higher prescribing rates. The intrinsic motivation for these doctors with lower antibiotic prescribing rates already is being part of a wider professional movement to reduce the future risk of AMR for the benefit of society.

Table 9.3 Incentives and disincentives for CRP POCT adoption in primary care in Ireland

Stakeholders	Reasons for adoption	Reasons against adoption	Recommendations
HSE	▪ Measure to help reduce antimicrobial resistance as part of iNAP AMR (2017-20). ▪ Reduced referrals to secondary care. ▪ Evidence of reduction in unnecessary antibiotic prescription when CRP tests are used without compromising patient safety. ▪ More efficient and effective healthcare.	▪ Funding mechanism needs to balance encouraging the adoption of CRP POCT versus appropriate use for acute RTIs with clinical uncertainty.	▪ Development of CRP POCT user guideline and SOPs. ▪ Promote societal awareness of the benefit of reducing antimicrobial resistance through tackling the inappropriate use of antibiotics in primary care.
General Practitioners	▪ Ameliorate the financial risk for the GP in adopting CRP POCT if a programme is part- or fully funded by the HSE. ▪ Incentivise the use of CRP POCT for antimicrobial stewardship via a reimbursed quality improvement framework for primary care. ▪ Enhanced antibiotic prescribing confidence and job satisfaction. ▪ Increased decision-making support when uncertain of diagnosis. ▪ Improved communication and discussion with patients on appropriate use of antibiotics.	▪ Financial risk if cost of the programme is GP funded. ▪ Negative effects on GP workload and clinic patient flow. ▪ Risk aversion to new technology adoption (behaviour inertia). ▪ The 'additional' time required to complete the CRP POCT.	▪ CRP POCT programme needs to be appropriately reimbursed and incentivised. ▪ Perception of time delays can be altered based upon completion of a successful pilot.

Stakeholders	Reasons for adoption	Reasons against adoption	Recommendations
Hospital Laboratories	▪ Active involvement in the CRP POCT programme for the development of SOPs and the training of users, along with the maintenance and quality control of CRP POCT devices.	▪ Potential resistance to change if funding loss due to CRP POCT performed in community (that is, transfer of lab funding to CRP POCT programme).	▪ Existing and future funding should be managed to promote the involvement of hospital labs in the protocol development, staff training, device maintenance and quality control roles.
Patients	▪ Education around antibiotic prescribing and awareness of self-management of self-limiting viral infections. ▪ Greater satisfaction, confidence and reassurance for patients in the prescribing decisions of GPs.	▪ Barrier to accessing antibiotics.	▪ Education campaign around the use of CRP POCT.

9.6 Discussion

The introduction of CRP POCT will have implications for practice management and workflow. For the adoption of CRP POCT to succeed, there may be a trade-off between the self-interest of the individual professional, patient or stakeholder groups versus the societal gain of reducing AMR.

Patients may not have access to antibiotics that they may have received for similar symptoms in the past. The benefits for patients include not being exposed to the side effects of unnecessary antibiotics that do not aid their recovery from self-limiting acute RTIs. It will also mean that antibiotics will be more likely to be reserved for severe bacterial infections. The education campaign for patients on the role of CRP POCT in improving antimicrobial stewardship in primary care will be crucial for acceptance by the general population.

Doctors and nurses are likely to experience an increase in consultation times when using CRP POCT. Where CRP POCT has been adopted, there is some evidence of reduced demand for consultations among patients for similar self-limiting RTIs. This would counterbalance initial demands on primary care resources over time. The scenario of reduced numbers of patients with acute RTIs attending general practice in the future needs to be considered when designing the reimbursement scheme for a CRP POCT programme. CRP POCT programmes have to be adequately funded and resourced to ensure uptake in general practice. If general practices had to recoup the costs of CRP by charging their patients, such as those for phlebotomy services, there could be a substantial risk to the acceptance of the technology among patients. This would in turn have a negative impact on achieving the goal of reducing antimicrobial resistance (AMR) in society as identified by the Department of Health and the HSE. However, the opposite may occur if all patients can access CRP POCT when there is uncertainty in the clinical assessment of an acute RTI, without any impediment by consult fees or copayments.

There must be confidence in the CRP results delivered from CRP POCT in primary care. Doctors and nurses managing acute infections require accurate and reliable technology that will deliver CRP results that their patients can trust. ISO accreditation of the CRP POCT sites signals to patients that the results are accurate and reliable, addressing issues relating to clinical governance, risk management, user competence training, internal quality control and external quality assurance of the testing.

The potential adoption of CRP POCT needs to be consistent with the current and future role of the hospital laboratory network in supporting the implementation of national POCT guidelines. This could involve the development of SOP documents and training programmes for the CRP POCT users by hospital laboratory POCT teams. An

accreditation scheme for CRP POCT facilities in the community would provide further quality assurance for technology users and patients. For example, this may include a competency assessment process which could be routinely audited and supported by the hospital laboratory POCT teams. The WHO recommends different strategies and options for organising a national EQA programme, which should be considered in the design of an EQA scheme to support CRP POCT. International examples include the Welsh CRP POCT programme, which relies on an external party (WEQAS) for external quality assurance of CRP POCT. The Welsh EQA programme is fully supported by the hospital laboratory network. Alternatively, IEQAS in collaboration with the hospital laboratories may be a similar structure for consideration in the Irish setting. However, such consideration needs to take into account the existing workload of the hospital laboratory network.

The review of pilot studies from the UK showed substantial heterogeneity in how CRP POCT programmes are implemented. Due to differences in data collection, it is difficult to determine the true effect on antibiotic prescribing, and whether the introduction of CRP POCT had a sustained effect. The pilot studies do highlight issues, particularly in relation to use of the devices and errors, but they also demonstrate a general acceptance of CRP POCT. The results of the identified pilot studies must be considered in the context of the health service structure within which they were introduced, and how that system may differ from Irish primary care services with its mixed public and private funding model.

In designing any national programme in Ireland, lessons from the practical experience on governance, oversight and logistical in other international programmes may be learned, including the recently implemented Welsh CRP POCT programme. Evaluation of the impact of CRP POCT on antibiotic prescribing could be based on attaining predetermined targets for antibiotic prescribing reductions at specific milestones. The successful adoption models of CRP POCT in other European countries were characterised by having a slow and long early adoption phase followed by policy changes that then triggered large-scale adoption. Thus, a pilot CRP POCT programme in a selection of primary care centres, out-of-hours clinics or long-term care facilities in a CHO that contains one of the four national hospital lab hubs, may be the most prudent approach to managing the challenges of adopting the technology.

The introduction of CRP POCT should be considered in the context of a potential national quality management system applicable across point-of-care testing in primary care. By supporting the quality assurance, governance, and training required, such a system would enable the delivery of a safe and effective service. A

centralised service would also facilitate the IT structures necessary to provide connectivity and traceability.

9.7 Key messages

- The implementation of CRP POCT will require changes to working processes and patient flow within the general practice. Individual practices and practitioners will need to consider their own staffing, infrastructure and culture when establishing a testing service.
- Practice resources would be impacted if adoption of the CRP POCT were to be self-funded by doctors. The rapid uptake of CRP POCT in primary care may be unlikely in the absence of a funded implementation programme. Funding will be required from the HSE to ensure the systematic adoption and use of CRP POCT technology by GP contractors in primary care.
- Procurement options include: purchase by a community health organisation (CHO) to cover practices in their region; block purchase or tender proposal by HSE procurement on a national level; purchase and ownership of devices by central or supporting hospital laboratory services, loaned or leased back to primary care practices; loan or lease agreements facilitated by industry; or direct purchase by the primary care practice.
- Non-financial incentives should be considered for the adoption of the technology. Consideration may be given to introducing clinical guidelines that recommend the use of CRP POCT for acute RTIs with associated clinical uncertainty.
- All healthcare professionals performing the CRP POCT will require training on how to use the analysers, how and where to record the results, how and why internal and external quality control is performed, and what to do if an analyser does not work properly. Communication training may also be suggested for GPs to ensure patient cooperation and satisfaction with a scenario of non-prescribing of antibiotics for acute RTIs.
- The quality assessment process is crucial to assuring the accuracy and reliability of a CRP POCT service in primary care. It would provide confidence in the CRP results for patients and prescribers. Examples of international external quality assurance schemes from Wales, Denmark and Norway, and the recommendations of the WHO manual for establishing an EQA programme, are outlined for consideration.
- The acceptance of the CRP POCT programme among the general public may be enhanced by an antibiotic prescribing awareness campaign for patients. This may take the shape of advertising campaigns and patient education leaflets.

10 Discussion

A health technology assessment (HTA) is intended to support evidence-based decision-making in regard to the optimum use of resources in healthcare services. Measured investment and disinvestment decisions are essential to ensure that overall population health gain is maximised, particularly given finite healthcare budgets and increasing demands for services provided. The purpose of this HTA was to examine the evidence for C-reactive protein (CRP) point-of-care testing (POCT) to guide antibiotic prescribing for acute respiratory tract infections (RTIs) in primary care settings in Ireland. This chapter reviews and discusses the key issues and limitations of the data identified in the HTA.

10.1 Technology

Which technologies are considered in a HTA is important, as it impacts on the relative effectiveness of the included technologies. A diverse range of interventions might be considered as part of antimicrobial stewardship and those interventions may be used in tandem or in isolation. The mix of interventions offered and the sequence of their introduction may impact on their effectiveness. This HTA focused specifically on CRP POCT for patients presenting with acute RTIs in the primary care setting.

10.1.1 CRP POCT as a tool to support clinical decision-making

The aim of the HTA was to establish the clinical and economic impact of providing point-of-care testing to inform prescribing of antibiotics for patients presenting with symptoms of acute RTIs in primary care. Where there is clinical uncertainty regarding the need for an antibiotic, the use of CRP POCT may be helpful in differentiating between bacterial and viral infections.

A CRP test result is based on a measure of the C-reactive protein levels in a blood sample. The test result is therefore not a direct measure of bacterial or viral infection, but rather of an acute-phase protein produced in response to infection or tissue inflammation. In healthy people, the serum or plasma CRP levels are low. Raised concentrations of serum CRP often occur in bacterial infections, while typically only minor elevations are observed in viral infections.

In patients with ambiguous clinical findings, CRP POCT may be useful when used in conjunction with clinical examination or as part of a clinical decision rule to identify those patients most likely to benefit from antibiotic therapy, particularly where there is diagnostic uncertainty based on clinical examination alone. The objective of CRP POCT is therefore to rule out serious bacterial infections, thereby supporting a

decision not to provide an antibiotic to those who are unlikely to benefit from treatment. It may also help to identify those patients who are most likely to benefit from an antibiotic.

10.1.1 Included technologies

In this HTA the only intervention considered was CRP POCT in the primary care setting, with or without additional enhanced communication skills training. CRP point-of-care tests that co-tested another biomarker were eligible for inclusion. While one such device was identified (FebriDx®, which also tests for the presence of the viral biomarker Myxovirus resistance protein A [MxA]), no studies that used this device were eligible for inclusion in the evidence review. Other point-of-care technologies, such as rapid antigen detection tests (RADT), which can be used in primary care to diagnose bacterial pharyngitis caused by group A streptococci (GAS), were not considered in this assessment. Most notably, enhanced communication skills training was included as a combined intervention (with CRP POCT), but was not included as a standalone intervention as the scope of this project was CRP POCT. The only trials identified were those that included a CRP POCT arm, so there may be a wider evidence base available regarding enhanced communication skills alone.

At the time of publication, the use of CRP POCT to inform treatment of patients with suspected LRTI has been included in guidelines in the UK, Norway, Sweden, the Netherlands, Germany, Switzerland, Czech Republic and Estonia.

10.2 Epidemiology

RTIs are the most frequent infections encountered in primary care, accounting for approximately one quarter of attendances. International data suggest that primary care accounts for 80% to 90% of all antibiotic prescribing, with RTIs accounting for approximately 60% of prescriptions for antibiotics issued in that setting. Most RTIs are self-limiting. The natural course of upper RTIs is typically shorter (ranging from four days for acute otitis media to 2.5 weeks for acute rhinosinusitis) than for lower RTIs (ranging from three weeks for acute bronchitis/cough to three to six months (to complete recovery) for community-acquired pneumonia). Overprescribing of antibiotics is common in this setting, with high levels of inappropriate prescribing documented in observational studies benchmarking antibiotic prescribing versus clinical guidelines. Of note, however, there is substantial international variation in the consumption of antibiotics for systemic use in the community, as measured by average defined daily doses (DDDs). European surveillance data indicate a greater than three-fold variation (10.4-36.3; mean 21.9 DDD) between countries, with Ireland appearing mid-range (23.1 DDD). Despite broad consistency between

national guidelines on the diagnosis and treatment of RTIs, given that the majority of community prescribing is for RTIs, it is likely that some of this variation is driven by differences in actual antibiotic prescribing practices for these conditions in primary care. Although DDDs are adjusted for population size, they are not age-sex standardised and hence they may show apparent trends that actually reflect shifts in demography. As such, the DDD data should be interpreted with caution.

10.2.1 Irish epidemiological data

Due to the lack of centralised data collection of primary care activity in Ireland, there are no data sets that provide diagnosis-linked prescribing information. Figures were available from a single survey carried out between 2008 and 2010 for a sample of Irish GPs. Whether the sample was nationally representative at the time and whether the findings could be applicable 10 years after the study are questionable. However, it represents the only substantial Irish data source available. The lack of centralised data collection for primary care activity has implications both for evidence-based decision-making and for subsequent monitoring of new programmes or interventions. Based on the existing data collection structures, it would be very challenging to determine if the introduction of a national primary care-based CRP POCT programme would have a positive impact on antibiotic prescribing for acute RTIs.

Primary care provision in Ireland is characterised by a distinction between public patients that are in possession of a GMS or GP visit card, and private patients. Public patients can access GP services for free at the point of care, while private patients must pay a consultation fee out of pocket. As the entitlement to a GMS or GP visit card is means tested for all those aged six years and older, public patients tend to be more socioeconomically deprived than private patients. These considerations impact on the incidence of RTIs, the likelihood of attending the GP, and prescribing behaviour. These distinctions may impact on the applicability of international data to the Irish setting and also on decisions regarding how CRP POCT might be funded if it is introduced.

10.2.2 Trends in antimicrobial prescribing

As noted, overprescribing of antibiotics for RTIs in primary care is common, with high levels of inappropriate prescribing documented in observational studies benchmarking antibiotic prescribing versus clinical guidelines. At the patient level, there is a clear link between antibiotic dose and duration and the emergence of AMR, and there is also evidence that patients who have been treated frequently with antibiotics are at greater risk of antibiotic resistance. AMR results in increased morbidity and mortality from bacterial infections as well as increased economic

burden on the healthcare sector in the treatment and care of patients infected with multidrug-resistant strains as well as a loss of productivity. AMR results in the death of approximately 50,000 people per year in the US and Europe, and in the region of 700,000 people globally.

The rate of antibiotic prescribing has changed over time, as evidenced by the numbers of defined daily doses (DDD) over time. Overall, the number of DDDs per 1,000 inhabitants in Ireland has increased between 2003 and 2018, although there has been a modest decline since the peak at the start of 2015. There is substantial regional variation in DDDs per 1,000 inhabitants in Ireland. Regional variation may be attributable to a range of factors, such as location of pharmacies, and therefore may only partially reflect variation in prescribing. As the data on DDDs is based on total counts, it is not possible to investigate the trends in antibiotic prescribing in Ireland in relation to acute RTIs.

10.3 Clinical effectiveness and safety

The systematic review of clinical effectiveness and safety looked at the impact of CRP POCT on antibiotic prescribing for acute RTIs, and whether there were any adverse outcomes associated with CRP POCT. The pooled estimate for the RCTs showed a statistically significant reduction in antibiotic prescribing in the CRP POCT group compared with usual care (RR: 0.76). In the cluster randomised trials, there was a statistically significant reduction in antibiotic prescribing in the CRP POCT group compared with usual care (RR: 0.68). The observational studies show a similar effect of CRP POCT on antibiotic prescribing with a pooled RR of 0.61. Given the high prescribing rate for acute RTIs, this reduction is likely to be clinically important given the association between antibiotic use and antimicrobial resistance. The observed reduction in antibiotic prescribing does not appear to lead to a reduction in patient safety, with no evidence identified of an increase in mortality or hospitalisations associated with CRP POCT.

10.3.1 Duration and magnitude of effect

The treatment effect of CRP POCT on antibiotic prescribing as measured in the trials was marked: a reduction of approximately 25% in the rate of prescribing. The trials generally followed patients for 14 to 28 days to determine whether there were subsequent consultations for the same episode of RTI and to monitor if prescriptions were given at a later date. The average recruitment period across trials was 6.5 months, or 7.5 months from the recruitment of the first patient to completion of follow-up for the last patient. The treatment effect was greater in more recently published trials and in those with higher rates of prescribing in the usual care arm;

however, there were insufficient trials available to analyse these associations. Prescribing in the control arm of the RCTs ranged from 46.2% to 63.5%, so while estimated prescribing for RTIs in primary care in Ireland (61.7%) is at the upper end of this range, these data are likely to be broadly applicable to the Irish healthcare setting.

An important question, however, is whether that treatment effect is sustained over a longer period of time. CRP POCT facilitates a change in behaviour for both GPs and patients. The GP has a tool that supports a conversation around the need for an antibiotic prescription and patients will become more knowledgeable about the appropriateness of antibiotics in treating viral infections. The introduction of CRP POCT may lead to initial changes in practice, but those benefits may be eroded over time. The use of CRP POCT will increase consultation times. There may be periods when the device is not working or, if it is shared by clinicians in a practice, it may not be immediately available. It is therefore possible that prescribing practice may return to usual care levels after a period.

In the absence of studies giving clear long-term follow-up data, it is difficult to know whether the impact is sustained. One study followed a patient cohort over 3.5 years, but did not look at the long-term prescribing rates in the participating GPs. One study providing 12 month audit data found very low rates of CRP POCT usage at 12 months. If usage of the test reduces over time, then investment in the programme might require regular and substantial training or incentives to maintain changes to prescribing patterns. Consideration will also have to be given to the seasonal nature of RTIs, and that the timing of training and public and clinician awareness campaigns may need to be timed to ensure usage is adequate at peak times. The volume of CRP testing at a practice level and at an individual user level will influence the intensity and frequency of training required. It should be acknowledged that there is substantial variation across practices in terms of the number of patients and available resources, such as staff. All of these factors may influence how CRP POCT might be integrated into a practice in terms of which staff will use the device and who will require training in the device and quality assurance.

10.3.2 Safety concerns

While the systematic review concluded that use of CRP POCT to inform antibiotic prescribing in primary care for acute RTIs leads to a significant reduction in antibiotic prescribing without compromising patient safety, it is recognised that changes in the incidence of rare serious suppurative complications of RTIs (for example, peritonsillar abscess, empyema, and intracranial abscess) arising from a failure to provide timely antibiotic treatment cannot be evaluated precisely in clinical trials. A 2016 UK cohort study that reviewed data (2005 to 2014) for patients presenting with acute RTIs

found no evidence found that mastoiditis, empyema, meningitis, intracranial abscess, or Lemierre's syndrome were more frequent in low prescribing practices. Reduced prescribing for RTIs at initial consultation may lead to a slight increase in the incidence of pneumonia and peritonsillar abscess, both of which would be expected to respond to treatment. However, caution may be required in subgroups at higher risk of pneumonia.

Antibiotic treatment of RTIs exposes patients to an increased risk of an adverse event, such as an episode of drug-associated toxicity. Adverse drug events from antibiotic exposure may occur in one out of every five patients. By prescribing an antibiotic to a patient with a viral RTI, there is no benefit but there is the prospect of harm through adverse drug events and it could potentially contribute to increased antimicrobial resistance at both the individual and community level.

While antibiotic-related adverse events (AEs) are common, serious AEs are rare. The relative merit of the benefits and harms of antibiotic treatment were considered in terms of the numbers needed to treat (NNT) and to harm (NNH). It was shown that harm may be a more likely outcome than benefit, depending on the type of RTI and choice of outcome. For example, in acute otitis media the NNT is 24 and the NNH is 13. That is, harm is more likely than benefit. Although the benefits and harms may not be considered of equal importance, patients should have an understanding of the relative potential for benefit and harm in the context of antibiotic prescribing for RTIs.

10.3.3 Applicability to children

Patient groups generally considered at the highest risk of acute RTI and their sequelae include: patients aged less than five years or greater than 70 years, those with a pre-existing lung condition (such as COPD or asthma), immuno-compromised patients, and long-term care (LTC) residents of nursing homes. The incidence of RTIs is highest in children, and cases in children are associated with prescribing rates in excess of 50%.

In terms of the data on clinical effectiveness, only two RCTs and one observational study included children. Two studies reported results separately for children and adults, with the effect of CRP POCT on prescribing antibiotics found to be similar in both adults and children. One study found a significant effect in both adults and children while the other reported no effect in either group. Given the limited data on children and the lack of consistency in results, it was not possible to state what the impact of CRP POCT testing is on antibiotic prescribing in children presenting with acute RTIs in primary care.

Another consideration is the potential challenges associated with taking blood

samples from children. The procedure of drawing blood may be painful for a child, so there may be low acceptability for both children and parents, potentially limiting the benefits of having the CRP test result available to support clinical judgment.

10.3.4 Impact on patient and clinician behaviour

The introduction of CRP POCT may have numerous impacts on behaviour that could be considered positive or negative.

A clear potential impact would be the reduction in future consultations for RTIs. That is, patients who attend with an acute RTI and are not prescribed an antibiotic on the basis of the CRP test result may be less likely to attend the GP with a subsequent acute RTI. The behaviour change would occur because of an increased understanding that antibiotics should not be used to treat viral infections. One study provided weak evidence that this may happen in practice, noting non-statistically significant reductions in subsequent RTI episodes for patients exposed to CRP POCT. The negative converse would be that patients may begin to believe that they need to have a CRP test done before it can be determined that an antibiotic is not required, and thus attendance for RTIs might plausibly increase for some patients.

If a CRP POCT programme was rolled out, a public awareness campaign could be included, which would help to increase knowledge about antibiotic prescribing. Such a campaign could increase awareness not just in relation to antibiotic prescribing for RTIs but across all indications, although it has already been noted that RTIs account for a large proportion of antibiotic prescribing in primary care. While there are existing awareness campaigns in relation to antibiotic prescribing, the link to a test available in the primary care setting might help enforce the message, particularly given the large cohort of patients who could potentially have the test in a consultation.

The introduction of a diagnostic test can have negative consequences for clinical practice. There is a risk that some clinicians may allow their clinical judgment to be led by the test result. For example, if the guidelines state that a delayed prescription should be considered for CRP test results between 20 and 50 mg/L and a patient's test result is close to the lower threshold, the clinician may automatically give a delayed prescription. As already stated, the CRP POCT is intended to support clinical judgment, not to replace it.

Similarly, access to CRP POCT could, in some instances, undermine professional confidence. A GP may become reliant on the CRP test result to support decision-making rather than limiting its use to cases of clinical uncertainty. Another related aspect is the use of testing for medical protection. That is, overuse of tests as a

means of ensuring an evidence base in the event of a future claim of medical negligence. For example, if a GP considers that a patient has a viral infection and hence an antibiotic is not appropriate, they may carry out the CRP test to have a record of the CRP levels to justify their decision.

The availability of a test that is potentially useful when distinguishing between viral and bacterial acute RTIs may be seen as a tool to inform prescribing for other infections. There is a potential for indication creep where it is used for other indications for which there is no evidence that it facilitates a reduction in inappropriate antimicrobial prescribing without any adverse effects for patients. However, wider usage of CRP POCT may also lead to other health system gains and cost savings in terms of specialist referral, although that possibility is beyond the scope of this report. Laboratory-based CRP testing is currently widely used by primary care practitioners to support the diagnosis and management of a range of inflammatory conditions. CRP POCT may be substituted for laboratory-based testing in these patients with potential consequences for patient care if the CRP levels are different to those observed in patients presenting with acute RTIs impacting device performance. While it may be possible to use clinical guidelines to give direction on the appropriate use of CRP POCT, it would be extremely challenging to monitor and ensure appropriate usage of the technology across all primary care settings.

The net impact of these behavioural changes can only be speculated on, as they are likely to interact with each other and will be a function of the culture within which CRP POCT is being introduced. Other factors, such as fee-per-item incentives, can further distort behaviour and impact on the effect of CRP POCT on consulting and antibiotic prescribing patterns. Countries that include CRP POCT as part of their suite of antimicrobial stewardship initiatives are noted, for the most part, to have relatively low rates of antibiotic prescribing. Despite the uncertainty, it is likely that CRP POCT supports a culture of appropriate antimicrobial prescribing.

10.3.5 Link to antimicrobial resistance outcomes

A key motivation for CRP POCT is to reduce inappropriate prescribing of antibiotics with a view to reducing the risk of antimicrobial resistance in the future. While the correlation between antibiotic usage and antimicrobial resistance can be seen at a population level, it is challenging to determine the exact nature of the relationship between the two. As such, it is not possible to state what impact a 5% reduction in antibiotic prescribing now would have on antimicrobial resistance in five or ten years' time. The inability to clearly quantify the link between antibiotic prescribing and antimicrobial resistance means it is not possible to determine what impact the introduction of CRP POCT might have on future antimicrobial resistance. For

example, there may be a substantial impact, but with a substantial time lag. In light of the uncertainty regarding whether the effect of CRP POCT on antibiotic prescribing is sustained, it is possible that the impact may be too short-term to meaningfully impact on antimicrobial resistance. It must be acknowledged that the appropriateness of antibiotic prescribing in a given clinical context is not limited to the nature of the presenting condition (bacterial or viral), but also to other factors such as the class of antibiotic used, the dose and the duration of treatment. An intervention might therefore increase the appropriateness of antibiotic prescribing without reducing it. Thus, if the introduction of CRP POCT leads to only a short-term reduction in antibiotic prescribing, it does not preclude a longer-term positive contribution to antimicrobial stewardship.

The issue to highlight here is that there is substantial uncertainty in the longevity of the effect of CRP POCT on antibiotic prescribing behaviour and also uncertainty in the link between antibiotic usage and antimicrobial resistance. The combination of those two uncertainties cannot be quantified and therefore it is not possible to estimate how CRP POCT may impact on antimicrobial resistance.

10.4 Diagnostic test accuracy

The systematic review of diagnostic test accuracy investigated the sensitivity and specificity of the CRP test. The sensitivity and specificity describe the ability of a test to correctly diagnose people who do and do not have the condition of interest, in this case acute bacterial RTI. Diagnostic test accuracy is ordinarily quantified relative to a gold standard test: a test that always provides a correct diagnosis. In the case of RTIs, the gold standard test depends on the type of acute RTI, and may be based on one or more of microbiological, laboratory or radiological confirmation. The evidence base was characterised by a high level of heterogeneity in patient populations, diagnostic criteria, CRP cut-points, how the performance of the test was reported and the absence of a universal reference standard for the diagnosis of RTIs requiring antibiotic treatment.

Sensitivity is the proportion of patients who are positive and who are classified as positive by the test. The specificity is the proportion of patients who are negative and who are classified as negative by the test. The CRP POCT measures the serum or plasma level of CRP in the patient, and that level is translated into a test result. As not everyone with high CRP has a bacterial infection and not everyone with low CRP has a viral infection, the test will lead to some misclassification. For most tests of this nature, sensitivity and specificity are negatively correlated. That is, a test that has good sensitivity has poor specificity, and vice versa, because a cut-point must be chosen for classifying a test result as positive. At a low cut-point, such as a CRP level

of 10 mg/L, the sensitivity will be high (it is unlikely that anyone with a bacterial infection will have had a negative test result), but the specificity will be low (many people with a viral infection may have a positive test result).

A key finding of the review was that the sensitivity and specificity of the test was generally poor. It would be possible to pick a cut-point such that either the sensitivity or specificity was high, but not where both are high. If a cut-point is chosen that ensures high sensitivity then the test may be better for ruling out, whereas setting it for high specificity is better for ruling in. The findings suggest that different cut-points might be suitable depending on the type of acute RTI with which the patient presents. The use of different cut-points could create confusion in the use of the test, while the use of a universal cut-point would entail different rates of misdiagnosis across RTI types. Taken at face value, based on the diagnostic test accuracy, CRP POCT is not a very good test for distinguishing between viral and bacterial RTIs. However, that finding is contradicted by the significant impact on antibiotic prescribing observed in the clinical effectiveness trials. It may therefore be that the accuracy of the test is of lesser importance, and what is more critical is that it facilitates a discussion between the clinician and the patient and perhaps a more conservative treatment approach to managing acute RTIs.

Only one of the included studies investigated the use of CRP POCT in children and the results showed that CRP levels in children can be quite different to adults. The application of cut-points used in adults to tests in children would likely lead to misclassification. The equivocal results of the clinical effectiveness trials that included children may be explained by the difficulty in applying a universal cut-point across children and adults.

Many of the diagnostic test accuracy studies used CRP POCT in combination with a clinical prediction rule, making it difficult to determine the effect CRP POCT had on its own. The extent to which the results of those trials are applicable depends on whether GPs naturally apply those clinical prediction rules in practice and how they would combine the rule with the CRP test result in the absence of a defined algorithm. Further validation of prediction rules incorporating CRP measurement is required.

10.5 Analytical performance

While diagnostic test accuracy considered the ability of the test to correctly distinguish between viral and bacterial RTIs, the analytical performance was concerned with the ability of the POCT to accurately and precisely measure CRP levels. Notwithstanding the issues of selecting a CRP cut-point for classifying a test

result as positive, a test device that does not accurately measure CRP levels will compound uncertainty. The studies reviewing analytical performance compared devices both to each other and to a laboratory CRP device.

10.5.1 Bias, accuracy and precision

For semi-quantitative devices, the agreement between the reference test and the POCT was found to be moderate to good. The accuracy of the test was shown to decrease after the optimal 5 minutes. Due to the upper limit of 80mg/L, the semi-quantitative tests included may be of limited use in terms of current guidelines that use a cut-point of ≥100 mg/L for antibiotic prescribing.

The majority of the evidence suggested acceptable performance for all 11 quantitative devices in the laboratory setting. Precision was also acceptable in the laboratory for six of the devices, suggesting that under idealised circumstances in the laboratory most of the devices are accurate and precise. When used at the point of care, the results for accuracy and precision of the devices were more variable. Very little data were available on precision at the point of care.

It was noted that issues with imprecision and inaccuracy tend to be apparent at low and high CRP levels. Whether those issues translate into misdiagnosis depends on the choice of cut-points. For example, if a device has accuracy issues at CRP levels of 10 mg/L and lower, then it is unlikely to cause problems with misdiagnosis. However, if the accuracy or precision issues occur around CRP levels that might be chosen as diagnosis cut-points, then consideration would have to be given to how to control for that inaccuracy or imprecision in a clinical judgment.

10.5.2 Sources of error

An issue was that the performance of POCT devices in the laboratory was not always replicated in the primary care setting. There can be a wide range of drivers of error for the POCT, such as the collection procedure, the sample quality, the competence of the sample taker, poor maintenance of the device and transcription or reading errors relating to the test result. While these sources of error can be moderated through regular training and the use of robust standardised operating procedures, they cannot be eliminated. The impact of these errors associated with collection of the sample and use of the device can easily dwarf issues relating to the accuracy or precision of the test device, which may only lead to a ±10% bias in the CRP level.

A balance must be struck between accuracy and ease of use in the primary care setting. A system that is difficult to use is likely to have limited application in a busy primary care practice. More importantly, a system that is difficult to use may

facilitate error. The importance of quality assurance processes was highlighted in the organisational chapter, and the extent to which they might moderate or control error must be carefully considered.

10.6 Economic evaluation

A systematic review was undertaken to identify studies estimating the cost-effectiveness of CRP POCT in a primary care setting. Five studies were found including both cost-utility and cost-effectiveness analyses. In terms of cost-utility, CRP POCT testing was found to be a cost-effective alternative to clinical judgment alone. The cost-utility analyses were underpinned by the assumption that reduced antibiotic prescribing will lead to fewer adverse drug reactions and thus a utility gain. The short-term and minor nature of many of the adverse reactions means that the impact on utilities might not be clinically meaningful.

10.6.1 Cost-effectiveness model

A cost-effectiveness model was developed for this HTA that compared CRP POCT with and without enhanced communication skills training to usual care. The model considered outcomes for the Irish population over a five-year time horizon taken from the cost perspective of the HSE. Relative to usual care, the model found both POCT strategies were more costly, largely due to the added cost of CRP tests, but both reduced antibiotic prescribing in the community. The strategy of CRP POCT with enhanced communication skills training was more effective and less costly than CRP POCT alone. This finding was, however, subject to substantial uncertainty.

The model did not incorporate the impact on antimicrobial resistance, which may have very substantial health and economic impacts in the future. Given the uncertainty around the longer-term impact of CRP POCT and the exact nature of the link between current antimicrobial prescribing and future antimicrobial resistance, it was not feasible to model the effect on AMR. As such, the intervention is likely to be more cost-effective than estimated in the model

10.6.2 Budget impact

The budget impact of GP CRP POCT was estimated at €23.9 million (95% CI €5.1 to €43.8 million) over five years, while the budget impact for GP CRP POCT + comm was €4.5 million (95% CI €-22.8 to €34.8 million) over the same period. The addition of enhanced communication skills training was associated with a reduced budget impact because of increased clinical effectiveness (resulting in fewer antibiotic prescriptions than CRP POCT alone). The very wide confidence intervals underline the magnitude of uncertainty in the budget impact estimates. An important

consideration was the number of devices that would have to be bought to achieve adequate coverage such that CRP POCT was available for any RTI consultations where there was clinical uncertainty. Another key factor impacting on uncertainty in the estimates was the reduced risk of prescribing associated with the intervention. Given the probable correlation between impact on prescribing and volume of testing, if the uptake of testing is lower than was assumed in the analysis then the budget impact is likely to be an overestimate.

A scenario analysis was used to explore the impact of including a reimbursement fee associated with carrying out CRP POC tests. A fee-per-item approach leads to a substantial increase in the budget impact: based on reimbursement fees used in Europe the five year budget impact increased by between €8.2 million and €54.3 million.

10.6.3 Uncertainty in health and economic impact of CRP POCT

The imprecision associated with the effect on antibiotic prescribing of introducing CRP POCT creates substantial uncertainty in the cost-effectiveness and budget impact. What was not included in the model was uncertainty in relation to the longer-term impact of the intervention on prescribing. As already stated, the length of the trials was typically short, so it may not have been possible to identify whether there was a tailing off of effectiveness over time or conversely whether there was a sustained change in provider behaviour that had other health benefits for patients.

A potentially critical source of uncertainty relates to the impact that CRP POCT will have on consultation time. While the test takes longer than a typical consultation, the device can be left to run while the consultation continues. The GP could ask the patient to move to the waiting area, for example, and the test result might be given after the next patient is seen. Or the test might be carried out by a practice nurse in a separate room. While practices are likely to seek out an approach that minimises disruption to workflow, it will still add to consultation times. In the main analysis it was assumed that carrying out the CRP POC test would add an average of 3 minutes to a consultation, based on data used in a previous economic model.

Extending consultation times has an opportunity cost in that activity will be displaced, and that displaced activity might be associated with a loss of income. The amount of displaced activity depends on the time added to a consultation and whether the test will be available to patients of all ages or only adults. If the test is for adults only, adding 3 minutes to a consultation displaces almost 2% of GP activity, while adding 6 minutes will displace almost 3.8% of activity.

The displaced activity was incorporated into the cost-effectiveness analysis as an

opportunity cost of GP time. Displaced activity was not incorporated into the budget impact analysis as the opportunity cost does not generate a direct cost to the HSE. The opportunity cost from increased consultation time may be counter-balanced over time by reduced consultations for acute RTIs. The opportunity cost must also be considered in the context of the contribution to antimicrobial stewardship. However, failure to acknowledge the impact on GP workload may adversely impact on the uptake and usage of CRP POCT, and diminish its potential impact on antibiotic prescribing. Some countries have introduced reimbursement for tests carried out. If CRP POCT is adopted in Ireland, consideration will have to be given to how best to minimise the impact of testing and the associated management and quality assurance on GP workload and capacity.

10.6.4 Limitations of the economic evaluation

An important limitation of the economic evaluation was the limited data available on the treatment of acute RTIs in primary care in Ireland. In the absence of nationally representative data, the proportion of attendances associated with RTIs, and the proportion of episodes resulting in an antibiotic prescription were both based on a single Irish study that was conducted almost 10 years before this HTA. Both of those parameters are important in the budget impact, and if the study figures are biased (either through no longer being applicable or because the sample was not nationally representative), then the budget impact may have been poorly estimated.

The economic evaluation it was assumed that a CRP POCT device would have to be supplied to each practice, with some larger practices requiring multiple devices. Additional analyses were used to consider scenarios of one device per GP and one device per practice, respectively. There is the potential for an investment in multi-test devices that are not limited to CRP POCT. Should combined devices be adopted, there would be a reduced investment in CRP as the cost would be spread over a number of tests. However, many practices might already have devices for the other tests, in which case the cost savings may not actually be realised unless the devices were replaced as they reached the end of their lifespan.

It is noted that the overall goal of CRP POCT is to improve antimicrobial stewardship and reduce AMR. The impact of CRP POCT on antimicrobial resistance was not included in the model given the complexity of estimating the effect of reduced antibiotic prescribing on antimicrobial resistance. As already outlined, such an analysis would require so many broad assumptions and uncertainties as to not be of any practical value in decision-making. Any decision to implement CRP POCT is likely to be based on a wide range of considerations. While budget impact may be an important consideration, it is recognised that the evidence of cost-effectiveness of

CRP POCT that excludes its impact on AMR may be of limited relevance to decision-making.

10.7 Organisational considerations

A range of considerations were identified in relation to organisational issues. CRP POCT is designed to take place in the primary care setting and is intended for use in patients for whom there is clinical uncertainty as to whether their acute RTI is viral or bacterial. Other antimicrobial stewardship initiatives may be directed at increasing public awareness and perhaps reducing consultations for acute RTIs, based on the knowledge that it is likely to be viral and that there is no specific treatment available. By facilitating an immediate test result, CRP POCT can reduce the number of immediate and delayed prescriptions. The alternative of the GP sending the sample for testing to a hospital laboratory would entail a delay of several hours before the test result is known. Such delays create a serious inconvenience for patients, may complicate provision of prescriptions for positive test results, and may also diminish the opportunity for a conversation between GP and patient on the benefits and harms of antibiotic prescribing.

10.7.1 Practice resources

Several point-of-care tests are already carried out in the primary care setting, and thus the introduction of CRP POCT could potentially capitalise on the structures already in place. Those structures relate to the funding and provision of consumables associated with testing.

It was highlighted that the use of CRP POCT in a consultation would add to consultation time. The time taken from sample taking to test result is relatively short in comparison to sending a CRP sample to a hospital laboratory for testing. However, it is longer than the time taken for a typical consultation, and it was estimated to add an average of 3 minutes to a consultation. It is estimated that approximately one quarter of consultations in primary care are for RTIs, and that approximately 34% of those would be associated with clinical uncertainty. Thus, the introduction of CRP POCT could add 3 minutes to about 8% of all consultations. As indicated in the economic evaluation, the implications for a busy practice are quite substantial, with 2% of activity displaced under base case conditions. Depending on how much time the test adds to a consultation and whether the test is available to all ages or just adults, the displacement could be 8% or higher. It is likely that larger practices may seek ways to maintain efficiency, such as delegating testing to a specific member of staff such as a practice nurse or healthcare assistant. For smaller practices there may be limited opportunity to delegate and thus adoption of CRP POCT may displace

some patient care.

Training in CRP POCT is required for all those who will use the device and there are considerations around the volume of usage needed to retain competency. Although basic training in device usage is typically provided by the manufacturer at the time of acquisition, this is unlikely to be sufficient to ensure competency as part of a rigorous quality assurance system. In a practice with a turnover of staff there will need to be training for new staff and potentially refresher training for existing staff.

In the economic evaluation it was assumed that the HSE would fund the procurement of testing devices and would also supply the consumables for the test at no cost to GP practices. The fact that the test will add to consultation time means that some GPs may elect to charge a fee for carrying out the test. From a patient perspective, it is unclear what the acceptability would be for such a fee, as the alternative may be to attend at a local hospital to have CRP levels checked. A fee to patients may distort use of the test as fewer patients might consent to its use, and may undermine the effectiveness of CRP POCT in reducing antibiotic prescribing.

10.7.2 Quality assurance

Quality assurance was identified as an important element of a CRP POCT service. The responsibility for the quality control of the CRP POCT lies with the primary care practice, although it can be complemented by outsourcing aspects of the process as part of an external quality assurance scheme. For internal quality control, a control sample is tested by the user to ensure that the device is performing within certain defined specifications. The objective of an external quality assurance scheme, on the other hand, is to monitor and document the analytical quality, identify poor performance, detect analytical errors and make corrective actions.

While both internal and external quality assurance are important for any POTC service, it is worth considering the potential impact of poor-quality testing. The implications in this instance is that there will be an increased risk of misdiagnosis within patients presenting with acute RTI for which there is clinical uncertainty as to whether the underlying infection is viral or bacterial. In the context of usual care, the GP will rely on clinical judgment based on symptoms and signs, patient history and characteristics, and other factors. The CRP POCT test provides an additional piece of information which the GP may or may not use to aid judgment. It is likely that there is overprescribing of antibiotics in this patient cohort at present, and poor-quality testing may reduce the effectiveness of CRP POCT to support reduced antibiotic prescribing. From a patient perspective, unnecessary prescribing of antibiotics increases the risk of adverse drug reactions and will expose the patient to harm

without any potential to benefit.

There is the potential for CRP POCT to be integrated into a wider quality-assured system of POCT. Such a system could enable centralised tracking of batches and controlled samples, test results, and potentially to track usage by individual practitioners. There are many reasons why such a system would be beneficial for POCT and for quality assurance. However, it would be difficult to justify the introduction of such a system for CRP POCT alone, and it would have to be considered across a range of tests. As such, the cost of the system and the potential benefits would also have to be spread across multiple types of test. The responsibility for managing quality assurance, and the governance of POCT, might naturally sit with the hospital laboratory network. To ensure that service meets acceptable standards, consideration should be given to the resources required to ensure a sustainable infrastructure of QA and governance.

Quality assurance processes as reviewed here are intended to support a system of testing that achieves an acceptable standard relative to the gold standard of hospital laboratory testing. That is clearly distinct from quality in the sense of appropriate prescribing of antibiotics in terms of whether or not they are indicated, and the type, dose and duration of antibiotic treatment. Hence quality assurance is just one facet of ensuring that CRP POCT makes a positive contribution to antimicrobial stewardship. To achieve a sustained and meaningful change in practice, there must be a commitment to continuous improvement through the identification of areas for improvement and through the adoption of changed behaviour and processes. While national initiatives play an important role in improvement, local-level recognition and ownership of improvement processes may be more likely to lead to effective and sustained change.

10.7.3 Potential implementation options

The HTA considered a national programme of CRP POCT for acute RTIs in primary care. In this case that meant a systematic provision of CRP POC test devices and associated consumables and training in primary care practices. There are more than 1,700 practices in Ireland and almost 3,000 GPs. In the absence of any centralised data collection from GP practices or from POCT devices, it would not be feasible to monitor the use of the test other than through the volume of consumables provided to each practice or through a fee-per-item system. There would also be no pre-existing method to monitor the impact on antibiotic prescribing other than through the number of defined daily doses (DDD), which is not available in an indication-specific classification. If a reduction in DDDs was observed, it would not be possible to state if that was in cases of RTI or if it was associated with CRP POCT.

It would be possible to consider alternative partial roll-out of the technology to a subgroup of practices for which diagnosis and prescription data are routinely collected and coded, such as the networks being established through the HRB Primary Care Clinical Trials Network that will be focusing on this type of activity.[300] Similar to the pilot programmes introduced in the UK, a pilot would provide an opportunity to determine how the technology disrupts workflow, whether it influences prescribing practice, and the extent to which it is acceptable to patients. It would also provide the possibility of tracking whether the effect of CRP POCT on antibiotic prescribing is maintained over a longer timeframe. Options for a partial roll-out include a random subset of practices, a group of sentinel practices, or through the out-of-hours (OOH) services. It would be essential that the included clinics could provide data on diagnosis, test usage, and prescribing for all patients presenting with acute RTI. Ideally the pilot would continue for long enough to determine if the effect is sustained and how the adoption of CRP POCT impacts on workflow and capacity. Through the OOH services there is the opportunity to introduce a large proportion of GPs to CRP POCT and the potential benefits in terms of behavioural change. However, the trial data underpinning clinical effectiveness was not based specifically on OOH services, hence the findings may not apply due to differences in the demography and illness profile of the patients presenting. In the OOH services there may be a higher volume of testing and potentially the availability of auxiliary staff dedicated to carrying out tests, which will support efficient processes and potentially reduce impact on workflow. The intervention may be more effective in the OOH setting, which would have implications for how the outcome of such a pilot programme might inform the decision to adopt the technology in general practices.

Another alternative to consider is introducing CRP POCT to practices on a short-term basis to change prescribing behaviour, and then to monitor whether the behaviour change is maintained after the device is taken out of the practice. It is important to stress that there are no trial data available at present to suggest that a short-term CRP POCT intervention is effective.

For practices with good access to hospital laboratories, it may be possible to consider a scheme to provide rapid turnaround laboratory-based testing as an alternative to point-of-care testing. It would reduce the burden of quality assurance on practices and may present a viable alternative to POCT in certain geographic areas. Such an approach would entail a different pathway, as it may place a greater reliance on delayed prescriptions, and it is therefore unclear whether it would achieve the same clinical effectiveness as POC testing.

Based on a single study including 12 month audit data, it is possible that enhanced communication skills training may have a more sustainable effect on antibiotic

prescribing than CRP POCT.[180] The scope of this HTA was to evaluate CRP POCT, and as such a comprehensive systematic review of the effectiveness of enhanced communication skills training was not carried out. Based on the limited data reviewed, a may offer a potentially cost-effective alternative to CRP POCT.

A partial roll-out of CRP POCT would provide an opportunity to assess the impact of testing on practice capacity and workload. It would also offer the possibility of exploring approaches to ensuring continued use of testing to inform antibiotic prescribing decisions in cases of acute RTI. It may also provide the possibility of evaluating different solutions for different areas depending on the local health service infrastructure. A pilot study could generate data for subgroups for which there are no data at present regarding CRP POCT, such as residents in long-term care facilities.

The lack of consistent and systematic data collection in Irish primary care means it is not possible to routinely analyse primary care activity. For example, it is not possible to alert a practice if their rate of prescribing is substantially higher than the national average for a given indication. Development of a primary care dataset with national coverage including both diagnosis and prescribing would provide a means to identify practises where prescribing could potentially be improved. It would also provide a more direct means to measure the impact of antimicrobial stewardship initiatives on antibiotic prescribing in primary care.

10.8 Summary

The objective of CRP POCT is to rule out serious bacterial infections, thereby supporting a decision not to provide an antibiotic to those who are unlikely to benefit from treatment. It may also help to identify patients who are most likely to benefit from an antibiotic.

There are limited Irish epidemiological data available on acute RTIs in primary care and associated antibiotic prescribing. The lack of centralised primary care data collection in Ireland will hinder the monitoring of the impact of introducing CRP POCT.

A CRP POCT programme may have both positive and negative impacts on patient and clinician behaviour. In light of the experience in countries that include CRP POCT as part of their suite of antimicrobial stewardship initiatives, it is likely that CRP POCT supports a culture of appropriate antimicrobial prescribing. The clinical effectiveness of CRP POCT is not clearly explained by the results of the analysis of diagnostic test accuracy. However, it is possible that the impact of CRP POCT is primarily due to

how it facilitates communication between the clinician and the patient, rather than by providing an accurate differentiation between a viral and bacterial infection.

The introduction of CRP POCT is likely to displace primary care activity through increased consultation times for patients who undergo the test. That displacement of activity may be counterbalanced by a reduction in future consultations for RTIs. The displacement of care must also be considered in the context of the contribution to antimicrobial stewardship. If primary care practices find that capacity is adversely affected through the provision of CRP POCT, then GPs may cease to use testing and the effect on prescribing will be reduced.

10.9 Key messages

- The objective of CRP POCT is to rule out serious bacterial infections, thereby supporting a decision not to provide an antibiotic to those who are unlikely to benefit from treatment. It may also help to identify those patients who are most likely to benefit from an antibiotic.
- There are limited Irish epidemiological data available on acute RTIs in primary care and associated antibiotic prescribing. The lack of centralised primary care data collection in Ireland will hinder the possibility of monitoring the impact of introducing CRP POCT.
- A CRP POCT programme may have both positive and negative impacts on patient and clinician behaviour. In light of the experience in countries that include CRP POCT as part of their suite of antimicrobial stewardship initiatives, it is likely that CRP POCT supports a culture of appropriate antimicrobial prescribing.
- The clinical effectiveness of CRP POCT is not clearly explained by the results of the analysis of diagnostic test accuracy. It is likely that the impact of CRP POCT is related to how it facilitates communication between the clinician and the patient, rather than by providing an accurate differentiation between a viral and bacterial infection.
- The introduction of CRP POCT is likely to displace primary care activity through increased consultation times for patients who undergo the test. That displacement of activity may be counterbalanced by a reduction in future consultations for RTIs. However, there could be opportunity costs and loss of income for GPs due to displaced activity.
- A carefully managed and evaluated pilot programme or partial roll-out of CRP POCT may offer the best prospect to reduce uncertainty about the effects of a national programme.

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Appendix A Technical features of the device

	Technology				
	Quantitative CRP analysers				
Device type	Assay kit & analyser instrument	Assay kit & analyser instrument	Assay kit & analyser instrument	Assay kit & analyser instrument	Assay kit & analyser instrument
Proprietary name	**QuikRead go® CRP assay** and **QuikRead go® Instrument**	**QuikRead go® CRP+Hb assay** and **QuikRead go® Instrument**	**QuikRead® CRP assay** and **QuikRead® 101 Instrument**	**Alere Afinion™ CRP assay** and **Alere Afinion™ AS100*** or **Alere Afinion™ 2****	**NycoCard™ CRP assay** and **NycoCard™ Reader II**
Manufacturer	Orion Diagnostica Oy	Orion Diagnostica Oy	Orion Diagnostica Oy	Abbott Diagnostic Technologies AS	Abbott Diagnostic Technologies AS
Reference codes	**QuikRead go® CRP assay**: 135171 (50 tests), 151461 (25 tests), 135174 (500 tests). Localised test versions: 133891, 145215,135172,135173,135283, 135174,125175 and **QuikRead go® Instrument**: 133893. Localised versions: 135867,149915,145218,136196 **QuikRead® CRP control**: 68296 **QuikRead go® CRP control High:** 137071	**QuikRead go® CRP+Hb assay**: 140068 (50 tests) and **QuikRead go® Instrument**: 133893. Localised versions: 135867,149915,145218,136196 **QuikRead® CRP control**: 68296 **QuikRead go® CRP control High:** 137071	**QuikRead® CRP assay**: 134191, 134193 (50 tests). Additional test versions: 67961, 128574,128577, 68798, 06160, 134194,134197,134195, 134198,128575,106161 and **QuikRead® 101 Instrument**: 06040, 06078 **QuikRead® CRP Control:** 68296	**Alere Afinion™ CRP:** 1116526, 1116522, 1116524, 1116023 (15 tests) and **Afinion™ AS100 Analyser:** 1116049 or **Alere ™ 2 Analyser:** 1116679, 1116680, 1116681 **Alere Afinion™ CRP control:** 1116057	**NycoCard™ CRP:** 1116078, 1116080 and **NycoCard™ Reader II:** 1116149 **Alere Afinion™ CRP control:** 1116057
Class/GMDN code	General IVD, based on directive 98/79/EC; GMDN code 53705.	General IVD, based on directive 98/79/EC; GMDN code 53705	General IVD, based on directive 98/79/EC; GMDN code 53705	General IVD, based on directive 98/79/EC; GMDN code 53707	General IVD, based on directive 98/79/EC; GMDN code 53707
Additional tests	Strep A, iFOB	Strep A, iFOB	iFOB, U-ALB	HbA1c, lipid panel, ACR	HbA1c, D-dimer, U-Albumin
Method	Immunoturbidimetric assay	Immunoturbidimetric assay	Immunoturbidimetric assay	Solid phase immuno-chemical assay	Solid phase immuno-metric assay
Sample size & type (+alternative	20 µL capillary blood (venous whole blood, plasma or serum)	20 µL capillary blood (venous whole blood, plasma or serum)	20 µL capillary blood (venous whole blood, plasma or serum)	2.5 µL capillary blood (venous whole blood, serum or plasma)	5 µL capillary blood (venous whole blood, serum or plasma)

Analytical range (whole blood)	5 – 200 mg/L CRP	5 – 200 mg/L CRP 50 – 245 g/L Hb	8 – 160 mg/L CRP	5 – 200 mg/L CRP	8 – 200 mg/L CRP
Calibration	No – automatic	No – automatic	Yes – 15 sec	No – automatic	Yes – 15 sec
Haematocrit auto-correction	Yes[a]	Yes[a]	No	Yes[a]	No – calibrated to read 40% Ht
Special storage requirements for test (e.g. refrigeration)	CRP Reagent caps (in opened and unopened aluminium tube): 2-8°C (until expiry); 15-25°C; 24 hrs per day (1 month) & 7.5 hrs per day (3 months) Prefilled cuvettes in unopened foil pouches: 2-25°C (until expiry). It will take 15 minutes for an individual refrigerated prefilled cuvette to reach room temp.	CRP Reagent caps (in opened and unopened aluminium tube): 2-8°C (until expiry); 15-25°C; 24 hrs per day (1 month) & 7.5 hrs per day (3 months) Prefilled cuvettes in unopened foil pouches: 2-25°C (until expiry). It will take 15 minutes for an individual refrigerated prefilled cuvette to reach room temp.	CRP Reagent caps (in opened and unopened aluminium tube): 2-8°C (until expiry); 15-25°C; 24 hrs per day (1 month) & 7.5 hrs per day (3 months) Prefilled cuvettes in unopened foil pouches: 2-25°C (until expiry). It will take 15 minutes for an individual refrigerated prefilled cuvette to reach room temp.	Test Cartridge must reach an operating temperature of 15-30°C before use. Upon removal from refrigerated storage, leave the test cartridge in unopened foil pouch for at least 15 mins.	Nycocard™ test tube with dilution liquid is stored in refrigerator. It must be brought to room temperature before analysis.
Analyser size and weight	14.5 x 15.5 x 27 cm 1.7 kg	14.5 x 15.5 x 27 cm 1.7 kg	8 x 14 x 22 cm 1.0 kg	17 x 19 x 34 cm and 5.0 kg* 20 x 19 x 33 cm and 3.4 kg**	20 x 17 x 7 cm instrument box 2.95 x 14.4 cm (reader pen) 0.54 kg
Analyser warm-up time	50 sec	50 sec	30 sec	Afinion™ AS100: 3 min Alere™ 2 Analyser: 1 min 30sec	25 sec
Performance time for pre- and actual analysis	4.5 min (= 2.5 min + 2 min)	4.5 min (= 2.5 min + 2 min)	5.5 min (= 2.5 min + 3 min)	Afinion™ AS100: 4.25 min (=30sec + 3.75min) Alere™ 2 Analyser: 3.30min (=30sec +3.0min)	8 min 35 s (= 3 min 35 s + 5 min)

Practical aspects of test	Pre-analytical handling: capillary with plunger, inner reagent cap pushed through while putting cap on cuvette	Same as for QuikRead go® CRP assay. 2 results from a single sample in a single run	Pre-analytical handling involves manual sample & reagent mixing performed prior to analysis on device	Auto-self check with integrated error detection. Error codes possible due to small sample volume that may dry out after the 1min limit instructed in the package insert). Analyser cannot be moved if on.	Manual sample dilution, conjugate application and washing prior to analysis. Also need to manually adjust and white calibrate the reader pen of the battery-operated instrument.
Connectivity	Yes to data transfer to electronic patient files. Measurement results can be sent to LIS.	Yes to data transfer to electronic patient files. Measurement results can be sent to LIS.	Yes to data transfer to electronic patient file and LIS/HIS using QuikRead® Quiklink.	Yes to data transfer to electronic patient files. Alere Afinion™ Data Connectivity Converter (ADCC) is also included for simple transfer of patient and controls results to	No to data transfer to electronic patient files.
Print function	Yes	Yes	No	Yes	No
Data storage on device	Yes	Yes	No	Yes	No
Device lifespan	Approx. 5 years or ≥ 50,000 measurements per device	Approx. 5 years or ≥ 50,000 measurements per device	Approx. 5 years or ≥ 50,000 measurements per	Not reported	Not reported
Maintenance	Designed to be free of regular maintenance with built-in self check operations	Designed to be free of regular maintenance built-in self check operations	Designed to be free of regular maintenance built-in self check operations	Cleaning of cartridge chamber with a swab once a month	The white calibration device, the pen tip and the pen ring of the instrument/pen should be inspected regularly and replaced if dirty or damaged.
Software updates	New software can be updated to the instrument with a USB stick	New software can be updated to the instrument with a USB stick	Software (version 7.0 or newer) shortens the assay reaction time. No detail on how software is updated.	USB stick upgrade process provides analyser with software updates	Not possible.

Quality checks	QuikRead® CRP control (68296) and QuikRead go® CRP control High (137071) are intended for routine quality control of CRP assays by the QuikRead go® instrument. Low and high conc. approx. 30 and 85 mg/L.	QuikRead® CRP control (68296) and QuikRead go® CRP control High (137071) are intended for routine quality control of CRP assays by the QuikRead go® instrument. Low and high conc. approx. 30 and 85 mg/L.	QuikRead® CRP control (68296) is intended for routine quality control of CRP assays by the QuikRead® 101 instrument. Target control conc. approx. 50 mg/L	Alere Afinion™ CRP Control from Alere is recommended for routine quality control testing with each new lot or delivery of new CRP test kits	Alere Afinion™ CRP Control is recommended for routine quality control testing with each new lot or delivery of new CRP test kits
Training & support	Additional costs associated with training. No details provided.	Additional costs associated with training. No details provided.	Additional costs associated with training. No details provided	Manufacturer provides online learning videos and on-site training at no extra cost.	Manufacturer provides online learning videos and on-site training at no extra cost.
Warranty	2 years	2 years	2 years	12 months	12 months

	Technology				
Semi-/quantitative	**Quantitative CRP analysers**				
Device type	Assay kit & analyser instrument	Assay kit & analyser instrument	Assay kit & analyser instrument	Assay kit & analyser instrument	Assay kit & analyser instrument
Proprietary name	**Eurolyser CRP assay** and **Cube S Analyser**	**ichroma™ CRP test cartridge** and **ichroma™ Reader**	**AFIAS™ CRP test cartridge** and **AFIAS 1™ Analyser**	**AQT90 FLEX® CRP assay** and **AQT90 FLEX ® analyser**	**Microsemi™ CRP reagent unit** and **Microsemi™ analyser**
Manufacturer	Eurolyser Diagnostica GmbH	Boditech Med	Boditech Med	Radiometer Medical ApS	Horiba Ltd
Reference codes	**Eurolyser CRP assay:** ST 0100 CRP test kit (32 tests) ST 0102 CRP test kit with integrated capillary (32 tests) ST 1000 CRP control kit (2 x 2ml)(low/high) **Cube S analyser:** CA 0110	**ichroma™ CRP test cartridge** for use with **ichroma™ Reader** Reference codes not reported.	**AFIAS™ CRP** for use with **AFIAS 1™ Analyser**	**AQT90 FLEX ® CRP Reagent pack** (capacity for 200 separate tests and waste disposals) **AQT90 FLEX ® immunoassay analyser** 393-838 Reference code from 2008 CE declaration (March 2015)	**Microsemi™ CRP Reagent Unit** (50 tests per cartridge, 2 cartridges per box) **Microsemi™ analyser**
Class/GMDN code	CE IVD Directive compliant	Declaration of conformity with directive 98/79/EC for IVD medical devices.	CE IVD Directive compliant	General IVD, based on directive 98/79/EC classification, GMDN code 53705.	CE IVD Directive compliant

Additional tests	Microalbumin, D-Dimer, Ferritin, iFOB, K^+ , Lipoprotein A, Troponin I, ASO, CRP, hsCRP, Cystatin C (GFR), Hb, HbA1c, PT (INR)	Troponin I, CK-MB, myoglobin, hsCRP, PSA, AFP, HbA1C, cortisol, malaria, reumafactor IgM, D-dimera, CEA[b], TSH[b], T4[b], FSH[b], hCG[b], LH[b], prolactin[b], testosterone[b], ferritin[b], iFOB[c], microalbumin[c]	Quantitative testing possible using c-tip for TSH, PCT, and HbA1c	D-dimer, beta-hCG, troponin I, troponin T, CK-MB, myoglobin, NT-proBNP	WBC, RBC, Hb, Ht, platelets, lymphocytes, monocytes, granulocytes (calculated: MCV, MCH, MCHC, RDW, PDW, MPV)
Method	Immunoturbidimetric assay	Fluorescence sandwich immunoassay	Fluorescence immunoassay	Solid phase sandwich immunoassay	Immunoturbidimetric assay
Sample size & type (+alternative materials)	5 µL capillary blood sample (venous blood/ serum)	10 µL capillary blood sample (venous blood/ plasma/serum)	10uL or 50uL capillary blood sample from finger or heel (whole blood/ plasma/serum)	2 mL venous blood sample (plasma)	18 µL capillary blood sample + dead volume in the tube to 100 µL. (venous blood)
Analytical range (whole blood)	2.0 – 240 mg/L CRP	2.5 – 300 mg/L CRP	0.5~200 mg/L CRP	5 – 500 mg/L CRP	2.0 – 230 mg/L CRP
Calibration	No – automatic	No	Yes. ID Chip recorded once for each specific lot.	Yes. Adjustment needed when using a new lot no. reagent pack (time needed: 48 mins).	No
Haematocrit auto-correction	Yes[a]	No	No	Yes[a]	Yes[a]
Special storage requirements for test (e.g. refrigeration)	Storage in refrigerator (2-8°C). Allow single test at least 10 mins to warm up to room temperature.	Storage in refrigerator (2-8 °C). Allow detection buffer (DB) tube to attain room temperature for 30 mins before performing test. 2-8ºC for DB / 4-30ºC for cartridge.	Storage in refrigerator (2-8°C).	No special storage requirements. Closed analysis system.	No special storage requirements stated on company brochure.
Analyser size and weight	Instrument: 16 x 13 x 14.5 cm 2.4 kg (Tablet 14.2 x 7.2 x 0.8 cm)	18.5 × 8 × 25 cm 1.3 kg	32 x 20 x 18 cm 3.9 kg	45 × 46 × 48 cm 35 kg	43 × 26 × 45 cm 19 kg
Analyser warm-up time	Not reported	Not reported	Not reported	Not reported	Not reported
Performance time for pre- and actual analysis	5 min (= 1 min + 4 min)	5 min (= 2 min + 3 min)	5 min (= 2 min + 3 min)	13.5 min (= 30 s + 13 min) Add 4 mins to install reagent pack if necessary	4.5 min (= 30 s + 4 min)

Practical aspects of test	Automated, maintenance-free analysis with pre-set calibration curves & auto-self-test routine. Integrated capillary not always easily filled with blood.	Allow detection buffer tube to attain room temperature for 30 mins before performing test. Relatively complicated preanalytical handling using sample with detection buffer. Requirement to shake 10 times and discard first 2 drops before adding 2 drops to test cartridge. Portable analyser.	Semi-automatic immunodiagnostic device which uses all-in-one cartridges; it automatically mixes and dispenses samples when user loads sample only. Desktop analyser (but easy to carry). Empty the C-tip waste box daily.	The system minimises pre-analytical sample handling and utilises a closed sample system for reagent mixing and measurement. No contact with blood or waste. Needs venous blood samples and involves considerable time for analysis. Up to 15 cartridges placed in inlet with up to 16 tests each.	CRP measurement only possible in combination with haematology parameters. All-in-one: 3 reagents in the same cartridge and no need for cartridge removal after use.
Connectivity	Yes. Eurolyser CUBE is suited for connecting to eHealth services due to its internet and network capable android application on the tablet PC.	Yes. Online connection indirectly possible with LIS.	Yes. LIS / HIS communication.	Yes. Online connection possible with HIS and LIS.	Yes. Online connection possible with LIS
Print function	Seiko DPU-414 thermal printer & Seiko Label Printer 650 SE are optional accessories	Printer (optional)	Data output via Internal Printer	Hardware includes 4" thermal-sensitive printer	Integrated thermal printer
Data storage on device	Yes. Data transfer is possible to external devices	No details reported	Yes. 5,000 patient results	Yes. 2,000 patient results	Yes. 180 patient results
Device lifespan	Not reported	Not reported	Not reported	Not reported	Not reported
Maintenance	Designed as maintenance-free. Instrument is calibrated at the factory and has an internal self-check procedure during every measurement.	No details reported	No details reported	No details reported	Refer to 'zero-maintenance' concept applicable to the technology.
Software updates	Embedded software and new versions are released for free when new features or functionality improvements are added. Updated via the CUBE	No details reported	No details reported	No details reported	No details reported

Quality checks	The CUBE system uses single-use reagents, and internal measurements are to be performed once a week. Integrated QC system.	No details reported	No details reported	Built in quality control for continuous analyser performance evaluation. Liquid quality control (LQC) materials for the AQT90 FLEX® analyser help estimate the precision of test results and detect systematic analytical deviations that may arise from reagent or analyser variation.	Quality control target values uploaded by flash card.
Training & support	Online video tutorials for analyser set up and training.	No details reported	No details reported	No details reported	No details reported
Warranty	No details reported	No details reported	No details reported	No details reported	No details reported

	Technology				
Semi-/quantitative	**Quantitative CRP analysers**		**Semi-quantitative CRP tests**		
Device type	Assay kit & analyser instrument	Assay kit & analyser instrument	CRP test strips		Single-use disposable test
Proprietary name	**spinit® CRP disposable disc** and **spinit® instrument**	**CRP IS® test kits** and **Innovastar® analyser**	**Actim® CRP dip sticks**	**Cleartest® CRP strips**	**FebriDx®**
Manufacturer	Biosurfit	DiaSys Diagnostic Systems	Medix Biochemica	Servoprax	RPS Diagnostics
Reference codes	**spinit® CRP disposable disc** (20 test kit size) Reference codes not reported	**CRP IS® test kits** 270699910761 (50 determinations per test kit) 270699910760 (100 determinations per test kit) and **Innovastar® analyser**	**Actim® CRP kit** 31031ETAC (20 CRP test packs)	**Cleartest® CRP strips** C3 4050 (10 and 20 CRP test packs)	**FebriDx®** BP0036 (25 CRP test kit)

Class/GMDN code	CE mark approval	Declaration of conformity with directive 98/79/EC for IVD medical devices for analyser and reagents.	Declaration of conformity with directive 98/79/EC for IVD medical devices.	CE mark for IVD medical devices on pack (complies with directive 98/79/EC)	Declaration of conformity with directive 98/79/EC for IVD medical devices. GMDN: 64042.
Additional tests	Hb1Ac and other blood components (total leucocytes, white blood cells and haematocrit)	Glucose, haemoglobin, HbA1c	No	No	MxA
Method	Multi-method combination of immunoassay, haematology and clinical chemistry targets in a disposable test panel	Immunoturbidimetric test	Immunochromatographic	Immunochromatographic	Lateral flow immunoassay
Sample size & type (+ alternatives)	5 µL capillary blood sample (whole blood (venous and capillary), serum and plasma)	10 µL capillary blood sample (whole blood and plasma)	10 µL capillary blood sample (can also sample from anti-coagulated whole blood)	10 µL capillary blood sample (can also sample from anti-coagulated whole blood)	5 µL capillary blood sample
Analytical range (blood)	4.0 – 200 mg/L CRP	5 - 400 mg/L CRP	0 – >80 mg/L CRP	0 – >80 mg/L CRP	Qualitative thresholds: CRP ≥ ~ 20 mg/L MxA ≥ ~40 ng/mL
Calibration	No	No – precalibrated tests. But original calibration stability for 9 months only. To ensure measuring accuracy of the parameter reagent lot in use, recalibration is recommended.	N/A	N/A	N/A
Haematocrit auto-correction	No	Yes[a]	No	No	No
Special storage requirements for test (e.g. refrigeration)	Storage in refrigerator (2 - 8 °C)	Ready-to-use unit dose test. Shelf life 18 months from production.	Storage at 2 to 25 °C. Stored unopened, Each component can be used until the expiry date marked on the component.	Storage at 2 - 30 °C.	No refrigeration or special storage conditions required. The shelf-life for the test kits is 2 years at room temperature.
Analyser size and weight	24 x 22 x 31 cm 4 kg	20 x 15 x 17 cm 4 kg	N/A	N/A	N/A
Analyser warm-up time	No details reported	No details reported	N/A	N/A	N/A

Performance time for pre- and actual analysis	5 min (= 11 min* + 4 min) (*however, wait-time of at least 3 mins after fridge removalbefore opening pouch)	8 min (= 1 min + 7 min)	7.5 min (= 2.5 min + 5 min)	7.5 min (= 2.5 min + 5 min*) (*analysis time should not be later than 10 min)	10 min (performance ++analysis time) Test result should be read within 3 hours
Practical aspects of test	Must remove disc from refrigerator and wait at least 3 minutes before opening pouch.	Fully automated system – no manual steps required during measurement. Single cartridge containing all reagents needed for testing. Precalibrated tests – no time-consuming calibration.	Relatively complicated pre-analytical handling, semiquantitative, inter-observer variation, cut-off at 80 instead of 100 mg/L	Relatively complicated pre-analytical handling, semiquantitative, inter-observer variation, cut-off at 80 instead of 100 mg/L	FebriDx® does not require any additional ancillary equipment. FebriDx® high CRP reading suggests ≥ 20mg/L.
Connectivity	Yes. LIS / HIS communication	No details reported	N/A	N/A	N/A
Print function	Print out of test results in standard labels with printer (optional accessory)	No details reported	N/A	N/A	N/A
Data storage on device	Yes	50 results			Results display for 3 hours.
Device lifespan	Not reported	Not reported	Single-use strip	Single-use strip	Single-use disposable test. Shelf life of 2 years at room temperature.
Maintenance	No maintenance as per manufacturer website	No details reported	N/A	N/A	N/A
Software updates	No details reported	Link to IS Software for software download and update instructions	N/A	N/A	N/A
Quality checks	A self-check is performed automatically when running a test	No details reported	N/A	N/A	External controls are available.
Training & support	No details reported	No details reported	Not reported	Not reported	Training provided through UK distributor as wells as RPS Detectors.com or FebriDx.com (NICE MIB July 2017)
Warranty	No details reported	No details reported	N/A	N/A	N/A

Footnotes: [a] If the Hct value is outside the range 20-60 %, no CRP test result will be reported and an information code will be displayed). In these cases serum or plasma samples are recommended for CRP analysis; [b] Only in serum/plasma, centrifuge step necessary; [c] Urine/faeces.

Key: ACR (Albumin/creatinine ratio); AFP (Alpha-fetoprotein); ASO (Anti-Streptolysin-O); CEA (oncofetal glycoprotein); CK-MB (Creatine Kinase either muscle or brain type); FSH (Follicle-stimulating hormone); GMDN (Global Medical Device Nomenclature); Hb (Haemoglobin); HbA1c (Glycated Haemoglobin); hCG (Human chorionic gonadotropin); HIS (Hospital Information System); hsCRP (high-sensitivity CRP); Ht (Haematocrit); iFOB (faecal immunochemical test for haemoglobin); IVD (In vitro diagnostic); K^+ (Potassium); LH (Luteinising hormone); LIS (Laboratory Information System); MCH (Mean Corpuscular Haemoglobin); MCHC (Mean Corpuscular Haemoglobin Concentration); MCV (Mean Corpuscular Volume); MPV (Mean Platelet Volume); MxA Myxovirus resistance protein A); N/A (Not Applicable); NT-proBNP (N-terminal pro b-type natriuretic peptide); PCT (Procalcitonin); PDW (Platelets Distribution Width); PSA (Prostate specific antigen); PT(INR) Prothrombin Time (international normalized ratio) ; RBC (Red Blood Cell); RDW (Red blood cells Distribution Width); Strep A (Streptococcus pyogenes); T4 (Thyroxine); TSH (Thyroid Stimulating Hormone); U-ALB (quantitative test for albumin in urine samples); WBC (White Blood Cell.

Sources included: Brouwer and van Pelt (2015)[214]; Minnaard (2013)[25]; NICE Medtech Innovation Briefing reports for QuikRead®[13], Alere Afinion™[12] and FebriDx®[14]; dossier submissions from Orion, Abbott, Medix Biochemica and RPS Diagnostics, and available information from manufacturers' websites.

Appendix B Definition and symptoms of conditions

Acute Respiratory Tract Infections (RTIs) – definition and symptoms of conditions, burden of disease and natural course in the individual patient[50, 301]

Type of RTI	Definition	Symptoms and burden of disease	Natural course of illness
Upper Respiratory Tract Infections			
Common cold	The **common cold** is a viral infectious disease of the upper respiratory tract that is marked by inflammation of the mucous membranes of the nose, throat, eyes, and eustachian tubes and by a watery then purulent discharge and is caused by any of several viruses (such as a rhinovirus or an adenovirus). The condition is associated with more than 200 virus subtypes. The condition is rarely characterised by a discrete set of specific symptoms, with the illness varying according to individual and causative pathogen. Occasionally, there is spread to the lower respiratory tract.	Symptoms include: blocked or runny nose; sore throat; headaches; muscle aches; coughs; sneezing; a raised temperature; pressure in ears and face; loss of taste and smell; malaise. Most of the population experience at least one episode per year; these are usually self-limiting illnesses and resolve within a few days.	One and a half weeks[62]
Acute sore throat/ pharyngitis	**Pharyngitis** is inflammation of the pharynx, also known as a sore throat, and can be caused by viral or bacterial illnesses.	Symptoms include: swollen tonsils; enlarged and tender lymph nodes (glands) in the neck; a painful, tender feeling at the back of the throat; discomfort when swallowing. 82% of cases resolve in 7 days, and pain is only reduced by 16 hours[302]	One week[62]

Acute tonsillitis	**Tonsillitis** is inflammation of the tonsils. The main symptom is a sore throat, and it can be caused by viral or bacterial illnesses – although most cases are viral. The viruses that cause tonsillitis include the flu virus, parainfluenza virus (which also causes laryngitis and croup), adenovirus, enterovirus and rhinovirus. Bacterial tonsillitis may be caused by a number of different bacteria, but is usually caused by group A streptococcus bacteria.	Symptoms include: red and swollen tonsils; pain when swallowing; high temperature (fever) over 38°C (100.4°F); coughing; headache; tiredness; pain in ears or neck; white pus-filled spots on the tonsils; and swollen lymph nodes (glands) in the neck. Illness comes on suddenly and gets worse during the first 3 days. Most cases are viral and resolve within a few days.	One week[62]
Acute laryngitis	**Laryngitis** refers to inflammation of the larynx. This can lead to oedema of the true vocal folds, resulting in hoarseness. Laryngitis can be acute or chronic, infectious or non-infectious. Accompanying signs of infectious laryngitis include pain on swallowing foods or liquids, cough, fever, and respiratory distress. The most common variant is acute viral laryngitis, which is self-limiting and usually related to an upper respiratory infection such as the common cold. Bacterial laryngitis often caused by Haemophilus influenza, and can be life threatening. Other causes can include tuberculosis (TB), diphtheria, syphilis, and fungi.	Symptoms include: hoarse (croaky) voice; sometimes losing the ability to speak; sore throat, cough, difficulty swallowing, and fever. Most patients make a full recovery within three weeks without developing complications.	One to two weeks
Acute otitis media	**Acute otitis media** (AOM) is defined as an infection of the middle-ear space and is a common complication of viral respiratory illnesses. It is associated with rapid onset of signs and symptoms (<48 hours) of inflammation, such as otalgia, fever, irritability, anorexia, vomiting, and otorrhea. Otoscopic findings include a yellow–red exudate behind the tympanic membrane (TM).	Symptoms include: severe earache (caused by the pressure of mucous on the eardrum); a high temperature (fever) of 38°C (100.4°F) or above; flu-like symptoms in children, such as vomiting and lethargy (a lack of energy); slight deafness. Most common in young children, with more than	Four days[62]

		75% of episodes occurring in children under 10 years of age. AOM resolves in 60% of cases in 24 hours without antibiotics.[302]	
Acute rhinosinusitis	**Acute sinusitis** (also commonly known as acute rhinosinusitis) is defined as symptomatic inflammation of the mucosal lining of the nasal cavity and paranasal sinuses for less than 4 weeks. This swelling of the sinuses is usually caused by either a viral or a bacterial infection.	Symptoms include: pain, swelling and tenderness around cheeks, eyes or forehead; a blocked nose; reduced sense of smell; green or yellow mucous from the nose; a sinus headache; a high temperature of 38C or above; toothache and/or bad breath. Most infections resolve in 14 days without treatment and antibiotics only offer marginal benefit after 7 days.[302]	Two and a half weeks[62]

Type of RTI	Definition*	Symptoms and burden of disease	Natural course of illness
Lower Respiratory Tract Infections			
Acute bronchitis/cough	An acute illness, occurring in a patient without chronic lung disease, with symptoms including cough, which may or may not be productive and associated with other symptoms or clinical signs that suggest LRTI (sputum production, dyspnoea, wheeze or chest discomfort /pain) and no alternative explanation (e.g. sinusitis or asthma).	Symptoms include: Cough with sputum production, dyspnoea, wheeze or chest discomfort /pain.	Three weeks[62]
Influenza	An acute illness, usually with fever, together with the presence of one or more of headache, myalgia, cough or sore throat.	The illness can be categorised into uncomplicated or complicated influenza.[303] **Uncomplicated influenza**: Influenza presenting with fever, coryza, generalised symptoms (headache, malaise, myalgia, arthralgia) and sometimes gastrointestinal symptoms, but without any features of complicated influenza. Symptoms peak after two to three days and most patients begin to feel much better within five to eight days. **Complicated influenza**: Influenza requiring hospital admission and/or with symptoms and signs of lower respiratory tract infection (hypoxaemia, dyspnoea, lung infiltrate), central nervous system involvement and/or a significant exacerbation of an underlying medical condition Immunocompromised patients and young children can experience prolonged durations of	One week (if uncomplicated)

		infection and/or greater viral burden, compared to other groups. Elderly patients may also develop pneumonia. While pregnant women are more likely to have complications if they become ill with influenza.	
Community-acquired pneumonia (CAP)	**Suspected CAP** An acute illness with cough and at least one of new focal chest signs, fever >4 days or dyspnoea/tachypnoea, and without other obvious cause. **Definite CAP** As above, but supported by chest radiograph findings of lung shadowing that is likely to be new. In the elderly, the presence of chest radiograph shadowing accompanied by acute clinical illness (unspecified) without other obvious cause.	Symptoms include: cough (dry or with thick mucous that is yellow, green, brownish or blood-stained); difficulty breathing; tachycardia; fever; feeling generally unwell; sweating and shivering; loss of appetite; chest pain. Every year between 0.5% and 1% of adults in the UK will have community-acquired pneumonia. It is diagnosed in 5–12% of adults who present to GPs with symptoms of lower respiratory tract infection, and 22–42% of these are admitted to hospital, where the mortality rate is between 5% and 14%. Between 1.2% and 10% of adults admitted to hospital with community-acquired pneumonia are managed in an intensive care unit, and for these patients the risk of dying is more than 30%. More than half of pneumonia-related deaths occur in people older than 84 years.[22]	After starting treatment for community-acquired pneumonia, the symptoms of patients should steadily improve, although the rate of improvement will vary with the severity of the pneumonia, and most people can expect that by: • 1 week: fever should have resolved; • 4 weeks: chest pain and sputum production should have substantially reduced; • 6 weeks: cough and breathlessness should have substantially reduced;

			• 3 months: most symptoms should have resolved but fatigue may still be present; • 6 months: most people will feel back to normal.[22]
Acute exacerbation of COPD (AECOPD)	An event in the natural course of the disease (COPD) characterised by a worsening of the patient's baseline dyspnoea, cough and/or sputum beyond day-to-day variability sufficient to warrant a change in management. If chest radiograph shadowing, consistent with infection, is present the patient is considered to have CAP.[44]	On the day of onset, symptoms can increase sharply with symptoms of dyspnoea (64%), increased sputum volume (26%), sputum purulence (42%), colds (35%), wheeze (35%), sore throat (12%) and cough (20%).[120]	Recovery of Peak Expiratory Flow (PEF) was achieved in only 75.2% of exacerbations within 35 days, and 7.1% of exacerbations had still not returned to baseline after 91 days.[120]

Definitions extracted from: the 2011 European Respiratory Society (ERS) in collaboration with The European Society for Clinical Microbiology and Infectious Disease (ESCMID) Guidelines for the management of adult lower respiratory tract infections, the 2017 Public Health England Antibiotic Guidance for primary care on the management and treatment of common infections, 2017 Public Health England guidance on use of antiviral agents for the treatment and prophylaxis of seasonal influenza HSE Health A-Z and other resources (NHS choices, HSE A-Z and BMJ best practice guidance)

Appendix C Guidelines for the diagnosis and management of acute RTIs in Europe

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
Respiratory Tract Infections				
(62)	2008	UK	**NICE RTIs (2008)**	
Upper Respiratory Tract Infections				
Acute sore throat/ pharyngitis /tonsillitis				
(304)	2012	Europe	The Centor clinical scoring system can help to identify those patients who have a higher likelihood of group A streptococcal infection. However, its utility in children appears lower than in adults because of the different clinical presentation of sore throat in the first years of life.	A-3
			Throat culture is not necessary for routine diagnosis of acute sore throat to detect group A streptococci.	C-3
			If rapid antigen testing (RAT) is performed, throat culture is not necessary after a negative RAT for the diagnosis of group A streptococci in both children and adults.	B-2
			In patients with high likelihood of streptococcal infections (e.g. 3–4 Centor criteria) physicians can consider the use of RATs. In patients with lower likelihood of streptococcal infections (e.g. 0–2 Centor criteria) there is no need to routinely use RATs.	B-3
			It is not necessary to routinely use biomarkers in the assessment of acute sore throat.	C-3
			Either ibuprofen or paracetamol are recommended for relief of acute sore	A-1

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			throat symptoms.	
			Use of corticosteroids in conjunction with antibiotic therapy is not routinely recommended for treatment of sore throat. It can however be considered in adult patients with more severe presentations, e.g. 3–4 Centor criteria.	A-1
			Zinc gluconate is not recommended for use in sore throat.	B-2
			There is inconsistent evidence of herbal treatments and acupuncture as treatments for sore throat.	C-1 to C-3
			Sore throat should not be treated with antibiotics to prevent the development of rheumatic fever and acute glomerulonephritis in low-risk patients (e.g. patients with no previous history of rheumatic fever.	A1
			The prevention of suppurative complications is not a specific indication for antibiotic therapy in sore throat.	A2
			Clinicians do not need to treat most cases of acute sore throat to prevent quinsy, acute otitis media, cervical lymphadenitis, mastoiditis and acute sinusitis.	A3
			Antibiotics should not be used in patients with less severe presentation of sore throat, e.g. 0–2 Centor criteria, to relieve symptoms.	A1
			In patients with more severe presentations, e.g. 3–4 Centor criteria, physicians should consider discussion of the likely benefits with patients. Modest benefits of antibiotics, which have been observed in group A b-haemolytic streptococcus-positive patients and patients with 3–4 Centor criteria, have to be weighed against side effects, the effect of antibiotics on the microbiota, increased antibacterial resistance, medicalization and costs.	A1
			If antibiotics are indicated, penicillin V, twice or three times daily for 10 days, is recommended.	A1

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			There is not enough evidence that indicates shorter treatment length.	
Finnish Medical Society Duodecim, the Finnish Association for Central Practice, the Finnish Otolaryngological Society, Infectious Diseases Society of Finland and the Clinical Microbiologists Society	2012	Finland	Sore throat (pharyngitis) is typically a viral infection. Patients should be informed that pharyngitis is usually a mild, self-healing disease. Throat swab is recommended for adults with two or more symptoms: fever over 38°C, swollen submandibular lymph nodes, tonsillar exudate and no cough. Children under 15 years of age with any of these symptoms should be tested. If antibiotic is indicated, penicillin is the preferred choice, whereas first generation cephalosporins are recommended for those with penicillin allergy. Antibiotics can be started for patients with high fever before culture results are available. Adequate pain medication is important.	
(66)	2016	Germany	**Diagnosis:** To estimate the probability of tonsillitis caused by β-haemolytic streptococci, a diagnostic scoring system according to Centor or McIsaac is suggested. If therapy is considered, a positive score of ≥3 should lead to pharyngeal swab or rapid test or culture in order to identify β-haemolytic streptococci. Routinely performed blood tests for acute tonsillitis are not indicated. After acute streptococcal tonsillitis, there is no need to repeat a pharyngeal swab or any other routine blood tests, urine examinations or cardiological diagnostics such as ECG. The determination of the antistreptolysin O-titer (ASLO titer) and other antistreptococcal antibody titers do not have any value in relation to acute tonsillitis with or without pharyngitis and should not be performed. **Management** First-line therapy of β-haemolytic streptococci consists of oral penicillin. Instead of phenoxymethylpenicillin–potassium (penicillin V potassium), also phenoxymethylpenicillin–benzathine with a clearly longer half-life can be used. Oral intake for 7 days of one of both the drugs is recommended. Alternative treatment with oral cephalosporins (e.g. cefadroxil, cefalexin) is indicated only in cases of penicillin failure, frequent recurrences, and whenever a more reliable eradication of β-haemolytic streptococci is desirable. In cases of allergy	

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			or incompatibility of penicillin, cephalosporins or macrolides (e.g. Erythromycin-estolate) are valuable alternatives.	
(65)	2011	Germany	**Management** Routine antibiotic treatment of sore throat for the prevention of complications is currently not indicated. The effect of antibiotics on symptoms and duration of disease is, at best, moderate. It is more pronounced in patients with typical clinical symptoms and signs of pharyngitis caused by group A streptococci (GAS) and slightly more pronounced again in cases of additional positive throat swab for GAS. An algorithm for decision-making is proposed. Rapid testing for streptococcal antigen or a culture for GAS is only recommended if the result is likely to influence therapeutic decision-making. Patients with more severe illness and signs of GAS pharyngitis can be given antibiotic therapy for symptomatic relief.	
	2016	France	No antibiotics in adults with: an acute nasopharyngitis; an acute strep throat with a McIsaac score < 2 or with a McIsaac score ≥ 2 and a negative rapid diagnostic test (RDT). In case of acute strep throat with a McIsaac score ≥ 2 and a positive RDT: amoxicillin, 2g per day for 6 days. https://www.has-sante.fr/portail/upload/docs/application/pdf/2017-05/dir82/memo_sheet_-_acute_nasopharyngitis_and_acute_strep_throat_in_adults.pdf No antibiotics in a child with: an acute nasopharyngitis; under the age of 3 years with an acute strep throat ≥3 years with an acute strep throat with a negative RDT. In a child ≥3 years with an acute strep throat and a positive RDT amoxicillin, 50mg/kg/days for 6 days.	

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			https://www.has-sante.fr/portail/upload/docs/application/pdf/2017-05/dir82/memo_sheet_-_acute_nasopharyngitis_and_acute_strep_throat_in_children.pdf	
(63)	2009	Croatia	For streptococcal sore throat diagnostics, the Working Group recommends evaluation of clinical presentation according to Centor criteria and for patients with Centor score 0-1, antibiotic therapy is not recommended nor bacteriological testing, while for patients with Centor score 2-4 bacteriological testing is recommended (rapid test or culture) as well as antibiotic therapy in case of positive result. The drug of choice for the treatment of streptococcal tonsillopharyngitis is oral penicillin taken for ten days (penicillin V) or in case of poor patient compliance benzathine penicillin G can be administered parenterally in a single dose. Other antibiotics (macrolides, clindamycin, cephalosporins, co-amoxiclav) are administered only in case of hypersensitivity to penicillin or in recurrent infections. Tonsillectomy is a widely accepted surgical procedure that decreases the number of sore throats in children and should be performed only if indications for this procedure are established. Absolute indications include five or more streptococcal infections per year, tonsillitis complications, permanent respiratory tract obstruction, obstructive sleep apnoea syndrome and suspected tonsillar malignancy. Relative indications include chronic tonsillitis and occlusion disturbances.	
	2012	Italy	None of the available scoring systems are sufficiently accurate to identify group A β-haemolytic streptococci (GABHS) pharyngitis in settings with low prevalence for rheumatic disease. RADT should be performed by trained personnel in every child with a history and signs/symptoms suggestive of GABHS pharyngitis. RADT is not recommended in children with a McIsaac score of 0 or 1 with ≥2 signs/symptoms suggestive of viral infection. Backup culture in children with negative RADT result is not recommended. Culture test with	

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			antibiotic susceptibility assay should be performed exclusively for epidemiologic purposes. Streptococcal antibody titers are of no value in diagnosing acute pharyngitis. Antibiotic therapy is recommended in microbiologically documented GABHS pharyngitis. Because penicillin V is not available in Italy, amoxicillin (50 mg/kg/d in 2–3 doses orally) for 10 days is the first choice of treatment. In noncompliant cases, benzathine penicillin may be administered. Although not routinely recommended due to the high cost and wide spectrum of activity, a 5-day course with a second-generation cephalosporin may be used in noncompliant cases. Macrolides should be limited to children with demonstrated type I hypersensitivity to penicillin. Ibuprofen or paracetamol is recommended for relief of pain or fever associated with discomfort. Because the carrier state is not associated with increased risk of suppurative complications and risk of GABHS transmission to contacts is minimal, the carrier state should never be investigated and treated.	
NICE RTIs (2008)[62] (https://www.nice.org.uk/guidance/cg69/evidence/full-guideline-196853293)	2008	UK	Treatment **Avoid antibiotics** as 82% of cases resolve in 7 days, and pain is only reduced by 16 hours. **Use FeverPAIN** Score: **Fever** in last 24 hours; **P**urulence; **A**ttend rapidly under three days; severely **I**nflamed tonsils; **N**o cough or coryza. **Score 0-1:** 13-18% streptococci - no antibiotic. **2-3:** 34-40% streptococci - 3 day delayed antibiotic. **4-5:** 62-65% streptococci - if severe, immediate antibiotic or 48-hour delayed antibiotic. **Advise** paracetamol, self-care, and safety net.	
Acute otitis media (AOM)				

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
Finnish Medical Society Duodecim, the Finnish association of otorhinolaryngology and head and neck surgery, the Finnish Paediatric Society, the Finnish Otolaryngological Society and the Finnish Association for General Practice	2017	Finland	The diagnosis of acute otitis media is based on the presence of middle-ear effusion, signs of inflammation of the tympanic membrane, and signs and symptoms of an acute infection. Effective treatment of ear pain is crucial in the management of the disease. Antibiotic treatment for 5–7 days with amoxicillin or amoxicillin/clavulanate is recommended as a rule, because antibiotics shorten the time to resolution of illness, and no individually applicable criteria to guide antibiotic use are available. The follow-up of children with acute otitis media should be tailored individually. http://www.kaypahoito.fi/web/english/guidelineabstracts/guideline?id=ccs00071	
NICE RTIs (2008)[62] (https://www.nice.org.uk/guidance/cg69/evidence/full-guideline-196853293)	2008	UK	Management **Optimise analgesia and target antibiotics.** AOM resolves in 60% of cases in 24 hours without antibiotics. Antibiotics reduce pain only at two days (NNT=15), and do not prevent deafness. **Consider 2 or 3 day delayed, or immediate antibiotics for pain relief if:** <2 years AND bilateral AOM (NNT=4),bulging membrane, or symptom score >8 for: fever; tugging ears; crying; irritability; difficulty sleeping; less playful; eating less (0 = no symptoms; 1 = a little; 2 = a lot). All ages with otorrhoea NNT=3. Antibiotics to prevent mastoiditis NNT>4000.	
HAS	2016	France	Adults:In a case of purulent acute otitis media confirmed by visualisation of the tympanic membranes: amoxicillin: 3 g/day for 5 days. If conjunctivitis-otitis syndrome (Haemophilus influenzae): amoxicillin-clavulanic acid, 3 g/day, for 5 days. https://www.has-sante.fr/portail/upload/docs/application/pdf/2017-05/dir82/memo_sheet_-_purulent_acute_otitis_media_in_adults.pdf Children: In case of congesitve or seromucinous acute otitis media: no antibiotlics If purulent acute otitis media: Children <2 years: amoxicillin 80-90mg/kg/day for 8-10 days. If conjunctivitis-	

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			otitis syndrome (Haemophilus influenzae): amoxicillin-clavulanic acid, 80mg/kg/day, for 8-10 days https://www.has-sante.fr/portail/upload/docs/application/pdf/2017-05/dir82/memo_sheet_-_purulent_acute_otitis_media_in_adults.pdf Chilren >2 years with mild symptoms: no antibiotics Children > 2 years with severe symptoms: 80-90mg/kg/day for 5days. If conjunctivitis-otitis syndrome (Haemophilus influenzae): amoxicillin-clavulanic acid, 80mg/kg/day, for 8-10 days https://www.has-sante.fr/portail/upload/docs/application/pdf/2017-05/dir82/memo_sheet_-_purulent_acute_otitis_media_in_children_over_3_months.pdf	
Acute rhinosinusitis				
Current Care Guidelines/Finnish Medical Society Duodecim	2018	Finland	Patients with common cold have often symptoms similar to sinusitis. Mild or moderate symptoms often resolve in time, but symptomatic treatment (e.g. analgesics, decongestants) may be used. If the patient has severe pain (unilateral), purulent excretion in nose and/or pharynx, pain radiating to teeth or fever, bacterial sinusitis should be suspected. Diagnosis is based on clinical findings. Symptomatic treatment is recommended for patients with mild or moderate symptoms. Those with purulent excretion may benefit from antibiotics. First line treatment for patients with chronic or recurrent sinusitis is conservative. http://www.kaypahoito.fi/web/english/guidelineabstracts/guideline?id=ccs00022	
HAS	2016	France	In case of maxillary sinusitis: • acute purulent, uncomplicated with suspected bacterial infection with at least 2 of the following 3 criteria: persistent or increased infraorbital sinus pain	

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			despite a prescribed symptomatic treatment for at least 48 hours; unilateral nature of pain and/or its increase when the head is tilted forward, and/or its pulsating nature and/or its peak in late afternoon and at night; increased rhinorrhoea and continued purulence. These signs are all the more significant because they are unilateral; amoxicillin, 3 g/day, for 7 days. unilateral maxillary sinusitis associated with an obvious dental infection of the upper dental arch: amoxicillinclavulanic acid, 3 g/day, for 7 days. In case of frontal, ethmoid, sphenoid sinusitis: amoxicillin-clavulanic acid, 3 g/day, for 7 days.	
AWMF Association of Scientific Medical Societies	2017	Germany	***Not in English***	
NHG Dutch College of General Practitioners	2014	Netherlands	***Not in English***	
NICE sinusitis (acute) (2017)[67]	2017	UK	***People presenting with symptoms for around 10 days or less*** Do not offer an antibiotic prescription. Give advice about: • the usual course of acute sinusitis (2 to 3 weeks) • an antibiotic not being needed • managing symptoms, including fever, with self-care (see the recommendations on self-care) • seeking medical help if symptoms worsen rapidly or significantly, do not improve after 3 weeks, or they become systemically very unwell. Reassess if symptoms worsen rapidly or significantly, taking account of:	

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			• alternative diagnoses such as a dental infection • any symptoms or signs suggesting a more serious illness or condition. ***People presenting with symptoms for around 10 days or more with no improvement*** 1.1.4 Consider prescribing a high-dose nasal corticosteroid[1] for 14 days for adults and children aged 12 years and over, being aware that nasal corticosteroids: • may improve symptoms but are not likely to affect how long they last • could cause systemic effects, particularly in people already taking another corticosteroid • may be difficult for people to use correctly. Consider no antibiotic prescription or a back-up antibiotic prescription (see the recommendations on choice of antibiotic), taking account of: • evidence that antibiotics make little difference to how long symptoms last, or the proportion of people with improved symptoms • withholding antibiotics is unlikely to lead to complications • possible adverse effects, particularly diarrhoea and nausea • factors that might make a bacterial cause more likely (see symptoms and signs). 1.1.6 When a back-up antibiotic prescription is given, give verbal and written advice about: • managing symptoms, including fever, with self-care (see the recommendations on self-care) • an antibiotic not being needed immediately • using the back-up prescription if symptoms do not improve within	

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			7 days or if they worsen rapidly or significantly at any time • seeking medical help if symptoms worsen rapidly or significantly despite taking the antibiotic, or the antibiotic has been stopped because it was not tolerated. ***People presenting at any time who are systemically very unwell, have symptoms and signs of a more serious illness or condition, or are at high risk of complications*** 1.1.8 Offer an immediate antibiotic prescription (see the recommendations on choice of antibiotic) or further appropriate investigation and management in line with the NICE guideline on respiratory tract infections (self-limiting): prescribing antibiotics. 1.1.9 Refer people to hospital if they have symptoms and signs of acute sinusitis associated with any of the following: • a severe systemic infection (see the NICE guideline on sepsis) • intraorbital or periorbital complications, including periorbital oedema or cellulitis, a displaced eyeball, double vision, ophthalmoplegia, or newly reduced visual acuity • intracranial complications, including swelling over the frontal bone, symptoms or signs of meningitis, severe frontal headache, or focal neurological signs.	
Lower Respiratory Tract Infections				
Acute bronchitis/cough				
The Dutch College of General Practitioners (NHG) guideline for	2011	Netherlands	The guideline covers the diagnosis, treatment, and education of patients with cough, pneumonia, bronchiolitis, croup, whooping cough, and Q-fever. Acute	

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
acute cough (2011)[68]			cough is defined as cough lasting less than 3 weeks at presentation. It is important to distinguish an uncomplicated respiratory tract infection from a complicated respiratory tract infection that requires antibiotic treatment. In most cases, cough is caused by an uncomplicated respiratory tract infection (viral or bacterial) A patient with an uncomplicated respiratory tract infection has no risk factors for complications (age > 3 months and < 75 years, no relevant comorbidity), is not very ill, doesn't have signs of a complicated respiratory tract infection and has a fever < 7 days. The symptoms (cough) can last up to 4 weeks. There is no effective therapy. There are two groups of patients with a complicated respiratory tract infection. **1** Patients with a pneumonia (severely ill [tachypnea, tachycardia, hypotension or confusion] OR moderately ill and one-sided auscultatory findings, CRP > 100 mg/l [a CRP of 20-100 mg/l doesn't exclude a pneumonia, [management depends on presentation and risk-factors], infiltrate on chest X-ray or sick > 7 days with fever and a cough). These patients are prescribed an antibiotic. **2** Patients with other risk factors for complications (age < 3 months or > 75 years and/or relevant comorbidity [in children cardiac and pulmonary disease not being asthma, in adults congestive heart failure, severe chronic obstructive pulmonary disease, diabetes mellitus, neurological disorders, severe renal failure, compromised immunity]). In these patients, the decision to prescribe antibiotics is based on the presentation, supported, if necessary, by measurement of CRP. The measurement of C-reactive protein can help differentiate between pneumonia and mild respiratory tract infection in moderately ill adults with general and/ or local symptoms. This recommendation does not apply to children. Specific management recommendations are made for croup, bronchiolitis and whooping cough. In cases of moderate croup, a single dose of corticosteroid (e.g. dexamethasone, 0.15 mg/kg, oral or intramuscular, or 2 mg of nebulized budesonide) should be given. Mild croup is self-limiting; children with severe	

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			croup should be referred to a paediatrician. Children with bronchiolitis and dyspnoea should be monitored regularly during the first few days. Use of medication has not proven to be effective. In whooping cough antibiotics might be useful in preventing secondary cases only Additional investigations should be performed if there is suspicion of whooping cough in a patient from a family with unvaccinated or incomplete vaccinated children younger than 1 year or with a pregnant woman of more than 34 weeks gestation. The increasing resistance to doxycycline and macrolide antibiotics makes amoxicillin (for 5 days) the drug of first choice for pneumonia, with doxycycline as second choice. Doxycycline remains the first-choice drug if there is an increased risk of pneumonia caused by Coxiella burnetii (Q-fever) or Legionella. Because of lack of evidence on the effectiveness of noscapine and codeine and their known side effects these drugs are not recommended.	
NICE diagnosis and management of pneumonia in adults (2014)[22]	2014	UK	For people presenting with **symptoms of lower respiratory tract infection** in primary care, consider a point of care C-reactive protein test if after clinical assessment a **diagnosis of pneumonia has not been made** and it is not clear whether antibiotics should be prescribed. Use the results of the C-reactive protein test to guide antibiotic prescribing in people **without a clinical diagnosis of pneumonia** as follows: **1** Do not routinely offer antibiotic therapy if the C-reactive protein concentration is less than 20 mg/litre. **2** Consider a delayed antibiotic prescription (a prescription for use at a later date if symptoms worsen) if the C-reactive protein concentration is between 20 mg/litre and 100 mg/litre. **3** Offer antibiotic therapy if the C-reactive protein concentration is greater than 100 mg/litre.	
ESCMID/ERS guidelines for adult LRTI (2011)[44]	2011	Europe	Elderly LRTI patients with relevant comorbidity should be followed-up 2 days after the first visit. All patients with LRTI should be advised to return to the	

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			doctor if the symptoms take longer than 3 weeks to disappear. Antibiotic treatment should also be considered for patients with LRTI and serious comorbidity such as: **1** selected exacerbations of COPD (see section 'acute exacerbation of COPD'); **2** cardiac failure; **3** insulin-dependent diabetes mellitus; or **4** a serious neurological disorder (stroke, etc.). Cough suppressants, expectorants, mucolytics, antihistamines, inhaled corticosteroids and bronchodilators should not be prescribed in acute LRTI in primary care.	
Finnish Medical Society Duodecim, the Finnish Respiratory Society, Infectious Diseases **Society of Finland and the Finnish Association for General Practice**	2015	Finland	Pneumonia is recognised in patients suffering from acute cough or deteriorated general condition. Patients with acute cough without pneumonia-related symptoms or clinical findings do not benefit from antimicrobial treatment. Those with suspected or confirmed pneumonia are treated with antibiotics, amoxicillin being the first choice. Most patients with pneumonia can be treated at home. Those with severe symptoms are referred to hospital. Patients are always encouraged to contact his/her physician if the symptoms worsen or do not ameliorate within 2–3 days. Patients aged 50 years or older and smokers are controlled by thoracic radiography in 6–8 weeks. http://www.kaypahoito.fi/web/english/guidelineabstracts/guideline?id=ccs00108	
Finnish Medical Society Duodecim, the Finnish Society of Pediatrics and the Finnish Society of General		Finland	Children: All respiratory viruses are capable of causing lower respiratory tract infections. Active testing of influenza viruses during influenza epidemics is recommended.	

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
Medicine			Antitussive medications are ineffective and should not be used. Croup presenting with inspiratory stridor is recommended to be treated with oral corticosteroids and inhaled racemic adrenalin. Corticosteroids and inhaled racemic adrenalin are ineffective for the treatment of bronchiolitis. Inhaled salbutamol administered by a spacer (with a mask) is recommended for wheezy bronchitis. Amoxicillin is recommended for treating pneumonia at home and intravenous penicillin in hospital (combined with macrolide if mycoplasma is suspected). Pertussis is treated with azithromycin or clarithromycin.	
Community acquired pneumonia				
ESCMID/ERS guidelines for adult LRTI (2011)[44]	2011	Europe	To differentiate between pneumonia and other respiratory tract infections: A patient should be suspected of having pneumonia when one of the following signs and symptoms are present: new focal chest signs, dyspnoea, tachypnoea, pulse rate >100 or fever >4 days. In patients with a suspected pneumonia a test for serum-level of C-reactive protein (CRP) can be done. A level of CRP 24 h, makes the presence of pneumonia highly unlikely; a level of >100 mg/L makes pneumonia likely'. 'In case of persisting doubt after CRP testing, a chest Xray should be considered to confirm or reject the diagnosi.' Should the primary care physician test for a possible microbiological aetiology of LRTI? Microbiological tests such as cultures and gram stains are not recommended Biomarkers to assess the presence of a bacterial pathogen are not recommended in primary care Patients with an elevated risk of complications should be monitored carefully and referral should be considered. In patients over 65 years of age the following characteristics are associated with a complicated course: presence of COPD, diabetes or heart failure, previous hospitalization in the past year, taking oral glucosteroids, antibiotic use in the previous month, general malaise, absence of upper respiratory symptoms, confusion/diminished consciousness, pulse >100, temperature >38, respiratory rate >30, blood pressure <90/60,	B1 B1 A1 A3

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			and when the primary care physician diagnoses pneumonia.	
			In patients under 65 the working group thinks that diabetes, a diagnosis of pneumonia and possibly also asthma are risk factors for complications. For all age groups, serious conditions such as active malignant disease, liver and renal disease and other disorders that are relatively rare in primary care but affect immunocompetence, do also increase risk of complications.	C3
			Cough suppressants, expectorants, mucolytics, antihistamines, inhaled corticosteroids and bronchodilators should not be prescribed in acute LRTI in primary care.	A1
			Antibiotic treatment should be prescribed in patients with suspected or definite pneumonia.	C1
			Antibiotic treatment should be considered for patients with LRTI and serious comorbidity such as: selected exacerbations of COPD; (see below) 2 cardiac failure; 3 insulin-dependent diabetes mellitus; 4 a serious neurological disorder (stroke etc.) .	C3
			An antibiotic should be given in exacerbations of COPD in patients with all three of the following symptoms: increased dyspnoea, sputum volume and sputum purulence. In addition, antibiotics should be considered for exacerbations in patients with severe COPD.	C1
			Amoxicillin or tetracycline should be used as the antibiotic of first choice based on least chance of harm and wide experience in clinical practice. In the case of hypersensitivity, a tetracycline or macrolide such as azithromycin, clarithromycin, erythromycin or roxithromycin is a good alternative in countries with low pneumococcal macrolide resistance. National/local resistance rates should be considered when choosing a particular antibiotic. When there are clinically relevant bacterial resistance rates against all first choice agents, treatment with levofloxacin or moxifloxacin may be considered.	C1
			The empirical use of antiviral treatment in patients suspected of having influenza is usually not recommended.	B1
			Only in high-risk patients who have typical influenza symptoms (fever, muscle ache, general malaise and respiratory tract infection), for <2 days and duringa	A1

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			known influenza epidemic, can antiviral treatment be considered	
			A patient should be advised to return if the symptoms take longer than 3 weeks to disappear'. 'Clinical effect of antibiotic treatment should be expected within 3 days and patients should be instructed to contact their doctor if this effect is not noticeable. Seriously ill patients, meaning those with suspected pneumonia and elderly with relevant comorbidity, should be followed-up 2 days after the first visit'. 'All patients or persons in their environment should be advised to contact their doctor again if fever exceeds 4 days, dyspnoea gets worse, patients stop drinking or consciousness is decreasing. In the following categories of patients, referral to hospital should be considered. 1 Severely ill patients with suspected pneumonia (the following signs and symptoms are especially relevant here: tachypnoea, tachycardia, hypotension and confusion). 2 Patients with pneumonia who fail to respond to antibiotic treatment. 3 Elderly patients with pneumonia and elevated risk of complications, notably those with relevant comorbidity (diabetes, heart failure, moderate and severe COPD, liver disease, renal disease or malignant disease). 4 Patients suspected of pulmonary embolism. 5 Patients suspected of malignant disease of the lung.	C3 C3
NICE diagnosis and management of pneumonia in adults (2014)[22]			**Management** When a clinical diagnosis of community-acquired pneumonia is made in primary care, determine whether patients are at low, intermediate or high risk of death using the CRB65 score. The CRB65 score guides mortality risk, place of care, and use of antibiotics. Each CRB65 parameter scores one: **C**onfusion (AMT<8 or new disorientation in person, place or time); **R**espiratory rate >30/min; **B**P systolic <90, or diastolic <60; age >**65**. Use clinical judgement in conjunction with the CRB65 score to inform decisions about whether patients need hospital assessment as follows: **Score 0:** low risk, consider home-based care; **1-2:** intermediate risk, consider hospital assessment; **3-4:** high risk, urgent hospital admission. **Give safety-net advice** and likely duration of different symptoms, eg cough 6	

Name of society/organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/ class of recommendation (I, IIa, IIb, III)
			weeks. Mycoplasma infection is rare in over 65s.	
Influenza				
ESCMID/ERS			See guidelines for LRTI	
National Institutes for Health (Italy) guidelines for the management of influenza in children (2002)[306]	2002	Italy	**Management** Rapid diagnostic tests are not recommended due to insufficient sensitivity and specificity. Etiological treatment with neuraminidase inhibitors or other antiviral agents is not recommended. Symptomatic treatment should be based on acetaminophen or ibuprofen. Antibiotics are not recommended unless fever persists for more than 7 days and signs of lower respiratory tract infection are present. Admission to hospital should be limited to cases with pre-existing risk conditions, young infants with bronchiolitis, cases with respiratory distress and oxygen desaturation, or cases where home management is difficult due to social reasons.	
NICE influenza prophylaxis (2008)[51] and treatment (2009)[307]			**At risk:** pregnant (including up to two weeks post-partum); children under six months; adults 65 years or older; chronic respiratory disease (including COPD and asthma); significant cardiovascular disease (not hypertension); severe immunosuppression; diabetes mellitus; chronic neurological, renal or liver disease; morbid obesity (BMI>40). **Annual vaccination is essential for all those at risk of influenza.** Antivirals are not recommended for healthy adults. **Treat at risk patients** with five days oseltamivir 75mg BD, when influenza is circulating in the community, and ideally within 48 hours of onset (36 hours for zanamivir treatment in children), or in a care home where influenza is likely. See PHE Influenza guidance for the treatment of patients under 13 years of age. **At risk:** In severe immunosuppression, or oseltamivir resistance, use zanamivir 10mg BD (two inhalations by diskhaler for up to 10 days) and seek advice.	

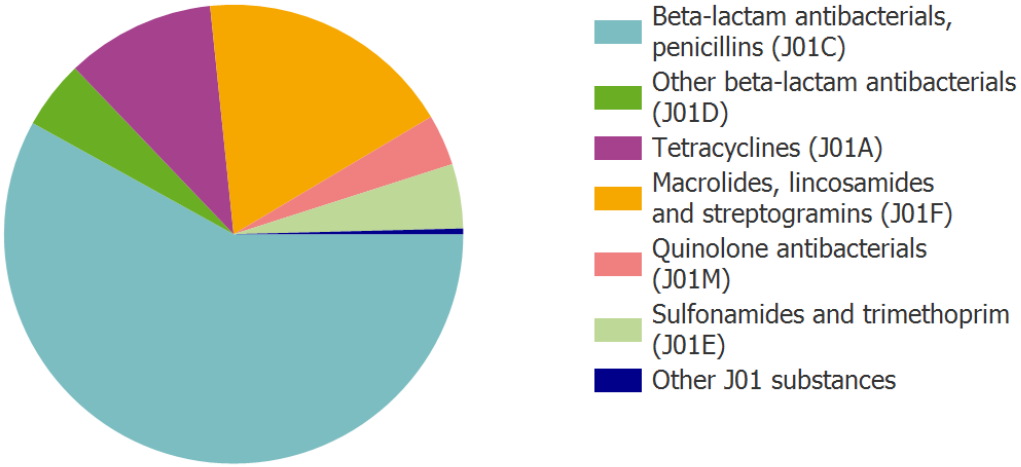
Appendix D Antibacterials for systemic use

Antibacterials for systemic use (ATC group J01)

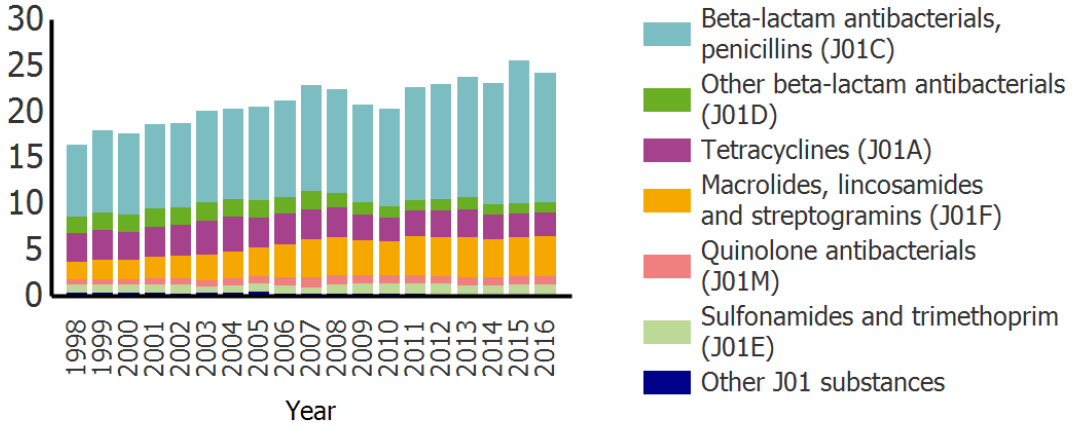
Consumption of antibacterials for systemic use (ATC group J01) in the community (primary care sector) and the hospital sector expressed in DDD per 1000 inhabitants and per day in 2016

ATC group J01	Community (primary care sector)	Hospital sector
Beta-lactam antibacterials, penicillins (J01C)	14.06	0.91
Other beta-lactam antibacterials (J01D)	1.17	0.20
Tetracyclines (J01A)	2.54	0.04
Macrolides, lincosamides and streptogramins (J01F)	4.38	0.26
Quinolone antibacterials (J01M)	0.87	0.11
Sulfonamides and trimethoprim (J01E)	1.10	0.05
Other J01 substances	0.09	0.25
Total	**24.23**	**1.83**

Distribution of the consumption in the community (primary care sector) of ATC group J01



Trend of the consumption in the community (primary care sector) of ATC group J01 expressed in DDD per 1000 inhabitants and per day



Appendix E Preferred antibiotics in primary care in Ireland

Preferred Antibiotics in Primary Care

In many cases in Primary Care the *Preferred Antibiotic* is *No Antibiotic*

See www.antibioticprescribing.ie/ Below are the **preferred first line** treatment choices when antibiotics are indicated and which antibiotics we should reduce the use of, to minimise resistance.

Respiratory Infections (upper and lower)	Urinary Tract Infections	Soft tissue infections – cellulitis, acne
Penicillin V (phenoxymethylpenicillin) Calvapen®	Trimethoprim	Flucloxacillin
Amoxicillin	Nitrofurantoin	Doxycycline
Doxycycline	Fosfomycin	Lymecycline (Tetralysal®)
Amoxicillin and Clarithromycin if Community Acquired Pneumonia (CAP)	Cephalexin	Trimethoprim
Clarithromycin if true penicillin allergy or specific clinical indication		

Antibiotics to be avoided First Line in Primary Care

Co- amoxiclav (unless animal or human bite, facial cellulitis, post partum endometritis, caesarean wound infections, pyelonephritis)	Azithromycin – only on advice of consultant or if treating STI
Ciprofloxacin (only in proven resistant UTI or acute prostatitis)	Moxifloxacin – only on consultant advice
Most third generation cephalosporins	Macrolides (unless TRUE PENICILLIN ALLERGY or specific indication e.g. mycoplasma, helicobacter eradication)
Clindamycin	

Reproduced courtesy of HSE (https://www.hse.ie/eng/services/list/2/gp/antibiotic-prescribing/antibicrobial-stewardship-audit-tools/campaign-materials/antibioticgpbooklet.pdf)

Appendix F PICOS for systematic review of clinical effectiveness and safety

Description	Project scope
Population	The population of interest is represented by patients of all ages who present with symptoms of acute respiratory tract infection in primary care. Subgroups of particular interest include: children, older adults (≥65 years of age), patients attending out-of-hours (OOH) services and those in long term care (LTC) facilities. ICD-10: J00 – J22 (upper and lower RTI), J40 (bronchitis not specified as chronic or acute), H65-H66 (Otitis media). MeSH: C01.539.739, C08.730 (respiratory tract infection), C09.218.705.663 (otitis media), C07.550.781, C08.730.561, C09.775.649 (pharyngitis), C08.618.248, C23.888.852.293 (cough)
Intervention	CRP point-of-care test for use in primary care setting (+/- communication training, +/- education component, +/- other biomarkers) in addition to standard care. Testing for CRP may assist the clinician in differentiating between bacterial and viral aetiology and therefore guide antibiotic prescribing. Point of care tests allow the test to be done at the time of consultation with results available within minutes. Twelve CE marked quantitative devices and three CE marked semi quantitative methods will be considered in this assessment. The names of products and the corresponding manufacturers are: <u>Quantitative devices:</u> QuikRead® CRP for use on QuikRead® 101 instrument; QuikRead go® CRP for use on QuikRead go® instrument; QuikRead go® CRP+Hb for use on QuikRead go® instrument (Orion Diagnostica Oy) Alere Afinion™ CRP for use on Afinion AS100™ analyser; NycoCard™ CRP test for use with NycoCard™ READER II (Abbott [Alere]) CRP assay for use with Cube S analyser (EuroLyser) CRP assay for ichroma™ instrument; AFIAS™ CRP for use with AFIAS 1™ (Boditech Med) CRP assay run on AQT90 FLEX® (Radiometer Medical ApS) CRP assay run on Microsemi™ instrument (Horiba) spinit® CRP (Biosurfit) InnovaStar® instrument (DiaSys Diagnostic Systems GmbH) <u>Semi-Quantitative devices:</u> Actim® CRP (Medix Biochemica) Cleartest® CRP strips (Servoprax) FebriDx® (RPS Diagnostics) MeSH-terms: D12.776.034.145, D12.776.124.050.120, D12.776.124.486.157 (CRP) , N04.590.874.500 (point of care tests
Comparison	Standard care alone
Outcomes	**Primary outcomes:** <u>Prescribing outcomes</u> ▪ Number of patients given antibiotic prescriptions (delayed +immediate) for acute RTI (at index consultation and at 28-days follow up) ▪ <u>Patient outcomes</u> ▪ Number of patients with substantial improvement or complete recovery at seven and 28-days follow-up

Description	Project scope
	▪ Patient mortality at 28-days follow up **Secondary outcomes:** Prescribing outcomes: ▪ Number of patients given an antibiotic prescription for immediate use versus delayed use ▪ Number of patients who redeemed a prescription for an antibiotic Patient outcomes: ▪ Time to resolution of acute respiratory infection symptoms ▪ ADR, including number of patients reconsulting or hospitalised due to ADR ▪ Number of patients with RTI complications resulting in reconsultation ▪ Number of patients with RTI complications in need of hospitalisation ▪ HRQOL ▪ Patient satisfaction ▪ Physician satisfaction Rationale; the included outcomes have been identified from systematic reviews.[29, 183] MESH terms: D27.505.954.122.085 (antibacterial agents)
Study design	RCTs, cluster RCTs, non-randomised studies, observational studies

Key: ADR – adverse drug reactions; CRP – C-reactive protein; HRQOL – Health related quality of life; LTC - Long term care; MeSH – Medical Subject Heading; OOH – Out-of-hours; RCT – randomised controlled trial; RTI – respiratory tract infection.

Appendix G Systematic review of clinical-effectiveness and safety: search terms

Medline OVID – Date of search 19/04/2018

51 34 and 50
50 or/35-49
49 exp Ciprofloxacin/
48 ciprofloxacin*.tw,nm.
47 quinolone*.tw,nm.
46 exp Quinolones/
45 tetracycline*.tw,nm.
44 exp Tetracyclines/
43 amoxacillin*.tw,nm.
42 (amoxicillin* or amoxycillin*).tw,nm.
41 exp Amoxicillin/
40 macrolide*.tw,nm.
39 exp Macrolides/
38 penicillin*.tw.
37 exp Penicillins/
36 antibiotic*.tw.
35 exp Anti-Bacterial Agents/
34 18 and 33
33 or/19-22
22 (c reactive protein or c-reactive protein or C-reactive protein).tw,nm.
21 c-reactive protein/
20 (("point of care" or "point-of-care" or "near patient" or poc or rapid or bedside) adj5 (test* or analys* or immunoassay* or technique* or immunofluorescence or "fluorescent antibody")).tw.
19 Point-of-Care Systems/
18 or/1-17
17 ((acute or exacerbation*) adj3 (copd or coad or chronic obstructive pulmonary disease or chronic obstructive airway* disease or chronic obstructive lung disease)).tw.
16 Pulmonary Disease, Chronic Obstructive/
15 croup.tw.
14 (severe acute respiratory syndrome or sars).tw.
13 (influenza* or flu or ili).tw.
12 ((acute or viral or bacter*) adj2 rhinit*).tw.
11 (common cold* or coryza).tw.
10 (sinusit* or rhinosinusit* or nasosinusit*).tw.
9 (nasopharyngit* or rhinopharyngit*).tw.
8 (pharyngit* or laryngit* or tonsillit* or sore throat* or cough*).tw.
7 (bronchit* or bronchiolit*).tw.
6 (otitis media or aom).tw.
5 exp otitis media/
4 (pneumon* or bronchopneumon* or pleuropneumon*).tw.
3 (ari or urti or lrti).tw.

2 (respiratory* adj3 (inflam* or infect*)).tw.
1 exp Respiratory tract infections/

EMBASE **Date of search: 19/04/2018**

#35#30 NOT #34
#34#31 NOT #33
#33#31 AND #32
#32 'human'/de
#31 'animal'/de OR 'animal experiment'/de OR 'nonhuman'/de
#30#20 AND #24 AND #28
#29#25 OR #26 OR #27 OR #27
#28 penicillin*:ab,ti OR macrolide*:ab,ti OR amoxicillin*:ab,ti OR amoxycillin*:ab,ti OR tetracycline*:ab,ti OR quinolone*:ab,ti OR ciprofloxacin*:ab,ti
#27 'quinolone derivative'/exp OR 'ciprofloxacin'
#26 antibiotic*:ab,ti
#25 'antibiotic agent'/exp
#24#21 OR #22 OR #23
#23 ('c reactive protein':ab,ti OR 'c-reactive protein':ab,ti OR 'c reactive') AND protein:ab,ti
#22 'c reactive protein'/de
#21 (('point of care' OR 'point-of-care' OR 'near patient' OR poc OR rapid OR bedside) NEAR/5 (test* OR analys* OR immunoassay* OR technique* OR immunofluores* OR 'fluorescent antibody' OR 'florescent antibodies')):ab,ti
#20#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#19 (((acute OR exacerbation*) NEAR/3 (copd OR coad OR 'chronic obstructive pulmonary disease' OR 'chronic obstructive airways disease' OR 'chronic obstructive lung disease')):ab,ti) OR aecb:ab,ti
#18 'chronic obstructive lung disease'/de
#17 croup:ab,ti
#16 'severe acute respiratory syndrome':ab,ti OR sars:ab,ti
#15 influenza*:ab,ti OR flu:ab,ti OR ili:ab,ti
#14 ((acute OR viral OR bacter*) NEAR/2 rhinit*):ab,ti
#13 'common cold':ab,ti OR 'common colds':ab,ti OR coryza:ab,ti
#12 rhinosinusit*:ab,ti OR nasosinusit*:ab,ti
#11 nasopharyngit*:ab,ti OR rhinopharyngit*:ab,ti
#10 'sore throat'/de
#9 phary AND ngit*:ab,ti OR laryngit*:ab,ti OR tonsillit*:ab,ti OR 'sore throat':ab,ti OR 'sore throats':ab,ti OR cough
#8 bronchit*:ab,ti OR bronchiolit*:ab,ti
#7 'otitis media':ab,ti OR aom:ab,ti
#6 'otitis media'/de OR 'acute otitis media'/exp
#5 pneumon*:ab,ti OR bronchopneumon*:ab,ti OR pleuropneumon*:ab,ti
#4 ari:ab,ti OR urti:ab,ti OR lrti:ab,ti
#3 (respiratory NEAR/2 (infect* OR inflam*)):ab,ti
#2 'respiratory tract inflammation'/exp
#1 'respiratory tract infection'/exp

CINAHL via EBSCOHOST

S29 S18 AND S23 AND S28
S28 S24 or S25 OR S26 OR S27
S27 TI (penicillin* or macrolide* or amoxicillin* or amoxycillin* or amoxacillin* or tetracyclin* or quinolon* or ciprofloxacin*) OR AB (penicillin* or macrolide* or amoxicillin* or amoxycillin* or amoxacillin* or tetracyclin* or quinolon* or ciprofloxacin*)
S26 (MH "Antiinfective Agents, Quinolone+")
S25 TI antibiotic* OR AB antibiotic*
S24 (MH "Antibiotics+")
S23 S19 or S20 or S21 or S22
S22 TI ("c reactive protein" or c-reactive protein or C-reactive protein) OR AB ("c reactive protein" or c-reactive protein or C-reactive protein)
S21 (MH "C-Reactive Protein")
S20 TI (("point of care" or point-of-care or poc or "near patient" or rapid or bedside*) N5 (test* or analys* or immunoass* or technique*or immunofluores* or "fluorescent antibody")) OR AB (("point of care" or point-of-care or poc or "near patient" or rapid or bedside*) N5 (test* or analys* or immunoass* or technique* or immunofluores* or "fluorescent antibody"))
S19 (MH "Point-of-Care Testing")
S18 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17
S17 TI ((acute or exacerbation) N3 (copd or coad or chronic obstructive pulmonary disease or chronic obstructive airway* disease or chronic obstructive lung disease)) OR AB ((acute or exacerbation) N3 (copd or coad or chronic obstructive pulmonary disease or chronic obstructive airway* disease or chronic obstructive lung disease))
S16 (MH "Pulmonary Disease, Chronic Obstructive+")
S15 TI croup OR AB croup
S14 TI (severe acute respiratory syndrome or sars) OR AB (severe acute respiratory syndrome or sars)
S13 TI (influenza* or flu or ili) OR AB (influenza* or flu or ili)
S12 TI ((acute or viral or bacter*) N2 rhinit*) OR AB ((acute or viral or bacter*) N2 rhinit*)
S11 TI (common cold* or coryza) OR AB (common cold* or coryza)
S10 TI (sinusit* or rhinosinusit* or nasosinusit*) OR AB (sinusit* or rhinosinusit* or nasosinusit*)
S9 TI (nasopharyngit* or rhinopharyngit*) OR AB (nasopharyngit* or rhinopharyngit*)
S8 TI (pharyngit* or laryngit* or tonsillit* or sore throat* or cough*) OR AB (pharyngit* or laryngit* or tonsillit* or sore throat* or cough*)
S7 TI (otitis media or aom) OR AB (otitis media or aom)
S6 (MH "Otitis Media+")
S5 TI (bronchit* or bronchiolit*) OR AB (bronchit* or bronchiolit*)
S4 TI (pneumon* or bronchopneumon* or pleuropneumon*) OR AB (pneumon* or bronchopneumon* or pleuropneumon)
S3 TI (ari OR arti OR urti OR lrti) OR AB (ari OR arti OR urti OR lrti)
S2 TI (respiratory N3 (inflam* or infect*)) OR AB (respiratory N3 (inflam* or infect*))
S1 (MH "Respiratory Tract Infections+")

COCHRANE LIBRARY **Date of search: 19/04/2018**

#1 (respiratory* near/3 (inflam* or infect*))

#2 Respiratory Tract Infections
#3 (ari or urti or lrti)
#4 (pneumon* or bronchopneumon* or pleuropneumon*)
#5 Otitis media
#6 (otitis media or aom)
#7 (bronchit* or bronchiolit*)
#8 (pharyngit* or laryngit* or tonsillit* or sore throat* or cough*)
#9 (nasopharyngit* or rhinopharyngit*)
#10 (sinusit* or rhinosinusit* or nasosinusit*)
#11 (common cold* or coryza)
#12 ((acute or viral or bacter*) near/2 rhinit*)
#13 (influenza* or flu or ili)
#14 (severe acute respiratory syndrome or sars)
#15 croup
#16 Chronic Obstructive Pulmonary disease
#17 ((acute or exacerbation*) near/3 (copd or coad or chronic obstructive pulmonary disease or chronic obstructive airway* disease or chronic obstructive lung disease))
#18 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
#19 Point-of-Care Systems
#20 (("point of care" or "point-of-care" or "near patient" or poc or rapid or bedside) near/5 (test* or analys* or immunoassay* or technique*or immunofluorescence or "fluorescent antibody"))
#21 C-Reactive Protein
#22 (c reactive protein or c-reactive protein or C-reactive protein)
#23 #19 or #20 or #21 or #22
#24 Anti-Bacterial Agents
#25 antibiotic*
#26 Penicillins
#27 penicillin*
#28 Macrolides
#29 macrolide*
#30 Amoxicillin
#31 (amoxicillin* or amoxycillin*)
#32 amoxacillin*
#33 Tetracyclines
#34 tetracycline*
#35 Quinolones
#36 quinolone*
#37 ciprofloxacin*
#38 ciprofloxacin
#39 #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38
#40 #18 and #23 and #39

Studies excluded at full text review for systematic review of clinical effectiveness

Reason for exclusion*		Study reference
1	Inappropriate patient group	De La Flor[308], Lemiengre 2018[309], Llor 2013[310], André 2005[311], Takemura 2005,[312] Van den Bruel 2016[32], Takemura 2005[313], Diar 2012[314], Verbakel 2016[315]
2.	Not set in primary care	Chauhan 2013[316], Gotta 2017[317], Fagan 2001[176], Gonzales 2011[177]
3.	Not CRP POCT	Atlas 2005[318], Christakis 2001,[319] Llor 2017[320], Llor 2011[321], Hopstaken 2003[193]
4.	No relevant Comparator	Lindstrom 2015[271], Muszyńska 2007[322], Neumark 2010[323], André 2004[324], Salwan 2015[325], Haldrup 2017[326], Schuijta 2018[327], Engstrom[328], Boonman De Winter 2016[329], Steurer 2011,[330] Minnaard 2016[27], Yebyo 2016[331], Streit 2015,[332] Hoffmann 2013[333], Davidson 2017[334]
5.	Inappropriate study design	Clinical laboratory news 2017[335], Schwartz 2017[336], Bjerrum 2010[337], Oppong 2013[240], Cals 2011[237]
6.	Study protocol	Altiner 2012[338],
7.	Con.ference abstract	Keitel 2016[339], Andreeva 2012 [340], Moreno 2014[341], Harmans 2015[342], Demir 2014[343], Herman 2015[344]
8.	Not original study	The Netherlands Organisation for Health Research and Development 2005[345], Andre 2008[346], Aabenhus 2016[347]
9.	Duplicate	Cals 2009[158], Diederichersen 2001[160], Strykowski 2015[161], Bjerrum 2005[157]
10.	Cannot extract outcome data	Llor 2013[348], Rebnord 2016[349], Bjerrum 2011[350], Rebnord 2017[351], Hughes 2016[38], Llor 2014,[352] Bjerrum 2006[353]

*****Studies may have been excluded for more than one reason. For studies with more than one reason for exclusion, the first reason identified is listed.

Appendix H Included studies in systematic review of clinical effectiveness

Author (year)	Andreeva (2014)
Country	Russia
Study design	RCT cluster
Number of participants	179
Length of follow-up	2 weeks
Gender	72% female in CRP arm and 74% female in Usual care group.
Inclusion criteria	Adult patients (≥ 18 years). Patients with acute cough/LRTI (including acute bronchitis, pneumonia, and infectious exacerbations of COPD or asthma) were included. An illness of less than 28 days duration, first consultation for the illness episode, being seen in a physician's office, and written consent to participate.
Exclusion criteria	Exclusion criteria were an inability to fill out study documentation, being previously included in the study, immunocompromised status (HIV patients, immunosuppressive treatment), and ongoing treatment with oral corticosteroids.
Funding source	None stated but authors declared no competing interests
Non responders/ loss to follow-up	9 out of 101 in CRP group. 77 out of 78 in usual group. 98 patients excluded from analysis as 2 GPs not completing forms.
Device type	Afinion™ test system (Axis Shield)

Author (year)	Bjerrum (2004)
Country	Denmark
Study design	Observational study
Number of participants	367 GPs
Length of follow-up	none
Gender	CRP arm 56% (55 to 57) female, No CRP arm 59% (57 to 60) female
Inclusion criteria	All ages, adults and children presenting with acute sinusitis, acute tonsillitis or acute otitis
Exclusion criteria	not reported
Funding source	Grant from The Health Insurance Foundation of Denmark

Non responders/ loss to follow-up	No follow-up period
Device type	Not reported

Author (year)	Cals (2009)
Country	Netherlands
Study design	RCT cluster
Number of participants	431 patients, 40 GPs from 20 practices
Length of follow-up	28 days
Gender	CRP group 59% female; no CRP test arm 64% female.
Inclusion criteria	Patients were eligible if they had a suspected lower respiratory tract infection with a cough lasting less than four weeks together with one focal and one systemic symptom.
Exclusion criteria	(from protocol) Immediate hospitalisation, previous hospitalisation within last 6 weeks, previous participation in the study, current or within past 2 weeks antibiotic use, insufficient understanding of Dutch language.
Funding source	Netherlands Organisation for Health Research and Development (grant 945-04010)
Non responders/ loss to follow-up	90% completed
Device type	NycoCard™ II reader

Author (year)	Cals (2010)
Country	Netherlands
Study design	RCT
Number of participants	258
Length of follow-up	28 days
Gender	CRP group 68.2% female, control group 70.1% female.
Inclusion criteria	Adult (≥ 18+ years) presenting with current episode of 1) LRTI or 2)rhinosinusitis. 1) For LRTI, cough duration < 4weeks with at least 1 focal

	sign and 1 systemic sign or symptom. 2) For rhinosinusitis, duration < 4 weeks with at least 2 symptoms or signs.
Exclusion criteria	1. Immediate requirement of admission to a hospital, 2. No understanding of the Dutch language, 3. Previous participation in the study, 4. Antibiotic use or hospitalisation in the past 2 weeks, 5. Immunocompromised status.
Funding source	Orion Diagnostica. Cals supported by grant of the Netherlands Organization for Health Research and Development.
Non responders/ loss to follow-up	100% for antibiotic follow-up data. 91% (CRP arm) and 97% (control arm) for patient reported outcomes.
Device type	QuikRead CRP analyser (Orion Diagnostica)

Author (year)	Diederichsen (2000)
Country	Denmark
Study design	RCT
Number of participants	812
Length of follow-up	7 days
Gender	57% female
Inclusion criteria	Patients: Children and adults. Patients who consulted their GP during normal working hours because of respiratory infections, and who belonged to the National Health Insurance Group 1, were eligible for participation. Practices: All GP's in single handed practices in the County of Fenen.
Exclusion criteria	Patients: Patients who had previously been seen by a GP as a result of the infection in question, patients who had a streptococcus test carried out, and patients known to have chronic inflammatory disease were excluded. Practices: GP's already using the CRP test
Funding source	NR
Non responders/ loss to follow-up	792 (98%) follow-up
Device type	NycoCard™ reader

Author (year)	Do (2016)

Country	Vietnam
Study design	RCT
Number of participants	2,037
Length of follow-up	14 days
Gender	60% (of 2036) female
Inclusion criteria	Children and adults aged 1-65 years with at least one focal and one systemic symptom lasting for less than 2 weeks for a non-severe acute respiratory tract infection.
Exclusion criteria	Patients with severe acute respiratory tract infection were excluded. Patients were also excluded if already taking antibiotics, convulsions, confusion, chronic disease e.g. Liver disease, cancer. No access to a telephone, not able to come for follow-up visit.
Funding source	Wellcome Trust, UK, and Global Antibiotic Resistance Partnership, USA. Alere Technologies provided reagents.
Non responders/ loss to follow-up	Out of 1019 in usual care arm (139 missed 14 day follow-up). Out of 1017 in the CRP POCT arm (123 missed 14 days follow-up).
Device type	NycoCard™ analyser used with NycoCard™ II reader (Alere Technologies)

Author (year)	Jakobsen (2010)
Country	Norway, Sweden and Wales
Study design	Observational study
Number of participants	803
Length of follow-up	none
Gender	CRP arm males = 37%, No CRP use arm males = 34%, no access to CRP arm males = 38%
Inclusion criteria	Adults (≥18 years). Consecutive patients presenting for consultation with first episode of acute cough. Duration of episode less than 28 days since onset of symptoms.
Exclusion criteria	Anyone who is immunocompromised.
Funding source	Funded through the GRACE study by the 6th Framework Program of the European Commission.

Non responders/ loss to follow-up	no follow-up period
Device type	NycoCard™ CRP Single Test (Axis-Shield) and QuikRead® CRP (Orion Diagnostica)

Author (year)	Kavanagh (2011)
Country	Ireland
Study design	Pilot cross sectional study
Number of participants	120
Length of follow-up	28
Gender	Not reported
Inclusion criteria	Adults (≥ 18 years). Participants presented with acute cough and/or sore throat with duration ≤ 1 month. Informed consent.
Exclusion criteria	Not reported
Funding source	Research Bursary funded by MSD
Non responders/ loss to follow-up	CRP arm 3/60 (5%) missing patient questionnaire, 1 patient completed questionnaire but refused CRP test. Usual care arm 3/60 (5%) missing patient questionnaire and 1 doctors questionnaire.
Device type	QuikRead® CRP kit (Orion Diagnostica)

Author (year)	Little (2013)
Country	European (Belgium, Spain, Wales, Poland, UK and Netherlands)
Study design	RCT cluster
Number of participants	4,264 patients 372 GPs in 228 practices
Length of follow-up	4 weeks
Gender	CRP arm 64% female; no CRP arm 64% female
Inclusion criteria	Practices needed to recruit more than 10 patients in baseline audit. Patients Adults (≥18 years). First consultation for acute cough of up to 28 days' duration or what the clinician believed to be an acute lower-respiratory-tract infection, despite cough not being the most prominent symptom; and diagnosis judged by the physician to be an acute upper-respiratory-tract

	infection (e.g., sore throat, otitis media, sinusitis, influenza, and coryzal illness).
Exclusion criteria	Exclusion criteria were a working diagnosis of a non-infective disorder (e.g., pulmonary embolus, heart failure, oesophageal reflux, or allergy); use of antibiotics in the previous month; inability to provide informed consent (e.g., because of dementia, psychosis, or severe depression); pregnancy; and immunological deficiencies.
Funding source	European Commission Framework 6 Programme and the National Institute for Health Research and the Research Foundation Flanders.
Non responders/ loss to follow-up	For primary outcome 100% follow-up. For patient diaries more than 95% follow-up. 18 GPs excluded as not enough patients recruited.
Device type	QuikRead® CRP kits

Author (year)	Llor (2012a)
Country	Spain
Study design	Non-randomised before–after study
Number of participants	Patients: 3,356 in full intervention group. 280 GPs
Length of follow-up	None
Gender	Not stated
Inclusion criteria	Patient presenting with LRTI
Exclusion criteria	None stated
Funding source	European Commission: DG SANCO under the Frame Program 6
Non responders/ loss to follow-up	No follow-up, but 14 physicians did not complete the intervention.
Device type	NycoCard™ CRP apparatus (Axis-Shield)

Author (year)	Llor (2012b)
Country	Spain
Study design	Non-randomised before–after study

Number of participants	Patients: 560 in full intervention group. GPs 175
Length of follow-up	None
Gender	2008 (pre) 36.1% men. 2009 (post) 34.2% men.
Inclusion criteria	Patients presenting with acute rhinosinusitis
Exclusion criteria	Not reported
Funding source	European Commission: DG SANCO under the Frame Program 6
Non responders/ loss to follow-up	No follow-up, but 14 physicians did not complete the intervention.
Device type	NycoCard™ CRP apparatus (Axis-Shield)

Author (year)	Melbye (1995)
Country	Norway
Study design	RCT
Number of participants	239
Length of follow-up	21 days
Gender	63% female
Inclusion criteria	Adults (≥ 18 years). Patients presenting with suspected pneumonia, bronchitis or asthma during normal office hours were included as well as those who presented the symptoms cough or shortness of breath, chest pain on deep inspiration or cough.
Exclusion criteria	Patients with sore throat, blocked nose or pain in ears or sinuses were excluded. Patients with angina or myocardial infarction like chest pain.
Funding source	Nycomed Pharma funded study. Melbye had scholarship from Norwegian Research council.
Non responders/ loss to follow-up	For antibiotic prescribing 100% follow-up over 3 weeks. For symptoms 98/108 (91%) in CRP arm and 121/131 (92%) in usual care arm.
Device type	NycoCard™ Reader (Axis Sheild)

Author (year)	Schot (2018)
Country	Netherlands
Study design	Pragmatic RCT (cluster randomisation for daytime general practice and individual randomisation for OOH setting)
Number of participants	309 randomised (301 for primary analysis; 180 for secondary analysis)
Length of follow-up	90 days
Gender	49% female
Inclusion criteria	Children (aged 3 months to 12 years) were eligible for inclusion if they had acute cough (<21 days), reported fever (>38 °C, < 5 days), and were suspected of having a non-serious LRTI by the treating GP.
Exclusion criteria	Children who were judged as severely ill by the GP based on symptoms and signs, and those whose referral to specialist or ED was deemed necessary by GP, or those highly suspect of pneumonia were excluded. Patients with impaired immunity, severe pulmonary disease and those who used systemic antibiotics and/or corticosteroids in past 4 weeks were excluded.
Funding source	Grant received from the Netherlands Organization for Health Research and Development (ZonMW grant number 837001008) and Alere Technologies AS. Further funding and logistic support was given by two participating laboratories, SALTRO and Star Medical Diagnostic Center.
Non responders/ loss to follow-up	Protocol violation (total n=32; CRP POCT n=2 and control n=30). Loss to follow-up for 2y outcomes (total n=129; CRP POCT n=60 and control n=69). Follow-up data were only available for 180 children (58% of total; 81/141 children [57%] in the intervention group and 99/168 children [59%] in control group).
Device type	Afinion™ test system (Alere)

Appendix I Algorithms used in studies

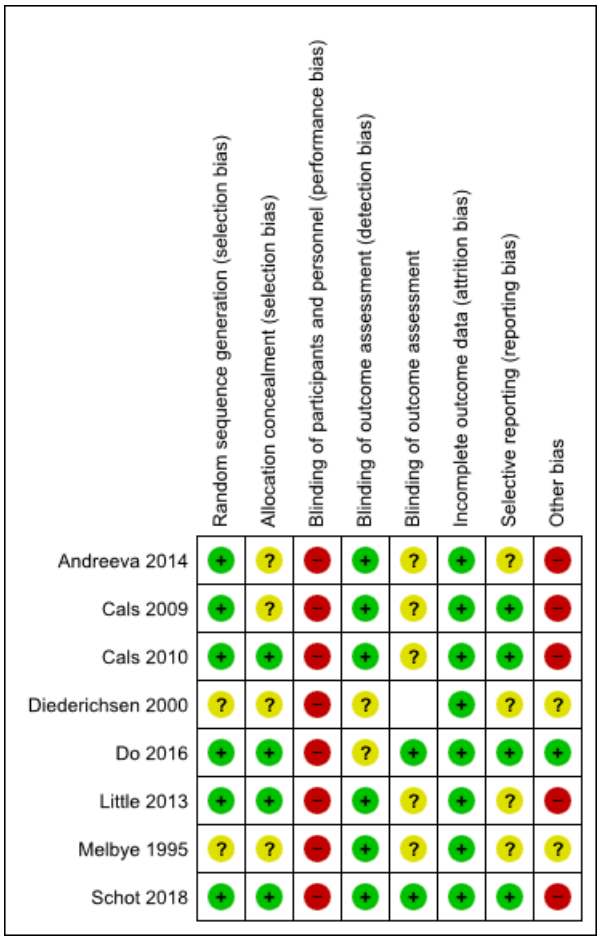
Author	Year	Algorithm, if used
Studies with clear recommendation to the GP		
Cals	2010	Advice was given based on CRP test values. No antibiotics if CRP <20mg/L, immediate antibiotics of CRP >100 mg/L and consider a delayed prescription for CRP levels between 20 and 99 mg/L. Physicians could deviate from the advice at any time
Do	2016	Recommend that antibiotics should not be prescribed if CRP ≤20 mg/L for patients aged 6–65 years and if CRP ≤10 mg/L for patients aged 1–5 years. Adults with CRP ≥100 mg/L and children with CRP ≥50 mg/L should generally receive antibiotics and hospital referral should be considered. Between these thresholds no specific recommendation was given and clinicians were advised to use their clinical discretion.
Llor	2012	Advice based on CRP cut-points. GPs were advised to use CRP test only in cases of doubt, and not as a standalone test, withholding antibiotic therapy for CRP values <20 mg/L and prescribing an antibiotic for values >100 mg/L.
Little	2013	Recommended cut-points for CRP. CRP ≤ 20 mg/l – self-limiting LRTI, withhold antibiotics. CRP 21-50 mg/L – majority of patients have self-limiting LRTI, assessment of signs, symptoms, risk factors and CRP is important, withhold antibiotics, in most cases. CRP 51-99 mg/L – assessment of signs, symptoms, risk factors and CRP is crucial, withhold antibiotics in the majority of cases and consider delayed antibiotics in the minority of cases. CRP ≥ 100 mg/L – severe infection, prescribe antibiotics
Other Algorithms used in studies		
Andreeva	2014	GPs were told that antibiotics were usually not needed when the CRP value was below 20 mg/L and that a prescription could be indicated for CRP values above 50 mg/L, taking into account the duration of illness, but that giving antibiotics should be decided on a case-by-case basis.
Bjerrum	2004	None reported.
Cals	2009	CRP <20 – pneumonia extremely unlikely. CRP 20 to 50 – pneumonia very unlikely. CRP 50 to 100 – clear infection, most likely bronchitis possibly pneumonia, combining clinical findings and CRP very important. CRP >100 – severe infection, pneumonia more likely.
Diederichsen	2000	Advice was given to the GPs that a normal CRP value (<10mg/L) and a CRP value <50 mg/L was seldom the result of bacterial infection.

Jakobsen	2010	None reported.
Kavanagh	2011	Based on CRP cut-points. CRP value of <20 was considered indicative of a viral or self-limiting infection. A value of 20 to 50 was taken to indicate a 'borderline' level (at which advice would usually be given to observe symptoms over 48 hours with explanation in relation to red flag symptoms and signs, and the possible issue of a delayed antibiotic prescription). A level of >50 was considered to be indicative of a bacterial infection.
Llor	2012	The GPs were informed about the evidence regarding CRP use in RTIs and it was emphasised that the test result should always be interpreted in combination with patient history recording and clinical examination. A CRP test result >40 mg/L was interpreted as a support for the decision to prescribe antibiotics, while a CRP test result <10 mg/L supported the decision on no antibiotic prescribing.
Melbye	1995	Disease duration 0-24 hours: CRP <50 mg/L – no change in clinical decision. Give antibiotics at CRP ≥50 mg/L. Disease duration 1-6 days: Do not give antibiotics at CRP <11 mg/L, CRP 11-49 mg/L no change in clinical decision, give antibiotics at CRP ≥50 mg/L. Disease duration seven days or more: Do not give antibiotics at CRP <11 mg/L, CRP 11-24 mg/L no change in clinical decision, give antibiotics at CRP ≥25 mg/L.
Schot	2018	GPs were not provided with strict decision rules based on CRP levels, but were given guidance on CRP cut points and likelihood of pneumonia in patients. CRP levels should be interpreted in combination with symptoms and signs. CRP levels <10mg/L make pneumonia less likely, but should not be used to exclude pneumonia when the GP finds the child ill, or when duration of symptoms is <6 hours. CRP levels >100mg/L make pneumonia much more likely; however, such levels can also be caused by viral infections. Between 10mg/L and 100mg/L, the likelihood of pneumonia increases with increasing CRP levels.

Appendix J Risk of bias and quality in systematic review of clinical effectiveness and safety

Table J.1 shows an overview of the risk of bias of the RCTs included in sytematic review of effectiveness and safety.

Table J.1 Risk of bias summary of included RCTs in systematic review 1 (clinical effectiveness and safety)



Most of the RCTs had adequate randomisation procedures.[162-165, 168, 178] In two studies it was unclear how the randomisation was done as no details were provided in the paper.[36, 171] It was often unclear from the description of the randomisation process if steps had been taken to ensure allocation concealment in the studies. All of the RCTs had a high risk of performance bias as it was not possible to blind clinicians as to which group a patient was in, as they had to know the CRP level

when it was available in order for it to influence their management of a patient. It would also be difficult to blind patients to which group they were in as a placebo (sham) procedure would need to be carried out instead of the CRP measurement. For the primary outcome of antibiotic prescribing, most of the outcome data were gathered from electronic databases or from forms filled out by clinicians and were judged to be at low risk of bias. Symptom duration and patient satisfaction were often recorded in patient diaries or by interview and it was often unclear how the data were extracted and if it was open to bias. For the primary outcome of antibiotic prescribing at index consultation, the data were complete and at low risk of attrition bias. For other outcomes, where data was collected up to 28 days later, the follow-up was good for most of the studies. When a protocol was available it was usually clear that there was no or low risk of reporting bias; however, a few older studies had no available protocol.[36, 171] Other sources of bias included the cluster randomised controlled design,[162, 163, 168, 178] stopping the study early,[171] and the method used to recruit patients.[36, 178]

Figure J.1 shows a summary graph of the risk of bias categories (low, unclear or high) across each of the the risk of bias domains. All studies score wither low or unclear risk of bias across the domains, except in the areas of performance bias and other bias where there is predominantly high risk of bias.

Figure J.1 Risk of bias summary graph of included RCTs in systematic review 1 (clinical effectiveness and safety)

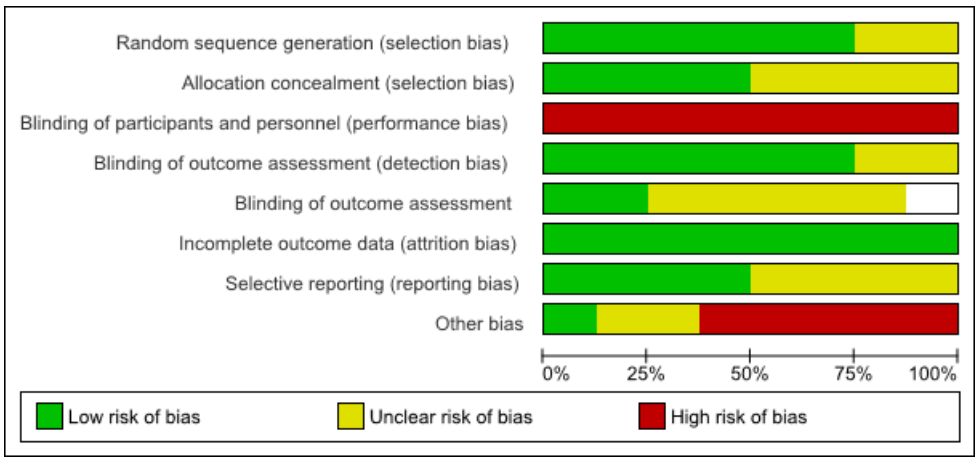


Table J.2 shows an overview of the risk of bias of included non-randomised studies in systematic review 1. All of the studies scored either a four or a five out of a possible seven, or in the case of Kavanagh et al.,[167] five out of a possible nine (as this study included a follow-up period). All of the studies scored a star for the representativeness of the cohort that underwent the CRP POCT. All bar the study by Jakobson et al.[166] also scored a star for selection of the control group. In the study

by Jakobson et al., the CRP POCT group included patients from Norway and Sweden, with Wales in the UK used as the control group as CRP POCT was not available in Wales at the time. The authors justified this choice stating that the countries have similar characteristics. However, as these countries have very different health systems and the presenting characteristics of the patients were different between the intervention and control groups, the suitability of the control group is questionable. For most studies it was unclear if antibiotics had been prescribed to any of the patients before the start of the study. Only the study by Jakobsen et al. stated that patients were only included if it was their first visit for the current RTI episode, suggesting that the outcome had not been present before the start of the study. For assessment of the outcome; in four out of five of the studies the antibiotic information was recorded by the clinician at the time of consultation, which means these studies do not score a star based on the Newcaste Ottawa scale, as a point is only scored for this domain if the assessment of the outcome is done independently and blinded or by record linkage. However, as the clinician must know the outcome of the CRP POCT for it to influence antibiotic prescribing, it seems unlikely that this would be a source of bias in this type of study. Also, it seems unlikely that there would be inherent bias in the clinician recording the antibiotic prescribing either in the medical records or on a form.

The GRADE summary of findings table is provided in Table J.3 below. The certainty associated with different outcomes ranged from ‘very low’ (Number of patients given antibiotic prescriptions for acute RTI at index consultation) to ‘high’ (Number of patients with substantial improvement or complete recovery at seven days follow up; Patient mortality at 28-days follow up; and Number of patients reconsulting).

Table J.2 Quality rating of included non-randomised studies (systematic review 1 – effectiveness and safety)

Study, Year	Selection				Comparability		Outcome			Overall quality score (Max. =9)
	Representativeness of exposed cohort?	Selection of the non-exposed cohort?	Ascertainment of exposure?	Demonstration that outcome of interest was not present at start of study?	Study controls for age/sex?	Study controls for at least 3 additional risk factors?	Assessment of outcome?	Was follow-up long enough for outcome to occur?	Adequacy of follow-up of cohorts?	
Bjerrum 2004	*	*	*	X	*	X	X	N/A	N/A	4 out of 7
Jakobsen 2010	*	X	*	*	*	X	*	N/A	N/A	5 out of 7
Kavanagh 2011	*	*	*	X	X	X	X	*	*	5 out of 9
Llor 2012(b)	*	*	*	X	*	*	X	N/A	N/A	5 out of 7
Llor 2012(a)	*	*	*	X	*	*	X	N/A	N/A	5 out of 7

Table J.3 Summary of findings table of the use of CRP POCT to guide antibiotic prescribing for patients presenting with acute RTI in primary care

Certainty assessment							**№ of patients**		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRP POCT	standard care	Relative (95% CI)	Absolute (95% CI)		
Number of patients given antibiotic prescriptions for acute RTI at index consultation												
7	randomised trials	serious [a,b]	not serious	not serious	not serious [a,c]	none	1072/2702 (39.7%)	1432/2618 (54.7%)	RR 0.76 (0.67 to 0.86)	131 fewer per 1,000 (from 77 fewer to 181 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Number of patients given antibiotic prescriptions for acute RTI at index consultation												
4	observational studies	not serious	not serious	not serious	serious [d]	none	1011/2326 (43.5%)	1784/2513 (71.0%)	RR 0.61 (0.54 to 0.69)	277 fewer per 1,000 (from 220 fewer to 327 fewer)	⊕◯◯◯ VERY LOW	CRITICAL

Number of patients given antibiotic prescriptions for acute RTI within 28 days*												
5	randomised trials	not serious	not serious	not serious	serious [c,d]	none	776/1368 (56.7%)	970/1376 (70.5%)	RR 0.81 (0.74 to 0.88)	134 fewer per 1,000 (from 85 fewer to 183 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Number of patients with substantial improvement or complete recovery at seven days follow up												
3	randomised trials	not serious	not serious	not serious	not serious	none	324/627 (51.7%)	336/637 (52.7%)	RR 1.03 (0.93 to 1.14)	16 more per 1,000 (from 37 fewer to 74 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Number of patients with substantial improvement or complete recovery at 28-days follow-up*												
3	randomised trials	not serious	not serious	serious [e]	not serious	none	207/264 (78.4%)	199/263 (75.7%)	RR 0.94 (0.69 to 1.28)	45 fewer per 1,000 (from 212 more to 235 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Patient mortality at 28-days follow up*												
5	randomised trials	not serious	not serious	not serious	not serious	none	Out of 7,165 patients in 5 RCTs there were no reported deaths				⊕⊕⊕⊕ HIGH	CRITICAL

Number of patients given an antibiotic for delayed versus delayed + immediate												
1	randomised trials	not serious		not serious		none	22/73 (30.1%)	29/81 (35.8%)	not pooled	see comment	-	IMPORTANT
Number of patients given an antibiotic for delayed versus delayed + immediate												
1	observational studies	not serious		not serious		none	10/27 (37.0%)	10/35 (28.6%)	not estimable		-	IMPORTANT
Time to resolution of RTI symptoms												
4	randomised trials	not serious	serious [f]	not serious	serious [f]	none	Studies were not pooled due to differences in the definition of the outcome. All four studies reported no significant difference in the time to resolution of symptoms between CRP POCT and usual care groups. Median time to resolution of symptoms in CRP POCT group ranged from 5 to 22 days. Median time in usual care group ranged from 4 to 22 days.				⊕⊕◯◯ LOW	CRITICAL
Number of patients reconsulting												
4	randomised trials	not serious	not serious	not serious	not serious	none	272/2322 (11.7%)	230/2202 (10.4%)	RR 1.09 (0.93 to 1.27)	9 more per 1,000 (from 7 fewer to 28 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Number of patients reconsulting												
1	observational studies	not serious		not serious		none	14/60 (23.3%)	9/60 (15.0%)	not estimable		-	
Number of patients in need of hospitalisation												
5	randomised trials	not serious	serious [g]	not serious	not serious	none	Three studies reported no hospitalisation of patients. One study reported no significant difference in hospitalisation between CRP POCT group and usual care group. One study reported significantly more hospitalisations in the CRP POCT group, but after controlling for all confounders this difference was no longer significant.				⊕⊕⊕◯ MODERATE	CRITICAL
Patient satisfaction												
3	randomised trials	not serious	not serious	not serious	serious [a]	none	794/894 (88.8%)	756/871 (86.8%)	RR 0.82 (0.55 to 1.21)	156 fewer per 1,000 (from 182 more to 391 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT

Patient satisfaction												
1	observational studies	not serious		not serious		none	51/60 (85.0%)	51/60 (85.0%)	not estimable		-	IMPORTANT

* Not all studies had 28 days follow-up, Two studies had a follow-up period of 14 days and one had a 21 days follow-up period.
CI: Confidence interval; RR: Risk ratio

Explanations

a. Heterogeneity
b. Difference in effect estimate from cluster randomised RCTs and individually randomised RCTs
c. 95% CI cross the line of no effect in a number of studies
d. Moderate heterogeneity
e. Follow up was less 14 days, 21 day and 28 days for the three studies, therefore the evidence for recovery at 28 days directly applies to only one study
f. No attempt was made to pool data as different definitions were given for resolution of symptoms
g. Effect of CRP POCT on hospitalisation differs substantially

Appendix K PICOS for systematic review of diagnostic test accuracy

Description	Project scope
Population	The population of interest is represented by patients of all ages who present with symptoms of acute respiratory tract infection in primary care. Subgroups of particular interest include: children, older adults (≥65 years of age), patients attending out-of-hours (OOH) services and those in long term care (LTC) facilities. ICD-10: J00 – J22 (upper and lower RTI), J40 (bronchitis not specified as chronic or acute), H65-H66 (Otitis media) MeSH: C01.539.739, C08.730 (respiratory tract infection), C09.218.705.663 (otitis media), C07.550.781, C08.730.561, C09.775.649 (pharyngitis), C08.618.248, C23.888.852.293 (cough)
Intervention	CRP POCT for use in primary care setting (+/- other biomarkers). Testing for CRP may assist the clinician in differentiating between bacterial and viral aetiology and therefore guide the prescription of antibiotics. Point of care tests allow the test to be done at the time of consultation with results available within minutes. Any CE marked CRP POC quantitative or semi quantitative method will be considered in this assessment: MeSH-terms: D12.776.034.145, D12.776.124.050.120, D12.776.124.486.157 (C reactive protein) , N04.590.874.500 (point of care tests)
Comparison	For the diagnostic test accuracy review, the diagnostic standard used for comparison will be dependent on the acute RTI of interest (microbiological/laboratory/radiological confirmation). Each disease group will be analysed separately.
Outcomes	Primary outcomes: ➢ Sensitivity and specificity ➢ PPV and NPV ➢ Likelihood ratio ➢ Area under the ROC curve (AUC) ➢ DOR
Study design	Diagnostic test accuracy studies

Key: AUC – Area under curve; CRP – C-reactive protein; DOR – Diagnostic odds ratio; DTA – Diagnostic test accuracy; LTC - Long term care; MeSH – Medical Subject Heading; OOH – Out-of-hours; NPV – negative predictive value; PPV – positive predictive value; RTI – respiratory tract infection; ROC – Receiver operating characteristic.

Appendix L Systematic review of diagnostic test accuracy: search terms

Embase search: Date of search: 17/05/18

No.	Query	Results
40.	#33 NOT #39	2,602
39.	#34 NOT #36	5,840,761
38.	#33 NOT #37	462
37.	#35 NOT #36	17,556,070
36.	#34 AND #35	1,732,020
35	'human'/de	19,288,090
34.	'animal'/de OR 'animal experiment'/de OR 'nonhuman'/de	7,572,781
33.	#32 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	2,621
32.	#27 AND #31	6,193
31.	#28 OR #30	7,371,204
30.	'diagnostic accuracy' OR 'diagnostic test accuracy' OR 'dta'	292,693
29.	#27 AND #28	6,193
28.	sensitiv* OR detect* OR accura* OR specific* OR reliab*	7,366,875
27.	#20 AND #24	19,694
26.	#25 AND #24 AND #20	14,685
25.	sensitiv* OR detect* OR accura* OR specific* OR reliab* OR positive OR negative OR diagnos*	12,746,185
24.	#21 OR #22 OR #23	174,668
23.	crp:ab,ti	77,014
22.	('c reactive protein':ab,ti OR 'c-reactive protein':ab,ti OR 'c reactive') AND protein:ab,ti	86,282
21.	'c reactive protein'/de	142,108
20.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	1,098,229
19.	(((acute OR exacerbation*) NEAR/3 (copd OR coad OR 'chronic obstructive pulmonary disease' OR 'chronic obstructive airways disease' OR 'chronic obstructive lung disease')):ab,ti) OR aecb:ab,ti	11,916
18.	'chronic obstructive lung disease'/de	108,899
17.	croup:ab,ti	1,729
16.	'severe acute respiratory syndrome':ab,ti OR sars:ab,ti	9,484
15.	influenza*:ab,ti OR flu:ab,ti OR ili:ab,ti	134,361
14.	((acute OR viral OR bacter*) NEAR/2 rhinit*):ab,ti	361
13.	'common cold':ab,ti OR 'common colds':ab,ti OR coryza:ab,ti OR coryza:ab,ti	5,105
12.	rhinosinusit*:ab,ti OR nasosinusit*:ab,ti	9,318
11.	nasopharyngit*:ab,ti OR rhinopharyngit*:ab,ti	2,216
10.	'sore throat'/de	13,685
9.	pharyngit*:ab,ti OR laryngit*:ab,ti OR tonsillit*:ab,ti OR 'sore throat':ab,ti OR 'sore	137,640

	throats':ab,ti OR cough*	
8.	bronchit*:ab,ti OR bronchiolit*:ab,ti	41,697
7.	'otitis media':ab,ti OR aom:ab,ti	26,302
6.	'otitis media'/de OR 'acute otitis media'/exp	26,423
5.	pneumon*:ab,ti OR bronchopneumon*:ab,ti OR pleuropneumon*:ab,ti	234,837
4.	ari:ab,ti OR urti:ab,ti OR lrti:ab,ti	6,126
3.	(respiratory NEAR/2 (infect* OR inflam*)):ab,ti	59,010
2.	'respiratory tract inflammation'/exp	485,474
1.	'respiratory tract infection'/exp	409,603

Cochrane library: Date of search: 17/05/18

ID	Search	Hits
1.	MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] this term only	3395
2.	(copd or coad or "chronic obstructive pulmonary disease" or "chronic obstructive airway disease" or "chronic obstructive airways disease" or "chronic obstructive lung disease"):ti,ab,kw (Word variations have been searched)	14023
3.	#1 or #2	14211
4.	"severe acute respiratory syndrome" or sars	141
5.	croup	210
6.	influenza* or flu or ili	2283
7.	common cold* or coryza	2160
8.	sinusit* or rhinosinusit* or nasosinusit*	3035
9.	nasopharyngit* or rhinopharyngit*	2942
10.	pharyngit* or laryngit* or tonsillit* or sore throat* or cough*	13359
11.	bronchit* or bronchiolit*	4962
12.	otitis media or aom	2708
13.	MeSH descriptor: [Otitis Media] this term only	714
14.	pneumon* or bronchopneumon* or pleuropneumon*	15364
15.	ari or urti or lrti	6655
16.	MeSH descriptor: [Respiratory Tract Infections] explode all trees	11801
17.	#3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16	57737
18.	MeSH descriptor: [C-Reactive Protein] this term only	4259
19.	"c reactive protein" or "c-reactive protein" or "C-reactive protein" or CRP	14874
20.	#18 or #19	14874
21.	"Diagnostic test accuracy" or "diagnostic accuracy" or dta	10166
22.	MeSH descriptor: [Sensitivity and Specificity] this term only	12095
23.	predict* or diagnose* or diagnosi* or diagnosti* or accura*	237612
24.	#21 or #22 or #23	240077
25.	#24 and #20 and #17	680

CINAHL (via EBSCOhost): Date of search: 17/5/18

No.	Query	Results
S28	s27 and s22 and s19	611
S27	s23 or s24 or s26	1,077,841
S26	(MH "Sensitivity and Specificity")	70,314
S25	"predict* or diagnose* or diagnosi* or diagnosti* or accura*"	0
S24	predict* or diagnose* or diagnosi* or diagnosti* or accura*"	1,056,784
S23	"Diagnostic test accuracy" or "diagnostic accuracy" or dta"	8,815
S22	s20 or s21	18,378
S21	TI (“c reactive protein” or c-reactive protein or C-reactive protein) OR AB (“c reactive protein” or c-reactive protein or C-reactive protein)	12,993
S20	(MH “C-Reactive Protein”)	12,758
S19	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17	115,467
S18	TI ((acute or exacerbation) N3 (copd or coad or chronic obstructive pulmonary disease or chronic obstructive airway* disease or chronic obstructive lung disease)) OR AB ((acute or exacerbation) N3 (copd or coad or chronic obstructive pulmonary disease or chronic obstructive airway* disease or chronic obstructive lung disease))	1,980
S17	(MH “Pulmonary Disease, Chronic Obstructive+”)	15,507
S16	TI croup OR AB croup	384
S15	TI (severe acute respiratory syndrome or sars) OR AB (severe acute respiratory syndrome or sars)	1,412
S14	TI (severe acute respiratory syndrome or sars) OR AB (severe acute respiratory syndrome or sars)	2,550
S13	TI (influenza* or flu or ili) OR AB (influenza* or flu or ili)	21,505
S12	TI ((acute or viral or bacter*) N2 rhinit*) OR AB ((acute or viral or bacter*) N2 rhinit*)	50
S11	TI (common cold* or coryza) OR AB (common cold* or coryza)	997
S10	TI (sinusit* or rhinosinusit* or nasosinusit*) OR AB (sinusit* or rhinosinusit* or nasosinusit*)	3,663
S9	TI (nasopharyngit* or rhinopharyngit*) OR AB (nasopharyngit* or rhinopharyngit*)	220
S8	TI (pharyngit* or laryngit* or tonsillit* or sore throat* or cough*) OR AB (pharyngit* or laryngit* or tonsillit* or sore throat* or cough*)	11,162
S7	TI (otitis media or aom) OR AB (otitis media or aom)	3,582
S6	(MH “Otitis Media+”)	4,416
S5	TI (bronchit* or bronchiolit*) OR AB (bronchit* or bronchiolit*)	3,781
S4	TI (pneumon* or bronchopneumon* or pleuropneumon*) OR AB (pneumon* or bronchopneumon* or pleuropneumon)	25,341
S3	TI (ari or arti or urti or lrti) OR AB (ari or arti or urti or lrti)	1,310
S2	TI (respiratory N3 (inflam* or infect*)) OR AB (respiratory N3 (inflam* or infect*))	8,504
S1	(MH “Respiratory Tract Infections+”	62,810

Studies excluded at full text review for systematic review of diagnostic test accuracy

Reason for exclusion*		Study reference
1.	Not set in primary care	Almirall 2014,[354] Chen 2006, [355] Elsammak 2006,[356] Flanders 2004,[357] Gan 2017,[358] Garcia Vazquez,[359] Higdon 2017,[360] Hu 2010,[361] Isaacman 2002,[362] Kang 2009,[363] Kaur 2013,[364] Kerttula 1987,[365] McCarthy 1978,[366] Melbye 1992,[367] Peng 2013,[368] Poyrazoğlu 2003,[369] Prat 2003,[370] Principi 1986,[371] Requejo 2003,[372] Stolz 2006[373] Shapiro 2018, Self 2017
2.	Study irretrievable	Babu 1989,[374] Hu 2003,[375] Khomerki 1966,[376] Udovicki 1980[377]
3.	Study outcomes not relevant to current systematic review	Broekhuizen 2012[378]
4.	Inappropriate study design	Schaaf 2006,[379] Searle-Barnes 2017,[380] Tomas 2015[381]
5	Abstract only	Rautakorpi 2008[382]
6.	Duplicate	Hopstaken 2004[383]
7.	Inappropriate patient population	Bielsa 2014[384]
8.	Data irretrievable	Young 2003

*Studies may have been excluded for more than one reason. For studies with more than one reason for exclusion,only one reason is listed.

Appendix M Included studies in systematic review of diagnostic test accuracy

Author year	Country and setting	Population	Reference test	CRP test	Other diagnostic /prognostic tests /clinical prediction rule	Groups (size)	CRP cut-off used (mg/L)
Calvino 2014	Primary care in Spain	Adults >18 years old with acute pharyngitis and the presence of the 4 Centor criteria	Microbiologic culture confirmed with posterior serogrouping	QuikRead®/go® devices	None	GAS (n = 83) GBS (n = 8) GCS (n = 13) GGS (n = 5) Other streptococcus (n = 10) No bacteria (n = 29)	None
Christensen 2014	General practice in Denmark	Acute tonsillitis patients aged 15-40 years with a Centor score of 1-4	Laboratory culture	Laboratory test		GAS (n = 29) Non-GAS (n=71)	6
Ebell 2017	General practice in Denmark	Adult patients aged 18-65 with suspected acute rhinosinusitis	Acute rhinosinusitis: • Abnormal CT finding OR • Abnormal CT finding + + purulent antral puncture fluid Acute bacterial rhinosinusitis: • Abnormal CT finding +purulent antral puncture fluid + positive bacterial culture of antral fluid.	Blood test	None	Acute rhinosinusitis (n = 91) Not acute rhinosinusitis (n = 84)	>15

Author year	Country and setting	Population	Reference test	CRP test	Other diagnostic /prognostic tests /clinical prediction rule	Groups (size)	CRP cut-off used (mg/L)
Gulich 2002	General practice in Germany	Patients aged ≥16 with newly developed sore throat	Microbiological culture of throat swabs	NycoCard™ CRP Whole Blood test	Clinical score of 4 parameters (throat mucosa, uvula, soft palate, tonsils), 2 points per criterion: High=6-8 Ambiguous=4-5 Low=0-3 . CRP test only in patients in ambiguous category	GAS (n = 73) non-GAS (n = 192)	≥35
Gulich 1999	General practice in Southern Germany	Patients 16-75 years presenting with sore throat	Microbiological culture of a throat swab. GPs clinical diagnosis	NycoCard™ CRP Whole Blood test	Routine physical exam	Bacterial pharyngitis (n = 38) Non-bacterial pharyngitis (n = 123)	≥35
Hansen 1995	General practice in Denmark	Patients 18-65 years suspected of having acute maxillary sinusitis.	CT + aspiration + laboratory culture	NycoCard™ CRP whole blood	Erythrocyte sedimentation rate	Acute maxillary sinusitis (n= 89) Not acute maxillary sinusitis (n = 79)	10
Heiskanen-Kosma 2000	Primary care in Finland	Children with radiologically confirmed pneumonia	EIA and immune complex assays (bacterial) Routine complement fixation (viral and mycoplasma)	Immunoturbidometric method (LKB 8600 Reaction rate analyser)	None	Pneumococcal (n = 57) Mycoplasmal /chlamydial (n = 43) Viral (n = 29) Unknown (n = 64)	None
Holm 2007	Primary care in Denmark.	Adults diagnosed with community-acquired LRTI	Chest radiography + laboratory culture	Laboratory test	None	Pneumonia (n = 48) Non-Pneumonia (n = 316)	20

Author year	Country and setting	Population	Reference test	CRP test	Other diagnostic /prognostic tests /clinical prediction rule	Groups (size)	CRP cut-off used (mg/L)
Hopstaken 2003	GP surgeries in southern part of The Netherlands.	Adults presenting with LRTI	Chest radiograph	Laboratory test	Signs and symptoms	Pneumonia (n = 32) Non-Pneumonia (n = 211)	10 20 50
Hopstaken 2009	General practice in The Netherlands	Patients presenting with signs and symptoms of LRTI	Chest radiograph (lateral and postero-anterior) + laboratory tests	Laboratory test	None	Pneumonia (n = 11) No pneumonia (n = 84)	10 50 100
Lagerström 2006	Primary care in Sweden	Adults with radiologically confirmed CAP	Chest X-ray	Laboratory based NycoCard™ reader	None	Pneumonia (n = 82) Non-pneumonia (n = 95)	None
Melbye 1988	General practices in Norway	Patients aged ≥15 years treated with antibiotics for clinically suspected pneumonia	Chest X-ray (postero-anterior and lateral projections)	Laboratory blood test	None	Pneumonia (n = 11) Non-pneumonia (n = 58)	> 11 > 50
Minnaard 2015	Primary care in 12 European countries	Adult out-patients presenting with acute cough	Chest radiograph + Laboratory culture	Afinion™ Nyco-Card™ Reader II Eurolyser Smart 700|340 QuikRead go® QuikRead® 101	Signs and symptoms	Pneumonia (n = 100) No pnuemonia (n = 100)	20 100

Author year	Country and setting	Population	Reference test	CRP test	Other diagnostic /prognostic tests /clinical prediction rule	Groups (size)	CRP cut-off used (mg/L)
Teepe 2016	GPs in 16 primary care research networks in 12 European countries (GRACE consortium)	At least 18 years of age presenting for the first time with the main symptom of acute or deteriorating cough (duration ≤ 28 days) or any clinical presentation considered by the GP to be caused by LRTI	Bacterial LRTI: The presence of prespecified bacteria in respiratory samples. Bacterial pneunomia: Chest radiography within 7 days of presentation in combination with the presence of prespecified bacteria from sputum or nasopharyngeal swab	Laboratory test	LRTI bacterial infection (CRP at 30 mg/l reported in combination with discoloured sputum). Bacterial pneumonia (CRP at 30 mg/L reported in combination with comorbidity, temperature greater or equal to 38 degrees centrigrade and crackles on lung ausculation)	All Patients (n=3,104) LRTI bacterial infection (n=539) Radiologically confirmed pneumonia (n=141) Bacterial pneumonia (n=38)	> 20 > 30 >100

Author year	Country and setting	Population	Reference test	CRP test	Other diagnostic /prognostic tests /clinical prediction rule	Groups (size)	CRP cut-off used (mg/L)
Van Vugt 2013	Primary care centres in 12 European countries	Adults presenting with acute cough	Chest radiograph	Laboratory test	Signs and symptoms	No Pneumonia: CRP level ≤20 (n=2039; 76.1%) 21-30 (n=214, 8%) 31-50 (n=230; 8.6%) 51-100: (n=135; 5%) >100 (n=62; 2.3%). Pneumonia: CRP level ≤20 (n=55; 39.3%) 21-30 (n=11, 7.9%) 31-50 (n=16; 11.4%) 51-100: (n=24; 17.1%) >100 (n=34; 24.3%). Diagnostic risk group*: Low: (n = 1,556; 55.2%) Intermediate: (n = 1132 40.1%) High: (n= 132; 4.7%)	> 30

Key: CRP – C reactive protein; GAS - group A streptococcus; GBS - group B streptococcus; GCS - group C streptococcus; GGS - group G streptococcus; CT – computed tomography; LRTI – Lower respiratory tract infection; CAP – community acquired pneumonia.

* Risk of radiologically confirmed pneumonia based on prediction model using signs and symptoms only. Risks defined a priori: low = <2.5%; intermediate = 2.5-20%; high = >20%.

Appendix O Risk of bias and quality in systematic review of diagnostic test accuracy

A tabular presentation of the QUADAS-2 quality assessment of the 15 studies included in this systematic review is shown in Table O.1. All studies reported clearly defined selection criteria. The majority of studies included either all patients presenting with symptoms of RTI or consecutive patients, therefore risk of bias and concerns regarding applicability were generally low. Potential risk of bias, or applicability concerns, was identified regarding patient selection in five studies. Exclusion of patients living in nursing homes by Lagerstrom et al. may reduce the applicability of the findings to the target population identified in our review question as this patient group is of particular interest due to high antibiotic prescribing rates in long-term care facilities in Europe.[185] Melbye et al. included only patients treated with antibiotics by a general practitioner for a suspected pneumonia.[196] Failure to include patients not treated with antibiotics introduces a potential risk of bias. Furthermore, patients who were too ill to attend the outpatient clinic for analysis of CRP levels were excluded which could lead to underestimation of diagnostic test accuracy. Van Vugt et al. reports that not all consecutive eligible patients were recruited.[198] The authors state that sequential recruitment was impossible given the high volume of patients presenting with LRTI during the winter period, and the time required to recruit and assess each patient. Given the large sample size in this study, clinically important selection bias was considered to be unlikely. Ebell et al. state that a large proportion of eligible patients declined to participate and data on non-participants were not available, introducing potential selection bias.[187]

Table O.1 Risk of bias findings

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Calvino 2014	Low	Low	Low	Low	Low	Low	Low
Christensen 2014	Low	Unclear	Low	Low	Low	High	Low
Ebell 2017	Unclear	Unclear	Low	Low	Unclear	High	Low
Gulich 2002	Low	Low	Low	Low	Low	Low	Low
Gulich 1999	Low	Low	High	Low	Low	Low	High
Hansen 1995	Low	Low	Low	Low	Low	Low	Low
Heiskanen-Kosma 2000	Low	High	Low	Low	Low	High	Low
Holm 2007	Low	Unclear	Low	Low	Low	High	Low
Hopstaken 2003	Low	Low	Low	High	Low	High	Low
Hopstaken 2009	Low	Unclear	Low	Unclear	Low	High	Low
Lagerstrom 2006	Low	Unclear	Low	Unclear	High	Unclear	Low
Melbye 1988	High	Unclear	Low	Low	High	High	Low
Minnaard 2015	Low	Unclear	Low	High	Low	High	High
Teepe 2016	Low	Low	Low	High	Low	High	Low
Van Vugt 2013	Low	Low	Low	High	Low	High	Low

In all included studies, patients received both the index and reference standard tests. The risk of bias and applicability of a number of included studies was judged to be unclear in terms of the index test. Insufficent information was provided in the majority of caes in order to determine if the results of the reference standard were available prior to interpretation of the index test. In studies where a CRP POC test was used, it was assumed that interpretation of the index test result was carried out during the consultation, eliminating the potential for the reference standard to influence interpretation of the test. Gulich et al. defined evidence of bacterial pharyngitis as throat swabs growing bacteria caused by group A- and C-β-haemolytic streptococci and haemophilus influenzae.[189] This has the potential to underestimate the prevalence of bacterial pharyngitis as infections may be attributable to other types of bacteria.

Variation in test technology or execution may affect estimates of diagnostic test accuracy. This systematic review aimed to evaluate the diagnostic test accuracy of CRP testing at the POC. An important limitation to the study conducted by Minnaard et al. was noted.[197] All tests were carried out in a laboratory setting by laboratory analysts, which may not be representative of the primary care setting where CRP POCT devices are intended for use. A number of studies used laboratory-based CRP testing and the findings of these studies may not be directly transferable to the primary care setting.[186, 187, 191-194, 196, 198] Studies for which CRP testing was carried out in a laboratory testing rated high in terms of concerns regarding the applicability of these findings to the primary care setting.

Three studies rated poorly in terms of patient flow and timing. Ideally, results of the index test and reference standard should be collected at the same time. The studies by Minnaard et al. and Teepe et al. reported that blood samples were taken on day one for analysis of CRP levels, however chest radiographs were obtained within seven days.[48, 197] Similarly, Hopstaken et al. report that blood samples were taken for analysis of CRP levels on the day of presentation to the GP, while chest radiographs were not obtained until three days after inclusion in the study.[193] The time interval between the execution of the index test and reference standard has the potential to introduce bias as a result of misclassification due to changes in patient condition or the potential of the results of one test to influence the results of another. A graphical summary of the overall quality assessment for each of the QUADAS-2 domains is illustrated in Figure O.2.

Figure O.2 Graphical overview of the overall quality rating of included studies in systematic review 2 (diagnostic test accuracy) for each of the key domains using the QUADAS-2 quality appraisal tool

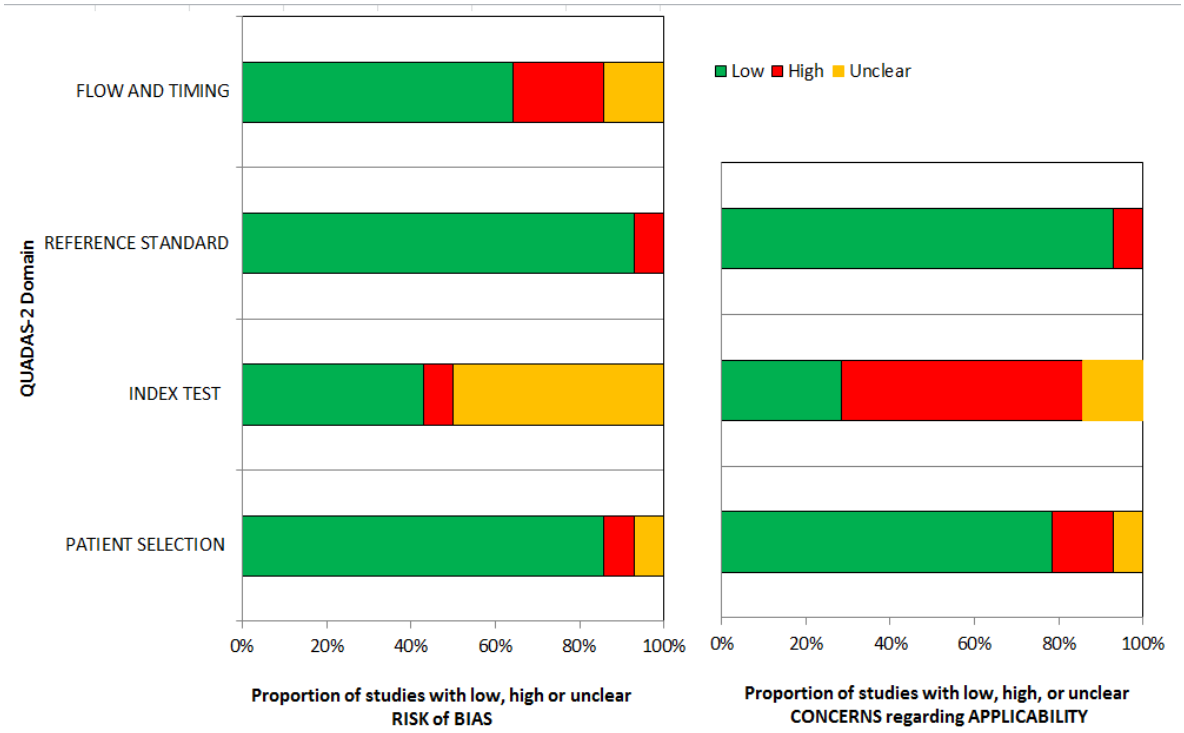


Table O.3 Summary of findings table of CRP POCT compared with the reference standard for the diagnosis of acute RTI in primary care

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
CRP levels (mg/L) **	Pharyngitis/Tonsillitis: Reported mean CRP levels in patients were inconsistent (GAS [range 34.4-40 mg/L]; Non-GAS [range 15-29.9]). Studies differed in the spectrum of patients due to differences in inclusion criteria. LRTI/Pneumonia: Only one study reported mean CRP levels in children. In studies in adults, measured CRP concentrations were more consistent in patients without pneumonia (range 17-19 mg/L (n=2)) than in pneumonia patients (range 62-145mg/L (n=3)).	Pharyngitis/Tonsillitis: (n=2) LRTI/Pneumonia: (n=4)	Pharyngitis/Tonsillitis: ⊕◯◯◯ VERY LOW [a,b,c] LRTI/Pneumonia: ⊕⊕◯◯ LOW [c, d]
CRP optimal threshold**	Sinusitis: The optimal cut-off point ranged from 10-17 mg/L. Pharyngitis/Tonsillitis: The optimal threshold was derived from the patient sample. A cut-off point of 35 mg/L was used to distinguish between bacterial and non-bacterial pharyngitis (n=1). A threshold of 6 mg/L was used to differentiate between GAS and non-GAS patients (n=1). Pneumonia/LRTI: Optimal cut-off points were chosen rather than derived and were 11, 20, 50 100 mg/L.	Sinusitis: (n=2) Pharyngitis/Tonsillitis: (n=2) RTI/Pneumonia: (n=5)	Sinusitis: ⊕⊕⊕◯ MODERATE[e] Pharyngitis/Tonsillitis: ⊕⊕◯◯ LOW [f,g] LRTI/Pneumonia: ⊕⊕⊕⊕ HIGH[h]
CRP alone at a specified threshold**	Sinusitis: CRP was significantly associated with a diagnosis of sinusitis at a cut-off point of 15 mg/L. At a threshold of 10 mg/L, CRP testing may be useful as a rule-out test. However, neither study recommended the use of CRP alone as a diagnostic tool. Pharyngitis/Tonsillitis: CRP testing was found to perform better in differentiating between bacterial and non-bacterial pharyngitis compared with clinical diagnosis only. LRTI/Pneumonia: At a cut-off point of 20 mg/L, in 3/4 studies the test demonstrated insufficient sensitivity to be used to reliably rule out pneumonia (sensitivity 0.48-0.79). At thresholds of 50 mg/L and 100 mg/L the test may be useful as a rule-in test (specificity 0.84-0.99).	Sinusitis: (n=2) Pharyngitis/Tonsillitis: (n=1) LRTI/Pneumonia: (n=5)	Sinusitis: ⊕⊕⊕◯ MODERATE[e] Pharyngitis/Tonsillitis: ⊕⊕⊕◯ MODERATE [h] LRTI/Pneumonia: ⊕⊕⊕◯ MODERATE [i]

Explanations

a. Downgraded by one level for inconsistency: Studies were inconsistent with regard to the spectrum of patients included and CRP levels reported in non-GAS groups.
b. Downgraded by one level for imprecision: Wide 95% confidence intervals
c. Downgraded by one level for indirectness: Blood or serum CRP concentrations are not a direct measure of diagnostic test accuracy.
d. Downgraded by one level for inconsistency: Studies were inconsistent with regard to mean or median CRP levels reported in pneumonia patients.
e. Downgraded by one level for indirectness: CRP testing was used either in combination with other clinical criteria (i.e. erythrocyte sedimentation rate) or as part of a clinical prediction rule.
f. Downgraded by one level for inconsistency: Studies were inconsistent with regard to thresholds used to define test positivity.
g. Downgraded by one level for risk of bias: 3/5 studies did not provide evidence or rationale for the cut-off points selected.
h. Downgraded by one level for indirectness: Current clinical guidelines recommend antibiotic treatment in patients with GAS pharyngitis only. The distinction between bacterial and non-bacterial pharyngitis may not be as useful.
i. Downgraded by one level for inconsistency: Studies report widely varying measures of sensitivity.
j. Downgraded by one level for indirectness: Studies evaluated the diagnostic test accuracy of CRP POCT in addition to other diagnostic tools. The effect of CRP POCT alone for the diagnosis of RTI cannot be determined.
k Downgraded by one level for inconsistency: Studies were inconsistent regarding the usefulness of CRP POCT in addition to a clinical score for the diagnosis of GAS infection.

**Measures of diagnostic test accuracy demonstrate clear threshold effects. That is, differences in accuracy are likely to be related to differences in the CRP cut-off point used in the study. It was therefore not appropriate to calculate summary estimates of accuracy for CRP POC tests as a group where a range of cut-off points have been used across studies. For this reason, the evidence is considered for each type of acute RTI identified in the systematic review.

***The signs and symptoms model is defined as a clinical prediction rule in which investigators identified the best combination of medical signs, symptoms, and other findings in predicting the probability of pneumonia with the aim of reducing uncertainty surrounding medical decision-making by standardising the collection and interpretation of clinical data.

Appendix P PICOS for systematic review of analytical performance

Description	Project scope
Population	The population of interest is represented by patients of all ages who present to primary care
Intervention	CRP point-of-care test for use in primary care setting (+/- other biomarkers) Twelve CE marked quantitative devices and three CE marked semi quantitative methods will be considered in this assessment. The names of products and the corresponding manufacturers are: <u>Quantitative devices:</u> QuikRead® CRP for use on QuikRead® 101 instrument; QuikRead go® CRP for use on QuikRead go® instrument; QuikRead go® CRP+Hb for use on QuikRead go® instrument (Orion Diagnostica Oy) Alere Afinion™ CRP for use on Afinion™ AS100™ analyser; NycoCard™ CRP test for use with NycoCard™ READER II (Abbott [Alere]) CRP assay for use with Cube S analyser (EuroLyser) CRP assay for ichroma™ instrument; AFIAS™ CRP for use with AFIAS 1™ (Boditech Med) CRP assay run on AQT90 FLEX® (Radiometer Medical ApS) CRP assay run on Microsemi™ instrument (Horiba)) Spinit® CRP (Biosurfit) InnovaStar® instrument (DiaSys Diagnostic Systems GmbH) <u>Semi-Quantitative devices:</u> Actim® CRP (Medix Biochemica) Cleartest® CRP strips (Servoprax) FebriDx® (RPS Diagnostics) MeSH-terms: D12.776.034.145, D12.776.124.050.120, D12.776.124.486.157 (CRP) , N04.590.874.500 (point of care tests
Comparison	Standard laboratory CRP measurement or another CRP POCT instrument
Outcomes	**Primary outcomes:** • Measures of accuracy (level of agreement between the result of one measurement and the true value) and precision (degree of reproducibility of the result) will be extracted for each CRP POCT device **Secondary outcomes** ▪ Where available, information on ease of use and suitability for primary care POCT will also be collected and summarised for each device
Study design	Any study reporting on analytical performance

Key: CRP – C-reactive protein; MeSH – Medical Subject Heading; POCT – Point of care testing

Appendix Q Systematic review of analytical performance: search terms

Embase: Date of search: 14/06/2018

No.	**Query**	**Result**
#23	AND 'HUMAN'	105
#22	#10 AND #14 AND #21	116
#21	#15 OR #16 OR #17 OR #18 OR #19 OR #20	52550
#20	'bedside'	36888
#19	'near patient'	883
#18	'point of care system'	1174
#17	'point of care testing'	11365
#16	POC	5235
#15	POCT	1968
#14	#11 OR #12 OR #13	52349
#13	'CRP'	79711
#12	'c-reactive protein'	150634
#11	'c reactive protein'	150634
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	1661450
#9	'Quality control'	196872
#8	'User friendliness'	1130
#7	'Ease of use'	503285
#6	Variability	25340
#5	'coefficient of variation'	25340
#4	Agreement	271299
#3	Accuracy	2707
#2	Precision	707237
#1	'analytical performance'	5381

EBSCO Host (Cinahl): Date of search: 14/06/2018

No.	Query	Result
#22	#10 AND #14 AND #21	17
#21	#15 OR #16 OR #17 OR #18 OR #19 OR #20	16502
#20	'bedside'	10623
#19	'near patient'	1801
#18	'point of care system'	631
#17	'point of care testing'	3656
#16	POC	751
#15	POCT	458
#14	#11 OR #12 OR #13	20541
#13	'CRP'	7816
#12	'c-reactive protein'	18683
#11	'c reactive protein'	18683
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	139332
#9	'Quality control'	10893
#8	'User friendliness'	231
#7	'Ease of use'	2823
#6	Variability	35908
#5	'coefficient of variation'	3477

#4	Agreement	35693
#3	Accuracy	53297
#2	Precision	10438
#1	'analytical performance'	346

PubMed: Date of search: 14/06/2018

#22	#10 AND #14 AND #21	152
#21	#15 OR #16 OR #17 OR #18 OR #19 OR #20	31260
#20	'bedside'	24820
#19	'near patient'	533
#18	'point of care system'	129
#17	'point of care testing'	3094
#16	POC	3271
#15	POCT	1094
#14	#11 OR #12 OR #13	78336
#13	'CRP'	40784
#12	'c-reactive protein'	68351
#11	'c reactive protein'	68351
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	694676
#9	'Quality control'	76926
#8	'User friendliness'	832
#7	'Ease of use'	7792
#6	Variability	235554
#5	'coefficient of variation'	20521
#4	Agreement	241587
#3	Accuracy	336396
#2	Precision	125382
#1	'analytical performance'	30070

Cochrane Library: Date of search: 14/06/2018

No.	Query	Result
#22	#10 AND #14 AND #21	60
#21	#15 OR #16 OR #17 OR #18 OR #19 OR #20	3565
#20	'bedside'	1855
#19	'near patient'	90
#18	'point of care system'	551
#17	'point of care testing'	431
#16	POC	345
#15	POCT	83
#14	#11 OR #12 OR #13	15649
#13	'CRP'	8244
#12	'c-reactive protein'	13218
#11	'c reactive protein'	13218
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	59736
#9	'Quality control'	2778
#8	'User friendliness'	98

#7	'Ease of use'	1287
#6	Variability	20831
#5	'coefficient of variation'	1327
#4	Agreement	12210
#3	Accuracy	25058
#2	Precision	6341
#1	'analytical performance'	62

Appendix R Included studies in systematic review of analytical performance

Author (Year)	Study Type & Country	Test setting(s) and operator(s)	Sample source(s) (n)	Population / Inclusion criteria	POCT device	Comparator device	Blood sample type(s)	Funding source
Bains (2017)[213]	UK - AP	Laboratory- Lab technician	Hospital Samples (n=44)	NR	ichroma™	Architect ci8200	Venous	NR
Brouwer (2014)[214]	Netherlands - AP	Laboratory – Lab technicians	Primary Care Samples (n=100)	Adults aged > 18 years. GP's patients, CRP concentrations from 5 to 200 mg/L	QuikRead® 101	Synchron	Venous	None – analysers were provided for free
					Smart Eurolyser		Venous	
					Afinion™		Venous	
					ichroma™		Venous	
					Microsemi™		Venous	
					AQT90 FLEX®		Venous	
					Actim®		Venous	
					Cleartest®		Venous	
Bukve (2016)[215]	Norway –EQA	Primary Care – GP & Nurses	Laboratory Samples (n=3) Primary Care Samples (n=2134) Hospital samples (n=22)	Healthy volunteers, blood stored in K2-EDTA and spiked with recombinant CRP (range 8-92 mg/L).	ABX Micros 200™	Cobas 600	Venous	None
					Afinion™			
					ichroma™			
					NycoCard™			
					QuikRead go®			
					QuikRead® 101			

Author (Year)	Study Type & Country	Test setting(s) and operator(s)	Sample source(s) (n)	Population / Inclusion criteria	POCT device	Comparator device	Blood sample type(s)	Funding source
Ciftci (2014)[216]	Turkey – AP	Laboratory – Lab technicians	Hopsital Blood Sample (n=96)	NR	ichroma™	Immage 800	Venous	None
Clouth (2009)[217]	Germany-AP	Laboratory – Not stated	Hospital Blood Samples (n=200)	NR	NycoCard™ Micros CRP™	Tina Quant	Venous	NR
De Graaf (2017)[218]	Netherlands-AP	Primary Care – GP	NR (n=100)	NR	spinit®	Roche Cobas 8000	EDTA anti coagulated whole blood	Device provided for free by manufacturer
Evrard (2005)[219]	France -AP	Laboratory – Lab technicians	(n=43)	NR	Actim®	Modular P900	Venous	NR
Ivaska (2015)[220]	Finland -AP	Laborartory – Lab technicians	Clinical blood samples (n=48)	NR	Afinion™	Modular P	Serum from EDTA venous blood	Turku University Research grant
Matheeusen (2018)[221]	12 European Countries -AP	Laboratory – Lab technicians	Primary Care (n=2922)	Adults > 18 years of age. Symptoms of LRTI, acute cough lasting less than 28 days, presenting to primary care	QuikRead® 101	Dimension Vista	Plasma from venous blood	EU funding Kits provided by manufacturers

Author (Year)	Study Type & Country	Test setting(s) and operator(s)	Sample source(s) (n)	Population / Inclusion criteria	POCT device	Comparator device	Blood sample type(s)	Funding source
Minnaard (2013)[25]	Netherlands - AP	Laboratory samples – Lab technicians	Hosptial Sampes	NR	Afinion™ NycoCard™ Reader II Smart Eurolyser QuikRead go® QuikRead® 101	Olyumpus AU 2700	Venous	None
Monteny (2006)[222]	Netherlands-AP	Primary care – GP	Primary Care (n=61)	Any child attending out of hours primary care service with a fever	NycoCard™ QuikRead® CRP	Tina Quant	Capillary Venous	ZonMW – health research/ development funding Distributor provided equipment
Nomura (2014)[223]	Japan -AP	Unclear	Hospital Samples (n=244)	NR	Microsemi™	Hitachi 7600	Venous	Authors employed by Horiba – manufacturers of Microsemi™
Semark (2003)[224]	UK-AP	Primary Care – Practice Nurse	Primary Care (n=124)	NR	QuikRead® 101	Vitros 950 dry slide	Venous & Capillary	Grant from Bio-Stat Ltd – supply QuikRead® system

Author (Year)	Study Type & Country	Test setting(s) and operator(s)	Sample source(s) (n)	Population / Inclusion criteria	POCT device	Comparator device	Blood sample type(s)	Funding source
SKUP (2001)[206]	Denmark -EQA	Hospital Laboratory – Lab Technicians & Primary Care Centres	Primary Care (n=40) Hospital samples (n=40)	Each hospital chose 40 samples with concentration of CRP in required range. Each GP selected 40 patients.	QuikRead® 101	Bayon, Cobas Integra, Hitachi	Venous	SKUP
SKUP (2002)[207]	Denmark-EQA	Hospital Laboratory – Lab Technicians & General Practice	Primary Care (n=160)	160 patients general practice and laboratory samples	ABX Micros™	Vitros 250, Axon, Cobas Integra 700, Vitros 950	Venous	SKUP
SKUP (2011)[209]	Denmark – EQA	Hospital Laboratory – Lab Technicians & Primary Care Centres	Hospital (n=109) venous (n=114) capillary Primary Care (n=80)	109 venous and 114 capillary bloods from same patients in hospital laboratory, 80 capillary blood in primary care	Smart Eurolyser	Cobas Integra 800	Capillary and Venous	SKUP
SKUP (2013)[211]	Denmark-EQA	Hospital Laboratory – Lab Technicians & Primary Care Centres	Hospital (n=100) Primary Care (n=86)	100 venous whole blood EDTA patient samples in a hospital laboratory and capillary samples from 86 patients in two primary health care centres.	ichroma™	Cobas Integra	Capillary and Venous	SKUP

Author (Year)	Study Type & Country	Test setting(s) and operator(s)	Sample source(s) (n)	Population / Inclusion criteria	POCT device	Comparator device	Blood sample type(s)	Funding source
Verbakel (2014) [225]	Belgium -AP	GP carried out the test in primary care	Primary care (n=35 adults)	(Adults aged 18-65 years attending a general practice sugery.	Afinion™	Cobas c702	Capillary	Fund for Scientific Research (FWO) devices were provided by the manufacturer

Appendix S Risk of bias and quality in systematic review of analytical performance

Figure S.1 QUADAS 2 – Risk of Bias for Analytical Performance

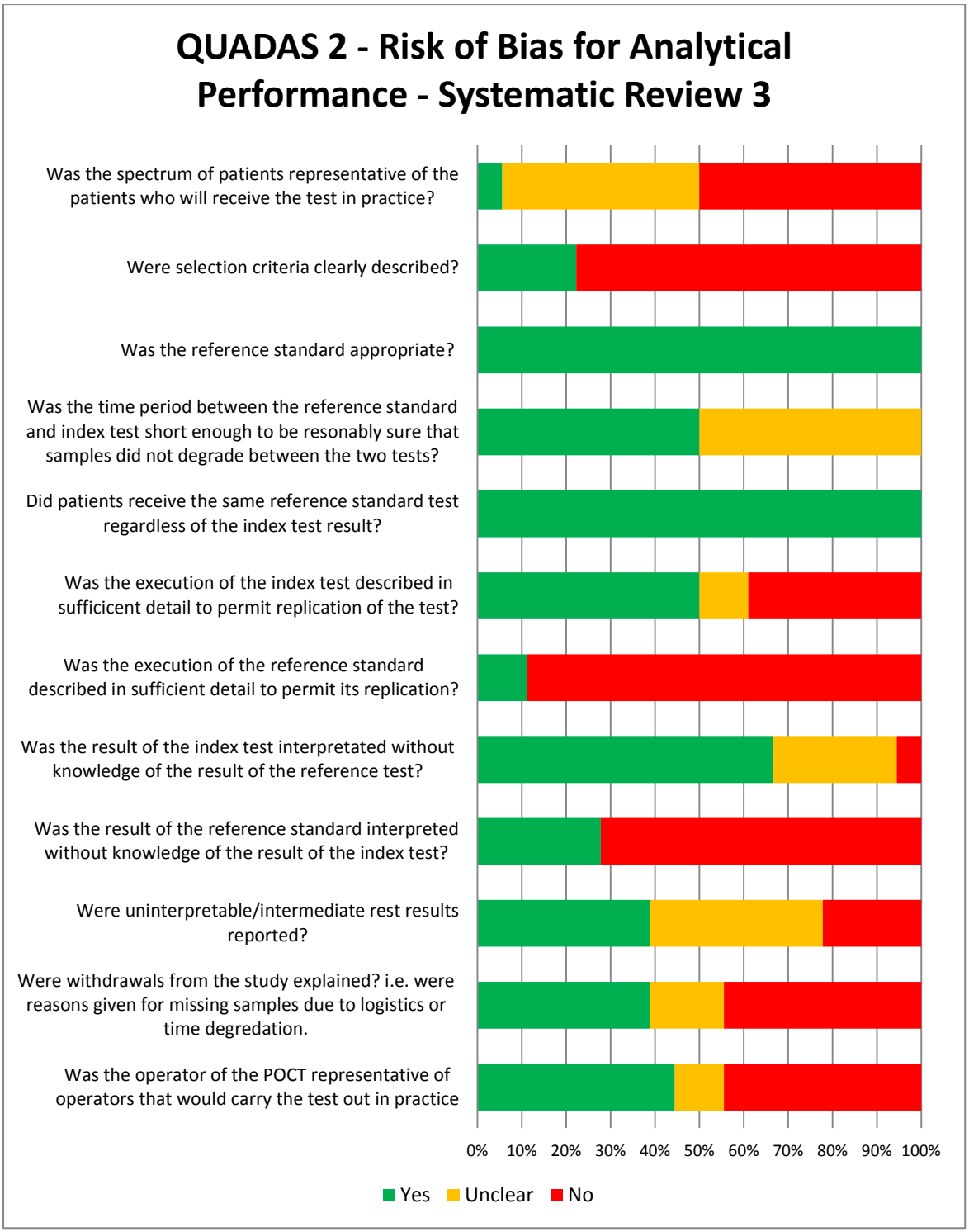


Table S.1 Risk of bias of included studies in systematic review 3 (analytical performance)

Author	Was the spectrum of patients' representative of the patients who will receive the test in practice?	Were selection criteria clearly described?	Is the reference standard appropriate?	Is the time period between reference standard and index suitable to ensure the sample did not degrade?	Did patients receive the same reference standard regardless of the index test result?	Was the execution of the index test described in sufficient detail to permit replication of the test?	Was the execution of the reference standard described in sufficient detail to permit its replication?	Were the index rest results interpreted without knowledge of the results of the reference	Were the reference standard results interpreted without knowledge of the results of the index test?	Were interpretable or intermediate test results reported?	Were withdrawals from the study explained?	Was the operator of the POCT representative of operator in practice?
Bains	●	●	●	●	●	●	●	●	●	●	●	●
Brouwer	●	●	●	●	●	●	●	●	●	●	●	●
Bukve	●	●	●	●	●	●	●	●	●	●	●	●
Ciftci	●	●	●	●	●	●	●	●	●	●	●	●
Clouth	●	●	●	●	●	●	●	●	●	●	●	●
De Graaf	●	●	●	●	●	●	●	●	●	●	●	●
Evrard	●	●	●	●	●	●	●	●	●	●	●	●
Ivaska	●	●	●	●	●	●	●	●	●	●	●	●
Matheeussen	●	●	●	●	●	●	●	●	●	●	●	●
Minnaard	●	●	●	●	●	●	●	●	●	●	●	●
Monteny	●	●	●	●	●	●	●	●	●	●	●	●
Nomura	●	●	●	●	●	●	●	●	●	●	●	●
Seamark	●	●	●	●	●	●	●	●	●	●	●	●
SKUP Smart Eurolyser	●	●	●	●	●	●	●	●	●	●	●	●
SKUP ichroma™	●	●	●	●	●	●	●	●	●	●	●	●
SKUP ABX Micros™	●	●	●	●	●	●	●	●	●	●	●	●
SKUP QuikRead® 101	●	●	●	●	●	●	●	●	●	●	●	●
Verbakel	●	●	●	●	●	●	●	●	●	●	●	●

●Low Risk ●High Risk ●Unclear Risk

* Two-part study involving initial testing of samples in laboratory and then at the point of care.

Table S.2 Summary of findings table of the analytical performance of CRP POCT compared with laboratory CRP testing for RTIs in primary care

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Accuracy	There was no systematic methodology for assessing accuracy and there was heterogeneity between studies in regard to the setting and operator of the device. Two studies assessed accuracy of semi quantitative devices; 17 studies assessed quantitative devices. The agreement with the reference standard for the semi quantitative devices ranged from 0.53 to 0.93, this deteriorated if the test was read after the optimal 5 minutes. There was also evidence or inter-observer disagreement. The accuracy of most quantitative devices was acceptable under idealised laboratory conditions, but was poorer when used at the point of care. The accuracy of the devices tended to be poorer at high CRP concentrations (> 100 mg/L), but this may not be clinically relevant.	(18 observational studies)	⊕◯◯◯ VERY LOW [a,b,c]
Precision	There was no systematic methodology for assessing precision. The acceptable level of imprecision was defined as a coefficient of variation less than 10%. The precision results were presented as within-day and between-day variation in the laboratory and primary care settings. Most devices reported acceptable precision in the laboratory setting (Smart Eurolyser, NycoCard Reader II & iChroma exhibited unacceptable precision [>10%] in at least one study). Only five studies had precision data measured at the point of care. Generally precision was comparable or poorer at the point of care.	(10 observational studies)	⊕◯◯◯ VERY LOW [a,b,c]
Ease of Use	There was no systematic methodology for assessing ease of use. The results were reported from laboratory and healthcare personnel. A survey or Likert scale was used or general statements were provided by participants. The overall time taken for the test was a major factor, but it was unclear from the studies what was considered an acceptable time period in the primary care setting. The Afinion and Smart Eurolyser were noted for their user friendliness.	(8 observational studies)	⊕◯◯◯ VERY LOW [a,c,d]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Using QUADAS 2, there was a risk of bias in a number of domains
b. The evidence for analytical performance was not consistent between studies; this may have been due to the operator or the setting in which the device was used
c. Some of the evidence is provided by studies in the laboratory setting with trained technicians as operators. These studies do not reflect the setting or operators that would use these devices in practice
d. For some devices there were inconsistent reports regarding their ease of use

Appendix T Systematic review of cost-effectiveness studies: search terms

MEDLINE (PubMed)

#1	"Respiratory tract infections"[mesh]
#2	((respiratory*[tiab]) AND (inflam*[tiab] OR infect*[tiab]))
#3	(ari[tiab] OR urti[tiab] OR lrti[tiab])
#4	(pneumon*[tiab] OR bronchopneumon*[tiab] OR pleuropneumon*[tiab])
#5	"otitis media"[mesh]
#6	(otitis media[tiab] OR "aom"[tiab])
#7	(bronchit*[tiab] OR bronchiolit*[tiab])
#8	(pharyngit*[tiab] OR laryngit*[tiab] OR tonsillit*[tiab] OR sore throat*[tiab] OR cough*[tiab])
#9	(nasopharyngit*[tiab] OR rhinopharyngit*[tiab])
#10	(sinusit*[tiab] OR rhinosinusit*[tiab] OR nasosinusit*[tiab])
#11	(common cold*[tiab] OR "coryza"[tiab])
#12	((acute[tiab] OR viral[tiab] OR bacter*[tiab]) AND (rhinit*[tiab]))
#13	(influenza*[tiab] OR flu[tiab] OR ili[tiab])
#14	(severe acute respiratory syndrome[tiab] OR sars[tiab])
#15	croup[tiab]
#16	"Pulmonary Disease, Chronic Obstructive"[mesh:noexp]
#17	((acute[tiab] OR exacerbation*[tiab]) AND (copd[tiab] OR coad[tiab] OR chronic obstructive pulmonary disease[tiab] OR chronic obstructive airway* disease[tiab] OR chronic obstructive lung disease[tiab]))
#18	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#19	"Point-of-Care Systems"[mesh:noexp]
#20	((point of care[tiab] OR point-of-care[tiab] OR near patient[tiab] OR poc[tiab] OR rapid[tiab] OR bedside[tiab]) AND (test*[tiab] OR analys*[tiab] OR immunoassay*[tiab] OR technique*[tiab] OR immunofluorescence[tiab] OR fluorescent antibody[tiab]))
#21	"c-reactive protein"[mesh:noexp]
#22	((c reactive protein[tiab] OR c reactive protein[nm]) OR (c-reactive protein[tiab] OR c-reactive protein[nm]) OR (C-reactive protein"[tiab] OR C-reactive protein"[nm]))
#23	#19 OR #20 OR #21 OR #22
#24	#18 AND #23
#25	"Anti-Bacterial Agents"[mesh]
#26	antibiotic*[tiab]
#27	"Penicillins"[mesh]
#28	penicillin*[tiab]
#29	"Macrolides"[mesh]
#30	(macrolide*[tiab] OR macrolide*[nm])
#31	"Amoxicillin"[mesh]
#32	((amoxIcillin*[tiab] OR amoxycillin*[nm]) OR (amoxycillin*[tiab] OR amoxycillin*[nm]))
#33	(amoxacillin*[tiab] OR amoxacillin*[nm])
#34	"Tetracyclines"[mesh]
#35	(tetracycline*[tiab] OR tetracycline*[nm])

#36	"Quinolones"[mesh]
#37	(quinolone*[tiab] OR quinolone*[nm])
#38	(ciprofloxacin*[tiab] OR ciprofloxacin*[nm])
#39	"Ciprofloxacin"[mesh]
#40	#25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39
#41	#24 AND #40
#42	((((((((((((((((((models, economic[mesh]) OR "economics, pharmaceutical"[mesh]) OR "economics, medical"[mesh]) OR "health care costs"[mesh]) OR "decision support techniques"[mesh]) OR "cost-benefit analysis"[mesh]) OR "Cost of illness"[mesh]) OR "cost savings"[mesh]) OR "Hospital costs"[mesh]) OR "economic"[ti]) OR ("costs and cost analysis"[mesh])) OR economic evaluation*[ti]) OR economic analy*[ti]) OR cost analy*[ti]) OR cost eff*[ti]) OR cost benefit*[ti]) OR cost utilit*[ti]) OR ("economics"[mesh])) OR cost*[ti/ab])
#43	#41 AND #42
#44	(((letter[Publication Type]) OR editorial[Publication type]) OR historical article[Publication Type]) OR animals
#45	#43 NOT #44

EMBASE

#1	respiratory tract infection'/exp
#2	respiratory tract inflammation'/exp
#3	(respiratory NEAR/2 (infect* OR inflam*)):ab,ti
#4	ari:ab,ti OR urti:ab,ti OR lrti:ab,ti
#5	pneumon*:ab,ti OR bronchopneumon*:ab,ti OR pleuropneumon*:ab,ti
#6	otitis media'/de OR 'acute otitis media'/exp
#7	otitis media':ab,ti OR aom:ab,ti
#8	bronchit*:ab,ti OR bronchiolit*:ab,ti
#9	phary AND ngit*:ab,ti OR laryngit*:ab,ti OR tonsillit*:ab,ti OR 'sore throat':ab,ti OR 'sore throats':ab,ti OR cough
#10	sore throat'/de
#11	nasopharyngit*:ab,ti OR rhinopharyngit*:ab,ti
#12	rhinosinusit*:ab,ti OR nasosinusit*:ab,ti
#13	common cold':ab,ti OR 'common colds':ab,ti OR coryza:ab,ti
#14	((acute OR viral OR bacter*) NEAR/2 rhinit*):ab,ti
#15	influenza*:ab,ti OR flu:ab,ti OR ili:ab,ti
#16	severe acute respiratory syndrome':ab,ti OR sars:ab,ti
#17	croup:ab,ti
#18	chronic obstructive lung disease'/de
#19	(((acute OR exacerbation*) NEAR/3 (copd OR coad OR 'chronic obstructive pulmonary disease' OR 'chronic obstructive airways disease' OR 'chronic obstructive lung disease')):ab,ti) OR aecb:ab,ti
#20	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#21	(('point of care' OR 'point-of-care' OR 'near patient' OR poc OR rapid OR bedside) NEAR/5 (test* OR analys* OR immunoassay* OR technique* OR immunofluores* OR 'fluorescent antibody' OR 'florescent antibodies')):ab,ti

#22	c reactive protein'/de
#23	('c reactive protein':ab,ti OR 'c-reactive protein':ab,ti OR 'c reactive') AND protein:ab,ti
#24	#21 OR #22 OR #23
#25	antibiotic agent'/exp
#26	antibiotic*:ab,ti
#27	quinolone derivative'/exp OR 'ciprofloxacin'
#28	penicillin*:ab,ti OR macrolide*:ab,ti OR amoxicillin*:ab,ti OR amoxycillin*:ab,ti OR tetracycline*:ab,ti OR quinolone*:ab,ti OR ciprofloxacin*:ab,ti
#29	#25 OR #26 OR #27 OR #28
#30	#20 AND #24 AND #29
#31	(models, AND economic OR 'economics'/exp OR 'economics, pharmaceutical'/exp OR 'economics, medical'/exp OR 'health care costs'/exp OR 'decision support techniques'/exp OR 'cost benefit analysis'/exp OR 'cost of illness'/exp OR 'cost savings'/exp OR 'hospital costs'/exp OR 'economic':ab,ti OR 'costs and cost analysis'/exp OR cost*:ab,ti OR (economic AND evaluation*:ab,ti) OR (economic AND analy*:ab,ti) OR (cost AND analy*:ab,ti) OR (cost AND eff*:ab,ti) OR (cost AND benefit*:ab,ti) OR (cost AND utilit*:ab,ti))
#32	#30 AND #31
#33	animal'/de OR 'animal experiment'/de OR 'nonhuman'/de OR 'editorial'/de OR 'letter'/de
#34	'human'/de
#35	#33 AND #34
#36	#33 NOT #35
#37	#32 NOT #36

EBSCOhost (Academic Search, CINAHL, EconLit)

S1	(MH "Respiratory Tract Infections+")
S2	TI (respiratory N3 (inflam* or infect*)) OR AB (respiratory N3 (inflam* or infect*))
S3	TI (ari OR arti OR urti OR lrti) OR AB (ari OR arti OR urti OR lrti)
S4	TI (pneumon* or bronchopneumon* or pleuropneumon*) OR AB (pneumon* or bronchopneumon* or pleuropneumon)
S5	TI (bronchit* or bronchiolit*) OR AB (bronchit* or bronchiolit*)
S6	(MH "Otitis Media+")
S7	TI (otitis media or aom) OR AB (otitis media or aom)
S8	TI (pharyngit* or laryngit* or tonsillit* or sore throat* or cough*) OR AB (pharyngit* or laryngit* or tonsillit* or sore throat* or cough*)
S9	TI (nasopharyngit* or rhinopharyngit*) OR AB (nasopharyngit* or rhinopharyngit*)
S10	TI (sinusit* or rhinosinusit* or nasosinusit*) OR AB (sinusit* or rhinosinusit* or nasosinusit*)
S11	TI (common cold* or coryza) OR AB (common cold* or coryza)
S12	TI ((acute or viral or bacter*) N2 rhinit*) OR AB ((acute or viral or bacter*) N2 rhinit*)
S13	TI (influenza* or flu or ili) OR AB (influenza* or flu or ili)
S14	TI (severe acute respiratory syndrome or sars) OR AB (severe acute respiratory syndrome or sars)
S15	TI croup OR AB croup
S16	(MH "Pulmonary Disease, Chronic Obstructive+")
S17	TI ((acute or exacerbation) N3 (copd or coad or chronic obstructive pulmonary disease or

	chronic obstructive airway* disease or chronic obstructive lung disease)) OR AB ((acute or exacerbation) N3 (copd or coad or chronic obstructive pulmonary disease or chronic obstructive airway* disease or chronic obstructive lung disease))
S18	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17
S19	(MH "Point-of-Care Testing")
S20	TI (("point of care" or point-of-care or poc or "near patient" or rapid or bedside*) N5 (test* or analys* or immunoass* or technique*or immunofluores* or "fluorescent antibody")) OR AB (("point of care" or point-of-care or poc or "near patient" or rapid or bedside*) N5 (test* or analys* or immunoass* or technique* or immunofluores* or "fluorescent antibody"))
S21	(MH "C-Reactive Protein")
S22	TI ("c reactive protein" or c-reactive protein or C-reactive protein) OR AB ("c reactive protein" or c-reactive protein or C-reactive protein)
S23	S19 or S20 or S21 or S22
S24	(MH "Antibiotics+")
S25	TI antibiotic* OR AB antibiotic*
S26	(MH "Antiinfective Agents, Quinolone+")
S27	TI (penicillin* or macrolide* or amoxicillin* or amoxycillin* or amoxacillin* or tetracyclin* or quinolon* or ciprofloxacin*) OR AB (penicillin* or macrolide* or amoxicillin* or amoxycillin* or amoxacillin* or tetracyclin* or quinolon* or ciprofloxacin*)
S28	S24 or S25 OR S26 OR S27
S29	S18 AND S23 AND S28
S30	SU Models, Economic
S31	SU Economics
S32	SU Economics, Pharmaceutical
S33	SU Economics, Medical
S34	SU Health Care Costs
S35	SU Decision Support Techniques
S36	SU Cost-Benefit Analysis
S37	SU Cost of Illness
S38	SU Cost Savings
S39	SU Hospital Costs
S40	TI economic OR AB economic
S41	SU Costs and Cost Analysis
S42	TI cost* OR AB cost*
S43	TI economic evaluation* OR AB economic evaluation*
S44	TI economic analy* OR AB economic analy*
S45	TI cost analy* OR AB cost analy*
S46	TI cost eff* OR AB cost eff*
S47	TI cost benefit* OR AB cost benefit*
S48	TI cost utilit* OR AB cost utilit*
S49	S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 or S47 OR S48
S50	S18 AND S23 AND S28

S51	S49 AND S50

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#1	(respiratory* near/3 (inflam* or infect*))
#2	Respiratory Tract Infections
#3	(ari or urti or lrti)
#4	(pneumon* or bronchopneumon* or pleuropneumon*)
#5	Otitis media
#6	(otitis media or aom)
#7	(bronchit* or bronchiolit*)
#8	(pharyngit* or laryngit* or tonsillit* or sore throat* or cough*)
#9	(nasopharyngit* or rhinopharyngit*)
#10	(sinusit* or rhinosinusit* or nasosinusit*)
#11	(common cold* or coryza)
#12	((acute or viral or bacter*) near/2 rhinit*)
#13	(influenza* or flu or ili)
#14	(severe acute respiratory syndrome or sars)
#15	15 croup
#16	Chronic Obstructive Pulmonary disease
#17	((acute or exacerbation*) near/3 (copd or coad or chronic obstructive pulmonary disease or chronic obstructive airway* disease or chronic obstructive lung disease))
#18	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17)
#19	Point-of-Care Systems
#20	(("point of care" or "point-of-care" or "near patient" or poc or rapid or bedside) near/5 (test* or analys* or immunoassay* or technique*or immunofluorescence or "fluorescent antibody"))
#21	C-Reactive Protein
#22	(c reactive protein or c-reactive protein or C-reactive protein)
#23	(#19 or #20 or #21 or #22)
#24	Anti-Bacterial Agents
#25	antibiotic*
#26	Penicillins
#27	penicillin*
#28	Macrolides
#29	macrolide*
#30	Amoxicillin
#31	(amoxicillin* or amoxycillin*)
#32	amoxacillin*
#33	Tetracyclines
#34	tetracycline*
#35	Quinolones
#36	quinolone*
#37	ciprofloxacin*
#38	ciprofloxacin
#39	(#24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or

	#36 or #37 or #38)
#40	(#18 and #23 and #39)
#41	MeSH descriptor: [Models, Economic] explode all trees
#42	MeSH descriptor: [Economics] explode all trees
#43	MeSH descriptor: [Economics, Pharmaceutical] explode all trees
#44	MeSH descriptor: [Economics, Medical] explode all trees
#45	MeSH descriptor: [Health Care Costs] explode all trees
#46	MeSH descriptor: [Decision Support Techniques] explode all trees
#47	MeSH descriptor: [Cost-Benefit Analysis] explode all trees
#48	MeSH descriptor: [Cost of Illness] explode all trees
#49	MeSH descriptor: [Cost Savings] explode all trees
#50	MeSH descriptor: [Hospital Costs] explode all trees
#51	economic:ti,ab,kw (Word variations have been searched)
#52	MeSH descriptor: [Costs and Cost Analysis] explode all trees
#53	cost*:ti,ab,kw (Word variations have been searched)
#54	economic evaluation*:ti,ab,kw (Word variations have been searched)
#55	economic analy*:ti,ab,kw (Word variations have been searched)
#56	cost analy*:ti,ab,kw (Word variations have been searched)
#57	cost eff*:ti,ab,kw (Word variations have been searched)
#58	cost benefit*:ti,ab,kw (Word variations have been searched)
#59	cost utilit*:ti,ab,kw (Word variations have been searched)
#60	(#41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59)
#61	(#40 and #60)

The following electronic sources were also searched for economic evaluations relevant to the research questions of this systematic review:

- Centre for Health Economics and Policy Analysis (CHEPA) http://www.chepa.org/
- Cost Effectiveness Analysis Registry http://healtheconomics.tuftsmedicalcenter.org/cear4/SearchingtheCEARegistry/SearchtheCEARegistry.aspx
- HTAi vortal https://www.htai.org/index.php?id=579
- Google Scholar and Google https://scholar.google.com/, https://www.google.ie
- Health Service Executive (HSE) https://www.hse.ie/eng/
- Health Information and Quality Authority (HIQA) https://www.hiqa.ie/
- Health Research Board (HRB) Ireland http://www.hrb.ie/home/

- Institute of Health Economics (Alberta Canada) https://www.ihe.ca/
- Lenus
  http://www.lenus.ie/hse/
- National Centre for Pharmacoeconomics (NCPE) http://www.ncpe.ie/
- National Coordinating Centre for Health Technology Assessment (NCCHTA)
  https://www.nihr.ac.uk/funding-and-support/funding-for-research-studies/funding-programmes/health-technology-assessment/
- National Institute for Health and Clinical Excellence (NICE)
  https://www.nice.org.uk/
- NHS Evidence database (UK)
  https://www.evidence.nhs.uk/
- Open Grey
  http://www.opengrey.eu/
- World Health Organization (WHO)
  http://www.who.int/en/

Appendix U Details of included studies in systematic review of cost-effectiveness

Authors (year); country	Population & Interventions	Analysis details	Costs	Clinical outcomes	Methods for dealing with uncertainty	Results
Cals et al. (2011); Netherlands	**Population:** Adults aged 18+ with acute cough/assumed LRTI **Intervention:** (1) GP plus CRP; (2) GP communication training; (3) GP plus CRP + GP communication training **Comparator:** Usual care (clinical judgment)	**Analysis type:** Alongside CEA (cost per percentage reduction in prescribing) **Perspective:** Health system **Time horizon:** 28 days **Discount rate:** N/A	**Currency & year:** Euro (€); 2004 prices **Cost components:** Direct health care costs and intervention costs (CRP and communication skills training)	Antibiotic prescribing at index consultation	The authors undertook scenario, rather than sensitivity analyses. Although proclaimed as a sensitivity analysis, the authors doubled staff costs in a scenario to reflect the budget impact of wider implementation; the authors conducted scenario analyses to look at varying degrees of adoption by GPs. No parameter sensitivity analysis undertaken; results were generated using bootstrapping.	Versus usual care (antibiotic prescribing: 68%), GP CRP: antibiotic prescribing 39%, ICER €5.79; communication skills: antibiotic prescribing 33%, dominant; GP CRP + communication skills: antibiotic prescribing 23%, ICER €4.15.

Authors (year); country	Population & Interventions	Analysis details	Costs	Clinical outcomes	Methods for dealing with uncertainty	Results
Oppong et al. (2013); Norway and Sweden	**Population:** Adults aged 18+ with acute cough/assumed LRTI **Intervention:** GP plus CRP POCT **Comparator:** No CRP point-of-care-test (clinical judgment)	**Analysis type:** Alongside CUA (cost per QALY) and CEA (cost per prescription avoided) to an observational study **Perspective:** Health system **Time horizon:** 28 days **Discount rate:** N/A	**Currency & year:** Euro (€); 2007 prices **Cost components:** Direct staff/service costs (e.g., GP/nurse visits, hospital admission) and medical investigation costs (e.g., CRP, X-ray, sputum culture, spirometry)	QALYs (EQ-5D); patient outcomes; and number of antibiotic prescribing	No sensitivity/scenario analyses were undertaken.	CRP POCT was associated with non-significant positive reductions in antibiotic prescribing (p = 0.078) and increased cost (p = 0.092). Despite the uncertainty, the authors reported CRP POCT was associated with a cost per QALY gain of €9,391. At €30,000 WTP, CRP POCT had a NMB of €25.20 and 70% probability of being cost-effective.

Authors (year); country	Population & Interventions	Analysis details	Costs	Clinical outcomes	Methods for dealing with uncertainty	Results
NICE (2014); UK	**Population:** Adults aged 18+ with LRTI **Intervention:** GP plus CRP POCT **Comparator:** Usual care (clinical judgment)	**Analysis type:** Crude CUA (cost per QALY) **Perspective:** Health system **Time horizon:** 28 days **Discount rate:** N/A	**Currency & year:** Sterling (£); 2012 prices **Cost components:** Direct staff/service costs (e.g., antibiotics, intervention costs, GP reconsultations, hospital admission)	QALYs (EQ-5D), derived from Oppong et al. (2013)	No sensitivity/scenario analyses were undertaken.	CRP POCT was associated with an ICER of £15,763 per QALY gained. The guideline concluded the strategy was likely cost-effective, but acknowledged large-scale implementation would be expensive and may outweigh the benefits of reduced antibiotic prescribing. On the basis of these findings, CRP POCT should be 'considered' rather than exclusively 'offered'.

Authors (year); country	Population & Interventions	Analysis details	Costs	Clinical outcomes	Methods for dealing with uncertainty	Results
Hunter (2015); UK	**Population:** Hypothetical cohort of 100 patients (aged 50, 62% female) with assumed RTI **Intervention:** (1) GP plus CRP; (2) nurse plus CRP; (3) GP plus CRP + communication training **Comparator:** Usual care (clinical judgment)	**Analysis type:** Decision model (NMB using QALYs) **Perspective:** Health system **Time horizon:** 3 years **Discount rate:** 3.5%	**Currency & year:** Sterling (£); 2013/14 prices **Cost components:** Direct health care costs and intervention (CRP and communication skills training), and hospital admissions	QALYs (EQ-5D), derived from Oppong et al. (2013); number of antibiotics prescribed; and number of RTIs over 3 years	Parameter and structural sensitivity analysis undertaken using PSA (for parameter uncertainty) and extended time horizon (for structural sensitivity analysis). One way sensitivity analysis undertaken for key parameters.	Versus usual care, GP plus CRP and practice nurse plus CRP strategies had highest NMB due to higher QALY gains and lower costs; GP plus CRP testing and communication training strategy had lowest NMB due to higher costs and lower QALY gains.

Authors (year); country	Population & Interventions	Analysis details	Costs	Clinical outcomes	Methods for dealing with uncertainty	Results
Oppong et al. (2018); Europe (Belgium, Netherlands, Poland, Spain, UK)	**Population:** Patients with assumed RTI (age not specified) **Intervention:** (1) GP CRP; (2) GP communication training; (3) GP CRP + GP communication training **Comparator:** Usual care (clinical judgment)	**Analysis type:** Alongside CUA (cost per QALY) and CEA (cost per percentage reduction in antibiotic prescribing) to a multinational, cluster, randomised, factorial controlled trial **Perspective:** Health system **Time horizon:** 28 days **Discount rate:** N/A	**Currency & year:** Euro (€); 2016 prices **Cost components:** Direct staff/service costs (e.g., primary and secondary care visits, hospital admission) and medical investigation costs (e.g., CRP, antibiotics, resistance)	QALYs (EQ-5D); patients outcomes; and percentage reduction in antibiotic prescribing	Two sensitivity analyses were undertaken: the first considered the cost-effectiveness of the different strategies in each country using country-specific cost-effectiveness thresholds (where applicable); the second excluded the cost of antibiotic resistance to assess the impact of this parameter on cost-effectiveness findings.	Overall, the results of both the CUA and CEA showed that training in communication skills is the most cost-effective option. Excluding the cost of antibiotic resistance in the CUA resulted in usual care being the most cost-effective overall. Country-specific results from the CUA showed that training in communication skills was cost-effective in Belgium, UK and Netherlands whilst training in CRP was cost-effective in Poland.

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