Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Report on the results of the public consultation on the health technology assessment of use of an enhanced inactivated influenza vaccine for those aged 65 years and older in the HSE Seasonal Influenza Vaccination Programme

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About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is an independent statutory body 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.

Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, 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 Chief Inspector of Social Services 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 permanent international protection accommodation service centres, health services and children's social services against the national standards. Where necessary, HIQA investigates serious concerns about the health and welfare of people who use health services and children's social 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 and social care services, with the Department of Health and the HSE.

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Introduction

Following a request from the Department of Health, the Health Information and Quality Authority (HIQA) agreed to undertake a health technology assessment (HTA) in relation to whether enhanced inactivated influenza vaccines (IIVs) should be funded for adults aged 65 years and older as part of the Health Service Executive (HSE) Seasonal Influenza Vaccination Programme. The aim of the HTA was to estimate the burden of disease associated with influenza and to assess the clinical effectiveness, cost effectiveness, budget impact, as well as the ethical, patient, social and organisational implications associated with changing the HSE Seasonal Influenza Vaccination Programme to include use of an enhanced IIV (instead of a standard IIV) for those aged 65 years and older.

The draft HTA report was published for public consultation in May 2024. This Summary of Outcomes report summarises the feedback received during the public consultation period and outlines HIQA's responses to the issues raised, including any changes that were made to the report as a result.

Methods

The aim of the public consultation was to seek feedback to identify any issues with the draft HTA report, to consider that feedback and to amend the report, as necessary.

The consultation process

The draft HTA was published on the HIQA website on 30 May 2024 and was available for public consultation until 11 July 2024. The consultation webpage contained a link to the draft technical report, a Plain Language Summary of the report, a link to the online survey (using the Qualtrics platform) for online submission of feedback, and a consultation feedback form that could be downloaded and returned via email or post. To ensure wide dissemination, a press release was issued at the beginning of the consultation period, and the findings of the draft HTA were reported in the media. E-mail requests for feedback were sent to a targeted list of stakeholder organisations with relevant expertise and those who are likely to be affected by the proposed change to the HSE Seasonal Influenza Vaccination Programme. Additionally, notifications of the public consultation were posted via social media sites (Twitter, Facebook, Instagram and LinkedIn).

Feedback form

The template for submission comprised a general request for feedback to enable respondents to flexibly provide their submission for any aspects of the report. A copy of the submission template is provided in Appendix A.

Synthesis

Each submission was recorded (excluding personal information), read in its entirety and, where appropriate, broken down into individual components. In cases where a question was skipped by the respondent, it was assumed that there were no issues of concern specific to that question.

The submissions were stratified according to whether they were from members of the general public or stakeholder organisations. Feedback considered broad in nature was described narratively. Verbatim personal responses and commentaries are summarised (Table 1). Feedback relating to specific content in the draft report is presented in tabular format alongside direct responses to the feedback (Table 2). To enhance readability and interpretation, specific comments pertaining to the content of the report were categorised under the following headings:

- epidemiology and burden of disease
- vaccine effectiveness and safety
- rapid review of economic modelling studies
- economic evaluation
- organisational issues
- ethical, patient and social considerations.

Where amendments were made to the report based on feedback, these are highlighted in the HIQA response.

Results

Overall, 18 unique and complete submissions were received during the public consultation period. In addition, 33 incomplete and 14 blank survey responses were received. As the incomplete responses contained no feedback, they have been excluded from the summary below. Of the 18 complete submissions, 10 were submitted via the online survey and eight were received by email. Seven of the 18 submissions were received from individual members of the general public, eight were submitted on behalf of stakeholder organisations or institutions and three were

submitted by a group of scientific and or health professionals acting in a personal capacity.

Summary of feedback

Members of the general public

Seven responses were received from members of the general public; each of these responses were from people in Ireland.

No respondent shared personal experiences with influenza-associated illness or disease. One respondent conveyed satisfaction with their personal experience of receiving the seasonal influenza vaccine, noting that they "would like to be protected to the best possible extent". The verbatim of responses is presented in Table 1.

Four respondents felt the information within the report was well explained or presented clearly. One respondent noted that the full report was too much to absorb, for reasons relating to its length and technical content. One respondent commented that the draft HTA report placed an emphasis on the costs relating to influenza vaccination, without "inclusion of good health or quality care". This point was not expanded on by the respondent. None of the respondents from the general public expressed disagreement towards the findings or conclusions of the HTA.

Table 1 Verbatim of personal experiences with influenza vaccination and commentary*

Number	Comment
Personal experiences	
1	My wife and I have been pleased and satisfied to be included in the annual flu injection process. This has been administered by either our local GP or pharmacy. We would like to be protected to the best possible extent.
Commentary	
1	I like the idea of an advanced vaccine for over 65s. It would be good for the individual and also the health service.
2	I find the proposal sensible and probably timely.
3	Thought the information was presented clearly.
4	Overall I think the article emphasises costs with no inclusion of good health or quality care.
5	The difference needs to be clear.
6	I regret that the full report of more than 300 pages was too much for us to absorb, both for reasons of the length of the reading and its technical content.

*Responses have been slightly amended to correct for minor grammatical errors and or typos.

Stakeholder organisations or institutions

Eight responses were received on behalf of the following stakeholder organisations or institutions:

- Department of Public Health HSE Dublin and Midlands
- Irish Pharmacy Union
- HSE National Immunisation Office
- National Network Of Older People's Councils – Age Friendly Ireland
- Nursing Homes Ireland
- CSL Seqirus – manufacturer of an adjuvanted quadrivalent influenza vaccine (Fluad Tetra®) and a cell-based quadrivalent influenza vaccine (Flucelvax Tetra®)
- Sanofi – manufacturer of a high-dose quadrivalent influenza vaccine (Efluelda®), a recombinant haemagglutinin (HA) quadrivalent influenza vaccine (Supemtek®), and a standard quadrivalent influenza vaccine (Quadrivalent Influenza Vaccine)

- Viatris – manufacturer of a standard quadrivalent influenza vaccine (Influvac tetra®).

Details of the feedback from these organisations and institutions, in addition to actions taken to address this feedback, where appropriate, are provided in Table 2. The feedback and corresponding responses are displayed by chapter.

The Department of Public Health HSE Dublin and Midlands provided feedback and perspectives based on their expertise and public health experience within the Dublin/Midlands region. They noted a lack of clarity from the HTA with respect to the impact that switching to enhanced influenza vaccines may have on vaccination uptake rates, noting also that adjuvanted influenza vaccines were offered to adults aged 65 years and older as part of the HSE Seasonal Influenza Vaccination Programme, in 2021-2022. They requested additional information relating to the expected adverse events associated with the enhanced influenza vaccines, such as from post-marketing surveillance studies. Thirdly, they highlighted the vulnerability of high-risk populations living in close quarters such as those in residential care facilities, as well as the potential benefit these populations may gain from enhanced influenza vaccines. Fourthly, the potential for vaccine administration errors was commented on, with reference to the National Immunisation Office's report on vaccine errors during the 2021-2022 influenza season.

The Irish Pharmacy Union commented in support of the use of an enhanced influenza vaccine for those aged 65 years and older in the HSE Seasonal Influenza Vaccination Programme. They described the contribution of community pharmacists throughout Ireland following the amendment of regulations in 2011 to enable registered pharmacists to supply and administer selected vaccines. They also commented with respect to pharmacists' experience of the negative impact of influenza and influenza-related complications on the lives of individuals. They noted that an adjuvanted influenza vaccine was previously offered as part of the HSE Seasonal Influenza Vaccination Programme during the 2021-2022 influenza season, and that the provision of this vaccine type was easily facilitated by pharmacists.

The National Immunisation Office provided feedback relating to Chapters 6, 7 and 8 that largely consisted of advice or clarification with respect to phrasing used in these chapters.

The National Network of Older People's Councils – Age Friendly Ireland expressed that, in general, the introduction of an enhanced vaccination programme for older adults in Ireland is viewed positively by members of the National Network of Older People's Councils. They highlighted the importance of addressing levels of disinformation that exist regarding vaccination, but expressed that personal choice is

important and older people should continue to have the option of receiving the standard vaccine if that is their preference. They expressed a desire for greater information relating to the adverse reactions associated with enhanced vaccines, in particular with respect to the Plain Language Summary. They shared that older people would like to be able to access a helpline or free phone support services in the event of experiencing adverse reactions to influenza vaccination, given the current demands and wait for GP appointments.

Nursing Homes Ireland expressed agreement with the conclusions made in the HTA indicating that an adjuvanted influenza vaccine for people aged 65 years and older would provide benefits in terms of a reduction in illness burden on the health and social care system. They expressed that older people would need to be provided with additional information about the potential side effects of vaccination from enhanced vaccines.

CSL Seqirus (who manufacture an adjuvanted quadrivalent influenza vaccine (Fluad Tetra®) and a cell-based quadrivalent influenza vaccine (Flucelvax Tetra®)) provided feedback that largely related to Chapters 4 and 6 of the HTA. This feedback included the provision of a list of studies relating to evidence supporting the use of adjuvanted influenza vaccines, including studies relating to both clinical and economic evidence. Responses to this feedback are provided in Table 2. Additionally, CSL Seqirus provided clarity with respect to cell-based influenza vaccines, highlighting that CSL Seqirus does not advocate for their use in the over-65-years age category.

Sanofi (who manufacture a high-dose quadrivalent influenza vaccine (Efluelda®), a recombinant HA quadrivalent influenza vaccine (Supemtek®), and a standard quadrivalent influenza vaccine (Quadrivalent Influenza Vaccine)) provided feedback that largely related to Chapters 4, 5, and 6 of the HTA. Detailed responses to this feedback are provided in Table 2. In summary, the first major comment from Sanofi related to concerns regarding the degree to which the HTA had highlighted the uncertainty surrounding the effectiveness estimate for adjuvanted influenza vaccines for the outcome of hospitalisation due to laboratory-confirmed influenza. This estimate was reported in Chapter 4 and informed the economic evaluation conducted in Chapter 6. The second major comment related to evidence supporting the effectiveness of high-dose influenza vaccines in reducing influenza-related hospitalisations, to which end a list of studies was provided.

Viatris (who manufacture a standard quadrivalent influenza vaccine (Influvac tetra®)) provided feedback that referred to Chapter 6 of the HTA. Detailed responses to this feedback are provided in Table 2. In brief, the feedback queried the transferability of evidence relating to the adjuvanted influenza vaccine to

Ireland, with reference to several studies comparing immunogenicity data of adjuvanted and non-adjuvanted influenza vaccines. Secondly, the company recommended that a sensitivity analysis be undertaken that incorporated lower relative vaccine efficacy estimates for the high-dose influenza vaccines. Thirdly, the hospitalisation rates were queried and noted to be high. Fourthly, it was suggested that there should be further elaboration of the increased risk of adverse events with both adjuvanted and high-dose influenza vaccines compared with standard influenza vaccines.

Specific comments on report content

Table 2 Comments received on report content and responses*

Organisation	Comment	Response
	Epidemiology and burden of disease	
Department of Public Health HSE Dublin and Midlands	Vaccine Uptake and Enhanced Inactivated Influenza Vaccines (IIVs) It is not clear from the HTA whether a transition to enhanced inactivated influenza vaccines would be expected to affect overall vaccine uptake rates. The authors could consider examining evidence from other countries that have adopted enhanced influenza vaccines, to help clarify whether the introduction of enhanced influenza vaccines influences public acceptance and uptake.	Text has been added to Section 3.5.1 to highlight that an adjuvanted quadrivalent influenza vaccine was offered to adults aged 65 years and older for a single season (2021-2022) as part of the HSE Seasonal Influenza Vaccination Programme. Text was also added to the discussion of Chapter 3 outlining the difficulties in interpreting the impact of this change on uptake in Ireland given other contextual factors (COVID-19, differences in the completeness of these data, and that the change was limited to a single season). Chapter 2 included an international review of influenza vaccine policy across 31 countries which identified countries that provide enhanced influenza vaccines as part of their immunisation programme for those aged 65 years and older. In this context, additional text was added to the Chapter 3 discussion regarding influenza vaccination uptake in the UK where adjuvanted influenza vaccines have been offered as part of the immunisation programme since the 2018-2019 season without evidence of a negative impact on uptake.
	Vaccine effectiveness and safety	
National Network of Older People's Councils - Age Friendly Ireland	Plain Language Summary - would benefit from more detail on serious adverse events, as full report quite detailed. (Specifically with regard to Section 4.5.2 and Table 4.3).	The main report, by its nature, is technical and very detailed. However, a high-level review of the safety of the vaccines is provided in the Plain Language Summary with a more detailed outline of the key findings of each chapter provided in the Executive Summary. In this section, the main adverse reactions are described for the various vaccines. Further text has been added to the Plain Language Summary to emphasise the importance of providing clear information on both the benefits and risks of the enhanced flu vaccines.

Organisation	Comment	Response
		Individuals should be supported to make informed choices about vaccination. The report highlights that, in the event of a policy decision to change from standard to enhanced influenza vaccines, updated training material and patient materials will be required to support informed choices about vaccination (see Advice, Plain Language Summary, Executive Summary, Chapter 7 and Chapter 8).
The Department of Public Health Dublin and Midlands	The authors could consider providing additional information on the real-world expected adverse effects of enhanced influenza vaccines based on post-marketing surveillance, if available. In addition, the authors could consider if there is any evidence that increased non-serious adverse events might affect influenza vaccine uptake.	Text has been added to Section 4.6.3 relating to post-marketing safety surveillance data. As outlined in an earier response, text was also added to the discussion of Chapter 3 regarding the impact of a switching to an enhanced influenza vaccine on uptake.
CSL Seqirus	The HTA report states that adjuvanted influenza vaccines may or may not reduce laboratory-confirmed influenza infection. The real-world evidence of the adjuvanted influenza vaccines demonstrates the robustness of the platform to address immunosenescence, demonstrating effective protection against standard egg vaccines and even equivalence with high-dose influenza vaccines, while providing superior cost effectiveness. Additionally, it is noted that the HTA concludes that cell-based influenza vaccines do not significantly reduce laboratory-confirmed influenza infection or laboratory confirmed influenza-related hospitalisation. Whilst this HTA is exclusively focused on the over 65 age group, references are made to a mixed age range effectiveness against influenza infection and hospitalisation. CSL Seqirus does not advocate for usage of cell-based influenza vaccines in the over-65 age category, however would challenge these findings if they are considered to be referring to the 6 months – 64 year age category, where there is a significant body of evidence demonstrating efficacy and effectiveness against	This HTA was informed by a systematic review of the safety, efficacy and effectiveness of the newer and enhanced vaccines published by the ECDC in March 2024. This systematic review included relevant randomised controlled trials as well as non-randomised studies (including prospective and retrospective cohort studies, case-control studies and test-negative design studies) provided they had a control group, with the search current to 24 July 2023. As such, the systematic review includes relevant real-world evidence (that is, observational studies) of the comparative effectiveness of these vaccines. Moreover, it is noted that the 2024 review is limited to the effectiveness of these vaccines compared with a standard trivalent or quadrivalent influenza vaccine or compared with another enhanced influenza vaccine. As such, it does not consider evidence relative to placebo or no vaccination. The statement 'that adjuvanted influenza vaccines may or may not reduce laboratory confirmed influenza infection' is taken directly from the summary of findings table (Table 4.3) which was reproduced (with permission) from the ECDC report and refers specifically to the effectiveness of adjuvanted influenza vaccines compared with standard influenza vaccines in adults. This table is not specific to adults aged 65 years and older, but rather includes all

Organisation	Comment	Response
	laboratory-confirmed influenza and influenza-related hospitalisations.	studies for those aged 18 years and older. Minor updates have been made to Chapter 4 to provide greater clarity with respect to data relevant to the population of interest to this HTA, that is, those aged 65 years and older and the comparator considered. These clarifications have also been made with respect to the evidence for the cell-based influenza vaccines.
Sanofi	We kindly ask for an amendment to the HTA report for enhanced influenza vaccines based on the following: We request that due consideration is given to all relevant RCT evidence for vaccine efficacy in the base case. Use of only statistically significant results can lend the assessment to potential bias and policy implications. Given available sources of data at the time of the assessment, we strongly suggest that the base case is amended to include assumptions based on more robust RCT data. The conclusions of the report do not currently reflect the sensitivity of cost-effectiveness results to efficacy inputs against hospitalisations for adjuvanted influenza vaccines. Considering the wider policy implications of the report, we recommend that these limitations are adequately represented to ensure decision-makers are fully informed of the caveats associated with cost-effectiveness model results, such as the high level of uncertainty.	As the model estimates the incremental benefits and costs arising from changing from a standard to an enhanced influenza vaccine, we believe that all relevant evidence for vaccine efficacy and effectiveness have been included in the base case, that is, where the available evidence indicated a difference in effect. In accordance with this evidence, the epidemiological model applied a reduced probability of laboratory-confirmed influenza cases (notified cases) for the high-dose influenza vaccine. The model then applied a hospitalisation rate to the notified influenza cases based on Irish data. This hospitalisation rate was not adjusted for the high-dose vaccine, and as such, the modelled outcomes include a proportional reduction in hospitalisation in line with the reduction in notified cases. Updates have been made to this chapter to clarify this. The report also acknowledges that, while the impact on hospitalisation from the systematic review of effectiveness and safety reported in Chapter 4 was not statistically significant, the p-value was borderline significant and the effect size was in line with the impact on incidence.
Sanofi	The Domnich et al. study results are used to define the effectiveness of adjuvanted influenza vaccines compared to standard dose non-adjuvanted influenza vaccines in the base case of the cost-effectiveness analysis and thus play a decisive role in the conclusions. More so, this variable is one of the most influential inputs as per the sensitivity analysis conducted within this assessment. We are concerned about the use of the Domnich et al. study in the base case of the HIQA model as these data are not reliable	In the assessment, evidence of improved effectiveness of adjuvanted (against hospitalisation with laboratory-confirmed influenza) and high-dose (against laboratory-confirmed influenza) influenza vaccines compared with standard influenza vaccines are both based on single studies, each using two seasons of data. The effectiveness observed in two seasons may not be representative of future seasons. As such, there are clear limitations to our understanding of vaccine effectiveness for both adjuvanted and high-dose influenza vaccines. A HTA is necessarily based on the best available evidence at a point in time. The uncertainty in the effectiveness estimates

Organisation	Comment	Response
	for such a critical decision impacting the health of the eligible Irish population. Base-case assessments of cost-effectiveness analysis should be anchored in the most reliable evidence. In this case it is clear that two critical RCTs (Beran et al. and Diaz-Granados et al.) provide the best available evidence for vaccine efficacy. Therefore, it is our recommendation that the report is amended to include evidence from these studies in the base case, and scenario analyses are conducted to understand the overall uncertainty in the health economic decision.	was acknowledged as we used a fully probabilistic model, supplemented with numerous sensitivity and scenario analyses. It is important to stress that another influential parameter was vaccine cost. The conditions under which each of the vaccine options may be considered the best use of resources is a function of both vaccine effectiveness and cost. This is clearly outlined in the new advice section which has been added to the report.
Sanofi	It must be noted that in one study, Diaz-Granados et al., a powered randomised trial has been misclassified as a non-randomised study of intervention (NRSI).	In the HTA, the study by Diaz-Granados et al. is classified as an RCT and used for the outcome of laboratory-confirmed influenza. With respect to the comparison between high-dose and standard influenza vaccines, a single NSRI by Doyle et al. was included that reported on hospitalisations for laboratory-confirmed influenza.
Sanofi	We wish to highlight that studies providing evidence of efficacy of high-dose influenza vaccines against hospitalisations have not been given due consideration within this assessment. These include RCTs and meta-analyses providing relevant evidence of high-dose influenza vaccines' efficacy against hospitalisations. Adequate justification should be provided for studies excluded from the evidence base: • Johansen, N. D., et al. (2024). "Effectiveness of high-dose versus standard-dose quadrivalent influenza vaccine against recurrent hospitalizations and mortality in relation to influenza circulation: A post-hoc analysis of the DANFLU-1 randomized clinical trial." Clinical Microbiology and Infection. • Palmu A. A., et al. (2024) High-Dose Quadrivalent Influenza Vaccine for Prevention of Cardiovascular and Respiratory Hospitalizations in Older Adults. Influenza Other Respir Viruses. 2024 Apr;18(4):e13270.	The listed studies were not included for a number of reasons. Specifically, the following publications were excluded as they did not include disaggregated data for any of the effectiveness outcomes of interest per the stated PICO (that is, laboratory-confirmed influenza, influenza-related hospitalisation or influenza-related death): • Johansen et al. (2024) • Palmu et al. (2024) • Johansen et al. (2023) • Vardeny et al. (2021). The following publications were systematic reviews; primary studies within these reviews were included, where relevant, within the ECDC systematic review used to inform this HTA. • Comber et al. (2023) This study is an academic publication by members of the HTA Directorate at HIQA. It relates to the 2020 ECDC systematic review which HIQA was commissioned to undertake for the ECDC.

Organisation	Comment	Response
	• Lee, J. K. H., et al. (2023). High-dose influenza vaccine in older adults by age and seasonal characteristics: Systematic review and meta-analysis update. Vaccine: X, 14, 100327. • Comber L et al. (2023). Systematic review of the efficacy, effectiveness and safety of high-dose seasonal influenza vaccines for the prevention of laboratory-confirmed influenza in individuals ≥18 years of age. Reviews in medical virology 33(3):e2330. • Johansen, N. D., et al. (2023). A Pragmatic Randomized Feasibility Trial of Influenza Vaccines. NEJM Evidence 2(2): EVIDoa2200206. • Diaz-Granados CA, et al. (2015). Robertson CA, Talbot HK, Landolfi V, Dunning AJ, Greenberg DP. Prevention of serious events in adults 65 years of age or older: a comparison between high-dose and standard-dose inactivated influenza vaccines. Vaccine. 2015;33(38):4988-4993. • Vardeny O et al. (2021). Effect of high-dose trivalent vs standard-dose quadrivalent influenza vaccine on mortality or cardiopulmonary hospitalization in patients with high-risk cardiovascular disease: A randomized clinical trial. JAMA. 2021;325(1):39-49.	• Lee et al. (2023) This study is a 2023 systematic review and meta-analysis with a search cut-off up to and including 30 April 2023. The ECDC report is more recent (search cut-off of 24 July 2023) and has a broader scope matching the aims of this HTA. • Diaz-Granados et al. (2015). This study is a supplementary analysis of the original efficacy trial that evaluated the effectiveness of high-dose influenza vaccines compared to standard dose influenza vaccines in preventing all-cause hospitalisations and serious cardio-respiratory events possibly related to influenza infection. The original efficacy trial (Diaz-Granados CA et al. 2014) was included in the ECDC review.
Sanofi	Whilst the ECDC review has been cited, we recommend that for clarity and transparency, this section should also include a summary table and PRISMA diagram with citations. We would like to highlight inconsistent use of citations in this section overall, and would recommend for transparency to provide citations throughout this section i.e., Sections 4.5.1 through Section 4.5.8.	Citations of the primary studies in Sections 4.5.1 to 4.5.8 have now been included to facilitate the reader and to improve transparency within these sections.
	Rapid review of economic modelling studies	
Sanofi	Section 5 in the draft HTA consultation document summarises the published economic evidence from various high-income countries. We would like to highlight that previous cost-effectiveness	Section 5 is a review of 19 modelling studies (15 of which were industry funded), reporting VE/rVE estimates that have been used previously, based on authors' choice of estimate. The chapter is intended to provide an

Organisation	Comment	Response
	assessments have taken a conservative approach to vaccine efficacy, and uncertainty has been tested using scenario analyses. The section further highlights the lack of face validity for the rVE estimate of 59.2% for adjuvanted influenza vaccines against hospitalisations, which has the potential to induce bias within the assessment. This section describes the previously published cost-effectiveness studies in high-income countries. Two key efficacy outcomes for influenza vaccines have been modelled in studies assessing cost-effectiveness across various countries. Clarity is needed in the description of efficacy evidence for both outcomes for some of the cost-effectiveness modelling studies discussed. Additionally, appropriate rationale for model choice, and assumptions related to inputs used in the model is lacking from this section. Additional rationale must be included for the topics; alternatively, the sensitivity of parameter uncertainty must be explored further by way of scenario analyses. Section 5.5.4 describes the cost-effectiveness studies which cite the meta-analysis conducted by Lee et al. (2021) used for estimates of rVE against hospitalisations. This is missing from the evidence summary. The discussion section outlines the potential benefits and challenges related to static and dynamic modelling to capture the impact of influenza vaccines. This section discusses static modelling being the more conservative modelling approach in the over-65 population. The use of dynamic model to this HTA has not been fully justified, given the target population of adults aged 65 years and older, and lack of clarity on an epidemiologically influential subgroup. We recommend further rationale is provided for final model choice, in the context of Section 5.	overview of modelling approaches and parameters used, but ultimately, it is the results of the ECDC report (that outlines the best available evidence and was objectively assessed by an independent research group) which informed HIQA's assessment of the safety and effectiveness of these vaccines and which was used to inform the economic model. By adopting this approach, the potential for bias in the assessment was minimised. Evidence for the clinical effectiveness of adjuvanted influenza vaccines against hospitalisation used in the HIQA economic model was based on the findings of the Domnich et al. study (published in December 2022). The search end date for the review of economic modelling studies was July 2023. This search identified only six studies (published after December 2022) for inclusion, four of which assessed an adjuvanted influenza vaccine against a comparator. The short time period between the publication of the Domnich study (December 2022) and search end date (July 2023) may be why this rVE estimate was not used as an input parameter in any of the published economic modelling studies included in this review. In Section 5, VE and rVE estimates are detailed as reported in the included studies. Where, for example, an estimate from the included studies are reported related to a specific outcome (for example, laboratory-confirmed influenza, symptomatic influenza, outpatient or medically-attended influenza, or influenza-related hospitalisation), this has been similarly reported in Chapter 5. Where an estimate has merely been reported in the included studies as an overall VE/rVE estimate, without any further clarification as to the specificity of the efficacy outcome, then it has been reported as such. Included studies have been reviewed, and amendments which provide further clarity were included in Table 5.4 (page 158) for three studies.

Organisation	Comment	Response
		Additional text has been added to Section 5.4.2 (page 148), outlining (and referencing) the number of models which included a rationale for model choice (9/19). Relevant assumptions relating to key economic modelling methodology and input parameters have been outlined throughout the chapter where clearly reported in the original studies, and where appropriate (for example, time horizon, discounting, VE/rVE estimates and waning). As such, no further amendments have been made to the report. The primary objective of this review was to gain up-to-date knowledge of economic modelling approaches. Details of sensitivity analyses conducted on model results and parameter uncertainty were not of specific interest in the review of modelling studies, and as such were not recorded. The approach undertaken by the HIQA evaluation team in relation to uncertainty in the cost-effectiveness analysis as detailed in Chapter 6 of this assessment is not informed by the results of previous modelling studies, but rather is informed by the sensitivity of model results to the unique combination of input parameters used, assumptions taken, and modelling approach. As such, no amendments have been made to the report. Section 5.5.4 in the report discusses the results, Section 5.4.5 Costs (direct and indirect) and Section 5.4.6 Effects (direct and indirect), within which rVE estimates are discussed. As such, no amendment has been made. Section 5.4.4 cites the sources of VE and rVE estimates used throughout the studies. The meta-analysis conducted by Lee et al. (2018) was cited in five of the included studies as a source of VE estimates, details of which are present on page 155. Lee et al. (2021) was not cited in any of the included studies as a source of estimates, and was cited in only one included study, as a reference used in the introduction, unrelated to VE estimates (Mattock et al.). No amendments have therefore been made to the report.

Organisation	Comment	Response
		Additional text has been added to Section 5.5.1 relating to epidemiological influential subgroups. With regard to the economic modelling of contagious diseases where the target population is not an epidemiologically influential subgroup, a static model may be acceptable. However, the lack of an epidemiologically influential subgroup does not preclude the use of a dynamic transmission model. Additionally, rationale as to why a dynamic transmission model was deemed appropriate is provided in Section 6.2.2.
	Economic evaluation	
CSL Seqirus	1. Economic evaluation stated 'that HD-IIV would be more effective than aIIV'. We would refer the following reviews and real-world evidence which demonstrate equivalency and potential superiority of aIIV to HD-IIV in hospitalisation and infection protection: • Relative Effectiveness of MF59 Adjuvanted Trivalent Influenza Vaccine vs Non-adjuvanted Vaccines During the 2019-2020 Influenza Season - PubMed (nih.gov) • Effectiveness of the MF59-adjuvanted trivalent or quadrivalent seasonal influenza vaccine among adults 65 years of age or older, a systematic review and meta-analysis - PubMed (nih.gov) • Comparative effectiveness of adjuvanted versus high-dose seasonal influenza vaccines for older adults: a systematic review and meta-analysis - PubMed (nih.gov) • Importance and value of adjuvanted influenza vaccine in the care of older adults from a European perspective - A systematic review of recently published literature on real-world data - PubMed (nih.gov) 2. Although HD-IIV has positive Phase 3 randomised clinical trial, the substantial body of real-world evidence for aIIV has	All comparisons in the results section of the economic evaluation chapter relate to the effectiveness of the vaccination strategies in generating quality-adjusted life years (QALY) gains which are achieved through reductions in both incidence of, and hospitalisation due to, cases of laboratory-confirmed influenza. The findings of the incremental cost-effectiveness analysis highlight a QALY gain with the high-dose influenza vaccines relative to the adjuvanted influenza vaccines.

Organisation	Comment	Response
	demonstrated its effectiveness in providing public health protection by reducing hospitalizations and infections that lead to healthcare utilisation. This equivalency will further demonstrate the cost effectiveness of aIIV in the over-65 population in Ireland. We have investigated the cost effectiveness of an aIIV public health strategy for Ireland as resourcing is an important component of effective vaccine recommendation. As such, we would also refer to the HTA, the specific Irish modelling paper which demonstrates QALY calculations with similar vaccine effectiveness, further reinforcing the cost effectiveness of aIIV. [Use of Adjuvanted Quadrivalent Influenza Vaccine in Older-Age Adults: A Systematic Review of Economic Evidence - PMC (nih.gov)]	
National Immunisation Office	• LAIV offered to those aged 2-17 years, rather than 0-18 years. • Would a % of adults not be prescribed an antiviral if eligible? • Why is "VE standard IIV 2-17 yrs" included in tornado plot, given this HTA for >65 years? • Clarify that results of BIA are based on list price of IIV of €10.99. • Relative vaccine prices - not clear in report whether 1.5 - 3.25 TIMES per dose. • Clarify that aIIV would dominate D-IIV AT IIV LIST PRICE (also needs to be clarified page 242).	• Amendment made in Section 6.2.1. to read: 'a LAIV to eligible individuals aged 2 to 17 yrs.' • Amendment made in Section 6.3.6 to include assumption that 28% would receive a prescription for antivirals, steroids and or expectorant. • This is a whole population model and given that influenza is a contagious disease, the effectiveness of a vaccine for one age group may impact on incidence of disease in another age group. • This clarification regarding the ex-VAT list price of the standard influenza vaccine has been added to Chapter 6 including the key points. • Amendment made in Sections 6.3.6 and 6.5.2 to include the word 'times'. • Amendment made to Sections 6.4.2 and 6.5.3 to clarify that the result is based on the cost of the standard influenza vaccine being the list price of €10.99 per dose.
Sanofi	• The impact of parameter uncertainty for relative vaccine effectiveness has not been captured adequately in the conclusions of the report.	In line with recommended practice for incremental analysis in economic evaluations, all possible strategies were ranked in order of increasing cost, with each strategy then compared with the preceding least costly strategy. Therefore in the incremental analysis, a strategy based on high-dose

Organisation	Comment	Response
	• The impact of parameter uncertainty needs to be further explored within this assessment by way of sensitivity (probabilistic sensitivity analyses (PSA) and one-way sensitivity analyses (OWSA)) and scenario analyses for a more nuanced interpretation of cost-effectiveness results, specifically related to the assessment of high-dose versus standard-dose influenza vaccines. • The PSA (Figure 6.5) for high-dose versus adjuvanted influenza vaccines indicates a high degree of uncertainty in estimates, with the majority of iterations lying in the north-west and south-west quadrants. The PSA (Figure 6.4) for adjuvanted versus standard influenza vaccines indicates a spread across all four quadrants of the CE plane. It must be noted that the spread of iterations is narrow. Nonetheless, a comparison of high-dose versus standard-dose influenza vaccines in a similar manner cannot be made as this assessment has not been included in the report. • The OWSA for adjuvanted versus standard influenza vaccines indicates a high level of uncertainty in incremental cost-effectiveness ratios (ICERs) contributed by relative risk of hospitalisation iterations, with ICERs ranging between -100k/QALY to 500k/QALY. In the OWSA for high-dose versus adjuvanted influenza vaccines, relative risk of hospitalisations is identified in the top 5 model drivers. These results indicate that the cost-effectiveness model is highly sensitive to the parameter for relative efficacy of adjuvanted influenza vaccines against hospitalisations, which are derived from one observational study. Based on recent publications it is determined that interpretation of results from Domnich et al. is uncertain and can lead to biased estimates. Thus, using complete and robust evidence in the cost-effectiveness assessment is crucial to ensure a high-quality assessment.	influenza vaccines (the most costly strategy) was compared with a strategy based on adjuvanted influenza vaccines (the second most costly strategy). The majority of iterations in Figure 6.5 do not lie in the north-west and south-west quadrants. As stated above, the incremental analysis ranked all possible strategies in order of increasing cost and compared each strategy with the preceding least costly strategy. Thus it was not appropriate to compare a strategy based on high-dose influenza vaccines with a strategy based on standard-dose influenza vaccines.

Organisation	Comment	Response
Sanofi	Section 6.2.8 Model input parameters This section is missing the base-case inputs for effects used in the modelling. For clarity, we recommend summarising the categories of utilities and disutilities used in the model base case within this section; the inputs used in the model are outlined in Section 6.5. Given variability in utility values identified in Section 5, rationale for choice of (dis)utility inputs needs to be provided.	Section 6.2 of the report relates specifically to the epidemiological model and Section 6.3 relates to the economic model. All epidemiological model inputs are included in Section 6.2, with a selection of inputs for the economic model included in Section 6.3. Given the volume of model inputs for the economic model, they are all included in Appendix A6.4.
Sanofi	Table 6.2 Vaccination input parameters This table does not provide a clear overview of the rVE inputs used in the model. Specifically, • rVE of adjuvanted influenza vaccines against laboratory-confirmed influenza cases. This information is available from RCTs. However, if assumptions are used, these should be made explicit for transparency • rVE of adjuvanted and high-dose influenza vaccines against hospitalisations. rVE of adjuvanted influenza vaccines has been used in the CE model, however it has not been reported within this table. rVE of high-dose influenza vaccines is available from RCTs and meta-analyses. However if assumptions are used, these should be made explicit for transparency.	The rVE of adjuvanted versus standard influenza vaccines against hospitalisation for influenza has been added to Table 6.2. Footnotes to this table note that the included rVE against laboratory-confirmed influenza cases was limited to high-dose influenza vaccines, and the rVE against laboratory-confirmed influenza hospitalisation was limited to adjuvanted influenza vaccines, as in each case this was the only enhanced vaccine for which a statistically significant reduction in laboratory-confirmed influenza in those aged 65 years and older was reported (Chapter 4). As outlined in an earlier comment, while the hospitalisation rate was not adjusted for the high-dose influenza vaccine, the modelled outcomes include a proportional reduction in hospitalisation in line with the reduction in laboratory-confirmed influenza cases. Updates have been made to this chapter to clarify this.
Sanofi	The results in Table 6.12 indicate 'Total costs' as a category, which does not provide sufficient information on the driver of costs. For transparency, we recommend the cost categories (for example, vaccine acquisition costs, vaccine administration cost, hospitalisation costs, etc.) be presented in addition to the total costs for each vaccine strategy.	When presenting the results of a cost-utility analysis, it is standard practice to present the total costs and utilities as used to determine the ICER. The costs in the budget impact analysis are disaggregated into incremental costs and costs averted (for example, through reductions in hospitalisation).
Sanofi	Section 6.4.2 Results: High-dose inactivated influenza vaccine compared with adjuvanted inactivated influenza vaccine	Additional text has been included in Section 6.4.2 to clarify the comparators.

Organisation	Comment	Response
	This section lacks clarity in the text as to the comparator that is, the text frequently switches between adjuvanted and standard influenza vaccines. Further context is needed within this section.	
Viatris Ireland	Switching to a strategy based on aIIV instead of standard IIV for those aged 65 years and older is recommended as result of the economic evaluation. However, a corresponding transferability of the evidence may not be given in Ireland. Regularly high vaccination rates in the Irish population ≥65 years of age should contribute to immune competence which makes the adjuvant effect rather unnecessary.	Evidence of the clinical effectiveness and safety for the enhanced influenza vaccines was informed by a systematic review of the evidence. The limitations of the available data and its applicability to the population aged 65 years and older in Ireland were considered. Chapter 3 of the report highlights the considerable burden of seasonal influenza in those aged 65 years and older in Ireland with this burden seen despite the existence of an established influenza vaccination programme that offers a standard influenza vaccine to adults, with high uptake in those aged 65 years and older. This evidence along with evidence in Chapter 4 of the lower effectiveness of standard influenza vaccines in older adults compared with those aged less than 18 years and in those aged 18 to 64 years, highlights the need for alternative vaccines that may provide improved effectiveness.
Viatris Ireland	For HD-IIV, the rVE value of 24.2% was used. Since findings from recent NRSI contradicted previous findings from RCTs regarding VE against laboratory-confirmed influenza, we would recommend adding a sensitivity analysis with lower rVE scenarios.	The rVE of HD-IIV versus standard IIV (rVE: 24.2% [95% CI: 9.7 to 36.5]) was subject to both probabilistic and one-way sensitivity analysis. See Figure 6.8 for the results of the OWSA.
Viatris Ireland	The hospitalisation rates in Table 6.3 appear very high. An overestimation may result from the fact that the DRGs for otitis media and or respiratory tract infections (page 94 of the draft HTA) were used which are not necessarily associated with influenza. One-way sensitivity analysis shows that the ICER is most sensitive to the following parameters: a. relative risk of hospitalisation with aIIV versus standard IIV in those aged 65 years and older b. probability of hospitalisation for influenza.	The hospitalisation rates used in the economic model relate to notified cases of influenza only and were estimated using HIPE discharge data with a principal diagnosis of influenza. Given that the data were obtained from an Irish source and extracted based on a principal diagnosis of influenza, these data represent the best available evidence.

Organisation	Comment	Response
Viatris Ireland	According to Table 6.4, a significantly increased risk of vomiting following vaccination with aIIVs and a significantly increased risk of combined systemic effects following vaccination with HD-IIVs was considered in the economic assessment, taken from the ECDC 2020 report. We understand the use of data from the subgroup analyses of older adults from the ECDC 2020 report. However, considering that aIIV demonstrated a significantly higher risk for fever, one should at least additionally consider AEs like fever and chills but also fatigue and myalgia in context with aIIV because of their much higher rates, and also pain at the injection site as local AE. In case of HD-IIV, we would suggest adding the local injection site reactions pain, erythema and swelling due to the huge difference in appearance compared to SD-IIV.	The outcomes analysed in the ECDC 2020 safety sub-group analyses for older adults of aIIV versus standard IIV included chills, fatigue, fever and myalgia. None of the results for these outcomes were statistically significant with the exception of chills (RR 1.43, 95% CI 1.26 to 1.63). There is a high degree of uncertainty associated with utility loss due to vaccine-related adverse events and specifically the utility loss attributable to each adverse event where an individual experiences multiple events. In the absence of supporting data, it was assumed that a vaccine-related adverse event results in influenza-related utility loss for one day. We adopted a conservative approach in the analysis and applied this utility loss to the systemic reaction with the highest statistically significant relative risk only.
Viatris Ireland	In the economic assessment, it remains unclear which rVE for hospitalisations due to laboratory-confirmed influenza was used for aIIV in the economic assessment.	The relative vaccine effectiveness of aIIV (versus standard IIV) in preventing hospitalisation for influenza is provided in Section 6.3.6 (model input parameters) and also in the list of economic model inputs provided in Appendix 6.4. The parameter has also been added to Table 6.2.
	Organisational issues	
The Department of Public Health HSE Dublin and Midlands	We appreciate the thoroughness and dedication evident in the HTA and offer our feedback and perspectives based on our expertise and the public health experience of the Dublin/Midlands region. The Health Technology Assessment (HTA) should also consider the potential clinical impacts (if any) of vaccine errors. The authors could consider highlighting the importance of proper training and protocols in vaccine administration to ensure optimal clinical outcomes.	Text has been added to Section 7.3 to note that an adjuvanted QIV was offered for the 2021-2022 influenza season. We have also referred to the National Immunisation Office's report on vaccine errors for this same influenza season in this section.
Irish Pharmacy Union	The IPU supports the use of an enhanced inactivated influenza vaccine for those aged 65 years and older in the HSE Seasonal	Thank you for the considered feedback and support of the findings of the HTA.

Organisation	Comment	Response
	Influenza Vaccination Programme. The IPU would welcome the full implementation of the National Immunisation Advisory Committee (NIAC) recommendation of an enhanced (adjuvanted) influenza vaccine for those aged 65 years and older. Previously, during the 2021/2022 season, an adjuvanted inactivated influenza vaccine was offered as part of the nationally funded HSE Seasonal Influenza Vaccination Programme. The provision of this vaccine type was easily facilitated. The existing infrastructure, resources and expertise are sufficient to support the roll out of this enhanced vaccine. Community pharmacists have the necessary skills and can undertake training as required to provide this enhanced vaccine type in a safe manner. The IPU welcomes the funding of an enhanced inactivated influenza vaccine for those aged 65 years and older as part of the HSE Seasonal Influenza Vaccination Programme, as it would ensure improved patient outcomes and reduce the burden on the health service.	
National Immunisation Office	Check if the target group of the Seasonal Programme in Ireland should be changed to 60+. Since that is who are eligible in 2024-2025.	As the terms of reference for the HTA related to the potential provision of enhanced vaccines for those aged 65 years and older, the population aged 60 to 64 years were considered outside the scope of the analysis. Updates have been added to Section 7.3 to highlight that if different vaccines are being offered to selected sub-groups within the adult population, care will be needed to ensure that individuals receive the correct vaccine. Reference to the Minister's decision to extend free influenza vaccination to those aged 60+ years has been made in text added to Section 7.3.
Nursing Homes Ireland	We have read the HTA on flu vaccines and are in agreement with the conclusions made indicating that an adjuvanted flu vaccine for people aged 65 and above would be of benefit in reducing illness burden and impact of flu illness across the wider health and social care system. We also agree that any change in the type of vaccine being administered to older people would need to be	Section 7.5.4 has been amended to include additional text highlighting the need to provide adequate information about potential side effects to enable informed consent.

Organisation	Comment	Response
	provided with additional information about the side effects as outlined in the HTA.	
	Ethical, patient and social considerations	
National Immunisation Office	"Community immunity" is preferred to "herd immunity"	Text has been changed accordingly throughout the report
The Department of Public Health Dublin and Midlands	In the Department of Public Health Dublin and Midlands, providing guidance, advice and surveillance for influenza outbreaks in residential care facilities is a considerable component of the workload during the influenza season. The high-risk population living in close quarters in residential care facilities make them particularly vulnerable to influenza outbreaks. Special attention should be given in the report to the possible advantages of enhanced vaccines in these populations to improve public health outcomes.	Text amendments have been made to Section 8.2.1 to highlight the importance of providing clear information about the potential benefits and harms to older adults to support informed consent. Additionally, text has been added to Section 8.2.2 relating to the potential benefit and importance of vaccination for older adults in residential and long-term care facilities.
National Network of Older People's Councils – Age Friendly Ireland	The National Network of Older People's Councils expresses appreciation for the Plain English version of the consultation documents. The Infographic was described as excellent. In general the approach to introducing an enhanced vaccination programme for older people is viewed positively by members of the National Network of Older People's Councils. However, older people should continue to have the option of receiving the standard vaccination if they prefer not to receive the enhanced version. Personal choice is important. In relation to older people who receive carers into their homes, an enhanced vaccination programme would be very beneficial, as many carers choose not to receive flu or Covid vaccinations. An enhanced vaccination programme would offer better protection for older people in the context that health and social care professional can opt out of vaccination schemes. It is very important to address the levels of disinformation and even conspiracy theory that exist in the general population (and also among carers).	In Section 7.3 text has been added emphasising the importance of clear information and communication regarding vaccines. Section 7.5.4 has been amended to highlight the requirement for additional information about potential side effects, and how these should be made available to the eligible population in an accessible manner. In Section 8.2.1, text has been added to highlight that an adult eligible to receive vaccination with an enhanced influenza vaccine may have a preference to be vaccinated with a standard influenza vaccine. Additionally, this section includes text discussing perceptions and expectations of influenza vaccination, and outlines that the source of information about vaccination can influence an individual's attitude towards vaccination and shape their decision-making. In Section 8.2.2 text has been added to highlight the potential benefit that enhanced vaccines may offer for individuals living in relatively close environments, as well as potentially benefiting carers and healthcare workers in such settings.

Organisation	Comment	Response
	The documents refer to increased risk of local issues from an enhanced vaccination programme. Older people would like more information on what types of local issues might be expected and the level of risk involved. Older people would like to be able to access a helpline or free phone support service in case they have adverse reactions, given how busy GP practices are and the difficulty in getting appointments. More information to be provided on possible side effects. While it is appreciated that the main document is very detailed due to the volume of research that is required to discuss enhanced vaccines, it was felt that the plain English version could benefit from more detailed discussion of factors such as SAE's to give older people a better understanding of the enhanced influenza vaccine (an example being Section 4.5.2 and Table 4.3 of the main report). Promotion and communication of any changes in the vaccination programme will be essential.	It can be difficult to balance the clarity and complexity of the information provided in the Plain Language Summary. As such, the Executive Summary provides a more detailed outline of the key findings of each chapter. In this section, the main adverse reactions are described for the respective vaccines. The HTA highlights the importance of an information campaign to educate individuals on the potential risk of complications from influenza and address concerns regarding the safety or efficacy of the vaccine.

*Comments have been slightly amended to correct for minor grammatical errors and or typos.

Scientific/Health professionals acting in a personal capacity

Three responses were received from scientific and or health professionals acting in a personal capacity. These comments and our responses are outlined in Table 3.

Table 3 Comments received from scientific and health professionals on report content and responses

Organisation	Comment	Response
	Vaccine effectiveness and safety	
Prof Anthony Staines	The recent ECDC review of influenza vaccine strategies (European Centre for Disease Prevention and Control. 2024) formed a key input for the draft HTA on influenza vaccination which HIQA produced (2024). The following criticisms were noted: The effect estimate relating to the efficacy of adjuvanted influenza vaccines against influenza-related hospitalisations is based on a single observational study of 512 participants from 2022. Correspondence was noted, including a letter to the editor by employees of Sanofi critiquing the methodology used by the study authors, and a response to these queries by the original study author. The results of the study were described as unreliable in this feedback. A comparison was drawn against the effect estimate relating to the efficacy of high-dose influenza vaccines against laboratory-confirmed influenza, which was based on a single RCT of 21,989 participants aged 65 years and older. This RCT was noted to be funded by Sanofi and its results considered as credible in this feedback. Additionally, the feedback noted the lack of head-to-head trials of these vaccines, which is described as an obvious deficiency in the evidence. The feedback also included that as long as drug regulators continue to accept such poor practice, we will remain uncertain of the benefits of novel vaccines.	Based on feedback, text has been added to the chapter to highlight that the estimates of relative vaccine efficacy or effectiveness for both the adjuvanted and high-dose influenza vaccines are based on the results of single studies and to note the uncertainty and limitations of the studies. See Section 4.6.3 for added text relating to this uncertainty.
Prof John Lambert	HIQA's acceptance and use of the ECDC 2024 report: ● The report and analysis by the ECDC is flawed. ● The study in question, Domnich et al 2022, relative effectiveness of adjuvanted vs non-adjuvanted seasonal influenza vaccines against severe laboratory-confirmed influenza among hospitalised Italian older adults	Based on feedback, text has been added to the chapter to highlight that the estimates of relative vaccine efficacy or effectiveness for both the adjuvanted and high-dose influenza vaccines are based on the results of single studies and to note the

Organisation	Comment	Response
	• Nealon et al 2024 Letter to the editor co-signed with international experts in epidemiology • Domnich 2024 Response to Letter to the Editor by first author Issue: Would like that HIQA do not accept the ECDC evaluation of the MF59 adjuvanted product. It does not appear to be efficacious and inferior to currently available products for influenza. To go into flu year with an inferior vaccine, knowing this study is flawed, will result in unnecessary morbidity to the Irish vaccinated population.	uncertainty and limitations of the studies. See Section 4.6.3 for added text relating to this uncertainty.
Prof Ciarán O'Neill	I note and welcome the conclusions of the report that enhanced vaccines offer a cost-effective option for vaccination of older adults in Ireland. The findings of the report accord with those of a systematic review published by myself and Grainne Crealey that examined in detail one sub-class of enhanced vaccines but considered the wider context. The paper was published in Vaccines and is entitled Use of Adjuvanted Quadrivalent Influenza Vaccine in Older-Age Adults: A Systematic Review of Economic Evidence O'Neill C, Crealey GE. Use of Adjuvanted Quadrivalent Influenza Vaccine in Older-Age Adults: A Systematic Review of Economic Evidence. Vaccines (Basel). 2024 May 10;12(5):523. doi: 10.3390/vaccines12050523. PMID: 38793774; PMCID: PMC11126004.	Thank you for the considered feedback and support of the findings of the HTA.
	Ethical, patient and social considerations	
Prof Ciarán O'Neill	As adjuvanted vaccines are considered to offer superior protection in this age group and are already available to those who can pay, I think the provision of public support will not only increase efficiency but also increase equity. The equity issue could perhaps have been given greater emphasis in the report.	Text in relation to the potential to improve equity has been added to 8.3.1

Changes to the report from the consultation process

The following changes were made to the draft report in response to comments and feedback received through the consultation process:

- Plain Language Summary, text has been added to emphasise the importance of providing clear information on both the benefits and risks of the enhanced flu vaccines.
- Chapter 3, text has been added to highlight that the adjuvanted QIV was offered to adults aged 65 years and older in Ireland for a single season (2021-2022). Text has also been added to the discussion regarding the potential impact of switching to an enhanced influenza vaccine has on vaccine uptake.
- Chapter 4, text has been updated to only report on studies that provided comparative estimates of effectiveness against any strain of influenza. Individual study citations from the updated ECDC systematic review have been added. Further discussion of the limitations of studies included in the updated ECDC systematic review have been included. Text has also been added to discuss post-marketing safety surveillance data for aIIVs and HD-IIVs.
- Chapter 5, the term "herd protection" has been updated to "community protection", details of studies that provided rationale for the model choice have been added, further clarification of the description of vaccine efficacy evidence added where possible, clarification on the term 'epidemiologically influential subgroup' added.
- Chapter 6, updated to clarify the assumptions, vaccine list prices, comparators and relative vaccine effectiveness estimates used in the economic model as well as clarifying the vaccine used in those aged less than 18 years (LAIV for 2- to 17-year-olds).
- Chapter 7, text added to include mention of potential programme expansion, adverse events, and vaccine errors, and that changes to the HSE Seasonal Influenza Vaccination Programme should be clearly communicated, including any difference in the risk of adverse events.
- Chapter 8, added text to highlight post-marketing safety data for aIIVs and HD-IIVs and to state that clear information should be communicated to individuals about the potential benefits and harms of receiving an enhanced influenza vaccine. Text added to highlight that an adult eligible to receive vaccination with an enhanced influenza vaccine may have a preference to be

vaccinated with a standard influenza vaccine. The possible advantages of enhanced vaccines in adults aged 65 years and older, particularly those living in long-term care facilities, and equity considerations have also been highlighted.

- Chapter 9, text added to highlight that the clinical effectiveness estimates of improved vaccine effectiveness for aIIV and HD-IIV with respect to laboratory-confirmed influenza hospitalisations and cases, respectively, are each based on single studies both of which collected data over two consecutive influenza seasons. Text also added to state that multi-season effectiveness data was unavailable but would provide a more accurate estimate of the true vaccine effectiveness.

In addition to the changes made above, the Key Findings and Advice to the Minister are presented in the final report. Every attempt has been made to further emphasise issues of importance that were highlighted during the consultation process in the Plain Language Summary, Executive Summary and Advice to the Minister.

Appendix A – Copy of submission feedback form

Health Information and Quality Authority
An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Health Technology Assessment of use of an enhanced inactivated influenza vaccine for those aged 65 years and older in the HSE Seasonal Influenza Vaccination Programme

For public consultation

Consultation Feedback Form

Your feedback is very important to us. We welcome comments you would like to make.

When commenting on a specific section of a document, it would help if you can identify which element you are commenting on and the relevant page number.

The consultation remains open until 5pm on 11 July 2024

You may email a completed form to us at consultation@hiqa.ie . Alternatively, you can post the completed form to: Health Information and Quality Authority, George's Court, George's Lane, Dublin 7, D07 E98Y. You may also complete and submit your feedback online here.

About you

Name	
Your or your organisation's country	
Today's Date	
Would you like your name and or that of your organisation to be kept confidential and excluded from the published summary of responses?	

General Information and Questions

You may provide us with feedback on the specific questions (see questions that follow), or alternatively you may provide us with general comments.

Part 1

Are you replying in a personal capacity or on behalf of an institution or organisation?

☐ Personal capacity

☐ On behalf of an institution *Please name*

☐ On behalf of an organisation *Please name*

Part 2

Please provide any general or specific feedback you have on the draft assessment. Where applicable, please specify the section of the assessment to which you are referring.

Please comment

Part 3

Please outline any issues with the clarity or presentation of the report. In your response, where applicable, please specify the section to which you are referring.

Please comment

Thank you for taking the time to give us your views.

After the closing date, we will assess all feedback and use it to finalise our documents. The final documents and the Statement of Outcomes (a summary of the responses) will be published on http://www.hiqa.ie.

If you wish to do so, you can request that your name and/or organisation be kept confidential and excluded from the published summary of responses. Please note that we may use your details to contact you about your responses. We do not intend to send responses to each individual respondent.

Please return your form to us either by email:

consultation@hiqa.ie

or you can post it to Health Information and Quality Authority, George's Court, George's Lane, Dublin 7, D07 E98Y:

or you can complete the form online at:
https://hiqa.qualtrics.com/jfe/form/SV_cU4x7xxSBIPmxQa

If you have any questions you can contact the consultation team by emailing consultation@hiqa.ie.

Please return your form to us either by email or post before

5pm on 11 July 2024

Please note that the Authority is subject to the Freedom of Information (FOI) Acts and the statutory Code of Practice regarding FOI.

For that reason, it would be helpful if you could explain to us if you regard the information you have provided as confidential. If we receive a request for disclosure of the information, we will take full account of your explanation, but we cannot give an assurance that confidentiality can be maintained in all circumstances.

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