SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLES AND FIGURES

Table S1. Glossary[1]

Cost-effectiveness analysis (CEA)	A comprehensive economic evaluation that estimates the incremental investment required to obtain an additional unit of benefit for a new intervention compared to the standard of care or another established intervention. The benefit could be any measure of efficacy or effectiveness, e.g., life years gained, reduction in blood pressure, cholesterol concentration, hospital stays, etc.
Cost-utility analysis (CUA)	A specific type of CEA in which the benefit is represented by QALY. This type of analysis allows decision-makers to compare cost-effectiveness results across different therapeutic areas. Thus, it may support decision-making for economic resource allocation within the broader frame of the healthcare system, instead of being limited to compare the efficiency of interventions within the specific frame of the disease for which each analysis was performed.
Deterministic sensitivity analysis (DSA)	Type of sensitivity analysis in which one or more parameters are varied each time within realistic limits, often from 95% confidence intervals. It clarifies potential uncertainties involving the parameter included in the model and facilitates understanding of the impact on the ICER.
Discount rate	In long-term analyses, the costs and benefits of any intervention change over time. To adjust to this, both terms of the analysis are discounted at a rate that is defined for each country. Discounting future benefits and costs accounts for the fact that society typically values immediate benefits more than those received in the future, and prefers to delay costs, i.e. there is a time preference in relation to costs and benefits. Thus, discounting compares costs and benefits that occur at different points in time by converting them into present values.

Friction cost approach	A method used to estimate the indirect costs derived from the loss of productivity attributable to the disease. It assumes that productivity is only lost when a worker needs to be replaced, considering that otherwise colleagues could make up for part of the work not performed by that sick employee. Thus, loss is adjusted to this proportion of the total time, which is called the "friction time". Its main limitation is that it is highly dependent on the type of job.
Healthcare direct costs	Refers to the costs of using healthcare resources that are directly attributable to illness and covered by the healthcare system, e.g. treatment, hospitalization, emergency department, physician visits, etc.
Health state	The building block of a health economic model that represents the subject's health at a given time point. Health states are interconnected by transition rates that are governed by either deterministic or stochastic rules predefined in the model.
Human capital approach	A method used to estimate the indirect costs derived from the loss of productivity attributable to the disease. It assumes that loss of productivity is proportional to time off work due to illness. Its main limitation is that it tends to overestimate loss of productivity.
Incremental Cost-Effectiveness Ratio (ICER)	This is the result of the CEA and is the difference in cost between two therapies divided by the difference in health gain. It estimates the additional cost of gaining one unit of clinical benefit (e.g., life years gained)
Incremental Cost-Utility Ratio (ICUR)	This is the result of the CUA and is the difference in cost between two therapies divided by the difference in health gain. It estimates the additional cost of gaining one unit of clinical benefit (e.g., QALY).
Indirect cost	The costs indirectly caused by the illness, such as loss of productivity due to sick leave, disability, early retirement, or premature death.

Perspective	The viewpoint from which the analysis is conducted. It defines the costs that should be included. Typical perspectives are the healthcare system perspective and the societal perspective.
Probabilistic sensitivity analysis (PSA)	A multivariate analysis that simultaneously varies all variables based on correctly chosen probability distributions, thereby creating cost-effectiveness planes and acceptability curves relative to a defined willingness-to-pay threshold for each country (33).
Quality-Adjusted Life Year (QALY)	A measure of effectiveness adjusted for quality of life, i.e., it takes into account the quantity and quality of life gained by the intervention. It has the advantage of being independent of the disease and thus provides a standardized method for comparing the effectiveness and cost-effectiveness of different healthcare interventions across a wide range of disease areas and patient populations.
Time horizon	Refers to the timeframe considered for the analysis: acute infections should be valued over the short term, while chronic conditions should consider the patient's entire lifespan.
Utility	Describes the degree of well-being associated with each health state. It is derived from the results of quality-of-life questionnaires and is used to estimate QALYs. Disutility is a decrement applied to the baseline utility when a specific event occurs.
Willingness-to-pay (WTP) threshold	The threshold with which ICUR is compared to decide whether the incremental price per QALY estimated for a new intervention is acceptable in a specific setting. It is country specific.

Abbreviations: CEA (cost-effectiveness analysis); CUA (cost-utility analysis); DSA (deterministic sensitivity analysis); ICER (incremental cost-effectiveness ratio); ICUR (incremental cost-utility ratio); PSA (probabilistic sensitivity analysis); QALY (quality-adjusted life years); WTP (willingness-to-pay)

Table S2. Example of an application of the critical reading algorithm to the Redondo et al.[2] cost-utility analysis

CRITICAL READING OF INFLUENZA VACCINE ECONOMIC EVALUATIONS			
Question	**Answer**	**Action**	***EVALUATION***
1. Assessing the model design: does it really answer the research question?			
1.1. Was the chosen type of model adequate to the addressed objective?	YES	Continue reading	*Yes (decision tree model for comparing seasonal vaccination strategies)*
	NO	You cannot decide based on the current EE	
	I don't know	Seek the help of an expert	
2. Assessing modelling methods: are they appropriate?			
2.1. Were both the healthcare provider and the societal perspective presented?	YES, both	Continue reading	*No (the assessment is carried out from the perspective of the healthcare system [NHS] and includes only direct healthcare costs)*
	Only the healthcare provider's perspective was presented	If evidence is incomplete, look for data on the impact on society as a whole	

CRITICAL READING OF INFLUENZA VACCINE ECONOMIC EVALUATIONS			
Question	**Answer**	**Action**	***EVALUATION***
	Only the societal perspective was presented	If evidence is incomplete, look for separate data from the perspective of the healthcare system	
	I don't know	Seek the help of an expert	
2.2. Were the results presented separately from each perspective?	YES, each payer's perspective was presented separately	Continue reading	
	NO, they were not	Look for data on separate perspectives	*NO (it does not apply)*
	I don't know	Seek the help of an expert	
2.3. Was the time at least one influenza season?	YES	Continue reading	
	NO	You cannot decide based on the current EE	*Yes (6-month time horizon [weeks 40 to 20])*

CRITICAL READING OF INFLUENZA VACCINE ECONOMIC EVALUATIONS			
Question	**Answer**	**Action**	***EVALUATION***
	I don't know	Seek the help of an expert	
2.4. Was the time horizon for the societal perspective the whole patient's lifetime?	YES	Continue reading	
	NO	Look for data for long-term vaccine consequences	*NO (it does not apply)*
	I don't know	Seek the help of an expert	
2.5. Was the population defined based on the local recommendations for influenza immunization and evaluated vaccine labels?	YES	Continue reading	*Yes (population: ≥65 years old; two subgroups 65-74 and ≥75, corresponding to local recommendations)*
	NO	You cannot decide based on the current EE	
	I don't know	Seek the help of an expert	
2.6. Were all the relevant comparators based on local recommendations included in the EE?	YES	Continue reading	*Yes (the main comparison is between aTIV (the vaccine currently used in many regions) and HD-QIV.* *SD-TIV/QIV was used as a common comparator to derive indirect results because there were no direct studies of HD-QIV vs. aTIV.*

CRITICAL READING OF INFLUENZA VACCINE ECONOMIC EVALUATIONS			
Question	**Answer**	**Action**	***EVALUATION***
	NO, only the most relevant comparator was included/only relevant comparators not previously assessed	Look for EEs assessing the comparator with other relevant comparators and treat the body of evidence as a whole	
	NO, the chosen comparator is not relevant	You cannot decide based on the current EE	
	I don't know	Seek the help of an expert	
3. Assessing the quality of the model input: were input parameters the best?			
	YES	Continue reading	

CRITICAL READING OF INFLUENZA VACCINE ECONOMIC EVALUATIONS			
Question	**Answer**	**Action**	***EVALUATION***
3.1. Was the burden of illness estimated over at least 5 seasons in static models?	NO	View the results with caution. The fewer the number of seasons included, the higher the uncertainty surrounding the results. Seek more evidence	*No (the 2010–2019 averages for A/B ratios were used, but the model assumes a single season and does not estimate the burden of disease over ≥5 seasons)*
	I don't know	Seek the help of an expert	
3.2. In a dynamic model, were good sources for epidemiologic parameters chosen?	YES	Continue reading	
	NO	View results with caution	*NO (it does not apply)*
	I don't know	Seek the help of an expert	
3.3. In a dynamic model, was the model calibration reported?	YES, completely	Continue reading	
	YES, but it was insufficient	You cannot decide based on the current EE	
	NO	View the results with caution	*NO (it does not apply)*
	I don't know	Seek the help of an expert	

CRITICAL READING OF INFLUENZA VACCINE ECONOMIC EVALUATIONS			
Question	**Answer**	**Action**	***EVALUATION***
	SR with meta-analysis of RCTs	Continue reading, it is probably the best evidence available; however, pay attention to the risk of bias and heterogeneity of included studies, as well as the confidence intervals	
3.4. What was the absolute and relative vaccine effectiveness rates source?	SR with meta-analysis of observational studies	Continue reading but pay attention to the risk of bias and heterogeneity of included studies. Observational studies are often very diverse in methodology. Remember that if heterogeneity is high, no conclusions should be drawn. Also pay attention to the width of confidence intervals: the wider they are, the greater the uncertainty of the results	

CRITICAL READING OF INFLUENZA VACCINE ECONOMIC EVALUATIONS			
Question	**Answer**	**Action**	***EVALUATION***
	Single RCT over more than one influenza season	Probably good evidence; however, an evidence quality check using an appropriate checklist could be useful. Also, checking coherence with observational data is advisable.	*Yes (vaccine effectiveness for HD-QIV from an RCT)*
	Single observational study over more than one season	Study design may be very variable, checking quality using an appropriate check list can be useful. You can seek more evidence for comparison.	*Yes (vaccine effectiveness for aTIV from an observational study)*
	Single season studies	Uncertainty is intrinsically high due to inherent inter-season virus variability. Checking coherence with other available studies is advisable.	
	I don't know	Seek the help of an expert	

CRITICAL READING OF INFLUENZA VACCINE ECONOMIC EVALUATIONS			
Question	**Answer**	**Action**	***EVALUATION***
	In any event, the help of an influenza expert is advisable		
3.5. Were the chosen utility values applicable for the specific population of the EE?	YES	Continue reading	*Yes (age-specific utility values for the Spanish population)*
	NO	Take the results with precaution	
	I don't know	Seek the help of an expert	
3.6. Were all relevant (differential) healthcare resources included in the cost analysis?	YES	Continue reading	*Yes (vaccination costs [price + administration], GP visits, ED visits, hospitalizations [influenza/pneumonia and alternative respiratory/cardiovascular scenario]; adverse events were not included)*
	NO	View the results with caution, and estimate the impact of missing resources on results	
	I don't know	Seek the help of an expert	
3.7. Was unit cost derived from appropriate official sources?	YES, and the mathematical treatment of the	Continue reading	*Yes (official sources from the Ministry of Health for hospital rates and costs and subscription databases for other unit costs; also updated to 2020 with CPI)*

CRITICAL READING OF INFLUENZA VACCINE ECONOMIC EVALUATIONS			
Question	**Answer**	**Action**	***EVALUATION***
	costs was clearly detailed		
	YES, but the treatment of different cost sources was not clearly explained	View the results with caution; check DSA for impact on results	
	NO	View the results with caution; check DSA for impact on results	
	I don't know	Seek the help of an expert	
3.8. Was the method used for productivity loss stated?	YES	Continue reading	
	NO	View the results with caution	*No (it does not apply)*
	I don't know	Seek the help of an expert	

CRITICAL READING OF INFLUENZA VACCINE ECONOMIC EVALUATIONS			
Question	**Answer**	**Action**	***EVALUATION***
3.9. In long term evaluations, were costs and benefits correctly discounted, according to national recommendations?	YES	Continue reading	*Yes, partially (costs and outcomes during the season were not discounted; LYs and QALYs due to deaths were discounted at 3% in accordance with Spanish recommendations)*
	No, they were not discounted, or they were discounted at a rate that is not appropriate for the setting and the reason is not justified	Results should be considered carefully; they could be over- or under-estimated.	
	I don't know	Seek the help of an expert	
3.10. Was DSA carried out?	YES, and reported in detail	Continue reading	*Yes, and reported in detail (an univariate analysis [Tornado] was performed with specified ranges)*

CRITICAL READING OF INFLUENZA VACCINE ECONOMIC EVALUATIONS			
Question	**Answer**	**Action**	***EVALUATION***
	YES, but reported detail is insufficient	View the results with caution, because you cannot estimate the impact of parameter variability on ICER/ICUR	
	NO	View the results with caution, because you cannot estimate the impact of parameter variability on ICER/ICUR	
	I don't know	Seek the help of an expert	
3.11. Was PSA carried out?	YES, and reported in detail	Continue reading	*Yes, and reported in detail (an PSA using beta/gamma/lognormal/uniform distributions (according to table) was presented, together with acceptability curves and probabilities)*
	YES, but reported detail is insufficient	View the results with caution, because you cannot estimate the global variability and robustness of results, and you cannot estimate	

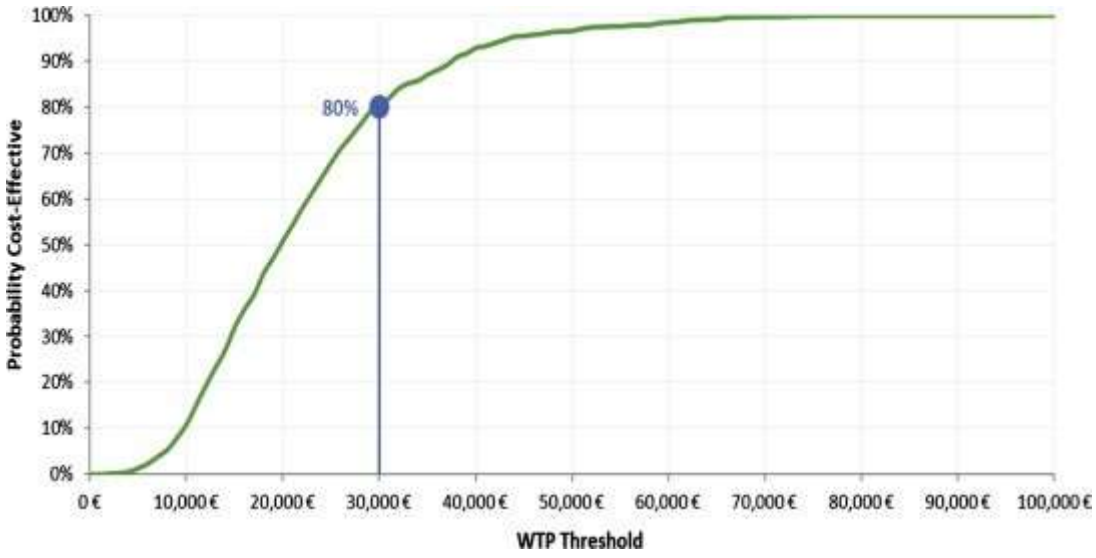
CRITICAL READING OF INFLUENZA VACCINE ECONOMIC EVALUATIONS			
Question	**Answer**	**Action**	***EVALUATION***
		acceptability based on your local WTP threshold	
	NO	View the results with caution, because you cannot estimate the global variability and robustness of results, and you cannot estimate acceptability based on your local WTP threshold	
	I don't know	Seek the help of an expert	
3.12. Was the acceptability curve presented?	YES	If you did not identify any critical flaws in the EE, you can interpret the acceptability curve	*Yes*
	NO	You cannot know the probability of the intervention being cost-effective with respect to the comparator in your setting	

CRITICAL READING OF INFLUENZA VACCINE ECONOMIC EVALUATIONS			
Question	**Answer**	**Action**	***EVALUATION***
	I don't know	Seek the help of an expert	

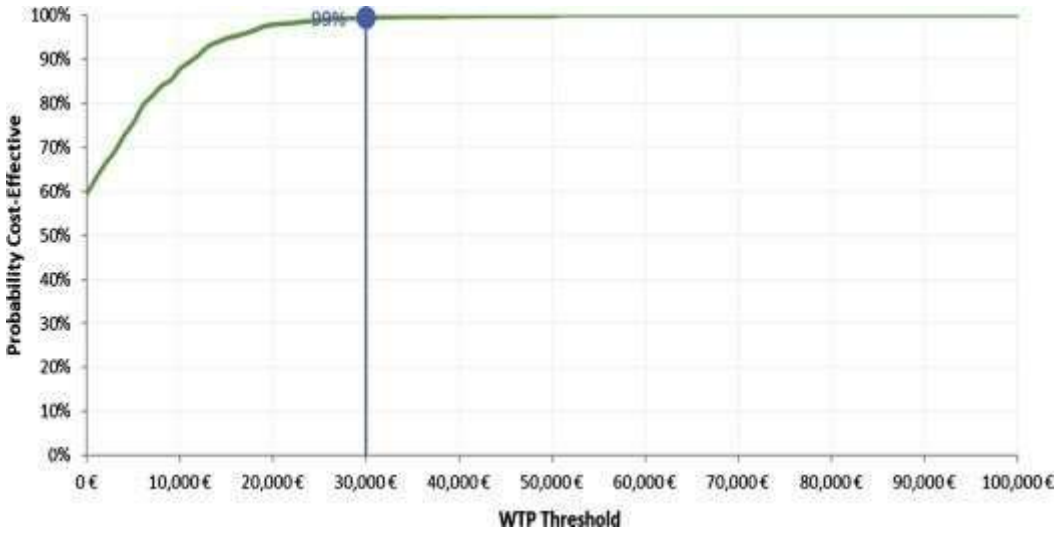
Abbreviations: aTIV (adjuvanted trivalent influenza vaccine); CHEERS (Consolidated Health Economic Evaluation Reporting Standards); COVID -19 (coronavirus disease 2019); CPI (consumer price index); DSA (deterministic sensitivity analysis); ED (emergency department); EE (economic evaluation); GP (general practitioner); HD-QIV (high-dose quadrivalent influenza vaccine); ICER (incremental cost-effectiveness ratio); ICUR (incremental cost-utility ratio); ILI (influenza-like illness); LY (life years); PCR (polymerase chain reaction); PSA (probabilistic sensitivity analysis); QALY (quality-adjusted life year); QIV (quadrivalent influenza vaccine); RCT (randomized controlled trial); R_0 (basic reproduction number); SR (systematic review); TIV (trivalent influenza vaccine); VE (vaccine effectiveness); WTP (willingness-to-pay).

Figure S1. Examples of a cost-effectiveness acceptability curves for the base case (A) and for the alternative scenario (B) for the Redondo et al.[2] cost-utility analysis

A



B



Abbreviations: WTP (willingness-to-pay)

The cost-effectiveness acceptability curve (CEAC) is a probabilistic sensitivity analysis (PSA) tool that shows the probability that one intervention is cost-effective relative to another, for different willingness-to-pay (WTP) thresholds per quality-adjusted life year (QALY) gained. In the base case (A), the CEAC shows that, for a threshold of

€30,000/QALY (the maximum adopted by decision-makers in Spain), the High-Dose inactivated influenza quadrivalent vaccine (HD-QIV) has approximately an 80% probability of being cost-effective compared to an adjuvanted trivalent inactivated vaccine (aTIV). This probability means that, considering all the uncertainty in the model parameters, 8 out of 10 PSA simulations indicate that investing in HD-QIV offers better value for money than continuing with aTIV. In the alternative analysis (B), the CEAC shows that in 99% of the 10,000 simulations of the probabilistic analysis, the HD-QIV option is more cost-effective than aTIV (at the threshold of €30,000/QALY). This result shows that the intervention remains cost-effective in virtually all simulations of the probabilistic analysis, reinforcing the robustness and credibility of the decision to adopt HD-QIV in people aged ≥65 years.

References

1. Fuentes F, Sánchez L, Navarro A, Gámez V, Fernández J, Benito H. Evaluación económica de medicamentos: puntos a considerar para no perderse. *Boletin Farmacoterapeutico de Castilla-La Mancha SESCAM*. 2014;
2. Redondo E, Drago G, López-Belmonte JL, Guillén JM, Bricout H, Alvarez FP, et al. Cost-utility analysis of influenza vaccination in a population aged 65 years or older in Spain with a high-dose vaccine versus an adjuvanted vaccine. *Vaccine*. 2021/08/23/ 2021;**3G** 5138-45. doi:https://doi.org/10.1016/j.vaccine.2021.07.048