Vaccine 41 (2023) 5518–5524

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Contributions of cost-effectiveness analyses (CEA) to influenza vaccination policy for older adults in Europe

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ARTICLE INFO

Keywords:
Cost-effectiveness analysis
Real-world evidence
Influenza vaccination
Enhanced vaccine

ABSTRACT

This review describes the importance of economic evaluations and real-world evidence (RWE) for the assessment of enhanced influenza vaccines for older adults in Europe. Individuals ≥65 years of age are at increased risk of severe influenza outcomes and many countries in Europe recommend enhanced vaccines for this population to mitigate immunosenescence. Some National Immunization Technical Advisory Groups (NITAGs) may preferentially recommend a specific enhanced vaccine, necessitating comparative economic evaluation and estimation of relative vaccine effectiveness between enhanced vaccine options in the absence of direct head-to-head efficacy data. Distinct approaches to economic modeling and cost-effectiveness analysis (CEA) guide national vaccination policies in Europe, including how underlying data, such as RWE, are used in these models. RWE is an important evidence source for input into CEA models based on disease factors (e.g., antigenic shift and seasonal variation) and practical factors (e.g., limitations of performing multiple randomized clinical trials to capture seasonal variation; the need to obtain relevant patient-oriented, real-world endpoints, such as hospitalizations). CEA is considered crucial to vaccine assessment among certain countries in Europe, but further harmonization of economic evaluations, including the use of RWE, across NITAGs in Europe may be of benefit, alongside standardized approaches for vaccine appraisal. In the future, more countries may use RWE as an input in CEA models to support NITAG recommendations for enhanced influenza vaccines in older populations, especially considering the value of RWE for the assessment of influenza epidemiology and vaccine effectiveness as stated by the World Health Organization, and the availability of a broad RWE base for certain enhanced vaccines.

Abbreviations: aQIV, adjuvanted quadrivalent influenza vaccine; aTIV, adjuvanted trivalent influenza vaccine; CEA, cost-effectiveness analysis; CEESP, Economic Evaluation and Public Health Commission; CEPS, The Economic Committee for Health Care Products; COVID-19, coronavirus disease 2019; CTV, Technical Vaccination Commission; EU, European Union; HAS, Haute Autorité de Santé; HD-QIV, high-dose quadrivalent influenza vaccine; HD-TIV, high-dose trivalent influenza vaccine; HTA, health technology assessment; JCVI, Joint Committee on Vaccination and Immunisation; NIP, national immunization program; NITAG, National Immunization Technical Advisory Group; QIV, quadrivalent influenza vaccine; QIVr, recombinant quadrivalent influenza vaccine; RCT, randomized controlled trial; rVE, relative vaccine effectiveness; RWE, real-world evidence; TC, Transparency Commission; TIV, trivalent influenza vaccine; UNCAM, National Union of Health Insurance Funds; VE, vaccine effectiveness; WHO, World Health Organization; UK, United Kingdom.

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https://doi.org/10.1016/j.vaccine.2023.07.073
Received 16 June 2023; Received in revised form 28 July 2023; Accepted 30 July 2023
Available online 5 August 2023

1. Introduction

In the European Union (EU), 88% of more than 27,000 influenza-related respiratory deaths each winter occur in people ≥65 years of age [1]. Mortality rates are 35 times higher in people ≥65 years of age than in those <65 years of age [1]; however, influenza vaccination rates in older individuals can be low, with less than half of those ≥65 years of age vaccinated in most EU countries, despite the goal for vaccine coverage of at least 75% of older individuals in these countries [2,3].

All 28 EU member states in 2018 recommended adult vaccination against seasonal influenza; of these, 21 states provided influenza vaccination on a voluntary basis free-of-charge at the point of delivery to older individuals [4]. Furthermore, several countries in Europe recommend that older individuals receive an enhanced influenza vaccine [5–7]. Enhanced influenza vaccines include adjuvanted, high-dose, and recombinant trivalent/quadrivalent influenza vaccine options (aTIV/aQIV, HD-TIV/HD-QIV, and QIVr, respectively), which have been developed to increase immunogenicity and relative vaccine effectiveness (rVE) compared with standard-dose influenza vaccines in older individuals who are at risk of potential age-related declines in immunity [5,8,9]. While quadrivalent influenza vaccines (QIVs) are currently available in the EU, information about the effectiveness of QIVs may be inferred from studies evaluating trivalent influenza vaccines (TIVs) with overlapping compositions and that are manufactured using the same processes [10].

Health economic analyses can be a valuable element of vaccine evaluation for inclusion in national programs [11], and many National Immunization Technical Advisory Groups (NITAGs) consider economic evidence in their review processes [11,12]. Distinct approaches to economic modeling and cost-effectiveness analyses (CEA) guide national vaccination policies in Europe, including how underlying inputs, such as real-world evidence (RWE), are used in these models [13]. Although not the primary focus of our review, budget impact analysis is another important tool that can be used in cost-constrained settings in circumstances in which a vaccine may offer value but budget limitations may pose a barrier to implementation [14]. This review discusses and provides expert opinion on the contributions of CEA to influenza vaccination public policy in the EU, focusing on enhanced vaccines indicated for older adults.

2. The value of CEA for vaccine policy

CEA is an economic evaluation that compares the costs and benefits of interventions to identify their productive efficiency [15]. CEA findings are produced from models that rely on the quality, accuracy, and transparency of a broad range of design choices, assumptions, and data inputs, including perspective (e.g., healthcare system, payer, societal), structure (e.g., time horizon, population, model type, vaccine strategies), costs (e.g., direct costs for vaccine acquisition, administration, in/outpatient hospitalizations, emergency department visits, general practitioner consultations, comedications), and outcomes (e.g., avoided costs, cases of influenza prevented, hospitalizations prevented, life-years saved, deaths averted, quality-adjusted life-years saved, productivity loss) [16,17] selected from evidence sources including randomized controlled trials (RCTs) and RWE. Examples of RWE can include prospective observational cohort studies and retrospective case–control analyses of patient outcome data in existing datasets, among other non-interventional designs. Uncertainty analyses, such as one-way and/or multivariate probabilistic analyses, and multiway scenario analyses, help ensure the validity, reliability, and robustness of results from CEA [16,17].

CEA are often used to evaluate the value of influenza vaccines, compared with no vaccination or compared with other similar vaccine alternatives, and involve estimating an incremental cost-effectiveness ratio and comparing it with a willingness-to-pay threshold or opportunity cost in a fixed budget [18]. Target audiences of CEA include health technology assessment (HTA) agencies, ministries of health, donor agencies, insurers, and private companies in some settings [16]. Findings from CEA may be used to negotiate vaccine prices, prioritize vaccine spending within health budgets, support inclusion of vaccines within national immunization programs (NIPs), and enable the implementation of recommendations, such as those made by NITAGs, to support vaccination of older adults with enhanced influenza vaccines.

Many CEA of enhanced influenza vaccines for older adults have been published [19–31], including several systematic reviews [32–34]. Meta-analysis techniques may not always be appropriate for summarizing economic modeling studies; however, systematic reviews may discuss how different investigators structured their models and estimated variables [35]. These choices may identify areas of uncertainty and reasons for differences between model findings, enabling decision-makers to identify studies most appropriate to their setting [35].

The coronavirus disease 2019 (COVID-19) pandemic accelerated the development of new vaccine technologies, including messenger RNA vaccine platforms [36,37], and demonstrated how societies are vulnerable to winter epidemics with multiple co-circulating pathogens [38,39]. These scenarios have encouraged further development of new combined vaccines against multiple viruses, such as vaccines containing antigens to elicit protection against influenza plus severe acute respiratory syndrome coronavirus 2 [40]. The effectiveness of potential new vaccines will need to be measured and compared with standards of practice using best-available methods. Evaluating vaccine effectiveness (VE) in the real-world setting is essential, as vaccine performance observed in routine clinical practice may differ from efficacy findings obtained from clinical trials, which are often powered to evaluate a small number of endpoints over a short duration of time [41].

3. CEA in NITAG assessments in the United Kingdom, France, and other countries

Most countries in Europe have a dedicated agency or ministry of health that is responsible for developing and overseeing implementation of national vaccination programs and relies on the advice of technical advisory groups to make recommendations [4]. Decisions can be made on a national or regional level [4]. NITAGs, which issue independent advice on vaccines for use in HTAs with the primary aim of providing advice for NIPs [12,42], increasingly consider economic evaluations, including CEA, to make recommendations [43,44].

3.1. United Kingdom and France

In the United Kingdom, the Joint Committee on Vaccination and Immunisation (JCVI) advises on vaccination recommendations. Attainment of cost-effectiveness is considered to be crucial and the “cornerstone of decision-making” for universal vaccination programs [45]. The JCVI considers a wide range of evidence when making recommendations on vaccines, including data from clinical trials, post-marketing surveillance, and RWE [41]. Subcommittees with specific expertise in modeling and economics review evidence, provide advice on parameters, and consider input from peer reviews performed by national and international experts [45] (Fig. 1**A**). For added rigor, the JCVI prefers that each CEA is performed by at least two groups using different methods; this process may be especially important for modeling work on influenza epidemiology and vaccination [45]. The committee provides advice or recommendations; it does not have a role in regulation, procurement, or running immunization programs, nor is the JCVI aware of the vaccine price or procurement processes, which are commercially confidential [45]. For 2023/2024, the JCVI recommended aQIV, HD-QIV, and QIVr for individuals ≥65 years of age [7]; aQIV and QIVr were reimbursed [46]. The JCVI states a preference for evaluating data obtained over multiple influenza seasons and anticipates that high-quality comparative data may be generated from real-world surveillance of influenza vaccination programs in primary and secondary care

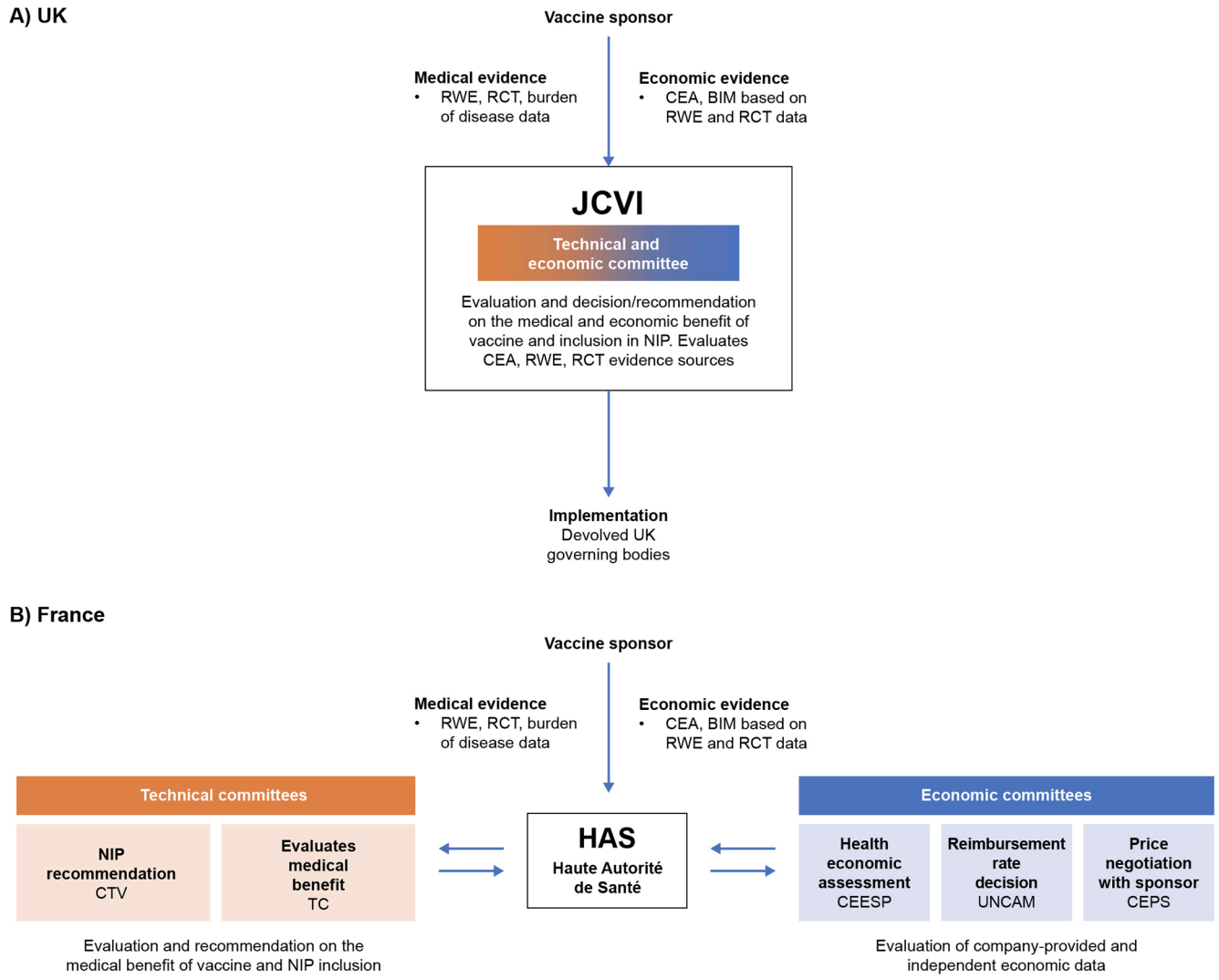

Fig. 1. Vaccine recommendation processes: stakeholders and evidence considered in (A) the United Kingdom [43,45] and (B) France [43,47,48,50]. BIM = budget impact model; CEA = cost-effectiveness analysis; CEESP = Economic Evaluation and Public Health Commission (Commission Evaluation Economique et de Santé Publique); CEPS = Economic Committee for Health Care Products (Comité Economique des Produits de Santé); CTV = Technical Vaccination Committee (Commission Technique des Vaccinations); JCVI = Joint Committee on Vaccination and Immunisation; NIP = national immunization program; RCT = randomized controlled trial; RWE = real-world evidence; TC = Transparency Commission (Comité Economique des Produits de Santé); UNCAM = National Union of Health Insurance Funds (Union Nationale des Caisses d'Assurance Maladie); UK, United Kingdom.

in the United Kingdom [7].

Other countries may have a different approach to the JCVI for evidence appraisal. In France, the Haute Autorité de Santé (HAS) is a key organization that coordinates vaccine assessment and issues vaccine recommendations that determine the NIP [47] (Fig. 1**B**). The Technical Vaccination Commission (CTV) is the expert advisory board that produces recommendations for the NIP based on epidemiological data, burden of disease evidence, the known risks and benefits of a vaccine, and economic analyses, including CEA and budget impact analysis [47]. Alongside CTV assessment, the Transparency Commission (TC) evaluates the medical benefit and/or added medical benefit of a vaccine, in consideration of the anticipated burden of disease, vaccine benefit–risk profile, and public health impact. A vaccine may be compared with an existing vaccine option, or no vaccination in the absence of existing recommendations.

In parallel with the TC assessment, the Economic Evaluation and Public Health Commission (CEESP) oversees how economic analyses are performed and reviews the quality and validity of analyses submitted by vaccines sponsors in reimbursement applications [48]. Submissions claiming a moderate-to-major additional medical benefit are highly scrutinized. One of the statutory vice-chairs of the CTV is the chair of the CEESP and, as such, is a qualified economist. The HAS board validates received recommendations and opinions, and submits a further recommendation to the government, which then decides whether to integrate a vaccine into the NIP. The Economic Committee for Health Care Products, informed by opinions from the TC and CEESP, negotiates the price with the vaccine sponsor, leading to a Managed Entry Agreement, in consideration of cost-effectiveness and budget impact estimates [49]. The statutory health insurance (UNCAM, the National Union of Health Insurance Funds) decides the rate of reimbursement [50].

The CTV has relied on "strong, evidence-based, decision-making procedures" when making recommendations [51]. As such, limited consideration of RWE, especially from studies performed outside of France, has been a distinctive feature of HAS policy. Recommendations for two recently approved influenza vaccines illustrate this approach. In 2020, HD-QIV was determined to provide "no medical benefit" by the TC in the absence of head-to-head comparisons with other influenza vaccines of the same valency. The company-submitted CEA claimed a significant additional medical benefit; however, the CEESP had strong reservations regarding the provided cost-effectiveness ratio estimates

Table 1
Strengths/limitations of RWE.

Strengths	Limitations
• RWE studies evaluate larger, more diverse, and more representative study populations than RCTs, potentially leading to more generalizable, clinically relevant results [64,65] • Influenza is a dynamic virus, making RWE crucial for assessing seasonal influenza epidemiology, VE, and rVE • Seasonal influenza epidemiology requires repeated VE studies to account for changing vaccine composition • There is a need to document all the aspects of influenza VE from protection against infection to protection against severe influenza, as well as the duration of this protection, which requires a large amount of data • RWE is needed to assess and obtain data on relevant patient-oriented, real-world endpoints, such as hospitalizations and medical visits, which provide valuable information to policy-makers [70] and reflect the severity of influenza that may be experienced by those ≥65 years of age • The real-time use of RWE for guiding vaccination policy was used during the COVID-19 pandemic [64,67–69,71] • Frameworks for modern usage and reporting of RWE are being introduced to expand the definition of high-quality evidence (e.g., EBM+) [69] • Advisory committees may prefer to evaluate data over multiple seasons from a single country to support recommendation decisions [7]	• Traditional evidence hierarchies and technology appraisal systems favor RCT data over other forms of data [64,65] • RWE can be prone to bias, and bias has been identified in RWE studies of influenza rVE, including determination of exposure and outcome, lack of information on confounders, and proper adjustment and analysis [72] • Non-randomized retrospective cohort studies assessing the effectiveness and relative effectiveness of adjuvanted influenza vaccines in older adults may exhibit moderate-to-high risk of bias, predominantly related to internal validity concerns and the potential for confounding [5] • RWE studies of aTIV/aQIV versus HD-TIV/HD-QIV have produced inconsistent rVE estimates [59]

aQIV = adjuvanted quadrivalent influenza vaccine; aTIV = adjuvanted trivalent influenza vaccine; COVID-19 = coronavirus disease 2019; EBM+ = evidence-based medicine +; HD-QIV = high-dose quadrivalent influenza vaccine; HD-TIV = high-dose trivalent influenza vaccine; RCT = randomized controlled trial; rVE = relative vaccine effectiveness; RWE = real-world evidence; VE = vaccine effectiveness.

because the model was based on an indirect comparison of rVE between HD-TIV and TIV. The HAS board recommended HD-QIV for inclusion in the NIP, but explicitly stated that although a reduction in influenza episodes and hospitalizations with HD-TIV was demonstrated, it was not possible to assess the clinical benefit or cost-effectiveness of HD-QIV in the absence of direct comparative data with other QIVs [52]. Similarly, in 2021, the TC determined that aQIV provides "no clinical added value" compared with other available vaccines indicated in individuals ≥65 years of age. A lack of head-to-head RCTs evaluating the efficacy of aQIV versus QIV or HD-QIV was identified as a factor for this appraisal [53]. No CEA was submitted by the company and no vaccine recommendation has been published by the HAS board as of April 2023.

3.2. Other countries

A review of NITAGs found a wide range of decision-making approaches used across countries [12,42]. Furthermore, a review of processes across 16 European countries identified diversity in vaccine assessment frameworks and high variance in seasonal influenza vaccine coverage rates in older adults [2]. Of the 16 countries evaluated, 11 conducted economic evaluations, 10 conducted systematic literature reviews and eight countries performed both steps as part of systematic frameworks for vaccine assessment. Once a decision is made, 10 countries publish the rationale for their positive or negative appraisal [2].

A specific example of diversity in vaccine decision-making between EU member states is that influenza vaccination is recommended for adults ≥60 years of age in the Netherlands and ≥65 years of age in France. A study comparing processes for seasonal influenza vaccine recommendations in France and the Netherlands found that, while both countries relied on clinical and epidemiological studies, CEA were considered minor sources of information, although were possibly more influential in the Netherlands than in France [44]. Whereas the ≥60-year-old threshold in the Netherlands was driven by cost avoidance, the ≥65-year-old threshold in France was driven by budget impact [44]. Systematic use of standard protocols was lacking in both countries. The personal judgment of experts, and cultural differences including broader societal views on healthy aging in the Netherlands versus France, may contribute to differences in recommendations [44].

To aid decision-makers, including NITAGs, HTA agencies, and ministries of health and finance, the World Health Organization (WHO) has published guidance on the standardization of economic evaluations for immunization programs [54], and specific guidance on the economic evaluation of influenza vaccines [55]. More broadly, an evaluation of EU vaccine market access pathways found that economic evaluations, such as budget impact assessment and CEA, were considered as part of NITAG recommendations in many EU countries, but also identified significant potential for collaboration across EU NITAGs and HTA bodies [43].

4. rVE data selected for use in CEA

Individuals ≥65 years of age are at increased risk of severe influenza outcomes and many countries in Europe recommend enhanced vaccines for this population to mitigate immunosenescence [5]. Furthermore, certain NITAGs may wish to preferentially tender a specific enhanced vaccine, creating a need for comparative economic evaluation and estimation of rVE between enhanced vaccines in the absence of head-to-head data.

The availability of RCT data and confidence in RWE may determine which rVE estimates are input into CEA models. Only one RCT provides relative efficacy data for HD-TIV versus standard-dose TIV [56,57]. Effectiveness estimates from RWE data over multiple seasons, but not efficacy data from an RCT, have been published for aTIV/aQIV [5,57–59]. rVE estimates from RWE for enhanced vaccines consistently demonstrate greater rVE versus non-adjuvanted, standard-dose vaccines, and aTIV/aQIV demonstrate comparable rVE to other enhanced vaccines over multiple seasons, including matched and mismatched

seasons [5,58,59].

On the other hand, despite the availability of rVE estimates from robust RWE studies [5,58,59], economic model base-case scenarios have used an input of 0% for the rVE of aTIV versus TIV [27,60] or aQIV versus QIV [28] when indirectly comparing against HD-TIV/HD-QIV, for which a rVE input of 24.2% for HD-TIV/HD-QIV versus TIV/QIV is used [61]. Although there are no RCT efficacy data comparing aTIV/aQIV with TIV/QIV, available RWE could be considered as an alternative approach. Meta-analyses of RWE may provide more robust estimates of VE and rVE based on pooled sources of evidence from multiple studies [58,59]. In an economic model, input variance within deterministic and probabilistic sensitivity analyses is essential to determine variables that drive CEA findings and the boundaries of cost-effectiveness estimates [16].

5. The increasing role of RWE

RWE is an important evidence source to input into CEA models based on disease factors (e.g., RWE datasets can account for antigenic shift and seasonal variation), and practical factors, such as the need to evaluate patient-oriented, real-world endpoints that may not be assessed as part of RCTs (Table 1) [62–65]. The WHO recognizes that observational VE studies have a larger role in policy for influenza vaccines than for other vaccines [63]. The US Food and Drug Administration also provides several framework and guidance statements that support the increasing role of RWE in healthcare decision-making [66].

RWE studies may produce more generalizable and clinically relevant results than RCTs, as RWE often emerges from diverse and large datasets [64,65]. The COVID-19 pandemic validated the importance and timeliness of RWE for making vital policy decisions rapidly [67–69]. Although RCTs remain the primary design to estimate the protective benefits of influenza vaccines, particularly at the pre-licensure stage, RWE analyses in the post-marketing setting can assess influenza VE across multiple influenza seasons. RWE is also needed to obtain data on real-world endpoints, such as hospitalizations and medical visits, which policymakers require [70].

Innovative approaches to controlling for bias and confounding in real-world studies are being implemented [73]. For example, multivariable instrumental methods have been developed to address unmeasured confounding and bias in an analysis of the rVE of HD-TIV versus TIV [74]. Modeling and adjustment methods used in RWE studies have improved with propensity scoring, inverse probability of treatment weighting, and Poisson regression modeling [72]. The WHO has published guidance on the evaluation of influenza VE from observational studies, including considerations for recognizing bias [63].

Policy decisions regarding influenza vaccination programs can be challenging, and RWE can be difficult to interpret and may be underutilized. Additional concerns may arise when country-specific data are not available and NITAGs may need to analyze RWE from neighboring countries or regions. RWE assessment is a relatively new element within technology appraisal, and the emergence of "early adopters" and "late adopters" within NITAGs is expected. Understanding the technology appraisal frameworks in use across Europe, and identifying strengths and weaknesses across different national technology appraisal frameworks, is of value [12,42]. NITAG decisions are made within political and budgetary contexts, and factors such as order to market and market access strategies can enhance the reimbursement potential of a specific vaccine beyond evidence presented in comparative technology assessments. To support collaborative engagements with NITAGs, rather than developing a single action plan, vaccine sponsors may wish to generate a general value demonstration toolkit, which includes RWE and that can be adapted to the priorities of different countries. NITAGs should recognize that the generation and assessment of economic evidence requires expertise, time, and resources [11].

6. Conclusion

In all countries, there is a need for increased focus on disease prevention, such as efforts to increase vaccination rates, including in older adults [2,4]. CEA is considered crucial to vaccine assessment among certain countries in Europe; further harmonization of economic evaluations, including the use of RWE, across NITAGs in Europe may be of benefit, alongside standardized approaches for vaccine appraisal. Furthermore, budget impact analysis of vaccines, which accompanies cost-effectiveness studies, can be a useful tool for decision-making authorities in each health system.

In the future, more countries may use RWE as an input in CEA models to support NITAG recommendations for enhanced influenza vaccines in older populations, especially considering the value of RWE for the assessment of influenza epidemiology and VE, and the availability of a broad RWE base for certain enhanced vaccines. The development of novel vaccines protecting against influenza will increase the number of comparators against which a new vaccine may be directly or indirectly assessed ahead of recommendation and/or reimbursement. Opportunities for more consistent approaches across EU countries for assessing clinical rVE and informing NIP decisions may result from the implementation of the EU HTA regulation, which will impact vaccine assessment by 2030.

Author contributions

All authors made substantial contributions to the conception, analysis, and interpretation of literature review findings; critically reviewed draft manuscripts for important intellectual content and provided input into draft manuscripts; and provided final approval of the version to be published.

Funding

CSL Seqirus USA Inc. provided funding to the medical communications agency Scion for medical writing support.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

AC has received honoraria for participating to scientific committees with GSK and Seqirus.

PC has received honoraria from Seqirus, Pfizer, and Sanofi for taking part in advisory boards.

VHN received funding for conducting RWE and CEA on vaccines from Takeda, Seqirus, Pfizer, and Moderna.

SM-P has received honoraria from Seqirus for taking part in advisory boards.

MP has received grants and honoraria from various pharmaceutical companies, inclusive of those developing, producing, and marketing vaccines (Seqirus, Sanofi, Moderna, Pfizer, AstraZeneca, Merck, MSD, and Janssen).

AP has received honoraria from Seqirus for taking part in advisory boards.

JR-A has received honoraria from Seqirus for taking part in advisory boards.

JM-Q is an employee of CSL Seqirus.

Data availability

All data included has been previously published.

Acknowledgments

Medical writing support was provided by Helene Wellington, MS, according to Good Publication Practice guidelines.

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