EXPERT REVIEW OF PHARMACOECONOMICS & OUTCOMES RESEARCH, 2017
VOL. 17, NO. 3, 249–265
https://doi.org/10.1080/14737167.2017.1343145

Taylor & Francis
Taylor & Francis Group

REVIEW

A systematic review of the health economic consequences of quadrivalent influenza vaccination

Pieter T. de Boer[a*], Britt M. van Maanen[a*], Oliver Damm[b], Bernhard Ultsch[c], Franklin C.K. Dolk[a], Pascal Crépey[d,e], Richard Pitman[f], Jan C. Wilschut[g] and Maarten J. Postma [a,h,i]

[a]Unit of PharmacoTherapy, -Epidemiology & -Economics (PTE2), Groningen Research Institute of Pharmacy, University of Groningen, Groningen, The Netherlands; [b]Department of Health Economics and Health Care Management, School of Public Health, Bielefeld University, Bielefeld, Germany; [c]Immunisation Unit, Robert Koch Institute, Berlin, Germany; [d]Department of Quantitative Methods in Public Health, EHESP Rennes, Sorbonne Paris Cité, Rennes, France; [e]UPRES-EA-7449 Reperes, University of Rennes 1, Rennes, France; [f]ICON Health Economics and Epidemiology, Oxford, UK; [g]Department of Medical Microbiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [h]Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [i]Institute of Science in Healthy Aging & healthcaRE (SHARE), University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

ABSTRACT

Background: Quadrivalent influenza vaccines (QIVs) contain antigens derived from an additional influenza type B virus as compared with currently used trivalent influenza vaccines (TIVs). This should overcome a potential reduced vaccine protection due to mismatches between TIV and circulating B viruses. In this study, we systematically reviewed the available literature on health economic evaluations of switching from TIV to QIV.

Areas covered: The databases of Medline and Embase were searched systematically to identify health economic evaluations of QIV versus TIV published before September 2016.A total of sixteen studies were included, thirteen cost-effectiveness analyses and three cost-comparisons.

Expert commentary: Published evidence on the cost-effectiveness of QIV suggests that switching from TIV to QIV would be a valuable intervention from both the public health and economic viewpoint. However, more research seems mandatory. Our main recommendations for future research include: 1) more extensive use of dynamic models in order to estimate the full impact of QIV on influenza transmission including indirect effects, 2) improved availability of data on disease outcomes and costs related to influenza type B viruses, and 3) more research on immunogenicity of natural influenza infection and vaccination, with emphasis on cross-reactivity between different influenza B viruses and duration of protection.

ARTICLE HISTORY
Received 3 March 2017
Accepted 13 June 2017

KEYWORDS
Economic evaluation; cost-effectiveness; influenza; vaccination; quadrivalent; vaccine; model

1. Introduction

Seasonal influenza is a contagious acute respiratory infection, causing every year up to five million cases of severe illness and half a million deaths globally [1]. In addition, the economic burden of seasonal influenza is considerable. In the United States (US) for instance annual costs of US $10.4 billion in health-care utilization and US $16.3 billion in work absenteeism are caused by influenza [2]. Seasonal influenza can be caused by influenza type A viruses and influenza type B viruses. Although the majority of influenza cases are caused by influenza type A viruses (A/H1N1 and A/H3N2), the burden of influenza type B viruses has been shown to be substantial. Since 2001, two antigenically distinct lineages of influenza B viruses, B/Victoria (B/Vic) and B/Yamagata (B/Yam), circulate worldwide on an irregular basis, being responsible for 20–25% of all influenza cases [3–5].

To reduce seasonal influenza epidemics, most industrialized countries implemented influenza immunization strategies. Trivalent influenza vaccines (TIVs) contain antigens derived from two influenza A virus subtypes (A/H1N1 and A/H3N2) and one influenza type B virus (either B/Vic or B/Yam). Each year it is decided which influenza B lineage should be included, based on predictions of the World Health Organization (WHO) about the anticipated dominant influenza type B virus [1]. However, in the seasons 2001–2002 until 2010–2011, mismatches between the vaccine and the circulating B viruses have occurred in half of the seasons, while in some seasons co-circulation of both lineages was noticed [3]. Therefore, quadrivalent influenza vaccines (QIVs) have been developed and were first licensed in 2012 [6], containing strains of both influenza B lineages (B/Vic as well as B/Yam).

Currently, some countries already include QIV next to TIV in their vaccination recommendations, like the US, Canada, and Australia [7–9]. The United Kingdom (UK) extended the influenza vaccination program to children using the quadrivalent live-attenuated influenza vaccine (Q-LAIV) [10]. However, in many other countries, including most European countries,

CONTACT Pieter T. de Boer p.t.de.boer@rug.nl University of Groningen, Groningen Research Institute of Pharmacy, PharmacoTherapy, - Epidemiology & -Economics, P.O. Box 196, 9700 AD Groningen, The Netherlands

*These authors contributed equally to this work

Supplemental data for this article can be accessed here.

TIV is still used because either QIV is not yet available, QIV procurement agreements with health-care providers might still be ongoing [11], or potential added benefits of QIV are not or not yet recognized by national immunization technical advisory groups (NITAGs).

A decision about switching from TIV to QIV is based on various criteria, of which a beneficial cost-effectiveness profile is often one of the principal aspects being considered by NITAGs in Europe [12]. Such cost-effectiveness assessments usually rely on mathematical models aiming to predict the impact of vaccination strategies on mortality, health-related quality of life, and costs to the health-care sector and society. In 2014, key issues and challenges relating to the determination of the impact and cost-effectiveness of quadrivalent influenza vaccination have already been described by Quinn et al. [13]. The authors recommended the use of subtype- and age-specific estimates of influenza disease burden and costs, because these estimates can differ between influenza A and B viruses across age-groups. Moreover, the existence of cross-protection from TIV against the unmatched B-lineage was discussed, potentially diminishing the relative impact of quadrivalent influenza vaccination. Finally, it was stated that the use of dynamic models would be important, as this modeling approach includes by definition indirect effects to the unvaccinated part of the population, which is of crucial relevance to the impact of vaccination.

To the best of our knowledge, two studies summarized the literature on the comparison of QIV versus TIV [13,14]. However, the corresponding searches seem not to be systematic. Moreover, a variety of economic evaluations of QIV versus TIV have subsequently been published. Therefore, we aimed to systematically review the literature on the economic value of QIV in order to analyze a potential switching from TIV to QIV, including the most recent publications. In addition, we aimed to identify gaps in the current knowledge and needs for future research.

2. Methods

2.1. Search strategy and study selection process

A literature search was performed in the Medline and Embase databases to identify relevant articles on the comparison of the health economic impact of QIV versus TIV that were published before 30 September 2016. Key words of the search included terms like influenza, quadrivalent, cost-effectiveness, cost-utility, cost-benefit, economic evaluation, and model. The full search strings can be found in the supplemental material and contained free text searching terms as well as controlled terms. We screened on titles and abstracts and eventually reviewed the full content of each eligible article. Also reference lists of eligible studies and review papers discussing the value of QIV were searched (snowballing).

Our selection criteria were that studies should contain original full economic evaluations of QIV versus TIV using a health-economic decision model. We considered studies of all age-groups and vaccine types. In order to be selected, studies had to include an economic comparison between QIV and TIV, or separately report outcomes for QIV and TIV that allowed calculation of this comparison by us. We limited our review to the English language. Abstracts of congress meetings, editorials, letters, and reviews were excluded.

2.2. Synthesis of results

The included papers were screened independently by two reviewers (BMvM and PTdB). First, the reporting quality of the studies was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist [15]. Then, the following information was systematically extracted if possible/reported: (1) country of study, funding source, general characteristics of the analysis (type of analysis, model type, perspective, time horizon, currency and price year, discount rate, type of sensitivity analyses, and model validation performances); (2) target group and main features of the vaccination program (coverage and vaccine price) and vaccine characteristics (vaccine efficacy, level of cross-protection of TIV against the opposite type B virus, and duration of protection); (3) influenza-related characteristics (attack rate, details on outcomes, duration of immunity, influenza-related health effects, details on health-care costs, and work days lost); and (4) main study outcomes (reduction of influenza cases, reduction of influenza-related deaths, incremental cost-effectiveness/cost-utility ratios, and key drivers of cost-effectiveness outcomes). It is important to note that the terms cost-effectiveness and cost-utility are interchangeably used in this review. Reported model validation techniques were assessed using the AdVISHE, a tool containing a structured list of relevant items for validation [16]. This checklist includes five validation categories, that is, validation of the conceptual model, input data, computerized model, model outcomes, and 'other' validation techniques. Any model validation effort that was described in the economic evaluation was then extracted. To enhance comparability between studies, cost-outcomes were transferred to the 2015 price year using national consumer price indexes [17] and then converted to US $ using purchasing power parities [18]. If the costing year was not provided in the study, we assumed a costing year of 'publication year minus 3 years.' The reporting of our review was performed according to the PRISMA statement [19]. However, not all items of the PRISMA statement are applicable to economic evaluations.

3. Results

3.1. Study selection

The initial search in the databases of Medline and Embase resulted in a total of 49 studies, of which 35 remained after removing duplicates. Of these 35 studies, 2 studies were excluded after screening titles and abstracts, and from 18 studies no full-text was available as these referred to conference abstracts only. As one additional study that met our inclusion criteria was identified outside the initial search, we ended up with 16 eligible studies [20–35]. The flowchart of the study identification process is displayed in Figure 1. One study comprised a main paper and a corrigendum [27,36]. Of these 16 studies, 2 did not primarily focus on the cost-effectiveness of QIV as compared with TIV, but on high-dose TIV [21] or

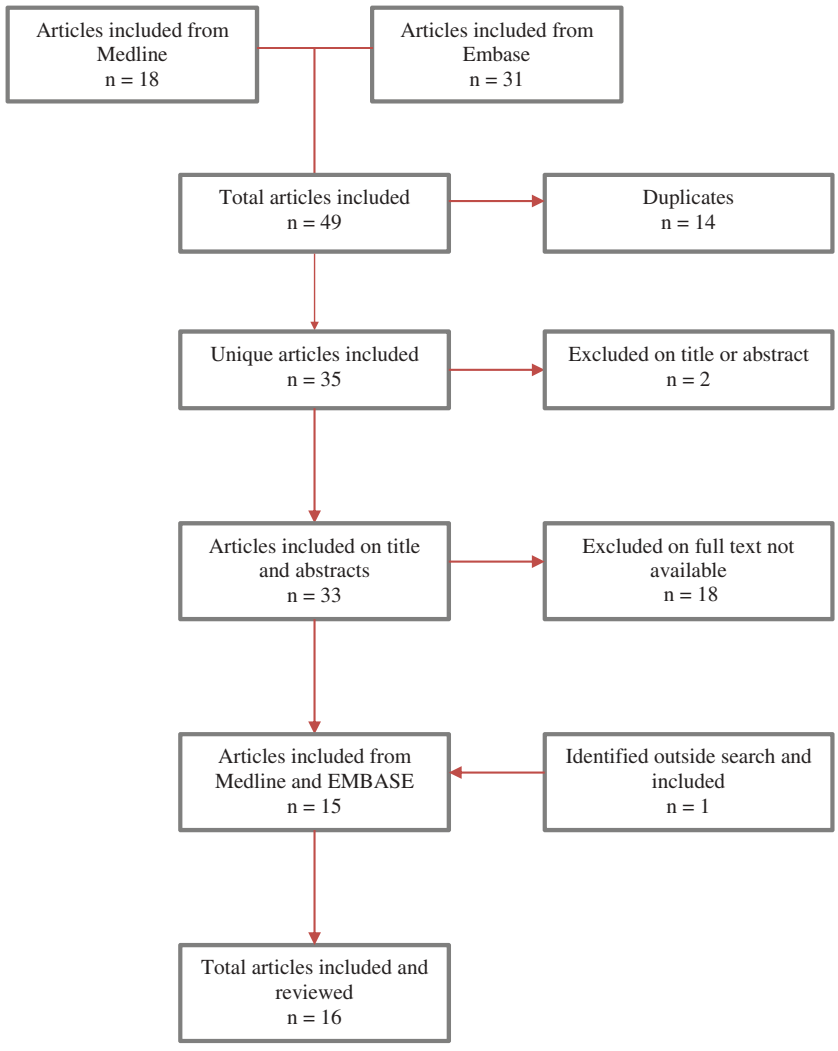

Figure 1. Flowchart of the study selection process.

adjuvanted TIV [29] as compared with TIV and QIV. However, as both studies reported detailed results of TIV and QIV, we included these studies in our review. Outcomes on QIV versus high-dose TIV or versus adjuvanted TIV were not included in this review, but are briefly described in the discussion section.

Overall, the reporting quality of the studies was found to be acceptable (see Table S1 for detailed scores per checklist item). A total of 13 out of 16 studies were ranked as good, adhering to more than 17 out of 24 items on the CHEERs checklist [20–26,28–31,33,35], while 3 studies were assessed as moderate, adhering to less than 17 out of 24 points [27,32,34]. Arguments for the choice of time-horizon and model-type were most often not reported. Also details on instruments used and populations involved to estimate the impact of influenza on quality-of-life were not presented in the majority of studies.

3.2. Study characteristics

A summary of the general study characteristics is given in Table 1. All studies were conducted in industrialized countries, including the US [21–23,27,29], UK [28,31,33], Canada [20,31], Spain [25], Finland [30], Australia [26], Germany [24], and Hong Kong [34,35]. One study analyzed the economic impact of QIV in 5 countries of the European Union (EU) and extrapolated this to all 27 EU countries [32]. Out of the 16 studies, 13 were funded by manufacturers [20–26,28–33], 1 was funded by public sources [27], and 2 studies were conducted without reporting any specific funding [34,35]. A total of 13 studies performed a cost-utility analysis [20–25,28–31,33–35], expressing results as costs per QALY gained. The remaining three studies conducted cost-comparisons [26,27,32].

Five studies used a dynamic modeling approach [23,24,29–31]. For three of these five studies, a more detailed description of the dynamic model was previously published [37–39]. Dynamic models simulate the transmission dynamics of influenza within the population and take into account age-stratified mixing patterns between different population groups, summarized in a 'contact matrix.' These models were compartmental SIR models (or extensions of such models), dividing the population between susceptible (S), infected (I), and recovered/immune (R), while adding a vaccinated compartment to account for those individuals protected by vaccination. By definition, dynamic models are able to account for both direct effects of vaccination and indirect effects on the vaccinated and the non-vaccinated

Table 1. Main characteristics and study design of the included studies.

Reference and country	Funding	Type of analysis	Modeling approach	Perspective	Time horizon	Currency (base-year), discount rate (costs/health effects)	Type of sensitivity analysis	Model validation
Chit [20], Canada	Industry	CUA	Static	Payer and society	1 season	CAD (2012), 5%/5%	Univariate, multivariate PSA	Cross-validation of model outcomes
Chit [21], United States	Industry	CUA	Static	Society	1 season	USD (2013), 3%/3%	Univariate, multivariate PSA	NR for QIV vs. regular TIV outcomes
Clements [22], United States	Industry	CUA	Static	Society	1 year	USD (2011), 3%/3%	Univariate, multivariate PSA	Cross-validation of model outcomes
de Boer [23], United States	Industry	CUA	Dynamic	Payer and society	20 years	USD (2013), 3%/3%	Univariate, multivariate PSA	Cross-validation of model outcomes
Dolk [24], Germany	Industry	CUA	Dynamic	Payer and society	20 years (following a 20-year burn-in period)	EUR (2014), 3.0%/1.5%	Univariate, multivariate PSA	Cross-validation of model outcomes
Garcia [25], Spain	Industry	CUA	Static	Society	Life-time	EUR (2014), 3%/3%	Univariate, multivariate PSA	Cross-validation of model outcomes
Jamotte [26], Australia	Industry	CC (CCA)	Static	Payer and society	10 years (2002–2012, 2009 excluded)	AUD (2014), no discounting	Univariate	Cross-validation of model outcomes
Lee [27], United States	Public	CC	Static	Payer and society	10 seasons (1999–2000 to 2008–09)	USD (2012), 3%/NA	Multivariate PSA	-
Meier [28], United Kingdom	Industry	CUA	Static	Payer and society	Life-time	GBP (2012/2013), 3.5%/3.5%	Univariate, multivariate PSA	Cross-validation of model outcomes
Mullikin [29], United States	Industry	CUA	Dynamic	Society	1 year	USD (NR), NA/3%	Univariate, multivariate PSA	Cross-validation of model outcomes
Nagy [30], Finland	Industry	CUA	Dynamic	Payer and society	20 years	EUR (2014), 3%/3%	Univariate, multivariate PSA	Model fit testing, cross-validation of model outcomes, validation against independent empirical data
Thommes [31], Canada and United Kingdom	Industry	CUA	Dynamic	Payer	10 years (following a 30-year burn-in period)	CAD (2013), 5%/5%. GBP (2013), 3.5%/3.5%	Univariate, multivariate, multivariate PSA	Face validity of input data, model fit testing, and cross-validation of model outcomes
Uhart [32], EU-5 and EU 27[a]	Industry	CC (CCA)	Static	Payer and society	10 seasons (2002–2003 to 2012–2013, 2009–2010 excluded)	EUR (NR), no discounting	Univariate	Cross-validation of model outcomes
van Bellinghen [33], United Kingdom	Industry	CUA	Static	Payer	Lifetime	GPB (2010), 3.5%/3.5%	Univariate, multivariate PSA	Cross-validation of the conceptual model and model outcomes, double programming
You [34], Hong Kong	No funding	CUA	Static	Society	9 seasons (2001–10, excluding 2009)	USD (2014), no discounting/3%	Univariate	Cross-validation of model outcomes
You [35], Hong Kong	No funding	CUA	Static	Payer and society	1 year	USD (NR), NA/3%	Univariate, multivariate PSA	Cross-validation of model outcomes

AUD: Australian dollar; CAD: Canadian dollar; CC: cost comparison; CCA: cost-consequence analysis; CUA: cost-utility analysis; EUR: Euro; GBP: Great British Pound, NA: not applicable, NR: not reported; PSA: probabilistic sensitivity analysis; QIV: quadrivalent influenza vaccine; TIV: trivalent influenza vaccine; USD: US dollar. [a]Uhart et al. [32] reported results of 5 European Union countries (EU5) (France, Germany, Italy, Spain, and United Kingdom) and extrapolations of these results of 27 European Union countries (EU27).

population, for example, herd protection or potential age shifts regarding incidence peaks [40,41]. The other 11 studies used static models [20–22,25–28,32–35]. Three of these 11 studies used the same Markov model [25,28,33] developed by van Bellinghen et al. [33], while 6 studies [20,21,26,27,32,34] followed and extended the approach that was explained in the online available spreadsheet-based model by Reed et al. [42]. All of the static modeling studies neglected indirect effects.

The societal perspective was the most considered perspective [20–30,32,34,35], including direct medical costs and indirect costs due to productivity losses. Other perspectives that were used concerned the payers perspective, comprising medical costs only [20,23,24,26–28,30–33,35]. Notably, some studies evaluated the decision problem from more than one perspective. Next to the perspective, the studies' time horizons present a core issue, with the longer time horizon generally being preferred but requiring long-term data and/or additional assumptions. The time-horizon varied across studies from one year to a lifetime. Four studies performed a retrospective analysis in which the additional benefit of QIV was estimated over 10 influenza seasons [26,27,32,34]. In some dynamic models, the total analysis time is longer than the time horizon (i.e. evaluation period) because of a 'burn-in'/'run-in' period [23,24,30,31]. This burn-in period is used to allow the model's dynamic behavior to settle down before the analysis between TIV and QIV is undertaken. For instance, in the study of Dolk et al. [24], each simulation ran for 40 years. The first 20 years were used for initializing age-dependent infection and immunity patterns in the population and the final 20 years for studying the intervention of QIV versus TIV.

All studies except one applied an equal discount rate for costs and health effects, ranging from 3% for the US [21,22,27,34,35], Finland [30], and Spain [25], to 5% for Canada [20,31]. Only the study for Germany used differential discount rates, that is, 3% for costs and 1.5% for health effects [24]. Three studies reported a discount rate for health effects only [29,34,35], as they limited discounting to life-years gained of influenza-related deaths. Two studies analyzing the impact of QIV retrospectively did not apply discounting [26,32].

To accommodate for uncertainty of relevant parameters in the model, most studies performed sensitivity analyses. A total of 13 studies performed a probabilistic sensitivity analysis (PSA) [20–25,27–31,33,35], 14 studies univariate sensitivity analyses [20–25,28–35], and 1 study a deterministic multivariate sensitivity analysis [31]. Descriptions on model validation were found to be scarce. The majority of studies performed cross-validation of the model outcomes to other studies [21–26,28–35]. Other reported validation efforts were double programming [33], face validity testing of the input data [31], and testing of the fit of the dynamic model to influenza incidence data [30,31]. In addition, Nagy et al. [30] reported that the temporal patterns of influenza incidence in Finland produced by the calibrated model were validated against Finnish national surveillance reports. For two studies, we did not find any model validation effort reported [20,27].

3.3. Characteristics of the vaccination programs and vaccines

Table 2 shows the characteristics of the vaccination programs/vaccines, used as main inputs for the models. Most studies focused on the whole population [20,22–24,27,29–33,35]. Two studies focused on the vaccination of the elderly aged ≥65 years [21,34], while three studies included elderly aged ≥65 years and people < 65 years with clinical risk conditions [25,26,28]. Vaccine coverage was predominantly based on current national uptake rates of the influenza vaccination program. Most studies focused on inactivated influenza vaccines only, while three studies also included a live-attenuated vaccine (LAIV) for age-groups where this vaccine is licensed [22,30,31].

All studies assumed equal vaccine efficacy of TIV and QIV against influenza type A viruses, as both vaccines contain the same influenza type A strains. Therefore, the vaccine efficacy against influenza A is not explicitly taken into consideration in this review. With regard to vaccine efficacy against influenza B, most studies used data from published meta-analysis by Tricco et al. [43] or DiazGranados et al. [44], while two studies [20,31] adopted the vaccine efficacy reported for the US vaccination program by Reed et al. [42]. Two studies did not differentiate between vaccine efficacy against influenza A and influenza B [24,29]. Almost all studies assumed that the vaccine efficacy of TIV against influenza B is proportional to the relative match with the circulating influenza B lineage in the last decade, with the match failing in approximately half of the seasons. In case of mismatched seasons, 11 studies assumed that TIV provides cross-protection against the mismatched influenza B lineage [20–24,26,28,31–34]. This level of cross-protection ranged between 60% and 70% of the matched vaccine efficacy. For QIV, studies predominantly applied the matched vaccine efficacy of TIV against both B-lineages. Chit et al. [21] increased the efficacy for 65+ year-olds from 49.0% for TIV to 50.7% for QIV. Four dynamic modeling studies reported information regarding the duration of the vaccine-induced protection [23,24,30,31]. Two studies set the average duration of vaccine protection at 1 year [23,31] and one study at 1.81 years [24] (presented in [39]). The study of Nagy et al. [30] used a probabilistic approach during the calibration process, sampling durations from a range of 0.5–3 years using a uniform distribution.

Figure 2 shows the incremental vaccine price of QIV over TIV. Seven studies based the vaccine price of QIV on published price lists [20,22–25,28,31], for instance, from the Centers of Disease Control and Prevention vaccine price list. Other studies assumed a hypothetical vaccine price for QIV [20,29,33,35], extrapolated the price increase from another country [31], or explored a range of vaccine price differences [27,34]. The incremental vaccine price varied considerably across studies, ranging from US $1.25 for Canada [20] to US $7.14 for the US [21]. Two studies assumed an equal vaccine price (price parity) of QIV and TIV [26,30], while the study of Uhart et al. [32] did not report vaccination costs, which, in interpreting their results, also reflects price parity between QIV and TIV. The three studies that included LAIV in their analysis

Table 2. Characteristics of the vaccination programs and its vaccines.

Reference and country	Included population	Vaccine type	Vaccine coverage (%)	Efficacy/effectiveness of TIV against influenza B (%)	Cross-protection of TIV against opposite B-virus (%)	Efficacy of QIV against influenza B (%)	Incremental vaccine price (2015 US $)
Chit [20], Canada	All ages	IIV	0–19 y: 31.0, 20–49 y: 27.0, 50–64 y: 47.0, 65–74 y: 71.0, 75–84 y: 81.0, ≥85 y: 78.0	Matched lineage: 47 Unmatched lineage: 28	Yes: 60	Matched efficacy of TIV against both B-lineages	1.25
Chit [21], United States	Elderly (≥65 y)	IIV (& high-dose IIV)	67	Overall influenza efficacy: 49.0	Yes: 60	Overall influenza efficacy: 50.7	7.14
Clements [22], United States	All ages	IIV for ≥50 y, IIV/LAIV market share for <50 y	< 5 y: 47.2, 5–17 y: 21.3,18–49 y: 30.5, 50–64 y: 44.5, ≥65 y: 66.6	Matched lineage: 66–77[a]. Unmatched lineage: 44–52[a]	Yes: 68	Matched efficacy of TIV against both B-lineages	TIV/QIV: 4.52. LAIV/QIV: −5.70[b]
de Boer [23], United States	All ages	IIV	0.5–2 y: 51.5, 2–4 y: 67.6, 5–10 y: 54.2, 11–14 y: 44.0, 15–18 y: 33.7, 19–49 y: 33.7, 50–64 y: 42.7, ≥65 y: 64.9	Matched: 49.2–80.0[a]. Unmatched: 34.4–56.0[a]	Yes: 70	Matched efficacy of TIV against both B-lineages	5.45–5.54[a]
Dolk [24], Germany	All ages	IIV	Healthy: 0–2 y: 19.2, 3–6 y: 22.4, 7–10 y: 23.6, 11–15 y: 11.0, 16–59 y: 16.9, ≥60 y: 48.8[c] At risk: 0–59 y: 33.0, ≥60 y: 64.9[c]	Matched: Overall influenza efficacy of 39–73[a]	Yes: 60[c]	Matched efficacy of TIV against both B-lineages	4.99
Garcia [25], Spain	All ages	IIV	Healthy: 65–69 y: 28.4, 70–74 y: 49.6, 75–79 y: 48.2, 80–84 y: 64.6, ≥85 y: 57.6 At risk: 0–17 y: 24.2, 18–49 y: 9.3, 50–64 y: 24.5, 65–69 y: 47.0, 70–74 y: 54.4, 75–79 y: 63.9, 80–84 y: 72.5, ≥85 y: 67.5	Matched lineage: 66.0–77.0[a]. Unmatched lineage: 44.0–52.0[a]	Yes: 67	Matched efficacy of TIV against both B-lineages	3.76
Jamotte [26], Australia	Elderly (≥65 y) and people 6 mo–64 y with clinical risk conditions	IIV	Healthy: 0–64 y: 0.0, ≥65 y: 74.6 At risk: 0–17 y: 41.3 18–64 y: 36.2, ≥65 y: 74.6	Matched: 66.0–77.0[a]. Unmatched: 44.0–52.0[a]	Yes: 67–68	Matched efficacy of TIV against both B-lineages	Price parity
Lee [27], United States	All ages	IIV	25[d]	Matched lineage: 47[d]. Unmatched lineage: 0	No	Matched efficacy of TIV against both B-lineages	Price parity: 5.16[e]
Meier [28], United Kingdom	Elderly (≥65 y) and people aged 18–64 y with clinical risk conditions	IIV	Healthy: 18–64 y: 0, ≥65 y: 71.1 At-risk: 18–49 y: 34.1, 50–64 y: 100, ≥65 y: 71.1	Matched lineage: 66.0–77.0[a]. Unmatched lineage: 54.3–63.7[a]	Yes: 68	Matched efficacy of TIV against both B-lineages	5.16
Mullikin [29], United States	All ages	IIV (& aIIV)	0–3 y: 72.2, 4–6 y: 63.4, 7–9 y: 61.0, 10–19 y: 49.3, 20–49 y: 32.3, 50–64 y: 45.3, ≥65 y: 65.0	Overall influenza efficacy of 0.40–0.65[a] in high match season, and 0.25–0.56[a] in low match season	NR	Overall influenza efficacy of high match season	4.34
Nagy [30], Finland	All ages	IIV for ≥18 y & IIV or LAIV for 2–17 y	0.5–2 y: 22.9, 3–4 y: 28.1, 5–14 y:24.0, 14–17 y: 22.9, 18–21 y: 12.0, 22–26 y: 0.091, 27–29 y: 10.9, 30–44 y: 13.0, 45–60 y: 18.0, 61–72 y: 40.9, ≥73 y: 70.1	Overall influenza efficacy: IIV: 48–59[a]. LAIV: 39–80[a]	No	Matched efficacy of TIV against both B-lineages	Price parity
Thommes [31], Canada and United Kingdom	All ages	Canada: IIV. UK: IIV for ≥18 y, LAIV for 2–17 y	Canada: 0 y: 16.8, 1 y: 32.9, 2–11 y: 28.3, 12–19 y: 22.9, 20–34 y: 16.1, 35–44 y: 20.7, 45–64 y: 31.4, ≥65 y: 64.4 UK: 0–1 y: 0, 2–17 y: 52.5 (UK1), 70.0 (UK2), 18–49: 3.9, 50–64 y: 17.6, ≥65 y: 71.1	Matched lineage: 66.0–77.0[a] for IIV, 53.0–73.0[a] for LAIV. Unmatched lineage: 44.0–52.0[a] for IIV, 34.0–53.0[a] for LAIV	Yes: 68	Matched efficacy of TIV against both B-lineages	Canada: 2.87. UK IIV: 5.22. UK LAIV: Price parity
Uhart [32], EU-5 and EU 27	All ages ≥ 6 mo	IIV	<2 y: 6.1–19.2, 2–17 y: 4.1–14.0, 18–49 y: 6.5–52.0, 50–64 y: 14.9–52.0, ≥65 y: 48.6–69.2[f]	Matched: 66.0–77.0[a]. Unmatched: 44.0–52.0[a]	Yes: 67	Matched efficacy of TIV against both B-lineages.	NA
van Bellinghen [33], United Kingdom	All ages	IIV	Healthy: 0–64 y: 0, ≥65 y: 71.2 Clinical risk conditions: 0–4 y: 17.2, 4–64 y: 44.5, ≥65 y: 71.2	Matched lineage: 66.0–77.0[a]. Unmatched lineage: 44.0–52.0[a]	Yes: 68	Matched efficacy of TIV against both B-lineages	1.37
You [34], Hong Kong	Elderly (≥65 y)	IIV	39.1	Matched lineage: 45–75[a]. Unmatched lineage: 32–53[a]	Yes: 70	Matched efficacy of TIV against both B-lineages	1.00–10.01
You [35], Hong Kong	All ages	IIV	0–4 y: 28.4, 5–14 y: 11.0, 15–64 y: 10.3, ≥65 y: 39.1	Matched lineage: 49.2–68.8[a]. Unmatched lineage: 0	No	Matched efficacy of TIV against both B-lineages	3.10

aIIV: adjuvanted inactivated influenza vaccine; IIV: inactivated influenza vaccine; LAIV: live attenuated influenza vaccine; NA: not applicable; NR: not reported. [a]Depending on age. [b]Switch from trivalent LAIV to quadrivalent IIV. [c]Adopted from Eichner et al. [39]. [d]Averaged over 10 seasons. [e]Results were derived from the corrigendum [36]. [f]Depending on country.

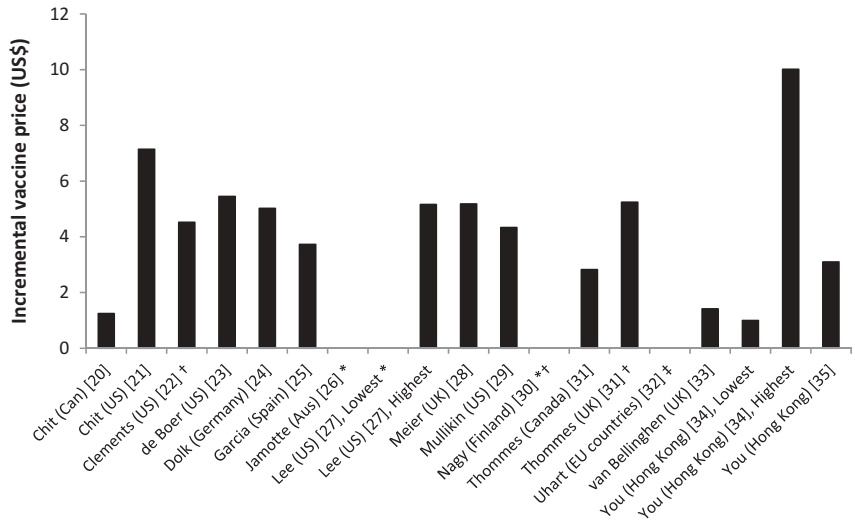

Figure 2. The incremental vaccine price of quadrivalent influenza vaccine (QIV) as compared with trivalent influenza vaccine (TIV) used across included studies. Prices are converted to 2015 US$. * These studies assumed price parity between QIV and TIV. † For these studies incremental vaccine prices of inactivated vaccines were shown only. For live-attenuated influenza vaccines (LAIV), price parity was assumed between LAIV and quadrivalent LAIV. ‡ The study of Uhart *et al.* [32] did not include vaccination costs, which reflects price parity.

used the same price for trivalent LAIV and Q-LAIV [22,30,31]. Vaccine administration costs were excluded in this review, as these costs are expected to be identical for TIV and QIV.

3.4. Influenza-related characteristics

Table 3 depicts an overview of the influenza-related input characteristics. An important epidemiological parameter concerns the probability to contract influenza among unvaccinated persons (attack rate). Half of studies reported this parameter [21,22,25–29,33]. In these studies, the probability of getting infected was age-dependent, being higher for children than for adults. Influenza cases were then split to subtype and lineage using laboratory data on influenza-positive tests. No distinction by age group was made in any study in the division of the influenza cases over influenza A and influenza B. Dynamic models estimated influenza incidence by subtype and lineage incidence by calibrating the model on time series of influenza-like illness incidences combined with laboratory data on influenza-positive tests [23,24,30,31]. Logically, studies with a dynamic modeling approach rather reported a basic reproduction number (R_0) than attack rates to demonstrate the spread of infection within the population. Notably, the R_0 reflects the average number of secondary infectious individuals produced by an average primary infectious case in a totally susceptible population.

The number of influenza-related hospitalizations or deaths was mostly calculated by multiplying the number of symptomatic influenza cases with the age-specific probabilities of these events, while some studies applied event rates on the study population directly. Other studies [34,35] used a top-down approach similar to the model of Reed et al. [42], estimating the number of influenza cases by dividing national influenza-associated death rates with influenza case-fatality ratios from the literature. Three studies used outcomes data that were specific for influenza B [30,34,35]. Two studies from Hong Kong used influenza B-specific hospitalization rates and/or influenza B mortality rates [34,35], while Nagy et al. [30] adapted subtype-specific outcomes estimated from the UK to Finland. All other studies used the same outcome probabilities across all influenza subtypes.

The QALY loss per influenza illness is calculated using two main parameters, that is, the quality of life estimate of influenza disease (utility) and the duration of the associated episode. Most studies split the duration and utility for influenza in two different categories, that is, uncomplicated and complicated influenza infections (including hospitalization) [21,23–25,28,31,33–35], while three studies applied average estimates of influenza-related QALY losses directly from the literature [20,23,30]. One study ignored QALY losses due to influenza illness assuming the disease to be transitory with negligible impact on the overall quality of life, but included QALY losses due to mortality [22]. We found that all studies based their QALY estimates on published data from non-subtyped influenza cases; that is, no studies used data specific for influenza type B infection.

Influenza-related costs can be separated into health-care and non-health-care costs. The health-care cost includes predominantly GP costs, hospitalization costs, and drug costs, while non-health-care costs include costs for travelling and productivity losses due to work loss. Overall, we found that on average the studies for the US had higher health-care costs than the studies from other countries. With regard to productivity losses of influenza-associated deaths, five studies [24,27,28,30,35] used the human capital approach valuing productivity losses until the age of retirement (Table 3). Three studies [20,21,23] applied the friction cost methods, assuming that an employee falling out of the production process will be replaced by an unemployed person after a friction period and that a certain elasticity of labor time and production applies. Again, no studies used data on resource use or absenteeism that was stratified by influenza subtype.

A final important parameter of interest concerns the duration of protection after natural infection. This parameter was implemented in four dynamic modeling studies [23,24,30,31].

Table 3. Influenza-related input parameters of the included studies.

Reference	Annual influenza attack rate (%)/R_0	Proportion influenza B of total influenza circulation, proportion influenza B unmatched	Health effects influenza morbidity	Health effects influenza mortality	Work days lost
Chit [20], Canada	NR	NR	QALY loss of 0.0146–0.0293[a] per influenza case	Life-expectancy corrected for age-specific utility	Illness: NR Mortality: friction period of 90 days
Chit [21], United States	≥65 y: 5.7	NR	Uncomplicated: utility of 0.25 for 6.0 days. Hospitalized: utility of 0.2 for 8.3 days	Life-expectancy corrected for age-specific utility	Uncomplicated: 1.9 days. Complicated 8.3 days. Mortality: friction period of 90 days
Clements [22], United States	<5 y: 20.3, 5–17 y: 10.2, 18–64 y: 6.6, ≥65 y: 9.0	21%, of which 50% unmatched	Not included	Life-expectancy corrected for age-specific utility	No complication: 0.5–1 day. Complicated: 1.15–4.89 days. Hospitalized: 9.43–16.68 days. Mortality: not included
de Boer [23], United States	R_0 B/Victoria: 1.10–1.77, R_0 B/Yamagata: 1.02–1.86	Intrinsic to calibration process	Uncomplicated: QALY loss of 0.005 for children and 0.007 for adults. Complicated: QALY loss of 0.042–0.076 for children[d] and 0.013 for adults	Life-expectancy corrected for age-specific utility	Uncomplicated: 0.5–1 days[b]. Complicated: 1–7 days[b] . Hospitalized: 8–31 days[b]. Mortality: friction period of 40 days
Dolk [24], Germany	R_0: 1.575[c]	Intrinsic to calibration process	Uncomplicated: disutility of 0.32 for 6.6–7.7 days (without antiviral treatment) or 5.6–6.7 days (with antiviral treatment). Outpatient visit: disutility of 0.127–0.262 for 3.3–10.1 days.[d] Hospitalized: disutility of 0.38 for 3.3–10.1 days.[d]	Life-expectancy corrected for age-specific utility	Uncomplicated: 2.6 days. Hospitalized: 8.8 days. Parental: 4.8 days. Mortality: human capital approach
Garcia [25], Spain	0–17 y: 19.2, 18–64 y: 6.55, ≥65 y: 6.17	25.7% of which 64.2% unmatched	Uncomplicated: disutility of 0.32–0.465[a] for 7.5 days. Outpatient complications: disutility of 0.32–0.465[a] for 5.4 days. Inpatient complications: 0.54–0.60[a] for 1.93–14.13 days[d]	Life-expectancy corrected for age-specific utility	Illness: NR. Mortality: not included
Jamotte [26], Australia	6 mo–4 y: 18.8, 5–17 y: 16.5, 18–64 y: 3.6, ≥65 y: 4.9	24.8% of which 52.6% unmatched	NA	NA	Illness: 4 days. Parental: 0.98 days. Mortality: not included
Lee [27], United States	Estimated combining age-specific influenza mortality rates with a case-fatality ratio[e]	23% of which 49.4% unmatched[e]	NA	NA	Illness: 3.2 days. Parental: 2.54 days. Mortality: human capital approach
Meier [28], United Kingdom	18–64 y: 6.6, ≥65 y: 6.2	25.7%, unmatched NR	Uncomplicated: Disutility of 0.68–0.88[a] for 7.5 days (without antiviral treatment) or 5 days (with antiviral treatment). Complicated: disutility of 0.80–0.98[a] for 14.3 days.	Life-expectancy corrected for age-specific utility	Illness: NR. Hospitalization: 7.0–10.6 days. Mortality: human capital approach
Mullikin [29], United States	0–4 y: 20.3, 5–17 y: 10.2, 18–64 y: 6.6, ≥65 y: 9.0	21.3%, unmatched NR	Uncomplicated: no QALY loss. Complicated: QALY loss 0.00904 to 0.10000[d]	Life-expectancy corrected for age-specific utility	Illness: NR. Mortality: not included
Nagy [30], Finland	R_0: 1.6–3.9	Intrinsic to calibration process	QALY loss of 0.0429 per influenza case	Life-expectancy corrected for age-specific utility	Uncomplicated: 1.56 days. Caregiver: 2.1–3.2 days. Hospitalized: 2.2 days. Mortality: Human capital approach
Thommes [31], Canada and United Kingdom	R_0 mean: 1.3, R_0 seasonal peak: 1.9	Intrinsic to calibration process	Canada: uncomplicated: QALY loss of 0.0041. Complicated: QALY loss of 0.0146–0.0293[a]	Life-expectancy corrected for age-specific utility	NA

(*Continued*)

Table 3. (Continued).

Reference	Annual influenza attack rate (%)/R_0	Proportion influenza B of total influenza circulation, proportion influenza B unmatched	Health effects influenza morbidity	Health effects influenza mortality	Work days lost
Uhart [32], EU-5 and EU 27	6 mo–17 y: 19.3, 18–64 y: 3.6, ≥65 y: 4.9	21.5–27.4%,[f] unmatched NR	NA	NA	Illness: 4 days. Parental: 0.98 days. Mortality: not included
van Bellinghen [33], United Kingdom	0–17 y: 19.2, 18–64 y: 6.55, ≥65 y: 6.17	24.8% of which 52.4% unmatched	Uncomplicated: disutility of 0.88 for 7.5 days (without antiviral treatment) or 5 days (with antiviral treatment). Complicated: disutility of 0.98 for 5.4 days.	Life-expectancy corrected for age-specific utility	NA
You [34], Hong Kong	Estimated combining age-specific influenza mortality rates with a case-fatality ratio	NR	Outpatient care: disutility of 0.40 for 7 days. Hospitalized: disutility of 0.5 (Non ICU care) or 0.62 (ICU care) for 10.8 days	Life-expectancy corrected for age-specific utility	Outpatient visit: 1 day for caregiver. Hospitalization: 10.8 days for caregiver. Mortality: not included
You [35], Hong Kong	Estimated combining age-specific influenza mortality rates with a case-fatality rate	NA, of which 53.5% unmatched	Outpatient care: disutility of 0.40 for 7 days. Hospitalization: disutility of 0.5 (Non ICU care) or 0.62 (ICU care) for 10.8 days	Life-expectancy corrected for age-specific utility	Outpatient visit: 1 day. Hospitalization: 10.8 days. Mortality: human capital approach

NA: not applicable; NR: not reported. QALY: quality-adjusted life-year; R_0: basic reproduction number. [a]Depending on age-group. [b]Depending on age-group and clinical risk-status. [c]Presented by Eichner et al. [39]. [d]Depending on complication. [e]Presented by Reed et al. [42]. [f]Varying by country.

All these studies assumed that the duration of naturally acquired immunity was longer than vaccination-acquired immunity. Two studies used an average duration of naturally acquired immunity for influenza B of 12 years [23,31], while one study used a duration of 7 years [24] (as presented in [39]). The study of Nagy et al. [30] used a probabilistic approach for this parameters during their calibration process, sampling input values between 0.5 and 75 years using a uniform distribution.

3.5. Study outcomes

The effectiveness and cost-effectiveness results of QIV versus TIV are summarized in Table 4. We found that the impact of QIV on influenza-related morbidity and mortality varied considerably across studies. Overall, dynamic models reported higher reductions of influenza-related morbidity as compared with static models. The impact of QIV on the total number of influenza cases (type A and B) as compared with TIV ranged from a reduction of 0.15% in the US using a static model [22] to 6.47% in the US using a dynamic model [29]. Studies presenting results for influenza B only found reductions of 29.2% for the US using a dynamic model [23] and 14.7% for Hong Kong using a static model [35]. One study focusing on elderly in Hong Kong presented incidence rates of averted influenza B cases, finding a total reduction of 118–508 per 100,000 person years [34]. Impact on influenza-related mortality was generally estimated somewhat higher than influenza morbidity (Table 4).

Figure 3 shows the cost-effectiveness results of QIV versus TIV, expressed as incremental cost-effectiveness ratios (ICERs). From a payer's perspective, a cost-effectiveness study for Finland [30] and cost-comparisons for Australia and the European Union [26,32] found that QIV would result in cost-savings (Figure 3A). However, these studies assumed price parity between QIV and TIV [26,30] or excluded vaccination costs in their analysis [32]. The highest ICER was found by Chit et al. [21] for the US, estimating an ICER of US $145,705/QALY using a static model. From a societal perspective, cost-savings were reported by one static cost-comparison model in the US [27] and two dynamic models in the US and Germany [24,29] (Figure 3B). The highest ICER was in a scenario found by You et al. [34] for Hong Kong, estimating that in a season with a good match and an incremental vaccine price of US $10, the ICER could increase to US $254,245 per QALY gained [34] from the societal perspective.

Most studies drew a conclusion on whether implementing QIV could be regarded as a cost-effective intervention. However, most countries do not have an official willingness-to-pay (WTP) threshold, whereas the National Institute for Health and Clinical Excellence (NICE) in the UK considers a WTP threshold of US$29,070–43,600 (£20,000–30,000) per QALY for vaccines [45]. When no official thresholds were available, studies often referred to WTP thresholds used in earlier published cost-effectiveness studies or to recommendations of the World Health Organization (WHO), suggesting that an intervention is cost-effective if the ICER is below three times the gross domestic product per capita of a country [46]. Applying this WHO recommendation on the

Table 4. Effectiveness and cost-effectiveness of QIV as compared with TIV and key parameters towards cost-effectiveness results.

Reference	Reduction of influenza cases	Reduction of influenza deaths	Payer's perspective results (2015, US $)	Societal perspective results (2015, US $)	Key parameters to cost-effectiveness outcomes[a]
Chit [20], Canada	1.25%	0.92%	78,303/QALY	52,169/QALY	QIV price, vaccine match, cross-protection of TIV, level of B circulation, hourly labor cost
Chit [21], United States	1.68%	0.72%	145,705/QALY	139,159/QALY	Not reported for QIV vs. TIV comparison
Clements [22], United States	0.15%	2.36%	NA	95,150/QALY	Cross-protection of TIV, vaccine match, level of influenza B circulation
de Boer [23], United States	29.2% (only influenza B)	31.7% (only influenza B)	31,934/QALY	27,891/QALY	Cross-protection of TIV, probabilities of death, vaccine efficacy
Dolk [24], Germany	4.02%	6.40%	18,760/QALY	CS	Probability of death, duration of natural immunity, disutility of influenza
Garcia [25], Spain	18,565 cases in one season	181 deaths in one season	16,695/QALY	13,054/QALY	Circulation influenza A, vaccine match
Jamotte [26], Australia	92 per 100,000 py (average)	0.92 per 100,000 py (average)	Total savings: 25.3 million	Total savings: 32.3 million	Influenza attack rate, cross-protection of TIV, proportion of influenza B, vaccine match
Lee [27], United States	1.40%[b]	1.40%[b]	Average annual costs: −30.5 to 344.7 million[c]	Average annual costs of −325.0 to 50.1 million[c]	QIV price
Meier [28], United Kingdom	1.17%	3.59%	21,615/QALY	19,921/QALY	Circulation influenza A, vaccine match
Mullikin [29], United States	6.47%	7.00%	5,188/QALY	CS	Vaccine match
Nagy [30], Finland	11.3%	18.2%	CS	CS	Influenza transmission coefficient/infectious period and QIV price
Thommes [31], Canada and United Kingdom	Can: 4.62% UK1: 1.44%[d] UK2: 1.83%[d]	Can: 6.78% UK1: 4.29%[d] UK2: 4.90%[d]	Can: 6,551/QALY UK1: 11,791/QALY[d] UK2: 10,676/QALY[d]	NA	QIV price, outcome probabilities, and inclusion of illness-related QALY loss
Uhart [32], European Union	EU5: 32.4 per 100,000 py[e]	EU5: 0.31 per 100,000 py[e]	Total savings: EU5: 117,437 million[e] EU27: 180,062 million[e]	Total savings: EU5: 325,354 million[e] EU27: 513,959 million[e]	Cross-protection of TIV, vaccine effectiveness, hospitalization costs
van Bellinghen [33], United Kingdom	0.69%	2.82%	8,611/QALY	NA	Distribution influenza A and B, vaccine match, QIV price
You [34], Hong Kong	65–79 y: 118 per 100,000 py. ≥80 y: 508 per 100,000 py (only influenza B)	65–79 y: 0.0589 per 100,000. ≥80 y: 0.254 per 100,000 py (only influenza B)	NA	65–79 y: 14,906–254,245/QALY[f].≥80 y: CS-70,147/QALY[f]	QIV price
You [35], Hong Kong	14.7% (only influenza B)	14.9% (only influenza B)	23,335/QALY	12,965/QALY	QIV price and proportion influenza B

Can: Canada; CS: cost saving; NA: not applicable; py: person years; QALY: quality-adjusted life-years; QIV: quadrivalent influenza vaccine; TIV: trivalent influenza vaccine; UK: United Kingdom. [a]Based on judgment of the reviewers. [b]For Lee et al. [27], reductions in influenza cases and deaths were directly adapted from Reed et al. [42]. [c]Shown for a QIV versus TIV price difference ranging from US $0 to US $5; Results were derived from the published corrigendum [36]. [d]UK1: Vaccine uptake rate of 52.5% in children aged 2–17 years. UK2: Vaccine uptake rate of 70% in children aged 2–17 years. [e]EU5 includes France, Germany, Italy, Spain, and United Kingdom. EU27 results were based on extrapolations of EU5. [f] Shown for a QIV versus TIV price difference ranging from US $1 to US $10. The season 2002 was excluded as no results were presented for this year.

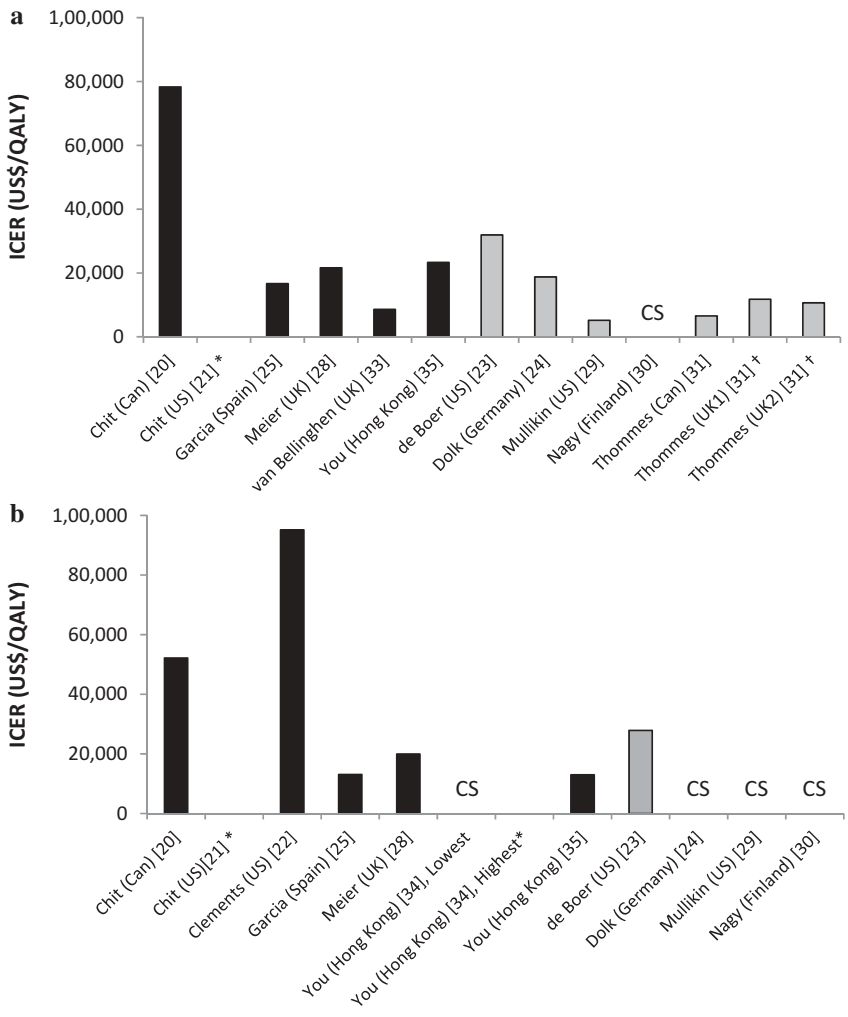

Figure 3. Incremental cost-effectiveness ratios (ICER) in US$/quality-adjusted life year (QALY) gained of quadrivalent influenza vaccine as compared with trivalent influenza vaccine. ICERs are converted to 2015 US$. Static models are presented in black and dynamic models in grey. Results are presented from a payer's perspective (Figure 3A) and the societal perspective (Figure 3B). CS: Cost-saving. *:The ICERs of Chit *et al* [20] . and You *et al*. [34] (highest) are not presented due to graphical issues. Chit *et al*. [20] found an ICER of US $145,700 per QALY from the healthcare payer's perspective and US $139,200/QALY from the societal perspective. You *et al*. [34] (highest) found an ICER of US $254,200/QALY from the societal perspective. †UK1: Vaccine uptake rate of 52.5% in children aged 2-17 years. UK2: Vaccine uptake rate of 70% in children aged 2-17 years.

US would result in a WTP threshold of US $150,000 per QALY gained. All cost-utility studies concluded that vaccination with QIV would be at least cost-effective as compared with TIV, when official or hypothetic thresholds were considered [20–25,28–31,33–35].

3.6. Key drivers of cost-effectiveness results

Parameters that were found to be of highest impact on cost-effectiveness outcomes are shown in Table 4. The four most reported key parameters were vaccine price of QIV, the level of cross-protection of TIV against the mismatched B virus strain, the distribution of influenza incidence between influenza A and influenza B, and the level of vaccine match of TIV with the circulating B lineages (Table 4). Obviously, higher vaccine price differences between QIV and TIV resulted in less beneficial cost-effectiveness outcomes. For instance, Nagy et al. [30] found that when an incremental vaccine price of US $3.96 for QIV over TIV would be assumed instead of price parity, the estimated amount of cost saving would be reduced by 30%. Also, the high ICER of US $139,027 per QALY gained for the US elderly by Chit et al. [21] could be explained by a relatively high vaccine price of QIV.

The impact of cross-protection of TIV to the opposite B virus strain on the cost-effectiveness was explicitly illustrated by the study of de Boer et al. [23], showing that decreasing the level of cross-protection from 70% to 50% in the US turned the ICER from US $27,891 per QALY gained into cost-saving/dominant. Furthermore, the circulation and distribution of, respectively, influenza A and influenza B and related vaccine matching/efficacy had also a strong effect on the ICER. For example, van Bellinghen et al. [33] noted that, in a scenario of 0.4% circulation of influenza B, the ICER would increase to US $587,000 per QALY gained and, in a scenario of 30% circulation of influenza B, the ICER would decrease to US $2,200 per QALY gained, both as compared to a base case of US $8,611 per QALY at 24.8% circulation. Additionally, in a scenario of 99.0% matching of TIV with the circulating influenza B virus strain instead of 52.3%, the ICER would rise to US $450,000 per QALY gained.

4. Expert commentary

This is the first systematic review concerning the health-economic value of QIV so far. According to the current literature, QIV appears to be a cost-effective intervention as compared with TIV. All studies found that QIV resulted in valuable health benefits as compared with TIV by reducing influenza related morbidity and mortality within a range of 0.15–6.5%. Additionally, QIV was estimated to save costs to the healthcare system and to society, partially or even fully compensating for the higher vaccine price of QIV compared to that of TIV. Although conclusions on cost-effectiveness were generally similar, we found substantial heterogeneity across cost-effectiveness results. ICERs varied from cost-saving to $146,000 from a health-care payer's perspective and cost-saving to $140,000 from a societal perspective. Identified key parameters to cost-effectiveness outcomes included vaccine price, circulation of the B-virus not included in TIV and cross-protection of TIV against the opposite B-virus.

Modeling approach was found to be important with regard to cost-effectiveness results. Despite the recommendations of Quinn et al. [13] and working groups on cost-effectiveness analyses of vaccines [40,47], only five studies used a dynamic transmission model. We found that dynamic models predicted a higher impact of QIV on influenza morbidity than static models, resulting in better cost-effectiveness outcomes. Vaccination reduces the overall influenza transmission within a population. As static models use a constant force of infection, they do not quantify the indirect impact of vaccination. Therefore, we recommend that, although static models can be informative for an initial preliminary analysis, dynamic models are required to study the full impact of QIV on health-economic outcomes. Obviously, the downside of this recommendation is that dynamic models demand more (fine-grained) input data than static models [41].

Notably, the impact of modeling approaches depends on the current vaccination policy of the studied country. Countries with universal influenza vaccination recommendations, such as the US, have relatively high vaccination coverage among children. As children seem to represent an important group in influenza transmission [48,49], the additional impact of dynamic models over static models will be higher in countries with universal vaccination as compared with countries restricting influenza vaccination to elderly and specific high-risk groups. Additionally, when – from a societal perspective – cost savings due to (parental) work loss are taken into account, potentially better cost-effectiveness outcomes may ensue. On the other hand, complication rates are highest among the elderly. Therefore, we would emphasize that cost-effectiveness outcomes might be highly influenced by the target group of the vaccination program.

An important key aspect to cost-effectiveness outcomes is whether cross-protection of TIV against the mismatched B virus is taken into account. As mentioned by Quinn et al. [13], recent evidence suggests that cross-protection of TIV to the opposite influenza B virus exists, potentially diminishing the impact of QIV significantly [43,44]. Our review shows that the majority of studies included cross-protection in their analyses. Most studies referred to systematic reviews by Tricco et al. [43] and DiazGranados et al. [44], estimating that the vaccine efficacy of TIV against the non-included B virus strain is 65–70% of the matched efficacy. Studies on single influenza seasons confirmed the finding of cross-protection during the 2012–2013 season in the US and Canada [50,51], but not during the 2011–2012 season in Canada [50]. Additionally, a recently published serological study demonstrated that antibodies elicited with inactivated TIV containing a Victoria-lineage strain were highly cross-reactive to a Yamagata-lineage strain [52]. As current evidence supports the existence of cross-protection, we endorse the inclusion of this aspect in cost-effectiveness models. However, as bias cannot be ruled out due to pre-existing immunity as a result of prior vaccination or natural infection, the exact estimate is unclear. Therefore, we highly recommend to perform sensitivity analyses on this parameter.

Another key parameter influencing cost-effectiveness outcomes is the vaccine price. Many studies had to make assumptions on the price premium of QIV as compared with TIV, since no official vaccine price was available at the moment of analysis. Therefore, the vaccine price should be taken into account when interpreting results, as for instance cost-effectiveness studies assuming a price parity between QIV and TIV will almost automatically result in cost-saving outcomes. On the other hand, assuming price parity in the absence of an official QIV price and just showing the expected net health benefit of QIV over TIV avoids drawing the wrong conclusion. Cost-effectiveness results could then be easily updated when a vaccine price becomes available. Currently, price lists of the US CDC show that the vaccine manufacturers increased the price of inactivated QIVs significantly, at around 50% higher than inactivated TIVs, although there was no price increase shown for Q-LAIV as compared with trivalent LAIV [53]. However, in large-scale public health programs, such as influenza vaccination, vaccines might be procured at relatively lower prices than indicated by the list prices.

Cost-effectiveness results also tend to be highly sensitive to the level of circulation of the influenza B virus. In seasons with a proper vaccine match and no co-circulation of both B lineages, the effect of QIV over TIV is likely to be negligible. This was highlighted in some studies that analyzed the impact of QIV retrospectively over the period 2001–2010, demonstrating a wide variation in cost-effectiveness results between different seasons [27,33,34]. As any influenza virus, influenza B incidence varies across countries and regions [4,5]. For instance, three studies estimated the proportion of mismatched influenza B infections at 50% of the total influenza B infections in the US between 1999 and 2009, in line with 52.6% in Australia between 2002 and 2012, and 52.4%, in the UK between 2000 and 2010 [22,26,33]. However, the study by Heikkinen et al. [54] found that this proportion was only 41.7% in Finland in the period 1999–2012. Therefore, studies analyzing the retrospective impact of QIV should aim to use country-specific data.

We noticed that most studies used equal estimates of resource use and costs across all influenza subtypes. As suggested by Quinn *et al*. [13], influenza B might be associated with higher morbidity in children as compared with the elderly. In the elderly, highest hospitalization and mortality

rates were found for the influenza A/H3N2 subtype, followed by influenza B virus and the A/H1N1 subtype. Usage of outcome estimates that are not specified by seasonal influenza subtype might therefore be considered nonoptimal. However, a study of Mosnier et al. [55] showed that despite differences in age-distribution between influenza A and influenza B, no differences on clinical severity were found between influenza virus types and subtypes among GP visiting influenza cases. Notably, when influenza B causes less severe disease in adults and the elderly as compared with influenza A, patients with influenza B will be underrepresented at medical facilities to undergo laboratory testing for subtype. This may complicate the split of influenza cases by subtype as performed in static models. A further complication might be that available data on laboratory tests were often subtyped between A and B, but not between B/Vic and B/Yam [56]. Regarding influenza-related mortality, the impact of QIV might be overestimated when A/H3N2 is indeed related to higher mortality in elderly than influenza B. As data on influenza B incidence and its resource use are still not widely available, more evidence on incidence and resource use by subtype would be desirable to improve the validity of cost-effectiveness results.

Next to nonlinear influenza epidemiology by age and subtype, pre-existing immunity due to prior natural influenza infection or vaccination history might induce inaccuracy. Duration of naturally acquired immunity is expected to be influenced by the natural waning of immunity within the individual as well as the drift of influenza viruses over time [57]. However, evidence on this aspect is, to the best of our knowledge, still scarce. Dynamic modeling studies included in this review, predominantly derived inputs for this parameter from a study of Vynnycky et al. [58]. This study calibrated a dynamic model on influenza incidence patterns of the UK, with optimal fit occurring when durations of naturally acquired immunity were set at 6 years for influenza A and 12 years for influenza B. Also a study by Eichner et al. [39], describing the influenza dynamics for Germany, assumed a longer naturally acquired immunity for influenza B as compared with influenza A/H3N2 (3.5 years versus 7 years). The study of Nagy et al. [30] found eligible simulations during their calibration process for durations of naturally acquired immunity against influenza B ranging between 0.5 and 75 years. A recent dynamic modeling study from Japan [59], however, estimated much shorter durations of natural immunity against influenza B than the above mentioned studies, estimating 1.15 years for B/Vic and only 0.08 years for B/Yam, although this does not align well with current knowledge on the relatively conserved antigenic nature of influenza B [60]. For the duration of vaccine-induced protection, a recent study by Kissling et al. [57] suggested that protection against influenza B was longer than that against influenza A/H3N2, possibly due to a more rapid antigenic drift of A/H3N2 [61]. Related to this aspect, Höpping et al. [62] recently presented an approach to optimize the effectiveness of TIV by choosing the included influenza B strain on the basis of the population's pre-existing immunity instead of taking the virus strain that circulated in the prior season. They argued that by taking into account the time since vaccination, antigenic drift, and serological parameters of each B virus strain, the level of residual protection against B/Yam and B/Vic could be estimated. By selecting the influenza B virus strain with the lowest residual protection, high protection levels against both influenza B viruses would be present after vaccination, potentially giving a better protection in case of a vaccine mismatch. Although this strategy is expected to be still inferior to QIV, Höpping et al. [62] suggested that it might at least partially capture the benefit of QIV, without any additional vaccine costs. So far, no study has ever compared the cost-effectiveness of QIV versus TIV using this 'Höpping' approach, which, however, might be of interest and complement existing studies.

With regard to the quality of reporting according to the CHEERS criteria [15], we found that adherence to this checklist was acceptable. However, we noticed that only a few studies provided arguments whether the chosen time horizon was appropriate to capture all the various effects and consequences of the intervention. Indeed, influenza is often considered a seasonal issue, with each year different types and/or subtypes of influenza predominantly circulating, varying in disease severity. Yet, considering the fact that influenza is an annual recurrent disease with potential crossover effects from season to season, a time horizon of more than one year is needed to capture all the various effects and consequences of vaccination policies. Hence, models should transparently argue whether their chosen time horizon is long enough to include relevant subsequent effects.

A second concern that emerged from the analysis using the CHEERS checklist relates to the exact descriptions of the population and instruments used to estimate the impact of influenza on quality-of-life. We noticed that many of the included studies used utilities from outdated studies (mostly other models) that were based on small sample sizes. Updating a systematic review on studies measuring the impact of quality-of-life estimated of influenza morbidity by Van Hoek et al. [63], we found that the evidence on this aspect is still limited [64]. Although two studies were published that used EQ-5D to measure quality-of-life of influenza morbidity based on larger sample sizes [63,65], generalizability might be limited as these analyses were conducted among patients infected with the pandemic H1N1 influenza strain. As pandemic H1N1 was generally seen as a milder variant of disease than A/H3N2 in adults, these values might not be truly representative for seasonal influenza in general [66]. Therefore, we recommend precise studies on estimating the quality-of-life in laboratory-confirmed seasonal influenza patients with standardized instruments.

The reporting regarding performed validation processes was found to be limited. A proper validation process of the model and its transparent reporting will improve the credibility of the model outcomes. Although most studies performed cross-validation of model outcomes to similar studies, these comparisons are mostly hampered by differences between model types and/or model inputs. Notably, as the inclusion of parameters such as waning of immunity or antigenic drift of viruses strongly enhance the complexity of (dynamic) models, validation techniques on the computerized model and its outcomes will become increasingly important. Obviously, the transparency of a model increases considerably by making the model publicly available, which – to the best of our

knowledge – was only done for the model used in the Canadian study by Chit et al. [20]. In addition, we would advocate the use of structured model validation checklists, as researchers tend to do more validation efforts than they report in their manuscripts [67].

Finally, we found that the majority of the studies were funded by pharmaceutical companies. We feel that, in addition to these sponsored studies, also publicly funded economic evaluations of QIV are needed to validate the findings from industry-funded studies. Furthermore, there were no studies performed in low- and middle-income countries (LMICs), where it would also be valuable to know if more restricted budgets could be better spent on QIVs or TIVs. Indeed, due to differences in demographics, comorbidities, and healthcare facilities, results from industrialized countries are not directly transferable to LMICs. For instance, as influenza B rather tends to infect adolescents and young adults than elderly, the impact might be higher in LMICs which generally have younger populations. An individual-based modeling exercise found that QIV would reduce influenza-related hospitalizations and deaths by 18% as compared with TIV in a community in South Africa between 2003 and 2013, while this was only 2% in Australia in the same period [68].

The main limitation of our study is that our search was restricted to the English language. A major strength of our study is that we systematically searched for economic evaluations of QIV using multiple databases. We converted study results to the same price year and corrected for differences in purchasing power to enhance comparability. Another strength is that we checked whether the key challenges mentioned by Quinn et al. [13] were addressed properly. We also included studies in which the primary goal was not to evaluate the cost-effectiveness of QIV as compared with regular TIV, but for instance with high-dose TIV or adjuvant TIV [21,29], with cost-effectiveness of QIV emerging as an additional result. Chit et al. [21] estimated that a high-dose TIV, containing four times higher viral-loads as compared with regular TIV, would be more effective in preventing influenza disease in US elderly as compared with QIV. From the societal perspective, the authors estimated that high-dose TIV would be cost-saving as compared with QIV or US $5,157 per QALY gained as compared with regular TIV. Mullikin et al. [29] found from a societal perspective that TIV adjuvanted with the squalene-containing oil-in-water emulsion MF59 would be cost-saving in US elderly as compared with regular TIV and QIV.

In conclusion, published evidence of the economic consequences found that quadrivalent influenza vaccination is expected to be a cost-effective intervention as compared with TIV. However, the cost-effectiveness potential is strongly related to the price difference between QIV and TIV, and the level of cross-protection that TIV provides against the B virus strain that is not included in the vaccine. In other words, the benefits of QIV will vary strongly by season according to the match of TIV with the circulating B virus strain. It is therefore recommended to assess the impact of QIV versus TIV using data from multiple influenza seasons, which on average will give a better reflection of influenza B virus strain circulation from one year to another. As previously discussed by Quinn et al. [13], we support the inclusion of cross-protection of TIV against the mismatched B virus, the use of influenza B-specific data to estimate the disease burden, and the use of dynamic models. As we noticed that influenza B-specific data on disease burden and costs remains scarce, we recommend more research into these topics.

5. Five-year view

With regard to the future, we endorse studies aiming to unravel the immunogenicity of natural influenza infection and vaccination. Uncertainty around potential influential aspects like cross-protection, duration of vaccine-induced and natural immunity is large. Further insight into these aspects will improve the understanding and modeling of influenza transmission dynamics. However, as modeling of the relationship between (drifting) influenza viruses and immunity in the human population will increase the complexity of dynamic modeling, we would also advocate proper and transparent model validation processes in order to guarantee continued adequate evidence-based immunization decision-making.

Although newly developed influenza vaccines, like high-dose vaccines and adjuvanted vaccines, have been shown to have improved immunogenicity and may, potentially, induce better cross-protection as compared with standard vaccines [69,70], their efficacy toward unmatched viruses remain to be analyzed. To definitively overcome this issue, the development of broad-spectrum influenza vaccines is currently widely explored [71]. These so-called 'universal' vaccines aim to induce a humoral response against viral antigens or antigenic epitopes which are not affected by antigenic drift or they may activate a different immune pathway like the cellular immune response [60]. Universal vaccines may thus provide protection against not only many different viral strains and drift variants, but also against antigenically shifted viruses with pandemic potential. A recent modeling exercise demonstrated that such broad-spectrum vaccines have the potential to interrupt influenza transmission even at moderate uptake levels [72]. Although some promising broad-spectrum vaccines have entered already the phase of testing in clinical trials [60], it remains uncertain whether and when such vaccines will become publicly available. Certainly, duration of vaccine-induced protection will become a very important aspect with regard to the public-health impact and cost-effectiveness of these vaccines.

Key issues

- Quadrivalent influenza vaccines (QIVs) contain one additional influenza B strain as compared with trivalent influenza vaccines (TIVs).
- Quadrivalent influenza vaccination is supposed to provide better protection in seasons with a mismatch between TIV and the circulating B virus lineage or in seasons with co-circulation of both influenza B lineage.

- In this review, we identified 13 cost-effectiveness studies and three cost-comparisons of QIV versus TIV.
- Studies predominantly estimated QIV to be a cost-effective or even cost-saving intervention from payer's and societal perspectives.
- Levels of mismatched influenza B circulation, cross-protection of TIV to the mismatched B virus and the QIV price premium were identified as key factors influencing health-economic outcomes.
- Enhanced use of dynamic transmission models is recommended as these models account for indirect effects of vaccination on unvaccinated individuals.
- As disease burden might differ by influenza subtype, cost-effectiveness studies should be improved with subtype-specific data and increased evidence on this aspect should be made available.
- Better understanding of influenza immunogenicity by natural infection and vaccination is needed to improve simulation of influenza dynamics.
- Given the increasing complexity of (dynamic) influenza models, systematic validation of the model and its outcomes is strongly recommended.

Funding

This paper was not funded.

Declaration of interest

The appointments of PT de Boer and FCK Dolk are partly supported by grants of different pharmaceutical companies, including companies involved in the subject matter of this study. BM van Maanen and B Ultsch report no conflicts of interest. O Damm conducted studies for pharmaceutical companies, including companies involved in the subject matter of this study. P Crépey, R Pitman, JC Wilschut and MJ Postma have received grants and honoraria from pharmaceutical companies, including companies involved in the subject matter of this study. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

ORCID

Maarten J. Postma http://orcid.org/0000-0002-6306-3653

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. World Health Organization. Influenza (seasonal) [Internet]. 2014. Available from: http://www.who.int/mediacentre/factsheets/fs211/en/.
2. Molinari NM, Ortega-Sanchez IR, Messonnier ML, et al. The annual impact of seasonal influenza in the US: measuring disease burden and costs. Vaccine. 2007;25:5086–5096.
3. Ambrose CS, Levin MJ. The rationale for quadrivalent influenza vaccines. Hum Vaccin Immunother. 2012;8(1):81–88.
4. Caini S, Huang QS, Ciblak MA, et al. Epidemiological and virological characteristics of influenza B: results of the global influenza B study. Influenza Other Respir Viruses. 2015;9:3–12.
5. Caini S, Andrade W, Badur S, et al. Temporal patterns of influenza A and B in tropical and temperate countries: what are the lessons for influenza vaccination? Plos One. 2016;11(3):1–15.
6. US Food and Drug Administration. FDA approves first quadrivalent vaccine to prevent seasonal influenza. 2012. http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm294057.htm
7. Grohskopf LA, Sokolow LZ, Broder KR, et al. Prevention and control of seasonal influenza with vaccines. Recommendations of the advisory committee on immunization practices — United States, 2016–17 influenza season. Mmwr. 2016;65(5):1–54.
8. National Advisory Committee on Immunization (NACI). Canadian immunization guide chapter on influenza and statement on seasonal influenza vaccine for 2016-2017 [Internet]. (2016). Available from: http://www.phac-aspc.gc.ca/naci-ccni/flu-2016-grippe-eng.php#footnote74.
9. Immunise Australia Program. Influenza (flu) [Internet]. (2016). Available from: http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/content/immunise-influenza.
10. Public Health England. Flu plan Winter 2016/17 [Internet]. London Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/525967/Annual_flu_plan_2016_to_2017.pdf.
11. European Centre for Disease Prevention and Control. Influenza vaccination [Internet]. (2016). Available from: http://ecdc.europa.eu/en/healthtopics/seasonal_influenza/vaccines/Pages/influenza_vaccination.aspx.
12. Takla A, Wichmann O, Carrillo-Santisteve P, et al. Characteristics and practices of National Immunisation Technical Advisory Groups in Europe and potential for collaboration, April 2014. Eurosurveillance. 2015;20:9.
13. Quinn E, Jit M, Newall AT. Key issues and challenges in estimating the impact and cost-effectiveness of quadrivalent influenza vaccination. Expert Rev Pharmacoecon Outcomes Res. 2014;14(3):425–435.

•• **Explains key issues on estimating the cost-effectiveness of the quadrivalent influenza vaccine.**

14. Tisa V, Barberis I, Faccio V, et al. Quadrivalent influenza vaccine: a new opportunity to reduce the influenza burden. J Prev Med Hyg. 2016;57:28–33.
15. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. Pharmacoeconomics. 2013;31:361–367.
16. Vemer P, Corro Ramos I, van Voorn GAK, et al. AdViSHE: a validation-assessment tool of health-economic models for decision makers and model users. Pharmacoeconomics. 2016;34(4):349–361.
17. Organisation for Economic Co-operation and Development. Consumer prices. http://stats.oecd.org/Index.aspx?querytype=view&queryname=221#. (2017).
18. Organisation for Economic Co-Operation and Development. PPPs and exchange rates. 2017 http://stats.oecd.org/Index.aspx?datasetcode=SNA_TABLE4
19. Moher D, Liberati A, Tetzlaff J, et al., PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Plos Med [Internet]. 2009;6(7):e1000097. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19621072
20. Chit A, Roiz J, Aballea S. An assessment of the expected cost-effectiveness of quadrivalent influenza vaccines in Ontario, Canada using a static model. Plos One. 2015;10(7):1–15.
21. Chit A, Roiz J, Briquet B, et al. Expected cost effectiveness of high-dose trivalent influenza vaccine in US seniors. Vaccine. 2015;33(5):734–741.
22. Clements KM, Meier G, McGarry LJ, et al. Cost-effectiveness analysis of universal influenza vaccination with quadrivalent inactivated vaccine in the United States. Hum Vaccines Immunother. 2014;10(5):1171–1180.
23. De Boer PT, Crépey P, Pitman RJ, et al. Cost-effectiveness of quadrivalent versus trivalent influenza vaccine in the United States. Value Heal. 2016;19(8):964–975.

• **Cost-effectiveness study of QIV versus TIV using a dynamic transmission model.**

24. Dolk C, Eichner M, Welte R, et al. Cost-utility of quadrivalent versus trivalent influenza vaccine in Germany, using an individual-based dynamic transmission model. Pharmacoeconomics. 2016;34(12):1299–1308.

- **Cost-effectiveness study of QIV versus TIV using a dynamic transmission model.**

25. García A, Lejarazu R, Reina J, et al. Cost–effectiveness analysis of quadrivalent influenza vaccine in Spain. Hum Vaccin Immunother. 2016;12(9):2269–2277.
26. Jamotte A, Chong CF, Manton A, et al. Impact of quadrivalent influenza vaccine on public health and influenza-related costs in Australia. BMC Public Health. 2016;16(1):630.
27. Lee BY, Bartsch SM, Willig AM. The economic value of a quadrivalent versus trivalent influenza vaccine. Vaccine. 2012;30(52):7443–7446.
28. Meier G, Gregg M, Poulsen Nautrup B. Cost-effectiveness analysis of quadrivalent influenza vaccination in at-risk adults and the elderly: an updated analysis in the UK. J Med Econ. 2015;18(9):746–761.
29. Mullikin M, Tan L, Jansen JP, et al. A novel dynamic model for health economic analysis of influenza vaccination in the elderly. Infect Dis Ther. 2015;4(4):459–487.
- **Cost-effectiveness study of QIV versus TIV using a dynamic transmission model.**

30. Nagy L, Heikkinen T, Sackeyfio A, et al. The clinical impact and cost effectiveness of quadrivalent versus trivalent influenza vaccination in Finland. Pharmacoeconomics. 2016;34(9):939–951.
- **Cost-effectiveness study of QIV versus TIV using a dynamic transmission model.**

31. Thommes EW, Ismaila A, Chit A, et al. Cost-effectiveness evaluation of quadrivalent influenza vaccines for seasonal influenza prevention: a dynamic modeling study of Canada and the United Kingdom. BMC Infect Dis. 2015;15:465.
- **Cost-effectiveness study of QIV versus TIV using a dynamic transmission model.**

32. Uhart M, Clay E, Largeron N. Public health and economic impact of seasonal influenza vaccination with quadrivalent influenza vaccines compared to trivalent influenza vaccines in Europe. Hum Vaccin Immunother. 2016;12(9):2259–2268.
33. Van Bellinghen LA, Meier G, Van Vlaenderen I. The potential cost-effectiveness of quadrivalent versus trivalent influenza vaccine in elderly people and clinical risk groups in the UK: a lifetime multicohort model. Plos One. 2014;9:6.
34. You JH, Ming WK, Chan PK. Cost-effectiveness analysis of quadrivalent influenza vaccine versus trivalent influenza vaccine for elderly in Hong Kong. BMC Infect Dis. 2014;14:618.
35. You JHS, Ming WK, Chan PKS. Cost-effectiveness of quadrivalent influenza vaccine in Hong Kong - a decision analysis. Hum Vaccines Immunother. 2015;11(3):564–571.
36. Lee BY, Bartsch SM, Willig AM. Corrigendum to "The economic value of a quadrivalent versus trivalent influenza vaccine." Vaccine. 2013;31:2477–2479.
37. Crépey P, De Boer PT, Postma MJ. Retrospective public health impact of a quadrivalent influenza vaccine in the United States. Influenza Other Respi Viruses. 2015;9(Suppl 1):39–46.
38. Thommes EW, Chit A, Meier GC, et al. Examining Ontario's universal influenza immunization program with a multi-strain dynamic model. *Vaccine* [Internet]. 2014;32(39):5098–5117. DOI:10.1016/j.vaccine.2014.06.005
39. Eichner M, Schwehm M, Hain J, et al. 4Flu - an individual based simulation tool to study the effects of quadrivalent vaccination on seasonal influenza in Germany. BMC Infect Dis. 2014;14:365.
40. Ultsch B, Damm O, Beutels P, et al. Methods for health economic evaluation of vaccines and immunization decision frameworks: a consensus framework from a European vaccine economics community. Pharmacoeconomics. 2016;34(3):227–244.
41. Van Maanen BM, De Boer PT, Dolk FCK, et al. Dynamic modelling approaches for the analysis of the cost-effectiveness of seasonal influenza control. Expert Rev Vaccines. 2016;16(1):1–4.
42. Reed C, Meltzer MI, Finelli L, et al. Public health impact of including two lineages of influenza B in a quadrivalent seasonal influenza vaccine. Vaccine. 2012;30(11):1993–1998.
43. Tricco AC, Chit A, Soobiah C, et al. Comparing influenza vaccine efficacy against mismatched and matched strains: a systematic review and meta-analysis. BMC Med. 2013;11:153.
44. DiazGranados CA, Denis M, Plotkin S. Seasonal influenza vaccine efficacy and its determinants in children and non-elderly adults: a systematic review with meta-analyses of controlled trials. Vaccine. 2012;31(1):49–57.
45. Rawlins M, Barnett D, Stevens A. Pharmacoeconomics: NICE's approach to decision-making. Br J Clin Pharmacol. 2010;70(3):346–349.
46. Marseille E, Larson B, Kazi DS, et al. Thresholds for the cost-effectiveness of interventions: alternative approaches. Bull World Health Organ. 2015;93(October 2014):118–124.
47. Pitman R, Fisman D, Zaric GS, et al. Dynamic transmission modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group-5. Med Decis Mak. 2012;32(5):712–721.
48. Hodgson D, Baguelin M, Van Leeuwen E, et al. Effect of mass paediatric influenza vaccination on existing influenza vaccination programmes in England and Wales: a modelling and cost-effectiveness analysis. Lancet Public Heal. [Internet]. 2017;6(16):1–8. Available from: http://linkinghub.elsevier.com/retrieve/pii/S2468266716300445
49. Weidemann F, Remschmidt C, Buda S, et al. Is the impact of childhood influenza vaccination less than expected: a transmission modelling study. BMC Infect Dis [Internet]. 2017;17(1):258. DOI:10.1186/s12879-017-2344-6
50. Skowronski DM, Janjua NZ, Sabaiduc S, et al. Influenza A/subtype and B/lineage effectiveness estimates for the 2011-2012 trivalent vaccine: cross-season and cross-lineage protection with unchanged vaccine. J Infect Dis. 2014;210(1):126–137.
51. McLean HQ, Thompson MG, Sundaram ME, et al. Influenza vaccine effectiveness in the United States during 2012-2013: variable protection by age and virus type. J Infect Dis. 2015;211(10):1529–1540.
52. Lee J, Boutz DR, Chromikova V, et al. Molecular-level analysis of the serum antibody repertoire in young adults before and after seasonal influenza vaccination. Nat Med [Internet]. 2016 November;22:1456–1464. Available from: http://www.nature.com/doifinder/10.1038/nm.4224
53. Centers for Disease Control and Prevention. VFC CDC vaccine price list archives [Internet]. (2017). Available from: https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/archive.html.
54. Heikkinen T, Ikonen N, Ziegler T. Impact of influenza B lineage-level mismatch between trivalent seasonal influenza vaccines and circulating viruses, 1999-2012. Clin Infect Dis. 2014;59(11):1519–1524.
55. Mosnier A, Caini S, Daviaud I, et al. Clinical characteristics are similar across type A and B influenza virus infections. Plos One. 2015;10(9):1–13.
56. Tafalla M, Buijssen M, Geets R, et al. A comprehensive review of the epidemiology and disease burden of influenza B in 9 European countries. Hum Vaccin Immunother [Internet]. 2016;12(4):993–1002. DOI:10.1080/21645515.2015.1111494
57. Kissling E, Nunes B, Robertson C, et al. I- move multicentre case – control study 2010/11 to 2014/15: is there within season waning of influenza type/subtype vaccine effectiveness with increasing time since vaccination? Euro Surv. 2016;21:16.
58. Vynnycky E, Pitman R, Siddiqui R, et al. Estimating the impact of childhood influenza vaccination programmes in England and Wales. Vaccine. 2008;26(41):5321–5330.
59. Nyirenda M, Omori R, Tessmer HL, et al. Estimating the lineage dynamics of human influenza B viruses. Plos One. 2016;11(11):1–14.
60. Wiersma L, Rimmelzwaan G, De Vries R. Developing universal influenza vaccines: hitting the nail, not just on the head. Vaccines. 2015;3:239–262.
61. Van De Sandt CE, Bodewes R, Rimmelzwaan GF, et al. Influenza B viruses: not to be discounted. Future Microbiol. 2015;10(9):1447–1465.
62. Mosterín Höpping A, Fonville JM, Russell CA, et al. Influenza B vaccine lineage selection - an optimized trivalent vaccine. *Vaccine* [Internet]. 2016;34(13):1617–1622. DOI:10.1016/j.vaccine.2016.01.042
63. Van Hoek AJ, Underwood A, Jit M, et al. The impact of pandemic influenza H1N1 on health-related quality of life: a prospective population-based study. Plos One. 2011;6(3):1–6.

64. Damm O, Scholz S, Ultsch B, et al. A systematic review of utility weights for influenza and influenza-like illness. Value Heal. 2016;19 (7):A419.
65. Hollmann M, Garin O, Galante M, et al. Impact of influenza on health-related quality of life among confirmed (H1N1)2009 patients. Plos One. 2013;8(3):1–10.
66. Hayward AC, Fragaszy EB, Bermingham A, et al. Comparative community burden and severity of seasonal and pandemic influenza: results of the Flu Watch cohort study. Lancet Respir Med [Internet]. 2014;2(6):445–454. DOI:10.1016/S2213-2600(14)70034-7
67. De Boer PT, Frederix GWJ, Feenstra TL, et al. Unremarked or unperformed? Systematic review on reporting of validation efforts of health economic decision models in seasonal influenza and early breast cancer. Pharmacoeconomics. 2016;34(9):833–845.
68. Milne GJ, Halder N, Kelso JK, et al. Trivalent and quadrivalent influenza vaccination effectiveness in Australia and South Africa: results from a modelling study. Influenza Other Respi Viruses. 2016;10(4):324–332.
69. Tetsutani K, Ishii KJ. Adjuvants in influenza vaccines. *Vaccine* [Internet]. 2012;30(52):7658–7661. DOI:10.1016/j.vaccine.2012.10.007
70. Falsey AR, Treanor JJ, Tornieporth N, et al. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. J Infect Dis [Internet]. 2009;200(2):172–180. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/175/CN-00719175/frame.html
71. Barberis I, Myles P, Ault SK, et al. History and evolution of influenza control through vaccination: from the first monovalent vaccine to universal vaccines. J Prev Med Hyg. 2016;57(3):E115-E120.
72. Subramanian R, Graham AL, Grenfell BT, et al. Universal or specific? A modeling-based comparison of broad-spectrum influenza vaccines against conventional, strain-matched vaccines. PLOS Comput Biol [Internet]. 2016;12(12):e1005204. doi: 10.1371/journal.pcbi.1005204