Economic evaluation of seasonal influenza vaccination in elderly and health workers: A systematic review and meta-analysis

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Summary

Background A number of cost-effectiveness analysis of influenza vaccination have been conducted to estimate value of influenza vaccines in elderly and health workers (HWs). This study aims to summarize cost-effectiveness evidence by pooling the incremental net monetary benefit (INMB) of influenza vaccination.

Methods A systematic review was performed in electronic databases from their inceptions to February 2022. Cost-effectiveness studies reporting quality-adjusted life year (QALY), or life year (LY) of influenza vaccination were included. Stratified meta-analyses by population, perspective, country income-level, and herd-effect were performed to pool INMB across studies. The protocol was registered at PROSPERO (CRD42021246746).

Findings A total of 21 studies were included. Eighteen studies were conducted in elderly, two studies were conducted in HWs, and one study was conducted in both elderly and HWs. According to pre-specified analyses, studies for elderly in high-income economies (countries) (HIEs) and upper-middle income economies (UMIEs) without herd effect could be pooled. For HIEs under a societal perspective, the perspective which identify all relevant costs occurred in the society including direct medical cost, direct non-medical cost and indirect cost, pooled INMB was \$217·38 (206·23, 228·53, I^2 =28.2%), while that for healthcare provider/payer perspective was \$0·20 (-11,908·67, 11,909·07, I^2 = 0.0%). For societal perspective in UMIEs, pooled INMB was \$28·39 (-190·65, 133·87, I^2 = 92.8%). The findings were robust across a series of sensitivity analyses for HIEs. Studies in HWs indicated that influenza vaccination was cost-effective compared to no vaccination or current practice.

Interpretation Influenza vaccination might be cost-effective for HWs and elderly in HIEs under a societal perspective with relatively small variations among included studies, while there remains limited evidence for healthcare provider/payer perspective or other level of incomes. Further evidence is warranted.

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Keywords: Influenza vaccination; Cost-effectiveness; Economic evaluation; Systematic review, Meta-analysis

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Research in context

Evidence before this study

Current evidence demonstrates that influenza vaccination is effective against influenza infection in high-risk population. Cost-effectiveness evidence of influenza vaccination is one of the important information for decision makers to consider whether influenza vaccination should be implemented. We searched PubMed, Embase®, CEA Registry of the center of the Evaluation of Value and Risk in Health, NHS-EED database, and DARE from their inceptions to February 2022 without any language restriction. Search terms were the combination of key words as "influenza vaccine" AND "economic evaluation" which were varied based on functions of the databases. Previous systematic reviews summarized available cost-effectiveness evidence of influenza vaccination in several high-risk population. However, no systematic reviews quantitatively summarized cost-effectiveness evidence of influenza vaccination in elderly and health workers.

Added value of this study

Only few cost-effectiveness studies of influenza vaccination for health workers were published. We found that influenza vaccination was cost-effective for health workers for high-income economies (countries). No cost-effectiveness evidence of influenza vaccination for health workers was found in low-and-middle income economies.

Several cost-effectiveness studies for elderly were published. We found that influenza vaccination was robustly cost-effective for elderly in high-income economies under a societal perspective the perspective which identify all relevant costs occurred in the society including direct medical cost, direct non-medical cost and indirect cost. The pooled incremental net monetary benefit was 271·38 with 95% confidence interval as 206·23 to 228·53. The variation for studies included in this pooling analysis was relatively small. On the other hand, influenza vaccination was likely to be not significantly cost-effective in high-income economies under a healthcare provider/payer perspective and upper-middle income economies under a societal perspective.

Implications of all the available evidence

Influenza vaccination might be cost-effective for health workers and elderly in high-income economies under a societal perspective However, there remains limited evidence for healthcare provider/payer perspective and for low- and middle-income economies. Further evidence is warranted.

Introduction

Seasonal influenza virus infection is associated with substantial morbidity and mortality worldwide, with causing an estimated 290,000–650,000 deaths each year.[1] Internationally available vaccines for the control of seasonal influenza have the potential to prevent significant influenza morbidity and mortality. The World Health Organization (WHO) made recommendations for annual influenza vaccination defining specific groups at risk of influenza disease and reconfirming the safety profile of influenza vaccines identifying several groups with high risk for influenza infection including health workers (HWs) and elderly.[2] HWs is considered a high priority group because they are not only at increased risk of infection but also at risk of influenza transmission to vulnerable patients in healthcare settings, while elderly is another high priority group because of their high risk of having serious complications.[2,3]

Previous systematic reviews of economic evaluation of influenza vaccination have been conducted providing summary evidence of economic value of influenza vaccination for HWs and elderly, but none of them summarized evidence quantitatively.[4–7] A quantitative summary of cost-effectiveness could provide the robust evaluation of economic outcomes across studies. A method for systematic review and meta-analysis of economic evaluation[8] has been developed and applied in several areas.[9–11] This method allows policy makers to make informed decisions according to pool evidence of cost-effectiveness from similar countries. This study aimed to synthesize overall cost-effectiveness evidence of influenza vaccination in elderly and HWs by pooling incremental net monetary benefits (INMBs) to assess the cost-effectiveness of influenza vaccination compared to no vaccination or current practice.

Methods

This systematic review followed the Preferred Reporting Items for Systematic Review and Meta-analysis guideline, and the protocol was registered at PROSPERO (CRD42021246746).

Data source and search strategy

We performed a systematic search via PubMed, Embase®, CEA Registry of the center of the Evaluation of Value and Risk in Health, NHS-EED database, and DARE from their inceptions to February 2022. Search terms were the combination of key words as "influenza vaccine" AND "economic evaluation". Keywords varied based on functions of the databases. (Supplement I)

Study selection

Studies were eligible if they met the following inclusion criteria: (1) conducted in elderly or HWs, (2) compared any pair among seasonal influenza vaccinations with no vaccination or current situation, (3) reported outcomes as life-year (LY), disability-adjusted life-years (DALY) or quality-adjusted life year (QALY). Titles and abstracts were independently screened, and the full texts were reviewed by PD and LML. Any discrepancies were discussed with NC and AT.

Data extraction and risk-of-bias assessment

Data were independently extracted by LML and PD, any disagreement was solved by a discussion with NC and AT. A standardized data extraction form was developed based on Consolidated Health Economic Evaluation Reporting Standard checklist.[12] Extracted information consisted of country, study design, population, type of vaccine and comparator, vaccine coverage, model type, time horizon, perspective, and outcomes. Incremental cost-effectiveness ratio (ICER) with its variance, incremental cost (ΔC), incremental outcomes (ΔE), and willingness-to-pay (WTP) were also extracted. The scatterplots representing ΔC and ΔE of probabilistic sensitivity analysis were also extracted using Web-Plot-Digitizer®. Authors were contacted to request for additional data if not available.

Risk-of-bias was assessed using the modified Economic Evaluations Bias (ECOBIAS) checklist[13] which consisted of two main parts with 22 items. Each item was rated as yes, partly, no, unclear, or not applicable. Three key items were selected for sensitivity analysis including limited sensitivity analysis bias, wrong model bias, and bias related to treatment effects because they were more relevant to overall validity assessment and the study context. Studies, which were assessed as yes for all three items, were classified as low risk-of-bias. Studies with one or multiple partly/unclear were classified as moderate risk-of-bias, while studies with at least one "No" were defined as high risk-of-bias.

Outcomes of interest

The outcome of interest was the INMB, which was calculated using the following equations:

$$\mathrm{INMB} = (\mathrm{K} \times \Delta\mathrm{E}) - \Delta\mathrm{C} \tag{1}$$

$$\mathrm{INMB} = \Delta\mathrm{E} \times (\mathrm{K} - \mathrm{ICER}) \tag{2}$$

where K is WTP, ΔC is incremental cost and ΔE is incremental outcome.

Variance of the INMB was calculated using the equations below.

$$\mathrm{Var}(\mathrm{INMB}) = \left(\mathrm{K}^2 \times \sigma^2_{\Delta E}\right) + \sigma^2_{\mathrm{ICER}} \tag{3}$$

$$\mathrm{Var}(\mathrm{INMB}) = \left(\mathrm{K}^2 \times \sigma^2_{\sigma c}\right) - 2\mathrm{K}\rho_{\Delta\mathrm{C}\Delta\mathrm{E}} \tag{4}$$

where $\sigma^2{}_{\Delta\mathrm{E}}$ is variance of incremental outcome, $\sigma^2{}_{\Delta\mathrm{c}}$ is variance of incremental cost, $\sigma^2{}_{\mathrm{ICER}}$ is variance of ICER, and $\rho_{\Delta\mathrm{C}\Delta\mathrm{E}}$ is covariance of ΔC and ΔE.

Positive INMB indicated cost-effective, while negative INMB indicated not cost-effective of influenza vaccination compared to comparator.[8,14]

Data preparation

Data were prepared according to five scenarios described in Supplement II. INMB and its variance were calculated accordingly. Variance was imputed using relative variance of studies with similar characteristics compared to its point estimate when not available. ICER, and ΔC were converted to 2019 value using consumer price index (CPI) and purchasing power parity (PPP).[15] The gross domestic product (GDP)-based WTP was also converted to 2019 value using CPI and PPP, while WTP from country-specific cost-effectiveness threshold was converted to current value according to their country using only PPP. WTP for studies not reporting their original WTP was imputed from similar studies. (Supplement II).

Data analysis

INMB and its variance were pooled across studies using a random-effects model by Der-Simonian and Laird method.[16] Each analysis was stratified by level of countries' income classified by World Bank,[17] WHO region, (societal or healthcare provider/payer), comparator (no vaccination or current practice), herd effect (incorporated or not incorporated), and vaccine administration. The societal perspective was the perspective which identify all relevant costs occurred in a society including direct medical cost, direct non-medical cost, and indirect cost. The healthcare provider/payer perspective identify cost occurred in healthcare system which including only direct medical cost. For studies comparing different types of influenza vaccination (e.g., trivalent influenza vaccine (TIV) or quadrivalent influenza vaccine (QIV)) with no vaccination, we calculated INMB for each comparison and average across vaccine types to represent the overall value of influenza vaccination and used the averaged INMB for pooling across studies. This approach was selected to avoid the violation of independence assumption of meta-analysis within study.

I^2 was used to assess heterogeneity across studies. Sources of heterogeneity were explored by meta-regression. Covariates were considered as a potential source of heterogeneity when I^2 decreased by ≥50% in meta-regression.

Subgroup analyses by types of vaccine (i.e., TIV or QIV), funders (public vs private), vaccine administration (bi-annual vs annual) were performed. A series of sensitivity analyses were also undertaken for a societal perspective as follows: (1) inclusion of studies reporting LY, (2) imputing variance using absolute variance instead of relative variance, (3) excluding studies with imputed variances, and (4) excluding studies with high risk-of-bias.

A funnel plot was constructed to assess small-study effect in our main pooling of INMB with societal and healthcare providers/payer perspective if a number of included studies is 3 or more. If any plot suggested asymmetry, a contour-enhanced funnel plot was further constructed to explore if the cause of asymmetry was heterogeneity or small-study effect.

Roles of the funding source

The funder of the study has no role for study design, data collection, data analysis, data interpretation, and

writing this report. PD, LML, and NC are responsible to data accessibility and jointly decide to submit this manuscript for publication.

Results

We identified 1923 articles, 21 studies were eligible for our systematic review, but 16 studies were included in meta-analysis (Figure 1).

Study characteristics

Study characteristics are presented in Table 1. Briefly, the included studies were conducted in 13 countries which comprised of five studies (23·8%) from the Americas Region (AMR),[18–22] ten studies[23–32] from Western Pacific Region (WPR) (47·6%), five studies[33–37] from European Region (EUR) (23·8%), and one study[38] (4·7%) from African Region (AFR). Four study (19·0%) was conducted in upper-middle income economies (UMIE),[24,30,31,38] one study[32] (4·7%) was conducted in lower-middle income economies (LMIE) and the other 16 studies were conducted in high-income economies (HIE) (76·2%).[18–23,25–29,33–37]

Four studies (19·0%)[20–22,28,33] used Markov model, nine studies[18,23,24,30–32,34,35,38] (42·9%) used decision tree, one study[26] (4·7%) used dynamic transmission model, and seven studies[19,25,27,29,33,36,37] (33·3%) did not mention the model. Only two studies[26,33] (11·8%) incorporated herd immunity in their analyses.

Ten studies[24,25,30-35,37,38] (47·6%) used one-year time horizon whereas one study[21] used six-month, one study[28] used five-year, and two studies[20,29] used ten-year time horizon, respectively. Some studies[22,23,26,27,36] did not mention time horizon. Fifteen studies (71·4%)[18–22,24-31,33,35,38,39] reported QALY as the final outcome, five studies (23·8%)[23,34,36,37] reported LY gained, and one study[32] (4·7%) reported disability-adjusted life year (DALY) saved (Table 1).

Eleven studies (52·3%)[18,21,22,24,29–33,35,38] reported vaccine types, while other studies (47·6%) did not. Of those, six studies[21,29,31-33,38] assessed TIV alone, while five studies[18,22,24,30,35] assessed both TIV and QIV. Eighteen studies[18–25,27–30,32,34–38] (85·7%) compared influenza vaccination to no vaccination, while three studies (14·2%)[26,31,33] compared influenza vaccination to

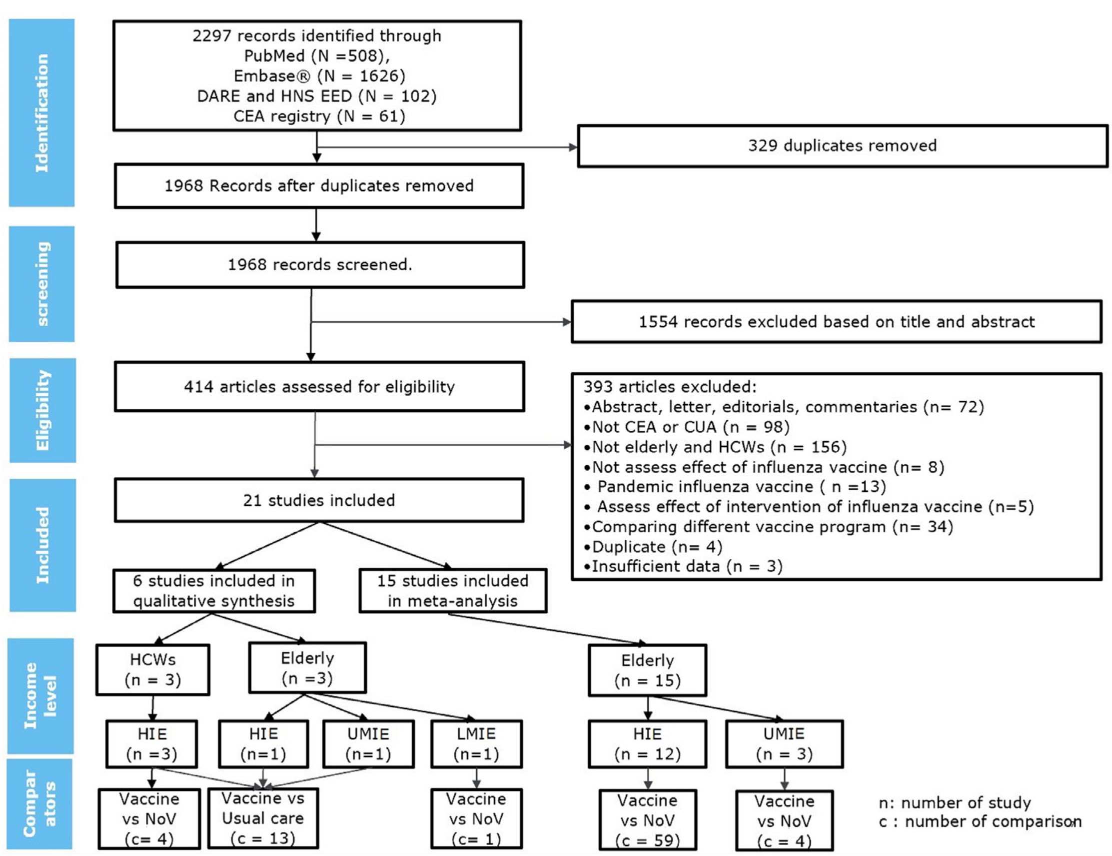

Figure 1. A flow diagram of selection of studies.

Abbreviations: CEA; cost-effectiveness analysis, CUA; cost-utility analysis, HCWs; health workers, HIE; high income economies, NoV; no vaccination, UMIE; upper-middle income economies.

	Country	WHO Region	Model type	WTP	GDP-based WTP	Time horizon	Herd effect	Discount rate	Perspective	Cost year	Type of CEA
Health workers											
Blommaert A (2014)[33]	Belgium	EUR	Static model	35,000 Euros	Yes	One-year	Yes	3%	Healthcare provider	2011	CUA
Burls (2006)[34]	UK	EUR	Decision analytic model	30,000 Pounds	Yes	One -year	No	3·5%	Healthcare provider	1999	CEA
Ortega-Sanchez (2021)	Lao	WPR	Decision tree model	2524 USD	Yes	One -year	No	3%	Societal	2020	CUA
Elderly											
Cai L (2006)[23]	Japan	WPR	Decision tree model	5 mil JPY	No	NR	No	NR	Societal	2002	CEA
Capri S (2018)[35]	Italy	EUR	Decision tree model	30,000 Euros	No	One -year	No	3%	Payer	2017	CUA
Chit A (2015)[18]	USA	AMR	Decision tree model	50,000 USD	No	Lifetime	No	3%	Societal	2013	CUA
Jiang M (2020)[24]	China	WPR	Decision tree model	29,580 USD	Yes	One -year	No	3%	Societal	2019	CUA
Maciosek (2006)[19]	USA	AMR	Simplified cost-effectiveness model	50,000 USD	No	Lifetime	No	3%	Societal	2000	CUA
Michaelidis CI (2011)[20]	USA	AMR	Markov model	50,000 USD	No	Ten-year	No	3%	Societal, Payer	2009	CUA
Newall (2014)[25]	Australia	WPR	NR	50,000 A$	No	One -year	No	3	Healthcare provider	2010	CUA
Patterson (2012)[21]	USA	AMR	Quasi-Markov model	50,000 USD	No	24-week	No	NR	Payer	2008	CUA
Postma MJ (1999)[36]	Netherland	EUR	NR	30,000 Euros	No	NR	No	4%	Provider	1995	CEA
Raviotta (2016)[22]	USA	AMR	Markov model	50,000 USA	No	NR	No	3%	Societal	2014	CUA
Tsuzuki (2019)[26]	Japan	WPR	SEIR model	50,000 USD	No	NR	Yes	2%	Payer	2018	CUA
Wang ST (2005)[27]	Taiwan	WPR	NR	68,264 USD	Yes	NR	No	5%	Societal	2001	CEA
Yue (2019)[29]	Singapore, Taiwan, Japan	WPR	Individual-based simulation model	Varied	No	Ten-year	No	3%	Societal	2018	CUA
You (2009)[28]	Hong Kong	WPR	Markov model	48,618 USD	No	Five-year	No	3%	Provider	2007	CUA
Reinders (1997)[37]	Netherland	EUR	Static cohort model	30,000 Euros	No	One -year	No	5%	Provider	1994	CEA
Edoka (2021)	South Africa	AFR	Decision tree model	3400 USD	No	One -year	No	5%	Societal/Provider	2018	CUA
Yan (2021)	China	WPR	Decision tree model	70,892 yuan	Yes	One -year	No	3%	Societal	2020	CUA
Yang (2020)	China	WPR	Decision tree model	8840 USD	Yes	One -year	No	3%	Societal	2017	CUA
Ortega-Sanchez (2021)	Lao	WPR	Decision tree model	2524 USD	Yes	One -year	No	3%	Societal	2020	CUA

***Table 1*: Study characteristics of included studies.**

Abbreviations: AMR; Region of the Americas, CEA; cost-effectiveness analysis, CUA: cost utility analysis, EUR; European Region, JPY; Japan Yen, NR; not reported, SEIR; Susceptible Exposed Infectious Recovered, USD, US dollars, WPR; Western Pacific Region, WTP, willingness to pay.

current practice. One study[29] compared different vaccine administration with no vaccination. A total of ten studies[18–20,22–24,27,29–32] (47·6%) and nine studies (42·8%)[21,25,26,28,33–37] were conducted under healthcare provider/payer perspective, respectively, while two study (9·5%)[20,38] applied both perspectives (Table 2).

Risk-of-bias assessment

Most studies had similar profile of bias for model structural assumption, comparators, and model type. Bias related to data, data identification, treatment effect, and quality of life used were varied across the included studies. For the three key items, two studies[27,34] were assessed as high risk-of-bias for limited sensitivity analysis bias. No study was assessed as high risk-of-bias for wrong model bias, while two studies were assessed as high risk-of-bias for bias related to treatment effects. Overall, twelve studies[18,19,21,24,26,28,30–33,35,38] (57·1%), four studies[20,22,23,29] (19·1%), and five studies[25,27,34,36,37] (23·8%) were assessed as low, moderate, and high risk of bias, respectively (Supplement III).

Overall cost-effectiveness analysis findings

Of the 21 included studies, two studies[33,34] were conducted in HWs, 18 studies[18–31,35–38] were conducted in elderly, and one study[32] was conducted in both HWs and elderly. The INMB in year 2019 was calculated. According to data preparation, five studies[26,29–31,33] with scenario 3, three studies[24,35,38] with scenario 4, and 13 studies[18–23,25,27,28,32,34,36,37] with scenario 5.

Health workers. Three studies[32–34] were conducted in HWs. Of those, two studies[33,34] were conducted in HIE, and another one study[32] was conducted in LMIEs. One study[34] in the United Kingdom (UK) conducted in year 2006 to estimate cost-effectiveness of influenza vaccination compared to no vaccination using a decision tree model with one-year time horizon without incorporation of herd immunity. The study used the LY as the outcome of interest under healthcare provider perspective. The study reported that ICER was 80·20 £/LY gained at WTP as 30000 £/LY gained. It concluded that influenza vaccine was cost-effective for HWs at the study year. The INMB at year 2019 was $9330·76 (9155·10, 9506·43) indicating influenza vaccination was highly cost-effective compared to no vaccination for HWs (Table 3).

A study[33] was conducted in Belgium in 2011 to assess cost-effectiveness of an increase in influenza vaccination coverage from 35% to 50% in HWs. The study used a static model with one-year time horizon and considered some degrees of herd immunity for older adult population. The QALY gained was the outcome under healthcare provider perspective. The ICER was 24,595 €/QALY without consider herd immunity (base-case) indicating influenza vaccination was cost-effective at the WTP as 35,000 €/QALY gained in HWs. In addition, they found that influenza vaccination was cost-effective for HWs when herd immunity was considered. The ICER ranged from €1833 to €37,849. However, the estimated INMB at 2019 value of the base-case was $1·84 (−0·63, 4·31) indicating influenza vaccination was likely to be cost-effective for HWs but not statistically significant. However, when herd immunity was considered, influenza vaccination was significantly cost-effective for all degrees of herd immunity applied with the INMBs of $5·18 to $112·22 (Table 3).

A study[32] was conducted in Lao People's Democratic Republic (Lao PDR) in 2020 to assess cost-effectiveness of routine annual influenza vaccination program for three subpopulations including pregnant women, elderly, and HWs. The study used a static decision tree model with one-year time horizon. The study did not consider herd immunity in the model. The DALY saved was the outcome of interest under a societal perspective. Specific to HWs, the study indicated that routine influenza vaccination was a cost-saving option for HW in Lao PDR at WTP of 81,490 Kips (₭)/day or 2542 $/year. The INMB at year 2020 was $222.23 (Table 3).

Elderly

A total of 19 studies[18–32,35–38] was conducted in elderly. Of those, 14 studies[18–22,24–26,28–31,35,38] reported QALYs, one study reported DALY,[32] while four studies[23,27,36,37] reported LY as the outcome (Table 2). Four study[24,30,31,38] was conducted in UMIEs, one study[32] was conducted in LMIE, while the rest was conducted in HIEs. A total of 13 studies was conducted in participants aged ≥ 65 years old. Five studies were conducted in participants aged ≥ 60 years old, while another one study was conducted in participants aged ≥ 69 years old.

High-income economies

Among HIEs, all seven studies[18–20,22,23,27,29] with nine comparisons, which were conducted under a societal perspective, indicated that influenza vaccination was cost-effective for original year at their respective WTPs. However, when INMBs for year 2019 were calculated, six of the nine comparisons had significantly positive INMB. A study[19] in the US had negative INMB of -$20·36 (−22·90, −17·82). A study[29] had three comparisons from three countries including Japan, Taiwan, and Singapore. The comparison from Taiwan had INMB of 0·12 (−0·12, 0·36), one from Japan had INMB of −0·08 (−0·27, 0·11), while the comparison from Singapore had INMB of 0·14 (−0·07, 0·35) (Table 4).

A total of eight studies[20,21,25,26,28,35–37] reported ICER from healthcare provider/payer perspective. Overall, seven studies[20,21,25,28,35–37] indicated that the

	Intervention	Comparators	Type of vaccine	Vaccine uptake	Vaccine efficacy	Vaccine price (USD 2019)	Original ICER (Base-case)	Unit of ICER	Conclusion
Health workers									
Blommaert A (2014)[33]	Trivalent 50%	Trivalent 35%	TIV	50%	59%	NR	24,595	€/QALY	High cost-effective
Burls (2006)[34]	Influenza vaccine	No vaccine	NR	51%	NR	12·62	80·2	£/LY	Cost-saving
Ortega-Sanchez (2021)	Influenza vaccine	No vaccine	TIV	100%	NR	3.597	Cost-saving	₭ /DALY	Cost-saving
Elderly									
Cai L (2006)[23]	Influenza vaccine	No vaccine	NR	NR	NR	40·73	516,331·6	¥/LY	Cost-effective
Capri S (2018)[35]	Influenza vaccine	No vaccine	TIV, MF59-TIV, ID-TIV, QIV	55·1%	Varied	14·8 – 19·3	10,733·8 – 19,655·2	€/QALY	Cost-effective
Chit A (2015)[18]	Influenza vaccine	No vaccine	IIV3, IIV4	67%	Varied	13·6 – 21·3	8833 – 15,001	$/QALY	Cost-effective
Jiang M (2020)[24]	Influenza vaccine	No vaccine	TIV, QIV	26·7%	NR	2·63 – 3·16	Cost-saving	$/QALY	Cost-effective
Maciosek (2006)[19]	Influenza vaccine	No vaccine	NR	57·4%	NR	18·69	980	$/QALY	Cost-effective
Michaelidis CI (2011)[20]	Influenza vaccine	No vaccine	NR	70%	NR	11·92	48,617	$/QALY	Cost-effective
Newall (2014)[25]	Influenza vaccine	No vaccine	NR	74·6%	Varied	23·55	1820 – 184,858	A$/QALY	Cost-effective
Patterson (2012)[21]	Influenza vaccine	No vaccine	TIV	36%	50%	40·6	13,084	$/QALY	Cost-effective
Postma MJ (1999)[36]	Influenza vaccine	No vaccine	NR	Varied	NR	35·2	Cost-saving	€/LY	Cost-effective
Raviotta (2016)[22]	Influenza vaccine	No vaccine	IIV3, IIV4	64·7%	39%	11·5 – 33·7	3693 – 8880	$/QALY	Cost-effective
Reinders (1997)[37]	Influenza vaccine	No vaccine	NR	75%	56%	NR	14,600	ƒ/LY	Cost-effective
Tsuzuki (2019)[26]	Influenza vaccine	Current practice	NR	Varied	37·6%	0·35	111,200 – 133,200	$/QALY	Not cost-effective
Wang ST (2005)[27]	Influenza vaccine	No vaccine	NR	35·6%	29%	NR	324·9 – 729·1	$/LY	Cost-effective
Yue (2019)[29]	Annual/ Biannual influenza vaccine	No vaccine	TIV	Varied	48%	1·83	Cost- saving – 0·2	$/QALY	Cost-effective
You (2009)[28]	Influenza vaccine	No vaccine	NR	NR	NR	0·43 – 6·23	5758·6	$/QALY	Cost-effective
Edoka (2021)	Influenza vaccine	No vaccine	TIV	3.11%	58%	3.04	2090 – 2034	$/QALY	Cost-effective
Yan (2021)	Influenza vaccine	No vaccine	QIV	47.5%	50.07%	NR	75.325 yuan	¥/QALY	Not cost-effective
Yang (2020)	Fully funded vaccination	Current practice (self-funded vaccination)	TIV	30%	12 – 50%	5.73	4.832	$/QALY	Cost-effective
Ortega-Sanchez (2021)	Influenza vaccine	No vaccine	TIV	100%	NR	3.597	782	$/DALY	Cost-effective

***Table 2*: Characteristics of interventions, comparators, and cost-effectiveness analysis findings.**

Abbreviations: ICER; incremental cost-effectiveness ratio, EE; economic evaluation, LY; life-year, QALY; quality-adjusted life year, DALY; disability-adjusted life year, QIV/IIV4; quadrivalent influenza vaccine, TIV/IIV3/ID-TIV; trivalent inactivated influenza vaccine, MF59-TIV; MF59®-adjuvanted trivalent influenza vaccine, NR; not reported.

$; US dollars, €; Euros, £; Pounds, ¥; Japanese Yen, A$; Australian dollars, ƒ; Dutch guilder, ₭; Lao PDR Kips.

	Intervention	Comparators	Scenario	Analysis	Perspective	Adjusted WTP threshold (2019 USD)	INMB	95% CI of INMB
High-income economies, provider perspective, no herd effect								
Blommaert A (2014)[33]	Trivalent IIV50%	Trivalent IIV35%	3	Base-case	Healthcare provider	45,378	1·84	−0·63, 4·31
Burls (2006)[34]	Vaccine	No vaccine	5	Base-case	Healthcare provider	38,683	9330·76	9155·10, 9506·43
Burls (2006)[34]	Vaccine	No vaccine	5	No absenteeism	Healthcare provider	38,683	9397·79	9221·50, 9574·09
Burls (2006)[34]	Vaccine	No vaccine	5	Pessimistic	Healthcare provider	38,683	2268·41	2181·79, 2355·02
High-income economies, provider perspective, having herd effect								
Blommaert A (2014)[33]	Trivalent IIV50%	Trivalent IIV35%	3	Herd effect on (1/3) in elderly 50 - 64	Healthcare provider	45,378	5·18	2·16; 8·20
Blommaert A (2014)[33]	Trivalent IIV50%	Trivalent IIV35%	3	Herd effect on (2/3) in elderly 50 - 64	Healthcare provider	45,378	8·53	4·20, 12·85
Blommaert A (2014)[33]	Trivalent IIV50%	Trivalent IIV35%	3	Herd effect on (1) in elderly 50 - 64	Healthcare provider	45,378	11·88	6·21, 17·55
Blommaert A (2014)[33]	Trivalent IIV50%	Trivalent IIV35%	3	Herd effect on (1/3) in elderly 65 - 74	Healthcare provider	45,378	10·97	5·55, 16·39
Blommaert A (2014)[33]	Trivalent IIV50%	Trivalent IIV35%	3	Herd effect on (2/3) in elderly 65 - 74	Healthcare provider	45,378	20·11	11·14, 29·08
Blommaert A (2014)[33]	Trivalent IIV50%	Trivalent IIV35%	3	Herd effect on (1) in elderly 65 - 74	Healthcare provider	45,378	29·25	16·29, 42·21
Blommaert A (2014)[33]	Trivalent IIV50%	Trivalent IIV35%	3	Herd effect on (1/3) in elderly 75+	Healthcare provider	45,378	38·63	27·89, 49·36
Blommaert A (2014)[33]	Trivalent IIV50%	Trivalent IIV35%	3	Herd effect on (2/3) in elderly 75+	Healthcare provider	45,378	75·42	56·68, 94·17
Blommaert A (2014)[33]	Trivalent IIV50%	Trivalent IIV35%	3	Herd effect on (1) in elderly 75+	Healthcare provider	45,378	112·22	84·58, 139·86
Lower-middle income economies, provider perspective, no herd effect								
Ortega-Sanchez (2021)	Vaccine	No vaccine	5	Base-case	Societal	2608	222.23	NA (Cost-saving)

***Table 3*: Estimation of INMB and its corresponding 95% confidence interval for each individual study in health workers.**

Note: Base-case analysis: main analysis of the study; No absenteeism: analysis excluded cost for replaced staff; *Pessimistic: worst-case scenario of influenza epidemic.

Abbreviations: CI; confidence interval, IIV; inactivated influenza vaccine, INMB; incremental net monetary benefit, quadrivalent inactivated influenza vaccine, USD; US dollars, WTP; willingness-to-pay.

	Intervention	Comparators	Scenario	Perspective	Adjusted WTP (2019 USD)	INMB	95% CI of INMB
Studies which could not be used to pool INMBs							
Upper-middle-income economies societal perspective, no herd effect							
Yang (2020)	Fully funded TIV program	Current practice	3	Societal	9285	1·4	−190·65, 133·87
Lower- middle-income economies, provider perspective, no herd effect							
Ortega-Sanchez (2021)	Vaccine	No vaccine	5	Provider	2608	4·48	0·58, 8·42
High-income economies, provider perspective, having herd effect							
Tsuzuki (2019)[26]	Vaccine for 60+	Current practice	3	Provider	50,000	−71·49	−72·60, −70·40
Tsuzuki (2019)[26]	Vaccine for 70+	Current practice	3	Provider	50,000	−46·92	−47·84, −46·00
Studies which were used to pool INMBs for both main analysis and sensitivity analysis							
High-income economies, societal perspective, no herd effect							
Cai L (2006)[23]	Vaccination	No vaccination	5	Societal	45,328	250·83	239·83, 261·85
Chit A (2015)[18]	Vaccination	No vaccination	5	Societal	50,000	45·94	26·55, 65·33
Maciosek (2006)[19]	Vaccination	No vaccination	5	Societal	50,000	2675·63	2646·52, 2704·74
Michaelidis CI (2011)[20]	Vaccination	No vaccination	5	Societal	50,000	−20·36	−22·90, −17·82
Raviotta (2016)[22]	Vaccination	No vaccination	5	Societal	50,000	54·37	51·07, 57·67
Wang ST (2005)[27]	Vaccination	No vaccination	5	Societal	68,264	2840·6	2804·48, 2876·73
Yue (2019)[29] (Singapore)	Vaccination	No vaccination	3	Societal	52,961	0·14	−0·07, 0·35
Yue (2019)[29] (Japan)	Vaccination	No vaccination	3	Societal	45,328	−0·08	−0·27, 0·11
Yue (2019)[29] (Taiwan)	Vaccination	No vaccination	3	Societal	68,264	0·12	−0·12, 0·36
High-income economies, healthcare provider/pay perspective, no herd effect for both main analysis and sensitivity analysis							
Capri S (2018)[35]	Vaccination	No vaccination	4	Payer	40,072	8·44	−96,275·01, 96,291·89
Michaelidis CI (2011)[20]	Vaccination	No vaccination	5	Payer	50,000	−22·74	−316,000·00, 316,001·06
Newall (2014)[25]	Vaccination	No vaccination	5	Provider	32,765	2·18	−97,887·24, 97,891·60
Patterson (2012)[21]	Vaccination	No vaccination	5	Payer	50,000	0·46	−48,880·36, 44,881·28
Postma MJ (1999)[36]	Vaccination	No vaccination	5	Provider	35,350	119·13	722,999·00, 723,406·42
You (2009)[28]	Vaccination	No vaccination	5	Provider	48,618	0·04	−12,566·47, 12,566·55
Reinders (1997)[37]	Vaccination	No vaccination	5	Provider	35,350	2·06	−95,053·84, 95,057·96
Upper-middle-income economies, societal perspective, no herd effect							
Edoka (2021)	Vaccine (TIV)	No vaccine	4	Societal	3400	0·12	−449.91, 450.15
Yan (2021)	Vaccine (QIV)	No vaccine	3	Societal	16.576	−117·88	−127.19, −108.57
Jiang M (2020)[24]	Vaccine (TIV)	No vaccine	5	Societal	29,580	57·96	−33·14, 149·10
Jiang M (2020)[24]	Vaccine (QIV)	No vaccine	4	Societal	29,580	64·83	−31·50, 161·2
Upper-middle-income economies, healthcare provider/pay perspective, no herd effect							
Edoka (2021)	Vaccine (TIV)	No vaccine	4	Provider	3400	0·12	−449.91, 450.15

***Table 4*: Estimation of INMB along with 95% CI of individual studies of elderly.**
Note: Base-case analysis: main analysis of the study.
Abbreviations: INMB; incremental net monetary benefit, TIV; trivalent influenza vaccination, QIV; quadrivalent influenza vaccine, USD; US dollars, WTP; willingness-to-pay.

influenza vaccination was cost-effective for original year. Only one study[26] in Japan indicated that influenza vaccination for elderly aged 60+ and 70+ was not cost-effective with the reported ICER/QALY of $133,200 and $111,200 exceeding the $50,000 WTPs threshold (Table 2). Of the eight studies, six studies[21,25,28,35–37] had positive INMB but not statistically significant. Two studies[20,26] had negative INMBs. One study[20] was conducted in the US and found that influenza vaccination was cost-effective at the original year 2011 value. However, when INMB was calculated, the conclusion was changed to not cost-effective in 2019 value. Another study[26] was conducted in Japan for elderly aged 60 + and 70+ in year 2018. They compared influenza vaccination with 90 vaccine coverage with current practice (vaccine coverage of 38% for elderly aged 60+ and 56% for elderly aged 70+). The calculated INMBs were -$71·49 (−272·60, −70·40) for elderly aged 60+, and -$46·92 (−47·84, −46·00) for elderly aged 70+. These indicated that influenza vaccination was not cost-effective for elderly in Japan (Table 4).

Upper-middle income economies

Among UMIEs, three studies[24,30,31] with four comparisons were conducted under a societal perspective, while one study[38] was conducted under both societal and healthcare provider perspectives. Under a societal perspective, two studies[24,38] indicated that influenza vaccination was cost-effective, while one study[30] in China indicated that the vaccination was not cost-effective comparing to no vaccination. One study[31] showed cost-effectiveness of influenza vaccination when fully funded comparing to current practice (self-funded vaccination). When INMB was calculated, four of five comparisons had non-significant positive INMB. A study[30] in China assessing QIV compared to no vaccination showed the significant negative INMB of -$117·88 (−127·19, −108·57) (Table 4).

Only one study[38] in South Africa was conducted under a healthcare provider perspective. The study originally reported that influenza vaccination was cost-effective in elderly. The INMB was $0·12 (−449·91, 450·15) (Table 4).

Lower-middle income economies

A study[32] in Lao PDR originally reported that influenza vaccination was cost-effective for elderly aged ≥ 60 year at its original WTP. It also showed a significant positive INMB of $4·48 (0.58, 8.42) (Table 4).

Meta-analysis findings in elderly

High-income economies: societal perspective. Seven studies[18–20,22,23,27,29] with 41 comparisons of influenza vaccination and no vaccination in elderly were included in meta-analyses. All studies were without no herd immunity. The vaccine uptake and efficacy ranged from 40% to 70% and 30% to 50%, respectively.

The pooled INMBs stratified by WHO regions indicated that INMBs were $687·60 (425·10, 950·10) and $0·05 (−0·10, 0·19) for Region of the Americas (AMR) and Western-Pacific region (WPR) with the corresponding I^2 of 100% and 28·2%, respectively (Figure 2). The positive INMB indicated that influenza vaccine was cost-effective in elderly for both regions, but statistical significance was observed for only AMR. A subgroup analysis of funder indicated that both public and private funders had positive INMB with statistical significance. The INMB for public funder was $238·37 (226·56,

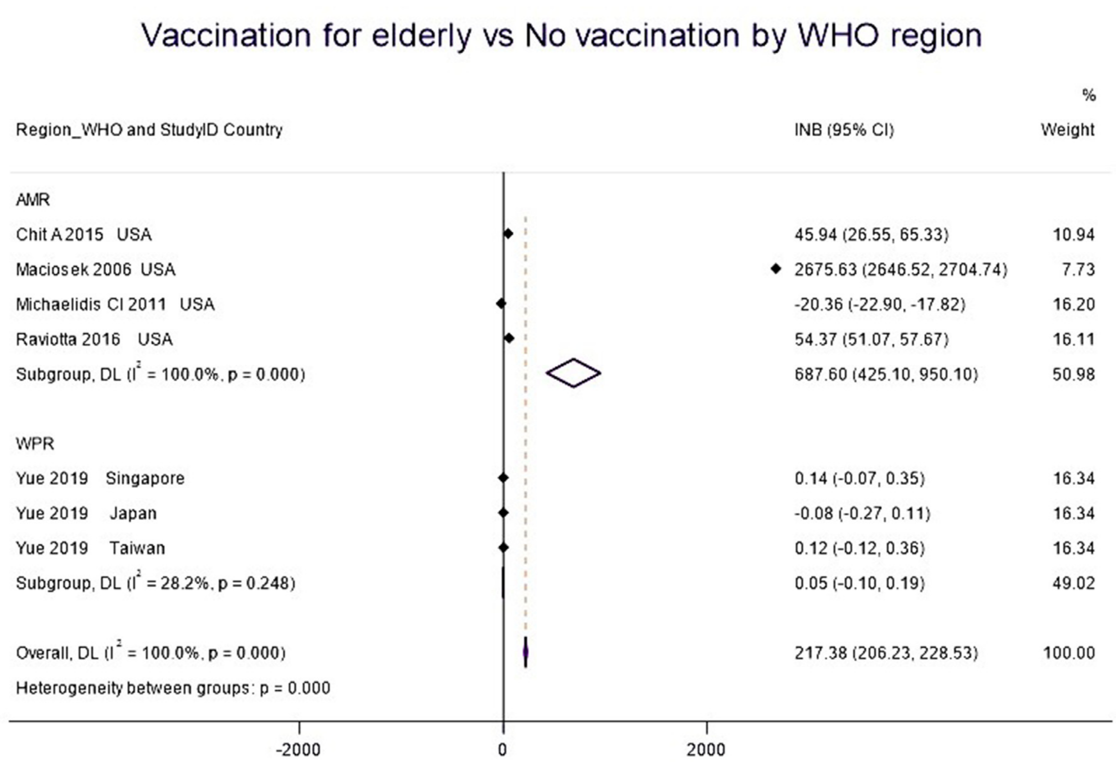

Figure 2. Meta-analysis of influenza vaccination compared to no vaccination in elderly under societal perspective in high-income economies

Note: Dashed line indicated the pooled estimate in a comparison with individual study estimates. $p < .05$ indicates statistical significance

Abbreviations: AMR; Regions of the Americas, CI; confidence interval, INB; Incremental net monetary benefit, WPR; Western Pacific Region.

250·18), while that for private funder was $45·94 (26·55, 65·33) (Supplement IV; Figure S1). Standard dose TIV, high-dose TIV and QIVs were also significantly cost-effective with the INMBs of $13·07 (10·67, 15·47), $62·97 (51·93, 74·0), and $43·74 (23·00, 64·48) (Supplement IV; Figure S2). Finally, an analysis of biannual influenza vaccination did not demonstrate cost-effective with the significantly negative INMB of -$1·40 (−1·68, −1·11) (Supplement IV; Figure S3).

High-income economies: healthcare provider/payer perspective. Five studies with 16 comparisons were included in meta-analysis. The INMBs were $8·44 (−96,275·01, 96,291·88), $0·00 (−44,434·96, 44,434·96), and $0·07 (−12,464·15, 12,464·29) for European Region (EUR), AMR, and WPR, respectively (Figure 3) indicating influenza vaccines were not cost effective in these regions under healthcare/payer perspective. A subgroup analysis of public funder indicated that INMB was $0·37 (−40,461·1, 40,461·84) (Supplement IV; Figure S1).

Upper-middle income economies: societal perspective. Three studies with 4 comparisons were included in meta-analysis. All studies did not include herd immunity. Vaccine uptake ranged from 3·11% - 47·5%. The pooled INMB was $0·12 (−449·91, 450·15) for AFR and $−31·46 (−206·85, 143·93) for WPR indicting that influenza vaccination were not significantly cost-effective in UMIEs in these regions (Figure 4).

Heterogeneity exploration, sensitivity analysis, and publication bias

High-income economies. Sources of heterogeneity were explored using univariate meta-regression of the following variables: funder, type of vaccine, model type, vaccine efficacy, vaccine price, and type of economic evaluation. None of them were found to explain heterogeneity with the I^2 ranging from 99·9% to 100% in meta-regressions. (Supplement V).

A series of sensitivity analyses were performed for both societal and healthcare provider/payer perspectives. For societal perspective, our observed INMBs were robust. A sensitivity analysis excluding studies with high risk of bias indicated that the pooled INMB was 226·16 (215·45, 236·87) with the I^2 of 100%. We also found that Maciosek's study[19] had INMB value

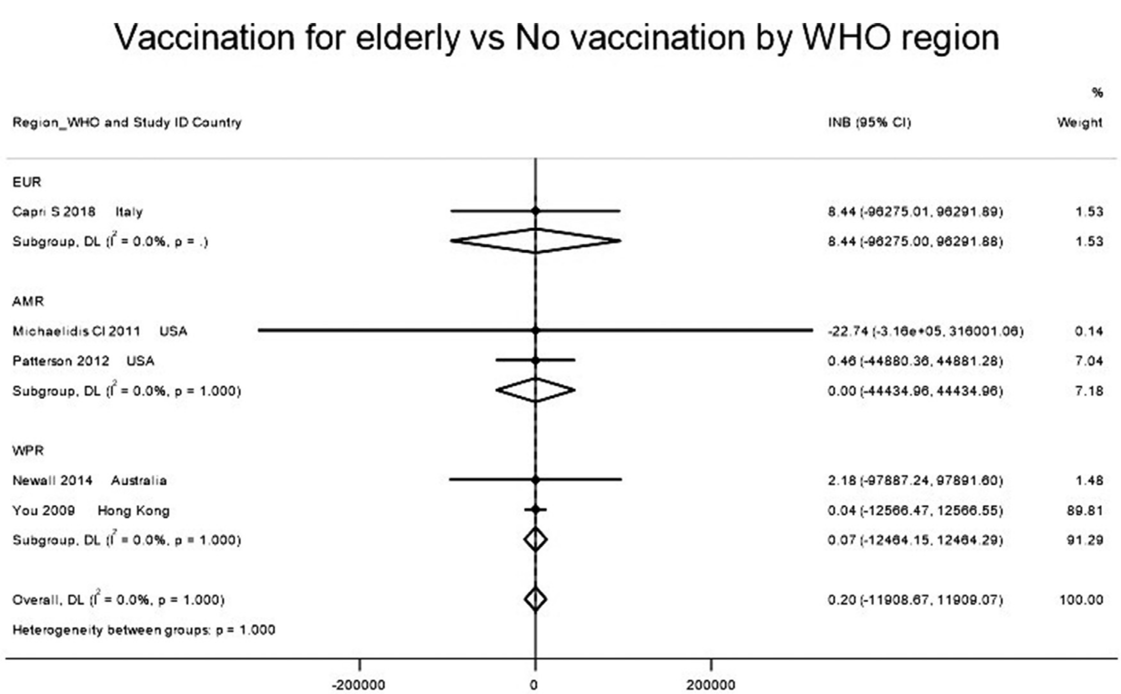

Figure 3. Meta-analysis of influenza vaccination compared to no vaccination in elderly under healthcare provider/pay perspective in high-income economies.

Note: Dashed line indicated the pooled estimate in a comparison with individual study estimates. $p < .05$ indicates statistical significance.

Abbreviations: AMR; Regions of the Americas, CI; confidence interval, EUR; European region, INB; Incremental net monetary benefit, WPR; Western Pacific Region.

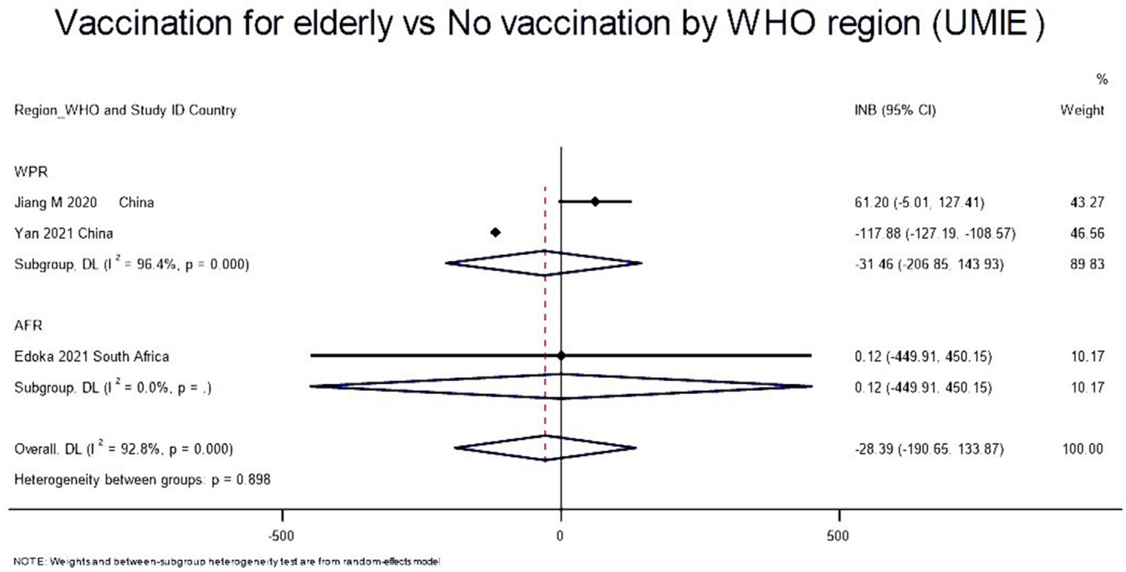

Figure 4. Meta-analysis of influenza vaccination compared to no vaccination in elderly for societal perspective in upper-middle income economies.

Note: Dashed line indicated the pooled estimate in a comparison with individual study estimates. $p < .05$ indicates statistical significance.

Abbreviations: AFR; African region, AMR; Regions of the Americas, CI; confidence interval, INB; Incremental net monetary benefit.

(2675) and QALY gained higher than those in other studies. This is possibly due to vaccine efficacy against death value used which was higher than those in other studies. We also performed a sensitivity analysis excluding the study and found that the pooled INMB had lowered from $217·38 to $5·74 but the I^2 remained unchanged (99·6%). Most sensitivity analyses indicated significant positive INMBs which were in-line with the main finding (Supplement VI).

A funnel plot indicated asymmetry for societal perspective but not for healthcare provider/payer perspective. A contour-enhanced funnel plot for societal perspective indicated that the asymmetry was more likely due to heterogeneity, not publication bias (Supplement VII).

Upper-middle income economies. Similar to heterogeneity exploration in HIEs, Sources of heterogeneity were explored using univariate meta-regression of the following variables: funder, type of vaccine, model type, vaccine efficacy, vaccine price, and type of economic evaluation. We found that type of vaccine and vaccine price might be the source of heterogeneity for UMIE under a societal perspective (Supplement V).

Discussion

We performed a systematic review and meta-analysis of cost-effectiveness of influenza vaccination compared to no vaccination or current practice in HWs and elderly. For HWs, our qualitative summary showed the cost-effectiveness of influenza vaccination in UK, Belgium, and Lao PDR. Our quantitative findings in elderly demonstrated favorable INMBs from influenza vaccination under a societal perspective with relatively robust results in HIEs. However, influenza vaccination was likely to be not significantly cost-effective in HIEs under a healthcare provider/payer perspective and UMIEs under a societal perspective.

Although, several systematic reviews[5–7,40,41] of cost-effectiveness of influenza vaccination have been reported, there was no quantitative summary of evidence of economic outcomes. To our knowledge, this study is the only systematic review which quantified value of influenza vaccination in terms of INMB and pooled them across studies. Country-specific WTP, purchasing power parity, and consumer price index were used to take into account the differences of costs between countries and year values. In addition, meta-regression analyses were also performed to explore sources of heterogeneity. We found no clear source of heterogeneity. Further, we were able to standardize monetary units to 2019 USD and used INMB instead of ICER to indicate value of influenza vaccination for decision making or policy analysis.[42,43] Our stratified analyses for elderly in HIEs under a societal perspective found that influenza vaccination was cost-effective for both WPR and AMR, but was significant in AMR region only due to limited number of studies in WPR. This evidence suggests that influenza vaccination is likely to show benefits over its cost for HIEs but evidence is limited in UMIEs and LMIEs.

The cost-effectiveness of influenza vaccination in elderly in HIEs under a societal perspective is robust. We also found that influenza vaccination was cost-effective regardless of the types of vaccines. Vaccination with standard-dose TIV and QIV showed significant positive INMBs compared to no vaccination but not for the high-dose TIV. The magnitude of cost-effective was higher in high-dose TIV and QIV than standard-dose TIV. This finding is similar to a previous systematic review[6] which summarized cost-effectiveness evidence of QIV compared to TIV. The systematic review indicated that most studies showed the cost-effective results of QIV over standard-dose TIV in any populations including elderly. A series of sensitivity analysis showed positive INMBs indicating a robustness of the findings leading to the increase in credibility of findings that influenza vaccination is a cost-effective strategy for elderly compared to no vaccination.

Despite robust evidence of cost-effectiveness of influenza vaccination in HIEs under a societal perspective, non-significant finding was observed in healthcare payer/provide perspective. We found non-significant positive INMBs with very wide variation. This might be because only one study provided variance, prompting imputation requirement for other studies. This led to high uncertainties around the analyses under healthcare payer/provide perspective.

We also found a non-significant positive INMB for UMIEs in AFR region, while we found non-significant negative INMB for UMICs in WPR region. In addition, we also found a significant positive INMB for LMICs in WPR region. However, those findings were from a small number of studies. INMBs for UMICs in AFR region and LMICs in WPR region were from only one study. One was from South Africa,[38] while another one was from Lao PDR.[32] In addition, INMB for UMIEs in WPR region was from only two studies which were conducted in China mainland. In addition, they reported opposite findings. Therefore, generalizability of INMB findings in those countries is limited and must be done with cautions.

Influenza vaccination is cost-effective in HWs especially when herd immunity is considered. This shows the value of influenza vaccination in HWs to prevent transmission of influenza to vulnerable patient groups in healthcare setting. However, only two studies in HWs from Europe were included. The value of seasonal influenza vaccination might be different from other countries, especially where the pattern of influenza transmission might differ from those in Europe.

Because of the scarce information on subpopulation of younger elderly and older elderly, we could not perform any subgroup analysis based on the difference ages. The INMB of different ages of participants might be different because of their expected life years and QALY gained.

Recently, Immunization and Vaccine related Implementation Research Advisory Committee (IVRAC-AC) had reviewed meta-analysis of economic evaluation approach and agreed that it could facilitate decision-making in countries without context-specific EE.[44] However, meta-analysis of economic evaluation should be methodologically improved in terms of data harmonization, and incorporating quality of studies in synthesizing economic evaluation estimates. For data harmonization, currency years for costs should be consistent across studies, normal distribution should not be assumed for incremental effectiveness, and prespecified stratified analysis should be based on contextual differences. Our study aligned with the recommendation for data harmonization. We converted all costs including ΔC, WTP, and ICER to currency year 2019. We also avoided the normal distribution assumption of ΔE and also ΔC by simulating variance and covariance of both ΔE and ΔC using Monte Carlo simulation (Scenario 3) instead of calculating variance using 95%CI (Scenario 2) which assumes normal distribution of ΔE and ΔC. We also performed hierarchically stratified analysis by country's income level and WHO region. We used them as proxies to contextualize economic evaluation studies. In addition to data harmonization, IVRAC-AC recommended that quality of studies should be taken into account for synthesizing economic evaluation estimates We also performed a sensitivity analysis by excluding studies with high risk of bias. We found that the pooled INMB was still significantly positive, indicating the robustness of our findings. However, meta-analysis of economic evaluation is a relatively new method which needs further research to improve data harmonization and synthesis of economic evaluation estimates to advance this field of research.

A small number of studies were included in the final meta-analysis for elderly in HIEs which might lead to less precise pooled INMBs. In addition, some studies did not provide variances of ΔC, ΔE, and ICER which are important for meta-analysis. Thus, we used scenario 5 which imputed the variance from other similar studies. Variance of 14 studies with 32 analyses must be imputed. This might lead to uncertainty of the findings. However, we performed a sensitivity analysis by excluding the studies with missing variance. We found that influenza vaccination remained significantly cost-effective.

Our study found only one CEA reported DALY as their clinical outcomes. It might be because we focused on elderly and HW. Most CEA studies using DALY as the clinical outcome might be in different population such as children.

There were a limited number of studies across WHO regions. Only AMR, WPR, and EUR among six regions were included. It limits the generalizability of our findings. In addition, the included studies were mostly from HIE with only three studies in UMIE. Generalizability of the findings in terms of the precision of cost-effectiveness findings should be for only HIEs. It could not be applied for countries with different income levels.

The meta-analysis of cost-effectiveness studies summarized all economic evidence globally in quantitative manner and stratified them in groups with similar characteristics. This study could be a valuable piece of evidence for policy makers to consider influenza vaccination for their national immunization program for HWs and elderly, especially for HIEs within AMR and WPR regions. The paucity of variances reported in cost-effectiveness studies suggested a strong need to encourage reporting of ΔC, ΔE, and ICER with their corresponding variance to facilitate meta-analysis of economic evaluation.

Influenza vaccination might be cost-effective for HWs and elderly under a societal perspective, especially for high-income economies within AMR, and WPR. However, there remains limited evidence for healthcare provider/payer perspective for low- and-middle-income economies and economies outside AMR, and WPR regions. Further evidence is warranted.

Data sharing statement

Review protocol has been available via PROSPERO website. All extracted and calculated data are available upon appropriate requests by emailing to co-corresponding authors.

Authors contribution

PD and LML reviewed literatures, extracted data for the study, synthesis, and quality assessment with inputs from AT, RH, PL, and NC. LML and PD performed the meta-analysis. PD and LML drafted the manuscripts and all authors made substantial contribution. All authors contributed to the study design, interpretation of findings, and critical revision of the manuscript. All authors approved the final version of the manuscript for submission.

Declaration of interests

PD, LML, AT, and NC declare no competing interest. RH and PL work the World Health Organization. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions, policy or views of the World Health Organization.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101410.

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