Costs and cost-effectiveness of influenza illness and vaccination in low- and middle-income countries: A systematic review from 2012 to 2021

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Abstract (300/300 words)

Introduction: Historically, lack of data on cost-effectiveness of influenza vaccination has been identified as a barrier to vaccine use in low- and middle-income countries. We conducted a systematic review of economic evaluations describing (1) costs of influenza illness, (2) costs of influenza vaccination programs, and (3) vaccination cost-effectiveness from low- and middle-income countries to assess if gaps persist.

Methods: We performed a systematic search in Medline, Embase, Cochrane Library, CINAHL, and Scopus using a combination of the following key words: "influenza" AND "cost" OR "economic." The search included studies with publication years 2012 through 2021. We abstracted general study characteristics and data specific to each of the three areas of review.

Results: Of 50 included studies, 24 presented data on cost-effectiveness, 23 on cost-of-illness, and four on program costs. Represented countries were classified as upper-middle income (UMIC; n=11), lower-middle income (LMIC; n=7), and low-income (LIC; n=3). The most evaluated target groups were children (n=26 studies), older adults (n=16), and persons with chronic medical conditions (n=12); fewer studies evaluated pregnant persons (n=8), healthcare workers (n=4), and persons in congregate living settings (n=1). Costs-of-illness were generally higher in UMICs than in LMICs/LICs; however, the highest total costs, as a percent of gross domestic product and national health expenditure, were reported from an LIC. Among studies that evaluated the cost-effectiveness of influenza vaccine introduction, most (83%) interpreted at least one scenario per target group as either cost-effective or cost-saving, based on thresholds designated in the study.

Conclusions: Continued evaluation of the economic burden of influenza illness and costs and cost-effectiveness of influenza vaccination, particularly in low-income countries and among underrepresented target groups (e.g., healthcare workers and pregnant persons), is needed; use of standardized methodology could facilitate pooling across settings. Robust, global economic data are critical to design and maintain sustainable influenza vaccination programs.

Summary box

What is already known on this topic: Prior systematic reviews and surveys have demonstrated a need for economic data on influenza vaccination from low- and middle-income countries to inform program implementation and expansion. Standardized tools and guidance have become available in recent years to guide economic evaluations for influenza illness and vaccination in low-and middle-income countries.

What this study adds: This article summarizes the literature on costs of influenza illness, costs of influenza vaccination programs, and vaccination cost-effectiveness from low- and middle-income country settings during 2012–2021.

How this study might affect research, practice, or policy: The findings suggest value-for-money for influenza vaccination and increased interest in economic evaluations in recent years, but continued, standardized evaluation of costs and cost-effectiveness is needed, particularly from low-income countries and for underrepresented target groups.

Article main text (4695/5000 words)

Introduction

Seasonal influenza vaccination is a key intervention to prevent morbidity and mortality from influenza virus infections [1]. The World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization (SAGE) recommends that countries starting or expanding influenza vaccination programs prioritize specific target groups at high risk for transmission or severe disease, including healthcare workers, individuals with chronic medical conditions, older adults, and pregnant persons. Additionally, depending on priorities, available resources, and feasibility, countries might consider additional target groups for vaccination, including young children, persons in congregate living settings, disadvantaged populations, and indigenous populations [1]. As of 2018, 118 of 194 (61%) WHO member states had an influenza vaccination policy [2]; nevertheless, while low- and middle-income countries represent 40% of the world's population and have a high burden of influenza illness [3-5], they constituted 85% of countries without a policy [2].

A 2019 survey indicated that lack of data on cost-effectiveness of influenza vaccination programs was a key barrier to initiating and expanding influenza vaccination programs in low- and middle-income countries [6]. Cost-effectiveness analyses and other economic evaluations can provide important information to guide evidence-based decision making, resource allocation, and long-term investment in vaccination by demonstrating value-for-money; however, these evaluations require accurate input data, including the costs of influenza illness, costs of vaccination, and impact of the vaccination program, in order to yield relevant and reliable results [7].

To help countries better assess the value of influenza vaccination, WHO and partners have developed standardized tools and updated guidance in recent years for economic evaluations regarding influenza illness and vaccination. These include 2016 guidance on estimating influenza economic burden [8, 9], 2016 guidance on economic evaluations for influenza vaccination, including cost-effectiveness analyses [10, 11], and a 2020 update to the Seasonal Influenza Immunization Costing Tool (SIICT) [12]. While previous systematic reviews have described economic data for influenza from low- and middle-income countries [13-17], these were generally conducted prior to the availability of these tools; more recent reviews have described data from high-income settings [16, 18, 19], focused on specific target groups [20-22], or addressed questions such as the comparative cost-effectiveness of quadrivalent and trivalent vaccines [23]. To summarize recent data and assess remaining gaps, we conducted an updated systematic review of studies describing the costs of influenza illness, costs of influenza vaccination programs, and influenza vaccination cost-effectiveness from low- and middle-income country settings within the last 10 years (2012–2021).

Methods

This review followed the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines for systematic reviews and was registered at PROSPERO (international prospective register of systematic reviews) under protocol number CRD42022304803.

Search strategy and study selection

We performed a systematic search using Medline, Embase, Cochrane Library, CINAHL, and Scopus in January 2022. The search included studies with a publication year of 2012 through 2021. Search terms were a combination of the following key words: "influenza" AND "cost" OR "economic;" specific search syntax for each database is provided in **Supplemental Table S1**.

Studies were eligible if they met the following inclusion criteria: (1) presented original, peer-reviewed findings on at least one of the following: (a) cost of illness, (b) cost of vaccination program, or (c) cost-effectiveness, cost-utility, or cost-benefit of vaccination (hereafter referred to as "cost-effectiveness studies") for seasonal influenza; and (2) included data for at least one low- or middle-income country based on World Bank income group classification during the study period [24]. We excluded studies that: (1) did not present original or peer-reviewed findings (e.g., literature reviews, conference abstracts, and editorials); (2) only presented data about infection with or vaccination for pandemic or novel influenza viruses (e.g., influenza A(H1N1)2009 pandemic strain); or (3) included data from mid-2009 through mid-2010 that could not be disaggregated from other results, as these months were considered to represent the global influenza A(H1N1)2009 pandemic period [25].

Specifically, cost-of-illness studies were required to use a case definition of laboratory-confirmed influenza (LCI) or syndromic definitions of influenza-like-illness (ILI) and/or severe acute respiratory infection (SARI), though estimates could then be extrapolated to include other disease presentations (e.g., non-medically attended illnesses). Program cost studies were required to present population-level estimates of vaccination program costs, i.e., studies that described only cost of vaccination to the individual were excluded. Cost-effectiveness studies were required to include a comparison of influenza vaccination versus no vaccination or modifications to current vaccination program (e.g., increase in vaccination coverage); studies that only compared the cost-effectiveness of different influenza vaccine products (e.g., quadrivalent versus trivalent, adjuvanted versus non-adjuvanted, or live attenuated versus inactivated) were not included.

Titles and abstracts were independently screened by 2 reviewers (RG, AC, MC, or WZ) for eligibility, with a third reviewer resolving any conflicting decisions. English-language full texts were again reviewed by 2 reviewers (RG, AC, MC, or WZ) for eligibility, with a third reviewer resolving any conflicting decisions. Publications in other languages (Mandarin Chinese, Russian, Spanish, and Bulgarian) were reviewed by a single native-language speaker. All screening procedures were performed using Covidence, a web-based collaboration software platform for systematic reviews [26]. We also reviewed references from included studies to identify additional relevant literature for inclusion.

Data extraction and quality assessment

Data from English-language publications were independently extracted by two reviewers (RG, AC, MC, or WZ), and disagreement was resolved by a discussion between the reviewers and consultation with a third reviewer if necessary. Data from publications in Mandarin Chinese were abstracted by a single native-language speaker (WZ); no other non-English publications met inclusion criteria.

A standardized Microsoft Excel-based data extraction form was developed to include the following information for all studies: country, study period, study methods, SAGE target group(s) represented, economic evaluation perspective, and funding source. Additionally, for cost-of-illness studies, we abstracted direct and indirect costs of all illnesses, outpatient visits, and hospitalizations. For program cost studies, we abstracted financial and economic costs both including and excluding vaccine procurement. Financial costs were incremental monetary expenditures made for the influenza vaccination program; economic costs included all financial costs as well as the value of existing resources and donations (as categorized by study authors). For cost-effectiveness studies, we abstracted the study intervention(s), comparator(s), incremental cost-effectiveness ratio (ICER), ICER interpretation, and cost-effectiveness threshold. If reported, we preferentially abstracted median values for economic variables; if medians were not reported, we abstracted mean values or ranges. We did not contact study authors to request additional unpublished data.

We used World Bank data to classify the income group of countries during the study period [24]; if countries changed income group classification during the study period, the higher classification was used. Additionally, we used World Bank data to obtain the gross domestic product (GDP) of countries during the study period [24]; for multi-year studies, the final year of the study period was used. For cost-of-illness and program cost studies, we also used World Health Organization data to obtain the Current Health Expenditure (CHE) and Domestic General Government Health Expenditure, respectively, of countries during the study period [27]. If no study period was specified, we used 3 years prior to the publication year for all relevant inputs as in prior systematic reviews [23].

For each English-language publication, two reviewers (RG, AC, MC, or WZ) assessed study quality and risk of bias using the Consolidated Health Economic Evaluation Reporting Standard (CHEERS) checklist

[28]; for non-English publications, one native speaker (WZ) completed the CHEERS checklist. The checklist includes 24 criteria developed to ensure standardized reporting across economic studies; all 24 were assessed for cost-effectiveness studies, and modified sets of 13 and 15 criteria were used for cost-of-illness and program cost studies, respectively (**Supplemental Table S2**).

Data conversion and analysis

We converted all currencies to US dollars (US$) using the International Monetary Fund official exchange rate for the nominal year [24] and then inflated all results to 2022 US$ using the U.S. Bureau of Economic Analysis GDP implicit price deflator [29, 30]. If a nominal currency year was not presented in the study, we used the final year of the study period or, if the study period was not stated, 3 years prior to the publication year. We calculated the gross national cost-of-illness and program cost, when reported, as a proportion of the national GDP and the national health expenditure. Additionally, we collated direct and indirect costs by SAGE target group and income group and reported ranges across strata. Similarly, we also collated ICER results by SAGE target group and income group and calculated the proportion of studies that interpreted findings as “cost-saving” (ICER<0), “cost-effective” (dependent on cost-effectiveness threshold specified in the study), or “not cost-effective.” All analyses were performed using SAS (version 9.4) and Microsoft Excel.

Results

Study characteristics and quality assessment

Of 6,614 total studies identified, 50 met eligibility criteria and were included in this review, including 43 English-language and 7 Chinese-language studies (**Figure 1, Supplemental Table S3**). Study characteristics are presented in **Table 1**; a total of 24 studies presented cost-effectiveness findings, 23 presented cost-of-illness, and four presented program costs. Studies included data from 20 country settings, which were classified as upper-middle income countries (UMICs; n=11), lower-middle income countries (LMICs; n=7), and low-income countries (LICs; n=3); one country, China, was classified as both UMIC and LMIC corresponding to multiple studies before and after an upward change in World Bank classification in 2010. These 20 countries represented 13% of 157 countries/territories classified as low- or middle-income countries in any year during 2005 (earliest year of data presented in included studies) through 2021. The most frequently evaluated SAGE target groups were children (n=26 studies, inclusive of children <18 years), older adults (n=16, inclusive of adults ≥60 years), and persons with chronic medical conditions (n=12); fewer studies evaluated pregnant persons (n=8), healthcare workers (n=4), and persons in congregate living settings (n=1).

Quality assessment scores indicated that the quality of included studies was acceptable; median scores by study type were 12 out of 13 (92%; interquartile range [IQR] 87–100%) for cost-of-illness, 14 out of 15 (93%; IQR 93–95%) for program costs, and 23 out of 24 (96%; IQR 86–100%) for cost-effectiveness studies (**Supplemental Figure S1**); only two of 50 studies (4%) scored <75%. Of 44 studies that reported a funding source, seven (16%) were supported by pharmaceutical industry and 20 (45%) by WHO or the US Centers for Disease Control and Prevention (CDC).

Cost-of-illness studies

The cost-per-episode of influenza illness ranged widely across studies (**Figure 2**). Twenty-three studies presented data about cost-per-episode, representing six UMICs (China [31-40], Colombia [41], Kazakhstan [42], Panama [43], Romania [42], South Africa [44, 45], and Thailand [46]), five LMICs (China [based on classification during study period] [47], El Salvador [43], India [48], Kenya [49], Ukraine [42], and Vietnam [50, 51]), and two LICs (Bangladesh [52] and Mali [53]). (**Supplemental Table S4**). Among the general population, the total cost-per-episode for outpatient visits, inclusive of direct and indirect costs, ranged from $6.24–155.92 (2022 US$); the total cost-per-episode for hospitalizations ranged from $106.85–1617.14. Among SAGE target groups, total cost-per-episode of outpatient visits and hospitalizations was $25.92–198.13 and $95.15–2202.74 for children, $38.17–164.52 and $282.37–2729.25 for older adults, $44.13–176.79 and $847.60–1578.86 for persons with chronic medical conditions, and $5.45–36.97 and $189.98–1088.92 for pregnant persons. Costs across all target groups were generally higher in UMICs than in LMICs/LICs (**Figure 2**). Nevertheless, indirect costs comprised a greater proportion of the total costs of outpatient visits compared with hospitalizations, and a greater proportion of total costs in LMICs/LICs compared with UMICs (**Supplemental Figure S2**). Details on costs abstracted from each study are described in **Supplemental Table S4.**

Four studies evaluated the cost-per-episode for multiple SAGE target groups [33, 38, 45, 50]. Studies from China and Vietnam found higher hospitalization costs among older adults compared with children [33, 38, 50], as well as higher costs associated with chronic medical conditions across age groups [33, 38]. In South Africa, total economic burden after incorporating rates of illness was highest for persons with chronic medical conditions, followed by children, older adults, and pregnant persons [45]. Across all studies, characteristics that impacted cost-of-illness included urbanicity (rural vs. urban) [33, 38, 47], facility type (public vs. private or level of care provision) [33, 52], and influenza season or circulating virus type [36, 39]. Only two identified studies quantified disability-adjusted life years [37] or quality-adjusted life days lost from influenza illness [35].

Seven of the 23 studies reported a total national economic burden of influenza illness for either the general population or specific SAGE target groups (**Table 2**), representing three UMICs (China [40], Romania [42], and South Africa [44, 45]), two LMICs (Kenya [49] and Ukraine [42]), and one LIC (Bangladesh [52]). Total annual costs of influenza illness in studies evaluating the general population (no specified SAGE target group) were equivalent to 0.02–0.19% of the national GDP and 0.32–7.16% of the national health expenditure; costs for any single target group were <0.01–0.02% of the national GDP and 0.01–0.42% of the national health expenditure. The highest total costs, as a percent of GDP and national health expenditure, were reported from Bangladesh [52]. Three studies accounted for non-medically attended illnesses in the estimation of national economic burden [42, 44, 45].

Program cost studies

Four studies evaluated the cost of influenza vaccination programs (**Table 3**): three with findings from UMICs (Albania [54], China [55], and Thailand [56]) and one from an LIC (Malawi [57]). Of these, two evaluated the cost of a program targeting pregnant persons [56, 57], one evaluated a program targeting healthcare workers [54], and one evaluated a program targeting multiple SAGE target groups (older adults, persons with chronic medical conditions, children <5 years, pregnant persons, and healthcare workers) [55]. Two studies used the WHO SIICT [12, 54, 57]. The total annual cost of program was equivalent to <0.01–0.04% of the national GDP and 0.06–4.78% of the national health expenditure; the highest proportion of health expenditure was reported in the study vaccinating multiple target groups. Vaccine procurement represented a large proportion of total costs (89% financial and 44% economic costs in Albania [54] and 1% financial and 82% economic costs, assuming donated vaccine, in Malawi [57]). Across studies, the total cost per dose administered ranged from $0.62–5.20 (financial) and $0.81–13.72 (economic), inclusive of vaccine purchase or donation.

Cost-effectiveness studies

Twenty-four studies presented data on cost-effectiveness of influenza vaccination (**Supplemental Table S5**), representing seven UMICs (Argentina [58], China [59-64], Colombia [65], Mexico [66-68], South Africa [69-71], Thailand [72-76], and Turkiye [77]), four LMICs (Kenya [78], Lao PDR [79], Ukraine [80], and Vietnam [69]), and one LIC (Mali [53]). Twenty (83%) studies evaluated influenza vaccine introduction (i.e., vaccination compared with no vaccination), two evaluated the effect of increased vaccination coverage on an existing program, and two evaluated combinations of new introduction and increased coverage for different target groups. Cost-effectiveness thresholds varied greatly across studies; most (n=15/24; 63%) used a threshold within one to three times the GDP per capita, three (13%) used other country-specific thresholds, one (4%) intentionally did not report a threshold, and the remaining five (21%) did not provide any details about thresholds.

Among the 20 studies that evaluated the cost-effectiveness of vaccine introduction, eight provided results for children, five for older adults, four for persons with chronic conditions, four for pregnant persons, two for healthcare workers, and one for persons in congregate living settings. Most (83%) interpreted at least one modeled scenario for each SAGE target group as either cost-effective (based on designated cost-effectiveness threshold) or cost-saving (ICER<0) (**Figure 3**). The number of studies that identified results as cost-saving were 3/8 (38%) for children, 1/5 (20%) for older adults, 2/4 (50%) for persons with chronic medical conditions, 1/4 (25%) for pregnant persons, and 2/2 (100%) for healthcare workers. Similarly, the number of studies that identified results as cost-effective were 3/8 (38%) for children, 3/5 (60%) for older adults, 2/4 (50%) for persons with chronic medical conditions, 3/4 (75%) for pregnant persons, and 1/1 (100%) for persons in congregate living settings. Only three studies interpreted all modeled scenarios for a particular target group as not cost-effective: 2/8 (25%) evaluating cost-effectiveness among children [71, 78] and 1/5 (20%) among older adults [64].

Two studies assessed the cost-effectiveness of influenza vaccine introduction for multiple target groups; of these, the target groups with the greatest value-for-money were healthcare workers in Laos (cost-saving; other groups evaluated were pregnant persons and older adults, found to be cost-effective) [79], and pregnant persons and persons with chronic medical conditions in South Africa (cost saving; other groups evaluated were older adults, found to be cost-effective, and children, not found to be cost-effective) [71]. The three variables most commonly identified to influence the ICER were annual incidence of influenza (n=9) [53, 58, 59, 69-71, 74, 77, 79], vaccine effectiveness (n=9 studies) [58, 63, 65, 70-73, 77, 79], and cost of vaccine (n=6) [53, 70, 71, 73, 74, 78]; some studies demonstrated that variation in the attack rate [59, 69, 71, 74] or vaccine effectiveness [71] change the interpretation of cost-effectiveness results (cost-saving, cost-effective, or not-cost-effective).

Additionally, seven papers looked at different prioritization strategies within SAGE target groups by underlying health conditions [70, 72] or age [58, 59, 73, 75, 78]; among pregnant persons in South Africa, prioritization of people living with HIV reduced the ICER (though not statistically significant) [70], and among persons with underlying coronary heart disease in Thailand, restricting to only persons with angina reduced the ICER, whereas restricting to persons with cardiac arrest/myocardial infarction increased the ICER (no longer cost-effective) [72]. Results by age were also mixed; two studies among children found lower ICERs for vaccinating younger children (6–23 months vs. 2–5 years or 6–14 years in Kenya [78] and 6–59 months vs. 5–14 years in China [59]), two studies among children found lower ICERs for vaccinating wider age ranges (6 months–5 years vs. 6–23 months or 6–36 months in Argentina [58]) or older children (12–17 years vs. 2–5 years or 6–11 years in Thailand [73]), and a study among persons with underlying heart disease in Thailand found a lower ICER for persons aged ≥50 years compared with ≥40 years or ≥60 years [75].

Discussion

The 50 studies identified in this review suggest an increased momentum to generate economic evidence about influenza illness and vaccination from low- and middle-income countries during 2012 – 2021; a previous review using a similar search strategy identified only 22 cost-of-illness or cost-effectiveness studies from low- and middle-income countries [15], and another identified nine cost-effectiveness/cost-benefit/cost-utility studies [13], both prior to 2012. The release of updated tools and guidance by WHO, as well as technical and financial support by WHO, CDC, and other international partners, have facilitated this expansion of the evidence base, emphasizing the utility of global and multinational collaborations in strengthening influenza vaccination programs worldwide. Recent additions to the literature include studies from LMIC/LICs, studies representing Sub-Saharan Africa, South Asia, and middle-income European countries, and studies focused on pregnant persons; none of these were represented in the previous reviews, which only identified data from UMICs in East Asia, Latin America, and Europe [13, 15]. However, disparities remain by income group and region; LICs are still very underrepresented, and no studies from low- and middle-income countries in the Middle East and North Africa region were identified in our review.

Additionally, pregnant persons, healthcare workers, and persons in congregate living settings remain especially underrepresented in economic evaluations. Healthcare workers are of particular interest because of the potential benefit of vaccination to themselves and the greater health system [81]; in

2018, Gavi, the Vaccine Alliance, expressed interest in assessing the feasibility and impact of routine influenza immunization of healthcare workers to support epidemic and pandemic influenza preparedness [82]. Additionally, the Gavi 5.1 strategy, presented in December 2022 [83], included a strategic focus on enhancing outbreak and pandemic response, to which healthcare worker vaccination might contribute. To date, global literature about cost-effectiveness and other evidence for influenza vaccination among healthcare workers remains limited [81, 84], but notably, we identified both a cost-saving result for healthcare worker vaccination in Lao PDR [79] and in Ukraine [80], suggesting high value-for-money. Additional data are needed to strengthen the evidence to optimize influenza vaccination in this target group.

Among all cost-of-illness studies, we found that the cost-per-episode estimates for influenza outpatient visits and hospitalizations varied widely. Per-episode costs were generally greater in higher income settings (i.e., UMICs compared with LMICs/LICs), likely reflecting higher costs of care, but the national economic burden among the general population, which ranged from <1%–7% of the national health expenditure, was highest in an LIC (Bangladesh [52]). More studies from LICs are needed to further evaluate disparities among income groups. As recommended by WHO, many studies used data from ILI/SARI sentinel surveillance sites for estimating economic burden; these surveillance systems can serve as a valuable data source but are not typically designed to capture non-medically attended illnesses [85] or non-respiratory disease outcomes [86], thereby likely underestimating the true economic burden of influenza. In South Africa for example, estimates obtained among patients meeting a SARI/ILI case definition underestimated the total economic burden by approximately 65% [44]; thus, comprehensive strategies and innovative strategies are needed to better characterize economic burden. Finally, characteristics of the underlying population in a particular setting, such as age structure and prevalence of underlying medical conditions, might affect costs across target groups; for example, in South Africa, where the highest burden was in individuals with chronic medical conditions, this was impacted by HIV and TB prevalence in the population [44, 45]. Thus, economic evaluations that address multiple target groups in a particular setting, rather than a single target group, can provide valuable evidence to inform local vaccination policy; given limited resources for vaccination programs, such comparisons could assist with target group prioritization.

We identified only four program cost studies within the last 10 years, indicating a need for more evaluations in low- and middle-income countries. Vaccine delivery cost studies can provide direct evidence to policymakers to make decisions on vaccine introduction, plan budgets and financing strategies for rollout, and identify efficiencies in service delivery [87]. In fact, the WHO SIICT [12] and other costing methods can be used even in the absence of an existing program, as performed in Malawi [57]. The four studies that we identified indicated that influenza vaccination programs generally cost a small fraction compared to the national GDP (≤0.04% in these studies) or national health expenditure (≤1% per each individual target group covered in these studies). Vaccine procurement was a major driver of program costs in both studies that disaggregated this component, representing 82% of the economic costs (including the value of donated resources) of the hypothetical maternal vaccination program using donated vaccine in Malawi [57], and 89% of the financial and 44% of the economic costs of a healthcare worker vaccination program utilizing a combination of government-procured and donated vaccines in Albania [54]. This underscores the importance of sustainable financing and procurement strategies to support access to influenza vaccines and enable successful program implementation, consistent with lessons learned from other vaccine introductions [88]. Again, as costs may vary across target groups, evaluating program costs in multiple groups within a given country context could provide useful data for resource prioritization.

Among cost-effectiveness studies identified in this review, most reported at least one cost-saving or cost-effective vaccination scenario per target group assessed; however, results were significantly impacted by variables such as influenza incidence, vaccine effectiveness, cost of vaccine, and vaccine coverage, as well as by prioritization within target groups (e.g., by age or specific underlying health conditions). Strategies to address this variability include use of at least 5 years of data to assess disease burden, if available, and use of sensitivity analyses among ranges of plausible values, for example including vaccine effectiveness estimates from years with high and low vaccine match [11]. Future studies could use innovative approaches to more completely characterize the total disease and economic burden of influenza, as well as additional endpoints for vaccine effectiveness (illness attenuation) and indirect protection from vaccination [7]. Finally, the use of appropriate cost-effectiveness thresholds in low- and middle-income settings warrants further discussion [89, 90]. In our review, among only three studies that did not identify any cost-effective scenarios, two used a cost-effectiveness threshold less than GDP per capita [71, 78]; however, using 1–3 times GDP per capita would have resulted in a cost-effective result in both. Use of context-specific thresholds reflecting local preferences [91], such as local health opportunity costs [92], might provide more valuable information to guide investment decisions than thresholds of 1–3 times GDP per capita [89, 90, 93, 94].

This review is subject to several notable limitations. First, the inclusion/exclusion criteria used (e.g., estimates derived from LCI or ILI/SARI case definition; no comparison of vaccine formulations) undercount the total number of economic studies from low- and middle-income countries within the past 10 years. Multiple other studies have evaluated costs of acute respiratory illness, of which influenza is an important etiology, or addressed other economic questions, such as the cost-effectiveness of quadrivalent vs. trivalent vaccine [23, 95], and were not captured here. Influenza illness might also present as non-respiratory outcomes [86], and thus the economic burden of influenza is underestimated in most studies that restrict to syndromic surveillance for ILI/SARI [85]. Second, target group definitions vary across countries, with variation in age cut-offs for children and older adults and prioritization of specific chronic medical conditions, but all results per target group were summarized together in this review due to the small numbers of publications, potentially missing nuances of within-group differences. Relatedly, although SAGE recommendations specifically reference children aged <5 years [1], all publications with data for children aged <18 years were included. Finally, we found substantial heterogeneity in the methodology and data inputs used across studies; in fact, as discussed previously, influenza itself intrinsically varies in annual incidence, disease severity, and vaccine effectiveness across seasons. As previously discussed, we did not conduct meta-analyses because of this variability, though methods for meta-analysis of economic data are available [96] and have been used in other reviews that focus predominantly on high-income settings [21].

This review also uncovered opportunities to provide evidence on policy-relevant questions that currently have limited evidence. First, we did not identify any studies taking an employer payer's perspective; however, studies utilizing this approach could provide valuable policy-relevant information to encourage vaccination among employees or to encourage employer-supported vaccination programs [97] as a pathway to broader influenza vaccine availability. Second, few studies quantified preference-based outcomes such as disability-adjusted life years [40] or quality-adjusted life days from influenza illness [38]; continued efforts for valuation of these outcomes could inform context-specific inputs for future cost-effectiveness analyses. Third, we only identified one included study that evaluated cost-effectiveness of influenza vaccination coadministered with another vaccine (pneumococcal vaccine) [65]; a few additional studies addressing coadministration were excluded because they did not provide results for influenza vaccination alone. Given opportunities to coadminister influenza vaccine with other vaccines across the life course, including COVID-19 vaccine [98], evaluation of shared costs in program cost or cost-effectiveness studies might incentivize integrated vaccine implementation. Fourth, we found only two studies that considered non-respiratory disease outcomes (cardiovascular disease events) in cost-effectiveness analyses, both among persons with underlying heart disease in Thailand [72, 75]; as previously discussed, inclusion of non-respiratory disease outcomes could better characterize the full impact of influenza vaccination [86]. Similarly, innovative strategies might address the broader impact of vaccines, such as impact on childhood development, household behavior, economic growth, political stability, and health equity [99, 100]

Conclusions

Continued evaluation of costs and cost-effectiveness is useful to drive evidence-based vaccine policy development, implementation, and refinement and global investment in influenza vaccination. Additional studies from low-income countries and underrepresented target groups (e.g., pregnant persons, healthcare workers, and persons in congregate living settings) would strengthen the evidence of value-for-money. Standardization of research agenda [1] and methodology across future evaluations, including considerations to capture the full spectrum of influenza-associated illness, could allow for pooled estimates and meta-analyses. Global, regional, and country-specific data on the economics of vaccination, including costs of vaccination programs, costs of avertable illnesses, and cost-effectiveness, are instrumental for policymaking, resource allocation, and investment for expanded and sustainable influenza vaccination programs.

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

Figure 1: PRISMA flow diagram of study selection process

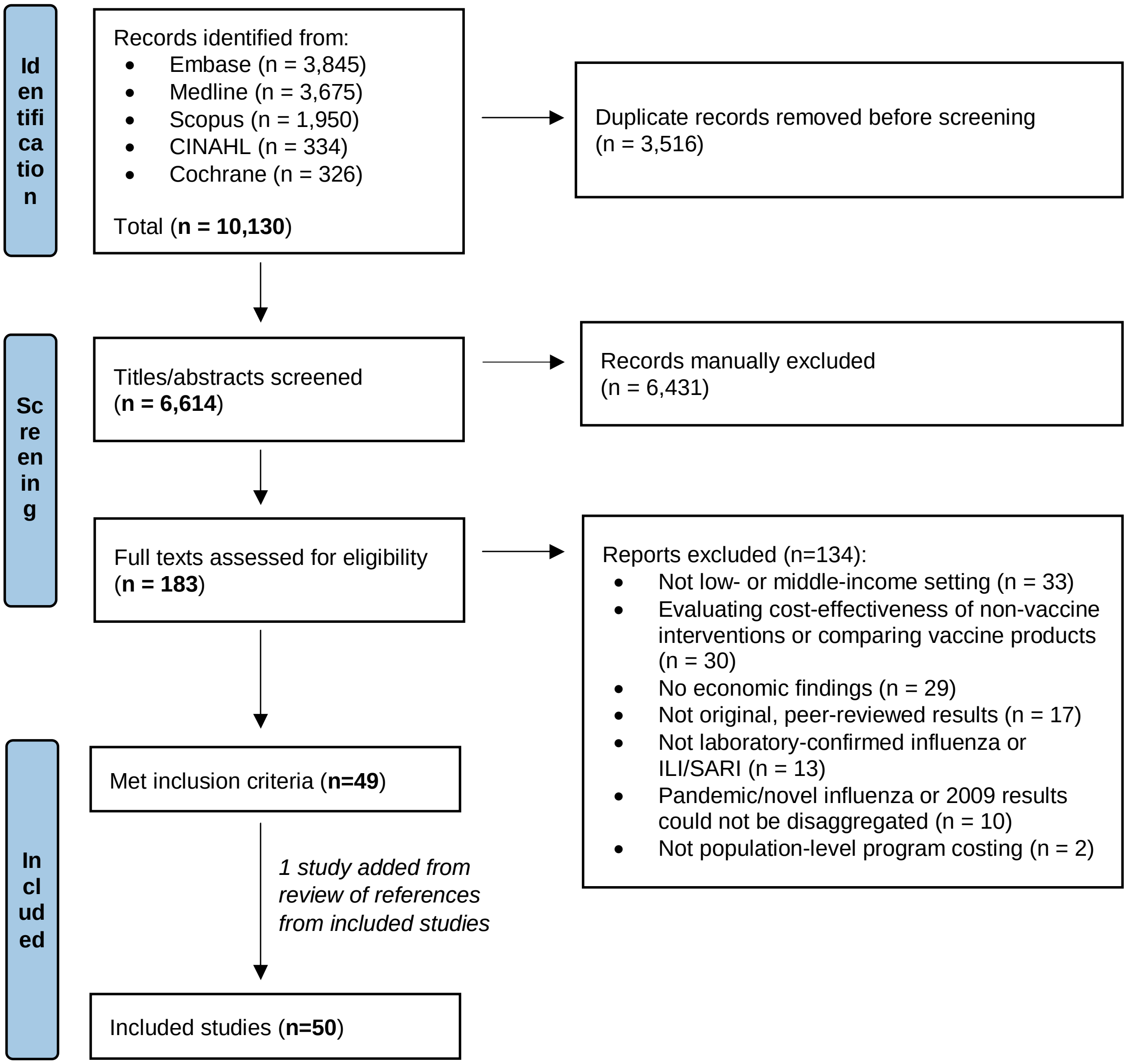


Table 1: Number of included studies by income group classification, region, Strategic Advisory Committee of Experts on Immunization (SAGE) target group, and study type

Income group and region	Total no. studies included	Total no. countries represented	No. studies by SAGE target group[1]							No. studies by study type		
			None (general population)	Children[2]	Older adults	Persons with chronic medical conditions	Pregnant persons	HCWs	Persons in congregate living settings	Cost-of-illness	Cost-of-program	Cost-effectiveness
Total	**50**[3]	**20**[4]	**13**	**26**	**16**	**12**	**8**	**4**	1	**23**[5]	**4**	**24**[5]
Upper-middle income countries (UMIC)	**40**	**11**	**7**	**22**	**13**	**11**	**5**	**2**	**1**	**17**	**3**	**20**
East Asia & Pacific	24	2	3	14	9	7	2	1	1	11	2	11
Latin America & Caribbean	7	4	2	6	0	1	0	0	0	2	0	5
Sub-Saharan Africa	5	1	2	2	2	2	3	0	0	2	0	3
Europe & Central Asia	4	4	0	0	2	1	0	1	0	2	1	1
Lower-middle income countries (LMIC)	**11**	**7**	**5**	**4**	**3**	**1**	**1**	**2**	**0**	**7**	**0**	**4**
East Asia & Pacific	5	3	4	1	2	0	1	1	0	3	0	2
Sub-Saharan Africa	2	1	1	2	0	0	0	0	0	1	0	1
Europe & Central Asia	2	1	0	0	1	0	0	1	0	1	0	1
Latin America & Caribbean	1	1	0	1	0	0	0	0	0	1	0	0
South Asia	1	1	0	0	0	1	0	0	0	1	0	0
Low-income countries (LIC)	**3**	**3**	**1**	**0**	**0**	**0**	**2**	**0**	**0**	**2**	**1**	**1**
Sub-Saharan Africa	2	2	0	0	0	0	2	0	0	1	1	1
South Asia	1	1	1	0	0	0	0	0	0	1	0	0

[1]Vaccination target groups as defined in WHO SAGE guidance [1]. Several studies reported data on >1 target group.

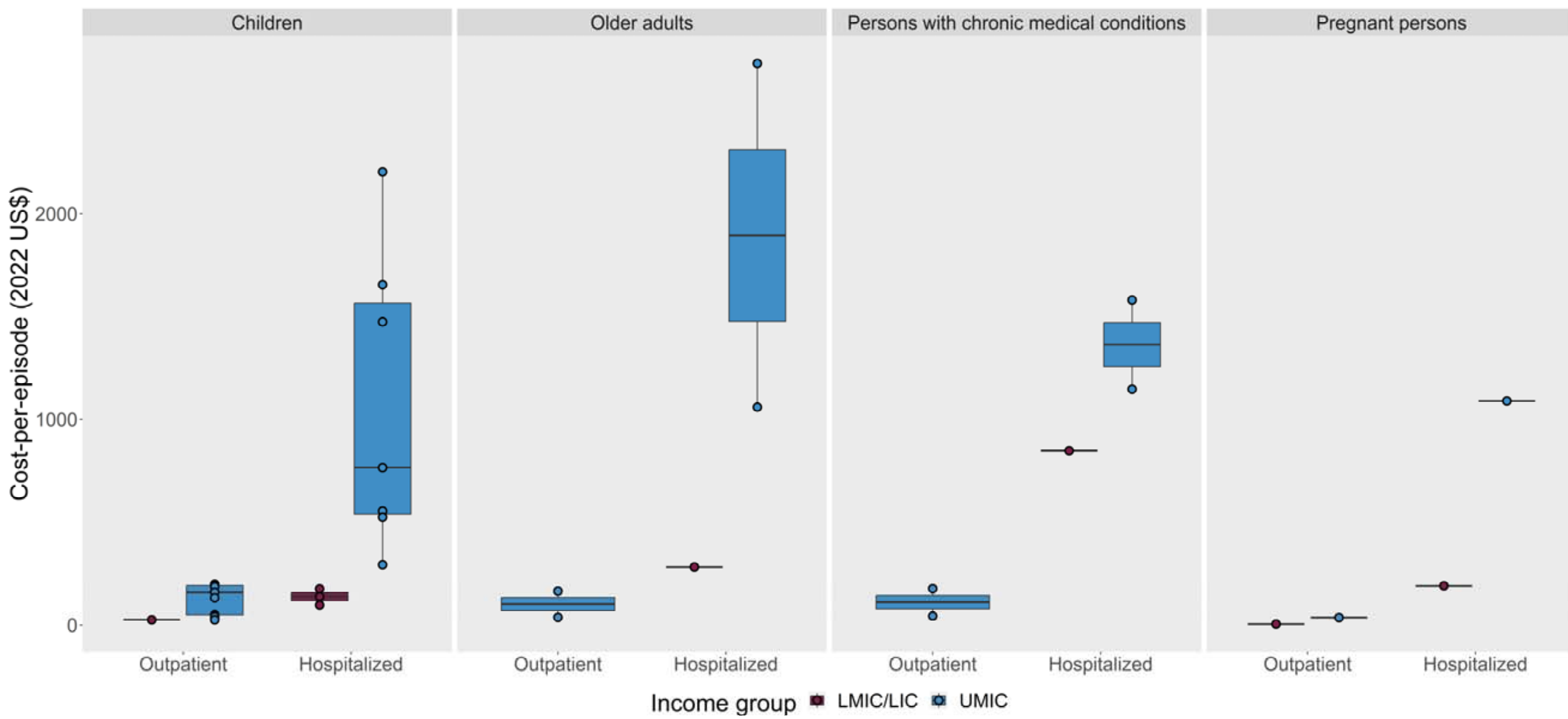
[2]Although SAGE recommendations specifically reference children aged <5 years [1], publications with data for children aged <18 years were included.

[3]Three studies [42, 43, 69] included countries from multiple income groups and/or regions.

[4]One country (China) changed income classification from LMIC to UMIC in 2010 and was counted in both groups corresponding to studies assessing time periods before and after this year.

[5]One study [53] reported original data for both cost-of-illness and cost-effectiveness.

Figure 2: Total costs-per-episode[1] of influenza illness, by disease severity (outpatient vs. hospitalized)[2], income group, and Strategic Advisory Committee of Experts on Immunization (SAGE) target group[3], in low- and middle-income countries



All costs presented in 2022 US$.

Abbreviations: LIC, low-income country; LMIC, lower-middle income country; UMIC, upper-middle income country; US$, US Dollars.

[1]Total costs inclusive of direct and indirect costs; direct costs were all medical and non-medical costs directly attributable to patient care. Indirect costs were all costs not directly attributable to patient care (e.g., lost earnings or lost productivity). Median costs were preferentially abstracted from source publications; if unavailable, mean costs were abstracted.

[2]No included papers reported hospitalization costs for older adults or persons with chronic medical conditions in LMIC/LIC.

[2]No cost-of-illness papers were identified for healthcare workers or individuals in congregate living settings in low- and middle-income countries.

Table 2: National economic burden of influenza illness, by Strategic Advisory Committee of Experts on Immunization (SAGE) target group[1], in low- and middle-income countries

Income group	Study	Country	Target group details	Data source for national extrapolation	Study period	Perspective	Total annual cost (2022 US$, millions)[2]	Total annual cost as % of total national GDP[2,3]	Total annual cost as % of national health expenditure[2,4]
General population									
UMIC	Tempia, 2019 [44]	South Africa	All ages	7 sentinel hospitals and 2 clinics	2013–15	Societal	$322.62[5]	0.09%	1.16%
UMIC	Gong, 2021 [40]	China	All ages	Not reported	2006–19	Societal	$4249.40	0.03%	0.55%
LMIC[6]	Emukule, 2019 [49]	Kenya	All ages	4 sentinel hospitals and 1 clinic	2013–14	Societal	$10.76–38.26	0.02–0.06%	0.32–1.14%
LIC[7]	Bhuiyan, 2014 [52]	Bangladesh	All ages	4 sentinel hospitals	2010	Societal	$219.68	0.19%	7.16%
Children[8]									
UMIC	Tempia, 2020 [45]	South Africa	6–59 months	7 sentinel hospitals and 2 clinics	2013–15	Societal	$39.97[5]	0.01%	0.14%
LMIC[6]	Emukule, 2019 [49]	Kenya	<5 years	4 sentinel hospitals and 1 clinic	2013–14	Societal	$6.19–14.21	0.01–0.02%	0.18–0.42%
Older adults									
UMIC	Kovacs, 2014 [42]	Romania	≥65 years	26 sentinel hospitals	2011–12	Payer[9]	$0.68[5]	<0.01%	0.01%
UMIC	Tempia, 2020 [45]	South Africa	≥65 years	7 sentinel hospitals and 2 clinics	2013–15	Societal	$18.75	0.01%	0.07%
LMIC	Kovacs, 2014 [42]	Ukraine	≥65 years	10 sentinel hospitals	2011–12	Payer[9]	$0.79	<0.01%	0.01%
Persons with chronic medical conditions									
UMIC	Tempia, 2020 [45]	South Africa	5–64 years with HIV, TB, or other UMC	7 sentinel hospitals and 2 clinics	2013–15	Societal	$102.15[5]	0.03%	0.37%
Pregnant persons									
UMIC	Tempia, 2020 [45]	South Africa	NA	7 sentinel hospitals and 2 clinics	2013–15	Societal	$7.24[5]	<0.01%	0.03%

Abbreviations: GDP, gross domestic product; HIV, human immunodeficiency virus; ILI, influenza-like illness; LCI, laboratory-confirmed influenza; LIC, low-income country; LMIC, lower-middle income country; NA, not applicable; SARI, severe acute respiratory infection; TB, tuberculosis; UMC, underlying medical condition; UMIC, upper-middle income country; US$, US Dollars.

[1]No cost-of-illness papers were identified for healthcare workers or individuals in congregate living settings in low- and middle-income countries.

[2]Calculated values not reported in source publication.

[3]National GDP obtained from World Bank [24], reported for final year of study period.

[4]Current Health Expenditure obtained from World Health Organization [27], reported for final year of study period.

[5]Included estimation of non-medically attended illnesses.

[6]Kenya changed classification from LIC to LMIC in 2014, during the study period [24], and was thus classified as LMIC.

[7]Bangladesh changed classification from LIC to LMIC in 2014, after the study period [24], and was thus classified as LIC.

[8]Although SAGE recommendations specifically reference children aged <5 years [1], publications with data for children aged <18 years were included.

[9]No indirect costs were included in the total estimate because of study perspective. The specific payer was not specified in the source publication.

Table 3: Costs of national influenza vaccination programs in low- and middle-income countries

Study characteristics							Scenario characteristics			Base scenario results			
Income group	Study	Country	Program year(s) costed[1]	Costing tool/method used	SAGE target group	Perspective	Base scenario: vaccine formulation and cost assumptions	Base scenario: coverage	Additional scenarios modeled	Total annual cost as % of total national GDP[2,3]	Total annual cost as % of national health expenditure[4]	Vaccine procurement cost[5] as % of total cost	Cost per dose administered (2022 US$)[3]
UMIC	Yang 2016 [55]	China	2015 (1 year)	Budget impact analysis using secondary data inputs	**Multiple**: (1) older adults ≥60y; (2) persons with chronic medical conditions; (3) children <5y; (4) pregnant persons; and (5) healthcare workers	Govt.	TIV for 0.25 ml formulation (infants aged 6–35 months) and $7.17 per dose for 0.50 ml formulation (all ages >35 months)	20%	Varied vaccine uptake and wastage rate	0.01%	4.78%	NR	NR
UMIC	Riewpaiboon 2021 [56]	Thailand	2018 (1 year)	Micro-costing approach sampling district health facilities	**Pregnant persons**	Health system	Unspecified seasonal vaccine: cost not reported	NR	NR	NR	NR	NR	$0.81–11.70 (economic) range across health facilities
UMIC	Pallas 2020 [54]	Albania	2018–19 (1 season)	SIICT[6] micro-costing approach	**Healthcare workers**	Govt.	TIV: $4.54/dose for donated single-dose vial presentation; $5.30/dose for government-purchased single-dose pre-filled syringe presentation	70%	Varied vaccine coverage, vaccine presentation, and purchase price	<0.01%	0.06%	89% (financial), 44% (economic)	$0.56 (financial), $7.68 (economic) excluding vaccine procurement; $5.20 (financial), $13.72 (economic) including vaccine procurement
LIC	Pecenka 2017 [57]	Malawi	2018–22 (5 years)	SIICT[6] micro-	**Pregnant persons**	Govt.	Unspecified seasonal vaccine:	47%	Varied vaccine	0.04%	1.09%	1% (financial),	$0.62 (financial),

	costing approach	$0/dose (financial cost) and $2.90/dose (economic cost) for donated single dose pre-filled vaccine presentation	uptake and purchase price		82% (economic) assuming donated vaccine	$5.46 (economic) assuming donated vaccine

Abbreviations: Govt., government; LMIC, lower-middle income country; NR, not reported; SAGE, Strategic Advisory Group of Experts on Immunization; SIICT, Seasonal Influenza Immunization Costing Tool; TIV, trivalent influenza vaccine; UMIC, upper-middle income country; US$, US Dollars; WHO, World Health Organization.

[1]Program years could be defined by calendar year or influenza season and are designated accordingly.

[2]National GDP obtained from World Bank [24], reported for final program year costed. Economic program costs were used for the calculation if both financial and economic total costs were reported.

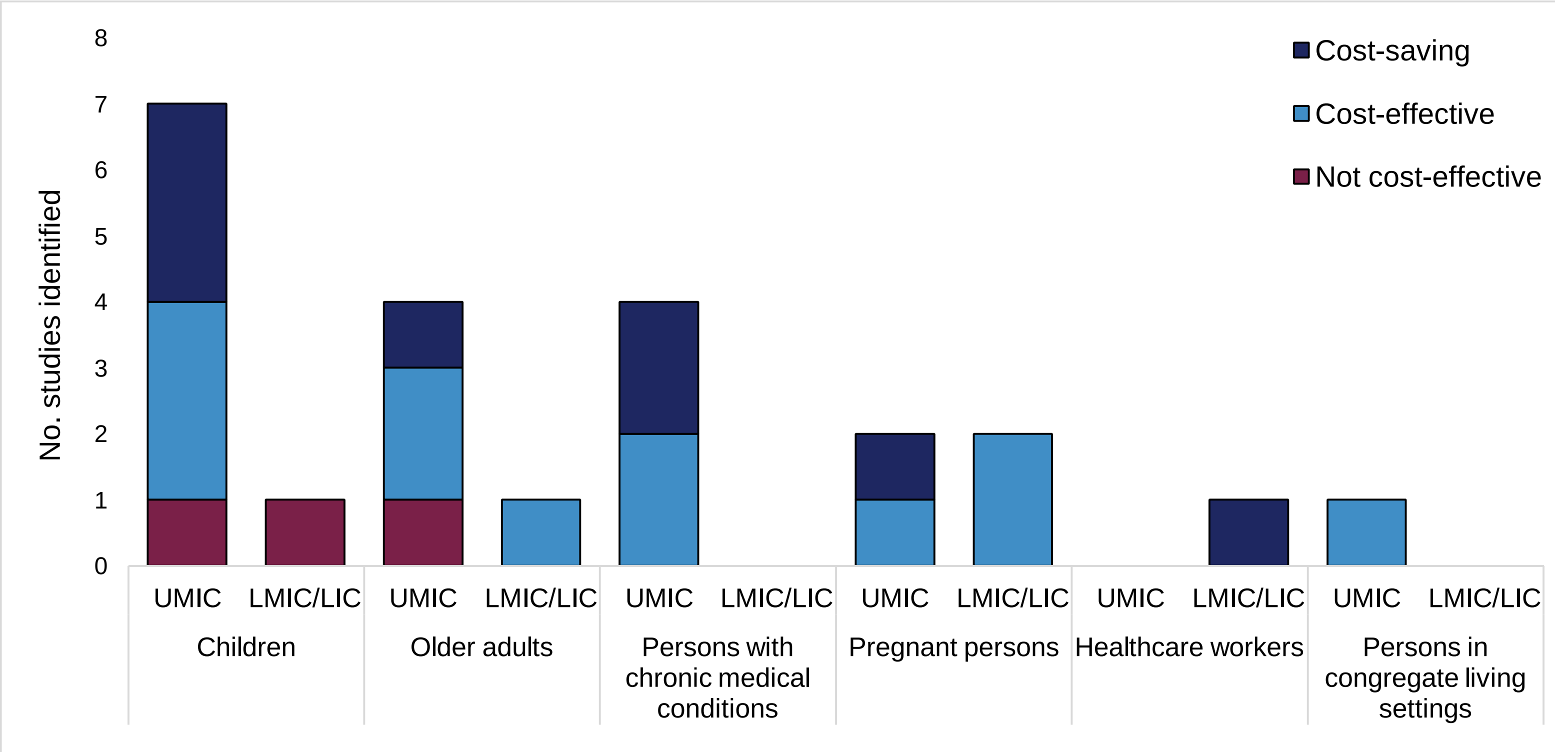
[3]Calculated values not reported in source publication.

[4]Percent of government health expenditure was obtained from the source publication if reported (Pallas and Yang); else, Domestic General Government Health Expenditure obtained from World Health Organization [27]. Economic program costs were used for the calculation if both financial and economic total costs were reported.

[5]Vaccine procurement cost includes cost of vaccine and vaccination supplies.

[6]The “WHO Flutool for planning and costing maternal influenza vaccination” was originally released in 2016; in 2019, the updated “Flutool plus – Seasonal Influenza Immunization Costing Tool (SIICT)” was released and allowed for influenza vaccination cost estimation in additional target groups [12]. Both tools are referred to as “SIICT” in this table.

Figure 3: Cost-effectiveness results of studies evaluating influenza vaccination[1], by Strategic Advisory Committee of Experts on Immunization (SAGE) target group, in low- and middle-income countries



Abbreviations: LIC, low-income country; LMIC, lower-middle income country; UMIC, upper-middle income country.

[1]Only includes studies comparing cost-effectiveness of influenza vaccination vs. no vaccination. Additional studies examining cost-effectiveness of modifications to a current vaccination program (e.g., increased coverage) are described in Supplemental Table S5. Categorization is based on the interpretation provided in the original study; if any modeled intervention was interpreted as cost-saving (ICER<0), the study was characterized as "cost-saving" and if any modeled intervention was interpreted as cost-effective, the study was characterized as "cost-effective." Interpretations of highly cost-effective and cost-effective were both combined as "cost-effective." Details on each scenario are provided in Supplemental Table S5.

Supplementary materials

Table S1: Search terms for systematic review, by database

Database	Strategy	Run Date
Medline (OVID) 1946-	(influenza* OR flu OR H1N1) AND Cost* OR economic* OR ec.fs AND Exp Animals/ NOT exp humans/ 2012 - 2021	01/31/2022
Embase (OVID) 1974-	Exp Influenza/ OR (influenza* OR flu OR H1N1).ti,ab. AND Cost* OR economic* AND Exp Animal/ NOT exp human/ NOT Conference abstract.pt 2012 – 2021; not Pubmed/Medline	01/31/2022
Cochrane Library	(influenza* OR flu OR H1N1):ti,ab AND (Cost* OR economic*):ti,ab 2012 – 2021	01/31/2022
CINAHL (EbscoHost)	(TI (influenza* OR flu OR H1N1)) OR (AB (influenza* OR flu OR H1N1)) AND (TI (Cost* OR economic*)) OR (AB (Cost* OR economic*)) 2012 – 2021; exclude Medline records	01/31/2022
Scopus	TITLE-ABS-KEY(influenza* OR flu OR H1N1) AND TITLE-ABS-KEY(Cost* OR economic*) AND NOT INDEX(medline) 2012 – 2021	01/31/2022

Table S2: Modified Consolidated Health Economic Evaluation Reporting Standard (CHEERS) criteria[1] used for quality assessment

CHEERS criterion	Description	Evaluated for cost-of-illness studies	Evaluated for cost-of-program studies	Evaluated for cost-effectiveness studies
Title	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	✓	✓	✓
Abstract	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	✓	✓	✓
Background and objectives	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	✓	✓	✓
Target population and subgroups	Describe characteristics of the base case population and subgroups analyzed, including why they were chosen.	✓	✓	✓
Setting and location	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	✓	✓	✓
Study perspective	Describe the perspective of the study and relate this to the costs being evaluated.	✓	✓	✓
Comparators	Describe the interventions or strategies being compared and state why they were chosen.			✓
Time horizon	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.		✓	✓
Discount rate	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.		✓	✓
Choice of health outcomes	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.			✓
Measurement of effectiveness	Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data. **OR** Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.			✓
Measurement and valuation of preference-based outcomes	If applicable, describe the population and methods used to elicit preferences for outcomes			✓ *(if QALY or DALY results presented)*
Estimating resources and costs	Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs. **OR** Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	✓	✓	✓

Currency, price date, and conversion	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.			
Choice of model	Describe and give reasons for the specific type of decision analytical model used. Providing a figure to show model structure is strongly recommended.			
Assumptions	Describe all structural or other assumptions underpinning the decision-analytical model.			
Analytical methods	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.			
Study parameters	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.			
Incremental costs and outcomes	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.			
Characterizing uncertainty	Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective). **OR** Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.			
Characterizing heterogeneity	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.			
Study findings, limitations, generalizability, and current knowledge	Summarize key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge.			
Source of funding	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.			
Conflicts of interest	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.			
Total possible score		**13**	**15**	**23–24**

[1]The full CHEERS criteria assessment [28] was performed for cost-effectiveness studies; a modified set of relevant criteria were assessed for cost-of-illness and cost-of-program studies.

Table S3: Description of included studies, by country

Country	Author, year	Study type	SAGE target group(s)							Reference
			None (general population)	Children	Older adults	Persons with chronic medical conditions	Pregnant persons	Healthcare workers	Persons in congregate living settings	
Albania (UMIC)	Pallas, 2020	Cost-of-program						✓		[54]
Argentina (UMIC)	Giglio, 2012	Cost-effectiveness (or cost-benefit, cost-utility)		✓						[58]
Bangladesh (LIC)	Bhuiyan, 2014	Cost-of-illness	✓							[52]
China (LMIC, UMIC)[1]	Chen, 2019	Cost-effectiveness (or cost-benefit, cost-utility)			✓					[60]
	Gong, 2021	Cost-of-illness	✓							[40]
	Guo, 2012	Cost-of-illness	✓							[47]
	Jiang, 2020	Cost-effectiveness (or cost-benefit, cost-utility)			✓					[62]
	Lai, 2021	Cost-of-illness		✓	✓	✓				[38]
	Wang, 2013	Cost-of-illness		✓						[31]
	Wang, 2015	Cost-of-illness		✓						[32]
	Wang, 2019	Cost-of-illness		✓						[37]
	Wang, 2021	Cost-of-illness		✓						[39]
	Yan, 2021	Cost-effectiveness (or cost-benefit, cost-utility)			✓					[64]
	Yang, 2015	Cost-of-illness	✓	✓	✓	✓				[33]
	Yang, 2016	Cost-of-program		✓	✓	✓	✓	✓		[55]
	Yang, 2017	Cost-of-illness	✓	✓	✓	✓				[35]

Country	Author, year	Study type	SAGE target group(s)							Reference
			None (general population)	Children	Older adults	Persons with chronic medical conditions	Pregnant persons	Healthcare workers	Persons in congregate living settings	
	Yang, 2019	Cost-effectiveness (or cost-benefit, cost-utility)				✓				[61]
	Yang, 2020	Cost-effectiveness (or cost-benefit, cost-utility)			✓					[63]
	Yu, 2018	Cost-of-illness		✓						[36]
	Zhang, 2017	Cost-of-illness		✓						[34]
	Zhou, 2014	Cost-effectiveness (or cost-benefit, cost-utility)		✓						[59]
Colombia (UMIC)	Lara, 2018	Cost-effectiveness (or cost-benefit, cost-utility)		✓						[65]
	Salcedo-Mejia, 2019	Cost-of-illness		✓						[41]
El Salvador (LMIC)	Jara, 2019	Cost-of-illness		✓						[43]
India (LMIC)	Koul, 2019	Cost-of-illness				✓				[48]
Kazakhstan (UMIC)	Kovacs, 2014	Cost-of-illness			✓					[42]
Kenya (LMIC)	Dawa, 2020	Cost-effectiveness (or cost-benefit, cost-utility)		✓						[78]
	Emukule, 2019	Cost-of-illness	✓	✓						[49]
Lao PDR (LMIC)	Ortega-Sanchez, 2021	Cost-effectiveness (or cost-benefit, cost-utility)			✓		✓	✓		[79]
Malawi (LIC)	Pecenka, 2017	Cost-of-program					✓			[57]
Mali (LIC)	Orenstein, 2017	Cost-of-illness **AND** Cost-effectiveness (or cost-benefit, cost-utility)					✓			[53]
Mexico (UMIC)	Betancourt-	Cost-effectiveness (or	✓							[67]

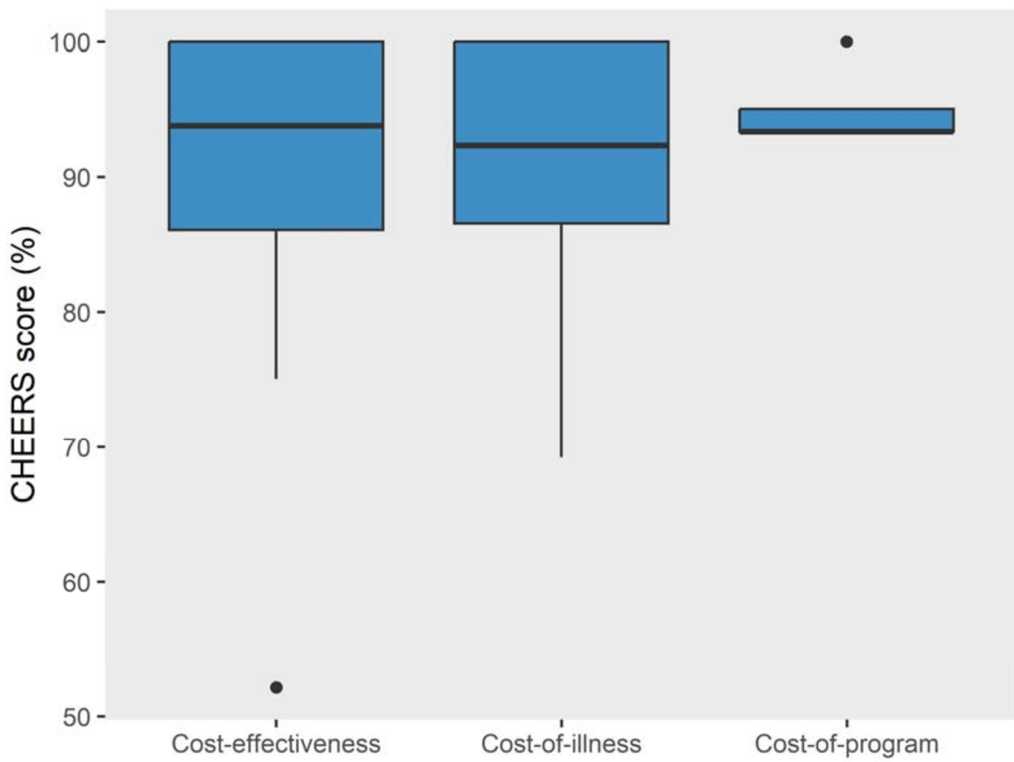
Country	Author, year	Study type	SAGE target group(s)							Reference
			None (general population)	Children	Older adults	Persons with chronic medical conditions	Pregnant persons	Healthcare workers	Persons in congregate living settings	
	Craviato, 2021	cost-benefit, cost-utility)								
	Falcon-Lezama, 2020	Cost-effectiveness (or cost-benefit, cost-utility)		✓						[66]
	Tapia-Conyer, 2021	Cost-effectiveness (or cost-benefit, cost-utility)	✓	✓		✓				[68]
Panama (UMIC)	Jara, 2019	Cost-of-illness		✓						[43]
Romania (UMIC)	Kovacs, 2014	Cost-of-illness			✓					[42]
South Africa (UMIC)	Biggerstaff, 2019	Cost-effectiveness (or cost-benefit, cost-utility)					✓			[70]
	Edoka, 2021	Cost-effectiveness (or cost-benefit, cost-utility)		✓	✓	✓	✓			[71]
	Tempia, 2019	Cost-of-illness	✓							[44]
	Tempia, 2020	Cost-of-illness		✓	✓	✓	✓			[45]
	de Boer, 2018	Cost-effectiveness (or cost-benefit, cost-utility)	✓							[69]
Thailand (UMIC)	Choosakulchart, 2013	Cost-effectiveness (or cost-benefit, cost-utility)				✓				[72]
	Kittikraisak, 2017	Cost-effectiveness (or cost-benefit, cost-utility)		✓						[74]
	Kittikraisak, 2018	Cost-of-illness		✓						[46]
	Meeyai, 2015	Cost-effectiveness (or cost-benefit, cost-utility)		✓	✓					[73]
	Riewpaiboon, 2021	Cost-of-program					✓			[56]
	Sribhutorn, 2018	Cost-effectiveness (or cost-benefit, cost-utility)				✓				[75]

Country	Author, year	Study type	SAGE target group(s)							Reference
			None (general population)	Children	Older adults	Persons with chronic medical conditions	Pregnant persons	Healthcare workers	Persons in congregate living settings	
	Suphanchaimat, 2020	Cost-effectiveness (or cost-benefit, cost-utility)							✓	[76]
Turkiye (UMIC)	Akin, 2016	Cost-effectiveness (or cost-benefit, cost-utility)				✓				[77]
Ukraine (LMIC)	Kovacs, 2014	Cost-of-illness			✓					[42]
	Kyi-Kokarieva, 2021	Cost-effectiveness (or cost-benefit, cost-utility)						✓		[80]
Vietnam (LMIC)	Vo, 2017	Cost-of-illness	✓	✓	✓					[50]
	Vo, 2017	Cost-of-illness	✓	✓	✓					[51]
	de Boer, 2018	Cost-effectiveness (or cost-benefit, cost-utility)	✓							[69]

Abbreviations: LIC, low-income country; LMIC, lower-middle income country; SAGE, Strategic Advisory Committee of Experts on Immunization; UMIC, upper-middle income country; US$, US Dollars

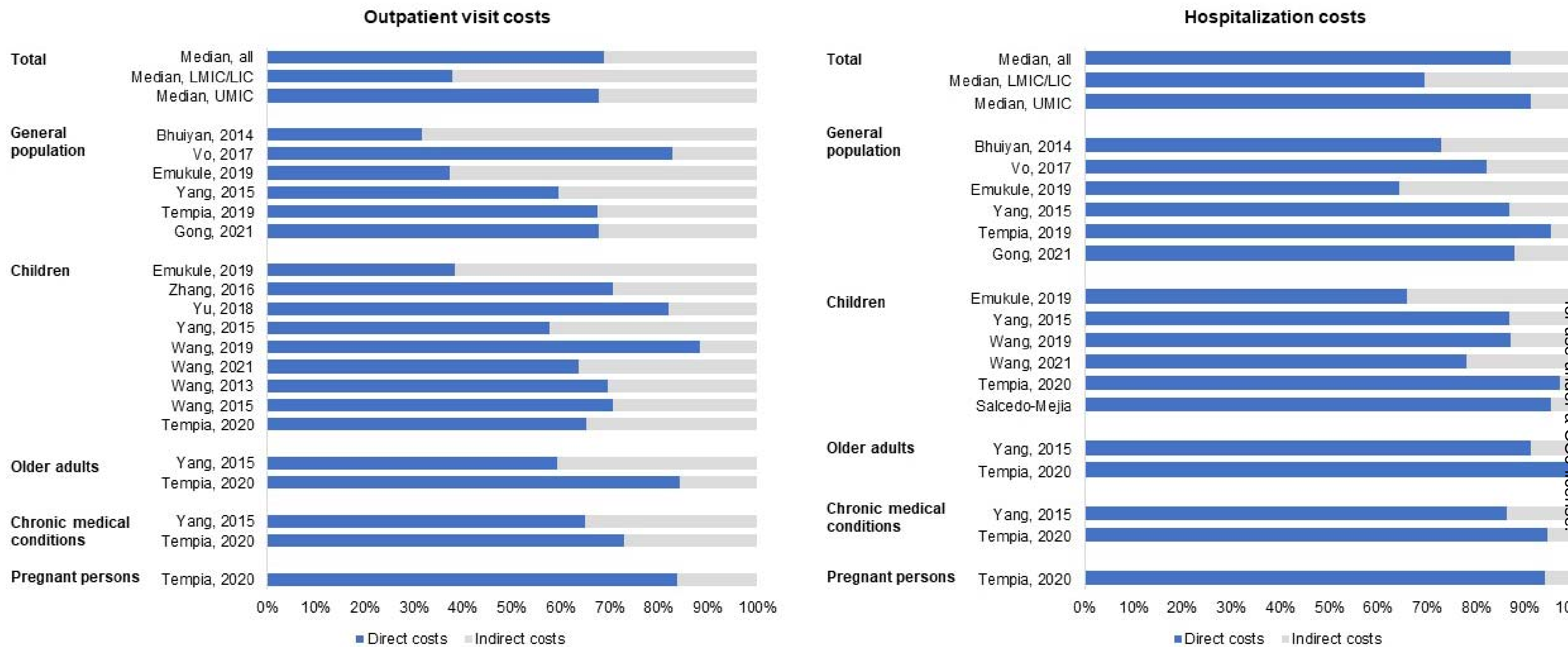
[1]China was classified as both UMIC and LMIC corresponding to studies before and after an upward change in World Bank classification in 2010.

Figure S1: Distribution of modified Consolidated Health Economic Evaluation Reporting Standard (CHEERS) quality assessment scores[1]



[1]The full CHEERS criteria assessment [28] was performed for cost-effectiveness studies; a modified set of relevant criteria were assessed for cost-of-illness and cost-of-program studies.

Figure S2: Contribution of direct[1] and indirect[2] costs to costs of influenza outpatient visits and hospitalizations, by Strategic Advisory Committee of Experts on Immunization (SAGE) target group, in low- and middle-income countries



Abbreviations: LIC, low-income country; LMIC, lower-middle income country; UMIC, upper-middle income country

[1]Direct costs were all medical and non-medical costs directly attributable to patient care, as reported in the study.

[2]Indirect costs were all costs not directly attributable to patient care (e.g., lost earnings or lost productivity).

Table S4: Costs of influenza illness[1], by Strategic Advisory Committee of Experts on Immunization (SAGE) target group[2] and disease severity (outpatient vs. hospitalized), in low- and middle-income countries

Study characteristics								Outpatient visits			Hospitalizations			
ncom e group	Study	Country	Target group details	Data source; public or private facilities	Illness case definition[3]	Study period	Perspective	Direct[4] cost per episode (2022 US$)[5]	Indirect[6] cost per episode (2022 US$)[5]	Total cost per episode (2022 US$)[5]	Direct[4] cost per episode (2022 US$)[5]	Indirect[6] cost per episode (2022 US$)[5]	Total cost per episode (2022 US$)[5]	Median length of hospitalization (days)
General population														
JMIC	Gong, 2021 [40]	China	All ages	NR	ILI/SARI	2006–19	Societal	$107.13	$50.75	$149.98	$1392.72	$193.97	$1617.14	--
JMIC	Yang, 2015 [33]	China	All ages	554 facilities; NR	LCI	2013–14	Societal	$77.35[7]	$52.79	$155.92	$1193.36[7]	$181.70	$1416.80	9
JMIC	Tempia, 2019 [44]	South Africa	All ages	7 hospitals and 2 clinics; public	ILI/SARI	2013–15	Societal	$32.20	$15.50	$47.71	$874.24	$42.94	$918.37	5.3
.MIC[8]	Guo, 2012 [47]	China	All ages	28 hospitals and clinics; public	ILI	2008–09	Payer[9]	$29.80	--	--	--	--	--	--
.MIC[10]	Emukule, 2019 [49]	Kenya	All ages	4 hospitals and 1 clinic; public and private	LCI	2013–14	Societal	$9.26	$15.49	$23.91	$90.99	$50.67	$142.17	4
.MIC	Vo, 2017 [50]	Vietnam	All ages	1 hospital; NR	SARI	2013–15	Healthcare system	--	--	--	$134.27[12]	--	--	7
.MIC	Vo, 2017 [51]	Vietnam	All ages	15 pharmacies, 3 clinics, and 1 hospital; private	ILI/SARI	2016	Societal	$104.46	$21.63	$128.35	$99.31	$21.63	$110.55	--
.IC[11]	Bhuiyan, 2014 [52]	Bangladesh	All ages	4 hospitals; public and private	LCI	2010	Societal	$5.47	$11.83	$6.24	$77.67	$28.92	$106.85	3
Children[13]														
JMIC	Zhang, 2017 [34]	China	<5 years	9 hospitals; NR	P&I	2005–09[14]	Payer[9]	--	--	--	$480.97[12]	--	--	7.1
JMIC	Wang, 2013 [31]	China	<5 years	1 hospital; NR	LCI	2011–12	Societal	$110.28	$48.39	$159.04	--	--	--	--
JMIC	Wang, 2015 [32]	China	6 months–11.5 years	1 hospital; NR	LCI	2011–12	Societal	$139.91	$58.22	$198.13	--	--	--	--
JMIC	Kittikraisak, 2018 [46]	Thailand	<5 years	1 hospital; public	LCI	2011–15	Societal	--	--	$26.24	--	--	$293.40	10
JMIC	Yu, 2018 [36]	China	<5 years	1 hospital; NR	LCI	2011–17	Patient	$107.86	$23.94	$131.80	--	--	--	--

UMIC	Wang, 2021 [39]	China	<5 years	1 hospital; NR	LCI	2011–17	Societal	$118.98	$67.85	$186.83	$1288.85	$365.42	$1654.23	7
UMIC	Jara, 2019 [43]	Panama	<10 years	2 hospitals; public	LCI	2012–13	Societal	--	--	--	--	--	$554.32	--
UMIC	Yang, 2015 [33]	China	<5 years	554 facilities; NR	LCI	2013–14	Societal	$95.76[7]	$69.98	$192.75	$1257.20[7]	$192.75	$1474.51	--
UMIC	Tempia, 2020 [45]	South Africa	6–59 months	7 hospitals and 2 clinics; public	ILI/SARI	2013–15	Societal	$33.40	$17.89	$50.09	$743.04	$21.47	$764.51	--
UMIC	Salcedo-Mejia, 2019 [41]	Colombia	<18 years	1 hospital; NR	LCI	2014	Societal	--	--	--	$1987.30	$99.03	$2202.74	8.9
UMIC	Wang 2019 [37]	China	3–17 years	NR	ILI/SARI	2016–18	Societal	$35.10	$4.55	$41.75	$471.46	$69.97	$524.62	--
UMIC	Lai, 2021 [38]	China	6–59 months	148 community health centers; public	ILI/SARI	2019	Societal	$102.18	--	--	$82.99	--	--	--
LMIC	Jara, 2019 [43]	El Salvador	<10 years	3 hospitals; public	LCI	2012–13	Societal	--	--	--	--	--	$176.30	--
LMIC[10]	Emukule, 2019 [49]	Kenya	<5 years	4 hospitals and 1 clinic; public and private	LCI	2013–14	Societal	$10.40	$16.73	$25.92	$90.98	$46.97	$137.81	4
LMIC	Vo, 2017 [50]	Vietnam	≤14 years	1 hospital; NR	SARI	2013–15	Healthcare system	--	--	--	$96.15[12]	--	--	--
Older adults														
UMIC	Kovacs, 2014 [42]	Kazakhstan	≥65 years	19 hospitals; NR	ILI/SARI	2011–12	Payer[9]	$19.49 (medical only)	--	--	$302.24[12]	--	--	--
UMIC	Kovacs, 2014 [42]	Romania	≥65 years	26 hospitals; NR	ILI/SARI	2011–12	Payer[9]	$26.93 (medical only)	--	--	$1048.11[12]	--	--	--
LMIC	Kovacs, 2014 [42]	Ukraine	≥65 years	10 hospitals; NR	ILI/SARI	2011–12	Payer[9]	$26.22 (medical only)	--	--	$110.73[12]	--	--	--
UMIC	Yang, 2015 [33]	China	≥60 years	554 facilities; NR	LCI	2013–14	Societal	$66.30[7]	$45.43	$164.52	$2499.66[7]	$236.95	$2729.25	--
LMIC	Vo, 2017 [50]	Vietnam	>64 years	1 hospital; NR	SARI	2013–15	Healthcare system	--	--	--	$282.37[12]	--	--	--
UMIC	Tempia, 2020 [45]	South Africa	≥65 years	7 hospitals and 2 clinics; public	ILI/SARI	2013–15	Societal	$32.20	$5.96	$38.17	$1056.72	$2.39	$1059.10	--
UMIC	Lai, 2021 [38]	China	≥60 years	148 community health centers; public	ILI/SARI	2019	Societal	$60.93	--	--	$167.08	--	--	--
Persons with chronic medical conditions														

JMIC	Tempia, 2020 [45]	South Africa	5–64 years with HIV, TB, or other UMC	7 hospitals and 2 clinics; public	ILI/SARI	2013–15	Societal	$32.20	$11.93	$44.13	$1084.15	$63.21	$1147.36	--
JMIC	Yang, 2015 [33]	China	All ages with UMC	554 facilities; NR	LCI	2013–14	Societal	$99.45[7]	$54.02	$176.79	$1357.87[7]	$213.63	$1578.86	--
JMIC	Lai, 2021 [38]	China	18–59 years with UMC	148 community health centers; public	ILI/SARI	2019	Societal	$37.92	--	--	$62.52	--	--	--
.MIC	Koul, 2019 [48]	India	≥18 years with diabetes	1 hospital; public	LCI	2015–17	Societal	--	--	--	--	--	$847.60	9
Pregnant persons														
JMIC	Tempia, 2020 [45]	South Africa	NA	7 hospitals and 2 clinics; public	ILI/SARI	2013–15	Societal	$31.01	$5.96	$36.97	$1024.52	$63.21	$1088.92	--
.IC	Orenstein, 2017 [53]	Mali	NA	6 community and referral health centers	LCI and ILI[15]	2011–14	Societal			$5.45 (LCI)[15]			$189.98 (ILI)[15]	

Abbreviations: HIV, human immunodeficiency virus; ILI, influenza-like illness; LCI, laboratory-confirmed influenza; LIC, low-income country; LMIC, lower-middle income country; NA, not applicable; NR, not reported; P&I, pneumonia and influenza hospitalization; SARI, severe acute respiratory infection; TB, tuberculosis; UMC, underlying medical condition; UMIC, upper-middle income country; US$, US Dollars

[1]Median costs were preferentially abstracted from source publications; if unavailable, mean costs were abstracted.

[2]No cost-of-illness papers were identified for healthcare workers or individuals in congregate living settings in low- and middle-income countries.

[3]For source publications presenting results for both LCI and syndromic illness, the results for LCI were used.

[4]Direct costs were all medical and non-medical costs directly attributable to patient care.

[5]Calculated or converted value; not presented in source publication.

[6]Indirect costs were all costs not directly attributable to patient care (e.g., lost earnings or lost productivity).

[7]Direct medical and non-medical costs were summarized separately in the source publication; medians were summed to obtain a total median direct cost.

[8]China changed classification from LMIC to UMIC in 2010 [24], after the study period, and was thus classified as LMIC for this study.

[9]No indirect costs were included in the total estimate because of study perspective. The specific payer was not specified in the source publication.

[10]Kenya changed classification from LIC to LMIC in 2014 [24], during the study period, and was thus classified as LMIC.

[11]Bangladesh changed classification from LIC to LMIC in 2014 [24], after the study period, and was thus classified as LIC.

[12]Included only direct medical costs (no non-medical costs).

[13]Although SAGE recommendations specifically reference children aged <5 years [1], publications with data for children aged <18 years were included.

[14]The full publication study period was 2005–2011; however, 2009–2010 and 2010–2011 were excluded because of H1N1 pandemic activity. Abstracted values represent the median of 2005–2009 annual values.

[15]Cost data were only available for one hospitalized LCI case; thus, ILI hospitalization costs were abstracted.

Table S5: Cost-effectiveness of influenza vaccination[1], by Strategic Advisory Committee of Experts on Immunization (SAGE) target group, in low- and middle-income countries

Study characteristics							Study results		
Income group	**Study**	**Country**	**Target group details**	**Intervention[2]**	**Comparator**	**Perspective**	**ICER or net benefit (in 2022 US$)[3]**	**Interpretation[4]**	**Cost-effectiveness threshold**
General population									
UMIC	de Boer, 2018 [69]	South Africa	All ages	Vaccination with TIV at 15% coverage	No vaccination	Societal	$1297.71– 2213.60 per QALY	None[5]	None[5]
UMIC	Betancourt-Craviato, 2021 [67] and Tapia-Conyer, 2021 [68][6]	Mexico	5–59 years	Vaccination with TIV at 50% coverage	No vaccination	Societal	NA	Cost-saving	NR
LMIC	de Boer, 2018 [69]	Vietnam	All ages	Vaccination with TIV at 15% coverage	No vaccination	Societal	$757.51–1306.31 per QALY	None[5]	None[5]
Children[7]									
UMIC	Giglio, 2012 [58]	Argentina	6–23 months	Vaccination at 50% coverage; product NR	No vaccination	Healthcare system	$2298.74 per QALY	Cost-effective	1–3 times GDP per capita
UMIC	Giglio, 2012 [58]	Argentina	6–36 months	Vaccination at 50% coverage; product NR	No vaccination	Healthcare system	$1441.45 per QALY	Cost-effective	1–3 times GDP per capita
UMIC	Giglio, 2012 [58]	Argentina	6 months–5 years	Vaccination at 50% coverage; product NR	No vaccination	Healthcare system	$937.01 per QALY	Cost-effective	1–3 times GDP per capita
UMIC	Meeyai, 2015 [73]	Thailand	2–11 years	Vaccination with TIV at 66% coverage	No vaccination	Societal	$5557.72 per DALY	Cost-effective	GDP per capita
UMIC	Meeyai, 2015 [73]	Thailand	2–11 years	Vaccination with LAIV at 66% coverage	No vaccination	Societal	$5662.74 per DALY	Cost-effective	GDP per capita
UMIC	Meeyai, 2015 [73]	Thailand	2–17 years	Vaccination with LAIV at 66% coverage	No vaccination	Societal	$7186.90 per DALY	Cost-effective	GDP per capita
UMIC	Meeyai, 2015 [73]	Thailand	2–5 years	Vaccination with LAIV at 66% coverage	No vaccination	Societal	$3702.23 per DALY	Cost-effective	GDP per capita
UMIC	Meeyai, 2015 [73]	Thailand	6–11 years	Vaccination with LAIV at 66% coverage	No vaccination	Societal	$2955.78 per DALY	Cost-effective	GDP per capita
UMIC	Meeyai, 2015 [73]	Thailand	12–17 years	Vaccination with LAIV at 66% coverage	No vaccination	Societal	$2301.86 per DALY	Cost-effective	GDP per capita
UMIC	Zhou, 2014 [59][8]	China	6–59 months	Vaccination at 12% coverage; product NR	No vaccination	Healthcare system	$0 per medically attended case	Cost-effective to cost-saving across seasons	GDP per capita
UMIC	Zhou, 2014 [59][8]	China	5–14 years	Vaccination at 11% coverage; product NR	No vaccination	Healthcare system	$48.10 per medically attended	Cost-effective	GDP per capita

							case		
UMIC	Kittikraisak, 2017 [74]	Thailand	6–60 months	Vaccination with TIV at 29–31% coverage	No vaccination	Societal	$668.25– 29,492.86 per QALY	Not cost-effective to cost-effective across seasons	1–3 times GDP per capita
UMIC	Lara, 2018 [65]	Colombia	<5 years	Vaccination with TIV; coverage NR	No vaccination	Healthcare system	NA	Cost-saving	1–3 times GDP per capita
UMIC	Lara, 2018 [65]	Colombia	<5 years	Vaccination with TIV; coverage NR	No vaccination	Societal	NA	Cost-saving	1–3 times GDP per capita
UMIC	Falcon-Lezama, 2020 [66] and Tapia-Conyer, 2021 [68][6]	Mexico	5–11 years	Vaccination with TIV at 50% coverage	No vaccination	Societal	NA	Cost-saving	NR
UMIC	Edoka, 2021 [71]	South Africa	6–59 months	Vaccination with TIV at 2% coverage	No vaccination	Healthcare system	$8507.71 per QALY	Not cost-effective	Country-specific threshold[9]
UMIC	Edoka, 2021 [71]	South Africa	6–59 months	Vaccination with TIV at 2% coverage	No vaccination	Societal	$5982.66 per QALY	Not cost-effective	Country-specific threshold[9]
LMIC	Dawa, 2020 [78]	Kenya	6–23 months	Vaccination with TIV (SH) at 30% coverage	No vaccination	Societal	$850.77–1573.19 per DALY	Not cost-effective	1–51% of GDP per capita
LMIC	Dawa, 2020 [78]	Kenya	2–5 years	Vaccination with TIV (SH) at 35% coverage	No vaccination	Societal	$1073.40–1786.73 per DALY	Not cost-effective	1–51% of GDP per capita
LMIC	Dawa, 2020 [78]	Kenya	6–14 years	Vaccination with TIV (SH) at 40% coverage	No vaccination	Societal	$1048.41–3539.39 per DALY	Not cost-effective	1–51% of GDP per capita
LMIC	Dawa, 2020 [78]	Kenya	6–23 months	Vaccination with TIV (NH) at 30% coverage	No vaccination	Societal	$502.06–2132.04 per DALY	Not cost-effective	1–51% of GDP per capita
LMIC	Dawa, 2020 [78]	Kenya	2–5 years	Vaccination with TIV (NH) at 35% coverage	No vaccination	Societal	$639.50–2122.95 per DALY	Not cost-effective	1–51% of GDP per capita
LMIC	Dawa, 2020 [78]	Kenya	6–14 years	Vaccination with TIV (NH) at 40% coverage	No vaccination	Societal	$1141.56–2525.05 per DALY	Not cost-effective	1–51% of GDP per capita
LMIC	Dawa, 2020 [78]	Kenya	6–23 months	Vaccination with TIV (SH and NH; biannual campaign) at 45% coverage	No vaccination	Societal	$770.12–4663.91 per DALY	Not cost-effective	1–51% of GDP per capita
LMIC	Dawa, 2020 [78]	Kenya	2–5 years	Vaccination with TIV (SH and NH; biannual campaign) at 50% coverage	No vaccination	Societal	$751.95–4640.05 per DALY	Not cost-effective	1–51% of GDP per capita
LMIC	Dawa, 2020 [78]	Kenya	6–14 years	Vaccination with TIV (SH and NH; biannual campaign) at 55% coverage	No vaccination	Societal	$1002.98–5369.29 per DALY	Not cost-effective	1–51% of GDP per capita
LMIC	Dawa, 2020 [78]	Kenya	6–23 months	Vaccination with TIV (SH and NH; year-round) at 60% coverage	No vaccination	Societal	$1302.85–9010.91 per DALY	Not cost-effective	1–51% of GDP per capita

LMIC	Dawa, 2020 [78]	Kenya	2–5 years	Vaccination with TIV (SH and NH; year-round) at 65% coverage	No vaccination	Societal	$1327.84–8970.02 per DALY	Not cost-effective	1–51% of GDP per capita
LMIC	Dawa, 2020 [78]	Kenya	6–14 years	Vaccination with TIV (SH and NH; year-round) at 70% coverage	No vaccination	Societal	$1666.33–7738.73 per DALY	Not cost-effective	1–51% of GDP per capita
Older adults									
UMIC	Meeyai, 2015 [73]	Thailand	≥60 years	Vaccination with TIV at 66% coverage	Current vaccination program (10% coverage)	Societal	$3612.20 per DALY	Cost-effective	GDP per capita
UMIC	Chen, 2019 [60]	China	≥60 years	Vaccination with TIV; coverage NR	No vaccination	Societal	$10313.18 per QALY	Cost-effective	3 times GDP per capita
UMIC	Chen, 2019 [60]	China	≥60 years	Vaccination with QIV; coverage NR	No vaccination	Societal	$28040.63 per QALY	Cost-effective	3 times GDP per capita
UMIC	Jiang, 2020 [62]	China	69 years[10]	Vaccination with TIV at 27% coverage	No vaccination	Societal	NA	Cost-saving	3 times GDP per capita
UMIC	Jiang, 2020 [62]	China	69 years[10]	Vaccination with QIV at 27% coverage	No vaccination	Societal	NA	Cost-saving	3 times GDP per capita
UMIC	Yang, 2020 [63]	China	≥60 years	Vaccination with TIV at 30% coverage (fully funded government program)	Current vaccination program (self-paid; 0% coverage)	Societal	$5605.57 per QALY	Cost-effective	GDP per capita
UMIC	Yan, 2021 [64]	China	≥60 years	Vaccination with QIV at 48% coverage	No vaccination	Societal	$12133.20 per QALY	Not cost-effective	GDP per capita
UMIC	Edoka, 2021 [71]	South Africa	≥65 years	Vaccination with TIV at 3% coverage	No vaccination	Healthcare system	$2373.98 per QALY	Cost-effective	Country-specific threshold[9]
UMIC	Edoka, 2021 [71]	South Africa	≥65 years	Vaccination with TIV at 3% coverage	No vaccination	Societal	$2310.37 per QALY	Cost-effective	Country-specific threshold[9]
LMIC	Ortega-Sanchez, 2021 [79]	Lao PDR	≥60 years	Vaccination with TIV at 100% coverage	No vaccination	Societal	$903.24 per life-year saved	Cost-effective	1–3 times GDP per capita
Persons with chronic medical conditions									
UMIC	Sribhutorn, 2018 [75]	Thailand	≤40 years with acute coronary syndrome[11]	Vaccination with TIV at 100% coverage	No vaccination	Societal	NA	Cost-saving	1–3 times GDP per capita
UMIC	Yang, 2019 [61]	China	Persons with diabetes	Vaccination with TIV at 40% coverage	No vaccination	Societal	$1798.51 per QALY	Cost-effective	GDP per capita
UMIC	Tapia-Conyer, 2021 [68]	Mexico	12–49 years with UMC[12]	Vaccination with TIV at 75% coverage	Current vaccination program (9–35% coverage)	Societal	NA	Cost-saving	NR

UMIC	Akin, 2016 [77]	Turkiye	>18 years with diabetes	Vaccination with 20% coverage; product NR	Current program (9% coverage)	Govt. (public payer)	$637.83 per QALY	Cost-effective	1–3 times GDP per capita
UMIC	Akin, 2016 [77]	Turkiye	>18 years with diabetes	Vaccination with 20% coverage; product NR	Current program (9% coverage)	Societal	$35.25 per QALY	Cost-effective	1–3 times GDP per capita
UMIC	Choosakulchart, 2013 [72]	Thailand	≥60 years with coronary heart disease[13]	Vaccination with product and coverage NR	No vaccination	Societal	$1386.98 per QALY	Cost-effective	Country-specific threshold[14]
UMIC	Edoka, 2021 [71]	South Africa	Persons living with HIV/AIDS	Vaccination with TIV at 5.51% coverage	No vaccination	Healthcare system	$1986.65 per QALY	Cost-effective	Country-specific threshold[9]
UMIC	Edoka, 2021 [71]	South Africa	Persons living with HIV/AIDS	Vaccination with TIV at 5.51% coverage	No vaccination	Societal	NA	Cost-saving	Country-specific threshold[9]
UMIC	Edoka, 2021 [71]	South Africa	Persons with other UMC	Vaccination with TIV at 3.14% coverage	No vaccination	Healthcare system	$2973.72 per QALY	Cost-effective	Country-specific threshold[9]
UMIC	Edoka, 2021 [71]	South Africa	Persons with other UMC	Vaccination with TIV at 3.14% coverage	No vaccination	Societal	NA	Cost-saving	Country-specific threshold[9]
Pregnant persons (including infants <6 months)									
UMIC	Biggerstaff, 2019 [70]	South Africa	NA	Vaccination prioritizing persons with HIV (70% coverage in HIV+ and 44% coverage in HIV-); product NR	No vaccination	Societal	$5550.81 per QALY	Potentially cost-effective[15]	GDP per capita
UMIC	Biggerstaff, 2019 [70]	South Africa	NA	Vaccination with 50% coverage; product NR	No vaccination	Societal	$7012.79 per QALY	Potentially cost-effective[15]	GDP per capita
UMIC	Edoka, 2021 [71]	South Africa	NA	Vaccination with TIV at 48.9% coverage	No vaccination	Healthcare system	$2283.11 per QALY	Cost-effective	Country-specific threshold[9]
UMIC	Edoka, 2021 [71]	South Africa	NA	Vaccination with TIV at 48.9% coverage	No vaccination	Societal	NA	Cost-saving	Country-specific threshold[9]
LMIC	Ortega-Sanchez, 2021 [79]	Lao PDR	NA	Vaccination with TIV at 100% coverage	No vaccination	Societal	$5797.15 per life-year saved	Cost-effective	1–3 times GDP per capita
LIC	Orenstein, 2017 [53]	Mali	NA	Vaccination with TIV; coverage NR[16]	No vaccination	Societal	$1033.76 per DALY	Cost-effective[17]	GDP per capita
Healthcare workers									
LMIC	Ortega-Sanchez, 2021 [79]	Lao PDR	NA	Vaccination with TIV at 100% coverage	No vaccination	Societal	NA	Cost-saving	1–3 times GDP per capita
LMIC	Kyi-Kokarieva, 2021 [80]	Ukraine	NA	Vaccination at 70% coverage; product NR	No vaccination	Societal	NA	Cost-saving	NR
Persons in congregate living settings									
UMIC	Suphanchaimat, 2020 [76]	Thailand	Incarcerated persons	Vaccination with TIV at 10% coverage[18]	No vaccination	Govt.	$2108.55 per DALY	Cost-effective	NR

Abbreviations: DALY, disability-adjusted life years; ICER, incremental cost-effectiveness ratio; Govt, government; HIV, human immunodeficiency virus; LAIV, live attenuated influenza vaccine; LIC, low-income country; LMIC, lower-middle income country; NA, not applicable; NR, not reported; QALY, quality-adjusted life years; QIV, quadrivalent influenza vaccine; TIV, trivalent influenza vaccine; UMIC, upper-middle income country; US$, US Dollars; WTP, willingness-to-pay.

[1]Cost-effectiveness, cost-utility, and cost-benefit analyses were eligible for inclusion if they included a comparison of influenza vaccination vs. either no vaccination or modifications to current vaccination program. Studies that only compared the cost-effectiveness of different influenza vaccine products were not included.

[2]Data for each base-scenario intervention or each perspective assessed are presented in individual rows. Sensitivity analyses are not presented. Vaccine coverage was rounded to the nearest integer.

[3]Calculated or converted value; not presented in source publication. Ranges represent annual seasonal estimates or varying illness attack rate.

[4]Interpretation per source publication. Interpretations of highly cost-effective and cost-effective were both combined as "cost-effective."

[6]Similar data sources and analysis methods used in both publications; these were counted collectively as one study for Figure 3.

[5]The study authors intentionally did not specify a cost-effectiveness threshold or interpretation because a country-specific threshold was not available.

[7]Although SAGE recommendations specifically reference children aged <5 years [1], publications with data for children aged <18 years were included.

[8]This study also modeled alternative strategies to increase vaccination rates; results are not shown.

[9]This study used a cost-effectiveness threshold for South Africa that reflects the health opportunity cost of health spending.

[10]The age of the hypothetical cohort was based on the mean age of the target population in China (69 years).

[11]Age groups of ≥50 years and ≥60 years were also modeled; only results for ≥40 years are shown as this was inclusive of all other groups. All scenarios were cost-effective.

[12]Medical conditions included diabetes, high blood pressure, morbid obesity, chronic renal failure, asthma, and pregnancy.

[13]Included patients with angina and cardiac arrest/myocardial infarction.

[14]A country-specific threshold of 100,000 Thai Baht was used (rationale not reported).

[15]The 90% uncertainty intervals for the ICER overlapped the cost-effectiveness threshold.

[16]Additional scenarios adjusted for poor access to care and increased severity of disease; all scenarios were cost-effective.

[17]Results were cost-effective when the cost per pregnant woman vaccinated was $1.00 or less.

[18]Additional scenarios modeled higher coverage of 30% and 100%; all scenarios were cost-effective.

References

1. World Health Organization, *Vaccines against influenza: WHO position paper—May 2022.* Wkly Epidemiol Rec, 2022. **19**: p. 185-208.
2. Morales, K.F., et al., *Seasonal influenza vaccination policies in the 194 WHO Member States: The evolution of global influenza pandemic preparedness and the challenge of sustaining equitable vaccine access.* Vaccine X, 2021. **8**: p. 100097.
3. Iuliano, A.D., et al., *Estimates of global seasonal influenza-associated respiratory mortality: a modelling study.* Lancet, 2018. **391**(10127): p. 1285-1300.
4. Lafond, K.E., et al., *Global burden of influenza-associated lower respiratory tract infections and hospitalizations among adults: A systematic review and meta-analysis.* PLoS Med, 2021. **18**(3): p. e1003550.
5. Lafond, K.E., et al., *Global Role and Burden of Influenza in Pediatric Respiratory Hospitalizations, 1982-2012: A Systematic Analysis.* PLoS Med, 2016. **13**(3): p. e1001977.
6. Kraigsley, A.M., et al., *Barriers and activities to implementing or expanding influenza vaccination programs in low- and middle-income countries: A global survey.* Vaccine, 2021. **39**(25): p. 3419-3427.
7. Jit, M., A.T. Newall, and P. Beutels, *Key issues for estimating the impact and cost-effectiveness of seasonal influenza vaccination strategies.* Hum Vaccin Immunother, 2013. **9**(4): p. 834-40.
8. World Health Organization, *WHO Manual for estimating the economic burden of seasonal influenza*. 2016, World Health Organization.
9. Chaiyakunapruk, N., et al., *Rationale and opportunities in estimating the economic burden of seasonal influenza across countries using a standardized WHO tool and manual.* Influenza Other Respir Viruses, 2018. **12**(1): p. 13-21.
10. World Health Organization, *Guidance on the economic evaluation of influenza vaccination*. 2016, World Health Organization.
11. Newall, A.T., et al., *WHO guide on the economic evaluation of influenza vaccination.* Influenza Other Respir Viruses, 2018. **12**(2): p. 211-219.
12. World Health Organization, *Flutool plus: WHO seasonal influenza immunization costing tool (SIICT), Pilot version 1.0*. 2020.
13. Ott, J.J., et al., *Influenza vaccines in low and middle income countries: a systematic review of economic evaluations.* Hum Vaccin Immunother, 2013. **9**(7): p. 1500-11.
14. de Francisco Shapovalova, N., et al., *A systematic review of the social and economic burden of influenza in low- and middle-income countries.* Vaccine, 2015. **33**(48): p. 6537-44.
15. Peasah, S.K., et al., *Influenza cost and cost-effectiveness studies globally--a review.* Vaccine, 2013. **31**(46): p. 5339-48.
16. D'Angiolella, L.S., et al., *Costs and effectiveness of influenza vaccination: a systematic review.* Ann Ist Super Sanita, 2018. **54**(1): p. 49-57.
17. Valcárcel Nazco, C., et al., *[Cost-effectiveness of vaccines for the prevention of seasonal influenza in different age groups: a systematic review].* Rev Esp Salud Publica, 2018. **92**.
18. Ting, E.E.K., B. Sander, and W.J. Ungar, *Systematic review of the cost-effectiveness of influenza immunization programs.* Vaccine, 2017. **35**(15): p. 1828-1843.
19. de Courville, C., et al., *The economic burden of influenza among adults aged 18 to 64: A systematic literature review.* Influenza Other Respir Viruses, 2022. **16**(3): p. 376-385.
20. Imai, C., et al., *A systematic review and meta-analysis of the direct epidemiological and economic effects of seasonal influenza vaccination on healthcare workers.* PLoS One, 2018. **13**(6): p. e0198685.

21. Dilokthornsakul, P., et al., *Economic evaluation of seasonal influenza vaccination in elderly and health workers: A systematic review and meta-analysis.* EClinicalMedicine, 2022. **47**: p. 101410.
22. Loong, D., et al., *Systematic Review on the Cost-Effectiveness of Seasonal Influenza Vaccines in Older Adults.* Value Health, 2022. **25**(8): p. 1439-1458.
23. Warmath, C.R., et al., *Comparisons in the Health and Economic Assessments of Using Quadrivalent Versus Trivalent Influenza Vaccines: A Systematic Literature Review.* Value Health, 2022.
24. The World Bank Group. *World Bank Open Data*. 2023 [cited 2022 November 1]; Available from: https://data.worldbank.org/.
25. World Health Organization, *Evolution of a pandemic: A (H1N1) 2009, April 2009–August 2010*. 2013.
26. Veritas Health Innovation, *Covidence systematic review software. Available at www.covidence.org.* Melbourne, Australia.
27. World Health Organization. *Global Health Expenditure Database*. 2023 [cited 2022 November 1]; Available from: https://apps.who.int/nha/database/Home/Index/en.
28. Husereau, D., et al., *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force.* Value Health, 2013. **16**(2): p. 231-50.
29. Dunn, A., S.D. Grosse, and S.H. Zuvekas, *Adjusting Health Expenditures for Inflation: A Review of Measures for Health Services Research in the United States.* Health Serv Res, 2018. **53**(1): p. 175-196.
30. Bureau of Economic Analysis. *GDP Price Deflator*. 2023 [cited 2022 November 1]; Available from: https://www.bea.gov/data/prices-inflation/gdp-price-deflator.
31. Wang, D., et al., *Socio-economic burden of influenza among children younger than 5 years in the outpatient setting in Suzhou, China.* PLoS ONE [Electronic Resource], 2013. **8**(8): p. e69035.
32. Wang, X., et al., *[Socio-economic impact of influenza in children:a single-centered hospital study in Shanghai].* Chung-Hua Liu Hsing Ping Hsueh Tsa Chih Chinese Journal of Epidemiology, 2015. **36**(1): p. 27-30.
33. Yang, J., et al., *The economic burden of influenza-associated outpatient visits and hospitalizations in China: a retrospective survey.* Infectious Diseases of Poverty, 2015. **4**: p. 44.
34. Zhang, X., et al., *Pneumonia and influenza hospitalizations among children under 5 years of age in Suzhou, China, 2005-2011.* Influenza Other Respir Viruses, 2017. **11**(1): p. 15-22.
35. Yang, J., et al., *The impact of influenza on the health related quality of life in China: an EQ-5D survey.* BMC Infectious Diseases, 2017. **17**(1): p. 686.
36. Yu, J., et al., *[Clinical characteristics and economic burden of influenza among children under 5 years old, in Suzhou, 2011-2017].* Zhonghua Liu Xing Bing Xue Za Zhi, 2018. **39**(6): p. 847-851.
37. Wang, S.Y., et al., *[Disease burden of influenza in schools and child care settings in rural areas of Hangzhou, 2016-2018].* Chung-Hua Yu Fang i Hsueh Tsa Chih [Chinese Journal of Preventive Medicine], 2019. **53**(7): p. 713-718.
38. Lai, X., et al., *The Economic Burden of Influenza-Like Illness among Children, Chronic Disease Patients, and the Elderly in China: A National Cross-Sectional Survey.* International Journal of Environmental Research & Public Health [Electronic Resource], 2021. **18**(12): p. 10.
39. Wang, Y., et al., *Economic burden of influenza illness among children under 5 years in Suzhou, China: Report from the cost surveys during 2011/12 to 2016/17 influenza seasons.* Vaccine, 2021. **39**(8): p. 1303-1309.
40. Gong, H., et al., *Estimating the disease burden of seasonal influenza in China, 2006-2019. [Chinese].* National Medical Journal of China, 2021. **101(8)**: p. 560-567.

41. Salcedo-Mejia, F., et al., *Economic Cost of Severe Acute Respiratory Infection Associated to Influenza in Colombian Children: A Single Setting Analysis.* Value in Health Regional Issues, 2019. **20**: p. 159-163.
42. Kovacs, G., et al., *Medical and economic burden of influenza in the elderly population in central and eastern European countries.* Human vaccines & Immunotherapeutics, 2014. **10**(2): p. 428-40.
43. Jara, J.H., et al., *Costs associated with acute respiratory illness and select virus infections in hospitalized children, El Salvador and Panama, 2012-2013.* J Infect, 2019. **79**(2): p. 108-114.
44. Tempia, S., et al., *Health and economic burden of influenza-associated illness in South Africa, 2013-2015.* Influenza & Other Respiratory Viruses, 2019. **13**(5): p. 484-495.
45. Tempia, S., et al., *Influenza economic burden among potential target risk groups for immunization in South Africa, 2013-2015.* Vaccine, 2020. **38**(45): p. 7007-7014.
46. Kittikraisak, W., et al., *Comparison of incidence and cost of influenza between healthy and high-risk children <60 months old in Thailand, 2011-2015.* PLoS ONE [Electronic Resource], 2018. **13**(5): p. e0197207.
47. Guo, R.N., et al., *Epidemiologic and economic burden of influenza in the outpatient setting: a prospective study in a subtropical area of China.* PLoS ONE [Electronic Resource], 2012. **7**(7): p. e41403.
48. Koul, P.A., et al., *Epidemiology and costs of severe acute respiratory infection and influenza hospitalizations in adults with diabetes in India.* Journal of Infection in Developing Countries, 2019. **13**(3): p. 204-211.
49. Emukule, G.O., et al., *The cost of influenza-associated hospitalizations and outpatient visits in Kenya.* BMC Public Health, 2019. **19**(Suppl 3): p. 471.
50. Vo, T.Q., et al., *Economic burden of influenza at a tertiary hospital in Vietnam.* Asian Pacific Journal of Tropical Disease, 2017. **7(3)**: p. 144-150.
51. Vo, T.Q., et al., *Social and economic burden of patients with influenza-like illness and clinically diagnosed flu treated at various health facilities in Vietnam.* Clinicoeconomics & Outcomes Research, 2017. **9**: p. 423-432.
52. Bhuiyan, M.U., et al., *Economic burden of influenza-associated hospitalizations and outpatient visits in Bangladesh during 2010.* Influenza & Other Respiratory Viruses, 2014. **8**(4): p. 406-13.
53. Orenstein, E.W., et al., *Cost-effectiveness of maternal influenza immunization in Bamako, Mali: A decision analysis.* PLoS ONE [Electronic Resource], 2017. **12**(2): p. e0171499.
54. Pallas, S.W., et al., *Program cost analysis of influenza vaccination of health care workers in Albania.* Vaccine, 2020. **38**(2): p. 220-227.
55. Yang, J., et al., *Seasonal influenza vaccination in China: Landscape of diverse regional reimbursement policy, and budget impact analysis.* Vaccine, 2016. **34**(47): p. 5724-5735.
56. Riewpaiboon, A., *Cost analysis of influenza vaccination for pregnant women in Thailand.* Pharmaceutical Sciences Asia, 2021. **48(2)**: p. 99-106.
57. Pecenka, C., et al., *Maternal influenza immunization in Malawi: Piloting a maternal influenza immunization program costing tool by examining a prospective program.* PLoS ONE [Electronic Resource], 2017. **12**(12): p. e0190006.
58. Giglio, N., et al., *Public health and economic benefits of new pediatric influenza vaccination programs in Argentina.* Human vaccines & Immunotherapeutics, 2012. **8**(3): p. 312-22.
59. Zhou, L., et al., *Cost-effectiveness of alternative strategies for annual influenza vaccination among children aged 6 months to 14 years in four provinces in China.* PLoS ONE [Electronic Resource], 2014. **9**(1): p. e87590.

60. Chen, C., et al., *[Cost-effective analysis of seasonal influenza vaccine in elderly Chinese population].* Chung-Hua Yu Fang i Hsueh Tsa Chih [Chinese Journal of Preventive Medicine], 2019. **53**(10): p. 993-999.
61. Yang, J., et al., *[Cost-effectiveness of potential government fully-funded influenza vaccination in population with diabetes in China].* Zhonghua Yu Fang Yi Xue Za Zhi, 2019. **53**(10): p. 1000-1006.
62. Jiang, M., et al., *Cost-effectiveness of quadrivalent versus trivalent influenza vaccine for elderly population in China.* Vaccine, 2020. **38**(5): p. 1057-1064.
63. Yang, J., et al., *Cost-effectiveness of introducing national seasonal influenza vaccination for adults aged 60 years and above in mainland China: a modelling analysis.* BMC Medicine, 2020. **18**(1): p. 90.
64. Yan, H., et al., *Cost-effectiveness analysis of quadrivalent influenza vaccination for older adults aged 60 and above in mainland China. [Chinese].* National Medical Journal of China, 2021. **101(30)**: p. 2405-2412.
65. Lara, C., D. De Graeve, and F. Franco, *Cost-Effectiveness Analysis of Pneumococcal and Influenza Vaccines Administered to Children Less Than 5 Years of Age in a Low-Income District of Bogota, Colombia.* Value in Health Regional Issues, 2018. **17**: p. 21-31.
66. Falcon-Lezama, J.A., et al., *Influenza in the school-aged population in Mexico: burden of disease and cost-effectiveness of vaccination in children.* BMC Infectious Diseases, 2020. **20**(1): p. 240.
67. Betancourt-Cravioto, M., et al., *Public Health and Economic Benefits of Influenza Vaccination of the Population Aged 50 to 59 Years without Risk Factors for Influenza Complications in Mexico: A Cross-Sectional Epidemiological Study.* 2021. **9**(3): p. 24.
68. Tapia-Conyer, R., et al., *A Call for a Reform of the Influenza Immunization Program in Mexico: Epidemiologic and Economic Evidence for Decision Making.* 2021. **9**(3): p. 19.
69. de Boer, P.T., et al., *The cost-effectiveness of trivalent and quadrivalent influenza vaccination in communities in South Africa, Vietnam and Australia.* Vaccine, 2018. **36**(7): p. 997-1007.
70. Biggerstaff, M., et al., *A cost-effectiveness analysis of antenatal influenza vaccination among HIV-infected and HIV-uninfected pregnant women in South Africa.* Vaccine, 2019. **37**(46): p. 6874-6884.
71. Edoka, I., et al., *A cost-effectiveness analysis of South Africa's seasonal influenza vaccination programme.* Vaccine, 2021. **39**(2): p. 412-422.
72. Choosakulchart, P., et al., *Cost-utility evaluation of influenza vaccination in patients with existing coronary heart diseases in Thailand.* Asian Biomedicine, 2013. **7(3)**: p. 425-435.
73. Meeyai, A., et al., *Seasonal influenza vaccination for children in Thailand: a cost-effectiveness analysis.* PLoS Medicine / Public Library of Science, 2015. **12**(5): p. e1001829; discussion e1001829.
74. Kittikraisak, W., et al., *Cost-effectiveness of inactivated seasonal influenza vaccination in a cohort of Thai children 60 months of age.* PLoS ONE, 2017. **12(8) (no pagination)**.
75. Sribhutorn, A., et al., *Influenza vaccination in acute coronary syndromes patients in Thailand: the cost-effectiveness analysis of the prevention for cardiovascular events and pneumonia.* Journal of Geriatric Cardiology, 2018. **15**(6): p. 413-421.
76. Suphanchaimat, R., et al., *Cost Effectiveness and Budget Impact Analyses of Influenza Vaccination for Prisoners in Thailand: An Application of System Dynamic Modelling.* International Journal of Environmental Research & Public Health [Electronic Resource], 2020. **17**(4): p. 14.
77. Akin, L., et al., *Cost-Effectiveness of Increasing Influenza Vaccination Coverage in Adults with Type 2 Diabetes in Turkey.* PLoS ONE [Electronic Resource], 2016. **11**(6): p. e0157657.
78. Dawa, J., et al., *Seasonal influenza vaccination in Kenya: an economic evaluation using dynamic transmission modelling.* BMC Medicine, 2020. **18**(1): p. 223.

79. Ortega-Sanchez, I.R., et al., *Cost-effectiveness of seasonal influenza vaccination in pregnant women, healthcare workers and adults >= 60 years of age in Lao People's Democratic Republic.* Vaccine, 2021. **39**(52): p. 7633-7645.
80. Kyi-Kokarieva, V.G., L.I. Padalko, and L.V. Kriachkova, *Socio-economic substantiation of expediency of seasonal influenza vaccine prophylaxis among medical workers.* Medicni Perspektivi, 2021. **26**(4): p. 205-212.
81. Jenkin, D.C., et al., *A rapid evidence appraisal of influenza vaccination in health workers: An important policy in an area of imperfect evidence.* Vaccine X, 2019. **2**: p. 100036.
82. Gavi, *Gavi board starts framing Alliance's approach to 2021–2025 period*. 2018, Gavi.
83. Gavi. *Gavi Board meeting, 7-8 December 2022*. 2022 [cited 2023 April 10]; Available from: https://www.gavi.org/governance/gavi-board/minutes/7-8-december-2022.
84. Cherian, T., et al., *Factors and considerations for establishing and improving seasonal influenza vaccination of health workers: Report from a WHO meeting, January 16-17, Berlin, Germany.* Vaccine, 2019. **37**(43): p. 6255-6261.
85. Thompson, M.G., et al., *Underdetection of laboratory-confirmed influenza-associated hospital admissions among infants: a multicentre, prospective study.* Lancet Child Adolesc Health, 2019. **3**(11): p. 781-794.
86. Macias, A.E., et al., *The disease burden of influenza beyond respiratory illness.* Vaccine, 2021. **39 Suppl 1**: p. A6-a14.
87. Levin, A., et al., *WHO-led consensus statement on vaccine delivery costing: process, methods, and findings.* BMC Med, 2022. **20**(1): p. 88.
88. Levine, O.S., et al., *A policy framework for accelerating adoption of new vaccines.* Hum Vaccin, 2010. **6**(12): p. 1021-4.
89. Turner, H.C., et al., *An Introduction to the Main Types of Economic Evaluations Used for Informing Priority Setting and Resource Allocation in Healthcare: Key Features, Uses, and Limitations.* Front Public Health, 2021. **9**: p. 722927.
90. Kazibwe, J., et al., *The Use of Cost-Effectiveness Thresholds for Evaluating Health Interventions in Low- and Middle-Income Countries From 2015 to 2020: A Review.* Value Health, 2022. **25**(3): p. 385-389.
91. Leech, A.A., et al., *Use and Misuse of Cost-Effectiveness Analysis Thresholds in Low- and Middle-Income Countries: Trends in Cost-per-DALY Studies.* Value Health, 2018. **21**(7): p. 759-761.
92. Ochalek, J., J. Lomas, and K. Claxton, *Estimating health opportunity costs in low-income and middle-income countries: a novel approach and evidence from cross-country data.* BMJ Glob Health, 2018. **3**(6): p. e000964.
93. Bertram, M.Y., et al., *Cost-effectiveness thresholds: pros and cons.* Bull World Health Organ, 2016. **94**(12): p. 925-930.
94. Robinson, L.A., et al., *Understanding and improving the one and three times GDP per capita cost-effectiveness thresholds.* Health Policy Plan, 2017. **32**(1): p. 141-145.
95. de Boer, P.T., et al., *A systematic review of the health economic consequences of quadrivalent influenza vaccination.* Expert Rev Pharmacoecon Outcomes Res, 2017. **17**(3): p. 249-265.
96. Crespo, C., et al., *Comparative efficiency research (COMER): meta-analysis of cost-effectiveness studies.* BMC Med Res Methodol, 2014. **14**: p. 139.
97. Ofori, S.K., et al., *Economic evaluations of interventions against influenza at workplaces: systematic review.* Occup Med (Lond), 2022. **72**(2): p. 70-80.
98. World Health Organization, *Coadministration of seasonal inactivated influenza and COVID-19 vaccines*. 2021.
99. Jit, M., et al., *The broader economic impact of vaccination: reviewing and appraising the strength of evidence.* BMC Med, 2015. **13**: p. 209.

100. Jit, M. and R. Hutubessy, *Methodological Challenges to Economic Evaluations of Vaccines: Is a Common Approach Still Possible?* Appl Health Econ Health Policy, 2016. **14**(3): p. 245-52.