An economic evaluation of Influenza and COVID -19 pandemic prevention and control interventions: a systematic review

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Abstract

Background: COVID-19 causes more 1.3 million deaths globally in just nine months. Influenza is a virus with respiratory symptoms, fever, and systemic symptoms very similar to COVID 19. Various public health measures have been taken by governments and health authorities to prevent and control the pandemics. This study aimed to review the economic evaluation of public health measures against COVID-19 and influenza pandemics.

Methods: We performed a systematic review of the literature to identify full economic evaluation studies on Influenza and COVID-19 pandemic published from 1998-2020. We built an exhaustive database search strategy. The search was done in Pubmed, Web of Science, EMBASE databases, and grey literature. We extracted data from selected studies using a structured data collection form after conducting a risk of bias assessment. Narrative summary tables were used to present the result and characteristics of eligible studies. Furthermore, we converted findings of studies that reported their outcome in costs per case averted and death averted into costs per life-year gained. All cost and Cost-effectiveness ratios were converted to 2019 US dollars using the exchange rate and GDP deflator. The study was registered in PROSPERO with registration No. CRD42020192384.

Results: The review revealed that most of the studies were conducted in high-income countries, and only few of the studies were on non-pharmaceutical interventions. Stockpiling drugs for the treatment of sick patients was found cost-effective in most of the studies. Treatment with antiviral drugs and vaccination were found very cost-effective. The addition of school closure to other interventions was considered cost-effective only for a pandemic with a high case fatality ratio. Almost all interventions were sensitive to the infectivity and severity of the pandemic. Most of the studies were also cost-effective from the societal perspective indicating a higher net societal benefit from the pandemic prevention and control strategies.

Conclusion: In conclusion, most of the interventions were cost-effective under various scenarios while school closure was cost-effective under a 'high case-fatality 'ratio' scenario only. Furthermore, the level of the pandemic's infectivity and severity were the key drivers of the cost-effectiveness of both pharmaceutical and non-pharmaceutical interventions.

Background

The coronavirus disease (COVID-19), an illness caused by a novel coronavirus, is the cause of an outbreak of respiratory illness, which was first discovered in Wuhan, Hubei Province, China beginning on 31st December 2019 and declared as a pandemic on 11th March 2020 [1, 2]. The virus has higher transmissibility and pandemic risk than SARS-COV and MERS-COV [3] with a reproduction number between 2 and 2.5 [1]. The virus is primarily transmitted among people through respiratory droplets and contact routes. Measures taken to prevent pandemics will lead to a substantial economic shock in addition to morbidity and mortality caused by the pandemic. Globally, the number of COVID-19 cases reached around 55 million, with more than 1.3 million deaths as of 15th November 2020.

Influenza, is similarly, is a virus with respiratory symptoms, fever, and systemic symptoms, and which can change its genetic makeup, making it liable to cause a pandemic. It is assumed that a global influenza pandemic can occur every 10 to 50 years interval [4]. There have been five influenza pandemics so far. For example, the Spanish flu pandemic killed 50–100 million people, and the Swine flu pandemic killed about a million people in 1998, and 2009, respectively [5].

Several pharmaceutical and non-pharmaceutical public health measures have been implemented against pandemics. Some non-pharmaceutical interventions include school closure, voluntary home isolation, work closure, working from home, and internal mobility restrictions [6]. Pharmaceutical interventions include vaccination, mass testing, treatment, and prophylaxis. Some countries effectively apply those measures in controlling the transmission of the pandemic, while some countries are less successful. For example, China has successfully slowed down the virus's spread through the lockdown of high-risk areas [7]. However, the cost associated with these public health interventions, especially with lockdown measures, is very high. For instance, Japan had lost about 27 trillion yen when Tokyo was under lockdown for a month, approximately 5.3% of its annual GDP [8]. Due to job losses and increased inequality between the rich and the poor [9]. School closure would increase time lost from work (productivity loss) for families and represented higher monthly household expenses because of the working day loss, especially for people with low socio-economic status [10-12]. Increasing food insecurity [13], mental health problems and suicide [14, 15], and death from other diseases are also associated consequences of these public health measures [16].

A robust health system led by evidence-based public health measures would minimise potential direct and indirect damages that a pandemic causes to the community and the government. Efficient and effective use of resources for containing and mitigating an epidemic is an area where policymakers lack substantial evidence. Because resources are scarce, policymakers need to prioritise measures that would save more lives than others. However, such kinds of evidence are scarce. There are two systematic reviews on pandemic preparedness measures' economic evaluation, including studies conducted only up to 2014 [17, 18]. There is a critical gap for an updated and comprehensive systematic review of the pandemics' full economic evaluation studies, which includes recent evidence and taking into account the COVID 19 pandemic. Therefore, this systematic review aimed to assess the economic evaluation of measures that have been used to prevent and control the Influenza and COVID-19 pandemic. The current review included studies conducted from 1998 to 2020.

Method

Inclusion and exclusion criteria for eligibility of studies

Full economic evaluation studies such as cost-minimisation, cost-effectiveness, cost-utility, and cost-benefit analyses focused on any interventions related to public health measures to prevent and control Influenza and COVID compared to no interventions or alternative course of actions. Outcome measues such as cost-benefit ratio, cost per infection prevented, cost per death prevented, cost per life-year gain, cost per quality-adjusted life years (QALY), cost-per disability-adjusted life years (DALY) averted, and average cost-effectiveness ratio (ACER) and incremental cost-effectiveness analysis (ICER) were used in full economic evaluation. We considered studies published from 1998 to 2020 for the review. We excluded partial economic evaluation studies such as economic burden or cost of illness that only reported health outcomes or only costs of the interventions; and commentaries, reviews, methodological articles, and editorials from the review.

Search methods for identification of studies

We built an exhaustive database search strategy in the global health cost-effectiveness analysis (CEA) registry, Embase, Scopus, PubMed, African Journal Online, and Elsevier for relevant studies according to the "Centre for Reviews and Dissemination's (CRD) Guidance" recommendations [19]. We did a manual-searching of reference sections of all identified relevant studies and searched for cited references. Besides, relevant internet sites were also searched for any useful findings. We first developed multiple search terms, and then we combined the search terms using "OR" and "AND." The search strategies used combined search terms relating to the terms Influenza pandemic, flu, COVID-19 as a class, relating to cost-effectiveness, cost-utility, and cost-benefit analysis. We also used filters to limit the search to studies conducted after 1998 and "Humans" and "English" for all databases. Search strategies on Pubmed were annexed on supplementary file 1.). In the figure below, we present the flow chart of the study selection process.

We used EndNote x9 to manage search results and remove duplicate records, and we also used Microsoft excel to select studies and extract data.

Selection of studies

Two authors (AY and ZG) selected potentially eligible titles and abstracts independently. A discussion was conducted on the selected titles and abstracts between the two authors. The authors performed a second stage screening for titles and abstracts approved by either of the authors. Disagreements concerning including eligible studies were approved by discussion in the presence of a third author (MY) based on established article selection criteria.

Data extraction and management

We designed data extraction form and included the following information: year of publication, country, setting, perspective, type of economic evaluation, analytic approach, intervention, comparator, outcome, time horizon, type of model, discount cost, a discount of effect, base year, consumer price index, currency, category of cost, data source of cost, a type of threshold used for ICER, a threshold value for the country, the infectivity of the pandemic, severity of the pandemic, ICER, cost-effectiveness of the interventions, type of sensitivity analysis, the parameters that were sensitive to the ICER. The tool was adopted from Consolidated Health Economic Evaluation Reporting Standards (CHEERS)" format [20] and NHS Economic Evaluation Database (NHS EED) guidelines [21]. Data extraction was undertaken by two reviewers and checked by the third author for accuracy.

Quality Assessment

The authors did a risk of bias assessment using recommended tools for health economic studies. The two authors (AY and ZG) independently assessed the risk of bias for methodological quality adopted from the CHEERS statement [20]. We evaluated ten domains, including whether the studies have clearly stated perspective of the study, time horizon, discounting, description of the intervention and comparator, description of costs used, source of the cost data, source of the effectiveness data, the base year of the report, clear description of the ICER, and sensitivity analysis. We gave a low, medium, and high score for studies and studies with severe limitations were excluded from the review. The criteria for quality assessment were annexed in supplementary file 2.

Data analysis and synthesis

Description of the characteristics of the studies and results was displayed using narrative summary and tables. The narrative summary was structured by the type of public health measure or intervention, the type of economic evaluation, and the country of study. Besides, parameters in the cost-effectiveness analysis examined for uncertainty in the cost-effectiveness ratio estimates were reported. For studies that report their findings in cost per case prevented and cost per death prevented, we changed the report to cost per life-year gained. We estimated the cost per death averted by multiplying the cost per case prevented by a case fatality ratio of 2% for COVID-19 and 0.5% for influenza pandemic [22, 23]. We calculated the cost per life-year gained by multiplying the costs per death averted by assumed remaining life years of 43, expecting a person would live up to 80 years. After converting the findings into costs per life-year gained, we then converted the costs to 2019 USD currency by first converting the currency to USD and then inflating the currency to the year 2019 using USA GDP deflator [24].

Results

Review profile

A total of 1300 records were identified through all methods. One hundred three studies met the inclusion criteria. Besides, we have also removed studies with different languages than English and those that describe only the disease's impact. We removed the studies by considering the Drummond checklist specifically if they have not mentioned the costs, the outcomes, and cost-effectiveness ratios and quality assessment tool we adopt. Fourteen studies were selected through cited reference searching and reference list screening, of which ten were excluded as they were not full economic evaluation studies. A total of 36 studies were finally included for the economic evaluation.

Description of the results

The studies were conducted mostly in developed countries. Among selected studies, only three studies, LMIC, South Africa, and China, were conducted in the developing countries, 33 studies were from the developed countries. The review indicated that 15 studies were conducted in the USA, followed by 3 in Singapore, 3 in the UK, 3 in China, 2 in the Netherlands, 1 in Australia, Canada, South Africa, Japan, France, Israel, and New Zealand. Two studies did not explicitly inform the country of the studies.

Among the studies, 14 of them were conducted on CUA, 15 on CEA, three on CBA, one on both CEA and CUA, two on both CBA and CEA, and one on both CBA and CUA. In terms of perspectives, 15 studies were conducted from a societal perspective, ten from a healthcare provider perspective, and eight from both a societal and a healthcare provider perspective. However, 3 of the studies did not clearly describe the perspective of the study. Most of the studies indicated the source of costs and the type of model used in the study. In table one below, we present a description of the reviewed studies.

Most of the studies have clearly described the costs used in the study. When using a societal perspective, there is a slight difference in the way productivity losses are estimated. For example, some studies have considered the future productivity loss due to death in the estimate [25], while other studies only considered the productivity loss at the time of infection, which might assume the future value of lost workers will be replaced [26-28]**.** The input cost for one study was not clearly described, and the link to other studies to see the estimate of the cost component did not work [29], and we failed in getting the information from the author. The cost input for one study was also based on the assumption that it should be interpreted with caution [30].

The cost-effectiveness of different interventions

Most of the studies have focused on pharmaceutical interventions related to antiviral treatment and vaccination, and some studies have conducted both pharmaceutical and non-pharmaceutical interventions. Generally, there are fewer studies conducted on non-pharmaceutical intervention.

In table two below, we present the cost-effectiveness of the reviewed studies.

In figure 3 below, we presented the cost-effectiveness of the interventions in 2019 USD. However, the interventions' findings are not consistent because of the settings of the studies and different assumptions, vaccinations, treatment of sick patients, and using personal protective equipment lie in a range of highly cost-effective interventions.

Cost-effectiveness of the reviewed studies

Stockpiling drugs and treatment of Antivirals

Seventeen studies were conducted on the stockpiling of drugs and treatment of patients with antivirals. Most of the studies used a do-nothing scenario as a comparator, and few have compared the interventions against the alternative course of actions or the addition of non-pharmaceutical interventions such as school closure. Stockpiling for the therapeutic use of the drugs to high-risk patients and post-exposure short term prophylaxis of all close contacts, including index patient treatment, is cost-saving. However, pre-exposure long term prophylaxis of entire patients is not cost-effective for stockpiling with less CFR.[26]**.** Prophylaxis was economically beneficial in high-risk subpopulations and pandemics with a case fatality rate greater than 0.6% [31]. It is cost-effective to stockpile drug when compared to no intervention at a pandemic reproductive rate of 1.8 and 20-40% population illness rate [32], and if the actual risk is less than 37% for 30 years but not cost-effective if less than 60% of the population would take the antiviral drugs or the attack rate is about 50% [33]**.** All the studies reviewed had estimated that the stockpiling of antiviral agents for only treating patients had optimal economic benefits.

Testing all symptomatic patients and treating those only with positive test results is less cost-effective when compared to treating all symptomatic patients for a pandemic influenza disease [34]. For stockpiling drugs and vaccine, antiviral treatment of those clinically infected is the most cost-effective, followed by population pre-pandemic vaccination, and then the combination of both antiviral treatment and population pre-pandemic vaccination when compared to a small stockpile of antiviral drugs for prophylaxis of case contacts and treatment of clinical cases and vaccine after six months [35]**.**

A combination of interventions such as a reduction in household contacts and 60% of work/school contacts and stockpiling drugs is more cost-effective compared to the same intervention by adding school closure for 26 weeks. At 1% influenza mortality, moderate infectivity (Ro of 2.1 or

greater), and 60% population compliance, a combination of adult and child social distancing, school closure, and antiviral treatment and prophylaxis is cost-effective. The addition of school closure is only cost-effective for pandemic with CFR of more than 1% and Ro higher than 1.6 [36].

The use of IV antiviral treatment for hospitalised patients with influenza-like illness is cost-effective for the smaller cost of antiviral treatment [37]. Using Oseltamivir for Influenza was cost-effective from a healthcare perspective and cost-saving from a societal perspective [29]. The empirical treatment of all sick patients with Oseltamivir costs less money and have higher effectiveness (dominant) when compared to the post rapid influenza diagnostic test treatment with Oseltamivir, and is cost-effective when compared with no intervention [38]. For high-risk groups, antiviral treatment, although less effective, seems more feasible and cost-effective than prophylaxis and should be chosen, mainly if limited drug availability [39].

For a variety of pandemic influenza scenarios (attack rate 20% or more, probability of preterm birth for women with Influenza 12% or more, mortality for a preterm neonate 2% or more, and the probability of influenza-attributable hospitalisation 4.8%), the use of antiviral medications for post-exposure prophylaxis among pregnant women in a pandemic influenza scenario is cost-effective compared to no intervention for pandemic influenza, but not in a seasonal influenza setting. As the probability of preterm death increases and CAR, the use of prophylaxis will be cost-saving [40]. PEP with Oseltamivir is probable to be a cost-effective strategy for family contacts when influenza-like illness contact attack rates are 8% or higher [27].

Most of the interventions related to stockpiling and treatment are cost-effective, given that there are higher infectivity and severity of pandemic influenza. The probability of pandemic in a given year and contact rate is also a determinant factor whether the treatment/stockpiling is cost-effective. In general, the cost-effectiveness of pandemic treatment/ stockpiling is determined by the probability of pandemic in a given year, contact rates, pre-existing immunity, age-specific mortality, changes in attack rates, case fatality rate, discount rate, and AV drug efficacy.

Stockpiling vaccines and vaccination

Among the reviewed studies, nine of them were conducted mainly on vaccination strategies. For influenza pandemic, early availability of vaccine before the peak time of pandemic determines its economic value. Vaccinating high-risk groups is highly cost-effective, followed by extending the vaccination to schools and then low-risk groups [41]. Vaccinating low-risk group is also cost-effective when compared to no intervention. When compared to seasonal prophylaxis, vaccination of the total population is preferred. Vaccinating the population at risk is very cost-effective, followed by a priority population. The least cost-effective scenario is vaccinating the total population for a pandemic with a 25% attack rate [39]. Under a wide range of scenarios, vaccination for pH1N1 for children and working-age adults is cost-effective compared to other preventive health interventions. The vaccine availability delays had a substantial impact on the cost-effectiveness of vaccination strategies [42].

At a lower cost ($21 per vaccine), there is a net saving to society if persons in all age groups are vaccinated, but at $62 per vaccine and gross attack rates of 25%, there will be a net loss if persons not at high risk for complications are vaccinated. At a lower vaccination cost, vaccinating all populations would be cost-effective. However, at higher vaccine costs, vaccinating high-risk populations would be cost-effective [43]. Vaccination initiated before the outbreak is also cost-saving [42], and pre-vaccination of 70% of the population with low efficacy vaccine is cost-effective [27].

Maternal influenza vaccination using either the single or two-dose strategy is a cost-effective approach when influenza prevalence greater than or equal to 7.5% and influenza-attributable mortality is greater than or equal to 1.05% (consistent with epidemic strains). This will be cost-saving as the prevalence of Influenza become more than 30% [44]. Assuming each primary infection causes 1.5 secondary infections, vaccinating 40% of the population would be cost-saving. Vaccination is even more cost-saving if more extended incubation periods, lower rates of infectiousness, or increased implementation of non-pharmaceutical interventions delay time to the peak of the pandemic. Vaccination saves fewer lives and is less cost-effective if the epidemic peaks earlier [45]. Mass vaccination was cost-effective and depended on the timing of vaccination and vaccine effectiveness [27]. Vaccination and stockpiling pneumococcal vaccine for the time of influenza pandemic are also very cost-effective [28, 46].

For severe pandemics or pandemics in which pre-pandemic influenza vaccine is unavailable, stockpiling of 23-valent pneumococcal polysaccharide vaccine (PPSV23) for a pneumococcal disease can be a cost-effective strategy for reducing the health and economic burden associated with secondary pneumococcal infections in a high-risk population. However, for a mildly severe pandemic in which pre-pandemic influenza vaccine is available, stockpiling of PPSV23 may not be cost-effective [28]. The cost-effectiveness of vaccine stockpile is determined by the vaccine efficacy and strain match and the costs of the vaccine. For higher vaccine efficacy, higher strain match, and lower vaccine cost, stockpiling vaccines are cost-effective [47].

This review showed that the cost-effectiveness of vaccination strategies is sensitive to the risk of death, CAR (the overall size of the epidemic), cost of vaccines, model assumptions, QALY loss per case, hospitalisation rates and costs, and case-fatality ratios, the number of vaccine doses needed, costs of vaccination, illness rates, and timing of vaccine delivery.

School Closure

Most of the reviewed studies related to school closure are conducted in combination with other studies. Closing school is a non-pharmaceutical response that is usually implemented at the early phase of a pandemic. Individual-based school closure with a lower threshold to trigger school closure is more cost-effective than district level or system level school closure [48]. Likewise, closing schools for a lower reproductive number, less than 1.6, is not considered economically efficient for society [25]. As most of the pandemic interventions are implemented in combination, the extent to

which adding schools closure to pharmaceutical interventions is also reviewed. Combination of antiviral prophylaxis for those with contact history and school closure is considered more efficient when compared to full targeted antiviral prophylaxis. Besides, a combination of pre-vaccination with a low-efficacy vaccine before the outbreak of a pandemic and school closure is more cost-effective than full targeted antiviral prophylaxis [49]. When compared to do nothing scenario, a combination of interventions such as adult and child social distancing, school closure, AV treatment, and prophylaxis is cost-effective for a pandemic with a reproductive number of 2.1 and a case fatality rate of 1%. The findings in those studies are sensitive to the infectivity, case fatality rate, level of population compliance, and antiviral effectiveness [36].

Tracking Exposed Persons, Testing, and Quarantines

A combination of healthcare testing, contact tracing, isolation centre, and mass symptom screen compared to only healthcare testing was found to be cost-effective with a reproductive number of 1.5 or with 0.1% prevalence of the disease to prevent COVID-19. The findings were sensitive to reproductive number, efficacies of contact tracing, isolation centres, and Mass screening to detect infections; cost of isolation of cases and quarantine centres [50]. At school for re-opening, weekly test with a test sensitivity of 80% (when compared to test sensitivity of 70% is cost-effective) with reproduction number of 2.5 and case fatality rate of 0.05% [30]. PCR for any symptomatic patients plus one-time PCR for the entire population is cost-effective when compared to PCR for any COVID-19-consistent symptoms with self-isolation if positive with an effective reproduction number of 2.0. The findings are sensitive to Varying rates of presentation to hospital care and ICU survival, input parameters on infections and deaths [51]. PCR testing with 90% sensitivity, and 100% specificity with a probability of Influenza-like illness being Influenza of 10%, 20%, 30% are cost-effective when compared to no interventions. Point of care test with 50% sensitivity and 95% specificity with the same probability is also cost-effective. The findings are sensitive to the probability of ILI being Influenza [52].

Personal protective equipment

Personal protective equipment in preventing COVID-19 cases was also assessed for some of the studies. For example, a study which compared N95 mask and face mask estimated the additional cost to be ranging from US$ 490 to USD 1230 per cases prevented with a clinical attack rate of 4.6. The findings were sensitive to the CRI attack rate and intervention effectiveness [53]. To protect healthcare workers, using personal protective equipment when compared with no intervention was 4,448 USD per HCW life saved for HCW infection as a percent of total infection of 9.6% and case fatality ratio of 1.38% [54]. For spontaneous and induced labour at a delivery service, universal screening is the preferred strategy given the high cost of universal PPE in the base case. However, for a planned cesarean delivery, universal PPE is cost-saving compared with universal screening. Universal screening is more cost-effective than PPE to prevent the transmission of COVID-19 to health workers for spontaneous and induced labour [55]. For a hospital protection measure response against respiratory infections, protection measures targeting only infected patients (hospitals full PPE for a suspected case, contact tracing, AV treatment for all cases for Pandemic (H1N1) 2009) yielded low incremental cost per death averted of $23,000 (US$) for pandemic (H1N1) 2009. Enforced protection in high-risk areas and full protection throughout the hospital averted deaths but came at a higher incremental cost [56].

Other non-pharmaceutical interventions

For interventions like border closure, the net present value is high if the case fatality rate is high. Border closure was relatively cost-effective when seen from the provider perspective and cost-saving from the societal perspective. The findings were sensitive to the number of deaths assumed, the value put on lost productivity, and the value of a monetised [57].

Discussion

This systematic review has identified 36 full economic evaluation studies that assessed prevention and control response interventions against pandemic influenza and COVID-19, and 10 of the studies were published from 2016 to 2020. Only two studies are conducted for LMIC countries[50, 54], and most of the studies are conducted in developed countries. There is a need for evidence in pandemic preparedness, control, and mitigation strategies in developing counties.

The evidence indicated that stockpiling antiviral drugs for the treatment of sick patients is cost-effective. Besides, stockpiling of antiviral drugs for prophylaxis can be cost-effective for diseases with a high reproduction number and case fatality rate. Empirical treatment of symptomatic patients was also cost-effective under a given scenario. Some of the studies show that the societal perspective is either cost-saving or cost-effective for stockpiling AV drugs or treatment of patients. Despite the high cost incurred by the health care provider for the pandemic control measures, the benefits from a societal perspective are mostly high.

This review shows that most of the studies are sensitive to clinical attack rate, case fatality rate, and cost of the drugs [26, 31, 34-39, 58]. The antiviral drug that was mainly used in the cost-effectiveness studies was Oseltamivir. However, the effectiveness of this drug against Influenza was disproved in recent studies and not recommended by WHO anymore as of 2017 [59]. Therefore, parameters related to the effectiveness of the drug will be affected mainly due to these recent findings, which will vastly reduce the cost-effectiveness of the drug.

Vaccination is also deemed cost-effective under various scenarios. Most of the studies consider vaccination as a very cost-effective intervention. However, studies also considered that the timing of the availability of the vaccines is very crucial. For example, the availability of the vaccine before

the peak of the pandemic period makes it affordable to provide. Vaccine effectiveness, vaccine costs, clinical attack rate, and case fatality rate are a determinant factor for the cost-effectiveness of the vaccination strategies [28, 39, 41-43, 45, 46, 60].

Adding school closure to different pharmaceutical interventions are cost-effective when the case fatality rate is high. The studies also mentioned that school closure is not cost-effective for pandemic with a small reproductive number and small case fatality rate. This is due to the higher societal cost of closing schools, like working hour loss to take care of children. Individual-based school closure for a shorter time might also be considered cost-effective when compared to system-based or district-based school closure. Overall the studies have sited that whether to close school or not should be guided by infectivity and case fatality rate of the pandemic[25, 36, 48, 49].

As for the other interventions, the cost-effectiveness of interventions related to healthcare testing, contact tracing, isolation centre, mass symptom screen, border closure, and PPE for health workers depend mainly on the reproductive number of the pandemic. In addition to the reproductive number, case fatality rate, and efficacies were also factors that tell if the interventions are efficient [30, 50, 52, 54, 55, 57].

There were limitations in this review, which requires care in its interpretation. First, the included studies are very heterogeneous in terms of methods applied. Secondly, the costs and effectiveness of the interventions are very context-specific, especially for the non-pharmaceutical interventions. In some countries, where human resource cost and prices of supplies and drugs were high, effectiveness was is high in general, while it is relatively low in some other countries for all interventions. This variation, therefore, makes it hard to disaggregate or aggregate (mean or median) the cost and ICER. Furthermore, since economic evaluations on pandemic preparedness heavily rely on crucial prospective assumptions on intervention effectiveness and unknown disease as risk, this makes the transferability of economic evaluation studies more challenging.

Conclusion

In conclusion, there is a shortage of evidence in low and middle-income countries on the economic evaluation of pandemic interventions. Most of the studies are performed for pharmaceutical interventions, and future researches should focus on non-pharmaceutical interventions. Whether an intervention against a pandemic is cost-effective is determined mainly by the infectivity and severity of the pandemic. According to most of the studies, stockpiling for the treatment of infected patients can be cost-effective. Vaccination is also cost-effective under different scenarios. Adding school closure to different pharmaceutical interventions is cost-effective only for a pandemic with a high case fatality rate. PPE for health workers is also an efficient strategy at LMIC. Overall most of the studies are cost-effective from the societal perspective than the healthcare provider perspective, which might imply the large societal gain due to the pandemic prevention and control strategy.

List Of Abbreviations

ACER: Average Cost-Effectiveness Ratio; CBA: Cost-Benefit Analysis; CEA: Cost-Effectiveness Ratio; CHEERS: Consolidated Health Economic Evaluation Reporting Standards; CRD: Centre for Reviews and Dissemination; DALY: Disability-Adjusted Life year; ICER: Incremental Cost-Effectiveness Ratio; LYG: Life year Gained; NHS EED: NHS Economic Evaluation Database; QALY: Quality Adjusted Life Year

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable

Availability of data and material

The data that support the findings of this study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

AY is the guarantor of the review. AY developed search strategies and prepared a data extraction form with the support of HITAP. AY and ZG conducted the preliminary searches. All authors participated in the review of the protocol and manuscript. All authors approved the data extraction form, the protocol, and the final version of the manuscript.

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Tables

Table 1: Description of the reviewed studies

Author	Country	Perspective	Type of EE	Time horizon	Type of model	Description of cost
Balicer et al., 2009 [26]	Israel	Societal (provider)	CBA	10 years	Static: Spreadsheet model	Direct medical cost and working days lost, but not include the lost value of life
Khazeni et al.,2009 [32]	USA	Societal	CUA	Life time	Dynamic: Compartmental epidemic model and the Markov model (deterministic SIRD model)	Vaccine cost (Antigen per μg ($)plus Adjuvant ($), μg Adjuvant per vaccine, Stockpiling (annual, $), administration, Patient Time, Oseltamivir, dispensing, Daily health care costs: Patient with severe side effects (treated in ICU), General medical hospitalised patient, and Long-term treatment facility cost
Lee VJ et al.,2006 [31]	Singapore	Societal	CBA and CEA	4 years	Decision tree model	Earnings lost per death, Hospital cost (USD$/day), Consultation and treatment cost (USD$), cost of vaccination, (USD$)
Lugner et al., 2009 [58]	Nether-lands	Societal	CEA	30 years	Dynamic: Deterministic SEIGR model	Outpatient GP visits, OTC drugs and antibiotics due to complications, hospitalisation, Production losses, telephone calls to GP, pharmacy fee for AV prescriptions, Stockpiling costs (One-time purchase, Oseltamivir, one-time purchase, combination Tamiflu and Oseltamivir, Yearly storing costs), purchase and storing, Oseltamivir
Siddiqui et al., 2008 [34]	UK	provider	CUA	30 years	Static: Decision tree	Mean unit costs per GP consultation, hospitalisation, and accident and emergency departments attendance for ILI, the unit cost of an AV treatment, Administration costs for the distribution of AV drugs or near-patient testing by visiting teams or call-in centre (equivalent to the mean cost of a home visit by a district nurse)
Sander et al., 2009 [49]	USA	Societal	CUA	1 year less	Dynamic: Discrete-time, stochastic, individual-level microsimulation	Cost of treatment of illness for children and adults, cost of prophylaxis cost of school closure. Cost of physician visits, hospitalisations, use of antibiotics, and use of over-the-counter medicines, drug and delivery cost for pre-vaccination, travel and time cost to obtain prophylaxis did not include the cost of premature death
Perlroth et al., 2010 [36]	USA	Societal	CUA	NCs	Dynamic: Networked individual level computational model ("Loki-Infect")	Outpatient visit to any medical site, hospitalisation with survival and influenza-related death, Alternative care site cost as a percentage of hospitalisation cost, Oseltamivir treatment per day, Oseltamivir prophylaxis per day, Antiviral dispensing cost (per course), Median daily wage rate, cost per student for each day of school missed (up to 64 maximum days.
Bruce Y. Lee., 2011 [37]	USA	provider and societal	CUA	NCs	A decision-analytic computer simulation model	IV antiviral Peramivir, Hospitalisation per day, ventilation per day, died in hospital, PCR test, median hourly wage,
Lugnér et al., 2010 [33]	Nether lands	Societal and provider	CEA	1 year	Static and Dynamic: Decision tree/deterministic SEIR model	GP visit, antiviral drugs, antibiotics, the counter drug, hospitalisation, and standard care, intensive care, productivity loss
D. B. C. Wu et al., 2018 [61]	USA	Societal	CUA	1 year	Decision-analytic model and dynamic transmission model	Transportation cost, daily work loss, GP visit, hospitalisation
Hiroko Nagase et al.,2009 [29]	Japan	Provider	CUA	53 days	Decision analytic model	Not found from a link
Kunling Shen et al., 2016 [38]	China	Provider	CUA	1 year	Decision-analytic model	Costs of outpatient visits, RIDTs, medications, emergency department visits, and hospitalisations
Baguelin et al., 2010 [62]	UK	Healthcare provider	CUA	Lifetime	An age and risk group structured deterministic transmission dynamic model	Calls to the National Pandemic Flu Service, GP calls and consultations, hospitalisations, stay on intensive care, antivirals, vaccine costs, vaccine delivery costs
Doyle et al., 2006 [39]	France	NCs	CEA	NCs	Static: Monte Carlo simulation	Cost of treatment, vaccine, and consultation
Lee BY et al.,	NCs	Societal	CUA	NCs	Static: Computer-	Antiviral medications, hospitalisation, costs of over-the-

2009 [40]					simulation decision tree	counter influenza medications and treatment of antiviral medication adverse effects,
Lee BY et al., 2010, [52]	NCs	Societal	CUA	NCs	Static: Monte Carlo decision-analytic computer simulation	Antiviral medications, clinic visit, hospitalisation, costs of over-the-counter influenza medications, death in hospital, PCR test, rapid test
Sander et al., 2006 [27]	UK	Health care provider	CUA and CEA	1 year	Static decision tree	General practitioner visit, specialist visit, Oseltamavir drug prescriptions, tests and investigations, primary and secondary care, hospitalisation
Lisa A. Prosser.,2011 [42]	USA	Societal	CUA	1 year	Computer simulation model	Vaccine cost, administration cost, cost of the vaccine, physician office settings
Lee VJ et al., 2009 [47]	Singapore	Societal	CEA and CBA	50 years	Static: Decision tree	Earnings lost per death, Hospitalisation cost, Value of 1 lost day, Consultation and treatment cost, outpatient care cost, cost of drug and vaccine
Meltzer et al., 1999 [43]	USA	Societal	CBA	Lifetime	Static: Monte Carlo simulation	Hospitalisations, outpatient visits, drug purchases, lost productivity including death, and cost of full vaccination (cost of the vaccine, as well as its distribution and administration (healthcare worker time, supplies); patient travel; time lost from work and other activities; and cost of side effects)
Newall et al., 2010 [35]	Australia	provider and societal	CEA	Lifetime	Dynamic: Hybrid transmission model and decision tree (deterministic SEIR model)	Age-specific hospitalisation cost, cost of emergency department visit, general practitioner visit, cost of vaccine and drug, vaccine and drug storage cost, productivity loss
Beigi et al., 2009 [63]	USA	Societal and third party perspective	CUA	NCs	Static: stochastic decision-analytic computer simulation	Cost of death, home treatment for mother and neonate, home treatment for vaccine side effect, hospitalisation for Influenza, influenza vaccine per dose, preterm birth productivity losses
Khazeni et al., 2009 [45]	USA	Societal	CUA	Lifetime	Compartmental epidemic model in conjunction with a Markov model of disease progression.	Vaccine (Antigen per microgram, Adjuvant, Adjuvant per vaccine, microgram, administration), patient time, Daily health care costs, including hospitalisation cost.
Beate Sander et al., 2010 [60]	Canada	Health care payer	CEA	Lifetime	A simulation model	Unit cost immunisation program(vaccine cost, medical supplies, personal and communication), the cost for a physician, emergency department, cost of hospitalisation, resource intensity weight
Jaime L Rubin et al., 2010 [46]	USA	Health care payer	CEA	1 year	Decision analytical	Vaccination cost, vaccine administration cost, cost of treating, cost of hospitalisation, (morbidity, mortality, and costs of Influenza without pneumococcal co-infection are not considered)
Praveen Dhankhar al., 2010 [28]	USA	Societal perspective	CEA		Decision (probability) tree model	Both direct and indirect costs (hospitalisation, outpatient, no medical care cost, vaccine cost, vaccine Admin cost, cost of recipient time), lost productivity to replace dead workers.
Nicholas Risko et al.,2020 [54]	LMIC	Societal	CEA	NCs	Decision-analytic model	Nitrile glove, polypropylene contact gown, plastic face shield, N95 mask, bleach wipe, hospital bed per day,
Mukerji et al., [53]	China	Societal	CEA	28 days	CEA model	Medical mask, N95 respirator, test kit, productivity cost of HCW time, antibiotics, Antitussives, Antipyretics, antiviral, traditional Chinese medicine, outpatient visit, emergency ward, monthly staff salary.
wong et al., 2016 [48]	China	Societal	CEA	16 weeks	Age-stratified region-specific disease-spread simulation model	Outpatient visit, hospitalisation, hospital cost for death, Over-the-counter cost, and productivity loss, including death
Boyd, M., et	New	Societal	CUA	Lifetime	Costing tool	NCs

al., 2018 [57]	Zealand	and provider	and CBA		developed by the New Zealand (NZ) Treasury (CBAx)	
Savitsky et al., 2020 [55]	USA	NCs	CEA	NCs	NCs	Cost of rapid test, cost of PPE for planned, unplanned, induced, and spontaneous delivery, cost of cesarean delivery, cost of vaginal delivery
Krishna P. Reddy et al., 2020 [50]	South Africa	Healthcare provider	CEA	1 year	A dynamic COVID-19 microsimulation model	Costs of PCR testing, contact tracing, and mass symptom screening, as well as daily costs of 265 hospitalisations, ICU stay, and IC/QC stays
Paltiel et al., 2020 [30]	USA	NCs	CEA	80 days	Decision and cost-effectiveness analysis linked to a compartmental epidemic 52 model	Cost per test with assumption
Anne M. et al 2020., [51]	USA	Health sector	CUA	180 days	A micro-simulation model	The model tallies tests, COVID-19-related use of hospital and ICU bed-days, as well as days spent self-isolating.
Brown et al., 2011 [25]	USA	Societal	CBA		Agent base model, Monte Carlo cost-benefit simulation	Outpatient Visit Costs, Hospitalization Given Influenza for different age group and productivity loss (Death Given Influenza)
Dan et al. [56]	Singapore	Healthcare provider	CEA	1 year	Static: Markov model	Cost based on alert policy, direct and indirect, cost of isolation, cost of treatment, cost of antiviral/day, cost of uncomplicated Influenza, cost of complicated Influenza, cost of respiratory failure with mechanical ventilation.

NCs: not clearly specified; CBA: cost-benefit analysis; CEA: cost-effectiveness analysis; CUA: a cost-utility analysis

Table 2: cost-effectiveness of the reviewed studies

Author	Intervention/ Comparator	Infectivity	Severity	ICER	Cost-Effectiveness	Parameters that affect the base-case findings most
Balicer et al., 2009 [26]	Stockpiling drug, therapeutic use to all patients/no intervention	attack rate 25%, probability of pandemic per year=3%	-	Societal (provider) 2.44 (0.33)	Societal cost saving	Not sensitive as long as the probability of pandemic is greater than one in 80 years.
Khazeni et al.,2009 [32]	Stockpile drug, and 25% reduction in contact./no intervention	Ro=1.8, 20-40% population illness rate	Clinical CFR=2.5	US$ 8,907/QALY gained	Yes	Contact rates, pre-existing immunity, age-specific mortality
Lee VJ et al.,2006 [31]	Stockpiling drug, treatment with Oseltamivir only/no intervention	CAR=30%	CFR=0.05%	CS	Yes	Changes in attack rate and case-fatality rate reduction with treatment and was sensitive to the variables of treatment and prophylaxis stockpiles.
lug'ner et al., 2009 [58]	stockpiling of antiviral oseltamivir and tamilfu/no intervention	CAR= 50%, Ro=1.73		Societal perspective: €15,000/LYG	Yes	Clinical attack rate, pandemic risk, drug efficacy
Siddiqui et al., 2008 [34]	Stockpiling drugs, Treating all symptomatic patients with antiviral drugs /no intervention	CAR= 25%	CFR=0.3%	€ 13, 668/QALY gained	Yes	The timing of the pandemic, the discount rate, and AV drug efficacy for reducing complications and hospitalisations
Sander et al., 2009 [49]	Full targeted antiviral prophylaxis (household contacts and 60% of work/school contacts), stockpile unlimited (FTAP), and closing all schools for 26 weeks /FTAP	Ro=2, CAR=50%	CFR=0.13%	US$ 48,472/QALY gained	No	The basic reproductive number and health care resource use
Perlroth et al., 2010 [36]	Adult and child social distancing, school closure, antiviral treatment and prophylaxis/ with no schools closed	Ro=2.1	CFR=1%	US$ 31,300/ QALY gained	Yes	The infectivity (Ro), case fatality rate, level of population compliance, and antiviral effectiveness
Bruce Y. Lee., 2011 [37]	Initiation of IV antiviral treatment for hospitalised patients, followed by PCR testing to determine whether the treatment should be continued/ no intervention	10% prevalence of Influenza	mortality by hospitalisation and age	US$ 39,674/QALY gained	Yes	The cost of IV antiviral agents
Lugnér et al., 2010 [33]	Treatment with AV-drugs/no intervention	CAR=38% Ro=1.73	CFR according to risk and age ($1.47*10^3$ to $3.36*10^2$)	€ 1637-1695/LYG	Yes	The proportion of cases that are treated and the age-specific clinical attack rates

D. B. C. Wu et al., 2018 [61]	Treatment of pandemic influenza with Oseltamivir 75 and 150 mg twice daily treatment/no treatment		Probability death from pneumonia in general ward=0.097, in ICU=0.5, sepsis=0.91 in GW and 0.74 in ICU; acute respiratory distress syndrome 0.998 in GW and 0.85 in ICU	CS	Yes	The proportion of inpatient presentation at the emergency visit and patients' quality of life
Hiroko Nagase et al.,2009 [29]	Oseltamivir treatment/ conventional treatment with a dose of febrifuge such as acetaminophen	60% prevalence among Influenza-like illness	-	JPY 398,571 (US$3,320) per QALY gained	Yes	The sensitivity of the rapid diagnostic test, the prevalence of the disease, the resistant virus rate, and the prevalence
Kunling Shen et al., 2016 [38]	Empiric treatment of cases of ILI with Oseltamivir (not testing)/ no treatment	probability of a child with ILI has influenza=39.5%	Probability of dying during influenza-related hospitalization=0.20%	RMB 4,438/QALY gained	Yes	Cost of Oseltamivir, probability of non-hospitalised pneumonia, and reduction in risk of pneumonia by Oseltamivir
Baguelin et al., 2010 [62]	Vaccinating low-risk groups begins on 23rd November (1-week delay)/No intervention	Prevalence of Influenza among ILI=37%		93% less than the threshold	Yes	Model assumptions, the overall size of the epidemic without vaccination, QALY loss per case, hospitalisation rates, costs, and case-fatality ratios
Doyle et al., 2006 [39]	Oseltamivir therapeutic for total population/No intervention	25% attack rate	Case fatality between 0.5% and 2% depending on age and risk group	€ 3,500/ death averted	Yes	Cost of treatment, vaccines, and consultations.
Lee BY et al., 2009 [40]	Antiviral medication use for pregnant women with contact history /no antiviral medication	20% attack rate	CFR for mothers=0.0105, preterm mortality=0.02	US$ 4,535/QALY gained	Yes	Attack rate, gestational age, and influenza-attributable preterm birth rate
Lee BY et al., 2010, [52]	Antiviral treatment of all patients presenting with ILI/no intervention	Probability of ILI being influenza=10%, (20%,30%)	CFR by age: 1.05% to 4.41%	US$ 60,028-84119, (22841-33040, 11,783-16,158)/QALY gained	No, (Yes, Yes)	Probability of preterm birth, antiviral efficacy, risk of birth defect, probability of ILI being Influenza
Sander et al., 2006	Post-exposure influenza prophylaxis with Oseltamivir/no intervention when infected.	The attack rate of 8%	Probabilities vary by complications.	£ 29,938)/QALY gained	Yes	The mechanism by which obtain a prescription for PEP (analysis C), cost-contacts access the drug, general practitioner visit
Lisa A. Prosser.,2011 [42]	Vaccination against pandemic influenza A/no vaccination	CAR=21%	Vary by age and risk status (0.134 to 61.97)/100,000	Depending on age and risk status-USD $8,000–52,000/QALY gained	Yes	Number of doses required for children, costs of vaccination, and timing of vaccine delivery

Lee VJ et al., 2009 [47]	Vaccine stockpile/no intervention	CAR=30%	CFR for high risk=137/100000	US$ 0.05 to 5.1)*10^6 per life saved	Vary according to vaccine efficacy and strain match.	Vaccine efficacy and vaccine strain matching, cost of the vaccine
Meltzer et al., 1999 [43] [43]	Vaccination for all age group/no vaccination	CAR=25%	Death rate for high risk group for age 0-19=9%, 20-64=40.9%, and 65-=34%	CS At $21 per vaccine	Yes	Risk of death, CAR, and cost of the vaccine.
Newall et al., 2010 [35]	Stockpile drug and vaccine, Antiviral treatment of those clinically infected/small stockpiles of antiviral drugs and vaccine after six months.	Ro=1.71 and CAR=31.1%	CFR =0.313%	AU$ 908/LYG	Yes	The R0 value and factors were impacting vaccine or antiviral effectiveness.
Beigi et al., 2009 [63]	Single-dose maternal influenza vaccination for mothers and neonates/no intervention	Prevalence of influenza=0.025	probability of death=0.0105	US$ 76,835/QALY gained	No	Influenza prevalence and severity of illness
Khazeni et al., 2009 [45]	Vaccinating 40% of the population early at the beginning of pandemic/no intervention	Ro=1.5	CFR=0.1%	CS	Yes	contact rate and vaccine efficacy
Beate Sander et al., 2010 [60]	Mass immunisation program/no intervention	clinical attack rate vary by vaccination status, vaccine effectiveness, vaccine time =0.17 to 0.4	CFR=0.01to 0.02 according to age for those I hospitalisation	Canadian $ 14,912/QALY gained.	Yes	Timing of mass vaccination program, vaccine administration cost, QALY gain
Jaime L Rubin et al., 2010 [46]	vaccination with PCV7 during influenza pandemic/ no vaccination	13/100 and 30/100 incidence rate	CFR vary by age and type of pneumococcal disease = 0 to 0.27.	CS	Yes	The incidence and case-fatality rates of bacteremic pneumonia and all-cause pneumonia and vaccine effectiveness.
Praveen Dhankhar al., 2010 [28]	Stockpiling 23-Valent Pneumococcal Polysaccharide vaccine, for 1957/68 type pandemic/ no intervention	20% attack rate	CFR=0.028	US$ 39,946/QALY gained	Yes	Probability of death rate, vaccine effectiveness, Proportion of secondary pneumococcal pneumonia cases, reduction of Attack rate
Nicholas Risko et al.,2020 [54]	Protecting health workers from COVID-19: PPE/no intervention	HCW infection as a percent of total infection=9.6%	CFR=1.38%	US$ 4,448 per HCW life saved	-	-
Mukerji et al., [53]	Protecting health workers from Influenza: N95/face mask	CAR=4.6%	-	US$ 490-$1230/infection prevented	-	The CRI attack rate and intervention effectiveness

Wong et al., 2016 [48]	Individual based School closure/system based school closure	attack rate=0.8%	prob. death for children, adult and old ages (10^4):0.15,1.2, 2.65	US$1,145 per cases prevented	Yes	Robust: not sensitive
Boyd, M., et al., 2018 [57]	Border closure /no intervention	-	-	societal(provider)$14,400 per QALY gained(51,300)	Yes	The number of deaths assumed, the value put on lost productivity (100% vs 25% of wages and tax revenue), and the value of a monetised QALY (in the CBA)
Savitsky et al., 2020 [55]	PPE for planned cesarean delivery/Universal screening	probability of covid-19=0.36%	-	cost saving	Yes	Chosen willingness to pay to prevent one COVID-19 infection in an HCW
Krishna P. Reddy et al., 2020 [50]	healthcare testing and contact tracing/Healthcare testing	Ro=1.5, infection prevalence=0.1	-	USD 220/LYG	Yes	Ro, efficacies of contact tracing, isolation centres, and Mass screening to detect infections; the cost of isolation of cases and quarantine of centres
Paltiel et al., 2020 [30]	weekly test, test sensitivity 80%/weekly test, test sensitivity 70%	Rt 2.5, 5 exogenous shock infections each week)	CFR=0.05%	USD 200/ infection averted	Yes	NC
Anne M. et al 2020., [51]	self-screen/ PCR-any-symptom	Effective Re=2.0	-	dominated	No	Varying rates of presentation to hospital care and ICU survival, input parameters on infections and deaths
Brown et al., 2011 [25]	School closure for 8 weeks/no intervention	Ro=1.2	CFR=0.01% to 0.04% (vary by age)	USD 14,185/ cases averted	No	Case fatality rate
Dan et al. [56]	Protection measures targeting only infected patients/no intervention	Secondary attack rate: 30% Spanish Influenza 10% SARS	Case fatality rate: Spanish influenza: 5%, SARS: 10%, Pandemic (H1N1) 2009: 4%	USD 23,644/Death averted	Yes	Case-fatality rate, patient exposure rate, and secondary attack rate

CFR: case fatality rate; CAR: clinical attack rate; BCA: cost-benefit analysis; ICER: incremental cost-effectiveness ratio; CS: cost-saving; Ro: basic reproductive number; ILI: Influenza-like illness; SARS: severe acute respiratory syndrome

Figures

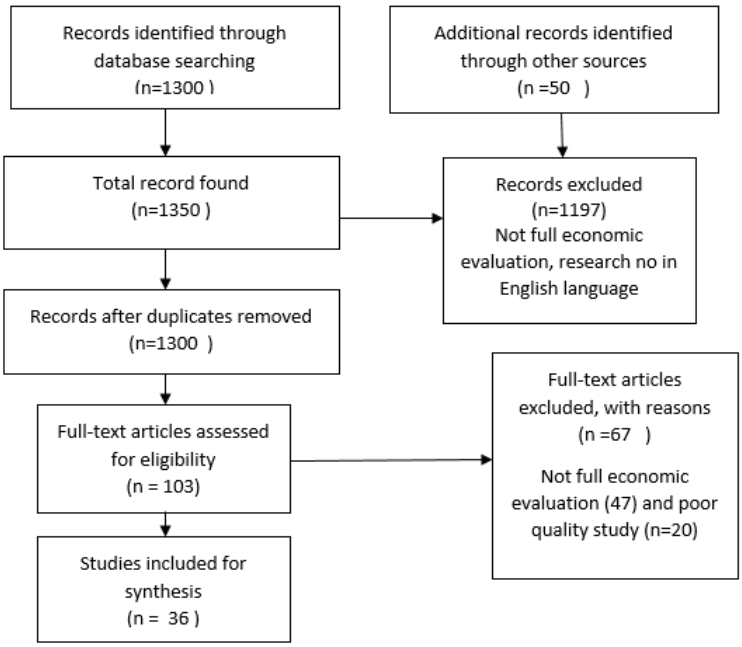

Figure 1

Review flowchart

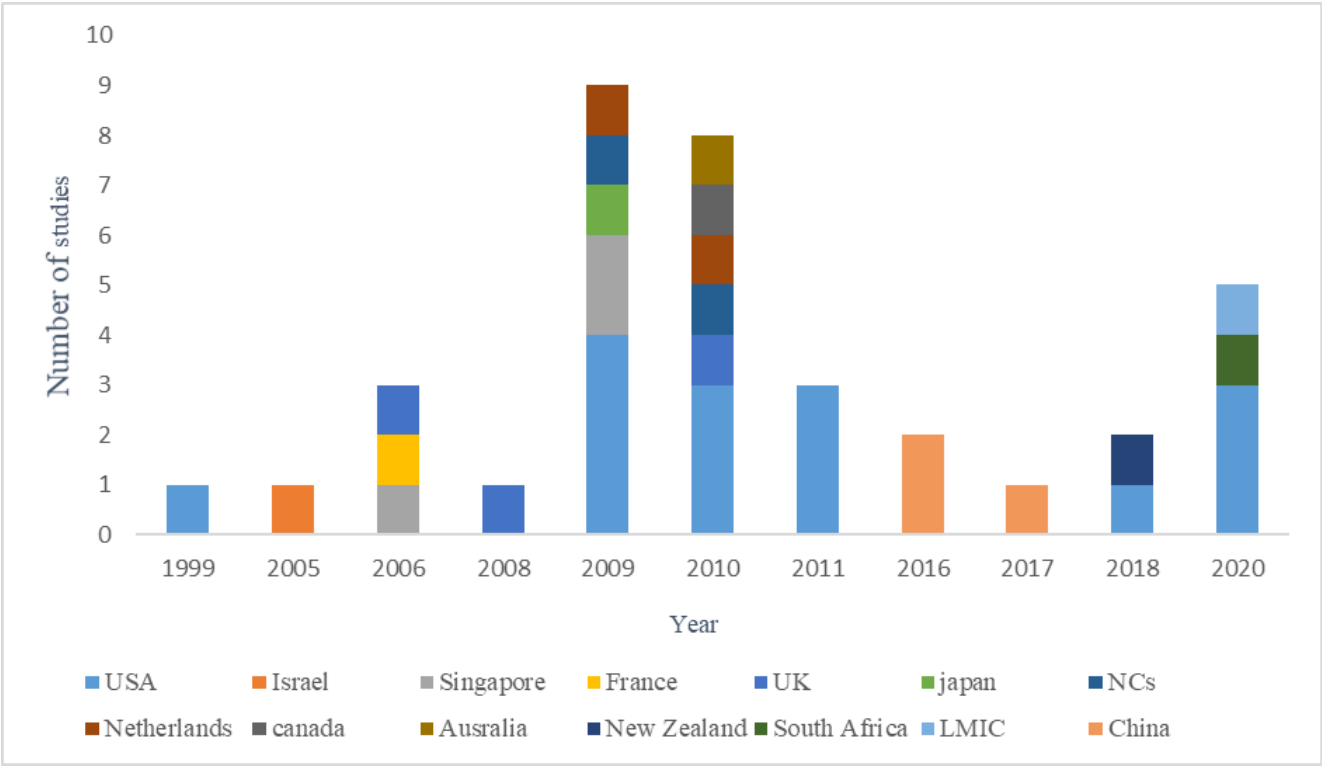

Figure 2

Number of studies and settings by year

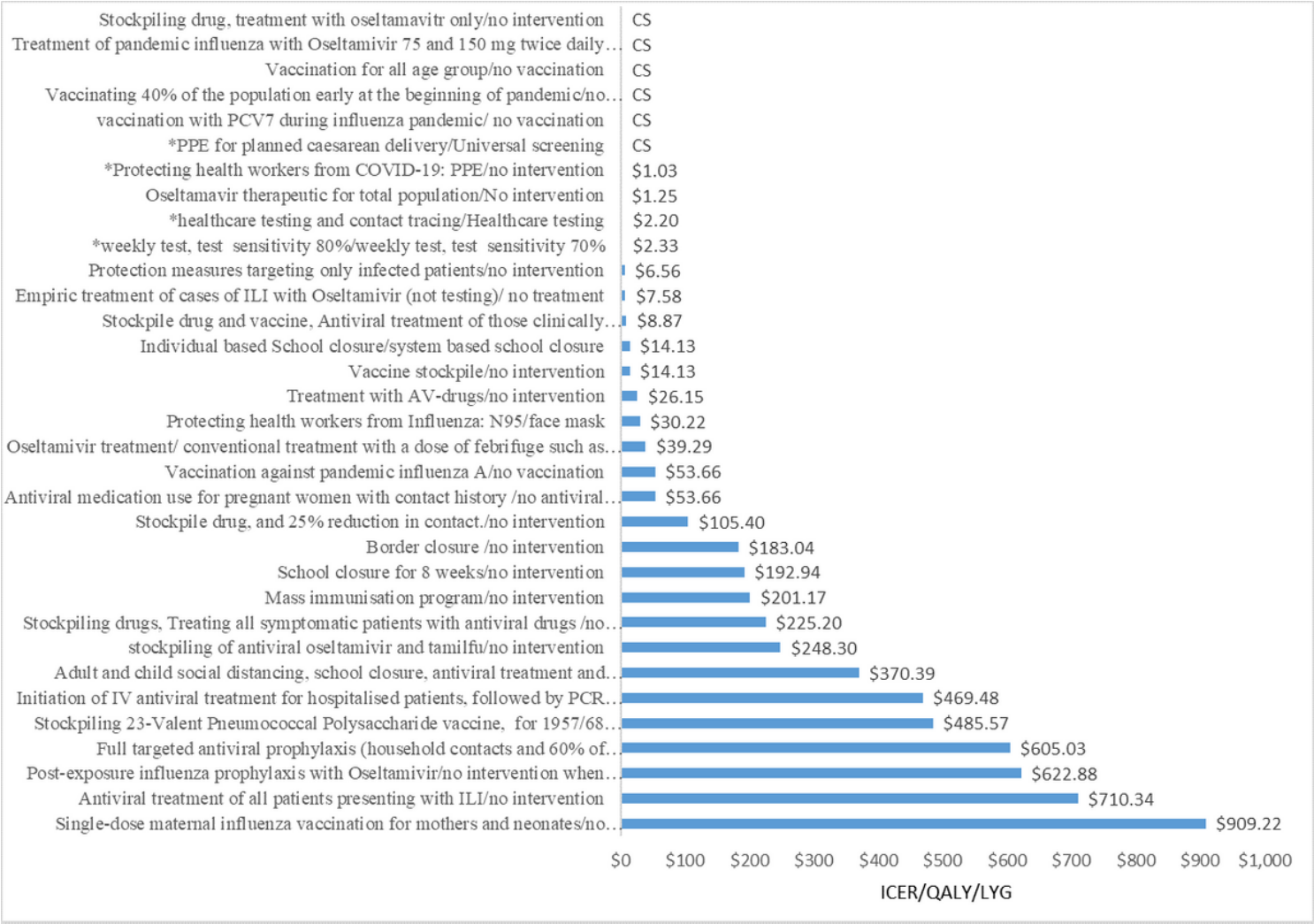

Figure 3

ICER of the interventions in (US$ 100 per QALY/LYG) in 2019; *studies conducted in 2020.

Supplementary Files

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- supplementaryfile1.doc
- supplementaryfile2.docx