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Systematic Literature Review

Model Comparisons of the Effectiveness and Cost-Effectiveness of Vaccination: A Systematic Review of the Literature

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ABSTRACT

Objectives: To describe all published articles that have conducted comparisons of model-based effectiveness and cost-effectiveness results in the field of vaccination. Specific objectives were to 1) describe the methodologies used and 2) identify the strengths and limitations of the studies. **Methods:** We systematically searched MEDLINE and Embase databases for studies that compared predictions of effectiveness and cost-effectiveness of vaccination of two or more mathematical models. We categorized studies into two groups on the basis of their data source for comparison (previously published results or new simulation results) and performed a qualitative synthesis of study conclusions. **Results:** We identified 115 eligible articles (only 5% generated new simulations from the reviewed models) examining the effectiveness and cost-effectiveness of vaccination against 14 pathogens (69% of studies examined human papillomavirus, influenza, and/or pneumococcal vaccines). The goal of most of studies was to summarize evidence for vaccination policy decisions, and cost-effectiveness was the most frequent outcome examined. Only 33%, 25%, and 3% of studies followed a systematic approach to identify eligible studies, assessed the quality of studies, and performed a quantitative synthesis of results, respectively. A greater proportion of model comparisons using published studies followed a systematic approach to identify eligible studies and to assess their quality, whereas more studies using new simulations performed quantitative synthesis of results and identified drivers of model conclusions. Most comparative modeling studies concluded that vaccination was cost-effective. **Conclusions:** Given the variability in methods used to conduct/report comparative modeling studies, guidelines are required to enhance their quality and transparency and to provide better tools for decision making.

Keywords: comparative modeling studies, effectiveness and cost-effectiveness, infectious diseases, systematic review of the literature, vaccination.

Introduction

Over the past 20 years, there has been a steep rise in the development of mathematical models predicting the effectiveness and cost-effectiveness of vaccination to help inform policy decisions [1]. Several elements have contributed to this rise. First, despite a considerable decrease in the burden of infectious diseases over the past decades, infectious diseases still account for 11.5% of all deaths worldwide (>6,000,000 deaths in 2012) [2]. The prevention/control of infectious diseases remains an important public health priority due to this burden, combined with pandemics and frequent outbreaks of emerging diseases. Second, advances in medicine have contributed to the development of new vaccines to prevent/control infectious diseases. Vaccination is potentially one of the most effective interventions at the population level and has historically been shown to be cost-effective [3–5]. Nevertheless, the higher price of recent vaccines has prompted a deeper examination of the effectiveness and cost-effectiveness of different vaccination strategies by decision makers [6]. Major funders and decision makers of vaccination programs such as Gavi The Vaccine Alliance, the Bill & Melinda Gates Foundation, the World Health Organization Strategic Advisory Group of Experts, as well as national immunization technical advisory groups in many countries such as the United Kingdom and the United States now require evidence of public health and economic impact at the population level before supporting vaccine introduction [7–12].

Mathematical models provide a formal framework to examine the effectiveness and cost-effectiveness of different interventions and to identify those that maximize health in the context of

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limited budgets [6]. Such models translate information from randomized clinical trials (i.e., vaccine efficacy at the individual level calculated over a short period of follow-up) into long-term predictions of the population-level effectiveness and cost-effectiveness of vaccination. They, however, require many simplifications and assumptions related to the model design, which may lead to variability in model predictions and uncertainty for decision makers [6,13]. There are several recent and ongoing efforts to standardize mathematical modeling studies [14,15]. Nevertheless, the increasing demand for these types of mathematical models still exceeds available expertise and the quality of models varies considerably, particularly in the prevention/control of infectious diseases [6].

Given the rise in the number of modeling studies and uncertainty, reviews or comparative modeling studies are increasingly being used to synthesize, compare, and/or understand different models' predictions of the effectiveness and cost-effectiveness of an intervention so as to assess model-based evidence for policy making. More specifically, these comparative modeling studies are undertaken to 1) describe the models that have been used to examine a policy question; 2) better understand the impact of model inputs, assumptions, and parameters on predictions; 3) characterize the robustness/variability of different model predictions to assess their suitability for policy recommendations; and/or 4) synthesize conclusions from several models to inform policy recommendations. Although several recognized guidelines are available for systematic reviews of epidemiological studies or randomized controlled trials (e.g., Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE)) [16,17], there are no such guidelines for reviews or comparative modeling studies. Consequently, comparative modeling studies vary greatly in the methodology used and the reporting of methods/results.

The aim of this systematic review was to identify and describe all published articles that have conducted comparisons of model-based effectiveness and cost-effectiveness results in the field of vaccination. Specific objectives are to 1) describe the different methodologies used and 2) identify the strengths and limitations of the comparative modeling studies identified.

Methods

Search Strategy and Selection Criteria

We systematically reviewed the global literature and reported it in accordance with the PRISMA guidelines [16]. Studies were eligible for inclusion if they fulfilled the following criteria: 1) they compared or reported the results of more than one mathematical model, 2) the intervention modeled was vaccination, and 3) the outcome was the population-level effectiveness or cost-effectiveness/cost-benefit of vaccination. We searched the MEDLINE and Embase databases in May 2016, with no restriction on the publication date or language of the publication. We used a combination of the following Medical Subject Heading terms, title, or abstract words: ("immunization programs," "immunization," "vaccination," "vaccine") and ("infection," "infectious disease," "communicable disease," "bacterial infections and mycoses," "parasitic diseases," "virus diseases") and ("mathematical model," "statistical model," "theoretical model," "nonlinear dynamics," "immunological models," "disease simulation," "computer simulation," "computer model," "cost-benefit analysis," "cost-effectiveness," "risk-benefit analysis") and ("comparison," "review," reviewed"). The exact searches for PubMed and Embase are presented in Appendix Table S1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.03.014. We identified eligible studies by reviewing titles and abstracts, and we also searched the reference lists of eligible articles. Two reviewers independently assessed the eligibility of all studies. Any discrepancy between the two investigators was resolved by discussion.

Data Extraction

Two reviewers used a standardized form (see Appendix Table S2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.03.014) to independently extract the characteristics of the comparative modeling studies. Studies were first categorized into two groups on the basis of their source of data for comparison: 1) comparisons that were based purely on results available in published articles (previously published results only) and 2) comparisons that were based on generating new simulations from the model reviewed that were not previously available in the published literature (results from new simulations). Then, the following characteristics were extracted: journal and year of publication, countries of the models included in each study, funding source, main objective (to describe model characteristics and parameter, to summarize/provide predictions and variability around prediction, or to understand variability in predictions), pathogen and vaccination strategy examined, procedure used for study identification (systematic review, nonsystematic review, or convenience sample), number of models included, presence and description of quality assessment of the studies/models included, main outcome used for comparison (effectiveness, cost-effectiveness/cost-benefit, or both), type of results synthesis (qualitative or quantitative), and main conclusions of the comparative modeling studies stated by the authors. See Appendix Table S2 in Supplemental Materials for more details on the standardized form used to extract the characteristics of the comparative modeling studies.

Data Synthesis

We conducted a qualitative synthesis of the published literature. Given the great variability in comparative modeling studies and our main objective to describe all published articles that have conducted comparisons of model-based effectiveness and cost-effectiveness/cost-benefit results, statistical heterogeneity analysis and pooling of data were not relevant. In addition, we decided a priori to stratify the presentation of results according to the type of results included in the comparative modeling study (previously published results only or results from new simulations). These two approaches are very different and our aim was to describe and compare their main strengths and limitations.

Results

In our search, we identified 1860 potentially relevant articles, of which 115 met the inclusion criteria (Fig. 1). Most of the comparative modeling studies (n = 109) presented a synthesis of previously published results, whereas only six studies presented the results obtained from new simulations performed specifically for the purposes of the comparative study. As illustrated in Figure 2A, there was a steep rise in the publication of comparative modeling studies since 2006. This rise is mostly attributable to the publication of comparative modeling studies of human papillomavirus (HPV) and influenza vaccination. The six comparative modeling studies using new simulations were published between 2010 and 2016 (Fig. 2B).

The main characteristics of the eligible comparative modeling studies are presented in Table 1. Although some studies were

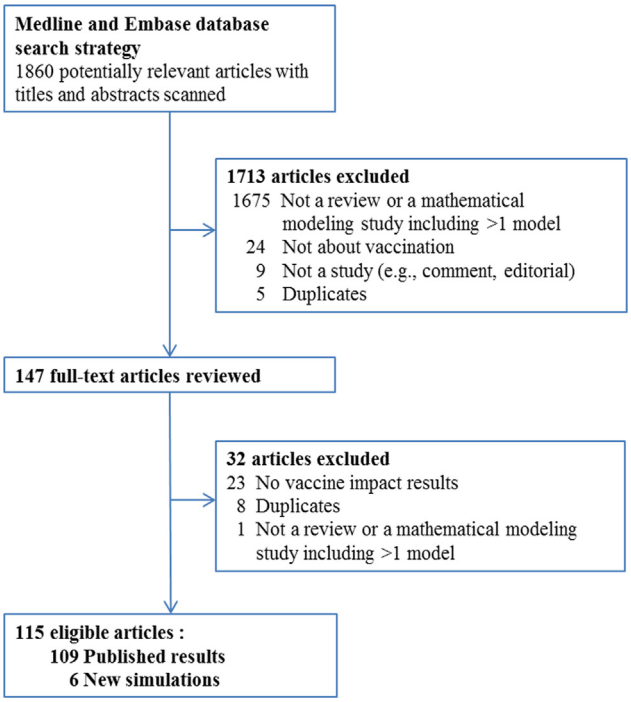

Fig. 1 – Study selection.

restricted to either high-income countries (HICs) or low- and middle-income countries (LMICs) only, 29% (32 of 109) of studies using published results and 50% (3 of 6) of studies using new simulations presented model outcomes representative of both country income groups [18]. Most of the studies were undertaken with the overall objective of summarizing existing evidence and providing predictions for decision makers (93% [101 of 109] published results/83% [5 of 6] new simulations). Of note, 67% (4 of 6) of comparative modeling studies using new simulations also aimed at describing model predictions/characteristics and understanding variability in predictions. Cost effectiveness/cost-benefit was the most frequently examined outcome (83% [91 of 109] published results/67% [4 of 6] new simulations). A quantitative synthesis of results was performed by only 1% (1 of 109) of studies using previously published results and 33% (2 of 6) of studies using new simulations. HPV, influenza, and pneumococcus were the three most frequently examined pathogens (69% [75 of 109] published results/50% [3 of 6] new simulations) and routine childhood vaccination was the vaccination strategy most frequently examined (55% [60 of 109] published results/67% [4 of 6] new simulations). Although several guidelines [16,17] recommend the use of a systematic approach to identify all potentially eligible studies and the assessment of the quality of studies, very few of the comparative modeling studies followed these recommendations. Only 35% (38 of 109) of studies using previously published results used a systematic approach to identify eligible articles and 26% (29 of 109) assessed the quality of studies, whereas none of the studies using new simulations followed these recommendations. When the quality of studies included in the comparative modeling study was assessed, the tool most frequently used was the Drummond checklist for assessing economic evaluations or an adaptation of this checklist (11 of 29 studies) [19–21]. Other tools used included the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [22] checklist and the Consensus on Health Economic Criteria list (CHEC-list) [23] (see Appendix Table S3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.03.014). These tools may have been less frequently used because the Drummond checklist was published in 1997, several years before the other tools.

The main conclusions of model comparisons are presented in Table 2 (see Appendix Table S4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.03.014). Of note, the conclusions presented in Table 2 and in Appendix Table S4 in Supplemental Materials represent the interpretation of the authors who conducted the comparative modeling studies and are rarely based on a quantitative pooled estimate of effectiveness or cost-effectiveness/cost-benefit. For all pathogens (except dengue), the comparative modeling studies identified at least one vaccination strategy that would be cost-effective. The main factor driving cost-effectiveness is identifying an optimal target population for vaccination: either age group, sex, disease-specific risk group, and/or region of the world. For example, the comparative modeling studies report that HPV vaccination is cost-effective for girls in HICs and LMICs. Nevertheless, HPV vaccination is not cost-effective for boys in countries with high vaccination coverage among girls. Comparative modeling studies find that influenza vaccination is cost-effective for elderly and high-risk groups in HICs, but results vary for working adults and children in HICs.

The modeling assumptions with the greatest impact on cost-effectiveness of vaccination identified by comparative modeling studies are natural history of diseases, herd effects, and duration of vaccine protection. For example, the duration of protection of the herpes zoster vaccine is a key driver of cost-effectiveness

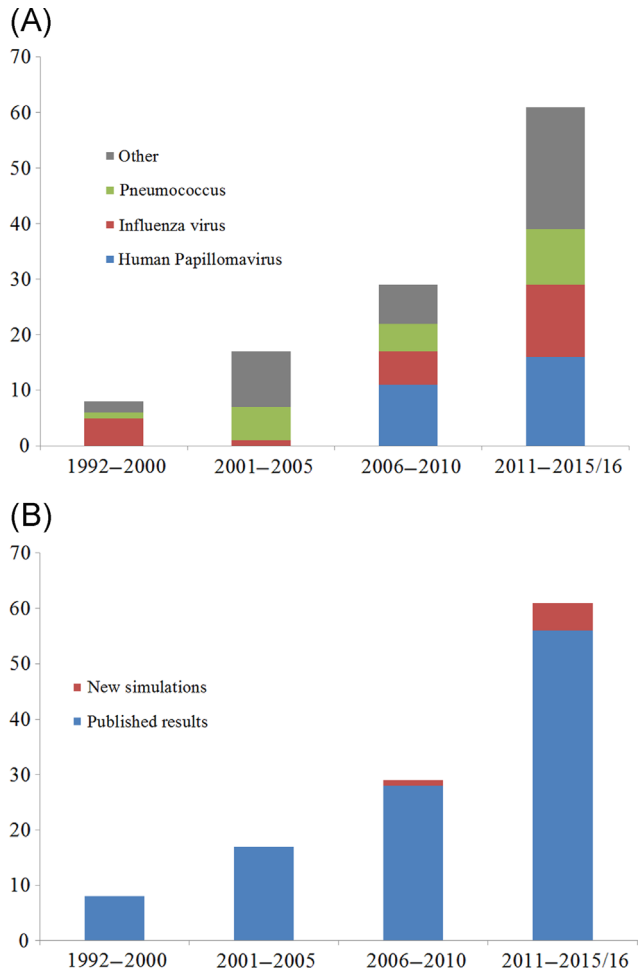

Fig. 2 – Number of comparative modeling studies over time according to (A) the pathogen examined and (B) the type of results presented.

Table 1 – Summary of characteristics of the 115 independent reviews included.

Characteristic	Published results (n = 109)		New simulations (n = 6)	
	% (n)	References	% (n)	References
		General information		
Publication date				
1992–2000	7% (8)	[26–33]	0% (0)	
2001–2005	16% (17)	[34–50]	0% (0)	
2006–2010	26% (28)	[51–78]	17% (1)	[135]
2011–2015/2016	51% (56)	[79–134]	83% (5)	[25,136–139]
Country				
HIC and LMIC	29% (32)	[27–29,34,37,43,47,49,53,57,65,66,70,71,75,79,81,85,86,91,93–99,106,112,116,125,131]	50% (3)	[135,136,138]
HIC only	58% (63)	[26,30–33,35,36,38–42,44–46,48,50–52,54–56,58–64,67,69,72–74,77,78,80,84,87–90,92,100,102–104,108–110,113,115,117–121,123,124,128,129,132,133]	17% (1)	[139]
LMIC only	12% (13)	[68,76,82,83,101,105,107,114,122,126,127,130,134]	33% (2)	[25,137]
Missing	1% (1)	[111]	0% (0)	
		Objectives		
Objectives of model comparison				
Describe model characteristics/parameters	39% (42)	[42,44,45,50,52,54–59,62,64,66–68,74,75,77,78,80,86,88,90,91,94,95,98,103,104,106,108,111,113,115,117,120,124,126,127,129,130]	67% (4)	[135–138]
Summarize/provide predictions and variability	93% (101)	[26–49,51–57,59–74,76–85,87–93,95–110,112–126,128,130–134]	83% (5)	[25,135,137–139]
Understand variability in predictions	16% (17)	[45,52,56,57,59,66,67,74,77,78,80,88,90,95,98,103,125]	67% (4)	[135–138]
		Intervention		
Pathogen examined				
Human papillomavirus	25% (27)	[52,54,56,58,60,61,67,69,72,77,78,80,84,89,96,100,101,103,114–116,121,126–128,133]	33% (2)	[137,139]
Influenza virus	23% (25)	[26,28,31–33,38,51,53,61,65,70,73,81,85,87,88,91,93,94,100,102,105,106,126,133]	0% (0)	
Pneumococcus	21% (23)	[30,35,36,40,43,45,48,55,59,62,74,79,83,86,102,111,120,124,126,127,131–133]	17% (1)	[135]
Varicella zoster virus (varicella vaccination)	9% (10)	[36,42,64,75,100,102,109,123,129,133]	0% (0)	
Hepatitis B virus	9% (10)	[27,29,34,61,76,100,102,104,126,133]	0% (0)	
Rotavirus	9% (10)	[49,66,82,83,98,100,125–127,133]	17% (1)	[138]
Hepatitis A virus	7% (8)	[36,39,41,57,61,100,107,126]	0% (0)	
Varicella zoster virus (herpes zoster vaccination)	6% (6)	[71,108,113,117,118,123]	0% (0)	
Bordetella pertussis	6% (7)	[46,61,63,90,92,95,119]	0% (0)	
Neisseria meningitidis	6% (6)	[44,47,50,61,100,133]	0% (0)	
Measles and rubella viruses	5% (5)	[37,99,100,110,127]	17% (1)	[136]
Dengue virus	2% (2)	[122,134]	0% (0)	
Haemophilus influenza serotype B	1% (1)	[68]	0% (0)	
Typhoid	1% (1)	[130]	0% (0)	
Other	5% (5)	[97,100,112,126,127]	17% (1)	[25]
Vaccination strategy				
Routine childhood	55% (60)	[27,29,34–37,39,41–47,49,50,55,57,59,61,62,64–66,68,70,75,76,79,81–83,86,91,93,94,97–100,102,104–107,109,110,112,120,122,123,125–127,129–134]	67% (4)	[25,135,136,138]
Routine adolescents	43% (47)	[27,29,34,35,37,39,41,42,44,46,52,54,56–58,60,61,67,69,72,76,77,80,84,89,93,94,96,99–106,109,110,112,114–116,119,121,126–128]	17% (1)	[137]
Routine adults	31% (34)	[27,29,32,34,35,38,39,44,46,48,57,70,71,74,76,87,88,92–94,99,100,102,104–106,111,112,119,120,123,124,127,134]	0% (0)	
Routine elderly	31% (34)	[26–28,30,31,33–35,39,40,43,46,48,53,57,70,71,73,76,85,93,94,100,102,104–106,108,112,113,117,118,124,127]	0% (0)	
Targeted high-risk groups (other than age)	31% (34)	[27,29,34,35,37,39,41–43,46,48,51,57,64,76,85,93,94,97,99,100,102,104–107,110,112,119,122,126,127,130,134]	0% (0)	
Other	6% (7)	[44,47,50,63,78,90,95]	17% (1)	[139]
		Methods of the comparative studies		
Search strategy/study identification				
Review	100% (109)		33% (2)	
Systematic	35% (38)	[30,51,57,61,63,68,71,72,74,76,77,79,83,86,93,94,96,99–102,104,105,108–110,114,115,117–123,126,132,133]	0% (0)	
Nonsystematic	65% (71)	[26–29,31–50,52–56,58–60,62,64–67,69,70,73,75,78,80–82,84,85,87–92,95,97,98,103,106,107,111–113,116,124,125,127–131,134]	33% (2)	[137,138]
Convenience sample	0% (0)		67% (4)	[25,135,136,139]
Number of modeling studies included				
2–10	28% (30)	[29,31–33,36,40,44,47,49,52,56,58,71,73,78,87,88,92,103–105,107,111,114,120,122,124,128,130,134]	100% (6)	[25,135–139]
11–20	39% (42)	[35,38,41–43,45,46,50,51,53–55,59,62,63,65–70,74,76,77,80–82,85,86,89–91,95,97,108,110,113,115,117,118,121,129]	0% (0)	
>21	29% (32)	[27,34,37,48,57,60,61,64,72,75,79,84,93,94,96,98–102,106,109,112,116,119,123,125–127,131–133]	0% (0)	
Missing	5% (5)	[26,28,30,39,83]	0% (0)	
Quality assessment of studies				
No	62% (68)	[27,29,31–39,41,42,44–48,50–56,58–62,64–67,70,73,75–78,80–82,84,86–92,94,95,97,98,101,102,105,106,112,113,116,120,124,128,131,132,134]	83% (5)	[25,136–139]
Yes	26% (29)	[43,49,57,63,68,69,72,74,79,85,93,96,99,100,103,104,107–109,114,117,119,121–123,126,127,130,133]	0% (0)	
Missing	11% (12)	[26,28,30,40,71,83,110,111,115,118,125,129]	17% (1)	[135]
Main outcome used for comparison				
Effectiveness	0% (0)		17% (1)	[136]
Cost-effectiveness/cost-benefit	83% (91)	[26,27,29,32–37,39–51,56–62,64–68,70,71,73–85,87–93,95–109,111–118,120–129,131,133]	67% (4)	[135,137–139]
Effectiveness and cost effectiveness/cost-benefit	16% (17)	[28,30,31,38,52–55,63,69,72,86,110,119,130,132,134]	17% (1)	[25]
Other	1% (1)	[94]	0% (0)	
Synthesis of results				
Quantitative	1% (1)	[133]	33% (2)	[25,135]
Qualitative	99% (108)	[26–132,134]	67% (4)	[136–139]

Table 2 – Summary of the conclusions of model comparisons.

Pathogen	Number of comparison studies	Mean number of modeling studies included	Main conclusions (as presented by authors of comparative modeling studies)
Human papillomavirus	27	16	• Cost-effective for girls (HICs and LMICs) • Not cost-effective for boys with high coverage among girls (HICs) • Variable cost-effectiveness results for boys with low coverage among girls (<40%–50%)
Influenza virus	25	16	• Cost-effective for elderly and targeted high-risk groups other than age in HICs (e.g., health care workers) • Variable cost-effectiveness results for working adults and children in HICs (generally cost-effective when taking into account work loss) • Lack of quality studies for MICs and no evidence for LICs (two reviews) • Methodology, perspective of analysis, model assumptions, and study quality vary greatly
Pneumococcus	23	16	• Variable cost-effectiveness results for children in HICs and LMICs (requires herd effects and limited serotype replacement to be cost-effective), but two reviews concluded that the vaccine was cost-effective in LMICs • Cost-effective in elderly in HICs • Variable cost-effectiveness results for adults and high-risk groups (one review)
Varicella zoster virus (varicella vaccination)	10	17	• Cost-effective in HICs (and may be cost-saving) if potential impact on herpes zoster is ignored • Not cost-effective in HICs (possible QALY losses) if herpes zoster shows large increases • Cost-effective for health care workers
Hepatitis B virus	10	14	• Cost-effective in areas of low to high endemicity • Variable cost-effectiveness results for routine vaccination in countries with very low endemicity • Targeted strategies are cost-effective in areas with very low endemicity (one review)
Rotavirus	10	24	• Cost-effective in LMICs • Variable cost-effectiveness results in HICs (requires herd effects and lower price to be cost-effective)
Varicella zoster virus (herpes zoster vaccination)	6	12	• Cost-effective in elderly for specific age groups in HICs (variable age groups provided: 60–75, 65–75, and >70-y- olds) (duration of protection is a key parameter)
Bordetella pertussis	7	14	• Cost-effective in children in HICs • Variable cost-effectiveness results for booster doses and vaccination of adolescents and adults in HICs (depends on herd immunity)
Hepatitis A virus	8	19	• Cost-effective in areas of low to high endemicity • Variable cost-effectiveness results for routine vaccination in countries with very low endemicity • Targeted strategies are cost-effective in areas with very low endemicity (one review)
Neisseria meningitidis	6	10	• Variable cost-effectiveness results for meningococcal group C vaccines in HICs (cost-effective if herd effects or high prevalence) • Vaccines cost-effective in the meningococcal belt in Africa (one review) • Conflicting results for mass vaccination during outbreaks
Measles and rubella viruses	5	18	• Cost-effective for both vaccines • More analyses for LMICs are required (one review)
Dengue virus	2	9	• Results not sufficient to support country-level decisions • More research required

HIC, high-income country; LIC, low-income country; LMIC, low- and middle-income country; MIC, middle-income country; QALY, quality-adjusted life-year.

results. Many comparative modeling studies concluded that supplementary work was required to have a clear picture of the cost-effectiveness of vaccination, particularly for LICs (e.g., influenza, dengue, measles, and rubella), given remaining uncertainties in assumptions or limited number of studies. Finally, HPV, influenza, and pneumococcal vaccines have been the objects of more comparative modeling studies in HICs than the actual number of mathematical models. We identified 27, 25, and 23 comparative modeling studies of HPV, influenza, and pneumococcal vaccination, respectively, and for each of these pathogens, there is a mean of 16 mathematical modeling studies included in the comparative modeling studies (Table 2).

Discussion

Our systematic review indicates that 95% of comparative modeling studies performed in the field of vaccination were based on previously published results without incorporating new harmonized assumptions to increase comparability of the models. These comparative modeling studies used a combination of systematic and nonsystematic approaches to identify eligible studies. The main outcome examined was the cost-effectiveness/cost-benefit of vaccination, and a qualitative synthesis of results was most often presented. The remaining 5% of comparative modeling studies identified were based on results from new simulations. These studies used a nonsystematic approach to identify eligible studies (mostly convenience samples); effectiveness and cost-effectiveness/cost-benefit of vaccination were both examined, and qualitative and quantitative synthesis of results were presented. Comparative modeling studies made it possible to identify cost-effective vaccination strategies for 13 of the 14 pathogens examined.

Most comparative modeling studies in the field of vaccination were based on previously published results of cost-effectiveness. This type of comparative modeling study has several advantages. First, it is relatively inexpensive and easy to conduct. Second, the main outcome examined, that is, cost-effectiveness, is a measure that is easy to identify and compare between studies. Third, it is possible to use a systematic approach to identify eligible studies, which minimizes potential reviewer selection biases. Nevertheless, this type of comparative modeling study also has important limitations. First, a quantitative synthesis of results (e.g., meta-analysis, pooling of results, and meta-regression) is likely to be misleading because of the different vaccination strategies examined or outcomes/outputs. Furthermore, because it is not possible to examine in detail and understand the impact of different model parameters and assumptions, these comparative modeling studies lead to very broad conclusions. For example, comparative modeling studies of model-based estimates of the effectiveness and cost-effectiveness of pneumococcal vaccination reported that cost-effectiveness results were variable for vaccination of children in HICs as well as adults and high-risk groups in all countries (the only consistently cost-effective strategy was vaccination of elderly in HICs). These reviews highlighted that results from different studies likely depended on a number of assumptions and methodological choices (e.g., including existence of herd effects, costs considered, and vaccine efficacy), without specifically teasing out the specific driving factors for the variability in conclusions.

Very few comparative modeling studies identified in our systematic review were performed with new simulations, even though this type of study has several strengths. First, because these comparative modeling studies use standardized vaccination scenarios and outcomes/outputs, it is easier to perform quantitative analyses and examine the impact of different model parameters and/or structural assumptions. Such model comparisons can also illustrate and examine parameter and structural uncertainty. Averaging over model with different structural assumptions has been proposed as one way to capture this aspect of uncertainty [24]. For example, Brisson et al. [140], with a group of 30 co-authors, recently conducted a comparative modeling study on the population-level impact of girls-only HPV vaccination combining data from 16 independent models. By requesting standardized outputs for prespecified vaccination scenarios, it was possible to conclude that HPV models were generally consistent in their predictions of the direct and herd effects of girls-only vaccination, even though models differed in structure, settings, and data used for calibration. Furthermore, by collecting detailed information on the models' characteristics, it was possible to perform a meta-regression, which identified three main sources of heterogeneity between model predictions: the predicted impact of HPV vaccination was higher when models did not include risk groups for sexual activity, assumed lower natural immunity among women, and/or included the natural history of cervical cancer. Another example is the comparative modeling study by Penny et al. [25]. The authors performed harmonized comparisons of the effectiveness and cost-effectiveness of the RTS,S/AS01 malaria vaccine using four different models. Although there were differences in the four models, they reached consensus about the predicted effectiveness and cost-effectiveness of vaccination in children aged 6 to 9 months. Furthermore, this work made it possible to understand the impact of the main differences between the models (e.g., baseline parasite prevalence, assumptions about rates of immune acquisition, and immunity). Nevertheless, comparative modeling studies using new simulations also have limitations. Most of these comparative modeling studies used a nonsystematic procedure to identify studies and are consequently more likely to be affected by reviewer selection bias. In addition, comparative modeling studies with new simulations are time-consuming, costly, require the collaboration of many modeling teams, and usually require funding for the extra simulations to be conducted. Finally, it is important to keep in mind that comparative modeling studies, with or without the use of new simulations, are strongly dependent on the quality of the models included. In this regard, there are several recent and ongoing efforts to standardize mathematical modeling studies [14,15] to increase their quality and comparability. Adherence to these mathematical modeling guidelines represents a first step toward providing better tools for decision making. Comparative modeling can then be used to help examine whether lack of quality of some models may have affected their results/conclusions in comparison with higher quality models (i.e., those with greater fidelity to guidelines). In addition, even though mathematical modeling guidelines can help ensure comparability between models, there are still structural assumptions in the models that cannot be standardized because they represent uncertainly about the underlying features of the disease/intervention and the best way to represent them mathematically. Hence, adequate comparative modeling, conducted according to standardized guidelines, can help explore the impact of these assumptions.

Conclusions

To our knowledge, this is the first systematic review to identify and examine comparative modeling studies of the effectiveness and cost-effectiveness of vaccination. We identified 115 different comparative modeling studies examining the effectiveness and cost-effectiveness of vaccination against 14 pathogens. Our results show a steep rise in comparative modeling studies examining the effectiveness and cost-effectiveness of vaccination, which is in line with the exponential rise in original

modeling studies and the demand for such analyses to help policy decisions. Nevertheless, contrary to other methods of data synthesis, such as systematic reviews and meta-analysis of empirical studies, there are no clear guidelines of how to conduct comparative modeling studies. Guidelines are thus required for comparative modeling studies to enhance their quality and transparency and to ultimately provide better tools for decision making.

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Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2018.03.014.

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