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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.

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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 limited budgets [6]. Such models translate information from randomized clinical trials (i.e., vaccine efficacy at the individual

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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 restricted to either high-income countries (HICs) or low- and middle-income countries (LMICs) only, 29% (32 of 109) of studies

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