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Review

Influenza cost and cost-effectiveness studies globally – A review

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ABSTRACT

Every year, approximately 10–20% of the world's population is infected with influenza viruses, resulting in a significant number of outpatient and hospital visits and substantial economic burden both on health care systems and society. With recently updated WHO recommendations on influenza vaccination and broadening vaccine production, policy makers in middle- and low-income countries will need data on the cost of influenza disease and the cost effectiveness of vaccination. We reviewed the published literature to summarize estimates of cost and cost-effectiveness of influenza vaccination. We searched PUBMED (MEDLINE), EMBASE, WEB of KNOWLEDGE, and IGOOGLE using the key words 'influenza', 'economic cost', 'cost effectiveness', and 'economic burden'. We identified 140 studies which estimated either cost associated with seasonal influenza or cost effectiveness/cost-benefit of influenza vaccination. 118 of these studies were conducted in World Bank-defined high income, 22 in upper-middle income, and no studies in low and lower-middle income countries.

The per capita cost of a case of influenza illness ranged from \$30 to \$64. 22 studies reported that influenza vaccination was cost-saving; reported cost-effectiveness ratios were \$10,000/outcome in 13 studies, \$10,000 to \$50,000 in 13 studies, and \geq \$50,000 in 3 studies. There were no studies from low income countries and few studies among pregnant women. Substantial differences in methodology limited the generalization of results.

Decision makers in lower income countries lack economic data to support influenza vaccine policy decisions, especially of pregnant women. Standardized cost-effectiveness studies of influenza vaccination of WHO-recommended risk groups' methods are urgently needed.

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Contents

1. Introduction	00
2. Methods	00
3. Results	00
3.1. Cost of medically-attended illness	00
3.2. Specific target groups	00
3.3. Cost effectiveness analyses	00
4. Discussion	00
5. Conclusion	00
Appendix A	00
References	00

1. Introduction

Annually, influenza viruses are associated with a substantial disease burden throughout the world. Estimates derived from data

in higher income countries suggest that seasonal influenza infections occur in approximately 10–20% of the world's population and may result in 3–5 million cases of severe illnesses and between 250,000 and 500,000 deaths worldwide [1]. Since the emergence of influenza H5N1 in 2003, increased investments into influenza surveillance and research has improved the quality and quantity of surveillance data globally especially from regions where previously no data had been available [2]. This accumulated data has helped

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to highlight the fact that influenza circulates globally, and that in some settings burden may be higher than experienced in higher income temperate regions due to a variety of factors that include lack of health care access, or specific co-morbidities such as HIV [3,4]. The World Health Organization's Strategic Advisory Group of Experts (SAGE) has recently recommended that all countries should promote vaccination to a number of risk groups including young children, the elderly, and those with underlying conditions, with specific priority given to pregnant women in order to protect the mother and the future young infant [5].

Global increases in manufacturing capacity [6], both in number of doses and in diversity of countries producing vaccine, may allow for many countries that previously had little or no influenza vaccine experience to seriously consider its introduction into routine immunization programs [7]. For instance, the Pan American Health Organization (PAHO) has added influenza vaccine to its revolving fund of vaccines available at discount prices to countries in the PAHO region [7], and several countries including Brazil, Thailand and India are embarking on developing domestic seasonal influenza vaccine production capacity [8]. For many countries not yet able to afford broad introduction of vaccines, maternal influenza immunization to protect the mother and unborn child may be the first step and could possibly be subsidized in the future through GAVI mechanisms as for other new vaccines.

However, a primary driver of vaccine policy is the cost of the influenza vaccine, its delivery, and the economic impact of influenza. Countries with long standing influenza vaccination programs have conducted a variety of economic evaluation studies that assess the number of visits and admissions, quality adjusted life years lost, cost-of-illness, cost-effectiveness, cost-benefit analysis, and loss productivity, and these data point to substantial economic burden. For example, one study estimated the annual cost of seasonal influenza in the United States between US\$71 and 167 billion from the societal perspective [1].

As influenza vaccine manufacturing capacity increases globally and countries consider introduction of one or more of the SAGE recommended groups, cost and cost-effectiveness studies will be crucial in decision-making.

We conducted a systematic review of the literature (a) to assess current available data globally on cost and cost-effectiveness of influenza especially in target groups mentioned in the SAGE recommendations, (b) to determine trends and general patterns that can be used to extrapolate published data to countries considering vaccination and (c) to identify gaps in cost and cost-effectiveness analysis.

2. Methods

We searched EMBASE, PUBMED (MEDLINE), WEB of KNOWLEDGE, and IGOOGLE for peer-reviewed studies that estimated the cost of seasonal influenza either for the entire population or for the following specific groups: children, elderly, healthcare workers, workers, and pregnant women. We used the search term "influenza" and narrowed the search with the following: 'economic burden', 'economic cost', 'cost of', 'cost of illness', and 'cost effectiveness'.

We excluded review articles, foreign language articles that did not summarize findings in English, and articles dealing predominantly with pandemic influenza. Articles were selected if they estimated the medical or non-medical cost of any severity of influenza illness either directly through a cost-of-illness study or as part of a cost-effectiveness or cost-benefit analysis of influenza vaccination. We summarized the number of studies per country, per geographic region (North America, South America, Europe, Asia, Africa, and Oceania), per World Bank [9] income group (high,

upper-middle, lower-middle, and low-income), and if the study was of the whole population (national) or of specific high-risk target groups. We classified as 'others' studies that did not fit into any of these categories, which included studies of subgroups such as cancer patients, renal patients, and other cost-effectiveness studies not targeted at specific groups or that did not estimate cost at the national level. We summarized the direct, indirect and total cost of influenza reported in these studies for the country and also per capita (based on population of country in the year of study) and as a percent of Gross Domestic Product (GDP) [9] to allow comparison between countries.

Since influenza activity and severity varies from year to year and costs can be measured in different ways, in order to understand possible reasons for differences in results between studies, we further extracted data about which assumptions authors made when estimating influenza disease burden (e.g. symptomatic attack rates, rate of outpatient visits and hospital admissions) and economic burden (e.g. the cost per hospitalization, clinic visit, and loss of work days), and the methods used to derive these estimates. We estimated the cost of hospitalization and outpatient visits per patient per country in studies with available information for children, elderly, and pregnant-women risk groups. Studies on working adults and healthcare workers were mostly studies of lost productivity and did not clearly give estimates of cost of influenza illness and so were not considered in this additional analysis.

We also recorded what the study authors concluded on the cost or cost-effectiveness of vaccination and stratified cost-effectiveness results by high-income and upper-middle income countries. Studies that concluded that the findings were cost-savings or had a benefit-cost ratio of more than 1 were classified as cost-savings. The other studies were classified based on their cost per outcome ratios (cost-effectiveness ratios, cost-benefit ratios, cost/QALY, cost/DALY, and cost/hospitalization averted) but not on their reported threshold used.

For studies where authors gave the cost of hospitalizations per day without giving the length of stay, we calculated the cost of hospitalization by use of the average length of hospitalization reported by other studies in the country. Where this was not available, we used 3 days for children, 4 days for adults, and 7 days for older adults. We converted all currencies to US dollars using the average exchange rate for the given year and converted all dollars to 2010 US dollars using the country specific consumer price index (CPI) [11,12] to account for inflation.

3. Results

We identified 140 articles from 27 countries that met our inclusion criteria: 60 articles from North America, 39 from Europe, 29 from Asia, 8 from South/Latin America, 4 from Oceania and none from Africa. Of 140 articles, 98 (70%) originated from temperate, 14 (10%) from subtropical, and 28 (20%) from tropical countries. One hundred and 18 articles (84%) articles were from countries classified as high-income and 22 (16%) articles from upper-middle income countries. We did not identify any published studies from low or lower-middle income countries. The median number of studies per country was 3 (range 1-55) (Table 1).

The majority of studies ($n=101$: 72%) reported a cost effectiveness/cost-benefit analysis of influenza vaccination, and the remainder ($n=39$: 28%) was cost-of-illness studies. A total of 11 studies were national cost estimates and 107 were studies on specific targeted risk groups and 12 were on 'others'. Twenty-seven countries contributed data on the cost of influenza; 2 from North America, 10 from Europe, 9 from Asia, 4 from South/Latin America, and 2 from Oceania. Eleven studies from 9 countries estimated the total cost of influenza either from the societal perspective

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