Cost-effectiveness analysis of pandemic influenza mitigation: What’s missing?

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Key Messages

Critique of scope
- Cost-effectiveness analysis of pandemic mitigation in developing countries is almost absent
- Research on non-pharmaceutical mitigation options is neglected in favour of vaccination and anti-viral stockpiling

Critique of methods
- Previous studies do not incorporate health system surge capacity
- Methods to model pandemic event uncertainty are highly variable

Abstract
Ideally pandemic influenza policy making would draw on a solid research base including cost-effectiveness analyses. This evidence base is currently small but has grown rapidly since 2009. However, currently research scope is narrow and there is considerable methodological variation between studies. To contribute to a discussion on improving quality and consistency within this emerging study area we identify four opportunities for improving scope and methods: i) increased focus on low resources settings ii) greater inclusion of non-pharmaceutical interventions iii) incorporation of health system surge capacity and iv) more robust analysis and presentation of pandemic event uncertainty.

Introduction
Highly pathogenic pandemic influenza poses a real if poorly defined risk to public health and economies. Murray et al. (2006) estimated that a pandemic event with excess mortality proportional to the 1918 Spanish influenza pandemic occurring in 2004 would result in 62 million excess deaths globally (1). In addition to mortality the United Nations System Influenza Coordinator (UNSIC) outlines impact to healthcare systems, animal health, agriculture, education, transport, tourism and the financial sector (2). In short, a pandemic event threatens all aspects of the economic and societal fabric.

In 2003 a strain of H5N1 highly pathogenic avian influenza (HPAI) re-emerged and continues to circulate. The risk of viral mutation facilitating human to human transmission and the likely
pandemic event resulting is the subject of much concern, debate and research. In this context the 2009 H1N1 swine influenza pandemic catalyzed action from public health decision makers and international donors. Many countries have drawn up Pandemic Preparedness Plans, invested in stockpiles of antivirals and equipped border points with heat scanners and virus neutralizing technology. In 2010, the United Nations System Influenza Coordinator (UNSIC) reported that between 2003 and 2009 international donors had pledged over US$ 4.3 billion for pandemic influenza preparedness (2). But how should such funds be used to maximize public health benefit? And in the context of existing resource constraints, especially in low and middle income countries, is pandemic preparedness a good use of funds compared with other public health investments options?

The total number of cost-effectiveness or economic evaluation studies of pandemic influenza mitigation options to date is small but has risen sharply since 2009. In a recent systematic review Perez Velasco et al. (2012) identified 44 economic evaluations of pandemic preparedness strategies (3). While the first of these was published 15 years ago in 1997, the majority (75%) were published from 2009 onwards. Perez Velasco et al evaluated these 44 studies against a check list of standard practices in economic evaluations but their stated aim was to summarize the literature and offer policy recommendations rather than examine methodological approaches. Prior to this, in 2009, Lunger and Postma (2009) conducted a review of 12 economic evaluations and recommended that decision models for pandemic influenza economic evaluation should be based on dynamic rather than static transmission models (4). This might also be turned around and noted that incorporating resource use or economic information to pandemic mitigation modeling would greatly increase the relevance to decision-makers.

The field of economic evaluation for epidemic or pandemic preparedness is at a nascent stage. However as control of endemic disease progresses, the importance of preparedness measures for epidemic events becomes increasingly important both due to the deceased burden of endemic disease and the increased risk of outbreaks in susceptible populations. The objective of the paper is to raise areas for improving the methods and scope of pandemic influenza economic evaluations. We offer a critique of four aspects of this emerging body of literature in two sections; firstly a critique of research scope followed by a critique of research methods. This paper is produced as part of a wider study of investment options for pandemic influenza mitigation in Cambodia.

**Critique of Scope**

*Low income countries are neglected*
Pandemic influenza presents the greatest risk in low and middle income countries. Murray et al. (2006) found that of the 62 million excess deaths estimated for a modeled pandemic in 2004, 96% occur in countries that are not part of the Organization for Economic Co-operation and Development (OECD). In this model there is also a strong negative correlation between income per-head and mortality; a 10% increase in income is matched by a 10% decrease in pandemic influenza associated mortality (1). Pandemic health impact in low income countries and regions can be compounded by lack of access to medical services, under nutrition, inadequate shelter, high population density, poor hygiene and a greater likelihood of co-infection with endemic disease.

Since poverty is widely associated with endemic disease burden it could be expected that poor countries will suffer a greater burden from pandemic disease. However, of the 44 pandemic influenza economic evaluations to date none focus specifically on low income countries (LICs) or lower middle income countries (LMICs), as defined by the World Bank. One study by Carrasco et al. (2011) evaluated the cost-effectiveness of anti-viral stockpiling in 10 countries including three LMICs and one LIC (5). They conclude that antiviral stockpiling is not estimated to be cost-effective for two thirds of the world’s population, recommending that “under perfect allocation higher resourced countries should aim to store antiviral stockpiles”. However this conclusion is problematic since the results does not necessarily reflect inferior effectiveness or greater costs of antiviral stockpiling in poorer countries but simply the affordability of the antivirals. Taking a global payer perspective (valuing health gains equally in all countries) would better reflect variation in cost-effectiveness between countries and would allow comparison with affordability. We argue that the concept of a global or international payer is a reality. International donors such as the Gates Foundation, the Global Fund, the World Bank and various national aid programmes, have considerable spending power.

**Pharmaceutical intervention selection bias**

Pharmaceutical interventions, principally vaccination and antiviral stockpiling, feature heavily in the pandemic economic evaluation literature. Of the 44 studies identified by Perez Velasco et al., 34 (77%) focus exclusively on pharmaceutical interventions. Only four studies (9%) focused exclusively on non-pharmaceutical interventions, namely school closure, air travel restriction, sick leave and facemasks. Perez Velasco et al. note the absence of considering public hygiene and disinfection. On the face of it this suggests intervention selection bias in the literature, with the potential to influence policy decisions and direct further research. It is possible that this bias is driven by the considerable financial implications of antiviral stockpiling policies. This further underscores the above point, that
research to date neglects the question of how scarce resources in poor countries can effectively save lives in favor of determining how more substantial funds might be efficiently allocated in high income countries. It would also be fair to say that economic evaluation of antiviral stockpiling presents a simpler research question that researchers might favor over complex analysis of non-pharmaceutical intervention options.

Critique of Methods

**No consideration of health system capacity**

The ability of the health system in general to cope with the sudden increase in demand, or *surge capacity*, is fundamental to minimizing pandemic influenza mortality and morbidity. Health system capacity has thus far not been incorporated into any pandemic influenza economic evaluations. Recent work by Rudge *et al.* highlights health system resource gaps for pandemic influenza scenarios in six South East Asian countries and perhaps not surprisingly the greatest gaps between demand and health system capacity were frequently found in the poorest areas (6). Ignoring health system capacity for a surge event implicitly assumes unlimited capacity, an assumption which is even less justifiable in a LIC or LMIC context. The question of whether health system strengthening in poor countries is the most cost-effective pandemic mitigation investment is still to be answered.

**Pandemic uncertainty is neglected**

Uncertainty is a characteristic feature of a pandemic event. By its very nature the incidence of disease, the associated morbidity, the fatality rate, or the year in which a pandemic might occur are unknown. Economic evaluations of endemic disease control rely on an implicit assumption of consistent public health burden over time, in order for the cost-effectiveness results for a control program to have relevance to future policy making. This is a reasonable assumption for endemic disease but for pandemic disease the uncertainty in disease burden and event timing is critical. However, pandemic economic evaluations typically use a fixed pandemic scenario to simplify the decision problem, for example assuming 1957 like pandemic characteristics. Some studies test these assumptions with fixed point univariate sensitivity analysis but few take a probabilistic approach and simulate multiple pandemics scenarios. Robust approaches to incorporating and presenting pandemic event uncertainty are key to improving methods for economic evaluation of pandemic mitigation options.

Conclusions

The evidence base for cost-effectiveness of pandemic influenza mitigation policy options is small but growing rapidly. Modeling methods vary considerably between studies and there are blind spots in
the literature scope. To contribute to a discussion on improving quality and consistency within this emerging study area we identify four opportunities for improving scope and methods: i) increased focus on low resources settings ii) greater inclusion of non-pharmaceutical interventions iii) incorporation of health system surge capacity and iv) more robust analysis and presentation of pandemic event uncertainty. In short, what’s missing from pandemic influenza cost-effectiveness analysis? Answer: poor countries, non-pharmaceutical interventions, health system capacity and pandemic uncertainty.
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Competing Interests
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