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Pharmaceutical interventions for mitigating an influenza pandemic: modeling the risks and health-economic impacts

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Model-based analyses built on burden-of-disease and cost–effectiveness theory predict that pharmaceutical interventions may efficiently mitigate both the epidemiologic and economic impact of an influenza pandemic. Pharmaceutical interventions typically encompass the application of (pre)pandemic influenza vaccines, other vaccines (notably pneumococcal), antiviral treatments and other drug treatment (e.g., antibiotics to target potential complications of influenza). However, these models may be too limited to capture the full macro-economic impact of pandemic influenza. The aim of this article is to summarize current health-economic modeling approaches to recognize the strengths and weaknesses of these approaches, and to compare these with more recently proposed alternative methods. We conclude that it is useful, particularly for policy and planning purposes, to extend modeling concepts through the application of alternative approaches, including insurers' risk theories, human capital approaches and sectoral and full macro-economic modeling. This article builds on a roundtable meeting of the Pandemic Influenza Economic Impact Group that was held in Boston, MA, USA, in December 2008.

KEYWORDS: cost–effectiveness analysis • economic impact • pandemic influenza

Several studies have shown that, in the case of an influenza pandemic, pharmaceutical interventions may be predicted to efficiently mitigate its impact. Using model-based analyses, these studies have demonstrated the potential for both vaccines and antiviral therapeutics to reduce both the epidemiologic impact (in terms of cases, complications and deaths) as well as the economic impact (in terms of medical resources, productivity changes and financial consequences for national economies) [1–5]. Generally, these models are built on firmly grounded concepts developed within burden-of-disease analysis and cost–effectiveness theory, suggesting beneficial effects for both pharmaceutical interventions and strategies directed at behavior, for example, school closures. In short, this might be labeled the 'health-economic approach' and, in general, these health-economic models adequately analyze the impact of pandemic influenza within the frameworks of these specific concepts. However, it is relevant to consider whether these concepts may present too limited an approach in order to capture the full macro-economic impact of pandemic influenza. Recently, suggested alternative modeling approaches have included insurers' risk theories, human capital theories and full macro-economic modeling. Most recently, Keogh-Brown, Smith and various co-authors have applied macro-economic modeling to epidemiological data on previous pandemics to analyze different scenarios [6–8]. These analyses have shown that, from the macro-economic point of view, different inferences may be drawn than from the cost–effectiveness approach and one specific aspect explicitly considered was the potential of school closure to add to, rather than mitigate, the economic impacts. Also, analyses from the World Bank, European Commission, the Asian Development Bank and the US Congressional Office all addressed economic consequences of avian influenza at global and continental levels [9,10,101,102].

With health economics being a multidisciplinary approach per se, and the general notion often expressed that health economics provides a comprehensive integration of the key aspects surrounding a decision whether or not to implement

a healthcare intervention, it is crucial to consider the health-economic analyses of pandemic influenza undertaken to date. The aim of this article is to summarize current health-economic modeling approaches for analyzing pharmaceutical interventions used to mitigate an influenza pandemic, to recognize the strengths and weaknesses of these approaches and to compare these with more recently proposed alternative methods. Pharmaceutical interventions typically encompass the application of (pre)pandemic influenza vaccines, other vaccines (notably pneumococcal), antiviral treatments and other drug treatment (e.g., antibiotics to target potential complications of influenza). Finally, we will delineate the usefulness of the current health-economic approach for policy and planning purposes, and comment on the further benefits of extending these concepts with new aspects derived through application of actuarial theories, human capital approaches and macro-economic modeling.

Pandemic influenza models & economic analysis

To begin with, we performed a systematic search for economic analyses in Medline and EMBASE, using various combinations of the terms 'cost–effectiveness', 'pandemic influenza', 'economic' and 'costs'. Further relevant papers were identified by snowballing on those papers initially found. A typical example of a health-economic approach identified, was published in *Vaccine* by Mylius *et al.* in 2008 [1]. The authors analyzed influenza infections, cases of influenza-like illness, deaths, hospitalizations and bed occupancy within the context of pandemic influenza in the local setting of The Netherlands. Assumptions for assessing these epidemiological and economic impacts were derived from seasonal influenza (e.g., regarding mortality and hospitalization rates [11,12]) and from analyzing historical information from previous pandemics in The Netherlands. For the analysis, a population dynamic structure was applied to simulate the spread of infection within the Dutch population. As opposed to a static model, dynamic models explicitly take into account the dynamics of infection transmission [13]. While static models have previously been applied for analyzing pandemic influenza [14], dynamic models are now seen as the 'gold standard' for analyzing influenza and often infectious diseases in general [2,15,16].

For dynamic models, one crucial parameter is R_0, formally defined as the number of infections caused by one infected person in a further fully susceptible population. Mylius *et al.* estimated R_0 as 1.73, based on information from the spread of the 1957/58 influenza A/H2N2 pandemic in the Dutch context [1]. Furthermore, information on contact patterns is important for these types of models that explicitly define who has most contact with whom, for example, in terms of age groups. Their analysis was limited to a pandemic vaccine, which is a vaccine that would become available at some point during the pandemic, and specifically developed on the actual pandemic strain, as isolated early in the pandemic. Depending on whether the vaccine would be available relatively early or rather late in the pandemic, the authors recommended targeting limited vaccine supplies to children, in order to optimally control the spread, or to the elderly, in order to mitigate consequences such as complications (e.g., pneumonia), hospitalizations

and deaths. This conclusion is certainly in line with other analyses on pandemic influenza performed by other research teams [17,18]. In addition, Germann *et al.* investigated a large set of potential control measures, indicating that for higher values of R_0 (>2.0) only an extensive combination of interventions – notably, vaccination, targeted antiviral prophylaxis (TAP), school closure, social distancing and travel restrictions – would exhibit a relevant impact on the size of the pandemic [19]. This highlights the fact that, under these circumstances, pharmaceutical interventions alone will not suffice. Ferguson *et al.* have also argued for the benefits of school closures if initiated around the peak of the pandemic [17]. Notably, the exact economic consequences of school closures were not analyzed in this research and such impacts are not necessarily as beneficial as the predicted epidemiological impact of school closure.

Cost–effectiveness analysis using dynamic modeling

In the absence of formal costing of items, the studies reviewed in the previous section cannot be seen as full cost–effectiveness analyses. A full cost–effectiveness analysis would typically relate monetary costs of investment, maintenance and monetary savings (net costs if subtracted from each other) to health gains, and, for nonbusiness audiences, in terms of quality-adjusted life years (QALYs) gained. Up to now, only a few formal cost–effectiveness analyses have been published that used a dynamic model, for example, studies undertaken in the USA [3] and The Netherlands [20]. The US study was extensive, including not only direct medical costs but also indirect costs of production losses. Alongside various other types of intervention, such as school closure, pharmaceutical interventions were also investigated. Of the single interventions investigated, school closure and prevaccination achieved the most reductions in illness attack rates. TABLE 1 summarizes some selected results from this study. For example, a wide range of options for TAP was analyzed, including the targeting of household members only, or full TAP in targeting work and school contacts as well, both with availability of antiviral treatments for 25 or 50% of the population. In addition, prevaccinating 70% of the population with a low-efficacy (prepandemic) vaccine was investigated. Findings indicated that prevaccination was more cost effective (lower net costs and more QALYs gained) than either a 'no intervention' strategy or school closure alone: however, the greatest effect was seen if prevaccination and school closure were combined. The combination of prevaccination and school closure provided extra QALYs if compared with full TAP, but at the expense of extra net costs. In particular, costs per QALY were approximately US$50,000 for the combination compared with full TAP. A very recent analysis – co-authored by one of the same authors – reinforced the previous findings for the 2009 H1N1 pandemic [2]. In particular, it was estimated that highly effective strategies in mitigating the pandemic's epidemiology would be school closure and especially vaccination. In fact, rapid vaccine deployment in the early stages of the pandemic would even render school closure unnecessary [21].

A second study targeted the setting of The Netherlands [15,20]. Outcomes from the afforementioned dynamic transmission model [1] were used in this health-economic calculation. In particular,

1432

Expert Rev. Anti Infect. Ther. 8(12), (2010)

Table 1. Pandemic influenza attack rates, mortality rates and cost–effectiveness in incremental costs per quality-adjusted life year gained (compared with no intervention in each case) using different mitigation strategies.

Intervention	Attack rate (%)	Deaths per 1000 individuals	Cost–effectiveness
No intervention	50	13	
School closure	39	10	US$37,000
Pre-vaccination	26	6	Dominates both above
FTAP	23	5	Dominates all above
School closure and FTAP	6	1	US$9300; dominates closure alone
School closure and prevaccination	4	1	US$9300; dominates closure alone

FTAP: Full targeted antiviral prophylaxis.
Data from [3].

outcomes from the dynamic model were compared in terms of money and health associated with stockpiling of antiviral drugs for treatment in the presence of a pandemic versus no stockpiling. Explicit scenarios for bulk generic oseltamivir versus the branded product Tamiflu® (Roche, Basel, Switzerland) were investigated, including combinations of bulk and brand. It was found that stockpiling oseltamivir alone versus 'doing nothing' is cost effective at a threshold of €20,000 per QALY if the risk of a pandemic outbreak is greater than 23% in 30 years. Including indirect costs of production losses, a risk of 10% during 30 years would already suffice as a favorable level of cost–effectiveness. Higher required risks were indicated for the combination of bulk and brand of oseltamivir [20]. The analysis assumed that no relevant resistance against these antiviral drugs would develop and the authors stress that, were this the case, an updated economic evaluation would be warranted.

A very recent US-based study applied a compartmental epidemic model and a Markov model of disease progression to the spread of H1N1 infection and complications [21]. The authors estimated that high mortality rates and lost QALYs could be averted and US$300 to almost US$500 million could be saved by vaccinating 40% of the US population in November or October, respectively. It was assumed that each primary infection would cause an average of 1.5 onward cases (R_0). It was concluded that full population coverage would not be necessary to achieve sufficient reduction in the R_0 to relevantly shorten the epidemic and thus achieve predicted QALY gains and mortality reductions, in addition to high potential cost savings. Results and conclusions were considered valid whether large-scale manufacture and distribution of either adjuvanted or nonadjuvanted vaccine was made available [21].

For other EU countries such health-economic information is currently lacking, although some projects are ongoing. In particular, given the specific interest in dynamic models, it is important to note that in the recent POLYMOD project (Improving Public Health Policy in Europe through Modelling and Economic Evaluation of Interventions for the Control of Infectious Diseases), empirical information on contact patterns has been gathered [22]. In a recent WHO project, these contact patterns have been generically applied to several EU countries for cost–effectiveness of pandemic and prepandemic vaccines within

the framework of a dynamic model [103]. We note that an urgent need exists to investigate contact patterns in other settings, in particular developing countries where data such as that gathered by Mossong et al. in European countries is as yet lacking [22].

For Australia, recent modeling research has investigated alternative vaccination strategies that exploit candidate prepandemic H5N1 vaccines that have shown potential for cross-strain protection [23,24]. This work uses an agent-based simulation model of an actual community of approximately 30,000 people in Australia as an example of a developed country, and has been used to determine the reduction in illness attack rate, hospitalizations and mortality due to mitigating interventions [25,26]. Assuming a two-dose vaccination regimen, they examined three separate vaccination strategies: pre-emptive, with vaccination applied prior to emergence of human-transmissible H5N1 influenza; reactive, where vaccination was initiated immediately after the first cases in the community were diagnosed; and, a split strategy, where the first dose was administered pre-emptively during the prepandemic phase and the second dose administered reactively. The authors showed that moving the first dose into the prepandemic period and administering the second dose once the pandemic had been recognized was more effective than the purely reactive strategy of giving two doses after recognition of the pandemic. By moving the delay between the first and second doses into the prepandemic period, the split vaccination strategy achieved a substantially better attack rate reduction than the reactive strategy, creating a cohort of immune individuals more rapidly following pandemic onset.

Further cost–effectiveness analyses using static models

Further cost–effectiveness studies targeted at the EU setting have been undertaken using static models rather than the dynamic approach. For example, Sadique et al. used a static model to illustrate the relatively high costs of school closures in the UK, in particular relating the indirect costs of productivity losses due to parental absenteeism during the period of closure [4]. From the same research group, Siddiqui and Edmunds analyzed the cost–effectiveness of antiviral treatment, both in the absence of, and combined with, near-patient testing [5]. Depending on the exact case-fatality rate assumed (either

2.29% according to data from the 1918 pandemic or 0.29% according to the 1957 and 1969 pandemics) cost–effectiveness per QALY gained ranged from GBP£1860–£13,700 for treatment and GBP£31,000–£228,000 for testing plus treatment. Earlier work by van Genugten *et al.* ranked pharmacological interventions for pandemic control in the specific Dutch setting by their potential in lowering overall hospitalizations. In particular, influenza vaccination ranked most favorable in this respect, followed by neuraminidase inhibitor treatment and pneumococcal vaccination [11]. The latter approach is now increasingly mentioned as one effective control strategy for pandemic influenza [27]. Finally, an analysis undertaken by Meltzer in the USA in 1999 focused on a variety of specific strategies to distribute a pandemic vaccine, namely: according to intra-pandemic use, adding 20 million essential service providers and distributing the vaccine to up to 40–60% of the total population [14]. Through the use of the human capital method for averted mortality, major financial benefits were estimated resulting in all specific strategies providing net cost savings. For example, for averted childhood deaths, full lifetime revenues due to production capacities were included. It could be debated whether this approach presents the most appropriate one, and other approaches have been suggested in the literature for limiting the impact of childhood deaths on the model results. In particular, friction costing and human resource approaches should be noted in this respect [28,29].

Some general inferences from cost–effectiveness analysis

Sensitivity analyses generally indicate that at least three parameters are crucial in cost–effectiveness models. The price, efficacy ratio attached to the pharmacological interventions is of prime importance. In order of magnitude, prices range from €5 (influenza vaccines), through to €20 (antivirals), up to €50 (newer generation pneumococcal vaccines). The efficacy and potential cost–effectiveness of neuraminidase inhibitors is well recognized [30,31], but varies per outcome considered, per age group targeted and by the specific brand. The efficacy of prepandemic vaccination may be limited, whereas a pandemic vaccine might exhibit similar efficacy to the average seasonal product. Notably, case fatality and overall mortality are crucial determinants of the denominator of the cost–effectiveness ratio, either life years or QALYs gained. Also, it has been shown that these vary tremendously by age group and health-economic models should take that into account. Finally, the likelihood of a new pandemic occurring within the specified time frame is important. Historical information – possibly hinting at three per century – may be taken into account to estimate this. However, circumstances for a rapid and worldwide spread of the virus have certainly changed. Improved influenza surveillance, for example, in South-East Asia, may influence the likelihood of a pandemic emerging and potential outbreaks may be subdued owing to early information being available. On the other hand, rapid and worldwide spread may be enhanced through increased travel movements over the globe, particularly air travel, as observed in recent decades.

Various pharmacological interventions have been investigated to date. In particular, influenza vaccination has been analyzed in four settings: as an upscaling of seasonal influenza, as a prepandemic vaccine, as a pandemic vaccine and in a split-vaccine approach. In addition, pneumococcal vaccination is considered to prevent complications from pneumonias and deaths arising from secondary bacterial infections. Antivirals, in particular neuraminidase inhibitors, are seen as appropriate both in the prophylactic and in the treatment setting. To complete this list, we note that some studies have investigated further pharmacological targeting of the influenza virus. It has been proposed that nonspecific agents with antiviral or anti-influenza properties could have a role in mitigating mortality in a pandemic, in particular statins, fibrates and chloroquine [32]. In a Danish study, pneumonia mortality was less in statin users (10%) than nonusers (16%) [33,34]. However, the potential economic impact of such agents has not yet been investigated and remains difficult to quantify until efficacy can be better established. Finally, we note that various studies have analyzed the properties of antibiotic use to prevent complications of influenza infection, including some tentative economic analysis (e.g., by Assink *et al.* [35]).

Limitations of conventional cost–effectiveness models

It is questionable as to whether the conventional approach to cost–effectiveness analysis, in those scarce studies performed to date on pharmaceutical interventions targeting influenza pandemic control, is able to comprehensively assess the full economic impact. Indeed, most analyses did include cost categories beyond direct medical costs only. For example, most studies included indirect nonmedical costs of production losses due to sickness absence and premature death, and often savings on these types of costs constitute the primary share of total savings due to control strategies. Inclusion of both medical and nonmedical costs, direct and indirect costs conform to health-economic guidelines specified by individual countries and the WHO [36,104]: that is, cost–effectiveness analysis should be performed from the societal perspective, including costs and savings irrespective of who pays and who benefits.

However, in the specific measurement of these cost categories, limitations already exist that may hamper our understanding of the full economic impacts. For example, regarding valuation of production losses, as yet unresolved discussions exist on what exact methodology to use, with various approaches being available. In particular, human capital, friction costing and human resource models are currently used, all potentially generating quite different results. For mortality, the human capital method typically focuses on lifetime earning capacities aggregated into a (discounted) net present value, whereas the friction costing approach is more conservative, only valuing lost earnings in the period until replacement of the absent person is achieved in the workplace, typically resulting in only 3–6 months of lost earnings [14,28]. Finally, some human resource models explicitly take into account that, for achieving lifetime earnings, investments have to be made in the early stages of life and should formally be subtracted from those earnings from a governmental and

1434

Expert Rev. Anti Infect. Ther. 8(12), (2010)

potentially societal perspective [29]. We could find no approaches or cost–effectiveness studies that consider the broader macro-economic impact on sectors of the economy (rather than on individuals with disease), medical costs, sickness absence and premature death. It should be appreciated that the actual impact of an influenza pandemic can far exceed the sum of the individual impacts. For example, while it is generally assumed in cost–effectiveness analyses that state-of-the-art medical care is provided, this might not be feasible in a real pandemic situation, where shortages in supplies, available beds and the absence from work of a significant proportion of healthcare workers could occur [37].

Despite providing important insights, it is relevant to consider some further limitations of the cost–effectiveness analyses currently available. Notably, modern cost–effectiveness relies heavily on the QALY concept, a subject that is not without dispute. In particular, for a highly prevalent disease such as pandemic influenza, it is obvious that large numbers of people with small decrements in quality of life may add up to huge QALY impacts, potentially much larger than QALY impacts related to mortality. Equal valuation of QALYs derived from quality-of-life reductions to those derived from mortality is one point of discussion in using the QALY concept [38]. One further point relates to equal valuation of QALYs over age groups, with some arguing that QALYs in the young should be valued higher than those in older individuals, referring to this principle as 'fair innings' [39].

Alternative models for pandemic influenza economic impact

Given some of these limitations in cost–effectiveness methodology, what alternatives do we have? Recently, some alternative approaches to estimate the economic impact have been taken. These reports aimed to either broaden the analytic scope to the whole macro-economy, or to explicitly take an alternative perspective. A recent analysis from the actuarial standpoint using an enterprise risk management perspective focused on production losses rather than mortality. A focus on the impact on businesses was justified by the notion that the economy is based on private employers and, ergo, that quantifying the meso-economic impacts on private employers would adequately aggregate to the full macro-economic impact. A focus on business impact may be justified as private enterprises make up a significant proportion of the economy, at least in developed countries. In particular, in this approach, economic impact on particular enterprises emerges from lost work time due to sickness, fear of contagion or caring for sick family members. Because industries have characteristic relationships between revenue and wages, this model allows individual employers to evaluate their risk and it produces national estimates consistent with macro-economic figures [40].

An Australian investigation explicitly adopted a sectoral approach by estimating the overall macro-economic impact based on estimates of the consequences of pandemic influenza for each individual sector in the economy [41]. In particular, the impacts in the sectors of energy, mining, agriculture, manufacturing and services were explicitly considered for various countries (e.g., the

UK and China), parts of the world (Europe and the USA), continents (Australia), organizations (Organization of the Petroleum Exporting Countries) and former alliances (Eastern Europe and the former Soviet Union). Spread of pandemic influenza was assumed to occur primarily through commercial airline travel and was based on actual aviation data [42].

The study by the Congressional Budget Office of the USA investigated two scenarios describing serious (1917/1918-like) and mild pandemics, respectively [10]. In the first scenario, 2 million deaths were estimated and there was an approximately 4% decrease in gross domestic product (GDP). This epidemic might cause a typical business-cycle recession in the USA, as often 'naturally' experienced during economic development. The second scenario would only involve limited numbers of deaths (~100,000) and a modest impact on GDP (~1% reduction). It was concluded that federal policies should be directed to ensure sufficient stockpiles of vaccines, improving access to antiviral drugs and enhancing availability of technology centers, allowing rapid and large-scale production of effective vaccines [10].

A recent analysis investigated the UK situation by applying a computable general equilibrium modeling experiment [7]. The authors showed that costs related to illness might range between 0.5 and 4.3% of GDP. However, a well-matched vaccine applied in a two-dose schedule was estimated to limit the overall economic impact to 1% of GDP maximally. Again, it was stressed that school closure and effective vaccination are essential in controlling the pandemic and its economic impact. The economic effects of school closure should be well balanced against the advantages and disadvantages of 'business as usual'. In addition, it was predicted that, for example, food industries and communications sectors would be affected most by the pandemic's economic consequences, whereas the lowest impact would be seen in the extraction sector, crops, utilities, and health and nonhealth services.

A similar macro-economic approach extending to comprise four EU countries by some of the same authors arrived at similar conclusions regarding the economic impacts and the effects of potential strategies for mitigating these impacts [8]. In particular, the authors applied a multisector single-country computable general equilibrium model for the UK, France, Belgium and The Netherlands. For various scenarios of alternative levels for disease severity, the authors show that school closures and preventive absenteeism significantly increase the negative impacts on the economy. Yet, in all cases prophylactic vaccination and antivirals seem worthwhile to limit the deteriorating effects of pandemic influenza on the economy. This again illustrates the additional findings that a macro-economic approach may provide over and above the traditional cost–effectiveness approach. Whereas overall, for pharmaceutical interventions, similar benefits are found in both approaches, school closure, for example, comes out quite differently in both approaches. In particular, in cost–effectiveness analysis school closure will occasionally come out as a worthwhile undertaking, whereas from the broader macro-economic perspective, this intervention often seems detrimental rather than beneficial for the economy.

Discussion

It requires a thorough knowledge of the weaknesses of an approach to fully understand and appreciate its strengths. With that in mind, we reviewed the cost–effectiveness analyses of pharmaceutical interventions directed at the control of pandemic influenza. We note that, current cost–effectiveness approaches may sometimes fail to adequately grasp the full extent of economic impacts. Also, communication of results with decision makers is a crucial aspect. Instead of merely aggregating and specifying the impact on QALYs, or defining cost–effectiveness ratios, more focus on adequately representing and communicating meaningful real-world outcomes may help decision makers better understand these models from a policy perspective. At least, in reporting cost–effectiveness analyses, strict distinction should be made in those QALYs obtained through quality-of-life improvements versus those related to survival improvements [43].

Improving cost–effectiveness analyses further will enhance applicability and face-validity, rendering more convincing analyses to policy makers. In addition, policy makers tend to favor transparent and not too complex models. Two types of models are currently employed in health-economic analyses of infectious diseases control, termed static and dynamic models [44]. In contrast to static modeling, dynamic modeling takes the spread of an infection within populations explicitly into account, and often involves complex modeling. Therefore, static models fall into the category of 'not too complex models' that are preferred by policy makers. It is, however, also known that static models may produce inaccurate results that deviate substantially from those obtained by applying a dynamic model [45]. This also appears to be the case for modeling pandemic influenza interventions.

Pandemic influenza warrants attention from policy makers, epidemiologists and health economists. It is already receiving attention from employers, for example, in the USA, who recognize that they can play an important role in pandemic preparedness within the business sector by assessing the likely business risks, such as the impact of worker absenteeism, developing continuity plans and basic prevention measures, and establishing policies to guide companies through a pandemic [105].

It is notable that the mortality from the 1957 and 1969 pandemics – both of which were considered mild – is still estimated to be approximately 100-fold the number of deaths due annually to cervical cancer, for which many European countries have now implemented large-scale universal vaccination schedules. Yet, decisions on pandemic control measures should be made carefully and must take into account the economic reality that resources are scarce. Cost–effectiveness of pandemic influenza interventions is thus warranted, but requires specific approaches, including dynamic modeling and extensions of traditional cost–effectiveness approaches to comprise all impacts within the broader economy and not just the healthcare sector.

We note that macro-economic approaches do present a relevant addition to cost–effectiveness, in particular in the area of pandemics. For capturing the full scope of pandemics and possible control measures it might even be argued that the macro-economic model is indispensable. Drawing on the previous example of SARS, for example, Keogh-Brown *et al.* showed the potential major economic effects of behavioral changes in the populations [46]. Willingness to alter shopping, travel and working habits may have consequences for the economy that go far beyond the costings included in traditional cost–effectiveness analyses. For SARS, it was shown that behavioral change, absenteeism and macro-economic production losses present huge macro-economic consequences, even within one single year [46].

Conclusion

We conclude that, to date, cost–effectiveness analyses have provided extremely relevant insights into the integrative value of the pharmaceutical interventions investigated. This applies to antiviral treatments, prophylactic use and prepandemic vaccination. There is a need for further cost–effectiveness analyses, for example, on quantifying the value of pneumococcal vaccination in pandemic control. Some weaknesses of cost–effectiveness analysis can be overcome to further enhance applicability, particularly to policy making. For such improvements, lessons can be learned from some alternative approaches that have now been applied, notably focusing on the macro-economy as a whole (either from the insurers' or the sectoral point of view), inclusive of monetarizing the various aspects concerned and/or even the health benefits. Also, issues paramount to the macro-economic perspective, such as absenteeism and behavioral changes, are ideally investigated in addition to cost–effectiveness, and would provide crucial insights in the full macro-economic impacts of pandemic influenza. Research in this area exists [47] and lessons can be learned from analyses after the SARS pandemic.

Expert commentary

In healthcare, cost–effectiveness analysis as a scientific technique has notably originated in the last three decades from the Medical and Sciences' faculties of universities all over the world. It has evolved as a multidisciplinary approach drawing on approaches and theories from cost–benefit analysis, statistics, mathematics, clinical research and pharmaceutical sciences. It is, therefore, certainly not surprising that in our analysis of health-economic modeling of pandemic influenza interventions a strong emphasis is laid on the economic aspects from the medical point of view. However, it is argued that this viewpoint may be too limited to capture the full macro-economic impact of pandemic influenza in all its dimensions. Alternative methods, comprising further dimensions, extending on the existing portfolio of methods and stronger embedded in macro- and micro-economic theories are warranted to support cost–effectiveness analyses. Whereas this may be true for all health-economic modeling, it seems most relevant in areas where health problems may occur on a scale that is beyond what is generally encountered, such as pandemic influenza. It would be very useful, particularly for policy and planning purposes, to extend modeling concepts through the application of alternative economic approaches, including insurers' risk theories, human capital approaches and sectoral and full macro-economic modeling.

Five-year view

Given the origin and evolvement of health-economic sciences in the last three decades, the limited view of cost–effectiveness analysis is not surprising. Currently, one might say that the science is mature in that cost–effectiveness is performed validly, coherently, consistently and reliably all over the world. It is seen as important that it is often well understood what inferences would be allowed to draw from the cost–effectiveness analyses and it relevantly contributes to healthcare policy making. With scientific developments surrounding cost–effectiveness having led to a clear set of methods, inclusive guidelines for 'good behavior in health-economic science' in many countries and institutes, development of additional methodologies seem appropriate and it seems timely to consider methods that go beyond 'classical' cost–effectiveness. From this it may be expected that in the next decade we will see methods from micro- and macro-economics being more integrated into health economics. Various potentials exist for this: drawing on other theories than welfare economics only, integrating macro-economic modeling into health-economic analyses and risk-based approaches from actuarial sciences. Many areas in health economics will benefit from such a development, for example, discounting theories and cost–effectiveness of infectious diseases. Notably, infectious diseases represent an area with potential involvement of risks for large-scale epidemics or pandemics and corresponding vast macro-economic impacts. Interventions for pandemic influenza will serve as an ideal case for developing and applying such methods.

Furthermore, development of such novel models should build on lessons learnt from the 2009 H1N1 pandemic. In several cases, cost–effectiveness of social distancing and pharmaceutical interventions to mitigate impacts in developed countries might have been overly optimistic due to the mild nature of the disease. Moreover, various models have neglected the capacity constraints that exist in the real world, limiting the potential for response, and have been too optimistic in potential intensities of infectious diseases' control measures. Opposite to what has often been assumed in models, pandemic vaccines were not available in any setting prior to the end of the first pandemic wave. Notably, the role of economic models – and indeed models in general – was limited as many of the decisions taken were merely related to politics, hurry and media attention, rather than to timely and rational analyses of efficacy, safety, cost–effectiveness, macro-economic impacts and opportunity costs. Opportunity costs may certainly have played a role as, next to targeting control measures, the need

existed to maintain ongoing routine medical services in outpatient and inpatient settings. In addition, mass immunization against H1N1 was designed next to routine influenza and other types of vaccination, with the explicit goal not to draw stakeholders away from those other settings. These aspects should be considered as pre-emptive to work to enhance designing proper, realistic and timely models to adequately assist healthcare policy makers in any future pandemic responses.

Key issues

- Cost–effectiveness analyses have provided extremely relevant insights into the integrative value of the pharmaceutical interventions in pandemic influenza control.
- There is a need for further cost–effectiveness analyses, for example, on quantifying the value of pneumococcal vaccination in pandemic control.
- Methodologically, cost–effectiveness analyses can be further strengthened by integrating approaches focusing on the macro-economy as a whole.
- There is a need for monetarizing the health benefits in the cost–effectiveness analysis to enhance applicability for policy making.

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