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Influenza

Cost of Illness and Considerations in the Economic Evaluation of New and Emerging Therapies

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Abstract

Influenza infection has been a burden to humans for thousands of years. Despite the fact that epidemics could be predicted with regularity, the lack of available prevention or treatment measures left humankind vulnerable to the harmful effects of this ubiquitous virus. While the pandemics of 1918 and 1957 are recent examples of the devastation that influenza may inflict, even in a typical year influenza infection and related complications cause significant morbidity and mortality.

The development of an influenza vaccine during the 1940s marked a major turning point in the management of this disease. Vaccination of the elderly and other high risk patients has been shown to reduce morbidity and mortality and to be a worthwhile investment from an economic perspective. Despite these benefits, vaccine use in this group remains suboptimal. The role of annual vaccination for individuals at lower risk for influenza-related complications remains controversial.

While prevention by vaccination is relatively straightforward, the treatment of symptomatic influenza-like illness with medication is more complicated. Differentiating symptoms caused by the influenza viruses from those caused by other common viruses is difficult. Currently available tests to document influenza as the cause of illness are either too expensive, too inaccurate or too time consuming to impact treatment. Symptom-based diagnosis remains the most commonly used strategy in clinical practice. The approval of the neuraminidase inhibitors (NIs) – zanamivir and oseltamivir – remind healthcare providers of the difficulties in diagnosing and treating influenza. NIs have been shown to reduce the duration of symptoms of individuals infected with influenza when prescribed within the first 2 days of symptoms. Whether these innovative agents are cost effective, however, requires a more detailed understanding of the benefits that these agents may offer above and beyond existing therapies.

In this review, we examine the burden of influenza infection, diagnostic challenges and the clinical and economic impact of available interventions. Clinical controversies and potential areas for further investigation are also explored.

1. Background

Influenza is a common disease that infects hundreds of millions of people each year. Although most of those who are infected recover quickly, older individuals and those with chronic medical conditions experience significant morbidity and mortality. Because the virus is ubiquitous and infection commonplace, influenza infection extracts tremendous economic costs both via direct medical costs and by indirect costs of lost productivity of those infected.

The burden of influenza can be decreased by protecting susceptible individuals, either by reducing the risk of infection with vaccination or medications or by using medications that reduce the severity of illness in infected individuals. An effective vaccine has been available since the 1940s. Thus, the focus of public health efforts has been to vaccinate individuals who are at greatest risk for influenza morbidity and mortality, i.e. the elderly and those with chronic illness. Despite patient education campaigns, practice guidelines and improved access to vaccine, the vaccination rate for high risk populations is still not optimal and the vaccination rate for the healthy, younger population (who may experience significant interruption in social function even in the absence of medical morbidity) is even lower. Antiviral medication specific for influenza has been available for over 4 decades, but until recently the utility of these drugs has been limited by a narrow spectrum of effectiveness (being active against influenza A virus only) and serious adverse effects.

The millennium heralded a tremendous change in the treatment armamentarium for influenza. In the course of a single year, the management of influenza changed dramatically with the approval of the neuraminidase inhibitors (NIs) zanamivir (Relenza®) and oseltamivir (Tamiflu™). For the first time, primary care providers had a competitively priced, well tolerated therapy capable of treating the full spectrum of influenza viruses.

The availability of new therapy is always accompanied by significant challenges. In the case of influenza, these challenges include difficulties in positively identifying infection, assessing the value of the benefit of treatment in different disparate populations and assigning payment responsibilities. These questions can be answered from an individual or a societal perspective. In this paper, we discuss the clinical and economic burden of influenza and the potential impact and economic trade-offs of emerging therapies.

2. Burden of Disease

Pandemic influenza is a notorious killer; the fact that the Spanish Flu pandemic of 1918 resulted in more deaths than World War I is dramatic evidence of the global impact of influenza.[1,2] More recently, the 1957 influenza pandemic killed 70 000 people in the US alone.[3] Pandemics occur when there is a complete change in one or more of the surface antigens of influenza ('antigenic shift'), leaving the majority of the population susceptible to infection; attack rates can approach 50%, resulting in significant loss of life and social disruption.[4] In most years, however, cases of influenza are associated with relatively minor changes in the surface antigens ('antigenic drift') and lower attack rates. These cases of influenza are defined as an epidemic if infection occurs in a given community with a frequency clearly in excess of normal expectancy.

The attack rate and severity of illness in a particular epidemic will depend on the susceptibility of the population to the prevalent influenza strains and, in particular, the amount of antigenic change in the strains themselves. Although the spectre of a future pandemic is alarming and public health agencies are developing plans to address this very real possibility, efforts to both quantify and control the annual epidemics are also critical.

2.1 Influenza-Related Mortality

Influenza-related mortality is difficult to accurately measure, primarily because of a lack of virological confirmation in most cases of suspected influenza. Furthermore, in many cases influenza infection may be the proximate, but not the ultimate, cause of death. For example, many patients infected with influenza die from bacterial pneumonia associated with the original influenza infection.

Investigators use the International Classification of Diseases code of 'pneumonia and influenza' (P&I) to classify influenza-related morbidity and mortality. To assess the impact of influenza epidemics on morbidity or mortality, the rate of weekly or monthly P&I hospitalisations and deaths can be analysed. The variation between baseline and influenza season P&I hospitalisations and mortality can be measured and classified as excess morbidity and mortality.

Lui and Kendal[5] used monthly P&I data to develop a cyclical regression model that, for the first time, allowed an accurate estimation of the impact of influenza on mortality in the US (using the years 1972 to 1985). Simonsen et al.[6] revised this methodology by using weekly, rather than monthly, P&I mortality data to refine the estimates of Lui and Kendal to compare the significance of annual influenza epidemics over the years 1972 to 1992. Their results generally confirmed the findings of Lui and Kendal for P&I mortality, and the use of weekly rates allowed these investigators to compare the impact of individual epidemics.

Although P&I mortality may be the most direct measure of the impact of influenza epidemics, investigators can also calculate influenza-related all-cause mortality. Just as influenza may be the proximate event in deaths from bacterial pneumonia, influenza may also be the inciting event in patients whose cause of death is recorded as cardiac or respiratory failure. As with P&I mortality, investigators have applied cyclical regression techniques to measure the impact of annual influenza epidemics on all-cause mortality. All-cause mortality figures provide a more comprehensive measure of deaths attributable to influenza, but the relatively smaller marginal increase between baseline and influenza season deaths may limit the precision of the measurement. Figure 1 illustrates the data of Lui and Kendal[5] and Simonsen et al.[6] regarding influenza mortality, both P&I and all cause, over the years 1973 to 1980.

2.2 Influenza-Related Morbidity

Measuring influenza-associated morbidity presents an even greater challenge than that posed by quantifying mortality. Morbidity spans the continuum from decreased functioning to hospitalisation and prolonged convalescence. Although hospitalisations attributable to influenza may be measured using the same methodology that is used to assess mortality, other manifestations of morbidity such as lost work days, lost productivity and use of outpatient physician care and medications are more difficult to capture.

Several well designed epidemiological studies have focused on hospitalisations attributable to influenza. In a study of influenza epidemics occurring from 1970 to 1978, Barker[7] measured hospitalis-

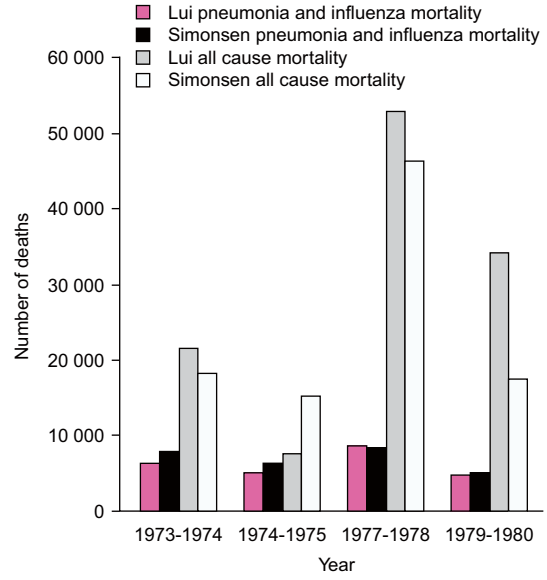

Fig. 1. Estimations of pneumonia and influenza, and all cause mortality by Lui and Kendal[5] and Simonsen et al.[6]

ation rates ranging from 25 excess P&I hospitalisations per 100 000 patients aged 0 to 14 years, to as many as 370 excess hospitalisations per 100 000 people aged 65 years and older. In a more recent study analysing data from the years 1970 to 1995, Simonsen et al.[8] found an average of 49 excess P&I hospitalisations/100 000 population per year in patients of all ages; patients greater than 65 years of age experienced an average excess hospitalisation rate of 174/100 000 patients per influenza season. Finally, Neuzil and colleagues[9] demonstrated that influenza-related morbidity and mortality is not confined to the elderly, but rather that younger women with many common clinical conditions, such as diabetes mellitus, heart disease and lung disease, may be at risk for complications from influenza. Using data from women on public assistance, she found that high risk women aged 45 to 64 years as well as those aged 15 to 44 years had a significantly increased risk of hospitalisation and deaths during influenza epidemics compared with the non-epidemic seasons.[9]

In addition to the complexity in measuring clinical burden, quantifying the economic impact of influenza is problematic. Direct costs, including physician visits, hospitalisations, nursing home care and medications, have been measured at $US17.5 billion in 1998.[9] Indirect costs, including the cost of lost earnings of ill workers and loss of future earnings from premature death, has been estimated to be $US5.4 billion (1998 values).[10] These costs, although impressive, represent figures for the US alone during a typical epidemic year. Furthermore, these indirect cost calculations do not take into account missed days of work to care for sick family members or decreased work output of ill individuals.

The costs of a typical epidemic, substantial as they may be, would be dwarfed by the potential costs of the impending influenza pandemic. Epidemiologists and infectious disease experts have warned that outbreaks such as the Hong Kong Flu (Avian-A H5N1) of 1997 are merely a harbinger of what is to come.[11] Meltzer et al.[12] attempted to model the potential costs to the US of a future influenza pandemic. Table I summarises the data. Assuming attack rates ranging from 15 to 35%, it is estimated that an influenza pandemic might be expected to cause anywhere from 314 000 to 734 000 hospitalisations and anywhere from 89 000 to 207 000 excess deaths. The total economic impact was estimated at $US71.3 to $US166 billion (1995 values).[12] This is likely to underestimate the true costs, as individuals with influenza who continued to work through their illness were not considered in the cost calculations.

There are no comparable analyses involving the impact of an influenza pandemic worldwide. Given that the US population of approximately 250 000 000 people represents less than 7% of the world's population, it is clear that the impact of a future pandemic on the global economy would be devastating.

3. Clinical Diagnosis of Influenza

In the outpatient setting, precise measurement of influenza incidence and attack rate remains elusive. Health professionals and the public at large can recite at least some of the signs and symptoms of 'the 'flu', but making a specific diagnosis of influenza in an individual patient is difficult. Symptoms such as fever, myalgias, malaise and cough are common in influenza, but are also common in a myriad of other viral and bacterial infections. Virological confirmation is problematic in the clinical setting because no single test provides optimal sensitivity and specificity. Recent advances in laboratory and clinical diagnostic methods may alleviate this difficulty. The ideal diagnostic method would have high sensitivity and specificity for influenza, be relatively simple and inexpensive to perform, and allow for diagnosis early in the course of infection (when antiviral therapy is still effective). There is currently no single test that fulfils these criteria, but improved technology may make an inexpensive, rapid and accurate test available in the near future.[13]

Clinical diagnosis has the advantages of being readily available and inexpensive, but its accuracy has been ill defined. A recent study by Monto et al.[14] has improved our understanding of the rela-

tionship between clinical presentation and likelihood of influenza infection. Retrospective data were used to evaluate the utility of a symptom-based prediction model derived from 3700 healthy adults enrolled in the zanamivir clinical trials. In a patient cohort with an average influenza incidence of 66%, multivariate analysis demonstrated that symptoms of fever and cough provided a positive predictive value (PPV) of 79%. The PPV was higher for individuals presenting with a temperature of ≥38°C at enrolment. Since PPV is dependent on the prevalence of the infection in the community, this prediction model may be less useful when the incidence of influenza is lower.

4. Cost Effectiveness of Interventions

4.1 Vaccination

Vaccination with annual intramuscular injection of inactivated influenza virus has been as the mainstay of population-based prevention. Since the early studies in the 1940s, research has demonstrated that an appropriate vaccine containing inactivated influenza virus delivered by injection can reduce the incidence of symptomatic infection in targeted populations.[15] If there is a good match between vaccine composition and circulating virus strains, the vaccine is 70 to 90% effective in reducing symptomatic influenza infection in healthy young individuals. While less effective in the elderly and patients with chronic illness, vaccination nonetheless reduces the risk of symptomatic influenza infection in these groups by 30 to 80%.[16,17] Multiple studies have demonstrated that vaccination of high risk elderly patients can reduce the risk of hospitalisation by 30 to 50% and also reduce mortality by greater than 50%.[18,19] The reduced risk of hospitalisation translates to a reduction in hospital costs, measured in several studies as ranging from $US10 to $US117 per vaccinee.[20,21]

Table I. Potential impact of future influenza pandemic

Disease measurement	Value
Estimated influenza attack rate	15-35%
Outpatient clinic visits	18-42 million
Hospitalisations	314 000-734 000
Infected and missing work	20-42 million people
Excess mortality	89 000-207 000 people
Direct and indirect costs	$US71.3-$US166 billion (1995 values)

Cost-effectiveness analysis of the vaccine in populations not at high risk have also been encouraging. In a randomised, double-blind placebo-controlled trial, Wilde et al.[22] demonstrated that influenza vaccination of healthcare workers resulted in a decrease in self-reported febrile respiratory illness and a reduction in work absences. Other investigators including Nichol et al.[23] and Campbell and Rumley[24] have shown that vaccination of healthy working adults significantly reduces sick days, and results in cost savings of up to $US45 per vaccinated worker.[23,24] However, a more recent analysis by Bridges et al.[25] found that influenza vaccination of healthy working adults actually costs $US66 per vaccinee. These varying results may, in part, be explained by variation in the attack rates of influenza, as well as in how costs are measured. The most important conclusion may be that, although the cost savings attributable to influenza vaccination in the elderly and infirm are well established, the cost effectiveness in other populations may depend on methodological considerations in the studies.

As data in support of routine vaccination have accumulated, guidelines encompassing this information have evolved. The 2000 Advisory Committee on Immunization Practices (ACIP) guidelines from the Centers for Disease Control and Prevention expanded the groups for whom vaccination is recommended.[26] In particular, the ACIP lowered the recommended age for annual vaccination from >65 years to >50 years, in an effort to better capture high risk individuals, increasing the target population by 28 million in the process. In addition, the ACIP continues to recommend annual vaccination of all adults and children with chronic medical conditions. Future studies are needed to determine whether this expansion of the recommendations is cost effective.

Since resources are limited, society must make choices about the most cost-effective manner to

combat influenza. Should vaccination programmes focus on the elderly who are most at risk of complications or should available resources be focused on the young, economically productive person whose illness may be even more costly to society? The relative value of vaccination must be weighed against alternative uses of scarce resources.

Although the role of the inactivated influenza vaccine is well established, the live, attenuated intranasal vaccine may have additional benefits. Studies have shown that the intranasal vaccine is safe and effective at reducing both serological and symptomatic influenza infections in children and adults.[27,28] Additional benefits may include improved mucosal immunity as well as improved compliance based on improved ease of administration.[4] At the present time, however, there has been only a single trial directly comparing the inactivated vaccine with the live intranasal vaccine and this study demonstrated no difference in immunological response.[29] However, until more direct comparative studies are completed, the inactivated vaccine is likely to remain the mainstay of influenza prevention.

4.2 Drug Treatment

Since vaccination may be refused and, even when given, may be ineffective, antiviral therapy remains an important weapon against influenza.[30] Although antiviral therapy was introduced over 30 years ago, the available drugs, amantadine and rimantadine, have not been widely accepted. These drugs, if given early in the course of disease, reduce the duration of symptoms and provide effective postexposure prophylaxis.[31] Major disadvantages, including serious adverse effects, rapid emergence of resistant strains and an absence of activity against influenza B encouraged pharmaceutical manufacturers to develop drugs whose activity and side effect profiles would encourage widespread use.[32,33] This research resulted in the 1999 release of the NIs.

The introduction of NIs such as zanamivir and oseltamivir represents a substantial change in influenza management. These NIs are active against both influenza A and B and are well tolerated by the majority of patients. By inhibiting neuraminidase, these drugs prevent viral replication and decrease the duration of influenza symptoms. *In vivo* studies have demonstrated that administration of an NI to patients within 48 hours of onset of symptoms reduces the duration of illness by approximately 1 to 1.5 days or 30% ($p = 0.05$).[34] Two recent placebo-controlled trials demonstrated that the NI oseltamivir, when given to patients with influenza-like symptoms during a period of known influenza presence in the community, reduced the duration of illness in those with laboratory proven influenza by 30% compared with placebo ($p = 0.06$).[35,36] Importantly, these studies also demonstrated evidence of decreases in influenza complications such as sinusitis and bronchitis, as well as reduction in the need for antibacterials amongst patients treated with NIs.

The rate of significant adverse effects was no greater in patients treated with NIs than those treated with placebo, although the rate of nausea with oseltamivir was significantly higher than with placebo (16 *vs* 5%; $p < 0.01$).[37] Emergence of resistant strains, a major problem of older antivirals, is felt to be less common with NIs. Nonetheless, prolonged treatment courses in immunocompromised individuals are likely to favour the emergence of resistant strains.[38] The best available evidence suggests that resistance, although uncommon, may occur in approximately 1% of isolates from individuals treated with NIs.[39]

In addition to their efficacy for decreasing the duration of symptomatic influenza infection, NIs have shown promise in preventing influenza infection in exposed individuals. Monto et al.[40] demonstrated that administration of zanamivir to individuals exposed to influenza resulted in an 84% decrease in episodes of febrile clinical influenza compared with placebo ($p = 0.01$); a study by Hayden and colleagues[41] demonstrated similar results with oseltamivir.

The efficacy trials of zanamivir and osteltamivir have been conducted largely in the healthy, nongeriatric population. Whether equal benefit is achieved in the elderly and those with chronic illnesses will have to be proven in postmarketing studies. None of the published studies has measured the

cost savings that might be achieved by shortening the duration of disease in healthy individuals. Thus, there is a critical need for additional research to address the cost effectiveness of these drugs.

4.3 Discussion

Influenza is common and costly. Vaccination of the elderly and patients with chronic illnesses reduces the risk of hospitalisation and death, while simultaneously resulting in cost savings to society.

Although the costs and benefits of influenza vaccination have been well documented, similar studies for NIs have not yet been conducted. These studies will have to address the clinical benefits and economic tradeoffs of both diagnosis and treatment. In order to be effective, NI therapy must be initiated within 48 hours of symptom onset, and ideally within 36 hours. Often, however, it is difficult to determine whether an individual has influenza or merely influenza-like illness. All currently available diagnostic algorithms, whether using laboratory-based testing or clinical diagnosis, contain potential shortcomings.

We attempted to evaluate the potential trade-offs involved with 3 alternative treatment strategies: empirical treatment of all patients with suspected influenza with an NI; laboratory-based testing followed by treatment of patients who tested positive; or no treatment offered at all. We found that, provided that a given patient had at least a 40% probability of having influenza and that the value placed on the benefits of treatment was $US125 or greater, empirical treatment with an NI is the most cost-effective strategy.[42] Although the monetary value may vary depending on the perspective (patient, clinician, employer, insurer), an explicit valuation of symptom reduction must occur.

Early data on NIs demonstrated that these drugs reduced transmission of influenza and reduced the duration of symptoms by approximately 30% (section 4.2). More recent studies have demonstrated additional benefits, including reductions in certain influenza-related complications as well as decreased use of antibacterials in patients treated with NIs.[36,43] Other potential benefits, such as reductions in P&I hospitalisations and deaths, and reduction in transmission of influenza between family members or co-workers, have not yet been adequately examined. The benefits of a reduction in duration of symptoms alone in healthy individuals with influenza could be considered akin to those associated with other 'lifestyle enhancing' pharmaceuticals, including sildenafil and nonsedating antihistamines.[44] Alternatively, if NIs can be shown to reduce additional end-points such as P&I hospitalisation and mortality, these new agents may revolutionise treatment of influenza. Ultimately, providers, payors and patients must determine how much they value the benefit afforded by treatment with any of these agents and whether these benefits outweigh the costs.

5. Conclusions

Influenza is ubiquitous but, for the majority of individuals infected, is unlikely to be life threatening. However, the high attack rate combined with the size of the susceptible population results in substantial excess morbidity, mortality and economic costs to society. Although emerging therapies have the potential to reduce the burden of influenza, further study is required to define which populations may benefit and the nature of the benefits that can be expected.

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