81 Pandemic Influenza: Potential Contribution to Disease Burden

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Abstract: Records of disease outbreaks resembling influenza date to the writings of Hippocrates (fifth century BPE). Since then, influenza has afflicted humans around the globe. The most severe ("Spanish Flu" pandemic) of three major outbreaks of the twentieth century killed approximately 20–50 million people worldwide. More recently, the global spread of highly pathogenic bird-adapted strain H5N1 is considered a significant pandemic threat. Since 2003, a total of 379 cases and 239 deaths have been reported. This chapter provides an overview of the genetic characteristics of the virus that elucidate its ability to continuously evade a host's immune system; it describes some of the approaches used to quantify the burden of influenza and discusses their implications for the prevention and containment of future pandemics. The preliminary findings of the studies discussed here suggest that influenza-related burden is highly underestimated in tropical and subtropical regions of the world. This implicates that proper assessment of influenza-related morbidity and mortality worldwide is essential in planning and allocating resources to protect against what could be one of mankind's most devastating challenges. A summary of learned lessons from past influenza pandemics are described and new intervention strategies aim at curtailing a future pandemic are discussed. More importantly, however, is the discussion of today's challenges such as antiviral resistance, limited resources in a world that is globally connected and the imminent gap between the capacity (resources available) of developed and developing parts of the world to respond to a pandemic.

List of Abbreviations: *CDC,* Center for Disease Control and Prevention; *FF, DM,* Currency Code for France and Germany; *Flu,* Influenza; *HA,* Hemmaglutinin; *H1N1,* *H2N2, H3N2, H5N1,* Influenza A Virus Subtypes; *ILI,* Influenza-Like-Illness; *NA,* Neuraminidase; *NB,* Influenza B Virus Glycoprotein; *NPI's,* Non-Pharmaceutical Interventions; *PB1-F2,* Proapoptotic Influenza A Virus Protein; *PI's,* Pharmaceutical Interventions; *P&I,* Pneumonia & Influenza; R_0, Basic Reproduction Number; *S-I-R Model,* Susceptible-Infected-Recovered Model

1 Introduction

Influenza (flu) is among the most ancient of pathogens of man and the most thoroughly studied of viruses, yet their rapid evolution makes control of epidemics and the prevention or even mitigation of pandemics a persistent public health challenge. The replication of the flu virus is noisy, i.e., offspring produced are remarkably variable. Flu viruses mutate continuously in so-called "antigenic drift," a strategy that allows the virus to evade the least experienced and adaptable immune systems in the human host population, the young and the very old.

This chapter is organized as follows:

- Section 1 provides a brief overview of the genetic basis for pandemics.
- Section 2
  - Provides a historical overview of the worldwide impact of flu epidemics and pandemics,
  - Describes approaches used in assessing flu related disease burden,
  - Highlights studies that have quantified morbidity, mortality and socioeconomic costs in countries around the world, and

  - Especially considers the burden in children, the most infected and infectious population group.
- Section 3 presents global and national modeling frameworks for evaluating the burden.
- Section 4 discusses the learned lessons from previous flu epidemics and pandemics, highlights new challenges facing humans today, and discusses preparation strategies for curtailing future pandemics.
- Section 5 concludes with thoughts on the future burden of flu.

2 The Genetic Basis of Influenza Pandemics

Epidemics caused by influenza viruses occur every winter in temperate regions of the globe. The size of these epidemics varies from year to year and from place to place. Very large epidemics associated with the widespread circulation of genetically novel influenza viruses, so-called pandemics, are caused only by influenza viruses of a single type (type A). Influenza (flu) virus, a member of the family Orthomyxoviridae is a segmented single-stranded RNA virus which exists in three types, A, B and C. Only types A and B cause disease of any consequence in humans. The genomes of both A and B viruses are comprised of eight gene segments which code for eleven viral proteins. Ten of these are functionally similar. The NB protein is unique to B viruses and the recently discovered PB1-F2 protein is found only in A viruses (Chen et al., 2001; McCullers et al., 2004; Steinhauer and Skehel, 2002).

Two of these proteins, hemaglutinnin (HA) coded for by the gene segment conventionally labeled #4, and neuraminidase (NA), coded for by the segment labeled #6, appear on the surface of the influenza virion, and are responsible for the greater portion of the immune response in humans. All B-type influenza viruses share variants of the same HA and NA proteins. The clinical attack rates for A and B type viruses are similar in children (McCullers et al., 2004); but the overall clinical attack rate is much lower in epidemics of B-type than A-type viruses. In addition, it has been recently demonstrated that mortality associated with influenza B epidemics has declined about linearly over the most recent 40 years (Reichert et al., 2007). This difference in epidemiology suggests that the circulation of influenza B viruses in human populations is determined by population-based immunity. Reassortment(genetic reassortment) among human influenza B viruses is believed to be the genetic basis for sporadic increases in observed attack rates for B-viruses (McCullers et al., 2004). A-type viruses, however, exhibit another dimension of genetic complexity. A-type viruses circulate not only in humans but in many non-human reservoirs, most notably aquatic birds. The sudden appearance in A-type viruses responsible for human influenza infections of one or more gene segments from influenza viruses that previously circulated only in non-human reservoirs produces chimeric influenza viruses that are sufficiently immunologically novel that very widespread illness and injury occurs among humans. It is also possible that a virus that previously circulated only in a non-human reservoir could mutate sufficiently that it becomes de novo capable both of producing disease in humans and being widely transmissible among humans. Such a virus is maximally different from previous human immunological experience (all gene segments are novel) and potentially could produce the most severe pandemics. Those newly emergent viruses whose genomes are comprised of a substitution of only some of the gene segments of viruses that previously circulated in humans are thought to have arisen via reassortment during dual infections involving both a non-human and human influenza virus.

The appearance of an influenza virus with a substituted gene segment is called "antigenic shift" (Hall et al., 1973; Monto and Kioumehr, 1975; Reichert et al., 2007).

Sixteen immunologically distinguishable forms of HA (H1-H16) have been identified and nine of NA (N1-N9). Because these two proteins are found on the surface of the virion, influenza has long been typed by reference to these two antigens. Only three HA subtypes and two versions of NA have been found in viruses that have circulated widely in humans. Pandemics of the twentieth century and their dates of emergence in the northern/southern hemispheres were caused by viruses of type H1N1 (1918/1918), H2N2 (1957/1958), and H3N2 (1968/1969). The 1918–1919 pandemic virus emerged en bloc as an avian virus the mutation and adaptation of which permitted replication in and transmission among humans (Taubenberger et al., 2005; Tumpey et al., 2005; Webster et al., 1992). The 1957 pandemic H2N2 virus emerged with substitutions of the HA, NA and PB1 gene segments into the evolved H1N1 viruses from an avian virus. The 1968 pandemic (H3N2) resulted from reassortments of the same avian sequences into multiple lineages of the evolved H2N2 viruses resulting in substitutions of HA and PB1 genes (Lindstrom et al., 2004). In each of the twentieth century pandemics, therefore, both the HA and the PB1 genes were substituted. The nomenclature for distinguishing immunologically and epidemiologically important influenza A-type viruses is, therefore, incomplete.

H1N1 viruses re-emerged in 1977 in what is widely believed to have been an accidental release from a research laboratory, probably in China. Currently the subtypes H1N1 and H3N2 are circulating widely in humans. A small number of isolates of H1N2 viruses have also been reported. Therefore, the only A-type influenza viruses not circulating at present are those with hemagglutinin of type 2, H2. In this context, we are all spectators to the brush with emergence of influenza A viruses of type H5N1 including a unique-to-human-experience PB1 gene, which is widely extant in the avian reservoir, causing massive disease in domestic poultry with a sporadic history of infecting small numbers of heavily exposed humans. With a case fatality rate of approximately 50%, these viruses pose the potential for a redux of the Great Pandemic of 1918 in which 1.5–3% of humanity perished.

Records of disease outbreaks resembling influenza date from the writings of Hippocrates (fifth century BPE). It is likely, however, that humans have suffered from influenza shortly, in evolutionary time, after the domestication of animals in which we now recognize the circulation of pathogenic influenza viruses, and in epidemic proportions since the rise of town-size urbanizations. The pandemic of 1580 is thought to be the first "confidently identified as (associated with) influenza" (Pyle, 1986); but "Clear" descriptions are attributed to authors in the tenth century (Langmuir and Farr, 1976). The first epidemiological level description of an influenza pandemic is due to William Farr who is credited with conceptualizing the burden of influenza as the mortality in excess that expected in the pandemic of that year in London. Detailed records begin with the pandemic of 1889–1892, with age-specific mortality, but serologic data became available only in the 1930s.

3 The Burden of Disease Attributable to Influenza

In 1847 William Farr described the burden of flu and developed methods to quantify its contribution to mortality (Farr, 1847; Langmuir and Farr, 1976). Since then, numerous studies have been proposed to quantify the burden of flu in humans.

Flu outbreaks in temperate climates occur from November through April in Northern and from May through September in Southern hemispheres. While seasonal periods characterize

flu outbreaks in Northern and Southern hemispheres, outbreaks in tropical climates are highly irregular and therefore more difficult to predict. Flu pandemics are worldwide epidemics that involve high morbidity and mortality resulting from major mutations in viral genome (antigenic shift). Unlike flu epidemics, pandemics do not necessarily occur in seasonal time. Some criteria for defining a major pandemic include the occurrence of a new emerging virus subtype for which humans have no immunity to and effective person-to-person contact. Three major pandemics have been observed in the last century. The first and foremost severe, the "Spanish Flu" (H1N1), occurred during 1918–1919. It is estimated that 20–50 million individuals succumbed to the disease worldwide (approximately 2% of a world's population), more than 25% of the US population became ill and 2.5% of those infected in the US died. The next major outbreaks, the "Asian Flu" (H2N2) and "Hong Kong Flu" (H3N2) emerged in 1957 and 1968, respectively. While the impact of these latter pandemics was considerably mild when compared to 1918–1919 pandemic, 2 and 1 million worldwide deaths were estimated to have come from the 1957 and 1968 pandemics, respectively (Simonsen et al., 1998).

3.1 Quantifying the Burden of Influenza

The concept of excess mortality was first introduced by William Farr (Farr, 1847; Langmuir and Farr, 1976) to describe influenza epidemics in London. This approach of excess mortality was later applied by Serfling in 1963 and various modifications of this approach are now widely used (Serfling, 1963). Based on the excess criteria, an epidemic occurs when the number of disease cases (mortality) exceeds the number expected. However, defining the term epidemic may differ mildly. For instance, the US denotes an epidemic threshold for mortality based on estimated of the expected number of deaths given in a particular week accompanied by 95% confidence intervals around the projected estimate. With this approach, an epidemic is reported when the upper 95% confidence interval is exceeded.

3.2 Mortality and Morbidity Burden

Prior to 1937, more than 90% of excess deaths were properly attributable to pneumonia. However, over the following decade total excess mortality has dropped to 1/3 that level and the fraction of the remainder attributable P&I dropped by 30%. Currently, this fraction has dropped to below 10% making the evaluation of flu-related burden a more challenging task. The burden associated with flu has been typically evaluated by a criterion that uses deaths recorded by physicians as caused by pneumonia and influenza (P&I) along with other measures such as influenza-like-illness (ILI). Excess mortality due to flu is calculated by estimating a baseline of deaths that would be expected in the absence of flu virus activity, and the number of deaths actually observed. This criterion, however, is not very sensitive as it fails to evaluate flu-related deaths that could have occurred outside the specified flu season or that could have been missed since several other diseases exhibit flu-like symptoms. Although P&I data has been widely used to evaluate excess mortality, it seems to account for about 25% of all flu related deaths; this suggests that estimates based on P&I may not be appropriate to measure the total impact of influenza on mortality (Simonsen et al., 1997). Further efforts aimed to improve excess mortality estimates due to flu have used all-cause mortality data instead.

The Serfling methodology (and various modifications of it) has been used to parameterize a baseline model based on statistical expectations (95% confidence interval of the baseline) by training data from non-epidemic years. A surveillance system based on the Serfling approach signals an epidemic whenever the observed time series data (e.g., P&I, all-cause mortality data) exceeds the established threshold. The model assumes an average mortality described by b_0, a linear trend denoted by b_1*t, 52-week cyclical period (or 52.1667 for adjusted leap years) denoted by $b_2\cos(2\pi t/52) + b_3\sin(2\pi t/52)$. This model can be denoted by the following equation:

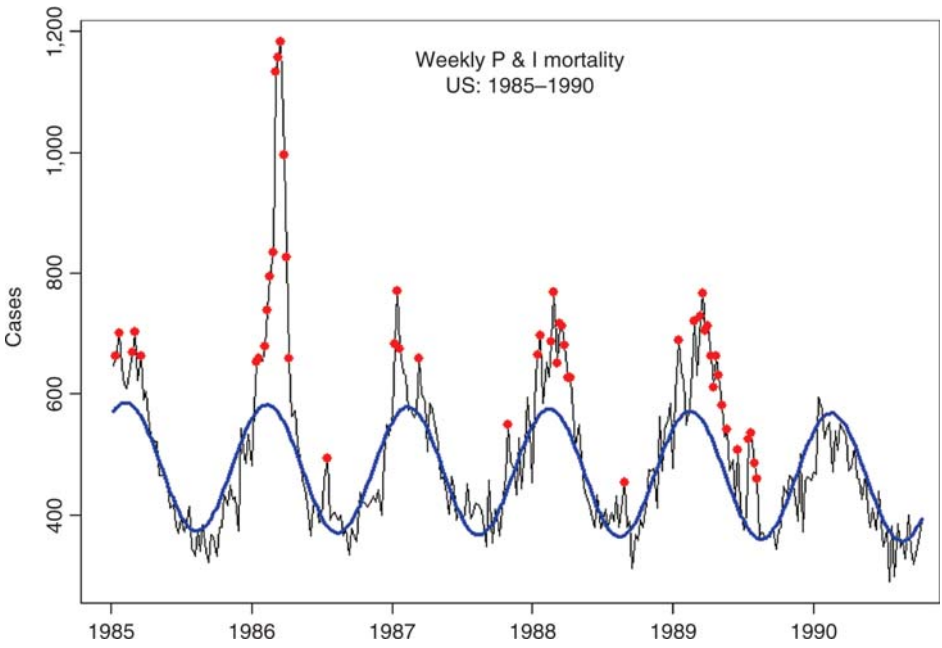
$$Y(t) = b_0 + b_1 * t + b_2 \cos(2\pi t/52) + b_3 \sin(2\pi t/52) + \text{error}$$

where Y(t) denotes the estimated mortality for week t. Variations of this model that account for potential deviations from a linear trend approach include a quadratic term b_1*t^2. We illustrate the proportion of deaths in the United States attributed to pneumonia and influenza (P&I) reported by the 122 cities mortality reporting system.

Figure 81-1 illustrates that the seasonal peaks observed for outbreaks in 1985–1989 seem to have exceed the epidemic threshold.

The sinusoidal function across denotes the seasonal baseline that is established based on periods outside the flu season. US estimates proposed by the Center of Disease Control (CDC) show that each year 5–20% individuals get infected with the virus, some 200,000 individuals get hospitalized and 36,000 die from the disease. Simonsen et al., modified this model to assess the burden of flu on mortality based on P&I and all-cause mortality weekly data for 20 years

Figure 81-1
Pneumonia and influenza mortality for 122 US cities during 1985–1989



(United States: 1972–1992). This study showed that excess mortality estimates were comparable to previous estimates that were based on monthly data (Simonsen et al., 1997). More significantly however, this study showed that P&I excess mortality data only captured 25% of the all-cause excess mortality estimates.

In a separate study, Simonsen et al. (Simonsen et al., 2000) estimated an average seasonal rate of excess P&I hospitalization of 49 cases in 100,000. This study further showed that the average risk of flu-related P&I hospitalization was twice as high during A (H3N2) seasons than those observed during seasons dominated by subtypes H1N1 and B. Individuals of age less than 65 had a 57% of all-flu-related hospitalizations, however the average seasonal risk of flu-related P&I hospitalization was significantly higher for this risk group. Further modifications of the Serfling model have been implemented. Thomson et al. proposed a Poisson regression model to predict excess cases of P&I during influenza epidemics (1979–2001). This study reported significant influenza-related hospitalizations among elderly (50–64 years) and children younger than 5 years old (Thompson et al., 2003). Their findings showed that a yearly average of 133,900 cases listed as P&I hospitalizations were actually associated with the flu virus. A more recent study implemented a Poisson extension of the seasonal type model to predict excess cases of P&I during 16 seasons of flu epidemics in France (Denoeud et al., 2007). This study showed that morbidity data (flu-like-illness and virological data) may be used to predict excess P&I. The implications of this study provide a real possibility of flu-related burden for countries in which specific pneumonia and flu mortality surveillance data is simply not available.

3.3 Evaluating the Burden in Non-Temperate Regions of the World

Most studies have focused on assessing the mortality of flu in regions of the world that exhibit temperate climates, however more recent efforts have demonstrated that burden of flu in the tropics/subtropics is significant. Singapore's yearly clinical infection from seasonal include are estimated at 20% (Ng et al., 2002). In a recent study, Lee et al. (Lee et al., 2007) implemented a linear regression model to evaluate the excess mortality due to flu pandemics of the last century. The authors estimated an excess mortality rate of 7.76 per 1,000 people during May–June and October–November of 1918. Using a similar approach (Murray et al., 2006) these estimates reached a rate of 18 per 1,000 people. Estimates of monthly excess mortality for the 1957 pandemic yield 0.47 per 1,000 people (mid May). Although excess mortality during the1968 pandemic seems mild when compared the 1918 and 1957 outbreaks, this pandemic exhibited two waves. The first wave occurred in mid August with estimated monthly excess mortality of 0.27 per 1,000 people (543 deaths in a population of 2,012,000). Excess deaths peaked again in May–June of 1970 and with an estimated excess mortally in the order of 0.15 per 1,000 people (309 deaths in a population of 2,074,500). Most significantly, this study showed that excess mortality estimates in Singapore are comparable, if not, higher than those observed in temperate regions. Their 1918 pandemic estimate of 1.80% (18 deaths in 1,000 people) exceeds global estimates of 1.06% and Taiwan's rate of 1.44% (Murray et al., 2006). Based on the findings in Lee et al. and studies referenced therein, *Table 81-1* summarizes the burden of flu in the 1918–1919 pandemic and it illustrates that tropical (sub-tropical) countries were affected more significantly than regions with temperate climates. These findings show that Kenya was the most affected country with an upper bound mortality rate estimate of 57.8%. Furthermore, four of the five highest affected countries corresponded to countries with tropical-subtropical climates.

Table 81-1

Estimated deaths and mortality rates attributed to influenza during the pandemic of 1918–1919. Countries are listed in order (highest to lowest) according to the estimated mortality rate

Country	Climate	No. deaths (in 1,000)	Mortality rate (per 1,000) %	Mortality rate ranking (high to low)
Kenya	Tropical	104–150	40–57.8	1
South Africa	Subtropical	300	44.3	2
India	Tropical	185	6.1–43.9	3
The Philippines	Tropical	81.0–288	8.0–28.4	4
Portugal	Temperate	59.0–159	9.8–26.4	5
Singapore	Tropical	2.87–6.66	7.8–18.0	6
Ceylon (Sri Lanka)	Tropical	51.0–91.6	10.0–17.9	7
Spain	Temperate	257–311	12.3–14.9	8
Taiwan	Subtropical	25.4–52.8	6.9–14.4	9
Japan	Tropical/ Temperate	368–517	6.7–9.4	10
United States	Temperate	402–675	3.9–6.5	11
Canada	Temperate	50.0–51.0	6.1–6.3	12
England	Temperate	116–200	3.4–5.8	13
Argentina	Temperate	10.2–46.0	1.2–5.4	14
British Honduras (Belize)	Subtropical	1.01–2.00	2.3–4.6	15
Denmark	Temperate	6.02–12.4	2.0–4.1	16
Australia	Temperate	14.5–15.4	2.7–2.9	17
Trinidad and Tobago	Tropical	0.30–1.00	0.1–0.2	18

This table was adapted from the results presented in Lee et al. (Lee et al., 2007)

3.4 Pediatric Burden

School-age children play a significant role in spreading the flu in a population. Children touch their noses, eyes, mouths, interact closely with other children and have contacts with members of their family. They intensify the spread of the disease since they shed the virus for longer periods of time and at higher virus titers than adults. In addition to their risk to others, the inexperience immune system of children enhances their risk of developing complications from an infection. Annual recommendations from the Center of Disease Control include the vaccination of children aged 6 months–5 years; however more recent discussions recommend vaccination of all-young age children.

Several studies have been reported on the burden of flu on morbidity and mortality in children (Neutzil et al., 2002; Reichert et al., 2001; Simonsen et al., 1998). A prospective surveillance study (1974–1999) of 1665 healthy children younger than 5 years showed annual

infection ranging between 15 and 42% (Neutzil et al., 2002). It was further shown that children younger than 2-year of age were more likely than older children to have serious complications such as pneumonia, croup, chonchiolitis and sepsis (Neutzil et al., 2002). A study assessing age-associated burden of flu in epidemic and pandemic periods showed that half of flu-related deaths during the 1968–1969, with larger proportions of those 1957–1958 and 1918–1919 were attributed to people younger than 65 years of age. This study further showed that the high number of cases observed in these pandemics decrease significantly in prospective outbreaks. More particularly, they found that after each pandemic, the absolute risk of flu-related mortality among people younger than 65 decreased from 7- to 28-fold over the following decade during severe epidemics. In contrast, the corresponding risk reductions among those people older than 65 years of age range from 2- to 3-fold or less (Simonsen et al., 1998). A multiple source data study of the UK during 1995–1999 showed that on average 10% of children contract clinical influenza while a further 20% may be asymptomatic for children younger than 5 years old (Watkins, 2004). While vaccination is the optimal choice for protecting young age children, and thereby, reducing the burden of flu in this group, it has also been shown that the risk to other members of the population can be reduced through children vaccination. Ahmed et al. showed that vaccinating young age children improved community level protection (Ahmed et al., 2001).

So far, our discussion of the burden of flu in children has been limited to countries in which flu outbreaks arise during the winter. However, recent studies of flu-related mortality in tropical and subtropical regions show that burden to children in these parts of the world could exceed the US estimates. Unlike developed countries, children in developing countries face additional challenges such as malnutrition, higher risks associated with bacterial infections, limited access to pharmaceuticals, limited health care, and poor living conditions (Simonsen, 2001). Studies of Cuba and Singapore reported 3–15% flu-related viral isolates in hospitalized children (Cancio et al., 2000; Chew et al., 1998).

Intervention plans aimed at protecting high-risk, as well as, all other members of a population against seasonal influenza have varied from country to country. Japan is the only country that has ever adapted a vaccination program based on children rather than adults. In a consequence to their most destructive pandemic experience in 1957 (approximately 8,000 deaths), Japan legislated a vaccination program that focused on school-age children (7–15 years). Under this program, vaccination levels reached 80%. *Figure 81-2* illustrates decreasing mortality trends from all-cause and pneumonia related mortalities. However, this figure also shows that as soon as vaccination measures were relaxed in 1987, flu-related mortality increased. The rising levels of excess mortality became even more evident after government discontinued the vaccination program in 1997. It has been estimated that the vaccination of children in Japan prevented about 37,000–49,000 deaths per year (Reichert et al., 2001). Other studies have shown that high (50–70%) levels of vaccination among children can provide effective protection to other members in a community (Elveback et al., 1976; Longini et al., 1978; Longini et al., 1988).

Chiu et al. showed that excess hospitalization in Hong Kong rates were higher that US estimates (Chiu et al., 2002). It is evident that influenza contributes significantly to hospitalization among children in both temperate and tropical regions. More particularly, these findings illustrate that the rates reported for Hong Kong exceed those of the US and that trends of decreasing hospitalization rates with increasing age are evident in both estimates. *Table 81-2* reports estimates of flu associated hospitalizations per 10,000 for children in various age groups.

Figure 81-2

Five-year moving average of excess deaths attributed to both pneumonia and influenza (P&I) and all-cause mortality, for Japan and the United States

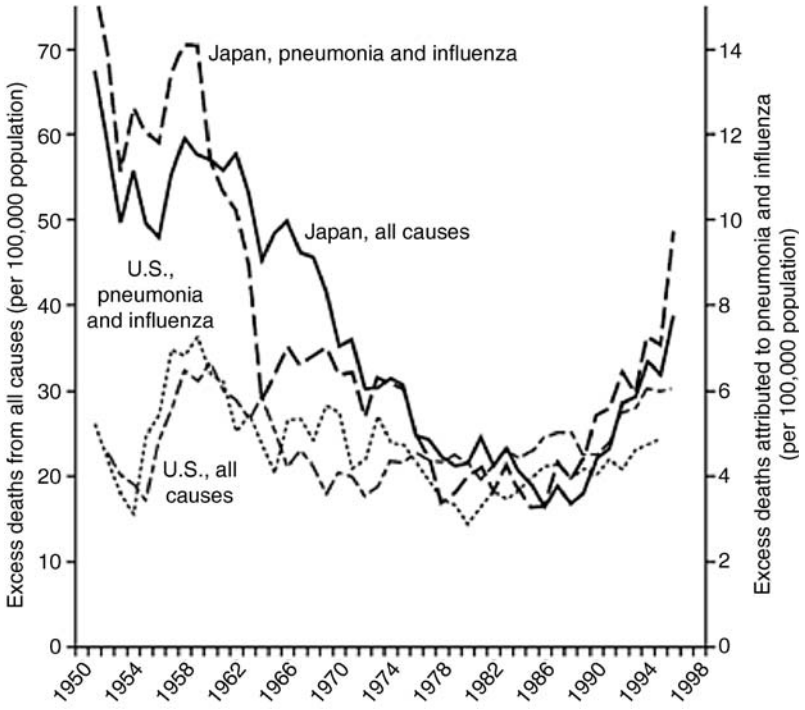


Table 81-2

Estimated flu associated hospitalization rates per 10,000 for the US and Hong Kong

United States	1979–1993
age <1 year	190/10,000
1< age <2	80/10,000
3< age <4	32/10,000
5< age <14	9.2/10,000
Hong Kong	**1998 :: 1999**
age <1 year	278.5/10,000 :: 288.5/10,000
1≤ age <5	218.4/10,000 :: 209.3/10,000
2≤ age <5	125.6/10,000 :: 77.3/10,000
5≤ age <10	57.3/10,000 :: 20.9/10,000
10≤ age <15	16.4/10,000 :: 8.1/10,000

This table was adapted form Rennels et al and the findings reported in Rennels et al and Chiu et al (Rennels et al., 2002; Chiu et al., 2002)

3.5 Socioeconomic Burden

Factors contributing to the socioeconomic burden of flu may be measured directly if they correspond to cost of hospitalization and pharmaceuticals (e.g., vaccine, antivirals). However, evaluating indirect costs such as loss of days of school and work, loss of productivity is significantly more challenging. During an influenza season it is likely that a large number of its members may be exposed to infection, particularly during the epidemic season. However, the highest risk of hospitalization occurs among infants (younger than 1 year) and the elderly (older than 65 years). Estimates of 90% of cases attributed to flu occur among the elderly. Although flu is not typically reported as the cause for hospitalization, it is most certainly a disease that sets the stage for the complication of other diseases such as pneumonia and chronic illness. Complications of already existing chronic long standing illness due to the flu are likely to result in increased hospitalization periods and more costly treatment, thereby increasing the cost for each person at risk.

In the US, flu contributes approximately 1–3 billion (US) in direct medical cost each year (US Congress, 1981). Estimates of 10–15 billion (US) for indirect costs related to mortality include lost earnings due to illness and lost of future earnings (US Congress, 1981). A French study (1989) estimated the direct and indirect contribution of influenza burden at FF1.9 billion (US: 300 million) and FF14.3 billion (US: 2.3 billion), respectively (Levy, 1996). A study in Germany estimated losses from absenteeism and medical treatment attributed to flu to almost DM2 billion (US: 1.1 billion) (Szucs, 1999). Another Dutch study further showed that flu-related burden could be as high as DM2.6 billion (Kressin and Hallauer, 1999).

4 Global/National Models for Evaluating the Burden

Further approaches used to study the burden of flu and evaluate the role of intervention measures to control the spread of disease involve epidemic mathematical models of disease transmission. These models assume a deterministic, stochastic or individual-level framework (among others) to capture the dynamics of disease transmission among individuals in a population of study. A deterministic compartmental epidemic model makes several assumptions. First, a model's behavior is determined (i.e., deterministic) precisely by initial conditions and parameter values (i.e., no elements of chance are involved). For instance, an initial population size of 500 susceptible and one infectious individual, fixed rates of disease transmission, recovery, and mortality. Second, compartmental implies that the state of the system is given by the number of people in each of the predetermined number of compartments (epidemiological states), for instance susceptible (S), infected (I), and recovered (R). A model is dynamic since the number of individuals in each epidemiological state (S, I, R) changes over time. The progression to disease is captured by the rate at which susceptible become infected and it depends on the number of currently infected hosts in a population. Although deterministic models do not capture random events, they can be extended to incorporate stochasticity. In this setting, events occur randomly, rather than deterministically. Stochastic models are particularly appealing when assessing the spread of disease in small populations where random events are likely to play an important role in the emergence dynamics of disease. Deterministic and stochastic models that characterize individuals in a population into subpopulations according to their current epidemiological state, for instance,

susceptible (S) and infected (I) are inappropriate to evaluate individual-level dynamics. For instance, rather than considering the subpopulation of all susceptible, one may be interested in accounting more specifically for age, gender or differences in risk (e.g. high-risk vs. low-risk) among individuals in a population. The level of detail that is observed in a heterogeneous population has been assessed using individual-level simulation models.

4.1 The Basic Reproduction Number

A key measure of the transmissibility of an infectious pathogen (i.e., flu virus) in these models is denoted by the threshold quantity, the basic reproduction number (R_0). This quantity measures the average number of secondary cases of infection generated by one primary case in a fully susceptible population. R_0 is composed of three contributions: the susceptible population available to have contact with a primary case (S^0), the length of time (D) the primary case is infectious to others (window of opportunity for infection), and the transmission coefficient β (rate of effective mixing). Together this yields the following formula: $R_0 = \beta D S^0$. A value of R_0 equal to one or below defines a transmission threshold under which the generation of new cases is insufficient to support spread of disease within a community. However, R_0 greater than one indicates that the infection will be able to spread in a population. A larger value of R_0 suggests the possibility of a more severe pandemic outbreak. For instance, estimates of R_0 between 2 and 3 were proposed for the 1918–1919 Spanish Flu pandemic (Mills et al., 2004).

4.2 Modeling/Quantifying the Burden of Influenza

Studies of the burden of past and potential future flu pandemics have been made accessible by mathematical models that vary in complexity and address a wide range of research challenges. A recent study reported the findings from three groups (UW/LANL, Imperial/Pitt and VBI group) that implemented individual-based stochastic simulation models to evaluate the effectiveness of a set of pharmaceutical and non-pharmaceutical interventions (NPIs) in reducing the burden of a potential pandemic influenza (Halloran et al., 2008). Comparisons were based on the simulation of a pandemic outbreak in a population similar to that of Chicago (approximately 3.6 million people). These simulations considered the following interventions: antiviral treatment and household isolation of identified cases, prophylaxis and quarantine of household contacts, closure of school, social distancing measures implemented in the workplace and the overall community. This study was aimed at evaluating the effectiveness of these measures as projected by each of the individual-based stochastic simulation models and to assess the robustness of these results to the model assumptions. The results from these three simulation models produced similar effectiveness of the interventions evaluated. More particularly, this study showed that the timely intervention of these measures reduces the final number of flu illness, for pandemics of moderate severity; all models show that NPIs are highly effective. Moreover, school closure is predicted to be highly important in all three model simulations. This study showed that under the levels of compliance (30–90%) and ascertainment (60–80%) assumed in these simulations, that it is quite possible to mitigate a pandemic, at least until a vaccine becomes available. The implications of these studies suggest possible routes that may be used to ameliorate the burden of a potential pandemic. However, the uncertainty involved ascertainment and compliance of cases is likely to play a significant role in the effectiveness of the proposed social distancing and targeted measures.

5 Learned Lessons and New Challenges

Influenza has a long history of affecting human populations. It has been nearly 90 years since the most severe flu pandemic (1918–1919) killed fifty million in a population size of two billion. Since then, we have learned about the virus evolutionary mechanisms, treatment and control interventions, and advances of vaccine research. Research of inter-pandemic and pandemic outbreaks of the twentieth century have shown that the virus undergoes antigenic shift mutations, the risk of infection and death seem to be age specific and related to a person's ability to mount an effective immune response. Although we have learned a great deal about the virus, our knowledge is still limited and the threat of a pandemic is still eminent.

5.1 Control Measures to Combat a Pandemic

Many studies have been proposed to evaluate the role of single, as well as combined intervention strategies that may be used to curtail the burden of a future pandemic. Although vaccine is the optimal approach at curtailing a flu pandemic, antivirals (therapeutic and prophylaxis) are likely to play an important role in reducing the burden. The use of multiple pharmaceutical interventions to reduce the burden of disease associated with a pandemic was evaluated in several studies (Ferguson et al., 2005; Germann et al., 2006, Longini et al., 2004, Longini et al., 2005). Choosing a plan that includes massive stockpiling of antivirals, targeted antiviral prophylaxis, massive pre-vaccination of high-risk individuals or a combination of any of these involves various levels of uncertainty and complexity. The foremost important factor in determining the approach to be implemented is to determine the level of resources available at the time that a pandemic virus emerges. Next, one must consider the potential complications that involve the use of antivirals. For example, should they be implemented as treatment or prophylaxis? Which of these two approaches is more economically efficient and likely to provide higher levels of community protection? Are there any implications of viral resistance with the use of antiviral treatment versus prophylaxis?

In efforts to prepare for a future pandemic, countries (worldwide) have drafted preparedness plans. These efforts include pharmaceutical interventions such as antiviral treatment and vaccine and non-pharmaceutical interventions such as isolation, quarantine, closing of public gatherings. To this end, several studies have been proposed to evaluate the role of these various interventions in minimizing the risk of a potential pandemic. A recent study assessed the current preparedness plans in the US, UK and the Netherlands and simulated single as well as combined intervention strategies during a pandemic (Nuño et al., 2007). The interventions proposed in this study included vaccine, antiviral treatment and prophylaxis, and basic hospital and community level transmission control measures. This study showed that while vaccine was optimal in reducing the burden during a pandemic, antiviral and basic control measures can be highly effective. The main findings in this study showed that the "optimal" plan for a particular country is contingent upon the resources available. That is, in countries with limited pharmaceutical interventions, the use of antivirals as treatment was preferred over prophylaxis. Moreover, in countries with little or no access to a vaccine or antivirals, the benefits of non-pharmaceutical interventions (NPIs) such as basic transmission control measures can be highly effective in reducing the burden due to influenza. This study proposed that the implementation of social behavioral measures that could effectively reduce a person's risk of infection were significant in reducing the burden of disease.

6 Concluding Remarks

Since the emergence of the highly pathogenic strain of avian flu H5N1 in Southeast Asia in 2003, a total of 379 cases and 239 deaths have been reported. Since its detection, the virus has mutated from a low pathogenic to a highly pathogenic strain with limited transmission to humans from infected poultry. Two of the three conditions necessary for a pandemic have been met, primarily, a new strain (H5N1) has emerged for which humans have very little immunity, strain can jump between species. The pending obstacle for a flu pandemic is its inability to be transmitted from human to human.

This chapter presented an overview of the genetic characteristics of the flu, discussed the properties of the virus that make it continuously challenging to humans, described some of approaches that have been used to quantify the burden, and concluded with a discussion on the current challenges that we face in preparing against a pandemic. As discussed, there are several challenges involved in evaluating the accurate burden of flu; the non-specific nature of the illness typically lends itself for an incomplete confirmation of cases that is likely to be attributed to the flu virus. For instance, it is possible that a person may experience an infection without the presence of symptoms and therefore escape surveillance systems. It is also possible that those infected individuals develop symptoms but choose to be cared for at home and therefore do not report to a clinic or hospital. Aside from the challenges involved in the surveillance and timely collection of data, this study emphasized that current methods for evaluating the burden of influenza are applicable in some cases to countries with temperate climates. A summary of the burden in tropical and subtropical regions of the world showed that in fact, the burden of flu has been highly underestimated. These findings suggest that an effective preparedness plan should be based on a global and accurate assessment of the burden. That is, building a capacity (pharmaceutical and non-pharmaceutical interventions) that is aimed at reducing the burden of developed and developing countries is essential for the well-being of communities worldwide.

New limitations that have evolved from advances in treating flu include antiviral resistance. A recent study showed that the benefits of antivirals during a flu pandemic are likely to be reduced by the presence of drug resistance (Lipsitch et al., 2007). As suggested in the evaluation of single and combined intervention plans for the US, UK and the Netherlands, Nuño et al. showed that the strategy of implementing antivirals in treatment or as prophylaxis will strongly depend on the level of resources available (Nuño et al., 2007). Countries with limited resources should opt for treatment rather than prophylaxis. An overwhelming conclusion from the studies that have evaluated various forms of interventions to curtail pandemic flu is that vaccine is clearly the optimal choice. However, there are practical limitations with the use of a vaccine. Foremost importantly, vaccine is unlikely to be available at the time a pandemic virus emerges in humans, as current methods for developing a flu vaccine require several months. Once a vaccine becomes available, it is uncertain how many doses each person would require for protection. With current manufacturing capabilities only about one third of the US population is likely to have access to a vaccine. Unfortunately, the level of resources that may be available for developing countries is likely to be much lower than the US and other developed parts of the world.

There are certainly numerous challenges that current public health systems face worldwide with the prospect of a flu pandemic. The main challenge includes the uncertainty

involved with the use of antivirals, vaccine and non-pharmaceutical interventions. Among the interventions that are likely to be readily available at the time of pandemic, non-pharmaceutical interventions (NPIs) will play an essential role in slowing the progression of an outbreak. However, the success of a NPI-based approach will likely be conditional on its timely and continuous implementation throughout the entire pandemic period (Bootsma and Ferguson, 2007; Hatchett et al., 2007; Markel et al., 2006; Markel et al., 2007). Early relaxation of these measures could further magnify the spread of a pandemic and yield devastating levels of morbidity and mortality. An optimal plan for preparing against a prospective flu pandemic is contingent upon the availability of pharmaceutical resources, its potential complications and the social demands that non-pharmaceutical interventions such as isolation, quarantine, closing of public gathering will have in a society.

The methods described in this chapter to evaluate the burden of influenza (seasonal or pandemic) can be easily implemented to study the spread and burden of other diseases such as SARS, smallpox, HIV, and others. Each disease involves different challenges (latency periods, different modes of transmission, infectiousness and mortality differences), however, the goal from a public health perspective is similar in all. That is, to develop appropriate methods to accurately assess the burden of disease and reduce/prevent the spread in a population.

Summary Points

- Flu-related morbidity and mortality is underestimated nationally and worldwide.
- The burden of seasonal influenza based on epidemics and estimates of excess mortality and morbidity is most significant among the young children, elderly individuals older than 65 years old, and the immunocompromised.
- Methods to evaluate the burden of influenza (excess mortality) in temperate regions relies on seasonally observed outbreaks, however evaluating the burden in parts of the world where most people live (tropics and subtropics) is a major concern because these regions have harbored previous pandemic strains.
- Cross-country studies that accurately evaluate the burden of flu epidemics and pandemics are essential in improving current preparedness plans and building appropriate resources (capacity).
- While vaccine is optimal for combating the flu, there are major logistical complications with this approach:
  - Vaccine will unlikely be readily available at the time when pandemic flu cases arise.
  - Resources will be insufficient to protect the population at risk, particularly in parts of the world that have limited-to-no access to a vaccine.
- Various challenges are also anticipated with the use of antivirals. Some of the challenges with the implementation of antivirals include:
  - Insufficient resources to provide protection throughout the pandemic period.
  - Resistance to antiviral has already been observed.
  - Early interruption of antivirals is likely to intensify transmission and magnify morbidity and mortality.

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Appendix

Key Facts

Pandemic influenza	Epidemic influenza
Global outbreak of disease resulting from the emergence of a novel virus	Local epidemic caused by a virus that has already circulated in the human population
Associated with major mutations (antigenic shift)	Associated with minor mutations (antigenic drift)
People have no immunity against this virus	People have partial immunity against this virus
40–60 millions deaths worldwide (based on 1918–1919 pandemic estimates)	250,000–500,000 deaths worldwide (yearly)

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