Lessons from Influenza Pandemics of the last 100 Years

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Running title: Lessons from Influenza Pandemics

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Abstract (148 words) (Text 2993 words)

Seasonal influenza is an annual occurrence, but it is the threat of pandemics which produces universal concern. Recurring reports of avian influenza viruses severely affecting humans have served as constant reminders of the potential for another pandemic. Review of features of the 1918 influenza pandemic and subsequent ones helps in identifying areas where attention in planning is critical. Key among such issues are likely risk groups and which interventions to employ. Past pandemics have repeatedly underscored, for example, the vulnerability of groups such as pregnant women and taught other lessons valuable for future preparedness. While a fundamental difficulty in planning for the next pandemic remains their unpredictability and infrequency, this uncertainty can be mitigated in part by optimizing the handling of the much more predictable occurrence of seasonal influenza. Improvements in antivirals and novel vaccine formulations are critical in lessening the impact of both pandemic and seasonal influenza.

Outbreaks of seasonal influenza are perennial occurrences in the temperate zones. Their impact on morbidity and mortality is highly variable but in some years can occur at levels that nearly disrupt the functioning of health care systems. [1,2] During such seasonal outbreaks, questions usually center around the severity and how well vaccine is protecting. But regardless of disruptions, their impact is quickly forgotten.

By contrast, pandemics of influenza occur much less often but are viewed as more threatening because of their relative unfamiliarity and potential for catastrophic impact. Even a century later, much of the concern stems from recognition of the sheer number of deaths attributable to the 1918 influenza pandemic. While estimates of death

have varied greatly, recent scholarship, largely based of previously omitted data from lower income countries, such as India, have revised global estimates upwards [3] Now, 50 million deaths is generally used as an overall global estimate, constituting nearly 3 percent of the world's population at the time. [4]

Pandemics are caused only by type A viruses. The current classification of A subtypes was developed in 1980, based on molecular evidence indicating that the previous nomenclature needed revision, with, in addition, inclusion of the neuraminidase. [5] Table 1 shows the terminology used pre-1980 and the current terminology. Years listed are either the start of virologically-confirmed pandemics or consensus dates reflecting when it was thought that a new subtype had emerged based on serology. [6-9] Influenza viruses were first isolated in the1930's and the etiology and timing of previous activity was based on testing of sera from individuals who had lived through the period in question. This approach, termed seroarcheology resulted in occasional controversy. Most identified the 1889 influenza as caused by A2 viruses and postulated that A3 viruses had started to circulate in 1902 with no recognized pandemic occurrence. Persons who lived through the 1918 pandemic were found to have antibodies against "swine" influenza viruses, now designated as A(H1N1). The more recent reconstruction of that virus confirms the overall validity of the seroarcheologic technique. [10,11]

Some implications of the 1918 pandemic

The most remarkable epidemiological feature of the 1918 pandemic was the unexpectedly high mortality among those 20-39 years of age. [3] Theories to explain this pattern abound but most involve an aberrant immune response. [12] One recent hypothesis postulates that prior infection of children in the 1889 pandemic rendered them particularly susceptible by immunologic imprinting to reinfection in 1918 when they were in their late 20's. [13]. Current evidence suggests that older individuals may have actually been protected in 1918. This is in contrast to the traditional belief in the W shaped epidemic curve, in which the high mortality in the elderly was a result of the erroneous inclusion of seasonal disease from early months of 1918. [14] Figure 1 shows the age-specific mortality in Philadelphia where the pandemic shut down the city and peaked at a weekly annualized rate of 140 per thousand. [3, 15-16] Another often overlooked but constant feature of all pandemics is the high mortality in the very young experiencing their first influenza infection. [14] These observations indicate that understanding the positive and negative effect of prior influenza exposure is critical. [17]

Other observations of relevance to planning efforts are indications of the usefulness of non-pharmaceutical interventions in mitigating community impact. [18] Susceptibility of pregnant women was well documented; it should not have been such a surprise during the 2009 influenza pandemic when it was rediscovered. [3] Sudden death has often been emphasized as a feature of 1918, but it took, on average, 9 or more days for death to occur. [19] (Figure 2) This stresses the need for health systems to have the surge capacity necessary to handle patients with the more typical prolonged illness regardless of the severity of a pandemic. A proportion of the deaths were

104 associated with bacterial complications. The global increase in antibiotic resistant
105 organisms is another major vulnerability. [20]
106
107 **An interval of nearly 40 years and the pandemic of 1957**
108
109 Most pre-1980 lists of influenza pandemics included one in 1947 despite lack of
110 documentation of global outbreaks. (Table 1) In that year, seasonal vaccine became
111 ineffective and it was thought that a new subtype named “A prime” had emerged. [21-
112 22] This understanding was important in developing the doctrine of original antigenic
113 sin. It is now understood that an intrasubtypic reassortment occurred in 1947 which
114 resulted in a major antigenic change of the A(H1N1) viruses. [23] A new subtype,
115 A(H2N2), actually emerged in 1957 when 3 gene segments coding for hemagglutinin
116 (HA), neuraminidase (NA) and an internal component moved from an avian virus into
117 the circulating A(H1N1) virus through genetic reassortment. [24-25] The resulting
118 A(H2N2) virus, which was called “Asian influenza” since it emerged from China, totally
119 replaced the A(H1N1) viruses. Since this was the first true pandemic since 1918, there
120 was immediate concern about its potential impact and great relief when it was found to
121 resemble seasonal influenza with morbidity highest in children and mortality at the
122 extremes of age. [26-27] (Figure 3) In the US, the virus emerged in the spring of 1957,
123 but outbreaks intensified only after schools in the Southern US opened in August,
124 underscoring the importance of children in dissemination. [28] Although vaccine was
125 available in the US late in the first wave, it had to be reformulated because of sub-
126 potency and standardization issues, concerns still being addressed. [29] (Figure 4)

With little vaccine available, attention was paid to other ways to reduce transmission. A controlled experiment conducted at the Veterans Administration hospital in Livermore, CA. demonstrated reduced transmission from the use of ultraviolet lights. [30] That tantalizing observation has been used recently to strengthen the suggestion that small particle aerosol transmission of influenza viruses is of importance.

Observations from the 1968 Pandemic

The A(H2N2) period lasted only 11 years until mid-1968. In July, a major outbreak in Hong Kong signaled that another reassortment event had occurred. [31] Avian influenza genes, one coding for the hemagglutinin and the other an internal component, replaced the existing counterparts in the circulating A(H2N2) virus; the neuraminidase gene was not replaced. [24-25] Emergence of A(H2N2) and A(H3N2) viruses and later events led to the concept that “novel” influenza viruses are most likely to come from East Asia. At the time, it was conjectured that reassortment (or “shift”) of avian and human influenza viruses occurred in a nonhuman “mixing vessel” because humans were believed not to have the right cellular entry receptors for avian influenza viruses. Pigs have receptors for both human and avian influenza viruses and since influenza viruses replicate in these animals, they were considered to be the “mixing vessel”. [32] This was further supported by the observation that humans, poultry, pigs and wild birds live in close proximity in East Asia providing ample opportunity for reassortment to occur there.

The A(H3N2) pandemic exhibited the same patterns of morbidity and mortality as the earlier A (H2N2) pandemic. In terms of reasons for emergence of a pandemic variant after only 11 years, it is of interest that the last outbreak of A(H2N2) in1967-68 was extensive, as measured by pneumonia and influenza (P and I) mortality. This indicates that a considerable percentage of the population still remained susceptible to A(H2N2) [33-34] However, the new A(H3N2) virus completely replaced the previous subtype and its variants, more than 50 years later, have been responsible for the greatest proportion of mortality from influenza viruses.

The first A(H3N2) pandemic wave occurred in the US in mid-winter 1968-9 at a time typical of seasonal influenza but in some parts of the world was delayed. There has been speculation that the delay was a result of protection from the unchanged neuraminidase (NA). Even in the US, contemporaneous studies showed reduction of infection in those with higher anti-NA titers, indicating an independent protective effect beyond anti-HA. [35] The role of anti-NA remains an issue in present day efforts to improve vaccine. [36]

The Swine Influenza Affair of 1976 and the Return of A(H1N1) in 1977

In January 1976, an outbreak of severe influenza occurred at the US military's Fort Dix, NJ. The causative virus was surprisingly found to be a variant of swine influenza, now recognized to be an A(H1N1) virus. [37] Since previous serologic studies had shown that the 1918 pandemic was probably caused by swine influenza (Table 1), there was strong concern that the Fort Dix outbreak could be the herald of another

severe pandemic. [38] In the US, vaccine production was begun after liability concerns of the manufacturers had been addressed. Even though no further human outbreaks were detected, mass vaccinations were begun and stopped only when a relationship between the vaccine and Guillain-Barre was identified. The “affair” has been studied extensively in terms of potential pitfalls in pandemic response and decision making. [39]

In the following year, a different A(H1N1) virus, one which had been circulating before 1957, was identified. [40] Transmission of this virus, termed Russian influenza since the reports first came from the far east of the Soviet Union, was unexpected because the virus had not been detected for 20 years. Infections were widespread, generally mild and limited to younger individuals; residual protection was nearly complete in older individuals. [41] This event has never been considered a true pandemic because so much of the world’s population was not susceptible and because of the uncertain origin of the virus. The re-emerged A(H1N1) virus remained in persistent circulation worldwide along with A(H3N2) viruses and continued to evolve until it disappeared in 2009. Before this, when a new A subtype began circulating, it completely replaced the previous one.

The Continuing Pandemic Threats of Avian Influenza Begin

The concept that avian influenza viruses could not directly infect humans ended in 1997 when avian A(H5N1) viruses spread directly from poultry to humans causing a small but highly important outbreak in Hong Kong. This event, which raised global concern, resulted in deaths of 6 of 18 patients with documented infection. [42-43] Once control measures, especially culling of poultry, were put into place, new cases abruptly

196 stopped. No further human cases were detected until, in 2003, when, in conjunction with
197 die offs of poultry, spread of A(H5N1) to humans occurred, mainly in Southeast Asia.
198 [44-46] Most human infections were the result of contact with poultry, but examples of
199 limited human to human transmission were documented. [47] Because human cases
200 were often severe and resulted in respiratory failure and death, there was high global
201 concern that a pandemic of this virus would be severe, should sustained human to
202 human transmission occur. [48] The nature of the threat, arising in animals but directly
203 of concern to humans, highlighted the generally poor coordination and often rigid
204 separation between animal and human health authorities at national and international
205 levels, as well as a general lack of national planning. The adoption of new International
206 Health Regulations in 2005, which was strongly influenced by the emergence of SARS
207 and re-emergence of A(H5N1) in 2003, constituted a major step forward. [49] In the
208 United States, there was particular attention directed to non-pharmaceutical
209 interventions, a result of the recognition that pandemic specific vaccines would be
210 available relatively late and that influenza-specific antiviral drugs, while important, would
211 be limited in quantity. There were discussions as to whether use of antivirals might be
212 able to contain human transmission of an emerging virus at the source; these plans
213 were mainly predicated on the emergence occurring in Asia. [50-51]
214
215 **The 2009 A(H1N1) Pandemic**
216
217 Continuing concern about outbreaks of avian influenza was interrupted when the
218 first pandemic of the 21st Century unexpectedly started in Mexico in 2009. [52] As a

result of intrasubtypic reassortment, the A(H1N1) variant involved was antigenically highly distinct from previously circulating influenza A(H1N1) viruses. [53] The prevailing dogma previously was that pandemic influenza was the result of emergence of a new virus subtype. However, the subsequent global spread indicates that a pandemic is better defined by the global population's immunological susceptibility and antigenic distance of the new virus from other influenza viruses, rather than rigid applications of virologic rules involving antigenic shift. [54]

The 2009 A(H1N1) virus was associated with lower attack rates in older individuals presumably because of prior exposure to older A(H1N1) viruses. Spread in North America in the spring extended quickly to other parts of the world, highlighting the importance of air travel in accelerating dissemination. In the United States, the spring wave slowed with the beginning of school summer vacations only to pick up again as schools opened in the autumn, re-confirming the importance of children in transmission.

This most recent pandemic has been extensively documented. Severe disease developed in a small proportion of healthy adults, many of whom had no underlying conditions, reminiscent of 1918 but at a much smaller scale. [55] Particularly vulnerable groups included indigenous populations, well-documented in Canada in the first spring wave. [56] This was not observed in the second wave, most likely related to modifications in response, including careful employment of antivirals. The association of severity with pregnancy was another clear reminder of the 1918 pandemic. A newly observed risk was morbid obesity. [57] The new pandemic virus completely replaced the prior circulating seasonal A(H1N1) but co-circulation of the influenza A(H3N2) virus continued.

A societal issue of considerable importance, which is essential to address for future pandemic, and also seasonal influenza planning efforts, was the perception promoted by some that the 2009 pandemic was a “fake pandemic”. [58-59] The claim, amplified by social media, was that the public health response was a conspiracy by governments and WHO to benefit the sale of influenza vaccines. The overall pattern of mortality, which was less extensive than in 20th century pandemics, was an important component. [55] But perhaps the more fundamental observation is that the accusations were consistent with a broader erosion of trust within society. The need to focus on communications and trust building in all phases of a pandemic is an essential lesson for improving planning for pandemics and responding to seasonal influenza.

General Observations from Past Pandemics

During the past 100 years since 1918, each of the four influenza pandemics have presented both common and unique challenges. None has been predictable in terms of timing, location of onset or the causative influenza virus. The ones starting in 1957 and 1968 had the most similar morbidity and mortality patterns, with severe complications and death highest at the extremes of age. The practical consequences for planning are the need to direct interventions to cover such groups while recognizing that other groups may also be higher than usual risk. [60] The age groups most at risk may be the same as in seasonal influenza but may not.

Questions about “severity” are to be expected early but determining such levels is particularly challenging. The impact on morbidity and mortality may differ, and perception of severity may also differ widely depending on place and time. During the start of events, the information available to health authorities is often limited and highly uncertain. Nonetheless, severity assessments are likely to be important for justifying the use of non- pharmaceutical interventions such as closing schools and restricting population movement. Such actions, which apparently had an effect in 1918, are socially disruptive and likely to be divisive. Reducing impact may benefit from using more resources early while communicating the uncertainties involved and the consequences of inaction.

Since 1957, vaccine has always been available late, often after the first wave. In 2009, the current system of virus sharing through frameworks already established at WHO worked well but vaccine was still not available widely nor equitably. New technologies such as a universal vaccine may eventual change this situation but not in the near term. The pre-pandemic use of vaccines containing known potential pandemic viruses, often with adjuvants, has been proposed but there are significant uncertainties in choosing what viruses might go into such a vaccine or for taking the inherent risks. [61-62]

Future approaches to mitigate influenza impact

Preparing for, and responding to, a pandemic is a complex phenomenon, combining science, societal beliefs, practical operational considerations and political will. Some countries and regions have continued to update plans, but others have not. This is a reflection in part of uncertainties following the 2009 pandemic but also what has been termed “pandemic fatigue.” The latter issue has been made worse by the repeated recognition of the pandemic potential of different avian influenza virus variants that have infected humans. [63-65].

Given this context, it is important to recognize that seasonal influenza occurs every year and many of the essential control measures for pandemics are based on those used for seasonal influenza. It is critical to avoid viewing pandemic and seasonal influenza as unrelated. Seasonal influenza is a cause of significant morbidity and mortality and the vaccine supply used for seasonal influenza sets, in a real-world sense,

the production capacity for a pandemic. Some countries that will want access to pandemic vaccine do not consider seasonal influenza as a priority. This will limit their capacities to vaccinate their most vulnerable sub-populations in a pandemic even if vaccine is available. This situation is especially true of lower resourced countries and continued efforts to document the impact of seasonal influenza and concomitantly, to develop the health system capabilities needed to support a pandemic response, remain high priorities. Determining the possible reduction in seasonal severe disease from use of vaccine can be evaluated in a vaccine probe study in which the vaccine is given under controlled conditions to young children in under-resourced areas, similar to studies which documented the need for pneumococcal vaccine. [66] The need for all countries to have and use vaccine in a pandemic is an issue of the equitable distribution of resources on both a national and global scale. Scientific advances have positioned the world to respond better to both seasonal and pandemic threats of influenza. However, to make the most of such advances before the next pandemic will still require consistent attention and both scientific and political leadership

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Table 1

Previous and Current influenza Type A Nomenclature for Subtypes Identified to be Circulating in Human Since 1889 (confirmed pandemics in bold)

Year of Identification	Activity	Pre1980 Nomenclature	Current Nomenclature
1889	**Pandemic**	**A2 (a)**	**H2N2(a)**
1902	Nonpandemic	A3(a)	H3N2(a)
1**918**	**Pandemic**	**Asw (Swine)(a)**	**H1N1**
1929	Nonpandemic	A (A0)	H1N1
1947	Nonpandemic	A'(A prime)	H1N1
1**957**	**Pandemic**	**A2 (Asian)**	**H2N2**
1968	**Pandemic**	**A3(Hong Kong)**	**H3N2**
1976	Nonpandemic	Asw (Swine)	H1N1
1977	Pseudopandemic	A1 (Russian)	H1N1
2009	**Pandemic**	**----------**	**H1N1pdm09**

a These strains were identified by serology but the specific identification is in dispute Some have the 1889 virus as H3N8 but without a different subtype identified starting in1902, a year when there was not a clear pandemic[6-9]

Figure legends

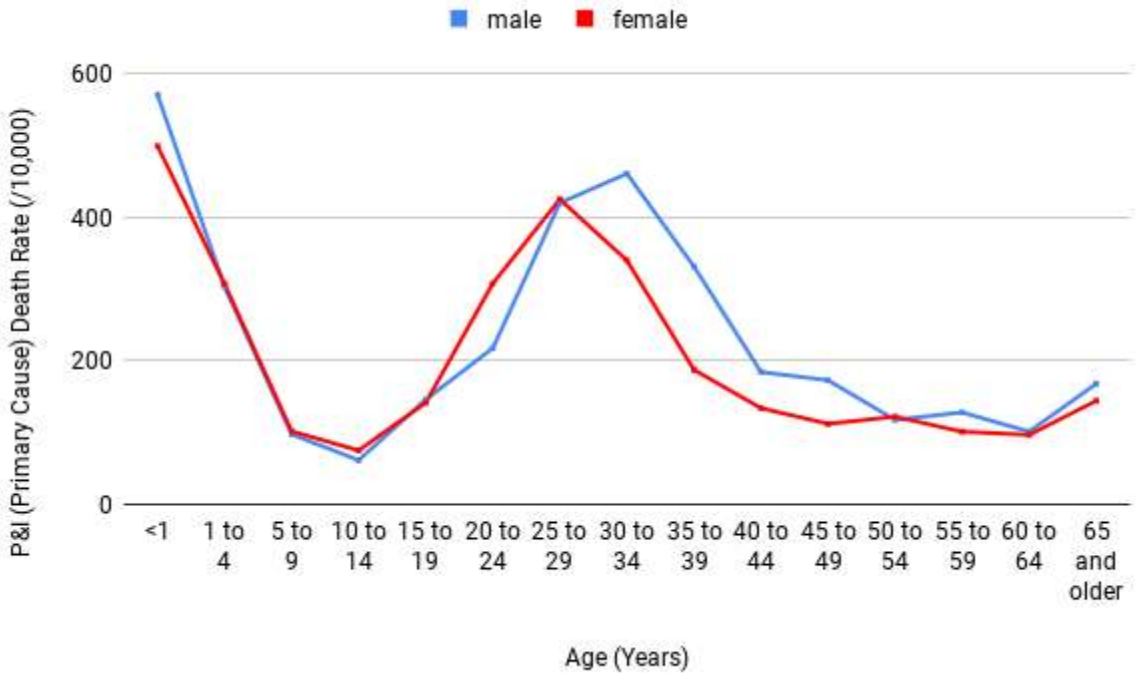
Figure 1. Sex and age specific annualized mortality rates for influenza and pneumonia (primary cause) Philadelphia, PA October-December, 1918 [15]

Figure 2. Distribution of day of death from influenza by day of disease as recorded at 2 US army general hospitals from the beginning of the pandemic until mid-December, 1918[19]

Figure 3. Incidence of influenza-like illness by age among 1,355 families, Kansas City, Mo July-Oct 1957 and pneumonia and influenza mortality by age, United States, 1957 (from [26-27])

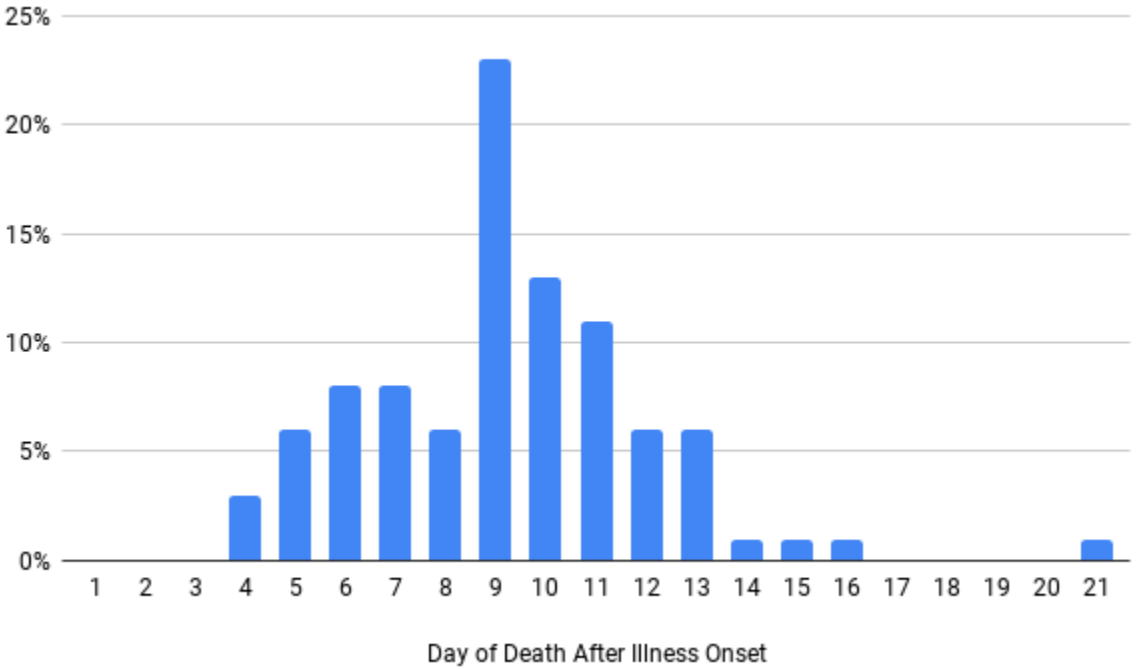
Figure 4. Asian (H2N2) influenza vaccine cleared for release in the US (millions of milliliters)[29]

Figure 1:



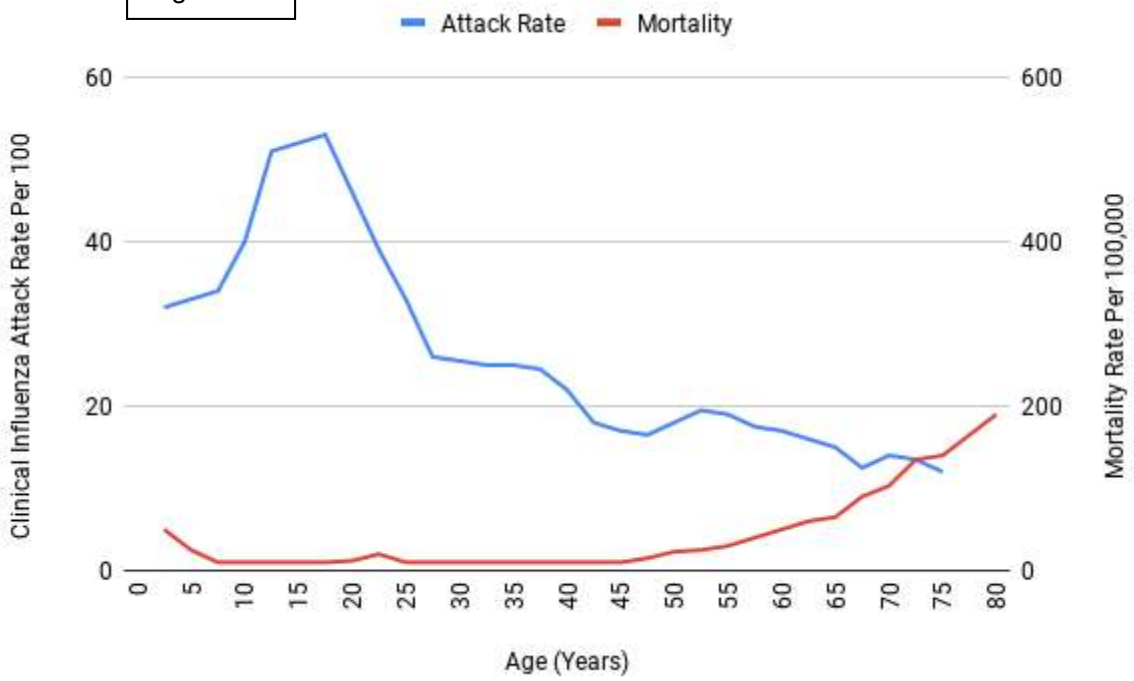
512

Figure 2:



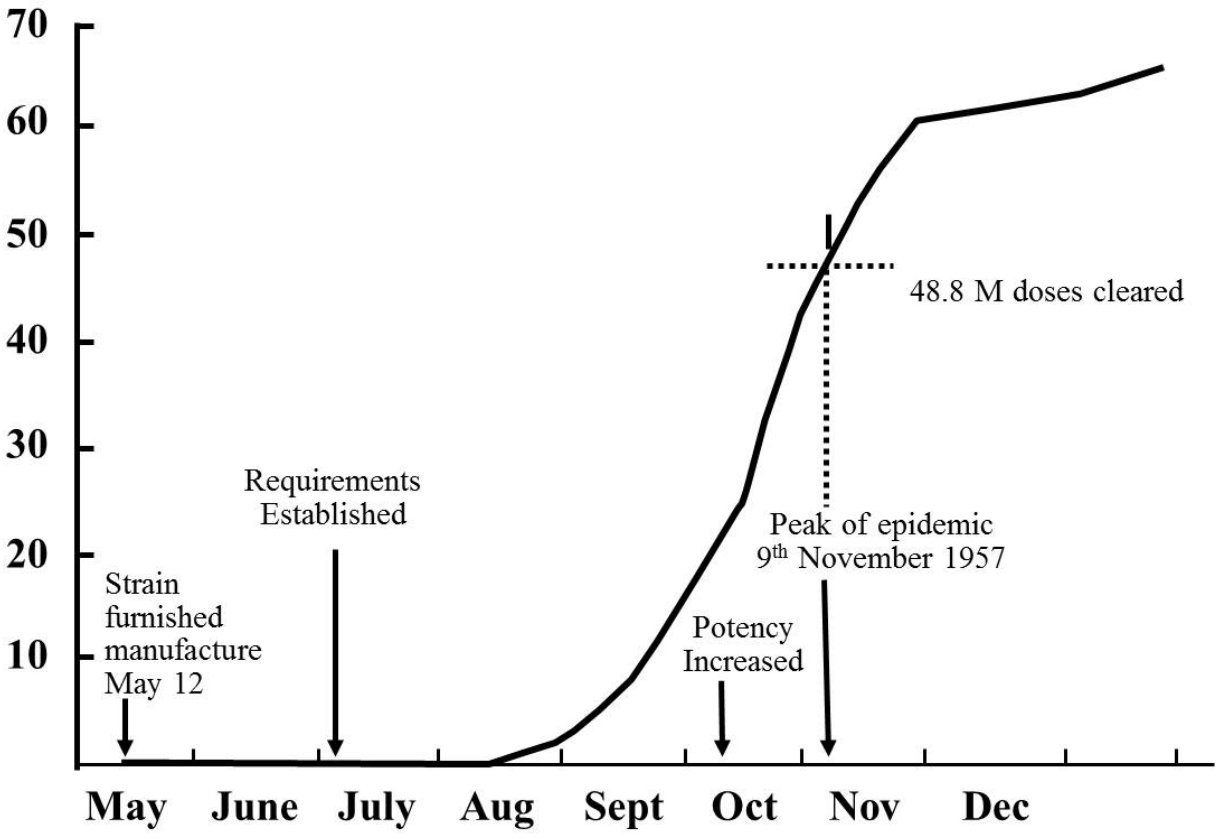
513

Figure 3:



514

Figure 4:



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