Novel Framework for Assessing Epidemiologic Effects of Influenza Epidemics and Pandemics

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The effects of influenza on a population are attributable to the clinical severity of illness and the number of persons infected, which can vary greatly between seasons or pandemics. To create a systematic framework for assessing the public health effects of an emerging pandemic, we reviewed data from past influenza seasons and pandemics to characterize severity and transmissibility (based on ranges of these measures in the United States) and outlined a formal assessment of the potential effects of a novel virus. The assessment was divided into 2 periods. Because early in a pandemic, measurement of severity and transmissibility is uncertain, we used a broad dichotomous scale in the initial assessment to divide the range of historic values. In the refined assessment, as more data became available, we categorized those values more precisely. By organizing and prioritizing data collection, this approach may inform an evidence-based assessment of pandemic effects and guide decision making.

Pandemic influenza results from the emergence of a new influenza A virus to which the population possesses little or no immunity (*1*). Past pandemic influenza viruses have spread rapidly worldwide, affecting persons of all ages and causing substantial illness and death. Influenza can result in a wide spectrum of clinical outcomes in infected persons, including asymptomatic infection, medically and non–medically attended respiratory illness, hospitalization, or death. The likelihood of these outcomes is variable and depends on many factors, including the age of the patient, the presence of underlying medical conditions, and characteristics of the virus itself (*2*).

The overall number of illnesses and deaths from influenza in the population may be primarily attributable to a combination of both the clinical severity of illness in infected persons and the transmissibility of the infection in the population. Figure 1 shows the increasing expected number of deaths in the US population as both the cumulative incidence of influenza in the population and the case-fatality ratio (CFR) increase.

Because the risk for severe outcomes and differences in the rates of transmission of the virus can vary, the effects on the population observed during pandemics have ranged from those similar to severe seasonal influenza epidemics to those experienced during the 1918 influenza pandemic. Depending on the overall population effects, a pandemic could overwhelm the capacities of public health and health care systems or result in societal disruption because of

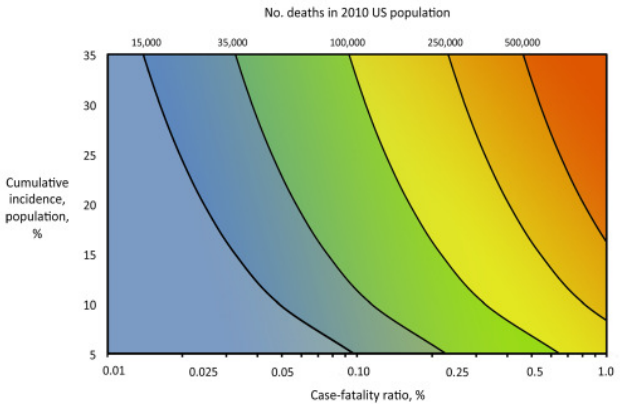

Figure 1. Estimates of influenza deaths in the 2010 United States population (308,745,538 persons) across varying values of case-fatality ratio and the cumulative incidence of infection in the population. Selected estimated numbers of deaths are indicated with a black line, across each relevant combination of case-fatality ratio and cumulative incidence. A color version of this figure is available online (wwwnc.cdc.gov/EID/article/19/01/12-0124-F1.htm)

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DOI: http://dx.doi.org/10.3201/eid1901.120124

school or workplace absenteeism, which could affect critical infrastructure (*1*,*3*).

Historically, assessment of influenza pandemic effects has been characterized by using an estimate of the overall CFR (*4*). Although this approach provided guidance for planning and projections of the expected number of deaths from pandemic influenza in the population, using that ratio alone presents several challenges. First, deaths from influenza may occur weeks after illness begins and can also be subject to reporting bias, delaying the ability of public health and government leaders to quickly issue recommendations for evidence-based public health interventions if they lack an accurate estimate of CFR. Second, a single overall CFR does not fully account for the varying effects a seasonal epidemic or pandemic could have on vulnerable population subgroups, which could include children or the elderly, those with chronic conditions, or certain racial and ethnic minorities. Finally, CFR does not address other societal effects, such as absenteeism or the demand on health care services from excess outpatient visits and hospitalizations, that could result from increased transmission. Because of these limitations, relying on CFR as a single measure of the effects on a population may make an assessment difficult if such data are not yet available early in a pandemic or misleading if the available data are not well characterized and the biases are not well understood.

The ability to synthesize epidemiologic data collected early during a pandemic to characterize its anticipated public health effects is of vital importance to public health officials in the United States and worldwide. Here we provide a conceptual framework with which to characterize the expected effects of a pandemic in the context of past experience with influenza epidemics and pandemics in the United States. We examined published data from past influenza seasons and pandemics to determine the range of effects of influenza in the United States. The framework provides a basic structure by which to synthesize epidemiologic data and on which preparedness plans can be developed to guide and communicate the pandemic influenza response.

Methods

We developed the assessment framework using a 4-step process. The steps included were the following: 1) identify and evaluate available measures of influenza transmissibility and severity, 2) create a standard scale for selected measures, 3) summarize and scale available measures, and 4) provide historical context.

Step 1: Identify and Evaluate Measures of Transmissibility and Severity

We first identified epidemiologic measures that may be indicators of either the transmissibility of a novel influenza virus or the clinical severity in infected persons. The identification of relevant measures within these categories was based on an extensive review of historical seasonal and pandemic influenza literature, including published articles and reports of surveillance data collected from the 1918 pandemic forward. Three criteria were used to evaluate the identified measures: 1) the availability and quality of data related to the measures during the early stages of past influenza pandemics and seasonal influenza epidemics; 2) the presence of enough variation in the measure to produce a biologically plausible and measurable scale; and 3) the epidemiologic strengths and limitations of the measure (online Technical Appendix, wwwnc.cdc.gov/EID/pdfs/12-0124-Techapp.pdf).

Step 2: Scaling Measures of Transmissibility and Severity

From the list of measures identified in step 1, we abstracted data from the literature review on the measures as reported during previous influenza seasons and pandemics. To create a comparable scale across the various measures of transmissibility and clinical severity, we first identified the range of values that had been observed historically for each measure. The data for each measure were then categorized into a uniform scale that was consistent across indicators of transmissibility and across indicators of clinical severity.

Because the availability and quality of epidemiologic information will increase throughout the course of a pandemic, we divided the assessment process into 2 assessment frameworks: 1) an "initial assessment" when data are sparse or very uncertain, and 2) a "refined assessment" when data are more available and more certain. A uniform scale of the transmissibility and clinical severity indicators was developed for each framework. When transmission of a novel influenza virus is identified, early epidemiologic measures provide a broad initial assessment, albeit with a high level of uncertainty, and were categorized by using a broad dichotomous scale. The assessment framework would become more refined as additional epidemiologic and clinical information are gathered and the biases in the earliest measures are better characterized. During this period, a similar general framework would incorporate a finer scale, allowing for more discrete separation of seasonal epidemics and pandemics.

Step 3: Summarize and Score Available Measures

During the initial assessment, a combination of the dichotomous scale for indicators of transmissibility and the dichotomous scale for indicators of severity results in a framework with 4 profiles (A, B, C, D) (Figure 2). An initial assessment can be made as soon as data on some measures become available and would continue to be reviewed and revised as the data warrant. As early data become available, issues of data quality are also essential to consider; we include a list of such considerations in

the online Technical Appendix. Once more robust data are available, the assessment could transition to the more detailed scale of the refined assessment framework, with scaled values of severity and transmissibility plotted along an x-axis and y-axis, respectively (Figure 3). Because the effects of an influenza pandemic may vary between age groups, the refined assessment could also be conducted with age-stratified data on indicators of transmissibility and clinical severity and then plotted by using the same scale and framework (Figure 4).

Step 4: Provide Historical Context

For the refined assessment, we scaled and plotted data from obtained from our literature riew for 4 pandemics (2009, 1968, 1957, 1918) and 3 nonpandemic influenza seasons that ranged in transmissibility and severity (1978–79, 2006–07, and 2007–08) (online Technical Appendix). When multiple measures for transmissibility or severity were present, we used the median score across all available measures. Age-stratified data from the 2009 influenza A (H1N1) pandemic were also similarly scaled and plotted by using the age categories <18 years, 18–64 years, and ≥65 years.

Results

Initial Assessment

Early in a pandemic, the spread of a novel virus is likely to be restricted to a particular geographic area, mostly in focal clusters of infections, and epidemiologic data are limited. To reflect the uncertainty in early data, we divided each measure of transmissibility and severity for the initial assessment framework into a dichotomous scale corresponding to the low-moderate and moderate-high ends of the range of values from the literature review. Scaled values for the initial assessment are shown in Table 1.

We recognized that early measures are likely to have substantial biases. Early measures of the transmissibility of the virus are likely to come from larger recognized outbreaks, which may lead to higher estimates than would eventually occur in the whole population. Likewise, early indicators of severity may be overestimated if severe illnesses are more likely to be recognized, as was seen worldwide early in the 2009 influenza A (H1N1) pandemic (*5*,*6*). For example, reports to the Centers for Disease Control and Prevention (Atlanta, GA, USA) of confirmed cases in the first few weeks of the 2009 pandemic indicated a crude CFR of 0.3% (*7*), »10-fold higher than it was estimated to be following adjustment for underdetection (*5*,*8*). To account for this bias in early measurements, we set the midpoint of the CFR in the initial assessment 10´ higher than the midpoint in the refined assessment.

Early measures of transmissibility were then scaled along a y-axis, and early measures of clinical severity were scaled along an x-axis. From the combination of these 2 dichotomous scales, the initial framework results in 4 quadrants (Figure 2). In quadrant A, for example, available indicators appear similar to the range seen in annual seasonal epidemics. For quadrant B, although clinical severity is in the range of that seen in seasonal epidemics, the transmissibility is greater and thus overall rates of severe outcomes may be greater. Conversely, in quadrant C, transmissibility is similar to that of seasonal epidemics, but severity is expected to be higher, again leading to increased expected rates of severe outcomes, but for a different reason. Finally, in quadrant D, both indicators are greater than expected during annual seasonal epidemics. Consequently, recommended guidance and interventions during the pandemic response may be different between the quadrants.

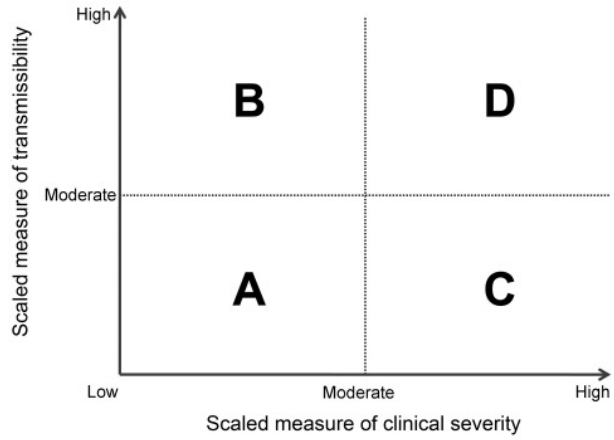

Figure 2. Framework for the initial assessment of the effects of an influenza pandemic.

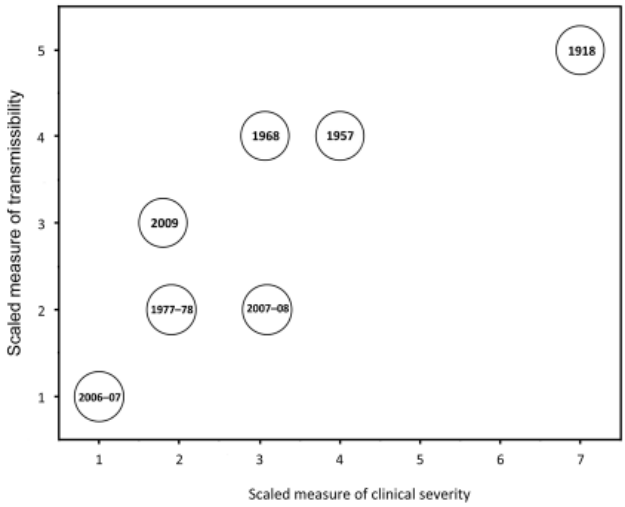

Figure 3. Framework for the refined assessment of the effects of an influenza pandemic, with scaled examples of past pandemics and past influenza seasons. A color version of this figure is available online (wwwnc.cdc.gov/eid/article/19/1/12-0124-F3.htm).

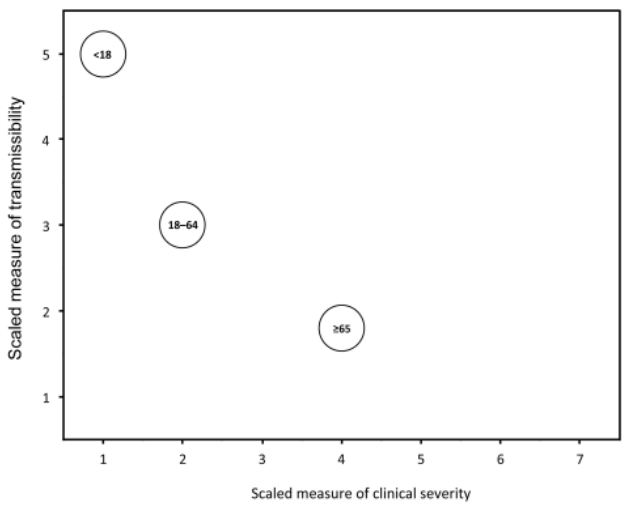

Figure 4. Framework for the refined assessment of the effects of an influenza pandemic, stratified by age group with scaled examples from the 2009 pandemic. A color version of this figure is available online (wwwnc.cdc.gov/eid/article/19/1/12-0124-F4.htm).

Refined Assessment

Although the assessment would be updated routinely as new data become available, an increase in the amount and quality of data will allow results to be presented in a more precise, refined assessment. For this framework, the range for each measure of transmissibility was divided into a 5-point scale while the range for each measure of clinical severity, which covered a broader range of values, was divided along a 7-point scale. To illustrate this assessment framework, we selected 5 measures of transmissibility and 3 measures of severity to scale on the basis of information obtained in our literature review. Detailed discussions of the measures and their strengths and limitations are in the online Technical Appendix. Table 2 displays the ordinal scales for the measures of transmissibility and clinical severity that we developed for the refined assessment. For example, a cumulative symptomatic attack rate of 12% would be classified as a 2 on the scale, whereas a cumulative symptomatic attack rate of 28% would be a 5 on the scale. Likewise, a CFR of 0.01% would be a 1 on the clinical severity scale, whereas a CFR of 1.2% would be a 7. Each measure followed this approach with a scale of 1, representing the lowest observed values for that parameter, with values increasing as the scale increases.

Using available measures of transmissibility and clinical severity and the scale in Table 2, we plotted the coordinates for several sample years on the refined assessment framework. For example, using the 2009 pandemic (Table 3), available measures of clinical severity included the symptomatic CFR, the symptomatic case-hospitalization ratio, and the ratio of deaths to hospitalizations (*5*,*8*). Each of these measurements was a 2 on the ordinal scale of clinical severity. Available measures of transmissibility from 2009 included a household secondary attack rate (*9*–*11*), an estimated population clinical attack rate (*12*), an estimated R_0 (*13*), and a peak percent of visits for influenza-like illness from national surveillance (*14*). Each of these measurements was a 3 on the scale of transmissibility. This is illustrated at the coordinate (*2*,*3*) in Figure 3. We likewise characterized data abstracted from past pandemics and selected previous seasons and also plotted them as shown in Figure 3. Further details are included in the online Technical Appendix.

In addition, we abstracted and scaled data from the 2009 pandemic by age group. These values were plotted in Figure 4, with the dashed box representing the overall

Table 1. Scaled measures of transmissibility and clinical severity for the initial assessment of pandemic influenza effects

Parameter no. and description	Scale: Low-moderate	Scale: Moderate-high
Transmissibility		
1. Secondary attack rate, household, %	≤20	>20
2. Attack rate, school or university, %	≤30	>30
3. Attack rate, workplace or community, %	≤20	>20
4. R_0: basic reproductive no.	1.0–1.7	≥1.8
5. Underlying population immunity	Some underlying population immunity present	No underlying population immunity present
6. Emergency department or other outpatient visits for influenza-like illness, %	<10	≥10
7. Virologic characterization	Genetic markers for transmissibility absent	Genetic markers for transmissibility present
8. Animal models—transmission studies	Less efficient or similar to seasonal influenza	More efficient than seasonal influenza
Clinical severity		
1. Upper boundary of case-fatality ratio, %	<1	≥1
2. Upper boundary of case-hospitalization ratio, %	<10	≥10
3. Ratio, deaths: hospitalizations, %	<10	≥10
4. Virologic characterization	Genetic markers for virulence absent	Genetic markers for virulence present
5. Animal models	Less virulent or similar to seasonal influenza	More virulent than seasonal influenza

Table 2. Scaled measures of transmissibility and clinical severity for the refined assessment of pandemic influenza effects

Parameter no. and description	Scale 1	2	3	4	5	6	7
Transmissibility							
1. Symptomatic attack rate, community, %	≤10	11–15	16–20	21–24	≥25		
2. Symptomatic attack rate, school, %	≤20	21–25	26–30	31–35	≥36		
3. Symptomatic attack rate, workplace, %	≤10	11–15	16–20	21–24	≥25		
4. Household secondary attack rate, symptomatic, %	≤5	6–10	11–15	16–20	≥21		
5. R_0: basic reproductive no.	≤1.1	1.2–1.3	1.4–1.5	1.6–1.7	≥1.8		
6. Peak % outpatient visits for influenza-like illness	1–3	4–6	7–9	10–12	≥13		
Clinical severity							
1. Case-fatality ratio, %	<0.02	0.02–0.05	0.05–0.1	0.1–0.25	0.25–0.5	0.5–1	>1
2. Case-hospitalization ratio, %	<0.5	0.5–0.8	0.8–1.5	1.5–3	3–5	5–7	>7
3. Ratio, deaths: hospitalization, %	≤3	4–6	7–9	10–12	13–15	16–18	>18

assessment of the 2009 pandemic. As shown, the available data indicated that persons <18 years of age had a high incidence of infection during the pandemic (an overall symptomatic attack rate of 26% [*12*], 5 on the transmissibility scale), but relatively few in that age group who became ill died (a CFR of 0.005% [*5*,*8*], 1 on the clinical severity scale). Those ≥65 years of age, however, had little illness (an overall symptomatic attack rate of 15% [*12*], 2 on the transmission scale), but more of those who became ill died (a CFR of 0.18% [*5*,*8*], 4 on the clinical severity scale). Persons 18–64 years of age had values that were similar to those of the overall assessment.

Discussion

A new framework to assess pandemic effects was developed to systematically assess the potential population effects of an influenza pandemic by characterizing data on both transmissibility and clinical severity and providing historical context from past pandemics and influenza seasons. We divided the framework into 2 periods. In the initial assessment, during the early stages of a pandemic, few epidemiologic data may be available and early indicators can be variable. These indications were thus categorized by using a broad dichotomous scale. In the refined assessment, as increased data become available later in a pandemic, the ranges of transmissibility and severity measures were more finely categorized.

Rather than rely only on a single measure, such as the CFR, to assess the potential effects of a pandemic, which may be misleading if those data are unavailable or not representative early in the pandemic, we incorporated several epidemiologic measures into the framework, although the CFR remains a valuable measure of clinical severity. With the creation of a standard scale that includes multiple epidemiologic measures, a variety of data may be incorporated to help synthesize these different measures into an overall indicator of transmissibility and clinical severity.

The visualization of epidemiologic data in the framework provides epidemiologists, public health officials, and policy makers with an evidence-based assessment of influenza transmissibility and clinical severity in the context of previous influenza seasons and pandemics. Although the 3 selected influenza seasons are positioned in a cluster in the lower left of Figure 3, discernible differences exist between the seasons. During the 2006–07 season, subtype A/H1N1 viruses predominated (*15*), producing what has been generally regarded as a milder season in the United States; this season received the lowest score for both transmissibility and clinical severity. Conversely, during the 2007–08 season, subtype A/H3N2 viruses predominated (*16*) to produce what has been generally regarded as a more severe season. This season is positioned toward the center of the graph, which indicates greater transmissibility and clinical severity than was seen in 2006–07. The 3 modern pandemics (2009, 1968, and 1957) are clustered in the upper center of the graph, indicating that these pandemics had higher transmissibility but that overall clinical severity was either at or moderately above the level observed during some recent influenza seasons. In contrast, the 1918 pandemic was positioned at the upper right corner of the graph, indicating a very transmissible and clinically severe pandemic with extensive effects in the population.

An evidence-based assessment of pandemic effects is essential to inform decision makers early in a pandemic and enable them to develop and communicate preventive recommendations to reduce illness and death. The context

Table 3. Indicators of severity and transmissibility from the 2009 influenza (H1N1) pandemic and the corresponding assessment scale

Parameter	Value	Score
Clinical severity		
Symptomatic case-fatality ratio, %	0.02	2
Symptomatic case-hospitalization ratio, %	0.05	2
Ratio, deaths: hospitalization, %	4.7	2
Overall		2
Transmissibility		
Household secondary attack rate, symptomatic, %	13	3
Symptomatic attack rate, community, %	20	3
Peak % visits for influenza-like illness	7	3
R_0: basic reproductive no.	1.4	3
Overall		3

provided by the assessment of transmissibility and severity can inform the selection of pharmacologic and nonpharmacologic interventions that may be appropriate to mitigate the anticipated effects of a pandemic. For example, although the early initial assessment was categorized into only 4 quadrants, this broad early assessment can help organize available information to facilitate early decision-making that may need to be initiated when data are still limited. When clinical severity is high (quadrants C/D), measures may be initiated to provide early treatment to all who are ill and to reduce spread to limit severe disease outcomes and demand on health systems. If clinical severity appears to be similar to seasonal epidemics, but incidence is high (quadrant B), measures may be taken to reduce transmission and prepare for the possibility of disruption in schools and workplaces due to absenteeism. As more data are collected, the assessment transitions into a more detailed refined assessment, and a better characterization of the risks of transmissibility and clinical severity. Subsequently, recommendations and communications may be refined to better reflect the potential effects of the evolving pandemic. Work is ongoing at the Centers for Disease Control and Prevention to use the assessment framework to select different combinations of transmissibility and clinical severity and develop prepandemic guidance on the basis of the potential effects in the population.

Although this framework provided an assessment of the potential population effects from an influenza pandemic, it should not be used in isolation of other epidemiologic data. As this study illustrated, the assessment may be stratified to incorporate data on transmissibility and severity by age group or other risk factors to assess how the expected effects might vary in and across these groups. In addition, decision makers should consider the potential effects in relation to the time at which the pandemic emerges and the particular course of the epidemic in an area (i.e., early vs. approaching peak activity). For example, although the United States experienced a peak of pandemic activity in the late spring of 2009, for most of the country that wave ultimately accounted for only ≈5%–8% of the total estimated burden of influenza during the first year of the pandemic (*5*,*12*). Decision makers should also consider additional factors that are relevant to their individual communities, regions, and states when formulating guidance for interventions based on the epidemiologic impact assessment. These considerations include factors such as access to adequate health care and public health interventions among the affected population, the demographic make-up, the presence of vulnerable populations, or the population density.

Our assessment is subject to some limitations. We conducted a literature review of published data on measures of transmissibility and clinical severity from past influenza seasons and pandemics. Some data were sparse or contradictory, making it difficult to fully understand the variability within measures and the comparability between measures. However, building the framework around a standard scale provides flexibility to refine how measures are categorized as additional data become available and allows for other measures to also be incorporated into the scale. This lack of data underscores the need for ongoing study of the epidemiology of annual epidemics of influenza to improve our ability to accurately characterize the variability in the transmissibility and severity of influenza. An increased understanding of the effects of seasonal influenza will help the public health community prepare for the potential effects of a novel influenza virus.

In addition, there will be biases and limitations in the measurement or availability of epidemiologic data to incorporate in the framework. The online Technical Appendix describes an evaluation of several epidemiologic measures and available data sources. We attempted to account for some of the known biases by adjusting the scales used in the initial assessment on the basis of the most recent experience of the 2009 pandemic. However, changes in care-seeking behavior or testing practices may require readjusting the scale to more accurately reflect future trends. It is also possible that severity could be underestimated initially because of the delay from illness to death, which we did not directly account for (*17*). In the case of influenza, however, this underestimation may have less bearing than the substantial underrecognition of community transmission (*6*).

Continued refinement of the methods by which we collect and analyze data annually on influenza will improve our ability to have accurate and reliable data during a pandemic. A key challenge in assessing the effects of an influenza pandemic is that many cases of influenza are mild, even in the most severe pandemics, and not all persons will seek medical care or be tested for influenza. This leads to an underestimation of the incidence by missing persons who do not seek medical care and biases estimates of severity by disproportionately detecting more severe cases. Developing novel methods to better characterize the community effects of influenza will be vital to define a more accurate case denominator. In addition, strengthening systematic surveillance methods and better characterizing existing systems will also help address some of the biases in the detection of influenza and the estimation of key epidemiologic parameters.

Although we used data from the United States, the framework provides a basic structure to synthesize epidemiologic data that may be useful in other settings as well. The measures used to characterize epidemics and pandemics of influenza have both strengths and limitations; thus, we developed a the framework that is flexible and can be adapted over time to incorporate or refine measures as more data become available or better characterized. Further evaluation of the framework will be needed to determine

whether it will be used as a formal policy for pandemic planning and response. This standardized approach informs the assessment of pandemic impact by organizing available epidemiologic information using a set of key parameters to prioritize data collection and facilitate decision making.

Acknowledgments

We thank the following persons for their helpful comments and contributions: Nancy Cox, Joe Gregg, Mark Frank, Martin Meltzer, Maria van Kerkhove, Tony Mounts, Neil Ferguson, Marc Lipsitch, Angus Nichol, Sylvie Briand, and participants in CDC's Pandemic Severity Summit and Workshop.

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References

1. Glezen WP. Emerging infections: pandemic influenza. Epidemiol Rev. 1996;18:64–76. http://dx.doi.org/10.1093/oxfordjournals.epirev.a017917
2. Fiore AE, Uyeki TM, Broder K, Finelli L, Euler GL, Singleton JA, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. MMWR Recomm Rep. 2010;59(RR-8):1–62.
3. Cox NJ, Subbarao K. Global epidemiology of influenza: past and present. Annu Rev Med. 2000;51:407–21. http://dx.doi.org/10.1146/annurev.med.51.1.407
4. Centers for Disease Control and Prevention. Interim pre-pandemic planning guidance: community strategy for pandemic influenza mitigation in the United States, February 2007 [cited 2012 Nov 19]. http://www.flu.gov/planning-preparedness/community/community_mitigation.pdf
5. Reed C, Angulo FJ, Swerdlow DL, Lipsitch M, Meltzer MI, Jernigan D, et al. Estimates of the prevalence of pandemic (H1N1) 2009, United States, April–July 2009. Emerg Infect Dis. 2009;15:2004–7. http://dx.doi.org/10.3201/eid1512.091413
6. Wilson N, Baker MG. The emerging influenza pandemic: estimating the case fatality ratio. Euro Surveill. 2009;14:pii: 19255. PubMed
7. Dawood FS, Jain S, Finelli L, Shaw MW, Lindstrom S, Garten RJ, et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med. 2009;360:2605–15. http://dx.doi.org/10.1056/NEJMoa0903810
8. Presanis AM, De Angelis D, Hagy A, Reed C, Riley S, Cooper BS, et al. The severity of pandemic H1N1 influenza in the United States, from April to July 2009: a Bayesian analysis. PLoS Med. 2009;6:e1000207. http://dx.doi.org/10.1371/journal.pmed.1000207
9. Cauchemez S, Donnelly CA, Reed C, Ghani AC, Fraser C, Kent CK, et al. Household transmission of 2009 pandemic influenza A (H1N1) virus in the United States. N Engl J Med. 2009;361:2619–27. http://dx.doi.org/10.1056/NEJMoa0905498
10. France AM, Jackson M, Schrag S, Lynch M, Zimmerman C, Biggerstaff M, et al. Household transmission of 2009 influenza A (H1N1) virus after a school-based outbreak in New York City, April–May 2009. J Infect Dis. 2010;201:984–92. http://dx.doi.org/10.1086/651145
11. Morgan OW, Parks S, Shim T, Blevins PA, Lucas PM, Sanchez R, et al. Household transmission of pandemic (H1N1) 2009, San Antonio, Texas, USA, April–May 2009. Emerg Infect Dis. 2010;16:631–7. http://dx.doi.org/10.3201/eid1604.091658
12. Shrestha SS, Swerdlow DL, Borse RH, Prabhu VS, Finelli L, Atkins CY, et al. Estimating the burden of 2009 pandemic influenza A (H1N1) in the United States (April 2009–April 2010). Clin Infect Dis. 2011;52(Suppl 1):S75–82. http://dx.doi.org/10.1093/cid/ciq012
13. Boëlle PY, Ansart S, Cori A, Valleron AJ. Transmission parameters of the A/H1N1 (2009) influenza virus pandemic: a review. Influenza Other Respir Viruses. 2011;5:306–16. http://dx.doi.org/10.1111/j.1750-2659.2011.00234.x
14. Brammer L, Blanton L, Epperson S, Mustaquim D, Bishop A, Kniss K, et al. Surveillance for influenza during the 2009 influenza A (H1N1) pandemic—United States, April 2009–March 2010. Clin Infect Dis. 2011;52(Suppl 1):S27–35. http://dx.doi.org/10.1093/cid/ciq009
15. Centers for Disease Control and Prevention. Update: influenza activity—United States and worldwide, 2006–07 season, and composition of the 2007–08 influenza vaccine. MMWR Morb Mortal Wkly Rep. 2007;56:789–94.
16. Centers for Disease Control and Prevention. Influenza activity—United States and worldwide, 2007–08 season. MMWR Morb Mortal Wkly Rep. 2008;57:692–7.
17. Garske T, Legrand J, Donnelly CA, Ward H, Cauchemez S, Fraser C, et al. Assessing the severity of the novel influenza A/H1N1 pandemic. BMJ. 2009;339:b2840. http://dx.doi.org/10.1136/bmj.b2840

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Article DOI: http://dx.doi.org/10.3201/eid1901.120124

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Technical Appendix

To develop the framework presented in the manuscript we evaluated several measures of influenza transmissibility and severity that have been characterized historically in the literature. In parts A and B, we provide a review of those measures that could be used to characterize novel influenza viruses and pandemics, including a detailed discussion of their strengths and limitations. Some measures did not have sufficient historical data, and were not able to be included in the assessment framework. Such measures may be incorporated into the framework in the future as they become better characterized. In Part C, we outline several data quality issues that should be considered in the inclusion of data in the assessment framework. Finally, in Part D we provide additional detail on the data abstracted from the literature on past pandemics and selected seasons that were used to scale examples provided in the manuscript.

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A. Evaluation of measures of transmissibility: Description of parameter sources, strengths, and limitations

1. R0 and serial interval

R_0 (the basic reproductive number) is defined as the average number of secondary cases per typical case in an otherwise susceptible population. Serial interval is the time between the onset of symptoms in a case patient and the onset of symptoms in the household contacts they infect.

Strengths: These measures help to characterize the speed with which a pathogen spreads throughout the population. The magnitude of R_0 may also inform the intensity of countermeasures that may be required to halt transmission. It is possible to estimate R_0 from case incidence data alone based on the pattern of the growing incidence of cases (1), and may have reasonable precision when the incidence of cases reaches only a few hundred (2).

Limitations: There is a delay before enough cases and generations of spread have occurred to estimate these parameters reliably. Additionally, these parameters are population specific and may not be generalizable from studies that occur in different populations.

2. Estimated attack rate (community, household, school, workplace)

Strengths: Attack rate is important to calculations of morbidity and overall societal disruption due to the pandemic influenza virus. The total number of estimated cases, estimated absenteeism, and potential economic impacts rely on an accurate understanding of the number of individuals who will become ill with the new virus. Field investigations can provide a well-defined population base in which to quickly assess illness and community disruption in an affected area. Approaches such as telephone or internet surveys may allow for a rapid assessment of a relatively large population. Household studies can be a reliable source of data for estimating the secondary attack rate of the disease in households (3).

Limitations: Accurate attack rates are often difficult to estimate early on, as the selected field location must have had enough transmission to get an accurate representation of the ultimate impact of a pandemic influenza virus, and be large enough to provide reliable estimates. In local settings where significant transmission has taken place, studies may not be representative of the total population, since attack rates can vary across geographic and demographic subgroups. Confirmation of pandemic virus infection may be unlikely among all ill participants, thus case definitions that do not rely on laboratory confirmation, such as influenza-like illness, may be used. Even a carefully selected syndromic case definition will miss cases of true pandemic influenza infection, will include cases that do not have true infection.

3. Medically-attended outpatient ILI visits

Presence of an influenza-like illness (routinely defined as fever [temperature >100°F /37.8°C] with cough or sore throat) among participants is currently ascertained through a wide variety of existing surveillance networks.

Strengths: These data provide regional and national views of current influenza activity, and many surveillance systems currently function year-round. Some of these systems have substantial historic data that allow for the development of well-characterized national and regional baselines. Electronic data sources may provide a near real-time snapshot of the number of people visiting outpatient providers or ERs for influenza-like illness. Indicators from these systems are likely going to be one of the first to reflect that a pandemic virus is widespread in a community. Electronic data sources are often available, allowing accurate baselines and trends to be calculated.

Limitations: A syndromic case definition will miss cases of true pandemic influenza infection that do not cause ILI, will include cases of ILI caused by other etiologies, and will exclude asymptomatic cases, giving a limited picture of the virus' activity. In addition, estimates of medically-attended ILI can be influenced by media attention on the spread of a pandemic influenza virus. Therefore, some increase in ILI visits will be a reflection of increased care-seeking behavior where the individual might not have sought care outside of a pandemic. It may be difficult to determine this effect in the early stages of a pandemic without additional field investigations.

Finally, electronic data sources are a new and expanding source of surveillance data. Electronic health record data are not governed by a single set of standards, so each system utilized will have specific caveats and data management issues that will need to be addressed. It may be difficult to find vendors that can provide data on short notice in specific geographical areas without a pre-existing relationship. Once data are received, it may be difficult to interpret and a careful consideration of the source is warranted. Further analysis and evaluation of these data sources during annual influenza seasons will help to identify the most useful sources of data and better characterize measures and trends that would be meaningful in a pandemic situation.

4. Underlying population immunity

Strengths: If representative baseline serum samples are available, limited serologic analysis could be done in a relatively short period of time after the detection of a pandemic virus to identify whether any underlying population immunity exists to the pandemic virus.

Limitations: A dedicated, representative collection of sera with adequate geographic distribution and which captures multiple birth cohorts may not be available for rapidly determining population immunity. Additionally, serology results can be delayed by the time required to develop and conduct virus-specific serologic assays, which may require significant time and resources.

5. Genetic markers of transmissibility

Strengths: Sequencing of the viral genome and antigenic characterization will occur soon after the discovery of a pandemic influenza virus. Information such as the presence of mutations for increased propensity for transmission may be identified from the results of these analyses.

Limitations: Few mutations within the influenza virus genome cause well-defined changes in transmissibility of the virus, nor is it currently known how these mutations correlate with expected attack rate in the population. Additional research will be needed to determine how a mutation or underlying population immunity affects the transmissibility of the virus.

6. Animal transmission experiments

Strengths: Once a novel influenza virus has been isolated, experiments using ferrets or other animal models can determine if contact and respiratory transmission of the novel virus differs from the observed transmission of other seasonal, novel, or pandemic influenza viruses. This work can be accomplished relatively soon after the first detection of a novel influenza virus.

Limitations: Currently, this capability exists in only a few laboratories in the world which can carry out animal studies in appropriate conditions. Results from ferret studies may not represent transmission dynamics in humans.

7. School/workplace absenteeism, including healthcare workers (HCW)

Strengths: Significant increases in school or industrial absenteeism and overall disruption may be detected in outbreak-affected populations. If timely data are available, this may provide some proxy indicators for attack rate before the time needed to organize and conduct a more detailed investigation. Additionally, HCWs in outbreak-affected areas are likely to be one of the first groups at risk for transmission and may provide some of the first opportunities to measure transmission.

Limitations: Currently, there is limited access to historic data on absenteeism and therefore was not included in the current impact assessment. Additional data and analysis of absenteeism records and their causes will be beneficial to determine historic baselines to assess excess absenteeism during a pandemic.

B. Evaluation of measures of clinical severity: Description of parameter sources, strengths, and limitations

1. Case-fatality and case-hospitalization ratios

Strengths: The case-fatality ratio and the case-hospitalization ratio could be estimated from reports of early laboratory-confirmed cases to CDC. In addition, field investigations in an affected area can provide a well-defined population base in which to assess rates of morbidity and mortality in relation to the full spectrum of illness (4).

In combination with statistical expectations about the number of severe outcomes and corresponding precision in a given sample size, the occurrence or lack of severe outcomes may provide a projected range of severity and may indicate an upper bound for the estimated ratios early on.

Limitations: Early in the course of a pandemic, the availability of laboratory confirmation of infection may be unavailable to define the total number of cases, which forms the denominator of these ratios. Since not all ill people are tested, laboratory-confirmed cases will be an underestimate of total cases, and detection is likely biased to more severe cases. As a result, calculations using confirmed cases will likely overestimate the true clinical severity of infection. Novel approaches to the collection(4) and adjustment(5, 6) of data on reported cases have been proposed and may provide avenues to improve the quality of related measures early in a pandemic.

The time to hospitalization and mortality lags behind the identification of illness in the population, and investigations undertaken too quickly in a population may not adequately capture the morbidity and mortality associated with the pandemic virus.

Finally, the threshold for hospitalization can vary broadly among populations/facilities, so it may be difficult to understand how generalizable measures may be that incorporate hospitalization.

2. Ratio of deaths to hospitalizations

Strengths: If influenza testing is likely to be biased toward persons with more severe illness, detection may be less biased between hospitalized cases and deaths than that of outpatient influenza. A ratio of the number of influenza deaths to the number of influenza hospitalizations in a given population may provide some information on the relative severity of a pandemic influenza virus if a greater proportion of severe illness results in death than previously expected.

Limitations: The threshold for hospitalization can vary between populations and over time, depending on the capacity of the health care system. It will be important to better characterize this measure historically to establish an appropriate baseline and variability in the measure. As influenza activity increases, however, an increasing likelihood of death compared to all those with severe illness may be an important measure to understand as a possible indicator of strain on the capacity of the health system to provide supportive care.

3. Genetic markers of virulence

Strengths: Laboratory analysis will be available quickly upon detection of a novel virus. Genetic markers potentially associated with increased propensity for virulence may be identified from the results of this analysis.

Limitations: The association between these markers and severity in human populations is not well-understood. A clear understanding of the presence and absence of certain mutations and their corresponding population-level impact on the virus' pathogenicity in humans is lacking.

4. Animal immunopathologic experiments

Strengths: Soon after isolation of a novel influenza virus, experiments in ferrets can be performed to determine the clinical features of infection. Pathologic and immunologic studies of tissues and biological markers can indicate the extent of infection and the morbidity and mortality of infection relative to experimental infection with other seasonal, novel, and past pandemic viruses.

Limitations: Currently, this capability exists in only a few laboratories in the world which can implement animal studies in appropriate conditions. Results from ferret studies may not represent virulence in humans.

5. Percent of ED visits that resulted in hospitalization

Strengths: Data from electronic data sources may be the earliest source of clinical data available to characterize the spectrum of illness associated with pandemic influenza virus infection. Early analysis of basic data in an outbreak-affected area may provide a sense of the proportion of people presenting to medical care that require hospitalization or other supportive care.

Limitations: The threshold for hospitalization is known to vary from setting to setting, thus it will be important to have a data source that has a well-characterized baseline for comparison. Currently, there is limited access to historic data and therefore was not included in the current impact assessment. As these data sources are relatively new and expanding, additional analysis of such existing data may be needed for interpretation.

6. Percent of hospitalizations admitted to ICU

Strengths: If influenza testing is likely to be biased to persons with more severe illness, detection may be less biased between all hospitalized cases and those requiring ICU admission. The smaller and more well-defined population may allow for more complete ascertainment, and thus a more valid measure of whether a greater proportion of hospitalized cases require critical care than would be expected.

Limitations: The threshold for hospitalization and ICU care may vary between populations and over time, depending on the capacity of the health care system. Currently, there is limited access to historic data and therefore was not included in the current impact assessment. It will be important to better characterize this measure historically to establish an appropriate baseline and variability in the measure.

7. Rate of hospitalization

Strengths: Because influenza testing is more likely to be performed for serious illness, hospitalization for influenza-related causes is less likely to be under ascertained. This measure may provide an assessment of whether the burden of hospitalization is higher than expected and whether specific risk factors exist that increase the rate of hospitalization.

Limitations: The rate of hospitalization is a combination of both the attack rate and risk of hospitalization among ill persons. As a result, without a corresponding measure of attack rate, it is difficult to interpret whether an increased rate of hospitalization represents increased clinical severity of illness or greater incidence of illness in the population.

8. Excess deaths

Strengths: These data have been used for many decades to define a baseline and epidemic threshold for mortality due to pneumonia and influenza (P & I), and provide a well-characterized means to compare P & I mortality from year to year.

Limitations: The number of excess deaths observed in a population can be a misleading indicator of severity because it is a combination of both the attack rate and risk of death among ill persons. As a result, without a corresponding measure of attack rate, it is difficult to interpret whether an increased number of deaths represents increased clinical severity of illness or greater incidence of illness in the population.

C. Data quality evaluation

Because of the uncertainty of early findings, the assessment will continue to be reviewed and revised as the data warrant. Issues of data quality should factor into decisions about the inclusion of epidemiologic data in the impact assessment. The following are some data quality considerations:

- **Type of estimates available**: What is the source population? Who is excluded and are there any impacts caused by these exclusions? Do the data measure the factors meant to be measured?

- **Timeliness**: What is the time period for which the data were collected?

- **Geographic detail**: What is the geographical source of the data? What geographic regions do these data represent? If international, is the population, culture, and medical infrastructure similar to the United States?

- **Availability of historic information**: Do the current data have a historic record with which to compare and benchmark?

- **Statistical standards**: Are there any serious accuracy or methodological problems with the statistics?

- **Revisions to data**: Has the data been revised or corrected because of data quality or analysis issues?

- **Presentation of the information**: Are key materials to support correct interpretation, such as concepts, sources, and methods, provided? Are the data and results presented clearly?

- **Other cautions**: Is there any other relevant issue or caution that should be exercised in the use of the data?

Adapted from: The Australian Bureau of Statistics Data Quality Framework (1520.0)

D. Data on measures of transmission and severity used to scale examples of past seasons and pandemics

Table D.1: Measures from 1918 pandemic, all age groups.

TRANSMISSION		**Range of observed values**			
Parameter		**Low**	**High**	**Score**	**Reference**
1	Cumulative incidence of ILI, community	8.8	39.1	5	(7)
2	R_o: Basic Reproductive Number	--	2	5	(8)
SEVERITY		**Range of observed values**			
Parameter		**Low**	**High**	**Score**	**Reference**
1	Symptomatic case-fatality ratio	--	2.04%	7	(*9*)

Table D.2: Measures from 1957 pandemic, all age groups.

TRANSMISSION		**Range of observed values**			
Parameter		**Low**	**High**	**Score**	**Reference**
1	Cumulative incidence of ILI, community	20%	48%	5	(*10, 11*)
2	Cumulative incidence of laboratory-confirmed illness	18.5%	56.8%	4	(*12, 13*)
3	Household secondary attack rate	8.4%	23.0%	4	(*10*)
4	R_o: Basic Reproductive Number	1.68	1.68	4	(*14*)
SEVERITY		**Range of observed values**			
Parameter		**Low**	**High**	**Score**	**Reference**
1	Symptomatic case-fatality ratio	0.1%	0.3%	4	(*15*)

Table D.3: Measures from 1968 pandemic, all age groups

TRANSMISSION		Range of observed values			
Parameter		**Low**	**High**	**Score**	**Reference**
1	Cumulative incidence of illness, non-confirmed	15%	43%	4	(*16-20*)
2	Cumulative incidence of illness, confirmed	10.4%	32%	4	(*16-18, 21*)
3	Cumulative incidence of infection, confirmed	15%	15%	2	(*22*)
4	Household secondary attack rate, non-confirmed	20%	20%	4	(*18*)
5	R_o: Basic Reproductive Number	1.06	2.01	4	(*23*)
SEVERITY		**Range of observed values**			
Parameter		**Low**	**High**	**Score**	**Reference**
1	Symptomatic case-fatality ratio	--	0.05%	3	(*24*)

Table D.4: Measures from 2009 pandemic, all age groups

TRANSMISSION		Range of observed values			
Parameter		**Low**	**High**	**Score**	**Reference**
1	Cumulative incidence of symptomatic illness, community, confirmed	--	19.9	3	(*25*)
2	Cumulative incidence of symptomatic illness, workplace, non-confirmed	--	17.5	3	(*26*)
3	Household symptomatic secondary attack rate, non-confirmed	11	24	3	(*3, 27-29*)
4	Household symptomatic secondary attack rate, confirmed	4	6	1	(*27, 28*)
5	Peak of ILI activity, percent of clinic visits	--	7.7	3	(*30*)
6	R_o: Basic Reproductive Number	1.0	3.3	3	(*31*)
SEVERITY		**Range of observed values**			
Parameter		**Low**	**High**	**Score**	**Reference**
1	Case-fatality ratio	0.007%	0.048%	2	(*5, 6*)
2	Case-hospitalization ratio	0.16%	1.44%	2	(*5, 6*)
3	Ratio, deaths:hospitalizations	1.8%	8%	2	(*6, 25, 32, 33*)

Table D.5: Measures from 1977-78 season, all age groups

TRANSMISSION		Range of observed values			
Parameter		**Low**	**High**	**Score**	**Reference**
1	Cumulative incidence of ILI, community, non-confirmed	--	48%	3	(*34*)
2	Cumulative incidence of symptomatic illness, community, confirmed	1.0%	20.1%	2	(*35, 36*)
3	Cumulative incidence of infection, community, confirmed	2.2%	31%	2	(*37, 38*)
4	Household secondary attack rate, infection	--	16%	2	(*37*)
SEVERITY		**Range of observed values**			
Parameter		**Low**	**High**	**Score**	**Reference**
1	Influenza excess mortality*	2.2 per 100,000	12.7 per 100,000	2	(*39-41*)
2	Case-hospitalization ratio	0.55%	1.60%	2	(*42, 43*)
3	Ratio, deaths:hospitalization	--	4.9%	2	(*43*)

*These measures to not directly estimate the clinical severity, thus the score for these measures was estimated accounting for the corresponding level of transmissibility.

Table D.6: Measures from 2006-07 season, all age groups

TRANSMISSION		Range of observed values			
Parameter		**Low**	**High**	**Score**	**Reference**
1	Peak of ILI activity, percent of clinic visits	--	3.5%	1	(*44*)
SEVERITY		**Range of observed values**			
Parameter		**Low**	**High**	**Score**	**Reference**
1	Influenza excess mortality*	--	1.55 per 100,000	2	(*39*)
2	Influenza excess hospitalization*	--	26.1 per 100,000	1	(*45*)
3	Ratio, deaths:hospitalizations	--	5.9%	2	(*45, 46*)

*These measures to not directly estimate the clinical severity, thus the score for these measures was estimated accounting for the corresponding level of transmissibility.

Table D.7: Measures from 2007-08 season, all age groups

TRANSMISSION		Range of observed values			
Parameter		**Low**	**High**	**Score**	**Reference**
1	Cumulative incidence of symptomatic illness, community, confirmed	3.1	10.8	2	(*47*)
2	Peak of ILI activity, percent of clinic visits	--	6%	2	(*48*)
SEVERITY		**Range of observed values**			
Parameter		**Low**	**High**	**Score**	**Reference**
1	Influenza excess mortality*	--	3.91 per 100,000	3	(*46*)
2	Influenza excess hospitalization*	--	66.8 per 100,000	3	(*45*)
4	Ratio, deaths:hospitalizations	--	5.9%	2	(*45, 46*)

*These measures to not directly estimate the clinical severity, thus the score for these measures was estimated accounting for the corresponding level of transmissibility.

E. References:

1. **Zachary, I.G. & Johnson, K.M.** Hong Kong influenza in the Panama Canal Zone. First epidemic by a new variant in the Western Hemisphere. *Am J Trop Med Hyg. 18* (6): 1048-56 (1969).

2. **Becker, N.G. et al.** Type and quantity of data needed for an early estimate of transmissibility when an infectious disease emerges. *Euro Surveill. 15* (26) (2010).

3. **Cauchemez, S. et al.** Household transmission of 2009 pandemic influenza A (H1N1) virus in the United States. *N Engl J Med. 361* (27): 2619-27 (2009).

4. **Garske, T. et al.** Assessing the severity of the novel influenza A/H1N1 pandemic. *BMJ. 339*: b2840 (2009).

5. **Presanis, A.M. et al.** The severity of pandemic H1N1 influenza in the United States, from April to July 2009: a Bayesian analysis. *PLoS Med. 6* (12): e1000207 (2009).

6. **Reed, C. et al.** Estimates of the prevalence of pandemic (H1N1) 2009, United States, April-July 2009. *Emerg Infect Dis. 15* (12): 2004-7 (2009).

7. **Frost, W.H.** Statistics of Influenza Morbidity: with special reference to certain factors in case incidence and case fatality *Public Health Records. 36*: 13 (1920).

8. **Mills, C.E. et al.** Transmissibility of 1918 pandemic influenza. *Nature. 432* (7019): 904-6 (2004).

9. **Collins, S.D.** Age and Sex Incidence of Influenza and Pneumonia Morbidity and Mortality in the Epidemic of 1928-29. *Public Health Records. 46* (33): 1909-1937 (1931).

10. **Chin, T.D. et al.** Morbidity and mortality characteristics of Asian strain influenza. *Public Health Rep. 75* (2): 149-158 (1960).

11. **Dunn, F.L. et al.** Epidemiologic studies of Asian influenza in a Louisiana parish. *Am J Hyg. 70*: 351-71 (1959).

12. **Jordan, W.S., Jr. et al.** A study of illness in a group of Cleveland families. XVII. The occurrence of Asian influenza. *Am J Hyg. 68* (2): 190-212 (1958).

13. **Carey, D.E. et al.** Community-wide epidemic of Asian strain influenza; clinical and subclinical illnesses among school children. *J Am Med Assoc. 167* (12): 1459-63 (1958).

14. **Longini, I.M., Jr. et al.** Containing pandemic influenza with antiviral agents. *Am J Epidemiol. 159* (7): 623-33 (2004).

15. **Payne, A.M.** Some aspects of the epidemiology of the 1957 influenza pandemic. *Proc R Soc Med. 51* (12): 1009-15 (1958).

16. **Mogabgab, W.J. & Leiderman, E.** Immunogenicity of 1967 polyvalent and 1968 Hong Kong influenza vaccines. *JAMA. 211* (10): 1672-6 (1970).

17. **Waldman, R.H. & Coggins, W.J.** Influenza immunization: field trial on a university campus. *J Infect Dis. 126* (3): 242-8 (1972).

18. **Davis, L.E. et al.** Hong Kong influenza: the epidemiologic features of a high school family study analyzed and compared with a similar study during the 1957 Asian influenza epidemic. *Am J Epidemiol. 92* (4): 240-7 (1970).

19. **Piraino, F.F. et al.** Outbreak of Hong Kong influenza in Milwaukee, winter of 1968-69. *Public Health Rep. 85* (2): 140-50 (1970).

20. **Sharrar, R.G.** National influenza experience in the USA, 1968-69. *Bull World Health Organ. 41* (3): 361-6 (1969).

21. **Waldman, R.H. et al.** An evaluation of influenza immunization: influence of route of administration and vaccine strain. *Bull World Health Organ. 41* (3): 543-8 (1969).

22. **Foy, H.M. et al.** Longitudinal studies of types A and B influenza among Seattle schoolchildren and families, 1968-74. *J Infect Dis. 134* (4): 362-9 (1976).

23. **Jackson, C. et al.** Estimates of the transmissibility of the 1968 (Hong Kong) influenza pandemic: evidence of increased transmissibility between successive waves. *Am J Epidemiol. 171* (4): 465-78 (2010).

24. **CDC.** Interim Pre-pandemic Planning Guidance: Community Strategy for Pandemic Influenza Mitigation in the United States. CS108488 (2007).

25. **Shrestha, S.S. et al.** Estimating the burden of 2009 pandemic influenza A (H1N1) in the United States (April 2009-April 2010). *Clin Infect Dis. 52 Suppl 1*: S75-82 (2011).

26. **Gindler, J. et al.** A model survey for assessing 2009 pandemic influenza A (H1N1) virus disease burden in the workplace. *Clin Infect Dis. 52 Suppl 1*: S173-6 (2011).

27. **Jhung, M.A. et al.** Epidemiology of 2009 pandemic influenza A (H1N1) in the United States. *Clin Infect Dis. 52 Suppl 1*: S13-26 (2011).

28. **Morgan, O.W. et al.** Household transmission of pandemic (H1N1) 2009, San Antonio, Texas, USA, April-May 2009. *Emerg Infect Dis. 16* (4): 631-7 (2010).

29. **France, A.M. et al.** Household transmission of 2009 influenza A (H1N1) virus after a school-based outbreak in New York City, April-May 2009. *J Infect Dis. 201* (7): 984-92 (2010).

30. **Brammer, L. et al.** Surveillance for influenza during the 2009 influenza A (H1N1) pandemic-United States, April 2009-March 2010. *Clin Infect Dis. 52 Suppl 1*: S27-35 (2011).

31. **Boelle, P.Y. et al.** Transmission parameters of the A/H1N1 (2009) influenza virus pandemic: a review. *Influenza Other Respi Viruses. 5* (5): 306-16 (2011).

32. **Skarbinski, J. et al.** Hospitalized patients with 2009 pandemic influenza A (H1N1) virus infection in the United States--September-October 2009. *Clin Infect Dis. 52 Suppl 1*: S50-9 (2011).

33. **Jhung, M.A. et al.** Preliminary results of 2009 pandemic influenza surveillance in the United States using the Aggregate Hospitalization and Death Reporting Activity. *Influenza Other Respi Viruses. 5* (5): 321-7 (2011).

34. **Sobal, J. & Loveland, F.C.** Infectious disease in a total institution: a study of the influenza epidemic of 1978 on a college campus. *Public Health Rep. 97* (1): 66-72 (1982).

35. **Monto, A.S. et al.** Prevention of Russian influenza by amantadine. *JAMA. 241* (10): 1003-7 (1979).

36. **Wright, P.F. et al.** Differing virulence of H1N1 and H3N2 influenza strains. *Am J Epidemiol. 112* (6): 814-9 (1980).

37. **Fox, J.P. et al.** Influenzavirus infections in Seattle families, 1975-1979. I. Study design, methods and the occurrence of infections by time and age. *Am J Epidemiol. 116* (2): 212-27 (1982).

38. **Monto, A.S. et al.** Tecumseh study of illness. XIII. Influenza infection and disease, 1976-1981. *Am J Epidemiol. 121* (6): 811-22 (1985).

39. Estimates of deaths associated with seasonal influenza --- United States, 1976-2007. *MMWR Morb Mortal Wkly Rep. 59* (33): 1057-62 (2010).

40. **Thompson, W.W. et al.** Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA. 289* (2): 179-86 (2003).

41. **Thompson, W.W. et al.** Estimates of US influenza-associated deaths made using four different methods. *Influenza Other Respi Viruses. 3* (1): 37-49 (2009).

42. **Barker, W.H. & Mullooly, J.P.** Impact of epidemic type A influenza in a defined adult population. *Am J Epidemiol. 112* (6): 798-811 (1980).

43. **Simonsen, L. et al.** The impact of influenza epidemics on mortality: introducing a severity index. *Am J Public Health. 87* (12): 1944-50 (1997).

44. Update: Influenza activity--United States and worldwide, 2006-07 season, and composition of the 2007-08 influenza vaccine. *MMWR Morb Mortal Wkly Rep. 56* (31): 789-94 (2007).

45. **Zhou, H. et al.** Hospitalizations Associated with Influenza and Respiratory Syncytial Virus (RSV) in the US from the 1993-94 through 2005-06 Seasons. *Options for the Control of Influenza VII*. Hong Kong, 2010.

46. **Cheng, P.Y. et al.** Timely Estimates of Seasonal Influenza-Associated Deaths in the United States Using CDC 122 Cities Mortality Reporting System Data. *Options for the Control of Influenza VII*. Hong Kong, 2010.

47. **Monto, A.S. et al.** Comparative efficacy of inactivated and live attenuated influenza vaccines. *N Engl J Med. 361* (13): 1260-7 (2009).

48. Influenza activity--United States and worldwide, 2007-08 season. *MMWR Morb Mortal Wkly Rep. 57* (25): 692-7 (2008).