A severe outbreak of pandemic influenza with a 25% gross clinical attack rate spreads across the U.S. populace.

Category	Description	Metric	Low	Best	High	
Health and Safety	Fatalities	Number of Fatalities ¹	77,000 154,000		230,000	
	Injuries and Illnesses	Number of Injuries or Illnesses ²	62 Million	77 Million	110 Million	
Feenemie	Direct Economic Loss	U.S. Dollars (2011) ³	\$71 Billion	\$110 Billion	\$180 Billion	
Economic	Indirect Economic Loss	U.S. Dollars (2011)	N/A			
Social	Social Displacement	People Displaced from Home ≥ 2 Days	/s 0 ⁴			
Psychological	Psychological Distress	Qualitative Bins	See text			
Environmental	Environmental Impact	Qualitative Bins ⁵	Low ⁶			
LIKELIHOOD	Frequency of Events	Number per Year	r per Year See Table			

Table 1A. Pandemic: SNRA Data Summary

Table 1B.	Conditional	and Absolute	Likelihood	Ranges for	Pandemic	Relative	Severitv
	• • • • • • • • • • • • • • • • • • •						

Frequency of All Influenza Pandemics				;	Low	Best	High	
Absolute Likelihood (Number Per Year) ⁷				′	0.017	0.033	0.10	
Conditional Likelihood of Severity, Given Pandemic Occurrence	Mild	Low	0.10		0.0017	0.0033	0.010	everity
		High	0.30		0.0051	0.0099	0.030	
	Middle	Low	0.50		0.0085	0.0165	0.050	
		High	0.80		0.0136	0.0264	0.080	
	Severe/	Low	0.10		0.0017	0.0033	0.010	e S
	Worst Case High 0.10		0.10		0.0017	0.0033	0.010	lativ
					A	bsolute Lik	elihood by	Re

¹ Fatality low, best, and high estimates were calculated using an attack rate of 25%, a U.S. population of 307 million, and a case fatality rate of 0.1%–0.3% (best: 0.2%). Reed et al (2013, January). Novel framework for assessing epidemiologic effects of influenza epidemics and pandemics; and Technical Appendix. *Emerging Infectious Diseases* 19(1) 85–91, at <u>http://wwwnc.cdc.gov/eid/article/19/1/12-0124_article;</u> Technical Appendix at <u>http://wwwnc.cdc.gov/eid/article/19/1/12-0124_techapp1.pdf</u> (retrieved June 2013).

² Illness low, best, and high estimates correspond to a U.S. population of 307 million and attack rates of 20%, 25%, and 35% respectively.

³ Sum of estimated hospitalization costs, business interruption from workdays lost, and one year's lost spending per fatality. See Direct Economic Impact for details.

⁴ Social displacement was assumed to be zero for the Human Pandemic Outbreak national-level event.

Event Background

There have been eight naturally caused influenza pandemics (including pandemics subsequently deduced to have been caused by influenza virus) since 1729.⁸ Thus, the historic frequency is once every 10 to 60 years. New influenza viruses that affect humans can emerge and spread rapidly. Influenza pandemics can occur at any time due in part to the following factors: the quality and scope of epidemiological and laboratory resources to identify and diagnose viruses with pandemic potential—both in the United States and globally; the complex reassortment of new influenza virus between animal and human hosts; potential lack of antibody resistance to new influenza virus strains in the population at large; potential resistance of new influenza virus strains to available antiviral medications; time needed to identify, develop, produce, and distribute an effective pandemic influenza vaccine; and countermeasure resources in the U.S. and globally to mitigate the transmission of a pandemic virus.

The frequency estimates (0.017/year, 0.033/year, 0.10/year) in the top row of Table 1A represent the likelihood of occurrence of the set of influenza pandemic events as a whole, not the conditional or absolute likelihoods of occurrence of the low, best, and high impact estimates in particular. (Low, best, and high impact estimates also do not necessarily correlate with each other across impact metric, e.g. the high estimates of fatalities, illnesses, and direct economic impacts do not necessarily correlate together in a single scenario.) The overall frequency of occurrence of an event and the conditional probabilities of an incident having low, moderate, or high impacts are independent variables. The top row frequency estimates are the low, best, and high frequencies indicated on the SNRA's comparative charts.

The approximate likelihoods of the 'mild' (10-30%), 'middle' (50-80%), and 'severe/worst case' (~10%) scenarios as described under "Additional Relevant Information" given occurrence of an influenza pandemic in the set as a whole, are listed in the first vertical column to the left. Similarly to the frequency of occurrence of pandemics as a whole, these conditional likelihoods have substantial uncertainties associated with them, and so are represented as ranges. Given the occurrence of an influenza pandemic, these represent the probabilities that the pandemic will be 'mild', 'middle', or 'severe/worse case'. Note that the designation 'mild' is strictly relative: the least severe historical instance of a 'mild' pandemic, the 2009 H1N1 influenza, killed more Americans than any other natural or accidental hazard incident or modeled scenario in the SNRA data set. Note also that these three categories do not correspond to the low, best, and high impact estimates of the SNRA Pandemic event as given in Table 1A the SNRA low, best, and high impact estimates reflect a broad 1957-like pandemic scenario, and the range of impacts described by the SNRA scenario straddle the boundary of the 'mild' and 'middle' categories described in Table 1Band "Additional Relevant Information." The range of impacts for the SNRA Pandemic event correspond to a high-'mild' to a 'middle' scenario.

The absolute frequency of each of the 'mild', 'middle', and 'worse case' scenarios described under "Additional Relevant Information" would be the product of the 0.017 - 0.10/year absolute frequency of the Pandemic event as a whole and their approximate conditional likelihoods of 10-30%, 50-80%, and 10% respectively, or 0.002-0.03, 0.008-0.08, and 0.002-0.01/year. These are presented in the body of Table 1B. Because of the multiple uncertainties involved with pandemic likelihoods, only the ranges (the high and low of each product) are considered to be informationally meaningful: these are colored in violet.

For additional detail, see "Additional Relevant Information" and associated discussion.

⁸ Different authors have different lists of which influenza years they consider to have been pandemics, but most modern writers' lists of likely influenza pandemics in the past three centuries include from about 8 to 12 events in total (when the 2009 H1N1 pandemic is included). Serological studies—blood tests to characterize antigens to surface proteins of influenza viruses a person may have been exposed to in his/her lifetime—have been successfully used to determine the serotypes (combinations of particular H and N surface proteins) of influenza outbreaks back to around 1900. However, making a determination of which historical outbreaks before that point were pandemics by the modern virological definition from past writers' observations indicative of a new influenza serotype (e.g., cross-continent spread, patterns of residual immunity from previous outbreaks) involves a great deal of inference and human judgment. Potter C. W. (2001, October), A history of influenza. *Journal of Applied Microbiology* 91(4) 572–579; Taubenberger et al (2009, April), Pandemic influenza—including a risk assessment of H5N1, *Revue Scientifique et Technique (Rev. Sci. Tech.)* 28(1) 187–202, at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2720801/ (accessed March 2013); Patterson, Karl D. (1986), Pandemic Influenza, 1700-1900: A study in historical epidemiology, Rowan & Littlefield, publishers; Dowdle, W. R. (1999), Influenza A virus recycling revisited. *Bulletin of the World Health Organization* 77(10) 820–828; at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC272381 (accessed April 2013); Norens et al (2010, November), Historical thoughts on influenza viral ecosystems, or behold a pale horse, dead dogs, failing fowl, and sick swine. *Influenza and Other Respiratory Viruses* 4(6) 327-337, at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC231

⁵ In 2011, the U.S. Environmental Protection Agency (EPA) convened an ad hoc group of environmental experts representing the fields of environmental science, ecological risk, toxicology, and disaster field operations management to estimate environmental impacts for this event. The comments and rankings presented in this Risk Summary Sheet have not undergone review by the EPA and only represent the opinions of the group. Estimates pertain to the potential for adverse effects on living organisms associated with pollution of the environment; they are grouped into high, moderate, low, and de minimus (none) categories.

⁶ Experts provided both first and second choice categories, allowing the experts to express uncertainty in their judgments as well as reflect the range of potential effects that might result depending on the specifics of the event. The experts provided a best estimate of 'Moderate' for a pandemic scenario with severe social impacts and a second best estimate of 'Low' for a less severe pandemic scenario (see Environmental Impacts). The SNRA used 'Low' as the best estimate and 'Moderate' as the second best estimate for the Pandemic national-level event, because the final numbers on other impact scales defined a scenario with social impacts corresponding to the less severe as opposed to the more severe pandemic scenario.

⁷ The SNRA data tables are presented differently for Pandemic than for other national-level events to address partner risk communication concerns that are specific for pandemic influenza. The same information is presented as in other data tables, but additional information is also presented.

Assumptions

The SNRA project team used the following assumptions to estimate health and safety impacts caused by a pandemic event:

- The scenario is based on a U.S. population of approximately 307 million. •
- Likelihood, fatality, and illness best estimates and ranges were provided to the SNRA project team by the U.S. Centers for Disease Control and Prevention (CDC).
- These experts stress that it is impossible to predict the timing or severity of the next pandemic.
- All of the estimates are given absent any intervention (i.e., before interventions are applied or attempted).9
- The modeled National-level Event is based on assuming a 25% attack rate¹⁰ and death rates associated with a scenario modeled on a 1957-scale pandemic if it were to occur in today's population.^{11,12}

Frequency

Low (1/60 years), best (1/30 years), and high (1/10 years) frequency estimates reflect the historic frequency of influenza pandemics of natural origin since 1729 of once every 10 to 60 years, averaging 1 in 30 years. These correspond to the absolute likelihood of the set of pandemics as a whole: the conditional likelihood of pandemic scenarios of different severities given occurrence of a pandemic event is discussed under "Additional Relevant Information".

Fatalities and Illnesses

Fatality low, best, and high estimates were calculated using an attack rate of 25%, a U.S. population of 307 million, and a case fatality rate of 0.1%–0.3% (best: 0.2%).¹³ Illness low, best, and high estimates correspond to the same U.S. population and attack rates of 20%, 25%, and 35% respectively.¹⁴

Comparisons to other estimates of health and safety impacts: Large uncertainties dominate any estimate of the human impacts of the next influenza pandemic.

⁹ See "Potential Mitigating Factors."

¹⁰ The attack rate is the percentage of population that becomes clinically ill due to influenza. Clinical illness is defined as a case of influenza that causes some measurable economic impact, such as one-half day of work lost or a visit to a physician's office.

¹¹ Reed et al (2013), op. cit.

¹² Medical technologies to improve survival probabilities in the elderly and health-compromised populations most at risk of dying from influenza have advanced in past decades. However, the larger fraction of these high-risk subpopulations in today's U.S. population-due in large part to these same advances—means that total fatalities from an influenza pandemic of similar virulence could be much higher today than in 1957. Melzer et al (1999). The economic impact of pandemic influenza in the United States: priorities for intervention, Emerging Infectious Diseases 5(5) 659-671, at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2627723/; with Appendix II, from http://wwwnc.cdc.gov/eid/article/5/5/99-0507-techapp2.pdf (accessed April 2013); Zimmerman et al (2010, September 7), Prevalence of high risk indications for influenza vaccine varies by age, race, and income, Vaccine 28(39) 6470-77, at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2939262/ (retrieved 17 June 2013).

The SNRA project team is not aware of any longitudinal study looking at the proportion of high-risk populations defined in comparable terms. However, the scale of this increase is apparent in studies of the U.S. populations covering shorter time periods. One illustration of this is the increase of the overall percentage of the U.S. population at high risk from complications of influenza from 15.5% to 20% in the five year period 1973-1978: Table 12, Office of Technology Assessment, U.S. Congress (1981, December), Cost Effectiveness of Influenza Vaccination. NTIS order #PB82-178492, also at http://ota.fas.org/reports/8112.pdf.

¹³ Melzer et al, Standardizing scenarios to assess the need to respond to an influenza pandemic, *Clinical Infectious Diseases* [forthcoming]; Reed et al (2013), *op cit.* ¹⁴ The 15%/25%/35% attack rate range used in CDC community planning tools (e.g., FluWorkLoss) was truncated below at 20% to correspond to the

lowest U.S attack rate of the naturally occurring influenza pandemics of the last century (19.9% for the 2009 H1N1 pandemic: Table D.4, technical appendix, Reed et al (2013). Although lower attack rates are reported for other historical pandemics these are reported only as the lower end of a range: the 19.9% attack rate is presented as a single estimate for the 2009 pandemic).

- Severity of virus: Although useful indications of the potential range of impacts may be inferred from records of the historical variability of the influenza virus (Figures 1, 2), patterns deduced from the historical record have been insufficient in themselves for constructing predictive models for the severity of the next pandemics.¹⁵ Many planning scenarios model experts' best judgment of a 'most representative' scenario, such as the 1957-scale pandemic model used for the SNRA and many other planning scenarios in this country; others model a 1918-scale pandemic as a maximal scenario for planning purposes.¹⁶ Current U.S. Government guidance is to plan to both a 'moderate' 1957/1968-style pandemic and a 'severe' 1918-style pandemic to ensure preparedness for a range of impacts.¹⁷
- Mitigation measures: In addition to the inherent characteristics of the virus, the actual impacts of a future pandemic will also depend upon the availability, speed of deployment, and effectiveness of medical and non-medical measures to mitigate disease spread and lethality. Despite extensive study in the literature,¹⁸ the extent to which the effects of the next pandemic will be mitigated in practice is dominated by open questions (see Potential Mitigating Factors).

Direct Economic Loss

Direct economic impacts as defined in the SNRA include decontamination, disposal, and physical destruction costs including property (structure, contents, physical infrastructure, and other physical property) and crop damage; one year's lost spending due to fatalities; medical costs; and business interruption directly resulting from the impacts of an event. For the 2015 SNRA, direct economic impacts were calculated based upon previous work done for the DHS RAPID model.^{19,20} This method was used, because it aligned better to the harmonized SNRA definition of direct economic impact than that used for the 2011 SNRA; however, given the 2015 SNRA fatality and illness inputs, both methods gave similar results (see below).

The SNRA project team used the following assumptions to estimate economic impacts caused by a pandemic event:

 ¹⁵ Dowdle, W. R. (1999), Influenza A virus recycling revisited. *Bulletin of the World Health Organization* 77(10) 820–828; at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2557748/ (accessed April 2013).
¹⁶ National Infrastructure Simulation & Analysis Center (NISAC), for the Office of Infrastructure Protection, U.S. Department of Homeland Security

¹⁶ National Infrastructure Simulation & Analysis Center (NISAC), for the Office of Infrastructure Protection, U.S. Department of Homeland Security (2007, October 10), National Population, Economic, and Infrastructure Impacts of Pandemic Influenza with Strategic Recommendations; also the 'high' scenario of the 2005 HHS Pandemic Influenza Plan (p. 18), and the 'high' and conservative fatalities planning factors of the UK Pandemic Influenza Strategy 2011 (pp. 16–17, 20–25) (overall, the UK strategy stresses a range of scenarios similar to HHS recommendations). Department of Health, United Kingdom (2011, November 10), UK Influenza Pandemic Preparedness Strategy 2011, at https://www.gov.uk/govemment/publications/ responding-to-a-uk-flu-pandemic (accessed June 2013); U.S. Department of Health and Human Services (2005, November), HHS Pandemic Influenza Plan, at https://www.flu.gov/planning-preparedness/federal/hhspandemicinfluenzaplan.pdf (accessed April 2013).

 ¹⁷ HHS Pandemic Influenza Plan, *op cit*; U.S. Centers for Disease Control and Prevention, CDC Resources for Pandemic Flu [Web portal], http://www.cdc.gov/flu/pandemic-resources/ (accessed June 2013).
¹⁸ Longini et al (2004, April 1). Containing pandemic influenza with antiviral agents. *American Journal of Epidemiology* 159(7) 623–633; Miller et al

¹⁸ Longini et al (2004, April 1). Containing pandemic influenza with antiviral agents. *American Journal of Epidemiology* 159(7) 623–633; Miller et al (2008, August 1). Prioritization of influenza pandemic vaccination to minimize years of life lost. *Journal of Infectious Diseases* 198(3) 305-311; Perlroth et al (2010, January 15). Health outcomes and costs of community mitigation strategies for an influenza pandemic in the United States. *Emerging Infectious Diseases* 50(2) 165–174; Meltzer et al (1999), *op cit.*; NISAC (2007), *op cit.*; Office of Technology Assessment (1981), *op cit.*; CDC (2011, May 10). Ten Great Public Health Achievements – United States, 2001–2010. *Mortality and Morbidity Weekly Report (MMWR)* 60(19) 619–623; CDC (2011, September 30), Notice to Readers: Revised Estimates of the Public Health Impact of 2009 Pandemic Influenza. *MMWR* 60(38) 1321; Atkins et al (2011, September). Estimating effect of antiviral drug use during pandemic (H1N1) 2009 outbreak, United States. *Emerging Infectious Diseases* 17(9) 1591–1598.

¹⁹ The Risk Assessment Process for Informed Decision Making (RAPID) 2010 (or RAPID II) was a strategic level, DHS-wide process to assess risk and inform strategic planning priorities developed by the DHS Office of Risk Management & Analysis (National Protection & Programs Directorate). The RAPID engine is a suite of computational tools for calculating human and economic measures of risk and the relative effectiveness of different DHS programs in risk reduction. Like the SNRA it is a quantitative tool for calculating and comparing risks in the homeland security mission space with each other, but unlike the SNRA it is designed for additionally calculating the comparative effectiveness of different programs in buying down risk. RAPID is presently maintained by the DHS Office of Policy.

²⁰ Note that the following is *based* on work done in developing the RAPID model, not the model itself. Common inputs include average hospitalization costs and direct business interruption costs per workday lost.

- All of the estimates are given absent any intervention (i.e., before interventions are applied or attempted).
- All estimates were converted to 2011 dollars for comparison with the existing events of the SNRA.
- **Decontamination, Disposal, and Physical Destruction costs** were assumed to be negligible in comparison with the other components of the SNRA direct economic loss measure for the Pandemic event.²¹
- Medical Costs: The SNRA project team made the assumption that hospitalizations would dominate the medical costs for the Pandemic event. A fatality/hospitalization ratio of 11%, the midpoint of the middle (Scale 4)-level scenario of CDC's current pandemic classification model²² was applied to the low, best, and high fatality estimates.²³ The resulting estimates of numbers hospitalized were multiplied by \$21,154, the average cost of influenza-related hospitalizations from the RAPID model adjusted to 2011 dollars, to obtain total estimated hospitalization costs.^{24,25}
- **Business Interruption** costs for the SNRA were estimated based on the workdays lost due to illnesses, including caregiver absences from work due to ill family members. The CDC FluWorkLoss model was used to estimate workdays lost for the SNRA.²⁶ FluWorkLoss is highly customizable to input assumptions and values.²⁷ However, for a given set of input assumptions, the output average total workdays lost per illness is a linear function of Case Fatality Rate (CFR) independent of attack rate, total fatalities, or pandemic duration. The relationship²⁸ corresponding to the FluWorkLoss default assumptions was used to estimate total workdays lost for each of the low/best/high fatality and illness scenarios. These totals, converted to total work-years lost,²⁹ were multiplied by the U.S. average annual output per worker of \$144,654³⁰ to produce estimates of total business interruption directly caused by a pandemic event.

²¹ This assumption may not hold true for an extremely severe pandemic causing social disruption on the scale of the 1918 pandemic: see Environmental Impact section below, discussion of Moderate impact estimate.

²² Scales as in Reed et al (2013).

 $^{^{23}}$ A constant ratio was used because the correlation of this measure to other measures across different scale scenarios was unknown: the different severity measures of the Reed model are used as inputs to determine a severity level and do not represent a prediction that these scenarios will be correlated in a real world pandemic event. As a sensitivity analysis, a functional relationship between this ratio and case fatality rates at the boundaries of each scenario (e.g. 0.05% CFR and 6.5% fatality/hospitalized ratio at the scale 2–scale 3 boundary) of (fatality/hospitalized) = 0.0374 ln(CFR) + 0.3516 [R² = 0.9986] was assumed and applied to the low/best/high fatality-illness scenarios to obtain fatality/hospitalized ratios of 9.3%, 11.9%, and 13.4% respectively. This resulted in total direct economic impacts of \$74/\$112/\$172 billion respectively, compared with \$71/\$114/\$180 billion total direct economic impacts of the final SNRA 2015 estimates.

²⁴ Similarly to the DHS Terrorism Risk Assessments, RAPID estimates of hospitalization costs were derived from the Nationwide Impatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality and are based on a five-day hospitalization (\$18,367 in \$2005). HCUP Nationwide Impatient Sample (NIS). Healthcare Cost and Utilization Project (HCUP) 2005. Agency for Healthcare Research and Quality, Rockville, MD: <u>http://www.hcup-us.ahrq.gov/nisoverview.jsp</u>.

²⁵ Low/best/high estimates 700,000/1.4 million/2.091 million hospitalizations and \$14.8/\$29.6/\$44.2 billion total medical costs from hospitalization. ²⁶ U.S. Centers for Disease Control and Prevention (2006). FluWorkLoss 1.0 [computer file]. At <u>http://www.cdc.gov/flu/pandemic-resources/tools/</u> <u>fluworkloss.htm</u> (retrieved 5 April 2013). ²⁷ Dherekher at al (2006). FluWith and FluWi

²⁷ Dhankhar et al (2006, September 29). FluWorkLoss: Software to estimate the impact of an influenza pandemic on work day loss [manual]. U.S. Centers for Disease Control and Prevention. At <u>http://www.cdc.gov/flu/pandemic-resources/tools/downloads/fluworkloss_manual_102306.pdf</u> (retrieved 5 April 2013).

 $^{^{28}}$ Total workdays lost/illness = 250.0×CFR + 1.192.

²⁹ Using relationship of 240 workdays/work-year (RAPID II standard value).

³⁰ Annual output per worker is taken from IMPLAN (2011) values for the average annual output per employee across all economic sectors (RAPID II standard value).

• Lost Demand from Fatalities: To estimate the costs of lost demand from deaths, the SNRA project team multiplied the number of deaths listed in the Data Summary Table by \$42,500, the same figure used across the SNRA 2011 events.³¹

Parameters	Low	Best	High
Fatalities	77,000	154,000	230,000
Illnesses	61,400,000 76,800,000		107,000,000
Factors	Low	Best	High
Decontamination/disposal/physical destruction (DDP)	\$0	\$0	\$0
Business interruption: Cost of workdays lost	\$53,364,548,000	\$78,270,471,000	\$125,769,360,000
Medical: Cost of hospitalizations	\$14,808,081,000	\$29,616,162,000	\$44,231,930,000
One year lost spending per fatality	\$3,272,500,000	\$6,545,000,000	\$9,775,000,000
	Low	Best	High
Total Direct Economic Loss	\$71,445,129,000	\$114,431,633,000	\$179,776,290,000

Comparisons to other estimates of economic impact: The economic loss model used by the 2011 SNRA included medical costs and a partial valuation of lost productivity due to time off work. Additionally, approximately 83% of the economic impacts from the 2011 model were associated with the value of lost productivity due to premature death, a component not included in the SNRA 2015 direct economic loss metric. However, when adjusted for the updated fatality/illness inputs of the 2015 SNRA, the 2011 model has a best estimate of \$116 billion, with a range of \$53 to \$157 billion. Although calculated by different loss estimation methods, these estimates closely coincide with those of the 2015 SNRA (\$114 billion, with a range of \$71 to \$180 billion).

In comparison to the 1957-scale scenario estimates of the 2015 SNRA, a 2006 study of the potential economic impact of an influenza pandemic gave an estimate of impact for a "mild" pandemic of 0.8% of global GDP, equivalent in the U.S. to approximately \$117.6 billion.³² Although calculated with a different methodology, this estimate is also within the range given in the "Data Summary" for the 1957 scenario.

A Congressional Budget Office (CBO)³³ study of a 1918-type outbreak scenario, assuming two million deaths, estimated that such a pandemic would cause the U.S. GDP (\$14.7 trillion) to decrease by 4.25%—equivalent to \$625 billion. This is above the range included in the Table, but it represents a comparatively less likely worst case scenario. The CBO's "mild" pandemic scenario, equivalent to the 1968 and 1957 pandemics, assumed 100,000 might die, and cause an impact of about 1 percent of GDP (\$147 billion). A detailed Canadian study³⁴ estimated that a

³¹ The SNRA and RAPID models use this figure to maintain comparability with the economic methodology of the 2008 Bioterrorism Risk Assessment (BTRA 2008) from which they derive. \$42,500 represents the midpoint (the expected value of a linear uniform distribution over the interval) of the \$35,000-\$50,000 median household income band in 2011. U.S. Department of Homeland Security (2008). Bioterrorism Risk Assessment: pp. E2.7–34. (BTRA assessment in its entirety is SECRET; Referenced appendix is UNCLASSIFIED//FOR OFFICIAL USE ONLY; Extracted information is UNCLASSIFIED.)

³² McKibinnin WJ and Sidorenko AA. Global macroeconomic consequences of pandemic influenza. Lowry Institute Analyses paper. Lowy Institute for International Policy. Feb. 2006.

³³ Congressional Budget Office (2006, July: updated/corrected from December 2005). A potential influenza pandemic: an update on possible macroeconomic effects and policy issues. At <u>http://www.cbo.gov/publication/17785</u> (accessed April 2013).

³⁴ James S and Sargent T. The economic impact of an influenza pandemic. Economic Analysis and Forecasting Division, Department of Finance – Canada. (unpublished paper) May 2006.

1918-type pandemic would reduce the Canadian economy by a maximum of 1.1% GDP—equivalent in the U.S. to US \$161.7 billion.

Social Displacement

Social displacement was assumed to be zero for the Human Pandemic Outbreak national-level event.³⁵

Note that hospitalization is not counted as social displacement for the purposes of the SNRA, since it would result in double counting with illnesses. Social distancing, quarantine, large-scale telework, and children and family staying home or college students returning home as a result of school closures are also not counted as social displacement, because they result in more people staying home rather than leaving home.

Psychological Distress

Psychological impacts for the SNRA focus on significant distress and prolonged distress, which can encompass a variety of outcomes serious enough to impair daily role functioning and quality of life. An index for significant distress was created that reflected empirical findings that the scope and severity of an event is more important than the type of event.³⁶ The equation for this index uses the fatalities, injuries, and displacement associated with an event as primary inputs. A multiplicative factor elicited (in 2011) from subject matter experts (SMEs) weights the index for differing psychological impact based on the type of event, but as a secondary input.

The Significant Distress Index is calculated from these inputs using a formula proposed by SMEs consulted for the SNRA project: $N_{SD} = C_{EF} \times (5 Fat + Inj + \frac{1}{2} D)$, where N_{SD} represents the number of persons significantly distressed, C_{EF} is the expert assessed Event Familiarity Factor, *Fat* is the number of fatalities, *Inj* is the number of injuries and/or illnesses, and *D* is the number of persons displaced (Social Displacement).

• In words, this formula suggests that there are 5 significantly distressed persons for each life lost; 1 for each person injured; and 1 for each 2 people displaced. This formula was constructed to reflect the empirical finding that the most severe stressor of a disaster is losing a loved one, followed by injury, followed by displacement.

The Event Familiarity Factor is intended to capture the extent to which the event entails an ongoing threat with uncertainty regarding long-term effects, is unfamiliar, or that people dread, exacerbating psychological impacts. This factor, ranging from 1.0 for familiar events to 1.3 for unfamiliar events, was provided by SMEs for each national-level event included in the SNRA: Human Pandemic Outbreak was given a C_{EF} of 1.0.

• Uncertainty was captured by applying the index formula to the low, best, and high estimates of these three human impact metrics.

The numerical outputs of this index formula were used to assign events to bins of a risk matrix for a semi-quantitative analysis of psychological risk in the SNRA.³⁷

³⁵ For the purposes of the SNRA, social displacement was defined as the number of people forced to leave home for a period of two days or longer. This measure does not capture the significant differences between temporary evacuations and permanent displacement due to property destruction. However, this distinction is less relevant for events with zero displacement on either measure.

³⁶ See Appendix G for references and additional discussion of the SNRA Psychological Distress metric.

³⁷ Page 57.

Environmental Impact

In 2011, the U.S. Environmental Protection Agency (EPA) convened an ad hoc group of environmental experts representing the fields of environmental science, ecological risk, toxicology, and disaster field operations management to estimate environmental impacts for this event in the first iteration of the SNRA. Estimates are based on the following assumptions:

- Experts were elicited to provide estimates in the environmental impact category based on assumptions. Actual environmental/ecological harm that occurs as a result of the events described in a given scenario may vary considerably, and will depend on numerous variables (e.g., chemical or biological agent, contamination extent, persistence, toxicity—both chronic and acute toxicity—and infectivity).
- EPA defined environmental consequence (impact)³⁸ as the potential for adverse effects on living organisms associated with pollution of the environment by effluents, emissions, wastes, or accidental chemical releases; energy use; or the depletion of natural resources.
- The experts provided a best estimate of 'Moderate' for a pandemic scenario with severe social impacts and a second best estimate of 'Low' for a less severe pandemic scenario.
- The 2015 SNRA reports the 'Low' environmental impact judgment as the best estimate for the Pandemic event because the social impacts of the best estimate scenario, as defined by the best estimates on other impact axes, correspond to the less severe pandemic scenario. The 2015 SNRA reports 'Moderate' as the second best judgment, because it describes the environmental impacts of a more severe pandemic scenario.
- Experts identified the impacts of a larger pandemic scenario as "Moderate" due to the potential for resources to be pulled from environmental protection activities, thereby allowing impacts to cascade and cause environmental impacts. If the pandemic were large enough, environmental protection could be deemphasized in order to divert resources towards higher priority response efforts, and impacts could be increased as service providers are afflicted with the pandemic (e.g., waste disposal efforts could be halted if workers require treatment).

Potential Mitigating Factors

Numerous medical and non-medical measures for mitigating the human impacts of an influenza pandemic, including social distancing, school closing, antiviral medications, antibiotics for secondary bacterial infections, and targeted vaccines, are known and would be expected to be deployed, at least in part. These measures' efficacy for those individuals who directly receive them is clearly indicated by the evidence in the literature. However, there is no consensus in the literature on what proportional or percentage reductions in total national fatalities and illnesses could be expected under the constraints and conditions of an actual pandemic.³⁹ Estimates of percentage reductions (mitigation effectiveness) in the literature range from 1.6%⁴⁰ to 96%⁴¹ for fatalities and 6%⁴² to 99%⁴³ for illnesses respectively.

³⁸ The 2011 SNRA referred to impacts as 'consequences' because of prior usage in quantitative risk assessment (Kaplan and Garrick [1981, March], On the quantitative definition of risk: *Risk Analysis* 1(1) 11-32). Except where it will cause confusion, 'impact' is used synonymously in this document because of pre-existing connotations of the word 'consequence' within FEMA.

 ³⁹ E.g. not everyone who is sick can afford going to the doctor or antiviral prescriptions; research and production times needed to mass produce vaccines targeted to the pandemic virus may delay their mass availability until after the pandemic's peak.
⁴⁰ CDC (2011, May 10). Ten Great Public Health Achievements—United States, 2001–2010. *Mortality and Morbidity Weekly Report (MMWR)*

⁴⁰ CDC (2011, May 10). Ten Great Public Health Achievements—United States, 2001–2010. Mortality and Morbidity Weekly Report (MMWR) 60(19) 619–623, at <u>http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6019a5.htm?s_cid=mm6019a5_w</u>; CDC (2011, September 30), Notice to Readers: Revised Estimates of the Public Health Impact of 2009 Pandemic Influenza. MMWR 60(38) 1321, at <u>http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6038a7.htm</u> (accessed June 2013).

The appropriate factor for converting the currently unmitigated impact numbers to mitigated equivalents is not known. However, recent CDC studies of the 2009-10 H1N1 pandemic suggest that any adjustment for mitigation under real-world societal and economic conditions would not substantially shift the numbers reported here.⁴⁴

Additional Relevant Information

The probability of impact due to a pandemic has two parts: the probability of a pandemic (any type) occurring, and then, once it has occurred, the severity of impact (essentially. the conditional probability that the "mild," "middle," or "worst case" scenario occurs).

Probability of a pandemic occurring: From 1729 through 2009 there have been 8–12 influenza pandemics (including pandemics subsequently deduced to have been caused by influenza virus).⁴⁵ They have thus historically occurred with a frequency of once every 10 to 60 years.

Probability of severity (probability of "mild," "middle," or "worst case" occurring once pandemic has started): The 1918 pandemic appears to have caused an exceptionally high case fatality rate. Such a pandemic could, in theory, reoccur but historically has only occurred once in approximately 8–12 pandemics. This historical frequency gives an approximately 10% chance that the next pandemic will be a 1918-type pandemic. Similarly, a "mild" pandemic, such as the 2009 pandemic, has only occurred once in 8-12 pandemics since 1700 and also has an approximate 10% probability of occurring. If one includes both the 1957 and 1968 pandemics as examples of "mild" impact pandemics, then the probability that such a scenario will occur rises to 30%. The probability of a "middle" scenario occurring is the residual after accounting for the probabilities of both "worst case" and "mild" scenarios (range for a "middle": 50%-80%).

Visualizing the time series of influenza pandemics, 1700-present

Quantitative study of mortality from historical influenza pandemics has focused almost entirely on the twentieth century. However, sufficient data on prior events exist for researchers to depict time series of historical pandemics over longer periods for mortality in selected populations. While differences in base population,⁴⁶ health, counting measures, and population age structures prevent precise comparisons, such estimates can be nonetheless arrayed together to get a rough picture of the historical variability of the influenza virus in terms of its effects on the human population (Figure 1).⁴⁷ The exceptional scale of the 1918–20 pandemic compared with other pandemics is immediately apparent.

⁴¹ Proportion of attack and mortality rates in the anticipated scenario to rates in the Baseline scenario, figure 3-1, p. 17. National Infrastructure Simulation and Analysis Center (NISAC) (2007, October 10). National Population, Economic, and Infrastructure Impacts of Pandemic Influenza with Strategic Recommendations. Office of Infrastructure Protection, U.S. Department of Homeland Security. ⁴² CDC (2011), Ten Great Public Health Achievements, *op cit*; CDC (2011), Revised Estimates, *op cit*.

⁴³ NISAC (2007), op cit.

⁴⁴ CDC (2011, May 10, September 30) op cit.; Atkins et al (2011, September). Estimating effect of antiviral drug use during pandemic (H1N1) 2009 outbreak, United States. Emerging Infectious Diseases 17(9) 1591-1598; at http://wwwnc.cdc.gov/eid/article/17/9/11-0295 article.htm (accessed June 2013).

⁴⁵ Porter (2001), Taubenberger et al (2009), Patterson (1986), Dowdle (1999), op. cit. Different authors count different events as pandemic or nonpandemic events. However, but most events on different authors' lists overlap, as does the 8 to 12 total number with different authors' pandemic event counts when the 2009 H1N1 pandemic is included.

⁵ 1729–1890 estimates are for England and Wales; 1918–present are for the U.S. (sources below).

⁴⁷ The eight pandemics of natural origin are the list of Potter (2001), op cit. Note that these eight pandemics will differ from the pandemic lists of many of the sources from which the chart data come, especially those of older sources.

Note that uncertainties reported in the data sources below are suppressed in the Figure for clarity of presentation.

Pre-1918: Estimates for the population of England and Wales, Eichel, Otto R. (1922, December). The long-time cycles of pandemic influenza. Journal of the American Statistical Association 18(140) 446–454; available via JSTOR Early Journals Free Content at http://www.jstor.org/stable 2276917 (accessed June 2013). 1729–33 (90/100,000) is the sum of Eichel's lines for 1729 (30–45) and 1733 (45–60); 1781-82, for 1782 (15); 1832– 33, for 1833 (45-60); 1889-90 (74/100,000), for 1889 (16) and 1890 (58). The midpoints of the dashed-line uncertainty ranges reported by Eichel were used as 'best estimates' (e.g. 37.5 + 52.5 = 90; 15; 52.5). Extrapolated to today's U.S. population without additional adjustments for factors



increasing or decreasing fatality rates compared with the past, these pandemics would have equivalent fatalities: 1729-33, 276,300; 1781-82, 46,050; 1832-33, 161,200; 1889-90, 522,000.

1918–20, 1957–58, 1968–69: Historical fatalities, National Institutes of Health, 2011. *Timeline of human flu pandemics* [electronic resource]. National Institute of Allergy and Infectious Diseases, National Institutes of Health, January 14, 2011; at http://www.niaid.nih.gov/topics/flu/research/pandemic/pages/timelinehumanpandemics.aspx (accessed March 2013). U.S. population, for population fatality rate: United States population including Armed Forces abroad, Table I: National Center for Health Statistics (1999). *Vital Statistics of the United States: 1999 Mortality Technical Appendix*. At http://www.chiad.nih.gov/topics/flu/research/pandemics/pages/timelinehumanpandemics.aspx (accessed March 2013). U.S. population fatality rate: United States: 1999 Mortality Technical Appendix. At http://www.chiad.nih.gov/topics/flu/research/pandemics/pages/timelinehumanpandemics.aspx (accessed March 2013). U.S. population fatality rate: United States: 1999 Mortality Technical Appendix. At http://www.cde.gov/ncbs/products/vsus/ta.htm (accessed April 2013). Extrapolated to today's U.S. population without additional adjustments for factors increasing or decreasing fatality rates compared with the past, these pandemics would have equivalent fatalities: 1918, 2.0 million; 1957, 125,900; 1968, 52,200.

2009–10: Fatalities (12,470 total), best estimate, Centers for Disease Control (2010, May 4), Updated CDC estimates of 2009 H1N1 influenza cases, hospitalizations and deaths in the United States, April 2009–April 10, 2010 [electronic resource]: at http://www.cdc.gov/h1n1flu/pdf/CDC_2009_H1N1_Est_PDF_May_4_10_fulltext.pdf (accessed April 2013); Shresta et al (1999, January 1), Estimating the burden of 2009 pandemic influenza (H1N1) in the United States (April 2009–April 2010), *Clinical Infectious Diseases* 52(S1) S75-82; at http://cid.oxfordjournals.org/content/52/suppl_1/S75.full.pdf+html (retrieved April 2014).

Influenza pandemics: Historical range of impacts

Each of the population attack rate (25%) and the case fatality rate (0.2%) selected as the basis of the best estimate pandemic scenario in the SNRA represents the geometric midpoint of the corresponding range (attack rate $20\%^{48}$ – $31.6\%^{49}$, CFR $0.02\%^{50}$ – $2.0\%^{51}$) observed in the influenza pandemics of the past century in the U.S. This suggests a logarithmic distribution on each axis of impact.

To represent a broader range of pandemic impacts beyond the comparatively narrow range of the SNRA Pandemic scenario and to permit comparisons and aggregations with other SNRA events, the uncertainty in each of these two parameters was represented by a log-uniform distribution over the historically observed intervals presented above. As fatalities represent the product of these two parameters (Table 3), the distribution of fatalities is given by the product of these two distributions (Table 4).⁵²

	Population Attack Rate						
CFR	20.0%	22.4%	25.1%	28.2%	31.6%		
0.020%	12,280	13,754	15,411	17,315	19,402		
0.036%	22,104	24,756	27,741	31,167	34,924		
0.063%	38,682	43,324	48,546	54,542	61,118		
0.11%	67,540	75,645	84,763	95,231	106,713		
0.20%	122,800	137,536	154,114	173,148	194,024		
0.36%	221,040	247,565	277,405	311,666	349,243		
0.63%	386,820	433,238	485,459	545,416	611,176		
1.12%	687,680	770,202	863,038	969,629	1,086,534		
2.00%	1,228,000	1,375,360	1,541,140	1,731,480	1,940,240		

Table 3: Fatalities,⁵³ Distribution Construction⁵⁴

⁴⁸ The 2009 pandemic (19.9%), Reed et al (2013).

⁴⁹ 1918 pandemic, U.S., best estimate historical fatalities of 675,000 (NIH (2011), *op. cit.*) divided by case fatality rate of 2.04% (Reed et al (2013)), 33,088,000 illnesses; divided by 1918 U.S. population of 104,550,000 (Vital Statistics of the United States (1999), *op. cit.*).

⁵⁰ 2009 pandemic, U.S., 12,219 best estimate fatalities (CDC (2010)) divided by 61,093,000 estimated illnesses from 19.9% population attack rate (Reed et al (2013)).

⁵¹ 1918 pandemic, U.S., 2.04% CFR (Reed et al (2013)).

⁵² Two log-uniform distributions, $U(20\%, 31.6\%) \times U(0.020\%, 2.0\%)$. Note that distributions such as these are not intended to represent known likelihoods of the occurrence of incidents of particular magnitudes: they are constructed to represent our uncertainty in the likely distribution of magnitudes for a hazard. In this case, since we do not know much about the true distribution other than the extremes which have been observed and our observation that more events have occurred between these extremes than at them, uniform distributions are the most accurate representation of our state of knowledge. The observation that events that have occurred between these extremes have tended to cluster nearer the lower end, and the span of orders of magnitude for CFR indicate that log-uniform distributions are a more appropriate model than linear uniform distributions. ⁵³ Product times 2009 U.S. population of 307 million (for consistency with primary estimates).

⁵⁴ Discretized (constructed in steps), five points for attack rate and nine points for CFR (an odd number of each was selected to ensure the central value [the SNRA best estimate] would be represented as a point in the set). Because the endpoints of the nominal ranges are included, the actual ranges are slightly broader than these (U(18.9%, 33.5%) × U(0.015%, 2.7%)).

			,		
CFR	Attack rate	Fatalities	Illnesses	Direct economic loss (2011\$ billion)	Probability of exceedance (fatalities)
20.0%	0.020%	12 300	61 400 000	54.3	0.989
22.4%	0.020%	13 800	68 800 000	60.9	0.967
25.1%	0.020%	15,400	77.200.000	68.3	0.944
28.2%	0.020%	17.300	86.500.000	76.6	0.922
31.6%	0.020%	19,400	97,000,000	85.9	0.900
20.0%	0.036%	21,800	61,400,000	56.8	0.878
22.4%	0.036%	24,500	68,800,000	63.7	0.856
25.1%	0.036%	27,400	77,200,000	71.4	0.833
28.2%	0.036%	30,800	86,500,000	80.0	0.811
31.6%	0.036%	34,500	97,000,000	89.7	0.789
20.0%	0.06%	38,800	61,400,000	62.4	0.767
22.4%	0.06%	43,500	68,800,000	70.0	0.744
25.1%	0.06%	48,800	77,200,000	78.4	0.722
28.2%	0.06%	54,700	86,500,000	87.9	0.700
31.6%	0.06%	61,400	97,000,000	98.6	0.678
20.0%	0.11%	69,100	61,400,000	72.4	0.656
22.4%	0.11%	77,400	68,800,000	81.2	0.633
25.1%	0.11%	86,800	77,200,000	91.0	0.611
28.2%	0.11%	97,300	86,500,000	102	0.589
31.6%	0.11%	109,000	97,000,000	114	0.567
20.0%	0.20%	123,000	61,400,000	89.6	0.544
22.4%	0.20%	138,000	68,800,000	100	0.522
25.1%	0.20%	154,000	77,200,000	113	0.500
28.2%	0.20%	173,000	86,500,000	126	0.478
31.6%	0.20%	194,000	97,000,000	142	0.456
20.0%	0.36%	218,000	61,400,000	119	0.433
22.4%	0.36%	245,000	68,800,000	134	0.411
25.1%	0.36%	274,000	77,200,000	150	0.389
28.2%	0.36%	308,000	86,500,000	168	0.367
31.6%	0.36%	345,000	97,000,000	188	0.344
20.0%	0.63%	388,000	61,400,000	170	0.322
22.4%	0.63%	435,000	68,800,000	190	0.300
25.1%	0.63%	488,000	77,200,000	213	0.278
28.2%	0.63%	547,000	86,500,000	239	0.256
31.6%	0.63%	614,000	97,000,000	268	0.233
20.0%	1.12%	691,000	61,400,000	257	0.211
22.4%	1.12%	774,000	68,800,000	288	0.189
25.1%	1.12%	868,000	77,200,000	323	0.167
28.2%	1.12%	973,000	86,500,000	362	0.144
31.6%	1.12%	1,090,000	97,000,000	406	0.122
20.0%	2.00%	1,230,000	61,400,000	408	0.100
22.4%	2.00%	1,380,000	68,800,000	457	0.078
25.1%	2.00%	1,540,000	77,200,000	513	0.056
28.2%	2.00%	1,730,000	86,500,000	575	0.033
31.6%	2.00%	1,940,000	97,000,000	644	0.011

Table 4: Pandemic, Modeled Distribution⁵⁵

⁵⁵ Median (the SNRA best estimate) and approximate 5th and 95th percentile intervals are highlighted.

This model was constructed so that the uncertainties in our knowledge of the conditional distribution of pandemic impacts can be represented in calculations comparing or combining human pandemic risk with other risks in the SNRA, as opposed to the use of point estimates or a narrowly defined scenario. However, a surprising and somewhat disturbing outcome is how closely this model parallels the actual historical variability of the influenza virus, in terms of fatalities projected to the U.S. population of today, over its known 300-year history (Figure 2).

The historical data (projected to current U.S. population) of Figure 1 is depicted in Figure 2 as an exceedance curve in semi-logarithmic space. When viewed on a logarithmic scale, the 1918 pandemic appears less exceptional compared with the other historical influenza pandemics of natural origin of the past three centuries.⁵⁶

While multiple factors affecting both likelihood and impacts substantially differ between the present day and the past, this comparative view can be useful for understanding the inherent variability of the influenza virus.



Figure 2: Fatalities, Historical and Modeled⁵⁷

*1977 H1N1 pandemic is not believed to be of natural origin, but is included for completeness.

⁵⁶ The logarithmic form of the best fit line, for both the theoretical and the historical distribution, is reflective of a single log-uniform distribution rather than a product. This is because the range for CFR (a power of 100 from end to end) is so much larger than the range of attack rates (a power of 2) that it effectively determines the shape of the product distribution.

⁵⁷ Historical incidents are identified by color to indicate data source or type. Blue, U.S. data 1918-present. Red, population fatality rates for England and Wales from Eichel (1922) *op. cit.*, original source the English Bills of Mortality 1729-1833. Purple, 1889-90 pandemic, population fatality rates for U.S. and European cities, predominantly European, applied to U.S. population: mean population fatality rate of 170/100,000 reported for major European and U.S. cities, Valleron et al (2010, May 11), Transmissibility and geographic spread of the 1889 influenza pandemic, *Proceedings of the National Academy of Sciences U.S.A.* 107(19) 8778-81, including Supporting Information files: at http://www.pnas.org/content/107/19/8778-80, including Supporting Information files: at http://www.pnas.org/content/107/19/8778-80, (accessed April 2013); 1890 U.S. population, U.S. Census Office (1896), Report on Vital and Social Statistics of the United States at the Eleventh Census: 1890, Part 1 – Analysis and Rate Tables, U.S. Department of the Interior: at http://www.cdc.gov/nchs/products/vsus/vsus_1890_1938.htm (accessed June 2013). The pink data point with astrix represents the accidental pandemic of 1977-78: Fatalities (860 total) in 1977-78 U.S. influenza esaon attributed to the 'frozen virus' A/USSR/90/77 (H1N1): Table 4, 1977 H1 excess fatalities (both age groups): Thompson et al (2009, February). Estimates of US influenza-associated deaths made using four different methods. *Influenza and Other Respiratory Viruses* 3(1) 37-49; at http://onlinelibrary.wiley.com/doi/10.1111/j.1750-2659.2009.00073.x/pdf (accessed April 2013). This is the only reference known to the SNRA project

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team which separates out fatalities attributed to each of the influenza virus strains circulating in 1977-78 (some other references appear to but in fact double count H1 and H2 fatalities). The returned virus primarily affected persons born after 1950, so mortality from H1N1 was low compared with the more lethal seasonal strain H3N2 (this pattern continued until a new H1N1 strain, directly descended from the 1918 virus, entered the human population in the 2009 pandemic).

For origin of A/1977/USSR, Chakraverty et al (1982, August), The return of the historic influenza A H1N1 virus and its impact on the population of the United Kingdom, *Journal of Hygiene* (London/Cambridge) 89(1) 89-100; Kendal et al, 1978, Antigenic similarity of influenza A (H1N1) viruses from epidemics in 1977-1978 to "Scandinavian" strains isolated in epidemics of 1950-1951, *Virology* 89 632-636; Kilbourne, Edwin D. (2006, January), Influenza pandemics of the 20th century, *Emerging Infectious Diseases* 12(1) 9-14; Nelson et al (2008), Multiple reassortment events in the evolutionary history of H1N1 influenza A virus since 1918, *PLoS Pathogens* 4(2) e1000012; Taubenberger et al (2006, January), 1918 influenza: the mother of all pandemics, *Emerging Infectious Diseases* 12(1) 15-22; Worobey, Michael (2008, April), Phylogenetic evidence against evolutionary stasis and natural abiotic reservoirs of influenza A virus, *Journal of Virology* 82(7) 3769-3774.