

## Supplemental Information— Data Supporting the Modeling of the Disease Course of Influenza

<b>Table S1. Seasonal Influenza Incubation Period Data Found in Literature</b>			
<b>Source</b>	<b>Number Observed</b>	<b>Incubation Period (Hours)</b>	<b>Incubation Period (Days)</b>
Alford et al. 1966 <sup>1</sup>	-	36	2
	4	48	2
Burnet et al. 1940 <sup>2</sup>	1	41	2
	1	51	3
Couch et al. 1971 <sup>3</sup>	-	48	2
	-	72	3
MacDonald et al. 1918 <sup>4</sup>	2	41	2
	2	48	2
Moser et al. 1979 <sup>5</sup>	1	24	1
	15	36	2
	7	48	2
	13	60	3
	1	72	3
Armstrong et al. 1921 <sup>6</sup>	42	24	1
	57	48	2
	37	72	3
	40	96	4
	17	120	5
	13	144	6
	3	168	7
Lessler et al. 2009 <sup>7</sup>	37	24	1
	16	36	2
	53	48	2
	13	60	3
	7	72	3
	7	96	4

<b>Table S2. Incubation Period of Pandemic Influenza</b>					
<b>Source</b>	<b>Number Infected in Study</b>	<b>Mean Incubation Period (Days)</b>	<b>Median Incubation Period (Days)</b>	<b>Min Incubation Period (Days)</b>	<b>Max Incubation Period (Days)</b>
Cao et al. 2009 <sup>8</sup>	125	-	2	1	7

<sup>1</sup> Alford RH et al. (1966) Human influenza resulting from aerosol inhalation. *Experimental Biology and Medicine*. 122 (3): 800-804.

<sup>2</sup> Burnet F, Foley M. (1940) The Results of Intranasal Inoculation of Modified and Unmodified Influenza Virus Strains in Human Volunteers. *Medical Journal of Australia*. 2 (25): 655-659.

<sup>3</sup> Couch RB et al. (1971) Correlated studies of a recombinant influenza-virus vaccine. III. Protection against experimental influenza in man. *Journal of Infectious Diseases*. 124 (5): 473-480.

<sup>4</sup> Macdonald P, Lyth JC. (1918) Incubation Period of Influenza. *British medical journal*. 2 (3018): 488.

<sup>5</sup> Moser MR et al. (1979) An outbreak of influenza aboard a commercial airliner. *American journal of epidemiology*. 110 (1): 1-6.s

<sup>6</sup> Armstrong C, Hopkins R. (1921) An epidemiological study of the 1920 epidemic of influenza in an isolated rural community. *Public Health Reports (1896-1970)*. 1671-1702.

<sup>7</sup> Lessler J et al. (2009) Incubation periods of acute respiratory viral infections: a systematic review. *The Lancet infectious diseases*. 9 (5): 291-300.

<sup>8</sup> Cao B et al. (2009) Clinical features of the initial cases of 2009 pandemic influenza A (H1N1) virus infection in China. *New England Journal of Medicine*. 361 (26): 2507-2517.

Source	Number Infected in Study	Mean Incubation Period (Days)	Median Incubation Period (Days)	Min Incubation Period (Days)	Max Incubation Period (Days)
Tuite et al. 2010 <sup>9</sup>	316	4.3	5	1	7
Ghani et al. 2009 <sup>10</sup>	16	2.05	-	1.9	-
Li et al. 2010 <sup>11*</sup>	15	-	4	1	7
Wang et al. 2012 <sup>12**</sup>	79	-	1.6	-	-
<b>Weighted</b>	<b>-</b>	<b>4.2</b>	<b>4.1</b>	<b>-</b>	<b>-</b>

\*Excluded from the weighted median because the study only examined hemodialysis patients.  
\*\*Excluded from the weighted median because these data were from a middle school, and thus over-represent children.

**Table S3. Percent of Individuals that Stop Shedding Virus Each Day after Symptom Onset**

Source	Day(s) after Symptom Onset	Percent that Stop Shedding
Doyle et al. 1998 <sup>13</sup>	1	0%
	2	0%
	3	17%
	4	10%
	5	15%
	6	27%
	7	26%
	8+	5%

**Table S4. Asymptomatic Seasonal Influenza Infections**

Source	Percent of Individuals who Shed Influenza Virus while Remaining Asymptomatic
Lau et al. 2010 <sup>14</sup>	14%
Loeb et al. 2012 <sup>15</sup>	10%
Suess et al. 2012 <sup>16</sup>	14%
<b>Mean</b>	<b>13%</b>

<sup>9</sup> Tuite AR et al. (2010) Estimated epidemiologic parameters and morbidity associated with pandemic H1N1 influenza. *Canadian Medical Association Journal*. 182 (2): 131-136.  
<sup>10</sup> Ghani A et al. (2009) The Early Transmission Dynamics of H1N1pdm Influenza in the United Kingdom. *PLoS currents*. 1: RRN1130.  
<sup>11</sup> Li H, Wang SX. (2010) Clinical features of 2009 pandemic influenza A (H1N1) virus infection in chronic hemodialysis patients. *Blood Purif*. 30 (3): 172-177.  
<sup>12</sup> Wang C et al. (2012a) Epidemiological and clinical characteristics of the outbreak of 2009 pandemic influenza A (H1N1) at a middle school in Luoyang, China. *Public Health*. 126 (4): 289-294.  
<sup>13</sup> Doyle WJ et al. (1998) Effect of rimantadine treatment on clinical manifestations and otologic complications in adults experimentally infected with influenza A (H1N1) virus. *J Infect Dis*. 177 (5): 1260-1265.  
<sup>14</sup> Lau LL et al. (2010) Viral shedding and clinical illness in naturally acquired influenza virus infections. *Journal of Infectious Diseases*. 201 (10): 1509-1516.  
<sup>15</sup> Loeb M et al (2012) Longitudinal study of influenza molecular viral shedding in Hutterite communities. *Journal of Infectious Diseases* 206: 1078-1084  
<sup>16</sup> Suess T et al. (2012) Comparison of shedding characteristics of seasonal influenza virus (sub) types and influenza A (H1N1) pdm09; Germany, 2007–2011. *PloS one*. 7 (12): e51653.

<b>Table S5. Weighted Mean Percentage of Influenza-Associated Symptoms</b>					
<b>Symptom</b>	<b>Prevalence in Individuals with Seasonal Influenza</b>			<b>Prevalence in Individuals with Pandemic Influenza</b>	
	<b>≤17 Years (sources 17-23)</b>	<b>18-64 Years (sources 24-40)</b>	<b>≥65 Years (sources 41-43)</b>	<b>≤17 Years (sources 44-58)</b>	<b>≥ 18 Years (sources 59-73)</b>
Abdominal Pain	N/A	N/A	N/A	11%	8%
Bronchospasm	N/A	N/A	N/A	4%	4% *
Chest Pain	N/A	N/A	N/A	8% *	8%
Chills	35%	55%	30%	27%	27%
Confusion	N/A	N/A	N/A	10% *	10%
Conjunctivitis	N/A	N/A	N/A	12%	15%
Cough	66%	81%	95%	85%	69%
Diarrhea	14%	5%	15%	10%	8%
Dyspnea	N/A	N/A	N/A	42%	39%
Fatigue or Malaise	87% *	87%	87% *	48%	49%
Fever	80%	72%	71%	93%	75%
Headache	38%	70%	54%	31%	36%
Loss of Appetite	N/A	N/A	N/A	21%	37%
Myalgia	23%	67%	33%	26%	27%
Nasal Congestion	89% *	89%	89% *	62%	21%
Nosebleed	N/A	N/A	N/A	17%	8%
Rhinorrhea	55%	78%	63% *	40%	41%
Sore Throat	46%	70%	14%	40%	40%
Vomiting	27%	15%	5%	18%	7%

- 
- <sup>17</sup> Cox NJ, Subbarao K. (1999) Influenza. *The Lancet*. 354 (9186): 1277-1282.
- <sup>18</sup> Leyer GJ et al. (2009) Probiotic effects on cold and influenza-like symptom incidence and duration in children. *Pediatrics*. 124 (2): e172-e179.
- <sup>19</sup> Long CE et al. (1997) Influenza surveillance in community-dwelling elderly compared with children. *Arch Fam Med*. 6: 459-465.
- <sup>20</sup> Kitamoto O. (1968) Therapeutic effectiveness of amantadine hydrochloride in influenza A2--double blind studies. *The Japanese journal of tuberculosis and chest diseases*. 15 (1): 17-26.
- <sup>21</sup> Kitamoto O. (1971) Therapeutic effectiveness of amantadine hydrochloride in naturally occurring Hong Kong influenza--double-blind studies. *The Japanese journal of tuberculosis and chest diseases*. 17 (1): 1-7.
- <sup>22</sup> Mizuta K et al. (1995) An outbreak of influenza A/H3N2 in a Zambian school dormitory. *East African medical journal*. 72 (3): 189-190.
- <sup>23</sup> Takeuchi Y. (1988) Epidemiological and clinical features of influenza and respiratory syncytial virus infections among children in Japan. *Acta paediatrica Japonica; Overseas edition*. 30 (3): 231-239.
- <sup>24</sup> Carrat F et al. (1997) Influenza and influenza-like illness in general practice: drawing lessons for surveillance from a pilot study in Paris, France. *The British Journal of General Practice*. 47 (417): 217.-220
- <sup>25</sup> Carrat F et al. (1999) Evaluation of clinical case definitions of influenza: detailed investigation of patients during the 1995–1996 epidemic in France. *Clinical infectious diseases*. 28 (2): 283-290.
- <sup>26</sup> Cowling BJ et al. (2008) Preliminary findings of a randomized trial of non-pharmaceutical interventions to prevent influenza transmission in households. *PloS one*. 3 (5): e2101.
- <sup>27</sup> Cox NJ, Subbarao K. (1999) Influenza. *The Lancet*. 354 (9186): 1277-1282.
- <sup>28</sup> Hayden FG et al. (1997) Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza virus infections. *New England Journal of Medicine*. 337 (13): 874-880.
- <sup>29</sup> Hayden FG et al. (1999) Use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza. *JAMA: the journal of the American Medical Association*. 282 (13): 1240-1246.
- <sup>30</sup> MIST. (1998) Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. The MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group. *Lancet*. 352 (9144): 1877-1881.
- <sup>31</sup> Monto AS et al. (2000) Clinical signs and symptoms predicting influenza infection. *Archives of Internal Medicine*. 160 (21): 3243.-3247
- <sup>41</sup> Boivin G et al. (2000) Predicting influenza infections during epidemics with use of a clinical case definition. *Clinical infectious diseases*. 31 (5): 1166-1169.
- <sup>42</sup> Cox NJ, Subbarao K. (1999) Influenza. *The Lancet*. 354 (9186): 1277-1282.
- <sup>43</sup> Long CE et al. (1997) Influenza surveillance in community-dwelling elderly compared with children. *Arch Fam Med*. 6: 459-465.
- <sup>44</sup> Zenciroglu A et al. (2011) Swine influenza A (H1N1) virus infection in infants. *European journal of pediatrics*. 170 (3): 333-338.
- <sup>45</sup> Husain EH et al. (2012) Hospitalization patterns and outcomes of infants with Influenza A (H1N1) in Kuwait. *Journal of infection in developing countries*. 6 (8): 632-636
- <sup>46</sup> Peiris M et al. (1999) Human infection with influenza H9N2. *The Lancet*. 354 (9182): 916-917.
- <sup>47</sup> Wang Z et al. (2012b) Clinical features of 167 children with the novel influenza A (H1N1) virus infection in Xi'an, China. *The Turkish journal of pediatrics*. 54 (2): 99-104.
- <sup>48</sup> Tran D et al. (2012) Comparison of children hospitalized with seasonal versus pandemic influenza A, 2004–2009. *Pediatrics*. 130 (3): 397-406.
- <sup>49</sup> Kinikar AA et al. (2012) Predictors of mortality in hospitalized children with pandemic H1N1 influenza 2009 in Pune, India. *The Indian Journal of Pediatrics*. 79 (4): 459-466.
- <sup>59</sup> Kawai N et al. (2011) Comparison of the clinical symptoms and the effectiveness of neuraminidase inhibitors for patients with pandemic influenza H1N1 2009 or seasonal H1N1 influenza in the 2007–2008 and 2008–2009 seasons. *Journal of Infection and Chemotherapy*. 17 (3): 375-381.
- <sup>60</sup> Winzer R et al. (2009) Early clinical experiences with the new influenza A (H1N1/09). *Deutsches Arzteblatt International*. 106 (47): 770.-776
- <sup>61</sup> Poepl W et al. (2011) Clinical aspects of 2009 pandemic influenza A (H1N1) virus infection in Austria. *Infection*. 39 (4): 341-352.
- <sup>62</sup> Yang TH et al. (2011) Early experience of the pandemic influenza H1N1 2009 epidemic in Taiwan. *J Chin Med Assoc*. 74 (7): 298-304.
- <sup>63</sup> Chien Y-S et al. (2010) Predictors and outcomes of respiratory failure among hospitalized pneumonia patients with 2009 H1N1 influenza in Taiwan. *Journal of infection*. 60 (2): 168-174.

- <sup>46</sup> Peiris M et al. (1999) Human infection with influenza H9N2. *The Lancet*. 354 (9182): 916-917.
- <sup>47</sup> Wang Z et al. (2012b) Clinical features of 167 children with the novel influenza A (H1N1) virus infection in Xi'an, China. *The Turkish journal of pediatrics*. 54 (2): 99-104.
- <sup>48</sup> Tran D et al. (2012) Comparison of children hospitalized with seasonal versus pandemic influenza A, 2004–2009. *Pediatrics*. 130 (3): 397-406.
- <sup>49</sup> Kinikar AA et al. (2012) Predictors of mortality in hospitalized children with pandemic H1N1 influenza 2009 in Pune, India. *The Indian Journal of Pediatrics*. 79 (4): 459-466.
- <sup>50</sup> McLean E et al. (2010) Pandemic (H1N1) 2009 influenza in the UK: clinical and epidemiological findings from the first few hundred (FF100) cases. *Epidemiology and infection*. 138 (11): 1531-1541.
- <sup>51</sup> Saha A et al. (2010) Swine-origin influenza A (H1N1) in Indian children. *Annals of Tropical Paediatrics: International Child Health*. 30 (1): 51-55.
- <sup>52</sup> Hawkes M et al. (2011) Natural history of pandemic H1N1 2009 influenza infection in healthy pediatric outpatients. *Academic pediatrics*. 11 (1): 66-74.
- <sup>53</sup> Yuen K et al. (1998) Clinical features and rapid viral diagnosis of human disease associated with avian influenza A H5N1 virus. *The Lancet*. 351 (9101): 467-471.
- <sup>54</sup> Feiterna-Sperling C et al. (2010) Pandemic influenza A (H1N1) outbreak among 15 school-aged HIV-1-infected children. *Clinical Infectious Diseases*. 51 (11): e90-e94.
- <sup>55</sup> Di Giambenedetto S et al. (2011) Clinical presentation, microbiological features and correlates of disease severity of 2009 pandemic influenza A (H1N1) infection. *European journal of clinical microbiology & infectious diseases*. 30 (4): 541-549.
- <sup>56</sup> Wang C et al. (2012a) Epidemiological and clinical characteristics of the outbreak of 2009 pandemic influenza A (H1N1) at a middle school in Luoyang, China. *Public Health*. 126 (4): 289-294.
- <sup>57</sup> Strong M et al. (2010) Adverse drug effects following oseltamivir mass treatment and prophylaxis in a school outbreak of 2009 pandemic influenza A (H1N1) in June 2009, Sheffield, United Kingdom. *Euro Surveill*. 15 (19): 19565-19570.
- <sup>58</sup> Louriz M et al. (2010) Clinical features of the initial cases of 2009 pandemic influenza A (H1N1) virus infection in an university hospital of Morocco. *Int Arch Med*. 3 (26): 1755-7682.
- <sup>59</sup> Kawai N et al. (2011) Comparison of the clinical symptoms and the effectiveness of neuraminidase inhibitors for patients with pandemic influenza H1N1 2009 or seasonal H1N1 influenza in the 2007–2008 and 2008–2009 seasons. *Journal of Infection and Chemotherapy*. 17 (3): 375-381.
- <sup>60</sup> Winzer R et al. (2009) Early clinical experiences with the new influenza A (H1N1/09). *Deutsches Arzteblatt International*. 106 (47): 770-776
- <sup>61</sup> Poepl W et al. (2011) Clinical aspects of 2009 pandemic influenza A (H1N1) virus infection in Austria. *Infection*. 39 (4): 341-352.
- <sup>62</sup> Yang TH et al. (2011) Early experience of the pandemic influenza H1N1 2009 epidemic in Taiwan. *J Chin Med Assoc*. 74 (7): 298-304.
- <sup>63</sup> Chien Y-S et al. (2010) Predictors and outcomes of respiratory failure among hospitalized pneumonia patients with 2009 H1N1 influenza in Taiwan. *Journal of infection*. 60 (2): 168-174.
- <sup>64</sup> Cao B et al. (2009) Clinical features of the initial cases of 2009 pandemic influenza A (H1N1) virus infection in China. *New England Journal of Medicine*. 361 (26): 2507-2517.
- <sup>65</sup> Al-Khuwaitir TS et al. (2009) H1N1 influenza A. Preliminary evaluation in hospitalized patients in a secondary care facility in Saudi Arabia. *Saudi medical journal*. 30 (12): 1532-1536.
- <sup>66</sup> Zhang G et al. (2011) Epidemiological and clinical features of 308 hospitalized patients with novel 2009 influenza A (H1N1) virus infection in China during the first pandemic wave. *Intervirology*. 54 (3): 164-170.
- <sup>67</sup> McLean E et al. (2010) Pandemic (H1N1) 2009 influenza in the UK: clinical and epidemiological findings from the first few hundred (FF100) cases. *Epidemiology and infection*. 138 (11): 1531-1541.
- <sup>68</sup> Elizondo-Montemayor L et al. (2012) Clinical and epidemiological features of 2009 pandemic H1N1 influenza differ slightly according to seroprevalence status during the second wave in the general population in Mexico. *Respir Care*. 57 (10): 1586-1593.
- <sup>69</sup> Mu Y et al. (2010) Clinical features, treatments and prognosis of the initial cases of pandemic influenza H1N1 2009 virus infection in Shanghai China. *Qjm*. 103 (5): 311-317.
- <sup>70</sup> Suryaprasad A et al. (2011) Virus detection and duration of illness among patients with 2009 pandemic influenza A (H1N1) virus infection in Texas. *Clin Infect Dis*. 52 Suppl 1: S109-115.
- <sup>71</sup> Gómez-Gómez A et al. (2010) Severe pneumonia associated with pandemic (H1N1) 2009 outbreak, San Luis Potosi, Mexico. *Emerging infectious diseases*. 16 (1): 27-34
- <sup>72</sup> Naseem A et al. (2011) A clinical account of hospitalized 2009 pandemic influenza A (H1N1) cases. *J Coll Physicians Surg Pak*. 21 (2): 97-102.
- <sup>73</sup> Shelke VN et al. (2012) Pathologic study of pandemic influenza A (H1N1) 2009 cases from India. *Pathology international*. 62 (1): 36-42.

\*Age specific data not available, weighted mean obtained from all age data points.

**Table S6. Estimated Annual Influenza-Associated Excess Mortality by Age<sup>81</sup>**

Age Range	Percent Excess Mortality
0 – 4 years	0.00025%
5 – 49 years	0.00020%
50 – 64 years	0.00130%
65+ years	0.02210%

**Table S7. Percentage of Pandemic Influenza Infected Individuals who Die, by Pandemic**

Pandemic	Percent Mortality of Infected Persons
1918 Spanish Flu <sup>82</sup>	2.5% - 10%
2009 H1N1 <sup>83</sup>	0.010% - 0.043%

<sup>74</sup> Louriá DB et al. (1959) Studies on influenza in the pandemic of 1957-1958. II. Pulmonary complications of influenza. *Journal of Clinical Investigation*. 38 (1 Pt 1-2): 213.-265

<sup>75</sup> Sohn CH et al. (2013) Comparison of clinical features and outcomes of hospitalized adult patients with novel influenza A (H1N1) pneumonia and other pneumonia. *Acad Emerg Med*. 20 (1): 46-53.

<sup>76</sup> Li H, Wang SX. (2010) Clinical features of 2009 pandemic influenza A (H1N1) virus infection in chronic hemodialysis patients. *Blood Purif*. 30 (3): 172-177.

<sup>77</sup> Low CY et al. (2010) Pandemic (H1N1) 2009 infection in adult solid organ transplant recipients in Singapore. *Transplantation*. 90 (9): 1016-1021.

<sup>78</sup> Armstrong M et al. (2012) [Morbidity and mortality associated to influenza A (H1N1) 2009 admissions in two hospitals of the Metropolitan area and analysis of its economic impact]. *Rev Chilena Infectol*. 29 (6): 664-671.

<sup>79</sup> Koopmans M et al. (2004) Transmission of H7N7 avian influenza A virus to human beings during a large outbreak in commercial poultry farms in the Netherlands. *Lancet*. 363 (9409): 587-593.

<sup>80</sup> Kawana A et al. (2007) Spanish influenza in Japanese armed forces, 1918–1920. *Emerging infectious diseases*. 13 (4): 590.-593

<sup>81</sup> Thompson WW et al. (2003) Mortality associated with influenza and respiratory syncytial virus in the United States. *Jama*. 289 (2): 179-186.

<sup>82</sup> Taubenberger JK, Morens DM. (2006) 1918 Influenza: the mother of all pandemics. *Emerging infectious diseases*. 12 (1): 15-22.

<sup>83</sup> National Institute of Allergy and Infectious Diseases. (2011) Pandemic Flu History. Washington, DC: Department of Health & Human Services.