# Detailed Parameters of the BARDA Interactive Flu Model

## Regional Vaccine Distribution Rates for Influenza

No data were available to quantify the typical and maximum possible flu vaccination rates in either the USA or other regions of the globe, and in lieu of available data, the rate of the USA was determined and then the rates for other regions were scaled based on the number of vaccine doses produced in those regions, presuming the same total amount of time was required to distribute the vaccine in every region. Additionally, because data regarding the rates of vaccine production outside the USA were unavailable, it was presumed that 100% of the vaccine doses became available on the first day the vaccine campaign began for both the USA and the regions in the model. For example, if the USA produced a total of 100 million doses and could distribute them at the rate of ten million per week, that would result in a ten-week distribution time. If another region produced 20 million doses and took that same ten weeks to distribute, the distribution rate in that region would have been two million per week.

The USA vaccine distribution rates were set to ten million and 30 million doses per week, based on a previous model.[1] An estimate that 46% of the US population was vaccinated against flu in the 2013-2014 flu season[2] was combined with an estimate of the US population of 310 million, to compute an estimated 142.5 million people were vaccinated that year. Using the ten and 30 million doses per week vaccine distribution estimates, and a total of 142.5 million people vaccinated, these data implied it would take 99.75 and 33.3 days to distribute all vaccines, respectively, in the United States. As mentioned, these durations of distribution were presumed to be held fixed across other regions, and the rates of vaccine distribution of each region were adjusted based on these values and the number of vaccine doses available in that region.

## Case Fatality Rates of Influenza

Seasonal influenza case fatality rates (CFRs) are difficult to directly measure, due to the way that flu cases and deaths are commonly recorded; deaths are instead typically reported in terms of excess mortality.[3] In lieu of a direct estimate, particularly for more distant historical flu seasons, baseline CFRs for seasonal influenza were based on severity ranges of flu pandemic scenarios defined in a previously-published modeling effort,[4] using, as a conservative assumption, the CFRs of scales 1-5 in the source, resulting in a range of 1E-4 to 3.5E-3 (the range in the source continues to 5E-3; however, this exact discrete value was not used in the parameter set). Baseline pandemic influenza CFRs began at the same rate of 1E-4, owing to the low CFR of the 2009pdm strain[5], but extended to 5E-2, the approximate CFR of 1918 influenza.[6]

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1 Biggerstaff M *et al* (2015) Estimating the potential effects of a vaccine program against an emerging influenza pandemic--United States. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 60 Suppl 1**:** S20-29

2 United States Centers for Disease Control and Prevention (2014) Flu Vaccination Coverage, United States, 2013-14 Influenza Season.

3 Centers for Disease Control. Estimating Seasonal Influenza-Associated Deaths in the United States: CDC Study Confirms Variability of Flu. http://www.cdc.gov/flu/about/disease/us_flu-related_deaths.htm. Last Update March 18th 2015. Accessed October 15th 2015.

4 Meltzer MI et al (2015) Standardizing scenarios to assess the need to respond to an influenza pandemic. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 60 Suppl 1: S1-8

5 Wong JY et al (2013) Case fatality risk of influenza A (H1N1pdm09): a systematic review. Epidemiology 24: 830-841

6 Taubenberger JK, Morens DM (2006) 1918 Influenza: the mother of all pandemics. Emerging infectious diseases 12: 15-22

Natural avian influenza strains show considerable variation in human case fatality rate, from zero to approximately 60% (6E-1).[7] As zero fatality strains have no risk in terms of human deaths, they were excluded and the minimum case fatality rate was set to the lowest for seasonal flu of 1E-4. The maximum was set to 6E-1.

For gain of function strains, it was presumed that seasonal influenzas could potentially be modified to be as deadly as 1918 flu, resulting in a maximum CFR of 5E-2. For pandemic strains, it was presumed that the case fatality rate of 1918 flu could be doubled, resulting in a maximum of 1E-1. For avian strains, it was presumed that strains could be made as deadly as the deadliest natural strain but no further, resulting in no additional CFRs beyond 6E-1.

## Summary Tables Containing All Values of Parameters Used

The following tables summarize all parameters used in the Interactive Flu Model. All possible combinations of parameters were exhaustively sampled.

**Table S1. Summary of Parameters Used for Global Flu Simulations**

| Parameter Description | Range of Values Used |
|---|---|
| $R_0$ Values (for natural and gain-of-function strains) | 0.1 to 2.5 in 0.1 increments |
| Case Fatality Rates (for natural strains) | All discrete values: [1E-4, 1.75E-4, 2E-4, 3.5E-4, 7.5E-4, 1.7E-3, 3.5E-3, 7.5E-3, 1E-2, 2.5E-2, 5E-2, 1E-1, 2E-1, 3E-1, 4E-1, 5E-1, 6E-1]<br><br>Seasonal: values from 1E-4 to 3.5E-3<br>Pandemic: values 1E-4 to 5E-2<br>Avian: values from 1E-4 to 6E-1 |
| Additional Case Fatality Rates for GOF Strains | Seasonal: [7.5E-3, 1E-2, 2.5E-2, 5E-2]<br>Pandemic: 1E-1<br>Avian: N/A |
| Seed Infections to Start Simulation | 100 |
| Simulation Length | 750 (days) |

[7] See Supporting Information section on Selected and Notable Avian Influenza Outbreaks

| Parameter Description | Range of Values Used |
|---|---|
| Latent Period | 2.6 (days)[8,9,10,11,12,13,14,15,16,17,18,19,20] (value is mean of sources investigated) |
| Infectious Period | 4 (days) [21,22,23] (value is mean of sources investigated) |
| Fractions of Cases with Symptoms | [0.87, 0.89, 0.91][24,25,26,27] (values are minimum, maximum, and midpoint of sources investigated) |
| Simulation Days When Vaccination Began | [182, 224, 266, 751]* (26, 32, 38 weeks) |
| Fractions of Population Vaccinated | {70.4%, 56%, 38%, 66.7%}[28**†] |
| Times to Distribute Vaccines | [33.3, 99.75] (days) |
| Vaccine Efficacies | [0.1, 0.442, 0.6][29] (values are minimum, maximum, and mean in source) |

8 Alford RH *et al* (1966) Human influenza resulting from aerosol inhalation. *Experimental Biology and Medicine* 122**:** 800-804

9 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**:** 655-659

10 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**:** 473-480

11 Macdonald P, Lyth JC (1918) INCUBATION PERIOD OF INFLUENZA. *Br Med J* 2**:** 488

12 Moser MR *et al* (1979) An outbreak of influenza aboard a commercial airliner. *American journal of epidemiology* 110**:** 1-6

13 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

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

15 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**:** 2507-2517

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

17 Tuite AR *et al* (2010) Estimated epidemiologic parameters and morbidity associated with pandemic H1N1 influenza. *Canadian Medical Association Journal* 182**:** 131-136

18 Wang C *et al* (2012) Epidemiological and clinical characteristics of the outbreak of 2009 pandemic influenza A (H1N1) at a middle school in Luoyang, China. *Public Health* 126**:** 289-294

19 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**:** 2507-2517

20 Tuite AR *et al* (2010) Estimated epidemiologic parameters and morbidity associated with pandemic H1N1 influenza. *Canadian Medical Association Journal* 182**:** 131-136

21 Carrat F *et al* (2008) Time lines of infection and disease in human influenza: a review of volunteer challenge studies. *American journal of epidemiology* 167**:** 775-785

22 Lau LL *et al* (2010) Viral shedding and clinical illness in naturally acquired influenza virus infections. *Journal of Infectious Diseases* 201**:** 1509-1516

23 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**:** 1260-1265

24 Lau LL *et al* (2010) Viral shedding and clinical illness in naturally acquired influenza virus infections. *Journal of Infectious Diseases* 201**:** 1509-1516

25 Loeb M *et al* (2012) Longitudinal study of influenza molecular viral shedding in Hutterite communities. *Journal of Infectious Diseases* 206**:** 1078-1084

26 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**:** e51653

27 Papenburg J *et al* (2010) Household transmission of the 2009 pandemic A/H1N1 influenza virus: elevated laboratory-confirmed secondary attack rates and evidence of asymptomatic infections. *Clinical Infectious Diseases* 51**:** 1033-1041

28 United States Centers for Disease Control and Prevention. Flu Vaccination Coverage, United States, 2014-15 Influenza Season. http://www.cdc.gov/flu/fluvaxview/coverage-1415estimates.htm. Last Update Accessed October 15, 2015.

29 United States Centers for Disease Control and Prevention. Seasonal Influenza Vaccine Effectiveness, 2005-2015. http://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm. Last Update Accessed October 8th, 2015.

| Parameter Description | Range of Values Used |
|---|---|
| Vaccine Efficacy in Preventing Further Transmission if Vaccinated Individual Infected | 0[30] |
| Fractions of Population that Seeks Clinical Care | {67.5%, 51.4%, 42.2%, 58%}[31,32] |
| Fractions of Population that Are Diagnosed and Prescribed Antivirals in High Income Regions | Baseline: {8.65%, 8.65%, 8.65%, 4.65%}[33,34]<br>10x (N. America only): {86.5%, 86.5%, 86.5%, 46.5%}[35] |
| Fractions of Population that Are Diagnosed and Prescribed Antivirals in Non-High Income Regions | {0%, 0%, 0%, 0%,}[36] |
| Antiviral Efficacies in Preventing Transmission | [0, 0.1, 0.25, 0.5][37] |
| Antiviral Efficacy in Preventing Death | 0.2[38] |
| Fraction of Population Adhering to Antiviral Regimen | 0.8[39,40] |
| Prior Immunities | [0, 0.1, 0.4] |
| Fraction of Cases Hospitalized | 0‡ |
| Community Mitigation Strengths | [0, 0.1, 0.25, 0.5] (zero implies no community mitigation) |
| Community Mitigation Start Day | 0 (i.e., immediately) |
| Community Mitigation Duration | (entirety of simulation) |
| * A start day of 751 implies that vaccination never begins, as the simulation will terminate prior | |
| ** Values given in {} indicate that each value corresponds to one of the four age categories, in order from youngest to oldest | |
| † The number of vaccine doses available in each region determines the total fraction of the population vaccinated; the numbers listed here were used to compute the relative proportion of the total vaccines each age group was given | |

[30] No data were available to support a value for this parameter; as a conservative assumption a value of zero was used

[31] Biggerstaff M *et al* (2012) Self-reported influenza-like illness and receipt of influenza antiviral drugs during the 2009 pandemic, United States, 2009-2010. *American journal of public health* 102**:** e21-26

[32] Biggerstaff M *et al* (2014) Influenza-like illness, the time to seek healthcare, and influenza antiviral receipt during the 2010-2011 influenza season-United States. *The Journal of infectious diseases* 210**:** 535-544

[33] Biggerstaff M *et al* (2012) Self-reported influenza-like illness and receipt of influenza antiviral drugs during the 2009 pandemic, United States, 2009-2010. *American journal of public health* 102**:** e21-26

[34] Biggerstaff M *et al* (2014) Influenza-like illness, the time to seek healthcare, and influenza antiviral receipt during the 2010-2011 influenza season-United States. *The Journal of infectious diseases* 210**:** 535-544

[35] A tenfold high distribution was added as a simulation parameter for North America to model the release of antivirals from the US stockpile. This parameter set was only used when investigating North America separately; for global figures the baseline was used for all regions, including North America.

[36] It was assumed that antivirals were not used in low income regions.

[37] Maximum value is the maximum observed reduction in symptom duration for patients taking antivirals (see Supporting Information Section on Antiviral and Vaccine Efficacy); other values were chosen to model intermediate ranges and antiviral resistant strains.

[38] Muthuri SG *et al* (2014) Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. *The Lancet Respiratory medicine* 2**:** 395-404

[39] Atkins CY *et al* (2011) Estimating effect of antiviral drug use during pandemic (H1N1) 2009 outbreak, United States. *Emerging infectious diseases* 17**:** 1591-1598

[40] O'Hagan JJ *et al* (2015) Estimating the United States demand for influenza antivirals and the effect on severe influenza disease during a potential pandemic. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 60 Suppl 1**:** S30-41

| Parameter Description | Range of Values Used |
|---|---|
| ‡ The interactive flu model provides functionality to track hospitalizations separate from cases; in this study the output was fatalities, so hospitalizations were not tracked and the hospitalization ratio was set to zero to simplify the number of required parameters | |

**Table S2. Summary of Parameters Used for Global SARS-CoV Simulations**

| Parameter Description | Range of Values Used |
|---|---|
| $R_0$ Values (for natural and gain-of-function strains) | [0.1:0.1:2.5 3.0 3.5 4.0] * |
| Case Fatality Rate (for natural strains) | [5E-2, 1E-1, 2E-1][41] |
| Additional Case Fatality Rates (for GOF strains) | [3E-1, 4E-1, 5E-1][42] |
| Seed Infections to Start Simulation | 100 |
| Simulation Length | 10000 (days) |
| Latent Period | 11 (days)[43] |
| Infectious Period | 16 (days)[44] |
| Fraction of Cases with Symptoms | [0.87, 0.94, 1.0][45,46] |
| Simulation Day When Vaccination Began | N/A |
| Fractions of Population Vaccinated | N/A |
| Time to Distribute Vaccines | N/A |
| Vaccine Efficacy | N/A |
| Vaccine Efficacy in Preventing Further Transmission if Vaccinated Individual Infected | N/A |
| Fraction of Population that Seeks Clinical Care | N/A** |
| Fraction of Population that Are Diagnosed and Prescribed Antivirals in High Income Regions | N/A |
| Fraction of Population that Are Diagnosed and Prescribed Antivirals in Low Income Regions | N/A |
| Antiviral Efficacy in Preventing Transmission | N/A |
| Antiviral Efficacy in Preventing Death | N/A |
| Fraction of Population Adhering to Antiviral Regimen | N/A |
| Prior Immunity | 0 |
| Fraction of Cases Hospitalized | 0† |
| Community Mitigation Strengths | [0, 0.1, 0.25, 0.5] (zero implies no community mitigation) |

41 Chan-Yeung M, Xu RH (2003) SARS: epidemiology. *Respirology* 8 Suppl**:** S9-14

42 These were presumed, as no data were available to estimate the possible increase by GOF

43 See Supporting Information section on CoV Disease Course

44 Ibid.

45 Le Vu S *et al* (2006) Absence of infection in asymptomatic contacts of index SARS case in France. *Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin* 11**:** 40-41

46 Wilder-Smith A *et al* (2005) Asymptomatic SARS coronavirus infection among healthcare workers, Singapore. *Emerging infectious diseases* 11**:** 1142-1145

| | |
|---|---|
| Community Mitigation Start Day | 0 (i.e., immediately) |
| Community Mitigation Duration | (entirety of simulation) |
| * Range is given in MATLAB notation, where x:y:z indicates all values from x to z in increments of y, inclusive of x and z. For example, [1:0.5:3 3.5] would expand to the set [1 1.5 2 2.5 3 3.5] | |
| ** As clinical visits were only tracked for distribution of antivirals, they were ignored for coronaviruses, which have no antivirals available | |
| † The interactive flu model provides functionality to track hospitalizations separate from cases; in this study the output was fatalities, so hospitalizations were not tracked and the hospitalization ratio was set to zero to simplify the number of required parameters | |

**Table S3. Summary of Parameters Used for Global MERS-CoV Simulations**

| **Parameter Description** | **Range of Values Used** |
|---|---|
| $R_0$ Values (for natural and gain-of-function strains) | 0.1 to 2.5 in 0.1 increments |
| Case Fatality Rate (for natural strains) | [4E-1, 5E-1, 6E-1][47,48,49] |
| Additional Case Fatality Rates (for GOF strains) | N/A[50] |
| Seed Infections to Start Simulation | 100 |
| Simulation Length | 10000 (days) |
| Latent Period | 5.5 (days)[51] |
| Infectious Period | 27 (days)[52] |
| Fraction of Cases with Symptoms | [0.87, 0.94, 1.0][53] |
| Simulation Day When Vaccination Began | N/A |
| Fractions of Population Vaccinated | N/A |
| Time to Distribute Vaccines | N/A |
| Vaccine Efficacy | N/A |
| Vaccine Efficacy in Preventing Further Transmission if Vaccinated Individual Infected | N/A |
| Fraction of Population that Seeks Clinical Care | N/A* |
| Fraction of Population that Are Diagnosed and Prescribed Antivirals in High Income Regions | N/A |
| Fraction of Population that Are Diagnosed and Prescribed Antivirals in Low Income Regions | N/A |

47 Hussain H (2014) Incidence and Mortality Rate of "Middle East Respiratory Syndrome"-Corona Virus (MERS-Cov), Threatens and Opportunities. *J Mycobac Dis* 4**:** 2161-1068.1000162

48 World Health Organization (2015) Middle East respiratory syndrome coronavirus (MERS-CoV): summary of current situation, literature update and risk assessment.

49 Assiri A *et al* (2013) Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. *The Lancet Infectious diseases* 13**:** 752-761

50 6E-1 was the highest value of the parameter used in the simulation; it was presumed no higher values were possible for GOF strains.

51 See Supporting Information section on CoV Disease Course

52 Ibid.

53 No data were available to support a range for this parameter. In lieu of primary data, the values of SARS-CoV were used as a proxy

| | |
|---|---|
| Antiviral Efficacy in Preventing Transmission | N/A |
| Antiviral Efficacy in Preventing Death | N/A |
| Fraction of Population Adhering to Antiviral Regimen | N/A |
| Prior Immunity | 0 |
| Fraction of Cases Hospitalized | 0† |
| Community Mitigation Strengths | [0, 0.1, 0.25, 0.5] (zero implies no community mitigation) |
| Community Mitigation Start Day | 0 (i.e., immediately) |
| Community Mitigation Duration | (entirety of simulation) |
| * As clinical visits were only tracked for distribution of antivirals, they were ignored for coronaviruses, which have no antivirals available | |
| † The interactive flu model provides functionality to track hospitalizations separate from cases; in this study the output was fatalities, so hospitalizations were not tracked and the hospitalization ratio was set to zero to simplify the number of required parameters | |