TECHNICAL APPENDIX. EPIDEMIOLOGICAL MODEL SUMMARY

Developed by: Jennifer Corbin, Ph.D.
& Rocco Casagrande, Ph.D., Gryphon Scientific

OVERVIEW OF THE MODEL

Akhmeta virus (AKMV), an orthopoxvirus first discovered in 2013 is known to infect both cattle and humans, though human-to-human transmission has not been observed. In this fictional scenario, the Akhmeta virus was deliberately modified to increase its virulence in cattle, a modification that inadvertently resulted in a virus which is also transmissible between humans.

The Akhmeta virus outbreak was modeled using a modified version of the Interactive Influenza Model (IIM), which is used by the U.S. Centers for Disease Control and Prevention and the U.S. Department of Health and Human Services Biomedical Advanced Research and Development Authority (HHS-BARDA) to evaluate the effectiveness of medical countermeasure strategies to control global disease outbreaks.[1] The IIM is a"Susceptible (S), Exposed (E), Infectious (I), Recovered (R)" (SEIR)-based model, which is a compartmental epidemiological model that tracks the progression of infections through various stages of a disease course. Deterministic compartmental models such as an SEIR model are appropriate for modeling large epidemics, such as this exercise fictional scenario. Variations of these models are commonly used by epidemiologists to forecast the course of epidemics.[2]

The model was written in and run using the R software package. Each compartment in the SEIR model is normalized so that the sum of all compartments equals 1. The S compartment consists of susceptible persons that become infected at a rate affected by the force of infection (βI), where β is the effective reproductive number (R_e) divided by the infectious period. The E compartment consists of latent infections, which progress to infectious cases at a rate affected by lambda (λ), which is the inverse of the latent period. The I compartment progresses to the R compartment at a rate affected by gamma (γ), which is the inverse of the infectious period. The IIM automatically initializes the model using the parameters for population, seed infections, latent period, and infectious period. All infections were assumed to be symptomatic. The seed infections are distributed into the E and I compartments according to the ratio of latent and infectious periods:

$$E_{initial} = \frac{latent\_period}{infectious\_period + latent\_period}$$

$$I_{initial} = \frac{infectious\_period}{infectious\_period + latent\_period}$$

These infections are accordingly deducted from the S compartment. Cumulative symptomatic cases are defined as sum of the S and R compartments, multiplied by the population. Cumulative deaths are defined as the R compartment multiplied by the mortality rate and population.

[1] For example, see Biggerstaff, M et al "Estimating the potential effects of a vaccine program against an emerging influenza pandemic--United States." Clin Inf Dis S1, S20-9 (2015).
[2] Tolles J, Luong T. (2020) Modeling Epidemics With Compartmental Models. JAMA. 323 (24): 2515-2516.

The IIM base model does not permit changes of the effective reproductive number (R_e) during a given model run, so changes of R_e were implemented by restarting the model and using active infections (E + I) of the previous model run as the seed infections for the new model run. The population was reduced by the recovered population of the previous run to account for the R compartment resetting to 0 during model initialization. This process was repeated for every change in R_e. Although this method is imperfect, it can effectively approximate the time course of cases resulting from variations in R_e.

MODEL PARAMETERS

The outbreak in the fictional country of Andoriban (population 210 million) was modeled with a seed of 200 initial human cases and an R_e of 1.3. In this early stage of the outbreak, the model uses a conservative R_e since the virus was not intentionally modified for human-to-human transmission. This R_e is slightly lower than the 1.5 reproductive number which has been noted in some outbreaks of monkeypox, another orthopoxvirus for which humans are not the reservoir host.

Another instance of the model is run in parallel for a global population of 8 billion (not including the fictional country Andoriban) with a seed of 10 cases and an R_e of 1.3. Global cases remain undetected until day 38 of the outbreak, when cases outside of Andoriban are identified. By day 46 the virus has adapted to the human host and mutated to become more transmissible (R_e of 2.0). Four months after the first human case, antivirals are available and used. The use of antivirals and social distancing result in a reduction in the R_e to 0.7. However, as the outbreak progresses the virus continues to mutate, rendering antivirals ineffective by month 6 and resulting in the effective R_e returning to 2.0 for the remainder of the exercise.

Since little data exists on the naturally occurring Akhmeta virus, and transmission between humans has not been observed, modeling parameters were derived from similar pox viruses including cowpox, monkeypox, and smallpox (Table 1).

Table 1: Parameters used in Akhmeta model for the fictional scenario in the exercise

Parameter	Value	Rational	Source
Effective reproductive number (R_e)	Varies from 0.7-2.0	Pox viruses that infect humans have been estimatedto have R0 values as low as ~1.5 (low estimate for monkeypox) to as high as 6 (high estimate for smallpox). Without antivirals, the model assumes an Re that falls between these two values, during the short period of antiviral use, the model assumes an Re that is less than 1.	2,3
Latent period	10 days	The latent period for pox viruses is typically more than a week but less than 2 weeks: Cow pox typically ranges from 7-12 days, monkeypox from 7-14 days, and smallpox from 10-14 days.	4,5,6
Transmissible period	12 days	The transmissible period for pox viruses is relatively long. For smallpox individuals have 2-4 days when they are mildly contagious, 4 days when they are extremely contagious, and 10 days when they are moderately contagious. The transmissible period for monkeypox is not known, but symptoms last 2-4 weeks. In non-survivors, the transmissible period lasts until death. For smallpox most individuals experience 2-4 days when they are mildly contagious and another 5-6 days of extreme contagiousness prior to death. The transmissible period for non-survivors of monkey pox lasts ~8-22 days.	7,8,9,10

Fraction Symptomatic	100%	Though asymptomatic circulation of pox viruses is possible, asymptomatic infection is not believed to be common.	11,12,13
Mortality	7%	The mortality rate in humans following infection with pox viruses ranges from 0% (cowpox) to 30% (smallpox). The model assumes a moderate mortality slightly lower than that seen in monkeypox (10%).	14,15

[1] Centers for Disease Control and Prevention. Thinking Outside the Cowpox: The Discovery of a Pox- Related Virus. https://www.cdc.gov/ncezid/dhcpp/featured_stories/cowpox.html. Accessed 12/2/2021.

[2] Grant R, Nguyen L-BL, Breban R. (2020) Modelling human-to-human transmission of monkeypox. *Bulletin of the World Health Organization*. 98 (9): 638-640.

[3] R, Leach S. (2001) Transmission potential of smallpox in contemporary populations. Nature. 414(6865): 748-751.

[4] Vorou RM, Papavassiliou VG, Pierroutsakos IN. (2008) Cowpox virus infection: an emerging health threat. *Curr Opin Infect Dis*. 21 (2): 153-156.

[5] Centers for Disease Control and Prevention. Monkeypox: Signs and Symptoms. https://www.cdc.gov/poxvirus/monkeypox/symptoms.html. Accessed 12/2/2021.

[6] Centers for Disease Control and Prevention. Smallpox: For Clinicians. https://www.cdc.gov/smallpox/clinicians/clinical-disease.html. Accessed 12/3/2021.

[7] Centers for Disease Control and Prevention. Smallpox: Signs and Symptoms. https://www.cdc.gov/smallpox/symptoms/index.html#earlyrash. Accessed 12/3/2021.

[8] World Health Organization. Monkeypox. https://www.who.int/news-room/fact- sheets/detail/monkeypox. Accessed 12/3/2021.

[9] Centers for Disease Control and Prevention. Smallpox: For Clinicians. https://www.cdc.gov/smallpox/clinicians/clinical-disease.html. Accessed 12/3/2021.

[10] Americo JL, Moss B, Earl PL. (2010) Identification of Wild-Derived Inbred Mouse Strains Highly Susceptible to Monkeypox Virus Infection for Use as Small Animal Models. *Journal of Virology*. 84 (16):8172-8180.

[11] Guagliardo SAJ et al. (2020) Asymptomatic Orthopoxvirus Circulation in Humans in the Wake of a Monkeypox Outbreak among Chimpanzees in Cameroon. *The American journal of tropical medicine andhygiene*. 102 (1): 206-212.

[12] Centers for Disease Control and Prevention. Pinkbook: Smallpox. https://web.archive.org/web/20100306053203/http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/smallpox.pdf. Accessed 12/3/2021.

[13] Vorou RM, Papavassiliou VG, Pierroutsakos IN. (2008) Cowpox virus infection: an emerging healththreat. *Curr Opin Infect Dis*. 21 (2): 153-156.

[14] Centers for Disease Control and Prevention. Smallpox: What is Smallpox? https://www.cdc.gov/smallpox/about/index.html. Accessed 12/3/2021.

[15] Sklenovská N, Van Ranst M. (2018) Emergence of Monkeypox as the Most Important OrthopoxvirusInfection in Humans. *Frontiers in public health*. 6: 241-241.