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Development of a New Contagious Disease Model for NATO Allied Medical Publication 7.5 (AMedP-7.5)

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Executive Summary

In October 2017, the North Atlantic Treaty Organization (NATO) Standardization Office published Allied Medical Publication 7.5 (AMedP-7.5) *NATO Planning Guide for the Estimation of Chemical, Biological, Radiological and Nuclear (CBRN) Casualties*, a document authored by the Institute for Defense Analyses (IDA) under tasking by the U.S. Army Office of the Surgeon General (OTSG). AMedP-7.5 describes a methodology for estimating the number and timing of casualties from CBRN agents and effects to "assist planners, logisticians, and other staff officers in quantifying contingency requirements for medical force structure, specialty personnel, medical materiel, and patient transport or evacuation."[1] Users of this methodology can estimate casualties resulting from exposure to 12 chemical agents, 15 biological agents (including 4 toxins), 13 radioisotopes, radioactive fallout, or prompt nuclear effects. A contagious disease model in AMedP-7.5 also allows users to account for the potential of secondary transmission of 2 of the 15 biological agents (the causative agents of pneumonic plague and smallpox).

As the custodian of AMedP-7.5, OTSG is obliged to review the document on a triennial basis and suggest updates or revisions as necessary to reflect changes in the state of knowledge or advancements in modeling approaches. In anticipation of the next review, OTSG tasked IDA to develop a new contagious disease model for possible inclusion in a future version of AMedP-7.5. Like the current AMedP-7.5 contagious disease model, the new model is a deterministic compartmental epidemiological model that simulates a contagious disease outbreak in a single randomly mixed population at risk (PAR). Compartmental epidemiological models categorize the PAR into cohorts that represent different disease states (e.g., infectious and capable of transmitting the disease). The model simulates the progression of the outbreak by tracking the changes in the portions of the population in each cohort over time.[2] To do this, a set of time-dependent, finite-difference equations are sequentially solved at discrete time steps.

To be consistent with the overarching AMedP-7.5 methodology, the new contagious disease model reports the number and the timing of casualties resulting from the outbreak in the same manner that it is done for the other CBRN agents in AMedP-7.5. At the same time, the new model overcomes three known limitations of the current contagious disease model: (1) the use of daily transmission rates that are unique to single historical outbreaks

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1 North Atlantic Treaty Organization, *AMedP-7.5: NATO Planning Guide for the Estimation of CBRN Casualties*, STANAG 2553 (Brussels, Belgium: NATO Standardization Office, 2017), 1-3.

2 This manner of tracking disease at the population level is in contrast to an individual-based contagious disease model that tracks the changes in disease state for every individual in the population.

of plague or smallpox, which may not be representative of future outbreaks, (2) the inability to model certain administrative control measures that reduce contact between infectious and susceptible individuals, and (3) the assumption that individuals transition between cohorts at a constant rate. Consequently, the new model is less reliant on individual historical outbreaks, incorporates administrative isolation of infectious individuals, and allows movement of individuals through the various stages of illness according to empirically derived distributions.

The incorporation of the new contagious disease model described in this paper is one of many potential revisions being considered for the next version of AMedP-7.5. At the start of the next AMedP-7.5 triennial review cycle, continued alignment of the data and assumptions associated with the new contagious disease model and the overarching AMedP-7.5 methodology should be confirmed. As the next step, the U.S. Army OTSG, as the custodian of AMedP-7.5, may propose to the NATO CBRN Medical Working Group recommended changes to AMedP-7.5, including the substitution of the new contagious disease model for the current AMedP-7.5 model. The process of validating the new contagious disease model to confirm that the representation of the system and its structural and data assumptions satisfactorily represent the process of contagious disease spread will fall to the subject matter experts (SMEs) within the CBRN Medical Working Group, who are tasked to formally review the entire AMedP-7.5 methodology. Finally, after the new contagious disease model has been validated, its software implementation must be verified. The AMedP-7.5 methodology (to include a new contagious disease model) is planned to be incorporated into the second part of the Medical Information and Coordination System (MEDICS) currently under development through NATO.[3] In support of OTSG, IDA is tasked to provide reach-back support during the NATO software development process and is prepared to help with the validation and verification process.

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[3] Erick Meinen, "MEDICS: CBRN Casualty Rate Estimation US," (presentation, January 2017); Sean Oxford, "Notes from 7–8 September 2017 CBRN CRE Workshop hosted by NCI Agency in the Hague, Netherlands," memorandum for the record (Alexandria, VA: Institute for Defense Analyses, September 13, 2017).

Contents

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1. Introduction

In October 2017, the North Atlantic Treaty Organization (NATO) Standardization Office published Allied Medical Publication 7.5 (AMedP-7.5), *NATO Planning Guide for the Estimation of Chemical, Biological, Radiological and Nuclear (CBRN) Casualties*, a document authored by the Institute for Defense Analyses (IDA) under tasking by the U.S. Army Office of the Surgeon General (OTSG). AMedP-7.5 describes a methodology for estimating the number and timing of casualties from CBRN agents and effects to "assist planners, logisticians, and other staff officers in quantifying contingency requirements for medical force structure, specialty personnel, medical materiel, and patient transport or evacuation."[1] Users of this methodology can estimate casualties resulting from exposure to 12 chemical agents, 15 biological agents (including 4 toxins), 13 radioisotopes, radioactive fallout, or prompt nuclear effects. A contagious disease model in AMedP-7.5 also allows users to account for the potential of secondary transmission of 2 of the 15 biological agents (the causative agents of pneumonic plague and smallpox).

As the custodian of AMedP-7.5, OTSG is obliged to review the document on a triennial basis and suggest updates or revisions as necessary to reflect changes in the state of knowledge or advancements in modeling approaches. In anticipation of the next review, OTSG tasked IDA to develop a new contagious disease model for possible inclusion in a future version of AMedP-7.5. The aim of the new contagious disease model is to overcome certain known limitations of the current AMedP-7.5 contagious disease model while remaining within the confines of the overarching AMedP-7.5 casualty estimation methodology. These limitations include (1) the use of daily transmission rates that are unique to single historical outbreaks of plague or smallpox, which may not be representative of future outbreaks, (2) the inability to model certain administrative control measures that reduce contact between infectious and susceptible individuals, and (3) the assumption that individuals transition between cohorts at a constant rate.

The purpose of this paper is to describe the motivation for deriving the new contagious disease model and to document the model's underlying assumptions and the equations that define the model. The paper can be used by subject matter experts (SMEs) on the NATO CBRN Medical Working Group to help inform the decision of whether to incorporate the new contagious disease model into a future version of AMedP-7.5 and by software developers trying to implement the model in a tool.

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[1] North Atlantic Treaty Organization, *AMedP-7.5: NATO Planning Guide for the Estimation of CBRN Casualties*, STANAG 2553 (Brussels, Belgium: NATO Standardization Office, 2017), 1-3.

Chapter 2 of this paper provides a brief summary of the current AMedP-7.5 contagious disease model, along with a discussion of its limitations and how the new contagious disease model overcomes those limitations. Chapter 3 describes the basic structure of the new contagious disease model; the adaptations to include prophylaxis, treatment, and isolation of infectious individuals; and the parameters and equations that specify the new contagious disease model for pneumonic plague and smallpox. Chapter 4 provides a summary of the model's advantages over the current AMedP-7.5 contagious disease model, reiterates all the modeling assumptions, and details the next steps required to include the new model into a future version of AMedP-7.5. Lastly, Appendix A summarizes the parameters in the new contagious disease model and provides recommended values to help a planner use the model. It is assumed throughout the paper that the reader has some knowledge of and access to AMedP-7.5.

2. Addressing Limitations of the AMedP-7.5 Contagious Disease Model

A. Current AMedP-7.5 Contagious Disease Model

The current AMedP-7.5 contagious disease model is a deterministic compartmental epidemiological model that simulates a contagious disease outbreak in a single randomly mixed population. Compartmental epidemiological models categorize the population at risk (PAR) into cohorts that represent different disease states (e.g., infectious and capable of transmitting the disease). This compartmental model is called a susceptible, exposed and infected, infectious, removed, prophylaxis efficacious (SEIRP) model after the names of the cohorts through which individuals move as their disease state changes. The susceptible (S) cohort represents the portion of the population that is not infected but is susceptible to infection. The exposed and infected (E) cohort represents the portion of the population that has become exposed and infected with the disease but is not yet infectious and capable of transmitting the disease. The infectious (I) cohort represents the portion of the population that is infectious and capable of transmitting the disease. The removed (R) cohort represents the portion of the population that is no longer infectious due to either recovery (and acquisition of a natural immunity to reinfection) or death due to the disease. Lastly, since the model allows for the consideration of medical countermeasures (MCMs) (antibiotics for plague and vaccination for smallpox), the prophylaxis efficacious (P) cohort represents the portion of the population that has received efficacious prophylaxis and is thereby protected from becoming infectious.

The current AMedP-7.5 contagious disease model simulates the progression of the outbreak by tracking over time the changes in the portions of the population corresponding to each disease state cohort.[2] To do this, a set of time-dependent, finite-difference equations are sequentially solved at discrete time steps. Disease transmission is modeled based on contact between the S and I cohorts and is governed by daily transmission rates derived from specific historical outbreaks of plague or smallpox. These transmission rates dictate the rate at which members of the S cohort become infected and transition to the E cohort.

[2] This manner of tracking disease at the population level is in contrast to an individual-based contagious disease model that tracks the changes in disease state for every individual in the population. Therefore, the model uses non-integer values to describe cohort sizes and the rate of movement between cohorts.

The disease-specific distribution of the incubation period duration dictates the rate at which individuals[3] from the E cohort transition to the *I* cohort. Likewise, the disease-specific distribution of duration of illness dictates the rate at which individuals from the *I* cohort transition to the *R* cohort. Finally, individuals in either the *S* or *E* cohorts can transition to the *P* cohort once prophylaxis is administered.

B. Limitations of the Current AMedP-7.5 Contagious Disease Model

A number of the features of the current AMedP-7.5 contagious disease model limit its utility in predicting casualties from future outbreaks. First, the daily transmission rates that drive the spread of disease over time are unique to single historical outbreaks of plague or smallpox, which may not be representative of future outbreaks. While these transmission rates could be used to reproduce the daily casualties from the historical outbreaks given the same starting conditions (number of initial infections and size of the PAR), the new contagious disease model uses data aggregated from multiple historical outbreaks to avoid overfitting to a single historical outbreak.

A second limitation of the current AMedP-7.5 contagious disease model is the inability to model certain administrative control measures that reduce contact between the infectious and susceptible cohorts. Planners may want to include these control measures in their planning process because these measures are likely to be administered during an outbreak. Possible administrative control measures include isolating infectious individuals, quarantining individuals suspected of being exposed, and reducing contact between distinct subpopulations (e.g., military units). Planners using the AMedP-7.5 methodology are not expected to provide information that characterizes the population beyond the total number of individuals. Therefore, the new model continues to model the PAR as a single, homogeneously mixing group of individuals. Given the lack of a specified population structure (i.e., one that has been divided into subpopulations), the new contagious disease model, like the current AMedP-7.5 model, does not allow planners to model the effects of reducing contact between subpopulations. Likewise, quarantining suspected contacts of infectious individuals is not included in either model, because no sensible contact tracing strategy is logically consistent with a homogeneously mixing population since everyone is equally likely to contact every other person in the population. The new contagious disease model overcomes the limitation of the inability to model isolating infectious individuals. To model isolation, planners are required to specify how soon after symptom onset individuals are assumed to continue contacting others before being isolated.

A third limitation of the current AMedP-7.5 contagious disease model results from the simplifying assumption that individuals transition between cohorts at a constant rate.

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[3] Since the model is a population-based model, the use of the term *individual(s)* throughout this paper does not necessarily mean an integer number of people.

This assumption, which is often incorporated into contagious disease models, specifies the rate of movement out of a cohort as "1" divided by the mean time in the cohort. This formulation of a constant rate of transition between cohorts implies that the distribution of time spent in each cohort is exponential.[4] In reality, the time distribution is often better described by other distributions (e.g., lognormal), and, in fact, the AMedP-7.5 technical reference manual (TRM)[5] specifies distributions for each stage of illness for plague and smallpox based on extensive literature reviews. By combining distributions using the mathematical operation of convolution, the new contagious disease model has the capability to exploit those empirically derived distributions and better reflect documented disease progression.

IDA conducted a literature review that focused on identifying ways to overcome the three aforementioned limitations: calculation of disease transmission, isolation of infectious individuals, and transition rates between model cohorts. The following subsections elaborate on the findings of the literature review and detail how the new model is less reliant on individual historical outbreaks, incorporates administrative isolation of infectious individuals, and allows movement of individuals through the various stages of illness according to empirically derived distributions.

1. Calculation of Disease Transmission

The defining feature of contagious disease models is the ability to represent the transmission of disease from infectious individuals to those who are susceptible to infection. In the most generalizable terms, the transmission rate, $p(t)$, is defined as the number of new infections per time step and is expressed as a function of the size of the susceptible population on a given time step, $S(t)$, and the size of the infectious population on that time step, $I(t)$:

$$p(t) = f(S(t), I(t)). \tag{1}$$

The right-hand side of Eq. 1 is sometimes called the transmission function, which relates the transmission rate to $S(t)$ and $I(t)$. Eq. 2 shows the transmission function used in the current AMedP-7.5 contagious disease model:

$$p(t) = \frac{\beta(t)S(t)I(t)}{N}. \tag{2}$$

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4 Emilia Vynnycky and Richard G. White, *An Introduction to Infectious Disease Modelling* (Oxford, UK: Oxford University Press, 2010), 33.

5 Sean M. Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5) NATO Planning Guide for the Estimation of CBRN Casualties*, IDA Document D-8122 (Alexandria, VA: Institute for Defense Analyses, October 2016).

The number of new infections is assumed to be proportional to the product of the size of the infectious population ($I(t)$) and the fraction of the total population, N, that is susceptible ($S(t)/N$). The constant of proportionality, $\beta(t)$, is called the transmission coefficient and is defined as the rate at which two individuals come into effective contact (i.e., contact effective for disease transmission to occur) per time step.[6]

In the current AMedP-7.5 model, the transmission coefficient varies as a function of time, with values derived from a single historical outbreak for each disease: a plague outbreak in Mukden, China, in 1946 and a smallpox outbreak in Yugoslavia in 1972. AMedP-7.5 uses a method described by Bombardt to derive the transmission coefficient values, which has been demonstrated to reproduce the original historical outbreaks with a high degree of accuracy.[7] Others have published alternative methods for deriving transmission coefficient values over time for specific outbreaks from incidence data (the rate of new infections or symptomatic individuals during a given period) and prevalence data (the proportion of the population that is infected or symptomatic during a given period) that have likewise shown success at reproducing the historical outbreaks.[8]

The applicability of the time-varying, historically derived transmission coefficient for modeling future outbreaks depends on the similarity in the epidemiological circumstances between the historical and future outbreaks. Unless the circumstances of the two cases are known to match, the "potential danger of overfitting an epidemic model with [a] time-dependent transmission rate"[9] could result in transmission rates that are not generalizable to the different circumstances in future outbreaks. Even with starting conditions (i.e., population size and number of initial infections) that differ from the historical outbreak, an outbreak modeled using the historically derived transmission coefficient values will behave similarly to the original outbreak. The overall spread of disease will rise and fall at the same times as the historical case. In addition, transmission for any outbreak modeled with the historically derived transmission coefficient values will end when those values reached

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6 Vynnycky and White, *An Introduction to Infectious Disease Modelling*, 26.

7 John N. Bombardt, Jr., *Primary Pneumonic Plague Transmission and BW Casualty Assessments*, IDA Paper P-3657 (Alexandria, VA: Institute for Defense Analyses, December 2001), FOR OFFICIAL USE ONLY; John N. Bombardt, Jr., *Smallpox Transmission and BW Casualty Assessments*, IDA Paper P-3550 (Alexandria, VA: Institute for Defense Analyses, October 2000), FOR OFFICIAL USE ONLY.

8 Mark Pollicott, Hao Wang, and Howard (Howie) Weiss, "Extracting the Time-Dependent Transmission Rate from infection Data via Solution of an Inverse ODE Problem," *Journal of Biological Dynamics* 6, no. 2 (2012): 509–523, https://www.tandfonline.com/doi/full/10.1080/17513758.2011.645510; Alexandra Smirnova, Linda deCamp, and Gerardo Chowell, "Forecasting Epidemics through Nonparametric Estimation of Time-Dependent Transmission Rates Using the SEIR Model," *Bulletin of Mathematical Biology* (May 2, 2017), https://link.springer.com/article/10.1007%2Fs11538-017-0284-3.

9 Pollicott, Wang, and Weiss, "Extracting the Time-Dependent Transmission Rate," 519.

zero,[10] meaning that no future outbreak can be modeled to last longer than the historical outbreak. Given that the transmission coefficient values derived from different historical outbreaks of the same disease can differ significantly,[11] the representativeness of any single set of values to unknown future outbreaks is limited.

To overcome the limitation of a transmission function that is overly specific to a particular historical outbreak of disease, the time-varying transmission coefficient was replaced with a time-invariant value that was derived by aggregating data from multiple historical outbreaks, which is analogous to how other disease-specific parameter values (e.g., incubation period, case fatality rate) were derived for AMedP-7.5. The new contagious disease model relies on a commonly used measure of transmissibility, the basic reproduction number, R_0, which is the average number of successful transmissions of disease per infectious person in an entirely susceptible population.[12] This number is more generalizable because it is not specific to a particular historical outbreak. Instead, information can be drawn from multiple historical sources. To derive a transmission coefficient value for a particular disease, the basic reproduction number was divided by the mean infectious period duration (in number of time steps)[13] for that disease, μ_I, as shown in Eq. 3.[14]

$$\beta = \frac{R_0}{\mu_I}. \tag{3}$$

Since R_0 is the average total number of new cases that infectious individuals are expected to cause over the duration of their infectious period, dividing this value by the number of time steps in the infectious period results in the number of new cases generated

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[10] The AMedP-7.5 time-varying transmission coefficient values derived from the 1946 Mukden plague outbreak were zero for all time points beginning on day 34 (see North Atlantic Treaty Organization, *AMedP-7.5*, Table 5-57). The AMedP-7.5 time-varying transmission coefficient values derived from the 1972 Yugoslavia smallpox outbreak were zero for all time points beginning on day 60 (see North Atlantic Treaty Organization, *AMedP-7.5*, Table 5-85).

[11] See Bombardt's calculated transmission coefficient values for the 1946 Mukden, China, and the 1919 Oakland, California, plague outbreaks (Bombardt *Primary Pneumonic Plague Transmission*, Figures 21 and 22). Not only do these values differ in the number of non-zero values (reflecting the different durations of the two outbreaks), but they also peak at different times.

[12] Vynnycky and White, *An Introduction to Infectious Disease Modelling*, 6.

[13] Since the model is run at discrete time steps, all durations, including the mean infectious period duration, must be specified as the number of time steps and are calculated by dividing the durations in units of days by the step size (e.g., 0.1 days).

[14] This formulation has been used in other publications. See, for instance, Bret D. Elderd, Greg Dwyer, and Vanja Dukic, "Population-Level Differences in Disease Transmission: A Bayesian Analysis of Multiple Smallpox Epidemics," *Epidemics* 5, no. 3 (September 2013): 1–27, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3869526/pdf/nihms510111.pdf.

per infectious individual per time step. Since the values for both parameters on the right-hand side of Eq. 3 can be derived from data accumulated from multiple outbreaks, these values are less likely to reflect the peculiarities of any single historical outbreak.

Thus the new contagious disease model uses the transmission function specified in Eq. 4:

$$p(t) = \frac{(R_0/\mu_I)S(t)I(t)}{N}. \quad (4)$$

Like the current AMedP-7.5 model, the new model features a transmission function that is bilinear with respect to $S(t)$ and $I(t)$. This assumption of bilinear incidence implies that the population mixes homogeneously, with individuals equally likely to contact any other individual in the population, regardless of either individual's cohort.

Several alternative transmission functions were also reviewed, including many that are nonlinear (see Table 1). Although the forms of the functions reported in Table 1 vary greatly, the phenomena that the various transmission functions attempt to capture are the same: a decline in the per capita transmission rate as the outbreak progresses or an upper bound on the rate of transmission in larger populations.

Table 1. Alternative Forms of the Transmission Function

Transmission Function[Note 1]	Description (Application)	References
$\frac{\beta(t)S(t)I(t)}{N}$	Bilinear incidence with time-varying transmission coefficient replicating transmission rates from historical outbreaks (reconstructing particular historical outbreaks)	Note 2
	Bilinear incidence with time-varying transmission coefficient that declines with each successive disease generation or with time since the start of the outbreak (modeling reduced contacts over time due to behavioral changes in the population)	Note 3
$\frac{\beta(I(t))S(t)I(t)}{N}$	Bilinear incidence with transmission coefficient that declines exponentially as a function of $I(t)$ (modeling reduced transmission over the course of the infectious period due to high-risk contacts being infected earlier)	Note 4
$\beta I(t)\left(N - \frac{I(t)}{q}\right)$	Refuge effect (modeling a population in which only segments of susceptible and infectious individuals mix homogeneously)	Note 5

Transmission Function[Note 1]	Description (Application)	References
$\frac{\beta S(t)^x I(t)^y}{N}$	Power function (modeling a population in which only segments of susceptible and infectious individuals mix homogeneously)	Note 6
$kS(t)ln\left(1+\frac{\beta I(t)}{k}\right)$	Negative binomial (modeling a heterogeneously mixing population in which the distribution of new infections is negative binomial)	Note 7
$\frac{\beta S(t)I(t)}{c+S(t)+I(t)}$	Asymptotic transmission/saturated incidence rate (modeling an upper limit to the number of contacts per infectious individual in large populations)	Note 8

Note 1: All variables not defined in the text are constants that must be tuned to the specific scenario of interest.

Note 2: John N. Bombardt, Jr., *Smallpox Transmission and BW Casualty Assessments*, IDA Paper P-3550 (Alexandria, VA: Institute for Defense Analyses, October 2000), FOR OFFICIAL USE ONLY; John N. Bombardt, Jr., *Primary Pneumonic Plague Transmission and BW Casualty Assessments*, IDA Paper P-3657 (Alexandria, VA: Institute for Defense Analyses, December 2001), FOR OFFICIAL USE ONLY; Mark Pollicott, Mark, Hao Wang, and Howard (Howie) Weiss, "Extracting the Time-Dependent Transmission Rate from infection Data via Solution of an Inverse ODE Problem," *Journal of Biological Dynamics* 6, no. 2 (2012): 509–523; Alexandra Smirnova, Linda deCamp, and Gerardo Chowell, "Forecasting Epidemics through Nonparametric Estimation of Time-Dependent Transmission Rates Using the SEIR Model," *Bulletin of Mathematical Biology* (May 2, 2017).

Note 3: David N. Fisman et al., "An IDEA for Short Term Outbreak Projection: Nearcasting Using the Basic Reproduction Number," *PLoS ONE* 8, no. 12 (2013): e83622; Gerardo Chowell et al., "Characterizing the Reproduction Number of Epidemics with Early Subexponential Growth Dynamics," *The Royal Society Publishing* 13, no. 123 (October 2016): 20160659.

Note 4: Brian G. Williams et al., "The Potential Impact of Male Circumcision on HIV in Sub-Saharan Africa," *PLoS Medicine* 3, no. 7 (July 2006), e262; Reuben M. Granich et al., "Universal Voluntary HIV Testing with Immediate Antiretroviral Therapy as a Strategy for Elimination of HIV Transmission: A Mathematical Model." *The Lancet* 373, no. 9657 (3–9 January 2009): 48–57.

Note 5: Hamish McCallum, Nigel Barlow, and Jim Hone, "How Should Pathogen Transmission Be Modelled?" *Trends in Ecology & Evolution* 16, no. 6 (June 2001): 295–300; T. Hoch et al., "Influence of the Transmission Function on a Simulated Pathogen within a Population," *Epidemiology and Infection* 136, no. 10 (October 2008): 1374–1382.

Note 6: Michael E. Hochberg, "Non-Linear Transmission Rates and the Dynamics of Infectious Disease," *Journal of Theoretical Biology* 153, no. 3 (7 December 1991): 301–321; McCallum, Barlow, and Hone, "How Should Pathogen Transmission Be Modelled?"; Sarah A. Orlofske et al., "Experimental Investigation of Alternative Transmission Functions: Quantitative Evidence for the Importance of Nonlinear Transmission Dynamics in Host-Parasite Systems," *Journal of Animal Ecology* 87, no. 3 (May 2018): 703–715.

Note 7: McCallum, Barlow, and Hone, "How Should Pathogen Transmission Be Modelled?"; Hoch et al., "Influence of the Transmission Function"; Orlofske et al., "Experimental Investigation of Alternative Transmission Functions."

Note 8: McCallum, Barlow, and Hone, "How Should Pathogen Transmission Be Modelled?"; Dongmei Xiao and Shigui Ruan, "Global Analysis of an Epidemic Model with Nonmonotone Incidence Rate," *Mathematical Biosciences* 208, no. 2 (August 2007): 419–429; Hoch et al., "Influence of the Transmission Function"; Juan Hou and Zhidong Teng, "Continuous and Impulsive Vaccination of SEIR Epidemic Models with Saturation Incidence Rates," *Mathematics and Computers in Simulation* 79, no. 10 (June 2009): 3038–3054; Abdelhadi Abta, Abdelilah Kaddar, and Hamad Talibi Alaoui, "Global Stability for Delay SIR and SEIR Epidemic Models with Saturated Incidence Rates," *Electronic Journal of Differential Equations* 2012, no. 23 (2012): 1–13.

Over the course of a real-world outbreak, the per capita transmission rate may diminish due to any combination of the following reasons.

- First, susceptible individuals are likely to change their behavior and take extra precautions to avoid exposure as more individuals around them show symptoms of illness. Some examples include "self-isolation, moving away from areas with high incidence, avoiding public transport, [and] children being kept away from school by their parents."[15] Such behavioral changes in the population have been modeled with a transmission coefficient that declines with each successive disease generation or with time since the start of the outbreak.[16]
- Second, a heterogeneity in susceptibility could cause more susceptible individuals to become infected earlier in an outbreak than those who are less susceptible, which would result in a deceleration of the transmission rate over time. Reflecting this distribution of susceptibility hypothesis, some researchers have modeled a transmission function with a transmission coefficient that decays exponentially as a function of the prevalence of disease in the population.[17]
- Third, the population could be mixing heterogeneously. A homogeneously mixing population is a simplification of reality, and outbreaks tend to cause clusters of infectious individuals such that individuals are each more likely to have contact with other individuals in the same cohort than in other cohorts. One attempt to model the "refuge effect" caused by a heterogeneity in the population, such as a spatial separation of the susceptible and infectious individuals within a population, assumes that only segments of the susceptible and infectious cohorts mix homogeneously.[18] The same effect has also been modeled by characterizing

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15 W. John Edmunds, Ken Eames, and Marcus Keogh-Brown, "Capturing Human Behaviour: Is It Possible to Bridge the Gap Between Data and Models?" in *Modeling the Interplay Between Human Behavior and the Spread of Infectious Diseases*, ed. Piero Manfredi and Alberto d'Onofrio (New York: Springer, 2013), 313.

16 David N. Fisman et al., "An IDEA for Short Term Outbreak Projection: Nearcasting Using the Basic Reproduction Number," *PLoS ONE* 8, no. 12 (2013): e83622, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3877403/pdf/pone.0083622.pdf; Gerardo Chowell et al., "Characterizing the Reproduction Number of Epidemics with Early Subexponential Growth Dynamics," *The Royal Society Publishing* 13, no. 123 (October 2016): 20160659, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5095223/.

17 Brian G. Williams et al., "The Potential Impact of Male Circumcision on HIV in Sub-Saharan Africa," *PLoS Medicine* 3, no. 7 (July 2006), e262, https://doi.org/10.1371/journal.pmed.0030262; Reuben M. Granich et al., "Universal Voluntary HIV Testing with Immediate Antiretroviral Therapy as a Strategy for Elimination of HIV Transmission: A Mathematical Model," *The Lancet* 373, no. 9657 (3–9 January 2009): 48–57, https://doi.org/10.1016/S0140-6736(08)61697-9.

18 T. Hoch et al., "Influence of the Transmission Function on a Simulated Pathogen within a Population," *Epidemiology and Infection* 136, no. 10 (October 2008): 1374–1382, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2870731/pdf/S095026880700979Xa.pdf; Hamish McCallum, Nigel Barlow, and Jim

the transmission function as a power function.[19] Others have modeled the effects of heterogeneity in the population by using a transmission function that generates new infections according to the negative binomial distribution.[20]

- Fourth, certain diseases with short generation times relative to the duration of the outbreak could mutate in such a way that the infectivity changes over the course of the outbreak. Evidence suggests that such changes may have affected the transmission of the Ebola virus in the West African Ebola outbreak.[21]

One way to capture the phenomenon of an upper bound on the rate of transmission in larger populations and to account for an upper limit on how many individuals an infectious person can contact in a given time is by assuming an asymptotic transmission function. Various forms of such a transmission function attempt to capture the saturated incidence rate between susceptible and infectious individuals in large populations by modeling transmission as proportional to the number of individuals in small populations but approaching an upper limit for larger populations.[22]

For estimating military casualties in a pre-event planning scenario, the transmission function in Eq. 4 was chosen over the alternatives listed in Table 1 for several reasons.

Hone, "How Should Pathogen Transmission Be Modelled?" *Trends in Ecology & Evolution* 16, no. 6 (June 2001): 295–300, https://doi.org/10.1016/S0169-5347(01)02144-9.

19 Sarah A. Orlofske et al., "Experimental Investigation of Alternative Transmission Functions: Quantitative Evidence for the Importance of Nonlinear Transmission Dynamics in Host-Parasite Systems," *Journal of Animal Ecology* 87, no. 3 (May 2018): 703–715, https://www.ncbi.nlm.nih.gov/pubmed/29111599; Michael E. Hochberg, "Non-Linear Transmission Rates and the Dynamics of Infectious Disease," *Journal of Theoretical Biology* 153, no. 3 (7 December 1991): 301–321, https://doi.org/10.1016/S0022-5193(05)80572-7; McCallum, Barlow, and Hone, "How Should Pathogen Transmission Be Modelled?"

20 When the negative binomial transmission function aggregation parameter k is low, individuals are assumed to be more likely to contact individuals in the same cohort than in other cohorts. See Orlofske et al., "Experimental Investigation of Alternative Transmission Functions"; Hoch et al., "Influence of the Transmission Function"; and McCallum, Barlow, and Hone, "How Should Pathogen Transmission Be Modelled?"

21 Richard A. Urbanowicz et al., "Human Adaptation of Ebola Virus during the West African Outbreak," *Cell* 167, no. 4 (November 2016): 1079–1087, https://doi.org/10.1016/j.cell.2016.10.013.

22 A representative form of an asymptotic transmission function (or saturated incidence rate) selected from among many published mathematical forms is shown in Table 1, where c is a constant. See McCallum, Barlow, and Hone, "How Should Pathogen Transmission Be Modelled?"; Dongmei Xiao and Shigui Ruan, "Global Analysis of an Epidemic Model with Nonmonotone Incidence Rate," *Mathematical Biosciences* 208, no. 2 (August 2007): 419–429, https://doi.org/10.1016/j.mbs.2006.09.025; Hoch et al., "Influence of the Transmission Function"; Juan Hou and Zhidong Teng, "Continuous and Impulsive Vaccination of SEIR Epidemic Models with Saturation Incidence Rates," *Mathematics and Computers in Simulation* 79, no. 10 (June 2009): 3038–3054, https://doi.org/10.1016/j.matcom.2009.02.001; Abdelhadi Abta, Abdelilah Kaddar, and Hamad Talibi Alaoui, "Global Stability for Delay SIR and SEIR Epidemic Models with Saturated Incidence Rates," *Electronic Journal of Differential Equations* 2012, no. 23 (2012): 1–13, http://emis.impa.br/EMIS/journals/EJDE/Monographs/Monographs/Volumes/2012/23/abta.pdf.

Given the uncertainties in the epidemiological circumstances (i.e., the disease, the environment, and the PAR) for a possible outbreak at an unknown time in the future, the transmission function incorporated in the new contagious disease model should be as generalizable as possible and divorced from any particular historical outbreak. The transmission function in Eq. 4, with its bilinear incidence and fixed transmission coefficient, makes few assumptions about the epidemiological circumstances and has few parameters for planners to select. All the alternative transmission functions have additional parameters that would need to be fitted for the diseases of interest to the new contagious disease model. None of the sources cited in Table 1 used the transmission functions for modeling plague or smallpox, so parameter values for these diseases are not readily available. While sufficient data on historical outbreaks of plague and smallpox exist to characterize the standard parameters used to derive the time-invariant transmission coefficient (i.e., R_0 and μ_I), deriving realistic values for the less common parameters would require more information than is currently available.

Even if values were available to parameterize the alternative transmission functions, the choice of transmission function might be trivial when also considering the effect of anticipated outbreak response measures. In reality, any observed cases of plague or smallpox in a deployed military population would undoubtedly trigger a large-scale response. Therefore, planners are expected to model response measures relatively early in the course of a modeled outbreak. Given the highly effective MCMs that are available for plague and smallpox, the modeled outbreak is expected to end shortly after the administration of medical response measures. Although the alternative transmission functions are expected to diverge progressively over time as small differences are compounded, the differences between outbreaks modeled with any of the transmission functions are expected to be negligible for the period of time early in the outbreak until response measures are implemented. If the user chooses not to model the use of MCMs or isolation of infectious individuals (described in the next section), then the modeled outbreak will not end until the susceptible population is depleted to the point at which the number of new infections is effectively zero. Given the potential magnitude of the divergence later in an outbreak between a constant and a time-varying transmission coefficient, it is recommended that the new contagious disease model not be used to estimate casualties in the absence of MCMs and isolation of infectious individuals.

2. Isolation of Infectious Individuals

Isolation is the practice of separating infectious individuals from the rest of the population to reduce or eliminate their contact with susceptible individuals. Before the recognition of an ongoing outbreak, medical staff would follow established procedures for identifying and potentially isolating patients suspected of being infected with a contagious disease. If suspicion is low, symptoms are nonspecific, or protocols dictate isolating

individuals only upon a laboratory (rather than clinical) diagnosis, then the implementation of an appropriate level of isolation may be delayed or omitted altogether. After a laboratory-confirmed diagnosis of a known contagious disease or several cases of disease suspected of being transmissible human-to-human, medical staff will recognize that an outbreak is ongoing, and procedures for identifying and managing suspected cases will likely be updated. This update may include the generation of a clinical case definition, with patients being isolated upon entry to the medical system if they display signs or symptoms that match the case.

The desired effect of isolating infectious individuals is that, once isolated, infectious individuals no longer spread disease to susceptible individuals, thus reducing the number of subsequent cases of infection compared to the non-isolation case. While contact with the infected individual may not cease entirely during isolation, *disease-causing contact* should be reduced since all individuals will be taking precautions to avoid infection when interacting with the isolated patient. In reality, imperfect isolation is possible, and transmission could still occur between infectious individuals and the medical staff, other patients, or visitors to the medical treatment facility.

In the new contagious disease model, isolation is assumed to be 100% effective once implemented. There is no partially effective isolation and no gradual transition from normal mixing within the population to complete isolation. Rather, there is a point in time for each infectious individual at which his or her ability to transmit the disease is terminated. Users of the new model specify the time after seeking medical care that an individual is modeled to be isolated effectively. For instance, if the user-specified time to reach effective isolation was 1 day, then every sick individual would be completely isolated within a day of seeking medical care. This period includes the time to reach the medical treatment facility and the time to identify the need for and implement the precautionary measures to effectively isolate the patient. Until the time at which individuals have become effectively isolated, they are assumed to be contacting other individuals at their normal rate. Once the time to become effectively isolated has been reached, individuals are modeled to have no more effective contacts with any susceptible individuals, and there is no further transmission from the isolated individuals.

For simplicity, the user-specified time to reach isolation in the model is treated as fixed. It varies neither by patient nor over the course of the outbreak. In reality, there would be a distribution of times to reach effective isolation dependent on the individuals' locations relative to the medical treatment facility and the speed at which the need for isolation was identified and implemented. However, this level of individual variation is not included elsewhere in the AMedP-7.5 casualty estimation methodology, and it is not clear what that distribution might look like if it were to be included. The choice to model the time to reach isolation as fixed over the course of the outbreak was also a simplifying assumption. As described previously, the time to isolation would likely decrease as the outbreak progressed

due to an increased awareness of the threat over time, perhaps abruptly at some specific point in time (e.g., when the outbreak was recognized). However, adding a changeover point would require three parameter values from the user rather than the single time to isolation value: an initial value for the time to isolation, a time at which that value changed, and the new value for the time to isolation. Minimizing the number of parameter values that users of the new contagious disease model are asked to provide as input is consistent with feedback from NATO military medical planners at the CBRN Casualty Rate Estimation Workshop held by NATO's Communications and Information Agency on September 7–8, 2017, in The Hague, Netherlands.[23] Participants at this workshop, which focused on user requirements for CBRN Casualty Rate Estimation software, indicated a preference that users be asked to provide general, high-level inputs and not be asked for too much detail.

3. Transition Rates between Model Cohorts

Inter-individual variation in response to exposure to disease-causing agents is dependent on a number of factors, including "gender, age, socioeconomic status, nutrition, and genetic background."[24] This variation affects the duration of the asymptomatic incubation period, the durations of subsequent stages of illness, and the probability of death. Each of these values can be described at the population level by a distribution across the individuals in the population, which was done for the development of AMedP-7.5 based on extensive literature review.

Unfortunately, despite the AMedP-7.5 TRM specifying the distribution for the durations of the incubation period and each subsequent stage of illness, a limitation of the current AMedP-7.5 contagious disease model is that those distributions cannot be used in full to describe the movement of individuals from one cohort to another. Instead, individuals transition between cohorts at a constant rate based on only the mean time that an individual is expected to spend in a given cohort. For example, the rate at which individuals develop symptoms (i.e., transition from the E cohort into the I cohort) is based on the mean incubation period duration of the disease, μ_E. More specifically, the symptom onset rate is equal to $\frac{1}{\mu_E}$. Therefore, the number of people transitioning from the E cohort to the I cohort at some time step t, $E \rightarrow I(t)$, is simply the expression shown in Eq. 5:

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[23] Sean Oxford (workshop attendee), e-mail message to authors, April 18, 2018.

[24] Kirsten C. Verhein, Heather L. Vellers, and Steven R. Kleeberger, "Inter-Individual Variation in Health and Disease Associated with Pulmonary Infectious Agents," *Mammalian Genome* 29, nos. 1–2 (February 2018): 38, https://www.ncbi.nlm.nih.gov/pubmed/29353387.

$$E \rightarrow I(t) = E(t-1) \times \frac{1}{\mu_E}. \quad (5)$$

Furthermore, the assumption that individuals transition between cohorts at a constant rate also implies that the dwell times in each cohort are described by exponential distributions.[25] To incorporate the empirically derived distributions described in the TRM, a more sophisticated approach was used to model the transition of individuals between cohorts.

In the new contagious disease model, the transition rates between cohorts are characterized with the mathematical operation of convolution. While the convolution appears in a range of mathematical applications, it is used in the new contagious disease model as an operation on the probability distributions that describe the stages of illness. If two random variables are independent, then the probability distribution that describes the sum of the two random variables is simply the convolution of the two variables' probability distributions. For example, let $F_1(t)$ be the probability distribution for the duration of the incubation period of a disease and let $F_2(t)$ be the probability distribution for the duration of stage 1 of illness for the same disease. Given these two distributions, the distribution that describes the combined time spent in the incubation period and stage 1 of illness is calculated as the convolution of $F_1(t)$ and $F_2(t)$ and is written as $(F_1 * F_2)(t)$. While the convolution of two (or more) functions can be calculated in multiple ways, the convolutions used in the new contagious disease model are formulated as discrete sums, as shown in Eq. 6:

$$(F_1 * F_2)(t) = \sum_{u=0}^{t} F_1(u) F_2(t-u). \quad (6)$$

To calculate convolutions as shown in Eq. 6, the distributions must be formulated as discrete probability mass functions instead of continuous probability density functions.

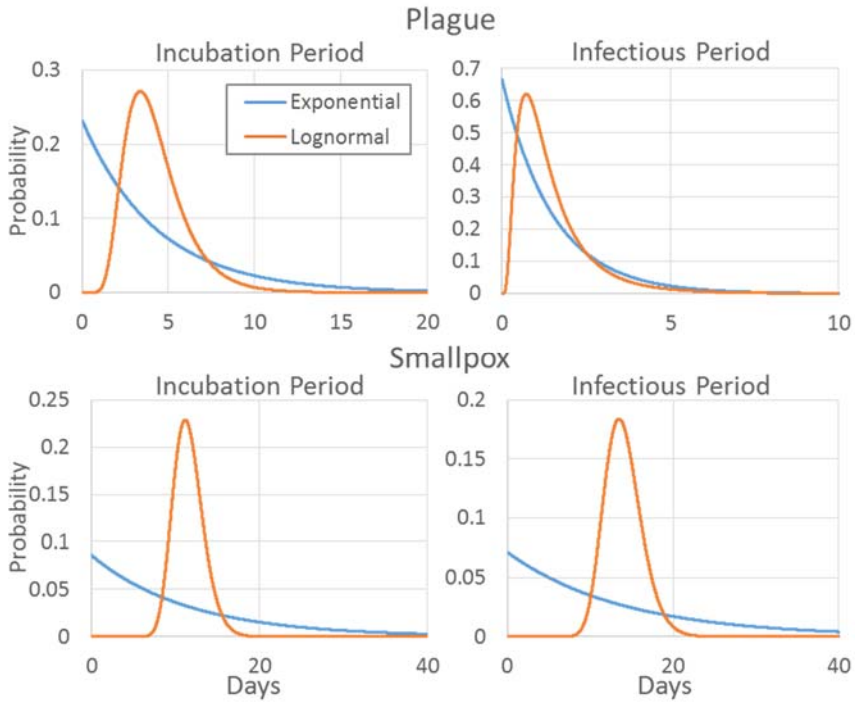
To return to the earlier example, using the convolution method, the number of individuals transitioning from the E cohort to the I cohort at some time step t, $E \rightarrow I(t)$, is given by Eq. 7:

$$E \rightarrow I(t) = (p * F_1)(t) = \sum_{u=0}^{t} p(u) F_1(t-u). \quad (7)$$

Note that this transition is not a movement of individuals according to an exponential dwell time, but rather a representation of the movement according to the likelihood of transitioning based on the known time of becoming infected, $p(t)$, and the specified distribution of dwell time in the incubation period, $F_1(t)$. For plague and smallpox, the incubation periods and the infectious periods are described by lognormal distributions. Figure 1 shows the difference between the probability density functions of the lognormal distributions

[25] Vynnycky and White, *An Introduction to Infectious Disease*, 33.

derived from the literature (see Appendix A for parameter values) and the exponential distributions implied by using the AMedP-7.5 model assumption of constant transition rates between cohorts for plague and smallpox incubation and infectious period durations. For both diseases, use of the exponential distribution would result in some fraction of individuals completing the incubation and infectious periods sooner than expected according to the lognormal distributions.



Note: The current AMedP-7.5 model assumes that individuals transition between cohorts at a constant rate based on only the mean time individuals stay in a given cohort. This assumption implies that the incubation and infectious periods follow exponential distributions. The new contagious disease model uses lognormal incubation and infectious period distributions that were empirically derived.

Figure 1. Comparison of Incubation and Infectious Period Distributions for Plague and Smallpox in the Current AMedP-7.5 Model (Exponential) and in the New Model (Lognormal)

For an example of how to interpret Eq. 7, consider a step size equal to 1 day. For this case, the transition of individuals from the E cohort to the I_1 cohort on time step (day) $t = 3$ is equal to the sum of four terms (i.e., the sum over u from 0 to 3):

- $u = 0$: the number of individuals who were infected on day 0 times the fraction of individuals who incubate for 3 days, $p(0)F_1(3)$,
- $u = 1$: the number of individuals who were infected on day 1 times the fraction of individuals who incubate for 2 days, $p(1)F_1(2)$,
- $u = 2$: the number of individuals who were infected on day 2 times the fraction of individuals who incubate for 1 day, $p(2)F_1(1)$, and

- $u = 3$: the number of individuals who were infected on day 3 times the fraction of individuals who incubate for 0 days, $p(3)F_1(0)$.[26]

As was true for Eq. 6, all components of the convolution in Eq. 7 must be formulated as discrete functions. The number of new infections is calculated once per time step, so the resulting time-dependent transmission rate, $p(t)$, is naturally a discrete function, and the incubation period distribution, $F_1(t)$, must be converted from a probability density function to a probability mass function. To convert a continuous probability density function to a discrete probability mass function, the user must first select a step size, dt. The probability mass function is defined for time steps equal to multiples of dt (with values being equal to the continuous probability density function evaluated at the same time steps multiplied by dt) and is undefined at all other values.

[26] The fraction of individuals who incubate for 0 days is always zero, so the fourth term in this list is always zero for this application.

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3. New Contagious Disease Model Formulation

A. New Contagious Disease Model Description

This section will first describe the features of the basic compartmental model framework shared by the new contagious disease model and the current AMedP-7.5 model. It will then introduce the features that were added to flesh out the new contagious disease model, including additions due to casualty status reporting requirements of the AMedP-7.5 methodology, prophylaxis and treatment for both diseases, and isolation of infectious individuals. The new model has plague and smallpox variants to account for some differences between the two diseases (e.g., a treatment cohort in the plague variant and a convalescent cohort in the smallpox variant). Each model variant has a unique set of equations, listed in Section 3.B, that specify the movement of individuals through the various cohorts to simulate the spread of that particular disease. Appendix A provides a table that summarizes all parameters required for implementing the model as well as recommended parameter values for plague and smallpox.

1. Basic Model Description and Model Inputs

Many of the assumptions that were made in the current AMedP-7.5 model are retained in the new contagious disease model. Both models are deterministic compartmental epidemiological models that simulate the spread of contagious disease at the population level by tracking the changes in the portions of the population corresponding to each disease state cohort over time.[27] Due to the unchanged assumptions for pneumonic plague and smallpox that (1) all individuals enter an asymptomatic incubation period before the development of symptoms and (2) once an infected individual ceases to be symptomatic, that individual is not susceptible to reinfection for the remainder of the modeled outbreak, a susceptible, exposed and infected, infectious, removed (SEIR) model was again selected as the foundation of the new contagious disease model before the inclusion of response measures described later in this subsection.

[27] Like the current AMedP-7.5 model, the new model uses non-integer values to describe cohort sizes and the rate of movement between cohorts. Therefore, the model will report non-integer numbers of casualties that can be rounded to integer numbers for reporting purposes. This treatment of non-integer people is consistent with the rest of the AMedP-7.5 methodology.

The disease progressions for plague and smallpox are also assumed to be the same in the new contagious disease model as those in the current AMedP-7.5 model. Following exposure and infection, both disease progressions begin with an asymptomatic, non-infectious incubation period. After the incubation period, individuals enter stage 1 of illness and exhibit moderate (severity level 2) symptoms.[28] Despite having developed symptoms, individuals in stage 1 of either plague or smallpox are not infectious and therefore are not capable of transmitting the disease.[29] Upon entering stage 2 of illness, individuals become infectious and begin exhibiting more severe symptoms. Individuals who will survive smallpox exhibit severe (severity level 3) symptoms in this stage and will progress to a period of convalescence before returning to duty. Individuals who will not survive smallpox exhibit very severe (severity level 4) symptoms in stage 2 of illness, which terminates in death. In the absence of treatment, all individuals will exhibit very severe (severity level 4) symptoms in stage 2 of plague, after which they die. Even with treatment (the full effect of which is discussed in the next subsection), some individuals will still die from plague after exhibiting very severe (severity level 4) symptoms in stage 2 of illness. For some treated plague cases, however, stage 2 of illness is characterized by moderate (severity level 2) symptoms, and, upon the termination of that stage of illness, these individuals will return to duty.

A traditional SEIR model would combine the asymptomatic incubation period with the symptomatic, non-infectious stage 1 of illness into the E cohort, as individuals in both stage are neither susceptible to infection (S) nor infectious and capable of transmitting the disease (I). However, the new contagious disease model, like the current AMedP-7.5 model, is subject to a number of casualty reporting requirements imposed by the AMedP-7.5 casualty estimation methodology. To track the change in symptom severity as individuals progress through the two symptomatic stages of illness for casualty reporting purposes, the current AMedP-7.5 model and the new contagious disease model split the traditional single I cohort into two cohorts (I_1 and I_2). The I_1 cohort consists of individuals who are in stage 1 of illness and are symptomatic but non-infectious, and the I_2 cohort contains individuals in stage 2 of illness who are infectious.[30] Another reporting requirement of the AMedP-7.5 methodology is that individuals in the R cohort be distinguishable as having

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[28] The AMedP-7.5 methodology rates the severity of symptoms on a scale from 0 (no observable symptoms) to 4 (very severe symptoms).

[29] Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5)*, 23-7–23-8, 26-10.

[30] An alternative to this approach would be to split the E cohort into two cohorts: an E_1 cohort for the non-symptomatic, non-infectious period (the current E cohort) and an E_2 cohort for the symptomatic, non-infectious period (the current I_1 cohort). The choice of variable name for the symptomatic, non-infectious period is purely semantic, since it has no effect on the actual simulation of the disease outbreak. In this case, the existing AMedP-7.5 naming convention was retained for consistency.

died of wounds, being in a period of convalescence, or having returned to duty. Thus the R cohort was split into three cohorts: DOW, $Conv$, and RTD, although the $Conv$ cohort is not applicable to modeling plague casualties, as survivors are capable of returning to duty after completing their course of antibiotic treatment in the medical treatment facility.[31]

The new contagious disease model has a number of inputs, some of which must be specified by the user and some of which have default recommended values that the user could change if desired. Required user-specified inputs include the disease to be modeled (plague or smallpox), the total fixed size of the population (N), and the number of initially exposed and infected individuals (E_0 in the absence of MCMs) that trigger the start of the outbreak and lead to all subsequent infections. The number of individuals initially exposed and infected can be postulated or can be derived using exposure estimates and the disease-specific infectivity model described in AMedP-7.5.

As part of the overarching AMedP-7.5 methodology, the user must specify the wounded in action (WIA) casualty criterion, the "injury severity threshold above which an individual is declared WIA"[32] from among the following three options.

- **WIA(1^+)**. An individual manifesting signs and/or symptoms of Severity Level 1 or greater is considered WIA.
- **WIA(2^+).** An individual manifesting signs and/or symptoms of Severity Level 2 or greater is considered WIA.
- **WIA(3^+).** An individual manifesting signs and/or symptoms of Severity Level 3 or greater is considered WIA.[33]

The effect of the casualty criterion for the two contagious diseases modeled in AMedP-7.5 is that for a user-specified casualty criterion of WIA(1^+) or WIA(2^+), individuals will be considered casualties upon entering stage 1 of illness since the first stage is characterized by symptoms of moderate (severity level 2) symptoms. For a casualty criterion of WIA(3^+), individuals will not be deemed casualties until entering stage 2 of illness, which is characterized by severe (severity level 3) symptoms for smallpox survivors and by very severe (severity level 4) symptoms for smallpox nonsurvivors and all plague casualties.

The model also requires that the step size between time steps at which calculations are made, dt, be specified. The benefit of a larger step size is a shorter simulation run time since fewer calculations are made over the course of a simulated outbreak. Since individuals can transition between disease states only once per time step, a smaller step size means that individuals can transition between disease states more rapidly and the duration of time

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31 Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5)*, 23-11. DOW = died of wounds, $Conv$ = convalescence, RTD = return to duty.

32 North Atlantic Treaty Organization, *AMedP-7.5*, 1-14.

33 North Atlantic Treaty Organization, *AMedP-7.5*, 1-10.

in any one state can be more precisely described (to the nearest fraction of a day). In reality, the transmission of disease from infectious individuals to susceptible individuals is a continuous process in time, which is more closely approximated with more closely spaced discrete time points (i.e., a smaller step size). Since casualties are reported on a daily basis, there must be an integer number of time steps per day. For the time-dependent model equations, the units of t are not days, but rather integer number of time steps. For instance, if the step size were equal to 0.1 days, then the expression for the number of new infections on day 3 (time step 30) would be $p(30)$, not $p(3)$.

For a given disease, a number of additional default parameter values could be modified by a knowledgeable user who wishes to use data from different sources. Among these values is the disease-specific basic reproduction number, R_0. The R_0 values recommended in the new contagious disease model are 1.3 for plague[34] and 5 for smallpox.[35] Disease-specific default parameters specify the distributions that dictate the time that individuals spend in each stage of illness. The AMedP-7.5 TRM specifies the distribution parameters that dictate the time spent in the incubation period, stage 1 of illness, stage 2 of illness, and (for smallpox) a convalescent period after the infectious period (stage 2 of illness).[36] The new contagious disease model continues to use these distributions to dictate the time spent in each cohort of the model. Appendix A provides the specific distributions.

2. Plague Prophylaxis and Treatment

According to the AMedP-7.5 TRM, "[m]edical management of pneumonic plague has two main objectives: avoiding mortality via early antibiotic intervention—before symptom onset if possible or as soon as possible thereafter if not—and controlling the risk of contagion."[37] To include the effects of medical interventions in the model, users must specify the time step relative to the start of the outbreak at which antibiotics are used to

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[34] J. O. Lloyd-Smith et al., "Superspreading and the Effect of Individual Variation on Disease Emergence," *Nature* 438, no. 7066 (December 2005): 355–359 (see Supplementary Table 1), http://www.nature.com/articles/nature04153#supplementary-information; Raymond Gani and Steve Leach, "Epidemiologic Determinants for Modeling Pneumonic Plague Outbreaks," *Emerging Infectious Diseases* 10, no. 4 (April 2004): 608–614. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3323083/pdf/03-0509.pdf.

[35] This value is the midpoint of the range 4–6 specified by Raymond Gani and Steve Leach, "Transmission Potential of Smallpox in Contemporary Populations," *Nature* 414, no. 6865 (13 December 2001): 750, https://www.nature.com/articles/414748a.pdf.

[36] See Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5)*, 23-12 (Table 185) for plague distributions and Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5)*, 26-19 (Table 210) for smallpox distributions.

[37] Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5)*, 23-9.

treat individuals in stage 1 of illness, t_{Tr}, and the time step relative to the start of the outbreak at which prophylactic antibiotics provide protection to susceptible or incubating individuals, t_{PEP}, which is presumably no earlier than t_{Tr}, since prophylactic use of antibiotics would almost certainly follow the recognition that antibiotics are effective in treating patients. If users do not wish to include the effects of medical interventions in the model, they must specify t_{Tr} and t_{PEP} to be arbitrarily large (beyond the time frame of interest to the user) such that they never trigger the use of medical interventions.

The administration of prophylactic antibiotics is modeled with the addition of a PEP cohort (analogous to the prophylaxis efficacious (P) cohort in the AMedP-7.5 model). At t_{PEP}, those individuals protected by prophylactic antibiotics transition from the S cohort and the E cohort to the PEP cohort, where they stay for the duration of the outbreak and do not return to the S cohort.[38] The fraction of individuals who were in the S cohort at time step t_{PEP} that are protected from infection is the product of the post-exposure prophylaxis (PEP) coverage rate, ψ_{PEP}, defined as the fraction of individuals in the S and E cohorts who were administered prophylactic antibiotics, and ϵ_S, the efficacy of the prophylaxis at preventing infection when administered to individuals in the S cohort. Similarly, the fraction of individuals who were in the E cohort at time step t_{PEP} that are protected from developing symptoms is the product of ψ_{PEP} and ϵ_E, the efficacy of the prophylaxis at preventing symptom onset when administered to individuals in the E cohort. The default recommended value for both ϵ_S and ϵ_E is 0.95, and the choice of value for ψ_{PEP} is left to the user since it depends on the scenario to be modeled.[39]

The administration of antibiotics to symptomatic individuals is considered treatment and is handled the same way that it was in AMedP-7.5. Once antibiotics are available (at time step t_{Tr}), they are assumed to be administered as treatment to all patients. Treatment initiated in stage 1 of illness is assumed to decrease the case fatality rate significantly, reduce the severity of stage 2 of illness for survivors to severity level 2, and change the duration of illness. Treatment initiated in stage 2 of illness has no effect on the model. Consequently, treatment is only significant if the casualty criterion is WIA(1^+) or WIA(2^+). Since individuals are not considered casualties until they enter stage 2 of illness if the casualty criterion is WIA(3^+), treatment could not be initiated until stage 2 of illness, at which point it has no effect and the value of t_{Tr} is inconsequential.

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[38] This assumption that prophylactic antibiotics will be available for the duration of the outbreak may seem unrealistic, but past analyses have shown that widespread use of highly efficacious prophylactic antibiotics (as are available for plague) have been effective at stopping the outbreak soon after antibiotic administration. PEP = post-exposure prophylaxis.

[39] North Atlantic Treaty Organization, *AMedP-7.5*, 5-60 (Table 5-56).

Modeling treatment to begin in stage 1 of illness has the effect of reducing the case fatality rate of individuals receiving treatment. In AMedP-7.5, the case fatality rate is modeled as 0% if treatment is initiated in stage 1 of illness. However, since the same antibiotics when administered prophylactically before symptom onset are modeled to be less than 100% effective at preventing the disease or aborting the infection, it seems reasonable to assume that these antibiotics would be no more effective at resisting the plague infection when administered after symptom onset. Accordingly, rather than using a fixed 0% case fatality rate, the new contagious disease model introduces the parameter ϵ_I, the efficacy of antibiotics when first administered in stage 1 of illness at reducing the severity of stage 2 of illness and preventing death (i.e., 1 minus the case fatality rate). The default recommended value for ϵ_I in the new contagious disease model is 0.95, which is equal to the recommended value for the efficacy of antibiotics when administered earlier in the course of infection and results in a case fatality rate of 5%. This case fatality rate value falls on the lower end of the range of 5 to 14% seen for streptomycin, a Food and Drug Administration (FDA)-approved antibiotic for plague, when administered early during the disease.[40] It is assumed that the case fatality rate for individuals who enter stage 1 of illness having already received prophylactic antibiotics (i.e., those for whom the antibiotics were ineffective at preventing disease) is 100%.

Once treatment is modeled to begin in stage 1 of illness, the fraction ϵ_I of individuals in the I_1 cohort who have not already received prophylactic antibiotics transitions to the treatment (T) cohort rather than the I_2 cohort upon completing stage 1 of illness. Individuals remain in the T cohort for a fixed number of time steps, D_{Tr}, which is recommended to be equal to 10 days.[41] During this time, their symptoms remain at severity level 2 (moderate) rather than severity level 4 (very severe), which untreated individuals experience in stage 2 of illness. After spending the fixed number of time steps in the T cohort, individuals transition to the RTD cohort. The fraction $(1 - \epsilon_I)$ of individuals in the I_1 cohort transition to the I_2 cohort and then to the DOW cohort as if untreated.

3. Smallpox Prophylaxis and Treatment

As specified in the AMedP-7.5 TRM, "[b]ecause smallpox is highly contagious, the objective of medical management is to limit the spread of the disease by isolating patients and vaccinating at-risk individuals. No antiviral drug treatment is available for smallpox."[42]

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[40] Thomas V. Inglesby et al., "Plague as a Biological Weapon: Medical and Public Health Management," *Journal of the American Medical Association* 283, no. 17 (2000): 2286, https://jamanetwork.com/journals/jama/fullarticle/192665.

[41] North Atlantic Treaty Organization, *AMedP-7.5*, 5-58 (Table 5-50).

[42] Oxford et al., *Technical Reference Manual to Allied Medical Publication 7.5 (AMedP-7.5)*, 26-12.

As a consequence of the lack of specific treatment, no changes to the new contagious disease model are made to account for treatment of smallpox casualties. Just like for the current AMedP-7.5 smallpox contagious disease model, "[m]edical treatment has no effect on the submodel parameter values."[43]

Responses that do affect the outputs of the model include vaccination and isolation of infectious individuals, the latter of which is discussed in the next subsection. For the subset of the PAR vaccinated against smallpox, vaccination is modeled to occur simultaneously at time step t_{vax}, which is measured relative to the start of the outbreak. Before t_{vax}, individuals are modeled to have no protection against smallpox, and, following t_{vax}, they are modeled as being protected. As with plague, if users do not wish to model medical interventions, they can set t_{vax} to some arbitrarily large value so that individuals are never vaccinated.

The effect of vaccination is twofold. First, vaccination changes the number of individuals who progress to the symptomatic stages of illness, transitioning individuals to the VAX cohort from either the S or E cohorts, analogous to the prophylaxis efficacious (P) cohort used in the current AMedP-7.5 model. The fraction of individuals who were in the S cohort at time step t_{vax} that are protected from infection is the product of the vaccine coverage rate, ψ_{vax}, defined as the fraction of individuals in the S and E cohorts who were vaccinated, and ϵ_{pre}, the efficacy of vaccination when administered pre-exposure. Similarly, of the individuals who were in the E cohort at time step t_{vax}, the fraction protected from developing symptoms of illness is the product of ψ_{vax} times $\epsilon_{post}(t)$, the vaccine efficacy when administered post-exposure, which depends on the number of days post-exposure vaccination occurs. The recommended value for ϵ_{pre} is 0.95, and the time-dependent recommended values for $\epsilon_{post}(t)$ are shown in Eq. 8.[44] Recall that t is specified as the number of time steps, so if the step size was 0.1 days, then individuals vaccinated at time steps 1 through 10 post exposure, for instance, would be protected at a rate of 0.9.

$$\epsilon_{post}(t) = \begin{cases} 0.95 & t = 0 \text{ days} \\ 0.9 & 0 \text{ days} < t \leq 1 \text{ day} \\ 0.8 & 1 \text{ day} < t \leq 4 \text{ days} \\ 0.25 & 4 \text{ days} < t \leq 8 \text{ days} \\ 0.02 & 8 \text{ days} < t \leq 15 \text{ days} \\ 0 & t > 15 \text{ days} \end{cases}. \tag{8}$$

The second effect of vaccination is reducing the case fatality rate for those individuals who still transition to the symptomatic stages of illness. As specified in AMedP-7.5, the case fatality rate for symptomatic individuals who were never vaccinated before symptom

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[43] North Atlantic Treaty Organization, *AMedP-7.5*, 5-70.

[44] North Atlantic Treaty Organization, *AMedP-7.5*, 5-71 (Table 5-78).

onset, θ_0, is estimated to be 0.30. The case fatality rate for individuals who became symptomatic after they were vaccinated while in the S cohort, θ_S, is estimated to be 0.03. Finally, the case fatality rate for individuals who became symptomatic after they were vaccinated while in the E cohort, θ_E, is estimated to be 0.20.[45]

4. Isolation of Infectious Individuals

The medical management of plague and smallpox includes isolating infectious individuals to reduce the spread of disease. As described in Chapter 2, isolation is assumed to be 100% effective and is applied to 100% of individuals who survive to be isolated. Users must specify the fixed number of time steps between individuals seeking medical care and being effectively isolated, D_{Iso}. For both diseases, if the casualty criterion is WIA(1^+) or WIA(2^+), then D_{Iso} is relative to the start of stage 1 of illness, when the first symptoms develop. If the casualty criterion is WIA(3^+), then D_{Iso} is relative to the start of stage 2 of illness, when more severe symptoms develop. If a user does not want to model isolation of infectious individuals, then D_{Iso} can be set to some arbitrarily large value, effectively letting individuals progress through all stages of illness without being isolated.

The new contagious disease model includes two additional cohorts to accommodate the isolation of infectious individuals: the Iso_1 cohort and the Iso_2 cohort. Individuals in either the Iso_1 cohort or the Iso_2 cohort have no contact with individuals in the S cohort, so they are not capable of transmitting disease. If the casualty criterion is WIA(1^+) or WIA(2^+), individuals with a stage 1 of illness duration longer than D_{Iso} transition from the I_1 cohort to the Iso_1 cohort D_{Iso} time steps after seeking medical care. Individuals with a stage 1 of illness duration shorter than D_{Iso} time steps transition to the I_2 cohort before being isolated, so they transition from the I_2 cohort to the Iso_2 cohort D_{Iso} time steps after seeking medical care. If the combined time spent in stage 1 and stage 2 of illness is less than D_{Iso} time steps, then individuals are never isolated. Being isolated does not affect the disease progression of individuals, so the severity level of individuals in the Iso_1 and Iso_2 cohorts are the same as those in the I_1 and I_2 cohorts, respectively. Furthermore, individuals transition out of the Iso_1 and Iso_2 cohorts on the same time steps that they would have transitioned out of the I_1 and I_2 cohorts, respectively.

If the casualty criterion is WIA(3^+), then nobody transitions into or out of the Iso_1 cohort because individuals are not considered casualties—and therefore are assumed to not seek medical care—until stage 2 of illness. Individuals transition from the I_2 cohort to the Iso_2 cohort D_{Iso} time steps after seeking medical care if the duration of stage 2 of illness is longer than D_{Iso} time steps. They are never isolated if the duration of stage 2 of illness is less than D_{Iso} time steps.

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[45] North Atlantic Treaty Organization, *AMedP-7.5*, 5-72 (Table 5-79).

B. New Contagious Disease Model Equations

This section describes the time-dependent equations that define the new contagious disease model plague and smallpox variants. In these equations, time is measured in units of the number of time steps (separated by step size dt) since the beginning of the outbreak, and parameters that represent durations of time (e.g., D_{Iso}) must be specified in units of the number of time steps. For example, if dt is chosen by the user to be 0.1 days, then the time step corresponding to 1 day is $t = 10$. Likewise, if the fixed duration between becoming a casualty and being effectively isolated is defined as 2 days, then $D_{Iso} = 20$.

1. Plague Model Variant Equations

The plague contagious disease model variant is characterized by the movements of individuals into and out of the various cohorts depicted in Figure 2, with the arrows specifying which movements are possible. The first step in using the new contagious disease model is to specify the number of individuals in each cohort at time step zero. To do this, the user must select N, the total fixed size of the population, and ω, the number of individuals initially exposed to a degree that they would become infected in the absence of MCMs. If the population was entirely susceptible at the time of the initial exposure, then all exposed individuals begin in the E cohort, and the remainder of the population is in the S cohort, resulting in the initial conditions specified by Eqs. 9 through 11:

$$p(0) = E(0) = \omega, \tag{9}$$

$$S(0) = N - \omega, \tag{10}$$

$$PEP(0) = I_1(0) = Iso_1(0) = I_2(0) = Iso_2(0) = DOW(0) = T(0) = RTD(0) = 0. \tag{11}$$

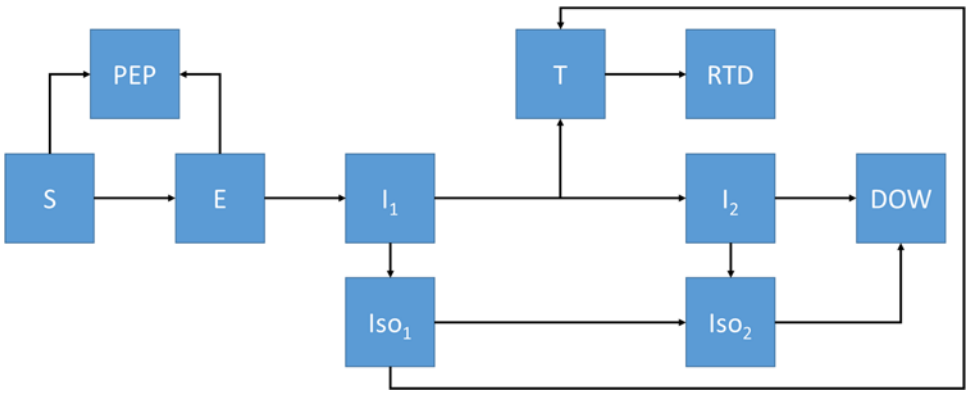

Figure 2. Plague Contagious Disease Model Diagram

If the population was administered prophylactic antibiotics before exposure, then some fraction of the number of initially exposed individuals who would become infected in the absence of MCMs is protected due to the prophylactic antibiotics and begins the

model in the PEP cohort. The resulting set of initial conditions for this case is specified in Eqs. 12 through 15 (in this case, t_{Tr} and t_{PEP} should be set to zero):

$$p(0) = E(0) = (1 - \psi_{PEP}\epsilon_S)\omega, \tag{12}$$

$$PEP(0) = \psi_{PEP}\epsilon_S\omega, \tag{13}$$

$$S(0) = N - E(0) - PEP(0), \tag{14}$$

$$I_1(0) = Iso_1(0) = I_2(0) = Iso_2(0) = DOW(0) = T(0) = RTD(0) = 0. \tag{15}$$

Once the initial conditions are set, then the numbers of individuals in each cohort at each subsequent time step are calculated sequentially beginning with the first time step. The number of individuals in a cohort at a given time step is equal to the number of individuals in that cohort at the previous time step plus the net change in the cohort size since that previous time step, as expressed in Eqs. 16 through 25:

$$S(t) = S(t-1) + \Delta S(t), \tag{16}$$

$$PEP(t) = PEP(t-1) + \Delta PEP(t), \tag{17}$$

$$E(t) = E(t-1) + \Delta E(t), \tag{18}$$

$$I_1(t) = I_1(t-1) + \Delta I_1(t), \tag{19}$$

$$Iso_1(t) = Iso_1(t-1) + \Delta Iso_1(t), \tag{20}$$

$$I_2(t) = I_2(t-1) + \Delta I_2(t), \tag{21}$$

$$Iso_2(t) = Iso_2(t-1) + \Delta Iso_2(t), \tag{22}$$

$$DOW(t) = DOW(t-1) + \Delta DOW(t), \tag{23}$$

$$T(t) = T(t-1) + \Delta T(t), \tag{24}$$

$$RTD(t) = RTD(t-1) + \Delta RTD(t). \tag{25}$$

For each cohort, the net change in the number of individuals at each time step is the sum of all individuals transitioning into that cohort minus the sum of all individuals transitioning out of that cohort, as shown in Eqs. 26 through 35:

$$\Delta S(t) = -S \to E(t) - S \to PEP(t), \tag{26}$$

$$\Delta PEP(t) = S \to PEP(t) + E \to PEP(t), \tag{27}$$

$$\Delta E(t) = S \to E(t) - E \to I_1(t) - E \to PEP(t), \tag{28}$$

$$\Delta I_1(t) = E \to I_1(t) - I_1 \to I_2(t) - I_1 \to Iso_1(t) - I_1 \to T(t), \quad (29)$$

$$\Delta Iso_1(t) = I_1 \to Iso_1(t) - Iso_1 \to Iso_2(t) - Iso_1 \to T(t), \quad (30)$$

$$\Delta I_2(t) = I_1 \to I_2(t) - I_2 \to DOW(t) - I_2 \to Iso_2(t), \quad (31)$$

$$\Delta Iso_2(t) = I_2 \to Iso_2(t) + Iso_1 \to Iso_2(t) - Iso_2 \to DOW(t), \quad (32)$$

$$\Delta DOW(t) = I_2 \to DOW(t) + Iso_2 \to DOW(t), \quad (33)$$

$$\Delta T(t) = I_1 \to T(t) + Iso_1 \to T(t) - T \to RTD(t), \quad (34)$$

$$\Delta RTD(t) = T \to RTD(t). \quad (35)$$

Thirteen possible movements can occur in the plague model, as indicated by the 13 arrows in Figure 2, each of which is represented as a term in Eqs. 26 through 35. For example, the rate of movement of individuals from the S cohort to the E cohort, $S \to E(t)$, appears as a term in the equations for $\Delta S(t)$ and $\Delta E(t)$, Eq. 26 and Eq. 28, respectively. The remainder of this section contains the derivations for each of the 13 unique movement rates.

a. Plague movement rates

1) $\boldsymbol{S \to E(t)}$

The movement of individuals from the S cohort to the E cohort is equal to the number of new infections per time step, which was defined as $p(t)$ in Chapter 2 and is shown in Eq. 36:

$$S \to E(t) = p(t) = \frac{(R_0/D_{I_2})S(t-1)I_2(t-1)}{N}. \quad (36)$$

Recall that only individuals in stage 2 of plague are infectious. Therefore, the number of new infections per time step—and thus the rate at which individuals in the S cohort transition to the E cohort—depends on the number of individuals in the I_2 cohort but not the I_1 cohort. Due to the discrete nature of the model calculations, new infections are calculated based on the number of individuals in the S and I_2 cohorts on the previous time step.

2) $\boldsymbol{S \to PEP(t)}$

Eq. 37 defines the number of individuals transitioning from the S cohort to the PEP cohort:

$$S \to PEP(t) = \begin{cases} 0 & t \neq t_{PEP} \\ \psi_{PEP}\epsilon_S[S(t-1) - p(t)] & t = t_{PEP} \end{cases}. \quad (37)$$

Note that the rate of protection conferred by prophylaxis for those individuals in the S cohort at t_{PEP} is the product of the PEP coverage rate, ψ_{PEP}, and the efficacy of prophylaxis when administered to individuals in the S cohort, ϵ_S.

3) $E \rightarrow PEP(t)$

Eq. 38 defines the number of individuals who transition from the E cohort to the PEP cohort:

$$E \rightarrow PEP(t) = \begin{cases} 0 & t \neq t_{PEP} \\ \psi_{PEP}\epsilon_E[E(t-1) + p(t) - \sum_{u=0}^{t} p(u)F_1(t-u)] & t = t_{PEP} \end{cases}. \quad (38)$$

Note that the rate of protection conferred by prophylaxis for those individuals in the E cohort at t_{PEP} is the product of the PEP coverage rate, ψ_{PEP}, and the efficacy of prophylaxis when administered to individuals in the S cohort, ϵ_E. The function $F_1(t)$ in Eq. 38 represents the probability mass function of incubation period durations, as it did in the examples in Chapter 2.

4) $E \rightarrow I_1(t)$

Eq. 39 defines the number of individuals who transition from the E cohort to the I_1 cohort:

$$E \rightarrow I_1(t) = \begin{cases} \sum_{u=0}^{t} p(u)F_1(t-u) & t \leq t_{PEP} \\ (1-\psi_{PEP}\epsilon_E)\sum_{u=0}^{t_{PEP}} p(u)F_1(t-u) + \sum_{u=t_{PEP}+1}^{t} p(u)F_1(t-u) & t > t_{PEP} \end{cases}. \quad (39)$$

For time steps up to and including t_{PEP}, the rate of individuals transitioning from the E cohort to the I_1 cohort is defined exactly as in Eq. 7. For time steps after t_{PEP}, the expression is split up to separately account for those who were infected before t_{PEP} (and were therefore in the E cohort at t_{PEP}) and those who were infected after t_{PEP} (and were therefore in the S cohort at t_{PEP}). The term representing those transitioning to the I_1 cohort who were infected before t_{PEP} includes only the fraction of individuals who were not already removed from the E cohort to the PEP cohort $(1-\psi_{PEP}\epsilon_E)$.

5) $I_1 \rightarrow Iso_1(t)$

Eq. 40 defines the number of individuals who transition from the I_1 cohort to the Iso_1 cohort:

$$I_1 \rightarrow Iso_1(t) = \begin{cases} \begin{cases} E \rightarrow I_1(t - D_{Iso}) & D_{Iso} \leq D_{I_1} \\ 0 & D_{Iso} > D_{I_1} \end{cases} & \text{WIA}(1^+) \text{ or WIA}(2^+) \\ 0 & \text{WIA}(3^+) \end{cases}. \quad (40)$$

This movement rate depends on two user-specified factors: the casualty criterion for determining whether an individual is WIA and the number of time steps until individuals are effectively isolated after seeking medical care, D_{Iso}. If the casualty criterion is chosen as WIA(1^+) or WIA(2^+), then individuals are assumed to seek medical care at the beginning of stage 1 of illness, and they are modeled as isolated while in stage 1 of illness only if D_{Iso} does not exceed the fixed duration of stage 1 of illness, D_{I_1}. Individuals transitioning from the I_1 cohort to the Iso_1 cohort would do so a fixed number of time steps, D_{Iso}, after entering the I_1 cohort, so the expression for $I_1 \rightarrow Iso_1(t)$ is written in terms of $E \rightarrow I_1(t)$. If D_{Iso} exceeds D_{I_1}, then no individuals transition from the I_1 cohort to the Iso_1 cohort, because they instead transition to either the I_2 cohort or the T cohort. If the casualty criterion is chosen as WIA(3^+), then individuals are assumed to seek care only when they enter stage 2 of illness, so no individuals transition from stage 1 of illness directly to isolation.

6) $I_1 \rightarrow T(t)$

Eq. 41 defines the number of individuals who transition from the I_1 cohort to the T cohort:

See page 33. (41)

For a casualty criterion of WIA(1^+) or WIA(2^+), the number of individuals transitioning from the I_1 cohort to the T cohort is zero when $D_{Iso} \leq D_{I_1}$ because even if individuals receive antibiotics while in stage 1, they are modeled to finish their time in stage 1 of illness before transitioning to the T cohort, by which time they are already isolated. When $D_{Iso} > D_{I_1}$, $I_1 \rightarrow T(t)$ is also zero before t_{Tr} because until that time step, by definition, antibiotics are not used to treat individuals. For time steps between t_{Tr} and t_{PEP}, no individuals entering stage 1 of illness are administered prophylactic antibiotics, so the fraction of individuals for whom antibiotic treatment is efficacious (ϵ_I) transitions to the T cohort D_{I_1} time steps after entering the I_1 cohort.

For time steps greater than t_{PEP}, the individuals in the I_1 cohort either were not administered prophylactic antibiotics or else were unreceptive to antibiotics administration while in either the S cohort or the E cohort. Those individuals in the latter group are assumed to be unreceptive to treatment with the same antibiotics that they were given as prophylaxis and therefore transition to the I_2 cohort rather than the T cohort. Therefore, the only individuals for whom treatment could be effective are those who were not previously administered prophylactic antibiotics. However, since treatment is not 100% effective, only a fraction (ϵ_I) of these individuals transitions from the I_1 cohort to the T cohort. Since the individuals who transition from the I_1 cohort to the T cohort were either in the S cohort or the E cohort at t_{PEP}, they are tracked separately in Eq. 41. The fraction of individuals in the E cohort at time step t_{PEP} who were not administered prophylactic antibiotics is $\left(\frac{1-\psi_{PEP}}{1-\psi_{PEP}\epsilon_E}\right)$, and the fraction of individuals in the S cohort at time step t_{PEP} who were not

administered prophylactic antibiotics is $\left(\frac{1-\psi_{PEP}}{1-\psi_{PEP}\epsilon_S}\right)$. Eq. 41 reflects the final, reduced expression when these coefficients are applied to the corresponding terms in the $E \rightarrow I_1(t)$ expression for $t > t_{PEP}$. If the casualty criterion is chosen as WIA(3^+), then individuals are assumed to seek care only when they enter stage 2 of illness, so no individuals transition from stage 1 of illness to the T cohort.

7) $Iso_1 \rightarrow T(t)$

Eq. 42 defines the number of individuals who transition from the Iso_1 cohort to the T cohort:

See page 33. (42)

The expression for this term, is similar to the $I_1 \rightarrow T(t)$ term described in Eq. 41. The only difference is that those individuals who transition from stage 1 of illness to the T cohort do so after having been isolated. As previously, if the casualty criterion is WIA(3^+), then individuals never enter the Iso_1 cohort, so the number of individuals transitioning from the Iso_1 cohort to the T cohort is likewise zero.

8) $Iso_1 \rightarrow Iso_2(t)$

Eq. 43 defines the number of individuals who transition from the Iso_1 cohort to the Iso_2 cohort:

See page 33. (43)

For a casualty criterion of WIA(1^+) or WIA(2^+), if the user-specified number of time steps to be effectively isolated, D_{Iso}, is longer than the fixed duration of stage 1 of illness, D_{I_1}, then individuals transition to stage 2 of illness before being isolated. Therefore, nobody enters the Iso_1 cohort, and nobody subsequently transitions from there to the Iso_2 cohort. If D_{Iso} is less than D_{I_1}, however, then individuals are isolated in stage 1 of illness and transition from the Iso_1 cohort to the Iso_2 cohort D_{I_1} time steps after having entered stage 1 of illness. Everyone leaving the Iso_1 cohort transitions either to the T cohort or the Iso_2 cohort; therefore, for every condition, Eqs. 42 and 43 sum to the total number of individuals leaving the Iso_1 cohort. Before t_{Tr}, all individuals in the Iso_1 cohort transition to the Iso_2 cohort. After t_{Tr}, the fraction of individuals for whom antibiotic treatment is ineffective $(1 - \epsilon_I)$ and all individuals who were not protected by prophylactic antibiotics transition from the Iso_1 cohort to the Iso_2 cohort rather than to the T cohort. Again, for a casualty criterion of WIA(3^+), individuals never enter the Iso_1 cohort, so the number of individuals transitioning from the Iso_1 cohort to the Iso_2 cohort is zero.

$$I_1 \to T(t) = \begin{cases} \begin{cases} 0 & D_{Iso} \le D_{I_1} \\ \begin{cases} 0 & t \le t_{Tr} \\ \epsilon_I E \to I_1\left(t - D_{I_1}\right) & t_{Tr} < t \le t_{PEP} \\ \begin{pmatrix} \epsilon_I (1-\psi_{PEP}) \sum_{u=0}^{t_{PEP}-D_{I_1}} p(u) F_1(t-u) + \\ \epsilon_I \left(\frac{1-\psi_{PEP}}{1-\psi_{PEP}\epsilon_S}\right) \sum_{u=t_{PEP}+1}^{t-D_{I_1}} p(u) F_1(t-u) \end{pmatrix} & t_{PEP} < t \end{cases} & D_{Iso} > D_{I_1} \end{cases} & \text{WIA}(1^+) \text{ or WIA}(2^+) \\ 0 & \text{WIA}(3^+) \end{cases} \tag{41}$$

$$Iso_1 \to T(t) = \begin{cases} \begin{cases} \begin{cases} 0 & t \le t_{Tr} \\ \epsilon_I E \to I_1\left(t - D_{I_1}\right) & t_{Tr} < t \le t_{PEP} \\ \begin{pmatrix} \epsilon_I (1-\psi_{PEP}) \sum_{u=0}^{t_{PEP}-D_{I_1}} p(u) F_1(t-u) + \\ \epsilon_I \left(\frac{1-\psi_{PEP}}{1-\psi_{PEP}\epsilon_S}\right) \sum_{u=t_{PEP}+1}^{t-D_{I_1}} p(u) F_1(t-u) \end{pmatrix} & t_{PEP} < t \end{cases} & D_{Iso} \le D_{I_1} \\ 0 & D_{Iso} > D_{I_1} \end{cases} & \text{WIA}(1^+) \text{ or WIA}(2^+) \\ 0 & \text{WIA}(3^+) \end{cases} \tag{42}$$

$$Iso_1 \to Iso_2(t) = \begin{cases} \begin{cases} \begin{cases} E \to I_1(t - D_{I_1}) & t \le t_{Tr} \\ (1-\epsilon_I) E \to I_1(t - D_{I_1}) & t_{Tr} < t \le t_{PEP} \\ \begin{pmatrix} \left((1-\epsilon_I)\left(\frac{1-\psi_{PEP}}{1-\psi_{PEP}\epsilon_E}\right) + \left(\frac{\psi_{PEP}(1-\epsilon_E)}{1-\psi_{PEP}\epsilon_E}\right)\right)(1-\psi_{PEP}\epsilon_E) \sum_{u=0}^{t_{PEP}-D_{I_1}} p(u) F_1(t-u) + \\ \left((1-\epsilon_I)\left(\frac{1-\psi_{PEP}}{1-\psi_{PEP}\epsilon_S}\right) + \left(\frac{\psi_{PEP}(1-\epsilon_S)}{1-\psi_{PEP}\epsilon_S}\right)\right) \sum_{u=t_{PEP}+1}^{t-D_{I_1}} p(u) F_1(t-u) \end{pmatrix} & t_{PEP} < t \end{cases} & D_{Iso} \le D_{I_1} \\ 0 & D_{Iso} > D_{I_1} \end{cases} & \begin{matrix} \text{WIA}(1^+) \\ \text{or} \\ \text{WIA}(2^+) \end{matrix} \\ 0 & \text{WIA}(3^+) \end{cases} \tag{43}$$

9) $I_1 \rightarrow I_2(t)$

Eq. 44 defines the number of individuals who transition from the I_1 cohort to the I_2 cohort:

See page 36. (44)

Whereas Eq. 43 represents the number of individuals who progress from stage 1 to stage 2 of illness after being effectively isolated ($D_{Iso} \leq D_{I_1}$ if the casualty criterion is WIA(1^+) or WIA(2^+)), Eq. 44 represents the number of individuals who progress from stage 1 to stage 2 of illness before being effectively isolated ($D_{Iso} > D_{I_1}$ or casualty criterion of WIA(3^+)). The two equations are therefore similar. For a casualty criterion of WIA(1^+) or WIA(2^+), the expression is identical to Eq. 43 except that the movement terms appear for the case when D_{Iso} is greater than D_{I_1}, and the no movement term corresponds to the case when D_{Iso} is less than or equal to D_{I_1}. For a casualty criterion of WIA(3^+), all individuals entering the I_1 cohort transition to the I_2 cohort after a fixed number of time steps, D_{I_1}, in stage 1 of illness.

10) $I_2 \rightarrow Iso_2(t)$

Eq. 45 defines the number of individuals who transition from the I_2 cohort to the Iso_2 cohort:

See page 36. (45)

This movement rate also depends on the user-specified WIA casualty criterion. For a criterion of WIA(1^+) or WIA(2^+), the number of individuals isolated while in stage 2 of illness is zero if $D_{Iso} \leq D_{I_1}$ since all individuals would be isolated in stage 1 of illness, and nobody would enter the I_2 cohort. If $D_{Iso} > D_{I_1}$, then all individuals transition from the I_1 cohort to the I_2 cohort before being isolated and the number that then transition to the Iso_2 cohort is proportional to the fraction of those individuals who have not yet entered the DOW cohort. The function $CDF_3(D_{Iso} - D_{I_1})$ represents the fraction of individuals who have already completed stage 2 of illness and transitioned to the DOW cohort.[46] For a criterion of WIA(3^+), the expression is nearly identical to that for a criterion of WIA(1^+) or WIA(2^+) when $D_{Iso} > D_{I_1}$. The only difference is that the delay in reaching isolation is relative to entering stage 2 of illness, so the $D_{Iso} - D_{I_1}$ terms are replaced with simply D_{Iso}.

[46] Since the distribution for the duration of stage 1 of illness for plague is a fixed value, D_{I_1}, evaluating the cumulative distribution function of stage 2 of illness durations at a time step $D_{Iso} - D_{I_1}$ is the same as evaluating the cumulative distribution function of the convolved stage 1 and stage 2 illness durations evaluated at D_{Iso}.

11) $\boldsymbol{I_2 \rightarrow DOW(t)}$

Eq. 46 defines the number of individuals who transition from the I_2 cohort to the DOW cohort:

See page 36. (46)

The expression for this term also differs depending on the casualty criterion chosen by the user. As stated previously, for a criterion of WIA(1^+) or WIA(2^+), individuals would not enter the I_2 cohort if $D_{Iso} \leq D_{I_1}$, since all individuals would be isolated in stage 1 of illness, so the number of individuals leaving the I_2 cohort for the DOW cohort is zero. If $D_{Iso} > D_{I_1}$, the individuals who transition from the I_2 cohort to the DOW cohort are those who have a stage 2 of illness duration shorter than $D_{Iso} - D_{I_1}$, the number of time steps spent in stage 2 of illness before being effectively isolated. For a casualty criterion of WIA(3^+), the individuals who transition from the I_2 cohort to the DOW cohort are those who have a stage 2 of illness duration shorter than D_{Iso} since individuals first seek medical care upon entering stage 2 of illness rather than stage 1 of illness (as for the other casualty criterion options.

12) $\boldsymbol{Iso_2 \rightarrow DOW(t)}$

Eq. 47 defines the number of individuals who transition from the Iso_2 cohort to the DOW cohort:

See page 36. (47)

This expression is similar to the expression for $I_2 \rightarrow DOW(t)$ for all but the first case, when $D_{Iso} \leq D_{I_1}$ for a criterion of WIA(1^+) or WIA(2^+). In that case, all individuals who entered the Iso_2 cohort transition to the DOW cohort after finishing their time in stage 2 of illness. If $D_{Iso} > D_{I_1}$, the individuals who transition from the Iso_2 cohort to the DOW cohort are those who have a stage 2 of illness duration greater than $D_{Iso} - D_{I_1}$ time steps and therefore are isolated before they die, so the only change is to the limits of the sum in the expression. Likewise, for a casualty criterion of WIA(3^+), the only change relative to Eq. 46 is to the limits of the sum. This change reflects the fact that this expression represents those individuals who die after spending at least D_{Iso} time steps in stage 2 of illness, so they are isolated before dying.

$$I_1 \to I_2(t) = \begin{cases} \begin{cases} \begin{cases} 0 & t \le t_{Tr} \\ E \to I_1(t - D_{I_1}) & t_{Tr} < t \le t_{PEP} \\ (1-\epsilon_I)E \to I_1(t - D_{I_1}) & t_{PEP} < t \end{cases} & D_{Iso} > D_{I_1} \end{cases} & D_{Iso} \le D_{I_1} \end{cases} \begin{matrix} \text{WIA}(1^+) \\ \text{or} \\ \text{WIA}(2^+) \end{matrix}. \quad (44)$$

$$I_2 \to Iso_2(t) = \begin{cases} \begin{cases} 0 & D_{Iso} \le D_{I_1} \\ (1 - CDF_3(D_{Iso} - D_{I_1}))I_1 \to I_2(t - (D_{Iso} - D_{I_1})) & D_{Iso} > D_{I_1} \end{cases} & \text{WIA}(1^+) \text{ or WIA}(2^+) \\ (1 - CDF_3(D_{Iso}))I_1 \to I_2(t - D_{Iso}) & \text{WIA}(3^+) \end{cases}. \quad (45)$$

$$I_2 \to DOW(t) = \begin{cases} \begin{cases} 0 & D_{Iso} \le D_{I_1} \\ \sum_{u=t-D_{Iso}-D_{I_1}+1}^{t} I_1 \to I_2(u)F_3(t-u) & D_{Iso} > D_{I_1} \end{cases} & \text{WIA}(1^+) \text{ or WIA}(2^+) \\ \sum_{u=t-D_{Iso}+1}^{t} I_1 \to I_2(u)F_3(t-u) & \text{WIA}(3^+) \end{cases}. \quad (46)$$

$$Iso_2 \to DOW(t) = \begin{cases} \begin{cases} \sum_{u=0}^{t} Iso_1 \to Iso_2(u)F_3(t-u) & D_{Iso} \le D_{I_1} \\ \sum_{u=0}^{t-D_{Iso}-D_{I_1}} I_1 \to I_2(u)F_3(t-u) & D_{Iso} > D_{I_1} \end{cases} & \text{WIA}(1^+) \text{ or WIA}(2^+) \\ \sum_{u=0}^{t-D_{Iso}} I_1 \to I_2(u)F_3(t-u) & \text{WIA}(3^+) \end{cases}. \quad (47)$$

13) $\boldsymbol{T \rightarrow RTD(t)}$

Eq. 48 defines the number of individuals who transition from the T cohort to the RTD cohort:

$$T \rightarrow RTD(t) = I_1 \rightarrow T(t - D_{Tr}) + Iso_1 \rightarrow T(t - D_{Tr}). \tag{48}$$

Since the number of time steps spent in treatment if initiated in stage 1 of illness, D_{Tr}, is fixed for plague, the number of individuals returning to duty at time step t is simply the same number that began treatment at time step $t - D_{Tr}$.

b. AMedP-7.5 casualty reporting outputs

In addition to the ability to calculate the number of individuals in each cohort at a given time step, the AMedP-7.5 methodology requires specific outputs for casualty estimation. In particular, a rate table presents "the number of *new* casualties in each category per day. It reports WIA without subdividing by Injury Severity Level."[47] The expressions for calculating the required data for the rate table are shown in Eqs. 49 through 52 (if the step size is less than 1 day, then the new casualties per day are calculated by summing the values for all time steps in each day):

$$\text{New WIA}(t) = \begin{cases} E \rightarrow I_1(t) & \text{WIA}(1^+) \text{ or WIA}(2^+) \\ I_1 \rightarrow I_2(t) & \text{WIA}(3^+) \end{cases}, \tag{49}$$

$$\text{New Conv}(t) = 0, \tag{50}$$

$$\text{New RTD}(t) = T \rightarrow RTD(t), \tag{51}$$

$$\text{New DOW}(t) = I_2 \rightarrow DOW(t) + Iso_2 \rightarrow DOW(t). \tag{52}$$

In addition to the rate table, a personnel status table reports "the number of total casualties in each category on each day, with WIA subdivided by Injury Severity Level."[48] Eqs 53 through 59 specify the expressions for calculating the daily category totals, which are simply the instantaneous number of individuals in one or more cohorts evaluated at each day:

$$\text{Daily WIA}(1)(t) = 0, \tag{53}$$

$$\text{Daily WIA}(2)(t) = \begin{cases} I_1(t) + Iso_1(t) + T(t) & \text{WIA}(1^+) \text{ or WIA}(2^+) \\ 0 & \text{WIA}(3^+) \end{cases}, \tag{54}$$

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[47] North Atlantic Treaty Organization, *AMedP-7.5*, 1-18.

[48] Ibid.

$$\text{Daily WIA}(3)(t) = 0, \tag{55}$$

$$\text{Daily WIA}(4)(t) = I_2(t) + Iso_2(t), \tag{56}$$

$$\text{Daily DOW}(t) = DOW(t), \tag{57}$$

$$\text{Daily Conv}(t) = 0, \tag{58}$$

$$\text{Daily RTD}(t) = RTD(t). \tag{59}$$

2. Smallpox Model Variant Equations

The smallpox contagious disease model variant is characterized by the movements of individuals into and out of the various cohorts depicted in Figure 3.

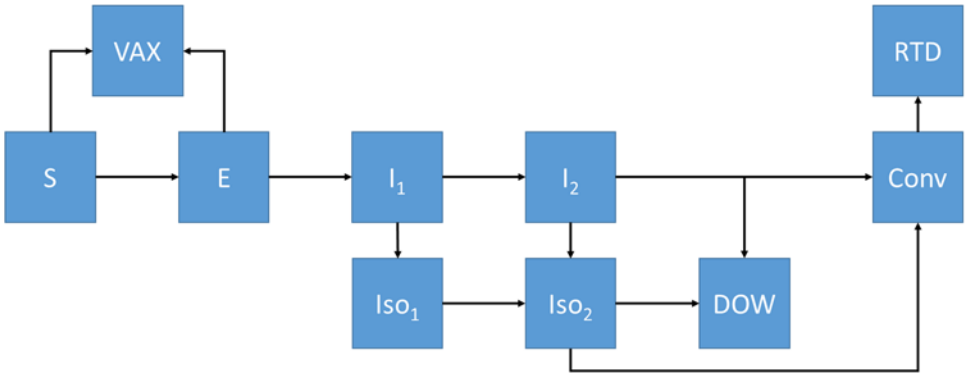

Figure 3. Smallpox Contagious Disease Model Diagram

Like the plague model variant, the first step in using the new smallpox model variant is for the user to specify N, the total fixed size of the population, and ω, the number of individuals initially exposed to a degree that they would become infected in the absence of MCMs, to set the number of individuals in each cohort at time step zero. If the population was entirely susceptible at the time of the initial exposure, then all exposed individuals begin in the E cohort, and the remainder of the population is in the S cohort, resulting in the initial conditions specified by Eqs. 60 through 62:

$$p(0) = E(0) = \omega, \tag{60}$$

$$S(0) = N - \omega, \tag{61}$$

$$VAX(0) = I_1(0) = Iso_1(0) = I_2(0) = Iso_2(0) = DOW(0) = Conv(0) = RTD(0) = 0. \tag{62}$$

If the population was vaccinated before exposure, then some fraction of the number of initially exposed individuals who would become infected in the absence of MCMs is protected due to the vaccine and begins the model in the VAX cohort, as reflected in Eqs. 63 through 66 (note that in this case, t_{vax} should be set to zero):

$$p(0) = E(0) = \left(1 - \psi_{vax}\epsilon_{pre}\right)\omega, \tag{63}$$

$$VAX(0) = \psi_{vax}\epsilon_{pre}\omega, \tag{64}$$

$$S(0) = N - E(0) - VAX(0), \tag{65}$$

$$I_1(0) = Iso_1(0) = I_2(0) = Iso_2(0) = DOW(0) = Conv(0) = RTD(0) = 0. \tag{66}$$

Once the initial conditions have been set, then the numbers of individuals in each cohort at each subsequent time step are calculated sequentially, beginning with the first time step. The number of individuals in a cohort at a given time step is equal to the number of individuals in that cohort at the previous time step plus the net change in the cohort size since that previous time step, as expressed in Eqs. 67 through 76:

$$S(t) = S(t-1) + \Delta S(t), \tag{67}$$

$$VAX(t) = PEP(t-1) + \Delta VAX(t), \tag{68}$$

$$E(t) = E(t-1) + \Delta E(t), \tag{69}$$

$$I_1(t) = I_1(t-1) + \Delta I_1(t), \tag{70}$$

$$Iso_1(t) = Iso_1(t-1) + \Delta Iso_1(t), \tag{71}$$

$$I_2(t) = I_2(t-1) + \Delta I_2(t), \tag{72}$$

$$Iso_2(t) = Iso_2(t-1) + \Delta Iso_2(t), \tag{73}$$

$$DOW(t) = DOW(t-1) + \Delta DOW(t), \tag{74}$$

$$Conv(t) = T(t-1) + \Delta Conv(t), \tag{75}$$

$$RTD(t) = RTD(t-1) + \Delta RTD(t). \tag{76}$$

For each cohort, the net change in the number of individuals at each time step is the sum of all individuals transitioning into that cohort minus the sum of all individuals transitioning out of that cohort, as shown in Eqs 77 through 86:

$$\Delta S(t) = -S \to E(t) - S \to VAX(t), \tag{77}$$

$$\Delta VAX(t) = S \to VAX(t) + E \to VAX(t), \tag{78}$$

$$\Delta E(t) = S \to E(t) - E \to I_1(t) - E \to VAX(t), \tag{79}$$

$$\Delta I_1(t) = E \to I_1(t) - I_1 \to I_2(t) - I_1 \to Iso_1(t), \tag{80}$$

$$\Delta Iso_1(t) = I_1 \to Iso_1(t) - Iso_1 \to Iso_2(t), \tag{81}$$

$$\Delta I_2(t) = I_1 \to I_2(t) - I_2 \to DOW(t) - I_2 \to Conv(t) - I_2 \to Iso_2(t), \quad (82)$$

$$\Delta Iso_2(t) = I_2 \to Iso_2(t) + Iso_1 \to Iso_2(t) - Iso_2 \to DOW(t) - Iso_2 \to Conv(t), \quad (83)$$

$$\Delta DOW(t) = I_2 \to DOW(t) + Iso_2 \to DOW(t), \quad (84)$$

$$\Delta Conv(t) = I_2 \to Conv(t) + Iso_2 \to Conv(t) - Conv \to RTD(t), \quad (85)$$

$$\Delta RTD(t) = Conv \to RTD(t). \quad (86)$$

There are 13 possible movements that can occur in the smallpox model, as indicated by the 13 arrows in Figure 3, each of which is represented as a term in Eqs. 77 through 86. The remainder of this section contains the derivations for each of the 13 unique movement rates.

a. Smallpox movement rates

1) $S \to E(t)$

The movement of individuals from the S cohort to the E cohort is equal to the number of new infections per time step and is shown in Eq. 87:

$$S \to E(t) = p(t) = \frac{(R_0/D_{I_2})S(t-1)I_2(t-1)}{N}. \quad (87)$$

Recall that only individuals in stage 2 of smallpox are infectious. Therefore, the number of new infections per time step—and thus the rate at which individuals in the S cohort transition to the E cohort—depends on the number of individuals in the I_2 cohort but not the I_1 cohort.

2) $S \to VAX(t)$

Eq. 88 defines the number of individuals transitioning from the S cohort to the VAX cohort:

$$S \to VAX(t) = \begin{cases} 0 & t \neq t_{vax} \\ \psi_{vax}\epsilon_{pre}[S(t-1) - p(t)] & t = t_{vax} \end{cases}. \quad (88)$$

Note that the rate of immunity for those individuals in the S cohort at t_{vax} is the product of the vaccine coverage rate, ψ_{vax}, and the efficacy of pre-exposure vaccination, ϵ_{pre}.

3) $E \to VAX(t)$

Eq. 89 defines the number of individuals who transition from the E cohort to the VAX cohort:

$$E \to VAX(t) = \begin{cases} 0 & t \neq t_{vax} \\ \sum_{u=0}^{t} \psi_{vax} \epsilon_{post}(t_{vax} - u) p(u) \big(1 - CDF_1(t-u)\big) & t = t_{vax} \end{cases}. \quad (89)$$

Note that the rate of immunity for those individuals in the E cohort at t_{vax} is the product of the vaccine coverage rate, ψ_{vax}, and the time-dependent efficacy of post-exposure vaccination, $\epsilon_{post}(t)$. The longer the delay between exposure and vaccination, the less efficacious the vaccine and the lower the probability that the individual will transition to the VAX cohort. The function $CDF_1(t)$ in Eq. 89 represents the cumulative distribution function of incubation period durations.

4) $E \to I_1(t)$

Eq. 90 defines the number of individuals who transition from the E cohort to the I_1 cohort:

$$E \to I_1(t) = \begin{cases} \sum_{u=0}^{t} p(u) F_1(t-u) & t \leq t_{vax} \\ \sum_{u=0}^{t_{vax}} \left[\left(1 - \psi_{vax} \epsilon_{post}(t_{vax} - u)\right) p(u) F_1(t-u) + \right] & t > t_{vax} \\ \sum_{u=t_{vax}+1}^{t} p(u) F_1(t-u) \end{cases}. \quad (90)$$

(1)

For time steps up to and including t_{vax}, the rate of individuals transitioning from the E cohort to the I_1 cohort is defined exactly as in Eq. 7, where the function $F_1(t)$ represents the probability mass function of incubation period durations. For time steps after t_{vax}, the expression looks much like the expression for $E \to VAX(t)$ when $t = t_{vax}$. One difference is that the rate of immunity ($\psi_{vax} \epsilon_{post}(t)$) has been replaced by 1 minus that term since those individuals who transition to the I_1 cohort are those who were not protected by vaccination. The second difference is that rather than all individuals successfully vaccinated transitioning instantaneously to the VAX cohort at time step t_{vax} (calculated using $1 - CDF_1(t)$), individuals not successfully vaccinated transition to the I_1 cohort after completing their time in the incubation period.

5) $I_1 \to Iso_1(t)$

Eq. 91 defines the number of individuals who transition from the I_1 cohort to the Iso_1 cohort:

$$I_1 \to Iso_1(t) = \begin{cases} \big(1 - CDF_2(D_{Iso})\big) E \to I_1(t - D_{Iso}) & \text{WIA}(1^+) \text{ or WIA}(2^+) \\ 0 & \text{WIA}(3^+) \end{cases}. \quad (91)$$

This movement rate depends on the user-specified casualty criterion. For smallpox, if the casualty criterion is WIA(1^+) or WIA(2^+), then individuals are assumed to seek medical care at the beginning of stage 1 of illness. The number of individuals isolated in stage 1 of

illness is proportional to the fraction of symptomatic individuals who have not already transitioned to stage 2 of illness before isolation. That fraction is calculated using $CDF_2(D_{Iso})$, the cumulative distribution function of stage 1 of illness durations evaluated at D_{Iso}, the number of time steps equal to the isolation delay. 1 minus this term is the fraction of symptomatic individuals who have durations of stage 1 of illness that exceed D_{Iso} and would therefore be isolated while in stage 1. Individuals transitioning from the I_1 cohort to the Iso_1 cohort would do so D_{Iso} time steps after entering the I_1 cohort, so the expression for $I_1 \rightarrow Iso_1(t)$ is written in terms of $E \rightarrow I_1(t)$. If the casualty criterion is chosen as WIA(3^+), then individuals are assumed to seek care only when they enter stage 2 of illness, so no individuals transition from stage 1 of illness directly to isolation.

6) $Iso_1 \rightarrow Iso_2(t)$

Eq. 92 defines the number of individuals who transition from the Iso_1 cohort to the Iso_2 cohort:

$$Iso_1 \rightarrow Iso_2(t) = \begin{cases} \sum_{u=0}^{t-D_{Iso}} E \rightarrow I_1(u)F_2(t-u) & \text{WIA}(1^+) \text{ or WIA}(2^+) \\ 0 & \text{WIA}(3^+) \end{cases}. \quad (92)$$

For a casualty criterion of WIA(1^+) or WIA(2^+), the individuals who transitioned from the I_1 cohort to the Iso_1 cohort transition into the Iso_2 cohort when they complete stage 1 of illness. The function $F_2(t)$ in Eq. 92 represents the probability mass function of stage 1 of illness durations (as it did in the plague model). As stated in the discussion of Eq. 91, if the casualty criterion is WIA(3^+), then individuals never enter the Iso_1 cohort, so the transition from the Iso_1 cohort to the Iso_2 cohort is likewise zero.

7) $I_1 \rightarrow I_2(t)$

Eq. 93 defines the number of individuals who transition from the I_1 cohort to the I_2 cohort:

$$I_1 \rightarrow I_2(t) = \begin{cases} \sum_{u=t-D_{Iso}+1}^{\mathrm{t}} E \rightarrow I_1(u)F_2(t-u) & \text{WIA}(1^+) \text{ or WIA}(2^+) \\ \sum_{u=0}^{\mathrm{t}} E \rightarrow I_1(u)F_2(\mathrm{t}-u) & \text{WIA}(3^+) \end{cases}. \quad (93)$$

Note that for a casualty criterion of WIA(1^+) or WIA(2^+), this expression is identical to Eq. 92 except for the limits in the sum. This expression represents all individuals who were not isolated in stage 1 of illness because they transition to stage 2 of illness before being isolated (i.e., their duration of stage 1 of illness is less than D_{Iso}). For a casualty criterion of WIA(3^+), all individuals entering the I_1 cohort transition to the I_2 cohort, and the timing is determined by convolving the number of individuals entering stage 1 of illness, $E \rightarrow I_1(t)$, with the distribution of stage 1 of illness, $F_2(t)$.

8) $I_2 \rightarrow Iso_2(t)$

Eq. 94 defines the number of individuals who transition from the I_2 cohort to the Iso_2 cohort:

$$I_2 \rightarrow Iso_2(t) = \begin{cases} \big(CDF_2(D_{Iso}) - CDF_2 * CDF_3(D_{Iso})\big)E \rightarrow I_1(t - D_{Iso}) & \text{WIA}(1^+) \text{ or } \text{WIA}(2^+). \\ \big(1 - CDF_3(D_{Iso})\big)I_1 \rightarrow I_2(t - D_{Iso}) & \text{WIA}(3^+) \end{cases} \quad (94)$$

For a criterion of WIA(1^+) or WIA(2^+), the number of individuals isolated while in stage 2 of illness is proportional to the fraction of symptomatic individuals who have already transitioned to stage 2 of illness before they could be isolated but have not yet entered the DOW or $Conv$ cohorts. The function $CDF_2 * CDF_3(D_{Iso})$ is the cumulative distribution function of the convolved stage 1 and stage 2 illness durations evaluated at D_{Iso}, the number of time steps equal to the delay in being effectively isolated after seeking medical care. This term represents the fraction of individuals who have already completed stage 2 of illness and transitioned to either the DOW cohort or the $Conv$ cohort.

For a criterion of WIA(3^+), the expression is analogous to Eq. 92 for the transition from the I_1 cohort to the Iso_1 cohort for a casualty criterion of WIA(1^+) or WIA(2^+). Instead of $CDF_2(D_{Iso})$, Eq. 94 uses $CDF_3(D_{Iso})$, the cumulative distribution function of stage 2 of illness durations evaluated at D_{Iso}. 1 minus this term is the fraction of symptomatic individuals who have durations of stage 2 of illness that exceed D_{Iso} and would therefore be isolated while in stage 2. The other change relative to Eq. 92 is that individuals are isolated D_{Iso} time steps after having entered stage 2 of illness rather than stage 1 of illness, so the term $I_1 \rightarrow I_2(t - D_{Iso})$ replaces $E \rightarrow I_1(t - D_{Iso})$.

9) $I_2 \rightarrow DOW(t) + I_2 \rightarrow Conv(t)$

Eq. 95 defines the total number of individuals who transition out of the I_2 cohort due to reaching the end of stage 2 of illness:

$$I_2 \rightarrow DOW(t) + I_2 \rightarrow Conv(t) = \begin{cases} \sum_{u=t-D_{Iso}+1}^{t} E \rightarrow I_1(u)F_2 * F_3(\mathrm{t} - u) & \text{WIA}(1^+) \text{ or } \text{WIA}(2^+)\cdot \\ \sum_{u=t-D_{Iso}+1}^{t} I_1 \rightarrow I_2(u)F_3(\mathrm{t} - u) & \text{WIA}(3^+) \end{cases} \quad (95)$$

These individuals transition into either the DOW cohort or the $Conv$ cohort depending on whether or not they become a fatality. To simplify the formulation of the model, these two transition rates are defined together.

10) $\boldsymbol{Iso_2 \rightarrow DOW(t) + Iso_2 \rightarrow Conv(t)}$

Eq. 96 is similar to Eq. 95, but it describes the transition of individuals out of the Iso_2 cohort instead of the I_2 cohort:

$$Iso_2 \rightarrow DOW(t) + Iso_2 \rightarrow Conv(t) = \begin{cases} \sum_{u=0}^{t=t-D_{Iso}} E \rightarrow I_1(u)F_2 * F_3(\mathrm{t}-u) & \mathrm{WIA}(1^+) \text{ or } \mathrm{WIA}(2^+) \cdot \\ \sum_{u=0}^{t-D_{Iso}} I_1 \rightarrow I_2(u)F_3(\mathrm{t}-u) & \mathrm{WIA}(3^+) \end{cases} \quad (96)$$

The expressions are identical to those in Eq. 95 except for the limits of the sums, as the individuals in the Iso_2 cohort rather than the I_2 cohort are those who were isolated before completing stage 2 of illness.

11) $\boldsymbol{I_2 \rightarrow DOW(t) + Iso_2 \rightarrow DOW(t)}$

Eq. 97 defines the total number of individuals who transition into the DOW cohort upon reaching the end of stage 2 of illness, whether or not they are isolated before their deaths:

See page 45. (97)

Individuals have different case fatality rates associated with the stage of illness in which they were vaccinated (if vaccinated at all). Unvaccinated individuals have a case fatality rate of θ_0. Individuals who were vaccinated while in the S cohort have a case fatality rate of θ_{S}. Lastly, individuals who were vaccinated while in the E cohort have a case fatality rate of θ_{E}. For time steps before t_{vax}, all individuals who completed stage 2 of illness (i.e., transitioned out of either the I_2 cohort or the Iso_2 cohort) would not have received the vaccine and therefore would have the unvaccinated case fatality rate, θ_0. For time steps after t_{vax}, individuals can fall into five groups depending on the cohort they were in at time step t_{vax} and whether or not they were among the vaccinated group: (1) those who were in the S cohort at t_{vax} and were vaccinated, (2) those who were in the S cohort at t_{vax} but were not vaccinated, (3) those who were in the E cohort at t_{vax} and were vaccinated, (4) those who were in the E cohort at t_{vax} but were not vaccinated, and (5) those who were not vaccinated because they were already symptomatic (in either stage 1 or stage 2 of illness).

12) $\boldsymbol{I_2 \rightarrow Conv(t) + Iso_2 \rightarrow Conv(t)}$

Eq. 98 is analogous to Eq. 97, but it describes the individuals who survive the disease:

See page 45. (98)

The case fatality rates that appear in Eq. 97 are replaced with 1 minus the case fatality rates to represent the survivors of the disease entering their convalescence period.

$$I_2 \to DOW(t) + Iso_2 \to DOW(t) = \begin{cases} \theta_0 \sum_{u=0}^{t} p(u)(F_1 * (F_2 * F_3))(t-u) & t \le t_{vax} \\ \theta_S \left(\frac{\psi_{vax}(1-\epsilon_{pre})}{1-\psi_{vax}\epsilon_{pre}}\right) \sum_{u=t_{vax}+1}^{t} p(u)(F_1 * (F_2 * F_3))(t-u) + & \\ \theta_0 \left(\frac{1-\psi_{vax}}{1-\psi_{vax}\epsilon_{pre}}\right) \sum_{u=t_{vax}+1}^{t} p(u)(F_1 * (F_2 * F_3))(t-u) + & \\ \theta_E \sum_{u=0}^{t_{vax}} \left[\left(\frac{\psi_{vax}(1-\epsilon_{post}(t_{vax}-u))}{1-\psi_{vax}\epsilon_{post}(t_{vax}-u)}\right) p(u) \sum_{w=t_{vax}-u+1}^{t-u} F_1(w)(F_2 * F_3)(t-u-w)\right] + & t > t_{vax} \\ \theta_0 \sum_{u=0}^{t_{vax}} \left[\left(\frac{1-\psi_{vax}}{1-\psi_{vax}\epsilon_{post}(t_{vax}-u)}\right) p(u) \sum_{w=t_{vax}-u+1}^{t-u} F_1(w)(F_2 * F_3)(t-u-w)\right] + & \\ \theta_0 \sum_{u=0}^{t_{vax}} \left[p(u) \sum_{w=0}^{t_{vax}-u} F_1(w)(F_2 * F_3)(t-u-w)\right] & \end{cases} . \quad (97)$$

$$I_2 \to Conv(t) + Iso_2 \to Conv(t) = \begin{cases} (1-\theta_0) \sum_{u=0}^{t} p(u)(F_1 * (F_2 * F_3))(t-u) & t \le t_{vax} \\ (1-\theta_S) \left(\frac{\psi_{vax}(1-\epsilon_{pre})}{1-\psi_{vax}\epsilon_{pre}}\right) \sum_{u=t_{vax}+1}^{t} p(u)(F_1 * (F_2 * F_3))(t-u) + & \\ (1-\theta_0) \left(\frac{1-\psi_{vax}}{1-\psi_{vax}\epsilon_{pre}}\right) \sum_{u=t_{vax}+1}^{t} p(u)(F_1 * (F_2 * F_3))(t-u) + & \\ (1-\theta_E) \sum_{u=0}^{t_{vax}} \left[\left(\frac{\psi_{vax}(1-\epsilon_{post}(t_{vax}-u))}{1-\psi_{vax}\epsilon_{post}(t_{vax}-u)}\right) p(u) \sum_{w=t_{vax}-u+1}^{t-u} F_1(w)(F_2 * F_3)(t-u-w)\right] + & t > t_{vax} \\ (1-\theta_0) \sum_{u=0}^{t_{vax}} \left[\left(\frac{1-\psi_{vax}}{1-\psi_{vax}\epsilon_{post}(t_{vax}-u)}\right) p(u) \sum_{w=t_{vax}-u+1}^{t-u} F_1(w)(F_2 * F_3)(t-u-w)\right] + & \\ (1-\theta_0) \sum_{u=0}^{t_{vax}} \left[p(u) \sum_{w=0}^{t_{vax}-u} F_1(w)(F_2 * F_3)(t-u-w)\right] & \end{cases} . \quad (98)$$

13) $\boldsymbol{Conv \rightarrow RTD(t)}$

Eq. 99 defines the number of individuals who transition from the $Conv$ cohort to the RTD cohort:

$$Conv \rightarrow RTD(t) = I_2 \rightarrow Conv(t - D_{Conv}) + Iso_2 \rightarrow Conv(t - D_{Conv}). \quad (99)$$

Since the convalescence duration, D_{Conv}, is fixed for smallpox, the number of individuals returning to duty at time step t is simply the same number that entered convalescence at time step $t - D_{Conv}$.

b. AMedP-7.5 casualty reporting outputs

Eqs. 100 through 103 specify the expressions for calculating the required data for the AMedP-7.5 methodology rate table (note that if the step size is less than 1 day, then the new casualties per day are calculated by summing the values for all time steps in each day):

$$\text{New WIA}(t) = \begin{cases} E \rightarrow I_1(t) & \text{WIA}(1^+) \text{ or WIA}(2^+) \\ I_1 \rightarrow I_2(t) & \text{WIA}(3^+) \end{cases}, \quad (100)$$

$$\text{New Conv}(t) = I_2 \rightarrow Conv(t) + Iso_2 \rightarrow Conv(t), \quad (101)$$

$$\text{New RTD}(t) = Conv \rightarrow RTD(t), \quad (102)$$

$$\text{New DOW}(t) = I_2 \rightarrow DOW(t) + Iso_2 \rightarrow DOW(t). \quad (103)$$

Eqs. 104 through 110 specify the expressions for calculating the daily category totals for the AMedP-7.5 methodology personnel status table.

$$\text{Daily WIA}(1)(t) = 0, \quad (104)$$

$$\text{Daily WIA}(2)(t) = \begin{cases} I_1(t) + Iso_1(t) & \text{WIA}(1^+), \text{WIA}(2^+) \\ 0 & \text{WIA}(3^+) \end{cases}, \quad (105)$$

See page 47. (106)

See page 48. (107)

$$\text{Daily DOW}(t) = DOW(t), \quad (108)$$

$$\text{Daily Conv}(t) = Conv(t), \quad (1092)$$

$$\text{Daily RTD}(t) = RTD(t). \quad (110)$$

$$\text{ily WIA(3)}(t) = \begin{cases} \sum_{x=0}^{t}[(1-\theta_0)\sum_{u=0}^{x} p(u)(F_1 * F_2)(x-u)] - \\ \sum_{x=0}^{t}[(1-\theta_0)\sum_{u=0}^{x} p(u)(F_1 * (F_2 * F_3))(x-u)] & t \le t_{vax} \\ \sum_{x=0}^{t}\left[\begin{array}{c} (1-\theta_S)\left(\frac{\psi_{vax}(1-\epsilon_{pre})}{1-\psi_{vax}\epsilon_{pre}}\right)\sum_{u=t_{vax}+1}^{x} p(u)(F_1 * F_2)(x-u) + \\ (1-\theta_0)\left(\frac{1-\psi_{vax}}{1-\psi_{vax}\epsilon_{pre}}\right)\sum_{u=t_{vax}+1}^{x} p(u)(F_1 * F_2)(x-u) + \\ (1-\theta_E)\sum_{u=0}^{t_{vax}}\left[\left(\frac{\psi_{vax}(1-\epsilon_{post}(t_{vax}-u))}{1-\psi_{vax}\epsilon_{post}(t_{vax}-u)}\right)p(u)\sum_{w=t_{vax}-u+1}^{x-u} F_1(w)F_2(x-u-w)\right] + \\ (1-\theta_0)\sum_{u=0}^{t_{vax}}\left[\left(\frac{1-\psi_{vax}}{1-\psi_{vax}\epsilon_{post}(t_{vax}-u)}\right)p(u)\sum_{w=t_{vax}-u+1}^{x-u} F_1(w)F_2(x-u-w)\right] + \\ (1-\theta_0)\sum_{u=0}^{t_{vax}}\left[p(u)\sum_{w=0}^{t_{vax}-u} F_1(w)F_2(x-u-w)\right] \end{array}\right] - & \\ \sum_{x=0}^{t}\left[\begin{array}{c} (1-\theta_S)\left(\frac{\psi_{vax}(1-\epsilon_{pre})}{1-\psi_{vax}\epsilon_{pre}}\right)\sum_{u=t_{vax}+1}^{x} p(u)(F_1 * (F_2 * F_3))(x-u) + \\ (1-\theta_0)\left(\frac{1-\psi_{vax}}{1-\psi_{vax}\epsilon_{pre}}\right)\sum_{u=t_{vax}+1}^{x} p(u)(F_1 * (F_2 * F_3))(x-u) + \\ (1-\theta_E)\sum_{u=0}^{t_{vax}}\left[\left(\frac{\psi_{vax}(1-\epsilon_{post}(t_{vax}-u))}{1-\psi_{vax}\epsilon_{post}(t_{vax}-u)}\right)p(u)\sum_{w=t_{vax}-u+1}^{x-u} F_1(w)(F_2 * F_3)(x-u-w)\right] + \\ (1-\theta_0)\sum_{u=0}^{t_{vax}}\left[\left(\frac{1-\psi_{vax}}{1-\psi_{vax}\epsilon_{post}(t_{vax}-u)}\right)p(u)\sum_{w=t_{vax}-u+1}^{x-u} F_1(w)(F_2 * F_3)(x-u-w)\right] + \\ (1-\theta_0)\sum_{u=0}^{t_{vax}}\left[p(u)\sum_{w=0}^{t_{vax}-u} F_1(w)(F_2 * F_3)(x-u-w)\right] \end{array}\right] & t > t_{vax} \end{cases}. \quad (106)$$

$$\text{Daily WIA}(4)(t) = \begin{cases} \sum_{x=0}^{t}[\theta_0 \sum_{u=0}^{x} p(u)(F_1 * F_2)(x-u)] - \\ \sum_{x=0}^{t}[\theta_0 \sum_{u=0}^{x} p(u)(F_1 * (F_2 * F_3))(x-u)] \end{cases} \quad t \le t_{vax}$$

$$\sum_{x=0}^{t} \begin{bmatrix} \theta_S \left(\frac{\psi_{vax}(1-\epsilon_{pre})}{1-\psi_{vax}\epsilon_{pre}}\right) \sum_{u=t_{vax}+1}^{x} p(u)(F_1 * F_2)(x-u) + \\ \theta_0 \left(\frac{1-\psi_{vax}}{1-\psi_{vax}\epsilon_{pre}}\right) \sum_{u=t_{vax}+1}^{x} p(u)(F_1 * F_2)(x-u) + \\ \theta_E \sum_{u=0}^{t_{vax}} \left[\left(\frac{\psi_{vax}(1-\epsilon_{post}(t_{vax}-u))}{1-\psi_{vax}\epsilon_{post}(t_{vax}-u)}\right) p(u) \sum_{w=t_{vax}-u+1}^{x-u} F_1(w)F_2(x-u-w)\right] + \\ \theta_0 \sum_{u=0}^{t_{vax}} \left[\left(\frac{1-\psi_{vax}}{1-\psi_{vax}\epsilon_{post}(t_{vax}-u)}\right) p(u) \sum_{w=t_{vax}-u+1}^{x-u} F_1(w)F_2(x-u-w)\right] + \\ \theta_0 \sum_{u=0}^{t_{vax}} \left[p(u) \sum_{w=0}^{t_{vax}-u} F_1(w)F_2(x-u-w)\right] \end{bmatrix} -$$

$$\sum_{x=0}^{t} \begin{bmatrix} \theta_S \left(\frac{\psi_{vax}(1-\epsilon_{pre})}{1-\psi_{vax}\epsilon_{pre}}\right) \sum_{u=t_{vax}+1}^{x} p(u)(F_1 * (F_2 * F_3))(x-u) + \\ \theta_0 \left(\frac{1-\psi_{vax}}{1-\psi_{vax}\epsilon_{pre}}\right) \sum_{u=t_{vax}+1}^{x} p(u)(F_1 * (F_2 * F_3))(x-u) + \\ \theta_E \sum_{u=0}^{t_{vax}} \left[\left(\frac{\psi_{vax}(1-\epsilon_{post}(t_{vax}-u))}{1-\psi_{vax}\epsilon_{post}(t_{vax}-u)}\right) p(u) \sum_{w=t_{vax}-u+1}^{x-u} F_1(w)(F_2 * F_3)(x-u-w)\right] + \\ \theta_0 \sum_{u=0}^{t_{vax}} \left[\left(\frac{1-\psi_{vax}}{1-\psi_{vax}\epsilon_{post}(t_{vax}-u)}\right) p(u) \sum_{w=t_{vax}-u+1}^{x-u} F_1(w)(F_2 * F_3)(x-u-w)\right] + \\ \theta_0 \sum_{u=0}^{t_{vax}} \left[p(u) \sum_{w=0}^{t_{vax}-u} F_1(w)(F_2 * F_3)(x-u-w)\right] \end{bmatrix} \quad t > t_{vax}$$

. (107)

For most categories, the daily total is simply the instantaneous number of individuals in one or more cohorts. For the daily number of individuals in the WIA(3) and WIA(4) categories, the calculation is not so simple, because the individuals in stage 2 of illness are split between these categories. Those individuals who survive the disease will experience severe (severity level 3) symptoms in stage 2 of illness, while those individuals who die will experience very severe (severity level 4) symptoms. For these categories, the daily totals are calculated by summing the total number of individuals who have ever entered stage 2 of illness with severe symptoms (for the WIA(3) category) or very severe symptoms (for the WIA(4) category) and subtracting from that value the sum total of individuals who have ever left stage 2 of illness for the $Conv$ cohort (for the WIA(3) category) or the DOW cohort (for the WIA(4) category).

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4. Summary and Next Steps

A. Summary

This document proposes a new contagious disease model to replace the one currently found in AMedP-7.5, which is nearing its triennial review cycle. The new contagious disease model conforms to the constraints of the AMedP-7.5 overarching methodology, generating deterministic estimates of the number of new plague or smallpox casualties in the same manner that it is done for the other CBRN agents in AMedP-7.5. At the same time, the new model overcomes three known limitations of the current contagious disease model: (1) the use of daily transmission rates that are unique to single historical outbreaks of plague or smallpox, which may not be representative of future outbreaks, (2) the inability to model certain administrative control measures that reduce contact between infectious and susceptible individuals, and (3) the assumption that individuals transition between cohorts at a constant rate. Consequently, the new model is less reliant on individual historical outbreaks, incorporates administrative isolation of infectious individuals, and allows movement of individuals through the various stages of illness according to empirically derived distributions.

The new model relies on a number of assumptions about the disease progressions of plague and smallpox, the available prophylaxis and treatment options, and the implementation of the isolation of infectious individuals:

- All individuals enter an asymptomatic incubation period before the development of symptoms of plague or smallpox.
- Despite having developed symptoms, individuals in stage 1 of either plague or smallpox are not infectious. Only individuals in stage 2 of illness are infectious and capable of transmitting the disease.
- Once an infected individual ceases to be symptomatic, that individual is not susceptible to reinfection for the remainder of the modeled outbreak.
- Data from multiple historical outbreaks can be aggregated to generate disease-specific parameters (e.g., the basic reproduction number (R_0), incubation period distribution, duration of illness distribution, and case fatality rate) that are applicable to predicting disease transmission in future outbreaks.
- The duration of time spent in a stage of illness is independent of the duration of time spent in other stages of illness.

- Once antibiotics are available, they are administered as treatment to all plague patients. However, only a user-specified fraction of the asymptomatic population receives the antibiotics as a prophylaxis.
- Antibiotics administered prophylactically protect a fraction of individuals from developing plague symptoms (determined by the efficacy of the antibiotics).
- Individuals who become symptomatic despite prophylactic antibiotics are also unresponsive to antibiotic treatment initiated in stage 1 of plague, so, even with subsequent antibiotic treatment, they follow the same disease progression as untreated individuals and DOW after finishing stage 2 of illness.
- Antibiotics first administered as treatment in stage 1 of plague decrease the case fatality rate, reduce the severity of symptoms in stage 2 of illness, and change the duration of illness. Individuals who do not receive any antibiotics until stage 1 of illness return to duty after finishing stage 2 of illness.
- Antibiotics first administered as treatment in stage 2 of plague have no effect on the model. Individuals who receive no antibiotics until stage 2 of illness follow the same disease progression as untreated individuals and DOW after finishing stage 2 of illness.
- All untreated plague cases DOW after finishing stage 2 of illness.
- Treatment has no effect on smallpox disease progression or outcome. The fraction of smallpox cases that DOW is the same for treated and untreated cases, as is the fraction that RTD after a period of convalescence.
- Before vaccination against smallpox, individuals have no protection against smallpox. Immediately following vaccination, a fraction of individuals vaccinated while in the S cohort is protected from infection, and a fraction of individuals vaccinated while in the E cohort is protected from developing symptoms of illness. Any delay between vaccination and the induction of immunity is built into the time-dependent post-exposure vaccine efficacy, which is a function of time between exposure and vaccination.
- Vaccination reduces the case fatality rate for individuals who become ill with smallpox despite being vaccinated.
- All plague and smallpox cases are isolated a fixed time after seeking medical care unless they die or recover before being isolated.
- Isolation is 100% effective once implemented. Before isolation, infectious individuals may transmit the disease to susceptible individuals. Immediately following isolation, the ability of infectious individuals to transmit the disease is terminated.

Further discussion and justifications are provided in the previous chapters. Many of these assumptions are not unique to the new contagious disease model but are applicable to the wider AMedP-7.5 methodology.

B. Next Steps

The incorporation of the new contagious disease model described in this paper is one of many potential revisions being considered for the next version of AMedP-7.5. At the start of the next AMedP-7.5 triennial review cycle, continued alignment of the data and assumptions associated with the new contagious disease model and the overarching AMedP-7.5 methodology should be confirmed. The U.S. Army OTSG, as the custodian of AMedP-7.5, may then propose to the NATO CBRN Medical Working Group recommended changes to AMedP-7.5, including the substitution of the new contagious disease model for the current AMedP-7.5 model.

The step of validating the new contagious disease model to confirm that the representation of the system and its structural and data assumptions satisfactorily represent the process of contagious disease spread will fall to the SMEs within the CBRN Medical Working Group, who are tasked to formally review the entire AMedP-7.5 methodology. Given the limited number of historical outbreaks that have occurred and been sufficiently recorded, a lack of appropriate data to validate the model may pose a risk. However, a comparison of the new contagious disease model results to the current AMedP-7.5 model results and to the few known cases of historical outbreaks could be done. Caution should be taken, however, not to judge the quality of the two contagious disease models solely on how well they reproduce historical outbreaks, since the current AMedP-7.5 model is designed to do precisely that for a limited set of outbreaks while the new model is intended to be more broadly applicable. The most useful assessment of the two models would be to compare predicted casualties over time to historical outbreaks not used to derive the transmission coefficient values in the current AMedP-7.5 model. The comparison of model outputs to historical outbreaks should be considered in combination with a theoretical evaluation of the merits of the data, assumptions, and structure of the new model.

After the new contagious disease model has been validated, its software implementation must be verified. The AMedP-7.5 methodology (to include a new contagious disease model) is planned to be incorporated into the second part of the Medical Information and Coordination System (MEDICS) currently under development through NATO.[49] Once this validation has been completed, the new contagious disease model written into the MEDICS

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[49] Erick Meinen, "MEDICS: CBRN Casualty Rate Estimation US," (presentation, January 2017); Sean Oxford, "Notes from 7–8 September 2017 CBRN CRE Workshop hosted by NCI Agency in the Hague, Netherlands," memorandum for the record (Alexandria, VA: Institute for Defense Analyses, September 13, 2017).

software should undergo a formal verification process to confirm that it reflects the validated version of the theoretical model described in this document. In support of OTSG, IDA is tasked to provide reach-back support during the NATO software development process and is prepared to help with the validation and verification process.

Appendix A.
Summary of Parameters and Recommended Values

As described in Chapters 2 and 3, a number of parameters are required to fully specify the new contagious disease model for plague and smallpox. Those parameters are defined in Table A-1, along with recommended values for use in the model. Unless specified in a table note, all recommended parameter values are from the AMedP-7.5 technical reference manual (TRM). Parameters that represent points in time (e.g., t_{PEP}) are explicitly stated to be the *time step* at which something happens and must be in units of the number of time steps (not days) since the beginning of the outbreak. Similarly, parameters that represent durations of time (e.g., D_{Iso}) are specified to be in units of the number of time steps. When values are recommended for these parameters, the conversion from days to time steps is made by dividing the value in days by the step size, dt, which is made explicit in Table A-1. Lastly, the probability mass functions for use in the model equations must be derived from the corresponding continuous probability density functions. To convert a continuous probability density function to a discrete probability mass function, the user must evaluate the continuous probability density function at multiples of dt and multiply each value by dt. The result is a probability mass function that is defined for time steps equal to multiples of dt and is undefined at all other values. Because the new contagious disease model is deterministic, the probability mass functions and cumulative distribution functions indicated in Table A-1 are used to deterministically calculate the fractions of the population that transition between cohorts at each time step as specified in the equations in Chapter 3. There are no random draws from these distributions as there would be in a stochastic model.

Table A-1. New Contagious Disease Model Parameters and Recommended Values for Smallpox and Pneumonic Plague

Definition	Variable	Recommended Plague Value	Recommended Smallpox Value
Wounded in action (WIA) casualty criterion	$\mathrm{WIA}(1^+)$, $\mathrm{WIA}(2^+)$, or $\mathrm{WIA}(3^+)$	Scenario-dependent	Scenario-dependent
Step size between time steps at which model calculations are executed	dt	User-specified	User-specified
Total fixed population at risk (PAR)	N	Scenario-dependent	Scenario-dependent

Definition	Variable	Recommended Plague Value	Recommended Smallpox Value
Number of individuals initially exposed to a degree that they would become infected in the absence of medical countermeasures (MCMs)	ω	Scenario-dependent	Scenario-dependent
Basic reproduction number	R_0	1.3[a]	5[b]
Probability mass function of incubation period durations	$F_1(t)$	Derived from log-normal distribution: Mean = 4.3 days Standard deviation = 1.8 days; μ = 1.378; σ = 0.402[c]	Derived from log-normal distribution: Mean = 11.6 days Standard deviation = 1.8 days; μ = 2.439; σ = 0.154[c]
Probability mass function of stage 1 of illness durations	$F_2(t)$	N/A	Derived from log-normal distribution: Mean = 3.0 days Standard deviation = 0.95 days; μ = 1.051; σ = 0.309
Cumulative distribution function of stage 1 of illness durations	$CDF_2(t)$	N/A	Cumulative distribution function of $F_2(t)$
Fixed stage 1 of illness duration (number of time steps)	D_{I_1}	1 day/dt	N/A
Probability mass function of stage 2 of illness durations	$F_3(t)$	Derived from log-normal distribution: Mean = 1.5 days Standard deviation = 1.2 days; μ = 0.158; σ = 0.703	Derived from log-normal distribution: Mean = 14.0 days Standard deviation = 2.24 days; μ = 2.626; σ = 0.159
Cumulative distribution function of stage 2 of illness durations	$CDF_3(t)$	Cumulative distribution function of $F_3(t)$	Cumulative distribution function of $F_3(t)$
Mean infectious period duration (number of time steps)	μ_{I_2}	1.5 days/dt	14.0 days/dt
Fixed treatment duration if initiated in stage 1 of illness (number of time steps)	D_{Tr}	10 days/dt	N/A
Fixed convalescence duration (number of time steps)	D_{Conv}	N/A	5 days/dt
Time step at which prophylactic antibiotics provide protection to susceptible or incubating individuals (relative to start of outbreak)	t_{PEP}	Scenario-dependent	N/A
Time step at which antibiotics are used to treat individuals in stage 1 of illness (relative to start of outbreak)	t_{Tr}	Scenario-dependent	N/A
Fraction of individuals in the S and E cohorts who were administered prophylactic antibiotics	ψ_{PEP}	Scenario-dependent	N/A

Definition	Variable	Recommended Plague Value	Recommended Smallpox Value
Efficacy of prophylactic antibiotics at preventing symptom onset when administered to individuals in the S cohort	ϵ_S	0.95	N/A
Efficacy of prophylactic antibiotics at preventing symptom onset when administered to individuals in the E cohort	ϵ_E	0.95	N/A
Efficacy of antibiotics administered while in stage 1 of illness at reducing the severity of stage 2 of illness and preventing death	ϵ_I	0.95	N/A
Time step at which vaccination provides protection to individuals (relative to start of outbreak)	t_{vax}	N/A	Scenario-dependent
Fraction of individuals in the S and E cohorts who were vaccinated	ψ_{vax}	N/A	Scenario-dependent
Rate of immunity conferred by pre-exposure vaccination	ϵ_{pre}	N/A	0.95
Rate of immunity conferred by post-exposure vaccination (dependent on number of time steps between exposure and vaccination)	$\epsilon_{post}(t)$	N/A	Time-dependent (see Eq. 8)
Case fatality rate for unvaccinated individuals	θ_0	N/A[d]	0.30
Case fatality rate for individuals vaccinated while in the S cohort	θ_S	N/A	0.03
Case fatality rate for individuals vaccinated while in the E cohort	θ_E	N/A	0.20
Fixed duration between becoming a casualty and being effectively isolated (number of time steps)	D_{Iso}	Scenario-dependent	Scenario-dependent

Notes for Table A-1:

[a] J. O. Lloyd-Smith et al., "Superspreading and the Effect of Individual Variation on Disease Emergence," *Nature* 438, no. 7066 (December 2005): 355–359 (see Supplementary Table 1), http://www.nature.com/articles/nature04153#supplementary-information; Raymond Gani and Steve Leach, "Epidemiologic Determinants for Modeling Pneumonic Plague Outbreaks," *Emerging Infectious Diseases* 10, no. 4 (April 2004): 608–614. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3323083/pdf/03-0509.pdf.

[b] This value is the midpoint of the range 4–6 specified by Raymond Gani and Steve Leach, "Transmission Potential of Smallpox in Contemporary Populations," *Nature* 414, no. 6865 (13 December 2001): 748–751, https://www.nature.com/articles/414748a.pdf.

[c] As discussed in Chapter 2, the assumption of a constant transition rate from the E cohort into the I cohort equal to the inverse of the mean incubation period implies an incubation period that follows an exponential distribution rather than the lognormal distribution derived from the historical data. Because of this assumption, the current AMedP-7.5 contagious disease model also includes a minimum incubation period for each disease to avoid reporting casualties earlier than would be expected if the incubation period dwell time followed the specified lognormal distribution. The new model does not require specifying a minimum incubation period value, because the use of convolutions to describe the transition of individuals between cohorts replaces the assumption of a constant transition rate and the associated exponentially distributed incubation period.

[d] Untreated plague is modeled with a case fatality rate of 100%. The model accounts for this case fatality rate, with all paths ending at the DOW cohort without treatment. If treatment is considered, the case fatality rate is modeled as 5%, which is incorporated into the model using the parameter ϵ_I, which is equal to 1 minus the case fatality rate and divides the population in stage 1 of illness into those that go to the T cohort (and later the RTD cohort) and those that go on to stage 2 of illness and later the DOW cohort.

Appendix B.
Illustrations

Figures

Tables

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Appendix C.
References

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Appendix D.
Acronyms

AMedP-7.5	Allied Medical Publication 7.5
CBRN	chemical, biological, radiological, and nuclear
DOW	died of wounds
FDA	Food and Drug Administration
IDA	Institute for Defense Analyses
MCM	medical countermeasures
MEDICS	Medical Information and Coordination System
NATO	North Atlantic Treaty Organization
OTSG	Office of the Surgeon General
PAR	population at risk
PEP	post-exposure prophylaxis
RTD	return to duty
SEIR	susceptible, exposed and infected, infectious, removed
SEIRP	susceptible, exposed and infected, infectious, removed, prophylaxis efficacious
SME	subject matter expert
SIR	susceptible, infectious, removed
STANAG	Standardization Agreement
TRM	technical reference manual
U.S.	United States
VAX	vaccinated
WIA	wounded in action

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NATO Allied Medical Publication 7.5 (AMedP-7.5), *NATO Planning Guide for the Estimation of Chemical, Biological, Radiological and Nuclear (CBRN) Casualties*, includes a contagious disease model for estimating the number of casualties resulting from an attack with a contagious biological agent. The current document describes a new contagious disease model developed by the Institute for Defense Analyses that overcomes certain known limitations of the AMedP-7.5 contagious disease model and could replace the existing model in future versions of AMedP-7.5. In particular, the new model relies on aggregated transmission data from multiple historical outbreaks of disease rather than transmission rates fitted to a single historical outbreak per disease. It includes the capability to model isolation of infectious individuals within a user-specified time after symptom onset. Lastly, the new model overcomes the simplifying assumption that individuals transition between cohorts at a constant rate equal to one divided by the mean time in a cohort. Instead, the new model incorporates convolutions to model the transition of individuals according to time distributions derived from extensive literature reviews.

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