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Assessment of Contagious Disease Surveillance & Outbreak Control Measures

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Executive Summary

Minimizing the operational disruption caused by an outbreak of contagious disease in a deployed military population requires that (1) disease surveillance capabilities rapidly trigger a response, and (2) the triggered response is rapidly implemented and effective. Exactly how rapidly surveillance and response capabilities must function depends on several disease related factors; some factors influence the *time available*[1] to detect and respond to the outbreak, some factors influence the *time it takes*[2] to detect and respond to the outbreak, and a few factors can influence both the *time available* and the *time it takes*. Figure ES-1 depicts the relationship between the *time available* and the *time it takes*.

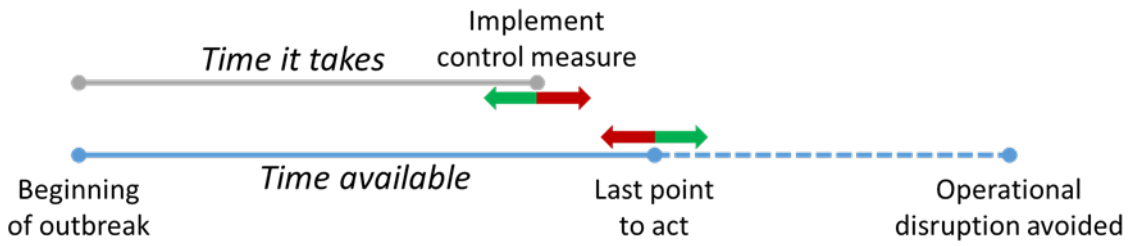

Figure ES-1. Notional Depiction of the *Time Available* and the *Time It Takes* to Detect and Respond to a Contagious Disease Outbreak

The level of operational disruption resulting from an outbreak depends on the difference between the *time available* and the *time it takes*. In general, operational disruption will be reduced if the *time available* is increased or if the *time it takes* is decreased, and vice versa (as indicated by the red and green arrows).[3] Table ES-1 summarizes the disease factors that influence either the *time available* or the *time it takes* to detect and respond to an outbreak.

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1 Defined as the time from the beginning of the outbreak to the last point in time that a given control measure could be implemented and still keep operational disruption below some threshold.

2 Defined as the time from the beginning of the outbreak to the point when a control measure is actually implemented.

3 In the figure, the *time it takes* to detect and respond to an outbreak is arbitrarily shown as shorter than the *time available*—a situation that would reduce operational disruption. The *time it takes* to detect and respond to an outbreak could also be greater than *the time available*—a situation that would increase operational disruption.

Table ES-1. Disease Factors Influencing Either the *Time Available* or the *Time It Takes* to Detect and Respond to an Outbreak

Time Available **to Detect and Respond**	***Time It Takes*** **to Detect and Respond**
Contagiousness of disease	
Duration of disease's latent period	
Number of initial infections	
Efficacy of response	Specificity of disease presentation
	Rarity of disease
	Prevalence of disease in region
	Availability of diagnostic tests

Figure ES-2 organizes the factors based on whether they provide more time, less time, or do not influence either the *time available* or *the time it takes* to detect and respond to an outbreak. Disease factors are color coded based on whether they reduce (green) or increase (red) operational disruption. The orange factors have the potential to either reduce or increase operational disruption, depending on the specifics of the disease outbreak. For a given disease, factors that increase operational disruption can be targeted for future capability development.

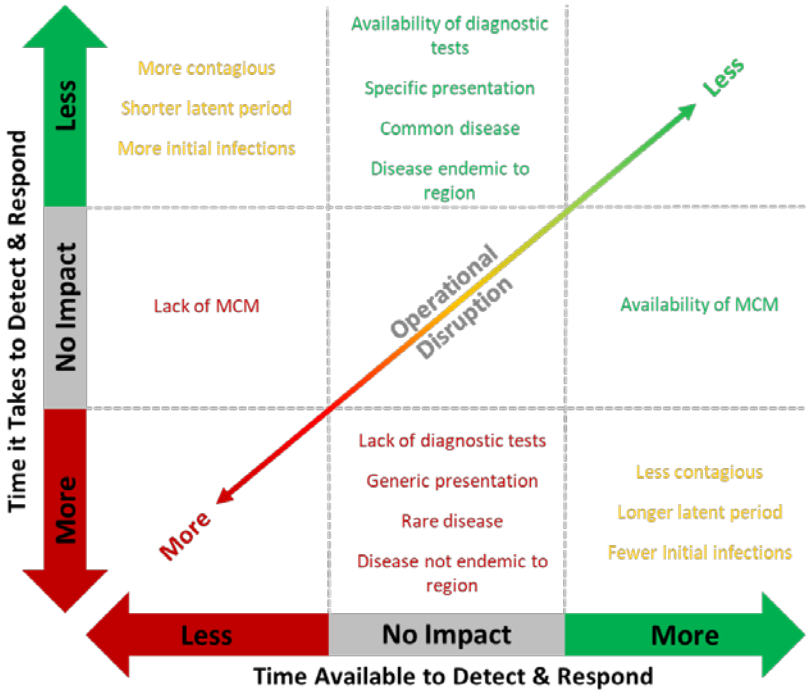

Figure ES-2. Framework to Assess Disease Factors' Influence on Disease Surveillance and Response

The Institute for Defense Analyses (IDA) team used a contagious disease model to quantitatively assess the ability of various disease surveillance triggers and control measure implementation strategies to minimize the percentage of the population at risk (PAR) that become a casualty due to infection with the disease (a surrogate for operational disruption). Lower levels of casualties (0.1% and 1% of the PAR) were used to represent the indirect operational disruption caused by the presence of contagious individuals in the PAR. Higher levels of casualties (5% and 10% of the PAR) were used to represent the direct operational disruption caused by personnel loss. To account for various ways in which an outbreak could begin, the IDA team analyzed outbreaks starting with 1, 10, and 100 initial infections.

Figure ES-3 shows modeling results for pneumonic plague. The gray bars represent a conservative characterization of how pneumonic plague would likely be detected in the PAR. From this baseline, the IDA team varied either the disease surveillance trigger that would initiate the response or the response itself. These variations are shown in the other bars in the figure.

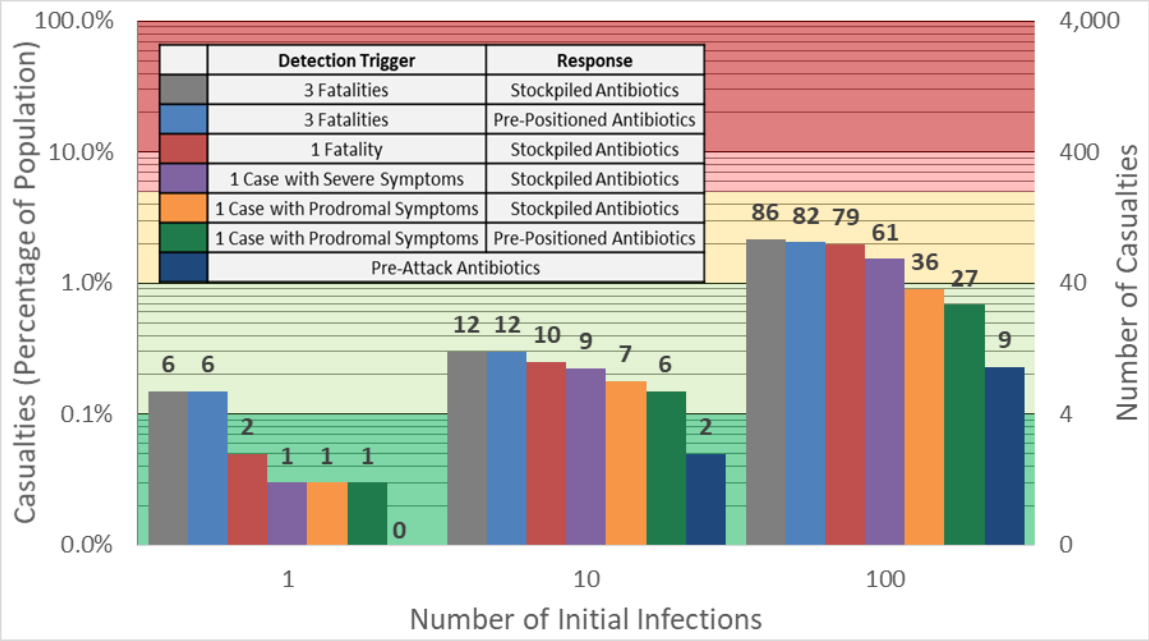

Figure ES-3. Number of Casualties Due To Infection with Pneumonic Plague (90th Percentile) for Various Disease Surveillance Triggers and Delays in Administering Population-Wide Antibiotics

To model an emerging infectious disease (EID), the IDA team used a parametric approach to determine the percentage of the population that would become a casualty for various combinations of the following:

- The minimum number of new cases that must occur in a 1-day time period to trigger the response process (i.e., *Threshold Number of New Cases in a Day to Trigger Response*),
- The efficacy of the control measure that is implemented (i.e., *Control Measure Efficacy*), and
- The number of days it takes to implement the control measure following the trigger to respond (i.e., *Control Measure Implementation Delay (Days)*).

Table ES-2 shows the results for outbreaks of a notional novel EID starting with 10 initial infections. The cells of the table are color coded to show the casualty thresholds that were used to measure the level of operational disruption: <1% (green), 1%–5% (orange), 5%–10% (red), >10% (dark red).

Table ES-2. Percentage of Population Becoming a Casualty (90th Percentile) for Varying Control Measure Efficacies and Delays in Implementation for Outbreaks starting with 10 Initial Infections

Control Measure Efficacy	Control Measure Implementation Delay (Days)	Threshold Number of New Cases in a Day to Trigger Response							
		1	2	3	4	5	8	10	15
95%	1	0.3%	0.4%	0.4%	1.0%	1.7%	3.8%	5.4%	9.5%
	3	0.4%	0.5%	0.5%	1.2%	1.9%	4.3%	5.8%	>10%
	7	0.7%	0.7%	0.8%	1.6%	2.6%	5.2%	7.1%	>10%
75%	1	0.7%	0.8%	0.8%	1.5%	2.4%	5.0%	6.7%	>10%
	3	0.8%	0.9%	1.0%	1.7%	2.7%	5.4%	7.3%	>10%
	7	1.1%	1.2%	1.4%	2.2%	3.5%	6.7%	8.9%	>10%
50%	1	3.6%	3.6%	3.8%	5.5%	7.6%	>10%	>10%	>10%
	3	3.7%	3.7%	4.1%	6.1%	8.2%	>10%	>10%	>10%
	7	4.6%	4.6%	5.1%	7.1%	>10%	>10%	>10%	>10%
25%	1	>10%	>10%	>10%	>10%	>10%	>10%	>10%	>10%
	3	>10%	>10%	>10%	>10%	>10%	>10%	>10%	>10%
	7	>10%	>10%	>10%	>10%	>10%	>10%	>10%	>10%

The analysis demonstrated that, in some cases, commanders have the ability to detect and respond to an outbreak of a known disease (e.g., plague or smallpox) in time to prevent direct operational disruption due to personnel loss, but in other cases, commanders will likely need to initiate high-consequence decisions with potentially incomplete knowledge of the situation to minimize operational disruption from an outbreak of an unknown disease—especially for a novel EID outbreak.

The IDA team made four recommendations:

- **Invest in Technologies that Facilitate Rapid Medical Countermeasure (MCM) Development.** Reducing the time to develop and field an MCM for a recently emerged disease increases the likelihood of having the drug available in the event that a deployed military population comes into contact with the disease. MCMs for diseases that lack one should be considered a high priority. In particular, diseases that may take longer to detect within a population—such as those with non-specific symptoms or those that lack diagnostic tests—should be targeted for MCM development. The availability of an MCM for these types of diseases would increase the time available to detect and respond to an outbreak, alleviating the disruption caused by the difficulties of detection.
- **Develop a Concept of Operations (CONOPS) for and Conduct a Cost-Benefit Analysis on Diagnostic Capabilities at Lower Roles of Medical Care.** Diagnostic testing at lower roles of medical care could facilitate earlier detection of outbreaks of diseases with generic presentations. Additional analyses should be conducted to fully characterize the benefit of fielding a diagnostic capability at lower roles of medical care, as compared to higher roles. The following questions should be considered as part of the assessment:
  - What is the concept of operations for determining who is tested?
  - Will samples taken during the early stages of illness contain a detectable quantity of infection indicators?
  - What are the fiscal, personnel, and operational costs of developing and fielding the capability?
  - What is the benefit of reducing the time it takes to run a diagnostic test by analyzing the sample at the patient's location, as compared to sending the sample to another facility?
- **Train/Educate Leadership on Value of Bidirectional Disease Surveillance Reporting.** The ability to detect atypical disease rates is facilitated by situational awareness of the prevalence of diseases in both the PAR and the surrounding environment. Maintaining up-to-date situational awareness requires timely reporting of information up and down the medical chain of command. IDA researchers observing recent North Atlantic Treaty Organization (NATO) exercises, which incorporated a contagious disease outbreak response, identified numerous challenges in obtaining situational awareness through timely disease surveillance reporting. The IDA team suggests training and leadership education on the value of timely and accurate disease surveillance reporting up and down the medical chain of command. This bidirectional reporting can create a disease surveillance feedback loop.

- **Develop Pre-Deployment Contingency Plans for Sustaining Isolated Units.** Pre-deployment planning for operations in high-risk regions should address contingency strategies for sustaining an isolated unit. Developing these strategies will likely require coordination between logistic and medical personnel. Additional analyses should be conducted to provide planners with analytically backed guidance on how long a unit may need to be isolated and measures that can be taken to minimize the risk of disease transmission when sustaining infected units.

Contents

1. Introduction

A. Background

The Institute for Defense Analyses (IDA) has conducted a variety of analyses investigating the impact of contagious disease outbreaks on military operations. Some of these analyses have focused on the risk posed by a specific disease—such as Ebola virus disease,[1,2] plague,[3] smallpox,[4,5] influenza,[6] or Severe Acute Respiratory Syndrome (SARS)[7]—while others have focused on larger categories of diseases—such as emerging infectious diseases (EID).[8] In general, the analyses have all led to similar conclusions: contagious disease outbreaks, whether the result of adversarial action or natural causes, can generate substantial disruption to military operations.

A contagious disease outbreak can disrupt an operation in multiple ways. First, given a sufficient number of ill individuals, an operation can be disrupted through a loss of personnel. The level of personnel loss required to disrupt a given operation may vary depending on the operation's tolerance for casualties, as well as the distribution of casualties across specific units or personnel types. In addition, the presence of even a few contagious individuals within a population at risk (PAR) may cause operational or strategic disruptions:

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1 John N. Bombardt, Jr., *Contagious Disease Dynamics for Biological Warfare and Bioterrorism Casualty Assessments*, IDA Paper P-3488 (Alexandria, VA: Institute for Defense Analyses, 2000).

2 Deena S. Disraelly et al., *Quick Reaction Analysis Series, No. 1301: Estimated Therapeutic Troop Equivalent Doses for Ebola and Marburg Hemorrhagic Fevers*, IDA Document NS D-4851 (Alexandria, VA: Institute for Defense Analyses, 2013).

3 John N. Bombardt, Jr., *Primary Pneumonic Plague Transmission and BW Casualty Assessments*, IDA Paper P-3657 (Alexandria, VA: Institute for Defense Analyses, 2001).

4 John N. Bombardt, Jr., *Smallpox Transmission and BW Casualty Assessments*, IDA Paper P-3550 (Alexandria, VA: Institute for Defense Analyses, 2000).

5 Deena S. Disraelly et al., *Quick Reaction Analysis Series, No. 1601: Assessment of Operational Risk Related to the Smallpox Vaccine Program (SVP)*, IDA Document NS D-5703 (Alexandria, VA: Institute for Defense Analyses, 2016).

6 John N. Bombardt, Jr. and Heidi E. Brown., *Potential Influenza Effects on Military Populations*, IDA Paper P-3786 (Alexandria, VA: Institute for Defense Analyses, 2003).

7 John N. Bombardt, "Congruent Epidemic Models for Unstructured and Structured Populations: Analytical Reconstruction of a 2003 SARS Outbreak," Mathematical Biosciences 203, no. 2 (2006): 171–203.

8 Julia K. Burr et al., *Emerging Infectious Disease Study*, IDA Paper P-5302 (Alexandria, VA: Institute for Defense Analyses, 2016).

- Operational logistics could become disrupted if movement into or out of the PAR is restricted in an effort to prevent the spread of the disease to other populations within the theater.
- Allied forces may reduce support of the operation to reduce the risk of the outbreak spreading to their forces.
- Host-nation civilians may reduce support to, or even directly oppose the presence of, U.S. forces in the area, due to the fear of becoming infected.

Operational disruption may be mitigated through the timely implementation of outbreak control measures. Further investigation is necessary to determine the feasibility of implementing outbreak control measures in time. This includes evaluating the type, availability, and timeliness of the disease surveillance information that is needed to trigger an outbreak response, and characterizing the consequence (or benefit) of delaying (or advancing) the time at which outbreak control measures are implemented.

B. Purpose and Analytic Approach

This analysis investigates how the timing of disease surveillance and the subsequently triggered control measures contribute to limiting operational disruption. Based on the analysis, the IDA team made capability development recommendations that could limit operational disruption. A two-part analytic approach was used to generate the recommendations. First, the IDA team developed a qualitative framework to assess how various disease-related factors influence the ability of disease surveillance to trigger a response in time to minimize operational disruption. The disease factors include both characteristics of the disease (e.g., contagiousness or duration of latent period) and current capabilities relating to the disease (e.g., availability of medical countermeasures or diagnostic tests).

Second, the IDA team used a contagious disease model to assess the ability of various disease surveillance triggers and control measure implementation strategies to minimize operational disruption.[9] By analyzing these simulations, the IDA team was able to determine the consequences of either delaying or hastening the detection and response processes. Additional details concerning the analytic approach can be found in Chapter 2.

C. Scope

This analysis focused on contagious disease outbreaks contained within a single deployed military PAR of 4,000 individuals (representative of a brigade-sized unit or a base). Therefore, in the context of the analysis, the term *disease surveillance* refers to the

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[9] The contagious disease model was developed by the IDA team specifically for use in this analysis. A synopsis of the model and its major assumptions can be found in Section 2.B.1. A complete technical description of the model can be found in Appendix B.

collection, interpretation, recognition, and dissemination of observations made by the medical personnel within the PAR. These observations could include: symptoms, case counts, clinical diagnoses, or the results of laboratory diagnostic tests. For some diseases, the diagnosis of a single patient may be adequate to trigger the response process, while for other diseases, commanders may only choose to act following the occurrence of a certain number of cases. While other sources of information—such as environmental sampling or intelligence reporting—could also inform disease surveillance, they are not the focus of this analysis. Similarly, the analysis focused on outbreak control measures that reduce disease transmission within the PAR. The IDA team did not directly analyze responses to mitigate the spread of the outbreak to populations outside of the PAR.[10]

The contagious disease outbreaks considered in the analysis were assumed to start with a single exposure event that introduced the disease into the PAR. Unless stated otherwise, the IDA team assumed that everyone in the PAR was unprotected and susceptible to infection at the start of the outbreak. The exposure event could be a result of an intentional dissemination of a weaponized pathogen, potentially infecting a large number of individuals. The exact number of initial infections would depend on the specifics of the attack's execution (agent preparation, munition choice, meteorological conditions, etc.), as well as the intent of the adversary. In addition to a large-scale attack, an adversary could also target a limited number of individuals to seed an outbreak while maintaining deniability of biological warfare (BW) use.

Inadvertent contact with a natural reservoir of the disease could also introduce the disease into the PAR. This could result from contact with infected individuals (e.g., host-nation civilians, allied forces, or adversarial combatants) or other natural reservoirs of the disease (e.g., local animal populations). An unintentional introduction of a disease of this type would likely result in a smaller number—or even a single individual—being initially infected.

The IDA team focused its analysis on two contagious BW agents: *Yersinia pestis*, the causative pathogen of plague, and *Variola major*, the causative pathogen of smallpox. In addition to the threat posed by traditional BW agents, previous IDA analyses identified EIDs as a threat to U.S. military forces.[11] Therefore, a notional EID was also considered in this analysis. While the term EID can describe a wide range of diseases, the IDA team focused on a notional novel pathogen to analyze how limited knowledge of a disease can impact disease surveillance. The conclusions drawn from analyzing these three diseases

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[10] See Burr et al., *Emerging Infectious Disease Study* for additional information on the ability of theater-level restriction of movement (ROM) to mitigate the impact of a contagious disease outbreak.

[11] Burr et al., *Emerging Infectious Disease Study.*

were used to provide capability development recommendations that are applicable to a range of diseases.

D. Paper Organization

The remainder of the paper is organized as follows:

- Chapter 2 describes the analytic approach.
- Chapters 3, 4, and 5 apply this approach to plague, smallpox, and the notional novel EID, respectively.
- Chapter 6 summarizes the observations and recommendations of the analysis.

2. Analytic Approach

A. Qualitative Framework to Assess Disease Factors' Influence on Disease Surveillance and Outbreak Response

The first part of the analytic approach was the development of a qualitative framework to assess how various disease-related factors either improve or impair the ability of disease surveillance to trigger a response in time to minimize operational disruption. The framework was then applied to specific diseases to inform the development of capabilities that could reduce operational impact. The framework categorizes disease factors based on whether they influence: (1) the *time available* to detect and respond to the outbreak or (2) the *time it takes* to detect and respond to the outbreak.

The *time available* to detect and respond to an outbreak is defined as the time from the beginning of the outbreak to the last point in time that a given control measure could be implemented and still keep operational disruption below some threshold. This time is notionally shown in Figure 1. The *time it takes* to detect and respond to an outbreak is defined as the time from the beginning of the outbreak to the point when a control measure is actually implemented. This time is also shown in Figure 1.

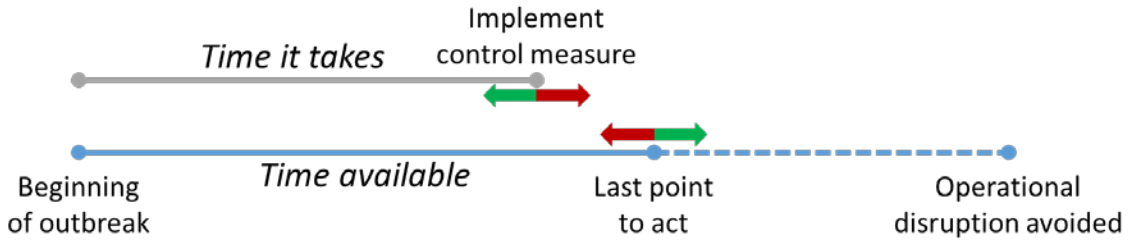

Figure 1. Notional Depiction of the Time Available and the Time It Takes to Detect and Respond to a Contagious Disease Outbreak

The level of operational disruption resulting from an outbreak depends on the difference between how long it takes to detect and respond to an outbreak and the time available. In general, operational disruption will be reduced if the *time available* is increased or if the *time it takes* is decreased. Conversely, operational disruption will generally increase if the

time available is decreased or if the *time it takes* is increased. These relationships are shown by the red and green arrows in Figure 1.[12]

1. Factors Influencing the *Time Available* to Detect and Respond to an Outbreak

The time available to detect and respond to an outbreak primarily depends on how quickly the disease spreads through the population, as well as how effective the response is at disrupting transmission. How quickly an outbreak grows primarily depends on three factors. First, outbreaks that start with a greater number of initial infections tend to grow faster than those starting with fewer initial infections. Therefore, an outbreak resulting from an adversarial release of weaponized pathogen will likely result in less time available for the disease surveillance and response process than an outbreak resulting from contact with a natural reservoir of the disease.

Second, diseases that are more contagious will result in a greater number of new cases in each generation of the outbreak than diseases that are less contagious. The contagiousness of a disease largely depends on its route of transmission. Diseases that can be transmitted from person to person via the respiration of pathogen-containing airborne droplets tend to be more contagious than those that are transmitted through other routes (e.g., direct contact with bodily fluids or fecal-oral). In addition, diseases that result in individuals being contagious for longer periods of time provide a greater opportunity for transmission.

Third, diseases that have shorter periods of time between successive generations will also result in a more rapid growth of the outbreak. In general, the time between successive generations of an outbreak is dictated by the disease's serial interval. The serial interval of a disease is the "time interval between successive infections in a chain of transmission"[13] and is sometimes referred to as the generation time. A disease's serial interval is often defined as the combined duration of its latent period and half of its contagious period. Therefore, diseases with shorter latent periods (and to a lesser extent, shorter contagious periods) will cause outbreaks with less time between successive generations than those with longer latent periods.

The influence of control measure efficacy on the time available to detect and respond to an outbreak is shown in Figure 2. The figure notionally shows the cumulative number of cases of a disease over time if no response is implemented (blue curve), if a highly

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[12] In Figure 1, the *time it takes* to detect and respond to an outbreak is arbitrarily shown as shorter than the *time available*—a situation that would reduce operational disruption. The *time it takes* to detect and respond to an outbreak could also be greater than the *time available*—a situation that would increase operational disruption.

[13] Emilia Vynnycky and Richard G. White, *An Introduction to Infectious Disease Modelling* (Oxford, UK: Oxford University Press, 2011), xxv.

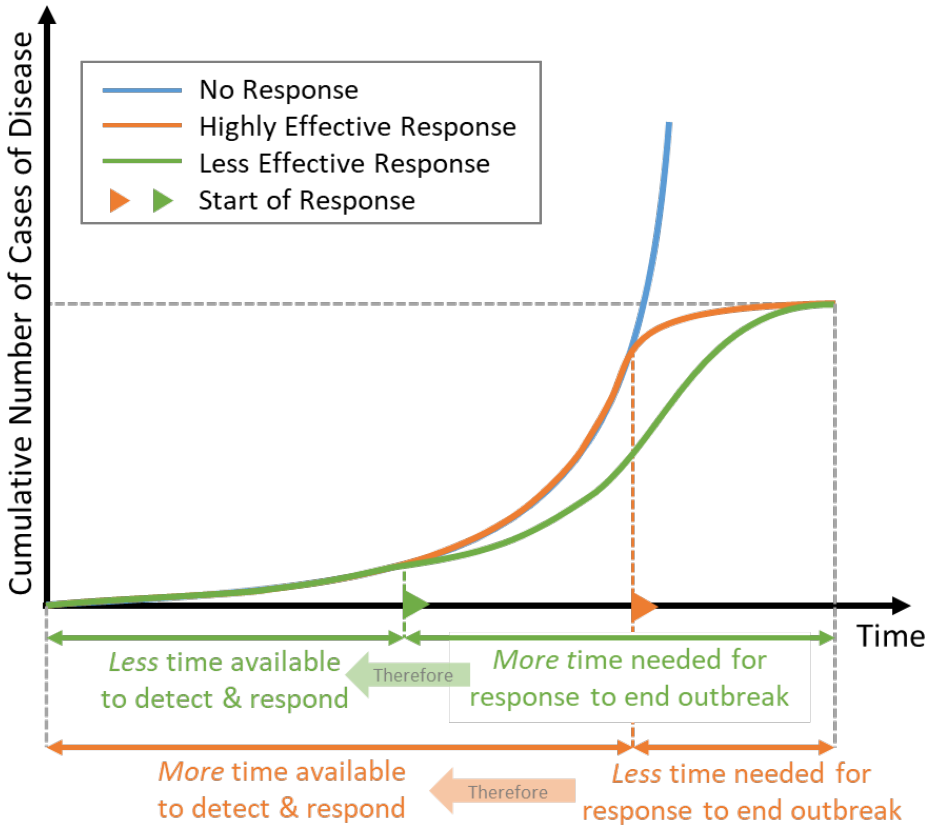


Figure 2. Notional Depiction of Control Measure Influence on the Time Available to Detect and Respond to an Outbreak

effective response is implemented (orange curve), and if a less effective response is implemented (green curve). Notice that the highly effective response rapidly truncates the progression of the outbreak following its implementation. This results in the outbreak ending (shown as the curve becoming horizontal) shortly after the start of the response. In contrast, the less effective response slowly diminishes the growth of the outbreak. Therefore, more time is needed for the response to end the outbreak. Because the less effective response requires more time to end the outbreak, it must be implemented earlier than the more-effective response. The need for earlier implementation results in less time available to detect and respond to the outbreak. In general, the time available to detect and respond to an outbreak is inversely related to the efficacy of the response that is used.

The relationship between response efficacy and the time available to detect and respond to an outbreak holds, regardless of the type of control measure. However, previous IDA work showed that medical countermeasures (MCMs) are generally more effective at disrupting disease transmission than other types of control measures (e.g., patient isolation

or quarantine).[14] Therefore, outbreaks of diseases for which vaccines or prophylactic drugs are not available will likely present a shorter window of time in which disease surveillance will need to trigger a response. Figure 3 summarizes the factors that influence the time available to detect and respond to an outbreak. Again, increasing the time available to detect and respond to an outbreak will reduce operational disruption.

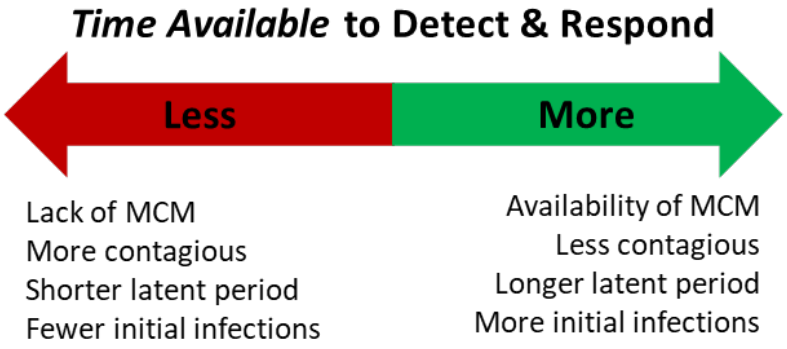


Figure 3. Factors Influencing the Time Available to Detect and Respond to an Outbreak

2. Factors Influencing the *Time It Takes* to Detect and Respond to an Outbreak

The time it takes for disease surveillance to trigger the implementation of control measures largely depends on how long it takes for the disease to be recognized in the PAR. In general, diseases that are harder to diagnose will be more difficult to detect than those that are easier to diagnose. Therefore, diseases that have generic presentations will be harder to detect than those with specific presentations. For example, diseases that present with generic influenza-like symptoms may be difficult to distinguish from other similarly presenting diseases. Likewise, rare or non-endemic diseases that medical personnel are less familiar with, or are not expecting to encounter, will be more difficult to detect. Finally, the availability of laboratory diagnostic tests can improve diagnostic capability, and therefore facilitate disease surveillance. However, the availability of a diagnostic test does not guarantee that medical personnel will use it. Medical personnel may have to suspect the disease based on clinical factors first to obtain the appropriate sample and execute the proper diagnostic test.

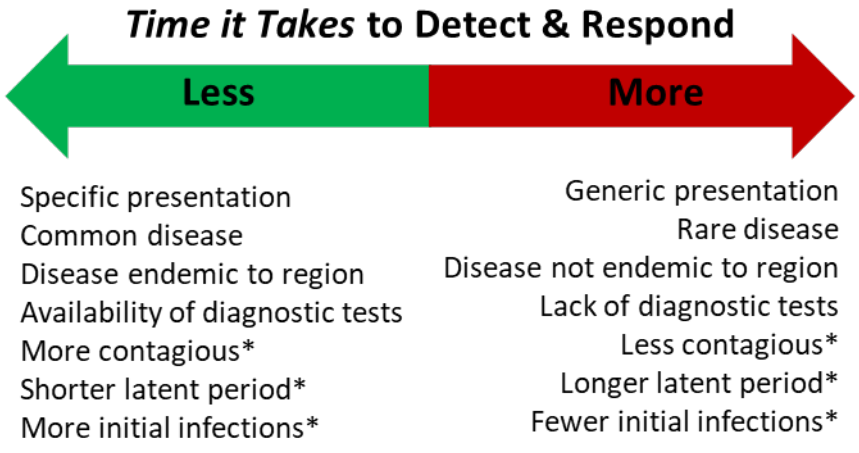
Recognition of an outbreak is also influenced by the prevalence of the disease within the PAR. Multiple individuals reporting to the medical system with a similar presentation over a short period of time will likely facilitate the disease surveillance process. In general, the shorter the time between the cases reporting to the medical system, the stronger the disease surveillance signal. For example, five individuals reporting with the same set of

[14] Burr et al., *Emerging Infectious Disease Study.*

symptoms on the same day will be more recognizable than the same individuals reporting over the course of multiple weeks.

In addition to the timing of individuals reporting to the medical system, the locations where they report can also influence the recognition of an outbreak. Multiple individuals with a similar presentation reporting to the same medical treatment facility (MTF) will provide a stronger disease surveillance signal than the same individuals reporting to multiple MTFs. By reporting to the same MTF, these individuals are more likely to be seen by the same medical personnel—increasing the likelihood of the outbreak being recognized. In contrast, if these individuals report to multiple MTFs, then case reporting and aggregation would likely be necessary to recognize the full extent of the cases—thus delaying the recognition of the outbreak.

Outbreaks that quickly generate larger numbers of simultaneous cases are more likely to result in multiple cases reporting to the same MTF. Therefore, faster-growing outbreaks are more likely to trigger the response process sooner than slower-growing outbreaks. The disease factors that contribute to the speed at which an outbreak grows (i.e., the number of initial infections, the contagiousness of the disease, and the duration of the disease's latent period) will also influence how long it takes to detect and respond to an outbreak. Figure 4 summarizes the factors that influence the time it takes to detect and respond to an outbreak. Again, factors that reduce the time it takes to detect and respond to an outbreak will reduce operational disruption.



*Factor that also influences the time available to detect and respond to an outbreak.

Figure 4. Factors Influencing the Time It Takes to Detect and Respond to an Outbreak

3. The Framework

The factors that influence the *time available* to detect and respond to an outbreak (i.e., those shown in Figure 3) and those that influence the *time it takes* to detect and respond to

an outbreak (i.e., those shown in Figure 4) make up the framework shown in Figure 5. The framework organizes the factors based on whether they provide more time, less time, or do not influence either the *time available* or *the time it takes* to detect and respond to an outbreak. For example, the factors that increase the *time available* to detect and respond to an outbreak (i.e., those shown on the right side of Figure 3) are shown in the far right *it takes* to detect and respond, it is located in the middle row of the framework. In comparison, the other three factors (i.e., less contagious, longer latent period, and fewer initial infections) increase the *time it takes* to detect and respond. Therefore, these three factors are located in the bottom row of the framework.

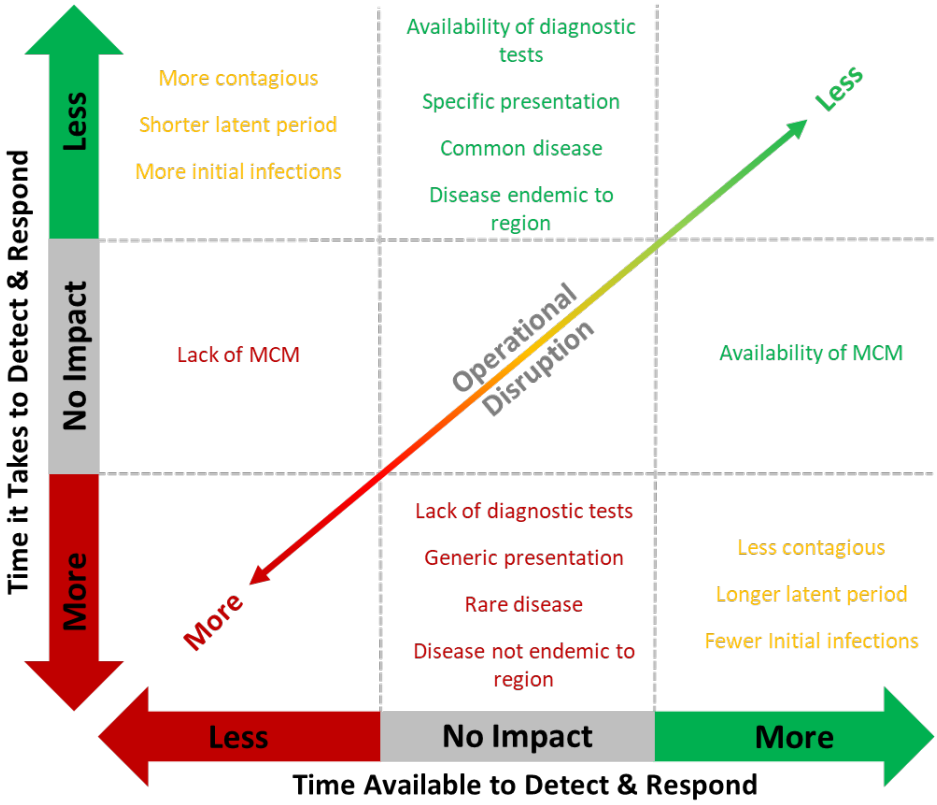


Figure 5. Framework to Assess Disease Factors' Influence on Disease Surveillance and Response

column of the framework. Because the availability of an MCM does not influence the *time* factors in the framework are color coded, based on how they influence the operational disruption caused by the outbreak. Factors that reduce operational disruption are shown in green. Factors that increase operational disruption are shown in red. Factors that have the potential to either reduce or increase operational disruption are shown in orange. These factors are those that influence both the *time available* and the *time it takes* to detect and respond to an outbreak.

The factors in the upper-left of the framework lead to a fast-growing outbreak. Such an outbreak can quickly generate large numbers of casualties, but the large number of cases will also make it easier for medical personnel to detect the outbreak. In comparison, the factors in the lower-right of the framework lead to a slow-growing outbreak. Although this type of outbreak will take longer to generate a large number of casualties, it may be harder to detect, given the smaller number of cases.

The IDA team applied the framework to specific diseases by identifying the combinations of factors that are applicable for a given disease. Some factors may not be applicable for a given disease. The applicable factors that either reduce the *time available* or increase the *time it takes* to detect and respond to an outbreak can then be targeted for future capability development. For example, fielding an MCM for a disease that lacks one can increase the time available to detect and respond to the outbreak. Similarly, fielding a diagnostic test for a disease that currently lacks one can reduce the time it takes to detect and respond to an outbreak of that disease. Even if a given factor cannot be directly targeted by a new capability (e.g., the duration of the disease's latent period), its influence on either the *time available* or the *time it takes* to detect and respond to an outbreak can still be improved. For example, training medical personnel to better recognize a disease that is rare, is not endemic to the region, or has a generic presentation could help reduce the time it takes to detect and respond to an outbreak of such a disease.

B. Quantitative Analysis of Operational Disruption

The second part of the analytic approach used a contagious disease model to assess the ability of various disease surveillance triggers and control measure implementation strategies to minimize operational disruption. The IDA team used this portion of the analysis to characterize the benefit—in terms of reducing operational disruption—of improving the disease surveillance and response process.

For each disease under consideration, the IDA team first conservatively characterized how an outbreak would likely be detected and what response would likely be taken. From this baseline starting point, the IDA team then systematically varied the disease surveillance trigger (i.e., how an outbreak would be detected) and the way in which the control measure was implemented (i.e., what response would be taken). The operational disruption of the various simulated outbreaks were then compared to characterize the consequence of each disease surveillance and response variation.

The IDA team used the total number of casualties due to infection with the disease as the primary metric of operational disruption. As discussed in Chapter 1, contagious disease outbreaks can disrupt operations in multiple ways. To account for this, a range of casualty thresholds were used. Lower thresholds (0.1% and 1% of the PAR) were used to represent the indirect disruption caused by a low number of contagious individuals, and higher

thresholds (5% and 10% of the PAR) were used to represent the direct disruption caused by personnel loss.

As mentioned in the scope of the analysis (Section 1.C), contagious disease outbreaks can start via adversarial action or contact with a natural source. To account for these different sources of infection, the IDA team simulated outbreaks that started with either 1, 10, or 100 initial infections. The term "initial infections" refers to individuals who were exposed and infected with the disease due to contact with the original source of infection (as compared to an infection resulting from transmission from another individual in the PAR). The initially infected individuals will eventually become ill, unless their infection is terminated via the administration of a post-exposure prophylactic (PEP). Given the ability of PEP to prevent infected individuals from becoming ill, some scenarios did not result in all of the initial infections becoming casualties. In other words, it is possible that an outbreak starting with 100 initial infections resulted in fewer than 100 casualties.

1. Contagious Disease Model Synopsis

As mentioned previously, a contagious disease model served as the primary quantitative analytic tool for the analysis. A complete technical description of the model, along with a list of assumptions, can be found in Appendix B. What follows is a brief overview of the model's critical features and assumptions.

The contagious disease model tracks each individual in the population at every time step (0.1 days) of the simulation. Random draws from previously defined disease-specific distributions determine: the durations of each individual's incubation period, first stage of illness, and second stage of illness; whether each individual dies; and the number of people each individual infects.[15] Because the model contains these random draws (i.e., is stochastic), running it multiple times with the same set of inputs results in different simulated outbreaks. Therefore, multiple trials were performed to characterize the variation in an outbreak due to the randomness inherent in individual disease progression and transmission.

Simulated outbreaks start with a specified number of initial infections, and unless explicitly specified, all other members of the population are susceptible to infection. Individuals can only become infected via transmission from another individual within the population—no external sources of infection are allowed. The population is assumed to be fixed throughout the duration of the simulation. The model assumes that all individuals in

[15] See Appendix B for specific distributions and corresponding citations.

the population are equally likely to contact—and therefore potentially infect—any other individual. This is a commonly used simplifying assumption.[16,17]

The contagious disease model considers response measures in two ways. First, it can account for certain disease-specific MCMs (i.e., antibiotics for plague and vaccine for smallpox). The model assumes that MCMs are simultaneously administered to the entire PAR, take 24 hours to become efficacious, and remain efficacious for the remainder of the outbreak. Second, it can account for a generic response capability that can reduce transmission by some specified amount. The latter ability is used to support "what if?" analyses. For example, what if a response could be implemented that reduced transmission by 95%, as compared to one that was only able to reduce transmission by 50%?

2. Summary of Fundamental Modeling Assumptions

The following are the fundamental assumptions relating to the contagious disease model:

- Outbreaks start with a single exposure event that introduces the disease into the PAR; all subsequent exposures are a result of person-to-person transmission.
- Unless stated otherwise, everyone in the PAR is unprotected and susceptible to infection at the start of the outbreak.
- The population is fixed throughout the duration of the simulation.
- All individuals in the population are equally likely to contact—and therefore potentially infect—any other individual.
- MCMs are simultaneously administered to the entire PAR, take 24 hours to become efficacious, and remain efficacious for the remainder of the outbreak.

A complete list of assumptions can be found in Appendix B.

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

[17] Matt J. Keeling and Pejman Rohani, *Modeling Infectious Diseases in Humans and Animals* (Princeton, NJ: Princeton University Press, 2008).

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3. Plague

A. Disease Overview

Human infection with the bacterium *Yersinia pestis* (*Y. pestis*) can result in three forms of plague: bubonic, septicemic, and pneumonic. Bubonic plague—the most common in naturally occurring infections—typically occurs via the bite of an infected flea. Individuals with the bubonic form of the disease can then develop the septicemic form of the disease if the bacterium spreads to their blood. The pneumonic form of the disease can occur in two ways. Individuals can experience secondary pneumonic plague if an existing plague infection spreads to their lungs. Primary pneumonic plague occurs when an individual's lungs become infected following the direct inhalation of the bacteria.[18]

Pneumonic plague is the only form of the disease that can result in person-to-person transmission. Individuals can become infected through the respiration of bacteria-containing droplets originating from a contagious individual. Although the occurrence of primary pneumonic plague is exceedingly rare, it is the form of the disease most likely to occur following an intentional release of the pathogen. Unless specifically stated otherwise, the use of the term "plague" in the remainder of the document refers to the primary pneumonic form of the disease (caused by either direct inhalation of disseminated agent or person-to-person transmission).

1. Disease Progression

Typical plague disease progression consists of the following:

- A 1- to 6-day incubation period (typically 2 to 4 days)[19];
- A brief prodromal period (approximately 1 day) characterized by moderate generic influenza-like symptoms, including: severe headaches, chills, nausea

[18] Mark R. Withers, ed., *USAMRIIDs Medical Management of Biological Casualties Handbook* (Fort Detrick, Frederick, MD: U.S. Army Medical Research Institute of Infectious Diseases, 2014).

[19] Ibid.

and vomiting, vertigo and general malaise; increased respiration, heart rate, and body temperature; and the appearance of a dry cough[20]; and

- A fulminant phase (approximately 1.5 days) characterized by the following very severe signs and symptoms: productive cough with hemoptysis (bloody sputum); increased respiratory rate and body temperature; dyspnea (difficulty breathing); weakness and exhaustion; weak pulse; cyanosis (blueish discoloration of the skin); frequent ataxia (uncoordinated movements); confusion; disorientation; restlessness and active delirium; possible coma; and eventual circulatory collapse or respiratory failure.[21]

Treatment with antibiotics is highly effective if initiated during the brief prodromal period (within 24 hours of symptom onset). Untreated plague (including treatment initiated after the prodromal period) has a case fatality rate (CFR) of nearly 100%.[22]

Person-to-person transmission of plague is most likely to occur during the fulminant phase of the disease. Transmission occurs via the respiration of bacteria-containing droplets originating from the coughing of an infected individual. Transmission typically requires direct and close contact (within six feet) with a contagious individual.[23] The average number of new infections caused per contagious individual in an entirely susceptible population is 1.3.[24]

2. Diagnosis

Early clinical diagnosis of a single individual with plague is unlikely. The nonspecific signs and symptoms associated with the prodromal stage of illness are not differentiable from similar—and substantially more common—bacterial or viral infections. Although the very severe and life threatening symptoms of the fulminant stage of the illness would likely motivate medical personnel to look for the cause, they alone may not be sufficient to lead to a rapid clinical diagnosis. On the other hand, multiple cases of previously

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[20] 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, 2016).

[21] Ibid.

[22] Withers, *USAMRIIDs Medical Management*.

[23] "Human Plague Transmission from Person to Person," Centers for Disease Control and Prevention, accessed April 12, 2019, https://www.cdc.gov/plague/index.html.

[24] Withers, *USAMRIIDs Medical Management*.

healthy individuals who develop fulminant pneumonia with hemoptysis leading to death would strongly suggest a plague outbreak.[25]

A presumptive laboratory diagnosis is possible via microscopic identification of the bacteria in blood or sputum. However, the identifiable "safety pin" appearance of the bacteria is only visible when prepared with certain stains (Wright, Giemsa, Wayson's, or methylene blue) and may not be apparent in others (Gram).[26] Cultured blood or sputum can provide a definitive diagnosis. However, diagnosis via culture can be complicated by slow bacterial growth at typical incubation temperatures, possible misidentification by automated systems, and intermittent presence in the clinical specimen. Ideally, multiple specimens should be taken and cultures should be performed at both a typical and higher temperature (28°C and 35°C). The process may take 48 to 72 hours.[27]

In addition, a confirmatory diagnosis can be made via polymerase chain reaction (PCR) analysis with the Next Generation Diagnostic System (NGDS) 1's Warrior panel. The Warrior panel allows for the simultaneous testing of a whole blood sample for the presence of six BW agents (*Bacillus anthracis*, *Yersinia pestis*, *Francisella tularensis*, *Coxiella burnetii*, Ebola virus, and Marburg virus). Although there are other assay panels for the NGDS 1, only the Warrior panel is able to identify *Y. pestis*. Therefore, NGDS 1 would likely only provide a plague diagnosis if medical personnel suspect plague or infection with a BW agent.[28]

3. Control Measures

There are no approved vaccines for pneumonic plague.[29] The primary method for controlling a plague outbreak is the rapid administration of antibiotics as a PEP and preexposure prophylaxis (PrEP). Antibiotics are highly effective at both terminating the infection of those who are incubating the disease (i.e., used as a PEP) and preventing infection in those who have not been infected (i.e., used as a PrEP).[30] Doxycycline is the

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25 Thomas V. Inglesby et al., "Plague as a Biological Weapon," *Journal of the American Medical Association* 283, no. 17 (2000): 2281–2190.

26 Withers, *USAMRIIDs Medical Management*.

27 Ibid.

28 Department of Defense, *Next Generation Diagnostic System (NGDS) Increment 1 Early Fielding Report* (Washington, DC: Director, Operational Test and Evaluation (DOT&E), 2017).

29 Withers, *USAMRIIDs Medical Management*.

30 Oxford et al., *Technical Reference Manual*.

preferred antibiotic for use as a PEP, with ciprofloxacin suggested as an alternative.[31,32] The IDA team modeled antibiotics as being 95% likely to[33]

- Provide protection against infection in those who were not already infected (i.e., those who were susceptible to being infected),
- Terminate the infection of those who were infected but had yet to develop symptoms (i.e., those who were incubating the disease), and
- Prevent development of the fulminant stage of the disease and contagiousness in those who were in the prodromal stage.

B. Qualitative Analysis of Factors Influencing Disease Surveillance

Figure 6 shows the qualitative framework as it applies to plague. Disease factors that are not applicable to plague are shown in gray. Disease factors that are applicable to plague are color coded, based on how they influence the operational disruption resulting from a plague outbreak. Factors that decrease operational disruption are shown in green and include the following:

- **Availability of diagnostic tests.** Confirmatory diagnosis can be made with PCR analysis (including the NGDS Warrior panel).
- **Specific presentation.** The rapid onset of fulminant pneumonia and death is a strong signal for disease surveillance.
- **Availability of MCM.** Antibiotics can both provide temporary immunity against infection and terminate infection in those who have yet to become ill.

Factors that increase operational disruption are shown in red and include the following:

- **Generic presentation.** The non-specific influenza-like symptoms of the prodrome will make early clinical diagnosis difficult.
- **Rare disease.** The primary pneumonic form of the disease occurs far less frequently than either the bubonic or the septicemic forms.
- **Disease not endemic to region.** Although plague outbreaks have occurred in regions across the globe, these outbreaks typically do not involve the primary pneumonic form of the disease.

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31 Withers, *USAMRIIDs Medical Management*.

32 Inglesby et al., "Plague as a Biological Weapon."

33 Oxford et al., *Technical Reference Manual*.

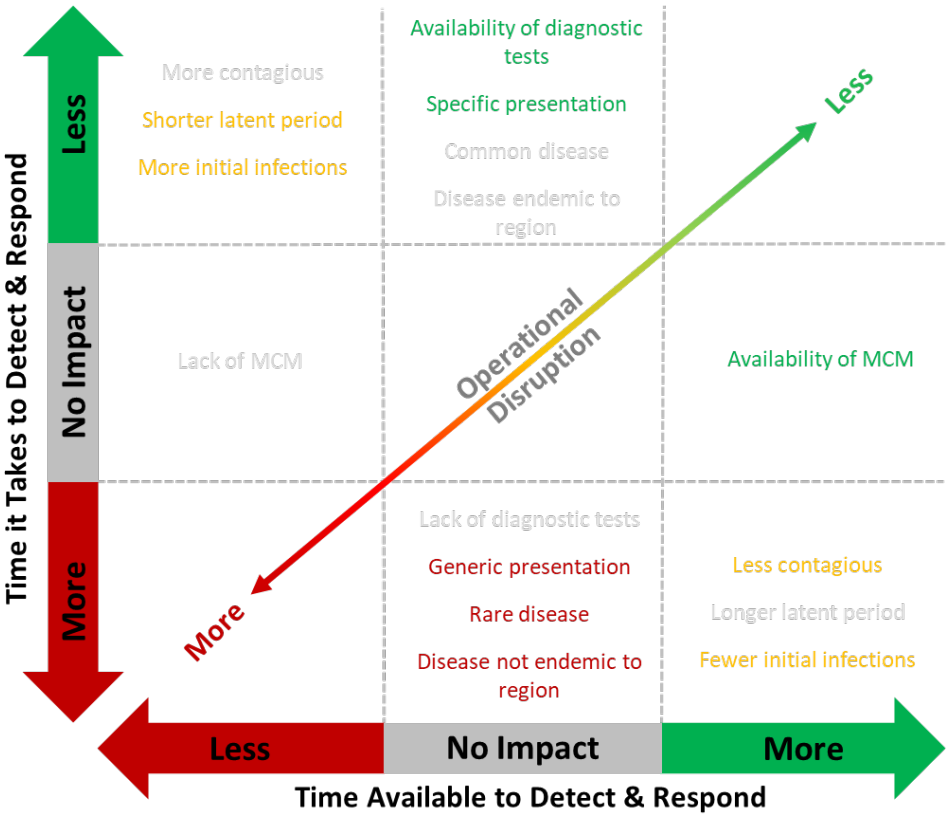

Figure 6. Framework to Assess Disease Factors' Influence on Disease Surveillance and Response: Plague

Factors that can either increase or decrease operational disruption are shown in orange and include the following:

- **Shorter latent period.** The latent period of plague is typically 3 to 5 days.[34]
- **More initial infections and fewer initial infections.** The number of initial infections may vary depending on the exposure source, route of exposure, and number of people in contact with the source.
- **Less contagious.** Person-to-person transmission typically requires close and direct contact with a contagious individual.

C. Quantitative Analysis of Operational Disruption

Recall that the first step of the quantitative portion of the analysis was to conservatively characterize how an outbreak of a given disease would likely be detected and what

[34] The latent period includes the incubation period (typically 2 to 4 days) and the symptomatic non-contagious prodrome (1 day).

response would likely be taken. From this starting baseline, the IDA team then systematically varied the disease surveillance trigger and the way in which the control measure was implemented. The goal of simulating these various responses was to determine the benefit—in terms of reducing operational disruption—of improving the timing of the disease surveillance and response processes.

Detecting a plague outbreak in the PAR would likely occur through a combination of the clinical diagnosis of cases in the fulminant phase of the illness and laboratory diagnostic tests. It is unlikely that an individual would be diagnosed with plague during their prodrome. The lack of disease-specific symptoms during the prodrome would provide clinicians with little evidence on which to make a presumptive diagnosis.[35] Even during the fulminant phase of the disease, a confirmatory diagnosis may not occur because of the following:

- Medical personnel may not conduct a diagnostic test if a suspected clinical diagnosis incorrectly suggests another disease.
- A sample could be taken at a point in the illness progression at which indicators of infection are not present.
- Medical personnel could fail to choose the appropriate panel to run in the PCR test. For the case of the NGDS 1, this could occur if neither plague nor another BW agent was suspected, and therefore the Warrior panel was not run.

These issues are further exacerbated by the lack of time to conduct such tests, due to the short duration of the fulminant stage of illness (average of 1.5 days). Most likely, medical personnel will need to witness multiple cases of the disease to recognize its presence within the population.

The exact number of cases of plague that would be required to trigger the response process is difficult to assess. On one hand, an astute clinician who is familiar with the signs and symptoms of infection with a BW agent could make a presumptive clinical diagnosis on the first case of the outbreak. On the other hand, if ill individuals report to different MTFs over an extended period of time, then the recognition that an outbreak is occurring could be delayed. A previous IDA analysis of a BW outbreak response in a civilian setting assumed that 10 cases of plague would be required to recognize that a mass casualty event had occurred in a major U.S. city.[36] In the PAR under consideration, the number of indi-

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[35] The IDA team assumed that all individuals report to the medical system as soon as they develop symptoms.

[36] Deena S. Disraelly et al., *Biodetection Technology Enhancements Alternatives Analysis (AA)*, vol. II: *Administration and Operational Effectiveness Analyses*, IDA Document NS D-9233 (Alexandria, VA: Institute for Defense Analyses, 2018).

viduals is substantially smaller than that of a major city (thousands as compared to millions). Therefore, fewer cases would likely be required to trigger the recognition of the disease. The IDA team made the assumption that medical personnel would detect an outbreak of plague by the time of the third fatality—regardless of the timing of fatalities and the MTF(s) in which they occur. An analysis of the sensitivity of this and other assumptions can be found in Appendix A, and a list of assumptions relating to the plague analysis can be found at the end of this chapter.

Following the detection of plague within the population, medical personnel would likely inform the commander of the outbreak and suggest the use of antibiotic PEP and PrEP. Given plague's high mortality rate and the relatively low operational burden of oral antibiotic administration, it is likely that the decision to administer antibiotics would be made rapidly. For the analysis, the IDA team assumed that the time required for the decision cycle following the detection of the outbreak would be negligible compared to the time to detect the outbreak and the time to administer population-wide antibiotics.

Once the decision to administer population-wide antibiotics has been made, the drugs need to be distributed to the individuals at risk of infection. The IDA team assumed that if the antibiotics are located within the population itself (e.g., within the Role 2 MTF), then they could be distributed to all members of the population within 6 hours of the decision to do so. This assumption is consistent with a previous IDA analysis.[37] If the antibiotics were not stored within the PAR, then their administration would be delayed. The IDA team assumed that antibiotics would be distributed to all non-symptomatic individuals in the PAR and that all individuals were completely compliant with the requisite dosing regimen. The benefits of PEP and PrEP were assumed to begin 24 hours following the first administration of antibiotics and were assumed to last for the duration of the outbreak.

To summarize, the IDA team used the administration of population-wide antibiotics within 6 hours of the third plague fatality as the baseline characterization of disease surveillance and response. The exact timing of this process—in terms of the number of days following the start of the outbreak—depends on how long it takes for three individuals to become infected and die. In general, this will occur sooner for outbreaks that start with more initial infections. However, even for a given number of initial infections, the timing of fatalities will depend on individual variation in disease progression. To illustrate this, the contagious disease model was run without the administration of antibiotics to determine the range in the timing of the third fatality. Table 1 shows the 10^{th}, median, and 90^{th} percentile delay from the first appearance of symptoms in the PAR to the third fatality.

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[37] Katherine M. Sixt et al., *Enhanced Viruses and Bacteria as Biological Weapons, Phase 1: An Analytic Framework for Understanding How Synthetic Biology Can and Cannot Enable an Adversary*, IDA Paper P-8465 (Alexandria, VA: Institute for Defense Analyses, 2017).

Table 1. Delay (Days) from First Appearance of Symptoms to Third Plague Fatality

Number of Initial Infections	10th Percentile	Median	90th Percentile
1	14.1	9.6	7.3
10	4.1	3.2	2.5
100	2.8	2.4	2.0

In addition to the baseline, the IDA team also analyzed six variations of how a plague outbreak could be detected and responded to. Each variation systematically changed either the disease surveillance trigger or the delay in administering antibiotics to the PAR. The six variations, as well as the baseline, are summarized below.

- **Outbreak detected after third fatality, population-wide antibiotics administered from stockpile in population.** Conservatively characterized baseline—multiple plague fatalities are required to trigger the implementation of population-wide antibiotics, which are stockpiled with the population (e.g., in the Role 2 MTF) and take 6 hours to distribute and administer.
- **Outbreak detected after third fatality, population-wide antibiotics pre-distributed to individuals.** Antibiotics are pre-distributed to individual service members or unit-level medical personnel, eliminating the six-hour delay in administering the drugs following the detection of the outbreak after the third fatality.
- **Outbreak detected after first fatality, population-wide antibiotics administered from stockpile in population.** The first plague fatality (instead of three fatalities) triggers the implementation of population-wide antibiotics, which are stockpiled with the population (e.g., in the Role 2 MTF) and take 6 hours to distribute and administer.
- **Outbreak detected after first case with severe symptoms, population-wide antibiotics administered from stockpile in population.** The first case to develop the fulminant stage of illness (instead of three fatalities) triggers the implementation of population-wide antibiotics, which are stockpiled with the population (e.g., in the Role 2 MTF) and take 6 hours to distribute and administer.
- **Outbreak detected after symptom onset of first case, population-wide antibiotics administered from stockpile in population.** The first case to develop prodromal symptoms (instead of three fatalities) triggers the implementation of population-wide antibiotics, which are stockpiled with the population (e.g., in the Role 2 MTF) and take 6 hours to distribute and administer.
- **Outbreak detected after symptom onset of first case, population-wide antibiotics pre-distributed to individuals.** The first case to develop prodromal symptoms (instead of three fatalities) triggers the implementation of population-wide antibiotics, which are pre-distributed to individual service members or

unit-level medical personnel, eliminating the six-hour delay in administering the drugs.

- **Pre-attack population-wide administration of antibiotics.** Antibiotics are administered to the population prior to the initial exposure event (instead of being administered in response to a disease surveillance trigger).

The contagious disease model was used to determine the level of operational disruption associated with each of the above seven disease surveillance and response variants. For each variant, the IDA team determined the 90th percentile case for the total number of casualties. The 90th percentile case was selected to show the level of operational disruption in all but the worst 10% of outbreaks. Figure 7 shows the number of casualties for each of the disease surveillance and response variants considered. The background of Figure 7 is color coded to facilitate comparison with the casualty threshold used to assess operational disruption (i.e., 0.1%, 1%, 5%, and 10% of the population).

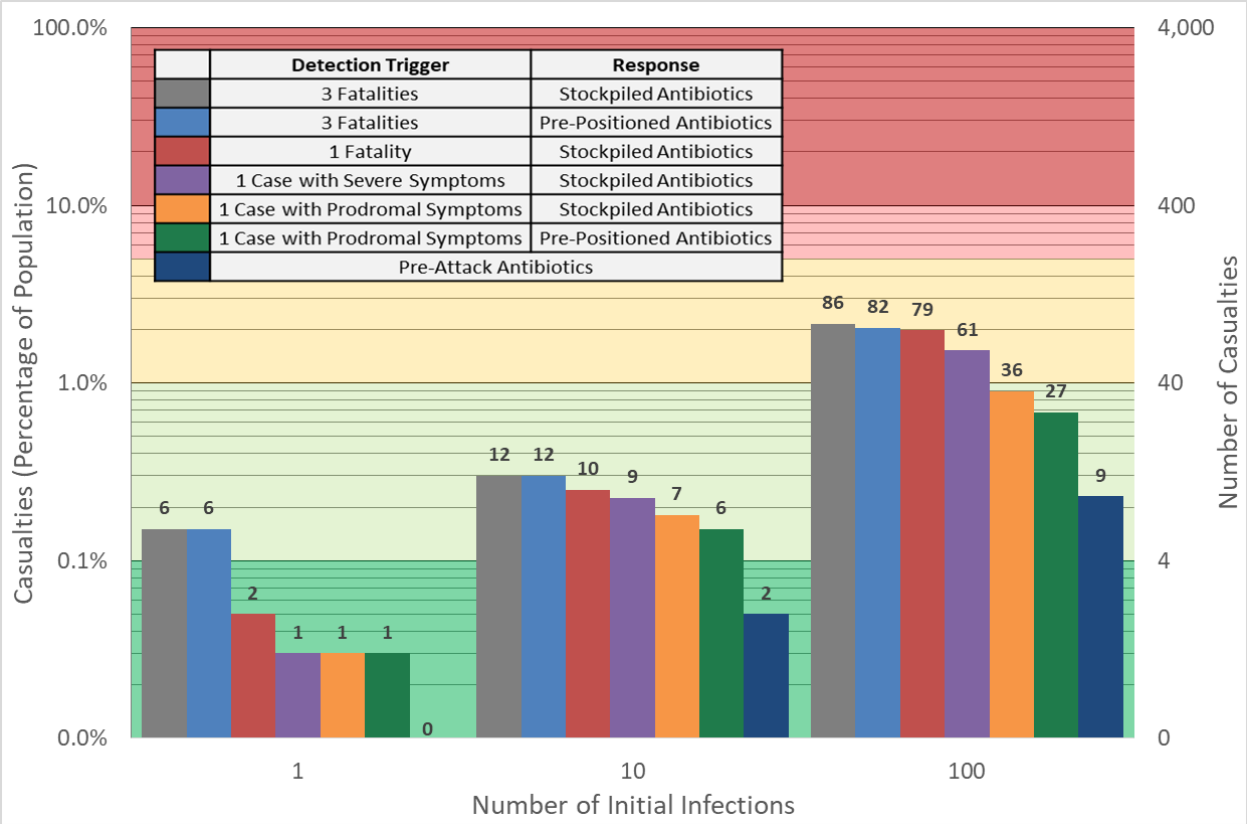

Figure 7. Number of Casualties Due To Infection with Pneumonic Plague (90th Percentile) for Various Disease Surveillance Triggers and Delays in Administering Population-Wide Antibiotics

The IDA team considered the various disease surveillance triggers in the context of a "what if?" analysis. The objective was to illustrate the level of operational disruption that would result if the outbreak could be detected through the various disease surveillance

triggers. The costs or feasibility of actually being able to detect the outbreak in such a way were not considered. As will be discussed in the subsequent section, this portion of the analysis can inform decision makers of the benefit of pursuing a capability that allows an outbreak to be detected through a given disease surveillance trigger. Additional analyses are required to characterize the costs and feasibility of such a capability.

The IDA team also assessed the consequence of delaying detection of the outbreak and the administration of antibiotics. This assessment served two purposes. First, it was a sensitivity analysis of the assumptions that underlie the characterization of the baseline scenario. Second, it showed the impact of responding to an antibiotic-resistant strain of plague. A full description of this assessment can be found in Appendix A. The IDA team found the operational disruption caused by a plague outbreak to be relatively insensitive to the assumed number of fatalities that would be required to trigger a response and the time required to administer antibiotics. Even if more than 20 fatalities were required to trigger the response process, outbreaks that cause more than 5% of the PAR (200 individuals) to become a casualty can be avoided. Similarly, even if the administration of population-wide antibiotics is delayed by 6 days, outbreaks that cause more than 5% of the PAR to become a casualty can be avoided. Therefore, if the strain of *Y. pestis* causing the outbreak was resistant to the first choice of antibiotics, then the resulting delay to obtain and administer a second choice of antibiotic would likely not be sufficient to cause a substantially greater level of operational disruption.

D. Discussion

In general, commanders have the ability to detect and respond to a plague outbreak in time to prevent the direct operational disruption caused by personnel loss. As shown in Figure 7, even when multiple fatalities are required to detect the outbreak, the administration of population-wide antibiotics is able to prevent 5% of the population from becoming casualties. That being said, the indirect operational disruption resulting from the presence of contagious individuals in the PAR may be unavoidable—even if population-wide antibiotics are administered prior to the exposure event.

As shown in the qualitative framework (see Figure 8), the availability of an MCM increases the time available to detect and respond to the outbreak. In addition, the strong disease surveillance and identification signals provided by the specific presentation of the fulminant stage of the disease and the availability of diagnostic tests decrease the time it takes to detect the outbreak. Having more *time available* to detect and respond in combination with a detection and response process that *takes less time* results in plague outbreaks that cause minimal direct operational disruption.

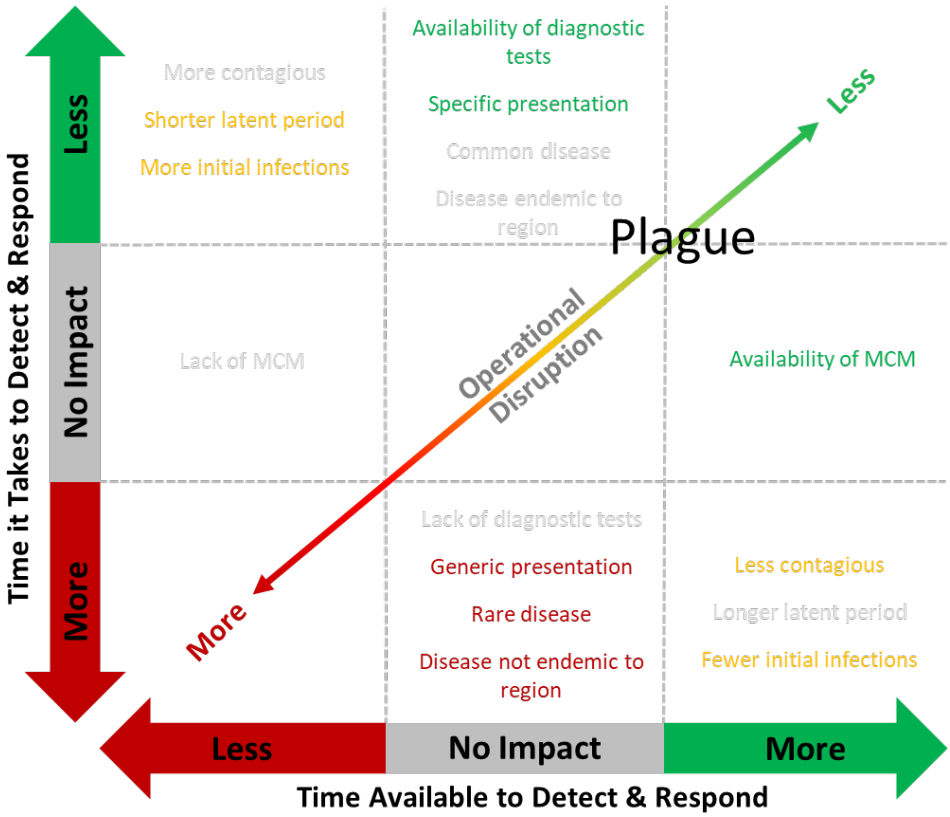

Figure 8. Framework to Assess Disease Factors' Influence on Disease Surveillance and Response: Plague

The results shown in Figure 7 show the benefits—in terms of reducing operational disruption—of both detecting the disease at various points during the outbreak and improving the time it takes to administer MCMs. These results can support decisions related to disease surveillance and response capabilities. For example, the results show a negligible benefit from pre-distributing population-wide antibiotics to individuals (blue and green bars in Figure 7), as compared to stockpiling the drugs within the PAR (gray and orange bars).

The benefit to reducing operational disruption by developing capabilities to facilitate early detection through disease surveillance can also be seen in Figure 7. These capabilities could include a future diagnostic test that can detect the disease during its very early stages or increasing medical personnel's familiarity with the clinical presentation of diseases that could be used as BW agents. Again, the IDA team did not assess the feasibility or costs of developing these types of capabilities; it only assessed the benefit to the disease surveillance and response processes. Figure 7 shows the benefit triggering the response process if the outbreak could be detected by recognizing plague's prodromal symptoms (orange bars), fulminant stage (purple bars), or the death of the patient (red bars).

Figure 7 also shows the benefit of medically protecting the PAR against infection prior to the initial exposure event (dark blue bars), as compared to triggering antibiotic administration following the detection of the outbreak through disease surveillance (all other bars). Of all the disease surveillance and response variations analyzed, administering pre-attack population-wide antibiotics resulted in the lowest level of operational disruption. In addition, proactively—as compared to reactively—administering an MCM lessens the need to detect the outbreak through disease surveillance to mitigate operational disruption.

Although the administration of population-wide antibiotics is able to prevent the direct operational disruption caused by personnel loss, it is unable to completely prevent cases of plague in the PAR. Even when the population is administered antibiotics prior to the exposure event (dark blue bars), cases of plague can still occur. Therefore, the indirect operational disruption caused by the presence of contagious individuals may be unavoidable.

E. Summary of Assumptions for Plague Analysis

In addition to the overarching contagious disease model assumptions listed in Section 2.B.2 and Appendix B, the following were assumed during the analysis of plague.

- All individuals report to the medical system as soon as they develop prodromal plague symptoms.
- For the conservatively characterized baseline, medical personnel would detect an outbreak of plague by the time of the third fatality, regardless of the timing of fatalities and the MTF(s) in which they occur.
- The time required for the decision cycle following the detection of the outbreak would be negligible compared to the time to detect the outbreak and the time to administer population-wide antibiotics.
- Antibiotics would be distributed to all non-symptomatic individuals in the PAR and all individuals were fully compliant with the requisite dosing regimen.
- Antibiotics stockpiled with the PAR can be distributed and administered within 6 hours of the decision to do so.
- Pre-positioned antibiotics can be administered immediately following the decision to do so.
- For the analysis of pre-attack antibiotic, individuals were administered antibiotics at some point prior to the exposure event to provide adequate time to be protected at the time of the exposure event.

4. Smallpox

A. Disease Overview

Smallpox is caused by infection with the *Variola* Orthopox virus. There are at least two strains of *Variola*: *Variola major*, which results in a more severe form of the disease with a CFR of around 30%, and *Variola minor*, which results in a milder form of the disease with a lower CFR of < 1%.[38] The *Variola major* strain of the virus can result in two clinical forms of the disease. Classical, or ordinary, smallpox—the more prevalent of the two—occurs approximately 90% of the time in unvaccinated individuals. Flat-type, or hemorrhagic, smallpox is less common—typically occurring in individuals with underlying immune deficiencies—and has a CFR of nearly 100% in unvaccinated individuals.[39] Given its higher prevalence, this analysis will focus solely on the ordinary type of the disease. Unless explicitly stated otherwise, the use of the term "smallpox" in the remainder of the document refers to the ordinary form of the disease caused by the *Variola major* virus.

1. Disease Progression

Typical smallpox progression consists of the following:

- A 7- to 19-day incubation period,[40]
- A 2- to 3-day prodromal period[41] characterized by high fever; malaise; vomiting; chills; headache; severe backache; possibly accompanied by abdominal pain and delirium,[42] and
- A clinical stage of the disease that lasts an average of two weeks and is characterized by difficulty swallowing, enanthem (rash) over pharynx; appearance of maculopapular rash first on the face, hands, and forearms (including mouth and pharynx) and subsequently on lower extremities; within days, vesicles form and

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38 Withers, *USAMRIIDs Medical Management*.

39 Oxford et al., *Technical Reference Manual*.

40 Withers, *USAMRIIDs Medical Management*.

41 Ibid.

42 Oxford et al., *Technical Reference Manual*.

progress to pustules and then scars; severe systemic toxemia leads to multiple organ failure and death in non-survivors.[43]

Treatment for smallpox consists primarily of supportive care. The U.S. Food and Drug Administration (FDA) recently approved the antiviral tecovirimat for the treatment of smallpox. However, due to a lack of human-subject testing, its benefit to an individual ill with smallpox is unknown.[44] Therefore, treatment with smallpox antivirals was not considered in this analysis. As will be discussed in additional detail later, a vaccine exists for administration as a PrEP and PEP.

Person-to-person transmission of smallpox occurs via the inhalation of respiratory secretions. Typically, individuals are most infectious during the time immediately following rash onset in the mouth and pharynx. It is the presence of these eruptions that lead to the exhalation of virus-containing droplets. Prior to this phase of the illness (i.e., during the prodrome), individuals are not typically considered infectious. Estimates on the number of new infections caused per infectious individual vary widely (1.5–20).[45] In a modern population with no immunity provided via the smallpox vaccine, each infectious individual could be expected to cause an average of 3.5 to 6 new infections.[46]

2. Diagnosis

The last recorded case of smallpox occurred in 1977, and the World Health Organization declared global eradication in 1980.[47] Given the decades since its eradication, medical personnel may not be familiar with the clinical presentation of the disease. The primary clinical feature of the disease—the rash—may be mistaken initially for other diseases, such as chickenpox, an allergic contact dermatitis, or another orthopoxvirus such as monkeypox or cowpox.[48] Laboratory diagnosis can be made via real-time PCR analysis. Unlike plague, smallpox is not included on the NGDS 1's Warrior panel.[49]

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43 Ibid.

44 "Smallpox: Prevention and Treatment," Centers for Disease Control and Prevention, last reviewed January 22, 2019, accessed April 12, 2019, https://www.cdc.gov/smallpox/prevention-treatment/index.html

45 Raymond Gani and Steve Leach, "Transmission Potential of Smallpox in Contemporary Populations," Nature 414, no. 6865 (2001): 748–751.

46 Ibid.

47 Oxford et al., *Technical Reference Manual*.

48 Withers, *USAMRIIDs Medical Management*.

49 Department of Defense, *Next Generation Diagnostic System (NGDS).*

3. Control Measures

The primary method for controlling a smallpox outbreak is the administration of the smallpox vaccine to potentially exposed individuals. Routine vaccination of American civilians ended in 1972. Routine vaccination of U.S. military personnel ceased in 1989 but was reinstated in 2003 for individuals deploying to either the U.S. Central Command (USCENTCOM) area of responsibility (AOR) or the Korean Peninsula.[50] The vaccination of individuals deploying to the USCENTCOM AOR subsequently ended in 2014.[51] Therefore, only individuals deploying to the Korean Peninsula currently receive the smallpox vaccine.[52]

Prior to the 2014 change in the CENTCOM AOR vaccination policy, IDA analyzed how vaccine protection rates would decrease over time following a decision to suspend the program. The analysis indicated that within 10 years of a decision to suspend routine smallpox vaccinations, none of the U.S. forces would be fully protected.[53] Given that routine vaccination of individuals deploying to the CENTCOM AOR ceased in 2014, the findings of the previous IDA analysis suggest that vaccination coverage levels—with the exception of those who have deployed to the Korean Peninsula—should fall to zero by 2024.

Given the evolution of the smallpox vaccination requirements, the level of vaccination coverage within the PAR under consideration depends on its individuals' deployment histories, as well as the year in which the exposure occurs. This analysis assumed that nobody within the PAR was protected via the smallpox vaccine at the time of the exposure. This assumption is consistent with a future scenario, in which a negligible portion of the PAR had deployed to the CENTCOM AOR prior to 2014 or had deployed to the Korean Peninsula. The presence of vaccinated individuals in the PAR would reduce the operational impact of a smallpox outbreak by preventing individuals from becoming infected and transmitting the disease. The operational impact of a smallpox outbreak on a population with a high level of vaccine coverage (e.g., a PAR operating within the Korean Peninsula) will be discussed below.

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50 Withers, *USAMRIIDs Medical Management*.

51 Defense Health Agency–Immunization Healthcare Branch, "U.S. Central Command Smallpox Vaccine Exception to Policy," DHA-IHB Information Paper (Arlington, VA: Defense Health Headquarters, 29 September 2017).

52 In addition to those deploying to the Korean Peninsula, a small number of individuals belonging to specialized chemical, biological, radiological, or nuclear units or certain medical personnel are vaccinated also. Individuals in these specialized units are not considered in this analysis.

53 Disraelly et al., *Quick Reaction Analysis Series, No. 1601: Assessment of Operational Risk*.

Due to the lack of vaccination prior to the initial exposure event, the smallpox vaccine will be administered in response to the detection of smallpox within the population. The vaccine is able to provide immunity to those who are not infected, as well as terminate the infection of those who have been infected but have yet to develop symptoms (i.e., those incubating the disease). The probability of an individual's infection being terminated due to vaccination depends on how quickly they are administered the vaccine following their exposure, as shown in Table 2. Individuals for whom the vaccine does not take (i.e., those who receive the vaccine and still become ill) generally experience a less severe form of the disease and have a reduced case fatality rate.[54] That being said, these individuals still experience symptoms of sufficient severity to cause them to be classified as a casualty and are still capable of transmitting the disease.

Table 2. Probability of Smallpox Vaccine Terminating Infection in Pre-Symptomatic Individuals

Delay from Exposure to Vaccination (Days)	Probability of Terminating Infection
0–0.25	93%
0.25–1	90%
1–3	80%
4–7	25%
8–14	2%
>14	0%

Source: Oxford et al., *Technical Reference Manual*.

As is the case for nearly all pharmaceuticals, the smallpox vaccine has certain contra-indications. Individuals who are immune-deficient, pregnant, or are experiencing eczema or psoriasis should not receive the vaccine.[55] However, in the event of an ongoing smallpox outbreak, the U.S. Centers for Disease Control and Prevention (CDC) recommend administering the vaccine to all potentially exposed individuals who are not severely immunodeficient (e.g., bone marrow transplant recipients or persons infected with the human immunodeficiency virus).[56] Because severely immunodeficient individuals would likely be medically unfit for deployment, the IDA team assumed that the smallpox vaccine would be administered to the entire PAR as a PEP.

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54 Oxford et al., *Technical Reference Manual*.

55 Disraelly et al., *Quick Reaction Analysis Series, No. 1601: Assessment of Operational Risk*.

56 Brett W. Petersen et al., "Clinical Guidance for Smallpox Vaccine Use in a Postevent Vaccination Program," *Morbidity and Mortality Weekly Report* (MMWR) 64, no. RR02 (February 20, 2015): 1–26.

B. Qualitative Analysis of Factors Influencing Disease Surveillance

Figure 9 shows the qualitative framework as it applies to smallpox. Disease factors that are not applicable to smallpox are shown in gray. Disease factors that are applicable to smallpox are color coded, based on how they influence the operational disruption resulting from a smallpox outbreak. Factors that decrease operational disruption are shown in green and include the following:

- **Availability of diagnostic tests.** Confirmatory diagnostic tests can be made with PCR analysis.
- **Specific presentation.** The unique presentation of the rash (i.e., starting on the face and hands before spreading centrally) is indicative of the disease.
- **Availability of MCM.** The smallpox vaccine can provide immunity against infection, as well as terminate the infection of those who receive the vaccine prior to symptom onset.

Factors that increase operational disruption are shown in red and include the following:

- **Lack of diagnostic tests.** Although PCR analysis can be used for confirmatory diagnosis, smallpox is not part of the NGDS Warrior panel.
- **Generic presentation.** Despite the iconic rash that characterizes the clinical stage of illness, the prodromal stage features generic symptoms.
- **Rare disease.** Smallpox has been globally eradicated since 1980.
- **Disease not endemic to region.** Smallpox has been globally eradicated since 1980.

Factors that can either increase or decrease operational disruption are shown in orange and include the following:

- **More initial infections and fewer initial infections.** The number of initial infections may vary depending on the exposure source, route of exposure, and number of people in contact with the source.
- **Longer latent period.** The mean time from exposure to contagiousness is 15 days.[57]

[57] Oxford et al., *Technical Reference Manual*.

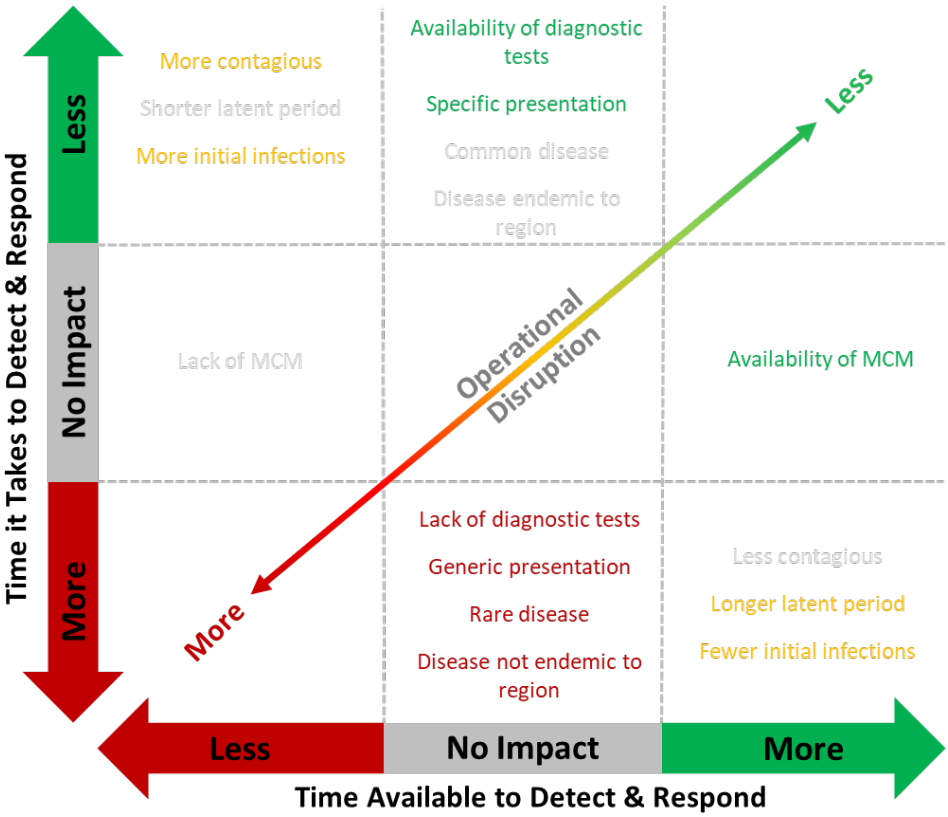

Figure 9. Framework to Assess Disease Factors' Influence on Disease Surveillance and Response: Smallpox

C. Quantitative Analysis of Operational Disruption

The quantitative analysis of smallpox was similar to that of plague. The IDA team first conservatively characterized how a smallpox outbreak would likely be detected and what response would most likely be taken. From this starting baseline, the IDA team then systematically varied the disease surveillance trigger and the way in which the control measure was implemented. Again, the goal was to determine the benefit—in terms of reducing operational disruption—of improving the timing of the disease surveillance and response processes.

Detecting a smallpox outbreak within the PAR will likely occur via the recognition of the iconic smallpox rash. Given the generic non-specific symptoms of the prodrome, it is unlikely that an individual would be diagnosed prior to the appearance of the rash. Although the progression of the rash presentation has uniquely distinguishing features that can facilitate its distinction from other diseases (e.g., first forming in the mouth, hands, feet, and face), medical personnel may misdiagnose it, due to unfamiliarity with the disease.

As was the case for plague, the IDA team decided that multiple cases of the disease would likely need to occur prior to medical personnel recognizing the disease as smallpox.

Again, the exact number of cases of smallpox that would be required to trigger detection is difficult to assess. The same previous IDA analysis that assumed 10 cases of plague would be required to recognize that a mass casualty event had occurred in a major U.S. city extended the same assumption to smallpox.[58] Again, given the smaller size of the PAR compared to a major city, fewer than 10 cases would likely be sufficient. The IDA team assumed that smallpox would be recognized in the PAR following the third case of rash—regardless of the timing of the cases and the MTF(s) in which they occur. The sensitivity of the results of the analysis to this assumption is discussed in Appendix A. A full list of assumptions relating to the smallpox analysis can be found at the end of this chapter.

The detection of smallpox within the PAR would represent a global health concern, likely triggering wide-ranging responses—many of which fall beyond the scope of this analysis. For the purpose of this analysis, the detection of smallpox would trigger the process of vaccinating individuals within the PAR. The IDA team assumed that a negligible amount of time would be required to decide to administer the smallpox vaccine following the detection of the disease. As discussed in Section 4.A.3, unless otherwise specified, the IDA team assumed that nobody in the PAR was vaccinated at the time of the initial exposure event.

Once the decision to administer the vaccine has been made, the vaccine must be transported to the PAR. Unlike the antibiotics used to respond to a plague outbreak, which were assumed to be available within the population itself, doses of smallpox vaccines will likely come from the Strategic National Stockpile (SNS). Vaccine doses from the SNS would need to be accessed at their location within the continental United States (CONUS), transported to the theater in which the PAR is operating, transported within the theater to the PAR, distributed to medical personnel within the PAR, and then finally administered to individuals within the population. The aforementioned IDA analysis of the smallpox vaccine assumed that 3 days were required to transport, distribute, and administer the vaccine.[59] This analysis made the same assumption. A discussion of the sensitivity of the analysis' results to this assumption is included in Appendix A.

To summarize, the IDA team used the administration of the smallpox vaccine within 3 days of the third case with rash as its baseline. As was the case for the plague response, the exact timing of the response will depend on how long it takes for three individuals to develop the rash, which itself will vary depending on individual variation in disease progression and transmission. Table 3 shows the 10th, median, and 90th percentile delay from the first appearance of symptoms in the PAR to the third case with rash. For outbreaks

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[58] Disraelly et al., *Biodetection Technology Enhancements Alternatives Analysis (AA)*, vol. II.

[59] Disraelly et al., *Quick Reaction Analysis Series, No. 1601: Assessment of Operational Risk*.

Table 3. Delay (Days) from First Appearance of Symptoms to Third Case with Smallpox Rash

Number of Initial Infections	10th Percentile	Median	90th Percentile
1	37.8	22.2	17.4
10	5.4	4.1	3.2
100	4.0	3.3	2.7

starting with 10 or 100 initial infections, the first three cases with rash are part of those who were initially exposed. Therefore, the delay only depends on the duration of their incubation and prodromal periods. On the other hand, for outbreaks starting with one initial infection, the second and third cases are a result of person-to-person transmission. Therefore, the delay depends on the timing of subsequent generations of the outbreak—resulting in a substantially longer delay.

In addition to the baseline, the IDA team also analyzed six variations of how a smallpox outbreak could be detected and responded to. Each variation systematically changed either the disease surveillance trigger or the delay in vaccinating the PAR. As was described during the plague analysis, even if the feasibility of implementing some of these changes is low, analyzing them can provide context as to the type of change that would be required to achieve a desired outcome. The six variations, as well as the baseline are summarized below.

- **Outbreak detected after third case with rash, population vaccinated with doses stockpiled in CONUS.** Conservatively characterized baseline—multiple cases with rash are required to trigger vaccination. Three days are required to transport and administer doses obtained from the SNS in CONUS.
- **Outbreak detected after third case with rash, population vaccinated with doses stockpiled in theater.** Multiple cases with rash are required to trigger vaccination. Two days (as compared to 3 days) are required to transport and administer doses obtained from a stockpile located within the theater in which the PAR is operating.
- **Outbreak detected after third case with rash, population vaccinated with doses stockpiled with the PAR.** Multiple cases with rash are required to trigger vaccination. One day (as compared to 3 days) is required to administer doses obtained from a stockpile located with the PAR.[60]

[60] Unlike most vaccines, which can be injected, the smallpox vaccine is administered percutaneously via puncturing the skin with a bifurcated needle. Medical personnel are unlikely to be familiar with this process and would require rapid training. The IDA team assumed that 24 hours would be required to administer the vaccine, even if it were stockpiled within the population.

- **Outbreak detected after first case with rash, population vaccinated with doses stockpiled in CONUS.** The first case with rash (as compared to three cases) triggers vaccination. Three days are required to transport and administer doses obtained from the SNS in CONUS.
- **Outbreak detected after symptom onset of first case, population vaccinated with doses stockpiled in CONUS.** The first case with prodromal symptoms (as compared to three cases with rash) triggers vaccination. Three days are required to transport and administer doses obtained from the SNS in CONUS.
- **Outbreak detected after symptom onset of first case, population vaccinated with doses stockpiled in with the PAR.** The first case with prodromal symptoms (as compared to three cases with rash) triggers vaccination. One day (as compared to 3 days) is required to administer doses obtained from a stockpile located within the PAR.
- **Pre-attack vaccination and vaccine doses from CONUS administered to exempt individuals following the third case with rash.** See discussion below.

When analyzing pre-attack vaccination, the IDA team assumed that individuals were vaccinated at some point prior to the exposure event to provide adequate time for immunity to develop. As was discussed earlier, the smallpox vaccine is contraindicated for certain individuals. Previous IDA work found that prior to the discontinuation of routine vaccination, 10% of forces deploying to the CENTCOM AOR were exempt from receiving the vaccine.[61] For any individual who is vaccinated, there is a 5% chance that the vaccine will not take (i.e., the vaccine is not efficacious and did not provide the appropriate immune response).[62] By combining both the exemption rate and the take rate, the IDA team modeled each individual who received the vaccine prior to the attack as having an 85.5% chance of being immune to infection at the time of the exposure event.

As discussed in the beginning of the chapter, the CDC recommendations for those who should not receive the smallpox vaccine depend on whether or not an outbreak is actively occurring. In the event of an ongoing outbreak, all individuals in the PAR would likely be administered the vaccine. In other words, individuals that were exempt from vaccination prior to the attack would not be considered exempt from post-attack vaccination. Therefore, for the analysis of pre-attack vaccination, the IDA team also modeled vaccination of exempt individuals in response to detecting the outbreak after the third case with rash. The vaccine was assumed to be stored in CONUS, and therefore 3 days are required to transport and administer the vaccine. Figure 10 shows the number of casualties for each of the disease surveillance and response variants considered.

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[61] Disraelly et al., *Quick Reaction Analysis Series, No. 1601: Assessment of Operational Risk*.

[62] Oxford et al., *Technical Reference Manual*.

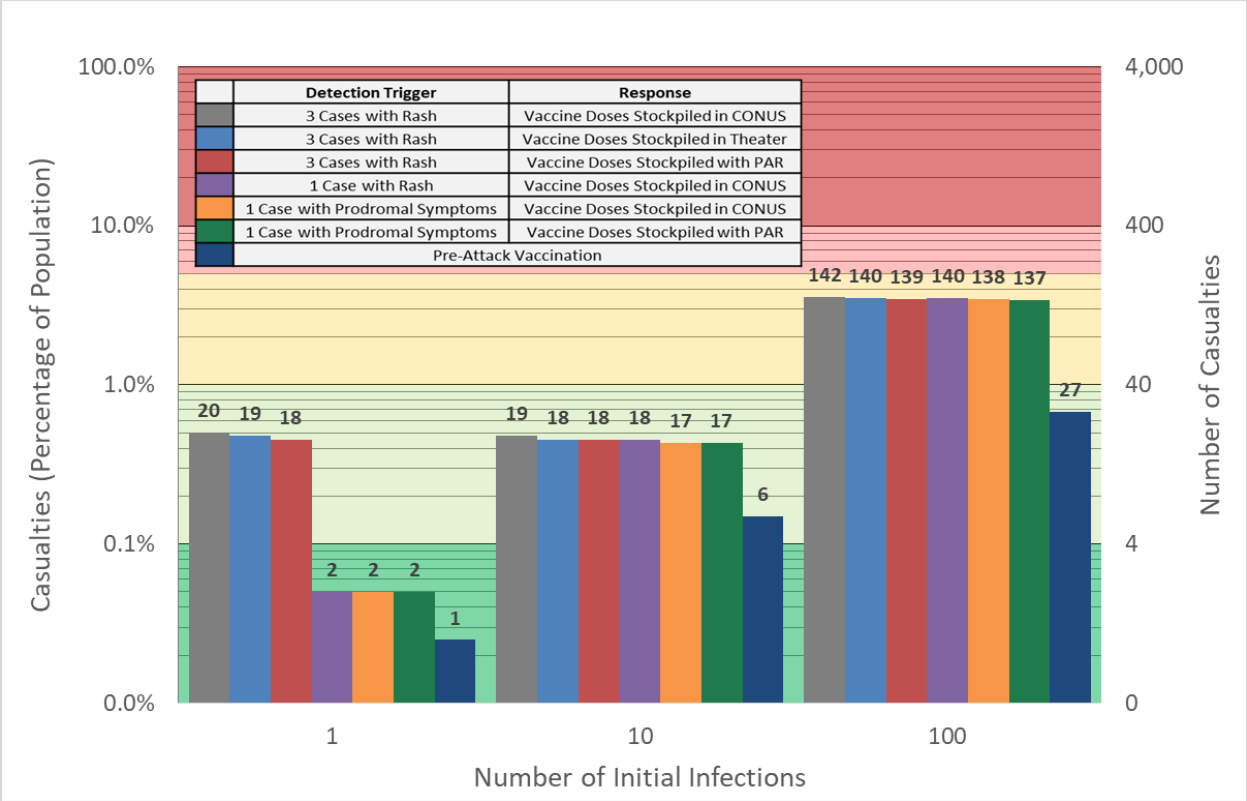

Figure 10. Number of Casualties due to Infection with Smallpox (90th Percentile) for Various Disease Surveillance Triggers and Delays in Vaccinating the Population

As discussed in the previous chapter, the IDA team considered the various disease surveillance triggers and responses in the context of a "what if?" analysis. The results presented in Figure 10 are intended to show the level of operational disruption that would result if the outbreak could be detected through the various disease surveillance triggers. What it would actually take to perform such a detection was not considered. As will be discussed in the subsequent section, these results can inform decision makers of the benefit of pursuing a capability that could detect an outbreak via a given disease surveillance trigger. Additional analysis is required to characterize the costs and feasibility of such a capability.

The IDA team also assessed the consequence of delaying the detection and response process. A full description of this assessment can be found in Appendix A. The IDA team found that the operational disruption caused by a smallpox outbreak was relatively insensitive to the assumed number of cases with rash that would be required to trigger the response process and the time required to transport and administer the vaccine. Even if 15 cases with rash were required to trigger the response process, outbreaks that cause more than 5% of the PAR (200 individuals) to become a casualty can be avoided. Similarly, even if the administration of the vaccine is delayed by 8 days following the third case with rash, outbreaks that cause more than 5% of the PAR from becoming a casualty can be avoided.

D. Discussion

The results of the smallpox analysis led to many of the same conclusions as the plague analysis. In general, commanders have the ability to respond to a smallpox outbreak in time to prevent the direct operational disruption caused by personnel loss. As shown in Figure 10, even when multiple cases with rash are required to trigger a response and multiple days are required to vaccinate the population, the response can limit casualties to less than 5% of the population. That being said, the indirect operational disruption caused by the presence of contagious individuals in the PAR may be unavoidable—even if the population is vaccinated prior to the exposure event.

As shown in the qualitative framework (see Figure 11), the availability of an MCM (i.e., the smallpox vaccine) increases the time available for the detection and response process. In addition, the strong disease surveillance signals provided by both the unique symptomology of smallpox and the availability of diagnostic tests to confirm suspected cases decrease the time it takes to detect the outbreak. Having more *time available* to detect and respond to the outbreak in combination with a detection and response process that *takes less time* results in smallpox outbreaks that cause minimal direct operational disruption.

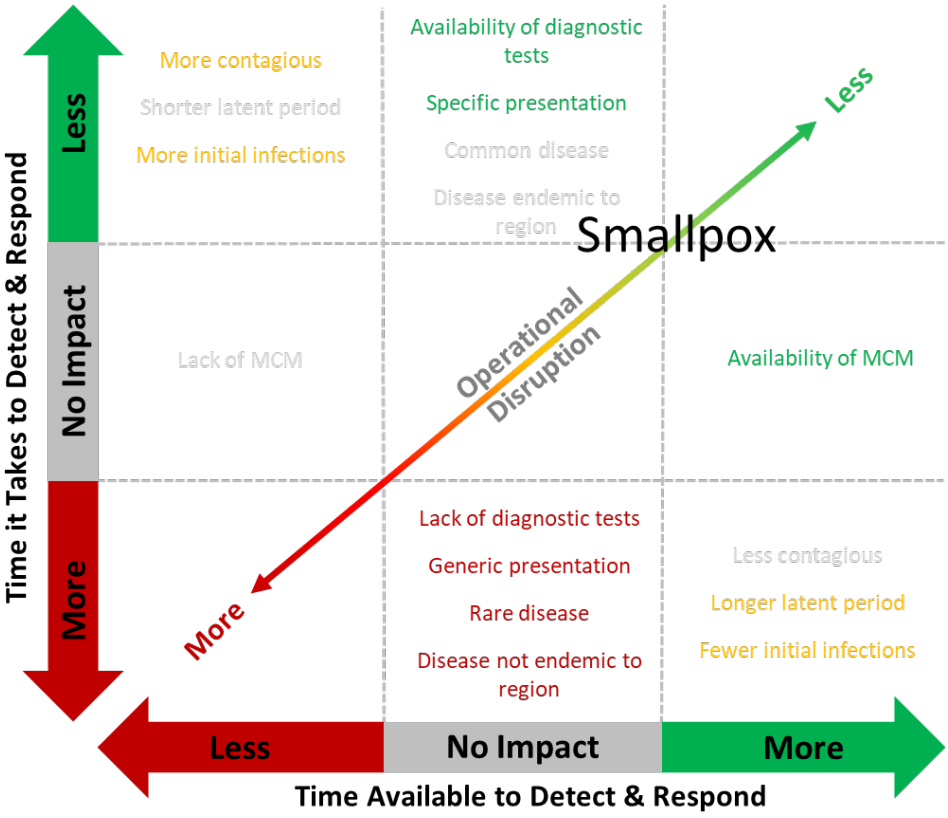

Figure 11. Framework to Assess Disease Factors' Influence on Disease Surveillance and Response: Smallpox

The results shown in Figure 10 can inform decisions related to the timing of the disease surveillance and response processes. For example, the results show a negligible benefit in stockpiling the smallpox vaccine in locations outside of CONUS. Reducing the time required to administer the vaccine by stockpiling it, either in the theater or with the PAR, reduced the size of the outbreak by, at most, two or three cases, respectively (as shown by comparing the blue and red bars to the gray bars in Figure 10). These results suggest that vaccine doses stored as part of the SNS can be accessed in time to prevent smallpox outbreaks from causing operational disruption due to personnel loss.

In general, the results shown in Figure 10 show that having an early diagnosis capability provides a negligible reduction in operational disruption. With the exception of outbreaks that start with one initial infection, detecting the outbreak at the time of either the onset of rash (purple bars) or prodromal symptoms (orange bars) of the first case results in outbreaks that are nearly the same size as those detected after three cases with rash (gray bars). For outbreaks starting with one initial infection, detecting the outbreak during the course of illness of the first case—as compared to requiring multiple cases—can prevent the outbreak from causing 0.1% of the PAR (four individuals) from becoming a casualty.

Vaccinating the population prior to the attack (dark blue bars) provided the greatest reduction in operational disruption. Pre-attack vaccination was the only response that was able to limit casualties to less than 1% of the PAR (40 individuals) for outbreaks starting with 100 initial infections. Even if the population was vaccinated prior to the attack, tens of cases of smallpox could still occur. Therefore, the indirect operational disruption caused by the presence of contagious individuals in the population may be unavoidable.

E. Summary of Assumptions for Smallpox Analysis

In addition to the overarching contagious disease model assumptions listed in Section 2.B.2 and Appendix B, the following were assumed during the analysis of smallpox:

- All individuals report to the medical system as soon as they develop prodromal smallpox symptoms.
- Unless stated otherwise, nobody within the PAR was protected via the smallpox vaccine at the time of the exposure.
- For the conservatively characterized baseline, medical personnel would detect smallpox in the PAR following the third case of rash—regardless of the timing of the cases and the MTF(s) in which they occur.
- The time required for the decision cycle following the detection of the outbreak would be negligible compared to the time to detect the outbreak and the time to administer the vaccine.

- The vaccine would be administered to all non-symptomatic individuals in the PAR.
- Three days are required to transport, distribute, and administer vaccine doses stored in CONUS.
- Two days are required to transport, distribute, and administer vaccine doses stored in the theater.
- One day is required to distribute and administer vaccine doses stored within the PAR.
- For the analysis of pre-attack vaccination, individuals were vaccinated at some point prior to the exposure event to provide adequate time for immunity to develop.

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5. Emerging Infectious Disease (EID)

A. Disease Overview

Although the term EID can be applied to a wide range of diseases, the IDA team focused its analysis on a novel disease. All EIDs—especially a novel pathogen—have some aspects that are unknown. When a novel pathogen first emerges, very little will be known about it. An understanding of the disease's presentation, incubation period, contagious period, contagiousness, and the availability of MCMs or diagnostic tests will likely be very limited or non-existent. The disease will become better characterized during the time following its initial emergence. During this time, the disease is still considered to be "emerging."[63] Therefore, a deployed military population's contact with a novel EID does not necessarily mean that the disease first emerged in the PAR; the population can come into contact with the disease during any point while the disease is still being characterized. The level of understanding of the disease at the time the PAR comes into contact with it will influence the ability of commanders to detect and respond to the outbreak in time to mitigate operational disruption.

To illustrate the challenges of detecting and responding to a poorly characterized disease, the IDA team analyzed a notional novel EID. The IDA team assumed that the PAR came into contact with the notional disease at some point shortly after the disease's emergence. Therefore, little would be known about the disease at the time of the outbreak. It is important to reiterate that this chapter only analyzes a single notional disease. The conclusions relating to this disease illustrate the challenges associated with responding to an outbreak of a poorly understood disease. That being said, the results—especially those from the quantitative analysis—are specific to this notional disease. These results may vary significantly for other diseases with different incubation periods, contagious periods, or contagiousness.

1. Disease Progression

The notional novel disease considered in this chapter was based on SARS. SARS was selected as the surrogate for the notional disease because its disease progression and transmission are relatively well understood. The notional novel EID analyzed by the IDA team

[63] Burr et al., *Emerging Infectious Disease Study*.

is characterized by the same disease progression and transmissibility as SARS. The disease progression is as follows:

- A 2- to 7-day incubation period; followed by
- A 2- to 7-day contagious febrile prodrome characterized by: fever, rigors (chills), myalgia (muscle pain), and headache; followed by
- A 3- to 7-day contagious lower respiratory phase characterized by: shortness of breath, dry nonproductive cough, and hypoxemia (low blood oxygen levels) in fatal cases.[64]

The CFR of the disease is approximately 10%. Individuals infected with the notional disease are contagious for the duration of their symptoms.[65] The average number of new infections caused per infectious individual in an entirely susceptible population is 1.63, although individual superspreaders may generate a substantially higher number of new infections.[66]

2. Diagnosis

The ability to diagnose a novel disease depends on how well the disease has been characterized since its emergence. During the early stages of a disease's emergence, there will be a period of time when little is known about the disease's clinical presentation. Diagnosis during this time may not be possible until a standardized case definition has been established. Even after a standardized case definition is developed, diagnostic tests would likely not be available to confirm clinically suspected or presumptive cases. In the event that the disease presents generic flu-like symptoms (as is the case for the notional novel EID under consideration here), medical personnel will likely have a difficult time differentiating the disease from similar, more common diseases and may therefore fail to recognize the disease and misdiagnose individuals as having a more common infection.

3. Control Measures

There is no guarantee that existing MCMs will be effective at preventing or terminating infection caused by a novel pathogen. Even if an existing MCM is effective, medical personnel may not know to administer it or have it available to support prophylaxis or

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64 "Preliminary Clinical Description of Severe Acute Respiratory Syndrome," Centers for Disease Control and Prevention, accessed March 7, 2019, https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5212a5.htm.

65 "Frequently Asked Questions About SARS," Centers for Disease Control and Prevention, accessed March 7, 2019, https://www.cdc.gov/sars/about/faq.html.

66 J. O. Lloyd-Smith et al., "Superspreading and the Effect of Individual Variation on Disease Emergence," *Nature* 438, no. 7066 (November 17, 2005): 355–359.

treatment needs. In the event that MCMs are unavailable for a novel disease, controlling the outbreak will likely require other forms of response, such as patient isolation or quarantine. Previous IDA work concluded that—in general—these non-pharmaceutical responses are less effective at mitigating the impact of a contagious disease outbreak than MCMs.[67] Furthermore, non-pharmaceutical control measures have the potential to disrupt operations themselves. For example, potentially exposed and infected individuals who are placed into quarantine may be unable to perform their duties.

B. Qualitative Analysis of Factors Influencing Disease Surveillance

Figure 12 shows the qualitative framework as it applies to the notional novel EID. As with plague and smallpox, disease factors that are not applicable to the disease are shown in gray. Disease factors that are applicable to the notional disease under consideration are color coded, based on how they influence the operational disruption resulting from an outbreak of the disease. Unlike plague and smallpox, none of the factors that reduce operational disruption are applicable to the notional novel EID (i.e., there are no green factors in the framework). Factors that the IDA team assumed could increase the operational disruption from the notional disease are shown in red and include the following:

- **Lack of MCMs.** MCMs were not available to control the spread of the novel EID under consideration
- **Lack of diagnostic tests.** Diagnostic tests were not available to diagnose infected individuals
- **Generic presentation.** The non-specific symptoms of the illness—along with the possibility of a poorly defined or nonexistent case definition—may confound diagnosis
- **Rare disease.** The prevalence of a novel disease may be low or unknown
- **Disease not endemic to region.** The global or regional distribution of the disease may be limited or unknown

Factors that the IDA team assumed could either increase or decrease the operational disruption from the notional disease are shown in in orange and include the following:

- **Shorter latent period.** The latent period of the notional disease is 2–7 days.[68]

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[67] Burr et al. *Emerging Infectious Disease Study*.

[68] Because infected individuals are contagious for the duration of their symptoms, the disease's incubation period (time from exposure to symptom onset) is the same as its latent period (time from exposure to contagiousness).

- **More initial infections and fewer initial infections.** The number of initial infections may vary depending on the exposure source, route of exposure, and number of people in contact with the source.
- **Less contagious.** Although the notional novel EID under consideration is relatively less contagious, at the time of the outbreak, a lack of knowledge about the disease could result in a limited understanding of the disease's contagiousness and route of transmission.

It is important to reiterate that Figure 12 shows the framework as applied specifically to the notional novel EID to illustrate the challenges of detecting and responding to a novel disease outbreak. In other words, the choice of which parameters are gray vs. green, red, or orange was based on SARS and may not be applicable to other EIDs. Other EIDs may have different applicable disease factors.

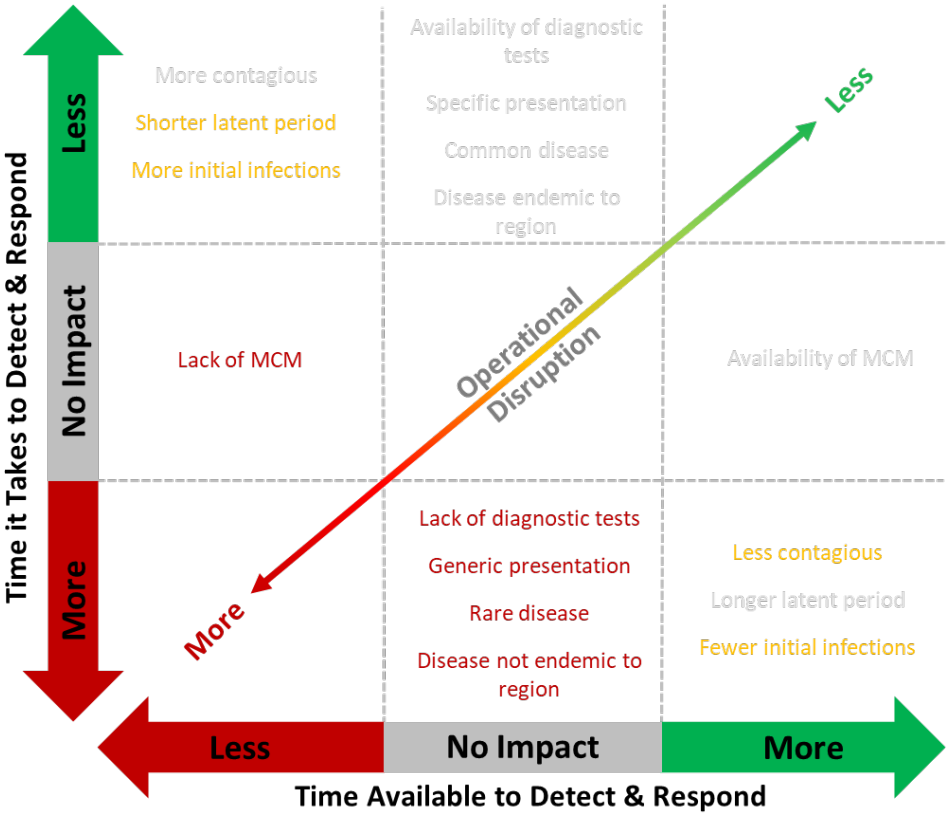

Figure 12. Framework to Assess Disease Factors' Influence on Disease Surveillance and Response: Notional Novel EID

C. Quantitative Analysis of Operational Disruption

The IDA team used a slightly different analytic approach for the quantitative assessment of the notional novel EID. Unlike the plague and smallpox analyses, which focused on specific individual diseases, the analysis of EIDs has a wider scope. Although the IDA team selected a single notional disease on which to focus, the goal of this section of the analysis is to assess how limited disease knowledge and capabilities influence the detection and response processes. Therefore, instead of simulating specific disease surveillance triggers and response strategies, as was done for plague and smallpox, the IDA team employed a parametric approach. This approach considered a range of possible

- Disease surveillance triggers,
- Delays in control measure implementation, and
- Overall ability of the control measure to disrupt disease transmission (i.e., control measure efficacy).

Parameters that describe the disease (e.g., latent period, contagious period, and contagiousness) were not varied. By parametrically varying the three components of the disease surveillance and response processes, the IDA team was able to characterize the circumstances that minimize operational disruption for the illustrative novel EID. A list of assumptions relating to the EID analysis can be found at the end of this chapter.

1. Disease Surveillance Triggers

As described previously, laboratory diagnostic tests will unlikely be available to provide a confirmatory diagnosis for a novel disease. Therefore, detection of the disease within the population would occur via symptom recognition. The ability to recognize the symptoms of the disease and diagnose infected individuals depends on the availability of information about the disease at the time of the outbreak. If the outbreak is occurring shortly after the emergence of the disease, then knowledge of its symptoms may be limited or nonexistent. Medical personnel will unlikely be able to correctly diagnose ill individuals. In this case, detection of the outbreak would likely occur via the observation of a higher than usual prevalence of illness in the population. In other words, even if medical personnel cannot determine the causative disease of the outbreak, they could still recognize that an outbreak of *something* was occurring.

The ability to recognize an atypical prevalence of disease requires an understanding of normal baseline levels of illness for the PAR. These baseline levels of illness would likely vary with time (e.g., increase during the influenza season), location (e.g., higher in regions with more endemic diseases), and operation (e.g., a spike in illness immediately following deployment to a new location). The better the baseline rates of illness are known, the easier it will be for medical personnel to recognize a deviation from these levels. To account for varying ability to recognize atypical disease prevalence in the population, the

IDA team parametrically varied the threshold number of new cases of disease presenting within a 1-day period to trigger the response process.

Using the number of new cases of disease within a 1-day period as the metric for the disease surveillance trigger has two limitations. First, it does not account for the impact of observing multiple new cases of disease over consecutive days—as compared to within a single day. Second, it does not consider where the cases report to the medical system. It assumes that all cases occur in the same local medical system or are all reported in a timely fashion to allow for rapid aggregation and identification of an outbreak.

To contextualize typical levels of illness in an operational setting, the IDA team analyzed disease and nonbattle injury (DNBI) admissions data from the United States Marine Corps (USMC) during Operation Iraqi Freedom (OIF).[69] The dataset defined "admissions" as casualties that required at least 24 hours of care in a medical treatment facility. The IDA team focused on DNBI rates that occurred from November through December 2004, which is the period of time when USMC forces were leading the offensive against the Iraqi insurgency stronghold of Fallujah. The data captured the number of battle injuries, non-battle injuries, and disease admissions per day.[70] Because the size of the USMC PAR considered in the data set (9,200 individuals) was different than the size of the PAR under consideration in this analysis, the IDA team scaled the data.

The corresponding daily disease admission rate (per 4,000 individuals) is shown in Figure 13. It is important to reiterate that the data shown in Figure 13 represent only individuals who were admitted and spent more than 24 hours in a Role 3 MTF. The data do not include individuals who reported to Role 1 or Role 2 MTFs and returned to their unit in the same day. Therefore, the data underestimate the number of individuals reporting to the medical system due to illness. The daily number of disease admissions varies. On many days, there were no new cases of disease, while on others, there were multiple. The IDA team used the range of daily disease admissions shown in Figure 13 to contextualize the incidence of illness in an operational environment.

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69 James Zouris, Edwin D'Souza, and Jay Walker, *Medical Planning Factors Used in Medical Requirements Processes Assessment* (San Diego, CA: Naval Health Research Center, 2010).

70 Ibid.

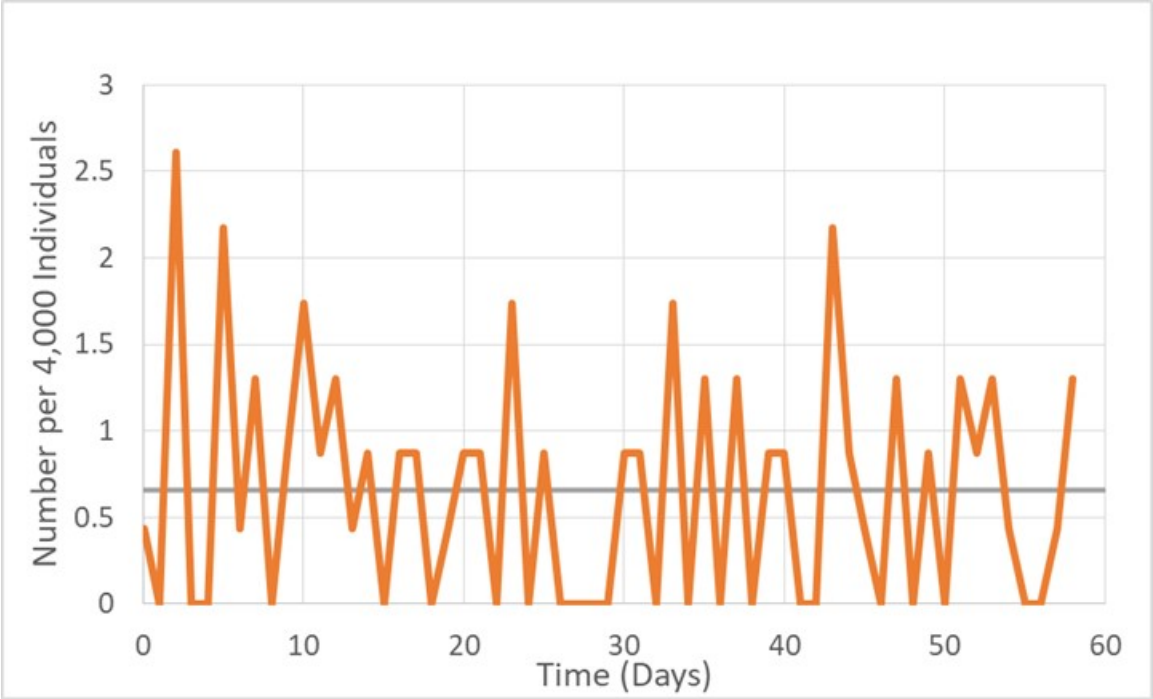

Figure 13. Daily (Orange) and Mean (Gray) Disease Admissions per 4,000 Individuals over 2 Months of USMC Maneuver Operations in OIF

2. Delays in Control Measure Implementation

Following the detection of an outbreak of a novel—and potentially unknown—disease in the population, medical personnel and commanders will need to decide how to respond. In the event that the disease has been detected but not identified, medical personnel may take only limited infection control measures. If so, the implementation of the most effective—and most high-risk—control measures may be delayed.

Medical personnel will likely use MCMs in an attempt to treat ill individuals and protect individuals from being infected. In the event that available MCMs are not effective for the disease, multiple days could pass as medical personnel try a variety of MCMs before realizing that a non-pharmaceutical response is needed to disrupt transmission.

Once the decision to implement a non-pharmaceutical control measure has been made, additional logistical constraints could further delay its implementation. For example, isolating contagious individuals could require: establishing isolation rooms or wards within pre-existing medical infrastructure; converting pre-existing medical facilities into isolation facilities; or establishing new specialized isolation facilities. Like isolation, quarantining potentially exposed or infected individuals could also require the establishment of specialized facilities. In addition, quarantine requires contact tracing of potentially exposed and infected individuals. The personnel required to implement and operate these responses would likely need to be obtained by reassigning individuals in the PAR or by augmenting

the PAR. Meeting these personnel requirements could further delay the implementation of these control measures.

3. Control Measure Efficacy

The overall ability of a non-pharmaceutical control measure to reduce disease transmission depends on the type of response and how it is implemented. For example, the effectiveness of an isolation or quarantine strategy is tied to the ability of medical personnel to correctly identify all infected and potentially exposed and infected individuals, respectively. A response that can isolate and quarantine a greater portion of the infected and potentially infected individuals will be better able to reduce disease transmission. During an outbreak of a novel pathogen, correctly identifying infected individuals may be complicated by a vague or non-existent case definition. In addition, the mechanism of disease transmission may not be well understood, and therefore identifying potentially exposed and infected individuals for quarantine may be a challenge.

Even if infected or potentially exposed and infected individuals can be identified, the specifics of how best to isolate or quarantine them may be unknown. If the mechanism of disease transmission is not well understood, inadequate isolation precautions may fail to effectively reduce transmission. Similarly, unless the duration of the incubation period of the disease is known, it may be difficult to know how long to quarantine potentially exposed and infected individuals. In addition to these challenges, operational circumstances can further limit the efficacy of a response. For example, a high operational tempo or large geographic distances between combat units and isolation facilities could further delay the isolation of infected individuals. Furthermore, a BW attack has the potential to generate a large number of near-simultaneous cases requiring isolation. Such a high demand could overwhelm pre-existing isolation capabilities, resulting in inadequate isolation of contagious individuals.

Instead of modeling a specific response, the IDA team considered a generalized control measure with various levels of efficacy (95%, 75%, 50%, and 25%). The efficacies represent the amount that disease transmission would be reduced once the response was implemented. By considering these various control measure efficacies, the IDA team could analyze the range of possible ways in which commanders could respond to the outbreak.

Although the IDA team analyzed a highly effective response efficacy (i.e., 95%), such a capability may not be possible as part of a response to a novel EID. Such a high response efficacy would be expected for a MCM response—as was the case for population-wide antibiotics administration in response to plague; however, it may be very difficult to obtain such an effective response with non-pharmaceutical control measures. For example, for a patient isolation response to be 95% effective, nearly every contagious individual would need to be completely isolated almost immediately after becoming contagious. Given all the aforementioned limitations associated with a lack of disease knowledge and operational

burdens, it is unlikely that such an effective isolation capability could be employed in response to a novel EID outbreak in a deployed setting.

4. Results of Parametric Analysis

Table 5, Table 6, and Table 7 show the results of the parametric quantitative analysis for outbreaks starting with 1, 10, or 100 initial infections, respectively. Each table shows the percentage of the PAR becoming casualties (90th percentile case) for various combinations of the following:

- The minimum number of new cases that must occur in a 1-day time period to trigger the response process (i.e., *Threshold Number of New Cases in a Day to Trigger Response*);
- The efficacy of the control measure that is implemented (i.e., *Control Measure Efficacy*); and
- The number of days it takes to implement the control measure following the trigger to respond (i.e., *Control Measure Implementation Delay (Days)*).

The cells of the table are color coded to show the casualty thresholds that were used to measure the level of operational disruption (see Table 4). It bears repeating that the results shown below are specific to the notional disease used in the analysis. Additional analysis would be required to generate a similar set of tables for additional diseases.

Table 4. Color Coding Used in Table 5, Table 6, and Table 7

Percentage of the PAR Becoming a Casualty	Number of Casualties
<0.1%	<4
0.1%-1%	4-40
1%-5%	40-200
5%-10%	200-400
>10%	>400

The following example illustrates the use of the tables for an outbreak starting with one initial infection (Table 5). Consider the case in which the response to the outbreak was not triggered until five new cases of the disease were reported to the medical system on the same day. If the implementation of the control measure was delayed by 3 days, then the outbreak would cause 1.0%, 1.2%, 1.9%, or 8.6% of the PAR to become a casualty if the control measure was 95%, 75%, 50%, or 25% effective, respectively.

Table 5. Percentage of Population Becoming a Casualty (90th Percentile) for Varying Control Measure Efficacies and Delays in Implementation for Outbreaks Starting with *One Initial Infection*

Control Measure Efficacy	Control Measure Implementation Delay (Days)	Threshold Number of New Cases in a Day to Trigger Response							
		1	2	3	4	5	8	10	15
95%	1	<0.1%	0.2%	0.4%	0.6%	0.8%	1.8%	2.6%	4.8%
	3	<0.1%	0.3%	0.4%	0.7%	1.0%	2.2%	2.9%	5.8%
	7	0.1%	0.4%	0.6%	0.8%	1.2%	2.7%	3.8%	6.8%
75%	1	<0.1%	0.3%	0.5%	0.8%	1.1%	2.5%	3.5%	6.4%
	3	0.1%	0.3%	0.6%	0.9%	1.2%	2.6%	4.1%	7.6%
	7	0.2%	0.5%	0.7%	1.0%	1.6%	3.3%	4.8%	8.8%
50%	1	0.2%	0.4%	0.8%	1.1%	1.6%	4.3%	6.3%	>10%
	3	0.2%	0.5%	0.8%	1.3%	1.9%	4.5%	7.1%	>10%
	7	0.3%	0.6%	1.1%	1.4%	2.6%	5.5%	7.7%	>10%
25%	1	0.5%	1.1%	2.0%	4.5%	8.9%	>10%	>10%	>10%
	3	0.5%	1.2%	2.1%	4.5%	8.6%	>10%	>10%	>10%
	7	0.6%	1.3%	3.1%	5.0%	>10%	>10%	>10%	>10%

Table 6. Percentage of Population Becoming a Casualty (90th Percentile) for Varying Control Measure Efficacies and Delays in Implementation for Outbreaks Starting with *10 Initial Infections*

Control Measure Efficacy	Control Measure Implementation Delay (Days)	Threshold Number of New Cases in a Day to Trigger Response							
		1	2	3	4	5	8	10	15
95%	1	0.3%	0.4%	0.4%	1.0%	1.7%	3.8%	5.4%	9.5%
	3	0.4%	0.5%	0.5%	1.2%	1.9%	4.3%	5.8%	>10%
	7	0.7%	0.7%	0.8%	1.6%	2.6%	5.2%	7.1%	>10%
75%	1	0.7%	0.8%	0.8%	1.5%	2.4%	5.0%	6.7%	>10%
	3	0.8%	0.9%	1.0%	1.7%	2.7%	5.4%	7.3%	>10%
	7	1.1%	1.2%	1.4%	2.2%	3.5%	6.7%	8.9%	>10%
50%	1	3.6%	3.6%	3.8%	5.5%	7.6%	>10%	>10%	>10%
	3	3.7%	3.7%	4.1%	6.1%	8.2%	>10%	>10%	>10%
	7	4.6%	4.6%	5.1%	7.1%	>10%	>10%	>10%	>10%
25%	1	>10%	>10%	>10%	>10%	>10%	>10%	>10%	>10%
	3	>10%	>10%	>10%	>10%	>10%	>10%	>10%	>10%
	7	>10%	>10%	>10%	>10%	>10%	>10%	>10%	>10%

Table 7. Percentage of Population Becoming a Casualty (90th Percentile) for Varying Control Measure Efficacies and Delays in Implementation for Outbreaks Starting with *100 Initial Infections*

Control Measure Efficacy	Control Measure Implementation Delay (Days)	Threshold Number of New Cases in a Day to Trigger Response							
		1	2	3	4	5	8	10	15
95%	1	2.9%	2.9%	2.9%	2.9%	2.9%	3.0%	3.0%	3.1%
	3	3.2%	3.2%	3.2%	3.3%	3.3%	3.4%	3.5%	3.6%
	7	4.5%	4.6%	4.7%	4.7%	4.8%	4.9%	5.1%	5.3%
75%	1	5.2%	5.2%	5.3%	5.2%	5.2%	5.3%	5.3%	5.4%
	3	5.5%	5.6%	5.6%	5.6%	5.6%	5.7%	5.8%	6.1%
	7	7.1%	7.2%	7.3%	7.3%	7.4%	7.5%	7.7%	8.0%
50%	1	>10%	>10%	>10%	>10%	>10%	>10%	>10%	>10%
	3	>10%	>10%	>10%	>10%	>10%	>10%	>10%	>10%
	7	>10%	>10%	>10%	>10%	>10%	>10%	>10%	>10%
25%	1	>10%	>10%	>10%	>10%	>10%	>10%	>10%	>10%
	3	>10%	>10%	>10%	>10%	>10%	>10%	>10%	>10%
	7	>10%	>10%	>10%	>10%	>10%	>10%	>10%	>10%

D. Discussion

A novel EID poses numerous challenges to disease surveillance. As shown in the qualitative framework (reproduced in Figure 14), the lack of a highly effective control measure—such as an MCM—reduces the time available for disease surveillance to trigger a response in time to mitigate operational disruption. In addition to having less *time available*, detecting and responding to a novel EID outbreak may take more time than it would for a well-understood disease. A lack of diagnostic tests, a generic presentation, and medical personnel's unfamiliarity with the disease can confound disease surveillance. Having less *time available* to detect and respond to the outbreak in combination with a detection and response process that *takes more time* can result in operational disruption.

For the notional novel EID, even if the outbreak is detected on the first case, large outbreaks may be unavoidable. Outbreaks that cause more than 10% of the PAR (400 individuals) to become a casualty may be unavoidable if the control measure efficacy is at most 25% or 50% effective for outbreaks starting with 10 or 100 initial infections, respectively—regardless of when the disease is detected.

If an outbreak of a novel EID occurred in a population with a background disease rate similar to that shown in Figure 13, detecting the outbreak via the observation of an atypical disease rate in time to prevent operational disruption may be difficult. Based on the

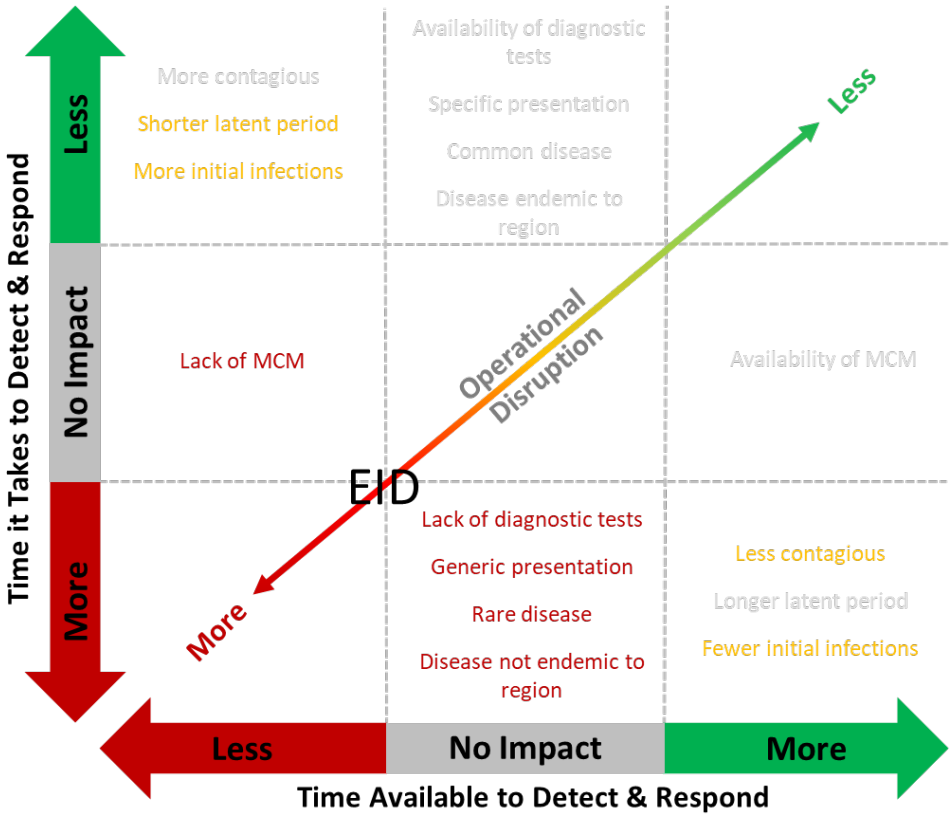

Figure 14. Framework to Assess Disease Factors' Influence on Disease Surveillance and Response: Notional Novel EID

background disease rate shown in Figure 13, it is possible that an additional one, two, three, or even four new cases per day across the PAR may not be considered atypical by medical personnel—especially if the cases report to multiple MTFs.

If five additional new cases of illness in 1 day are required to trigger a response, then preventing 1% of the population (40 individuals) from becoming a casualty may not be possible for outbreaks of the notional disease starting with 10 or more initial infections; for outbreaks starting with one initial infection, it is only possible if the response is 95% effective.

The results presented in Table 5, Table 6, and Table 7 show that the level of operational disruption resulting from an outbreak of this notional EID depends most on the efficacy of the control measure, followed by how quickly the outbreak is detected, and then by the delay in implementing the control measure. Therefore, developing more effective control measure capabilities (e.g., fielding an MCM) would likely provide a greater benefit to reducing operational disruption than developing capabilities that improve how quickly an outbreak can be detected, or how quickly a control measure can be implemented. Again, these results apply to this notional EID only, and may vary significantly depending on the actual disease presentation.

Given the constrained time available for disease surveillance, commanders may need to respond at the first sign of an outbreak. Time may not be available to wait to gain more information about the disease and the outbreak. Commanders may need to implement control measures with limited knowledge of the outbreak. However, given the potentially disruptive nature of some non-pharmaceutical control measures, commanders may wish to delay their implementation to gain additional situational awareness. Unfortunately, such a delay may result in a response missing the limited window of opportunity to minimize operational disruption.

E. Summary of Assumptions for EID Analysis

In addition to the overarching contagious disease model assumptions listed in Section 2.B.2 and Appendix B, the following were assumed during the analysis of the novel EID:

- The PAR comes into contact with the notional disease at some point shortly after the disease's emergence.
- MCMs are not available to control the spread of the novel EID.
- Diagnostic tests are not available to diagnose infected individuals.
- All individuals report to the medical system as soon as they develop the prodromal symptoms of the EID.
- All cases occur in the same local medical system or are all reported in a timely fashion to allow for rapid aggregation and identification of an outbreak.

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6. Observations and Recommendations

A. General Observations

The analysis of the three diseases led to a dichotomous conclusion on the ability of disease surveillance to trigger a response in time to minimize the operational disruption resulting from a contagious disease outbreak. On one hand, although the indirect operational disruption due to the presence of contagious individuals may be unavoidable, commanders have the ability to detect and respond to an outbreak of a known disease (e.g., plague or smallpox) in time to prevent direct operational disruption due to personnel loss. On the other hand, commanders will likely need to initiate high-consequence decisions with potentially incomplete knowledge of the situation to minimize operational disruption from an outbreak of an unknown disease—especially for a novel EID outbreak.

The conclusions relating to the plague and smallpox surveillance and response processes are driven primarily by two factors. First, because available MCMs for these diseases are highly effective at disrupting disease transmission, there is a long time window in which they can be implemented and still minimize operational disruption. This allows more time for disease surveillance to trigger the detection and response processes. As shown in the qualitative framework (reproduced in Figure 15), the availability of an MCM provides more time available to detect and respond to the outbreak and still mitigate operational disruption.

Second, both diseases feature a period of specific and severe symptoms. Although the severe symptoms pose a life-threatening risk to the casualty, their presence serves as a strong signal for disease surveillance and identification. This signal is then amplified by the presence of multiple cases with similar presentation. Furthermore, the diagnostic tests that are available for both diseases can confirm a suspected or probable clinical diagnosis. As shown in Figure 15, these disease surveillance signals decrease the time it takes to detect and respond to the outbreak.

Together, the benefits afforded by the availability of an MCM and the disease surveillance signals can compensate for the potential delays in the detection and response processes due to medical personnel's possible unfamiliarity with these two diseases. Therefore, commanders will likely be able to detect an outbreak of either plague or smallpox in time to implement a response that can prevent direct operational disruption due to personnel loss.

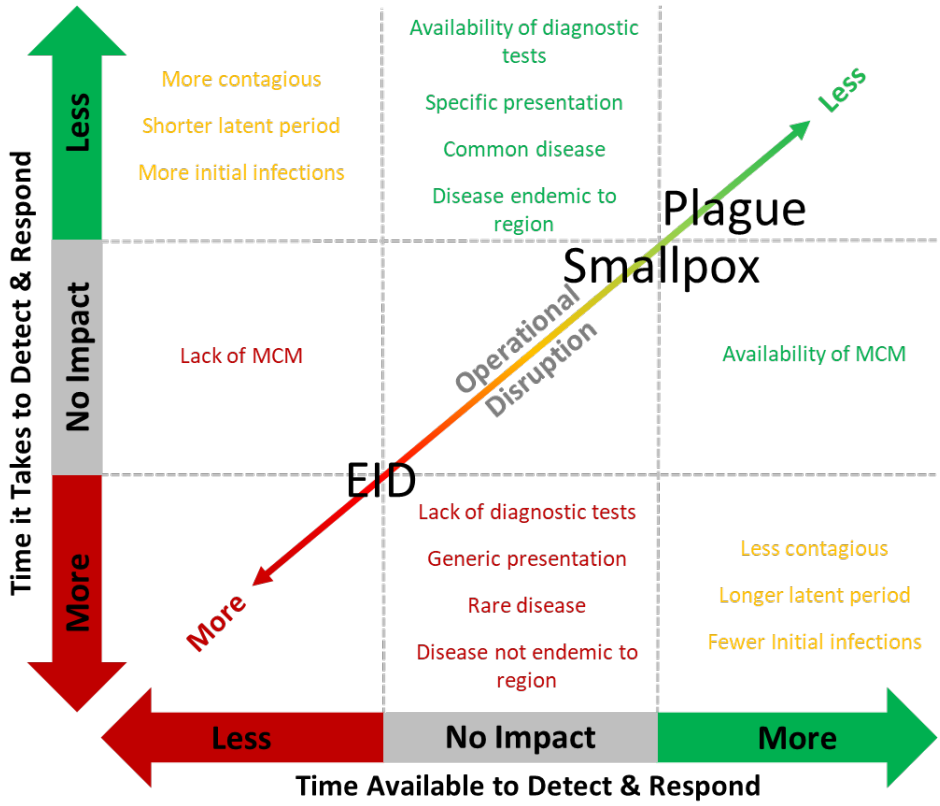

Figure 15. Framework to Assess Disease Factors' Influence on Disease Surveillance and Response

Although disease surveillance is capable of triggering a response in time to minimize the operational disruption resulting from a plague or smallpox outbreak, the impact of the disease on the population may be unavoidable. The outbreak can still result in tens (or more) of contagious individuals, whose mere presence can disrupt operations. The presence of a contagious disease within the population could cause allies or a host nation to withdraw support in fear of the disease spreading to their own personnel. In addition, theater-level restriction of movement (ROM) into or out of the PAR could impact the logistics and support the PAR receives. Because a low number of contagious individuals may be unavoidable, commanders should be prepared to conduct their missions under these constraints.

In contrast to plague and smallpox, reducing the operational disruption caused by a novel EID outbreak may be substantially more difficult. If the MCM for the EID is unknown—as would likely be the case for a novel viral disease—or ineffective—as would likely be the case for a drug-resistant strain of an existing disease—the window of opportunity to intercede is reduced. Even if an outbreak is detected quickly, the available control measures may lack the requisite efficacy to prevent operational disruption. In such a case, substantial personnel loss (e.g., > 10% of the PAR) may be unavoidable.

The clinical presentation of an EID may confound surveillance. Diseases may present with only generic influenza-like symptoms or may lack a well-characterized case definition. Furthermore, medical personnel may be unfamiliar with the presentation of a novel disease. All of these factors would increase the time it takes to detect the outbreak. In such a case, an outbreak may only be detected once it has infected a sufficient number of people to be noticeable above the typical rate of disease within the population. This delay in detecting the outbreak, in combination with the limited time available to detect and respond, can result in substantial operational disruption.

These challenges are further complicated by the potential for operational disruption caused by non-pharmaceutical control measures—such as patient isolation or quarantine. Commanders may wish to delay implementing these types of control measures to ensure that the threat posed by the outbreak warrants such a response. However, postponing the response to gain more information about the outbreak may result in more operational disruption. To minimize operational disruption, commanders may have to make the high-consequence decision of implementing a response based on the limited information available when the outbreak is first detected.

B. Recommendations for Capability Development

The IDA team provides the following recommendations relating to mitigating operational disruption caused by contagious diseases. While these recommendations may not be surprising, they remain important. The order in which the recommendations are presented does not reflect their priority or importance.

1. Invest in Technologies that Facilitate Rapid MCM Development

Of the factors that influence the time available to detect and respond to an outbreak, the existence of a highly effective MCM is one of the most critical. Even when their administration is substantially delayed, antibiotics and the smallpox vaccine can quickly stop an outbreak of plague and smallpox, respectively.

The lack of a highly effective MCM—as would likely be the case for a novel viral EID outbreak—reduces the time in which commanders can respond and mitigate casualties. In general, the lower efficacy of non-pharmaceutical control measures means the response can only be effective if it is implemented sooner. This lack of time requires rapid detection of the outbreak within the population.

The IDA team recommends investment in technologies that facilitate rapid MCM development. Reducing the time to develop and field an MCM for a recently emerged disease increases the likelihood of having the drug available in the event that a deployed military population comes into contact with the disease. MCMs for diseases that lack one should be considered a high priority. In particular, diseases that may take longer to detect

within a population—such as those with non-specific symptoms or those that lack diagnostic tests—should be targeted for MCM development. The availability of an MCM for these types of diseases would increase the time available to detect and respond to an outbreak, alleviating the operational disruption caused by difficulties associated with detection.

2. Develop CONOPS for and Conduct a Cost-Benefit Analysis on Diagnostic Capabilities at Lower Roles of Medical Care

In general, the plague and smallpox analysis showed that having the ability to hasten MCM administration by detecting the outbreak through an early diagnosis provided limited improvement in reducing the size of the outbreak. Therefore, fielding a diagnostic capability that can detect outbreaks of these diseases while the patient is at a lower role of care may provide a limited benefit to reducing operational disruption. Diseases with distinguishable and severe symptoms (such as plague and smallpox) provide medical personnel with a strong signal for disease surveillance. This strong signal—especially in combination with the availability of a highly effective MCM—can prevent outbreaks from causing operational disruption due to personnel loss.

In contrast, the ability to perform diagnostic testing at lower roles of medical care could assist in the detection of outbreaks of diseases with generic presentations. Such a capability could allow outbreaks to be detected earlier than they would be if disease surveillance relied solely on the recognition of atypical disease rates. Additional analyses should be conducted to fully characterize the benefit of fielding a diagnostic capability at lower roles of medical care, as compared to higher roles. The following questions should be considered as part of the assessment:

- What is the concept of operations for determining who gets tested?
- Will samples taken during the early stages of illness contain a detectable quantity of infection indicators?
- What are the fiscal, personnel, and operational costs of developing and fielding the capability?
- What is the benefit of reducing the time it takes to run a diagnostic test by analyzing the sample at the patient's location, as compared to sending the sample to another facility?

3. Train and Educate Leadership on the Value of Bidirectional Disease Surveillance Reporting

Detection of an outbreak of a disease that lacks a specific presentation or diagnostic tests will likely depend on the recognition of a higher-than-normal disease rate in the population. The ability to detect atypical disease rates is facilitated by situational awareness of the prevalence of diseases in both the PAR and the surrounding environment. Maintaining

up to date situational awareness requires timely reporting of information up and down the medical chain of command. IDA researchers observing recent North Atlantic Treaty Organization (NATO) exercises, which incorporated a contagious disease outbreak response, identified numerous challenges in obtaining situational awareness through timely disease surveillance reporting.

Medical personnel should routinely report case counts up the chain of command for aggregation across the PAR.[71] This routine reporting helps characterize the typical rate of disease in the population. Ideally, medical personnel should have an understanding of how disease rates vary from day to day, given the time of year and operational tempo. A well-characterized baseline disease rate can improve both the speed and confidence of detecting the atypical prevalence of disease associated with a contagious disease outbreak. During the early part of an operation, a lack of data may prevent the characterization of such a baseline. In this case, a baseline may need to be estimated by extrapolating data from operations in similar climates and environments.

Disease surveillance information should also be directed down the medical chain of command. Medical personnel at lower roles of medical facilities need to be aware of the most up-to-date information relating to the following:

- Case definitions for diseases of concern;
- Potential sources of infection, such as natural reservoirs of endemic diseases or specific infected populations (e.g., host nation individuals or allied units);
- Reporting requirements, such as the disease surveillance observations that need to be reported, the frequency of the reporting, and the recipient of the reported information;
- Protective measures that should be taken, such as increasing the standard level of personnel protective equipment, reinforcing hygiene practices, or educating personnel on identifying pertinent symptoms and the importance of promptly reporting to an MTF when ill; and
- Control measures, such as the level of isolation required for contagious individuals or contact tracing

The IDA team suggests training and leadership education on the value of timely and accurate disease surveillance reporting up and down the medical chain of command. This bidirectional reporting can create a disease surveillance feedback loop (illustrated in

[71] Reporting may include automated or manual reporting of ICD-10 codes.

Figure 16). Disease surveillance observations made by Role 1 MTFs can be reported to the Role 2 MTF for aggregation across the PAR. From these observations, Role 2 MTF personnel can then provide updated disease surveillance guidance and response actions back down to the Role 1 MTFs. In addition, the observations from the Role 2 MTF can be reported to the theater-level command, where they can be aggregated across the theater and supplemented with observations from a Role 3 MTF and medical intelligence. The theater-level command can then provide updated disease surveillance guidance and response actions to all lower-role MTFs. The updated guidance can increase their situational awareness about disease risks and ongoing outbreaks. That increased awareness should result in increased vigilance in forward medical providers, and, in turn, increase theater staff awareness of new disease information.

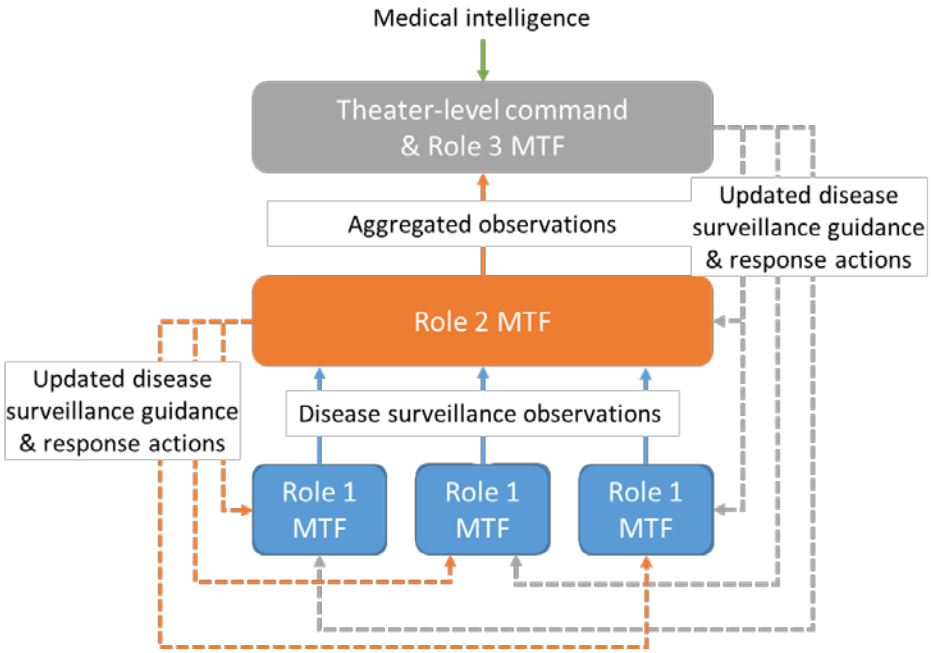

Figure 16. Diagram of Disease Surveillance Feedback Loop

4. Develop Pre-Deployment Contingency Plans for Sustaining Isolated Units

As mentioned at the beginning of this chapter, the operational disruption resulting from the mere presence of contagious individuals in the population may be unavoidable. Commanders may have to operate under the constraint of limited direct contact with individuals outside of the PAR. This limited contact could restrict or interfere with logistics support, allied-nation support, and host-nation support. Under these circumstance, the extent to which the PAR can continue its mission largely depends on its ability to be sustained while avoiding direct contact with individuals from uninfected units or populations.

The possibility of sustaining an isolated unit should be considered as part of pre-deployment planning for regions that pose a high risk for contagious disease exposure.

Commanders should develop contingency strategies for sustaining an isolated unit. Developing these strategies will likely require coordination between logistic and medical personnel. Additional analyses should be conducted to provide planners with analytically backed guidance on how long a unit may need to be isolated and measures that can be taken to minimize the risk of disease transmission when sustaining infected units.

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Appendix A.
Assessment of Delaying Disease Surveillance and Response Processes

As part of its quantitative analysis of plague and smallpox, the Institute for Defense Analyses (IDA) team assessed the consequence of delaying the detection and subsequent implementation of control measures. This appendix details the assessment.

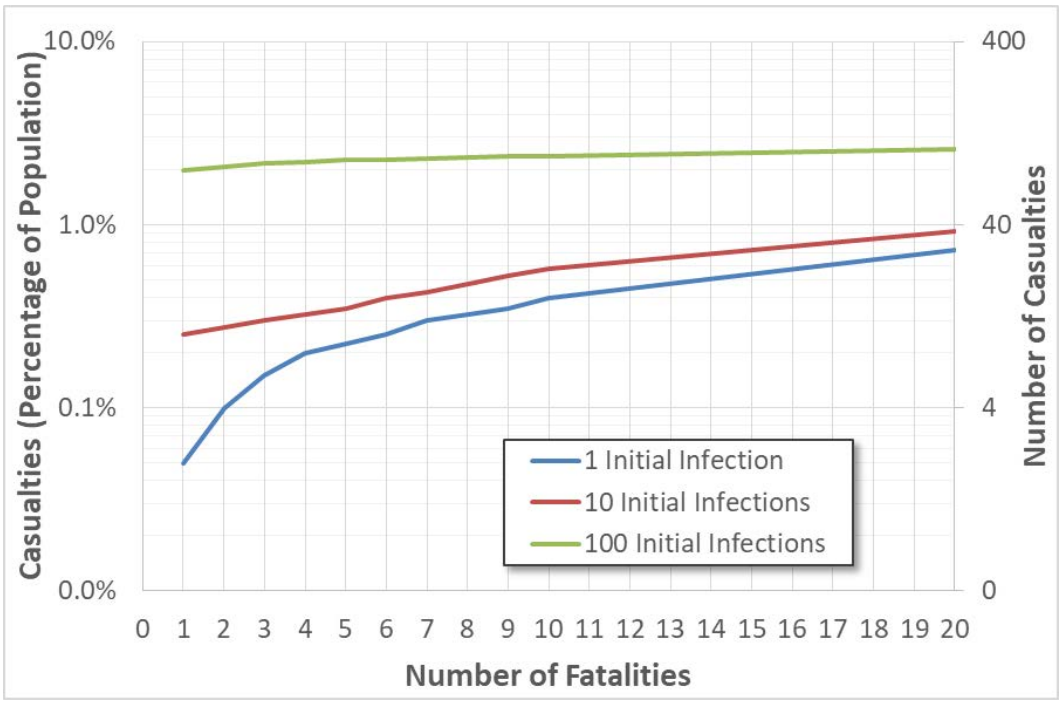
Plague

The assessment of the consequence of delaying the detection of a plague outbreak and the implementation of population-wide antibiotics served two purposes. First, it was a sensitivity analysis of the assumptions that underlie the characterization of the baseline scenario. Second, it showed the impact of responding to an antibiotic resistant strain of plague.

Sensitivity of Outbreak Size to Disease Surveillance Delays

The characterization of the baseline surveillance trigger and control measure implementation was based on two assumptions. First, plague would be recognized in the population following the third fatality. Second, the decision to administer population-wide antibiotics and the time to distribute the drugs would take 6 hours. If the first assumption underestimated actual disease surveillance capabilities, then the administration of antibiotics would be delayed. Figure A-1 shows the 90^{th} percentile case of the total percent of the population at risk (PAR) that would be infected if various numbers of fatalities were required to trigger the administration of antibiotics.

Even if 20 fatalities were required to trigger the response process, the outbreak would not cause more than 1% of the population (40 individuals) to become a casualty if it started with 1 or 10 initial infections, and it will not cause more than 5% (200 individuals) of the population to become a casualty if it started with 100 initial infections. In other words, even if the disease surveillance process required 20 plague fatalities to trigger a response, it would not cause a substantial increase in operational disruption, as compared to if it was detected after the third fatality.



Note: Six hour delay from response trigger to PEP administration assumed

Figure A-1. Percentage of PAR Becoming a Casualty due to Infection with Plague (90th Percentile Case) for Population-Wide Antibiotics Response Triggered by Various Numbers of Fatalities

Likewise, if the second assumption underestimated either the time for the decision cycle or the time to distribute antibiotics, then the administration of population-wide antibiotics would be delayed further. Figure A-2 shows the total percentage of the population becoming a casualty (90th percentile case) for various delays in antibiotic administration following the third fatality. Even if the administration of the medical countermeasure (MCM) is delayed by 6 days (as compared to the assumed 6 hours), the response can still prevent 1% of the population (40 individuals) from becoming a casualty for outbreaks starting with either 1 or 10 initial infections, and it can still prevent 5% of the population (200 individuals) from becoming a casualty for outbreaks starting with 100 initial infections. Again, the ability of disease surveillance to minimize operational disruption is insensitive to the exact characterization of the delay in response implementation.

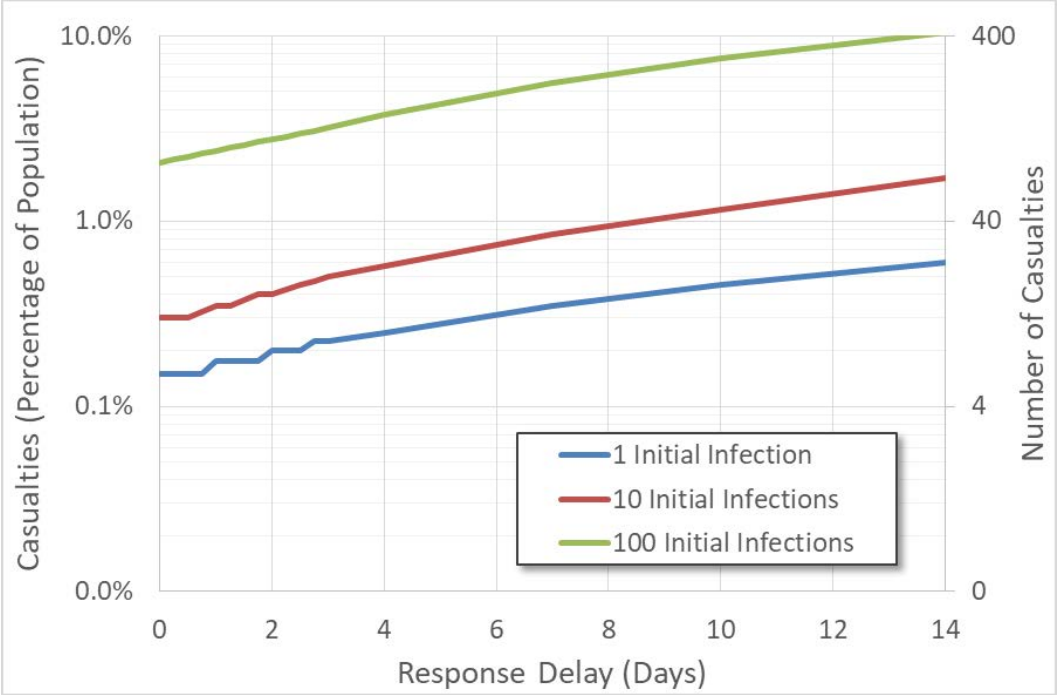


Figure A-2. Percentage of PAR Becoming a Casualty due to Infection with Plague (90th Percentile Case) for Various Delays in Administering Population-Wide Antibiotics Following Third Fatality

Impact of Antibiotic Resistance

Antibiotic resistance could occur naturally or be engineered by an adversary. Clinical isolates of *Y. pestis* from infected individuals in Madagascar have shown antibiotic resistance to either a single drug (e.g., streptomycin) or to a wide range of drugs used for treatment and prophylaxis.[1] The remainder of this section assess the operational impact of antibiotic resistance on the disease surveillance and response capabilities described previously.

The IDA team assumed that antibiotic resistance would not impact disease progression, transmission, or diagnosis. Therefore, the assumption that baseline capabilities would detect the presence of plague within the PAR following the third fatality is still valid. Although the disease surveillance process would likely not be impacted by antibiotic resistance, the response process would. The IDA team assumed the following in regards to the administration of antibiotics in response to an outbreak of antibiotic-resistant plague:

- The strain of plague is completely resistant to the first choice of antibiotic.
- Twenty-four hours are required to realize that the first choice of antibiotics is ineffective. This assumption is consistent with the assumed delay from drug

[1] Marc Galimand, Elisabeth Carniel, and Patrice Courvalin, "Resistance of *Yersinia pestis* to Antimicrobial Agents," *Antimicrobial Agents and Chemotherapy* 50, no. 10 (October 2006): 3233–3236.

administration to effect. In other words, medical personnel will realize that the first choice of antibiotic is ineffective when they do not observe the anticipated effect within the population (i.e., an improvement of the condition of ill individuals or a reduction in the number of new cases).

- Following the realization that the first choice of antibiotic is ineffective, 24 hours are required to obtain and administer a second choice of antibiotic.
- The second choice of antibiotic is highly effective.

These assumptions are consistent with a previous IDA analysis that considered responding to outbreaks of antibiotic-resistant strains of biological warfare (BW) agents.[2]

Given these assumptions, an antibiotic-resistant strain of plague would delay the administration of an effective antibiotic by 48 hours. Therefore, baseline disease surveillance and response capabilities result in the administration of a highly effective antibiotic 2.25 days following the third plague fatality (as compared to 6 hours after the third fatality if the strain was not antibiotic resistant). Table A-1 shows the number of casualties, given the baseline disease surveillance and response capabilities against an antibiotic-resistant strain of plague. Although antibiotic resistance results in a 2-day delay in the administration of population-wide antibiotics, the overall impact on the size of the outbreak is negligible. Even when faced with an antibiotic-resistant strain of the disease, disease surveillance and response capabilities are able to prevent operational disruption due to personnel loss.

Table A-1. Number of Casualties (90th Percentile): Baseline Disease Surveillance and Response Capabilities—Antibiotic Resistance

	Number of Casualties (% of Population)	
Number of Initial Infections	**No Resistance**	**Resistance**
1	6 (0.15%)	8 (0.20%)
10	12 (0.30%)	17 (0.43%)
100	86 (2.15%)	103 (2.85%)

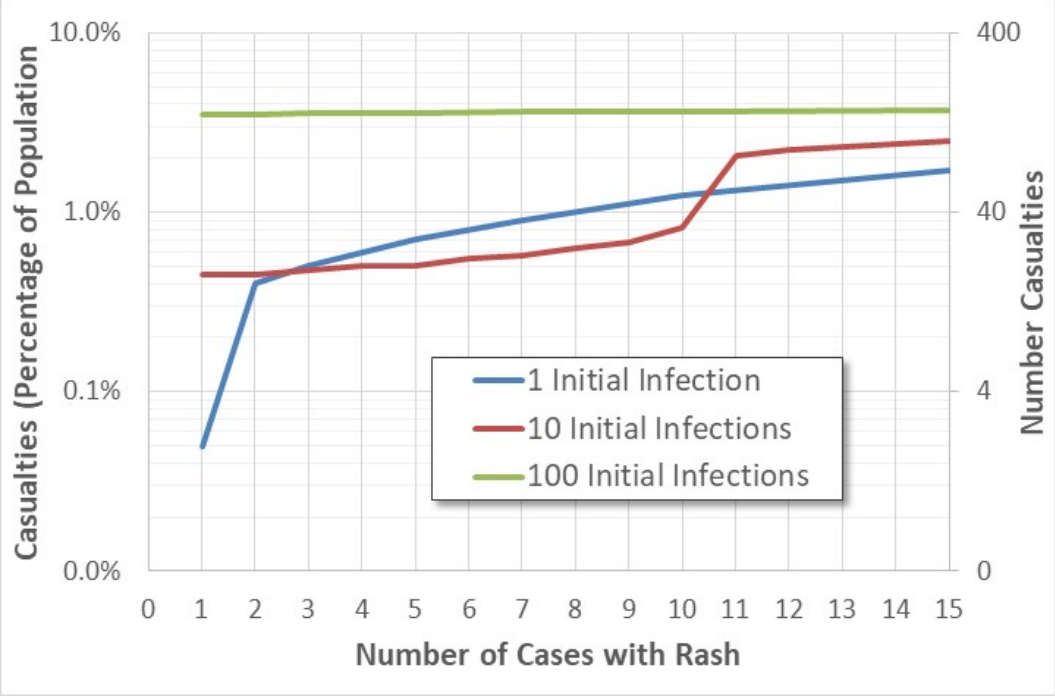
The previous discussion focused on a scenario in which the strain of *Y. pestis* was only resistant to the first choice of antibiotics. In the event that the pathogen is resistant to multiple choices of antibiotics, additional time would be required before an effective antibiotic could be administered. Figure A-2 can be used to determine the percent of the population that would become a casualty if a longer period of time is required to identify and administer an effective antibiotic. For example, if the pathogen is resistant to the first two

[2] Katherine M. Sixt et al., *Enhanced Viruses and Bacteria as Biological Weapons, Phase 1: An Analytic Framework for Understanding How Synthetic Biology Can and Cannot Enable an Adversary*, IDA Paper P-8465 (Alexandria, VA: Institute for Defense Analyses, 2017).

choices of antibiotic, then the administration of an effective antibiotic would be delayed by 4 days following the third fatality. The inclusion of this additional delay in the response process results in a minimally larger outbreak.

Smallpox

Recall that the characterization of the baseline smallpox disease surveillance and response capability was based on two assumptions. First, the outbreak would be detected following the third case with rash. Second, 3 days would be required to transport and administer the smallpox vaccine to individuals in the PAR. If either of these assumptions are underestimates, then the administration of the vaccine would be delayed. Figure A-3 shows the sensitivity of the total size of the outbreak to the number of individuals with rash that are required to trigger the response. Even if seven cases with rash are required to trigger the response (as compared to baseline assumption of three), the outbreak will still not cause more than 1% of the population (40 individuals) to become a casualty if it started with one or 10 initial infections, and it will still not cause more than 5% (200 individuals) of the population to become a casualty if it started with 100 initial infections.



Note: A 3-day delay from response trigger to vaccine administration is assumed.

Figure A-3. Percentage of the PAR Becoming a Casualty due to Infection with Smallpox (90th Percentile) for Vaccination Response Triggered by Various Numbers of Cases with Rash

Figure A-4 shows the sensitivity of the results to the assumption that 3 days would be required to transport and administer the vaccine. As was the case with the first assumption, the total size of the outbreak is relatively insensitive to the assumed delay in vaccine administration. Even if vaccine administration was delayed by 8 days following the third case with rash (as compared to the baseline assumption of 3 days), the outbreak will still not cause more than 1% of the PAR to become a casualty if it started with 1 or 10 initial infections and it will still not cause more than 5% of the PAR to become a casualty if it started with 100 initial infections.

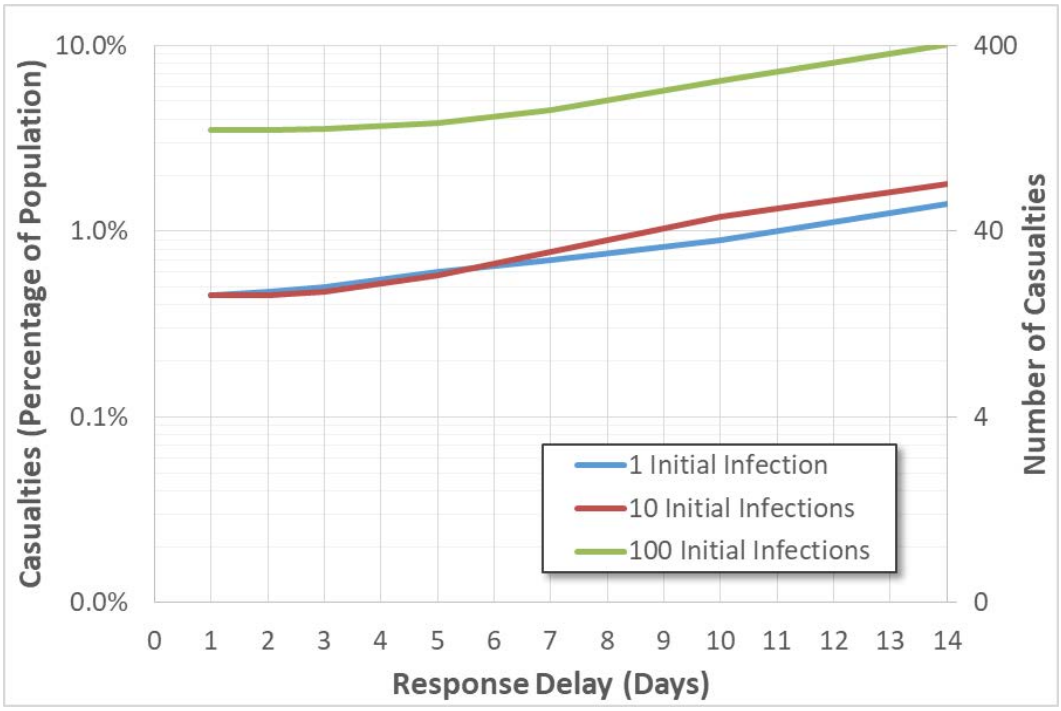


Figure A-4. Percentage of PAR Becoming a Casualty due to Infection with Smallpox (90th Percentile) for Various Delays in Vaccine Administration Following Third Case with Rash

In both of the results shown, as well as those shown in Figure 10, outbreaks starting with 1 initial infection sometimes resulted in larger outbreaks than the corresponding outbreak beginning with 10 initial infections. This counterintuitive result is due to two analytic choices made by the IDA team. First, presenting the 90th percentile result. Second, accounting for individual variation in contagiousness in the model. For many simulated outbreaks, the 90th percentile result corresponds to an outbreak that starts with individuals who transmit the disease to a higher-than-average number of people (i.e., outbreaks starting with superspreaders).

When the outbreak starts with 10 initial infections, the impact of having superspreaders among the initial infections is reduced, because the disease surveillance threshold (e.g., third case with rash) is reached in the first generation of the outbreak. Therefore, the

smallpox vaccine can disrupt the transmission of the initial infections. In comparison, when the outbreak starts with a single initial infection, the disease surveillance threshold is not reached during the first generation of the outbreak—unless, of course, the threshold is a single individual. Therefore, the single initial infection has the opportunity to transmit the disease for the full duration of their contagious period prior to the administration of the vaccine. In the event that the single initial infection is a superspreader (as is expected in the 90^{th} percentile result), this individual can cause more infections during the full duration of their contagious period than the 10 initial infections can in the vaccinated population.

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Appendix B.
Technical Description
of Contagious Disease Model

Model Overview

The Institute for Defense Analyses (IDA) team developed a stochastic, individual-based, compartmental contagious disease model for simulating outbreaks, which was implemented in the programming language python. The model uses a single homogenously mixed population. The size of the population is assumed to be fixed for the duration of the outbreak. As a compartmental model, the population is divided into cohorts based on the health state of each individual. The model simulates an outbreak by tracking the progression of individuals through these cohorts over time. The cohorts are as follows:

- S: individuals who are susceptible to infection;
- E: individuals who are exposed and infected, but have yet to develop symptoms (i.e., are incubating the disease);
- I_1: individuals who are symptomatic but have yet to become infectious;
- I_2: individuals who are infectious and capable of transmitting the disease;
- R: individuals who are removed as a source of infection, either because they died due to the disease—in which case, they can be further categorized as a member of the fatality cohort (FAT)—or because they recovered—in which case, they can be further categorized as a member of the recovered cohort (REC); and
- Post-exposure prophylactic (PEP): individuals who are either protected from infection or had their infection terminated due to administration of a PEP or pre-exposure prophylaxis (PrEP).

These six cohorts are mutually exclusive and collectively exhaustive, such that the number of individuals in each cohort sums to the total size of the population, N, at all times.

The amount of time an individual spends in the E, I_1, and I_2 cohorts is determined by random draws from previously defined disease-specific distributions. The probability of an individual dying as a result of their infection is determined from the disease's case fatality rate (CFR). These disease-specific parameters are shown in Table B-1.

Table B-1. Distributions Used to Determine Dwell Times and CFR

Cohort	Plague[a]	Smallpox[b]	SARS[c]
E	Lognormal Mean: 4.3 days Standard deviation: 1.8 days	Lognormal Mean: 11.6 days Standard deviation: 1.8 days	Gamma Mean: 4.49 days Standard deviation: 2.63 days
I_1	Fixed 1 day	Lognormal Mean: 3 days Standard deviation: 0.95 days	N/A
I_2	Lognormal Mean: 1.5 days Standard deviation: 1.2 days	Lognormal Mean: 14 days Standard deviation: 2.24 days	Gamma Mean: 12.5 days Standard deviation: 5.6 days
CFR	100% if untreated or treatment initiated after prodrome; 5% if treatment initiated during prodrome	30% if unvaccinated, 3% if vaccinated before exposure, 20% if vaccinated after exposure	0.109%

[a] 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, 2016).

[b] Oxford et al., *Technical Reference Manual*.

[c] John N. Bombardt, "Congruent Epidemic Models for Unstructured and Structured Populations: Analytical Reconstruction of a 2003 SARS Outbreak," Mathematical Biosciences 203, no. 2 (2006): 171–203.

Note: SARS is not modeled with a symptomatic non-contagious period.

Disease Transmission Rates

In addition to accounting for the individual variation in the various stages of illness, the model also accounts for individual variation in infectiousness. By including variation in individual infectiousness, the model can simulate the low-probability but high-consequence impact that superspreaders have on outbreak dynamics. The model's consideration of individual variation in infectiousness follows closely from the work of Lloyd-Smith et al.[1] Lloyd-Smith et al. demonstrated that the extent of individual variation in infectiousness depends on the disease. One of the products of the analysis by Lloyd-Smith et al. was the quantification of the extent of individual variation in infectiousness for a variety of diseases (or in some cases, specific outbreaks of a given disease). For each disease (or disease outbreak) considered, Lloyd-Smith et al. provided a distribution for the basic reproductive number, R_0. The R_0 distributions used for this analysis are shown in Table B-2.

[1] J. O Lloyd-Smith et al., "Superspreading and the Effect of Individual Variation on Disease Emergence," *Nature* 438, no. 7066 (November 17, 2005): 355–359.

Table B-2. R_0 Distributions

Plague	Smallpox*	SARS
Geometric Mean: 1.32 Standard Deviation: 1.75	Negative Binomial Mean: 5 Standard Deviation: 8.52	Negative Binomial Mean: 1.63 Standard Deviation: 4.27

Source: J. O Lloyd-Smith et al., "Superspreading and the Effect of Individual Variation on Disease Emergence," *Nature* 438, no. 7066 (November 17, 2005): 355–359.

* The smallpox distribution reported in Lloyd-Smith et al. was based on a partially vaccinated population, and therefore did not represent a true R_0 distribution. The IDA team scaled the reported distribution using a methodology presented by Lloyd-Smith et al. to generate a distribution with a mean that matches the R_0 estimate in Gani and Leach, "Transmission potential of Smallpox."

The R_0 distributions provided by Lloyd-Smith et al. needed to be adapted for use in IDA's contagious disease model. The R_0 distributions represent the probability of an individual infecting a given number of individuals over the entirety of their infectious period. However, IDA's contagious disease model tracks the number of new infections per time step. Therefore, the IDA team needed a way to characterize the daily number of new infections caused per infectious person. To do this, the R_0 distributions provided by Lloyd-Smith et al. were converted into distributions for daily disease transmission rates.

The IDA team assumed that an individual's infectiousness was due to two separate and independent factors: the duration of their infectious period, D, and their individual transmission rate β. The model assumes that individuals are equally infectious through the duration of their infectious period. Therefore, β is a constant that represents the daily number of new infections caused by an individual in an entirely susceptible population. These two factors were assumed to contribute equally to an individual's infectivity, such that $R_0 = \beta \times D$.

The IDA team used a "guess and check" approach to derive a disease-specific distribution for β from a disease's known distributions for R_0 and duration of infectious period. In general, the approach centered on systematically "guessing" a possible distribution for β and "checking" to see if it could generate a R_0 distribution that matched the distribution reported in Lloyd-Smith et al. The following procedure was used to derive the β distribution for each disease:

1. Guess possible distribution type for β (e.g., normal, lognormal, exponential, gamma)
2. Parametrically vary parameter values for guessed distribution type; for each set of parameter values:
    a. Take a random sample from the guessed β distribution and multiply it by a random sample from the known duration of infectious period distribution to obtain a R_0 value

b. Continue to sample from guessed β distribution and known distribution for duration of infectious period to generate a R_0 distribution corresponding to the guessed β distribution

c. Compare generated R_0 distribution to the known R_0 distribution to check guessed β distribution[2]

3. Identify the set of β distribution parameter values that generated the R_0 distribution that most closely matches the known R_0 distribution
4. Repeat steps 1-3 with a different distribution type
5. Identify β distribution (in terms of both distribution type and parameter values) that generated the R_0 distribution that most closely matched the known distribution

Table B-3 shows the β distributions that were selected for use in the contagious disease model. To reiterate, the β distributions shown below represent the variation among infectious individuals in the expected daily number of new infections each would cause in an entirely susceptible population.

Table B-3. β Distributions

Plague	Smallpox*	SARS
Normal Mean: 0.90 Standard Deviation: 0.61	Gamma Mean: 0.35 Standard Deviation: 0.58	Negative Gamma Mean: 0.14 Standard Deviation: 0.33

Control Measures

The contagious disease model can account for two types of control measures: specific medical countermeasures (MCMs) for plague and smallpox, and a generic reduction in transmission that can represent a range of possible responses. Control measures are initiated a specified number of days after the outbreak reaches one of the following thresholds:

- The first appearance of symptoms in the population,
- The total number of cases with prodromal symptoms,
- The total number of cases with severe symptoms,
- The total number of fatalities, or
- The number of new cases within a 24 hour period.

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[2] The generated R_0 distribution was compared to the known R_0 distribution by summing the square of the differences of the distributions at each integer on the range of 0–99. The smaller the resulting sum, the more similar the two distributions were considered to be.

For example, the model can simulate the administration of the smallpox vaccine 3 days following the third case with rash (i.e., severe symptoms).

The plague MCM is antibiotics for use as a PrEP, PEP, and treatment. Antibiotic PrEP is administered to the entire population at some point prior to the outbreak, such that it becomes efficacious prior to the start of the outbreak. PrEP is modeled to have a 95% probability of protecting an individual from infection.[3] For PEP, the model assumes that the entire population is simultaneously administered antibiotics and the drugs require 24 hours to become efficacious. PEP was modeled as having a 95% probability of both preventing susceptible individuals from becoming infected and terminating the infection of those who are infected but not yet symptomatic (i.e., those in the E cohort).[4] The model assumes that the benefits of antibiotics (as either a PrEP or PEP) do not cease until the end of the outbreak. Therefore, individuals remain protected against infection for the remainder of the outbreak (i.e., never return to the S cohort). As a treatment, antibiotics are modeled as having a 95% probability of preventing an individual from becoming infectious if administered during the 1-day symptomatic non-infectious period and provide no benefit if administered after that point.[5] The model assumes that the administration of antibiotics as a PEP and treatment occur at the same time.

The smallpox MCM is the smallpox vaccine as a PrEP or PEP. Antivirals and treatment were not included in the model. Smallpox vaccine PrEP is assumed to be administered at some point prior to the outbreak, such that it becomes efficacious prior to the start of the outbreak. The user can specify a percent of the population that is exempt from receiving the vaccine as a PrEP.[6] Those who do receive the vaccine have a 95% probability of becoming immune to infection.[7] As a PEP, the smallpox vaccine is administered to the entire population and requires 24 hours to become efficacious. The vaccine has a 95% probability of providing immunity to susceptible individuals.[8] The efficacy of the vaccine for terminating infection in those that are pre-symptomatic depends on the delay between exposure and vaccination, as shown in Table B-4. Vaccinated individuals who still become symptomatic have a reduced probability of death, as shown in Table B-1.

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3 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, 2016).

4 Ibid.

5 Ibid.

6 As discussed in Section 4.A.3, an exemption rate of 10% was used to account for individuals for whom the vaccine was contraindicated.

7 Oxford et al., *Technical Reference Manual*.

8 Ibid.

Table B-4. Probability of Smallpox Vaccine Terminating Infection in Pre-Symptomatic Individuals

Delay from Exposure to Vaccination (Days)	Probability of Terminating Infection
0–0.25	93%
0.25–1	90%
1–3	80%
4–7	25%
8–14	2%
>14	0%

Source: Oxford et al., *Technical Reference Manual*.

The final control measure included in the model is a generic reduction of transmission used to account for a range of possible responses. This model feature was used for the analysis of emerging infectious diseases (EIDs); however, it can be applied toward plague and smallpox outbreaks, as well. The model accounts for this generic response by simply reducing the expected number of new infections per infectious individual, β, by a user-specified amount.

Detailed Description of Model Algorithm

The final section of this technical appendix is a walk-through of the contagious disease model algorithm.

Initialize Cohorts

The first step of the model is to initialize the number of individuals in each cohort.

- If PrEP is not being modeled,
  - The number of individuals in the E cohort at the start of the outbreak, $E(t = 0)$, is the user specific number of initial infections, E_0.
  - All other individuals in the population are in the S cohort; $S(t = 0) = N - E_0$, where $S(t = 0)$ is the number of individuals in the S cohort at the start of the outbreak and N is the user-specified number of individuals in the population.
  - No individuals are in the I_1, I_2, R, and PEP cohorts at the start of the outbreak: ($I_1(t = 0)$, $I_2(t = 0)$, $R(t = 0)$, and $PEP(t = 0)$, respectively).
- If PrEP is being modeled, then some individuals who would have been in either the E or the S cohort in the absence of PrEP are in the PEP cohort instead.
  - For each individual who would have been an initial infection (E_0) in the absence of PrEP,

- A random draw is used to determine if the individual was exempt from receiving PrEP.
  - If a single draw from continuous uniform distribution over the interval [0-1) is less than the PrEP exemption rate (0 for plague and 0.1 for smallpox), then the individual is considered exempt from PrEP and starts the outbreak as a member of the E cohort;
  - Else, the individual is considered non-exempt from PrEP and an additional draw from the same continuous distribution is done to determine if the PrEP was efficacious.
    - If the result of the draw is less than the PrEP efficacy, then the individual is protected from infection and starts the outbreak as a member of the PEP cohort;
    - Else, the individual starts the outbreak as a member of the E cohort.

– The same logic is applied for each individual who would have been in the S cohort in the absence of PrEP.
  - Individuals start the outbreak in the S cohort if
    - They are exempt from PrEP, or
    - They are non-exempt from PrEP, but the PrEP is non-efficacious.
  - Individuals start the outbreak in the PEP cohort if they are non-exempt from PrEP and the PrEP is efficacious.

– All other cohorts start with zero individuals.

Determine Individuals' Attributes

Once the cohorts are initialized, the next step is to conduct random draws to determine individuals' attributes.

- For each individual in the population, random draws from the distributions in Table B-1 and Table B-3 are used to determine the following:
  – The duration of the individual's incubation period,
  – The duration of the individual's symptomatic non-infectious period,
  – The duration of the individual's infectious period, and
  – The individual's transmission rate, β_i.

Iterate through Each Time Step in the Simulation

Following the initialization of the cohort sizes and individuals' attributes, the next step is to iterate through each time step of the outbreak to track the movement of individuals between cohorts. The model can be run with any user-specified time step, Δt. The IDA team used a 0.1 day time step for this analysis.

Determine the number of new infections

The first process in each time step is to determine the number of new infections generated by each individual who was infectious on the previous time step.

- The number of new infections per infectious individual in a given time step, $p_i(t)$, is determined via a random draw from a Poisson distribution:[9]

$$\text{Poisson}\left(\frac{k\,\beta_i\,S(t-1)}{N}\Delta t\right).$$

- The scaling parameter k is used to represent the impact of a generic control measures
  - If the time step is before the implementation of the control measure, $k = 1$;
  - Else, $k = 1 - \epsilon_{ROM}$, where ϵ_{ROM} is the efficacy of the control measure.
- The total number of new infections for the time step, $p(t)$, is the sum of the new infections caused by each infectious individual:

$$p(t) = \sum_{i=1}^{I_2(t-1)} p_i(t).$$

Transition individuals to new cohorts

Once the number of new infections for the current time step is determined, the next step is to determine which individuals need to transition to a new cohort. The model iterates through every individual in the population to determine who needs to transition between cohorts. For each individual in the population,

- If the individual is in the S cohort at this time step:
  - If the total number of individuals who have transitioned from the S to the E cohort on this time step is less than the total number of new infections for

[9] The Poisson distribution was used to avoid having non-integer numbers of new infections that would need to be converted to integers for use in the individual-based model. Although the number of new infections caused per individual will vary over the course of the individual's infectious period (due to the changing size of the susceptible population and the use of random draws), the individual is still considered to be equally infectious through the course of his or her infectious period because of his or her fixed transmission rate.

the time step, then the individual is considered to have been infected and transitions to the E cohort.

- If the individual is not infected on this time step and if this is the time step on which PEP becomes efficacious:
  - If PrEP had not been administered prior to the start of the outbreak:
    - If a random draw from a continuous uniform distribution over the interval [0-1) is less than the efficacy of the PEP, the individual transitions from the S cohort to the PEP cohort;
    - Else, the individual remains in the S cohort.
  - If PrEP had been administered prior to the start of the outbreak:
    - If the disease is plague, then the PrEP was not efficacious for this susceptible individual (if it had been, the individual would be in the PEP cohort, not the S cohort), and therefore, it is assumed that PEP would also not be efficacious; the individual remains in the S cohort.
    - If the disease is smallpox:
      - If the individual was exempt from PrEP vaccination (individuals exempt from PrEP vaccination are still considered eligible for PEP vaccination):
        - If a random draw from a continuous uniform distribution over the interval [0-1) is less than the efficacy of the PEP, the individual transitions from the S cohort to the PEP cohort;
        - Else, the individual remains in the S cohort
          - If the individual was not exempt from PrEP vaccination, then the individual was administered the vaccine, but it was non-efficacious. It is assumed that the vaccine would still be non-efficacious if administered again and therefore the individual remains in the S cohort.
  - If the individual is not infected on this time step and if this is not the time step on which PEP becomes efficacious, then the individual remains in the S cohort.
- If the individual is in the E cohort at this time step:
  - If the time the individual has spent in the E cohort is greater than or equal to the duration of the individual's incubation period, then the individual transitions from the E cohort to the I_1 cohort.

- If the individual is still in the incubation period, and if this is the time step on which PEP becomes efficacious:
  - If PrEP had not been administered prior to the start of the outbreak
    - If a random draw from a continuous uniform distribution over the interval [0-1) is less than the efficacy of the PEP, the individual transitions from the E cohort to the PEP cohort
    - Else, the individual remains in the E cohort
  - If PrEP had been administered prior to the start of the outbreak:
    - If the disease is plague, then the PrEP was not efficacious for this susceptible individual (if it had been, the individual would be in the PEP cohort, not the E cohort), and therefore, it is assumed that PEP would also not be efficacious; the individual remains in the E cohort.
    - If the disease is smallpox:
      - If the individual was exempt from PrEP vaccination (individuals exempt from PrEP vaccination are still considered eligible for PEP vaccination):
        - If a random draw from a continuous uniform distribution over the interval [0-1) is less than the probability of aborting infection specified in Table B-4 (which is dependent on the delay between exposure and vaccination), the individual transitions from the E cohort to the PEP cohort;
        - Else, the individual remains in the E cohort.
      - If the individual was not exempt from PrEP vaccination, then the individual was administered the vaccine, but it was non-efficacious. It is assumed that the vaccine would still be non-efficacious if administered again, and therefore the individual remains in the E cohort.
  - If the individual is still in the incubation period, and if this is not the time step on which PEP becomes efficacious, then the individual remains in the E cohort.

- If the individual is in the I_1 cohort at this time step:
  - If the time the individual has spent in the I_1 cohort is greater than or equal to the duration of the individual's symptomatic non-infectious period:
    - If the disease is plague, and if antibiotic treatment was administered to the individual while they were in the I_1 cohort:

        - If a random draw from a continuous uniform distribution over the interval [0-1) is less than the efficacy of antibiotic treatment, the individual transitions from the I_1 cohort to the REC cohort;
        - Otherwise, the individual transitions from the I_1 cohort to the I_2 cohort
    - If the time the individual has spent in the I_1 cohort is less than the duration of the individual's symptomatic non-infectious period, then the individual remains in the I_1 cohort.
- If the individual is in the I_2 cohort at this time step:
    - If the time the individual has spent in the I_2 cohort is greater than or equal to the duration of the infectious period:
        - If a random draw from a continuous uniform distribution over the interval [0-1) is less than the disease's CFR, then the individual transitions from the I_2 cohort to the FAT cohort;
        - Else, the individual transitions from the I_2 cohort to the REC cohort
    - If the time the individual has spent in the I_2 cohort is less than the duration of the infectious period, then the individual remains in the I_2 cohort.
- If the individual is in either of the R cohorts—FAT or REC, then nothing needs to be done since they will remain in that cohort for the remainder of the outbreak

Determine when control measures are implemented

As the model iterates through every individual in the population, it also tracks the events that can trigger the implementation of control measures:

- The first appearance of symptoms in the population,
- The total number of cases with prodromal symptoms,
- The total number of cases with severe symptoms,
- The total number of fatalities, and
- The number of new cases within the previous 24 hours.

Once the outbreak has reached the user-specified threshold for the selected trigger event, the day on which the control measure will go into effect is calculated by adding the user-specified delay between the trigger and the control measure implementation to the current time step. If the control measure is an MCM, an additional 24 hours is added to account for the time between drug administration and onset of efficaciousness.

Determine if simulation should continue

The model proceeds to the next time step, unless either of the following termination conditions are satisfied:

- The E, I_1, and I_2 cohorts are empty. If all three of these cohorts are empty, then additional cases are not possible and the outbreak has come to an end.
- The R cohort has reached a user-specified size. This termination condition can reduce run time by ending simulations that result in a certain fraction of the population being infected.

Output Reporting

When the simulation ends, the model reports the time histories of the following:

- Size of the S cohort,
- Size of the E cohort,
- Size of the I_1 cohort,
- Size of the I_2 cohort,
- Size of the R cohort,
- Size of the FAT cohort,
- Size of the REC cohort,
- Cumulative number of new infections (individuals that have entered the E cohort),
- Cumulative number of symptomatic individuals (individuals that have entered the I_1 cohort), and
- Cumulative number of contagious individuals (individuals that have entered the I_2 cohort).

These outputs can then be aggregated over multiple trials to determine summary statistics. A minimum of 5,000 trials was run for each simulation.

Summary of Assumptions

- Outbreaks start with a single exposure event that introduced the disease into the PAR. All subsequent exposures are a result of person-to-person transmission.
- Unless stated otherwise, everyone in the PAR was unprotected and susceptible to infection at the start of the outbreak.
- The population is fixed throughout the duration of the simulation.

- All individuals in the population are equally likely to contact—and therefore potentially infect—any other individual.
- MCMs are simultaneously administered to the entire PAR, take 24 hours to become efficacious, and remain efficacious for the remainder of the outbreak.
- An individual's infectiousness is due to two separate and independent factors: the duration of their infectious period, D, and their individual transmission rate β.
- Individuals are equally infectious throughout the duration of their infectious period.
- Individuals for whom an MCM was not efficacious as a PrEP will also not benefit from the same MCM administered as a PEP.

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Appendix C.
Illustrations

Figures

Tables

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Appendix D.
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Appendix E.
Abbreviations

AMedP	Allied Medical Publication
AOR	area of responsibility
BW	biological warfare
CDC	Centers for Disease Control and Prevention
CFR	case fatality rate
CONOPS	concept of operations
CONUS	continental United States
DHA	Defense Health Agency
EID	emerging infectious disease
FAT	fatality cohort
FDA	Food and Drug Administration
ICD	International Statistical Classification of Diseases and Related Health Problems
IDA	Institute for Defense Analyses
IHB	Immunization Healthcare Branch
MCM	medical countermeasure
MTF	medical treatment facility
NATO	North Atlantic Treaty Organization
NGDS	Next Generation Diagnostic System
OIF	Operation Iraqi Freedom
PAR	population at risk
PCR	polymerase chain reaction
PEP	post-exposure prophylactic
PrEP	pre-exposure prophylaxis
REC	recovered cohort
ROM	restriction of movement
SARS	Severe Acute Respiratory Syndrome
SNS	Strategic National Stockpile
U.S.	United States
USCENTCOM	U.S. Central Command
DNBI	disease and nonbattle injury
USMC	United States Marine Corps

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14. ABSTRACT

The Institute for Defense Analyses (IDA) investigated how the timing of disease surveillance and the subsequently triggered control measures contribute to limiting the operational disruption caused by a contagious disease outbreak in a deployed military population. A qualitative framework assessed how disease related factors influence the time available and the time it takes to detect and respond to an outbreak. A contagious disease model was used to assess the ability of various disease surveillance triggers and control measure implementation strategies to minimize operational disruption. Commanders may have the ability to detect and respond to an outbreak of a known disease in time to prevent direct operational disruption due to personnel loss. However, commanders will likely need to initiate high consequence decisions with potentially incomplete knowledge of the situation to minimize operational disruption from an outbreak of an unknown disease. Accordingly, the IDA team recommends: 1) investing in technologies that facilitate rapid medical countermeasure development, 2) developing concepts of operations for and conducting a cost-benefit analysis on diagnostic capabilities at lower roles of medical care, 3) training and educating leadership on the value of bidirectional disease surveillance reporting, and 4) developing pre-deployment contingency plans for sustaining isolated units.

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