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Critical Factors for Parameterisation of Disease Diagnosis Modelling for Anthrax, Plague and Smallpox

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ABSTRACT

This paper undertakes a technical review of the properties of three diseases often associated with the threat of bioterrorism: anthrax, plague and smallpox. While the literature on these agents is extensive, the information is not generally available in a concise form for the purpose of modelling the course of spread of disease through a population, including the emergence of observable indicators of community infection. The focus here is to extract from the literature information describing these agents for the purpose of developing models of symptoms emergence and disease progression in individual people, as well as parameters describing how the diseases may spread in a community and be observable. This information can be used to parameterise models of disease diagnosis in a community, for the purpose of analysing candidate syndromic surveillance systems. Information is also provided on common diseases that may be misdiagnosed in the early stages of an outbreak due to an act of bioterrorism, namely, influenza, chickenpox, and community acquired pneumonia. Where information is not available in precise quantitative form, semi-quantitative graphs are provided, which provide a useful summary for developers of probabilistic models of disease diagnosis.

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Executive Summary

The threat from terrorist groups using biological agents has been the subject of intense debate since the Amerithrax incident in 2001. The Australian Government shares similar concerns and has directed relevant Departments to develop a 'Whole-of Government' (WoG) strategy to prepare the nation against biological attacks. The Defence Science and Technology Organisation (DSTO) has initiated the development of a 'detect-to-treat' capability so that appropriate countermeasures can be deployed in a timely manner. A key element of this strategy is to leverage on the JeHDI system to be commissioned by Joint Health Command (JHC) at the end of 2012. It was hoped that the system will allow for an early indication of a disease outbreak.

Prompt and accurate reporting of disease symptoms from hospitals, GP and other health care providers are the backbone of an effective syndromic surveillance system. Individual reports may not contain sufficient information to raise an alarm, but when large data sources are pooled together, the analysis possesses significant statistical power for indication of a biological attack. As such they can potentially be used to raise an alert earlier than the medical community would have done

Many different approaches have been adopted to track the propagation of an infectious disease. The major objective of this review is to describe the epidemiological and clinical parameters for three biological agents, namely anthrax (caused by *Bacillus anthracis*), plague (caused by *Yersinia pestis*) and smallpox (caused by variola virus) that are often considered as potential bioterrorism agents. The results have been used to parameterise the critical functions of a disease diagnosis model that will be a part of the syndromic surveillance system.

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Contents

1. INTRODUCTION.....	1
2. INHALATIONAL ANTHRAX	2
2.1 Background	2
2.2 Vaccination.....	2
2.3 Natural Infection.....	2
2.4 Differential Diagnosis and Syndromes.....	3
2.5 Diagnosis	3
2.6 Prognosis	3
3. PNEUMONIC PLAGUE	3
3.1 Background	3
3.2 Vaccination.....	4
3.3 Clinical Features.....	4
3.3.1 Natural Infection	4
3.4 Differential Diagnosis Syndromes.....	5
3.5 Diagnosis	5
3.6 Prognosis	6
4. SMALLPOX.....	6
4.1 Background	6
4.2 Vaccination.....	6
4.3 Clinical Features.....	7
4.3.1 Natural Infection	7
4.4 Vaccination.....	7
4.5 Differential Diagnosis and Syndromes.....	8
4.6 Diagnosis	8
4.7 Prognosis	8
5. CONCLUSION	9
6. REFERENCES	10
7. FIGURES AND TABLES	13

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1. Introduction

There are increasing concerns that biological agents could be used as a weapon of choice by terrorists to inflict casualties and disrupt daily life of the general populace. The Amerithrax incident has highlighted the vulnerability of an unsuspected community and the enormous medical and consequence management costs incurred by such an attack [1-3]. The Australian Government holds similar views and has directed relevant Departments to develop a 'Whole-of Government' (WoG) strategy to strengthen the nation's preparedness against biological attacks. The Defence Science and Technology Organisation (DSTO) is developing a 'detect-to-treat' system so that appropriate and timely countermeasures can be implemented to minimise the impact of the bioterrorist attacks to the Australian community. DSTO is seeking, through collaboration with Defence's Joint Health Command (JHC), to use the military electronic health record system to monitor disease outbreaks. A key element of this strategy is to develop a disease diagnosis model for a community following the initial release of the biological agent causing the disease. This could facilitate a rigorous analysis and comparison of an awareness system based on syndromic surveillance to more intrusive detection and mitigation options.

The power of syndromic surveillance systems comes from their ability to analyse data from many sources, for example from reports of multiple clinicians, which individually may not contain sufficient information to raise an alarm, but taken together may contain a signal indicative of an attack of statistically significant strength. As such they can potentially be used to raise an alert earlier than the medical community would have done [4]. Fig. 1 is an illustration of the benefits of syndromic surveillance when coupled with an electronic health record system over conventional disease surveillance. Implementation of a range of syndromic surveillance systems has been adopted by the US as a primary means of detecting dangerous epidemic outbreaks [1].

There are different approaches to track the propagation of an infectious disease. Information on the symptoms, timeline of the expression of the symptoms, the probabilities of occurrence and stages of contagiousness etc are needed to delineate the extent that the disease could spread and what the outbreak signal will look like within an electronic health record. The purpose of this review is to describe epidemiological and clinical parameters for three biological agents that are often considered as potential bioterrorism agents. The results will be used to parameterise the critical functions of a disease diagnosis model that will be a part of the syndromic surveillance system which could potentially differentiate the occurrence of a bio-weapon induced illness from the more common and prevailing endemic diseases that show similar symptoms in those deliberately infected. The biological agents included in this study are one non-contagious disease, anthrax (caused by *Bacillus anthracis*) and two contagious diseases, plague (caused by *Yersinia pestis*) and smallpox (caused by variola virus). This approach will allow for the development of algorithms to detect suspicious events, better understanding of how disease is transmitted and assist in resource planning in the event of a biological agent release.

2. Inhalational Anthrax

2.1 Background

Bacillus anthracis, the causative agent of anthrax, is a gram-positive, spore forming bacterium. Anthrax is a worldwide disease of domesticated and wild animals that secondarily may occur in humans. Numerous products have been implicated in transmission to humans including wool, hair, bone, horns and hides. Within Australia, there are few naturally occurring cases of cutaneous anthrax. Globally, it is estimated that there are between 2000 and 20,000 human cases per year [6]. Cutaneous anthrax is the most common naturally occurring form [5]. The largest reported epidemic occurred in Zimbabwe between 1979 and 1985, with some 10,000 reported cases and 182 deaths [6]. Naturally occurring anthrax is more common in some regions, including the Middle East, Africa and Latin America [6].

2.2 Vaccination

Effective use of live attenuated veterinary vaccines has been associated with the decrease in animal and human cases. The currently approved US human vaccine (Anthrax Vaccine Adsorbed (AVA), Emergent BioDefense Operations Lansing, Inc) has been used for pre-exposure prophylaxis of veterinarians, laboratory, textile, and other workers who may be occupationally exposed, as well as US military personnel [6]. The role of post-exposure vaccination as an adjunct to antibiotics is not yet known. [7].

2.3 Natural Infection

Naturally occurring anthrax in humans is acquired from contact with anthrax-infected animals or anthrax-contaminated animal products. Cutaneous anthrax is the most common form (95% of cases). It follows the deposition of anthrax spores into the skin, often following trivial trauma [6]. The mean incubation period is 5 days. The lesion is characteristic and consists of a red pruritic macula, which develops into a papular-vesicular stage in 2-3 days [5, 8]. Vesicles, 1 to 3 mm in size, may appear and discharge clear or serosanguineous fluid. A painless depressed black eschar then follows and dries and falls off in the next 1 to 2 weeks. Eschars usually occur on exposed skin (fingers, forearm, and neck) and are associated with extensive oedema. Painful lymphadenopathy can occur with associated systemic symptoms. When bacteremia develops, it leads to high fever and death. Spontaneous healing occurs in 80% to 90% of untreated cases [5, 8]. Gastrointestinal anthrax is rare, and found in only 1% of cases. Like inhalational anthrax, this form is more likely to be associated with bacteraemia and sepsis and is associated with a mortality of around 40% [6].

Naturally occurring inhalational anthrax is now rare and the occurrence of a single case would be considered highly unusual and suspicious of bioterrorism. Table 1 provides the Australian case definitions for anthrax. The clinical features and key differential

diagnoses of inhalational anthrax and its comparison with influenza pneumonia, pneumococcal pneumonia and pneumonic plague are detailed in Table 2.

2.4 Differential Diagnosis and Syndromes

Acute severe pneumonia with sepsis would be the most common initial diagnosis of inhalational anthrax. The most common pathogens implicated include influenza virus (pneumonia) and bacterial causes of severe community acquired pneumonia, including pneumococcal pneumonia.

2.5 Diagnosis

The diagnosis of inhalational anthrax is based on:

- i. epidemiological and clinical data with the sudden appearance of several cases of severe acute febrile illness with respiratory symptoms with fulminant course and death or acute febrile illness in persons identified as being at risk following a specific attack;
- ii. results of the chest radiograph and the chest CT scan, which may show a widened mediastinum with hyperdense hilar and mediastinal nodes, infiltrates and pleural effusion, and results of the thoracentesis with hemorrhagic pleural effusions; and
- iii. microbiological cultures of blood, pleural fluid, cerebrospinal fluid and preserve biopsies which grow with large gram-positive bacilli, with preliminary identification of *Bacillus* species [5].

2.6 Prognosis

Without treatment, the mortality of inhalational anthrax approaches 100%. The mortality rate decreases by 30% if patients receive antibiotics and/or immune serum therapy at any time during the illness. The mortality is even lower, at around 40%, if early treatment is commenced during the prodromal phase of treatment [7]. Fig. 2 provides a summary of the time course of the expression of epidemiological features, symptom manifestations and recovery of patients exposed to anthrax.

3. Pneumonic Plague

3.1 Background

Yersinia pestis, the causative agent, is a Gram negative bacillus or coccobacillus. It is relatively slow growing and thus *Y. pestis* may sometimes be unrecognized [10]. *Yersinia pestis* has been isolated from all continents, but in 2000 and 2001 more than 95% of reported human cases were from the African region, including a well documented focus

in Madagascar accounting for more than 41% of the world's reported cases. [9]. Plague occurs in irregular periodic epizootics with inter-epidemic periods of up to 10 years or more [12]. Contacts with rodents harbouring infective fleas are often unrecognized and allow the transmission of the vector to humans. Very close contact (less than 2 metres) with a person who suffers from primary pulmonary plague is required to transmit it between humans [12]. The more common form of plague, bubonic plague, is thought to be the result of inoculation of bacteria through abrasions or other breaks in the skin.

3.2 Vaccination

No vaccines are currently available, but several vaccines are currently in development [9], including a subunit vaccine is being developed.

Historically, killed whole bacilli and live attenuated vaccines have been used, but its clinical utility is limited by high rates of local and systemic adverse reactions and short duration of protective immunity.

3.3 Clinical Features

3.3.1 Natural Infection

The incubation period from inoculation to the first clinical symptom has been estimated at 4.3 ± 1.8 days [11], consistent with previous data reporting an incubation period of between 2 and 8 days from inoculation to the first symptoms [10]. The initial symptoms are usually non-specific 'flu-like' symptoms which include fevers, chills, headaches and weakness [12]. Clinical plague infection manifests itself in three forms depending in the route of infection: bubonic, septicaemic and pneumonic [12]. Table 3 details the Australian case definitions for pneumonic plague. Table 2 shows the clinical features and key differential diagnoses of pneumonic plague and its comparison with influenza pneumonia, pneumococcal pneumonia and inhalational anthrax.

Worldwide, bubonic plague is the predominant form reported (80-95% of suspected cases). Following inoculation, bacteria drain to cutaneous lymphatics to regional lymph nodes where establishment of infection causes destruction and necrosis of lymph nodes ("buboes"). Progressive infection and inflammation progresses to enlargement of the lymph glands (classically armpits, neck and groin) of up to 10 cm, which develops into necrosis and spontaneous drainage. General symptoms including fever, weakness and chills are common. Untreated, patients develop bacteraemia and endotoxemia with shock, disseminated intravascular coagulation, multi-organ failure, coma and death [10].

The pneumonic form of plague is the most virulent and the least common. Pulmonary symptoms appear when infection spreads to the lung and may be primary (where infection is acquired by inhalation) or secondary (following bubonic or primary septicaemic plague) [10]. The incubation period of primary pneumonic plague is shorter

and has been estimated at 24 to 48 hours after exposure. Symptoms of pneumonic plague include productive cough with muco-purulent sputum, haemoptysis, dyspnea, and chest pain [13]. Non-specific gastrointestinal symptoms including nausea, vomiting, and diarrhoea may be reported [10].

The duration of the infectious period is reported as 2.5 ± 1.2 days [11]. The time from respiratory exposure to death in humans has a mean of 2 to 4 days in most epidemics [10]. In primary pneumonic plague, the extent of spread from human to human is not certain, with some reports suggesting that it is highly transmissible, others suggesting transmission is rare, and others suggesting intimate contact is required [11]. A modelling study estimated an R_0 at 0.8 to 3.0 [11].

Other uncommon forms of plague are described. Primary septicaemic plague occurs in patients who develop *Y. pestis* septicaemia without a discernable bubo. Although described in all age groups, it appears to be more common in the elderly [12]. Pharyngeal plague results from contamination of the oropharynx with *Y. pestis*-infected material and plague meningitis can also occur [12].

3.4 Differential Diagnosis Syndromes

The plague starts with 'flu-like' symptoms. Differential diagnoses depend on the site of infection. Bubonic plague may be confused with streptococcal or staphylococcal lymphadenitis, infectious mononucleosis, cat-scratch fever, and other cause of acute lymphadenopathy.

The primary pneumonic form cannot be easily distinguished from other causes of pneumonia on clinical grounds. Other similar causes of community-acquired pneumonia occurring in Australia include pneumococci, streptococci, leptosporia, burkholderia,, acinetobacters and influenza viruses [12]. Symptoms may also be similar to inhalational anthrax [10]. When present, cervical lymphadenitis may be more suggestive of plague pneumonia (and tularaemia) than other causes of pneumonia [12].

3.5 Diagnosis

Diagnosis and confirmation of plague requires laboratory testing. Isolation and identification of *Y.pestis* from clinical specimens are required for diagnosis confirmation [12]. However, the identification of *Y. pestis* may be problematic, with reports of misidentification by automated systems. Other investigations often reveal non-specific findings suggestive of severe infection, including leukocytosis with toxic granulation, coagulation abnormalities, abnormal liver functions, acute renal failure and other evidence of multi-organ failure. In addition, chest radiographic findings are also non-specific and variable but are most often described as bilateral infiltrates and consolidation.

There are no widely available rapid diagnostic tests for plague. A rapid antigen detection of soluble F1 capsular antigen in many clinical specimens of patients has been used in Madagascar, but is not widely available [14]. A serological diagnosis can only be made by demonstrating a diagnostic change in antibody titre in paired serum specimens over several weeks [10].

3.6 Prognosis

The prognosis depends on the site of infection and timeliness of treatment. A combination of tetracycline or doxycycline together with an aminoglycoside is used [15]. In the absence of treatment half of bubonic plague victims will die within 4 to 7 days [11]. The early use of active antibiotics has led to a decrease in mortality to under 10-20%. In 2003, among the 2,118 cases reported by 9 countries, 182 died [12]. The case fatality of primary septicaemic plague is higher [9]. Primary pulmonary plague, the most uncommon form, has the highest case fatality which approaches 100% if untreated and is still more than 50% with antimicrobial treatment [9]. The time course of the expression of epidemiological features, symptom manifestations and post-exposure recovery is explained in Fig. 3.

4. Smallpox

4.1 Background

Smallpox virus (also called *variola*) is a poxvirus that only infects humans. It is associated with a severe disease form, (variola major) and a milder form (variola minor) [16]. Smallpox was declared by the World Health Assembly to have been eradicated in 1980. Prior to eradication, smallpox was noted to spread most readily during the cool, dry winter months but could be transmitted in any climate and in any part of the world [18].

Transmission occurs mainly from person to person by droplets and aerosols. Contaminated clothing or bed linen can also spread the virus [16]. Historically, smallpox transmission throughout the population was usually restricted to household members and close friends, as cases were often bedbound with the prodromal illness prior to being contagious.

4.2 Vaccination

After ensuring the worldwide eradication of smallpox, smallpox vaccination ceased by 1984 [17]. A reserve of vaccine doses is held in many countries. Smallpox vaccine is associated with post vaccine encephalitis in 3 cases per million, with a mortality rate of 40% [18]. In immunosuppressed patients, the vaccination may lead to progressive vaccinia infection which is fatal in the absence of immunoglobulin therapy [18].

Currently, routine vaccination is only recommended for laboratory staff who may be exposed to poxviruses.

4.3 Clinical Features

4.3.1 Natural Infection

More than 90% of smallpox cases are clinically characteristic and readily diagnosed in the context of a known outbreak. Natural infection occurs following contact between the virus and the oropharyngeal or respiratory mucosa [16]. Patients are most infectious during the first week of illness when virus titers in saliva are highest. The initial viraemia, which develops on the third and fourth day, is asymptomatic as the virus migrates to the spleen, bone marrow and lymph nodes before a second viraemic phase occurring around the eighth day after exposure [16]. The incubation period lasts 10 to 14 days (range 7-17 days) [15, 16, 18]. The initial prodromal illness is non-specific, with symptoms including high fever, malaise, weakness, severe aching, pains and prostration, with abdominal pain, nausea and vomiting less commonly reported [15, 16, 18]. Two to three days later (i.e about 15 days after infection), the classic rash appears, with small reddish spots in the mouth and throat. This papular rash develops over the face (including mucosa of the mouth and pharynx) where it is most pronounced and subsequently spreads to the extremities [15, 16]. Within 1 to 2 days, the rash becomes vesicular, and then pustular. Patients remain febrile throughout the evolution of the rash and customarily experience considerable pain as the pustules grow and expand. Crusts begin to form about the eighth and ninth day of rash. Gradually, scabs form which eventually separate, leaving pitted scars. Encephalitis sometimes ensues due to acute perivascular demyelination [16]. Death usually occurs during the second week of illness [16, 18].

In 5 to 10% of smallpox patients, 2 other forms of smallpox may be present and may be difficult to recognise: hemorrhagic and malignant [16, 18]. In the hemorrhagic forms, patients exhibit bleeding into the skin and intestinal tract [18]. Pregnant women appear to be unusually susceptible. The incubation period is usually shorter, and more intense. Death occurs by the fifth or sixth day after onset of rash [16]. In the malignant form, disease develops which is more rapidly progressive and almost always fatal within 5 to 7 days. In such patients, the lesions are confluent and never progress to the pustular stage. Lesions remain soft, flattened, and velvety to touch, with the appearance of a reddish-coloured crepe rubber [16, 18].

4.4 Vaccination

The only vaccine available in Australia is the ACAM2000 (Sanofi Aventis) which was approved for use in September, 2010. Older stocks of the previous vaccinia vaccine are in limited quantities in the Australian stockpile.

4.5 Differential Diagnosis and Syndromes

From a clinical perspective, the disease most commonly confused with smallpox is chickenpox (primary *varicella*), and during the first 2 to 3 days of rash it may be impossible to distinguish between the two [15]. However, all smallpox lesions develop at the same phases, and on any part of the body appear identical. Chickenpox lesions are much more superficial, and scabs, vesicles and pustules may be seen simultaneously on adjacent areas of skin. Chickenpox rash is denser over the trunk (the reverse of small pox) and is not found on the palm or soles [16]. Epidemiologically, chickenpox does not usually occur in outbreaks, as the majority of the population are immune following childhood infection or immunisation. Tables 4 and 5 contain the Australian case definitions for smallpox. The clinical features of smallpox and a comparison with chickenpox are listed in the Table 6.

Monkeypox infection is rare but may clinically resemble smallpox. It occurs mostly in central and western Africa, but imported cases have been described in the United States. Symptoms are usually milder than for smallpox, and monkeypox causes lymphadenopathy [19]. Hemorrhagic smallpox cases were most often initially identified as meningococemia or severe acute leukaemia. Malignant smallpox, particularly associated with severe abdominal pain may be mistaken for non-infectious causes of severe abdominal pain [16].

4.6 Diagnosis

Specimens are obtained from vesicular or pustular fluid. Smallpox infection can be rapidly confirmed in the laboratory by electron microscopic examination, appearing as brickshaped virions [16]. Although smallpox and monkeypox virions are indistinguishable, naturally occurring monkeypox is found mainly in tropical rain forest areas of Africa [16]. Definitive laboratory identification and characterization of the virus involves growth of the virus in cell culture and characterization of strains by use of various biological assays, including polymerase chain reaction techniques and restriction fragment-length polymorphisms. Because of the infectivity of the virus, diagnostic studies should only be performed in high level bio-secured facilities.

4.7 Prognosis

The mortality rate depends on disease severity. *Variola* major is the most serious type, historically killing 30 to 35% of victims [15]. In case of hemorrhagic or malignant forms the mortality rate reaches almost 100% [16].

No specific antiviral treatments have been proven to be effective [16]. Current optimal care is through supportive therapy with antibiotic treatment in the event of secondary bacterial infections.

Vaccination administered within the first few days after exposure and perhaps as late as 4 days may prevent or significantly ameliorate subsequent illness [16]. The time course of the expression of epidemiological features, symptom manifestations and recovery post-infection is illustrated in Fig. 4.

5. Conclusion

The world is today confronted with potential biological attacks, be they sponsored by state-run programs or less sophisticated terrorist and/or special interest groups. The accidental release of *Bacillus anthracis* from a Soviet military base [20] and the contamination of salad bars with *Salmonella typhimurium* [21] by the Rajhneeshee serve as a reminder of our vulnerability to such attacks. The US Department of Homeland Security (DHS) has put in significant investments to set up the National Biosurveillance Integration Centre (NBIC) to provide early detection and warning of natural and deliberate release of biological agents. By integrating and bridging interagency resources and efforts, a capability based on new health information technology was fully functional in 2008 and is expected to be upgraded at the beginning of 2010 [1]. The Australian military is also establishing an integrated and digitized health information system. This initiative provides an opportunity to commission a syndromic surveillance capability (detect-to-treat) into the military e-Health system to strengthen the ADF's defence against biological attacks [22].

This paper reviewed data from published literature on critical factors that describe the symptoms, contagiousness and transmissibility of anthrax, plague and smallpox. As these diseases are rare or have been declared eradicated, reported case series and reviews were drawn to delineate symptom evolution following exposure semi-quantitatively, although quantitative data are provided wherever available. The epidemiology and temporal progression of symptoms are contrasted with common diseases that present in similar ways. It is intended that by parameterizing the data presented, a diagnosis model to aid syndromic surveillance for anthrax, pneumonic plague and smallpox will be accomplished.

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7. Figures and Tables

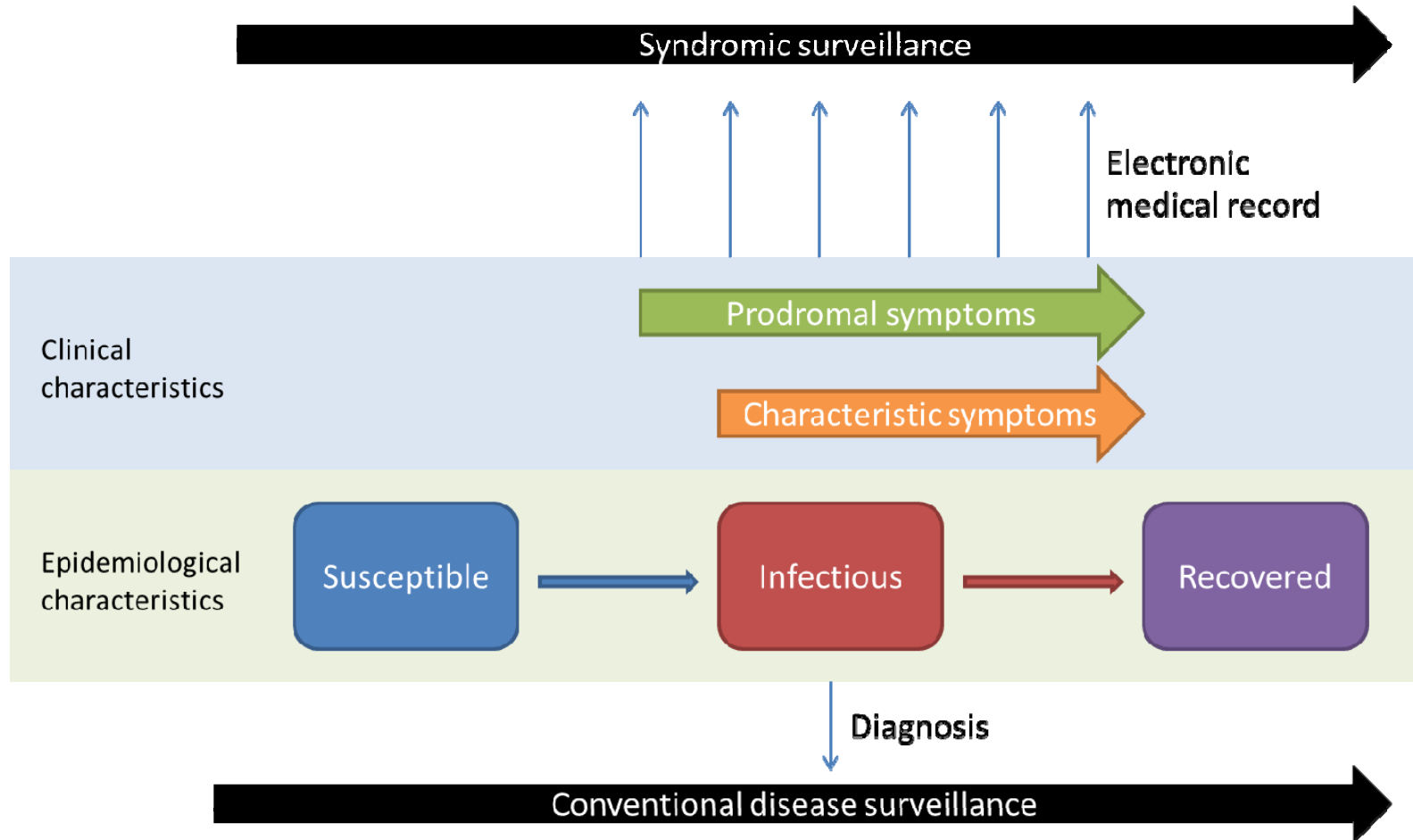


Figure 1: Syndromic surveillance utilising full electronic health record data versus conventional disease surveillance

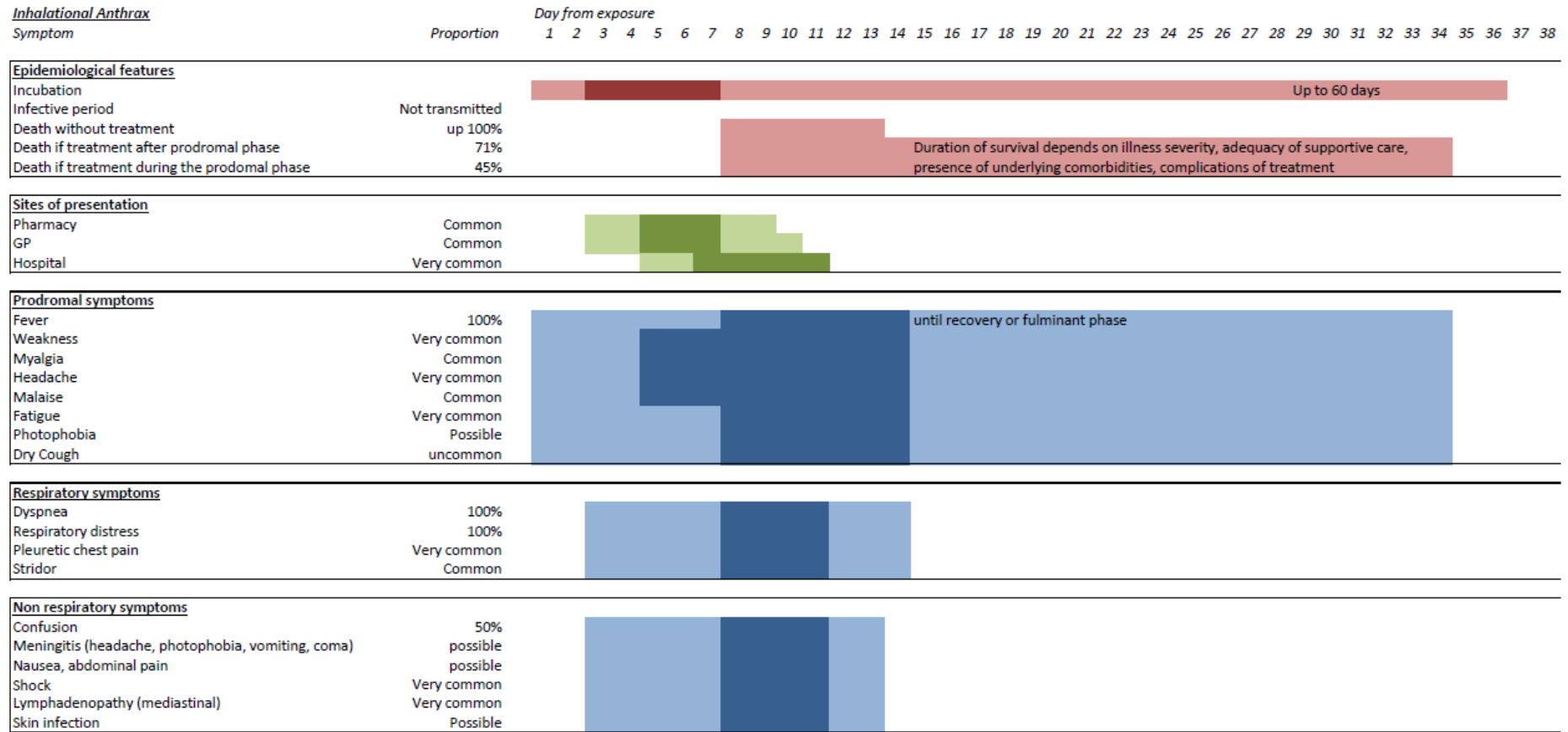


Figure 2: Time course of clinical and epidemiological features of inhalational anthrax from day of exposure. Dark colours indicate the range of time where symptoms or events are most likely to occur, with lighter colours indicating the range of time where symptoms or events may be present. Prodromal symptoms refer to non-specific and usually milder symptoms that may be reported prior to the onset of the symptoms and signs that are more characteristic of the disease.



Figure 3: Time course of clinical and epidemiological features of pneumonic plague from day of exposure. Dark colours indicate the range of time where symptoms or events are most likely to occur, with lighter colours indicating the range of time where symptoms or events may be present. Symptom onset in pneumonic plague is reported as sudden and severe with no prodromal symptoms.

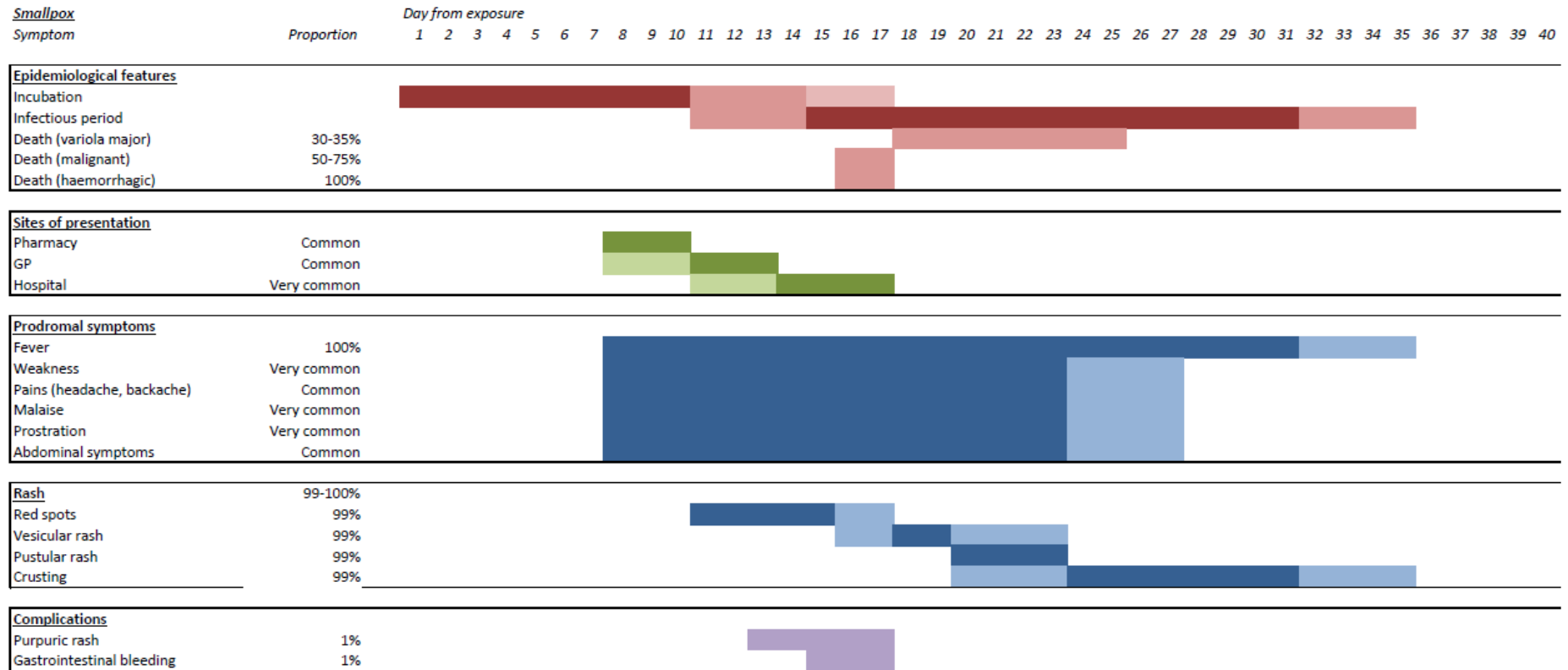


Figure 4: Time course of clinical and epidemiological features of smallpox from day of exposure. Dark colours indicate the range of time where symptoms or events are most likely to occur, with lighter colours indicating the range of time where symptoms or events may be present. Prodromal symptoms refers to non-specific systemic symptoms that occur prior to the onset of the rash which is characteristic of the disease.

Table 1: Australian case definition for anthrax (National Notifiable Disease Surveillance System)

LEVEL OF CERTAINTY	DEFINITION OF COMPONENTS
<p>Confirmed case A confirmed case requires either:</p> <ol style="list-style-type: none"> 1. Laboratory definitive evidence <p>OR</p> <ol style="list-style-type: none"> 2. Laboratory suggestive evidence AND clinical evidence. 	<p>Clinical evidence</p> <ol style="list-style-type: none"> 1. Cutaneous: skin lesion evolving over 1-6 days from a papular through a vesicular stage, to a depressed black eschar invariably accompanied by oedema that may be mild to extensive <p>OR</p> <ol style="list-style-type: none"> 2. Gastrointestinal: abdominal distress characterised by nausea, vomiting, anorexia and followed by fever <p>OR</p> <ol style="list-style-type: none"> 3. Rapid onset of hypoxia, dyspnoea and high temperature, with radiological evidence of mediastinal widening <p>OR</p> <ol style="list-style-type: none"> 4. Meningeal: acute onset of high fever, convulsions, loss of consciousness and meningeal signs and symptoms.
	<p>Laboratory evidence</p> <p>Laboratory definitive evidence Isolation of <i>Bacillus anthracis</i> -like organisms or spores confirmed by a reference laboratory.</p> <p>Laboratory suggestive evidence</p> <ol style="list-style-type: none"> 1. Detection of <i>Bacillus anthracis</i> by microscopic examination of stained smears <p>OR</p> <ol style="list-style-type: none"> 2. Detection of <i>Bacillus anthracis</i> by nucleic acid testing.

Table 2: Clinical characteristics of anthrax, pneumonic plague, influenza pneumonia and pneumococcal pneumonia used in differential diagnosis

VARIABLES	INHALATIONAL ANTHRAX	PNEUMONIC PLAGUE	INFLUENZA PNEUMONIA	PNEUMOCOCCAL PNEUMONIA
References	(5)(6)(7)(23)(24)	(9)(10)(11) (25)	(26)(27)(28)(29)	(30)(35)
Prodromal symptoms Low grade fever High grade fever Weakness Headache, myalgia Photophobia Dry Cough Sore throat Gastrointestinal symptoms	Common Uncommon Common Very common Very common Possible Uncommon NR NR	No (Sudden onset of illness)	Very common Very common Common Very common Very common NR Quite often Quite often Possible	No (Sudden onset of illness)
Respiratory symptoms Cough Sputum production Bloody sputum Dyspnoea Respiratory distress Pleuritic chest pain	100% Common Rare NR 100% Very common Very common	Very common Very common Possible 100% 100% Common	100% 70% Possible NR Quite often Possible Uncommon	100% Very common Possible Possible Common Possible Common
<i>Upper respiratory symptoms</i> Sore throat Stridor	NR NR Common	Rare Rare NR	Common Common NR	Uncommon Uncommon
<i>Non respiratory symptoms</i> Fever Fatigue Confusion Meningitis Gastrointestinal symptoms Sepsis Shock	Very common Very common 50% Possible Very common	Very common Very common Quite often Very rare Possible	70% Very common Uncommon Very rare 10%	Very common Very common Possible Rare Rare

Multiorgan failure	Very common	Very common	Possible	Common
Lymphadenopathy	Very common	Very common	Rare	
	Very common	Common	Uncommon	5-13%
Skin infection	Very common (Mediastinal)	Possible (cervical 'buboes')	Possible	No
Arthritis	Possible	NR	NR	Herpes labialis ("cold sore")
	Possible	NR	NR	Rare

Very common= 80 to 99%, common = 60 to 79%, quite often = 30 to 59%, possible 10 to 29%, Uncommon 5-9%, rare 1 to 4%, very rare<1%

Table 3: Australian case definition for plague (National Notifiable Disease Surveillance System)

LEVEL OF CERTAINTY	DEFINITION OF COMPONENTS
Confirmed case A confirmed case requires Laboratory definitive evidence only.	Laboratory definitive evidence Isolation of Yersinia pestis.

Table 4: Smallpox case definitions (National Notifiable Disease Surveillance System).

LEVEL OF CERTAINTY	DEFINITION OF COMPONENTS
<p>Confirmed case A confirmed case requires Laboratory definitive evidence only.</p> <p>Probable case A probable case requires either: 1. Clinical evidence AND Laboratory suggestive evidence OR 2. Clinical evidence AND epidemiological evidence.</p>	<p>Laboratory definitive evidence 1. Isolation of variola virus, confirmed at the Victorian Infectious Diseases Reference Laboratory. OR 2. Detection of variola virus by nucleic acid testing, confirmed at the Victorian Infectious Diseases Reference Laboratory.</p> <p>Laboratory suggestive evidence 1. Detection of a poxvirus resembling variola virus by electron microscopy. 2. Isolation of variola virus pending confirmation. 3. Detection of variola virus by nucleic acid testing pending confirmation.</p> <p>Clinical evidence Credible clinical smallpox as judged by an expert physician.</p> <p>Epidemiological evidence An epidemiological link to a confirmed case.</p>

Table 5: *Infectious Disease Emergency Response (IDER) Working Group Guidelines (2003) (36)*

SITUATION	DEFINITION
<p>A. First cases of smallpox in a non-affected geographical region</p> <p>Index case A first case of smallpox or unrelated cases in a new geographical area.</p>	<p>Confirmed case A case of fever and rash consistent with the clinical definition, plus laboratory confirmation by polymerase chain reaction (PCR) or viral isolation.</p> <p>Probable case A case of fever and rash consistent with the clinical definition plus electron microscopy identification of orthopoxvirus.</p> <p>Suspected case A case of fever and rash consistent with the clinical definition, without laboratory confirmation or an epidemiological link to other cases, in the absence of other laboratory diagnosis and reviewed by an infectious diseases physician.</p>
<p>B. Outbreak situation (subsequent cases in a cluster)</p> <p>Confirmed case within an outbreak</p>	<p>A case of fever and rash consistent with the clinical definition, plus either: (a) electron microscopy identification of orthopoxvirus; or (b) a case with strongly suspicious clinical features and no other diagnosis.</p> <p>Probable case within an outbreak A case of fever and rash consistent with the clinical definition, plus an epidemiological link to a confirmed case during an outbreak.</p> <p>Possible case Acute onset of fever but no rash in a person with an epidemiological link to a confirmed case, and reviewed by an infectious diseases physician.</p>

Table 6: *Clinical Characteristics of smallpox and chickenpox used in differential diagnosis*

SYMPTOMS	SMALLPOX	CHICKENPOX
References	(16)(17)(18)(32)-	(33)(34)
Prodromal symptoms		Unusual in children Less important than for smallpox
High Fever	100%	Possible
Low grade fever	0%	Common
Weakness	Very common	Possible
Headache, backaches	Common	Rare
Malaise	Very common	Possible
Prostration	Very Common	Uncommon
Abdominal symptoms	Common	Rare
Fever	Very common	Common early but resolves quickly
Respiratory symptoms	0%	Rare (Varicella pneumonitis occurs in 1/400 adults; more common in immunocompromised patients)
Gastrointestinal symptoms	Uncommon	Uncommon
Intestinal tract bleeding	1%	0
Purpuric rash	1%	Uncommon(20)
Encephalitis	Uncommon	0.1% to 0.2%

Cerebral ataxia	0%	Very rare (1/4000 in children <15 years) (20)
Rash	99%-100%	Very common
Initial small red spot	By day 5 of the rash(19)	
Subsequent vesicular rash	By day 7 of the rash(19)	
Subsequent pustular rash	100%	
- Facial involvement	100%	
- Face predominance	Initial	Later in illness
- Found on the palm and soles	Yes	Uncommon
- Lesions develop in the same phases	Yes	No

Very common= 80 to 99%, common = 60 to 79%, quite often = 30 to 59%, possible 10 to 29%, Uncommon 5 to 10%. rare 1 to 4%,very rare <1%

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19. ABSTRACT This paper undertakes a technical review of the properties of three diseases often associated with the threat of bioterrorism: anthrax, plague and smallpox. While the literature on these agents is extensive, the information is not generally available in a concise form for the purpose of modelling the course of spread of disease through a population, including the emergence of observable indicators of community infection. The focus here is to extract from the literature information describing these agents for the purpose of developing models of symptoms emergence and disease progression in individual people, as well as parameters describing how the diseases may spread in a community and be observable. This information can be used to parameterise models of disease diagnosis in a community, for the purpose of analysing candidate syndromic surveillance systems. Information is also provided on common diseases that may be misdiagnosed in the early stages of an outbreak due to an act of bioterrorism, namely, influenza, chickenpox, and community acquired pneumonia. Where information is not available in precise quantitative form, semi-quantitative graphs are provided, which provide a useful summary for developers of probabilistic models of disease diagnosis.					