INTERNATIONAL JOURNAL OF MULTIDISCIPLINARY RESEARCH AND STUDIES

VOLUME04ISSUE04

# ''RE-ASSESSMENT OF MITIGATION STRATEGIES FOR DELIBERATE RELEASES OF ANTHRAX EMPLOYING A REAL-TIME OUTBREAK CHARACTERIZATION TOOL''

DR.G.PARIC; PRO.DS. ZORIC

## ABSTRACT

responding rapidly and appropriately to a covert anthrax release is a crucial public health challenge. a strategy to help the geographical targeting of such a response has recently been published; as have several independent studies that investigate mitigation strategies. Here, we review and mix a number of these published techniques to more realistically assess how key aspects of the general public health response might impact the outcomes of a bioterrorist attack. We combine a within-host mathematical model with our spatial back-calculation method to research the consequences of several important response variables. These include how previously reported levels of adherence with taking antibiotics might affect the full outbreak size compared to assuming full adherence. Post-exposure vaccination is additionally considered, both with and without the employment of antibiotics. Further, we investigate a variety of delays (2, 4, and eight days) before interventions are implemented, following the Last Day of symptomatic onset of some number of observed initial cases (5, 10, and 15). Our analysis confirms that outbreak size is minimized by implementing prophylactic treatment after having estimated the exposed area supported 5 observed cases; however, imperfect (rather than full) adherence with antibiotics leads to approximately 15% additional cases. Moreover, of these infected individuals who only partially adhere to a prophylactic course of antibiotics, 86% remain disease-free; a result that holds for scenarios within which infected individuals inhale much higher doses than considered here. Increasing logistical delays have a very detrimental effect on lives saved with an optimal strategy of early identification and analysis. Our analysis shows that it's critical to own systems and processes in situ to rapidly identify, geospatially analyze then swiftly reply to a deliberate anthrax release.

**Keywords**

Bacillus Anthracis Bioterrorism Computer simulation disease out breaks Statistical model public health practice

## Introduction

In the event of covert aerosolized anthrax released within the UK, public health authorities would try to provide antibiotics to exposed individuals to attenuate the amount of casualties and deaths (HPA website, 2010). Our recent spatial back-calculation study (Legrand et al., 2009) has shown that it would be possible to spot those individuals sufficiently exposed to warrant prophylactic treatment using data on the primary few cases (symptomatic onset dates and home/work locations) together with recent environmental condition. To estimate the potential good thing about using this method, we previously assumed that prophylactic antibiotic treatment would be administered to exposed individuals after a set logistical delay (4 days) following the symptomatic onset of some number (5 to 15) of observed initial cases, like could be required to prompt recognition of a covert attack and also to allow the statistical analysis of the geographical extent of the discharge. We also assumed that antibiotics would completely prevent disease altogether those that were symptom-free at the time of antibiotic administration. As we highlighted previously, a number of these assumptions are uncertain and need sensitivity analysis — indeed, several research papers (Brookmeyer et al., 2004, Wein et al., 2003, Wein & Craft, 2005, Baccam & Boechler, 2007, Fowler et al., 2005, Craft et al., 2005, Braithwaite et al., 2006, Zaric et al., 2008, Wilkening, 2008) have considered such outcomes but only from a contingency planning perspective instead of one among a real-time response situation, which we consider here. during this study, we briefly review the substantial amount of modeling work that has been performed regarding anthrax mitigation strategies. We then combine aspects of those modeling approaches with our own work on spatial back-calculation approaches to judge more realistic treatment outcomes. Additionally to examining antibiotic prophylaxis, the likelihood of implementing prophylactic vaccination is additionally assessed.

**Background**

Brookmeyer et al. (2004) developed a mechanistic within-host model describing the human dose-response relationship of anthrax supported germination and clearance rates of B spores inhaled into the lungs. This model was wont to analyze the advantages of antibiotic prophylaxis with varying response times, durations of drug administration, and patient adherence levels following an aerosolized anthrax release. it had been found that “even if the mass distribution of antibiotics is completed within six days of the initial exposure, then at the most about 70% of cases may be prevented”. Post-exposure vaccination was shown to possess limited preventative effects thanks to the delay of roughly one month after vaccination before achieving immunity. However, other factors like antibiotic-resistant strains or low adherence to long-term antibiotic therapy mean that post-exposure vaccination could sway be a vital secondary intervention. it had been also shown that any additional benefits gained from pre-exposure vaccination would require very high population coverage.

Wein et al. (2003) assessed the impact of a large-scale anthrax attack on a typical U.S. city and similarly highlighted the necessity for rapid antibiotic distribution to exposed individuals, especially as hospitalization proved to be a bottleneck within the healthcare system. Their model was further developed to assess the relative benefits of administering a vaccine before or after an anthrax attack (Wein and Craft, 2005). This latter paper, however, features a slight error whereby an equation describing exposed individuals was applied to infected individuals (see Eq. (A4) within the Appendix). Fortunately, this only includes a relatively small effect on the quantitative results and doesn't change the qualitative conclusion that, with or without pre-exposure vaccination, a post-exposure strategy that combined both antibiotics and anthrax vaccine was superior to antibiotic prophylaxis alone. A recent simulation study undertaken by Baccam and Boechler (2007) found complementary results to those presented within the analytical study of Wein and Craft (2005) favoring a post-exposure response with combined antibiotic and vaccine treatment.

A cost-effectiveness study by Fowler et al. (2005) similarly found that “use of vaccine plus antibiotic prophylaxis is that the simplest and least expensive therapy” when considering post-attack strategies only. This was because the extra vaccine-related cost was shown to be but the high cost of medical aid for those individuals who would otherwise become symptomatic thanks to the assumed imperfect antibiotic efficacy. Fowler et al. also suggested that pre-exposure vaccination may become cost-effective if the antibiotic distribution or adherence was substantially impaired but interestingly found that “antibiotic prophylaxis would still be an economical component of post-attack therapy, even for people who had previously received vaccination” because of a but 100% effective vaccine. Conversely, Braithwaite et al. (2006) found that pre-event vaccination was less cost-effective than post-event strategies primarily thanks to the assumed low rates of adherence with anthrax immunization programs.

Interestingly, Craft et al. (2005) only considered pre-event vaccination and not post-event vaccination “because of the non-negligible probability of another anthrax event, and since of the good cost and difficulty of mounting a good post-event response” (Wein and Craft, 2005). Although the anthrax vaccine appears safer than the smallpox vaccine, moderate and severe side effects would likely occur with a large-scale vaccination program. The resistance to smallpox and anthrax vaccination among front-line workers and therefore the military, respectively, suggests that it'd be difficult to attain the high levels of coverage required for pre-event vaccination to be effective (Wein and Craft, 2005). Note that we don't consider pre-event mass vaccination within the following analysis since we believe that the associated problems outweigh any potential benefits.

The mass treatment strategies considered within the above studies essentially follow an assumption that “the true exposed population soon after the event is unknown” (Baccam and Boechler, 2007). Moreover, 3 further modeling papers (Braithwaite et al., 2006, Zaric et al., 2008, Hupert et al., 2009) addressing the relative logistical and operational merits of anthrax bioterrorism surveillance and response have all highlighted the im-

portance of identifying exposed individuals once an attack has been detected. Our recent work (Legrand et al., 2009) has shown that it should indeed be possible to satisfactorily estimate the placement and geographic extent of an anthrax attack supported spatial and temporal information from early cases and up to date meteorological data. This was supported a way that combined a spore dispersion model, within-host dynamics, and daily movement data. within the work presented below, we use this previously developed method to analyze a wider and more realistic range of mitigation strategies and assumptions than considered previously.

**Methods**

Our previous model of an anthrax outbreak (Legrand et al., 2009) incorporates the within-host dynamics of spore germination and clearance (first described by Brookmeyer et al. (2004)) to calculate the probability of infection given a selected inhaled dose. Both prophylactic antibiotics and vaccination can reduce this probability of infection by destroying spores as they begin to germinate and multiply, thus preventing the assembly of disease-inducing toxins. Here we adapt previously published methodologies (Brookmeyer et al., 2004, Wein & Craft, 2005) to match the impact of antibiotics and/or vaccination within the context of getting estimated those individuals requiring prophylactic treatment via our back-calculation method (Legrand et al., 2009). To compute the outbreak size for every mitigation strategy we applied the treatment effectiveness (detailed within the Appendix) to infected individuals who had been identified for treatment but who were yet to develop symptoms at the time of treatment administration. within the text that follows we describe the parameterization of those various mitigation strategies.

**Treatment strategies**

Previously we considered that every one individuals identified as having an exposure risk of a minimum of 1/100,000 (via our spatial back-calculation methodology) would receive antibiotics following a 4-day logistical delay after the primary 5, 10, or 15 cases had occurred (Legrand et al., 2009). Although Wein et al. (2003) similarly believed that

"antibiotics are often distributed to the complete population in 4 days" it had been important to research how uncertainties during this delay between outbreak detection and prophylactic treatment would impact upon the full number of cases; therefore, we considered delays of two, 4 and eight days.

Calculation of the outbreak size in our earlier study was supported the simplifying assumption that adherence with, and efficacy of, antibiotic prophylaxis for 60 days was 100% if initiated before the onset of symptoms (termed full antibiotic adherence). However, experience from the 2001 anthrax attacks suggests that several individuals will only partially adhere to a prophylactic course of antibiotics (Shepard et al., 2002). To account for this behavioral effect we followed Wein and Craft (2005) in order that among individuals offered antibiotics, 10% take no antibiotics, 15% take antibiotics for exactly 15 days, 25% take them for exactly 30 days, 25% take them for 45 days, and 25% take them for the total 60 days. Hereafter this behavior is collectively spoken as imperfect antibiotic adherence.

In addition to prophylactic treatment based purely on antibiotics, we also considered the impact of post-exposure prophylactic vaccination (termed vaccination). The vaccine efficacy was assumed to be 90%, with 50% of these receiving the vaccine acquiring immunity after 21 days and therefore the other 50% after 28 days (Wein and Craft, 2005). Five post-exposure treatment outcomes were therefore investigated:

1)No treatment;

2)Vaccination;

3)Imperfect antibiotic adherence;

4)Vaccination + imperfect antibiotic adherence; and

5)Full antibiotic adherence.

Whilst outcomes 1 and 5 had been compared in our earlier study (Legrand et al., 2009) and outcomes 2–4 had been considered in some earlier modeling studies elsewhere (Brookmeyer et al., 2004, Wein & Craft, 2005), crucially these latter outcomes had not been investigated in a very modeling context that included a practical prospect of having the ability to statistically estimate the population requiring prophylactic treatment.

**Scenarios**

We examined the impact of the treatment strategies under the Reference scenario employed in our previous work and also the 5 misspecification scenarios that account for the potential effects of uncertainties in parameter values, data, and model structure. Here we offer a quick description of those scenarios; see Legrand et al. (2009) for further details. For the Reference scenario, 40 anthrax outbreaks were simulated following airborne releases of 1010 spores from a height of 100 m into a 5 m/s westerly wind. In these simulations, the time period of infected individuals was supported a continual exposure model but the following back-calculation assumed a direct exposure for the sake of simplicity. Scenario a second user the Reference scenario simulations but performed the back-calculation with individuals' symptomatic onset times rounded to the closest half-day instead of the closest hour. Scenario B also used the Reference scenario simulations but with a median delay between spore germination and therefore the symptomatic onset of 5 days within the back-calculation model instead of the two days wont to simulate the outbreak. for every of scenarios C to E, we simulated 40 outbreaks as before but with three modified versions of the simulation model; the within-host dynamics component was replaced by the model proposed by Brookmeyer et al. (2005) for a coffee dose exposure (scenario C), the puff model of airborne dispersion was replaced by the Hazard Prediction and Assessment Capability (Sykes et al., 2007) model (scenario D), and occasional movements were added to the daily commuting data (scenario E). for every of those three scenarios parameter inferences were performed with the Reference scenario back-calculation model.

## Results

Fig. 1 shows the extent to which imperfect antibiotic adherence would lead to slightly larger outbreaks (colored box-plots) than within the case of assuming full adherence (yellow box-plots) (Legrand et al., 2009). Although imperfect antibiotic adherence is maybe realistic given differences in human behavior, the relatively small differences within the number of cases highlight that our previous assumption of complete antibiotic protection is fairly accurate for the tiny outbreaks considered here. More importantly, however, Fig. 2 shows how imperfect, as hostile full, antibiotic adherence encompasses a larger effect on outbreak size when antibiotic prophylaxis is initiated after atiny low number of cases have occurred; on the average approximately 15% more cases are expected when antibiotics are implemented after 5 observed cases whereas only ~ 5% more cases result when intervening after 15 observed cases. this happens because starting interventions earlier in a plague implies that more individuals can receive prophylactic treatment and thus more individuals can fail to stick to the total course of antibiotics. Thus, although our results confirm that implementing interventions supported fewer cases continues to be likely to forestall more cases than awaiting further cases (Fig. 1), the effect of imperfect adherence is to minimize this relative benefit (Fig. 2).

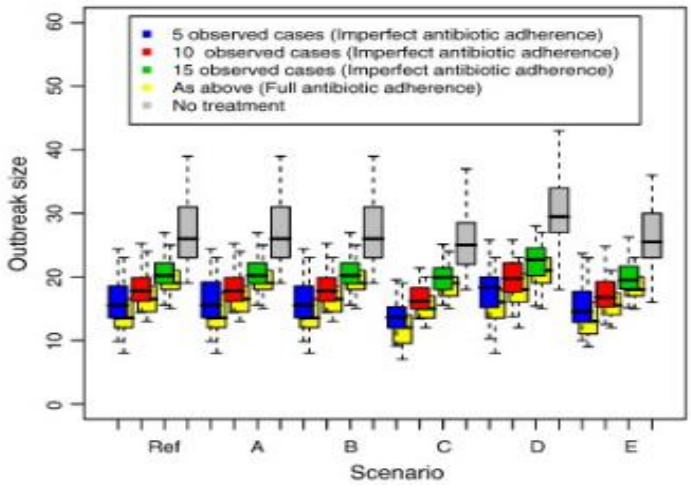

Fig. 1. Impact of administering prophylactic antibiotics to individuals living or working during a ward exposed to a risk of a minimum of 1/100,000 inhabitants with Reference scenario (Ref) and scenarios A to E: outbreak size with no treatment (grey boxes), with imperfect antibiotic adherence (colored boxes) and with full antibiotic adherence (yellow boxes) administered 4 days after the primary 5, 10 or 15 cases occurred. Each box plot represents the 25th, 50th, and 75th percentiles of the distribution of the entire number of cases from 40 simulations (whiskers reach 1.5 times the inter-quartile range).

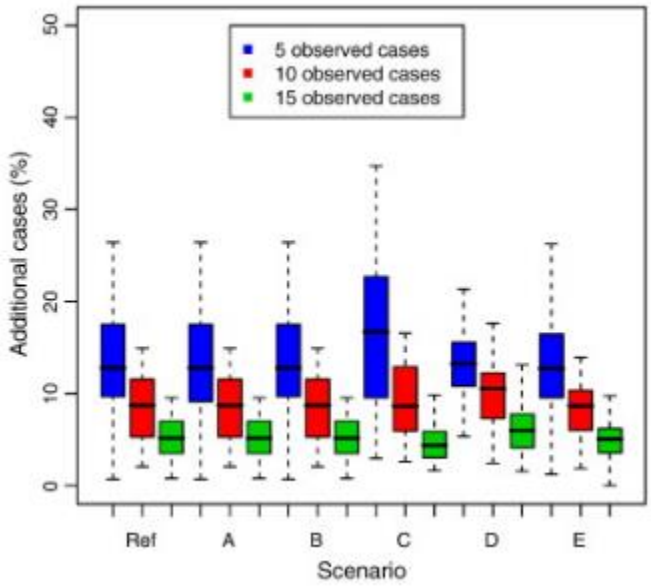


Fig. 2. The relative difference in outbreak size between outcomes of imperfect antibiotic adherence and full antibiotic adherence. Antibiotics administered 4 days after the primary 5 (blue boxes), 10 (red boxes), or 15 (green boxes) cases have occurred with Reference scenario (Ref) and scenarios A to E. Each box plot represents the 25th, 50th, and 75th percentiles of the distribution from 40 simulations (whiskers touch 1.5 times the inter-quartile range).

Given that the delay from vaccination to the acquisition of functional immunity corresponds to a high percentile of the period distribution, a technique based purely on post-exposure vaccination of affected areas is probably going to be only marginally better

than providing no treatment in the slightest degree (Fig. 3). Although public health authorities would likely provide antibiotic treatment following an aerosolized anthrax release, it is, however, possible that the anthrax strain might be proof against antibiotics and thus vaccination alone might represent a 'worst-case' outcome under these circumstances. With no antibiotic resistance, a combined antibiotic and vaccination strategy is realistically optimal (Fig. 3), provided that it's likely there'll be imperfect antibiotic adherence. However, as shown in Fig. 1, Fig. 2 and supported in Fig. 3, if logistical constraints meant that vaccination couldn't be performed then rapid administration of antibiotics alone would still be a highly effective prophylactic treatment strategy.

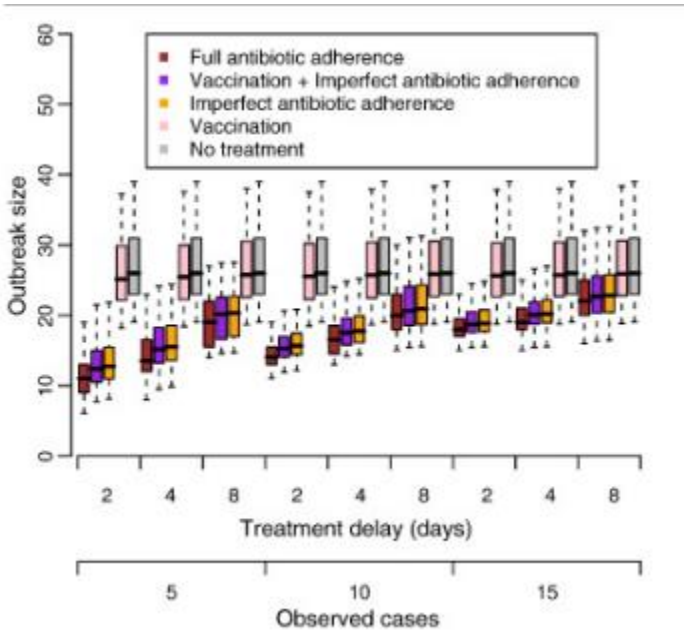


Fig. 3. Impact of assorted prophylactic treatment outcomes to individuals living or working in a very ward exposed to a risk of a minimum of 1/100,000 inhabitants with Reference scenario (Ref): outbreak size when treatment is run 2, 4, or 8 days after the primary 5, 10, or 15 cases occurred. Each box plot represents the 25th, 50th, and 75th percentiles of the distribution of the full number of cases from 40 simulations (whiskers touch 1.5 times the inter-quartile range).

Treatment delays have way more of an impression if interventions are initiated after 5 observed cases than after 15 observed cases (Fig. 3). this can be because, with a final expected outbreak size of about 25–30 cases, the primary five cases would likely come from the first tail of the time period distribution meaning that, with from now on delays, interventions might miss the majority of people yet to present with symptoms. However, intervening after 15 cases means there are fewer cases still to become symptomatic and so subsequent delays beyond this can have less effect on the ultimate outbreak size (though the increased delays overall will obviously have resulted in more cases). These results highlight the importance of a mix of early estimation of the geographic targeting of prophylactic treatment with its rapid distribution; delays with either are likely to possess a detrimental impact on the lives saved overall.

Using Eq. (A3) within the Appendix we note that the typical treatment effectiveness (i.e. the efficacy of treatment when combined with the timing of antibiotic adherence and/or vaccination immunity) for those infected individuals who received treatment before displaying symptoms was:

•No treatment: 0%.

•Vaccination: 7%.

•Imperfect antibiotic adherence: 86%.

•Vaccination + imperfect antibiotic adherence: 89%.

•Full antibiotic adherence: 100%.

These values are constant across all delays, the observed number of cases, and scenarios outlined during this paper. Furthermore, these values remain stable for inhaled doses of up to approximately 10,000 spores (see Fig. 4) and would therefore apply for an excessive amount of larger releases than considered here (where those infected

inhaled approximately 10 spores). For very large doses (> 10,000 inhaled spores) the effectiveness of full/imperfect antibiotic adherence in preventing disease decreases (Fig. 4) since it's increasingly likely that spores will remain within the lungs even after 60 days of taking antibiotics. Fig. 4 also shows the effectiveness of the vaccination alone strategy similarly decreasing with increasing dose; a results of the increasing probability of spore germination before gaining immunity. Only the 'Vaccination + imperfect antibiotic adherence' outcome remains somewhat effective at very high doses because immunity is achieved whilst taking antibiotics for a proportion of people. This effect is taken into account further within the discussion.

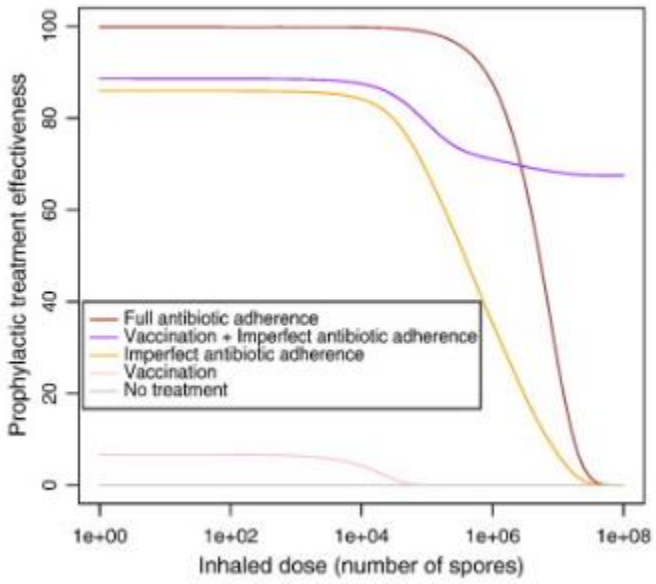


Fig. 4. the common effectiveness of varied prophylactic treatment outcomes at preventing disease for infected individuals. We conservatively set t1 = 0 in Eq. (A3) within the Appendix to get a bound on the effectiveness. Values of t2 and t3 are provided within the Methods.

## Discussion

Hupert et al. (2009) recently summarised the inputs and outputs of eight US-based an-

thrax modeling studies and highlighted the importance of comparing and contrasting the results of complementary work-streams to realize a consensus regarding optimal mitigation strategies. Fittingly, we've built on earlier research by combining our spatial back-calculation methodology results (Legrand et al., 2009) with various post-exposure prophylactic treatment strategies proposed by others (Brookmeyer et al., 2004, Wein & Craft, 2005). Our results confirm that rapid identification of a covert anthrax release after the tiniest number possible of early cases; a direct statistical assessment of its geographic extent supported their case histories; and a rapidly targeted antibiotic prophylaxis strategy for those deemed exposed is critical if casualties are to be minimized.

In this study, we examined potentially more realistic (i.e. poorer) adherence with antibiotics than considered previously and located that such imperfect adherence might end in approximately 15% extra cases with early implementation of treatment. absolutely the differences in outbreak size here were small thanks to the low inhaled doses (and thus the little outbreak sizes) that result from the scenarios considered. However, for larger releases, the impact of adherence is probably going to be significant especially when combined with rapid interventions, where large numbers of lives could potentially be saved. Indeed, even at high exposure levels (~ 10,000 spores), the previously assumed 100% effectiveness of antibiotics falls to 86% when assuming the adherence levels observed during the 2001 anthrax attacks. for people inhaling particularly large doses (> 10,000 spores), antibiotics can be required for 4 months or longer (Brookmeyer et al., 2003); in such scenarios, vaccination might be wont to shorten the antibiotic course (Brookmeyer et al., 2004). Thus, although full antibiotic adherence would be optimal for the bulk of cases in many release scenarios, additional vaccination may need to be considered for people experiencing very high exposure levels, furthermore as for mitigating against imperfect antibiotic adherence (and any strain resistance to antibiotics).

Although we will generalize our results somewhat, modeling larger 'worst-case' anthrax releases would require slightly different assumptions to those considered during

this study. for instance, because of the little outbreak sizes here we assumed that cases would receive antibiotics at approximately the identical time but distributing antibiotics during much larger outbreaks is probably going to require several additional days (Brookmeyer et al., 2004, Wein & Craft, 2005, Baccam & Boechler, 2007, Zaric et al., 2008, Wilkening, 2008, Hupert et al., 2009), potentially leading to more cases. On the opposite hand, with larger outbreaks and thus a bigger number of early cases, it's important to think about that outbreak detection may occur sooner which adherence rates could increase thanks to a greater perceived risk of infection (Braithwaite et al., 2006). In reality, and maybe most significantly, although a better number of cases is probably going to produce improved estimates of the situation and spatial extent of a deliberate release, there'll be significant public health challenges in rapidly and reliably collecting the desired epidemiological data, especially from individuals (or their relatives/friends) that are already seriously ill.

**Appendix**

With the time of exposure to anthrax spores at t = 0, we denote a method without interventions as S0 and a technique with interventions, starting at time t1, as S1. Under S0, we denote the amount of cases developing symptoms before t1 as C1 and also the number of cases developing symptoms after t1 as C2. the full number of cases, C, is then given by:

$$C = C_1 + C_2.$$

Under $S_1$ we have:

$$C = C_1 + C_2(1 - d)$$

where $d$ is the *effectiveness* of treatment given by:

$$d = 1 - \frac{P(\text{developing symptoms with } S_1 | \text{no symptoms before } t_1)}{P(\text{developing symptoms with } S_0 | \text{no symptoms before } t_1)}.$$

Derivation of the effectiveness

The probability, p, of infection given an inhaled dose, D, (also referred to as the dose-

response function or attack rate) of anthrax in humans will be described by the subsequent equation:

where $\lambda = 1 * 10^{-4}$ days$^{-1}$ and $\theta = 0.109$ days$^{-1}$ are the spore germination and clearance rates, respectively, from the lung (Brookmeyer et al., 2004). We note that:

$$P(\text{developing symptoms before } t_1) = 1 - \exp\left(-D\frac{\lambda}{\lambda+\theta}\left(1 - e^{-(\lambda+\theta)t_1}\right)\right)$$
$$\Rightarrow P(\text{no symptoms before } t_1) = \exp\left(-D\frac{\lambda}{\lambda+\theta}\left(1 - e^{-(\lambda+\theta)t_1}\right)\right).$$

Conditioning on the attack rate we find that:

$$\begin{aligned} p_{\text{condition}} &= P(\text{developing symptoms with } S_0 | \text{no symptoms before } t_1) \\ &= \frac{P(\text{developing symptoms with } S_0 \cap \text{ no symptoms before } t_1)}{P(\text{no symptoms before } t_1)} \\ &= \frac{P(\text{developing symptoms with } S_0 \text{ after } t_1)}{P(\text{no symptoms before } t_1)} \\ &= \frac{p - P(\text{developing symptoms before } t_1)}{P(\text{no symptoms before } t_1)} \\ &= \frac{1-\exp\left(-D\frac{\lambda}{\lambda+\theta}\right) - \left(1-\exp\left(-D\frac{\lambda}{\lambda+\theta}\left(1-e^{-(\lambda+\theta)t_1}\right)\right)\right)}{\exp\left(-D\frac{\lambda}{\lambda+\theta}\left(1-e^{-(\lambda+\theta)t_1}\right)\right)} \\ &= 1 - \exp\left(-D\frac{\lambda}{\lambda+\theta}e^{-(\lambda+\theta)t_1}\right). \end{aligned} \quad \text{(A1)}$$

The modified attack rate, c, for a personal who starts and stops taking antibiotics at t1 days and t2 days, respectively, and so acquires immunity (via vaccination) at t3 days is given by:

$$c = P(\text{developing symptoms with } S_1) = 1 - \exp\left(-D\frac{\lambda}{\lambda+\theta}\left(1 - e^{-(\lambda+\theta)t_1} + e^{-(\lambda+\theta)t_2} - e^{-(\lambda+\theta)t_3}\right)\right).$$

Here we assume that antibiotic distribution and vaccination occur at the identical time. Note that for a method of vaccination alone, t2 = t1, for a technique of antibiotics alone, t3 → ∞, and that we set t3 = t2 if immunity develops before a personal stops taking antibiotics (Brookmeyer et al., 2004). As before it holds that:

$$P(\text{developing symptoms before } t_1) = 1 - \exp\left(-D\frac{\lambda}{\lambda+\theta}\left(1 - e^{-(\lambda+\theta)t_1}\right)\right)$$
$$\Rightarrow P(\text{no symptoms before } t_1) = \exp\left(-D\frac{\lambda}{\lambda+\theta}\left(1 - e^{-(\lambda+\theta)t_1}\right)\right).$$

Conditioning on the modified attack rate we discover that:

Combining Eqs. (A1), (A2) we discover that the effectiveness of treatment is then given by:

Conditioning on the modified attack rate we find that:

$$c_{\text{condition}} = P(\text{developing symptoms with } S_1 | \text{no symptoms before } t_1) \quad \text{(A2)}$$
$$= \frac{P(\text{developing symptoms with } S_1 \cap \text{no symptoms before } t_1)}{P(\text{no symptoms before } t_1)}$$
$$= \frac{P(\text{developing symptoms with } S_1 \text{ after } t_1)}{P(\text{no symptoms before } t_1)}$$
$$= \frac{c - P(\text{developing symptoms before } t_1)}{P(\text{no symptoms before } t_1)}$$
$$= \frac{1-\exp\left(-D\frac{\lambda}{\lambda+\theta}\left(1-e^{-(\lambda+\theta)t_1}+e^{-(\lambda+\theta)t_2}-e^{-(\lambda+\theta)t_3}\right)\right)-\left(1-\exp\left(-D\frac{\lambda}{\lambda+\theta}\left(1-e^{-(\lambda+\theta)t_1}\right)\right)\right)}{\exp\left(-D\frac{\lambda}{\lambda+\theta}\left(1-e^{-(\lambda+\theta)t_1}\right)\right)}$$
$$= 1 - \exp\left(-D\frac{\lambda}{\lambda+\theta}\left(e^{-(\lambda+\theta)t_2} - e^{-(\lambda+\theta)t_3}\right)\right).$$

Combining Eqs. (A1), (A2) we find that the *effectiveness* of treatment is then given by:

$$d = 1 - \frac{c_{\text{condition}}}{p_{\text{condition}}} \quad \text{(A3)}$$
$$= 1 - \frac{1-\exp\left(-D\frac{\lambda}{\lambda+\theta}\left(e^{-(\lambda+\theta)t_2}-e^{-(\lambda+\theta)t_3}\right)\right)}{1-\exp\left(-D\frac{\lambda}{\lambda+\theta}e^{-(\lambda+\theta)t_1}\right)}.$$

We applied Eq. (A3) to those infected individuals who had been identified for treatment via the spatial back-calculation methodology (Legrand et al., 2009) and who were yet to present with symptoms at the time of treatment administration. Note that an equivalent equation for exposed (rather than infected) individuals is given by:

$$e = 1 - c_{\text{condition}} \quad \text{(A4)}$$

## References

Baccam & Boechler, 2007

P. Baccam, M. Boechler

Public health response to an anthrax attack: an evaluation of vaccination policy options

Biosecur. Bioterror., 5 (1) (2007), pp. 26-34
CrossRefView Record in ScopusGoogle Scholar

Braithwaite et al., 2006
R.S. Braithwaite, D. Fridsma, M.S. Roberts
The cost-effectiveness of strategies to scale back mortality from an intentional release of aerosolized anthrax spores
Med. Decis. Mak., 26 (2) (2006), pp. 182-193
View Record in ScopusGoogle Scholar

Brookmeyer et al., 2003
R. Brookmeyer, E. Johnson, R. Bollinger
Modeling the optimum duration of antibiotic prophylaxis in an anthrax outbreak
Proc. Natl Acad. Sci. USA, 100 (17) (2003), pp. 10129-10132
View Record in ScopusGoogle Scholar

Brookmeyer et al., 2004
R. Brookmeyer, E. Johnson, R. Bollinger
Public health vaccination policies for holding an anthrax outbreak
Nature, 432 (2004), pp. 901-904
CrossRefView Record in ScopusGoogle Scholar

Brookmeyer et al., 2005
R. Brookmeyer, E. Johnson, S. Barry
Modeling the period of anthrax
Stat. Med., 24 (2005), pp. 531-542
CrossRefView Record in ScopusGoogle Scholar

Craft et al., 2005
D.L. Craft, L.M. Wein, A.H. Wilkins

Analyzing bioterror response logistics: the case of anthrax
Manage. Sci., 51 (2005), pp. 679-694
CrossRefView Record in ScopusGoogle Scholar

Fowler et al., 2005
R.A. Fowler, et al.
Cost-effectiveness of defending against bioterrorism: a comparison of vaccination and antibiotic prophylaxis against anthrax
Ann. Intern. Med., 142 (2005), pp. 601-610
CrossRefView Record in ScopusGoogle Scholar

HPA website, 2010
HPA website, 2010. Available at:
http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947395481.
Google Scholar

Hupert et al., 2009
N. Hupert, et al.
Predicting hospital surge after a large-scale anthrax attack: a model-based analysis of CDC's cities readiness initiative prophylaxis recommendations
Med. Decis. Mak., 29 (4) (2009), pp. 424-437
View Record in ScopusGoogle Scholar

Legrand et al., 2009
J. Legrand, et al.
Estimating the situation and spatial extent of a covert anthrax release
PLoS Comput. Biol., 5 (1) (2009), p. e1000356, 10.1371/journal.pcbi.1000356
CrossRefGoogle Scholar

Shepard et al., 2002
C.W. Shepard, et al.
Antimicrobial post exposure prophylaxis for anthrax: adverse events and adherence
Emerg. Infect. Dis., 8 (2002), pp. 1124-1132
CrossRef View Record in Scopus Google Scholar

Sykes et al., 2007
R. Sykes, et al.
SCIPUFF Version 2.3, Technical Documentation
(2007)
Google Scholar

Wein & Craft, 2005
L.M. Wein, D.L. Craft
Evaluation of public health interventions for anthrax: a report back to the secretary's council on public health preparedness
Biosecur. Bioterror., 3 (2005), pp. 348-356
CrossRef View Record in Scopus Google Scholar

Wein et al., 2003
L.M. Wein, D.L. Craft, E.H. Kaplan
Emergency response to an anthrax attack
Proc. Natl Acad. Sci. The USA, 100 (2003), pp. 4346-4351
View Record in Scopus Google Scholar

Wilkening, 2008
D.A. Wilkening
Modeling the time period of anthrax
Med. Decis. Mak., 28 (2008), pp. 593-605

View Record in Scopus Google Scholar

Zaric et al., 2008

G.S. Zaric, et al.

Modeling the logistics of response to anthrax bioterrorism

Med. Decis. Mak., 28 (3) (2008), pp. 332-350

View Record in Scopus Google Scholar

**AUTHOR AFFILIATION**

DR.G.PARIC

PRO.DS. ZORIC