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Predicting Hospital Surge after a Large-Scale Anthrax Attack: A Model-Based Analysis of CDC's Cities Readiness Initiative Prophylaxis Recommendations

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Background. *After a major bioterrorism attack, the US Centers for Disease Control and Prevention (CDC) Cities Readiness Initiative (CRI) calls for dispensing of medical countermeasures to targeted populations within 48 hours. The authors explore how meeting or missing this 48-hour goal after a hypothetical aerosol anthrax attack would affect hospital surge, in light of the multiple uncertainties surrounding anthrax-related illness and response.* ***Design***. *The authors created a discrete-time state transition computer model representing the dynamic interaction between disease progression of inhalational anthrax and the rate of dispensing of prophylactic antibiotics in an exposed population.* ***Results***. *A CRI-compliant prophylaxis campaign starting 2 days after exposure would protect from 86% to 87% of exposed individuals from illness (assuming, in the base case, 90% antibiotic effectiveness and a 95% attack rate). Each additional day needed to complete the campaign would result in, on average, 2.4% to 2.9% more hospitalizations in the exposed population; each additional day's delay to initiating prophylaxis beyond 2 days would result in 5.2% to 6.5% additional hospitalizations. These population protection estimates vary roughly proportionally to antibiotic effectiveness but are relatively insensitive to variations in anthrax incubation period.* ***Conclusion***. *Delays in detecting and initiating response to large-scale, covert aerosol anthrax releases in a major city would render even highly effective CRI-compliant mass prophylaxis campaigns unable to prevent unsustainable levels of surge hospitalizations. Although outcomes may improve with more rapid epidemiological identification of affected subpopulations and increased collaboration across regional public health and hospital systems, these findings support an increased focus on prevention of this public health threat.* ***Key words:*** *anthrax; emergency preparedness; antibiotic prophylaxis; hospital bed capacity; models, decision support; models, theoretical.* ***(Med Decis Making 2009;29:424–437)***

BACKGROUND

The release of anthrax (*Bacillus anthracis*) spores over a major metropolitan region, an event with the potential to cause massive casualties on the scale of a small nuclear detonation, had received considerable federal attention even before the 2001 US mail attacks that killed 5 people and sickened 22.[1,2] With the creation of the Strategic National Stockpile (SNS) in 1999, the US government directed significant financial and human resources to the development of countermeasures and strategies to mitigate the effects of intentional and natural outbreaks of disease.[1] In 2004, the Department of Health and Human Services (DHHS) convened the Anthrax Modeling Working Group (AMWG) of the Secretary's Council on Public Health Emergency Preparedness to provide quantitative guidance on the purchase and use of medical countermeasures to minimize the health impact of anthrax release over

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civilian populations. The Centers for Disease Control and Prevention (CDC) also unveiled the Cities Readiness Initiative (CRI), the nation's first attempt to standardize public health actions—notably mass prophylaxis dispensing tactics—to minimize casualties in the aftermath of such an event.[3]

Three independent reports from AMWG members have been published since 2004, each using distinctive modeling approaches to estimate the effectiveness of preexposure and postexposure antibiotic dispensing and vaccination strategies in preventing inhalational anthrax.[3–5] Brookmeyer and colleagues[5] formulated a mathematical "competing risk" model of spore germination v. immunological clearance to gauge the risk of illness after exposure, Wein and Craft[3] combined that risk estimation method with a complex analytic queuing model of prophylaxis and medical treatment to determine casualties after exposure, and Baccam and Boechler[4] estimated casualties using a discrete-time compartment model representing both incubation and disease progression under different prophylaxis and medical treatment interventions. All 3 reports (and additional papers[6–9]) support the conclusion that delay to campaign initiation has a greater impact on casualties than campaign duration. However, they do not directly address key operational questions for planning the health system response to an anthrax attack, such as what the expected surge on hospital resources would be. In this article, the fourth and final report of the 2004 AMWG, we present a new model that directly evaluates the impact of current CRI guidance for mass prophylaxis campaigns on population-level outcomes.

The CRI mass prophylaxis recommendations center on a "48-hour goal" for countermeasure distribution.[10,11] Specifically, CRI grantees, which now comprise the 72 largest cities in the United States, must demonstrate the ability to dispense countermeasures to all designated at-risk populations within 48 hours of the decision to do so. Although the CRI addresses urban centers, this 48-hour performance goal has assumed near-universal currency in countermeasure dispensing strategies across the United States. Massachusetts, for example, recently described how its statewide public health response infrastructure was essentially completely reinvented since 2004 to meet the CRI requirement.[11] However, no published reports have quantitatively evaluated how outcomes vary in relation to meeting or missing the 48-hour goal; in fact, one recently published model assumed that the first 48 hours of an anthrax response dispensing campaign would constitute just the "ramp-up" time to full dispensing capacity, with the actual mass prophylaxis campaign taking over 11 days.[12]

The model presented here, first developed in 2002–2003 for the Agency for Healthcare Research and Quality (AHRQ), was used during the initial formulation of the CRI to provide quantitative assessments of the effect of mass prophylaxis interventions on expected hospital surge arrivals in the aftermath of an aerosol anthrax attack (Dr. William Raub, DHHS, personal communication, September 10, 2008.).[13] Here we use an updated version of the model to explore 2 interrelated questions: what are the consequences of missing the CRI 48-hour goal for postexposure prophylaxis, and what impact do initial response time, anthrax incubation period, and antibiotic effectiveness have on expected hospitalizations? Unlike other AMWG models, ours does not attempt to predict survival after hospitalization because our objective was to clarify the impact of public health interventions on patient arrivals to hospitals (or other health care delivery locations). How that load is handled, and with what expected outcomes, is an important but separate modeling issue, which has been ably addressed elsewhere.[14]

METHODS

We created a discrete-time state transition model representing the dynamic interaction between the rate of progression to symptomatic inhalational anthrax and the rate of successful dispensing and effective use of prophylactic antibiotics in a defined population after a large-scale anthrax attack. We focus on the first week of response after population exposure.

Model Structure

The model is based on recently published epidemiological analyses of the 1979 aerosol anthrax release in Sverdlovsk, Russia, which represents the only documented population-level anthrax exposure in modern history.[15–17] The state transition model applies to a hypothetical population that has been exposed to sufficient anthrax spores to cause symptomatic illness. The probability of becoming symptomatic changes due to 3 factors: the probability distribution for the incubation period for inhalational anthrax (see below), the particular prophylaxis strategy undertaken, and the effectiveness of the countermeasures given. A prophylaxis strategy is defined by 2 tactics, the delay until countermeasure dispensing starts ("time to first pill") and the length of time

needed to successfully prophylaxis all those eligible for treatment ("time to last pill"). Once prophylaxis begins, we assume, along with Craft and colleagues,[14] a uniform rate of countermeasure dispensing with no ramp-up period. The model incorporates transitions between asymptomatic but exposed, symptomatic, and prophylaxed states on a daily basis and calculates the area under the incubation distribution curve (i.e., the number of potentially symptomatic individuals). Some patients in this at-risk cohort will by chance be offered prophylaxis on the same day that they happen (probabilistically, due to the incubation distribution) to become symptomatic. For these patients, the model assumes that 38.1% will be hospitalized, based on data in Holty and others[18] suggesting that this is the rate of progression to critical illness for inhalational anthrax if antibiotics are initiated during the prodromal phase of infection.

The model output is the number of individuals who are expected to develop symptomatic inhalational anthrax requiring hospital-based intravenous antibiotic treatment. The inverse of this is the "save rate," or the percentage of exposed and "at-risk" individuals who successfully avoid developing illness due to the prophylaxis campaign.

Model Assumptions and Parameters

Table 1 compares critical modeling assumptions of the model with those of the 3 other AMWG teams as well as those of recent cost-effectiveness, logistical, and mathematical models of anthrax mass prophylaxis by Braithwaite, Fowler, Zaric, and Wilkening.[3–5,12,17,19,20]

Exposure

The model does not explicitly consider spore dispersal. Modeling aerosol plumes involves complex interactions between spore size, charge, and additives; weather conditions; release characteristics; population demographics; building protection factors; time of day; and other factors. Recently, Brookmeyer and colleagues[7] demonstrated the relative insensitivity of the incubation period distribution to dose of inhaled anthrax spores over roughly the range from ID_1 (dose sufficient to cause symptomatic disease in 1% of those exposed) to ID_{50}. Their finding lends pathophysiological support to our simplifying assumption of dose independence of the incubation period for the user-defined exposed population. Instead of relying on a model to determine population exposure, we have configured it as a user input: a definable subfraction of the prophylaxed population is assumed to have inhaled sufficient anthrax spores to cause symptomatic infection. Data support the assumption that 95% of exposed individuals would develop inhalational anthrax in the absence of intervention.[20]

Anthrax Incubation Distribution

The baseline probability distributions for the incubation (or latency) period for inhalational anthrax come from analyses of the Sverdlovsk outbreak by Brookmeyer and colleagues[15] that have recently been revised by Wilkening.[17] Brookmeyer and others fit the timing of hospitalization of 70 cases of inhalational anthrax to a lognormal distribution with a mean of 2.398 and a standard deviation of 0.713, corresponding to a median time to onset of symptoms of 11.0 days with a dispersion factor (e^{σ}) of 2.04 days. Although there has been controversy about the integrity of the Sverdlovsk data and consequently the true shape of an inhalation anthrax latency curve (see, e.g., Inglesby and others[21]), recent comparative analyses by Wilkening provide strong support for using a modified Brookmeyer curve (with a median incubation period of 9.5 days and a dispersion factor of 1.91 days) as a basis for population-based exposure modeling.[16,17,21] Because the Brookmeyer curve forms the basis for other AMWG models, we present and compare results using both estimates, labeled (W) for Wilkening and (B) for Brookmeyer. Brookmeyer's most recent analysis of the Sverdlovsk data suggests that there likely is no "one" anthrax incidence curve but rather multiple rates of disease progression from exposure to symptomatic illness for different demographic subpopulations, with median durations ranging from approximately 8 to 14 days.[7] In light of this demographic variation, we also performed sensitivity analyses varying the mean time to onset of symptoms from 8 to 14 days (modeled as a lognormal distribution with a mean range of 2.079–2.639) combined with different campaign tactics.

Time Horizon

The model calculates expected hospitalizations during the first 60 days after exposure. The right-hand "tail" of the Brookmeyer lognormal curve predicts that 0.9% of casualties will occur after 60 days, so results for scenarios with late casualties (e.g., with low effectiveness antibiotics) are marginally positively biased.

Effectiveness

Prophylactic interventions for anthrax will have a theoretical efficacy (the ability to halt disease

Table 1 Summary of Anthrax Response Modeling Approaches and Assumptions, 2005–2008

	Brookmeyer and Others[7] (AMWG)	Wein and Craft[3] (AMWG)	Baccam and Boechler[4] (AMWG)	Fowler and Others[20]	Braithwaite and Others[19]	Zaric and Others[12]	Wilkening[17]	Hupert and Others (AMWG)
Publication date	2005	2005	2007	2005	2006	2008	2008	2008
Model type	Mathematical (competing risk)	Mathematical (competing risk + queuing)	Compartmental	Decision analytic (cost-effectiveness)	Simulation (cost-effectiveness)	Compartmental (cost-effectiveness)	Mathematical (competing risk)	Compartmental
Exposure level	$ID_{1,\sim10,50}$	ID_{50}	Variable	ID_{10}	ID_{50}	Variable	Variable	Variable
Anthrax epidemiology source data	Mathematical analysis of Sverdlovsk data and competing risk model (Brookmeyer and others[8,15])	Brookmeyer and others[8]	Rickmeier and others[33] (no citation given in article but used; Baccam, personal communication, 2008	Data from medical review articles (e.g., Inglesby and others[21])	Original analysis of 2001 US attacks	Holty and others[18] (systematic review of published cases 1900–2001)	Mathematical reanalysis of Sverdlovsk data and competing risk model (Brookmeyer and others[8,15])	Wilkening[17]; Brookmeyer, and others[5,7,8,15]
Incubation distribution	Lognormal	Lognormal	Lognormal	Undefined	Uniform 11% daily risk of transition to prodrome (5%–50%)	Lognormal	Lognormal	Lognormal
Incubation period (median ± dispersion factor)	11 ± 2.04 days	10.95 ± 2.04 days	2.3 to 12.7 days (dose dependent)	Undefined	Mean 6.2 days	Mean 10.95 ± 2.04 days	Mean 9.5 ± 1.9 days	9.5 ± 1.9 days (W) and 11 ± 2.04 days (B)
Prodromal period (median ± dispersion factor and/or transition probability)	NA	1.75 ± 2.04 days	Undefined	Undefined	Mean 3 days (23% daily risk of transition to fulminant; range, 10%–100%)	Mean 3.8 days (6.2% daily risk of transition to fulminant for first 3 days, then 43.3%/day)	Mean 3.35 ± 0.54 days	NA

(continued)

Table 1 (continued)

	Brookmeyer and Others[7] (AMWG)	Wein and Craft[3] (AMWG)	Baccam and Boechler[4] (AMWG)	Fowler and Others[20]	Braithwaite and Others[19]	Zaric and Others[12]	Wilkening[17]	Hupert and Others (AMWG)
Antibiotic efficacy during incubation period (range)	100% (0%, 90%, and 100%)	100%	100%	80% (50%–90%)	80% (25%–100%)	100%	98% (called "effectiveness" but not summary measure)	Not separately modeled (summary effectiveness measure used)
Initial antibiotic adherence	100% (for first 15 days)	90% (for first 15 days)	90% (for first 15 days)	100% (<50%–100%)	90% (80%–100%)	65% (65%, 90%)	95% of exposed population prophylaxed	Not separately modeled (summary effectiveness measure used)
Summary baseline antibiotic effectiveness (Efficacy × Adherence)	100%	90%	90%	80%	72%	65%	93%	90%
Delay until start of campaign	3 or 6 days	2, 3.5, or 6 days	2, 3.5, or 6 days	Undefined	Undefined	2.2 days (range, .6–2.2 days)	Variable	Variable
Duration of campaign	3 or 6 days	2, 6, or 10 days	2, 6, or 10 days	Undefined	Undefined (mean rate of dispensing 10,000/day; range, 1000-100,000/day)	11.3 days	2 days	Variable
Probability of symptomatic illness with no antibiotic prophylaxis	100%	100%	100%	95%	Variable (dependent on attack probability)	100%	100%	95%

AMWG, Anthrax Modeling Working Group; NA, not applicable.

progression under ideal circumstances) and a practical effectiveness (how this efficacy plays out under lifelike conditions, including such patient-related factors as adherence). Because effectiveness ultimately is what matters in calculating both patient-level and population-wide outcomes (i.e., probability of symptomatic illness and regional hospital surge), we include only the latter as a variable in the model. For consistency with both the Wein and Baccam/Boechler models, in the base case, we assume 90% effectiveness of interventions for individuals who receive their antibiotics prior to becoming symptomatic.[3,4]

Ramp-Up

We explored the impact of ramp-up to maximal dispensing speeds by evaluating a 1-day ramp-up to a 48-hour dispensing campaign at various delays to initiation of prophylaxis, as well as 1- to 7-day ramp-ups in conjunction with the baseline assumption of a 2-day delay to campaign initiation.

Modeling Software

To maximize usability, our model is a Microsoft Excel workbook running a Visual Basic for Applications (VBA) macro, the code for which is available in full in the Web Appendix at http://mdm.sagepub.com/supplemental.

RESULTS

Under baseline assumptions of a CRI-compliant 48-hour mass prophylaxis campaign with a delay of 2 days between exposure and initiation of response, 90% antibiotic effectiveness, and 95% progression to disease in the absence of treatment, between 86% (Wilkening curve, W) and 87% (Brookmeyer curve, B) of exposed individuals would be protected from developing symptomatic inhalational anthrax (Table 2a,b). If antibiotic effectiveness were 100%, population protection with these same response parameters would range from 95.6% (W) to 96.5% (B) (Table 2c,d). In contrast, at the extreme end of the timeframe of interest here (i.e., if detection and response were delayed by 1 week and the campaign took 7 days instead of 48 hours), population protection with 90% antibiotic effectiveness would range from 39.5% (W) to 49.3% (B).

Figure 1a,b illustrates, for the Wilkening and Brookmeyer incubation distributions, respectively, the increase in expected hospitalizations due to missing the CRI goal of a 48-hour dispensing campaign. These figures show that the detrimental effect of longer campaigns varies with the delay to campaign initiation. On average, each additional campaign day beyond the CRI goal leads to an additional 2.4% (B) to 2.9% (W) of the exposed population requiring hospitalization (range, 0.5%–3.6%, depending on the delay to campaign initiation). The largest effect of missing the CRI goal comes on the first missed day, with a 3-day campaign causing an additional 2.9% (B) to 3.6% (W) of the exposed population to be hospitalized.

In contrast, every additional-day delay in campaign initiation beyond 2 days would lead to an additional average 5.2% (B) to 6.5% (W) of the exposed population requiring hospitalization (range, 2.9%–7.5%, depending on campaign duration). For example, if dispensing were carried out according to the CRI, a delay in response of 4 days after exposure leads to an additional 11.4% (B) to 15.2% (W) increase in the proportion of exposed population requiring hospitalization. The greatest marginal increase in hospitalizations is seen with delays of 4 to 5 days, after which the marginal effect of each additional-day duration declines. Figure A1 in the Web appendix (http://mdm/sagepub.com/supplemental) shows that, compared to the Brookmeyer distribution, using Wilkening's data leads to 0.1% to 3.6% more hospitalizations in the first week after the attack, depending on delay and campaign duration.

Population protection declines in a roughly linear fashion with decreasing antibiotic effectiveness, but this relationship is modulated by delay to campaign initiation (Figure 2). For the baseline case of a 2-day delay to campaign initiation and a 48-hour campaign, every 1% decrease in antibiotic effectiveness leads to a 0.95% increase in expected hospitalizations. The timing of these hospitalizations, however, is highly nonlinear, as shown in Figure 3. For the baseline scenario with 90% effectiveness and a 2-day delay, hospitalizations are temporally distributed as a "double hump" peaking on postexposure days 3 and 7 with an extended right-hand "tail" of late hospitalizations. Delay to campaign initiation determines the size of the initial surge, which may merge into the second "hump" if antibiotic dispensing does not occur within the first 7 days.

Figure 4 shows expected hospitalizations with a 48-hour campaign while varying both the delay to campaign initiation and the median anthrax incubation period (from 8 to 14 days using a lognormal distribution). With an immediate response, population protection is highly insensitive to incubation

Table 2 Proportion of Exposed Population Protected against Hospitalization under Different Mass Prophylaxis Tactics Varying Start and Duration of Campaign (in %)

a. 90% Antibiotic Efficacy, 95% Attack Rate, Wilkening Curve

			Delay in Initiating Dispensing Campaign after Exposure						
		Immediate	1 Day	2 Days	3 Days	4 Days	5 Days	6 Days	7 Days
Campaign duration	1 day	90.0	89.7	88.0	84.0	78.1	71.0	63.6	56.2
	2 days	89.8	88.8	86.0	81.1	74.6	67.4	60.0	52.9
	3 days	89.2	87.2	83.4	77.8	71.0	63.8	56.6	49.8
	4 days	87.9	85.0	80.3	74.3	67.4	60.3	53.4	46.9
	5 days	86.0	82.2	77.0	70.8	63.9	57.0	50.4	44.2
	6 days	83.5	79.1	73.6	67.3	60.6	53.9	47.6	41.8
	7 days	80.7	75.9	70.3	64.0	57.4	51.0	45.0	39.5

b. 90% Antibiotic Efficacy, 95% Attack Rate, Brookmeyer Curve

			Delay in Initiating Dispensing Campaign after Exposure						
		Immediate	1 Day	2 Days	3 Days	4 Days	5 Days	6 Days	7 Days
Campaign duration	1 day	90.1	89.8	88.4	85.5	81.1	75.8	70.1	64.2
	2 days	89.9	89.1	87.0	83.3	78.5	73.0	67.2	61.4
	3 days	89.4	87.9	85.0	80.8	75.7	70.1	64.4	58.7
	4 days	88.5	86.2	82.7	78.2	72.9	67.3	61.7	56.2
	5 days	87.0	84.2	80.2	75.4	70.1	64.6	59.1	53.8
	6 days	85.1	81.8	77.6	72.7	67.3	61.9	56.6	51.5
	7 days	83.0	79.3	74.9	70.0	64.7	59.4	54.2	49.3

c. 100% Antibiotic Efficacy, 95% Attack Rate, Wilkening Curve

			Delay in Initiating Dispensing Campaign after Exposure						
		Immediate	1 Day	2 Days	3 Days	4 Days	5 Days	6 Days	7 Days
Campaign duration	1 day	99.99	99.6	97.7	93.4	86.8	78.9	70.6	62.5
	2 days	99.8	98.7	95.6	90.1	82.9	74.8	66.6	58.8
	3 days	99.1	96.9	92.6	86.4	78.9	70.8	62.9	55.3
	4 days	97.7	94.4	89.2	82.5	74.9	67.0	59.3	52.1
	5 days	95.5	91.3	85.6	78.6	71.0	63.3	56.0	49.1
	6 days	92.8	87.9	81.8	74.8	67.3	59.9	52.9	46.4
	7 days	89.6	84.3	78.0	71.1	63.8	56.7	50.0	43.8

d. 100% Antibiotic Efficacy, 95% Attack Rate, Brookmeyer Curve

			Delay in Initiating Dispensing Campaign after Exposure						
		Immediate	1 Day	2 Days	3 Days	4 Days	5 Days	6 Days	7 Days
Campaign duration	1 day	99.99	99.7	98.2	94.9	90.1	84.2	77.7	71.2
	2 days	99.8	98.9	96.5	92.5	87.1	81.0	74.6	68.2
	3 days	99.3	97.6	94.4	89.7	84.0	77.8	71.4	65.2
	4 days	98.2	95.7	91.8	86.8	80.9	74.7	68.4	62.3
	5 days	96.6	93.4	89.1	83.7	77.8	71.6	65.5	59.7
	6 days	94.5	90.8	86.1	80.7	74.7	68.7	62.8	57.1
	7 days	92.1	88.1	83.2	77.6	71.8	65.9	60.1	54.7

duration, ranging from 89.5% (median 8-day incubation period) to 90.1% (median 14-day incubation period). As delay to response increases, so does variation in predicted outcomes; for a 7-day delay, protection varies from 46.1% under the fastest incubation assumption to 71.3% under the slowest. For

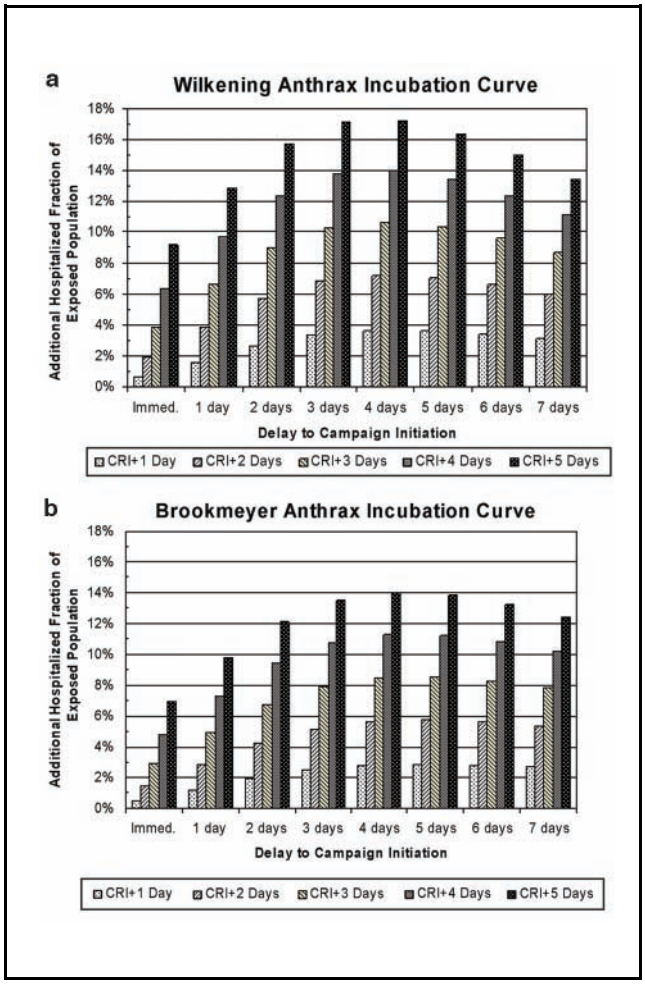

Figure 1 Increase in hospital surge with mass prophylaxis campaigns that exceed the Cities Readiness Initiative (CRI) 48-hour campaign goal: (a) Wilkening and (b) Brookmeyer incubation distributions, 90% antibiotic effectiveness, 95% attack rate.

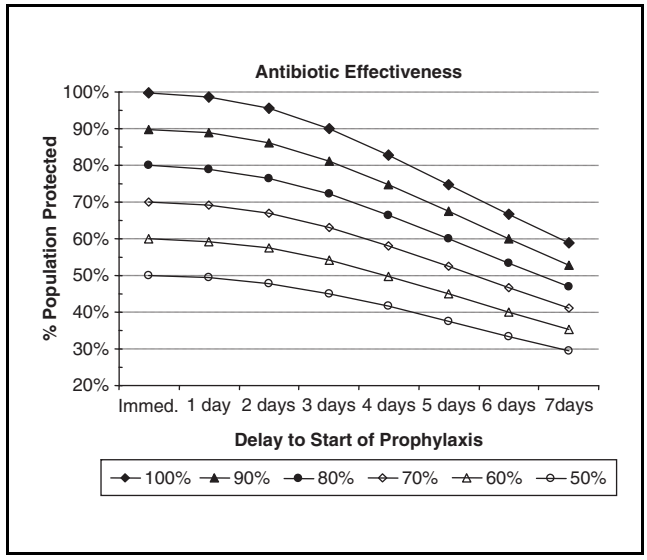

Figure 2 Effect of antibiotic effectiveness on population protection with a Cities Readiness Initiative (CRI)–compliant 48-hour campaign and variable delay to start of prophylaxis (Wilkening anthrax incubation distribution, 95% attack rate).

the base case assumption of a 2-day delay in response (i.e., the third curve from the top in Figure 4), population protection ranges from 82.7% to 88.7% (for 8- to 14-day incubations). This yields an absolute difference of 6% change in expected hospitalizations despite an almost doubling of the anthrax incubation period for the base case mass prophylaxis campaign.

The impact of adding a ramp-up period to full dispensing capability was small: a 1-day ramp-up in conjunction with a CRI-compliant mass prophylaxis campaign decreased the proportion of exposed population protected by between 0.5% (immediate start) and 3.6% (with a 5- or 6-day delay to start; Figure 5). Longer ramp-up periods for CRI-compliant campaigns that start on postexposure day 2 are associated with a 1.6% to 2.7% decrease in population protection per additional ramp-up day.

Overall, our results track closely to those of previously published models (Table 3). On the basis of published results, we can directly compare our base case with only the Wein and Baccam models, and these demonstrate $< 5\%$ difference in estimated outcomes under both incubation distributions. Using the Brookmeyer distribution, our model's results are within 10% of those reported by Wein and colleagues[3] across a range of prophylaxis campaign tactics. Using Wilkening's distribution leads to progressive underestimation of symptomatic illness by our model compared with Wein's model, especially with slower campaigns. In contrast, agreement between the current model and those of Baccam, Zaric, and, interestingly, Brookmeyer improves with the use of the Wilkening distribution.[4,5,12] Although agreement with the Baccam model is variable and does not exhibit any clear trend, results of the Zaric and Brookmeyer models align more closely with our model for slow campaigns.

DISCUSSION

We investigated the capability of the mass antibiotic prophylaxis component of the CDC's Cities Readiness Initiative (CRI) to prevent illness after a

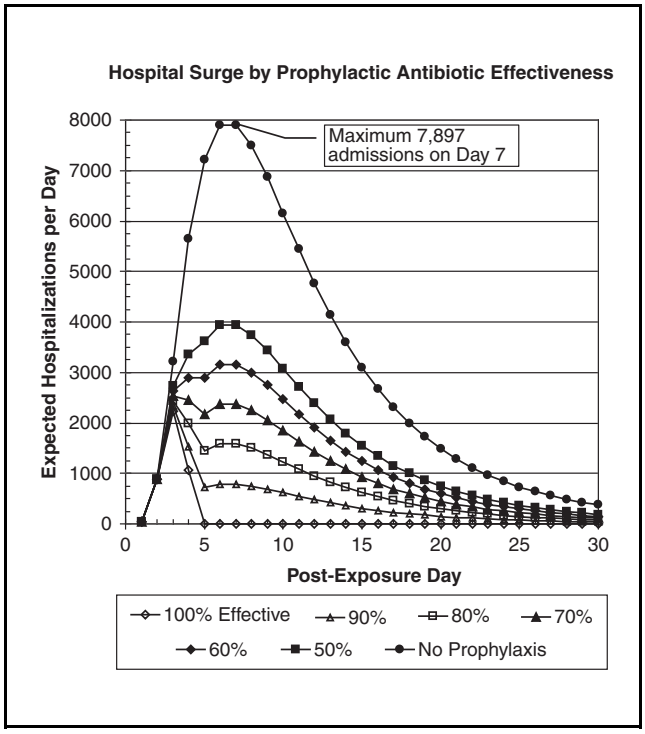

Figure 3 Effect of antibiotic effectiveness on the magnitude and timing of expected hospital surge after Cities Readiness Initiative (CRI)–compliant 48-hour mass prophylaxis campaign (example of 100,000 exposed, 2-day delay to initiation, 90% antibiotic effectiveness, 95% attack rate, Wilkening incubation distribution).

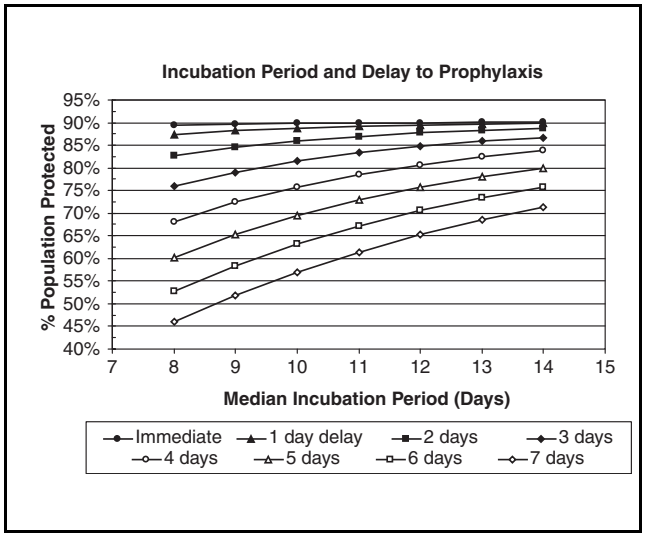

Figure 4 Effect of anthrax incubation period and delay to prophylaxis initiation on population protection (Cities Readiness Initiative [CRI]–compliant 48-hour dispensing campaign, 95% attack rate, 90% antibiotic effectiveness, Wilkening incubation distribution).

large-scale release of anthrax spores over a major urban locale.[22] Using a computer model to quantify the ability of such campaigns to prevent hospitalizations due to inhalational anthrax, we conclude that the current CRI emphasis on reducing campaign duration to 48 hours or less constitutes important but insufficient guidance to ensure adequate protection of exposed populations in the aftermath of such an attack. Specifically, our model sheds light on 2 additional factors relating to antibiotic prophylaxis—delay in campaign initiation and effectiveness of dispensed medications (which, in turn, is dependent on patient adherence and efficacy of the treatment)—that have a greater relative impact on projected hospitalizations than campaign duration. If an optimistic public health goal is the prevention of >80% to 85% of expected hospitalizations in such a scenario (i.e., the population protection assumed by Fowler and others[20] in their cost-effectiveness analysis of anthrax countermeasure dispensing tactics and less than the 90% protection level proposed by Wilkening[23]), we estimate that the delay until commencement of a CRI-compliant campaign can be no more than 3 days and that antibiotic effectiveness must be greater than 90%. These parameters, furthermore, appear to be relatively insensitive to underlying uncertainties about the incubation distribution of inhalational anthrax.

Our results both confirm and extend key findings of the DHHS Anthrax Modeling Working Group (AMWG) participants and others showing that delay to initiation of prophylaxis has roughly twice the impact on outcomes as campaign duration. The CRI focus on prophylaxis campaign duration is understandable because the design and conduct of these campaigns are presumably directly under the purview of local or state public health authorities. In contrast, shortening the time to bioterrorism attack detection and to the decision to engage in population-wide mass prophylaxis entails a complex interplay of clinical and biosurveillance activities that may be outside of the direct control of local public health planners.[24–26] Nevertheless, the now-unanimous findings of members of the AMWG suggest that effective counter-bioterrorism planning warrants at least equal emphasis on, and perhaps national standard-setting for, improving response times.

Along with campaign initiation delay and duration, antibiotic effectiveness had a major impact on

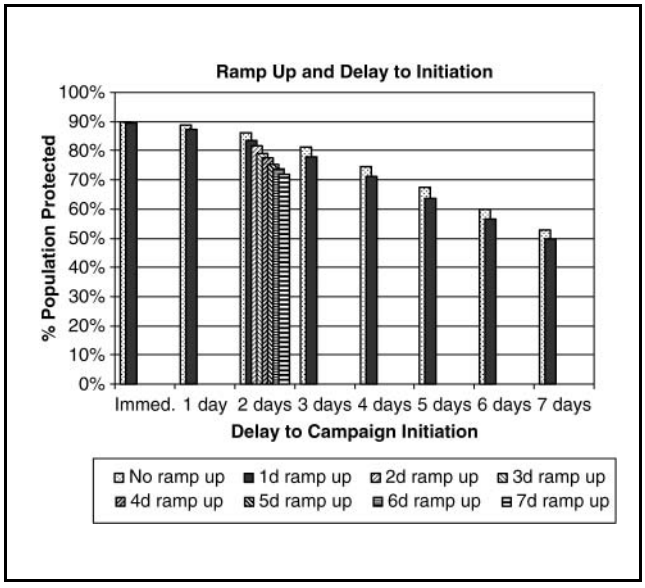

Figure 5 Effect of ramp-up on population protection with 2-day campaign and variable delay to start of prophylaxis (Wilkening curve, 90% antibiotic effectiveness, 95% attack rate).

outcomes from our model, supporting increased public health efforts to improve the correct use of dispensed antibiotics through adherence education and outreach.[3] Other studies have evaluated alterations in antibiotic effectiveness, mainly through changes in adherence, but none has heretofore described the multiphasic temporal surges in expected hospitalizations that may result after a major aerosol anthrax attack, results that we believe have important ramifications for hospital-based response planning.[27–29]

Given considerable uncertainty about the delay from exposure to symptomatic illness due to inhalational anthrax, we find it reassuring that population protection from rapid mass prophylaxis campaigns appears to be relatively stable over a broad range of modeled incubation periods.[7] Comparing the Wilkening and Brookmeyer distributions, we found generally $< 5\%$ difference in projected population outcomes over a range of response tactics, suggesting that general guidance for CRI-type campaigns may be obtained from models using either curve.

Although the prior AMWG reports estimate population-level survival rates from modeled hospital-based treatment of sick individuals, our model focuses solely on estimated hospital surge arrivals, which we believe is a critical metric linking public health interventions such as mass

Table 3 Comparison of Published Models for Prophylaxis against Inhalational Anthrax (% of Exposed Population Protected by Antibiotic Prophylaxis, ID_{10}, 90% Antibiotic Effectiveness, and Wilkening or Brookmeyer Anthrax Incubation Distributions)[7,17]

Delay to Initiate Prophylaxis (Days)	Duration of Prophylaxis Campaign (Days)	Hupert (Wilkening/ Brookmeyer Curves, %)	Anthrax Modeling Working Group					Other	
			Brookmeyer and Others[5] (%)	Difference (W/B) (%)	Wein and Craft[3] (%)	Difference (W/B) (%)	Baccam and Boechler[4] (%)	Difference (W/B) (%)	Zaric and Others[12] (%)	Difference (W/B) (%)
2	2	86.0/87.0			83.0	3.6/4.8	84.0	2.4/3.6		
2	6	73.6/77.6			76.4	–3.7/1.6	68.0	8.2/14.1		
2	10	60.8/67.1			66.8	–8.9/0.5	61.0	0.3/10.0		
3	3	77.8/80.8	67.0	16.1/20.6						
5	2	67.4/73.0			77.4	–12.9/–5.7	57.0	18.2/28.1		
5	6	53.9/61.9			62.9	–14.3/–1.6	51.0	5.7/21.4		
5	10	43.6/52.5			53.3	–18.2/–1.5	49.0	–11.0/7.1		
6	6	47.6/56.3	46.0	3.5/22.4						
2	3	60.3/61.7[a]							54.7[a]	10.2/12.8
2	5	55.7/58.2[a]							53.0[a]	5.1/9.8
2	10	44.0/48.7[a]							43.9[a]	0.2/10.9

a. 65% antibiotic effectiveness.

prophylaxis to health care delivery system planning. This model may therefore help "bridge the gap" between public health and hospital-based emergency response planning for anthrax and other bioterrorism attacks, with specific applications for 2 types of users: 1) public health and emergency management personnel with responsibility for developing effective regional mass prophylaxis campaigns and 2) hospital or health system managers whose facilities would have responsibility for managing the resulting surge in inhalational anthrax cases.

As with all model-based studies, this work has several potential limitations. First, our model is incomplete: we do not consider anthrax spore dispersal, plume formation, patient respiration, or host-pathogen interaction, instead simplifying these into 2 inputs: the total size of the population requiring prophylaxis and the expected percentage of that group that has received an infectious dose of anthrax.[30] This simplified approach has 2 justifications. For the purpose of examining policy-level decisions about public health emergency response, using a defined target population makes practical sense because policy makers ultimately may want to ensure that planning encompasses their specific jurisdictions, which will be of known size. Furthermore, using simple population exposure estimates (i.e., not those modified by incidental effects such as atmospheric conditions) may allow more transparent planning for worst-case scenarios that involve entire target populations.

Second, to better characterize the relationship between the particular public health intervention of mass antibiotic prophylaxis and the potential surge in demand for hospital-based care after an anthrax event, our model estimates the daily number of individuals becoming symptomatic with inhalational anthrax. As noted, other AMWG reports provide casualty counts or rates that are the result of combinations of interventions at both the public health (i.e., mass prophylaxis) and hospital (i.e., treatment of sick individuals) levels. Calculating mortality in this context inflates the number of assumptions for which there is a relatively thin evidence base, first regarding the success at preventing symptomatic illness before it starts (i.e., through prophylaxis, as we have done) and second regarding the reversal of symptomatic illness after a patient gains access to advanced hospital-based care. Determining the potential availability and effective use of such medical capability is, we believe, an important and complex modeling problem in its own right. One consequence of this simplification is that our model may be better suited for use in clarifying the relative benefits of different detection and response strategies than for prediction of the absolute number of hospitalizations resulting from a single scenario. Wein and Craft[3] first noted this linearity between number of casualties and those infected, which along with the multiple uncertainties associated with modeling specific attack scenarios led the AMWG members to focus on fraction infected rather than overall number of casualties.

Our model assumes homogeneous mixing, both of the exposed population within the general population and among various patient types within the exposed population (i.e., each exposed individual shares the same daily risk of progression to symptomatic disease). Although the former assumptions appear justified by the heterogeneity of cases in the Sverdlovsk data, it leaves the potential for inaccurate predictions in particular subpopulations (e.g., geriatric or pediatric populations).[17] Zaric and others[12] and Bravata and colleagues[31] have shown elegantly the dependency of mass prophylaxis outcomes on demand—namely, the willingness and ability of individuals in an anthrax exposure zone to access prophylactic medications either through mass dispensing sites (i.e., Points of Dispensing) or alternative means (US Postal Service, MedKits, etc.).

Finally, we did not consider mass or targeted preevent vaccination to be a component of the CRI prophylaxis approach (although other AMWG members explicitly modeled the impact of this intervention). Given the remote likelihood of a large-scale anthrax attack and both the known and perceived risks of adverse events with the currently available anthrax vaccine, we consider general public acceptance of such an intervention to be unlikely.[5]

This concluding report of the 2004 AMWG modeling initiative affords an opportunity to reflect on the broader implications of its collected results. Models may serve many functions in emergency preparedness and planning, including assisting emergency planners in understanding the scope of complex problems, providing insights into the downstream effects of proposed interventions, and evaluating cost, risk, and outcome tradeoffs under different attack and response scenarios. More fundamentally, models can force reconsideration of basic beliefs, which, when confronted by evidence, may need to be altered, yielding important policy ramifications. In this light, the AMWG models can serve to refocus biodefense policy discussions around a newly delimited set of optimistic outcomes against this type of catastrophic bioterrorist

attack; what is notable is how bad the "best case" is and how rapidly things can get much, much worse.

Taken together, the results of the AMWG suggest that for an unannounced aerosol anthrax attack, emergency planners should assume at baseline that roughly 15% to 20% of exposed individuals will require hospitalization, *despite* rapid detection, an excellent tactical response, and optimal medication adherence. Given the potential scale of population exposure from bioterrorist attacks (i.e., from the hundreds, as in 2001, to hundreds of thousands or even millions of individuals[22]), this implies potentially thousands of anthrax hospital admissions per day, surge levels that would exceed medical capability and would be associated with potentially massive loss of life even in the largest, best-prepared cities.

Federal emergency planners convened the original AMWG in part to determine which countermeasures the federal government should purchase to ensure optimal population protection after an anthrax attack. What the resulting models reveal is that it may not be possible to avoid a medical catastrophe in the aftermath of such an attack, despite the efficient use of stockpiled countermeasures in rapid population-wide dispensing practices. A second round of the AMWG currently is under way to consider alternative outcomes under additional dispensing regimes, such as home-based MedKits or postal system delivery, but even these innovations do not fully resolve the pivotal issues of time to detection and antibiotic effectiveness that can, in light of this and other reports, be considered key drivers of medical outcomes.

So where does this pessimistic picture of anthrax biodefense leave us? Half a century ago, a similar, though more pronounced, conclusion was reached concerning the medical response to a thermonuclear attack.[31] Sidel and others[32] predicted the devastation of the health care system and its inability to care for victims in the aftermath of such an attack, and their writings subsequently sparked a number of initiatives aimed at reducing the threat of nuclear war, ultimately leading to the formation of the Nobel Prize–winning International Physicians for the Prevention of Nuclear War (IPPNW). Although dependent on the size of a hypothesized anthrax release, the AMWG's results suggest that casualties from such an attack could rapidly escalate into the thousands, which, in conjunction with potential contamination of the health care infrastructure, could bring regional systems of medical care to a halt, threatening both health and civil order. This seeming inevitability of severe, if not necessarily nuclear weapon–level catastrophic, consequences leads us to 3 policy-related conclusions pertaining to detection, response, and prevention of bioterrorist events.

First, the federal government should continue to promote and fund research to improve rapid detection of a biological attack and pinpointing of population exposure patterns once an attack is identified. New initiatives might investigate the comparative effectiveness of devoting time to traditional "shoe leather" epidemiological investigation in the early hours of attack response to tailor more limited prophylaxis efforts to those who are more likely to have suffered medically significant exposure, compared to devoting all resources to population-wide "shotgun" efforts, as prescribed in the CRI.

Second, new programmatic and conceptual approaches to bioterrorism response should attempt to integrate both funding and planning for public health preparedness (e.g., currently funded through the CRI and other mechanisms) and health care delivery system preparedness (e.g., funded through the ASPR Hospital Preparedness Program) at the federal, state, regional, and local levels to better coordinate and sustain mass care capability for hospitalized victims. These programs should focus on ensuring collaborative planning for expected hospitalizations, addressing, for example, the anticipated timing for augmenting surge capacity and the durability of hospital supply chains during emergencies.

Finally and most important, these findings indicate that efforts to prevent bioterrorist attacks from occurring should receive at least equal priority to that given to the development of reactive defense mechanisms such as mass prophylaxis. Following in IPPNW's footsteps, this may be addressed by placing primary focus on peer-to-peer interaction among international medical and scientific societies and on multilateral covenants such as the 1972 Biological and Toxin Weapons Convention.[23] However, given the likelihood that bioterrorism would be a non-state-sponsored activity, both diplomatic and nondiplomatic efforts in interdiction and deterrence will be required (aided by initiatives such as the US-Russian Cooperative Threat Reduction Program).

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