1 Introduction

Since the September 11, 2001, terrorist attacks in New York and Washington and the subsequent anthrax outbreaks on the east coast of the United States, bioterror concerns have focused on smallpox. Routine smallpox vaccinations in the United States ended in 1972. The level of immunity remaining from these earlier vaccinations is uncertain but is assumed to be degraded substantially. For present modeling purposes, we assume it to be nil.

As a weapon, smallpox would be very different from anthrax. Anthrax is not a communicable disease. Smallpox is highly communicable. With a case fatality rate of roughly 30 percent (meaning that 30 percent of infected individuals die), it is also very deadly. Many of those who survive the disease, furthermore, are permanently disfigured, their well-being compromised for life.

There is now heated debate on the appropriate national strategy for smallpox bioterror.[1] Who should be vaccinated?

1. In the summer of 2001, researchers at the Johns Hopkins Center for Civilian Biodefense Strategies, in collaboration with several other organizations, formulated a policy exercise known as Dark Winter, which raised many important questions for bioterror attack response; see O'Toole, Mair, and Inglesby (2002).

Everyone who volunteers? Targeted subpopulations? When should immunization begin? Immediately? Only after a confirmed attack? What is the role of quarantine?

In this monograph, we present a county-level individual-based computational model of a smallpox epidemic.[2] We review and criticize the two main vaccination strategies currently under discussion: trace and mass vaccination. Based on the model, we then develop a distinct "hybrid" strategy that differs sharply from both, while combining useful aspects of each. It involves both preemptive (that is, pre-release) and reactive measures. As the basis for a national smallpox containment strategy, we believe it offers important advantages over the alternatives.

MODELS

In gauging the scale of a smallpox bioterror threat, and in designing an effective policy response, it is crucial to have *epidemic models* depicting the spatial spread of the disease in a relevant setting. Without the use of explicit models, there is no systematic way to gauge uncertainty or to evaluate competing intervention strategies. Building on previous work, we have developed an individual-based computational modeling environment for the study of epidemic dynamics in general (see appendix A).[3] This can be

2. Individual-based modeling is also called agent-based modeling. To avoid confusion between our agents (individual people) and infectious disease agents, we use the term individual-based modeling predominantly.

3. See Burke (1998); Grefenstette and others (1997); Burke and others (1998); Epstein and Axtell (1996); Epstein (1997).

applied to an indefinite variety of pathogens and social structures. Here, we develop an individual-based model of smallpox at the county level (an application to genetically modified smallpox is also noted).[4]

In contrast to compartmental epidemic models, which assume perfect homogeneous mixing and mass action kinetics,[5] the individual-based approach explicitly tracks the progression of the disease through *each individual* (thus populations become highly heterogeneous by health status during simulations) and tracks the contacts of each individual with others in relevant social networks and geographical areas (for example, family members, co-workers, schoolmates). All rules for individual agent movement (for example, to and from workplace, school, and hospital) and for contacts with and transmissions to other people are explicit, as is stochasticity (for example, in contacts). No homogeneous mixing assumptions are employed at any level. The prime social units that loom largest in the smallpox data,[6] such as hospitals and families, are explicitly represented, and our vaccination (and isolation) strategy is focused on these units of social structure. Calibration of our model to these data, and statistical analysis of core model runs, are discussed below.

Our model differs from the primary (and valuable) competing approaches, in a number of ways. For example,

4. For an introduction to the individual-based modeling technique, see Epstein and Axtell (1996). For diverse applications of the methodology, see Brian and others (2002).

5. Anderson and May (1991); Kaplan, Craft, and Wein (2002).

6. Mack (1972).

it differs from that of Halloran and coauthors in its explicit inclusion of hospitals. Most fundamentally, as a "pure" individual-based model, it eschews all homogeneous mixing assumptions at any level, in contrast to the models of both Halloran and coauthors and Kaplan, Craft, and Wein.[7]

7. Halloran and others (2002); Kaplan, Craft, and Wein (2002). There are further differences, including parametric ones. For useful remarks comparing continuous and discrete individual approaches in the present connection, see Koopman (2002).