Reviewer’s report

Title: Transmission patterns of smallpox: systematic review of natural outbreaks in Europe and North America since World War II

Version: 2 Date: 21 February 2006

Reviewer: Mike Bray

Reviewer’s report:

General

Review of "Transmission patterns of smallpox", by Bhatnagar et al.

The authors perform an extensive literature search to identify and characterize smallpox outbreaks since World War II that resulted from importation of the disease into areas of Europe and North America previously free of it. Their analysis focuses on assessment of the “effective first generation reproduction rate,” as an index of how swiftly bioterrorist-introduced smallpox would spread through a modern target population.

The authors’ study extends the earlier work of Thomas Mack, but reaches the same conclusions: most natural re-introductions of smallpox into areas long free of the disease resulted in small outbreaks that did not exceed two generations of cases; such outbreaks were almost always centered in hospitals; and failure to recognize the disease when it first appeared was a contributing factor in the development of larger epidemics. The authors’ work somewhat improves on that of Mack, by adding to the number of outbreaks examined and performing a more rigorous numerical analysis. However, a weakness of this manuscript is the authors’ apparent lack of curiosity as to the factors that caused a few epidemics to have a much larger initial R. A detailed examination of those cases would be useful to the reader. The authors also place excessive reliance on the pattern of past introductions of smallpox as a reliable predictor of the nature and outcome of future bioterror attacks, and fail to consider how a massive, multifocal release of aerosolized variola virus could produce an entirely different pattern, characterized by huge waves of initial infections that would have catastrophic consequences in their own right.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Background:

In the first paragraph, the authors note that the transmissability of smallpox is "a key factor" in determining the size of an outbreak resulting from bioterrorism. Although transmissibility is a factor in predicting how an epidemic would play out, I would consider the factors of overwhelming importance to be the magnitude of the initial attack (quantity of agent in each aerosol release, number and timing of such releases and the number of persons exposed) and the efficiency with which the aerosolized virus causes human infections. There is no doubt that a smallpox outbreak commencing with only one or a few cases will be recognized and contained quickly. However, the real threat of concern to biodefense planning is of a simultaneous, multifocal assault by a team of terrorists as pitiless and determined as those who carried out the 9/11 jetliner attacks, who could release small-particle aerosols into the ventilation systems of numerous large enclosed areas, such as crowded shopping malls, subways, train stations and other transportation hubs in sites across the
country. Such an attack could produce a huge initial wave -- a tsunami -- of hundreds of thousands of cases of smallpox that would immediately overwhelm our health care system, bring interurban transportation and commerce to a halt, and do irreparable damage to the country. The 10-14-day incubation period following the first wave would be employed in vaccinating the unexposed population, monitoring those exposed to the initial cases, and employing postexposure antiviral prophylaxis, if available.

No discussion of the threat of smallpox is complete without acknowledging that variola virus could be used for this type of catastrophic terror attack. The introductory section of the Background, the last line of that section and line 5 of the first paragraph of the Discussion are therefore incorrect, since modern smallpox control efforts cannot be guided solely by past experience of naturally occurring disease.

Page 18, last paragraph: The authors suggest that their findings will provide insights into smallpox bioterror attacks "under different attack scenarios", but they don't describe what any of those scenarios might be. As stated above, the scenario of greatest concern for planning defenses against smallpox is a massive multifocal release of airborne variola virus in urban areas in the US and other countries. The authors’ examination of natural introductions of smallpox in the past is of little help to those contemplating the response to such an event.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Results and Discussion:

Page 9, paragraph 2: It is conjectured, but not proven, that the Aralsk outbreak was the result of testing aerosolized smallpox.

Page 16, last line: The statement that mass vaccination was used in New York City in 1947 appears to suggest that that strategy was responsible for bringing the outbreak to an end. In fact, transmission occurred only within a few hospitals, which responded once the disease was recognized by vaccinating their staff and other persons exposed to the smallpox patients and instituting traditional infection control measures. Mass vaccination had little, if anything to do with preventing the spread of smallpox into the surrounding city.

Many of the authors' observations in this section are either inherently obvious or already form part of general knowledge of smallpox. For example, the fact that outbreaks were larger when the initial case was not recognized to be smallpox, or that smallpox was recognized more quickly when the initial case showed typical features of the disease, will not be news to most people who read this paper.

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Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:
I declare that I have no competing interests.