Reviewer's report

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

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Reviewer: Joel Breman

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General. This paper refreshes our memory that smallpox importations into northern countries have generally not been highly explosive. However, the Kosovo, Yugoslavia, experience and several exportations within and into India, Bangladesh and elsewhere in poor countries have spread widely, without the same rapid detection and control measures found in the north (see Fenner et al, Smallpox and its eradication, ref 21; and the India and Bangladesh primary sources cited in Fenner). It is bioterrorism within poor countries that are of great concern now (see Breman, Arita, Fenner, Preventing the return of smallpox, NEJM, 2004). Further, the authors need to consider in more detail the immunologic status of the population in the period discussed. While vaccination coverage was incomplete in all countries mentioned, there was a vaccination policy (generally every 3 years) and some protection existed in all communities, whereas today that is not the case for virtually all persons under 30 years of age, and many older than 30. The authors refer to reference 21 (Fenner et al) as the source of most of their outbreaks: this is a secondary source, coming from the Mack papers (ref 12) and others. Better to use and cite Mack rather than an interpretation of his important work. What has this paper added that Mack et al do not address?

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

1. p2, Abstract, Results, sentences beginning line 2. Need more precision on "...small..." and "...low initial R values and were prolonged; higher initial R values and were shorter" and others. The atypical cases seems milder. Are these Variola minor?

2. p3, "Most outbreaks..." As above, most outbreaks occurring in poor countries might not be contained in a few generations. In fact monkeypox, the main orthopoxvirus occurring now in central Africa is alleged to be spreading up to six generations (see AJTMH report from the Republic of Congo by Inger Damon's group from the CDC. published in 2005). Monkeypox, looks exactly like smallpox clinically.

3. p4, Background, end 2nd para. Need more information on whether the patients and their contacts were vaccinated or not, and if so when.

4. p4, 2nd to last sentence. What is evidence that "...immunity was...similar to a contemporary US population...a priori"? I disagree. See above re: vaccination policies at the time of the outbreaks described. Why not discuss this issue and make a table with any measured or estimated vaccination coverage at the time of the imports in the areas affected.

5. p5, last 2 sentences, refer to rich countries. Bioterrorists may actually go to poor countries as has occurred with explosive devices. Incumbent on scientists and public health officials to assure that terrorists can't get smallpox virus.
6. p7, 1st incomplete para. Again, vaccination status of vulnerable groups (contacts) important to note. "Atypical" is defined in two ways: milder (possibly V. minor or vaccine attenuated) and "rash not characteristic of smallpox". The latter can be severe. V. minor appears to have the same secondary attack rates as V. major, but vaccine attenuated smallpox probably does not spread as readily.

7. p7, Analysis. Use numbers, instead of qualitative descriptions of outbreaks and R values, etc. (not "small").

8. p9, 2nd para, line 8. The USSR outbreak in 1972 is anecdotal, and not well documented despite ref 23.

9. p11, line 4. should be "...median values for the...

10. p11, Characteristics..., line 7. What is "...The majority...and most had a certificate..." Be more precise.

11. p13, 2nd full para, case fatality rates. The rates of 0.24, 0.20, and 0.17 indicate severe smallpox, probably due to V. major. There is no discussion of this in the paper and it should be included that most importations came from Asia where V. major was prevalent. No discussion of patient management is included. In fact with attention to fluids, nutrition, electrolytes, and bacterial suprainfection the CFR might be lower, even with V. major.

12. p15, Discussion, line 6. Delete "what were effectively". 3rd para last line, delete "effective". 2nd para. Discuss the Kosovo outbreak because it was special and might resemble what would happen today in a poor country. Also what can we learn from the "small" outbreak (R=2, 28 cases, 9 generations)?

13. p16, line 6. The nosocomial nature of imported smallpox is mirrored in other diseases that elicit chaos, panic and civil disruption--Ebola, Marburg, Lassa come to mind.

14. p17, 1st para, 1st sentence. The mixing of atypical (milder) and hemorrhagic "...versus a typical presentation" as having "...more cases and deaths..." needs explanation.

16. On p. 7 reference is made to efficacy of control measures including VIG (refs 16-17); there is no subsequent discussion of this unproven control measure, nor of alleged smallpox-specific treatments, some new, some old.

17. Tables. It would be useful to have consecutive numbering of all 51 outbreaks in 1 table with identifiers, including measured and estimated immune status of target contacts and population. Also add what control measures were taken. For instance in Birmingham, UK, in 1978 only a few thousand vaccinations were given despite the population having an estimated immunity level of less than 50%.

18. Table 1b. Need more detail as to what the "Atypical" presentation really was.

19. Table 2. The "Number of Outbreak" and "Total Cases" don't seem to match. Do the authors mean "Mean number of cases"?
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.