Author's response to reviews

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

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Author's response to reviews: see over
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Re: Transmission Patterns of Smallpox

From: Vibha Bhatnagar MD MPH

Dear Editorial Team

Biomed Central Public Health

We appreciate this opportunity to re-submit our manuscript, “Transmission Patterns of Smallpox: Systematic Review of Natural Outbreaks in Europe and North American since World War II.” The reviewers have made several important suggestions and we have been able to address most of them in this revision. Below you will find an itemized response and an indication of where the text has been changed. Please note that all changes have been made in blue.

We look forward to your reply.

Sincerely,

Vibha Bhatnagar MD MPH
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Reviewer 1
We appreciate your feedback – thanks!

Reviewer 2

Major Compulsory Revisions

Background:
In the first paragraph, the authors note that the transmissibility 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.

- We agree with the reviewer that the initial reproductive rate is one of several factors that determine the impact of an outbreak. We have attempted to clarify this
in first paragraph of the “Background”: “A number of issues, such as the amount of virus released and the number of people exposed, need to be considered in order to estimate the impact of a bioterrorist attack with smallpox.”

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 post exposure 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.

• We agree with the reviewer and have modified these statements.

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.

• This was an omission on our part. Our prior work focused on the impact of an attack with smallpox and we have now briefly described some of the attack scenarios of the attack scenarios that we modeled. The reviewer has correctly pointed out that this review alone cannot be solely used to guide planning in the event of a bioterrorist attack. However, we feel that this review did define transmission patterns of smallpox.

Minor Essential Revisions
Results and Discussion:
Page 9, paragraph 2: It is conjectured, but not proven, that the Aralsk outbreak was the result of testing aerosolized smallpox.

• We thank the reviewer for noting this. This statement has been corrected.

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.

• We agree with the reviewers and did not mean to imply that mass vaccination was an effective control strategy. We have taken out “these outbreaks were limited to 2 and 3 generations, respectively” in order to avoid this implication.
Reviewer 3:
Major Compulsory Revisions

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).

........ 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.

...........Discuss the Kosovo outbreak because it was special and might resemble what would happen today in a poor country.

- This is an extremely important point and we thank the reviewer for bringing this to our attention. We agree with the reviewer and have added a paragraph on the Kosovo outbreak in the discussion. Our focus, however, was on transmission patterns in a contemporary U.S. population but we agree that the discussion is incomplete without acknowledging the potential impact of a smallpox outbreak in a less developed country.

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.

........... p4, 2nd to last sentence. What is evidence that "...immunity was...similar to a contemporary U.S. 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 importations in the areas affected.

- The reviewer has raised an important issue. The vaccination status of the population is an important consideration. Our literature review, however, was structured on identifying smallpox outbreaks. We did not come across detailed information on immunization policies for specific countries, except for as noted above, vaccination was required in childhood, every three years and with travel to smallpox endemic countries.

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

- This would be an interesting addition, but many of the papers that we reviewed did not present this information, or did not present it in a comprehensive fashion that was comparable across outbreaks. Since our review was motivated by the need to estimate parameters for the epidemiologic model used in Bozzette et al., 2003, and this information was not needed for that model, and we could not get the data comprehensively, we did not include it in our review.

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?
- The work of Mack has now also been cited. Thank you for bringing this to our attention.

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.

p7, Analysis. Use numbers, instead of qualitative descriptions of outbreaks and R values, etc. (not "small").
- We apologize if this sounded ambiguous; we have substituted numbers as you have suggested.

The atypical cases seem milder. Are these Variola minor?
- We again apologize for this ambiguity. We have now specified what “atypical” is and have stated that we considered Variola Major (not minor, as often seen in South America and Australia).

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.
- The reference to European and North American countries has been clarified. We again appreciate the concern for less developed countries and have added a new discussion paragraph as noted above.

p9, 2nd para, line 8. The USSR outbreak in 1972 is anecdotal, and not well documented despite ref 23.
- We agree with the reviewer that this outbreak was not as well documented as some of the other detailed outbreaks. However, it had all the items documented required for a “detailed” outbreak by the definition used in this review.

p11, line 4. should be "...median values for the..."
- Thanks for bringing this typo to our attention.

p11, Characteristics..., line 7. What is "...The majority...and most had a certificate..." Be more precise.
- We agree that this statement is not precise; this has been modified.

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.
- The reviewer is correct, outbreaks of V. minor were not reviewed. We are in agreement that medical management has changed and with supportive care, the mortality rates may be quite different in a contemporary population. On the other hand, the use of steroids and immunosuppressive drugs may make a contemporary outbreak more severe. Therefore, it is hard to speculate what a modern day case may look like.
p15, Discussion, line 6. Delete "what were effectively". 3rd para last line, delete "effective".
2nd para.
• We apologize for the use of “effective” – we have used this term in order to
differentiate between the number of documented outbreaks (45) and number of
outbreaks after breaking several into epidemiological components (effective of 51
outbreaks). At this time we are still not able to find clear, alternative wording.

p17, 1st para, 1st sentence. The mixing of atypical (milder) and hemorrhagic "...versus a
typical presentation" as having "...more cases and deaths..." needs explanation.
• We have taken out reference to the number of deaths. We agree that the inclusion
of “more deaths” is confusing. We were attempting to state what we observed. The
number of deaths was higher in these outbreaks because of the higher case-load
(the death rate was not necessarily higher).

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.
• This is an important point and we have tried to clarify this. We have now mentioned
to potential use of cidofovir but a detailed discussion on the smallpox management
may be beyond the scope of this text.

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%.
• We agree with the reviewer that these are important issues. As noted above it is
difficult to estimate the immune status of each population at this time.
• On review of the outbreaks, ring vaccination and case isolation were routinely used
and alternative measures such as mass vaccination, VIG and quarantine were
rarely used. Therefore, in order to simplify the tables, this additional information
was not included.

Table 1b. Need more detail as to what the "Atypical" presentation really was.
• This has been clarified.

Table 2. The "Number of Outbreak" and "Total Cases" don't seem to match. Do the
authors mean "Mean number of cases"?
• Thank you for bringing this to our attention. The table headings have been
changed. They now read “Number of Outbreaks Identified” and “Median for
Number of Total Cases.”