Author’s response to reviews

Title: Risk of serious complications and death from smallpox vaccination: A systematic review of the United States experience, 1963-1968

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Dear Ms. Veitch,

After discussions regarding the division of labor we have changed the author order to be Dr. Aragón, Dr. Ulrich, Dr. Fernyak, and Dr. Rutherford. Dr. Aragón remains the corresponding author.

We are grateful to the reviewers for their excellent comments and suggestions.

**Responses to Paolo Bonanni:**

Discretionary revisions:

**Bonanni:** While changing the Conclusions section (see Compulsory revisions), the Authors could expand their considerations on the policy of voluntary vaccination of public officials in the light of the results of their review. It would be interesting to know their opinion on the balance between risks and benefits of smallpox immunization in selected groups of population.
**Response:** We agree that the Conclusions does not add much. The topic of balancing risks and benefits is a complex one which could not be addressed adequately in a concluding paragraph.
**Action:** The conclusion was deleted and our concluding comments are in the last paragraph of the discussion.

Compulsory revisions

**Bonanni:** Page 8, Methods section, sub-heading 'Quantitative data synthesis': the Authors should explain more clearly how they solved the different classification of age groups in the study by Ratner.
Response: We agree.

**Action:** “Data were stratified by vaccination status and by age groups (age <1 year, ages 1 to 4 years, ages 5 to 19 years, ages 20+ years, and all ages combined). For the Ratner study [Ratner70], data in the age groups “Age 5 to 14” and “Age 15+” were counted in the groups “Age 5 to 19” and “Age 20+”, respectively.” changed to “Data in all the studies, except the Ratner study, were stratified by vaccination status and by the following age groups (age <1 year, ages 1 to 4 years, ages 5 to 19 years, ages 20+ years, and all ages combined). For the Ratner study [Ratner70], data in the age groups “Age 5 to 14” and “Age 15+” were counted in the groups “Age 5 to 19” and “Age 20+,” respectively.”

**Bonanni:** Page 10, Results section, lines 3-10. There is a mistake in the counting of excluded studies. Their total number (to be subtracted from 18) is 11 and not 10, as erroneously reported.

**Response:** We agree.

**Action:** “Using our selection criteria we excluded 10 studies:” changed to “Using our selection criteria we excluded 11 studies:”

**Bonanni:** Page 13, Results section, sub-headings Generalized vaccinia and Accidental infection (inadvertent autoinoculation). There is a mistake in the reporting of data of risk range of accidental infections (the same values of generalized vaccinia are erroneously reported). Table 5 probably supplies the right values (please check).

**Response:** We agree.

**Action:** “In the Lane study, the risk ranged from 133.3 to 1647 cases per million vaccinations, and was highest in infants aged <1 year.” changed to “In the Lane study, the risk ranged from 371.2 to 2118 cases per million vaccinations, and was highest in infants aged <1 year.”

**Bonanni:** Page 15, Discussion section, first line. The sentence should be change as follows: 'To our knowledge, this is the first systematic review of the severe complications of smallpox vaccination in the USA'.

**Response:** We agree.

**Action:** “This is the first systematic review of the severe complications of smallpox vaccination.” changed to “To our knowledge, this is the first systematic review of the severe complications of smallpox vaccination in the USA.”

**Bonanni:** Page 18, Discussion section, paragraph starting with 'Fifth (limitation)'. While explaining why the CDC approach not to combine risk estimates from different studies is probably correct, the Authors should also give the reasons for maintaining the pooled summary measures in the article despite some drawbacks they may present.

**Response:** Because we cannot explain the heterogeneity in estimates we thought is was best to present both to the reader and to warn them that “the pooled summary measures presented may not be appropriate.”

**Action:** None.

**Bonanni:** Page 20, Conclusions section. All the section should be re-written, since in its present form all Conclusions are an unnecessary duplication of information and considerations already reported in the Discussion section. It may be useful to use the section to express an opinion on the current policy of immunization in USA (see Discretionary revisions).

**Response:** Addressed above.

**Action:** No additional.
Responses to William C Thompson:

Thompson: 1) Abstract - Need to summarize what the inclusions criteria were for the initial 348 studies and the seven studies that met your final inclusion criteria.
Response: We agree.
Action: Abstract Methods changed to “Using a MEDLINE search strategy, we identified 348 articles, of which seven studies met our inclusion criteria (the number of persons that were primary and re-vaccinations were reported, sufficient data were provided to calculate complication or case-fatality risks, and comparable case definitions were used). For each complication, we estimated of the complication, death, and case-fatality risks.”

Thompson: 2) Background - Needs to be edited. For example, many instances where the word risk should be plural
Response: We agree.
Action: This has been corrected.

3) Methods

Thompson: Explain why you didn't do additional literature searches before 1965 using data sources other than Medline.
Response: The inclusion criteria was based on the “Neff criteria” which were not published until 1967; prior to that work there were no consistent case definitions for smallpox vaccine adverse events.
Action: The following sentence was added to the end of paragraph 1 of the Methods section: “Based on this consultation [with Neff and Lane] and our inclusion criteria (described below) we did not pursue articles published before 1965 or from additional US databases.”

Thompson: Explain why the Neff criteria were used.
Response: We agree.
Action: “… one or more vaccination complications were consistent with case definitions as defined by Neff and colleagues [neff67a].” changed to “… one or more vaccination complications were consistent with case definitions as defined by Neff and colleagues [neff67a]. Prior to this publication there were no consistent case definitions of smallpox vaccine complications.”

Thompson: Explain why the abstractors were not blinded. Otherwise drop that sentence.
Response: We agree.
Action: Done.

Thompson: Describe why the age groups were selected. For example, it would be been interesting to see data for persons aged > 50 years. My guess is that there are not any data broken out by those age groups.
Response: Addressed in response to Dr. Bonanni above.
Action: No additional action (see response to Dr. Bonanni above).

4) Results

Thompson: Provides a nice summary of the data.
Response: We agree.
Action: None

5) Discussion

Thompson: The discussion is too long and should be shortened.
Response: We agree.
Action: Discussion section shortened as described below.

Thompson: Second paragraph could be dropped.
Response: This paragraph summarizes the important case fatality risks and should be kept.
Action: This paragraph has been shortened.

Thompson: The limitations section is too long.
Response: We agree.
Action: The last paragraph in Discussion shorted and the Conclusions deleted.

Thompson: On page 18, the authors agree with the CDC authors who did not combine risk estimates for the 2 Lane studies, but the authors of this paper did combine those estimates. Big contradiction that needs to be addressed.
Response: Addressed in response to Dr. Bonanni above.
Action: No additional action (see response to Dr. Bonanni above).

Thompson: 1st Paragraph on page 19 could be cropped.
Response: We agree.
Action: Most of paragraph deleted.

Sincerely,

Tomás Aragón, MD, DrPH