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Title	Intradermal pre-exposure rabies vaccination: a six-year retrospective observational study in a Canadian travel clinic
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Reviewer 1	Dr. Stephen Toovey
Institution	Royal Free and University Medical School, Academic centre for travel medicine and vaccines, Bottmingen, Switzerland
General comments (author response in bold)	<p>This is a useful paper, the main strength I think being the demonstration of 99.9% seroconversion with ID immunisation.</p> <p>1. The comparison of PrEP vs non-PrEP recipients is could benefit from stratification by risk, as it is not clear if the risk profile of the two groups is similar. We thank the reviewer for this suggestion. Risk factors for injury caused by potentially rabid animals identified in the literature include young age, traveling to Southeast Asia, India, and North Africa, and traveling for tourism (Reference: Gautret P, Parola P. Rabies in travelers. Curr Infect Dis Rep 2014;16:394). These are covariates in our logistic regression model. Stratifying by risk would mean identifying and applying a risk score which has not been described in the literature to our knowledge. We believe that for the purposes of our paper, usage of these covariates provides an adequate comparison of the two groups.</p>
Reviewer 2	Dr. Judy MacDonald
Institution	Alberta Health Services, Calgary, Alta.
General comments (author response in bold)	<p>This interesting paper adds important data to the literature, especially in terms of effectiveness of ID PrEP. It would be helpful to provide a comparison to effectiveness of IM PrEP measured by serological response.</p> <p>General comments: This interesting paper adds to the literature in providing evidence of the effectiveness of intradermal rabies pre-exposure prophylaxis (PrEP) in travellers, and some comparisons between those travellers that get PrEP and those who don't. It is generally well-written and flows well.</p> <p>To improve clarity and statistical appropriateness in the paper, please consider the following:</p> <p>1. In sections where you are talking about PrEP and both IM and ID PrEP, it would be helpful to differentiate amongst these by using the terms "any PrEP" rather than just PrEP, as well as IM or ID PrEP (which is already being done). "Any PrEP" was adopted at several places in the text for clarification (e.g. page 5, line 13; page 7, line 2 among others).</p> <p>2. Making it clear that ID PrEP is indicated for immunocompetent travellers who are not taking chloroquine, according to NACI recommendations. You did not mention this when you were describing the discussion with travellers for whom PrEP was recommended, nor in some other sections where reference was made to NACI's endorsement of the ID route for PrEP. This was clarified on page 4, lines 22-23 and page 5, line 1.</p> <p>3. In Tables 1 and 3, I don't believe you can state a single P-value for a whole section where you have broken this variable down into subsets of age. Example Table 3 Age (years), you give one P-value but you have multiple age groups to compare in terms of ID and IM PrEP. What does that mean? Following the Editor's recommendation, we have replaced the p-values with standardized differences. For categorical variables, standardized differences apply to the entire group. Reference: http://support.sas.com/resources/papers/proceedings12/335-2012.pdf</p> <p>4. I have not commented on the univariate and multivariate analyses presented in Tables 2 and 4 as I do not have the expertise to assess their validity and correctness. We believe that the analyses are valid and correct.</p> <p>5. Throughout the paper, you have used "ml" as the abbreviation for millilitres. Consider using "mL" as is done in the Canadian Immunization Guide and other references to improve clarity. This was corrected throughout the text (e.g. page 4, line 18).</p> <p>6. Did you ever do serology for travellers getting IM PrEP? Also, clearly explain why serology is required for ID PrEP. We did not perform serological testing for IM PrEP recipients, as it is not recommended by the Canadian Immunization Guide based on known excellent serological response in immunocompetent recipients. Serological testing is recommended by the Canadian Immunization Guide if PrEP is given by the ID route to ensure an acceptable level of protective antibodies, as it is not the "gold standard". This has been clarified in the text (page 6, lines 13-14).</p> <p>7. Provide some explicit comment on how the uptake of PrEP reflects the recommendation of the travel clinic practitioner based on their risk assessment of the proposed trip, which would consider things like duration of trip, destination, type of activity, etc. This was adjusted in the text (page 6, lines 7-9).</p> <p>I have specific comments or suggested edits as follows:</p> <p>Page 3:</p> <p>8. Line 4 (and also in abstract): delete "with vaccination" or change wording to say "...with other vaccines" or "when getting other vaccines". We have deleted "with vaccination" in the abstract.</p> <p>9. Line 15: IM – use full wording the first time this term is used This was corrected.</p> <p>Page 5:</p> <p>10. Lines 16-17: Brand names of vaccine should have ® or ™. Suggest a slight wording change – rather than "...the human diploid cell vaccine" and "...the purified chick embryo cell vaccine" use "...a human diploid cell vaccine" etc, as these two vaccines are not the only HCDV or PCECV available globally. This was corrected.</p> <p>Page 6:</p>

	<p>11. Line 1: do you have a reference to cite for the 6-hour period the vaccine vial can be used? Our reference was the Québec provincial immunization guide: Ministère de la Santé et des services sociaux. Protocole d'immunisation du Québec. Québec: Gouvernement du Québec; 2013:407. This reference was added to the text.</p> <p>12. Line 4: should be "appointments" This was corrected.</p> <p>Page 7: 13. Line 11: should be "...of IM ..." This was corrected.</p> <p>14. Lines 11-12: would improve clarity to explicitly state that PrEP is a 3-dose vaccine series, with doses given on days 0, 7, and 21 or 28. This was corrected.</p> <p>Page 9: 15. Line 7: capitalize "Figure 1" This was corrected.</p> <p>16. Line 13: identify when the single IM booster dose was given for interest sake – prior to travel? Yes, it was given prior to travel. This was added to the text.</p> <p>17. Organization of paragraphs: suggest lines 9-13 follow lines 15-19 for improved flow. This was adjusted.</p> <p>18. Line 22: add "years of age" after "18" This was corrected.</p> <p>Page 10: 19. Line 13: was age difference statistically significant between ID and IM groups? Yes. This was added to the text.</p> <p>Page 12: 20. Lines 5-7: by mentioning number of patient visits in the same sentence that you are talking about proportion of travellers receiving PrEP, it almost sounds like you are suggesting they are the same. Suggest stating the number of patient visits in a separate sentence. Proportion should not vary simply because of decreased patient visits. This was adjusted.</p> <p>Page 14: 21. Line 5: should be "travelers" This was corrected.</p> <p>Page 15: References 22. #3 – link to CIG seems to be broken. The link appears to be functional to us.</p>
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