Author's response to reviews

Title: Measles vaccination coverage estimates from surveys, clinic records, and immune markers in oral fluid and blood: A Population-based cross-sectional study

Authors:

Kyla T Hayford (khayford@jhsph.edu)
Mohammed S Shomik (mshomik@icddrb.org)
Hassan M Al-Emran (alemranmb27@hotmail.com)
William J Moss (wmoss@jhsph.edu)
David Bishai (dbishai@jhsph.edu)
Orin S Levine (olevine@jhsph.edu)

Version: 3 Date: 16 May 2013

Author's response to reviews: see over
Dear Editorial Board of BMC Public Health,

Thank you for the thoughtful comments on our manuscript “Measles vaccination coverage estimates from surveys, clinic records, and immune markers in oral fluid and blood: A Population-based cross-sectional study.” We responded to the reviewer comments (see below) and have enclosed a tracked and clean version of the revised manuscript. We look forward to your response.

Regards,
Kyla Hayford

Comments, Reviewer 1
1 - Could you please expand the abbreviation "ICDDR,B," (I suppose this means “International Centre for Diarrhoeal Disease Research, Bangladesh”)?
Thank you. We corrected this.

2 - I think the work by Lessler et al. reported in PLoS Med. 2011 should be cited as it is an important work in the field. Briefly, they have developed a method by which administrative coverage estimates can be combined with a cross-sectional survey to estimate the effectiveness of measles (or other) vaccination programs.

We agree that Lessler et al.’s paper on improving administrative coverage estimates is an important contribution to immunization metrics literature. Their study models measles containing vaccine (MCV) coverage at the national level and uses supply side variables (e.g. number of vaccine doses distributed, system efficiency). Because our study is an individual level analysis and lacks supply-side data, we limited our references in the intro section to similar studies. We now have added Lessler et al.’s paper to our discussion section.

3 - Please, could you clarify what you mean by “consenting children”? Did you seek the consent of parents or guardians?
Written parental permission was obtained from all enrolled children. The methods section was revised to clarify this.

4 - Please, could you add to the text the explanation given in the legend of Figure 1 concerning the difference between the 1450 children announced in the Methods section and the 1389 children effectively selected?
We updated the results section with following revision: “1450 children were randomly selected from the DSS database, of whom 1389 were living in the DSS area at the time of the study. Of these children, 1260 (89.8%) were enrolled in the study from September 2010 to January 2011 (Figure 1).”

5 - Please, could you clarify how you have considered children aged of 12-16 months have refused OF collection?
We revised this sentence as “The parent of one child refused OF collection...”

6 - Please, could you clarify why no adjustment were done to the raw blood prevalence to account for differences between vaccination history and immunologic status?

Two types of adjustments were done to the MCV1 coverage estimate from oral fluid, which were not done with MCV1 estimate from blood. Explanations are below:

1) Adjustment for sensitivity and specificity of the assay (using equation on pg. 6) - Because the serum assay had a reported sensitivity and specificity of 99.6% and 100%, respectively, adjustment to the MCV1 coverage would have resulted in a 0.3% change in coverage from 88.6% to 88.9%. The small difference was negligible, did not affect inferences and therefore we opted to present the raw number without any adjustment.

2) Adjustment for primary vaccine failure – We adjusted MCV1 coverage by oral fluid with a conservative seroconversion rate (85%) for children vaccinated with MCV at ages 9-10 months (our study population) based on a review by Moss et al. 2009 (WHO Immunological Basis for Immunization Series. Module 7: Measles). We did not apply this adjustment to the blood MCV1 coverage because it would have resulted in >100% MCV coverage (88.6%/85% = 104%) and been difficult to interpret. Although our results suggest that an 85% seroconversion rate may be too conservative for the oral fluid results, a less conservative adjustment would only exacerbate the differences between the MCV1 coverage by oral fluid versus other coverage estimation methods and would not have affected the overall inferences in the paper.

7 – It would be nice that you can discuss your findings in comparison with administrative coverage data reported to the World Health Organization and the WHO-UNICEF estimates? Public health experts extensively use these two sets of data.

We agree with the reviewer. In fact, this study was conceived with the goal of understating and improving the comparability of vaccination coverage estimates from various data sources (e.g. administrative data, DHS surveys and WHO-UNICEF estimates). Because the study is not nationally representative, we did not directly compare national MCV1 coverage from administrative records or WHO-UNICEF data. Instead we collected all MCV1 coverage estimates from the population under study – including administrative coverage and coverage evaluation surveys by the government – and compared them to our estimates in the Discussion section (paragraph 1, discussion section, pg. 11). Using the raw data we collected, we also applied the same methods for calculating administrative coverage and DHS-based coverage and developed table 2 as a generalizable tool that policymakers and public health experts could use to improve the comparability between MCV1 coverage indicators. We revised our discussion section to put our findings in the context of national and WHO-UNICEF efforts to estimate vaccination coverage.

8 - Please, could you add this term to the abbreviations list: socioeconomic status (SES)?

Yes, we added SES to the list.
Comments, Reviewer 2

1. Title & Abstract: The authors were measuring both coverage and seroconversion of measles. As with serum assays, oral fluids EIA for measles measure serum based measles specific IgM. This should be made clear in the title, since cold chain problems and undernutrition can, among other factors, cause a mismatch between measles vaccination coverage and measles vaccination seroconversion.

We would like to highlight that this study measured measles-specific IgG and not measles-specific IgM. As the reviewer suggests, measles-specific IgM would not be an appropriate biological marker of vaccination history more than 1 month after vaccination. However, measles-specific IgG is an accepted measure of vaccination history in the absence of circulating wild-type virus because measles-specific IgG levels are high after vaccination and do not wane substantially throughout an individual’s lifetime. Measles IgG in oral fluid and serum has been used by many studies as a metric of previous vaccination history and a correlate of protection against measles virus. (http://www.ncbi.nlm.nih.gov/pubmed/18644417; http://www.ncbi.nlm.nih.gov/pubmed/19211140; http://www.ncbi.nlm.nih.gov/pubmed/21396902; http://www.ncbi.nlm.nih.gov/pubmed/11477961; http://www.ncbi.nlm.nih.gov/pubmed/17262908).

Cold chain and biological factors (e.g. undernutrition) are important considerations for discrepancies between vaccination history and seroprotection, which we address on pg. 12, paragraph 1. In this study, we collected data on nutritional status (e.g. mid-upper arm circumference for all children and height/weight in a subset of children) but did not observe a clinically or statistically significant association between undernutrition and having a discrepant vaccination status (positive history of MCV1 but seronegative). We believe serosurveillance in conjunction with vaccination history indicators could be a powerful tool for monitoring problems with the cold chain that could be fixed before an outbreak occurs.

2. Study origins: This study is based on Kyla Hayford’s 2012 Dissertation: http://gradworks.umi.com/35/24/3524826.html and should be stated as such in the manuscript's text or acknowledgment. We added this to the acknowledgment section.

3. Methods and Results: A major deficiency of this study is that it does not stratify Oral Fluid (OF) testing samples by age of vaccination against measles. It is well known that oral fluid testing is time dependent, with highest positive predictive value within the first month of vaccination. Since children with prior history of measles vaccination studied in this cohort were 12 - 16 months old, it is very likely that they had been vaccinated against measles several months earlier. http://www.ncbi.nlm.nih.gov/pubmed/10694156 I cannot recommend this study for publication if the authors are unable to revise their methods to highlight time of vaccination and provide results based on time of OF test following first dose of
measles vaccination as a separate table. Given that it is already well known that the positive predictive value of OF testing for measles IgM wanes one month or later following measles vaccination, this study has not advanced our knowledge of the usefulness & limitations of the test.

We would like to clarify that measles-specific IgG was measured in this study, not measles-specific IgM (see #1 above). Because of this, we did not age stratify in the analysis. To ensure that measles-specific IgG was an appropriate correlate of protection in the population, we confirmed that MCV1 receipt occurred at least 1 month prior to oral fluid collection in enrolled children (based on clinic records, vaccination card records and maternal report).

4. OF testing is known to have a high negative predictive value: http://jid.oxfordjournals.org/content/187/Supplement_1/S283.long this attribute was not tested in the authors' study, for the 10% - 15% that were documented as negative using cards and self-report by mothers.

Results should report on positive and negative predictive value of OF at various months following receipt of MCV1. Stratifying PPV and NPV by time since MCV1 is an important concern for an IgM assay but not for an IgG assay (see #1 above).

Minor Essential Revisions

5. Introduction: Some information on measles epidemiology globally and in Bangladesh is important. Also pertinent is description of Bangladesh's measles vaccination schedule.

We made revisions to the introduction within the limitations of the word count. We also highlighted the implications of vaccination timing in Bangladesh on the validity of the assay in the methods section (penultimate paragraph, methods section, pg. 6-7).

Discretionary revisions

6. Since the main point of the authors relates to OF validity, it is important to include more pertinent references on OF sensitivity and predictive value in the results section, and list appropriate references.

We wrote a related paper that is currently under peer review, which validated the OF results against blood results from this study. Because we did an in-depth analysis of sensitivity and predictive accuracy of the OF assay in this paper, we did not focus on it here. We added a reference to our unpublished work in this paper.