Author's response to reviews

Title: Measles Vaccine Coverage and Factors Related to Uncompleted Vaccination among 18-month-old and 36-month-old Children in Kyoto, Japan

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Version: 3 Date: 14 February 2005

Author's response to reviews: see over
Thank you very much for reviewers' constructive comments on our manuscript titled “Measles Vaccine Coverage and Factors Related to Delayed Immunization among 18-month-old and 36-month-old Children in Kyoto, Japan”.

We responded to each of the Reviewer’s comments as follows.

1 16 November 2004 Version: Date:
Barbara Bardenheier Reviewer:

Reviewer’s report:
General
This paper presents important, relevant information about measles vaccination coverage in a country where immunizations were mandatory until 1994. Results of this study should be used to target the children most at risk for not being immunized.

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

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1) I could not find where the outcome measure was defined. It should be in the methods section, but it only says (pg 5) that logistic regression was carried out to assess the factors related to measles vaccine coverage.

We added the following sentence to the methods section, “This study’s outcome measure is defined as measles vaccine coverage among 18 and 36-month-old children.” (pp. 5, ln 21).

On page 7 it says predictors of low coverage but doesn’t define what is low coverage.

The revised version reads, “Predictors of uncompleted vaccine coverage.” (pp. 7).

So is the referent group for the odds ratios in tables 3 and 4 being vaccinated or not
being vaccinated? It should be made more clear.

For more clarity, we changed the direction of both referent group and variables.
The referent group is being unvaccinated, so we changed the title of tables 3 and 4 to:
“Factors related to uncompleted measles vaccination.”

Also, on page 6 it says the coverage rate among 18 month olds is 73.2% which isn’t rare so relative risks should be presented or at least mention that odds ratios might be inflated. The ORs presented for the 36-month olds is fine because the rate was 88.9% (only about 11% unvaccinated is rare).

We added the sentences to the results section, “Among the 18-month-old group, measles vaccine coverage was 73.2%, The odds ratio may be inflated as an approximate value of the risk ratio.” (pp. 8, ln 20; Predictors of completed measles vaccination).

2) On page 3, first paragraph: In the US, indigenous measles transmission has been interrupted by supplementary mass vaccination campaigns.2-5 has been misquoted. None of the articles cited mention anything about the United States doing mass vaccination campaigns. Rather, they discuss ways of improving the existing infrastructure to increase vaccination coverage. The paper by Ciro de Quadros mentions that Since 1991, all the PAHO member countries in the Americas, with the exception of Canada and the United States, have conducted catch-up measles vaccination campaigns... Hence, maybe the authors confused all the Americas except Canada and the U.S with the U.S.? This needs to be corrected.

In light of your commentary, we have revised the background section on page 3. Thank you.

3) On pg. 3 first paragraph, last sentence: it says Japan is reported to be the principal exporting country of measles to the U.S.- this should be clarified to say in 2000 because that was the only year it was reported to be so.

We added “In 2000” on page 3, line 26.

4) On page 10 first paragraph, last sentence: the vaccine risks discussed are what is used by WHO Expanded Programme on Immunization. Is that what is being used in
Japan? I am not the expert in this area, but I do know that in some countries WHO uses a measles only vaccine and not the MMR which is mentioned in other cited papers (Lieu, et al). Which vaccine is used in Japan should be mentioned.

In Japan, a total of three different measles vaccines are available (AIK-C, Schwartz FF8, CAM). BIKEN-CAM is supplied to the WHO Expanded Programme on Immunization. On page 11, line 6, we quote Reference 19, a publications that notes the frequency of adverse events related to measles vaccines.

5) On page 8, the second sentence in the Discussion section the authors mention that since 1994 vaccination was no longer mandatory. That should also be mentioned in the introduction when the Immunization Law is first brought up, on page 3 in the second paragraph.

In the introduction, we added a sentence on the recent changes in measles immunization policy in Japan (pp. 3).

6) On Table 2 above the columns it says 'percentage of respondents answering correctly'. Because some readers might not know what 'correctly' is I think they that the authors should put the percentage that said either 'yes' or 'no'.

We changed “correctly” to “yes” on Table 3. (previously Table2 in original version)

Discretionary Revisions (which the author can choose to ignore)

1) On page 5 the first two sentences in the results section: describes Kyoto City and its population, which really is background, not results, and should be moved to the introduction section.

We moved the description of Kyoto City to the method sections (pp. 4).

2) On page 9, third paragraph last sentence is awkward. may be probably lower is redundant. Need to reword.

We changed “may be probably lower” to “may also be lower.” (pp. 10, ln 6)
Reviewer's report
Measles Vaccine Coverage and Factors Related to Delayed Immunization among Title:
18-month-old and 36-month-old Children in Kyoto, Japan.
1 30 November 2004 Version: Date:
Glenda Lawrence Reviewer:

Reviewer's report:
All of my comments in the report below that relate to data analysis and presentation, including issues around the validation of parent report of vaccination status are 'major compulsory revisions'. The others are at the authors' discretion.

Measles vaccine coverage and factors related to delayed immunization among 18-month-old and 36-month-old children in Kyoto, Japan

This paper describes a cross-sectional survey to assess measles vaccine coverage and related factors among a large sample of children presenting to health clinics in Kyoto for routine health checks at 18 and 36 months of age. Parents provided information, in a self-completed questionnaire, about their child’s immunisation status, their knowledge and beliefs about immunisation and socio-demographic factors.

The study parallels similar studies in other affluent developed countries to identify factors related to the non-uptake of measles vaccine by parents. This has relevance both nationally and internationally because, since 1996, there has been a global initiative to eliminate measles. In this era of measles elimination, the paper provides some interesting and relevant information from a developed country that appears to have some way to go before they achieve measles elimination, which as many comparable countries have achieved.

The methods are generally well described and appropriate to answer the research question. The results section, and particularly the tables presenting the logistic regression results, requires some editing to assist the reader. The discussion is generally well balanced and is relevant. It would be improved if the results of this study were discussed more broadly in the international context (in addition to the USA).

Abstract
• The authors conclude that a system to enhance access to vaccination is required. It seems to me from the paper, that other factors are also important, including communication with parents about the changing vaccination schedule.

We changed to “Efforts to enhance access to vaccination services and to communicate with
Introduction
The authors imply that the global strategy for the elimination of measles commenced in 2001. This is not so – it commenced in the 1990s and many countries implemented immunization and enhanced measles surveillance policies related to this during the late 1990’s. Some (e.g. the Americas) achieved measles elimination quite early. The two dose strategy came later, in 2000 when it was realized this would be necessary for elimination in many countries due to insufficient coverage with the first dose, plus failure by some vaccines to seroconvert. Two doses prevents the build-up of number of people in the population who are susceptible to measles infection to a level that is able to sustain outbreaks of disease.

In light of your commentary, we revised the background section on page 3. Thank you.

The phrase that 2 doses maximizes “both individual and population immunity” could be misunderstood by readers not familiar with this subject. The purpose of the 2nd dose of measles-containing vaccine is not to increase the level of immunity, but to increase the total number of people who are immune. A two dose policy provides an opportunity for vaccination of those who missed the first dose and to re-immunize those who failed to sero-convert with the first dose, usually because circulating maternal antibody levels inhibited sero-conversion.

We revised the sentence to read, “to increase the total number of people who are immune.” (pp. 3, ln 14)

It would also help readers if more information was included in the introduction about recent changes in measles immunization policy in Japan as they affect the birth cohorts were selected for this study. It was only when I read the discussion section that I realized that at the time the study was conducted in late 2002, the children in the 18 month age-group may not have considered overdue for measles vaccine until they reached the age of 24 months.
We revised the background section on page 5.

The 2000 national survey – reference [9] is unlikely to be accessed by international readers. Could the authors please indicate how coverage was estimated in the national survey (parent-report, validation, reliability etc).

The 2000 national survey was a collection of reports from local governments (response rate was 97.6%). We have no information about the validation of this survey.

Methods

Parent questionnaires: what were the response options? Did they include ‘unsure’ and ‘refusal’?

Response options were “yes” and "no". They didn’t include ‘unsure’ and ‘refusal’. When there was no response, we omitted the data. (30 in the 18 month group; 55 in the 36 month group)

Logistic regression analysis: there is no mention of the multivariate analysis or the methods used to construct the dummy of variables to combine knowledge and concern about adverse events (as reported in Table 4).

We added the following sentence to the methods section: “This logistic regression analysis was carried out using three dummy variables, namely, X1, X2 and X3” (pp. 8, ln14)

Validation study: how many records were assessed and on what basis were they selected (random sample, convenience sample etc)?

In the 18-month-old group, 110 respondents were assessed, and in the 36-month-old group, 119 respondents were assessed. (described in the results section on pp. 7) The sample was one of convenience. All respondents’ children received a health checkup at Kami-gyo Public Health Center during the survey period. Our present survey was conducted in cooperation with the Kami-gyo Public Health Center. We checked all respondents’ answers
from the Kami-gyo Public Health Center.

Results
Paragraph 1, lines 5,6: it would be clearer for readers if the authors specified that the response rates of 88% and 82.5% were for the immunisation survey (i.e. denominator is the number who attended for the health check).

We changed the sentence to, “The response rate was 88.1% (2707 respondents out of 3072 patients who received a health checkup) and 82.5% (2340 respondents out of 2836 patients who received a health checkup)” (pp 6, ln 13)

Page 6: Quite a lot of the text describing measles coverage and incidence could be put into a table if the authors wished to reduce the amount of text. It may be easier to follow in a table.

We have discussed this point, but would like to keep it as text.

Validation of vaccination status: did those who were included in the ‘validation’ group differ in characteristics compared to parents who were not included in the ‘validation’ group?

Kami-gyo Public Health Center is situated in the middle of Kyoto City. Although this area is socioeconomically upper-middle class within the confines of Kyoto City, parent characteristics are likely to be quite similar. (health checkup rate is similar.)

Page 6, paragraph 1, line 12: the authors indicate that measles incidence was ‘significantly’ higher among children who interacted with other children but no p value is provided to indicate whether the difference was statistically significant.

We added the 95% confidence interval on pp. 6, ln 27.
We changed the incidence of measles in the 18 month group from 1.8% to 1.9%, because we were miswritten.

Reasons for not receiving measles vaccine: was the difference in the percentage reporting concern about adverse events in the unimmunised children statistically
significantly different for the 18 month group (2.9%) versus the 36 month group (9.5%).

We surmised that the parents who showed concern about adverse events would not make their children have a vaccine shot until 36 month. Accordingly, we categorized “concern about adverse events” as a cause, and “not completed vaccination” as an outcome.

There is no reference to table 2 in the text (page 7)

We added the reference for Table 3 (previously Table 2) on pp.7, ln24.

Predictors of low coverage: This section is not written very clearly; there is no indication of the direction of association and the titles of paragraph and table appear to be contradictory i.e. are you focusing on factors associated with children being immunised or factors associated with incomplete immunization? Was age mother’s age of <30 years associated with the child being immunized or not immunized? This is not clear from the table or the text.

For more clarity, we changed the direction of both referent group and variables. The referent group is unvaccinated. We changed the title of tables 3 and 4 to “Factors related to uncompleted measles vaccination.

The logistic regression analysis was conducted focusing on factors associated with children not being immunized. Mother’s age of <30 years was also associated with incomplete immunization.

Tables 3 and 4 would be clearer for readers if the direction of association was shown (see suggestion below)

Factors related to completed measles vaccination (18 month group)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prevalence</th>
<th>Odds Ratio (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=1836)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother’s age (&gt;30 years)</td>
<td>63.3%</td>
<td>1.11 (0.93, 1.32)</td>
<td>0.26</td>
</tr>
<tr>
<td>Mother working</td>
<td>25.1%</td>
<td>0.60 (0.50, 0.73)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>First born child</td>
<td>54.5%</td>
<td>1.93 (1.62, 2.30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interact with other children</td>
<td>21.3%</td>
<td>0.57 (0.46, 0.69)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Presence of allergy 17.8 1.11 (0.89, 1.40) 0.37
Concerned about adverse events 30.0 0.77 (0.64, 0.93) 0.007
Knowledge score: 7-12 points 39.3 2.09 (1.73, 2.53) <0.001
(Also, it is easier for the reader if all variables are in the same direction – i.e. No concern about adverse events OR = 1.30; Mother not working OR= 1.67)

We revised the content of Table 4. (previously Table 3)

**Table 4:** It would be clearer to give the adjusted OR of G1 as 1.0 (referent) and to indicate what G1 is (i.e. low knowledge, high concern), then state the OR values for each of the other groups e.g.
Low knowledge, high concern (G1) 1.00 (referent)
High knowledge, high concern (G2) 2.70
Low knowledge, low concern (G3) 1.71
High knowledge, low concern (G4) 3.65

We revised Table 5. (previously Table 4)

**How many respondents were in each of the 4 groups?**

The new version shows numbers in Table1. (created Table1 for explanation of dummy variables in this version)

**These results suggest that the level of knowledge is more highly correlated with immunization status than the level of concern about adverse events. Would the authors care to comment on this in the discussion?**

We added the following sentence to the Discussion, “These results suggest that the level of knowledge is more highly correlated with immunization status than the level of concern about adverse events” (pp10, In 28).

**What happened to the adjusted OR values when the ‘child allergy’ variable was removed from the final model? It isn’t statistically significantly associated with measles immunization status in the univariate or multivariate analyses.**

The adjusted OR values when the ‘child allergy’ variable were removed from the final model
as shown in the table below. The adjusted OR values were quite similar.

<table>
<thead>
<tr>
<th>variable</th>
<th>18 month group</th>
<th>36 month group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI) P value</td>
<td>Odds Ratio (95% CI) P value</td>
</tr>
<tr>
<td>Mother's age ( &lt; 30 years)</td>
<td>1.32 (1.08, 1.62) 0.01</td>
<td>1.66 (1.14, 2.39) 0.007</td>
</tr>
<tr>
<td>Mother working</td>
<td>1.42 (1.04, 1.94) 0.04</td>
<td>1.76 (1.17, 2.67) 0.007</td>
</tr>
<tr>
<td>Not first born child</td>
<td>2.24 (1.84, 2.73) &lt;0.0001</td>
<td>2.40 (1.73, 3.37) &lt;0.0001</td>
</tr>
<tr>
<td>Interaction with other children</td>
<td>1.51 (1.09, 2.10) 0.008</td>
<td>1.93 (1.27, 2.93) 0.002</td>
</tr>
<tr>
<td>High knowledge, low concern (G1)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Low knowledge, low concern (G2)</td>
<td>2.18 (1.71, 2.80) &lt;0.0001</td>
<td>2.04 (1.36, 3.12) 0.001</td>
</tr>
<tr>
<td>High knowledge, high concern (G3)</td>
<td>1.35 (0.96, 1.88) 0.08</td>
<td>1.67 (1.00, 2.76) 0.05</td>
</tr>
<tr>
<td>Low knowledge, high concern (G4)</td>
<td>3.62 (2.71, 4.87) &lt;0.0001</td>
<td>3.70 (2.32, 5.93) &lt;0.0001</td>
</tr>
</tbody>
</table>

CI: Confidence Intervals

**Did the authors check for colinearity in the multi variate regression model– eg mother’s age and first born child?**

We checked for colinearity in the multi variable regression model. The correlation coefficient among mother’s age (<30) and not first born child was 0.29 in the 18 month group and 0.26 in the 36 month group. The correlation coefficient, except among unemployed mothers and “no interaction with other children”, was 0.01-0.29. Although the correlation coefficient among “mother working” and “interaction with other children” was high (0.75 in the 18 month
group and 0.66 in the 36 month group), these are different and we are interested in both of them. We put both of them into the final model.

Discussion

The explanation of the coverage calculation used for the national survey (reference 9) is not clear. The denominator does not seem to be appropriate.

We explain our reasoning for mentioning the denominator as follows: “This survey’s methodology, however, is problematic. The definition of denominator (total number of persons who were going to receive vaccination per year) differs across individual local governments. To obtain vaccine coverage is important for each local government.” Most local governments define the denominator as total number of persons who reached the vaccination age per year, but some local governments define it as the number added the number of persons not vaccinated until the year before when they reached the vaccination age.