Author's response to reviews

Title: Health burden and economic impact of measles-related hospitalizations in Italy in 2002-2003.

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Dear Dr Phillips,

Thank you for the reviewer’s comments. Please find attached a revised version of the manuscript, in which all comments have been addressed.

Below is a list of the changes made with respect to each point.

1. Please shorten the introduction. E.g. the last paragraph regarding the national database could be described in the Methods section and mentioned in the Discussion. The part that hospitalizations are only 40-50% of costs of measles cases etc. is double with discussion. Please only mention it in the Discussion section.

The Introduction has been shortened by making the requested changes. The section regarding the national database is now partly mentioned in the Methods section (first paragraph) and partly in the Discussion section. The point regarding the percentage of hospitalizations costs is now mentioned only in the Discussion.

2. The results should be presented in a more structured manner. The first part of the results has overlap with other headings e.g. diagnoses/complications. Please make sure that you structure the results section in a way that no overlap exists. This could probably be best done by leaving out the first part of the results.

As suggested, the Results section has been substantially modified. In particular, the following major changes have been made:

- A new subtitle was added (“Main discharge diagnosis”).
- A new table (Table 1) was added, describing the main discharge diagnoses in measles hospitalizations. The original text was modified accordingly.
- Table 4 was expanded and now includes all clinical diagnoses by age. The corresponding text was modified accordingly.
- Length of stay and cost sections were expanded.

3. In Table 2 too much detail is given with respect to region. Please leave out. This would be useful when you have information with regard to susceptibility level in the population or vaccine coverage and relate this to the incidence. You could make a geographical figure of Italy showing with different colours the incidence. This would make the north-south gradient visible.
Table 2 has been removed as requested and a figure showing the 2002 and 2003 regional standardised rates of measles hospitalizations has been added (Figure 1).

4. In Table 5 the length of hospital stay differs somewhat between regions. Why? Age-difference, different complication rate?

According to the referee’s suggestion, we replaced the mean with the median length of stay by geographical area. Despite the fact that a longer median length of stay was observed in Central Italy (5 days) compared to Northern and Southern Italy (4 days), this difference is modest, and cannot apparently be related to differences in age-specific hospitalization rates nor to differences in complication rates.

5. Length of hospital stay; please relate this to age

The following sentence was added to the text: “Median length of stay was 4 days in all age groups ≤19 years, and 5 days in cases aged >19 years (p<0.001).”

6. The information with regard to diagnoses/complications could be better summarized in a table and only shortly described in the text.

See response to Point 2. As suggested, diagnoses/complications are summarized in Table 4 and only briefly described in the text.

7. In Table 4 the columns do not add up to 100, is this because one row has been left out?

Table 4 now lists all recorded diagnoses by age. Percentages for each diagnosis are calculated over the number of hospitalizations in each age group and total percentages for each column exceed 100 because more than one discharge diagnosis may be listed for each hospitalization. A note has been added below the table to explain this.

8. Do you have information with regard to the secondary discharge diagnoses? What is meant by no associated secondary diagnosis?

All clinical diagnoses (main and secondary diagnoses) reported for the 5154 hospitalizations are now described in Table 4.

“No associated secondary diagnosis” means that only one discharge diagnosis is listed in the discharge abstract form. To avoid confusion, however, the first sentence under the subheading “Complications” (Methods) was changed as follows: “For the purposes of this study, non-complicated measles cases were defined as cases with a main discharge diagnosis of “measles without mention of complication (code 055.9).”

9. The costs part is very short: please specify it according to measles with and without complication when that is possible.

This analysis has been performed, and the results have been added to the cost section.

10. Why is using DRGs an advantage? Easy to apply but less accurate? Is it applicable to other countries? Otherwise what is the reason for mentioning it as a unique characteristic of the study?
The advantage of using DRGs to calculate the costs incurred by the National Healthcare System for hospitalizations is now explained in the Discussion section (paragraph 2), and a reference regarding countries that use DRGs for reimbursement of hospital costs has been included (Reference n. 22).

11. Please shorten the paragraph on page 14 (In Italy… and their related costs).

This paragraph has been shortened, as requested.

12. The number of reported deaths is lower than that found in the Campania region. As a reason, reporting of a different discharge diagnosis is given. What does this observation imply for the rest of the observations in terms of completeness?

This is one possible reason and implies that some measles-related diagnoses may have been missed. The discussion regarding the limitations of the study has been modified to better explain this point. As mentioned in the text however, another explanation for the discrepancy may be that the patient died outside of the hospital setting.

13. What is the possible reason for many hospital admissions without a complication? What is the reason for admission?

The following sentence was added to the Discussion: “Although we cannot precisely identify the reason for admission in these cases, and we cannot exclude that at least part of these admissions may have been inappropriate, these findings confirm that measles can be severe enough to require hospitalization even in industrialised countries and even when specific complications are not present (6).”

14. At what frequency do you expect that readmission in the hospital occurred?

Unfortunately, we have no way of calculating the rate of hospital readmission for measles. Nevertheless, we have clearly discussed as a limitation of the study the fact that our data refers to hospitalizations, and not to patients.

15. Please discuss the difference found between regions; e.g. relate it to vaccination coverage, susceptibility level. This could make the message, that high vaccination coverage is essential, more pronounced.

The difference in hospitalization rate found between regions is discussed in the Conclusions section. We had already stated in the previous version that the greater number of hospitalizations in central and southern regions reflect the different regional vaccination strategies adopted in the past which had led, with a few exceptions, to higher coverage levels in northern regions with respect to regions in the Centre and south of Italy. To further reinforce the point made by the referee, however, the following sentence has been added: “A seroprevalence study conducted in the late 1990s found a significantly higher proportion of children susceptible to measles in regions with vaccination coverage rates below 70%, and these regions were, in fact, prevalently located in central and southern Italy (3, 31).”

16. Please shorten the part of the conclusion with regard to the elimination plan for measles and CRS.

This part of the conclusion has been shortened.
17. Would it not be better to calculate the median ages as well as median hospital stay and give the range? Was the length of stay normally distributed?

Median age and median hospital stay are now reported in the text. The length of stay was not normally distributed, but approximately 95% of admissions lasted \( \leq 10 \) days. This information has been added to the text.

Regarding the editorial issues, we have added a “Competing interests” section as well as an “Author’s contribution” section. This study was performed by using routinely available data and did not require to be evaluated by an ethics committee.

Kind regards,

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