Author's response to reviews

Title: Geographical differences in whooping cough in Catalonia, Spain, from 1990 to 2010.

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Author's response to reviews: see over
Dear Sir,
Please find enclosed the revised manuscript. We have made the changes suggested by the reviewers as far as possible. The manuscript has been reviewed by a native English speaker.

Sincerely yours,

Reviewer 1:

Major comments

1. Categorization of rural and urban areas around mean population density may not be completely efficient. In several countries the rural and urban communities are classified by a National statistic entities putting together several indexes. Does a similar classification exist in the area under study?

   We have changed our classification of rural and urban counties according to the Spanish law 45/2007 LDSMR (Law of Sustainable Development in Rural Areas) definition. According to this classification, counties are considered rural when the population density is lower than 100 inhabitants/km² and the population is < 30,000 inhabitants (on page 4, lines 20 and 21).

2. I understand that the setting in the entire area under study is pretty homogeneous. However I think it is very important to investigate a number of factors that may act as confounders in the analysis:

   - sociodemographics: it may be that the number of households differs between rural and urban areas thus affecting the matrix of contacts. Age may be different as well;

     Unfortunately we do not have information on the age of the reported cases for all the study period (this is explained in the methods section on page 4, lines 13 and 14).

   - immunization coverage;

     The difference in immunization coverage is not statistically significant between rural and urban areas in the region of the study as is now discussed in the manuscript (see page 9 paragraph 2).

   - attitude to diagnose pertussis: it may be that lab resources are used more frequently in urban areas.

     Since 2003, the surveillance system of Catalonia provides a messenger system for each physician who wants to send samples related to suspected cases of whooping cough. This is now stated in the manuscript (see page 9 paragraph 3).
The Authors should include these factors in the models or at least provide some discussion on their potential effect.

Some comments about vaccination coverage and the surveillance system are included in the revised manuscript (on page 9).

3. Seasonality does not seem to follow a precise pattern. However the Authors may have tested seasonality by age group. I would expect a more pronounced seasonality in infants and children. Are these data available?

As explained above, we do not have the age for all the cases included in the study.

Reviewer 2:

Major Compulsory Revisions

1- A map of the Catalonia with counties limits and different colors for urbans vs rural counties and location of Big cities should be informative to help the interpretation of the results (rural counties aggregated ? isolated ?).

We agree. We have included a map with the required information (see Figure 1).

2- Results section. « In 1990, 33 counties were considered as rural, 8 as urban. In 2010, 31 counties were rural and 10 urban »…. The definition implies a change in number of rural/rural counties every year… how thus was built the rural and urban time series…. Data from one county can be included in rural aggregation in few years and in urban aggregation for the other years…. That is not clear… please clarify this point and provide more details in supplementary material for instance… A time series is supposed to be the number of cases in the same spatial unit…

We agree. We have classified the counties as rural or urban at the beginning of the study and have continued with this classification during the whole period. There were 27 rural and 14 urban counties.

3- Fig 2 : it looks that the dynamics are different in rural and urban counties, which is interesting to explore but frustrating since it is not done fully in the manuscript. A single graph with the 2 curves (urban vs rural) would help to see the differences (e.g. the epidemics in 1996 that we see at the Catalonia level is largely due to an epidemics in rural counties but does not concern the urban countries…

We have changed figure 2 to a graph with rural and urban incidences to better show the differences. Information about whooping cough outbreaks is not available before 1996, and therefore we cannot know if there were some specific outbreaks in rural counties. We have explained this in the discussion section in the manuscript (on page 7, last paragraph).

4- The only information given by the authors is incidence globally higher in urban (I am surprised with that when I see Fig 2) and the trend (methods used to define it = the red lines in fig 2, not clear) is different between rural and urban… A graph showing the proportion of cases by year in rural vs in urban counties should be interesting. We do not see the results of seasonality test or spectral analyses of both time series to look at periodicity. A cross analysis would be informative on the synchrony or delay between the time series. The results shown are poor and do not
bring very relevant information. Additional analyses of the 2 time series should be performed to make the manuscript rich enough in new insights for publication.

In this revised manuscript, figure 2 has been modified in order to be clearer. P values for seasonality analyses and the results of binomial regression of seasonality are included in the manuscript (on page 7, lines 2-5). We have now included adjusted models for four-week periods in order to assess the association of the two time series.

5- Vaccination data are not presented… it should be crucial to have an idea about the evolution/change of VC over time and the difference between urban and rural. Authors mention that DTP3 coverage is similar between rural and urban… is that true during the whole period ? what about the vaccine coverage of boosters ? That should be added to the manuscript. We do not have this data available for each case. We have included in the discussion a paragraph with data available about differences in coverage between rural and urban settings in Catalonia (on page 9, paragraph 2).

6- Results sections : » In 20 years of the study, the incidence rate was higher in urban countries for 9 years and in rural for 4 years. … What about the 7 other years ? With the classification used in this revised manuscript, these results have changed. The new results are described and discussed in the revised manuscript (Results, paragraph 2 and discussion, paragraph 2).

7- In the whole period, the rate was higher in urban counties »…. How can it be the case if that happens only 9 years among 20 years…. ? please clarify this paragraph.. We have excluded the comparison of the whole period because it was difficult to interpret (in some years the incidence was higher in urban counties and in other years the opposite was true).

8- Authors mention a specific study for the period 2003-2010 with individual data… it is a pity that did not consider the age distribution of cases since it is a crucial research question in the pertussis field currently in the context of boosting questioning. As explained before, the surveillance system of the disease in Catalonia did not include the age for the whole study period.

Minor Essential Revisions

1- Abstract: « WC is a communicable disease whose incidence has increased in recent years »… please add « in some vaccinated countries », since it is not systematic everywhere… We have added this sentence.

2- Background section : « Introduction of the vaccine reduced the incidence but did not change these intervals, suggesting endemic circulation of Bp. » I guess, « intervals » mean « periodicity »… periodicities did increased after vaccination in all countries (you cite Broutin et al 2010 later in your ms but there are also country-specific paper that showed that). Vaccination reduced incidence and increased periodicity, also changed the age distribution of cases (increasing mean age at infection for instance) and that argues for the impact of vaccination on transmission too, not only on disease. We have included new references for other studies (ref 24).
3- Table 1 is supposed to present incidences for rural and urban and thus correspond to the Figure 1 /figure 2… which is not the case for 1990-1991 and 1992… with high incidences in the table. Figure 3 shows the incidence in four-week periods and table 1 shows the global annual incidence. Therefore, the incidences in table 1 are the sum of the incidences in figure 2 year-by-year. We now include more details in the legends in the axis.