Author’s response to reviews

Title: Definition and characterization of localized meningitis epidemics in Burkina Faso: a longitudinal retrospective study

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Author’s response to reviews: see over
Definition and characterization of localised meningitis epidemics in Burkina Faso: a longitudinal retrospective study

Authors’ reply to reviewers’ comment, September 19, 2011

1. Reviewer’s report

General comments:
In this study, authors use a novel dataset, with a thin geographical specification of disease counts, and investigate a definition of an epidemic at a lower level than currently used in public health policies. This is of prime importance in the management of meningitis in the African Belt, and could allow improving vaccination efficiency and saving scarce resources. Yet, how the current vaccination policy could evolve relatively to the results shown here should be better described and enhanced, mostly in the discussion. The manuscript needs reviewing, in terms of language and of re-organising.

Specific:
Globally:
- My concern about the English language expression applies especially to the "Results" section. This section should be re-organised and it should be clarified what some results are expected to show (for instance, ‘The interquartile range of ACI among health centres of the same district year was on median 1.41% (range 0.72-2.29%) in district years with epidemic declaration and 0.03% (0.01-0.09%) in district years without epidemic declaration’, ‘The median population size in
individual localised epidemics was 6,702’).

Authors’ reply:
We have revised both sequences in the manuscript to facilitate the interpretation of the results.

In addition, a few sentences should be removed for not being informative, if not confusing (i.e. ‘We used the interquartile range of ACI as a measure of heterogeneity among health centres in the same district and year’, ‘We use two ACI at the health centre level to define a localized epidemic’).

Authors’ reply:
We have removed both sentences from the methods section.

- In order to have a better idea of the potential interest of downscaling from the district to the health-centre level for defining an epidemic, it would be great to describe population size at both levels. Including a map in the figures would help visualising the studied area and mostly the results in terms of localized epidemic.

Authors’ reply:
In reply to both reviewers’ 1 and 3 comments, we have expanded the table to include a more exhaustive description of all districts, with or without epidemic declaration, including population size. Furthermore, we have added a map representing the localised epidemics in the Hauts-Bassins region during 2006-8.

- Vaccination policy is the problem you are tackling in this study, without detailing it enough in my opinion. You should discuss how your results could impact the current policy. For instance, would epidemic episodes at a health centre level be sufficiently long for efficiently launching vaccination campaigns?

Authors’ reply:
Apart from better understanding the overall epidemiology of meningitis in the belt, characterising localised epidemic might be useful to evaluate the impact of the newly introduced conjugate A vaccine (as explained in the discussion (6th paragraph) and
also, as rightly pointed by the reviewer, to inform epidemic response strategy, as explained in the 8th paragraph of the discussion. The overall response strategy depends on the capacity of the surveillance system to detect outbreaks, and the availability of vaccines. Considering that vaccines usually cannot be prepositioned at country or district level due to the limited worldwide production, the time required to bring the vaccine to respond to a localised outbreak exceeds the duration of the outbreak and the campaign will have no impact. However, in the ideal situation where the surveillance system is timely and the vaccines readily available, then the response may be targeted, as explained for Mali and Chad. We added a sentence to clarify this issue in the 8th paragraph.

It would also be interesting to evaluate the number of vaccine that would have been administered over the study period according to both policies, the current district level policy, and the one you propose

Authors’ reply:

We agree that the number of vaccine doses required is an important criterion for comparing vaccine strategies. However, we do not believe that this manuscript should include such estimation for precise policies, although the calculation is technically feasible (the respective estimates are 1 mio for RT@HC and 2.5 mio for the district level decision, assuming a vaccine target of age 1-20 yrs, vaccination only in the concerned health centre (RT@HC) and repeated vaccination if repeated threshold crossing). A vaccination policy and the required number of doses would depend on several other factors, such as target age range, size of the area vaccinated in each instance, the decision to vaccinate populations repeatedly in consecutive years. We believe that readers may be confused whether we suggest here a concrete vaccination policy, which we definitely would not like to do in this paper. Any concern and disagreement in readers knowledgeable in policy making would distract their attention from the main message, which is the fact that epidemic definition and surveillance should be done at the health centre level. Further detailed and exhaustive evaluations are needed to inform policy making.

To nevertheless follow-up with the reviewer’s idea, we re-wrote the respective paragraph in the discussion, which reads now:

"While the proposed definition of localised epidemics at the health centre level (LE75) did not improve timeliness of epidemic declaration at the health centre level compared to the current practice of district level analysis, our study showed that if RT@HC was used, epidemics could be identified geographically precisely and in one quarter of instances at least one week earlier than by district level analysis. This may be important for the timeliness of reactive mass vaccine campaigns, which will remain necessary after MenAfriVac introduction, at least for occasional serogroup W135 epidemics. Some countries, such as Mali and Togo, do organize reactive vaccine campaigns based on health centre level incidence data and therefore hold vaccine stocks at district level. Many factors influence the effectiveness and costs of a reactive vaccination campaign (speed of data transmission,
campaign logistics, target population) and the usefulness of health centre level analysis of surveillance data for informing vaccination strategies need to be evaluated in more detail on larger data sets.

It would also be clearer to readers if you were explaining what is expected from the introduction of the new conjugate A vaccine.

Authors’ reply:

The introduction of this new vaccine is expected to dramatically change the epidemiology of meningitis in the belt and will hopefully eliminate the large meningitis A outbreaks as a public health problem. This issue is obviously very important and interesting, but not tightly related to the main study question. We initially did not mention this issue to avoid confusing the reader and lengthen the manuscript. We added a short paragraph in the discussion and leave it to the editor’s discretion whether we should expand further. The discussion section reads now: “The disappearance of these localised epidemics could be used for quantifying the impact that meningococcal serogroup A conjugate vaccine (MenAfriVac®) will have on epidemic meningitis. The introduction of MenAfriVac® in the meningitis belt is expected to substantially change the meningitis epidemiology and a key issue will be to evaluate the impact of the vaccine on the frequency and extend of epidemics. It is possible that the presented definition of epidemics at the health centre level will allow quantifying the long-term impact in a sensitive and economic way, especially in areas where no widespread laboratory surveillance is conducted.”

Finally, you should discuss what impact might have had the past vaccination campaigns on the dynamic of the disease and thus on your data: it could partly explain why epidemics are so localized (vaccination might have stop it from spreading in the district), and how it could be related to some districts/health center declaring epidemics in 2 consecutive years. Another issue of vaccination is the susceptibility of the population which could be originating a good part of the local interannual variability of cases (to be linked with the interval epidemics at health district level might occur at).

Authors’ reply:

Prior vaccination campaigns and carriage are certainly very important drivers of epidemics. Individual data on immunization status was not available as per policy data are aggregated per week and district. In addition, the vaccination coverage at
the health centre level was not available either. However, level of immunity may explain why outbreaks are localised, but should not impact on the thresholds. We added this point as a limitation of the study: “Data on past vaccination campaigns and coverage at the health centre level were not available. Population immunity likely is an important factor of epidemic occurrence and heterogeneous vaccination coverage across the district may explain why some outbreaks remain localised and why outbreaks may occur several years in a row despite vaccination campaigns.”

- You could simplify your incidence rates definitions: weekly incidence rate (WIR) is the weekly number of cases per 100,000 inhabitants, and annual incidence rates (AIR) the annual number of cases per 100 inhabitants (cumulative means your cumulate counts with time, which is not the case here).

Authors’ reply:

We have simplified the terminology and dropped the term cumulative throughout the manuscript. The definition in the methods section reads now: “We calculated weekly incidence rates (WIR) as number of weekly cases per 100,000 inhabitants and annual incidences (%) as annual cases per 100 inhabitants.”

- You should better explain the concepts you are using, such as’ years with epidemic declaration’ (at a district or a health centre level?), ‘epidemiogenic’, ‘separate epidemic wave factors’

Authors’ reply:

We have revised these terms and use more detailed or intuitive wording. For example, the sentence on “separate epidemic wave factors” reads now: “While no strong evidence exists on what makes these localised epidemics occur, specific spatially restricted factors other than climate ...”

- Be careful with acronyms being wrongly spelt. You should be more consistent in writing percentage. I would advice to give them in numbers and use the % symbol
Authors’ reply:

We have made these changes throughout the manuscript. The acronym ACI was dropped.

- Did you not try to have data about viral infections in the studied health centres?

It would have been a great opportunity to test a hypothesis that was exposed in a previous publication.

Authors’ reply:

No, the data are not available but we are preparing to collect information on respiratory infections in a specific project.

Abstract:

A few words should be replaced to better describe the study: ‘spatiotemporal’ instead of ‘temporo-spatial’, ‘definition of localized epidemics to be used in real time surveillance’ instead of ‘real-time definition of localized epidemics’ (the definition is not time varying) and avoid the term ‘demographic characteristics’ since the only variable analysed is the population size. You should also specify that the threshold LE75 is defined on two consecutive weeks.

Authors’ reply:

We have made these changes.

Finally, when you say ‘where no widespread laboratory surveillance exists’, I imagine you refer to quantifying the reduction of the burden of the disease after the introduction of the conjugate A vaccine, but the message is not clear.

Authors’ reply:

We have not mentioned MenAfriVac introduction in the abstract, so it would take many more words to introduce here the problematic of surveillance, which exists in most countries in the meningitis belt.
To improve the wording nevertheless, we extended the sentence which says now: “...and help documenting vaccine impact against epidemic meningitis where no exhaustive laboratory data exist for quantifying incidence reduction.”

Methods:

- I would rather talk about ‘predominantly NmA or NmX epidemics’ rather than what could sound purely ‘NmA /X epidemics’.

Authors’ reply:

We have made this change, the sentence reads now: “Both regions experienced epidemic waves with meningitis predominantly due to NmA during 1996-1998 and 2006-2008, and predominantly due to NmW135 during 2002-2003.”

- When you mention the median, specify what it refers to (for ‘median peak WIR and median AIC’ : does it refer to all health districts or only to epidemic ones)

Authors’ reply:

It refers to median peak WIR and median annual incidence in health centres with localised epidemics, we clarified this in the text.

Results:

- Be careful with using percentiles on too small samples

Authors’ reply:

We made sure no inappropriate proportions are indicated.

- The paragraph on location of localized outbreaks and relation between epidemics at a districts/health center level is unclear and should be split into two according to the 2 topics. Considering epidemic definition, it needs rephrasing for it is confusingly presented (for instance, ‘In 9 out of the 12 district years which were declared as epidemic, at least one localized epidemic was identified at a
health center level; in the sole district year declared as non epidemic two
localized epidemics were recorded’).

Authors’ reply:

We rewrote the paragraph for more clarity, it reads now: “In 9 out of 12 district years with declaration of an epidemic at the district level a localised epidemic was identified in at least one health centre. By contrast, two localised epidemics were identified in one district year without epidemic declaration (Table 1).”

Considering the distance, you should first inform what you are talking about, and make it clear that you first describe the Hauts bassins region, then the Boulsa district (is that correct?).

Authors’ reply:

We have split in two parts and given the precision on the region in the text.

Finally, the fact that a given health center declares an epidemic over 2 consecutive years deserves more attention, mostly in the discussion, where it should be related to vaccination.

Authors’ reply:

We now have addressed this point in the discussion: “Population immunity likely is an important factor of epidemic occurrence and heterogeneous vaccination coverage across the district may explain why some outbreaks remain localised, and why outbreaks may occur several years in a row despite vaccination campaigns.”

- It is surprising and not very consistent to present results in terms of timing of epidemic declaration for the RT@HC criterion, when you had previously selected the LE75 criterion. You should at least present both.

Authors’ reply:

We have added this information to the results section.

- It is surprising to mention lab testing in the discussion without mentioning it in
the results.

Authors’ reply:

We have added this information to the results section.

Discussion:

- You should better explain how your proposed definition could help overcome
the limitation of routine surveillance data and allow analyses that are specific for
meningococcus.

Authors’ reply:

The proposed definition and thresholds do not aim to overcome limitations of the
surveillance system, but to suggest an additional analytic approach that provides a
more refined description of the outbreaks. In addition, although the shape of an
epidemic curve may be suggestive of a meningococcal outbreak, what we propose
does not replace microbiological documentation, and would not be sufficient to
launch a vaccination campaign. We opted not to further address this point in the
manuscript, as an in-depth analysis of timing of vaccine response and operational
implications would be required, which would go beyond of the format of this
manuscript. As we discuss in the end of the fifth discussion paragraph, the
hypothesis that this kind of routine surveillance data analysis can provide information
on meningococcal meningitis specifically, requires further confirmation by studies
targeting this research question.

Tables and figures

- Table 1 needs reorganisation and title simplification. I would give first the district
level variables then the health centre variables (defined as such in a top row). To
help simplifying the names, you should give more explanations in the text (i.e.
epidemic (non-epidemic) HC are health centres for which the LE 75 criterion was
(wasn't) met in the given year, weeks are given as calendar weeks, all cases are
not laboratory confirmed). I am not sure the information about the week of WIR
peak is of primary necessity. Reorder the rows for easier to read.

Authors’ reply:
We have made three major changes in the table. First, we split into two tables to illustrate first the importance of health centre level analysis and definition of epidemics; and second to show which characteristics thus defined localised epidemics have. Then, we reordered the columns to separate district level from health centre level information. Finally, following the recommendation by reviewer 3, we completed the information for all district years included in the analysis, epidemic or not.

The tests results should better be given in the manuscript than in the table.

**Authors’ reply:**

The Mann-Whitney test result (Poisson model in the revised manuscript) is indicated in the fourth paragraph of the result section. We would like to keep it in the table as complementary information to the descriptive difference that appears when reading the table.

I would not include in the epidemic duration the first week before definition was met.

**Authors’ reply:**

For the purpose of describing the nature of the identified epidemics, we believe it is necessary to include the week preceding the accomplished definition, as, in retrospective, its incidence can be assumed to be epidemic.

- **Figure 1:** Excel is not the most satisfying software for drawing graphs, and explicit legend.

**Authors’ reply:**

In fact, the graph was prepared by STATA, not Excel. We now have prepared another version using Excel, which yields a better graphics result.

- **Figure 2:** This is a ROC curve. You could draw two lines linking the symbols relative to predicting the annual cumulative incidences of >0.4 and >0.8 respectively;
Authors’ reply:

We have tried out drawing lines between the symbols, but individual data points got difficult to perceive. Therefore, we opted to keep the graph as it was.

A legend on the graph would explain what each symbol represent

(you do not need to describe the different definitions RT@HC and LE25-LE250, since those are explained in the manuscript)

Authors’ reply:

We appreciate the recommendation; however, adding the definition labels in the graph overloaded the graph and made it difficult to read. As the general recommendation is to provide all information necessary to understand a figure in the legend, we opt for keeping the explication of definitions in the legend.
2. Reviewer's report

Reviewer's report:

The manuscript by Tall et al describes a new method of identifying meningitis epidemics in Burkina Faso, part of ‘the meningitis belt’ with high incidence of mostly meningococcal meningitis and frequent epidemics. It is an interesting and according to the presented data adequate method of identifying epidemics which can be useful for quick intervention by means of vaccination.

The manuscript is well written and of significant interest to researchers in the field and health care policy makers in the region.

In my opinion there is one crucial issue missing from the discussion, which should be addressed before the manuscript can be accepted. For this method of identifying (localised) epidemics the authors use data from local health centres. The authors should comment on the quality of the reports of suspected meningitis from health centres. If reporting is biased, this may explain the heterogeneity found in incidence rates among health centres of the same district during epidemic years. This may for instance be analysed by looking at the average number of reported cases outside epidemic seasons, which should be comparable if the quality of the reports are similar.

Authors’ reply:

Following this comment, we have analysed the interquartile range of case counts and weekly incidence rates of suspected meningitis reports outside the meningitis season (June through October). No systematic differences were observed, but this analysis is limited by the fact that there are generally very few cases during this season (most health centres report zero suspected cases). We have added a discussion of data quality to the limitations section: “We used data from a surveillance system without routine
quality control and some biases may arise. For example, heterogeneity between health centre level incidences may result from differences in reporting practices. Incidences during the rainy season were comparable in health centres across all districts, but differences in practices may arise specifically during the meningitis season.”
3. Reviewer's report

Reviewer's report:

Major compulsory revisions.

1. Figure 1 shows the results of the 6 districts. However, a summary of the results of the 201 different health centres should be provided as well together with a description of the relationship between results at the health centre level and the district level.

Authors’ reply:

We have prepared an additional series of six graphs which we suggest to include in the manuscript (Figure 2). The graphs are boxplots of the annual incidences at the health centre vs. district level, specifically for each year and district. This format illustrates quite well the relation between the two levels of analysis.

The statistical tests used presented in Table 1 only provides data on health centres within epidemic districts. Similar results should be presented for non-epidemic health districts. The complete table, ideally should provide the number of Health Centres with and without epidemics and relate that the overall district figure. This would highlight the potential ability of health centre data to predict district results.

Authors’ reply:

We have expanded Table 1 to include all district years, and added the number of health centres and population size per district. Further modifications were done according to comments by reviewer 1.

2. The analysis suggests that spatio-temporal clustering has been found in their data. However, they do not provide robust statistical analysis to justify their
conclusions. It is not clear whether the size of the geographical units described (90kmx50km) was derived from their data or pre-determined.

Authors’ reply:

As suggested by reviewer 1, we add a map to illustrate the findings qualitatively.

Indeed, we have not used any advanced biostatistics methods to evaluate clusters quantitatively. The geographical units underlying the definition of localised epidemics are the health centre areas defined by the health administration. We described geographically contingent zones that experienced localised epidemics at the same time.

Apart from the objective to evaluate the diagnostic performance of our definition for localised epidemics, we took a descriptive approach with basic statistical methods to describe the epidemiology of these localised epidemics, without any methods of spatial epidemiology. First, we felt that given the relatively small number of district years included, this data set did not yet allow the application of spatial statistical methods. Even more so, we intended to provide a proof of concept with simple but robust statistical methods. We are starting to expand the present data base with data from larger parts of the country and a longer time period, including geographical information, which will allow us to do formal spatial statistics. We now mention this issue in the discussion of limitations: “To validate the approach, similar analyses should be conducted on a wider geographical area and include more recent years that were characterized by low serogroup A incidence and high serogroup X or pneumococcal incidence, use spatial epidemiological methods and include more systematic laboratory information on the aetiology of meningitis epidemics and vaccination.”

3. The authors conclude that there was great heterogeneity in weekly and AIC among health centres of the same district. The Kruskall Wallis test does not determine true heterogeneity. The population size of each health centre (and number of observed cases) is needed to determine whether the variation of results can be explained by chance alone.

Authors’ reply:

Following the reviewer’s comment on the need to include the population size for significance testing, we decided to use a Poisson model to evaluate whether the
variable “health centre” contributes significantly to differences between incidence rates within district years. Similarly, we now used a Poisson model to test for differences in incidence rates between health centres the met the epidemic definition and those that did not.

The paragraph in the Methods section now reads: “For descriptive analyses, we calculated weekly incidence rates (WIR) as weekly number of cases per 100,000 inhabitants and annual incidences (%) as annual number of cases per 100 inhabitants. We used Poisson models to test the variability of annual incidences within district years (Wald test) and to test the difference of annual incidences between health centres with and without localised epidemics. “

Discretionary revisions:

4. The discussion states that ‘localized epidemics concerned suprisingly small population groups. Why were the authors surprised. Is it possible that this is a statistical quirk of the analysis used.

Authors’ reply:

The use of the word “surprisingly” was misleading. The fact that the basic unit of epidemics often concerns only very small communities was our hypothesis to start with; it is rather by reading the general literature on the topic that one would think that epidemics only concern entire countries or sub-regions. We have revised the sentence, which reads now:

“Secondly, in most years, localised epidemics concerned small communities (<5,000 inhabitants in several instances), small portions of the district population (as low as 1%), restricted geographic areas (individual health centre areas) and short periods (as short as three weeks).“