Author's response to reviews

Title: Measuring the Burden of Arboviral Diseases: The Spectrum of Morbidity and Mortality of Four Widely Prevalent Infections

Authors:

A Desiree LaBeaud (alabeaud@chori.org)
Fatima Bashir (drfatima08@hotmail.com)
Charles H King (chk@case.edu)

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Author's response to reviews: see over
Dear Drs. Murray and Lopez:

Thank you for your recent decision letter on the manuscript titled, "Measuring the Burden of Arboviral Diseases: The Spectrum of Morbidity and Mortality of Four Classic Infections." (MS: 1597752740422565) I appreciate the reviewers’ insight and the opportunity for revision. According to your recommendations, I have since revised the manuscript incorporating the comments.

I appreciate the effort and time your reviewers have taken in reviewing our manuscript. The comments were helpful and relevant, particularly the DALY calculation clarifications. Below I have provided detailed responses to each comment. My responses are in italics on the following pages.

There are relatively sparse data about these infections and the diseases that they cause. Because of temporal fluctuations in transmission, and wide variation in the quality of local case reporting, some information requested by reviewer #3 is just not available. At present, there is no mechanism for validation. Therefore, we have used credible ranges for the incidence inputs for our DALY calculations, based on published high and low values for these rates. While our estimates are broad, they are evidence-based, and our analysis provides a first-approximation, quantitative estimation of the likely DALY burden for these infections. The analysis also points up the necessary targets for future research. That is, the need for detailed vital statistics and demographic breakdowns of cases by age and sex, so that accurate planning and investment can be done for arbovirus disease burden control.

Thank you again for this opportunity.

Sincerely,

Angelle Desirée LaBeaud, MD, MS
Assistant Scientist
Center for Immunobiology and Vaccine Development
Children’s Hospital Oakland Research Institute
Referee 1:
Essential revision: Tables and figures: Year should be mentioned. DALY is estimated for each year.

As mentioned in the methods section, our estimates were based on 2005 population data. ‘2005’ has been added to the title and headings of Table 4.

Discretionary revision
(1) This is reasonably a good manuscript and deserves publication in Population Health Metrics considering the paucity of data available and nature of squeal of the diseases reported.

(2) The research question is well defined and precise.

(3) Methods are appropriate. However, some further explanation is required on the following aspects.

a. There are few assumptions in the methodology like using disability weights (DW) for some disease sequelae with analogue DW taken from GBD studies. Some more discussion is needed in this aspect to tell the readers that in absence of published DW for these conditions other closely similar conditions were used.

We have added a new table (Table 3) in the Methods section to detail our ‘unofficial’ estimation of DW’s for the arbovirus sequelae for which official DWs are not formally established. The choices were based on the GBD Program’s 1996 DW’s for very similar outcomes (visual impairment, blindness, polyarthritis, paresis, etc.) for other GBD diseases. The new Table 3 lists the DWs that were used for infection YLD burden calculations, and their likely ranges (given the absence of official DW point estimates).

b. It will be appropriate to explain the reasons for excluding 172 studies for analysis.

Before commencing our review, we established formal inclusion/exclusion criteria for papers to be included. The 172 papers mentioned as excluded either did not meet the time criterion (completed after 2000), did not include population-based prevalence or incidence data for infection, complications, or cause-specific mortality. The 38 papers included in this paper’s analysis did meet these criteria. Details explaining the selection are now included in the Methods section.

172 PAPERS WERE EXCLUDED BECAUSE THEY DID NOT MEET INCLUSION CRITERIA (DISCUSSION OF COMPLICATIONS THAT LEAD TO MORTALITY, POPULATION-BASED INFORMATION AND INCIDENCE/PREVALENCE RATES, STUDIES COMPLETED AFTER 2000). 38 STUDIES WERE INCLUDED SINCE THEY MET INCLUSION CRITERIA. OUR PURPOSE WAS TO TAKE THOSE STUDIES INTO ACCOUNT THAT TOLD US ABOUT MORTALITY RATES AND WHAT AGE GROUPS AND GENDER WAS COMMONLY AFFECTED. IN ORDER TO CALCULATE THE DALY SCORE, INCLUSION CRITERIA WERE ADDED TO THE METHODS SECTION.

c. DALY is usually estimated on the basis of age and gender class and is presented in thousands (,000), not in range. A discount of 3% is also adopted to maintain uniformity for comparison because DALY is a measure generally to prioritize diseases for intervention.

BECAUSE SOME OF THE DALY estimates in this paper include values well under 1000/year-OUR DALY ESTIMATE RANGES INCLUDED VALUES <1000. Because of this, for better precision, we have reported WE HAVE REPORTED ABSOLUTE THE actual numbers of VALUES OF DALYS, rather than thousands. The reader can easily make the transition to thousands for comparison to other documents.
We did, indeed, include discounting in our DALY calculations—DALY estimates values with and without with and without the discount weight of 3% discounting were included in the original manuscript, and can now be found in Table 4 were included in our original manuscript and can be found in Table 4.

(4) Data well controlled and presented well.
(5) Standards are maintained
(6) Discussion and conclusion satisfactory
(7) Abstract is well balanced
(8) Writing is acceptable.

Referee 2:
1. Is the question posed by the authors new and well defined?
   Yes
2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
   Yes
3. Are the data sound and well controlled?
   Yes
4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
   Yes
5. Are the discussion and conclusions well balanced and adequately supported by the data?
   For the most part, although there is a section of the Discussion which requires remediation (see specific comments)
6. Do the title and abstract accurately convey what has been found?
   Yes, although use of the term 'classic infections' seems like conversational language and lacks definition

The title was changed to: "Measuring the Burden of Arboviral Diseases: The Spectrum of Morbidity and Mortality of Four WIDELY PREVALENT Infections."

7. Is the writing acceptable?
   Yes
Reviewer's report
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Please number your comments and divide them into:
- Major Compulsory Revisions
  None.
- Minor Essential Revisions
  Title: I find the term 'classic infections' as used in the title to be uninformative, and conversational in tone. Might it be better to actually name the infections in the title? What is a 'classic infection'? I'm sure this can be easily remedied.

The title was changed to: "Measuring the Burden of Arboviral Diseases: The Spectrum of Morbidity and Mortality of Four WIDELY PREVALENT Infections."

Discussion: pg 13 para 2. The statement on line 3 of this paragraph, that "...infections that were once contained in remote tropical locations are likely to spread to new areas." is uninformative, unsupported and one of debatable validity. The authors betray a lack of reading of modern, quality literature on this topic.
While this point is merely used to add weight to the argument about the extent of
impact of vector borne diseases, it is not well used here. Growing population size
and increases in inter-regional air travel are much more important factors. This
section should be revised, and authors need to exercise caution before
perpetuating semi-truths about vector-borne disease and climate change.

Although we believe that the range of some vector-borne diseases is expanding due to climate change, (for example, bluetongue virus in Europe) we have removed all reference to climate change from the manuscript, and have revised the section in question. ALTHOUGH WE BELIEVE THAT THE RANGE OF VECTOR-BORNE DISEASES HAS CHANGED DUE TO CLIMATE CHANGE (FOR EXAMPLE, BLUETONGUE), WE HAVE REMOVED ANY REFERENCE TO CLIMATE CHANGE IN THE MANUSCRIPT AND HAVE REVISED THIS SECTION.

Also, in the same paragraph, the authors imply that the Indian Ocean
chikungunya outbreak of 2005 was related to warmer temperatures and shorter
EIPs. While this may have been one factor, they have neglected the important
issue of the increased virulence of the strain due to an envelope change related
to a point mutation.


All up, the discussion of the impact of climate change on
vector borne disease epidemiology reads as very broad-brush and uninformed.
Perhaps this section was written quickly.
This said, I'm confident these problems can be readily fixed, as they present no
great problem for the publishability of the paper.

Referee 3:
• Major Compulsory Revisions:
1- are there any validation process for these results, especially for number of
death or clinical occurrence of these four diseases in around 2005 for some
counties with very good notification data or death registry? If there are these
validator results, authors should explain, if there are not these process, authors
should explain how they can validate their results.

There are relatively sparse data about these infections and the diseases that they cause. Because of temporal fluctuations in transmission, and wide variation in the quality of local case reporting, the information requested by the reviewer is just not available. At present, there is no mechanism for validation. Therefore, we have used credible ranges for the incidence inputs for our DALY calculations, based on published high and low values for these rates. While our estimates are broad, they are evidence-based, and our analysis provides a first-approximation, quantitative estimation of the likely DALY burden for these infections. The analysis also points up the necessary targets for future research. That is, the need for detailed vital statistics and demographic breakdowns of cases by age and sex, so that accurate planning and investment can be done for arbovirus disease burden control.

2- Authors should put their estimation in a table by age (in grouping format), sex
and by each disease for clinical (or symptomatic) incidence rate (or number),
death, YLD, YLL and DALYs. This table is big, but we can have that as an
electronic attach to the paper in this journal

<table>
<thead>
<tr>
<th>AGE</th>
<th>SEX</th>
<th>INCIDENCE</th>
<th>DEATH</th>
<th>YLD</th>
<th>YLL</th>
<th>DALYs</th>
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<th>YLL</th>
<th>DALYs</th>
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</table>
3- it would be better if authors addressed that after all literature review and using reported data; for which countries or regions they fined data point (by year). In other words they should show what are the sources for these estimations.

4- Their estimation for DALY (3, 0) is between 120000-2380000, this range is very big. This big interval needs more explanation in discussion part. Also a very big interval for estimated deaths per year for Chikungunya in table 1 (33-25761) or for yellow fever 675-30000. What is the logic behind of these big intervals?

THERE IS VERY SPARSE INFORMATION REGARDING THESE INFECTIONS AND THEREFORE THE RANGES ARE BROAD AND REFLECT LOW AND HIGH ESTIMATES BASED ON CURRENT INFORMATION ABOUT THE INCIDENCE AND RANGE OF DISEASE SEQUELAE. THE ESTIMATES ARE BROAD BUT EVIDENCE BASED AND ARE THE BEST WE HAVE TO DATE. THE POINT OF OUR MANUSCRIPT IS TO HIGHLIGHT THE LACK OF DETAILED INFORMATION AND INSIST ON FUTURE STUDIES TO ADDRESS THESE NON-CORE GBD DISEASES.

• Minor Essential Revisions :
  1- in page 10 first paragraph it is not clear that lower mortality due to Chikungunya virus infection 1 per 1000 mortality is in general population or in infected population.

This is the reported mortality rate for the general population. The point is now clarified in the revised manuscript.

MORTALITY RATE FOR THE GENERAL POPULATION IS 1 PER 1000 AND WAS CLARIFIED IN THE MANUSCRIPT.

2- In table2 what is the reference for 0-2% “Survivor’s risk for multi-year or permanent disability”

We have added a citation to reference 78 to the rTable.

• Discretionary Revisions :
  1- It will be better if we had a table that shows in one column each Sequelae (selected by authors and attributed) for each diseases and appropriate sequelae from GBD DW table in other column. In last column of this table they should put DW for each adjusted sequelae.

This table is now provided as Table 3 in the revised manuscript.

THIS TABLE WAS CONSTRUCTED AND ADDED TO THE MANUSCRIPT (TABLE 3).

Level of interest: An article of importance in its field