Author's response to reviews

Title: Treating cutaneous leishmaniasis patients in Kabul, Afghanistan: cost-effectiveness of an operational program in a complex emergency setting.

Authors:

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Author's response to reviews: see over
Dear Dr Phillips,

Thank you for sending us your and the reviewers’ comments on our manuscript MS 1767261107111933 [Reithinger and Coleman. Treating cutaneous leishmaniasis patients in Kabul, Afghanistan: cost-effectiveness of an operational program in a complex emergency setting].

I sincerely apologize for the slight delay in revising the manuscript, which was due to overseas travel of one of us. We have revised the manuscript according to forwarded comments and we hope that the current version addresses your and the reviewers’ concerns. A point-by-point reply to editorial and reviewers’ comments is attached.

On behalf of all authors, I look forward to hearing from you soon.

Best regards,

Richard Reithinger, PhD
Epidemiologist
Clinical Trials Area
Reviewer 1 (Theo Vos, TV) made a total eleven comments:

**Major comments**

1. TV noted that the manuscript did not clearly stipulate what the research questions is and what the comparator in the economic evaluation is, whether 'no treatment' or 'alternative treatment'.

   We have attempted to clarify the objective of the study [Page 5, Lines 12-18]. First, we aimed –for the first time- to estimate the cost-effectiveness of an operational cutaneous leishmaniasis (CL) treatment program. TV is right to assume that our comparator for presented data is ‘no treatment’ [P5, L14]. Our second aim was to discuss potential policy implications of our results for CL treatment in Afghanistan and elsewhere (e.g. should we be treating CL at all?’) highlighting characteristics associated with cost-effectiveness studies of health programs in complex emergency environments such as Afghanistan.

2. TV commented that the data for the triangular distribution of CL disease may underestimate true figures, as the data was based on a prevalence survey and would not take into account duration of disease past the survey date. He also noted that the cited reference was numbered incorrectly and that the numbers on lesion duration should be changed.

   We corrected the reference and thank TV for highlighting the incorrect lesion duration as presented in Table 2 in our manuscript – this has been amended [P21]; however, this did not affect the cost-effectiveness estimate because our models used the correct numbers.

   We agree with TV that data from cross-sectional studies may underestimate the true lesion duration and have included a statement to this effect in the discussion [P10]. Unfortunately, data on the duration of the natural evolution of CL lesions due to *Leishmania tropica* is unknown and the data from our cross-sectional studies is a best estimate.

3. It was noted that whilst there was no concerns regarding the methodological approach, some of the data used in the calculations was erroneous, specifically data on intralesional treatment efficacy extrapolated from Ref 20 and Ref 22. TV also noted that estimates from reference 22 were for meglumine antimoniate and not sodium stibogluconate.

   The references were numbered incorrectly and have been changed accordingly in the revised version of the manuscript. We thank TV for highlighting the fact that some of the estimates were from studies evaluating meglumine antimoniate and not sodium stibogluconate, the drug of choice used in Afghanistan.

   Both meglumine antimoniate and sodium stibogluconate are the first line, WHO-recommended drugs for cutaneous leishmaniasis treatment, and both are so-called pentavelent antimonials [P6]. There is no documented difference in the therapeutic efficacy for CL between the two drugs [P11]. Thus, we decided to keep current estimates used in our analyses. However, in the revised manuscript we now generally refer to pentavelent antimonials (SbV) rather than SSG; in Table 2 we also highlight that estimates from (former) Ref 20 and 22 are based on the use of meglumine antimoniate.
In response to TV’s comment, the cited 50% efficacy from the study by Asilian et al (Ref 20) was for the patient group treated with intralesional meglumine antimoniate.

4. **TV noted that the criteria that we used to judge whether an intervention is cost-effective is outdated, and that the more recent, country-specific WHO-CHOICE criteria should be used, i.e. 1*GDP per capita for very cost-effective interventions and 1*3 GDP per capita for cost-effective interventions.**

We have revised our manuscript according to the WHO-CHOICE guidelines: GDP per capita of Afghanistan in 2004 was US$ 165 (U.S. Department of State) [P10]. According to this criteria CL treatment is cost-effective and we have amended the discussion and conclusions in the revised manuscript accordingly.

**Minor comments**

5. **TV suggested changing the term ‘reference treatment’ as ambiguous.**

We have changed the wording from ‘reference treatment’ to ‘standard treatment’ throughout the manuscript.

6. **It was commented to be more specific in the conclusion, i.e. with regards of whether leishmaniasis treatment is cost-effective or not (in line with comment 4 by the same reviewer).**

We have made the conclusion more specific [P13]; see also comment 4.

7. **Similar to comment 2 by TV, it was noted to clarify the duration of disease data used in the analyses.**

There is no published data on the natural history and duration to self-cure of CL due to *Leishmania tropica* [P10]. Thus, the data from our cross-sectional studies is a best estimate, though –as we now outline- in the discussion, we are fully aware of the caveats using this figure [P10].

8. **TV noted that if we wanted to conclude that CL treatment is not cost-effective, especially when using systemically-administered drugs, our methods should reflect that statement, i.e. making explicit comparison of CE for IM SSG vs no treatment, IL SSG vs no treatment and preferably also IL SSG vs IM SSG.**

Using the criteria of WHO-CHOICE, CL treatment, as implemented by HNI in Kabul, is cost-effective. We are now planning to conduct cost-effectiveness analyses comparing various CL diagnostic and therapeutic approaches, which we, however, felt was beyond the scope of this manuscript.

9. **TV enquired from where the estimate of 16 years came from [Page 9].**

This estimate was arbitrary. It was obtained by doubling the maximum lesion time (8 years) obtained from our prevalence surveys. This sentence has now been deleted in the revised manuscript [P11].

10. **TV doubted that Ref 7 referred to interventions in complex emergencies.**

Yes, indeed the numbering for that reference was incorrect – this has been amended in the revised manuscript.
11. TV noted that the Ref 7 was incorrect.
The numbering for that reference was incorrect, it should have referred to the study by Meddings et al – this has been amended in the revised manuscript.

Reviewer 2 (Charles King, CK) made a total six comments:

Major comments

1. CK commented that one problem with our investigation and manuscript is the rigid adherence to leishmaniasis DALY weights given by the Global Burden of Diseases Program. CK suggested including a formal assessment of the impact of alternative disability weights on the outcome of our analyses accompanied by graph (tornado diagram).

Yes, we could not agree more with CK that the disability weights for cutaneous leishmaniasis are not representative of the perception of local communities affected by the disease.

Following CK’s suggestion we simulated our calculations using different disability weights (including the ones used for elephantiasis and leprosy), included a graph of the results as well as expanded our discussion on disability weights [P11]. See also tornado diagram that has been included in the revised version of the manuscript (Figure 2).

2. CK enquired whether there are economies of scale based on clinic size and population level served and whether there are likely to be economies of scope in multispeciality vs primary care clinics. CK also enquired whether we could estimate the leverage obtained by reduction in transmission due to the treatment of the human reservoir.

Current HNI program is a vertical program exclusively delivering health services for the diagnosis, treatment, prevention and control of leishmaniasis. It is clear that our program is an economy of scale, i.e. a higher patient turnover would lead to higher cost-effectiveness.

Unfortunately, data measuring or estimating the impact of treatment of the anthroponotically-transmitted leishmaniases (whether cutaneous or visceral) does not exist. Whilst we agree with CK that such data would be highly relevant for our analyses and also within the wider policy context, obtaining such data would be very difficult due to the requirement to accurately determine several clinical, parasitological, entomological and epidemiological variables. Thus, whilst we for example know that transmission occurs in certain hotspots (Ref 2) we have no data how treatment affects infectiousness to the sandfly vector.

3. CK enquired that if the cost per DALY averted is $407, which is above the $150 threshold, this would mean that we should not treat CL and commented that our discussion was ambiguous about this statement. He added that our discussion was not really clear as to what alternatives were to solve this problem and whether it was fair to say that current strategy is not cost-effective, if no comparison is explicitly given (the implication being that the comparison strategy is to do nothing). CK also
added that it would be useful to recommend where CL treatment would stand on the priorities for treatment in a complex health emergency recovery operation.

See also comments 4 and 6 by TV. According to the WHO-CHOICE criteria, CL treatment in Kabul is cost-effective – our discussion and conclusion of the revised manuscript have been modified accordingly. Alternatives to reduce the cost of treatment or increase drug efficacy (see also tornado diagram) would increase cost-effectiveness.

Whilst we may assume that $407 per DALY averted is less cost-effective as other health interventions, we cannot emphasize enough that data on the cost-effectiveness of health interventions in a complex emergency settings is extremely scarce and caution should be taken to compare studies due to either variations in analytical protocol and locality-specific parameter values [P10-12].

Minor comments

1. CK noted that we did not justify the choice of triangular distributions for the variation of the input parameters used in our calculations, and that the rationale should be included in the revised manuscript.

We have included an explanation to use triangular distributions in our calculations in the legend to Table 2 [P21].

2. It was suggested to include a tornado diagram in the manuscript to indicate the relative influence of each parameter on outcomes.

We have carried out relevant analyses and a tornado diagram has been included in the revised manuscript (Figure 2).

3. Ck commented that the phrase ‘The majority of staff...’ [Page 7, Line 5] did not make sense and should be revised.

This sentence has been deleted from the manuscript text [P8].