Additional file I: Protocol systematic review

Proposed title: Leptospirosis in sub-Saharan Africa: a systematic review

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Background

Leptospirosis is regarded as an emerging zoonosis worldwide, with the majority of cases in the tropics, in part due to climate change and demographic shifts. It is caused by free-living spirochetes of the *Leptospira* genus (order Spirochaetales). Several mammals serve as a vector for this organism and shed leptospires into urine for prolonged periods. Humans are usually infected after contact with contaminated water or meat; infection is associated with highly variable clinical manifestations, ranging from asymptomatic, undifferentiated fever to complex illness with high morbidity and mortality rates. Leptospirosis is under-diagnosed worldwide because of the non-specific symptoms, the lack of quick and simple diagnostic tests and unawareness amongst clinicians. The extent of the disease in the tropics has been shown in several studies. Epidemiological data for most of the African continent is scarce, but not unavailable, both for humans and mammalian species. A recent study amongst hospitalized febrile patients in Moshi, Northern Tanzania, showed evidence of antibodies reacting to pathogenic leptospires in 41.6% (346/831) of the patients; 70 of those 831 patients (8.4%) met the definition of either confirmed or probable leptospirosis (*Biggs et al. 2011*). In banded mongooses (*Mungos Mungo*) in Northern Botswana, which live in close proximity to humans, 41.5% (17/41) had PCR-proven leptospiral DNA in kidney tissue (*Jobbins et al. 2013*). Furthermore, earlier studies from the mid 1930s and 1999 describe human leptospirosis to be endemic in Gabon (*Bertherat et al. 1999*).
The aim of our review is to summarize the data for leptospirosis available from sub-Saharan Africa, and to best describe present knowledge of the epidemiology of this infectious disease in the region and options for treatment and prevention.

**Objectives**

1) To summarize the data available for leptospirosis in sub-Saharan Africa, which includes the epidemiology of human leptospirosis infection, outbreaks, clinical manifestations, diagnostics, control and prevention measures and recommendations for further research.

2) To summarize the data of Leptospirosis in mammals in sub-Saharan Africa.

**Outcome(s)**

*Primary outcomes*

The primary objective is to investigate the prevalence (and/or incidence) of leptospirosis and leptospiral antibodies in both humans and animals in all countries of sub-Saharan Africa.

*Secondary outcomes*

Secondary objectives include risk factors, circulating serogroups, serovars and/or strains, clinical manifestations, treatment, prevention measures, seasonal influences and mortality.

**Identifying research evidence**

We will conduct a systematic review according to the PRISMA guidelines to summarize the data for leptospirosis available from each country of sub-Saharan Africa. We will search Ovid Medline, Embase, Cochrane Library (including DARE and Central) CINANL, Web of Science, Biosis Previews, African Index Medicus, African Journals Online, Google Scholar and Pubmed (non-Medline citations) for studies published up to 25 October 2013 without language restrictions. If necessary, we will update the search before submission. Studies conducted in the western Indian Ocean islands were excluded because of an extensive systematic review that was performed recently on this topic (*Devars et al. 2013*). Any study in which the epidemiology of leptospirosis in any country in sub-Saharan Africa was reported
will be included, as well as case series and case reports. Experimental microbiological studies will be excluded.

**Trial registration**

The review will be registered in advance with PROSPERO (International prospective register of systematic reviews).

**Risk of bias (quality) assessment**

Risk of bias will be assessed separately for each eligible study, using an assessment tool, extracted and modified from an evidence based developed tool designed to assess the risk of bias in population-based prevalence studies (*Hoy et al. 2012*). This tool will be used to code and provide consistency for selection. We will decide to perform a meta-analysis (if data allows) according to the quality assessment scores and risk of bias assessments.

**Data extraction (selection and coding)**

The first author (S.G. de Vries) will screen titles and abstracts for location, study population and general correlation with our research objectives. Full versions of potentially relevant articles will be obtained to assess eligibility. These will then be independently evaluated for inclusion by the first and second author (B.J. Visser). The last and senior author (M.P. Grobusch) will adjudicate any disagreements and make the final decision on selection. We will also search cross-references of the full text retrieved articles. Data will be collected independently from each publication and captured using a standardised Word document form. We plan to extract data from text, tables and figures. Study investigators will be contacted in cases of unclear data or eligibility criteria.

Data from eligible studies in humans will be extracted based on the following:

i. **Methodological information**: year of publication, year of research, country of study, study setting (rural/urban, in/out hospital), design, objectives / measure of primary outcome, target population and selection criteria, total enrolment, attrition rate (if applicable), sample size

ii. **Case definition**: diagnostic methods used to prove leptospiral antibodies and cut-off values.

iii. **Study outcomes**:

   - Prevalence of leptospirosis / leptospiral antibodies, numbers per group
Data from eligible studies in animals will be extracted based on the following:

i. **Methodological information**: year of publication, year of research, country of study, study setting (wild/domestic/cattle, urban or rural), objectives / measure of primary outcome, target population (e.g. species) and selection criteria/methods, total enrolment, attrition rate (if applicable), sample size.

ii. **Case definition**: diagnostic methods used to prove leptospiral antibodies and cut-off values.

iii. **Study outcomes**:
   - Prevalence of leptospirosis / leptospiral antibodies, numbers per group
   - Leptospiral serovars / serogroups / strains
   - Risk factors, possible exposure sites (if applicable)

**Data synthesis**

Data will be collected independently from each publication and captured using a standardised form. Data will be extracted from text, tables and figures and a narrative synthesis is planned.

**Synopsis systematic review article**

- **Abstract**

- **Introduction**:

- Leptospirosis: General, diagnosis, treatment and prevention

- **Methods section**
- Results:
- Human leptospirosis in sub-Saharan Africa: West / East / Central / Southern Africa
- Leptospirosis in mammals in sub-Saharan Africa: West / East / Central / Southern Africa
- Discussion: recommendation for further (clinical) research
- Conclusion

Suggested tables/figures/data:
- Overview surveys (human) leptospirosis in sub-Saharan Africa, sorted and described by region
- Overview epidemiological data (human) leptospirosis in sub-Saharan Africa, sorted and described by region
- Flow diagram PRISMA selection of studies
- Appendix search strategy; inclusion and exclusion criteria
- Appendix other additional information

Time schedule:
October 2013: Preparing protocol, reading literature & prepare search strategy (S.G. de Vries, B.J. Visser & I.M. Nagel)
October 2013: Searching the literature. Screening of records by two independent reviewers (Sophia G. de Vries & Benjamin J. Visser)
November / December 2013: Data extraction in standardized Word 2003 document form, data-entry, meta-analysis with Review Manager 5 and drafting the manuscript.
December 2013 / January 2014: Finalizing manuscript (all authors) and submit to peer-reviewed medical journal with preferably an open-access option.
January / February / March 2014: If applicable, revising the manuscript for re-submission.

Literature
