Report of the Second Meeting of the Leptospirosis Burden Epidemiology Reference Group

World Health Organization

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This report is available in electronic format from **http://www.who.int/zoonoses/diseases/lerg/en/.**

Acronyms and abbreviations

AFI	acute febrile illness
ALI	acute lung injury
ARI	acute renal injury
DALY	disability-adjusted life year
ELISA	enzyme-linked immunosorbent assay
FAO	Food and Agriculture Organization of the United Nations
FERG	Foodborne Disease Epidemiology Reference Group
FOS	WHO Department of Food Safety and Zoonoses
GOARN	WHO Global Outbreak Alert and Response Network
GBD	global burden of disease
HSI	WHO Department of Health Statistics and Informatics
ICD	International Classification of Diseases
IFA	immunofluorescence assay
LERG	Leptospirosis Burden Epidemiology Reference Group
MBD	WHO Mortality and Burden of Disease Unit
MAT	microscopic agglutination test
MDG	Millennium Development Goal
NGO	nongovernmental organization
NIH	National Institutes of Health (United States)
NTD	neglected tropical disease
NZD	neglected zoonotic disease
OIE	World Organisation for Animal Health
PCR	polymerase chain reaction
SROC	summary receiver operating characteristic
UN	United Nations
WHO	World Health Organization
YLL	years of life lost
YLD	years lived with a disability

Executive summary

The second meeting of the Leptospirosis Burden Epidemiology Reference Group (LERG) was held on 22–23 September 2010 in Geneva, to further the work to estimate the global burden of human leptospirosis. Human leptospirosis is a neglected disease, mostly affecting vulnerable populations in rural settings and semi-urban slums. A systematic literature review estimated the median global annual incidence of endemic human leptospirosis, i.e. excluding outbreaks, as 5 cases per 100 000 population. It is highly probable that this is a gross underestimate, since many cases of leptospirosis are undiagnosed or misdiagnosed, because of lack of awareness of the disease and difficulties in carrying out laboratory confirmation tests. Studies have shown that leptospirosis may represent up to 20% of febrile illness of unknown origin. Limited studies have suggested that the highest median annual incidence occurs in the African Region (95.5 per 100 000 population) followed by the Western Pacific (66.4), the Americas (12.5), South-East Asia (4.8) and Europe (0.5). In some areas, incidence is as high as 975 cases per 100 000. An estimated 17% of hospitalized patients suffer acute lung injury, of which 25% die as a result. Existing data on leptospirosis incidence and disease sequelae are limited, but suggest that Africa, the Western Pacific, and the Americas have the greatest burden of disease, and that fewer economic resources are associated with a higher burden of disease.

An improved understanding of the risk factors and drivers for leptospirosis transmission and infection is needed to devise improved integrated interventions for reduction of sources of infection. Work has started to develop a transmission model, to aid the translation of the burden of disease estimates into contextualized support for decision-making by policy-makers.

The results of the systematic literature review, with estimates of global incidence, sequelae and the global burden of human leptospirosis, will be published in peer-reviewed journals. A report on the preliminary work to develop a transmission model for leptospirosis is expected to be published in 2011.

1. Introduction

1.1 Overview of LERG

The Leptospirosis Burden Epidemiology Reference Group (LERG), an advisory group to the Director-General of the World Health Organization (WHO) on the epidemiology of leptospirosis, was established in 2009 following an informal WHO consultation in 2006. The first meeting of LERG (LERG 1) took place on 2–4 December 2009 in Geneva. The LERG comprises ten advisors serving in their individual capacities, with a broad range of expertise in burden of disease methodology, epidemiology, clinical laboratory techniques, infectious diseases, zoonoses, disease modelling and international public health. In addition, resource advisors are invited to participate in specific meetings to complement the expertise and skills in the Group. The Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE) are also invited to participate in the work of LERG as partners at the human–animal–ecosystems interface.

The LERG secretariat is based in the WHO Department of Food Safety and Zoonoses (FOS) and works in partnership with other WHO clusters and departments at Headquarters and in the regional offices. The role of the secretariat is to facilitate, coordinate, guide and monitor the work of the LERG and to provide logistic, administrative and technical support.

The overall objectives for efforts to estimate the global burden of human leptospirosis are:

- to provide estimates for human leptospirosis worldwide, according to age and sex and by WHO region;
- to encourage countries to use burden of diseases estimates for cost-effectiveness analyses of intervention and control measures; and
- to increase Member States' awareness of, and commitment to, interventions to prevent and control leptospirosis.

1.2 Objectives and expected outcomes of the meeting

The second meeting of the LERG (LERG 2) was held on 22–23 September 2010. The list of participants is given in Annex 1. Dr Arthur Reingold chaired the meeting and Dr Wendy Harrison acted as rapporteur. Dr Bernadette Abela-Ridder welcomed the participants on behalf of WHO, presented a draft agenda for the meeting (see Annex 2), and outlined the objectives and expected outputs.

The specific objectives of the second LERG meeting were:

- to review and appraise the revised systematic review of mortality, morbidity and disability from human leptospirosis;
- to review a draft disease transmission model for leptospirosis and provide technical input for the further development and refinement of the model;
- to assemble preliminary estimates of the disease burden;
- to identify gaps in knowledge and research; and
- to advise WHO on the next steps for estimation of the burden of human leptospirosis and the implications for policy.

The expected outputs were: a summary of the LERG peer review input on the systematic literature review and draft transmission model; a workplan outlining next steps for estimation of the burden of disease, including work to be commissioned; and recommendations on the translation of burden estimates into policy for the secretariat.

1.3 Declarations of interest

The secretariat reported that all experts participating in LERG 2 had completed declaration of interest forms. Dr Albert Ko had been involved in two patent applications for use of *leptospira* antigens as potential diagnostic reagents, as part of a collaboration between three universities and a nonprofit organization. The institutions are collaborating with a company that makes rapid

diagnostic tests to develop an assay for leptospirosis. The collaboration is funded by a national public health institution. The patent applications have not been licensed to the company or any other third party, and the product is not commercially available. It was concluded that these interests did not warrant exclusion from the discussions of the meeting. No other potential conflicts of interest were identified.

2. Background to the current meeting

2.1 Leptospirosis – a neglected disease[a]

Endemic zoonotic diseases perpetuate poverty by attacking not only people's health but also their livelihoods. They remain neglected in most endemic countries because of a lack of information and awareness about the extent of the problem. An absence of suitable diagnostic tools and sustainable strategies for prevention and control worsens the problem.

The result is often a false perception that the burden and impact on society are low, such that they attract neither the health resources nor the research needed for their control – effectively putting them in the category of neglected zoonotic diseases (NZDs).

Control of NZDs offers a highly cost-effective opportunity to alleviate the widespread poverty that exists in remote rural areas and marginalized periurban communities. In many countries, the roles and responsibilities of the different sectors in investigating and controlling NZDs are unclear. As NZDs affect both humans and animals, interventions require concerted action between human health, veterinary, and other relevant sectors.

The complex nature of efforts to prevent and control zoonotic disease means that partners have to share responsibilities and coordinate activities to address health risks at the human–animal–ecosystem interface. The partnerships formed can better direct translational research and policy development for intervention.

2.2 Leptospirosis – an emerging disease driven by climate and environment

Climate can affect the transmission of infectious diseases. Changes in, for example, temperature, humidity and rainfall, and a rise in sea-level, can alter the transmission dynamics of a disease; these changes act in combination with anthropogenic factors, such as population density, housing location and type, water and sanitation, and waste management.[1,2] The combination of multiple variables and their interactions makes it difficult to describe transmission pathways and predict disease trends and outbreaks. Research has linked key climatic factors, particularly rainfall, to the transmission of disease. The movement of pathogens in animal populations and the environment is also affected by changes in climate and the environment.

The incidence of leptospirosis, which is in part a rodent-borne disease, depends on environmental and climatic conditions that influence rodent population dynamics, size and behaviour. The Intergovernmental Panel on Climate Change (IPCC)[3] has suggested that the predicted increase in heavy rainfall in the twenty-first century could increase the risk of leptospirosis through contamination of flood waters or run-off by rodent populations. In the past decade alone, leptospirosis has proven to be an endemic disease with epidemic potential. Recent reported outbreaks in Guyana, India, Kenya, Lao People's Democratic Republic, New Caledonia, Nicaragua, the Philippines and Thailand have highlighted the strong links between leptospirosis and extreme weather events.

a Based on: Neglected tropical diseases, hidden successes, emerging opportunities. Geneva, World Health Organization, 2009 (http://whqlibdoc.who.int/publications/2009/9789241598705_eng.pdf).

3. Progress since LERG 1

3.1 Revision of the systematic review of existing evidence

A systematic review was conducted by the Gonçalo Moniz Research Centre, Oswaldo Cruz Foundation/ Brazilian Ministry of Health, Salvador and Bahia, Brazil.

The initial objectives of the systematic review were:

- to produce a comprehensive, standardized tabulation of available data on leptospirosis disease incidence, mortality estimates and disease sequelae; and
- to identify gaps in information to be addressed through modelling or future research.

During this review, 29 databases were searched for reports published between January 1970 and October 2008 that included 50 or more cases of human leptospirosis. At its first meeting, the LERG recommended broadening the scope of the review by amending the criteria for inclusion and appraisal of scientific evidence to estimate the burden of disease.

The review had therefore been re-run with the following amendments:

1. revised inclusion criteria;
2. use of an updated disease definition;
3. revised study quality criteria;
4. increased number of languages evaluated.

3.1.1 Revised inclusion criteria

Disease incidence

To assist the assessment of the burden of disease, the LERG had suggested that level IV studies (see Box 1) should be included, in addition to levels I-III, provided that the report described the population base on which the study was performed or the geographical region, for which an estimate of the population base could be obtained (i.e. from the national census).

Triangulation and validation with other data sources were also sought to improve accuracy. For example, authors of published studies that did not entirely fulfil the level of evidence criteria for the systematic literature review protocol were contacted to enquire if there were any additional unpublished community-based data. Researchers were also asked to submit other appropriate unpublished data. In addition, where available, data for other diseases of similar severity in the same geographical location were requested, to give some indication of hospital admission rates and to assist in the interpretation of health facility-based incidence and prevalence studies. Data from studies of different types, e.g. health facility studies, passive surveillance and mortality reporting, were also requested as a way of increasing accuracy and confidence in disease burden estimates.

Some outbreak and surveillance investigations of less than one year in duration met the inclusion criteria for this review. However, these investigations are likely to introduce higher estimates of disease because they were most likely performed during epidemics or in periods of high seasonal leptospirosis transmission. Incidence and mortality rates from outbreak studies were compared with those from non-outbreak studies using the Wilcoxon rank sum test to evaluate differences between these two groups. Outbreak studies were found to have a significantly higher median incidence than non-outbreak-related studies ($P \leq 0.05$); they were therefore excluded from the analysis of endemic incidence and mortality rates. It was, however, recognized that exclusion of these studies would also introduce a degree of bias.

Box 1

For incidence and prevalence data, the standard levels of evidence are as follows:
Level I – nationally representative incidence and prevalence studies with all indicators.
Level II – community-based (likely representative) incidence and prevalence studies.
Level III – large cohort studies with likely representativeness.
Level IV – national surveillance studies, health care facilities-based studies and outbreak reports.
Level V – case reports, series with fewer than 20 subjects, editorials, letters, etc.

Sequelae

At its first meeting, LERG had decided that the inclusion of studies of level IV, as well as those of levels I-III (see Box 2), would be beneficial. However, some concerns had been raised by members regarding the appropriateness of using level IV studies to determine the development of sequelae. Specifically, the LERG was concerned that the sequelae recorded in health facilities may not be representative of those in the community, either in nature or duration, especially where access to health care is limited. However, it was decided that, in some settings, the data would be more reflective of the broader population, e.g. in Thailand, where health care is free and available to all.

Box 2.

For sequelae data, the standard levels of evidence are as follows.
Level I – longitudinal follow-up studies with individual ascertainment of sequelae and confounding factors.
Level II – cross-sectional studies without individual ascertainment of sequelae and confounding factors.
Level III – retrospective cohort studies of disease sequelae.
Level IV – national surveillance studies, health care facility-based studies and outbreak reports.
Level V – case reports, series of fewer than 20 subjects, editorials, letters, etc.

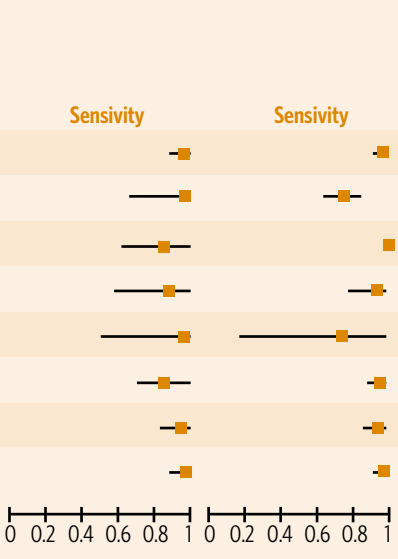
It was considered appropriate to include data from studies that described the disease sequelae and case-fatality for 50 or more suspected cases of leptospirosis. Leptospirosis acquired during an outbreak is not expected to have atypical disease manifestations or mortality, and reports that describe outbreak events often include detailed descriptions of leptospirosis sequelae. Therefore, outbreak studies were included in the analysis of disease sequelae.

3.1.2 Immunofluorescence assay (IFA)

Professor Yupin Suputtamongkol, on behalf of Dr Wanruchada Katchamart, Dr Rujipas Sirijatuphat and Dr Anupop Jitmuang from the Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Thailand, presented the results of a meta-analysis performed to compare the accuracy of the immunofluorescence assay (IFA) and the microscopic agglutination test (MAT) for the diagnosis of leptospirosis. Three major databases, MEDLINE, SCOPUS and the Cochrane Library, were searched for studies published between January 1960 and May 2010 that evaluated serological diagnosis as a diagnostic test for leptospirosis, using MAT, culture or polymerase chain reaction (PCR) as the gold standard, and that provided sufficient data to calculate sensitivity and specificity. Twelve studies were initially identified, of which eight fulfilled the quality criteria for diagnostic test accuracy and were included in the statistical analysis.

Figure 1. Forest plot showing the results of eight studies to assess the accuracy of IFA

Reference *	Study	True positive	False positive	True negative	False negative	Sensivity	Sensivity
4	Appassakij et al I 995	58	3	0	114	1.00 (0.94, 1.00)	0.97 (0.93, 0,99)
5	Chimsumang et al 2005	11	16	0	53	1.00 (0.72, 1.00)	0.77 (0.65, 0.86)
6	Florez et al 2006	17	0	2	163	0.89 (0.67, 0.99)	1.00 (0.98, I ,00)
7	Hirschberg et al 1968	12	2	1	30	0.92 (0.64, I 00)	0.94 (0.19, 0.99)
8	Joshi S el al 2002	6	1	0	3	1.00 (0.54, 100)	0.75 (0.19, 0.99)
9	Pradudkanchana S 2003	33	7	4	136	089 (0.75, 0.97)	0.95 (0.90, 0,98)
10	Torten et al 1966	42	4	1	73	0.98 (0.88, 1.00)	0.95 (0.87, 0,99)
11	Udomsakdl I972	50	2	0	98	1.00 (0.93, 1.00)	0.98 (0.93, 1.00)



* References 4, 5, 6, 7, 8, 9, 10, 11

The results, summarized in Figure 1, indicated that IFA is a highly sensitive and specific diagnostic test, compared with the gold standard test for the diagnosis of leptospirosis. The summary receiver operating characteristic (SROC) curve, which represents the relationship between the true positive rate and the false positive rate of a test. The limitation of this analysis is that the statistical tests for meta-analysis of diagnostic test accuracy are not as well established as other types of meta-analysis and the interpretation of confidence regions of the SROC curve can be problematic.

The LERG concluded that the analysis of IFA was limited to too few countries to be generalizable to the global level.

Laboratory-confirmed cases of leptospirosis were defined as:

clinical signs and symptoms consistent with leptospirosis and any one of the following:

- fourfold increase in MAT titre in acute and convalescent serum samples;
- MAT titre ≥1:400 in single or paired serum samples;
- isolation of pathogenic *Leptospira* species from normally sterile site;
- detection of *Leptospira* species in clinical samples by histological, histochemical or immunostaining technique;
- pathogenic Leptospira species DNA detected by PCR;

Probable cases of leptospirosis were defined as:

clinical signs and symptoms consistent with leptospirosis and one of the following:

- presence of IgM or a fourfold increase in IFA antibody titre in acute and convalescent serum samples;
- presence of IgM antibodies by enzyme-linked immunosorbent assay (ELISA) or dipstick;
- MAT titre ≥1:100 in single acute-phase serum sample in non-endemic regions.

No significant difference was found between the number of studies identified using the case definition of laboratory-confirmed and probable cases and the number of studies using only laboratory-confirmed cases. Therefore, studies reporting laboratory-confirmed cases were used.

3.1.3 Revised quality criteria

The quality of studies was ranked according to the revised criteria outlined in Table 1. Both high and medium quality studies were included in the analysis.

Table 1. Revised quality assessment criteria used for incidence and sequelae studies.

Major criteria for incidence studies	Quality rank		
	High	Medium	Low
Population-based	Yes	Yes	No
Recently and reliably estimated	Yes	No	-
Laboratory confirmation	Yes	Yes	No
LERG case definition	Yes	No	-
Systematic case ascertainment	Yes	Yes	No
Active case ascertainment	Yes	No	-
Study period U1 year	Yes	No	-
Rates calculated or extrapolated	Yes	Yes	No
Major criteria for sequelae studies	**High**	**Medium**	**Low**
Laboratory confirmation	Yes	Yes	No
Use of LERG case definition	Yes	No	-
Representative population	Yes	Yes	No
Identification method	Yes	No	-
Rates calculated or extrapolated	Yes	Yes	No

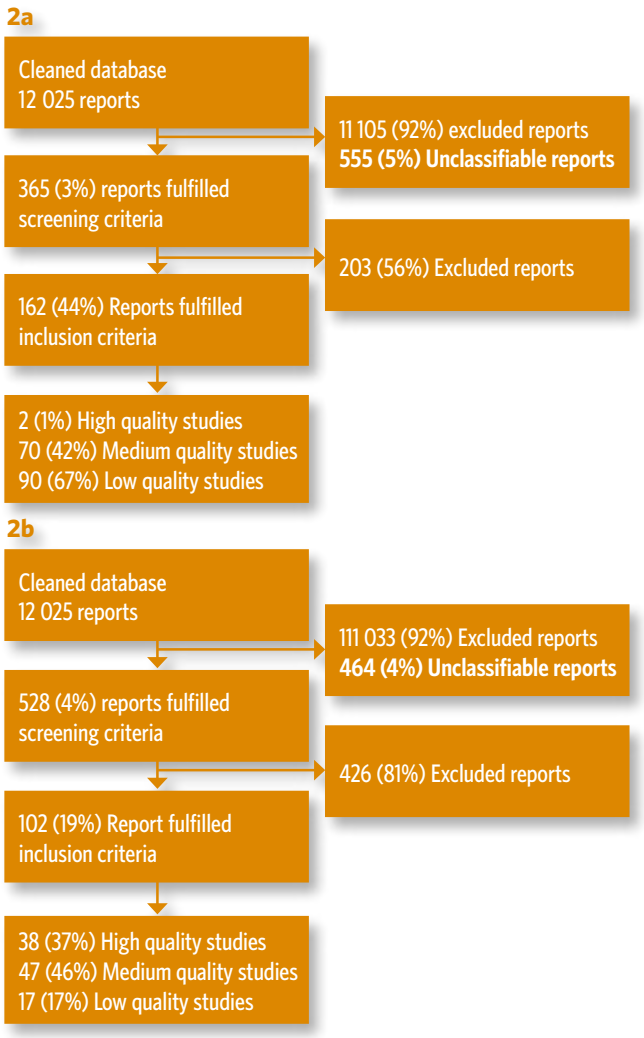
3.1.4 Language restriction

There was no language restriction for the search strategy; the full text of the reports was obtained and, where necessary, translated into English for inclusion in the analysis.

3.2 Results of the 2010 systematic review

Of the 12 025 reports on leptospirosis that were identified, 264 fulfilled the revised inclusion criteria for incidence and sequelae studies (see Annexes 3–6), with a total of 157 (72 incidence and 85 sequelae studies) being classified as high or medium quality (Figure 2). This contrasted with the total of 67studies identified in the 2009 systematic review in this category.

Figure 2 Summary of studies included in the 2010 systematic review.



2a: Disease incidence studies
2b: Disease sequelae studies.

Estimates of incidence by WHO region were obtained, and are summarized in Table 2.

Table 2. Median incidence of leptospirosis by WHO region, high and medium quality studies

WHO region	N°. of data-sets	Median incidence per 100 000 persons (range)
Africa	4	95.5 (62.8-160.2)
Eastern Mediterranean	0	-
Europe	21	0.5 (0.1-15.8)
Americas	26	12.5 (0.1-306.2)
South-East Asia	5	4.8 (0.3-7.3)
Western Pacific	13	66.4 (1.1-975.0)
World	69	5.1 (0.1-975.0)

The median global incidence of endemic human leptospirosis, excluding cases due to outbreaks, was 5 cases per 100 000 population, but in some areas the incidence was as high as 975 cases per 100 000. The mean annual global incidence of epidemic leptospirosis, as reported in outbreak reports, was 14 cases per 100 000 population. Some concern was expressed at the significant lack of data, especially from Africa and the Eastern Mediterranean Region, and at the substantial heterogeneity in the data. It was suggested that caution is needed in generalizing these data to a regional or global level; WHO subregions may be more appropriate geographical units when considering extrapolation of the data. LERG members highlighted the need to take into consideration leptospirosis peaks and the seasonality of outbreaks, as well as the need to quantify the proportion of the burden that is due to outbreaks. The LERG also acknowledged that the estimates would be minimum values, because of the under-ascertainment implicit in the use of passive surveillance studies and the diagnostic criteria applied.

The available incidence and case-fatality data were stratified by age and sex, as shown in Tables 3 and 4.

Table 3. Incidence data stratified by age and sex (2 studies)

Age range (years)	Median incidence (per 100 000 population)	
	Males	Females
0-9	1.4	2.0
10-19	19.2	4.8
20-29	57.0	15.4
30-39	44.6	20.3
40-49	32.7	8.4
50-59	51.5	38.9
>59	73.6	28.3

Table 4. Case-fatality data stratified by age and sex (2 studies)

Age (years)	Median case-fatality (%)	
	Males	Females
0-9	0	12
10-19	10	5
20-29	0	6
30-39	0	14
40-49	10	37
50-59	12	0
60-69	31	0
>70	0	0

Studies determining the frequency of sequelae and the associated case-fatality are summarized in Table 5.

Table 5. Frequency of sequelae and associated case-fatality

Sequela	N°. of reports	N°. of cases	Median incidence of sequela (%) (range)
Acute renal injury	49	2963	36 (0-88)
Acute lung injury	36	1069	17 (0-62)
	N°. of reports	**N°. of cases**	**Median case-fatality (%) (range)**
Acute renal injury	7	49	12 (0-67)
Acute lung injury	25	159	25 (2-87)

The duration of sequelae was also estimated from appropriate studies, as shown in Table 6.

Table 6. Duration of sequelae

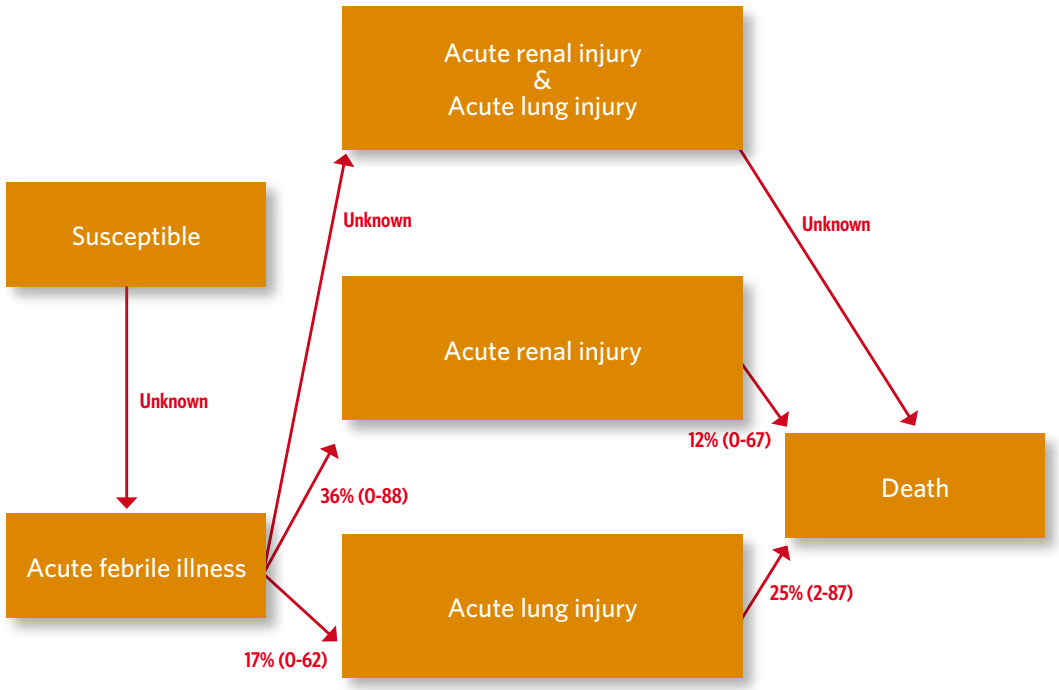
Sequela	No. of datasets	Median duration (days) (range)
Fever	6	6 (4-13)
Acute renal injury	3	12 (7-21)
Acute lung injury	4	6 (4-7)

The LERG concluded that further data were required for a number of disease model parameters; these are identified as "unknown" in Figure 3. Data are needed on the relative frequencies of mild disease (acute febrile illness) and the more severe sequelae. LERG recognized such data would not be easily available, because the majority of studies were of hospitalized cases. For the calculation of disability-adjusted life years (DALYs), there is also a need to estimate the duration of each of the sequelae, with and without treatment. Information about the populations that received treatment in the different regions would also be required.

Figure 3: The disease model showing the frequency and case fatality proportions of acute lung and renal injury

LERG members discussed the need to assess the probability of acute lung injury and acute renal injury occurring in the same patient. A consensus was also needed on the disability weight to be assigned in such cases: either the higher disability weight of the two sequelae could be used, or the disability weights for the two sequelae could be added together, or an adjusted disability weight could be developed. The inclusion of long-term muscular and neuropsychiatric sequelae was also discussed.

Members of LERG recognized that data on incidence and duration of sequelae will also be valuable to health authorities for planning use of health resources, especially in an outbreak setting.



3.3 Results of the WHO questionnaire

As part of efforts to estimate the global human leptospirosis disease burden, a grey literature search was initiated by WHO in early 2010 to assemble the available epidemiological data. Questionnaires were sent to countries in all WHO regions, asking for available data on the incidence of human leptospirosis since 1970 and the level of surveillance – active or passive surveillance, sentinel studies, or other methods. As was the case with the systematic literature review, the questionnaire identified a lack of information for the African and Eastern Mediterranean Regions.

Table 7. Summary of responses to questionnaire and availability of data at regional level

WHO Region	N°. of Member States	N°. of country responses	Proportion of countries that responded (%)	Country responses with no data
Americas	35	20	57.1	3
Africa	46	6	13.0	4
Eastern Mediterranean	21	1	4.8	0
Europe	53	7	13.2	1
South-East Asia	11	5	45.5	1
Western Pacific	26	19	73.1	2
Total	**192**	**58**	**30.1**	**11**

The level of surveillance for leptospirosis varies by region. In the Americas and the Western Pacific, active and passive surveillance methods are commonly used, as there have been several reported outbreaks in these areas in the past few decades. However, insufficient information is available on the surveillance methods of many countries, especially in Africa, the Eastern Mediterranean and Europe. The observed limited capacity for monitoring leptospirosis in developing countries, and the low priority assigned to it, could explain the limited surveillance in certain areas.

3.4 Modelling approaches

The risk of leptospirosis in a population can be predicted on the basis of a number of environmental and socio-economic factors (see Box 3). Given the lack of globally representative epidemiological data, the first LERG meeting had considered that modelling approaches based on these risks would be a useful mechanism for extrapolating the existing data to other regions.

Box 3. Important risk factors for leptospirosis

- Increased rainfall and flooding
- Inadequate floodwater drainage
- Poor housing or slum dwellings
- Proximity to open sewers
- Overcrowding
- Contact with animals
- Poor hygiene and sanitation
- Workplace exposure

In addition to their use as predictive tools, modelling approaches have been shown to be useful in evaluating potential interventions, understanding epidemiological processes and identifying important gaps in knowledge. Models based on subdividing the population into departments (e.g. susceptible, infectious, recovered and immune) were considered to be currently unsuitable for leptospirosis, because of a lack of sufficient data and imprecise understanding of disease ecology. It would also be difficult to use this type of modelling to predict morbidity in other regions, because of: the different transmission cycles, which are linked to environmental, animal, agricultural or occupational cycles; the survival of leptospires in the environment and the effect on survival of environmental variables and seasonality; and the variation in clinical manifestations.

Mapping the risk of leptospirosis to categorized regions on the basis of defined profiles was considered a possibility. WHO and others have previously produced risk maps for a number of diseases, including malaria, neglected tropical diseases and dengue fever.[12] Existing climatic data and data collected in Demographic and Health Surveys,[13] which are currently carried out in 84 countries, were considered useful in the development of risk maps.

Data from passive surveillance for leptospirosis in Thailand from 2000 to 2006[b] were initially considered as a basis for developing a model. Basic demographic data included sex and age of patients (from 2003 to 2006) and occupational data (from 2000 to 2003) (see Box 4).

Box 4. Thailand dataset for 2003–2006 used to develop the model

Total cases: 46338 (ffi 1.24 per 10000 person per year)
Median age of cases: 38 years (interquartile range: 26–49)
Median age of population in Thailand: ~ 33 years
24% of all patients were females
77% of patients worked in the agricultural sector
~ 46% of Thai population employed in agriculture

The following were assessed:

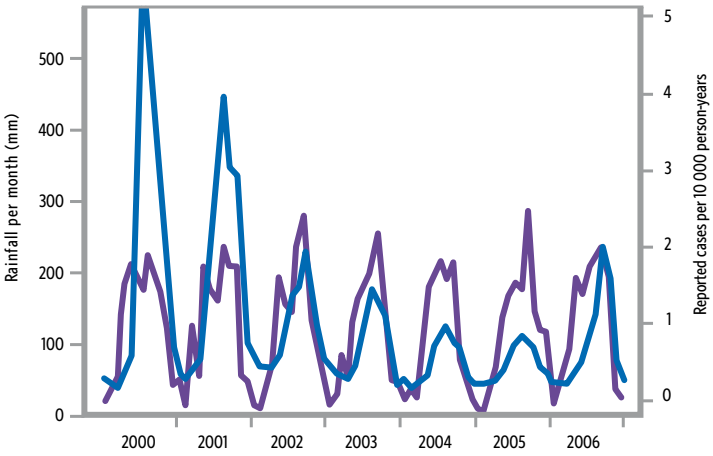
- temporal distribution of leptospirosis cases;
- spatial distribution of leptospirosis cases at regional and provincial level;
- correlation between number of leptospirosis cases and:
  - age, sex, occupation,
  - population density,
  - altitude, and
  - major and minor rice production season.

The data for the different years were highly heterogeneous. It was difficult to identify variables that had a high predictive power. For example, the level of rainfall per month was not predictive of the number of reported cases per year, as illustrated in Figure 4. In addition, it was not possible to identify independent variables that could be measured using a practical unbiased method, that gave a meaningful average or summary at the provincial level, and that were biologically or sociologically plausible. The impact of floods was also difficult to include in the model.

It was concluded that the current model based on the Thailand dataset could not be used to predict disease burden in other geographical areas. Further development would require analysis of additional datasets from other settings to identify common determinants that could predict the risk of leptospirosis.

However, newer data are now available from the Bureau of Epidemiology of the Ministry of Public Health of Thailand that seem to be based on more consistent reporting behaviour. It is also possible that a comprehensive dataset from Brazil would be useful in further developing the model, especially because some predictive indicators have been identified in this region.

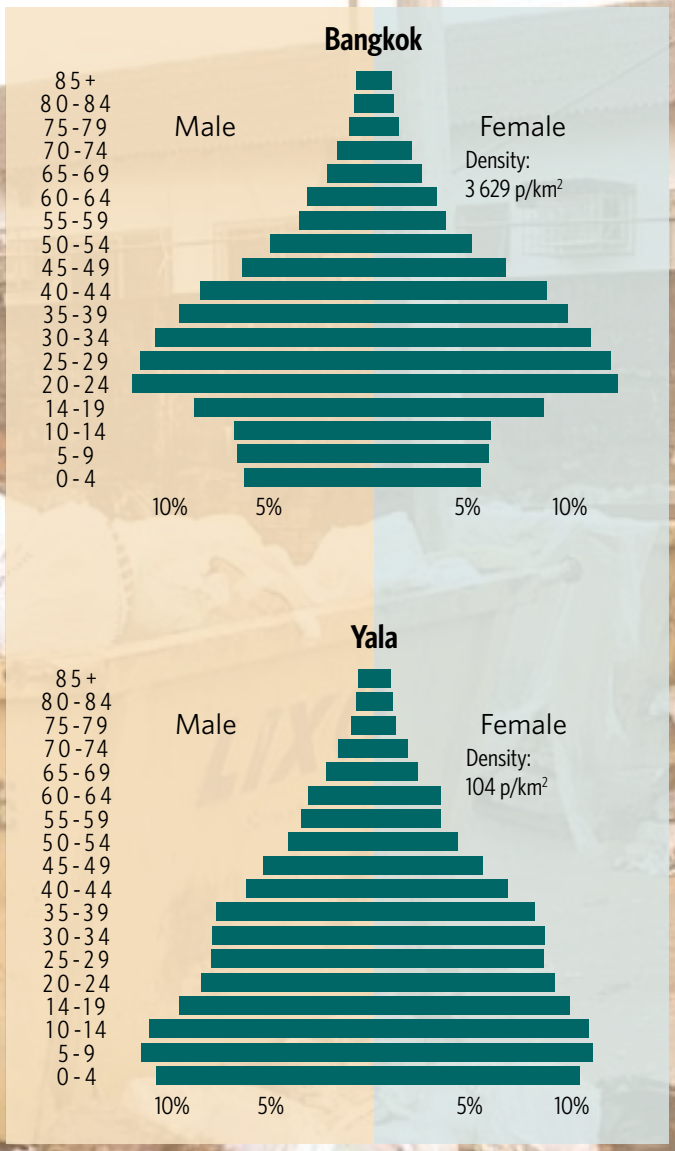
Figure 4. Mean monthly rainfall (arithmetic mean of 76 provinces, black line) and mean number of reported cases per 10 000 person-years (red line).



The LERG acknowledged that model development was critical to further understanding the ecology of the disease and assessing the impact of demographic factors, such as age distribution, which were reported as showing significant regional variation in the current Thailand dataset (see Figure 5). The important role of models in determining cost-effectiveness of interventions was also recognized.

b Unpublished data from The Bureau of Epidemiology, Ministry of Public Health, Thailand.

Figure 5. **Age structure of the population in two provinces of Thailand.**



4. Knowledge management

4.1 Identification of knowledge gaps

A number of gaps in scientific knowledge were identified by the LERG and the need for further information for the development of more effective strategies for control and prevention was highlighted. While it is outside the remit of LERG to consider actions to address these gaps, the Group considered it important to record them for the benefit of the wider community of leptospirosis researchers.

Point-of-care diagnostic tests

The existing gold standard serological tests are difficult to perform, and it is not easy to demonstrate the presence of leptospires during active infection. In addition, the high background level of leptospirosis antibodies in endemic regions means that diagnostic assay results cannot easily differentiate between current and past infection. The lack of evidence regarding the long-term sequelae means that the DALYs attributed to leptospirosis may be underestimated.

Animal models and the known biological behaviour of leptospires suggest that infection may become chronic and that leptospires may persist in the kidneys, liver, lung and central nervous system. The medical implications of this are unknown. Leptospiral diversity and the biological differences underlying different forms of severe leptospirosis also make it difficult to characterize sequelae. The difficulty of demonstrating the organisms in certain tissues (e.g. in the eye in uveitis) also contributes to the lack of reliable diagnosis.

Protocols for surveillance for disease and infection sources

There is a need for low-cost effective surveillance mechanisms for leptospirosis in endemic countries. It will be important to ensure that appropriate capacity and resources are available to implement surveillance in a sustainable way.

Incidence data and long-term studies to assess the burden of disease

Lack of awareness and funding may contribute to the scarcity of large-scale studies on leptospirosis. There is a need to develop integrated disease, ecology, and risk-model approaches and to establish standardized protocols and centres of excellence for clinical, epidemiological and laboratory studies. Banks of well characterized serum, urine and other specimens would allow new diagnostic tests, based on antibody and antigen detection, to be validated and used in the field. Incidence and long-term studies in regions representative of different epidemiological contexts and clinical manifestations would lead to a better understanding of the impact of leptospirosis.

Appropriate guidelines for outbreak response and clinical management

The LERG will continue to work closely with the Global Outbreak Alert and Response Network (GOARN) and other partners in WHO on the response to leptospirosis outbreaks, to develop clinical management protocols, including care paths, and to adapt these for use in settings with a range of available resources. Further data on the effectiveness of mass prophylaxis in outbreak settings would facilitate the development of these guidelines.

Targeted intervention based on the improved knowledge of disease ecology

It is crucially important to continue to advocate for a cross-sectoral systems approach to the control and prevention of leptospirosis. Further knowledge of the natural ecology of the disease and the animal–human–ecosystem interface will help to identify the most effective points for intervention, from both the human and veterinary public health perspective.

4.2 Knowledge transfer and policy implications

Despite the gaps in scientific knowledge, it is expected that an estimate of the global burden of human leptospirosis will be available in 2011. There will then be a need to consider how to translate this knowledge into relevant policy and intervention strategies.

Bearing in mind the Group's third objective,[c] LERG members discussed the opportunities for use of esti-

c "To increase Member States' awareness of, and commitment to, interventions to prevent and control leptospirosis."

mates of the global burden of leptospirosis at country level, to develop the most appropriate and cost-effective interventions for control and prevention of the disease. They identified a number of areas where further tools need to be developed to assist responsible authorities in endemic countries (see Figure 6). While the transmission model cannot generate estimates of disease burden, it may be a useful tool for policy-making, determining appropriate interventions, and assessing the likely cost-effectiveness of interventions.

Tanja Kuchenmüller, from the WHO Department of Food Safety and Zoonoses, presented approaches to bridging the research–policy gap and tools for knowledge translation (see Box 5). The LERG recognized the importance of investigating how the burden of disease estimate could be used in working with other groups, such as the WHO Foodborne Disease Burden Epidemiology Reference Group (FERG) and the Evidence-Informed Policy Network (EVIPNet), to analyse the policy situation in endemic countries. Knowledge translation is a cyclical process (see Figure 6), feeding back the lessons learned throughout the implementation cycle. Some of the knowledge gaps recognized by LERG have an important effect on the translation process and will require investment. For the evaluation of outcomes, point-of-care diagnostic capacity and protocols for surveillance need to be developed to ensure that the success of interventions is accurately assessed.

Box 5. Knowledge translation

Knowledge translation (KT) is a dynamic and iterative process that includes synthesis, dissemination, exchange and ethically sound application of knowledge to improve health outcomes, provide more effective health services and products, and strengthen the health care system. Evaluation and monitoring of KT initiatives, processes, and activities are key components of the KT process. This process takes place within a complex system of interactions between researchers and knowledge users, which may vary in intensity, complexity and level of engagement depending on the nature of the research and the findings, as well as the needs of the particular knowledge user.

Synthesis, in this context, means the contextualization and integration of findings from individual research studies within the larger body of knowledge on the topic. A synthesis may use quantitative or qualitative methods and must be reproducible and transparent. It can take the form of a systematic review, following the methods developed by the Cochrane Collaboration, or result from a consensus conference or expert panel. Realist syntheses, narrative syntheses, meta-analyses, meta-syntheses and practice guidelines are all forms of synthesis.

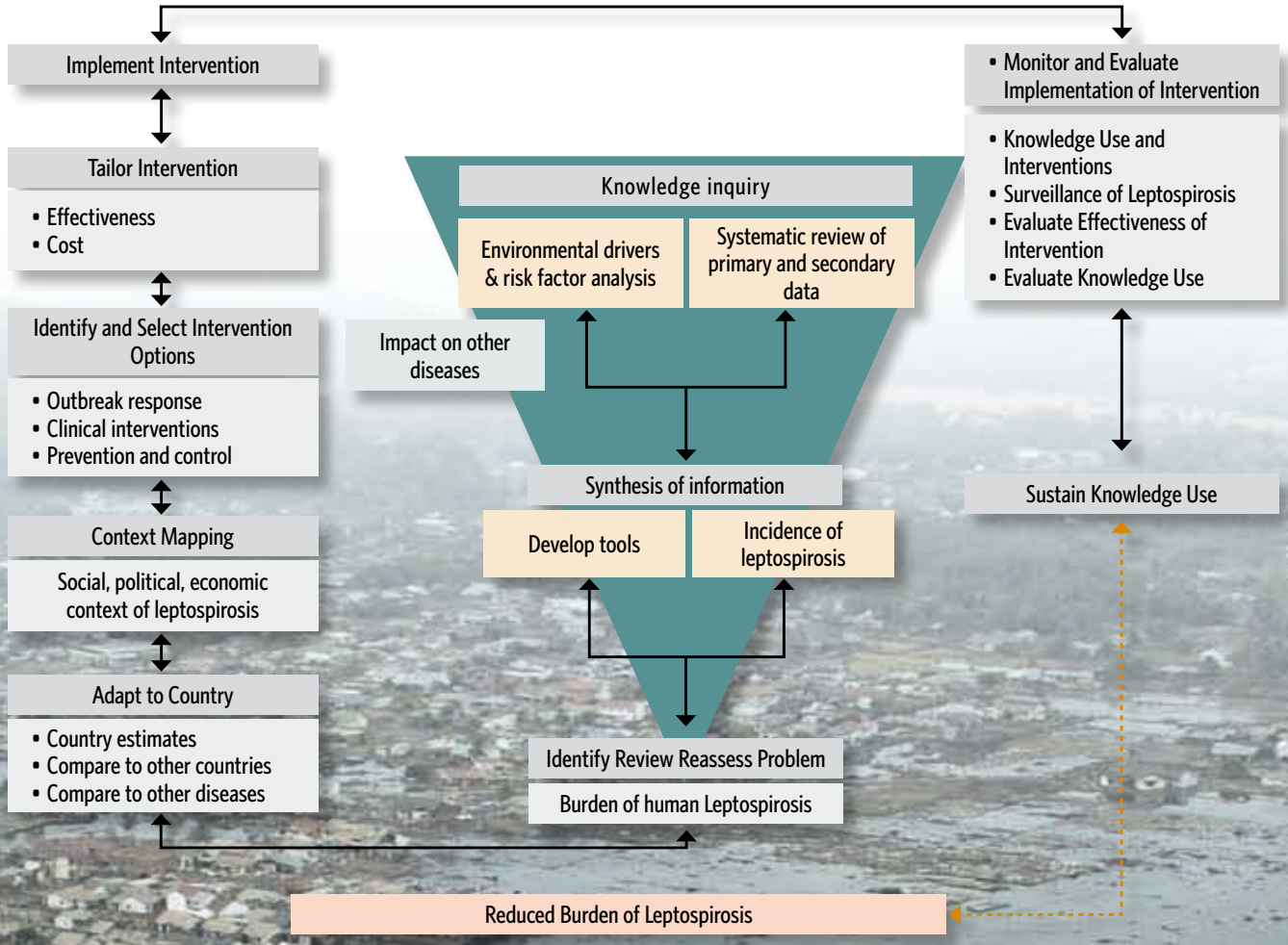
Dissemination involves identifying the appropriate audience and tailoring the message and medium to that audience. Dissemination activities can include such things as summaries and briefings for stakeholders, educational sessions with patients, practitioners or policy-makers, engagement of knowledge users in developing and executing dissemination and implementation plans, creation of tools, and engagement Of the media.

Exchange of knowledge refers to the interaction between the knowledge user and the researcher. Knowledge exchange involves collaborative problem-solving among decision-makers and researchers. Effective knowledge exchange fosters mutual learning through interaction in all stages of policy design, including producing, planning, disseminating, and applying research in decision-making.

Ethically sound application of knowledge for improved health comprises activities that are consistent with ethical principles and norms, social values, and legal and other regulatory frameworks. It is worth keeping in mind, however, that principles, values and laws may not always be completely concordant. The term application is used to refer to the iterative process by which knowledge is put into practice.

Based on: Canadian Institutes of Health Research (http://www.cihr-irsc.gc.ca/e/39033.html).

Figure 6. Framework for knowledge translation for leptospirosis



Modified by Asim Qasim, from Canadian Institutes of Health Research (http://www.cihr-irsc.gc.ca/e/39033.html).

Table 8. Enabling and constraining factors in translating knowledge to policy and practice[a]

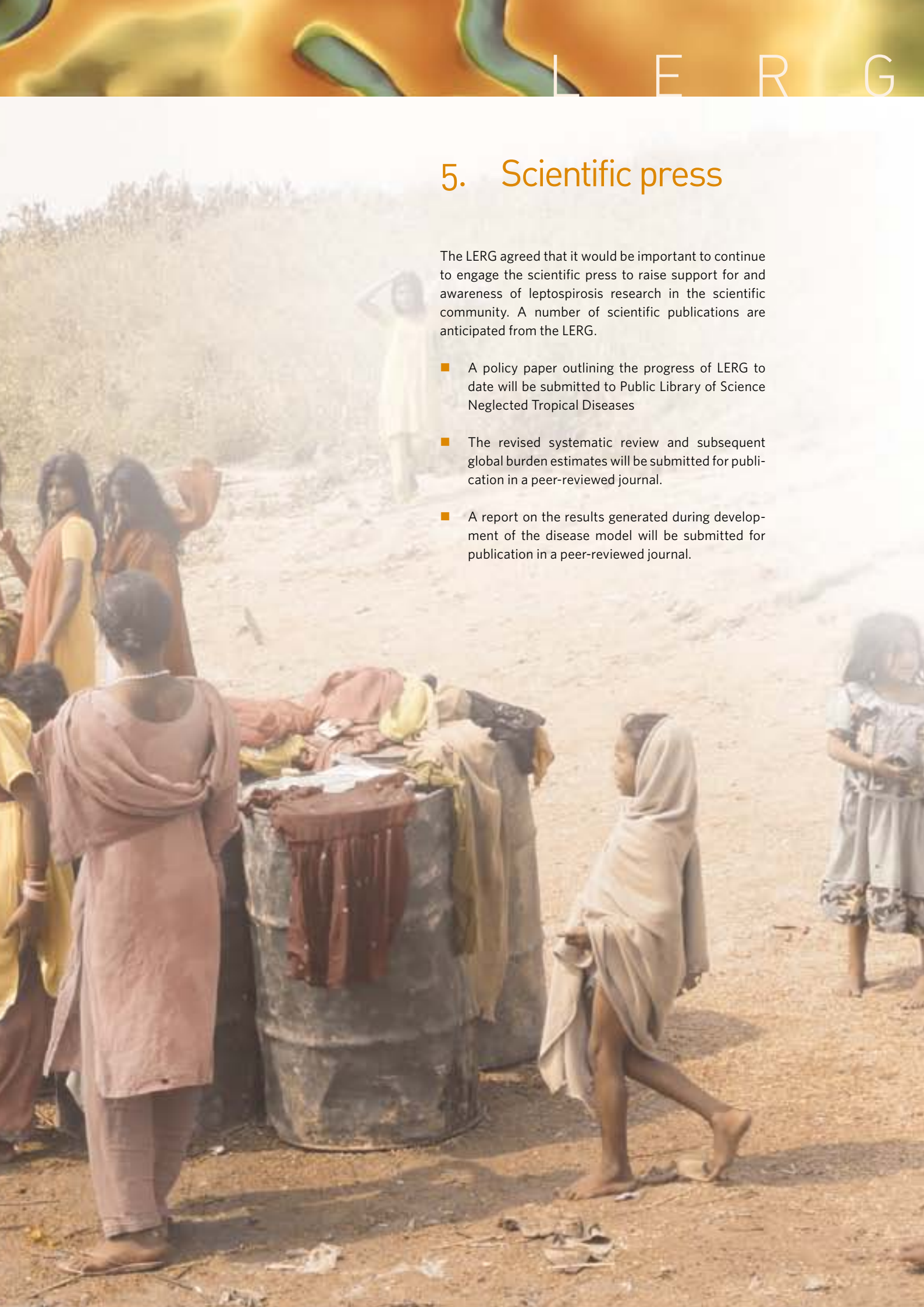
Enabling factors	Constraining factors
Push factors (supply side)	**Push factors (supply side)**
■ Production of relevant and good evidence ■ Timely and understandable repackaging and synthesis of the evidence, evidence-based actionable messages (EBAMs) ■ Credible knowledge mediators/brokers/messengers, opinion leaders ■ Availability of and access to knowledge ■ Knowledge mapping ■ Donor/ funding agencies' support for KT	■ Lack of a common framework for knowledge translation ■ Limited integration of quantitative and qualitative methods for synthesis of evidence ■ Costly and slow process of knowledge production and synthesis ■ Lack of and poor access to relevant evidence ■ Competing sources of knowledge that may be distorted or biased ■ Donor-driven research agenda
Pull factors (demand side)	**Pull factors (demand side)**
■ Political commitment and local knowledge champions ■ Political mapping and understanding of the sociopolitical environment ■ Problem-based evidence and user-initiated policy questions ■ Integration of social actors in local decision-making bodies (social participation) ■ User-friendly access to knowledge and searchable databases	■ Low demand for scientific evidence by policy-makers ■ Different paradigms for evidence and policy among decision-makers, practitioners and researchers ■ Political or financial reasons for not acting on good evidence
Exchange	**Exchange**
■ Education of and dialogue with users and media on high-impact stories on the use of knowledge ■ Innovative ways of knowledge sharing, especially tacit knowledge	■ Lack of interactive communication between producers and users of scientific evidence ■ Lack of knowledge sharing, especially with policy-makers and the community

[a] Adapted from WHO, 2006.[14]

5. Scientific press

The LERG agreed that it would be important to continue to engage the scientific press to raise support for and awareness of leptospirosis research in the scientific community. A number of scientific publications are anticipated from the LERG.

- A policy paper outlining the progress of LERG to date will be submitted to Public Library of Science Neglected Tropical Diseases
- The revised systematic review and subsequent global burden estimates will be submitted for publication in a peer-reviewed journal.
- A report on the results generated during development of the disease model will be submitted for publication in a peer-reviewed journal.



6. Outcomes, recommendations and action plan

6.1 Systematic review

LERG members recommended that, following the planned revisions, the data from the systematic review would be appropriate for use in the calculation of DALY figures for a preliminary estimate of the leptospirosis disease burden. These initial figures could then be assessed for plausibility as part of wider burden of disease initiatives.

LERG members were, therefore, requested to use their networks to gather the additional data required to complete the suggested revisions (see Annex 7 for data collection form to be used). LERG recognized that obtaining detailed clinical information may be time-consuming. In order to allow timely data analysis, members were invited to provide whatever information is readily available, and indicate if further data will be forthcoming later.

Data will be requested from areas with currently poor coverage (e.g. China). Data will be required separately for male and female patients, stratified by age, to calculate age- and sex-specific rates for disease incidence, mortality, case-fatality and sequelae.

In addition, data on study design and patient characteristics will be requested, such as whether the study was performed during an outbreak, and whether it included only hospitalized cases, only outpatient cases, or a mix of the two. These data will be crucial in allowing further aggregation with similar studies, and to calculate more accurate incidence and sequelae rates. Information is also requested about whether the study's case definition corresponded to those recommended by the LERG.

The number of laboratory-confirmed cases and deaths with either ARI, ALI, or both will also be requested, in order to obtain information that will be required for the calculation of years lived with a disability. LERG will consult with FERG and other global burden of disease initiatives to identify the best strategies for incorporating co-morbid sequelae into disease burden estimates.

On completion of the systematic literature review, it will be submitted, together with the accompanying databases and burden of disease calculation, to the WHO Mortality and Burden of Disease Unit, for review and consideration for the WHO global report and atlas.

6.2 Disease model

The existing disease model was not able to identify independent variables that could act as a proxy for disease incidence for use in estimating the burden of leptospirosis. However, LERG recognized the value of the model in further elucidating the ecology of the disease, and requested a report summarizing the efforts to establish a leptospirosis transmission model, including the potential for use of more recent data, and recommended possible refinements to the model. The authors were also encouraged to submit the report for publication in a peer-reviewed journal and further explore the opportunities for use of the model as a tool to help endemic countries to select cost-effective interventions.

6.3 Knowledge transfer

LERG recommended further investigation of how WHO could use the LERG burden of disease estimate in knowledge translation and bridging the research–policy gap.

6.4 Strategic partnerships

The LERG also recognized the benefits of liaising with other groups, such as the Global Outbreak Alert and Response Network and other disease burden groups, to coordinate efforts and learn from their experience. Both policy-makers and funding agencies should be targeted with information on the accumulating knowledge on the burden of leptospirosis and experiences acquired during management of outbreaks. The reports and summary documentation produced by the secretariat should continue to be used to raise awareness and sensitize governments and other agencies, and as the basis of grant proposals, seminars and presentations.

6.5 Funding

Funding opportunities will continue to be explored and a range of possible donors identified.

6.6 Summary of action plan

Table 9 presents a summary of the items on the LERG action plan. A more detailed workplan is given in Annex 8.

Table 9. Summary of action items.

Systematic review of literature	
Revise systematic literature review	Feb 2011
Submit systemic review for publication in peer-reviewed journal	Mar 2011
Calculate DALYs for human leptospirosis and submit report to peer-reviewed journal	June 2011
Risk/transmission model	
Produce a report for publication in peer-reviewed journal	Feb 2011
Translating research knowledge into policy and interventions	
Investigate possible next steps	To be determined
Communication and advocacy	
Submit policy platform paper for the Public Library of Science Neglected Tropical Disease Journal (PLoS NTD)	Jan 2011

References

1 McCarthy JJ, Canziani OF, Leary NA, Dokken DJ, White KS. *Climate change 2001: impacts, adaptations, and vulnerability.* Working Group II. Intergovernmental Panel on Climate Change (IPCC). New York: Cambridge University Press; 2001.

2 Lau CL, Smythe LD, Craig SB, Weinstein P. Climate change, flooding, urbanization and leptospirosis: fuelling the fire? *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 2010; 104: 631-638.

3 Solomon S, Qin D, Manning M, Marquis M, Averyt K, Tignor M et al., eds. *Climate change 2007. The physical science basis.* Contribution of Working Group I to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change 2007. Cambridge & New York: Cambridge University Press (http://www.ipcc.ch/publications_and_data/ar4/wg1/en/contents.html).

4 Appassakij H, Silpapojakul K, Wansit R, Woodtayakorn J. Evaluation of the immunofluorescent antibody test for the diagnosis of human leptospirosis. *Am J Trop Med Hyg,* 1995; 52:340-343.

5 Chimsumang S, Chettanadee S, Jitrathai S, Wongchotigul V. Indirect immunoperoxidase test for the diagnosis of leptospirosis. *Southeast Asian J Trop Med Public Health,* 2005; 36(2): 296-301.

6 Agudelo-Flórez P, Restrepo-Jaramillo BN, Arboleda-Naranjo M. Leptospirosis in Uraba, Antioquia, Colombia: a seroepidemiological and risk factor survey in the urban population. *Cad Saude Publica,* 2007; 23(9):2094-2102

7 Hirschberg N, Galton MM, Sulzer CR. Experiences with the indirect fluorescent antibody test in the serodiagnosis of leptospirosis. *Health Lab Sci,* 1968; 5(2):89-94.

8 Joshi S, Bal A, Bharadwaj R, Kumbhar R, Kagal A, Arjunwadkar V. Role of IgM specific indirect immunofluorescence assay in diagnosing an outbreak of leptospirosis. *Indian J Pathol Microbiol.* 2002; 45(1):75-77.

9 Pradutkanchana S, Pradutkanchana J, Khuntikij P. Detection of IgM specific antibody using indirect immunofluorescent assay for diagnosis of acute leptospirosis. *J Med Assoc Thai,* 2003; 86: 641-647.

10 Torten M, Shenberg E, van der Hoeden J. The use of immunofluorescence in the diagnosis of leptospirosis by a genus-specific antigen. *J Infect Dis,* 1966; 116: 537-543.

11 Udomsakdi S, Potha U. The diagnosis of leptospirosis by fluorescent antibody technique using saprophytic leptospira as a genus specific antigen. *Journal of the Medical Association of Thailand,* 1972; 55:101-104.

12 Esteva L, Vargas C. Analysis of a dengue disease transmission model. *Mathematical Biosciences,* 1998; 150: 131-151.

13 Demographic and Health Surveys (http://www.measuredhs.com/).

14 Bridging the "know-do" gap. Meeting on knowledge translation in global health, 10-12 October 2005. Geneva: World Health Organization; 2006 (http://www.who.int/kms/WHO_EIP_KMS_2006_2.pdf; accessed 5 November 2010).

Annex 1. Participants in the meeting

LERG advisors

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Annex 2. Agenda of the meeting

Wednesday, 22 September 2010

09:00-9:30	Premeeting with rapporteur and chair Coffee served outside meeting room
09:30-10:00	Welcome by ADG/HSE and WHO Secretariat
10:00-10:30	Report on progress WHO Secretariat
10:30-11:00	*Coffee break*
11:00-12:30	Systematic literature review Juan Calcagno and Federico Costa
12:30-14:00	*Lunch break*
14:00-15:30	Transmission model Jakob Zinsstag and Jan Hattendorf
15:30-16:00	*Coffee break*
16:00-1700	Translating burden estimates to policy and EVIPNET Tanja Kuchenmuller and Ulysses Panisset

Thursday, 23 September 2010

09:00-9:30	Summary of Day 1 by Chair and Rapporteur
09:30-9:45	Review of immunofluorescent antibody test (IFA) Yupin Suputtamongkol
9:45-10:30	Discussion: Systematic review, transmission model, and preliminary burden of disease estimation for human leptospirosis
10:30-11:00	*Coffee break*
11:00-12:30	Next steps and LERG workplan
12:30-14:00	*Lunch break*
14:00-15:30	Next steps and LERG workplan
15:30-16:00	*Coffee break*
16:00-17:30	Brief summary of Day 2 by Chair and Rapporteur Summary and formal closure of LERG 2 by WHO Secretariat

Annex 3. Quality assessment criteria for disease incidence studies

Criteria	Surveillance studies not associated with outbreaks	Outbreak-associated studies	Cohort studies (including randomized controlled trials)
Methods for identifying study population			
Study population	1) Was the study a population-based investigation? 2) Was the population base recently and reliably estimated (i.e. census)?	1) Was the study a population-based investigation? 2) Was the population base recently and reliably estimated (i.e. census)?	1) Were inclusion and exclusion criteria defined for the cohort? 2) Was the cohort representative of the population to be studied?
Methods for measuring incidence			
Outcome	1) Was laboratory confirmation performed for suspected cases? If so, were standard diagnostic methods and criteria used according to LERG recommendations? 2) Was case ascertainment active or passive? 3) Was case ascertainment hospital-based or outpatient/community-based? 4) Did changes occur in the way that case ascertainment was performed or incidence measured during the study period?	1) Was laboratory confirmation performed for suspected cases? If so, were standard diagnostic methods and criteria used according to LERG recommendations? 2) Was case ascertainment active or passive? 3) Was case ascertainment hospital-based or outpatient/community-based? 4) Did changes occur in the way that case ascertainment was performed or incidence measured during the study period	1) Was laboratory confirmation performed for suspected cases? If so, were standard diagnostic methods and criteria used according to LERG recommendations?* 2) Was case ascertainment active or passive? 3) Was case ascertainment hospital-based or outpatient/community-based? 4) Did changes occur in the way that case ascertainment was performed or incidence measured during the study period?
Study period	1) Was the study period defined? 2) Was surveillance performed for at least a year in order to address seasonal variation in incidence?	1) Was the study period defined?	1) Was the study period defined? 2) Was the cohort followed for at least a year in order to address seasonal variations in rates?
Sources of bias			
Follow-up of suspected cases	1) Is there information on the proportion of suspected and confirmed cases for which single and paired sera were collected?	1) Is there information on the proportion of suspected and confirmed cases for which single and paired sera were collected?	1) Is there information on the proportion of suspected and confirmed cases for which single and paired sera were collected?
Drop-outs and deaths	1) Not applicable	1) Not applicable	1) What was the proportion of drop-outs during follow-up?
Data analysis			
Analytical methods	1) Were rates calculated? If not, can they be extrapolated or estimated from the data reported by the author? 2) Were age- and sex-specific attack rates determined or can they be calculated from the data?	1) Were rates calculated? If not, can they be extrapolated or estimated from the data reported by the author? 2) Were age- and sex-specific attack rates determined or can they be calculated from the data?	1) Were rates calculated? If not, can they be extrapolated or estimated from the data reported by the author? 2) Were age- and sex-specific attack rates determined or can they be calculated from the data?

Annex 4. Quality assessment checklist for disease incidence studies[1]

	Quality		
	High	**Medium**	**Low**
	Major criteria		
	The study fulfils all of the following criteria:	The study does not fulfil the criteria for high or low quality, and in general has the following characteristics:	The study fulfils one or more of the following criteria
Study population	1) Population-based study 2) Population base recently and reliably estimated	1) Population-based study 2) Population base not recently or not reliably estimated	1) Study not population-based
Measuring incidence	1) Laboratory confirmation performed with standard methods and definitions, as defined by LERG 2) Active case ascertainment, whether community- or hospital/provider-based 3) Study period was 1 year or more	1) Laboratory confirmation performed, but standard methods and definitions not used 2) Passive hospital/provider-based case ascertainment 3) Study period less than 1 year	1) Laboratory confirmation not performed. 2) Case ascertainment not performed as a systematic or continuous process during the study period.
Analysis	1) Rates calculated or can be extrapolated from the data	1) Rates calculated or can be extrapolated from the data	1) Rates cannot be calculated or extrapolated from the data
	Minor criteria (to be coded in order to discriminate reports within a quality rank)		
Measuring incidence	1) Community-based case ascertainment 2) No changes in case ascertainment during the study period	1) Hospital-based case ascertainment 2) Changes in case ascertainment cannot be determined from the report	1) Hospital-based case ascertainment 2) Changes in case ascertainment cannot be determined from the report
Bias	1) Information available on proportion of subjects for whom paired and single samples were evaluated during laboratory confirmation	1) Information not available on proportion of subjects for whom paired and single samples were evaluated during laboratory confirmation	1) Information not available on proportion of subjects for whom paired and single samples were evaluated during laboratory confirmation
Analysis	1) Age- and sex- specific attack rates calculated or can be extrapolated	1) Age- and sex-specific attack rates cannot be calculated or extrapolated	1) Age- and sex-specific attack rates cannot be calculated or extrapolated

[1] Includes surveillance studies not associated with outbreaks, outbreak-associated studies, and cohort studies, including randomized controlled trials

Annex 5. Quality assessment criteria for disease sequelae studies

Criteria	Disease sequelae
	Methods for selecting study population
Study population	1) Were standard diagnostic methods and criteria used to identify leptospirosis cases according to LERG recommendations? 2) Were the cases studied representative of the population of leptospirosis patients in the epidemiological setting?
	Methods for measuring sequelae
Outcome	1) Were sequelae defined and, if so, were the definitions in accordance with those recommended by the LERG. If not, are there adequate data to estimate sequelae rates according to the LERG definition? 2) Were sequelae identified prospectively by clinical evaluations performed while under medical care for the illness or retrospectively by medical chart review?
	Sources of bias
Case confirmation	1) Is there information on the proportion of suspected cases for which single and paired sera were collected? 2) Were sequelae determined for unconfirmed cases of suspected leptospirosis, including deaths?
	Statistical methods
Statistical methods	1) Were sequelae and case-fatality rates calculated? If not can they be extrapolated or estimated from the data reported by the author? 2) Were age- and sex-specific sequelae and case-fatality rates determined or can be calculated from the data?

Annex 6. Checklist for quality evaluation of disease sequelae studies.

	Quality		
	High	**Medium**	**Low**
	Major criteria		
	The study fulfils all of the following criteria:	The study does not fulfil the criteria for high or low quality and in general has the following characteristics:	The study fulfils one or more of the following criteria:
Study population	1) Laboratory confirmation performed with standard methods and definitions, as defined by LERG 2) Cases representative of the patient population in the study setting (i.e. consecutive cases enrolled)	1) Laboratory confirmation performed but standard methods and definitions were not used 2) Cases representative of the patient population of in the study setting (i.e. consecutive cases enrolled)	1) Laboratory confirmation not performed 2) Convenience sample of cases, which is not representative of the patient population in the study setting
Sequelae	1) Sequelae identified prospectively during clinical evaluations performed while under medical care for the illness.	1) Sequelae identified retrospectively during medical care for the illness	1) No description of the protocol used to evaluate sequelae
Analysis	1) Sequelae and case-fatality rates can be calculated or extrapolated from the data	1) Sequelae and case fatality can be calculated or can be extrapolated from the data	1) Sequelae and case-fatality rates cannot be calculated or extrapolated from the data
	Minor criteria (to be coded in order to discriminate reports within a quality rank)		
Bias	1) Information available on proportion of subjects for whom paired and single samples were evaluated during laboratory confirmation 2) Sequelae determined for unconfirmed cases of leptospirosis	1) Information not available on proportion of subjects for whom paired and single samples were evaluated during laboratory confirmation 2) Sequelae not determined for unconfirmed cases of leptospirosis	1) Information not available on proportion of subjects for whom paired and single samples were evaluated during laboratory confirmation 2) Sequelae not determined for unconfirmed cases of leptospirosis
Analysis	1) Age- and sex-specific sequelae rates calculated or can be extrapolated	1) Age- and sex-specific sequelae rates cannot be calculated or extrapolated	1) Age- and sex-specific sequelae rates cannot be calculated or extrapolated

Annex 7. Simplified protocol for collecting age- and sex-specific information on leptospirosis

This annex provides a data collection form for use by LERG members in collecting information to improve the systematic literature review on leptospirosis, to refine the data on incidence, mortality, age–sex distribution, mild/severe presentation and, where available, co-morbidity. There are two primary goals:

1. to calculate age- and sex-specific incidence and mortality rates;

2. to calculate age- and sex-specific case-fatality and sequelae rates.

It is recognized that obtaining detailed clinical information on sequelae may be time-consuming. In order to allow timely data analysis, please provide whatever information is readily available, and indicate if further data will be forthcoming later (please specify an estimated date).

The first section of the form is designed to collect information on study design and patient characteristics. This includes whether the study was performed during an outbreak, and whether it included only hospitalized cases, only outpatient cases, or both. This information is important in order to allow aggregation with similar studies, and to calculate incidence and sequelae rates using the correct denominator. Additionally, the form requests information about whether the study's case definition corresponded to that recommended by the LERG. The LERG case definitions for probable and confirmed cases are given on the form.

The second section of the form requests information on the identified cases. Data are requested separately for male and female patients, stratified by age group.

1. Age groups and population base: please input, if available, the estimated population base for each age group. If census information or number of cases is available for different age ranges, please modify the form to include the age ranges for which you have information.

2. Clinically suspected vs laboratory-confirmed cases: please indicate the number of cases and deaths in each category. Laboratory-confirmed cases are a subset of all clinically suspected cases. If only laboratory-confirmed data are available, please enter an X in the "Clinically Suspected" column.

3. Disease sequelae: please provide the number of laboratory-confirmed cases and deaths with either ARI, ALI, or both. Note that this information is valuable even if population estimates are not available. The clinical definition for these sequelae is given on the form. We wish to obtain information that distinguishes patients with either sequelae from those with both. We recognize that, in some cases, it may only be possible to report the total number of ARI and ALI cases without distinguishing those with both sequelae. In this case, please enter X in the "Both ARI and ALI" column.

Please complete the information in the yellow cells whenever possible

Study characteristics				
Study site country				
Study site region				
Study start date (dd/mm/yy):				
Study end (dd/mm/yy):				
	Yes	**No**	**Unknown**	**Comments**
Cases representative of the patient population in the study setting (i.e. consecutive cases enrolled)				
Study performed during an outbreak				
Study used active surveillance to identify cases				
Study protocol prospectively identified cases				
Study performed in an exclusively urban setting				
Study performed in an exclusively rural setting				
Study performed in a mixed rural and urban setting				
Study included only hospitalized cases				
Study included only outpatient cases				
Study included both outpatient and hospitalized cases				
Laboratory confirmation of cases performed using LERG defined criteria*				

* The following definitions are used by the LERG:

Confirmed case of leptospirosis: Clinical signs and symptoms consistent with leptospirosis and any one of the following: (1) fourfold increase in MAT titre in acute and convalescent serum samples;
(2) MAT titre ≥1:400 in single or paired serum samples; (3) isolation of pathogenic *Leptospira* spp from normally sterile site; (4) detection of *Leptospira* spp in clinical samples by histological, histochemical or immunostaining technique; (5) pathogenic *Leptospira* DNA detected by PCR; (6) presence of IgM or IgA antibodies in the immunofluorescence assay;

Probable case of leptospirosis: Clinical signs and symptoms consistent with leptospirosis and any one of the following: (1) Presence of IgM antibodies by ELISA or dipstick; (2) MAT titre ≥1:100 in single acute-phase serum samples.

Instructions: please indicate in each column the number of cases or deaths within each age range. When reporting the number of cases or deaths associated with ARI or ALI, please record cases with only ARI, only ALI or both conditions. If this level of stratification is not available, please record the number of cases with either ALI or ARI, and mark X where asked to record the cases with both conditions.

Age range	Population base (each age group)	Clinically suspected cases		Laboratory confirmed cases							
		Nº. of cases	Nº. of deaths	Nº. of cases	Nº. of deaths	Nº. of ARI cases[1]	Nº. of ALI cases[2]	Nº. of cases with both ARI and ALI[3]	Nº. of deaths due to ARI	Nº. of deaths due to ALI	Nº. of deaths due to both ARI and ALI[3]
0–9 years											
10–19 years											
20–29 years											
30–39 years											
40–49 years											
50–59 years											
60–69 years											
≥70 years											

1 ARI (acute renal injury): acute onset of oliguria, uraemia, or abnormally elevated serum creatinine or blood urea nitrogen.

2 ALI (acute lung injury): respiratory distress, as indicated by the finding of dyspnoea or respiratory frequency ≥ 28 per minute; bilateral crepitus; bilateral infiltrates in chest X-ray examination; a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2) < 300mm; or report of the use of mechanical ventilation as a therapeutic intervention.

3 Please insert X in this column if it cannot be distinguished how many patients had both ALI and ARI.

Annex 8. Follow-up action

		Estimated completion date
1 Systematic review of published literature		
1a	LERG members to provide additional data on information gaps in systematic literature review on incidence, mortality, age–sex distribution, mild/severe presentation and, where available, co-morbidity. Request for the required information to be sent to relevant countries.	Nov 2010
1b	Examine available data for leptospirosis peaks and seasonality to identify outbreaks and quantify proportion of burden due to outbreaks.	Feb 2011
1c	Revise systematic literature review by including new data based on new definition and new information supplied by LERG members.	Feb 2011
1d	Submit systematic literature review for publication in peer-reviewed journal.	March 2011
1e	Use data from systematic review to calculate DALYs and burden of disease.	May 2011
1f	Review preliminary burden estimates and assess for plausibility.	June 2011
1g	Submit burden of disease estimate for publication in peer-reviewed journal.	Mar 2011
2 Risk/transmission model		
2a	Prepare a report summarizing efforts to establish a leptospirosis transmission model, including using more recent data and reasons why prediction of burden is not feasible, and recommend potential uses of more refined models.	Dec 2010
2b	Submit research on leptospirosis transmission model for publication in peer-reviewed journal.	Feb 2011
3 Translating research knowledge into policy and interventions		
3a	Investigate possible next steps for WHO to use LERG burden of disease estimate in knowledge translation.	To be determined
3b	Discuss with EVIPNet/WHO whether country policy situation analyses are required.	To be determined
4 Communication and dissemination of findings to key government staff, researchers and policy-makers		
4a	Submit policy platform paper to the Public Library of Science Neglected Tropical Disease Journal (PLoS NTD).	Nov 2010

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