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

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World Health Organization

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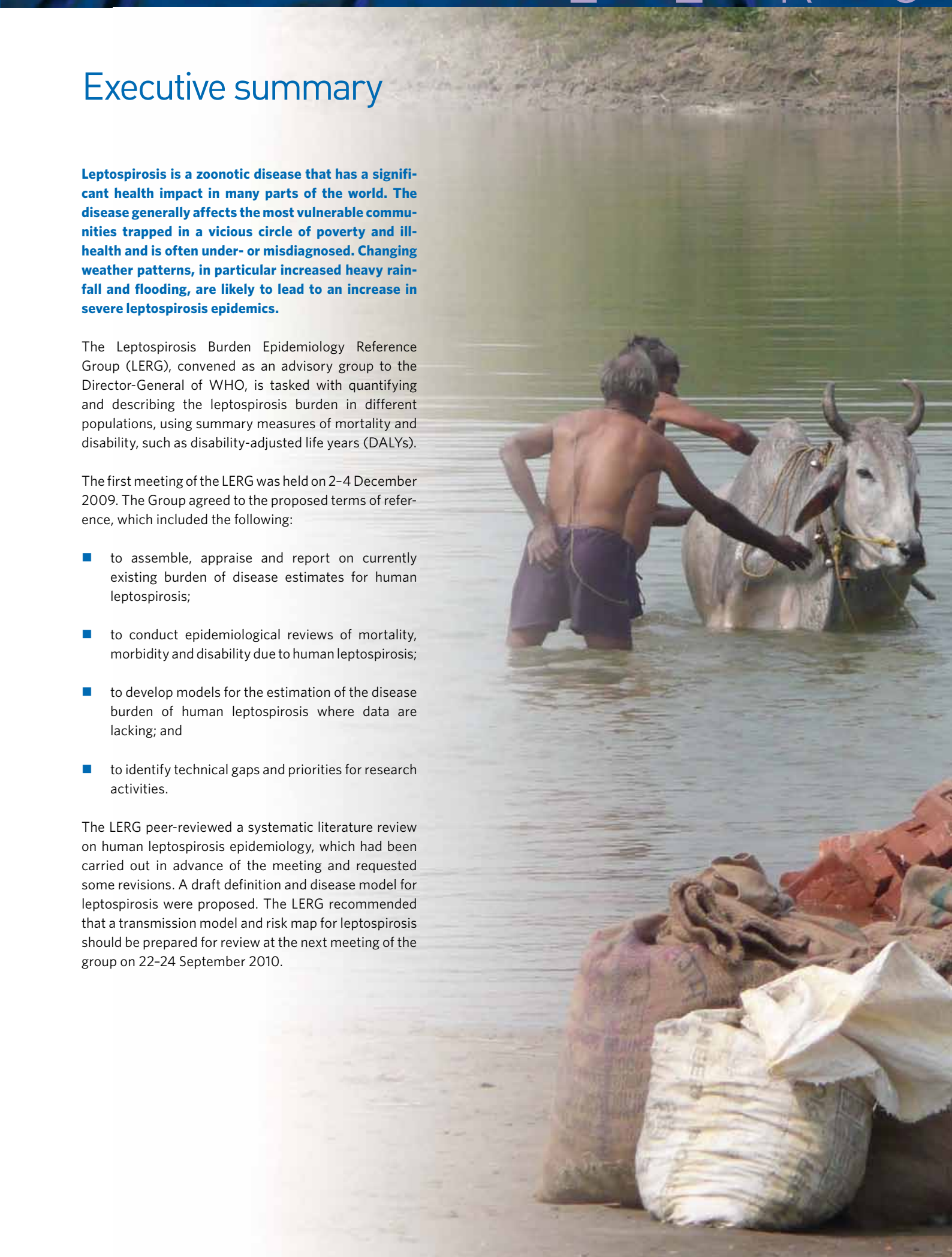
This report is available in electronic format from **www.who.int/zoonoses/diseases/lerg/en**

Acronyms and abbreviations

AFI	acute febrile illness
DALY	disability-adjusted life year
ECDC	European Centre for Disease Prevention and Control
ELISA	enzyme-linked immunosorbent assay
FERG	Foodborne Disease Epidemiology Reference Group
FOS	WHO Department of Food Safety and Zoonoses
GBD	global burden of disease
GBD 2004	WHO Global Burden of Disease Study, 2004 update
GBD 2005	Global Burden of Disease, Injuries and Risk Factors Study, 2005
GLR	grey literature review
ICD	International Classification of Diseases
IFA	immunofluorescence assay
LERG	Leptospirosis Burden Epidemiology Reference Group
MAT	microscopic agglutination test
MDG	Millennium Development Goal
NGO	nongovernmental organization
NIH	National Institutes of Health (United States)
NTD	neglected tropical disease
OIE	World Organisation for Animal Health
ORD	Office of Rare Diseases
PCR	polymerase chain reaction
SR	systematic review
UN	United Nations
WHO	World Health Organization
YLL	years of life lost
YLD	years lived with a disability

Executive summary



Leptospirosis is a zoonotic disease that has a significant health impact in many parts of the world. The disease generally affects the most vulnerable communities trapped in a vicious circle of poverty and ill-health and is often under- or misdiagnosed. Changing weather patterns, in particular increased heavy rainfall and flooding, are likely to lead to an increase in severe leptospirosis epidemics.

The Leptospirosis Burden Epidemiology Reference Group (LERG), convened as an advisory group to the Director-General of WHO, is tasked with quantifying and describing the leptospirosis burden in different populations, using summary measures of mortality and disability, such as disability-adjusted life years (DALYs).

The first meeting of the LERG was held on 2–4 December 2009. The Group agreed to the proposed terms of reference, which included the following:

- to assemble, appraise and report on currently existing burden of disease estimates for human leptospirosis;
- to conduct epidemiological reviews of mortality, morbidity and disability due to human leptospirosis;
- to develop models for the estimation of the disease burden of human leptospirosis where data are lacking; and
- to identify technical gaps and priorities for research activities.

The LERG peer-reviewed a systematic literature review on human leptospirosis epidemiology, which had been carried out in advance of the meeting and requested some revisions. A draft definition and disease model for leptospirosis were proposed. The LERG recommended that a transmission model and risk map for leptospirosis should be prepared for review at the next meeting of the group on 22–24 September 2010.

1. Introduction

The first meeting of the Leptospirosis Burden Epidemiology Reference Group (LERG) was held on 2–4 December 2009. The participants are listed in Annex 1. The meeting was opened by Dr Jørgen Schlundt, Director of the Department of Food Safety and Zoonoses (FOS) of the World Health Organization (WHO). Dr Bernadette Abela-Ridder welcomed the participants on behalf of WHO, presented a draft agenda for the meeting (see Annex 2), explained procedural issues and outlined the expected outputs of the meeting.

Dr Arthur Reingold was elected as Chair of the meeting and Dr Wendy Harrison as Rapporteur.

1.1. Objectives and expected outcomes of the meeting

The objectives of the meeting were:

- to formally adopt the terms of reference and working procedure of the Group;
- to receive a briefing on global burden of disease methodology;
- to review and appraise a recent systematic review of the published literature on human leptospirosis;
- to review and appraise a review of the grey literature on human leptospirosis;
- to develop a definition and disease model for leptospirosis;
- to advise the WHO secretariat on the next steps and timeframe for estimation of the leptospirosis disease burden; and
- to advise the WHO secretariat on communication and fund-raising efforts.

It was also hoped that the meeting would raise awareness of the need for intersectoral and interdisciplinary input to the development of policies for the control of leptospirosis and other zoonotic diseases of public health importance (see Box 1).

Box 1. Intersectoral and interdisciplinary approaches to control of zoonotic diseases

Leptospirosis – like other zoonoses – has a complex transmission cycle. Prevention and sustainable control require strong partnerships between human and animal public health sectors and a number of other disciplines like water and sanitation management.

These partnerships need to include international organizations, nongovernmental organizations (NGOs), national governments, civil society and donors. Disease control activities by all partners should be coordinated, to reduce the number of monitoring, reporting and delivery systems, and to avoid duplication of efforts and fragmented results.[1]

Strategies that build and strengthen existing efforts to improve intersectoral coordination and communication should be promoted, in both disease-specific initiatives and horizontal programmes. The LERG includes individuals and organizations representing different sectors and disciplines, and is well placed to promote policy development that recognizes the need to generate and maintain appropriate intersectoral links.

2. Background to the current meeting

In October 2006, WHO convened an informal consultation to discuss how the burden of disease associated with human leptospirosis could be assessed, recognizing that surveillance data were inadequate in this regard.[2] One major outcome of that consultation was the establishment of the Leptospirosis Burden Epidemiology Reference Group, to implement the recommendations of the consultation and to estimate the global burden of leptospirosis.

2.1. LERG composition

The members of the LERG were appointed by the Director-General of WHO, following a public call in the scientific press. The LERG comprises ten advisors, who serve in their individual capacity, not representing any specific institution or Member State. The members of the group have been selected to ensure a broad skill base, including expertise in burden of disease methodology, epidemiology, clinical laboratory techniques, infectious diseases, zoonoses, disease modelling and international public health. The selection of advisors also took into account the need for geographical and gender balance.

In addition, resource advisors may be invited to participate in LERG meetings, to provide specific ad hoc advice, as needed.

The World Organisation for Animal Health (OIE) is a key partner in the work of the LERG, providing expertise on the subject and allowing the work to advance in a more complete and intersectoral way. The WHO secretariat is based within FOS, and works in partnership with other WHO clusters and departments at Headquarters and in the regional offices (see Box 2). The secretariat's role is to facilitate, coordinate, guide and monitor the work of the LERG, and to provide logistic, administrative and technical support.

Box 2. Partnering with other WHO Regions, clusters and international organizations

African Region
Region of the Americas
South-East Asia Region
European Region
Eastern Mediterranean Region
Western Pacific Region

Clusters at WHO Headquarters

- Health, Security and Environment Cluster
- HIV, TB, Malaria and Neglected Tropical Diseases Cluster
- Health Action in Crisis Cluster

International organizations

- Food and Agriculture Organization of the United Nations (FAO)
- OIE

2.2. LERG terms of reference and functions

The LERG is an expert advisory group to the Director-General of WHO on the epidemiology of leptospirosis.

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

- to provide estimates for human leptospirosis worldwide, according to age and sex of patients and by WHO region;
- to encourage countries to use burden of disease 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.

The functions of the LERG are:

- to assemble, appraise and report on existing burden of disease estimates for human leptospirosis;
- to conduct epidemiological reviews for mortality, morbidity and disability due to human leptospirosis;
- to develop models for the estimation of the disease burden of human leptospirosis, where data are lacking;
- to use the models to develop user-friendly tools for burden of disease studies at country level;
- to identify technical gaps and priorities for research activities; and
- to make recommendations to WHO regarding the establishment of LERG task forces and other means of addressing scientific and technical matters.

It is expected that the efforts of the LERG will ultimately lead to:

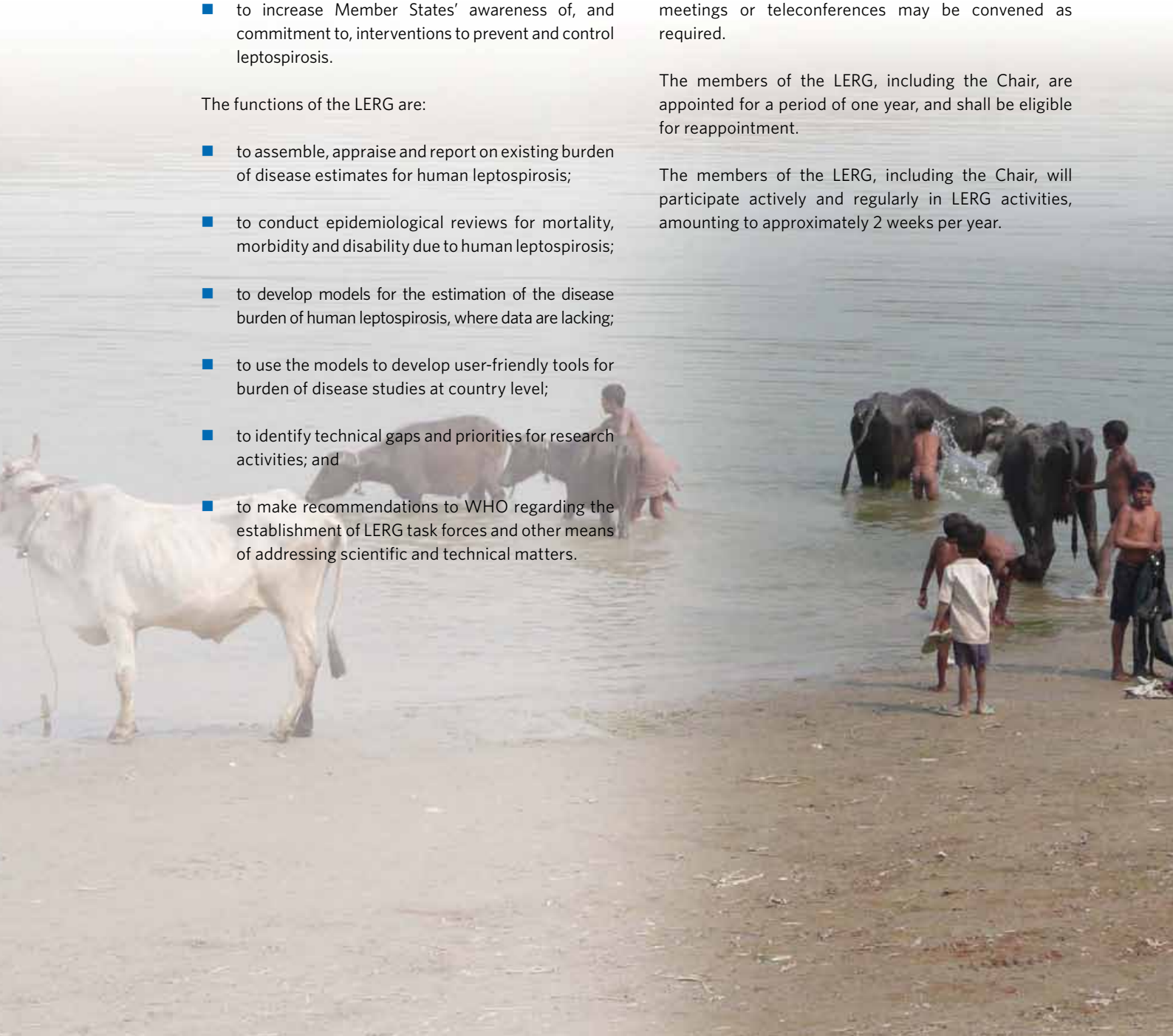
- the production of a global report and atlas of the disease burden of human leptospirosis;
- the identification of research gaps that need to be addressed;
- a contribution to estimates for human leptospirosis in the Global Burden of Disease (GBD) study for the year 2005.

2.3. Working procedures

The LERG will convene once or twice a year; additional meetings or teleconferences may be convened as required.

The members of the LERG, including the Chair, are appointed for a period of one year, and shall be eligible for reappointment.

The members of the LERG, including the Chair, will participate actively and regularly in LERG activities, amounting to approximately 2 weeks per year.



3. Epidemiology of leptospirosis

Leptospirosis is a zoonotic disease that has a significant health impact in many parts of the world, particularly the Americas and Asia. It can present in life-threatening forms, such as Weil's disease and severe pulmonary haemorrhage syndrome. Recent estimates indicate that there are more than 500000 cases of leptospirosis each year worldwide.[4] The majority of reported cases have severe manifestations, for which mortality is greater than 10%. Furthermore, studies in Thailand have shown that leptospirosis may represent up to 20% of febrile illness of unknown origin.[5]

Epidemics of leptospirosis often occur during seasonal heavy rainfall and flooding[6] and are associated with extreme weather events, as exemplified by the outbreak in the Philippines in 2009.[7] The Intergovernmental Panel on Climate Change has suggested that many regions are likely to suffer heavier and more frequent flooding as a consequence of increased frequency of heavy precipitation linked to global climate change.[8] As a result, leptospirosis can be expected to increase in importance.[9,10,11]

In Latin America, the two primary risk groups for leptospirosis are urban slum-dwellers and subsistence farmers. The relative proportions of these risk groups in the population vary from country to country as a result of differences in underlying conditions of poverty. There is often a constant force of infection as a result of infected animal reservoirs, including rodents, livestock and dogs. In other regions, such as Asia, the disease is mostly associated with outbreaks following flooding, as occurred in Thailand in August 2006. Occupational exposure is also common. In Europe, leptospirosis has shifted from being an occupational disease to one associated with recreational activities, particularly water sports and travel.

At present, one billion of the world's population live in slum settlements; this number is expected to double in the next 25 years.[12] The growth of large urban populations, who are marginalized and unable to access basic medical services, may have a significant impact on the leptospirosis disease burden.[8]

3.1. Rationale for WHO action

Surveillance and reporting of leptospirosis vary significantly from country to country, depending on the surveillance capacity, whether reporting of the disease is mandatory, and whether the necessary laboratory infrastructure is available to perform the standard, but technically demanding, diagnosis. The disease is notifiable in most countries of the Western Pacific Region; for example, in China leptospirosis has been notifiable since 1955. However, in other parts of Asia, and in most African and some Latin American countries, the disease is not notifiable. There is a significant lack of information on leptospirosis, especially in Africa, where few, if any, countries report the disease and little research has been performed to assess the potential disease burden. The disease in animals, with specific criteria, is notifiable to the OIE.

Despite the lack of reliable incidence data, increasing reports of outbreaks suggest that leptospirosis is emerging as an important public health problem.

Vulnerable populations are the most severely affected by leptospirosis, which – although it occurs throughout the world – remains a neglected disease. The neglected tropical diseases (NTDs) have been recognized as having a profound impact on health and productivity, particularly in poor rural communities.[11] Occupational exposure, often of the main wage earner, can significantly reduce family income; this situation is often compounded by the fact that other members of the family are unable to work because they have to care for the patient. Medical costs can push families into debt. In addition, as a zoonotic disease, leptospirosis reduces livestock productivity, compromising food security and further reducing income, thus trapping populations in a vicious circle of poverty and disease. Control of leptospirosis, and other neglected tropical diseases, could therefore have a broad impact on development in general and on progress towards the Millennium Development Goals (MDGs), particularly MDG1 (eradication of extreme poverty and hunger) and MDG6 (combating of HIV/AIDS, malaria and other diseases) (see Box 3).[12]

Box 3. Millennium Development Goals

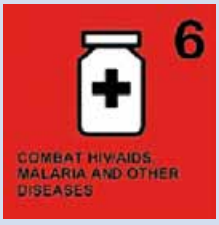
MDG1: Eradicate extreme poverty and hunger

Indicators

Target 1: Halve, between 1990 and 2015, the proportion of people whose income is less than $1 a day.

Target 2: Achieve full and productive employment and decent work for all, including women and young people.

Target 3: Halve, between 1990 and 2015, the proportion of people who suffer from hunger.



MDG 6: Combat HIV/AIDS, malaria and other diseases

Target 1: Have halted by 2015 and begun to reverse the spread of HIV/AIDS.

Target 2: Achieve, by 2010, universal access to treatment for HIV/AIDS for all those who need it.

Target 3: Have halted by 2015 and begun to reverse the incidence of malaria and other major diseases.

4. The global burden of disease

Even the best surveillance systems cannot capture all cases of disease, and leptospirosis will remain underestimated without a thorough analysis of the burden of disease. The term "burden of disease" is widely used to describe a variety of efforts that seek to quantify health outcomes attributable to specific diseases. The description of the disease burden in this context follows the principles used in the original Global Burden of Disease Study of 1990 and the Global Burden of Disease, Injuries and Risk Factors Study[13] (see Box 4). Global burden of disease analyses provide a comprehensive and comparable assessment of mortality and loss of health due to diseases, injuries and risk factors in all regions of the world, quantifying mortality, morbidity and disability complications in a single summary measure, the disability-adjusted life year (DALY). The information obtained to construct this summary measure can be used to describe disease and syndrome occurrence, magnitude of risk factors, and economic or cost burden.

The parameters required for calculation of DALYs are:

- number of deaths from acute disease and all sequelae;
- incidence and age at onset of acute disease and all sequelae;
- average duration of acute disease and all sequelae;
- remission rates of acute diseases and all sequelae;
- disability weight for acute disease and all sequelae (reflects the severity of disease on a scale from 0 [perfect health] to 1 [equivalent to death]).

If these data are not available, models may be developed to provide feasible and validated estimates. If modelling does not yield accurate and representative results, country studies may be performed as a last resort.

Box 4. Global burden of disease methodology[14]

Health policies should be based on accurate and meaningful health information. Much of the information collated, however, cannot be directly translated into policy. Health data from routine statistics or epidemiological studies are often fragmented, frequently concentrate on fatal health outcomes, and may not be complete. Studies that investigate particular conditions may exaggerate mortality, often because several co-existing pathologies actually contribute to – and compete for – the cause of death. Moreover, traditional statistics use a variety of different measures, which do not permit direct comparisons of the cost-effectiveness of different interventions.

The GBD approach addressed these problems and proposed a single metric, the disability-adjusted life year (DALY). DALYs reflect the years of life lost to premature death (YLL) and the years lived with disability (YLD) taking account of varying degrees of severity, making time itself the common metric for death and disability. The DALY is therefore a health gap measure, equating to one year of healthy life lost. DALYs for a disease or health condition are calculated as the sum of YLL in the population and YLD for incident cases of the health condition.

YLL is calculated as the number of deaths at each age multiplied by the standard life expectancy at the age at which death occurs. To estimate YLD for a particular cause for a particular time period, the number of incident cases in that period is multiplied by the average duration of the disease and a disability weight that reflects the severity of the disability experienced in the particular disease state on a scale from 0 (perfect health) to 1 (dead). DALYs are internally consistent and disaggregate co-morbidity, hence decoupling epidemiological estimates from advocacy. A particular strength of the GBD approach is that it permits disability associated with disease to be estimated, which is particularly important where mortality is low but disabling long-term sequelae may arise. Disadvantages of the DALY approach include the need for strong value judgements on disability and age, thus placing emphasis on death and morbidity in young adulthood. Burden of disease studies include elements of disease modelling, risk assessment and burden projections, which inform policy-makers about the likely future nature of disease burdens, enabling preventive strategies to be targeted accordingly. They should, where possible, capitalize on existing information and translate it into a single measure.

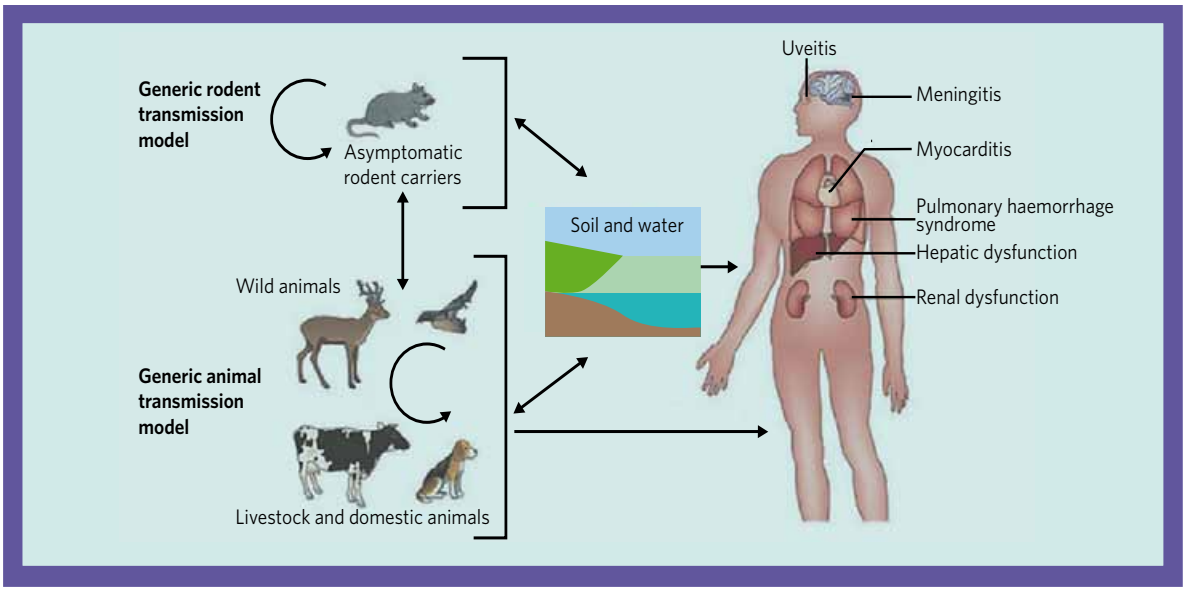
The LERG wished to take advantage of the increased awareness and expertise that has arisen from the various global burden of disease studies. In recent years, a consortium led by the Institute for Health Metrics and Evaluation (IHME) at the University of Washington, with the collaboration of a number of key institutions, including WHO, Harvard University, Johns Hopkins University, and the University of Queensland, has been revising global burden of disease estimates for nearly 160 causes for the year 2005 (GBD 2005). The consortium is also revising the disability weights and adding new risk factors. WHO's global burden of disease updates for 1999–2004 have been incremental, and have not included all causal factors. New data, methods and estimates are expected to provide an opportunity to stimulate the further development of estimation methods and generate improved official statistics. There are small differences between the acceptance criteria of the WHO-generated figures and the GBD 2005 study (to be completed in late 2010), primarily as a result of differences in interpretation of causality of conditions. The estimates generated by LERG will inform in both the WHO and the GBD 2005 studies.

5. Approaches to estimation of the global burden of leptospirosis

5.1. Definition of leptospirosis

Leptospirosis is a bacterial disease caused by *Leptospira* spp. and occurs all over the world. It has multiple modes of transmission and presentations (see Figure 1) and presents a **number of diagnostic challenges, which make disease definition problematic.**

Figure 1. The transmission cycle of leptospirosis (image reproduced with the permission of the authors[15])



Leptospirosis is clinically defined as an illness characterized by fever, headache and myalgia, and may cause jaundice, acute renal failure, bleeding including pulmonary haemorrhage syndrome, meningitis, myocarditis and uveitis.

The LERG agreed a definitive case definition, as follows: Symptoms consistent with leptospirosis *and* any one of the following:

- a 4-fold increase in microscopic agglutination test (MAT) titre between acute and convalescent serum samples;
- a single MAT ≥ 1:400 (or single MAT ≥ 1:100 in non-endemic regions);
- isolation of *Leptospira* spp. from a normally sterile site;
- detection of *Leptospira* spp. in clinical samples using histological, histochemical or immunostaining techniques; or
- *Leptospira* DNA detected by a method based on the polymerase chain reaction (PCR).

The LERG also agreed a presumptive case definition, as follows:

Symptoms consistent with leptospirosis *and* any one of the following:

- presence of IgM antibodies, as shown by enzyme-linked immunosorbent assay (ELISA) or dipstick; or
- presence of IgM or IgG antibodies, as shown by immunofluorescence assay (IFA).

The Group discussed whether it would be appropriate to include a positive IFA as a criterion for the definitive diagnosis; however, it considered that a comprehensive review of the literature was required to determine whether this diagnostic technique is applicable in all settings.

5.2. Disease model

The disease model, or outcome tree, depicts the natural history of the disease in diagrammatic form. In this case, it shows the acute and chronic disease states that an infection with leptospirosis may cause, as well as death, and helps define the different outcomes for which burden of disease estimates need to be derived. These include a number of potential complications or sequelae of leptospirosis that can produce a subsequent condition associated with morbidity, disability or mortality. In developing the disease model, the aspects listed below need to be considered.

Overall number of sequelae

In order to ensure that estimates can reasonably be derived, most groups working on burden of disease studies have limited themselves to a manageable number of sequelae. The LERG agreed to select a maximum of three sequelae.

Frequency and duration of sequelae and contribution to DALYs

The LERG agreed to focus on the sequelae that occur most frequently in patients with leptospirosis. The LERG also assessed and evaluated the contribution that the different sequelae make to the overall burden of disease, in terms of severity and duration. For example, uveitis occurs in relatively few cases, has been reported in only a few countries, is of variable duration, and would have a relatively low disability weight. In addition, the LERG considered that, in many settings, it was often difficult to confirm whether leptospirosis was the causal agent of uveitis. The LERG therefore decided not to include uveitis as a sequela in the leptospirosis disease model. For similar reasons, it was also decided not to include meningitis, myocarditis or hepatic dysfunction.

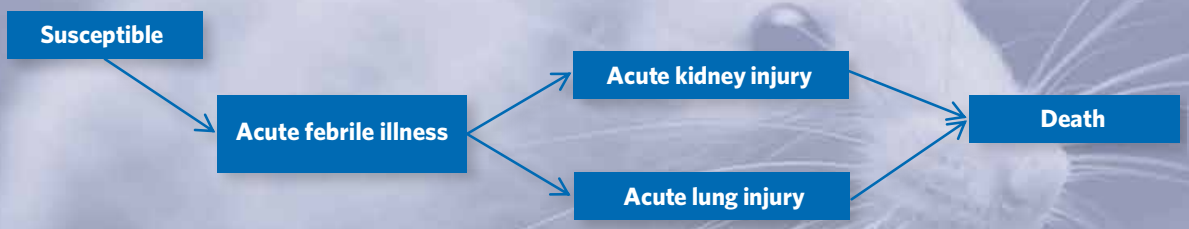
Disaggregating syndromes

Groups of clinical signs that are aggregated into syndromes, e.g. Weil's syndrome (includes nephritis, pneumonitis or myocarditis with or without hepatic insufficiency), need to be disaggregated and the conditions described individually to ensure that an adequate disability weight can be assigned. Subsequently, the sequelae associated with the largest disability can be identified individually and included in the leptospirosis disease model.

Multiple co-existing sequelae and synergy

Determination of the cause of death often does not take into account co-morbidities or potential synergies between co-existing sequelae. This is a criticism often levelled at the use of the DALY as a disease burden metric.16 The LERG considered that, where multiple sequelae exist simultaneously, only those with the highest disability weight should be included in estimation of DALYs. The Group also did not try to include any estimation of the impact of negative synergies between sequelae The above criteria were used to identify sequelae that would significantly contribute to the burden of disease. The working model that was agreed on is shown in Figure 2.

Figure 2. Working disease model for leptospirosis



5.3. Required inputs

In order to obtain an accurate estimate of disease burden for leptospirosis, data are needed for all the parameters mentioned in section 4. A number of different methods are proposed to obtain the necessary inputs.

5.3.1. Systematic review of existing evidence

5.3.1.1. Systematic review of the published literature

The group assessed the results of a systematic review of the literature on human leptospirosis, which was carried out in 2009 by the Gonçalo Moniz Research Centre, Oswaldo Cruz Foundation/Brazilian Ministry of Health, Salvador, Bahia, Brazil. The objectives of the systematic review were (1) to produce a comprehensive, standardized tabulation of available data on disease incidence, mortality estimates and disease sequelae, and (2) to identify gaps in information to be addressed through modelling or future research.

The review had searched 29 databases (Annex 3. List of databases used in the systematic review) to identify reports published between January 1970 and October 2008 that included 50 or more cases of human leptospirosis.

A total of 12 033 reports on leptospirosis were identified in English, French, Italian, Portuguese or Spanish (see Figure 3). The levels of evidence and the inclusion and exclusion criteria were modified for leptospirosis using a the standard WHO review protocol for inclusion and appraisal of scientific evidence to estimate the burden of disease were adapted for use in the review (available on request). These were then categorized as high, moderate or low risk of bias, in accordance with the criteria.

In brief the steps of the analysis are as follows.

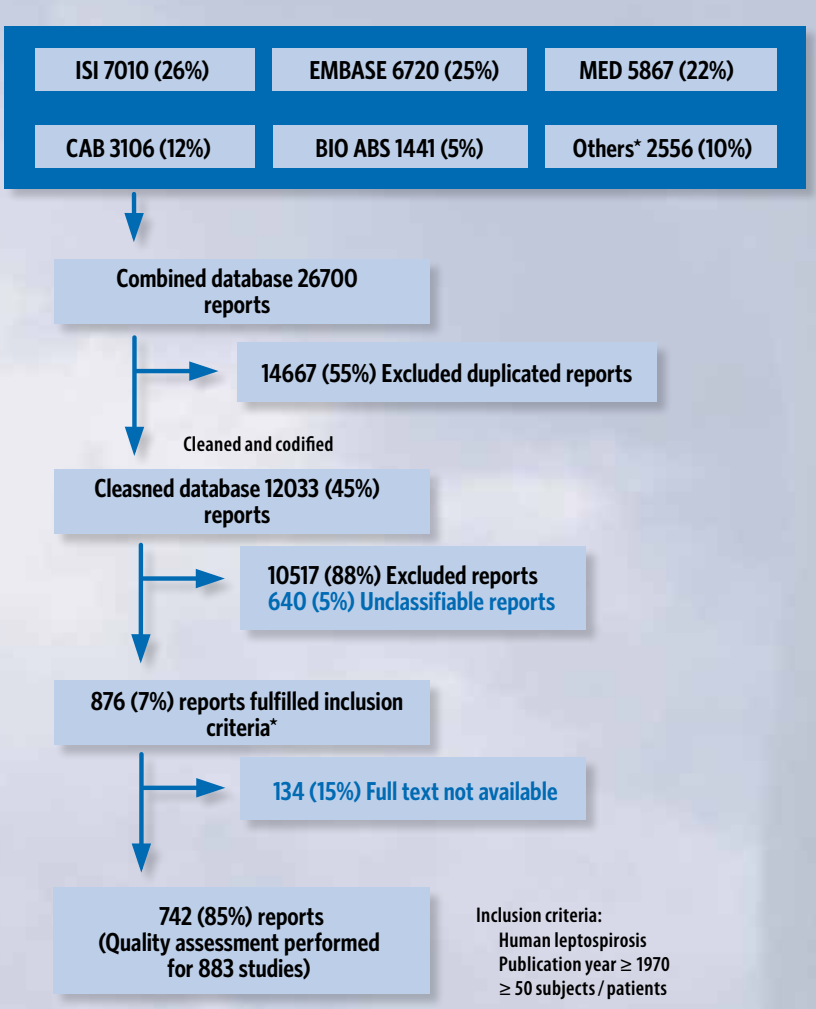
Step 1. Analysis of the level of evidence provided.
Step 2. Assessment against general inclusion and exclusion criteria.
Step 3. Assessment against study quality criteria that evaluated:

a. sample and setting;
b. measurement;
c. bias;
d. data analysis and results

for the following

a. disease incidence studies;
b. disease sequelae studies;
c. disease prevalence studies of leptospirosis among acute febrile illness cases;
d. prevalence of prior infection studies;
e. randomized controlled trials.

Figure 3. Summary of yield of literature search, filtered by inclusion and exclusion criteria and quality criteria



In all, 65 studies were identified as having a low or moderate risk of bias; these are listed by region in Table 1.

Table 1. Summary distribution of studies with low, moderate and high risk of bias according to WHO GBD regions

Region *	Study designs				Total
	Disease Incidence	Disease preval.	Disease sequelae	Preval. of prior infection	
	No. of Low-Moderate risk of bias studies / Total studies				
High Income Asia Pacific (Region 1)	0/3	0/5	0/2	0/3	**0/13**
Central Asia (Region 2)	0/1	—	—	—	**0/1**
East Asia (Region 3)	0/3	0/1	0/2	0/2	**0/8**
South Asia (Region 4)	2/42	2/40	1/23	3/22	**8/127**
Southeast Asia (Region 5)	1/33	2/39	2/15	3/21	**9/108**
Australasia (Region 6)	1/13	0/1	...	1/12	**2/26**
Caribbean (Region 7)	1/62	1/7	0/8	7/23	**9/100**
Central Europe (Region 8)	0/12	0/2	0/4	0/5	**0/23**
Eastern Europe (Region 9)	0/7	—	—	—	**0/7**
Western Europe (Region 10)	3/73	0/5	1/20	3/37	**7/135**
Andean Latin America (Region 11)	0/13	6/11	0/1	3/10	**9/35**
Central Latin America (Region 12)	1/29	0/7	0/3	5/22	**6/61**
Southern Latin America (Region 13)	0/11	0/3	0/1	1/7	**1/22**
Tropical Latin America (Region 14)	2/48	0/5	4/33	5/27	**11/112**
North Africa/Middle East (Region 15)	0/3	0/8	0/1	0/4	**0/16**
High Income North America (Region 16)	0/20	0/1	0/2	0/11	**0/34**
Oceania (Region 17)	2/11	0/11	0/3	0/3	**2/27**
Central Sub-Saharan Africa (Region 18)	—	0/1	—	1/2	**1/3**
East Sub-Saharan Africa (Region 19)	0/5	0/1	—	0/4	**0/10**
Southern Sub-Saharan Africa .(Region 20)	—	—	—	0/2	**0/2**
West Sub-Saharan Africa (Region 21)	0/1	0/3	0/1	0/4	**0/8**

* See Annex 5. for complete list of countries/territories in WHO GBD regions.

Disease incidence were obtained from the following WHO regions: South Asia (India); South east Asia (Seychelles); Australasia (New Zealand); Caribbean (Barbados); Western Europe (Ireland and France); Central Latin America (Panama); Tropical Latin America (Brazil); and Oceania (New Caledonia). Disaggregated data by study period was available for Barbados, Brazil, France, and New Caledonia.

Disease incidence data was classified by i) disease incidence from surveillance data; and ii) disease incidence from outbreaks (an outbreak represents the occurrence, in a community or region, of cases of illness with a frequency clearly in excess of normal expectancy. Outbreaks may be cyclic. Incidence rates from outbreaks can be expected to be higher than the ones obtained using surveillance data).

In view of the poor global coverage of the literature, the LERG considered that the inclusion criteria should be revised and the systematic review re-run. Additional methods should also be explored to provide the appropriate worldwide data necessary for the estimation of the burden of disease. The LERG compared the suggested WHO review protocol with the level of evidence applied in the systematic review, in order to identify opportunities to broaden the inclusion criteria.

For incidence and prevalence data, the suggested WHO review protocol levels of evidence are as follows.

Level I – nationally representative incidence and prevalence studies;
Level II – community-based incidence and prevalence studies;
Level III – large cohort studies;.
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.

In the WHO review protocol, studies fulfilling the criteria for levels I to III are included for further analysis. Reassessment of the leptospirosis studies identified in the systematic review found no further studies that could be classified as level I-III. Ten further studies could be classified as level IV: one outbreak study and nine studies in endemic settings, of which six were considered to be nationally representative and four representative of a subnational region. The geographical distribution of these ten studies is given in Table 2.

Table 2. Studies fulfilling review protocol level of evidence IV criteria for disease incidence and prevalence

Country or territory	Diagnosis	Year
Trinidad and Tobago	MAT 1:800	1977–1982
New Caledonia	NA	1983–1985
Seychelles	Autopsy, serological test.	1988–1990
Barbados	MAT (1:50), ELISA	1980–1991
India	MAT 1:200	1987–1994
Seychelles	PCR, MAT (seroconversion 1:100, fourfold rise)	1995–1996
Peru	ELISA, ISOLATION,MAT	2003–2004
Brazil	MAT, ELISA	1996
Thailand	MAT (1:400, fourfold rise)	2003–2004
French Polynesia	PCR, ELISA, MAT (seroconversion, 1 significant titre)	2004–2005

The LERG decided that inclusion of these level IV studies would assist in assessing the leptospirosis disease burden. However, the LERG identified a number of concerns, including the need to ensure that appropriate denominator data were available for estimation of incidence, and that the data were representative of the population, especially in studies based in health care facilities. The broader problem of under-reporting was also considered a potential issue. Concerns were expressed over the use of seroprevalence data alone, since these reflect exposure and not active disease.

The LERG considered that the inclusion of level IV surveillance studies would be appropriate if the data could be validated using existing community-based studies and if a calculated adjustment factor could be used to give an accurate approximation of the denominator. Triangulation with other data sources would also improve accuracy. For example, authors of published studies that do not entirely fulfil the review protocol level of evidence criteria could be contacted to enquire if there were any additional unpublished community-based data. Or researchers might be asked to submit appropriate unpublished data. In this way, a more complete data set could be produced for the burden of disease estimates. In addition, where available, data on other diseases of similar severity in the same geographical location may give some indication of hospital admission rates, to assist in the interpretation of health facility-based incidence and prevalence studies.

Triangulation of data from studies of different types, e.g. health facility studies, passive surveillance and mortality reporting, was also suggested as a way of increasing accuracy and confidence in disease burden estimates. Uneven data quality was identified as a potential pitfall; however, solutions have been developed to address this in other burden of disease studies, which may prove useful for this study.

The development of transmission and risk models (see sections 5.3.2. and 5.3.3.) was considered to be very useful for estimating the disease burden in regions where few or no data exist or where studies are of poor quality. These models could be validated using existing studies.

The LERG was concerned at the geographical bias of the data, in particular because large regions were not represented. This was partly due to the limited number of selected languages used in the literature search: 118 reports identified as relating to human leptospirosis were not included as they were in other languages. The LERG decided that these studies should be translated and assessed for inclusion. This may go some way to addressing the regional gaps in the data.

For sequelae, the review protocol 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.

Table 3. Studies fulfilling review protocol level of evidence IV criteria for sequelae

Country or territory	Diagnosis	Year
New Caledonia	NA	1983–1985
India	MAT 1:200	1987–1994
West Indies	ELISA, MAT	1989–1993
Seychelles	PCR, MAT (seroconversion 1:100, fourfold rise)	1995–1996
Brazil	MAT, ELISA	1996
Peru	ELISA, isolation, MAT	2003–2004

No further studies were identified that fulfilled the criteria for levels I to III. However, six further studies with more than 50 subjects could be classified as level IV: three were nationally representative and three were representative of a subnational region. The geographical distribution of these studies is given in Table 3.

The LERG considered that inclusion of these studies would be beneficial; however, some concerns were identified 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 considered 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.

5.3.1.2. Systematic review of grey literature

Grey literature is any material not formally published by commercial publishers or in peer-reviewed journals, and includes reports, fact sheets, conference proceedings and other relevant documents from institutions, organizations and government agencies. A grey literature review was conducted by WHO[a] in collaboration with the Gonçalo Moniz Research Centre, Brazil. The aim of the review was to complete the epidemiological data on human leptospirosis and contribute to the global burden of disease estimate for human leptospirosis.

a Review carried out by Reina Sikkema and Tineke Kramer (Netherlands), Eleni Pantiori (Greece) and Faisal Abbas (Pakistan).

A systematic Internet search was conducted for national morbidity and mortality data on human leptospirosis cases from 1970 to October 2008. Government ministry of health and agriculture Websites from 193 WHO Member States were consulted, and the Google search engine was used to find other relevant sites. All numerical data found were entered into a database. The researchers are in the process of identifying additional international sources e.g. the European Centre for Disease Prevention and Control (ECDC), OIE, Institut Pasteur, Leptonet, and the Global Infectious Disease and Epidemiology Network (GIDEON), and national sources other than the ministries of health and agriculture.

The review did not locate any targeted grey literature in 142 of the 193 WHO Member States. No epidemiological data were found for the African and Eastern Mediterranean Regions; however, a relatively high number of case reports were found for South-East Asia, South America, Europe and the Western Pacific Region. Differences were noted in the stratification levels used by countries to describe the available data.

To supplement these data, in November 2009 a questionnaire was sent out to 41 ministries of health to obtain government data that may not be available online (see Annex 4). At the time of the LERG meeting, responses had been received from Bangladesh, India, Sri Lanka, Thailand and Turkey. Further responses are expected.

The grey literature review required a large investment of time and effort, and has so far yielded a relatively low number of quantitative reports. However, the LERG considered that the inclusion of the grey literature was useful for identifying data gaps . In addition, these data could be used to check the plausibility of data collected using other methods and to validate epidemiological models.

The LERG agreed to continue to collate any information received from the remaining 38 Member States in response to the questionnaire, and to complete the review of data from international and national sources. It would not, however, proceed further with the Internet search for data from ministries of health and agriculture.

The LERG members agreed to contribute data on human leptospirosis available to them through their networks and their own unpublished data.

5.3.1.3. Systematic review of existing databases

A number of existing databases may provide valuable

data for the calculation of DALYs. WHO maintains the largest database of cause-of-death registration data in the world. Since the 1950s, countries have been reporting to WHO on their causes of death; currently, over 130 countries provide such data, classified according to the International Classification of Disease (ICD).[17] The quality and completeness of the data vary, but time series are consistently available for both developed and developing countries, allowing detailed analyses of causes.

Where data on incidence are not easily available, they may be derived from mortality data from vital registration databases. In the WHO Global Burden of Disease Study, 2004 update (GBD 2004), incidence rates for cancers in some regions were imputed from mortality rates, using incidence:mortality ratios from countries with cancer registries[18]. The incidence of first-ever stroke was imputed from country-level stroke mortality estimates, using a model that took into account 28-day case-fatality rates and average long-term risk of death for 28-day survivors. Incidence of injury was generally estimated from mortality rates using incidence:mortality ratios derived from hospital and emergency department data from a number of countries. Although it is not always easy to estimate case-fatality rates for leptospirosis in a population, as data often come from health care facility studies, it would be useful to examine whether case-fatality rates could be used to estimate leptospirosis incidence.

Other disease burden epidemiology groups have used existing databases to provide valuable information on health and non-health predictor variables that can be used to model missing data.[19] The Foodborne Disease Burden Epidemiology Reference Group (FERG) carried out a systematic search of all publicly available databases (e.g. from United Nations organizations, other international agencies and NGOs) to find country data on potential predictor variables applicable to food- and waterborne diseases. The databases had to comply with agreed criteria, for example, that they were validated and based on solid epidemiological information, and that the country data had been approved by the country in question. The FERG recognized that these national data did not capture within-country variation. There may be opportunities for the LERG to capitalize on this work to identify predictor values that could be applicable to leptospirosis and provide inputs for risk mapping of this disease

5.3.2. Modelling approaches

5.3.2.1. Risk mapping

The risk of leptospirosis in a population can be predicted on the basis of a number of environmental and socioeconomic factors (see Box 5). The LERG considered that risk maps would be a useful predictive mechanism, given the lack of appropriate epidemiological data that are globally representative.

Box 5. Risk factors for leptospirosis

- Increased rainfall and flooding
- Inadequate floodwater drainage
- Poor housing or slum dwellings
- Proximity to open sewers[20]
- Overcrowding
- Contact with animals
- Poor hygiene and sanitation
- Workplace exposure[21]

WHO and others have produced risk maps for a number of diseases, including malaria, neglected tropical diseases and dengue fever.[22] Mapping the risk of leptospirosis would allow regions to be categorized on the basis of defined risk profiles. Transmission models could then be developed to reflect regional differences in the force of infection. Existing climatic data and data collected for Demographic and Health Surveys[23], which are currently carried out in 84 countries, could be used to develop the risk map. Recognized socioeconomic metrics, such as gross national income[24] and the human development index,[25] could also be included.

A project conducted in the context of the work of the FERG examined dozens of potential predictor variables for mortality from food- and waterborne diseases. The predictors included child mortality, vaccine coverage, and health personnel coverage, but also non-health variables from the sectors of agriculture, trade, the environment, population, nutrition, consumption habits and animal health. The modelling exercise found that non-health variables were stronger predictors of foodborne disease than many classical health indicators. Non-health indicators are likely to be a useful new tool in the effort to estimate the global burden of mortality from potentially foodborne infections. If validated for leptospirosis, these indicators could also be used in the development of a risk model.

Data on the incidence of acute febrile illnesses (AFIs), collected for other disease control and surveillance programmes, may also be used where the proportion of AFI attributable to leptospirosis is known, for example in India.[26] However, the LERG acknowledged that a comprehensive standardized methodology for the study of febrile disease was required.

The complexity and sophistication of risk models should reflect the availability of data for the input parameters and the required outputs. The risk models could be validated with existing data from epidemiological studies and triangulated with available surveillance data. The LERG agreed to use the available expertise in WHO to develop a leptospirosis risk map, with oversight from a member of the Group (Dr Joseph Vinetz).

5.3.2.2. Transmission model

Transmission models are being used with increasing frequency to help characterize patterns of endemic diseases and epidemics and to evaluate the impact of interventions.[27] Such models can also be used to predict and quantify morbidity and mortality from infectious diseases. Modelling approaches are also able to include the impact of epidemics on estimation of burden of disease. A number of the burden estimates for neglected tropical diseases are hampered by under-reporting and misdiagnosis. Attempts have been made to quantity this error for other diseases.[28]

The LERG agreed that it would be appropriate to develop a transmission model for leptospirosis. The studies identified in the systematic review could be used to assign values to the inputs and to validate the model. A conceptual model, which identified the required parameters and constants, was presented to the group by Professor Jakob Zinsstag to guide the discussions (Figure 5).

Taking into account the complexity of the transmission cycle, the model in Figure 5 could be further elaborated to differentiate between different forces of transmission. In conjunction with risk maps, a number of regionally appropriate transmission models could be developed. This would allow a more accurate understanding of the likely disease burden in various risk settings. The LERG considered that one model per WHO region would be a feasible goal but recognized that taking a regional approach would have some limitations and that adjustments for focality of disease would need to be made, where possible.

Figure 4. A transmission model for leptospirosis based on SIR model - S: susceptible, I: infectious and R: recovered (reproduced with the permission of Jakob Zinsstag).

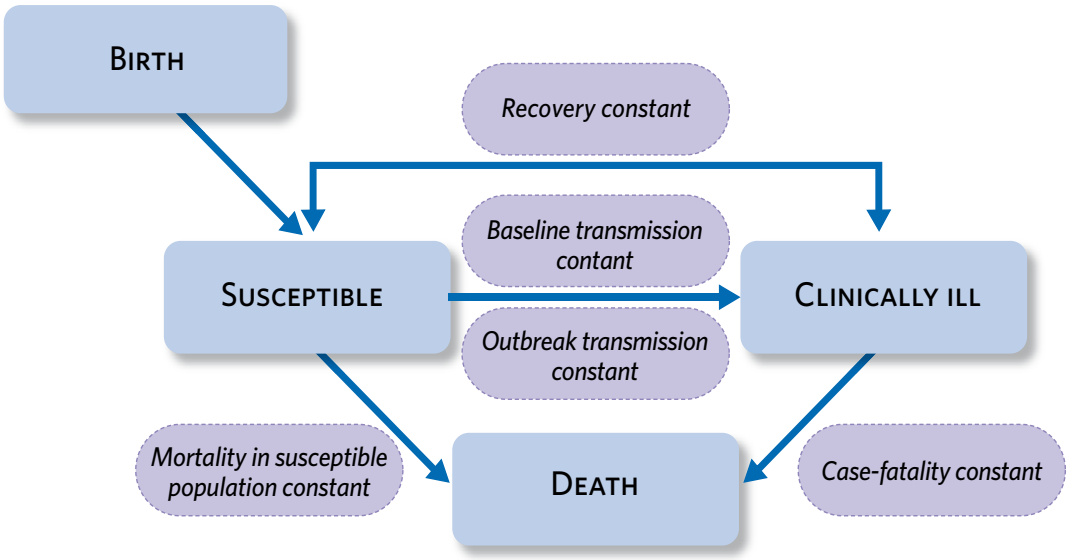
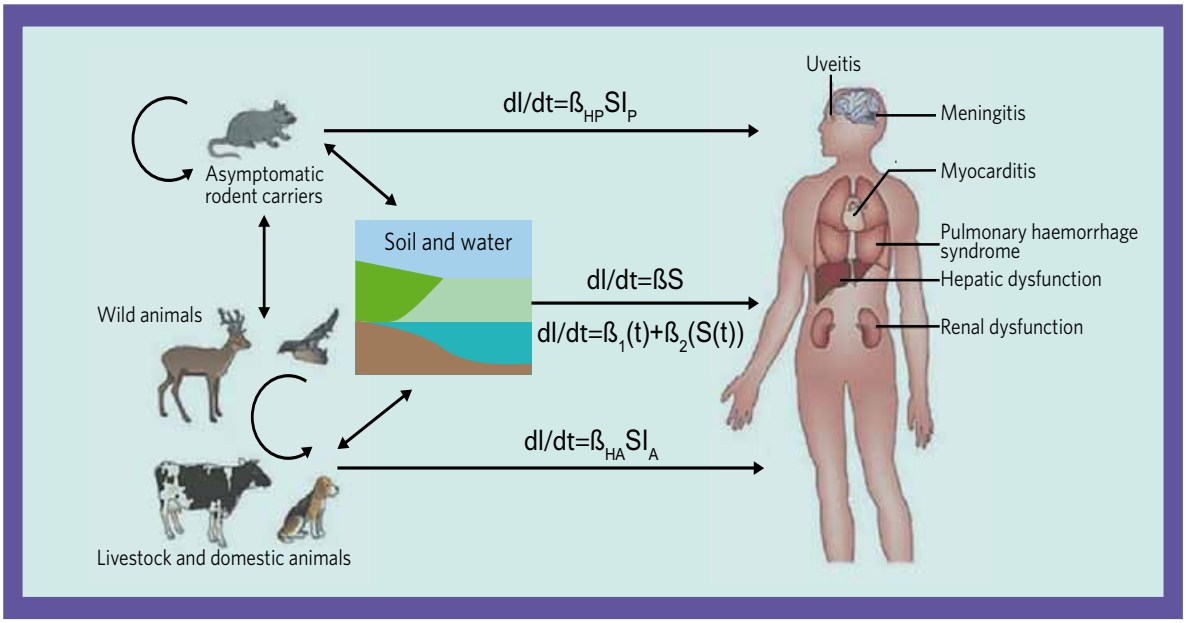


Figure 5. A transmission model for leptospirosis, taking into account the different modes of transmission (image reproduced with the permission of the authors[15]).



Based on variation of Susceptible (S), Infection (I), Recovered (R) model, β: Infection rate, A: animal, d: derivative, H: human, P: rodents, t: duration of disease

Leptospirosis is clinically defined as an illness characterized by fever, headache and myalgia, and may cause jaundice, acute renal failure, bleeding including pulmonary haemorrhage syndrome, meningitis, myocarditis and uveitis.he LERG requested the WHO secretariat to commission a suitable group to produce a model for leptospirosis transmission. The LERG focal point for the development of the model would be Jakob Zinsstag.

5.4. Identification of gaps

During the deliberations of the LERG, a number of gaps in scientific knowledge were identified. While it is outside the remit of the LERG to consider actions to address these gaps, the Group considered that it was important to record them for the benefit of the wider leptospirosis disease community.

Lack of point-of-care diagnostics to identify cases of acute leptospirosis

The existing "gold standard" serological tests are difficult to perform,[29] and it is not easy to demonstrate the presence of leptospires during the active infection. In addition, the background level of antibodies in endemic regions means that diagnostic assay results cannot easily differentiate between current and past infection.

Lack of evidence regarding strongly suspected long-term sequelae of direct relevance to determination of DALYs for leptospirosis

Animal models and the known biological behaviour of the organism suggest that infection may become chronic and leptospires may persist in kidneys, liver, lungs and the central nervous system. The medical implications of this are unknown.[30] Leptospiral diversity and the biological differences underlying different forms of severe leptospirosis also make characterization of sequelae problematic. The difficulty of demonstrating the organisms in certain tissues, e.g. in uveitis, also contribute to the lack of reliable evidence.

Insufficient incidence and long-term studies for directly assessing the burden of disease.

Lack of awareness and funding may have contributed to the lack of large-scale studies in this area. 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. Well-defined banks of serum, urine and other specimens would allow new diagnostic tests, based on antibody and antigen detection, to be validated and used in a field context. Targeting incidence and long-term studies in regions representative

of different epidemiological contexts and of the range of clinical severity would lead to a better understanding and assessment of the impact of leptospirosis.

5.5. Communication and advocacy strategy

5.5.1. Communication and advocacy

The LERG agreed that a communication and advocacy strategy was essential to the success of this project. Communications needed to be appropriate for the audience and it would be important to engage key stakeholders at all levels.

The LERG also saw benefits in liaising with other disease burden expert groups and learning from their experiences. Both policy-makers and funding agencies should be targeted and maximum use made of existing logistic infrastructure. The extensive professional networks of the LERG advisors should also be used.

The LERG asked the secretariat to prepare a summary document, outlining the activities of the LERG and including a budget for ongoing work. This could be used for awareness-raising and sensitization of governments and other agencies, and as the basis for grant proposals, presentations and seminars.

5.5.2. Scientific press

The LERG agreed that it would be important to engage the scientific press early to raise awareness of and support for the activity in the scientific community. A number of potential opportunities were identified:

- proposing a symposium focusing on leptospirosis at the annual meeting of the American Society of Tropical Medicine and Hygiene;
- aiming for an editorial on the first meeting of the Group in the Public Library of Science Neglected Tropical Diseases journal; and

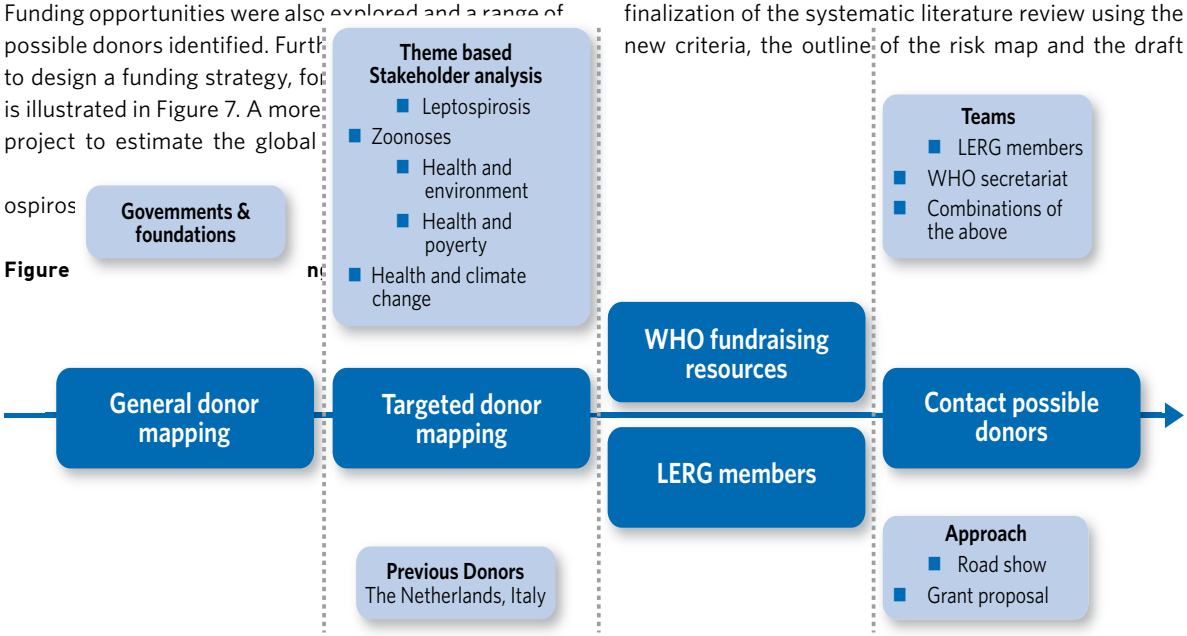
- aiming for a perspectives article on LERG activities in the American Journal of Tropical Medicine and Hygiene.

5.5.3. Funding

Funding opportunities were also explored and a range of possible donors identified. Furth
to design a funding strategy, for
is illustrated in Figure 7. A more
project to estimate the global

ospiros

Figure n



6. Follow-up

The next LERG meeting is planned for 22–24 September 2010. It will review progress and the results of the work performed since the first meeting, including the finalization of the systematic literature review using the new criteria, the outline of the risk map and the draft

A summary document outlining the activities of the LERG is in development to illustrate that a relatively small investment in the work of LERG that builds on other health initiatives, could trigger significant change.

transmission model. There will also be assessments of actions every three months.

Table 4 Follow-up actions required

	Summary of recommendations and action required	Completion date
1	Complete disease definition criteria. Evaluate IFA on the basis of systematic literature review	31 Dec 2009
2	Re-analyse systematic literature review in light of new criteria and additional data available from LERG advisors	19 May 10
3	Develop risk map for review at LERG 2	31 Aug 10
4	Develop draft transmission model for review at LERG 2	31 Aug 10
5	Develop advocacy materials for LERG	15 March 10

Annex 1. Participants

LERG advisors

Dr Gholamreza Abdollahpour, Leptospira Research Laboratory, University of Tehran, Tehran, Islamic Republic of Iran.

Dr Rudy Hartskeerl, Research Coordinator of Royal Tropical Institute (KIT) Biomedical Research and Head of WHO/FAO/OIE Leptospirosis Reference Centre, Amsterdam, Netherlands.

Dr Albert Ko, Visiting Researcher, Gonçalo Moniz Research Center, Oswaldo Cruz Foundation/Brazilian Ministry of Health, Salvador, Bahia, Brazil.

Dr Arthur Reingold, Professor of Epidemiology and Head of the Division of Epidemiology, School of Public Health, University of California, Berkeley, United States of America.

Dr Yupin Suputtamongkol, Professor, Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand.

Dr Paluru Vijayachari, Director, WHO Collaborating Centre for Diagnosis, Research, Reference and Training in Leptospirosis, Regional Medical Research Centre (ICMR), Port Blair, India.

Dr Joseph Vinetz, Professor of Medicine, Division of Infectious Diseases, Department of Medicine, University of California, School of Medicine, San Diego, United States of America.

Dr Paul Yip, Professor and Director, Social Work and Social Administration Department, The University of Hong Kong, Hong Kong SAR, China

Dr Jakob Zinsstag, Assistant Professor in Epidemiology, Faculty of Science of the University of Basel, and Project Coordinator at the Swiss Tropical Institute, Basel, Switzerland.

Unable to attend:

Dr Colette Diguimbaye, Laboratoire de Recherches Vétérinaires et Zootechniques de Farcha, N'Djamena, Chad.

Resource advisors

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Dr Eric Bertherat, Department for Global Alert and Response

Dr Pierre Formenty, Department for Global Alert and Response

Dr Robert Bos, Department for Public Health and Environments

Dr Luis Fernando Leanes, WHO Regional Office for the Americas

Dr Hilde Kruse, WHO Regional Office for Europe (by teleconference)

Dr Christopher J. Oxenford, WHO Regional Office for the Western Pacific

World Organisation for Animal Health

Dr Alex Thiermann, Advisor and President of the Terrestrial Animal Health Code

Annex 2. Agenda

Wednesday, 2 December 2009 LERG Briefing and Technical meeting

9.00 - 10.00	Pre-meeting with Rapporteur and Chair Coffee served outside meeting room
10.00 - 11.00	Welcome by ADG/HSE and WHO Secretariat and Election of Chair and Rapporteur
11.00 - 12.30	Introduction LERG: Purpose, procedures and expected outcomes Role and Terms of Reference of LERG members
12.30 - 13.30	Lunch
13.30 - 15.00	Estimating the Global Burden of Disease at WHO - from GBD to LERG
15.00 - 15.30	Coffee break
15.30 - 16.30	Leptospirosis BoD assessment - Discussion Outline day 2 and 3
16.30 - 17.00	An example: Intersectoral burden estimation of brucellosis and rabies Jakob Zinsstag
17.00-17.30	Leptospirosis surge after typhoon in Philippines

Thursday, 3 December 2009 LERG Technical meeting

9.00 - 10.30	Summary from Chair and Rapporteur on Day 1 Presentation of systematic literature review on human leptospirosis Discussion
10.30 - 11.00	Coffee break
11.00 - 12.30	Systematic Review - Discussion cont. Presentation of grey literature data search and country questionnaire - Discussion
12.30 - 13.30	Lunch
13.30 - 14.00	A possible disease model for human leptospirosis Albert Ko
14.00 - 15.00	Examination of data - usability, data gap identification
15.00 - 15.30	Coffee break
15.30 - 16.00	The GBD 2005 Study Colin Mathers
16.00 - 17.30	Examination of data - assess needs for burden estimation including modelling

Friday, 4 December 2009 LERG Technical meeting

9.00 - 10.30	Summary from Chair & Rapporteur on Day 2 Agree on work plan for LERG Advise on individual work to be commissioned
10.30 - 11.00	Coffee break
11.00 - 12.00	Immediate LERG outputs Advocacy and fundraising needs Agreement on next steps LERG schedule 2010
12.00 - 12.30	Summary and formal closure of LERG 1
13.30 - 15.00	Post-meeting with Rapporteur and Chair

Annex 3. List of databases used in the systematic review

Database	Site	Comments
Global databases		
Medline	http://www.ncbi.nlm.nih.gov/pubmed/	Included
Popline	http://db.jhuccp.org/ics-wpd/popweb/	Included
CAB	http://www.promedmail.org	Included
BiologicalAbstracts	http://www.periodicos.capes.gov.br/portugues/index.jsp	Included
CINAHL	http://www.cinahl.com/	Included
EMBASE	Provided by WHO	Included
PAISInternational	http://www.csa.com/factsheets/pais-set-c.php	Included
ProMed	http://www.promedmail.org	Included
ISIWebofKNOWLEDGE	http://isiwebofknowledge.com/	Included
Cochrane	http://www.cochrane.org/	Included
WHOLIST	http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=WHOLIS&lang=p	Included
Regional WHO databases		
African Index Medicus (AIM)	http://indexmedicus.afro.who.int/cgi-bin/wxis.exe/iah/	Included
Index Medicus for the Eastern Mediterranean Region (IMEMR)	http://www.who.int/bookorders/anglais/detart1.jsp?sesslan=1&codlan=1&codcol=46&codcch=15	Included
Western Pacific Region Index Medicus (WPRIM)	http://wprim.wpro.who.int/SearchBasic.php	Included
Other regional databases		
LILACS (Latin American and Caribbean Health Science Information)	http://bases.bireme.br/cgi-bin/wxislind.exe/iah/cys/?IsisScript=iah/iah.xis&base=LILACS&lang=p	Included
KoreaMed	http://www.koreamed.org/SearchBasic.php	Included
Metasearch from HELLIS Network Libraries	http://www.hellis.org/modules.php?op=modload&name=metasearch&file=hellismeta	Included
Health Research and Development Information Network	http://www.herdin.ph/old/	Included
AMICUS Canadian union catalogue	http://amicus.nlc-bnc.ca/aaweb/amilogine.htm	Included
Institute of Tropical Medicine (ITM) in Antwerp Belguim	http://lib.itg.be:8000/webspirs/start.ws	Included
Japan Science and Technology Information Aggregator, Electronic	http://www.jstage.jst.go.jp/browse/	Included
l'Ecole nationale de la santé publique	http://www.bdsp.tm.fr/	Included
Turkish Medline	http://www.turkishmedline.com/	Included
La bibliothèque de Santé Tropicale	http://www.santetropicale.com/resume/catalogue.asp	Included
Cuiden	http://www.index-f.com/	Included
Databases that could not be used		
SocioFile	http://www.nisc.com/factsheets/soci.asp	Not available
Econlit	http://www.econlit.org/	Not available
BIOSIST	http://www.biosis.org/	Not available
African Health Line	http://www.nisc.com	Not available
IMSEAR	http://library.searo.who.int/modules.php?op=modload&name=websis&file=imsear	Not available

Annex 4. Questionnaire to collect country data on the burden of human leptospirosis

The questionnaire below was sent to 41 countries to obtain data on human leptospirosis that could provide input to the estimation of the global burden of the disease.

Country: _____

Department or office responsible
for surveillance of human leptospirosis: _____

Contact details: _____

Date: _____

1. Is human leptospirosis a disease of mandatory notification in your country?

   ☐ No ☐ Yes Since when? Year: _____

2. What is the number of human leptospirosis suspected cases, confirmed cases and deaths of leptospirosis in the country? If available, detail the information by year from 1970 to 2008 in the attached data entry sheet.

3. How are the data on human leprospirosis gathered?

Passive surveillance	☐ No	☐ Yes
Active surveillance	☐ No	☐ Yes
Sentinel studies	☐ No	☐ Yes

   Other (please specify) _____

4 If available please share any documents or reports on human leptospirosis in your country that may not be published, may have restricted circulation or not be indexed in bibliographic databases

Country data sheet for epidemiological data on human leptospirosis

Year	Suspect human cases	Confirmed human cases	Human deaths attributable to leptosirosis
1970			
1971			
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2009			

Please return to Dr Bernadette ABELA-RIDDER abelab@who.int or fax: +41 22 791 4807
Department of Food Safety and Zoonoses, World Health Organization, Avenue Appia 20,
CH-1211 Geneva 27, Switzerland

Annex 5. Regions used in burden of disease studies

High Income Asia Pacific (Region 1): Japan, Republic of Korea, Singapore
Central Asia (Region 2): Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Mongolia, Tajikistan, Turkmenistan, Uzbekistan
East Asia (Region 3): China, Democratic Republic of Korea
South Asia (Region 4): Afghanistan, Bangladesh, Bhutan, India, Nepal, Pakistan
Southeast Asia (Region 5): Cambodia, Indonesia, Lao's Democratic Republic, Malaysia, Maldives , Mauritius, Mayotte, Myanmar, Philippines, Seychelles, Sri Lanka, Thailand, Timore Leste, Vietnam, (Réunion)
Australasia (Region 6): Australia, New Zealand
Caribbean (Region 7): Anguilla, Antigua and Barbuda, Aruba, Bahamas , Barbados., Belize, Bermuda, British Virgin Islands, Cayman Islands, Cuba, Dominica, Dominican Republic, French Guiana, French Polynesia, Grenada, Guadalupe, Guyana, Haiti, Jamaica, Martinique, Montserrat, Netherlands Antilles, Saint Kitts and Nevis, St Lucia, St Vincent, Suriname, Trinidad and Tobago, Turks and Caicos Islands
Central Europe (Region 8): Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, Montenegro, Slovakia, Slovenia, Former Yugoslavia Republic of Macedonia, (Kosovo)
Eastern Europe (Region 9): Belarus, Estonia, Latvia, Lithuania, Republic of Moldova, Russian Federation, Ukraine
Western Europe (Region 10): Andorra, Austria, Belgium, Channel Islands, Cyprus, Denmark, Faeroe Islands, Finland, France, England, Germany, Gibraltar, Greece, Greenland, Holy See, Iceland Ireland, Isle of Man, Israel, Italy, Liechtenstein, Luxembourg, Malta, Monaco, Netherlands Norway, Portugal, Saint Pierre et Miquelon, San Marino, Spain, Sweden, Switzerland, United Kingdom
Andean Latin America (Region 11): Bolivia, Ecuador, Peru
Central Latin America (Region 12): Colombia, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Venezuela
Southern Latin America (Region 13): Argentina, Chile, Falkland Islands (Malvinas), Uruguay,
Tropical Latin America (Region 14): Brazil
North Africa, Middle East (Region 15): Algeria, Bahrain, Egypt, Islamic Republic of Iran, Iraq, Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Morocco, Occupied Palestinian Territory, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, Turkey, United Arab Emirates, Western Sahara, Yemen
High Income North America (Region 16): United States of America, Canada
Oceania (Region 17): American Samoa, Cook Islands, Fiji, French Polynesia, Guam, Kiribati, Marshall Islands, Federated States of Micronesia, Nauru, New Caledonia, Niue, Northern Mariana Islands, Palau, Papua New Guinea, Pitcairn, Samoa, Solomon Islands, Tokelau, Tonga, Tuvalu, pei, Raiatea, Vanuatu, Wallis and Fortuna.
Central Sub-Saharan Africa (Region 18): Angola, Central African Republic, Congo, Democratic Republic of the Congo, Equatorial Guinea, Gabon
East Sub-Saharan Africa (Region 19): Burundi, Comoros, Djibouti, Eritrea, Ethiopia, Kenya, Madagascar, Malawi, Mozambique, Rwanda, Somalia, Sudan, Uganda, United Republic of Tanzania, Zambia
Southern Sub-Saharan Africa .(Region 20): Botswana, Lesotho, Namibia , South Africa, Swaziland, Zimbabwe
West Sub-Saharan Africa (Region 21): Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Côte d'Ivore, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Nigeria, Saint Helena, São Tomé and Principe, Senegal, Sierra Leone, Togo

Annex 6. Follow-up action

	Action	Activity implemented or commissioned by	LERG member responsible for monitoring activity	Time required to complete the output
1	**Complete disease definition criteria**			
1a	Review existing literature to determine the appropriateness of including IFA as a diagnostic criterion for definitive diagnosis of leptospirosis	YS	YS	31-Dec-09
2	**Systematic review of published and grey literature**			
2a	LERG members to identify all relevant published, unpublished and grey literature data (at review protocol evidence levels I, II, III, and IV) focusing on disease incidence and sequelae, and make available for inclusion in the systematic review.	All LERG members	All LERG members	Supply data 31 Jan 2010
2b	LERG members to review results of systematic review and identify any further published or unpublished data that may be included.	WHO	AR	31-Jan-10
2c	Translate abstracts of 118 papers identified in the systemic review written in non-selected languages. Identify and translate full text of papers fulfilling inclusion criteria and include in further analysis.	WHO	BA-R	19-Feb-10
2d	Review quality criteria used for inclusion of studies.	Brazil	BA-R	31-Jan-10
2e	Re-run literature review using WHO standard GDB level of evidence 1–IV criteria and revised quality criteria and agreed disease definition and diagnostic criteria.	Brazil	BA-R	19-May-10
2f	Set up a "sharepoint site" to allow efficient and effective sharing of information	WHO	WHO	31-Jan-10
2g	Continue to collate information from Ministry of Health grey literature questionnaires and make available to LERG for review	WHO	WHO	31-Mar-10
3	**Risk/transmission model**			
3a	Commission transmission model	WHO	JZ	Aug-10
3b	Commission risk model	WHO	JV	Aug-10
3c	Provide draft model and define inputs	WHO	JV, JZ	Aug-10
3d	Run draft model	WHO	JV, JZ	Aug-10
3e	Calibrate /validate models using existing data for regions with different risk profiles.	WHO	JV, JZ	to be announced
4	**Communication and dissemination of findings to key government staff, researchers and policy-makers**			
4a	Prepare a summary document outlining the activities of the LERG to use for awareness-raising and sensitization of governments and other institutions and organizations and to act as the basis for grant proposals, seminars and presentations and for dissemination on the Internet.	WHO	WHO	15-Mar-10
4b	Symposium focusing on leptospirosis at the 2010 annual meeting of the American Society of Tropical Medicine and Hygiene	JV, AK, JZ	JV, AK, JZ	18-Nov-10
4c	Editorial summary of the first meeting of the LERG to be published in Public Library of Science Neglected Tropical Diseases journal	AK	JV, AK, JZ	31 Feb 2010
4d	Perspective article in the American Journal of Tropical Medicine and Hygiene	JV	JV	31 Feb 2010
4e	Explore funding opportunities	WHO	JV	

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