Informal Consultation on Global Burden of Leptospirosis: Methods of Assessment

Geneva, 25-27 October 2006
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**INTRODUCTION**  

**CONSULTATION OBJECTIVES**

**DEFINITION AND SCOPE**

**EPIDEMIOLOGY OF LEPTOSPIROSIS**

**THE GLOBAL BURDEN OF DISEASE (GBD) APPROACH**

**GLOBAL BURDEN OF DISEASE STUDIES PERFORMED TO DATE FOR ZOONOTIC DISEASES**

- Rabies
- Echinococcosis

**DISCUSSION OF TECHNICAL STEPS TO ESTIMATE THE GLOBAL BURDEN OF LEPTOSPIROSIS**

- Demographic baseline
- Cause of death analysis
- Epidemiological description of non-fatal outcomes of leptospirosis
- Internal consistency of epidemiological estimates
- Comparative risk assessment
- Sensitivity analysis
- Final report and dissemination of results

**BURDEN OF DISEASE ASSESSMENT - THE INTERNATIONAL LEPTOSPIROSIS SOCIETY (ILS)**

**CONCLUSIONS AND RECOMMENDATIONS**

**ANNEX 1: LIST OF PARTICIPANTS**

**ANNEX 2: AGENDA**

**ANNEX 3: WORKING GROUPS**

**ANNEX 4: PRESENTATIONS**
List of Acronyms

BOD   Burden of Disease
CE    Cystic echinococcosis
DALY  Disability-Adjusted Life Year
FOS   Department of Food Safety, Zoonoses and Foodborne Diseases
GBD   Global Burden of Disease
ILS   International Leptospirosis Society
NTD   Department of Control of Neglected Tropical Diseases
OIE   Office International des Epizooties (World Organisation for Animal Health)
PAHO  Pan American Health Organization/WHO Regional Office for the Americas
SDE   Sustainable Development and Environmental Health
WHO   World Health Organization
YLL   Years of Life Lost (to premature death)
YLD   Years Lived with Disability
Introduction

The meeting was opened by Dr François-Xavier Meslin, Department of Food Safety, Zoonoses and Foodborne Diseases (FOS), on behalf of its Director Dr Jørgen Schlundt.

Dr Rudy Hartskeerl, of the Dutch Royal Tropical Institute (KIT), and currently President of the International Leptospirosis Society (ILS), was elected Chairperson. Dr Joseph Vinetz, of the Division of Infectious Diseases, University of San Diego, was elected Rapporteur (Annex 1).

Dr Meslin introduced the draft agenda (Annex 2) which was adopted following some additional suggestions provided by the Chairperson.

Consultation objectives

The main objective of the meeting was to discuss the current state of evidence available to conduct a global burden of disease study on leptospirosis.

The goal of the meeting was to develop a strategic framework and identify the next steps required to estimate the global burden of leptospirosis.

Definition and scope

Leptospirosis is a disease with a significant health impact in many parts of the world, particularly in the Americas and Asia. This zoonotic disease causes life-threatening manifestations such as Weil’s Disease and Severe Pulmonary Haemorrhage Syndrome. The most recent estimates indicate that there are more than 500 000 annual cases of leptospirosis worldwide\(^1\). The majority of reported cases have severe manifestations for which mortality is greater than 10%. Furthermore, studies conducted in Thailand show that leptospirosis may represent up to 20% of febrile illness of unknown (undiagnosed/misdiagnosed) origin\(^2\).

Leptospirosis is mostly regarded as an epidemic disease with large visible outbreaks associated with floods or unusually high rainfall. However, the burden of endemic leptospirosis is thought to be very significant for people living in rural areas involved in farming (crops/animals) and urban area settlements with inappropriate sanitation (slums). Although the disease is a neglected tropical disease it is not currently considered as such by the Global Network for Neglected Tropical Diseases Control (GNNTDC) which was recently launched in collaboration with the Department for the Control of Neglected Tropical Diseases (NTD).

This Consultation was organized in close collaboration with the ILS, which resulted in a heterogeneous group of 10 experts on leptospirosi s from throughout the world. The professional background of these experts varied from control and prevention of clinical

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Informal Consultation on Global Burden of Leptospirosis: Methods of Assessment.

disease, epidemiology and diagnostics. The group was joined by mathematical modellers and also by a WHO expert in Global Burden of Disease studies.

Epidemiology of Leptospirosis

Leptospirosis is a zoonosis of worldwide distribution, endemic mainly in countries with humid subtropical or tropical climates with epidemic potential.

Although the most important epidemiological risk groups for leptospirosis vary, all countries have both endemic leptospirosis and epidemics in certain conditions. Epidemics in urban settings will mainly be associated with high rainfall while rural epidemics are also associated with harvest seasons.

In Latin America, the two primary epidemiological risk groups are urban slum-dwellers and subsistence farmers although the proportion of these risk groups may vary across countries due to regional differences in underlying conditions of poverty (Annex 4, presentation A. Ko). Data from Peru show that the disease may be endemic in the Amazonian jungle (Annex 4, presentation J. Vinetz). There is often a constant force of infection due to infected reservoirs such as rodents, livestock and dogs as is also the case for several African countries were rodents and shrews have been established as reservoirs of *Leptospira* spp (Annex 4, presentation R. Machang'u). In other regions such as Asia, the disease is mostly associated with outbreaks following flooding such as in Thailand in August 2006. However, occupational exposure is also very common (Annex 4, presentation S. Sehgal, W. Tangkanakul, J. Xiugao). In Europe we see a shift from leptospirosis being an occupational disease to one where recreational activities, particularly water sports and travel, are major risk factors (Annex 4, presentation W. Ellis).

Humans are not important in maintaining the transmission of leptospirosis but are continuously exposed if awareness, surveillance and control measures are lacking or fail. The clinical course in humans ranges from mild to lethal with a broad spectrum of symptoms and clinical signs. Infection and severe outcome rates in humans vary geographically and case ascertainment relies on recognition of severe manifestations. Since symptoms for mild leptospirosis cases and possible chronic sequelae of acute episodes are not disease specific (i.e. similar to dengue and malaria), the disease is often misdiagnosed and presumably contributes to a significant underestimation of the total burden due to leptospirosis.

The surveillance and reporting of leptospirosis in the world varies significantly depending on whether countries have mandatory reporting for the disease, have the laboratory infrastructure to perform standard technically-demanding diagnostic methods, and have the surveillance capacity to effectively report cases to the health authorities. In China, leptospirosis has been notifiable since 1955. The disease is also notifiable in most countries of the Western Pacific Region while in most African, other Asian and in some Latin American countries the disease is not notifiable at all (Annex 4, abstract L. Smythe, presentations A. Ko, R. Machang'u, J. Xiugao). There is a significant lack of information on leptospirosis in Africa, where few, if any countries report leptospirosis and little research has been performed to assess the potential disease burden. In animals, and with specific criteria, the disease is notifiable to the World Organisation for Animal Health (OIE).
Although data on annual occurrence of leptospirosis is lacking in most countries, especially in Africa, the increasing reports of outbreaks suggest that leptospirosis is emerging as an important public health problem. Countries like Australia, which have active surveillance, can easily identify changing demographics and accurately update health authorities on the disease. An ongoing long-term cohort study in the Brazilian city of Salvador will certainly help to understand the disease epidemiology better in this region and may give an indication of the extent of mild leptospirosis cases (Annex 4, presentation A. Ko). Initial findings demonstrate that 5% of urban slum-dwellers are infected each year with leptospirosis. Research from the Peruvian Amazon suggests that under-diagnosis of leptospirosis is common in a region of high endemicity and grave pulmonary complications are often under-recognized. The epidemiology of leptospirosis is complex and the role of immunity is not understood fully. For example, when assuming that individuals are continuously exposed, it is not easily explained why outbreaks only occur on some occasions (Annex 4, presentation J. Vinetz). The presented surveillance data from China showed a very sharp decrease in the disease incidence over the last 10 years. The data should be interpreted with caution, although a possible explanation for this decrease includes (but is not limited to) agricultural mechanization and improved public awareness. (Annex 4, presentation J. Xiugao).

Overall, both basic bacteriology and serology studies and national burden studies are needed to determine the prevalence of leptospirosis in both human and animal populations. This will give an indication of the extent of the cost of leptospirosis to the health-care system and society as a whole. Such figures would help in the setting of priorities for prevention and control of the disease. In areas such as Australia and Europe, a decrease in human incidence is being achieved through education campaigns targeted at high-risk groups as well as animal disease control programmes (including vaccination). This has been achieved through active surveillance and research programmes which facilitate the availability of timely and accurate data. (Annex 4, presentations W. Ellis and L. Smythe). In many areas of the world the most effective gains will be made by directly addressing the underlying conditions of poverty, which have led to the emergence of leptospirosis. However, the lack of information on the disease burden has been a major impediment in convincing health authorities (a) to allocate resources and implement control measures that have been employed successfully in developed countries and (b) to develop new intervention strategies that target high-risk population groups.

It emerged from the discussions that to date a cohesive global estimate for the burden of leptospirosis is lacking and discussions therefore focused on how this global estimate could be obtained. It was agreed that a strategic plan for a GBD study on leptospirosis should be developed and initiated without delay.

**The Global Burden of Disease (GBD) Approach**

Claudia Stein presented the rationale and methods for the Global Burden of Disease (GBD) which was adopted by WHO for its reporting on health information in the late 1990s (Annex 4, presentation C. Stein).

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 only be partially available. Studies which investigate particular conditions may exaggerate claims on mortality. This is largely a reflection of co-morbidity where several co-existing pathologies 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 Study\(^3\) approach addressed these problems and proposed a single metric, the Disability Adjusted Life Year (DALY). DALYs express the years of life lost to premature death (YLL) and the years lived with disability (YLD) for varying degrees of severity, making time itself the common metric for death and disability. One DALY is therefore a health gap measure, equating to one year of healthy life lost. DALYs for a disease or health condition are the sum of the years of life lost due to premature mortality (YLL) in the population and the years lost due to disability (YLD) for incident cases of the health condition:

\[
\text{DALY} = \text{YLL} + \text{YLD}
\]

The years of life lost (YLL) correspond to the number of deaths multiplied by the standard life expectancy at the age at which death occurs. The basic formula for YLL (excluding other social preferences discussed below), is the following for a given cause, age and sex:

\[
\text{YLL} = N \times L
\]

where:

- \(N\) = number of deaths
- \(L\) = standard life expectancy at age of death in years

Because YLL measure the incident stream of lost years of life due to deaths, an incidence perspective is also taken for the calculation of YLD. To estimate YLD for a particular cause in 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). The basic formula for YLD is the following (again, without applying social preferences):

\[
\text{YLD} = I \times \text{DW} \times L
\]

where:

- \(I\) = number of incident cases

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Informal Consultation on Global Burden of Leptospirosis: Methods of Assessment.

- \( DW \) = disability weight
- \( L \) = average duration of the case until remission or death (years)

DALYs are internally consistent and disaggregate co-morbidity, hence de-coupling epidemiological estimates from advocacy. One particular strength of the GBD approach is that it permits the estimation of disability associated with disease, particularly where mortality may be low but disabling long-term sequelae arise. Disadvantages of the DALY approach include the need for strong value judgments on disability and age, thus placing emphasis on death and morbidity in young adulthood.

While the GBD study did not specifically examine the burden of leptospirosis, it assessed (in its second round in the year 2000) the global burden of unsafe water and poor sanitation using nationally representative household-level exposure data on water quality and hygiene[^1]. This burden was calculated using estimated disease reductions from multiple community intervention studies. The risk assessment thus relied on the impact of interventions rather than characterization of the burden of disease per se.

Burden of disease studies should not produce a plethora of new research but instead capitalize on existing information and translate it into a single measure. Burden of Disease studies include elements of disease modelling, risk assessment and burden projections; the latter inform policy-makers where to target preventive strategies and what to expect in terms of future disease burden. Missing elements in the traditional GBD approach are the downstream effects on trade, agriculture and social costs. Using the DALY metric, however, these can be developed and should be incorporated in the global burden study of leptospirosis.

Global burden of disease studies performed to date for zoonotic diseases

The following two studies were presented and discussed as good examples of how the GBD approach could be used for zoonotic diseases. WHO was involved in a study aimed at quantifying the public health and economic burden of endemic canine rabies in Africa and Asia. The Institute of Parasitology, at the University of Zurich, Switzerland, conducted a study to assess the global socioeconomic impact of echinococcosis.

The most significant difference between these diseases and leptospirosis is the fact that for both diseases dogs are the primary hosts, although sheep also play an important role in the epidemiology of echinococcosis. This has an advantage for disease control purposes since only a limited number of species have to be targeted. This is in contrast to leptospirosis in which many wild and domestic animal species are reservoirs and often only play an indirect role owing to water contamination with their infected urine.

It also has an advantage for modelling purposes: dealing with zoonotic diseases with only one host allows for estimation of possible human cases based on available information on the animal disease situation. This is again not applicable for leptospirosis which is mainly, but not exclusively, a water-associated disease of multiple animal origin.

a. Rabies
Rabies remains an important yet neglected disease in Africa and Asia\(^5\) (Annex 4, presentation F. Meslin). Disparities in the affordability and accessibility of post-exposure treatment and risks of exposure to rabid dogs result in a skewed distribution of the disease burden across society, with the major impact falling on those living in poor rural communities, in particular children. Deaths due to rabies are responsible for 1.74 million DALYs lost each year (90% CI = 0.75–2.93). An additional 0.04 million DALYs are lost through morbidity and mortality following side-effects of nerve-tissue vaccines. The estimated annual cost of rabies is US$ 583.5 million (90% CI = US$ 540.1 – US$ 626.3 million).

The value of providing a quantitative estimate of disease impact due to rabies should not be under-estimated. Rabies is often perceived as a rare or insignificant disease of humans in developing countries; this perception has been a major factor hampering the development of disease control initiatives. Furthermore, control of rabies is often seen as the responsibility of veterinary authorities, but demonstration of the public health importance of rabies and the benefits of disease control to the public health authorities (both in terms of DALYs saved and reduced costs of postexposure prophylaxis) will encourage involvement of the health sector in control efforts.

b. Echinococcosis
Cystic echinococcosis (CE) is a condition of livestock and humans that arises from eating infective eggs of the cestode *Echinococcus granulosus*\(^6\) (Annex 4, presentation P. Torgeson). Dogs are the primary definitive hosts for this parasite, with livestock acting as intermediate hosts and humans as occasional intermediate hosts. The outcome of infection in livestock and humans is cyst development in the liver, lungs, or other organ system.

The distribution of *E. granulosus* is considered worldwide. Disability-adjusted life years (DALYs) and monetary losses, resulting from human and livestock CE, were calculated from recorded human and livestock cases. Even without correcting for the underreporting of human and livestock cases, CE has a substantial global disease impact in terms of DALYs and monetary losses. When no underreporting is assumed, the estimated human burden of disease is 285 407 (95% confidence interval [CI] 218 515–366 133) DALYs or an annual loss of US$ 193 529 740 (95% CI US$171 567 331–US$ 217 773 513).

When the number of DALYs lost, taking into account the recognized underreporting of human cases, is compared with those of other parasitic conditions evaluated by WHO, worldwide losses due to CE are slightly less than those caused by African trypanosomiasis (1 525 000) and more than those caused by onchocerciasis (484 000) or Chagas disease (667 000)\(^7\).

In addition, experiences from the Swiss Tropical Institute with regard to zoonotic disease control programmes on brucellosis and rabies were also presented at the meeting (Annex 4, presentation J. Zinsstag). This highlighted important issues when attempting to control, and possibly to eliminate, zoonoses:

- Simultaneous surveillance in animals and humans are most appropriate to demonstrate pathways of transmission and costs to society.
- Benefits to public health and society by controlling the disease in animals need to be demonstrated, particularly in countries with scarce resources.
- Cost-sharing scenarios stimulate cooperation between animal and public health sectors.
- Animal-human transmission models allow simulation of the effect of interventions in animals on human health.

**Discussion of technical steps to estimate the global burden of leptospirosis**

In the working groups, as well as the subsequent plenary, participants discussed how best to take the efforts of a global burden study forward (Annex 3). In both working groups, extensive discussions took place to develop a “disease model” for leptospirosis. The importance of different animals in the model (both native and domestic animals and pests), as well as the environment, was discussed. Working Group 1 also considered whether or not the animal health costs should be considered, as was done in the echinococcosis study. The following steps (which are not necessarily sequential) were highlighted by WG 1:

**a) Demographic baseline**

The required demographic inputs to the study are:

1. population by age, sex and geographical region for the reference year; and
2. total mortality by age, sex and geographical region for the reference year.

WHO is using the UN Population Division estimates for all countries in the world. It is proposed to use these for the leptospirosis study.

**b) Cause of death analysis**

For countries with a good vital registration system, data are available which can be used to make adjustments for incompleteness and miscertification either because of misidentification or poor ascertainment. For countries without a good vital registration system, a collation of all available data sources is recommended:

- health surveys (including DHS, MICS, other community based surveys),
- hospital discharges,
- medical registries,
- police records, etc.

**c) Epidemiological description of non-fatal outcomes of leptospirosis**

The basic steps in describing the epidemiology of non-fatal health outcomes include:
1) systematic review of current knowledge of the selected disease and sequela;
2) construction of a diagram of the natural history of the disease and sequela; the "disease model" (for draft models please see Annex 3);
3) identification of the epidemiological indicators to be estimated;
4) review of the published and non-published epidemiologic data available;
5) collation of all available data sources: health surveys, hospital discharges, medical registries, police records, etc.; and
6) creation of the first set of estimates.

d) Internal consistency of epidemiological estimates
   1) check of internal consistency of the first set of estimates (see Chapter 8 of National Burden of Disease Manual, WHO);
   2) expert consultation; and
   3) production of a second set of estimates, which are internally consistent.

e) Comparative risk assessment
It may not be possible to conduct a disease/syndrome based burden study as outlined above owing to unavailability of data. Therefore, a risk-based approach may be used where information on exposure to risk is used to predict outcome. This applicability and feasibility of this alternative approach needs to be determined for leptospirosis. If indicated, the following steps would be required:

   1) select the risk factors for analysis;
   2) gather information on prevalence and relative risks from local studies (i.e. surveys, epidemiological studies);
   3) search in the international literature for complementary information and relative risk data;
   4) estimate the burden attributable to the selected risk factor.

f) Sensitivity analysis
The sensitivity analysis of the final results to the social preferences used in YLL and YLD should be examined by recalculating the entire set of estimates using different values of discount rate and age weighting.

g) Final report and dissemination of results
This will involve careful planning to ensure maximum dissemination and understanding of results. Apart from preparation of a report, there will be a need for seminars to explain findings to key government staff and health researchers and planners. Additionally, thought should be given to dissemination of results through the Internet and in electronic form. In the interests of transparency and accountability, it is highly recommended to make YLD worksheets and documentation of disease models and assumptions publicly available.
Burden of Disease Assessment - The International Leptospirosis Society (ILS)

The International Leptospirosis Society (ILS) is a worldwide organization of mostly research groups working on leptospirosis and is a critical partner in burden of disease (BOD) efforts related to leptospirosis (Annex 4, presentation R. Hartskeerl). The ILS also includes interested clinicians, veterinarians, epidemiologists and public health officials, and, in collaboration with WHO, it has produced guidelines on diagnosis, surveillance and control of leptospirosis.8

One objective of the ILS is to provide up-to-date epidemiological information on leptospirosis to international and national health authorities as requested. The ILS organized different worldwide surveys of which the one covering the period 1987-997 was published in WHO's Weekly Epidemiological Record in 1999.9

With support provided by the Dutch Royal Tropical Institute a password-protected website was created, LeptoNet, to compile leptospirosis data worldwide. It allows for online input and analysis of epidemiological data. Unfortunately, the system does not work optimally, possibly because it relies on volunteer input with no personal gain and is not universally accepted by all ministries of health. It was discussed that active input of data from publications and sources on Internet might help to re-vive this site. If the site contains reliable data, it will be more attractive to be consulted and might stimulate institutions to update the information. The Global Burden of Leptospirosis Initiative and ILS will need to discuss further collaboration to avoid possible duplication.

Conclusions and recommendations

Participants recommended that an estimate of the global burden of human leptospirosis is the most important priority in addressing this public health problem. A first draft model and methodology for the BOD analysis was suggested during the meeting (Annex 4, Working Group 1). It was recognized that:

- Although no burden study would be complete without addressing the BOD in animals, this was considered to be beyond WHO's scope of work. It was suggested that the World Organisation for Animal Health (OIE) should be contacted to explore whether this could be taken forward by them through one of their working groups.
- There may be significant limitations with respect to information available for a BOD study, especially in regions such as Africa.
- Leptospirosis is an endemic disease but epidemics are expected to contribute significantly to the overall disease burden. A BOD study would need to include time or time-space modelling of the contribution that outbreaks make to the disease burden.

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• Leptospirosis is known to be significantly influenced by climactic factors. A BOD study may need at some stage to incorporate climate into the mathematical models, especially in regions for which there is limited data (Africa and South-East Asia, especially India and Indonesia). As a future step, the BOD study may involve forecasting given the long-term climactic and socioeconomic (urbanization) changes that are predicted to occur.

• Another limitation is the current lack of information on resistance and susceptibility to leptospirosis (i.e., naturally-acquired immunity to re-infection). This will need to be addressed in future proposed disease models.

• An analysis of cost-effectiveness should be performed in a second phase in the BOD study. This analysis should also consider veterinary costs. It was felt to be important because clearly-defined intervention measures that can be used in disease control strategies, especially in developing countries have not been identified yet.

• Performance of national BOD studies for leptospirosis only, or as part of a study to address the national burden of NTDs, are strongly encouraged by WHO and will be needed to validate the estimates generated by the global BOD study.

The process for implementing the BOD study was defined as follows: WHO should provide the platform and act as the coordinating agent for assembling the relevant core group which coordinates the BOD process. Within WHO, different departments will be involved in the initiative, especially NTD, since inclusion of the leptospirosis BOD study into a broader NTD initiative would enhance its credibility.

This is a similar approach to the one used for estimating the global burden of foodborne diseases, for which WHO provides the lead.

Furthermore, the Consultation proposed the establishment of a Leptospirosis Epidemiological Reference Group (LERG) that will bring together all the necessary expertise in different areas. It is thought that LERG will meet at least twice a year and will collate, commission and critically appraise all relevant burden of leptospirosis work. WHO should provide any necessary scientific, technical and other support to LERG including the preparation of meeting reports. FOS should provide secretarial support.

WHO would seek financial and institutional support, both within WHO and with other international organizations such as the OIE.

A timeline for the next six months was drafted:

November 2006 briefing to internal WHO partners to discuss outcomes of this meeting;
January 2007 drafting WHO strategy map for BOD analysis process;
February 2007 WHO to identify a core reference group;
March 2007 editorial by informal committee in ASTMH journal on Global BOD initiative; (editorial to be disseminated to other international journals in the area for potential publication);
March-May 2007 WHO to coordinate preparation of the proposal for core reference group;
collaborators should identify sources of funding;
May 2007 WHO to prepare proposals to submit for funding.
Annex 1: List of Participants

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Dr Claudia STEIN, Medical Officer, Department of Food Safety, Zoonoses and Foodborne Diseases
Annex 2: Agenda

Wednesday, 25 October 2006

09:00 - 09:15 Opening:

- Dr Jørgen Schlundt, Director, Department of Food Safety, Zoonoses and Foodborne Diseases (SDE/FOS)
- Dr François Meslin, Department of Food Safety, Zoonoses and Foodborne Diseases (SDE/FOS)
- Dr Rudy Hartskeerl, President, International Leptospirosis Society, and Head, WHO Collaborating Centre for Reference and Research on Leptospirosis, Royal Tropical Institute, Amsterdam
- Introductions

09:15 - 10:30 Review of regional situation (15 minutes each):

- in Africa (Professor R. S. Machang'u)
- in the Latin America - except Peru, Caribbean and North America - (Dr Albert Ko)
- in Peru (Dr Joseph M. Vinetz)
- PAHO/AMRO activities in the Americas (Dr Alejandro Lopez)

10:30 - 11:00 Coffee break

11:00 - 12:30 Review of regional situation (continued):

- in Europe (Professor W. A. Ellis)
- in South-East Asia - except Thailand (Professor Subhash Sehgal)
- in Thailand (Dr Waraluk Tangkanakul)
- in the Western Pacific - except China (Dr Lee Smythe)
- in China (Dr Jiang Xiugao)

12:30 - 14:00 Lunch break

14:00 - 15:30 Burden measurement (45 minutes each):

- methods of Burden Assessment (Dr Claudia Stein)
- collecting information on leptospirosis at global level (Dr Rudy Hartskeerl)

15:30 - 16:00 Coffee break

16:00 - 17:30 Methods used for evaluation of burden of other zoonoses (30 minutes each):

- Report on meeting of global burden of foodborne diseases (Dr Claudia Stein)
Informal Consultation on Global Burden of Leptospirosis: Methods of Assessment.

- Reassessing the burden of rabies in Africa and Asia (Dr François Meslin)
- Global Socioeconomic Impact of Cystic Echinococcosis (Dr Paul Torgeson)

Thursday, 26 October 2006

09:00 - 10:00  Measuring the burden of leptospirosis:
  - Assessing human health and social benefits of interventions in livestock; also the case for leptospirosis? (Dr Jakob Zinsstag)

10:00 - 10:30  Introduction to working groups (Dr François Meslin)

10:30 - 11:00  Coffee break

11:00 - 12:30  Working Groups (Rooms X7 and L328)

Working group 1:
  To develop a plan to determine the global disease burden of human leptospirosis
  - What is missing to assess the burden of the disease?
  - What can we do to develop a standard model?
  - What is missing to prevent and control the disease?

Working group 2:
  - Leptospirosis as a disease of domestic and wild animals:
  - The complexities of leptospirosis epidemiology with its various hosts/reservoirs.
  - How to construct the various "dynamic disease models", and identify and provide an estimate for the required epidemiological indicators.

12:30 - 14:00  Lunch break

14:00 - 15:30  Working groups (continued)

15:30 - 16:00  Coffee break

16:00 - 17:30  Report of working groups and discussion

Friday, 27 October 2006

09:00 - 10:30  Conclusions and recommendations

10:30 - 11:00  Coffee break

11:00 - 12:30  Identification of tasks and partners
  - development of research proposal
  - funding mechanisms
Annex 3: Working groups

Objective:
To develop a plan to determine the global disease burden of human leptospirosis

Working group 1

Different points need to be addressed:

Define population:
- global
- by country and region
- whole population
- all age groups
- male and female

Possible Natural History Model

* Includes depression and other mental health problems.

Define case definitions (what does my disease look like)?
- Asymptomatic infection: absence of fever, myalgias, and headache
- Acute febrile illness: Fever, myalgias, headache
- Weil's syndrome: Nephritis or pneumonitis or myocarditis with or without hepatic insufficiency
- Pulmonary haemorrhage: Respiratory failure
- Meningitis
- Uveitis

Define what burden to measure?
- DALYS (summary)
Informal Consultation on Global Burden of Leptospirosis: Methods of Assessment.  

- Incidence
- Monetary costs
  - Patient treatment costs
  - Human morbidity: salary lost
  - Human mortality costs
  - Animal health costs

What are the basic measures to do a Global Burden of Disease analysis? DALYS
- Proportion of risk groups in the population
  - Urban slum dwellers, subsistence farmers, occupational-risk groups, travel/recreation
- Infection rate
- Proportion with symptomatic disease
- Proportion of symptomatic patients who develop complications
- CFR for each syndrome

What are the basic measures to do a Global Burden of Disease analysis? DALYS
- Proportion of assymptomatic patients who develop uveitis and other chronic sequelae
- Duration of each syndrome
- Disability weight for each syndrome
- Age and gender structure of patient's with each syndrome
- Animal population and transmission measures

What are the basic measures to do a Global Burden of Disease analysis?
- Human monetary costs
  - Treatment costs for each syndrome
  - Per capita GNI or GDP
  - Loss of income due to death
  - OR Willingness to pay
- Animal health costs (when applicable)
  - Decrease productivity of agricultural animals
  - Treatment costs
  - Vaccination costs
  - Trade restrictions

What are the basic measures to do a Global Burden of Disease analysis?
- Human monetary costs
  - Treatment costs for each syndrome
  - Per capita GNI or GDP
  - Loss of income due to death
  - OR Willingness to pay
- Animal health costs (when applicable)
  - Decrease productivity of agricultural animals
  - Treatment costs
  - Vaccination costs
  - Trade restrictions

Burden measurements for background vs epidemic situations?
- Background rate
- Epidemic rate
  - Model based on past epidemics and predictors such as climactic factors
  - Calculate infection rates from outbreak/disaster situations
Do we have the data sources for a Global Burden of Disease analysis?

- Strategy will be to obtain specific rates for risk populations to obtain a global rate:
  - Urban slum dwellers
    - Prospective: 5% per year in Salvador
    - Inference from cross-sectional studies? one study 30 years ago
  - Subsistence farmers or sharecroppers
    - Prospective data: Available from Thailand, Spain, Barbados, China (RCTs), Cuba (RCTs), Nicaragua
      - Inference from cross-sectional studies
  - Occupational risk groups
    - Livestock workers: May be old published data
    - Fisherman?: Data unknown
  - Recreational/travel related risk groups
    - Case report information, Prospective data from Dutch tourists

Do we have the data sources?

- Proportion of symptomatic infections
  - Infer from outbreak investigations and RCTs: Buriman outbreak, India (Orissa, Andaman [RCT]), Panama (RCT)
  - Take in account geographical differences in proportions (due to serovars, etc?)

Do we have the data sources?

- Proportion of symptomatic patients who develop:
  - Weil's syndrome
  - Develop SPHS
  - Meningitis
  - Uveitis
  - There is no data for the proportion of complications among symptomatic infections

Do we have the data sources?

- Strategy
  - Calculate the heath care seek behaviour of patients with acute febrile illness
  - Exists information on the proportion of complication among clinical leptospirosis cases (those who seek health care assistance)

- CFR for each syndrome: Exists data from cross-sectional studies of leptospirosis patients from a wide geographical distribution
- Proportion of assymptomatic patients who develop uveitis and other chronic sequelae
  - Information from outbreak from Tamil Nadu, India?
- Duration of each syndrome
  - Exists information from cross-sectional studies of patients
- Disability weight for each syndrome
  - Can consider using weights for similar syndromes (dengue fever)
- Age and gender structure of patient's with each syndrome
  - Exists information from cross-sectional studies of patients

How to access the data sources?

- Published papers
- Reports

How to deal with missing data sources?

- Modelling
- Validating in sentinel studies for different risks groups
Working group 2

S - I - (R) model for Leptospirosis

A start was made in the development of a SI(R) model for Leptospirosis. It is known that humans can get re-infected with a different serovar of Leptospirosis.

\[
\frac{dI}{dt} = \beta_{HA} S_{HA} + \beta_{HP} S_{HP} + \beta_{ES} f(E)
\]

In which:
\(\beta\) is the transmission coefficient
\(S_{HA}\): susceptible human population
\(I_{HA}\): Infectious animals
\(I_{HP}\): Infectious pests
\(f(E)\): ??? shouldn't this be \(I_E\)??

Potential source of infection:

<table>
<thead>
<tr>
<th>Source</th>
<th>% Population at risk in RURAL area</th>
<th>% Population at risk URBAN (slums) area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pests</td>
<td>95%</td>
<td>0</td>
</tr>
<tr>
<td>Domestic animals</td>
<td>5%</td>
<td>0</td>
</tr>
<tr>
<td>Environment</td>
<td>0</td>
<td>100%</td>
</tr>
</tbody>
</table>

To calculate the disability DALY's as a summary measure, the data should be stratified by: age and sex as well as by urban/rural

\[
\text{DALY} = aE^2 = YLL + YLD
\]
In which:

\[ YLL = N \times L \]

where:

- \( N \) = number of deaths
- \( L \) = standard life expectancy at age of death in years

Duration of untreated disease:

<table>
<thead>
<tr>
<th>Form of disease</th>
<th>Minimum duration</th>
<th>Most likely duration</th>
<th>Maximum duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>7 days</td>
<td>12 days</td>
<td>365 days</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Disability weight factor ~ Dengue, Influenza

Mortality rate:

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimum</td>
<td>Most likely</td>
</tr>
<tr>
<td>&lt;10 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-15 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 15 yr</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ANNEX 4: PRESENTATIONS
Rodents and leptospirosis in Tanzania

- Rodents, and shrews (Crocidura spp) are major reservoirs for leptospirosis in Tanzania.
- Over 20 different genera of rodents of diverse species have been described in Tanzania, therefore, potential reservoirs of leptospires are prevalent (Leirs, 1984; Kilonzo et al., 2003).
- Leptospirosis was first reported in Tanzania from a dog in a veterinary clinic (Semuguruka et al., 1974).
- However, serological studies carried out in sugarcane and rice farms in early 1990s have demonstrated a broad seroprevalence of leptospirosis in rodents, humans and domestic animals.

Bacteriological studies (1997) have led to the (first) isolation of the pathogen from cattle at a slaughterhouse (Machang’u et al., 1997).

Within the Ratzooman Project (2003-2006), studies were carried out on the epidemiology of leptospirosis (alongside plague and toxoplasmosis) in selected areas of Tanzania (Fig 2).

The findings from this study have shown that, rodents (M. natalensis, Cricetomys gambianus) and shrews are the prominent reservoirs of the leptospires.

Serogroups Icterohaemorrhagiae and Ballum are possibly the most prevalent in Tanzania.

Within the serogroup Icterohaemorrhagiae, an endemic sorovar, named Sokoine, has been described for the first time.

Research methodology

The study involved three major stages:

1. Seroprevalence of leptospirosis in rodents, shrews, humans and domestic animals in selected areas.
2. Identification of seropositive (reservoirs) rodents and shrews to genus/species levels.
3. Isolation and characterization of the leptospire isolates from the rodents, shrews and humans.

Research areas

- Investigations were primarily focused in and around Morogoro town, where major human activities are farming and livestock keeping (Fig 2).
- Other areas included Chunya, Lower Moshi, Kongwa and Mvomero districts.
- Rodent trapping sites included: indoors (human residences), peri-domiciles, home gardens, cultivated fields (rice, sugar cane and maize), fallow swamps and the town slaughterhouse.

Farming: Rice, sugar cane and maize
SEROLOGICAL STUDIES

- Serum samples from rodents and shrews (n = 500), humans (n = 400), and domestic animal (n = 364) were randomly selected and analysed for antibodies to most common *Leptospira* spp serogroups by the microagglutination assay (MAT).
- The antigens tested were serogroups (serovariants in brackets): *Icterohaemorrhagiae* (Sokoine), *Grippotyphosa* (RM4), *Ballum* (Ballum), *Canicola* (Canicola), *Sejroe* (Hardjo) and *Pomona* (Pomona).
- *Serovars* Sokoine and RM4 were the local isolates previously obtained from rodents and cattle, respectively, in Morogoro and subsequently typed.

ISOLATION OF LEPTOSPIRES FROM RODENTS AND SHREWS

- Isolation of leptospires were attempted from representative samples of kidneys and urine of rodents and shrews.
- Out of a total of 2165 tissues and urine specimens cultured, 35 spirochetes were isolated from *M. natalensis*, *Crocidura* spp and *C. gambianus* captured in the Morogoro area (Table 5).
- Out of the 35 spirochaetal isolates, 21 have been identified as leptospires by MAT (Table 6).
- Of the 21 isolates, five belong to a new serovar Sokoine of serogroup *Icterohaemorrhagiae*.

CHARACTERIZATION OF LEPTOSPIRA ISOLATES

- Upon serological characterization (MAT) of the isolates it was revealed that serogroups Ballum and *Icterohaemorrhagiae* are the most prevalent (Table 6). A number of isolates are yet to be characterized.
- Total of 993 kidney samples were further analysed by PCR of which 31 were positive and 4 samples were inconclusive.
- The PCR results of rodent tissues correlate well with the serological (MAT) results of the isolates (Table 7).

ISOLATION AND CHARACTERIZATION OF LEPTOSPIRES FROM HUMANS

- The serological studies for leptospirosis in humans were complemented with an attempt to isolate leptospires in blood samples (n = 358) and urine samples (n = 589).
- One suspect leptospira isolate from the urine sample of a patient at Health Centre (Mikumi).
- Two suspected isolates were from the urine of clinically healthy slaughter men at the Morogoro abattoir.
- The human isolates are yet to be fully characterized.
- No attempts were made to isolate the leptospires from domestic animals.
RESULTS.

➢ A total of 3298 rodents were captured. These were predominantly *M. natalensis* (62.7%), *Rattus rattus* (15.68%) and *Mus musculus* (12.67%) (Table 1).

➢ Shrews (n = 371) were also relatively high in prevalence in Morogoro (consisted 10.1% of all captures).

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**Table 1:- Rodents and shrews captured in Morogoro (2003 – 2005)**

<table>
<thead>
<tr>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1029</td>
<td>953</td>
<td>86</td>
<td>2068</td>
</tr>
<tr>
<td>Crocidura spp</td>
<td>144</td>
<td>130</td>
<td>77</td>
</tr>
<tr>
<td><em>R. rattus</em></td>
<td>313</td>
<td>92</td>
<td>112</td>
</tr>
<tr>
<td><em>R. norvegicus</em></td>
<td>33</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><em>Mus spp</em></td>
<td>368</td>
<td>38</td>
<td>12</td>
</tr>
<tr>
<td><em>C. gambianus</em></td>
<td>121</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td><em>Lentrus spp</em></td>
<td>16</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td><em>Lemmuscomys spp</em></td>
<td>11</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><em>Grammomys spp</em></td>
<td>10</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td><em>Leggada spp</em></td>
<td>9</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Other spp</td>
<td>8</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>2082</td>
<td>1284</td>
<td>303</td>
</tr>
</tbody>
</table>

**Table 2 :- Rodent and shrew sera (n = 500) tested by MAT for antibodies to leptospires**

<table>
<thead>
<tr>
<th>Titres</th>
<th>Icterohaemorrhagiae</th>
<th>Pomona</th>
<th>Canicola</th>
<th>Grippo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:20</td>
<td>9</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>1:40</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1:80</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1:160</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1:320</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:640</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:1280</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:2560</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1:20480</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 3:- Human sera (n = 400) tested for antibodies to leptospira (2004)**

<table>
<thead>
<tr>
<th>Titres</th>
<th>Grippo.</th>
<th>Sokoine.</th>
<th>Hardjo</th>
<th>Pomona</th>
<th>Canicola</th>
<th>Ballum</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:20</td>
<td>0</td>
<td>12</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1:40</td>
<td>1</td>
<td>10</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1:80</td>
<td>0</td>
<td>11</td>
<td>3</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>1:160</td>
<td>1</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1:320</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1:640</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1:1280</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1:2560</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 4:- Domestic animals sera positive for leptospirosis 2005**

<table>
<thead>
<tr>
<th>Source</th>
<th>Icterohaemorrhagiae</th>
<th>Pomona</th>
<th>Canicola</th>
<th>Ballum</th>
<th>Grippo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheep &amp; Goats (n = 100)</td>
<td>38</td>
<td>24</td>
<td>9</td>
<td>9</td>
<td>34</td>
</tr>
<tr>
<td>Pigs (n = 100)</td>
<td>41</td>
<td>26</td>
<td>6</td>
<td>6</td>
<td>27</td>
</tr>
<tr>
<td>Dogs (n = 100)</td>
<td>39</td>
<td>9</td>
<td>9</td>
<td>5</td>
<td>26</td>
</tr>
<tr>
<td>Cat. (n=64)</td>
<td>9</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>

**Table 5: Spirochetal isolates from rodents and shrews captured in Morogoro (2003 to 2006)**

<table>
<thead>
<tr>
<th>Rodent and shrew species</th>
<th>Total cultures</th>
<th>Positive</th>
<th>% Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>M. natalensis</em></td>
<td>1582</td>
<td>8</td>
<td>0.51</td>
</tr>
<tr>
<td>Crocidura spp</td>
<td>346</td>
<td>16</td>
<td>4.62</td>
</tr>
<tr>
<td>C. gambianus</td>
<td>237</td>
<td>11</td>
<td>4.64</td>
</tr>
<tr>
<td>TOTAL</td>
<td>2165</td>
<td>35</td>
<td>1.62</td>
</tr>
</tbody>
</table>
LEPTOSPIROSIS IN MOZAMBIQUE

- The sites identified in Mozambique were in three urban/periurban provinces: Maputo, Tete and Zambézia Provinces.
- A total of 572 rodents were captured: Maputo (466), Tete (47), Zambézia (59).
- The captured animals were identified as *R. norvegicus*, *Mus spp*, *Mastomys spp*, *Tatera spp* and *Crocidura spp*.

ANALYSIS OF ANIMAL SPECIMENS

The tests carried out included:

- Serology (MAT testing)
- Culture of kidney tissues for leptospires
- PCR on some of the kidney tissues.

RESULTS

- Overall seroprevalence of the disease was 20.6 %
- Out of 197 tissue samples tested by PCR for leptospirosis, 3.6 % were positive and 3.6 % were doubtful.
- Cultures were not successful (contamination) hence isolation was not attempted

LEPTOSPIROSIS IN SOUTH AFRICA

- The studied sites were in the provinces of Limpopo and Durban, and from the city of Port Elizabeth.
- Samples were collected from rodents, and dogs and were tested for antibodies by MAT and Dri Dot (Table 8)
- Kidney tissues were cultured for *Leptospira spp* and also screened for leptospiral DNA by PCR
### RESULTS

- Serogroups obtained from serology were: Bratislava, Canicola, Australis, Pomona, and Grippotyphosa.
- Leptospira cultures failed, possibly due to contamination.
- PCR results for leptospirosis from Limpopo (Rodents and dogs), Durban (Rodents) and Port Elizabeth (Rodents) ranged ± 5-10 % positive (Table).
- Leptospirosis Dri Dot tests are questionable because Dri Dot is designated for human serum testing only.
- Sera tested by Dri Dot were further tested by MAT.

### LEPTOSPIROSIS IN ZIMBABWE

- Three sites were selected for the Ratzooman Project in Zimbabwe, namely Mbare, Hatcliffe and Nkayi.
- The studies involved the screening of sera from rodents and dogs for antibodies by MAT (Table 9).

### CONCLUSION

- Rodents and shrews have been established as reservoirs of *Leptospira spp*.
- The prevalence of leptospirosis in the four African countries studied has been established serologically and by culture.
- Serogroups Icterohaemorrhagiae and Ballum appear among prevalent serogroups, in rodents, domestic animals and humans.
- Studies of leptospirosis prevalence and leptospires on the African continent need to be intensified.

---

#### Table 8. Seroprevalence of leptospirosis in rodents and dogs

<table>
<thead>
<tr>
<th>Place/Animal spp</th>
<th>Samples tested</th>
<th>Dri Dot (+ve)</th>
<th>MAT (+ve)</th>
<th>Culture (+ve)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limpopo (Rodents)</td>
<td>202</td>
<td>37 (18.5 %)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Limpopo (Dogs)</td>
<td>34</td>
<td>33 (97.1 %)</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>Durban (Rodents)</td>
<td>223</td>
<td>22 (9.9 %)</td>
<td>10 (4.5 %)</td>
<td>0</td>
</tr>
<tr>
<td>Port Elizabeth (Rodents)</td>
<td>1200</td>
<td>27 (2.3 %)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

#### Table 9. Seroprevalence of leptospirosis in rodents and dogs

<table>
<thead>
<tr>
<th>Location</th>
<th>Animal spp</th>
<th>Samples</th>
<th>MAT (+ve)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mbare</td>
<td>Rodents</td>
<td>96</td>
<td>31 (32.3 %)</td>
</tr>
<tr>
<td></td>
<td>Dogs</td>
<td>18</td>
<td>15 (83.3 %)</td>
</tr>
<tr>
<td>Hatcliffe</td>
<td>Rodents</td>
<td>96</td>
<td>35 (36.5)</td>
</tr>
<tr>
<td></td>
<td>Dogs</td>
<td>15</td>
<td>13 (86.7%)</td>
</tr>
<tr>
<td>Nkayi</td>
<td>Rodents</td>
<td>56</td>
<td>22 (39.3%)</td>
</tr>
<tr>
<td></td>
<td>Dogs</td>
<td>17</td>
<td>16 (94.1%)</td>
</tr>
</tbody>
</table>
Informal Consultation on Global Disease Burden of Leptospirosis: Review of Situation in Latin America (Except Peru)


Fundação Oswaldo Cruz (FIOCRUZ)
Ministério da Saúde
Salvador, Brasil

Division of International Medicine and Infectious Disease
Weill Medical College of Cornell University
New York, USA

Case for Disease Burden Analysis in Latin America

- Leptospirosis disease burden approaches or may exceed that of other priority diseases for the region.
  - Passive surveillance
  - Outbreaks
  - Population-based investigations
  - Cohort studies

- Disease burden analyses are feasible.
  - Dengue, meningitis

Definable risk factors can be targeted for intervention and are likely to be cost-effective.
  - Improved sanitation
  - Reservoir control
  - Early case detection and treatment to prevent severe disease

Model for the Natural History of Leptospirosis

<table>
<thead>
<tr>
<th>Population</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed/Infected</td>
<td>Prob ( k_1 )</td>
</tr>
<tr>
<td>Symptomatic infection</td>
<td>Prob ( k_2 )</td>
</tr>
<tr>
<td>Clinical disease</td>
<td>Prob ( k_3 )</td>
</tr>
<tr>
<td>Severe disease forms</td>
<td>Prob ( k_4 )</td>
</tr>
<tr>
<td>Weil’s disease</td>
<td>Passive case reporting</td>
</tr>
<tr>
<td>Pulmonary hemorrhage</td>
<td>Active outpatient surveillance</td>
</tr>
<tr>
<td>Death</td>
<td>Passive case reporting</td>
</tr>
</tbody>
</table>

Surveillance Information for Latin America: Surveys of Leptospirosis Case Reporting

- 1998-2000, LeptoNet

2001-2005, Fiocruz, work-in-progress

20 countries (pop., 494 million) not including Peru

6 countries: Not listed as a reportable disease?
  - Bolivia, Colombia, Ecuador, Honduras, Panama, Paraguay

4 countries: Information not found
  - Belize, French Guiana, Guyana, Suriname

Caveats in Applying the Model in Latin America

- Two primary epidemiological risk groups in Latin America (population, 552 million):
  - Urban slum dwellers
  - Subsistence farmers
  - Occupational risk groups
  - Travel and recreation

- Proportion of these risk groups vary by country

- Type of environmental exposures (i.e., inoculum dose effects)
- Pathogen-related factors (i.e., infecting serovar)
- Host factors
- Bias in case ascertainment

Country | Ministry of Health Website | Leptospirosis Case Notification Website
---------|--------------------------------|---------------------------------|
Argentina | h... | h... |
Bolivia | h... | h... |
Brazil | h... | h... |
Colombia | h... | h... |
Costa Rica | h... | h... |
Ecuador | h... | h... |
El Salvador | h... | h... |
Guatemala | h... | h... |
Honduras | h... | h... |
Nicaragua | h... | h... |
Panama | h... | h... |
Peru | h... | h... |
Paraguay | h... | h... |
Uruguay | h... | h... |
Mean Annual Cases of Confirmed Leptospirosis

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ILS</td>
<td>805</td>
<td>2,620-3,638</td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>2,836</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argentina</td>
<td>10</td>
<td>0</td>
<td>187-377</td>
</tr>
<tr>
<td>Costa Rica</td>
<td></td>
<td>136-300</td>
<td></td>
</tr>
<tr>
<td>Mexico</td>
<td>441</td>
<td>94-109</td>
<td></td>
</tr>
<tr>
<td>El Salvador</td>
<td>8-85</td>
<td>(deaths)</td>
<td></td>
</tr>
<tr>
<td>Uruguay</td>
<td>32</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>Nicaragua</td>
<td>55</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>Chile</td>
<td>9</td>
<td>12-84</td>
<td></td>
</tr>
<tr>
<td>Guatemala</td>
<td>5</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Guyana</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suriname</td>
<td>154</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Panama</td>
<td>7</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3,000</td>
<td>1,294</td>
<td>3,165-4,789</td>
</tr>
</tbody>
</table>

Surveillance Data for Leptospirosis: Interpretation and Issues

- Information available for 83% of at-risk population in LA.
- Case ascertainment relies on recognition of severe manifestations.
  - Case definition for severe leptospirosis.
  - Burden attributed to mild leptospirosis, which may account for the majority of DALYs, remains undefined.
- Confirmed case numbers underestimate burden.
  - Standard diagnosis is inadequate.
  - Deaths often can not be confirmed.
  - In Brazil, >12,000 suspected cases each year
  - 75% of the severe disease burden may be missed.
- Irregardless, burden based on confirmed cases is high.
  - Leptospirosis, Brazil: 2,620-3,638 cases, CFR 12%
  - DHF, Latin America: 5,720-15,433 cases, CFR<1%

Cyclic Urban Epidemics of Severe Leptospirosis:
Population-Based Surveillance in Salvador, Brazil, 1996-2004 (N=2,300)

Validation of Clinical Case Definition for Surveillance in Salvador, Brazil 1996-1999

<table>
<thead>
<tr>
<th>Definition</th>
<th>Paired Sample* (n = 298)</th>
<th>Single Sample (n = 332)</th>
<th>Without Sample (n = 398)</th>
<th>Total (n = 1028)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed</td>
<td>255 (86)</td>
<td>65 (20)</td>
<td>--</td>
<td>320 (31)</td>
</tr>
<tr>
<td>Probable</td>
<td>13 (04)</td>
<td>135 (41)</td>
<td>--</td>
<td>148 (14)</td>
</tr>
<tr>
<td>Unconfirmed</td>
<td>30 (10)</td>
<td>132 (39)</td>
<td>398 (100)</td>
<td>520 (55)</td>
</tr>
</tbody>
</table>

* Positive predictive value for the clinical case definition was 90%
Burden of Severe Leptospirosis in Salvador, Brazil, 1996-2000

Annual incidence 10.2/100,000 pop
Males 23.8/100,000 pop
Females 4.7/100,000 pop
Mean age of cases (years) 34.8 +/- 15.2
Case fatality rate 15% (151)
Duration of hospitalization (days) 9.1 +/- 10.4
ICU admissions 25% (258)
Dialysis 24% (245)
Blood transfusions 6% (61)
Annual per capita health care expenditures: US$25.44

Model for the Natural History of Leptospirosis

<table>
<thead>
<tr>
<th>Population</th>
<th>Prob (x1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed/Infected</td>
<td>Prob (x2)</td>
</tr>
<tr>
<td>Symptomatic infection</td>
<td>Prob (x3)</td>
</tr>
<tr>
<td>Clinical disease</td>
<td>Prob (x4)</td>
</tr>
<tr>
<td>Severe disease</td>
<td>Prob (x5)</td>
</tr>
<tr>
<td>Well's disease</td>
<td>Passive surveillance</td>
</tr>
<tr>
<td>Pulmonary hemorrhage</td>
<td>Active sentinel surveillance</td>
</tr>
<tr>
<td>Death</td>
<td>Sequelae</td>
</tr>
</tbody>
</table>

Natural History of Urban Leptospirosis: Outcome Measurements for the Pau da Lima Cohort

- **Severe leptospirosis**
  - Hospital-based surveillance of 9,862 subject cohort
  - Laboratory-confirmed cases
  - Incidence: 9.5 per 100,000 pop.

- **Leptospira infection**
  - Annual surveys of a 2,003 member sub-cohort
  - MAT seroconversion or 4-fold titer rise
  - Infection rate:
    - All subjects: 4.9% per year
    - Seronegative at baseline: 3.4% per year
    - Seropositive at baseline: 11.1% per year

- **Severe disease:infection ratio is estimated to be 1:516**

Addressing Leptospirosis Disease Burden: Recommendations

- Stratify cases according to an easily applied definition for severe disease.
- Apply clinical case definitions to address under-reporting due to poor laboratory confirmation.
- Measure burden associated with mild clinical leptospirosis.
  - May be the major contributor to overall DALY
  - Cohort studies being initiated in Salvador, Brazil
  - Sentinel approach recruiting sites with serum banks
- Urgent need to estimate health care system costs.
- The most effective gains will be made by directly addressing the underlying conditions of poverty which have led to the emergence of leptospirosis in Latin America.
  - Research focused on evaluating interventions targeting specific risk factors

Risk Associations with Leptospira Infection

<table>
<thead>
<tr>
<th>Variable</th>
<th>Past infection (N=3166)</th>
<th>New infection (N=1576)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Reside &lt;10m open sewer</td>
<td>1.35 (1.10-1.67)</td>
<td>1.89 (1.09-3.27)</td>
</tr>
<tr>
<td>Reside in flood region</td>
<td>1.96 (1.43-2.68)</td>
<td>1.67 (1.05-4.78)</td>
</tr>
<tr>
<td>Peri-domiciliary contact</td>
<td></td>
<td></td>
</tr>
<tr>
<td>garbage</td>
<td>1.51 (1.21-1.88)</td>
<td>1.86 (1.10-3.10)</td>
</tr>
<tr>
<td>mud</td>
<td>1.47 (1.20-1.79)</td>
<td>2.10 (1.30-3.40)</td>
</tr>
<tr>
<td>flood water</td>
<td>1.38 (1.10-1.68)</td>
<td>2.15 (1.30-3.55)</td>
</tr>
<tr>
<td>sewage</td>
<td>1.63 (1.32-2.01)</td>
<td>2.04 (1.24-3.34)</td>
</tr>
<tr>
<td>Digging/cleaning open sewers</td>
<td>1.70 (1.40-2.18)</td>
<td>2.39 (1.45 – 3.94)</td>
</tr>
</tbody>
</table>
One billion individuals, representing 32% of the world’s urban population, live in slums.

The UN Millennium Declaration pledged to achieve “significant improvement in the lives of at least 100 million slum dwellers by the year 2020.”

The world’s urban slum population will double to 2 billion in the next 25 years.

Collaborating Network Institutions:
- Fundação Oswaldo Cruz / MS
- Associações dos Moradores da Pau da Lima
- Secretaria da Vigilância da Saúde / MS
- Secretaria da Saúde do Estado da Bahia
- Secretaria Municipal da Saúde / Salvador
- Universidade Federal da Bahia
- Hospital Emílio Ribas
- Universidade de São Paulo
- University of California at Los Angeles and Berkeley
- Weill Medical College of Cornell University

Support:
- Ministério da Saúde (Brasil)
- Conselho Nacional da Pesquisas (Brasil)
- NIAID, NIH (USA)
- Fogarty International Center, NIH (USA)
Regional Leptospirosis
Situation: Peru

Joseph M. Vinetz, M.D.
University of California, San Diego
On Behalf of the Peru-United States Leptospirosis Consortium

Key Collaborators

- Manuel Cespedes
  - Director, Zoonotic Diseases Laboratory Instituto Nacional de Salud, Lima, Peru
- Eduardo Gotuzzo, M.D.
  - Director, Alexander von Humboldt Institute of Tropical Medicine, Universidad Peruana Cayetano Heredia, Lima Peru
- Robert H. Gilman, M.D.
  - Professor, Johns Hopkins University
  - Research Professor, Universidad Peruana Cayetano Heredia

Contributions of Peru to Global Research in Leptospirosis

- Peru-US Leptospirosis Consortium
- Defined leptospirosis hyper-endemicity and patterns of transmission
- Demonstrated first cases of pulmonary involvement in leptospirosis in Peru
  - Brought to Peruvian MOH attention
- Discovered new species
- Developed new approach for environmental risk assessment for severe leptospirosis
- Developed training and research collaborative infrastructure in Peru

Leptospirosis en Perú 1994 - 2005

Casos confirmados de Leptospirosis en PERÚ 1994 – 2004

<table>
<thead>
<tr>
<th>Region</th>
<th>Incidencia</th>
<th># Casos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madre de Dios</td>
<td>19.0</td>
<td>140</td>
</tr>
<tr>
<td>Loreto</td>
<td>3.45</td>
<td>261</td>
</tr>
<tr>
<td>Ucayali</td>
<td>2.69</td>
<td>93</td>
</tr>
<tr>
<td>Cusco</td>
<td>1.57</td>
<td>178</td>
</tr>
<tr>
<td>Cajamarca</td>
<td>0.77</td>
<td>107</td>
</tr>
</tbody>
</table>

Casos notificados de leptospirosis Perú 2003-2005*

*Fuente: Noti-OGHE-BENAC-U-NHNA *SE 37
Outbreaks 2006

Amazonas (30 casos lepto, 1 caso sin fiebre amarilla ha muerto, 94 analizado 35 con fiebre amarilla, 13 muertos), Cañete, Lima (21 casos, 1 muerto entre 38 personas investigadas) Rimac, Lima, (150 casos sin muerto) (Pucalpa, Ucayali, en 2002, 2004, 2005, 2006, number of cases ??)

Serogrupos mas prevalentes detectados por MAT en Humanos 2001

Brotes epidémicos de Leptospirosis en Perú (1)
Personal militar en Pichanaqui (1999)

Brotes epidémicos de Leptospirosis en Perú (2)
Escolares de San Pedro de Huacarpana (2005)

Leptospirosis epidémica brote en Perú (2)
Escolares de San Pedro de Huacarpana (2005)

Leptospirosis endémica en Perú
Leptospirosis endémica en Perú

Prevalencia de anticuerpos de inmunoglobulina antileptospiral (IgM/IgG) por grupo de edad

The trend of increasing prevalence by age is significant for Belen and the rural communities (p = 0.018 and p = 0.012, respectively).


Photo B by Dorothy Whittembury http://www.victoria-adventure.org/more_than_links_images/dorothy/part_1.html

Vigilancia Sindrómica

<table>
<thead>
<tr>
<th>Nivel</th>
<th>Síndrome febril icterico-hemorágico</th>
<th>IgM Malara</th>
<th>IgM Anti HBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td></td>
<td>Positivo</td>
<td>Positivo</td>
</tr>
<tr>
<td>Regional</td>
<td>IgM Lepto.</td>
<td>Positivo</td>
<td></td>
</tr>
<tr>
<td>Nacional</td>
<td>Evaluas muestras al INS (IgM, MAT y PCR)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Norma Técnica para la Atención Integral de la Leptospirosis Humana, MINSAL, PERÚ

Reported case of Leptospirosis in PERÚ

1994-2004 2005

Patterns of Transmission

- Sporadic
  - Baltimore
  - EcoChallenge Sabah, Indonesia
  - Triathlon in Illinois
- Endemic
  - Iquitos, probably all tropical regions
  - Protective immunity vs. severe disease
- Epidemic
  - Brazil, Korea, India, Andaman and Nicobar Islands, more
  - Protective immunity vs. severe disease

Urban vs. Rural Leptospirosis

<table>
<thead>
<tr>
<th>Location</th>
<th>Number Resident</th>
<th>Number with Clinical Followup</th>
<th>Number with Leptospiral Serology, Antibodies Available</th>
<th>Number with Leptospiral Antibodies*</th>
<th>Number of Serum Positive Cases**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital (inpatient)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inpatient</td>
<td>45</td>
<td>24 (53.3%)</td>
<td>44 (97.8%)</td>
<td>24 (55.5%)</td>
<td>3</td>
</tr>
<tr>
<td>Outpatient</td>
<td>344</td>
<td>298 (87.0%)</td>
<td>306 (99.2%)</td>
<td>165 (55.9%)</td>
<td>2</td>
</tr>
<tr>
<td>FE (inpatient)</td>
<td>39</td>
<td>37 (94.9%)</td>
<td>39 (97.4%)</td>
<td>31 (81.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Outpatient</td>
<td>72</td>
<td>68 (93.1%)</td>
<td>72 (100%)</td>
<td>44 (61.1%)</td>
<td>0</td>
</tr>
<tr>
<td>Sócrates (inpatient)</td>
<td>114</td>
<td>96 (83.9%)</td>
<td>107 (95.0%)</td>
<td>57 (53.2%)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>180</td>
<td>210 (10.2%)</td>
<td>250 (90.0%)</td>
<td>180 (86.0%)</td>
<td>2</td>
</tr>
<tr>
<td>Rural</td>
<td>244</td>
<td>213 (87.3%)</td>
<td>238 (97.5%)</td>
<td>182 (65.1%)</td>
<td>1</td>
</tr>
<tr>
<td>General Total</td>
<td>624</td>
<td>523 (83.6%)</td>
<td>588 (96.6%)</td>
<td>562 (89.9%)</td>
<td>1</td>
</tr>
</tbody>
</table>

Epidemiology of Highly Endemic Leptospirosis

- Related to daily activities of living
  - Frequent exposure, ubiquitous
- Zoonotic Reservoirs
  - Difer between urban and rural settings
  - Is biodiversity in rural area vs. urban areas related to transmission?
    - Serovars/strains/species regionally distributed
      - Copenhageni in Salvador, Brazil dominant
    - Multiple serovars/species co-exist in Iquitos, Peru
    - New species/serovars being discovered
      - L. fainei serovar Hurstbridge
      - Serovar Sehgal in Andaman Islands
      - VAR10, dominant species/serovar in Iquitos, Peru
Proportion of Leptospirosis Cases Due to Varillal 10

- Varillal only: 205 cases (21%)
- Cross infection (Varillal + others): 93 cases (10%)
- Non-Varillal: 127 cases (13%)
- Negative: 549 cases (56%)

Determining Risk for Severe Leptospirosis by Molecular Analysis of Environmental Surface Waters for Pathogenic Leptospira

Christian A. Ganoza, Michael A. Matthias, Devon Collins-Richards, Kimberly C. Brauwer, Calaveras B. Cunningham, Eddy R. Segura, Robert H. Gilman, Eduards Gotuzzo, Joseph M. Vinetz*
Table 2: Distribution of L. interrogans strains with location

<table>
<thead>
<tr>
<th>Location</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urban/peri-urban</td>
<td>9</td>
<td>3</td>
<td>0</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Rural</td>
<td>2</td>
<td>7</td>
<td>9</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>10</td>
<td>9</td>
<td></td>
<td>30</td>
</tr>
</tbody>
</table>

The relative proportion of L. interrogans serovars varied significantly with location (p=0.03, Fisher's exact test)

* Includes leptospiral genomospecies L. noguchii, L. santarosai and L. genmospecies 1.

A Proposed International Leptospirosis Research Agenda

- Creation of regional, national and international networks of leptospirosis diagnostic laboratories
  - Development of an international registry of cases
    - Critical for guiding public health policy decisions
- Establishment of central repositories
  - Leptospiral strains, hybridomas, reference polyclonal antisera and monoclonal antibodies, available at nominal cost
- Creation of an international, internet-queriable, up-to-date, comprehensive leptospiral database
- Development of an international, multi-center, prospective population-based study of leptospirosis
  - Human genetic susceptibility
  - Leptospiral virulence
  - Creation of well-characterized specimen bank for refinement of diagnostics and therapeutics
CEPANZO

Created through an agreement with the Government of Argentina, the Pan American Zoonoses Center (CEPANZO) began operations in Buenos Aires in August 1956 “to promote and strengthen Governments’ activities to combat the zoonoses in the countries of America.”


CEPANZO PROGRAM OF ACTIVITIES

- Training
- Laboratory studies
- Research
- Demonstration and information work

IN THEORY Research activities were guided toward the animal reservoir rather than the human infection, concentrated on the analysis of outbreaks to determine the dissemination and extension of the disease in order to identify risk groups on the basis of the characterization of the corresponding ecosystems.

IN PRACTICE Activities were guided toward training of human resources and the laboratory implementation of diagnoses for national reference in regard to the typing and characterization of serovars.

Course on leptospirosis at the Pan American Zoonoses Center (CEPANZO) in Azul, Argentina, in 1961.
OUTCOME OF THE ACTIVITIES IN CEPANZO

- 1960’s - Resolutions of the PAHO Directing Councils systematically describe financing difficulties.
- 1970’s - Begins to release activities in Leptospirosis.
- 1979 - “urge the participating Governments to assume a larger share of the operating costs…”
- 1982 - “accelerate negotiations, including those involving the financial situation”

The Pan American Zoonoses Center was disestablished on April 30, 1990.

The Pan American Institute for Food Protection and Zoonoses (INPPAZ) was established on November 15, 1991.

OUTCOME OF THE ACTIVITIES IN LEPTOSPIROSIS

- INPPAZ transfers reference strains to 8 laboratories within the region.

By 1997, Leptospirosis was not mentioned among the diseases included in the specific objectives of the Program on Veterinary Public Health.

NOWADAYS

- End of 2003 - A focal point in Leptospirosis is designated
- February 2004 – Meeting in Mexico
- May 2004 – 2006 - Meetings in Cuba

AIMS

- Promote standardization and harmonization of laboratory procedures
- Identify needs and set regional mechanisms of provision for supplies
- Identify reference laboratories for the region
- Promote technical cooperation among countries
- Develop a regional information and surveillance system
- Standardize protocols for the attention of emergencies
- Standardize protocols for the development of vaccines
- Promote basic and applied research projects
- Seek financing to sustain the activities

SURVEY

- July 2004 – A survey is distributed to the 27 countries
- Feedback from 24
- 87 laboratories – Answers from 68

United States and Canada not included
NEEDS

- Unify reference strains
- Harmonize rapid tests
- Training and supplies for isolation
- Epidemiological studies
- Treatment protocols
- Control and quality assurance procedures

TASKS

- Identify national reference laboratories
- Distribute reference strains
- Identify regional reference laboratories
- Define control and quality assurance procedures
Leptospirosis: European Perspective

W. A. Ellis

Veterinary Sciences Division, Stormont, Belfast

OIE Leptospira Reference Lab

Want to discuss both human and animal leptospirosis in Europe

Former very dependant on knowledge of latter

Implications for developing countries of difficulties in Europe

Different aspects important

Human

Important for their acute clinical consequences – may be chronic sequels

Animals

Chronic infection by Host maintained leptospires are MOST important in food producing animals
Give rise to economic loss through reproductive wastage

Nidality very marked in Europe

Only a small number of species containing only a few of the serovars found worldwide

L. interrogans
L. borgpetersenii
L. kirchneri

Major domestic animal maintained leptospira infections in Europe:

L. borgpetersenii serovar Hardjo – cattle, sheep
L. interrogans serovar Bratislava/Muenchen? – pigs, horses and dogs plus various wildlife reservoirs,
L. interrogans serovar Canicola - dogs

Human infections

Caused by incidental infections ie direct or indirect transmission from animal hosts

Animal leptospirosis

Animals act both as maintenance and incidental hosts

Veterinary Sciences Division

Veterinary Sciences Division, Stormont, Belfast
Other leptospires found in Europe – largely rodent maintained:

- *L. interrogans* serovars *Icterohaemorrhagiae* (rat), Sejroe, Saxkoebing, Pomona (Dania), Autumnalis, Lora and Broomi
- *L. borgpetersenii* serovars Ballum/Arborea/Castellon, Tarassovi and Javanica
- *L. kirschneri* serovars Grippotyphosa and Mozdok/Tsarasovo

Only a small number of serogroups represented

- Australis, Autumnalis, Ballum, Canicola, Grippotyphosa, *Icterohaemorrhagiae*, Javanica, Pomona, Sejroe and Tarassovi

Has in the past reduced the number of antigens required for serological confirmation

Human:

- Incidence of confirmed clinical disease
  - Very low
  - Falling – complex but factors affecting decrease out-weight those which would cause an increase

Human incidence – factors contributing to decrease:

- Living and working conditions – mechanisation in agriculture
- Legislation – e.g. Health and Safety and Control of Substances Hazardous to Health (COSHH) in the UK.
- Control of maintenance hosts populations – rat control programmes
- Control of infection in some maintenance hosts eg cattle have reduced exposure in farmers

Human incidence – factors contributing to decrease:

- Education
- Vaccination
- Control programmes

Shift from being an occupational disease to one where recreational activities (a), particularly water sports, and travel are major risk factors (b)

(a) often a feature of (b)

However, working with animals still a major risk factor – veterinarians, abattoir workers, farmers, hunters
Human incidence – factors contributing to increase:

**Recreation**
- Water sports
  - Canoeing, raft racing, jet skiing
- Adventure sports where there is increased exposure to infected water and risk of skin abrasions
  - Pot-holing
- Iron-man and triathlon events

**Travel**
- Exposure through travel has had the effect of greatly increasing the number of species and serovars to which Europeans can be exposed relative to the short list which I have shown earlier
- Makes confirmatory serodiagnosis more difficult

**Reported Incidence**
- Higher in eastern Europe than in West
- Range: 0.3 (Spain) to 18 (Russia) cases per 1,000,000
- Major differences between similar countries:
  - e.g. France has an incidence of c 6-10x that of the UK or Germany
- And in different ecosystems:
  - e.g. Azores c 11x higher incidence than mainland Portugal

**Human**
- Serological evidence suggests higher levels of undiagnosed and or subclinical leptospirosis particularly in certain high risk groups
- Polish study (2004) – 14% seroprevalence in people with contact with cattle and pigs
- Spain (1999) – 11.5% veterinary students seropositive

**Human**
- Rat still the major source of infection across Europe with Icterohaemorrhagiae infection major cause, both in terms of confirmed diagnoses but also in severity
- Mortality rates vary within Europe
  - e.g. very rare in UK but Italy was reporting a >20% mortality rate in the late 90's
**Reporting v Surveillance**

**Human**
- Notifiable (UK-RIDDOR 1995-
  Reporting of Injuries, Diseases and
  Dangerous Occurrences Regulations)
- Reporting systems but not surveillance

**Animal**
- Neither reporting nor surveillance

---

**Animal Leptospirosis in Europe**

National veterinary regulatory authorities primary interest is in OIE List A diseases
- Leptospirosis is List B
- Therefore control measures are voluntary.
- Their implementation falls to the individual owners or to sectors of the agricultural industry
- Surveillance is increasingly being funded by vaccine manufacturers to support product marketing
- **Lack of good current prevalence data**

---

**Major domestic animal maintained leptospira infections in Europe:**
- *L. borgpetersenii* serovar Hardjo – cattle, sheep
- *L. interrogans* serovar Bratislava/Muenchen – pigs, horses and dogs plus various wildlife reservoirs,
- *L. interrogans* serovar Canicola - dogs

---

**Hardjo and Bratislava are not just European but global infections of cattle and pigs respectively**

- Genital infection and venereal spread are important aspects of both host parasite interactions
- Evidence that Hardjo and Bratislava have the ability to persist for very prolonged periods in CNS of sheep and pigs respectively – **could this have read across for humans- NZ study**

---

**Hardjo infection:**

Disease of the susceptible pregnant cow (abortion) or the recently calved cow (infertility and occasionally agalactia)

- Primarily a disease of Holstein/Friesian dairy cattle.
- ? Genetic susceptibility or management practices ensuring the supply of susceptible animals

---

**Hardjo infection – prevalences variable in Europe**

- Prevalences low in some of the older more traditional beef breeds eg in Portugal there are high prevalences in dairy cattle(H/F) in the plains of NW Portugal yet in the Alto Duro it is almost absent (traditional beef breeds)
### Hardjo Prevalence

Endemic in cattle in the UK, Ireland and Netherlands. Was the cause of the increase in human leptospirosis in the UK in the mid 1980’s. Incidence in man reduced by farmer education and the widespread use of effective monovalent vaccine in dairy cattle. Control schemes - Netherlands.

### Hardjo Infection in Cattle Elsewhere in Europe

Prevalence decreases from south to north – High levels of infection in Italy and south eastern Europe as far as Turkey but apparently absent from Scandinavia. German work in the 1980’s suggested that it was common in cattle in Bavaria but uncommon in the north. Recent work indicates that prevalence has now fallen in the south.

### Inappropriate Antigens - Hardjo in France

Never isolated in France (but in French exports as long ago as 1965). Long argued by French authorities that prevalences were very low. However recent evidence of surprisingly high sero-prevalences in beef cattle following the switch to using a UK hardjo isolate as antigen. Similar story when French switched from Australis to Bratislava for pig testing.

### Bratislava Infection

Ubiquitous host range, but specific pig adapted strains. No evidence of pig strains being a significant zoonoses – very poor urinary excretion. Evidence from Spain that it could be adapting to cattle.

### Canicola Infection


### Incidental Infections

Not significant in most domestic animal species but one exception – Horse – very susceptible, often very valuable. Most cause abortion. Grippotyphosa, Pomona and Bratislava associated with recurrent uveitis. No investigations of horses as source of human infections.
Problems in Europe

Loss of skill base - particularly acute in Eastern Europe where it was historically strong
Very few specialist labs
Molecular tools are improving rapidly but need underlying base of isolates
Lack of surveillance data, particularly animal data with knock-on consequences for human diagnosis

General problems

Air transport regulations
Security considerations
Finance – full economic cost
Collapse of limited facilities in Africa – Onderstepoort
Major epidemic of Grippotyphosa infection in Kenya. Nowhere in Africa to do testing

Summary

Low incidence in people
Knowledge base of strains present is old/ out of date
Much that we do not know about animal hosts and the strains they maintain
Scenario of Leptospirosis in Southeast Asia

Subhash C Sehgal
MD, MAMS, FAMS, FIMSA, FNASc, FRC PATH (UK)

Transmission Cycle: Leptospirosis
Factors facilitating transmission

- Environmental factors
  - High rainfall
  - High humidity
  - Temperature between 28°C - 35°C
  - Neutral or slightly alkaline pH of soil
  - Large forest cover
  - Poor environmental sanitation
  - Increased agricultural activity
- Animal factors
  - Rodent density
  - Farm animals
  - Domestic animals
- Human factors
  - Occupation involving animal contact
  - Poor personal hygiene

Risk groups

- Contact with contaminated environment
  - Agricultural workers
  - Sewage workers
  - Bare-foot walkers
  - Sports persons
- Contact with animal urine
  - Cattle farming
  - Pig farming
  - Veterinarians
- Contact with animal tissue
  - Butchers
  - Veterinarians
  - Laboratory personnel

Situation in Southeast Asia

- Existence of Weil’s disease was suspected during late 19th century and early 20th century
- Bacteriologically confirmed cases first detected in Andaman Islands in 1929
- Cases were detected in Bombay, Calcutta and Assam during 1930s and 1940s
- Very few reports between 1940s and 1980s
- Sudden upsurge of reports since 1980s

Population at risk

<table>
<thead>
<tr>
<th>Country</th>
<th>Population</th>
<th>Work force (million)</th>
<th>Agricultural labor share (%)</th>
<th>Agri. workers (million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangladesh</td>
<td>133,470,000</td>
<td>66.2</td>
<td>60.0</td>
<td>80,000</td>
</tr>
<tr>
<td>Brunei</td>
<td>373,788</td>
<td>0.14</td>
<td>15.0</td>
<td>49,104</td>
</tr>
<tr>
<td>Cambodia</td>
<td>7,904,392</td>
<td>6</td>
<td>30.0</td>
<td>2,346,700</td>
</tr>
<tr>
<td>China</td>
<td>1,284,897,690</td>
<td>744</td>
<td>60.0</td>
<td>491,300</td>
</tr>
<tr>
<td>India</td>
<td>1,025,103,500</td>
<td>816</td>
<td>80.0</td>
<td>825,000</td>
</tr>
<tr>
<td>Indonesia</td>
<td>197,735,600</td>
<td>99</td>
<td>40.0</td>
<td>44,710</td>
</tr>
<tr>
<td>Laos PDR</td>
<td>4,698,337</td>
<td>28</td>
<td>30.0</td>
<td>1,398</td>
</tr>
<tr>
<td>Malaysia</td>
<td>19,435,368</td>
<td>8.9</td>
<td>10.0</td>
<td>1,898</td>
</tr>
<tr>
<td>Myanmar</td>
<td>31,435,953</td>
<td>20.7</td>
<td>70.0</td>
<td>16,719</td>
</tr>
<tr>
<td>Philippines</td>
<td>66,464,366</td>
<td>33.7</td>
<td>40.0</td>
<td>15,185</td>
</tr>
<tr>
<td>Singapore</td>
<td>5,504,333</td>
<td>2.09</td>
<td>8.1</td>
<td>456</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>19,742,459</td>
<td>6.6</td>
<td>40.0</td>
<td>2,870</td>
</tr>
<tr>
<td>Thailand</td>
<td>68,772,457</td>
<td>33.8</td>
<td>20.0</td>
<td>13,939</td>
</tr>
<tr>
<td>Vietnam</td>
<td>91,757,699</td>
<td>36.2</td>
<td>40.0</td>
<td>36,644</td>
</tr>
<tr>
<td>Total</td>
<td>2,031,497,811</td>
<td>168.85</td>
<td>63.84</td>
<td>922,000</td>
</tr>
</tbody>
</table>

Environment and people

- Most countries in Southeast and South Asia have tropical hot and humid climate with monsoons
- A significant part of the land area is low lying wetlands
- Rice is a major crop cultivated and a large proportion of the 922 million agricultural labourers in these countries are involved in rice cultivation
- Agricultural techniques are by and large conventional
- All these countries have large domestic and free living animal populations
- These factors lead to high incidence of leptospirosis in these countries

Situation in different countries

- Existence of Weil’s disease was suspected during late 19th century and early 20th century
- Bacteriologically confirmed cases first detected in Andaman Islands in 1929
- Cases were detected in Bombay, Calcutta and Assam during 1930s and 1940s
- Very few reports between 1940s and 1980s
- Sudden upsurge of reports since 1980s
National task force study (ICMR)

States where leptospirosis was detected

Annual Leptospirosis outbreaks

States where leptospirosis was detected

Leptospirosis as a cause of fever (ICMR task force study)

<table>
<thead>
<tr>
<th>Place</th>
<th>Suspects</th>
<th>+ve</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhubaneswar</td>
<td>357</td>
<td>29</td>
<td>8.1</td>
</tr>
<tr>
<td>Kashmir</td>
<td>72</td>
<td>15</td>
<td>20.8</td>
</tr>
<tr>
<td>Jodhpur</td>
<td>241</td>
<td>6</td>
<td>2.3</td>
</tr>
<tr>
<td>Manipal</td>
<td>518</td>
<td>60</td>
<td>11.6</td>
</tr>
<tr>
<td>Kolkata</td>
<td>273</td>
<td>15</td>
<td>5.5</td>
</tr>
<tr>
<td>Dibrugarh</td>
<td>295</td>
<td>12</td>
<td>4.1</td>
</tr>
<tr>
<td>Kerala</td>
<td>582</td>
<td>290</td>
<td>49.8</td>
</tr>
<tr>
<td>Wardha</td>
<td>306</td>
<td>14</td>
<td>4.6</td>
</tr>
<tr>
<td>Lucknow</td>
<td>134</td>
<td>13</td>
<td>9.7</td>
</tr>
<tr>
<td>Chandigarh</td>
<td>77</td>
<td>16</td>
<td>20.8</td>
</tr>
<tr>
<td>Pune</td>
<td>549</td>
<td>40</td>
<td>7.3</td>
</tr>
<tr>
<td>Hyderabad</td>
<td>186</td>
<td>22</td>
<td>11.8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>3611</strong></td>
<td><strong>532</strong></td>
<td><strong>14.7</strong></td>
</tr>
</tbody>
</table>

Situation in different countries: Malaysia

- Several reports of isolation pathogenic leptospires from water bodies have originated from Malaysia
- Much of the information about the ecological background of leptospirosis was gained through studies conducted in Malaysia and nearby countries during 1940s, 50s and 60s
- An outbreak of leptospirosis was reported among the participants of a multi sport expedition in Malaysia in 2000

Situation in Philippines

- Philippines is astride the typhoon belt and every year five to six cyclones strike the country
- Flash floods are common during monsoon
- First case was identified in 1932
- No nationwide data on disease occurrence
- Seroprevalence as high as 43% has been reported among the farmers
- A 266% increase in reported cases was observed in 1999

Situation in Indonesia

- Indonesia has a tropical humid climate and most of the land area are coastal low lands
- Agriculture is an important economic activity accounting for 20% of GDP and employing 50% of the workforce
- Leptospirosis is a common occurrence in Indonesia
- As many as 17 serovars were first isolated in Indonesia
- A seroprevalence of 11.8% had been observed in Jakarta
- Seroprevalence among rodents was high at 47%
Situation in other countries

- **Vietnam**: There have been several reports of leptospiral infection among animal populations.
  - In a study involving 1,400 participants from Mekong delta, a seroprevalence rate of 18% was observed.
- **Sri Lanka**: Leptospirosis has been one of the common epidemics.
  - Recently a large outbreak occurred in which more than 1,500 persons were affected.
- **Bangladesh**: Seroprevalence rate of 38.2% was observed in flood prone area.
- **Pakistan**: 11% non-A, non-B hepatitis cases showed 4-fold rise in titre of IgM anti-leptospiral antibodies (Bryan JP et al, 1996).

Emerging public health problem

- Although data on annual occurrence of leptospirosis lacks in most countries, the increasing reports and frequent outbreaks suggest that leptospirosis is emerging as an important public health problem.
- The reasons could be:-
  - Expansion of agriculture to more areas
  - Environmental impact of deforestation
  - Frequent floods
  - Migration of population to cities and overcrowding
  - Unplanned expansion of cities
- A multicentric study conducted in four SEA nations showed that leptospirosis accounts for 17% of non-hepatitis A-E jaundice, 13% non-malarial fever and 3% of haemorrhagic fevers.

What needs to be done

- A strengthened surveillance and notification to detect early warning signals of outbreaks and rapid response.
- A higher priority for leptospirosis in National & WHO (TDR) health programmes.
- Networking of institutions working in the field of leptospirosis.
- Development of better diagnostic tests, particularly antigen detecting system.
- Making diagnostic facilities available at regional level by establishing regional reference centres.

THANKS
Burden of Leptospirosis in Thailand
Waraluk Tangkanakul, MD, MPH
Department of Disease Control
Ministry of Public Health
Thailand

Topics
- Epidemiology of Leptospirosis during epidemic (since 1996), Thailand
- Leptospirosis outbreak after flooding (19 to 22 August 2006) in Nan province, Thailand

Reported Cases and Morbidity rate (Per 100,000 Population) of Leptospirosis by year in Thailand, 1988-2006 (up to 29 July)

Death cases and case fatality rate of Leptospirosis by year in Thailand, 1990-2006 (up to 29 July)

Morbidity rate of Leptospirosis by province, 1995 - 2000

Source: Disease Notification Report, Ministry of Public Health, Thailand
Morbidity rate of Leptospirosis by province, 2000 - 2005

<table>
<thead>
<tr>
<th>Year</th>
<th>Morbidity rate per 100,000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>72</td>
</tr>
<tr>
<td>2001</td>
<td>71</td>
</tr>
<tr>
<td>2002</td>
<td>70</td>
</tr>
<tr>
<td>2003</td>
<td>66</td>
</tr>
<tr>
<td>2004</td>
<td>66</td>
</tr>
<tr>
<td>2005</td>
<td>70</td>
</tr>
</tbody>
</table>

Morbidity rate per 100,000 population
- None = ,  < 2.5 = , 2.5 - 15 = , 15 - 50 = , > 50 =

Source: 506 Notification report, BOE, Ministry of Public Health, Thailand

Epidemiology of Leptospirosis during epidemic, Thailand (1)

Place: In village level, one year cohort study in Korad found decreased in incidence rate from reported area (11.8% to 9%) whereas incidence rate in non-reported area (2.6%) did not change.

Time: rainy season (Jul.- Dec., peaked in Sep.- Oct.)

Person: Male farmers and age groups between 41-60 were at high risk of getting infection. M:F case ratio was 3:1 in 2006.

Clinical: Fever, headache and myalgia are common manifestations. Pulmonary haemorrhage was frequently reported and a major cause of death.

Proportion of Leptospirosis in fever of unknown origin ranged from 17.5 to 37.4% (details in Ref. 1-7).

Epidemiology of Leptospirosis during epidemic, Thailand (2)

Immunity: Prevalence of leptospiral antibody in population was 2 times lower than in 1970 (71 provinces 28%, 1,028/3,737).

In 1998, in general population and military personnel were 13.5% (33/245) and 8.1% (30/369).

Asymptomatic infection: Prevalence in agriculturist was 8.4% but increased during outbreak, 60.4 up to more than 90%.

Risk factors: Working in paddy field and exposure to natural water resources were also risks of leptospiral infection.

It cannot be confirmed that exposure to animals was strongly associated with the human infection.

Epidemiology of Leptospirosis during epidemic, Thailand (3)

New serovar: Bratislava was first recognized in 1997 and had serologic reactivity by MAT in cases from many provinces (9 NE, 11 North and 1 South provinces). It was also found from buffalo, dog and pig by MAT in Korad. (Ref. 8,9) Saigon was first reported in Sonkhla, 2000.

Changing of serovars: has documented in Mahasarakam (pyrogenes, 1998 to bratislava), Sakon Nakhon (ranarum, 2000 to bratislava, 2001) and 11 lower north provinces (pyrogenes to bratislava).

Isolation in same provinces: Predominant serovar in human was Autumnalis (Ref.10). Autumnalis was also be isolated from B.indica’s kidney (Ref.11).

Leptospirosis outbreak after flooding (19 to 22 August 2006) in Nan province
Ubosod Wat Phumin (at the front)
Wat Chang Khom Worawihan, Amphoe Muang Nan

Affected areas
-12 out of 14 districts (85.7%) were flooded.
-52 out of 99 Tambons (52.5%) and 262 out of 885 (29.6%) villages were destroyed.

Level of destruction
Red: high
Pink: Moderate
Green: Mild

Investigators
-Thai Field Epidemiology Training Program (Principle Investigator: Dr. Derek Sutdan)
-Bureau of General Communicable Diseases
-National Institute of Health
-National Animal Institute of Health
-Mahidol university
-Armed Forced Research of Medical Science
-Nan Provincial Health Office
-Tha Wang Pha Hospital

Objectives
- Verify diagnosis.
- Verify outbreak and extending of the outbreak.
- Identify source and risk factors of outbreak.
- Technical support for prevention and control of outbreak.
- Logistic support: glove, doxycycline etc.
Methodologies

• Descriptive study: reviewed medical records of all admitted cases, trapped rodent and culture leptospires from kidneys of 11 rodents, 1 buffalo, 1 cow, blood drawn from chicken, dog, cat, cows, pig and culture from soil and water of death cases house
• Unmatched case control study (27 cases: 108 control, 1:4) under analysis process

Preliminary results of Leptospirosis outbreak in Nan province

• Number of cases: 410 cases (54 confirmed cases by PCR or IFA, 140 probable cases and 216 suspected cases) with 6 deaths (3 confirmed cases by PCR)
• Place: Tha Wang Pha district had highest attack rate, followed by Muang district. 35 out of 43 villages (81.4%) in Tha wang Pha reported suspected leptospirosis cases.
• Time: Peaked of outbreak was 3 weeks (37th) after flooding.
• Person: Male to Female case ratio was 1.6:1. Median age of cases was 38 years old (range 2 to 77 years)
Clinical manifestations of Leptospirosis cases in Nan province, 18 August – 25 September 2006

Number of Leptospirosis cases by district in Nan province, 18 August – 25 September 2006

Preliminary Laboratory results

<table>
<thead>
<tr>
<th>Type of Lepto. Test</th>
<th>+ve Results (%)</th>
<th>Serovar (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lepto latex test</td>
<td>2.7 (101/3,700)</td>
<td>-</td>
</tr>
<tr>
<td>2. IFA</td>
<td>2.7 (42/1,596)</td>
<td>-</td>
</tr>
<tr>
<td>3. PCR</td>
<td>3.0 (2/66)</td>
<td>-</td>
</tr>
<tr>
<td>4. culture</td>
<td>1 human sample</td>
<td>-</td>
</tr>
<tr>
<td>5. MAT</td>
<td>32.2 (18/55)</td>
<td>Sejroe 43.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Australis 26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Louisiana 17.3</td>
</tr>
</tbody>
</table>

Source: Chiang Mai regional office, Department of Medical Science tested sample during 7 – 16 September 2006
Medical cost for Leptospirosis, Nan province 7 to 25 Sep. 2006

<table>
<thead>
<tr>
<th>Categories</th>
<th>bahts</th>
<th>$ (37 bahts)</th>
<th>number</th>
<th>Total $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lepto latex *</td>
<td>50</td>
<td>1.35</td>
<td>3,700</td>
<td>4,995</td>
</tr>
<tr>
<td>IFA*</td>
<td>200</td>
<td>5.41</td>
<td>1,596</td>
<td>8,634.36</td>
</tr>
<tr>
<td>PCR*</td>
<td>500</td>
<td>13.51</td>
<td>66</td>
<td>891</td>
</tr>
<tr>
<td>MAT*</td>
<td>200</td>
<td>5.41</td>
<td>55</td>
<td>297.55</td>
</tr>
<tr>
<td>Outpatients**</td>
<td>143.75</td>
<td>3.89</td>
<td>3,700</td>
<td>14,393</td>
</tr>
<tr>
<td>Inpatients**</td>
<td>2,288.28</td>
<td>61.85</td>
<td>250</td>
<td>15,462.5</td>
</tr>
<tr>
<td>Cost/ day**</td>
<td>671.71</td>
<td>18.15</td>
<td>1,750</td>
<td>31,762.5</td>
</tr>
</tbody>
</table>

Total Cost = 2,828,128.67 bahts / 76,435.91 $

Source: *National Institute of Health (cost for only reagent)

Investigation and prevention cost for Leptospirosis, Nan province from DDC, 10 to 25 Sep. 2006

<table>
<thead>
<tr>
<th>Categories</th>
<th>bahts</th>
<th>$ (37 bahts)</th>
<th>number</th>
<th>Total $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perdium, 7 Day</td>
<td>8,400</td>
<td>227.01</td>
<td>10</td>
<td>2,270.1</td>
</tr>
<tr>
<td>Transportation</td>
<td>6,000</td>
<td>162.16</td>
<td>20</td>
<td>3,243.2</td>
</tr>
<tr>
<td>media</td>
<td>50</td>
<td>1.35</td>
<td>100</td>
<td>135</td>
</tr>
<tr>
<td>Logistic supports (Department of Disease Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boots</td>
<td>100</td>
<td>2.7</td>
<td>10,000</td>
<td>27,000</td>
</tr>
<tr>
<td>Edu. material</td>
<td>100</td>
<td>2.7</td>
<td>10,000</td>
<td>27,000</td>
</tr>
<tr>
<td>Doxycycline (2)</td>
<td>10</td>
<td>0.27</td>
<td>10,000</td>
<td>27,000</td>
</tr>
</tbody>
</table>

Total Cost = 2,543,613.5 bahts / 68,746.3 $

Total cost

- Medical cost
  - 76,435.91 $ (2,828,128.67 bahts)
  - 68,746.3 $ (2,543,613.5 bahts)

- Investigation and Medical cost from Department of Disease Control
  - Total 145,182.21 $ (5,371,741.77 bahts)

Distribution of FUO, Leptospirosis cases by month in Thailand, 1996-16 Oct. 2006

Source: 506 Disease Notification Report, MOPH

What is FUO?

Fever > 2 days

Non-specific symptoms: myalgia, nausea, vomiting, etc.

Pyrexia of Unknown Origin

Non-specific signs: Lymphadenopathy, hepatomegaly, splenomegaly, etc.

Non-specific lab: CBC, U/A, CXR etc.

Khop Khun
Thank you

Ref.1

Ref.2
Cases of FUO in working age group (more than 15 years) in Thailand, 1990 – 16 Oct. 2006

<table>
<thead>
<tr>
<th>Year</th>
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<tr>
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<tr>
<td>1991</td>
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<tr>
<td>1994</td>
<td>200,000</td>
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</table>

Source: 506 Disease Notification Report, MOPH, Thailand

Ref.3

Diagnosis of Leptospirosis cases in Udon Thani (Oct 2000 – Dec 2002)

- Total 204 patients were diagnosed as having leptospirosis based on MAT and/or culture isolation
- 96 patients (47%) were culture positive
- Identified leptospira serovars were:
  - autumnalis (85%)
  - pyogenes (5%)
  - medemision (5%)
  - javanica (4%)
- Time to culture detection of leptospires ranged from 7-66 days, median 22 days.

Wuthiekanun, et al. ILS 2005, Thailand

Ref.5

Diagnosis of Leptospirosis cases in Maharat Nakhon Rachasima, Loei, Banmai Chaiyaprod and Chumphon, July 2001 – June 2002

- Total 845 acute febrile illness patients
- Diagnosis
  - Leptospirosis: 249 (29.5%)
  - Leptospirosis & influenza: 14 (1.7%)
  - Leptospirosis & other rickettsial infections: 8 (0.9%)
  - Leptospirosis & scrub typhus: 33 (3.9%)
  - Scrub typhus: 99 (11.7%)
  - Scrub typhus & influenza: 20 (2.4%)
  - Scrub typhus & other viral infections: 4 (0.5%)
  - Murine typhus: 13 (1.5%)
  - Murine typhus & influenza: 2 (0.2%)
  - Others: 115 (13.6%)


Ref.6

Distribution of bratislava by province in human and swine (MAT), B. indica (culture), 1999-2000

Human
- Rice field rat (B. indica)
- Swine

Ref.8
Cohort study (integrated Human - Animal Studies) March to December 2004, Nakorn Ratchasima

<table>
<thead>
<tr>
<th>Serovar found in Human (2,207)</th>
<th>Serovar found in Buffalo (103)</th>
<th>Serovar found in Cattle (100)</th>
<th>Serovar found in Dog (100)</th>
<th>Serovar found in Pig (100)</th>
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<td>Ranarum</td>
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<tr>
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<td>Shermani</td>
<td>Shermani</td>
<td>Shermani</td>
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<tr>
<td></td>
<td>Tarassovi</td>
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<tr>
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Serovar found in Buffalo (100)

<table>
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<th>Serovar found in Pig (100)</th>
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<tr>
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Serovar found in Pig (100)

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<tr>
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</table>


| Source: Phulsuksombati D, et al.2002 Ref.11 |

Rattus norvegicus 36.7% 62.6%
Bandicota indica 13.1% 14.6%
Rattus losea 7.7% 16.7%
Rattus ratus 7.1% 1.7%
Rattus argentiventer 6.2%
Bandicota savilei 6.0%
Rattus exulans 1.0%
Epidemic: Buri Rum, Surin, Khon Kaen, Kalasin, control: Nakhon Panom
R.Norvigicus: Pyrogenes
B.indica: Autumnalis, Bataviae, Pyrogenes, Javanica and Australis
The surveillance and reporting of leptospirosis in the Western Pacific Region varies significantly depending on the notifiable status of the disease, the disease diagnostic capability and methods for reporting cases to the health authorities.

Australia has a well defined surveillance program which captures confirmed cases from around the country. Questionnaires are used to provide enhanced surveillance and reports are generated by the WHO/FAO/OIE Collaborating Centre for Reference & Research on Leptospirosis as hardcopy and published on a website. The Australian Department of Health and Ageing also collects notifiable data and issues reports quarterly and annually. Others such as New Caledonia and New Zealand also have very effective surveillance schemes which notify and report on epidemiological aspects of the disease, this information is collated into their Annual Reports and can be made available on request. Other countries in the region vary in their surveillance and reporting levels for the disease but where needed have the potential to develop their capability.

The range of serovars or representative serogroups infecting humans and animals in the region varies significantly. There are new serovars emerging in the region which have the potential to change the disease landscape depending on their ability to adapt to new hosts and virulence to humans. Australia has seen 2 new serovars emerge in recent years and the region of Micronesia another. Abilities of countries to investigate disease outbreaks, collect diagnostic specimens from human and animal sources and to collaborate with reference facilities determines largely the collective effectiveness of authorities to locate newly emerged or emerging serovars of Leptospira in the region.

The ability of all countries in the region to accurately report on and monitor leptospirosis hinges strongly on their respective abilities to provide diagnostic and reporting services which are timely and informative of trends. The provision of targeted laboratory training, database development with enhanced surveillance against well defined and adopted notifiable disease criteria well help resolve some of the issues.
Early Discovery and Investigations of Leptospirosis in China

- The presence of leptospirosis in China was first discovered in Guangzhou city from one of the three patients suffering from fever with unknown reason.
- By means of silver staining, leptospires were seen microscopically in liver preparations of guinea pig inoculated with the patient’s blood.
- Two leptospirosis cases with meningoencephalitis were observed by Zhong Huilan in 1939. Meanwhile, an investigation of the infectious source was conducted.

The serious outbreaks and study on geographical epidemiology of leptospirosis, 1955-1993.

Geographical Features of China

- China is at the eastern tip of Eurasia with latitude ranging from 18°N to 53°34’N and longitude from 73°E to 135°06’E. The higher western part and lower eastern part are the main topographical features of the country. Qinghai-Xizang plateau is the highest and descends eastwards. There are many mountains, rivers, hills, basins and plains all over the whole country.
General Features of Climate in China

• The climate of China varies extremely. In summer, air temperature in the south and north is high and difference in temperature is small. In winter, this difference in temperature is big. Generally, air temperature in the north is lower than that in the south. The annual rainfall also varies greatly. Leptospirosis mainly distributes over the areas with latitude from 20°N to 35°N and longitude from 100°E to 120°E. There is a decline in rainfall from 1600mm in the southeast to 300mm in the northwest. Within various geographical distributions many kinds of animals and plants exist.

Epidemic Intensity and Tendency of Leptospirosis, 1955-1993

• Leptospirosis was recognized as a notifiable infectious disease in 1955. According to national statistics, 2,424,057 cases of leptospirosis were reported during the period 1955-1993. Average year incidence was 7.0384/10^5, and 24,637 dead cases were reported. Average year fatality rate was 1.02%. The data was collected from 26 provinces.

Incidence Records of Leptospirosis (1)

• There were more than thirty outbreaks of leptospirosis during the period 1955-1993. A large-scale outbreak of leptospirosis was documented in Wenjiang District, Sichuan province in 1958. During the harvest season in autumn more than ten thousand people (mainly farmers and students) were infected through contact with the urine of field rodents. The incidence rate was 19.89/10^5.

Incidence Records of Leptospirosis (2)

• In 1963, parts of Hebei province were heavily flooded. The environments in the flooded area were contaminated with urine of swines. A great number of cases (mainly farmers taking parts in the flood fighting) occurred several days later. The incidence rate was 295.91/10^5.

Incidence Records of Leptospirosis (3)

• During the early 1970s, Huaihe river valley was flooded due to heavy rainfall. Outbreaks of leptospirosis occurred several times. The highest incidence rate was 255.91/10^5 among the outbreaks.

Incidence Records of Leptospirosis (4)

• In 1987, there was an outbreak of leptospirosis in the northeast part of Sichuan province. During the harvest season, more than ninety thousands of farmers were infected. The incidence in Guangan county was 3400/10^5.
The Epidemic Area Can Be Divided into Three Regions

- The area south to 25°N and east to 105°E covering 3 epidemic provinces of Guangdong, Guangxi and Hainan has the total of 129,197 cases with an average incidence of 4.25/10,000.
- The area between 25°N and 35°N covers 13 epidemic provinces of Hubei, Hunan, Jiangxi, Fujian, Shanghai, Jiangsu, Anhui, Zhejiang, Sichuan (including Chongqing), Yunnan, Guizhou, Henan and Tibet etc, which has the total cases of 1,985,898 with an average incidence of 12.00/10,000.
- The area north to 35°N but east to 105°E consists of 10 prevalence provinces such as Shanxi, Hebei, Shandong, Beijing, Tianjing, Inner Mongolia, Liaoning, Jilin and Heilongjiang etc, across which the total cases have been examined with the average incidence of 2.85/10,000.
Seasonal Distribution of Leptospirosis in Different Years in China

- The patients that appear to the north of the Yellow River valley are mostly hobbleddehoys with age group under 20y, accounting for 65% of the total local figure.

Age Distribution of Leptospirosis in China (1)

- The cases that appear in provinces situated at the middle and lower reaches of the Yangtze river such as Hubei, Hunan are mostly consist of a elder and strong laborers.

Age Distribution of Leptospirosis in China (3)

- The main part of Chinese leptospirosis patients are peasants, who then, the percentage contributed by employees and preschool children is lower.
Gender Distribution

- According to the analysis of 402,664 patients in China, the ratio of male/female is 2.01:1, but for 3,168 patients in the north of Yellow River valley this sex ratio is 3.19:1.
- Male patients occupy 76% versus females 24% in the Yellow River valley while in the Yangtze River delta males account for 67% with females for 33%.

Epidemic Forms of Leptospirosis in China

- The paddyfield-form
- Flood-form
- Rain-form
- Other forms

Paddyfield-form

- The paddyfield-form leptospirosis dominates in south China, infections got during farming work in paddy fields, swamplands, glebes and the like. Its chief epidemic source is rats and *Lai*, its dominant serovar. Reports also emerge in Henan, Anhui, Jilin province in recent years especially during the harvest time when cadres, factory workers, teachers and students, adventitious peasants and soldiers come down to the fields to help of reaping.

Flood-form

- The flood-form leptospirosis prevails almost in plain regions where floods frequently occur. *Swine* is its main infectious source and its serovar is *pomona*, but *dogs* could also be the main infectious source in some specific areas with *canicola* as its serovar, and in recent years rats have been also reported as the dominant infectious source in some mountain areas where mountainous flood occurs from time to time with complicated serovars of *Icterohemorrhagiae, Grippotyphosa* and *Bataviae*, etc.

Rain-form

- The rain-form leptospirosis dominates in plain and downfolds. Local people infected leptospirosis by contacting the contaminated water and so as lead to the long time prevalence of leptospirosis. The rain-form has taken place in most provinces in China with *swine* as its main infectious source and also some other host animals reported.

Other forms

- Swimming
- Swine or other animals breeding
- Others
Reservoirs

- During the past four decades, extensive studies have been made. Eighty-five species of animals have been examined. 66 species of animal reservoirs have been discovered in China. They are 30 species of Rodentia, 6 of Insectivora, 6 of Carnivora, 2 of Lagomorpha, 6 of Artiodactyla, 2 of Perissodactyla, 2 of Squamata, 8 of Anura, 1 of Synbranchi, and 1 of Acarina. Rallus aquaticus, Bubulcus ibis and Laelaps echidninus are reservoirs.

- Among these natural carriers, wildlife, especially small rodents as well as swine and canines play a very important role in the epidemiology of leptospirosis. Wild rodentia is the main reservoir of Paddyfield-form, especially Apodemus agrarius, Rattus flavipectus, Rattus losea, and Rattus norvegicus. The carrier rates in rodents are very high along the Yangtze River valley and in the southern part. The carrier rates vary in different localities. Domestic animals, swine and canines are the main reservoirs of Flood and Rain form along Yellow River valley and in the northern part. humans is an infectious source for leptospirosis.

Serogroups and Serovars

- According to the analysis of 12,310 strains isolated from patients blood and 18,691 strains from kidneys of domestic and wild animals, there existed 18 serogroups and 74 serovars of Leptospira interrogans.

- Of the 18 serogroups of pathogenic leptospira, 13 serogroups are most widely distributed in China. Serovar Lai is mainly distributed in the Yangtze River valley, serovar pomona is mainly in Yellow River valley and in the northern part.

15 China Representative Reference Strains

<table>
<thead>
<tr>
<th>Serovar</th>
<th>Strain</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Lai</td>
</tr>
<tr>
<td>javanica</td>
<td>M.14</td>
</tr>
<tr>
<td>canicola</td>
<td>L.im</td>
</tr>
<tr>
<td>fallus</td>
<td>Pkala</td>
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<td>pyrogenes</td>
<td>Hain</td>
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<td>seromani</td>
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<tr>
<td>australis</td>
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<tr>
<td>pomona</td>
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<tr>
<td>harasseri</td>
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<td>wild</td>
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<tr>
<td>Bini</td>
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<table>
<thead>
<tr>
<th>Year</th>
<th>No. Cases</th>
<th>Incidence</th>
<th>No. Deaths</th>
<th>Mortality</th>
<th>Case-Fatality (%)</th>
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Epidemic Intensity and Tendency of Leptospirosis in China, 1994-2005

- 26 surveillance spots in 6 provinces
- Each spot contains 1-2 villages in a county
- Collecting epidemiologic data, investigating density of rats, isolating pathogenic Leptospira, case-study, serological detection, etc.


Month Distribution of the Cases of Leptospirosis in 2005 and Comparing with that in 2004

Month Distribution of the Dead Cases of Leptospirosis in 2005 and Comparing with that in 2004

Geographical Distribution of Leptospirosis in 2005 in China
Distribution of Leptospirosis in Provinces in 2005 in China

Age Distribution of Leptospirosis in 2005 in China

Occupational Distribution of Leptospirosis in 2005 in China

Reservoir investigation


No. Cases of Leptospirosis in 2006, Jan to Sep
### Distribution of Leptospirosis in Provinces in 2006 in China, Jan-Sep

<table>
<thead>
<tr>
<th>Province</th>
<th>No. Case</th>
<th>No. Death</th>
<th>Province</th>
<th>No. Case</th>
<th>No. Death</th>
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<td>Henan</td>
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<td>Guangxi</td>
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<td>46</td>
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<td>Chengdu</td>
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<td>Sichuan</td>
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<tr>
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<td>0</td>
<td>Yunnan</td>
<td>48</td>
<td>8</td>
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<tr>
<td>Shandong</td>
<td>10</td>
<td>0</td>
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### Age Distribution of Leptospirosis in China in 2006, Jan-Sep

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<tr>
<td>10-20</td>
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<tr>
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<td>30-40</td>
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<td>60-70</td>
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<td>70-80</td>
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### Occupational Distribution of Leptospirosis in China in 2006, Jan-Sep

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<td>Housework/unemployment</td>
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</tr>
<tr>
<td>Unknown</td>
<td>5</td>
</tr>
<tr>
<td>Others</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>460</td>
</tr>
</tbody>
</table>
Informal Consultation on Global Disease Burden of Leptospirosis: Methods of Burden Assessment

Claudia Stein, MD, MSc, PhD, FFPH
World Health Organization
Department of Food Safety, Zoonoses and Foodborne Diseases
Geneva, 25-27 October 2006

Weil's disease
Diarrhoeal disease
Hepatic disease
Cancer

Bacterial
Viral
Parasitic
Chemical
Other

Unsafe water
Poor food hygiene
Poor sanitation
Habitation

What do we mean by 'burden'?

ECONOMIC BURDEN
Societal
Particular constituencies
Individual

Which approach to use?

DALYs
Surveillance systems
HALE & others
Intervention impact
$ Costs (DALYs)

Global Burden of Disease (GBD)

GBD 1990 Study
World Development Report 1993
Murray and Lopez 1996
~130 diseases by age, sex and regions of the world

WHO Updates 2000-2004
Annual revisions GBD 1998 to 2002
World Health Reports 1999 to 2004
Comparative Risk Assessment
Generalized Cost-Effectiveness (WHO-CHOICE)
National BOD manual and tools
www.who.int/evidence/bod

GBD Disease classification

Group I: Communicable, maternal, perinatal and nutritional conditions
Group II: Non-communicable diseases
Group III: Injuries

Group I. Communicable, maternal, perinatal and nutritional conditions
A. Infectious and parasitic diseases
1. Tuberculosis
2. Sexually transmitted diseases excluding HIV
   a. Syphilis
   b. Chlamydia
   c. Gonorrhea
   d. Other STDs

Leptospirosis not specifically considered under other conditions following ICD classification system
**GBD Goals**

- Measure loss of health in a comparable way
- Decouple epidemiological assessment and advocacy
- Avoid double counting
- Inject non-fatal health outcomes into health policy debate
- Use a common metric for burden of disease assessment and cost-effectiveness analysis ("summary measure of population health")

**Summary Measures of Population Health (SMPH)**

“Measures that combine information on mortality and non-fatal health outcomes to represent the health of a particular population as a single number”

Murray CJL, Salomon JA, Mathers C, 1999

**A typology of Summary Measures**

- **A** = Time spent in perfect health
- **B** = Time spent in less than perfect health
- **C** = Time lost due to mortality

Health Expectancy = **A** + \( f(B) \)

(Example: HALE)

Health Gap = **C** + \( g(B) \)

(Example: DALY)

**Disability Adjusted Life Years**

\[ \text{DALY} = \text{YLL} + \text{YLD} \]

- **YLL** Years of life lost due to mortality
- **YLD** Equivalent years of healthy life lost due to disability

**Time** as the common metric for mortality and imperfect health
The essence of DALYs

Mortality, Morbidity, and more...

- **Mortality** = Years of life lost (YLL):
  - Mortality and age at death
- **Morbidity** = Years lived with disability (YLD):
  - Incidence, Remission, Duration, Sequelae, Disability, Severity

  for ~130 diseases and their sequelae

YLD - Years Lived with Disability

\[ YLD = \text{Incidence of cases/sequelae} \times \text{average duration} \times \text{disability weight} \]

\[ \text{DALY} = YLL + YLD \]

YLL - Years of Life Lost (mortality)

\[ YLL_x = \text{Number of deaths at age}_x \times \text{standard years of life lost at age}_x \]

\[ \text{DALY} = YLL + YLD \]

What you need (by age and sex)

- Decision on type of burden to be assessed!
- Incidence
- Duration
- Disability weight
- Age at onset

What you (often) have

- Single measure of prevalence
- Limited knowledge of the natural history
- Limited info on severity not matching disability weights

GBD Data sources

**Mortality**

- Vital registration, sample registration systems, household surveys, surveillance systems, epidemiological studies, population laboratories

**Morbidity/disability**

- Disease registers, population based studies, epidemiological (longitudinal studies), health facility data (injuries)
Sources of information on Cause of Death

- Vital registration systems
- Sample registration systems
- Household surveys
- Population laboratories
- Epidemiological estimates
- Cause of death models
- Hospital deaths
- Cancer registries
- (Verbal autopsy)

AVAILABILITY OF NEW OR RECENT VITAL REGISTRATION DATA (complete or partial) WHR2000 & WHR2002

<table>
<thead>
<tr>
<th>Region</th>
<th>WHR2000</th>
<th>WHR2002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>The Americas</td>
<td>21</td>
<td>33</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Europe</td>
<td>43</td>
<td>51</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>8</td>
<td>21</td>
</tr>
<tr>
<td>World</td>
<td>82</td>
<td>128</td>
</tr>
</tbody>
</table>

DALYs - summary of data needs

- Incidence (prevalence) of condition
- Description and quantification of all sequelae
- Age of onset of condition and sequelae
- Duration of episode and all sequelae
- Disability weight for episode and sequelae
- Case fatality ratio or relative risk of mortality

DALYs: Iodine deficiency disorders

YLD calculated for boxes with bold outline and orange shading.

Interpretation of DALYs

\[ \text{DALY} = \text{YLL} + \text{YLD} \]

- High number deaths
- Young adult deaths
- High LE assumed
- High incidence
- Sequela +++
- High DW
- Long duration

Global Burden of Leptospirosis

- Which 'burden'?
- Background &/o epidemic burden?
- Animal/human effects
- Which measures – traditional/summary?
Leptospirosis

GBD approach - conclusions

Advantages
• De-couple epidemiological assessment and advocacy
• Combines fatal and non-fatal health outcomes
• Presents health outcome as single number
• Complies with ICD convention
• Avoids double counting
• Common currency for burden and cost-effectiveness analyses

Disadvantages
• Includes strong value judgements (disability, age)
• All aspects of disease 'buried' in a single number
• Ignores biological reality of co-morbidity and -mortality (risk factors)

Extra Slides
CoDMoD - distributing deaths over cause groups

Inputs (for ~ 3000 registration years, WHO database):
• General & age-specific mortality
• Proportional cause-specific mortality
• GDP

Output (by country):
• Age- and sex-specific cause of death patterns
Measurement methods/questions

• Visual analog
• Time-trade off
• Standard gamble
• Person-trade-off
• Willingness-to-pay

Table 1. Pearson’s Correlation Coefficients for Median Disability Weights for Ten Exercises, Based on 14 Conditions Common to All Exercises

<table>
<thead>
<tr>
<th></th>
<th>Int’l I</th>
<th>Netherlands</th>
<th>Maghreb</th>
<th>Japan</th>
<th>GBD</th>
<th>Int’l II</th>
<th>CDC</th>
<th>Brazil</th>
<th>Int’l III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Int’l I</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Netherlands</td>
<td>0.58</td>
<td>1.00</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Maghreb</td>
<td>0.96</td>
<td>0.96</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>0.94</td>
<td>0.91</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GBD</td>
<td>0.97</td>
<td>0.96</td>
<td>0.92</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Int’l II</td>
<td>1.00</td>
<td>0.98</td>
<td>0.96</td>
<td>0.93</td>
<td>0.97</td>
<td>1.00</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CDC</td>
<td>0.99</td>
<td>0.99</td>
<td>0.95</td>
<td>0.90</td>
<td>0.94</td>
<td>0.96</td>
<td>1.00</td>
<td></td>
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<td>Brazil</td>
<td>0.96</td>
<td>0.92</td>
<td>0.96</td>
<td>0.92</td>
<td>0.96</td>
<td>0.93</td>
<td>0.97</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Mexico</td>
<td>0.98</td>
<td>0.93</td>
<td>0.93</td>
<td>0.92</td>
<td>0.96</td>
<td>0.97</td>
<td>0.97</td>
<td>0.96</td>
<td>1.00</td>
</tr>
<tr>
<td>Int’l III</td>
<td>0.98</td>
<td>0.95</td>
<td>0.92</td>
<td>0.93</td>
<td>0.97</td>
<td>0.96</td>
<td>0.97</td>
<td>0.96</td>
<td>1.00</td>
</tr>
</tbody>
</table>
Collecting information on leptospirosis at global level

Rudy A. Hartskeerl

Leptospirosis

Zoonosis with considerable worldwide public and veterinary health (and thus economic) impact

Fundamental differences in what are the important aspects of human and animal leptospirosis give rise to differences in:
- Requirements of diagnostic methods used
- Control methods applied

Worldwide emerging (last decade)
- Marked increase and outbreaks in Thailand
- Several outbreaks in India
- Outbreaks in Australia, Malaysia, Indonesia, China
- Outbreaks in the Americas e.g. Nicaragua, Brazil, Peru, Colombia, Ecuador, USA/Hawaii
- Outbreaks in Europe
- Africa

UNDERESTIMATION
- Difficult diagnosis (not recognised)
- Cases not reported (no notification)
- Unawareness (not considered in the diagnosis)
- Zoonoses with a complex and dynamic epidemiology
Leptospirosis, dengue and hantavirus infections worldwide (2002)

<table>
<thead>
<tr>
<th></th>
<th>Leptospirosis</th>
<th>Dengue</th>
<th>Hantavirus infections (HFRS)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number annually</td>
<td>Unknown</td>
<td>50,000,000</td>
<td>Unknown</td>
</tr>
<tr>
<td>Severe forms**</td>
<td>300,000 – 500,000</td>
<td>400,000</td>
<td>150,000 – 200,000</td>
</tr>
<tr>
<td>Mortality (severe forms)**</td>
<td>5-20%***</td>
<td>5-15%</td>
<td>3-10%***</td>
</tr>
</tbody>
</table>

* HFRS: Haemorrhagic Fever with Renal Syndrome  
** Leptospirosis and hantavirus infection with hospitalization; Dengue, Dengue Haemorrhagic Fever (DHF)  
*** Mortality of 40% and higher reported for a number of outbreaks and/or strains or forms of disease

What is needed?

- Increased awareness
- Proper diagnostics
- Education (courses, meetings)
- International Leptospirosis Society (ILS)
- Notification and surveillance (prevention and control measures)
- Assessment of BoD (idem)

ILS TERMS OF REFERENCE

- To stimulate international leptospirosis research meetings worldwide mainly through liaison and collaborating with other microbiological groups either in leptospirosis or other fields of microbiology.
- To maintain an executive committee to plan, monitor and guide future meetings.
- To organise a meeting of the ILS every second year.
- To provide up-to-date epidemiological information on leptospirosis to international and national health authorities as requested.

ILS meetings

- 1996 Nantes, France
- 1999 Marysville, Australia
- 2002 Bridgetown, Barbados
- 2005 Chiang Mai, Thailand
- 2007 Quito, Ecuador
- 2009?
up-to-date epidemiological information

- ILS worldwide surveys
  - 1998-2000
  - 2001-2004
- WHO-ILS initiative: LeptoNet
  (on-line input and output of data; to replace the surveys)

Notification and surveillance (1)

- Knowledge of (global) incidence and distribution forms the basis to awareness (break the vicious cycle: unawareness, underdiagnosis and under-reporting)
- Awareness is linked to alert attitude of health authorities and financial resources towards prevention and control (no leptospirosis = no problem)

Notification and surveillance (2)

- Notification is a national decision; few countries have notification systems

Status

- Human leptospirosis: profile of leptospirosis falls rapidly after outbreaks
- Veterinary leptospirosis: lack of interest by state veterinarians & researchers
  - Developed economies: problem of industry
  - Developing world: something caused by rats

GENERAL DATA

- Responses covered about 5% of the world population
- In total 47,260 human cases reported in the period 1998-2000 (corresponds to 320,000 cases annually worldwide (100%).
  - male 62%, female 38%
- Relation between incidence and temperature & (seasonal) rainfall

ILS Worldwide survey

1998-2000

HIGHEST INCIDENCE

2000

<table>
<thead>
<tr>
<th>Country</th>
<th>Region</th>
<th>Incidence Per 100.000</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>Andaman</td>
<td>50.0</td>
<td>21.0</td>
</tr>
<tr>
<td>Thailand</td>
<td></td>
<td>23.1</td>
<td>2.5</td>
</tr>
<tr>
<td>India</td>
<td>Chennai</td>
<td>10.5</td>
<td>-</td>
</tr>
<tr>
<td>France</td>
<td>Ile de la Reunion</td>
<td>6.0</td>
<td>-</td>
</tr>
<tr>
<td>India</td>
<td>Kerala</td>
<td>5.6</td>
<td>10.1</td>
</tr>
<tr>
<td>USA</td>
<td>Hawaii</td>
<td>4.0</td>
<td>0</td>
</tr>
<tr>
<td>Brazil</td>
<td>Sao Paulo</td>
<td>1.9</td>
<td>12.3</td>
</tr>
<tr>
<td>Uruguay</td>
<td></td>
<td>1.6</td>
<td>100</td>
</tr>
<tr>
<td>Indonesia</td>
<td>Semarang</td>
<td>1.2</td>
<td>16.7</td>
</tr>
</tbody>
</table>
### HIGHEST MORTALITY 2000

<table>
<thead>
<tr>
<th>Country</th>
<th>Region</th>
<th>Incidence</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uruguay</td>
<td></td>
<td>1.6</td>
<td>100</td>
</tr>
<tr>
<td>India</td>
<td>Andaman</td>
<td>50.0</td>
<td>21.0</td>
</tr>
<tr>
<td>Indonesia</td>
<td>Semarang</td>
<td>1.2</td>
<td>16.7</td>
</tr>
<tr>
<td>Panama</td>
<td></td>
<td>2.0</td>
<td>16.7</td>
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<tr>
<td>Brazil</td>
<td>Sao Paulo</td>
<td>1.9</td>
<td>12.3</td>
</tr>
<tr>
<td>India</td>
<td>Kerala</td>
<td>5.6</td>
<td>10.1</td>
</tr>
<tr>
<td>Chile</td>
<td></td>
<td>0.07</td>
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</tr>
</tbody>
</table>

### OUTBREAKS (1) 1998, 1999, 2000

<table>
<thead>
<tr>
<th>Country/Reg</th>
<th>1998</th>
<th>1999</th>
<th>2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thailand</td>
<td>2230</td>
<td>6080</td>
<td>14,285</td>
</tr>
<tr>
<td>India/Chennai</td>
<td>353</td>
<td>344</td>
<td>624</td>
</tr>
<tr>
<td>Mexico</td>
<td>269</td>
<td>264</td>
<td>789</td>
</tr>
<tr>
<td>India/Kerala</td>
<td>160</td>
<td>206</td>
<td>278</td>
</tr>
<tr>
<td>India/Andem</td>
<td>126</td>
<td>149</td>
<td>157</td>
</tr>
<tr>
<td>Uruguay</td>
<td>21</td>
<td>24</td>
<td>51</td>
</tr>
<tr>
<td>Panama</td>
<td>1</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

Outbreaks indicated for each year. Number of cases in bold/italics indicate markedly increased numbers.

### OUTBREAKS (2) 1998, 1999, 2000

<table>
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<th>Country/Reg</th>
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<th>1999</th>
<th>2000</th>
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</thead>
<tbody>
<tr>
<td>China/Hubei</td>
<td>1,267</td>
<td>259</td>
<td>253</td>
</tr>
<tr>
<td>USA/Hawaii</td>
<td>65</td>
<td>39</td>
<td>48</td>
</tr>
<tr>
<td>France/I.Reun</td>
<td>52</td>
<td>25</td>
<td>42</td>
</tr>
<tr>
<td>Australia</td>
<td>168</td>
<td>273</td>
<td>207</td>
</tr>
<tr>
<td>France (cont.)</td>
<td>684</td>
<td>759</td>
<td>534</td>
</tr>
<tr>
<td>Japan</td>
<td>0</td>
<td>21</td>
<td>3</td>
</tr>
</tbody>
</table>

Outbreaks indicated for one or two years. In bold/italics, number of cases for the year that an outbreak was indicated.

### MOST IMPORTANT SEROGROUPS AND HOSTS

- Ictero 49.1%
- Pomona 10.9%
- Sejroe 10.9%
- Australis 7.3%
- Autumnalis 5.5%
- Grippotyph. 5.5%
- Canicola 3.6%
- Celledoni 1.8%

- Rats 32.7%
- Cattle 16.3%
- Rodents 12.7%
- Dogs 9.1%
- Pigs 9.1%
- Mice 5.5%
- Horses 3.6%
- Racco/bandic 1.8%

### DISTRIBUTION OF CASES ACCORDING TO OCCUPATION

Surveillance; up-to-date epidemiological information

- **ILS worldwide surveys**
  - WER 1999 (1987-1997; ±100 submissions/36 countries)
  - 1998-2000 (basic data on LeptoNet; 56 submissions/28 countries)
  - 2001-2004 (participation very low; 7 submissions)

- **Trend**
  - Participation decreases each round

- **Reasons**
  - Too much work with no direct profit
  - Fear for economy (tourist industry)
  - Unjustified national proud
Why LeptoNet?

- ILS worldwide surveys
  - takes a lot of time and work for the ILS volunteers
  - Does not provide up-to-date information
- WHO-ILS initiative: LeptoNet
  (to replace the surveys)
  - Up-to-date: on-line input and output of data
  - Workload divided
Interactive LeptoNet participation

- Preferably one institution per country (mostly national reference laboratory or Ministry of Health)
- Preferably one contact person

LeptoNet since 2002

- LeptoNet is to replace the surveys
- Success depends on the input of data of participants
- Many applications (96) from participants from many countries
LeptoNet since 2002

- LeptoNet is to replace the surveys
- Success depends on the input of data of participants
- Many application (96) from participants from many countries

- Input of data very low

Why little input?

- LeptoNet is not known
- National regulations form bottleneck
- National notification absent
- National notification in big countries difficult
- Intention of LeptoNet (application) is not well understood
- Questionnaire too complicated/detailed
- What is a case?
- Primarily for human leptospirosis

Notification and surveillance

- International efforts are largely ignored

What is needed?

- This meeting
- Finishing and publishing ILS survey 1998-2000
- Upgrading (simplifying) LeptoNet and questionnaire?
- Strengthening ILS (TDR and NGO recognition?)
WHO Consultation to Develop a Strategy to estimate the Global Burden of Foodborne Diseases

World Health Organization
Department of Food Safety, Zoonoses and Foodborne Diseases

The plan

• Estimate % foodborne disease among overall global burden of disease
• Consider multiple causes (infectious/zoonotic, parasitic, Chemical)
• Launch alliance of multiple national and international partners
• Assimilate previous efforts to estimate burden
• Identify gaps in foodborne disease burden estimates
• Triangulate various methods and approaches
• Use BoD summary measures that are internationally understood (incidence, prevalence, mortality, DALYs)
• Encourage BoD studies at country level

What has been done so far?

• Incidence & mortality studies of diarrhoeal disease (various infective agents)
• Comparative Risk Assessment (CRA) studies of water-borne diseases (various causes)
• Foodborne disease burden in OECD countries (WHO)
• Comparative Risk Assessment of foodborne diarrhoeal disease (unpublished)
• Prevalence studies of zoonotic foodborne diseases
• Burden studies of parasitic diseases
• Studies often hospital, passive surveillance system or outbreak based
• Causes not complete (especially in chemical area)
• Few developing countries’ studies
• Multiple epidemiological methods applied
• % foodborne not always identified
• Work often limited to children
• Estimates often not aggregated by sex, age or region

Objectives of the meeting

• Bring together > 50 international experts in epidemiology/chemicals/parasites/zoonoses from around the world to:
  - Develop strategy for global foodborne BOD estimates involving relevant partners
  - Use meeting as launch event for wider collaboration
  - Prepare detailed action plan and time frame for BOD work – completing the evidence base
  - Develop a standard protocol/manual for conducting BOD studies in countries to obtain estimates

Things hoped for …

• Proposals for composition of core reference group
  - Develop estimates for global foodborne BOD for all relevant causes and risk factor
  - Convene group regularly to report to and advise WHO

• Suggestions for sponsorship/potential donors

→ Summary of efforts in meeting report (end of year ‘06)
What was done

<table>
<thead>
<tr>
<th>Monday 25 Sept</th>
<th>Tuesday 26 Sept</th>
<th>Wednesday 27 Sept</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>Session 2: Mapping the evidence (plenary)</td>
<td>Session 3: National Burden Studies (plenary)</td>
</tr>
<tr>
<td>Lunch</td>
<td>Session 3: National Burden Studies (presentations)</td>
<td>Session 4: Strategy, action plan &amp; next steps (plenary)</td>
</tr>
<tr>
<td>Lunch</td>
<td>Session 2: Mapping the evidence (group work 1)</td>
<td>Global Salm-Surv workshop</td>
</tr>
<tr>
<td>Lunch</td>
<td>Session 3: National Burden Studies &amp; Strategy (group work 2)</td>
<td>Global Salm-Surv workshop</td>
</tr>
</tbody>
</table>

Plenary

Group work

Presentations in plenary

- WHO Global Burden of Disease approach
- Foodborne disease burden work to date, including:
  - Enteric/diarrhoeal disease burden
  - Waterborne disease burden
  - Zoonoses & parasites
  - Chemicals
- WHO National Burden of Disease studies (data needs)
- World Health Surveys (WHIS)
- WHO Burden of enteric disease strategy
- Burden of disease country protocols
- Burden of disease studies: Jordan and Netherlands

Outcome 1: Draft evidence map

Shift in terminology

"To estimate the global burden of disease by causes commonly transmitted through food"

Outcome 2: Strategy & time frame

<table>
<thead>
<tr>
<th>Disease</th>
<th>Risk Factor</th>
<th>Specific</th>
<th>Immediate</th>
<th>Mid-term</th>
<th>Long-term</th>
<th>Some potential Collaborators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious diseases - acute</td>
<td>Top pathogen specific causes - children &lt;5 adult</td>
<td>Identify % foodborne</td>
<td>Establish % foodborne</td>
<td>Intervention studies</td>
<td>CHESP, CHERG Network, Levine et al, Nat Institutes, FAO</td>
<td></td>
</tr>
<tr>
<td>Infectious diseases - chronic</td>
<td>Expert group to identify whether this is correct list</td>
<td>% foodborne</td>
<td>Expert group to evaluate burden</td>
<td>Nat Institutes, WHO, ICASA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemicals</td>
<td>Acute and chronic</td>
<td>Safety audit to identify the leading causes, particularly for developing countries</td>
<td>% foodborne</td>
<td>Expert group to establish burden</td>
<td>Nat Institutes, ICPA, U.S. FDA, EFSA, GEMS Food, FDA</td>
<td></td>
</tr>
</tbody>
</table>

Outcome 3: National BoD protocols

Outcome 4: Epi Reference Group

General Burden of Disease expert (Chair)
FOS Secretariat
Epidemiologists in the area of:
- Microbiology/enteric diseases
- Chemicals/Toxicology
- Parasitic diseases
- Zoonotic diseases

→ To form sub-groups by area

Outcome 5: Donor list

Outcome – unscheduled:
Statement of Support from floor

- Acknowledgement of importance of recognition of burden of foodborne diseases
- Acknowledgement of importance in considering multiple causes of foodborne diseases, including chemical and zoonotic causes
- Endorsement of the FOS/WHO initiative to estimate the Global Burden of Foodborne Diseases
- Calling upon FOS/WHO to continue to provide the leadership for this effort

→ To be sent by Chair of Consultation to DG, ADG and Director FOS
→ To form preamble of meeting report
### Time frame for implementation

<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/01/2023</td>
<td>Initial planning</td>
</tr>
<tr>
<td>02/02/2023</td>
<td>Gathering of stakeholders</td>
</tr>
<tr>
<td>03/03/2023</td>
<td>Field data collection analysis</td>
</tr>
</tbody>
</table>

**Thank you**
Assessing the burden of rabies in Asia and Africa

Darryn Knobel
F X Meslin et al
for the
WHO Rabies Burden of Disease
Working Group

Rabies: a fatal disease

• Every 15 minutes a patient dies of rabies in Asia
• Children aged less than 15 years are involved in 40% of the cases

Rabies: a dog mediated disease in Asia and Africa

• In closer contact with "street" dogs
• More likely to be severely bitten
• Less likely to report exposure

Aims of the study: correct for the lack of data

• Underreporting of rabies cases: gross under-reporting as shown by S. Cleaveland et al
• Discrepancies in reported figures:
  - India 30,000 before 2000 and now a few hundred.
• Reasons for underreporting:
  - Patients do not seek hospital treatment (hospital records useless)
  - Lack of laboratory confirmation
  - Breakdown in reporting system
  - Not always recognized clinically (death register no useful)

Working Group Members:

• Dr Darryn Knobel, CTVM
• Dr Sarah Cleaveland, CTVM
• Dr Eric Fèvre, CTVM
• Dr Paul Coleman, LSHTM
• Dr Francois-Xavier Meslin, WHO
• Dr Elzabeth Miranda, WHO
• Dr Jakob Zinsstag, STI
• Dr Alexandra Shaw, consultant
• Dr Martin Meltzer, CDC

Co-authors of Article "re-assessment of the burden of rabies in Africa and Asia WHO Bulletin July 2003"
How to compensate for the lack of data.

• Environmental/climatological surrogates to infer burden of disease, e.g. malaria, T.B.
• Rabies – dog bite injury data
• Why dog bite injuries?
  – Incentive for people to report animal bites
  – Government records of PET expenditure
  – Accessible data source
  – Records of suspect rabid dog bites
• Range: 15-240/100,000 humans/year

Model drivers:

• Main parameters driving the model are
  – Annual incidence of suspect rabid dog bites
  – Rabies recognition probability \( P_1 \)
  – Probability of receiving successful post-exposure treatment \( P_{10} \)

  – For incidence of dog bites: from 10 to 250 per 100,000 most likely 100
  – For \( P_1 \): 39% to 64% most likely 50%
  – For \( P_{10} \): 55% to 100% most likely 60 to 80%

Parameter values

• Monte Carlo simulation
• Incorporates parameter variability & uncertainty
• Assign distribution to each parameter

![Parameter values diagram]

Model inputs

• Scenarios considered
  – Africa/Asia and Urban/Rural (4 scenarios)
  – Endemic disease vs epidemic

  – Estimate of the human population at risk
  – Based on dog population density threshold for rabies virus circulation
  – Dog ubiquitous and size of population people dependant
  – Dog population studies
• Laboratory data and special studies data where available (literature)
• Expert opinion

![Model inputs diagram]
Human populations at risk

Figure 2a. Human populations at risk from canine rabies in Africa

Figure 2b. Human populations at risk from canine rabies in Asia

Model outputs
tested against mortality data in countries with good rabies reporting systems

- Total predicted PET cases
  - Africa 560,000
  - All Asia 3,250,000
  - India 1,100,000
- Total predicted human rabies deaths
  - Africa 24,000
  - All Asia 31,000 (28,500 excluding China)
  - India alone 20,000

Total deaths: 55,000

DALY score

- Disability-adjusted life-years
- DALY = YLL + YLD

- YLL: years of life lost (rabies affects young people; 40% below 15 years)
- YLD: years of life lived with disability (rabies is an acute fatal disease; no disability incurred and in most developing countries no hospitalization)

Factors considered:
  i) Deaths due to rabies
  ii) and as "morbidity": Fear & anxiety following suspect rabid dog bite and Side-effects & fatalities after NTV vaccination

DALY score

Total rabies DALY score: 2,081,625

Global infectious disease burdens


Financial burden of rabies (US$)

<table>
<thead>
<tr>
<th></th>
<th>Asia</th>
<th>Africa</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET costs (direct)</td>
<td>126,805,875</td>
<td>5,822,680</td>
</tr>
<tr>
<td>PET transport costs</td>
<td>22,472,156</td>
<td>471,945</td>
</tr>
<tr>
<td>PET income loss</td>
<td>314,610,188</td>
<td>3,530,149</td>
</tr>
<tr>
<td>Dog vaccination costs</td>
<td>39,000,000</td>
<td>8,710,000</td>
</tr>
<tr>
<td>Total costs:</td>
<td><strong>502,888,219</strong></td>
<td><strong>18,534,774</strong></td>
</tr>
<tr>
<td>GRAND TOTAL:</td>
<td><strong>520,000,000</strong> US$</td>
<td></td>
</tr>
</tbody>
</table>
Methods for Burden Assessment: Echinococcosis

Paul Torgerson
Universität Zürich
Institut für Parasitologie

Echinococcosis
- Methods for global burden assessment
- DALYs
- Uncertain data
- Financial estimates
- Echinococcosis burden in Switzerland

Economics
- Costs-Livestock
  - Animal production losses
  - Decreased food conversion efficiency
  - Mortality or morbidity
  - Lower reproductive performance
  - Lower milk yield

Economics
- Costs-Human Disease
  - Cost of Treatment
    - Surgery
    - Medical treatment
    - Convalescence
  - Morbidity
    - Time off work
    - Less productive
  - Mortality
    - Economic effects of death
**Data Sources**

- **OIE reports**
  - Gross underreporting
- **Literature reports**
  - Method of collection
  - Biased
- **Representative surveys**

**Data from literature**

<table>
<thead>
<tr>
<th>Country</th>
<th>Years evaluated</th>
<th>Human incidence (annual incidence per 100,000 pop.)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>1983-1992</td>
<td>0.22±0.37 (mean±SD)</td>
<td>Arai and Aoyama, 1993</td>
</tr>
<tr>
<td>Costa Rica</td>
<td>1981-1994</td>
<td>0.23</td>
<td>Langefors and Haggman, 1985</td>
</tr>
<tr>
<td>Japan</td>
<td>1983-1990</td>
<td>0.22</td>
<td>Landers and Trinick, 1990</td>
</tr>
<tr>
<td>Greece</td>
<td>1984</td>
<td>2.4</td>
<td>Chatebopoulos and Thorns, 1999</td>
</tr>
<tr>
<td>Italy</td>
<td>1989-1992</td>
<td>1.82</td>
<td>Colenica et al., 1997</td>
</tr>
<tr>
<td>Italy (region)</td>
<td>Early 2000, 1.57-Eraclea Rangoni, 2.91-Milan, 2.33-Appuli</td>
<td>Colenica et al., 2006</td>
<td></td>
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<tr>
<td>Portugal</td>
<td>1989-1993</td>
<td>1.82</td>
<td>Ser方にa, 2001</td>
</tr>
<tr>
<td>Spain</td>
<td>1991-1996</td>
<td>0.80</td>
<td>Arora, 1997</td>
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<tr>
<td>Northern Italy</td>
<td>1988-1992</td>
<td>0.79 (0.69-0.89, median, 1.28-2.89, range)</td>
<td>Colletti et al., 1995</td>
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<tr>
<td>U.K. (England)</td>
<td>1984-1990 June</td>
<td>0.73</td>
<td>McLaughlin et al., 1998</td>
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**OIE Data**

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<td>11</td>
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<td>Jordan</td>
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<td>15</td>
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<td>Italy</td>
<td>478</td>
<td>472</td>
<td>566</td>
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<td>Liberia</td>
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<td>Lebanon</td>
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<td>144</td>
<td>144</td>
<td>144</td>
</tr>
</tbody>
</table>

**Sources of Data Uzbekistan**

- **OIE reports**
  - 1999 - 1428 cases
  - 2002 - 1500 cases
- **Government figures**
  - 2000 - 1435 cases
  - 2001 - 819 cases
- **Hospital records search and case finding**
  - 2000 - 4636 cases
  - 2001 - 4089 cases

**Sources of Data Jordan**

- **OIE reports**
  - 1996-2004
  - 0-21 cases per year
- **Hospital records search and case finding**
  - 1995 - c 128 cases per year

**Uncertainty**

- Some costs well defined
- Other costs ??
  - May represent the largest losses
- Poor or inadequate reporting
- Sample size
- Diagnostic test efficiency
- Attributable morbidity
- Monte-Carlo techniques
  - Randomly vary each “unknown”
Estimating unknown data

Other modelling techniques
- From published prevalence in
  - Dogs < 10%
  - Sheep < 50%
- Estimate Incidence in humans
  - c10 cases/100,000/year
  - Over estimates some (eg Muslim)
  - Under estimates eg Chinese

Hospital Costs
- Cost of treatment and medication

Annual number of cases = mean (± SEM)  
\[ x \]
Cost of representative sample = mean (± SEM)

Other Human Health Costs
- Long term ill health
- Do patients fully recover?
- Perhaps not?
- Permanent decrease in quality of life
  - How much?
  - Needs good studies to accurately define
- Infected but not treated
- Sub clinical disease
- Some patients die
  - Capital Approach
  - Willingness to pay

Echinococcosis in Jordan

Total Costs
- All calculations should be discounted for future values
Non financial instruments

- HALYs, DALYs, QALYs
- All measures of loss of health
- WHO preferred measure is DALY
  - Disability Adjusted Life Year
  - Measures number of “years of full health” lost due to disease

DALY

- Length of time lived with morbidity
- Discounted for
  - Disability weight
  - Age of onset
  - Losses in future years at today’s rates
- Numbers of healthy years lost

China

Serchu County

- 3135 subjects
- 178 positive for CE (5.7%)
- 180 positive for AE (5.7%)
- Adjusted prevalence for CE 4.9%
- Adjusted prevalence for AE 4.6%
Disability Weights

- Echinococcosis
  - Disease free liver cancer (0.200) (improve after surgery)
  - Preterminal liver cancer (0.239) (Post surgical conditions)
  - Terminal liver cancer (0.809) (Recurrent disease, multiorgans etc)
  - Death 1
- Weights and duration assigned using a multinomial distribution with relative proportions based on published surgical studies.

Results of treatment for CE

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of patients</th>
<th>Cure</th>
<th>Morbidity</th>
<th>Relapse</th>
<th>Death</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greece (1984-1999)</td>
<td>56</td>
<td>40</td>
<td>13 (23%)</td>
<td>3 (5%)</td>
<td>0 (0%)</td>
<td>(15)</td>
</tr>
<tr>
<td>Italy (1956-1987)</td>
<td>298</td>
<td>244</td>
<td>27 (9%)</td>
<td>15 (5%)</td>
<td>12 (4%)</td>
<td>(14)</td>
</tr>
<tr>
<td>Turkey (1992-1999)</td>
<td>95</td>
<td>32</td>
<td>18 (40%)</td>
<td>24 (25%)</td>
<td>1 (1%)</td>
<td>(16)</td>
</tr>
<tr>
<td>Turkey (1990-1995)</td>
<td>108</td>
<td>88</td>
<td>19 (18%)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td>(17)</td>
</tr>
<tr>
<td>Greece (1985-1990)</td>
<td>67</td>
<td>59</td>
<td>4 (6%)</td>
<td>3 (6%)</td>
<td>1 (2%)</td>
<td>(18)</td>
</tr>
<tr>
<td>Italy (1982-1994)</td>
<td>89</td>
<td>70</td>
<td>17 (19%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>(19)</td>
</tr>
<tr>
<td>Total</td>
<td>713</td>
<td>533</td>
<td>116 (19%)</td>
<td>46 (6%)</td>
<td>36 (5%)</td>
<td></td>
</tr>
</tbody>
</table>

Data used for age weightings

<table>
<thead>
<tr>
<th>Country</th>
<th>Years</th>
<th>Average age of onset/detection</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>2001-2003</td>
<td>35</td>
<td>(3)</td>
</tr>
<tr>
<td>Jordan</td>
<td>1994-2000</td>
<td>31-43</td>
<td>(22)</td>
</tr>
<tr>
<td>Kenya (Turkana)</td>
<td>1980s</td>
<td>21-30</td>
<td>(23)</td>
</tr>
<tr>
<td>Morocco</td>
<td>2000-2001</td>
<td>32</td>
<td>(24)</td>
</tr>
<tr>
<td>Turkey</td>
<td>1992-1999</td>
<td>44</td>
<td>(16)</td>
</tr>
<tr>
<td>Kyrgyzstan</td>
<td>1991-2000</td>
<td>22</td>
<td>(26)</td>
</tr>
</tbody>
</table>
**Economic losses**
- Attributable loses only
- True losses are only those that are preventable
- Cystic echinococcosis
  - Eliminated by veterinary public health programmes
  - Essentially entire burden is preventable

**Global Burden of Echinococcosis**
- 1.0 million DALYs
  - c 200,000 cases per year
- US$4.1 Billion (adjusted for underreporting, PPE estimate)
  - 46% Human costs
  - 54% Animal health costs

**Echinococcosis compared to other diseases**

<table>
<thead>
<tr>
<th>Disease</th>
<th>DALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptospirosis</td>
<td>199,000</td>
</tr>
<tr>
<td>Onchocerciasis</td>
<td>564,000</td>
</tr>
<tr>
<td>Dengue</td>
<td>816,000</td>
</tr>
<tr>
<td>Chagas</td>
<td>867,000</td>
</tr>
<tr>
<td>Toxocariasis</td>
<td>1,529,000</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>1,702,000</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>2,060,000</td>
</tr>
<tr>
<td>Lymphatic filariasis</td>
<td>2,777,000</td>
</tr>
<tr>
<td>TB</td>
<td>34,729,000</td>
</tr>
<tr>
<td>Malaria</td>
<td>46,486,000</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>702,000</td>
</tr>
<tr>
<td>Trachoma</td>
<td>2,529,000</td>
</tr>
<tr>
<td>Onchocerciasis</td>
<td>1,877,000</td>
</tr>
<tr>
<td>Trichuriasis</td>
<td>1,006,000</td>
</tr>
<tr>
<td>Hookworm</td>
<td>59,000</td>
</tr>
</tbody>
</table>

**Alveola Echinococcosis in Switzerland**
- 20-30 cases per year
- Life expectancy c 7-10 years if untreated
- Treatment is surgery and chemotherapy
- Chronic disease

**Burden analysis of AE in Switzerland**
- Fox numbers are increasing
- Potential increase threat of transmission to humans
- Baiting foxes can reduce the prevalence rates in urban foxes
- Is baiting cost effect?
- Needs a burden assessment
Burden Assessment of AE

- DALYs
- Economic (financial) assessment
- Modelling techniques
  - Estimate life expectancy of patients treated now
  - Relatively small sample size as a rare disease
  - Good data is available that can be extrapolated to other endemic areas

Methodology

- Case searching
- Data bases of Swiss hospitals
- 330 suitable cases identified 1963-2005
- Details of each case
  - Treatment
  - Years of follow up
  - Eventual outcome

Methodology

- Survival analysis
- Assess the life expectancy of patients diagnosed today
- Years of life lost
- Medical records indicate length of treatment
- Disability weights

Survival Analysis

- Relative survival analysis
- Relative to Swiss normal population
  - 2005 Swiss life tables
- Multivariate
  - Gender
  - Age of diagnosis
  - Year of diagnosis

Relative Survival Analysis

|                     | Estimate | Std. Error | Z value | Pr(>|z|) |
|---------------------|----------|------------|---------|----------|
| Age of patient at time of diagnosis | 0.03802  | 0.0177     | 3.230   | 0.001237 |
| Year of Diagnosis   | -0.08723 | 0.02395    | -3.643  | 0.000270 |
| Gender (male)       | 0.32325  | 0.33799    | 0.956   | 0.338880 |

Relative survival analysis

- Lower hazard for more recently diagnosed cases
- Lower hazard if the patient is diagnosed at a young age than at an old age
Relative Survival Analysis

- Project the model forward to cases diagnosed in 2005
- Estimate the survival times of patients diagnosed with AE

Relative survival

- Mean age of diagnosis 52 years
- Life expectancy of 52 year old male
  - Normal Swiss male population 28.95 years
  - AE positive 31.3 years (CI 29.2-32)
- Model suggests that c 1.85 years of life lost
- YLLs is 32.4 (16.6-59.1)

YLDs

- Case records suggest that treatment is for 7-10 years
- Hepatic resection followed by chemotherapy
- Disability weight suggested:
  - Liver cancer in remission
  - 0.2 for duration of chemotherapy

YLDs

- Age weighted and discounted
- Bootstrap analysis to model uncertainty
- YLDs = 15.9 (CI 12.1-20.1)

DALYs

- YLDs + YLLs
- = 48.5 DALYs lost per year
  - CIs 30.8-77.1
- Total cost CHF 4.2 million (US$ 3.3 million)
  - CIs CHF2.5 million - CHF6.7 million

DALYs lost without treatment

- Estimated from life expectancies of patients before mid 1970s
- 5-7 years with pre-terminal liver cancer
- 2-3 years with terminal liver cancer
- DALYs lost c 582
- This can be extrapolated to endemic areas where treatment is not available
  - China
Comparative life expectancy at age 52 years for AE patients compared to Swiss population norms

Red-males, green-females. Dashed line population norms, solid line AE patients

Cost Effectiveness

- Total medical treatment CHF 2.0 million per year
- DALYs saved c 535
- CHF3740 per DALY (US$2950)

Conclusions

- Burden estimates possible with data from a variety of sources
- DALYs for zoonoses can indicate priorities compared to other diseases
- Modelling techniques can be powerful to estimate unknown or unobtainable data
- Stochastic and risk analysis techniques are powerful tools to model uncertainty.
- Financial estimates for zoonoses can give an overall burden of disease including animal health costs
  - Purchasing power equivalents give a better idea of disease burden in poor countries
  - Such results can be used to implement cost sharing between sectors
- Results of cost sharing can indicate the true cost benefit to health services

Thank You

- Dr Christine Budke
- National Institutes of Health (U.S.A.) and the National Science Foundation (U.S.A.) (Ecology of Infectious Diseases Programme)
- European Union
- INTAS
- Swiss National Science Funds
Assessing human health and societal benefits of interventions in livestock

Also a case for Leptospirosis?

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Starting point

- Occurrence of emerging and re-emerging zoonoses not interrupted
- Well contained in industrialized countries
- Problem for developing and transition countries
- Humans not important maintaining transmission, but continuously exposed if surveillance and control fails
- Elimination only possible by interventions in the animal reservoir
- What is the public health benefit from interventions in livestock? (MoH)

WHO ministerial summit

November 2004

- Pivotal role of strengthened health systems to achieve the Millennium Development Goals (MDG)
- Health systems research to include broader societal dimensions
- One such extension includes a closer interaction between human and animal health
- 1960s Calvin Schwabe coins the term „one medicine”

Examples

- Example of an intersectoral economic analysis of brucellosis
- Preliminary results on rabies
- Analytical framework and data requirements for bovine tuberculosis
- Study types
- Options for Leptospirosis
Human Brucellosis in Mongolia

WHO: Is livestock mass vaccination profitable for the public health?

Epidemiologic and economic considerations

- Animal to animal transmission dynamics
- Simulation of interventions
- Animal to human transmission
- Linkage of disease prevalence to
  - livestock productivity
  - health cost
Fitting the model to human brucellosis

![Graph showing prevalence in sheep](image)

Fitting the model to sheep brucellosis

![Graph showing prevalence in sheep](image)

Simulation of the vaccination campaign in the future as a basis for the economic analysis

![Graph showing prevalence in sheep](image)

Synoptic view of benefits and costs of animal brucellosis mass vaccination in Mongolia

![Graph showing distribution of benefits](image)

Proposed cost sharing scenario

<table>
<thead>
<tr>
<th>Sector</th>
<th>Agriculture sector</th>
<th>Human Health</th>
<th>Total overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breeder</td>
<td>5,174.9</td>
<td>1,009.4</td>
<td>3,782.4</td>
</tr>
<tr>
<td>Public sector</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total Agriculture sector</td>
<td>5,174.9</td>
<td>1,009.4</td>
<td>3,782.4</td>
</tr>
<tr>
<td>MoH, Central Government</td>
<td>1,009.4</td>
<td>3,240.3</td>
<td>2,230.9</td>
</tr>
<tr>
<td>HIS, Health Insurance Fund</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Patients</td>
<td>1,669.3</td>
<td>1,103.7</td>
<td>3,782.4</td>
</tr>
<tr>
<td>Total overall Human Health</td>
<td>3,782.4</td>
<td>12,141.8</td>
<td>8,359.4</td>
</tr>
<tr>
<td>Total private sector</td>
<td>7,947.9</td>
<td>25,513.1</td>
<td>17,565.2</td>
</tr>
<tr>
<td>Total society</td>
<td>8,957.3</td>
<td>28,753.4</td>
<td>19,796.1</td>
</tr>
</tbody>
</table>

1) 1 USD = about 1'080.-- MNT (October 2000)
2) Net Present Value (= benefits minus costs)
3) Benefit Cost Ratio (= benefits over costs); (min: 2.27, max: 4.37)

DALY estimate of brucellosis and cost-effectiveness for human health

- Urgent need for consensus on zoonoses DALY estimate at WHO
- Public health perspective (Disability class II) 19.1 US$, 11% of total cost
- Societal perspective, including private sector 71.4 US$, 42% of total cost
- Is there a DALY estimate for Leptospirosis?
**Brucellosis in China (Shang et al. 2002) „Separated phenomenon“**

- The reason why the “separated phenomenon” appeared was that the time, place, tests and sampling methods of the surveys on human and animal brucellosis were not standardized and uniform (Shang, 1996).

**Mixed animal and human health team**

- Identification of possible sources of exposure of pastoralists
- Being a camel breeder was a significant risk factor for Q-fever seropositivity in humans
- Brucellosis seroprevalence cattle 7% and positive association with history of abortions
- Human brucellosis seroprevalence 2%: professional risk and raw milk consumption

**Need for standardized simultaneous surveys in animals and humans**

- The reason why the “separated phenomenon” appeared was that the time, place, tests and sampling methods of the surveys on human and animal brucellosis were not standardized and uniform (Shang, 1996).

**Zoonotic seroprevalences of nomadic pastoralists and their livestock**

- Identification of possible sources of exposure of pastoralists
- Being a camel breeder was a significant risk factor for Q-fever seropositivity in humans
- Brucellosis seroprevalence cattle 7% and positive association with history of abortions
- Human brucellosis seroprevalence 2%: professional risk and raw milk consumption

**Study design for a simultaneous animal and human brucellosis assessment in Kyrgyzstan (Cross-sectional cluster sampling)**

<table>
<thead>
<tr>
<th>Species</th>
<th>per Oblast</th>
<th>No of Oblast</th>
<th>No of Repetitions</th>
<th>Total N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheep</td>
<td>600</td>
<td>3</td>
<td>1</td>
<td>1800</td>
</tr>
<tr>
<td>Goat</td>
<td>600</td>
<td>3</td>
<td>1</td>
<td>1800</td>
</tr>
<tr>
<td>Cattle</td>
<td>600</td>
<td>3</td>
<td>1</td>
<td>1800</td>
</tr>
<tr>
<td>Human</td>
<td>600</td>
<td>3</td>
<td>2</td>
<td>3600</td>
</tr>
<tr>
<td>Total No. Of samples</td>
<td>9000</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Kyrgyzstan**

- Health authorities record increasing number of brucellosis cases and dispute with the veterinary services to intervene
- Veterinary services do intervene but control seems not effective enough
- Switch from S19 to Rev1 in Small Ruminants

Schelling et al., 2003
What is the public health and societal benefit of rabies control?

**Simplified deterministic model of rabies transmission between dogs and humans**

- $S = \text{susceptible dogs}$
- $L = \text{latent infected dogs}$
- $I = \text{rabid dogs}$
- $R = \text{vaccinated dogs}$
- $X = \text{susceptible humans}$
- $Y = \text{exposed humans}$
- $Z = \text{rabid humans}$

**Comparative cost-effectiveness of PET against PET + dog vaccination**

- $\mu_1$: Cost per DALY with dog vaccination
- $\mu_2$: Cost per DALY without dog vaccination

What is the public health and societal benefit of bovine tuberculosis control?
African network on bovine tuberculosis >2007

Conclusions I

• Simultaneous surveillance in animals and humans are most appropriate to demonstrate pathways of transmission an cost to society
• Societal perspective shows that brucellosis control is profitable also in developing and transition countries
• Cost-sharing scenarios help to cooperate between animal and public health sectors
• Vaccination interventions could be potentially linked (e.g. to Echinococcosis)

Options for Leptospirosis

• Depends on disease system:
  • Rodent, Pig, Cattle, Dog derived?
  • Constant force of infection from reservoir
    • E.g. Rodent, Slaughterhouse situations
  • Dynamic force of infection considering transmission process in animals
    • Data intensive
    • Allows to simulate interventions in animals
Example of a new rodent-human model

A model of Leptospirosis infection in an African rodent to determine risk to humans: Seasonal fluctuations and the impact of rodent control

(Holt et al. 2006) Seasonal dynamics of force of infection from rodents in Tanzania

Simulating interventions:
- Dotted line: Environmental management
- Closed line: Rodent control

Human component not included

Tentative framework for a livestock-human Leptospirosis model

Susceptible Humans (at Risk) → Infectious Pigs → Recovered Humans

Intervention

Tentative framework for a livestock-human Leptospirosis model (slaughter house exposure)

Susceptible Humans (at Risk) → Proportion of Infectious Pigs → Recovered Humans

Intervention

Conclusion II

- Animal-human transmission model allows simulation of the effect of interventions in animals on human health
- Needs simultaneous datasets from animals and humans
- Existing data?
- New case studies?
- Stochastic models