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ARTÍCULO ESPECIAL

International Leptospirosis Society: objectives and achievements*

Dr. Rudy A. Hartskeerl[1]

INTRODUCTION

Leptospirosis is a zoonotic disease of increasing global importance. It has a considerable public health and economic impact. Primarily, leptospirosis is an occupational disease affecting many labourers (e.g. rice field workers, [cattle]farmers, sugarcane cutters, fishermen, meat- and sewer workers) in their productive age. Apart from the costs of treatment, this generates economic losses by a decreased income both at the personal and national level. Leptospirosis also is a disease of animals affecting many domestic and farm animals. There is an enormous economic impact on the international trade of animals and semen. Economic losses are also caused by cost for treatment and control and by reduced milk yields and reproductive failures.

DIFFICULT DIAGNOSIS AND UNDERESTIMATION

In spite of its significant medical and economic impact, leptospirosis is one of the most overlooked and neglected diseases. The main reason for that is probably because leptospirosis is difficult to diagnose both in the clinic and at the laboratory. Leptospirosis has protean manifestations, mimicking many other diseases such as influenza, hepatitis, dengue, Hantavirus infections and other viral haemorrhagic fevers, yellow fever, hepatitis, malaria, typhoid fever and other enteric diseases, and pneumonia. Therefore it is often confused with any of these other disease that generally encounter more alertness. Confirmation of a clinically suspected leptospirosis at the laboratory also has many bottlenecks. Conventional methods such as isolation, darkfield microscopy, Microscopic Agglutination Test (MAT), ELISA, IFAT, and quick tests such as IHA and MSAT are slow, unreliable (notably darkfield microscopy), have a low detection threshold, are difficult to standardize, need well-trained personnel, and/or require expensive media and equipment. Thus, diagnosis of leptospirosis is difficult and this forms an obvious reason for the underestimation of leptospirosis.

Two worldwide surveys performed by the International Leptospirosis Society (ILS) revealed that 300,000 to 500,000 recorded cases of leptospirosis occurred annually. Only few countries have a notification system and mainly hospitalised cases are recognised. The recorded cases thus represent severe forms of leptospirosis with fatality rates typically ranging from 5-20 % (Table). Because of lacking notification systems in most endemic countries, it can de argued that the real number of severe cases is much higher. Hantavirus infections and, notably dengue are two viral haemorrhagic fevers that are better known and receive much more attention than leptospirosis. When comparing the numbers of severe cases and the fatality rates of leptospirosis with

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[1] Physician Doctor. President of International Leptospirosis Society. WHO/FAO/OIE Leptospirosis Reference Center. KIT (*Koninklijk Instituut voor de Tropen/Royal Tropical Institute*)

those of dengue and Hantavirus infections, leptospirosis equals both as a public health hazard (Table).[1-8] As indicated above, leptospirosis - as a zoonosis - has an additional economic impact at the agricultural level. Thus, while there is a reason for underestimation of leptospirosis, a justification is missing.

TABLE. Leptospirosis, dengue and hantavirus infections worldwide

	Leptospirosis	Dengue	Hantavirus infection (HFRS)*
Total number annually	Unknown	50,000,000	Unknown
Severe forms**	300,000-500,000	400,000	150,000-200,000
Mortality (severe forms)	5-20 %***	5-15 %	3-15 %***

* 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

INCREASED AWARENESS

What can be done about this marked underestimation? Clearly increased alertness of the clinicians, the ones who see the patients, is of paramount importance. This can only be achieved by making them aware that leptospirosis is around, thus by implementation of proper laboratory diagnostics and notification systems, preferably associated with surveillance. Additionally, the public should be informed about the hazards via the papers, radio and television and alertness of notably clinicians, health care workers and decisionmakers should be created e.g. by targeted education and courses.

NOVEL DIAGNOSTIC TESTS

What really is needed for improved laboratory diagnosis are tests that are easy-to-perform, robust, reliable, quick, stable, and affordable. In recent years, several rapid tests have been published and become commercially available. Two of these tests are the LeptoTek Lateral Flow test (LFA) and the LeptoTek Dri Dot test. Basically, the LFA is an ELISA albeit that a dye instead of an enzymatic reaction is used to obtain the colour.[9] The test detects human anti-*Leptospira* IgM antibodies in 10 minutes. The Dri Dot is a latex agglutination test with the coated latex particles dried on a card to obtain maximum stability.[10] This test detects human anti-*Leptospira* antibodies, likely IgM, and takes 30 seconds.

In serum samples taken during the first 10 days after onset of the disease, LFA has a sensitivity of 66 % and a specificity of 93 %. In sera taken after 10 days the sensitivity and specificity are 81 % and 90 %, respectively. As expected, these figures are similar to those obtained with the IgM ELISA.[9]

The Dri Dot gives a sensitivity and specificity in convalescent sera (88 % and 90 %, respectively) similar to those of the ELISA but has a marked higher and sensitivity in the sera taken in the first 10 days of disease (72 % compared to 60 % for ELISA).[10] The Dri Dot thus may be a particularly valuable early in the disease.

INTERNATIONAL LEPTOSPIROSIS SOCIETY (ILS)

The ILS is instrumental to the increase of awareness of leptospirosis worldwide. The society was established in 1994 to promote knowledge on leptospirosis through the support and (co)organisation of scientific meetings. Consistently, the terms of reference indicate the maintenance of an executive committee to plan, monitor and guide meetings, with an ILS meeting held every third year or as appropriate. Provision of up-to-date epidemiological information on leptospirosis to international and national health authorities is another ILS task.

Scientific meetings: Since the formation of the ILS, there have been three successful international meetings; i.e. in 1996 in Nantes, France, in 1999 in Marysville, Australia, and in 2002 in Bridgetown, Barbados. The next meeting will be organised in November 2005 in Chiang Mai, Thailand (www.ils2005.org).

WHO-ILS guidelines: As a contribution to distribute knowledge on leptospirosis, in 2003, the WHO-ILS guidelines 'Human Leptospirosis; Guidance for Diagnosis, Surveillance and Control'[11] was published. The guidelines are mainly intended for health workers (clinicians, laboratory technicians, microbiologists, public health care workers and - decision makers, veterinarians and biologists with an interest in zoonosis) having no specialized knowledge of leptospirosis but wishing to be generally informed about the microorganism and the disease. For interested readers the guidelines provide further information in its Annexes and bibliography. There are currently plans to translate the guidelines into Spanish and Japanese.

Worldwide surveys: As mentioned above, ILS performed two rounds of surveys. One covered 1987--1997 and results have been published in Weekly Epidemiological Records.[12] A summary of the results from the survey for 1998, 1999, 2000 is available on LeptoNet (see below). Here follow some interesting data from that survey. The response covered 5 % of the world population (leptoNet incorrectly mentions 8 %). 47,260 human cases were reported in the three years. This extrapolates to 320,000 cases per year in total (100 % world population covered). Worldwide 62 % of the cases were male and 38 % were female and as expected there is a clear relationship between incidence and temperature. Leptospirosis is particularly a disease of humid tropical and subtropical countries.

The highest incidence in 2000 was reported by India, Andaman Islands (50.0 per 100,000 population) followed by Thailand (23.1 per 100,000). Brazil was the first ranking Latin American country with an incidence of 1.9. Highest mortality rate (100 %) was reported for Uruguay (51 patients) in 2000. Next Latin American country was Panama (16.7 %). Usually low /mediate incidences combined with high mortality rates are associated with a low awareness. Only the very severe cases are recognised! Seven countries and states reported an outbreak in each of the three years while an additional six countries/states had outbreaks in one or two years.

The most common infecting serogroup was Icterohaemorrhagiae (49.1 %) followed by Pomona and Sejroe (both 10.9 %), Australis (7.3 %), Autumnalis and Grippotyphosa (both 5.5 %), and Canicola (3.6 %). Rodents, rats and mice composed half of the reported main infection source. However, almost 40 % was formed by domestic and farm animals (cattle 16.3 %, dogs 9.1 %, pigs 9.1 %, and horses 3.6 %). Other feral animals than rodents seem to present a group of minor in the epidemiology of leptospirosis (11 %).

LeptoNet: LeptoNet is a WHO-ILS initiative financed by WHO and sponsored by KIT Amsterdam, The Netherlands. LeptoNet is an epidemiological website with the possibility of on-line data input, data output and data collation. The website has become available half 2003 and can be contacted at www.leptonet.net

There are two main reasons to construct LeptoNet. (i) Execution of the ILS surveys and collation of the data takes a lot of time and work for the ILS volunteers. By the set-up of the website the workload is divided over several contributors. (ii) Collection and generation of data by the surveys takes time and is not up-to-date. LeptoNet is on-line available and has the potential to provide recent information. For the input of data, LeptoNet uses a questionnaire that basically is adapted from the questionnaire used for the surveys. Possibilities are offered to produce tables and graphics about the distribution of cases according to sex, age and profession. The page thus provides an excellent tool for worldwide (but also national) surveillance. The need of proper surveillance is substantiated by several examples of reports with inconsistent and incomplete data on outbreaks, often underestimating the leptospirosis problem.

One example. At the beginning of 2004, an outbreak of dengue and dengue haemorrhagic fever occurred in Indonesia. At the end of March about 30,000 cases were reported with over 600 fatalities. However, information was received from two hospitals (among the few aware of leptospirosis) that indicated that at the same time a leptospirosis outbreak with a mortality rate of approximately 20 % occurred (R.A. Hartskeerl, personal information). It appeared that alertness for leptospirosis among clinicians in Indonesia was very low and proper diagnostic tests required to reveal this leptospirosis outbreak were available only in limited amounts.

Considering the confusion of leptospirosis with dengue and dengue haemorrhagic fevers in several other parts of the world, it is tempting to assume that a substantial proportion of the so-called dengue haemorrhagic

fever cases and fatalities were actually due to leptospirosis. Except by LeptoNet, there was no mentioning of this putative leptospirosis outbreak in international reports. Apparently, the leptospirosis outbreak was neglected by the panic of the concomitant dengue outbreak, once again demonstrating the current 'obsession' for viral diseases. Clearly, the web page has the potential to play an important role in surveillance, ultimately leading to the implementation of adequate control measures and a proper treatment of leptospirosis patients.

Although the site is open for everyone who is interested, the on-line input of data (and some data collation functions) is only accessible after successful application. Interactive participation is preferably done by one institute per country (mostly the national reference centre or the epidemiological section of the Ministry of Health) and preferably by one contact person. Application is possible via LeptoNet. Since June 2003, 48 persons have applied, with 18 applicants coming from 13 countries from Latin America and the Caribbean.

International MAT proficiency testing: The MAT with its still unsurpassed sensitivity and specificity is the gold standard in diagnostic testing of leptospirosis. Unfortunately, the test is difficult to standardise. It requires live *Leptospira* cultures and the estimation of the end-point titre is done by eye and thus subjective. For quality assurance it is therefore of utmost importance that the test has an international quality control on its performance. Under the umbrella of the ILS, the National Serology Reference Laboratory, Australia, the Leptospira.

Reference Unit, County Hospital, United Kingdom and the WHO/FAO/OIE Leptospirosis Reference Centre, KIT Biomedical Research, The Netherlands organised a worldwide MAT proficiency testing in 2002. The proficiency test, which will be held each year, is now in its 3rd round. Results show the need for international MAT proficiency testing for many laboratories and reveal a significant benefit for the participants in repeated rounds (manuscript in preparation).

IMPORTANT ADDRESSES

ILS homepage: www.med.monash.edu.au/microbiology/staff/adler/ilspage.htm
LeptNet: www.leptonet.net
MAT proficiency testing: Roderick@nrl.gov.au
4th ILS meeting: www.ils2005.org

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Dr. *Rudy A. Hartskeerl*. Department Biomedical Research, Meibergdreef 39, 1105 AZ Amsterdam, The Netherlands. E-mail: r.hartskeerl@kit.nl, Phone: +31-20-5665438, Fax: +31-20-6971841