3rd Global Leptospirosis Environmental Action Network (GLEAN) Meeting

March 12 – March 14, 2013
Brasilia, Brazil

Meeting Report

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Acknowledgements

The third Global Leptospirosis Environmental Action Network (GLEAN) meeting took place at the World Health Organization (WHO)/Pan American Health Organization (PAHO) Country Office in Brasilia, Brazil on March 12-14, 2013. The host of this meeting was the Secretariat of Health Surveillance/Ministry of Health of Brazil; organized with the support of WHO, PAHO and the Health and Climate Foundation.

The organizers would like to thank the Secretariat of Health Surveillance/Ministry of Health of Brazil and the Joint Research Center (JRC)/European Commission for their financial support for the third GLEAN meeting.

Gratitude should also be extended to the WHO/PAHO country office staff, meeting coordinators, report committee, and to all of the participants/attendees for making this meeting a great success.

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Executive Summary

Launched in 2010, the Global Leptospirosis Environmental Action Network (GLEAN) gathers representatives from international organizations and foundations as well as researchers. The initiative provides direction and coordination to fill the many gaps in leptospirosis knowledge with the ultimate goal of translating the research findings into operational guidance for communities and countries affected by leptospirosis outbreaks. A technical framework document, decided at the first GLEAN meeting in 2011, identified existing knowledge along with research gaps. It also identified urban leptospirosis outbreaks linked to natural catastrophes as a priority for action.

At the second GLEAN meeting in 2012, short-term and long-term objectives were developed and a preliminary guideline for outbreak control finalized. Since this meeting, several key projects have been completed including:

- a systematic review of leptospirosis outbreaks based on scientific literature from 1970 onward,
- a systematic review of the rapid diagnostic tests, and
- a GLEAN website.

From 12-14 March 2013, the third GLEAN meeting was held in Brasilia, Brazil. The meeting was hosted by the Secretariat of Health Surveillance, Ministry of Health of Brazil, and organized by the Pan American Health Organization, World Health Organization, Health and Climate Foundation and European Joint Research Centre. Nearly 30 international experts from 13 countries participated in the meeting, representing international organizations and foundations, academic institutions, vaccine manufactures and research laboratories. Additionally, nearly 40 Brazilian public health and laboratory specialists from 15 states participated.

Case studies and operational research projects were presented enabling the identification of additional needs in terms of knowledge and practice, including: i) to demonstrate the effectiveness of antibiotherapy and chemoprophylaxis, ii) to evaluate the potential of using PCR for routine laboratory confirmation, iii) to determine the effectiveness of rodent control on reducing leptospirosis incidence in humans.

Four working groups related to disease prediction, prevention, detection and intervention, were formalized. Each of them agreed on a 2013-2016 work plan that aligns with the identified public health priorities and the current research being conducted by the participants. Deliverables include training, field studies, literature reviews, and evaluation of the current practices. Missing expertise and additional potential collaborations were also identified.

The guidelines for leptospirosis outbreak control were updated.

The meeting also enabled a fruitful exchange of experiences among international and national professionals who work in different levels and institutions in the fight against leptospirosis.

Introduction

From 12-14 March 2013, an international multidisciplinary meeting on Leptospirosis was held in Brasilia, Brazil. The meeting was hosted by the World Health Organization (WHO) and the Pan American Health Organization (PAHO) in partnership with the Ministry of Health of Brazil.

Experts on leptospirosis were brought together from academia, research institutes, non-profit organizations, and non-governmental organizations from around the world to share knowledge on the state of leptospirosis and develop an action plan for minimizing the global human disease burden.

The objectives of the 2013 GLEAN meeting were to update participants on the GLEAN activities undertaken in 2012, develop the 2013-2016 GLEAN work plan, formalize the four working groups (detect, predict, prevent, intervene), and review case studies and operational research. The meeting enabled an exchange of experiences among international and national professionals who work in different levels and institutions in the fight against leptospirosis.

Session 1: Setting the Stage

Welcome and Opening Remarks

J. Barbosa da Silva, Secretariat of Health Surveillance, Ministry of Health of Brazil
Michel Jancloes Jancloes, Health and Climate Foundation
Eric Bertherat, WHO
Cristina Schneider, PAHO; in representation of J. Molina, PAHO

Overview of GLEAN

Michel Jancloes, Health and Climate Foundation

GLEAN (Global Leptospirosis Environment Action Network) has been developed as an interdisciplinary initiative to better inform preventive and control strategies against leptospirosis. The magnitude of this deadly human disease, which is also the second most prevalent zoonosis in the world, has been overlooked and systematic disease control efforts have been neglected so far. Disease burden has been estimated at more than 1,500,000 cases and 100,000 deaths per year, when adjusted for underreporting. This public health threat is likely increasing due to climate change through severe post disaster and flood outbreaks, affecting slums and subsistence farmers. Almost no operational guidelines exist because the transmission dynamics are badly understood, symptoms are not specific, detection is not made early enough and the biology of the pathogens is very complex (several species and more than 250 different serovars exist). GLEAN has identified four strategic pillars to mobilize the national and international partners, in particular research and development institutions. More specifically, the following issues have been recognized as priorities to be the basis for GLEAN short- and medium- term plans of actions. 1) Prediction: defining main drivers of transmission and their ability to predict significant changes in human infection risk and of outbreaks. 2) Detection: identifying case definition and outbreak thresholds, working out an algorithm for detection. 3) Prevention: assessing the effectiveness of preventive measures, developing rodents control strategies and measuring the impact of animal and human vaccines. 4) Intervention: working out preparedness and control operational guidelines. At last, some key institutional challenges were identified and are to be kept in mind for the new GLEAN developments. New members should be identified from the medical, climatology, veterinary, and economic sciences. At a country level, next efforts are going to be made for validating research results and translating tests and experiments into policy formulation and program capacity building.

GLEAN: From Marseille to Brasilia (and meeting objectives)

Eric Bertherat, WHO

Launched in 2010, the Global Leptospirosis Environmental Action Network (GLEAN) gathers representatives from international organizations and foundations as well as researchers. The initiative provides direction and coordination to fill the many gaps in leptospirosis knowledge with the ultimate goal of translating the research findings into operational guidance for communities and countries affected by leptospirosis outbreaks. The first GLEAN meeting was held in 2011 in Marseille, France. The meeting was hosted by the Institut de Médecine Tropicale du Service de Santé des Armées. At the meeting, the need was recognized for a collaborative initiative on leptospirosis along with the development of a technical framework document identifying research gaps as it

is related to disease prediction, prevention, detection and intervention. It was also agreed that urban outbreaks of leptospirosis linked to natural catastrophes should be addressed as a priority.

JRC hosted the second meeting in 2012 in Ispra, Italy. The GLEAN initiative was finalized organized, short-term and long-term objectives were defined and a preliminary guideline for outbreak control drafted. Since this last rendezvous, several projects have been finalized. They include: i) a preliminary systematic review of outbreaks based on scientific literature from 1970, ii) a systematic review of the rapid diagnostic tests and iii) a dedicated website.

The third GLEAN meeting was hosted by the Brazilian Ministry of Health. The primary objectives were to update participants on the GLEAN activities undertaken in 2012; develop the 2013-2016 GLEAN Plan of Action; formalize the four working groups (detect, predict, prevent, intervene); as well as review case studies and operational research in progress. The meeting also enabled an exchange of experiences among international and national professionals who work in different levels and institutions in the fight against leptospirosis.

Leptospirosis outbreaks worldwide: An overview from 1970 to 2012
Presenter: Claudia Munoz-Zanzi
Claudia Muñoz-Zanzi, University of Minnesota, Federico Costa: FIOCRUZ
Bozena Morawski, University of Minnesota, Federico Costa: FIOCRUZ

A systematic literature review of occurrence of leptospirosis outbreaks is underway. The objectives of the review include:

Primary:

- Present complete overview of human leptospirosis outbreak-related data by country from 1970 to 2012.
- Quantify human leptospirosis outbreak incidence by country and over time.
- Quantify outbreak size, duration, and human morbidity and mortality, by country and over time.
- Determine environmental or social factors associated with outbreaks.

Secondary:

- Identify gaps in scientific knowledge and improve our understanding of the determinants of outbreaks.
- Identify gaps and biases in reporting (quantity and quality).

The review is considering scientific literature, informal reports (e.g. ProMed), and other grey literature. A clearly defined protocol is being followed consisting of inclusion and exclusion criteria and application of a specific outbreak definition. For reports that fulfill the outbreak definition, information is being extracted to characterize the outbreak and potential risk factors (e.g. number of cases, place and time, case detection mechanism, fatality, exposures, and quality assessment of the report). Application of the review protocol to the existing Leptospirosis Burden Epidemiology Reference Group (LERG) database (1970-2008) of 26,704 records yielded 298 reports (including 97 ProMEd references) meeting the outbreak definition. There is a marked increase in the number of

reports over the years, which probably reflect the combined effect of improved detection and reporting, as well as of drivers of a potential true increase in outbreak occurrence.

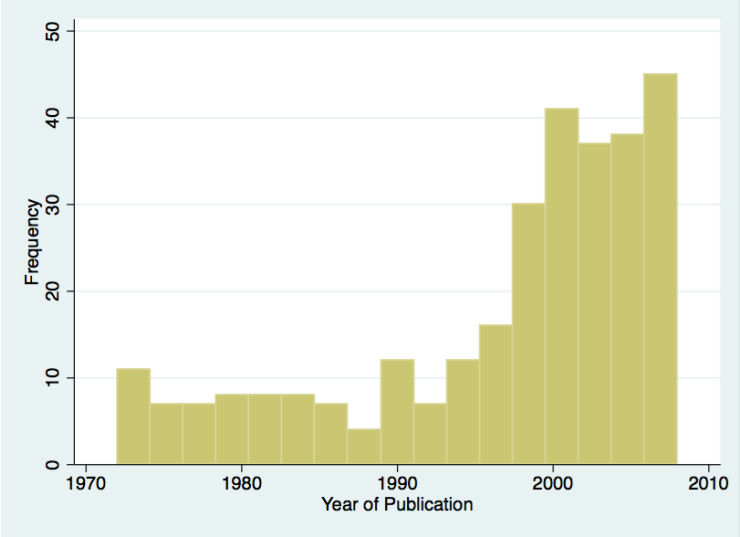

Figure 1. Number of outbreak reports per year (from LERG 1970-2008 database)

Preliminary analysis of the extracted reports shows that 33% of the reports are classified as high quality (major criteria) and having exposure to contaminated water as a predominant risk factor. Furthermore, water-associated outbreaks show to be larger in size. Global distribution of outbreaks shows important gaps in reports (lack of data) from Africa and other regions which are likely due to considerable under-diagnosis and under-reporting (Figure 2). Next steps include completion of data extraction of the LERG reports and review of searches from 2008-2012 (approximately 3,000 records for application of outbreak definition). The level of effort and approach for obtaining data from non-published reports/data need to be discussed.

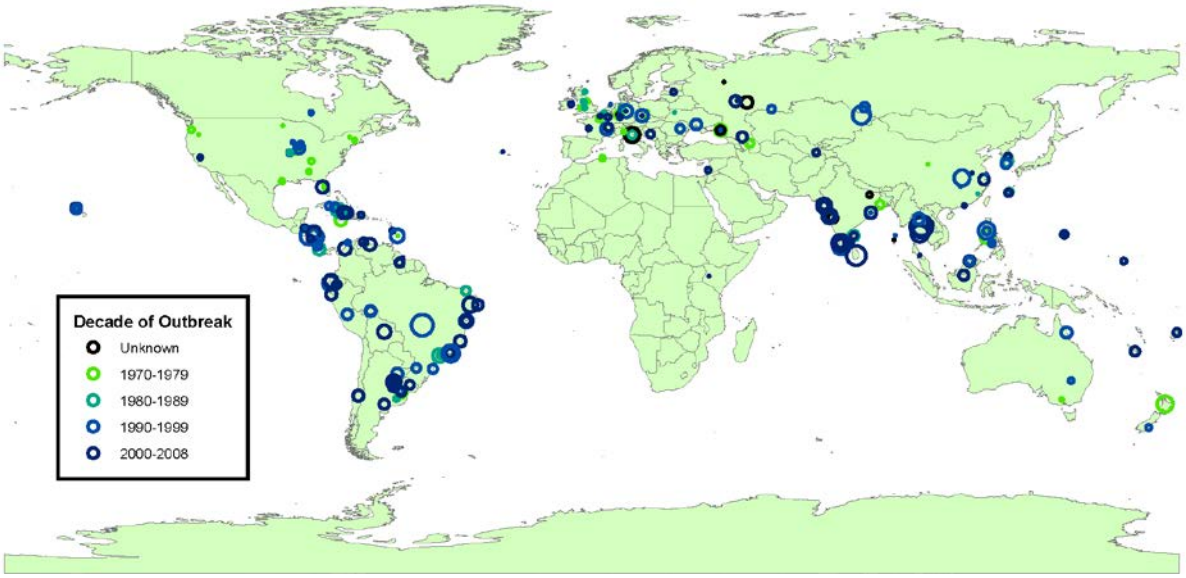

Figure 1. Distribution of leptospirosis outbreaks worldwide (LERG database 1970-2008) (reports of all quality included)

Leptospirosis in Latin America and the Caribbean: State-of-the-art knowledge
Martha Maria Pereira, WHO Collaborating Center for Leptospirosis, Oswaldo Cruz Institute/FIOCRUZ, Rio de Janeiro, Brazil

Background – Leptospirosis is a zoonosis widely distributed around the world. The human disease has been mentioned as an emerging, re-emerging, or neglected disease according to the geographical area and time. The gaps in knowledge may cross the major areas of the actual biological research. There are challenges in the diagnosis and treatment of severe forms characterized by clinical signs and symptoms of hemorrhage and renal failure. Surveillance and control measures are challenging due to the gaps in technical knowledge and lack of proper field samples and cases, which also limit advancement of technical knowledge. This cycle impedes making true progress in comprehensive disease control and awareness despite the emerging situations caused by climatic changes and recent epidemic outbreaks in Latin America and Caribbean countries.

Methodology – All relevant information concerning the scientific literature has been used to produce a realistic report on the current state of knowledge. The search has been focused in the region of Latin America and Caribbean countries in the period between the years 2002 and 2012. The available information has been searched in Pubmed/NCBI, BIREME/BVS (LILACS) and ISI Web of Knowledge. Original papers in English, Spanish, French and Portuguese were considered. Country health information systems and documents from international scientific bodies were used for complimentary data. Databases were managed by EndNote X5 software.

Conclusions – There are gaps in scientific knowledge that lead to gaps in information regarding the burden of human leptospirosis. This is true both from a global and regional perspective. Promising and relevant information is being produced in areas of great scientific development such as genomics and proteomics, which may lead to new findings and products such as simple tests for diagnosis and vaccines. The findings in these areas involve inter-institutional and international cooperation mainly with countries outside the region. Fields such as pathology, immunology, and pathogenesis need more attention since these are of most importance to therapeutic alternatives.

Leptospirosis in Brazil
Eduardo P. Caldas, MoH Brazil -Zoonotic Disease

The objectives of the Brazilian National Epidemiological Surveillance are to: (1) reduce case fatality rate by timely diagnosis and appropriate treatment; (2) monitor the occurrence of cases and outbreaks and determine its spatial and temporal distribution; (3) identify the serotype circulating in each area; and (4) apply preventive and control measures for people, the environment and animal reservoirs.

The case definition of a suspected leptospirosis case involves clinical and epidemiological components. It encompasses the presentation of signs and symptoms characteristic of leptospirosis, such as fever and myalgia, in addition to previous exposure (30 days) to mud/flood, contact with contaminated water, sewer water or sewer system, garbage and agriculture/animals possibly contaminated. The confirmed case

definition includes clinical and epidemiological aspects, as well as laboratory confirmation by ELISA-IgM reactive, microagglutination (MAT), immunohistochemistry positive in death cases, isolation of leptospires in blood, fluid cerebrospinal, urine or tissue, or pathogenic leptospirosis DNA detected by PCR.

The Brazilian Ministry of Health (MoH) has published fact-sheets, guidelines and manuals for leptospirosis, which are available to the public through the MoH website. In addition, it counts with the Brazilian National Information System, an information system for notifiable diseases (SINAN) that employs universal and passive methods, and includes general, housing, clinical and laboratory data, individual notification, epidemiological history, treatment, conclusion and further information. All data are compiled in a database performed by DATASUS.

About 72% of cases of leptospirosis occur in the urban areas of Brazil, especially in association with domestic environment situations. Rains and floods increase exposure and in urban settings *Rattus norvegicus* (sewage rat) and *Rattus rattus* (roof rat) are the primary rodent reservoirs for leptospirosis. Rural areas account for about 28% of the cases, primarily due to occupational risk situations.

In 2007, six municipalities were designated as priorities municipalities in Brazil to reduce leptospirosis' case fatality rate: Rio de Janeiro/RJ, São Paulo/SP, Salvador/BA, Curitiba/PR, Recife/PE and Belém/PA. The specific objectives of this project are to define risk areas, strengthen surveillance and disease control, establish control methodologies in leptospirosis reservoirs, and train health professionals in diagnosis and clinical management. The main goals for 2013 include training of clinicians in referral hospitals and to finalize the guidelines for leptospirosis surveillance and control.

Session 2: Predict

Leptospirosis outbreaks in Nicaragua: Identifying critical areas and exploring drivers for evidence-based planning

Presenter: Maria Cristina Schneider
Maria Cristina Schneider; Patricia Nájera; Sylvain Aldighieri; Matthew Moynihan; Marcos Espinal, Pan American Health Organization, Health Surveillance and Disease Prevention and Control
Jorge Bacallao, Universidad de Ciencias Médicas de La Habana
Aida Soto; Wilmer Marquiño; Lesbia Altamirano, Pan American Health Organization Nicaragua
Carlos Saenz; Jesus Marin; Eduardo Jimenez, Ministerio de Salud de Nicaragua

Leptospirosis is an epidemic-prone zoonotic disease that occurs worldwide. In Central America, leptospirosis outbreaks have been reported in almost all countries; Nicaragua in particular has faced several outbreaks. The objective of this study is to stratify the risk and identify “critical areas” for leptospirosis outbreaks in Nicaragua, and to perform an exploratory analysis of potential “drivers”. This ecological study includes the entire country (153 municipalities). Cases from 2004 to 2010 were obtained from the country’s health information system, demographic and socioeconomic variables from its Census, and environmental data from external sources. Criteria for risk stratification of leptospirosis were defined. Nicaragua reported 1,980 cases of leptospirosis during this period, with the highest percentage of cases (26.36%) in León, followed by Chinandega (15.35%). Forty-eight municipalities were considered critical areas, 85 were endemic, and 20 were silent. Using spatial and statistical analysis, the variable presenting the most evident pattern of association with critical areas defined by the top quintile of incidence rate is the percentage of municipal surface occupied by the soil combination of Cambisol (over pyroclastic and lava bedrock) and Andosol (over volcanic ash foundation). Precipitation and percentage of rural population are also associated with critical areas. These methodologies and findings could be used for Nicaragua’s Leptospirosis Intersectoral Plan, and to identify possible risk areas in other countries with similar drivers.

Eco-Epidemiology study of leptospirosis in Chile

Claudia Munoz-Zanzi, University of Minnesota

The eco-epidemiology of leptospirosis is being investigated in 12 communities from southern Chile representing slums, villages, and farms. Results revealed high levels of *Leptospira* contamination (18% of positive samples) in water from the peri-domestic environment (e.g. puddles, containers, canals, ponds) in all community types. Furthermore, human drinking water sources showed evidence of contamination. Overall, 20% of rodents trapped in the households were positive for *Leptospira*. *Leptospira* occurrence in rodents and water is higher in rural communities than in urban slums. The most important determinants found so far are climatic and temporal (yearly and seasonal changes). Notably, dynamics of infection in urban slum communities from this temperate area show distinct patterns of infection. These slums have few rodents and with lower prevalence than rural areas. Conversely, prevalence of infection is the highest in dogs from urban slums compared with rural households. This is consistent with evidence of prior exposure to serovar Canicola in people from the slums.

Preliminary molecular analysis of the positive water and rodent samples from the same communities is not showing a high level of similarity indicating that other hosts may be playing a role in environmental contamination. Molecular (sequence) diversity in positive samples at the community level is the highest in farms and the lowest in slums. Data on infection in people, livestock, and other domestic animals in rural communities, as well as human risk behaviors are being analyzed. Preliminary findings highlight the need to examine transmission at a local level and using a "systems" approach.

Digital-earth information systems for post-disaster assessment of leptospirosis and for anticipating consequences at local scales
Andreas Skouloudis, Institute for Environment & Sustainability, DG-JRC

Leptospirosis became recently a major public-health problem that is closely related with the environment. This disease can claim many victims with large outbreaks during natural disasters or seasonal floods. This presentation examined the availability of information for predicting the assessment of disease on the basis of geographical information suitable for exposure mapping. In particular, the elements shown in the table below were covered.

Table 1. Elements needed for spatial assessment of leptospirosis occurrence and risk exposure mapping

Infrastructural equipment	Predict	Prevent	Detect	Intervene
DEM and Catchment Areas	√	●		
Corine Land-use Assessment	√	√	●	
Animal density	●		●	●
Population density	√		●	●
Meteorological sensor devices	√	√	●	
Biosensors in lab	√		●	●
Biosensors in the field	●		●	●

Elements marked with √ are areas incorporated already. Elements marked with ● are operations that could be accurately carried out by GLEAN for enabling solutions to problems that were previously irresolvable due to their high degree of complexity. The need for cheap and easy-to-operate monitoring systems for early warnings and verify the effectiveness of actions during disasters or during "interventions" for containment was emphasized. Additionally, Digital Elevation data and the identification of the water catchment areas in less than 50x50m^2 or even in finer resolutions should be used. Improved animal and population density data are already in the pipeline and improved meteorological water quality monitoring techniques and instruments that can enhance our ability to perceive and monitor the aquatic environment. Biosensors are capable of providing specific, high spatial resolution information and allow unattended operation that will be particularly useful for water borne related diseases.

Sensor networks enable sensitive monitoring systems and allowing real-time monitoring of pollutants and facilitates data transmission between the measurement points and central control stations for continuous surveillance and early warning capability. Such data are: local temperature, pressure, humidity, dew point, wind speed and direction, rain and rain-rate, solar and UV radiation that can be also associated with water level sensors in rivers. More sensitive systems within flowing water allow real-time monitoring of contaminants and pathogens associated with outbreaks of specific diseases.

The implementation of sensor networks for data collection and exposure mapping relies on identification of locations where such networks could be of use. Systematic monitoring from satellite images is utilized for increasing the potential areas of application, for assessing the geographical representativeness of the measurements of the sensors, and proposing the methodology on assessing the environmental conditions that are associated with outbreaks of leptospirosis. Unfortunately, several combined deployments of earth observations with ground sensors are required for understanding the connections between hydrology and human health.

Improved spatial resolution and higher sensitivity allow for localized detection of outbreaks and simplified operation with reduced costs compared to conventional methods. Ultimately, this will lead to the establishment of early warning systems that might investigate the effectiveness of key control measures, including vaccination (when it becomes available) and affront the water decontamination, and animal control issues.

Session 3: Detect

Update on laboratory diagnosis tests and strategies, in particular towards early testing and confirmation

Rudy A. Hartskeerl, Royal Tropical Institute (KIT)

Disease burden: Leptospirosis is a major neglected infectious disease. A current systematic review on the burden of leptospirosis indicates >1.7 million severe cases of human leptospirosis occur annually with a fatality rate of about 8%. In addition, a DfID report on poverty and zoonoses hotspots ranks leptospirosis as the second most important zoonosis, only preceded by a group of zoonotic gastrointestinal diseases. Similarly, in a recent GeoSentinal multicenter study on tropical diseases in Western travelers reflecting global exposure risks, leptospirosis was placed third highest, following malaria and, again, gastrointestinal diseases. In both studies, leptospirosis far outranks the burden of dengue, revealing an unjustified balance disparity of attention towards these two diseases.

Standard diagnostic tests: In spite of a growing awareness of leptospirosis, the disease still remains underreported. This is due largely to the difficult diagnosis. Protean manifestations make the disease challenging to diagnose on clinical grounds while standard laboratory techniques are arduous, expensive, or unreliable. Standard “antigen detection” approaches include darkfield microscopy (DFM) and isolation by culture. While DFM is notoriously unreliable, isolation, the true gold standard, takes weeks to months to become positive and hence is not beneficial for the management of the individual patient.
Other standard tests are based on serology. The microscopic agglutination test (MAT) is the reference test while in many situations the IgM (Enzyme-Linked ImmunoSorbent Assay) ELISA would be a more feasible approach. A recent paper on the laboratory case definition shows that serology is not applicable in the first five days post onset (DPO) of disease because antibodies are not present in detectable levels. Sensitivity increases rapidly in the late acute phase (till 10 DPO) with the following observations: (i) IgM ELISA is earlier positive then MAT and maintains a higher sensitivity in the late acute phase (sensitivity >95%, specificity 100%). The MAT, at the best, reaches a sensitivity of 80% (specificity 100%). (ii) The availability of a paired sample greatly increases the sensitivity of serological testing already at an early acute phase. Based on these findings, the WHOCC in Amsterdam has revised their algorithm, now applying IgM ELISA together with PCR and culturing on samples collected up tot 10 DPO. MAT is performed only on samples collected more than 10 DPO.

Rapid diagnostic tests: Numerous rapid diagnostic tests (RDT) are currently commercially available, mostly based on lateral flow or latex agglutination formats. A prospective evaluation of three of such tests (manuscript published in PLoS NTD 2013) reveals the following: (i) as expected, the sensitivity of these tests is low at the early stage of the disease, (ii) sensitivity increases in the late acute phase to early convalescence phase up to 70-80% with an appreciable specificity of >98%, (iii) sensitivity increases markedly (>95%) when paired samples are available, and (iv) the diagnostic accuracy of tests varies from year to year; one cannot rely on a consistent performance.
The performance of (sero) diagnostics, whether reference or screening tests, depend on the local epidemiological situation. A high exposure pressure to infection with several

Leptospira serovars or other infectious agents that cause cross-reactions might require more stringent criteria for a positivity threshold to define a case.
Early diagnostic tests: An early test is different from a rapid test. Early treatment (or early outbreak registration) requires early testing and hence would require future focus on 'early' tests. Such tests are antigen detection-based. Conventional formats of antigen detection tests (e.g. antigen capture ELISA) have a sub-optimal sensitivity of 100 to 1000 leptospires per milliliter (ml) sample. This detection threshold could be considerably improved by applying nanotechnology but would make tests expensive. Currently, amplification techniques of nucleic acids (NA), mostly the polymerase chain reaction (PCR), applied on early acute blood samples seem to be a promising approach. Real time PCR has the potential to detect a single copy in a reaction and prospective validation reveals a high level of diagnostic accuracy. Improvements might focus on improved NA extraction methods concentrating target DNA of high purity or on isothermal amplification methods that require less pure NA.
Technical developments make this approach increasingly affordable. Currently, battery driven hand-held PCR machines are available at reasonable prices, whereas isothermal amplification requires even more simple and cheap devices. While portable real-time machines can generate direct online data, the use of Taqman-like probes allows capturing and detection in lateral flow formats. Images can be sent by SMART phone to the national epidemiological center for case and early outbreak registration. Providing tests with a Quick Response (QR) code will at the same time allow the storage and access to relevant data, only limited by (inter)national privacy restrictions.

Diagnostic accuracy: Because epidemiological situations are locally different, any test requires local validation to assess the diagnostic accuracy prior to implementation. RDTs should be evaluated against reference tests. Moreover, since quality assurance during production of RDTs is often poor, causing performance inconsistencies, local evaluations need to be executed on a regular basis. It is often argued that the use of crude antigens is the cause of false positive test outcomes and that the use of recombinant antigens will increase the specificity. The use of a species-derived antigen, however, also implies a concomitant reduction of the global sensitivity where infections with a variety of heterologous species and serovars occur. Thus far, convincing evidence of a better global performance of recombinant antigen-based serological tests is lacking. When confirming RDT positive sera from various parts of the world, the WHOCC in Amsterdam often finds these samples negative both in the reference tests and in the same RDT. Good performance of RDTs might frequently be an issue of the test performer/reader rather than of the test itself or the local epidemiological situation.

In summary: (i) the use of an early test (applicable the first five days of illness) is to be preferred above the use of a rapid one since the speed of case finding is essential. To date, (real-time) PCR is the most feasible option for accurate early diagnosis but needs further elaboration to make it more cost-effective and to generate early registration at national epidemiological centers. PCR might be substituted by isothermal amplification approaches. (ii) Current RDTs are a suitable option for screening cases at peripheral levels, albeit that these only enable confirmation in the late acute phase (> 5DPO). (iii) Currently available data do not show that recombinant antigen-based RDTs have a better global performance than crude antigen-based ones. (iv) Confirmation by arduous or more expensive standard tests such as isolation by culturing, MAT and (real-time) PCR is to be done at a national reference center in close contact or associated with the national epidemiological center to contribute to early outbreak warning. (v) All tests, whether antigen detection-based, serological, point-of-care, or standard tests, need

validation before implementation. Local validation is critical for serological tests as their diagnostic accuracy will depend on distinct local epidemiological situations. Epidemiological background will affect genus specific molecular tests to a lesser extent.

Laboratory diagnosis in Brazil
Leandro Queiroz Santi, MoH - CGLAB/SVS/MS

The National System of Public Health Laboratories (SISLAB) in Brazil includes a network of laboratories at national, regional, state, municipal and local levels. The objectives of the National Network of laboratories surveillance of leptospirosis are to confirm suspected cases, monitor the circulating serovars, and provide support for the epidemiological surveillance and control.

The state reference laboratories perform serology tests (IgM ELISA), the regional reference laboratories perform serology tests (IgM ELISA, MAT), culture and PCR, and the national reference laboratory performs MAT, immunohistochemistry, PCR and culture. Leptospirosis confirmation occurs at the national reference laboratory. Brazil has five regional labs and one national reference lab (FIOCRUZ, RJ).

The mains goals faced by the laboratory network regarding the challenges of epidemiological surveillance of leptospirosis are to strengthen the responsiveness of the network, strengthen the laboratory information system, increase access to laboratory information system, and apply technological innovations (real time PCR and rapid tests).

The changing face of Leptospirosis diagnosis in New Caledonia
Presenter: Cyrille Goarant
Cyrille Goarant and Ann-Claire Gourinat, Institut Pasteur de Nouvelle-Calédonie

With an average incidence of 38 cases per 100,000 inhabitants, leptospirosis is endemic in New Caledonia, a small island country in the South Pacific. It has a typical seasonal pattern, with inter-annual variations under a very strong influence of the El Niño Southern Oscillation. Its epidemiology is typically rural and exposure risk factor analysis point to a number of animal reservoirs. Leptospirosis surveillance is based on our single reference laboratory for the biological confirmation of human cases and relies on the mandatory notification of all cases to the New Caledonian Health Authority. At the laboratory level, we follow a diagnostic algorithm based on the number of days since onset of symptoms: from the onset to day 10, real time PCR is implemented on serum specimens. MAT is conducted from day 6 on. Additionally, real time PCR can also be run on urine specimens from day 8 on. All biological results are properly interpreted in order to make conclusions rigorous and clear. As an example, the result for a negative PCR stresses the usefulness of submitting a convalescent serum for MAT to assess seroconversion.

For the past 7 years, we have observed a major change in the relative contribution of qPCR and MAT to the diagnosis of human cases: whereas MAT accounted for 74% of the diagnosed cases in 2006, it only accounted for 8% in 2012 and none of the 20 first cases in 2013. This major shift has several possible causes. First, we have worked at improving both the analytical sensitivity and the turnaround time to provide results in a timely manner. Additionally, we possibly achieved an increased awareness of the

availability and benefits of qPCR in terms of early diagnosis and treatment by both medical staff and general population. Notably, a consequence of this shift to early, single sample diagnosis has been the loss of the epidemiological information provided by MAT. MAT can provided a putative identification of the serogroup of the infecting *Leptospira* strain which is useful for source determination. We therefore developed a molecular typing scheme that is usable directly on patients' specimen DNA extracts. Taken together with the identification provided by MAT, this has allowed identifying the putative infecting strain and corresponding animal reservoir in more than 95% of human cases over the past three years. The algorithm, technical improvements, and optimizations are discussed together with the contribution to a better knowledge of the animal reservoirs involved in human leptospirosis in New Caledonia.

Using the Dual Path Platform (DPP^{TM}) for rapid diagnostics in Leptospirosis
Edmilson Domingues da Silva, Fiocruz/RJ

Diagnosis of leptospirosis by the reference serologic assay, the microscopic agglutination test (MAT), requires paired sera and is not widely available. We developed a rapid assay using immunodominant *Leptospira* immunoglobulin-like recombinant proteins in an immunochromatographic lateral flow dual path platform (DPP, Chembio Diagnostic Systems, Inc.). In this study, the novel DPP assay developed and produced by Bio-Manguinhos (Fiocruz, RJ) and the Center for Research Gonçalo Moniz (CPqGM, Fiocruz, BA) detected 81-85% of severe acute clinical leptospirosis using the initial clinical specimen collected at hospital presentation and its diagnostic performance was comparable to a commonly used IgM-ELISA. Furthermore, the DPP assay produces a result in 20 minutes and can be more easily implemented in field settings than existing diagnostic technologies. The assay performed well for diagnosis of severe acute clinical cases and it can be easily introduced into hospitals and health posts where leptospirosis is a major public health problem.

Session 4: Prevent

Vaccine Session

Lessons from 30 years' experience of human vaccination against leptospirosis in France

Jérôme Denis, IMAXIO SA, France

A human vaccine against leptospirosis was developed in the 1960s/1970s in France as a response to the sewer workers in Paris being strongly affected by this zoonosis. The vaccine, made of one inactivated bacterial strain (serovar Icterohaemorrhagiae, strain Verdun), received its market authorization in 1979. Since then, human vaccination against leptospirosis has been extensively practiced in France in the most exposed adult populations, mainly workers in sewage collection and treatment, pisciculture, agriculture, construction, and also among emergency responders such as firemen. The vaccine efficacy was originally shown by the disappearance of Icterohaemorrhagiae-associated leptospirosis cases in the first vaccinated sewer population in the 1980's in Paris. The high level of seroconversion rate (more than 90%) after each vaccination boost was also shown in different studies. Additionally, several publications reported good tolerance of this vaccine, mentioning mainly expected minor local and systemic reactions after vaccination. Altogether, the vaccination experience in France over the 30 past years illustrates the possible contribution of human vaccination to leptospirosis prevention in high-risk populations.

Impact of vaccination of animals on the human populations

Presenter: Jackie Benschop

Jackie Benschop; Julie Collins-Emerson; Cord Heuer; Peter Wilson, Massey University

The incidence of notified leptospirosis cases in New Zealand in the last quarter of 2012 was three per 100,000, the highest among OECD countries. Leptospirosis in New Zealand is an occupational disease with livestock farmers and abattoir workers most at risk. Serovars Hardjobovis and Pomona have consistently been responsible for at least 50% of human cases and these serovars are found in New Zealand pastoral livestock species. A 2010 survey of 237 farms found serological evidence of exposure to Hardjobovis and/or Pomona in over 50% of adult sheep and beef cattle and in 34% of adult deer. Two important serovars that are seen internationally, Canicola and Icterohaemorrhagiae, are exotic to New Zealand.

Globally the major burden of human leptospirosis derives from contact with rodents. Control measures to reduce exposure to rodents include reducing their numbers by poisoning and trapping, and rodent-proofing buildings and feed stores. However in New Zealand, given the role domestic species play in transmission to humans, livestock vaccination is a mainstay for the control of human leptospirosis and it has a long history. In the 1960s and 1970s increasing concern over "dairy farm fever" coupled with the realization that cows were silently infected with Hardjobovis were key drivers for the governmental support of an animal vaccine to protect humans from leptospirosis. In 1973-74, voluntary vaccination of dairy cattle began and there was a subsequent decline in cases: in the early 1970s the incidence risk was approximately 25 cases per 100,000; in 1979, the incidence risk was 19 cases per 100,000; and in 1982, this had dropped to 4.5 per 100,000. In New Zealand today approximately 85% of dairy herds are

vaccinated. Coincident with the uptake of vaccination in dairy herds, the New Zealand pork industry also made a strong push for leptospirosis control and this was supported by slaughterhouses. However, only a small proportion of sheep (<1%), beef (18%) or deer farmers (10%) currently vaccinate against leptospirosis.

Animal vaccination as an option for the control of human leptospirosis is feasible if the predominant serovars found in human cases are few, and they are maintained in domestic species. Other important considerations include that vaccines are efficacious (prevent shedding in naïve animals and reduce it in those previously exposed); vaccination is incentivized (includes legislation, enforcement and proven benefits to animal owners beyond human protection); vaccination is practical (timing fits in with animal production and movement cycles, the cold chain can be maintained and staff are trained to deliver it); and that animal vaccination is recognized by all as a long term prospect.

Opportunities and challenges currently facing New Zealand within the sphere of animal vaccination to control human leptospirosis include the timely and appropriate delivery of vaccine in dairy herds as herd size increases and young stock are grazed away from the home farm; the emergence of serovar Ballum as the single most predominant serovar in human cases; the recent findings in a pilot study that leptospiral challenge of calves at an early age and potential human exposure still exists on dairy farms using vaccines; and incentivizing all appropriate livestock industry sectors to vaccinate. With regard to the latter, vaccination of sub-clinically infected deer has been shown to improve reproductive and growth outcomes and be cost-effective for farmers. A current PhD project is underway to investigate this in sheep flocks and beef breeding herds.

Human-Animal-Environment Interface Session

Rodent control in urban settings – Brazil: Favorable evidence to pulsed baiting strategies in programmed treatment blocks

Eduardo de Masi, Municipal Health Secretary, Municipal Government of São Paulo

The Campo Limpo Borough is located in the South Region of São Paulo city (Geographical coordinates: -23.64° and -46.77°). The resident population is 607,115 inhabitants in approximately 170,000 dwellings. Based on epidemiological risk factors and GIS information, 21 program areas for leptospirosis control were identified which consist of 36,872 linear meters of stream, 2,066 sewers, 6,977 dwellings, and an estimated population of 25,000 householders. These areas are generally considered slums and are characterized by high population density, poor socioeconomic and environmental sanitation conditions, and are located in the borders of streams. According to the Leptospirosis and Rodent Control Program of São Paulo, these areas annually received three blocks of deratization; each block consisting of a three-pulse application of rodenticide. The time interval between each block is four months and between each pulse is one week. Fifteen zoonosis agents work daily to conduct rodent control measures in streams, sewers, and human dwellings. The result of these strategies shows temporal reduction in infestations after each subsequent pulse within the same block. The annual reduction in the number of rodent burrows was 48.4% and in roof rat infestation rate was 58.8%. Moreover, the reduction in rodenticide consumed between the first and third block was 34.7%, equivalent to 81.7kg. As a consequence of the pulsed bait strategies, the reduction in leptospirosis incidence in the period from

2004 to 2011 was 50.8%, despite of an increase in pluviosity from 2007 to 2010. In conclusion, the pulsed bait strategies in treatment blocks were effective, but the time interval between blocks (four months) was too long. Therefore, it is advised to reduce the interval to three months.

Ecological aspects of *Leptospira* reservoir in Salvador, Brazil
Federico Costa, Instituto de Saude Colectiva-UFBA (Fiocruz)

In Brazil, more than 10,000 cases of leptospirosis are reported every year. Most cases are identified in urban slum areas, especially in large cities, and are related to epidemics during the rainy season, which is from May to July in Brazil. Major risk factors for leptospirosis are the presence of open sewers, accumulated trash, and rats. Rats are thought to be the primary reservoir in urban areas. Three different studies were conducted related leptospirosis in Salvador; Rodent Control Program (RCP), environmental reservoir, and rat leptospirosis reservoir.

Rodent Control Program (RCP):
In 2007, the Zoonosis Control Centers, made up of municipal organizations responsible for reservoir control, from Salvador and FIOCRUZ, together with Yale University and Liverpool University, started a collaboration called the Rodent Control Program (RCP). The main objective of this collaboration was to develop a systematic prevention program to decrease incidence of leptospirosis in Salvador, Brazil. The RCP utilized a multidisciplinary approach including Epidemiology, Ecology, and a Geographic approach and modeling of the results.

Residences of laboratory confirmed leptospirosis cases (years 2005-2010) were delocalized. Their spatial distribution defined 11 areas (15% of the area of the city), containing 2,078 blocks, of equal risk for leptospirosis. From January to April 2007, the pre-epidemic season, households from treated blocks were visited, surveyed for signs of rat infestation, and received rodenticide applications and the distribution of educational materials.

The efficacy of the RCP was evaluated by assessing two different outcomes; level of rodent infestation and treatment intensity. The level of rodent infestation was evaluated by surveying 10% of treated blocks after intervention. The treatment intensity was measured by kilograms of rodenticide applied and proportion of chemically treated houses in a block. Kilograms of rodenticide applied and the proportion of chemically treated houses in a block were used to build two mathematical models that evaluated the risk ratio of incidence of severe leptospirosis between pre- and post-intervention periods. Of the 2,078 total blocks, 671 blocks were treated in 2009 and 1,129 blocks in 2010. Pre-intervention surveys identified rat infestation rates of 25% and 26% in 2009 and 2010, respectively. Of the total of households infested in 2009, 92% had evidence of *Rattus norvegicus*. After intervention, rat infestation decreased from 25% to 7% ($p<0.001$) in 2009 and from 26% to 15% ($p<0.001$) in 2010. Using the models, the predicted impact of maximum rodent intervention, as measured by either block coverage or kg of rodenticide application, had large confidence intervals limiting our ability to evaluate the efficacy of RCP. Our study indicates that high proportions (>25%) of households are infested with *R. norvegicus*. The RCP was able to decrease rat infestation but, because severe leptospirosis cases are rare events, was not able to evaluate its impact on decreasing incidence.

Environmental Reservoir:
In 2011, we performed a one-year survey of leptospires in environmental surface water in an urban slum community. The study site was situated in a valley of 0.12 km2 in the city of Salvador, Brazil. We systematically collected pooled water and sewage samples from 14 points during the months of July and October (two weeks each). DNA was extracted from 50 ml of water samples. A qPCR assay based on the gene lipL32 was used to determine genome equivalents from the water samples. Pathogenic leptospires were detected in 12% (61) of 498 surface water samples. The proportion of qPCR positive samples (18% vs. 9%, $P<0.05$) and leptospiral concentration (10.1 vs. 6.6/ml, $P<0.05$) were significantly increased for the month where rainfall was greater (October vs. July; 230mm vs. 81mm). The proportion of positive samples was significantly higher in samples collected during the morning when compared with afternoon samples (17% vs. 6%). Samples collected from sewage also had significantly higher positivity proportion and *Leptospira* concentration (18%; 8.8/ml) than pooled water (6%; 6.2/ml). Our findings suggest that the diurnal and seasonal variations influence the dynamics of leptospires in the environment. Furthermore, interventions targeting sewer will be necessary for effective prevention.

Rat Leptospirosis Reservoir:
Rats were captured during 2010 in an urban slum situated in a valley of 0.12 km2 in the city of Salvador, Brazil. A seasonal- and sex-matched sample from urban Baltimore, MD, USA (year 2010) was captured in order to compare population parameters between tropical and temperate rats during winter. Trap success was similar between Salvador (11.6%) and Baltimore (10.8%). Juvenile rats (<200g) were more frequently captured in Salvador (20%) compared with Baltimore (2%). In Brazil, leptospiral carriage among juvenile animals was high (35%) and increased to 68% in young adults and 76% in adults. This infection pattern in rats is different of the pattern observed in U.S. rats and may indicate important differences in how infection is acquired in these temperate and tropical locations.

Animal leptospirosis: towards a changing epidemiology
Angeli Kodjo, VetAgro Sup

Most of the debate around animal leptospirosis associated with large-scale outbreaks tends to present animals as factors contributing to the spread of the disease due to their role as reservoir of certain *Leptospira* serovars. This is true with most rodents, particularly with the rat which is one of the most efficient vectors of the pathogen. Of course, it is justified to give priority to human beings during such dramatic events, but as victims, many domestic animals are affected similarly to humans, with possible changes in the epidemiology of their disease. This situation has two major impacts, a social impact which is not debatable with animals regarded as pets, and economic losses for the farm industries which may directly impair the situation post disaster. In the case of leptospirosis, it is well known that economic losses occur, but this has never been quantified, the GLEAN initiative can be an opportunity to start such investigations.

The social anthropology of rodents and their management
Steven Belmain, Natural Resources Institute, University of Greenwich, Chatham

Rodents are widely accepted as one of the main underlying ecological drivers of leptospirosis infection in livestock and human populations. Evidence from many other vector-borne diseases clearly indicates that sustainably reducing vector populations can reduce chronic and acute outbreaks of disease. Despite this, there have been few attempts to manage rodent reservoirs as a means of reducing risk of disease transmission in the context of leptospirosis or, indeed, any rodent-vectored disease. This talk argues that the reasons for failing to manage rodent pest populations is largely due to human attitudes, pre-conceived notions, and the anthropomorphizing of rodent behaviors and abilities which affect the design and implementation of rodent control actions. Non-human behaviors inherent in rodents, such as neophobia, are not easily understood by people and can lead to wrong choices and wrong conclusions when trying to control rodent populations. Ultimately, many people try and fail to control rodents, becoming apathetic and accepting of rodents, tolerating the problems they cause due to beliefs that "rodents are too clever to control." Changing people's attitudes and practices through training and capacity building by providing access to knowledge about rodents and raising peoples' awareness about technology and actions that are proven to be cost-beneficial and environmentally sound can lead to major improvements to the livelihoods of the rural and urban poor. This is because rodents can transmit many different diseases as well as damage agriculture (pre and post-harvest), personal possessions (clothes, fishing nets, blankets) and infrastructure (electrical wires, sanitation); therefore, reducing rodent numbers affects many aspects of peoples' lives. The new paradigm of ecologically-based rodent management argues that the use of poisons is not the exclusive solution to rodent pests, with a need to integrate social anthropology and rodent biology knowledge for the design of sustainable pest management solutions.

Leptospirosis, water, and sanitation in Brazil
Adriana Rodrigues Cabral, MoH - CGVAM/SVS/MS

Leptospirosis is recognized as a disease of social relevance. In Brazil, sustainable development indicators (IDS 2012) and occurrence of diseases related to inadequate environmental sanitation result in a persistent high number of hospitalizations for these diseases linked to poor sanitation, especially in the North and Northeast of Brazil
The risk factors associated with leptospirosis transmission depend on the characteristics of the spatial organization and the living and working conditions of the population. Therefore, it is important to know the role of demographic, social and economic factors as determinants of the disease.

Leptospirosis transmission has a strong relationship with the improper disposal of solid waste and deficient drainage systems. Together, these two factors directly affect the occurrence of floods and hence possible increase in the risk of contamination. Therefore, the adverse effects of these two variables, when put together, represent a higher risk when compared to their isolated effects.

In Brazil, there have been important advances in social policies, which are directly related to public health. The national policy for sanitation (Law 11.445/2007) establishes four essential components for sanitation (drinking water supply, sewerage, urban cleanness and solid waste management, drainage and storm water management of

urban areas) and defines that basic sanitation plans are mandatory for all Brazilian municipalities. The National Policy on Solid Waste (Law No. 12.305/2010) brings together all principles, objectives, instruments, guidelines and goals, aiming for an integrated and environmentally sound management of solid waste.
However, from the four components of the sanitation sector, the drainage and urban storm water management services are the ones in most need of policies and institutional organization. According to the National Sanitation Plan, about 45 billion dollars are expected for investment in the sector between 2011 and 2014.

Session 5: Intervene

Antibiotic Prophylaxis and Therapy Session

Antibiotic prophylaxis for leptospirosis (Cochrane review)
Marc Morillon, Institut de Médecine Tropicale Du Service De Sante

Administration of antibiotics as prophylaxis (Doxycycline 200 mg weekly) to persons exposed to leptospirosis, especially in the case of occupational exposure or after disasters such as flooding, is common. A Cochrane review has been conducted by Brett Major DM and collaborators in order to determine if this practice was based on scientific evidence. The search resulted in 500 citations in the literature. Further assessment identified 24 unique relevant studies, including only three randomized trials. Two were related to pre-exposure prophylaxis in different populations and a third to post-exposure prophylaxis. The latter was not investigated any further because it did not show significant difference between treatment and placebo. All trials were affected by bias, the most important being incomplete outcome data since it had not been conducted based on “intention to treat”. The study population in one of the pre-exposure trials consisted of 954 non-immune US soldiers deployed to Hawaii for a short time. The study population of the second pre-exposure trial included 995 people, likely partially immune adults and adolescents, residing in Andaman Islands (Indian Ocean) and to whom prophylaxis was given for several weeks. A prophylaxis failure was identified in the two studies by seroconversion and in the second one also by clinical symptoms. No evidence of the benefit of doxycycline has been shown overall; except maybe in the non-immune population (OR = 0.05). The second study suggests (OR= 0.015) that doxycycline may prevent deaths (3 deaths in placebo arm and no deaths in treatment arm). More significant findings were the mild adverse effects (nausea and vomiting) associated with doxycycline. These results are disappointing and limit the ability to make conclusions. Obviously further studies are needed. It has been suggested that the strict selection criteria such as those used in a Cochrane review may be too strict and lead to eliminating results that are nevertheless interesting from an operational point of view.

Antibiotic therapy for leptospirosis (Cochrane review)
Yupin Suputtamongkol, Siriraj Hospital - Mahidol

Whether or not antibiotics should be used for the treatment of leptospirosis, and if used which antibiotic, have been matters for debate for many years. A Cochrane review, conducted by Brett Major DM and collaborators, identified and assessed seven clinical trials that tested antibiotics in patients with leptospirosis. Four of these trials compared intravenous penicillin to a placebo. Three of the trials looked at differences between different antibiotics. All trials had high risk of systematic errors and of random errors. When looked at together, these trials do not answer the basic questions about whether or not antibiotics should be used. Part of the reason for this is that there is a wide range of severity among people ill with the disease. Additional randomized clinical trials are needed. Nonetheless, these trials suggest that antibiotic therapy in sick patients may result in faster recovery (2 days earlier). Despite the lack of evidence, if a clinician chooses to treat leptospirosis with an antibiotic, there does not seem to be any difference between the use of intravenous penicillin, intravenous cephalosporin, doxycycline, or azithromycin. These antibiotics, however, have not been tested to the same extent as intravenous penicillin.

Case management of suspected leptospirosis in Thailand
Yupin Suputtamongkol, Siriraj Hospital - Mahidol

Leptospirosis is a common cause of acute undifferentiated fever in Thailand and Southeast Asia. Malaria and dengue infection must be initially excluded in all patients presenting with this syndrome. The lack of sensitive and rapid methods for the laboratory confirmation of a tentative diagnosis has been a major problem.
Early recognition and appropriate treatment reduce morbidity and mortality of the patients. Doxycycline would usually be an appropriate initial antimicrobial treatment for an individual with either suspected rickettsioses or leptospirosis. Azithromycin could be considered as an alternative treatment whenever doxycycline allergy is suspected.

Our experience during the outbreak of leptospirosis in Thailand and results of clinical studies show that empirical treatment with doxycycline would be the most cost-effective option for these patients. This strategy was also beneficial for patients with other diseases which clinically mimic leptospirosis such as scrub typhus. It should be noted that this strategy applies only to adult patients with acute fever suspected of mild leptospirosis. Patients with potentially more serious diseases should be treated more aggressively as an inpatient basis.

Disaster Plan and Response to Outbreaks Session

Disaster plan and response to outbreaks - The Brazilian experience
Melina Érica Santos, MoH - CIEVS/SVS/MS

CIEVS represents the National Focal Point of Brazil for International Health Regulations and it is responsible for preparedness, report, monitoring, and timely response for situations of risk of disease spread and events that may constitute Public Health Emergency of National and International Concern. According to Presidential Decree N. 7616 November 17th 2011, a Public Health Emergency of National Concern in Brazil occurs when urgent coordinated measures for prevention, control and containment are necessary and when there are disease outbreaks, disasters or lack of health assistance to the population. The Emergency Operations Plan is composed by procedures that support the local level response and the early development of emergency preparedness plans to reduce the impact of health related emergencies. The response operation is based on the Incident Command System strategy and the Emergency Operations Center structure. The leptospirosis events of National Public Health Concern are commonly constituted by epidemic situations, aggregation of cases or uncommon epidemiological patterns. In Brazil, there have been eight leptospirosis events monitored by the Secretariat of Health Surveillance since 2006. The Emergency and Disaster Plan establishes the effective structure and basic response to emergencies and disasters and promotes appropriated institutional capability for preparedness and response to emergencies.

Session 6: Regional Initiatives

Leptospirosis in the Southwest Indian Ocean islands

Frederic Pagès, Cellule de l'Institut de Veille Sanitaire de l'Océan Indien (Cire Océan Indien)

Leptospirosis burden can be very high in tropical areas, especially in tropical islands. Islands of the southwest Indian Ocean are very different in terms of geological origin, animal and population settlements, socio-economic development, health system, and health priorities. The situation of human and animal leptospirosis, pathogen characteristics and the perception, surveillance and control are very different across the islands as well. Nevertheless, all these islands face each year, during the cyclonic period and the rainy season, heavy rains and sometimes extensive flooding. In Madagascar and Union of Comoros, the presence of human leptospirosis was questioned and it is currently not considered as a priority disease by the health authorities, therefore, it is not routinely detected or reported. Now, human cases have been reported on both islands and the presence of an important animal reservoir has been highlighted. In Mauritius, limited data are available but human leptospirosis has already been described and cases are detected and reported each year with apparently low burden (2.5 cases per 100,000 inhabitants). Seychelles Islands were considered in the nineties as the hottest spot of leptospirosis in the world with an incidence of 101/100,000. Currently, the burden of leptospirosis has decreased with an incidence rate these last two years of 17/100,000 inhabitants. However, fatality remains high with and estimated as 16% for the last three years. In Réunion island, the incidence of leptospirosis is lower (9.1/100,000 inhabitants) but fatality rate is still important (3%) despite the high technical level of the hospital and the early detection of cases. In Mayotte Island, since the implementation of a specific surveillance system of leptospirosis in 2008 similar to Seychelles and Réunion, the reported number of leptospirosis has exploded and Mayotte is currently the high spot for leptospirosis in the area with an incidence rate ranging from 59 to 87 cases for 100,000 inhabitants in the last years. In Mayotte as well as in Seychelles and Réunion, the occurrence of leptospirosis is clearly linked to the seasonal rainfalls and the burden of leptospirosis varies between years and between districts. Notably, the clinical situation is very different in Mayotte with a case fatality rate of only 0.7 %, a high proportion of affected women (26%) and a high proportion of people under 15 years (20%). These differences could be explained in part by the predominance of *Leptospira* strains other than serovar Icterohaemorragiae both in human and animal, and also by the habits of the population. Leptospirosis is present in all islands of the south west Ocean Indian with very different burden according to the islands. Part of those differences could be attributed to a surveillance bias; nevertheless, the role of endemic reservoirs, unique transmission dynamics in the different islands needs to be assessed.

Leptospirosis in the Americas region: From an outbreak perspective

Presenter: Maria Cristina Schneider
Maria Cristina Schneider; Patricia Nájera; Sylvain Aldighieri; Deise Galan, Pan American Health Organization

Leptospirosis could be considered an emerging disease of epidemic prone in the Americas. The PAHO framework from an outbreak perspective for this disease includes: the International Health Regulations, GLEAN, importance of the animal/human interface, risk and drivers analysis, importance of natural disasters and analysis of their relation

with communicable diseases, and the WHO Burden of Leptospirosis. Reviewing Healthmap, a real-time open access database, 530 global alerts of leptospirosis were registered from January of 2010 to December 2013, with more than half (341 alerts) located in the Americas. Leptospirosis is the top 6 infectious hazard reported in the WHO Event Management System (EMS/IHR) globally and the top 3 for the Americas Region. Seventy percent of the natural disasters in the Americas are floods and storms (including hurricanes), and it is well known that many times after floods and heavy rain outbreaks of leptospirosis occur. PAHO/HS/IR working objectives are related to the prediction, detection, prevention and response to outbreaks of leptospirosis, thereby reducing mortality and severe cases during outbreaks, as well as reducing the number of cases in risk areas, especially those related to the environment. Examples of current PAHO activities include: analysis of which are the priority countries in the Region related to leptospirosis outbreaks; study conducted with Nicaragua to identify risk areas and drivers for leptospirosis outbreaks; support to WHO and GLEAN initiatives; support countries in technical cooperation; development of tools to support countries to predict, detect, prevent and respond to outbreaks of leptospirosis; organization of a national and international meeting in Nicaragua; and development an intersectoral webpage for this topic.

America region: Burden of disease perspective
Prevention and control activities in Central America
Victor J. Del Río Vilas, PAHO/WHO Panaftosa

The present paper introduces prevention and control activities for leptospirosis led by the Pan American Health Organization (PAHO) in Central America. In recent years contextual variables, such as inadequate sewage systems to properly address the increasing demands of migrant populations around big cities, have evolved to increase the likelihood of leptospirosis occurrence in the region. Since 2006, PAHO has coordinated three short-term projects to help addressing this increased risk. The target countries are Cuba, Honduras, Guatemala, Nicaragua, and Republican Dominican. The first project (2006 to 2008) built basic laboratory capacities to support differential diagnosis of leptospirosis. The second (2008 to 2009) and third projects (2012 to 2013) had an eco-health and multisectoral focus, and aimed to strengthen formal mechanisms for collaboration between the Ministries of Agriculture and Health. Specifically, the projects delivered planning workshops, improved laboratory capacity, strengthened leptospirosis detection in the environment (farms and abattoirs), and identified priorities among other activities. Future efforts against leptospirosis in the region must build on the outputs delivered to date to ensure sustainable policy changes, and feed into tractable impact indicators for the improvement of health.

Incidence of leptospirosis in French West Indies, 2011
Sylvie Cassadou, Cellule de l'Institut de Veille Sanitaire aux Antilles-Guyane (Cire Antilles Guyane)

Leptospirosis is a neglected zoonotic disease, which affects all tropical regions, particularly South America and the Caribbean. Its incidence and case-fatality rates are poorly known and probably highly underestimated. The public health impact of the disease in the French West Indies is believed to be much higher than in mainland France, but the currently available epidemiologic indicators lack reliability and precision. A study was carried out in Guadeloupe and Martinique during 2011 in order to precisely

estimate the incidence of leptospirosis using all the currently available biologic tests for diagnosis, mainly PCR test.

The incidence of leptospirosis was estimated at 69 and 61 annual cases per 100,000 inhabitants in Guadeloupe and Martinique, respectively, which is more than 100 times the incidence observed in mainland France. The epidemiology of the disease has also been described in terms of severity, demographic characteristics, and seasonal patterns. Using PCR-real time for diagnosis has allowed identifying cases that would not have been detected without having recourse to this test. As this test contributes to detect the disease early, antibiotics can be administered and successfully treat the disease. The use of this test, recommended by the French National Authority for Health, should thus be generalized within the French West Indies.

Additionally, these results support the need to develop an integrated management strategy for surveillance, prevention and control of the disease in the French West Indies.

Session 7: The Brazil Experience

Leptospirosis outbreak investigation in Várzea Alegre, CE

Patrícia Pereira Vasconcelos de Oliveira, MoH - EPISUS/SVS/MS

Currently in Brazil, 28% of the reported cases of leptospirosis are associated with rural areas. In these areas, leptospirosis transmission occurs indirectly, usually linked to the work activities of people that deal with the production of grains and cereals. In 2008, an outbreak of leptospirosis occurred in farmers engaged in rice cultivation in the municipality of Várzea Alegre/CE. At the time, a cross-sectional study was developed in which some hypotheses were raised; among them that leptospirosis occurred due to the work activity carried out by rice farmers. The objective of this study was to identify the risk factors for leptospirosis related to work activities in the outbreak of the municipality of Várzea Alegre through a population based case-control study (1:2) from January to July of 2008.

Confirmed cases of leptospirosis were defined by individuals who presented antibody titers for leptospirosis greater than or equal to 1:100 by the microscopic agglutination test and controls were healthy individuals with negative laboratory results for leptospirosis antibodies using the same test. Bivariate and multivariate analyzes were developed and two theoretical models were prepared and assessed. In the first theoretical model, the risk factors associated were being male and having worked in rice farming. Therefore, to identify the risk factors intrinsically linked to rice farming that could be related to the outcome, it was decided to conduct a second model between cases who reported having worked in the rice fields. In the second model, the use of short unprotected clothes (OR = 5.3; 95% CI = 1.6-17.5) and work shifts over eight hours (OR = 3.9; 95% CI = 1.1-14.6) were independently associated with infection by *Leptospira*.

Epidemiological investigation of possible leptospirosis outbreak in a middle and high school in Rio Grande, RS, Brazil

Luciane Cougo dos Santos, SMS/Rio Grande/RS

The Municipality of Rio Grande is located in the state of Rio Grande do Sul, in the southern part of Brazil, situated in the Hydrographic Basin L40. It has a land area of 2,710 km^2, with a population of approximately 197,228 inhabitants (IBGE, 2010), although estimations project a population of 250,000 in 2013. Rio Grande is a coastal plain with ecosystems of dry fields, dunes, forest, fields (in Portuguese, capões de mata), wetlands, marshes, lagoons and coastal lagoons, which are home to wildlife rodents such as: *Hydrochoerus hydrochaeris, Myocastor coypus, Calomys laucha and Ctenomys sp.*, potential reservoir species for *Leptospira interrogans* of wild variants. In this environment, the interaction between reservoir species, livestock and family farming can bring a high risk of epidemics and outbreaks of leptospirosis to the region.

At the end of the 2012, an outbreak of leptospirosis was reported in a private middle and high school in the central area of Rio Grande, which has an average of 500 students. The first case was reported on October 10, 2012 to the Municipal Epidemiologic Surveillance with symptoms of fever, myalgia, headache, prostration, diarrhea and abdominal pain that started on September 9, 2012.

Laboratory tests were performed in LACEN/RS (test performed: ELISA-IgM) and FIOCRUZ/RJ (microscopic agglutination test - MAT) to confirm cases. In total, 47 suspected cases (n = 47) were reported, with 35 non-reactive, 1 indeterminate and 11 reactive for leptospirosis (IgM-ELISA). The most common symptoms in reactive cases were headache (90.9%), abdominal pain (81.8%), fever, prostration, and diarrhea (63%), besides vomiting (45%), myalgia (36%) and calf pain (36%). During the investigation in the school, evidence of the presence of rats was found in a small playground in the inner court, a place that was frequented by groups of the lower grades. Many burrows, puddles of water, and high humidity were observed. Forty-one samples were analyzed using MAT, which were non-reactive for all strains tested. The panel consisted of Copenhageni (M20), Canicola (Hond Utrech IV), Crippothyphosa (Moska V), Pomona (Pomona), *Australis* (Ballico), *Bataviae* (Swart), *Castellonis* (Castellon 3), *Cynopteri* (3522 C), Javanica (Veldrat Batavia 46), Panama (CZ 214K), Pyrogenes (Salinem), Hardjo (Hardjoprajitno), Sejroe (M84), Patoc (Patoc I), Tarassovi (Perepelitsin), Autumnalis (Akiyami A), Hebdomadis (Hebdomadis), Wolffi *(*3705), Icterohaemorrhagiae (RGA).

Work Plan

Work Plan

To provide focused guidance and operational accountability for the advancement of the GLEAN mission, the need for a four-pillar work plan was agreed upon at the previous GLEAN annual meeting.

The Four Pillars of GLEAN

The pillars were developed to provide a holistic, multidisciplinary approach with the aim of reducing the overall impact leptospirosis outbreaks have on communities from early detection to timely intervention.

Predict

Predicting when and where outbreaks will occur while extremely complex and not fully understood, may be invaluable in preventing the large-scale human health, animal health and socio-economic issues associated with leptospirosis. Prediction of outbreaks involves an in-depth understanding between and within various sectors including climate and weather, rodent and small mammal populations, domestic animals, and water and sanitation systems.

Prevent

Preventing leptospirosis outbreaks involves a concerted effort between multiple sectors. Vaccination of animal and human populations needs to be further explored for both effectiveness and cost-effectiveness. Additionally, communication, health education, and social mobilization play critical roles in educating the population on risk factors and increasing awareness of the disease among health care providers. Improving country level capacities, including water distribution and sanitation systems, is paramount in preventing disease transmission and cost-effective and sustainable solutions need to be developed. Additionally, understanding when and how to use weather alerts and forecasts to disseminate the information to the general public needs to be assessed.

Detect

The rapid detection of leptospirosis is a critical step to effectively manage the disease and to control outbreaks (in both human and animal populations). Without accurate and available rapid confirmation techniques and appropriate surveillance and alert systems, distinguishing outbreaks from endemic events becomes difficult. Additionally, making the diagnosis of leptospirosis becomes arduous, particularly in mild cases when the differential is wide. Furthermore detecting leptospirosis in rodent, small mammal, and domestic animal populations and in the water supply maybe important in controlling the disease and minimizing the impact to the human population, yet it needs to be further evaluated.

Intervene

Understanding how to effectively respond to leptospirosis outbreaks requires further evaluation. A standardized outbreak protocol needs to be developed, implemented, and evaluated. There are also many questions including how to properly manage cases, when and/or if mass chemoprophylaxis should be administered, and how rodent, small mammal, and domestic animals control should be carried out.

2013-2014 GLEAN Work Plan

Details of the work plan's implementation (responsibilities, chronogram, etc.) will be determined within each of the pillar groups.

PREDICT

1. **Progress report** on on-going research projects as it relates to identifying drivers of transmission, persistence, environmental contamination, and spillover (cross-species transmission) in humans and animals in rural and urban settings in Nicaragua, Seychelles, Brazil, Chile, and New Zealand.

2. **Website development**. Development of a page within the GLEAN website with information on the predict pillar as it relates to members, goals, activities, and reports.

3. **Literature review on needs and approaches to predict transmission and outbreaks.** A draft of a comprehensive review of the current knowledge, data gaps, parameters needed, and modeling approaches or methods.

4. **Identification of collaborators** necessary in order to move forward.
    a. Gaps in areas of expertise: mathematical transmission modeling, spatial analysis and GIS, hydrology, climatology, and anthropology.
    b. Gaps in geographical representation: Africa, Middle East, Western Asia.

5. Creation of a "**leptospirosis investment case**" which incorporates:
    a. Systematic review of outbreaks 1970-2012
    b. Global map of outbreaks
    c. Economic impact, if available

PREVENT

1. **Conduct rodent control training** (urban and rural context) in Brazil.

2. **Evaluate the effectiveness of rodent control** to decrease leptospirosis incidence based on on-going studies in urban areas.

3. **Evaluate and determine preventive measures to be included into a written protocol** to be implemented during leptospirosis outbreaks.

4. **Systematic review on human vaccines** that are currently available and provide recommendation of future studies to be conducted.

5. **Identification of collaborators** necessary in order to move forward.

DETECT

1. **Determine case definition, baseline data/epidemiological threshold, and epidemiological profiles** through conducting needs assessment through collection and collation of existing surveillance systems, developing a systematic protocol and evaluating. Focus initially on Brazil and Colombia, to be extended with other countries such as Thailand and New Caledonia, when possible.

2. Publish the **descriptive review of diagnostics.**

3. **Cochrane review on diagnostics** (serology only).

4. **Cochrane Review on diagnostics** (PCR only)
   This will be done jointly by WHO CC, Amsterdam with help of WHO, using the templates designed for the serodiagnostics. It has been decided not to focus on PCR but to review antigen detection tests in general.

5. **Identification of collaborators** necessary in order to move forward.

INTERVENE

A planning framework with phased activities and the production of "milestones" and "intermediate" deliverables. The time frame is tentative as most activities depend on other groups' work and on an intensive interactive consultation process.

Produce guidelines on:

a. Clinical case management of leptospirosis
b. Mass /selected chemoprophylaxis of Leptospirosis
c. Outbreak investigation and control

SECRETARIAT

Coordinators: World Health Organization, Health and Climate Foundation, European Joint Research Centre, UNANGO

1. **Write publication**: international, multi-disciplinary, multi-sectorial initiative to combat leptospirosis: Global Leptospirosis Environmental Action Network (GLEAN)
2. Continue **Advocacy and fund raising efforts** through talks, donor meetings, updated website

PROJECTS AND IDEAS BEYOND 2014 (to be reviewed at next GLEAN meeting)

Predict:

1. Report on publications in peer-reviewed journals of existing projects from Predict members that provide new knowledge on the drivers of transmission, persistence, environmental contamination, and spillover (cross-species transmission) in humans and animals in rural and urban settings in Nicaragua, Seychelles, Brazil, Chile, and New Zealand.
2. Identify and compile current studies and available data as it relates to spatial/temporal statistical models used to predict and inform risk stratification approaches.
3. Develop a framework for developing mathematical models
4. Plan a "case study" for each of the selected (3b) ecological and sociological systems. Determine options to propose and fund a prospective study in an appropriate location to address some of the data gaps and to validate models.

Prevent:

1. Evaluate the rodent control training in Brazil
2. Provide GLEAN rodent control recommendations for leptospirosis prevention based on the results of the effectiveness evaluation and the feedback of the first training course
3. Expand rodent control training program globally
4. Develop the preventive measure protocol for leptospirosis prevention and validate in different epidemiological contexts.
5. Design an integrated surveillance system which links reservoir with human health
6. Write a clinical trial protocol for the use of vaccines to be used during outbreaks
7. Evaluate the impact of animal vaccination on shedding and the transmission of leptospirosis to humans

Detect:

Help countries in developing and implementing policies and tools for early outbreak detection, with a focus on surveillance and diagnostics.

1. Surveillance: Continuation of project started in in 2013 to be expanded to additional countries such as French West Indies
2. Diagnostics: Develop a global leptospirosis serum bank

Intervene:

1. Investigate the impact of chemoprophylaxis through animal models and observational case control studies.
2. Produce Leptospirosis case management guidelines
3. Develop guidelines for Mass /selected chemoprophylaxis of Leptospirosis (based on animal models and observational case-control studies)
4. Develop a Leptospirosis outbreak investigation and control guideline

Recommendations for Outbreak Control

Recommendations for outbreak control were updated and are included in the annexes.

Meeting Discussion

The management of leptospirosis may be different depending on whether we consider cases occurring in an endemic context or during an outbreak. To achieve the main goal of GLEAN which is to mitigate the risk and impact of outbreaks of leptospirosis in high-risk populations, a comprehensive approach is needed. Identification of underlying gaps of knowledge and difficulties within the areas of the bacterial agent, disease epidemiology, and control strategy can be done.

1. Bacterial agent

The complexity of this disease lies in the diversity of the *Leptospira* bacterial agent. Surface antigens are used to define more than 250 serovars and genome studies have divided the genus into 20 species, each one species having its own ecology (with some variation worldwide). Many mammals, including humans, may be victims of this infection while others may be asymptomatic carriers. A greater understanding of the variety of animal carriers, the global ecological variation of the bacteria, and the complex ecosystems associated with leptospirosis must be gained at both country and regional levels.

Bacterial agent: Diagnosis and diagnostics

Much of the knowledge gap surrounding this disease is related to the fact that diagnosis, especially early diagnosis, remains difficult. The presence of bacteria in blood or other samples is difficult to detect, direct examination is unreliable, bacterial culture is fastidious and slow, and antigen detection is hampered by antigenic variability.

Ongoing studies aim to evaluate tests using the most common antigens. Detection of specific DNA is a relevant alternative and some laboratories have routinely adopted PCR. Real-time PCR appears to be more reliable than other techniques. Today, these tests are the most convenient, fitting with the objective of a diagnosis during the first (four) days of the disease. This is critical since results will be negative within 24-48 hours of antibiotic treatment. Some commercial PCR systems are available, and may be used in standard laboratories. Other techniques using low temperature or isothermal amplification are in development.

Current tests are not ideal for early diagnosis for several other reasons. Tests for detection of IgM by immunochromatography become positive several days after the onset of infection. The presence of IgM may be the result of heterotypic reactions leading to false positive results. The reliability of the tests depends on specificity of the antibodies, which is complicated by the variety of serovars and their variable ecology based on region. The general recommendation is to have a local validation of each test because of varying performance within distinct local epidemiological backgrounds. Alternatively, the establishment of globally representative serum collections will enable WHO CCs performing (comparative) evaluations of existing and new tests. IgM test accuracy is also impacted by time variations (fluctuating production quality). For these reasons, ELISA tests, including RDTs, are no longer used in places where PCR and MAT are preferred. Attempts have been made to develop new tests using lateral flow chromatography and new antigens however their performance is still limited by the same aforementioned factors.

Status of the MAT as the “gold standard” diagnostic methods for leptospirosis appears to be overrated especially from an operational perspective. Agglutination antibodies appear

very late and this test requires a panel of living strains of bacteria which limits its use to reference laboratories. Leptospirosis diagnosis may not be excluded after one MAT, especially if performed early after symptom onset. Additionally, convalescent samples are often very difficult to obtain. Therefore, there is a need to re-define diagnosis strategies

Despite the limitations identified, the discussion of diagnostic methods still centers on serological rapid tests. Even if not ideal, RDTs may be used in some circumstances to at least define probable cases. It should not be considered as a confirmation test and may be evaluated in each environment given that positive and negative predictive values are highly influenced by local prevalence.

To help address the issues with diagnostic methodology, the "Detect" pillar working group has been tasked with establishing a case definition and considering development of a serum bank, a tool necessary to compare the performance of different tests worldwide. A meta-analysis has to be done to review all diagnosis tests, excluding PCR. A specific Cochrane review on PCR methods shall be requested. There is a network for leptospirosis diagnosis and research called the Inter-American Network for Leptospirosis Diagnosis and Research (RINDILEPTO), which could be utilized.

2. Epidemiology

The most frequent way of disease transmission to humans is by skin (most often via abrasions or wounds) or mucosa contact with contaminated water, usually contaminated by urine from infected animals. Leptospirosis is often closely linked to poverty, especially in urban settings, but may also be a result of occupational exposure in rural environments through jobs such as farming and slaughter house work. It has been evocated that some fertilizing products may foster penetration of the bacteria through skin in farmers. Rice culture is also an activity associated with disease exposure, especially during planting season when planters' arms and legs are immersed in water. Exposure through contaminated drinking water in rural and urban areas also remains possible.

Epidemiologic patterns:

Due to the difficulties in biological confirmation and the existence of numerous mild and clinically silent forms of infection, epidemiologic and geographical descriptions are limited and rely on estimation. As a result, knowledge of the endemic situation of leptospirosis is limited. In tropical areas of Latin America and in Brazil, leptospirosis is the third largest event of epidemiologic emergency after dengue and flu. Conversely, in Africa, the disease has not been widely documented, although imported cases from Madagascar suggest the disease is present.

Even in countries in which leptospirosis is a reportable disease, variability still exists due to inconsistency of medical teams' awareness and lack of access to proper laboratories for confirmation. In hyper-endemic areas such as Brazil, 72% of leptospirosis cases occur in urban environments (housing situations) and 28% in rural environments (working situations). Similarly, studies in Nicaragua show heterogeneous distribution with "hot spots." of high infection risk. In temperate regions, such as New Zealand and Chile, most, but not all, of human leptospirosis cases are associated with rural occupational activities involving animals (farmers, slaughterhouse, and other agricultural

workers. Regardless of location, the influences of geographical and temporal factors on disease distribution are observed even in small countries and isles.
Rodent population dynamics appear to be a key determinant in the epidemiology of leptospirosis, in particular in tropical or sub-tropical areas. However, very little is known about their proliferation and migration, especially after disasters such as flooding, and how those processes impact infection risk in various communities. The exact nature of inter-relationships between leptospirosis in rodents and other animal hosts, environment, and people that can result in outbreaks are complex and not completely understood. Furthermore, the detection of outbreaks requires an outbreak definition, which in turn depends on knowledge of the endemic baseline. Aside from spectacular outbreaks, many of the outbreaks may be missed in the absence of an established baseline. In addition, discrimination between seasonal increase and outbreaks may be difficult. Understanding of how the animal, environment and human components interact under baseline and increase risk or outbreaks conditions is critical to improve our ability to forecast changes in incidence.

3. Control strategy

Intervention: Clinical management

In humans, clinical diagnosis (syndromic approach) is difficult since presentation is non-specific. Symptoms can range from a mild and flu-like illness to severe forms with pulmonary hemorrhage and meningitis. It is believed that > 9% multi organ dysfunction of unknown cause admitted in Taiwan ICU may be due to leptospirosis. In non-severe forms, clinical diagnosis has a weak (20%) predictive value. Differentiating between diseases with similar symptoms (dengue, malaria and typhus, etc.) when diagnostic tools are not available creates further complications for clinicians.

Leptospira are very sensitive to a broad list of antibiotics. Doxycycline is the most often used antibiotic therapy for leptospirosis, but there is a lack of strong scientific evidence for its efficacy. A Cochrane review of antibiotic treatment has been conducted and concluded that treatment does not significantly impact outcome. It appears that too stringent facets of meta-analysis may be an obstacle for operational decisions. The consensus among clinicians is that antibiotic treatment at least shortens the duration of symptoms. A lack of positive results from these studies may be the result of late antibiotic treatment linked to a delayed diagnosis. In addition, there is also a need for a better knowledge of leptospirosis pathophysiology. There is a need to conduct additional studies; however, experts suggested the need to analyze data that has already been published such as non-randomized trials before conducting new studies.

Chemoprophylaxis

Chemoprophylaxis is has been used (both pre- and post-exposure) in scenarios that may indicate the beginning of an outbreak. A Cochrane review, however, concluded that regular use of doxycycline (200 mg oral) therapy increases odds for nausea and vomiting with unclear benefit in reducing seroconversion or clinical consequences. Treatment by doxycycline appears to be more efficacious in non-immune populations with short exposure, such as travelers, and militaries personnel. It has been suggested that a less stringent review might be made without restricting examination only to randomized case-control trials.

Vaccination
Very few human vaccines are available for leptospirosis. A French vaccine was developed in the 1980's after requests from Paris' sewers associations. Its immunogenicity is moderate and it requires two injections separated by one month, one booster between 4 and 6 months, followed by boosters every two years. Since the vaccine contains *L. interrogans* serovar Icterohemorragiae, it protects against the homologous serogroup. Limited to protection of professional groups, this vaccine is not adapted for mass vaccination or for emergency situations. Chinese and Cuban vaccines exist, but limited information is available.

Vaccines for animals are available (for instance serovar Canicola for dogs) and are widely used. Vaccination of domestic animals has demonstrated a decrease of carriage for homologous serovars in animals and leptospirosis infection in humans.

Rodent population control
Results on the incidence of disease among rodent populations are discordant in urban environments. *Leptospira* dynamics between rat and environmental reservoirs and their relation to human transmission is unavailable. While current methods need to be evaluated and protocols developed, relying on one control method isn't ideal and using several methods appears to be the most effective. Additionally, performing risk stratification using environmental, social and spatial analysis to determine areas of highest risk and to guide effective interventions is necessary. Education and training is important including using innovative ideas such as Leptospirosis Net and Day L (leptospirosis day).

4. Collaboration
There is a need for an integrated management strategy to tackle leptospirosis, which includes social communication, laboratory, vector control, clinical management, and epidemiological surveillance. Moving forward, the shift should be from a vertical approach to a one-health, multi-sectorial approach.

In Brazil, veterinarians, biologist, nurses, and microbiologists are integrated and hold positions within the Ministry of Health, thus a multidisciplinary approach is utilized which allows for an integrated response.

Conclusion

The importance of GLEAN and its multi-disciplinary approach to reducing the impact of leptospirosis is becoming increasingly evident. The case studies and operational research projects presented throughout the meeting enabled fruitful discussions between experts and led to the identification of future collaborations. Moreover, the exchange of experiences between country level response and global policy leaders proved invaluable.

Additionally, critical gaps surrounding detection, prevention, prediction and intervention were identified and strategies to address them were developed. Through formalizing the working groups, experts are now able to work together to accomplish the set forth goals over the coming years.

Annex 1: Meeting Agenda

2013 Global Leptospirosis Environmental Action Network Meeting
12-14 March 2013 ☐Brasilia, Brazil ☐PAHO/WHO Country Office

Day 1: Tuesday, 12 March 2013

Setting the Stage		
Time	**Topic**	**Speaker**
08:30 – 09:00	Registration	
09:00 – 10:00	Welcome and opening remarks	J. Barbosa da Silva J. Molina
10:00 – 10:15	Overview of leptospirosis and GLEAN	M. Jancloes
10:15 – 10:30	From Marseille to Brasilia… and meeting objectives	E. Bertherat
10:30 – 11:00	*Coffee Break*	
11:00 – 11:30	Leptospirosis outbreaks worldwide: an overview from 1970 to 2012	C. Munoz-Zanzi
11:30 – 11:45	Leptospirosis in Latin America and the Caribbean: State-of-the-art knowledge	M. Pereira
11:45 – 12:00	Leptospirosis in Brazil	E. Caldas
12:00 – 13:30	*Lunch*	
Predict		
13:30 – 13:45	Leptospirosis outbreaks in Nicaragua: Identifying critical areas and exploring drivers	C. Schneider
13:45 – 14:00	Eco-Epidemiology study in Chile	C. Munoz-Zanzi
14:00 – 14:15	Digital earth information systems for post-disaster assessment of leptospirosis and for anticipating consequences at local scales	A. Skouloudis
14:15 – 14:45	Open session for bilateral discussions	
14:45 – 15:00	*Coffee Break*	
Detect		
15:00 – 15:15	Update on rapid diagnostic tests	R. Hartskeerl
15:15 – 15:30	Laboratory diagnosis in Brazil	L. Queiroz Santi
15:30 – 15:45	The changing face of leptospirosis diagnosis in New Caledonia	C. Goarant
15:45 – 16:00	Using the DPP™ platform for rapid diagnostics in leptospirosis	E. da Silva
	Close of meeting for day	
16:30-18:30	**GLEAN member management meeting**	

Day 2: Wednesday, 13 March 2013

Prevent		
Time	**Topic**	**Speaker**
09:00 – 09:15	Opening remarks	
	Vaccine session	
09:15 – 09:30	Lessons from 30 years' experience of human vaccination against leptospirosis in France	J. Denis
09:30 – 09:45	Impact of vaccination of animals on human pop	J. Benshop
09:45 – 10:00	Open session for bilateral discussions	
10:00 – 10:15	*Coffee Break*	
	Human-Animal-Environment Interface session	
10:15 – 10:30	Rodents control in urban setting – Brazil	E. Masi
10:30 – 10:45	Ecological aspects of the urban rat reservoir	F. Costa
10:45 – 11:00	Animal leptospirosis; towards a changing epidemiology	A. Kodjo
11:00 – 11:15	The social anthropology of rodents and their mgt	S. Belmain
11:15 – 11:30	Leptospirosis, Water and sanitation in Brazil	A. Cabral
11:30 – 12:00	Open session for bilateral discussions	
12:00 – 13:15	*Lunch*	
Intervene / Respond		
	Antibiotic prophylaxis and therapy	
13:15 – 13:30	Antibiotic prophylaxis (Cochrane review)	M. Morillon
13:30 – 13:45	Antibiotic Therapy (Cochrane review)	Y. Suputtamongkol
13:45 – 14:00	Case management in Thailand	Y. Suputtamongkol
	Disaster Plan and response to outbreaks	
14:00 – 14:15	The Brazilian experience	W. Kleber de Oliveira
14:15 – 14:30	Leptospirosis in Nicaragua and Intersectorial Plan	E. Sánchez
14:30 – 14:45	*Coffee Break*	
Regional Initiatives		
14:45 – 15:00	Leptospirosis in the South West Indian ocean islands	F. Pages
15:00 – 15:15	Leptospirosis in the Americas Region: From an outbreak perspective	C. Schneider
15:15 – 15:30	America region (burden of disease perspective)	V. Del Río
15:30 – 15:45	French West Indies	S. Cassadou
15:45 – 16:00	Open session for bilateral discussions	
	Close of meeting for day	
16:00-18:30	**GLEAN member management meeting**	

Day 3: Thursday, 14 March 2013

Brazil experience		
Time	**Topic**	**Speaker**
	Leptospirosis in Brazil	
09:00 – 09:15	Leptospirosis outbreak investigation in Várzea Alegre/CE	P. Vasconcelos
09:15 – 09:30	Leptospirosis outbreak investigation in Rio Grande/RS	L. C. dos Santos
09:30 – 10:30	Panel discussion (Interdisciplinary)	
10:30 – 11:00	*Coffee Break*	
11:00 – 12:00	Open session for bilateral discussions	
12:00 – 12:30	Closing remarks	
	Closing of meeting	
12:30 – 13:45	*Lunch*	
13:45 - 18:30	**GLEAN member management meeting and working group**	

Annex 2: Meeting Participants

International Participants

Name	Organization	Location	Email
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Detect
Rudy Hartskeerl, Eric Bertherat, Marta Maria Pereira, Federico Costa, Mathieu Picardeau, Jiri Wagenaar, Ingrid Milena Bedoya, Andreas Skouloudis, Bill Ellis, Michel Jancloes, Albert Ko, Angeli Kodjo, Cyrille Goarant, Kara Durski, Guilhermo Ribeiro, Jonas Brant, Ingrid Milena Rodriguez Bedoya, Sylvie Cassadou, and Yupin Suputtamongkol.

Prevent
Federico Costa, Eduardo Caldas, Victor Del Rio Vilas, Steve Belmain, Cyrille Goarant, Frederic Pages, Jerome Denis, Michael Jancloes, Rudy Hartskeerl, Jackie Benschop Eric Bertherat, Kara Durski, Claudia Munoz-Zanzi.

Intervene
Michel Jancloes, Albert Ko, Angeli Kodjo, Eric Bertherat, Cyrille Goarant, Kara Durski, Guilhermo Ribeiro, Jonas Brant, Rudy Hartskeerl, Sylvie Cassadou, Yupin Suputtamongkol.

Annex 3: Recommendations for Outbreak Control

April 2013

Global Leptospirosis Environmental Action Network (GLEAN)*
Preliminary GLEAN recommendations for the control of disaster related leptospirosis outbreaks

While it was acknowledged that additional research needs to be conducted in order to provide evidence-based recommendations, GLEAN experts developed a preliminary set of recommendations in order to advise public health leaders if an outbreak occurs prior to formal recommendations being developed.

- Laboratory specimen collection:
  - A case definition should be used in accordance with local diagnostic capabilities (probable/suspect/confirmed case)
  - As many laboratory specimens as possible should be collected
  - Screening should be done for all suspect cases
  - High quality specimens using serum (if possible whole blood) and sent to appropriate reference laboratory for confirmation
    - MAT, PCR
      - Identification of agent
  - In parallel to reference laboratory confirmation, perform in country tests
    - ELISA or commercial RDT
- Empiric treatment of probable cases:
  - Use empiric treatment for probable cases to reduce morbidity and mortality related to leptospirosis
- Individual prevention:
  - Use barrier protection if there is a potential to come into contact with contaminated materials. If individual exposure occurs when cleaning up after disasters, immediately clean the affected body areas.
  - Treated water should be provided according to water treatment guidelines
- Community prevention:
  - Mass Chemoprophylaxis:
    - There is no current evidence that mass chemoprophylaxis given to the whole population reduces morbidity or mortality
    - There is evidence that pre-exposure chemoprophylaxis decreases morbidity in controlled target populations with individuals of high risk such as military workers, disaster relief workers, sewage and sanitation workers
  - Decontamination of water:
    - There is no indication for mass decontamination of water (based on current evidence).
- Vaccination (human and animals):
  - Based on current evidence, mass immunization with current vaccines does not impact the course of an outbreak.
- Risk communication:
  - Follow a risk communication plan that targets the public sector as well as the health service sector
  - Communicate early to improve awareness among the community and health care providers
  - Communicate risk in a professional and non-exaggerated format
- Rodent control:
  - Rodent control should not be implemented once an outbreak has occurred as it is too late to have a significant impact on human disease transmission

* www.glean-lepto.org

Annex 4: Commonly Used abbreviations

ELISA - Enzyme-linked immunosorbent assay

IgM - Immunoglobulin M

LAMP PCR - Loop mediated isothermal amplification

MAT - Microscopic agglutination test

PCR - polymerase chain reaction

RDT - Rapid Diagnostic Test

RPA - Recombinase polymerase amplification