The Homœopathic Prevention of Leptospirosis in Cuba

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Abstract: The water borne parasitic disease Leptosporisis is endemic in Cuba. It peaks, especially in three Eastern provinces of the country, every hurricane season when there is often massive flooding and destruction of infrastructure. The Finlay Institute in Cuba manufactures a vaccine against the disease, but it is of moderate efficacy (around 80%) and whenever there is a change in the active strain of the disease, there is a significant lead time needed to prepare a new vaccine. In 2007, the three Eastern provinces were hit by two severe hurricanes in quick succession, and the incidence of the disease rose despite use of the vaccine. The Finlay Institute homeopathically immunized over two million people with immediate success. The program was repeated in 2008 with equal success. The available data is presented to show the impact of the interventions, and the value of homoeoprophylaxis in providing a rapid, economical, effective and safe option to vaccination.
Keywords: Leptospirosis endemics in Cuba, homeoprophylaxis for; leptospirosis, a homeopathic clinical study

Introduction

This article summarizes the results obtained from a study[1] initiated by the Cuban government when using homeoprophylaxis (HP) to prevent an outbreak of leptospirosis in three regions of Cuba that were struck by hurricanes in 2007 and 2008.

Overview of Leptospirosis

Leptospirosis is a serious disease caused by infection with pathogenic strains of the Gram-negative bacterium *Leptospira* spp. In recent years, leptospirosis has emerged as one of the most important zoonotic (transmitted from animals to humans) diseases worldwide and a severe health problem in developing countries and the tropics.

Human infection usually occurs through contact with water contaminated with the urine of domestic and wild animals which are natural bacteria reservoirs. Infection enters through the mucosa or open skin lesions. Leptospirosis normally affects farmers and individuals involved in agriculture or animal breeding. There have been an increasing number of leptospirosis infections in urban areas in Cuba, and among adventure travellers practicing water sports.

The symptoms may include meningitis, pneumonitis, hepatitis, nephritis, mastitis, myocarditis, hemorrhagic crisis and multi-organ failure. Misdiagnosis is common, especially in regions where Dengue fever and Dengue hemorrhagic fever, and other diseases with similar symptoms, are endemic.

It is worse in countries with deficient surveillance, sanitary and health structures, with inadequate diagnostic tools and poor medical awareness, leading to misdiagnosis, as well as in tropical countries where leptospirosis incidence appears to be closely related to high rain fall and flood seasons when ecological conditions are favorable for the transmission of zoonotic diseases.

During natural disasters in endemic regions, such as strong rainfall and hurricanes causing extensive flooding, the risk of leptospirosis infection increases for all populations exposed to polluted water.

Diagnosis

Leptospirosis diagnosis is based on antibody detection in sera samples by HAT (hemagglutination test) and hemocultures. Antibody detection by microagglutination test (MAT) has been considered the gold standard for early diagnostic serology, although antibodies are not often detected in very early phases of infection, and the presence of antibodies is not a direct predictor of infection in endemic areas. Viral diseases like hepatitis viruses A and B and Dengue infection were eliminated in this study by serum analysis for antibodies using standard ELISA methodology.

Common Control Measures

The main control measures used in Cuba are:

1. Chemoprophylaxis: Doxycycline, given in a weekly oral dose of 100 mg, has been demonstrated to be usually effective in outbreak control but is not always useful for the prevention of large at-risk groups.

2. Vector control: The control of animal reservoirs to interrupt the transmission chain has to be effective and sustained to decrease infection, a difficult task when natural disasters occur.

3. Education: Raising awareness of prevention strategies within the community is helpful.

4. Vaccination: A common control measure in Cuba, *vaxSpiral*® is a triple-valent leptospirosis inactivated vaccine that was developed by and is being produced at the Finlay Institute, Cuba. *vaxSpiral*® has been included on the national immunization program since 1998 for individuals over fifteen years old in at-risk groups. Clinical trials conducted in Cuba demonstrated a 78.1% efficacy and agood safety profile. The immunization schedule includes two intramuscular injections six to eight weeks apart. It is a realistic long-term measure, but ineffective in preventing sudden outbreaks in previously unvaccinated populations.

5. Homeoprophylaxis: In 2007 and 2008, the Cuban government decided to use the leptospira bacterium in highly potentized formulations as an additional preventative measure to control leptospirosis epidemics. (See study below.)

The Study

Material and Methods

Population

The Cuban researchers identified two broad geographic regions:

IR (intervened region): three western provinces (Las Tunas (LT), Holguín (HG) and Granma (GR)) comprising 21.4% of the total population of the country, with 49.1% of the cases of leptospirosis reported from 2005 to 2007. The numbers of individuals per province were: LT: 528,687, HG: 1,023,633 and GR: 826,047. The total number of individuals was 2,378,367. The whole population over one year of age, independent of their physical, psychological or social status, were considered at-risk groups and included in the target universe. Individuals with severe symptoms of leptospirosis disease, mostly patients admitted to intensive care units, were excluded.

RC (the rest of the country): twelve provinces comprising 78.6% of the population, with 50.9% of leptospirosis cases in Cuba from 2005 to 2007.

Homœoprophylactic Strategies

Complete homœoprophylactic treatment included an intial administration of two doses of *NosoLEP* 200C (see below) in week 46 in 2007, followed by a booster administration of two doses of *NosoLEP* 10M in 2008. The two oral doses were 7-9 days apart, and each dose consisted of five drops administrated sublingually te minutes removed from eating, smoking or drinking.

All homœoprophylactic products were developed and produced at the Finlay Institute following Good Fabrication Practices and National Regulations established for homœopathic products.

The application of *NosoLEP* was carried out by family doctors, nurses, social workers and paramedic personnel previously trained in the administration procedure. The intervention was stratified, addressing the highest at-risk localities as the first priority, but targeting the complete population in the shortest time possible.

NosoLEP formulations

NosoLEP is prepared from four strains of inactivated leptospiras (10^6 bacteria/ml), selected on the basis of the frequency of isolation, viability and virulence. Inactivated bacteria obtained by incubation in 70% ethanol for 24 hours were used as raw material for mother tinctures. The four strains were processed independently. From mother tinctures, 1/100 serial potencies were prepared using the Korsakovian method. Between each dilution step, the solution was succussed 100 times using a continuous dynamizer (Dino) up to 200C and 10M. Potencies of the four strains were mixed equally in the final product. *NosoLEP* consisted of a 30% alcoholic solution containing the homœopathically potentized leptospires. The final products were controlled for alcohol content, water quality and microbiologic load by a quality system previously established for vaccine production control.

Data Collection and Analysis

The incidence of leptospirosis disease is assessed on a regular basis by the National Surveillance Program (NSP) for zoonotic diseases under the Minister of Public Health of Cuba (MPHC). A national weekly report is generated based on provincial data integrated at the Trend Analysis Unit from the Vice-Minister of Epidemiology of the MPHC. Data on rain quantities was obtained from the National Institute of Hydraulic Resources (http://www.hidro.cu/).

Statistical Analysis

All data were analyzed by combining tools from: *Microsoft Excel* (Professional Edition 2003), *StatGraphics Plus* (Version 5.0), *GraphPad Prims 4* for Windows (Version 4.00) and *SPSS* for Windows (Version 15.0.1)2.

Results

	2005	2007	2007	2008
IR - Cases	143	266	401	64
% of all Cuba	33%	52%	56%	15%
RC - Cases	290	241	309	376
% of all Cuba	67%	48%	44%	85%

Table 1: Leptospirosis Cases 2005 to 2007 in IR

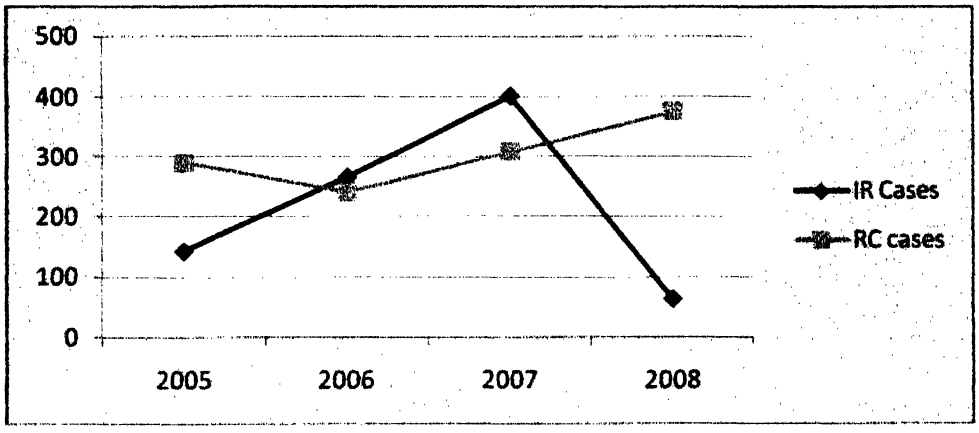

Figure 1: Leptospirosis Cases 2005 to 2008

Leptospirosis and Rainfall

Correlation analysis from 2004 to week 46 of 2007 showed that the two variables – leptospirosis incidence and rainfall - are significantly related, and variability within the data should not be attributed to random effects. The Spearman correlation factor of 0.69 ($p<0.05$) showed that the number of confirmed cases was positively related to the increase of rainfall levels, and therefore rainfall should be considered as an important risk factor for leptospirosis infection, especially in high risk regions. However, in 2008 this correlation was not observed in IR since the decrease in confirmed cases was not proportional to the rain accumulation, unlike in RC, where the relationship between rain and confirmed cases recorded in 2008 was similar to 2007.

Trends of Leptospirosis Disease in Cuba

The data of reported cases from 1990 to 2006 was analyzed in a weekly temporal series to study the historic trends across the year. The following common trend was observed:

Weeks 1- 40: the median number of reported cases remained lower than 13 cases/week (except week 26, with 20 cases/week). No significant differences were observed between weeks during this period.

Weeks 45-52: the months of October, November and December contain up to 45% of the cases per year, when the higher rain accumulates are being reported historically.

Weeks 49-52: the medians were significantly higher than the medians of previous weeks; the dispersion of the data in these weeks was also higher, increasing weekly and being highest at week 52 (see Figures 2 and 3).

Table 1 shows the leptospirosis cases from 2005 to 2007, and the data is graphed in Figure 1.

2007 Experience

In October-November 2007 the region was hit with extreme rainfall (peaks of 400 mm/hour) causing extensive flooding. The intense rains collapsed the drain systems and rivers, and water reservoirs overflowed to cause major flooding over the provinces of IR. Consequently, the risks of leptospirosis infection dramatically increased and extended the estimated risk groups to the full population.

Surveillance data revealed that a significant epidemic of leptospirosis occurred in the IR during 2007, the incidence of leptospirosis increasing to 7.2 per 10^5 inhabitants, and was deemed due to a sustained increase in the rainfall accumulates from 2004 to 2007. An abrupt incremental trend was observed in the IR from week 39 to 46, when the number of cases was greater than the historic median of the country and of the region (IR)

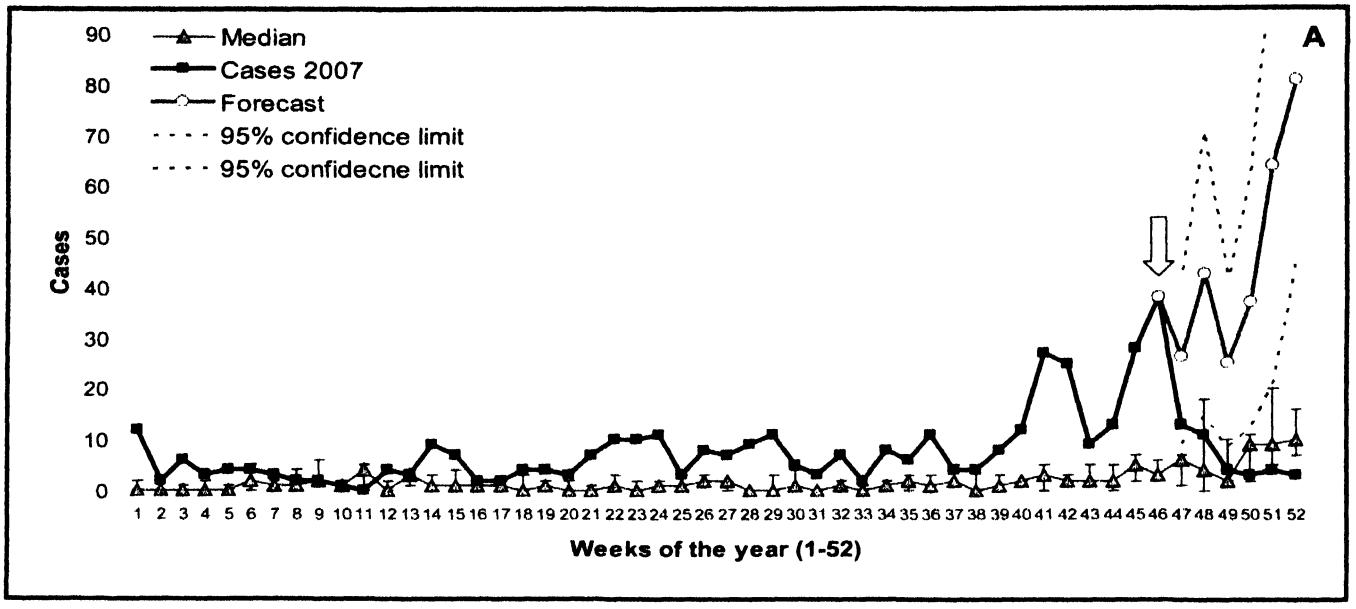

Figure 2: Trends in Leptospirosis in IR in 2007

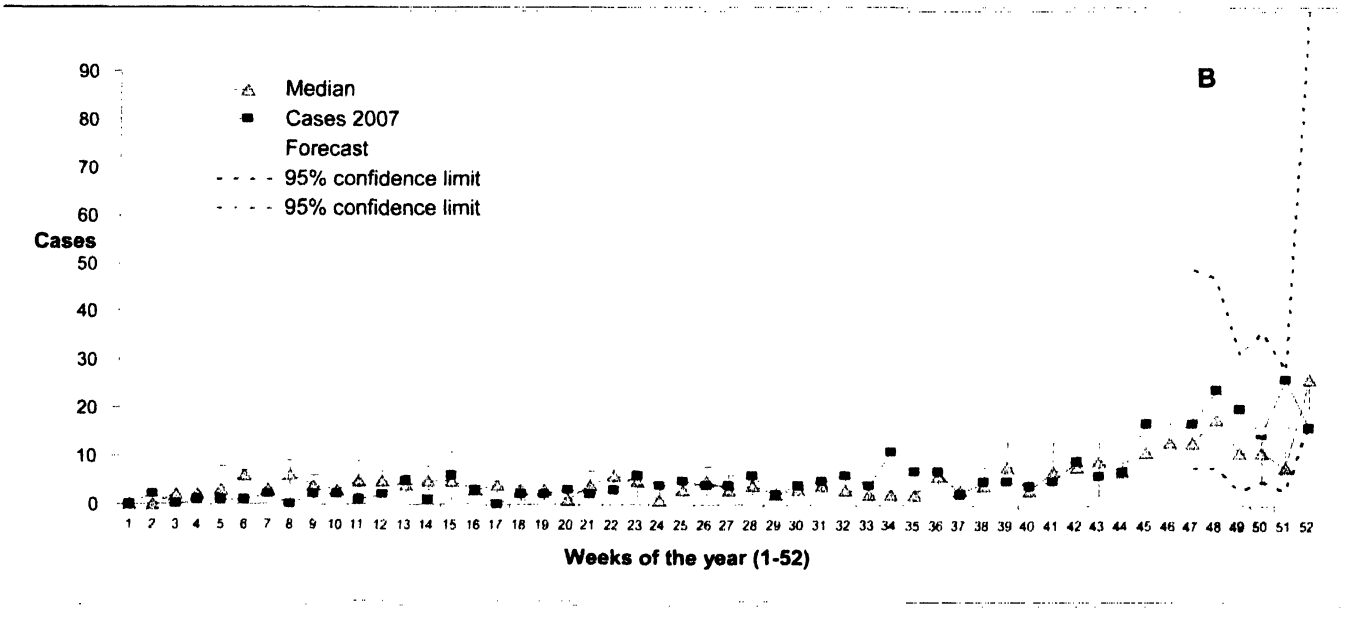

Figure 3: Trends in Leptospirosis in RC in 2007

for this time of the year. (Figure 2)

A simple exponential smoothing model was adjusted to the data from 2004-2007 and used to estimate the probable number of cases during weeks 47-52 in 2007 (with 95% confidence limits). The estimates showed a trend similar to the historic observations but at a higher incidence than previously observed, including a dramatic increase in weeks 51 and 52. (Figure 2) However, instead of a forecasted 111 to 461 cases, there were only 38 in weeks 47-52. In contrast to the expected trend (forecast model), after week 47, the reduction in the leptospirosis cases from 38 to 4 cases/week in IR was achieved in only three weeks and was coincident with the application of the *NosoLEP* 200C. (Figure 2)

Similar analysis was done in RC in order to confirm whether the observations from IR were unique or also observed in the untreated regions. From weeks 1 to 46, the number of reported cases per week in RC was similar to the historic median. The forecast model applied to RC suggested that no difference in trend in RC could be expected from that observed historically. The numbers of confirmed cases after week 47 in 2007 in RC were not statistically different from the historic medians (since 1990) and were included in the confidence

limits of the forecast model.(Figure 3).

2008 Experience

The incidence of leptospirosis in 2008 was strongly influenced by two factors:

(1) Two high intensity hurricanes that hit the country in August-September. Hurricane "Gustav" struck the eastern province of Cuba (Pinar del Rio) while hurricane "Ike" caused severe damage in central and western regions, including the provinces of IR.

(2) Two doses of *NosoLEP* 10M C were given to 2,308,562 people (96%) in IR in September 2008.

The following trends were observed in 2008:

Weeks 1- 41: the number of confirmed cases in both RC and IR were similar to the historic median and thus accorded with that expected.

Week 42: a significant outbreak of the disease was reported in a closed population (116 infected people) of RC, but was quickly controlled by the application of chemoprophylaxis.

Week 43-52: In RC, the number of cases remained similar to the historic median with a high number of infected people in the last weeks of the year, suggesting no changes in the trend in infection rates.

Weeks 45-52: the number of cases in IR remained significantly lower than the historic median. (Figure 2).

Weeks 51 and 52: both 2007 and 2008 experienced 42 confirmed cases.

From 2005 to 2007, the incidence of leptospirosis in IR increased very quickly and reached the highest value in 2007 with 16.6 cases per 10^5 inhabitants, higher than in RC. In 2008, the incidence of leptospirosis in IR (2.7 per 10^5 inhabitants) was significantly lower than in RC and Cuba.

The data from week 46, 2007, to week 52, 2008, pointed out major differences between RC and IR regarding leptospirosis incidence. When compared with historic trends, the disease attack rate was modified in IR but remained as expected in RC. The main factors that should be considered to explain the above result should be focussed on the strategies for prevention implemented in these regions since no other conditions were significantly different. (Table 2) Despite the increased risks of leptospirosis infection in IR and the impact of four meteorological disasters, a reduction of 84% in the number of cases/year was observed from 2007 to 2008 in IR.

2007 Compared to 2008

In RC, the last weeks (49-50) of both 2007 and 2008 recorded an increase in the number of confirmed cases, showing a trend similar to the historic median and to that predicted by the forecast model applied to this region (validating the accuracy of the model to predict disease prevalence).

IR showed a reduction of 84% in the number of cases from 2007 (401 cases) to 2008 (64 cases). RC reported an increase of 22% on the number of leptospirosis cases from 2007 (309 cases) to 2008 (376 cases). Consequently, the incidence of the disease in IR dropped from 16.7 per 10^5 (2007) to 2.7 per 10^5 (2008).

Finally, the correlation between rain accumulates and incidence was disrupted in IR in 2008, while the relation of these two variables remained similar in RC.

Region	2007	2008
IR	16.6	2.7
RC	3.5	4.3

Table 2: Leptospirosis cases per 10^5 Inhabitants

Discussion

The trend in leptospirosis disease in IR was significantly altered in 2007 and 2008, showing a strong reduction in the number of confirmed cases plus no increases at the end of the year, in contrast to the number of cases expected. In 2007, strong rains and large flooded areas caused by four meteorological disasters produced extensive damage to the environment. The data showed that the HP (homœoprophylactic) intervention to about 2.3 million people significantly reduced the incidence and modified the historical trend of this disease in IR even though no modification was observed in the rest of the country (RC). During 2008, the IR reported 24 out of 52 weeks with no confirmed cases and 40 out of 52 with 0-2 cases/week.

Important facts to consider when attributing causation for the observed reduction in leptospirosis incidence in IR are:

Leptospirosis risk groups are distributed all across the country.

Both high circulation of the pathogen (epidemic levels) and environmental conditions (impact of four natural disasters) increased the risk of infection more in IR than in RC. During 2007, RC was not affected by strong rainfall or by high epidemic rates of leptospirosis infection. However in 2008, both regions were affected by the impact of hurricanes and similar rainfall, but no increase in leptospirosis incidence was observed in IR, unlike the increase in RC.

The coverage of vaccination and chemoprophylaxis were similar in both regions since their application followed the current guidelines from the Minister of Public Health of Cuba. The main difference regarding prevention measures was the massive HP intervention in IR.

The HP intervention covered over 96% (2,308,562 people) of the target population in IR while the coverage of vaccination was limited by the lack of the Cuban vaccine *vaxSpiral*®. Therefore, the relative effect of HP significantly outweighed the effect of vaccination in reducing the number of infected individuals.

The reduction in the number of confirmed cases in IR occurred as rapidly as two weeks (coincident with the achievement of 70% of coverage of HP), but was also sustained for the next 57 weeks to the end of 2008. Considering the large time needed to induce a protective immune response by vaccination and the short temporal effect of chemoprophylaxis, the reduction caused by these measures should not be expected in the short time observed.

These facts suggest that the HP intervention in IR could be the main factor causing a significant reduction in leptospirosis incidence, thus supporting the value of HP in epidemic situations.

Conclusions

The effectiveness of homœopathy has been widely discussed and still remains controversial despite decades of research and clinical testing. Double-blinded, controlled and randomized clinical trials have been seen by some as the golden test to demonstrate effectiveness of any health intervention. However one of the limitations of such trials is the size of the population and the levels of exposure to risk factors. Thus, even when successful results are obtained from controlled trials, the real effectiveness of a given product needs to be tested in large open populations with high exposure to the target disease or pathogen, preferably in endemic areas. The results from phase four clinical trials are frequently not good enough to support the introduction of the assayed product for general application, thus forcing researchers to revisit previous stages of investigation.

The Cuban government has applied an HP formulation in a large population in an endemic area with increased risk of exposure; the results strongly suggest high effectiveness of the HP intervention and support the use of such an alternative for epidemic control. The massive application of HP in IR also showed its potential regarding feasibility, time savings, cost savings, and general usefulness. When properly trained and organized personnel are involved in the HP application, large coverage can be achieved in a very short time with modest resources.

Further studies in IR should give new evidence to support stronger conclusions. A comparative study of mechanisms of immunity within the HP treated, vaccinated or unvaccinated, population could provide important data to complement the epidemiological observations. Nonetheless, the surveillance of the leptospirosis incidence in Cuba over the next years should provide the most valuable proof of the efficacy of HP intervention in IR. Finally, the results support the extension of HP as a useful alternative to help control other diseases in epidemic situations.

About the authors: Dr. Gustavo Bracho is Advisor to the President and General Director of the Finlay Institute, Havana, Cuba, and head of the Homeopathy and Biotherapic Projects at the Institute. He is an experienced researcher in molecular and cellular biology and has headed the Adjuvant Group within the Immunology Department of Finlay. In 2005-2006, he was a researcher in a Collaboration Project with the Flinders Medical Centre, Adelaide, Australia, examining vaccine production methods. He has pioneered the use of homeoprophylaxis in Cuba as both an adjunct and an alternative to orthodox vaccination. He is widely published in his area.

Dr. Isaac Golden is Business Manager, Academic Operations, at Endeavour College of Natural Health. He has been in practice since 1984, and has conducted the world's largest long-term trial of homeoprophylaxis, which formed the basis for his Doctorate in 2004, the first time a mainstream Australian University awarded a PhD in a homeopathic topic. He has authored ten books on homeopathy and many articles in Australia and internationally.

Endnotes

1 Gustavo Bracho, Enrique Varela, Rolando Fernández, Barbara Ordaz, Natalia Marzoa, Jorge Menéndez, Luis García, Esperanza Gilling, Richard Leyva, Reynaldo Rufín, Rubén de la Torre, Rosa L Solis, Niurka Batista, Reinier Borrero and Concepción. "Large-scale application of highly-diluted bacteria for Leptospirosis epidemic control." Homeopathy 99: pp. 156-166. 2010.

2 Central tendency and dispersion of weekly reports were explored by using the median, interquartile range and range of data. Normality of the data was assessed by Kolmogorov-Smirnov test. Differences between medians were determined by Wilcoxon signed rank test and Kruskal-Wallis test for grouped data.

Nonparametric Spearman correlation test was performed between rains accumulates and leptospirosis cases.

Five forecast models were tested for best adjustment to temporal series of leptospirosis cases (dependent) and rain accumulates (independent variable). Simple exponential smoothing model was selected as no significant differences were observed between adjusted curves and real data when the residual errors were analyzed in 5 different tests with a 95% confidence level. Adjusted forecast curves, lower and upper confidence limits were validated with different data sets.

Chi-squared (c2) test was used to compare the frequency of leptospirosis infection expressed in cases x 105 inhabitants.

All tests were performed using a 95% confidence level (p=0.05). AJH