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ORIGINAL PAPER

Large-scale application of highly-diluted bacteria for Leptospirosis epidemic control

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Background: **Leptospirosis is a zoonotic disease of major importance in the tropics where the incidence peaks in rainy seasons. Natural disasters represent a big challenge to Leptospirosis prevention strategies especially in endemic regions. Vaccination is an effective option but of reduced effectiveness in emergency situations. Homeoprophylactic interventions might help to control epidemics by using highly-diluted pathogens to induce protection in a short time scale. We report the results of a very large-scale homeoprophylaxis (HP) intervention against Leptospirosis in a dangerous epidemic situation in three provinces of Cuba in 2007.**

Methods: **Forecast models were used to estimate possible trends of disease incidence. A homeoprophylactic formulation was prepared from dilutions of four circulating strains of Leptospirosis. This formulation was administered orally to 2.3 million persons at high risk in an epidemic in a region affected by natural disasters. The data from surveillance were used to measure the impact of the intervention by comparing with historical trends and non-intervention regions.**

Results: **After the homeoprophylactic intervention a significant decrease of the disease incidence was observed in the intervention regions. No such modifications were observed in non-intervention regions. In the intervention region the incidence of Leptospirosis fell below the historic median. This observation was independent of rainfall.**

Conclusions: **The homeoprophylactic approach was associated with a large reduction of disease incidence and control of the epidemic. The results suggest the use of HP as a feasible tool for epidemic control, further research is warranted.** *Homeopathy* (2010) **99**, 156–166.

Keywords: Homeoprophylaxis; Prevention; Leptospirosis; Epidemics; Cuba

Introduction

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 diseases worldwide

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and a severe health problem in developing countries and the tropics.[1–3] According to antigenic determinants, *Leptospira spirochetes* are classified into 25 serogroups and over 250 serovars that affect almost all mammals. Human infection usually occurs when contact with the urine of domestic and wild animals (mainly rodents, dogs, pigs and horses) which are natural bacteria reservoirs secreting spirochetes in the urine, the animal vectors often remain symptom free.[4] Infection occurs through the mucosa or open skin lesions and the contact urine contaminated water.[5–7]

Under normal conditions, Leptospirosis is an occupational disease affecting individuals living in rural regions, mainly farmers involved in agriculture or animal breeding which are considered the main at-risk groups. However, an increasing number of Leptospirosis infections in urban areas and among adventure travellers practising water-sports has being reported in recent years.[8–11] Leptospirosis epidemics are a greater concern in developing countries where poor sanitary conditions, health structures, medical awareness and misdiagnosis have contributed to keep Leptospirosis as a major, but poorly recognised, threat. In tropical countries, the incidence of Leptospirosis is closely related to rainfall and flooding seasons when ecological conditions are favourable for the transmission of zoonotic diseases.[1,2] When infected urine contaminates water reservoirs, the bacteria can survive for long periods in water at neutral pH.

The symptoms caused by Leptospirosis infection are extremely variable and potentially dangerous, they include meningitis, pneumonitis, hepatitis, nephritis, mastitis, myocarditis, haemorrhagic crisis and multi-organ failure.[12] The broad spectrum of symptoms caused by Leptospirosis infection frequently leads to misdiagnosis, incorrect selection of medical treatment and high mortality rates, especially in regions where other infectious diseases with overlapping symptoms are also prevalent (eg, Dengue fever).[13,14]

The laboratory tests for Leptospirosis diagnosis are mainly based on demonstration of spirochetes in clinical samples (blood, urine and organ samples), or detection of serum antibodies. Leptospirosis cultures from clinical samples grow very slow and are a very late confirmatory method that should not be use to decide medical treatments.[7,12] Antibody detection by Indirect Hemagglutination Assay (HIA) has been considered the 'gold' standard for early diagnostic serology, although antibodies are often not detected in early phases of infection and the presence of antibodies is not a direct predictor of infection in endemic areas. The detection of bacterial DNA in blood samples by PCR is a sensitive and rapid method to confirm the infection but is not widely available and mostly limited to regional labs.[15]

Given the difficulties of confirming Leptospirosis infection, medical awareness and appropriate management of suspicious patients are key aspects to decreasing mortality rates. However, disease control strategies should be based mainly on prophylactic approaches addressing immune protection, transmission chain disruption and risk amelioration. Among the most commonly used prevention alternatives, chemoprophylaxis has been demonstrated to be effective in outbreak control. However, considering the short half life of doxycycline in blood stream (18 h), its prophylactic effect is limited and unfeasible for large groups at risk in endemic areas.[16,17] In addition the effectiveness of doxycycline prophylaxis after severe climatic phenomena has still to be demonstrated.[13] The control of animal vector represents another strategy to disrupt the transmission chain but it has to be effective and sustained to significantly decrease infection risks. In view of the diversity of vector animal species and complexity of the ecosystems, especially after the severe damage caused by natural disasters, vector control is still far from being a realistic alternative.

Vaccination represents, to date, the most effective option for disease control despite the fact that Leptospirosis vaccines are not widely available.[18] vaxSpiral® is the commercial name of the only three-valent Leptospirosis vaccine available in the market. It is a whole cell inactivated preparation developed and produced at Finlay Institute, Cuba.[19] vaxSpiral® demonstrated a 78.1% efficacy and good safety profile in clinical trials conducted in Cuba has been included in the national immunization program since 1998 for immunization of individuals over 15 years old in at-risk groups (mainly farmers and animal breeding workers).[20–24] However, because of the time needed to complete the immunization schedule and to reach high coverage the effects of vaccination on decreasing the incidence are significant only over the long term.[24] Particularly in endemic regions suffering sudden-onset epidemics, the effect of vaccination programmes can be very slow because of the high circulation of pathogens and the continuous modification of group at risk.[25]

There are few published trials of disease control using homeopathic medicine as preventive method, homeoprophylaxis (HP).[26–29] These approaches involve the use of highly-diluted and succussed (potentised) material from different sources including plants, animals, minerals and bacteria. HP has been used in epidemic situations since 1798 and as an alternative to routine vaccination programs for the prevention vaccine-preventable and non-preventable diseases.[27,30–33] Potentised pathogens or disease products known nosodes or biotherapies have been reported to be effective in controlling epidemic diseases, but homeopathy and HP are the focus of strong debate and more research is required.[26,29] In accordance with the basis of HP, leptospira bacterium in highly potentised formulations might be an effective and accessible prevention alternative for the control of Leptospirosis epidemics.[28,29,34,35] This approach combines knowledge from homeopathy, immunology and epidemiology resulting in a possible alternative in epidemic settings.

Natural disasters cause drastic modifications of the habitat of animal vectors that increase the probability of direct contact, and of contamination of water reservoirs supplies, thus generating a sudden increase of the risk of infection of animal-borne and water-transmissible diseases.[36] When Leptospirosis endemic areas are affected by climatic events

producing heavy rainfall and flooding, the risk of Leptospirosis infection is dramatically boosted and challenges all prevention options.[7,37–41] After natural disasters in endemic regions, urgent measures are needed to control and prevent Leptospirosis epidemics but these should be based on rational and feasible strategies that integrate all available options.[38,39,41]

From 2005 to 2007, environmental, socio-economic and climatic changes in Cuba caused modifications of infection risks that resulted in an increase in the disease incidence. Particularly, since the beginning 2007, Leptospirosis incidence of epidemic levels was observed in a region comprising three adjacent provinces of Cuba. In October–November 2007, these three provinces were severely affected by high intensity meteorological events which caused widespread flooding, further increasing the risk of infection for the population. To confront this emergency situation, from November 2007 an intervention based on the principles of HP was carried out on this region by using a Leptospirosis nosode, based on the hypothesis that massive application of this homeopathic product would have an impact on disease incidence. This article reports the results of disease surveillance before and after this HP intervention.

Material and methods

Population

The entire population over 1 year of age from the provinces of Las Tunas (LT), Holguín (HG) and Granma (GR) in eastern region of Cuba, independent of their physical, psychological or social status was considered as risk group and target population. These three provinces were considered as one single geographical area, designated the Intervention Region (IR). The total population at the beginning of the study was 2,404,787 persons (LT: 534,018 HG: 1,035,388 and GR: 835,381). All the remaining provinces of Cuba were considered as another geographical area (designated Rest of the Country, RC): a total of 8,834,547 persons. The analysis involving these populations constitutes a large-scale epidemiological cohort study.

Epidemiological surveillance

The history of Leptospirosis incidence in Cuba is recorded by an efficient National Surveillance Program (NSP) for zoonotic diseases of the Ministry of Public Health of Cuba (MPHC) established in 1980. The NSP is based on Municipal and Provincial Centres for Hygiene and Epidemiology (PCHE), connecting all Health Assistance Institutions into a national network. Regional PCHE centres have their own laboratory facilities for diagnosis and confirmation of Leptospirosis patients. After detection of suspicious cases at emergency services of Local and Provincial Hospitals, Polyclinics and Family Doctor Clinics, patient data are recorded and blood samples are submitted to PCHE for differential diagnosis. Each PCHE generates a weekly report including; suspicious cases, confirmed cases, mortality, infection risk, exposure factors and geographical–demographical distribution of cases. A national weekly report based on provincial data is generated by the Trend Analysis Unit from the Vice-Minister of Epidemiology of the MPHC. For this paper we used the data generated by the NSP.

Laboratory diagnosis of Leptospirosis

Leptospirosis diagnosis was assessed following the national protocol used by all diagnostic laboratories of the NSP, based on antibody detection in serum samples by HIA and haemoculture. Leptospirosis antigens for HIA were produced at the Finlay Institute, Havana, Cuba. For haemocultures, blood samples were cultured in vials containing EMHJ culture medium. Vials were incubated for several weeks at 28–30°C and checked weekly for the presence of spirochetes using dark field microscopy. Confirmed cases were reported according to the first day of symptoms. Differential diagnosis to exclude viral diseases with overlapping symptoms like hepatitis A and B and Dengue infection was performed by analysis of serum antibodies using standard ELISA methods.

Prevention and control strategies

Conventional measurements: Conventional prevention strategies are based mainly on vaccination and chemoprophylaxis. The individuals treated with either vaccination or chemoprophylaxis in the IR amounted to about 3% of the population. Individuals within risk groups were vaccinated when identified with two intramuscular doses (6–8 weeks apart) of vaxSpiral® following manufacture's instructions (Finlay Institute, Havana, Cuba). This vaccine comprises three pathogenic strains (*L. interogans* Serovar *Canicola*, *L. interogans* Serovar *Copenhageni* and *L. kirschneri* Serovar *Mozdok*) which circulate in Cuba and Latin America. Chemoprophylaxis was applied mainly for focal treatment and outbreak control to high-risk groups when identified and consisted of a weekly oral dose of Doxicycline 100 mg.

Homeoprophylactic strategies: HP intervention was implemented for the entire population, over 1 year of age, of the IR. It consisted in the application of the homeopathic product nosoLEP in two different potencies. HP started in week 45 of 2007 with two oral doses of nosoLEP 200C with an interval between doses of 7–9 days. Ten to twelve months later, the schedule was completed by the administration of another two oral doses (7–9 days apart) of nosoLEP 10MC. Each dose consisted of five drops (250–300 μL) administred sublingually 20 m away from eating, smoking or drinking. It was administered by about 5000 personnel of public health system of Cuba which included family doctors, nurses, social workers and paramedics that were trained in the administration procedure. The intervention was organized and stratified in order to achieve the highest coverage in the shortest time as possible.

nosoLEP preparation

nosoLEP is a registered product (Registration numbers: nosoLEP 200C: N-09-184-S01, nosoLEP 10MC: N-09-182-S01) developed and produced at Finlay Institute

following Good Manufacturing Practice and National Regulations for homeopathic products. nosoLEP comprises four highly-diluted strains of inactivated leptospiras: *L. interogans* Serovar *Canicola*, *L. interogans* Serovar *Copenhageni*, *L. kirschneri* Serovar *Mozdok* and *L. borgpetrsenii* Serovar *Ballum*. The strains were selected on basis of the frequency of isolation (circulation rate), viability and virulence. Inactivated bacteria (10^6 bacteria/ml) were used as source material for mother tinctures obtaining.

From the mother tinctures, 1/100 serial dilutions were prepared using homeopathic pharmaco-technical methods (Korvsakovian dilutions). Between each dilution step, the solution was succussed 100 times using an automatic dynamizer up to 200°C (200 × 1:100 dilutions) and 10 MC (10^4 × 1:100 dilutions). The four strains were processed independently and mixed in equal proportions in the final products (nosoLEP 200C and nosoLEP 10MC), in 30% ethanol. The quality of final products was controlled by measuring the alcohol content, water quality, pH and microbiologic load.

Strains preparation: Leptospirosis strains isolated from patients were classified at Finlay Institute using monoclonal and polyclonal reference antibodies. Virulence was checked in challenge experiments on Golden Sirius hamsters (CENPALAB, Havana, Cuba). Viable and virulent strains were cultured in EMHJ liquid media at 28–30°C until stationary phase. The cultures were harvested by centrifugation, inactivated at 56°C for 30 min and adjusted to cellular concentration of 10^6 bacteria/ml. Adjusted preparations were analysed for identity and inactivity by the quality control procedures established at Finlay Institute.

Data collection

Weekly reports on Leptospirosis incidence were collected from PCHEs and the Trend Analysis Unit, parts of the NSP of the MPHC. Data on rainfall were obtained from the National Institute of Hydraulic Resources (http://www.hidro.cu/). Population data were provided by the National Statistic Office of Cuba (http://www.one.cu).

Ethical considerations

nosoLEP is a registered product and its application is fully regulated by National Regulatory Agency according to International and National regulations for homeopathic products; it is also monitored by the National Centre for Pharmacology Surveillance. The intervention consisted in the very large-scale application of nosoLEP to the population of IR as a response to an emergency needs to confer protection to a large population exposed to an increased risk of Leptospirosis infection. We complied with international ethic standards for interventions in humans.

The massive application of nosoLEP was approved by the National Regulatory Agency and both National and Provincial Public Health Authorities. Information about the product and the intervention was provided by local TV, radio programs, newspapers and was also free available through information desks spread over the IR. Every participant was verbally informed by the person in charge of the application and consent from each individual was obtained before administration. Consent from non-competent persons was obtained from next of kin or the person in charge. Inclusion was absolutely voluntary and free. No attempt was made to influence individuals refusing to be included.

Statistical analysis

The data were analysed by combining tools from: StatGraphics Plus (Version 5.0), GraphPad Prims 4 for Windows (Version 4.00) and SPSS for Windows (Version 15.0.1). Central tendency and dispersion of weekly reports data were assessed using the median, inter-quartile range and range of data and represented by Box and Whiskers plots to explore the historic course of Leptospirosis disease. 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. The Spearman correlation test was performed between cumulative rainfall and Leptospirosis cases. The Chi-squared (χ^2) test was used to compare the frequency of Leptospirosis infection expressed in cases $\times 10^5$ inhabitants. Statistical significance was considered to be a 95% confidence level.

Forecast models: Although no model can predict exactly the future incidence of Leptospirosis, adjusted models are useful to forecast probable incidence trends and epidemics.[42] Five available forecast models were tested for best fit to temporal series of Leptospirosis cases (dependent) and rainfall (independent variable). To select the best fitting model, all were tested to determine how well they predicted the real temporal series of 2000–2004. The differences between forecast and real values (residual error) were analysed for statistical significance. All models gave similar forecast curves, but simple exponential smoothing was selected as no significant differences were observed when the residual errors were analysed in five out of five different tests with a 95% confidence level while the other five models all failed in one or more tests. Adjusted forecast curves, lower and upper confidence limits were validated with real data sets from different years.

Results

Trends of Leptospirosis incidence in Cuba

In order to better understand the behaviour of Leptospirosis infection in Cuba, the data of reported cases from 1990 to 2006 were analysed in a weekly temporal series to study the historic trends across the year. Despite the data year by year being very variable, three main periods showing a common yearly trend could be identified. The first period from weeks 1 to 40 showed a low and stable incidence with median number of reported cases remained <13/week, no significant differences were observed between weeks except week 26 (Figure 1). The data from this period also showed low variability (short inter-quartile ranges). The second period, from weeks 41 to 48 showed a slowly rising trend in the median of reported cases. In the last period (weeks 49–52), even though the dispersion

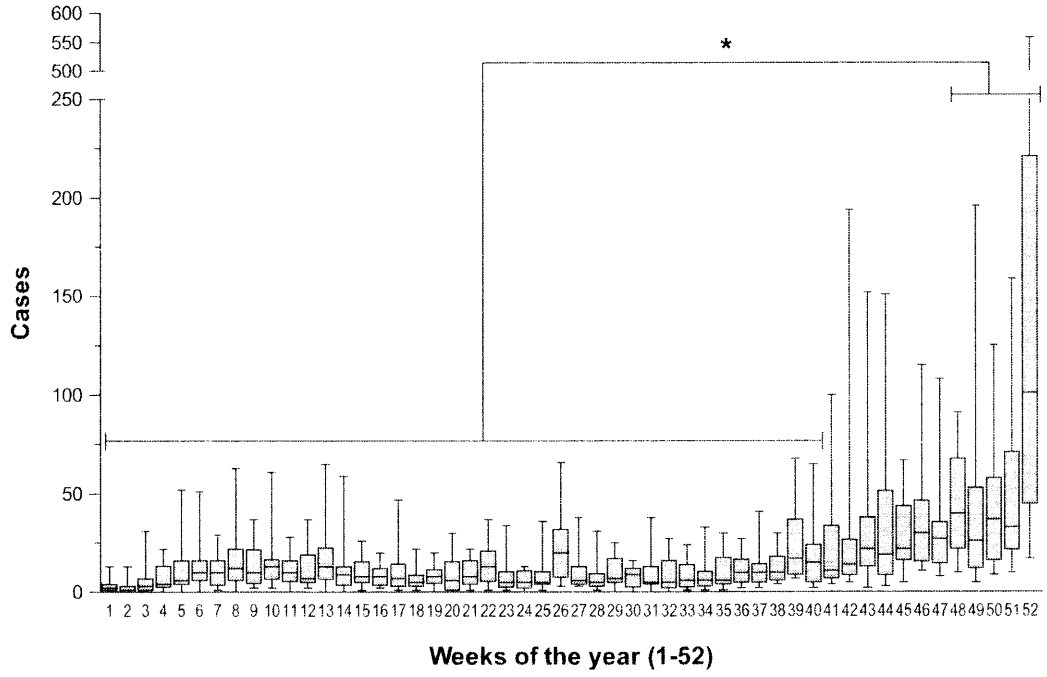

Figure 1 Leptospirosis historic course across the year in Cuba by week (1990–2006). Box and Whisker plot of the number of cases reported by week from 1990 to 2006 in Cuba. Filled boxes showed the inter-quartile range from 75 percentile (top) to 25 percentile (bottom). Median is represented by horizontal lines in the filled boxes. Error bars showed the range of the data (maximum and minimum). * represented significant differences between the median $p < 0.05$ (Kruskal–Wallis test).

of the data was higher, the median values were significant higher than the medians of previous weeks and a rapid increase was observed towards the last week of the year (Figure 1).

This analysis showed that from 1990 to 2006 the historic tendency was for a higher number of confirmed cases in the last two periods of the year (weeks 41–52) with the highest infection rate in weeks 49–52. Up to 52.4% of the annual cases were reported in the last 12 of 52 weeks, and of those 53.1% were reported in the last 4 weeks of the year (weeks 49–52). The last two periods comprises from October to December, when rainfall is at its highest levels of the year.

Leptospirosis incidence and rains

Given the apparent relationship of Leptospirosis incidence and rains, a further correlation analysis was performed between these two variables. Unfortunately, no data on rainfall are available before 2004. However, correlation analysis from 2004 to week 46 of 2007, showed that the number of confirmed cases was significantly related to the increased rainfall (Spearman correlation factor 0.69, $p < 0.05$). This suggests that the variability within the data should not be attributed to random effects and that rainfall should be considered an important risk factor for Leptospirosis infection, especially in high-risk regions.

The emergency

From 2005 to 2006, 43.5% of the cases of Leptospirosis reported in Cuba were concentrated in the three provinces of the IR which comprise only 21.4% of the total population of the country. The incidence trend during the year in IR is similar to those observed historically in Cuba with the largest number of cases being reported in weeks 49–52 of the year (Figure 2A). In 2007, the incidence of Leptospirosis in the IR was higher than the historic median from the beginning and throughout the year. However, an abrupt increase was observed in the IR from weeks 39 to 46 when the number of cases increased to more than 19/week (Figure 2A).

The situation was further exacerbated by two meteorological events in October–November causing extreme rainfalls (peaks of 400 mm/h) and extensive flooding. Consequently the risks of Leptospirosis infection dramatically increased and extended the risk to the whole population.

A simple exponential smoothing model based on the 2004–2007 data was used to estimate the probable trend of the number of cases in weeks 47–52 of 2007. According to the model, no significant reduction in the confirmed cases could be expected during weeks 47–50 but a further increase in weeks 51 and 52 was forecast (Figure 2A). The forecast curves showed a trend similar to the historic observations but at higher levels than previously observed: the 95% confidence interval was 111–461 cases expected for this period.

In contrast, in the RC no significant differences were recorded between the number of cases reported in 2007 and the historic trend. In addition, the RC was not affected by any natural disasters in 2007; normal levels of rains were recorded and the model predicted a normal course of the disease (historic median and the inter-quartile ranges were included within the confidence limits of prognostic curve) for the end of the year (Figure 3A). Therefore the

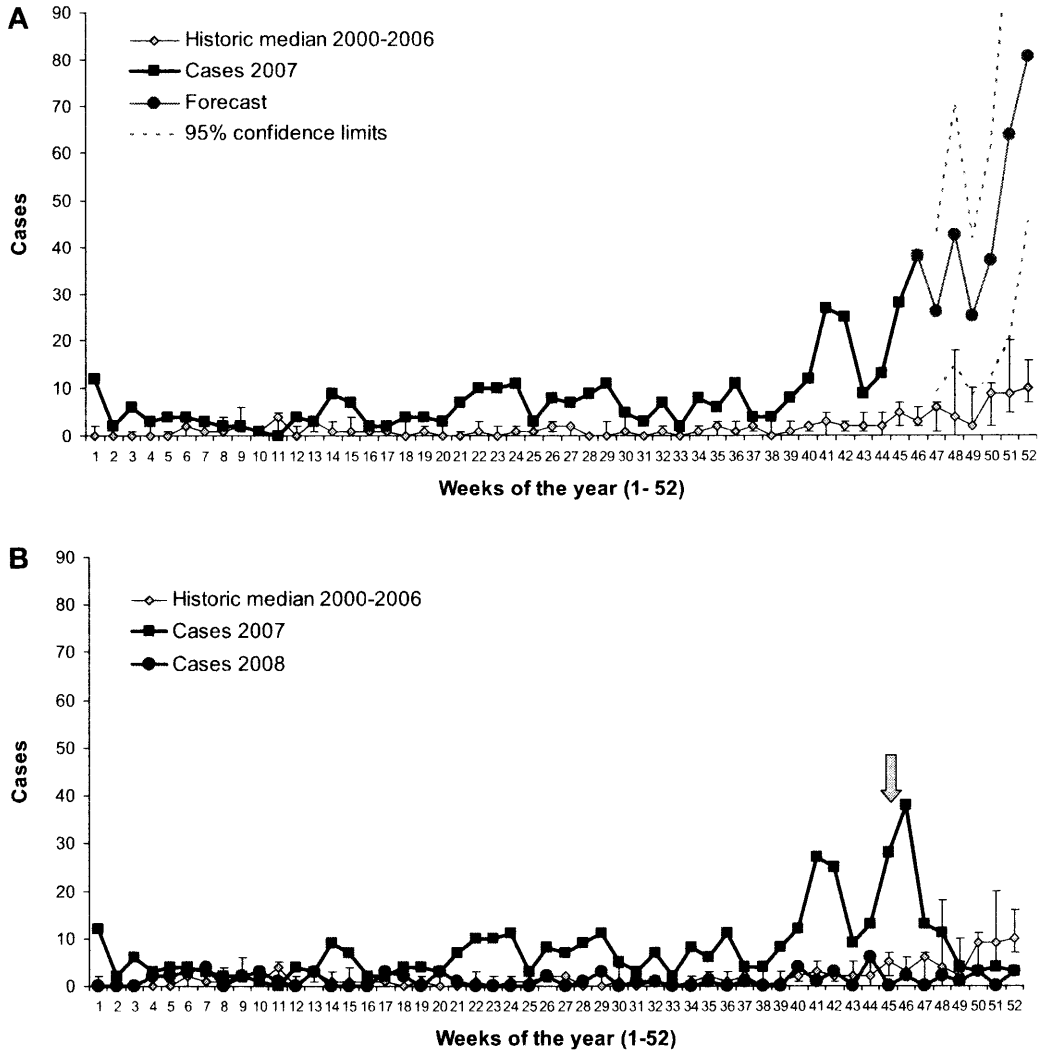

Figure 2 Leptospirosis incidence and trends in the IR. The historic course of Leptospirosis disease in the IR from 2000 to 2006 is showed for comparison in both graphics by means of the median (grey filled diamonds) of weekly confirmed cases. Errors bars represented the interquartile range of the median. **A.** The situation of disease at IR prior to the intervention and the predicted trend from forecast model. The black filled squares represent the number of cases reported from week 1 to 45 of 2007. After week 45, the red filled circles represent the forecast trend predicted by simple exponential smoothing model adjusted to the data of the region (2000–week 45 of 2007). Dotted lines represent the 95% confidence limits for the forecast curve. **B.** Shows the follow up of confirmed cases after the start of large-scale application of HP leptospira nosode (nosoLEP) in the IR from week 45 of 2007. The black filled squares represent the number of cases reported before and after the start of the intervention in 2007. The start of the intervention in 2007 is denoted by the vertical arrow. The number of cases reported in the following weeks of the whole 2008 year is represented by blue filled circles. At week 48 2007 the coverage was over 70% and 92% at week 50. Significant differences ($p < 0.05$) were detected at weeks 50–52 of both 2007 and 2008 when compared with the corresponding historic medians (Wilcoxon signed rank test).

probability of occurrence of a major epidemic was extremely high in the IR while normal historic behaviour of the disease was expected in the RC.

The intervention in 2007

Considering the epidemic situation in the IR, the unfavourable prognosis and the emergency caused by natural disasters, a massive HP application of nosoLEP 200C was started at week 45, 2007. vaxSpiral® vaccination and chemoprophylaxis in high-risk groups were continued but because of the limited availability of vaccines, vaccination coverage among newly exposed population was limited to 15,000 individuals in the IR (0.6% coverage). In contrast, HP coverage reached over the 92% of total population of IR at week 50 representing 2,112,257 individuals treated with two doses of nosoLEP 200C.

Surveillance results from 2007 (end of the year)

The impact of the intervention was followed through the surveillance system of MPHC. Two weeks after the intervention started, a dramatic decrease in the number of confirmed cases was observed in the IR, falling from 38 cases in week 46 to 3–4 cases/week during weeks

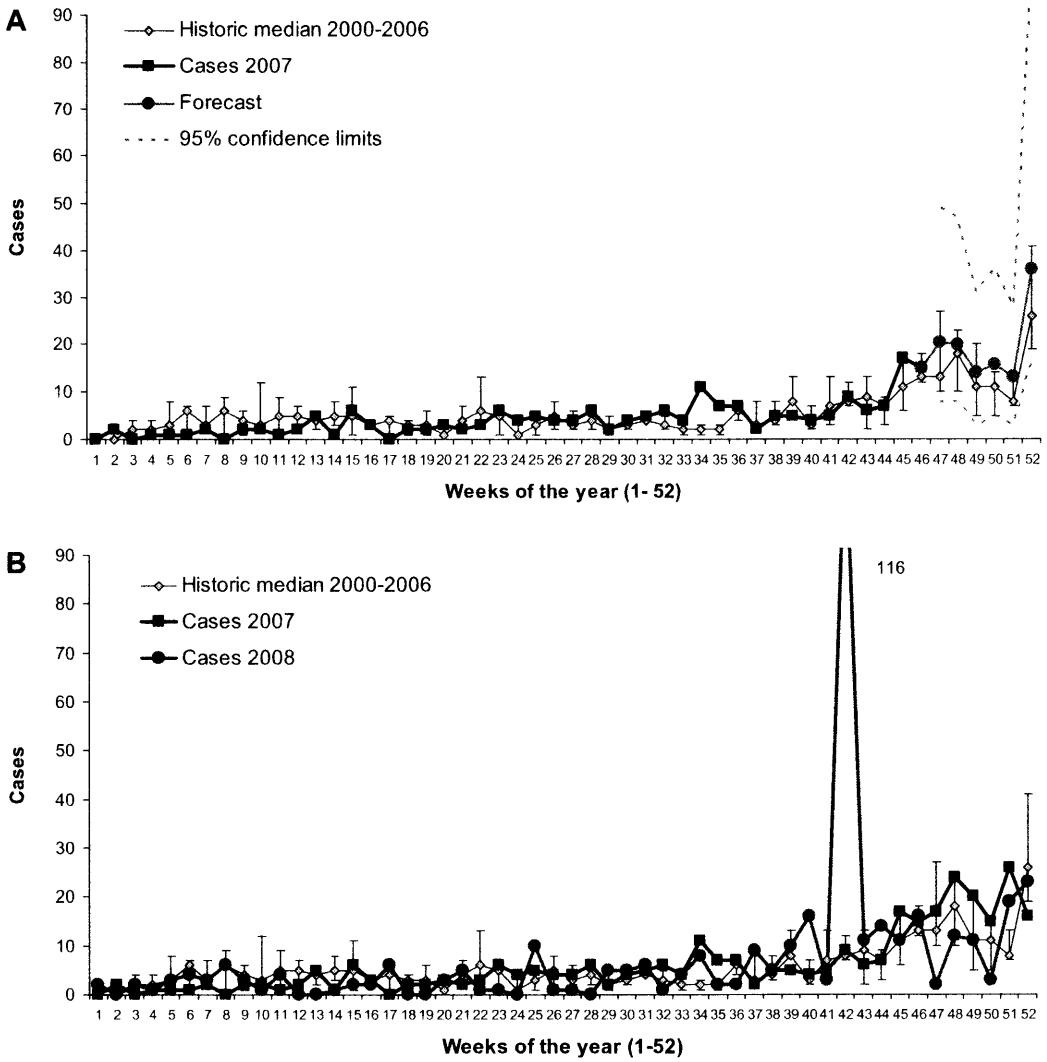

Figure 3 Leptospirosis incidence and trends at the RC (no intervened region, RC). The historic course of Leptospirosis disease in the RC from 2000 to 2006 is shown for comparison median (grey filled diamonds) of weekly confirmed cases. Errors bars represented the inter-quartile range of the median. **A.** The RC from week 1 to week 45 of 2007 (the time frame before the intervention in the IR) is shown in black filled squares. After week 45, the probable trend of cases predicted by simple exponential smoothing model adjusted to the data of the region (2000–week 45 of 2007) is plotted in red filled circles. Discontinuous lines represent the 95% confidence limits for the forecast curve. **B.** The weekly confirmed cases during 2007 in the RC are represented by black filled squares while the number of cases of 2008 is represented by filled blue circles. Only conventional measurements and no HP approaches were applied in this region (RC). No significant differences were detected between the number of reported cases on weeks 49–59 of both 2007 and 2008 and the corresponding historic medians (Wilcoxon signed rank test).

49–52. The number of cases detected in weeks 49–52 of 2007 was significantly lower than the historic median for these weeks (Figure 2B). A noteworthy finding was that this reduction in the Leptospirosis cases occurred in only 3 weeks and was coincident with the achievement of a 70% coverage of the population treated with nosoLEP 200C (Figure 2B). When comparing with the predicted trend, the total confirmed cases after intervention (weeks 47–52) was reduced from a forecast 111–461 (95% confidence limits) to 38 representing a reduction of 91.8–65.8% (Figure 2B).

Similar analysis was done for the RC to determine whether a similar phenomenon was observed in the untreated regions. In the same time period (weeks 47–52, 2007) the numbers of confirmed cases in RC were not statistically different from the historic medians. In agreement with the prediction, the number of confirmed cases in RC remained over 16 cases/week at the end of 2007 (Figure 3B).

Surveillance results from 2008

The incidence of Leptospirosis was also followed in 2008 to examine the incidence over a full year. Two outstanding factors should be considered for the analysis in 2008. The first is the impact of three high intensity hurricanes that affected almost all the country in August–September and generated very heavy rain (Hurricanes