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Original

Operative Definitions for Prevention and Control of Leptospirosis in Costa Rica

Virginia Rodríguez-Moreno[1], Juan José Romero-Zúñiga[2]

Abstract

Aim: Leptospirosis is the most frequent zoonotic disease worldwide and it requires an efficient epidemiologic surveillance. This study evaluated the operative definitions of the Costa Rican Protocol for the prevention and control of leptospirosis.

Methods: this work is a two-stage (descriptive, analytic) cross-sectional study using a clinical-predictive model by means of logistic regression. Data were obtained from the National Reference Center for Virology and Leptospirosis, Costa Rican Institute for Research and Education in Nutrition and Health (January 2001 to June 2003).

Results: Five hundred and sixty-eight records were initially found. One hundred and fifty-four were eliminated for not having the correct information for the classification of the leptospirosis protocol. The other 414 records were analyzed and none of them complied with the criteria for a confirmed case. For this reason, a broader definition taken from the literature was used (confirmed case = serology of 1:800). Consequently, 52 cases were confirmed and 368 were classified as suspicious. Only cefalalgia (OR=0.5; CI 95% 0.2 -1.1) and male gender (OR=3,01; CI 95% 1.2-8.1) showed a significant association with the diagnosis of leptospirosis. When clinical and epidemiologic variables were grouped, the combinations of cephalalgia+myalgia+epidemiologic history(OR=3,8; CI 95% 1.1-14.9) and systemic symptoms+epidemiologic history (OR=0.01; CI 95% 1.2-18.9) showed significant association with the diagnosis, although with a high correlation between them (Kappa > 0.8).

Conclusion: with the existing data and by means of the methodology used for the analysis it was not possible to validate the definitions established by the protocol or to generate operative definitions that could be applied on a national scale. It was also impossible to establish a definition of a probable case.

Keywords:leptospirosis, epidemiologic surveillance, Costa Rica.

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1. Costa Rican Social Security Authority, San Carlos Hospital, Ciudad Quesada, Alajuela, Costa Rica.
2. Program for Research in Population Medicine, School of Veterinary Medicine, National Autonomous University, Heredia, Costa Rica.
Abbreviations: CNRVL, National Reference Center for Virology and Leptospira; INCIENSA, Costa Rican Institute for Research and Education in Nutrition and Health; SVE-Lepto, Epidemiologic Surveillance System for Leptospirosis; MAT, Microagglutination Test; WHO, World Health Organisation; CDC, Centers for Disease Control; OR, Odds ratio.
Correspondence:
Virginia Rodriguez Moreno,
vrmoreno@hotmail.com
Juan-Jose Romero-Zuniga,
jromero@medvet.una.ac.cr

Leptospirosis is the most widely distributed zoonosis in the world. It is found mainly in warm and humid regions. The reported incidence reflects not only the disease's incidence, but also the availability of laboratory diagnostics and the clinical suspicion index.[1] Additionally, the diagnostic confirmation of leptospirosis can only be done by laboratory methods, mainly serologic due to the high cost and low sensibility of culture and molecular tests.[2-5]

The microagglutination test (MAT) is the cornerstone of diagnostic confirmation of this disease. However, it is laborious, expensive, it requires trained staff and it is not able to detect antibodies until the 6th or 7th day of the disease onset.[4.5]Even though there is a great variety of tests in the market their sensibility during the acute phase is low.[5]

The great variability in clinical features, the wide range of differential diagnoses, and the difficulties in laboratory diagnosis have prompted the apparition of multiple case definitions in the epidemiologic surveillance systems. Consequently, the World Health Organization (WHO) has established case definitions for leptospirosis: suspected and confirmed cases.[6] In a study by Katz & Effler (2003) the authors concluded that a broader confirmed case definition can be used in the interest of increasing the effectiveness of the epidemiologic surveillance systems for human leptospirosis.[7]

In 2002, the Ministry of Health of Costa Rica presented the *Protocol for the prevention and control of leptospirosis*,[8] in which the authorities established the following operative definitions: a) suspected case: acute fever with cephalalgia, myalgia and arthralgia, vomiting, shivering, with or without conjunctival injection and, in some cases, jaundice or signs of bleeding, with a history of exposure to water bodies (lakes, ponds, rivers) or rodents, domestic or wild animals in the last month;b) confirmed case: i) case confirmed by clinical criteria and epidemiologic investigation when no suitable laboratory sample is available; ii) suspected case confirmed by serologic tests or a positive culture of any of the recognized pathogenic serovariants with a minimum 4-fold increase in the antibody titer of one or more of the leptospiral antigens detected by the MAT in a second sample taken 15 days after the first one.

There is a considerable proportion of the medical community in our country that thinks that the case definitions in this Protocol are too specific and that this factor has impaired the effectiveness of the Costa Rican epidemiologic surveillance system for leptospirosis (SVE-Lepto). Thus, the aim of this study was to identify the effect of the results of the serologic tests used by the system on the classification of cases as required by the Protocol and to INTEGRATE?? The clinical, epidemiologic and laboratory features for each case in a predictive clinical model for a new definition of probable case which would be more useful for our country.

Methods

We carried out a cross-sectional observational research on the data collected in the registry of the Leptospirosis Diagnosis Laboratory at the National Reference Center for Virology and Leptospirosis (CNRVL)of the Costa Rican Institute for Research and Education in Nutrition and Health (INCIENSA). Cases included were those for which an initial blood sample was obtained between January 2001 and June 2003 and which served as basis for the criteria included in the *Protocol for the prevention and control of leptospirosis* in Costa Rica. This repository included samples from population from all the national territory and all samples analyzed complied with the following inclusion criteria: a)having been studied for leptospirosis during the specified period, b) having at least 2 consecutive serologic testsregardless of their results or the time between their collection, c) no distinction on the grounds of socio-demographic characteristics.

The collection, edition and analysis of the data was done with EpiInfo 2000 (CDC, 2000) by means of a purposely created and validated database.The study did not require an informed consent because of it observational nature. Nevertheless, it was carried out under the

supervision of the CNRVL at INCIENSA and the confidentiality of the data was assured at all times.

At first, all the records were considered to be suspectedcases of leptospirosis. We classified cases as confirmed when they complied with the operative definitions included in the current Protocol. In order to extend the analysis, we used Katz &Effler's 2003 proposedbroader definition of confirmed case[7] which considered the following criteria: a) records with antibody titers of 1:800 or greater in one sample; b) records in which a minimum 4-fold increase in the levels of specific antibodies between two samples, regardless of the time between their collection.

A descriptive analysis was done on both the suspected and the confirmed cases. We calculated the sensibility, specificity, positive predictive value and negative predictive value of the definition of suspected case by means of 2X2 tables using the WinEpiscope software version 2.0.9. All calculations were done considering a 95% confidence level. The same procedure was used to evaluate the performance of the broader definition of confirmed case. We also conducted an analysis of de quality of the surveillance system in terms of the timing of the sampling for serology tests and the quality of the records. Finally, we conducted a multivariate analysis by means of a backward/stepwise regression including those variables that had $p < 0.25$in the univariate analysis. This analysis was carried out using EpiInfo 2000.10. Statistical significance of the model was based on p values from the likelihood ratios.

Results

As shown in Figure 1, of 568 records we were able to identify for this study, 154 were eliminated because they lacked the minimal information for their classification.

Using the current Protocol there was not a single confirmed case of leptospirosis in the country during the period we studied and only one case complied with the specifications for serology. When we used the broader case definition a total of 52 cases were confirmed and 362 were classified as suspected.

Both the sensibility and the positive predictive value of the operative definitions given by the current Protocol were 0%, whereas the specificity and negative predictive value were, respectively, 98.3% and 99.8%.

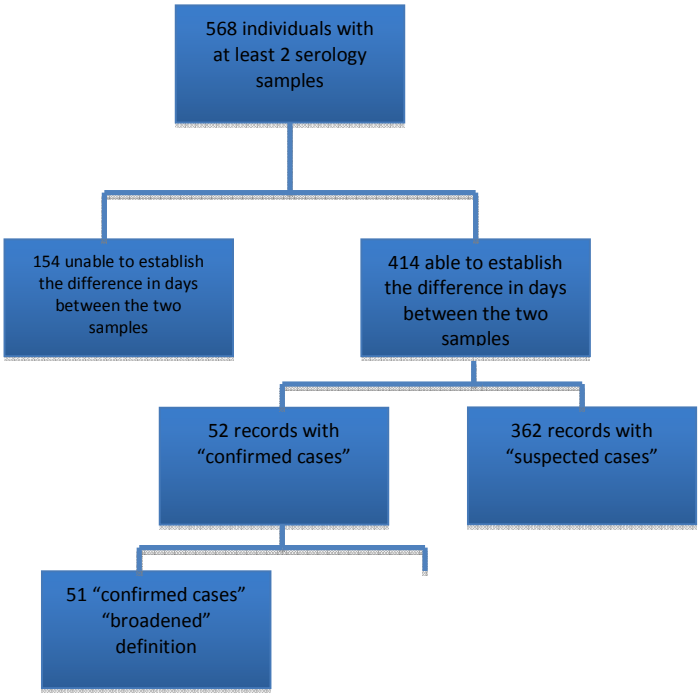

Figure 1. Classification of the leptospirosis records at the Laboratory of diagnosis at CNRVL, as established by the current SVE-lepto Protocol in Costa Rica.

Regarding the timing of the SVE-Lepto, the Protocol considers that an adequate primary sample for serology is that taken after 8 days of the onset of symptoms. With this criteria, 9.2% of the samples (52/568) did not have any information regarding the quantity of days of evolution on the date of sample collection and in 71.5% the primary samples were inadequate because they had been taken before the 8th day of onset. Moreover, 33% of the cases had a secondary sample that did not comply with the recommended timing either.

Furthermore, in order to be able to get a reliable serologic diagnosis one must allow 15 days between the dates of collection of the primary and secondary blood samples, but this was observed in

only 6 records of the 414 we analyzed while 138 (33.3%) had samples with a shorter interval and 23 (5.6%) had secondary samples taken after 90 days of onset. The mean interval between the dates of sampling was 29.7 days, ranging from 0 to 269 days.

In regards of the quality of the information, in addition to those records that were eliminated because it was not possible to determine the interval between samples, 233 (56.3%) of the records we analyzed lacked information on the epidemiologic history of the patient. This information is part of the criteria included in the operative definitions of the current Protocol for both the suspected case and the confirmed case.

Univariate analysis

In this phase of the analysis only cephalalgia showed a significant association with leptospirosis (OR=0.5; CI 95%: 0.2-1.1), implying that those who did not have the disease had twice the probability of having cephalalgia than those who did have leptospirosis. No other factor, either clinical or epidemiologic, showed any significant association with the diagnosis of leptospirosis (tables 1 and 2). Also, when clinical manifestations and epidemiologic history were grouped by system and frequency no group showed any clear association with the disease (tables 3 and 4).

Men had 3 times the chances of suffering leptospirosis than women (OR=3.0; CI95% 1.2-8.1). Additionally, we found a weak association between agricultural and livestock occupations and the diagnosis of leptospirosis (OR=1.7; CI 95%: 0.7-4.1).

Using the 0-15 years age group as the reference group, there was no association of the different age groups with the diagnosis of leptospirosis, although we observed a tendency to increasing risk with increasing age: 16-45 years (OR=1.5; CI 95%: 0.7-3.4); over 45 years (OR=2.4; CI 95%: 0.9-6.2).

In the third part of the univariate analysis, we looked at the linkage between the epidemiologic history, regardless of its nature (contact with potentially contaminated waters, contact with animals or others), and some groups of symptoms depending on their frequencies or the affected system and we found some significant associations. Specifically, we found that the occurrence of cephalalgia and myalgia and of an epidemiologic history correlated with the diagnosis of leptospirosis, and also that there is an association between systemic symptoms (anorexia, arthralgia, myalgia or shivers) and epidemiologic history and the dependent variable. Nevertheless, there is a lack of precision despite statistical significance (Table 4).

Multivariate analysis

When we analyzed all the clinical, epidemiologic and laboratory characteristics in the information derived from SVE-Leptowe were unable to validate the definitions included in the current leptospirosis diagnosis Protocol (Costa Rican Ministry of Health, 2002). Neither was possible to generate, by means of a clinical-predictive model, new operative definitions which could be applied to our country, nor to elaborate a definition of probable case.

Table 2. Results of diagnostic imaging for patients included in the study, type 3 health facility, 2008.

Type of imaging test	Diagnoses	N	%
Radiology	Bilateral arthrosis	1	3.6
	Scapulo-humeral arthrosis	1	3.6
	Sclerosis of the acromion	1	3.6
	Sclerosis of the major tuberosity	1	3.6
	Displaced fragment	1	3.6
	Osteopenia	1	3.6
	Sub-chondral sclerosis	2	7.1
	Acromio-clavicular arthrosis	2	7.1
	Cyst of the head of the humerus	2	7.1
	Normal limits	16	57.1
Ultrasound	Rupture of the rotator cuff	17	29.3
	Rotator cuff tendinitis	8	13.8
	Bursitis	7	12.1
	Sprain of the rotatorcuff	4	6.9
	Collection	1	1.7
	Pinching	1	1.7
	Tendinosis of the rotator cuff	1	1.7
	Normal limits	19	32.8

Source:medical records, type 3 health facility.

Discussion

In view of the multiple clinical presentations of leptospirosis, the variety in the differential diagnoses and the difficulties of an early diagnosis diverse studies have attempted to identify the suspected cases in a timely fashion in order to provide adecuate treatment and to apply epidemiologic surveillance strategies. The majority of these studies relate to the use and implementation of rapid tests.[2-5] However, some studies have analyzed clinical parameters as the present work has.[7,10-11]

In an attempt to validate the case definitions generated by the CDC using data from the epidemiologic surveillance system in Hawaii from 1974 to 1998, Katz and Effler (2003)[7] reported that the confirmed cases present more severe clinical manifestations than probable cases, and than probable cases with higher antibody levels clinically and epidemiologically comparable with confirmed cases. An association between a confirmed diagnosis of leptospirosis and the following factors: hospitalization, fever, shivers, myalgia, vomiting, thrombocytopenia and hematuria.In this study it was not possible to evaluate laboratory data since these were not available. But, of the clinical data which were associated with the diagnosis of leptospirosis in another study,[7] none of these aspects showed an association with confirmed cases, despite the fact of using a broader definition. Of note, fever, myalgia, vomit and shivers are actually included in the definition of suspected case according to the current Protocol.

In a study done in Puerto Rico, the authors reported an increase in the cases of leptospirosis during an outbreak of dengue fever after a hurricane.[10] They identified an association between leptospirosis, occular pain, arthralgia, diarrhoea, and jaundice. The association between occular pain and diarrhoea and leptospirosis is interesting since these symtoms are included in the national guidelines for the definition of suspected cases of dengue fever,[12] but not for those applied to leptospirosis. Given the fact that both diseases are considered to be endemic in our country and in view of the evidence,[10] the clinical spectrum for the diagnosis of leptospirosis is broadened and this underscore the importance of differential diagnoses which rely on the fundamental interrogation for epidemiologic history applied to patients. Moreover, the authors of this work found that people exposed to the effects of a hurricane had a higher probability of suffering leptospirosis (RR=4.4; CI 95% 1.6-12.4).[10]
Other authors have demonstrated that dyspnea, oliguria, alveolar infiltrates, abnormalities in repolarization and leukocytosis of over 12 900 leucocytes per mm^3 were independently associated with mortality following leptospirosis.[11] With this evidence the authors could establish clinical and laboratory parameters to early identify patients with leptospirosis who could develop complications due to their illness and to provide them with a more specialized care in an intensive care unit. In the mean time, in Costa Rica, we continue our attempts to improve the ability of our surveillance system to detect suspected cases of leptospirosis.

This is the first study in our country to attempt a validation of the operative definitions established by the national guidelines for leptospirosis using local cases. We originally intended to establish a definition of suspected case which would be highly sensitive, specific and with the highest predictive values, based on clinical, epidemiologic and laboratory data in the records of the Laboratory for Leptospirosis Diagnosis at CNRV-INCIENSA and to validate it with the confirmed cases according to the Protocol for prevention and control of leptospirosis.[8] Also, we aimed at proposing a definition of probable case, in order to improve the performance of the surveillance system. However, because of the quality of the records, the specificity of the operative definitions, and, consequently, the low number of confirmed cases, we were unable to complete this work and the results are distant from what was expected.

Of the 18 clinical variables and the 10 epidemiologic variables that were included in our univariate analysis, only cephalalgia showed an association with a confirmed diagnosis of

leptospirosis (OR=0.5; CI 95% 0.2-1.1). It was necessary to group different variables and even add the epidemiologic history to the clinical manifestations, in order to be able to work with a lower amount of independent variables in view of the reduced number of cases. Even after this, the univariate analysis done with these grouped variables proved successful only for two sets which showed association with a diagnosis of leptospirosis: cephalalgia+myalgia+epidemiologic history (OR=3.8; CI 95% 1.1-14.9) and systemic symptoms+epidemiologic history (OR=0.01; CI 95% 1.2-18.9). Nevertheless, these two variables were highly correlated. Of note, epidemiologic histories were of high relevance whereas when symptoms were analyzed, either independently or grouped by their frequency of the affected system, none of these variables showed a significant association to the diagnosis of leptospirosis.

The most important problem that significantly influenced our results was the fact that there were no confirmed cases as specified by the Protocol for the prevention and control of leptospirosis,[8]and for this we had to use a broader definition of case which had been reported in the literature. Thus, we considered a case as confirmed (for epidemiologic surveillance purposes but not for final clinical diagnosis) when a patient showed antibody titers of 1:800 or more in a single sample as suggested by Katz and Effler (2003).[7]

Several reasons can explain why we were unable to detect a single confirmed case of leptospirosis as established in the current guidelines:

Incomplete information in the records and the laboratory requests: the clinician is directly responsible for making a good history for every patient, which should include symptoms and epidemiologic data. Despite this, only 178 records of the total 414 we analyzed had any information regarding epidemiologic history of the patient. According to the Protocol, the epidemiologic history is a fundamental criterium for the establishment of a suspicion of leptospirosis. This reduced the number of records available for epidemiologic analysis to just 15. One could question the source of the data since they were obtained from test requests sent to the reference laboratory at INCIENSA. However, a revision of the medical records did not yield any more useful information than the one already obtained from the original source. On the other hand, the date of sample collection was not recorded for 154 subjects and this prompted their exclusion from the analysis. Again, this information is fundamental if one is to use the criteria enforced by the Protocol. Remarkably, almost 60% of the eliminated records came from the Brunca region (south), where nearly 50% of the records had to be excluded from the analysis because it was impossible to determine the span between the dates of sample collection due to the inexistence of these data.It is clear that measures should be implemented in order to ameliorate this deficiency, because this omission is sufficient to destroy all the clinical, diagnostic and epidemiologic work done with each patient.

Date of collection of samples for serology: responsibility is shared in this aspect. The clinician is suppossed to indicate the collection of the sample at a right time in relation with the date of the onset of symptoms and the days of evolution of the disease, whereas the microbiologist (i.e. clinical pathologist) is responsible for the collection and processing of the sample. As proved in the first stage of this research, there is a high percentage of samples that are collected and processed before the right time and this could generate false negative results and hinder the interpretation of secondary samples.

Processing of the samples: this is direct responsibility of INCIENSA as stated by the current Protocol. One of the parameters in the evaluation of the surveillance system for leptospirosis is the percentage of inadequate samples. The Protocol defines a sample as adequate if it is collected after 8 days of onset for the primary one, and at 15 days after the primary sample for the secondary one. However, INCIENSA is not entitled to refuse processing of inadequate samples, causing an inefficient use of technical and economic resources, a disregard for the clinical pathologists' judgment, and compromises the ability of the system tomake definitive diagnoses.

Systematic process of investigation and data analysis: national statistics related to this study seem to overestimate the leptospirosis problem. According to the records of the Ministry of Health,[14-15] between 2001 and 2002 487 cases of leptospirosis were reported nationwide.These data would constitute a valuable source for a study similar to this one, but in view of our results, the reality seems to be different because national statistics seem not to be processed in accordande with the criteria established by th Protocol for the prevention and control of leptospirosis.[8] If this is correct, the health authorities would be discrediting their own norms.

All these situations explain why there is a lack of the necessary starting material, i.e. a sufficient number of confirmed cases, to develop modelling strategies which allow for the achievement of this studie's initial objectives.

This study reveals that in practice there is no true implementation of the current Protocol. It is not possible to conclude, with such results, if the operative definitions are applicable nationwide or not, or if there are clinical or epidemiologic parameters that could help improve the sensibility of the system. It is possible, however, to question the real situation of our leptospirosis surveillance system. In a study done in Costa Rica, in an attempt to adapt the definition of suspected case for dengue fever based on clinical parameters, the authors concluded that, regardless of the proposed case definition, the real problem lies with its application.[13] This appears to be, at least in part, the situation with the Protocol for the prevention and control of leptospirosis, which is not applied in the clinical setting nor to the diagnosis of cases.

With this work we conclude that it is not enough to protocol if this information is not going to reach those who are suppossed to apply them. It is thus fundamental that, after the issue of any protocol or guideline, the education of the healthcare staff, its applicability and its compliance are guaranteed. Also, its results must be verified by means of a process of tracking and constant evaluation of the surveillance system. It is necessary to reinforce and, why not, rethink the surveillance system for leptospirosis in Costa Rica. A fundamental part of this would be the modification of the operative definitions in the Protocol, in order to improve the sensibility and positive predictive value of the system by means of, for example, the relaxation of the confirmed case definition based on serologic aspects.7 Finally, all this process must be accompanied by an improvement of the quality of the information that feeds the registries of the systema nationwide.

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Translate by: Esteban Arrieta

Table 1. Univariate analysis for clinical manifestations in confirmed* and suspected leptospirosis cases. Costa Rica, Januray 2001 – June 2003.

Manifestation	Confirmed case (%)	Suspected case (%)	OR	CI 95%	P
Anorexia	1.9	6.1	0.3	0,0 – 1,9	0,19
Arthralgia	9.6	15.5	0.6	0,2 – 1,6	0,18
Cephalalgia	23.1	36.5	0.5	0,2 – 1,1	0,04
Diarrhoea	1.9	1.1	1.8	0,0 – 18,2	0,49
Abdominal pain	1.9	4.4	0.4	0,0 – 2,9	0,35
Epistaxis	0.0	0.6	0.0	0,0 – 37,3	0,76
Shivers	3.8	6.4	0.6	0,1 – 2,5	0,37
Exanthema	9.6	15.5	0.6	0,2 – 1,6	0,18
Hematuria	0.0	0.6	0.0	0,0 – 37,3	0,76
Hepatomegaly	1.9	0.0	Indef.	0,2 – Indef.	0,13
Jaundice	19.2	17.1	1.2	0,5 – 2,5	0,42
Conjunctival injection	15.4	14.9	1.0	0,4 – 2,4	0,53
Myalgia	23.1	30.4	0.7	0,3 – 1,4	0,18
Nausea	0.0	5.0	0.0	0,0 – 1,6	0,08
Petechiae	0.0	1.9	0.0	0,0 – 4,9	0,39
Retroocular pain	5.8	10.8	0.5	0,1 – 1,7	0,19
Bleeding	3.8	2.5	1.6	0,2 – 7,9	0,41
Vomit	1.9	6.6	0.3	0,0 – 1,8	0,15

* Following the broadened criteria for confirmed case.
Indef = Indefinite

Table 2. Univariate analysis for epidemiologic history in confirmed* and suspected leptospirosis cases. Costa Rica, Januray 2001 – June 2003.

History	Confirmed case (%)	Suspected case (%)	OR	CI 95%	P
Stagnant waters	26,7	16,0	1,9	0,4 – 7,1	0,23
Sewage	6,7	6,1	1,1	0,0 – 8,8	0,63
Warehouses	0,0	0,6	0,0	0,0 – 423,8	0,92
Pigs	6,7	8,6	0,8	0,0 – 5,8	0,63
Equines	0,0	8,6	0,0	0,0 – 3,4	0,28
Floods	6,7	9,8	0,7	0,0 – 4,9	0,57
Dogs	33,3	17,8	2,3	0,6 – 8,1	0,13
Wells	0,0	0,6	0,0	0,0 – 423,8	0,92
Rivers	6,7	6,1	1,1	0,0 – 8,8	0,63
Rodents	20,0	16,6	1,3	0,2 – 5,1	0,48
Waters**	40,0	23,3	2,2	0,6 – 7,4	0,13
Animals**	33,3	31,3	1,3	0,3 – 4,8	0,44

* Following the broadened criteria for confirmed case.
** Grouped

Table 3. Univariate analysis for clinical manifestations in confirmed* and suspected leptospirosis cases. Costa Rica, Januray 2001 – June 2003.

Manifestation	Confirmed case (%)	Suspected case (%)	OR	CI 95%	P
Headache+myalgia	19.2	27.1	0.6	0.3-1.4	0.15
Headache+myalgia+jaundice	7.7	5.8	1.4	0.3-4.3	0.39
Headache+myalgia+conjunctiva injection	11.5	11.0	1.1	0.3-2.7	0.53
Bleeder	5.8	6.1	1.0	0.2-3.3	0.61
Skin and mucosa	34.6	37.8	0.9	0.4-1.7	0.39
Systemic	25.0	35.0	0.7	0.3-1.4	0.19
Gastrointestinal tract	5.8	11.6	0.5	0.1-1.6	0.15

* Following the broadened criteria for confirmed case.
Indef = Indefinite

Table 4. Univariate analysis for clinical manifestations in confirmed* and suspected leptospirosis cases. Costa Rica, Januray 2001 – June 2003.

Manifestation	Confirmed case (%)	Suspected case (%)	OR	CI 95%	P
Headache+mialgia+epide.	66.7	34.4	3.8	1.1-14.9	0.02
Headache+myalgia+jaundice+epide,	26.7	12.3	2.6	0.6-9.9	0.12
Headache+myalgia+ conjunctiva injection +epidem	40.0	17.8	3.1	0.8-10.5	0.05
Bleeder+epidem	0.0	8.6	0.0	0.0-3.4	0.28
Skin and mucosa +epidem	60.0	39.3	2.3	0.7-8.3	0.09
Systemic +epidem	73.3	39.3	4.2	1.2-18.9	0.01
Gastrointestinal tract+ epidem	20.0	13.5	1.6	0.3-6.6	0.35

* Following the broadened criteria for confirmed case.
Indef = Indefinite