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Leptospirosis in Mesoamerica

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Abstract
Purpose of Review Leptospirosis is recognized as a globally re-emerging zoonosis. Despite historical evidence of this bacterial infection dating back centuries, very few studies have looked at the specific geographic distribution of historical leptospirosis outbreaks of public health importance in Mesoamerica. This article aims to review the pertinent outbreaks in this region, in an effort to influence future public health campaigns targeted at eradication.
Recent Findings Mesoamerica is a geographical and culture area of the western hemisphere which has a uniform subtropical and tropical climate that covers since the middle part of Mexico, from its high plains, to the southern forest, and jungles extending to Central America to what is now known as Costa Rica. Leptospirosis is an infectious disease present in the people and fauna of Mesoamerica since many centuries, and an emergent illness nowadays. It is caused by bacteria of the genre *Leptospira*, which affects humans and domestic and wilds animals, causing multiples outbreaks in different countries of this region. Leptospirosis occurs in tropical and tempered regions and its incidence rise tenfold during the rainy season.
Summary Leptospirosis, also known as Weil's disease, porker's disease, rice field fever, or cane fields fever, names that reflect the relevance of affected people activities. There are reports describing alike illness outbreaks in ancient civilizations in Mesoamerica: cocoliztli (Nahuatl word for pest) epidemic outbreaks registered in ancient Mexico (New Spain) from the sixteenth to eighteenth centuries in impoverished indigenous communities after the conquest, were described with characteristics of leptospirosis, with fever, jaundice, and neurologic disorders.

Keywords Leptospirosis · Historical review · Cocoliztli epidemics · Mexico · Central America

This article is part of the Topical Collection on *Leptospirosis in Mesoamerica*

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Introduction

Mesoamerica (from the Greek in the middle) is a geographical area of the western hemisphere which has a uniform subtropical and tropical climate that covers since the middle part of Mexico, from its high plains, to the southern forest, and jungles extending to Central America to what is now known as Costa Rica. However, Mesoamerica is better defined by its culture, where 5000 years ago, large civilizations with highly complex societies developed a great knowledge of architecture, engineering, astronomy, and philosophy, settled in large cities. These cultures still have an influence on many forms of the societal thoughts, and immaterial goods that have permeated even today societies. Mesoamerica includes the half south of Mexico, Guatemala, El Salvador, and Belize; the west of Honduras, Nicaragua, and Costa Rica.

The etymological meaning of the word origin came from the Latin verb *oriri*, that means "rise, arise; or the Greek "ornýnai" meaning "start, awake". Our "awakening", the start of our civilization, merges from the mixture of ancient cultures, which share ideology, knowledge, believes, and custom and gives us a unique identity. This universal meaning of Mesoamerica is reflected in the poem by Netzahualcoyotl in 1400 AC:

"I love the sing of the zenzontle
Bird of four hundred voices
I love the color of jade
And the enervous perfume of the flowers
But the most I love, is my brother
The man"

The previous poem [1] belongs to the postclassic Mesoamerican period, when the conception of man, animals, and flowers is referred in a unique identity, and with the same importance. This syncretism results in elements necessary for the development of zoonotic diseases.

Thus, when talking about leptospirosis, it is necessary to refer to the origins of our civilization, which has a deep root in the Nahuatl, Olmeca, or Mayan cultures, and other pre-Columbian complex societies, all of them give rise to current social behaviors. Nowadays, they are a mixture of ancient beliefs and multicultural enrichment.

Leptospirosis is an infectious disease present in the people and fauna of Mesoamerica since many centuries, and an emergent illness nowadays. It is caused by bacteria of the genre *Leptospira*, which affects humans and domestic and wilds animals, causing multiples outbreaks in different countries of this region. Occurs in tropical and tempered regions, and its incidence rise tenfold during the rainy season [2•].

History

Leptospirosis, also known as Weil's disease, porker's disease, rice field fever, or cane fields fever, names that reflect the relevance of affected people activities. There are reports describing alike illness outbreaks in ancient civilizations: there are vestiges of Mesopotamia that matches with pathologic signs of leptospirosis; in the Egyptian papyri of 2500 BC are descriptions of this disease, the same in Greek of Hippocrates and Galen; and in the campaigns of Napoleon [3]. Morover, cocoliztli (Nahuatl word for pest) epidemic outbreaks registered in ancient Mexico (New Spain) from the sixteenth to eigthteenth centuries in impoverished indigenous communities after the conquest, were described with characteristics of leptospirosis, with fever, jaundice, neurologic disorders, and only during the rainy seasons [4] (Fig. 1).

In 1802, Lacereaux made the first description of leptospirosis, and in 1883, Landarouzi describes a case report of jaundice and hemorrhage that named "hepatic typhus". In 1886, at the same time, Mathieu in France and Adolf Weil in Germany described clinical cases of fever, jaundice, and renal failure, naming in 1887 Weil's disease by Goldschmidt [5••]. In 1907, Stimpson visualize the microorganism in a kidney fragment of a patient, who died of yellow fever, owing to their morphology, he named it *Spirochaeta interrogans*. At 1914, Inada and Ido, in Japan, found spirochetes in the liver of guinea pigs

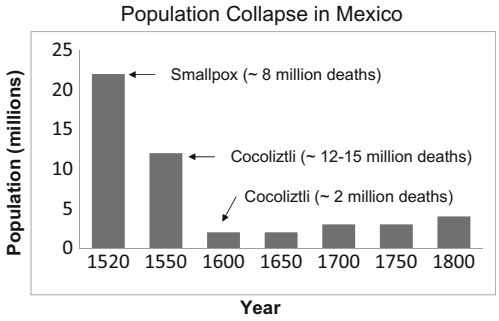

Fig. 1 The sixteenth century population collapse in Mexico, based on estimates of Cook and Simpson. The 1545 and 1576 cocoliztli epidemics appear to have been hemorrhagic fevers caused by an indigenous unknown agent and aggravated by unusual climatic conditions. The Mexican population did not recover to pre-Hispanic levels until the twentieth century. Image from Acuna-Soto et al. [4], https://dx.doi.org/10.3201/eid0804.010175. Used with permission

infected with blood of mineworkers which present high fever, jaundice, and hemorrhagic events, named it *Spirochaeta icterohaemorrhagiae* [3]. In 1915, these authors achieve isolates and cultures of this agent. [5]

Between 1917 and 1918, Noguchi, proposed the genre *Leptospira*, giving the definitive name to the causal agent. During the World War I, in Europe occurred outbreaks of leptospirosis among German soldiers [3]. In 1922, there was a first report of this disease in the USA, and until 1946, it has been reported in 46 countries [5]. In 1947, Wood isolates *Leptospira* from rat feces in the USA. [6]

Situation in Mexico

In Mexico, leptospirosis was firstly reported in an epidemics of yellow fever by Noguchi and Kligler in Yucatan at 1920, and after by Pérez-Grovas and LeBlanc in Veracruz in the same decade [7–9]. It is interesting to observe that in the outbreak of jaundice investigated by Pérez-Grovas, the probes of Pfeiffer and serological agglutination were positive in 117 of 183 patients [8]. Further on, in 1937, Bustamante notified 3 cases of Weil's disease in oyster's workers [10]in the city of Tampico, and in the next year, Castañeda, in the same city, isolate *Leptospira* in Norway rats [11]. Along many years, Varela and coworkers studied leptospirosis in Mexico, revealing the presence of *Leptospira icterohaemorrhagiae* in a high proportion of Norway rats, coming from the ports of Tampico and Veracruz, as well as their description of *L. canicola* in 2 of 8 sick dogs, and in a cattle, confirmed by serologic samples [12].

In the 1950s, Varela et al. made large serologic surveys including 1323 blood donor samples of apparently healthy persons, and 458 samples of healthy hogs from Central Mexico and Mexico City, also studied a few numbers of

horses and dogs. These samples were examined in search of reactivity to *L. icterohaemorrhagiae*, *L. canicola*, and *L. pomona antigens* by microscopic agglutination. Four of 15 horses shown reaction to *L. icterohaemorrhagiae*, and approximately 26% of the dogs were positive, mostly to *L. icterohaemorrhagiae* and in less degree to *L. canicola* and *L. pomona.* Hogs of three districts showed a high proportion of reactions that oscillate from 33 to 52%. The relative frequency of reactivity to the three antigens varies per geographic origin of the samples and the reactions for; *L. pomona* were more frequent from animals coming from Mexico City and Guerrero; while those coming from Oaxaca showed more reactions to *L. icterohaemorrhagiae* and less to *L. pomona* and *L. canicola*. On the other hand, approximately 15% of the human samples were positive, especially for *L. icterohaemorrhagiae* and in less frequent to the other two species antigens. The proportions of seropositive by districts vary from 2 to 29% approximately. In Mexico City, 15% of 150 blood samples were positive [13]. Nevertheless, other investigators have performed serological surveys with inconclusive results; Mendoza-Hernandez et al. did not obtain any positive reaction in 25 human samples of people from Mexico City, studied in the 1950s, but obtain 10% of positive samples from 91 blood subjects with clinical hepatitis (Fig. 2).

In the 1960s, Varela et al. assessed 10,362 serological samples of 21 (of the 32 states of Mexico) with 18% of positive reactions. In 1997, Colin-Ortiz et al., reported a 14.4% of positive reactions among the 9876 blood samples obtained from Yucatan and the Valley of Mexico including Mexico city, from 1961 to 1995 [14]. In 1991, Caballero and coworkers found a 39% of prevalence among farmers [15]. In 1995, Gavaldon and his group analyzed by agglutination 206 samples of blood donors; 7% were positive, from this, 53% of disclosed reaction to the Shermani serovar, 33% for *L. canicola*, 20% for *L. pyrogens*, 13% for *L. pomona*, and 6% for *L. icterohaemorrhagiae*, being the highest frequency in the age group of 20 to 39 years [16]. In the 2006, Navarrete-Espinosa and coworkers made a transversal study from 500 people of Jaltipan, a rural town of south Veracruz, patients fulfilled a structured questionnaire and a blood sample was taken at home. They found a global seroprevalence of 4%, with a major positive tests among people in their productive age; 85% of the positive samples were also positive for dengue fever, demonstrating the coexistence of both agents in the same population [17].

In 2002, Vado-Solis et al. made a clinical and epidemiological study in humans and animals of Yucatan, using the IgM Leptospira dipstick, and MAT for serological samples; study was made in 400 healthy people, 439 cases of probable leptospirosis, and 1060 reservoirs (cows, hogs, dogs, rats, and possums). Seroprevalence in this study was of 14.2% in humans, with predominance of serovars *L. tarassovi*, *L. hardjo*, *L. pomona*, and *L. panama* [5].

In 2007, Navarrete and coworkers completed a prospective study in 204 suspected infected people in the city of Izamal, Yucatan; 88% were positive to direct observation in dark field, 87 and 50.5% were positive to MAT to titles of 1:40 and 1:80, respectively. The predominant serovar was *L. hardjo* (94%), with prevalence of 72% in women, and higher in those older than 45 years (95.7%); the more important risk factors were home maid, contact with backwater, and animal feces deposits close to home [18].

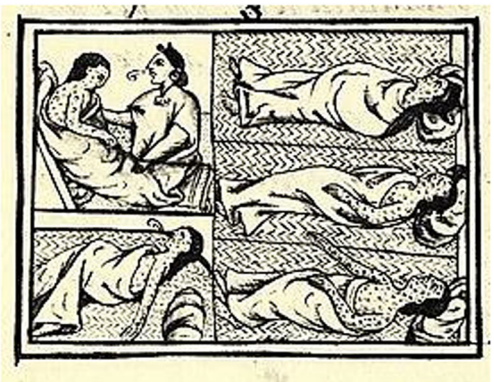

Fig. 2 Indigenous victims, Florentine Codex (compiled 1540–1585). The cocoliztli epidemic of 1576 refers to millions of deaths in the territory of New Spain in present-day Mexico in sixteenth century attributed to one or more illnesses collectively called cocoliztli. The cause of the epidemic remains unknown though it might have been an indigenous viral hemorrhagic fever, perhaps exacerbated by the worst droughts to affect that region in 500 years and living conditions for indigenous peoples of Mexico in the wake of European invasion. Some historians have suggested it was typhus, measles, or smallpox, though the symptoms did not match

Central American Endemics

In the countries of Central America, Guatemala, Belize, Honduras, El Salvador, Nicaragua, and Costa Rica, weather conditions of this tropical area, with prolonged rainy seasons, economy mainly based on livestock and agriculture, irregular human settlements, and low access to medical services outline a higher prevalence of leptospira infection. As we describe for Mexico before, there are only small efforts to assess the true burden of this disease, mostly with seroprevalence surveys, and reports of outbreaks when occurs. Recently, Heidi Wood lead a group of investigators of English-speaking Caribbean countries including Belize, they report the seroprevalence of seven zoonotic diseases in pregnant women, and found a mean of $8.0 \pm 7.5\%$ of population positive for tested *Leptospira* species [19]; meanwhile in an old survey carried out in 1984 in urban and rural areas, prevalence of positive test elapsed from 11.5% in school pupils, to 37% in people of rural communities, with predominance of *L. sejroe*, followed by *L. pyrogenes*, and *L. australis* [20]. In Guatemala, a graduate

thesis for Chemical Sciences by Herrera-García demonstrated a prevalence of 30.3% positive serological test for *Leptospira* in an irregular suburban settlement of Guatemala City, mainly of *L. australis*, *L. lanka*, and *L icterohaemorrhagiae*. Furthermore, in Honduras, Naranjo and colleagues reported an outbreak of leptospirosis disease after the torrential rains associated with the Mitch hurricane, patients were largely men aged from 15–50 years, recalling a plague of rodents during recovery of hurricane, serovars frequency was 44.4% for *L. icterohaemorrhagiae*, 22.2% for *L. hardjo*, and 11.1% for each, *L. canicola*, *L. pyrogenes*, and *L. tarassovi* [21]; importantly, they report a good protection with the Cuban vaccine against leptospira infection.

In Nicaragua, there have been reported severe outbreaks with high morbidity and mortality due to leptospirosis after hurricanes or heavy flooding; in 1995, an outbreak of pulmonary hemorrhage was described affecting a large rural population, in which 26 of 51 fatal cases has demonstrated leptospira infection [22]. More recently, Reller recognized leptospira infection as a cause of at least the 6.3% of acute febrile illness in patients presented at emergency departments in Nicaragua, emphasizing the importance of diagnosis and early treatment [23]. From the smallest country of Central America, El Salvador, Sabek et al. reported 17.5% of positive sera of 984 humans found 13 serogroups, and predominance of men, an increase with age and rural communities [24]. Finally, in the south limit of Meosamerica, in Costa Rica, infection due to *Leptospira* is considered endemic; an outbreak of travelers returning to the USA from a white-water rafting trip on flooded rivers in Costa Rica in the middle of 1990s highlight the importance of this disease among Costa Rican people and travelers visiting tropical areas [25]; furthermore, leptospirosis is also mentioned as a possible contributor to the chronic condition known as Mesoamerican nephropathy, entity that is discussed regionally due to its burden in the region [26].

Hence, evidence suggests that this entity has predilection for the tropical regions with an incidence in humans depending the geographical zone, rating between 0.1 and 1/100,000 habitants in tempered climate to 10–100/100,000 habitants in tropical countries [27]. In Mesoamerica, there is a high prevalence of positive sera of its population as a whole, with 30–40% of tests in high-risk subjects. Animal surveys also revealed a high prevalence of infections either in domestic or wild species; moreover, outbreaks are seen along the last two decades related to rainy seasons, and more importantly associated with hurricanes, which are frequently between August and November in this region [28, 29]. Leptospirosis seems to be also an occupational disease, mainly of men and women engaged in farm work, livestock, sugar cane cultivation, animal husbandry, poverty, overcrowding, and poor sanitary facilities in their communities. The real magnitude is perhaps underestimated because of the wide clinical spectrum, and the lack of accessible diagnostic methods for the entire population (Fig. 3).

Vectorial Structure of the Leptospirosis in Mesoamerica

In the daily searching for the subsistence, the man takes a place too close with the nature. From ancient time, man and animal made an unsolvable league; at the beginning due to economic reasons, and lately, the human being has understood their ecologic environment, the physical qualities of the fauna, and its association with natural events. In that coexistence with the nature, they attribute to the animals some energy and sacred powers; making the animals some deity, god epiphanies, messengers, or symbols of diverse ideas and universal scope [30].

In Mesoamerican people, this perception acquires relevant levels, giving the animals an important place in the configuration of their religion. They became present in the

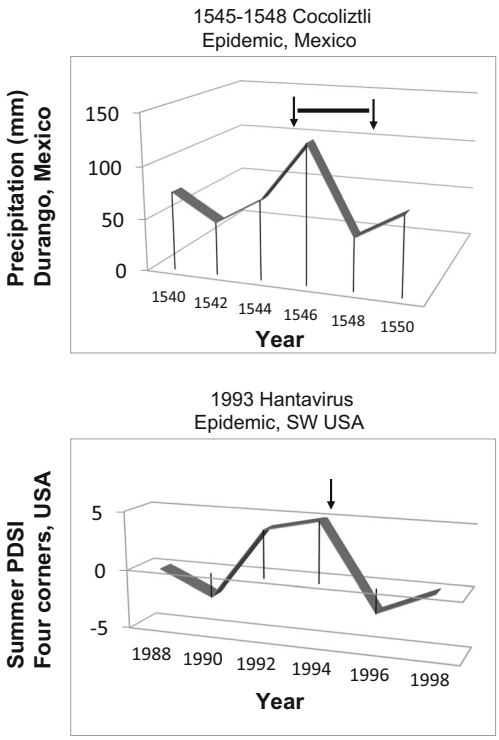

Fig. 3 The winter-spring precipitation totals estimated for year in Durango, 1540–1548 (*top*), compared with the Palmer drought index, southwestern USA 1988–1995 (*bottom*). The tenfold increase in deer mice was witnessed in the southwestern USA during the 1993 outbreak, a year of abundant precipitation following a prolonged drought. The similar dry-wet pattern reconstructed for the 1545 epidemic of cocoliztli may have impacted the population dynamics of the suspected rodent host to aggravate the epidemic. Image from Acuna-Soto et al. [4], https://dx.doi.org/10.3201/eid0804.010175. Used with permission

myths of the creation of the universe, also in the complex symbology associated with different deity or natural forces [31]. Very wide is the importance of the Mesoamerican fauna, like the configuration of their own vision of the universe, and responsible in the transmission of some disease like leptospirosis. Throughout centuries, Mesoamerican cultures depended on the products of the generous nature of their region, with abundance of animal and vegetal products, and a constant interaction with the wild animals, since the same nature conditioned that they did not require the domestication of animals on a large scale. Therefore, frequent outbreaks of leptospirosis permit serovar modifications throughout the entire region, and along the time, as observed in several serological studies. Nowadays, activities related with nature remains a source of important economic resources that continue to place large populations at risk for this infection. There is still a lot to do in this region, especially, to have clinical guidelines applicable to all levels of medical attention in this area; to identify cases early, using simple tests that must be available at first hand, which might administer early and effective treatments. Vaccination against this illness also seems to be a resource that needs to be evaluated more intensively.

Conclusion

Mesoamerica, talking from this rich region, shown through all this years, that the relation of the human being and the nature is essential for the enrichment and the evolution. *Leptospira* is just one example of the evolution, showing us the importance of the mixture of the population from Europe and America, the detection of this illness has become an important diagnostic exercise, because of its high incidence in our region. We also have to consider that this illness is related with poor hygiene and related jobs. The importance of these studies is to make consciousness of the high risk that this entity offer. Preventive medicine is the clue, to fight against *Leptospira*, but first we have to understand the surrounding ambient and the clinical conditions, to offer a better health service to the entire world.

Compliance with Ethical Standards

Conflict of Interest Alejandro E. Svarch, Cesar Alejandro Arce-Salinas, and Jose L. Amaya declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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