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Opinion

Leptospirosis and Extensive Urbanization in West Africa: A Neglected and Underestimated Threat?

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Abstract: Leptospirosis affects 1 million and kills 60,000 people annually, but it remains poorly documented in Africa. We aim to describe the large West African Conurbation Corridor where the omnipresence of slums, water and close animal/human interactions may result in high leptospiral risk. Though scarce, data from this region point towards the wide circulation of pathogenic leptospires in the urban environment as well as in humans. However, because of the absence of reliable surveillance systems together with lack of awareness, the absence of reference laboratory and/or a high number of infected people showing only mild manifestations, it is likely that the burden is much higher. We believe raising awareness of leptospirosis may have a positive impact on many vulnerable African city dwellers, as the disease is a preventable and treatable.

Keywords: urbanization; neglected tropical diseases; *Leptospira*; zoonoses; public health

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1. Leptospirosis: A Widespread but Poorly Documented Disease

Leptospirosis is caused by more than 250 serovars of spirochetes distributed among 10 pathogenic species that can infect and cause severe disease in humans and animals, as well as 5 intermediate species with unclear pathogenicity status that may cause a variety of mild clinical manifestations. It is the most common bacterial zoonosis in mammals and evidence suggests birds, amphibians, reptiles, and fish also carry pathogenic leptospires [1]. Pathogenic *Leptospira* colonize the kidneys of reservoir hosts, especially rodents, and they are excreted via urine into the environment where they can survive in water for several months, and humans usually get infected through contact with contaminated water (reviewed in [2]). Leptospirosis infects at least one million and kills 60,000 people in the World annually, although it remains a poorly documented disease [3]. As an illustration, a recent wide-scale survey of causative infectious agents in 1578 Asian patients showing sepsis found that

95 (6%) of them were infected with leptospires [4]. Yet, despite its obvious impact on public health worldwide, leptospirosis is still not included in the international programs targeting the neglected tropical diseases such as the one supported by WHO (http://www.who.int/neglected_diseases/diseases/en/). Its complex epidemiology and difficult diagnosis [5] pushed experts from various fields to gather within the International Leptospirosis Society (www.leptosociety.org/) and the Global Leptospirosis Environmental Action Network (https://sites.google.com/site/gleanlepto/home; [6]) to fill the numerous gaps of knowledge that limits accurate prediction, prevention, and detection of the disease as well as interventional measures.

Leptospirosis is associated with water exposure, contact with animals (farm and agricultural workers) and poor sanitation [5]. Floods and heavy seasonal rainfall in tropical countries have been demonstrated to be a major cause of outbreaks [7,8]. Little is known about the circulating etiological agents of leptospirosis in most of the regions of the World but there is increasing evidence that leptospires are not only circulating in wetlands, as is commonly accepted, but also in arid regions (e.g., Niger: [9]) or dry non-floodable habitats (e.g., Southeast Asia: [10]).While traditionally associated with rural environments(e.g., [11,12]), leptospirosis is now also considered as an emerging disease in urban slum communities with poor sanitation infrastructure (e.g., [13–16]).

Additional focus should be made on the African continent where data on leptospirosis are scarce (reviewed in [17,18]) compared to other continents [3]. In parts of Africa, health services may be poorly developed with limited treatment and diagnostic testing capacities. This probably contributes to the many so-called ‘fevers of unknown origin’ that may often be inaccurately diagnosed as malaria (e.g., [19]). Beyond its role in the pseudo-malaria fevers, leptospirosis is also a differential diagnosis of several epidemic diseases of particular importance in Africa, such as dengue [20], yellow fever [21], viral hemorrhagic fevers [22,23] or pneumonic plague [24]. This adds to the existence of an occupational risk like on other continents, as suggested by the study conducted among kennel workers in Nigeria [25]. We here aim at pointing towards the high leptospiral risk that may exist in African urban environment which has been particularly poorly investigated for the disease.

2. Highly Favorable Conditions for Leptospirosis Propagation in the West African Coastal Conurbation

Urbanization, especially in developing countries, has been quick and massive, with the current population projections moving from 3,960,000,000 urban citizens to 6,340,000,000 by 2050 [26]. A clear illustration of rapid urbanization is the West African Coastal Conurbation (WACC), a 700 km-long limitless urban corridor between Abidjan, Côte d’Ivoire, and Lagos, Nigeria, with large cities merging to form a vast urban mega-region (Figure 1). The WACC currently houses more than 25 million people who are structured within and around large adjacent cities such as Abidjan (3 million inhabitants), Accra (5 million), Lomé (1 million), Cotonou (1 million), Porto-Novo (500,000) and Lagos (10 million). It is also close to other Nigerian megacities such as Ibadan (4 million), Benin City (1.5 million), Port Harcourt (1.5 million) and Calabar (500,000) (Figure 1). The WACC population is expected to grow to 34 million people by 2025 [27]. This rapid urbanization and uncontrolled urban sprawl raises important concerns related to access to basic health care services, sanitation, waste management, housing, etc. Leptospirosis incidence is expected to increase following global changes that include uncontrolled city expansion ([7,16]. The WACC area is also considered by the Intergovernmental Panel on Climate Change to be highly vulnerable regarding climate change [28]. It is comprised of lakes, swamps and mangroves, and the numerous bowls and the extremely dense hydrographic networks are responsible for many flooding events, either following rainfall accumulation or through lakes and rivers overflows. For example, each year, 43% of Cotonou, Benin, is flooded one to two months long either by Lake Nokoué overflow or by rainfalls that cannot be drained due to a defective sanitation network [29], thus directly affecting 200,000 poor urban dwellers and indirectly affecting many others through service interruption, resource unavailability, degraded water quality, etc. [30]. In addition, coastal West Africa undergoes an equatorial climate with 800–1600 mm annual rainfalls and ca. 27 °C mean annual temperature, thus being highly compatible with *Leptospira* survival and proliferation [7,8,31]. Furthermore, future predictions on climatic trends suggest continuing favorable conditions for such pathogens [32].

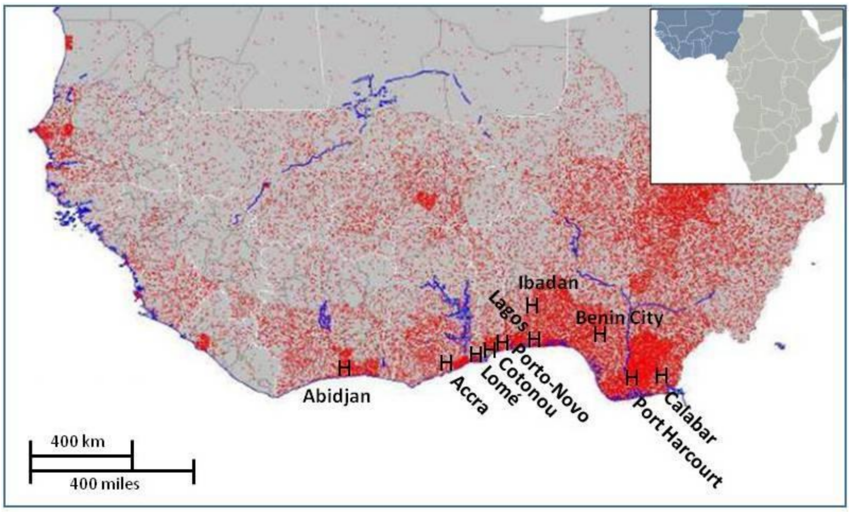

Figure 1. Predicted urbanization in West Africa in 2020. Each red dot represents 10,000 inhabitants. Modified from [33].

3. What We Know about *Leptospira* in the WACC

Published and grey literature reports have documented pathogenic *Leptospira* spp. circulating in Benin, Ghana, Ivory Coast and Nigeria, but, to our knowledge, no studies have been performed in Togo (reviewed in [17,18]).

In Nigeria, surveys in healthy populations showed between 13.5% and 18% of leptospirosis seroprevalence in the Eastern and Plateau States, respectively [34,35]. The two latter states are several hundred kilometers away from the WACC, but a national survey including southern regions found a 20.4% seroprevalence using Microscopic Agglutination Test (MAT) [36,37], thus demonstrating that *Leptospira* pathogenic strains are present in most parts of Nigeria, especially in the south of the country which has a warmer and wetter climate. The most frequent serogroup in MAT-positive people was Icterohaemorrhagiae (18.3%), followed by Sejroe (15.7%), Grippotyphosa and Pyrogenes (15%). When at risk populations were investigated, higher seroprevalences were observed (i.e., 4.5% in hospital laboratory personnel, 20.2% in farmers, 29.5% in abattoir workers and up to 46% in coal mine workers; [34,35]). To our knowledge, no survey has ever been conducted in febrile patients, but one symptomatic case has been recently described (Isa et al., 2014): a student infected by *L. borgpetersenii* serogroup Tarassovi who displayed fever and profound jaundice who was residing in a hostel recently flooded and infested by rats and with proximity to roaming livestock.

In Ghana, several ELISA-based studies have shown high seroprevalence in rural areas ([38]: 33% of positive human sera out of 460 from Southern Ghana; [39]: 21% out of 657 human sera from ten rural localities) while studies focusing specifically on urban areas are scarcer. Rothstein [40] conducted a MAT survey on 117 febrile patients initially hospitalized for a suspected viral hepatitis: 65 (55.6%) of them were *Leptospira*-seropositive. Unfortunately, serogroups could not be identified due to the use of pooled antigens. Another MAT-based survey of 99 febrile patients originating from the Ashanti and Volta districts, both in the Southern half of the country, led to 21.2% of seropositive people, with serogroups Icterohaemorrhagiae and Tarassovi being identified with the highest titers (1:3000 and 1:1000, respectively) in patients showing acute phase in hospitals from the Atlantic Coast [41]. Finally, Kronmann et al. [42] and Tagoe et al. [43] investigated *Leptospira* antigens in 198 and 166 febrile patients hospitalized in Accra, respectively, and found that 1.7% and 7.8% of them were seropositive (no data on serovars available).

In Côte d'Ivoire, there is one documented study of 93 vaccinated and 65 unvaccinated dogs from Abidjan and two surrounding cities [44]. MAT analyses (focusing on titers >1:320) showed that 58.7% and 47.7%, respectively, were seropositive. The absence of significant difference in seroprevalence between the vaccinated and non-vaccinated animals together with the circulation of serogroups Icterohaemorrhagiae and Canicola was interpreted as the result of a high infectious pressure in the Abidjan area, suggesting that human beings are at risk, as well (Roqueplo et al. 2015). Accordingly, a recent survey has been conducted on 384 patients randomly selected from the 2014 national surveillance system for yellow fever. Four patients (1.04%) were found infected by either PCR, or ELISA IgM and MAT: they were three adult males and one adult female, all coming from the Western part of Côte d'Ivoire and occurring in the rainy season. Although these febrile cases of leptospirosis were all of rural origin, they show that acute leptospirosis exists in Côte d'Ivoire where it is a differential diagnostic of yellow fever (Bourhy, Koffi and colleagues, in prep.).

In a recent qPCR-based survey from southern cities of Benin, namely Cotonou, Porto-Novo and Ouidah, we found that 111 (12.9%) out of 858 rodents and shrews were carrying pathogenic leptospires that were then identified as *L. interrogans*, *L. kirschneri* and *L. borgpetersenii* through DNA sequencing (our unpublished data). This agrees with another study of 90 small mammals from Cotonou showing 18.9% of positive animals [45]. In addition, although no serogroup could be identified, several pathogenic *Leptospira* positive cultures could be settled from various waterholes within Cotonou and its neighborhood [46]. Two independent ELISA-based surveys of IgG agree in suggesting that human seroprevalence is also quite high in Cotonou (15.4% and 15.8% in 175 and 266 randomly selected people within eight and twelve districts of the city, respectively; [47,48]). It may even reach 33.3% in some very poor and crowded urban areas [48] and up to 42.9% in at risk professionals such as fishermen [47]. Accordingly, a MAT-based investigation of 503 at risk professionals (i.e., 279 urban market gardeners, 30 fish farmers and 194 abattoir workers showed 54.3% seropositive [46]. In the same study, 244 undiagnosed febrile patients were also investigated and 76% of them were found MAT-positive. In both at risk professional and febrile patient samples, 12–15 serogroups were identified, with Icterohaemorrhagiae and Grippostyphosa being the most predominant. However, such results should be considered with great caution since a titer 1:20 was used [46], thus potentially leading to an over-estimate of seroprevalence. Another study conducted in 734 hospitalized children found that 1.9% of them were *Leptospira*-seropositive (ELISA and dipstick tests), while the search for IgM together with Faine's [49] score >26 suggested an incidence of 4.9‰ per year in this particular population [50]. Finally, a symptomatic and MAT-positive (MAT titer and serogroup not available) case of leptospirosis was recently described from Cotonou (Kpossou et al., submitted), thus strongly suggesting that leptospires do induce human disease in the country.

4. Conclusions

Until now, data on the burden of leptospirosis has been very focused on serological studies that occur in specific geographical areas and regions. Moreover, positivity cut-offs are usually quite low, thus suggesting an over-estimation of seroprevalence. However, looking at the numerous studies together, a picture emerges of a wide circulation of pathogenic leptospires in coastal West Africa, especially in the large, still expanding and increasingly crowded WACC. We hypothesize that the low number of reported cases in the WACC region is due to (i) the absence of reliable surveillance systems together with lack of awareness of the medical community; (ii) the absence of reference laboratory and rapid diagnostic tests for the diagnosis of leptospirosis in the area; and/or (iii) an usually high number of infected people showing only asymptomatic or mild manifestations who do not seek health care.

Therefore, One Health investigations on leptospirosis should be considered in West Africa where a well-designed sentinel system could be used to signal trends, identify outbreaks, and monitor the burden of the disease in communities. Further, robust epidemiological studies are urgently needed in order (i) to identify the *Leptospira* strains that indeed infect human locally; (ii) to investigate the sources of contamination as well as (iii) the uses and habits of person that may be at risk for infection. As an example, collaborative research that involve medics, biologists, hydrologists, and geographers is currently conducted in Cotonou, Benin, and aims at identifying severe cases in hospitalized malaria-negative febrile patients as well as describing leptospires diversity and distribution within the urban environment. Such studies are expected to be helpful in demonstrating the potential importance of the disease for local public health, and in characterizing areas where, and seasons when inhabitants are most at risk. We believe that raising awareness of leptospirosis may have a large positive impact on the health of millions of people residing in West Africa, particularly the vulnerable urban city dwellers in WACC, as the disease is largely treatable.

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