

Getting leptospirosis onto the lists of neglected tropical diseases

openaccessgovernment.org/article/getting-leptospirosis-onto-the-lists-of-neglected-tropical-diseases/177928

7 June 2024

Leptospirosis is a globally important infectious disease, but neglected to the extent that it's not on WHO's or FDA's neglected tropical diseases lists; this needs to change

What is leptospirosis, and why is it so bad for global health?

Leptospirosis, caused by spirochetes of the bacterial genus *Leptospira*, poses a significant yet poorly recognized global public health threat. Incomprehensibly, this disease remains neglected by the global health agenda. Leptospirosis is estimated to cause more than a million cases and over 60,000 deaths annually, with case fatality rates of up to 20%.⁽¹⁾ Hence, leptospirosis is the most important zoonotic bacterial disease worldwide. It is common in tropical regions of low- and middle-income countries such as Brazil, India, China, Indonesia, Peru, Sri Lanka, and Thailand, and it affects high-income countries, too, including the United States and Europe.

Leptospirosis disproportionately affects individuals living in impoverished and resource-poor settings, both urban and rural^(2, 3, 4) especially those affected most by climate change.⁽⁵⁾ Signs and symptoms of infection are initially nonspecific (i.e., fever) that can progress to severe, life-threatening disease, particularly fulminant shock, lung hemorrhage, jaundice, and renal failure; in some places, severe leptospirosis is the most common reason for intensive care unit admission. To this day, the lack of actionable diagnostic tests (i.e., rapid tests) is the primary reason that leptospirosis is misdiagnosed and underreported. Recent advances in leptospirosis vaccines and diagnostics—key interventions—mandate that leptospirosis is prioritized on the global health agenda and added to the two NTD lists of highest importance: those of the World Health Organization (WHO) and the United States Food and Drug Administration (FDA).

Why is it so hard and relevant to count leptospirosis cases?

The lack of effective, accessible point-of-care diagnostics for leptospirosis, which typically presents with non-specific clinical manifestations, leads to poor disease recognition. Public health authorities, such as the CDC and the US Council of State and Territorial Epidemiologists, currently require reporting leptospirosis, but this has not always been so because of the lack of actionable diagnostics.⁽⁶⁾ Cases are generally diagnosed by centralized reference laboratories or clinical laboratories.

Current diagnostics are primarily serology-based and are indirect; culture, PCR, and antigen detection are direct and highly useful, but either is not actionable or not yet available, and results are delayed, even in high-income settings. The absence of a rapid

and reliable antigen detection test further complicates early diagnosis. Taken together, due to vast underreporting, positioning leptospirosis as a global health priority could catalyze the development of innovative, simple, and inexpensive point-of-care (or nearly so) diagnostic tests needed for early detection and management of the disease and necessary for epidemiological reporting.

What are the WHO and FDA NTD *lists*?

Inclusion on the WHO NTD *list* is largely driven by policy groups that have regional and international interests and advocate for specific diseases. Current guidelines for advocacy are based on WHO's centralized Sustainable Development Goals: a road map for neglected tropical diseases 2021–2030, and subject to formal STAG-NTD review and recommendation. ⁽⁷⁾

The WHO NTD *list* includes the following: Buruli ulcer; Chagas disease; dengue and chikungunya; dracunculiasis; echinococcosis; foodborne trematodiasis; human African trypanosomiasis; leishmaniasis; leprosy; noma; rabies; schistosomiasis; soil-transmitted helminthiasis; snakebite envenoming; and yaws. While these diseases are important health challenges in certain impoverished populations, they do not fully encompass the scope of diseases, which are focused on areas defined by WHO's NTD department. Few of the NTDs on the WHO list have actionable strategies for prevention, diagnosis, and treatment; such strategies are not criteria for being on this list. The process by which diseases are added is overseen by the WHO's standing Strategic and Technical Advisory Group for NTDs (STAG-NTDs), which reports directly to the WHO Director General.

Similarly, Section 524 of the Federal Food, Drug, and Cosmetic Act outlines the FDA's list of NTDs (another list), which is more extensive. ⁽⁸⁾ Under this provision, sponsors of approved vaccines and therapeutics for these designated NTDs receive Priority Review Vouchers (PRVs), which enable them to introduce and market their products within the US. PRVs provide financial incentives for the commercialization of vaccines and therapeutics for under-addressed NTDs that would otherwise not be pursued due to a lack of an adequate business model or financial justification.

Why is it so important for leptospirosis to be on the global agenda via the WHO's and FDA's neglected tropical disease *lists*?

In 2021-2022, we requested that the Secretary of the Department of Health and Human Services of the United States consider adding leptospirosis to the current list of tropical diseases in the Federal Food, Drug and Cosmetic Act. We cited key elements of our proposal in accordance with Section 524(a)(3)(R) of the Federal Food, Drug and Cosmetic Act, which authorizes the US Secretary of Health and Human Services to designate by order 'any other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalized populations' as a tropical disease. Leptospirosis fulfills all criteria.

Recognizing leptospirosis on the lists secures the necessary visibility and attention that drives philanthropic and governmental support, which is needed for advancing research and development. The inclusion in these lists signifies to national and international health agencies, as well as the pharmaceutical industry that there is a public health necessity and potential market for developing effective diagnostics, vaccines, and treatments. This recognition would potentially stimulate industry interest by creating incentives like the Priority Review Voucher system, which encourages the development of treatments for neglected diseases. The commercial development of novel therapeutics could then be expedited, making interventions against leptospirosis possible on a large scale.

The global mandate to address the leptospirosis threat within One Health and climate change contexts

Animal leptospirosis is a major livestock concern worldwide, in industrialized and LMICs, affecting health, food security, and gross domestic product. ⁽⁹⁾ In agricultural communities, leptospirosis compromises livestock health, exacerbating food insecurity and decreasing livestock productivity and economic value; production animals also transmit infection to humans. ⁽¹⁰⁾ As an environmentally transmitted zoonosis, mitigating leptospirosis requires an integrated One Health approach that explicitly accounts for important economic, i.e., GDP effects, public health effects, and clinical effects on humans and animals. Such control measures include improved diagnostics, vaccines, and therapeutics for humans and livestock.

Leptospirosis is increasingly a concern in the context of climate change ^(5, 11) as warmer temperatures and more frequent extreme weather events enhance the growth and spread of *Leptospira*, putting larger populations at risk. These conditions increase human exposure to contaminated waters, particularly where sanitation and healthcare are inadequate. Drought increases risk by exposure to concentrated, contaminated water sources. These factors further contribute to a rising incidence of leptospirosis, marking it as a critical health issue linked to climate change. ⁽⁵⁾

The compelling case for getting leptospirosis onto WHO's and FDA's NTD *lists*

Formally recognizing leptospirosis as an NTD will enable key opportunities for funding and research on the burden, costs, and prophylactic/therapeutic interventions necessary to reduce its global impact. Such science-based tools are critical in battling any public health threat. NTD status would not only elevate the disease's profile but would also mobilize international resources and increase the attention needed to combat its spread, ultimately leading to substantial economic gains and reducing food insecurity in affected regions.

The barriers to getting onto the *lists* can be overcome by data

The lack of policy interest from both the human and animal health sectors stems from a lack of awareness and unclear perceived economic benefit in addressing leptospirosis's severity and impact. ^(1, 12) Difficulty in diagnosis means less awareness of potential action. Actionable and inexpensive diagnostic tools are critical to better document the global burden of leptospirosis, a metric commonly utilized to present a disease's global impact. Similarly, economic data from a One Health perspective needs to be developed and consolidated.

Being on the *lists* is necessary but not sufficient to ameliorate the global burden of leptospirosis

Properly deployed diagnostics within formal programs to quantify the global burden of leptospirosis underlies the business argument for investing in vaccine discovery, translational, commercial development, and deployment through public agencies and private health systems. Vaccines are pivotal in controlling leptospirosis. The widespread deployment of such vaccines will require substantial investment, leveraging of public resources, and coordinated international support.

Adding leptospirosis to the WHO and FDA NTD *lists* is more than a bureaucratic formality; it is a necessary step to acknowledge the disease's severity, socioeconomic impact, and global reach and to obtain financial support from important global health funding agencies. For global health, economic stability, and humanitarian equity, we advocate for adding leptospirosis as a neglected tropical disease onto the *lists*.

Authors

Joseph M. Vinetz,^{1,2,3} Alyssa N. Chetrick,¹ Katie E. Steimel,¹ Carla E. Devillers,³ Jean-Louis Excler,⁴ Jerome H. Kim,⁴ and Suneth Agampodi⁴

1. Yale University, New Haven, CT, USA
2. Alexander von Humboldt Institute of Tropical Medicine and Faculty of Sciences, Universidad Peruana Cayetano Heredia, Lima, Peru
3. Luna Bioscience, Inc, New Haven, CT, USA
4. International Vaccine Institute, Seoul, South Korea

References

1. Costa F, et al. 2015. Global morbidity and mortality of leptospirosis: a systematic review. PLoS Negl Trop Dis 9: e0003898.
2. Ganoza CA, et al. 2006. Determining risk for severe leptospirosis by molecular analysis of environmental surface waters for pathogenic *Leptospira*. PLoS Med 3: e308.
3. Ko AI, et al. 1999. Urban epidemic of severe leptospirosis in Brazil. Lancet 354: 820-825.
4. Segura ER, et al. 2005. Clinical spectrum of pulmonary involvement in leptospirosis in a region of endemicity, with quantification of leptospiral burden. Clin Infect Dis 40: 343-51.

5. Kim CL, A et al. 2023. Mitigating the effects of climate change on human health with vaccines and vaccinations. *Front Public Health* 11: 1252910.
6. Guerra MA, 2013. Leptospirosis: public health perspectives. *Biologicals* 41: 295-7.
7. Control of Neglected Tropical Diseases, WHO, 2020. Ending the neglect to attain the Sustainable Development Goals: a road map for neglected tropical diseases 2021–2030. Available at: <https://www.who.int/publications/i/item/9789240010352>. Accessed May 18, 2024.
8. FDA, 2024. Tropical Disease Priority Review Voucher Program. Available at: <https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/tropical-disease-priority-review-voucher-program#:~:text=To%20qualify%20for%20a%20PRV,been%20approved%20in%20any%20other>. Accessed May 20, 2024.
9. Riediger IN, et al. 2017. Rapid, actionable diagnosis of urban epidemic leptospirosis using a pathogenic *Leptospira* lipL32-based real-time PCR assay. *PLoS Negl Trop Dis* 11: e0005940.
10. Bharti AR, et al. 2003. Leptospirosis: A zoonotic disease of global importance. *Lancet Infect Dis* 3: 757-771.
11. Douchet L, M et al. 2024. Climate-driven models of leptospirosis dynamics in tropical islands from three oceanic basins. *PLoS Negl Trop Dis* 18: e0011717.
12. Agampodi S, et al. 2023. Global, regional, and country-level costs of leptospirosis due to loss of productivity in humans. *PLoS Negl Trop Dis* 17: e0011291.

Please Note: This is a Commercial Profile



This work is licensed under [Creative Commons Attribution 4.0 International](https://creativecommons.org/licenses/by/4.0/).