Editorial

The Paradox of the Chicken and the Egg: Lack of Actionable Diagnostics Prevents Global Burden of Disease Assessment and Deployment of Public Health Preventive Measures

Vinetz JM [1*]

[1] Division of Infectious Diseases, Department of Medicine, University of California, San Diego La Jolla, California, USA

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***Correspondence:** jvinetz@ucsd.edu

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Leptospirosis, a bacterial zoonosis, is a globally important emerging infectious disease. The magnitude of its public health importance in most regions and countries remains unknown, both in terms of clinical diagnosis and overall burden of disease, which supports the designation of leptospirosis as a neglected tropical disease. Indeed, the Director of the World Health Organization formally appointed an advisory council, the Leptospirosis Epidemiology Reference Group (LERG), to assess the global burden of leptospirosis. (www.who.int/zoonoses/diseases/lerg/en/index.html).

The work of LERG has been preliminarily reported (1). An essential finding from the LERG reports is that systematic data to assess the global burden of disease are lacking. The lack of clinically responsive diagnostic tests combined with insufficient systematic study of affected human populations remains a major impediment to understanding the impact of leptospirosis on affected human populations at the clinical, public health and policy levels. This difficulty in diagnosis leads to a paucity of data so that leptospirosis is usually not recognized as a public health threat. Hence, public health approaches to prevent and ameliorate this disease through environmental remediation of hot spots of transmission or novel vaccine or other preventive interventions do not receive programmatic priority by governmental and private research funding organizations or by public health agencies. This story is typical of neglected tropical diseases. However, in the case of leptospirosis, which has the capability of causing explosive epidemics (and predictably and regularly does so around the world) of acute febrile illness, jaundice, renal failure, pulmonary hemorrhage, refractory shock and death, the stakes are too high not to develop new ways to identify, treat, and prevent this disease.

The overall strategy of any global research effort to develop new, globally applicable leptospirosis diagnostic tools has to based on organizing epidemiology and clinical research groups in a diversity of leptospirosis-endemic setting. The current state of diagnostic testing for leptospirosis is poor and relies primarily on decades-old testing methods that are inexact, slow, and not useful at the point of care, hence leading to delayed or missed opportunities for timely clinical care and public health interventions. In the developing world, reference laboratories are generally based at government-supported entities; in the industrialized world, reference laboratories are far removed from the field setting where the burden of disease is highest. Leptospirosis has sporadic,(2,3,4) highly endemic(5, 6, 7, 8) and explosively epidemic patterns of disease,(9, 10, 11) which are related to how humans interact with the environment around them and the diversity of *Leptospira*due to the presence of mammalian reservoir hosts such as rodents, dogs and livestock. Sporadic leptospirosis occurs dramatically in the context of intermittent activities in which people come into contact with *Leptospira*-contaminated environmental surface waters and wet soils, for example during the EcoChallenge Sabah in 2000(12) or other adventure traveler events such as triathlons.(13)

Progress in addressing the global threat of leptospirosis rests on the premise that the development of new clinically timely diagnostics for acute leptospirosis is an essential tool for controlling this disease. Major efforts need to be

deployed at the level of laboratory-based discovery to develop rapid, robust and reliable diagnostic tests that are accurate in different globally representative epidemiological settings and that reflect the high diversity of infectious members of the genus *Leptospira*, which is an important potential barrier to diagnosis.(2, 14, 15)Key to diagnostics development is studying diverse and representative patient populations to produce a well-characterized specimen bank.(16)The diversity of infecting *Leptospira* will make it essential to prioritize diagnostic reagents to those that detect the most clinical significant infecting species/serovars. The recent genome-level protein microarray work pioneered and led by the Felgner and Ko groups(17, 18) will need to focus not only *Leptospirainterrogans* serovar Copenhageni (the globally most important infecting strain but not the only cause of severe leptospirosis), but also take into account the existing and forthcoming comprehensive genomic information which indicates some cross-reactive protein antigens among pathogenic *Leptospira*, but also significant differences in ortholog and paralog content at the genomic level (http://gcid.jcvi.org/projects/gsc/leptospira/).Current commercially-available serological assays use soluble sonicated antigens from the saprophytic (non-infectious) *Leptospira biflexa* as antigen;(19) assays based on this antigen have relatively poor sensitivity (ranging from 20-60% on the acute serum sample) and have neither prognostic nor epidemiological implications in terms of progression to severe disease nor zoonotic source of infection, respectively.

The gold standard diagnosis of leptospirosis has traditionally been the microscopic agglutination test (MAT) that primarily detects antibodies to leptospiral surface lipopolysaccharide. Using the MAT as the gold standard has recently been called into question(20) because molecular tests (conventional and quantitative real time PCR) detect more cases than does MAT.(20, 21) Isolation of *Leptospira* from clinical samples requires specialized medium,(22, 23) equipment and handling, and is poorly sensitive, time-intensive, inefficient and difficult, even though essential for understanding many aspects of *Leptospira*biology. Molecular testing, while clearly the newest gold standard, is relatively expense and, hitherto, has required fairly sophisticated facilities, expertise and training, not typically easily available and clinically actionable in leptospirosis-affected settings.

A new generation of leptospirosis diagnostic testing is urgently needed. The leptospirosis field considers this disease to be woefully neglected with significant burden of disease related not only morbidity but to mortality. New diagnostic tests need specifically to identify acute leptospirosis, predict the need for antibiotic treatment (all *Leptospira*are susceptible to most (24, 25, 26, 27, 28), and indicate the need for hospitalization. New tests must be able to quantify endemicity, identify infection hotspots, identify infecting *Leptospira*species/serovars and strains, towards the goal of interrupting transmission at the public health level. Such tests need to provide the essential data to be actionable in clinical practice and to underlie key data for enabling public health policy makers to make decisions for intervention. The chicken and the egg paradox is this: funding is needed for diagnostics development in leptospirosis, but without having the data to justify such funding—whether from governmental or philanthropic sources—such diagnostics development will be difficult to pursue.

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