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Leptospirosis: time to move to molecular epidemiology

Comments on “Reassessment of MLST schemes for *Leptospira* spp. typing worldwide” by Varni and colleagues

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For decades, our knowledge of leptospirosis epidemiology was built from serological studies. Isolates were typed using the reference cross-agglutinin absorption technique into more than 250 serovars, grouped into more than 20 serogroups. Human and animal cases diagnosis as well as animal reservoir studies most frequently identified the putative infecting strain using the reference Microscopic agglutination test, a technique shown to have a low individual predictive value but still useful at a population level (Levett, 2001; Levett, 2003). More recently, *Leptospira* typing has moved to the study of DNA sequence polymorphisms using the molecular tools developed and used widely in most bacterial genera, notably Multi Locus Sequence Typing. In parallel, the advent of highly sensitive and highly specific real time PCR techniques has revolutionized the field of human leptospirosis diagnosis. When positive, they allow a confirmatory diagnosis of acute leptospirosis in a couple of hours using a single

blood specimen (cerebrospinal or urine are also usable later in the course of the disease).

This change was particularly notable in our laboratory in New Caledonia, where the contribution of PCR to the diagnosis of human leptospirosis has increased from 20-30% to more than 90% in less than 10 years. Despite our recommendation of presumptive antibiotic treatment, this rapid turnaround time is probably beneficial for the patients; at very least it allows minimizing medical uncertainty and useless medical explorations before seroconversion. On another hand, this shift in diagnosis techniques is also prone to restrict our knowledge on the contribution of the various *Leptospira* strains to human cases (and therefore the importance of the various animal reservoirs) both by abandoning the time-consuming and fastidious culture and strain isolation and by depriving reference laboratories of convalescent sera, because they become useless for diagnosis or medical purpose.

Molecular techniques were also used for characterizing uncultured *Leptospira* from clinical (Agampodi et al., 2013) or animal (Perez et al., 2011) specimens or even from the environment (Ganoza et al., 2006; Viau and Boehm, 2011). However, reconciling the historical serological knowledge with this modern molecular epidemiology data is a real need until animal reservoir studies also move to molecular approaches, but remains very challenging.

In a recently published study, Varni and colleagues (Varni et al., 2013) re-assessed *Leptospira* MLST data from studies published earlier, together with new sequence sets from regional isolates. Interestingly enough, they noted a unidirectional correlation between sequence types and serogroup, where sequence types contained isolates belonging to a single (or at most two) serogroup. In our lab, we also developed and now routinely use DNA sequence polymorphism to putatively identify the infecting *Leptospira* from human cases, based on the assumption that our island environment hosts a limited number of *Leptospira* strains and

reservoir hosts (Perez and Goarant, 2010). One next challenge, besides going back to culture and isolation for collecting and typing reference isolates, is to identify the best DNA targets and amplification techniques for this purpose. These should fulfill two hardly compatible needs: (i) a need to be highly sensitive to account for the frequently very low bacterial burden of clinical specimens and (ii) a need to generate DNA products with a sequence polymorphism of epidemiological relevance. Additionally, these should still take into account the wide diversity of the genus *Leptospira*.

Because leptospirosis as a public health and veterinary concern is moving from serological to molecular tools (Levett, 2007) reconciling historical serological data with DNA sequence polymorphisms will allow bridging the gap between our historical and upcoming knowledge of leptospirosis, notably linking animal reservoirs and human infections, an indubitable key to control strategies.

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