Reply to Lee and Howden

Manson, Abigail L.; Abeel, Thomas; Galagan, James; Chandrabose Sundaramurthi, Jagadish; Shanmugam, Siva Kumar; Palaniyandi, Kannan; Narayanan, Sujatha; Swaminathan, Soumya; Earl, Ashlee M.

DOI
10.1093/cid/cix751

Publication date
2018

Document Version
Final published version

Published in
Clinical Infectious Diseases

Citation (APA)
Manson, A. L., Abeel, T., Galagan, J., Chandrabose Sundaramurthi, J., Shanmugam, S. K., Palaniyandi, K., Narayanan, S., Swaminathan, S., & Earl, A. M. (2018). Reply to Lee and Howden. *Clinical Infectious Diseases*, *66*(1), 160-161. https://doi.org/10.1093/cid/cix751

genomics for resistance prediction in India and potentially other endemic regions with diverse lineages of *M. tuberculosis.* By extension, this study emphasizes the critical need to collect strains and categorize the mutations circulating in these regions to better inform such predictions.

Although we reiterate the importance of this work, we have some considerations that warrant further attention. First, we note that the authors apply a threshold of 10 single nucledotide polymorphisms (SNPs) distance for "recent transmission," stating this threshold was derived in previous publications. Given this, they then conclude that transmission "was occurring among patients from the same and not different regions." We would argue that this inference cannot be made from the data available in this study. The sampling fraction, which corresponds to the proportion of total cases included in the study, is an essential (yet often overlooked) consideration in genomic epidemiology. Previous studies have shown that, as sampling fraction decreases, clustering is underestimated [5, 6]. With a low sampling fraction, numerous potential transmission events may be missed due to failure to observe source or secondary cases. When making inferences about transmission in genomic epidemiology (or deciding which inferences should be made), this is therefore a critical consideration [7]. In the Manson et al study, the authors included samples from 196 unique patients from 2 districts of India that were collected over a 6-year period. Because India accounts for >2 million cases of tuberculosis per year [8], the Manson et al study clearly includes only a small proportion of the total cases that would have been diagnosed in this time. We therefore argue that transmission between districts cannot and should not be excluded. To do so not only sends a potentially erroneous message to regional public health units but also risks promoting a "silo effect," wherein public health officials within regions overlook risk factors for transmission beyond their administrative borders, which may ultimately prove detrimental to tuberculosis control in India and elsewhere.

We would also caution about the general application of SNP thresholds derived from external studies. Although such thresholds are useful from a public health perspective, it is important to note that their sensitivity and specificity for transmission often depends on local strain diversity (eg, [9]) and may not be readily transferrable across settings. We agree that ≤10 SNPs distance does suggest a close genetic relationship; however, it is important to keep in mind that direct person-to-person transmission cannot be ruled in absent more detailed epidemiologic and contextual data.

Notes

Financial support. R. S. L. is supported by a Fellowship from the Canadian Institutes of Health Research (Funding Reference Number 152448). B. P. H. holds a Practitioner Fellowship from the National Health and Medical Research Council, Australia (GNT1105905).

Potential conflicts of interest. Both authors: No reported conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Clinical Infectious Diseases® 2018;66(1):159–60

DOI: 10.1093/cid/cix750

Reply to Lee and Howden

To the Editor—We thank Dr Lee and Prof Howden for their letter and for giving us an opportunity to better articulate our interpretation of findings, especially with respect to transmission of *Mycobacterium tuberculosis* among patients within 2 southern Indian districts. Based on analysis of single nucleotide polymorphism (SNP) differences between 223 *M. tuberculosis* strains from 196 patients within the Thiruvallur and Madurai districts of Tamil Nadu, we report recent intradistrict, but no recent interdistrict, transmission of strains among patients. In drawing these conclusions, we limited our interpretation to the data available to us, which showed that the closest SNP distance between *M. tuberculosis* isolated from patients in different districts was 85 SNPs, which is substantially higher than the very small numbers of SNPs (as few as 0) observed when comparing isolates from patients treated in the same district and treatment center.

However, the absence of highly related *M. tuberculosis* between the 2 districts (Madurai and Tiruvallur) does not exclude the possibility of interdistrict transmission. We fully agree that our sample size was extremely small relative to the number of isolates circulating in either studied region and that a larger sample size could

point to cases of interdistrict transmission. In fact, we and others have used similar whole-genome sequences and SNP thresholds to show that strains of *M. tuberculosis* can be carried across great distance, both within countries and even between different continents [1–8]. We also agree that transmission chains are exceedingly difficult to establish across any distance without detailed epidemiological data, which we did not have for this study, and we, therefore, did not attempt to model specific transmission links. We regret that we did not emphasize the limitations of our data for inferring interdistrict transmission because we agree that misinterpretation of our results could have unintended consequences for tuberculosis control efforts. However, our results suggest that attention to local infection control is in order.

Notes

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Clinical Infectious Diseases® 2018;66(1):160-1

DOI: 10.1093/cid/cix751