Published in final edited form as:

Int J Tuberc Lung Dis. 2016 March ; 20(3): 423–424. doi:10.5588/ijtld.15.1024.

The Impact of Mixed Infections on the Interpretation of Molecular Epidemiology Studies of Tuberculosis

Sanghyuk S. Shin, PhD,

Department of Epidemiology, Fielding School of Public Health, University of California Los Angeles; Los Angeles, CA, USA

Chawangwa Modongo, MD, and

Botswana-Upenn Partnership; Gaborone, Botswana

Nicola M. Zetola, MD, MPH

Department of Radiation Oncology, University of Pennsylvania, Philadelphia; Pennsylvania, USA

Keywords

nosocomial transmission; MDR TB; heteroresistance; infection control

We read with great interest Crudu *et al.*'s article on nosocomial transmission of multidrug-resistant tuberculosis (MDR TB) in Moldova.¹ While we agree with the authors' overall conclusion that nosocomial transmission of MDR TB is likely to be common in Moldova and requires urgent attention, we believe that the authors could be underestimating the impact of mixed-strain *M. tuberculosis* (MTB) infections and community-based MTB transmission in their study.

Tuberculosis patients can have concomitant infection with non-MDR and MDR TB strains at diagnosis.² If multidrug resistance is not detected and first-line anti-TB drugs are initiated, selective amplification of the MDR TB strain could occur, resulting in the "unmasking" of MDR TB during the course of treatment.³ While we agree with Crudu *et al.* that the epidemiological significance of such occurrence is currently unknown, mixed infections can be highly prevalent in certain populations and, therefore, could significantly impact the interpretation of molecular epidemiology findings such as theirs.²

Crudu *et al.* argues that development of MDR TB during treatment is not likely to be due to mixed infections because of the high rate of clustering of the URAL 163-15 genotype among follow-up samples.¹ While a hospital outbreak of a multidrug-resistant URAL 163-15 strain could have led to the study findings, the evidence provided by Crudu *et al.* is insufficient for drawing that conclusion. In hyperendemic settings, DNA fingerprinting using MIRU-VNTR and spoligotyping alone could misclassify recent MTB transmission events versus reactivation of latent infections caused by prevalent strains in the community.⁴ It is, therefore, possible that the URAL 163-15 genotype comprises multiple strains prevalent in

the community.⁴ High transmission rates of the multidrug-resistant URAL 163-15 genotype in the community could have led to high prevalence of mixed-strain infections involving the URAL 163-15 genotype, which were identified at the hospital. In addition, the URAL 163-15 genotype was found in three of the four hospitals in Crudu *et al.*'s study, which argues against a single ongoing clonal transmission chain as the primary cause of URAL 163-15 MDR TB incidence during follow-up.¹ Furthermore, a prior study from the same group found rapid development of MDR TB (less than 3 months of treatment) for half of the patients, which seems more consistent with “unmasking” of previously undetected MDR TB strains than rapid progression to active disease after nosocomial transmission of MDR TB.⁵ It is worth noting that nosocomial MDR TB transmission among patients with tuberculosis could lead to mixed infections that could progress to active disease or reactivate at a later time. Hence, nosocomial MDR TB transmission might be a significant driver of mixed infections. Unfortunately, Crudu *et al.* do not report sufficient clinical and epidemiological data (e.g. overlapping hospital stays between patients, time to MDR TB development, prior history of TB treatment and hospitalization) to shed light on these alternate explanations.

Molecular epidemiology studies such as Crudu *et al.*'s provide invaluable insights into tuberculosis transmission. However, improved understanding of mixed infections is needed to increase our ability to interpret and draw robust conclusions from molecular epidemiological data.

Acknowledgments

This work was supported in part by National Institutes of Health [grant numbers K01AI118559, R21AI120838, R01AI097045, MH58107, 5P30AI028697, UL1TR000124]. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

References

1. Crudu V, Merker M, Lange C, et al. Nosocomial transmission of multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis.* 2015; 19(12):1520–1523.10.5588/ijtld.15.0327 [PubMed: 26614195]
2. Cohen T, van Helden PD, Wilson D, et al. Mixed-Strain Mycobacterium tuberculosis Infections and the Implications for Tuberculosis Treatment and Control. *Clin Microbiol Rev.* 2012; 25(4):708–719.10.1128/CMR.00021-12 [PubMed: 23034327]
3. van Rie A, Victor TC, Richardson M, et al. Reinfection and Mixed Infection Cause Changing Mycobacterium tuberculosis Drug-Resistance Patterns. *Am J Respir Crit Care Med.* 2005; 172(5): 636–642.10.1164/rccm.200503-449OC [PubMed: 15947286]
4. Lee RS, Radomski N, Proulx J-F, et al. Reemergence and Amplification of Tuberculosis in the Canadian Arctic. *J Infect Dis.* 2015; 211(12):1905–1914.10.1093/infdis/jiv011 [PubMed: 25576599]
5. Jenkins HE, Crudu V, Soltan V, Ciobanu A, Damente L, Cohen T. High risk and rapid appearance of multidrug resistance during tuberculosis treatment in Moldova. *Eur Respir J.* 2014; 43(4):1132–1141.10.1183/09031936.00203613 [PubMed: 24558181]