‘Resistance’ to tuberculous immunoreactivity conversion: considering the evidence for its inclusion in *Mycobacterium tuberculosis* annual risk of infection estimates

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We thank Dowdy and Behr for their recent article,[1] and agree with their conclusion that annual risks of *Mycobacterium tuberculosis* infection (ARTI) in high-incidence settings are underestimated. The three reasons provided are omission of increased infection risks in adolescence and young adulthood, reversion of TB immunoreactivity and resistance to conversion. While there is evidence to support the first two reasons,[2-4] we believe the assumption that 20% are ‘resistant to…conversion’ despite ‘intense exposure’ requires scrutiny.

First, the source of the 20% figure is unclear. The primary result of the cited Uganda study of household contacts of pulmonary culture-positive TB, found that only 8.3% (198/2,381) were ‘persistently negative’ for 1-2 years post-contact.[5] A later follow-up study of all ‘persistently negative’ contacts, ≥15 years of age in 2014, labelled those who ‘remained’ negative as ‘resisters’, and although ‘resisters’ made up >20% in this study, only a selection of ‘matched’ immunoreactive participants were included, so ‘resisters’ were overrepresented.[6] Second, to believe any study’s claim that ‘resisters’ exist, the proxy used to determine they have been ‘highly exposed’ must be beyond reproach. However, the only proxy used by the Uganda study was past household contact, with no consideration of exposure or source case infectiousness (e.g. smear-positivity). While participant exposure was assessed using a ‘risk score’ (based on ten questions regarding contact), none were resultantly excluded. Finally, and crucially, suggesting 20% could be resistant to conversion, is inconsistent with studies demonstrating reactivity can reach 98-100% in populations that are, evidently, highly-exposed.[7,8] Given the contribution of Dowdy and Behr’s 20% ‘resister’ assumption to their final quantification of underestimation, their estimates may need revising.

Another issue is the authors’ emphasis on the identification and treatment of ‘recently infected’ individuals, in response to higher ARTI estimates. Recent infection cannot be diagnosed, and evidence presented by the authors themselves, including high community transmission, low long-term progression risks and reversion, do not support the efficiency of this approach. We would argue that rather than individually treating infection, the priority should be to reduce population infection risk, by discovering and treating infectious and soon-to-be infectious individuals. Twentieth century achievements in high-income settings[9] and recent evidence[10] support the effectiveness of this approach.

We agree with the authors that it is important to revisit assumptions regarding ARTI, the evidence for reversion alone supports this. However, as we do, we should carefully consider all existing evidence and link recommendations to what could and has worked.

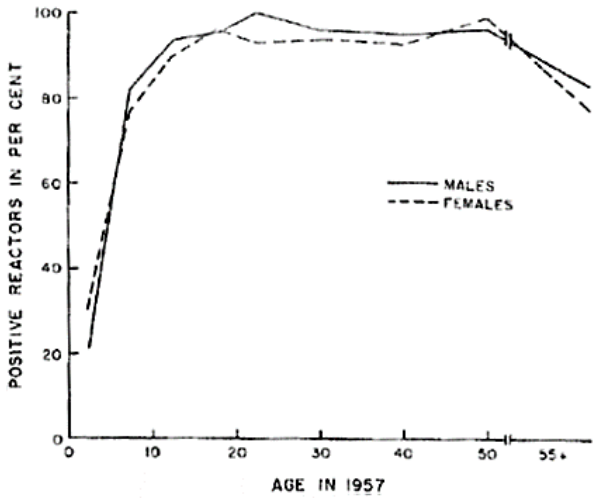

Figure 1 TST reactivity in an Inuit population of Alaska, 1957, by sex and age (≥5mm to 5 TU PPD).[7] Comstock GW, Ferebee SH, Hammes LM/1967/A controlled trial of community-wide isoniazid prophylaxis in Alaska/ The American Review of Respiratory Disease/95(6)/935-43/Figure 2, page 93.

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