

Elsevier Editorial System(tm) for The Lancet
Manuscript Draft

Manuscript Number:

Title: Response to Lange C, Dheda K, Chesov D, Mandalakas AM, Udwadia Z, Horsburgh CR. Management of drug-resistant tuberculosis. The Lancet. 2019 Sep 14;394(10202):953-66.

Article Type: Correspondence

Keywords: Management of drug-resistant contacts
MDR TB
household contacts
Preventive therapy
surveillance

Corresponding Author: Dr. Katherine M Gaskell, MBChB MSc

Corresponding Author's Institution: LSHTM

First Author: Katherine M Gaskell, MBChB MSc

Order of Authors: Katherine M Gaskell, MBChB MSc; David A Moore, MBChB MD

Manuscript Region of Origin: UNITED KINGDOM

Response to Lange C, Dheda K, Chesov D, Mandalakas AM, Udwadia Z, Horsburgh CR. Management of drug-resistant tuberculosis. *The Lancet*. 2019 Sep 14;394(10202):953–66.

KM Gaskell & DAJ Moore

Whilst pleased to read ‘Management of drug-resistant tuberculosis’ by Lange et al(1) we were disappointed that the section on management of multidrug-resistant tuberculosis contacts perpetuates unsubstantiated platitudes, confusing clinicians, and misrepresenting guidance.

Current evidence for preventive therapy (PT) effectiveness is extremely thin with three RCTs awaited. The cited ‘evidence from 2017’ describes old data for which the abstract reads ‘Few studies met inclusion criteria, therefore results should be cautiously interpreted’ and in which 3/5 studies included showed no effect at all(4).

WHO recommend ‘In selected high-risk household contacts of patients with MDRTB, PT may be considered based on individualized risk assessment and a sound clinical justification’ with ‘informed consent’(2). The article neglects to mention that core management remains ‘strict clinical observation and close monitoring ... for at least 2 years’ (2). The authors state proof of infection is not required to initiate PT. The 2018 WHO guideline explicitly states, ‘Confirmation of infection with LTBI tests is required’.

Drug susceptibility index-contact concordance was seen in only 76.6% of pairs (278/363), 11 of the 16 studies these data come from include 10 pairs (3). Is this high enough to guide PT?

Long-term paediatric exposure to levofloxacin is not definitively safe. In 2018 the EMA and FDA warned that all fluoroquinolone use should be suspended or used cautiously in life threatening conditions(5). Does this apply to PT where most children do not need treatment?

Efforts should be targeted to deliver interventions supported by a strong evidence-base, whilst continuing to gather complementary evidence.

References

1. Lange C, Dheda K, Chesov D, Mandalakas AM, Udwadia Z, Horsburgh CR. Management of drug-resistant tuberculosis. *The Lancet*. 2019 Sep 14;394(10202):953–66.
2. WHO. Latent TB infection: Updates and consolidated guidelines for programmatic management [Internet]. World Health Organisation. Geneva, Switzerland; 2018. Report No.: ISBN 978-92-4-155023-9. Available from: <https://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/>
3. Shah NS, Yuen CM, Heo M, Tolman AW, Becerra MC. Yield of Contact Investigations in Households of Patients With Drug-Resistant Tuberculosis: Systematic Review and Meta-Analysis. *Clin Infect Dis*. 2014 Feb 1;58:381–91.

4. Marks SM, Mase SR, Morris SB. Systematic Review, Meta-analysis, and Cost-effectiveness of Treatment of Latent Tuberculosis to Reduce Progression to Multidrug-Resistant Tuberculosis. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2017 Jun 15;64(12):1670–7.
5. Anonymous. Quinolone- and fluoroquinolone-containing medicinal products [Internet]. European Medicines Agency. 2018 [cited 2019 Sep 19]. Available from: <https://www.ema.europa.eu/en/medicines/human/referrals/quinolone-fluoroquinolone-containing-medicinal-products>