The Journal of Infectious Diseases

LETTER TO THE EDITOR

Re: Estimating the Early Transmission Inhibition of New Treatment Regimens for Drug-Resistant Tuberculosis

Tom A. Yates [1,2,*], David A. Barr [3]

[1]UCL Institute of Health Informatics, University College London, UK; [2]Division of Infection and Immunity, University College London, UK; [3]Department of Infectious Diseases, Queen Elizabeth University Hospital, Glasgow, UK

We read with interest this paper by the late Anton Stoltz and colleagues[1] and think the method described could generate useful information for TB programmes. However, we think the precision of these estimates of infectiousness has been overstated; that, given the limits of the current evidence around duration of infectiousness after initiation of effective treatment, we favour an approach to deisolation that prioritises an overall risk assessment; and that, before such experiments are repeated, we need better methods for ensuring the safety of research participants.

The purpose of the study[1] was to estimate differences in infectiousness between people with tuberculosis, not differences in susceptibility to *Mycobacterium tuberculosis* between guinea pigs. As it was not possible to ascertain which person infected which guinea pig, this was a comparison between 1 vs 1 cohort rather than a comparison between 5 vs 9 people. Either way, $p<0.0001$ is implausible.

Taking multiple, presumably correlated, measures of the infectiousness of each cohort, by having 90 guinea pigs per cage, can reduce variance due to measurement error but cannot reduce variance due to between cohort differences in infectiousness. Infectiousness among people with

t.yates@ucl.ac.uk

DOI: 10.1093/infdis/jiaf655

TB is known to be highly heterogenous.[2] To give an illustrative example, a trial in which two groups of 90 people each had their blood pressure measured once would yield more information than a trial in which one individual from each group had their blood pressure measured 90 times.

The authors present two comparisons against baseline, rather than a between cohort comparison. If - as it appears - the intention is to contrast the ability of regimens to reduce infectiousness, the authors will again have overstated the precision of their estimates.[3]

Given the limitations of current data on duration of infectiousness after initiation of effective treatment, from both this study[1] and from previous animal experiments[4], we have concerns that they were given such weight in recent guidelines.[5] In our view, unless better data emerge, recommendations regards deisolation should emphasise overall risk assessments rather than time since initiation of effective therapy alone. Returning home to live with people with whom you had been living for months prior to starting effective treatment is not the same as being moved from a side room into a bay on a transplant ward.

Finally, it is critical that people volunteering as research participants are protected from avoidable harm. Whilst taking measures of infectiousness prior to initiating treatment can help address between individual variation in infectiousness, e.g. by adjusting for infectiousness during the baseline period, treatment should not be intentionally delayed unless we can safely identify a group of patients who will not be harmed - or be seen to be harmed - as a result. In this study, a young man with a CD4 count of 16 cells/ul and bilateral cavitary disease never started treatment and *'was removed from study after 2.76 patient-days and did not return due to acute tuberculosis-related illness, resulting in death.'*[1] We cannot know whether this man with advanced HIV and extensive untreated XDR-TB would have died irrespective of treatment. However, given 'acutely unwell' patients were not eligible to participate in the study, it seems likely that he deteriorated while therapy was being withheld.

It is unclear from this manuscript what action was taken to prevent people with MDR TB acquiring XDR TB whilst participating in the study. Within healthcare facility transmission of strains harbouring additional drug resistance is well described.[6] This risk is highest prior to initiation of effective treatment. Prior publications indicate that the Airborne Infections Research facility housed patients in two-bedded rooms with shared communal spaces.[7]

Funding sources: TAY is an NIHR Clinical Lecturer, funded by the National Institute for Health and Care Research. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health and Social Care.

Conflict of interest: TAY has worked on studies that received material support from Pasante, GSK, and Sanofi, and was Associate PI on the RECOVERY trial. He did not benefit financially from these relationships. He sits on the TB Prevention Taskforce at TB Think Tank. He is on the steering committee of the International Tuberculosis Host Genetics Consortium. DAB declares no relevant conflicts of interest.

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