access to care, screening strategies, continuum of care, preventive measures for high-risk populations, improving liver health literacy on the prevention of new infections and reinfections, liver disease management, outcome evaluation of policy and interventions, and innovation, research, and development.

I strongly believe that the Taiwanese experience of the control of hepatitis C can be shared by other countries where infection is equally prevalent and the socioeconomic status is similar.

Ding-Shinn Chen
chends@ntu.edu.tw

Department of Internal Medicine, National Taiwan University College of Medicine, Taipei City, Taiwan; Hepatitis Research Center, National Taiwan University Hospital, Taipei City, Taiwan; Genomics Research Center, Academia Sinica, Taipei City, Taiwan

1 Burki T. Eliminating hepatitis C. *Lancet Infect Dis* 2019; **19:** 246–47.
2 WHO. Global Hepatitis Report 2017. Geneva: Word Health Organization, 2017. http://apps.who.int/iris/bitstream/handle/10665/255017/1/WHO-HIV-2017.06-eng.pdf (accessed March 21, 2019).
3 Chen DS. Fighting against viral hepatitis: lessons from Taiwan. *Hepatology* 2011; **54:** 381–92.
4 Alter H. To have B or not to have B: vaccine and the potential eradication of hepatitis B. *J Hepatol* 2012; **57:** 715–17.
5 Chiang CJ, Yang YW, Chen JD, et al. Significant reduction in end-stage liver diseases burden through the national viral hepatitis therapy program in Taiwan. *Hepatology* 2015; **61:** 1154–62.
6 Taiwan Hepatitis C Policy Guideline 2018–2025. Taipei City: Ministry of Health and Welfare, Executive Yuan ROC (Taiwan), 2019.

Ceftriaxone-resistant *Salmonella* Typhi in a traveller returning from a mass gathering in Iraq

The large outbreak of ceftriaxone-resistant *Salmonella enterica* serovar Typhi in Hyderabad, Pakistan, reported by Farah Naz Qamar and colleagues[1] highlights the substantial public health risk associated with a contaminated water supply in the absence of adequate vaccination. Public Health England has increased surveillance on returning travellers from Pakistan presenting with enteric fever, using whole-genome sequencing to type the strains from confirmed cases. Since the first imported case associated with this outbreak strain reported in September, 2017, we have seen 13 further cases from Pakistan.[2]

A 45-year-old resident of London, UK, who attended the Arba'een pilgrimage in Iraq in October, 2018, presented in January, 2019, with short diarrhoeal illness followed by daily fevers, night sweats, and weight loss. Further investigations identified *S* Typhi in blood cultures. The strain was phenotypically an extended-spectrum β lactamase (ESBL) producer and resistant to quinolones. Whole-genome sequencing confirmed presence of the resistance genes $bla_{CTX\text{-}M\text{-}15}$, *aac(6′)-Iy*, and the 83:S-F mutation in the *gyrA* quinolone resistance-determining region. The individual was successfully treated with oral azithromycin. Phylogenetic analysis showed that the strain was indistinguishable from another imported case of *S* Typhi, in which the individual presented in January, 2019, after a trip to Al Diwaniyah, Iraq. The second individual was successfully treated with oral co-trimoxazole.

When compared with the Public Health England database of *S* Typhi genomes collected through routine surveillance of English cases (n=1250 as of Feb 1, 2019, Bioproject, PRJNA248792), The two strains cluster within the H58 haplotype of which the recent outbreak in Pakistan is a member.[3] The phylogeny reveals the Iraqi isolates are more closely related to an ESBL-negative strain recovered from an imported case from India in 2017. This finding suggests introduction of the Indian strain into Iraq and probable acquisition of the ESBL genotype in situ (appendix). Two Iraqi strains from 2019 are distinct from a previously described ESBL-producing, quinolone and azithromycin-resistant strain from Iraq.[4] Although these ESBL strains are less resistant than the extensively drug-resistant strain from Pakistan, they highlight the escalating problem of multidrug resistance in Asia.

Mass gatherings including pilgrimages have long been a public health concern.[5] In 2018, over 15 million pilgrims from across the globe took part in the Arba'een pilgrimage, many travelling overland from India and Pakistan. Improved public health measures, including better sanitation and vaccination are essential for preventing ongoing transmission.

We declare no competing interests.

**Gauri Godbole, Naina McCann, Stephen Morris Jones, Timothy J Dallman, Michael Brown*
gauri.godbole@phe.gov.uk

Infection Division, Hospital for Tropical Diseases, London, UK (GG, SMJ, MB); Clinical Research Department, London School of Hygiene and Tropical Medicine, London, UK (GG, NM, SMJ, MB); and Gastrointestinal Bacteria Reference Unit, National Infection Service, Public Health England, London NW9 5EQ, UK (GG, TJD)

1 Qamar FN, Yousafzai MT, Khalid M, et al. Outbreak investigation of ceftriaxone-resistant *Salmonella enterica* serotype Typhi and its risk factors among the general population in Hyderabad, Pakistan: a matched case-control study. *Lancet Infect Dis* 2018; **18:** 1368–76.
2 Godbole GS, Day MR, Murthy S, Chattaway MA, Nair S. First report of CTX-M-15 *Salmonella* Typhi from England. *Clin Infect Dis* 2018; **66:** 1976–77.
3 Klemm EJ, Shakoor S, Page AJ, et al. Emergence of an extensively drug-resistant *Salmonella enterica* serovar Typhi clone harboring a promiscuous plasmid encoding resistance to fluoroquinolones and third-generation cephalosporins. *mBio* 2018; **9**.
4 Pfeifer Y, Matten J, Rabsch W. *Salmonella enterica* serovar Typhi with CTX-M beta-lactamase, Germany. *Emerg Infect Dis* 2009; **15:** 1533–35.
5 Gautret P, Steffen R. Communicable diseases as health risks at mass gatherings other than Hajj: what is the evidence? *Int J Infect Dis* 2016; **47:** 46–52.

Advanced immunodiagnostic tests for paediatric tuberculosis

See **Online** for appendix

We read with interest the Article by Hilary Whitworth and colleagues,[1] comparing the accuracy of commercially available interferon-γ release assays (IGRAs) with second-generation IGRAs incorporating novel antigens.[1]

This large multicentre study is a valuable contribution towards efforts to improve the diagnostic evaluation of suspected tuberculosis disease. The authors reported that second-generation IGRAs (incorporating the additional antigens Rv3615c or Rv3879c) had higher sensitivity than T-SPOT.*TB* assays. They concluded that in low-incidence settings these tests "might have sufficiently high sensitivity...to facilitate prompt rule-out of tuberculosis".

As highlighted by the authors, this study did not include children, and therefore this conclusion might not necessarily apply to this age group. Substantial differences exist between the immune response to *Mycobacterium tuberculosis* in children and adults, and results from studies in adults cannot simply be extrapolated to children. These differences could explain why a study evaluating novel IGRAs in children younger than 5 years in India reported that enhanced enzyme-linked immunospot assays, using Rv3615c-encoded and Rv3879c-encoded antigens, did not improve the diagnostic performance of the standard enzyme-linked immunospot assay (which makes use of ESAT-6 and CFP-10 antigens).[2]

Furthermore, the study used the QuantiFERON-TB (QFT) Gold in-Tube assay that has since been replaced by the QFT-Plus assay, which was developed to improve sensitivity for detecting active tuberculosis by differentially stimulating CD4 and CD8 T cells. However, a 2019 study in children in a high-tuberculosis burden setting found no difference in performance between these two assays,[3] and similar results have been reported in adults.[4]

Several promising new immunological biomarkers (other than interferon-γ) that might enable the development of improved tuberculosis immunodiagnostic tests for children, have been identified in the past few years.[5] These biomarkers include various mycobacteria-specific cytokine responses that have better performance characteristics than interferon-γ and might simultaneously facilitate the distinction between latent and active tuberculosis.[6] A test with the ability to make this distinction would be a major advance in facilitating clinical management. In addition, high rates of indeterminate (ie, uninterpretable) assay results in young children remain a major issue. As current IGRAs do not have sufficiently high sensitivity to exclude tuberculosis disease in children, and microbiological diagnosis in this age group is difficult, developing a reliable triage test remains a high priority. In the search for next-generation immunodiagnostic tests for tuberculosis that perform more robustly across all age groups, it is therefore vital that children are included in future early-phase studies.

MT has received assays for research at reduced pricing from Cellestis, and support for conference attendance from Cepheid and GlaxoSmithKline. The other authors have nothing to disclose.

Paola Villanueva, Eva Sudbury, Rinn Song, Marc Tebruegge, Nigel Curtis
paola.villanueva@rch.org.au

Department of Paediatrics, University of Melbourne, Parkville, VIC 3052, Australia (PV, ES, MT, NC); Infectious Diseases Research Group, Murdoch Children's Research Institute, Parkville, Australia (NC); Infectious Diseases Unit, The Royal Children's Hospital Melbourne, Parkville, Australia (NC); Department of Paediatric Infectious Diseases and Immunology, Evelina London Children's Hospital, Guy's and St Thomas' National Health Service Foundation Trust, London, UK (MT); Department of Infection, Immunity, and Inflammation, University College London Great Ormond Street Institute of Child Health, University College London, London, UK (MT); Oxford Vaccine Group, Department of Paediatrics, University of Oxford and the National Institute for Health Research Oxford Biomedical Research Centre, Oxford, UK (RS); Division of Infectious Diseases, Boston Children's Hospital, Boston, MA, USA (RS); and Department of Pediatrics, Harvard Medical School, Boston, MA, USA (RS)

1 Whitworth HS, Badhan A, Boakye AA, et al. Clinical utility of existing and second-generation interferon-γ release assays for diagnostic evaluation of tuberculosis: an observational cohort study. *Lancet Infect Dis* 2019; **19:** 193–202.

2 Shaikh N, Gupte A, Dharmshale S, et al. Novel interferon-gamma assays for diagnosing tuberculosis in young children in India. *Int J Tuberc Lung Dis* 2017; **21:** 412–19.

3 Kay AW, DiNardo AR, Dlamini Q, et al. Evaluation of the QuantiFERON-Tuberculosis Gold Plus Assay in children with tuberculosis disease or following household exposure to tuberculosis. *Am J Trop Med Hyg* 2019; **100:** 540–43.

4 Petruccioli E, Vanini V, Chiacchio T, et al. Analytical evaluation of QuantiFERONPlus and QuantiFERON-Gold In-tube assays in subjects with or without tuberculosis. *Tuberculosis* 2017; **106:** 38–43.

5 Togun TO, MacLean E, Kampmann B, Pai M. Biomarkers for diagnosis of childhood tuberculosis: a systematic review. *PLoS One* 2018; **13:** e0204029.

6 Tebruegge M, Dutta B, Donath S, et al. Mycobacteria-specific cytokine responses detect tuberculosis infection and distinguish latent from active tuberculosis. *Am J Respir Crit Care Med* 2015; **192:** 485–99.

Linezolid for drug-susceptible tuberculosis

We appreciate the interest in and comments on our trial by Hüseyin Bilgin and colleagues[1] and Saiam Ahmed and colleagues,[2] which was done to assess the substitution of ethambutol with linezolid during the intensive phase of treatment of pulmonary tuberculosis.[3] Several concerns were raised regarding our analysis of the results.

The first concern was our exclusion of 27 participants from the modified intention-to-treat analysis. As illustrated in figure 1 of the Article,[3] 18 participants were excluded because they did not take the trial medication at all, and nine were excluded because of protocol violations, including absence of information regarding HIV antibody concentration or urine human chorionic gonadotropin concentration and enrolment despite the presence of leucopenia ($<3{\cdot}0 \times 10^3/\mu L$). Another concern was our inclusion of patients with a positive Xpert MTB/RIF assay but negative sputum culture at baseline for analysis of the primary outcome. In fact, our trial involved patients with pulmonary tuberculosis with a positive Xpert MTB/RIF assay regardless of the culture status at baseline. We assumed a 10% culture failure rate in our calculation of the sample size, but