

test as a unifying indicator for an acceptable safety profile of a pre-vaccination screening strategy. A high PPV ensures that a high proportion of individuals who test positive are not truly dengue-naïve. The required sensitivity to achieve a high PPV will depend on the seroprevalence in the population on which the test is done and on the test specificity. Charts can be used to determine—for tests with different specificities and in different seroprevalence situations—the minimum sensitivity needed to ensure that, for example, less than 10% of test positives are actually dengue-naïve (appendix).

See Online for appendix

We think that an additional reasonable criterion for the selection of a diagnostic test is that individuals who are deemed ineligible for vaccination as a result of the test should be at a lower risk of hospitalised or severe dengue disease if they are left unvaccinated than if they are vaccinated.

High sensitivity ensures a low proportion of misclassifications among those who test negative, particularly in high-prevalence settings. In the Dengvaxia trials,⁴ the 5-year cumulative incidence of dengue hospitalisation in vaccinees aged 9 years or older was reduced by 1.50 percentage points relative to the control group for seropositive participants (1.88% [95% CI 1.54–2.31] in seropositive controls vs 0.38% [0.26–0.54] in seropositive vaccinees), and increased by 0.48 percentage points relative to the control group for seronegative participants (1.09% [0.53–2.26] in seronegative controls vs 1.57% [1.13–2.19] in seronegative vaccinees). Hence, if more than 25% of individuals who test negative in a pre-vaccination screening strategy are misclassified (ie, are not dengue-naïve) then, on average, the individuals with a test-negative result would benefit from vaccination (appendix). In other words, a meaningful rapid diagnostic test will need a negative predictive value of at least 75%. This implies the need for high test sensitivity in

highly endemic settings because of the few true seronegative individuals (appendix).

As manufacturers develop rapid diagnostic dengue tests to achieve an optimal balance between sensitivity and specificity they will need to prioritise specificity to ensure the safety of vaccinees. However, we argue that it is important that test sensitivity is of the order of 90% (appendix) or more as otherwise those who test negative might be, on average, at higher risk of hospitalised or severe dengue than they would be if they were vaccinated.

SF is supported by a Sir Henry Dale Fellowship jointly funded by the Wellcome Trust and the Royal Society (Grant number 208812/Z/17/Z). PGS is partly supported by a grant jointly funded by the UK Medical Research Council (MRC) and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement, is part of the EDCTP2 programme supported by the European Union, and is a member of the Independent Data Monitoring Committee for trials of the Sanofi-Pasteur dengue vaccine (Dengvaxia). Sanofi Pasteur sponsored, in part, a meeting on diagnostic tests for dengue organised by the Global Dengue & Aedes Transmitted Diseases Consortium (GDAC) at which some of the ideas for this work were developed. GDAC covered travel and accommodation costs.

*Stefan Flasche, Peter G Smith
stefan.flasche@lshtm.ac.uk

Vaccine Centre, London School of Hygiene & Tropical Medicine, London, UK (SF); and MRC Tropical Epidemiology Group, London School of Hygiene & Tropical Medicine, London, UK (PGS)

- 1 Capeding MR, Tran NH, Hadinegoro SRS, et al. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial. *Lancet* 2014; **384**: 1358–65.
- 2 Villar L, Dayan GH, Arredondo-García JL, et al. Efficacy of a tetravalent dengue vaccine in children in Latin America. *N Engl J Med* 2015; **372**: 113–23.
- 3 Hadinegoro SR, Arredondo-García JL, Capeding MR, et al. Efficacy and long-term safety of a dengue vaccine in regions of endemic disease. *N Engl J Med* 2015; **373**: 1195–206.
- 4 Sridhar S, Luedtke A, Langevin E, et al. Effect of dengue serostatus on dengue vaccine safety and efficacy. *N Engl J Med* 2018; **379**: 327–40.
- 5 Ferguson NM, Rodríguez-Barraquer I, Dorigatti I, Mier-y-Teran-Romero L, Laydon DJ, Cummings DAT. Benefits and risks of the Sanofi-Pasteur Dengue vaccine: modeling optimal deployment. *Science* 2016; **353**: 1033–36.
- 6 Wilder-Smith A, Hombach J, Ferguson N, et al. Deliberations of the Strategic Advisory Group of Experts on Immunization on the use of CYD-TDV dengue vaccine. *Lancet Infect Dis* 2018; **19**: e31–38.

- 7 Rodríguez-Barraquer I, Salje H, Cummings DA. Dengue pre-vaccination screening and positive predictive values. *Lancet Infect Dis* 2019; **19**: 132–34.

Taiwan commits to eliminating hepatitis C in 2025

I read with great interest Talha Burki's report¹ "Eliminating hepatitis C", in which he described situations in Egypt, Pakistan, Mongolia, China, Australia, and Rwanda. He reiterated that drugs alone are not enough for elimination, and that countermeasures, such as screening and accessibility of harm reduction services, are also needed. Elimination of chronic viral hepatitis is an ambitious task that needs national and international efforts, as was indicated by WHO.²

Because of its heavy disease burden, Taiwan has been fighting hepatitis B since the late 1970s,³ with successful results.^{4,5} Despite the fact that Taiwan is not a member of WHO and, for political reasons, WHO never helps Taiwan in the control of infectious diseases, Taiwan still took serious actions to follow the WHO guidelines on control of viral hepatitis.³ When the World Health Assembly adopted the Global Health Sector Strategy on viral hepatitis in 2016, it immediately caught the attention of the Taiwanese people and government, and efforts towards the elimination of chronic hepatitis C were seriously considered. After 2 years, the efforts from experts, public health officers, legislators, and the government leaders have culminated in a consensus of reaching the WHO goals in 2025—ie, 5 years earlier than the 2030 deadline set by WHO. Accordingly, the Taiwan Hepatitis C Policy Guideline 2018–2025⁶ was approved and published at the beginning of 2019. The government will provide US\$1.7 billion in the coming 8 years for the control of hepatitis C. Actions will include lowering the barriers of

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: World 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 colleagues¹ 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-M-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

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



See Online for appendix