

duration of viraemia in humans) are similar to dengue, which has spread around the world aided by human travel. By contrast with dengue, most yellow fever infections in the past occurred when humans encroached the sylvatic cycle outside urban areas, and were not associated with a high risk of dispersal through air travel. However, major urban epidemics have occurred in both Africa and tropical America in the past decade. In parallel, we have seen an unprecedented growth in air travel intensity between Africa or Latin America directly to Asia.⁴ These factors combined increase the probability that travellers infected with yellow fever will introduce the virus to Asia at a time when conditions are aligned—ie, the presence of *Aedes* spp mosquitoes in an urban area during a suitable seasonal window. Application of the International Health Regulations (IHR), which require mandatory yellow fever vaccination for all travellers from yellow fever-endemic areas to permissive non-endemic areas, should prevent such introductions. However, hundreds of thousands of people have circumvented the IHR, as evidenced during the yellow fever outbreak in Angola,⁵ which should serve to highlight the need for action.

Is Asia prepared for a yellow fever epidemic? Many countries strengthened their pandemic preparedness capabilities in the wake of the 2009 influenza pandemic, guided by WHO. Country capacity building under the IHR, supported by the Joint External Evaluation, has increased preparedness and response capabilities to a range of public health threats. However, whether preparedness for epidemic vector-borne diseases such as yellow fever has been increased is uncertain.

Among the key issues that need to be addressed are the strengthening of laboratory-based surveillance capable of detecting imported yellow fever, effective vector control programmes, and plans to scale-up mass-vaccination

programmes, including the capacity to rapidly import vaccines, training of health-care workers to conduct such programmes, and clinical management of severe yellow fever disease.

We advocate for a call to action to urgently identify gaps and develop preparedness plans in all Asia-Pacific countries that are at risk of yellow fever virus introduction.

We declare no competing interests.

*Annelies Wilder-Smith, Vernon Lee, Duane J Gubler
anneliesws@gmail.com

Department of Disease Control, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK (AW-S); Heidelberg Institute of Global Health, University of Heidelberg, Heidelberg 69120, Germany (AW-S); Ministry of Health, Singapore (VL); and Global Dengue and Aedes-transmitted Diseases Consortium, Seoul, Korea (DJG)

- 1 Wilder-Smith A, Gubler DJ, Weaver SC, Monath TP, Heymann DL, Scott TW. Epidemic arboviral diseases: priorities for research and public health. *Lancet Infect Dis* 2017; **17**: e101–06.
- 2 Gubler DJ. Pandemic yellow fever: a potential threat to global health via travelers. *J Travel Med* 2018; **25**: tay097.
- 3 Wilder-Smith A, Leong WY. Importation of yellow fever into China: assessing travel patterns. *J Travel Med* 2017; **24**: tax008.
- 4 Glaesser D, Kester J, Paulose H, Alizadeh A, Valentin B. Global travel patterns: an overview. *J Travel Med* 2017; **24**: tax007.
- 5 Brent SE, Watts A, Cetron M, et al. Identifying global vulnerabilities to urban transmission of yellow fever virus. *Bull World Health Organ* 2018; **96**: 343–354.
- 6 Wilder-Smith A, Massad E. Estimating the number of unvaccinated Chinese workers against yellow fever in Angola. *BMC Infect Dis* 2018; **18**: 185.

Extensively drug-resistant typhoid fever in Pakistan

We read the Article by Farah Qamar and colleagues¹ about the outbreak of ceftriaxone-resistant *Salmonella enterica* serotype Typhi in Hyderabad, Pakistan, with great interest. *S Typhi* was observed as being twice as prevalent in the Qasimabad subdistrict of Hyderabad City (attack rate 15 per 1000 residents) as in the Latifabad subdistrict (seven per 1000 residents), two areas that differ

socioeconomically. In most cases, children younger than 15 years were affected.¹ The main reason for the outbreak was the mixing of drinking water and sewage in two subdistricts.¹

Up to 21 million people contract typhoid each year, often by consuming food or water contaminated by faeces, of whom up to 161 000 die.^{2,3} 3–6 cases of typhoid per 100 000 persons-years are estimated to occur in south Asia, which includes Pakistan.⁴ Among the 16 countries in Asia where typhoid is prevalent, inhabitants of the Punjab and Sindh provinces of Pakistan were at the highest risk of developing typhoid.⁴

Extensively drug-resistant typhoid fever is spreading in Pakistan, raising fears of antibiotic failure at global level.⁵ Experts believe that Pakistan's abysmal sewage and water systems coupled with low vaccination rates and overpopulated city dwellings are the root causes of the spread of extensively drug-resistant typhoid.^{3,6} In a 10-month period between 2016 and 2017, health authorities in Pakistan detected more than 800 cases of extensively drug-resistant typhoid in the city of Hyderabad alone.^{5,7} A new typhoid conjugate vaccine, Typbar-TCV, recently pre-qualified by the WHO, has been used by the public health officials in the province of Sindh to vaccinate 250 000 children in Hyderabad.² However, the local population is reluctant to use vaccination as rumours are circulating that vaccination is a foreign plot to poison Pakistan's children, and vaccinators face refusals almost every day.³

Extensively drug-resistant typhoid has the potential to spread globally by replacing less resistant strains where they are endemic.^{2,3,5,7} One remaining oral antibiotic, azithromycin, is still active against extensively drug-resistant typhoid; however, further genetic mutation could make typhoid untreatable in some areas.²

The provincial government of Sindh, Pakistan, which deals with the water and sanitation issues has

started revamping the water filtration plant of Jamshoro, Hyderabad, after the judicial commission appointed by the Supreme Court of Pakistan ordered an inquiry into mixing of sewage water into natural waterways.^{8,9} The provincial government has also sanctioned 399.74 million Pakistani rupees for restoration of the water distribution network and 414.13 million Pakistani rupees for revival of the sewage system in Hyderabad.⁹ These initiatives can also curb the practices of using hand-operated water pumps in the vicinity of affected areas, which was one of the reasons cited in the paper, causing mixing of sewage and drinking water.¹ Another initiative that should be started by the government is the education of local people, particularly children, about hygiene practices and use of boiling water in cooking food and drinking through pictorial pamphlets and school education programmes. Another major step that should be made by the newly established Sindh Food authority is the inspection of the local restaurants and eateries for unhygienic practices.

The spread of extensively drug-resistant typhoid should be an alarming sign that the world is slowly moving towards a pre-antibiotic era because of widespread overuse of antibiotics. This has become a serious concern in developing nations such as Pakistan, where antimicrobial surveillance is poor and in urgent need of strengthening. Both governmental and non-governmental organisations in Pakistan need to actively promote vaccination campaigns and healthy hygiene habits and discourage irrational use of antibiotics to prevent the mortality and morbidity associated with increasing antibiotic resistance in pathogens.

We declare no competing interests.

Muhammad Kamran Rasheed,
Syed Shahzad Hasan,
Zaheer-Ud-Din Babar,
*Syed Imran Ahmed
sia194@yahoo.com

Department of Pharmacy Practice, Qassim University, Saudi Arabia (MKR); Department of Pharmacy, University of Huddersfield, Huddersfield, UK (SSH, ZUB); and School of Pharmacy, International Medical University, Kuala Lumpur 57000, Malaysia (SIA)

- 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 Baumgaertner E. "We're out of options": doctors battle drug-resistant typhoid outbreak. *The New York Times*, April 13, 2018. <https://www.nytimes.com/2018/04/13/health/drug-resistant-typhoid-epidemic.html> (accessed July 7, 2018).
- 3 Ahmad M. Pakistan is racing to combat the world's first extensively drug-resistant typhoid outbreak. *Sci Am*, March 14, 2018. <https://www.scientificamerican.com/article/pakistan-is-racing-to-combat-the-worlds-first-extensively-drug-resistant-typhoid-outbreak> (accessed May 7, 2018).
- 4 Antillón M, Warren JL, Crawford FW, et al. The burden of typhoid fever in low- and middle-income countries: a meta-regression approach. *PLoS Negl Trop Dis* 2017; **11**: e0005376.
- 5 Dalton J. Typhoid superbug in Pakistan raises fears of global antibiotic failure. Independent, April 17, 2018. <https://www.independent.co.uk/news/world/asia/typhoid-superbug-pakistan-global-antibiotic-failure-a8307836.html> (accessed July 5, 2018).
- 6 US warns Pakistan against outbreak of drug-resistant typhoid fever. *Dawn*, July 5, 2018. <https://www.dawn.com/news/1418058> (accessed July 5, 2018).
- 7 WHO. Joint external evaluation of IHR core capacities of the Islamic Republic of Pakistan. Mission report: 27 April–6 May 2016. Geneva: World Health Organization, 2016. <http://www.who.int/ihr/publications/WHO-WHE-CPI-2017.9/en/> (accessed July 20, 2018).
- 8 Inquiry ordered into disposal of sewage into natural waterways. *Dawn*, Dec 24, 2018. <https://www.dawn.com/news/1453181> (accessed Dec 24, 2018).
- 9 Water Commission's interim report identifies measures taken. *Pakistan Observer*, Dec 13, 2018. <https://pakobserver.net/water-commissions-interim-report-identifies-measures-taken/> (accessed Dec 24, 2018).

Macrolide resistance in *Streptococcus* spp

In their Review in *The Lancet Infectious Diseases*, Kieran O'Brien and colleagues¹ extensively examined antimicrobial resistance following mass azithromycin distribution for trachoma. Their results were of great interest, particularly with regards to macrolide resistance in *Streptococcus*

pneumoniae, the main target organism of the studies included in the Review.

As they discussed, the use of azithromycin might induce macrolide resistance in other organisms. They mentioned *Escherichia coli* and *Staphylococcus aureus* as examples of macrolide-resistant organisms other than *S pneumoniae*. However, several other organisms might be appropriate candidates for continued surveillance of antimicrobial resistance.

According to a report from the Japan Nosocomial Infections Surveillance,² 34.4% of *Streptococcus pyogenes* and 33.5% of *Streptococcus agalactiae* showed macrolide resistance. *S pyogenes* is a major cause of bacterial pharyngitis and rheumatic fever in children and sometimes causes severe infection such as necrotising fasciitis. *S agalactiae* is the most important causative organism of neonatal sepsis. Both are sensitive to penicillin, so usually treatment selection is not difficult. Nevertheless, macrolides are a useful option for patients with penicillin allergy.³ This alternative has unfortunately been lost in clinical settings in Japan, and the same thing might happen in other countries in the near future.

Japan Antimicrobial Consumption Surveillance and the AMR Clinical Reference Center provide statistical information about antimicrobial consumption.⁴ They reported that larger amounts of macrolide are consumed in Japan than in EU and European Economic Area member states (4.84 defined daily doses per 1000 inhabitants per day [DID] in 2013 in Japan and 3.1 DID in 2013–14 in the EU and European Economic Area).^{4,5} Although further research is required to understand the factors that contribute to this high proportion of macrolide resistance, the association between larger amounts of consumption and high proportions of resistance is difficult to deny.

We intend to continue longitudinal antimicrobial resistance surveillance, including *Streptococcus* spp other than