### Comment

## Globalisation of antibiotic-resistant bacteria at recurring mass gathering events

Antimicrobial resistance is associated with an estimated 4.95 million deaths annually and is currently a leading cause of death worldwide.1 Despite numerous global initiatives to control the surge of antimicrobial resistance, at the current rate of increase, annual deaths from antimicrobial resistance are estimated to rise to 10 million by 2050. This puzzling conundrum indicates that there are unknown factors that continue to increase antimicrobial resistance at a global scale and that identifying them will be crucial in controlling the ongoing antimicrobial resistance pandemic. There are also scarce data about the geographical distribution and evolution of antimicrobial resistance over time in settings outside of health-care facilities,<sup>2,3</sup> and more accurate scientific evidence is required to promote optimal policies to combat antimicrobial resistance.

Opportunities for reviewing knowledge gaps and refocusing scientific, political, and funder attention

on priority antimicrobial resistance research will arise during World Antimicrobial Awareness Week, Nov 18-24, 2022. During World Antimicrobial Awareness Week, the quadripartite organisations-WHO, the Food and Agriculture Organization of the UN, the UN Environment Programme, and the World Organisation for Animal Health-will promote the multisectoral approach of preventing antimicrobial resistance together. Although the focus will be on conventional antimicrobial resistance agendas, the neglected issue of the globalisation of antimicrobial resistance through mass gathering religious and pride festival events<sup>4</sup> must now be a priority agenda at the upcoming World Antimicrobial Awareness Week, given that these events could yield substantial exacerbating factors driving the antimicrobial resistance pandemic. Over the past two decades, individual case and small



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cohort reports indicate transmission of various See Online for appendix

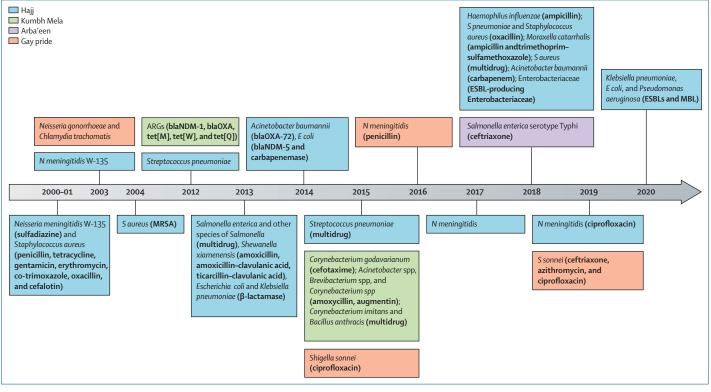


Figure: Bacterial pathogens and antimicrobial resistance associated with religious and gay pride events

The studies that inform this figure are listed in the appendix. Text in bold denotes the antibiotics to which the bacteria are resistant. ARGs=antibiotic resistance genes. ESBL=Extended-spectrum beta-lactamase. MBL=metallo beta-lactamase. MRSA=methicillin-resistant *Staphylococcus aureus*.

pathogens in both symptomatic and asymptomatic travellers from across the world attending recurring mass gathering events (figure).<sup>4-11</sup> These findings expose huge scientific knowledge gaps on the cryptic carriage, transmission dynamics, and ongoing evolution of antimicrobial resistance genes in people who attend mass gathering events, and their eventual effect on amplifying the global spread of antimicrobial resistance.<sup>5-710.11</sup>

The Kumbh Mela (India), Arba'een (Iraq), Hajj (Saudi Arabia), Grand Magal of Touba (Senegal), and global gay pride events attract millions of people to the host countries from across the world.4-7 Attendees of mass gathering events live and interact together, generating a vast amount of biological waste, such as faeces, urine, sweat, and sputum, with billions of microorganisms contaminating the environment, water, food, surfaces, and skin. Thus, mass gathering events create ideal conditions for transmission between attendees, organisers, and local residents of a range of pathogens, including multidrug-resistant bacteria that affect the respiratory tract, gastrointestinal tract, and genitalia.4.7 Men who have sex with men (MSM) are known to be at increased risk of acquiring multidrugresistant enteric pathogens and other sexually transmitted infections through close contact and exchange of secretions and excreta during unprotected anal, oral, and other sexual practices.<sup>8,9</sup> Repeated and frequent courses of antibiotic treatments in MSM with recurrent sexually transmitted infections drive antimicrobial resistance further, diminishing antibiotic treatment options.8-10 Clinico-epidemiological studies over the past decade have reported Neisseria gonorrhoea, Mycoplasma genitalium, Giardia intestinalis, HIV-1, and multidrug-resistant strains of foodborne gut pathogens Shigella sonnei and Campylobacter coli in MSM populations across diverse geographical locations.<sup>6,8-10</sup>

Antimicrobial resistance is also a neglected but important issue at the Kumbh Mela and requires proper scientific definition. Kumbh Mela is the world's largest religious mass gathering event<sup>7</sup> and is held every 4 years at locations across India, with over 100 million pilgrims from across all continents bathing together in the holy rivers of Ganga, Godavari, Kshipra, and Sangam. The Kumbh Mela thus carries the combined risk of antimicrobial resistance transmission from the carriage of bacteria in the skin, urinary, genital, or gastrointestinal tracts of pilgrims during mass communal worshipping that involves bathing together in contaminated river water under poor sanitary conditions. In 2021, a spatiotemporal meta-analysis of bacterial communities detected in water samples from the Godavari River showed anthropogenic multidrugresistant bacterial strains generating in real time during the Kumbh Mela.12 The 2022 Indian Council of Medical Research Antimicrobial Resistance Surveillance Network annual report<sup>13</sup> showed an upward trajectory of antimicrobial resistance across India. Resistance of Escherichia coli to imipenem increased from 14% in 2016 to 36% in 2021; methicillin-resistant Staphylococcus aureus rates increased from 28.4% in 2016 to 42.6% in 2021. Whether the Kumbh Mela contributes to exacerbating antimicrobial resistance within India and globally remains to be defined by case-controlled cohort studies of pilgrims. The disruptions to regular health care in India and across the world because of COVID-19 appear to have worsened challenges with antimicrobial resistance control worldwide.<sup>14</sup>

During World Antimicrobial Awareness Week, in addition to advancing a multisectoral, transdisciplinary approach that recognises the connection between people and their shared environments, the organisations and international stakeholders must prioritise and emphasise the urgent need for more political and funder investments in antimicrobial resistance research at mass gathering events. Coordinated action must be inclusive, and mass gatherings must be incorporated into the global antimicrobial resistance research agenda and more broadly in action plans, to prevent antimicrobial resistance. Given that millions of people from across the world attend recurring religious and gay pride events, they provide unique cohorts for taking forward a range of research and operational studies, such as defining the prevalence of antimicrobial resistance; risk factors for the evolution of antimicrobial resistance genes; transmission between participants; globalisation after the event; efficacy of infection control measures; antibiotic stewardship; and trials of new rapid diagnostics, vaccines, antibiotics, and novel therapeutic agents. Although the initiation and coordination of these studies might appear a logistical nightmare that is seemingly impossible, as the unprecedented but successful COVID-19 response illustrated, stakeholder support is required to to take forward these studies.

Overcoming these challenges will require increased political will; approval by the governments of countries hosting mass gathering events; adequate resources, including funding, to establish cross-continental networks, coordinate, and conduct these studies; developing common study and ethics protocols; and the availability of interventions at an affordable cost. To advance optimal participation by attendees of religious and gay pride events in research studies will be to avoid indirect or direct anti-religious, homophobic and racist stereotypes. This will require human-rightsbased study protocols, developed with full engagement of representatives from relevant religious, gay pride communities and host countries organisers, to avoid stigmatization, and use of unacceptable, prejudicial language, and content.

At the UN General Assembly on Sept 22, 2022, an important side event addressed antimicrobial resistance; heads of government and state, government ministers, and relevant stakeholders declared that urgent action is required to stop the spread of antimicrobial resistance. Antimicrobial resistance is a consistent agenda item in G7 and G20 presidencies. With such strong political support, the quadripartite organisations and relevant stakeholders need to take up strategic organisational and visionary leadership, create capability and capacity, and generate the required funding to advance research through cross-continental networks. This process could be underpinned by adapting, repurposing, and utilising the extensive existing research infrastructures, including genomics, epidemiological, communication, and data management expertise developed across the world for COVID-19. The quadripartite organisations must act now to find the missing data to formulate more effective policies than we have currently and avoid another global pandemic that could cause millions of deaths from antimicrobial resistance.

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- Murray CJL, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* 2022; **399:** 629–55.
- 2 Hay SI, Rao PC, Dolecek C, et al. Measuring and mapping the global burden of antimicrobial resistance. BMC Med 2018; 16: 78.
- Luz CF, van Niekerk JM, Keizer J, et al. Mapping twenty years of antimicrobial resistance research trends. Artif Intell Med 2022; **123:** 102216.
- 4 Zumla A, Azhar EI, Hui DS, Shafi S, Petersen E, Memish ZA. Global spread of antibiotic-resistant bacteria and mass-gathering religious events. *Lancet Infect Dis* 2018; **18**: 488–90.
- Hoang VT, Dao TL, Ly TDA, et al. Acquisition of multidrug-resistant bacteria and encoding genes among French pilgrims during the 2017 and 2018 Hajj. Eur J Clin Microbiol Infect Dis 2021; 40: 1199–207.
- Day MJ, Jacobsson S, Spiteri G, et al. Significant increase in azithromycin "resistance" and susceptibility to ceftriaxone and cefixime in Neisseria gonorrhoeae isolates in 26 European countries, 2019. BMC Infect Dis 2022; 22: 524.
- Memish ZA, Steffen R, White P, et al. Mass gatherings medicine: public health issues arising from mass gathering religious and sporting events. *Lancet* 2019; **393:** 2073–84.
- Lister NA, Smith A, Tabrizi S, et al. Screening for Neisseria gonorrhoeae and Chlamydia trachomatis in men who have sex with men at male-only saunas. Sex Transm Dis 2003; 30: 886–89.
- Gaudreau C, Bernaquez I, Pilon PA, Goyette A, Yared N, Bekal S. Clinical and genomic investigation of an international ceftriaxone- and azithromycinresistant Shigella sonnei cluster among men who have sex with men, Montréal, Canada 2017–2019. Microbiol Spectr 2022; 10: e0233721.
- 10 Greninger AL, Addetia A, Starr K, et al. International spread of multidrugresistant *Campylobacter coli* in men who have sex with men in Washington state and Québec, 2015–2018. *Clin Infect Dis* 2020; **71**: 1896–904.
- 11 D'Souza AW, Boolchandani M, Patel S, et al. Destination shapes antibiotic resistance gene acquisitions, abundance increases, and diversity changes in Dutch travelers. *Genome Med* 2021; **13**: 79.
- 12 Jani K, Bandal J, Shouche Y, et al. Extended ecological restoration of bacterial communities in the Godavari river during the COVID-19 lockdown period: a spatiotemporal meta-analysis. *Microb Ecol* 2021; 82: 365–76.
- 13 Indian Council of Medical Research. Antimicrobial resistance research and surveillance network annual report. 2021. https://main.icmr.nic.in/sites/ default/files/upload\_documents/AMR\_Annual\_Report\_2021.pdf (accessed Oct 26, 2022).
- 14 Tomczyk S, Taylor A, Brown A, et al. Impact of the COVID-19 pandemic on the surveillance, prevention and control of antimicrobial resistance: a global survey. J Antimicrob Chemother 2021; 76: 3045–58.

# THE LANCET

## Supplementary appendix

This appendix formed part of the original submission. We post it as supplied by the authors.

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#### Supplementary references for figure 1

- 1. Wilder-Smith A, Goh KT, Barkham T, Paton NI. Hajj-associated outbreak strain of Neisseria meningitidis serogroup W135: estimates of the attack rate in a defined population and the risk of invasive disease developing in carriers. *Clin Infect Dis.* 2003;36(6):679-683.
- 2. Fatani MI, Bukhari SZ, Al-Afif KA, Karima TM, Abdulghani MR, Al-Kaltham MI. Pyoderma among Hajj Pilgrims in Makkah [published correction appears in Saudi Med J. 2002;23(10):1296.
- 3. Balkhy HH, Memish ZA, Almuneef MA, Osoba AO. Neisseria meningitidis W-135 carriage during the Hajj season 2003. *Scand J Infect Dis.* 2004;36(4):264-268.
- 4. Lister NA, Smith A, Tabrizi S, et al. Screening for Neisseria gonorrhoeae and Chlamydia trachomatis in men who have sex with men at male-only saunas. *Sex Transm Dis.* 2003;30(12):886-889.
- 5. Memish ZA, Balkhy HH, Almuneef MA, Al-Haj-Hussein BT, Bukhari AI, Osoba AO. Carriage of Staphylococcus aureus among Hajj pilgrims. *Saudi Med J.* 2006;27(9):1367-1372.
- 6. Lynch JP 3rd, Zhanel GG. Streptococcus pneumoniae: epidemiology and risk factors, evolution of antimicrobial resistance, and impact of vaccines. *Curr Opin Pulm Med*. 2010;16(3):217-225.
- 7. Ahammad ZS, Sreekrishnan TR, Hands CL, Knapp CW, Graham DW. Increased waterborne blaNDM-1 resistance gene abundances associated with seasonal human pilgrimages to the upper ganges river. *Environ Sci Technol.* 2014;48(5):3014-3020.
- 8. Leangapichart T, Hadjadj L, Gautret P, Rolain JM. Comparative genomics of two Shewanella xiamenensis strains isolated from a pilgrim before and during travels to the Hajj. *Gut Pathog.* 2021;13(1):9.
- 9. Olaitan AO, Dia NM, Gautret P, et al. Acquisition of extended-spectrum cephalosporinand colistin-resistant Salmonella enterica subsp. enterica serotype Newport by pilgrims during Hajj. *Int J Antimicrob Agents*. 2015;45(6):600-604.
- Leangapichart T, Dia NM, Olaitan AO, Gautret P, Brouqui P, Rolain JM. Acquisition of Extended-Spectrum β-Lactamases by Escherichia coli and Klebsiella pneumoniae in Gut Microbiota of Pilgrims during the Hajj Pilgrimage of 2013. *Antimicrob Agents Chemother*. 2016;60(5):3222-3226. Published 2016 Apr 22.
- 11. Leangapichart T, Gautret P, Griffiths K, et al. Acquisition of a High Diversity of Bacteria during the Hajj Pilgrimage, Including Acinetobacter baumannii with blaOXA-72 and Escherichia coli with blaNDM-5 Carbapenemase Genes. *Antimicrob Agents Chemother*. 2016;60(10):5942-5948. Published 2016 Sep 23.
- Chiou, C. S., Izumiya, H., Kawamura, M., Liao, Y. S., Su, Y. S., Wu, H. H., Chen, W. C., & Lo, Y. C. (2016). The worldwide spread of ciprofloxacin-resistant Shigella sonnei among HIV-infected men who have sex with men, Taiwan. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*, *22*(4), 383.e11–383.e16. <u>https://doi.org/10.1016/j.cmi.2015.12.021</u>

- 13. Jani K, Khare K, Senik S, et al. Corynebacterium godavarianum sp. nov., isolated from the Godavari river, India. *Int J Syst Evol Microbiol*. 2018;68(1):241-247.
- 14. Jani K, Bandal J, Rale V, Shouche Y, Sharma A. Antimicrobial resistance pattern of microorganisms isolated and identified from Godavari River across the mass gathering event. *J Biosci.* 2019;44(5):121.
- Harimurti K, Saldi SRF, Dewiasty E, et al. Streptococcus pneumoniae carriage and antibiotic susceptibility among Indonesian pilgrims during the Hajj pilgrimage in 2015. *PLoS One*. 2021;16(1):e0246122. Published 2021 Jan 26. doi:10.1371/journal.pone.0246122
- 16. Neri A, Palmieri A, Prignano G, et al. Molecular characterisation and antibiotic susceptibility of meningococcal isolates from healthy men who have sex with men. *Sex Transm Infect*. 2022;98(6):420-426.
- Alasmari, A., Houghton, J., Greenwood, B., Heymann, D., Edwards, P., Larson, H., Assiri, A., Ben-Rached, F., Pain, A., Behrens, R., & Bustinduy, A. (2021). Meningococcal carriage among Hajj pilgrims, risk factors for carriage and records of vaccination: a study of pilgrims to Mecca. *Tropical medicine & international health : TM & IH*, *26*(4), 453–461.
- Bokhary H, Research Team H, Barasheed O, et al. Evaluation of the rate, pattern and appropriateness of antibiotic prescription in a cohort of pilgrims suffering from upper respiratory tract infection during the 2018 Hajj season. *Access Microbiol.* 2022;4(4):000338. Published 2022 Apr 25.
- Hoang, V. T., Dao, T. L., Ly, T., Gouriet, F., Hadjadj, L., Belhouchat, K., Chaht, K. L., Yezli, S., Alotaibi, B., Raoult, D., Parola, P., Baron, S. A., de Santi, V. P., Rolain, J. M., & Gautret, P. (2021). Acquisition of multidrug-resistant bacteria and encoding genes among French pilgrims during the 2017 and 2018 Hajj. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology*, 40(6), 1199–1207.
- 20. Godbole G, McCann N, Jones SM, Dallman TJ, Brown M. Ceftriaxone-resistant Salmonella Typhi in a traveller returning from a mass gathering in Iraq. *Lancet Infect Dis.* 2019;19(5):467.
- 21. Yezli S, Yassin Y, Mushi A, Bukhari M, Banasser T, Khan A. Carriage of *Neisseria meningitidis* Among Umrah Pilgrims: Circulating Serogroups and Antibiotic Resistance. *Infect Drug Resist.* 2022;15:4685-4696. Published 2022 Aug 23.
- 22. Chiou CS, Izumiya H, Kawamura M, et al. The worldwide spread of ciprofloxacinresistant Shigella sonnei among HIV-infected men who have sex with men, Taiwan. *Clin Microbiol Infect*. 2016;22(4):383.e11-383.e16.
- 23. Ahmed OB, & Asghar AH. The Coexistence of Extended-Spectrum β-lactamase and Metallo-β-Lactamase Genes in Gram-Negative Bacteria. Archives of Pharmacy Practice, 2022;12(3), 22-28.