

# The genetics behind drug resistant enteric fever

Enteric fever is a potentially life-threatening bacterial infection caused by i) *Salmonella* Typhi, which causes typhoid fever, and ii) *Salmonella* Paratyphi types A, B and C, which cause paratyphoid fever. It is commonly transmitted via contaminated water and food and is endemic in regions of southeast Asia and sub-Saharan Africa. As an indication of the scale of this global public health threat, there were an estimated 14.3 million cases worldwide in 2017 and ~136,000 associated deaths<sup>1</sup>.

*Salmonella* is no exception to the trend of increasingly observed antimicrobial resistant (AMR) pathogens. In the past 6 years, an extensively drug resistant (XDR) type of typhoid fever began to spread worldwide; in addition to physical suffering, this places an increased burden on healthcare services and is of great concern due to limited treatment options. Dr Gemma Langridge leads a team at Quadram Institute (QI) who have been collaborating with the UK Health Security Agency (UKHSA) formerly known as Public Health England (PHE), the Child Health Research Foundation in Bangladesh, and the Allama Iqbal Medical College & Jinnah Hospital and Government College University in Pakistan, using genome sequencing and analysis to better understand and track cases of enteric fever, including both paratyphoid and typhoid variants, providing an evidence base for clinical management and targeted interventions.



## 1990 – 2018

Outbreaks of typhoid fever increasing in frequency and size, and also being observed in non-endemic regions<sup>2</sup>.

## 1997

Standard treatment for typhoid fever is antibiotics<sup>3</sup> (uncomplicated cases: ciprofloxacin or azithromycin / severe cases: ceftriaxone).



## 1999 – 2000

*Salmonella* Typhi strains highly resistant to ceftriaxone and ciprofloxacin are observed by Dhaka Shishu Hospital, Bangladesh<sup>4,5</sup>.

## Pre 2015

PHE's standard method of detecting *Salmonella* Typhi is serotyping, which relies on antibody preparations. In 2014, PHE undertake parallel testing of phenotypic and genotypic methods for identification<sup>6</sup>



## 2015

Whole Genome Sequencing (WGS), providing more detailed information, is validated with antibiotic phenotypic testing for identification and AMR surveillance in *Salmonella*<sup>7</sup>.

## 2016

Outbreak of Extensively Drug Resistant (XDR) typhoid fever identified in Sindh province, southern Pakistan<sup>8</sup>



“This XDR outbreak led to a need to identify imported drug resistance for typhoid *Salmonella* that are resistant to the primary treatment for enteric fever in England, ceftriaxone, in order to inform the national treatment guidelines.”  
Marie Chattaway, UKHSA

## 2017

First isolate of ceftriaxone resistant *Salmonella* Paratyphi A is obtained from a traveller returning to England from Bangladesh<sup>9</sup>. Prompts a ‘Health resistance alert’ and advisory action from PHE<sup>10</sup>



## 2017

From November 2017 to April 2020 XDR *Salmonella* Typhi consistent with the ongoing outbreak in Pakistan was isolated by PHE from 68 cases of travellers returning to the UK<sup>11</sup>. Cases are increasing, and treatment options are decreasing<sup>12</sup>.

## 2018

PHE developed and implemented a real-time PCR test for the identification and differentiation of typhoid from non-typhoid *Salmonella* enabling same day testing to support case management and public health intervention.

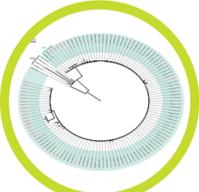
“Increased number of XDR *Salmonella* Typhi cases in Lahore, Pakistan were creating panic in the medical community but sequencing some of these isolates by Quadram Institute Bioscience has helped in understanding the origin and management of XDR cases”  
Dr Farhan Rasheed, Allama Iqbal Medical College & Jinnah Hospital

## 2019

Jinnah Hospital, Lahore observed a dramatic rise in XDR typhoid fever cases (27 cases in 10 weeks)

## 2019

QI researchers generated WGS data for local clinicians in Pakistan, confirming that an outbreak in Lahore was linked to that in Sindh Province in 2016<sup>13</sup>.



## 2019

This WGS data is being used to support the case for mass typhoid vaccination being put forward to Pakistan government.



## 2020

Tracking the spread of antibiotic resistant enteric fever infections also assists in outbreak response by health authorities in Pakistan



“This genetic mobility may lead to the maintenance of resistance even in the absence of antibiotic selection pressure. Treatment guidelines may have to change to reflect this.”  
Satheesh Nair, UKHSA

## 2021

In multiple cases, the key antibiotic resistance gene responsible for XDR had integrated into the *Salmonella* Typhi genome<sup>11</sup>

## 2022

Updated clinical guidelines for management of enteric fever in England are published, and include treatment with meropenem and azithromycin for complicated cases from XDR regions<sup>14</sup>

## Where next?

Continue sequencing efforts of water specimens, potentially contaminated waterways and looking for asymptomatic carriers.

The whole WGS process, from growing bacterial cells to interpreting sequence data for identification, Antimicrobial Resistance (AMR) characterisation and high throughput single nucleotide polymorphism typing for surveillance can take as little as 5 days. A rapid turnaround time considering the amount of data obtained.

### References

- GBD 2017 Typhoid and Paratyphoid Collaborators (2019). The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet Infectious Diseases* 19 (4):369-81. [https://doi.org/10.1016/S1473-3099\(18\)30685-6](https://doi.org/10.1016/S1473-3099(18)30685-6)
- Kim, S., Lee, K. S., Pak, G. D., Excler, J. L., Sahastabudde, S., Marks, F., Kim, J. H., & Magosale, V. (2019). Spatial and Temporal Patterns of Typhoid and Paratyphoid Fever Outbreaks: A Worldwide Review, 1990-2018. *Clinical Infectious Diseases: an official publication of the Infectious Diseases Society of America*, 69(Suppl 6), S499-S509. <https://doi.org/10.1093/cid/ciz705>
- MSF Clinical guide. <https://medicalguidelines.msf.org/viewport/CG/english/enteric-typhoid-and-paratyphoid-fevers-16689926.html>
- Saha, S. K., Talukder, S. Y., Islam, M., Saha, S. A highly Ceftriaxone-resistant *Salmonella* Typhi in Bangladesh, *The Paediatric Infectious Disease Journal* (1999). Volume 18- Issue 4- p 387. <https://doi.org/10.1097/00006454-199904000-00018>
- Djehout, B., Saha, S., Sajib, M., Tanmoy, A. M., Islam, M., Kay, G. L., Langridge, G. C., Endtz, H. P., Wain, J., & Saha, S. K. (2018). Ceftriaxone-resistant *Salmonella* Typhi carries an IncI1-ST31 plasmid encoding CTX-M-15. *Journal of medical microbiology*, 67(5), 620-627. <https://doi.org/10.1099/jmm.0.000727>
- Chattaway, M.A. et al (2019). The transformation of Reference Microbiology Methods and Surveillance for *Salmonella* With the Use of Whole Genome Sequencing in England and Wales. *Front. Public Health* <https://doi.org/10.3389/fpubh.2019.00317>
- Day, M. et al (2018). Comparison of phenotypic and WGS-derived antimicrobial resistance profiles of *Salmonella enterica* serovars Typhi and Paratyphi. *J Antimicrob Chemother* 1;73(2):365-72 <https://doi.org/10.1093/jac/dkx379>
- Klemm, E.J. et al (2018). Emergence of an extensively drug resistance *Salmonella enterica* serovar Typhi clone harbouring a promiscuous plasmid encoding resistance to fluoroquinolones and third generation cephalosporins. *mBio* 9(1).
- Nair, S., Day, M., Godbole, G., Saluja T, Langridge GC, Dallman TJ & Chattaway MA (2020). Genomic surveillance detects *Salmonella enterica* serovar Paratyphi A harbouring bla<sub>CTX-M-15</sub> from a traveller returning from Bangladesh. *PLoS ONE* <https://doi.org/10.1371/journal.pone.0228250>
- UK Public Health Resistance Alert: *Salmonella* Typhi. [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/715430/hpr4517\\_slml-typi\\_AR\\_A.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/715430/hpr4517_slml-typi_AR_A.pdf)
- Nair, S., Chattaway M., Langridge, G.C. et al (2021). Extended spectrum beta lactamase producing strains isolated from imported cases of enteric fever in the UK reveal multiple chromosomal integrations of bla<sub>CTX-M-15</sub> in XDR *Salmonella* Typhi. <https://doi.org/10.1093/jac/dkab049>
- Herdman, M. T. et al (2021). Increasingly limited options for the treatment of enteric fever in 10 travellers returning to England, 2014-2019: a cross-sectional analytical study. *J Med Microbiol* 70(8):001359 <https://doi.org/10.1099/jmm.0.001359>
- Rasheed, F., Saeed, M., Ali Khan, N. F., Baker, D., Khurshid, M., Ainsworth, E. V., Turner, A. K., Imran, A. A., Rasool, M. H., Saqalein, M., Nisar, M. A., Fayaz Ur Rehman, M., Wain, J., Yasir, M., Langridge, G. C., & Ikram, A. (2020). Emergence of Resistance to Fluoroquinolones and Third-Generation Cephalosporins in *Salmonella* Typhi in Lahore, Pakistan. *Microorganisms*, 8(9), 1336. <https://doi.org/10.3390/microorganisms8091336>
- Nabarro, L.E. et al (2022). British Infection Association guidelines for the diagnosis and management of enteric fever in England. <https://doi.org/10.1016/j.jinf.2022.01.014>