



# Global Typhoid Genomics Consortium Overview

ReLAVRA+ Meeting 11 July 2023

Megan Carey, PhD, MSPH

Consortium Coordinator, AMRnet Policy Fellow - London School of Hygiene & Tropical Medicine & Associate Director, AMR Strategy - IAVI

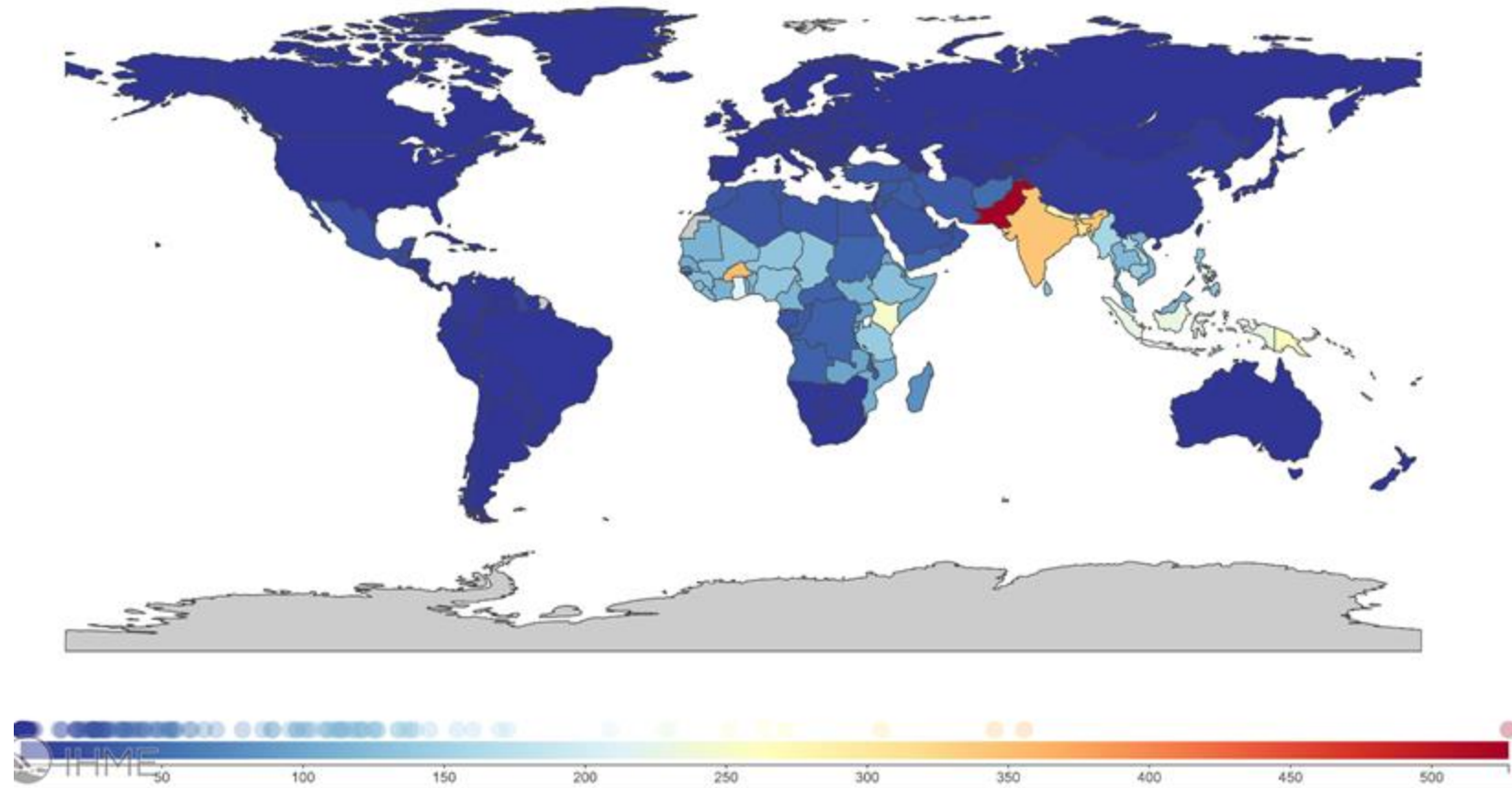


@meganecarey

# TYPHOID FEVER EPIDEMIOLOGY

- Typhoid fever is a systemic infection caused by the bacteria *Salmonella enterica* serovar Typhi (*S. Typhi*)
- *S. Typhi* human-restricted, transmitted via fecal-oral route
- 9,237,224 million cases, 110,029 deaths annually<sup>1</sup> – major regional data gaps
- Typically diagnosed using blood culture (55% sensitive)
- 1% case fatality rate, but AMR is a major concern

## Typhoid Fever DALYs per 100,000 (2019)

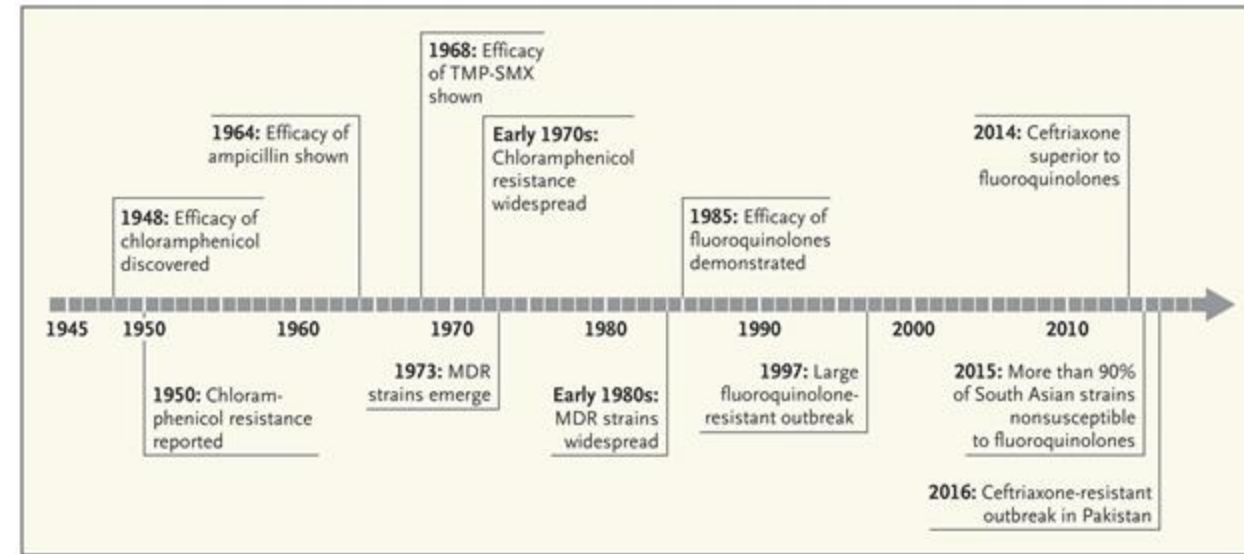


1. Global Burden of Disease Study 2019 (GBD 2019) – Institute for Health Metrics and Evaluation Global Health Data Exchange (GHDx).

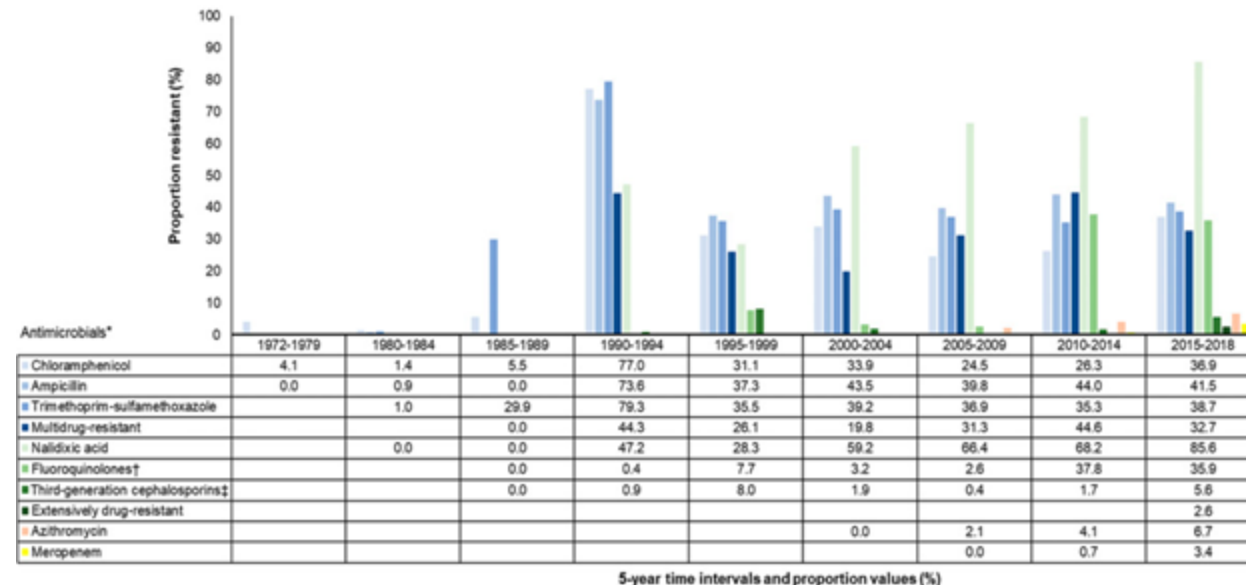
# Antimicrobial Resistance

- **Multidrug resistance** (MDR; resistant to chloramphenicol, co-trimoxazole, ampicillin) became common in the 1990s
- **Fluoroquinolones** became first-line treatment, resistance became common in South & Southeast Asia in the 2000s
- This led to use of **third-generation cephalosporins** for treatment of typhoid in Asia, but the emergence & spread of **extensively-drug resistant** (XDR; MDR + resistant to fluoroquinolones, and third-generation cephalosporins) typhoid in Pakistan left azithromycin as the only available oral antimicrobial in South Asia
- **Azithromycin-resistant typhoid** has since emerged in [Bangladesh](#), [Pakistan](#), [India](#), [Nepal](#), [Samoa](#), and [Singapore](#)
- **We are rapidly approaching the end of effective oral antibiotics for treatment of typhoid fever**

## Timeline of AMR in *S. Typhi*

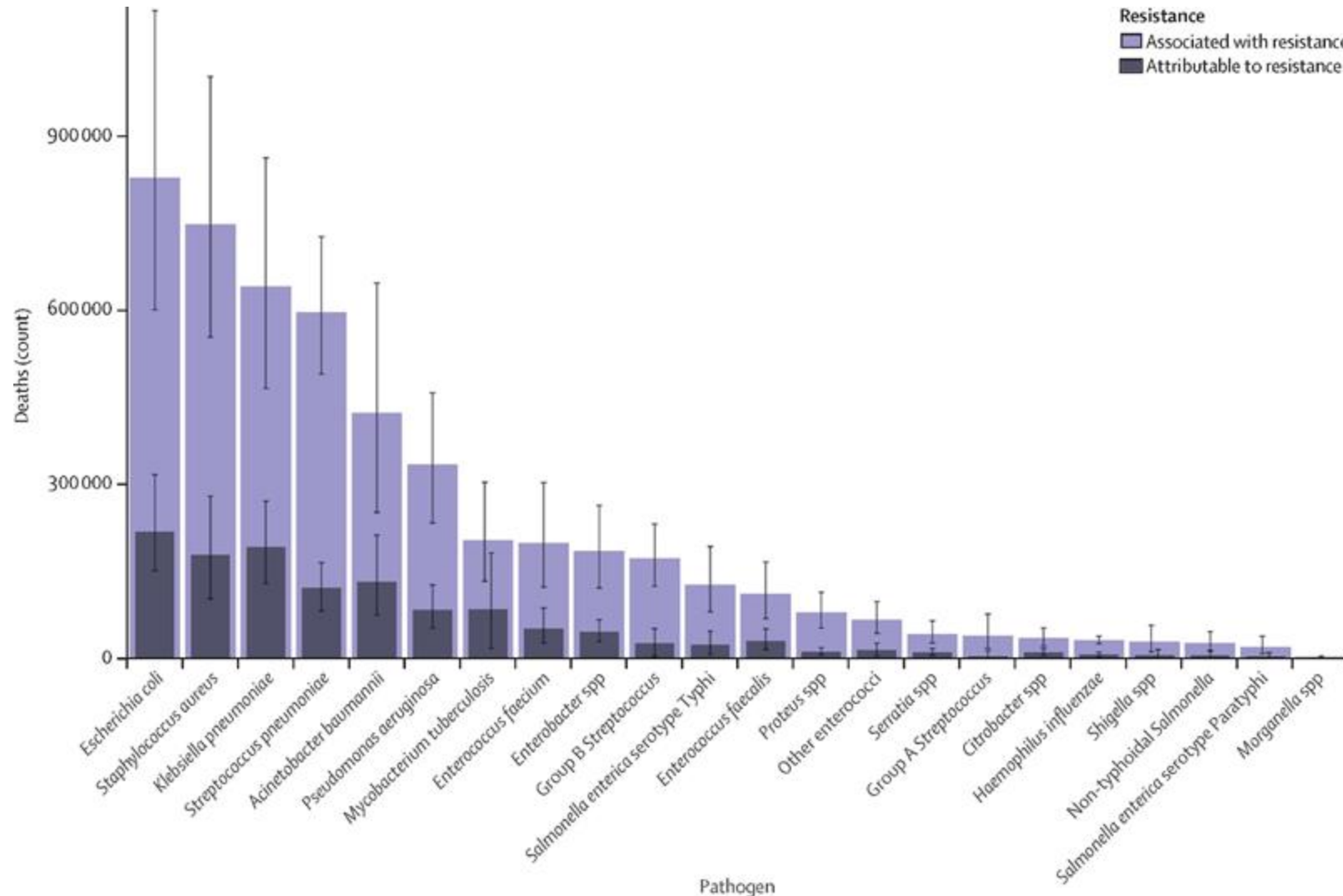


## AMR *S. Typhi* isolates (global) 1972-2018



Figures from: Andrews JR, Qamar FN, Charles RC, Ryan ET. **Extensively drug-resistant typhoid—are conjugate vaccines arriving just in time?** N Engl J Med 2018; 379:1493–5. & Marchello CS, Carr SD, Crump JA. **A systematic review on antimicrobial resistance among *Salmonella Typhi* worldwide.** American Journal of Tropical Medicine and Hygiene. 2020;103(6):2518-2527. doi:10.4269/ajtmh.20-0258

# AMR *S. Typhi* and attributable mortality



Recent estimates suggest that 23,700 deaths were attributable to drug-resistant *S. Typhi*. This analysis only considered MDR and fluoroquinolone resistant *S. Typhi*, so is likely to be an underestimate, and the problem is likely to get worse with the continued emergence and spread of AMR.

# Challenges with phenotypic AMR data

---

Not always widely or consistently reported

---

Repeat testing is difficult

---

Hard to standardize across labs – different methods & breakpoints may be used, and technicians may interpret results differently

---

Not all breakpoints extensively validated with clinical data

---

Provide no information about relatedness or transmission dynamics

# The case for WGS data in informing typhoid control

## RESEARCH ARTICLE

Informal genomic surveillance of regional distribution of *Salmonella* Typhi genotypes and antimicrobial resistance via returning travellers

Danielle J. Ingle<sup>1,2\*</sup>, Satheesh Nair<sup>3</sup>, Hassan Hartman<sup>3</sup>, Philip M. Ashton<sup>3</sup>, Zoe A. Dyson<sup>4,5</sup>, Martin Day<sup>3</sup>, Joanne Freedman<sup>6</sup>, Marie A. Chattaway<sup>3</sup>, Kathryn E. Holt<sup>5,7,8</sup>, Timothy J. Dallman<sup>3</sup>

Standardized AMR outputs

Information about international transmission & emergence & spread of drug-resistant strains

Repeatable

Facilitates investigation of new mechanisms of resistance and pathogen discovery

Extrapolation possible from returning traveler data

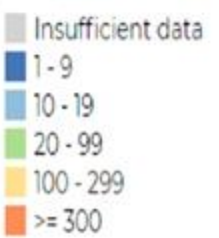
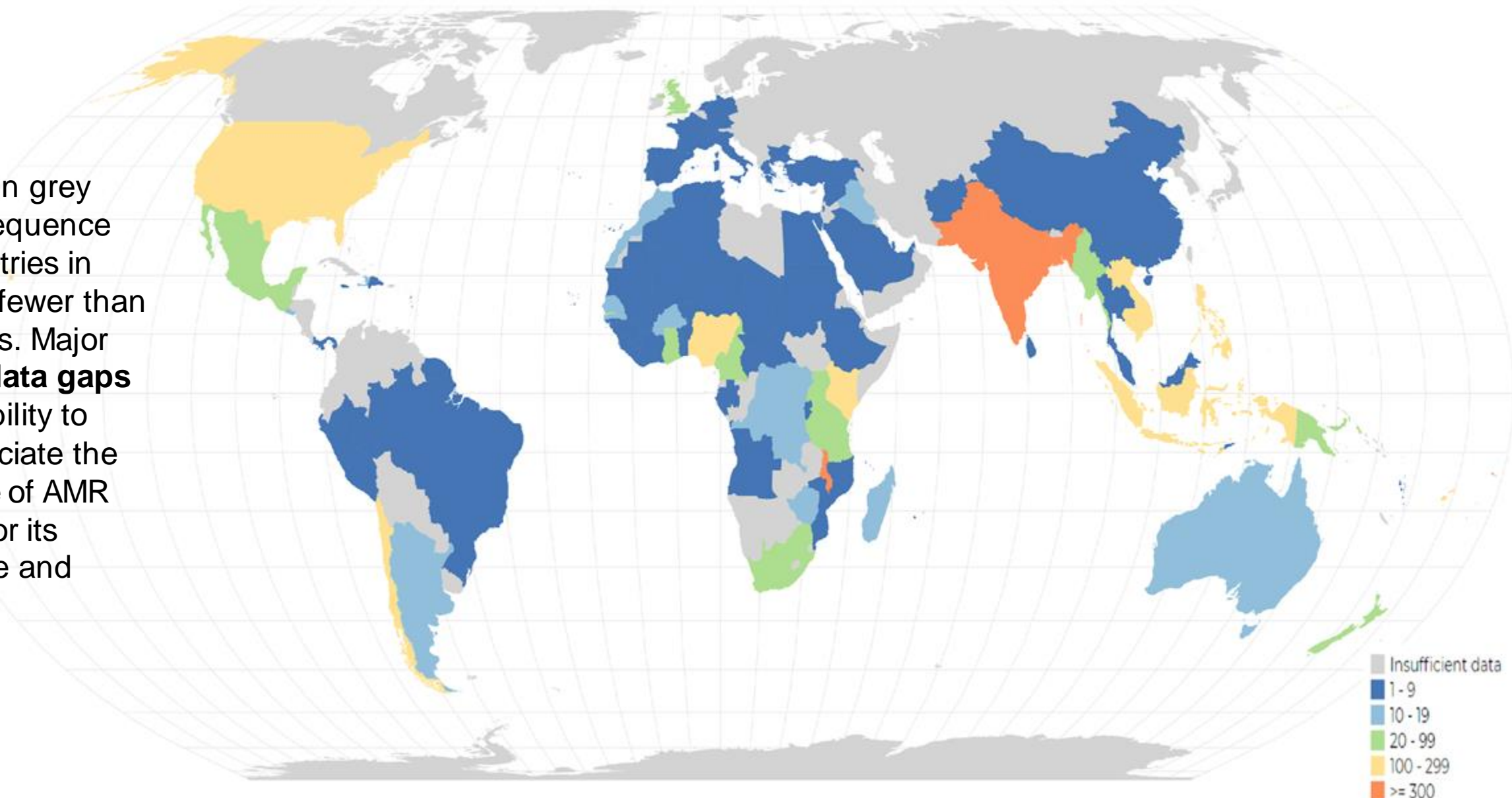
# Global Overview of Salmonella Typhi

Map view: No. Samples

Dataset: All

Time period: 1958 to 2021

Countries in grey have no sequence data; countries in blue have fewer than 20 samples. Major **regional data gaps** limit our ability to fully appreciate the magnitude of AMR and monitor its emergence and spread





**GLOBAL  
Typhoid Genomics  
CONSORTIUM**

## Overview of Goals & Activities

### **Our Mission:**

We aim to engage the global typhoid research community in order to aggregate *Salmonella* Typhi genomic data to monitor the emergence and spread of drug resistance and inform targeted public health action.

### **Consortium goals:**

1. Encourage prompt sharing of typhoid genome data for public health benefit
2. Facilitate the extraction and reporting of key data of public health relevance
3. Promote and facilitate the dissemination and use of information derived from typhoid genomic data to monitor antimicrobial resistance and post-vaccination impact

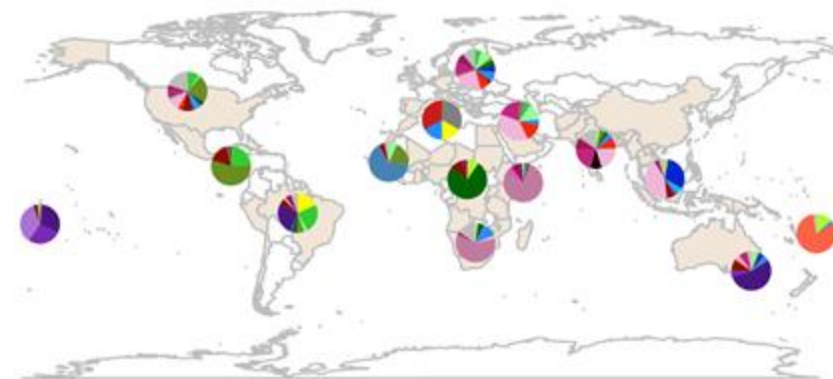


## Global diversity and antimicrobial resistance of typhoid fever pathogens: insights from 13,000 *Salmonella* Typhi genomes

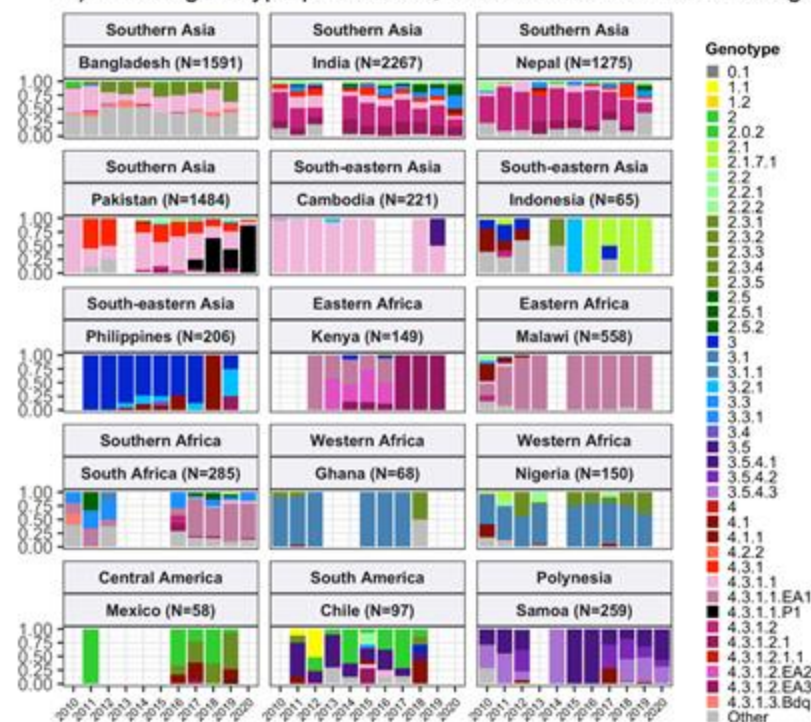
ID Megan E. Carey, ID Zoe A. Dyson, ID Danielle J. Ingle, ID Afreenish Amir, ID Mabel K. Aworh, ID Marie Anne Chattaway, ID Ka Lip Chew, ID John A. Crump, ID Nicholas A. Feasey, ID Benjamin P. Howden, ID Karen H. Keddy, ID Mailis Maes, ID Christopher M. Parry, ID Sandra Van Puyvelde, ID Hattie E. Webb, ID Ayorinde O. Afolayan, ID Shalini Anandan, ID Jason R. Andrews, ID Philip M. Ashton, ID Buddha Basnyat, ID Ashish Bavdekar, ID Isaac I. Bogoch, ID John D. Clemens, ID Kesia E. da Silva, ID Anuradha De, ID Joep de Ligt, ID Paula Lucia Diaz Guevara, ID Christiane Dolecek, ID Shanta Dutta, ID Louise Francois Watkins, ID Denise O. Garrett, ID Gauri Godbole, ID Melita A. Gordon, ID Andrew R. Greenhill, ID Chelsey Griffin, ID Madhu Gupta, ID Rene Hendricksen, ID Robert S. Heyderman, ID Yogesh Hooda, ID Juan Carlos Hormazabal, ID Odion O. Ikhimiukor, ID Junaid Iqbal, ID Jobin J. Jacob, ID Claire Jenkins, ID Dasaratha Ramaiah Jinka, ID Jacob John, ID Gagandeep Kang, ID Abdoulie Kanteh, ID Arti Kapil, ID Abhilasha Karkey, ID Samuel Kariuki, ID Robert A. Kingsley, ID Roshine Mary Koshy, ID A. C. Lauer, ID Myron M. Levine, ID Ravikumar Kadahalli Lingegowda, ID Stephen P. Luby, ID Grant A. Mackenzie, ID Tapfumane A. Mashe, ID Chisomo Msefula, ID Ankur Mutreja, ID Geetha Nagaraj, ID Savitha Nagaraj, ID Satheesh Nair, ID Take K. Naseri, ID Susana Nimarota-Brown, ID Elisabeth Njamkepo, ID Iruka N. Okeke, ID Sulochana Putli Bai Perumal, ID Andrew J. Pollard, ID Agila Kumari Pragasam, ID Firdausi Qadri, ID Farah N. Qamar, ID Sadia Isfat Ara Rahman, ID Savitra D. Rambocus, ID David A. Rasko, ID Pallab Ray, ID Roy Robins-Browne, ID Temsunaro Rongsen-Chandola, ID Jean Pierre Rutanga, ID Samir K. Saha, ID Senjuti Saha, ID Karnika Saigal, ID Mohammad Saiful Islam Sajib, ID Jessica C. Seidman, ID Jivan Shakya, ID Varun Shamanna, ID Jayanthi Shastri, ID Rajeev Shrestha, ID Sonia Sia, ID Michael J. Sikorski, ID Ashita Singh, ID Anthony M. Smith, ID Kaitlin A. Tagg, ID Dipesh Tamrakar, ID Arif Mohammad Tanmoy, ID Maria Thomas, ID Mathew S. Thomas, ID Robert Thomsen, ID Nicholas R. Thomson, ID Siaosi Tupua, ID Krista Vaidya, ID Mary Valcanis, ID Balaji Veeraraghavan, ID François-Xavier Weill, ID Jackie Wright, ID Gordon Dougan, ID Silvia Argimón, ID Jacqueline A. Keane, ID David M. Aanensen, ID Stephen Baker, ID Kathryn E. Holt, ID

Global Typhoid Genomics Consortium Group Authorship

a) Genotype prevalence by world region, 2010-2020



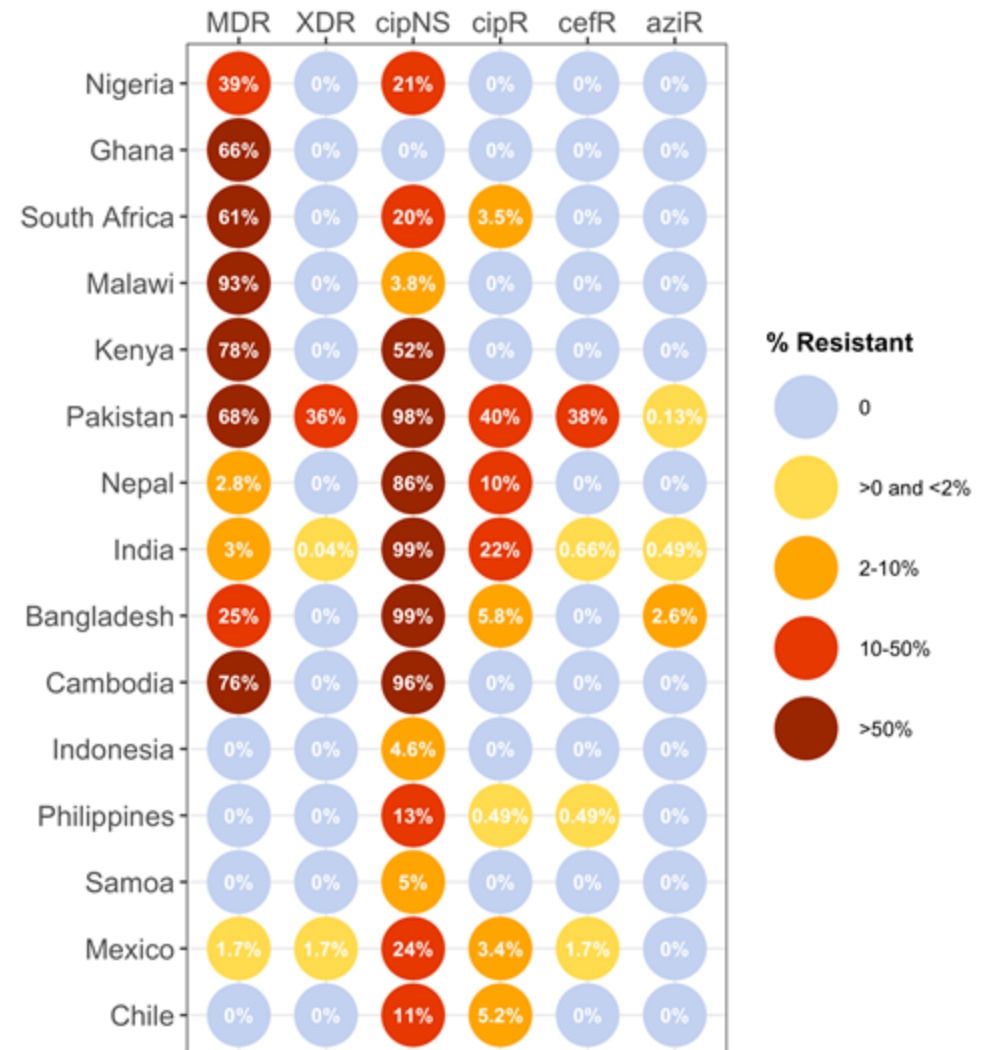
b) Annual genotype prevalence, for countries with at least 50 genomes



## Global diversity and antimicrobial resistance of typhoid fever pathogens: insights from 13,000 *Salmonella* Typhi genomes

ID Megan E. Carey, ID Zoe A. Dyson, ID Danielle J. Ingle, ID Afreenish Amir, ID Mabel K. Aworh,  
 ID Marie Anne Chattaway, ID Ka Lip Chew, ID John A. Crump, ID Nicholas A. Feasey, ID Benjamin P. Howden,  
 ID Karen H. Keddy, ID Mailis Maes, ID Christopher M. Parry, ID Sandra Van Puyvelde, ID Hattie E. Webb,  
 ID Ayorinde O. Afolayan, ID Shalini Anandan, ID Jason R. Andrews, ID Philip M. Ashton, ID Buddha Basnyat,  
 ID Ashish Bavdekar, ID Isaac I. Bogoch, ID John D. Clemens, ID Kesia E. da Silva, ID Anuradha De, ID Joep de Ligt,  
 ID Paula Lucia Diaz Guevara, ID Christiane Dolecek, ID Shanta Dutta, ID Louise Francois Watkins,  
 ID Denise O. Garrett, ID Gauri Godbole, ID Melita A. Gordon, ID Andrew R. Greenhill, ID Chelsey Griffin,  
 ID Madhu Gupta, ID Rene Hendricksen, ID Robert S. Heyderman, ID Yogesh Hooda, ID Juan Carlos Hormazabal,  
 ID Odion O. Ikhimiukor, ID Junaid Iqbal, ID Jobin J. Jacob, ID Claire Jenkins, ID Dasaratha Ramaiah Jinka, ID Jacob John,  
 ID Gagandeep Kang, ID Abdoulie Kanteh, ID Arti Kapil, ID Abhilasha Karkey, ID Samuel Kariuki, ID Robert A. Kingsley,  
 ID Roshine Mary Koshy, ID A. C. Lauer, ID Myron M. Levine, ID Ravikumar Kadahalli Lingegowda,  
 ID Stephen P. Luby, ID Grant A. Mackenzie, ID Tapfumane A. Mashe, ID Chisomo Msefula, ID Ankur Mutreja,  
 ID Geetha Nagaraj, ID Savitha Nagaraj, ID Satheesh Nair, ID Take K. Naseri, ID Susana Nimarota-Brown,  
 ID Elisabeth Njamkepo, ID Iruka N. Okeke, ID Sulochana Putli Bai Perumal, ID Andrew J. Pollard,  
 ID Agila Kumari Pragasam, ID Firdausi Qadri, ID Farah N. Qamar, ID Sadia Isfat Ara Rahman, ID Savitra D. Rambocus,  
 ID David A. Rasko, ID Pallab Ray, ID Roy Robins-Browne, ID Temsunaro Rongsen-Chandola, ID Jean Pierre Rutanga,  
 ID Samir K. Saha, ID Senjuti Saha, ID Karnika Saigal, ID Mohammad Saiful Islam Sajib, ID Jessica C. Seidman, ID Jivan Shakya,  
 ID Varun Shamanna, ID Jayanthi Shastri, ID Rajeev Shrestha, ID Sonia Sia, ID Michael J. Sikorski, ID Ashita Singh,  
 ID Anthony M. Smith, ID Kaitlin A. Tagg, ID Dipesh Tamrakar, ID Arif Mohammad Tanmoy, ID Maria Thomas,  
 ID Mathew S. Thomas, ID Robert Thomsen, ID Nicholas R. Thomson, ID Siaosi Tupua, ID Krista Vaidya, ID Mary Valcanis,  
 ID Balaji Veeraraghavan, ID François-Xavier Weill, ID Jackie Wright, ID Gordon Dougan, ID Silvia Argimón,  
 ID Jacqueline A. Keane, ID David M. Aanensen, ID Stephen Baker, ID Kathryn E. Holt,  
 Global Typhoid Genomics Consortium Group Authorship

Fig 2. Prevalence of key AMR genotype profiles by country





Data generators in research & public health labs submit genome & source data to sequence DBs (NCBI/ENA)



Analytics to extract AMR and genotype data from sequence, store with source data in DB



Source, AMR & genotype data pulled into dashboard for interactive data-viz



## GLOBAL Typhoid Genomics CONSORTIUM

- Metadata & sampling
- Genome assembly & QC
- Genotype scheme
- AMR dictionary
- Pathogenwatch DB





## Resource development

- [GenoTyphi scheme](#)
- AMR library
- Code for Nanopore data
- Expansion to Paratyphi, iNTS

## Data sharing

- [Metadata standards](#)
- QC standards
- Pathogenwatch collections
- [TyphiNET dashboard](#)

# GLOBAL Typhoid Genomics CONSORTIUM

typhoidgenomics.org

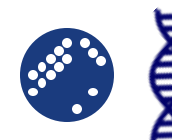
## Advocacy



- Policy advisory group
- Public health lab group
- Case studies

## *Training & capacity building (future)*

- *Lab & informatics*
- *Protocols and tutorials*
- *Workshops*



# External Oversight

## Steering Committee

*Multidisciplinary international experts who oversee Consortium activities (chair: Kat Holt)*

- Buddha Basnyat (OUCRU, Nepal)
- Josefina Campos (Administración Nacional de Laboratorios e Institutos de Salud, Argentina)
- Marie Chattaway (Public Health England)
- Alan Christoffels (South African National Bioinformatics Institute, South Africa)
- Danielle Ingle (Microbiological Diagnostic Unit Public Health Laboratory, Australia)
- Sam Kariuki (Kenya Medical Research Institute, Kenya)
- Ana Lauer (US Centers for Disease Control and Prevention, USA)
- Chisomo Msefula (University of Malawi College of Medicine, Malawi)
- John Nash (Public Health Agency of Canada, Canada)
- Iruka Okeke (University of Ibadan, Nigeria)
- Firdausi Qadri (icddr,b, Bangladesh)
- Farah Qamar (Aga Khan University, Pakistan)
- Senjuti Saha (Child Health Research Foundation, Bangladesh)
- Sonia Sia (Research Institute for Tropical Medicine, Philippines)
- Balaji Veeraraghavan (CMC Vellore, India)
- Francois-Xavier Weill (Institut Pasteur, France)

## Advisory Group

*Global public health experts who ensure Consortium activities to maximize public health benefit (chair: Megan Carey)*

- Adwoa Bentsi-Enchill (World Health Organization, Switzerland)
- Denise Garrett (Sabin Vaccine Institute, USA)
- Jacob John (Christian Medical College, Vellore, India)
- Elizabeth Klemm (Wellcome Trust, UK)
- Francisco Luquero (Gavi, the Vaccine Alliance, Switzerland)
- Jason Mwenda (World Health Organization AFRO, Republic of Congo)
- Kathy Neuzil (Center for Vaccine Development and Global Health, University of Maryland School of Medicine, USA)
- Carmem Pessoa-Silva (World Health Organization, Global Antimicrobial Resistance Surveillance System, Switzerland)
- Pilar Ramon-Pardo (Pan American Health Organization)
- Jeff Stanaway (Institute for Health Metrics and Evaluation, USA)
- Duncan Steele (Bill & Melinda Gates Foundation, USA)
- Sofonias Tessema (Africa Pathogen Genome Initiative, Ethiopia)



Prof. Kathryn Holt  
London School of  
Hygiene & Tropical  
Medicine &  
Monash University  
[@DrKatHolt](#)



Dr. Zoe Dyson  
London School of  
Hygiene & Tropical  
Medicine  
[@msmicrobiocode](#)



Dr. Megan Carey  
London School of  
Hygiene & Tropical  
Medicine  
[@meganecarey](#)



Prof. Stephen  
Baker University of  
Cambridge/IAVI  
[@Baker Lab Cam](#)



Prof. David  
Aanensen  
University of Oxford  
Big Data Institute  
[@daanensen](#)

## Global Typhoid Genomics Consortium Coordinators

# To get involved



Check out our webpage: [www.typhoidgenomics.org](http://www.typhoidgenomics.org)



Read our Memorandum of Understanding ([bit.ly/typhiMOU](http://bit.ly/typhiMOU)) and Code of Ethics ([bit.ly/typhiCOE](http://bit.ly/typhiCOE)) for members



Register as a member ([bit.ly/typhiREG](http://bit.ly/typhiREG)) and send your signed MoU to [info@typhi.net](mailto:info@typhi.net)



Try out Typhi Pathogenwatch ([pathogen.watch](http://pathogen.watch)) and read about it here: <http://bit.ly/TyphiPW>



Explore the TyphiNET data visualization dashboard ([typhi.net](http://typhi.net))



Learn more about the GenoTyphi genotyping scheme ([bit.ly/GenoTyphi](http://bit.ly/GenoTyphi))



Sign up to our mailing list: <http://eepurl.com/htFATr>



Follow us on Twitter @TyphiNET

Backup slides



# New activities



Planned  
Publications:

Commentary - global update paper  
Working Group 2 paper  
Mykrobe paper  
TyphiNET paper



Working  
Groups:

Paratyphi A  
Typhi Mykrobe Implementation  
Genotypi  
Data management  
Public health laboratories



New  
initiatives:



# Digital infrastructure for typhoid genomics

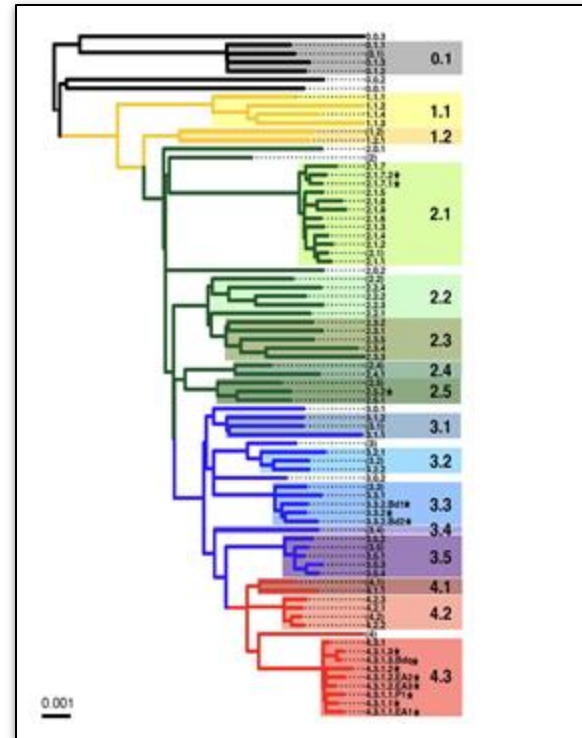
# GLOBAL Typhoid Genomics CONSORTIUM

## Metadata

Accession
Date
Country sequenced
Travel associated
Country of travel
→ Country of origin
Purpose of sampling
Source
Symptomatic
Isolating lab

[bit.ly/TyphiMeta](https://bit.ly/TyphiMeta)

## Genotype scheme



[github.com/typhoidgenomics](https://github.com/typhoidgenomics)

## AMR dictionary

<i>bla</i> CTXM-15	→ ceftriaxone
<i>bla</i> TEM-1D	→ ampicillin
<i>catA1</i>	→ chloramphenicol
<i>dfrA1</i>	→ trimethoprim
<i>dfrA5</i>	→ trimethoprim
<i>sul1</i>	→ sulfonamides
<i>acrB</i> -R717L	→ azithromycin
<i>gyrA</i> -S83F	→ ciprofloxacin
<i>parC</i> -E84G	→ ciprofloxacin

[github.com/pathogenwatch](https://github.com/pathogenwatch)  
[github.com/typhoidgenomics](https://github.com/typhoidgenomics)

## Platform & DB



### Analytics platform

- Genome QC
- Confirm species, serotype
- Assign genotype
- Predict AMR

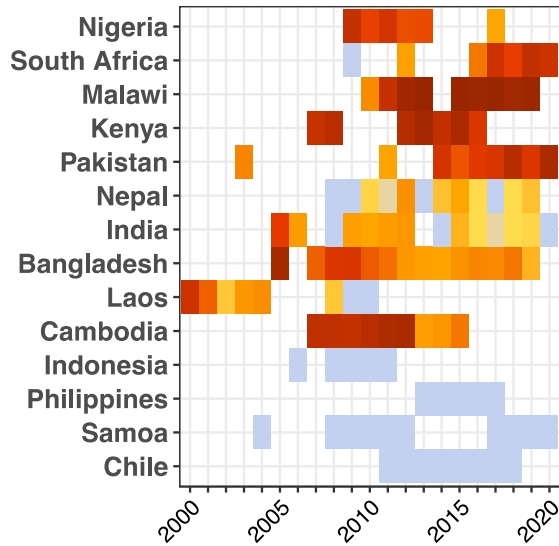
### Database

- Store QC'd genomes, analytics & metadata

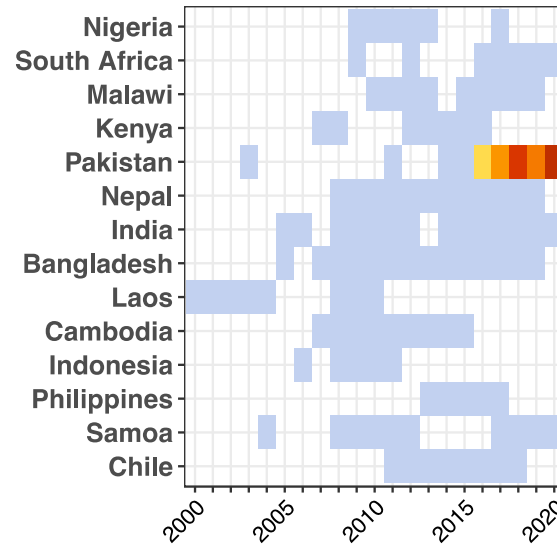
[pathogen.watch/Typhi](https://pathogen.watch/Typhi)

# AMR Frequencies by Country (2000 – 2020)

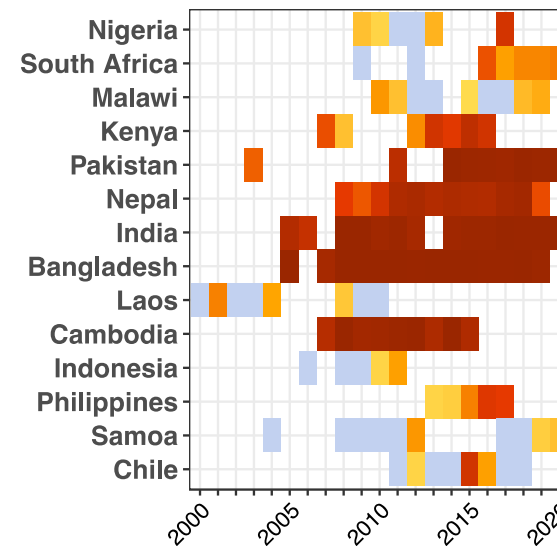
a. MDR



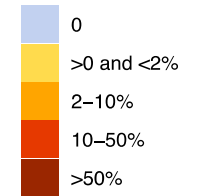
b. XDR



c. CipIR

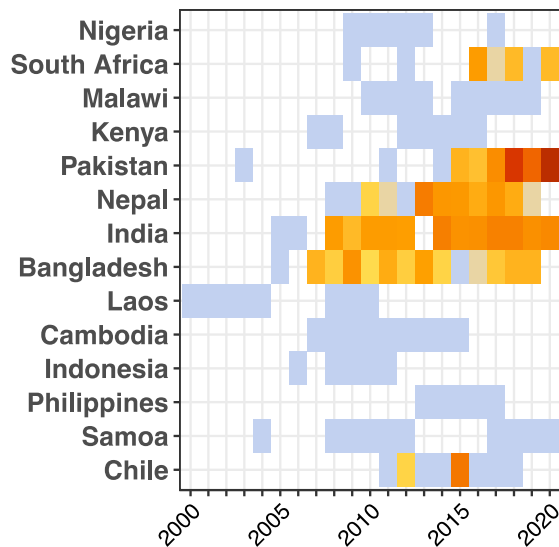


% Res

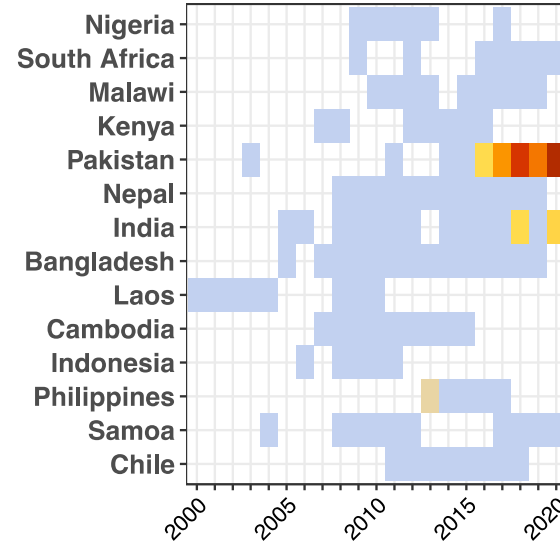


Countries with  $\geq 3$  years of  $\geq 10$  representative genomes

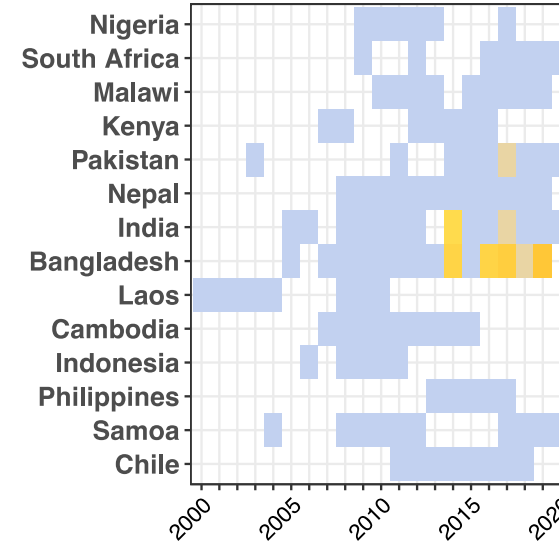
d. CipR



e. CefR

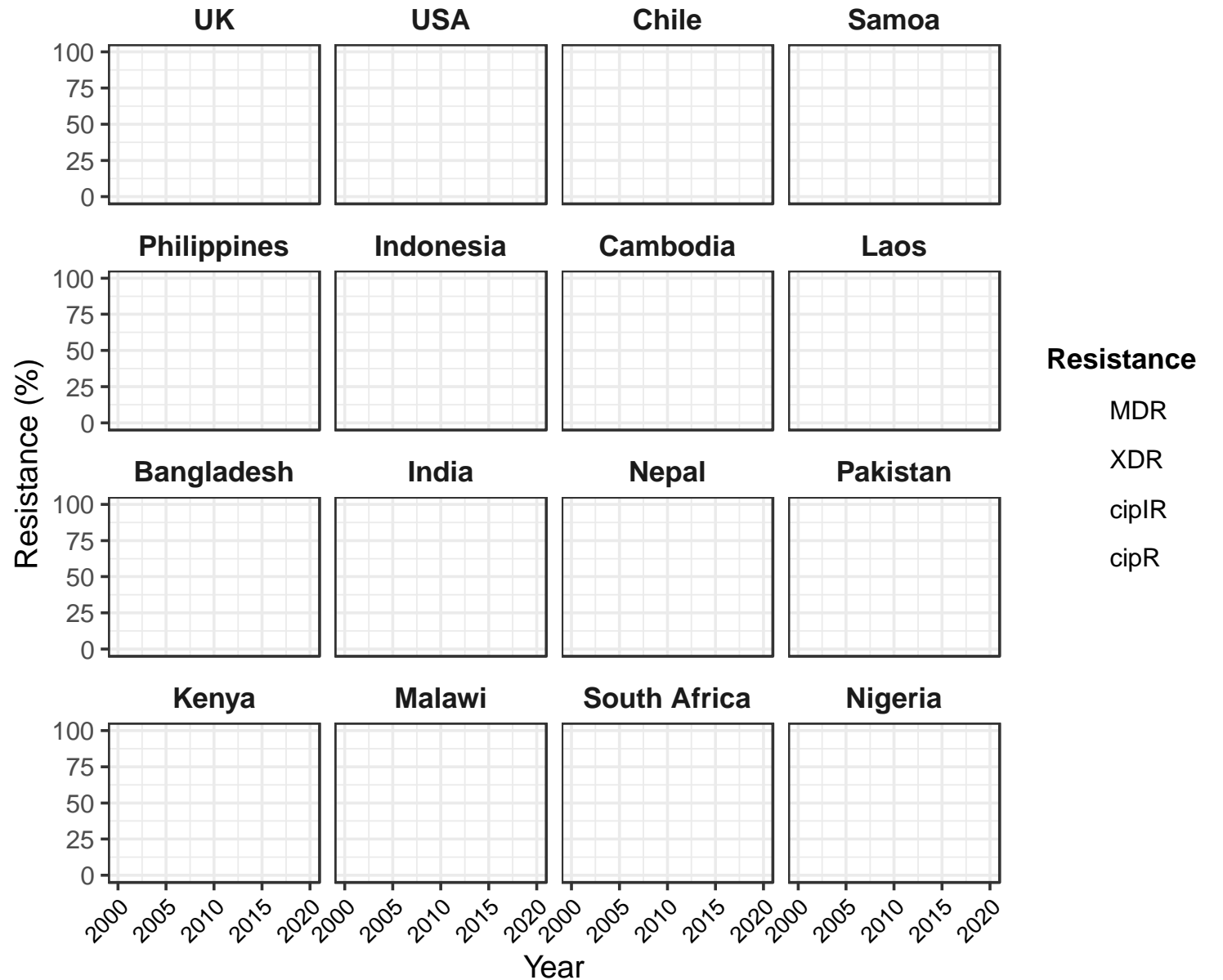


f. AziR



# Resistance frequencies by country over time

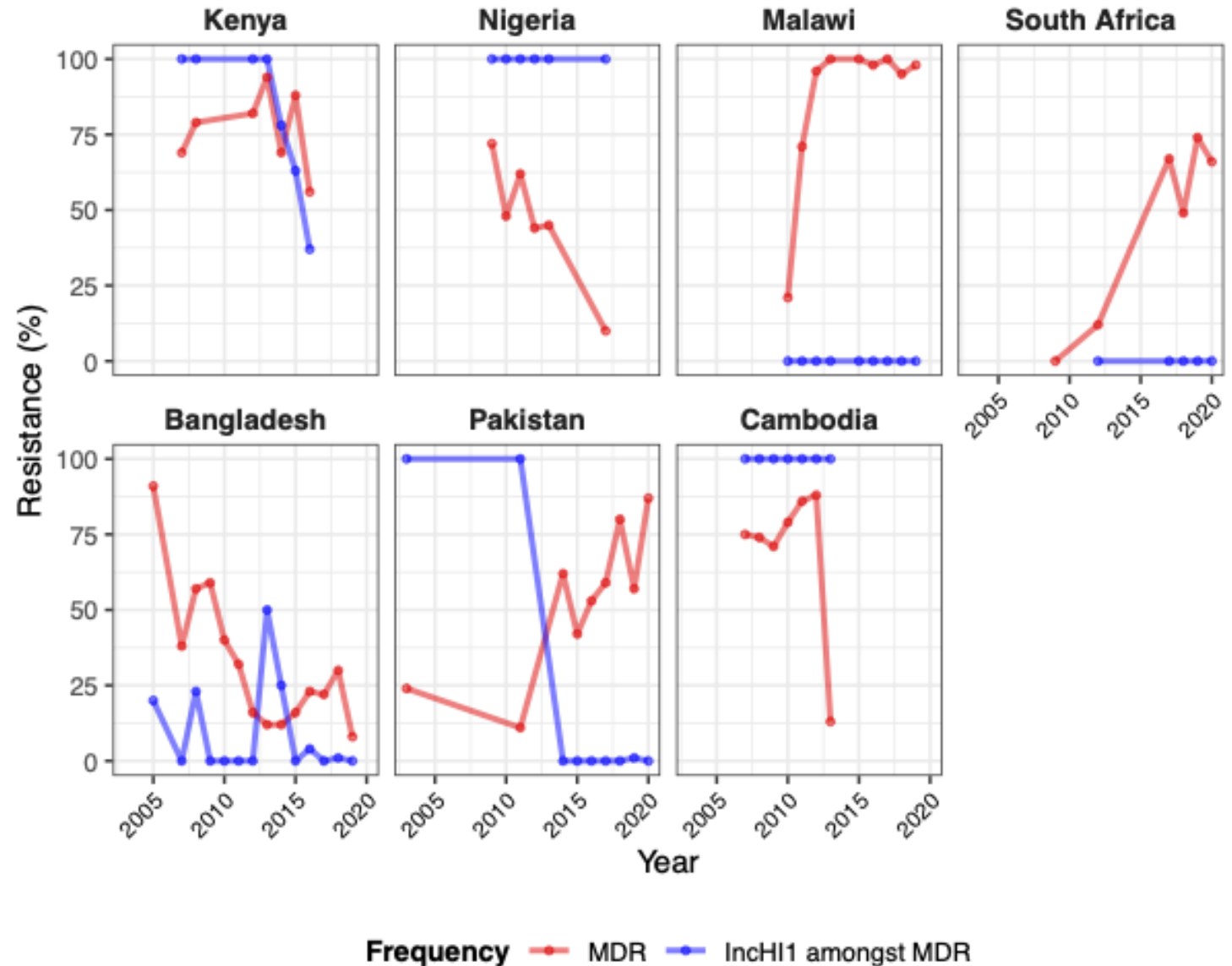
Temporal trends in AMR frequency from 2000 – 2020 in countries w/ 10+ genomes for 3+ years



# MDR frequency over time

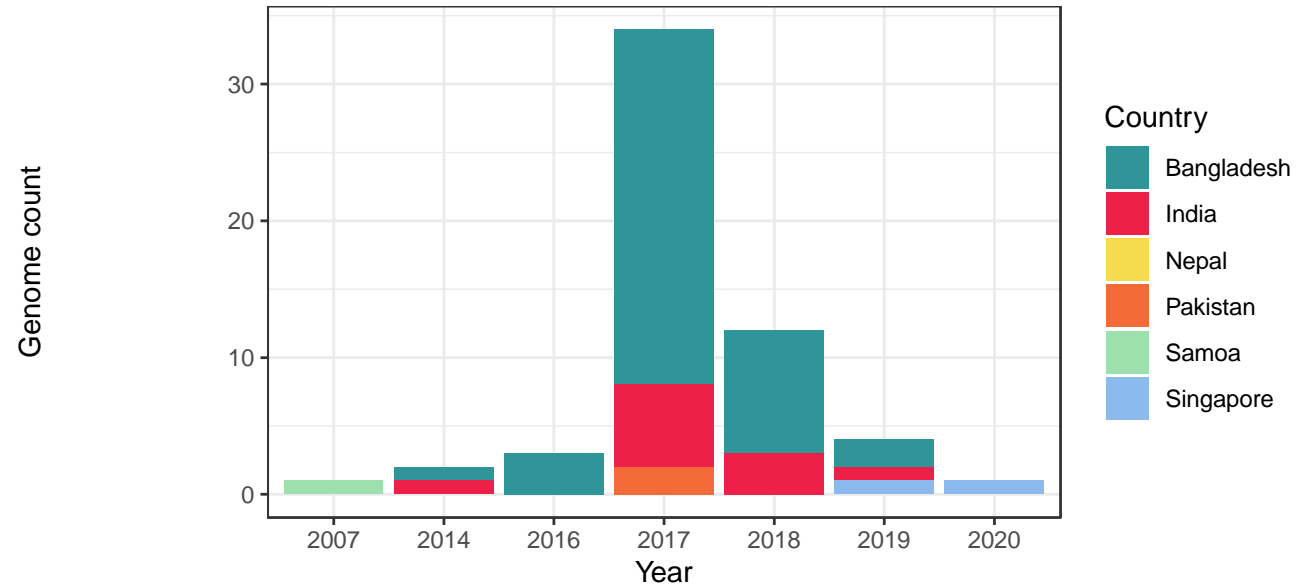
Trends in annual MDR frequency (red) and proportion of MDR explained by IncHI1 plasmids (blue).

- MDR prevalence high in Malawi & Kenya, declining in Nigeria & South Asia

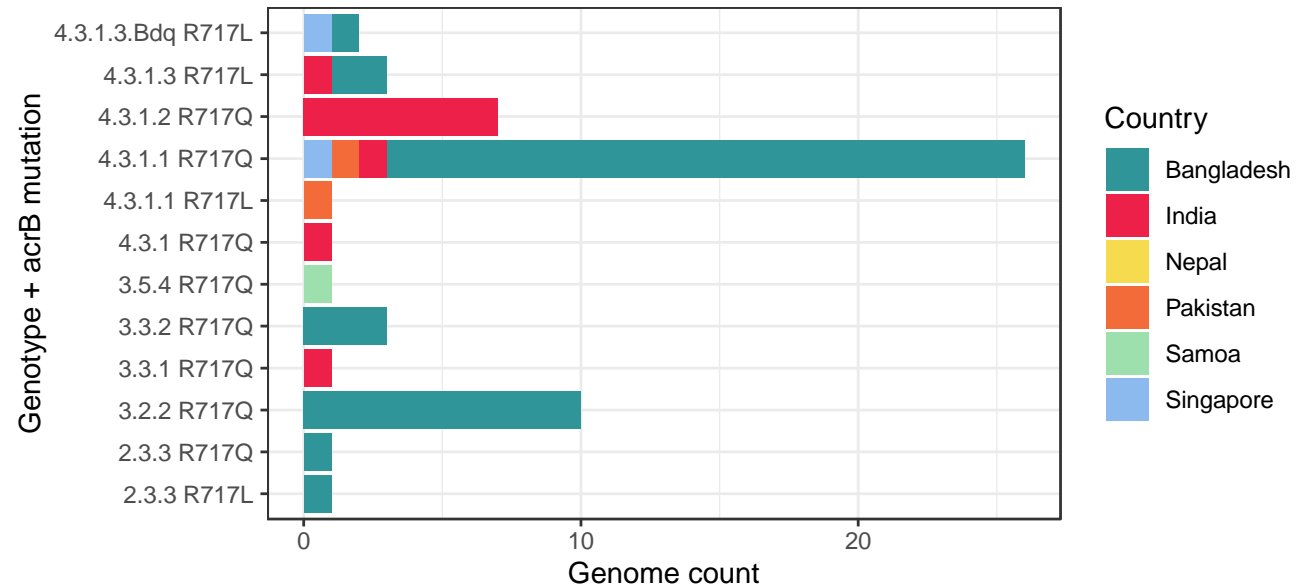


# Distribution of *acrB* mutants

a) Distribution of *acrB* mutants



b) *acrB* mutants by country



# XDR *S. Typhi* in Pakistan

- Rwp1-PK1 isolated from Rawalpindi in July 2015 from a 17-year-old male
  - Following ceftriaxone treatment failure, strain [was found to be phenotypically XDR](#)
- Strain [was later sequenced](#) and shares the full set of AMR determinants typical of 4.3.1.1.P1, but was not included in previous genotyping or comparative genomic analyses
- **XDR strain was present in northern Pakistan for at least a full year before ceftriaxone outbreaks in the southern province of Sindh**

