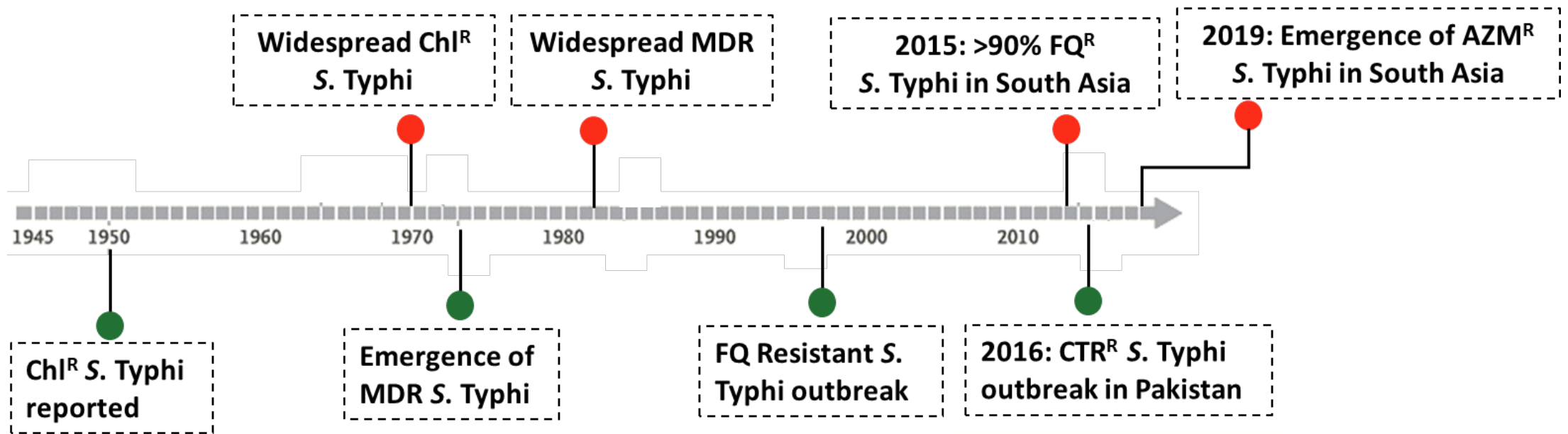


# Recent emergence of cephalosporin-resistant *Salmonella* Typhi carrying IncFIB(K) plasmids encoding *bla*<sub>CTX-M-15</sub> gene in India

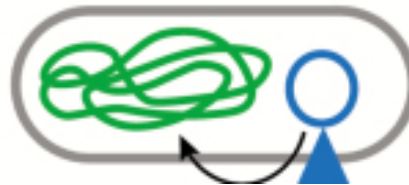


**Tharani Priya T**  
**Doctoral student | Christian Medical College, Vellore**

# Drug Resistant S. Typhi: The timeline



AMR genes on IncHI1 plasmid

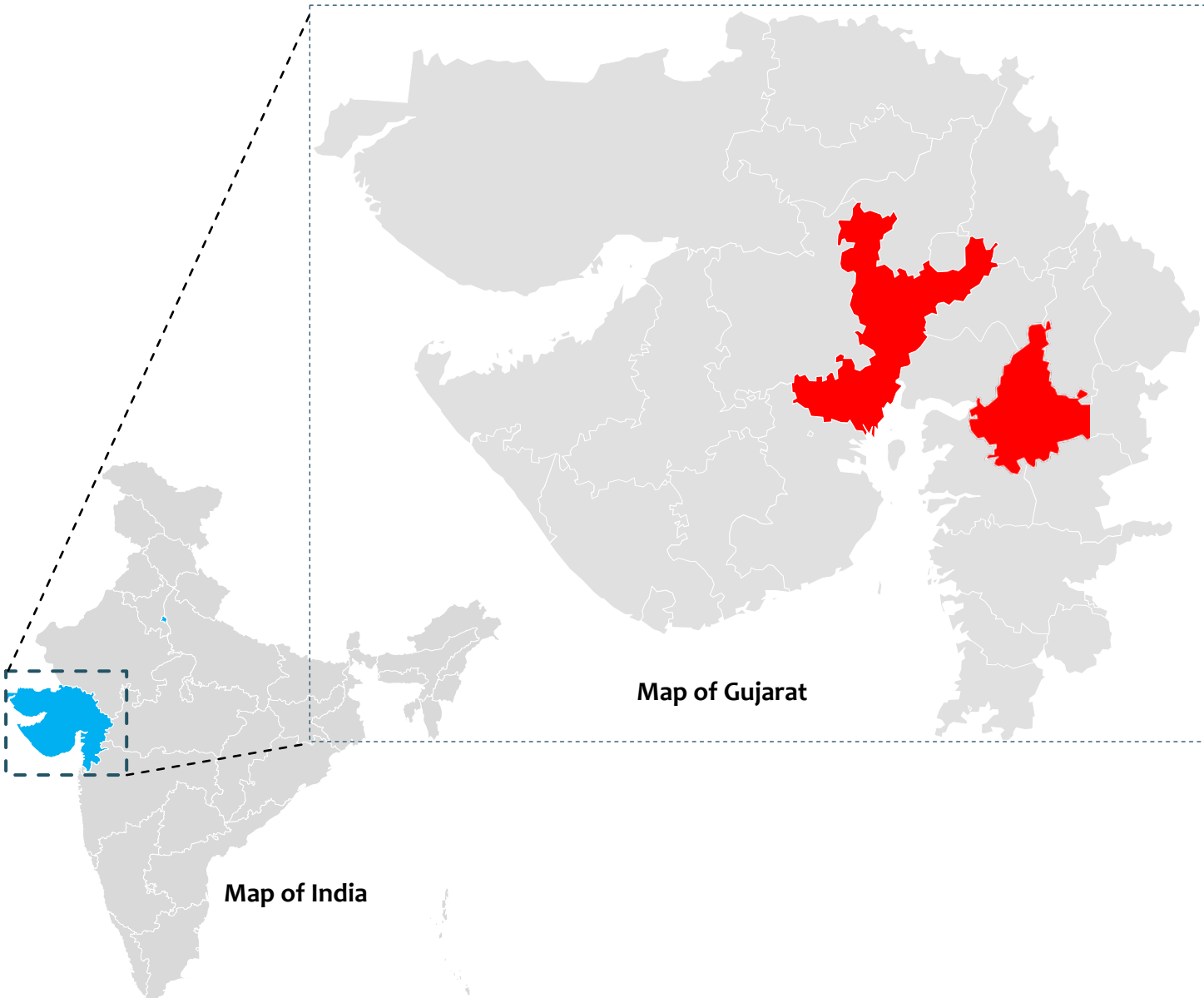


AMR genes on IncY plasmid and chromosome



XDR S. Typhi

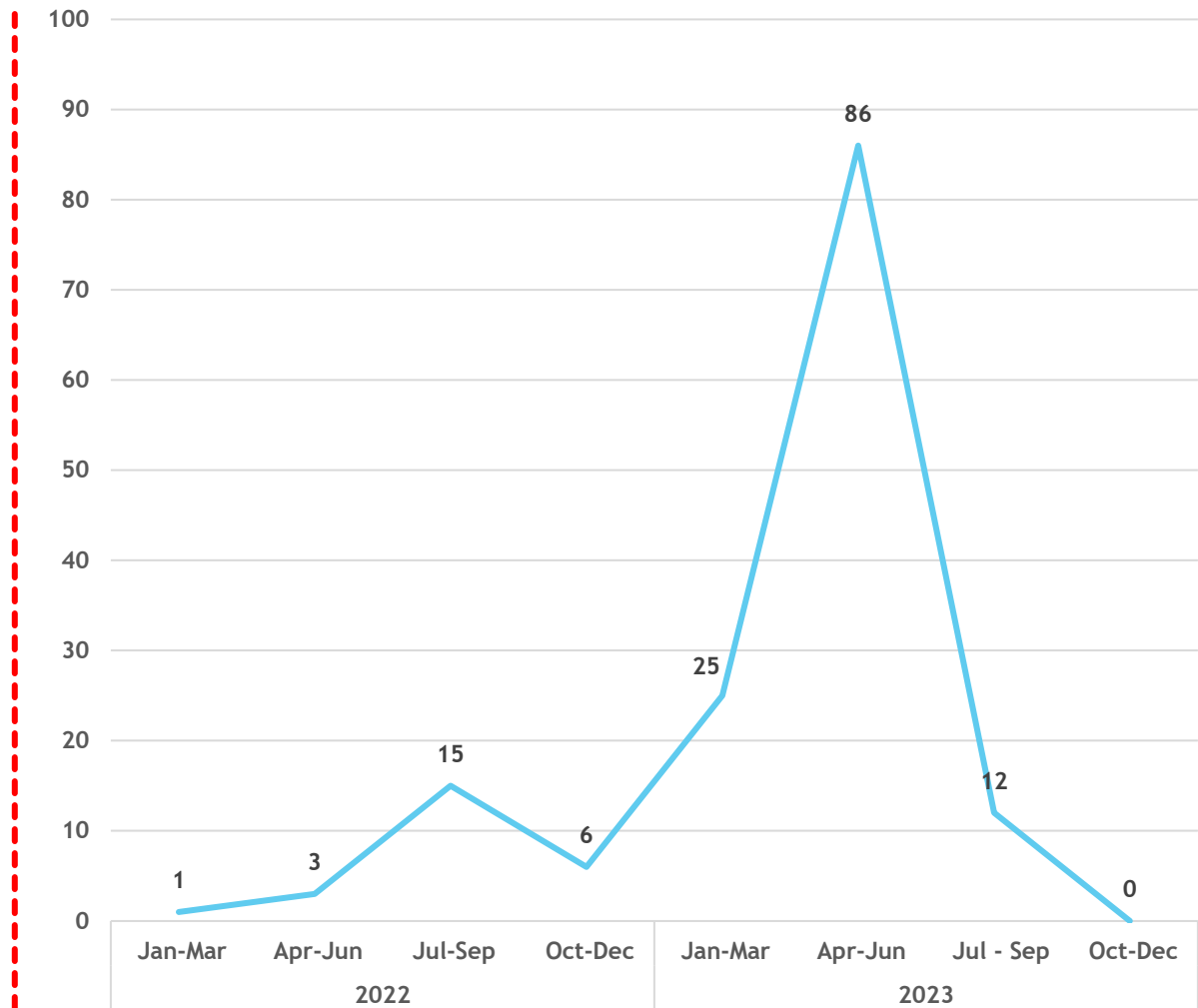
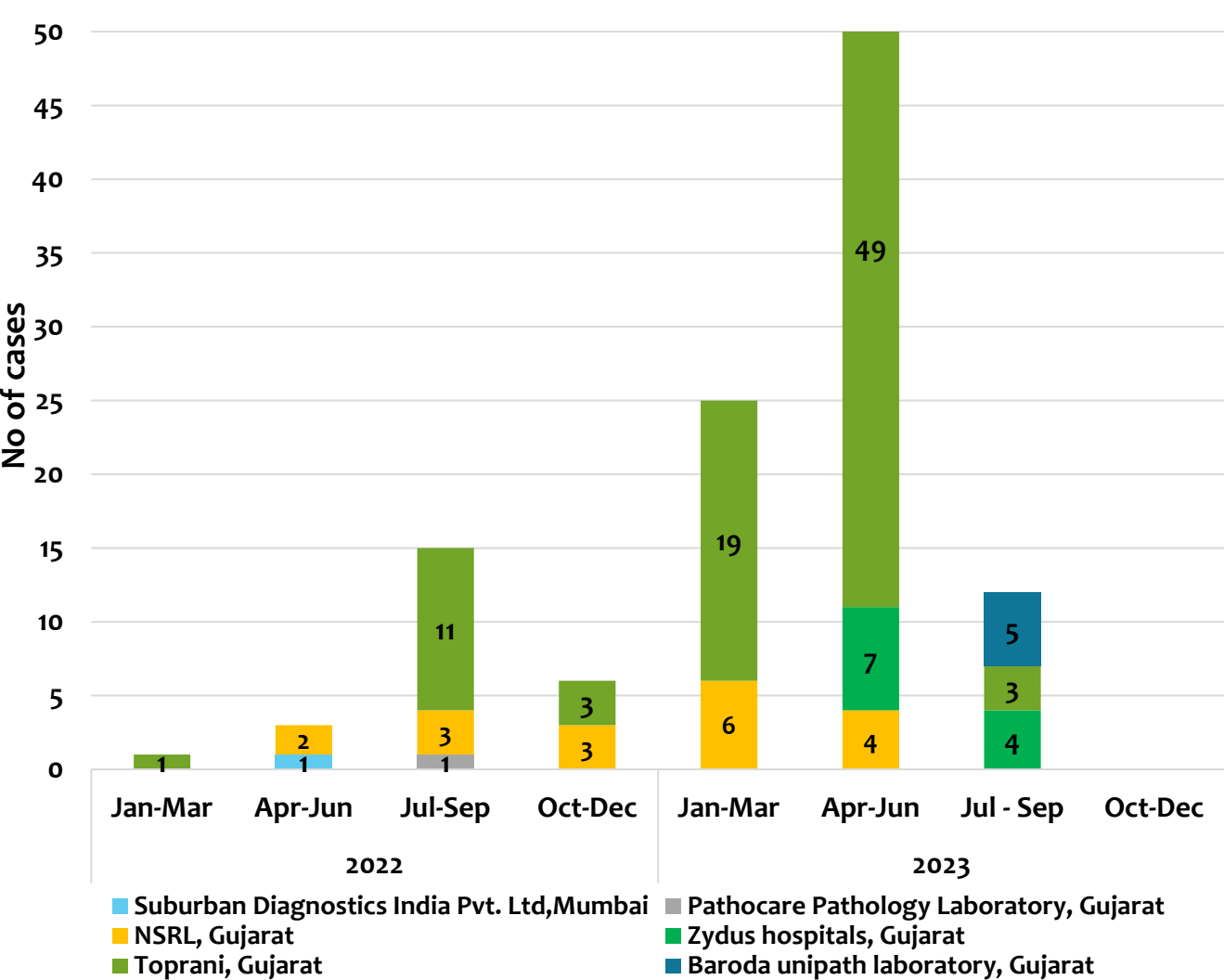
# Outbreak of Ceftriaxone Resistant *S. Typhi* in India?



- 08/2022: **Single isolate** of Ceftriaxone resistant *S. Typhi* from Pathocare lab
- 11/2022: 8 isolates from NSRL lab were confirmed as Cef<sup>R</sup> @ CMC (June onwards)
- 05/2023: 11 isolates from Zydus hospital were confirmed as Cef<sup>R</sup> @ CMC
- 06/2023: 10 isolates from the 2<sup>nd</sup> Batch (NSRL) confirmed as Cef<sup>R</sup>
- 06/2023 onwards: ~100 isolates of Ceftriaxone resistant *S. Typhi* from different diagnostic centres across Vadodara

# Timeline of the emergence of CEF-R S. Typhi

## from diagnostic centres in Gujarat, India



# In the News: CEF-R S. Typhi outbreak in Vadodara, Gujarat

11/29/23, 4:08 PM

Typhoid getting stubborn, recovery taking longer now - Times of India

Printed from

**THE TIMES OF INDIA**

## Typhoid getting stubborn, recovery taking longer now

TNN | Jul 14, 2023, 09.53 AM IST



VADODARA: Typhoid, which is otherwise widely prevalent and treatable with known medicines is fast becoming become a nightmare for doctors and patients alike.

Alarming, the bacterial infection is showing stubborn resistance to multiple drugs that have been used for decades to treat this disease that is caused by consuming contaminated water or food. As a result, the symptoms, which usually subside within seven to 10 days, are giving patients a harrowing time for as long as 20-25 days.

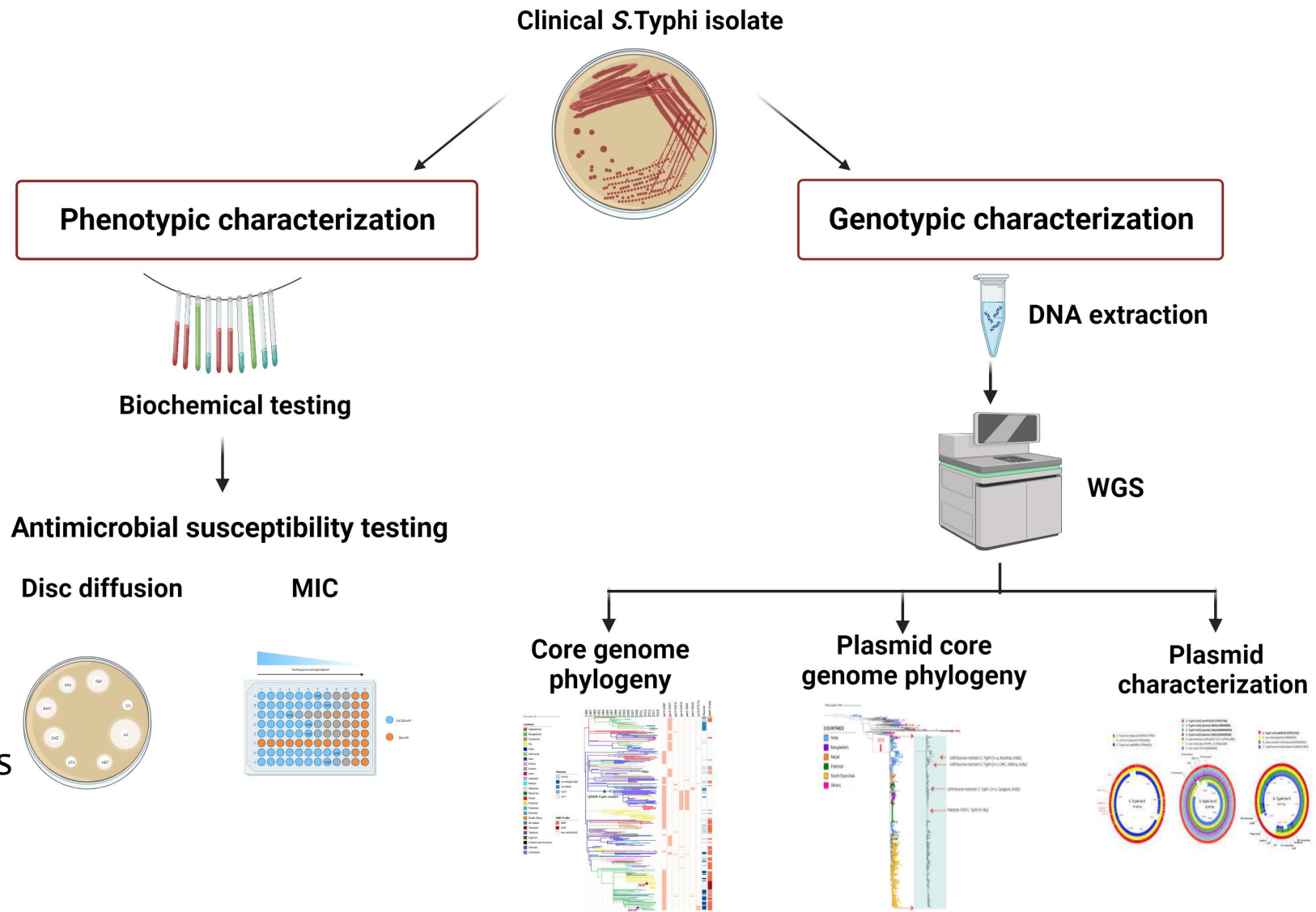
# Methodology

## Phenotypic characterization

- Antimicrobial susceptibility testing (DD, MIC)

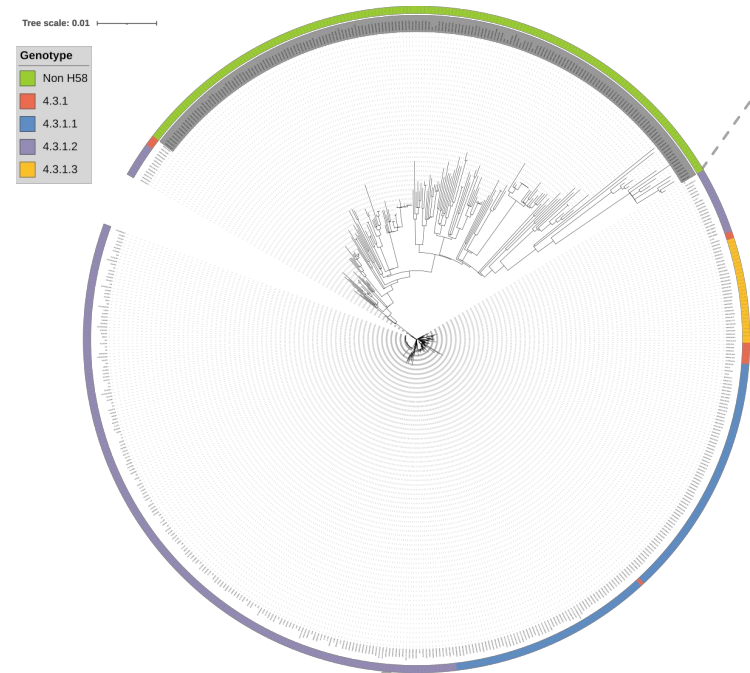
## Molecular characterization

- Whole Genome Sequencing
  - S. Typhi - 148 isolates
  - 16 contemporary isolates
- Genomic analysis
  - Comparative genomic analysis
  - Phylogenetic analysis
  - Plasmid characterization





# Core Genome Phylogeny of global H58 *S. Typhi* isolates



Maximum likelihood tree of 553 *S. Typhi* (H58 and non-H58)

Tree scale: 0.1

**Genotype 2**

- 4.3.1
- 4.3.1.1
- 4.3.1.2
- 4.3.1.3

**Location**

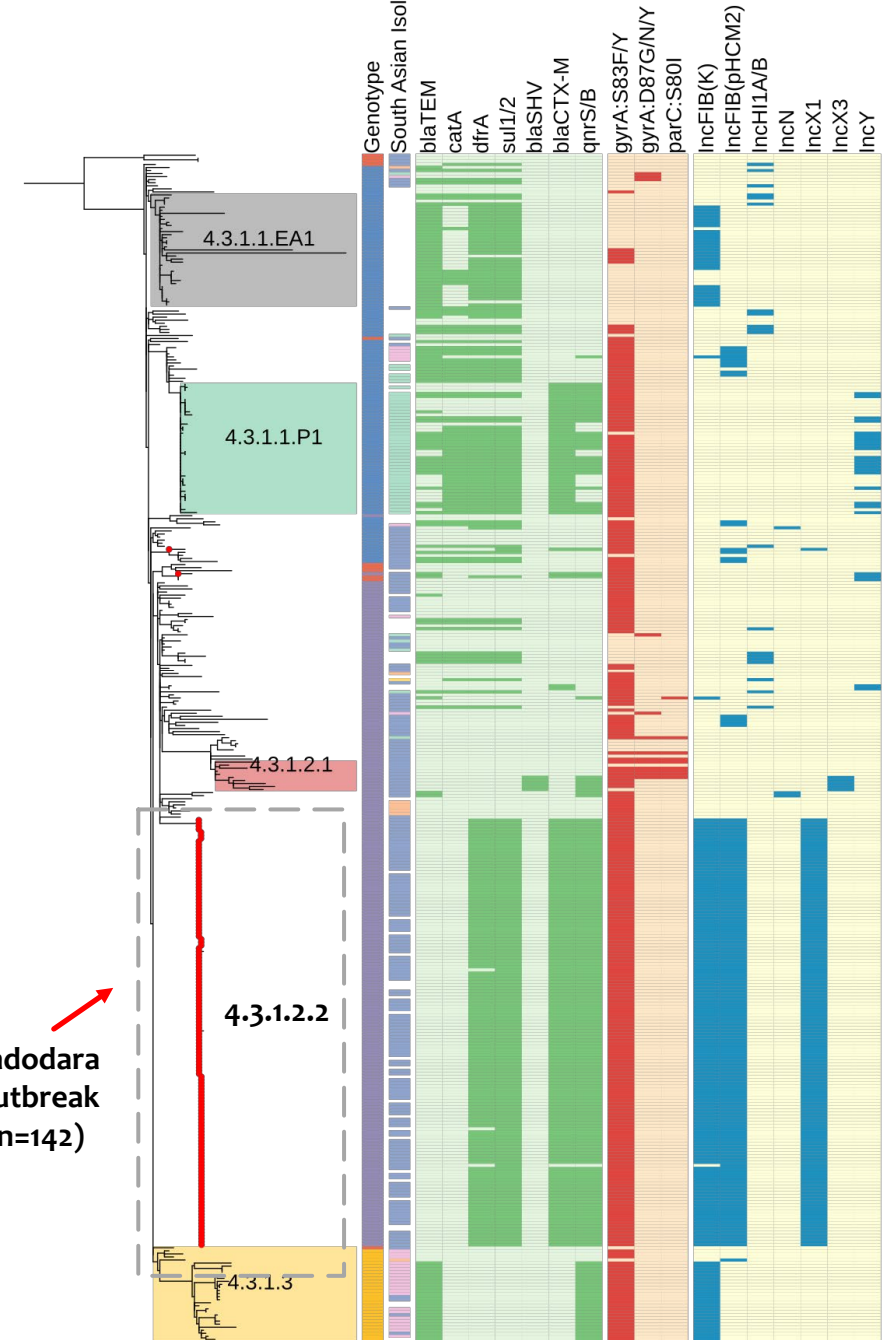
- India
- Pakistan
- Bangladesh
- Nepal
- Sri Lanka

**Lineage**

- 4.3.1.1.P1
- 4.3.1.1.EA1
- 4.3.1.3
- 4.3.1.2.1

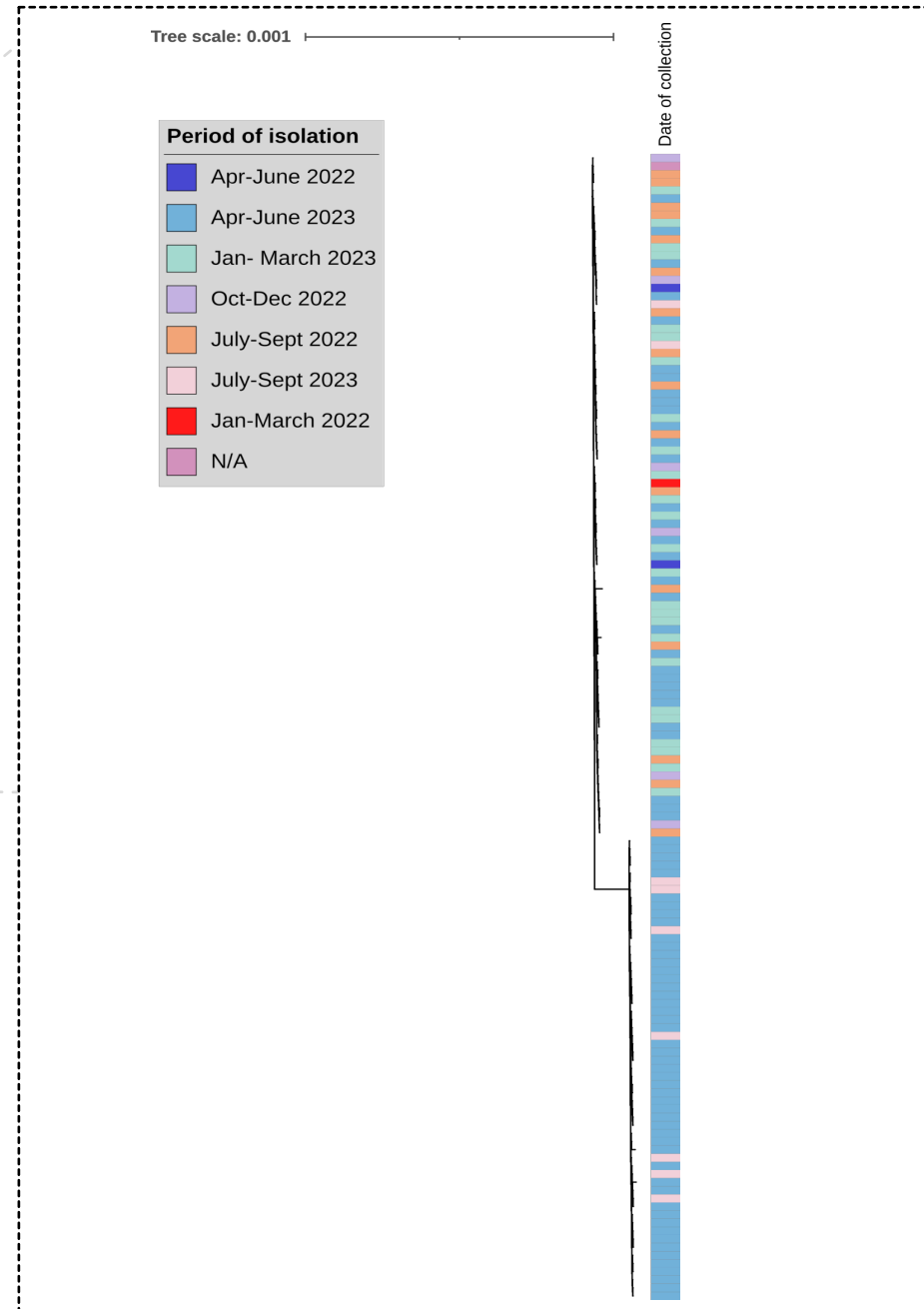
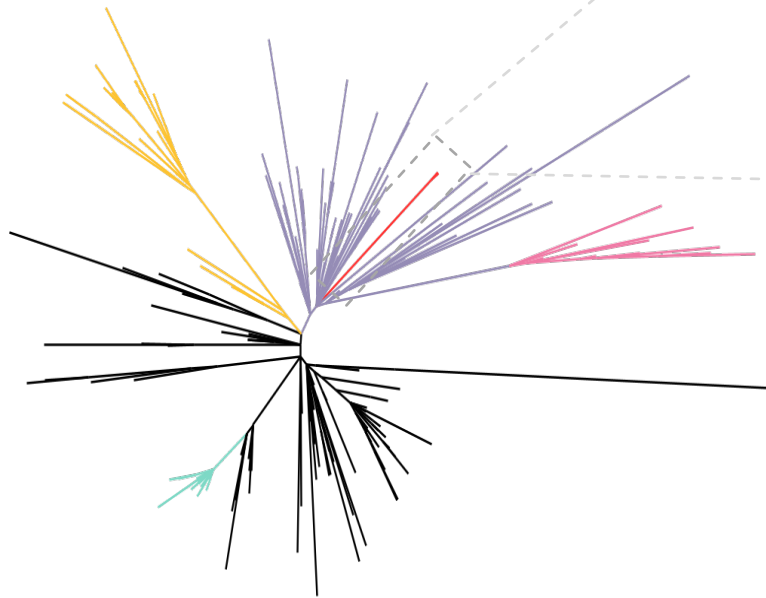
**Study Isolates**

- Study Isolates



Population structure of H58 *S. Typhi* isolates (n=371)

# Unrooted phylogenetic tree of CTR-R *S. Typhi* outbreak isolates

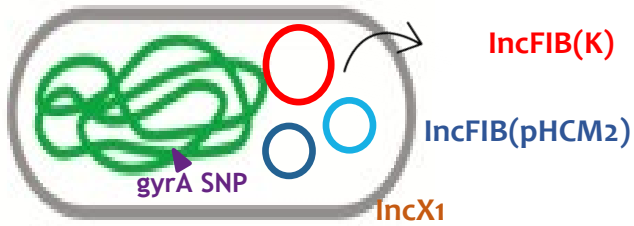


EF



# Genomic Characterization of Cef<sup>R</sup> *S. Typhi* in India

## Vadodara Outbreak



AMR genes in  
**IncFIB(K)** Plasmid

H58 (4.3.1.2)

Plasmid: AMR genes  
**IncFIB(K):** CTX-M, dfrA, sul,  
qnrS

**QRDR**  
gyrA: S83F

## Reported from Delhi



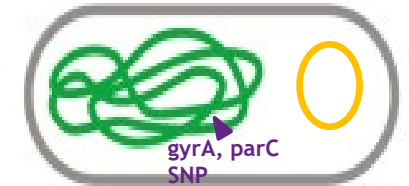
AMR genes in **IncY**  
Plasmid

H58 (4.3.1)

Plasmid: AMR genes  
**IncY:** TEM1B, CTX-M, dfrA,  
sul, tet, qnrS

**QRDR**  
gyrA: S83F

## Reported from Mumbai



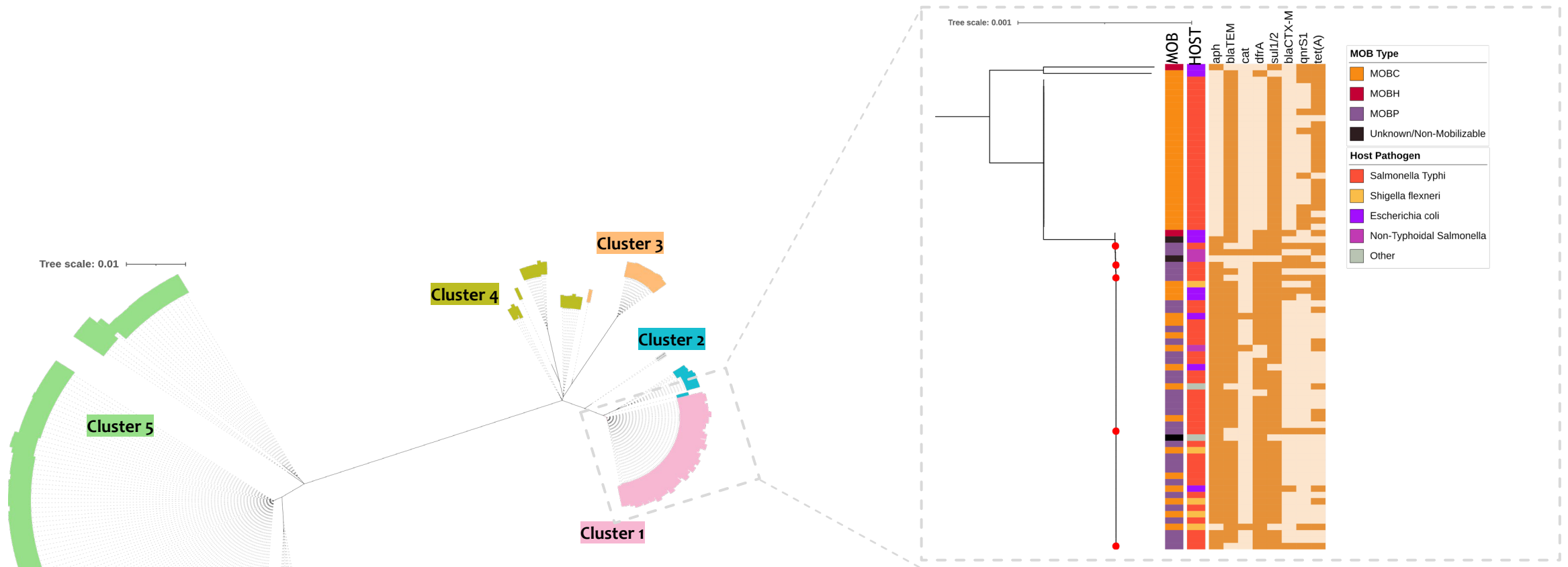
AMR genes in **IncX3**  
Plasmid

H58 (4.3.1.2)

Plasmid: AMR genes  
**IncX3:** , SHV-12, qnrB

**QRDR**  
gyrA: S83F, D87N, S80I

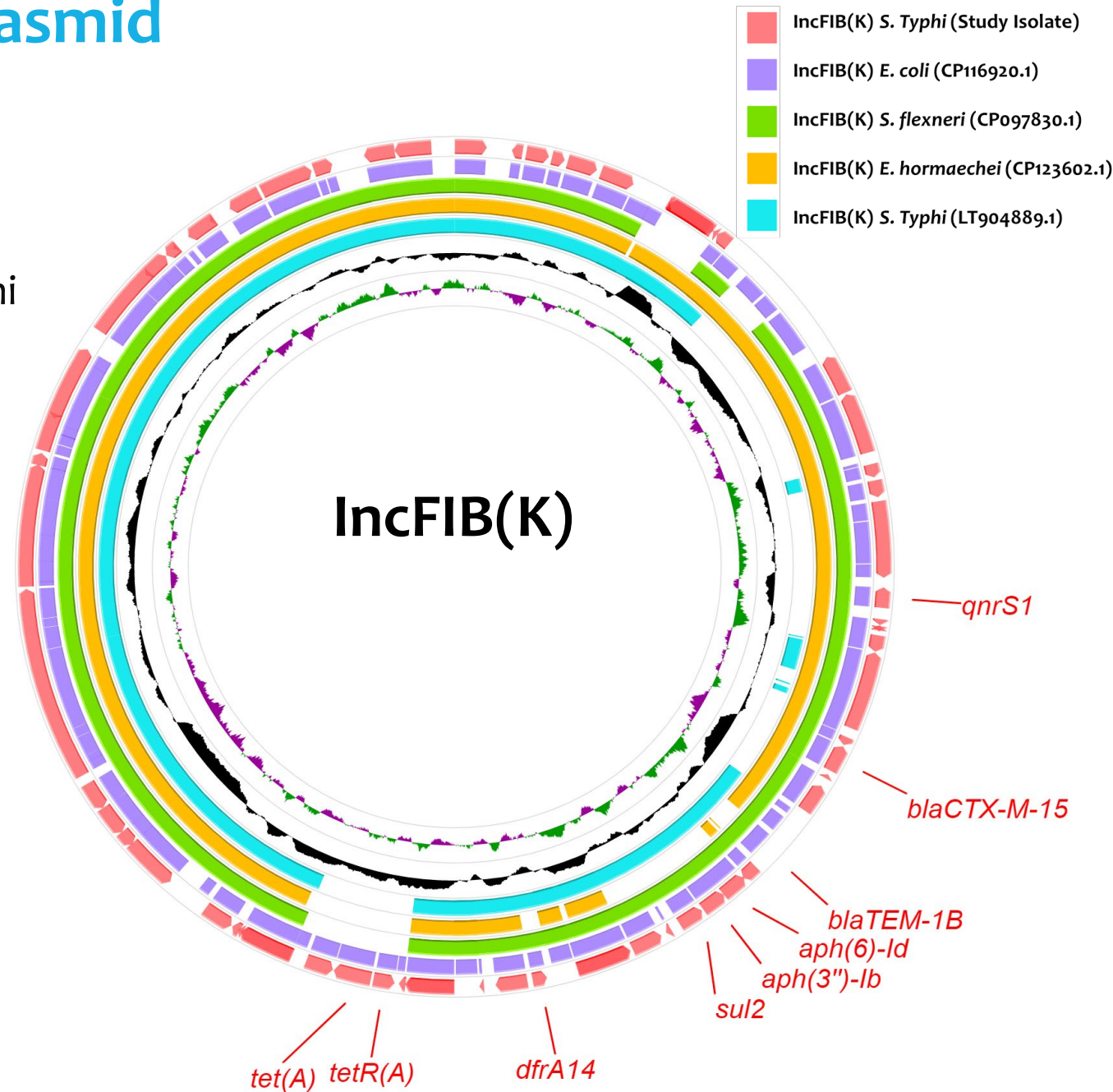
# Core Phylogenetic tree of global IncFIB(K) plasmids (n=276)



- ✓ Dataset includes plasmids from diverse bacterial hosts *K. pneumoniae*, *S. Typhi*, *E. coli* and other bacterial spp
- ✓ Cluster 1 carried IncFIB(K) plasmid from global collection similar to study isolates
- ✓ Core gene SNP of IncFIB(K) plasmid from other Enterobacteriales were similar to that of study isolates

# Characterisation of IncFIB(K) plasmid

- ✓ **IncFIB(K)** plasmid confers resistance to 3GC by means of *bla*<sub>CTX-M-15</sub> gene
- ✓ Closer to IncFIB(K) plasmid of Tanzanian *S. Typhi* strain (LT904889) (isolated on 2008) and European *E. coli* (CP116920)
- ✓ IncFIB(K) plasmids carried by *S. Typhi* from Bangladesh showed less similarity
- ✓ Possible transmission from other Enterobacteriales



# Key observation

- ✓ Outbreak of ceftriaxone-resistant *S. Typhi* detected from Vadodara & Ahmedabad, India
- ✓ These isolates carried **three plasmids: IncFIB(K)**, IncX1 and IncFIB(pHCM2) where **IncFIB(K)** plasmid confers resistance to 3GC by means of *bla*<sub>CTX-M-15</sub> gene
- ✓ Other resistance determinants such as *aph(3'')*, *aph(6')*, *sul2*, *dfrA14* and *tetA* were identified
- ✓ Genotyping and phylogenetic analysis revealed that the outbreak isolates (*n*=142) belong to a **distinct subclade (4.3.1.2.2)** within genotype 4.3.1.2 (H58 lineage II)
- ✓ SNP-based phylogenetic analysis of the core genes in IncFIB(K) revealed the plasmid backbone is **closely related to** that of IncFIB(K) from **other Enterobacteriales**
- ✓ Possible transmission from other Enterobacteriales



# Conclusion

- **S. Typhi continues to improve its ability to remodel its genome**
  - Acquisition of various mobile genetic elements and different genetic structures which are related to antibiotic resistance
- **Exposure of third-generation cephalosporins during the treatment**
  - Beginning of a new wave of ceftriaxone-resistant S. Typhi in India
- **Measures to reduce the emergence of increasingly resistant strains of S. Typhi**
  - Introduction of new typhoid conjugate vaccines as well as other control measures such as improved water, sanitation, and hygiene (WASH) systems





# Acknowledgement



BILL & MELINDA  
GATES foundation



Dr. Balaji Veeraraghavan

Ankur Mutreja

Dr. Jobin John Jacob

Megan Carey

Dr. Gagandeep Kang

Anton Spadar

Dr. Jacob John

Mr. Aravind V

Ms. Monisha

Ms. Pavithra

Ms. Yamini



# Thank you...!

