Assessment of population structure and antimicrobial resistance pattern of *Salmonella* Typhi isolates using whole genome sequencing data in Bangladesh

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11th International Conference on Typhoid and other Invasive Salmonelloses
Hanoi, Vietnam
March 2019
Estimates of typhoid burden in Bangladesh

- Typhoid fever remains a public health threat especially in South Asia including Bangladesh due to poor access of safe water and sanitation system.

- In Bangladesh, an overall population incidence of typhoid estimated between 292 - 395 per 100,000 people per year (Theiss-Nyland et al. 2019)

- The indiscriminate use of antibiotics is accelerating the reports of multi-drug resistance.

- Whole genome sequence based study emphasizes the importance of surveillance to understand the AMR trend to facilitate patient management.
S. Typhi strains isolated from Bangladesh (1998 - 2016)

A total of 818 S. Typhi strains were utilized for genomic analysis

- 202 S. Typhi strains from 3 urban areas inside Dhaka city (2003 - 2016)
  - icddr,b Dhaka Hospital (n= 43)
  - icddr,b Kamalapur field site (n= 130)
  - icddr,b Mirpur field site (n= 29)

- Also 616 previously published sequence data were included (1998 - 2016)
  - From Wong et al. 2016 (n= 88)
  - From Tanmoy et al. 2018 (n= 528)
Genomic analysis workflow

Raw read data (fastq format)

Quality check (fastqc)

Population structure

Genotyping framework

AMR, Plasmid analysis

Insertion sites

Phylogenetic tree construction

RedDog Pipeline: http://github.com/katholt/RedDog
Spatial analysis of 202 S. Typhi strains of this study

Microreact: https://microreact.org/project/S1a1IWN7N
Genotypic distribution of 818 S. Typhi strains

- Revealed 17 distinct genotypes
- Genotype 4.3.1 (H58) dominant
- H58 lineage I (4.3.1.1) more common among Bangladeshi strains than lineage II
- New H58 lineage called “lineage Bd” (4.3.1.Bd) reported in Tanmoy et al. 2018 was also found in our collection
Timeline of Bangladeshi Typhi strains sequenced from 1998 - 2016

- Rapid increase of genotypes 3.3.0, 3.2.2, and 2.3.3 carrying only 1 QRDR in recent years
Bangladeshi 818 S. Typhi population structure with AMR

Acquired AMR genes (defined as MDR)

- $\text{bla}_{\text{TEM}-1}$ (ampicillin)
- $\text{catA1}$ (chloramphenicol)
- $\text{dfrA7, sul1, sul2}$ (cotrimoxazole)

- MDR genes without evidence of IncHI1 plasmids observed in only H58 lineage I isolates

- QRDR mutation in $\text{gyrA}$ (S83F or S83Y) was the most prevalent

**AMR and plasmid analysis:**

- ariba: [https://github.com/sanger-pathogens/ariba](https://github.com/sanger-pathogens/ariba)
- SRST2: [https://github.com/katholt/SRST2](https://github.com/katholt/SRST2)
Newly defined “lineage Bd” in Bangladeshi S. Typhi strains

• A newly defined H58 lineage reported in Tanmoy et al. 2018 as “lineage Bd” (4.3.1.Bd) was found in 138 Typhi strains

• Revealed **two major patterns** in terms of AMR gene and plasmid association
  - Strains harbouring IncHI1-PST6 plasmid contained 8 AMR genes \( \text{cat}A1, \text{dfr}A, \text{sul}1, \text{bla}_{\text{TEM}-1}, \text{str}AB, \text{sul}2, \text{tet}B \)
  - Strains carrying IncFIBK plasmid associated with only 4 AMR genes \( \text{bla}_{\text{TEM}-1}, \text{sul}2, \text{qnr}S1, \text{tet}A \)
Insertion sites of transposons in S. Typhi isolates

- Two separate integration event of IS1 site observed in H58 lineage I isolates
  - STY3618 and STY3619 locus near gene cyaA
  - STY3947 locus near gene yidA

- Acquired AMR genes encoded within Tn2670 composite transposon, comprising Tn6029 (blaTEM-1, strB, strA, sul2) and Tn21 (dfrA7, sul1) inserted within Tn9 (catA1)

ISMapper: [https://github.com/jhawkey/IS_mapper](https://github.com/jhawkey/IS Mapper)
Global and regional S. Typhi strain circulation patterns
Conclusions

WGS data of S. Typhi strains representative of the past 18 years from Bangladesh suggest that:

- H58 lineage I (39.1%) most common in Bangladeshi strains followed by H58 lineage Bd strains (16.8%)
- MDR phenotype strongly correlated with H58 isolates than non-H58 isolates
- Reported for the first time two different patterns of AMR and plasmid association in lineage Bd isolates (4.3.1.Bd)
- Rapid spread of genotype 2.3.3, 3.2.2,3.3.0 carrying only QRDR mutation led to reduce fluoroquinolone susceptibility
- Highlights the need for laboratory and molecular based surveillance to monitor acquisition of AMR and ongoing evolution in endemic regions
Acknowledgments

• icddr,b
Farhana Khanam, Saruar Bhuiyan, Taufiquur Rahman Bhuiyan, Firdausi Qadri

• Wellcome Trust Sanger Institute, University of Cambridge
Zoe Dyson, Elizabeth Klemm, Pathogen informatics team, Gordon Dougan
15th International Asian Scientific Conference on Diarrheal Disease & Nutrition (ASCODD)

Date: January 28-30, 2020

Venue: icddr,b, Dhaka, Bangladesh

Theme: Humanitarian Crisis and Impact on Diarrhoeal diseases and Nutrition