A NGS Approach to Characterize Drug Resistance of *Salmonella enterica* serovar Typhi

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Background: Enteric fever is a systemic illness, predominantly caused by *Salmonella enterica* serovar Typhi. Globally, it affects an estimated 17-22 million people/year, with about 200,000 deaths, especially in the developing countries including Bangladesh. Timely treatment with appropriate antibiotics is crucial. However, the emergence of antimicrobial resistance (AMR), specifically to ampicillin(AMP), chloramphenicol(CHL), cotrimoxazole(SXT) and ciprofloxacin(CIP) has reached an alarming level and become major public health threat. AMR is encoded on multiple chromosomal and extra-chromosomal genes that can be identified by the Next Generation Sequencing (NGS). So, our study aimed to detect the molecular pathways responsible for AMR & predict the phenotypic-susceptibility from Whole Genome Sequence (WGS).

Methods: During 1999-2013, >3000 *Salmonella* Typhi were isolated from blood of enteric fever patients at Dhaka Shishu (children) Hospital, Bangladesh. 551 strains were selected (337 hospitalized & 214 attending outpatient facility) for the study. Strains were confirmed by biochemical and specific-antisera tests. Antimicrobial susceptibility was measured by disk-diffusion (CLSI-2016). WGS was done with Illumina-Hiseq and is being analyzed using de-novo assembly (Newbler), own-scripts to attain closed genome, comparative-genomics (Mauve) and annotation (SABIA).

Results: 39%(215/551) of selected strains was multidrug resistant (MDR, resistant to AMP-CHL-SXT), from 38%(6/16) in 1999, to 26%(12/47) in 2013. In contrast, 87%(481/551) of selected *S.* Typhi strains was CIP-non-susceptible, ranging from 50%(8/16) in 1999, to 89%(42/47) in 2013. Preliminary mapping results showed presence of plasmid pHCM1 (contains AMR-genes) and pHCM2 in 9%(50/551) and 41%(228/551) of selected strains respectively. A *Salmonella* Genomic Island (SGI11, contains AMP/CHL/SXT-resistance genes) was found in 98%(211/215) of MDR strains. In contrast, only 22%(47/215) MDR strains had pHCM1.

Conclusion: Successful analysis of the WGS data, combined with the clinical and laboratory metadata will help us to identify the molecular pathways for AMR. This could also serve as the preliminary step to design a real-time characterization tool for enteric pathogens based on genomic information on AMR.