

## RESULTS

We investigated the capacity of NET release ex vivo upon stimulation with PMA by microscopy and observed that 2 hrs of PMA stimulation induced maximum NET release. A range of multiplicity of infection (MOI) was tested (0.5 to 20) and MOI 10 was the highest for efficient killing. NET-mediated killing of *S. Typhi* was highest (42%) at acute stage of typhoid fever. This killing capacity of NET was reducing from infective stage to acute convalescence stage (36%). At late convalescence, the killing capacity was further reduced (21%) that was close to healthy controls (15%). NET-mediated killing capacity of neutrophils isolated from typhoid fever patients coincided with the recovery of patients.

## CONCLUSIONS

Our results show that neutrophils isolated from typhoid fever patients are active in entrapping and killing of *S. Typhi* by NET ex vivo. NET assay could be an useful marker to correlate with prognosis of typhoid fever. Further analysis is ongoing in more patients as well as typhoid vaccine recipients (Tybar-TCV).

### 14. Developing Enterprise Level Multi-Layered National Data Management System for Near Real-Time Surveillance of Enteric Fever Data at Indian Sites

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## BACKGROUND

Electronic data capture systems experience challenge while synchronizing different locations' data at near real-time intervals with appositeness, quality and reporting. By leveraging technology advancement, we built robust data collection system for Tier I community surveillance for enteric fever across four sites in India.

## METHODS

The system was designed for community-based cohorts in diverse locations across India for active fever surveillance. People from IT science, Android developers and public health scientists worked together in developing the Application. It was designed on a multi-layered architecture to run on Android tablets, web-browser and secured cloud infrastructure; providing server-side services hosting robust object-relational database.

The android app "EntericFev" was developed using *androidstudio*, Java programming language. Version controlling for development process was done on GitHub platform with manual testing for every version. The web-browser based forms for capturing suspected typhoid cases (STF) and clinical lab reports were designed using *Codelgniter* PHP framework and hosted on Apache web services. Data are pushed to *PostgreSQL*, secured object-relational database configured to provide standard security with fine-grained access control, audit trails, logs and regular backups. User-friendly interface using Adminer database management tool supports Data Managers. An online data visualization tool, *Amazon QuickSight* was deployed with site-level access which provided a good graphical

representation of data and some quick pre-defined results of analysis for continued monitoring data quality. Summary tables for visualization process got populated at pre-defined time intervals using *Pentaho Data Integration* tool. Server-side infrastructure is hosted on EC2 instance on Amazon Web Services (AWS). We chose a t2.large type instance with two virtual CPUs, one elastic IP, 300 GiB volume and installed Red Hat Enterprise Linux 7.3 on it.

## RESULTS

The architecture works in unison to achieve flawless quality data capture. Since its deployment in July 2017, *EntericFev*, used by 184 users has generated 20,41,230 data points from four sites capturing information of 25,304 participants. Excellent audit trails are instituted that have captured 41,81,614 trails.

## CONCLUSIONS

*EntericFev* provided a robust software for data management of National Surveillance System and is easily scalable to National or Global level for any number of sites with minimal efforts.

### 15. Geospatial Mapping of the Global Prevalence of Antimicrobial Resistant *Salmonella Typhi* and *Paratyphi A* Isolates

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## BACKGROUND

Antimicrobial resistance of *Salmonella Typhi* and *Paratyphi A* strains has been reported from multiple countries, negatively impacting our ability to treat and control infections. However, there are gaps in our understanding of the geographic distribution and prevalence of resistant *S. Typhi* and *Paratyphi A*. Understanding the distribution of resistance is vital for informing policy and combating the spread of disease.

## METHODS

We are compiling a dataset of the proportion of *S. Typhi* and *Paratyphi A* isolates resistant to key antimicrobials, linked to specific times and locations. Data have been extracted from published literature from 1990 to 2017; this will be supplemented by data from additional sources.

A geospatial modelling framework will be used to predict the proportion of *S. Typhi* and *Paratyphi A* isolates with multidrug resistance and fluoroquinolone non-susceptibility, at a high spatial resolution. Briefly, a stacked generalisation ensemble model will capture the associations between selected covariates and the resistance data; then a Bayesian model based geostatistical model will be fit to the data, accounting for the remaining spatial and temporal correlation and producing pixel level estimates of resistance. Additional covariates on antibiotic use and treatment seeking behaviour are being produced to inform the model.

**RESULTS**

The majority of data obtained from published literature is from South Asia, with a paucity of microbiological data identified from Africa and the Middle East, and large data gaps in Southeast Asia.

These data show large variations in resistance by antimicrobial, geographic location, year of isolation, and *Salmonella enterica* serovar. Trends of decreasing multidrug resistance and increasing fluoroquinolone non-susceptibility in *S. Typhi* are evident in South Asia, however high heterogeneity within the region is noted. High-resolution maps of resistance will enable a more thorough analysis of resistance patterns.

**CONCLUSIONS**

We discuss methodological plans to leverage existing data and geospatial modelling techniques to produce robust, validated estimates of resistance in *S. Typhi* and Paratyphi A globally. Heterogeneity within published data highlights the importance of these techniques and the need for additional data to inform the model. A collaborative effort is required to produce accurate estimates of the prevalence of antimicrobial resistant *S. Typhi* and Paratyphi A.

## 16. Ceftriaxone Resistance in *Salmonella* – The New Threat in *S. Paratyphi A*

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**BACKGROUND**

Concern is growing that widespread carriage of extended spectrum beta-lactamases by *Salmonella Typhi* is spreading. An outbreak in Pakistan of ceftriaxone resistant typhoid fever and surveillance on travellers returning to the UK suggests this fear is being realised. The new Vi-conjugate vaccine for typhoid fever offers real hope for the control of typhoid fever but no human vaccine is available for other invasive salmonellosis. CTX-M enzymes are the most commonly reported from salmonella and so screening for these enzymes is prudent.

**METHODS**

We have screened all available salmonella referred to PHE between 2014 - Oct 2018 for CTX-M carriage by whole genome sequencing using Illumina Hi-seq protocols (47,872 sequence datasets), analysed in detail the plasmids from enteric fever pathogens and compared them to previously reported cases.

**RESULTS**

387 *Salmonella* were found to encode CTX\_M enzymes in their genomes, with CTX-M-9, CTX-M-14 and CTX-M-65, CTX-M-55/TEM-1 & CTX-M-15/TEM-1 as the most common markers. One of these was a *S. Paratyphi A*. Examination of the plasmid revealed close identity to a CTX-M-15 encoding plasmid (PRJEB211992) isolated from a child in Bangladesh. The new plasmid (pSPA440915) was very similar in every respect and also contained the TEM191 gene. We must consider the transmission between these two predominant enteric fever pathogens as highly likely.

**CONCLUSIONS**

Here report the emergence of ceftriaxone resistant *S. Paratyphi A* seen in a traveller returning to the UK from Bangladesh. Given the lack of a vaccine for paratyphoid fever the surveillance for this strain of *S. Paratyphi A* needs to be prioritised in Bangladesh.

## 17. Distinct Susceptibility and Invasiveness Profiles in *Salmonella Infantis* From South Africa and the United Kingdom

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**BACKGROUND**

Amongst *Salmonella* serovars, *S. Infantis* has become the fourth commonest cause of human salmonellosis in the EU (including the UK), causing 30% of *Salmonella* infections in Israel and is the commonest serovar in domestic fowl worldwide. In South Africa, little is known about the epidemiology of *S. Infantis*.

**METHODS**

Invasive index of was calculated as the number of all sequenced isolates from blood culture divided by isolates from stool referred to the UK reference laboratory and included historical isolates and all data since 2014. Sequence type was designated according to the standard *Salmonella* MLST scheme (mlsst.net). To investigate this we further sequenced *S. Infantis* isolates from Public Health England between 2004 and 2017 and from the National Institute for Communicable Disease between 2003 and 2016. Whole genome sequencing of isolates was performed on an Illumina NextSeq machine at the Quadram Institute or on a HiSeq at PHE.

**RESULTS**

The Invasive Index of selected serovars from 2018 were as follows: *Salmonella Paratyphi A* = 64.79, *Salmonella Typhi* = 61.34, *Salmonella Dublin* = 34.62, *Salmonella Typhimurium* ST313 = 16.22 and *Salmonella Infantis* = 1.49.

The Invasive Index of *S. infantis* according to Sequence Type were as follows: ST603 = 18.2, ST32 = 3.2 and ST2283 = 1. Preliminary results from the sequencing of South African isolates suggests a higher burden of resistance in the UK (52.2% MDR) compared to South Africa (19.0%).

**CONCLUSIONS**

*S. Infantis* as a serovar is not considered invasive. Of 2579 isolates received with metadata by PHE only 40 were invasive. Interestingly when ST603 and ST32 were analysed separately the invasiveness index (23/888, 2.5%) was much higher suggesting that sub-groups of the *S. Infantis* serovar may be highly invasive. Furthermore antimicrobial resistance appears to be driven by the presence of the pESI plasmid and we are currently exploring this further.