Typhoid fever in urban Dhaka, Bangladesh: associated factors and antimicrobial resistance pattern

Farhana Khanam
icddr,b

TyVAC Typhoid Vaccine Acceleration Consortium
CENTER FOR VACCINE DEVELOPMENT • OXFORD VACCINE GROUP • PATH

Photo: PATH/Asad Zaidi

Background

- Urbanization has resulted in inadequate access to clean water and sanitary facilities, increasing the incidence of typhoid fever in many parts of the world, including Bangladesh
- A study conducted in urban Dhaka between 2016 to 2019 showed a higher typhoid burden; 161 cases per 100,000 person-years of observation
- Previous studies demonstrated various risk factors for developing typhoid fever including close contact with an infected person, consuming food that someone with typhoid fever has handled, and being a carrier of *S*. Typhi after recovery from typhoid fever
- Changes in risk factors and associations between risk factors and typhoid fever may occur with changes in expenditure for health, health-seeking behaviors, personal hygiene, and other related social factors
- It is crucial to understand the epidemiological and clinical aspects of typhoid fever since this will help scientists and public health experts develop evidence-based preventive measures

Objectives

- To determine the factors associated with typhoid fever
- To evaluate the attributes of each suspected typhoid case to predict who would be a confirmed case using the random forest classification model
- To determine the current antimicrobial resistance (AMR) pattern

Trial methods

- We analyzed the dataset of a cluster-randomized trial of Vi-TT vaccine conducted in a densely populated urban area of Dhaka, Bangladesh

- For the Vi-TT trial, a baseline census and biannual census updates were conducted to enumerate the study population and to collect household- and individual-level demographic, socioeconomic, and WASH information

- 205,760 population were enumerated at baseline and 239,493 population were active at the end of the study

- After the baseline census, the whole study area was divided into 150 clusters, which were randomized at a 1:1 ratio to a single dose of either the intervention (Vi-TT, Typbar-TCV) or control (SA 14-14-2 Japanese encephalitis [JE]) vaccine) given to children aged 9 months to <16 years

Trial methods (cont.)

- Individuals with a history of fever for ≥2 days or axillary temperature of ≥38°C were enrolled in the passive surveillance after obtaining informed consent
- Blood samples were collected from enrolled participants and assessed by microbiological cultures for *S*. Typhi
- Febrile episodes in which *S*. Typhi was isolated from blood culture and a home visit by the study staff confirmed the identity of the patient was defined as typhoid fever
- Antimicrobial susceptibility test was done by using the disk diffusion method and interpreted as per the Clinical and Laboratory Standards Institute (CLSI) guideline

Statistical analysis

- The dataset including the two-year follow-up of the study population of JE clusters was used for this analysis

- Demographic (i.e., age, gender, and religion), socioeconomic (i.e., monthly HH expenditure and construction material of house), and household WASH information (i.e., shared toilet, shared kitchen, hand wash practices, source of drinking water) were collected at baseline census

- Clinical data (i.e., temperature, duration of fever) from all suspected typhoid patients was collected during enrollment in the passive surveillance

- AMR data of culture-confirmed typhoid patients was also included in this analysis

Statistical analysis (cont.)

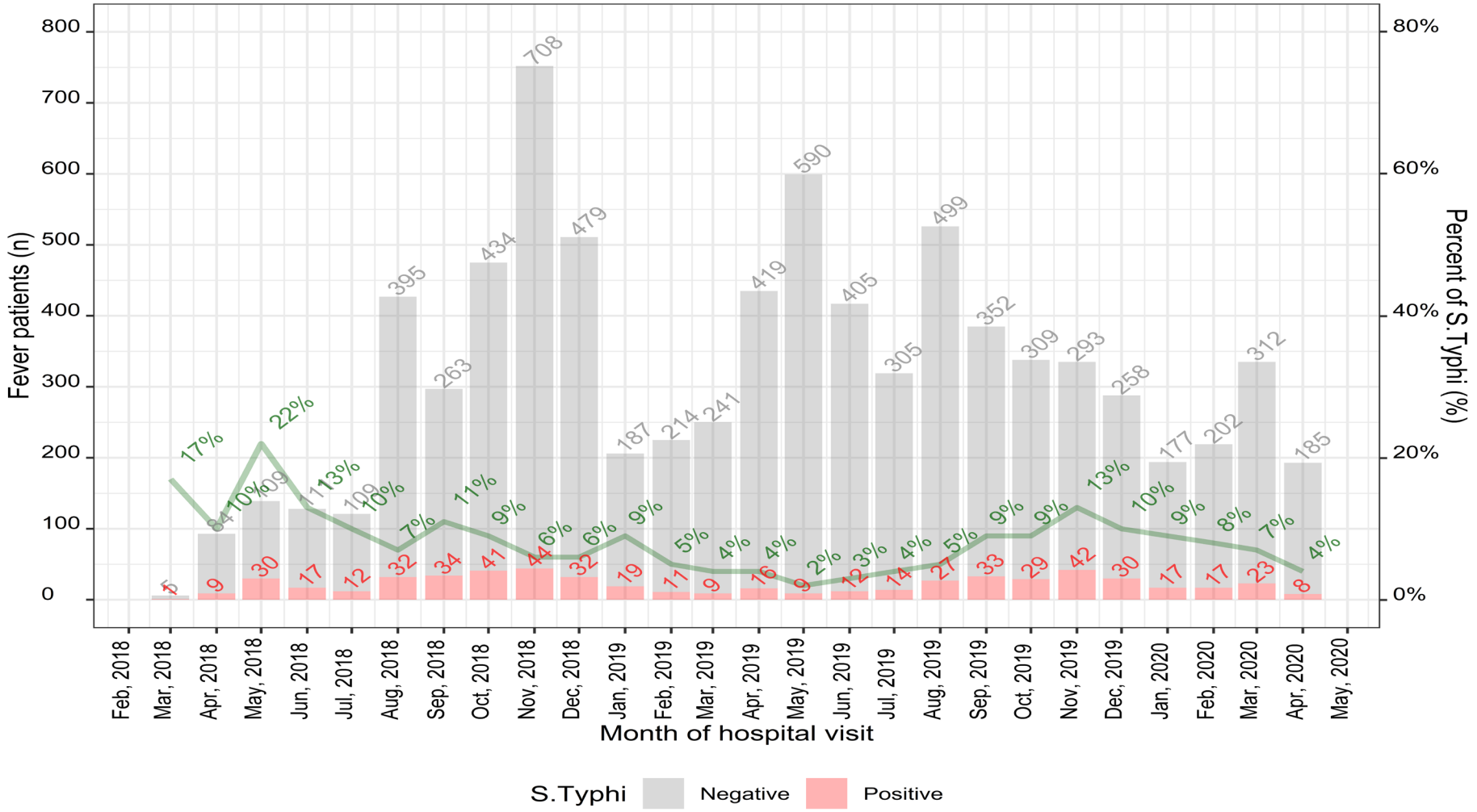
- A bivariate analysis was performed to determine the relationship between typhoid fever and different contributing factors
- The relevant applications of the Wilcoxon rank-sum, Fisher exact, and Pearson's Chi-squared tests were used to evaluate the statistical significance between categorical variables and typhoid fever
- The variables included in the multiple regression models were those that demonstrated a relationship (p-value ≤0.10) with typhoid fever in the bivariate analysis
- Crude and adjusted odds ratios were estimated to evaluate the relationship between independent variables and typhoid fever by using simple logistic regression
- A 2-tailed p-value <0.05 was considered as the threshold for significance

Statistical analysis (cont.)

- To prioritize the factors based on their importance in predicting typhoid fever
  - A random forest classification model was used to understand the predictive power of the factors
    - ✓ The model gave a mean decrease Gini score for each factor
    - ✓ The factors were ordered based on the Gini score
- AMR data was categorized as susceptible and non-susceptible (resistant and intermediate) and the multidrug-resistant (MDR) was defined if any *S*. Typhi isolate showed resistance to three antibiotics (ampicillin, chloramphenicol, and cotrimoxazole)

Results

Month-wise enrollment of patients and isolation of *S. Typhi*



Baseline characteristics of enrolled patients in the passive surveillance from JE clusters (Cont.)

Characteristics	Blood culture negative patients (N=7,645)	Blood culture positive patients (N=568)	p-value
Age in years	14 (15)	11 (11)	0.008
Age groups			<0.001
<2 yrs	1,025 (97%)	37 (3.5%)	
2-4 yrs	1,548 (92%)	139 (8.2%)	
5-17 yrs	2,746 (91%)	283 (9.3%)	
18+ yrs	2,326 (96%)	109 (4.5%)	
Gender			0.400
Female	3,867 (93%)	276 (6.7%)	
Male	3,778 (93%)	292 (7.2%)	
Religion			0.400
Others	43 (98%)	1 (2.3%)	
Muslim	7,602 (93%)	567 (6.9%)	
Temperature (°C)	37.65 (0.98)	37.90 (0.95)	<0.001
Two or more days of fever			<0.001
No	998 (98%)	16 (1.6%)	
Yes	6,647 (92%)	552 (7.7%)	
Antibiotics taken in last 2 weeks			<0.001
No	6,672 (94%)	438 (6.2%)	
Yes	973 (88%)	130 (12%)	

Baseline characteristics of enrolled patients in the passive surveillance from JE clusters (Cont.)

Characteristics	Blood culture negative patients (N=7,645)	Blood culture positive patients (N=568)	p-value
General symptoms			0.072
No	6,956 (93%)	504 (6.8%)	
Yes	689 (92%)	64 (8.5%)	
Symptoms of gastrointestinal tract diseases (i.e., diarrhea/vomiting)			<0.001
No	6,028 (94%)	385 (6.0%)	
Yes	1,617 (90%)	183 (10%)	
Symptoms of upper respiratory tract diseases (i.e., coughing)			<0.001
No	6,012 (93%)	485 (7.5%)	
Yes	1,633 (95%)	83 (4.8%)	
Symptoms of lower respiratory tract diseases (i.e., sneezing, sore throat)			<0.001
No	3,928 (91%)	380 (8.8%)	
Yes	3,717 (95%)	188 (4.8%)	
Symptoms of urinary tract diseases			0.200
No	7,556 (93%)	565 (7.0%)	
Yes	89 (97%)	3 (3.3%)	

Baseline characteristics of enrolled patients in the passive surveillance from JE clusters

Characteristics	Blood culture negative patients (N=7,645)	Blood culture positive patients (N=568)	p-value
Headache			<0.001
No	7,104 (93%)	506 (6.6%)	
Yes	541 (90%)	62 (10%)	
Symptoms of orthopaedic diseases			0.500
No	7,551 (93%)	563 (6.9%)	
Yes	94 (95%)	5 (5.1%)	
Symptoms of skin diseases			0.200
No	7,606 (93%)	563 (6.9%)	
Yes	39 (89%)	5 (11%)	
Shared kitchen			0.300
No	2,630 (93%)	184 (6.5%)	
Yes	5,015 (93%)	384 (7.1%)	
Shared toilet			0.008
No	2,831 (94%)	179 (5.9%)	
Yes	4,814 (93%)	389 (7.5%)	
Safe source of drinking water			0.200
No	5,138 (93%)	396 (7.2%)	
Yes	2,507 (94%)	172 (6.4%)	
Treated drinking water			0.400
No	2,019 (93%)	141 (6.5%)	
Yes	5,626 (93%)	427 (7.1%)	

Baseline characteristics of enrolled patients in the passive surveillance from JE clusters (Cont.)

Characteristics	Blood culture negative patients (N=7,645)	Blood culture positive patients (N=568)	p-value
Hand wash before meal			0.600
No	2,215 (93%)	159 (6.7%)	
Yes	5,430 (93%)	409 (7.0%)	
Hand wash after defecation			0.800
No	228 (93%)	18 (7.3%)	
Yes	7,417 (93%)	550 (6.9%)	
Place of waste disposal			0.700
No	418 (94%)	29 (6.5%)	
Yes	7,227 (93%)	539 (6.9%)	
Distance of source of the drinking water	15 (10, 20)	14 (10, 20)	0.094
Water filter in the household			0.700
No	6,986 (93%)	516 (6.9%)	
Yes	659 (93%)	52 (7.3%)	
Monthly HH expenditure in Taka	15,000 (12,000, 20,000)	15,000 (11,500, 20,000)	0.400
Construction materials			0.900
No	3,565 (93%)	267 (7.0%)	
Yes	4,080 (93%)	301 (6.9%)	

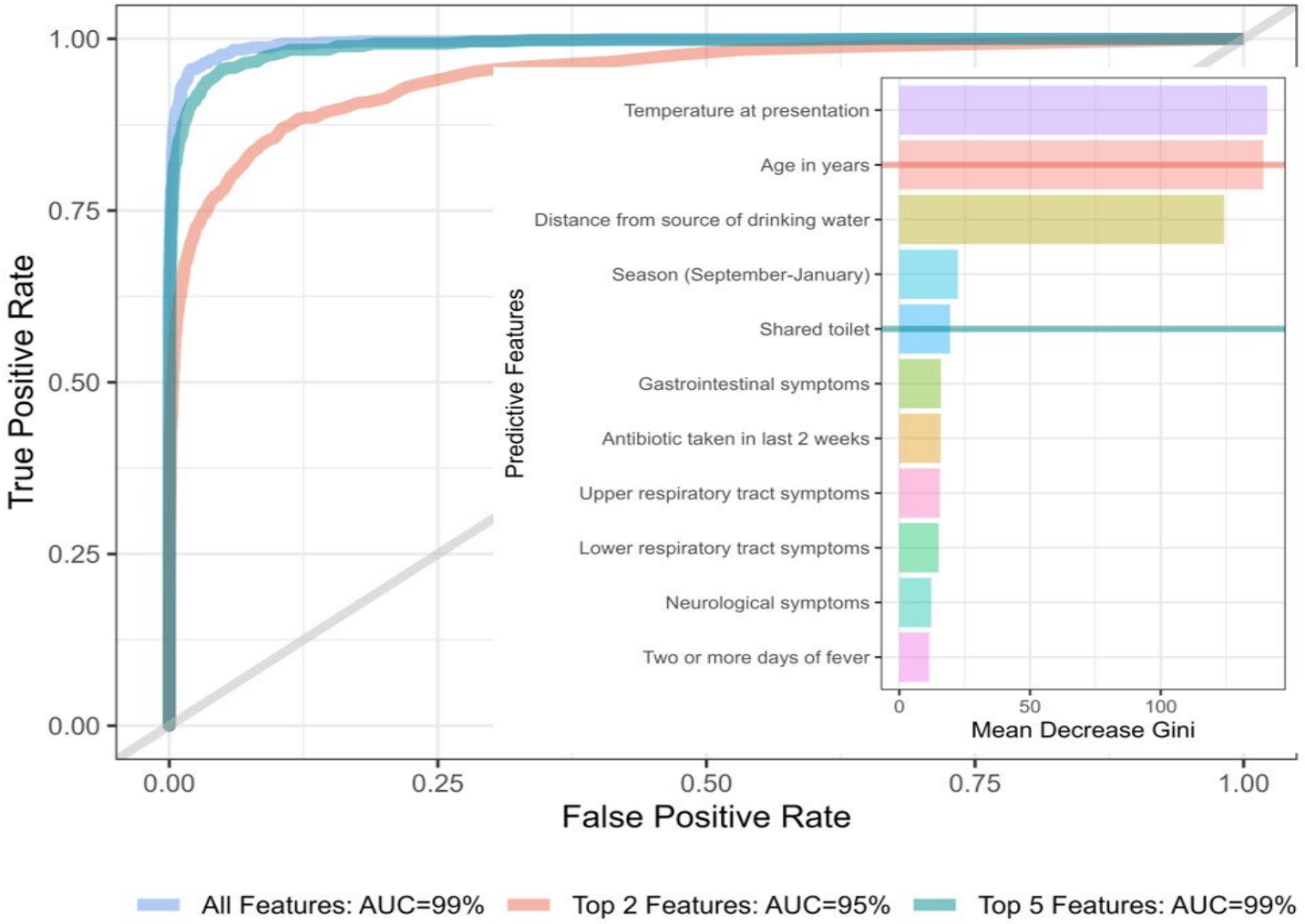
[1]Mean (SD); n (%); Median (IQR)
[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Factors associated with typhoid fever

Factors*	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age groups (Ref: 18+ years)				
<2 years	0.77 (0.52, 1.12)	0.178	0.86 (0.57, 1.27)	0.456
2-4 years	1.92 (1.48, 2.49)	<0.001	2.35 (1.79, 3.09)	<0.001
5-17 years	2.2 (1.76, 2.77)	<0.001	2.44 (1.93, 3.09)	<0.001
Temperature at presentation	1.3 (1.19, 1.42)	<0.001	1.49 (1.36, 1.63)	<0.001
Two or more days of fever	5.18 (3.25, 8.92)	<0.001	7.49 (4.64, 13)	<0.001
Antibiotics taken in the last 2 weeks	2.04 (1.65, 2.5)	<0.001	1.92 (1.55, 2.38)	<0.001
Gastrointestinal symptoms	1.77 (1.47, 2.13)	<0.001	1.24 (1, 1.54)	0.052
Upper respiratory tract symptoms	0.63 (0.49, 0.8)	<0.001	0.5 (0.38, 0.65)	<0.001
Lower respiratory tract symptoms	0.52 (0.44, 0.63)	<0.001	0.46 (0.37, 0.57)	<0.001
Headache	1.61 (1.21, 2.11)	0.001	1.32 (0.97, 1.79)	0.073
Shared toilet	1.28 (1.07, 1.54)	0.009	1.27 (1.05, 1.53)	0.014
Distance from source of drinking water	1 (1, 1)	0.693	1 (1, 1)	0.454

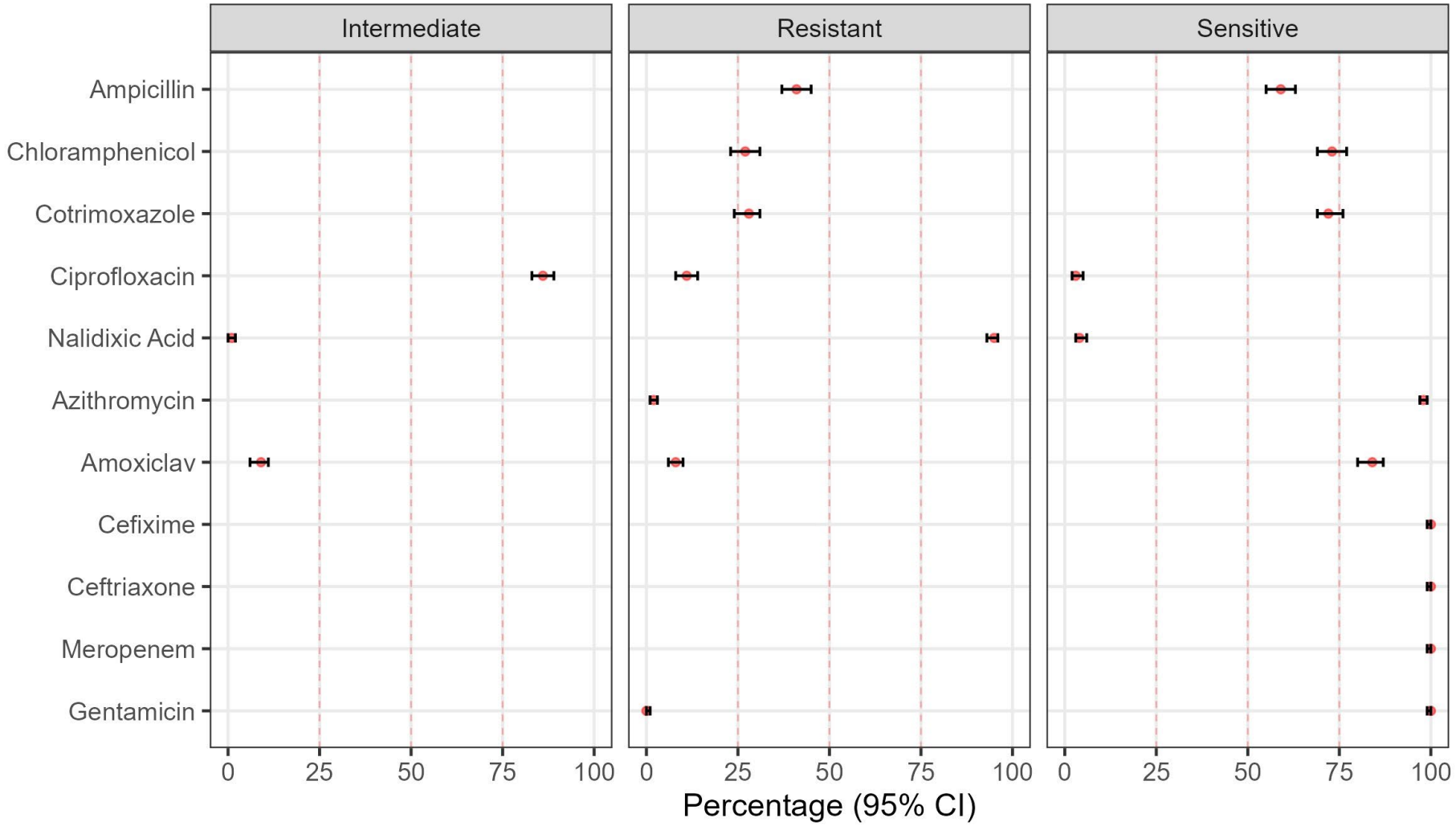
***Factors associated with typhoid at 10% level of significance in the bi-variable analysis**
OR: Odds ratio
CI: Confidence interval

ROC curve and variables importance from random forest classification model



ROC= Receiver operating characteristic curve
AUC= Area under the curve

Antimicrobial susceptibility pattern of isolated *S.* Typhi strains



MDR: 22%

Summary of findings

- 7-8% of febrile patients were identified as having typhoid fever throughout the year in the passive surveillance and an average of 22 cases were identified monthly

- The most significant attributes for typhoid fever included age, temperature at presentation, distance to the source of drinking water, sharing a toilet, and history of antibiotic use

- This analysis showed that 22% MDR and a high frequency of resistance to commonly used antibiotics were present

Limitations and strengths of the study

- The study was conducted in a defined urban slum area, so the identified factors are not likely to be representative nationally
- Also, environmental factors were not included as those were not collected during the census and enrollment in the passive surveillance
- A major strength of this analysis was the use of a machine-learning algorithm with higher sensitivity and specificity to confirm the top associated factors
- A comprehensive dataset was used in this analysis and the data was rigorously collected during the census and passive surveillance over the course of two years

Implication of the study findings

- Clinical management of typhoid patients will benefit from the associated clinical factors identified by the prediction model used in this analysis, particularly in hard-to-reach areas without access to diagnostic facilities
- Clinicians treating suspected typhoid patients in resource-poor settings will benefit from the current AMR and MDR data
- The high burden of AMR and MDR *S*. Typhi will draw the attention of policymakers and enhance the antibiotic stewardship programmes in Bangladesh
- Scientists and public health experts will find the study findings useful in developing evidence-based preventive interventions

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TyVAC works closely with global partners

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