Incidence of Enteric Fever in Bangladesh, Nepal and Pakistan and Vaccination Implications: Results of the Surveillance for Enteric Fever in Asia Project

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Surveillance of Enteric Fever in Asia Project (SEAP)

Multi-country, multi-site surveillance study

Study Sites

- **Bangladesh**
  Dhaka Shishu Hospital (DSH), Shishu Sasthya Foundation (SSF)
- **Pakistan**
  Aga Khan University Hospital (AKUH), Kharadar General Hospital (KGH)
- **Nepal**
  Kathmandu Medical College (KMC), Dhulikhel Hospital (DH)

Utilizing a facility-based surveillance and health care utilization survey (HCUS) hybrid framework

Main objective to characterize the burden of enteric fever including:

- **Population-based incidence**
- **Patterns of antimicrobial susceptibility**
- **Clinical spectrum of the disease, including severity, complications and outcome**
- **Cost of illness from a health care and societal perspective**

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Methods Overview

HCUS

- To ascertain occurrence of febrile illness and associated care-seeking

Hospital and laboratory-based surveillance

- Enroll suspected enteric fever and blood culture-confirmed cases

Outpatient
Fever for ≥3 consecutive days within the last 7 days

Inpatient
Clinical suspicion or a confirmed diagnosis of enteric fever

Hospital Laboratory
Laboratory Networks
Blood culture for Salmonella Typhi or Paratyphi

Surgical Wards
Ileal perforation of unknown origin, even in the absence of laboratory confirmation

- Measure blood culture positivity rates
- Follow-up to assess long-term sequelae

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Methods
Incidence Calculation

The Journal of Infectious Diseases

SUPPLEMENT ARTICLE

Integrating Facility-Based Surveillance With Healthcare Utilization Surveys to Estimate Enteric Fever Incidence: Methods and Challenges

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Cohort studies and facility-based sentinel surveillance are common approaches to characterizing infectious disease burden, but present trade-offs; cohort studies are resource-intensive and may alter disease natural history, while sentinel surveillance underestimates incidence in the population. Hybrid surveillance, whereby facility-based surveillance is paired with a community-based healthcare utilization assessment, represents an alternative approach to generating population-based disease incidence estimates with moderate resource investments. Here, we discuss this method in the context of the Surveillance for Enteric Fever in Asia Project (SEAP) study. We describe how data are collected and utilized to adjust enteric fever incidence for blood culture sensitivity, facility-based enrollment, and healthcare seeking, incorporating uncertainty in these parameters in the uncertainty around incidence estimates. We illustrate how selection of surveillance sites and their coverage may influence precision and bias, and we identify approaches in the study design and analysis to minimize and control for these biases. Rigorously designed hybrid surveillance systems can be an efficient approach to generating population-based incidence estimates for infectious diseases.

Keywords. typhoid; enteric fever; surveillance; incidence; methods; bias.

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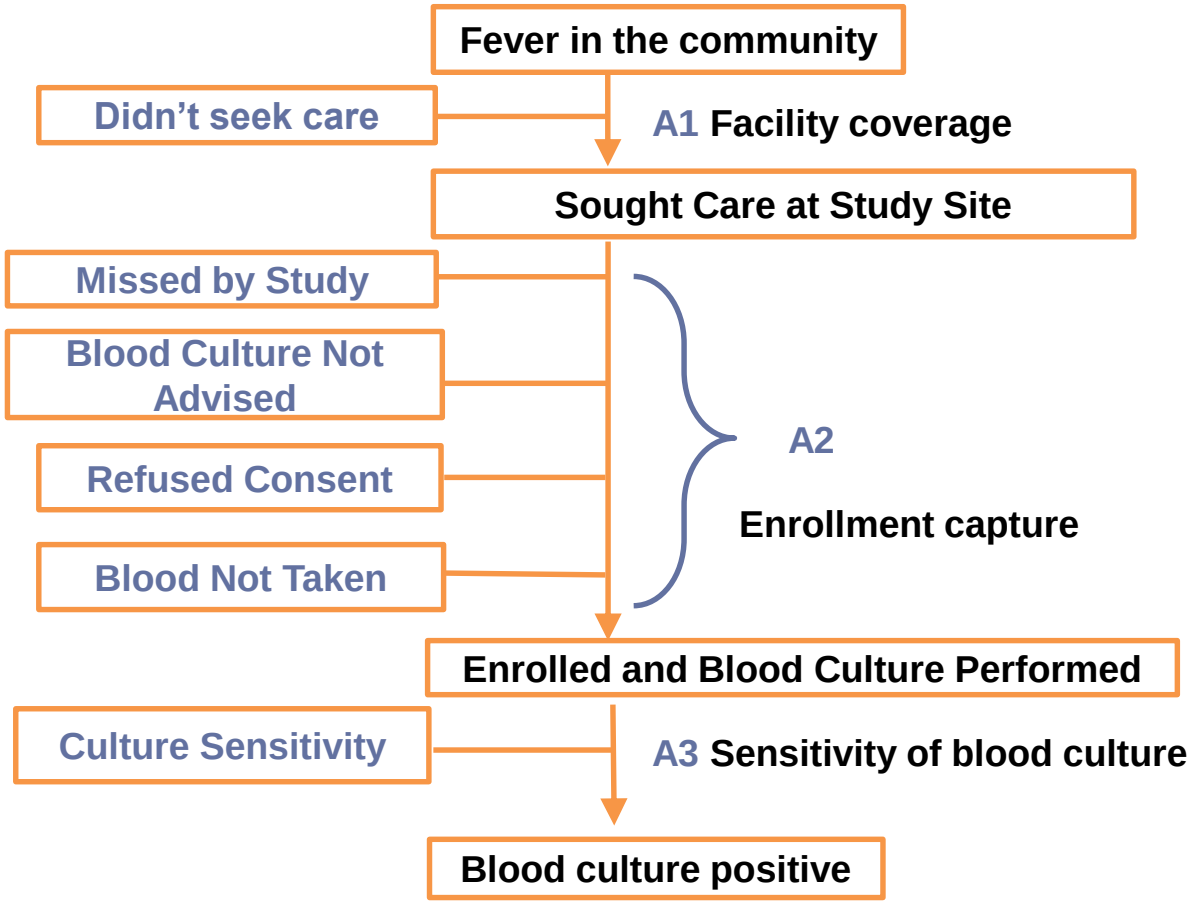
Population-Based Incidence Calculations

Crude Incidence = $\frac{cases}{catchment\ population}$

Adjusted Incidence = $\frac{Crude\ incidence}{Total\ Adjustment}$

Total Adjustment = A1*A2*A3



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Population-Based Incidence Calculations

Characterize uncertainty in incidence

- Monte Carlo simulation from distributions of cases and adjustment factors
  - 1,000,000 simulations for each site and age group
  - Generate median and 95% confidence interval for incidence

Possible bias in adjusted incidence

- Established a surveillance network with good facility coverage to capture high proportion of typhoid-like illness
- Action to minimized selective enrollment
  - Education of providers
  - Rigorous quantification of missed eligible cases

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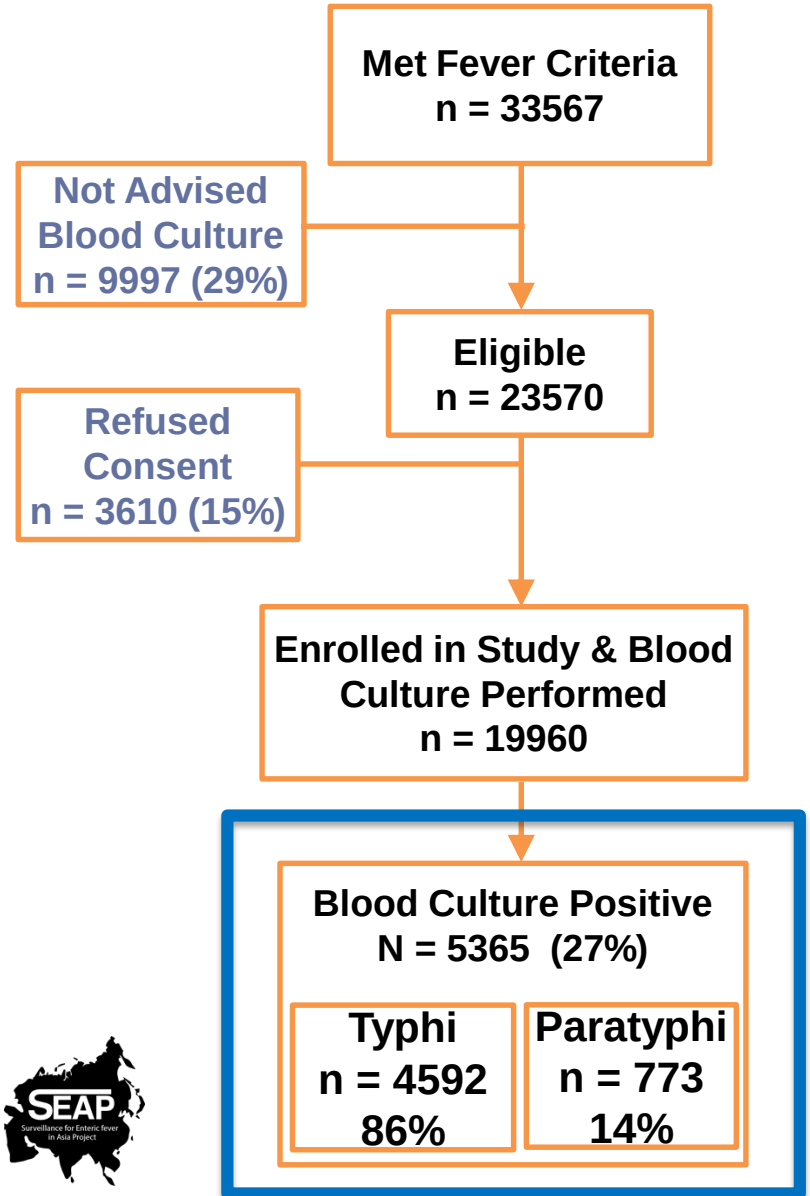
Characteristics of Enrolled Patients (Sep 2016 – Sep 2018)



	Bangladesh* n=10090	Nepal n=4549	Pakistan n=5321
Male	58%	58%	57%
Age, median (25th -75th percentile)	4 (2-8)	20 (9-31)	9 (3-25)

* Pediatric hospital

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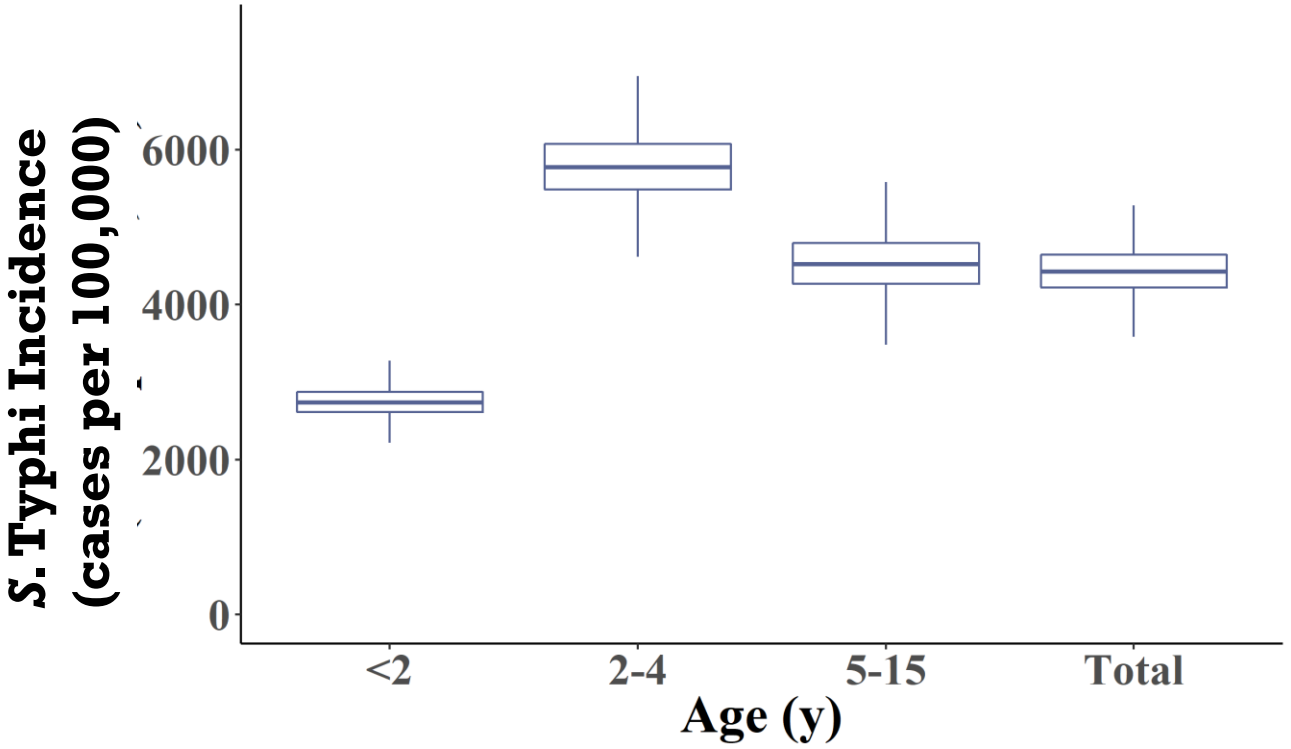
S. Typhi Incidence by Age: Bangladesh



Age Group	Dhaka Shishu Hospital + Sasthya Foundation Hospital	
	Crude Rate per 100,000 (95% CI)	Adjusted Incidence Rate per 100,000 (95% CI)
<2 years	168 (143, 194)	2738.9 (2387.3, 3162.6)
2 to 4 years	321 (287, 357)	5772.4 (4998.5, 6704)
5 to 15 years	125 (104, 147)	4523.5 (3831.2, 5363.4)
Total	167 (142, 193)	4425.7 (3859.5, 5100.3)

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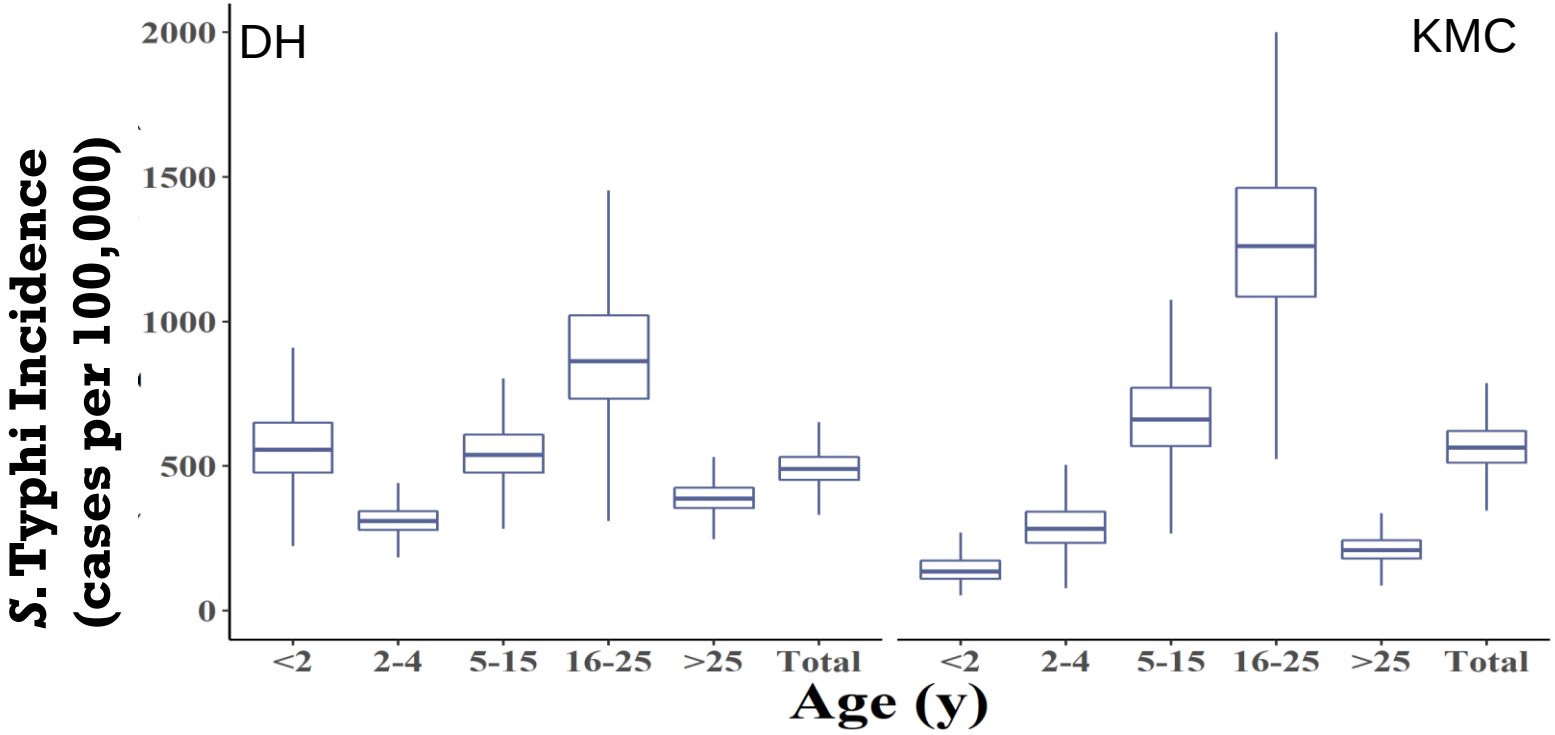
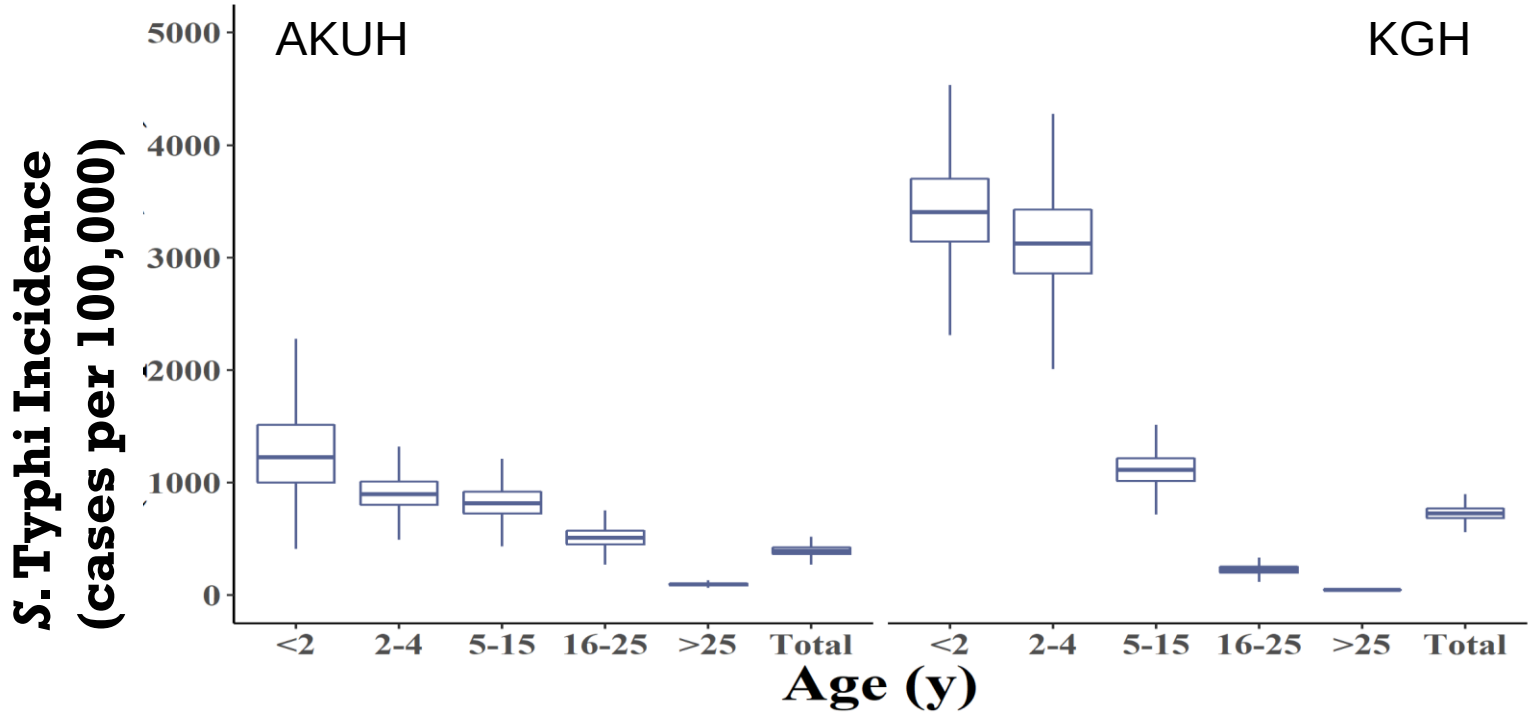
S. Typhi Incidence by Age: Nepal



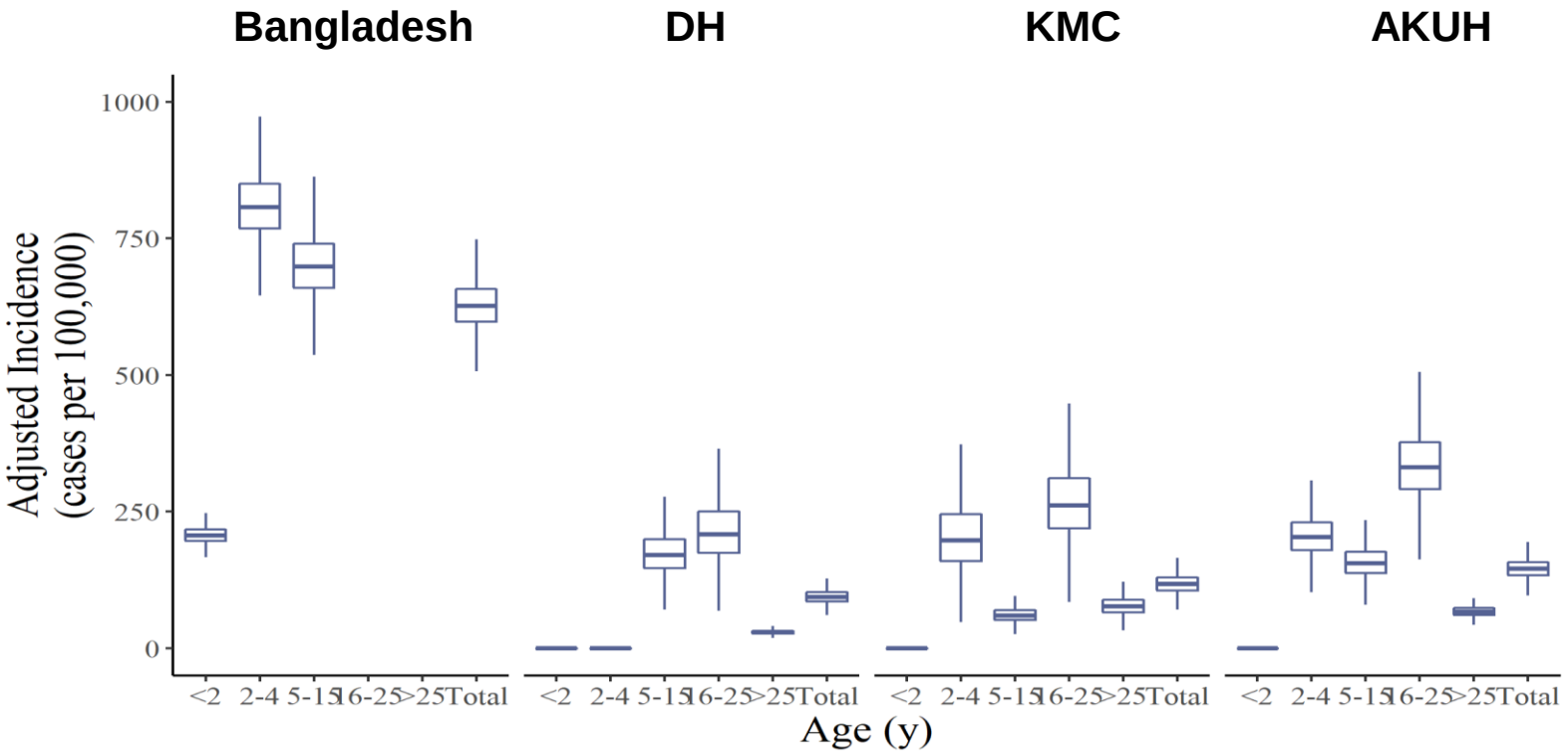
Age Group	Dhulikhel Hospital		Kathmandu Medical College	
	Crude Rate per 100,000 (95% CI)	Adjusted Incidence Rate per 100,000 (95% CI)	Crude Rate per 100,000 (95% CI)	Adjusted Incidence Rate per 100,000 (95% CI)
<2 years	59 (45, 75)	556.5 (364.2, 886.9)	19 (11, 29)	136.1 (78.2, 292.9)
2 to 4 years	31 (21, 42)	309.7 (232.2, 424.2)	11 (5, 18)	282.5 (165.8, 502.9)
5 to 15 years	68 (53, 85)	538.1 (386.4, 777)	72 (56, 89)	661.6 (432.9, 1046.5)
16 to 25 years	96 (78, 116)	863.5 (549.9, 1432.9)	120 (99, 142)	1270.9 (824.6, 2009.7)
>25 years	21 (13, 31)	387.9 (298.9, 508)	14 (7, 21)	209.4 (137.2, 325.3)
Total	48 (35, 62)	489.8 (389.3, 624.3)	53 (40, 68)	563.4 (426.5, 752.9)

S. Typhi Incidence by Age: Pakistan



Age Group	Aga Khan University Hospital		Kharadar General Hospital	
	Crude Rate per 100,000 (95% CI)	Adjusted Incidence Rate per 100,000 (95% CI)	Crude Rate per 100,000 (95% CI)	Adjusted Incidence Rate per 100,000 (95% CI)
<2 years	72 (56, 90)	1222.9 (710.9, 2343.3)	186 (60, 213)	3404.8 (2726.5, 4388)
2 to 4 years	48 (35, 62)	896.8 (648.5, 1264.2)	140 (118, 164)	3126.3 (2426.6, 4102.4)
5 to 15 years	29 (19, 41)	816.2 (581.3, 1161.3)	35 (24, 47)	1110.3 (860.4, 1448.4)
16 to 25 years	12 (6, 20)	508.4 (363.5, 723.7)	4 (1, 9)	223.7 (160.5, 318.2)
>25 years	3 (3, 7)	96.6 (75.2, 125.4)	1 (0, 4)	47.9 (38.1, 61.1)
Total	15 (8, 23)	393.5 (314, 497)	25 (16, 35)	726.8 (615.5, 864)

S. Paratyphi Incidence by Age



Age Group	Crude Rate per 100,000 (95% CI)			
	Bangladesh	Dhulikhel Hospital	Kathmandu Medical College	Aga Khan University Hospital
<2 years	26 (16, 36)	0	12 (6, 19)	0
2 to 4 years	50 (37, 65)	0	11 (5, 18)	3 (0, 7)
5 to 15 years	21 (13, 31)	11 (5, 18)	10 (4, 17)	4 (1,8)
16 to 25 years		19 (11, 28)	12 (6, 20)	6 (2, 11)
>25 years		1 (0, 4)	3 (0, 8)	2 (0, 5)
Total	27 (18, 38)	7 (2, 13)	7 (3, 13)	3 (0, 7)

Summary

High burden of enteric fever in our study sites

- **Burden varies between countries and within a country**
- **Enteric fever occurs in both high-density urban areas and lower density peri-urban/rural settings (e.g., Kathmandu vs. Dhulikhel in Nepal)**
- **Age-specific incidence rates vary by country (e.g., incidence rates higher in 15-25yo in Nepal)**

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Limitations

Relying on blood culture introduces uncertainty to our estimates at many levels

- **Sensitivity of the assay**
- **Difficulty with changing clinical practice for advising blood culture**
- **Refusal of blood collection by patients**

Connecting sero-epidemiologic assays and/or environmental surveillance to blood culture may increase the precision of incidence estimates

Data may not generalizable to other areas within the country outside our surveillance

- **Incidence estimates are from large populations**
- **Rates may vary in lower-density cities in the same country**

More assessment in rural areas is needed

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Implications for Vaccine Introduction

High burden of disease in our study sites highlights the need for the implementation of the new typhoid conjugate vaccine (TCV)

Understanding local epidemiology is key

- **Successful implementation plan for TCV needs to be informed by accurate, context-specific data**

Robust surveillance is essential to monitor TCV impact and areas for improvement in the implementation

As we move towards elimination, new methods to identify individuals and populations at risk are necessary

- **Immunological and molecular markers of *S.* Typhi and Paratyphi have potential as lower cost alternative methods for detection**

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Thank you!

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SEAP Presentations & Posters

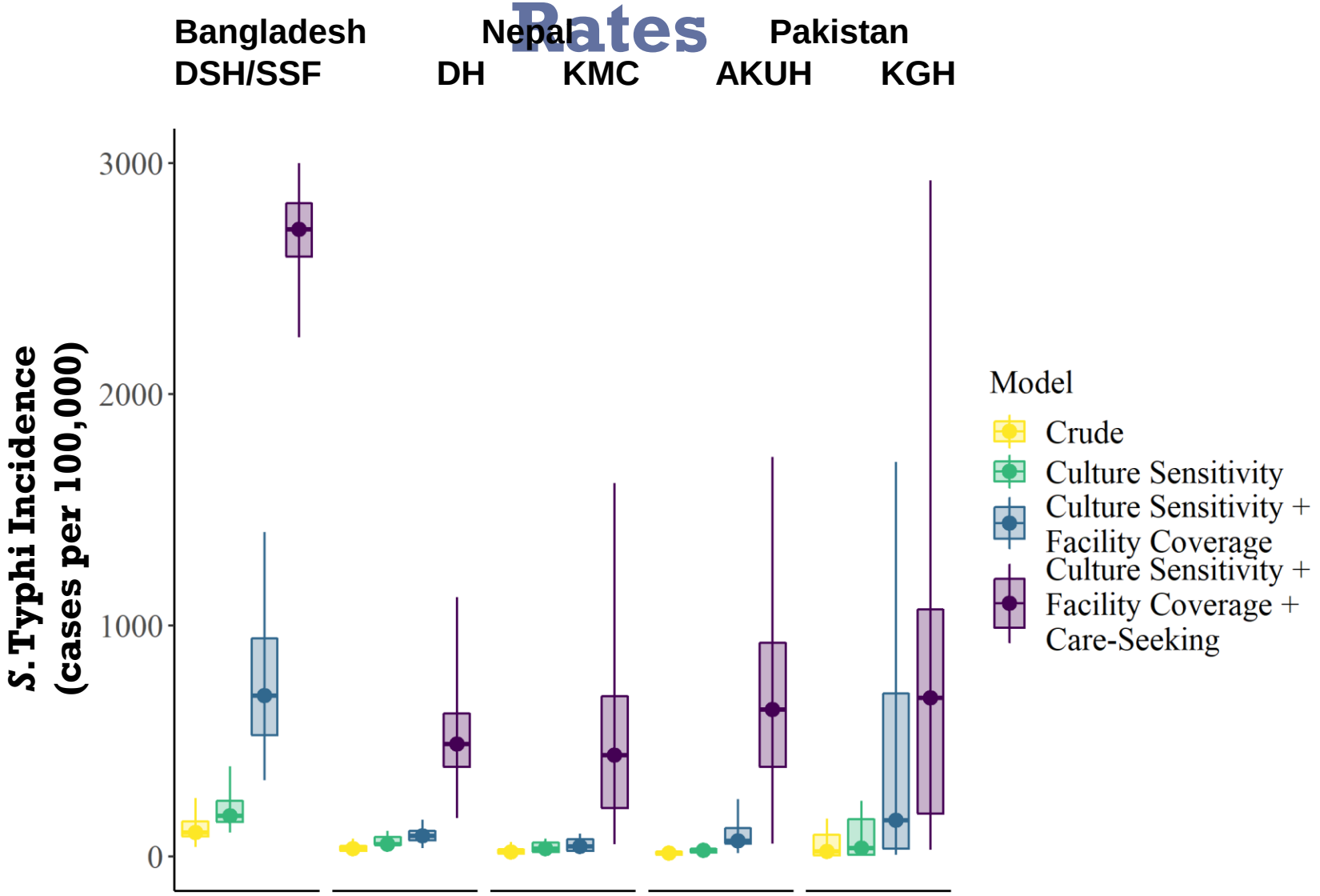
Oral Presentations

- Antimicrobial non-susceptibility Among Salmonella Typhi and Paratyphi A Isolates – Preliminary Results from SEAP project (presented by Muhammad Tahir Yousafzai)
- Geo-Spatial reporting of Ceftriaxone resistant Salmonella typi outbreak investigation in Hyderabad and spread to Karachi (presented by Abdul Momin Kazi)
- Mortality attributed to ileal perforations: Prospective data from a multi-centers enteric fever surveillance project in Pakistan (presented by Saqib Qazi)
- Illness Severity and Outcomes among Enteric Fever Cases - Data from the Surveillance for Enteric Fever in Asia Project (SEAP) (presented by Caitlin Barkume)
- Validity of reported antibiotic use among suspected enteric fever cases in Nepal, Bangladesh and Pakistan (presented by Krista Vaidya)
- Healthcare-seeking patterns for individuals with suspected enteric fever (presented by Alex Yu)
- Incidence of Enteric Fever in Bangladesh, Nepal and Pakistan and Vaccination Implications: Results of the Surveillance for Enteric Fever in Asia Project (presented by Denise Garrett)

Posters

- Clinical predictors for culture-positive enteric fever in patients presenting with febrile illnesses in South Asian settings (presented by Kristen Aiemjoy)
- Comparison of cost of illness of extensively drug-resistant (XDR) vs. non-XDR typhoid fever in Pakistan: policy implications for typhoid vaccine (presented by Muhammad Tahir Yousafzai)
- Hospitalization of pediatric enteric fever cases during 2016-2018: Surveillance for Enteric Fever in Asia Project (SEAP), Bangladesh (presented by Shampa Saha)
- Intestinal perforations from enteric fever among children and adults: Data from prospective surveillance in Karachi, Pakistan (presented by Nasir Saddal)
- Use of geo spatial technique to identify catchment area of patient with typhoid fever – a hybrid utilization technique (presented by Momin Abdul Kazi

Impact of Adjustments on Incidence Rates



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