

High rates of enteric fever diagnosis and low burden of culture-confirmed disease in rural Nepal

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High burden of enteric fever in Kathmandu

Kathmandu, Nepal: Still an enteric fever capital of the world

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25 Years after Vi Typhoid Vaccine Efficacy Study, Typhoid Affects Significant Number of Population in Nepal

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Emerging trends in enteric fever in Nepal: 9124 cases confirmed by blood culture 1993–2003

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Burden in rural Nepal?

- ViPS vaccine trial in 5 villages west of Kathmandu in 1986-7 (Acharya et al, NEJM 1987)
- Incidence of culture-confirmed disease was 6.5 per 1,000 person-years

Few other data, in part due to limited laboratory infrastructure

Sparse data on enteric fever burden in rural areas

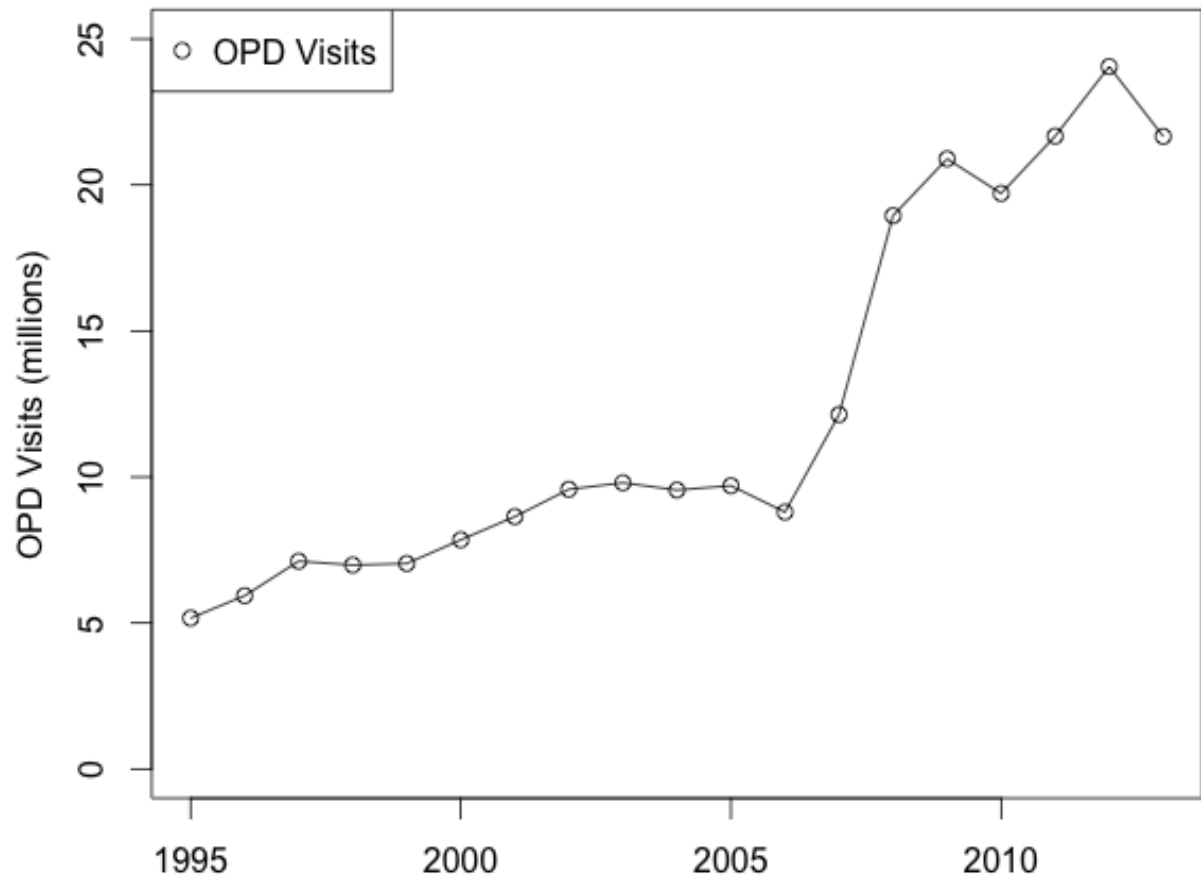
- Global estimates of the burden of typhoid largely drawn from urban areas
- Incidence: 5-20 cases per 1,000 in high burden slums

Recent Studies

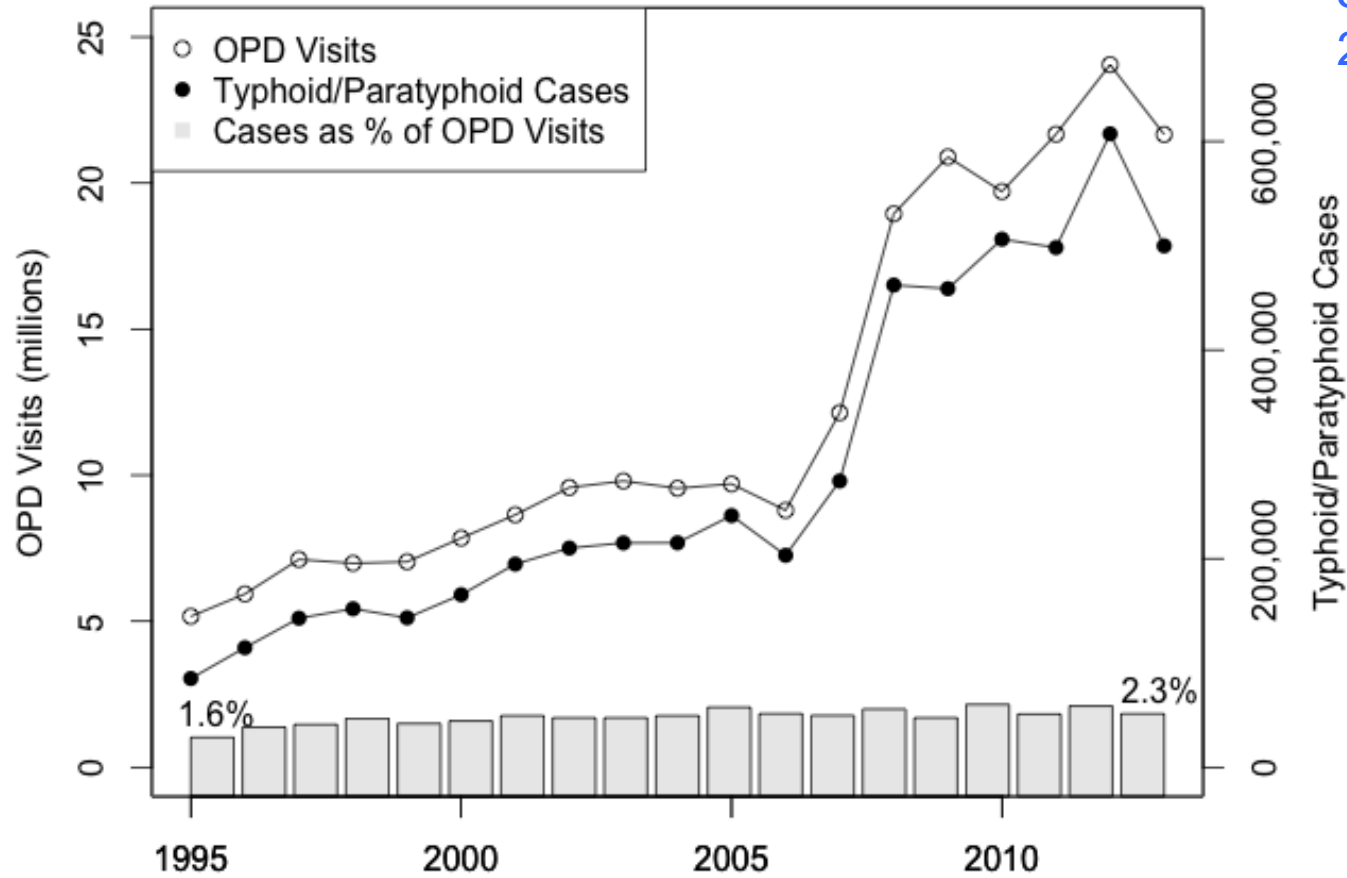
- 2.0 / 1,000 in rural Vietnam (Lin et al, 2000)
- 1.5-2.5 / 1,000 in rural Bangladesh (Rahman et al)
- Urban incidence in children >15x rural incidence, Kenya (Breiman et al, 2012)

Review of Health Management Information System Data

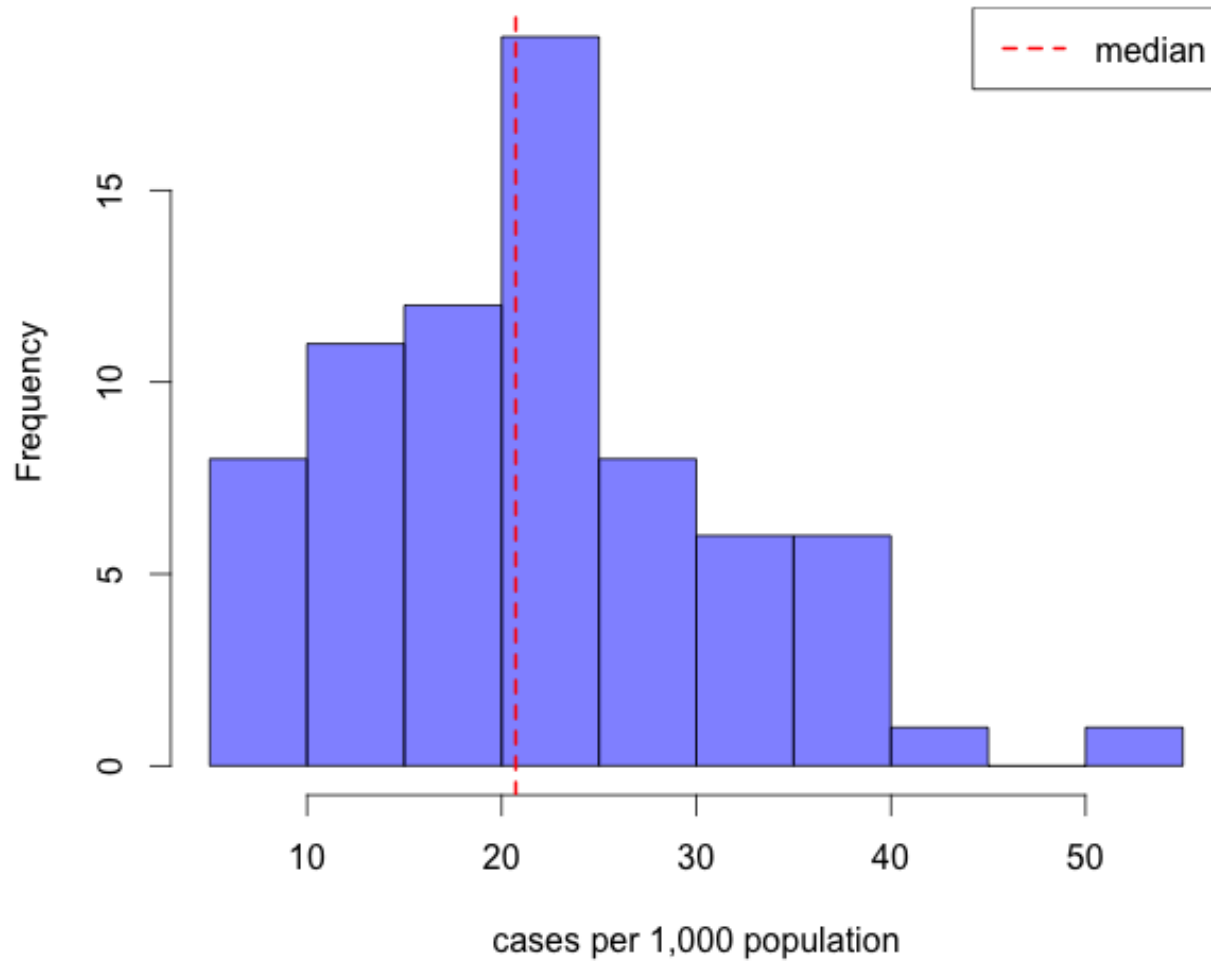
- National reporting system for all levels of formal health-care system
- Reviewed data on outpatient department (OPD) visits and reported typhoid/paratyphoid cases from 1995-2014
- Most sites do not perform blood cultures
- There is no formal clinical/case definition for typhoid/paratyphoid



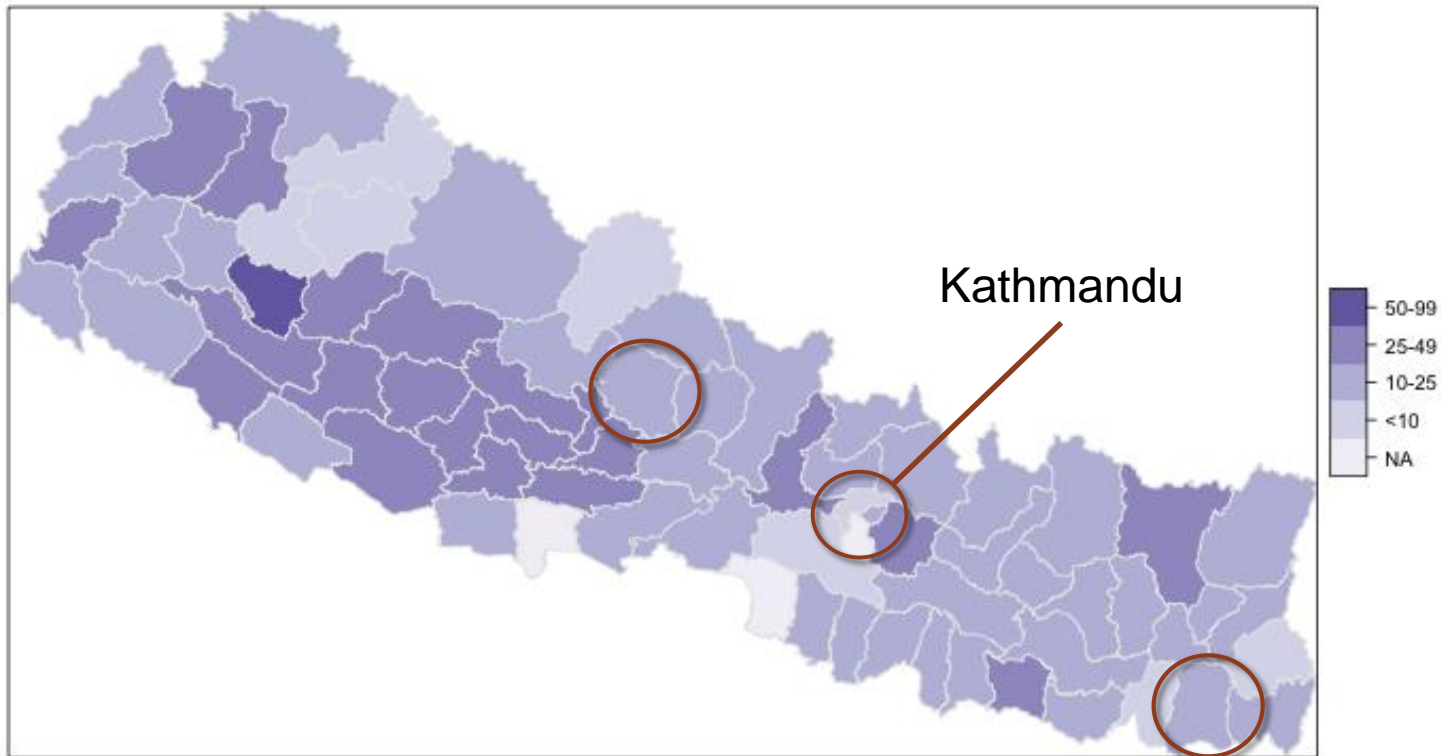
500,000 cases/year
2% of population



Distribution of incidence by district



Incidence of reported typhoid/paratyphoid by district, 2010-2014 (cases/1000 population)



In 2013-2014, enteric fever #1 diagnosis cited for hospitalization

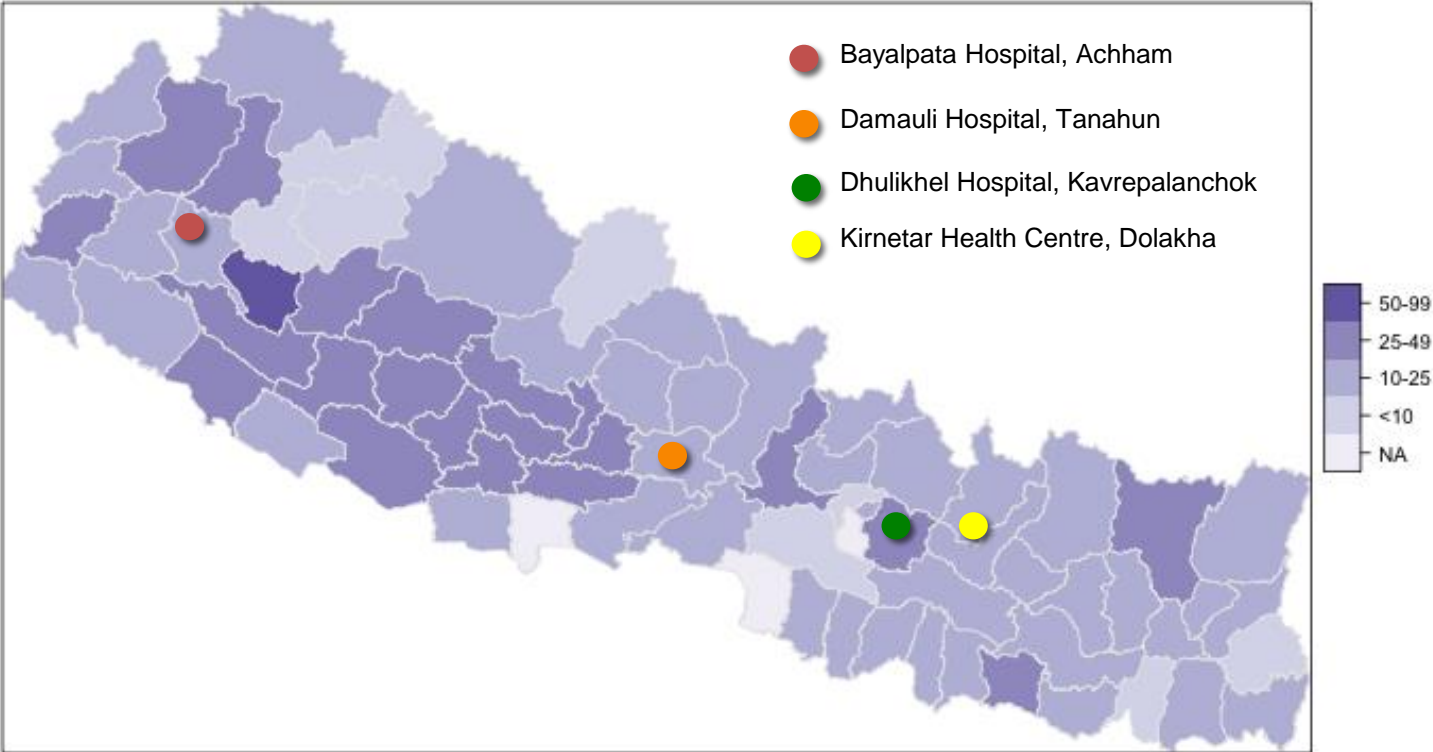
How much of this is actually enteric fever?

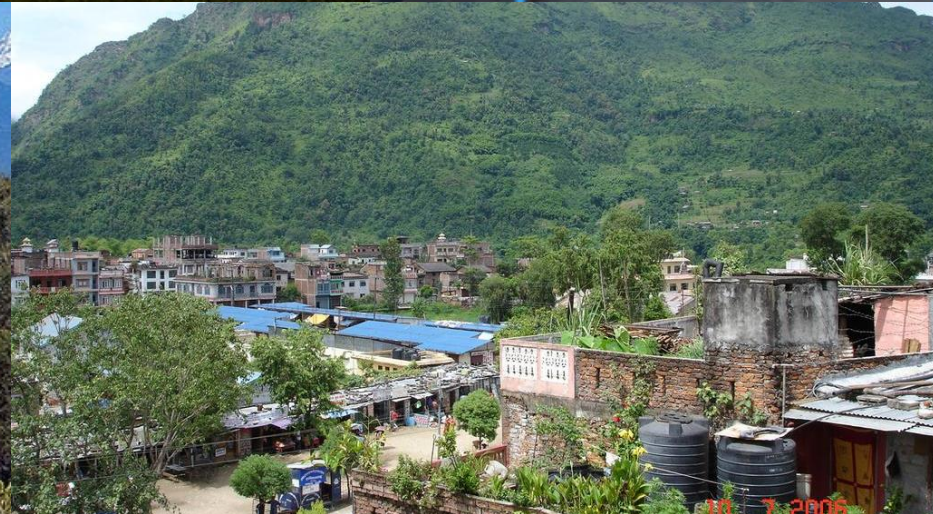


Methods

- Prospective surveillance study among all individuals >1 year of age with fever ≥ 72 hours
- Demographic, clinical history, clinical signs/symptoms and antibiotic exposure captured by questionnaire
- 5-10 cc blood drawn from adults (1-5 cc from children < 5)
- Blood culture performed using tryptic soy broth or Bactec bottles (majority)
- Antimicrobial susceptibility testing performed by disk diffusion

Study Sites





Results – Study Population

- >98% of patients meeting criteria and approached agreed to participate
- 1,821 participants from August 2013-April 2015
- Participants drawn from 14 districts
- 54% women
- Median age: 25 years (IQR: 13-47)

Prior Treatment-Seeking



48% of participants had sought prior care during this episode (most at pharmacies or private clinics)

31% of participants had received antibiotics

Clinical Diagnoses

Diagnosis	Number	% of diagnoses
Enteric Fever	648	54%
LRTI/Pneumonia	121	10%
UTI	79	7%
Viral Fever	67	6%
URTI	61	5%
Pharyngitis	31	3%
Tonsillitis	19	2%
Tuberculosis	13	1%
Total with Diagnosis	1201	--

Enteric fever was the leading diagnosis at all 4 study sites

Prevalence of Typhoidal *Salmonella* among participants

Site	Typhoidal <i>Salmonella</i> / Number Tested	%
Bayalpata Hospital	1 / 193	0.5%
Damauli Hospital	0 / 111	0.0%
Dhulikhel Hospital	35 / 1345	2.6%
Kirnetar Health Centre	1 / 172	0.6%
Total	37 / 1,821	2.0%

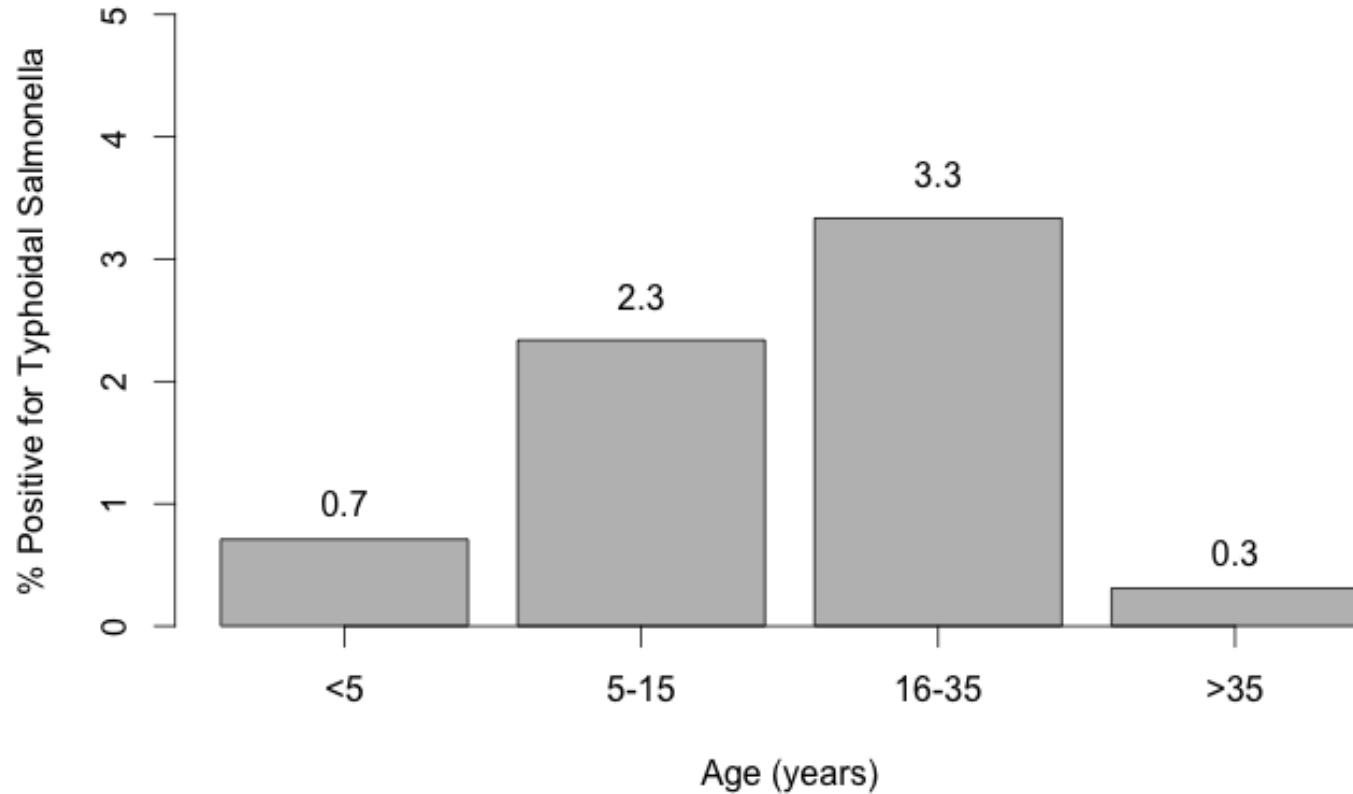
Comparisons of typhoidal *Salmonella* positivity among febrile participants:

- 4-14% in Kathmandu Valley (Bajracharya et al, 2014)
- 4-6% in urban Bangladesh (Brooks et al 2005; Naheed et al, 2010)
- 0.85% in rural Bangladesh (Rahman et al)
- Most <1% in rural Africa (Mweu and English 2008)

Bacterial Pathogens Isolated

Organism	Number of isolates	% among pathogens
<i>Salmonella</i> Typhi	23	31%
<i>Staph aureus</i>	17	23%
<i>Salmonella</i> Paratyphi	14	19%
<i>E coli</i>	10	13%
<i>Streptococcus spp</i>	4	5%
<i>Enterococcus</i>	3	4%
<i>Acinetobacter</i>	2	3%
<i>Klebsiella</i>	1	1%
<i>Proteus</i>	1	1%
Total	75	100%

Typhoidal Salmonella Culture Positivity by Age



Additional Key Findings

- Individuals with an empiric diagnosis of enteric fever were more likely to have enteric fever than those without (2.8% vs 1.3%, $p=0.03$).
- Individuals who had previously received antibiotics had trend towards being *more likely* to be culture positive for typhoidal *Salmonella* (2.7% vs 1.3%, $p=0.07$).
- 48% of patients were prescribed antibiotics (site range 41%-81%)
- Lowest antibiotic prescription rates at Dhulikhel Hospital, where highest burden of culture-confirmed enteric fever

Antimicrobial Susceptibility and Treatment

- All *Salmonella* isolates tested (n=32) had intermediate susceptibility (27/32) or over resistance (5/32) to Ciprofloxacin
- Fluoroquinolones were the most common antibiotic prescribed among culture-confirmed enteric fever cases, followed by Azithromycin and Cefixime





Limitations

- Diverse geography, climate and living conditions within Nepal not all represented by these sites
- Small blood volumes limit sensitivity
- Nearly 1/3 of participants had prior antibiotic exposure
- Limited data from children < 5 years of age
- Alternative etiologies of febrile illnesses not yet known

Future Steps

- Addition of 3-5 sites with broader geographic representation
- Community surveys to determine treatment-seeking patterns, enable incidence calculations
- Identification of alternative etiologies by serologic and molecular testing of banked samples
- Assess outcomes according to etiology of illness

Conclusions

- 2% of the Nepali population is empirically diagnosed with enteric fever each year in the formal sector alone
- Enteric fever diagnosis rates are particularly high in rural areas, while culture-confirmed cases were sparse
- High levels of antibiotic use in rural areas targeting the wrong disease
- Need to identify alternative etiologies of infections (e.g. rickettsia, leptospirosis, influenza, viruses) responsible for acute febrile illnesses in rural Nepal
- Establish sustained, geographically representative surveillance for typhoid throughout Nepal, including peri-urban/rural areas

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