Multiple Modalities to Explore Typhoid among Children: implication in vaccination policy

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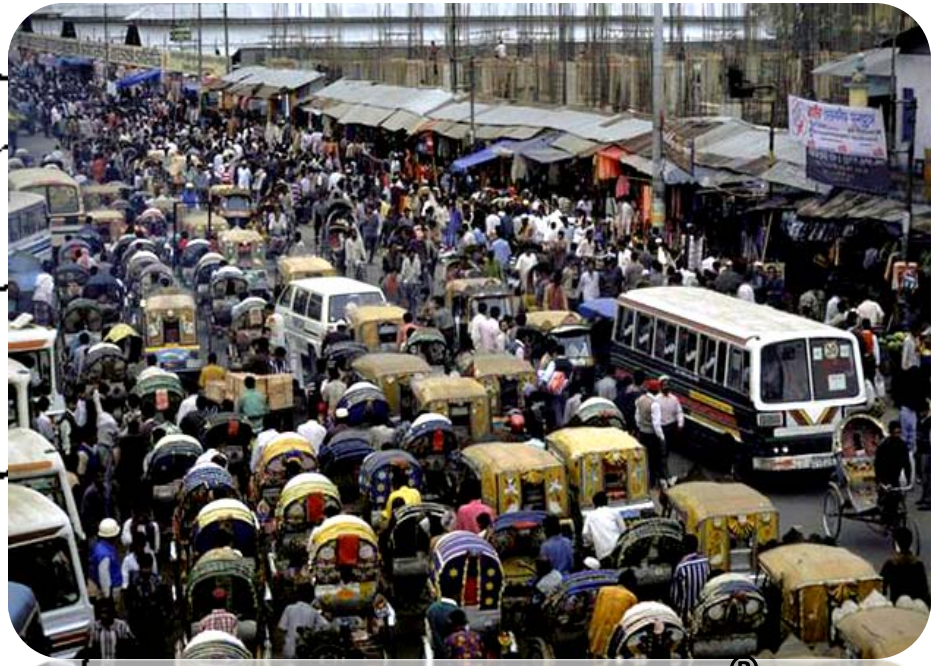
BANGLADESH

- ~150 million people
  - 7th most populous country in the world
- Population density ~2,000 persons/square kilometer
  - Highest among any country
    - Global mean 42 persons/ km^2
    - Per capita income - US$ 840



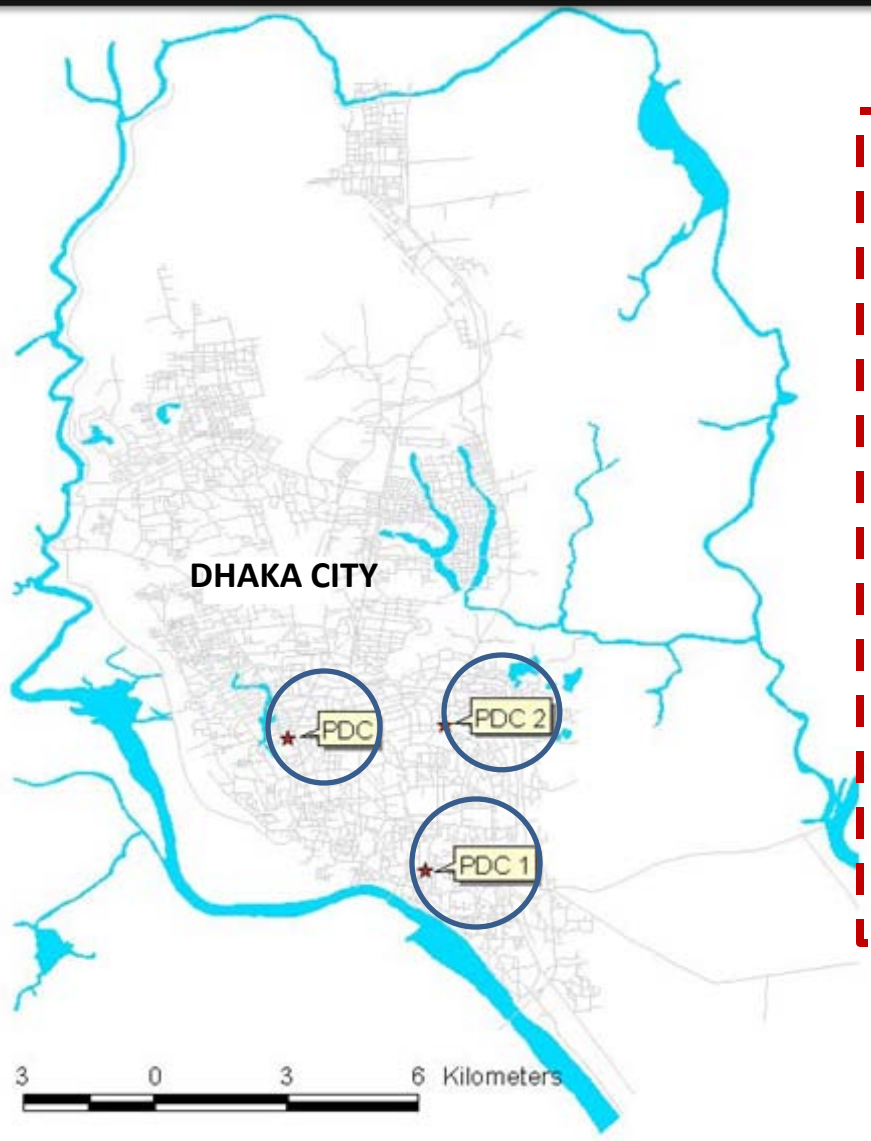
Dhaka Trade Mark®

Prior Antibiotic – Community and Hospital	
Before coming to hospital	32%
At hospital, prior to specimen collection	20%
Overall cases without prior antibiotic	48%

Surveillance for Invasive Bacterial Infections – Multiple Modalities

- Multicentre laboratory based surveillance in Dhaka city
- Multicentre hospital based surveillance – Urban and Rural
- Population based surveillance in a rural community
- Population based surveillance in an urban slum

Multicentre Laboratory Based Surveillance in Dhaka City (1994 – 2011)



Out patient based diagnostic centers

- Expensive private facilities
- Cases referred by senior pricey practitioners
- Higher SES

Multicentre Laboratory Based Surveillance in Dhaka City (1994 – 2011)

Total Blood Culture = 74,210

↓

Positive Cases = 6,678 (9%)

↓

Salmonella Typhi = 4,111 (62%)

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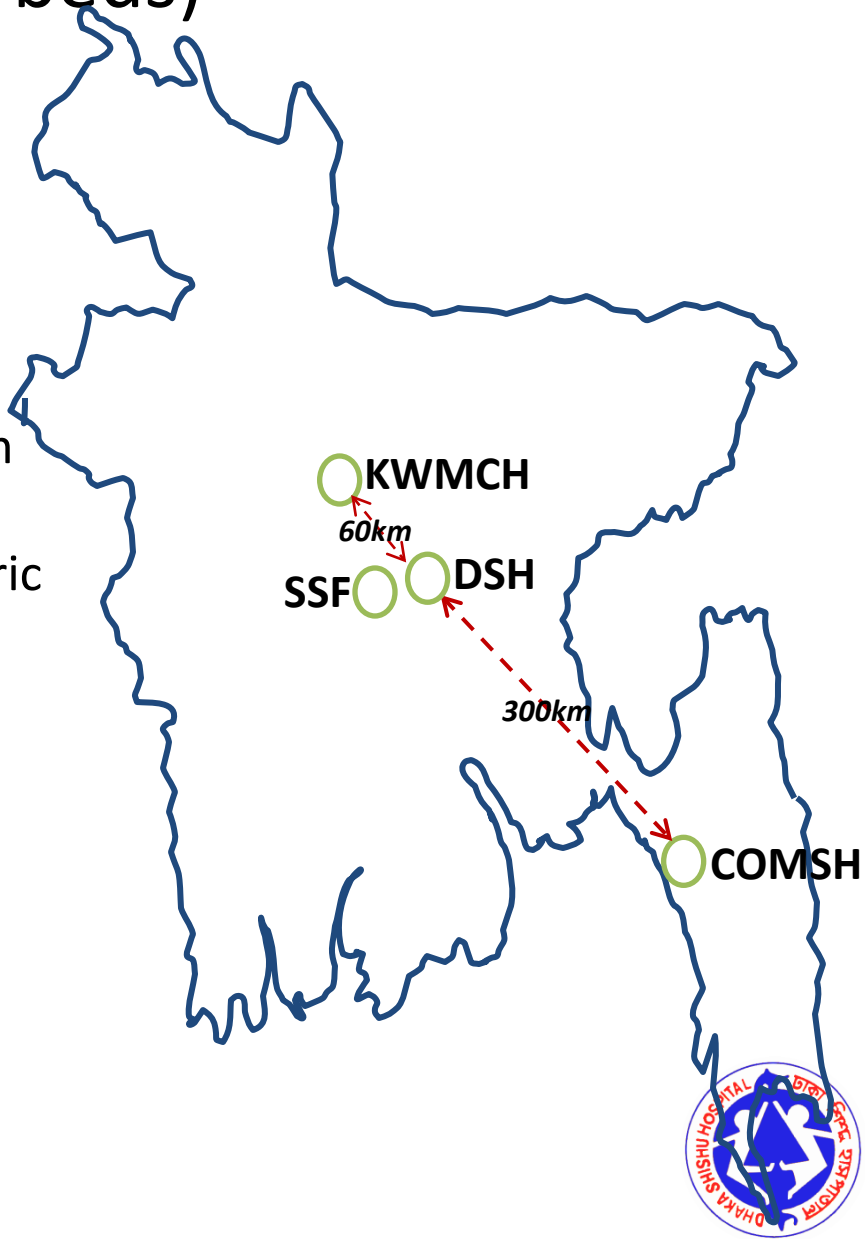
Hospital Based Surveillance - Network of 4 Hospitals (1,055 beds)

- 60 Km from Dhaka
- 80 Paediatric Beds

- 300 Km from Dhaka
- 200 Paediatric beds

Dhaka Shishu Hospital
600 Paediatric Beds
WHO Sentinel Site

- Dhaka
  - 175 Paediatric Beds



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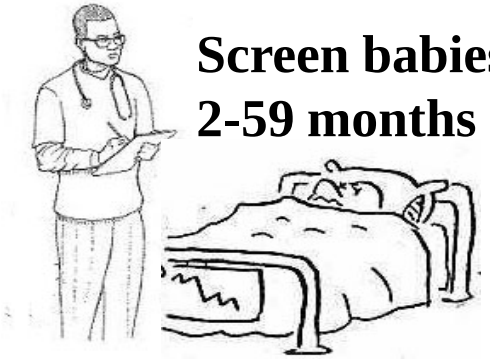
Multicentre Hospital Based Surveillance for invasive bacterial diseases



Screen babies of 2-59 months

IF MEET INCLUSION EXCLUSION CRITERIA

ELIGIBLE

Consent taken

BLOOD COLLECTION

ENROLLED

CULTURE

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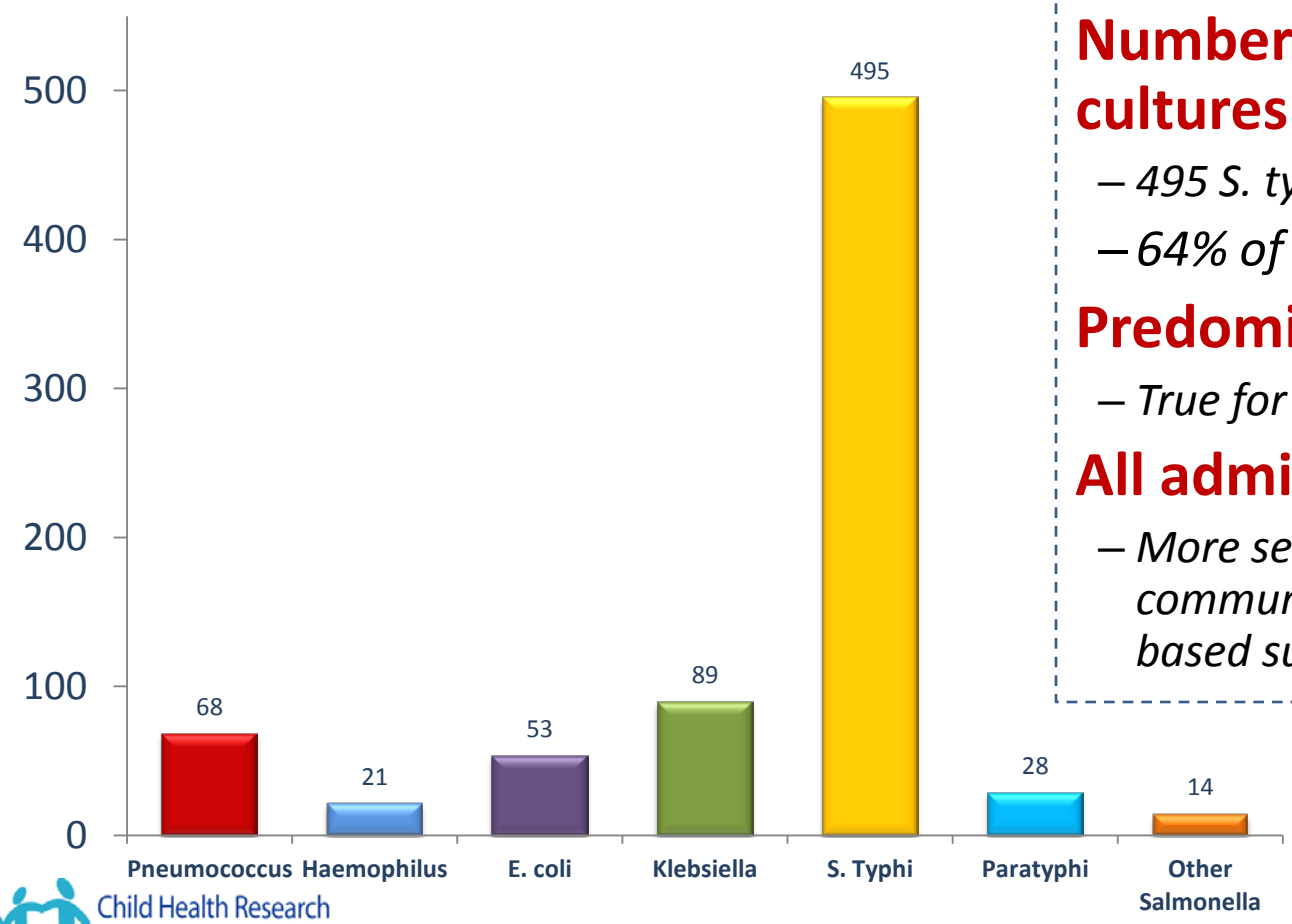
Multicentre Hospital Based Surveillance for Invasive Bacterial Diseases – 3 urban hospitals



Number of blood cultures (18,652)

- *495 S. typhi*
- *64% of all isolates*

Predominance of *S. typhi*

- *True for other hospitals*

All admitted cases

- *More severe cases than community patients in lab based surveillance*

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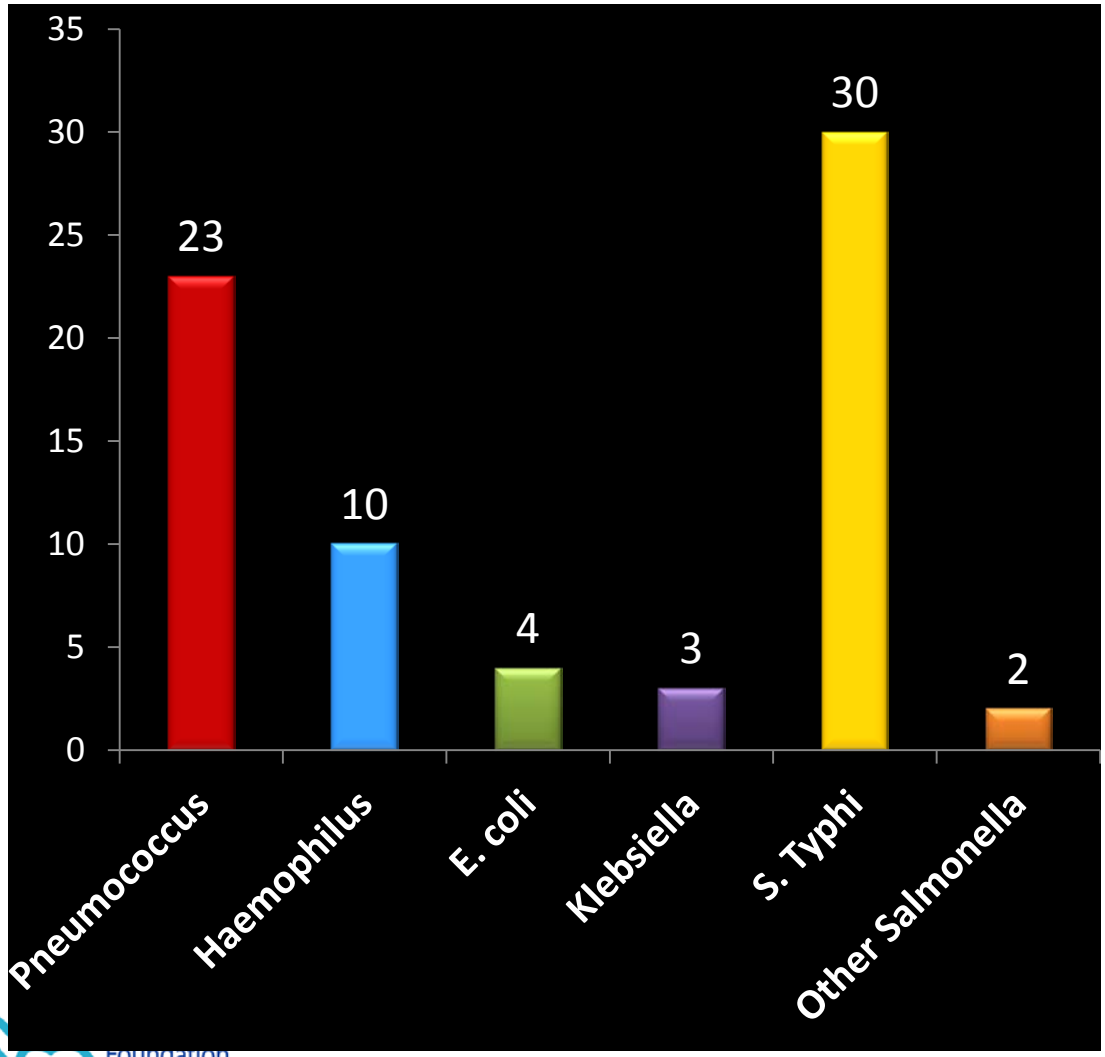
Multicentre Hospital Based Surveillance for Invasive Bacterial Diseases – Rural hospital



- Total blood culture – 4,203
- Relatively low rate of isolation
  - 42% of all isolate
  - Relatively low prevalence

Mirzapur, Rural Bangladesh

POPULATION BASED FIELD SITE

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Integrated Rural Field Site

- Mirzapur
  - 63 kilometers north of Dhaka city
  - Population: 400,000
- Health facilities:
  - Kumudini Hospital (750 beds)
    - ~120 pediatric patients at OPD daily
    - >500 patients a day
    - Pediatric ward of 80 beds
  - Upazilla Health Complex (31 beds)

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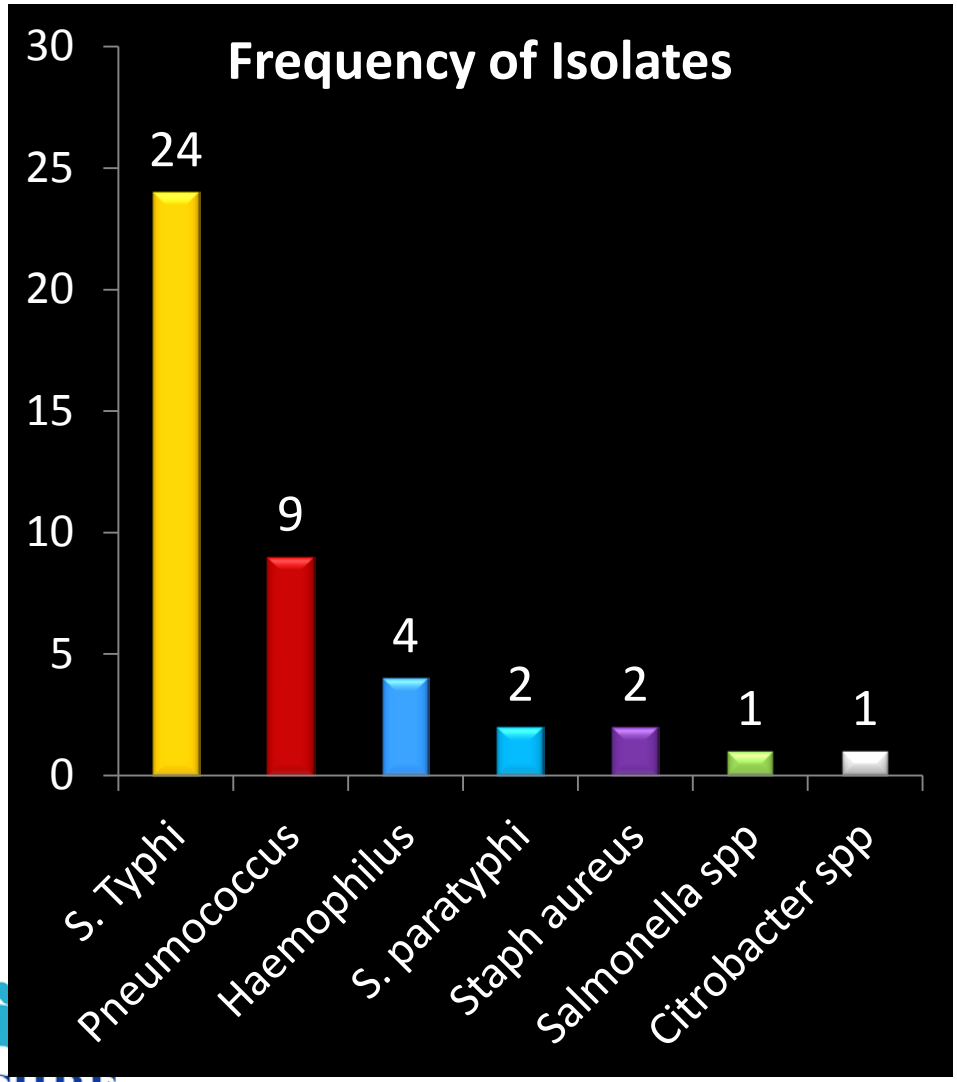
Distribution of Blood Culture in Rural Bangladesh



Variables	No.
Population	144,000
Total enrolled	11,439
Episodes with temp ≥100.4^{0}F	3,978
Blood Culture done	3,724

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Age-specific Incidence of typhoid fever <5 children in rural Bangladesh

Age groups (months)	Culture confirmed cases	Typhoid incidence/ per 100,000 person-years
0 – 11	0 (0)	0
12 – 23	3 (12.5)	94
24 – 35	6 (25)	145
36 – 47	13 (54.2)	304
48 – 59	2 (8.3)	64
Total	24 (100)	151

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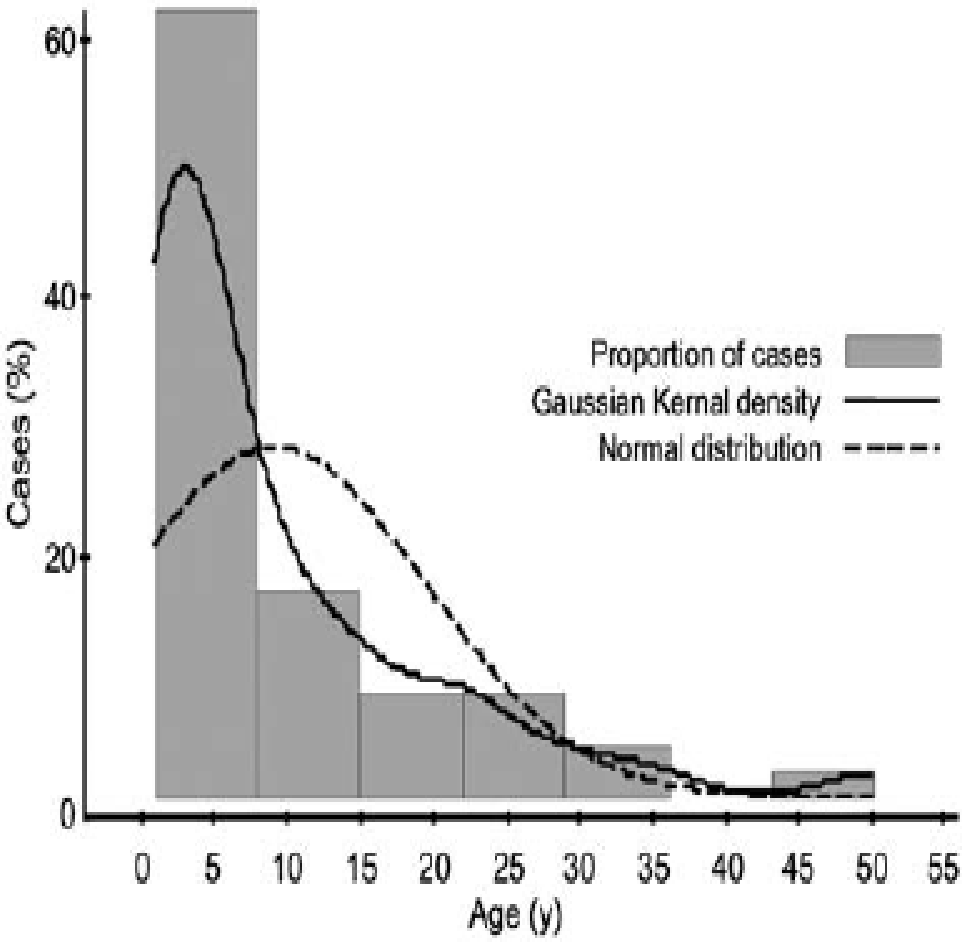
Population Based Surveillance in Urban Slum

Population Based Surveillance in Urban Slum



Active surveillance
all age group
Fever ≥38^{0}C – blood culture

Total blood culture – 888
Total positive – 65 (7%)
***S. typhi* – 49 (75%)**
Predominant cause of bacteraemic fever

Incidence
<5 years – 19 episodes/1000 person-years
≥5 years – 4 episodes/1000 person-years

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Brooks et al 2005

The specter of anti-microbial resistance

DO WE KNOW THE DYNAMICS?

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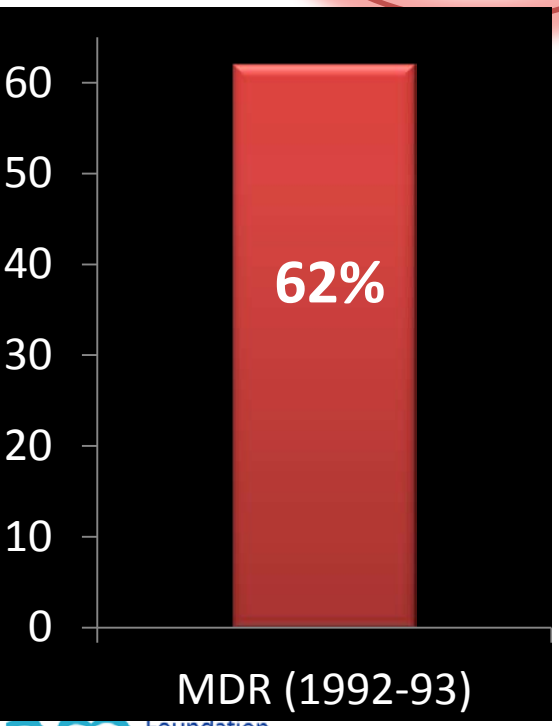
Treatment of Typhoid Fever

- 1st line of Antibiotic
  - Amoxycillin
  - Chloramphenicol
  - Cotrimoxazole

- Problem since 1990s
  - Slow epidemic of multi-drug resistant *S. Typhi* in the subcontinent



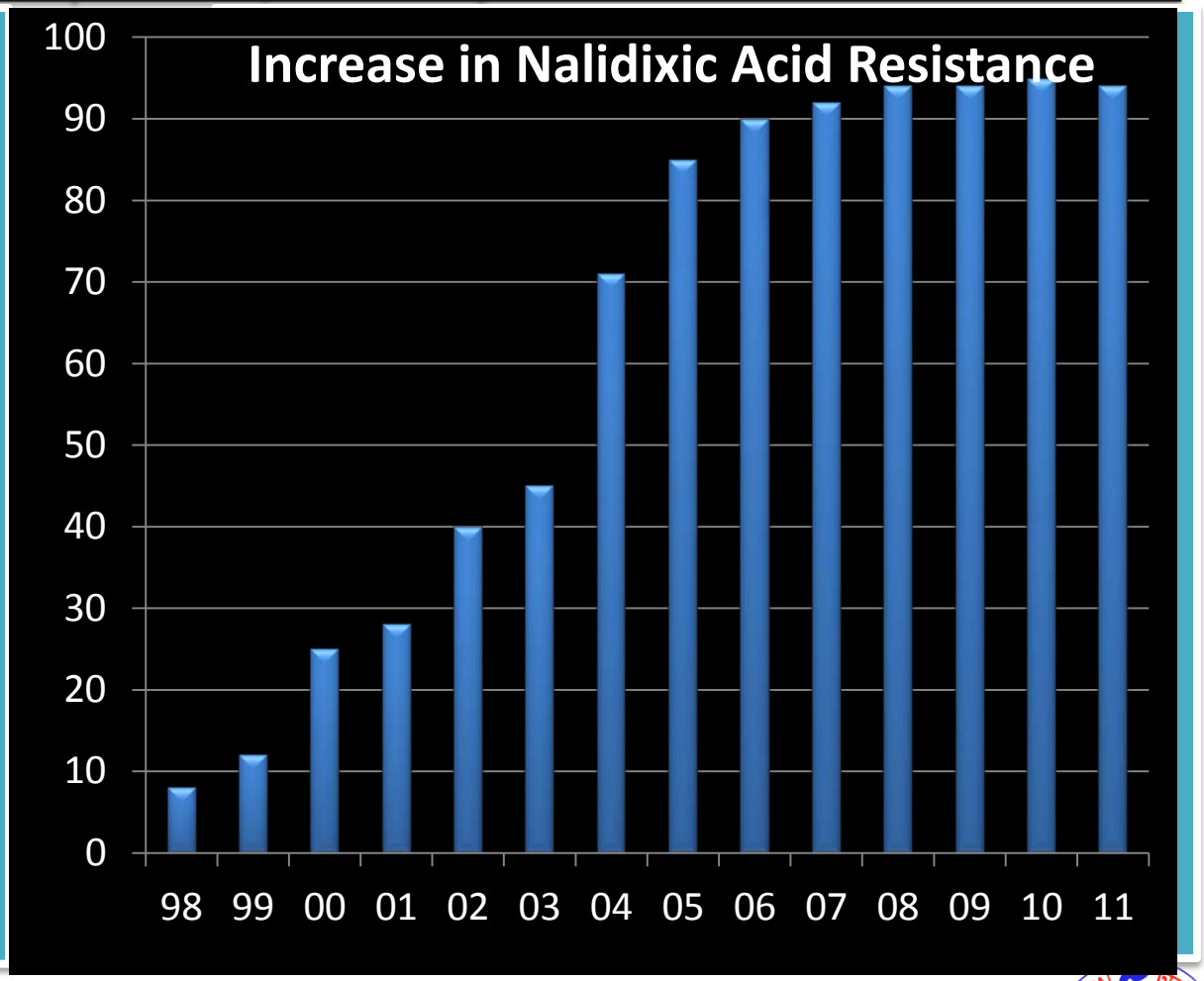
- Concern for the public health practitioners
- Confusion between clinicians and microbiologists

- 2nd line of antibiotic
  - Ceftriaxone - Expensive
  - Ciprofloxacin – Widely Used

Saha et al. 1995

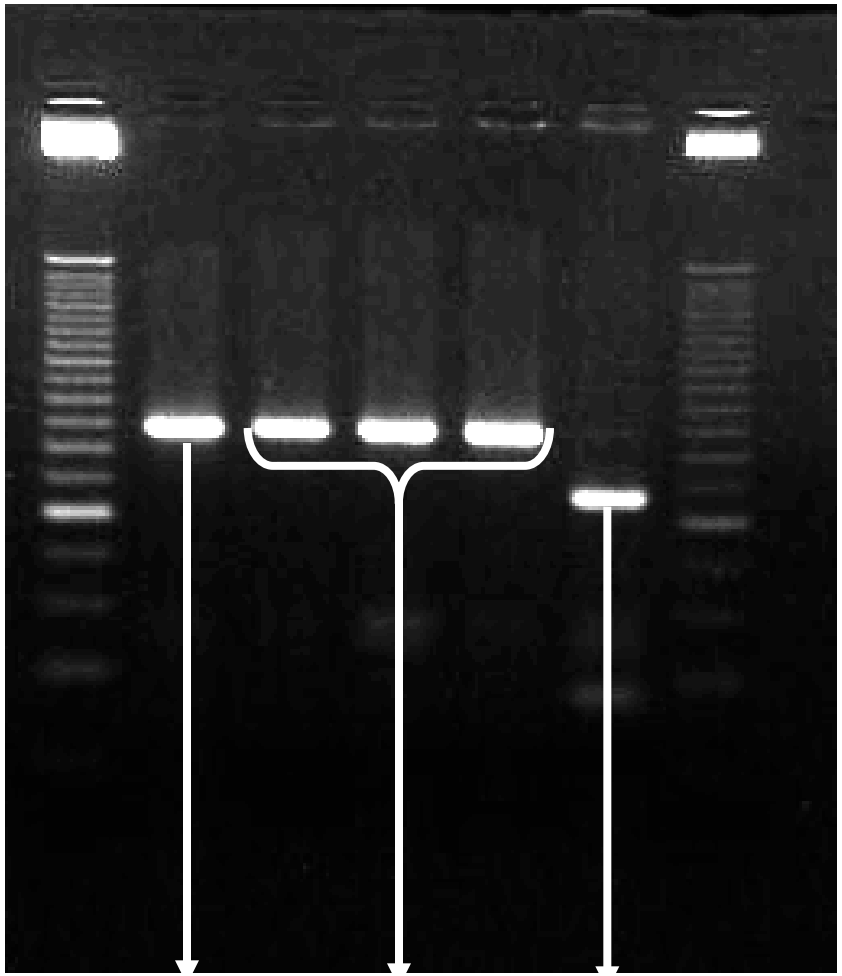
Trend of Drug Resistance '94-'11 (N=5,937)

- Progressive increase in relative resistance to ciprofloxacin
  - Delay in clinical response
  - Treatment failure
  - Recurrences



Saha et al Antimicrobial Agents Chemother1990, Saha et al Antimicrobial Agents Chemother1995

Emergence of Highly Cipro-Resistant *S.* Typhi: Molecular Basis of Resistance



- Highly ciprofloxacin resistant S. Typhi
  - MIC 512 μg/ml
  - Double mutation at point 83 and 87 of gyrase genome
  - Contrast to "No mutation" in sensitive strains

Saha et al. J. Clin Microbiol 2006

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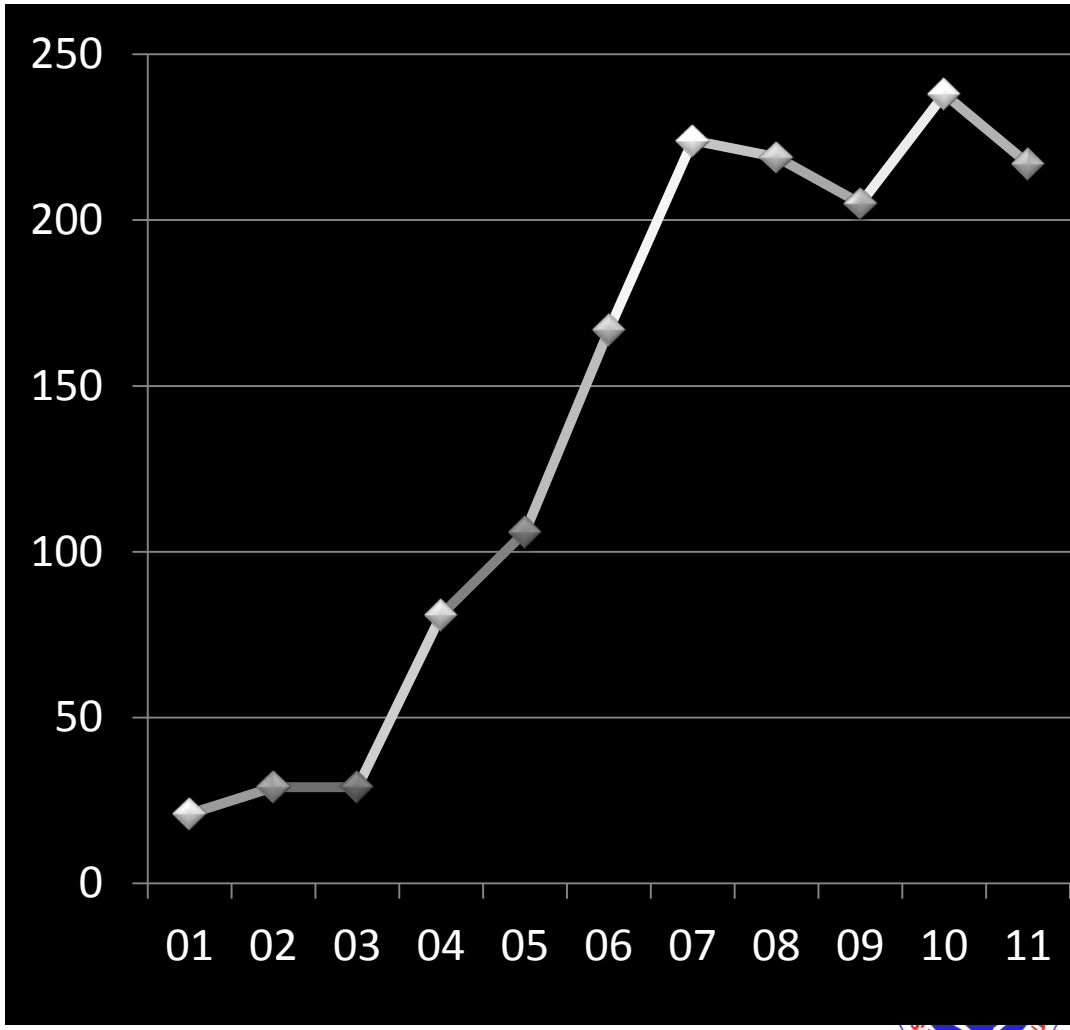
Financial Implications of Drug Resistance

- High prevalence of MDR and Nalid^{R}
- Increasing trend isolation at hospital
  - Hospitalization lead to 10 times increase in direct cost ($22-29 Vs $172-286)
    - Mean income of typhoid cases - $73
  - Indirect cost – absence from the business, food for attendants, missing schools, etc.



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Improved Living Conditions – sanitation, hygiene, piped water and so on

WHAT COULD BE THE POSSIBLE IMPACT ON TYPHOID?

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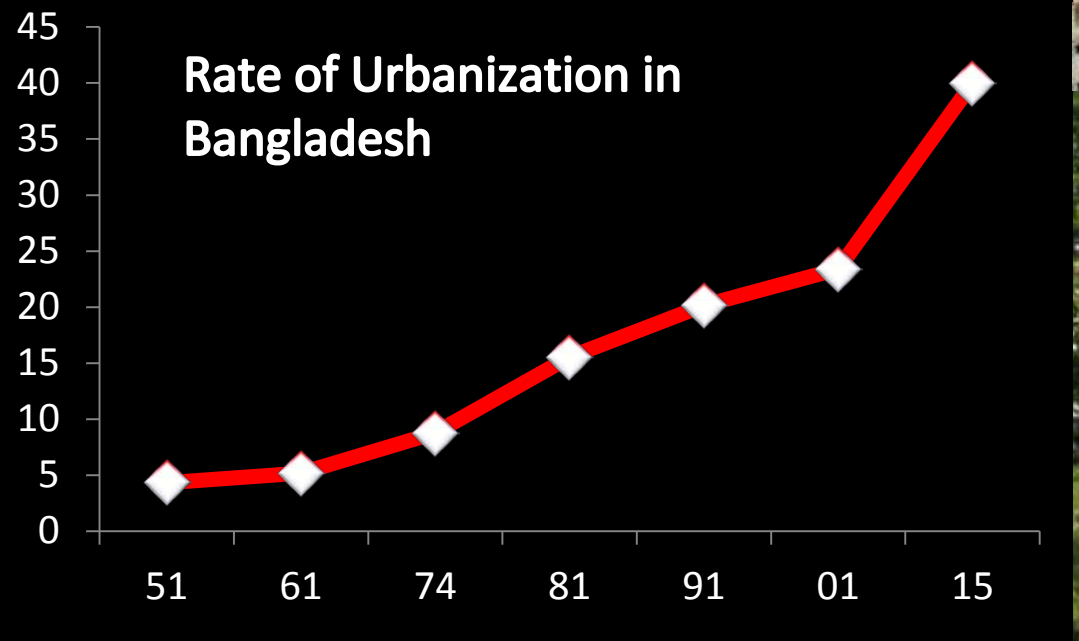
Comparative Prevalence of Typhoid in Urban and Rural Bangladesh

	Urban	Rural
Among blood cultures Hospital	2.7%	0.80%
Among blood cultures - Community	5.4	0.64%
Among isolates - Hospital	64%	41%
Among isolates - Community	75%	56%
Incidence/100,000	1,900	151



Immunization against Typhoid

PERSPECTIVE FOR BANGLADESH AND BEYOND

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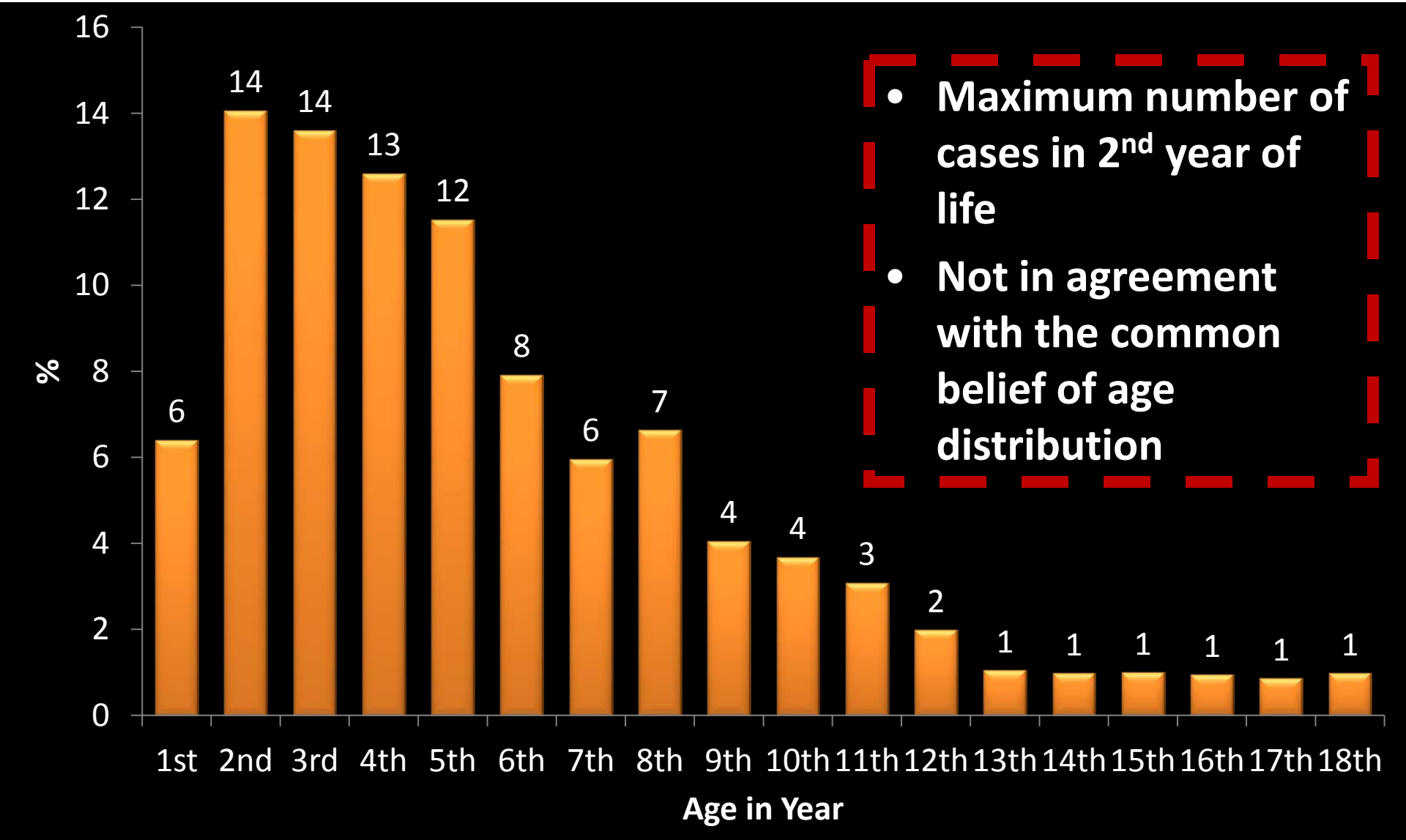
Typhoid: Dogma of Recent Past

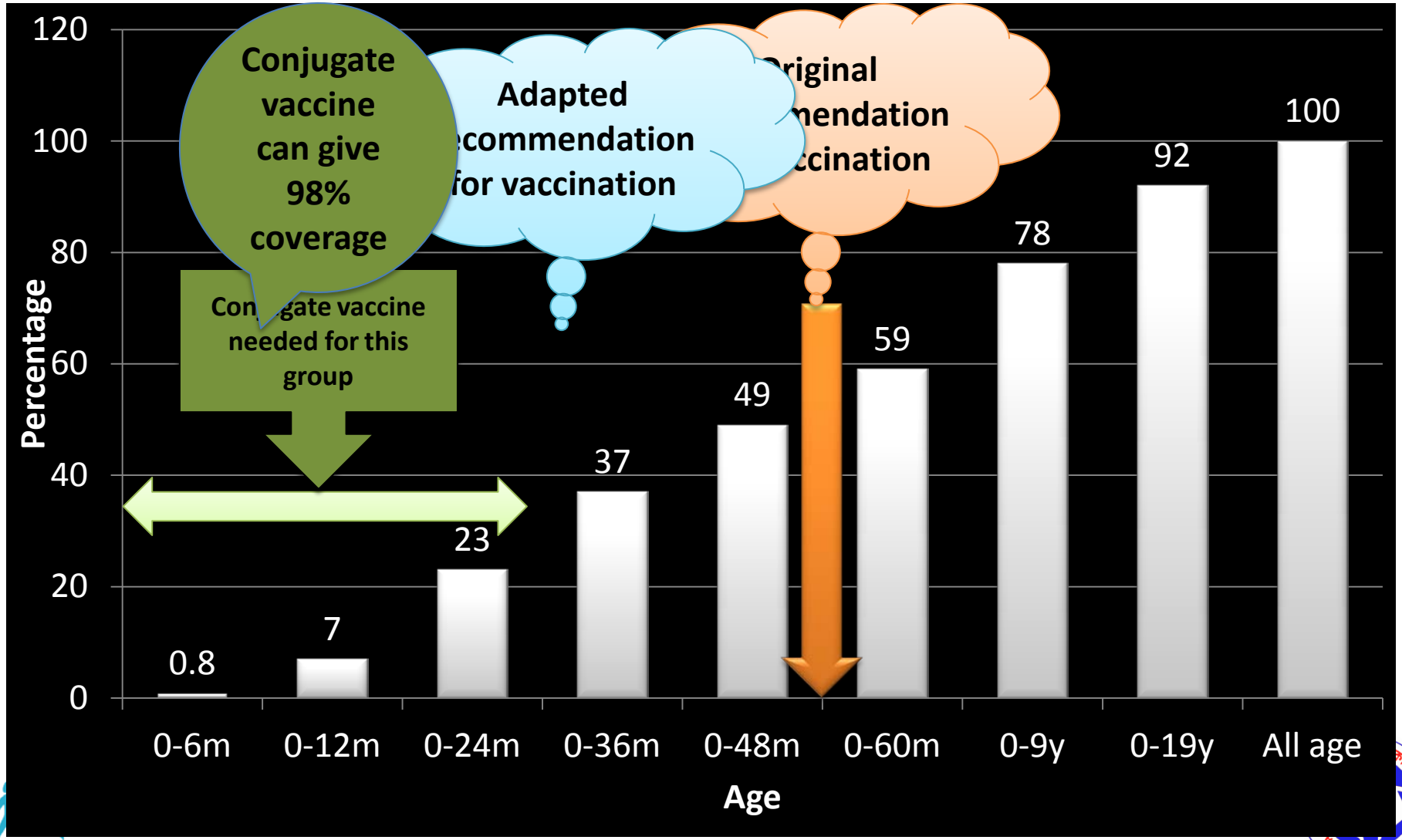
The disease is not prevalent among Preschool Children

Even if it is there, the disease episodes are benign

Age Group Distribution of Typhoid Cases (N= 5,937)



Age Group Distribution (N= 5,937) – impact on typhoid vaccination policy



Typhoid in Early Age

IS IT REALLY SEVERE IN YOUNGER AGE GROUP?

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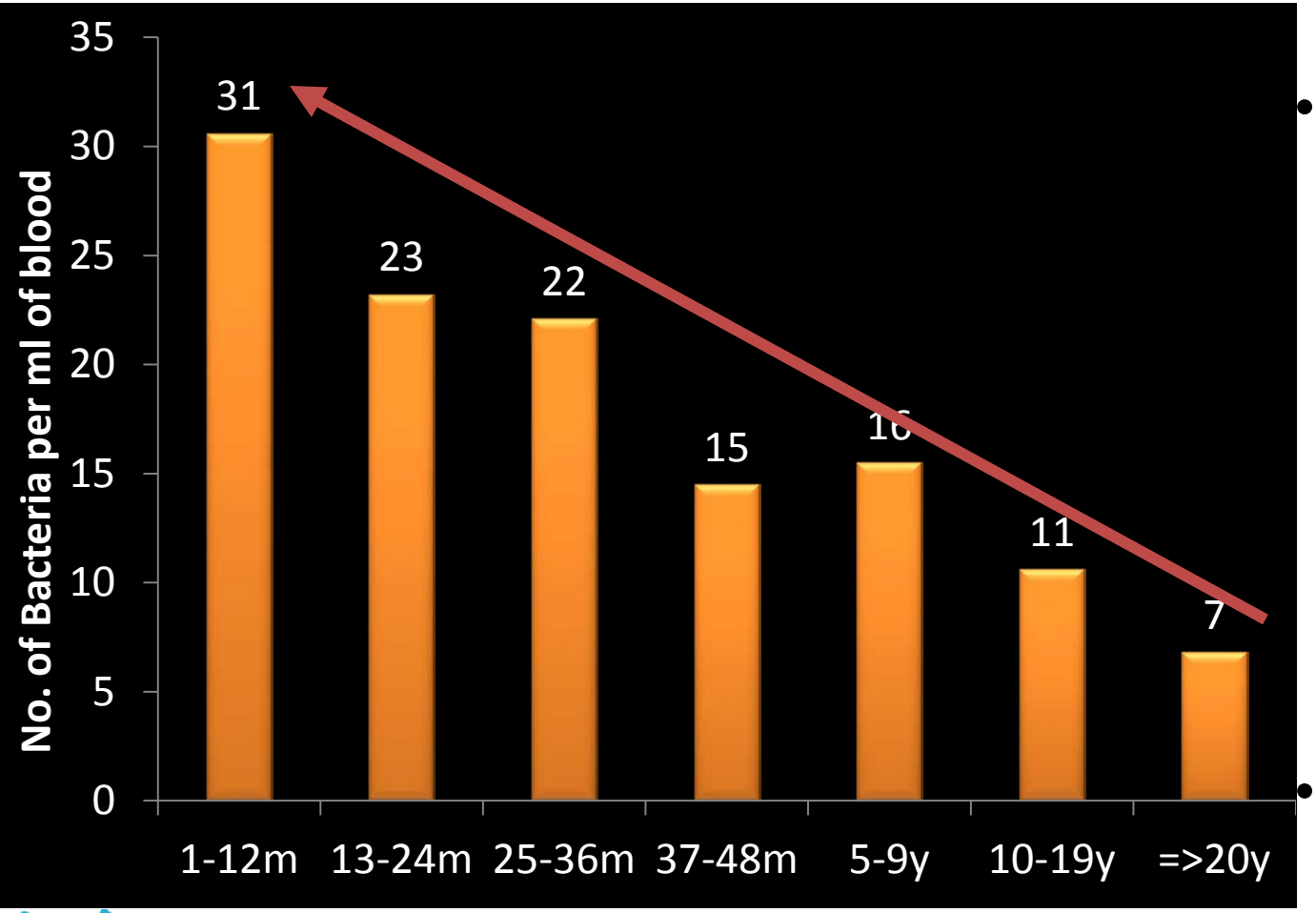
Magnitude of S. Typhi bacteraemia



- Previous concept: Less severe in young infants?
  - High magnitude of bacteremia
  - Facility based study
    - Care seeking behavior
    - Access to health
  - We dealt with sicker children
- Severity in young children is no less

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Saha et al PIDJ, 2000

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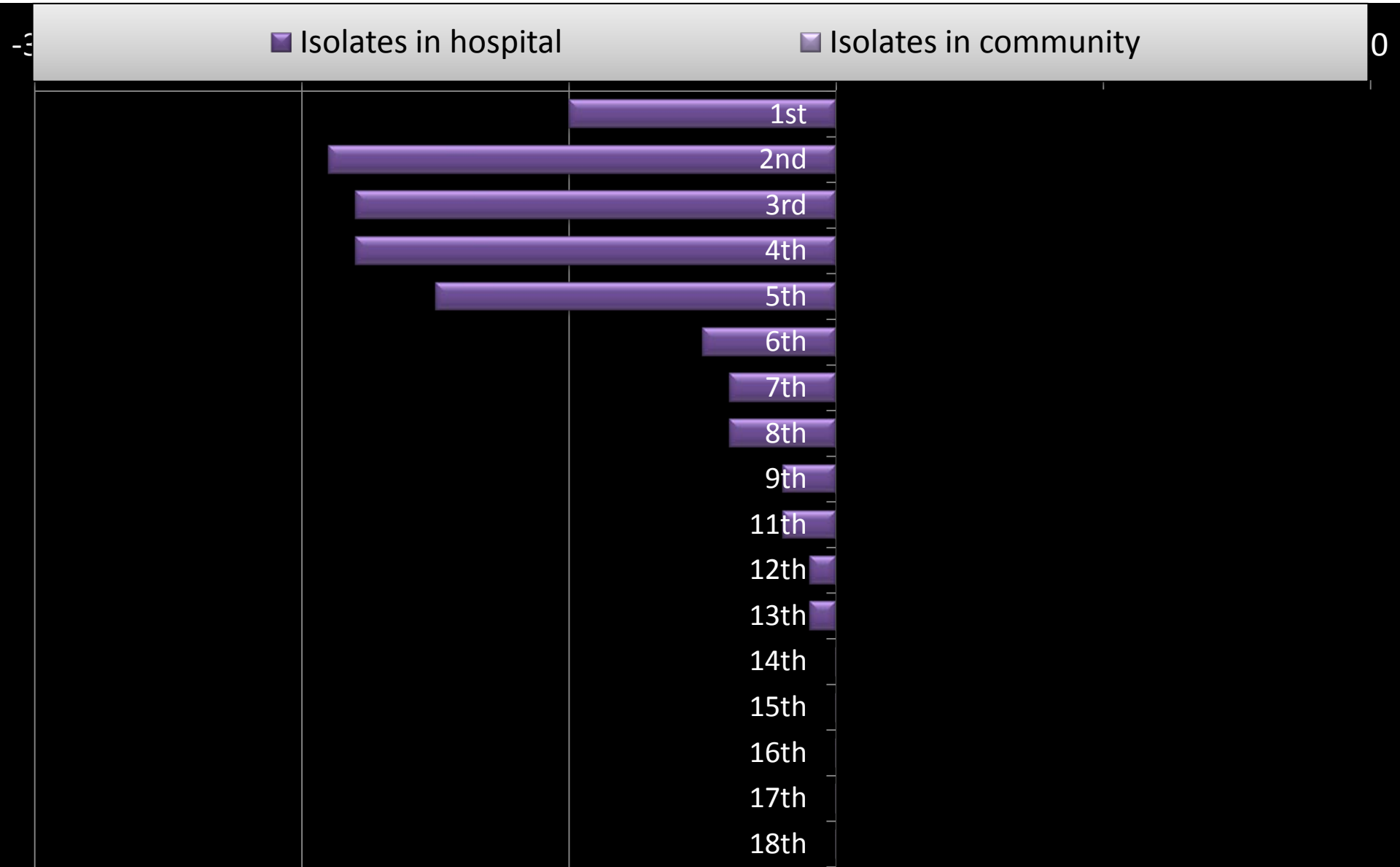
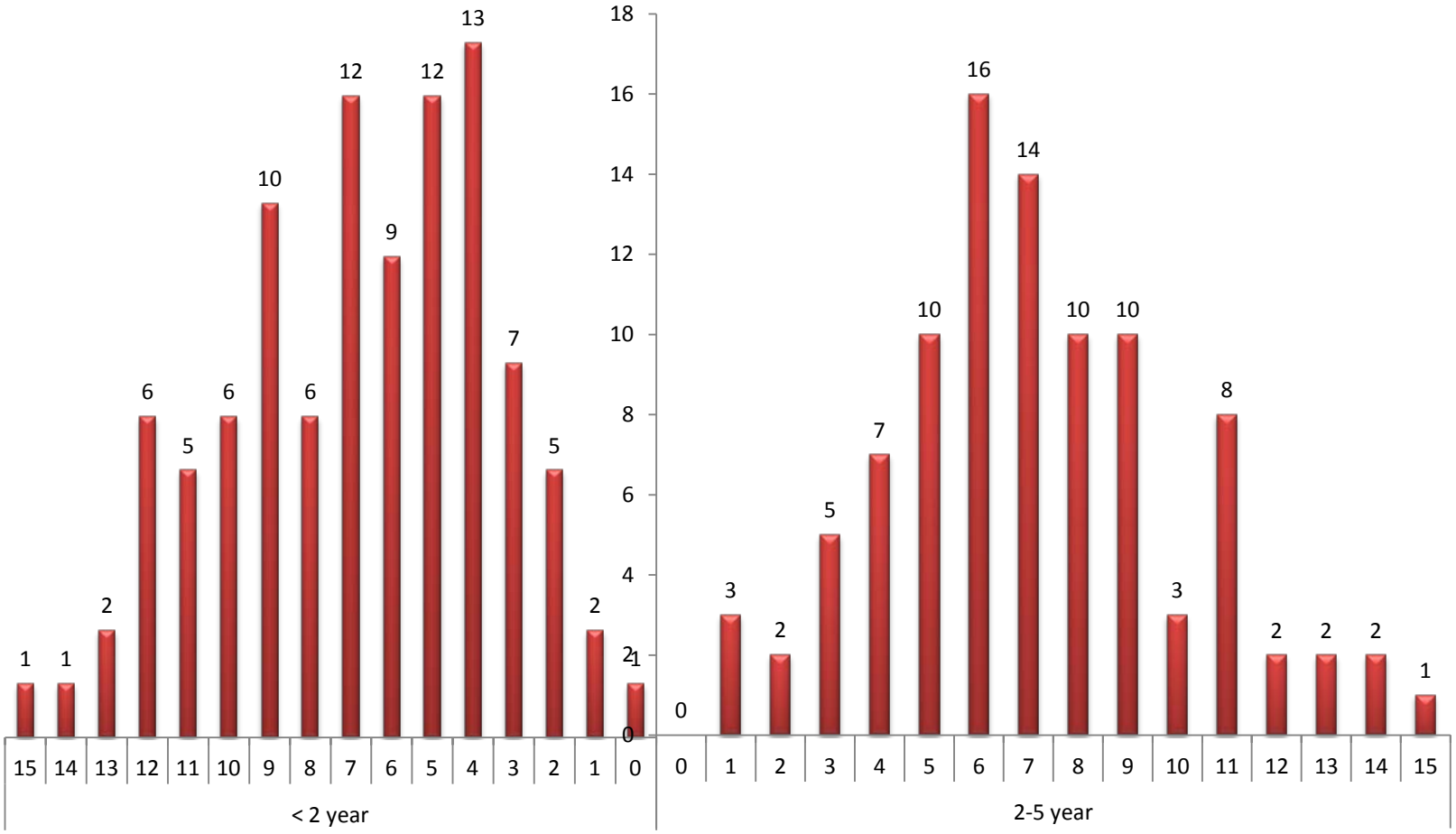
Age Distribution of Typhoid Cases in Hospital and Community



Duration of Hospital Stay by Age Group



<2 years

2-5 years

- Similar duration of hospital stay irrespective of age group

So we can not just escape the children

THESE ARE NOT THE POPULATION WE ARE LOOKING FOR

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What needs to be done to prevent Typhoid

IMPROVED SANITATION AND IMMUNIZATION

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Highest Price Tag for Child Survival

WATER AND SANITATION

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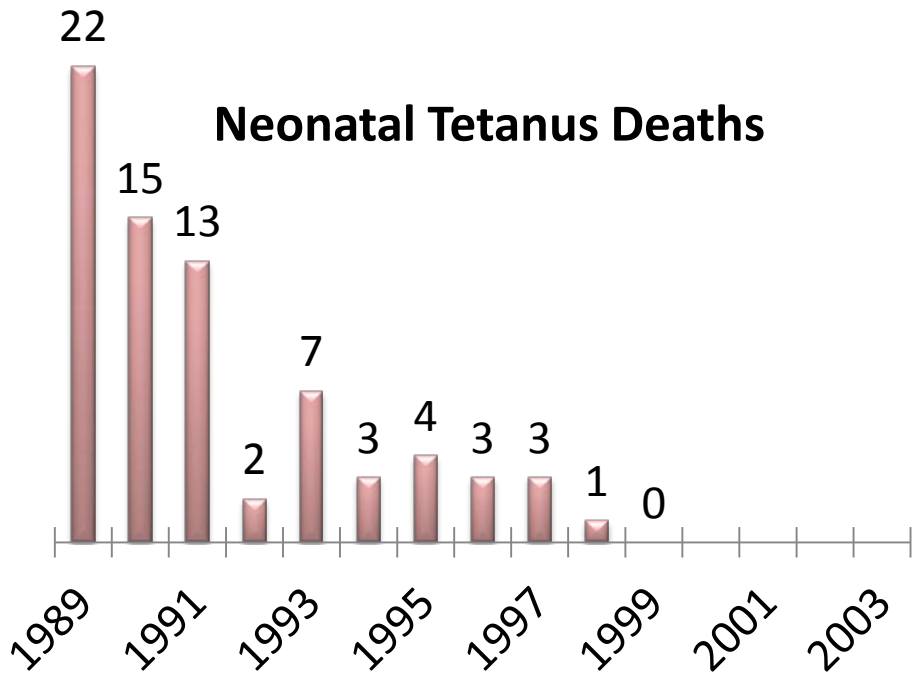
Impact of Immunization is Straight Forward



- Bangladesh has Few Things to be Proud
  - Our Immunization Program
  - a success story e.g. near disappearance of Tetanus, Diphtheria, Polio, Hib, etc.
- In the process of introducing Pneumo vaccine

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Issues with Typhoid Vaccines – Polysaccharide vs Protein Conjugated Vaccine

When conjugation technology is available for last 3 decades

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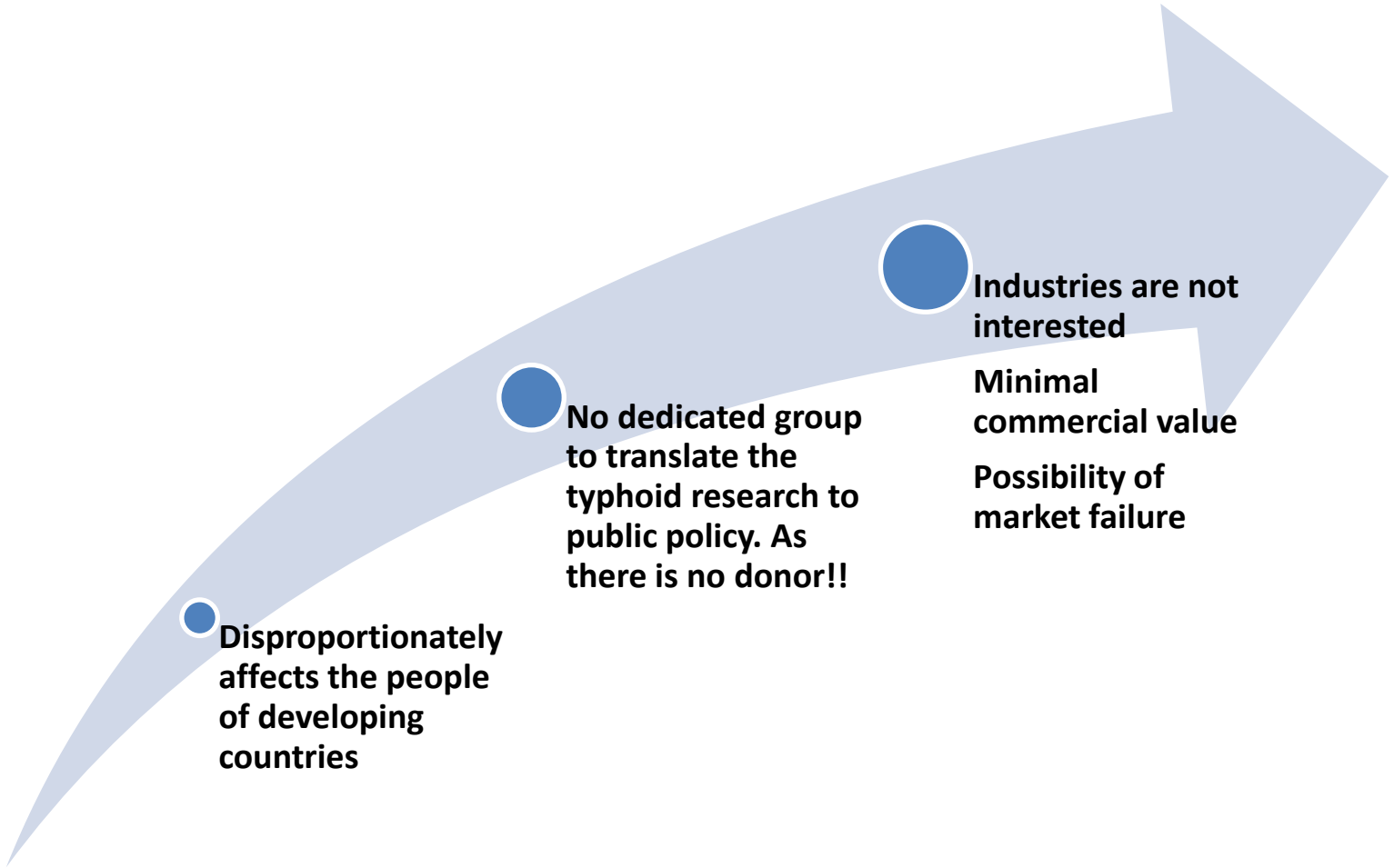
Why the Uncertainty about Conjugate Vaccine for Typhoid?



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New Hope in Preventing Typhoid

COALITION AGAINST TYPHOID

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Thank You

Are we too much focused to our own agenda?

HOPE TO GET BACK THE PERIPHERAL VISION SOON

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Expectations from this Meeting

- Bangladesh will be part of Global Health Work of UoT focusing on
  - Infectious Diseases
  - Translation of Science to Public Policy

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Donor Driven Research

WE DIDN'T INTEND TO DO ANY RESEARCH ON TYPHOID SPECIFICALLY

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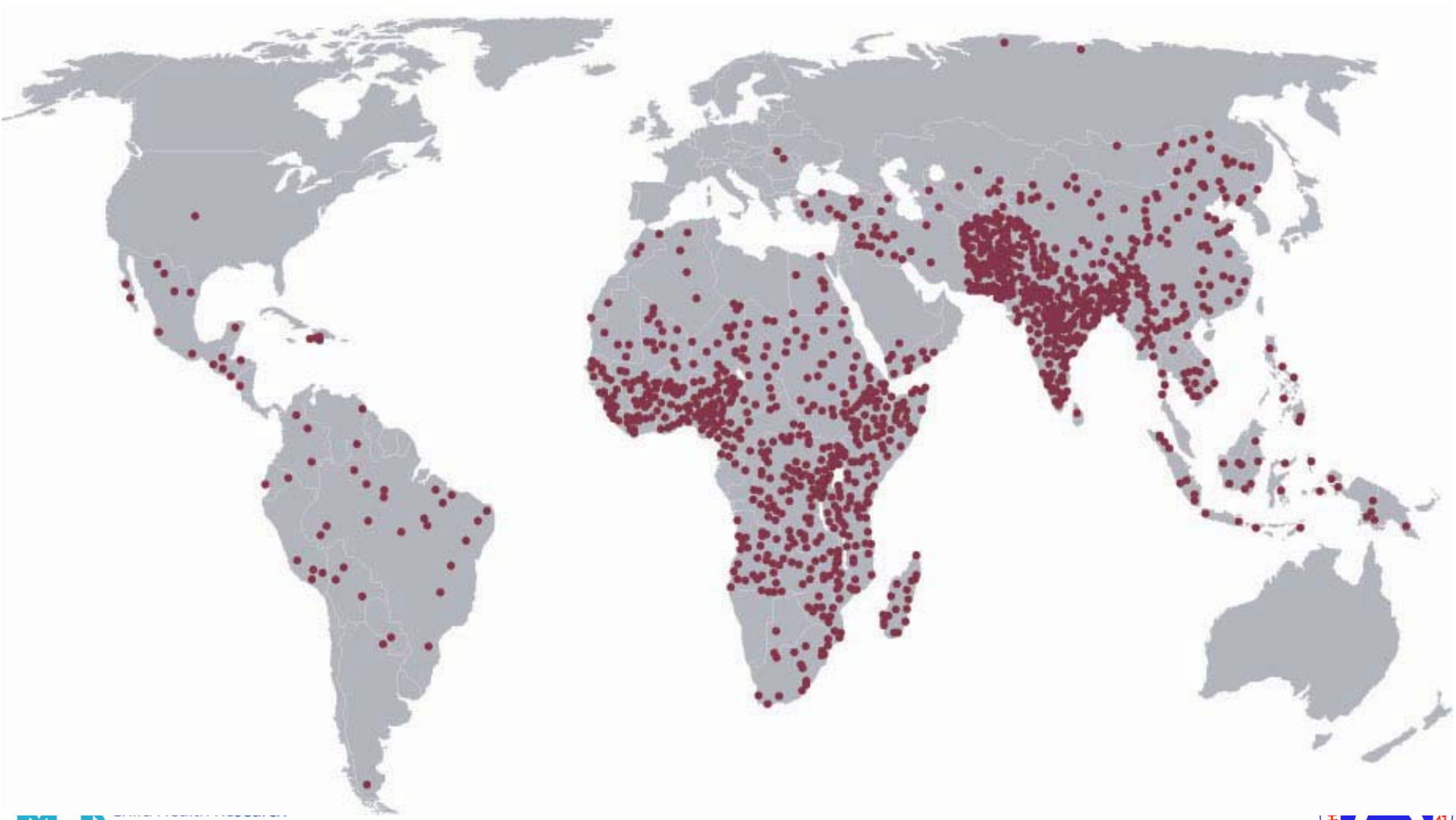
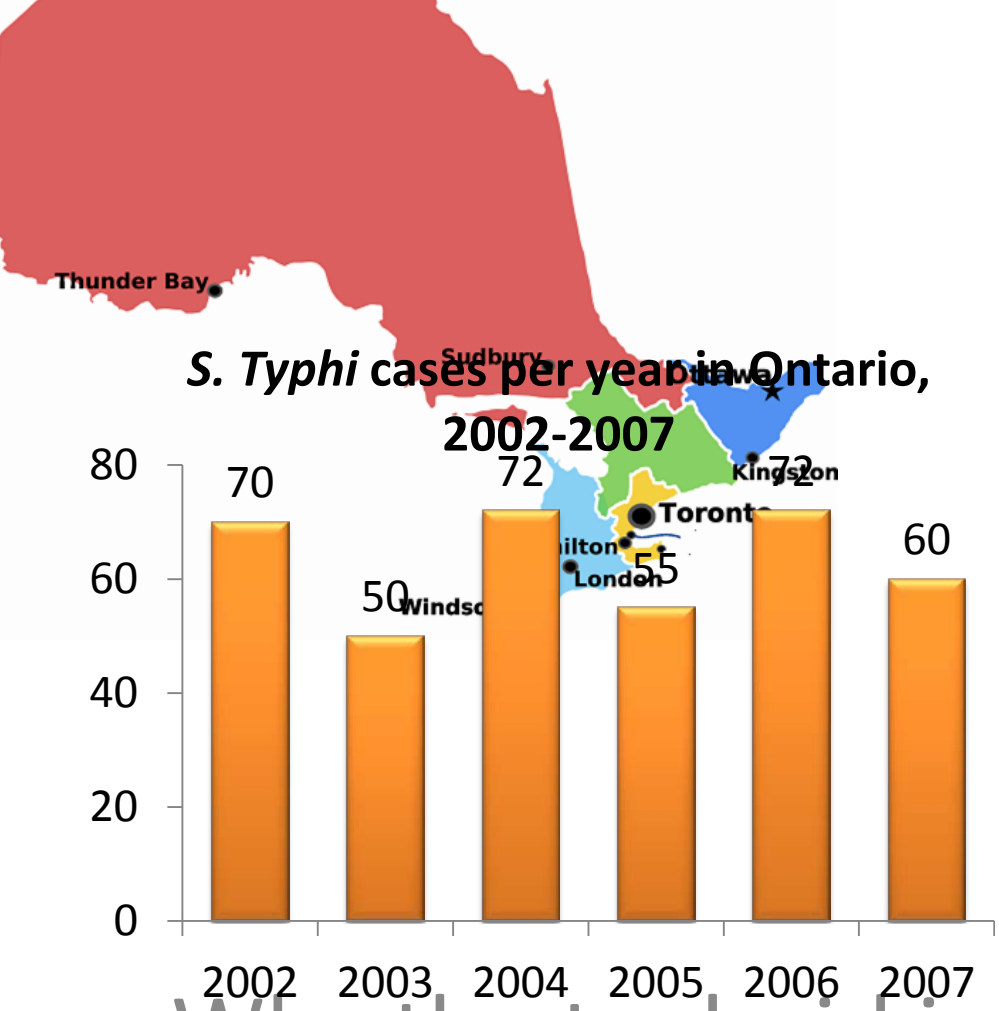
Key Issues for this Talk

- Child Health
- Infectious Diseases
- Typhoid
- Surveillance
- Vaccines

Illogical Distribution of Technologies





***S. Typhi* cases per year in Ontario, 2002-2007**

Why the typhoid issue at Toronto?

DIDN'T WE ERADICATE TYPHOID YEARS AGO?

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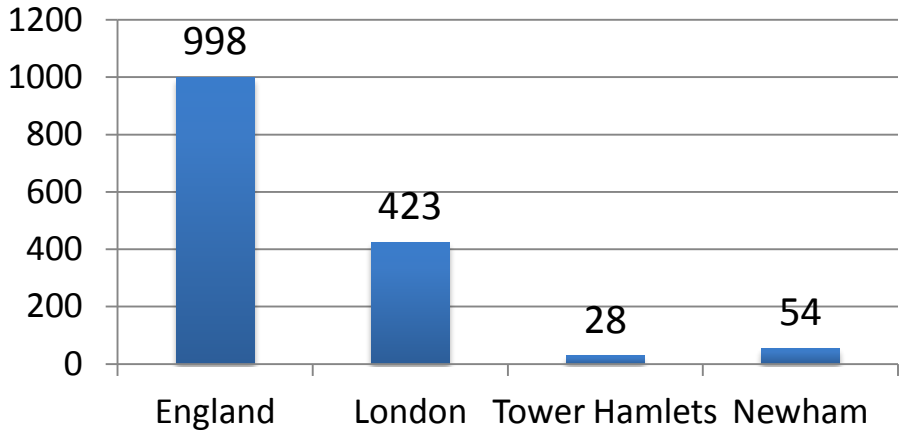
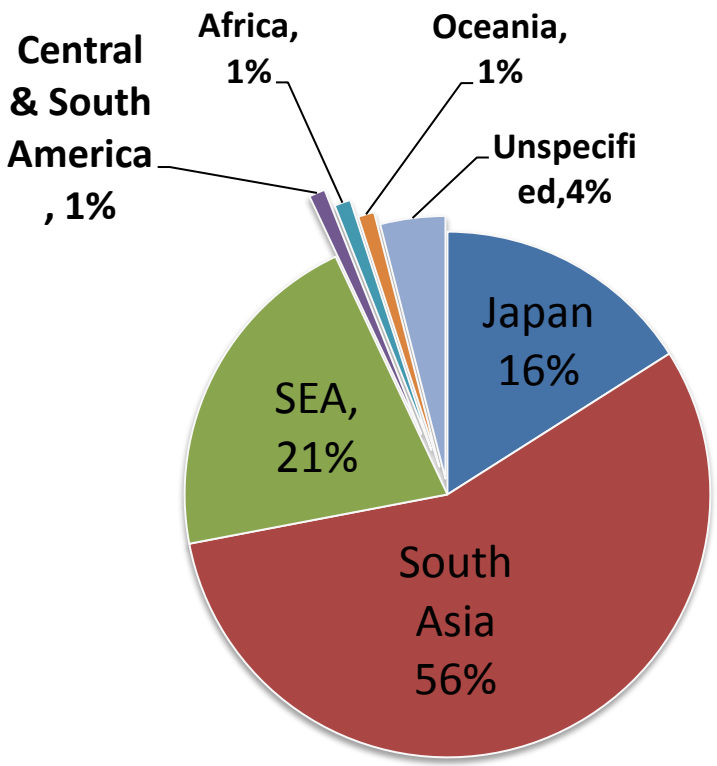
Morris et al 2009

Typhoid Travels Across the World

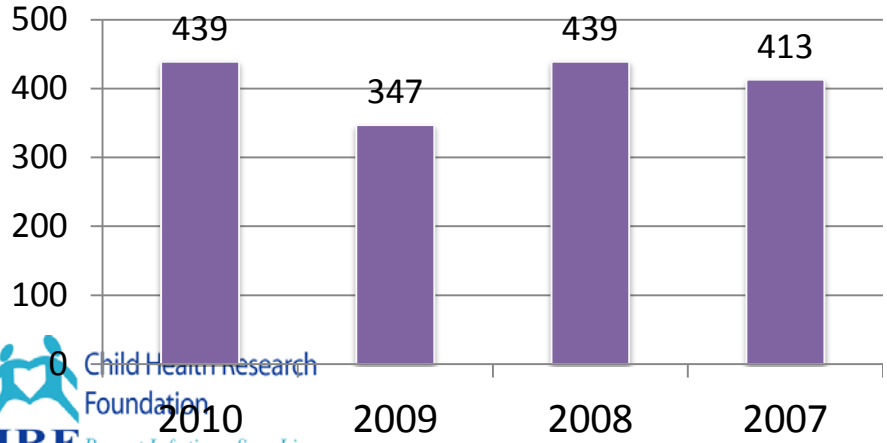
1,503 Typhoid cases in UK, 2006-09



227 Typhoid Cases in Japan, 2005-08



Typhoid cases in USA



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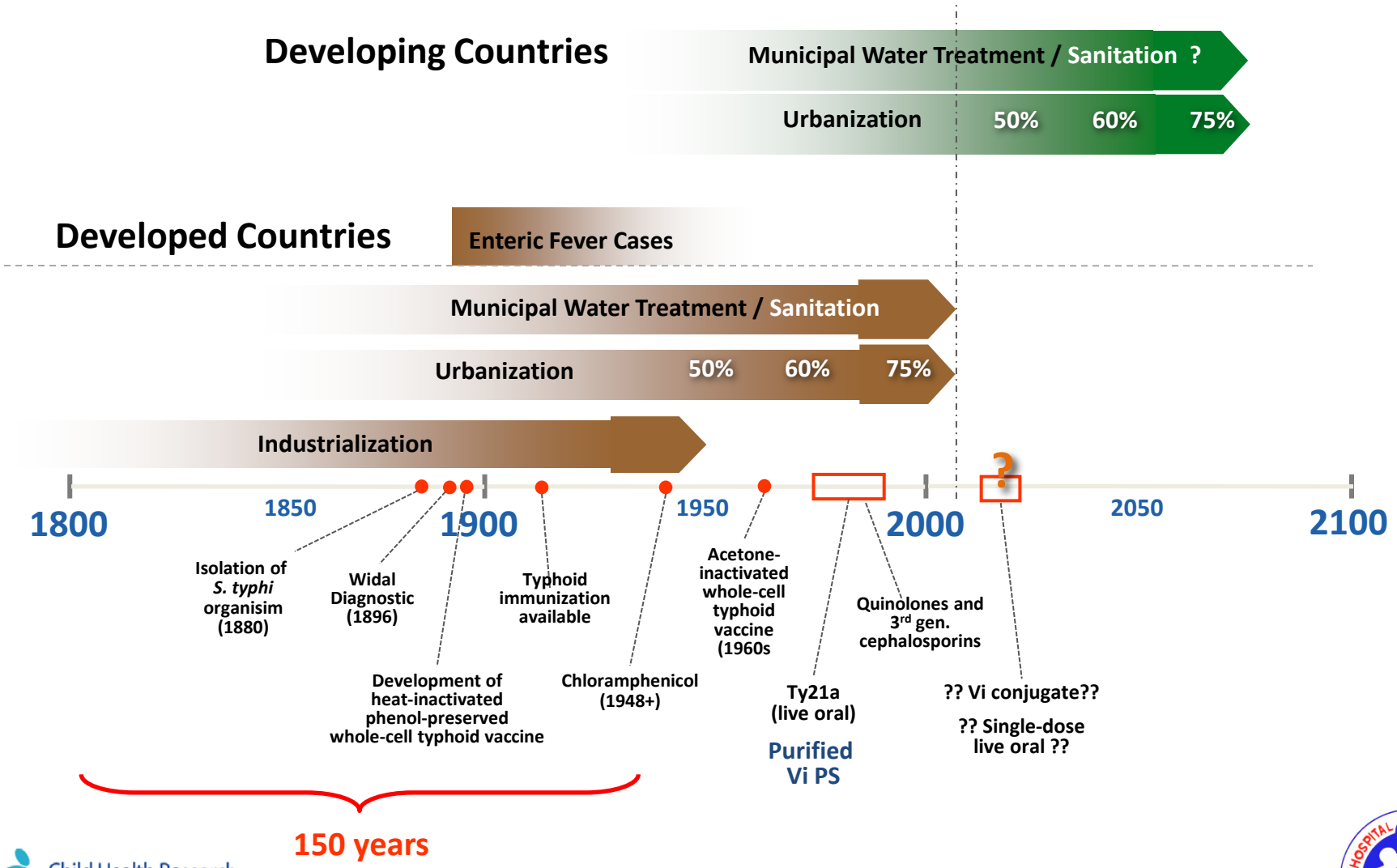
Typhoid – A Global Disease

IT CAN NOT BE FOOLED BY SAYING - THESE ARE NOT THE POPULATIONS YOU ARE LOOKING FOR!

Typhoid Through the Centuries



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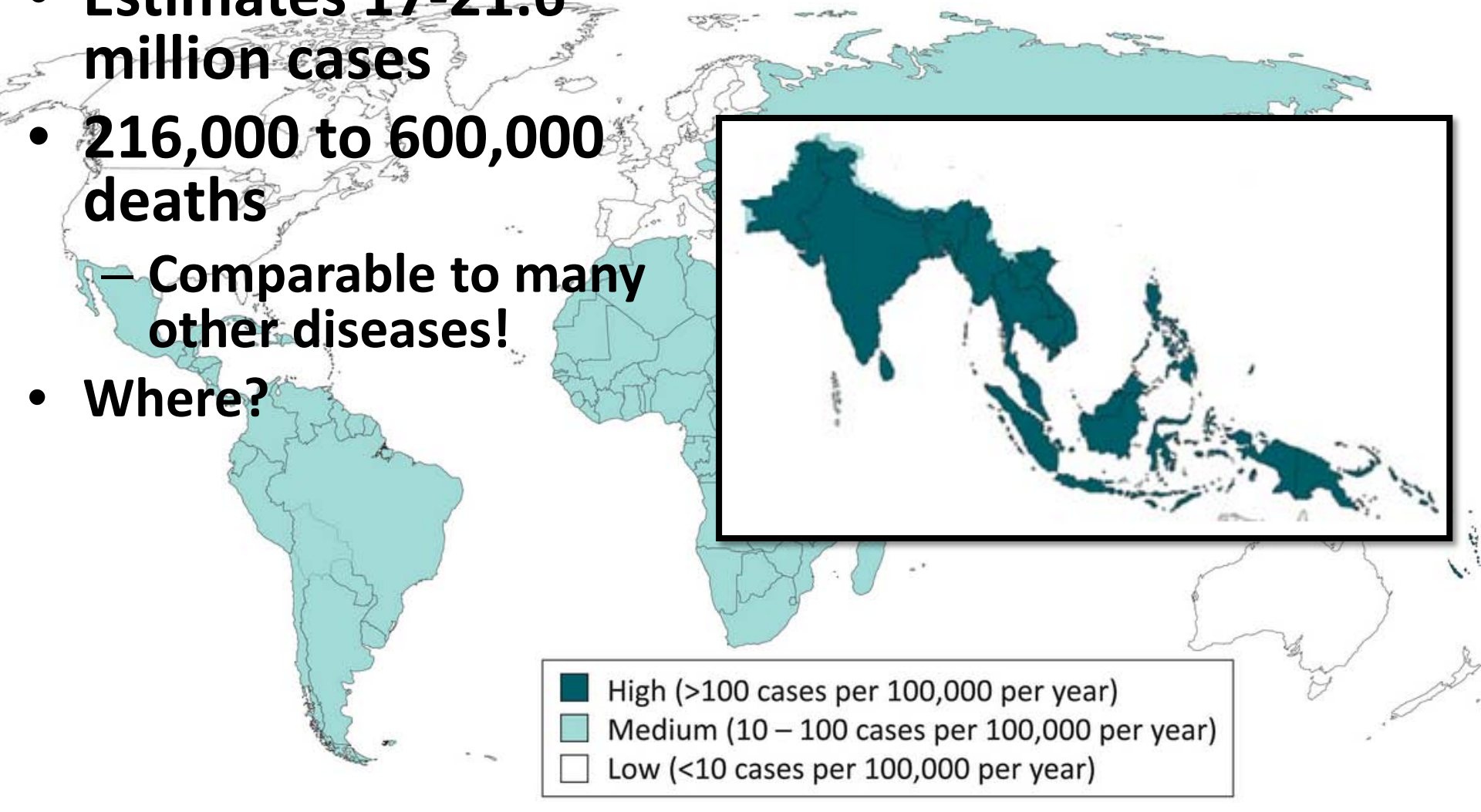
How Big a Problem Is This and Where?

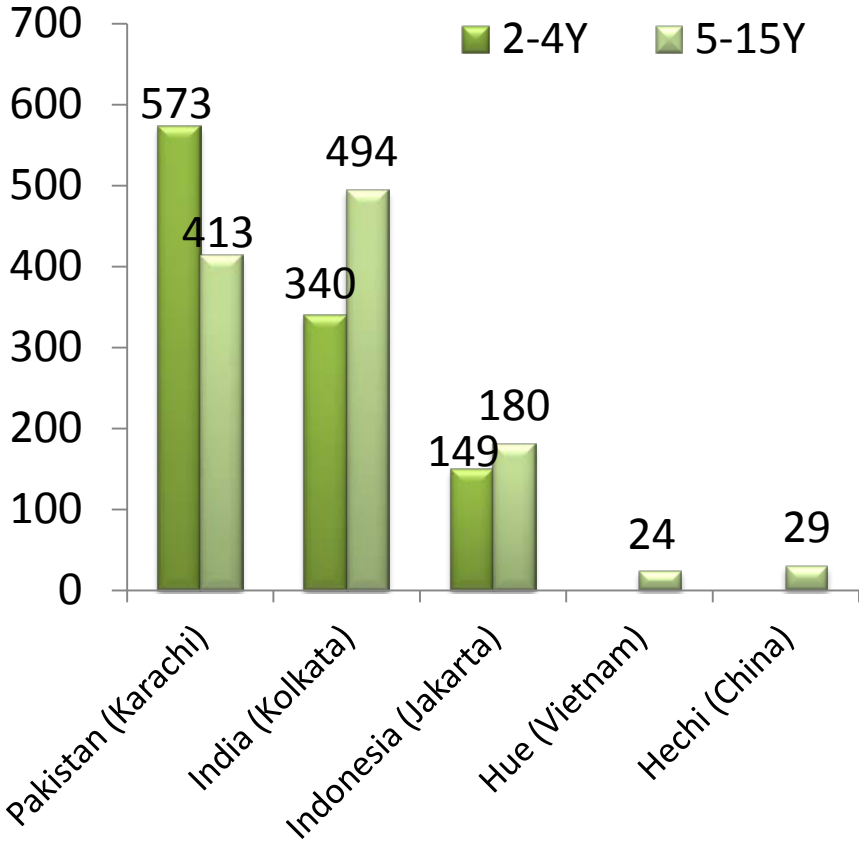
- Estimates 17-21.6 million cases
- 216,000 to 600,000 deaths
  - Comparable to many other diseases!
- Where?



Typhoid Remains Neglected

- None at WHO
- No GAVI Initiative,
- Recent initiative from BMGF – DOMI (Diseases of the most impoverished) programme
- More Recently “Coalition Against Typhoid”

DOMI TYPHOID PROGRAM
Population-based studies



CHINA, INDIA, INDONESIA, PAKISTAN, VIETNAM

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Tunnel Versioned!

I HOPE THESE INITIATIVES COULD BE WITH BROADER PERSPECTIVES

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Bangladesh Team

TAKEN THEIR VISION OUT OF THE TUNNEL TO UNDERSTAND TYPHOID

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