

Enteric Fever Outbreaks in Africa: Same old Foe but Emerging New Challenges in Management

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Lecture outline

- **Epidemiology of typhoid in Africa**
- **New clonal expansions and Antimicrobial Resistance**
- **Current issues on diagnosis**
- **Prospects for vaccine use in disease prevention strategies**

Introduction

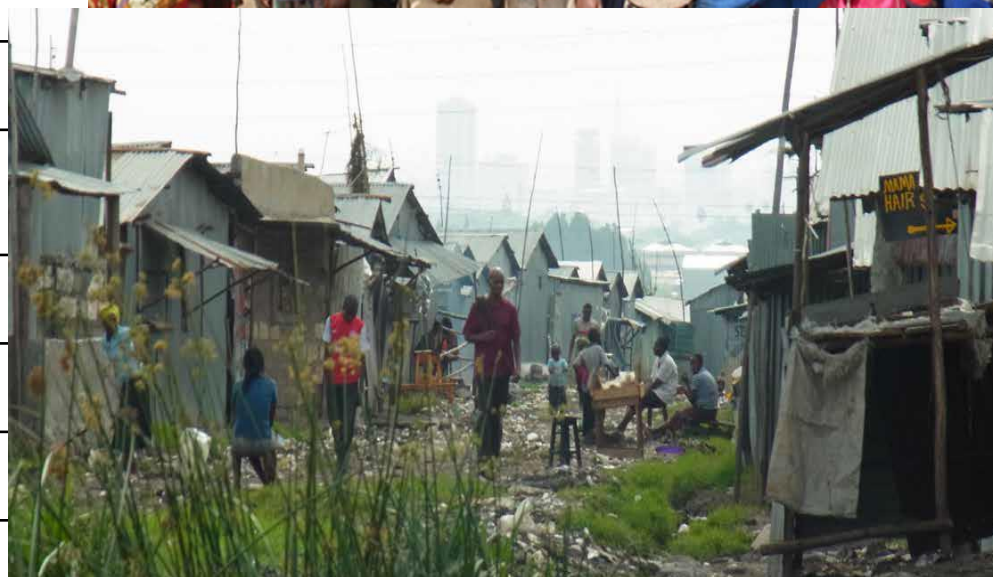
- **Few population-based data on incidence and mortality due to salmonellosis in Africa (SETA initiative)**
- **Most data from hospital-based studies of community-acquired bloodstream infection**
 - **Non-Typhi *Salmonella* predominate in west, central, east, and southern Africa**
 - **More cases of S. Typhi now reported from informal settlements in sub-Saharan Africa**
 - **Differences in regional prevalence and epidemiology is poorly understood**

A long way to go on matters overcrowding and sanitation

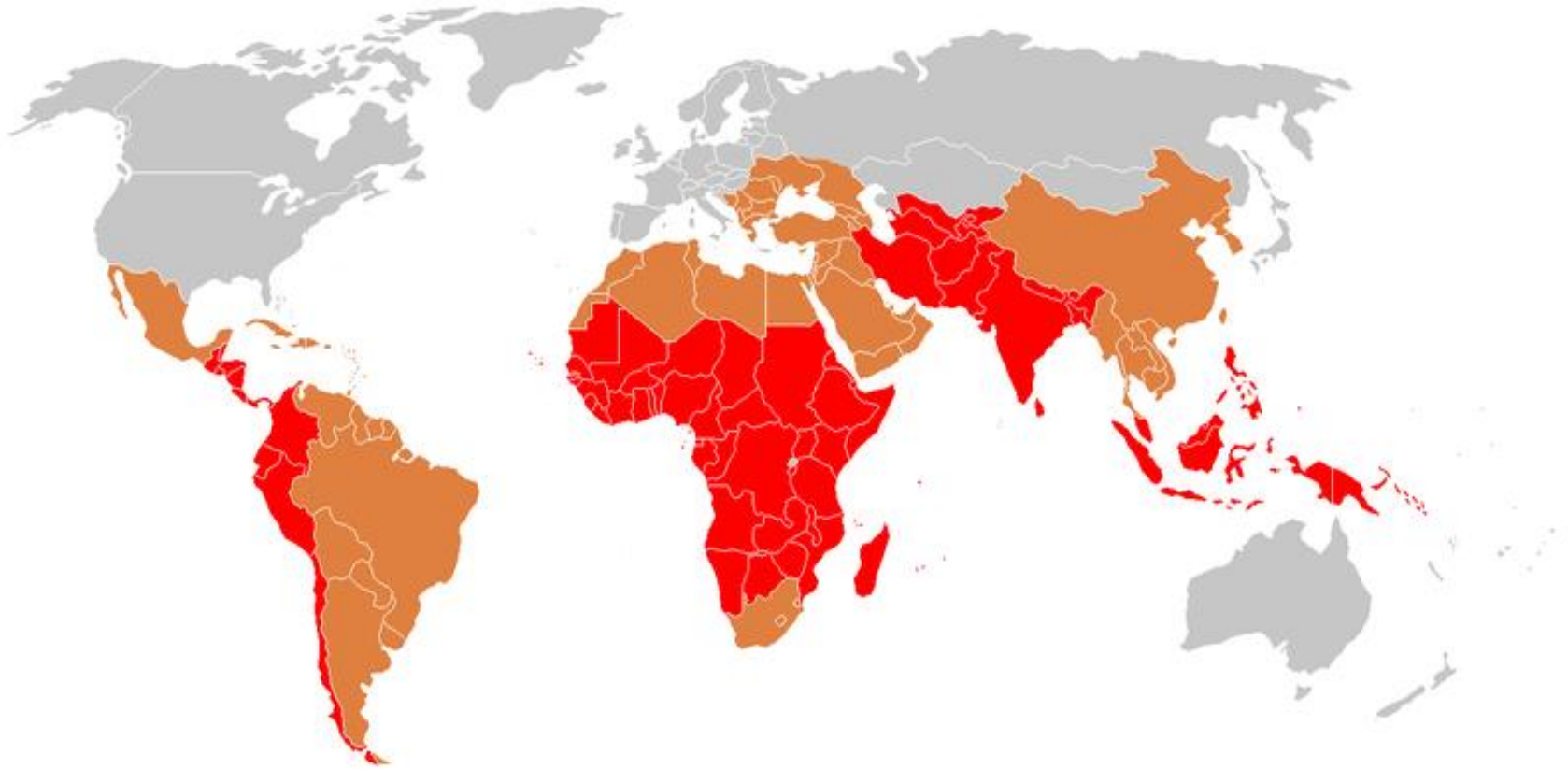
Mukuru kwa Njenga and Mukuru Reuben are among the many villages in the larger slum

Catchment population for Mukuru

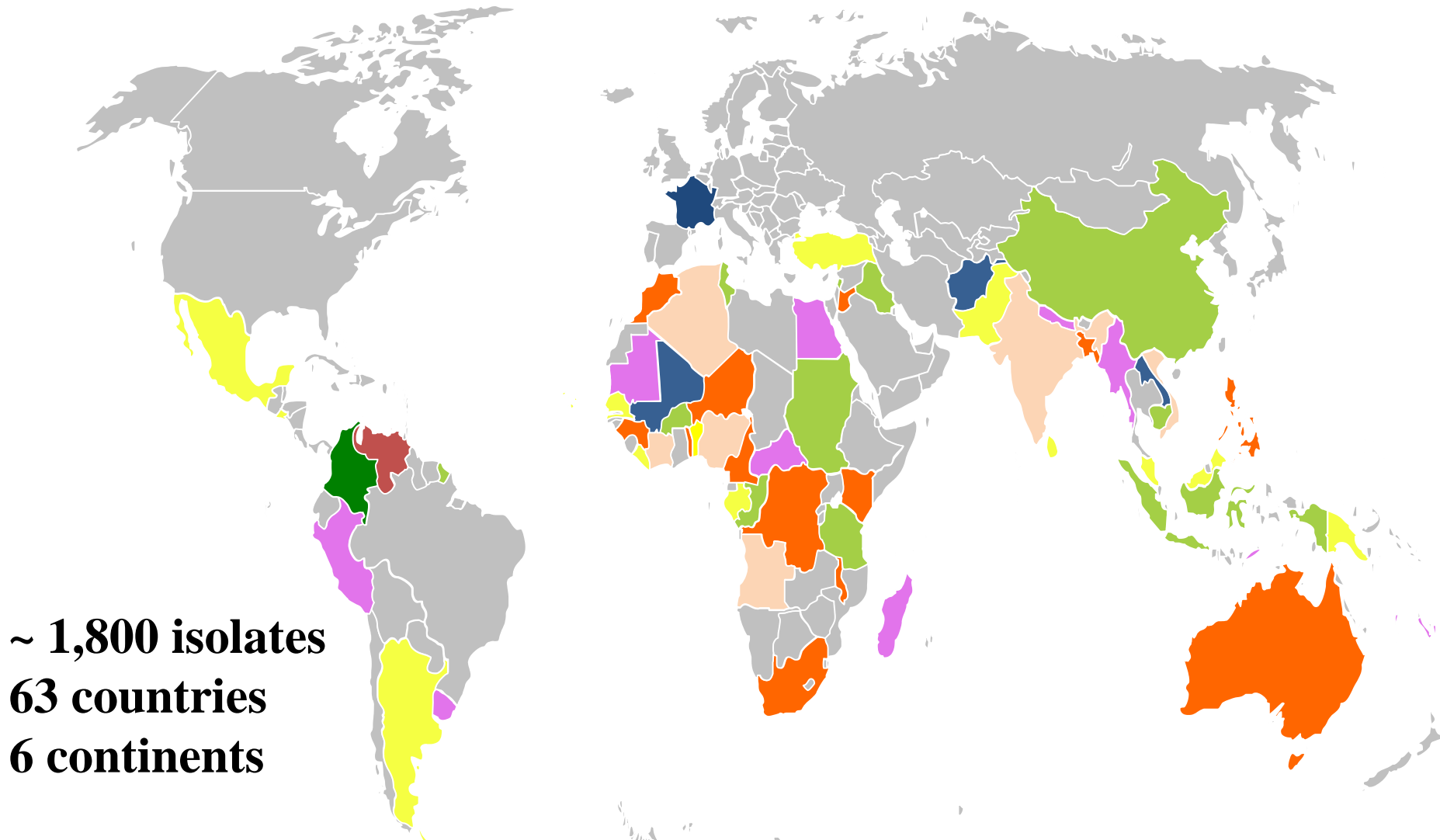
Description	Population
Total catchment population	150,000
Children under 1yr(12months)	22,000
Children under 5 yrs (60months)	30,000
Children under 15 yrs	37,000
Adults (24-59yrs)	50,000
Elderly (over 60yrs)	11,000



Endemic and Hyperendemic typhoid regions





Global Collection and analysis of *S. Typhi*



Wong VK, et al. Nat Genet. 2015 Jun;47(6):632-9.

In sub-Saharan Africa, where does Typhoid Fever cluster?

-  Non-H58 S. Typhi
-  H58 S. Typhi



West Africa:

Molecular Surveillance Identifies Multiple Transmissions of Typhoid in West Africa.

International Typhoid Consortium., Wong VK, et al. PLoS Negl Trop Dis. 2016 Sep 22;10(9):

South Africa:

Typhoid Fever in South Africa in an Endemic HIV Setting.

Keddy KH, et al; GERMS-SA..PLoS One. 2016 Oct 25;11(10):.

Carriage prevalence of Salmonella enterica serotype Typhi in gallbladders of adult autopsy cases from Mozambique.

Lovane L, et al. J Infect Dev Ctries. 2016 Apr 28;10(4):410-2.

A Qualitative Study Investigating Experiences, Perceptions, and Healthcare System Performance in Relation to the Surveillance of Typhoid Fever in Madagascar.

Pach A, et al. Clin Infect Dis. 2016 Mar 15;62 Suppl 1:S69-75.

Rapid emergence of multidrug resistant, H58-lineage Salmonella Typhi in Blantyre, Malawi.

Feasey NA, et al PLoS Negl Trop Dis. 2015 Apr 24;9(4):.

Central Africa:

Salmonella Typhi in the Democratic Republic of the Congo: fluoroquinolone decreased susceptibility on the rise.

Lunguya O, et al PLoS Negl Trop Dis. 2012;6(11):e1921

East Africa:

Typhoid in Kenya is associated with a dominant multidrug-resistant *Salmonella enterica* serovar Typhi haplotype that is also widespread in Southeast Asia.

Kariuki S, et al. J Clin Microbiol. 2010 Jun;48(6):2171-6.

Diagnosis of imported Ugandan typhoid fever based on local outbreak information: A case report.

Ota S, et al. J Infect Chemother. 2016 Nov;22(11):770-773.

A large and persistent outbreak of Typhoid fever caused by consuming contaminated water and street-vended beverages: Kampala, Uganda, January - June 2015.

Kabwama SN, et al. BMC Public Health. 2017 Jan 5;17(1):23.

A large outbreak of typhoid fever associated with a high rate of intestinal perforation in Kasese District, Uganda, 2008-2009.

Neil KP, et al. Clin Infect Dis. 2012 Apr;54(8):1091-9.

Massive lineage replacements and cryptic outbreaks of *Salmonella* Typhi in eastern and southern Africa.

Wirth T. Nat Genet. 2015 Jun;47(6):565-7.

Diagnosis and Treatment of Typhoid Fever and Associated Prevailing Drug Resistance in Northern Ethiopia.

Wasihun AG, et al Int J Infect Dis. 2015 Jun;35:96-102.

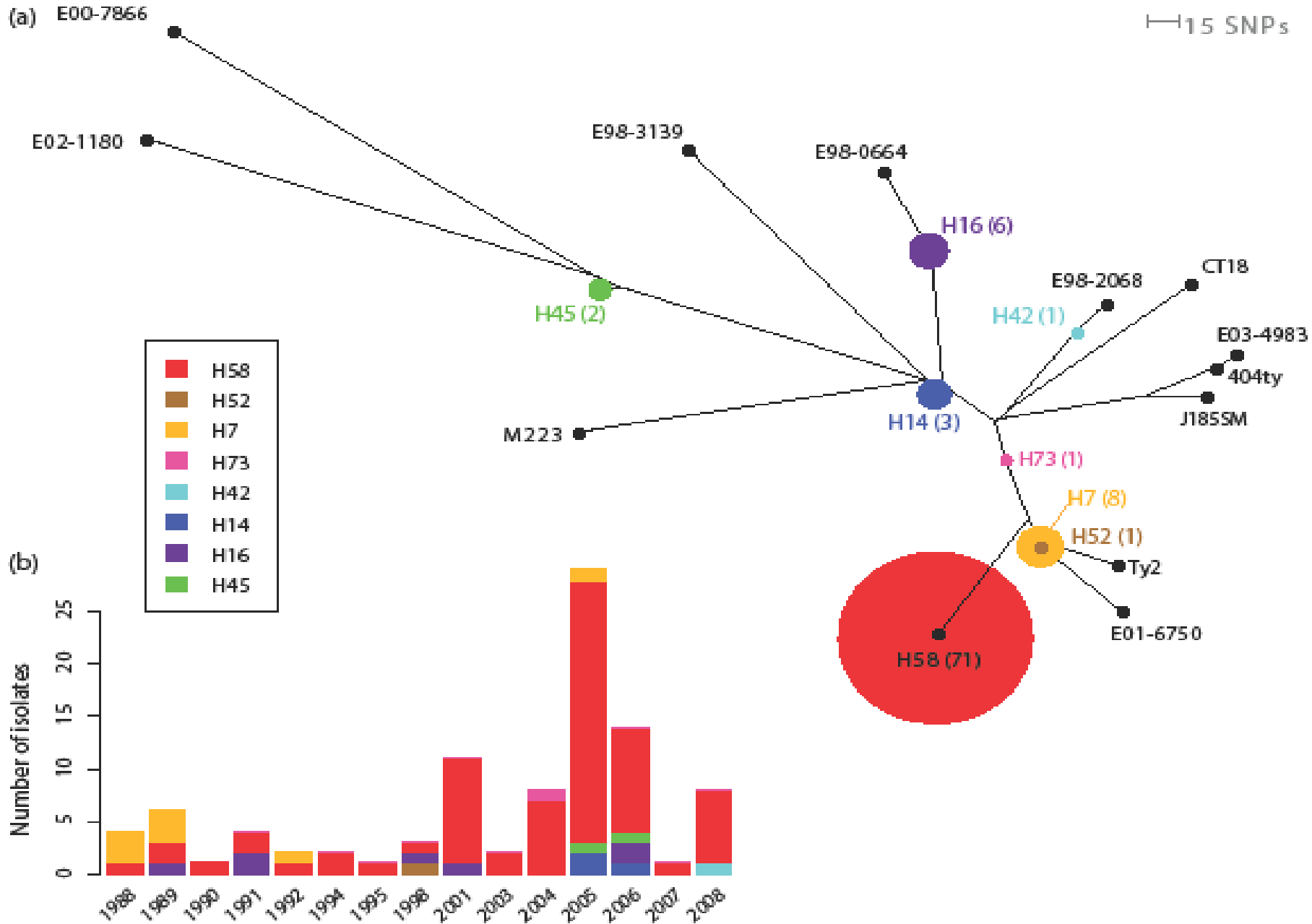
Transcontinental MDR spread:

A Multicountry Molecular Analysis of *Salmonella enterica* Serovar Typhi With Reduced Susceptibility to Ciprofloxacin in Sub-Saharan Africa.

Al-Emran HM, et al Clin Infect Dis. 2016 Mar 15;62 Suppl 1:S42-6.

In all endemic settings MDR is a major challenge in Africa

Kenya as an early hub of *S. Typhi* H58 from SE Asia



What are the major challenges in tackling
Typhoid in SSA?

Challenges in Diagnosis

•Clinical Diagnosis

- High index of suspicion
- Knowledge of the local epidemiology
- Clinical presentation is usually non specific



Laboratory tests: from when are they useful?

- Blood culture or BM culture : Week 1
- Serological Methods : Week 2
(Widal Test most common)
- Stool Ag Test : Week 2
- Urine culture : Week 4
- PCR : Week 1
- WGS and metabolomics technology can be adopted for bedside Dx

Diagnostic accuracy of the TUBEX-TF and OnSite Typhoid IgG/IgM Combo tests with culture as the gold standard

(Zimbabwe outbreak of 2014)

Test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
TUBEX-TF (n = 131)	100	94.12	63.16	100
OnSite Typhoid IgG/IgM Combo (n = 136)	100	94.34	63.16	100



Only point-of-care rapid tests available, but **LOW** to **MODERATE** sensitivity and specificity

- Challenges in treatment options and vaccine use in Africa

Issues of antibiotic Rx in face of MDR

S. Typhi

- For MDR infections fluoroquinolones widely used for treatment.
- For fully susceptible *S. Typhi* (ciprofloxacin MIC < 0.06 µg/mL) Rx very effective
- Later generation fluoroquinolone, gatifloxacin, clinically more effective against MDR infections
- Azithromycin MIC ≤ 16 µg/mL
- Ceftriaxone and cefotaxime, reliable reserve drugs particularly for hospital admitted cases

Vaccines

- WHO recommends targeted vaccination of high risk populations as a short- to medium-term measure.
- Locally, only private clinics stock Vi conjugate vaccine for travel vaccination and for workers in hospitality industry
- Prices still too high for widespread public health use
- Governments in Africa have not prioritized use of vaccine even in endemic settings

Conclusion 1

- With increasing informal settlements with little or no infrastructure, we will continue to experience outbreaks, we have to prepare!
- Accurate diagnosis a major challenge in our settings – we need to adopt simple affordable rapid kits that can be deployed under field conditions.
- Burden of disease data and economic implications important to document as these mobilize action!

Conclusion 2

- Resistance to commonly available antibiotics and high cost of effective alternatives should persuade policy makers to consider low cost vaccine, with options for technology transfer and bulk purchase
- Improving hygiene, clean water supply and reduced overcrowding long term goals

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