# Epidemiology of NTS and S. Typhi in Kenya and E. Africa region

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# Outline of my talk

1. **Introduction**
2. **What we know about field epidemiology of adult and paediatric iNTS in the region**
3. **iNTS and Typhoid contrasting epidemiology**
4. **Conclusion and planned studies**

# Background

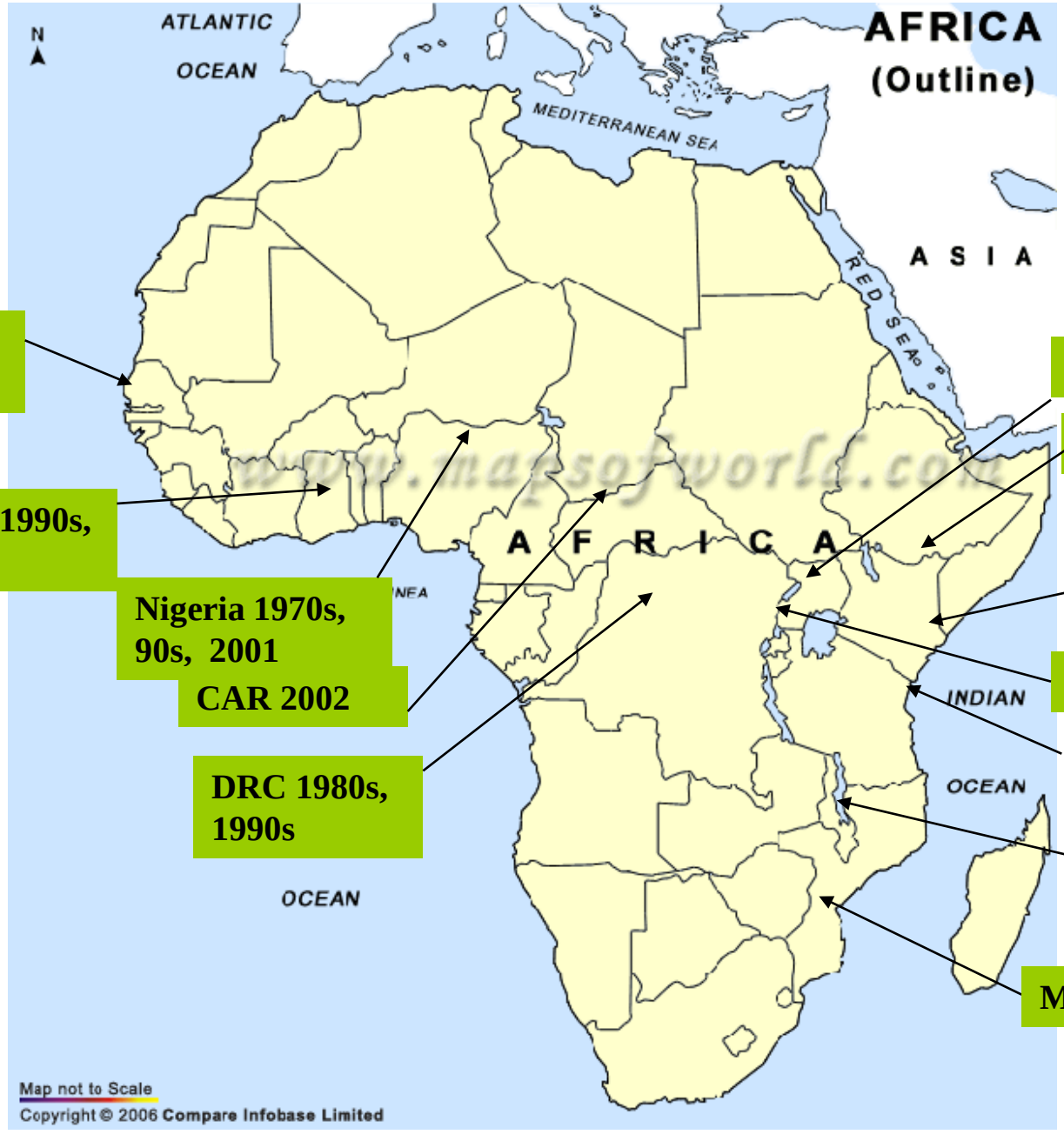
# Invasive NTS in adults

- **NTS bacteraemia is a common, recurrent illness in HIV-infected adults, after TB and pneumococcal bacteremia.**
- **NTS bacteraemia has a high mortality (47%) and recurrence (43%) rate in HIV-infected adults.**
- **Recurrence is caused by recrudescence rather than re-infection.**
- **Predominant serovar from seropositive patients, S. Typhimurium at 58%.**
- **MDR strains are now common in this population (68%)**

# Several documented studies on NTS in children

- ***Tanzania:*** 5/24 children with suspected meningitis and/or septicemia, had meningitis caused by S. Enteritidis, all of whom died.
- Septicemia caused by NTS was associated with very high fatality rates. ***Vaagland et al.*** *BMC Infect Dis. 2004 ; 14;4:35;* ***Blomberg et al.*** *J Clin Microbiol. 2005 ; 43: 745–749*;
- ***Uganda:*** Bacteraemia affects 1 / 6 severely malnourished children
- High mortality especially among the HIV-positive.
- High level of resistance to common antibiotics: ***Bachou et al****. BMC Infect Dis. 2006; 7;6:160.*
- ***South Africa*****:** 59% [94 of 160]) of NTS were blood culture isolates.
- High levels of antibiotic resistance. ***Kruger et al****. Antimicrob Agents Chemother. 2004; 48(11):4263-70.*
- ***Malawi:*** Case-fatality rates for childhood NTS are also high (21–24%), even when appropriate antibiotics are available ***(Gordon et al.CID 2008)***
- ***Gambia:*** incidence of invasive bacterial infections in children - 1009 (95% CI, 903-1124) cases per 100,000 person-years
- Community-acquired invasive NTS among children aged 2-29 months in rural Gambia *:* ***Ikumapayi et al****. J Med Microbiol. 2007; 56:1479-84*

# Reports from tropical Africa of NTS as a major cause of paediatric bacteraemia




The Gambia 1980s and 2005

Ghana 1990s, 2002

Nigeria 1970s, 90s, 2001

CAR 2002

DRC 1980s, 1990s

Uganda 2006, 2009

Ethiopia 2010-2012

Kenya 1980s, 1990, 2005, 2006, 2010

Rwanda 1980s

Tanzania 2007, 2010

Malawi 1996-2010

Mozambique 2001-2006

# Recent studies in Kenya

- **Differing burden and epidemiology of non-Typhi Salmonella bacteremia in rural and urban Kenya, 2006-2009. Tabu C, et al. PLoS One. 2012;7(2):e31237.**

**NTS accounted for 60/155 (39%) of blood culture isolates in the rural and 7/230 (3%) sites. The adjusted incidence in the rural site was 568/100,000 person-years**

- **Invasive bacterial infections in neonates and young infants born outside hospital admitted to a rural hospital in Kenya. Talbert AW, et al. Pediatr Infect Dis J. 2010 Oct;29(10):945-9.**

**Of the 4467 outborn young infants admitted, 748 (17%) died. 11% had IBI (10% bacteremia and 3% bacterial meningitis), with a case fatality of 33%**

- **Bacteraemia in Kenyan children with sickle-cell anaemia: a retrospective cohort and case-control study. Williams et al. Lancet. 2009 Oct 17;374(9698):1364-70.**

**iNTS at 18% for children with sickle cell disease**

- **Characterisation of community acquired non-typhoidal Salmonella from bacteraemia and diarrhoeal infections in children admitted to hospital in Nairobi, Kenya. Kariuki S, BMC Microbiol. 2006 Dec 15;6:101.**

**Overall 170 (51.2%) of children presented with iNTS alone, 28 (8.4%) with gastroenteritis and bacteraemia and 134 (40.4%) with gastroenteritis alone.**

# Documented Risk Factors

# Host factors

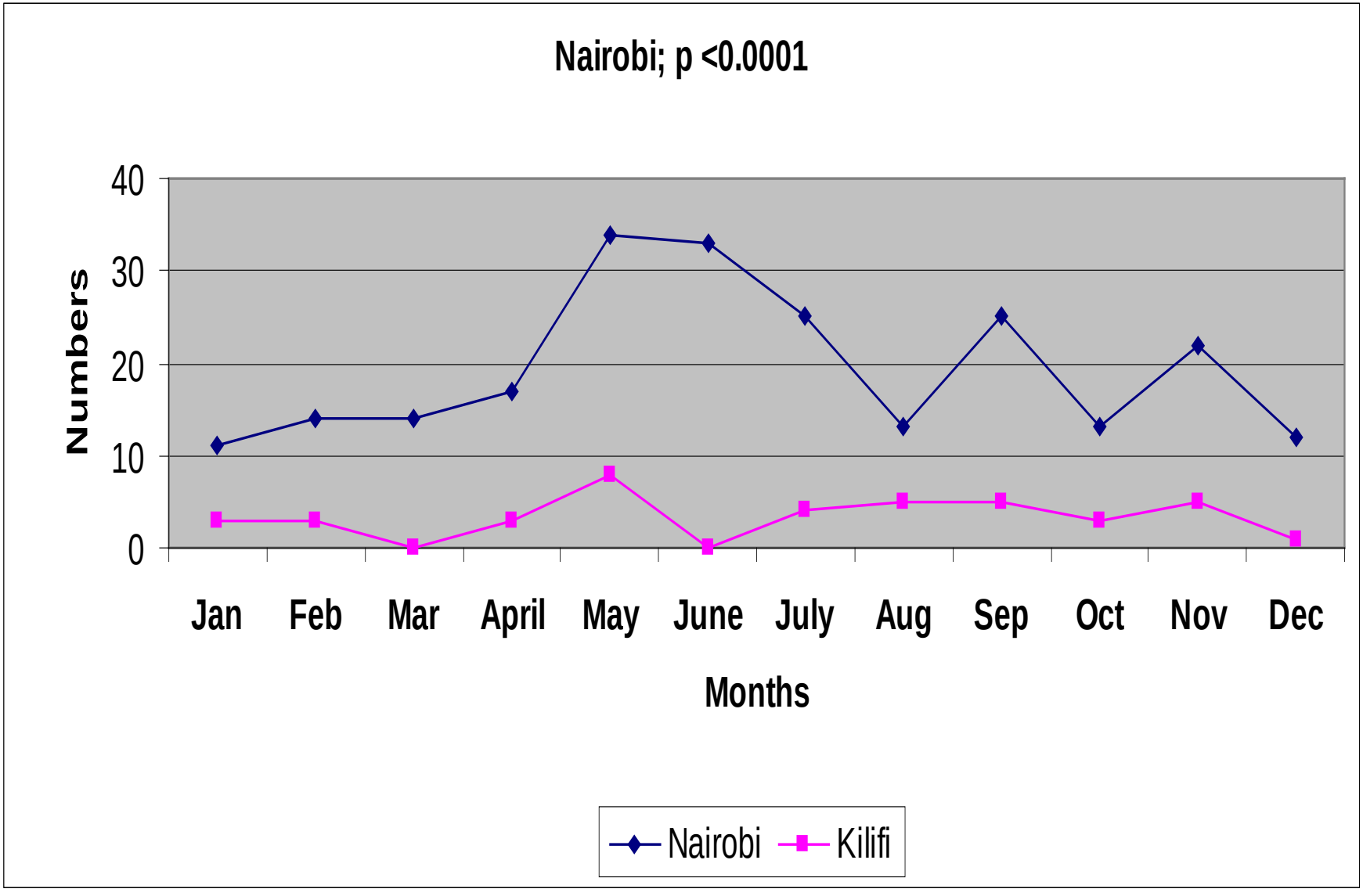
- Young age
- Anaemia
- Malaria
- Malnutrition
- HIV

- Sickle cell disease
- Schistosomiasis
- Diabetes
- Malignancy

# Environmental factors

- Rainy season
- Water supply
- Crowding
- Hygiene

# Seasonal variation of NTS infections



# Pathogen factors

– Virulence characteristics have been mapped in PIs: type III secretion systems, Vi antigen, lipopolysaccharide and other surface polysaccharides, flagella, and various factors essential for the intracellular life cycle of NTS.

DeJong et al. PLoS Pathog. 2012;8(10):e1002933

– Antibiotic resistance, initially chloramphenicol resistance and now emerging fluoroquinolone resistance on the MGE.

Kariuki *et al*., BMC Microbiol. 2006 Dec 15;6:101.

Okoro *et al*, Nature Genetics Dec 2012

# MDR phenotype is a feature of iNTS

| Antimicrobial Agent | Range | MIC (µg/ml) Mode | MIC50 | MIC90 | % R |
|---|---|---|---|---|---|
| Ampicillin | 0.25->256 | >256 | 82 | 64 | 48 |
| Co-amoxyclav | 0.75->256 | 4 | 1 | 16 | 8 |
| Cefuroxime | 2->256 | >256 | 8 | 32 | 30 |
| Ceftriaxone | 0.094-16 | 0.064 | 0.5 | 2 | 0 |
| Gentamicin | 0.06->256 | 4 | 1 | 8 | 16 |
| Co-trimoxazole | 0.064->32 | >32 | 8 | 32 | 46 |
| Chloramphe | 0.19->256 | >256 | 4 | 32 | 26 |
| Tetracycline | 0.064->256 | 3 | 16 | 128 | 49 |
| Nalidixic acid | 1.5->256 | 3 | 3 | 3 | 12 |
| Ciprofloxacin | 0.064-4 | 0.16 | 0.06 | 0.125 | 0 |

***Kariuki et al. J Med Micro 2006; 55:585***

# Emergence of ceftriaxone resistant S. Typhimurium in 2010

- Isolate 1. 43 year old hospitalized male Feb, 2010, stool culture done due to diarrhea and septic screen.
- Isolate no 2. date of isolation May 2010 from a hospitalized 1 month old baby, urine and blood culture
- Both Identified as S. Typhimurium
- Sensitive to – Chlor, Ciproxin and Cefoxitin.
- Resistant to Nalidixic acid, Septrin, Ampi, Ceftriaxone and aztreonam. MIC ceftriaxone >256 ; MIC Cipro 0.012
- ESBL CTX-M-18

# Environmental reservoirs and transmission routes remain elusive !

*Journal of Medical Microbiology* (2006), 55, 585–591 DOI 10.1099/jmm.0.46375-0

## Invasive multidrug-resistant non-typhoidal *Salmonella* infections in Africa: zoonotic or anthroponotic transmission?

Samuel Kariuki,[1,2] Gunturu Revathi,[3] Nyambura Kariuki,[3] John Kiiru,[1] Joyce Mwituria,[1] Jane Muyodi,[1] Jane W. Githinji,[4] Dorothy Kagendo,[1] Agnes Munyalo[1] and C. Anthony Hart[2]

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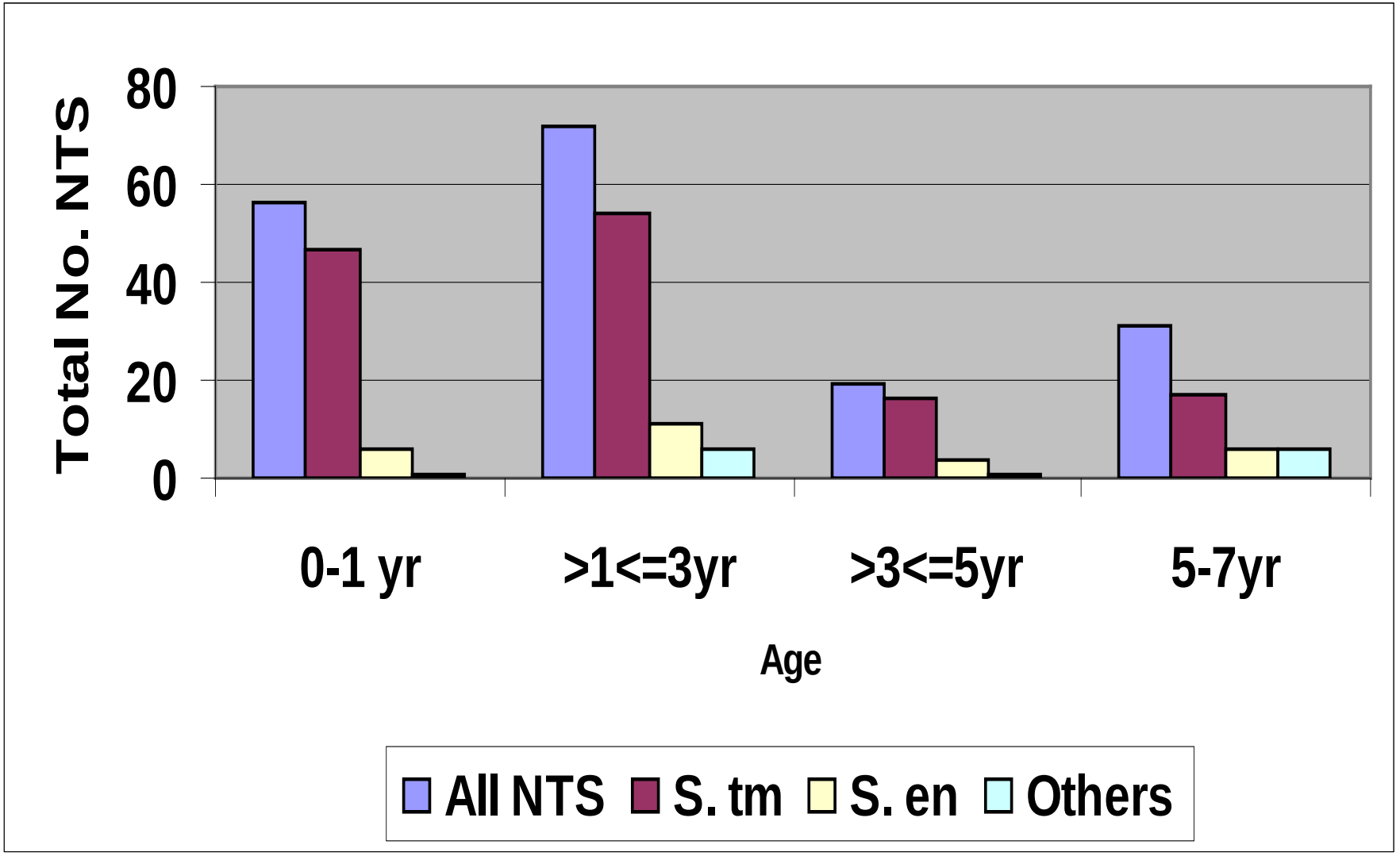
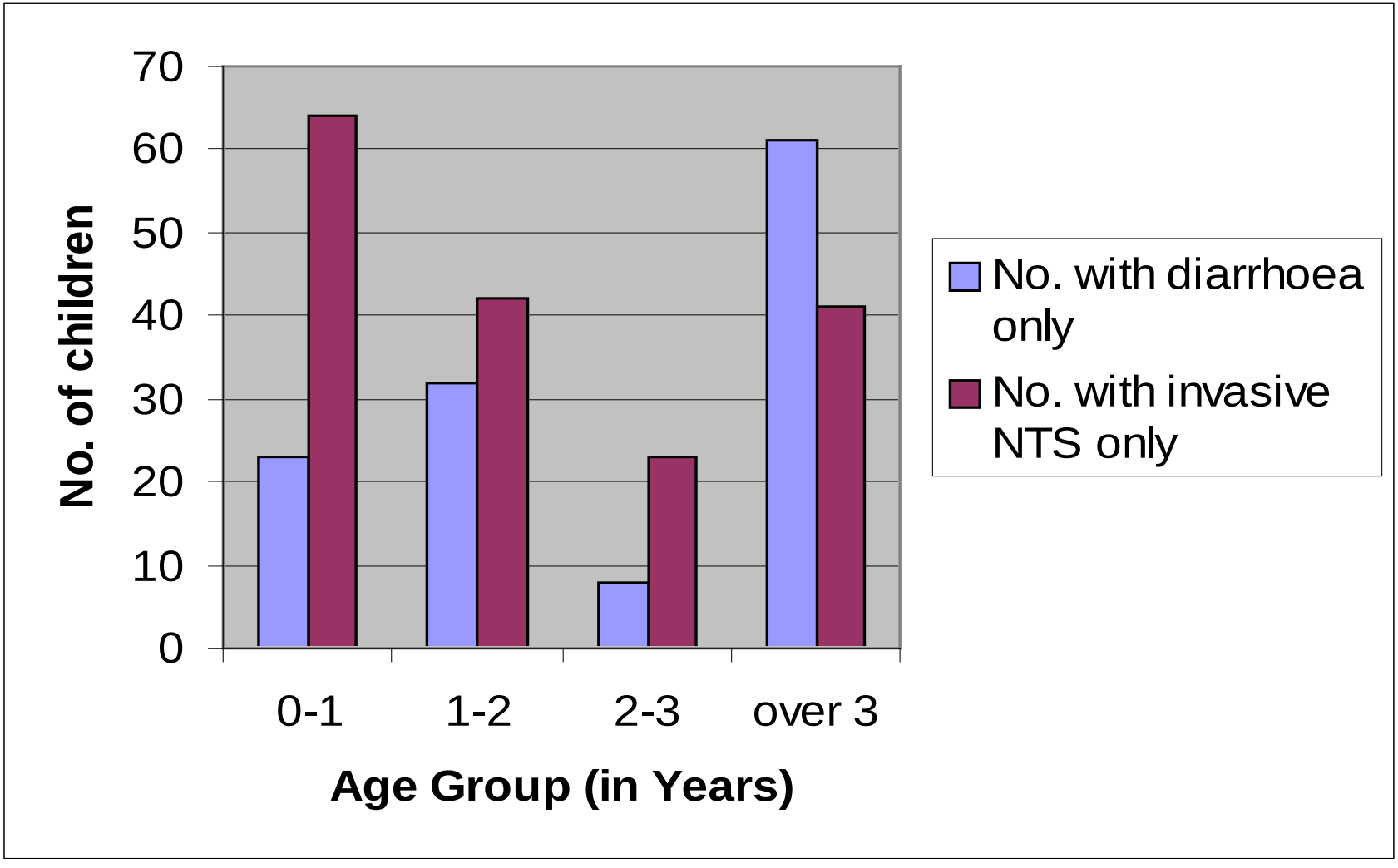
# NTS by age group – Nairobi

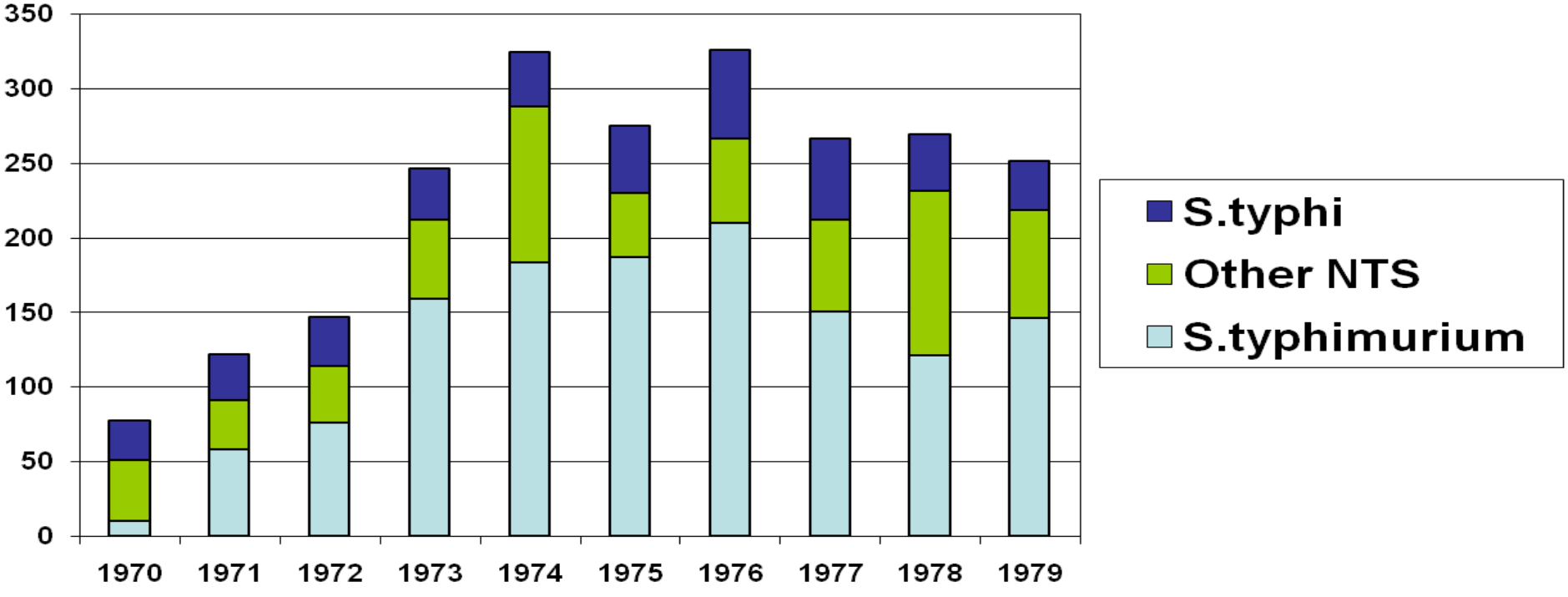



Kariuki *et al*., Int. J. Antmicrob Agents 2005, 25: 39-45

# Clinical presentation of NTS infection according to age group



# We believe NTS was a problem starting way back in 1970s?




Wamola IA, Mirza NB. Salmonella infections at Kenyatta National Hospital, 1970-80. E Afr Med J 1981; 58: 677-683

| 1975-79: 297 invasive isolates | |
|---|---|
| < 2 years | 45% |
| 2-12 years | 32% |
| > 13 years | 23% |

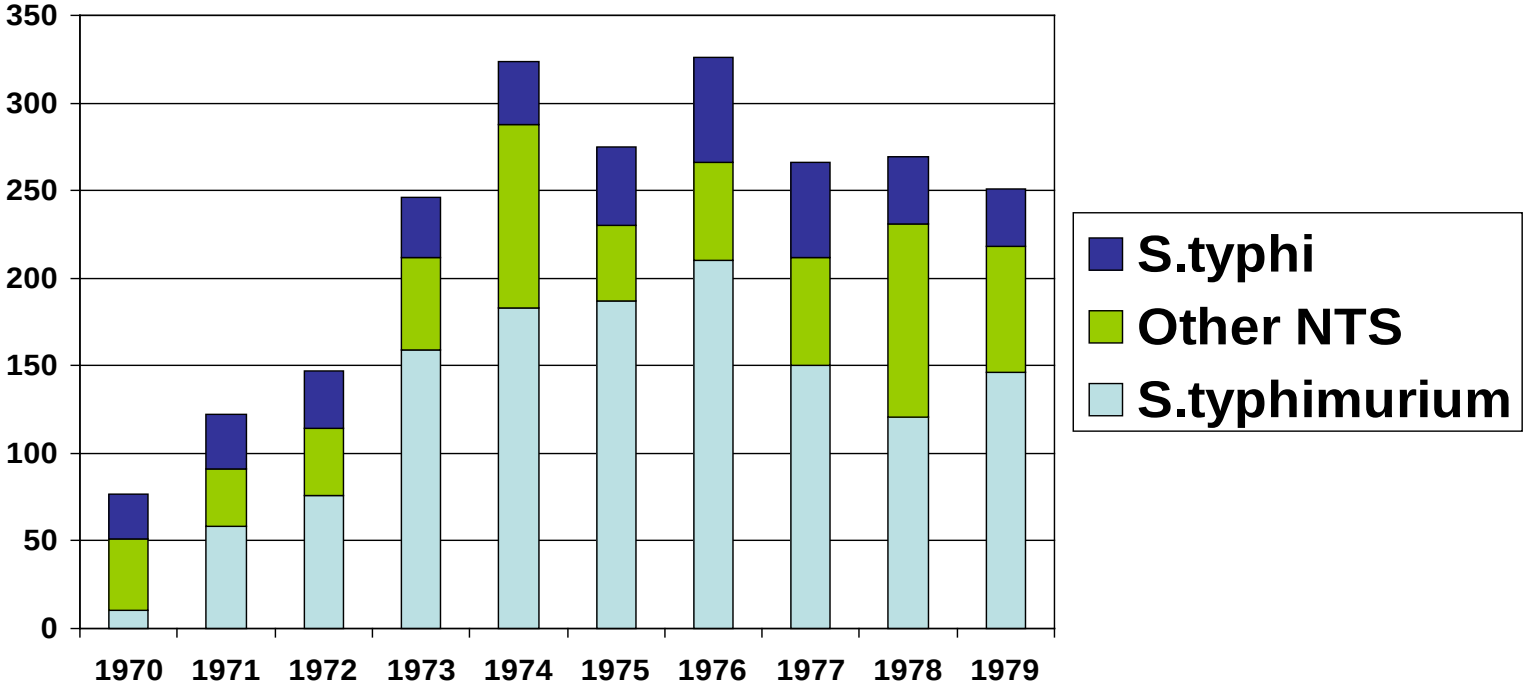
Mortality for *S.typhimurium*

blood isolates (n=93) 18%

CSF isolates (n=26) 96%

# Salmonella infections Kenyatta National Hospital 1970-80

Wamola IA, Mirza NB. E Afr Med J 1981; 58: 677-683




| % antibiotic resistance | | | |
|---|---|---|---|
| | Ampicillin | Cotrimoxazole | Chloramphenicol |
| *S.tyhimurium* | 63 | 13 | 30 |
| *S.typhi* | 22 | 6 | 0 |

# Contrasting Typhoid/NTS incidence

- In urban informal settlement studies:
- crude incidence of blood culture-confirmed typhoid fever was 247 cases per 100,000 pyo, highest in children 5-to-9 and 2-4 yo (596 and 521 /100,000 pyo)
- No seasonality noted
- Not HIV-related
- In typical rural community
- Crude incidence was 29 cases per 100,000 pyo in Lwak 18–34 year age group (63 cases per 100,000 pyo) and low in 2-4 and 5–9 yo(28 and 18 cases per 100,000 pyo, respectively)

# Conclusions

1. ST313 iNTS clade is fast expanding throughout SSA
2. Is iNTS athroponotic? We think so in SSA
3. With Hib and pneumococcal vaccine available, iNTS is likely to be the major bacterial infection in both adults and children
4. MDR phenotype will complicate management
5. Improved detection and early treatment will save lives

# Proposed iNTS Project

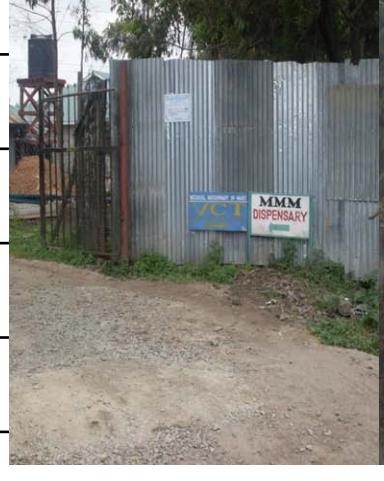
- To determine geospatial distribution of cases of invasive salmonellosis (iNTS and Typhoid) treated at the clinics in Mukuru slum 15 km east of Nairobi city
- To determine the hotspots for invasive salmonella infection according to genotypes in circulation and evaluate the risk factors associated with high incidence of disease in specific endemic zones.

# Study site and population

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

## Catchment population for Mukuru clinic

| Description | Population |
|---|---|
| Total catchment population | 89,258 |
| Children under 1yr(12months) | 2,678 |
| Children under 5 yrs (60months) | 11,336 |
| Children under 15 yrs | 27,045 |
| Adults (24-59yrs) | 21,690 |
| Elderly (over 60yrs) | 625 |




# The Invasive Salmonella Study

Expected outcomes of the study will include:

(1) incidence, prevalence, and spatial and spatio-temporal clustering of strain types/genotypes of invasive salmonellosis and NTS diarrhea

(2) incidence, prevalence, and spatial and spatio-temporal clustering of strains with different antibiotic resistance profiles, and of strains with different resistance genes;

(3) maps showing hotspots for the ST and iNTS phenotypes in space and in space-time,

(4) associations between potential risk factors and the risk of TF and iNTS disease

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