Non-typhoidal *Salmonella* invasive disease as a leading cause of child death in Africa

Challenges and Opportunities for Management and Control

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KENYA MEDICAL RESEARCH INSTITUTE
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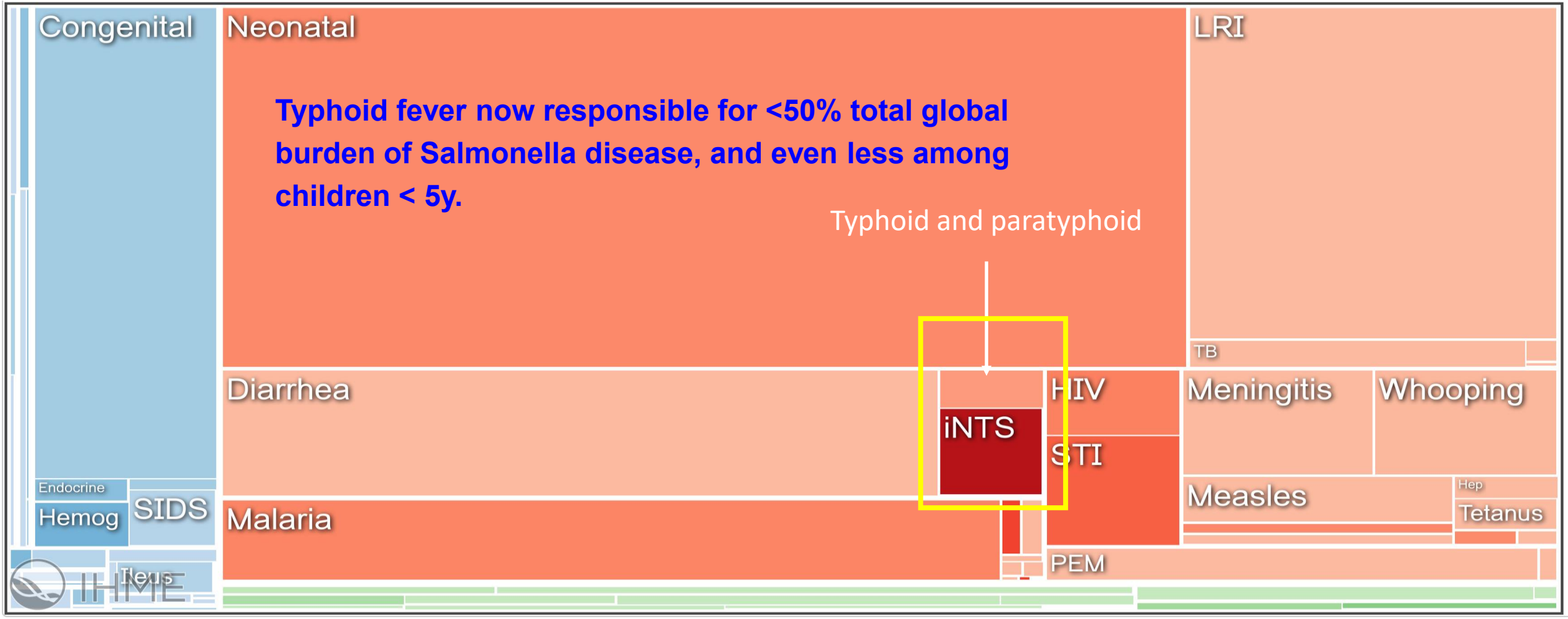
DNDi
Best Science for the Most Neglected
20 Years

What we know so far on Epi and Genomics of iNTS

Global deaths by cause, <5 years of age, 2019



https://vizhub.healthdata.org/gbd-compare/

Epidemiology of Invasive NTS disease in SSA

- In 2017: Approx 535,000 iNTS illnesses and 77 500 deaths; 422,000 (78.9%) illnesses and 66 500 (85.9%) deaths occurred in SSA.
- Lineages of *S.* Typhimurium (ST) 313 and S. Enteritidis ST11 dominate
- iNTS in children: severe febrile illness with non-specific clinical signs and symptoms (resembling those of severe falciparum malaria).
- Respiratory symptoms in ca. 50% of the cases.
- ***iNTS bacteraemia in young febrile children has poor outcome***
    - *Upto 28-35% may die within 48h*
- *No zoonotic source for key iNTS Lineages identified, but transmission is enhanced in poor WASH environment*
- **WHO syndromic guidelines for antibiotic treatment only predict 60% of iNTS.**
- Challenges lab Dx of iNTS, leads to Ab misuse/overuse and increasing AMR


nature communications

Article

A genomic appraisal of invasive *Salmo*
Typhimurium and associated antibioti
resistance in sub-Saharan Africa

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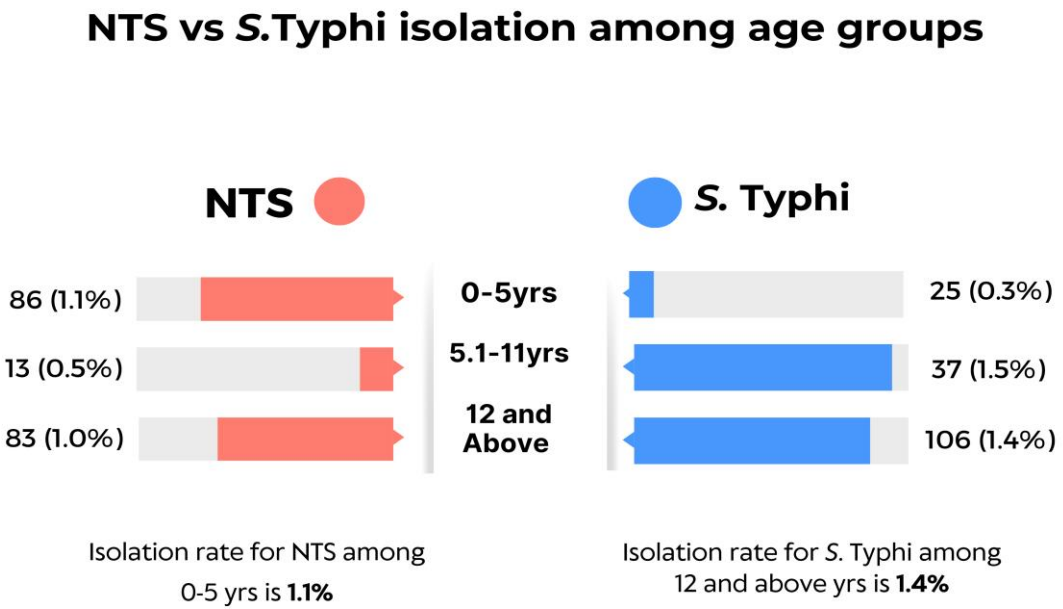
Invasive non-typhoidal *Salmonella* (iNTS) disease manifesting
infection with high mortality is responsible for a huge public h
sub-Saharan Africa. *Salmonella enterica* serovar Typhimurium
ium) is the main cause of iNTS disease in Africa. By analysing
sequence data from 1303 *S.* Typhimurium isolates originating
countries and isolated between 1979 and 2017, here we show
scaled appraisal of the population structure of iNTS disease c
Typhimurium across many of Africa's most impacted countrie
invasive *S.* Typhimurium clades have already emerged, with ST
ST313-L2 driving the current pandemic. ST313-L2 likely emerg
Democratic Republic of Congo around 1980 and further spre
1990s. We observed plasmid-borne as well as chromosomally
oquinolone resistance underlying emergences of extensive-dru
resistance. Our work provides an overview of the evolution of

Informal settlements are a constant source of iNTS transmission

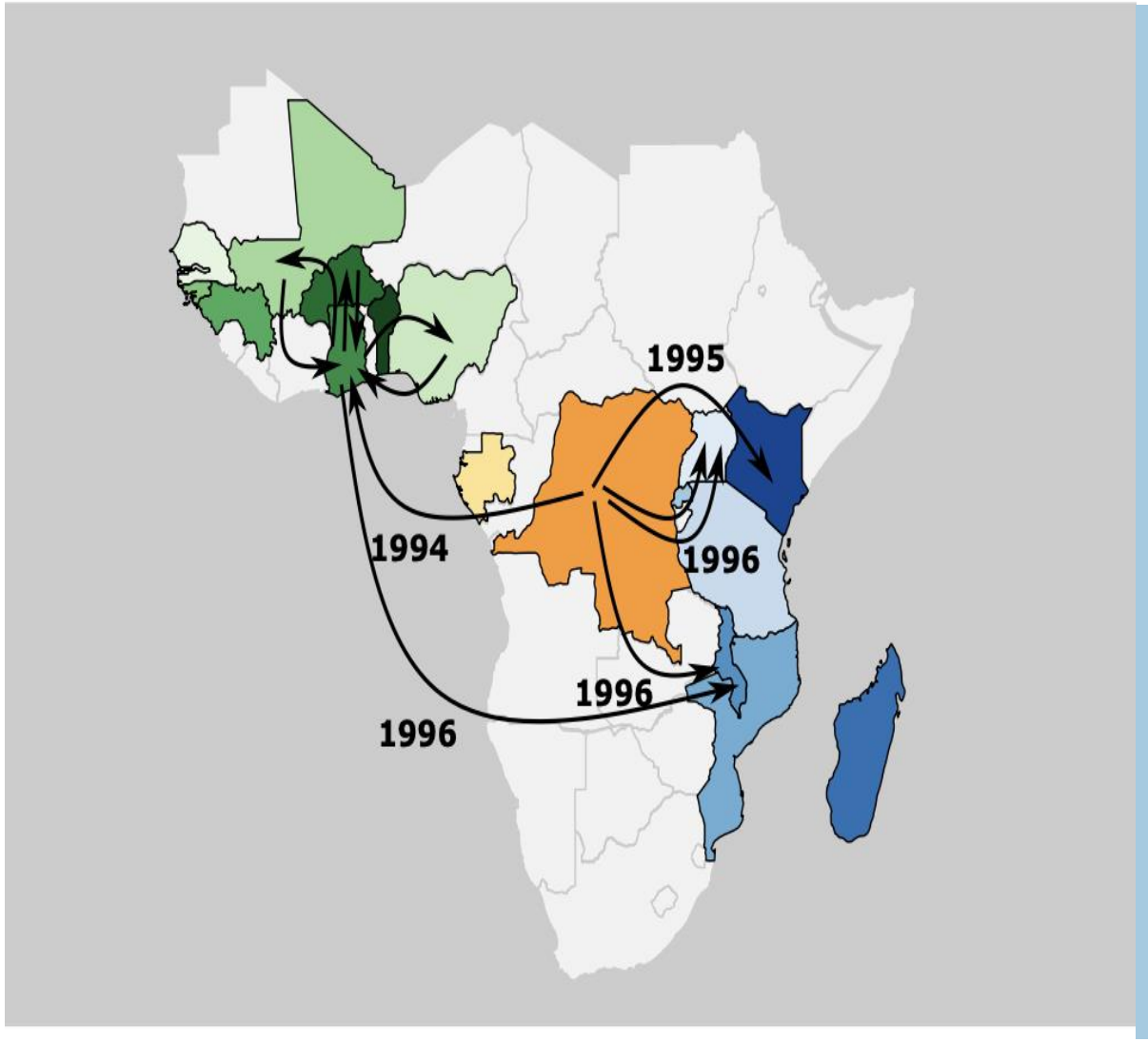
Catchment population for Mukuru DSS (3km^2)

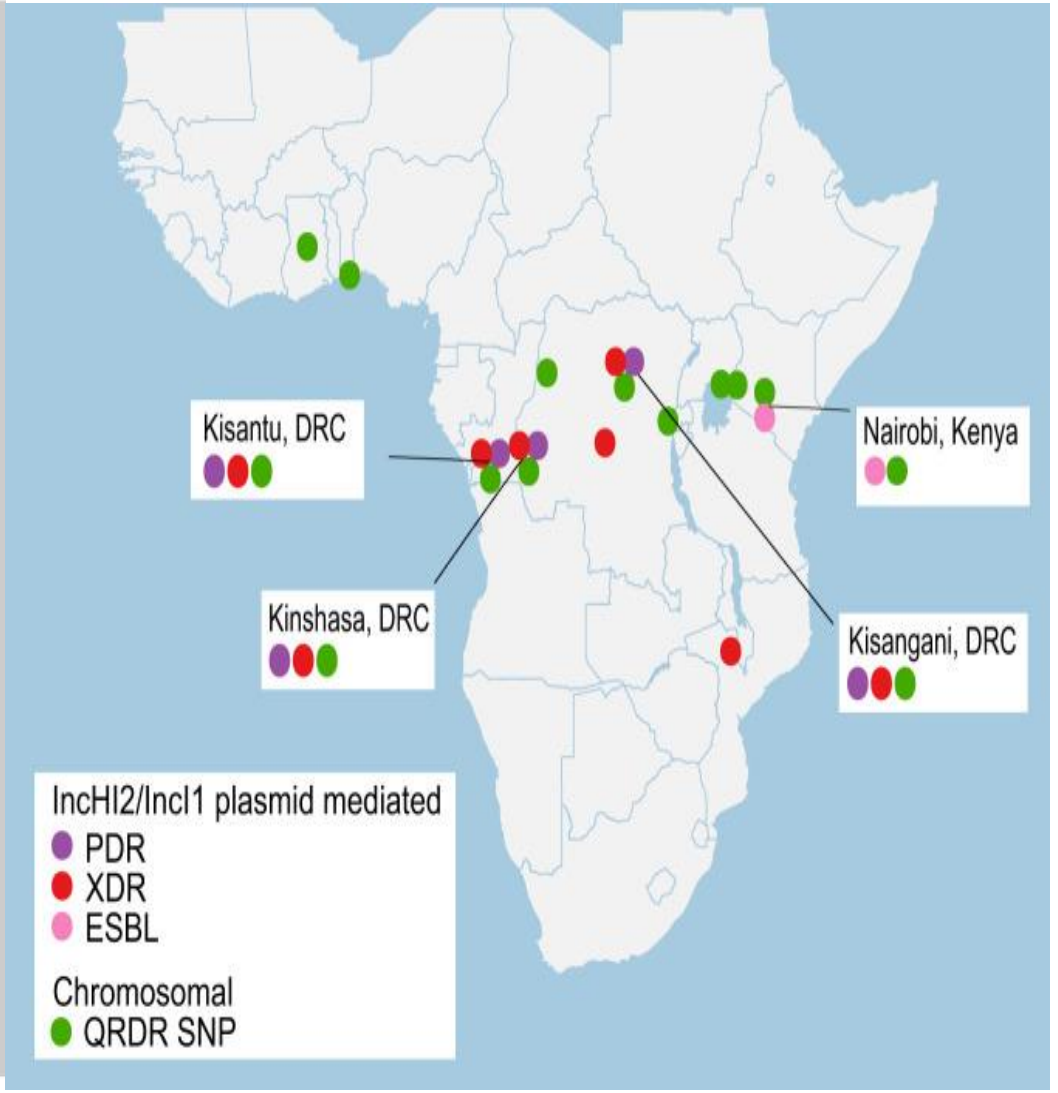
Incidence in urban settings in Kenya ranges from 366 to 625 per 100,000 per year

Clustering of iNTS serotypes and *S.* Typhi in hotspots!



Transmission events between the African regions (East, Central and West) and the respective predicted years of transmission.





We postulate that the current pandemic ST313-L2 clade emerged in the DRC in 1980 and has spread across sSA , plus attendant AMR burden!

Puyvelde *et al*-2023-Nature Comm

Several independent clades of iNTS have emerged in Africa

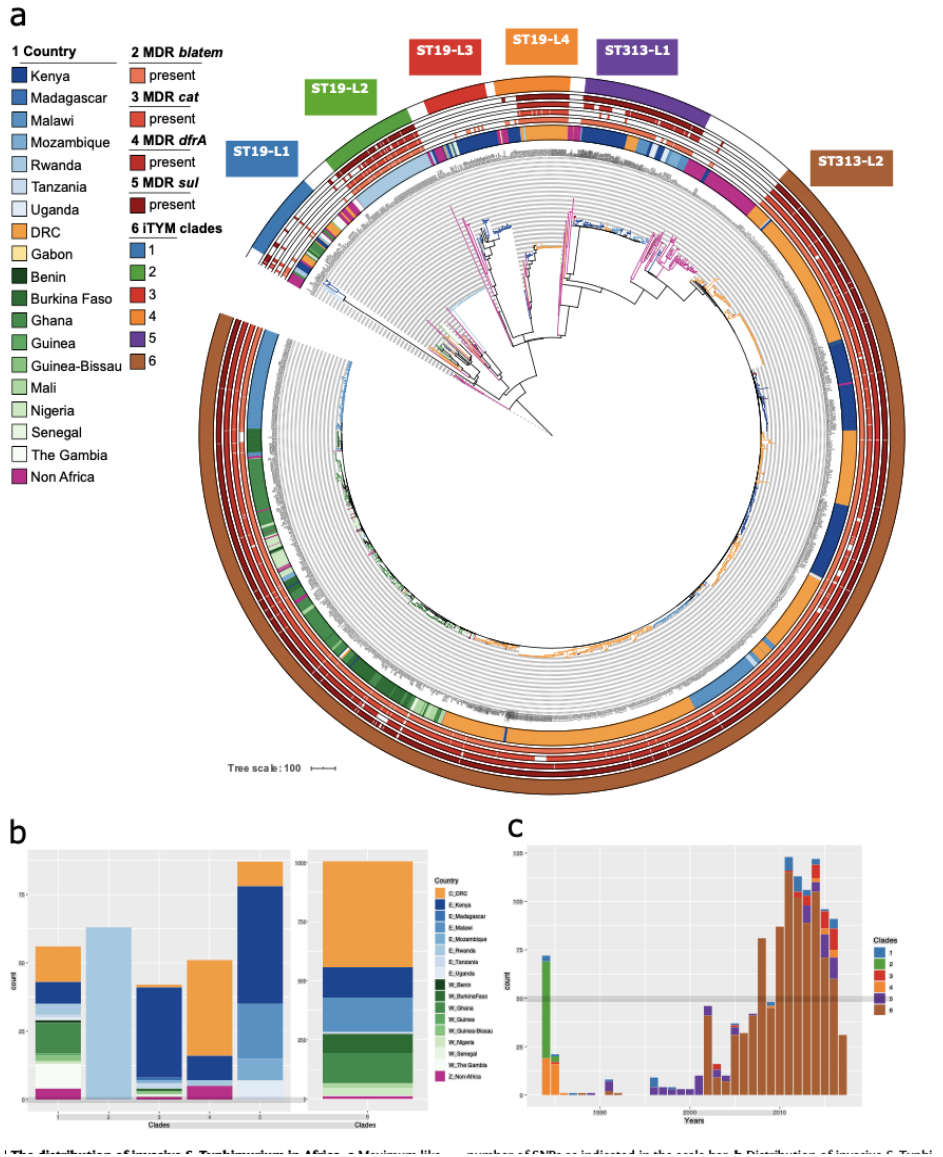
- 6 major clades associated with invasive S. Typhimurium infections.
- 4 clades were ST19 (ST19-L1 to L4) while 2 clades were ST313-L1 and ST313-L2.

- 5 of the clades older in most countries, ST313-L2 isolates became most dominant since 2001 and is driving the current pandemic in sSA.

- ST313-L2 has seven subclades, with each subclade associated to one country, i.e., DRC (n = 5), Kenya (n = 1) and Malawi (n = 1), suggesting local clonal expansions.

Widespread detection of ESBLs and other MDR genotypes

Puyvelde *et al*-2023-Nature Comm.



NTS carriage and shedding as source of infection in households and community

Kering, PhD

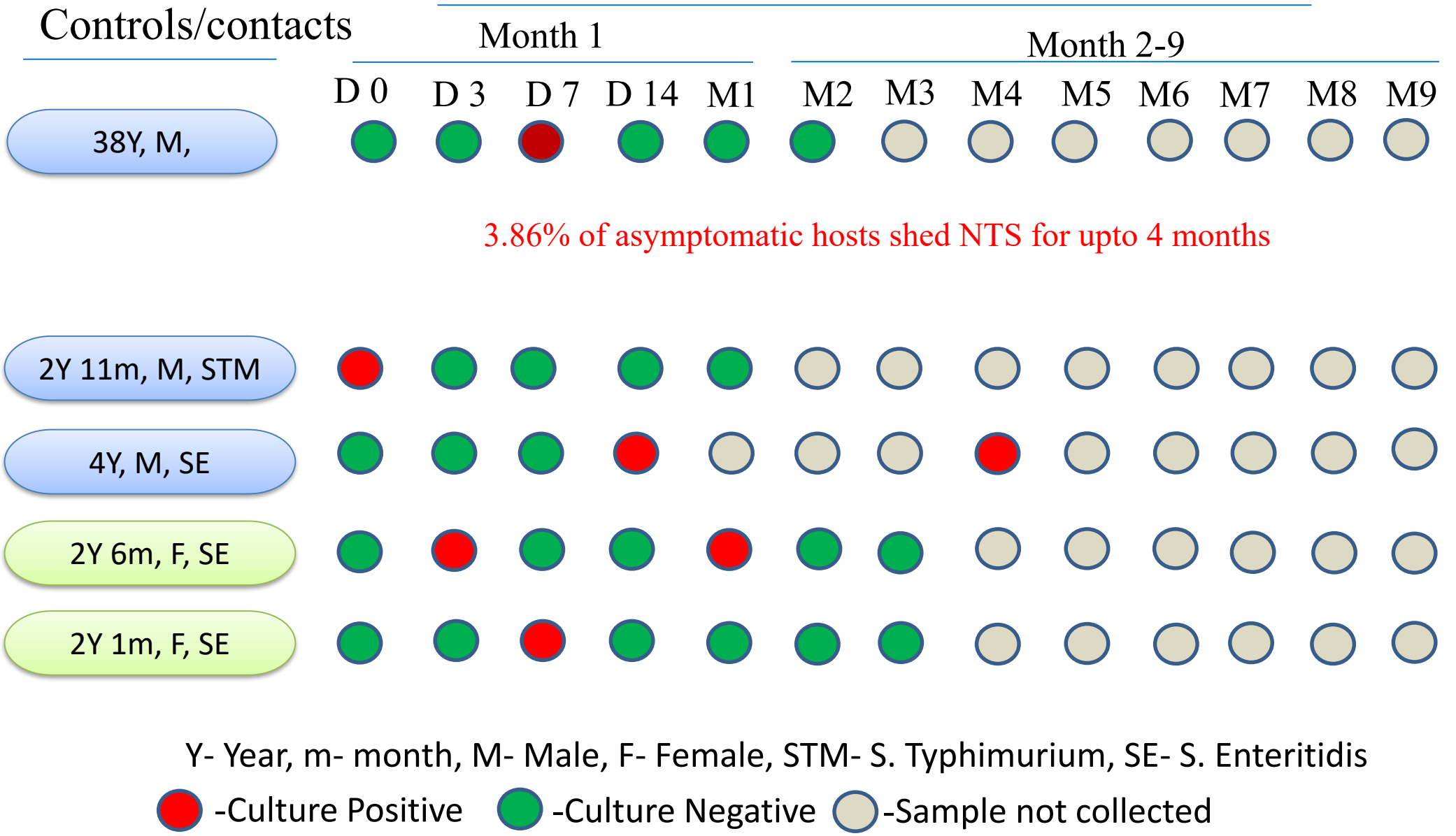
Patient results at recruitment

Longitudinal follow-up (stool shedding after end of R_x)

		Month 1					Month 2-6				
		D0	D3	D7	D14	D28	m2	m3	m4	m5	m6
Patient 1	8m, F, SE	●	●	●	●	●	●	●	●	●	●
Patient 2	4Y 9m, M, SE	●	●	●	●	●	●	●	●	●	●
Patient 3	1Y, M, SE	●	●	●	●	●	●	●	●	●	●
Patient 4	1Y, F, SE	●	●	●	●	●	●	●	●	●	●
Patient 5	1Y 10m, M, SE	●	●	●	●	●	●	●	●	●	●
Patient 6	1Y 1m, M, SE	●	●	●	●	●	●	●	●	●	●
Patient 7	2Y 11m, F, SE	●	●	●	●	●	●	●	●	●	●
Patient 8	1Y 2m, F, STM	●	●	●	●	●	●	●	●	●	●

Upto 26.5% of the NTS patients shed iNTS after treatment for upto 4 months

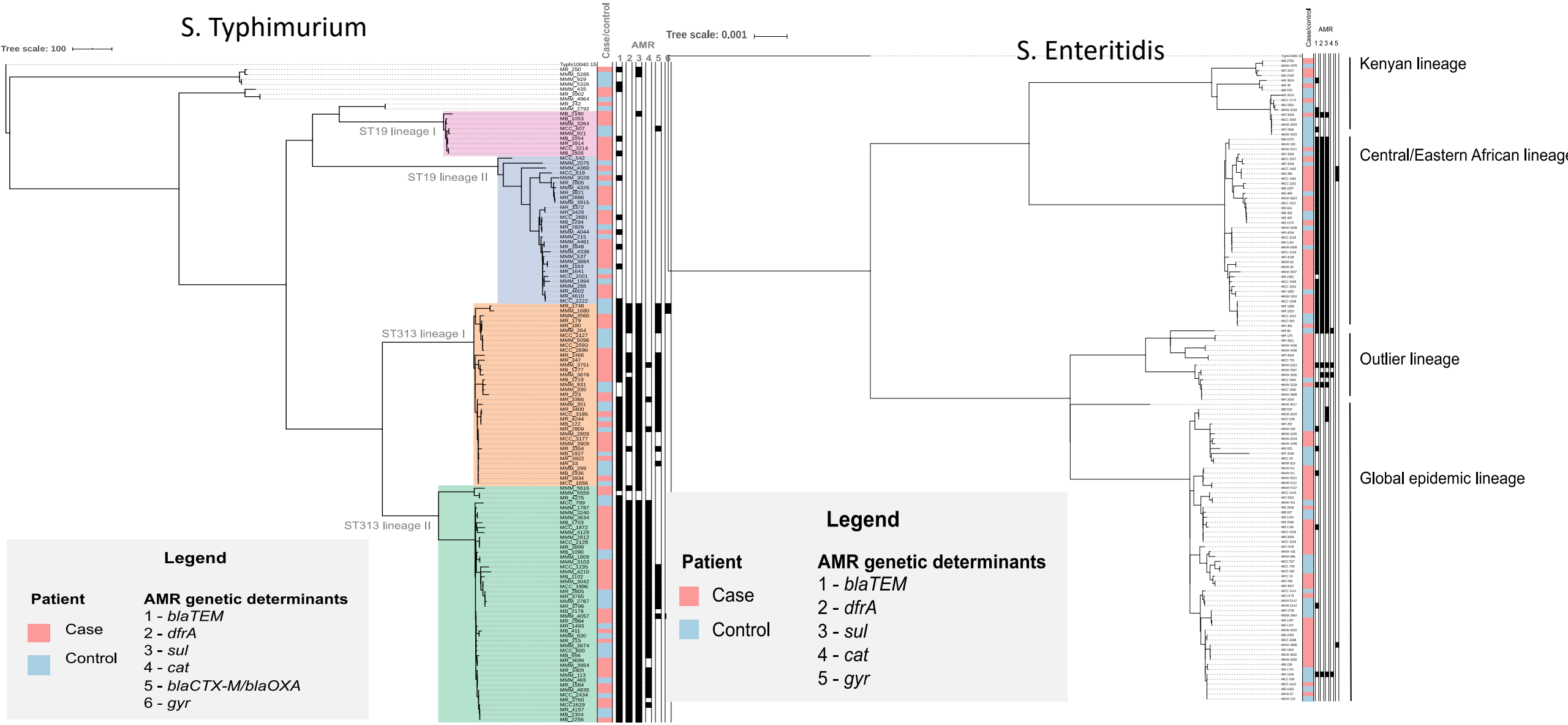
Carriage/ Shedding in asymptomatic children



Y- Year, m- month, M- Male, F- Female, STM- S. Typhimurium, SE- S. Enteritidis

-Culture Positive -Culture Negative -Sample not collected

AMR and clonal diversity of iNTS strains in disease and carriage/shedding



Vaccine approaches for management of iNTS, especially MDR

1. Live attenuated *Salmonella* vaccines - highly immunogenic and **easy to administer.**

* **F**ecal shedding of NTS vaccine strains would raise **regulatory concerns**

2. Conjugate based vaccines - Consist of **COPS chemically linked to phase 1 flagellin proteins (FliC),**

*Highly **immunogenic currently being evaluated in a Phase 1 clinical trial**

3. Outer membrane vesicles (OMVs) based Vaccines - Generalized modules for membrane antigens (GMMA) for increased OMV yield for vaccine production, through gene deletions.

*GMMAs purified from *S.* Typhimurium and *S.* Enteritidis currently going through evaluation

Data gaps and challenges for invasive NTS disease management and prevention

2014 and 2019 BMGF convenings and current findings

Gaps in Epidemiology

1. Robust understanding of NTS reservoirs, sources, and modes of transmission in high iNTS disease incidence.
2. Clear and unbiased data on the proportion of iNTS disease attributable to key host risk factors including HIV, malaria, and malnutrition.
3. Detailed knowledge of risk for NTS infection and iNTS disease by age from birth through infancy into early childhood to inform age for vaccine administration.
4. Environmental risk factors, AMR trends and implications for transmission.

Gaps in Carriage/shedding and Immunology

1. Duration of NTS shedding after infection and disease, as both a source for onward transmission and as a potential endpoint for vaccine trials.
2. Does asymptomatic NTS shedding following infection or disease have beneficial/harmful possible outcomes, either to develop protective immunity, or to develop invasive disease?
3. Robust data to support the iNTS vaccine value proposition, including on iNTS disease incidence, disability, and death.
4. Huge burden of iNTS in children 6 weeks to 6 months, despite the protection from maternal antibodies. Stratification of age-specific data on iNTS occurrence by month helpful in deciding how early a NTS vaccine should be administered.

What is needed to answer key questions?

- Birth cohort study in area(s) of high iNTS incidence.
- Primary outcome: acquisition of relevant NTS strain in stool.
- Secondary outcome: iNTS disease.
- Analyses:
  - Reservoir- and source-assigned case-control study on fecal acquisition
  - Understanding of age at first exposure and patterns of shedding
  - Host risk factors for iNTS disease at community level
  - Data on incidence, disability, death at community level
  - Serologic changes with colonisation and disease
  - Immune correlates of protection
  - Site development for vaccine trials

Conclusion

1. iNTS now a major cause of mortality>typhoid in <5y olds in endemic settings
2. Over the last 15 years, new technologies including WGS has contributed to great progress on understanding of NTS and iNTS epi and genomics, but gaps in R&D remain
3. Vaccine initiatives will interrupt transmission and reduce AMR spread
4. Critical gaps in R&D persist, addressing these will accelerate strategies for management, prevention and control of iNTS disease

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- **The field and Lab Teams**


• Thank you!