

**Lethal invasive non-typhoidal
Salmonella infections in young
children in sub-Saharan Africa**

Myron M. (Mike) Levine, M.D., D.T.P.H.

**Grollman Distinguished Professor & Director,
Center for Vaccine Development (CVD),
University of Maryland School of Medicine
Baltimore, MD**

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other Invasive Salmonellosis**

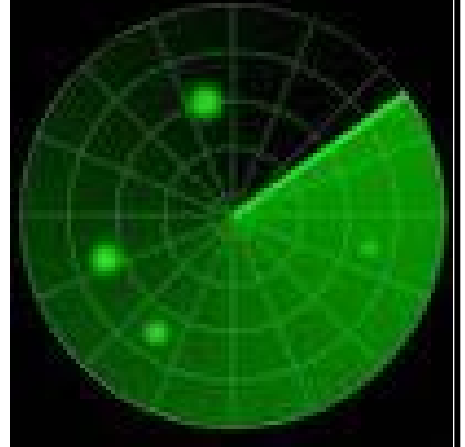
Dhaka, Bangladesh, March 1, 2013



Invasive bacterial infections among children < 5 years of age in sub-Saharan Africa

Blood-borne pathogens on the radar screen

- *Haemophilus influenzae* type b (Hib)
- *Streptococcus pneumoniae* (“pneumo”)
- *Neisseria meningitidis* (interest in Group A)



A blood-borne pathogen not on the radar

- Non-typhoidal *Salmonella* (“NTS”)



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Annual incidence of invasive pneumo & NTS disease in 3 African sites

Site (Period)	Age group	Inc. inv. pneumo /10 ⁵	Inc. inv. NTS /10 ⁵
Kilifi, Kenya (1998-02) J Berkley et al, 2005 (7% HIV prevalence)	0-11 mos.	241	170
Basse, Gambia (2000-4) G Enwere et al, 2006 (~1% HIV prevalence)	2-5 mos.	363	408
	6-11 mos.	576	360
	12-17 mos.	526	334
Manhica, Mozambique (2001-6) B Sigauque et al, 2009 (15% HIV prevalence)	0-11 mos.	403	388
	12-59 mos.	187	262

Incidence of NTS sepsis disease during the controlled field trial of RTS,S malaria vaccine in 7 African countries

	<i>Salmonella</i> sepsis (cases/10³)	
Age group on enrollment	RTS,S malaria vaccine (N=5949)	Rabies vaccine (N=2974)
5-17 mos.	6.9/10 ³ /18 mos fu	7.7/10 ³ /9 mos fu
	RTS,S malaria vaccine (N=4358)	Menin. Vaccine (N=2179)
6-12 wks.	3.7/10 ³ /9 mos fu	4.6/10 ³ /9 mos fu

Annualized incidence of NTS sepsis disease during the controlled field trial of RTS,S malaria vaccine in 7 African countries

	<i>Salmonella</i> sepsis (cases/10⁵/12 mos of follow-up)	
Age group	RTS,S malaria vaccine (N=5949)	Rabies vaccine (N=2974)
5-17 mos.	460	770
	RTS,S malaria vaccine (N=4358)	Mening. Vaccine (N=2179)
6-12 wks.	493	613

Invasive NTS disease

Industrialized countries

- Invasive disease as a complication of gastroenteritis
- Severe invasive disease:
 - Infants < age 3 months
 - The elderly
 - Immunocompromised
- Incidence is increasing
- Typhimurium (ST19), Enteritidis, Heidelberg, Dublin, Schwarzengrund
- Animal reservoir
- Promiscuous host range



Clinical features among young children in sub-Saharan Africa with invasive NTS disease

- Most cases do not present with gastroenteritis, nor do they have a history of recent gastroenteritis!!
- Children with invasive NTS disease are clinically indistinguishable from young children with invasive pneumococcal infections

Clinical features of invasive NTS infections among children < age 2 years in Gambia

- ~ 90% non-focal – bacteremia/septicemia
- ~ 10% focal – meningitis, septic arthritis, etc.

Symptom	Pneumo (N=74)	NTS (N=92)
Very sick	88%	79%
Diarrhea	16%	38%
Vomiting	58%	62%
Resp. sx	95%	67%
↑ Resp. rate	96%	77%

**What non-typhoidal
Salmonella (NTS) serovars
are causing invasive NTS
disease in sub-Saharan
Africa?**



Invasive NTS infection serovars among children < age 3 yrs in sub-Saharan Africa – early studies

- ***Salmonella* Typhimurium**
- ***Salmonella* Enteritidis**

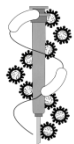
These two serovars account for ~ 75-95% of the cases of invasive pediatric NTS disease in Kenya, Malawi, Gambia, Mozambique & Mali



Surveillance at l'Hôpital Gabriel Touré (HGT), Mali



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CVD-MALI

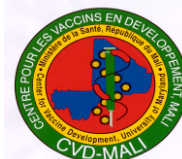
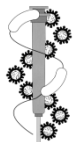


Surveillance at l'Hôpital Gabriel Touré (HGT), Mali

- **71% of pediatric admissions had presumed infections** (J Campbell, S Sow, et al 2004)
- 50% had a clinical dx of malaria
- **21% of admissions died in hospital**
- **Clinical Bacteriology Laboratory** established by CVD in 2002
- Malian personnel were trained at CVD in Baltimore and locally in Mali in clinical microbiology, GCP & data management
- Blood cultures or body fluid cultures (e.g., CSF) systematically (7 days/week) obtained from hospital admissions with:
 - ✓ Age: 0-15 years
 - ✓ Fever: $\geq 39^{\circ}\text{C}$ and/or
 - ✓ Clinical syndrome compatible with invasive bacterial disease (e.g., sepsis, meningitis, septic arthritis, etc.)

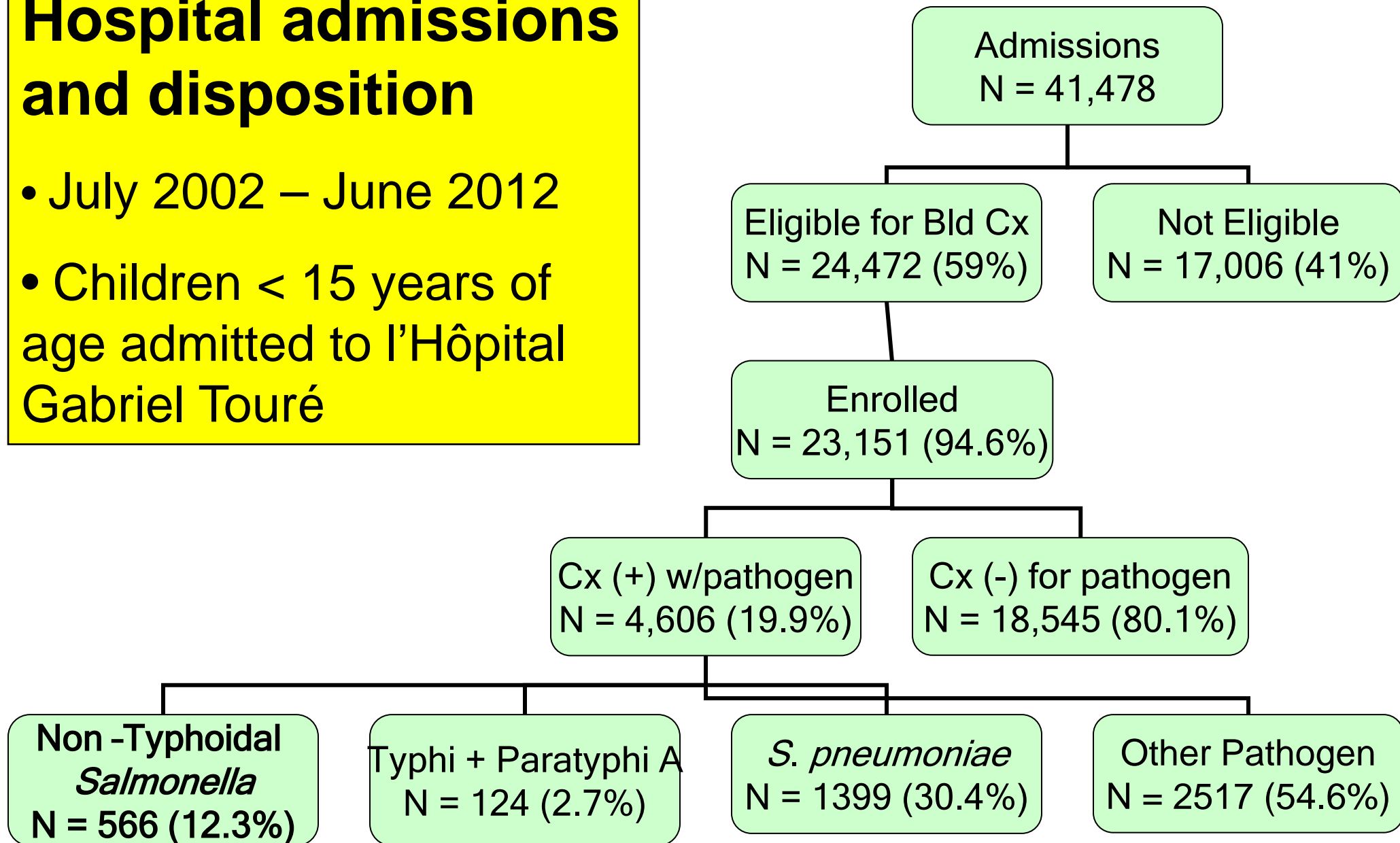


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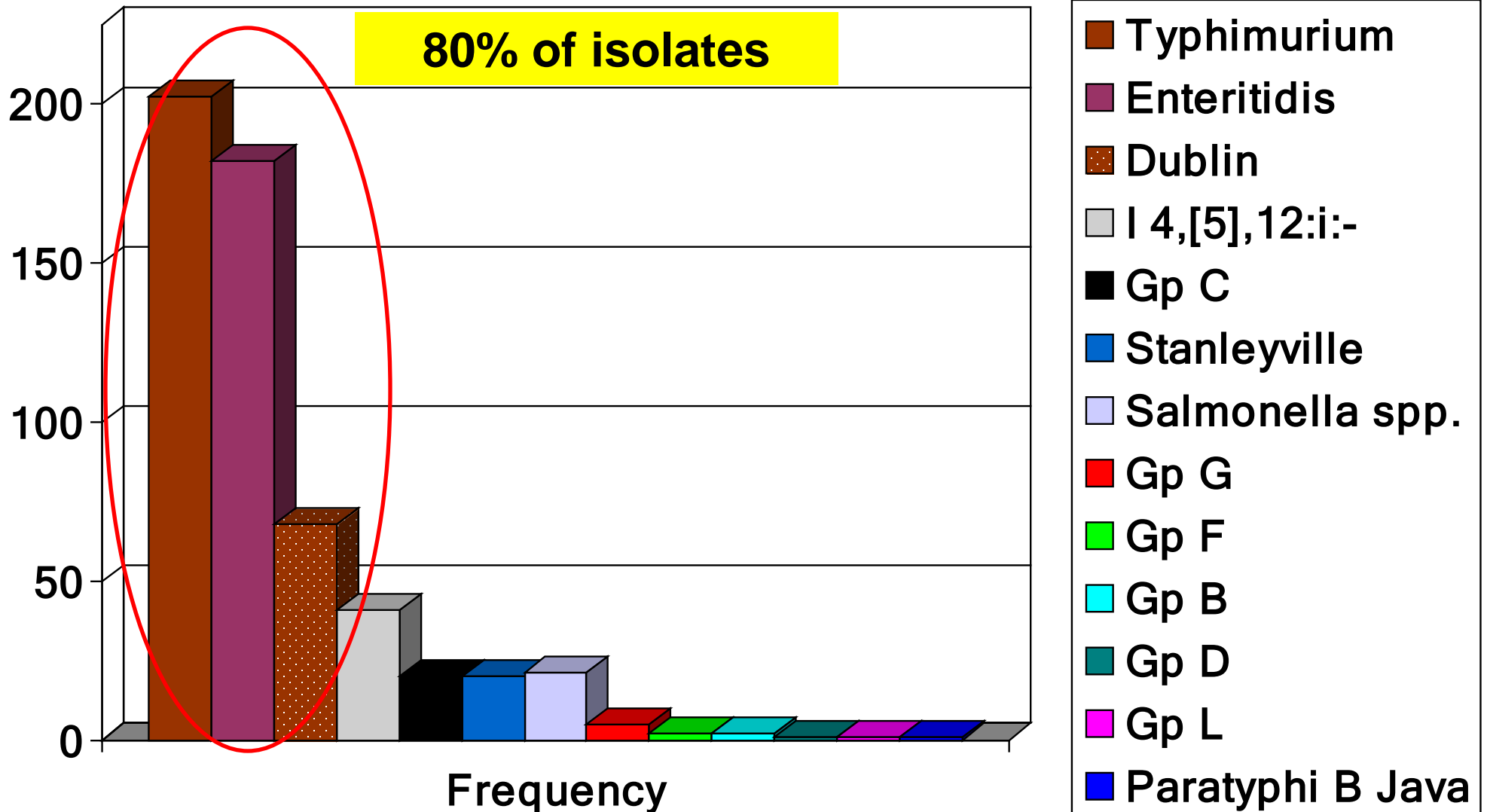


Hospital admissions and disposition

- July 2002 – June 2012
- Children < 15 years of age admitted to l'Hôpital Gabriel Touré

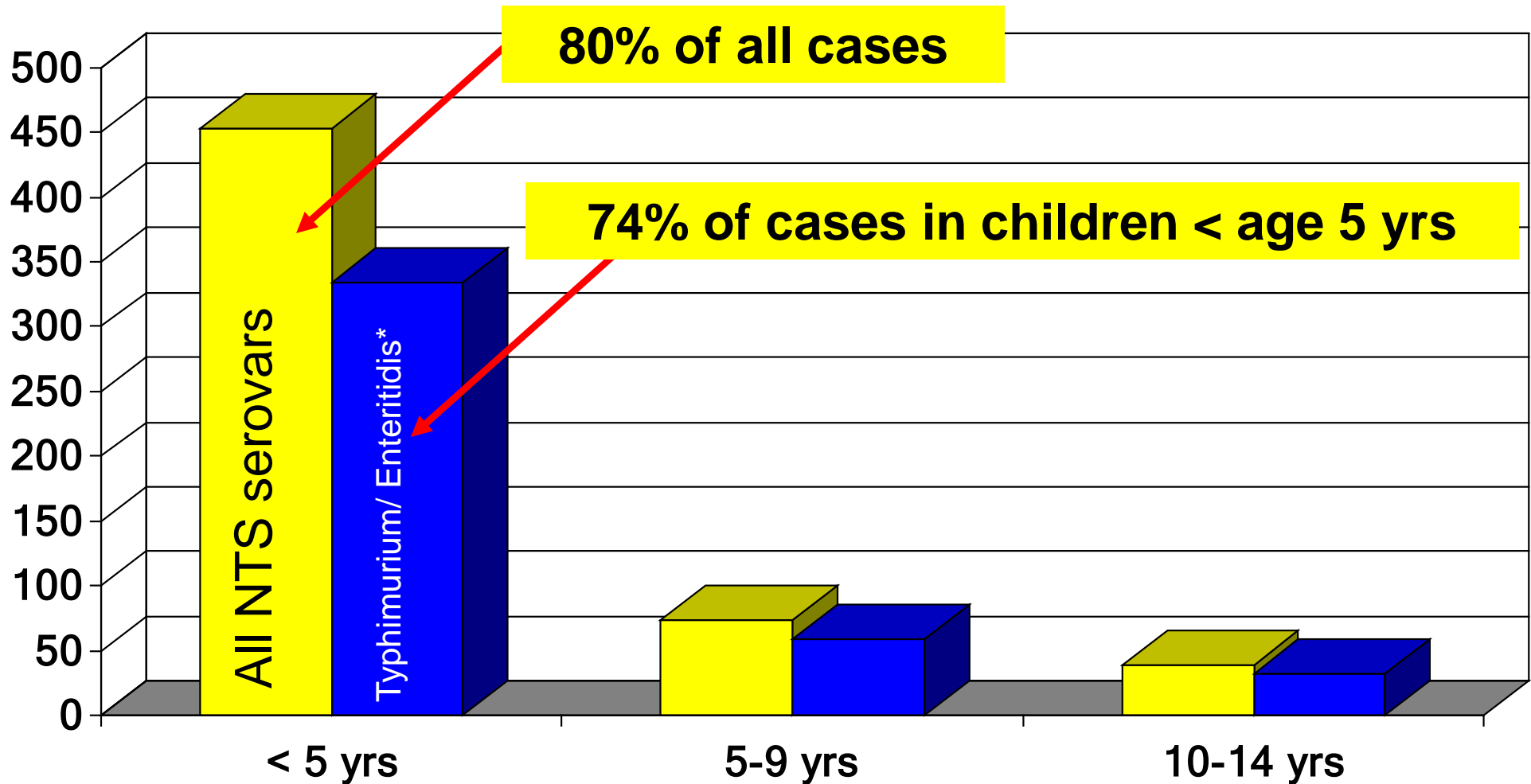


Serovars of the 566 NTS isolates



Typhimurium and monophasic variants (I 4,[5],12:i:-) are mostly ST 313.

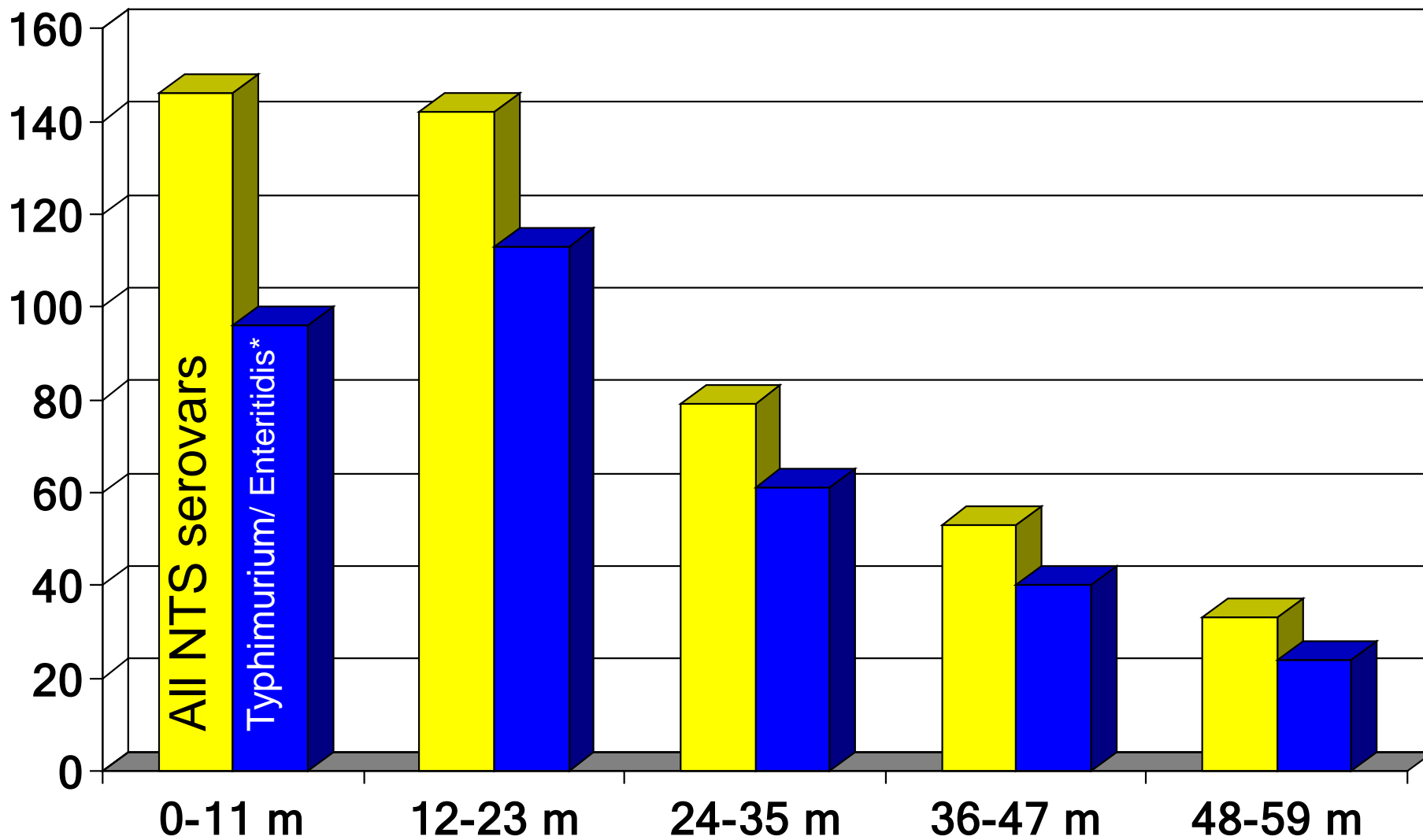
Total NTS and Typhimurium*/Enteritidis cases by age groups



* Includes Typhimurium and monophasic variants

M Tapia et al 2012

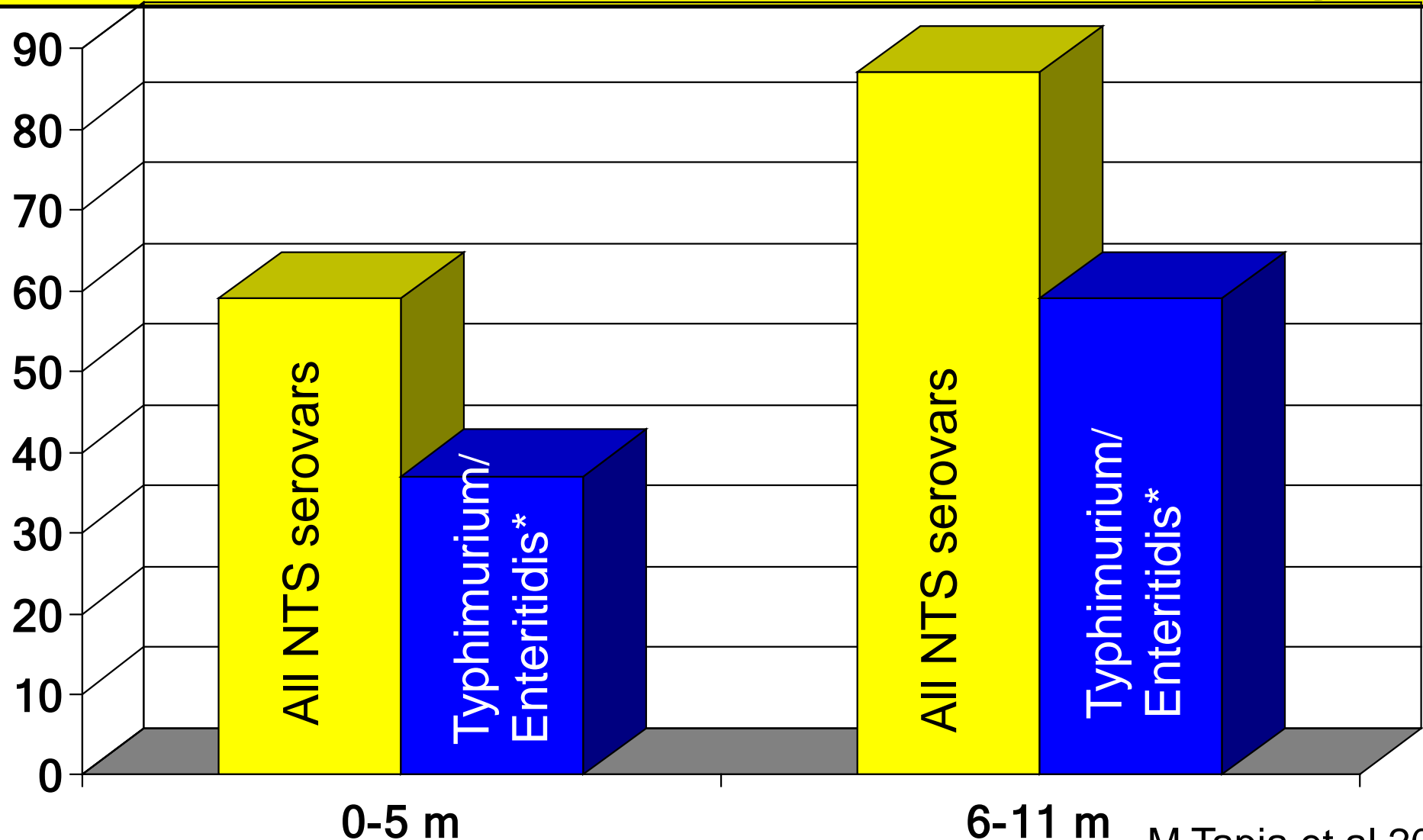
Total NTS and Typhimurium*/Enteritidis cases < 60 months of age



* Includes Typhimurium and monophasic variants

M Tapia et al 2012

Total NTS and *S. Typhimurium** & *S. Enteritidis* cases < 12 months of age



* Includes Typhimurium and monophasic variants

M Tapia et al 2012

Clinical presentation of hospitalized NTS cases, 7/02 - 6/12, Mali

	Bacteremia/ Septicemia	Meningitis
Number of cases	509 (90%)	47* (8.3%)
% of cases due to Typhimurium or Enteritidis	74.7%	83%
Median age	23 months	11 months
Case Fatality Rate (CFR)	22%	23%**

- 1 case also had (+) culture of soft tissue ** 7 of 10 deaths were < 12 months of age
Remaining cases included 1 septic arthritis, 1 peritonitis & 8 soft tissue infections.
- Total = 566 cases

Case fatality rate (CFR) by serovar of hospitalized cases of invasive NTS, Mali, 7/02 - 6/12

Serovar	Cases	CFR
Typhimurium	202	16%*
Enteritidis	182	28%*
I 4,5,12:i:-	41	19%
Dublin	68	19%
Stanleyville	20	20%
Group C	20	13%
All others	33	41%
TOTAL	566	22%



* p=0.005

Case fatality rate by age among invasive NTS inpatients, Mali, 7/02-6/12

Age (mos.)	Typhimurium*		Enteritidis	
	Cases	CFR	Cases	CFR
0-11	52	19%	44	38%
12-23	66	14%	47	24%
24-35	28	22%	33	31%
36-47	25	17%	15	43%
48-59	15	17%	9	25%
< 60	186	17%	148	35%



* Includes *S. Typhimurium* and monophasic variants

M Tapia et al 2012

Antibiotic resistance of NTS isolates

Serovar	N	Amp	Chlor	Ceftr	TMP/ SMZ
Typhimurium	191	96%	100%	5%	94%
Enteritidis	70	97%	39%	17%	61%
Dublin	54	4%	0%	2%	4%
Stanleyville	28	0%	0%	0%	0%



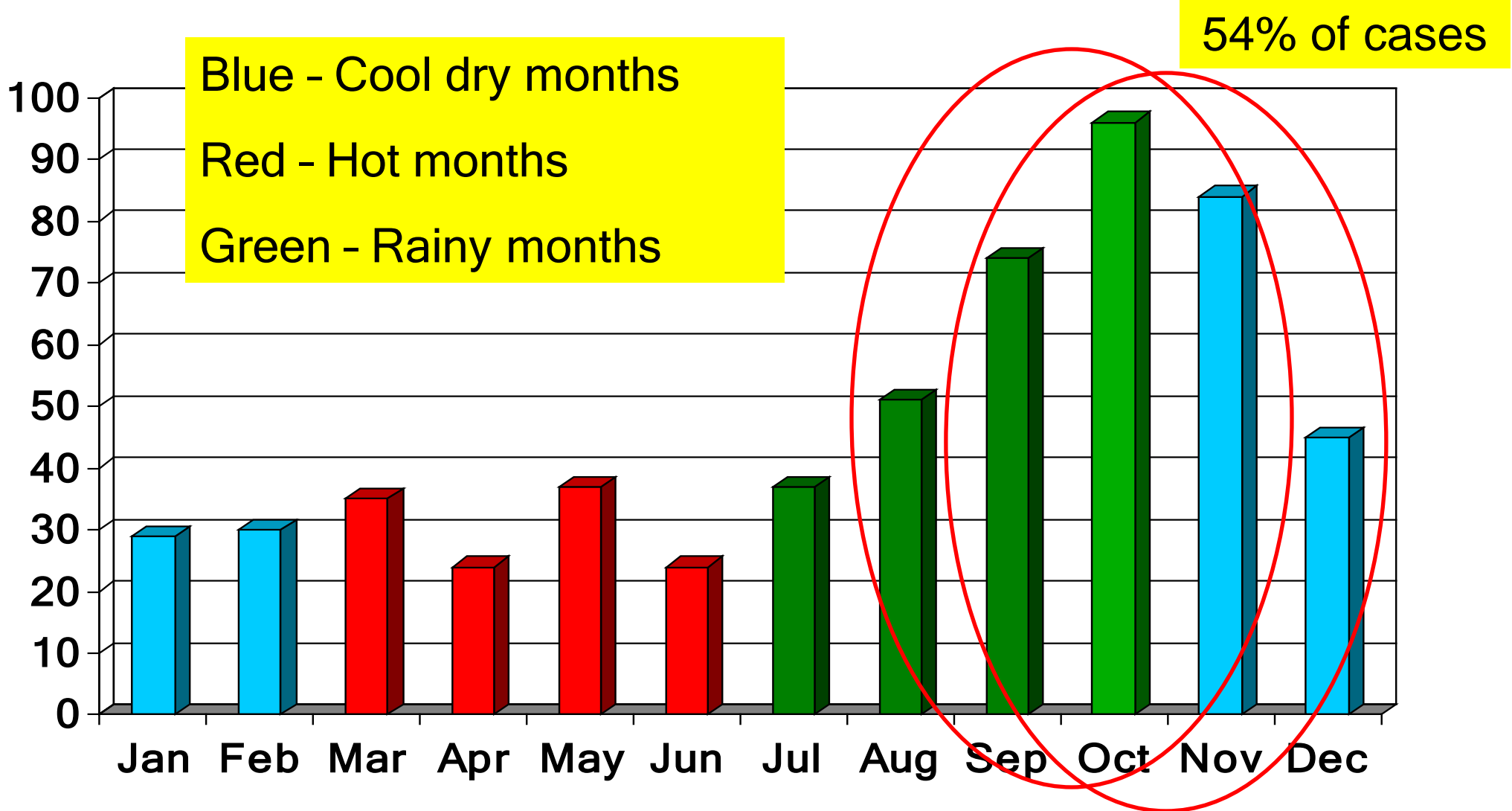
Severe invasive NTS disease in Africa

Host risk factors

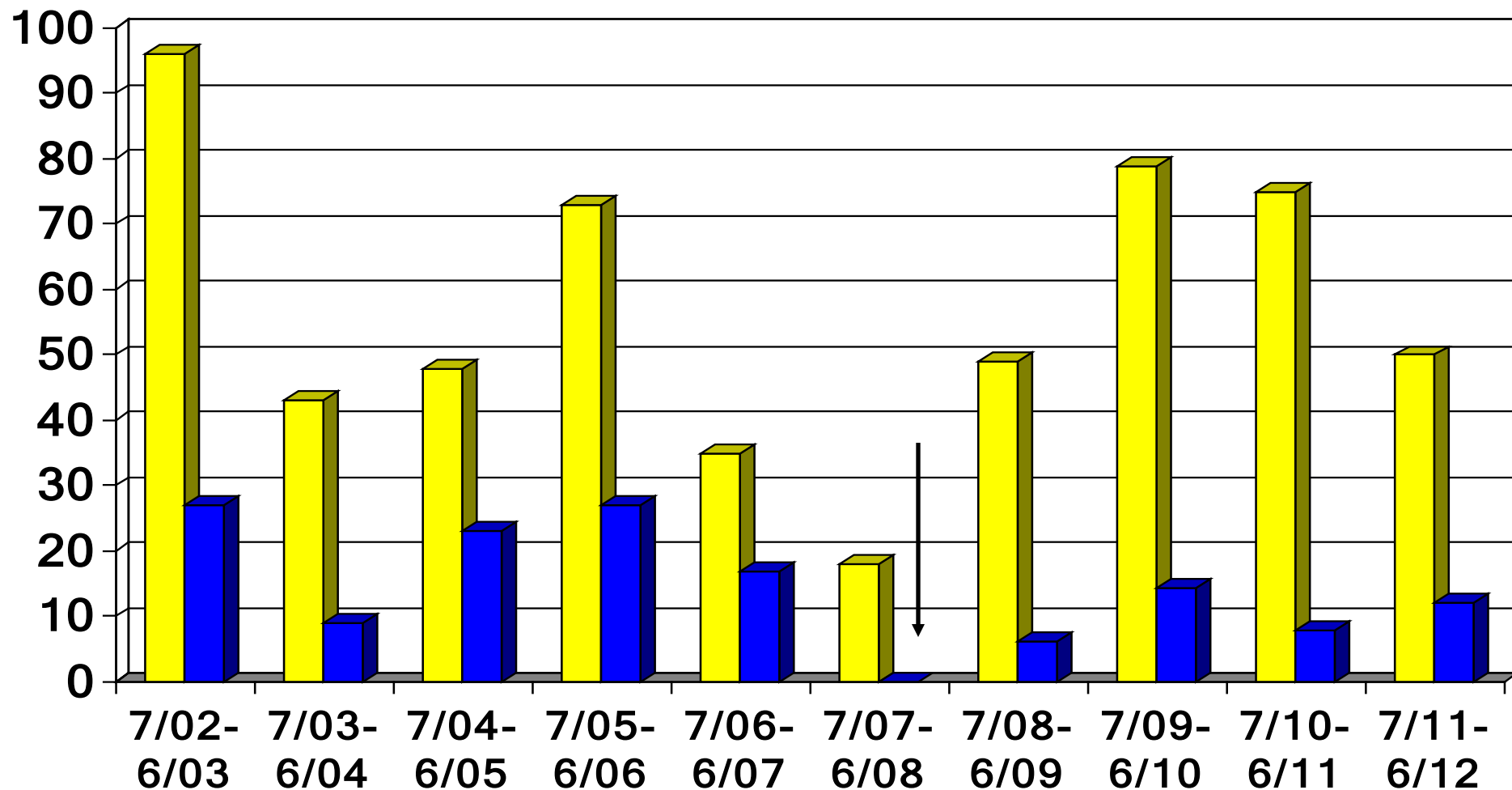
- Reticuloendothelial system blockade
 - Severe anemia of malaria
 - Hemolytic anemias (e.g., sickle cell hemoglobinopathy, etc.)
- HIV (where prevalent)
- Malnutrition



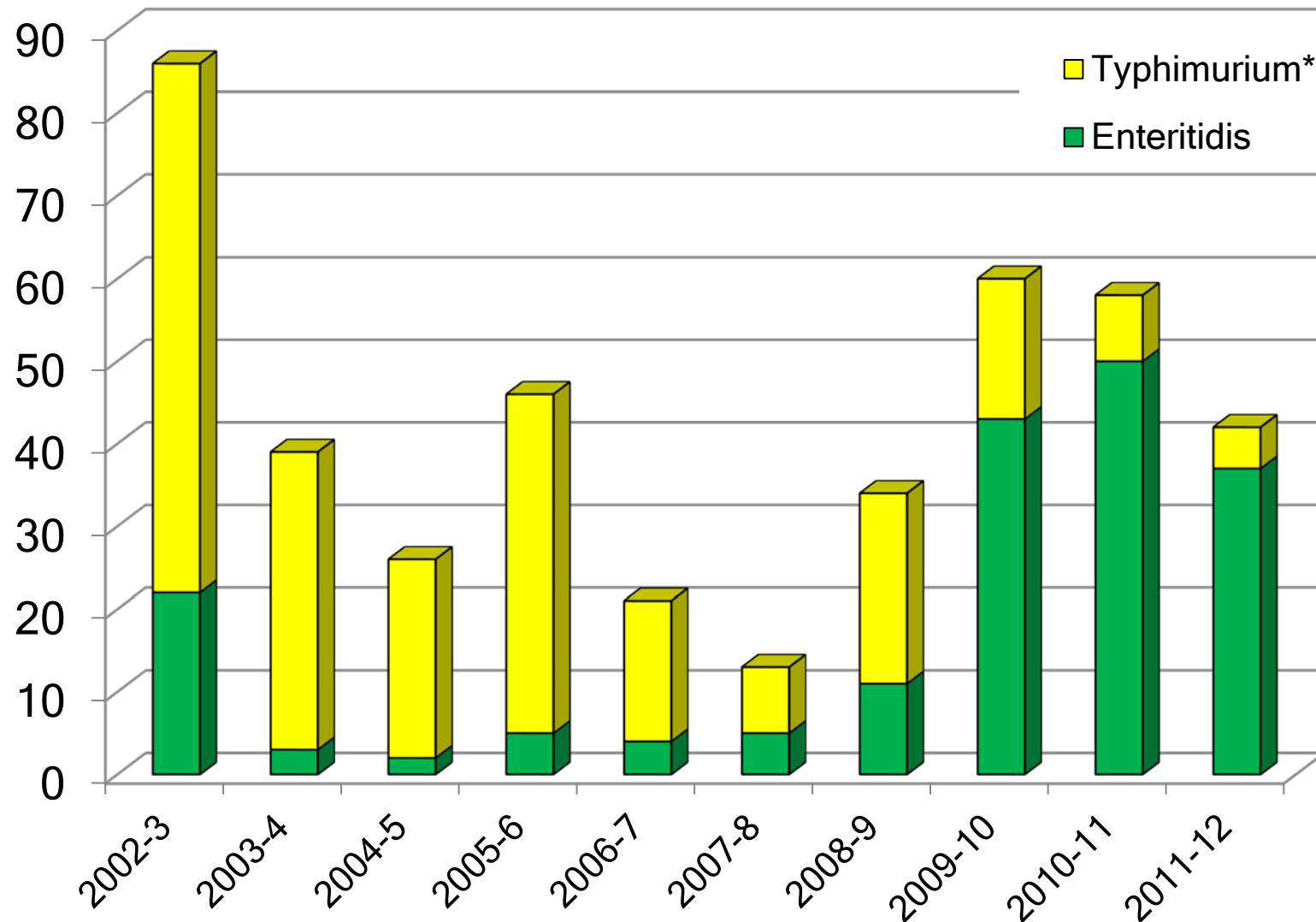
Seasonality- NTS cases, Mali, 7/02 – 6/12



Year-to-year variability of invasive NTS infections & malaria smear positivity (blue), Mali, 7/02 – 6/12



Year to year variability of serovar composition, Mali, 7/02 – 6/12



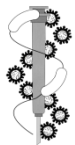
* Includes Typhimurium and monophasic variants

**Are the *S. Typhimurium* and
S. Enteritidis isolates from
pediatric invasive NTS
patients distinctive?**

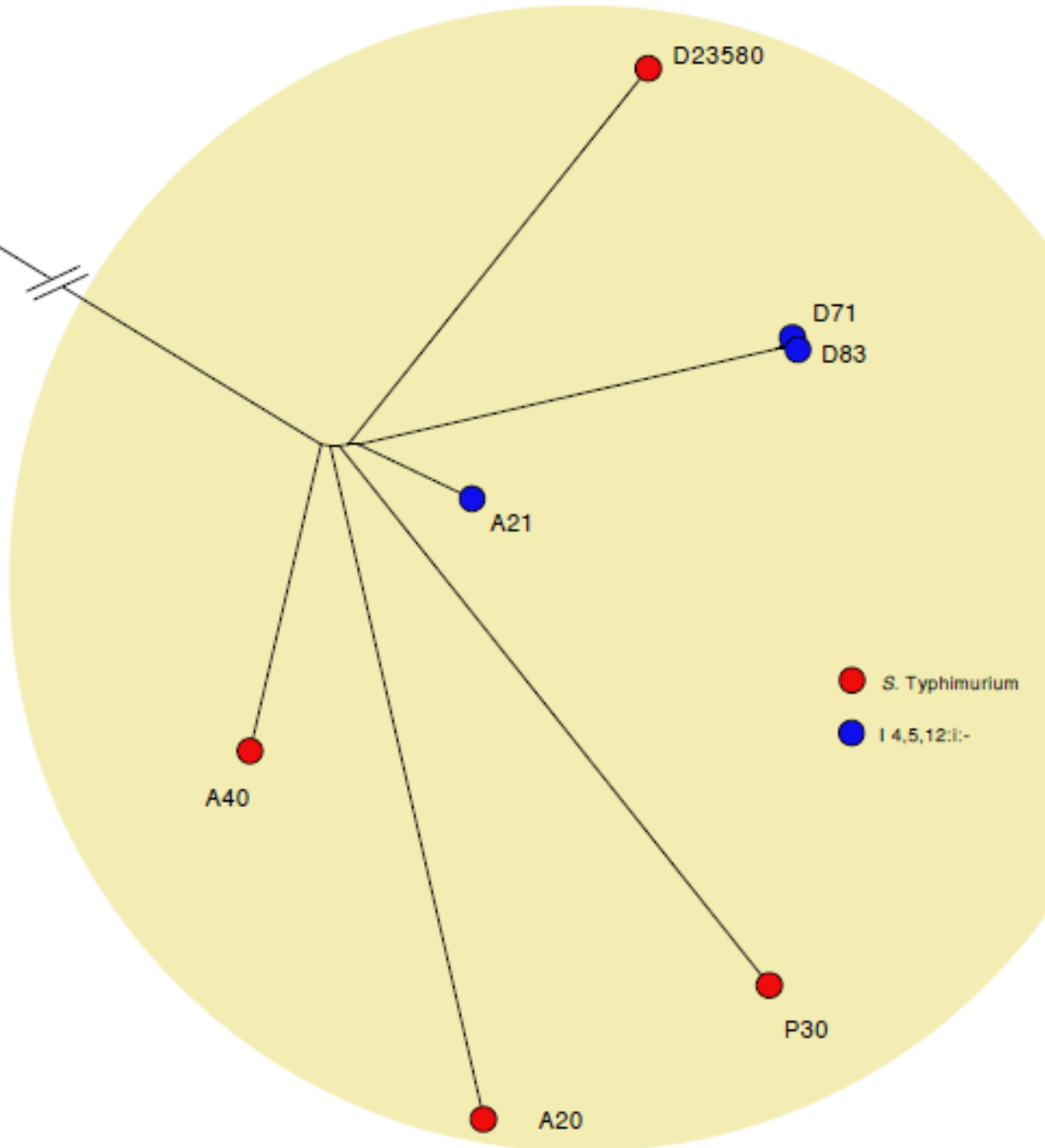


Changing our views about NTS

- Invasive MDR NTS isolates from Malawi & Kenya are mainly of an **unusual MLST type (ST313)**
- Malawian strain D23580 sequenced by R Kingsley & G Dougan at the Sanger Institute, UK
- Compared to genome sequences of “classic” Typhimurium strain LT2 & Typhi, D23580 showed:
 - **Genome degradation & convergence- Typhi-like**
 - **34 pseudogenes** not in LT2
 - **17 kb deleted**; total coding **loss of 61 genes**
 - **32 of 61 lost genes are also degraded in Typhi or Paratyphi A**



SL1344
DT104
LT2
DT2



**Malian *S.*
Typhimurium
and
monophasic
mutants are
also ST313
clade & closely
resemble the
Malawi
prototype**

CVD



S Tennant &
R Kingsley

Can we make a safe, effective & affordable vaccine to prevent invasive NTS disease among infants & toddlers in Africa?

Lessons learned from successful typhoid vaccines serve as a guide



Immune responses likely to mediate protection against NTS & strategies to elicit the responses

SIgA mucosal ABs

Prevent invasion from gut

Serum antibodies

Targets for antibodies:

OPS; flagella; core PS, OMP?

Biological activity of ABs:

Opsonophagocytic killing -

Bactericidal - complement-mediated killing

Cell-mediated immunity

Eliminates intracellular bugs

Best for eliciting gut SIgA

Live oral vaccine

Best for serum IgG ABs

Parenteral conjugate or protein vaccines

Best for stimulating CMI

Live oral vaccines

Clinical development of the bivalent (S. Typhimurium/S. Enteritidis) conjugate NTS vaccine: a public-private partnership

- **CVD, University of Maryland, Baltimore**
 - Vaccine design, preclinical, process development, clinical trials, project coordination
- **Wellcome Trust, London UK**
 - Funding (Strategic Translation Award), advocacy
- **Bharat Biotech, Hyderabad, India**
 - GMP pilot lots of the 2 monovalent conjugates & the bivalent conjugate; commercial manufacture post-licensure

Deploying a vaccine against invasive NTS

Target age by disease burden

- Children < 36 months of age

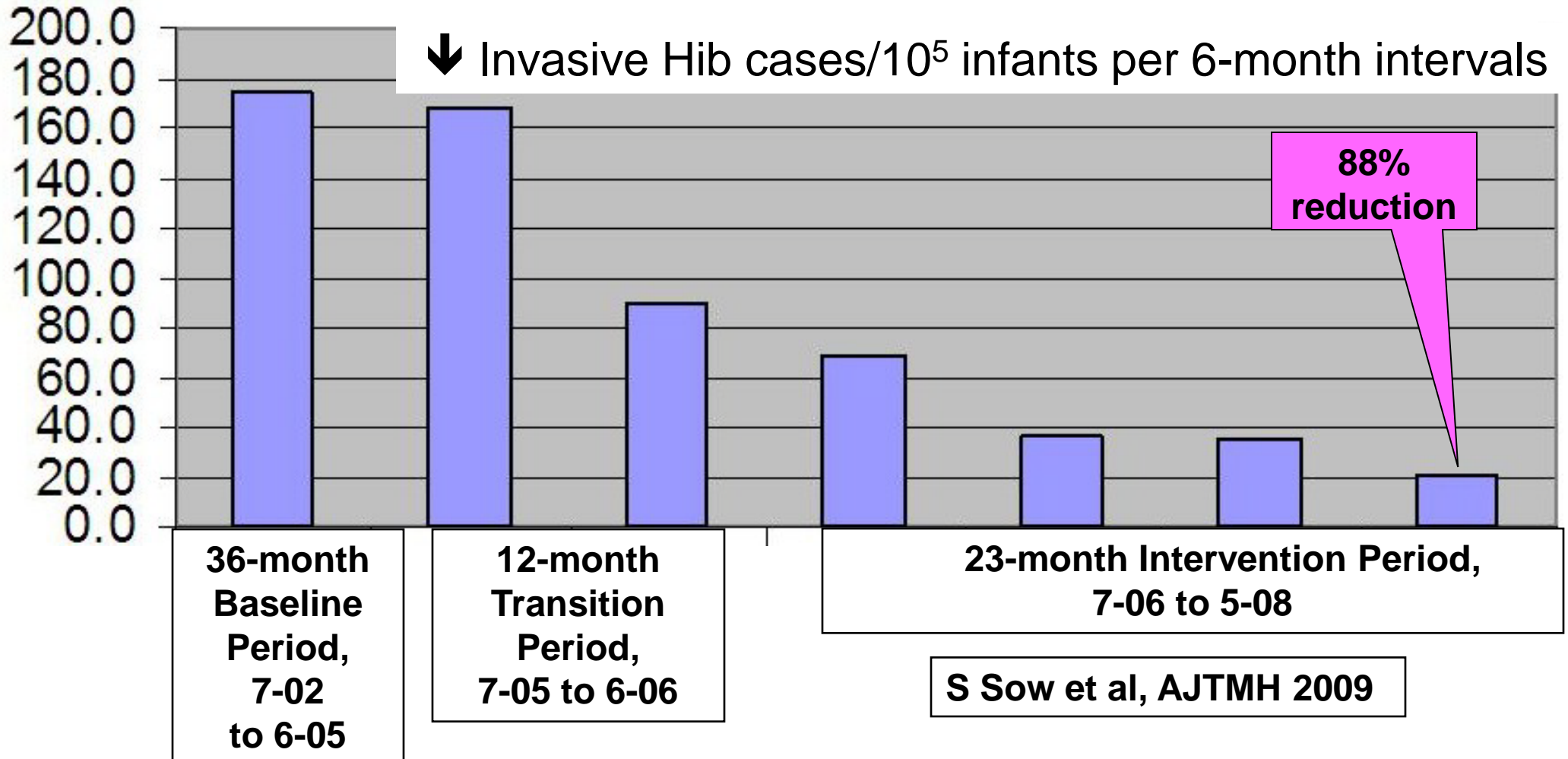
Target age population by practicality of vaccine delivery

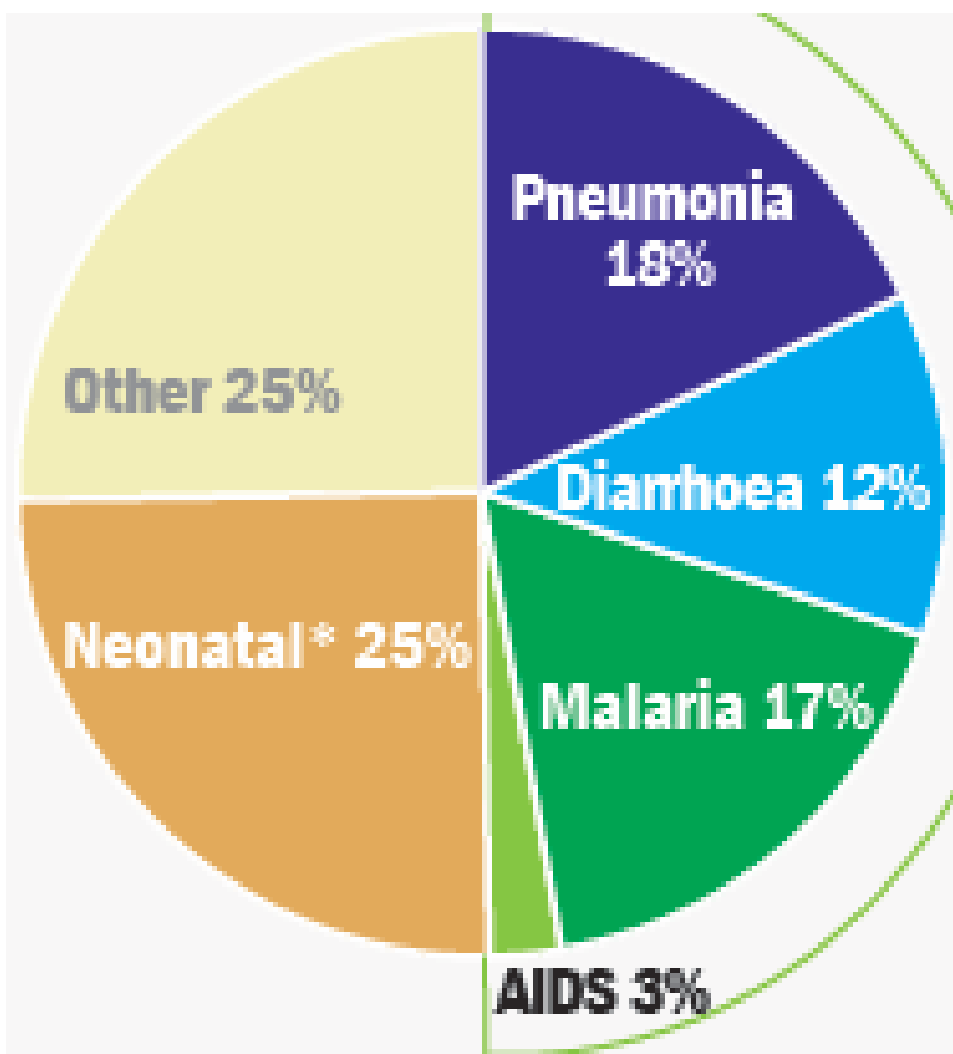
- Expanded Program on Immunization (**EPI**)
 - ~ Age 6, 10 and 14 weeks in most of sub-Saharan Africa
 - NTS vaccine must be compatible with other EPI vaccines



**EPI Unit in
Health Center,
Kangaba, Mali**

Impact of Hib vaccine introduction on invasive Hib disease in infants, Bamako, Mali





**Very-high-mortality countries
(U5MR ≥ 100)**

Sub-Saharan Africa		
Countries and territories	U5MR	U5MR rank
Sierra Leone	185	1
Somalia	180	2
Mali	176	3
Chad	169	4
Democratic Republic of the Congo	168	5
Central African Republic	164	6
Guinea-Bissau	161	7
Angola	158	8
Burkina Faso	146	9
Burundi	139	10
Cameroon	127	11
Guinea	126	12
Niger	125	13
Nigeria	124	14
South Sudan	121	15

Cases & deaths from bacterial invasive infections in children < 5 yrs of age in sub-Saharan Africa



Above the water
– the cases & deaths that we detect among children seen at hospitals & health centers

Below the water
– the cases & deaths among children in the community who do not access health care facilities

Invasive NTS disease

Industrialized countries

- Invasive disease as a complication of gastroent.
- Severe invasive disease:
 - Infants < age 3 months
 - The elderly
 - Immunocompromised
- Incidence is increasing
- Typhimurium (ST19), Enteritidis, Heidelberg, Dublin, Schwarzengrund
- Animal reservoir

Sub-Saharan Africa

- Serendipitous discovery
- Children < age 3 years
- Most do not present with gastroenteritis
- High case fatality $\geq 20\%$
- Novel strains:
 - ST313 (by MLST)
 - genomic degradation
- 75-95% of invasive NTS
 - *S. Typhimurium* (including variants), *S. Enteritidis*

Acknowledgments (partial listing)

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**Thank you for your
attention**

