A broad spectrum vaccine to prevent invasive *Salmonella* Infections for sub-Saharan Africa

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Epidemiology of invasive *Salmonella* infections

Enteric fevers

- *Salmonella* Typhi
- *Salmonella* Paratyphi A
- *Salmonella* Paratyphi B
- *Salmonella* Paratyphi C (rare)

Invasive NTS disease (septicemia, meningitis, etc.)

- *Salmonella* Typhimurium
- *Salmonella* Enteritidis
- I:4,[5],12:i:-
- *Salmonella* Dublin

Focal metastatic infections

- *Salmonella* Choleraesuis
- *Salmonella* Paratyphi C

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Relative importance of the *Salmonella* serovars varies by global region and over time

Asia

- *Salmonella* Typhi
- *Salmonella* Paratyphi A (emerging)

Africa

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

South America (1970s & 1980s)

- *Salmonella* Typhi
- *Salmonella* Paratyphi B
- *Salmonella* Paratyphi A

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Invasive *Salmonella* epidemiology, RWANDA

Age (mos)	No. of Children	*S.* Typhi	Non-typhoidal *Salmonella**	*Strep. pneumo.*	Other Bacteria
<12	255	2 (0.8%)	14 (5.5%)	3 (1.2%)	6 (2.4%)
12-23	239	6 (2.5%)	12 (5.0%)	5 (2.1%)	4 (1.7%)
24-47	191	7 (3.7%)	7 (3.7%)	2 (1.0%)	2 (1.0%)
48-71	77	5 (6.5%)	0 (0.0%)	1 (1.3%)	2 (2.6%)
≥72	138	27 (19.7%)	3 (2.2%)	3 (2.2%)	1 (0.7%)
Total	900	47 (5.2%)	36 (4.0%)*	14 (1.6%)	15 (1.7%)

* 13 *S.* Typhimurium, 22 *S.* Enteriditis & 1 *S.* Dublin

LePage P, Bogaerts J, Van Goethem C, Ntahorutaba M, Nsengumuremyi F, Hitimana DG, Vandepitte J, Butzler JP, Levy J, et al. Lancet 1987

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Case fatality by pathogen, RWANDA

All Pathogens	*S.* Typhi	*S.* Typhimurium	Other *Salm.*	*Strep. pneumo.*
10/107	2/46	2/11	2/22	0/14
9.3%	4.3%	18.2%	9.1%	0%

* Patients lost to follow-up were dropped from denominator

LePage P et al. Lancet 1987

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

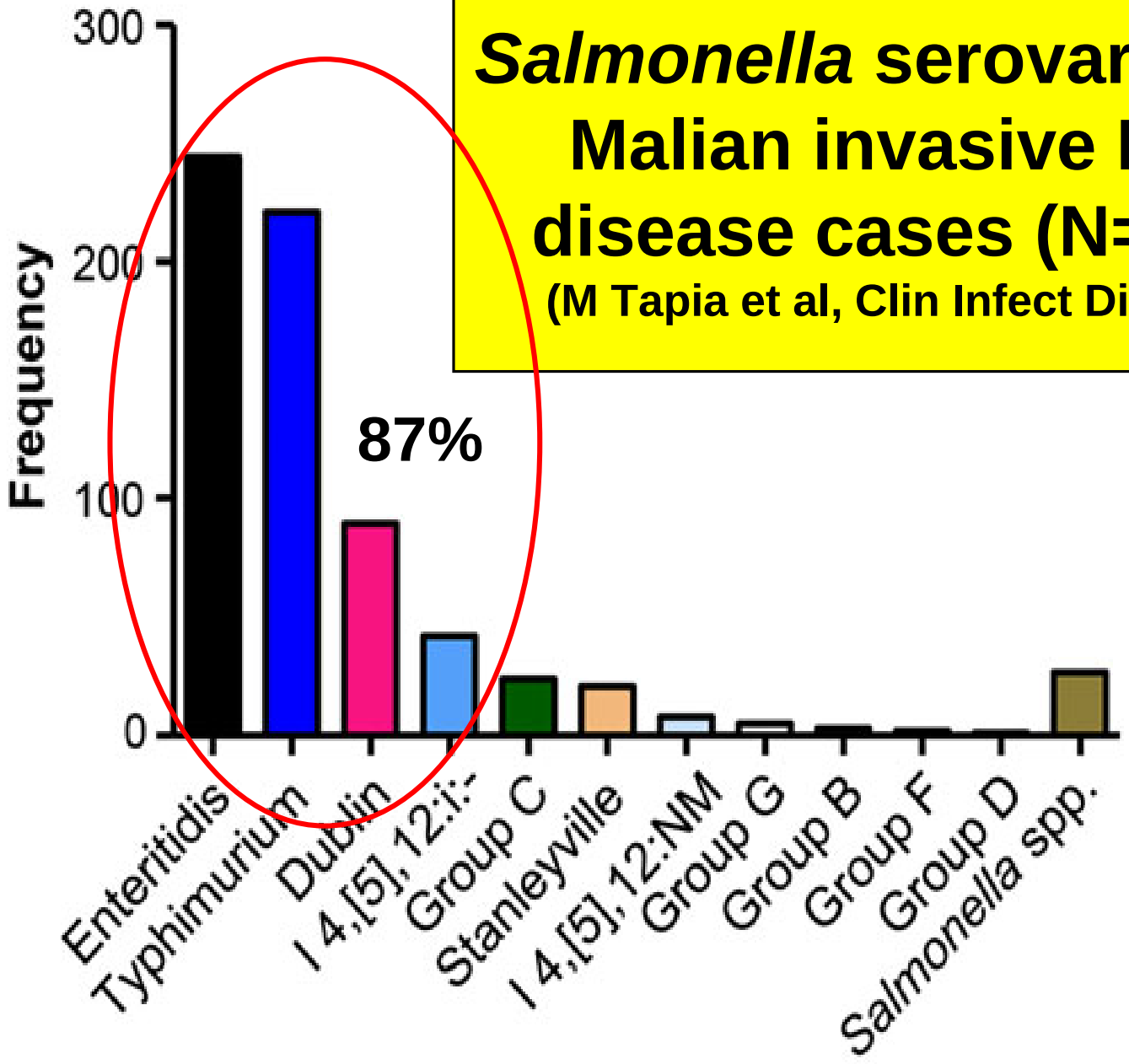
Site (Period)	Age group	Inc. inv. pneumo /10^5	Inc. inv. NTS /10^5
Kilifi, Kenya (1998-02) J Berkley et al, 2005 **(7% HIV prevalence)**	0-11 mos.	241	170
Basse, Gambia (2000-4) G Enwere et al, 2006 **(~1% HIV prevalence)**	2-5 mos.	363	408
	6-11 mos.	576	360
	12-17 mos.	526	334
Manhiça, Mozambique (2001-6)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

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

Surveillance at l'Hôpital Gabriel Touré, Bamako, Mali

Salmonella serovars from Malian invasive NTS disease cases (N=687)

(M Tapia et al, Clin Infect Dis 2015)



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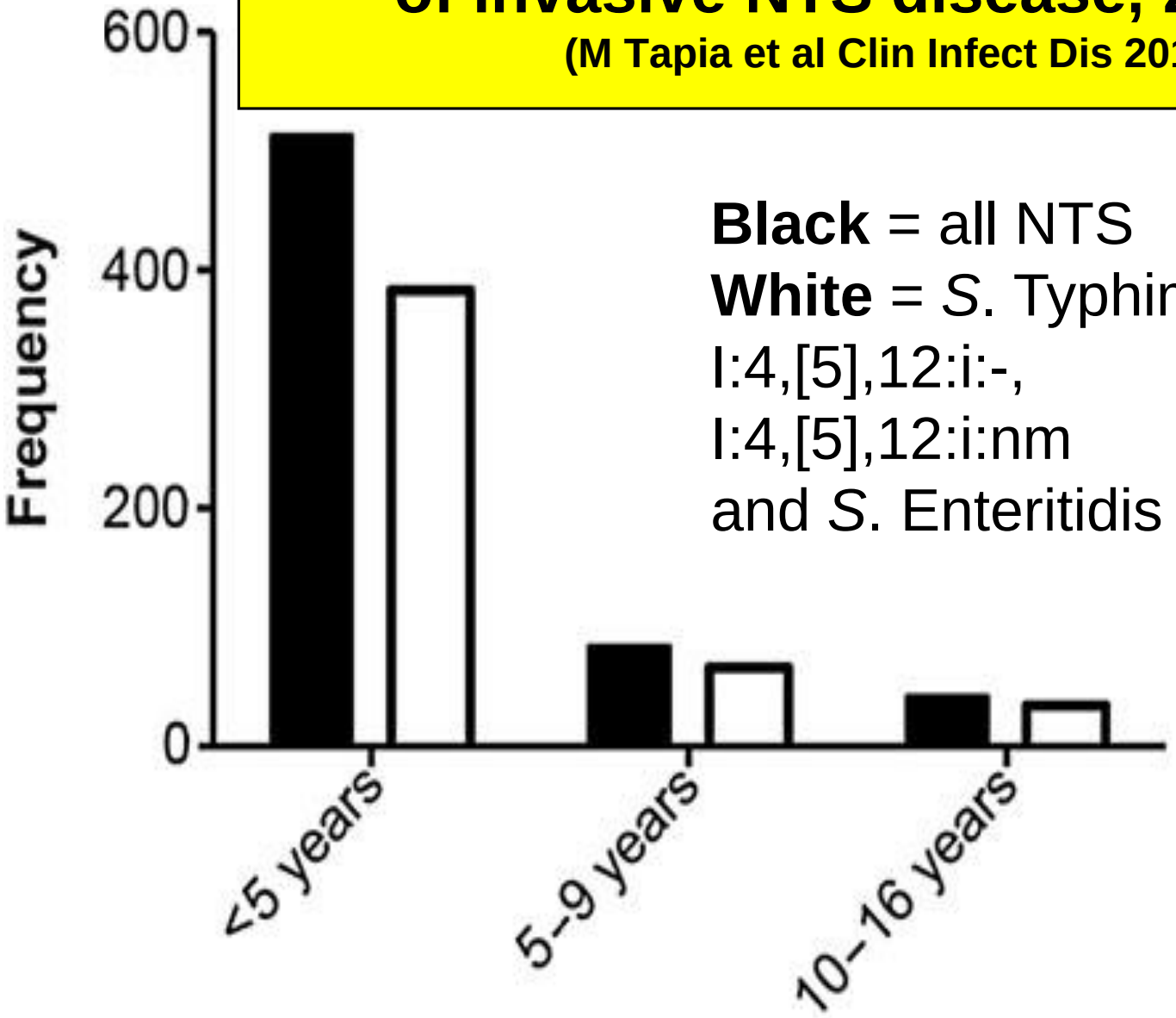
Age groups That need to be protected against invasive NTS disease in sub-Saharan Africa

Age distribution of Malian pediatric cases of invasive NTS disease, 2002-13

(M Tapia et al Clin Infect Dis 2015)



Black = all NTS
White = *S*. Typhimurium, I:4,[5],12:i:-, I:4,[5],12:i:nm and *S*. Enteritidis

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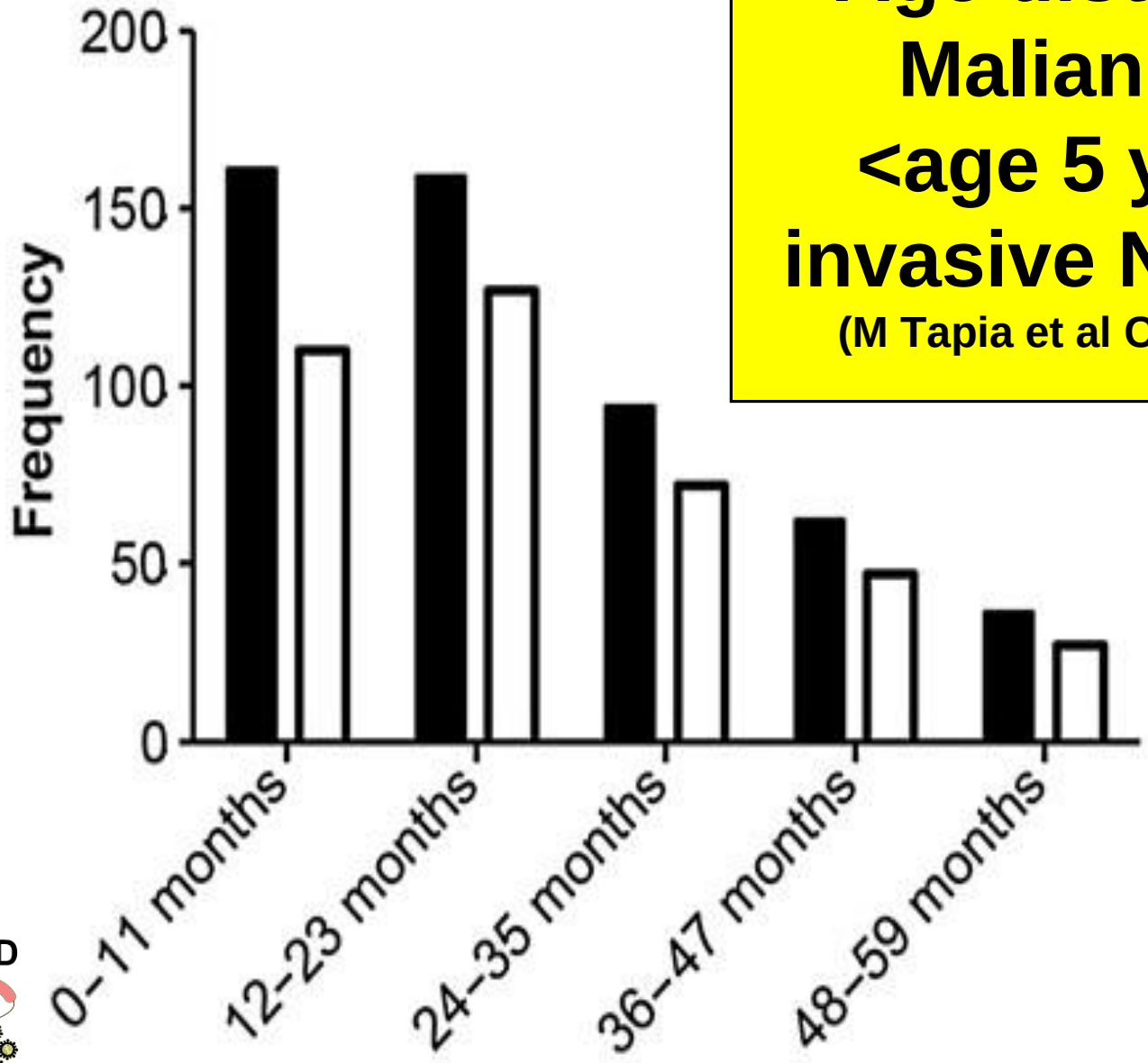
Age distribution of Malian children <age 5 years with invasive NTS disease

(M Tapia et al Clin Infect Dis 2015)



Black = all NTS
White = *S.* Typhimurium, I:4,[5],12:i:-, I:4,[5],12:i:nm
S. Enteritidis

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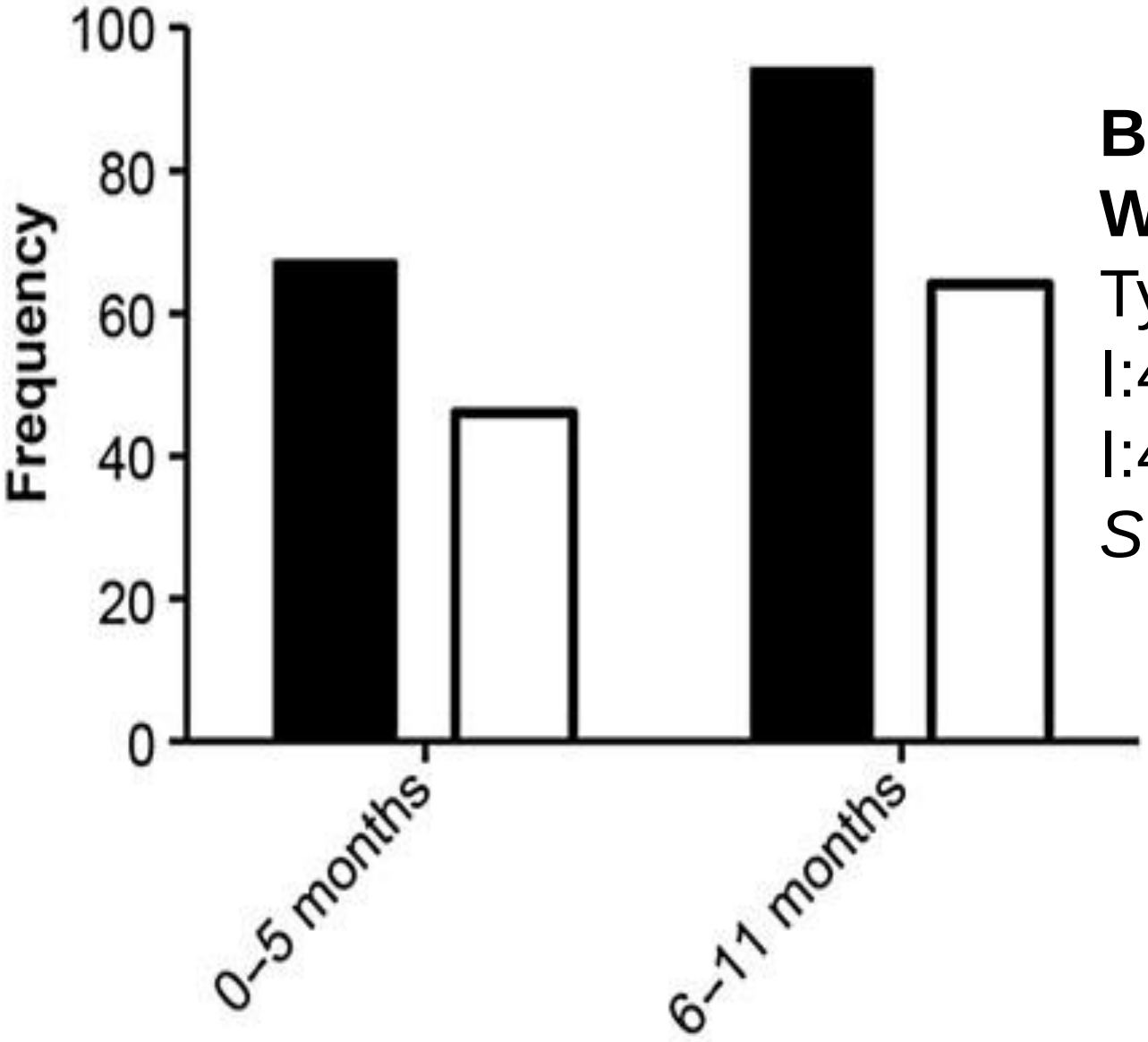
Ages of Malian infants with invasive NTS disease

(M Tapia et al, Clin Infect Dis 2015)



Black = all NTS
White = *S.* Typhimurium, I:4,[5],12:i:-, I:4,[5],12:i:nm
S. Enteritidis

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High case fatality rates (CFR) among hospitalized cases of invasive NTS in Malian children <5 years of age, 2002-14, by serovar

Serovar	Cases	CFR
Typhimurium* I 4,5,12:i:-* I 4,5,12:i:-NM*	187	14%$
Enteritidis	196	28%$
Dublin+	65	15%

* Multiple antibiotic-resistant

\+ Antibiotic sensitive

$ p=0.005

M Tapia et al 2015

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Case fatality rate by age among invasive NTS inpatients, Mali, 7/02-6/13

Age (mos.)	Typhimurium*		Enteritidis	
	Cases	CFR	Cases	CFR
0-11	53	15%	57	33%
12-23	66	12%	61	21%
24-35	28	18%	44	25%
36-47	25	16%	22	36%
48-59	15	13%	12	25%
< 60	187	14%	196	28%

M Tapia et al 2015

* Includes *S*. Typhimurium and monophasic and non-motile variants

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Deaths from invasive *Salmonella* infections among children <5 yrs of age in sub-Saharan Africa

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

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

CVD strategies for a broad-spectrum vaccine to prevent invasive *Salmonella* disease in sub-Saharan Africa

- Trivalent parenteral conjugate vaccine:
  - *S.* Typhimurium conjugate Baliban SM et al. PLoS NTD 2017
  - *S.* Enteritidis conjugate Simon R et al. PLoS One 2013
  - *S.* Typhi Vi-TT conjugate Mohan K et al. CID 2015
- Trivalent attenuated live oral vaccine:
  - *S.* Typhimurium (CVD 1931) Tennant S, et al I&I 2015
  - *S.* Enteritidis (CVD 1944) Tennant S, et al I&I 2015
  - *S.* Typhi (CVD 909) Wang J et al. I&I 2000; Tacket C et al. JID 2004; Wahid R et al. Mucosal Immunol 2008; Wahid R et al. CVI 2014
- Vaccines must be compatible with EPI

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Potentially relevant immune responses to CVD NTS conjugate vaccines in pre-clinical studies

- Binding antibodies against COPS & flagella (ELISA)
- Opsonophagocytic antibodies
- Serum bactericidal antibodies

RESEARCH ARTICLE

Modeling the Potential for Vaccination to Diminish the Burden of Invasive Non-typhoidal *Salmonella* Disease in Young Children in Mali, West Africa

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PLOS | NEGLECTED TROPICAL DISEASES

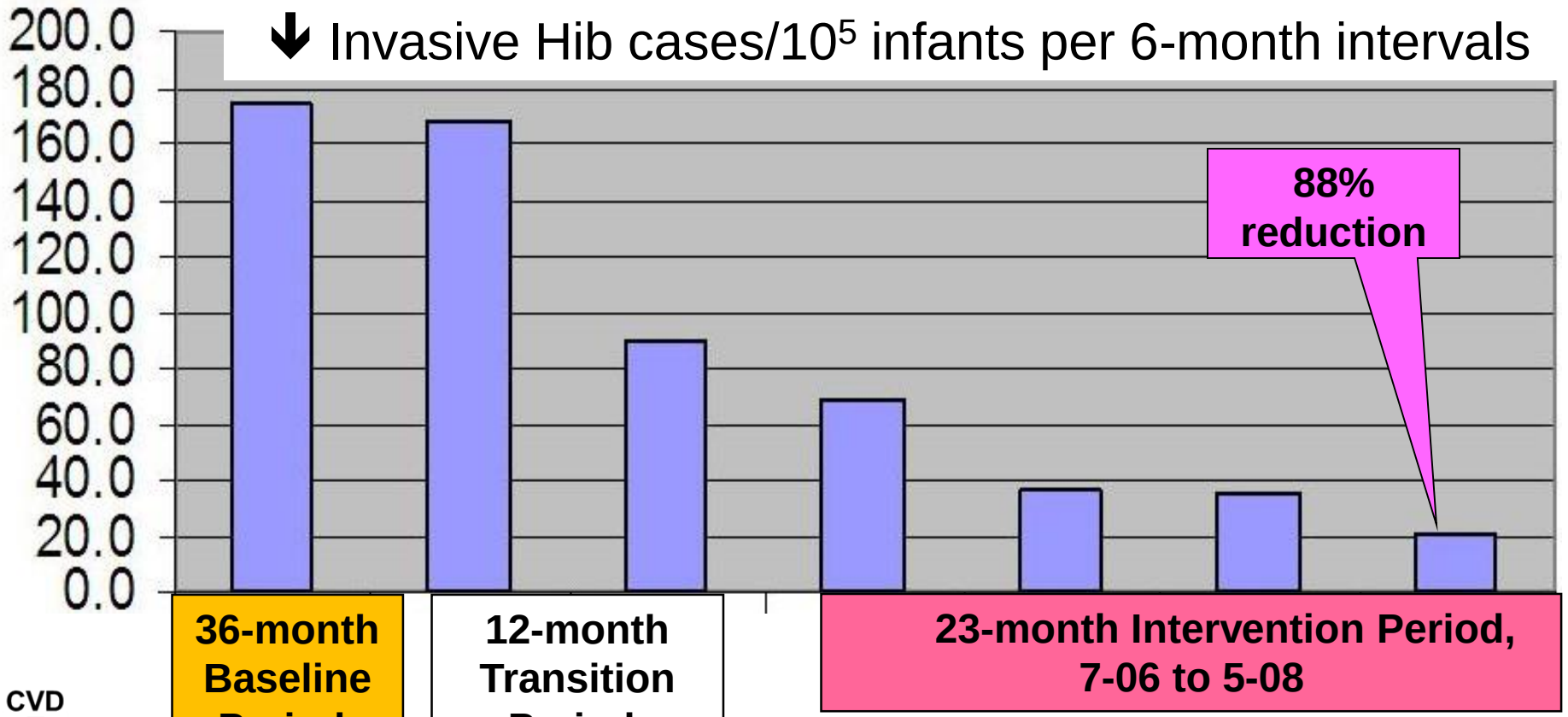
2017

Incidence of invasive Hib disease per 100,000 7/2002 - 6/2005

(S Sow et al, Pediatr Infect Dis J 2005)

Age group	Year 1	Year 2	Year 3	Mean Annual
0-1 m	21.9	10.6	10.3	14.2
2-3 m	22.3	43.4	63.4	43.4
4-5 m	133.1	270.7	263.3	223.6
6-7 m	**411.5**	**341.4**	**377.8**	**376.6**
8-9 m	175.2	275.2	446.1	301.3
10-11 m	134.7	117.9	127.5	126.6
0-11 m	145.5	171.0	206.5	174.9

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



S Sow et al, AJTMH 2009

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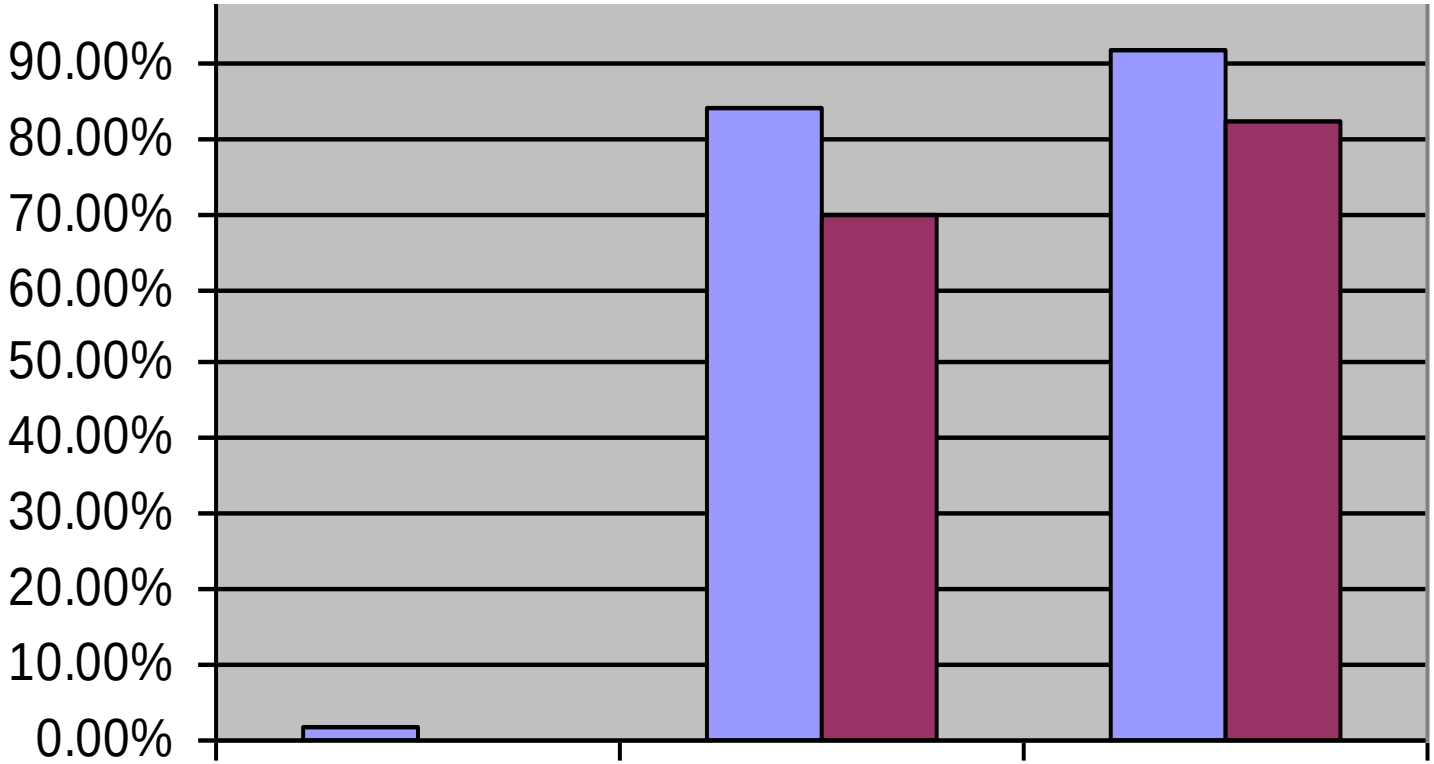
Prevalence of serum Hib PRP antibodies in Malian infants 6-7 months of age before and 18 & 30 months after the introduction of Hib conjugate into the EPI for Malian infants



S Sow et al, AJTMH 2009

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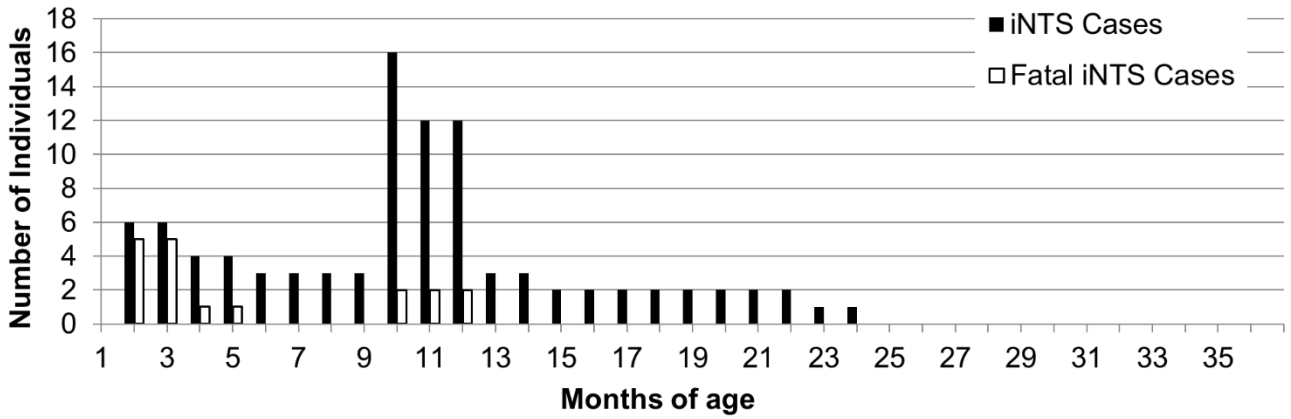
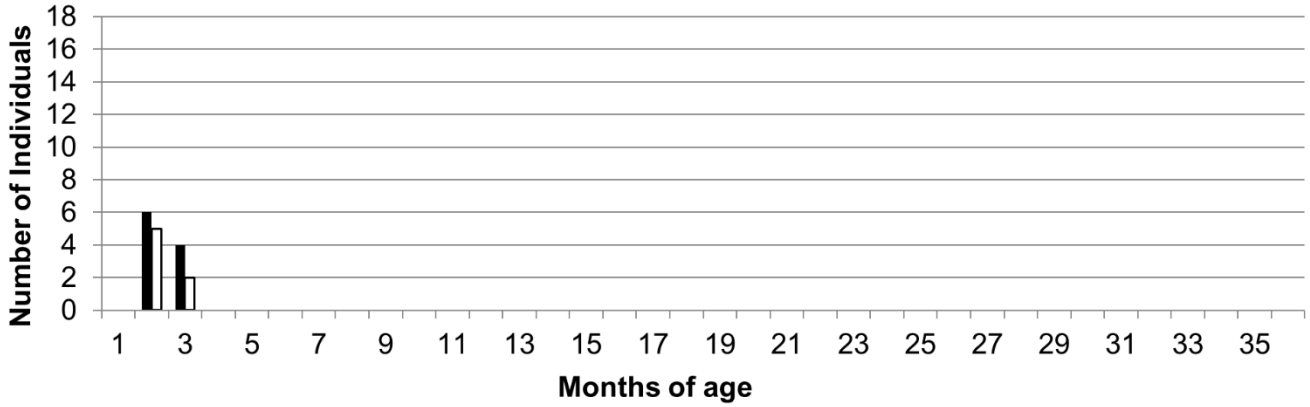
(a)



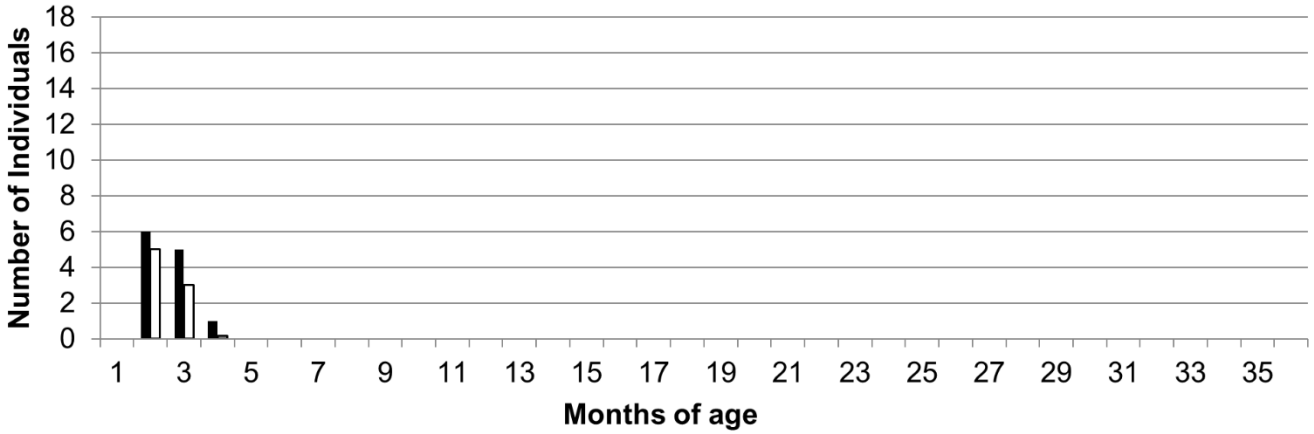
Bamako cohort, no vaccine (K Bornstein et al PLoS NTD 2017)

(b)



Cohort with NTS vaccine, 100% VE, 100% coverage

(c)



Cohort with NTS vaccine, 95% VE, 90% coverage

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EPI schedule in sub-Saharan Africa

Infant vaccines (0-11 months of age)

- Pentavalent (DwPT/Hib/HBV) vaccine - 6, 10 & 14 wks
- Pneumococcal conjugate – 6,10 & 14 wks
- IPV – 14 wks
- Oral rotavirus – 6, 10, 14 weeks (2 or 3 doses)
- OPV – 6, 10 & 14 weeks
- Measles or MR – 9 mos (YF, MenAfrivac)
- Coming – RTS,S

Toddler vaccines (12-23 months of age)

- MCV2 (2^{nd} measles containing vaccine) - 15-18 mos
- RTS,S
- TT or dT
- Pneumococcal conjugate?

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Multivalent vaccines against invasive *Salmonella* disease by different regions and globally

Asia	**Africa**	**Developing Countries**	**Global**
Typhi	Ty'murium	Typhi	Typhi
Paratyphi A	Enteritidis	Paratyphi A	Paratyphi A
	Typhi	Ty'murium	Ty'murium
		Enteritidis	Enteritidis
			Group C
			(e.g., Newport)

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Components of vaccines against invasive *Salmonella* disease by different regions and globally

Asia	**Africa**	**Developing Countries**	**Global**
Typhi	Ty'murium	Typhi	Typhi
Paratyphi A	Enteritidis	Paratyphi A	Paratyphi A
	Typhi	Ty'murium	Ty'murium
		Enteritidis	Enteritidis
			Group C
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Thank you