

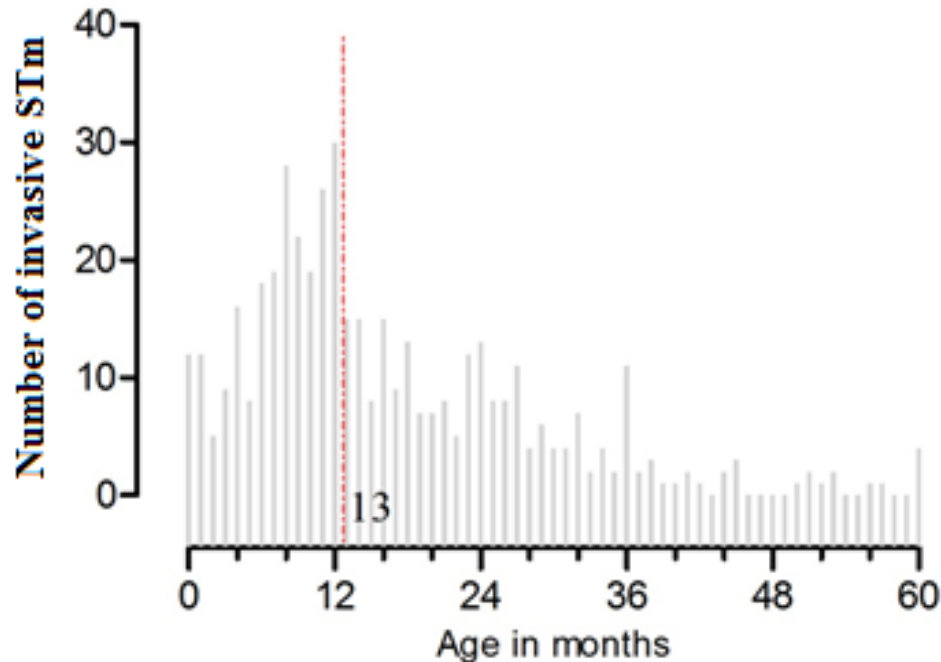
Dissecting immune responses against iNTS

Tonney Nyirenda, Wilson Mandala, Rob Heyderman,
Melita Gordon

Malawi-Liverpool-Wellcome Trust
Clinical Research Programme



Risk factors of iNTS disease in African children



Risk factors

- Infancy
- Malaria
- Malnutrition
- HIV

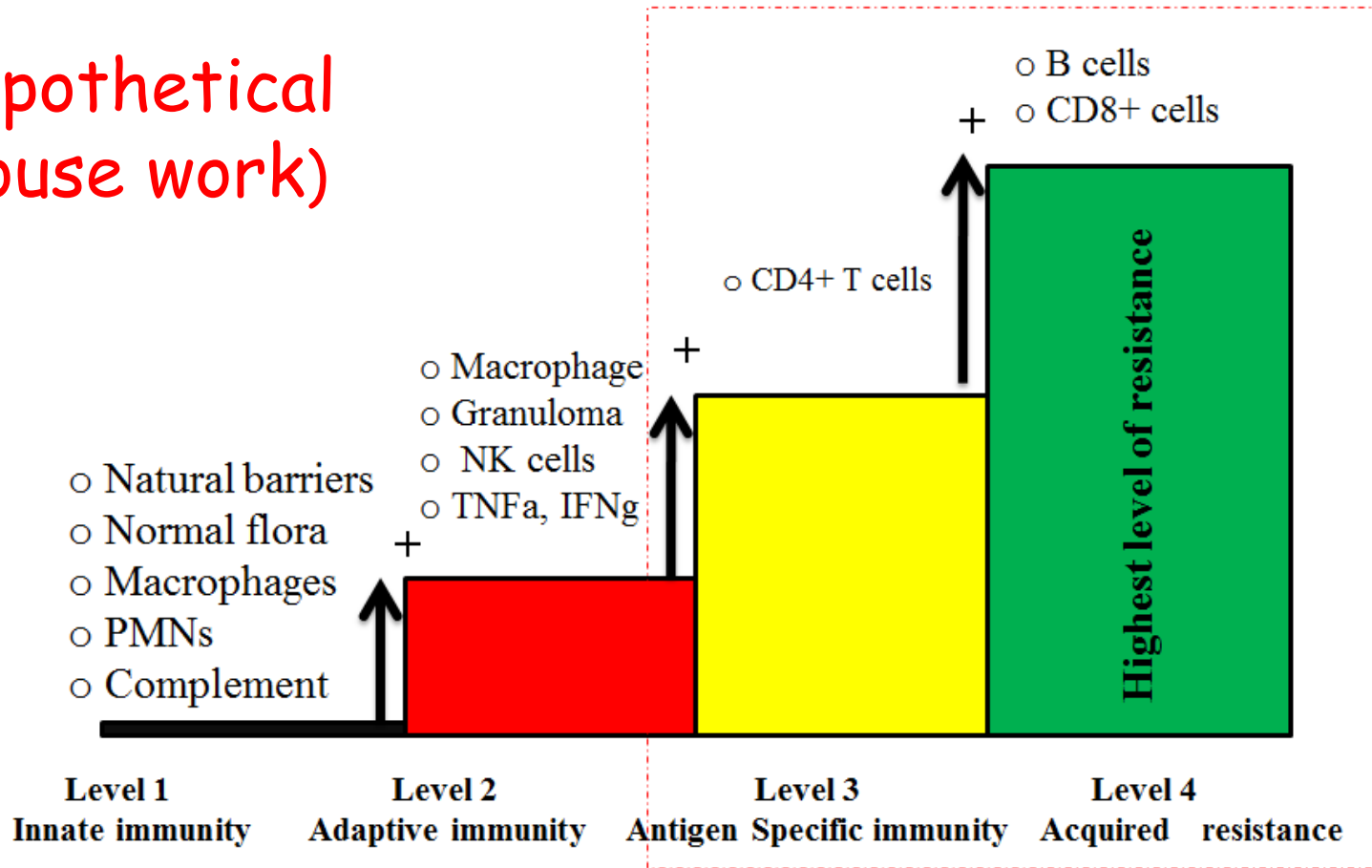
- Median age 13 months
- 80% of cases were <2 yrs

Nyirenda TS, JID 2014

Morpeth SC, CID 2009

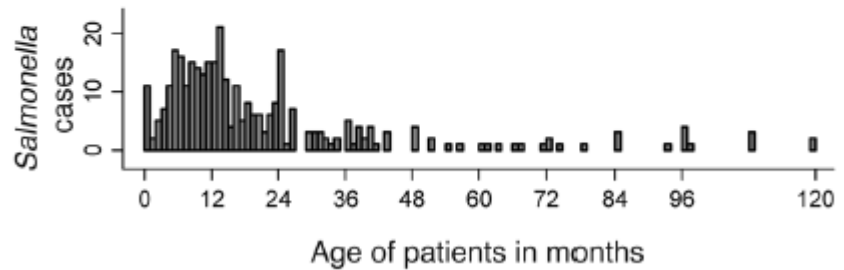
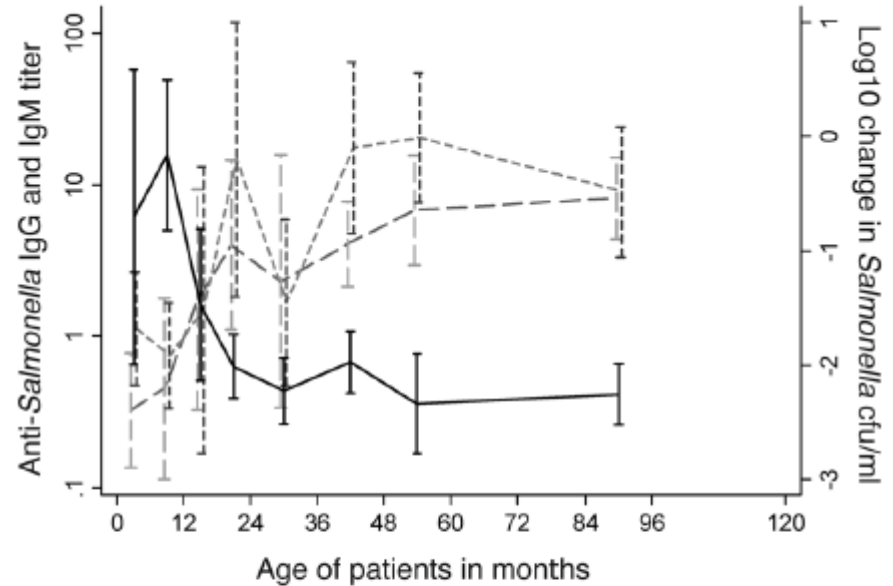
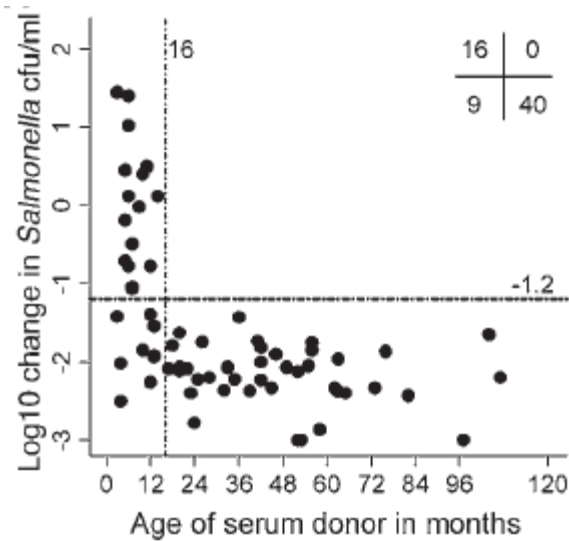
Immunity to *Salmonella* is complex

Hypothetical
(Mouse work)



Adapted from Mastroeni P, Curr Mol Med 2002

Antibody mediated serum immunity to NTS in Malawian children



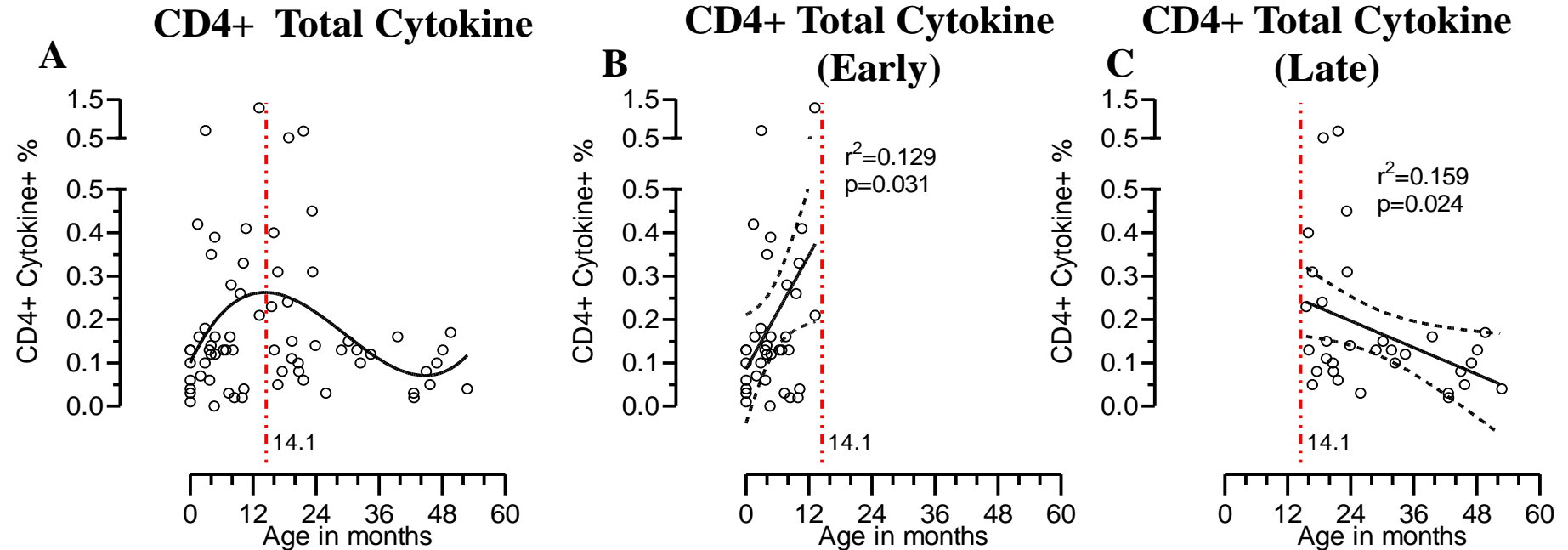
Hypothesis 1

CD4+ T cell immunity to NTS develop in parallel to antibody immunity in the first 2 years of life

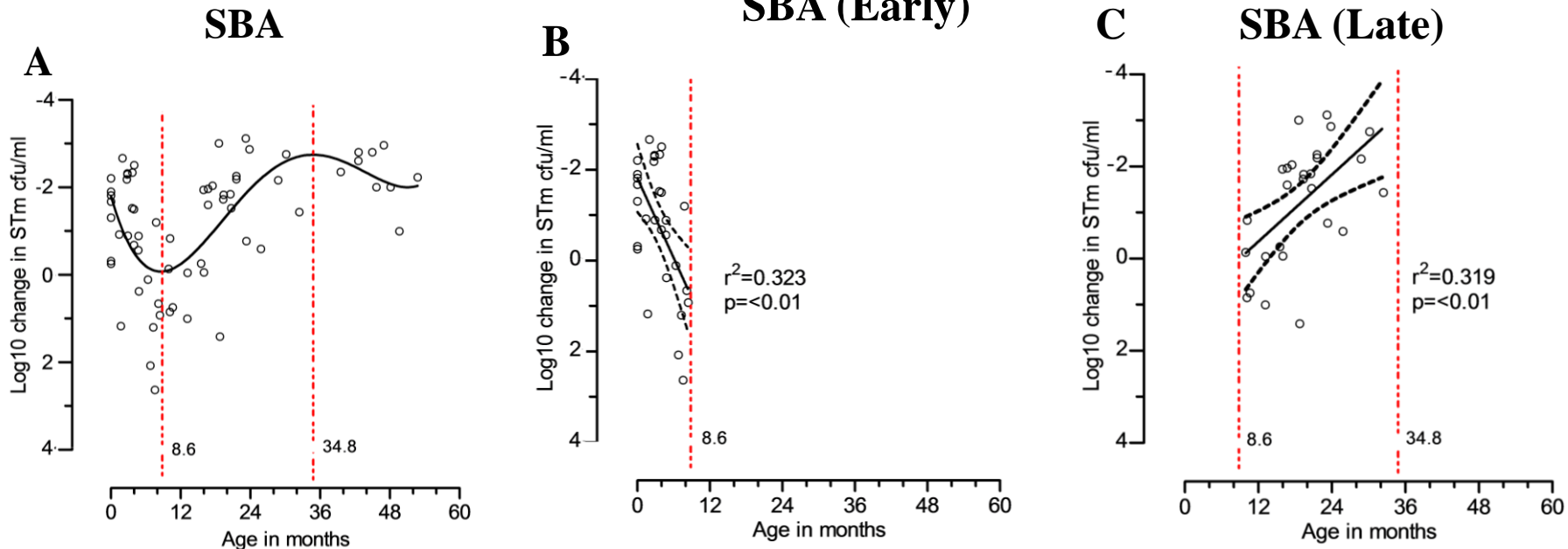
Method

- Cross section study
- Healthy children (n=80, age 0-60 months)
- CD4+ T cell ICS; IFN- γ , TNF- α , IL-2
- Serum killing and antibody by ELISA

Early acquisition of STm-specific CD4+ T cells



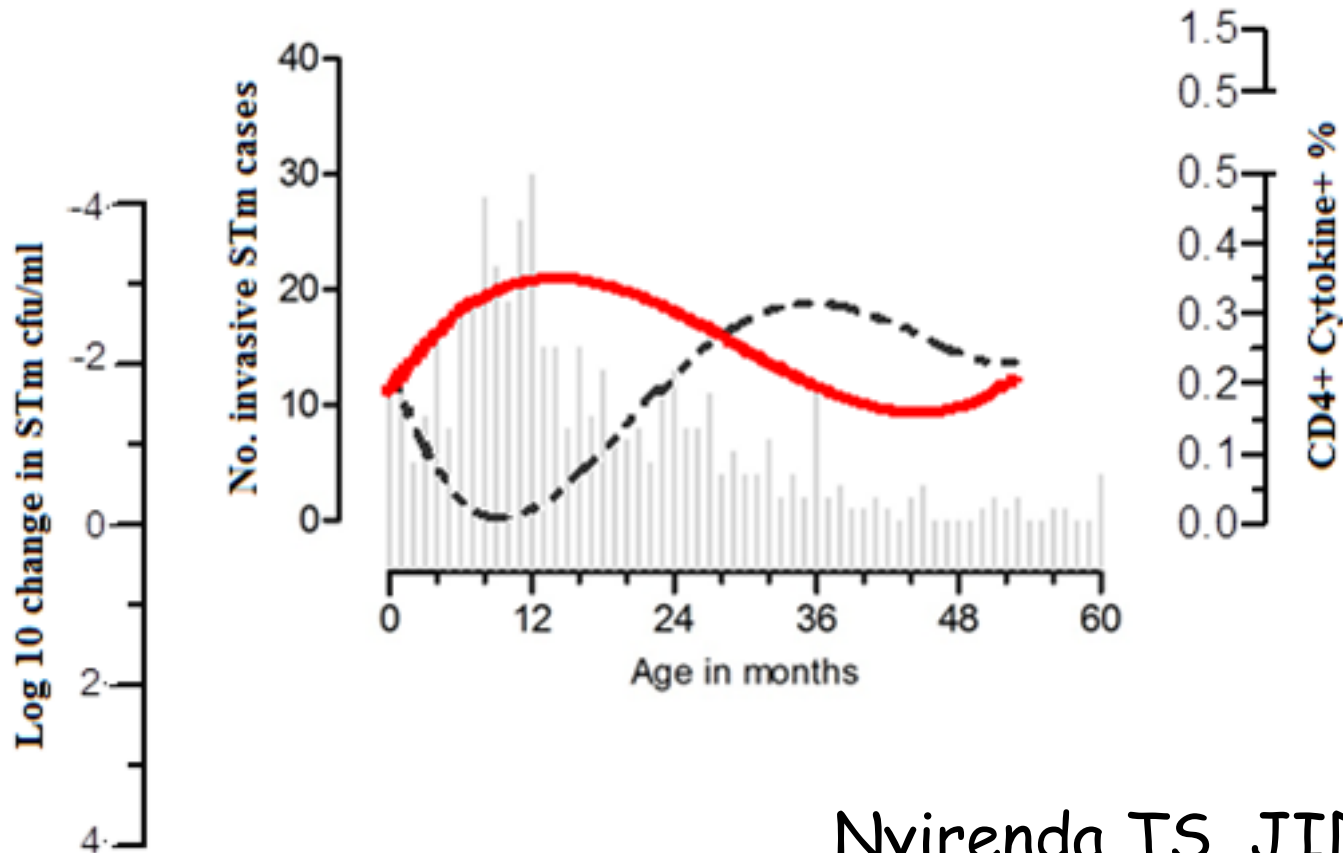
Delayed acquisition of STm D23580 serum killing



- SBA to STm D23580 mainly correlate with IgG antibodies targeting LPS O 4;5

Sequential acquisition of T cells and antibodies to STm is associated with a decline of iNTS cases

No. invasive STm — · — SBA (Ab immunity) — CD4+ T cell immunity



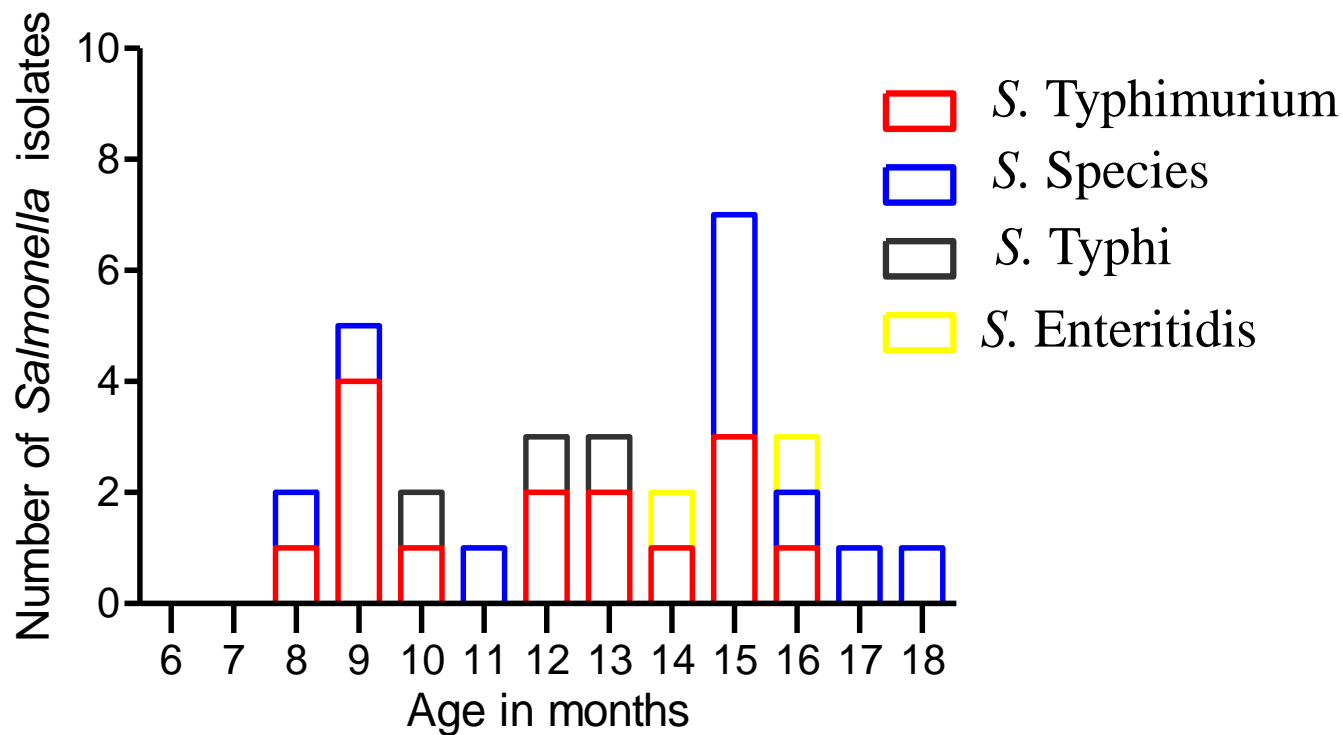
Hypothesis 2

Salmonella exposure within the GIT facilitates the acquisition of specific-antibody mediated serum killing

Methods

- Cohort study
- Healthy children (n=60, age 6-18 months)
- Stool culture or PCR for *Salmonella* (1 month interval)
 - PCR targets; FliC (STm) and Fimbriae (STy)
- Serum killing (SBA) (3 months interval)

Frequency of *Salmonella* exposure events

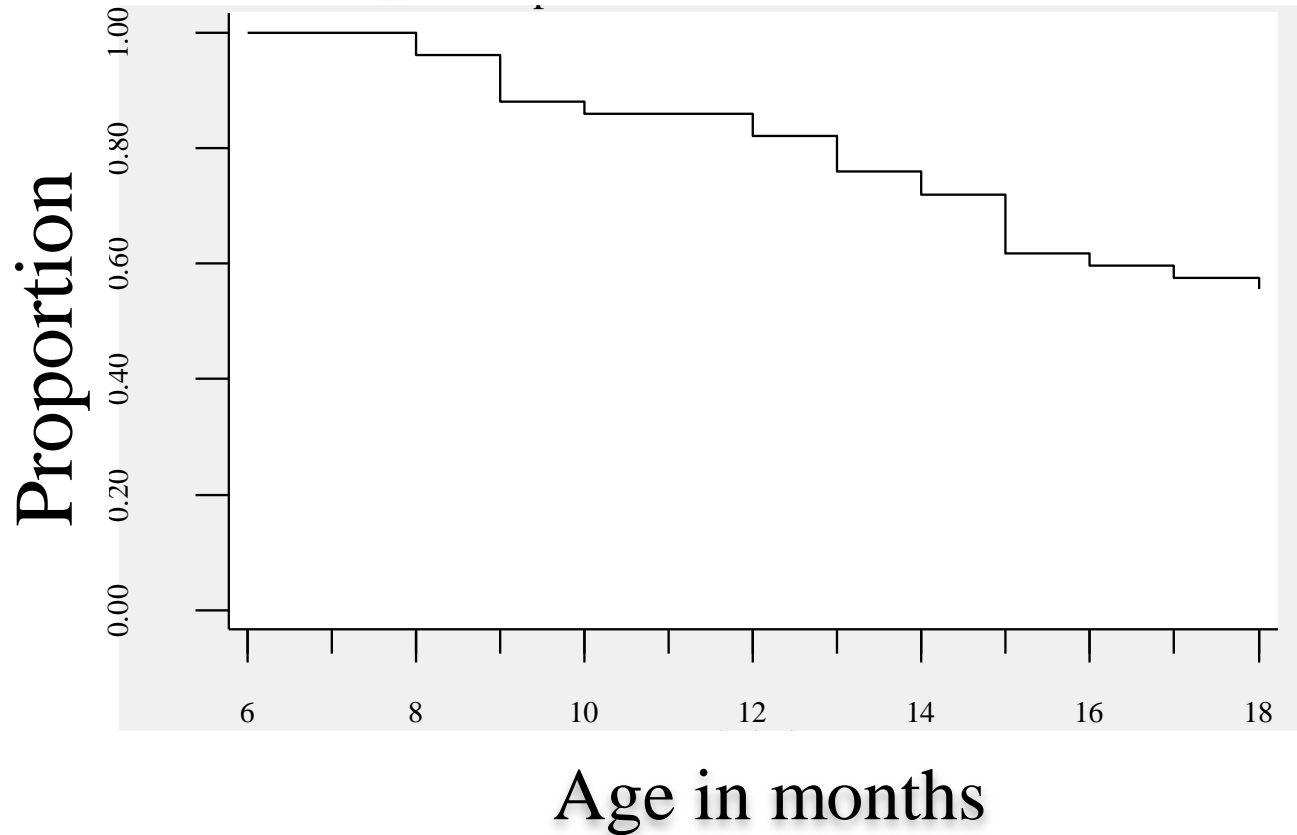


Stool samples tested (630)

- 29 *Salmonella* detected (culture or PCR)
- 23 culture positive
- 6 PCR only (208 samples tested)

Incidence of *Salmonella* within the GIT

Kaplan-Meier survival estimate



- 47% (22/47) exposed to *Salmonella* at least once within the GIT (6-18 months)

Salmonella exposure within GIT is associated with acquisition of potentially protective SBA

Definition; SBA $\geq -1 \log 10$ (potentially protective)

Age = 6-18 months (N= 229)

Exposed = 35/42

Non exposed = 108/187

OR 3.65 95% CI (1.54, 8.65)

Summary

- Sequential acquisition of T cells and antibodies to STm is associated with a decline of iNTS cases
- *Salmonella* exposure within GIT is associated acquisition of potentially protective SBA
- Children under-two are more vulnerable to iNTS disease and require vaccine intervention

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