Acquisition of Immunity to Non-Typhoidal Salmonella in Malawian Children to Inform Vaccine-Derived Immunity; a Serological Catalytic Model

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5th December 2023, CAT Conference

Overview

Background

Serological catalytic model structure

Model comparison

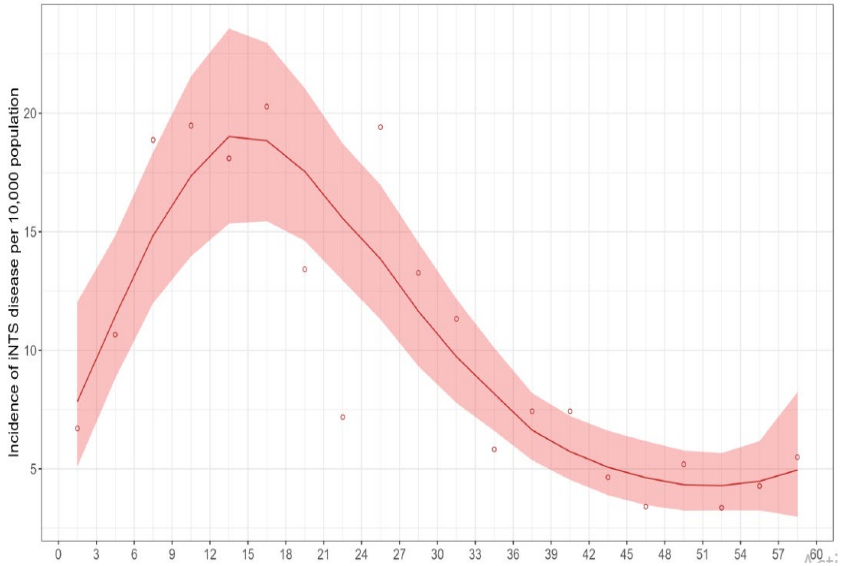
- Constant force of infection
- Changing force of infection by age

Conclusions

Background

- Natural immunity appears to be highly effective
- Anti O-antigen IgG antibodies have been shown to be able to mediate protection in vitro and in animal models[1, 2]
- Antibodies may be useful as correlates of protection
- Asymptomatic enteric NTS infections in the
- community appear to result in protection
- Commonest serovar causing invasive disease in Malawi is *S*. Typhimurium

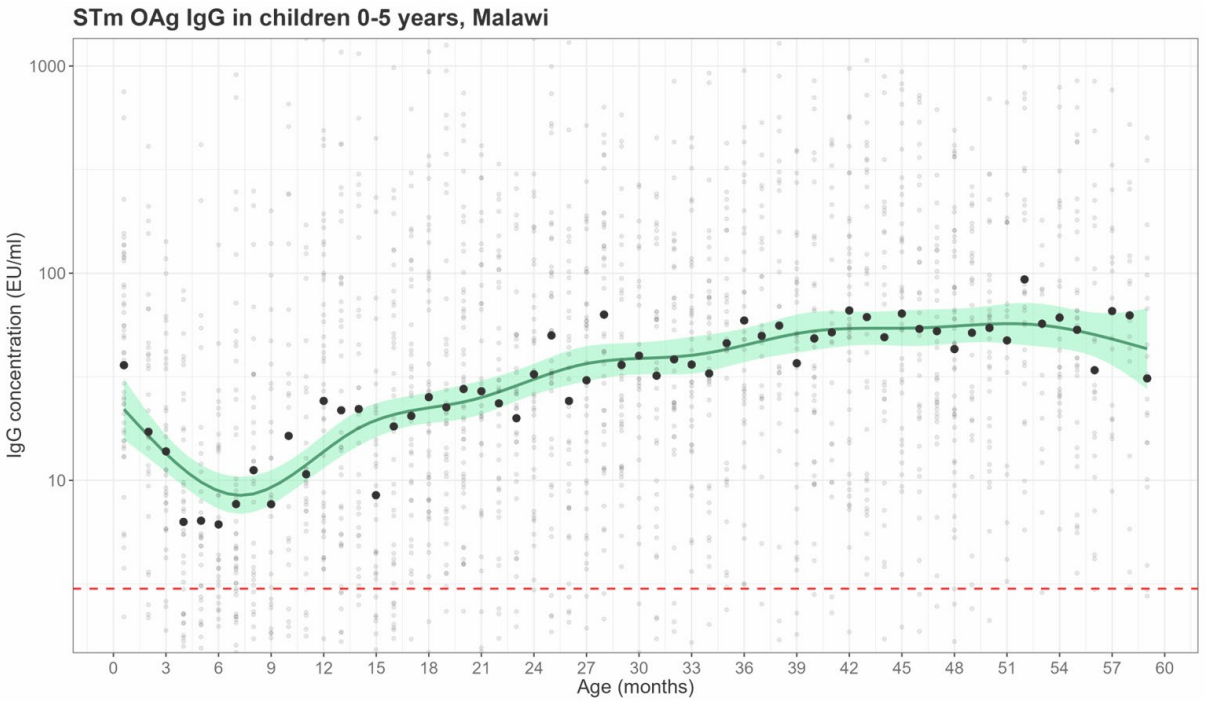
Age incidence of iNTS Blantyre, Malawi, 2010-2021



1. Elsheimer-Matulova M, et al. Vaccine. 2020, 2. Simon R, Infect Immun. 2011

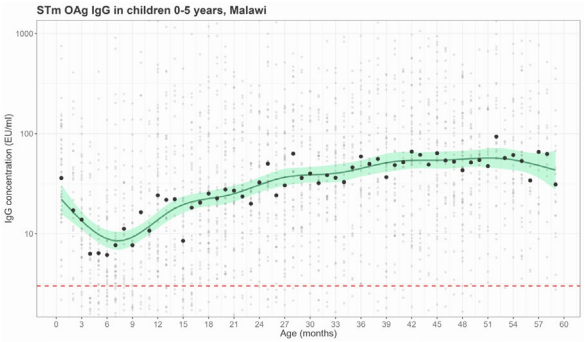
SAINTS study: Malawi

- 2400 children (paired serum samples)
- Randomly sampled from community census
- ELISA *S.* Typhimurium OAg LPS[3]
- Additional samples:
  - Stool MC&S/ PCR/ sequencing
  - Malaria (MRDT/ film)
  - Anaemia (Hb)
  - Malnutrition (MUAC/ z-score)



3. Aruta MG, et al. BioTech. 2023

Serological Catalytic Model for Geometric Mean Concentration (GMC) of STm OAg IgG acquisition by age



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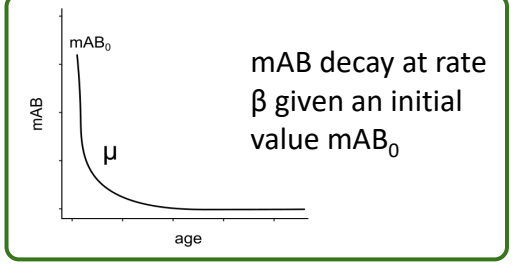
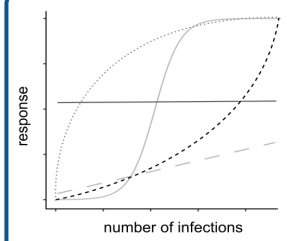
age number of infections

$$GMC(a, ni) = mAB(a) + \Phi(\theta(a))$$



mAB decay at rate β given an initial value mAB_0



induction of IgG by a person who has experienced *i* infections

Generalised logistic curve can take any shape

Estimated **number of exposures *θ*** for individuals at age *a*

Adaptation to models for pneumococcal carriage and immunity J. Lourenco

Fitting model to data (MCMC)

Three parameters that will be fitted to the data:

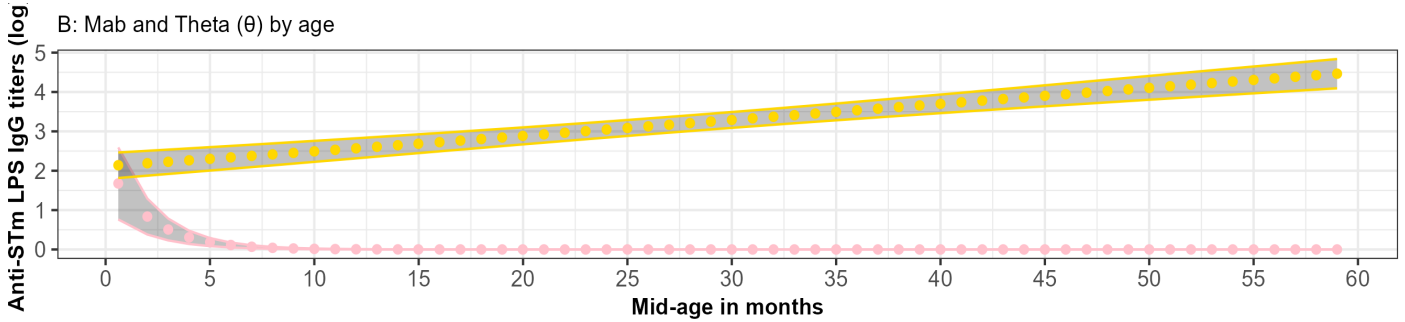
- Initial maternal antibody level
- Growth rate (exponential phase)
- Number of exposures above which the antibody response will enter the growth function

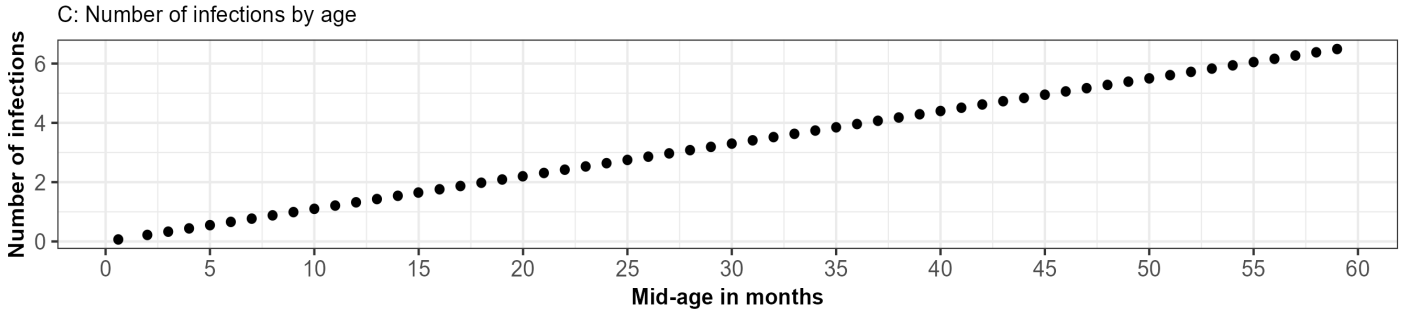
Force of infection (FOI) is assumed to remain constant over time and age

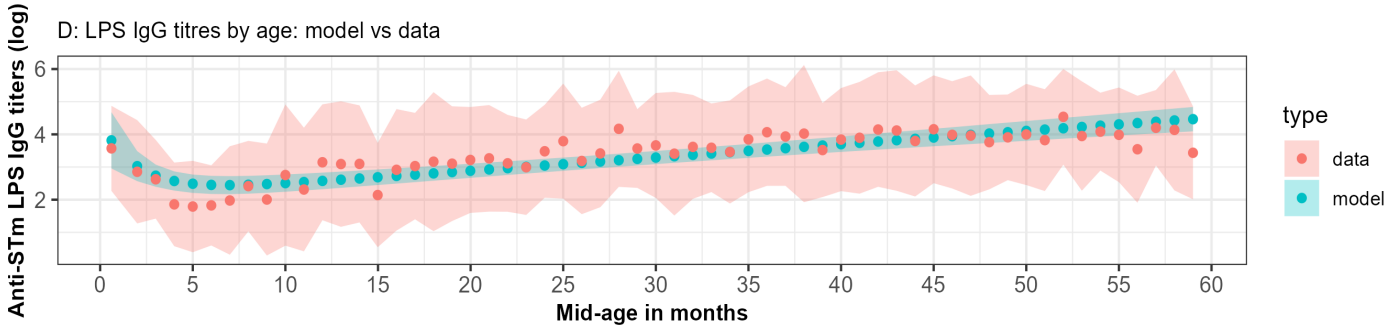
- Limited data from literature[4]

4. Arnold BF, et al. Elife. 2019

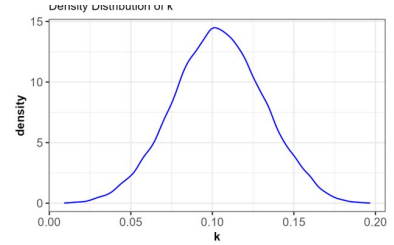
Model 1 components:
Constant FOI



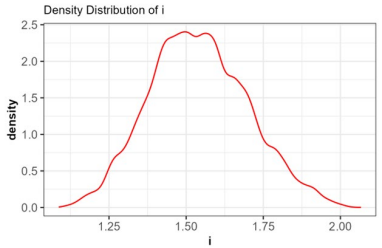




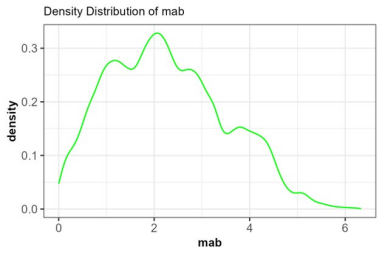
Growth Rate



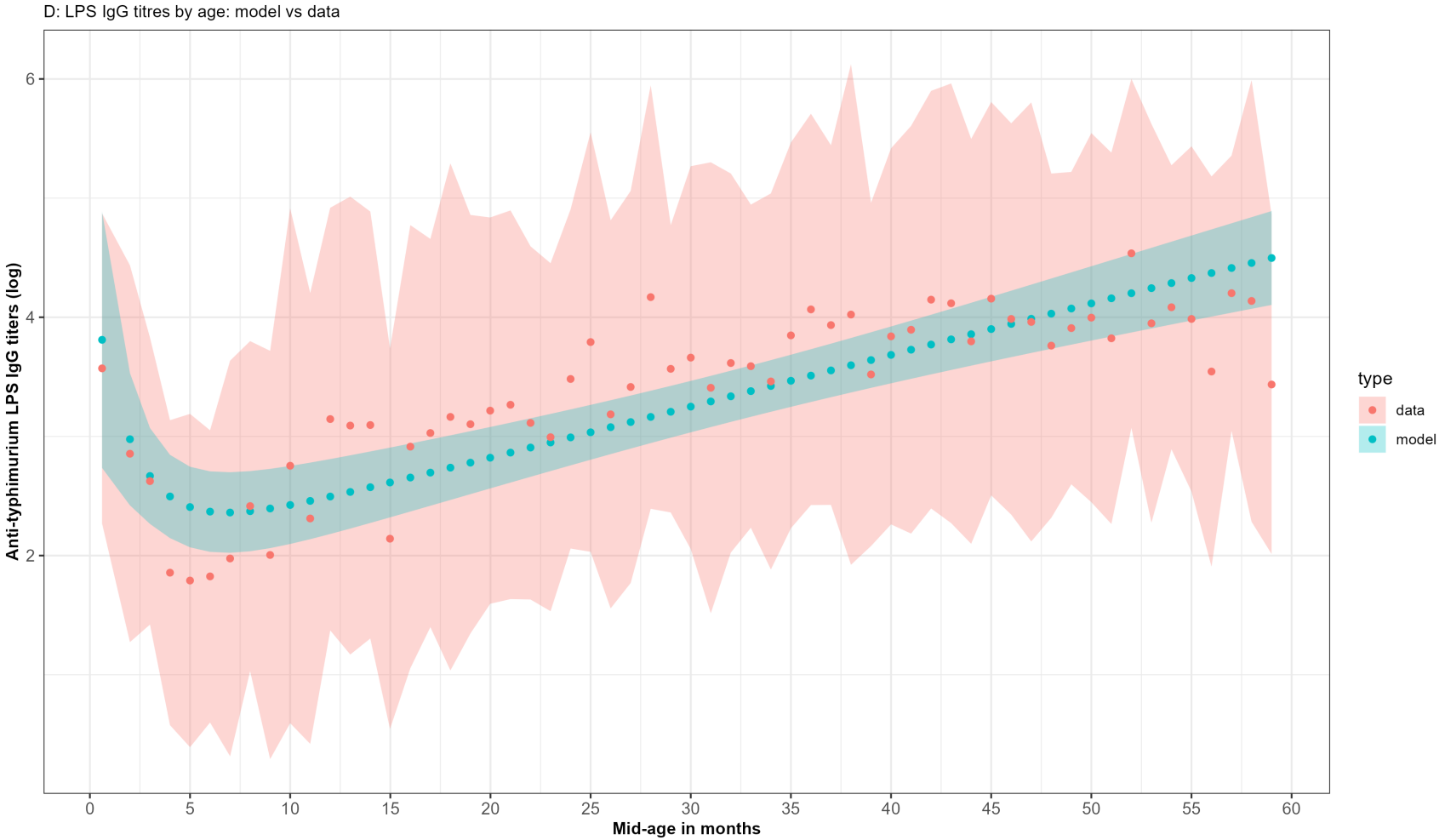
Enter exponential phase



Maternal Ab



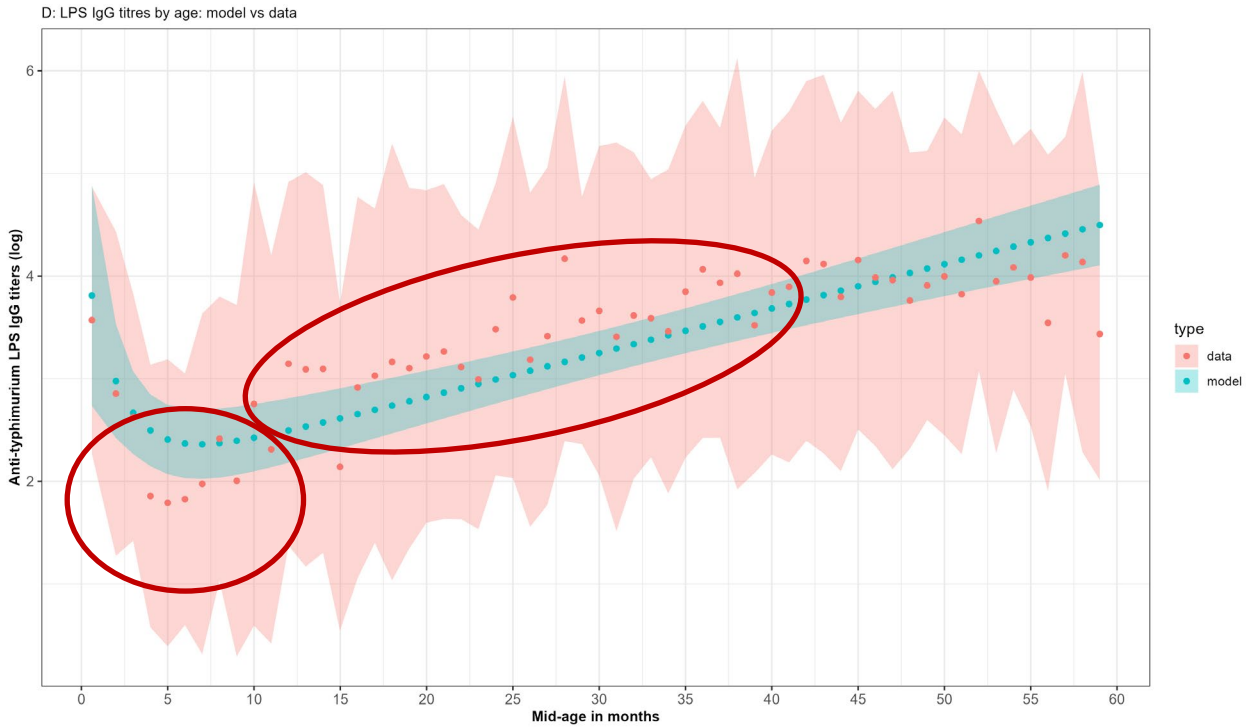
Model 1 fit:
Constant FOI



Problems

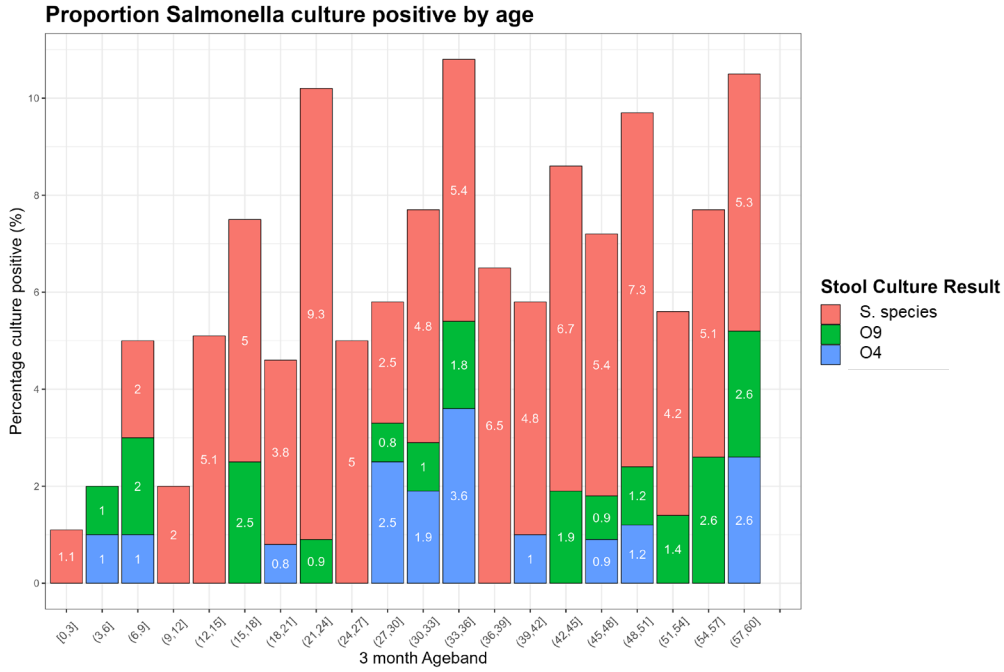
- Not capturing nadir of IgG level or speed of increase of acquisition of antibodies

- Assumption of constant FOI is not correct?

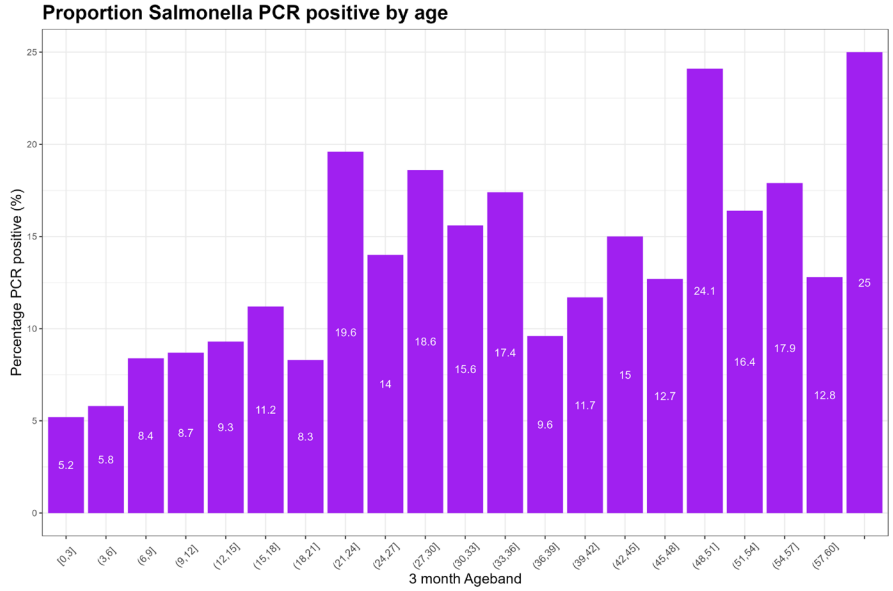


Justification for changing FOI with age

Stool Microbiology



Pan-Salmonella PCR (TTR primer)



Fitting model to data (MCMC)

Four parameters that will be fitted to the data:

- Initial maternal antibody level
- Growth rate (exponential phase)
- Number of exposures above which the antibody response will enter the growth function
- Baseline FOI

Force of infection (FOI) is assumed to vary by age

- Exponential growth at weaning

FOI of other enteric pathogens

Cumulative incidence of Shigella infection and Shigella-attributable diarrhoea episodes in 1715 children in MAL-ED cohort

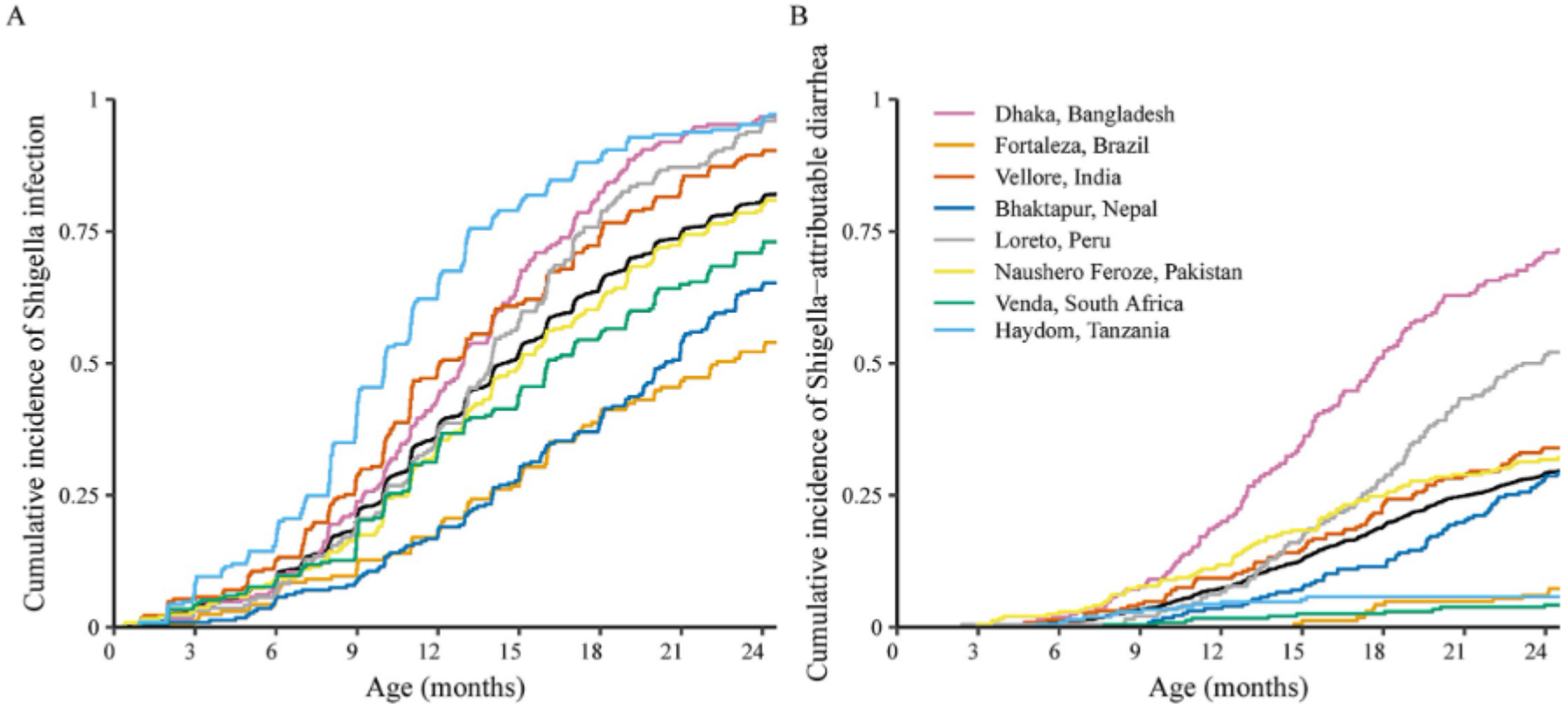
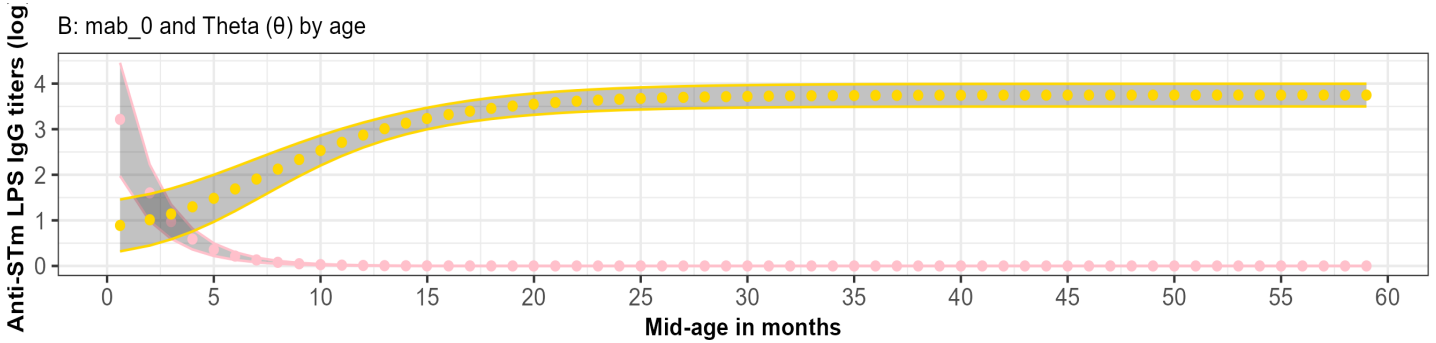
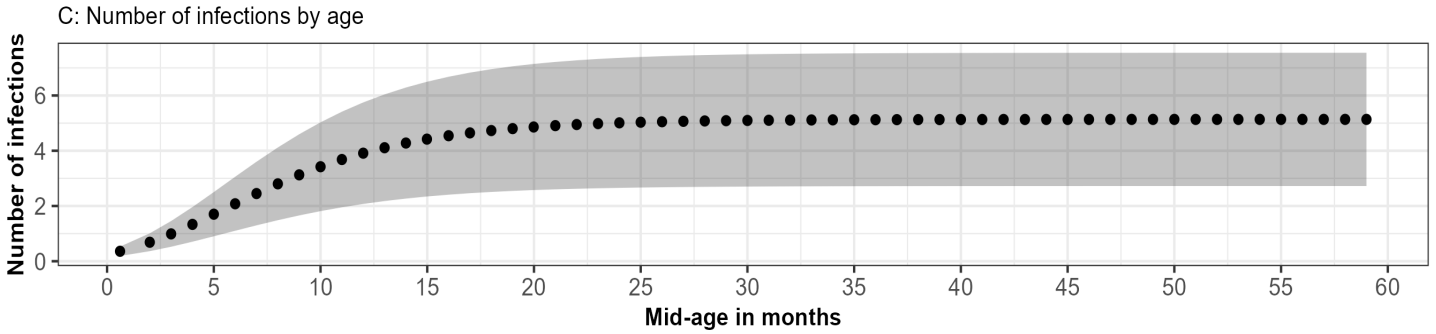


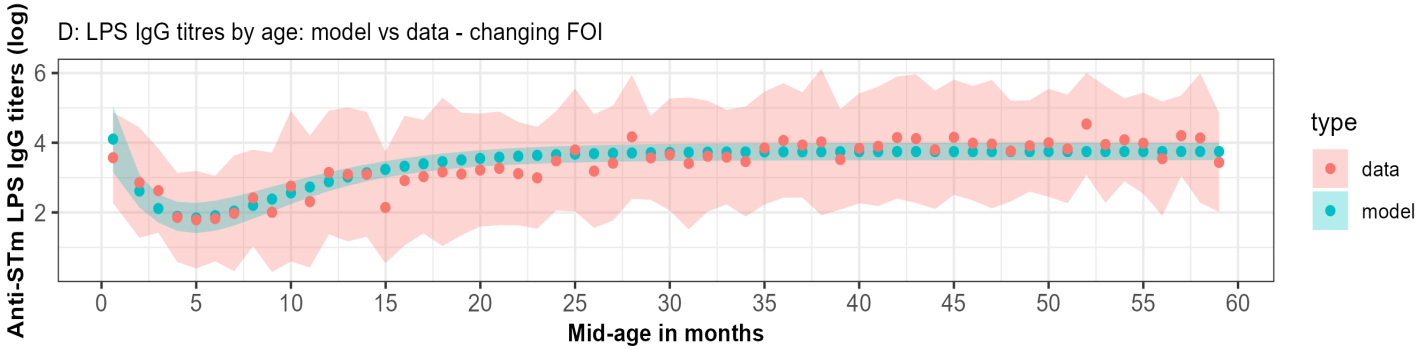
Fig 1. Cumulative incidence of *Shigella* infection (A) and *Shigella*-attributable diarrhea episodes (B) among 1715 children in the MAL-ED cohort.

Model 2 components:

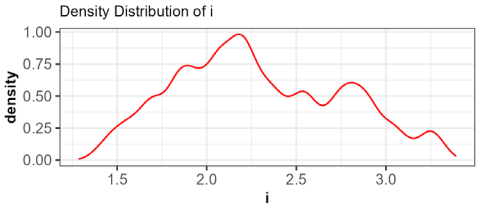
Age-dependent FOI



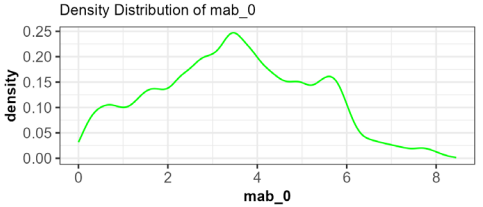




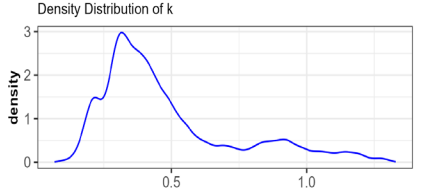
Enter exponential phase



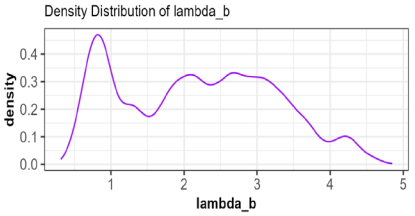
Maternal Ab



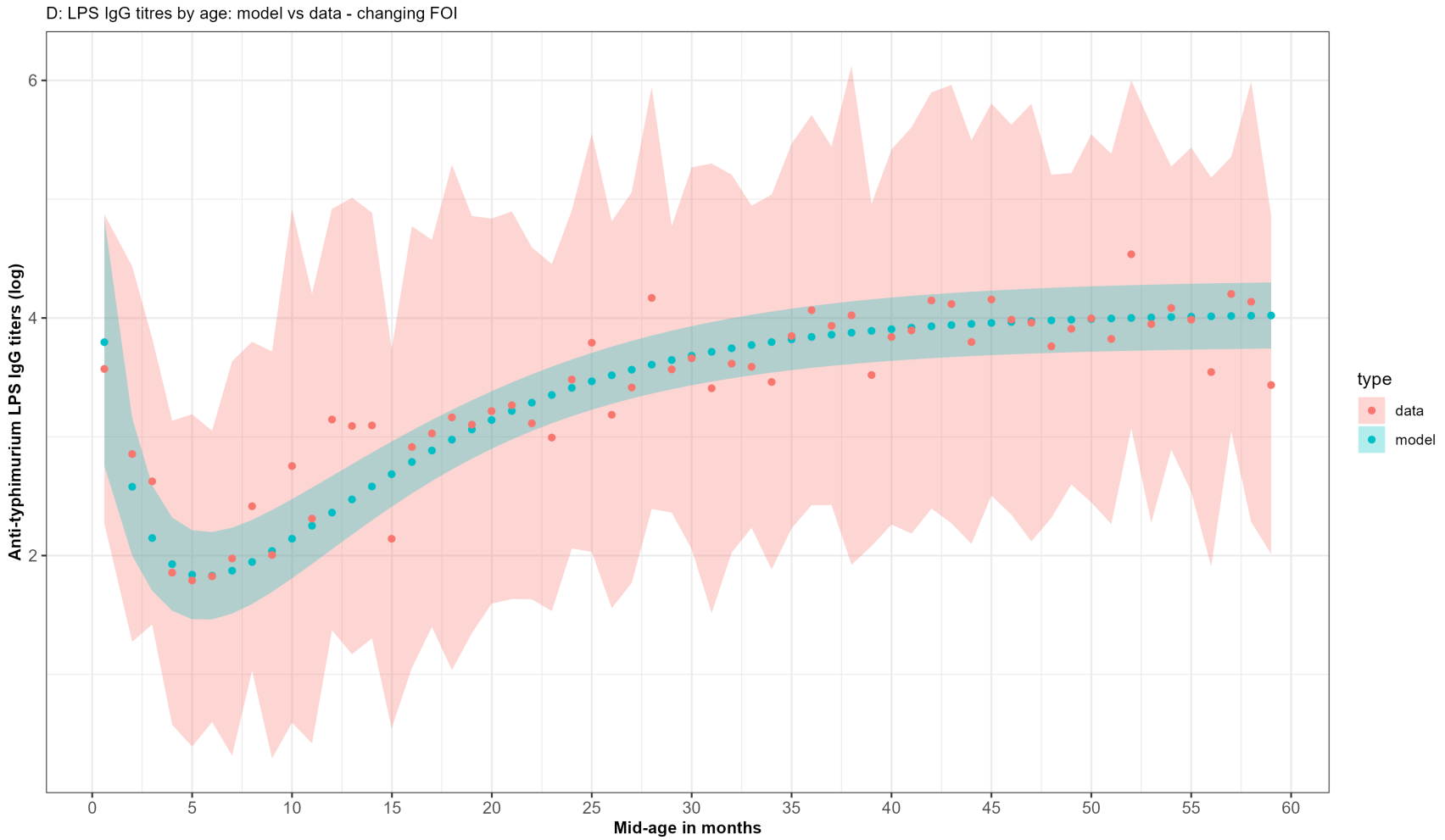
Growth Rate



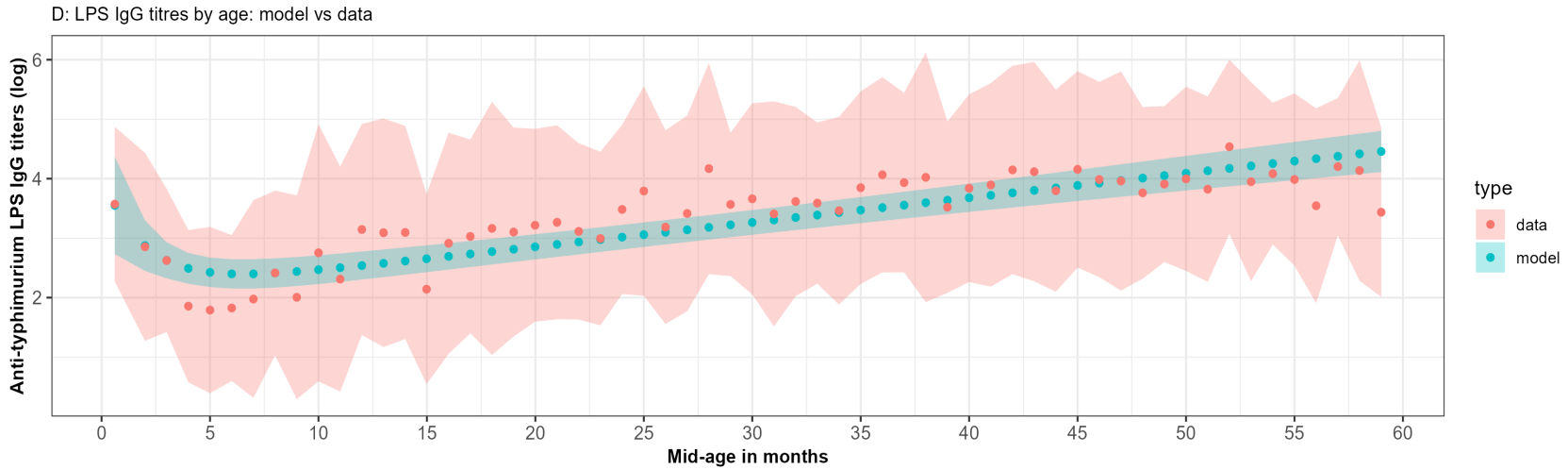
Baseline Lambda

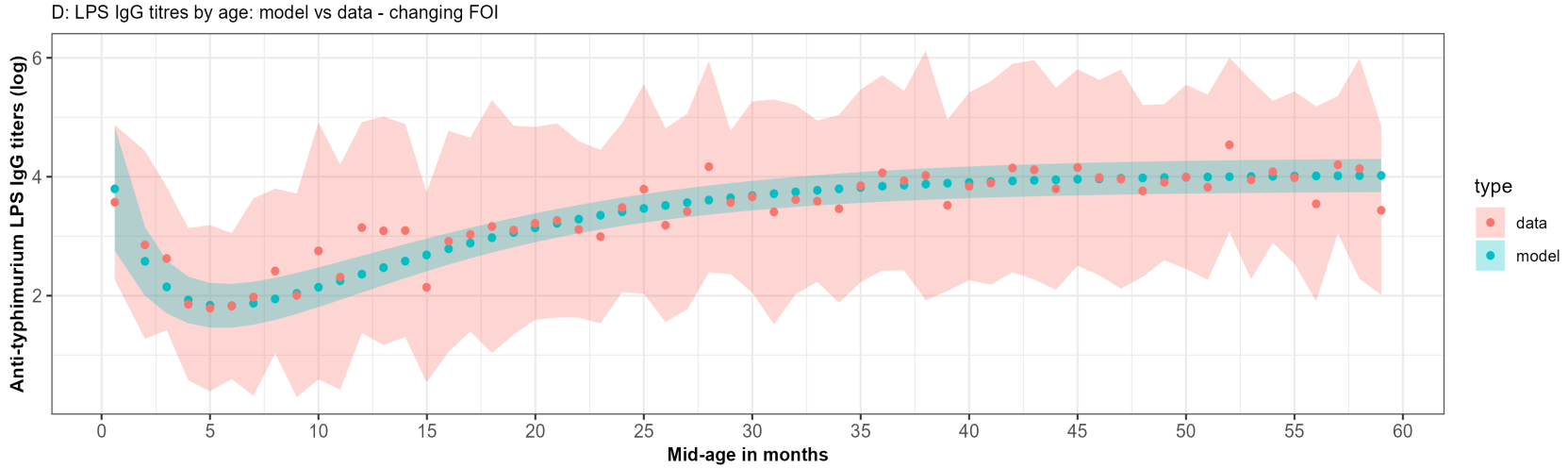


Model 2 fit:
Age dependent FOI



Model 2 selected as best fit (WAIC/ LOO)





Supporting the hypothesis that the relationship of exposure to eNTS is consistent with an age-dependent FOI (sigmoidal)

Conclusions

- Model fit was improved assuming FOI increased around age of weaning (4-6 months)
- Consistent with the observed age-stratified point prevalence of eNTS detected on stool microbiology in the same study cohort
- Immunity may be derived from asymptomatic S. Typhimurium but may be cross-protection from non-pathogenic NTS strains carrying same O-Ags
- Antibody levels likely reflect exposure to asymptomatic NTS and therefore community protection, rather than reflecting the burden of invasive disease

Next steps

- Modeling age-stratified serological responses versus disease incidence
- Cross-validation considering risk factors and epidemiological setting
- Compartmental models parameterized by output of serocatalytic model

Acknowledgments

Supervisors:
Professor Melita Gordon
Professor Neil French
Dr Tonney Nyirenda
Dr Jose Lourenco
Dr Marc Henion

Lab team:
Innocent Kadwala
Maurice Mbewe
Happy Banda
Niza Silungwe
Kenneth Chizani

Georgina Makuta &
Field team

GVGH:
Omar Rossi
Rocio Canals
Maria Grazia Aruta
Elisa Lari
Daniele De Simone

Data:
Paul Kambiya
Richard Wachepa
Alfred Muyuya

Vacc iNTS

wellcome

GSK

Thank You!

References

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Maternal antibody

$$mAb = m_s0\, e^{-\beta_s(a)}$$

Where:

- m_s0 = Maternal Ab at baseline (serotype specific)
- e = euler's constant
- β_s = exponential decay (serotype specific)
- a = age

Natural acquisition of IgG

$$\Phi(\theta(a))$$

Φ = relationship between number of exposures and induction of IgG

θ = number of exposures experienced at age (a)

Natural acquisition of IgG

Using Gompertz function for growth, which exhibits exponential decay of relative growth rate:

$$f(t) = ce^{-ke^{-rt}}$$

Where

- c = upper asymptote (carrying capacity) of f(t): $lim_{t\to\infty} ke^{-ce^{-rt}} = ke^0 = k$
- e = Euler's constant
- k = sets displacement along the x-axis (translates graph to left or right)
- r = sets the growth rate (y scaling)
- t = time

Calculate natural acquisition of IgG to OAg LPS

Using Gompertz function, can calculate acquisition of IgG with age (Φ)**:**

$$\Phi\left(i_s, ks, \theta(a)\right) = ce^{-i_s e^{-k_s \theta(a)}}$$

Where:

- θ(a) = average number of serotype-specific (s) exposures experienced by age a
- c = will be set at constant as highest antibody titre measured in the population - if had an infinite number of exposures this would be the plateau of antibody response (upper asymptote/ carrying capacity of f(Φ))
- k_s = growth rate (y scaling)
- i_s = age (months) above which antibodies begins to enter exponential phase (displacement along x-axis)
- e = Euler's constant
- a = age

Number of exposures

$$\theta = \lambda(a)$$

Where:

- θ = number of exposures
- λ = lambda
- a = age

Force of infection assumed to be constant:

- By age
- Over time

} ?valid assumption

Changing FOI with age

Gompertz formula to model increased risk of infection at weaning age

$$\theta = \lambda_0 m e^{-we^{-ra}}$$

Where:

- θ = number of exposures
- λ_0 = baseline force of infection
- m = upper limit of new infections by age 60 months (scaled to 1 to make gompertz into probability distribution (0 to 1))
- e = Euler's constant
- w = age in months before enter exponential phase (x-axis displacement) - weaning
- r = exponential phase/ growth rate -> enter high feco-oral transmission after weaning age
- a = age