Longitudinal analyses of serological data

May 23, 2025

Seroanalytics Training
Blantyre, Malawi

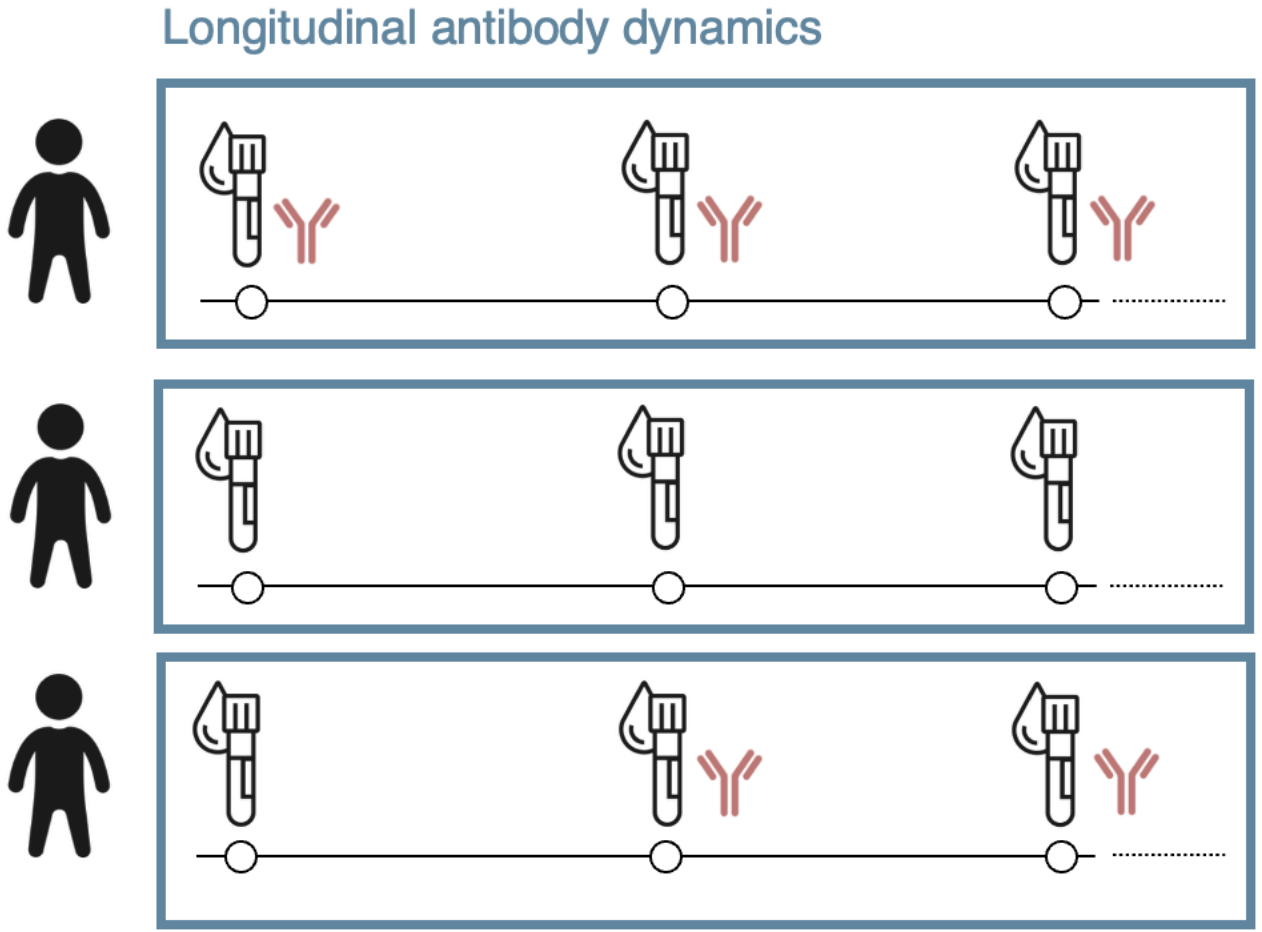
Outline

- Longitudinal data
- Antibody kinetics
- Value of analyses of quantitative titers

Reminder: longitudinal data

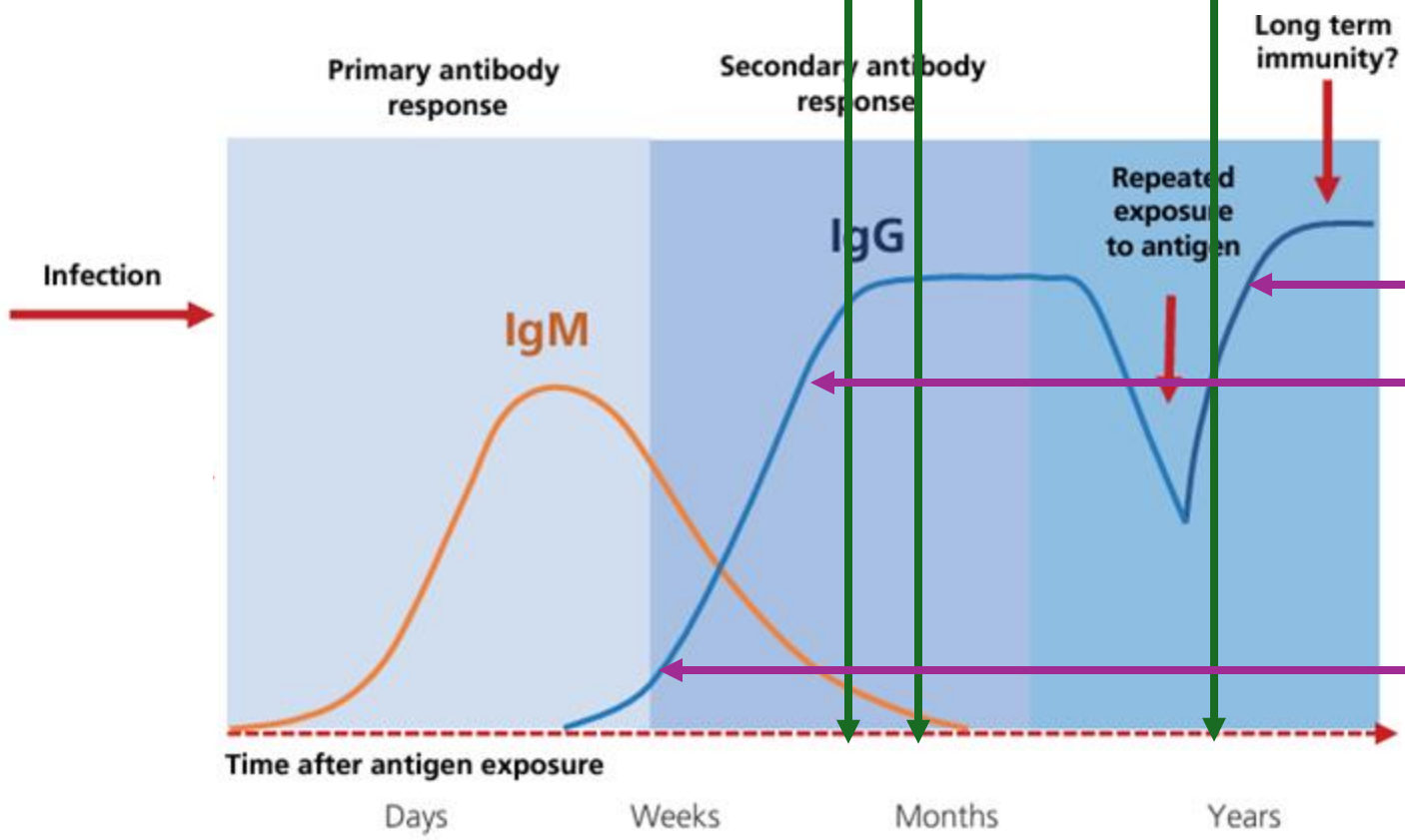
(From Lecture 0)

- Repeated samples from the same individuals
- Could be days, weeks, months, years apart
- Could span various time periods



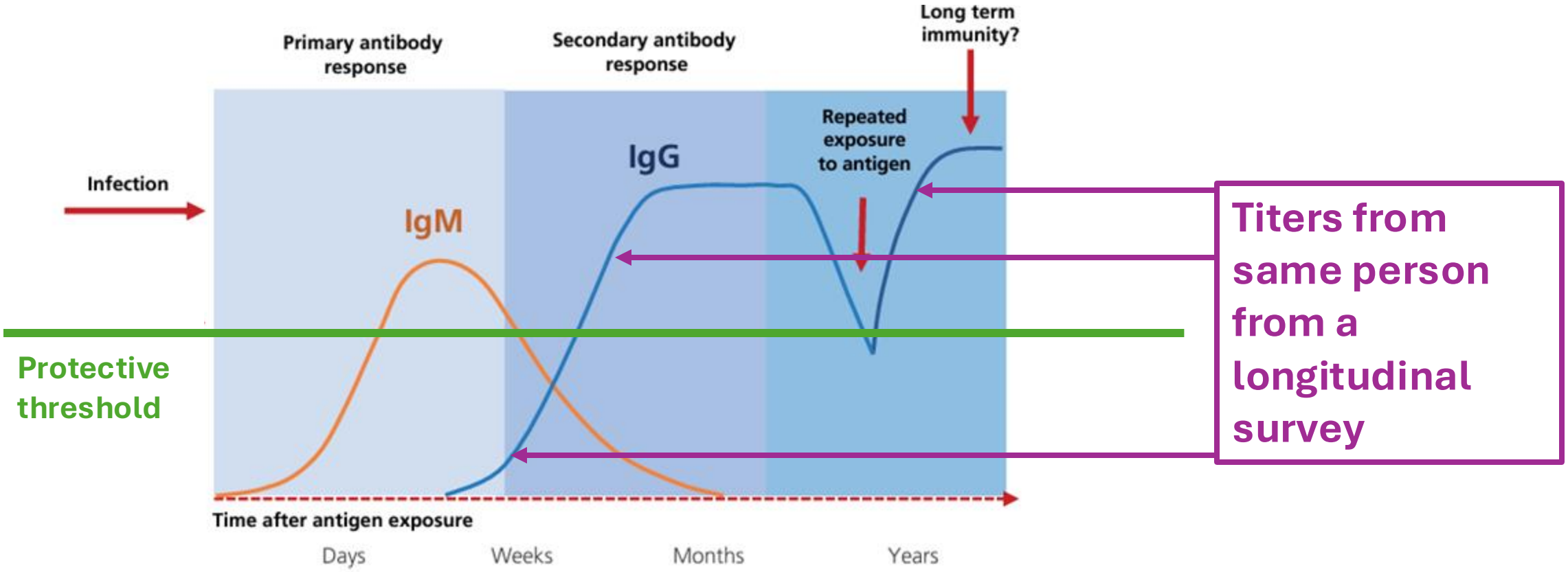
Antibody kinetics

Titers from individual people within cross sectional survey

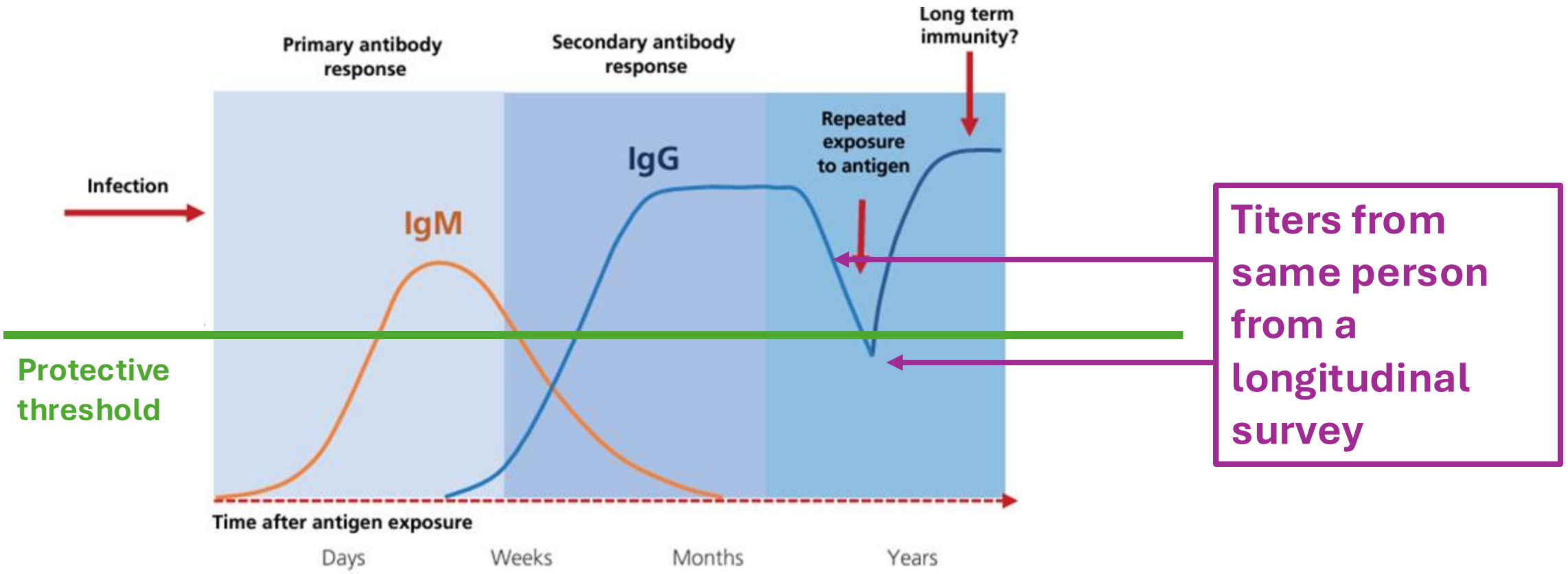


Titers from same person from a longitudinal survey

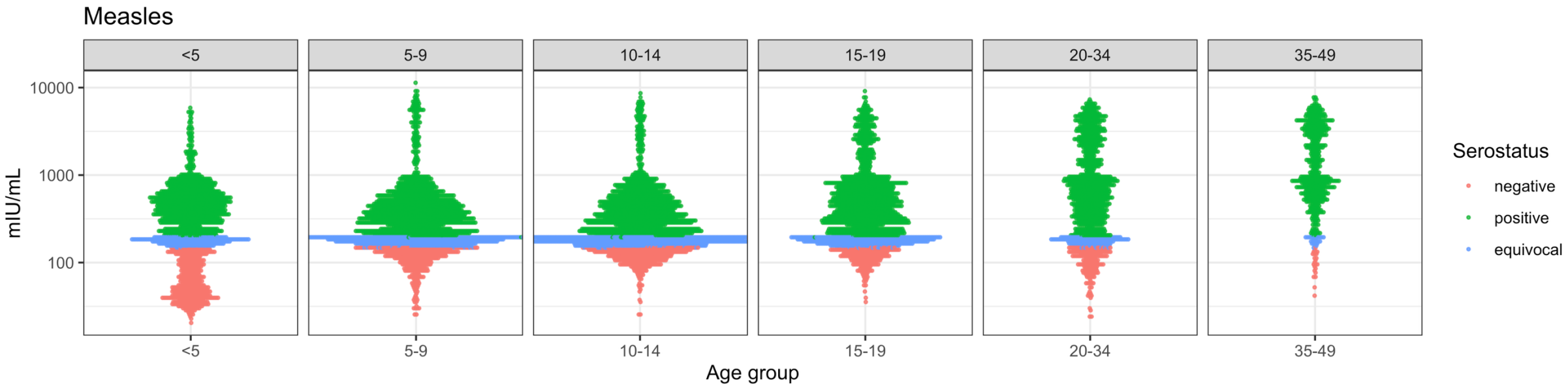
Binary serostatus often does not tell the full story



Binary serostatus often does not tell the full story



Even without longitudinal data, there is still value in analyzing quantitative titers



Carcelen, Winter, *et al*. (2022) *Sci Reports*.

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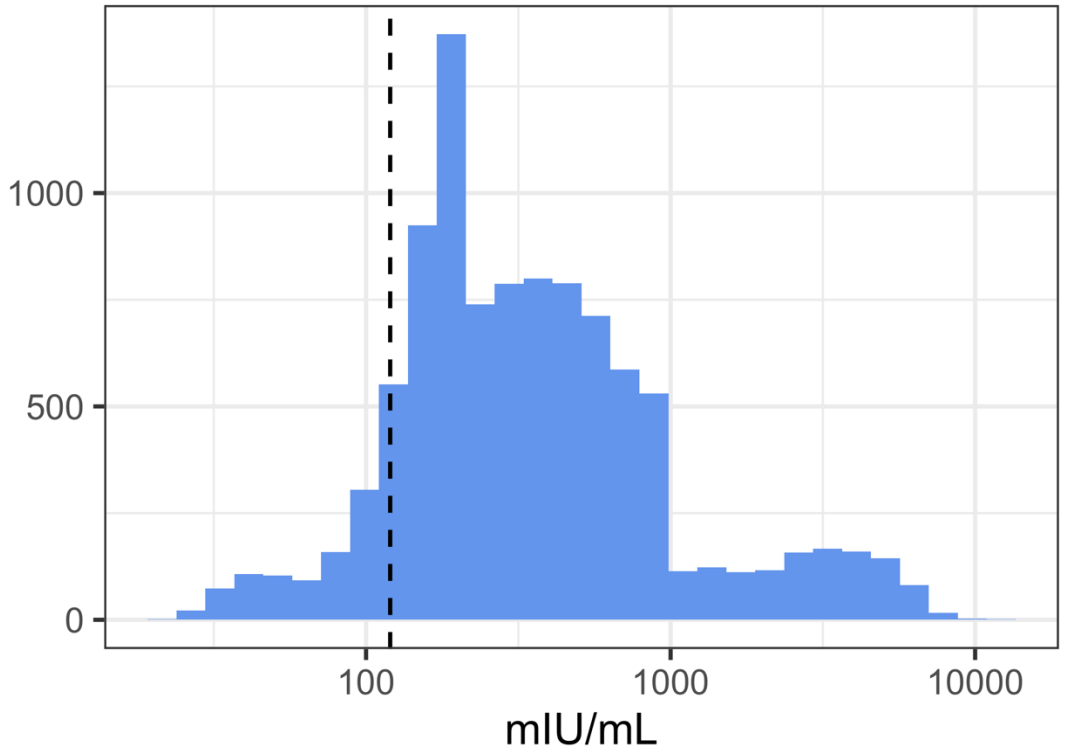
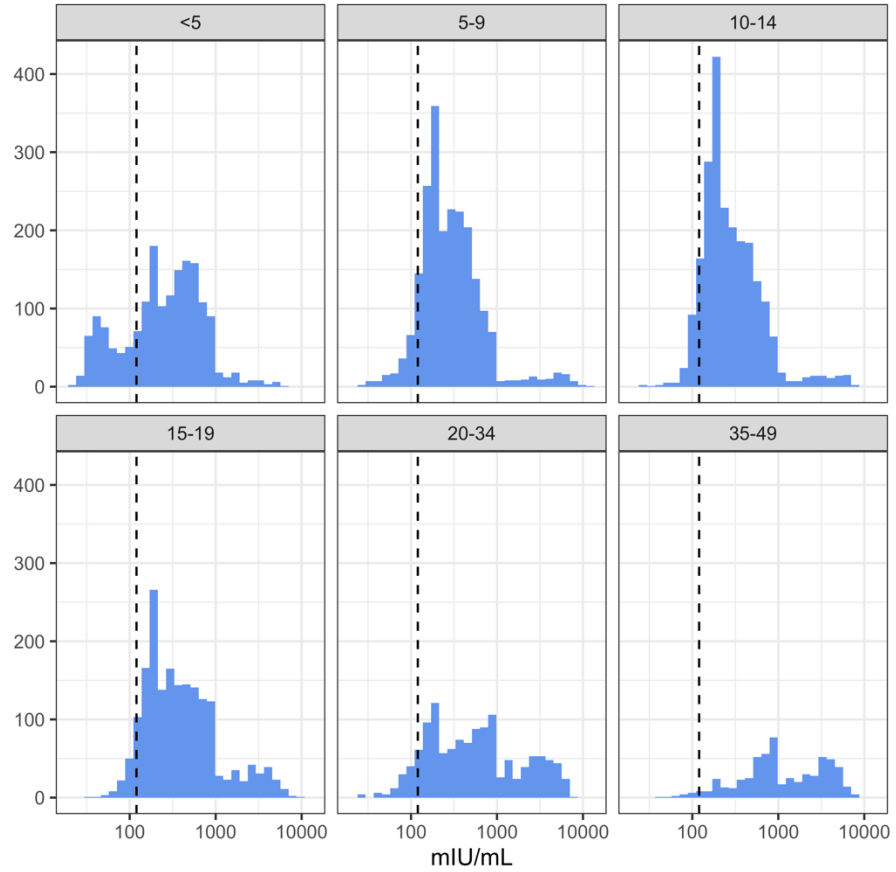




Carcelen, Winter, *et al*. (2022) *Sci Reports*.

Longitudinal data can help us analyze…

- Initial response to infection/vaccination
- Incidence and time-since-infection (TSI)
- Boosting (from exposure or vaccination)
- Waning or decay

Initial response to infection / vaccination

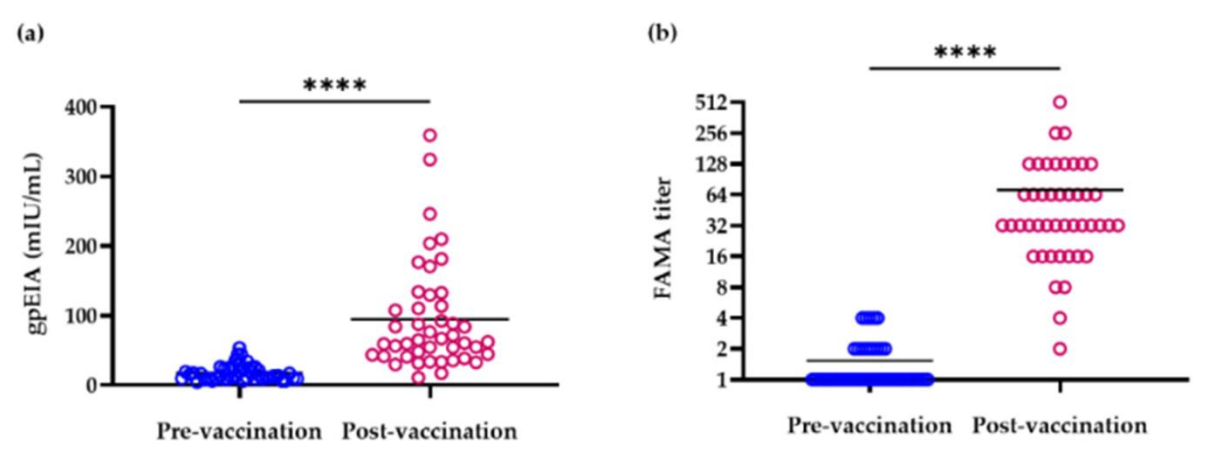
Including immunogenicity studies

Open Access Article

Cross-Sectional Study of Varicella Zoster Virus Immunity in Healthy Korean Children Assessed by Glycoprotein Enzyme-Linked Immunosorbent Assay and Fluorescent Antibody to Membrane Antigen Test

by Yunhwa Kim [1], Ji-Young Hwang [1], Kyung-Min Lee [1], Eunsil Lee [2] and Hosun Park [1,3,*]

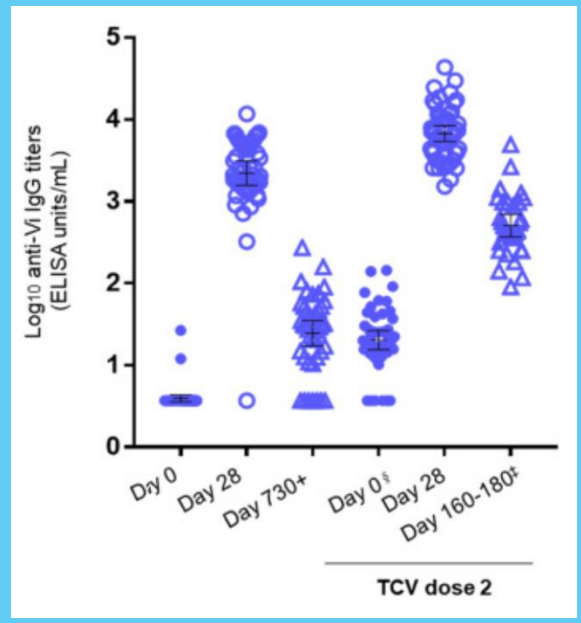
[1] Department of Microbiology, College of Medicine, Yeungnam University, Daegu 42415, Korea
[2] Department of Pediatrics, College of Medicine, Yeungnam University, Daegu 42415, Korea
[3] Immunogenicity Evaluation Laboratory, Clinical Trial Center, Yeungnam University Medical Center, Daegu 42415, Korea
* Author to whom correspondence should be addressed.



Immunogenicity and reactogenicity of a booster dose of a typhoid conjugate vaccine (TCV) in Malawian pre-school children

Nginache Nampota-Nkomba,[a,b] Osward M. Nyirenda,[a] Shrimati Datta,[b] Victoria Mapemba,[a] Priyanka D. Patel,[c] Theresa Misiri,[c] Felistas Mwakiseghile,[c] John M. Ndaferankhande,[c] Bright Lipenga,[c] Jennifer Oshinsky,[b] Marcela F. Pasetti,[b] Leslie P. Jamka,[b] Melita A. Gordon,[c] Matthew B. Laurens,[b] and Kathleen M. Neuzil,[b,d,*] on behalf of the TyVAC team

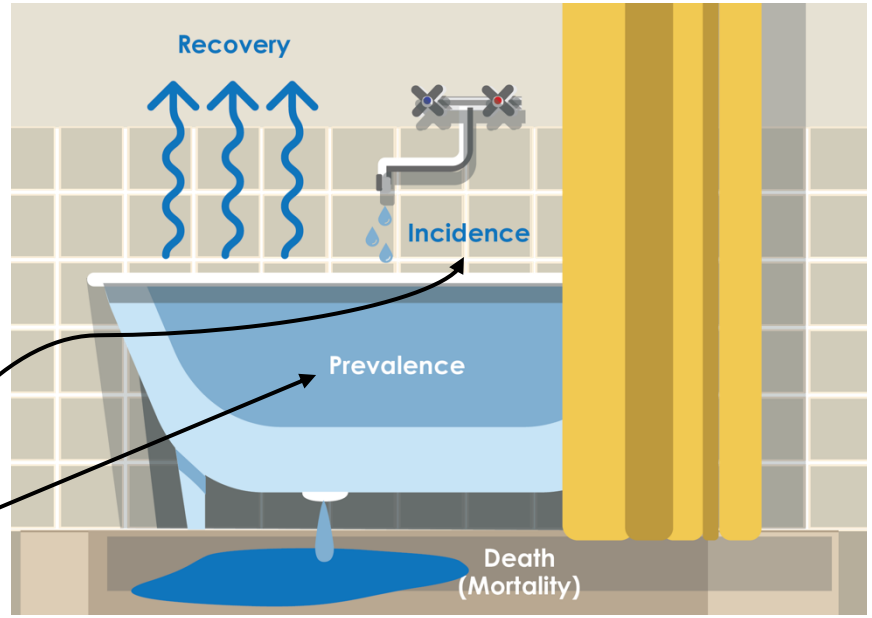
[a]Blantyre Malaria Project, Kamuzu University of Health Sciences, Blantyre, Malawi
[b]Center for Vaccine Development and Global Health, University of Maryland School of Medicine, Baltimore, MD, United States
[c]Malawi-Liverpool-Wellcome Program, Kamuzu University of Health Sciences, Blantyre, Malawi
[d]Fogarty International Center, National Institute of Health, Bethesda, MD, United States

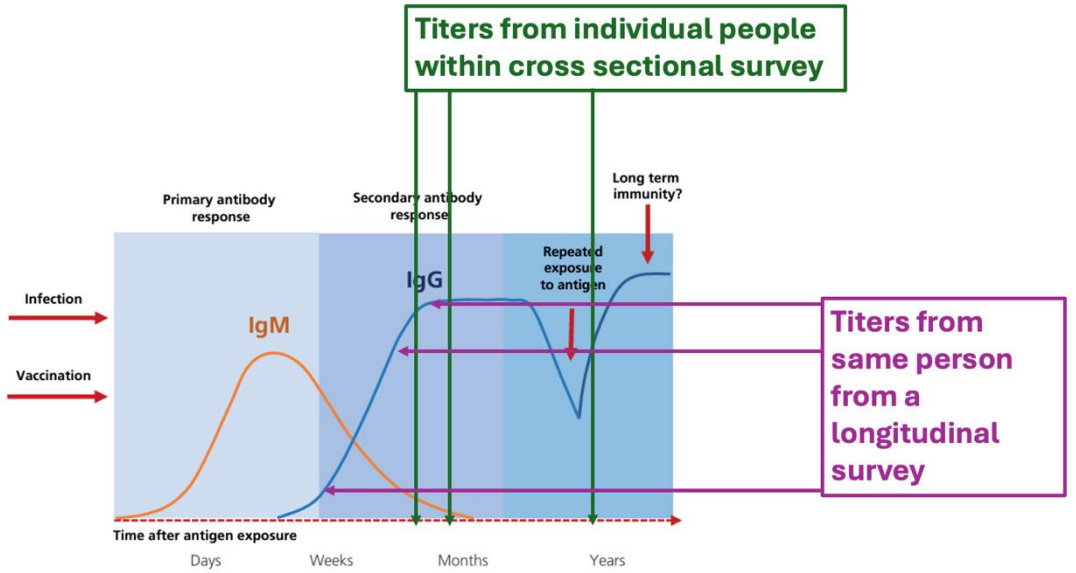


Seroincidence estimation

- Cross sectional data can show us the proportion of people seropositive / above some threshold at any given time
  - **This is a metric of prevalence**

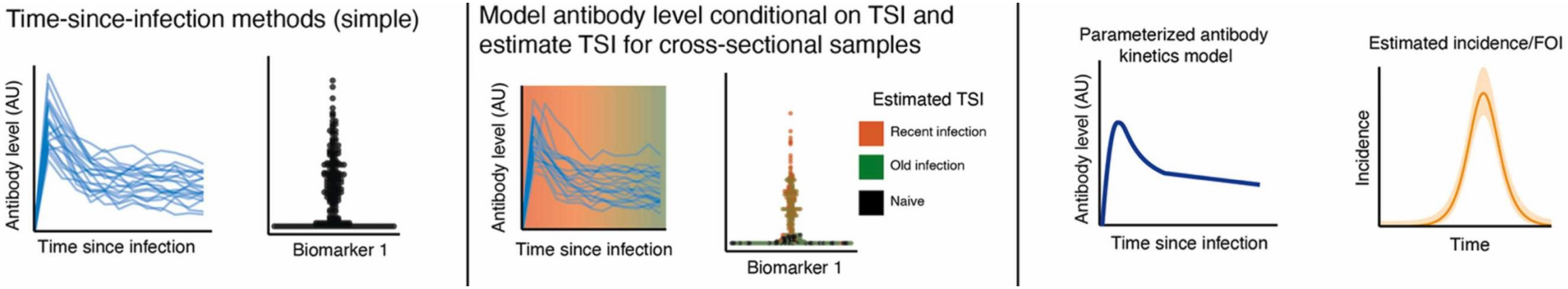
- Longitudinal data can show us changes within individuals in the population which allows us to estimate new infection/exposure
  - **This is a metric of incidence**



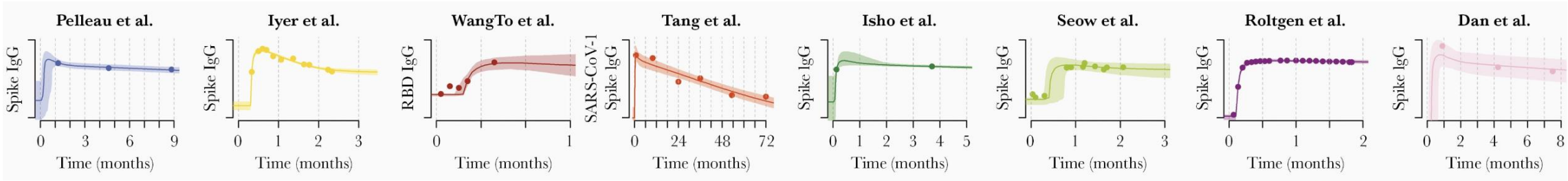


Time-since-infection (TSI)

- Use mathematical model to predict antibody level as a function of TSI (or vaccination)
- Requires longitudinal samples following known exposure
- Can use information from one or more antigens / biomarkers simultaneously



Example: TSI



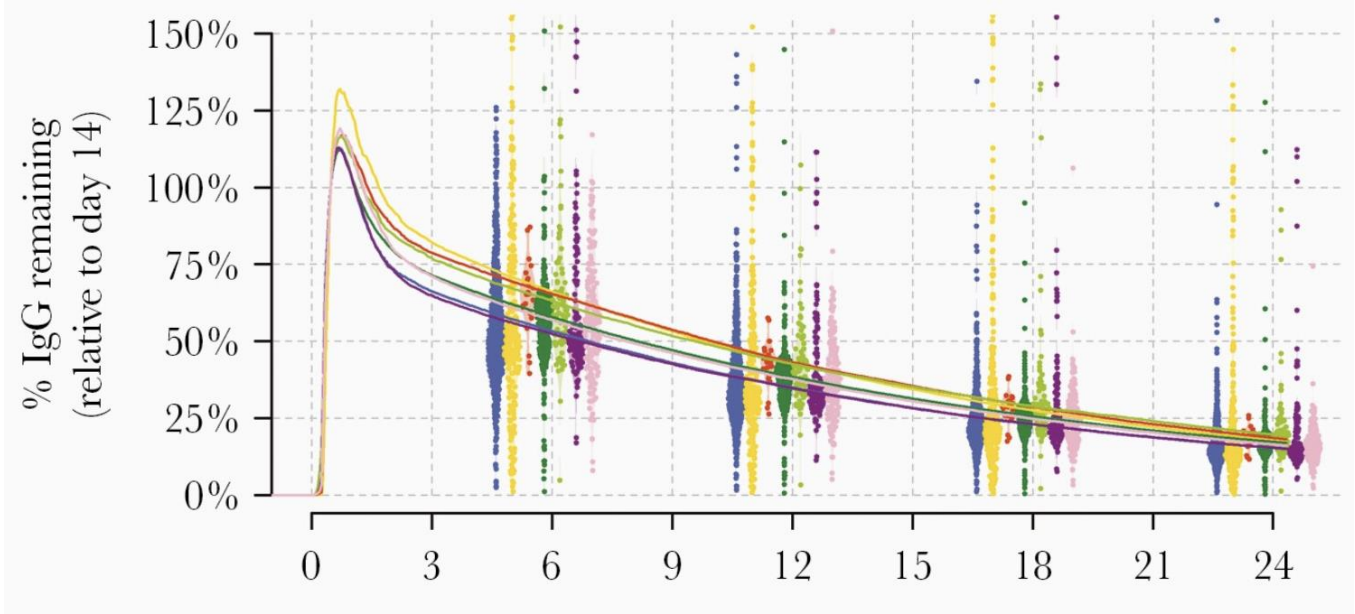
JOURNAL ARTICLE

Kinetics of the Severe Acute Respiratory Syndrome Coronavirus 2 Antibody Response and Serological Estimation of Time Since Infection

Stéphane Pelleau , Tom Woudenberg , Jason Rosado , Françoise Donnadieu , Laura Garcia , Thomas Obadia , Soazic Gardais , Yasmine Elgharbawy , Aurelie Velay , Maria Gonzalez ... Show more

The Journal of Infectious Diseases, Volume 224, Issue 9, 1 November 2021, Pages 1489–1499, https://doi-org.proxy1.library.jhu.edu/10.1093/infdis/jiab375

Published: 19 July 2021 **Article history** ▾



Boosting

- Can use kinetics to understand rate of boosting following vaccination or infection
- Additionally, asymptomatic cases or carriage

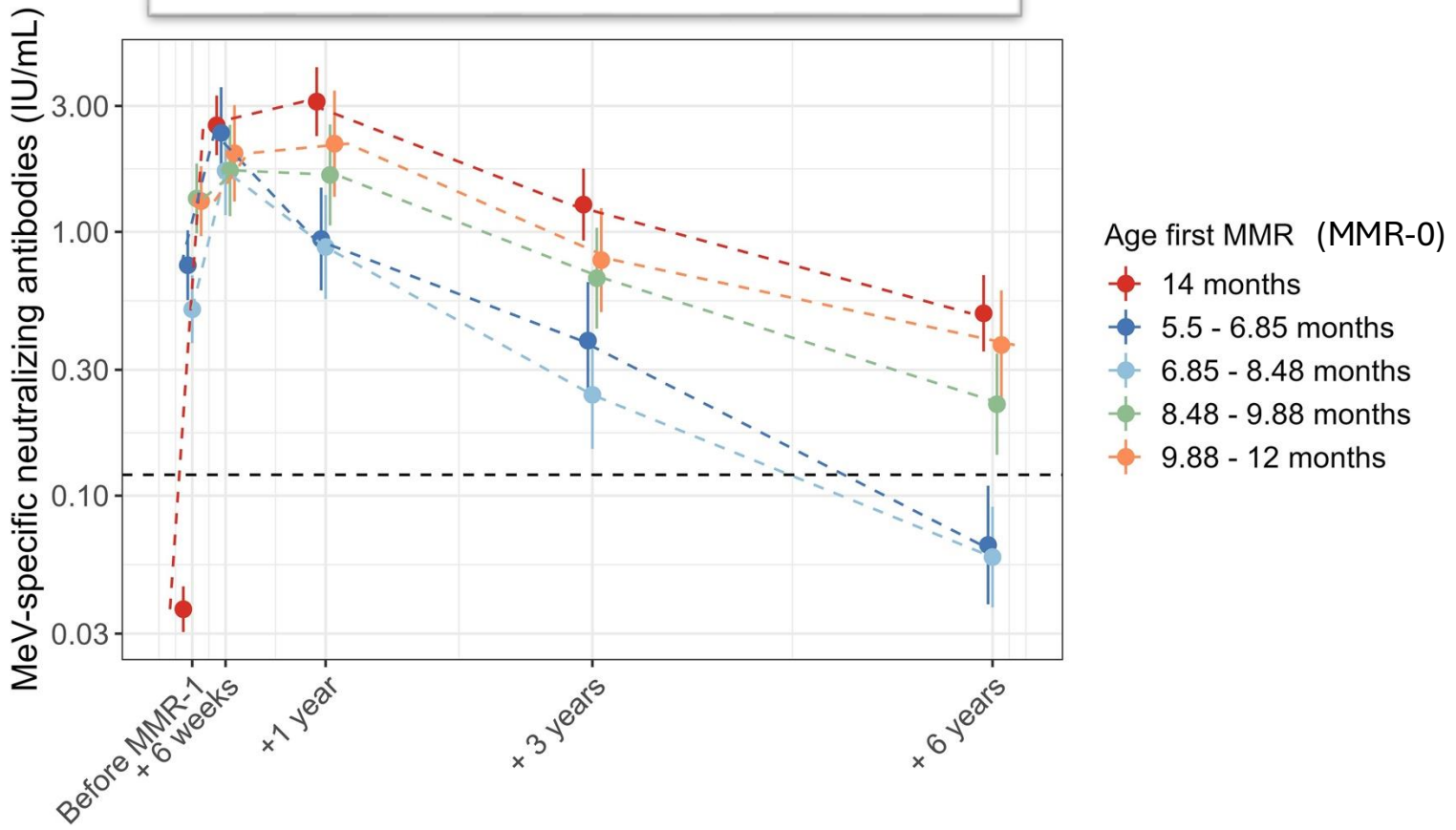
JOURNAL ARTICLE EDITOR'S CHOICE

Long-term Dynamics of Measles Virus–Specific Neutralizing Antibodies in Children Vaccinated Before 12 Months of Age

Maaike van der Staak , Hinke I ten Hulscher , Alina M Nicolaie , Gaby P Smits , Rik L de Swart , Jelle de Wit , Nynke Y Rots , Robert S van Binnendijk ✉ Author Notes

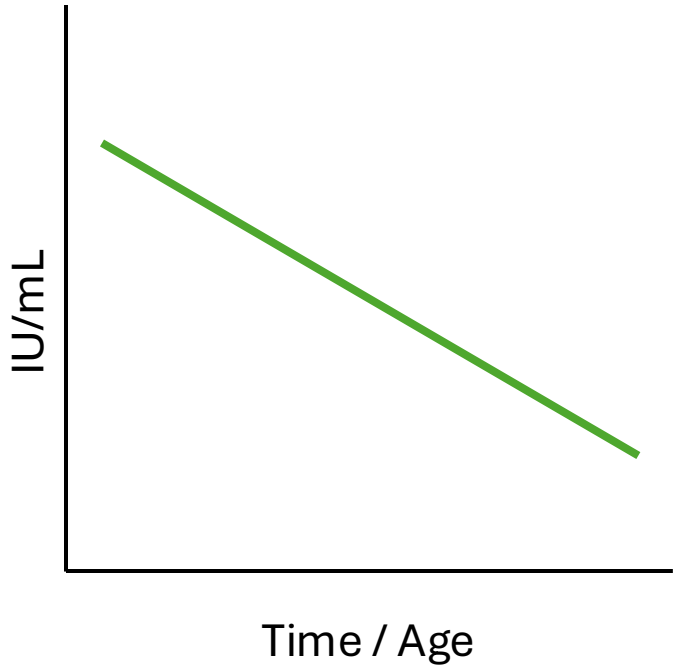
Clinical Infectious Diseases, Volume 80, Issue 4, 15 April 2025, Pages 904–910, https://doi-org.proxy1.library.jhu.edu/10.1093/cid/ciae537

Published: 04 November 2024 **Article history** ▾

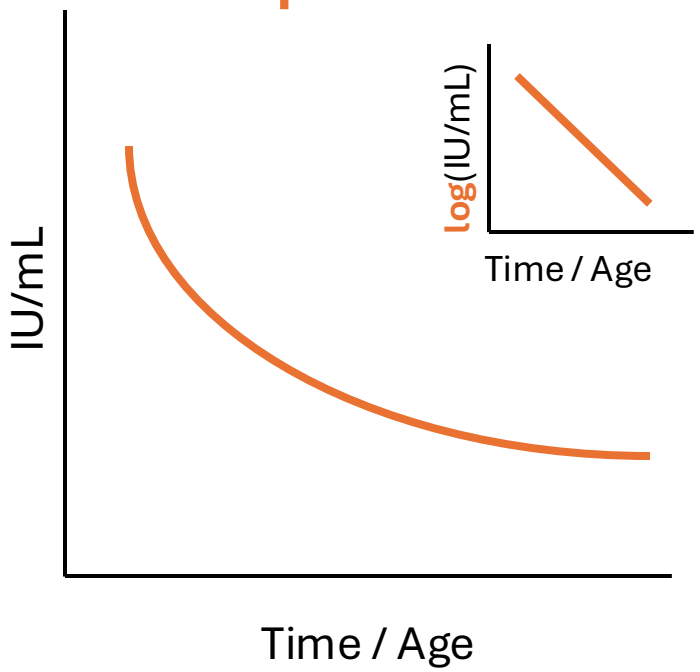


Waning models

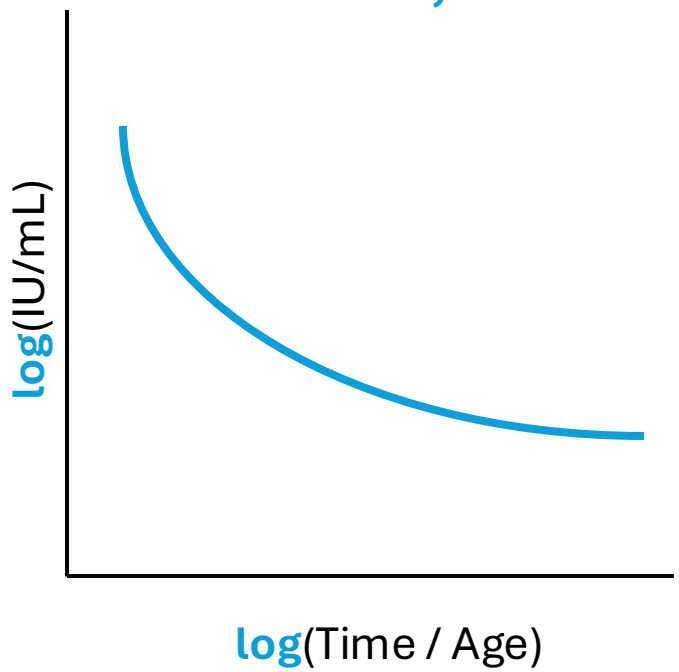
Linear



Exponential

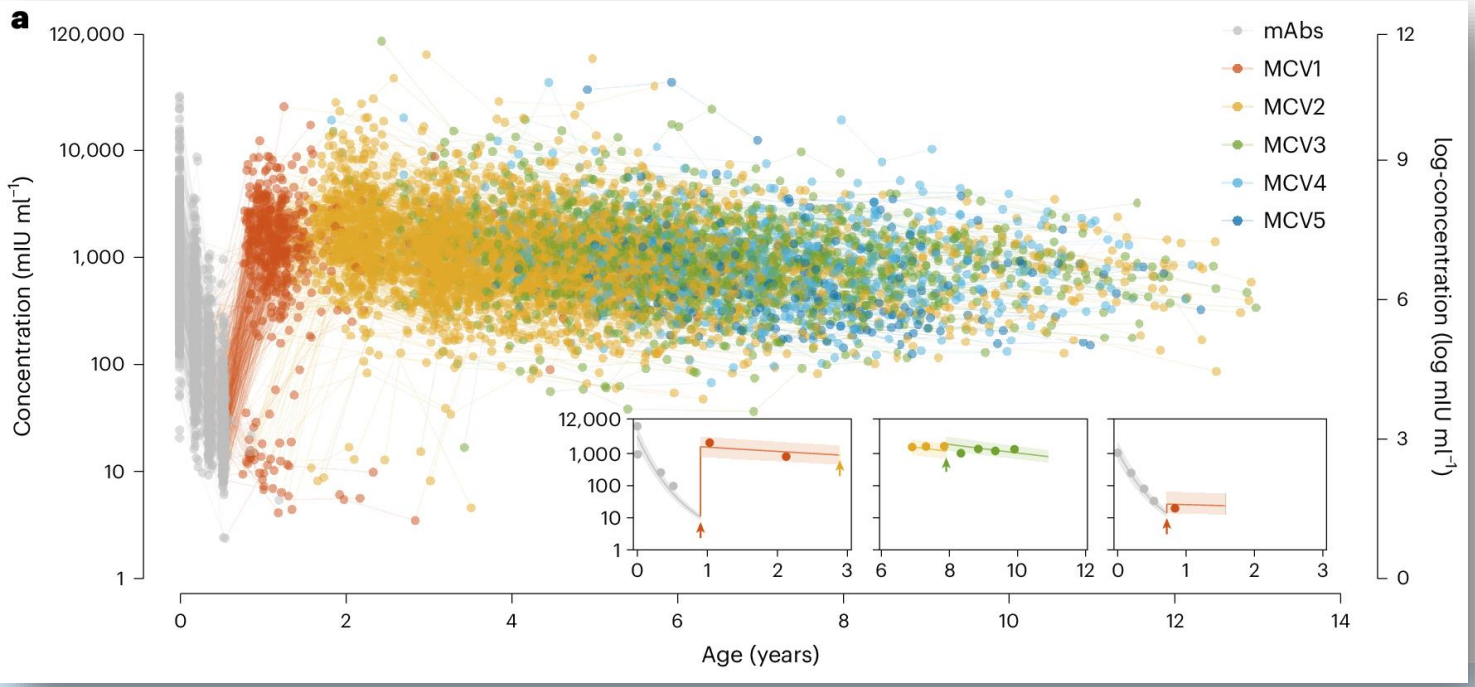


Power, etc…



Application: Longitudinal VPD titers

- **Decay expected, but infrequently quantified**
  - Explicit mechanisms affecting rate of decay hypothesized but also not often quantified (especially in low- and middle-income settings)



Declining measles titers (IU/mL) across age:

- 2 years: 1465 (1353 – 1604)
- 5 years: 889 (837 – 953)
- 8 years: 645 (584 – 713)

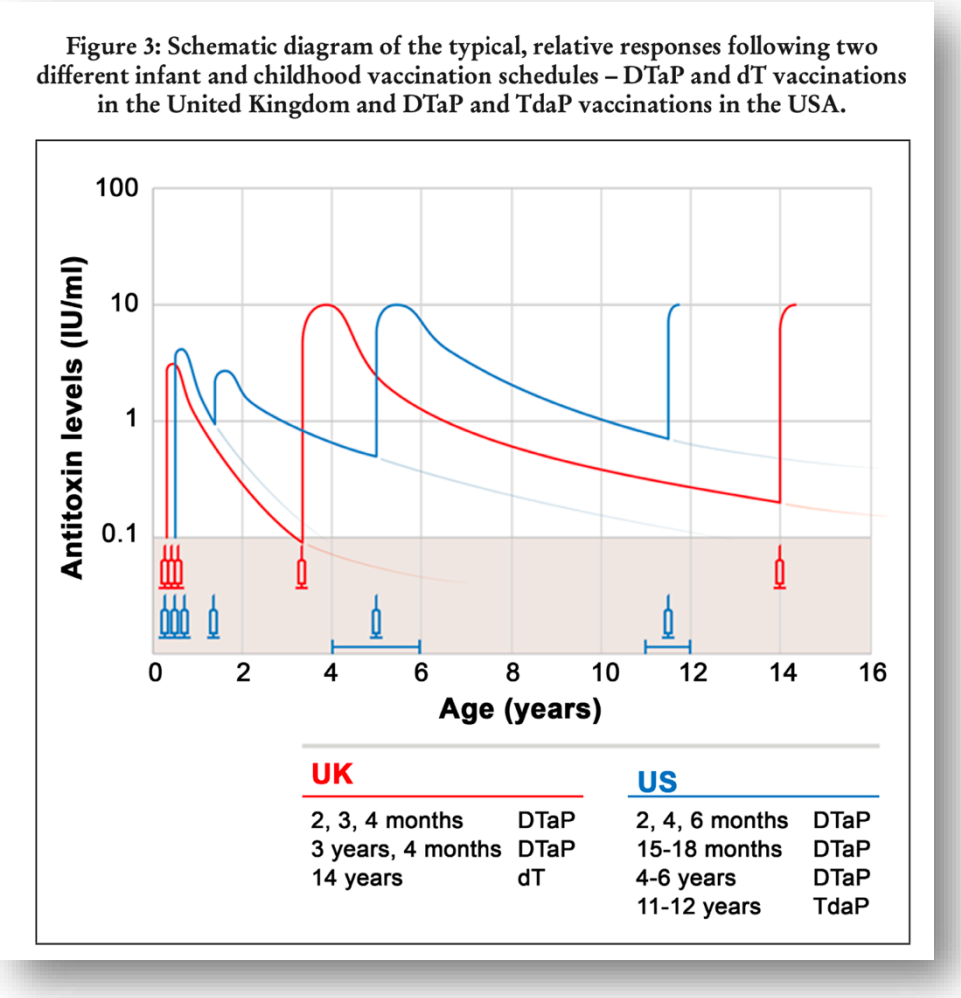
Current titer related to maternal antibody concentration and date of vaccination

- Did not examine additional factors that might influence rate of decay (e.g., nutritional status)

Wang W, *et al*. *Nat Microbiol* (2024). DOI:10.1038/s41564-024-01694-x

Longitudinal tetanus titers

- Tetanus primary series: 3 doses before age 6 months
- **Substantial waning expected**
- WHO recommends 3 boosters
  - Prevent outbreaks
  - Achieve and maintain maternal and neonatal tetanus elimination (MNTE)
  - Relatively low cost (between $0.40 - $1.49 for all boosters per child)
- EPI programs per country determine booster schedule

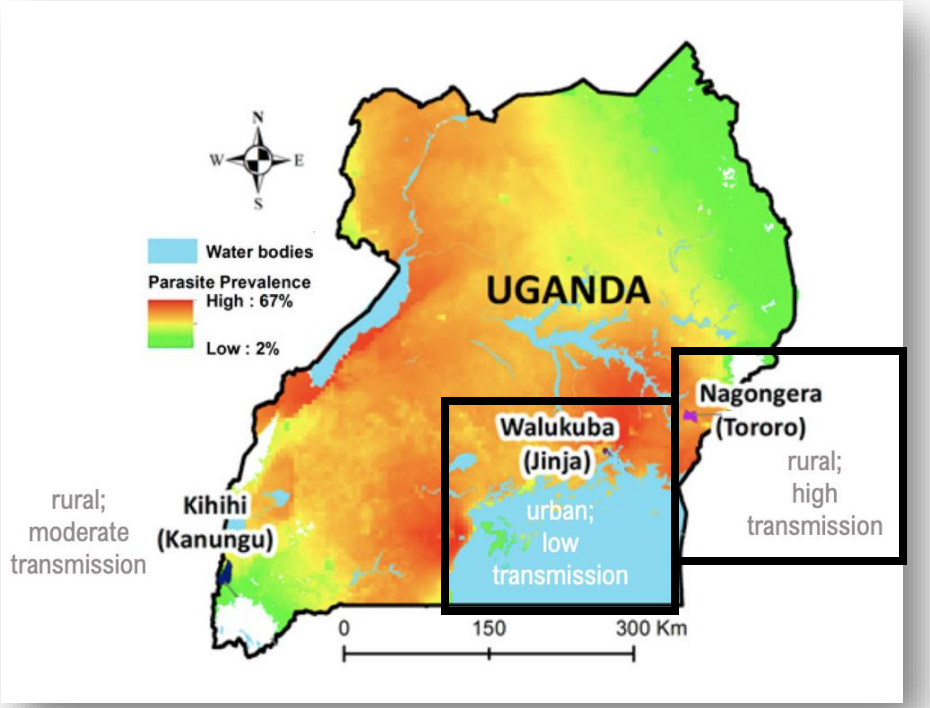


WHO Immunological Basis for Immunization Series Module 3: Tetanus (Update 2018)

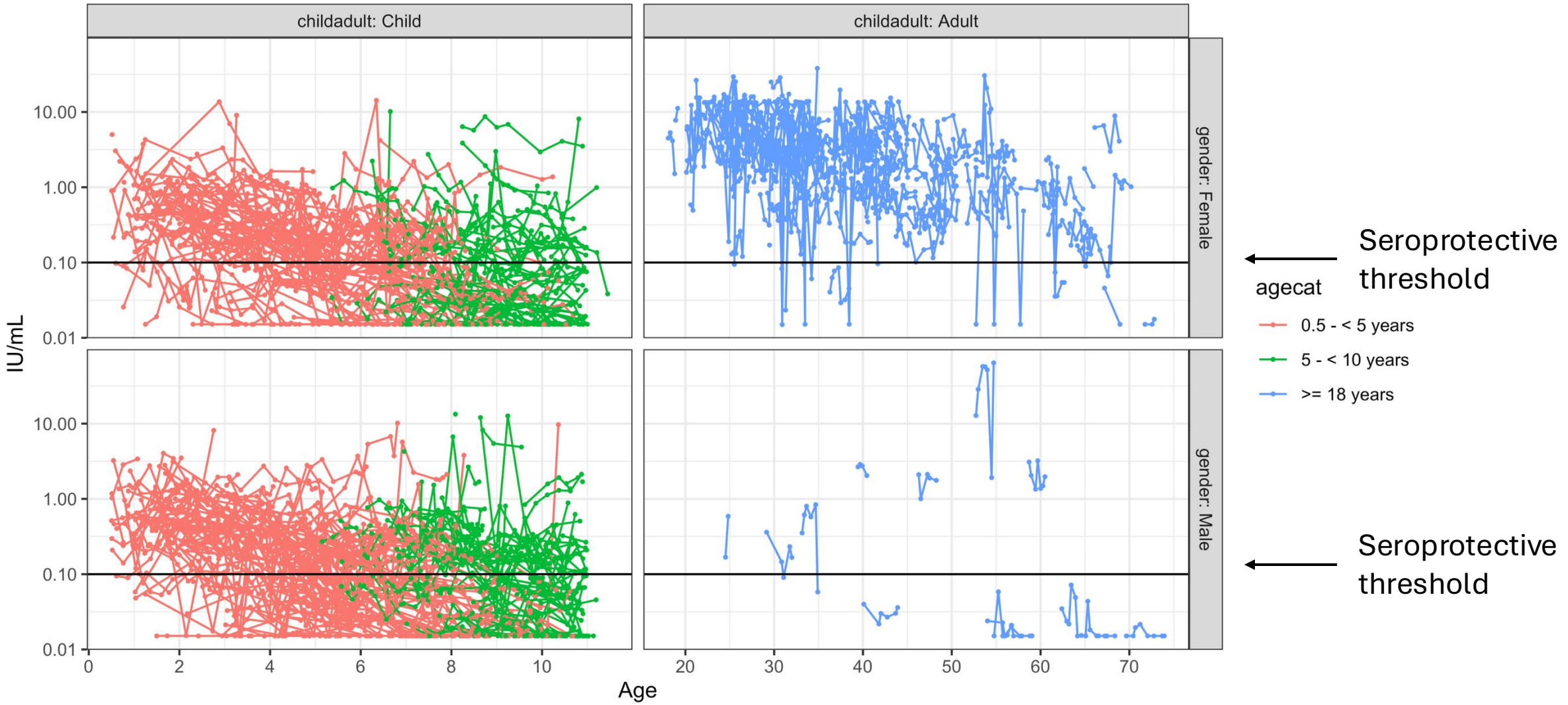
Application: assessing tetanus antibody decay

- Program for Resistance, Immunology, Surveillance, and Modelling of Malaria (PRISM)
  - Longitudinal cohort with quarterly sampling

- **Objective**: characterize tetanus antibody waning overall and by key study characteristics



Kamya, *et al*. (2015) *AJTMH*.



Sbarra, *et al.* (in preparation)

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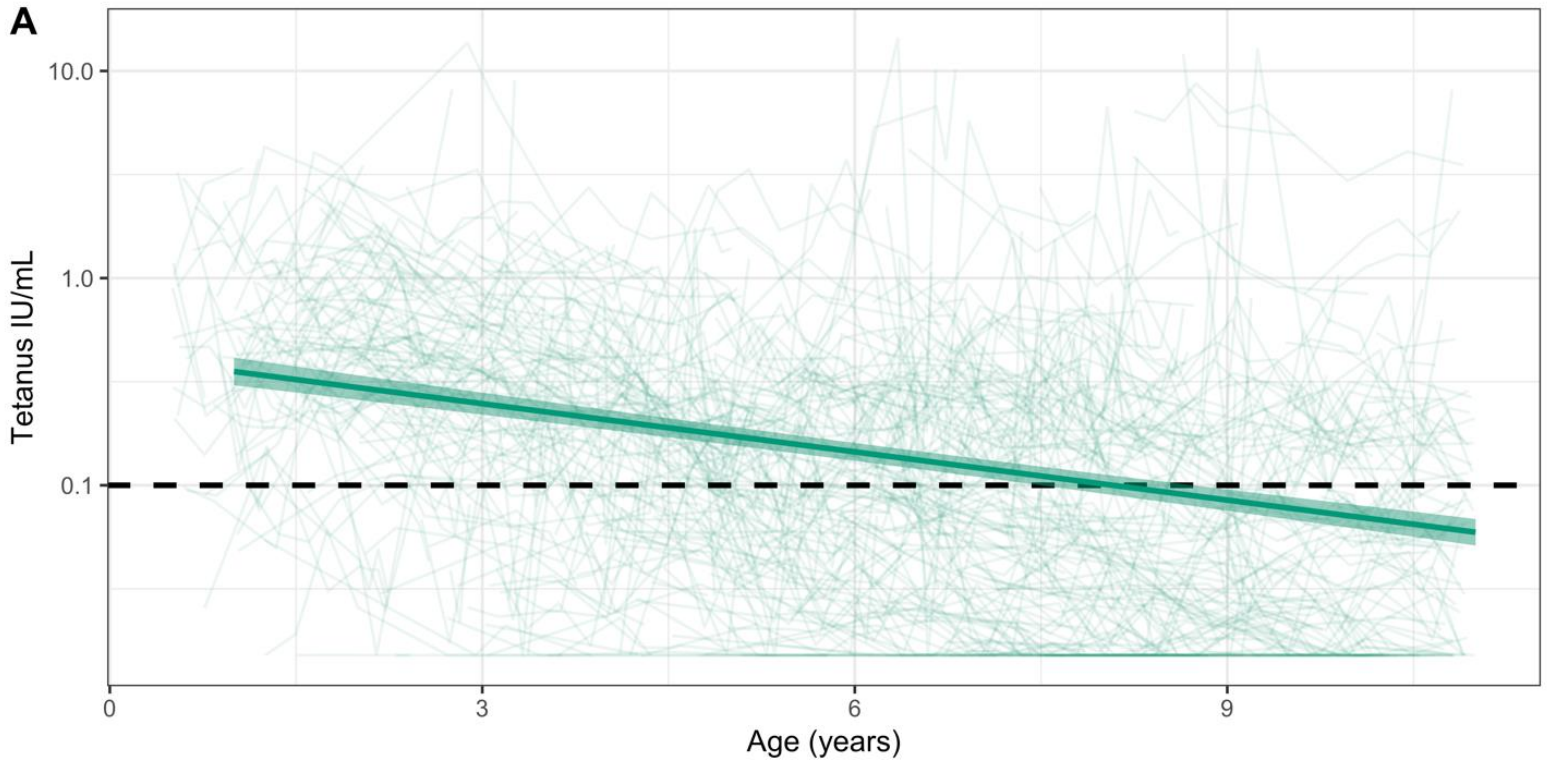
Tetanus antibody decay

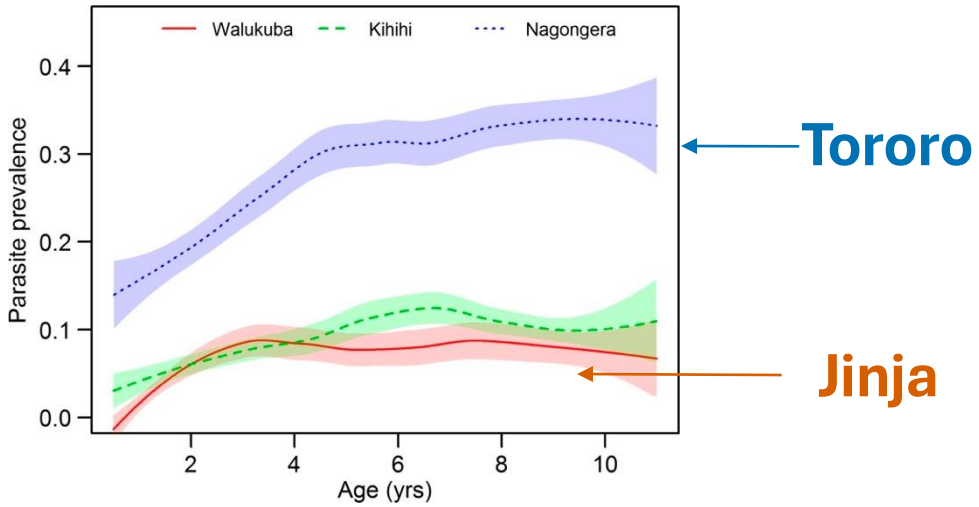


Half-life of antibody titers is 3.9 years (95% CI: 3.5–4.4 years).

Estimated **age of sero-reversion** is 8.1-years-old (95% CI: 7.2- to 9.2-years-old).

Sbarra, *et al.* (in preparation)

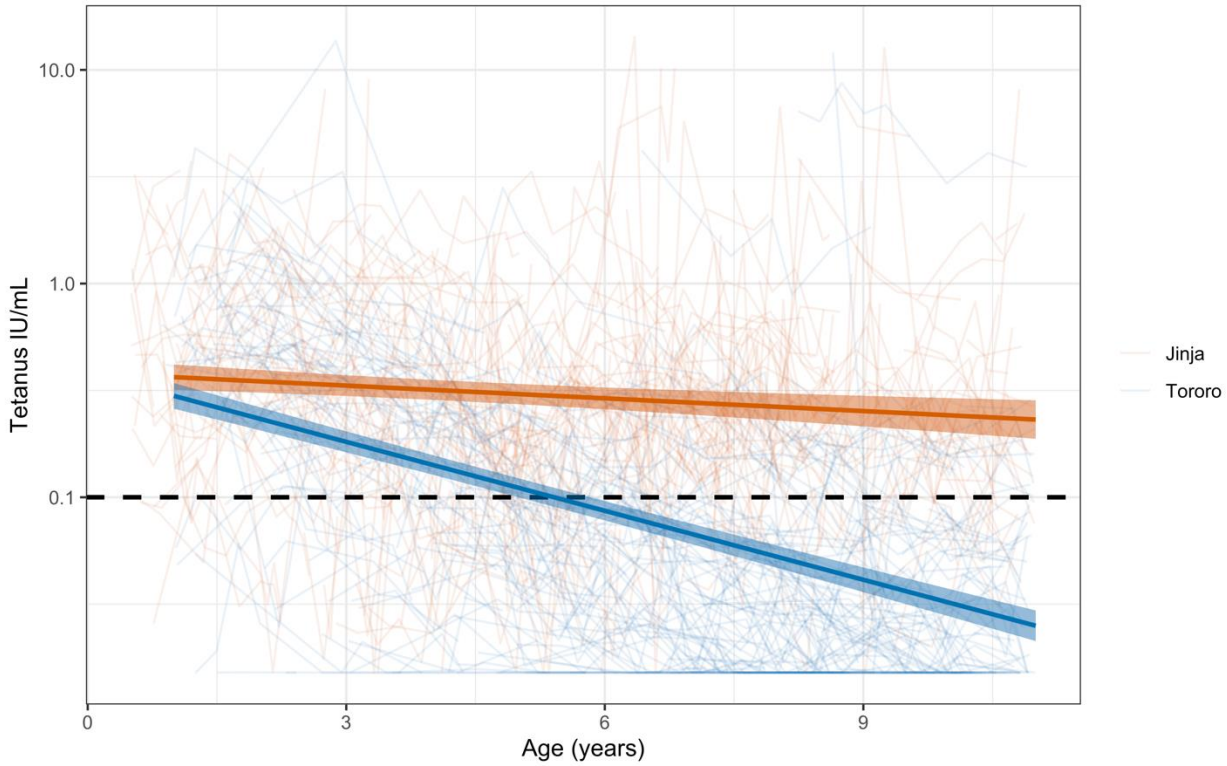
Decay by study site



Tororo

Jinja

Kamya MR, *et al. Am J Trop Med Hyg* (2015).



Half-life of tetanus antibody titers in **Jinja (15.2 years [95% CI: 9.7 to 34.6 years])** is statistically more than **in Tororo (2.8 years [95% CI: 2.6 to 3.1 years])**.

Sbarra, *et al.* (in preparation)

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We can still consider the correlate of protection when evaluating longitudinal data

	Jinja	Tororo	Total
Sero-reversion event during study period	37	52	89
No sero-reversion event during study period	161	70	231
Total	198	122	320

Hazard model: estimates the probability that an event will occur during a specified time period

- Among children who were seropositive at the start of the study period, there was a 2.35 (95% CI: 1.53 to 3.62) times increased risk of sero-reversion in Tororo relative to Jinja ($p < 0.001$).

Questions?