Longitudinal analyses of serological data

May 23, 2025

Seroanalytics Training
Blantyre, Malawi

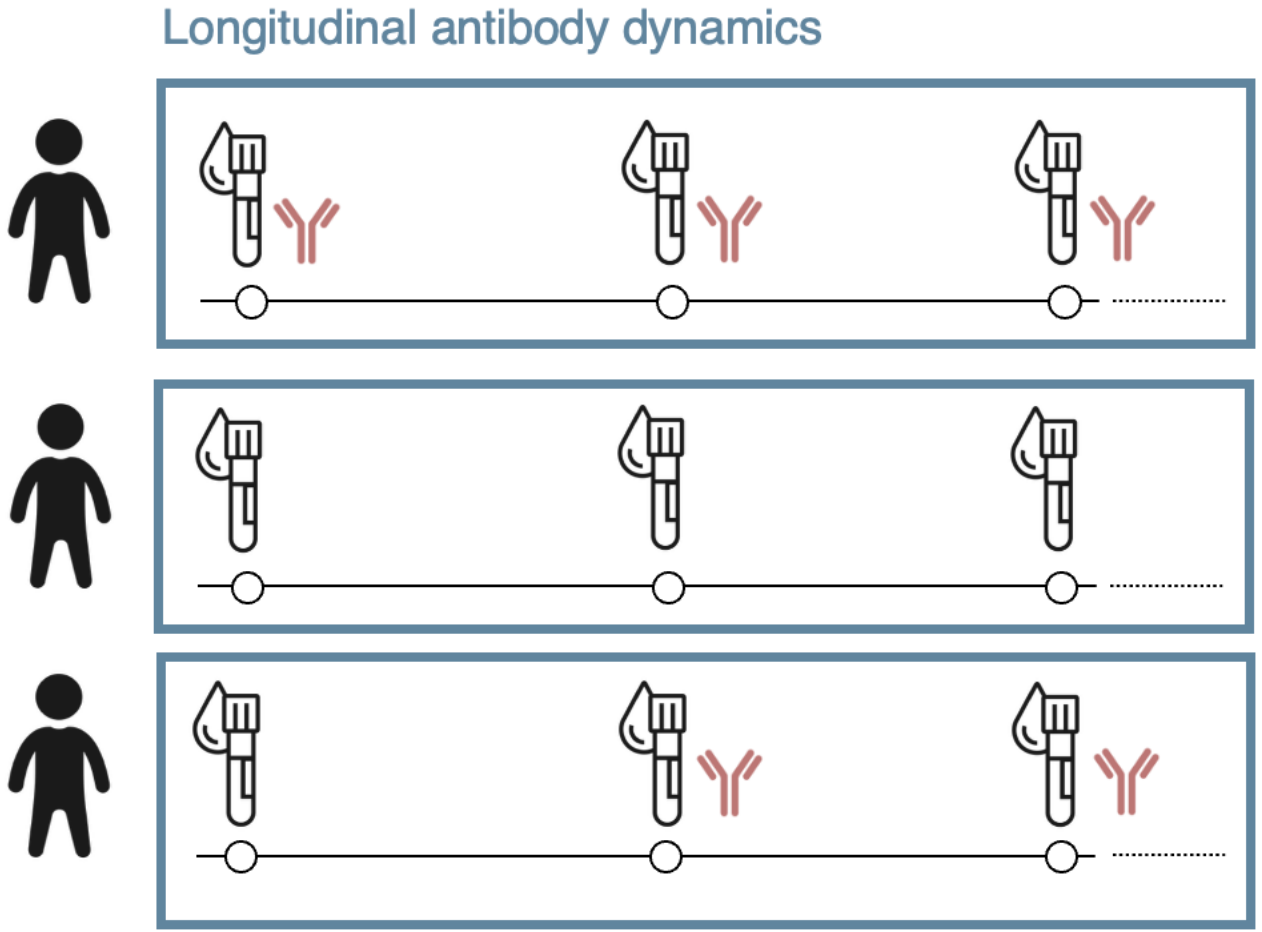
Outline

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

Reminder: longitudinal data

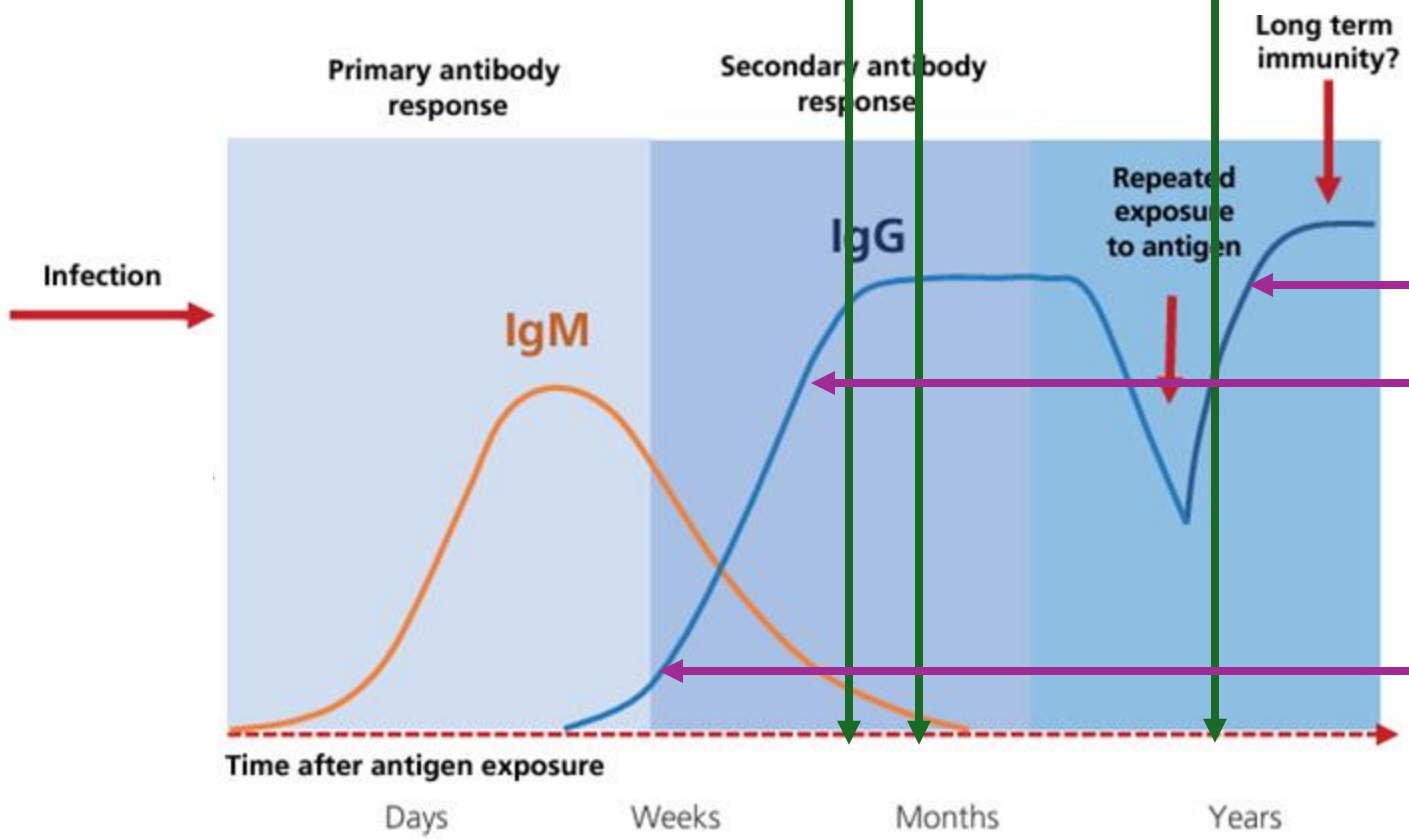
(From Lecture 1)

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



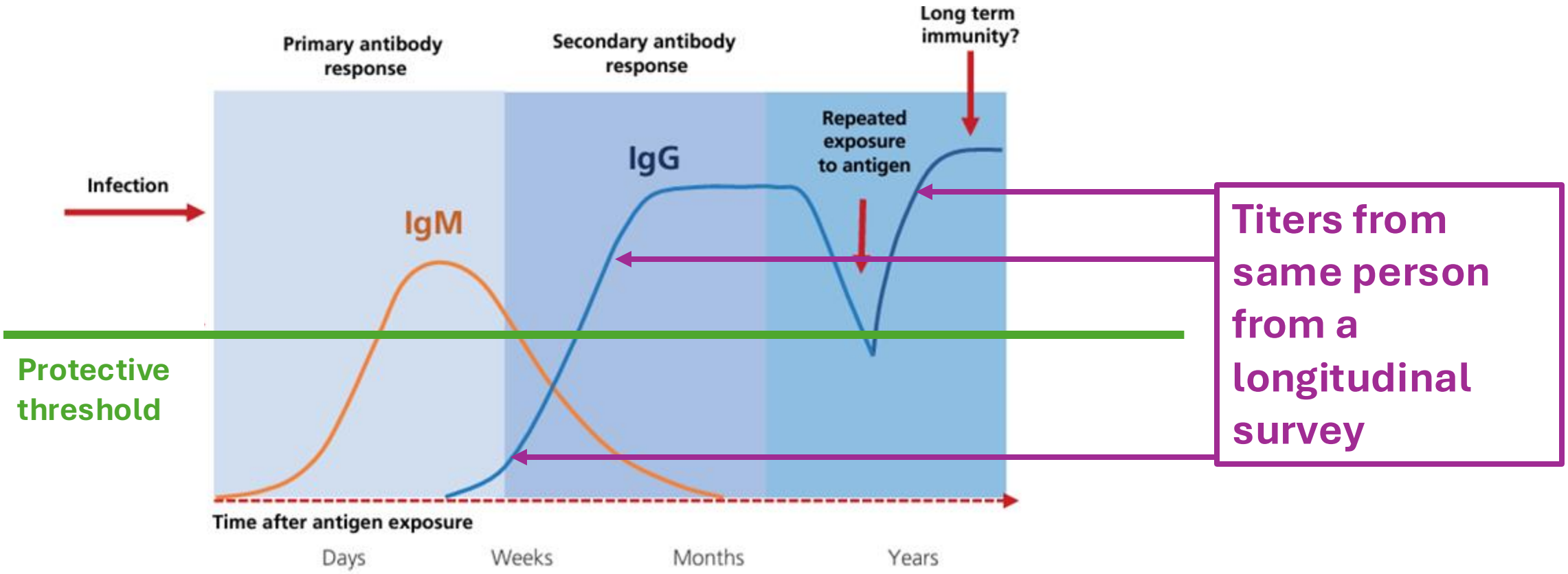
Antibody kinetics

Titers from individual people within cross sectional survey

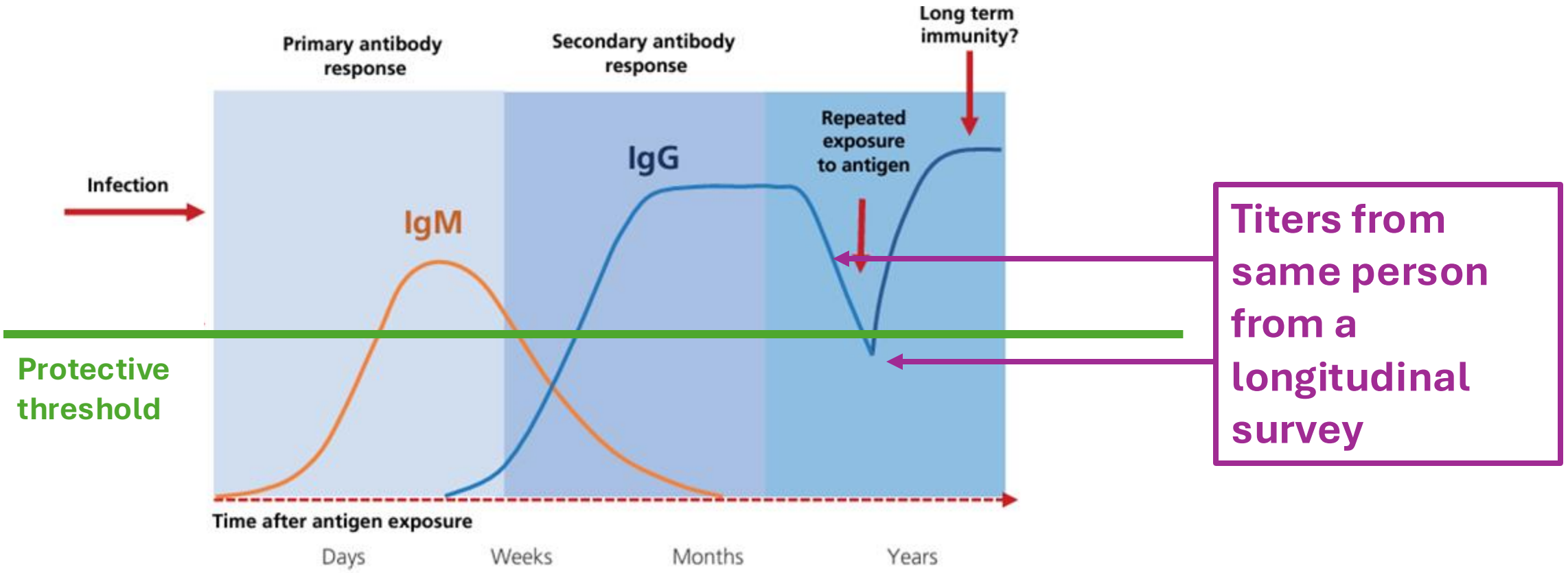


Titers from same person from a longitudinal survey

Binary serostatus often does not tell the full story

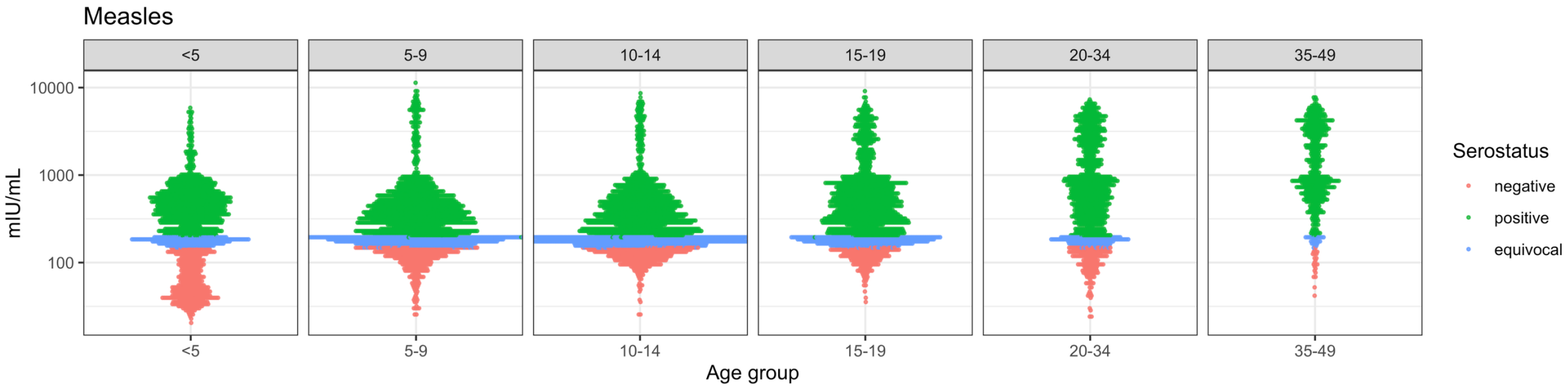


Binary serostatus often does not tell the full story



Titers from same person from a longitudinal survey

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



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

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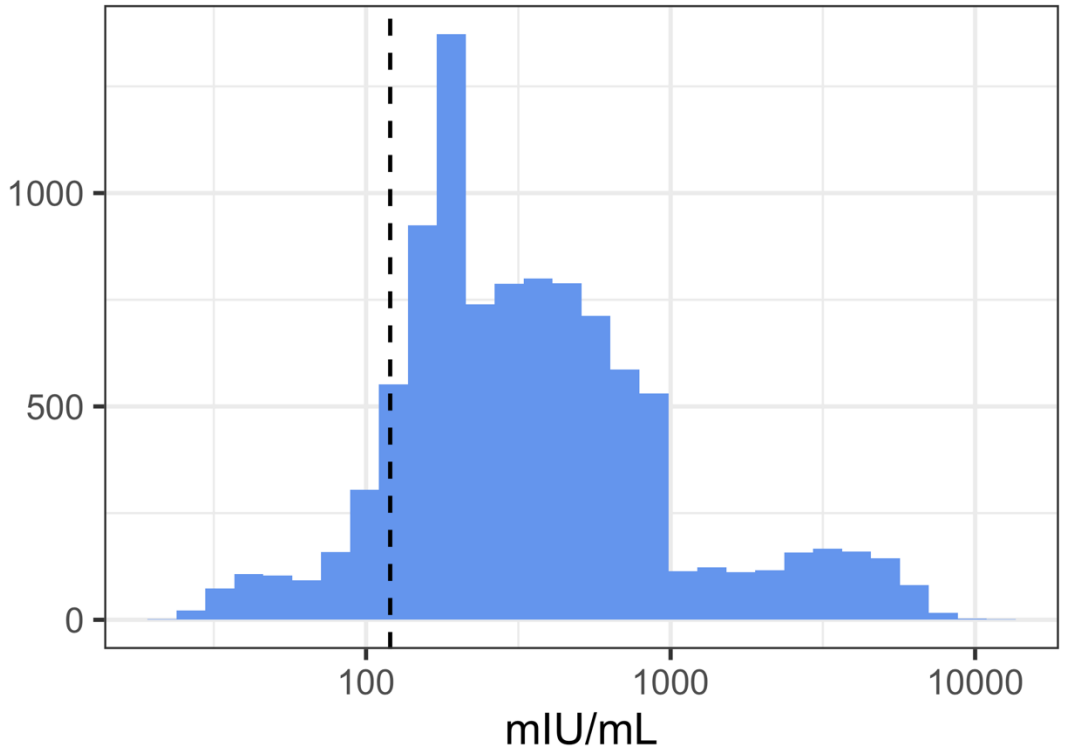
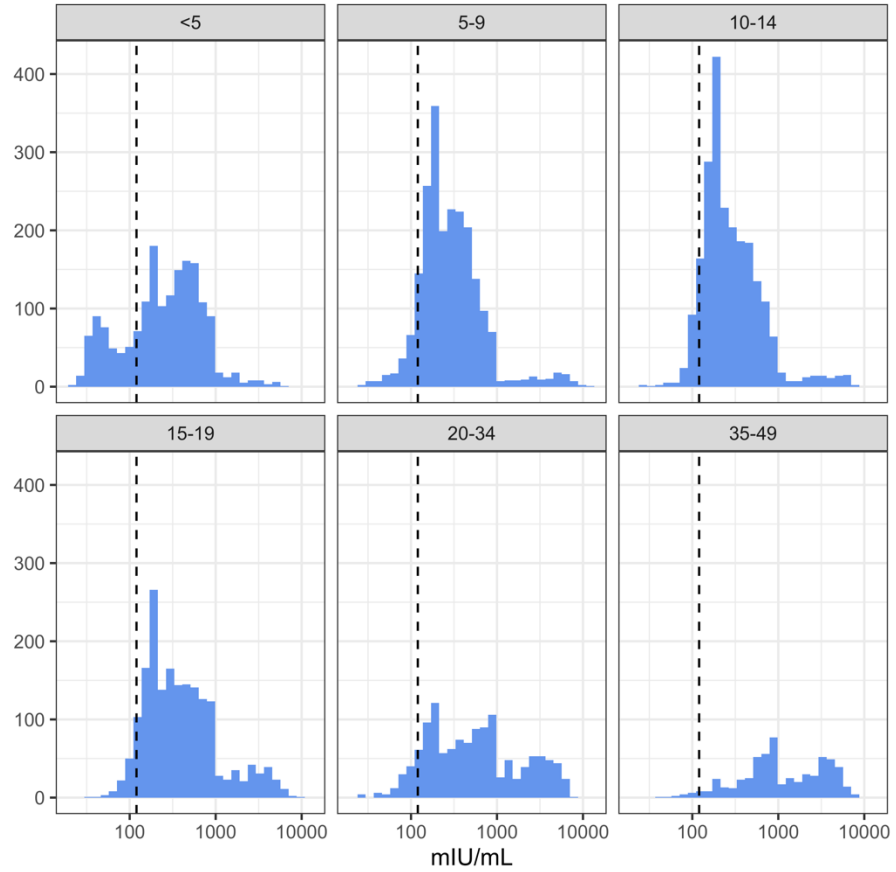




Carcelen, Winter, *et al*. (2022) *Sci Reports*.

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

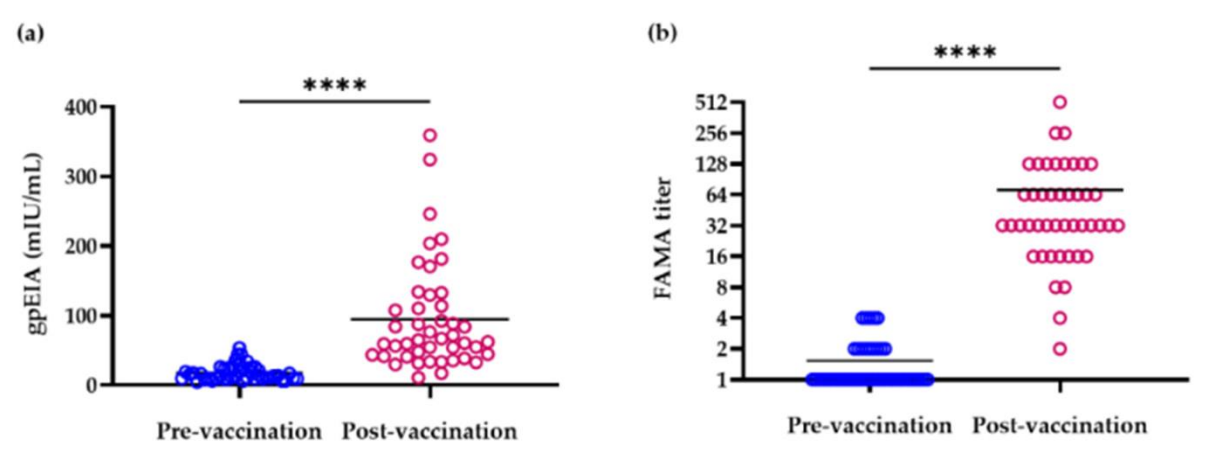
Including immunogenicity studies

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,*]

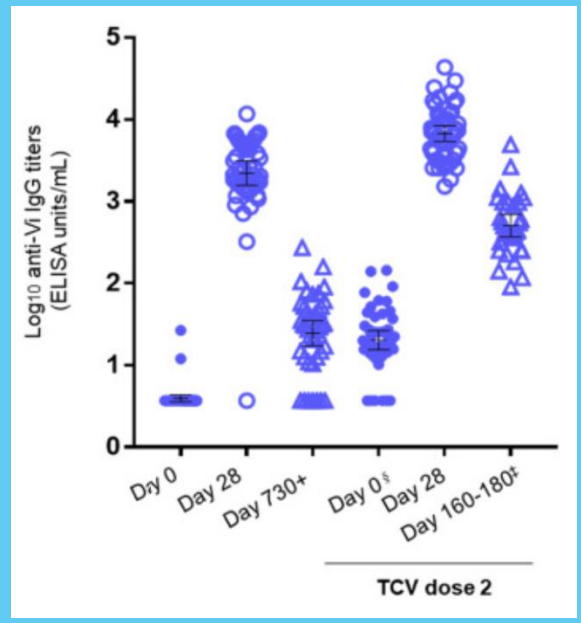
[1] Department of Microbiology, College of Medicine, Yeungnam University, Daegu 42415, Korea
[2] Department of Pediatrics, College of Medicine, Yeungnam University, Daegu 42415, Korea
[3] Immunogenicity Evaluation Laboratory, Clinical Trial Center, Yeungnam University Medical Center, Daegu 42415, Korea
* 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

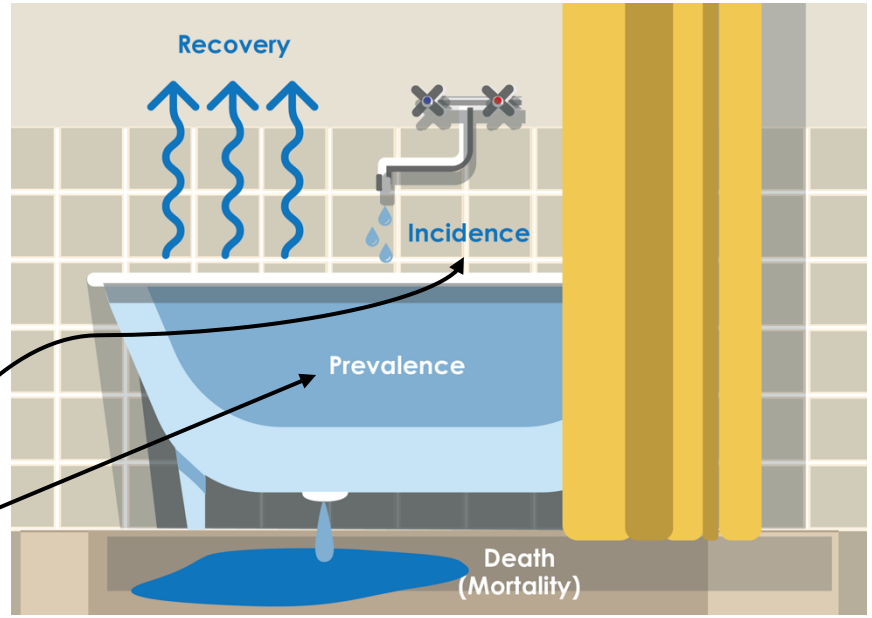
[a]Blantyre Malaria Project, Kamuzu University of Health Sciences, Blantyre, Malawi
[b]Center for Vaccine Development and Global Health, University of Maryland School of Medicine, Baltimore, MD, United States
[c]Malawi-Liverpool-Wellcome Program, Kamuzu University of Health Sciences, Blantyre, Malawi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

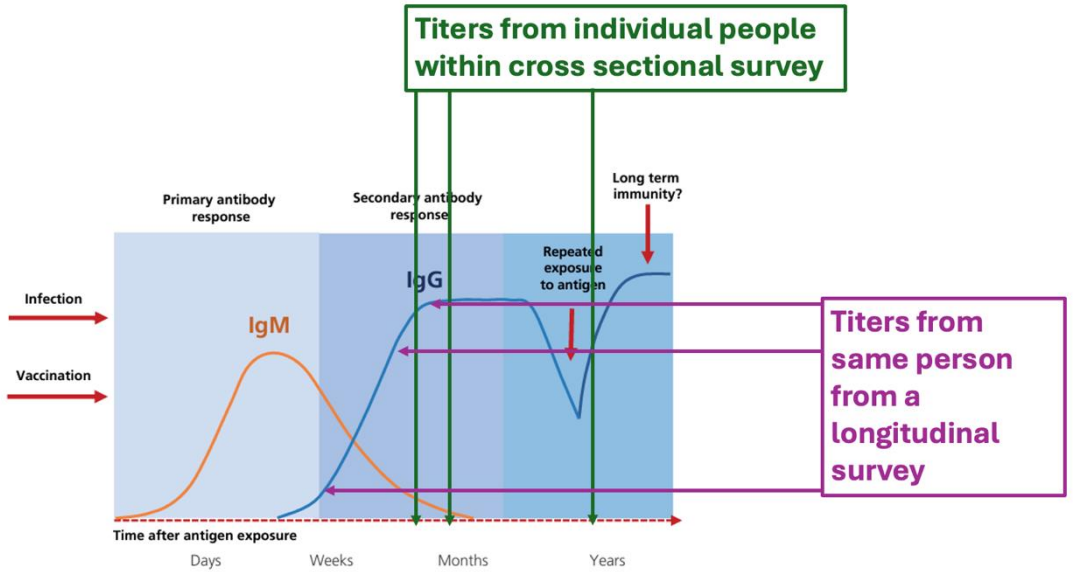


Seroincidence estimation

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

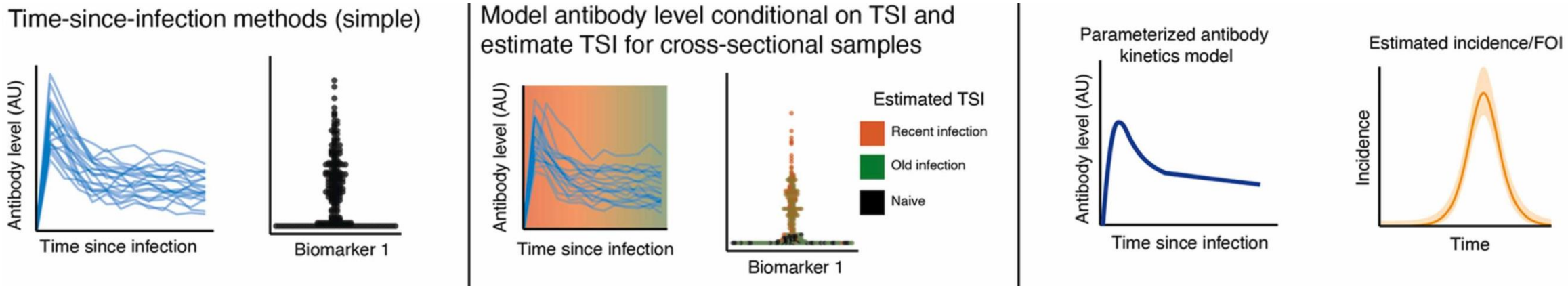
- Longitudinal data can show us changes within individuals in the population which allows us to estimate new infection/exposure
  - **This is a metric of incidence**



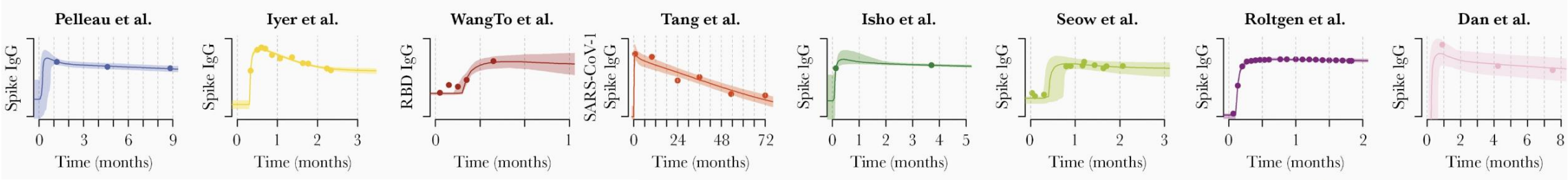


Time-since-infection (TSI)

- 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



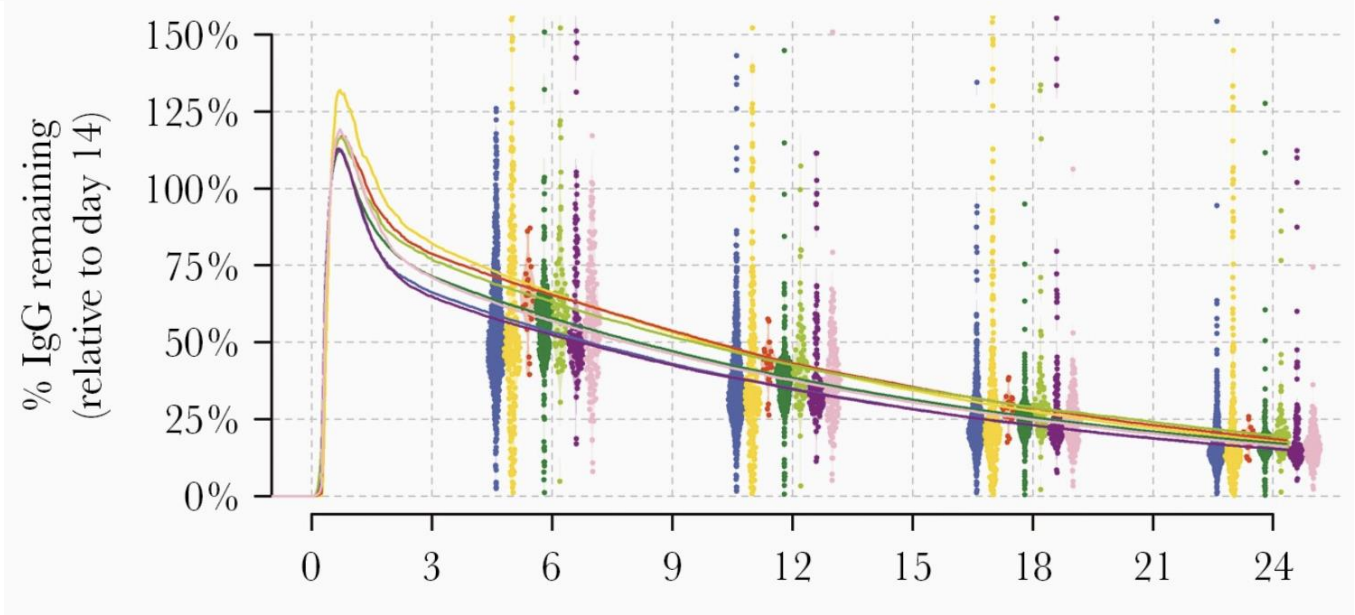
JOURNAL ARTICLE

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

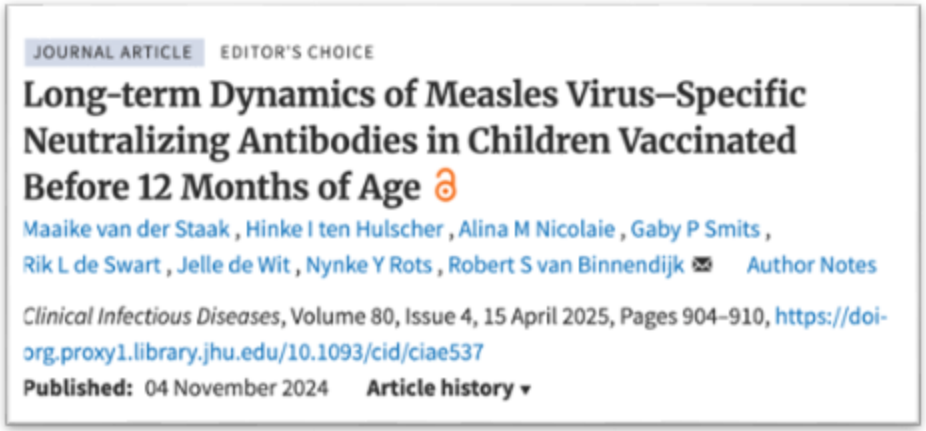
The Journal of Infectious Diseases, Volume 224, Issue 9, 1 November 2021, Pages 1489–1499, https://doi-org.proxy1.library.jhu.edu/10.1093/infdis/jiab375

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



Boosting

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



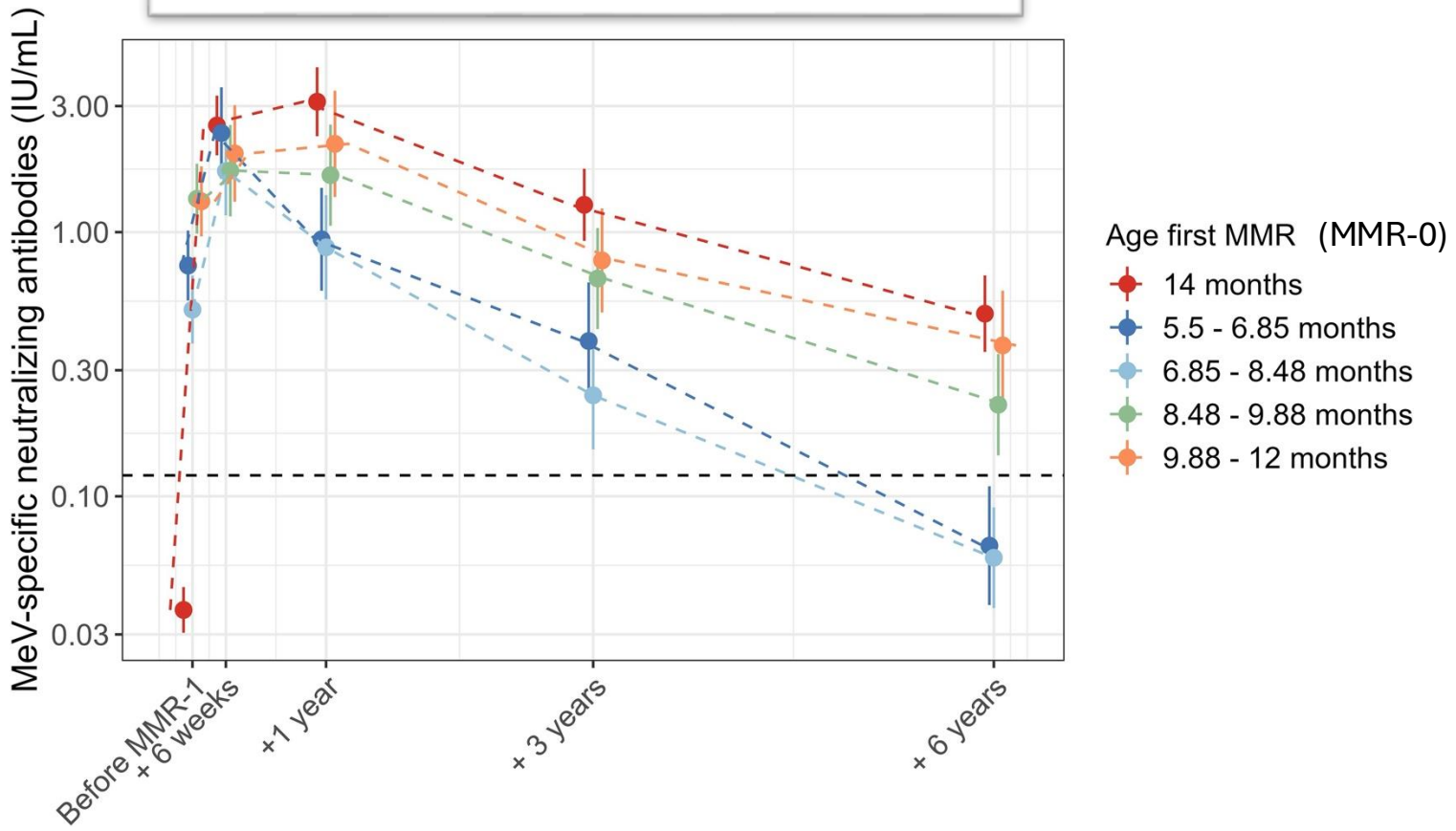
JOURNAL ARTICLE EDITOR'S CHOICE

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

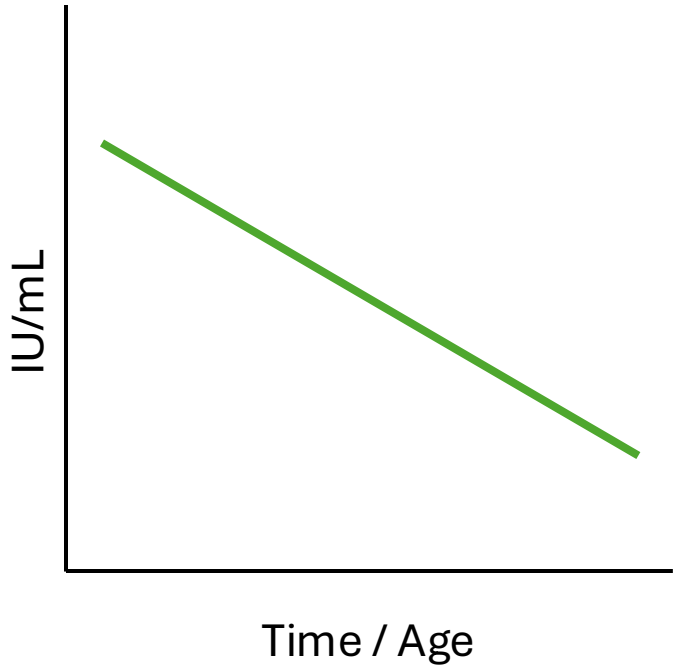
Clinical Infectious Diseases, Volume 80, Issue 4, 15 April 2025, Pages 904–910, https://doi-org.proxy1.library.jhu.edu/10.1093/cid/ciae537

Published: 04 November 2024 **Article history**

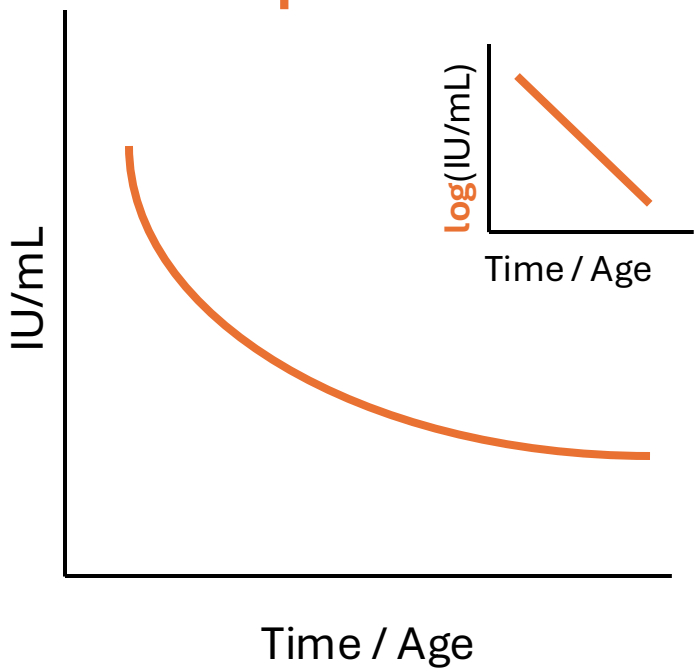


Waning models

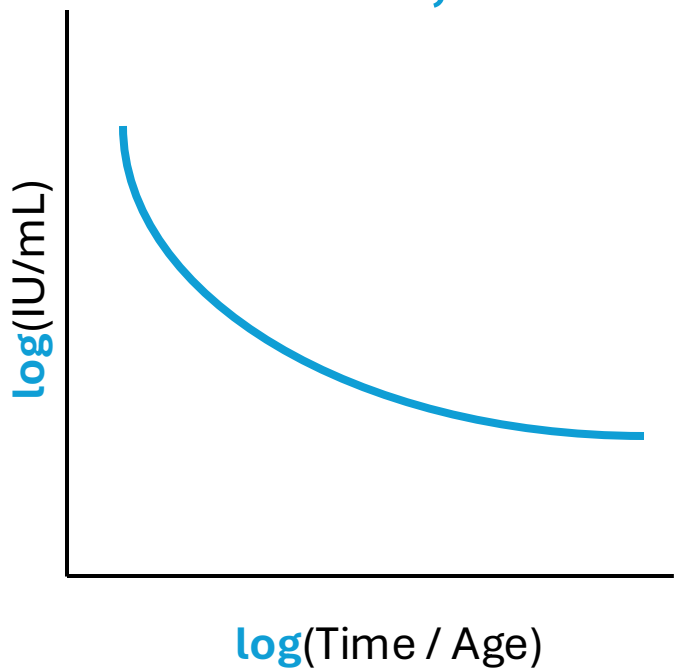
Linear



Exponential

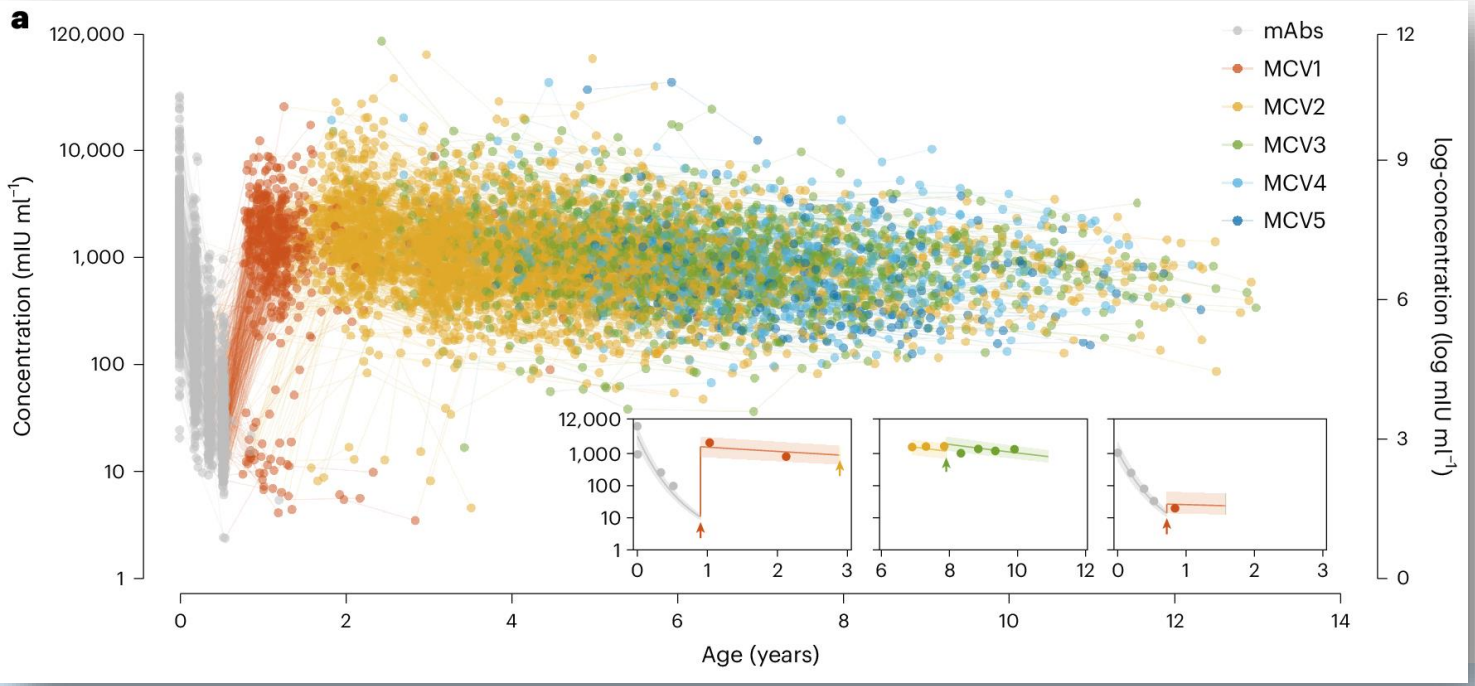


Power, etc…



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)

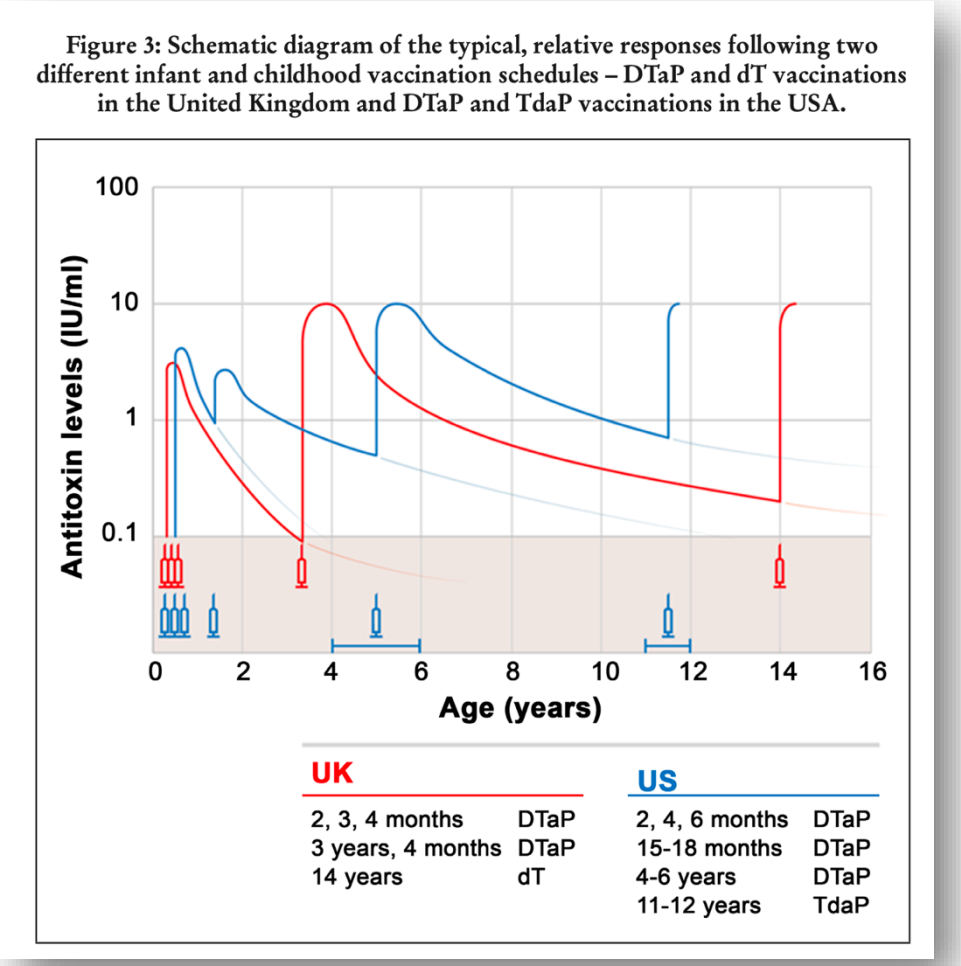
Current titer related to maternal antibody concentration and date of vaccination

- 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

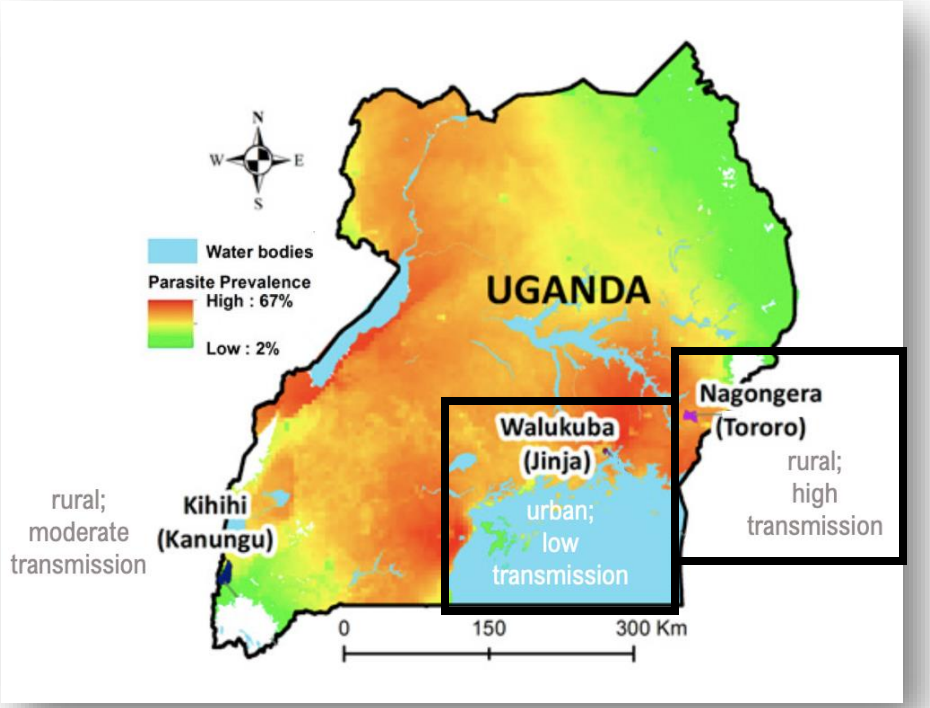


WHO Immunological Basis for Immunization Series Module 3: Tetanus (Update 2018)

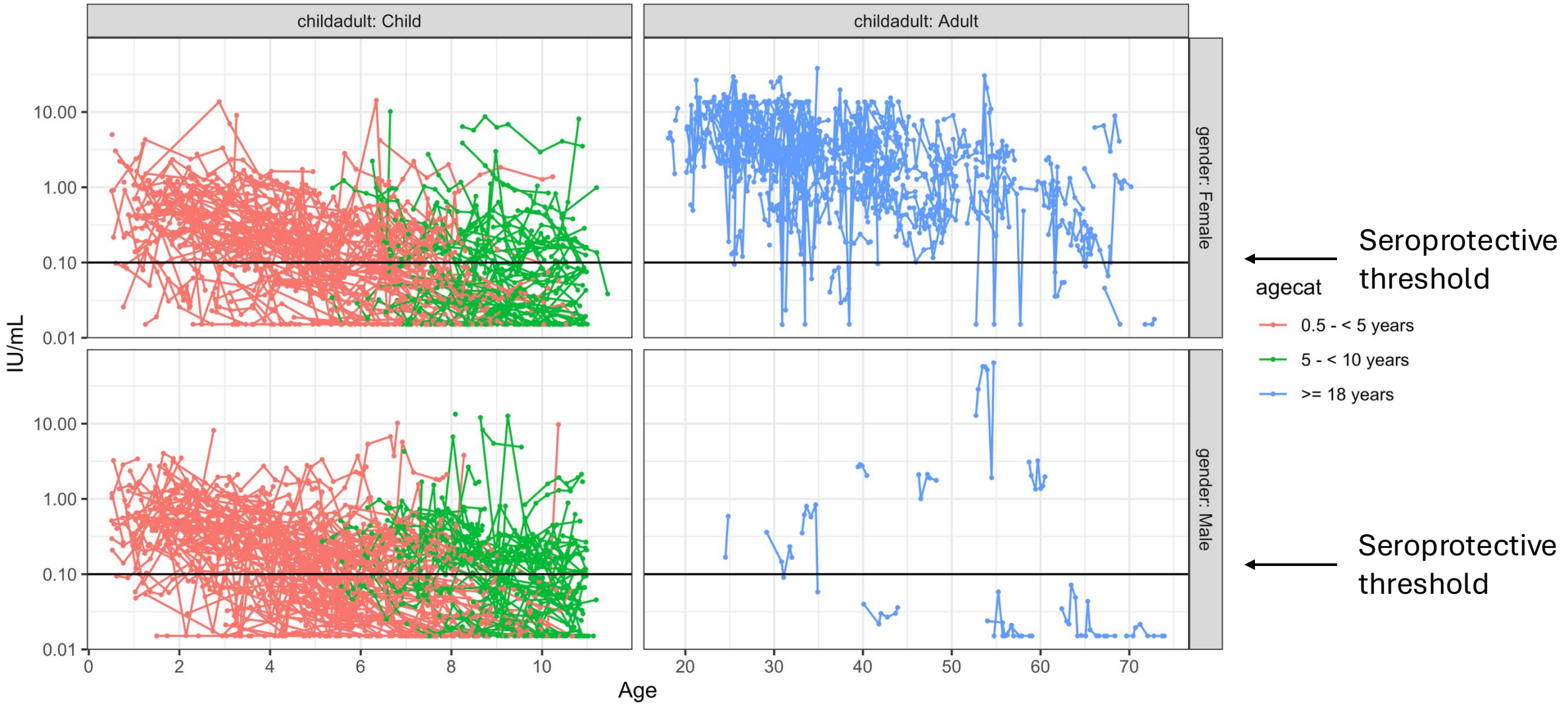
Application: assessing tetanus antibody decay

- 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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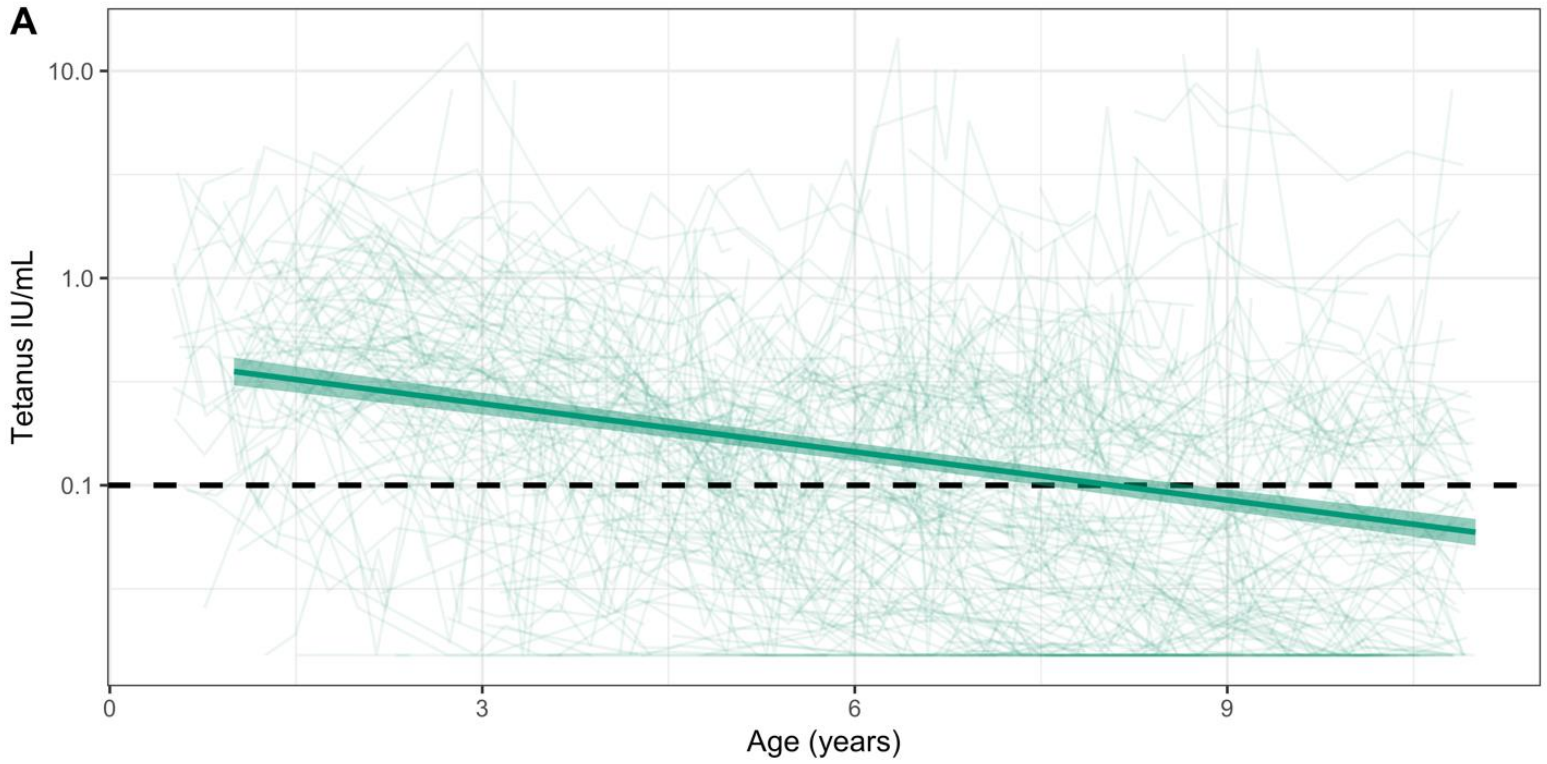
Infectious Disease DYNAMICS
Johns Hopkins Bloomberg School of Public Health

Tetanus antibody decay

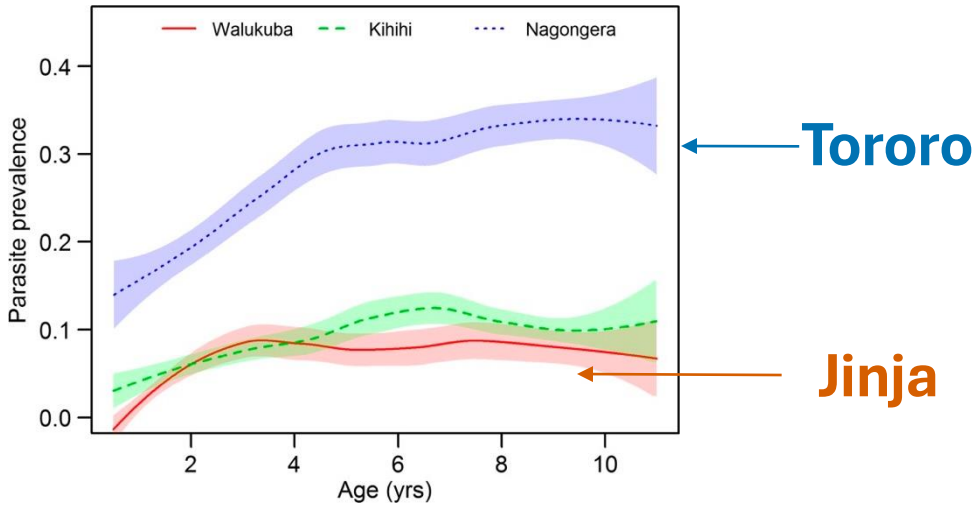


Half-life of antibody titers is 3.9 years (95% CI: 3.5–4.4 years).

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

Sbarra, *et al.* (in preparation)

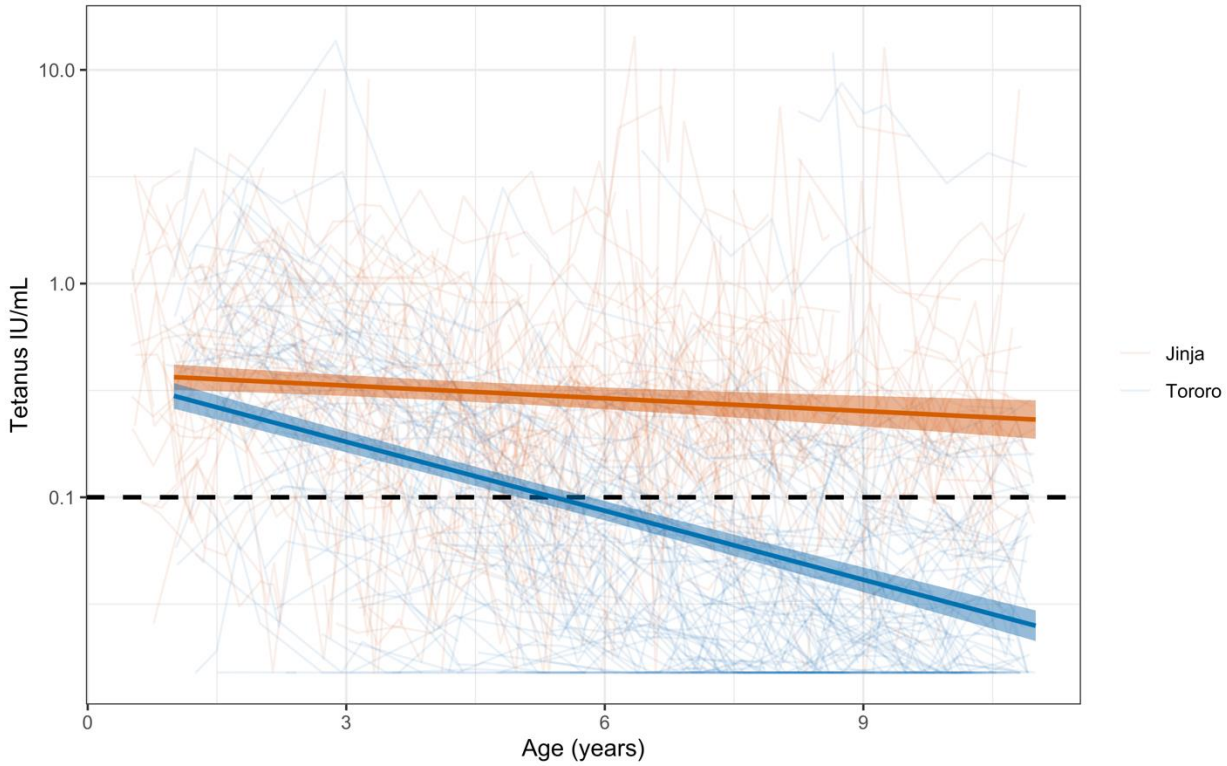
Decay by study site



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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Infectious Disease DYNAMICS

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?