Quantitative antibody levels as a measure of exposure to helminths and other neglected tropical diseases

Computational notebooks and (most) data used to make this presentation:
https://github.com/ben-arnold/quantAb-annecy

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Big picture:

We are working on seroepidemiologic methods that generalize to diverse pathogens and could be useful for integrated serosurveillance

PERSPECTIVE

Integrated Serologic Surveillance of Population Immunity and Disease Transmission

Benjamin F. Arnold, Heather M. Scobie, Jeffrey W. Priest, Patrick J. Lammie

Emerging Infectious Diseases, 2018; 24(7):1188-1194

Topics

Seroprevalence can be difficult to interpret for antibody responses that boost and wane with repeated exposures

Population mean antibody levels reflect differences in exposure, even for pathogens with complex immunology

Mean antibody levels and seroprevalence measure the same heterogeneity in exposure regardless of antibody distribution and cutoff

Comparison of antibody levels with other measures of transmission

Advantages, limitations and the bottom line

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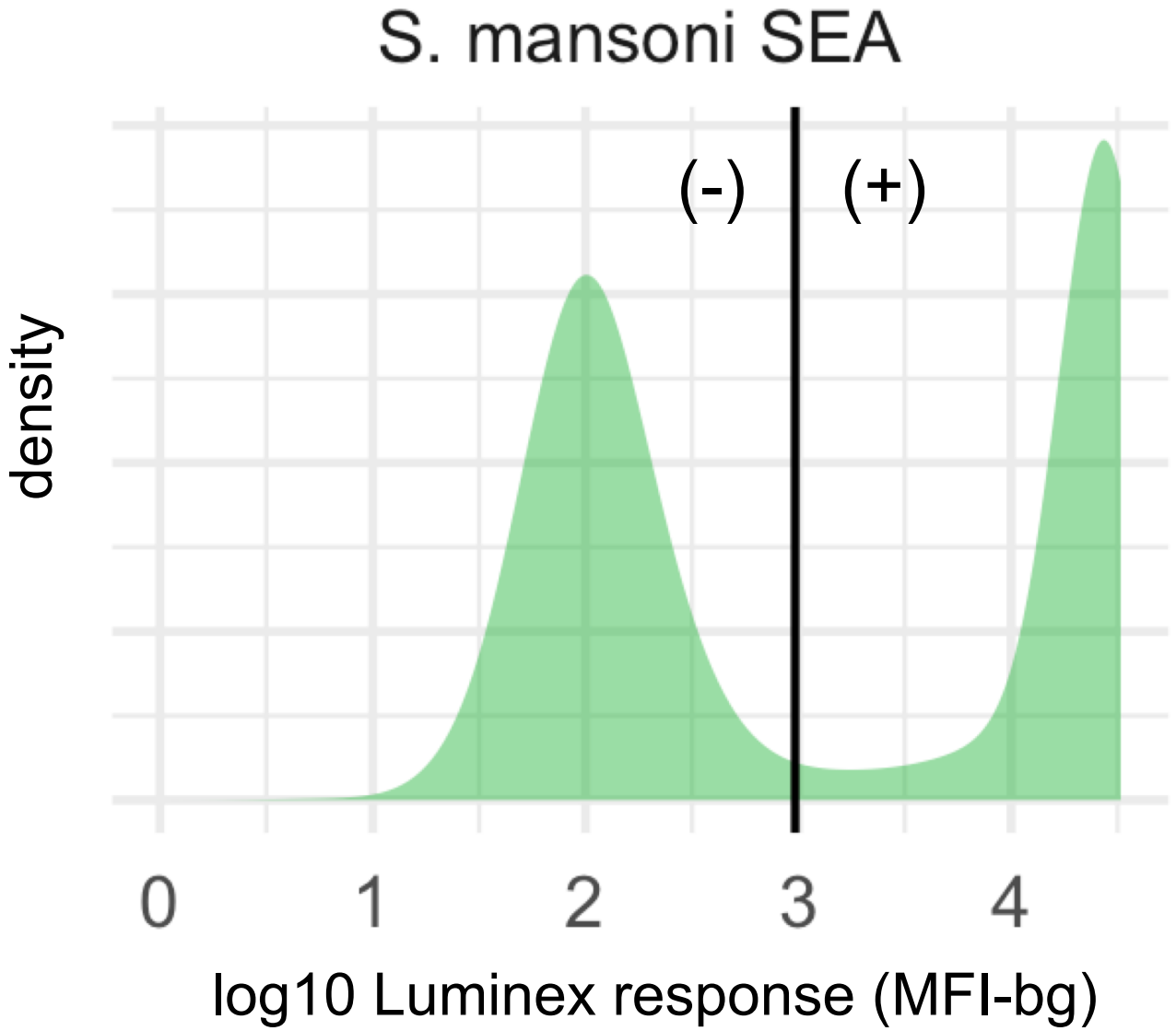
Many antibody assays provide a quantitative readout

The staple of analyzing antibody data for decades has been to classify quantitative levels as seropositive (**+**) or seronegative (**–**)

Ideal example: *Schistosoma mansoni* SEA



There are benefits to reducing antibody response to + / –

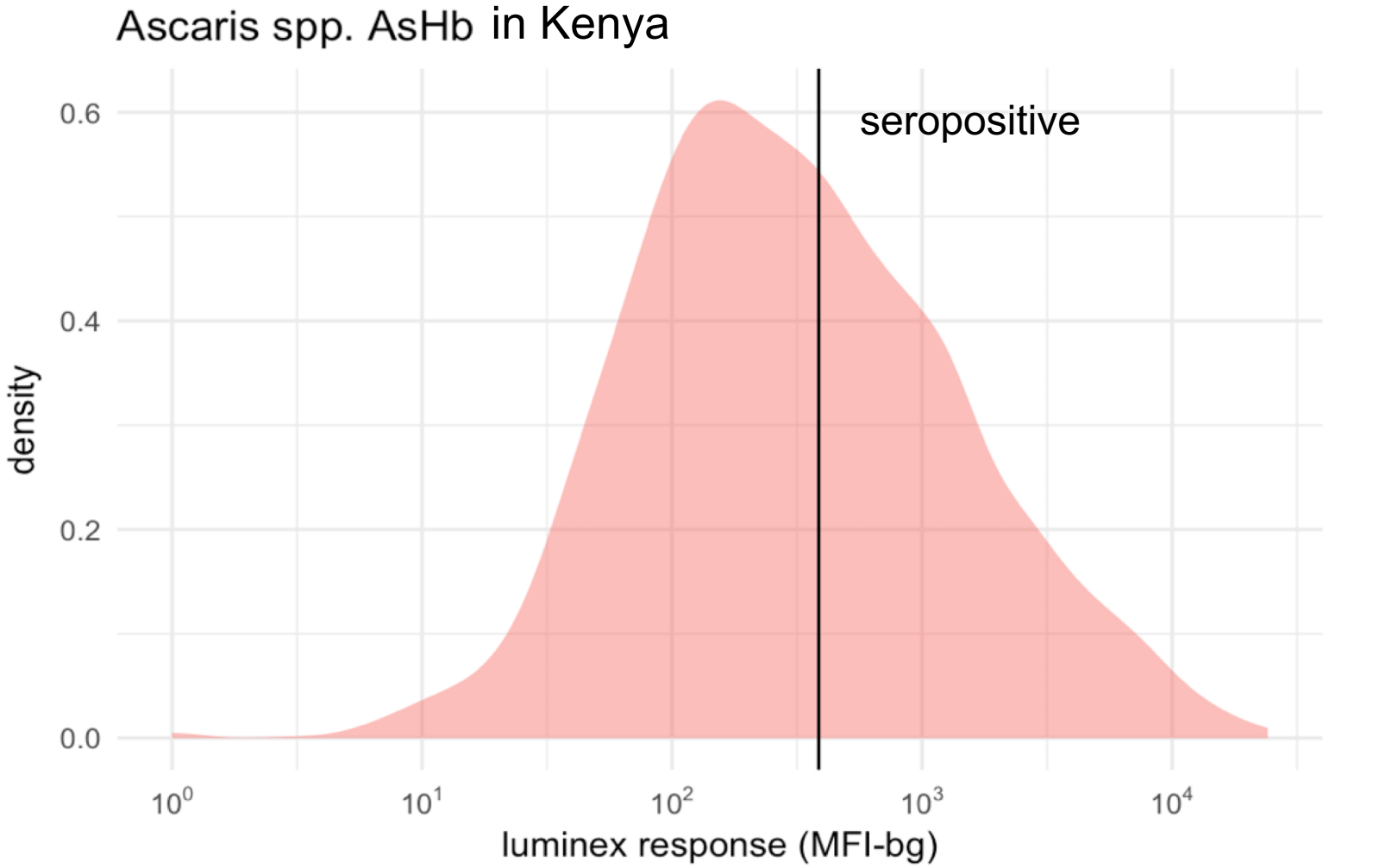
Seroprevalence is a standard epidemiologic parameter

- Can estimate seroconversion rates from seroprevalence as one measure of the force of infection

Converts arbitrary units of antibody assays to a common scale

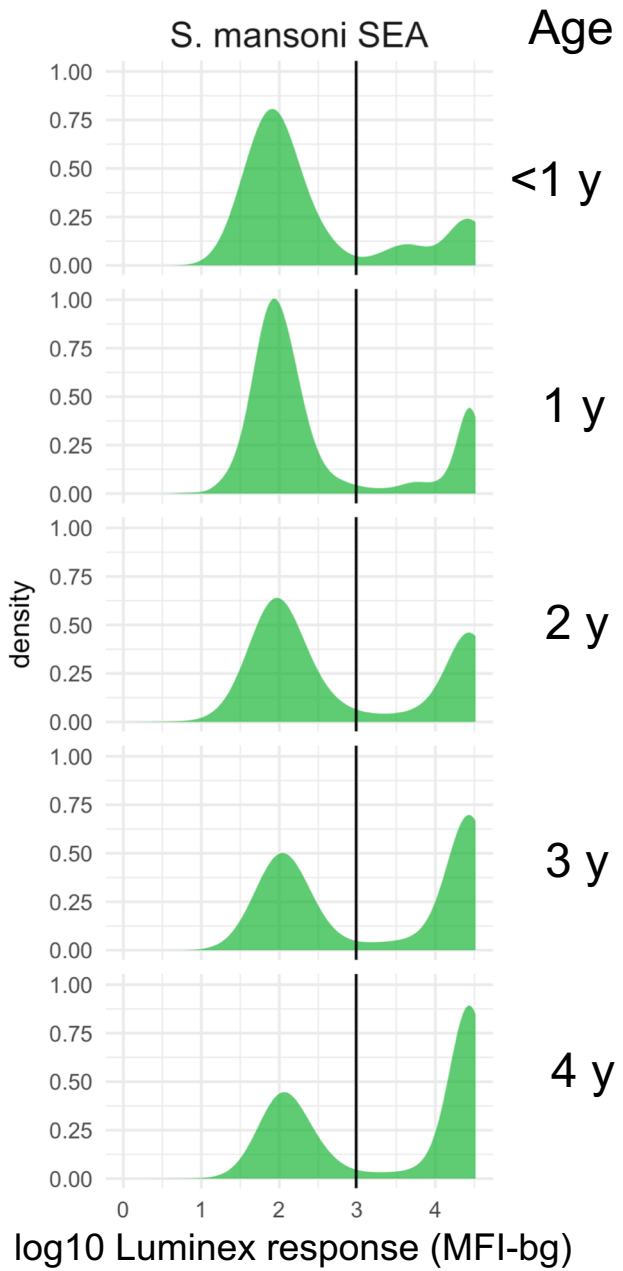
- Easier to compare estimates across pathogens and populations

But, in many examples seropositivity cutoffs do not clearly distinguish subpopulations of exposed and unexposed



Njenga et al. *in review*

Stable versus shifting antibody distributions in Mbita, Kenya



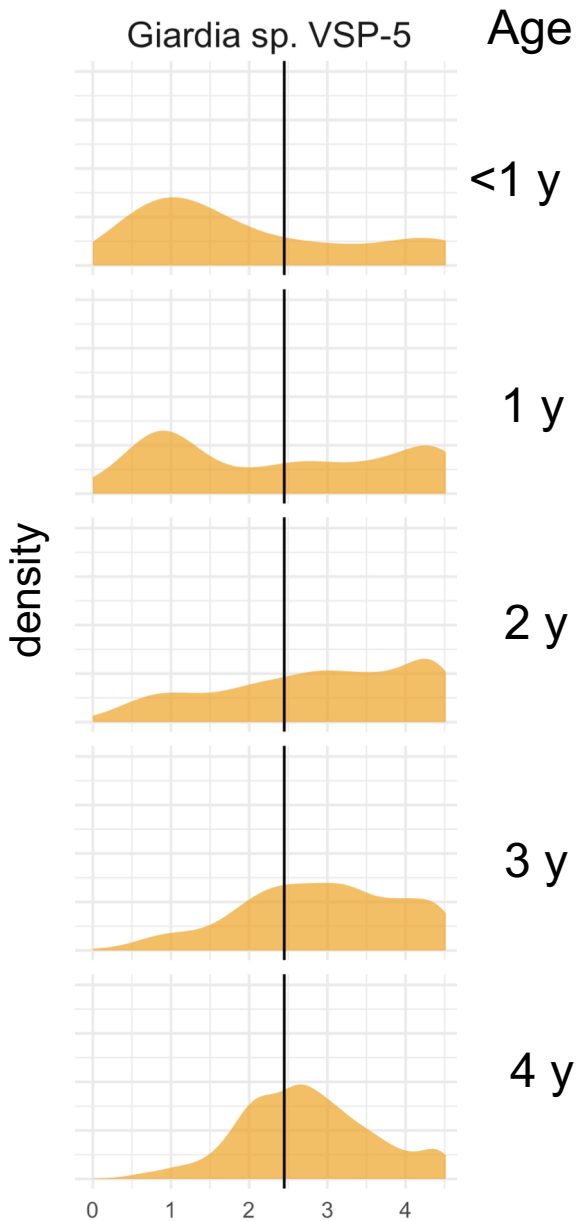
Schistosoma mansoni SEA

Clear differentiation between seronegative and seropositive distributions

Stable: does not change as children age

Seronegative indicates never exposed

Stable versus shifting antibody distributions in Mbita, Kenya



Giardia sp. VSP-5

Some differentiation between seronegative and seropositive distributions among <1 y

As children age, distribution shifts from bimodal to unimodal through antibody boosting and waning

By 3-4 years, seronegative does not necessarily indicate never exposed

Giardia is typical of enteric pathogen responses among children

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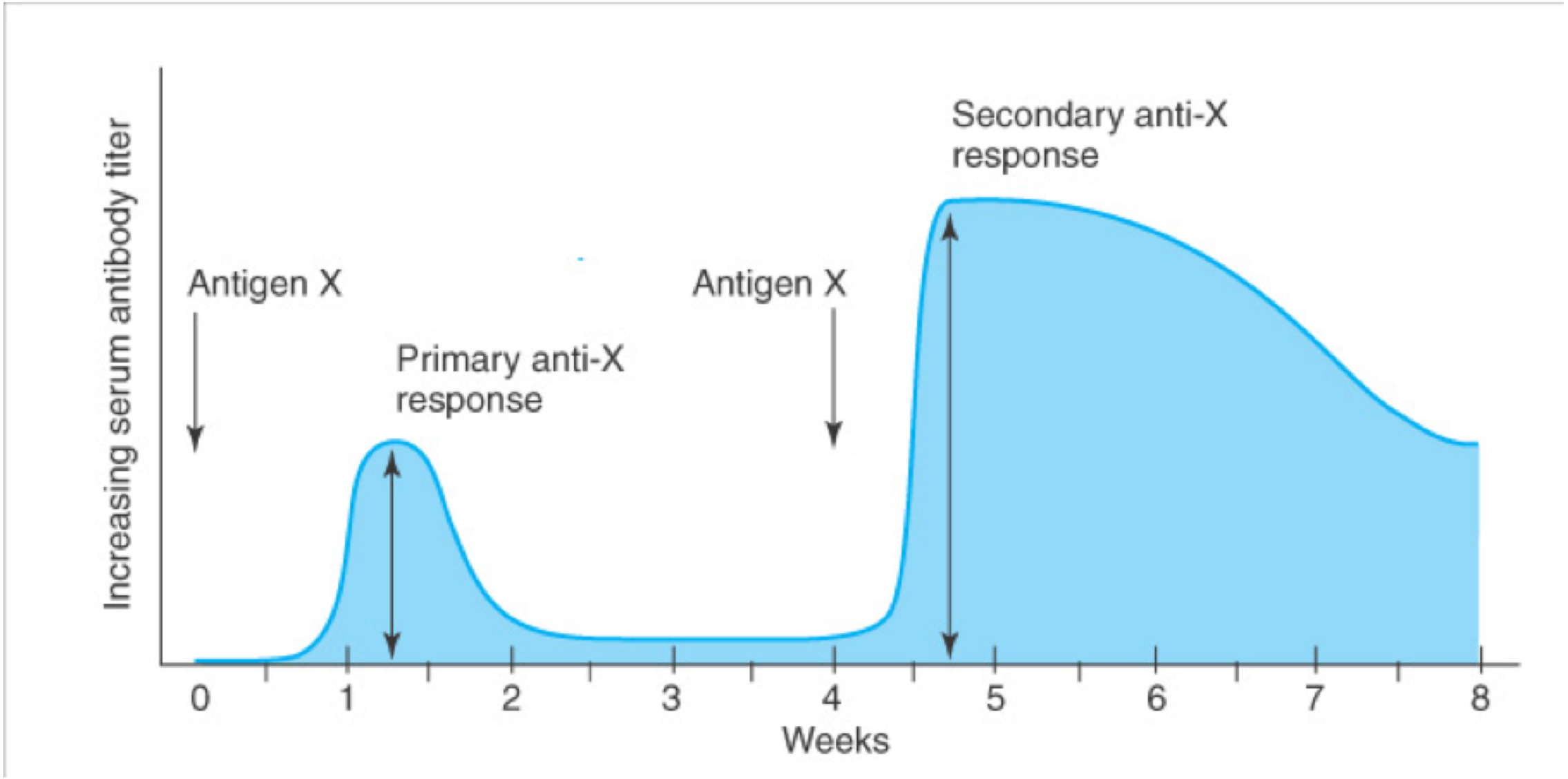
Comparison of antibody levels with other measures of transmission

Advantages, limitations and the bottom line

Adaptive immune response



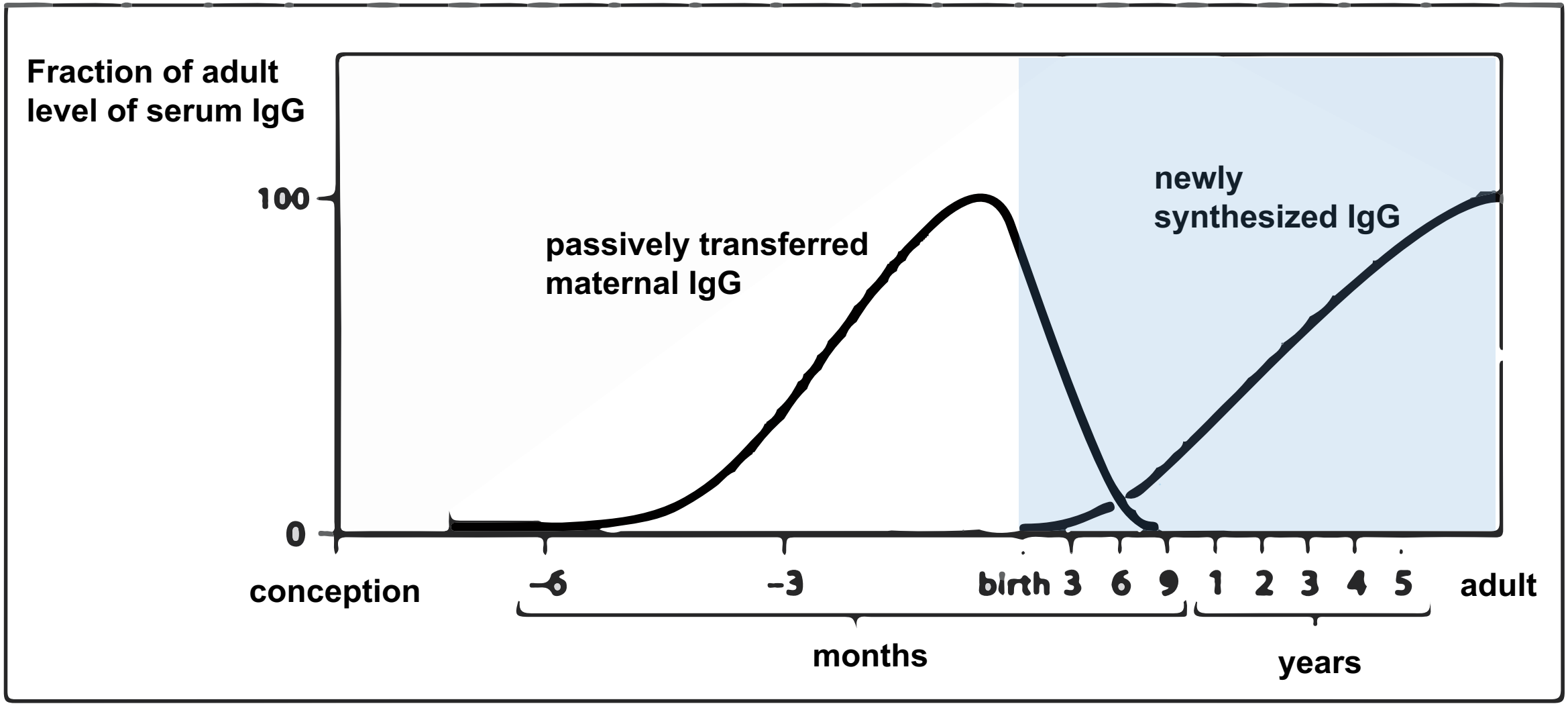
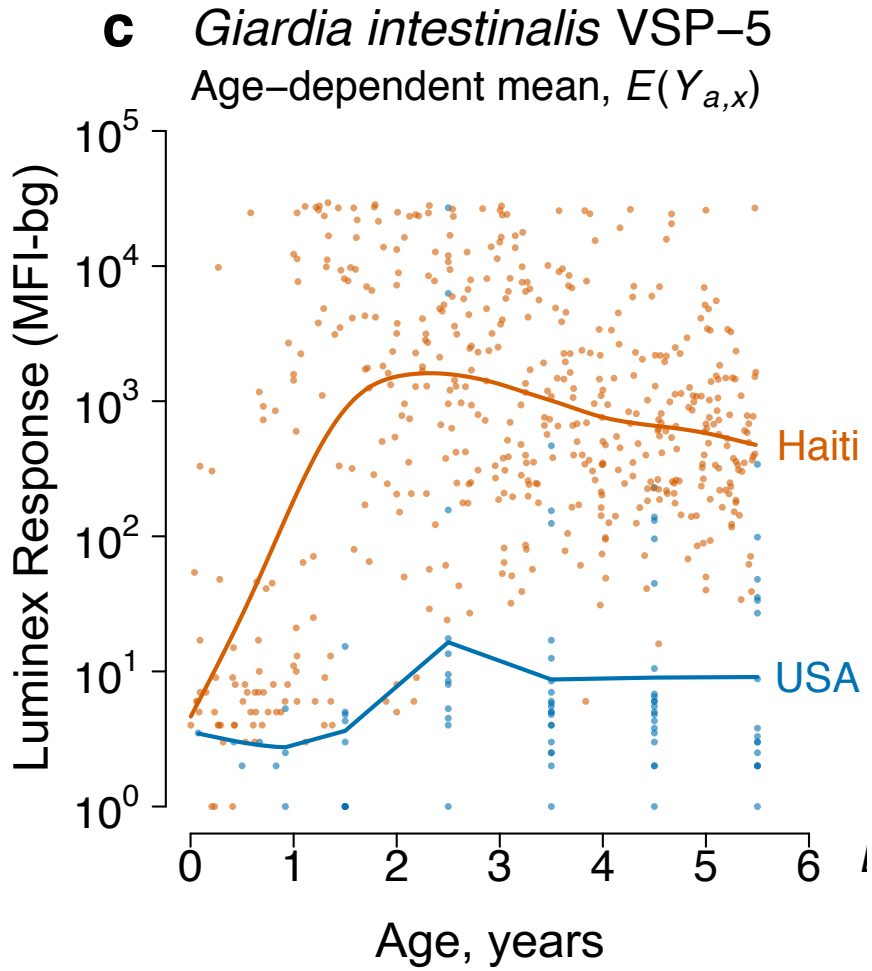


Figure 9.24 (edited), The Human Immune System, 3rd ed. (© Garland Science 2009)

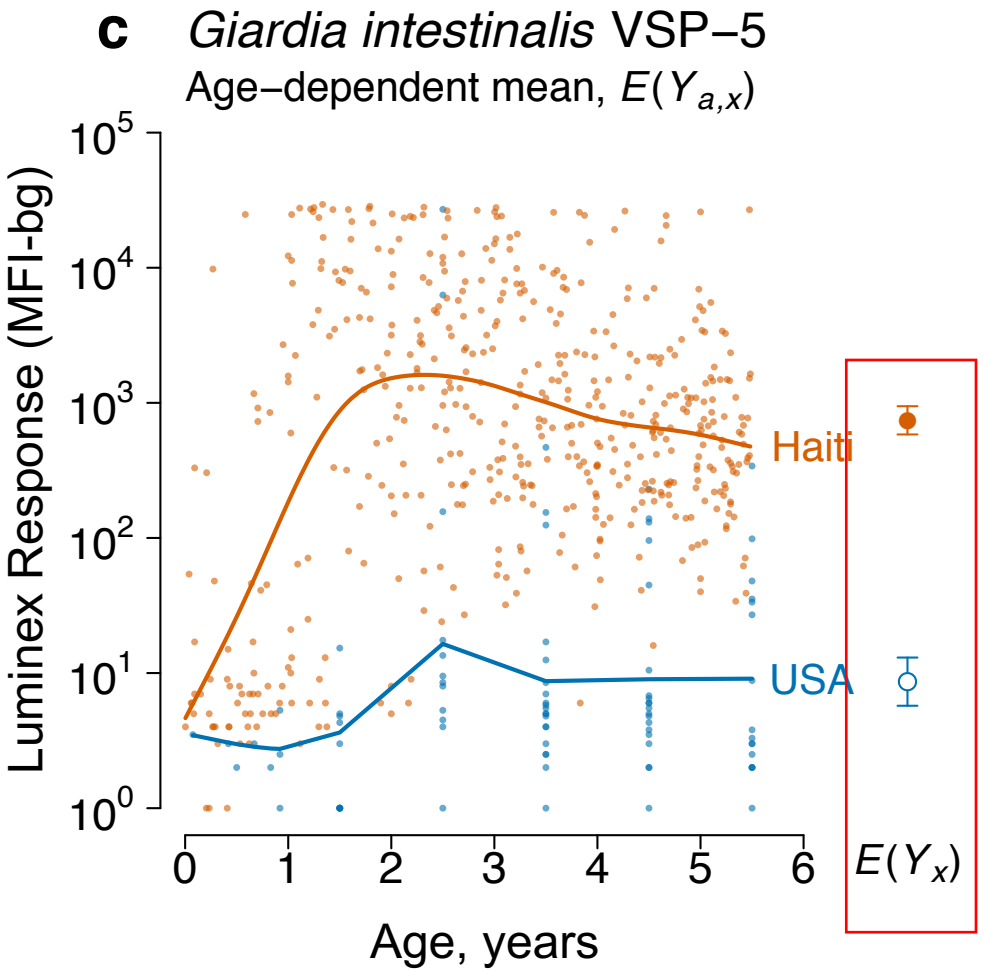
Population mean antibody levels reveal consistent patterns despite enormous between-individual variation in response



Lower transmission = curve shift

- Slower rise
- Lower plateau

Population mean antibody level summarizes the curve

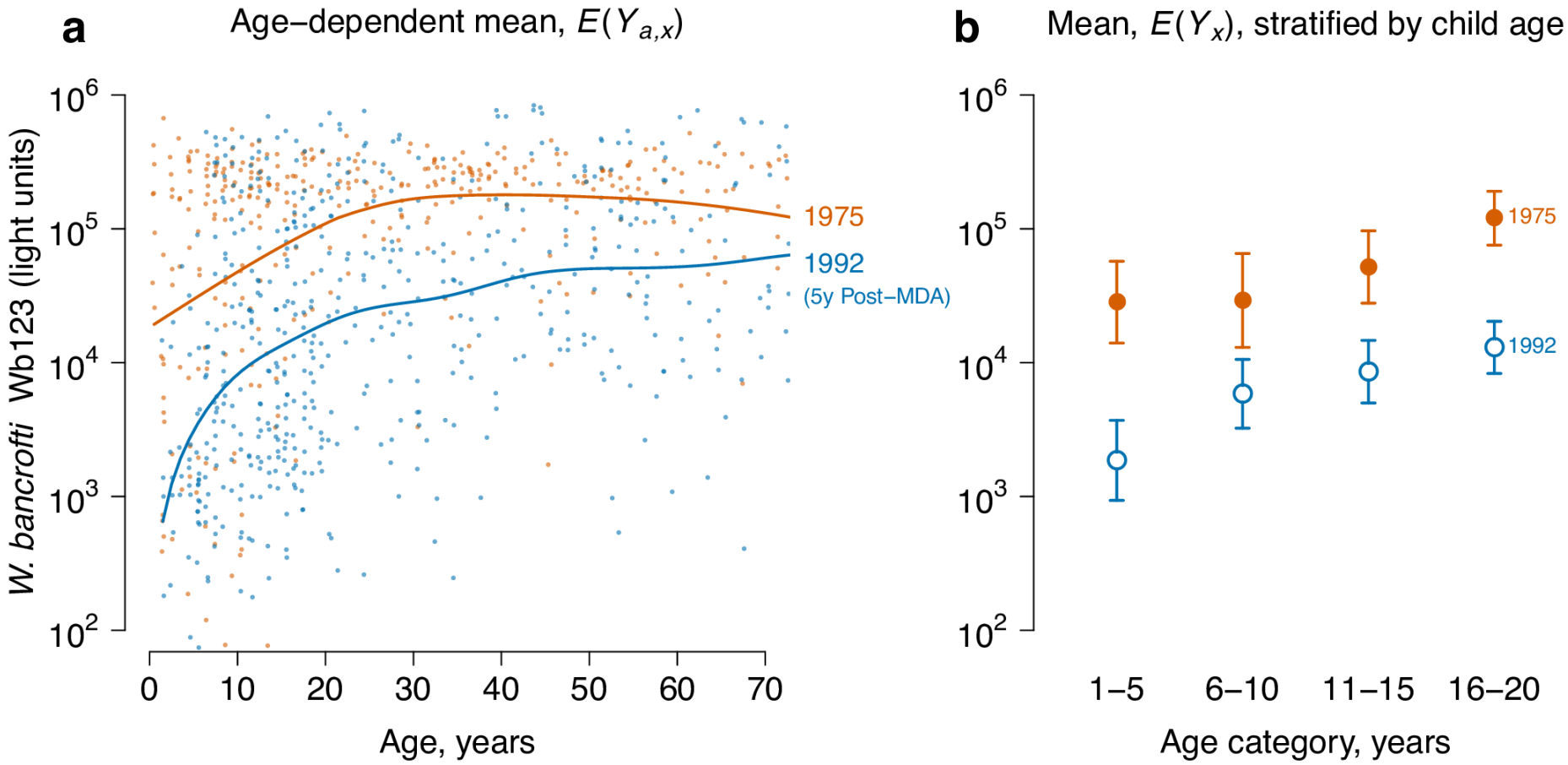


Nice interpretation:

The mean equals the area under the curve, so it captures the steepness of its rise and its sustained height

Arnold et al. *PLOS NTDs*, 2017; 11(5): e0005616. S1 Text: https://doi.org/10.1371/journal.pntd.0005616.s001

W. bancrofti antibody curves before and after mass drug administration, Mauke (Cook Islands)



Arnold et al. *PLOS NTDs* 2017; 11(5): e0005616. Steel et al. *PLOS NTDs* 2012; 6(12): e1940.

Topics

Seroprevalence can be difficult to interpret for antibody responses that boost and wane with repeated exposures

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Advantages, limitations and the bottom line

Mbita, Kenya study

Am. J. Trop. Med. Hyg., 96(6), 2017, pp. 1460–1467
doi:10.4269/ajtmh.16-0665

Multiplex Serologic Assessment of Schistosomiasis in Western Kenya: Antibody Responses in Preschool Aged Children as a Measure of Reduced Transmission

Kimberly Y. Won,[1]* Henry M. Kanyi,[2] Faith M. Mwende,[2] Ryan E. Wiegand,[1] E. Brook Goodhew,[1] Jeffrey W. Priest,[3] Yeuk-Mui Lee,[1] Sammy M. Njenga,[2] W. Evan Secor,[1] Patrick J. Lammie,[1] and Maurice R. Odiere[4]

Mbita, Kenya study

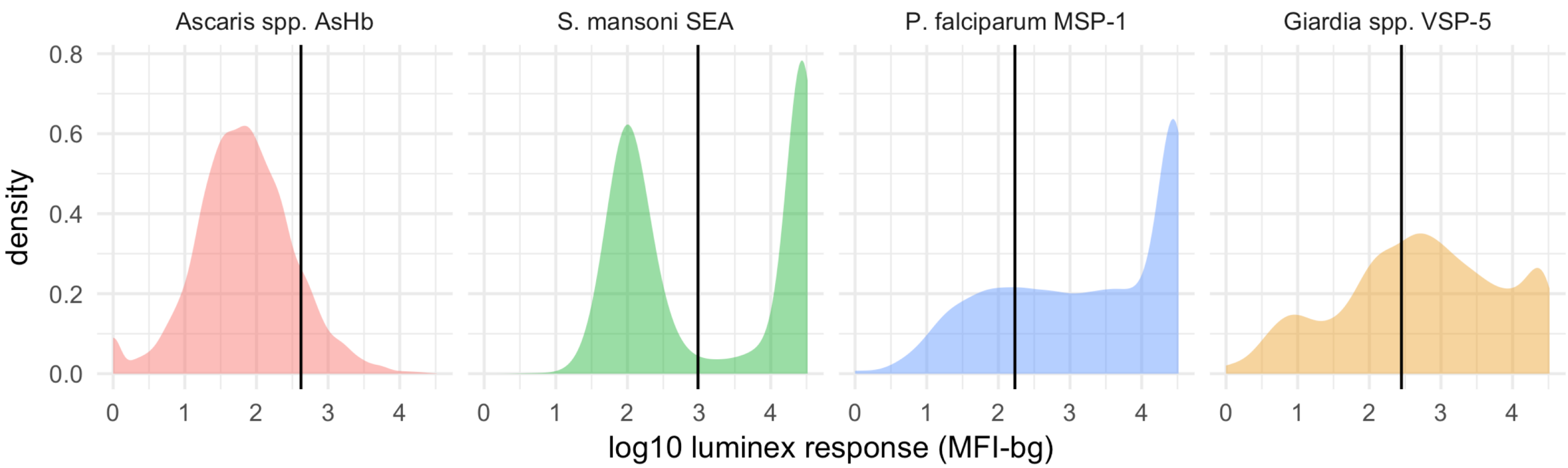
30 villages, repeated cross sectional surveys, 2012, 2013, 2014

3,663 children, ages 1 to 4 years

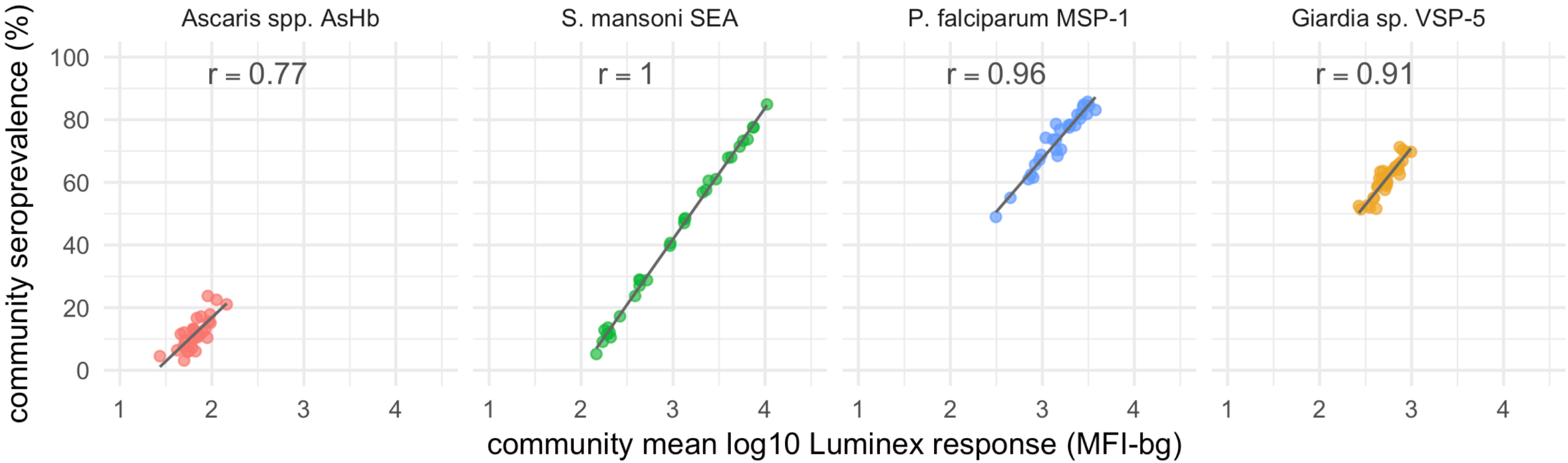
Tested blood in multiplex, including

- *Ascaris spp.* AsHb purified native hemoglobin from *Ascaris suum*
- *Schistosoma mansoni* SEA native soluble egg antigen
- *Plasmodium falciparum* MSP-1
- *Giardia intestinalis* VSP-5

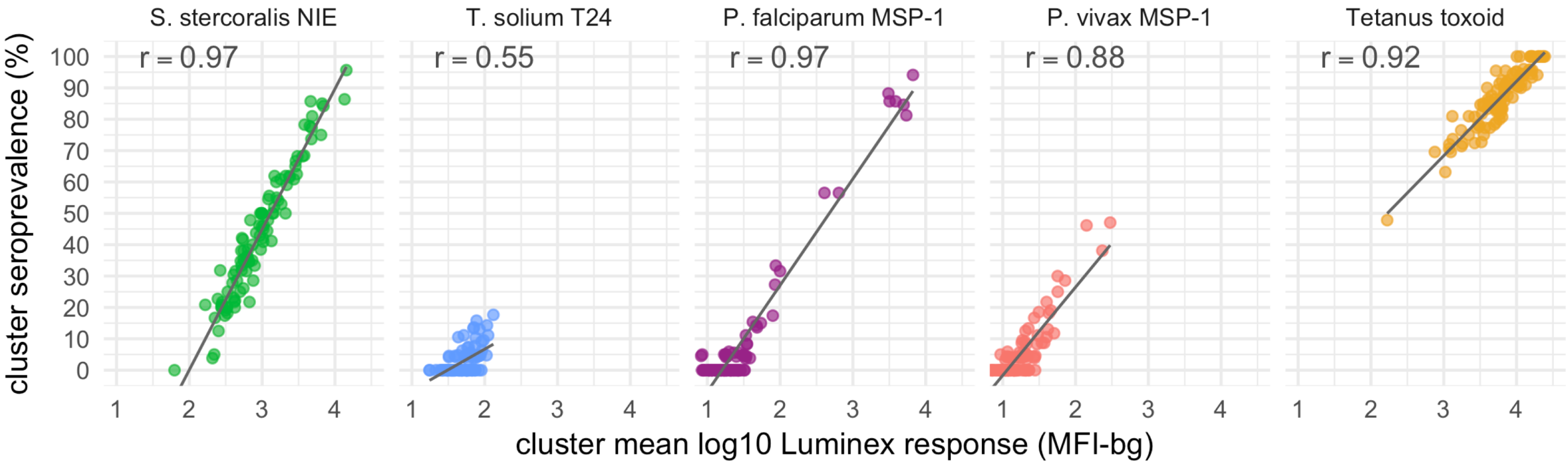
Distribution of antibody levels



Linear relationship between community-level mean MFI and seroprevalence



Linear relationship between cluster-level mean MFI and seroprevalence



Mao et al. *Epidemiol. Infect.* 2015; 143, 1858–1867
Priest et al. *PLOS NTDs.* 2016; 10(5): e0004699.
Arnold et al. *Emerg. Infect. Dis.* 2018; 24(7):1188-1194

Mean antibody levels and seroprevalence measure the same heterogeneity in exposure regardless of antibody distribution and cutoff

This is helpful to keep in mind because often we have no seropositivity cutoff, or we have a cutoff but it doesn't have a meaningful interpretation

Topics

Seroprevalence can be difficult to interpret for antibody responses that boost and wane with repeated exposures

Population mean antibody levels reflect differences in exposure, even for pathogens with complex immunology

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Comparison of antibody levels with other measures of transmission

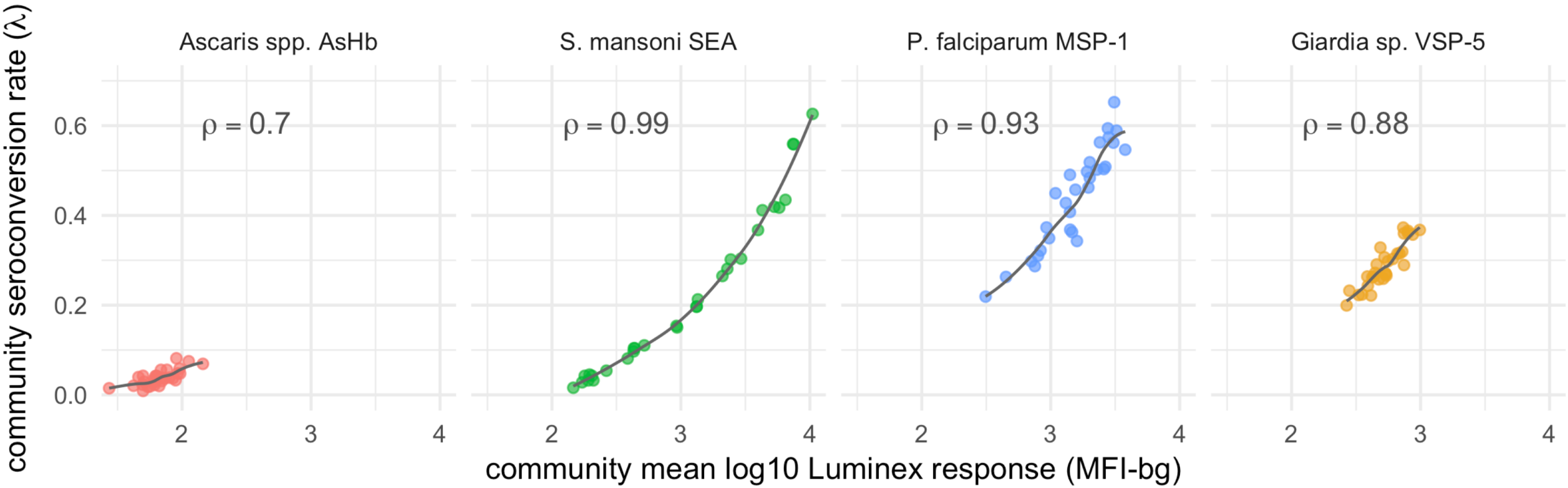
Advantages, limitations and the bottom line

Additional comparisons in Mbita, Kenya:

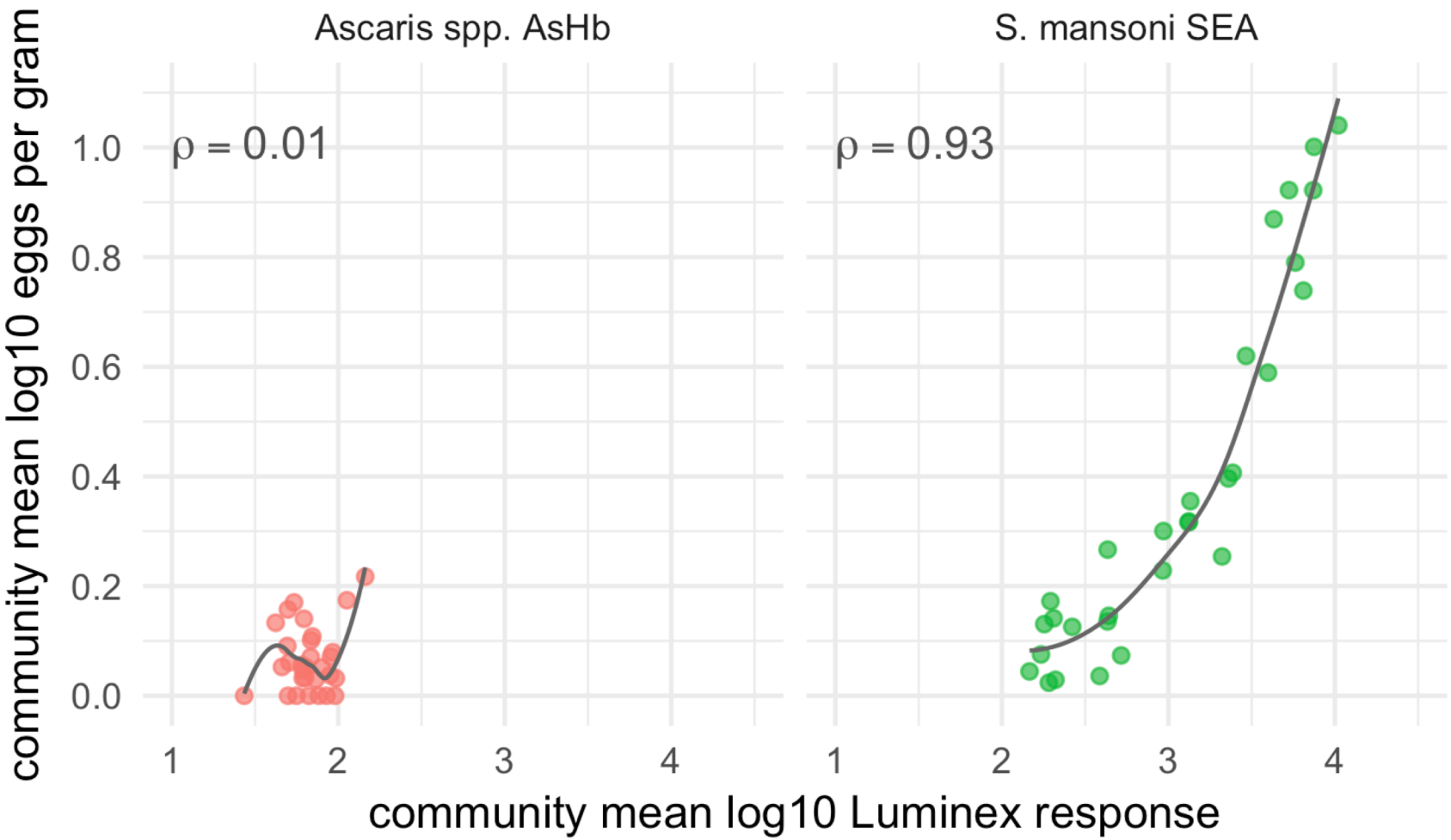
- Seroconversion rate (λ), a measure of force of infection
  - Average incidence of seroconversion among preschool aged children, estimated from age-structured seroprevalence

- Eggs per gram and prevalence measured by Kato-Katz
  - *Ascaris lumbricoides*, Kato-Katz community % range: 0% to 7%
  - *Schistosoma mansoni*, Kato-Katz community % range: 2% to 55%

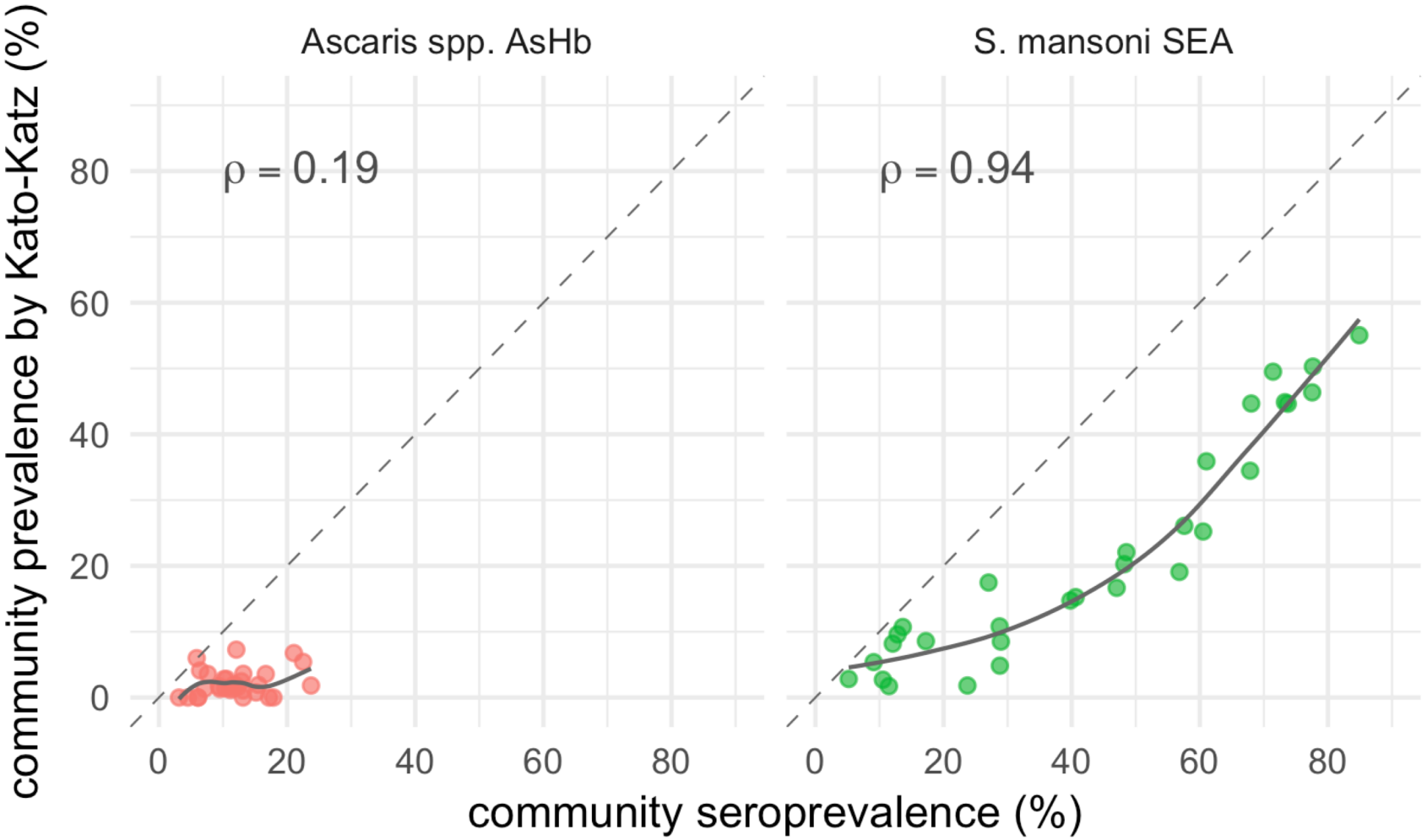
Quantitative antibody levels provide the same information about heterogeneity in exposure as the seroconversion rate



Community-level mean antibody response strongly associated with eggs per gram in stool for *S. mansoni*



S. mansoni : more resolution and higher levels of seroprevalence compared with prevalence by Kato-Katz



Topics

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Comparison of helminth antibody levels with other measures of transmission

Advantages, limitations and the bottom line

Advantages of quantitative antibody levels

Comparing population exposure using quantitative antibody levels is a general approach that requires almost no assumptions

By integrating exposure over time, antibody response can provide more information than measures of patent infection

In some examples, quantitative antibody levels embed more information than binary seroprevalence (not shown today)

- Malaria example: Helb et al. *PNAS* 2015; 112: e4438-47
- LF & malaria examples: Arnold et al. *PLOS NTDs* 2017; 11(5): e0005616

Limitations of using quantitative antibody levels:

1. Only provides an indirect measure of transmission
   - versus patent infection or seroconversion rates

2. No reference standards exist for most antigens, so quantitative levels remain in arbitrary units and are assay-dependent
   - Difficult to make direct comparisons between pathogens and between studies
   - Reference standards exist for vaccine preventable disease antigens – an inspiration for other disease groups!

Bottom line:

Quantitative antibody levels are a robust summary measure of exposure when you cannot estimate seroprevalence or you cannot interpret it

Use seroprevalence when you can for epidemiologic interpretation

…. but you are asking more of the data so check your assumptions to ensure that seroprevalence actually means something useful, such as “recently exposed”

contributors and funders

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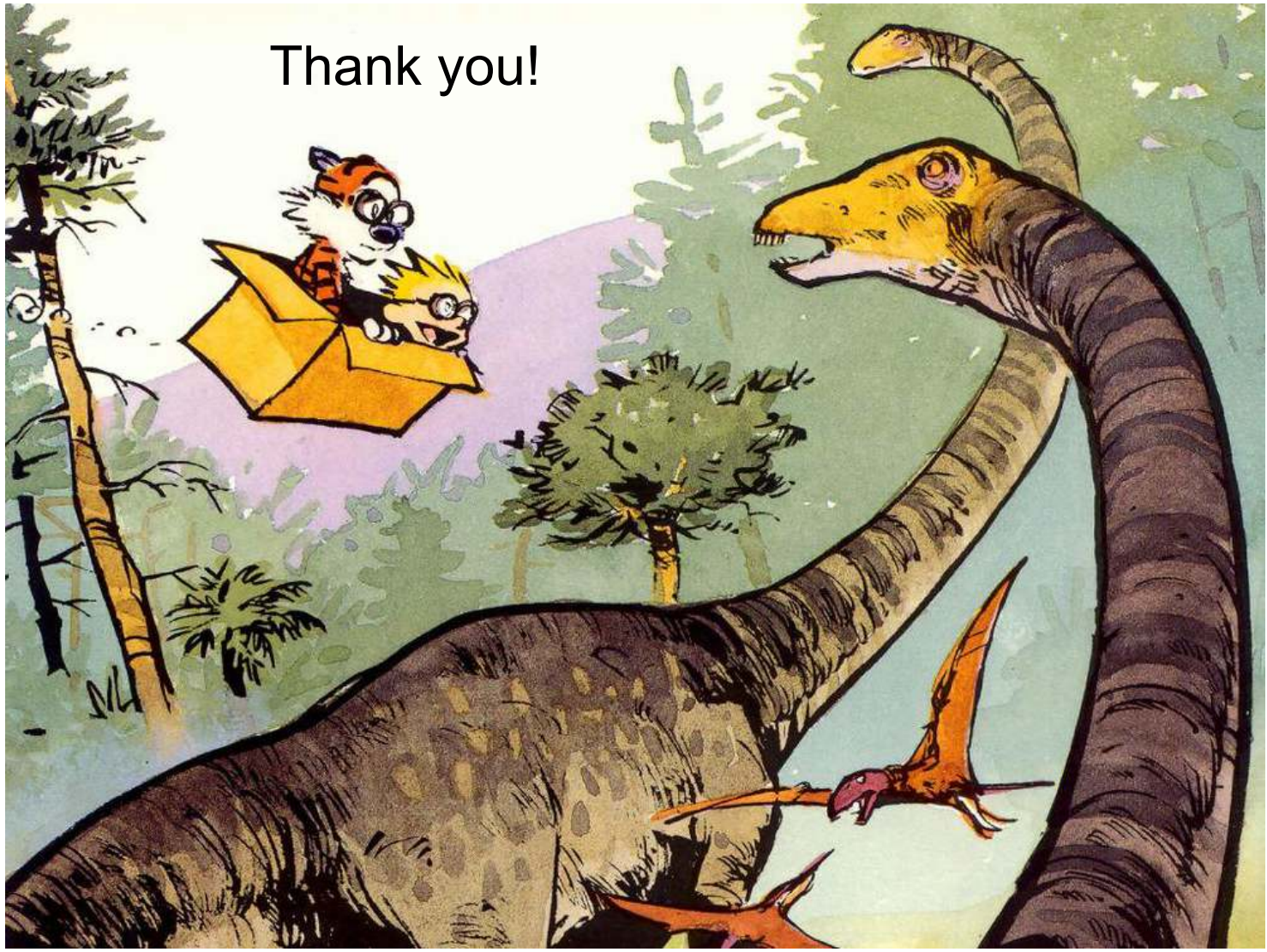
Principal funding for this work

NIH / NIAID: K01-AI119180

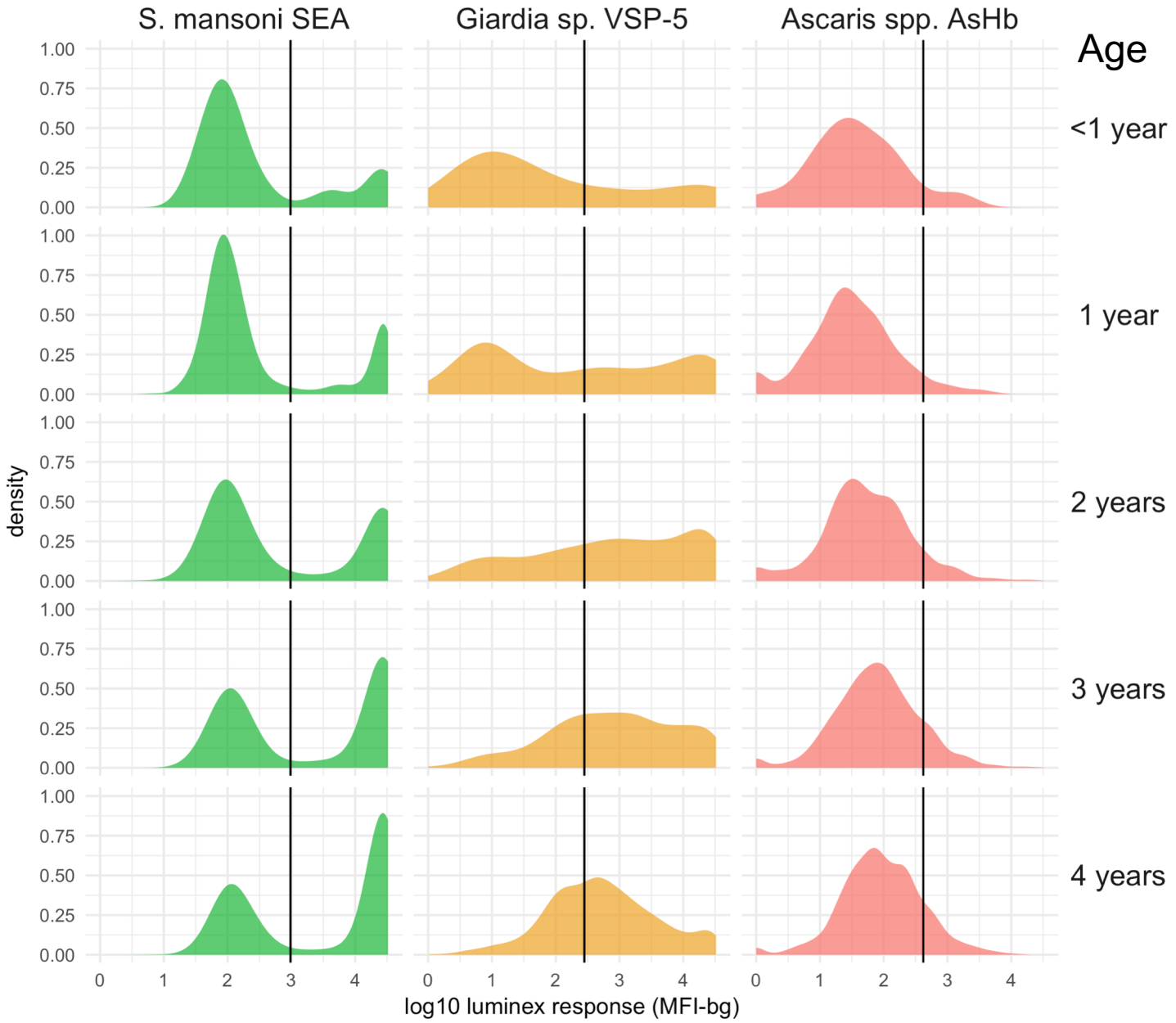


Watterson

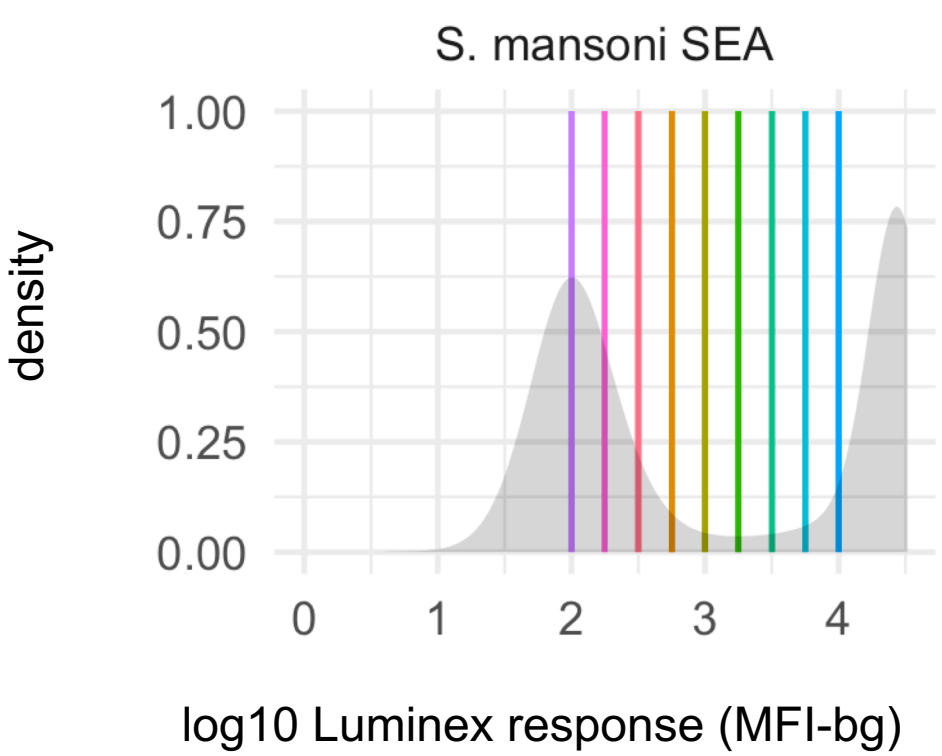
extra slides

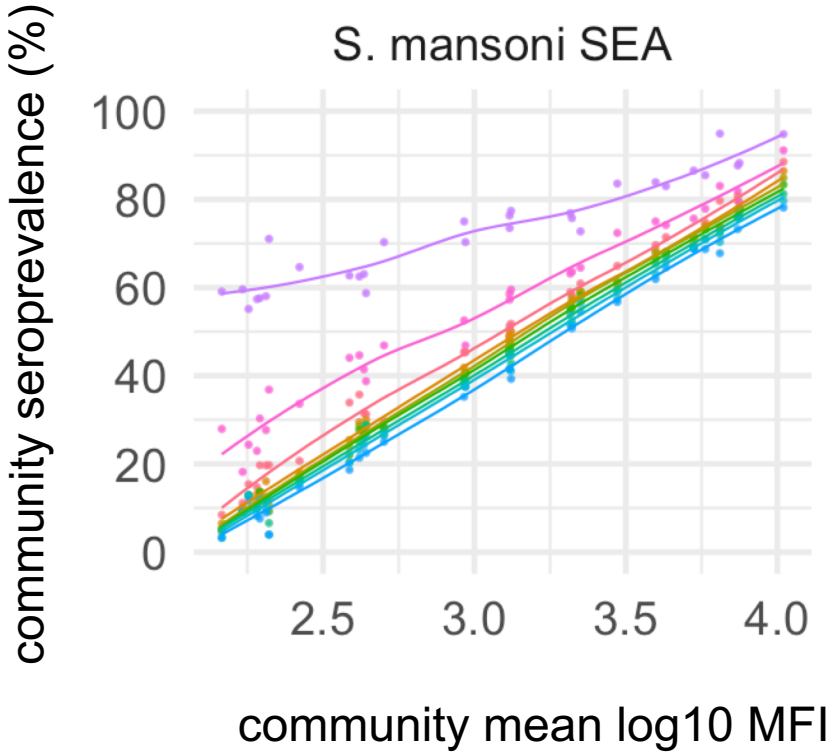
Pathogen / disease	Antigens included in multiplex	Well Characterized?
Lymphatic filariasis (*W. bancrofti*)	Bm14, Bm33, Wb123	YES
River blindness (*O. volvulus*)	Ov16, Ov17, Ov33	YES
Schistosomiasis (*S. mansoni*)	SEA, Sm25	YES
Cysticercosis (*Taenia solium*)	T24H	YES
Strongyloidiasis (*S. stercoralis*)	NIE	YES
Ascariasis (*Ascaris spp.*)	AsHb	NO
Trachoma (*C. trachomatis*)	Pgp3, CT694	YES
Cryptosporidium spp.	Cp17, Cp23, CpP2	YES
Giardia intestinalis	VSP1-5,7	YES
Entamoeba histolytica	LecA	YES
Norovirus	VLP GI.4, VLP GII.4 NO	NO
Campylobacter jejuni	p18, p39	NO
Salmonella, serotype Typhimurium	LPS Group B	NO
Salmonella, serotype Enteriditis	LPS Group D	NO
Enterotoxigenic *E. coli* (ETEC)	heat labile toxin β subunit	NO
Vibrio cholerae	Cholera toxin β subunit	IN PROGRESS

Stable versus shifting antibody distributions in Mbita, Kenya



Sensitivity analysis of the effect of different cutoffs on the relationship between community mean MFI and seroprevalence





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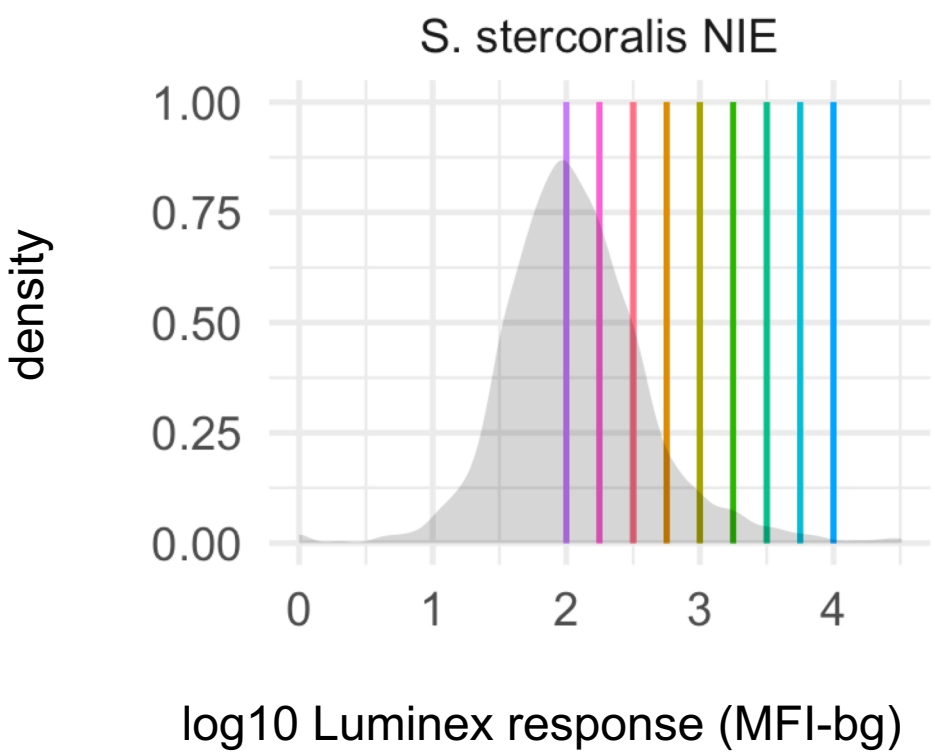

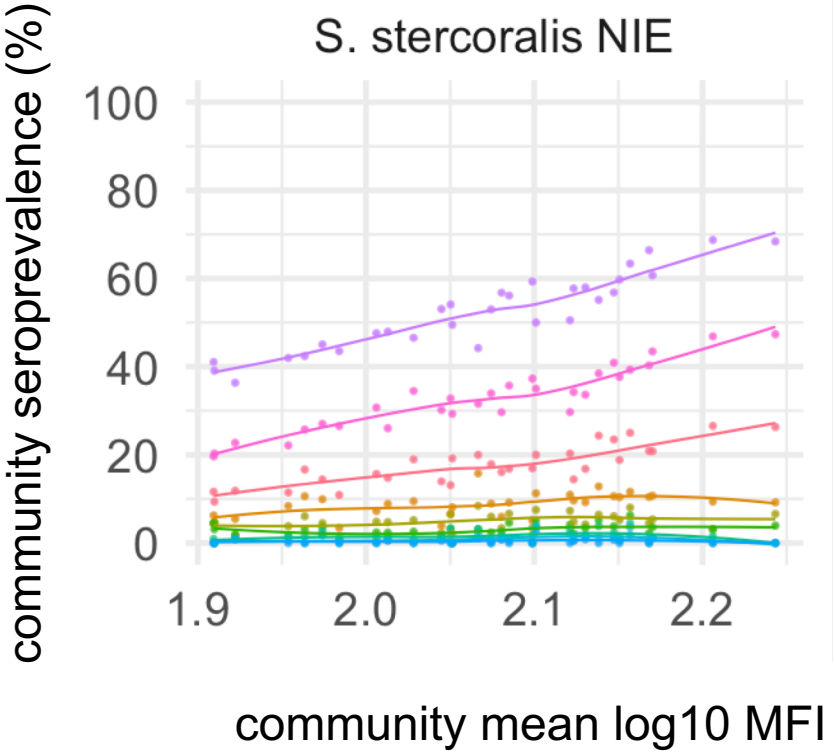

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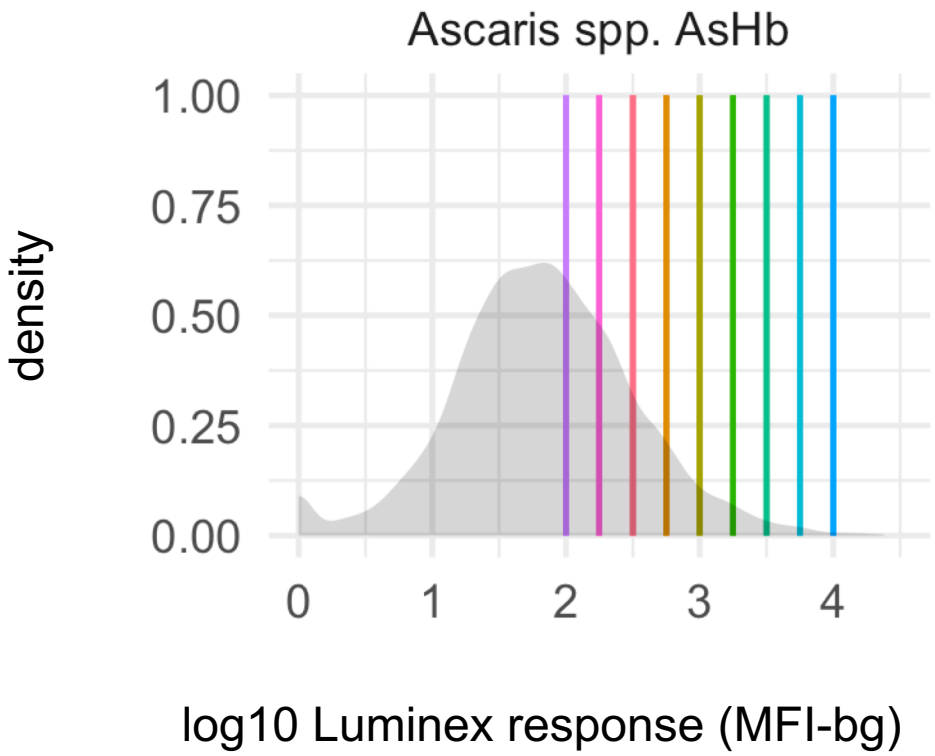

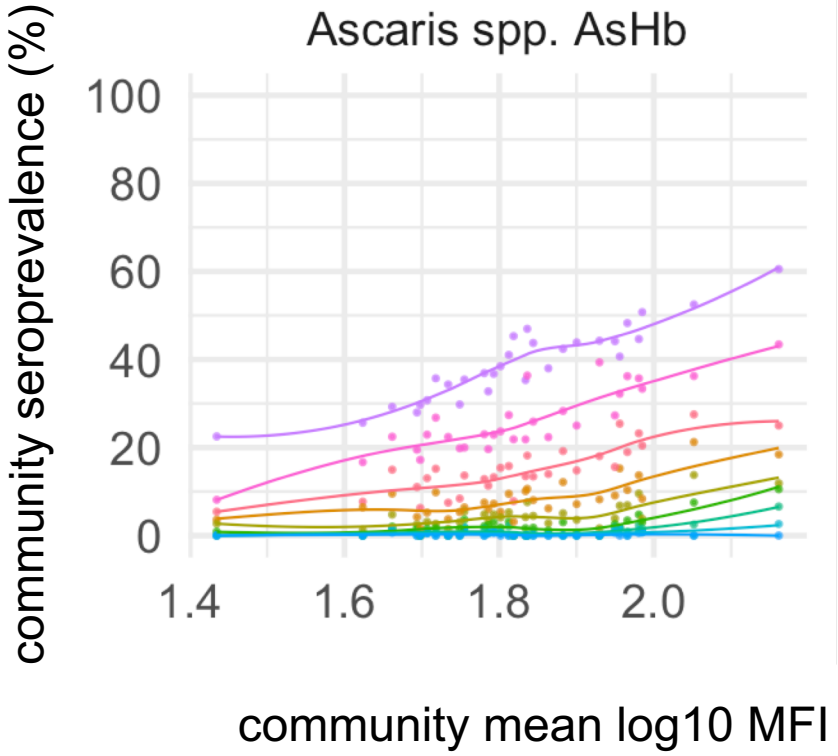

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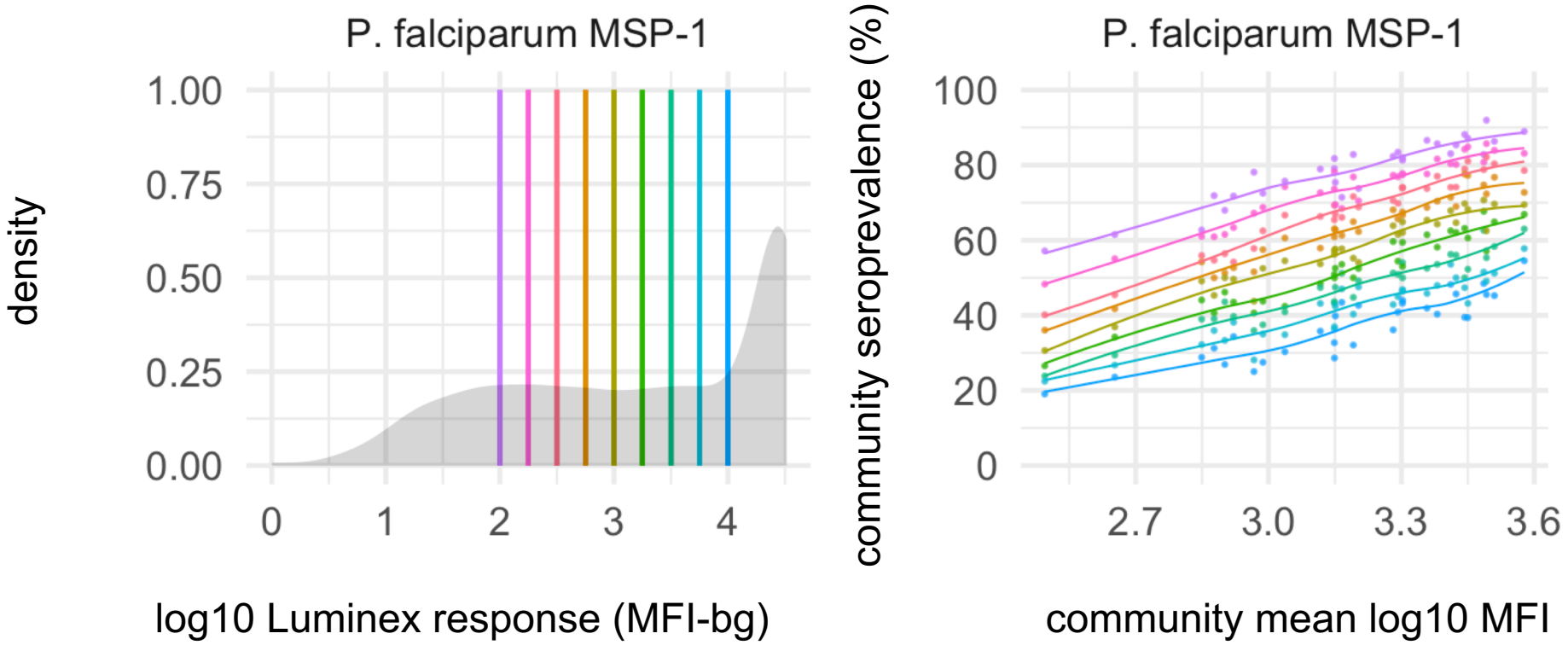

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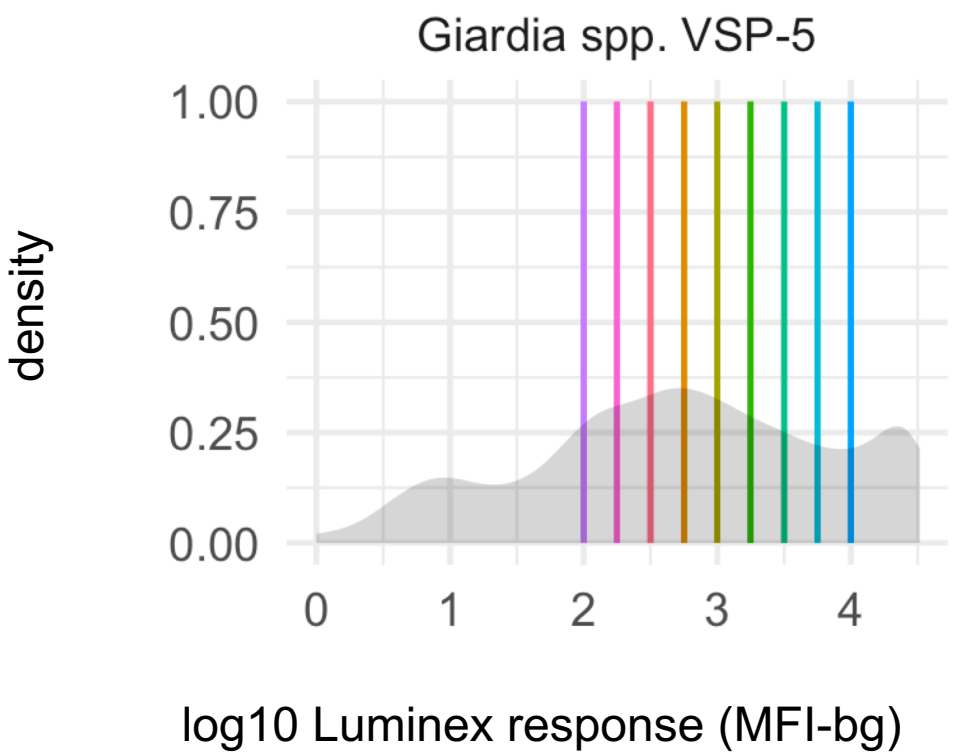
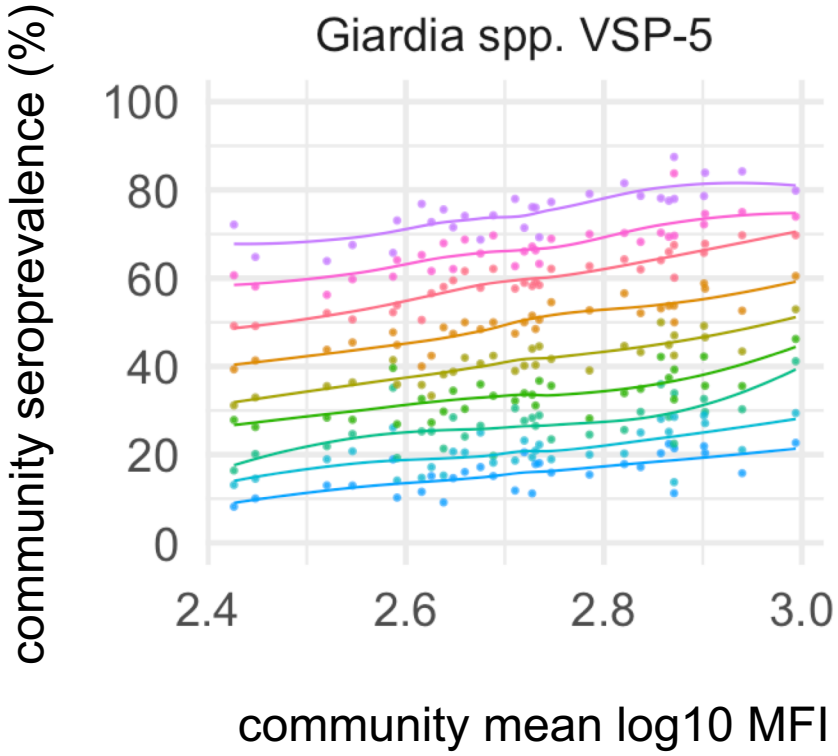
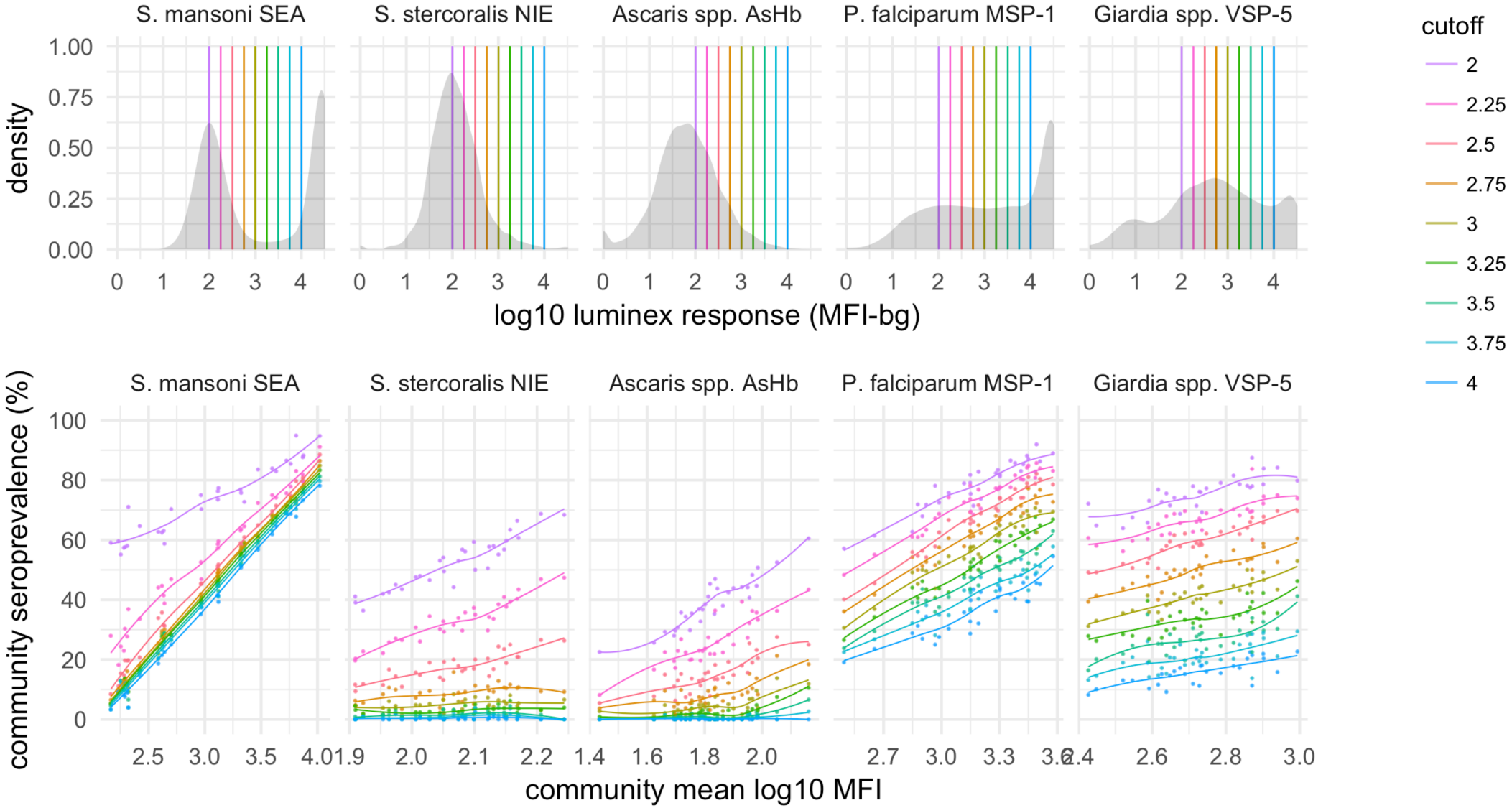
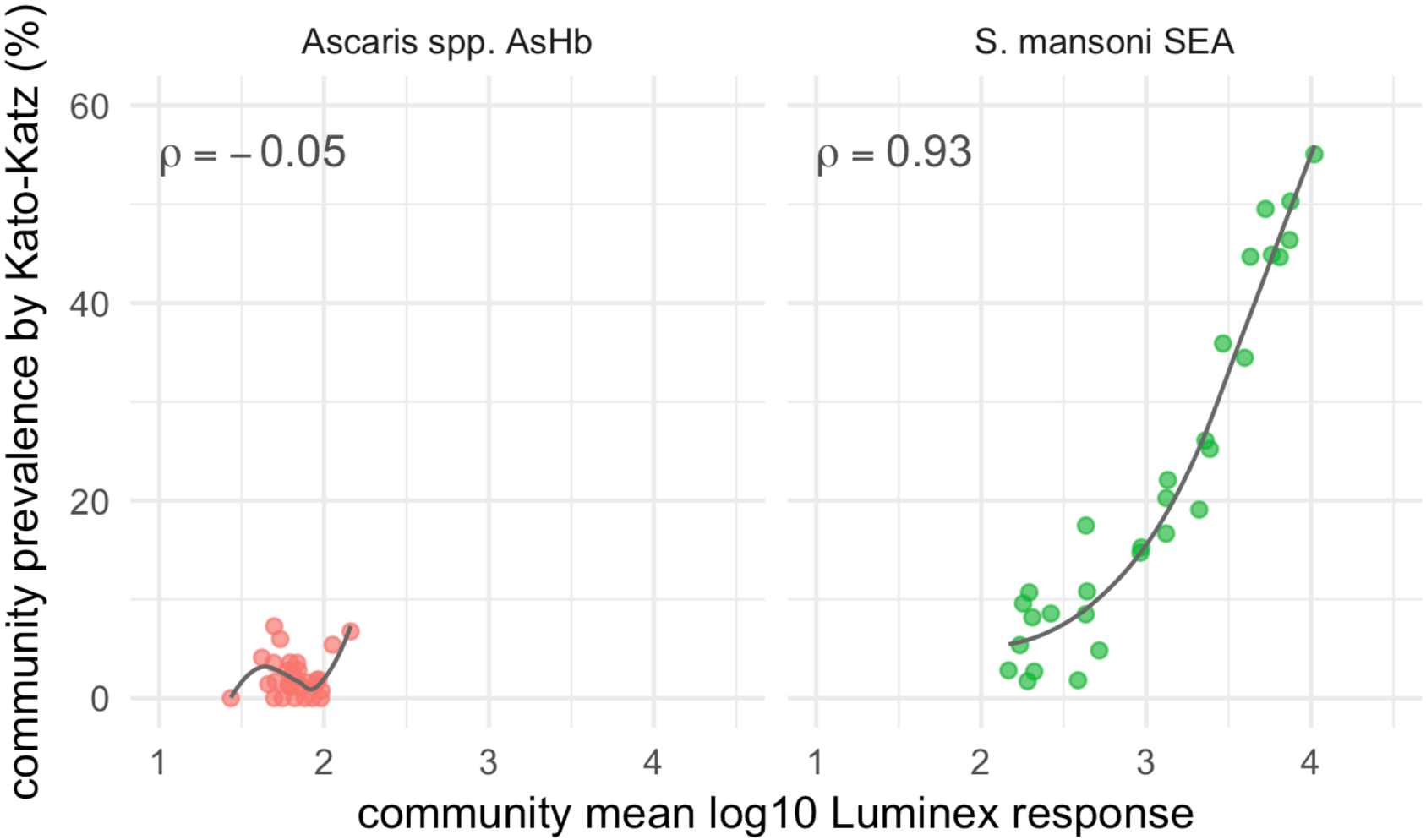




Linear relationship between mean MFI and seroprevalence across all cutoffs, but there is a change in level (intercept)



Community-level mean antibody response strongly associated with infection prevalence by Kato-Katz in stool for *S. mansoni*



Implications:

Community mean antibody levels strongly related to seroconversion rates

- An extension of the relationship with seroprevalence
- Must assume that “seronegative” indicates an individual was not previously seropositive over the age period
- This assumption is questionable for at least *Giardia* in this example

For schistosomiasis, antibody-based measures provide similar community-level information as stool based measures of infection using Kato-Katz.

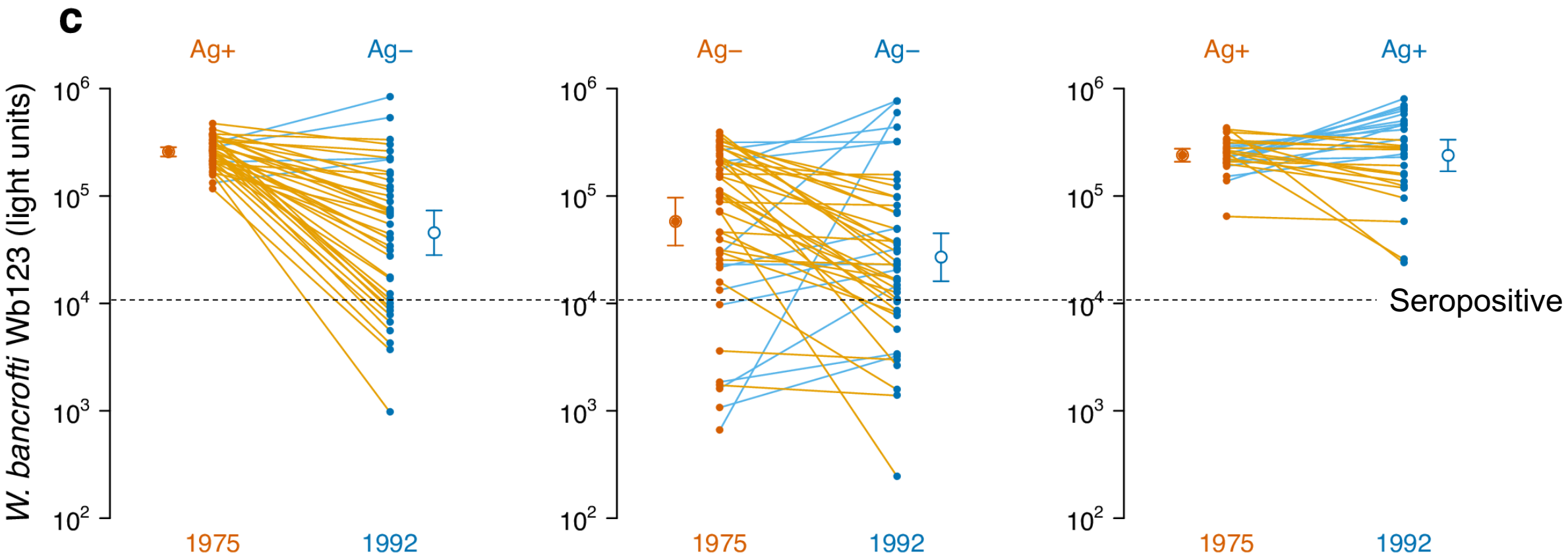
Example of a well-validated antigen with a durable response that can still result in an ambiguous antibody distribution:

W. bancrofti Wb123 on Mauke, Cook Islands

Steel et al. *PLOS NTDs* 2012; 6(12): e1940.
Arnold et al. *PLOS NTDs* 2017; 11(5): e0005616.

Individual-level Wb123 trajectories by whether they were antigenemic (Ag +/-), a measure of active infection in 1975 and 1992

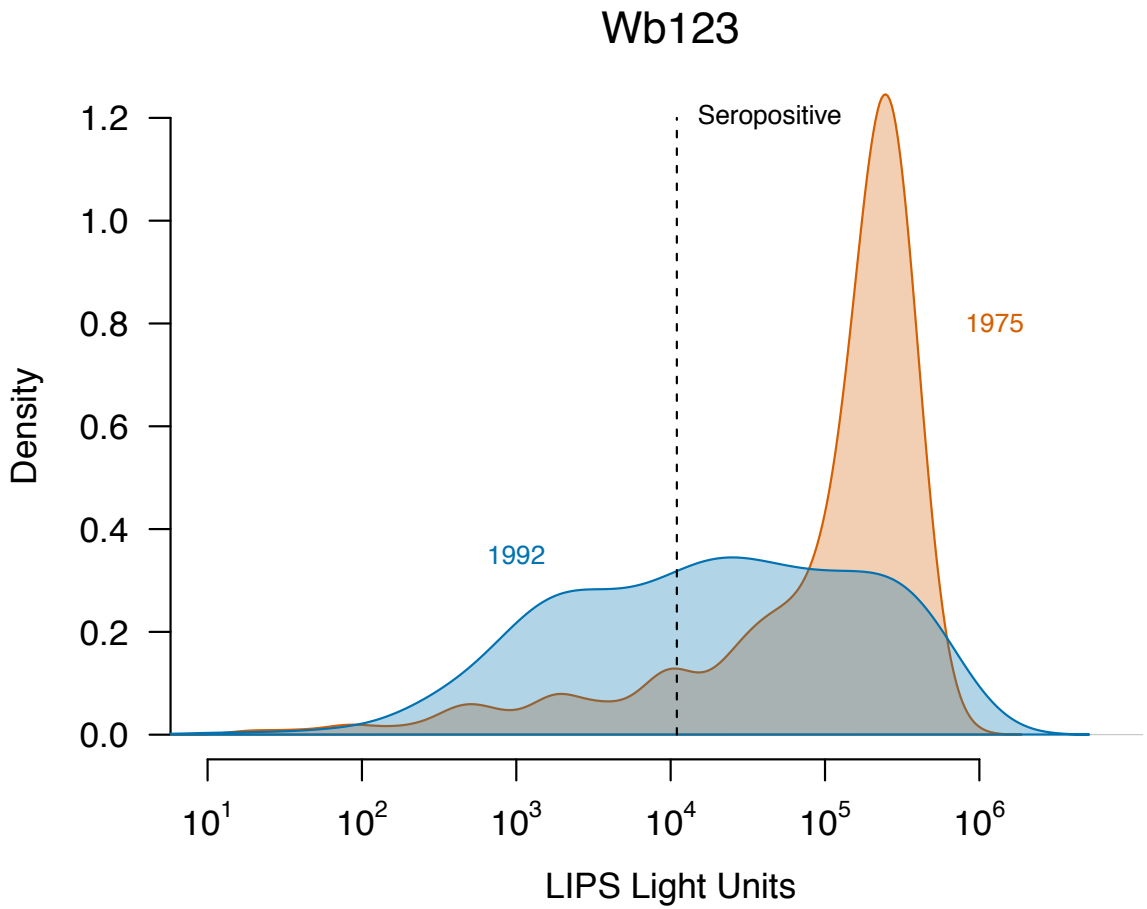
Evidence of slowly waning antibody levels between surveys



Arnold et al. *PLOS NTDs* 2017; 11(5): e0005616.

Wb123 distribution by 1992 was likely a complex mixture of unexposed, previously exposed, and currently infected

Complicates the interpretation of “seronegative”



Arnold et al. *PLOS NTDs* 2017; 11(5): e0005616.

Example 2: Cambodia immunoprotection survey, 2012

Nationally representative, population-based survey

100 sampling clusters

Enrolled 2,150 women

Ages 15-39 years

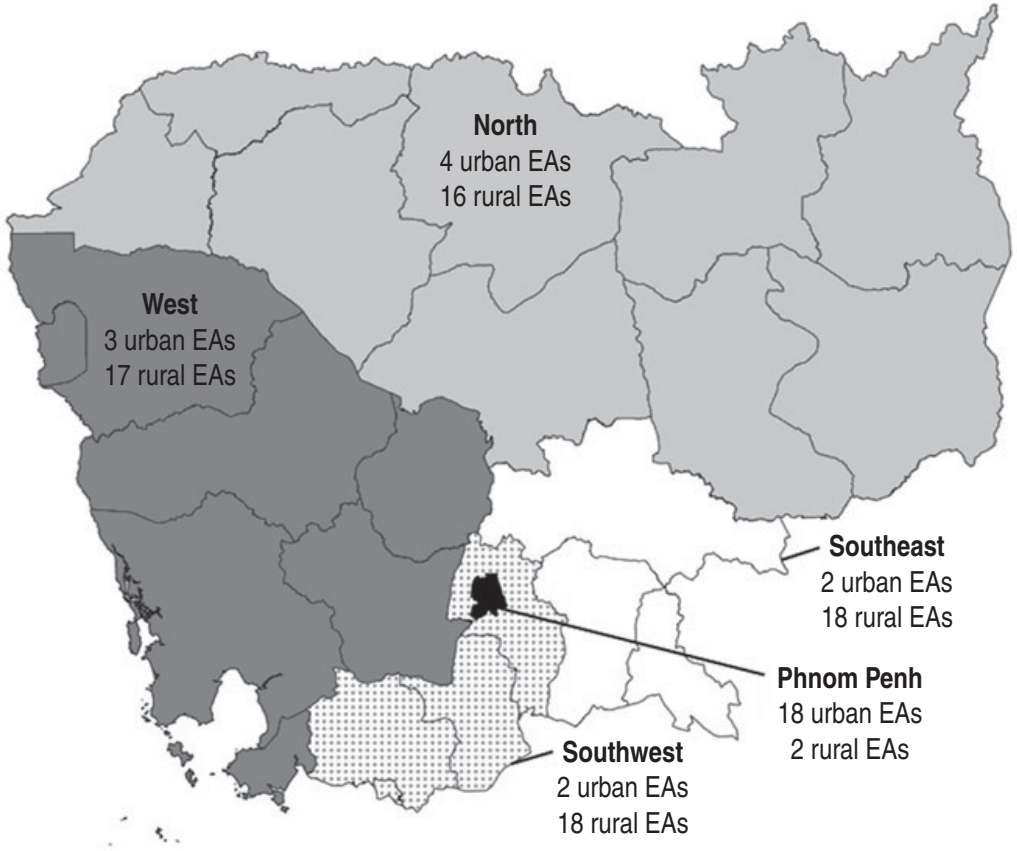


Fig. 1. Map of Cambodia illustrating the five regions for the 2012 vaccine-preventable disease serological survey and the number of urban and rural enumeration areas (EA) included the survey for each region. Cambodian provinces by region:

Mao et al. *Epidemiol. Infect.* 2015; 143, 1858–1867
Priest et al. *PLOS NTDs.* 2016; 10(5): e0004699.
Arnold et al. *Emerg. Infect. Dis.* 2018; 24(7):1188-1194

Example: Coastal Kenya LF survey

Njenga *et al. Parasites & Vectors* (2017) 10:99
DOI 10.1186/s13071-017-2044-5

Parasites & Vectors

RESEARCH Open Access

Assessment of lymphatic filariasis prior to re-starting mass drug administration campaigns in coastal Kenya

Sammy M. Njenga[1*], Henry M. Kanyi[1], Faith M. Mutungi[1], Collins Okoyo[1], Hadley S. Matendechero[2], Rachel L. Pullan[3], Katherine E. Halliday[3], Simon J. Brooker[3], C. Njeri Wamae[4], Joyce K. Onsongo[5] and Kimberly Y. Won[6]

Coastal Kenya LF survey (Njenga et al. *in review*)

Cross sectional survey, 2015

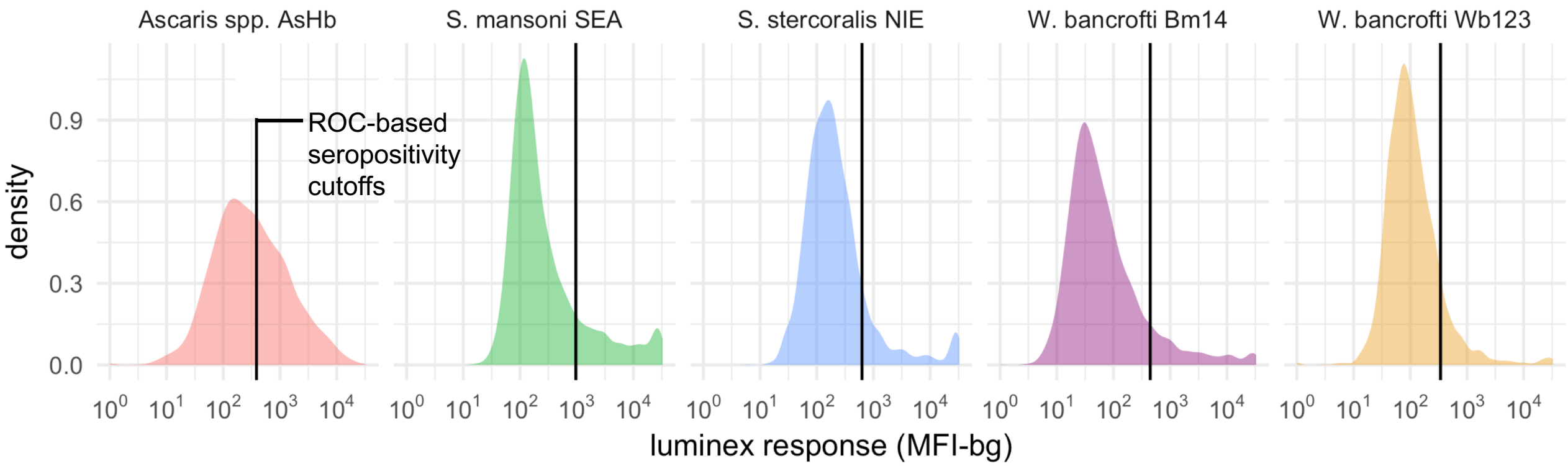
10 villages in coastal Kenya

2,837 participants, ages 2 to 100 y

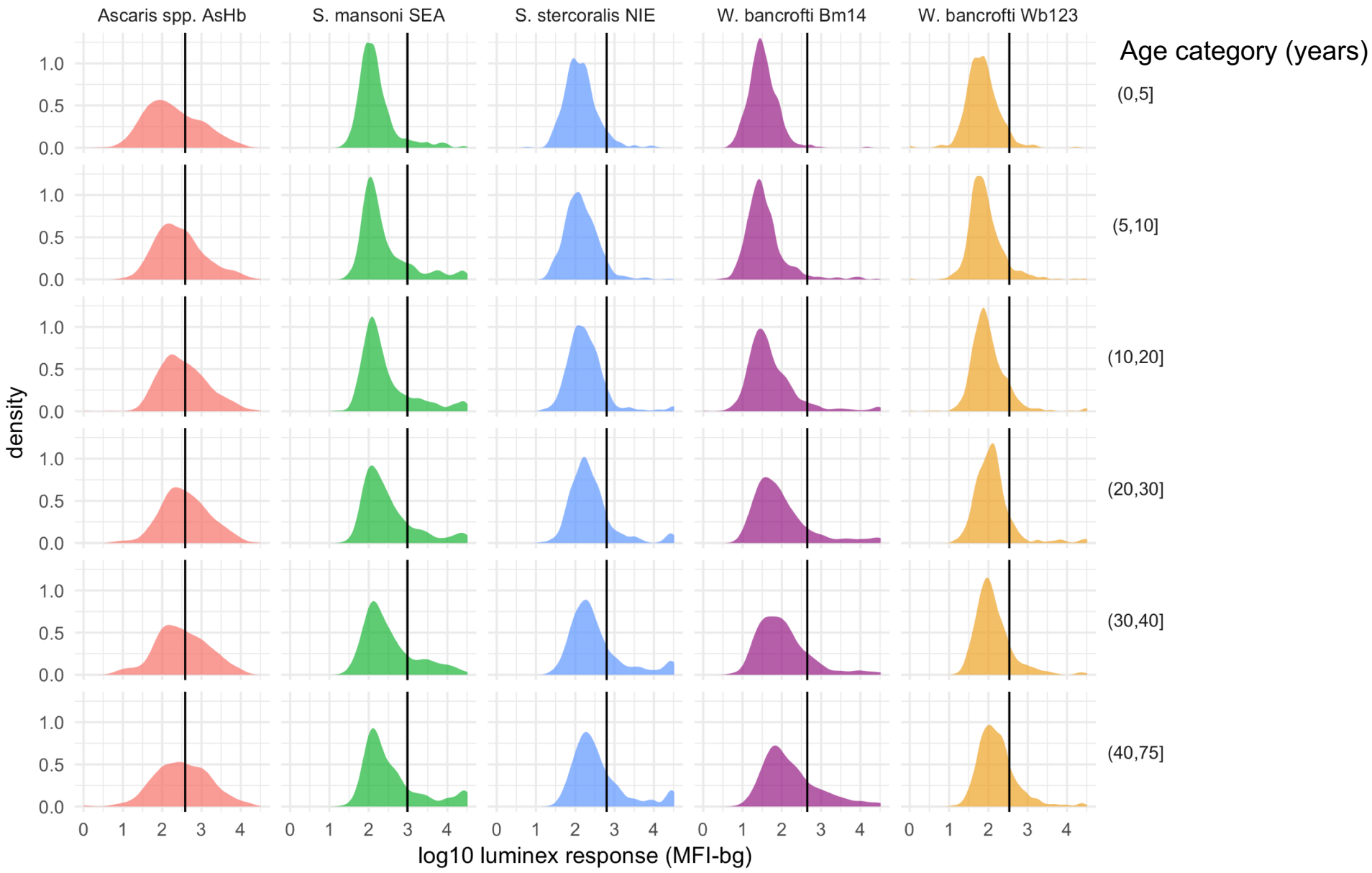
Tested blood in multiplex with many antigens, including:

- *Ascaris spp.* AsHb : purified native hemoglobin from *Ascaris suum*
- *Schistosoma mansoni* SEA : native soluble egg antigen
- *Strongyloides stercoralis* NIE
- Lymphatic filariasis Bm14, Wb123

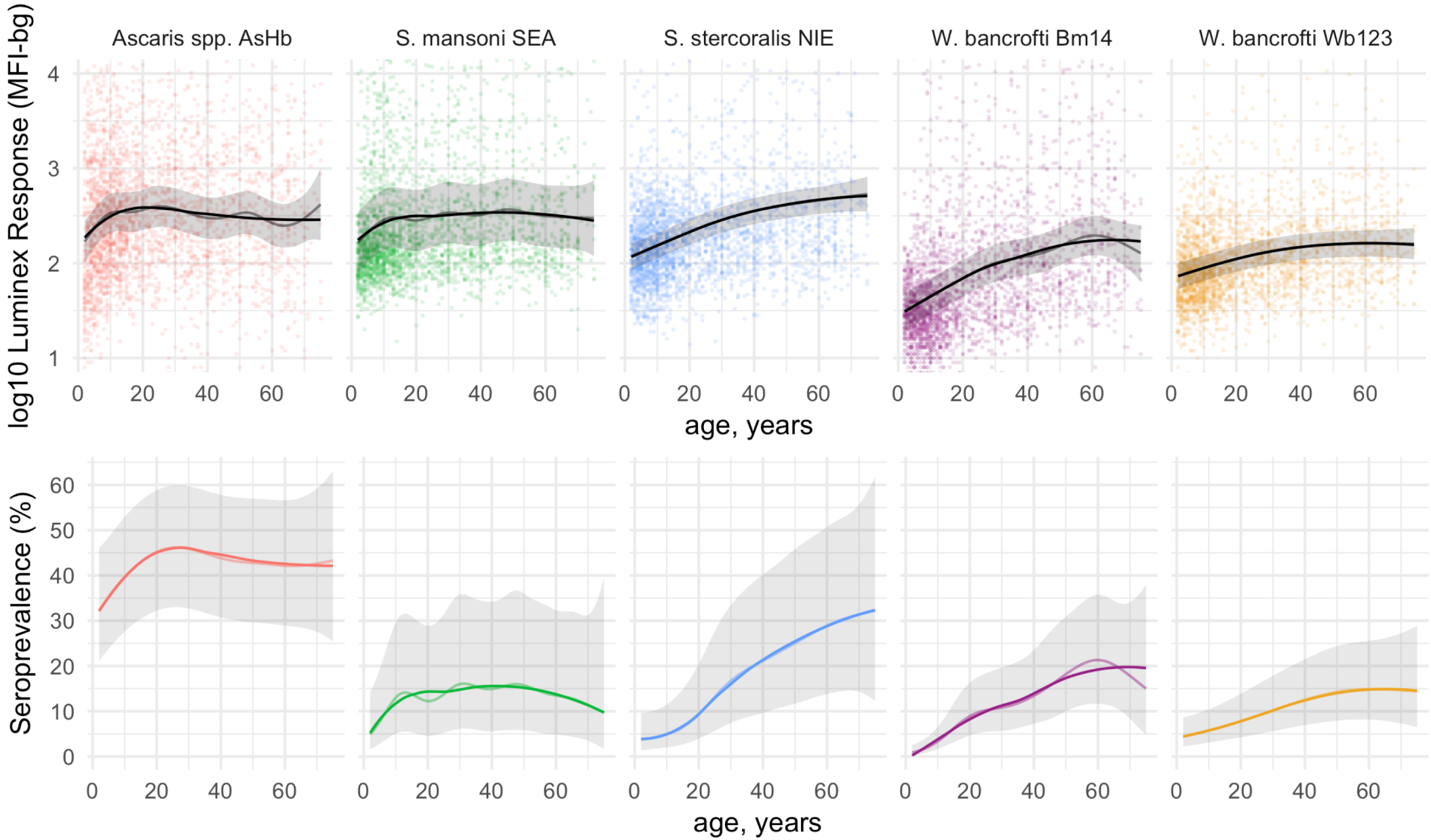
Distribution of antibody levels



Age-stratified antibody distributions, coastal Kenya



Age-dependent means and seroprevalence, coastal Kenya



Linear relationship between community-level mean MFI and seroprevalence