Bridging the Gap: Environmental and Sero-surveillance for Estimating Typhoid Burden

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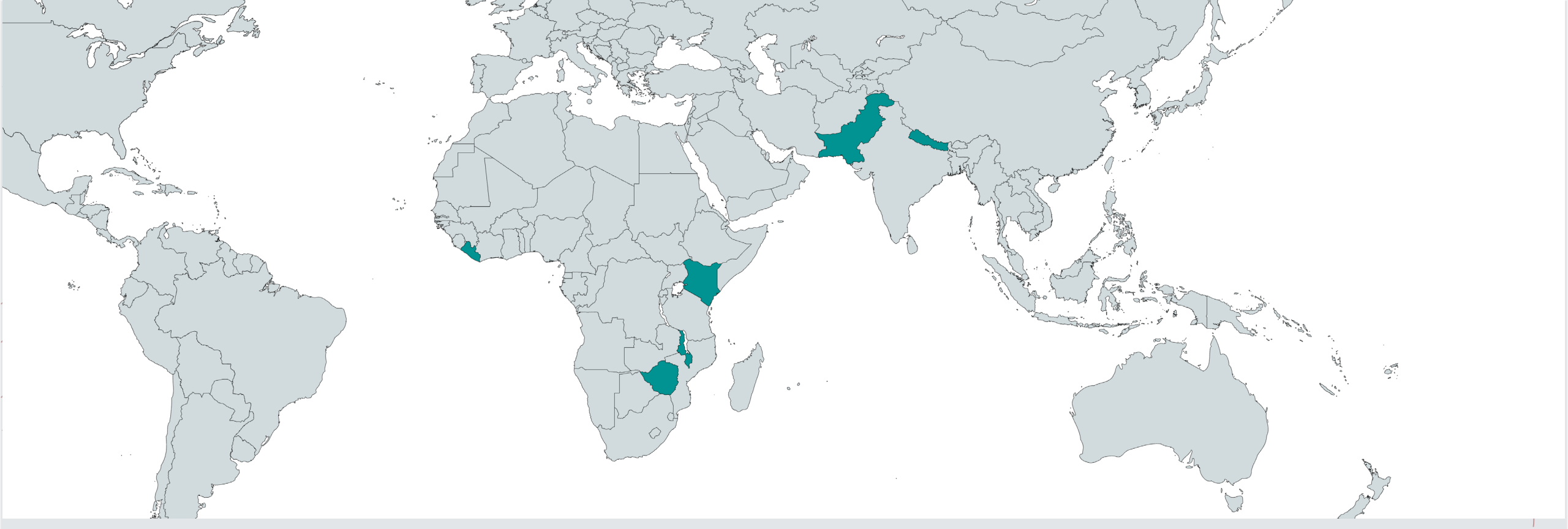
December 06, 2023

Together We Can Take on Typhoid

COALITION AGAINST TYPHOID
a program of the Sabin Vaccine Institute



Typhoid conjugate vaccines are effective but have yet to be widely adopted

Together We Can

Take on Typhoid

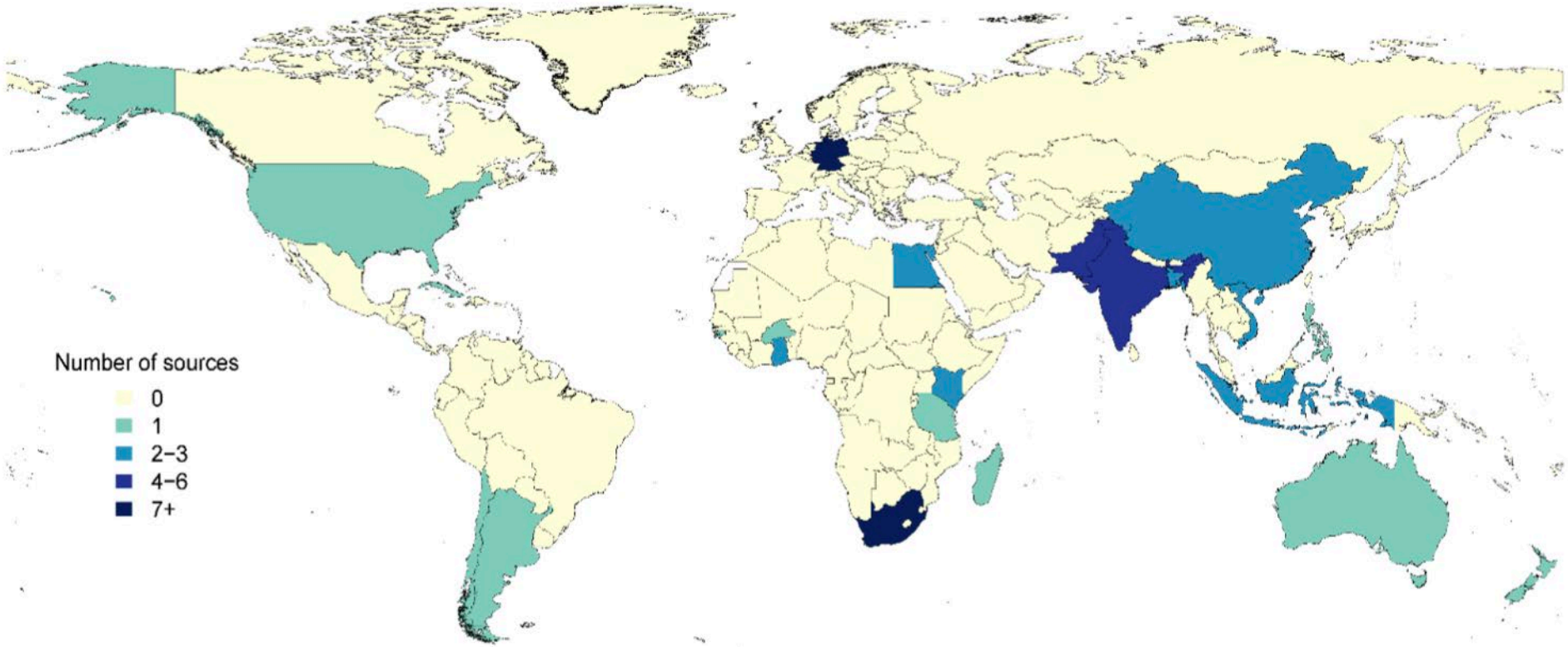
“Data inequality is our biggest challenge moving forward”

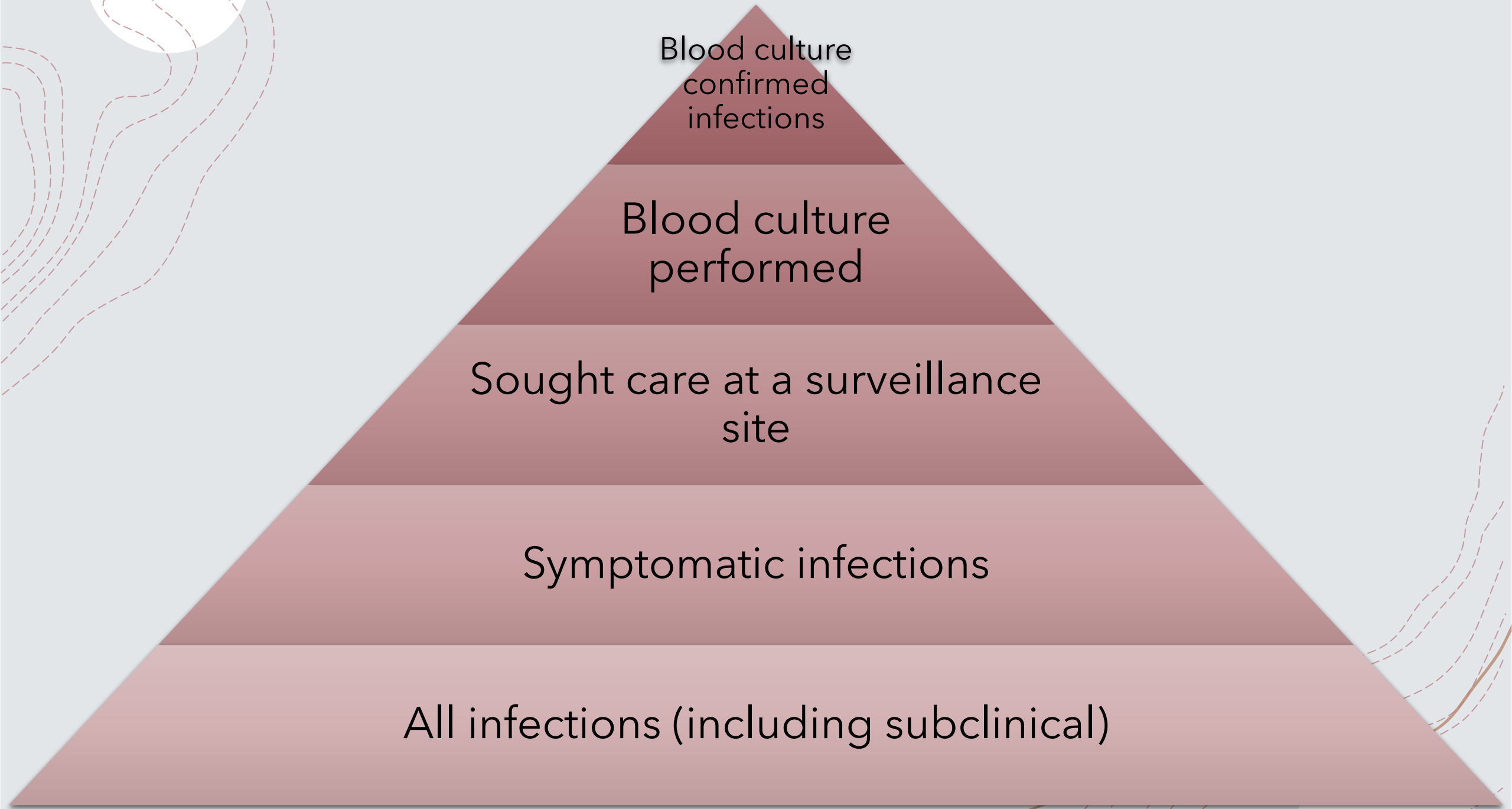
- Kathy Neuzil, ASTMH 2023

TyVAC Typhoid Vaccine Acceleration Consortium

The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017

*GBD 2017 Typhoid and Paratyphoid Collaborators**




Blood culture confirmed infections
Blood culture performed
Sought care at a surveillance site
Symptomatic infections
All infections (including subclinical)

LATEST ADVANCES IN SEROEPIDEMIOLOGY FOR ENTERIC FEVER

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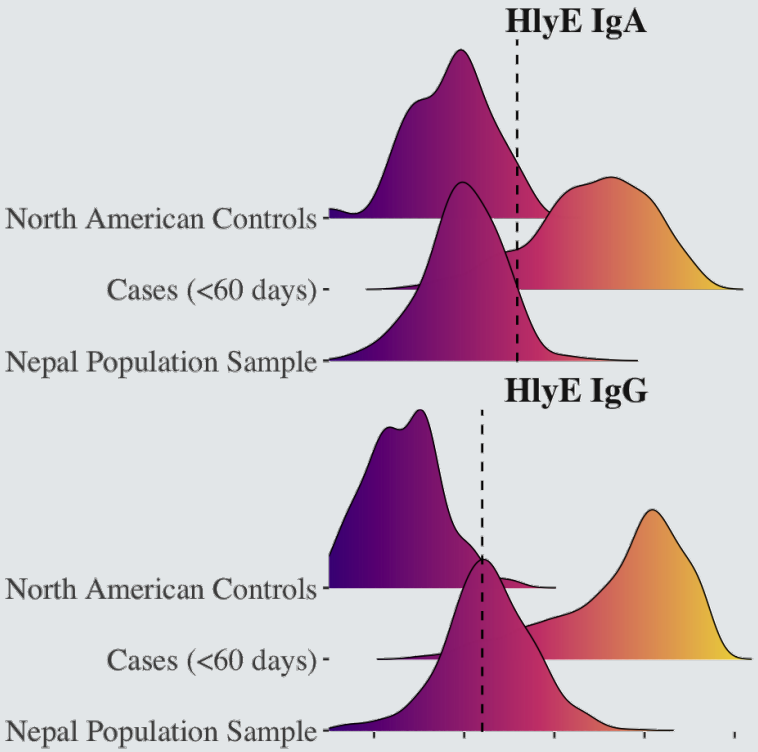
Department of Public Health Sciences
UC Davis School of Medicine
Department of Immunology and Microbiology
Mahidol University Faculty of Tropical Medicine
kaiemjoy@ucdavis.edu

UC DAVIS HEALTH

Mahidol University
Wisdom of the Land

Seroepidemiology & Environmental Surveillance for Enteric Fever (SEES)



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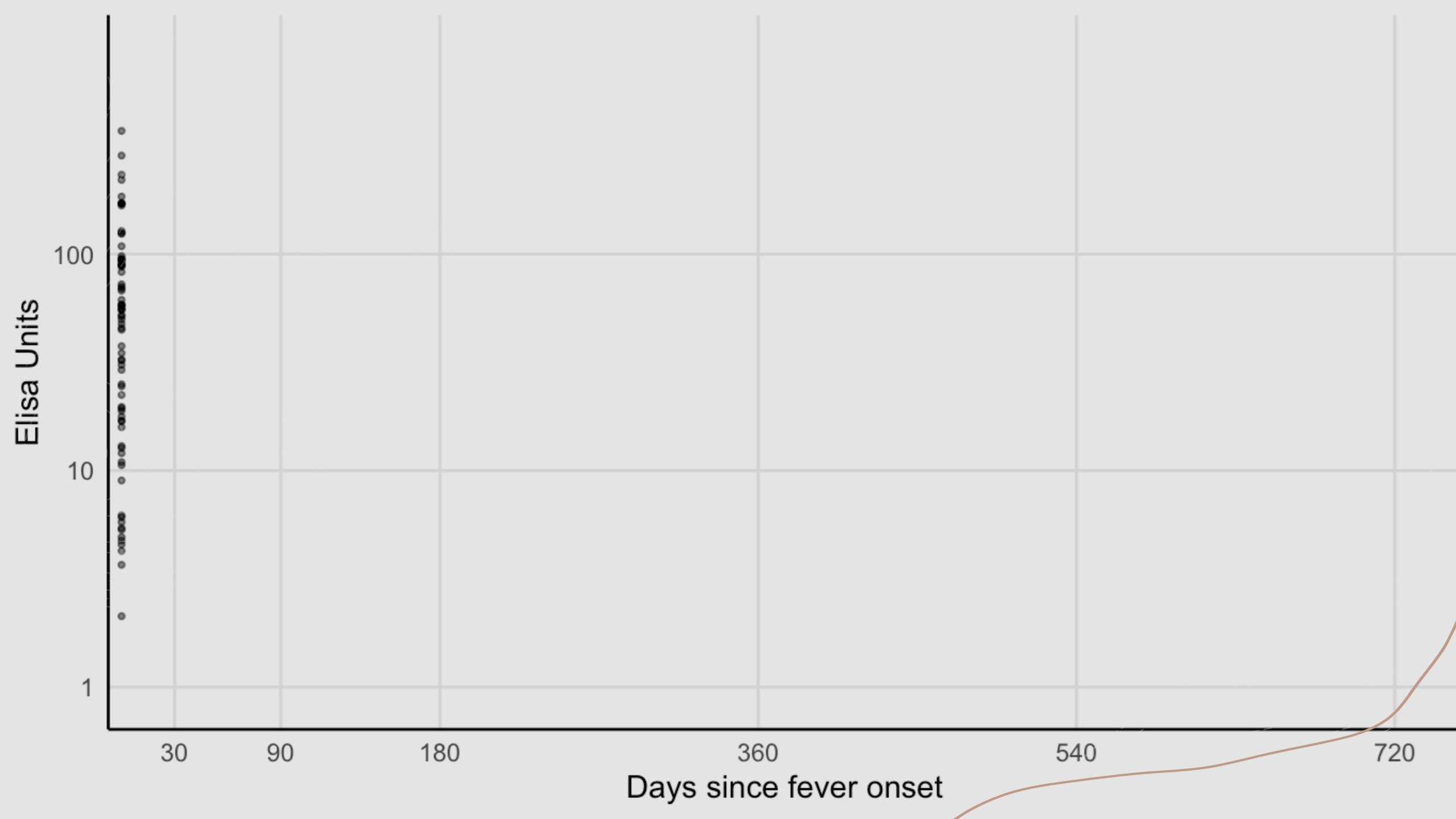
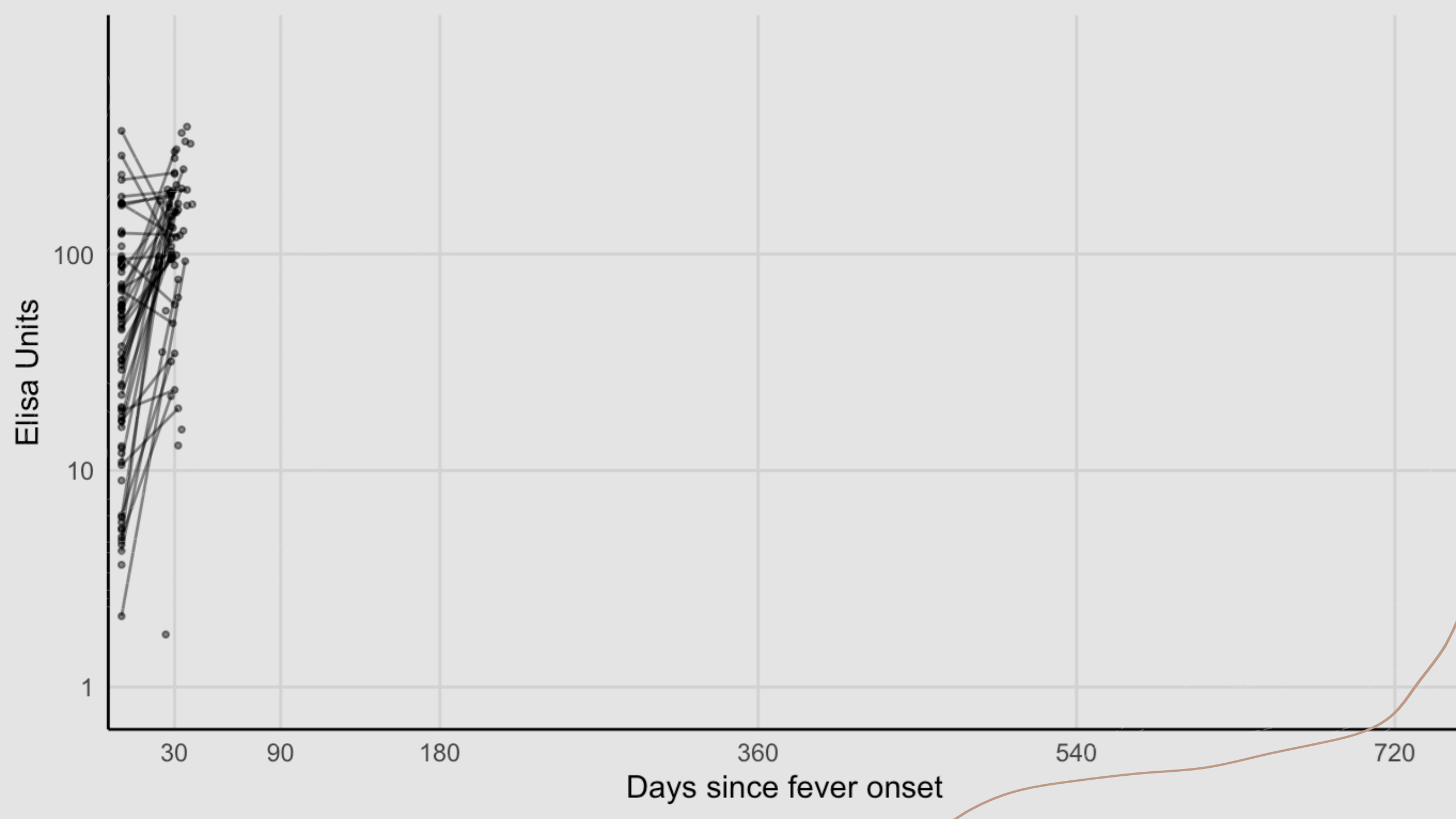

Elisa Units
100
10
1
30
90
180
360
540
720
Days since fever onset


Elisa Units
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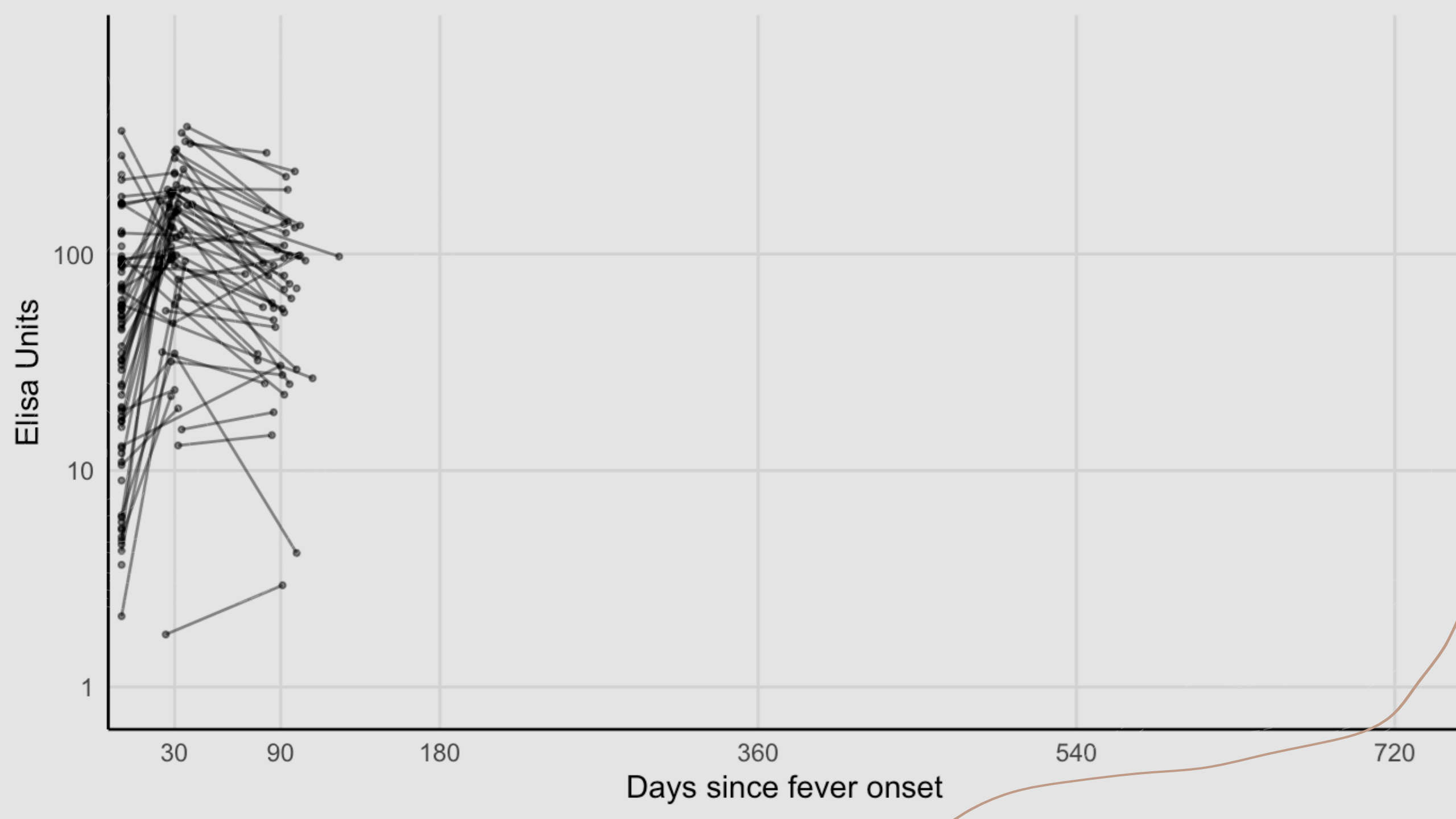
Days since fever onset


Elisa Units
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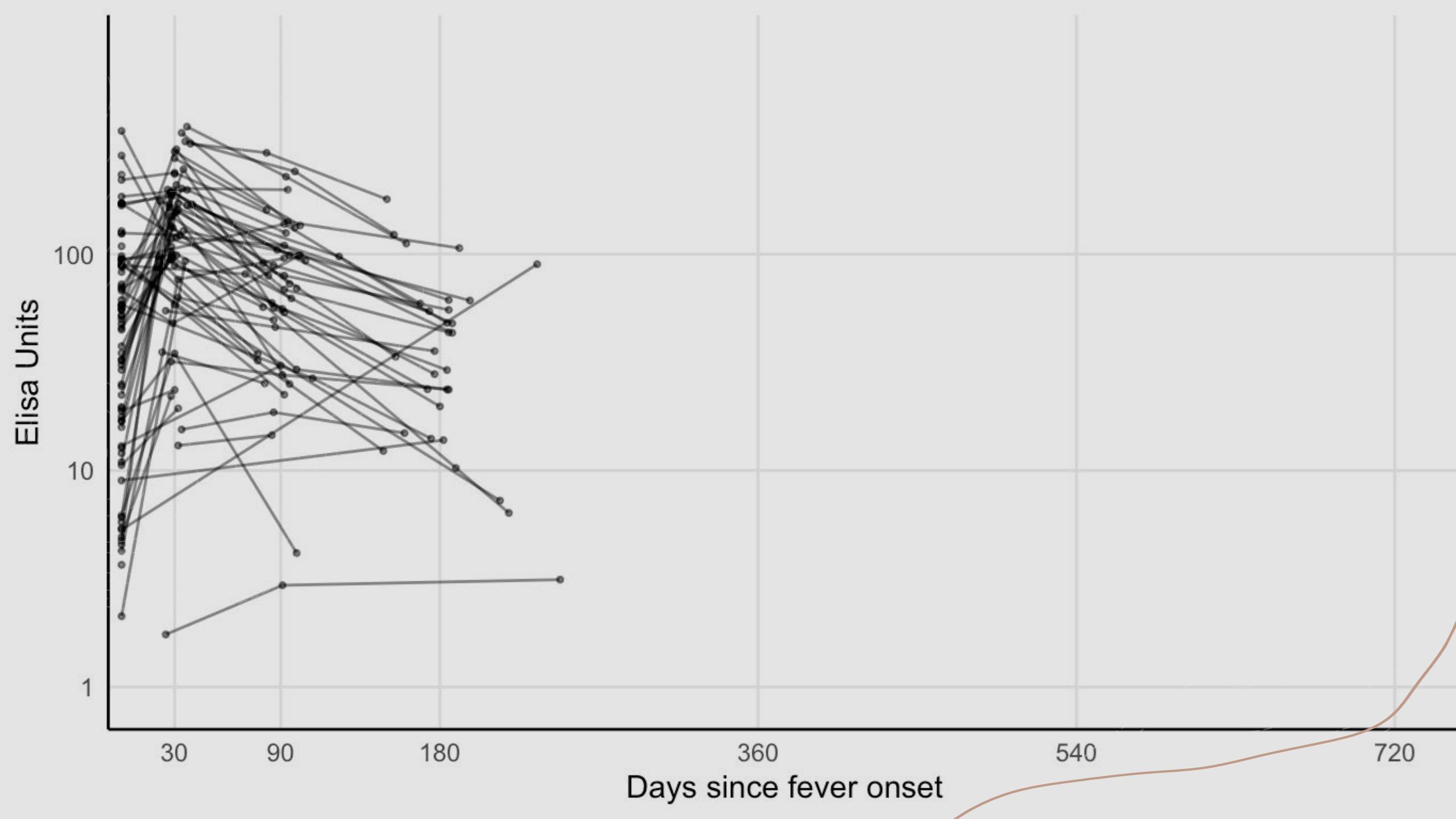
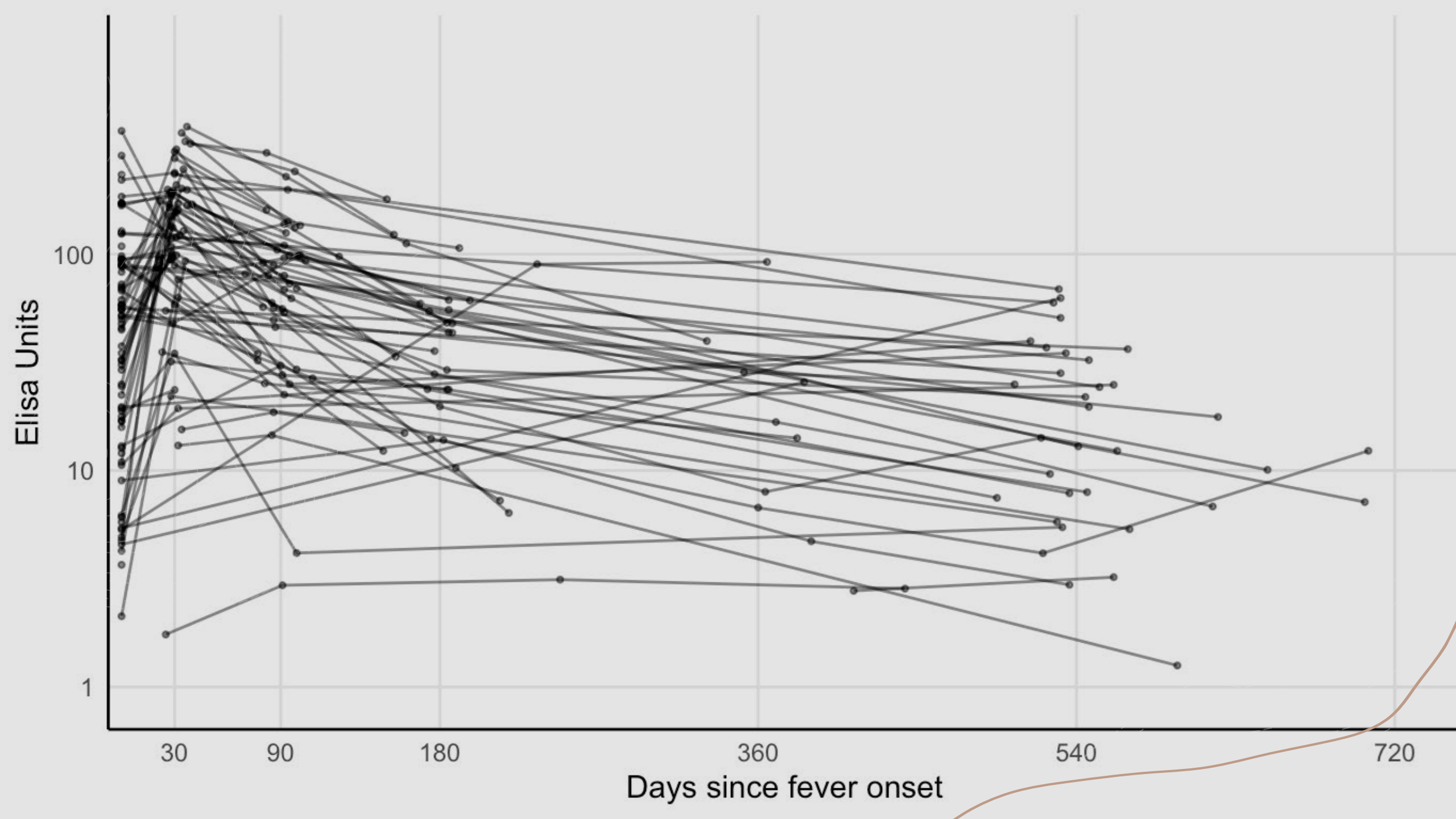
Days since fever onset


Elisa Units
100
10
1
30
90
180
360
540
720
Days since fever onset


Elisa Units
100
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1
30
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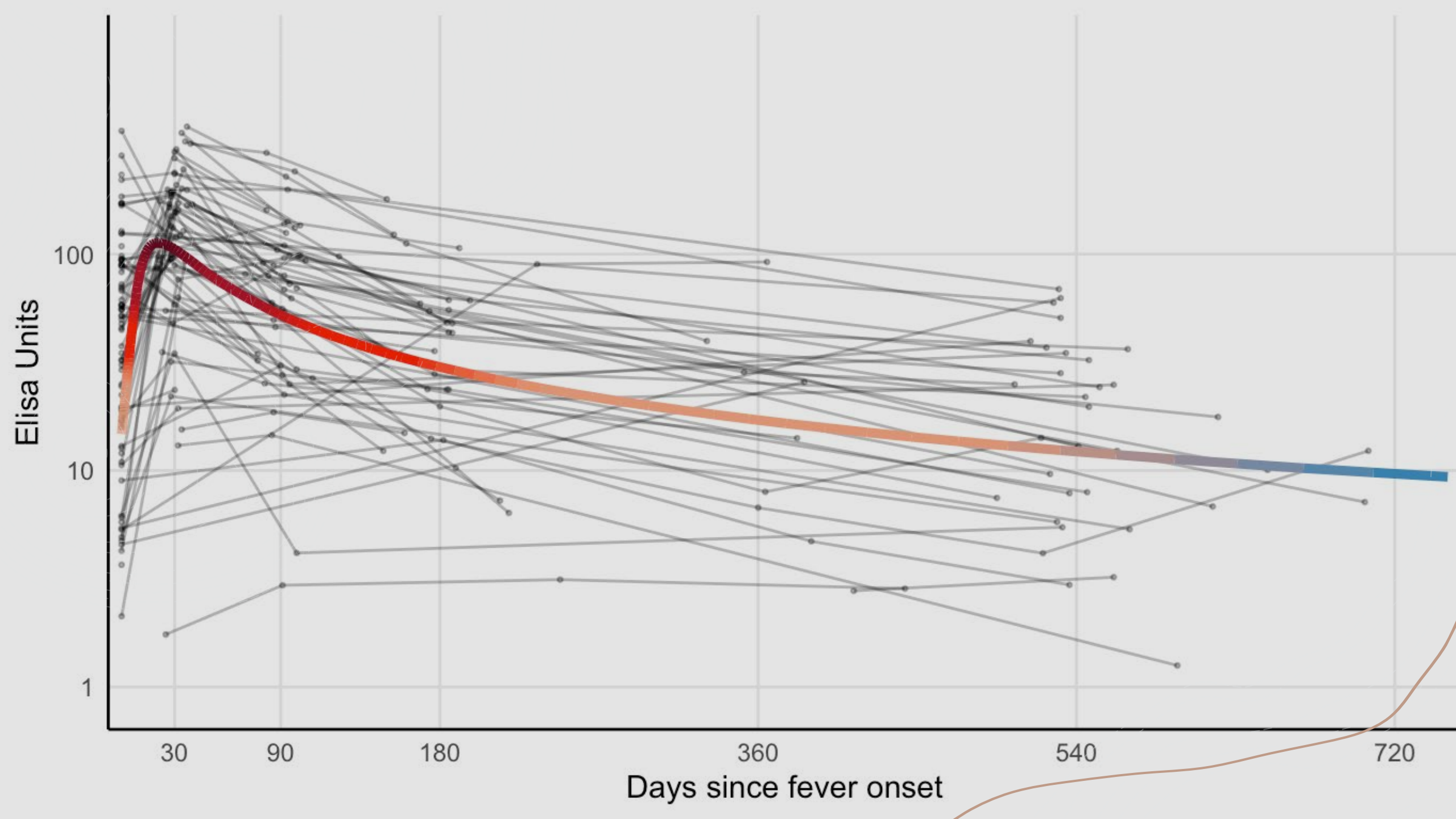
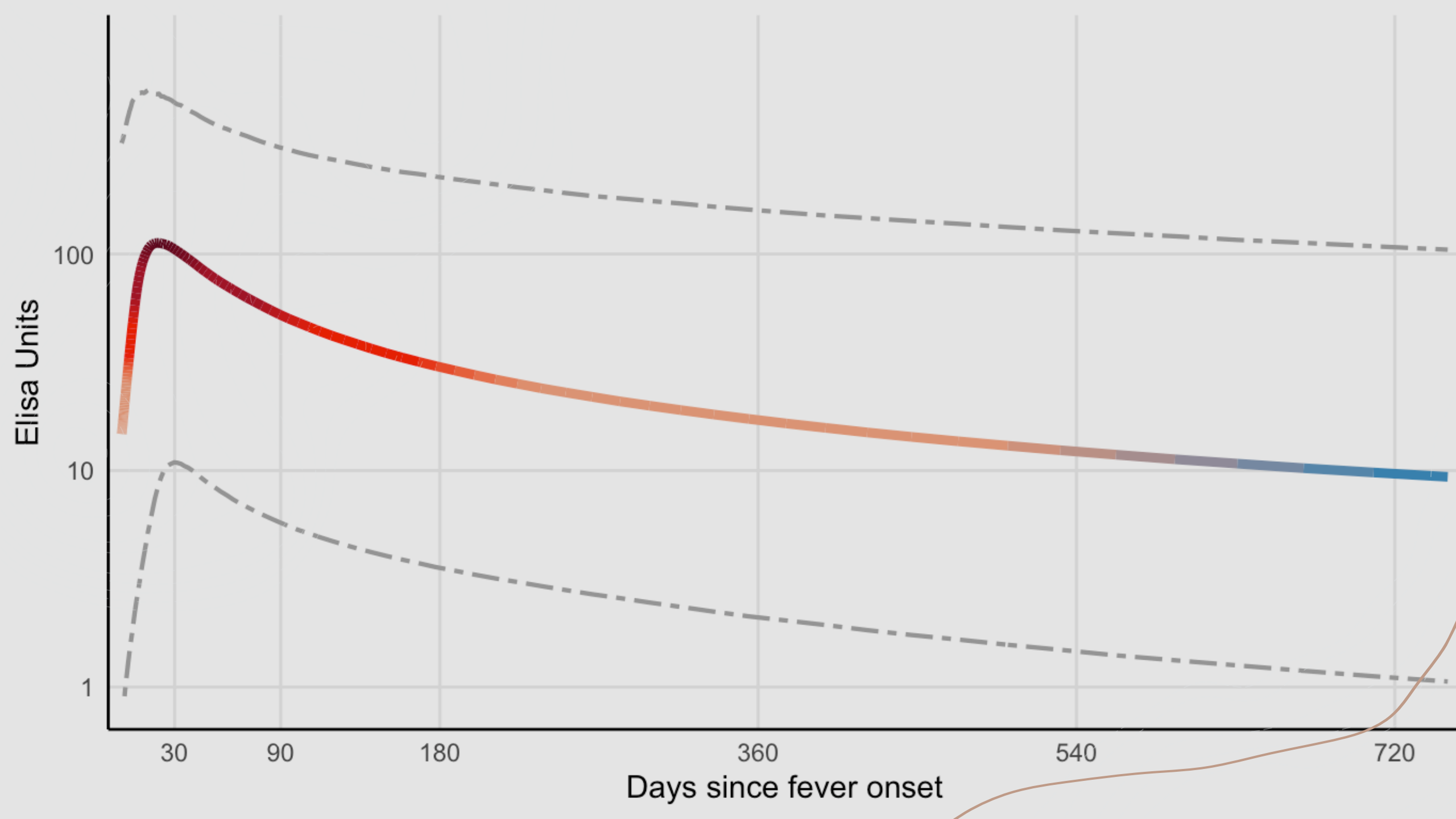
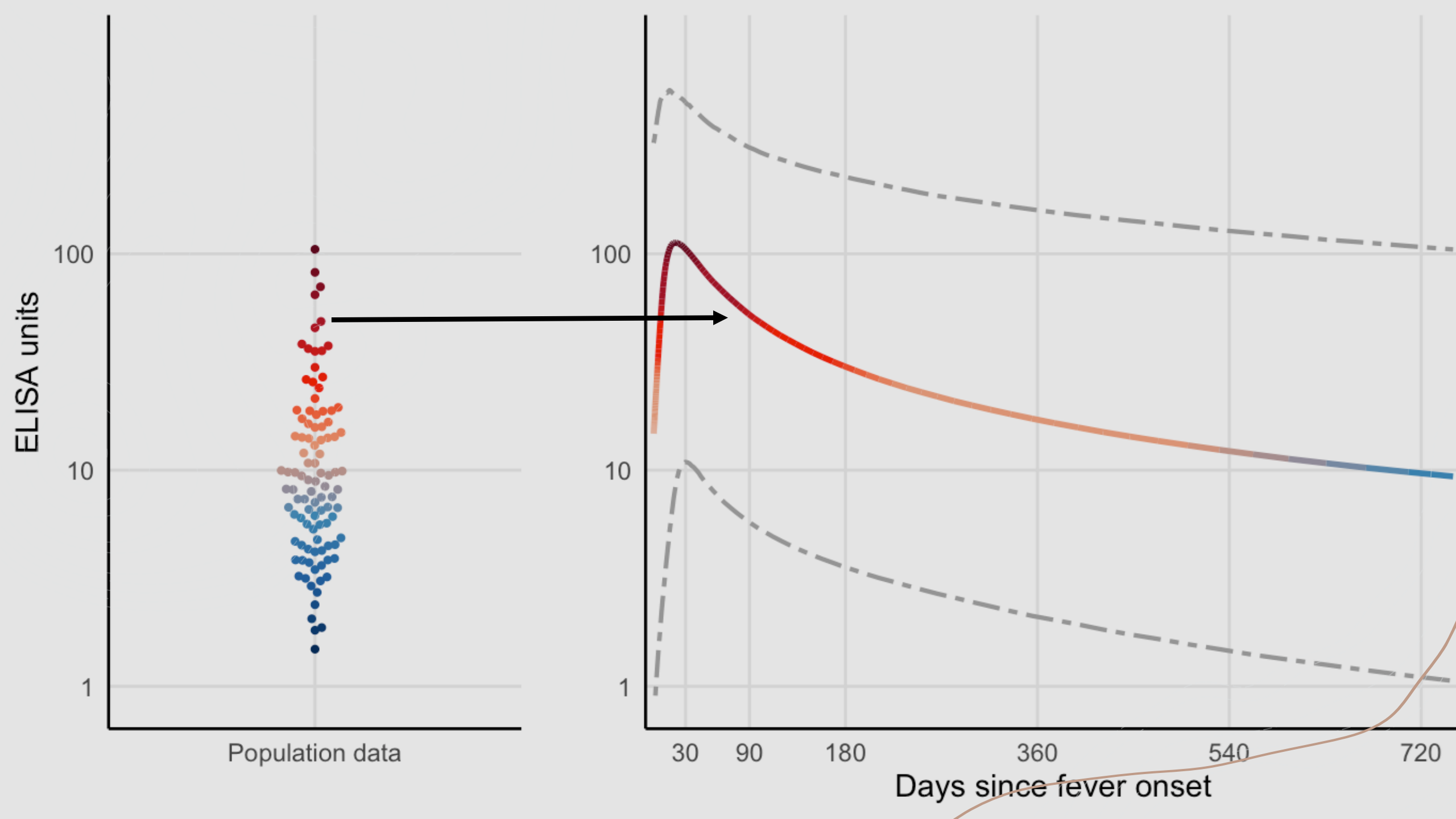
Days since fever onset


Elisa Units
100
10
1
30
90
180
360
540
720
Days since fever onset

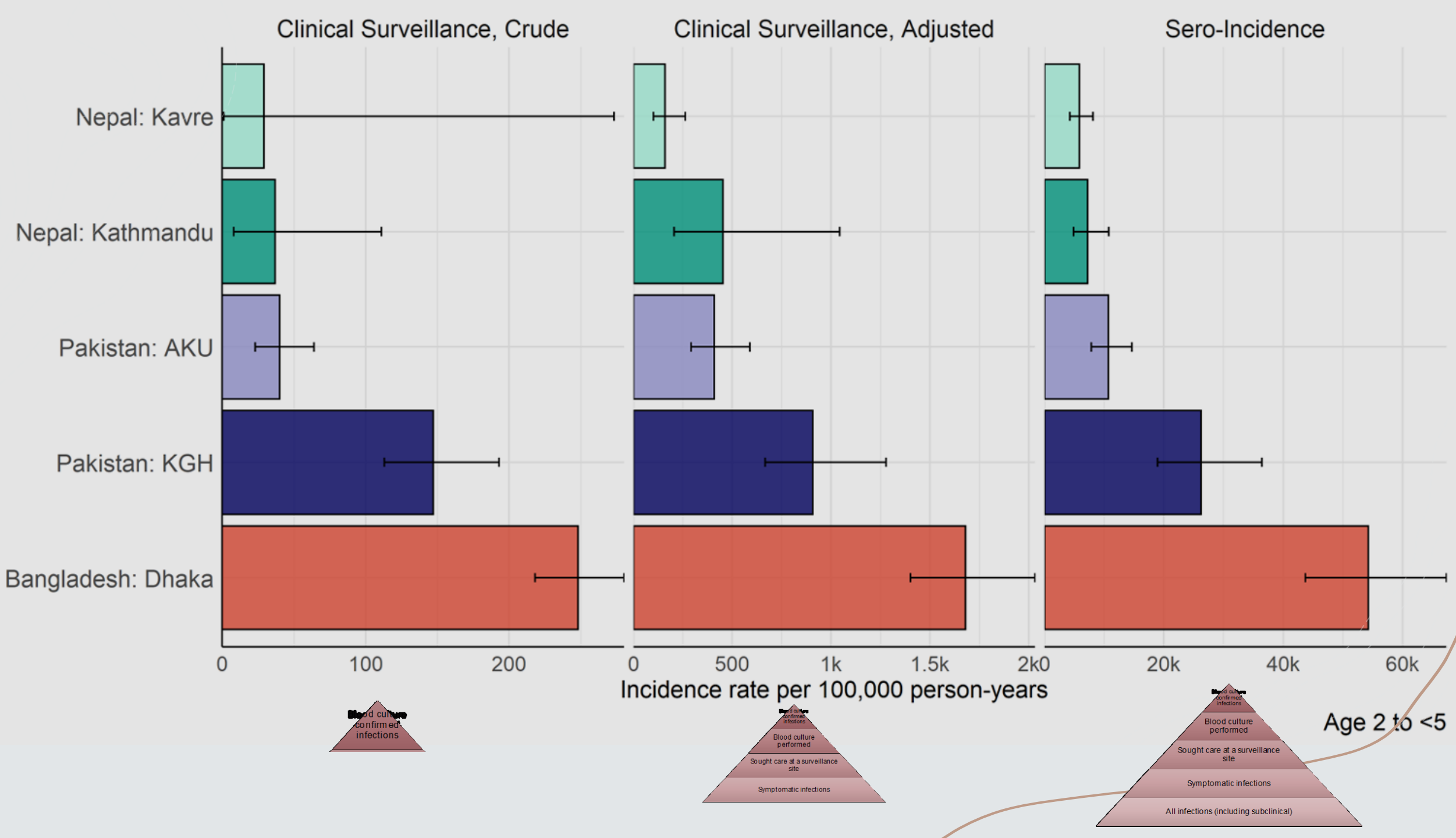

Elisa Units
100
10
1
30
90
180
360
540
720
Days since fever onset


ELISA units
100
10
1
Population data
100
10
1
30
90
180
360
540
720
Days since fever onset

Estimating seroincidence using antibody dynamics

- Seroincidence provides actionable evidence:
  - "The number of **new** infections in this population per year"
- Antibody dynamics only need to be modeled once
- Incorporate heterogeneity in antibody responses (instead of ignore)
- Incorporating signal from multiple antigens/isotypes to improve precision
- Accommodate biological noise and measurement error

Teunis et al, Stats in Medicine, 2020
Teunis et al, Epidemics, 2016


Clinical Surveillance, Crude
Clinical Surveillance, Adjusted
Sero-Incidence
Nepal: Kavre
Nepal: Kathmandu
Pakistan: AKU
Pakistan: KGH
Bangladesh: Dhaka
0
100
200
0
500
1k
1.5k
2k0
20k
40k
60k
Incidence rate per 100,000 person-years
Blood culture confirmed infections
Blood culture performed
Sought care at a surveillance site
Symptomatic infections
All infections (including subclinical)
Age 2 to <5

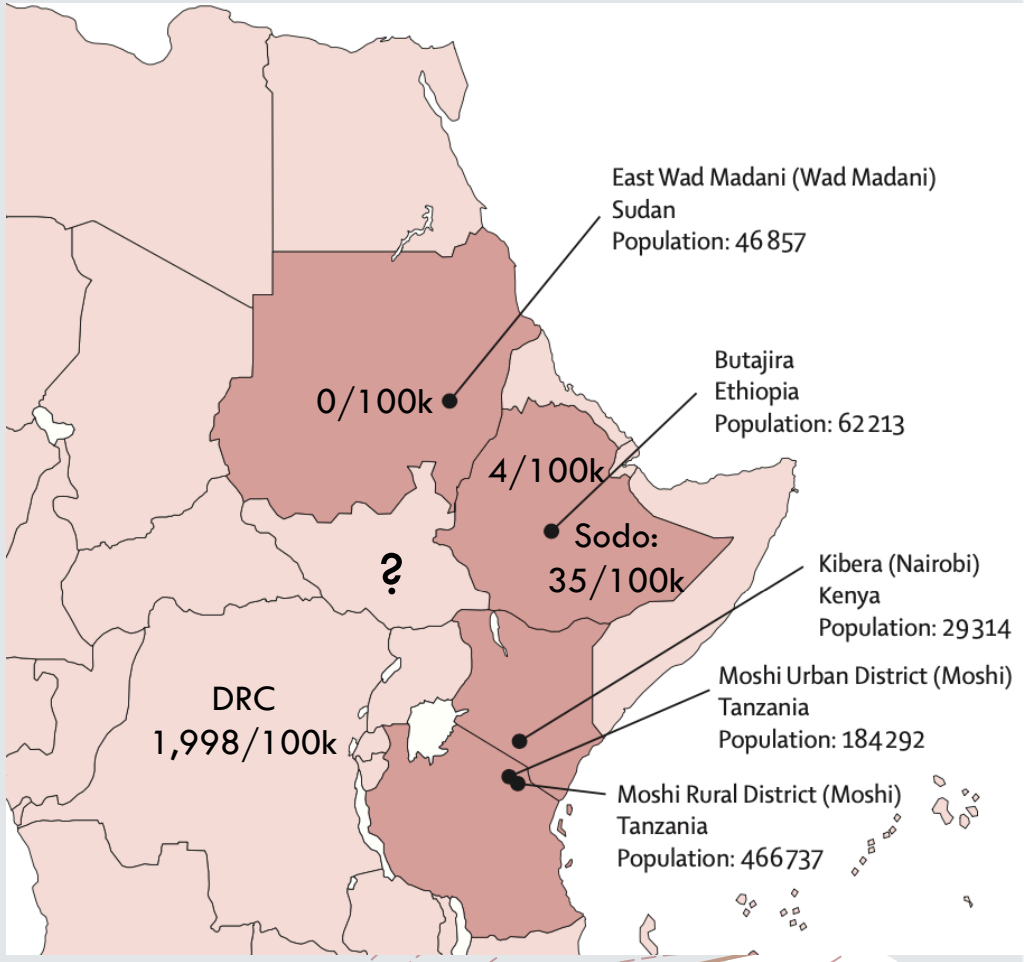
Settings where blood culture surveillance is not available

+Covid serosurvey (DBS) 2020

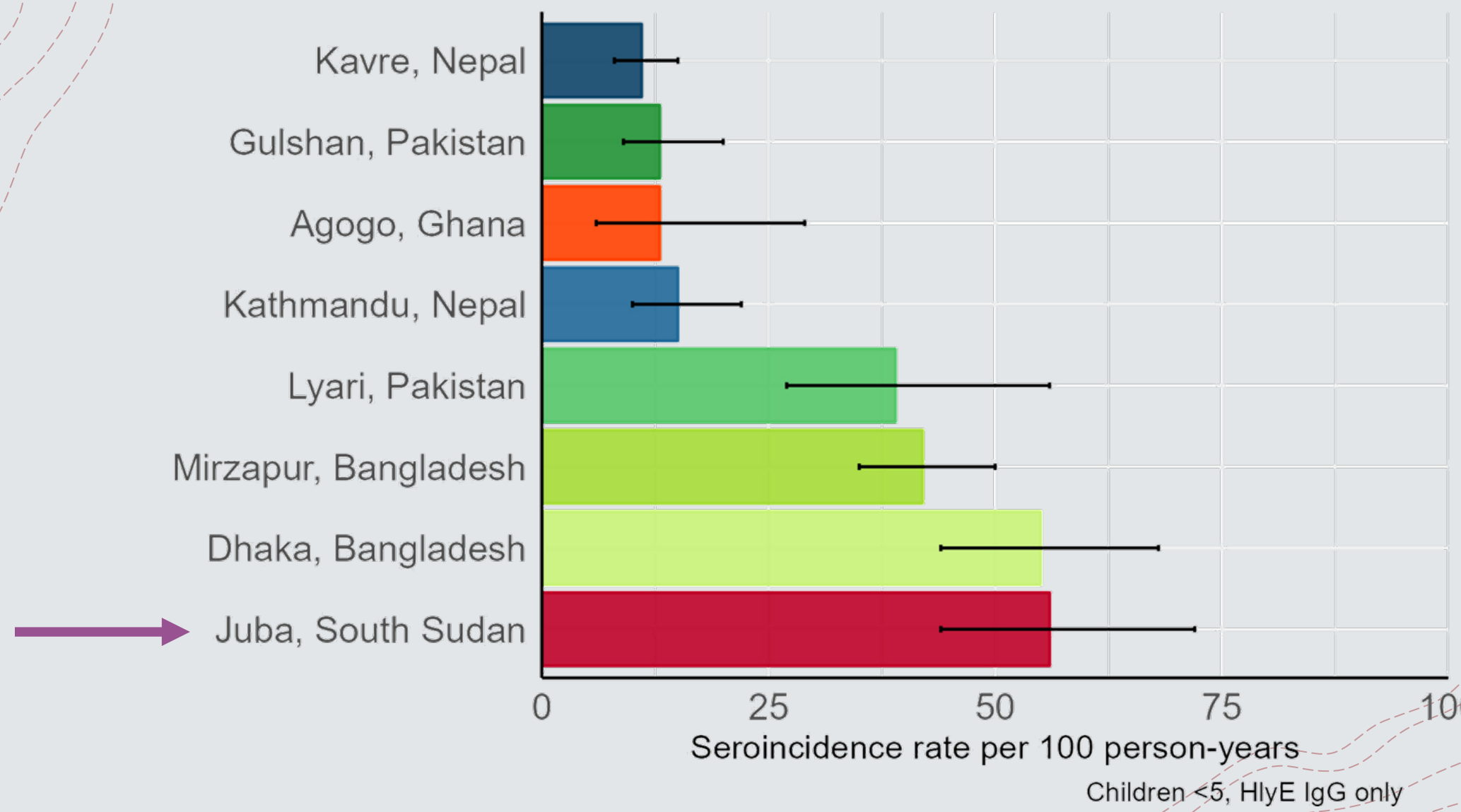
+397 samples

World Health Organization
South Sudan

JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH



Marks et al, *LGH* 2017


Kavre, Nepal
Gulshan, Pakistan
Agogo, Ghana
Kathmandu, Nepal
Lyari, Pakistan
Mirzapur, Bangladesh
Dhaka, Bangladesh
Juba, South Sudan
0
25
50
75
100
Seroincidence rate per 100 person-years
Children <5, HlyE IgG only

Filling the gaps

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Toronto Western
Princess Margaret
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Michener Institute

Francis I. Proctor Foundation
for Research in Ophthalmology

KENYA MEDICAL RESEARCH INSTITUTE
KEMRI

TECHNICAL UNIVERSITY OF MOMBASA

Stanford University

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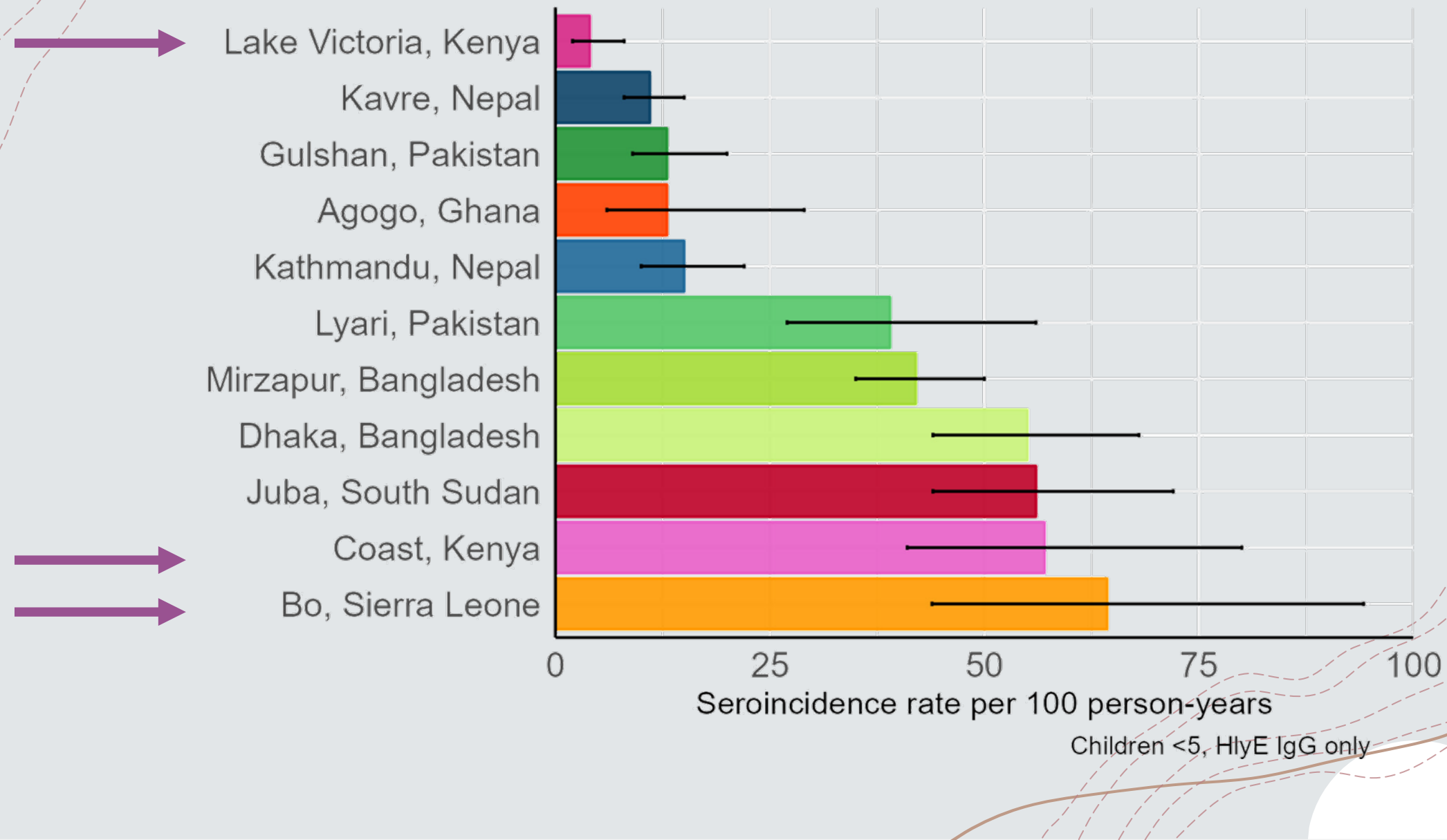
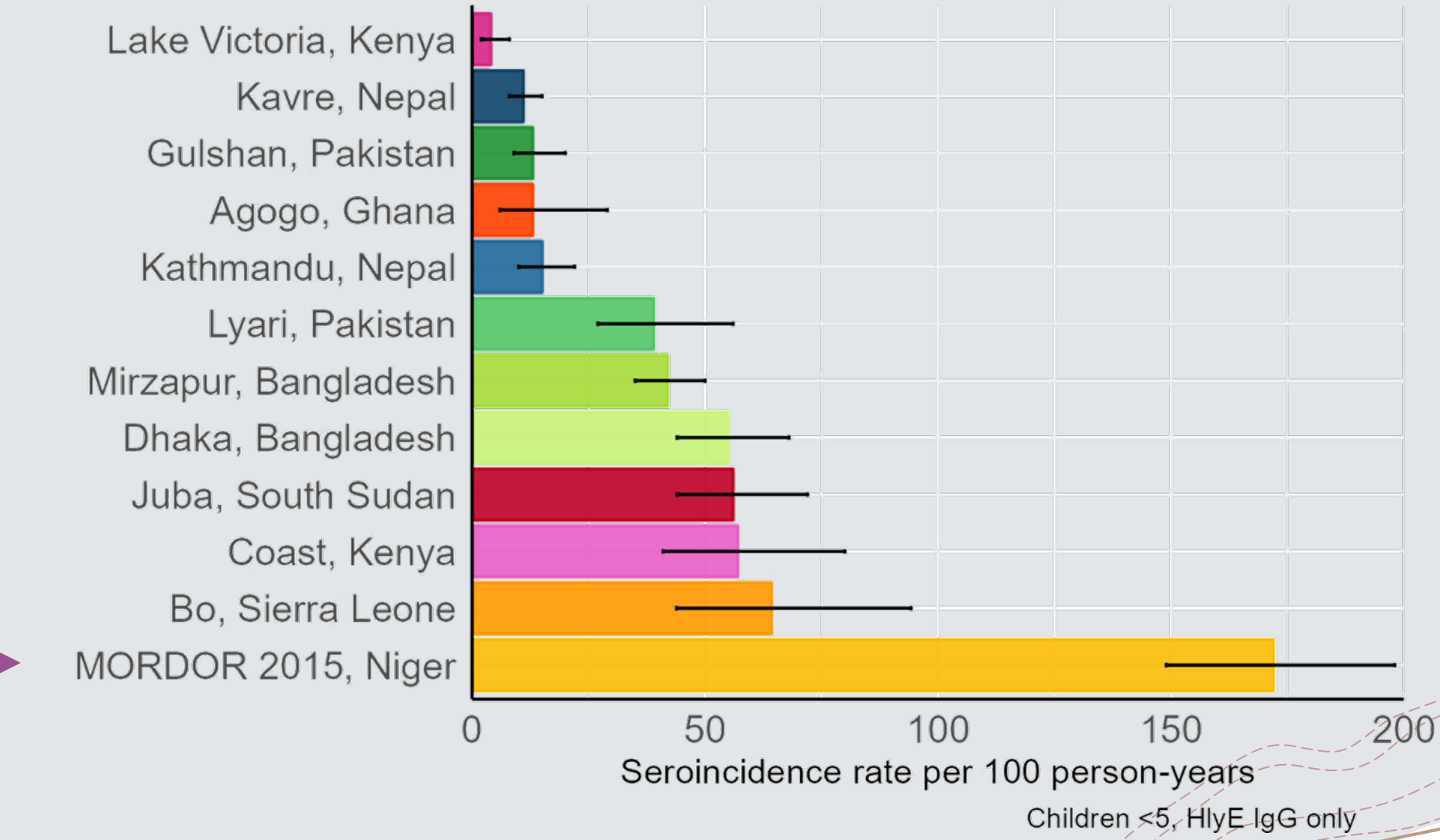
TyVAC
Typhoid Vaccine
Acceleration Consor


Lake Victoria, Kenya
Kavre, Nepal
Gulshan, Pakistan
Agogo, Ghana
Kathmandu, Nepal
Lyari, Pakistan
Mirzapur, Bangladesh
Dhaka, Bangladesh
Juba, South Sudan
Coast, Kenya
Bo, Sierra Leone
0
25
50
75
100
Seroincidence rate per 100 person-years
Children <5, HlyE IgG only


Lake Victoria, Kenya
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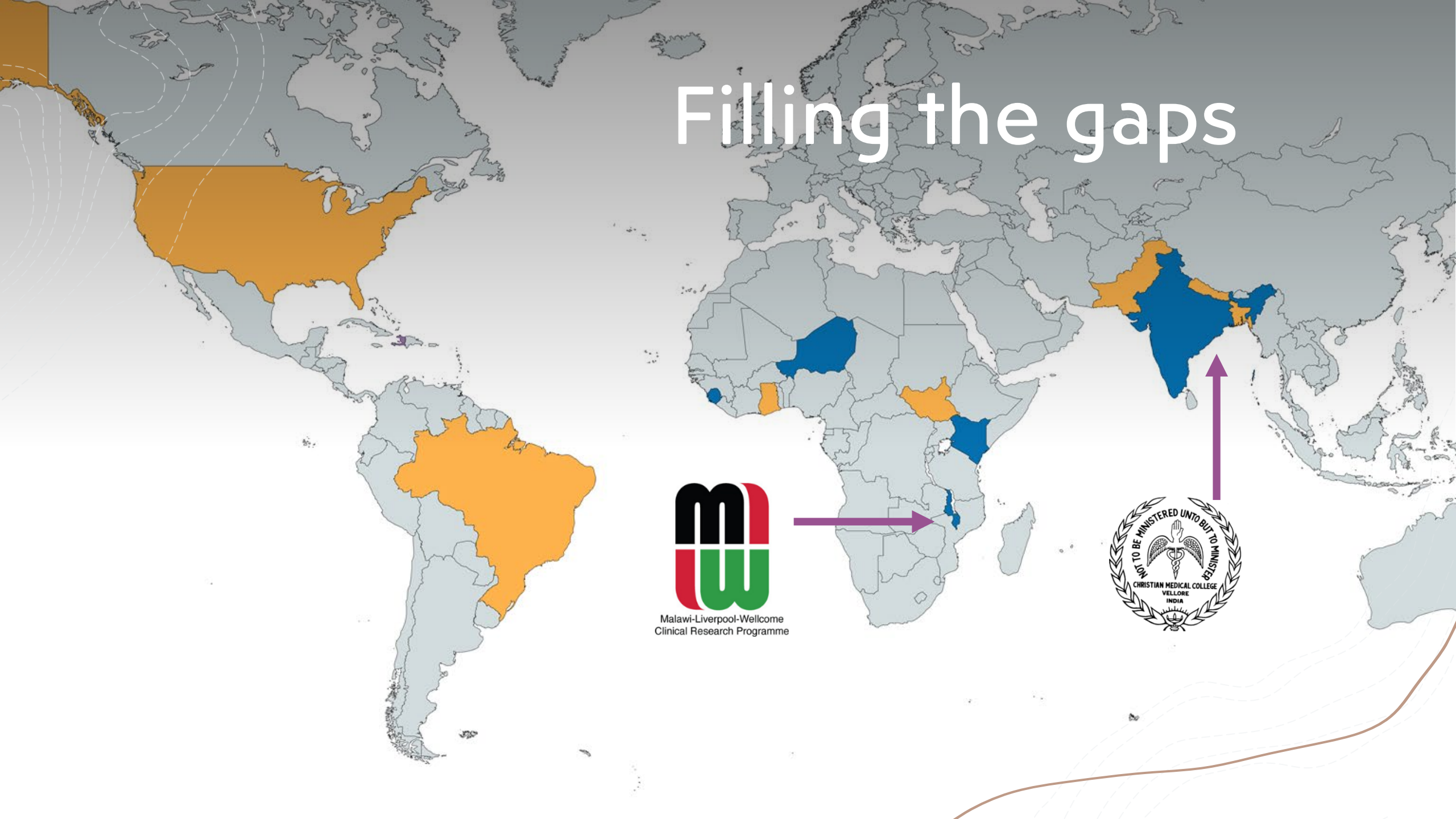
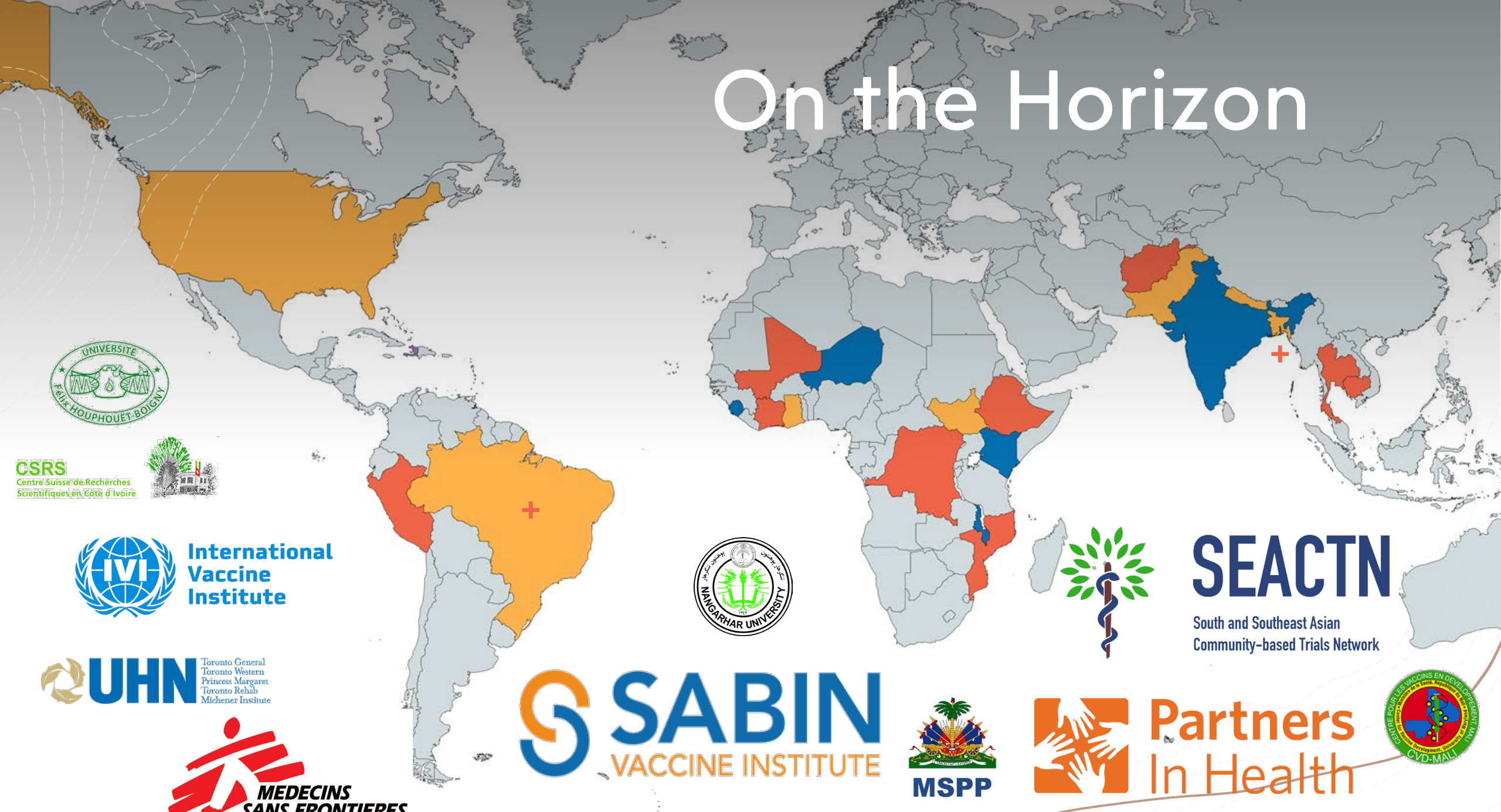
Agogo, Ghana
Kathmandu, Nepal
Lyari, Pakistan
Mirzapur, Bangladesh
Dhaka, Bangladesh
Juba, South Sudan
Coast, Kenya
Bo, Sierra Leone
MORDOR 2015, Niger
0
50
100
150
200
Seroincidence rate per 100 person-years
Children <5, HlyE IgG only

Filling the gaps



On the Horizon



Université Félix Houphouët-Boigny

CSRS
Centre Suisse de Recherches Scientifiques en Côte d'Ivoire

International Vaccine Institute

Nangarhar University

SEACTN
South and Southeast Asian Community-based Trials Network

UHN
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Toronto Western
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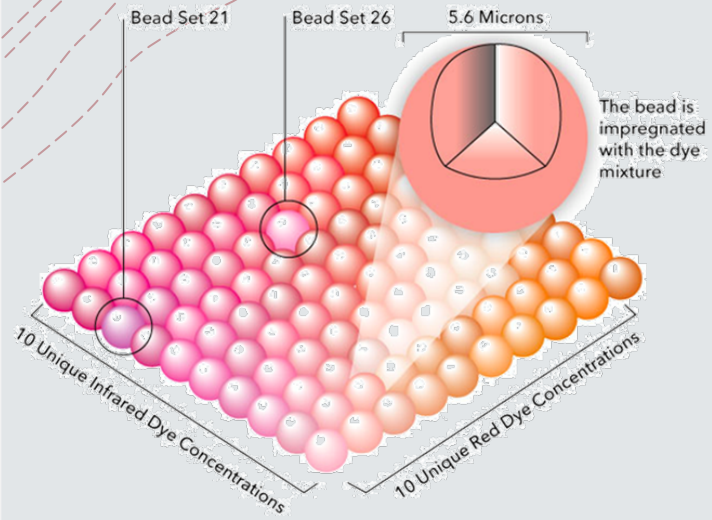
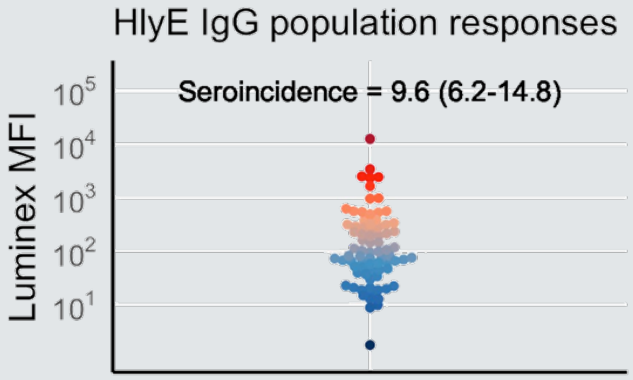
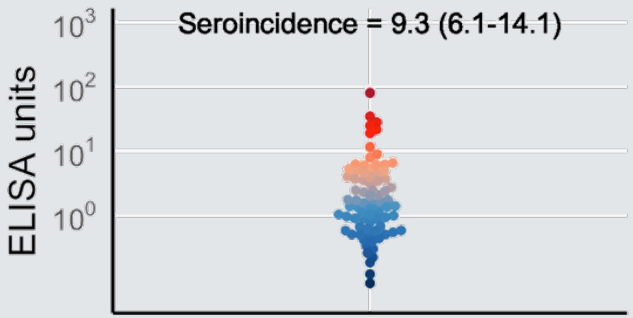
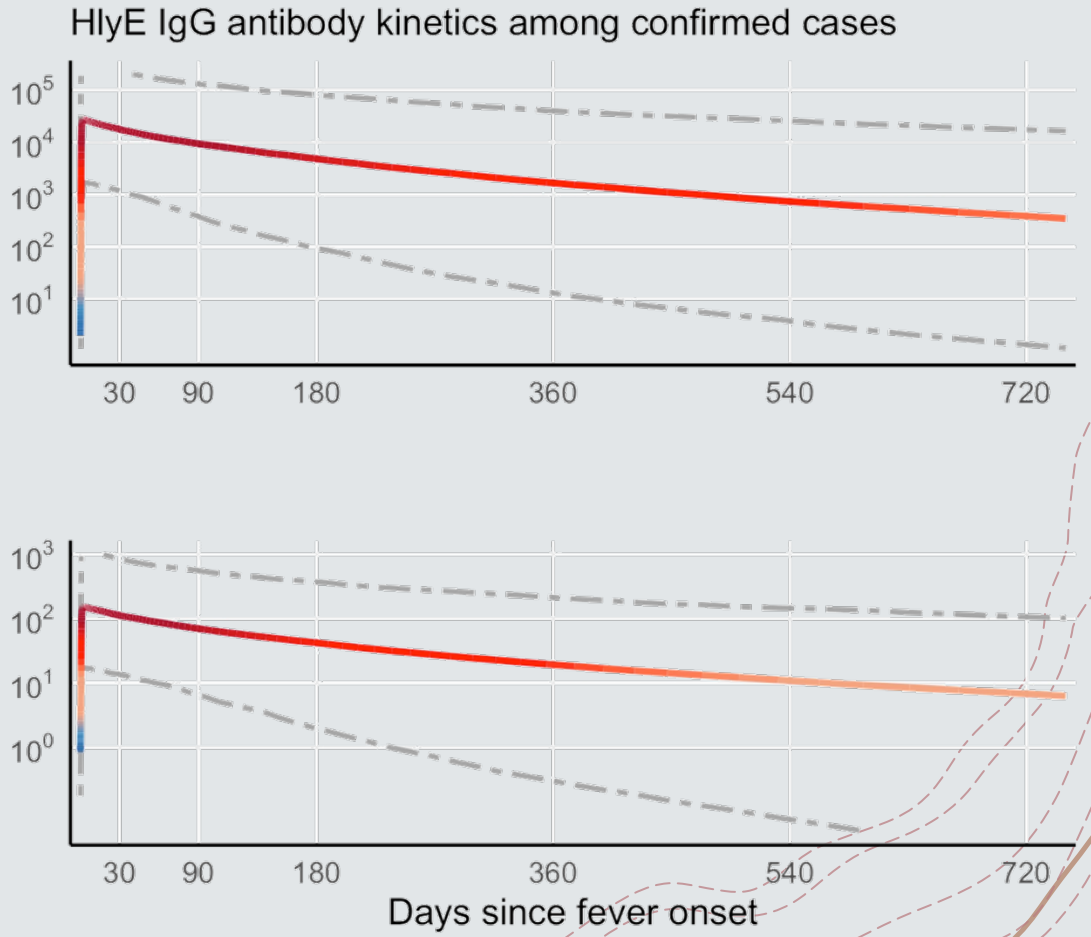
Centre pour les vaccins en développement, Mali
CVD-MALI

Integrating HlyE into bead-based multiplex assays







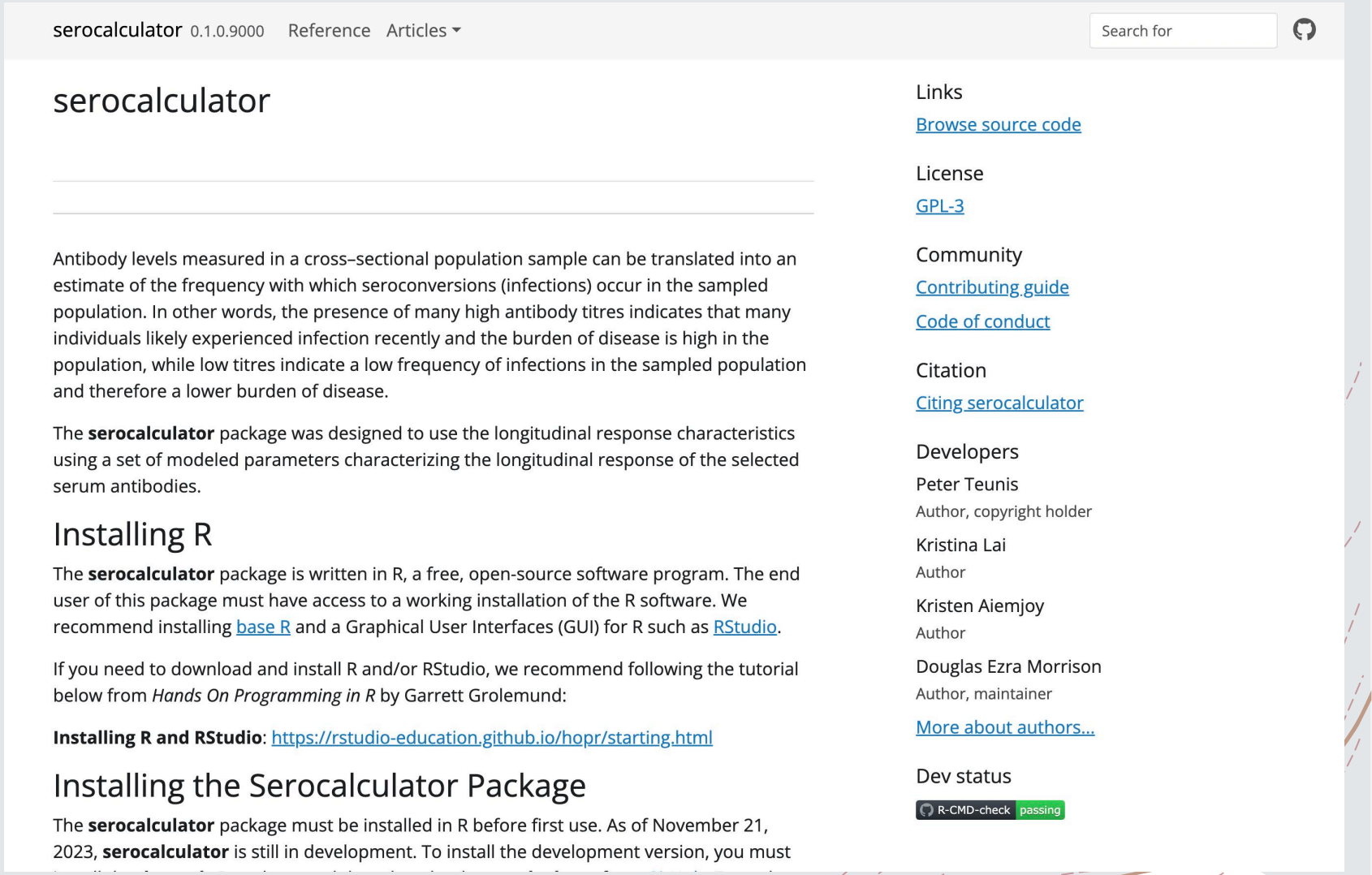


Scaling enteric fever serosurveillance: Analytical tools

Open source analytical package for R available on GitHub https://github.com/UCD-SERG/serocalculator

Analytical training workshops

- Bangkok Aug 2022
- Kigali Dec 2023
- **Anywhere you invite us**



National Institute of Allergy and Infectious Diseases

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ACKNOWLEDGEMENTS

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KENYA MEDICAL RESEARCH INSTITUTE
KEMRI

TECHNICAL UNIVERSITY OF MOMBASA

International Vaccine Institute

UCSF

MORU
Tropical Health Network

MGH
1811

Stanford University

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CHRISTIAN MEDICAL COLLEGE
VELLORE
INDIA

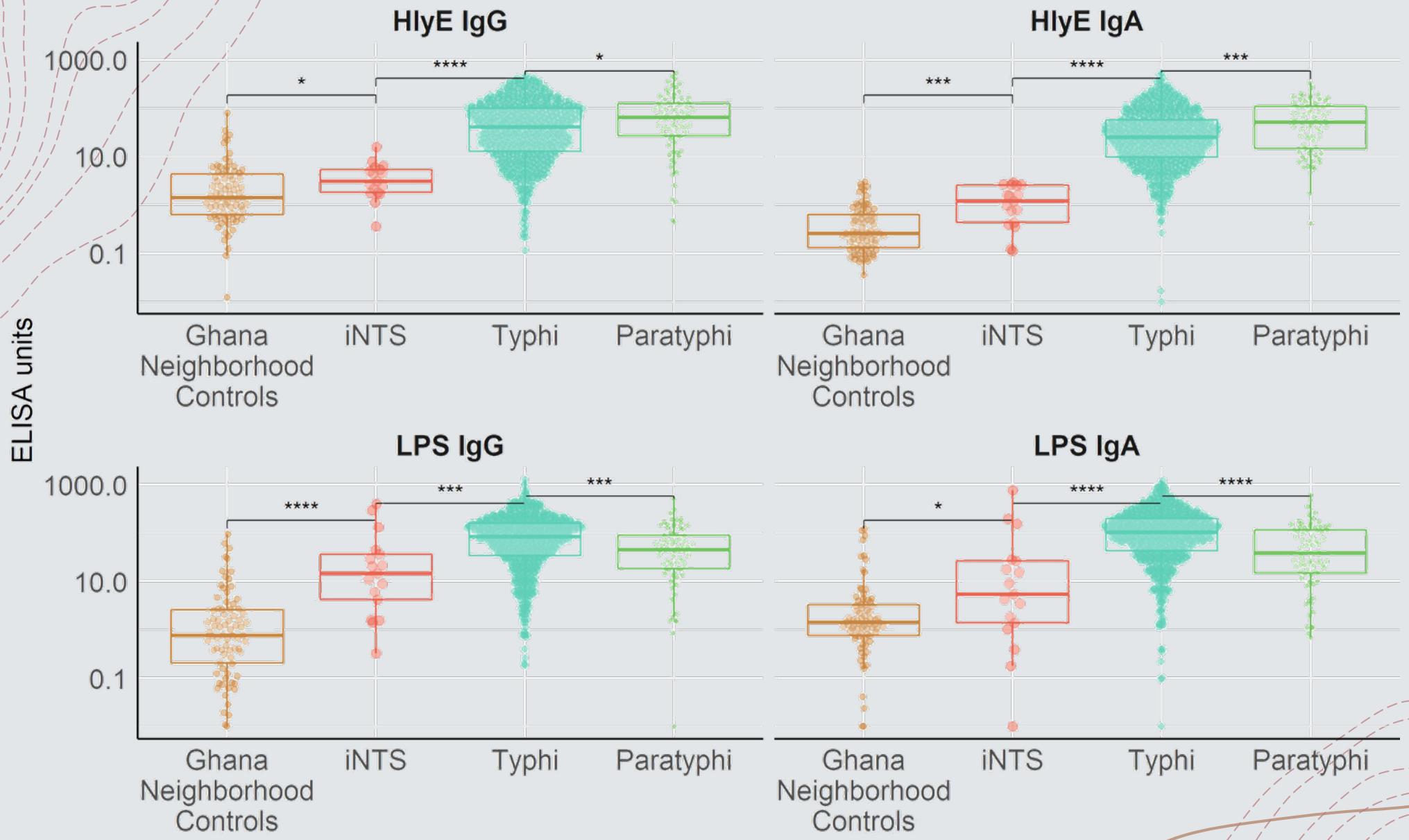
NIH
National Institute of Allergy and Infectious Diseases

Got DBS?
Call us

Extra slides

Study Site	Study Name	Age Range (y)	Age< 5 (n)	Total (n)	Year	Reference
Bangladesh **Dhaka** **Mirzapur**	SEES	0.5-18	101 151	401 596	2019-2021	https://doi.org/10.1016/S2666-5247(22)00114-8
Kathmandu Valley, Nepal	SEES	0.5-25	186	846	2019-2020	https://doi.org/10.1016/S2666-5247(22)00114-8
Pakistan **Karachi** **Hyderabad**	SEES	0.5-25	126	494	2019-2020	https://doi.org/10.1016/S2666-5247(22)00114-8
Agogo Ghana	SETA	2-19	18	79	2016	https://doi.org/10.1016/S2666-5247(22)00114-8
Juba, South Sudan	COVID	1-70	66	1244	2020	https://wwwnc.cdc.gov/eid/article/28/11/22-0239_article
Dosso, Niger **2015** **2020**	MORDOR	0-5	449 558	449 558	2015 2020	https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2787602
Kenya **Coastal (Ukunda, Msambweni)** **Western sites (Chulaimbo, Kisumu)**	CHIKV, DENV	3-18	31	1401	2017	https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-023-08157-4
Vellore, India		0-21	364	1217	2022	
Blantyre, Malawi		1-14	387	937	2023	
Bo, Sierra Leone	HEAL-SL	2-95	35	455	2022	Jha P et al, in preparation
Araraquara, Brazil	Dengue cohort	2-16	150	432	2014-2015	https://doi.org/10.1016/j.actatropica.2019.105313
United States **California - COVID serosurvey** **Boston-Pediatric cohort**	CA-FACTS	3-50 1-18	3 54	205 80	2021 2017-2020	https://www.researchsquare.com/article/rs-2548374/v1

Cross-reactive antibody responses in iNTS?



HlyE IgA
Typhi vs iNTS
AUC: 0.97
(95% CI: 0.96-0.99)

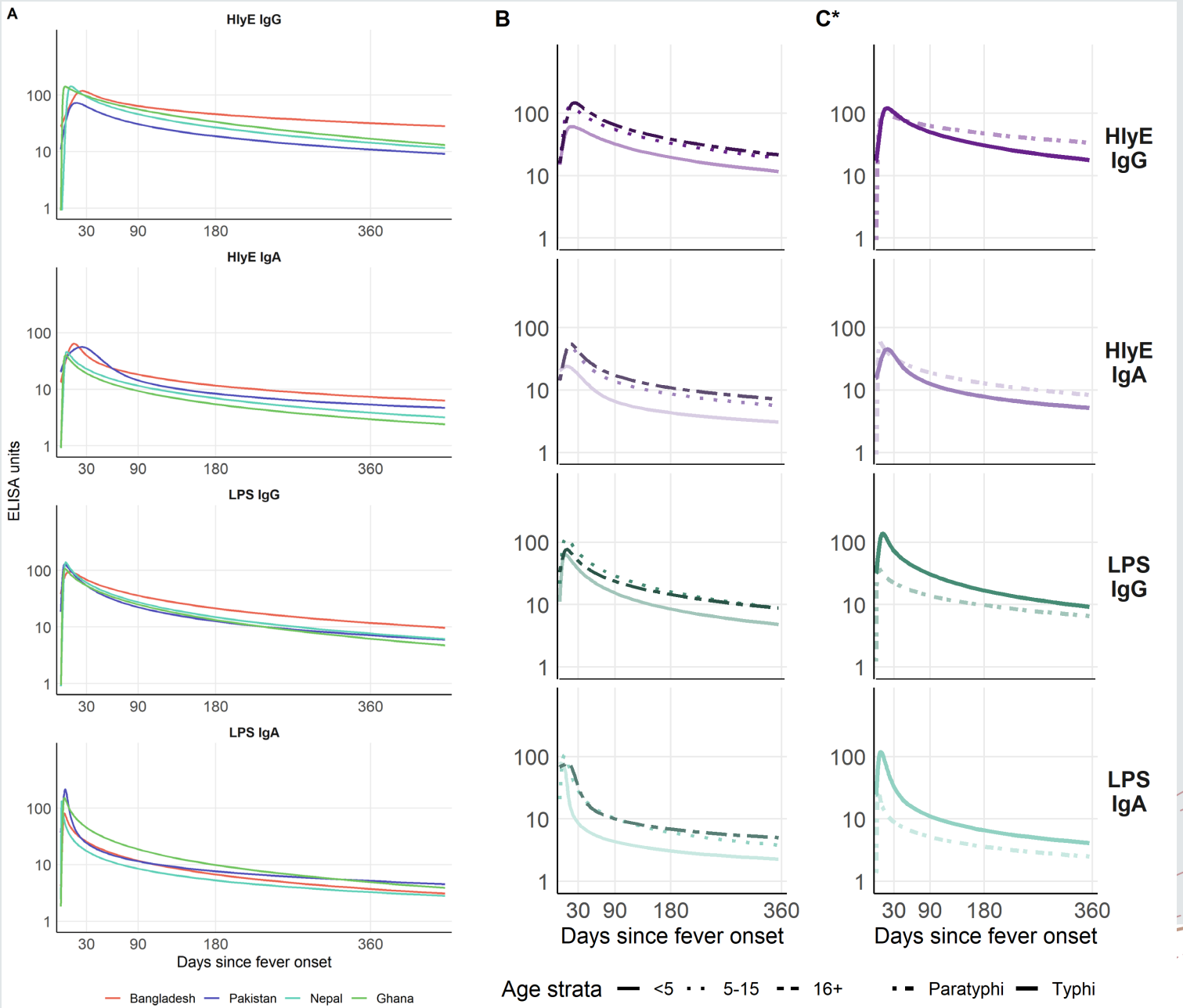
LPS IgA
Typhi vs iNTS
AUC: 0.88
(95% CI: 0.78-0.99)

Variation in antibody kinetics by:

Country

Age

Typhi/Paratyphi A



Schools as a Platform for Rapid Typhoid Seroepidemiological Assessments: Evidence from Nepal

Shiva Ram Naga
Dhulikhel Hospital, Kathmandu University Hospital

Background

- High typhoid burden in Kathmandu Valley; limited evidence in the other regions of Nepal.
- Blood culture surveillance studies are expensive, logistically intensive, and take many years to complete
- Serologic surveys are an alternative approach to generate accurate typhoid incidence estimates
- Schools are a potential alternative population to quickly estimate typhoid burden, but it's unclear whether they provide a representative sample for assessing community exposure to *S.* Typhi

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Objectives

- Determine the feasibility of using a school-based sampling frame for typhoid sero-epidemiology, evaluating participation rates and resource requirements

- Compare school-based and population-based seroincidence estimates from the same communities to determine whether school-based estimates provide unbiased estimates compared with household-based surveys

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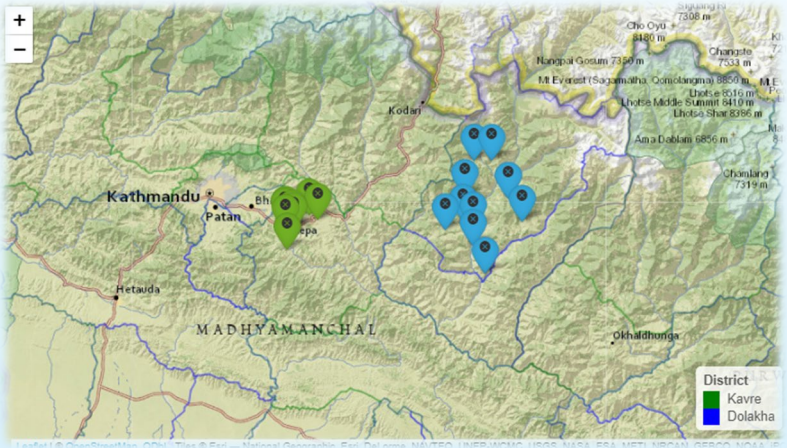
Methods

- Random sample of 18 primary and secondary schools
  - 8 in Kavre district
  - 10 in Dolakha district
- Up to 100 children randomly selected from each school
- Inclusion criteria: Age between 4 and 18 years
- Fingerstick capillary blood collected onto filter paper
- HlyE IgG and IgA antibody levels determined by kinetic ELISA
- Estimated seroincidence in each community using previously published methods (Aiemjoy et al, 2022)



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School and Population Sample

	Population		School	
	Kathmandu	Kavre	Kavre	Dolakha
Median age (IQR)	12·0 (5·8–17·8)	10·2 (5·1–15·7)	11(8-14)	9(7-12)
Sample size	353	481	816	522
Duration of study, Months	24	24	4	2
Research Staff Required	8	8	4	4
Consent Rate	76.5%	86.4%	**88.3%**	**98.3%**

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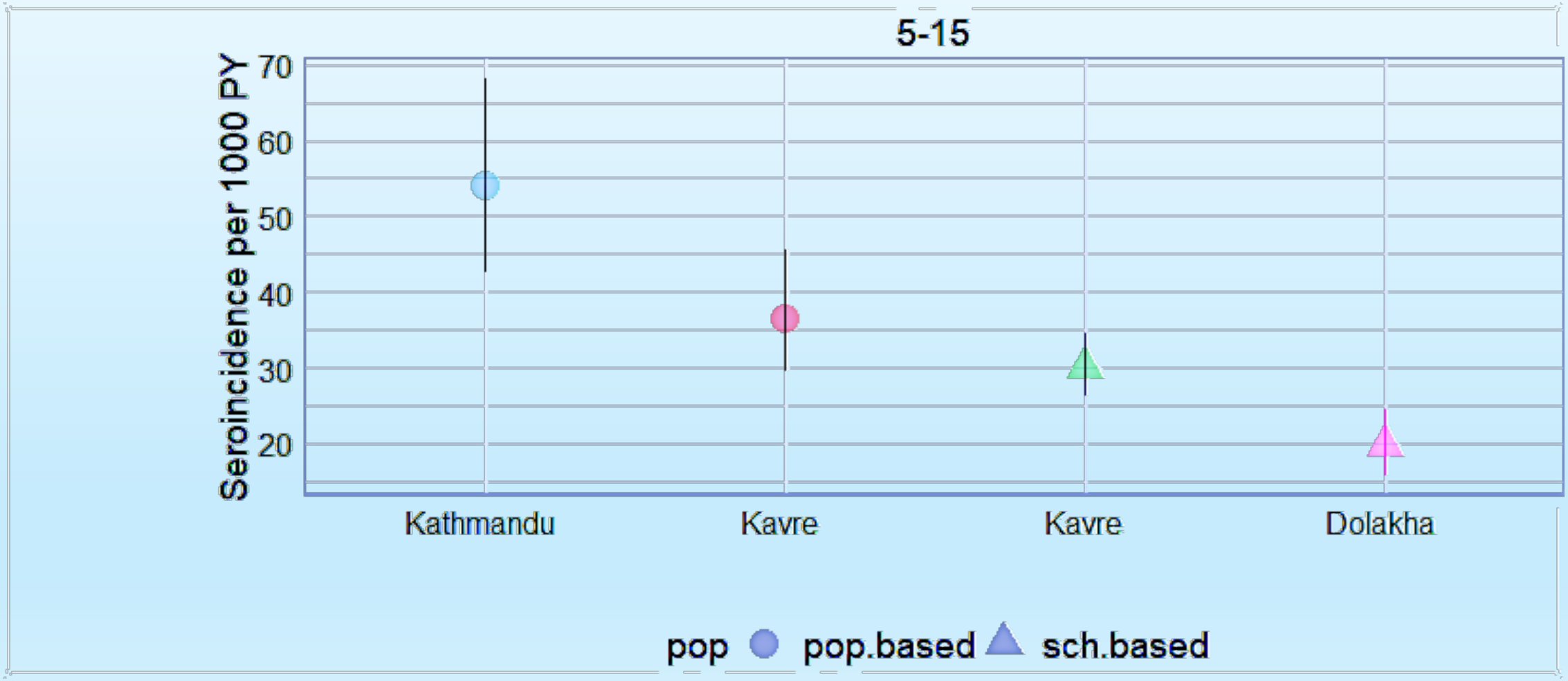
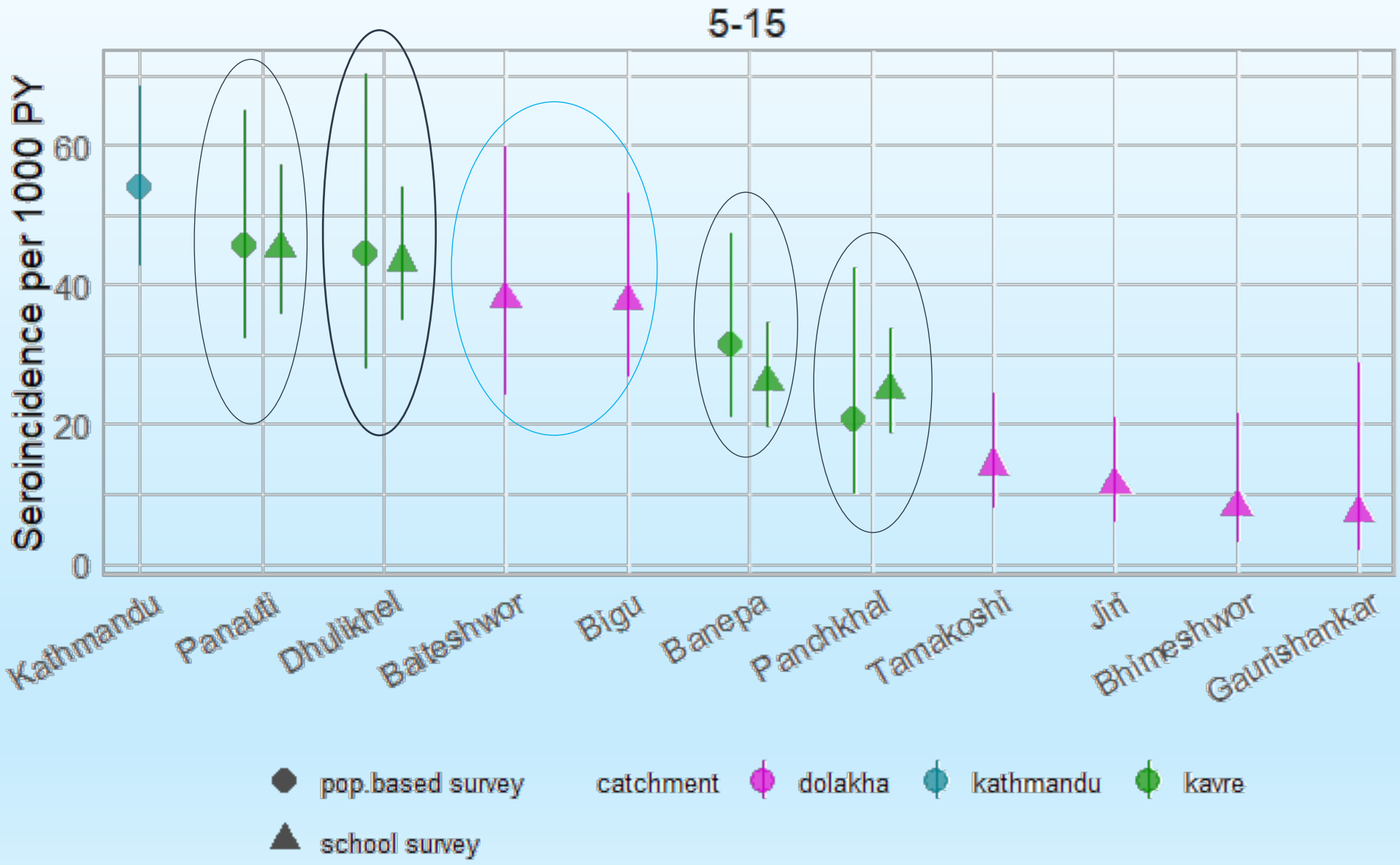
RESULTS

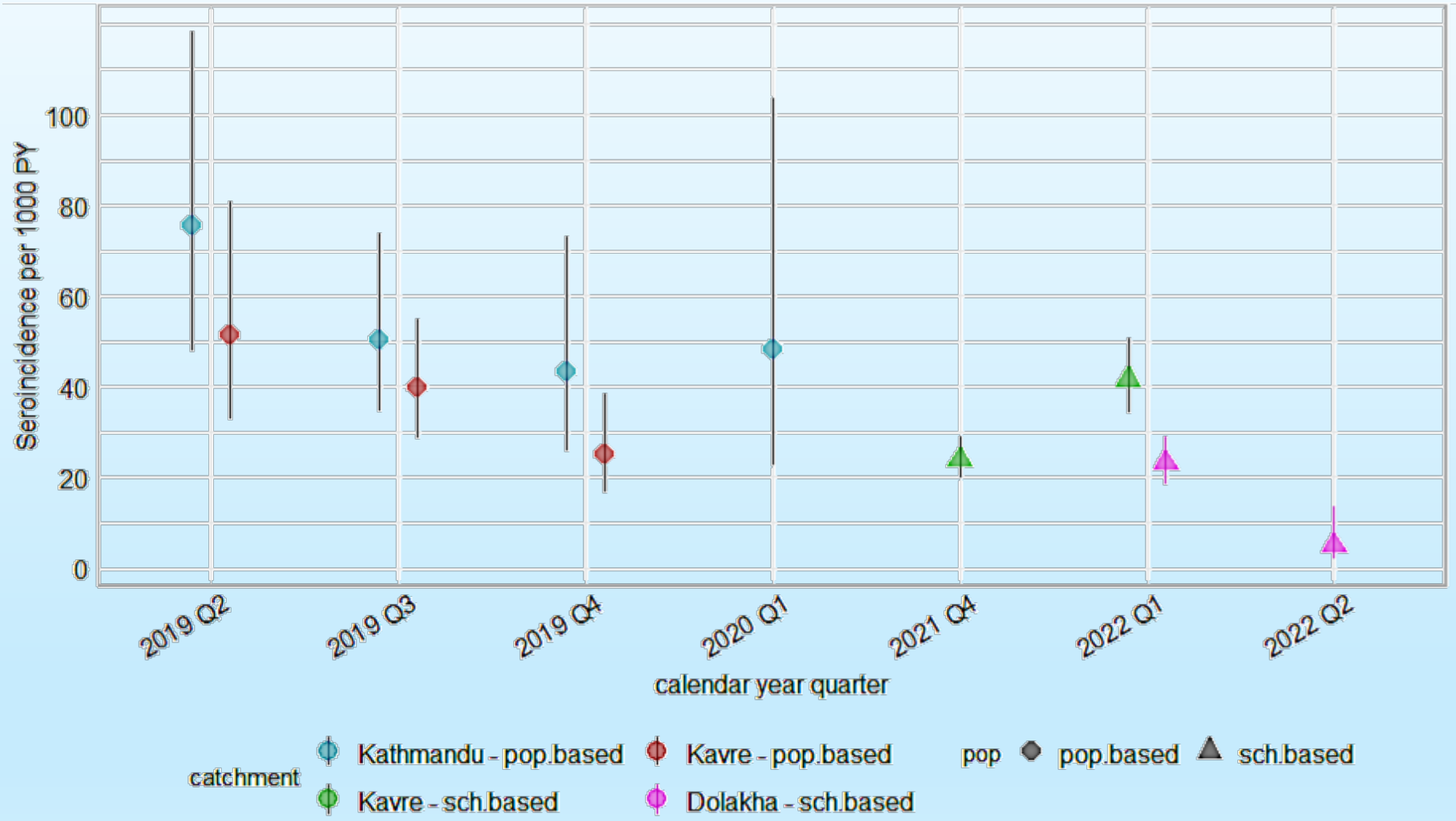
Seroincidence by District and Sampling frame



Seroincidence by Municipality and Sampling frame



Seroincidence by Timepoints and Sampling site



Conclusions

- Seroincidence estimates derived from school based sampling were similar to those derived from household surveys
- Participation rates were higher in school based surveys compared with household surveys, and sampling was able to be performed in a fraction of the time and with fewer personnel, markedly reducing costs
- School-based surveys could enable rapid mapping of typhoid risk in communities where blood culture-based surveillance is not available, as well as monitoring of typhoid exposure trends following vaccine introduction
- In settings where surveys for helminths or other infections are performed at school, typhoid surveys could be part of an integrated surveillance system to leverage resources and enhance scalability

Acknowledgements

Nepal Team:-

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Harvard Medical School

Dr. Richelle Charles

Stanford Team:-

Dr. Jason Andrews, Christopher Leboa

SABIN Team:-

Dr. Denise Garrett, Dr. Jessica Seidman, Alice Carter, Kate Doyle

Funded by:-

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Thank You

Enteric fever seroincidence estimates using cross-sectional rapid serosurveys in Bangladesh

Presented by

Sira Jam Munira

Child Health Research Foundation

CHRF

Child Health Research Foundation

Prevent Infections, Save Lives

Study design

For Dhaka and Mirzapur*

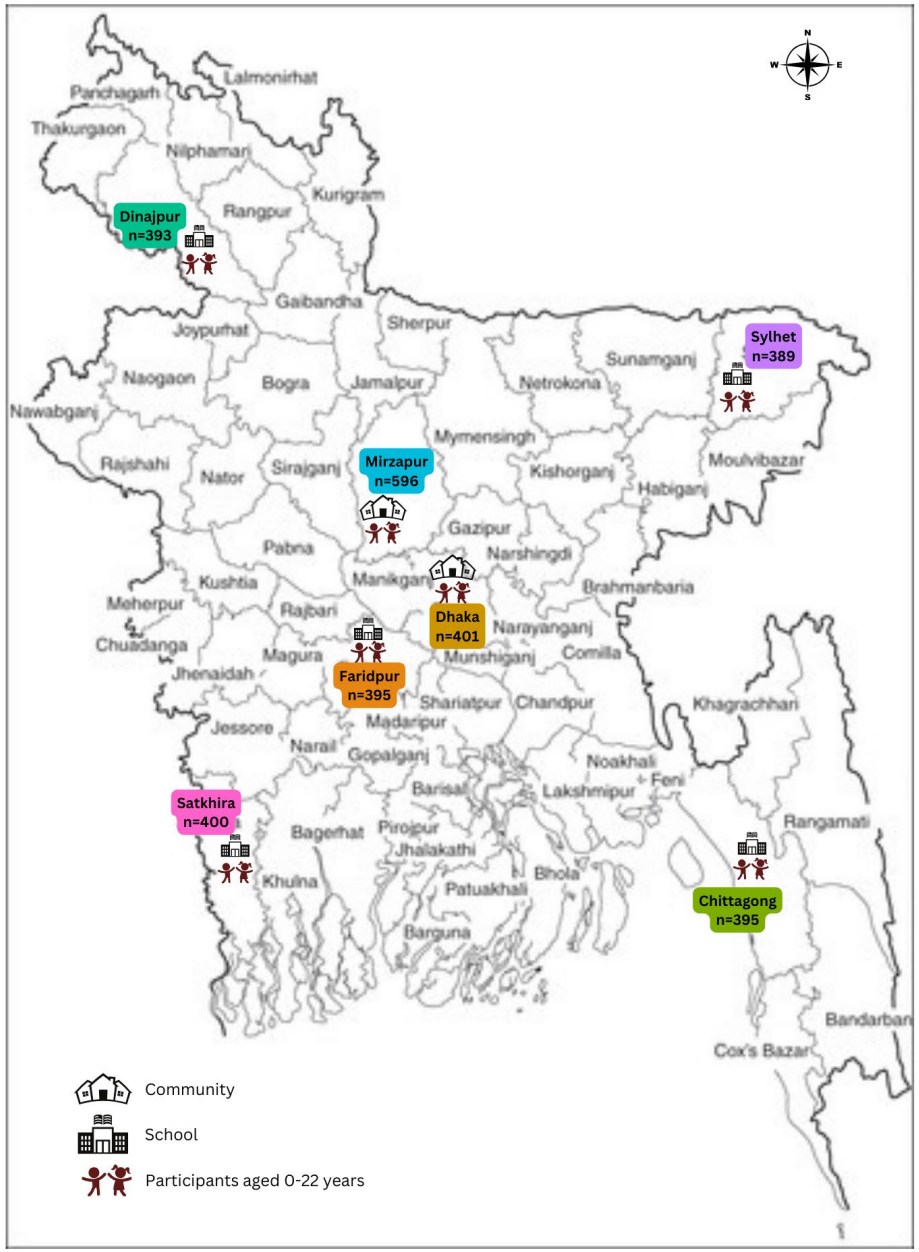
- ✓From June 2019 to June 2021
- ✓Collected dried blood spot samples

For the remaining areas

- ✓January to June 2022, 3-5 days for each survey
- ✓Collected venous whole blood samples
- ✓Additional benefits to participants-

Blood grouping and Hepatitis B/C tests,

Science camps



*Aiemjoy et al., The Lancet Global Health, 2022

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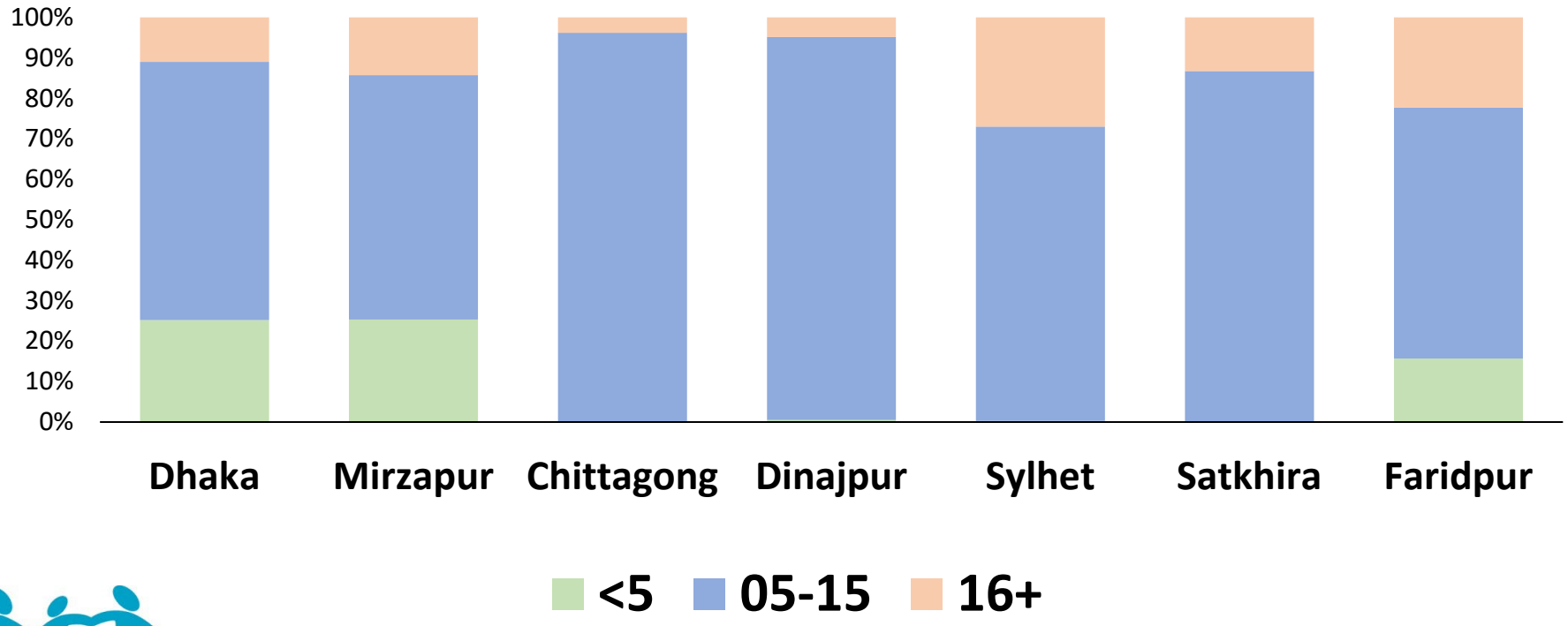
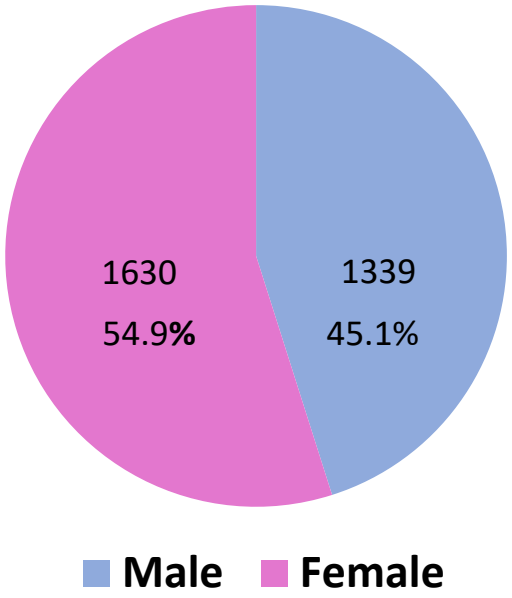
Characteristics of the study participants

Age distribution



Sex distribution



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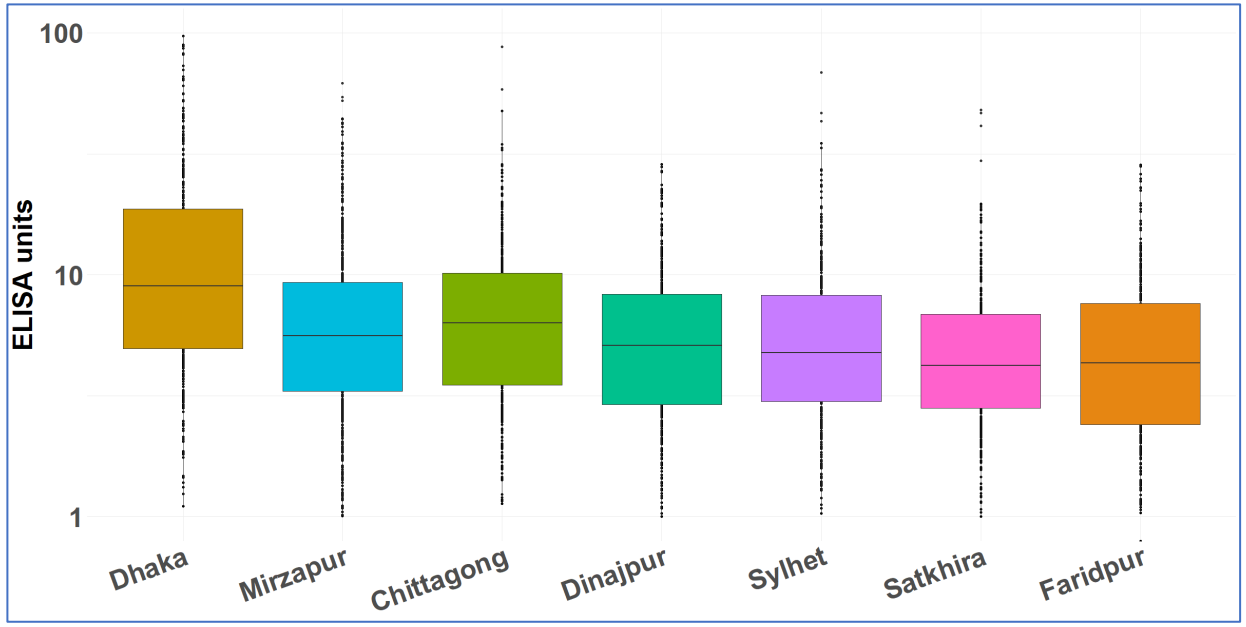
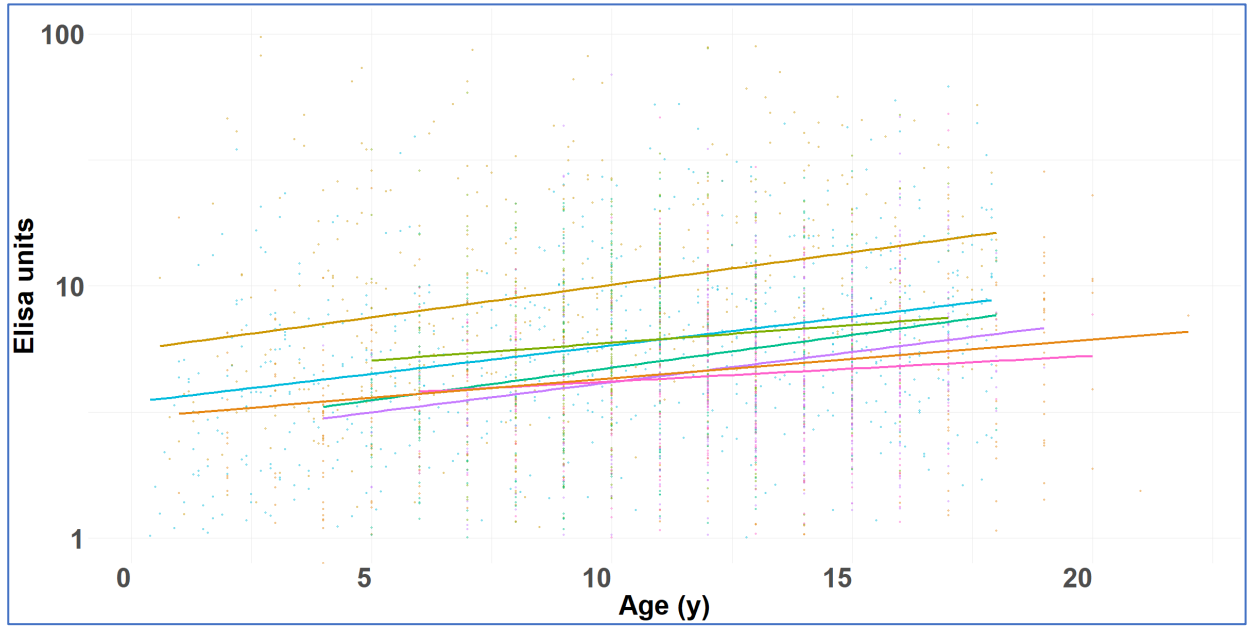
Prevent Infections, Save Lives

Anti-HlyE IgG response among study participants

By study communities

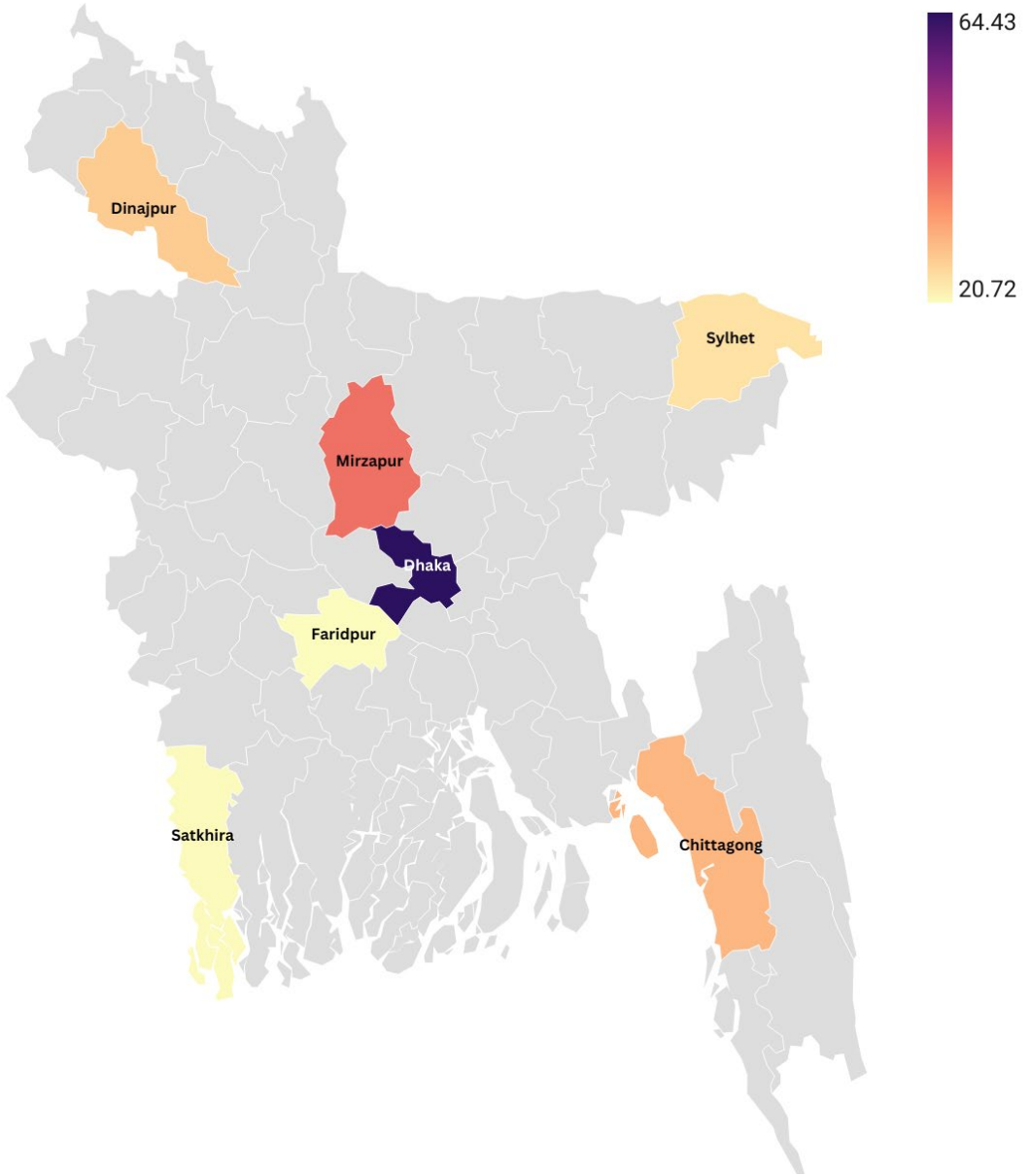


By age



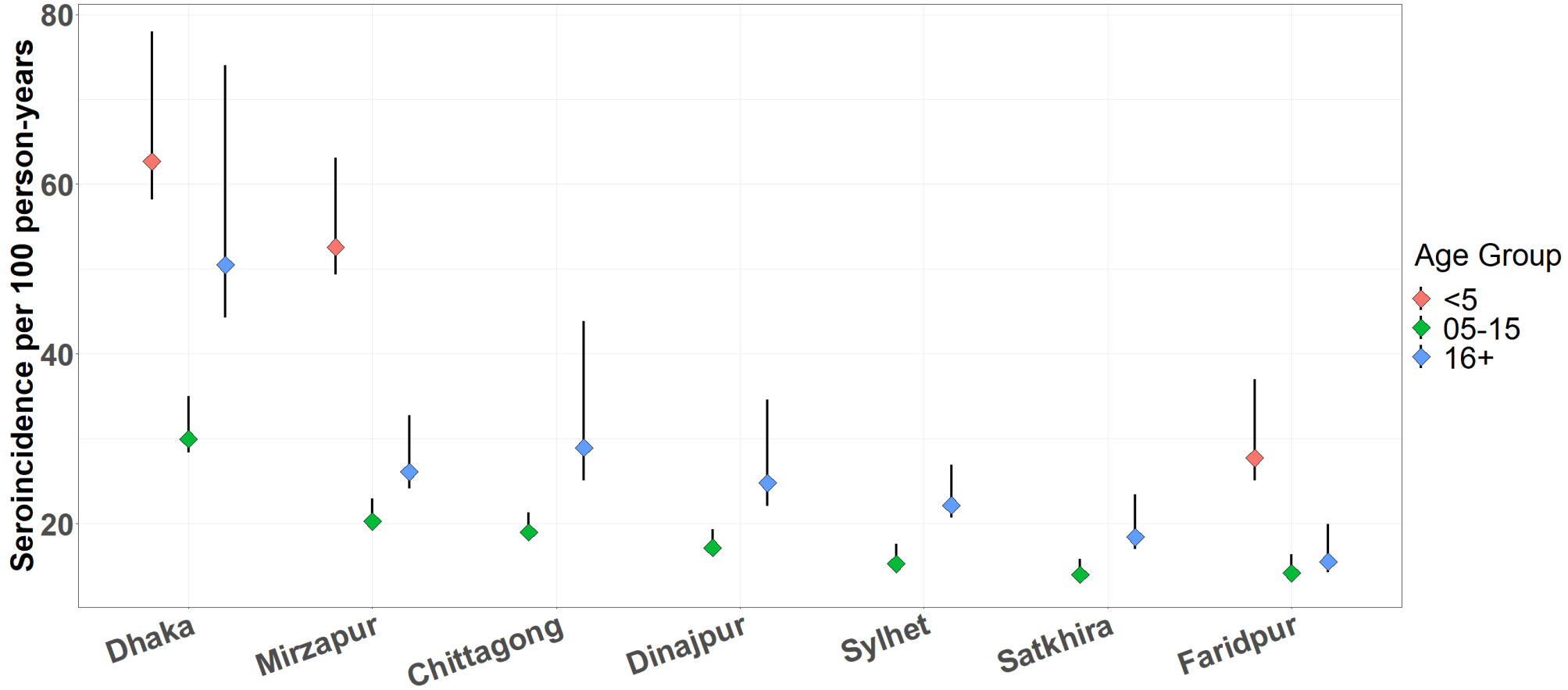
Enteric fever seroincidence among study participants

Study areas	Seroincidence per 100 person-years (95% CI)
Dhaka	64.4 (55.4- 75.0)
Mirzapur	39.0 (34.8- 43.8)
Chittagong	30.1 (26.4- 34.4)
Dinajpur	27.3 (23.9- 31.1)
Sylhet	24.3 (21.3- 27.8)
Satkhira	21.0 (18.5- 23.9)
Faridpur	20.7 (18.2- 23.6)



Seroincidence per 100 person-years (Age 0 to 22 years)

Enteric fever seroincidence by age group



Child Health Research Foundation

Prevent Infections, Save Lives

This tool enables us..

- To detect high enteric fever burden areas
- To detect priority age groups for enteric fever

Thank you

CHRF

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BILL & MELINDA GATES foundation

13th INTERNATIONAL CONFERENCE TYPHOID & OTHER INVASIVE SALMONELLOSES
December 5-7, 2023 | Kigali, Rwanda

COALITION AGAINST TYPHOID
a program of the Sabin Vaccine Institute

Mapping Typhoid Transmission Geospatial Analysis and Seroepidemiology for TCV Prioritization

Dr. Abdul Momin Kazi, MBBS, MPH, PhD (Cand)
Assistant Professor (Research)
Department of Pediatrics & Child Health
The Aga Khan University, Karachi, Pakistan

آغا خان یونیورسٹی
THE AGA KHAN UNIVERSITY

Data Sources

1. Impact Assessment of Typhoid conjugate vaccine following introduction in Routine Immunization Program of Pakistan (IATRP)	October 2020 to September 2023 • Total cases tested : 30,503 • XDR-positive: 18603	Hospital and Lab based data
2. Serosurveillance and Environmental Surveillance for Enteric Fever (SEES)	March 2018 to June 2022 • Population-based: 794 • School-based: 1363	Campaign • November 2019 Routine Immun • January 2020
3. (SEAP) Phase II & III, and ITRIPP study	January 2017 to September 2023 • Total cases tested : 61,936 • XDR-positive: 35,543	

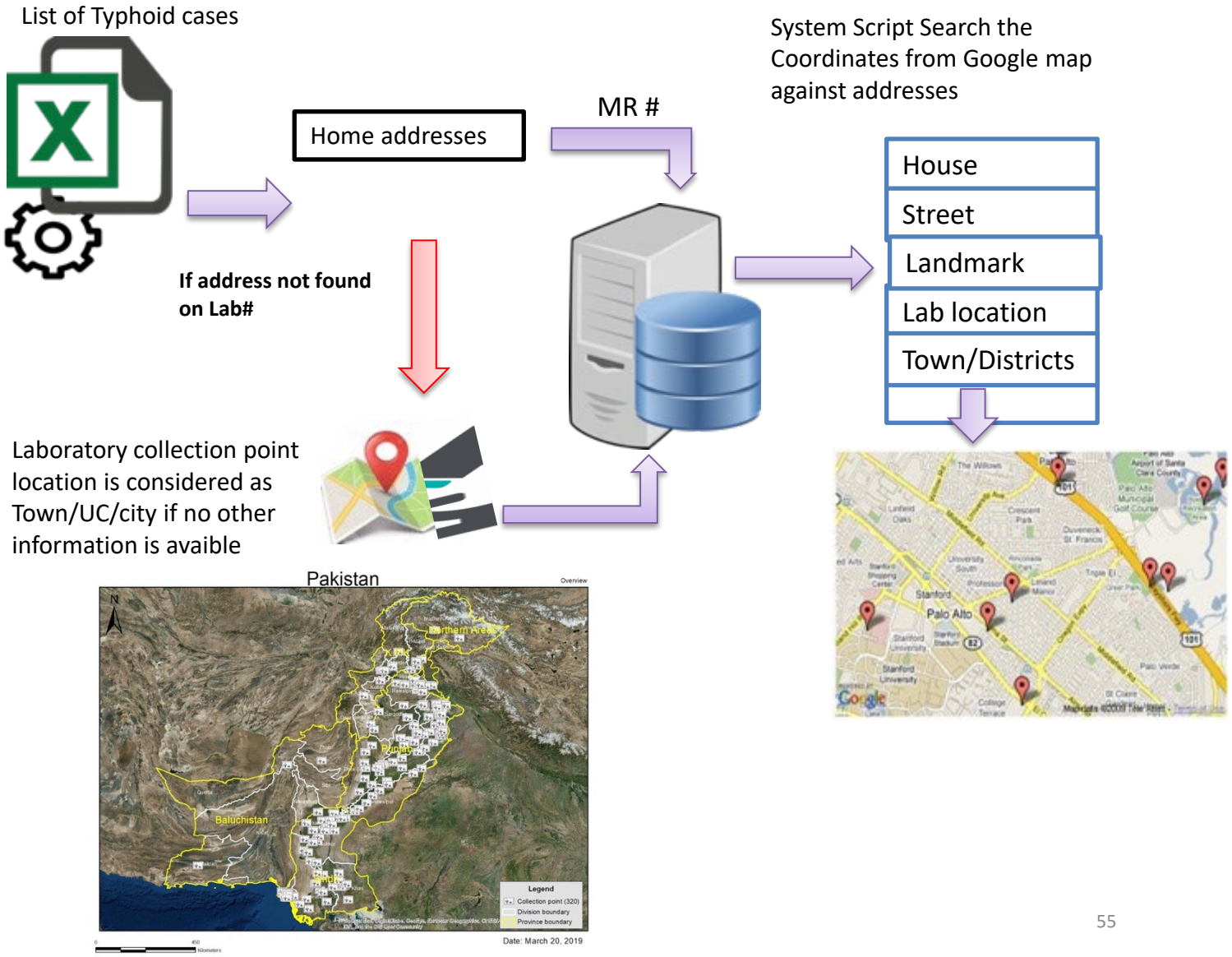
Extracting Geospatial information from Hospital and Lab Data

Hospitals

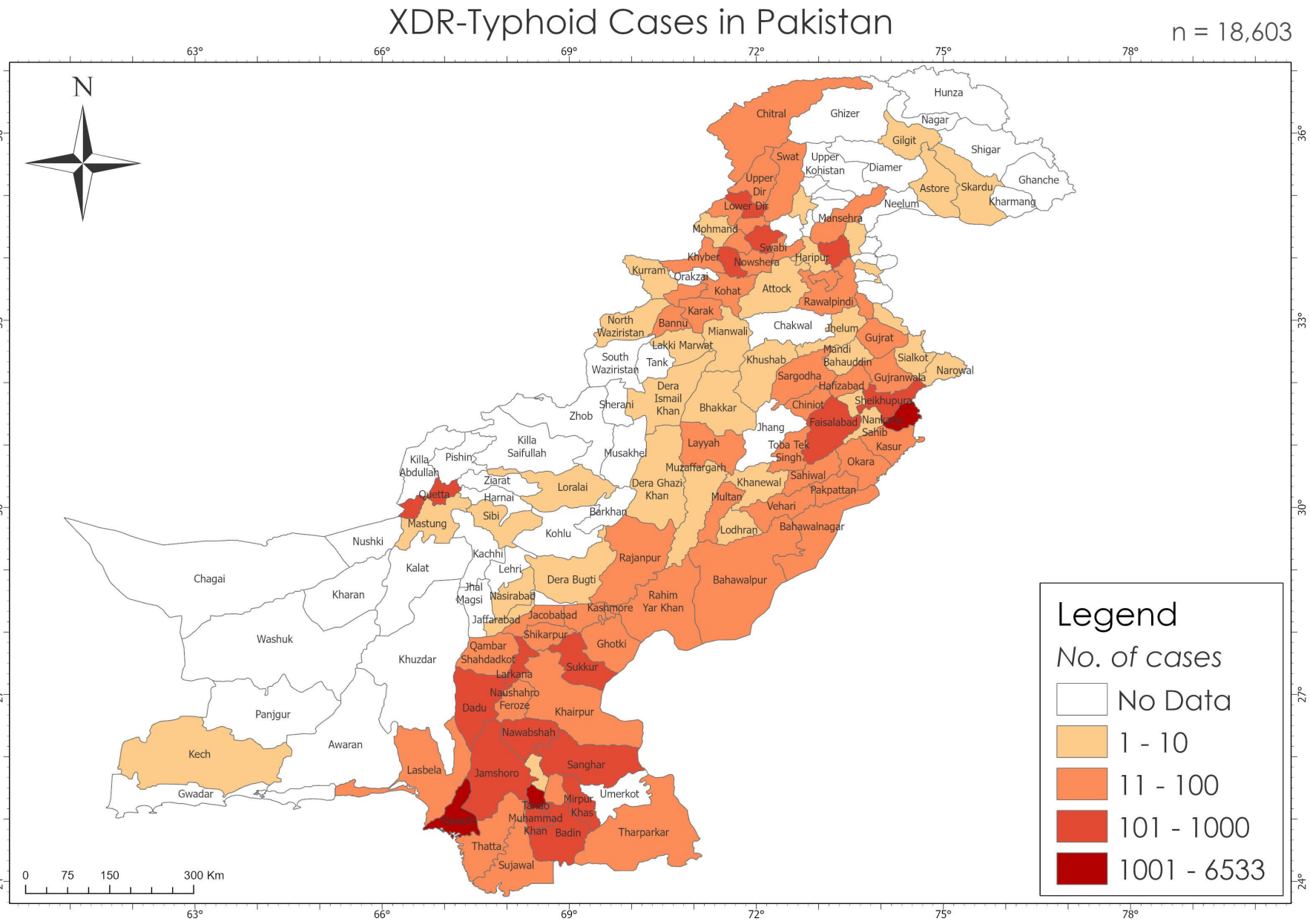
- Aga Khan University Hospital
- Liaquat University of Medical and Health Science Hospital, Hyderabad
- Aga Khan Maternal and Childcare Center AKMCCC, AKU
- Children's hospital and Institute of Child Health
- Shifa International Hospital
- Qasimabad Hospital, Hyderabad
- Bhittai Hospital, Hyderabad
- Kharadar General Hospital
- National Institute of Child Health
- Jinnah Postgraduate Medical center

Labs

- Aga Khan University Lab network – allover Pakistan
- Liaquat University of Medical and Health Science (LUMHS) Laboratory Network
- Chughtai Lab Network
- Shaukat Khanum Hospital Laboratory Network



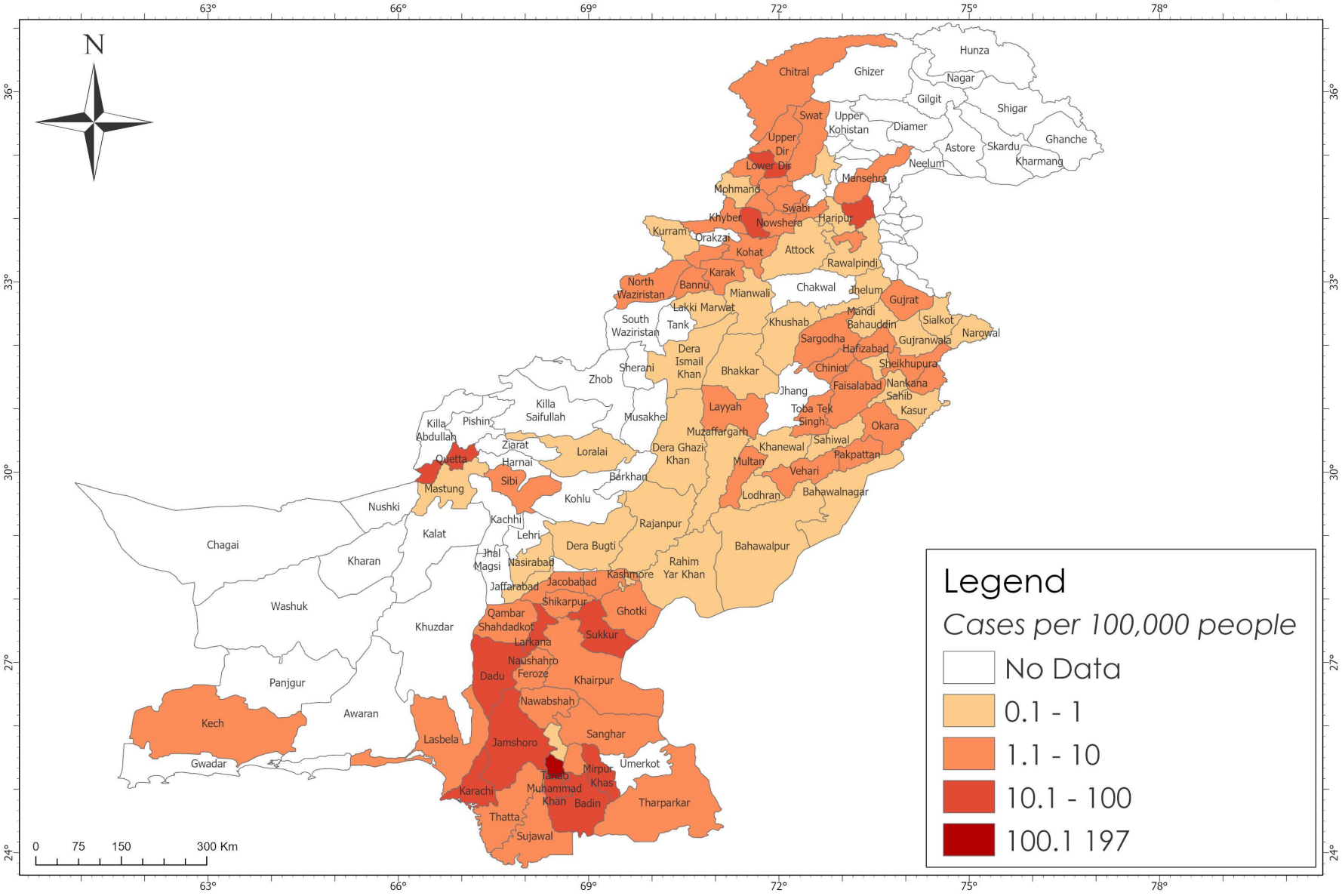
October 2020 to September2023



Sindh Cities	XDR Cases
Karachi	6533
Hyderabad	4342
Jamshoro	462
Larkana	498
Dadu	158
Sanghar	180
Nawabshah	158
Mirpur Khas	289
Thatta	29
Sukkur	149
Qambar Shahdadkot	65
Tando Allahyar	45
Tando Muhammad Khan	99
Punjab Cities	**XDR Cases**
Lahore	1010
Faisalabad	108
Gujranwala	41
Multan	67
Rawalpindi	34
Sargodha	41
Sheikhupura	108
Bahawalnagar	14
Bahawalpur	14
Chiniot	13
Hafizabad	12
Kasur	25

XDR-Typhoid Cases in Pakistan (Density over Population)

n = 18,603

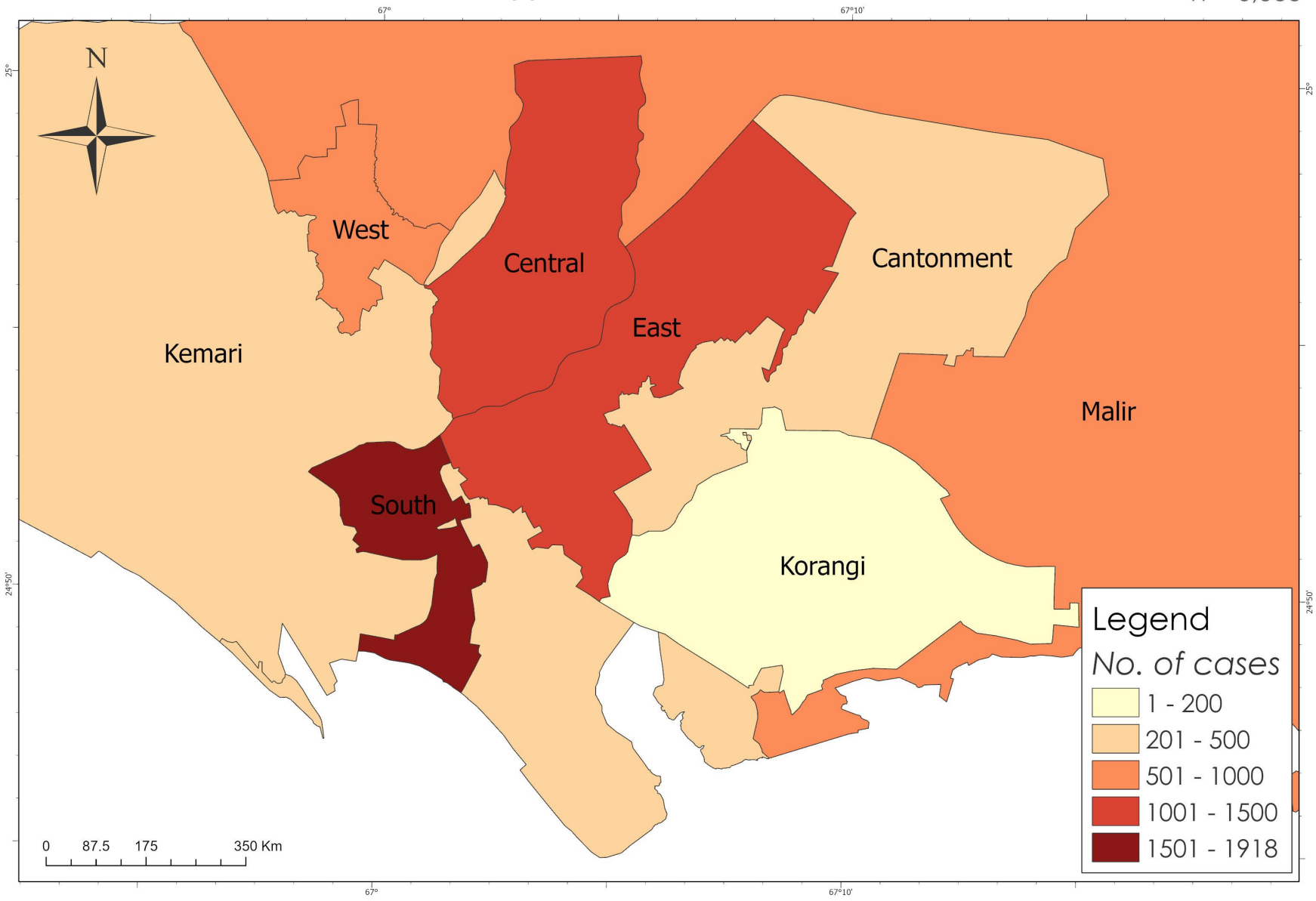


Sindh Cities	Density over 100,000 people
Hyderabad	197
Karachi	41
Jamshoro	47
Larkana	33
Mirpur Khas	19
Sukkur	10
Qambar Shahdadkot	5
Sujawal	2
Tando Allahyar	5
Tando Muhammad Khan	16

Punjab Cities	Density over 100,000 people
Lahore	9
Faisalabad	1
Gujranwala	1
Multan	1
Rawalpindi	1
Sheikhupura	3
Chiniot	1

XDR-Typhoid Cases in Karachi

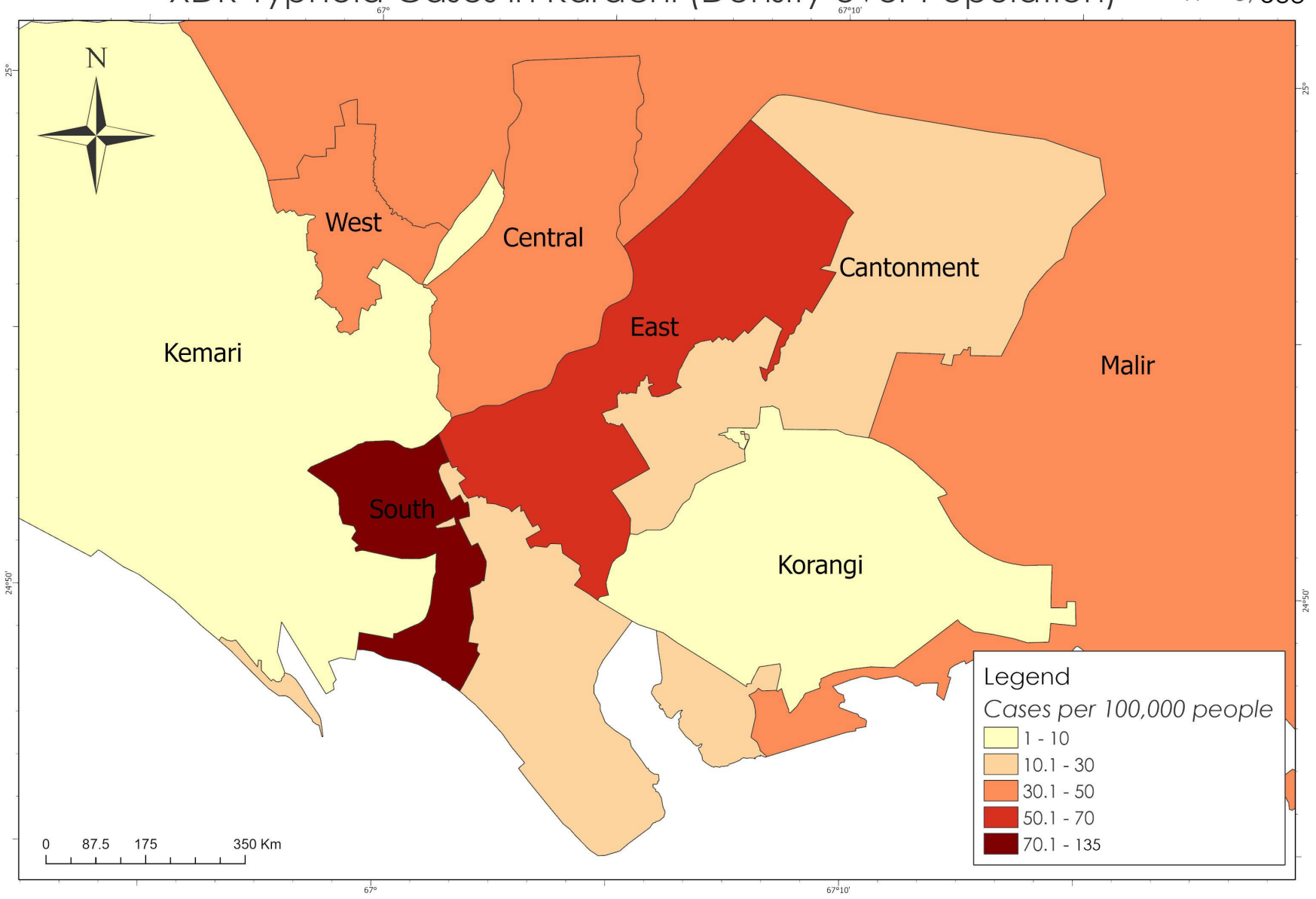
n = 6,533



Karachi Districts	XDR Cases
Karachi South	1918
Karachi East	1426
Karachi Central	1221
Karachi West	722
Malir	619
Karachi Cantonment	258
Kemari	202
Korangi	167

XDR-Typhoid Cases in Karachi (Density over Population)

n = 6, 533

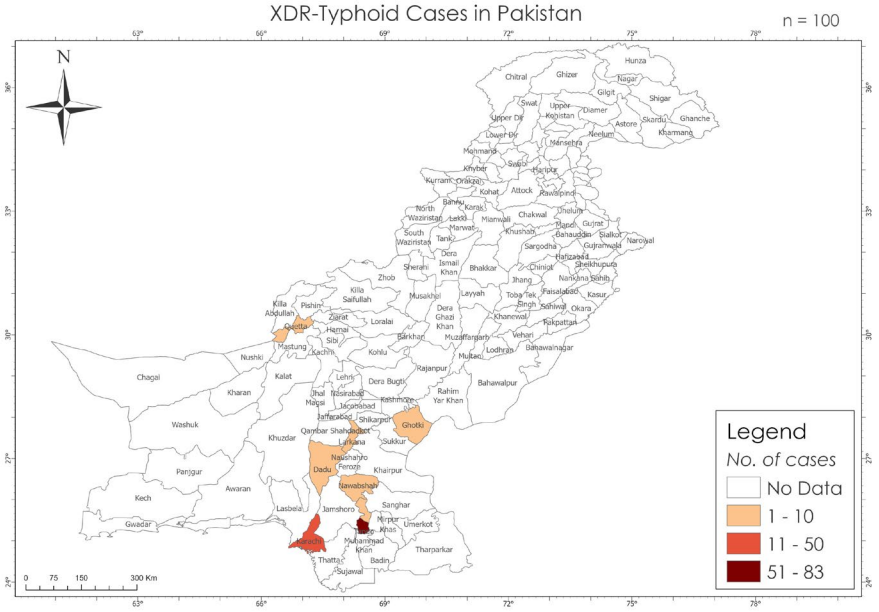


Karachi Districts	Population	Cases per 100,000 people
Karachi South	1,416,936	135
Karachi East	2,610,998	55
Karachi West	1,560,284	46
Karachi Central	2,971,626	41
Malir	1,812,104	34
Karachi Cantonment	873,955	30
Kemari	2,348,599	9
Korangi	2,457,019	7

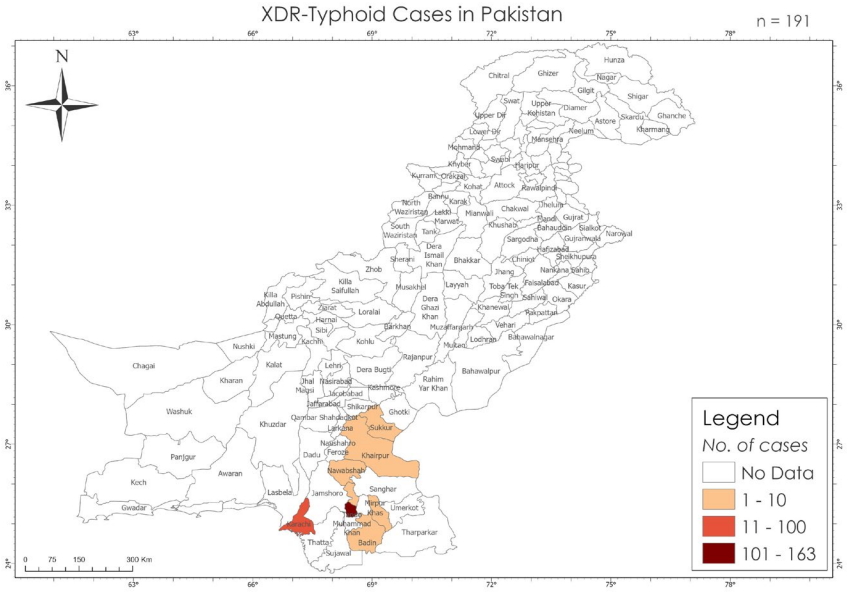
Number of XDR-positive Cases
Seasonality Maps

2017

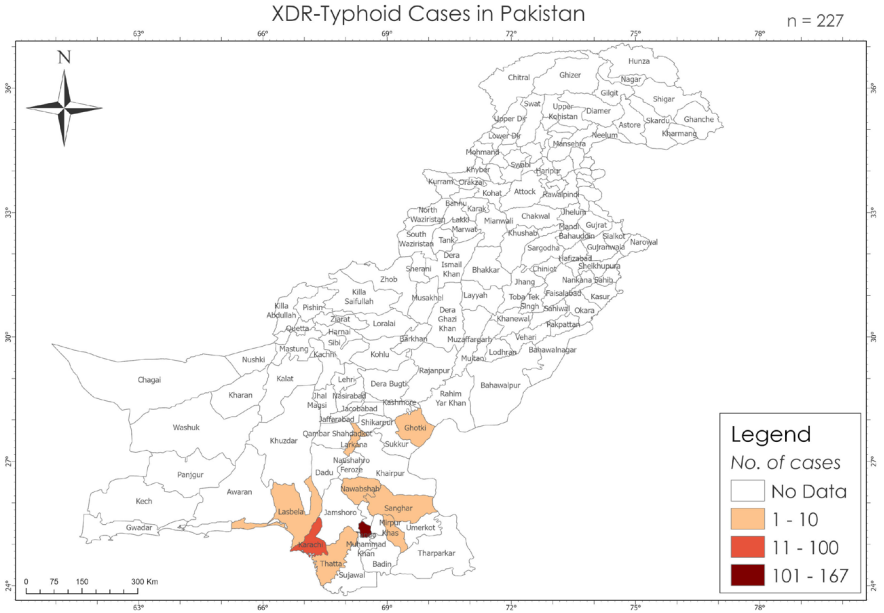
January - March



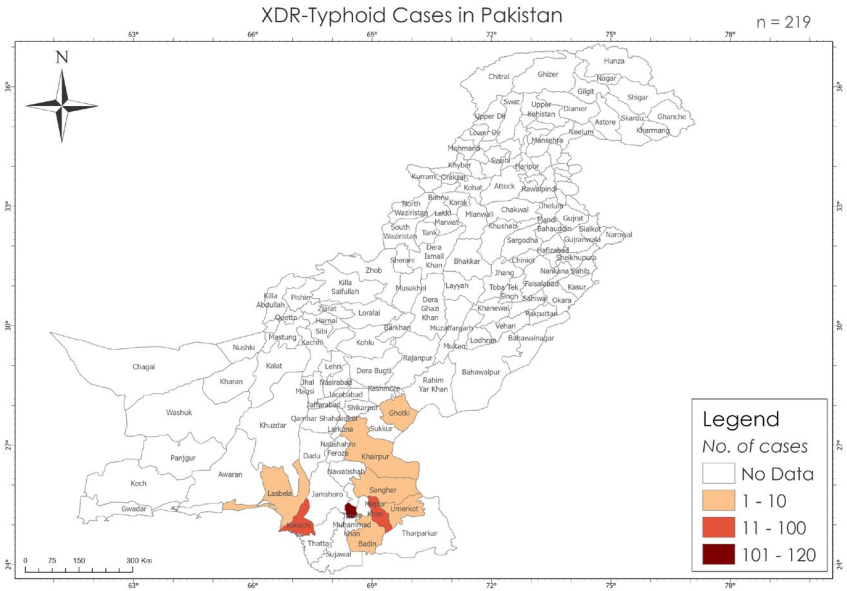
April - June



July – September

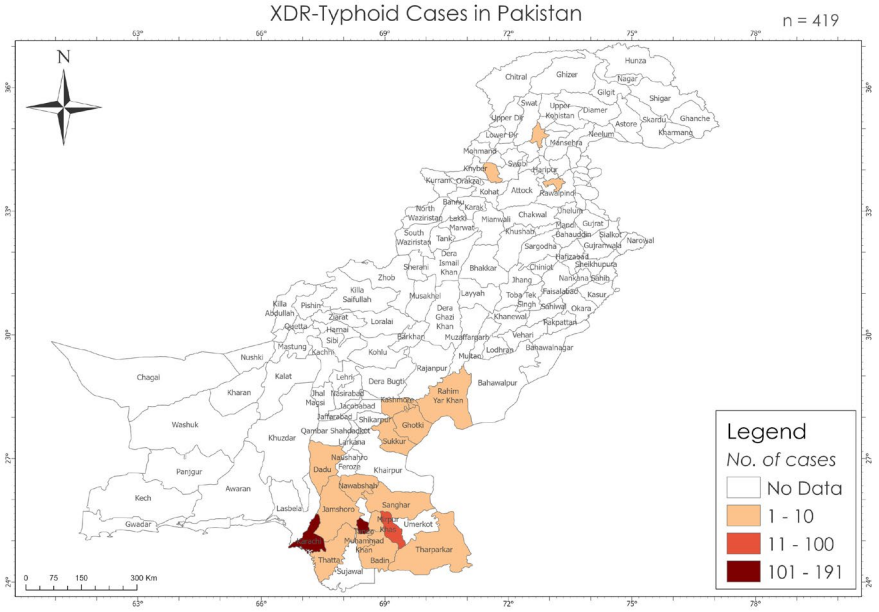


October - December

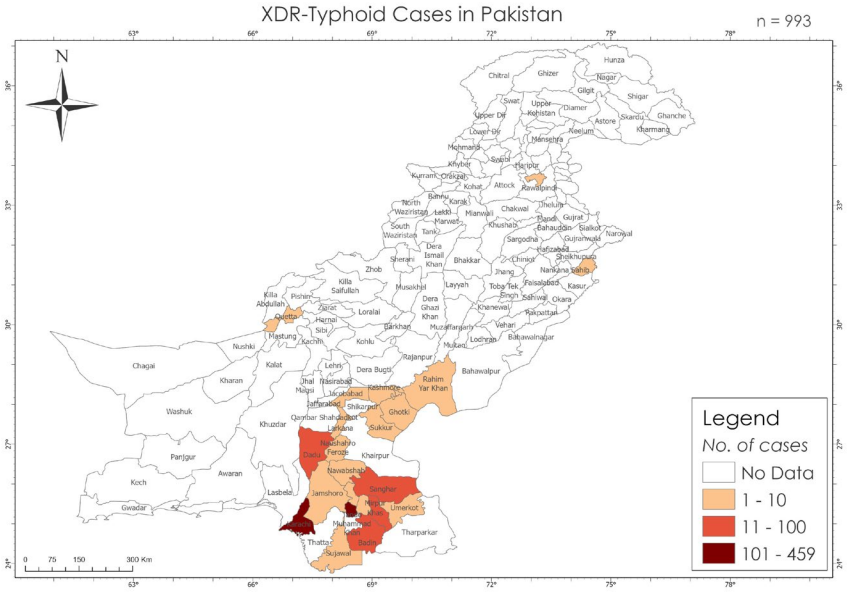


2018

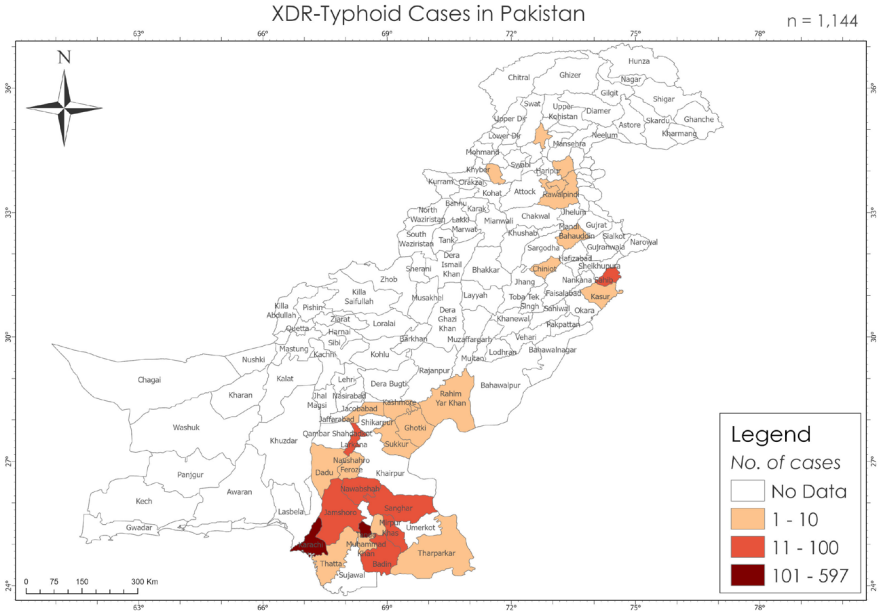
January - March



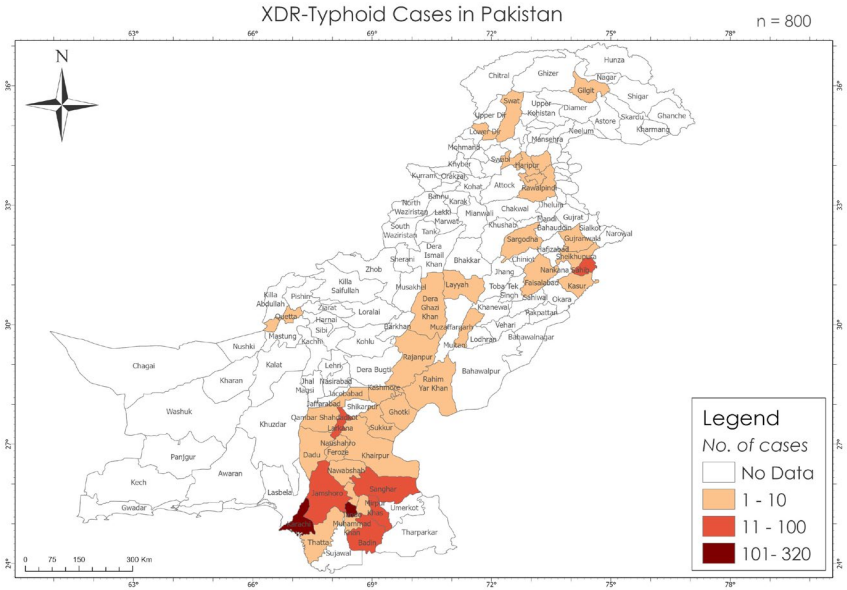
April - June



July – September

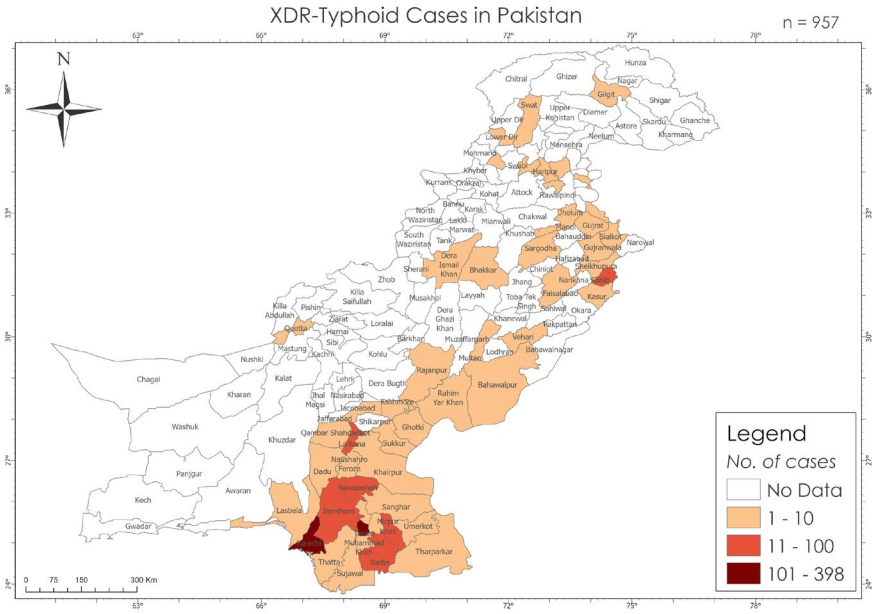


October - December

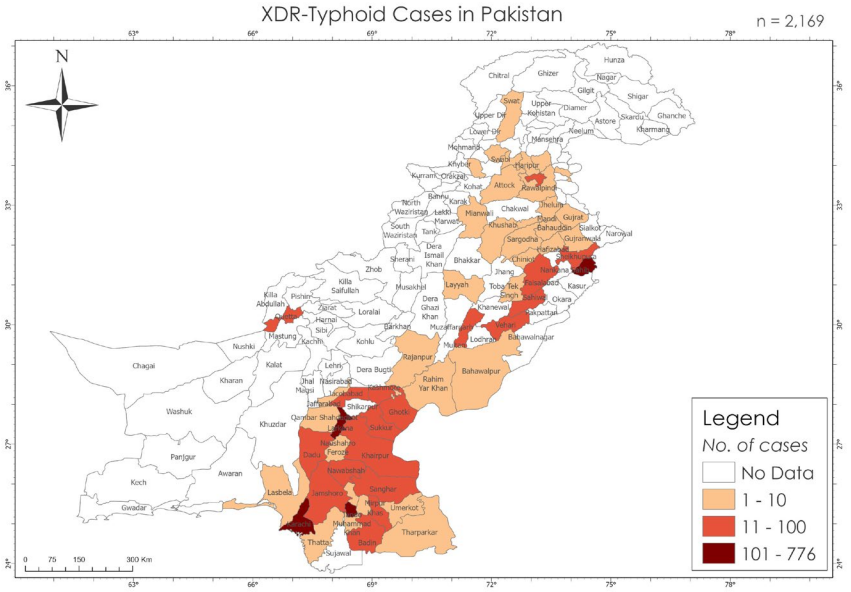


2019

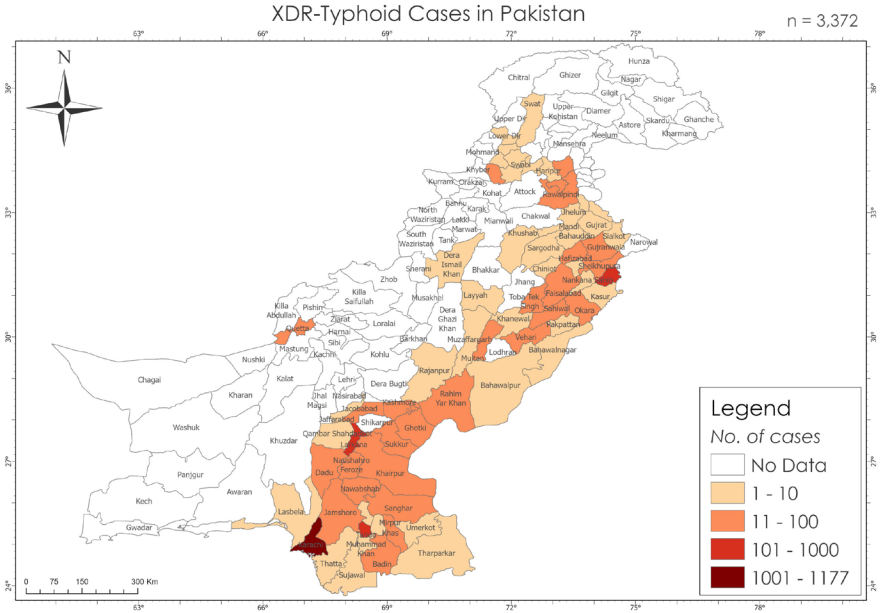
January - March



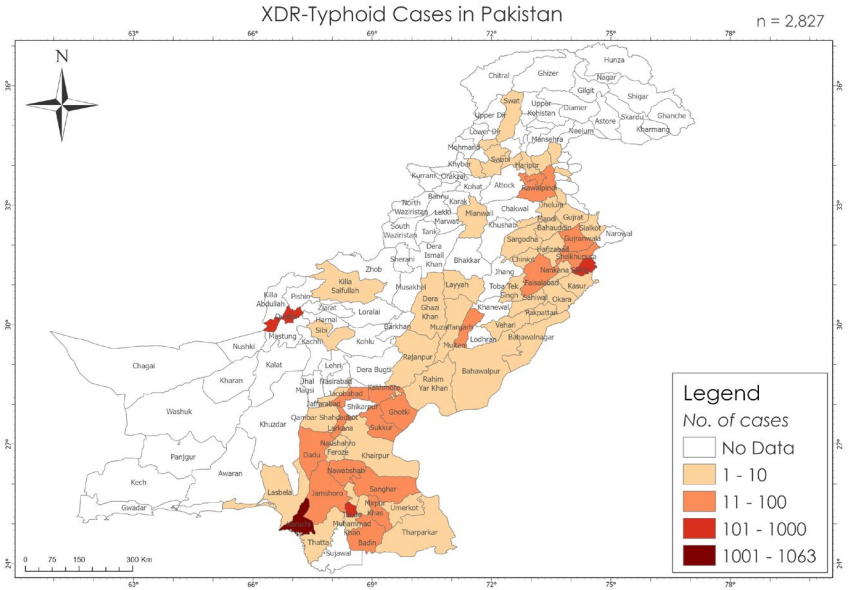
April - June



July – September



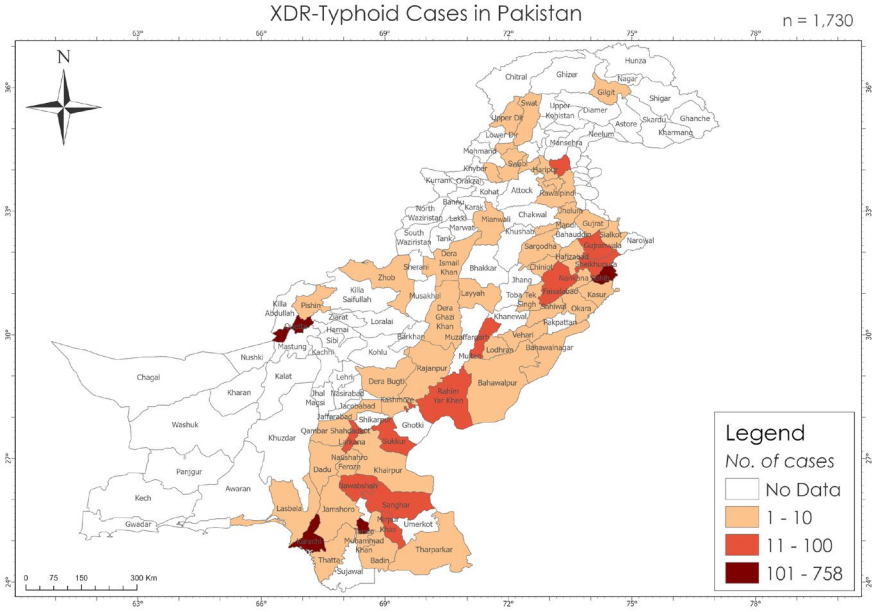
October - December

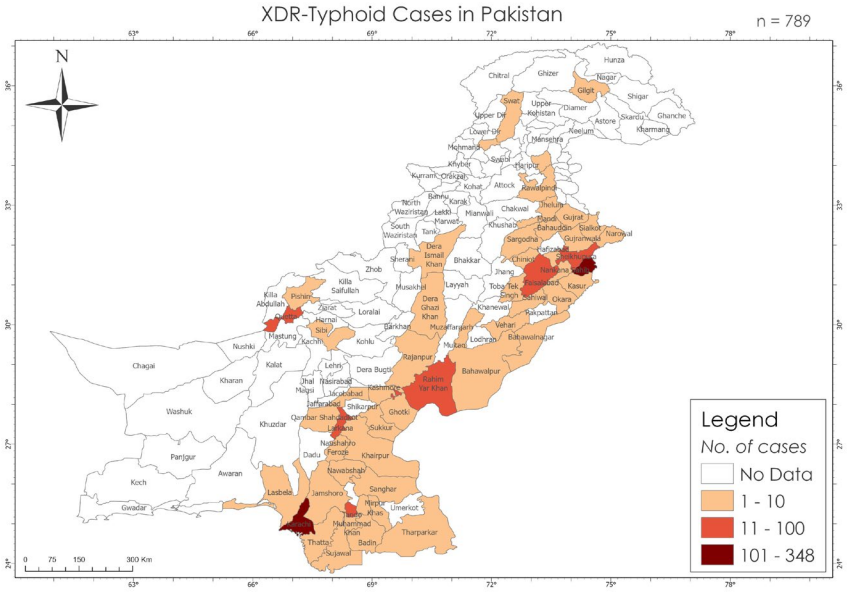


2020*

*Vaccine introduced

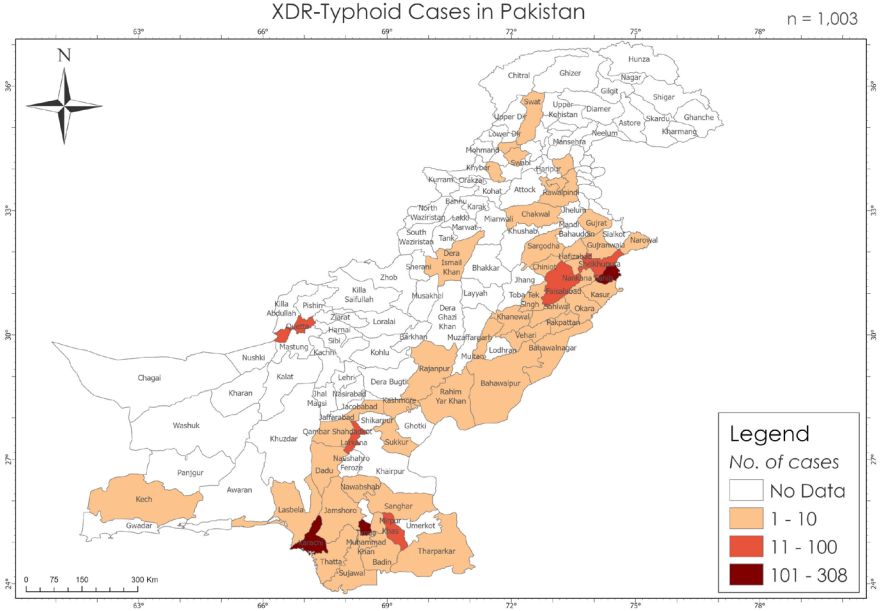
January - March

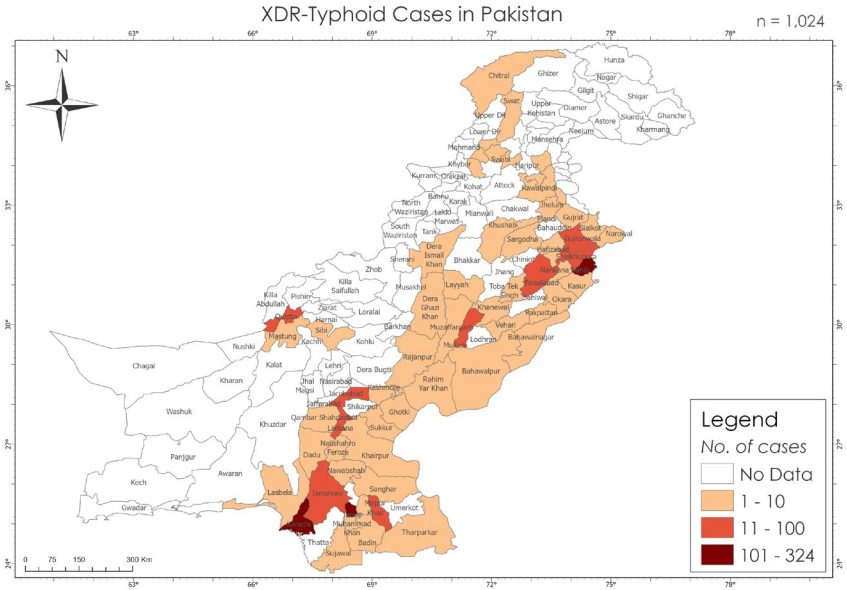




April - June

July – September

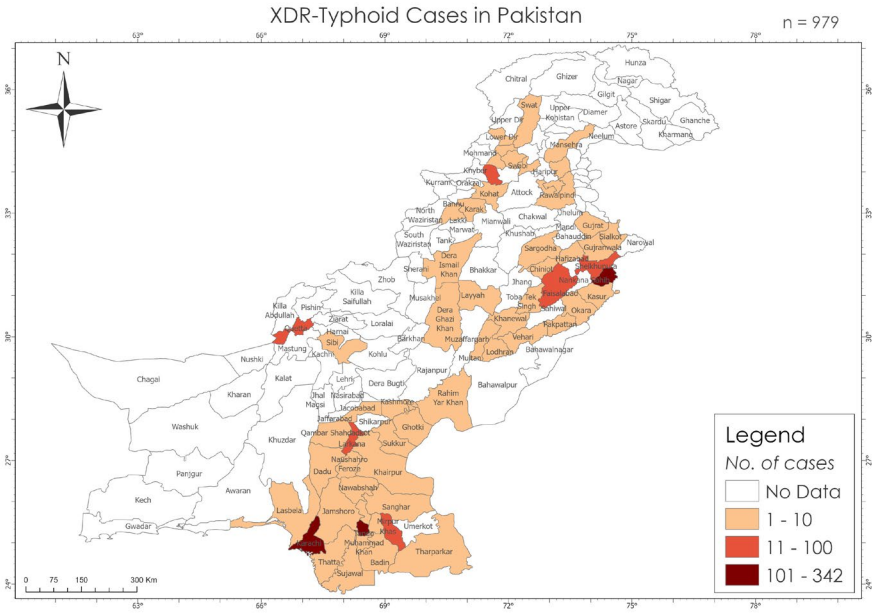




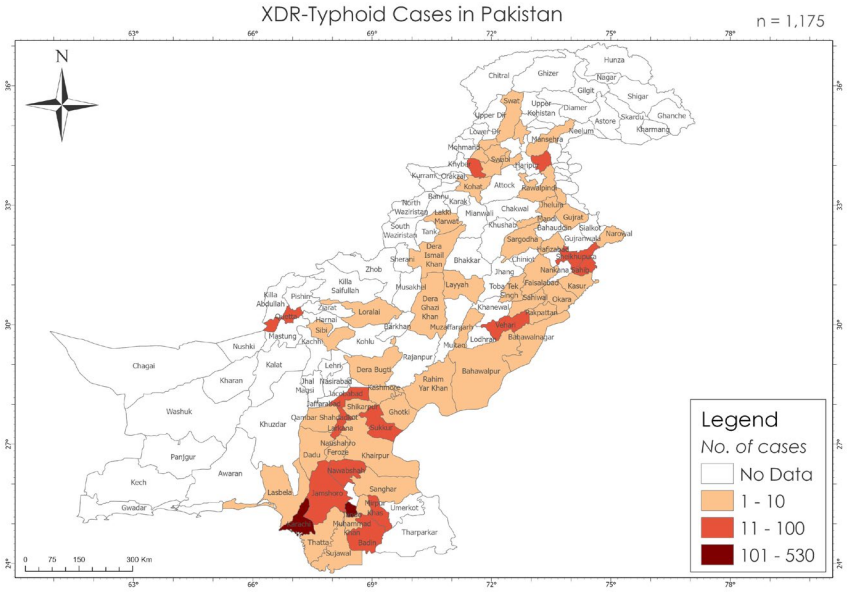
October - December

2021

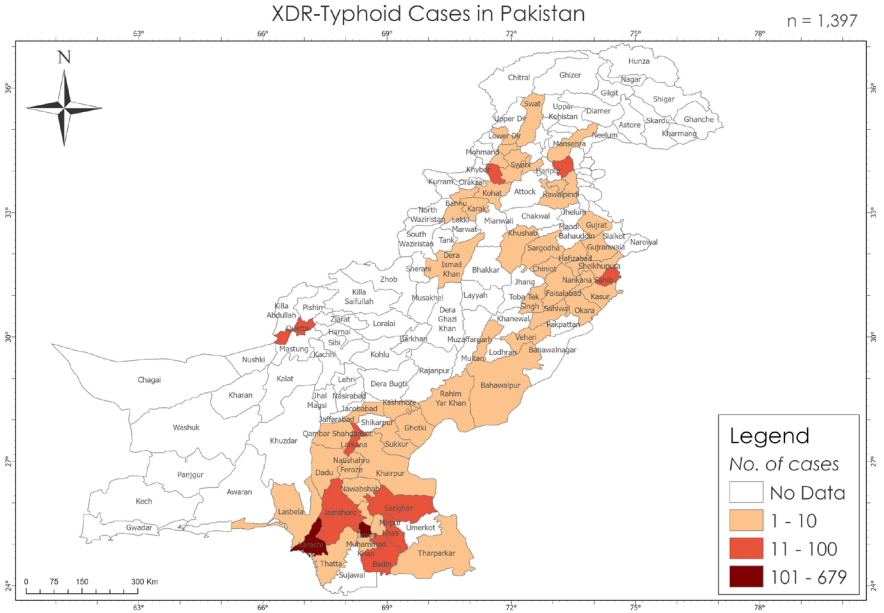
January - March



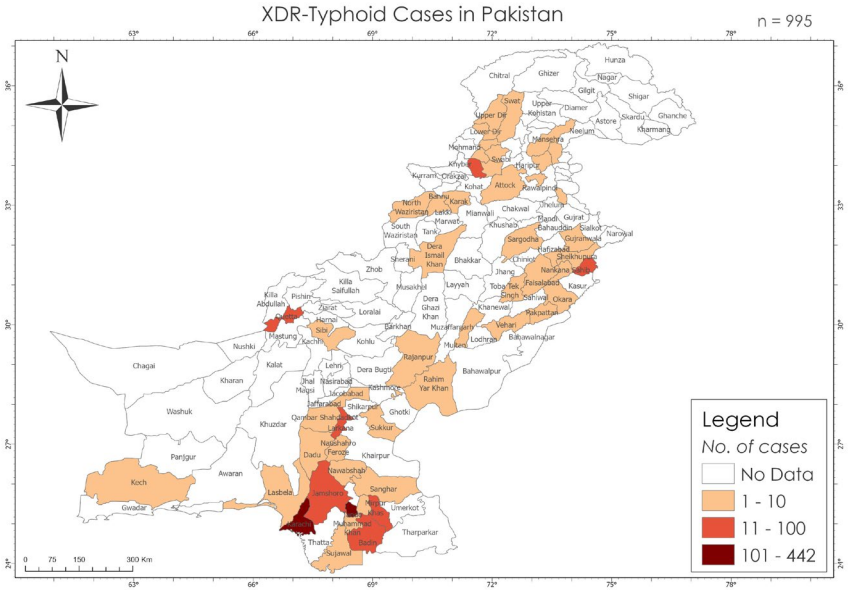
April - June



July – September

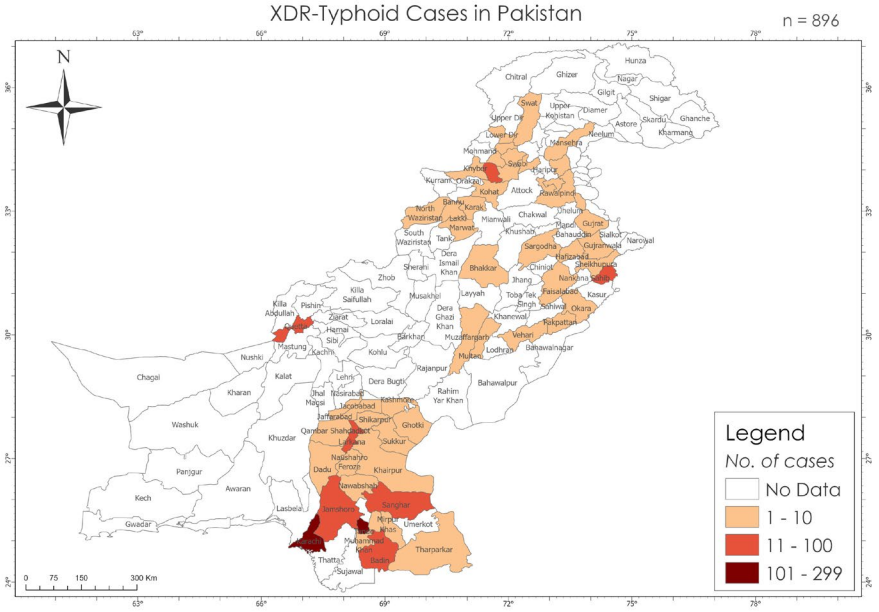


October - December

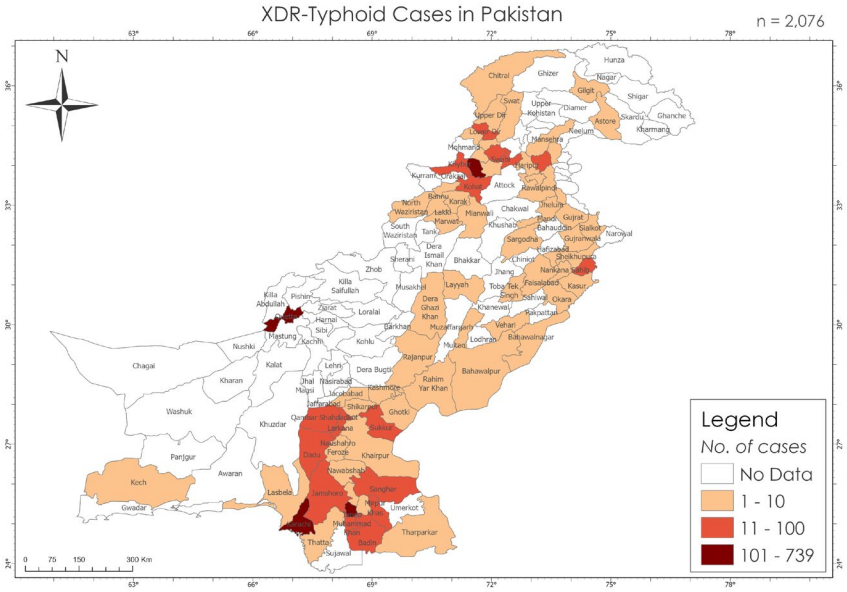


2022

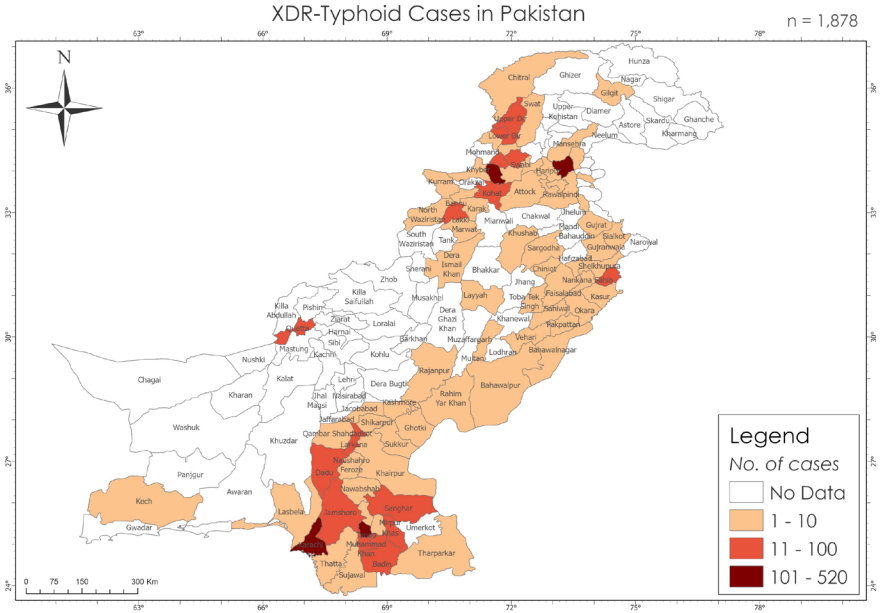
January - March



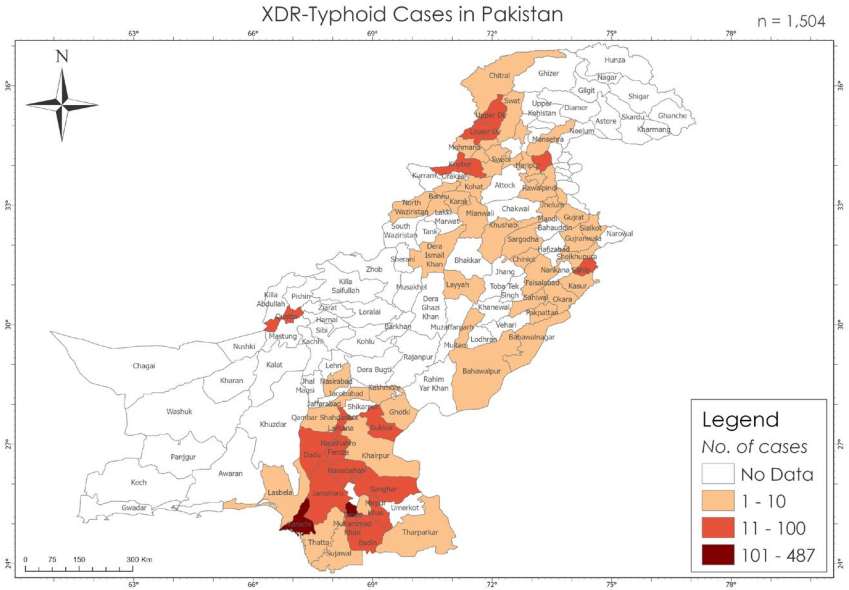
April - June



July – September

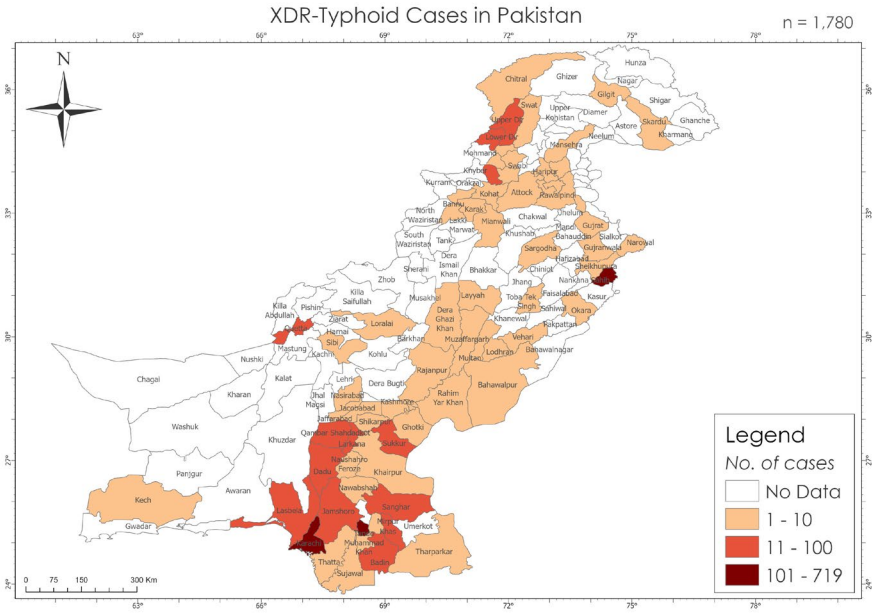


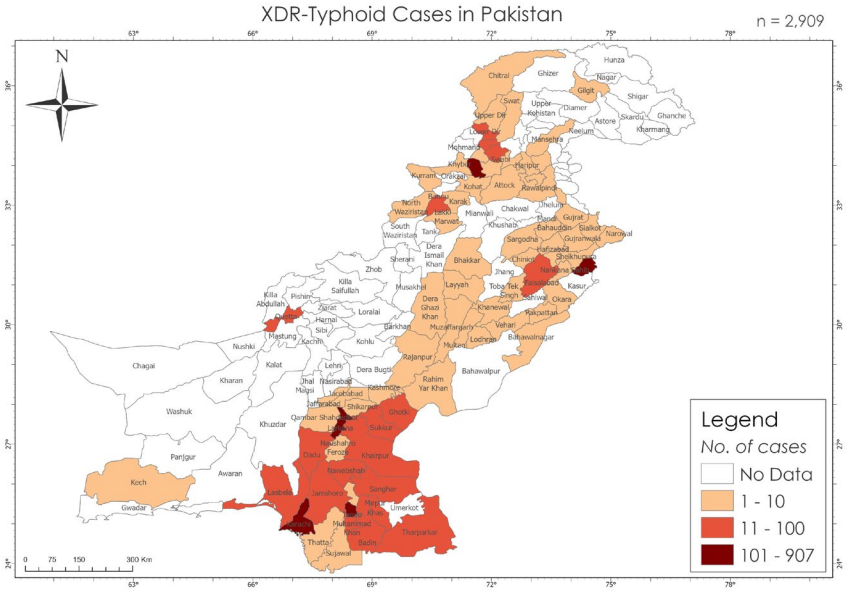
October - December



2023

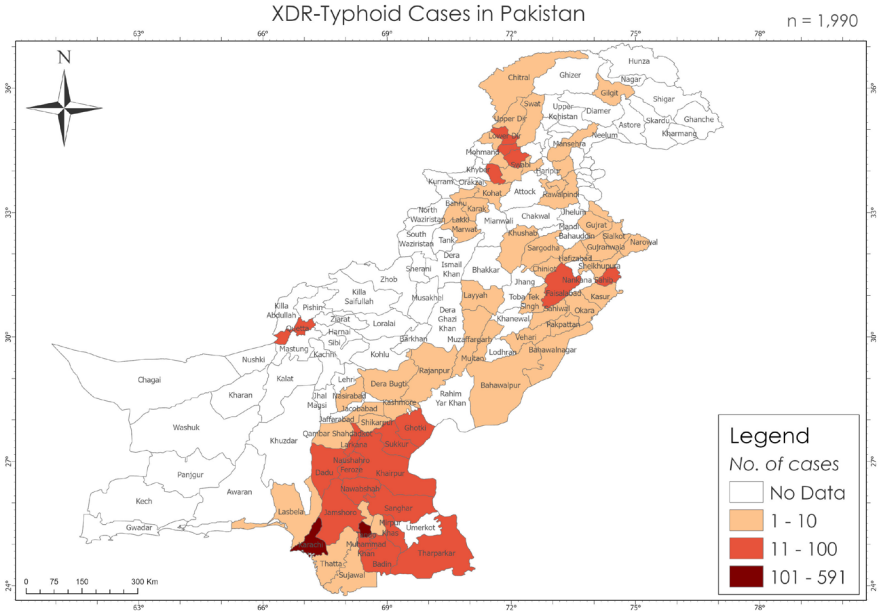
January - March





April - June

July – September



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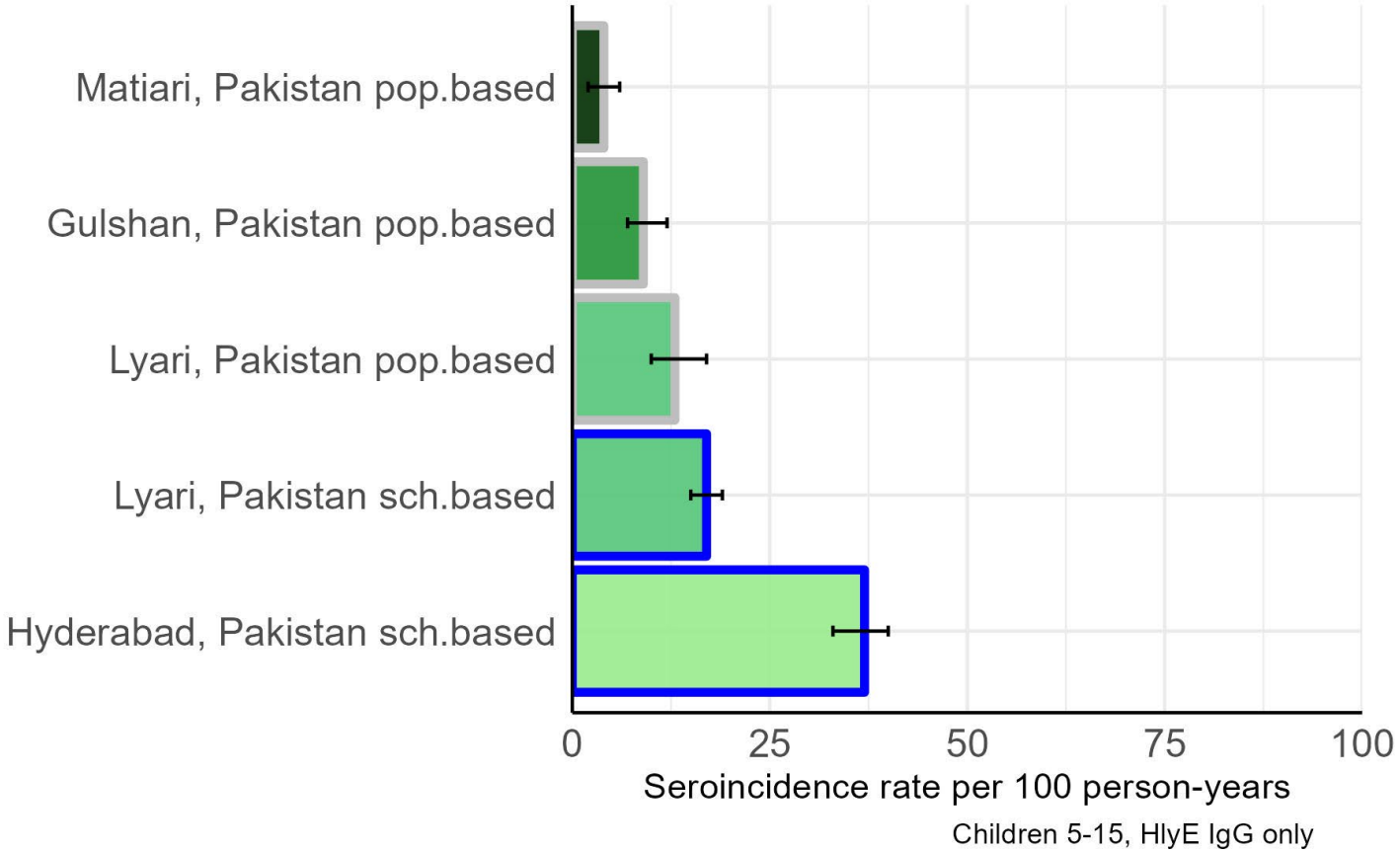
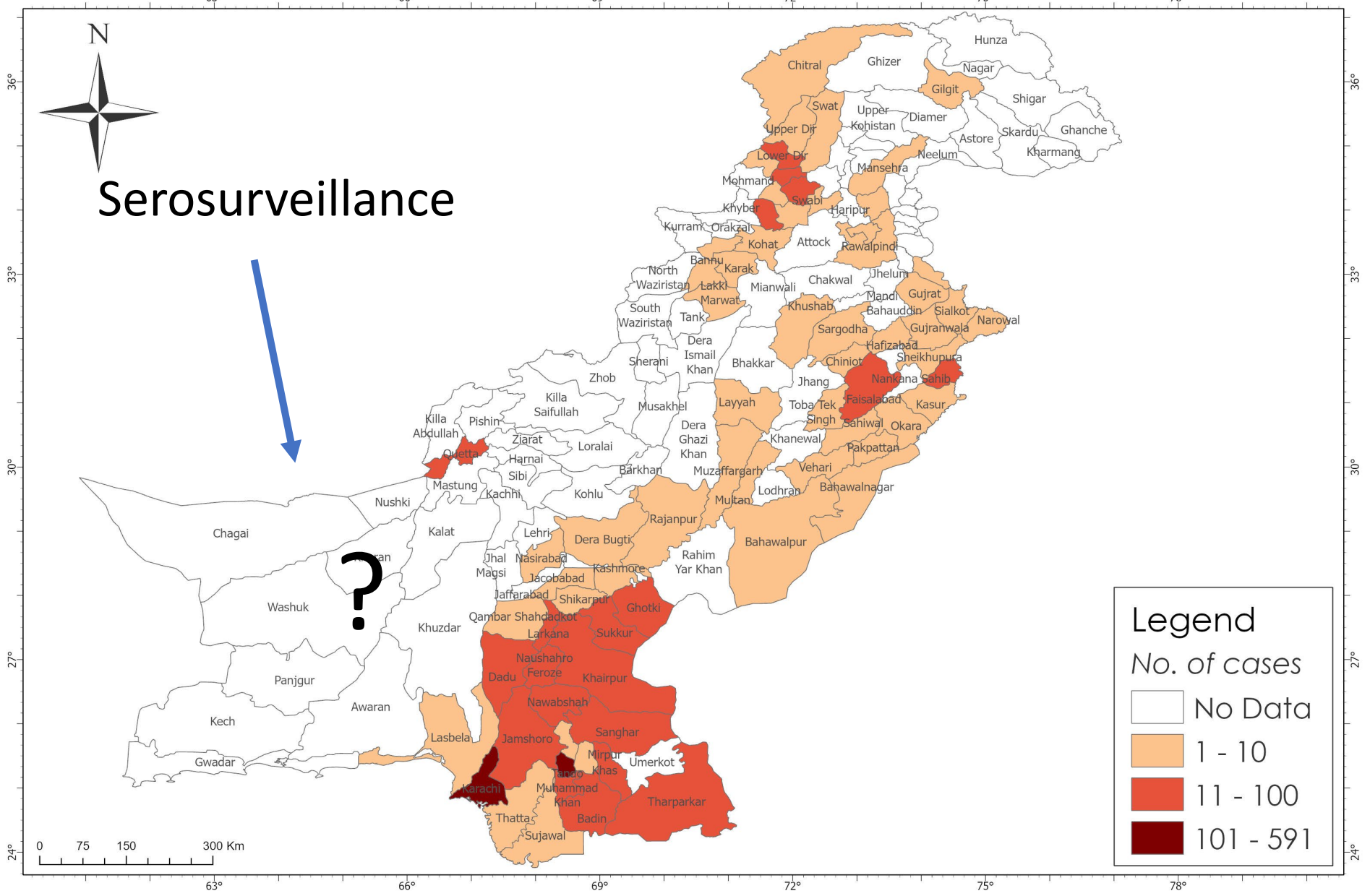


XDR-Typhoid Cases in Pakistan

n = 1,990



Conclusions

- Hyderabad had the highest clinical (blood culture) incidence and seroincidence

- Serosurveillance is a strategy to efficiently fill in the gaps in areas where blood culture is not available

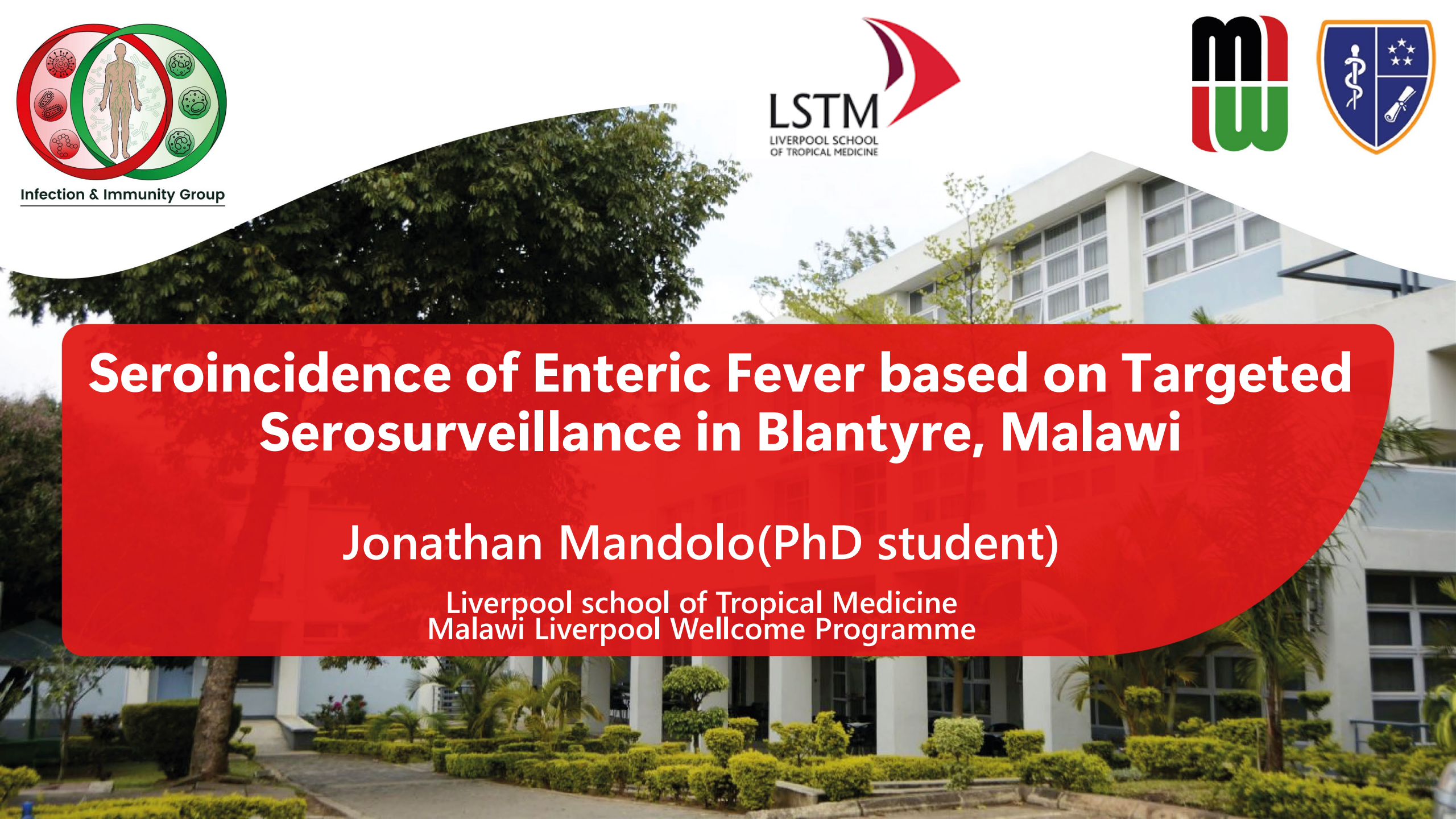
- In Lyari, where we had both population-based and school-based serosurveys, seroincidence estimates were comparable

Acknowledgements

Dr. Farah Qamar
Study and field team

Parents and families

GIS team
Syeda Aliya Hassan
Ayub Khan



Infection & Immunity Group

LSTM
LIVERPOOL SCHOOL
OF TROPICAL MEDICINE

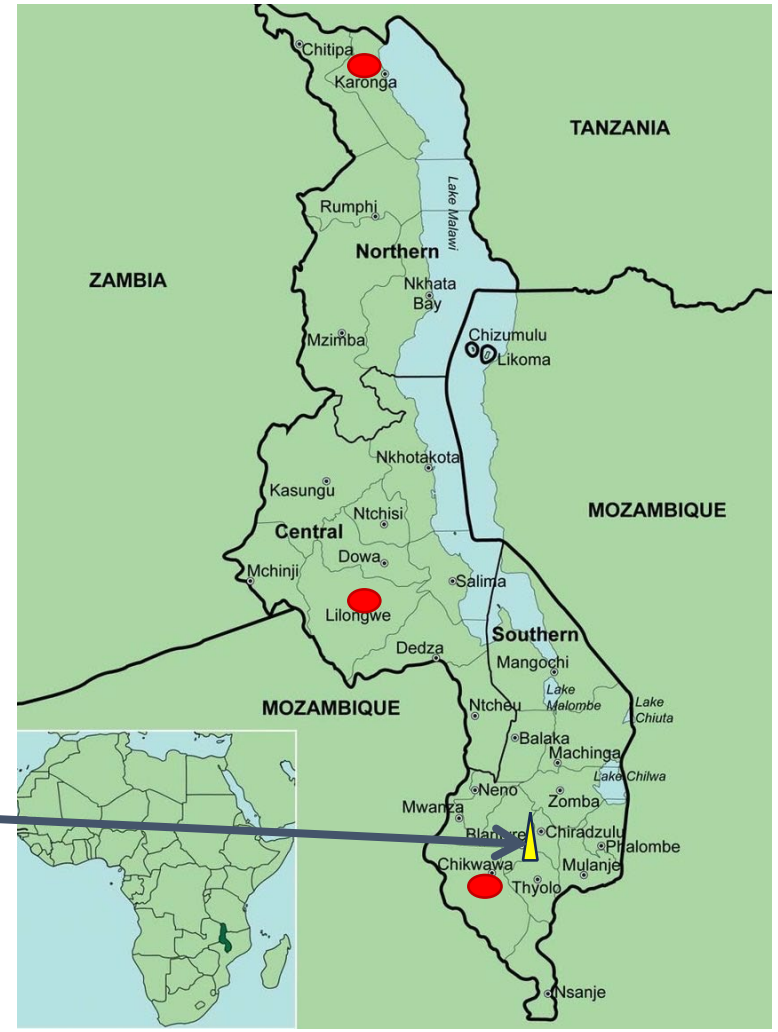
Seroincidence of Enteric Fever based on Targeted Serosurveillance in Blantyre, Malawi

Jonathan Mandolo(PhD student)

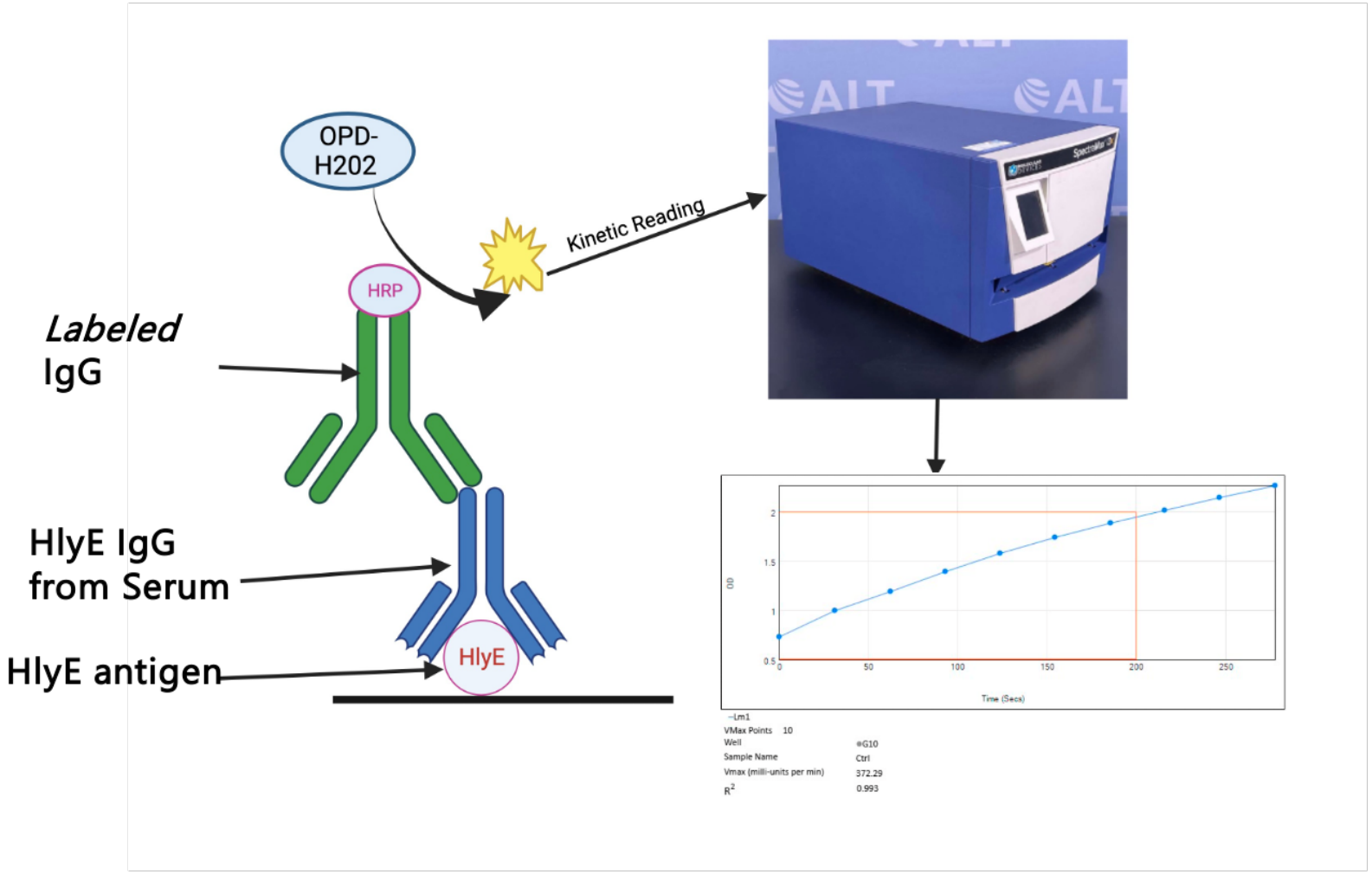
Liverpool school of Tropical Medicine
Malawi Liverpool Wellcome Programme

Study Design

- This was a cross sectional study in Ndirande, Blantyre , Malawi between Dec 2022 to June 2023
- The target was to recruit 1300 individuals of 1 to 14 years based on adjusted clinical incidence
- Recruited 966 of age groups 1-2 and 3-4, 5-9, 10-14 years



Laboratory Methods



Created with BioRender.com , Aiemjoy et al, BPLoS Negl Trop Dis., 2020

Data Analysis

Infection & Immunity Group

- Antibody dynamics from a longitudinal cohort of 1,420 blood culture–confirmed enteric fever cases in Nepal, Ghana, Bangladesh, Pakistan were used
- Age- stratified incidence rates were estimated using the age-specific antibody response parameters

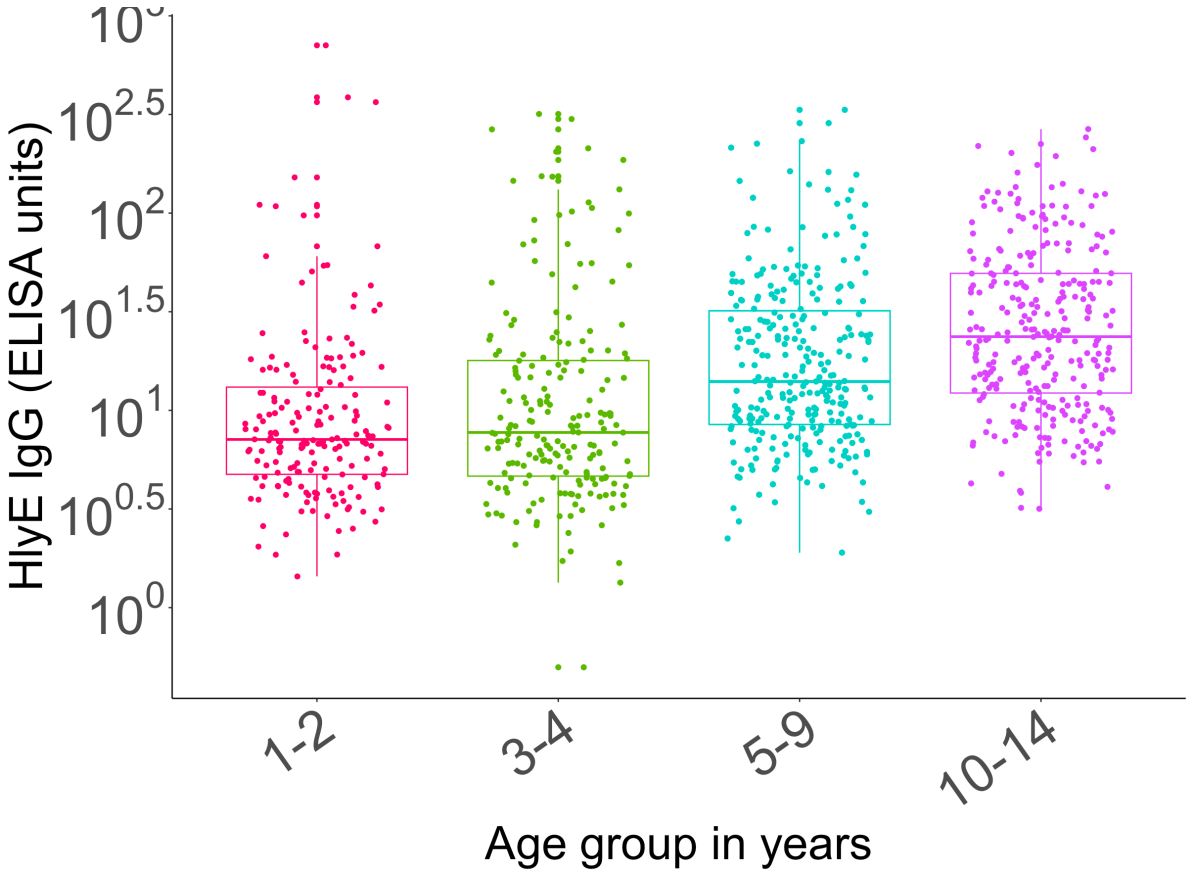
Aiemjoy et al, BPLoS Negl Trop Dis., 2020

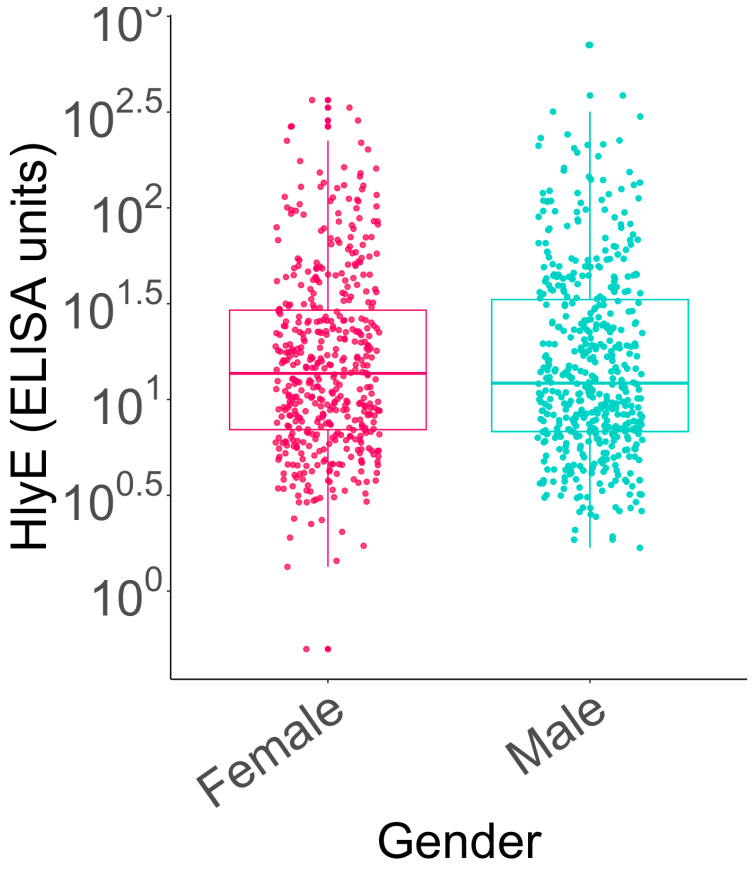
Participants demographic characteristics

Infection & Immunity Group

Characteristic	Category	Value, N = 966 (%)
Age, y, median (IQR)		6 (3 -11)
Age group	1 to 2 years	183 (18.94)
	3 to 4 years	204 (21.12)
	5 to 9 years	287 (29.71)
	10 to 14 years	292 (30.23)
Sex	Female	476 (49.28)
	Male	490 (50.72)

HlyE IgG ELISA units by Demographic Characteristics



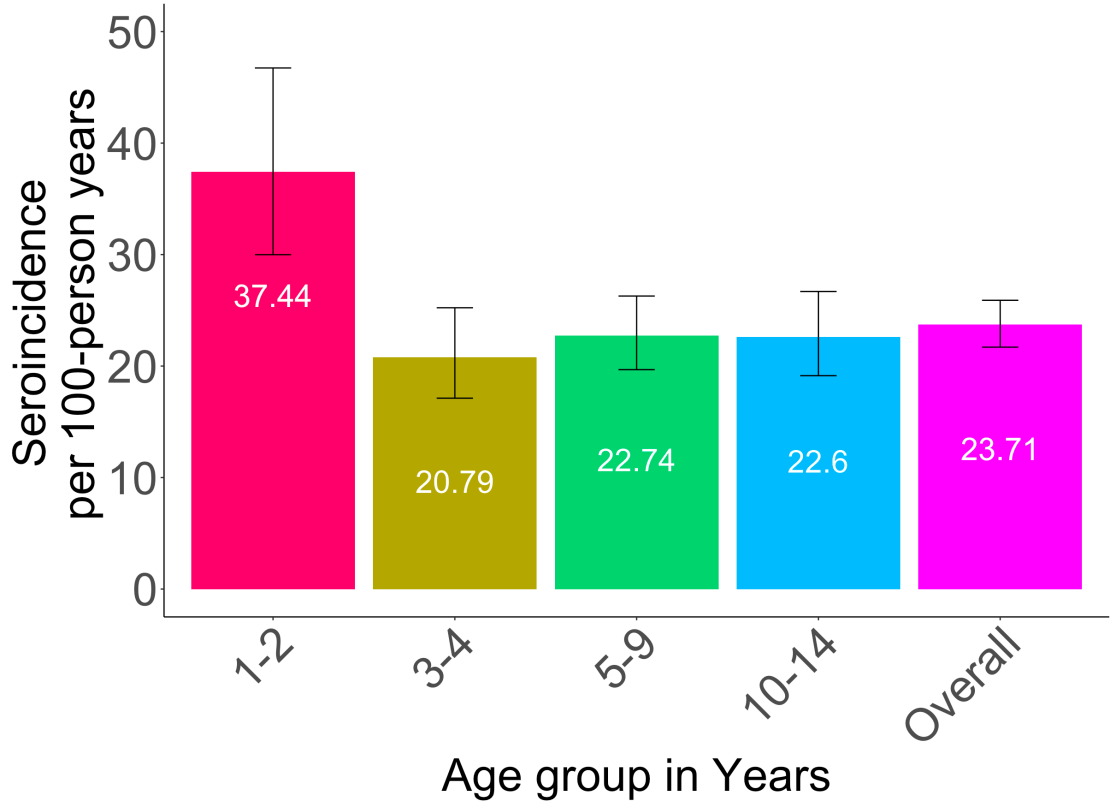


Increase in HlyE IgG levels by age suggesting hyperendemicity

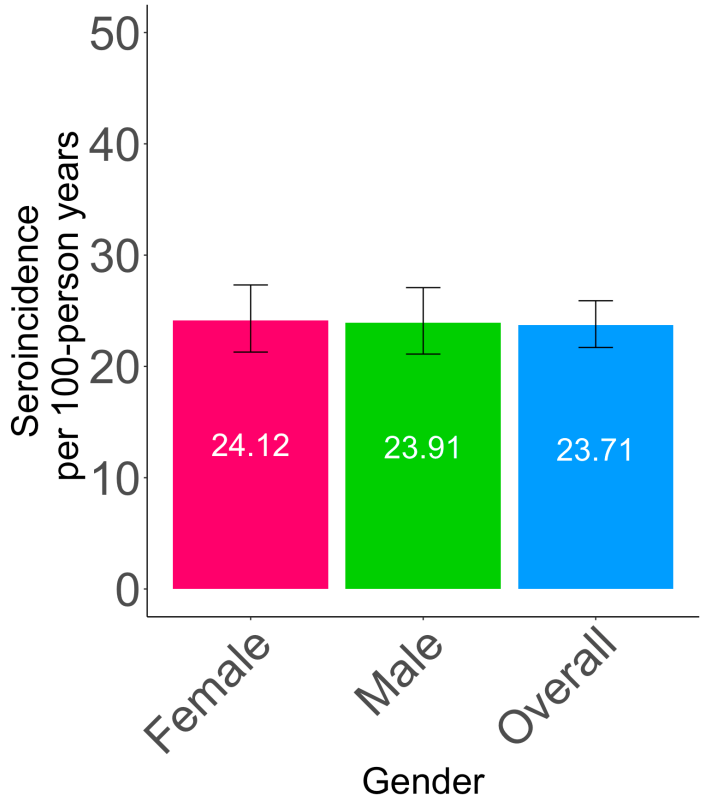
Seroincidence by demographic characteristics

Infection & Immunity Group

A



B



Higher force of infection in younger Children

Case-based incidence vs Seroincidence

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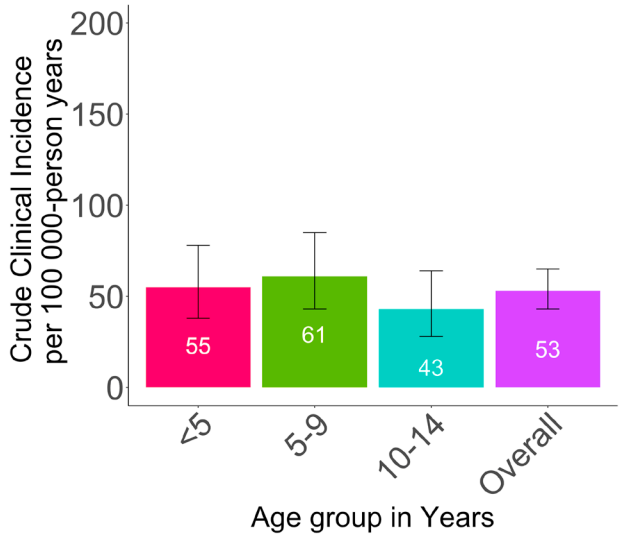
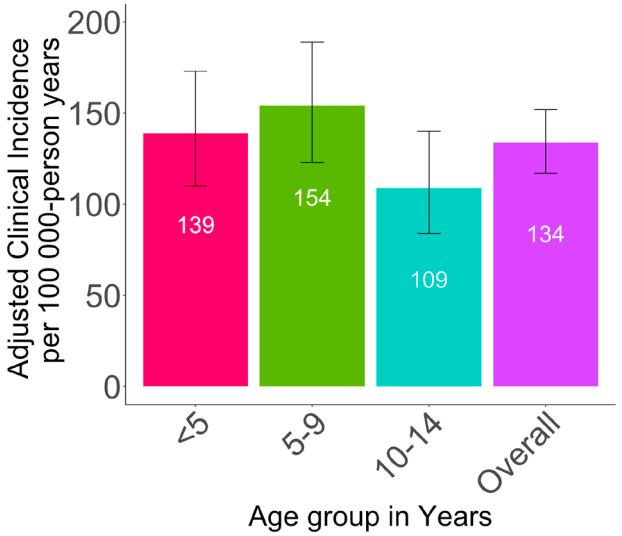
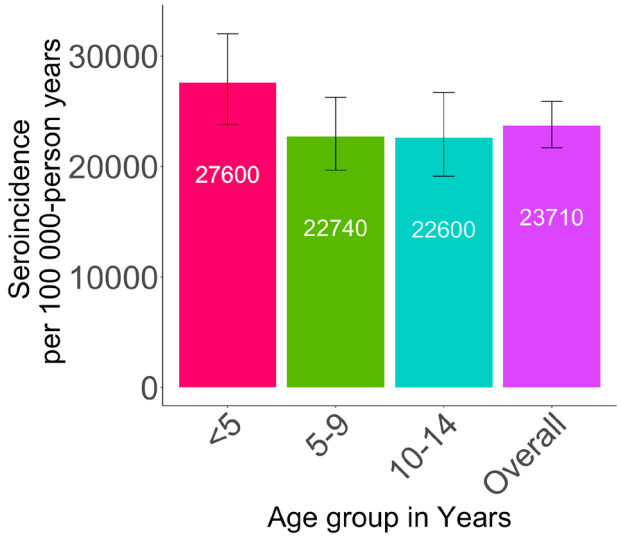
Clinical Incidence (Crude)



Clinical Incidence (Adjusted)



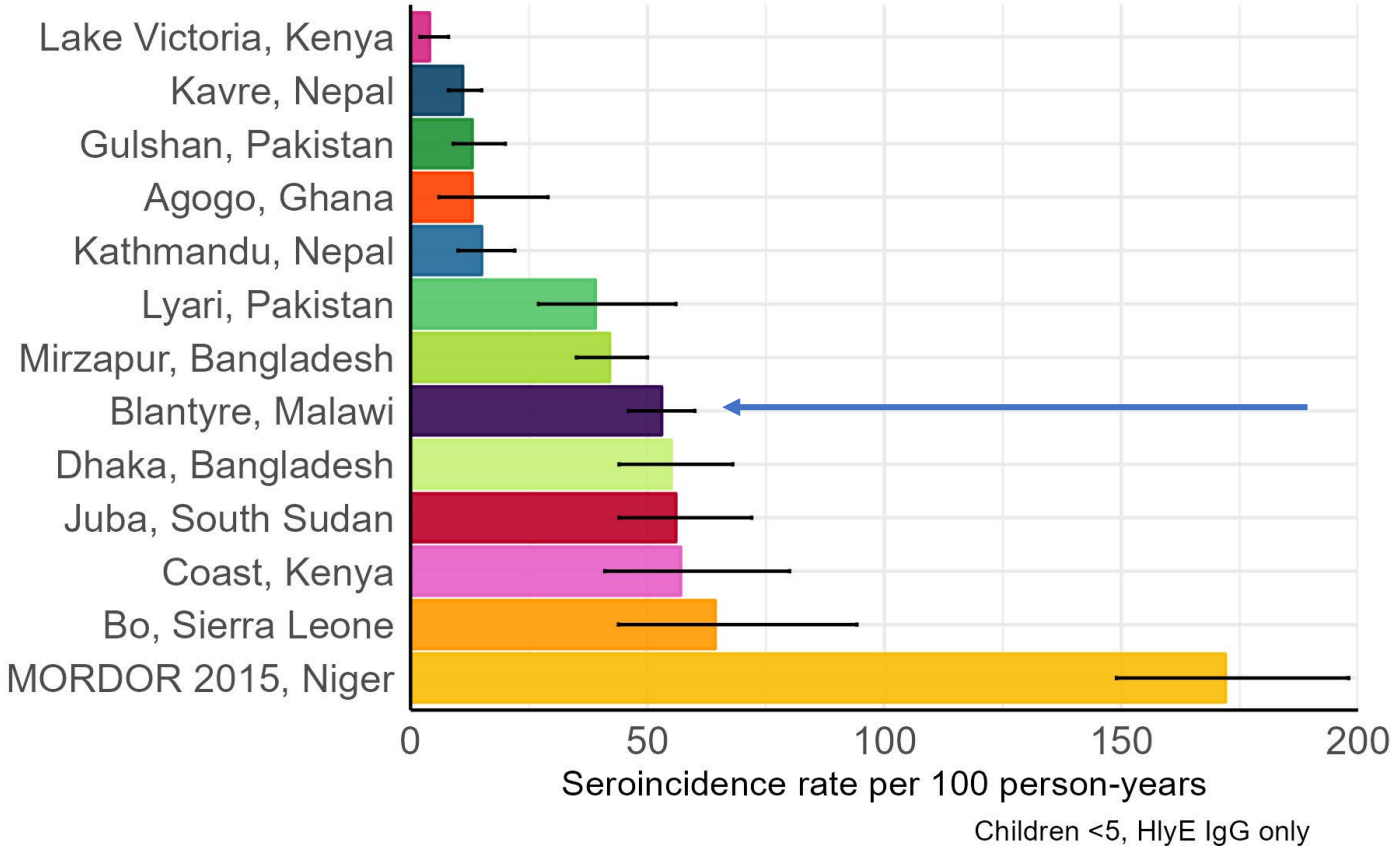
Seroincidence



Higher Seroincidence rate than clinical-incidence rate in Urban Malawi

(Feasey et al. unpublished)

Malawi Seroincidence vs other Countries



courtesy of Assoc Prof Richelle Charles

Conclusion

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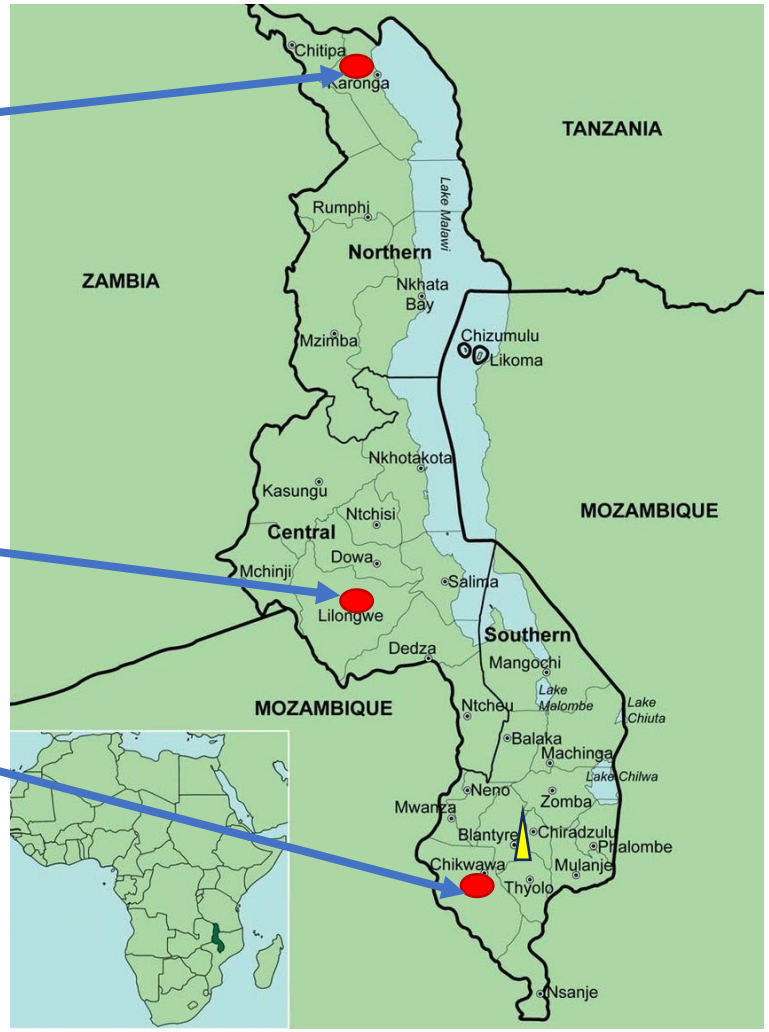
- Higher Salmonella typhi Seroincidence rate than clinical incidence estimates in Urban Malawi
- Malawi amongst the high Enteric fever burden countries
- The approach has a potential to expand the geographical scope of typhoidal Salmonella surveillance and generate incidence estimates in Malawi

Way Forward

- Analyse samples from other sites of Malawi to have a proper national burden of Enteric fever



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