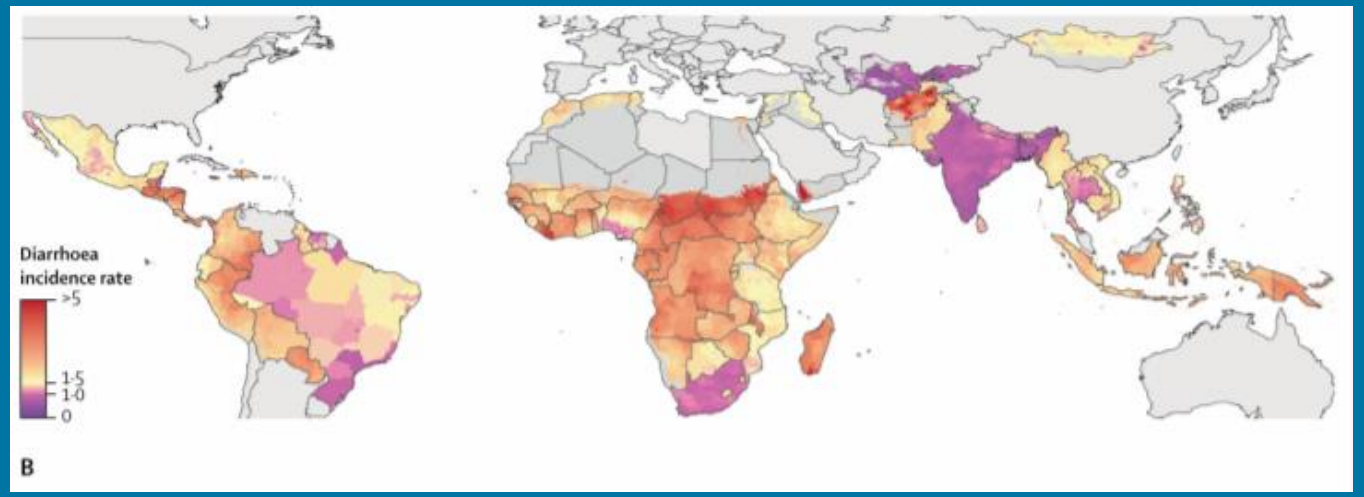
Summary of workstreams related to assessing U5 mortality of enteric pathogens:

Update from the burden of enteric disease (BoED) working group

PDVAC virtual session 2

11th May 2020

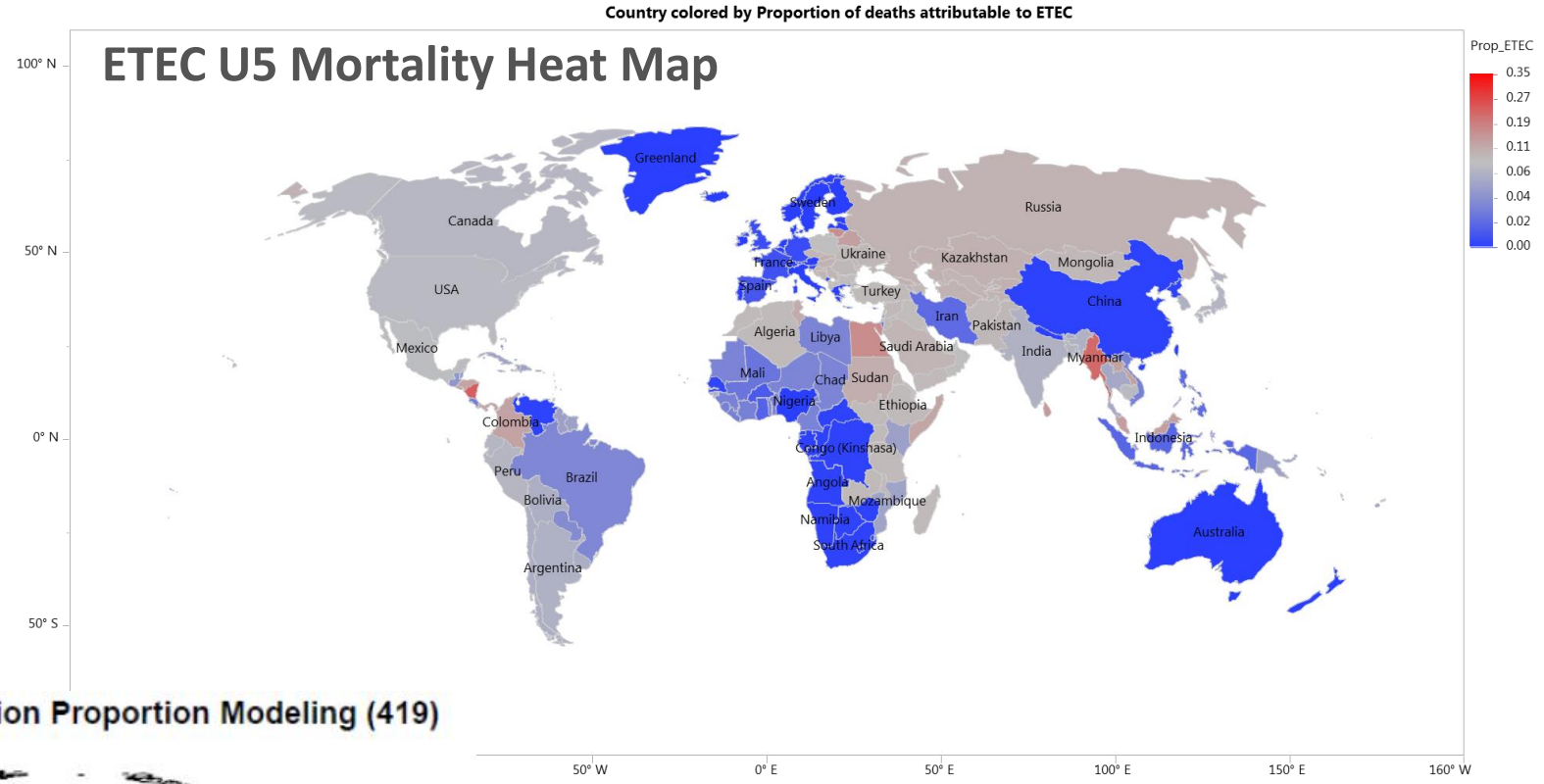


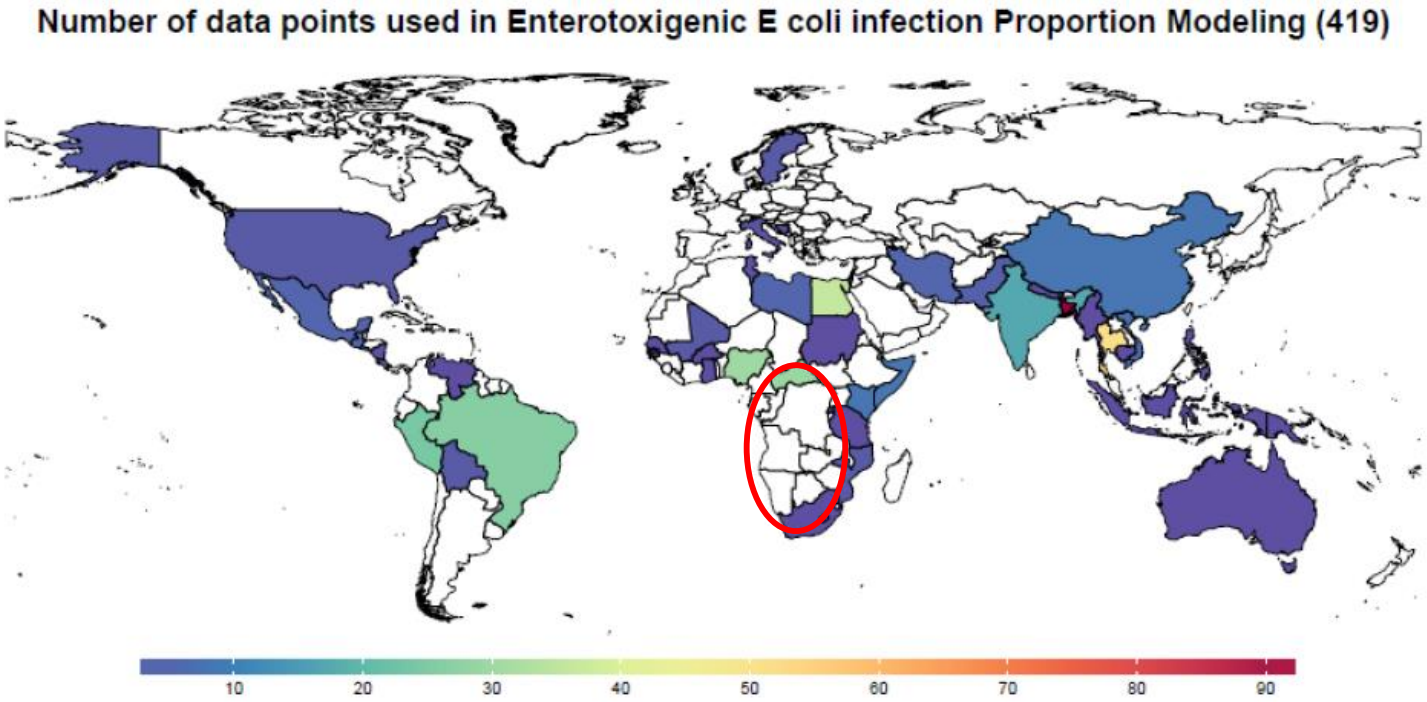
Rationale for the formation of the BoED working group

Outcome	CHERG/MCEE 2010	MCEE 2017 (Unpublished)	GBD 2010	GBD 2013	GBD 2015	GBD 2016
ETEC deaths U5 (uncertainty range)	42,000 (20,000 – 76,000)	44,078 (32,848 - 58,054)	38,700	23,100 (17,000 – 30,400)	23,600 (9,600 – 44,300)	18,669 (9,800-30,659)
Shigella deaths U5 (uncertainty range)	28,000 (12,000 – 53,000)	25,008 (17,148 - 35,878)	42,600	33,400 (24,900 – 43,500)	54,900 (27,000 – 94,700)	63,713 (41,191-93,611)

- In 2017, there was a shift in the funding envelop for development of ETEC and Shigella vaccines on the basis of the U5 mortality estimates

Is data paucity a potential issue?

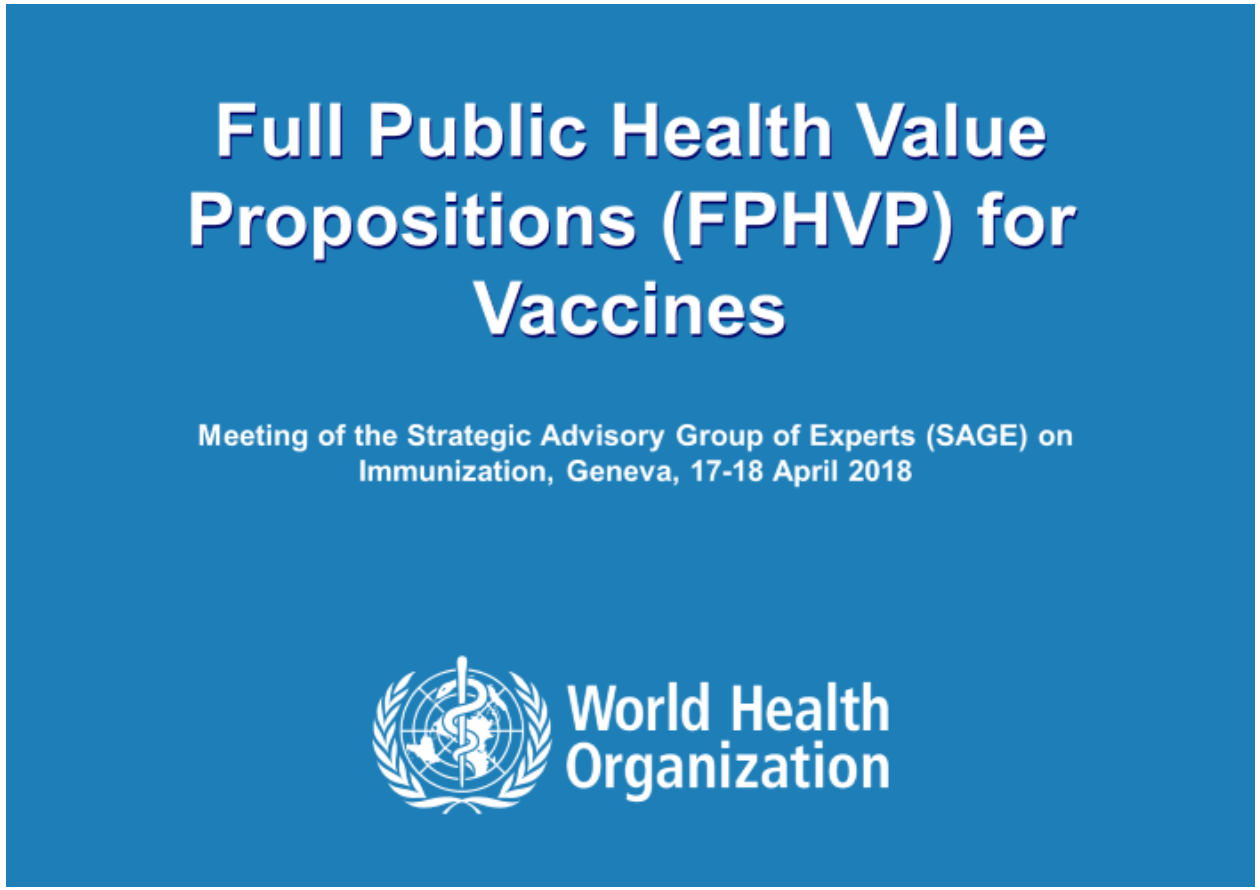




Presented at PDVAC 2018
Courtesy of Chad Porter and Mark Riddle

USU
Uniformed Services University

Concept of the Full Value of Vaccine Assessment (FVVA)



The FVVA for vaccines is a concept that describes the **global value of a vaccine, including from an LMIC perspective**. It aims to articulate the full direct (individual) and **indirect (population) effects** of a vaccine.

The intent of FPVV assessment is to **support decision-making across the continuum of vaccine development and uptake**, with a line-of-sight to **sustainable socio-economic and public health impact**.

Rationale for the formation of the BoED working group

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- In 2017, there was a shift in the funding envelop for development of ETEC and Shigella vaccines on the basis of the U5 mortality estimates

PDVAC Recommendation 2018:

"To further investigate understanding and credibility of Burden of Disease estimates, through the formation of a joint IVIRAC/PDVAC independent working group to evaluate diarrheal burden models, and particularly to assess the level of uncertainty regarding ETEC mortality estimates."

Guiding principles of BoED working group

- The goal of this work was to improve understanding, robustness and credibility of data inputs and methodology that underpin enteric disease mortality estimates
- From the outset, we sought inclusion of and collaboration with the two groups that develop mortality estimates (IHME and MCEE)
- The goal **was not** to decide what is the true burden of ETEC or Shigella, nor to prioritise either pathogen or set of estimates; it was to focus on strengthening good modelling practices
- The BoED WG has reported progress to WHO's Immunization and vaccines related implementation research advisory committee (IVIR-AC) throughout
- Measures of morbidity were acknowledged as being crucial inputs from the outset, but were not included in this initial scope

Objectives of this session

- Review the status of workstreams related to improving quantification of the under 5 mortality, caused by individual enteric pathogens;
- Discuss the impact of findings and their potential implications to future under 5 mortality estimates;
- Provide an overview of the proposed expansion of the working group scope to evaluate the data and methodology to quantify the morbidity burden of enteric pathogens
- Presentations today are ‘hot off the press’ as context for PDVAC sessions that will follow on Shigell and ETEC in the coming weeks

Overview of this session

Topic	Detail	Moderators, speakers
Session overview & objectives	Highlight of PDVAC's 2018 recommendations related to this work	Birgitte Giersing (WHO)
Summary of workstreams related to mortality of enteric pathogens	High-level description of all workstreams that investigated the differences in the burden of U5 mortality for enteric pathogens.	Mateusz Hasso-Agopsowicz (WHO)
Results of the study grading analysis	Quality assessment of studies that were used to calculate mortality estimates	Mateusz Hasso-Agopsowicz (WHO)
Analysis of the systematic review of odds ratios	Analysis of the systematic review of odds ratios of developing diarrhoea when a pathogen is detected in stool.	Benjamin Lopman (Emory)
Analysis of the systematic review of case fatality rates	Analysis of the systematic review of pathogen specific case fatality rates.	Virginia Pitzer (Yale)
Results from the meta analysis of input studies	Meta-analysis of studies used to calculate mortality estimates, and the impact of IHMEs model adjustments on mortality estimates.	James Platts-Mills (U. of Virginia)
Perspective of the PDVAC members on the BoED WG		Cherry Kang (THSTI) Peter Smith (LSHTM) Claudio Lanata (IIN)
Perspectives from the mortality modelling groups	Potential implications from the systematic reviews and meta-analysis on future mortality estimates	Hmwe Kyu (IHME) Bob Black (MCEE)
Discussion		Rob Breiman (Emory)
Anticipated outcomes, timelines, next steps	Expected outcomes, their timelines, and next steps	Mateusz Hasso (WHO)
Expansion of scope to morbidity	**For discussion and endorsement:** Review and agree on the proposed scope of work to measure the impact of enteric infections on morbidity	Ibrahim Khalil (WHO)
Closed session		PDVAC ONLY

Overview of this session

World Health Organization

For information and discussion

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Perspective of the PDVAC members on the BoED WG	Brief reflections from PDVAC members who are also members of the BoED working group	Cherry Kang (THSTI) Peter Smith (LSHTM) Claudio Lanata (IIN)
Perspectives from the mortality modelling groups	Potential implications from the systematic reviews and meta-analysis on future mortality estimates	Hmwe Kyu (IHME) Bob Black (MCEE)
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Overview of workstreams related to mortality of enteric pathogens

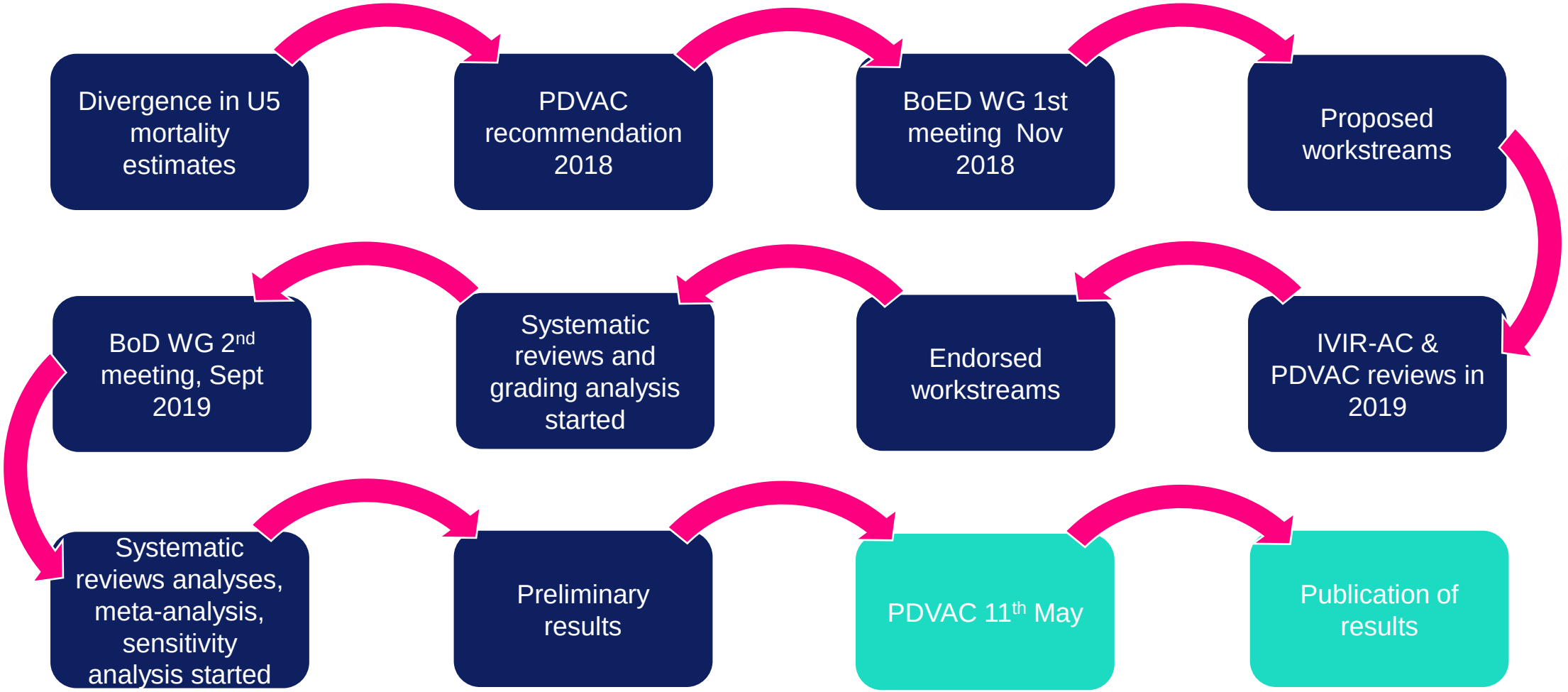
World Health Organization

Mateusz Hasso-Agopsowicz

PDVAC Virtual session 2

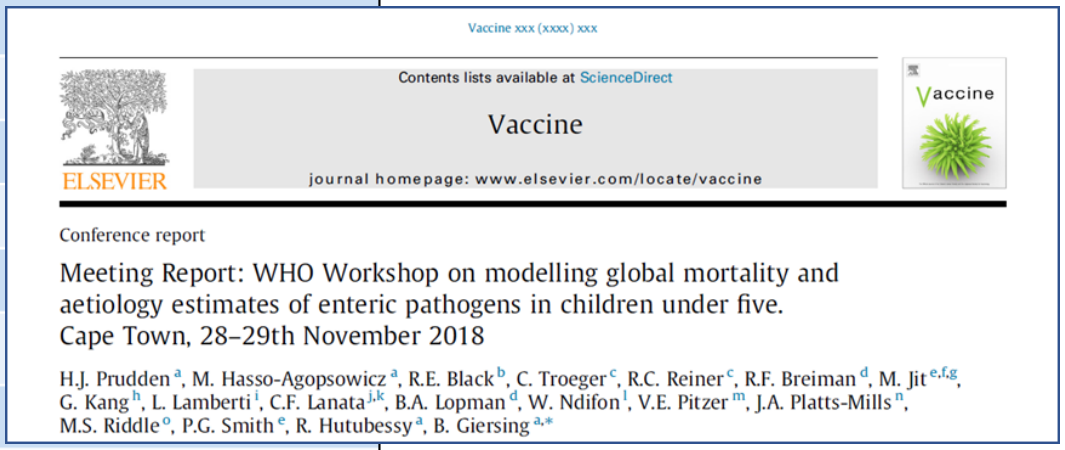
11 May 2020

Development and progress of Enteric BoED WG workstreams



BoED Working Group

Participant	Affiliation
Ben Lopman	Emory, USA
Cherry Kang (PDVAC)	Translational Health Science and Technology Institute, India
Claudio Lanata (PDVAC)	Nutritional Research Institute, Peru
Mark Jit (IVIR-AC)	LSHTM, UK
Mark Riddle	Uniformed Services University, USA
Peter Smith (PDVAC)	LSHTM, UK
Robert Breiman (Chair)	Emory, USA
James Platts-Mills	University of Virginia
Virginia (Ginny) Pitzer	Yale University, USA
Wilfred Ndifon (IVIR-AC)	African Institute for Mathematical Sciences, South Africa



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Conference report

Meeting Report: WHO Workshop on modelling global mortality and aetiology estimates of enteric pathogens in children under five. Cape Town, 28–29th November 2018

H.J. Prudden [a], M. Hasso-Agopsowicz [a], R.E. Black [b], C. Troeger [c], R.C. Reiner [c], R.F. Breiman [d], M. Jit [e,f,g], G. Kang [h], L. Lamberti [i], C.F. Lanata [j,k], B.A. Lopman [d], W. Ndifon [l], V.E. Pitzer [m], J.A. Platts-Mills [n], M.S. Riddle [o], P.G. Smith [e], R. Hutubessy [a], B. Giersing [a,*]

Summary of workstreams

1. **Data Gaps – to identify and address areas where additional evidence may improve future U5 mortality estimates.**

   A) Systematic review of odds ratios of developing diarrhoea when a pathogen is detected in stool: Ben Lopman, Julia Baker (Emory University)

   B) Systematic review of pathogen specific case fatality rates: Ginny Pitzer, Ernest Asare (Yale University)

Summary of workstreams

1. **Data Gaps – to identify and address areas where additional evidence may improve future U5 estimates.**

2. **Study Quality Exercise – to improve understanding of the studies, and the quality of the studies, included in the modelling process.**

   A) Grading analysis of input studies: Egle Butkeviciute (LSHTM), finalised

   B) Sensitivity analysis of low quality studies: IHME, on hold due to Covid

Summary of workstreams

1. **Data Gaps – to identify and address areas of commonality where additional evidence may improve future estimates. Gaps where new data is needed**

2. **Study Quality Exercise – to improve understanding of the studies, and the quality of the studies, included in the modelling process.**

3. **Data Processing Exercise – a high level assessment of similarities and differences in study data included in the models, how it is processed**

   A. Meta-analysis of input studies and the impact of model adjustments: James Platts-Mills, Sarah Elwood (University of Virginia)

Summary of workstreams

1. **Data Gaps – to identify and address areas of commonality where additional evidence may improve future estimates. Gaps where new data is needed**
2. **Study Quality Exercise – to improve understanding of the studies, and the quality of the studies, included in the modelling process.**
3. **Data Processing Exercise – a high level assessment of similarities and differences in study data included in the models, how it is processed**
4. **Model Comparison Exercise – to address structural and methodological differences in models:** on hold, pending results from workstreams 1-3

Results of the study grading analysis

Mateusz Hasso-Agopsowicz, Egle Butkieviciute, Birgitte Giersing

PDVAC Virtual session 2

11 May 2020

Summary of workstreams

1. **Data Gaps – to identify and address areas of commonality where additional evidence may improve future estimates. Gaps where new data is needed**

2. **Study Quality Exercise – to improve understanding of the studies, and the quality of the studies, included in the modelling process.**

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Study Quality Exercise: Aim and Objectives

Aim: To conduct a grading review to improve our understanding of the quality of studies and data used by both IHME and MCEE groups.

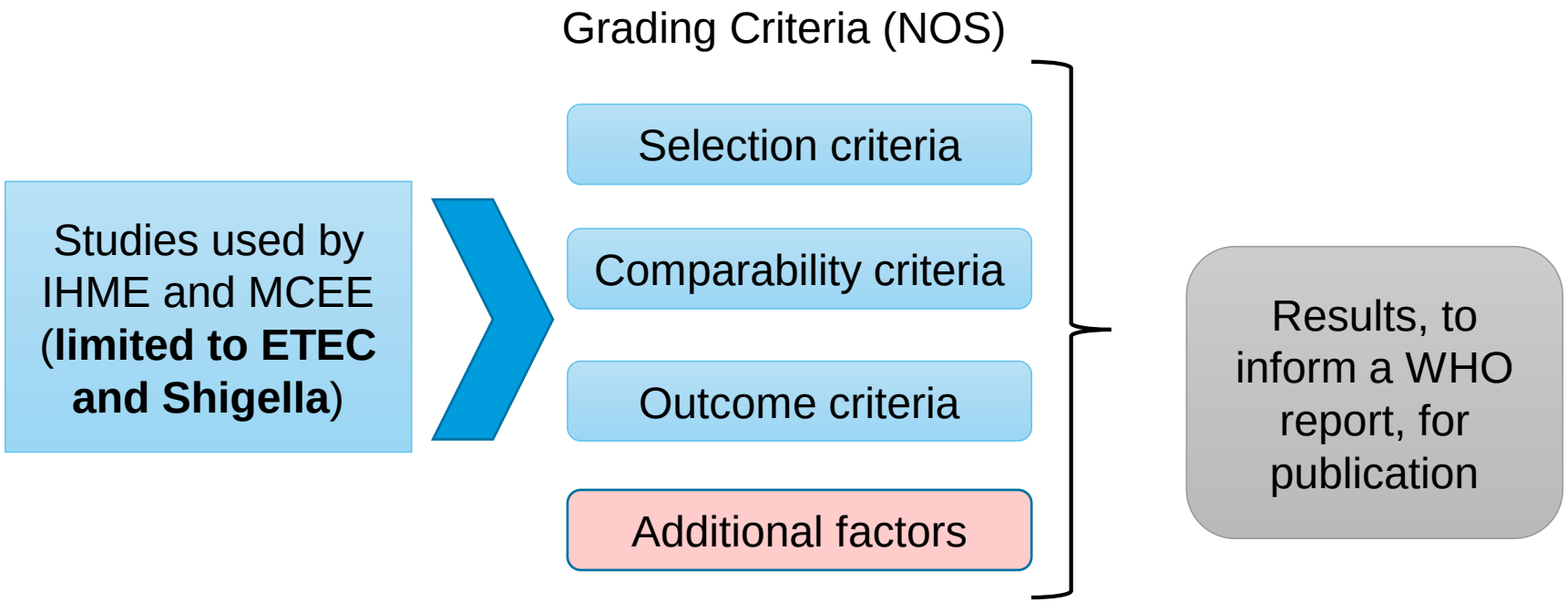
The analysis includes only **ETEC** and **Shigella** studies.

Objectives:

- To develop a standardised grading assessment tool;
- To determine the quality of the studies used by each of the groups;
- To conduct a sensitivity analysis of low quality studies and measure their impact on mortality estimates

Study Quality Exercise: Methodology

Together with the BoED WG, a modified Newcastle-Ottawa Scale to assess the quality of IHME and MCEE studies was developed

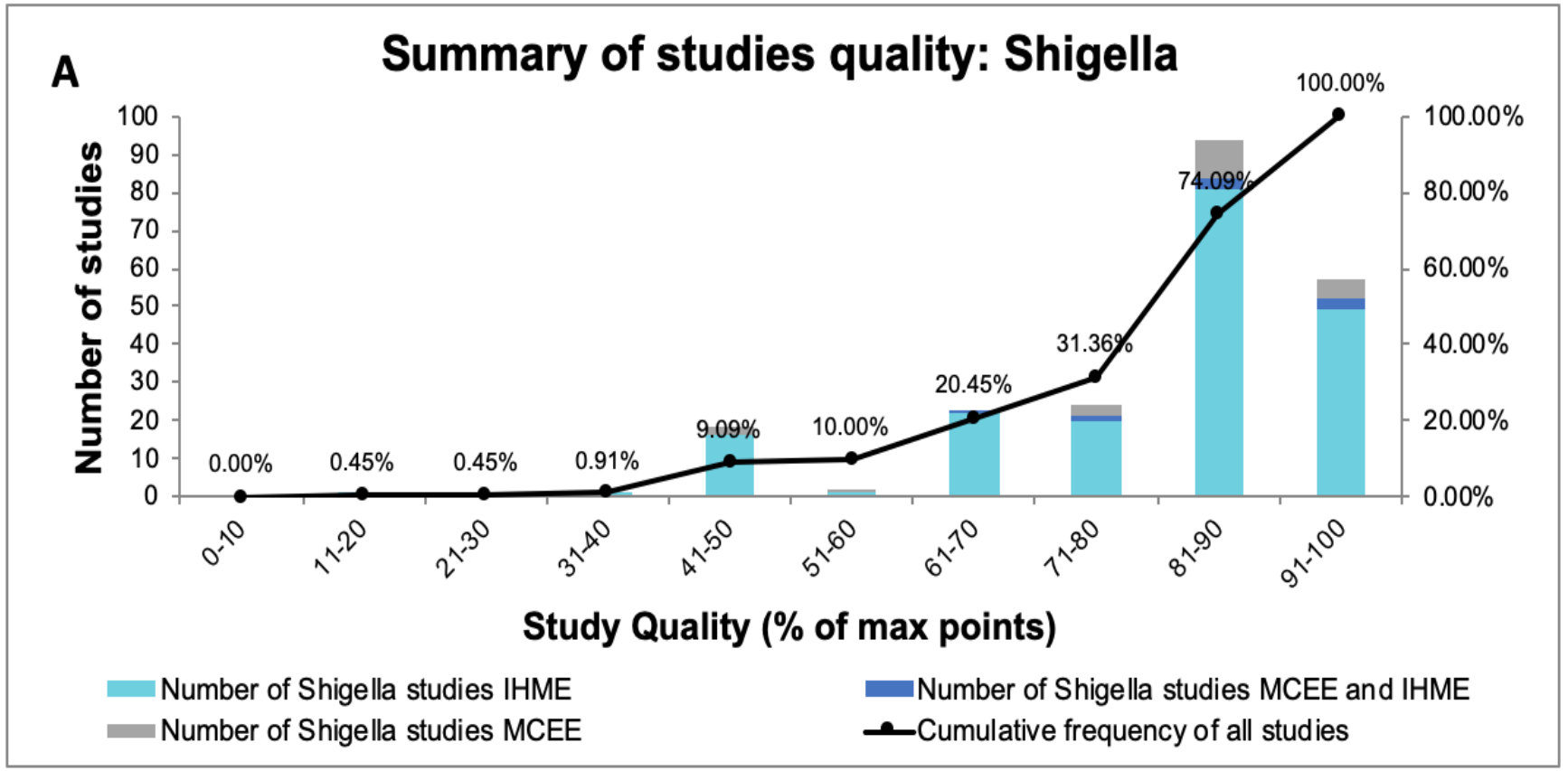


Study Quality Exercise: Results

Pathogen	Total number of studies	No of studies in MCEE only	No of studies in IHME only	No of studies in IHME and MCEE
ETEC	119	5	112	2
Shigella	220	21	191	8

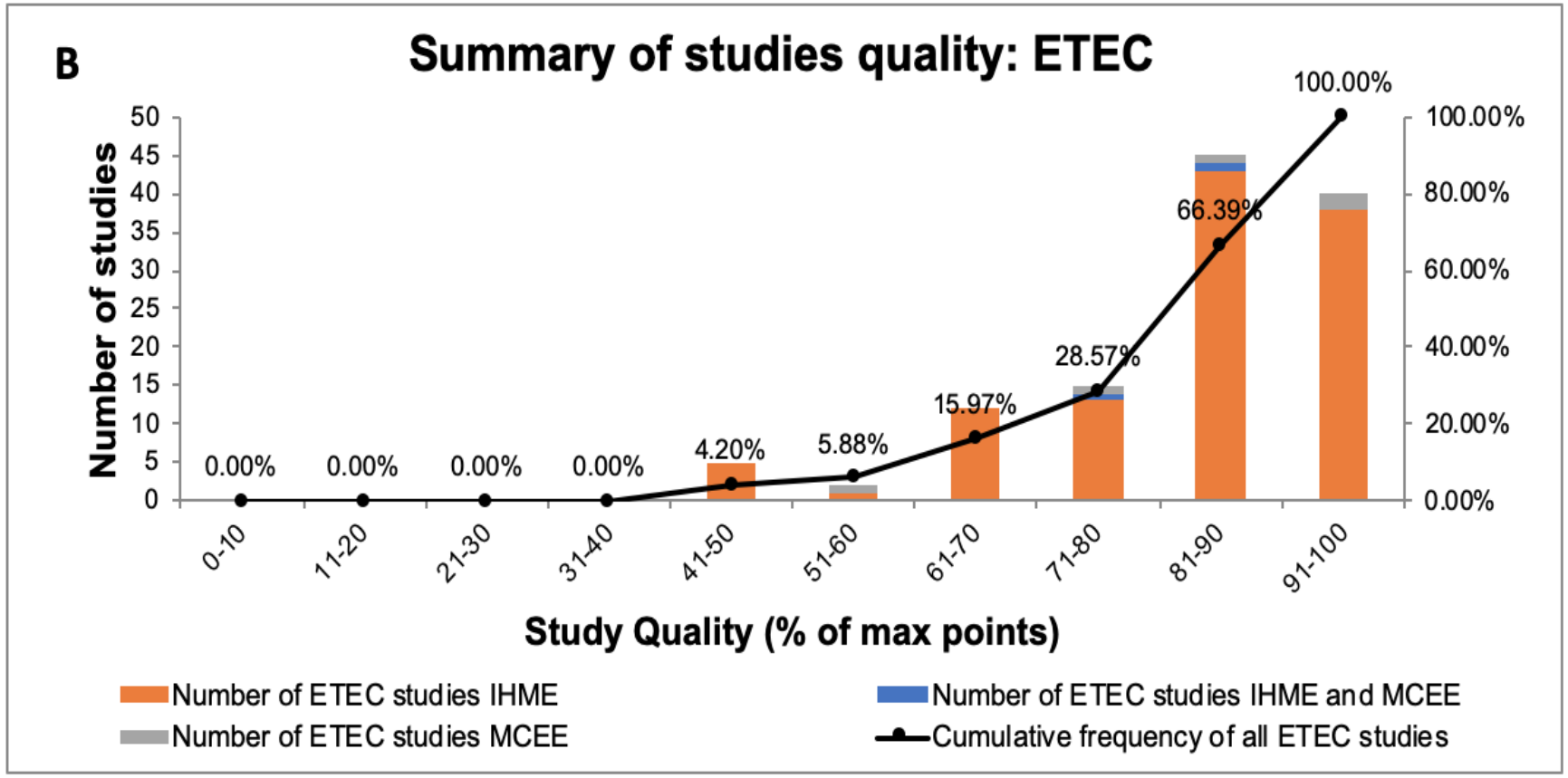
- Only a small number of studies that overlap
- Reflect different inclusion criteria applied by both groups

Study Quality Exercise: Shigella results



- Majority of studies received a high quality score
- Only 20.45% of studies scored less than 70/100 quality score
- Similar quality scores observed for studies used by both groups

Study Quality Exercise: ETEC results



- Majority of studies received a high quality score
- Only 15.97% of studies scored less than 70/100 quality score
- Similar quality scores observed for studies used by both groups

Study Quality Exercise: Next steps

- IHME agreed to conduct a sensitivity analysis of low quality studies to measure their impact on mortality estimates
- WHO and BoED WG are preparing a publication that summarizes outcomes of study quality and sensitivity analyses.
- The publication will include high level recommendations about inclusion and exclusion criteria for studies to be included in mortality estimates.

META-ANALYSIS OF ODDS RATIOS

BENJAMIN LOPMAN & JULIA BAKER

EMORY UNIVERSITY

PDVAC Virtual Consultation 2
May 11, 2020

EMORY

ROLLINS
SCHOOL OF
PUBLIC
HEALTH

IMPLICATIONS & USE OF ODDS RATIOS

- GBD: # of episodes and deaths attributable to each pathogen is the product of the total # of diarrhea episodes and deaths, and the PAF for that etiology
- PAF = proportion * (1-1/OR)
  - Proportion = proportion of pathogen detection in diarrhea samples (based on a molecular diagnostics)
  - ORs are based on molecular diagnostic results from GEMS
    - OR for children <1 year
    - OR for all age groups >1 year (based on OR for children ages 1-5 years)

Source: GBD 2016 Diarrhoeal Disease Collaborators, *Lancet ID* 2019, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6202444/

STUDY OBJECTIVES

- Aim: Examine the relationship between the presence of pathogens and the occurrence of diarrhea
- Conduct a meta-analysis to determine pathogen-specific OR
- Provide pathogen specific ORs stratified by:
  - Age group
  - Under 5 child mortality level
  - Pathogen detection method

DATA & STATISTICAL ANALYSIS

- Data on the presence of 15 pathogens in diarrhea & non-diarrhea stool samples
  - Systematic review of literature (1990-2019), University of Washington START Center
  - MAL-ED and GEMS data
  - 145 studies, 1,324 observations, 15 pathogens
- Random effects meta-analysis
  - Model OR for each pathogen

Model	Stratified by	Adjusted for
Model 1	• None	• None
Model 2	• Age group • Child mortality level	• Pathogen detection method • Study design
Model 3	• Age group • Child mortality level • Pathogen detection method	• Study design

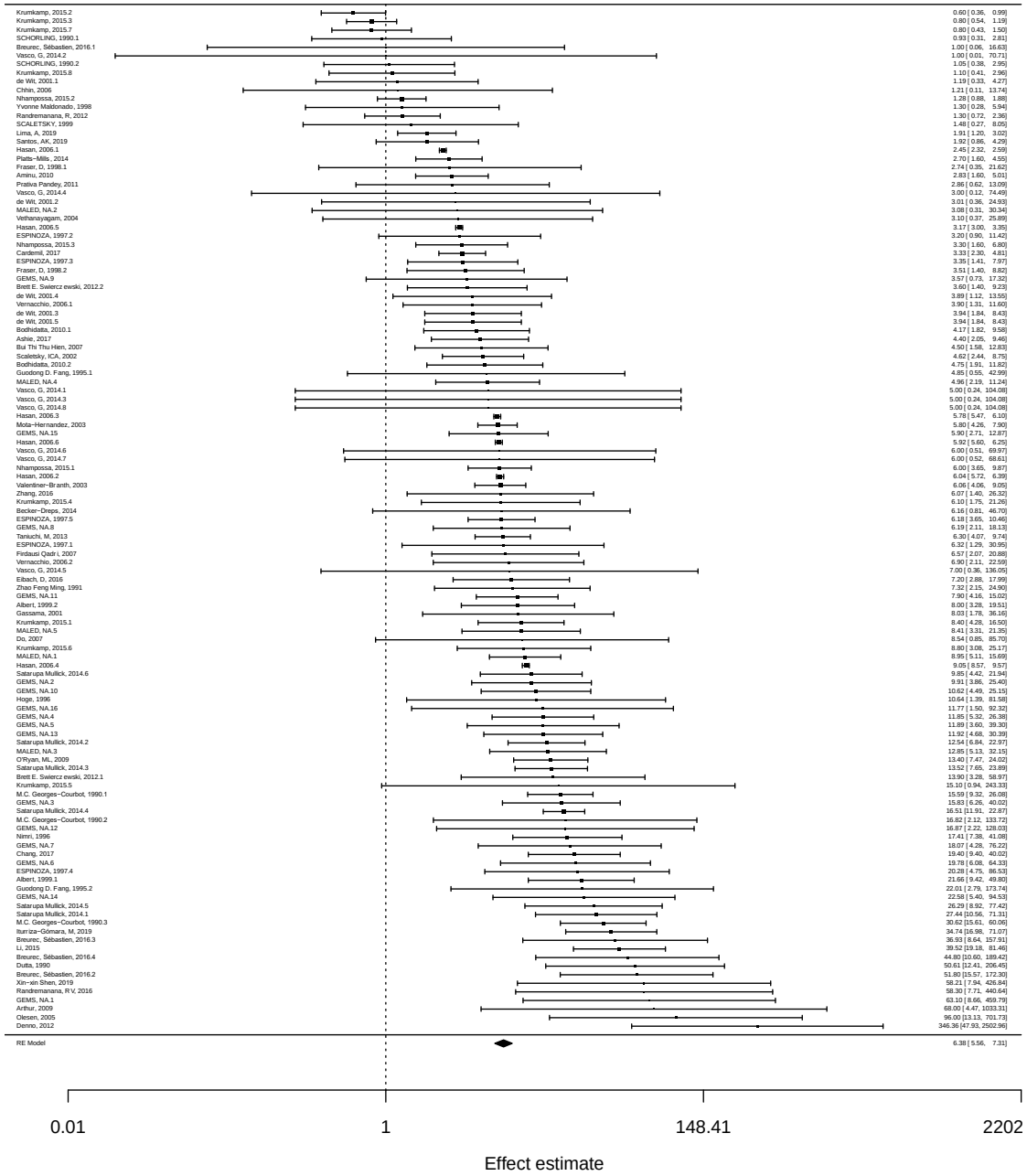
MODIFIERS CONSIDERED

Variable	Definition
Age group	• 0-5 years of age • >5 years of age • Mixed- combination
Child mortality level	Based on quintiles of under 5 child mortality (UNIGME estimates from 2003) • Very low: lowest quintile • Low: next two quintiles • High: two highest quintiles
Pathogen detection method	• EIA/ELISA • Culture/isolation • Microscopy (electronic) } Combined into "conventional methods" • PCR • Other/unspecified/missing
Study design	• Case-control: standard (n=877) or nested (n=135) • Cohort: prospective (n=300), retrospective (n=6), cross-sectional (n=1), RCT (n=5)

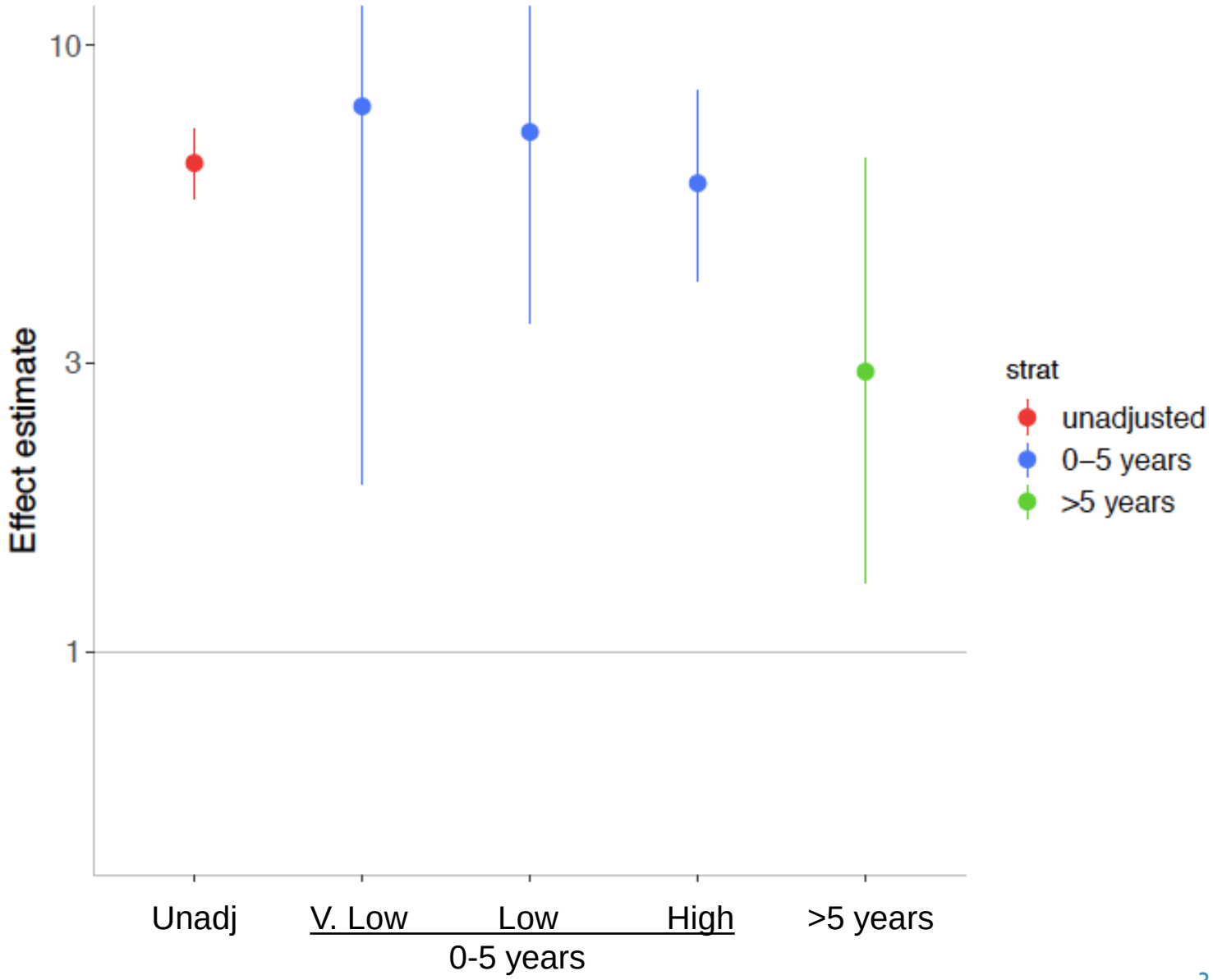
ROTAVIRUS

(N=119)

OR = 6.4 (5.6, 7.3) →

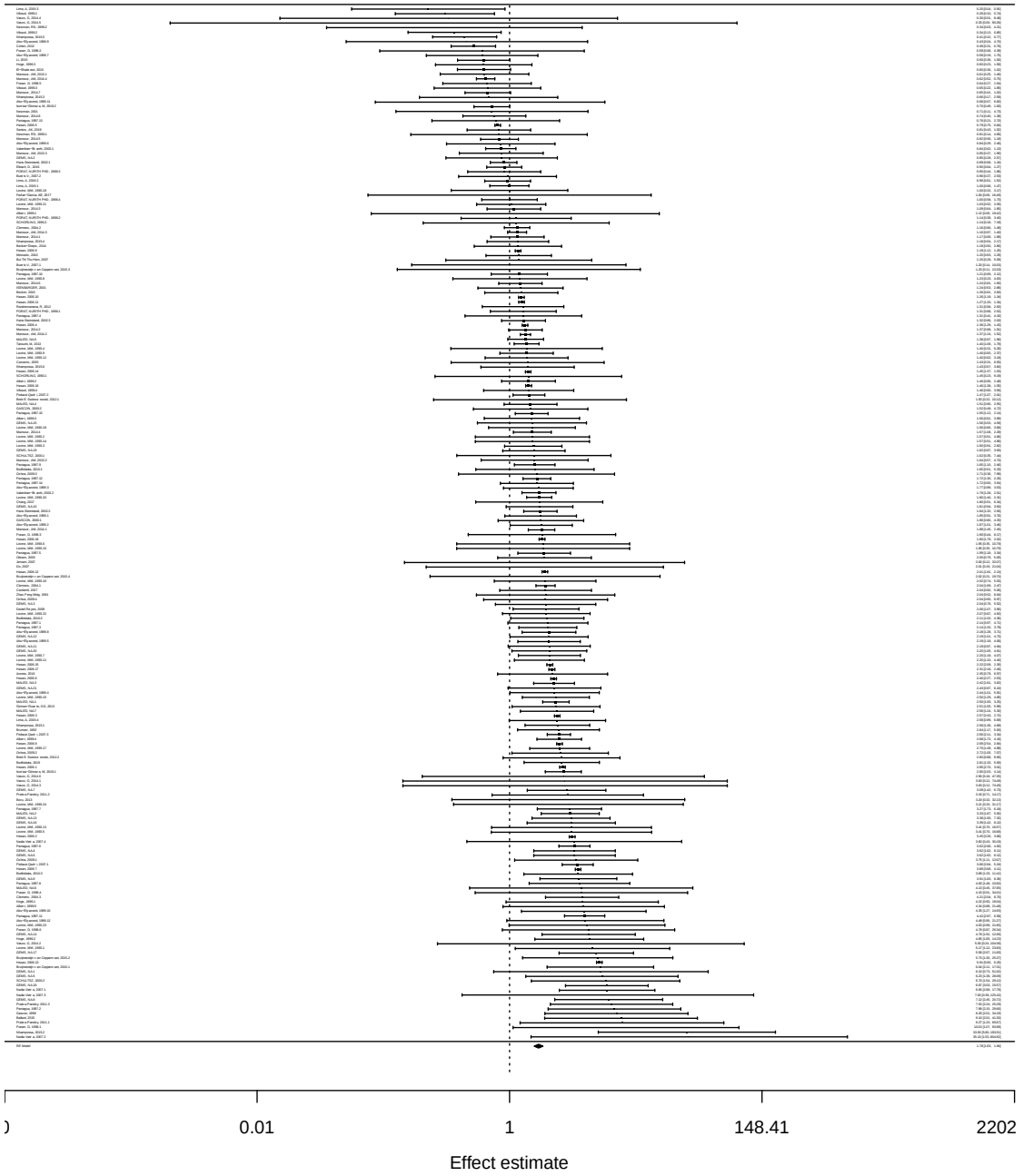


ROTAVIRUS
(N=119)

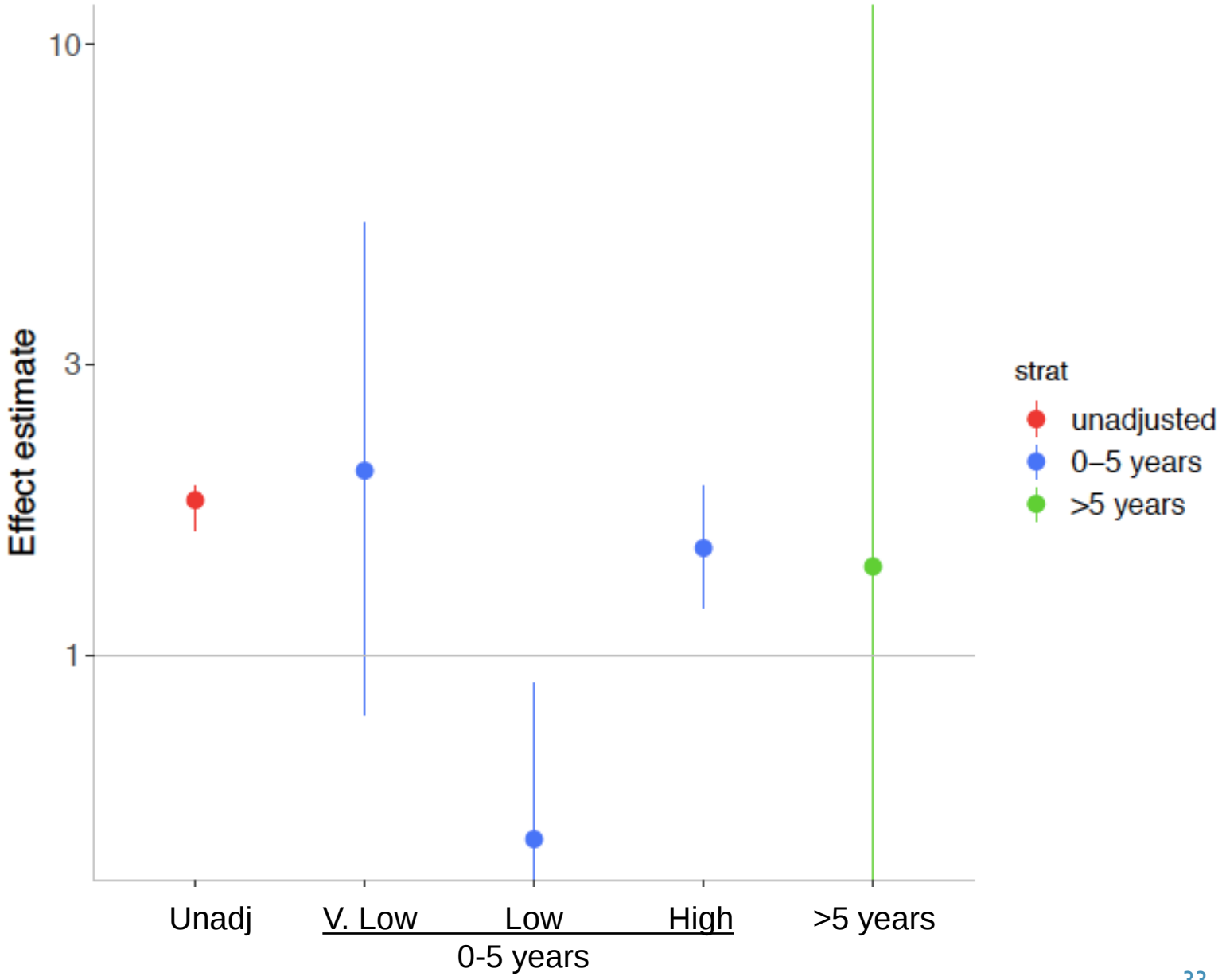


ETEC
(N=212)

OR = 1.8 (1.6, 1.9) →



ETEC
(N=212)


10
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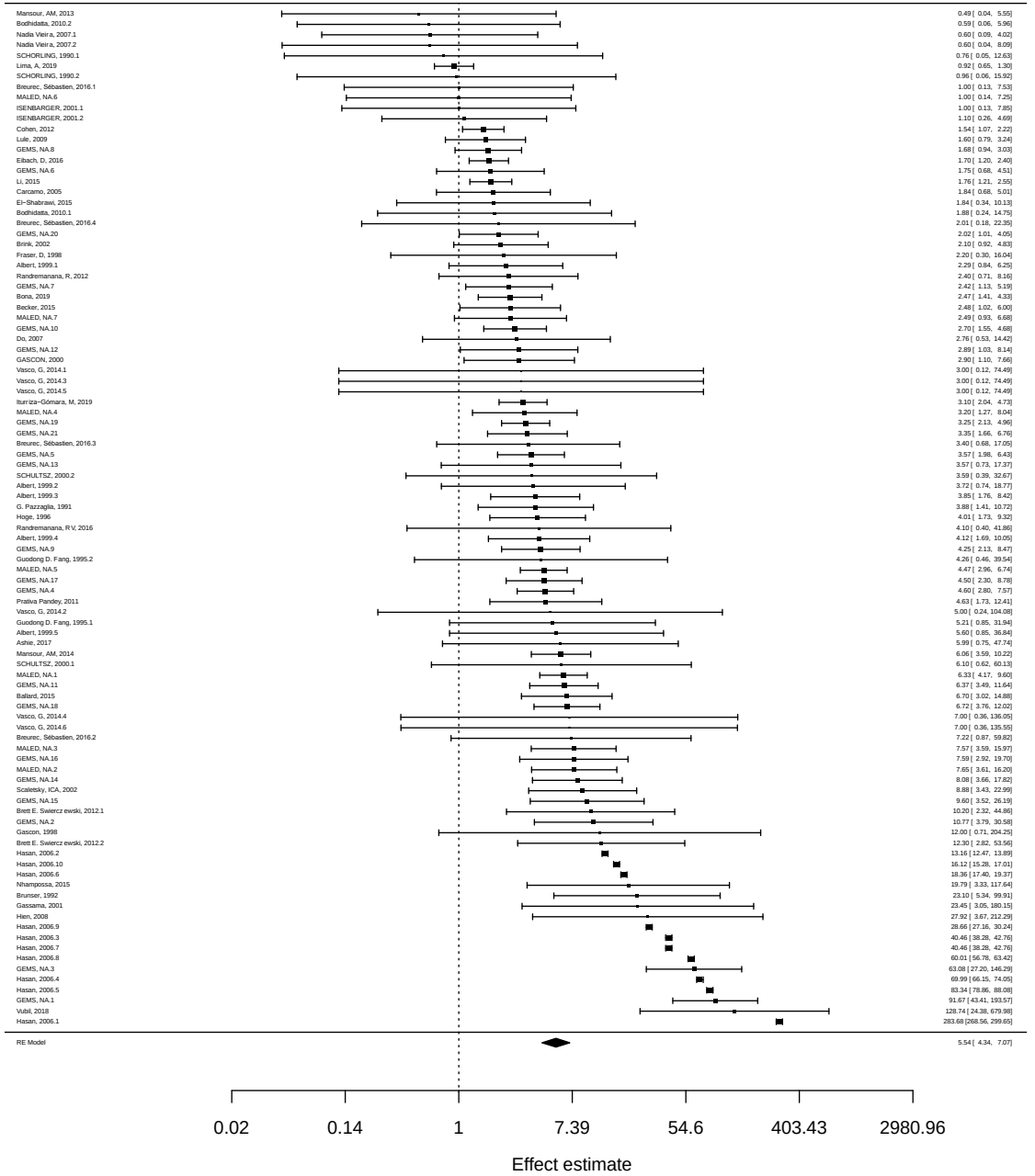
1
Effect estimate
Unadj
V. Low
Low
High
>5 years
0-5 years
strat
unadjusted
0–5 years
>5 years

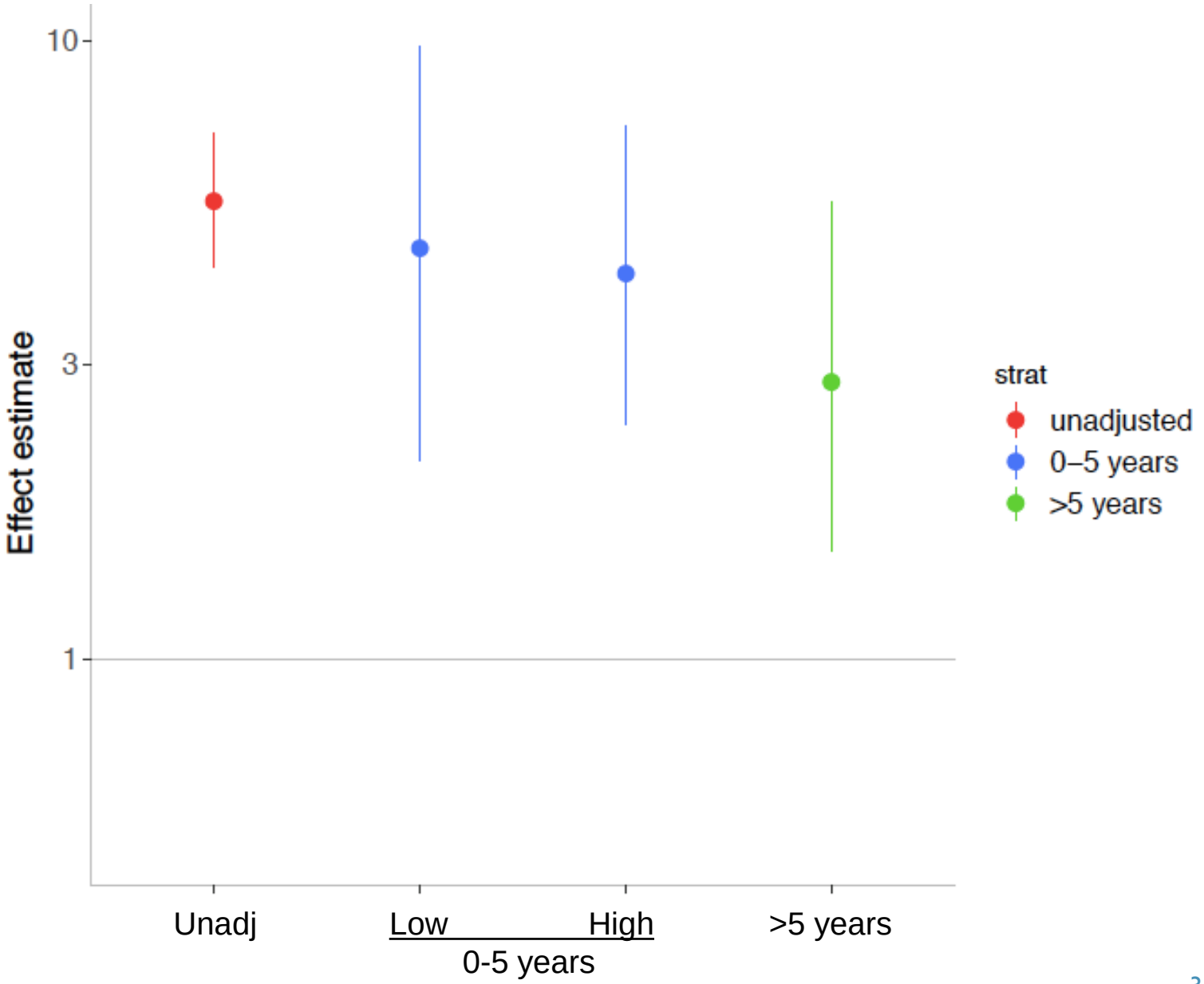
SHIGELLA

(N=97)

OR = 5.4 (4.3, 7.0) →



SHIGELLA
(N=97)



SUMMARY ODDS RATIOS

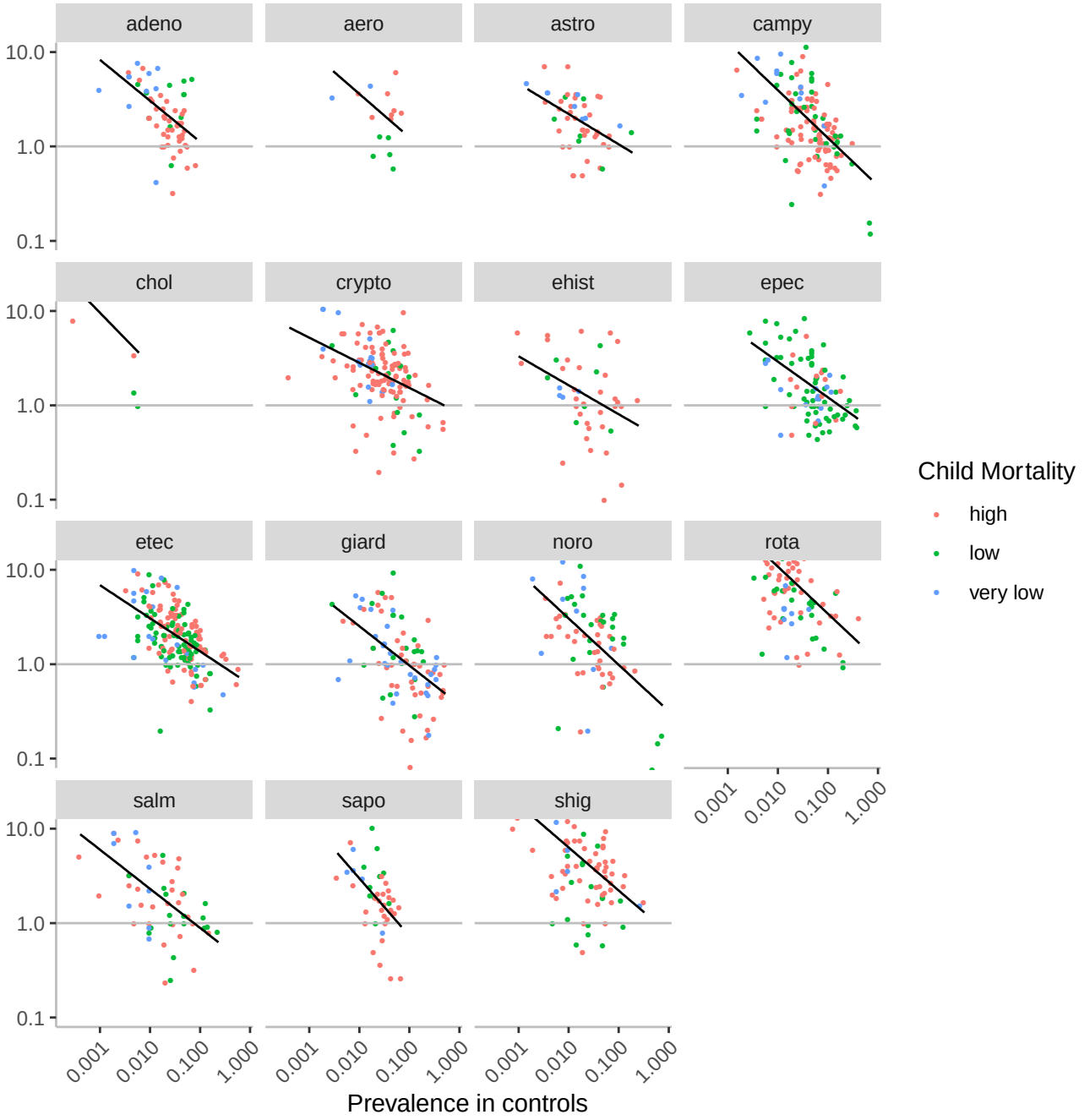
Pathogen	Unadjusted		0-5 years*						> 5 years*	
			V. low mortality		Low morality		High mortality			
	Est.	CI	Est.	CI	Est.	CI	Est.	CI	Est.	CI
Adenovirus	2.1	1.8-2.6	6.4	1.0-38.8	4.1	1.9-8.8	1.3	0.8-2.1		
Astrovirus	1.9	1.6-2.3			0.6	0.1-3.0	1.7	0.9-3.1		
Norovirus	1.7	1.4-2.0			9.8	1.7-57.3	2.9	1.4-6.0	3.2	1.3-7.6
Rotavirus	6.4	5.6-7.3	7.9	1.9-32.9	7.2	3.5-15.2	5.9	4.1-8.4	2.9	1.3-6.5
Sapovirus	1.8	1.5-2.1			2.0	1.4-2.8	1.0	0.5-1.8		
Aeromonas	2.4	1.7-3.3					3.7	3.2-4.2		
Campylobacter	1.7	1.5-1.9	8.8	1.3-59.2	2.3	1.2-4.4	1.7	1.3-2.2	5.1	2.6-10.0
Cholera	5.3	1.6-17.1								
EPEC	1.4	1.2-1.6	1.8	1.2-2.7	2.8	0.6-13	1.4	0.9-2.0	1.2	0.9-1.7
ETEC	1.8	1.6-1.9	2.0	0.8-5.1	0.5	0.3-0.9	1.5	1.2-1.9	1.4	0.1-24.7
Salmonella enterica	1.9	1.4-2.5			1.4	0.9-2.0	1.4	0.8-2.5	0.9	0.6-1.3
Shigella	5.5	4.3-7.1			4.6	2.1-9.8	4.2	2.4-7.3	2.8	1.5-5.5
Cryptosporidium	2.2	1.9-2.4	2.5	1.2-5.2	1.0	0.3-3.2	1.9	1.7-2.2	3.4	1.2-9.6
E. histolytica	1.3	1.1-1.6			0.6	0.2-1.9	1.7	1.1-2.7	1.2	0.6-2.3
Giardia lamblia	1.0	0.9-1.1	1.1	0.4-3.0	2.0	0.9-4.4	0.8	0.6-1.1	1.2	0.6-2.3

*Controlling for pathogen detection method, study design

ODDS RATIOS- BY PATHOGEN DETECTION METHOD

Pathogen	0-5 years												> 5 years			
	Very Low Child Mortality				Low Child Mortality				High Child Mortality				All Mortality Levels			
	Conven.		PCR		Conven.		PCR		Conven.		PCR		Conven.		PCR	
	Est.	CI	Est.	CI	Est.	CI	Est.	CI	Est.	CI	Est.	CI	Est.	CI	Est.	CI
Adenovirus					4.1	1.9-8.8			1.3	1.0-1.8						
Astrovirus									1.7	0.9-3.2	2.0	0.8-5.2				
Norovirus			3.7	1.7-8.1			2.8	1.6-4.9	3.0	1.6-5.3	1.1	0.9-1.3			3.2	1.3-7.6
Rotavirus	3.9	1.1-13.6	96.0	13.1-701	7.1	3.9-12.9			6.5	4.4-9.7	6.5	3.1-13.3	2.9	1.3-6.5		
Sapovirus			3.0	1.2-7.5			2.0	1.4-2.8			0.9	0.5-1.9				
Aeromonas																
Campylobacter	8.8	1.3-59.2			2.3	1.1-4.8	2.1	1.0-4.3	1.6	1.2-2.2	1.3	0.8-2.0	4.9	2.3-10.6	3.8	2.3-6.3
Cholera																
EPEC			1.8	1.2-2.7			1.4	1.1-1.7			1.4	0.9-2.0			1.2	0.9-1.7
ETEC			2.0	0.5-7.9	2.0	0.4-11.2	1.2	0.9-1.7	1.3	1.0-1.7	1.5	1.1-2.1			3.6	1.1-11.4
Salmonella ent.					1.4	0.9-2.0			1.3	0.9-2.1	1.9	0.8-4.6	0.9	0.6-1.3		
Shigella					4.6	2.1-9.8	1.5	0.9-2.7	4.2	2.8-6.4			2.8	1.5-5.5		
Cryptosporidium					0.9	0.2-4.8			1.9	1.7-2.2	3.3	2.4-4.7	3.4	1.6-7.2	1.8	0.5-5.6
E. histolytica					0.6	0.2-1.9			1.9	1.0-3.5	1.2	0.6-2.1	1.2	0.6-2.3		
Giardia lamblia	1.1	0.4-3.0			2.0	0.9-4.5			0.8	0.6-1.0	0.8	0.5-1.3	1.2	0.6-2.3		

All models controlling for study design
*Excludes 'other/unspecified' detection method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0.100
1.000
Prevalence in controls
Child Mortality
high
low
very low

SUMMARY OF MAIN FINDINGS

- Substantial heterogeneity by pathogen
- When stratified:
  - Difference in OR by age, child mortality status, pathogen detection method
  - ORs reflect frequency of exposure, asymptomatic infection, development of immunity
- These ORs may be (adapted and) used as inputs in burden models
- However, the strong inverse relationship with prevalence in controls raises the question
  - **Is the OR is a good indicator of pathogenicity for all pathogens?**

IMPLICATIONS & USE OF ODDS RATIOS

- Important variations in OR not captured in models using one measure across ages/mortality levels

- GBD: # of episodes and deaths attributable to each pathogen is the product of the total # of diarrhea episodes and deaths, and the PAF for that etiology
- PAF = proportion * (1-1/OR)
  - Proportion = proportion of pathogen detection in diarrhea samples (based on a molecular diagnostics)
  - ORs are based on molecular diagnostic results from GEMS
    - OR for children <1 year
    - OR for all age groups >1 year (based on OR for children ages 1-5 years)

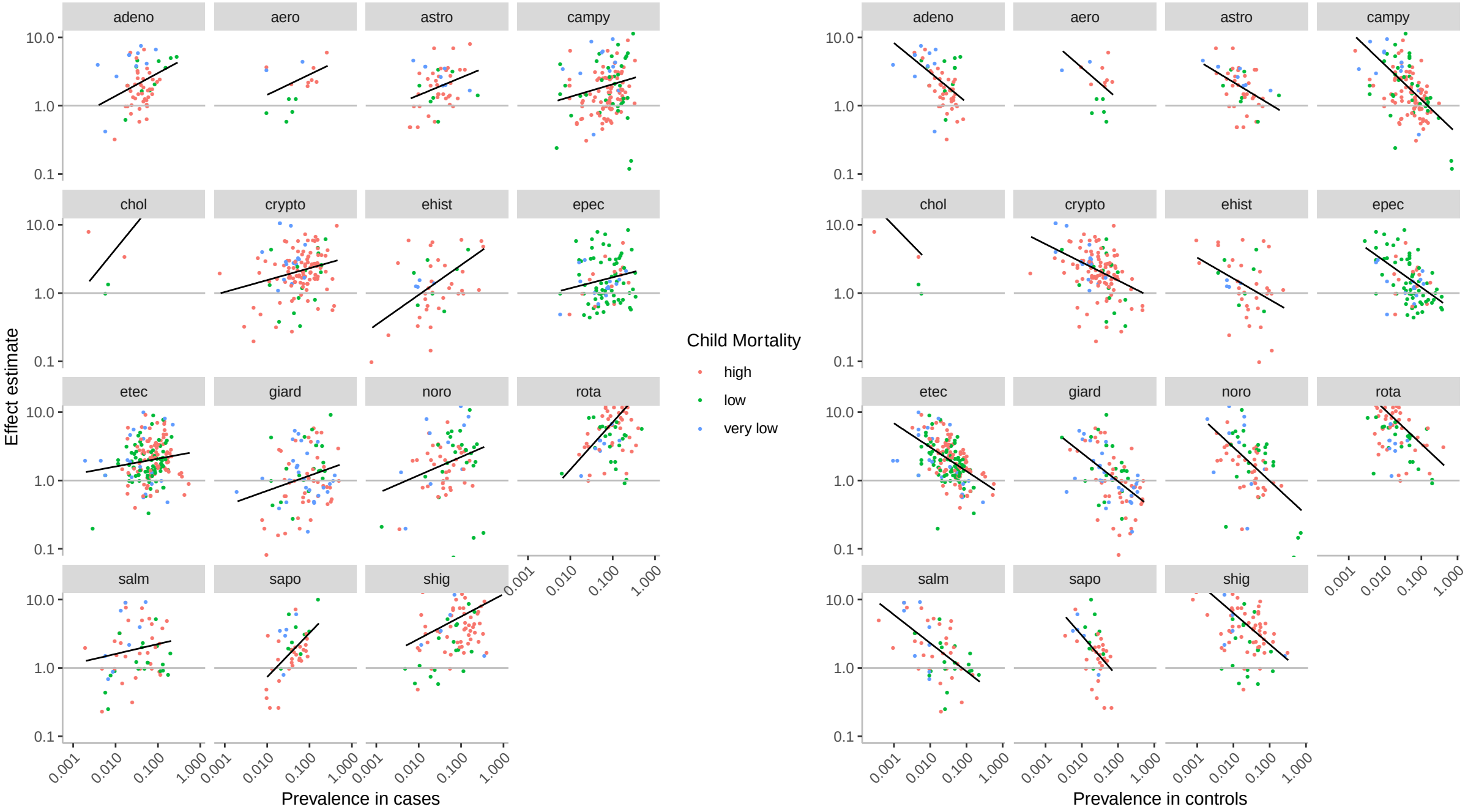
Source: GBD 2016 Diarrhoeal Disease Collaborators, *Lancet ID* 2019, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6202444/

THANK YOU!

EXTRA SLIDES

DISTRIBUTION OF MODIFIERS

	All	Adeno	Astro	Noro	Rota	Sapo	Aero	Campy	Chol	EPEC	ETEC	Salm	Shigel	Crypto	E. hist	Giardia
Total obs.	1324	64	50	85	119	44	16	148	6	97	222	65	97	136	65	110
Age group																
0-5 years	973	55	44	59	87	42	12	105	5	78	184	43	74	98	27	60
Mixed	253	8	5	20	27	2	2	28	0	12	24	16	16	28	30	35
>5 years	98	1	1	6	5	0	2	15	1	7	14	6	7	10	8	15
Child mortality status																
Very low	158	10	8	10	12	5	2	13	0	14	20	9	5	17	4	29
Low	411	12	7	32	38	10	5	41	3	67	89	19	26	16	18	28
High	755	42	35	43	69	29	9	94	3	16	113	37	66	103	43	53
Pathogen detection method																
EIA	229	19	12	9	67	0	0	2	0	3	41	0	0	44	11	21
Culture	181	0	0	0	0	0	5	70	3	3	3	31	48	5	4	9
Microscopy	81	0	0	0	0	0	1	6	0	0	0	6	3	20	15	30
PCR	402	11	13	55	23	16	2	37	1	72	86	16	6	25	22	17
Other/Unspec	201	5	1	1	8	1	8	7	2	19	62	12	12	18	12	33
Missing	230	29	24	20	21	27	0	26	0	0	30	0	28	24	1	0
Study design																
Cohort	312	4	4	13	33	4	3	39	1	21	99	12	18	23	7	31
Case-control	1012	60	46	72	86	40	13	109	5	76	123	53	79	113	58	79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0.100
1.000
Effect estimate
Prevalence in cases
Prevalence in controls
Child Mortality
high
low
very low

Case fatality rate of diarrheal pathogens: a meta-analysis

Prepared by
Ernest O. Asare & Virginia E. Pitzer
Yale School of Public Health
for the WHO BoED Working Group

Motivation

- Global burden of diarrheal models assume that deaths from enteric pathogens occur in proportion to the distribution of pathogens in hospitalized (MCEE) or severe (IHME) cases
- Do not take into account potential differences in the risk of death from different pathogens

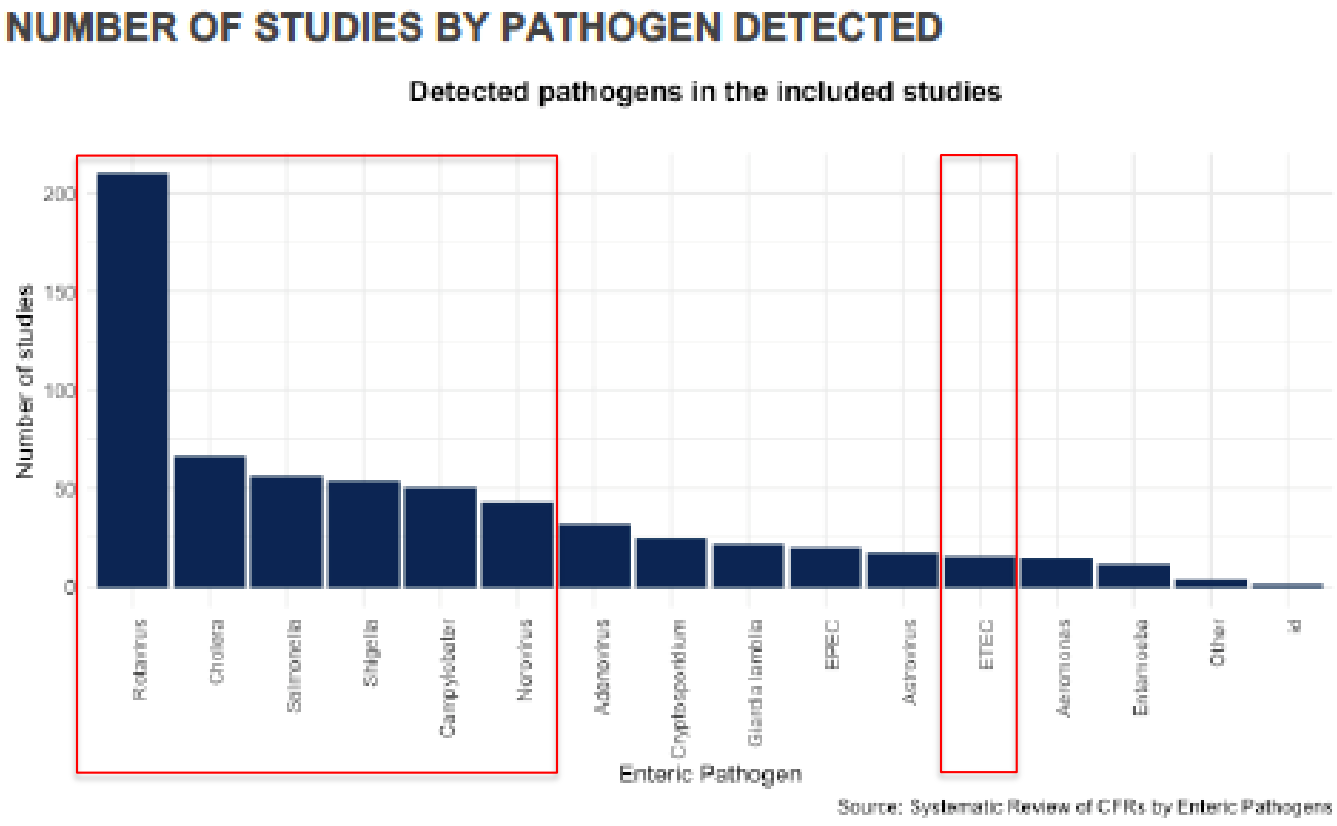
Our Goal

1. To investigate heterogeneity in the case-fatality rate (CFR) of different diarrheal pathogens

2. To examine how the CFR varies by WHO region, age group, and setting (hospital or community)

3. To develop a model to estimate the CFR overall and for each pathogen, controlling for predictors of heterogeneity

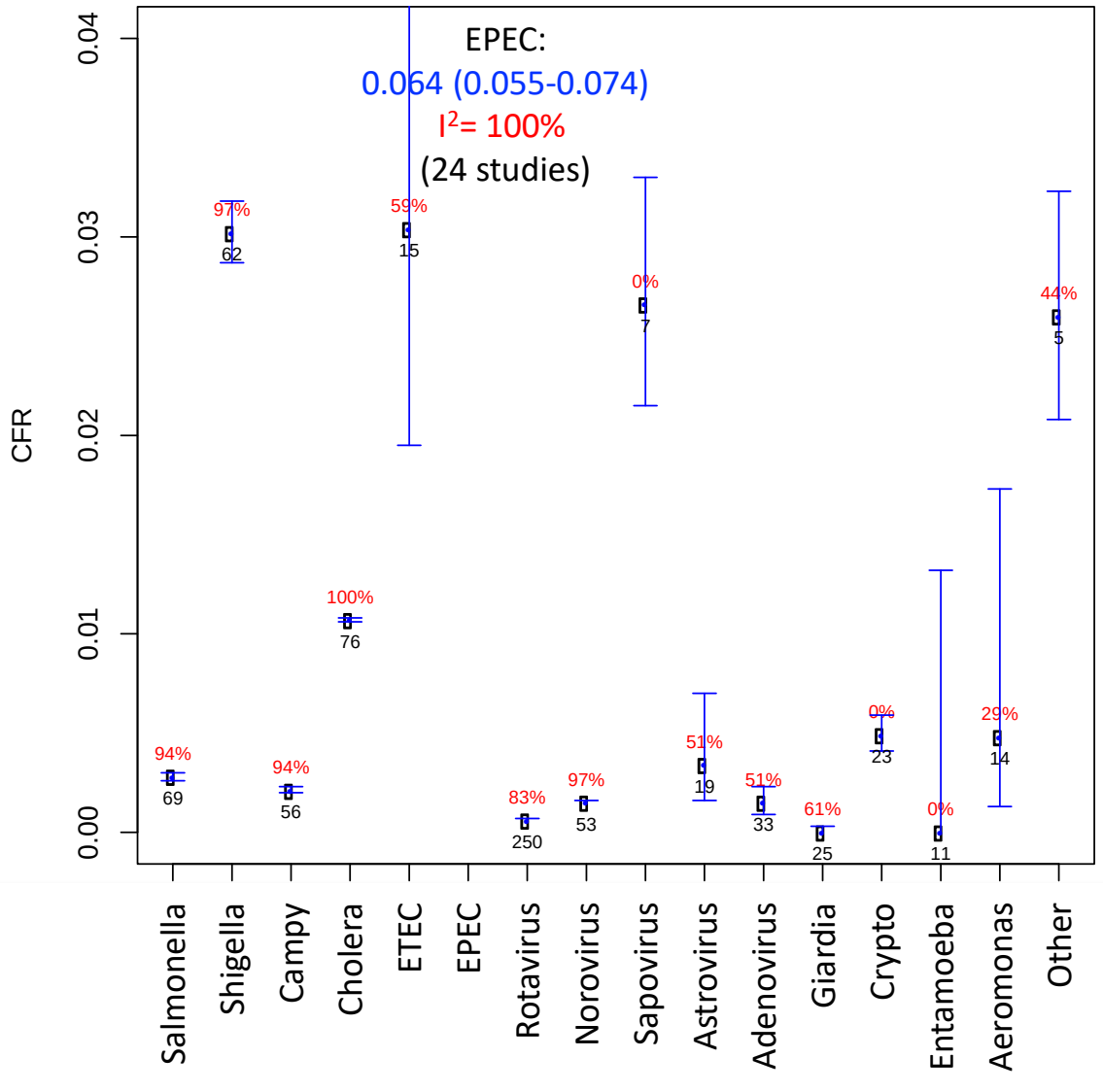
Systematic review data



- Excluded studies among "special" populations (e.g. HIV+ individuals, malnourished children) and for iNTS
- Potential predictors:
  - Age group (<1, <5, ≥5, other)
  - WHO region
  - Setting (hospital, community, other)

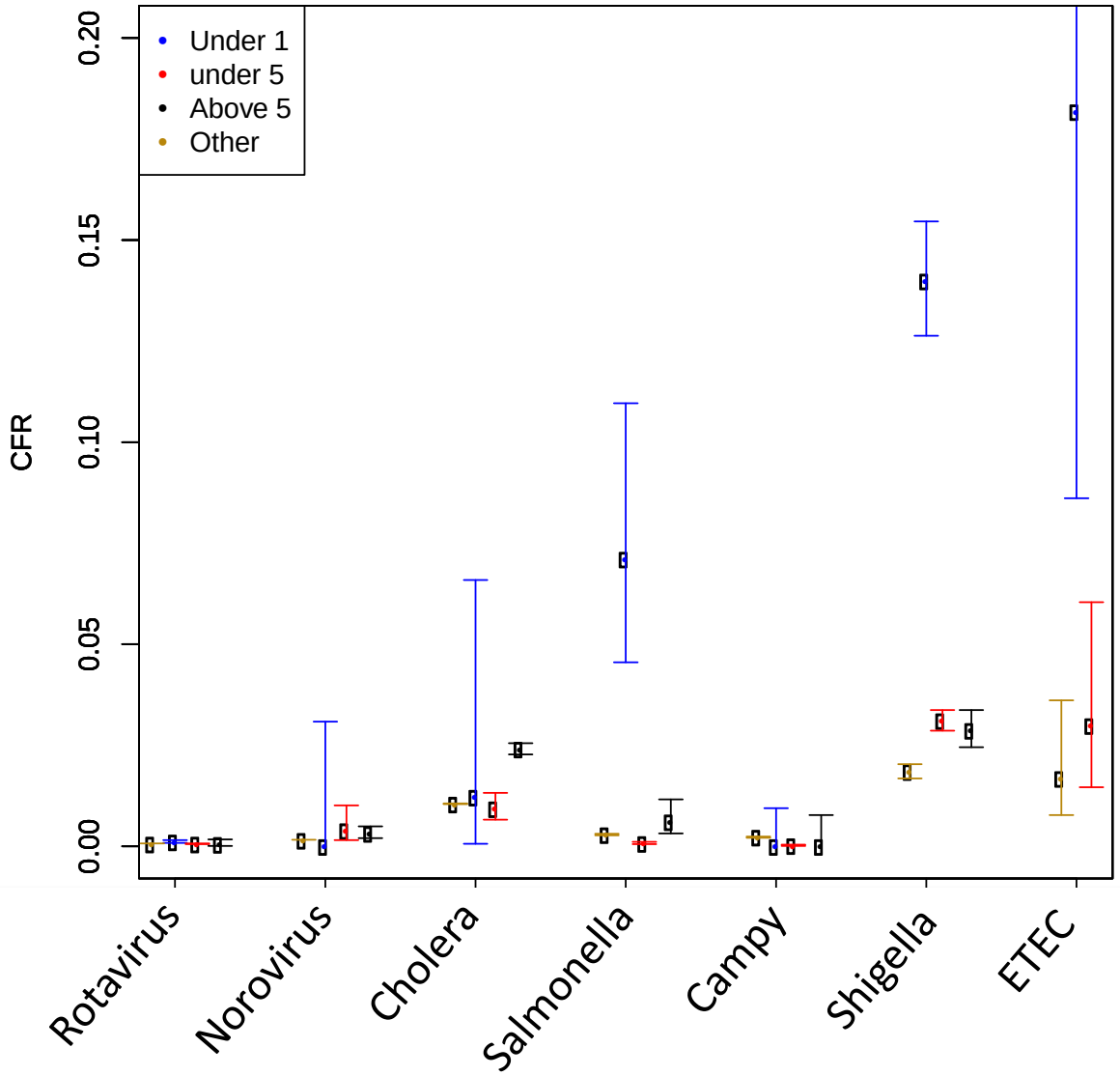
START CENTER
STRATEGIC ANALYSIS, RESEARCH & TRAINING CENTER
Department of Global Health | University of Washington

Results – CFR by pathogen



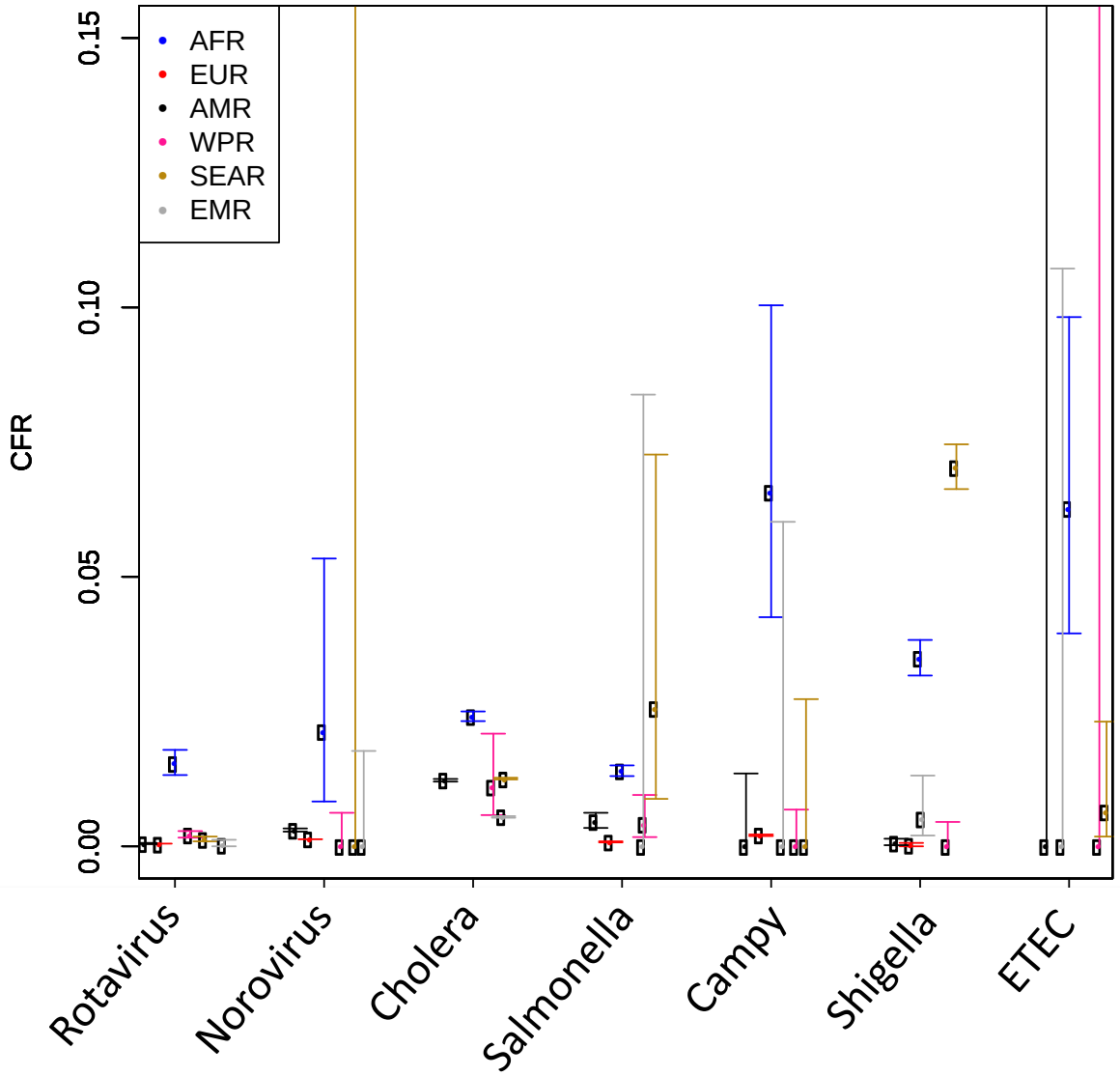
- **Overall CFR:** 0.65% (0.58-0.73%)
- Significant heterogeneity both within and between pathogens

Potential predictors: age group



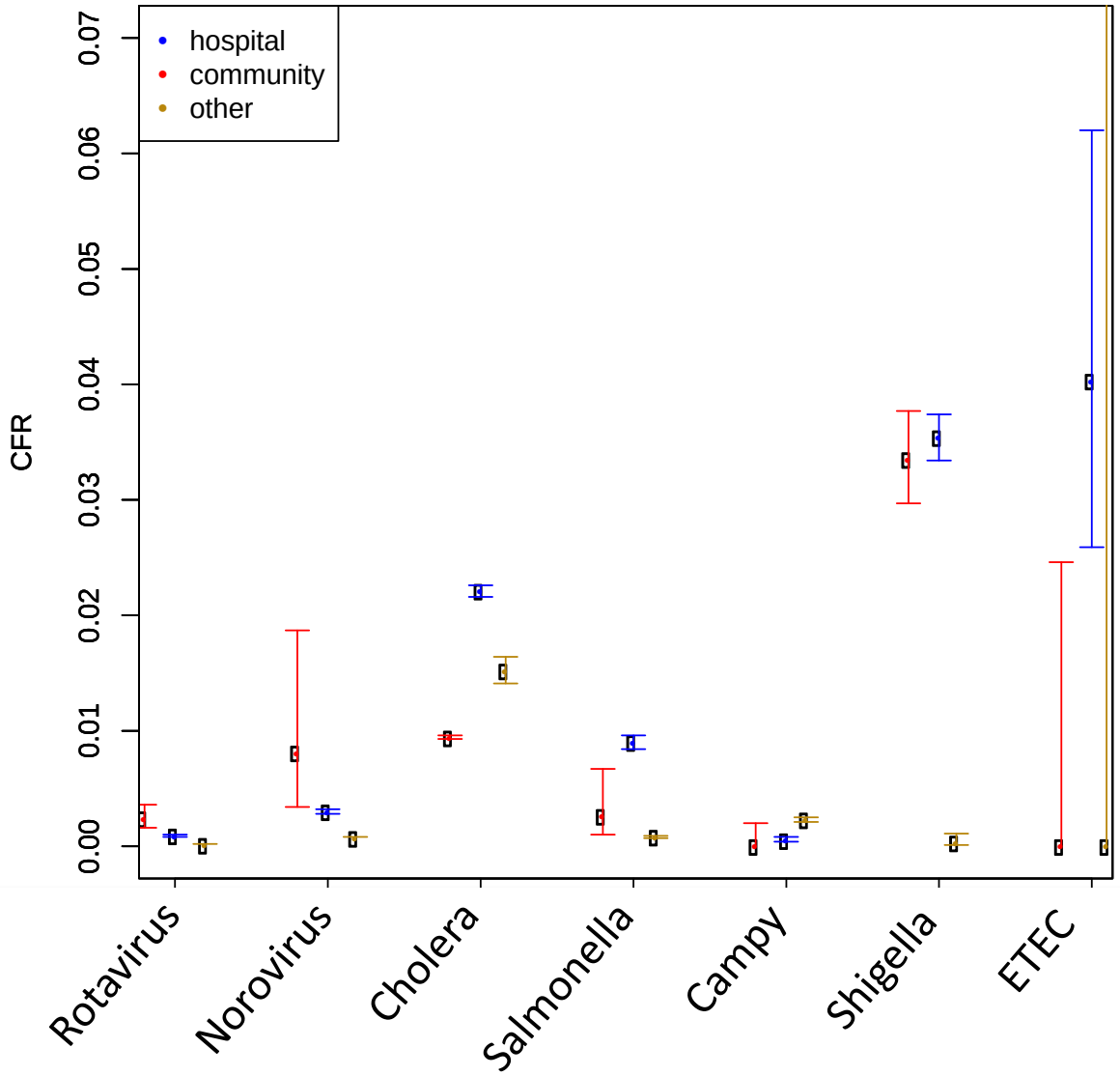
- Higher case fatality rates among infants (<1 yr old) for some pathogens
  - Salmonella
  - Shigella
  - ETEC
- Higher case fatality rate among ≥5 yr olds for cholera

Potential predictors: WHO region



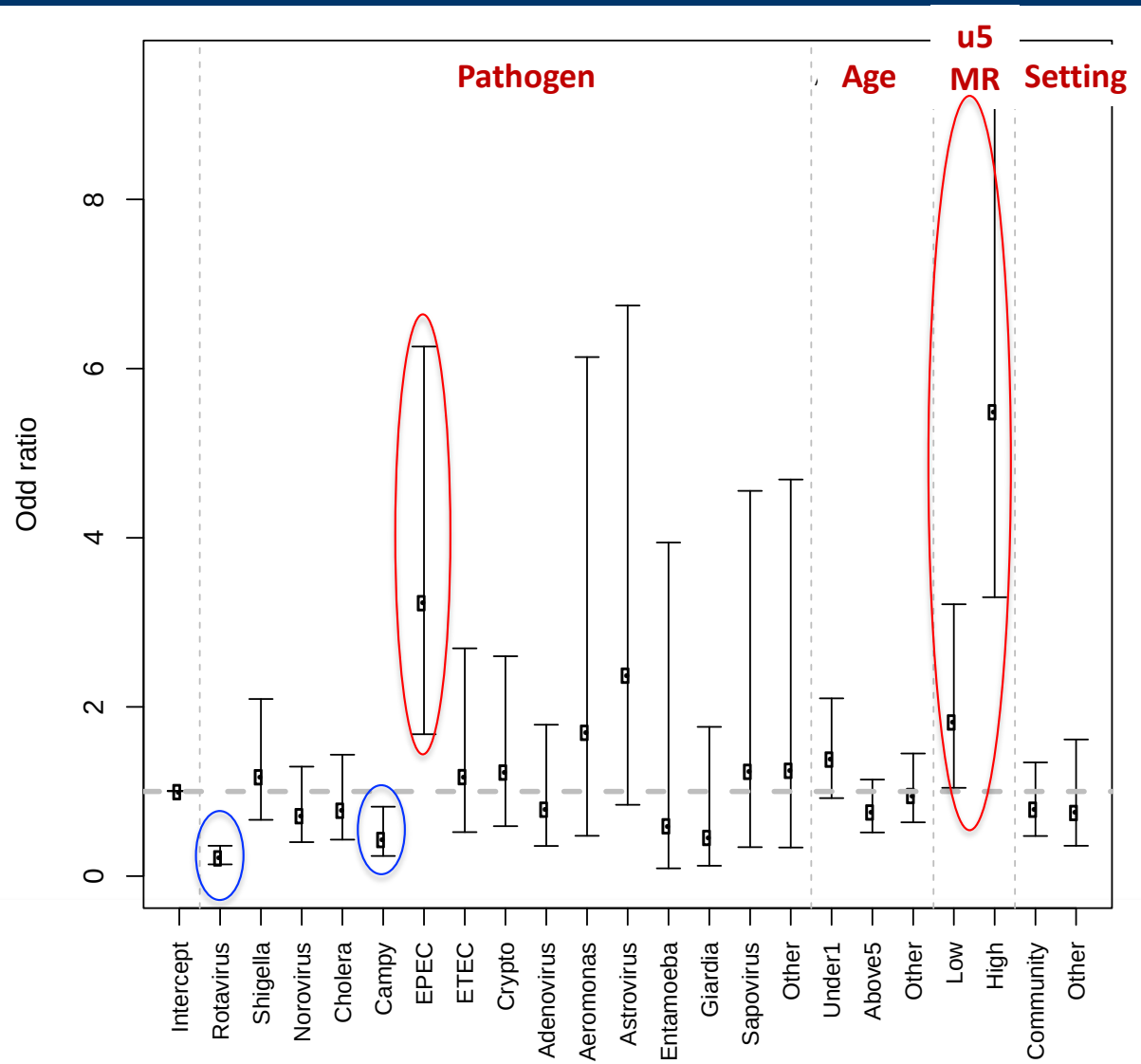
- Higher case fatality rates in AFRO for all pathogens
- Higher CFR in SEARO for
  - Salmonella
  - Shigella

Potential predictors: setting



- No consistent variation in case fatality rate by setting
- Higher CFR in community-based studies for rotavirus, norovirus
- Higher CFR in hospital-based studies for:
  - Cholera
  - Salmonella
  - ETEC

Meta-regression analysis results



- Reference group:
  - Salmonella
  - <5 year age group
  - very low mortality strata
  - hospital-based studies
- CFR is **lower** for rotavirus, campylobacter, **higher** for EPEC
- CFR is **higher** in high under-5 mortality countries

Summary

- Substantial heterogeneity in the estimated CFR both within and between pathogens
- For some pathogens, CFR was higher for:
  - Age group <1 yr
  - AFRO region/higher u5 mortality rate strata
  - Community-based studies (viral pathogens) or hospital-based studies (bacterial pathogens)
- Heterogeneity is not fully explained by age, WHO region/u5 mortality rate strata, or setting

Implications of results for BoED models

- Distribution of diarrheal pathogens among hospitalized patients is a reasonable proxy for those causing death
  - But our analysis shows there is additional heterogeneity in risk of death among inpatients with different pathogens
- Potentially could use ORs from this analysis to account for additional differences in risk of death among inpatients
  - This would decrease deaths attributed to rotavirus, campylobacter; increase deaths attributed to EPEC, astrovirus, etc.
  - However, analysis should account for additional uncertainty in risk of death among those who do not seek care

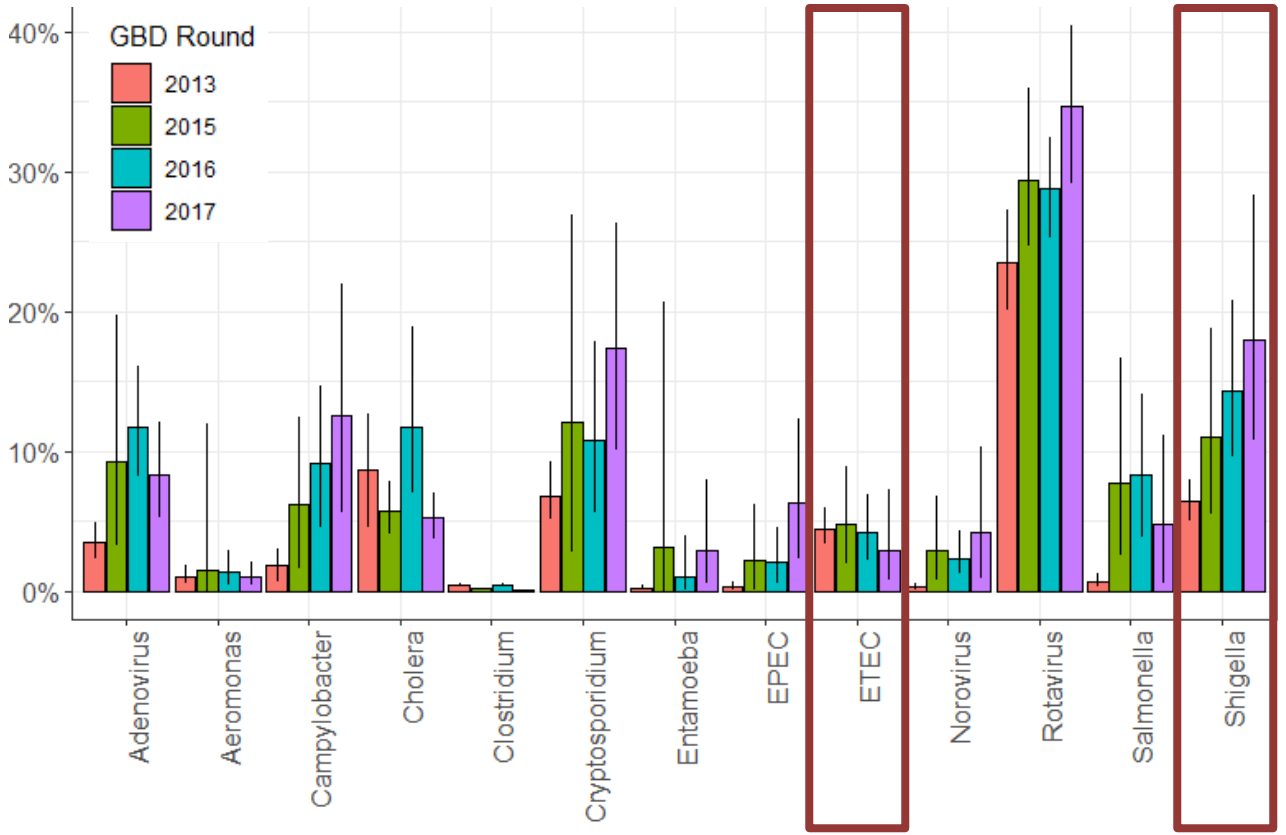
Meta-Analysis of IHME/MCEE study input data and IHME model-based adjustments

Sarah Elwood and James Platts-Mills
for the WHO Burden of Disease Working Group
PDVAC session of diarrhea mortality estimates
11th May, 2020

Global mortality estimates for *Shigella* and ETEC (children < 5 years of age)

Pathogen	MCEE 2017 (unpublished)	IHME GBD 2016 (Lancet 2018)
ETEC	44,078 (32,848 – 58,054)	18,700 (9,800 – 30 659)
Shigella	25,008 (17,148 – 35,878)	63,700 (41 191 – 93 611)

GBD 2010 estimates – four iterations



Courtesy of Chris Troeger/IHME, Bob Black/MCEE, Birgitte Giersing/WHO

Components of global burden estimates – a simple schema

Group	Pathogen prevalence AKA "proportion"	Inference to etiology	Diarrhea mortality incidence
IHME	Prevalence in hospitalized diarrhea in multi-pathogen studies with qPCR diagnostics (by applying adjustments for 1) "community diarrhea" (non-hospitalized) studies, 2) single-pathogen studies, 3) studies with non-qPCR diagnostics)	Calculate population attributable fractions (AFs) using GEMS odds ratios	National/sub-national incidence of fatal diarrhea
MCEE	Proportion of diarrhea positive by meta-analysis from multi-pathogen studies of hospitalized children using "standard" diagnostics	Use pathogens associated with diarrhea in GEMS, force sum of proportions to 1 (include % unknown)	Regional incidence of fatal diarrhea

Components of global burden estimates – a simple schema

Group	Pathogen prevalence AKA "proportion"	Inference to etiology	Diarrhea mortality incidence
IHME	Prevalence in hospitalized diarrhea in multi-pathogen studies with qPCR diagnostics (by applying adjustments for 1) "community diarrhea" (non-hospitalized) studies, 2) single-pathogen studies, 3) studies with non-qPCR diagnostics)	Calculate population attributable fractions (AFs) using GEMS odds ratios	National/sub-national incidence of fatal diarrhea
MCEE	Proportion of diarrhea positive by meta-analysis from multi-pathogen studies of hospitalized children using "standard" diagnostics	Use pathogens associated with diarrhea in GEMS, force sum of proportions to 1 (include % unknown)	Regional incidence of fatal diarrhea

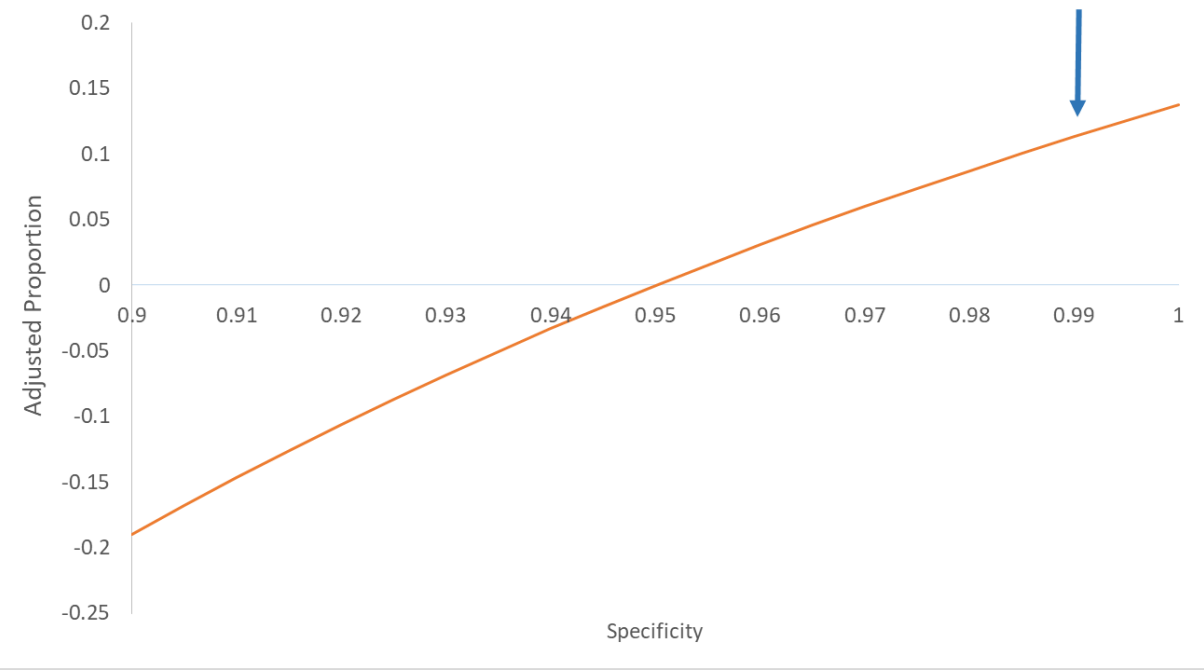
Methods

- High-level meta-analysis of both groups' age-adjusted data
  - Random effects meta-analysis using the Tukey-Freeman double arcsine transformation for the raw proportion data (internally validated with simulations)
  - Weighted by the product of the inverse variance and country-level mortality for each study
- Apply IHME adjustments and examine impact on prevalence estimates
  - Scalar adjustment applied on the logit scale to studies in community settings (0.042 for Shigella, 0.130 for ETEC)
  - Scalar adjustment applied on the logit scale for single pathogen studies (-0.343 for Shigella, -0.125 for ETEC)
  - Diagnostic adjustment – after deriving a qPCR cutoff from GEMS+MAL-ED data, sensitivity and specificity of culture vs PCR is calculated and used to adjust non-PCR observed prevalence to the expected "true" prevalence using PCR
  - Apply odds ratios from GEMs to get population attributable fraction (OR 9.1 for Shigella, 7.7 for ETEC)

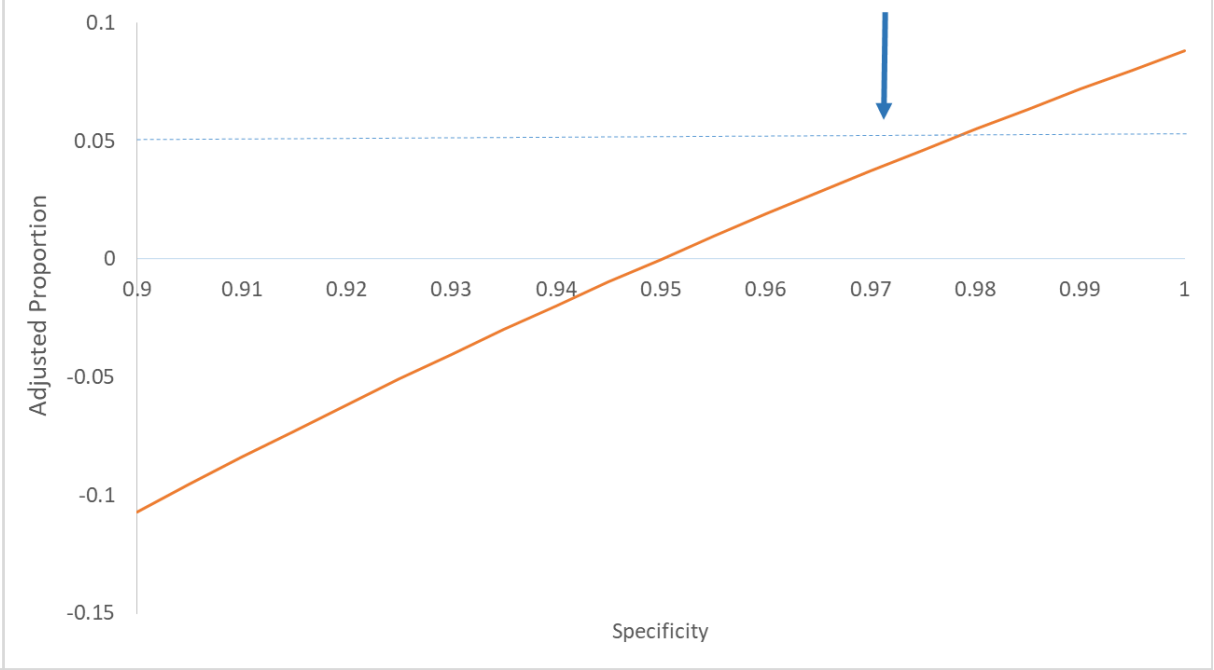
Calculation of adjusted proportion (what would have been found using PCR) from observed proportion (what was found using culture)

$$True\ proportion = \frac{(Proportion_{Observed} + Specificity - 1)}{(Sensitivity + Specificity - 1)}$$

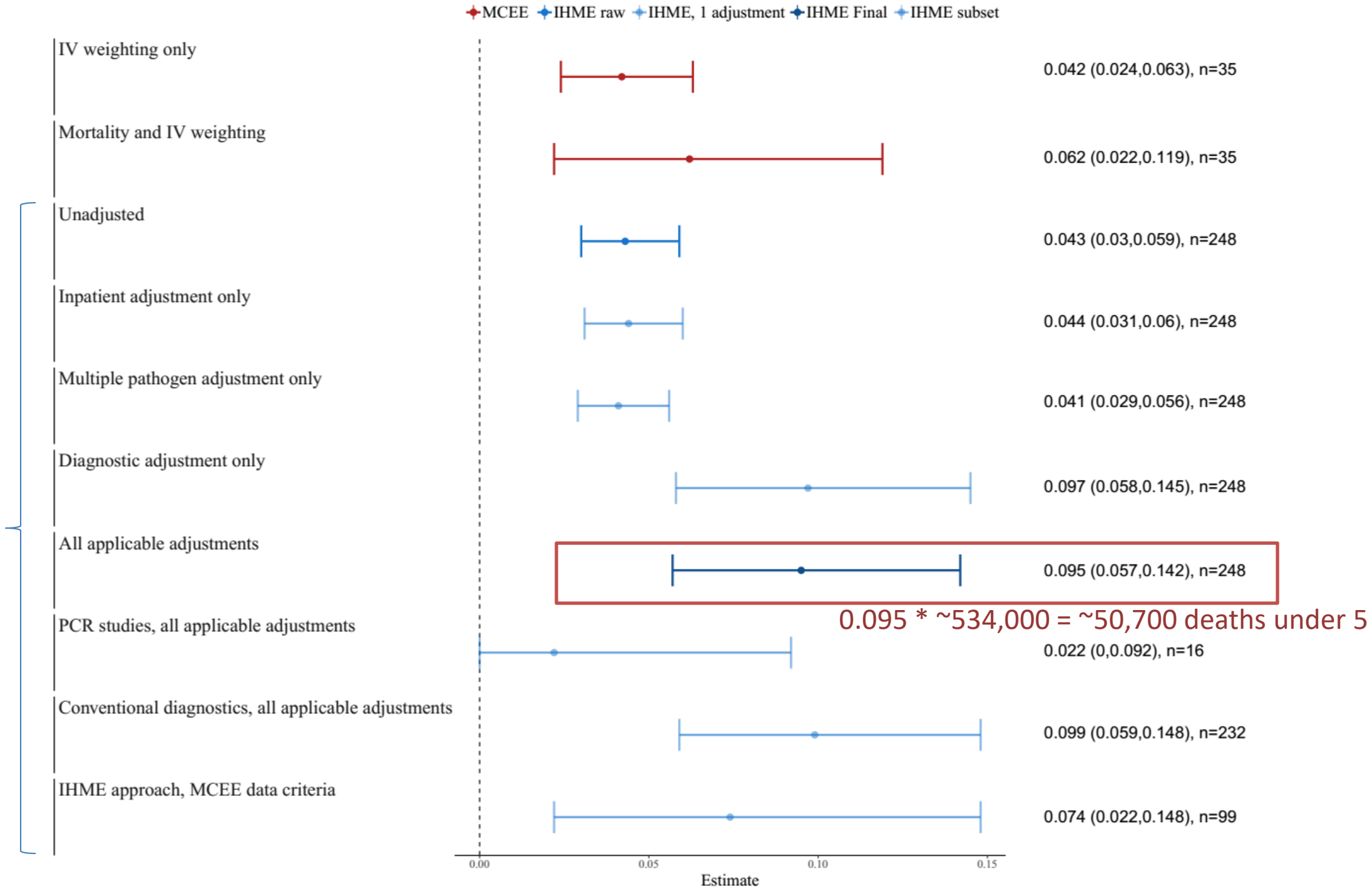
Shigella
-- Observed proportion: 0.05
-- Sensitivity = 0.363
-- Adjusted ("True") proportion: ~0.12



ETEC
-- Observed proportion: 0.05
-- Sensitivity = 0.567
-- Adjusted ("True") proportion: ~0.045



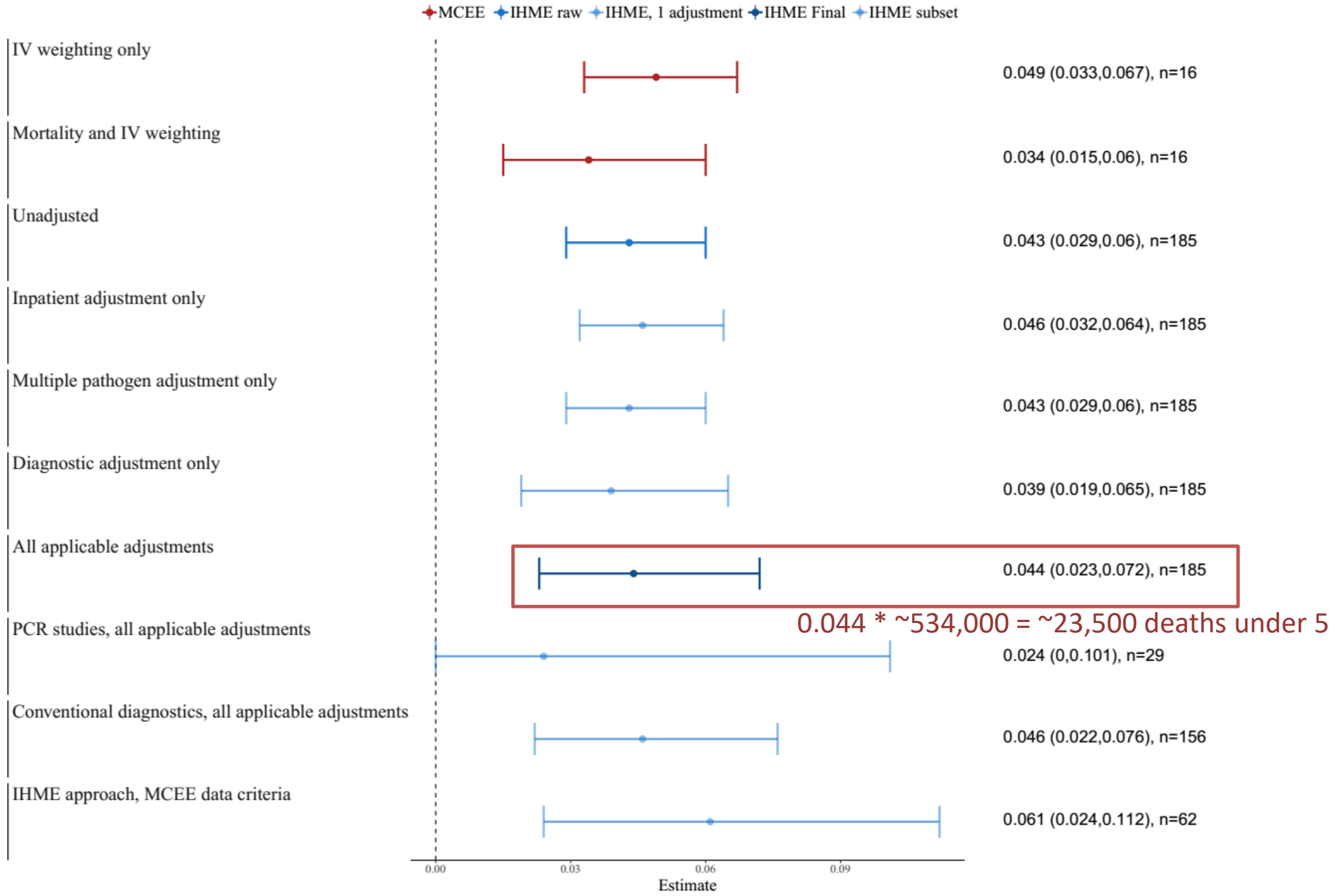
Shigella



All IHME estimates are mortality-weighted attributable fractions

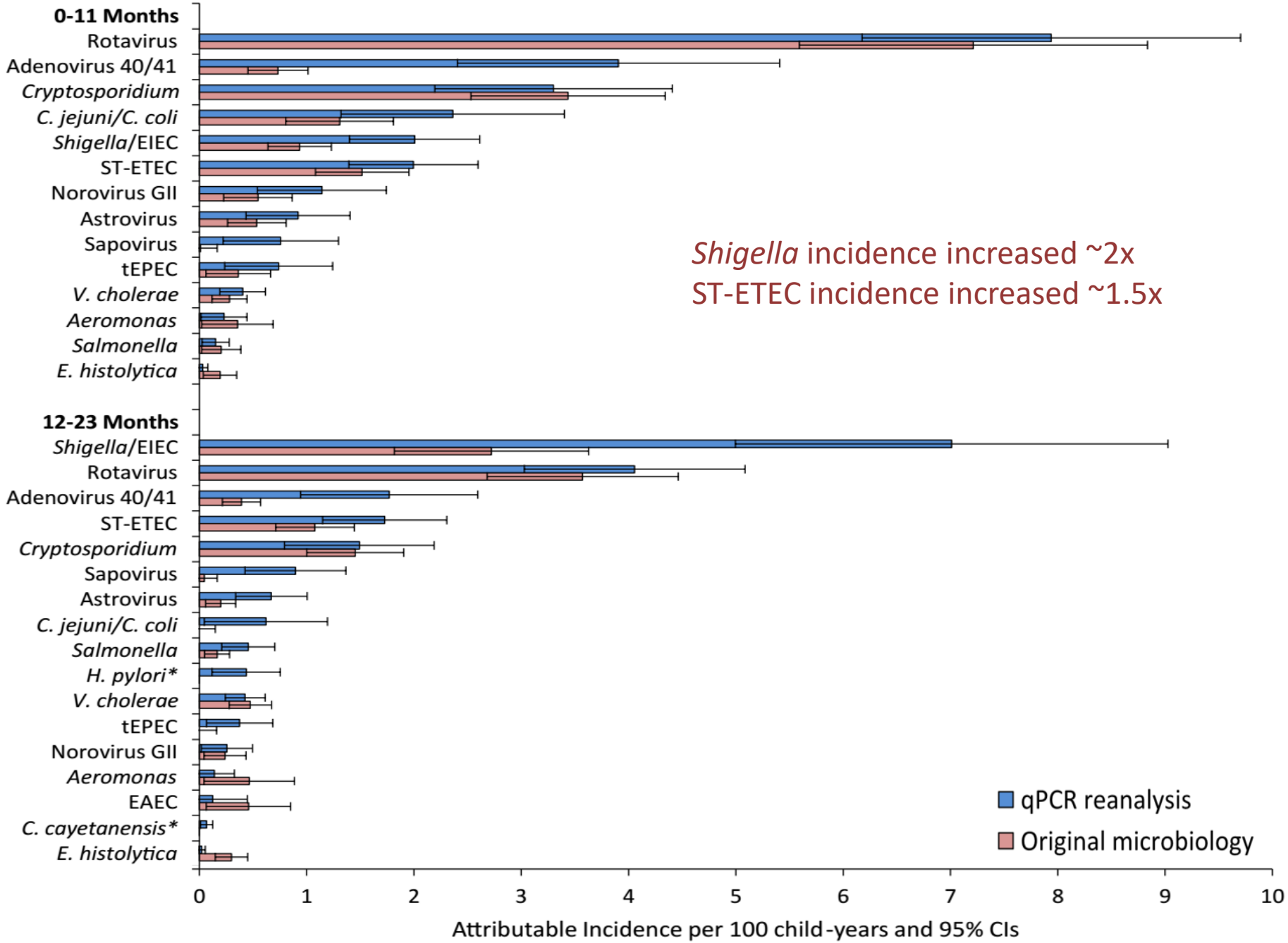
0.095 * ~534,000 = ~50,700 deaths under 5

ETEC



0.044 * ~534,000 = ~23,500 deaths under 5

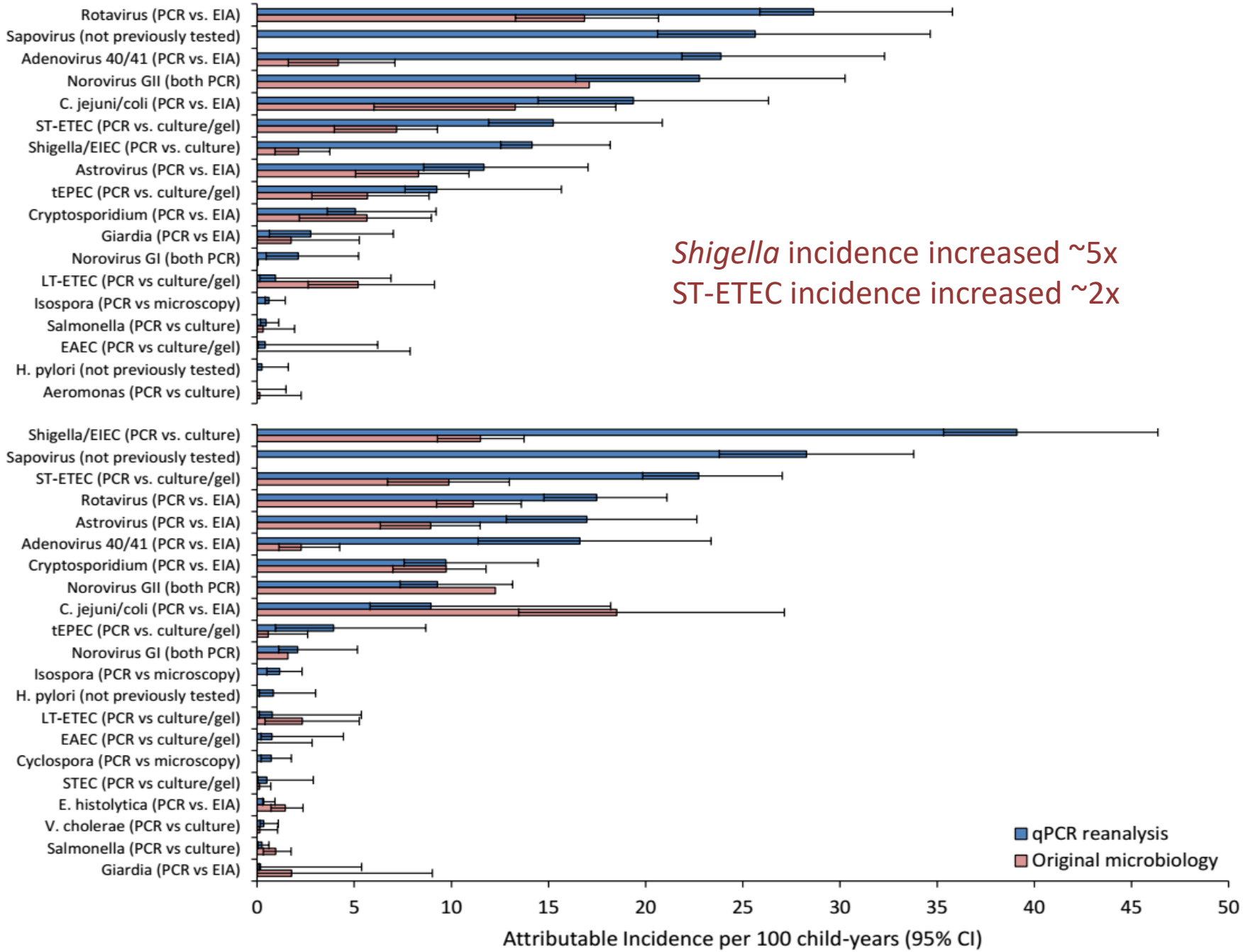
GEMS re-analysis findings



Shigella incidence increased ~2x
ST-ETEC incidence increased ~1.5x

Liu J and Platts-Mills JA, et al. Lancet 2016

MAL-ED re-analysis findings



Shigella incidence increased ~5x

ST-ETEC incidence increased ~2x

Platts-Mills JA and Liu J, et al. Lancet Global Health 2018

Conclusions

1. The IHME diagnostic test adjustments have by far the largest impact on literature-derived pathogen prevalence; still, the burden increase remains conservative (~2x for *Shigella* and essentially unchanged for ETEC) when compared to the GEMS/MAL-ED re-analysis findings
2. Alternative approaches to making these adjustments could be considered and would likely further increase the gap between *Shigella* and ETEC burden for GBD
3. The application of etiology proportions to different envelopes (national/sub-national by IHME, regional by MCEE) may also lead to differences in the estimates

Perspectives from PDVAC members of the BoED WG

World Health Organization

Claudio Lanata, Cherry Kang, Peter Smith

PDVAC Virtual session 2

11 May 2020

IHME

Perspectives on findings from the mortality modelling groups

Hmwe Kyu

May 11, 2020

UNIVERSITY of WASHINGTON

Institute for Health Metrics and Evaluation

Perspectives and potential next steps

- Thanks to the modeling groups for the valuable analyses and findings!
- How the analyses may be useful in future estimates?

(1) Validation exercise using CFRs

- Compare implied CFRs based on GBD results and the CFRs from systematic review

(2) Incorporate odds ratios (ORs) into PAF calculation

- Determine the ratio of reference (PCR) to non-reference (conventional methods)
  - Use *within-study* comparisons when possible
- Adjust non-reference data to the expected value if conducted using same study design
- Explore the possibility of predicting ORs by country as a function of sociodemographic development

Anticipated outcomes, timelines, next steps

World Health Organization

Mateusz Hasso-Agopsowicz, Birgitte Giersing

PDVAC Virtual session 2

11 May 2020

Next steps

1. **Finalize ongoing analyses and workstreams**
    1. WS1: Data gaps
        1. Analysis of odds ratios of developing diarrhoea when pathogen is detected in stool, **COMPLETED**
        2. Analysis of pathogen specific CFRs, **NEAR COMPLETION**
    2. WS2: Study quality exercise
        1. Study quality analysis, **COMPLETED**
        2. Sensitivity analysis of low quality studies, **PENDING**
    3. WS3: Data processing exercise
        1. Meta-analysis of input studies and the impact of model adjustments, **COMPLETED**
    4. WS4: Model comparison exercise, **PAUSED**

Estimated finalisation of workstreams 1-3, Summer 2020

Next steps

1. Finalize ongoing analyses and workstreams
2. **Work with IHME and MCEE to inform future iterations of U5 mortality estimates**
    1. Continued discussion with IHME and MCEE
    2. Sharing results and accompanying databases

Next steps

1. Finalize ongoing analyses and workstreams
2. Work with IHME and MCEE to inform future iterations of mortality estimates
3. **Dissemination of results, proposed list of articles:**
    1. Results from the OR systematic review
    2. Results from the CFR systematic review
    3. Results from the meta-analysis
    4. A high-level document that describes inclusion and exclusion criteria for mortality estimates studies (incorporating results from the grading analysis and IHME sensitivity analysis)
    5. An overarching publication that describes the exercise, binds all workstreams together and summarises conclusions and recommendations

Next steps

1. Finalize ongoing analyses and workstreams
2. Work with IHME and MCEE to inform future iterations of mortality estimates
3. Dissemination of results, proposed list of articles
4. **Continued monitoring for additional data to inform models that calculate mortality estimates, i.e. CHAMPS, GPDS**

Next steps

1. Finalize ongoing analyses and workstreams
2. Work with IHME and MCEE to inform future iterations of mortality estimates
3. Dissemination of results, proposed list of articles
4. Continued monitoring for additional data to inform models that calculate mortality estimates
5. **Expansion of work to measure the impact of enteric pathogens on morbidity (2020-2023)**

Discussion

World Health Organization

Questions for PDVAC

- Have the outcomes of the BoED WG led to improved understanding of the data inputs and data processing that inform the mortality estimates?
- (How) could the outcomes of this work improve robustness and credibility of mortality estimates?
- Does PDVAC have any recommendations as to how this work can be incorporated into future mortality estimates and to inform research agenda around enteric pathogens?

Proposed expansion of BoED WG scope to include morbidity assessment

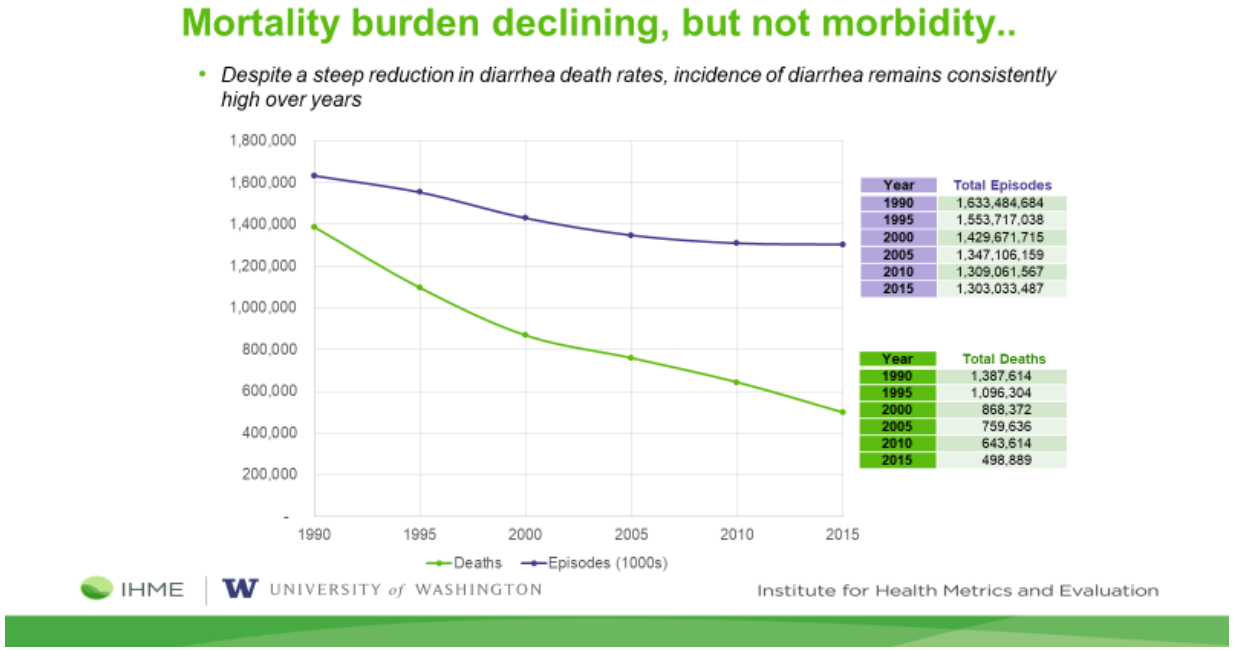
Ibrahim Khalil

PDVAC Virtual session 2

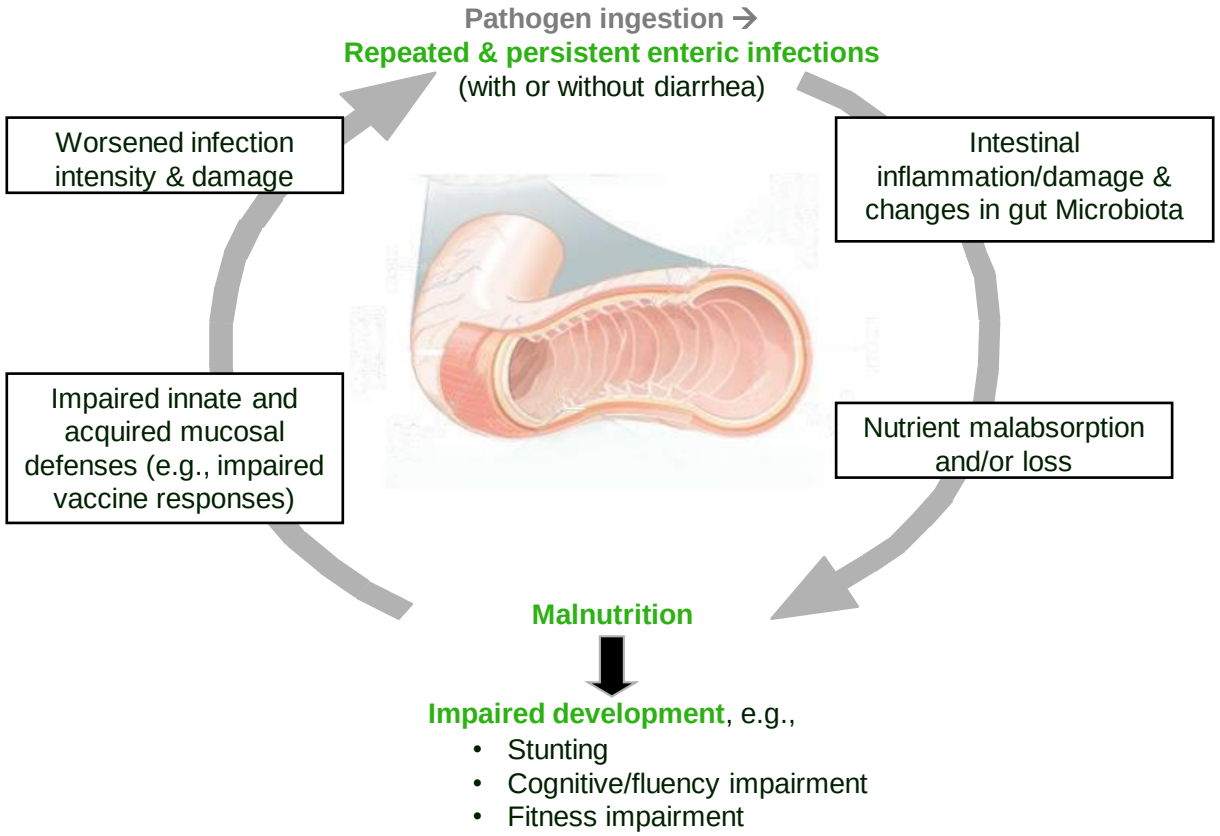
11 May 2020

Underestimation of Overall Diarrhea Burden: the need to quantify long term sequalae

- Diarrheal diseases burden estimates have been dominated by childhood deaths
- Public health policy decisions are mainly based on mortality estimates
- It is suggested that stunting, wasting, cognitive impairment, decreased school performance, and other consequences, disrupt the trajectory of a child's potential development
- Assessment of long-term effects of diarrheal diseases is challenging
- Improved data and careful analyses to define and quantify the diarrhea long term sequalae, is needed for a more precise assessment of the full costs of diarrhea and enteric vaccines FVVA



The little we know; Diarrhea, Malnutrition, and impaired development…



Existing diarrheal morbidity modelling estimates

World Health Organization

- Diarrhoea episodes are significantly associated with childhood growth faltering
- After addition of the DALYs due to the long-term sequelae as a consequence of undernutrition, the burden of diarrhoeal diseases increased by 39·0% among children younger than 5 years

Global disability-adjusted life-year estimates of long-term health burden and undernutrition attributable to diarrhoeal diseases in children younger than 5 years

Christopher Troeger, Danny V Colombara, Puja C Rao, Ibrahim A Khalil, Alexandria Brown, Thomas G Brewer, Richard L Guerrant, Eric R Houpt, Karen L Kotloff, Kavita Misra, William A Petri Jr, James Platts-Mills, Mark S Riddle, Scott J Swartz, Mohammad H Forouzanfar, Robert C Reiner Jr, Simon I Hay, Ali H Mokdad

- The expanded effects of non-fatal ETEC and shigella-related diarrhoeal episodes can have lasting consequences
- Prevention of these infections could reduce the risk of direct death and stunting and deaths due to other infectious diseases

Burden of enterotoxigenic *Escherichia coli* and shigella non-fatal diarrhoeal infections in 79 low-income and lower middle-income countries: a modelling analysis

John D Anderson IV*, Karoun H Bagamian*, Farzana Muhib, Mirna P Amaya, Lindsey A Laytner, Thomas Wierzba, Richard Rheingans

Evidence of Sub-Clinical Enteric Infection Burden

MAL-ED study (prospective community cohort)**:**

- 76.9% diarrheal stools and 64.9% of non-diarrheal stools had at least one pathogen
- 41.0% diarrheal stools and 29.0% non-diarrheal stools, had at least two

(Platts-Mills JA et al. Lancet Glob. Health. 2015)

GEMS Study (Case Control):

- 83% of cases and 72% of controls had at least one pathogen
- 45% cases and 31% controls had at least two

(Kotloff KL et al. The Lancet. 2013)

Why do we need to quantify sub-clinical enteric infections and EED Burden?

World Health Organization

- Studies focused on clinical diarrhea-- emerging evidence of underestimation of exposure to enteropathogens and their long-term consequences
- Both diarrhea and enteropathogen infection have been associated with growth faltering, reduced cognitive development, and reduced vaccine efficacy
- Continual challenge by pathogens in the gut, alters the structure, metabolic and immunological pathways and changes the microbiome
- Quantifying the contribution of individual pathogens to growth shortfalls has been less frequently examined
- Recognizing the importance of enteric infections, will direct efforts to reduce the compounded damage due to inadequate diet and infection

Proposed activities for the BoED WG

- Conduct a landscape analysis of the available and forthcoming data, and methods used to measure morbidity (variables, metrics, types of tests performed, etc.)
- Examine the evidence for the pathologic pathway leading to long term sequalae of enteric infections and diarrhea (inflammation biomarkers, EED, stunting…etc.)
- Collaborate with / track the ongoing efforts of the AMR vaccine value attribution framework to incorporate contribution of AMR, when appropriate
- Identify critical data gaps and propose research studies that may improve understanding, including mining existing data sets from past studies

- **Output 1:** Identification of data and research gaps to quantify morbidity, recommendations communicated through publication
- **Output 2:** Assess whether the evidence collected on disease impact, and the existing studies/methods to measure morbidity could inform the development of a standardised framework to quantify the burden

Question to PDVAC

- Does PDVAC endorse the proposed scope of work for the BoED working group, to include evaluation of morbidity data and estimates?

***Please note:**

- the BoED WG will continue to collaborate with the global enteric disease burden modellers to incorporate analysis from the mortality workstreams and assess new data that becomes available, i.e. GPDS and CHAMPS (Child Health and Mortality Prevention Surveillance Network)
- this work should be complemented and coordinated with cost estimation, including societal and economic impacts but this is beyond the scope of this WG