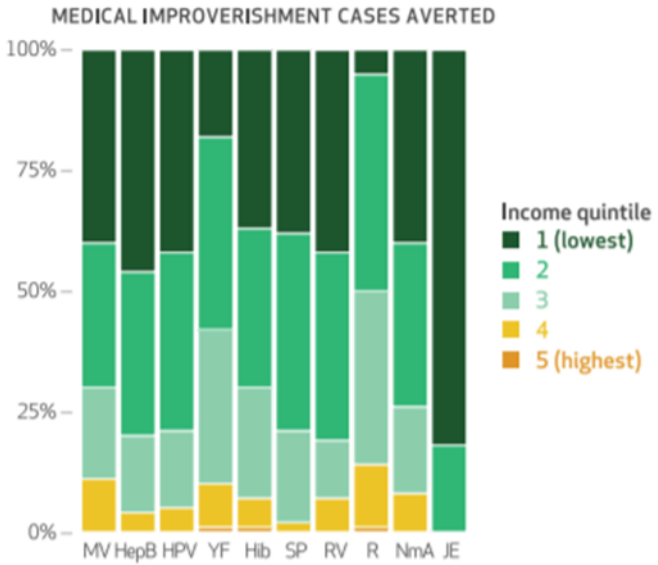
Full Value of Vaccine Assessment (FVVA) for *Shigella* vaccines

World Health Organization



2020 WHO Product Development for Vaccines Advisory Committee (PDVAC)

Virtual Consultation 3

18 May 2020

Moving beyond mortality to articulate vaccine value

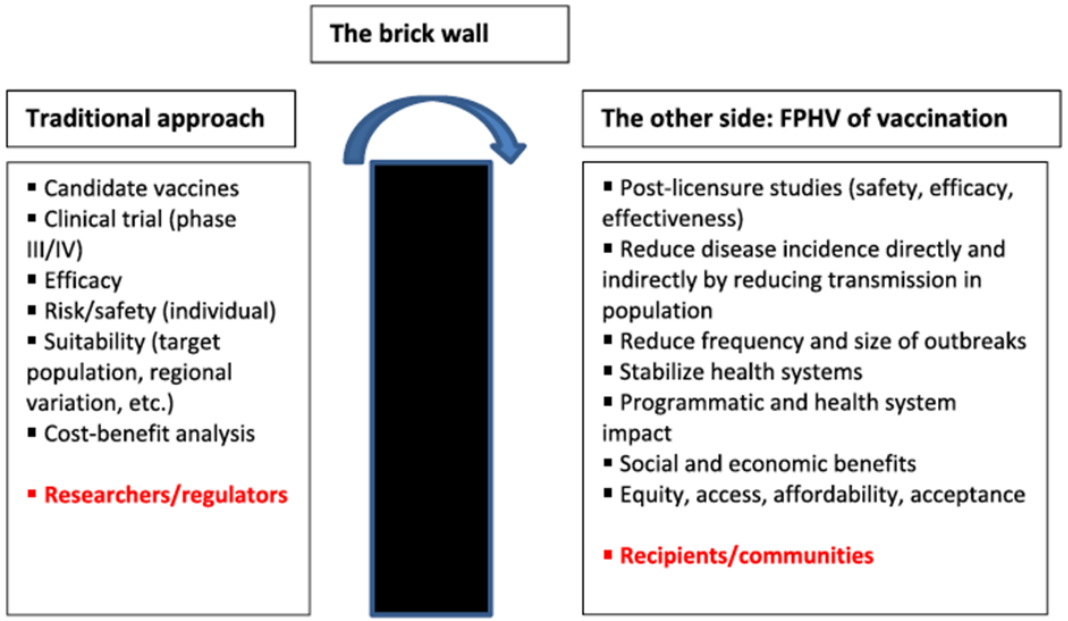
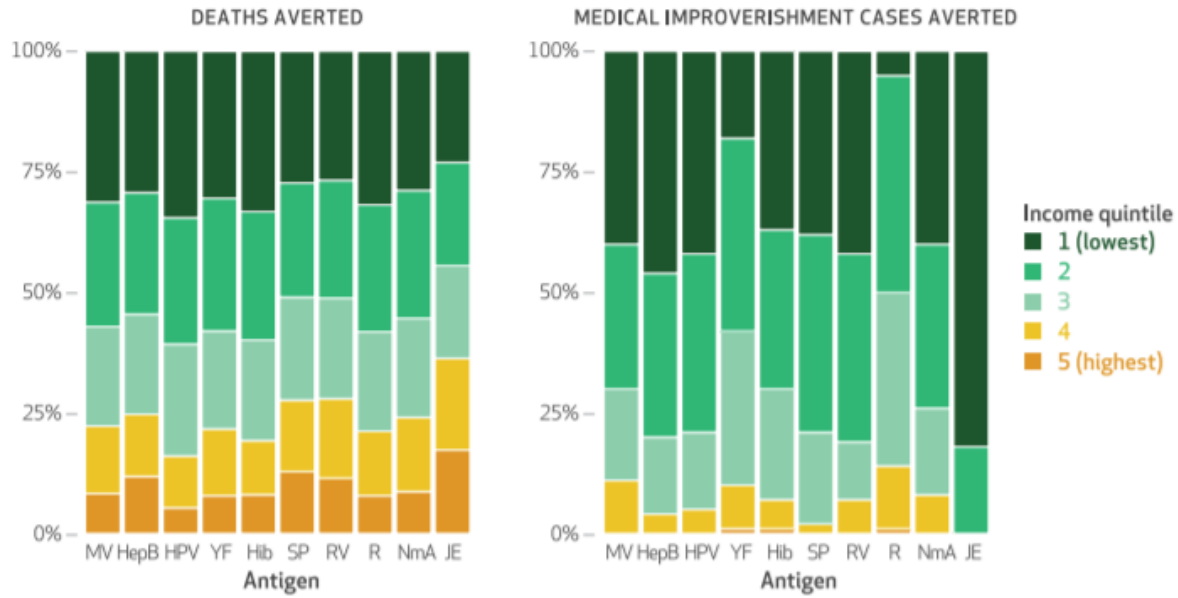
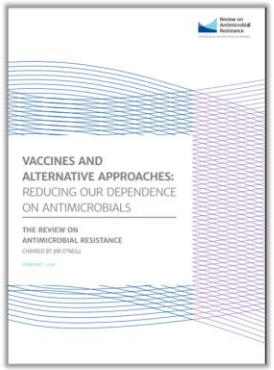
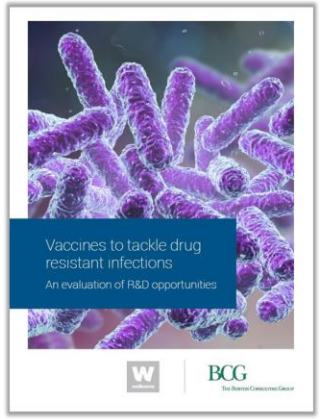


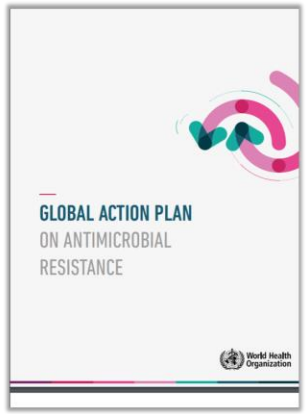
Fig. 2. The brick wall: Moving from vaccines to vaccination.

Sources:
Gessner B et al. Estimating the full public health value of vaccination. Vaccine 2017; 35:6255
Chang et al. The Equity Impact Vaccines May Have On Averting Deaths And Medical Impoverishment In Developing Countries, Health Affairs 37, No. 2 (2018): 316–324



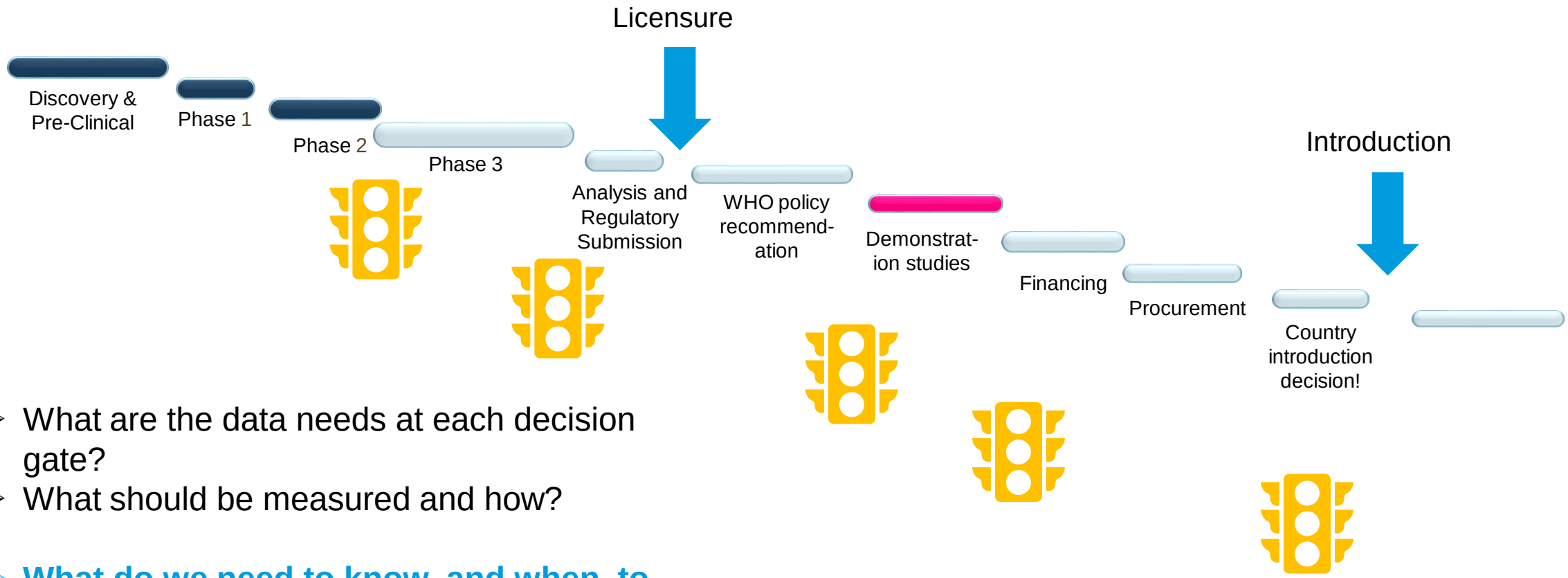






VoVRN
VALUE OF VACCINATION RESEARCH NETWORK

Product development continuum to access and impact



- What are the data needs at each decision gate?
- What should be measured and how?

- **What do we need to know, and when, to avoid a delay to impact?**

https://www.who.int/immunization/research/ppc-tpp/PPC_Shigella_draft_for_review_april2020.pdf?ua=1

DRAFT WHO Preferred Product Characteristics for Vaccines against *Shigella*

Written comments proposing modifications to this text must be received by **28 May 2020** and entered in the Comment Form (available separately), and should be addressed to the Responsible Officer: Dr Birgitte Giersing at giersingb@who.int.

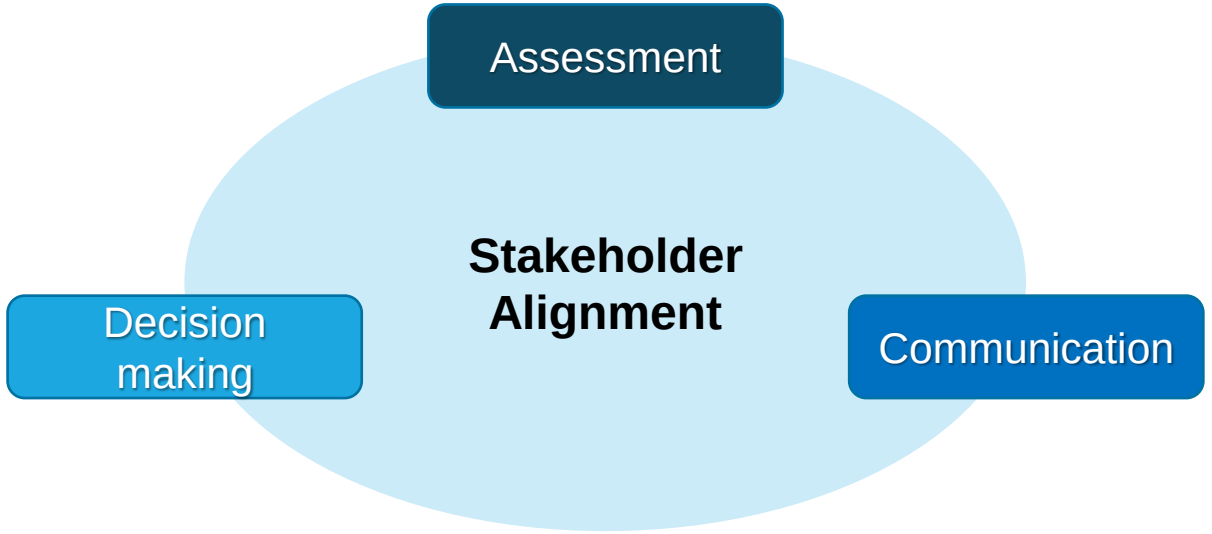
Current WHO concept of "full value of vaccines assessment"

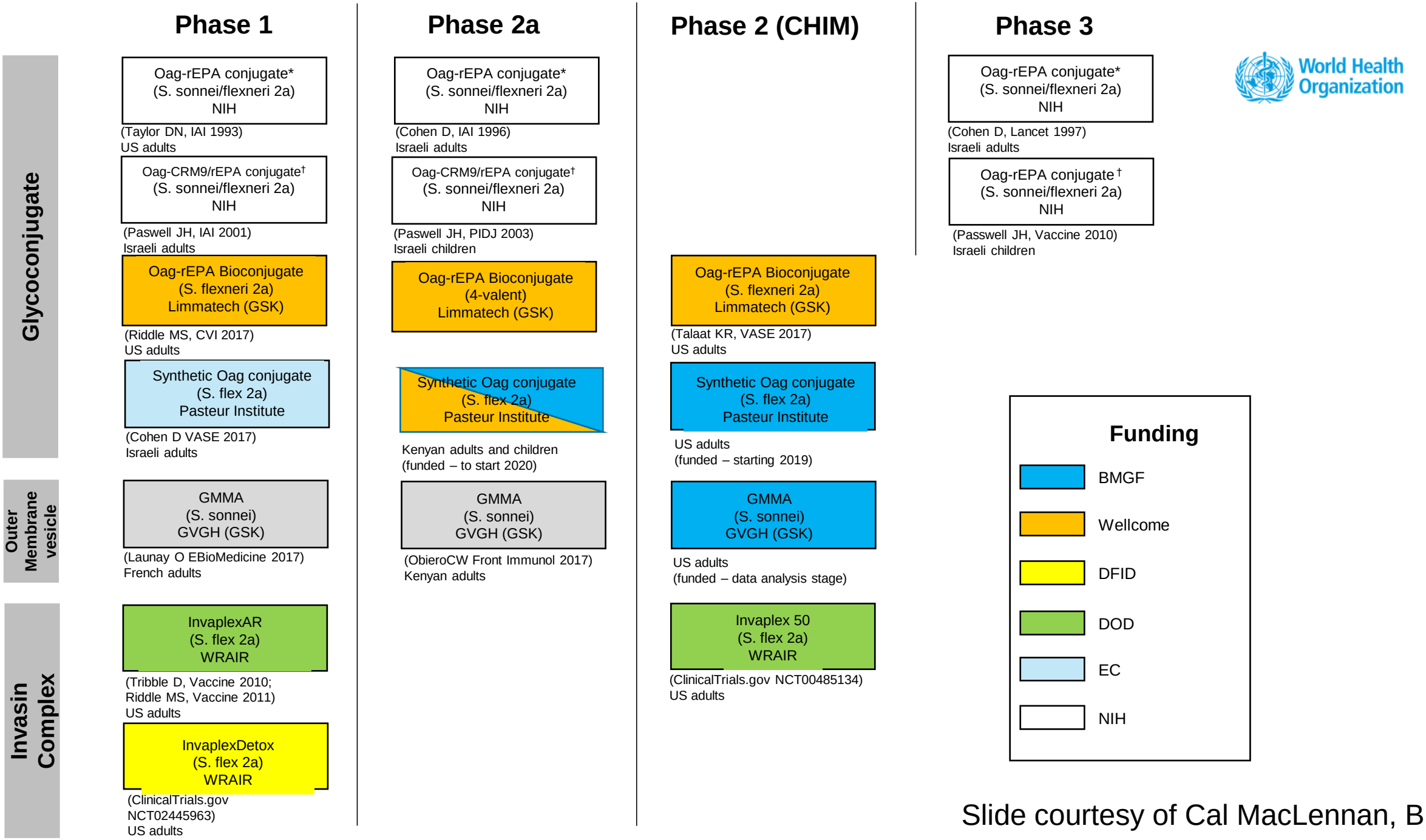
The FVVA for vaccines is a concept that describes the **global value of a vaccine, including from an LMIC perspective**.

It aims to articulate the full direct (individual) and **indirect (population) effects** of a vaccine.

The intent of FVVA 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**.





Slide courtesy of Cal MacLennan, BMGF

Why do we need a FVVA for Shigella, now?

World Health Organization

Shigella candidates are here.

- Vaccine development and opportunity costs, and therefore risk, increase substantially beyond phase II – **how is further investment justified?**
- Key stakeholders expand/diversify beyond POC, with different agendas – **how do we align on priorities?**
- The decision making environment is changing: other disease priorities, full new vaccine pipeline, evolving criteria and metrics – **do we know what data we need? Do we have it?**
- We need a vaccine that is licensed, recommended, procured and accessible – **how can we work together most effectively across the continuum?**
- There's a long way from product development to impact for a global health vaccine – **how will the environment change?**

Objectives of this meeting

PATH have identified the major themes to inform a FVVA for Shigella vaccines.

This session is to discuss the critical questions that should inform the assessment, **from the PDVAC perspective**, and their relative importance, *at this point in time*.

The purpose of this session is:

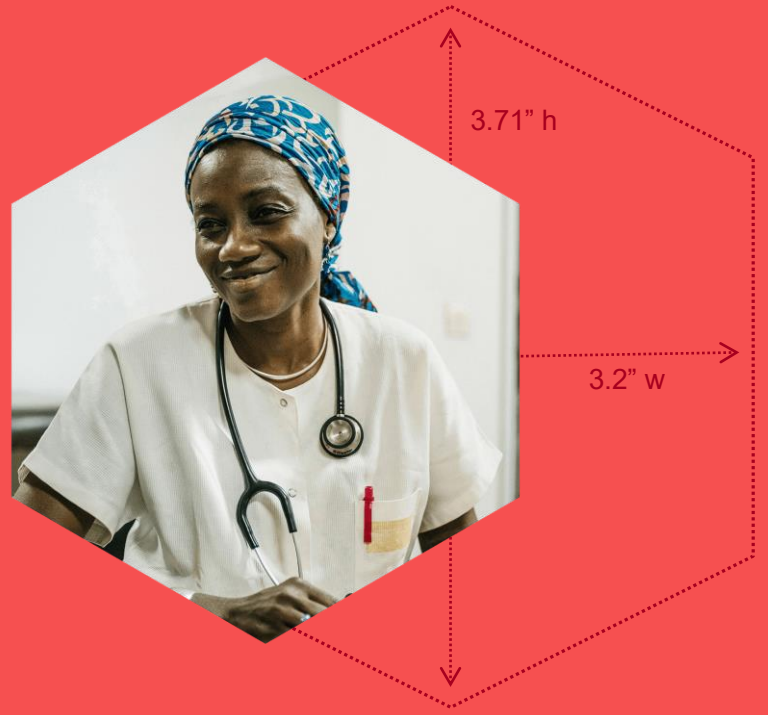
- To seek feedback on the proposed questions to be addressed by the Shigella FVVA.
- To identify gaps or other questions that could be addressed as part of the Shigella FVVA.

Agenda overview

Topic	Duration	Detail	Moderators, speakers
Introduction: session overview & objectives			David Kaslow / Birgitte Giersing
Why do we need a FVVA for Shigella vaccines?	10’	Overview of proposed key elements that are needed to define the Shigella vaccine value assessment	Bill Hausdorff (PATH)
Questions for clarification			
What has changed in our perception of Shigella burden in the last decade?	15 + 10	Evolving mortality estimates, subnational vs national heterogeneity, recent data or models that many inform impact of stunting	Karen Kotloff (UMD)
AMR as an incentive for vaccine development/use	10 + 5	○ Overview of ongoing studies of potential impact of a Shigella vaccine on AMR	Mateusz Hasso (WHO)
The potential impact and cost-effectiveness of a Shigella vaccine.	10’ + 5’	Includes an overview of key impacts considered and omitted and the rationale for considering the relationship between stunting, cognition, learning and macroeconomic effects.	Farzana Muhib (PATH)
Questions for consideration*	5’	Questions to frame discussion, and for input from PDVAC: ➢ How robust are the data on stunting to long term morbidity that impacts socio-economic outcomes? ➢ What modifications, if any, to current cost effectiveness analyses should be included based on new data? ➢ How, and when, should we engage with / gather information on national stakeholder perceptions of Shigella burden and of a vaccine’s potential impact?	Birgitte Giersing (WHO)
Discussion (open session)			
Discussion (closed session)			

Public Health Value Propositions

Full Value of Vaccines Assessments



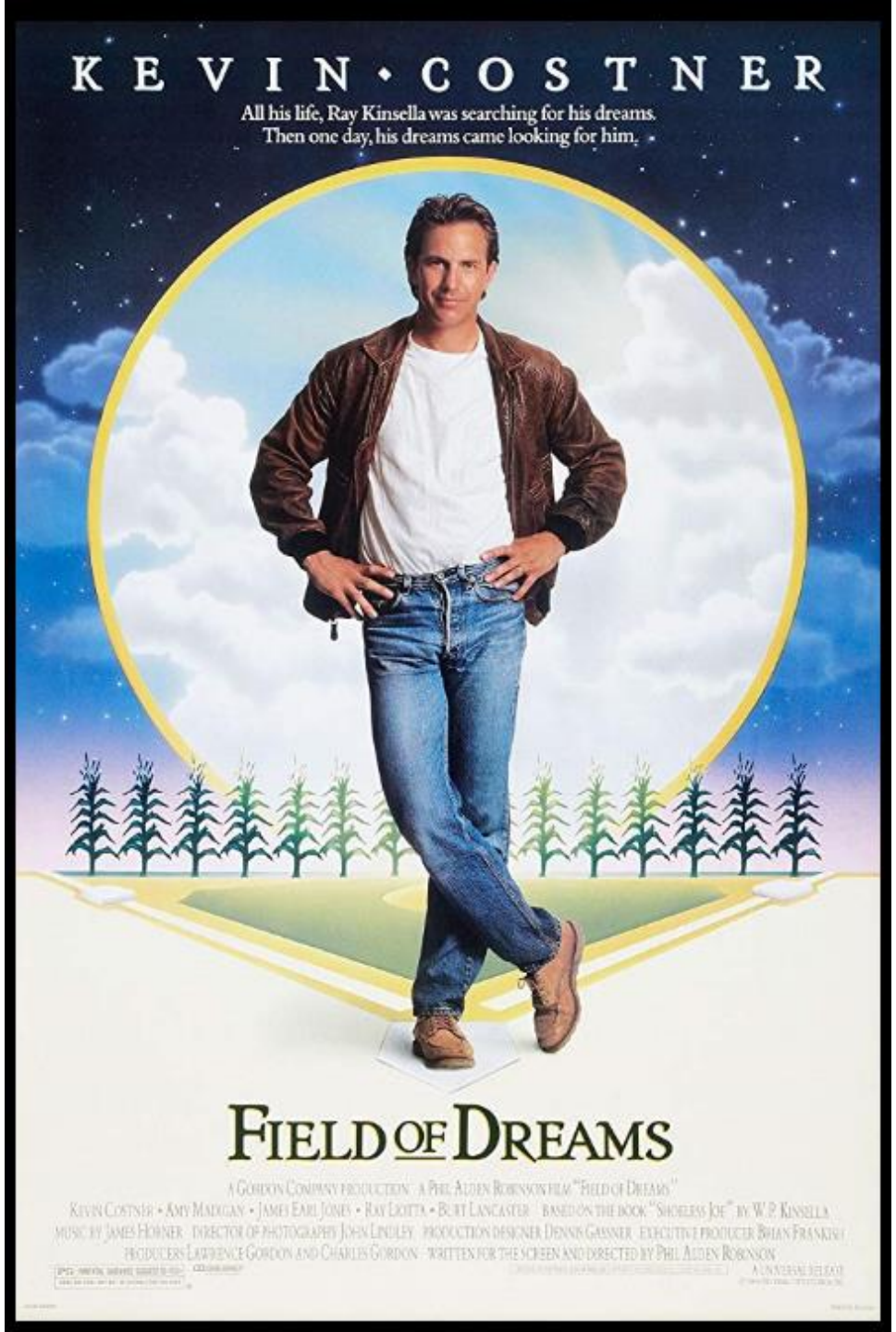
William Hausdorff, PhD

Lead, Public Health Vaccine Proposition

PATH, Washington DC

PDVAC, 18 May 2020

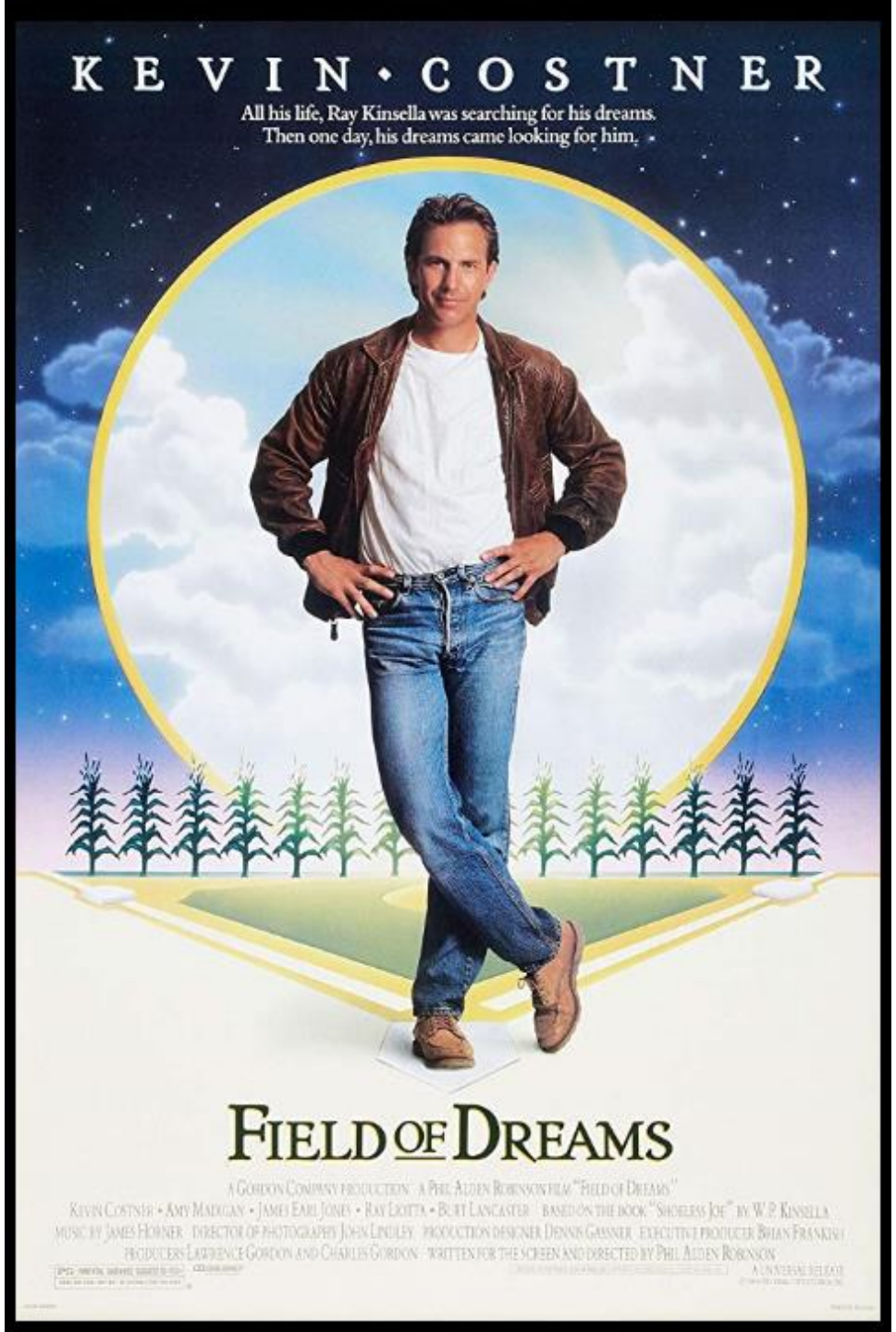
PATH



“Build it and they will come”

or, translated into vaccine-ese

“Develop a good vaccine against an important disease and they will use it”



"Build it and they will come"

or, translated into vaccine-ese

"Develop a good vaccine against an important disease and they will use it"

Except:

--**Typhoid conjugates**

- clinical efficacy established in 2001, 1st country introducing 2019

--**Malaria vaccine (RTS,S)**

- You know the story

--**HPV vaccines**

- Implementation lagging in too many countries

Plus:

--Other vaccine development efforts abandoned or proceeding at a glacial pace despite promising scientific results

Public health value proposition/Full Value of Vaccines Assessment

Critical, evidence-based analysis to ensure our efforts align with needs and capacity of intended beneficiaries

Influence vaccine design and inform planning for evidence generation during vaccine development

↓

Help estimate likely demand for the vaccine

↓

Facilitate policy recommendations and successful vaccine adoption & introduction

PATH

Illustrative elements of this critical, evidence-based analysis

- Target population and feasibility of delivery
  - Who, exactly, is the vaccine for? Is it feasible to deliver it to that target group?
- Disease target: the Need
  - What, exactly, are you trying to prevent, and why? How effective does the vaccine have to be? What is the benefit to the overall population?
- Competitive context
  - Based on a critical analysis of other options and interventions, would the vaccine be a preferred, cost-effective solution?
- Perspectives of national and local stakeholders
  - They are the ones who would have to prioritize and use their own resources to adopt and introduce
- Demand
  - Credible demand forecasts
- Truly critical information gaps and unknowns
  - What do we still need to know to decide whether there is a compelling value proposition for this vaccine?
  - No “nice-to-haves,” please.

Shigella vaccine candidates are entering advanced clinical stages but…

- **Perception of disease burden changing**
- **Cost-effectiveness changing**
- **National policy maker/end user perceptions unknown**

What would be the likely demand for an effective Shigella vaccine?

These raise a number of questions (illustrative)

Is role of Shigella sufficiently convincing?

- **Perception of disease burden changing**
  - Less mortality, more watery diarrhea, stunting, antibiotic resistance, older age groups…
- **Cost-effectiveness changing**
- **National policy maker/end user perceptions unknown**

These raise a number of questions (illustrative)

Is this of sufficient magnitude to "move the dial" on a Shigella vaccine?

- **Perception of disease burden changing**
  - Less mortality, more watery diarrhea, stunting, antibiotic resistance, older age groups…
- **Cost-effectiveness changing**
- **National policy maker/end user perceptions unknown**

- **Perception of disease burden changing**
- **Cost-effectiveness changing**
  - Need to reevaluate with revisited disease burden
  - National vs sub-national programs
  - Macroeconomic assessment needed to handle stunting
- **National policy maker/end user perceptions unknown**

How would these change CE?

- **Perception of disease burden changing**
- **Cost-effectiveness changing**
  - Need to reevaluate with revisited disease burden
  - National vs sub-national programs
  - Macroeconomic assessment needed to handle stunting
- **National policy maker/end user perceptions unknown**

Is this sufficiently robust and important to be a game changer?

- Perception of disease burden changing
- Cost-effectiveness changing
- **National policy maker/end user perceptions unknown** → *Why don't we ask them?*
  - Especially in light of increasingly crowded EPI schedule and vaccine costs

Shigella vaccine demand

- **Perception of disease burden changing**
- **Cost-effectiveness changing**
- **National policy maker/end user perceptions unknown**

What would be the likely demand for an effective Shigella vaccine?

- How effective, and against what endpoint, does it have to be?
- Demand for standalone vs a combination: lessons from Hib and HepB experiences?

Why consider Shigella combinations now?

- At present, not obvious a Shigella standalone would be a high priority
- A combination would likely optimize cost-effectiveness, avoid additional injections, minimize incremental costs, and could have positive effects on uptake of both antigens
- Late stage development or licensed candidates already exist:
  - Typhoid conjugates
  - Cholera vaccines
  - Non-replicating rotavirus vaccines (?)
- Could convince developers to alter development strategies to accommodate combination

Goal of a Shigella FVVA

Assess—and possibly enhance--the probability that a safe and effective Shigella vaccine would be developed, widely recommended, produced and adopted

What has changed in our perception of *Shigella* burden in the last decade?

Karen L. Kotloff, MD

2020 WHO Product Development for Vaccines Advisory Committee (PDVAC) Virtual Consultation: Full Value of Vaccine Assessment (FVVA) for *Shigella* vaccines

18 May 2020

UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE
CENTER FOR VACCINE DEVELOPMENT AND GLOBAL HEALTH

CVD·GH
CENTER FOR VACCINE DEVELOPMENT AND GLOBAL HEALTH

What we need to know (1)

- Disease burden
  - Global incidence and mortality
  - Target population (age, SES), benefits and expectations for herd protection
  - Universal coverage in LMIC versus high risk populations
  - Given antigenic heterogeneity, how much shigellosis is preventable
- Disease manifestations that should be prevented
  - All Shigella-associated acute watery diarrhea and dysentery
  - Sought health-care
  - Moderate-to-severe disease – how should this be defined
  - Asymptomatic disease
    - Must a vaccine induce sterile immunity to interrupt transmission of this human-specific pathogen
    - Is asymptomatic infection clinically significant

What we need to know (2)

- Potential Secondary and Indirect effects
  - Nutritional faltering, especially stunting – how much stunting could be prevented/ameliorated
  - EED
  - Acute and subacute mortality
  - Cost benefit – is there a dual market (military, travelers, high risk groups)
  - Antimicrobial resistance
    - If dysentery decreases, will antibiotic use for diarrheal diseases do the same?
    - Induction and broad transmission of highly AMR strains could render a growing proportion of *Shigella* infections untreatable
  - Hospitalization
  - Outbreak control, pandemic control
- What does a *Shigella* vaccine look like? Multivalent? Cost? Cold chain? Opportunity?
- What do policy-makers need to know and what is the clearest evidence to inform them
  - Acute disease burden
  - Cost
  - Equity
  - Is *Shigella* an important component of the causal chain that leads to stunting, other infection, mortality
  - AMR

Disease Burden: *Shigella*-specific Morbidity

Shigella morbidity

- Global incidence <5 years is 11.6/100 c-y (95% CI 6.4-19.9)

(Khalil I. *Lancet Infect Dis* 2018; 18: 1229–40)

Study Sites: GEMS, GEMS 1A, and VIDA

Case-control, population-based studies to measure the incidence, etiology, and adverse clinical outcomes of diarrheal illness among children <5 years of age living in developing countries with moderate-high under 5 mortality before (GEMS, GEMS 1A) and after (VIDA) rotavirus vaccine introduction

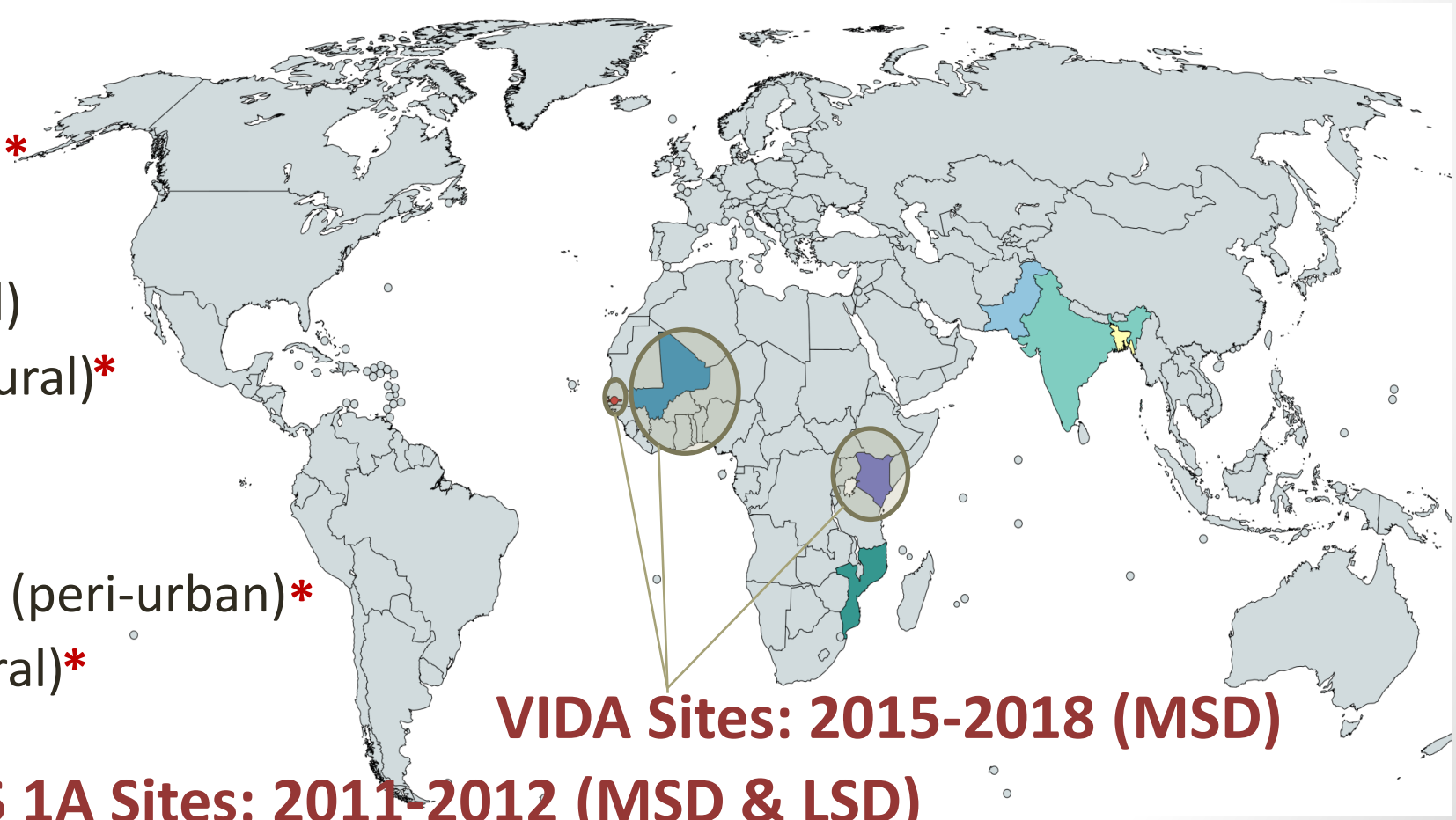
GEMS: 2008-2010 (MSD)

Africa:

- Basse, The Gambia (rural)*
- Bamako, Mali (urban)*
- Siaya County, Kenya (rural)
- Manhiça, Mozambique (rural)*

Asia:

- Bin Qasim Town, Pakistan (peri-urban)*
- Mirzapur, Bangladesh (rural)*
- Kolkata, India (urban)*

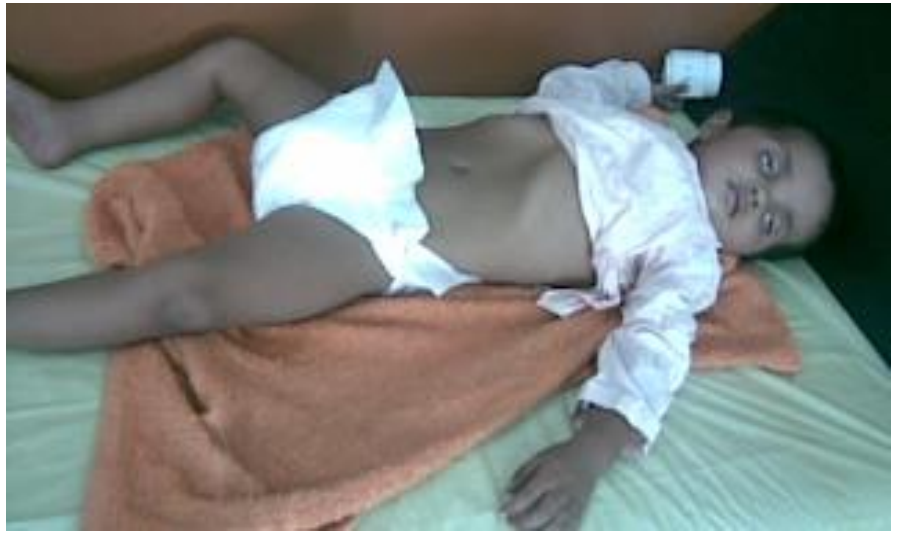


VIDA Sites: 2015-2018 (MSD)

***GEMS 1A Sites: 2011-2012 (MSD & LSD)**

Methods: GEMS, GEMS 1A, and VIDA

- GEMS: MSD: Eligible cases sought healthcare with new onset, acute diarrhea with at least one of the following signs (7 sites):
  - Sunken eyes
  - Loss of skin turgor
  - IV rehydration
  - History of bloody diarrhea
  - Hospitalization (Actual or recommended)

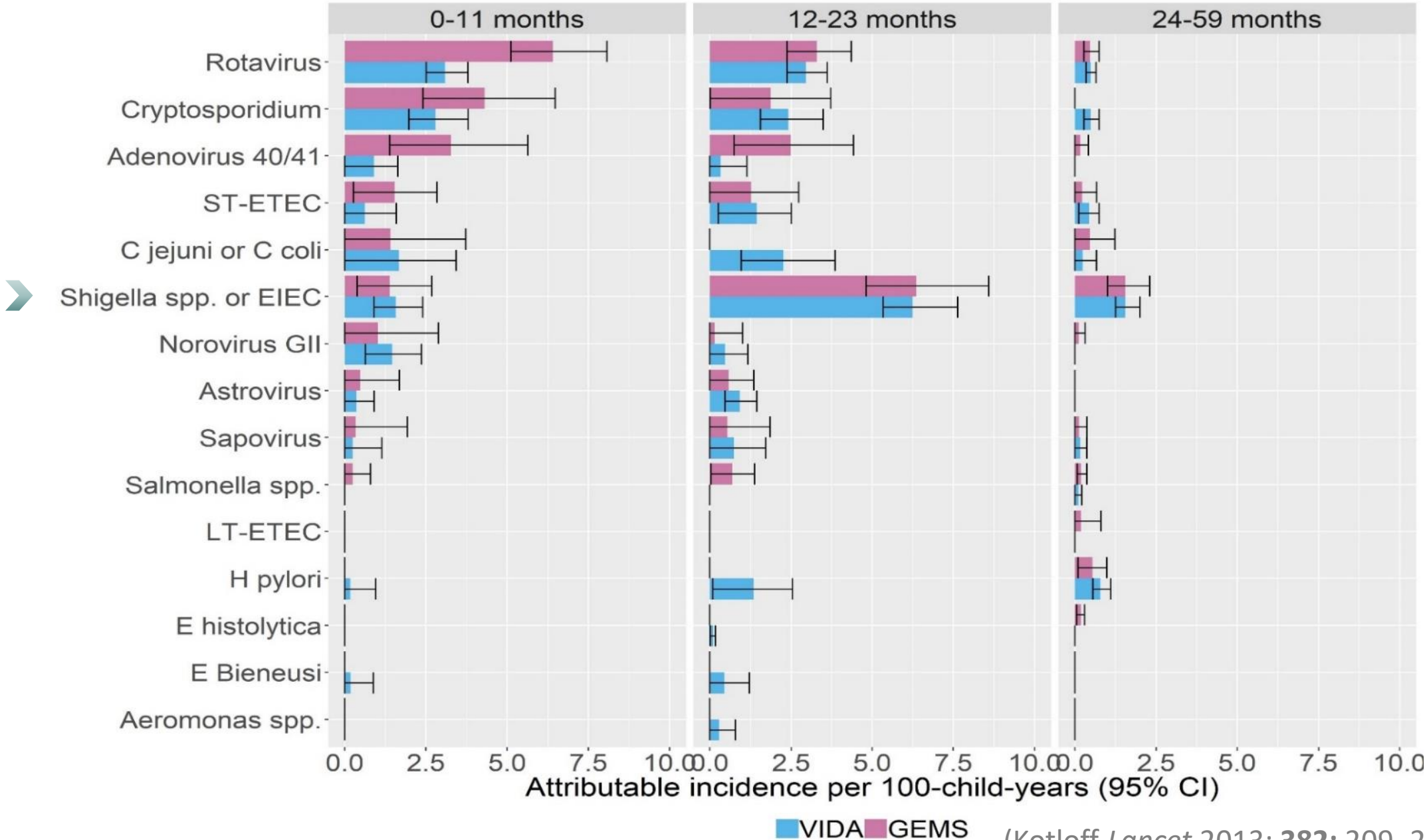


- GEMS 1A: LSD: Eligible cases sought healthcare with new onset, acute diarrhea without any of the MSD signs

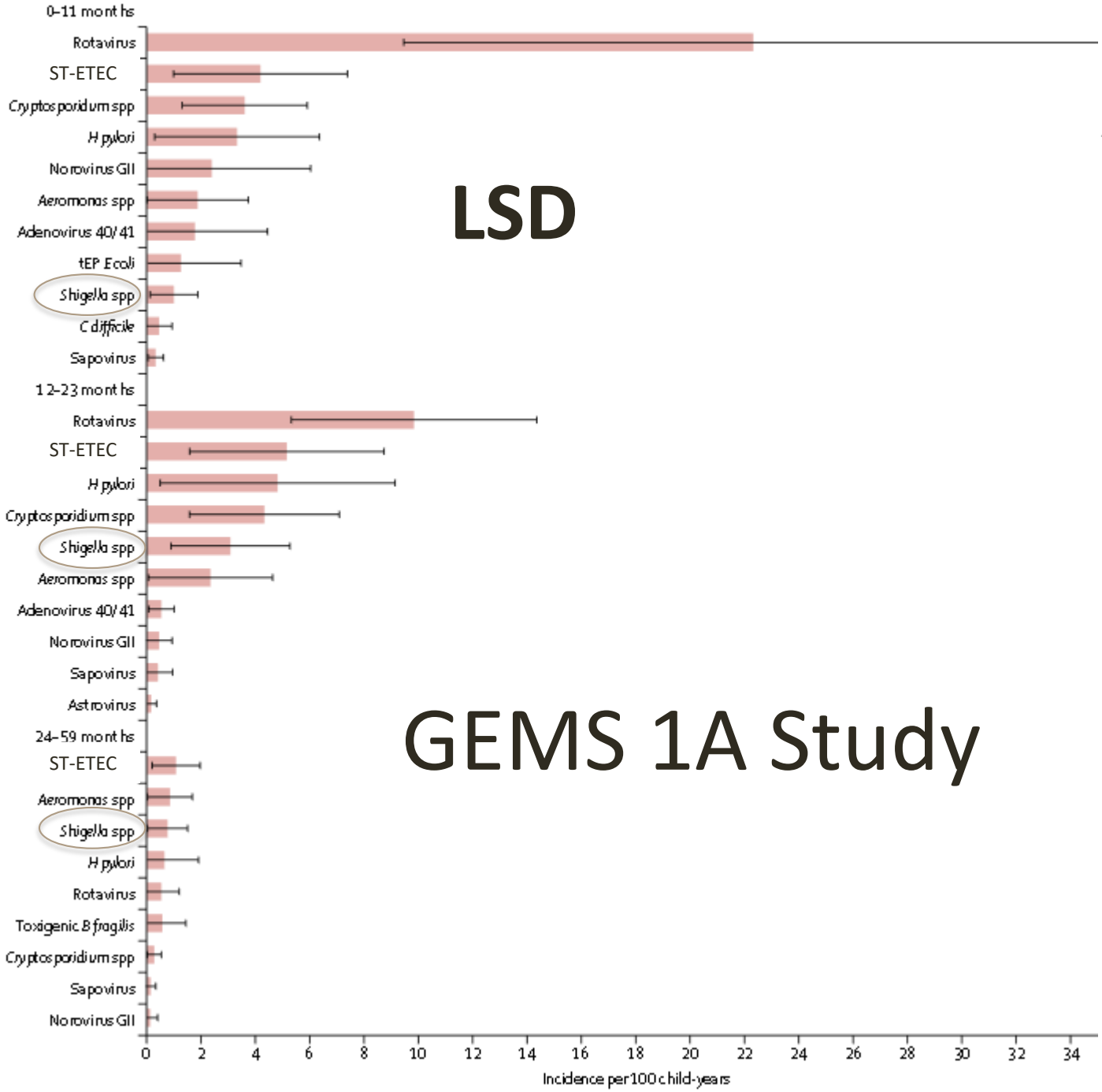
- VIDA: MSD at 3 GEMS sites in Africa that introduced rotavirus vaccine

(Kotloff *Lancet* 2013; **382:** 209–22); Kotloff *Lancet Glob Health* 2019;7:e568-84; Kotloff unpublished

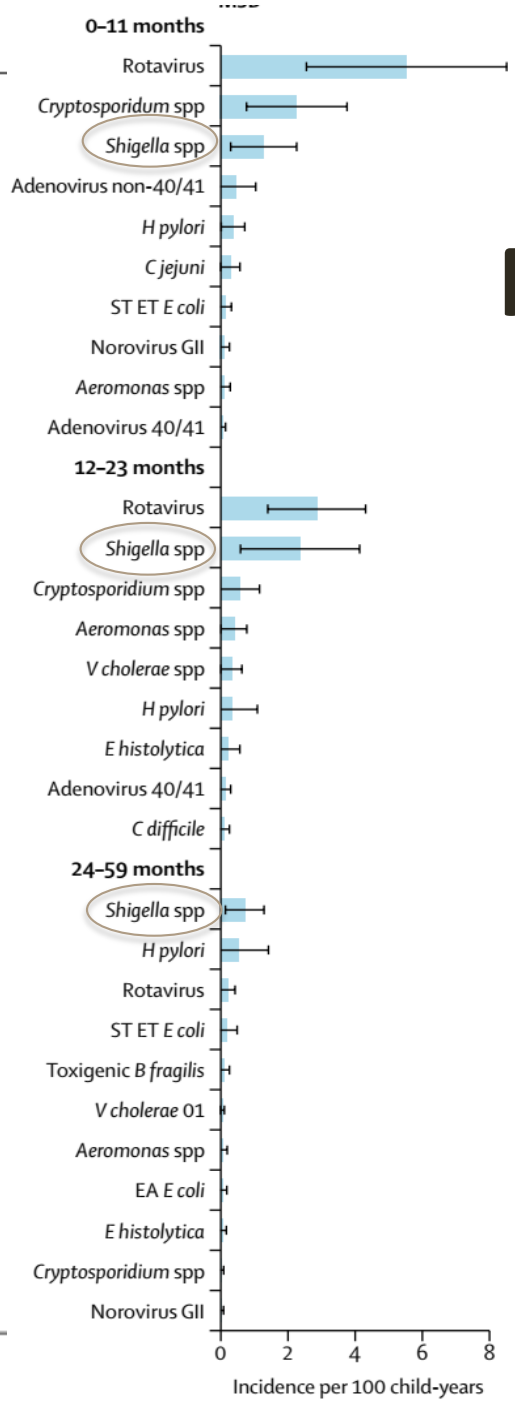
Attributable incidence (qPCR) by age (All sites): GEMS vs VIDA



(Kotloff *Lancet* 2013; **382:** 209–22; unpublished)



LSD

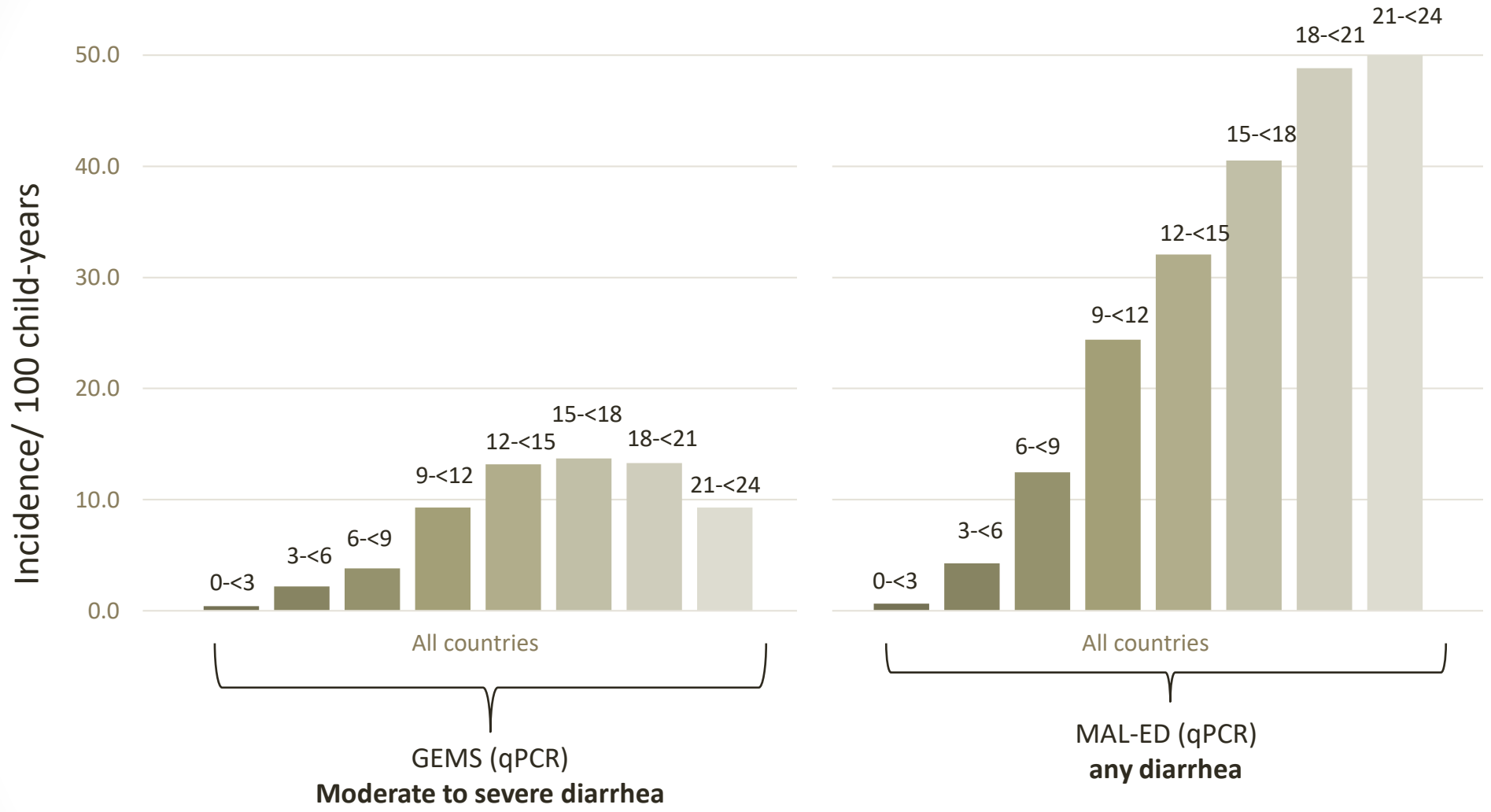


MSD

GEMS 1A Study

(Kotloff *Lancet GH* 2019)

Shigella- attributable diarrhea **incidence** in under 2's



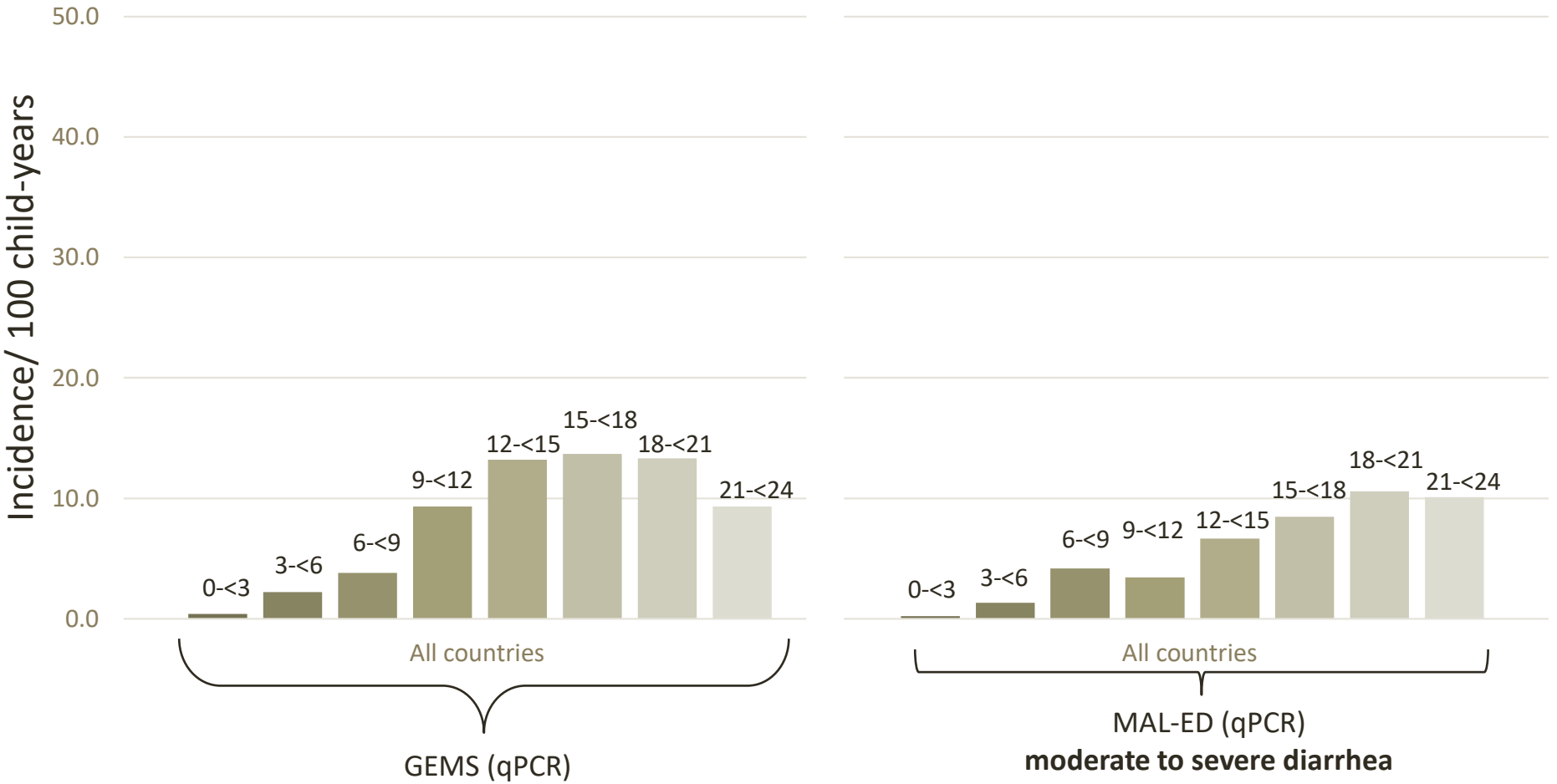
GEMS
Bangladesh
Gambia
India
Kenya
Mali
Mozambique
Pakistan

MAL-ED
Bangladesh
Brazil
India
Nepal
Peru
Pakistan
South Africa
Tanzania

Kotloff, unpublished

Platts-Mills, unpublished

Shigella- attributable diarrhea (MSD and all diarrhea) incidence in under 2's



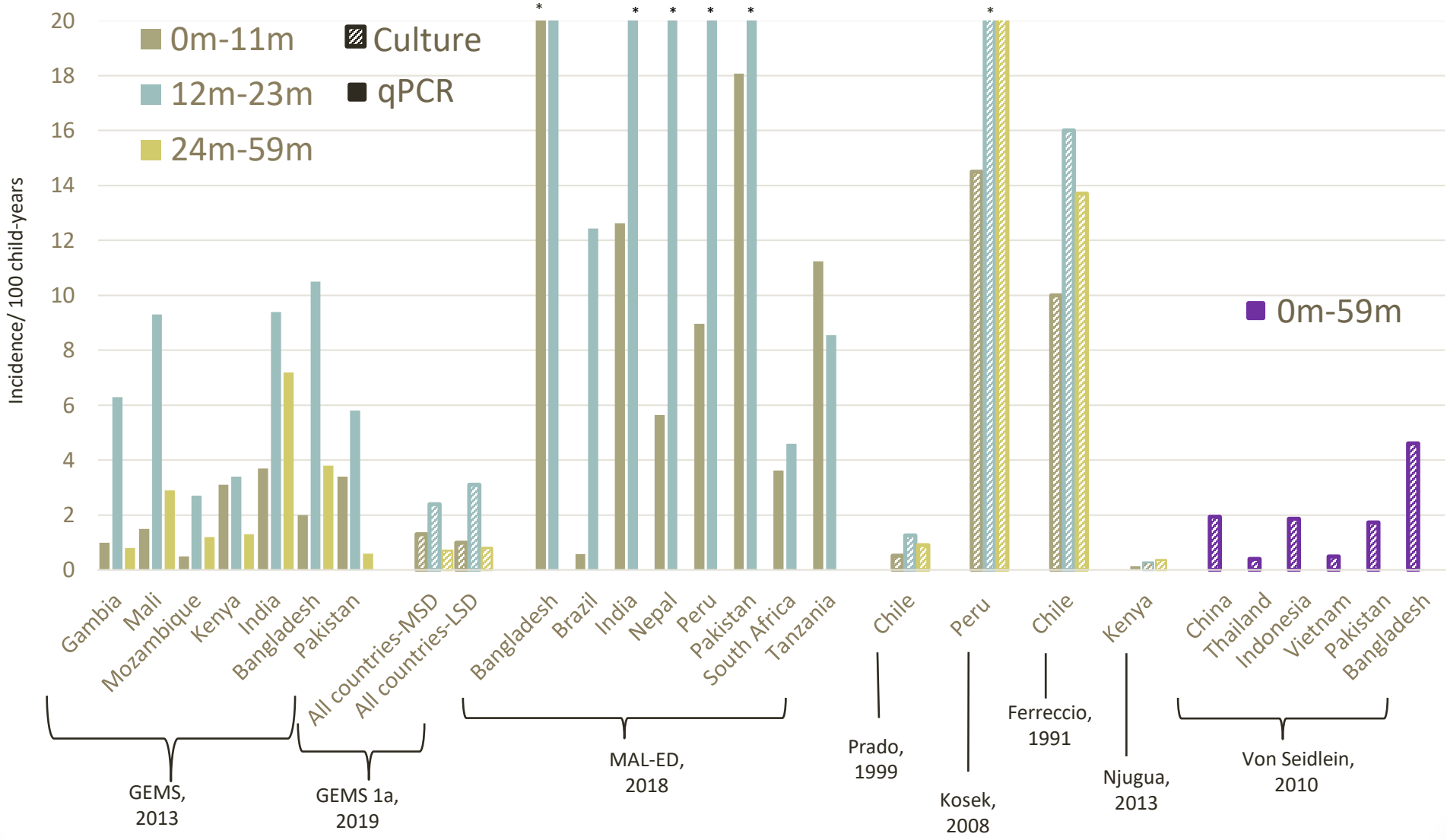
GEMS
Bangladesh
Gambia
India
Kenya
Mali
Mozambique
Pakistan

MAL-ED
Bangladesh
Brazil
India
Nepal
Peru
Pakistan
South Africa
Tanzania

Kotloff, unpublished

Platts-Mills, unpublished

Shigella diarrhea incidence in under 5's



*estimates >20 episodes/100 Child-Years

ABCD Trial Network

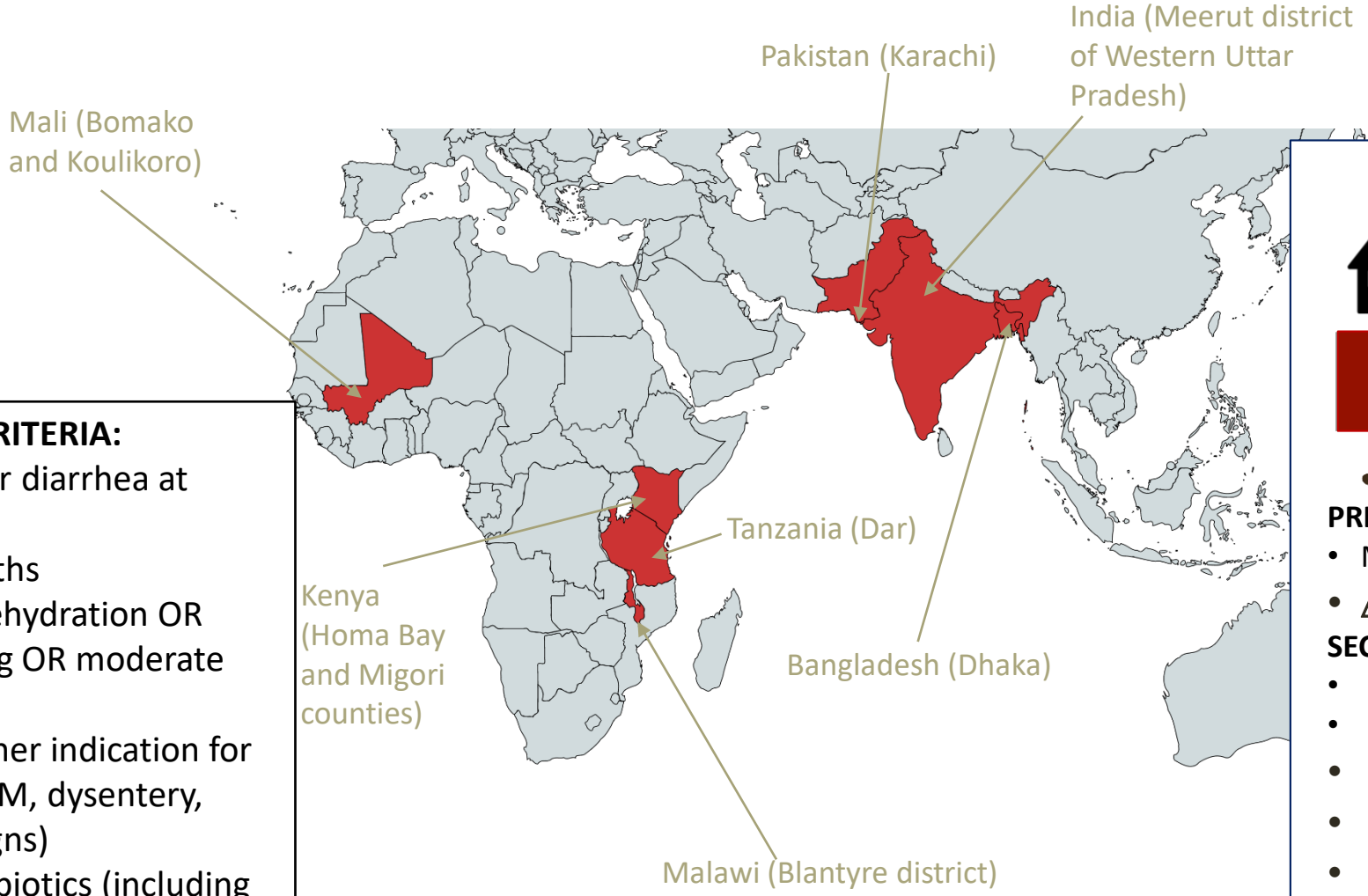
The ABCD study team *Trials* (2020) 21:71
https://doi.org/10.1186/s13063-019-3829-y

Trials

STUDY PROTOCOL Open Access

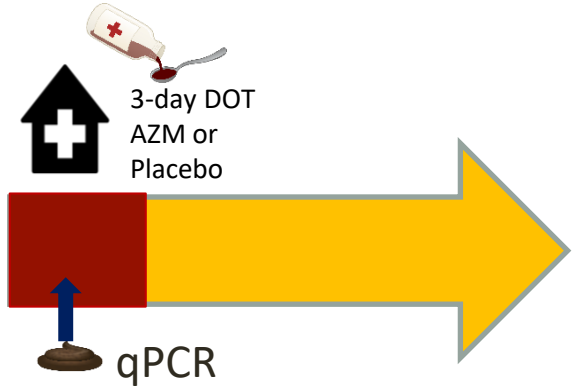
A double-blind placebo-controlled trial of azithromycin to reduce mortality and improve growth in high-risk young children with non-bloody diarrhoea in low resource settings: the Antibiotics for Children with Diarrhoea (ABCD) trial protocol

The ABCD study team



ENROLLMENT CRITERIA:

- Sought care for diarrhea at health facility
- Age 2-23 months
- AND one of dehydration OR severe stunting OR moderate malnutrition
- Absence of other indication for antibiotics (SAM, dysentery, pneumonia signs)
- No use of antibiotics (including metronidazole) in last 14-days



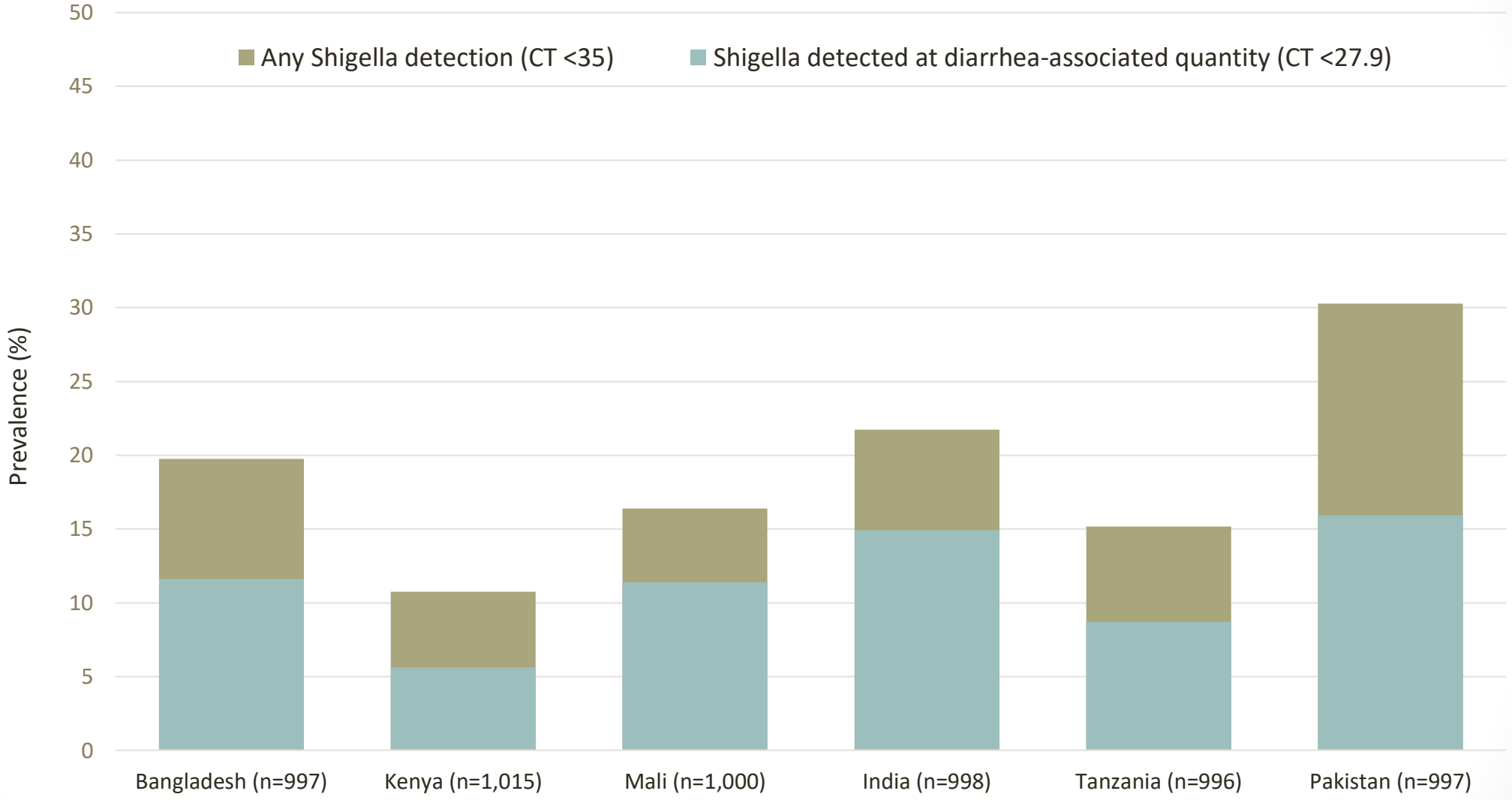
PRIMARY OUTCOMES:

- Mortality
- Δ Length-for-age z-score (LAZ)

SECONDARY OUTCOMES:

- Hospitalization
- Day 2/3 diarrhea
- Δ MUAC
- Δ WHZ
- Δ WAZ
- AMR in *E.coli* & *S. pneumoniae*

Preliminary* prevalence of *Shigella* detection of children enrolled in ABCD

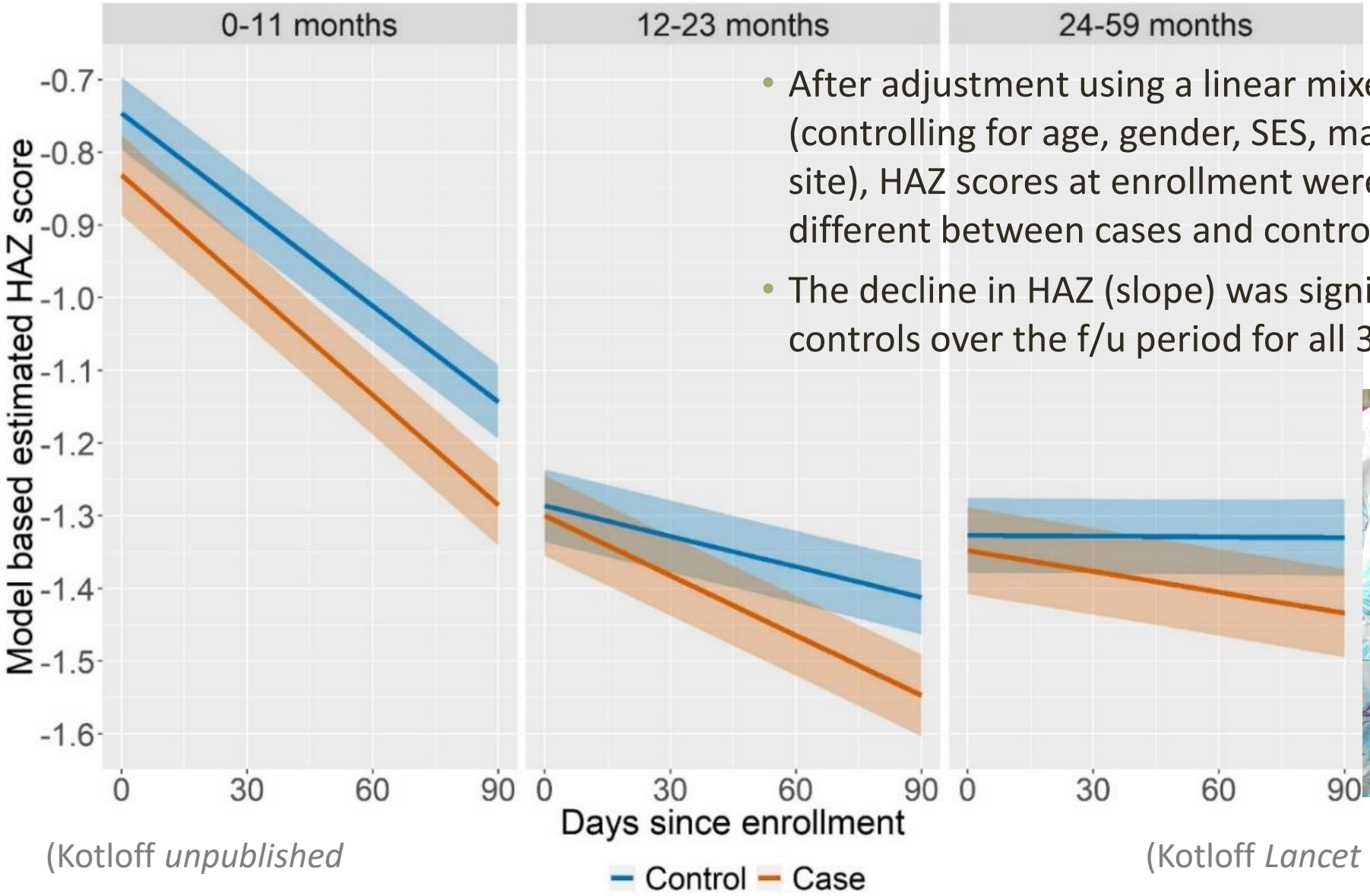


ABCD study team, unpublished

*To be eventually presented as attributable fractions (with confidence intervals) borrowing control information from GEMS & MAL-ED. Malawi data is forthcoming.

Disease Burden: Long term outcomes: All MSD and LSD, and Shigella-specific MSD

Height for age (HAZ)-scores at enrollment and follow-up for MSD cases & controls (VIDA)



- After adjustment using a linear mixed effects model (controlling for age, gender, SES, maternal education, and site), HAZ scores at enrollment were not significantly different between cases and controls.
- The decline in HAZ (slope) was significantly greater in cases vs controls over the f/u period for all 3 age groups ($p \leq 0.003$).

(Kotloff *unpublished*

(Kotloff *Lancet* 2013; **382:** 209–22; unpublished)

Diarrheal episodes may increase risk of ALRI

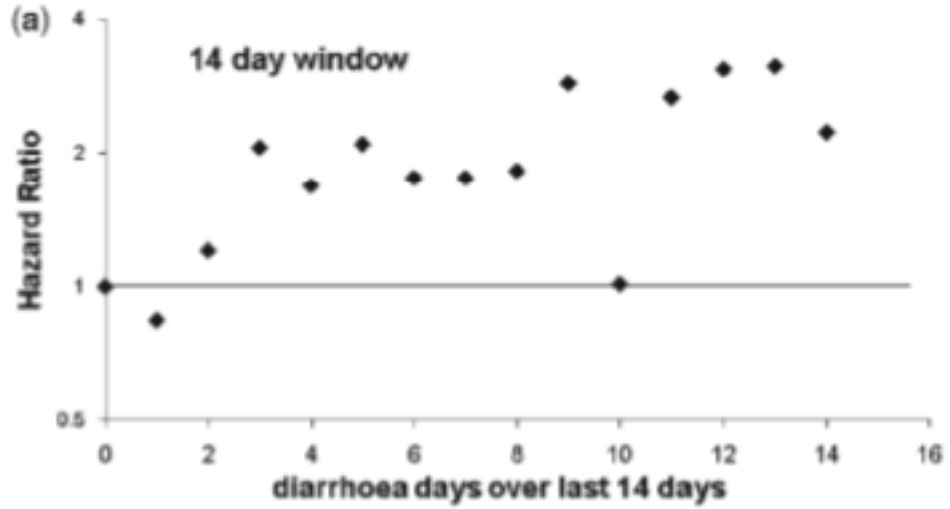


Figure 3 The risk of ALRI in Ghana depending on the number of diarrhoea days during (**a**) the last 14 and (**b**) the last 28 days prior to the index day (time window closest to the index day). To avoid convergence problems, the number of diarrhoea days during the 28-day window was collapsed into groups of four

Estimate 26% of ALRI cases in Ghana may be due to diarrhea in previous 2 weeks

Schmidt, 2008, IJE

Comparison of enrollment HAZ and ΔHAZ between LSD cases and their controls

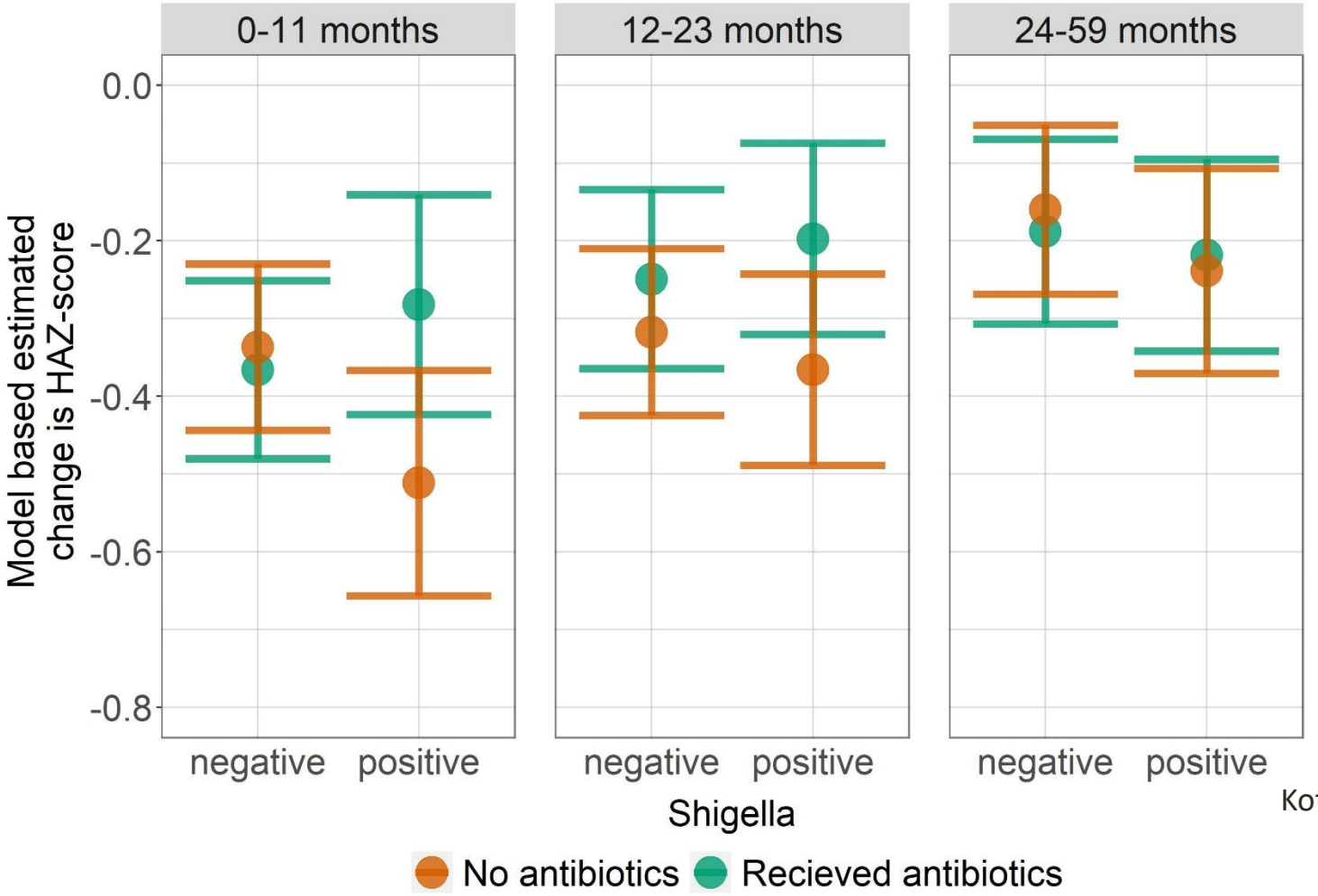
	0–11 months		12–23 months		24–59 months	
	Weighted mean (95% CI)	p value	Weighted mean (95% CI)	p value	Weighted mean (95% CI)	p value
(Continued from previous page)						
All sites combined						
Number of participants	1070 patients; 1268 controls	..	982 patients; 1275 controls	..	755 patients; 1142 controls	..
Enrolment HAZ						
Patients	−0·98 (−1·07 to −0·88)	0·70	−1·47 (−1·58 to −1·37)	0·96	−1·79 (−1·94 to −1·64)	0·87
Controls	−0·95 (−1·04 to −0·85)	..	−1·55 (−1·63 to −1·47)	..	−1·88 (−1·98 to −1·77)	..
ΔHAZ						
Patients	−0·16 (−0·21 to −0·12)	0·23	−0·18 (−0·21 to −0·15)	0·0040	−0·04 (−0·07 to −0·01)	<0·0001
Controls	−0·18 (−0·22 to −0·14)	..	−0·11 (−0·14 to −0·09)	..	0·03 (0·01 to 0·55)	..

Enrolment HAZ in patients versus controls was compared by weighted paired *t* test; ΔHAZ in patients versus controls was compared by weighted linear regression, adjusting for enrolment HAZ and duration to follow-up. HAZ=length-for-age or height-for-age Z score. ΔHAZ=change in HAZ (ie, HAZ at follow-up visit [50–90 days after enrolment] minus HAZ at enrolment).

Kotloff LGH 2019

40

Effect WHO-recommended antibiotics for dysentery at enrollment on change in HAZ between enrollment and follow-up in *Shigella* positive vs *Shigella* negative MSD



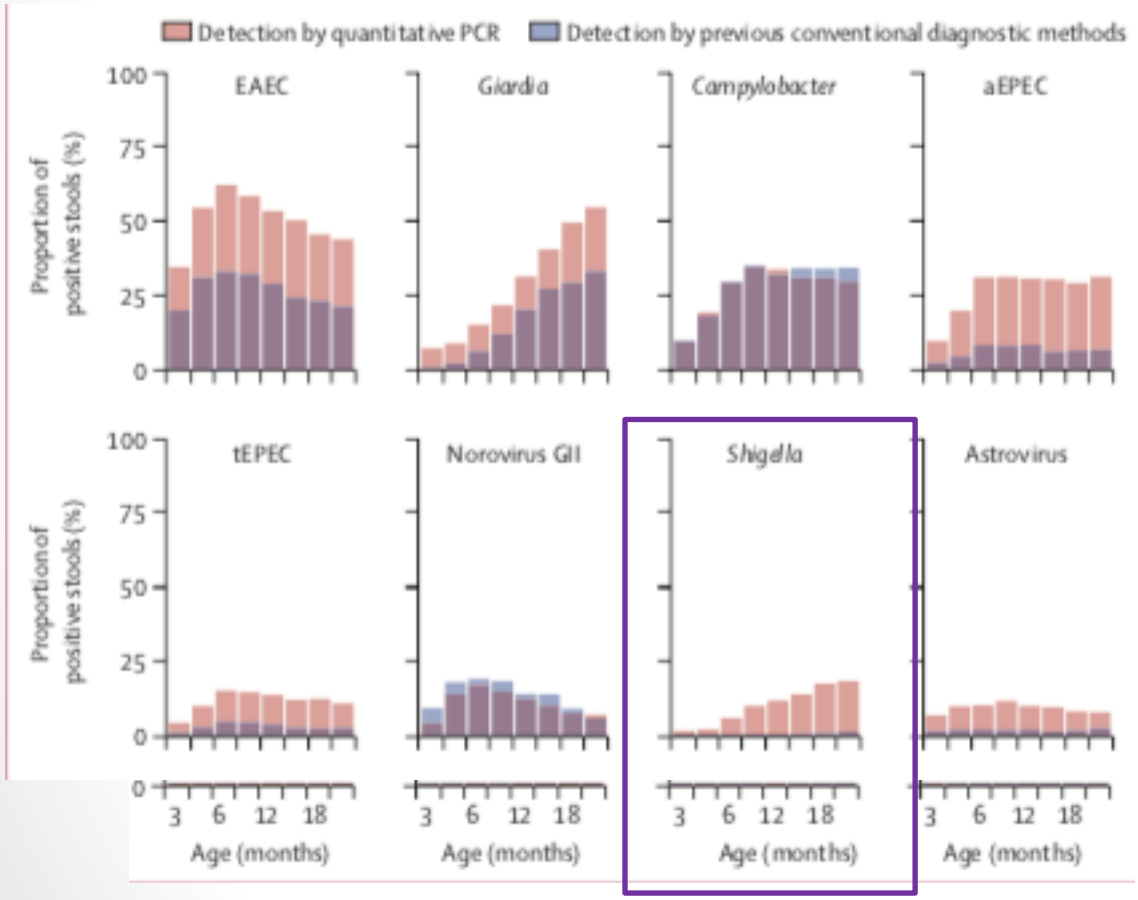
2-way interaction: abx by *Shigella (*p-value <0.001)

3-way interaction: abx by *Shigella* by age (p-value =0.06)

Kotloff, unpublished

*model adjusted for baseline HAZ, duration to follow up, gender, site, caretaker had at least primary school education, Household used clean cooking fuels, Household has at least 3 working assets, household has access to improved water, household has access to improved sanitation, household had a finished floor, household was crowded (> 3 people per sleeping room), caretaker cared for >2 children under the age of 5, other pathogens – ST only ETEC, LT only ETEC, EAEC, tE

Shigella associated with linear growth shortfalls even in the absence of diarrhea



Rogawski, Lancet GH, 2018

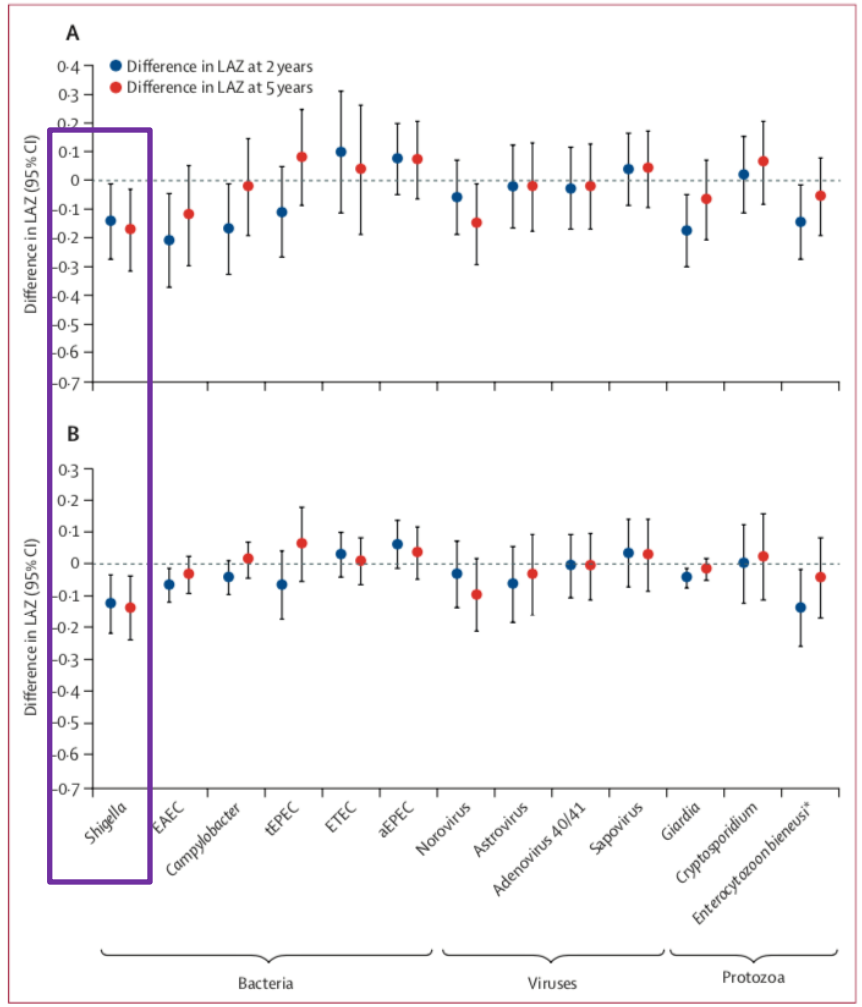


Figure 4: **Effect of specific enteropathogen infections on height attainment at age 2 and 5 years**
Difference in LAZ according to high and low pathogen prevalence (A) and per one log increase in the mean quantity of pathogen per g of stool (B) in non-diarrhoeal stools. Data were available for 1469 children at 2 years and 1202 children at 5 years in the Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development cohort. Estimates were adjusted for site, enrolment LAZ, sex, SES, exclusive breastfeeding in the first 6 months, and maternal height. LAZ=length-for-age Z scores. EAEC=enteroaggregative *Escherichia coli*. tEPEC= typical enteropathogenic *E coli*. ETEC=enterotoxigenic *E coli*. aEPEC=atypical enteropathogenic *E coli*. **Enterocytozoon bieneusi* is an intracellular parasitic fungus.

Should microbiological protection be an endpoint?
-Shigella-

Efficacy (p value adjusted for multiple comparisons): Veterans vs naives:			
Any illness	**Fever**	**Diarrhea**	**Dysentery**
70% (0.003)	89% (0.0006)	89% (0.0006)	78% (0.003)

Microbiologic response to challenge according to prior experience with shigellosis			
Group	**No. (%) with + stool culture**	**Geometric mean peak excretion**	
Veterans	11/11 (100%)	1.1×10^6 cfu*	*P=0.04, Kruskal -Wallis
Naives	12/12 (100%)	1.4×10^7 cfu*	

Kotloff Vaccine 1995

Disease Burden: Mortality

Relationship between an episode of MSD and death

	GEMS			VIDA		
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
The Gambia	3.8%	0.6%	7.5 (3-7.5)	1.0%	0.05%	20.6 (2.7-155.8)
Mali	1.1%	0.2%	4.3 (1.8-6.5)	0.4%	0.05%	7.4 (0.9-61.3)
Kenya	3.5%	0.5%	5.3 (2.8-10.7)	1.1%	0.05%	22.0 (2.9-165.9)
Total	2.5%	0.4%	**5.9 (3.7-9.22)**	0.8%	0.05%	**16.4 (5.1-53.2)**

GEMS: Conditional logistic regression using Firth's penalized likelihood.
VIDA: Generalized linear mixed effects model with logit link. Both applied separate analyses by site and then overall.

(Kotloff *Lancet* 2013; **382:** 209–22; unpublished)

Mortality of LSD and MSD for GEMS-1A

	MSD deaths	HR (95% CI)	LSD deaths	HR (95% CI)
Cases	23/2,212 (1.04%)	11.91* (3.5, 40.5)	12/2,962 (0.41%)	2.8 ** (0.95, 8.11)
Controls	3/3,433 (0.09%)		7/4,074 (0.17%)	

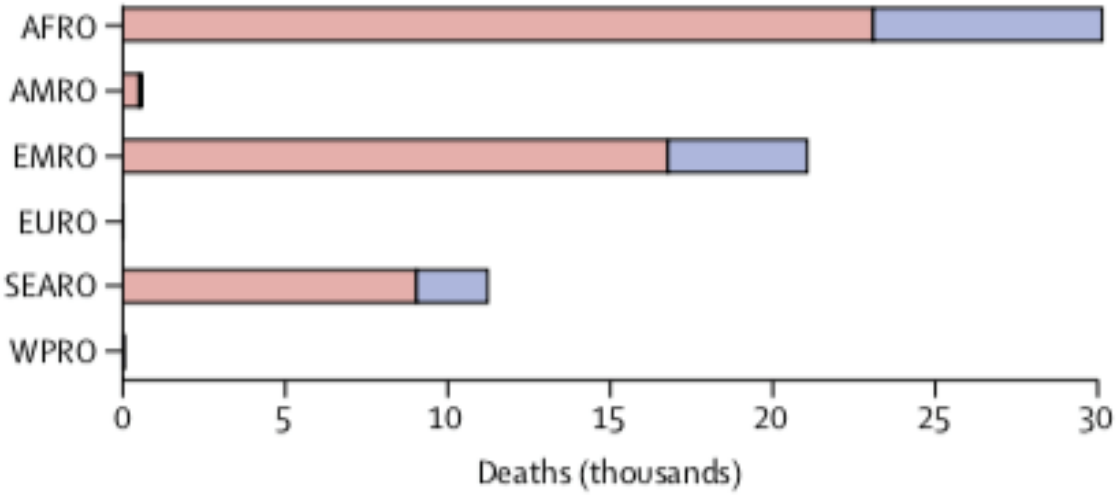
HR = Hazard ratio from a Cox regression which takes into consideration days from enrollment to death.

*Statistically significant (p-value < 0.05); **p=0.06

(Levine MM, *Lancet GH* 2020)

Shigella mortality

- 2nd leading cause of diarrhea-mortality (13.2% of diarrheal deaths (95% CI 9.2-17.4))
- >50,000 deaths in children under 5 each year
- **Indirectly** (via stunting) causes an additional ~13,000 deaths (28% increase over direct deaths)



igure 1: Mortality due to enterotoxigenic *Escherichia coli* (A) and shigella B) diarrhoea and other infectious diseases in children younger than 5 years, by WHO region

Anderson, Lancet GH, 2019

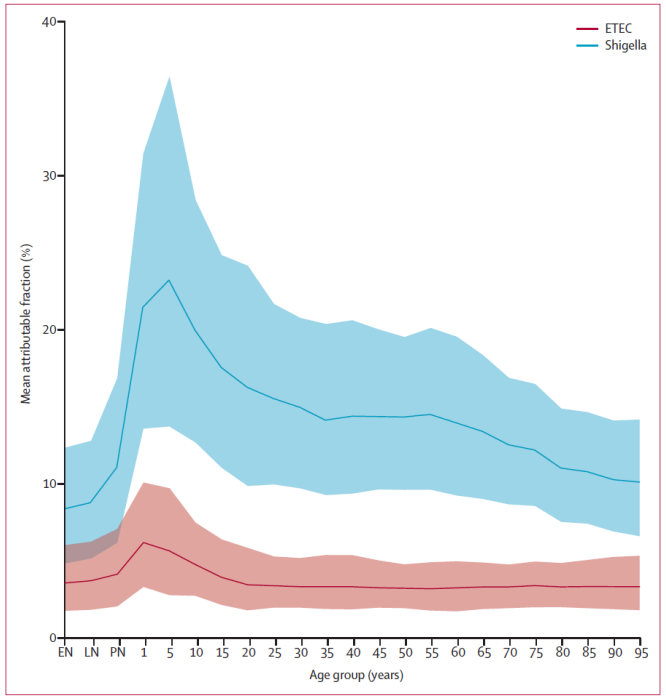
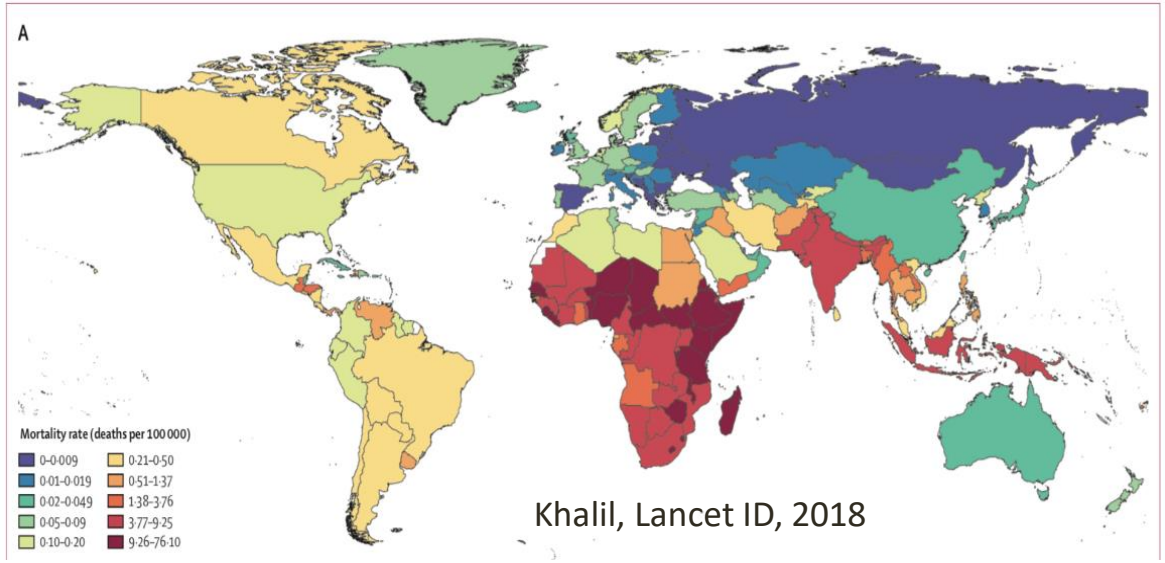


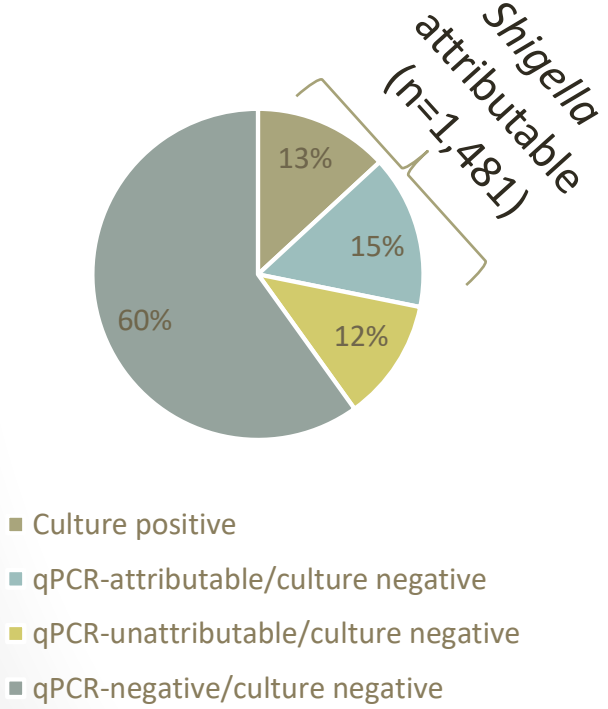
Figure 1: The age distribution of the population attributable fraction of diarrhoea mortality at the global level in 2016 for shigella and ETEC
The population attributable fraction represents the proportion of diarrhoea deaths that are due to each pathogen. Ribbons are 95% uncertainty intervals around the mean estimates. ETEC=enterotoxigenic *Escherichia coli*. EN=early neonatal. LN=late neonatal. PN=postnatal.

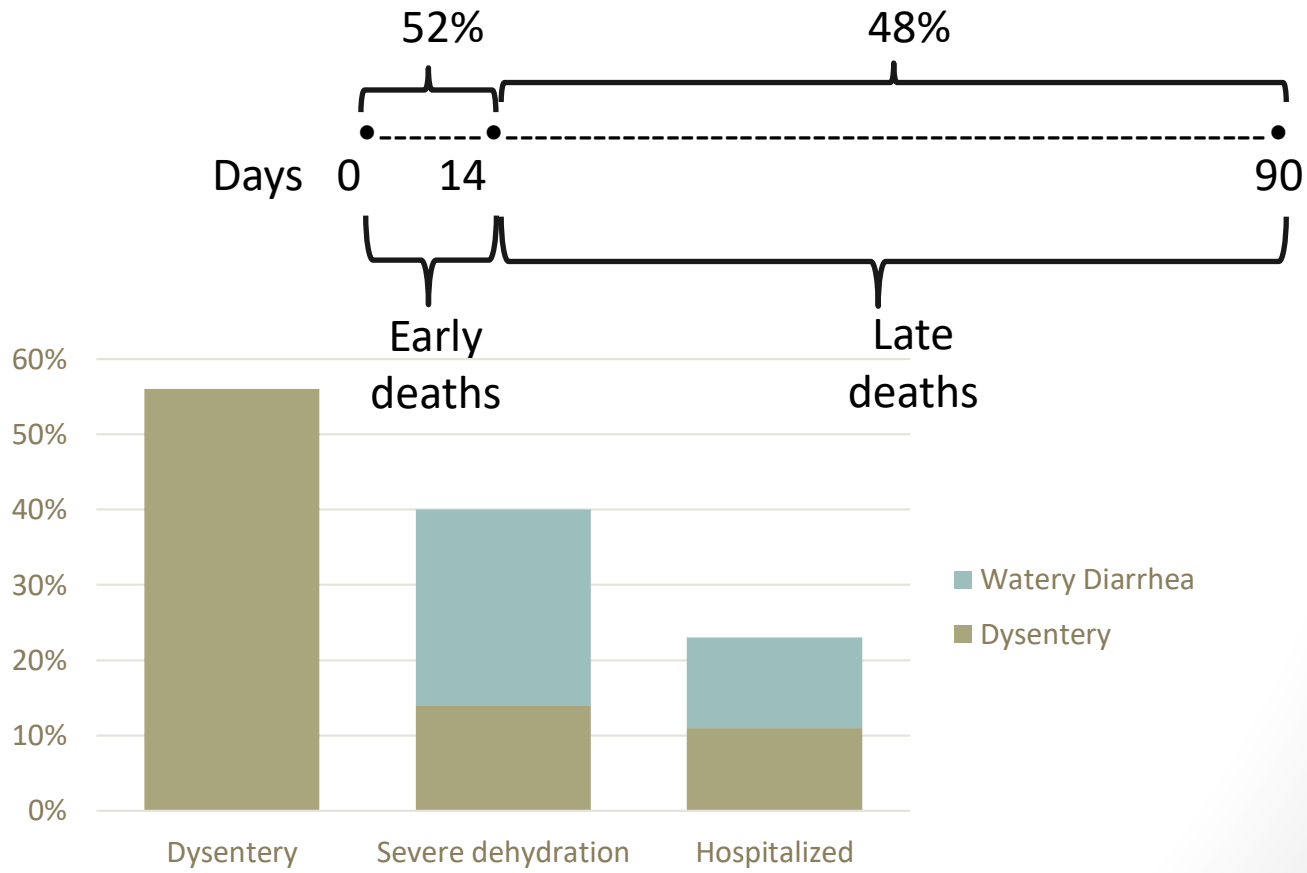


Khalil, Lancet ID, 2018

Clinical Findings and Death among *Shigella* MSD cases in GEMS

- 42/ 1481 (2.8%) *Shigella* cases died in 60-90 days (analysis limited to MSD cases whose stool sample underwent culture and qPCR testing)
  - 27/ 42 (64%) deaths in culture-negative/ qPCR-attributable *Shigella* cases

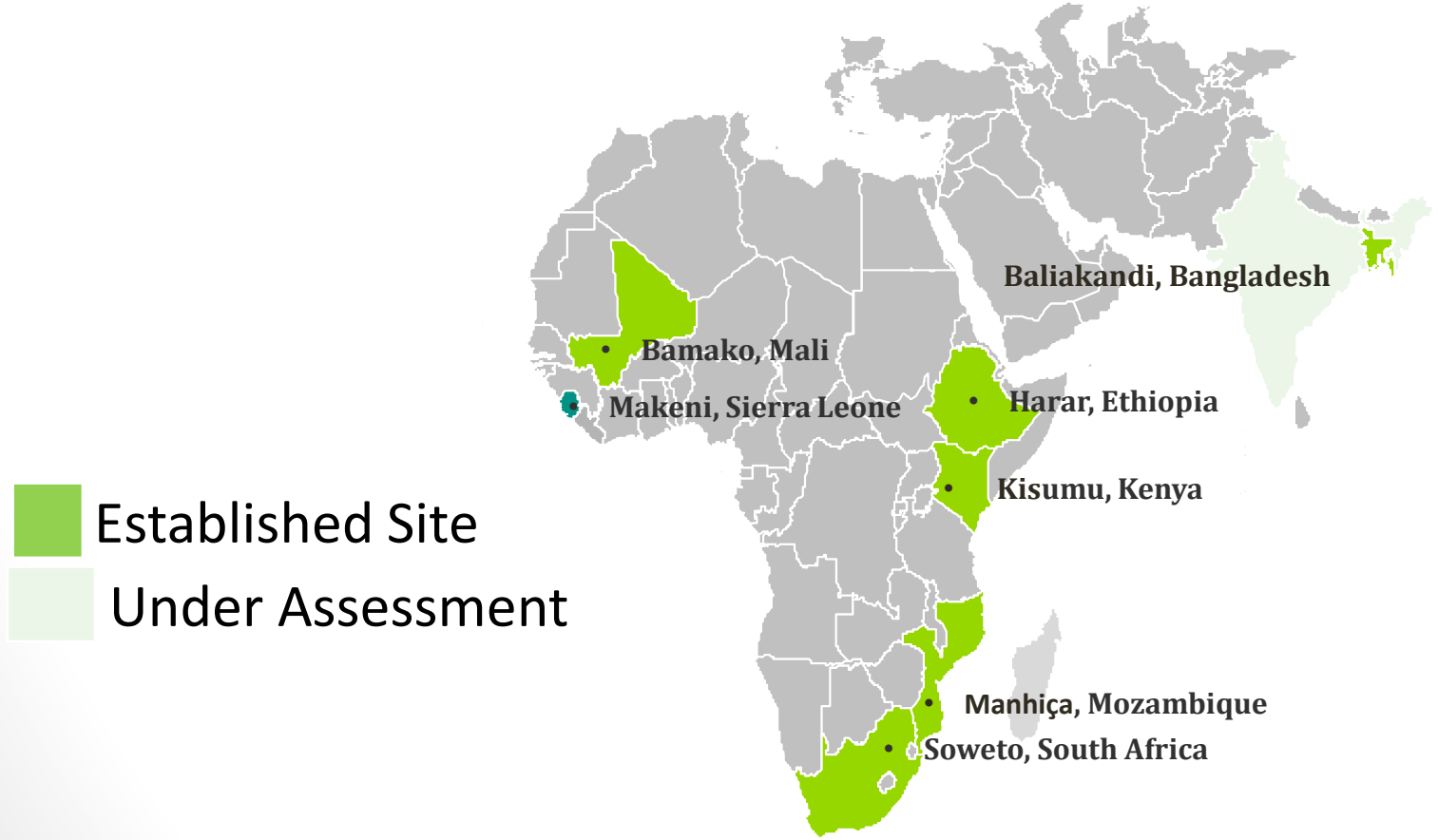




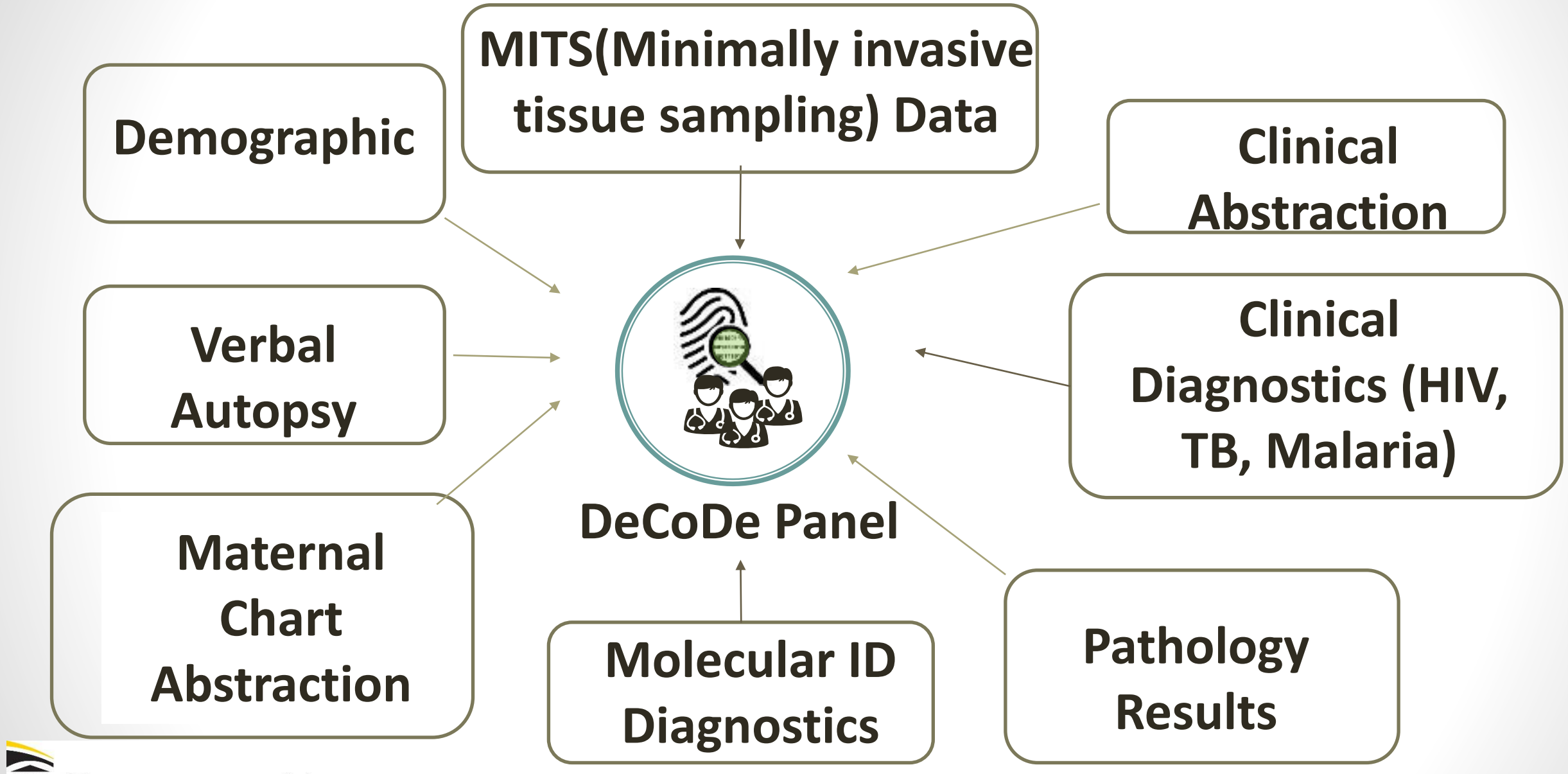
7/8/2020

Child Health and Mortality Prevention Surveillance (CHAMPS) Program Objectives

Focus: Identify the most-preventable causes of mortality among children under 5 years of age in high mortality countries of sub-Saharan Africa and South Asia to inform policy and public health action

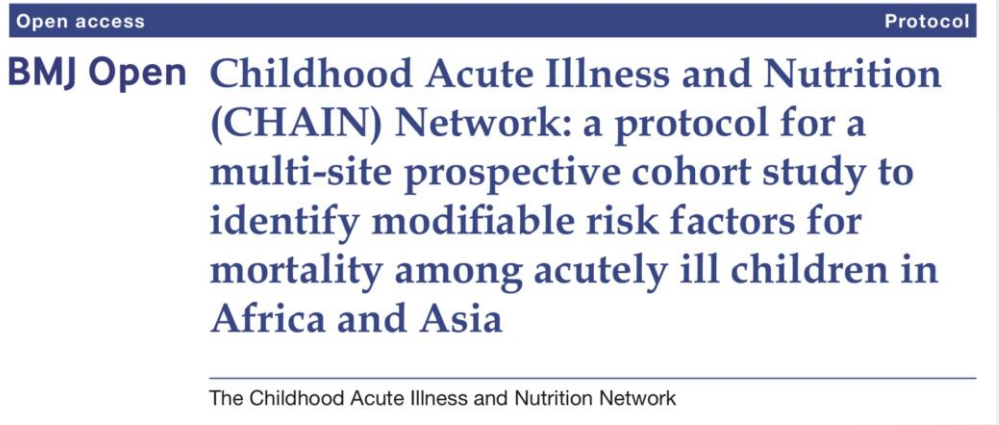


CHAMPS: Determination of the Cause of Death<5 y

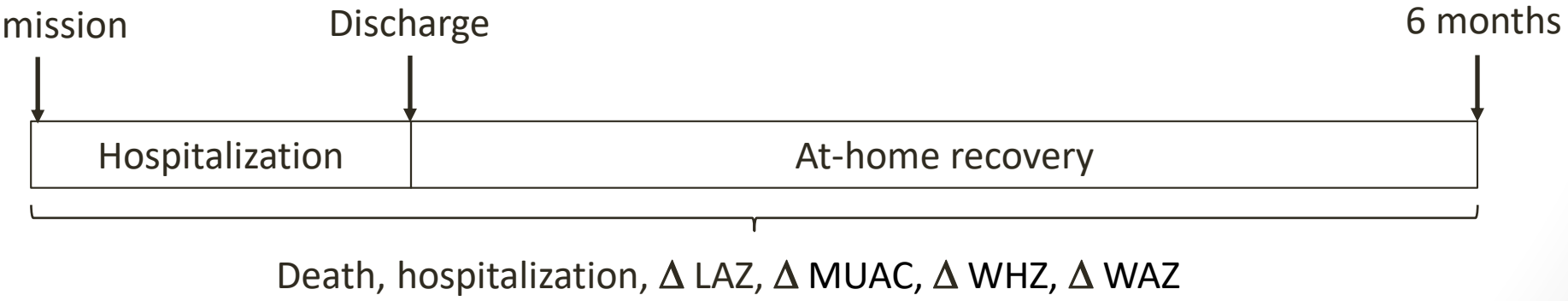


Upcoming data of *Shigella* outcomes- CHAIN

- **CHAIN**-Bangladesh, Burkina Faso, Kenya, Malawi, Pakistan, Uganda (PI's Jay Berkley and Judd Walson, BMGF-funded)
- ~3000 hospitalized children with oversampling of malnourished children (~1700 children admitted with diarrhea)
- High mortality rate (350 deaths [>10%]) in subsequent 6 months
- qPCR testing of stool at admission and discharge and culture + AST in subset of participants

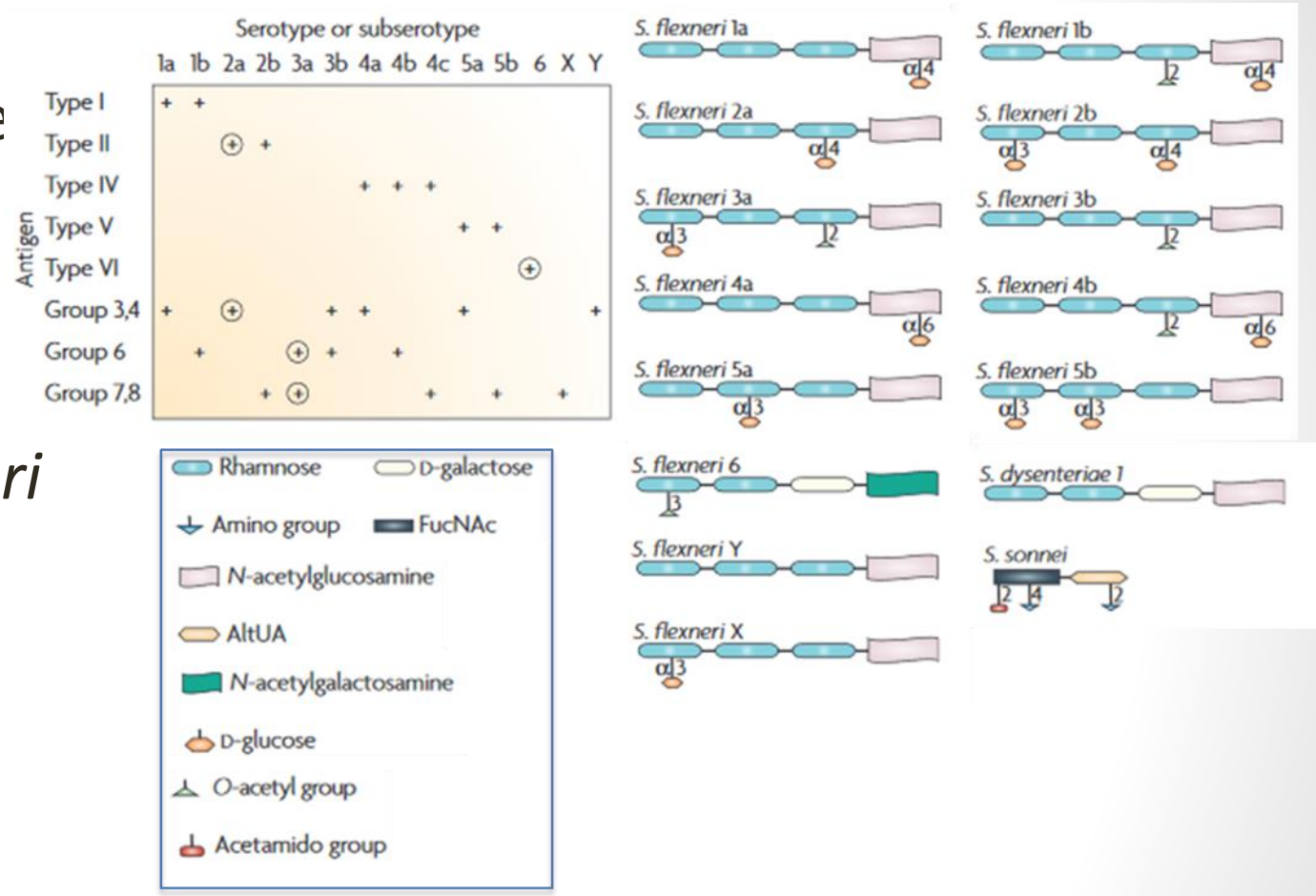


- 19% *Shigella* detected
- 14% *Shigella* detection at CT<27.9



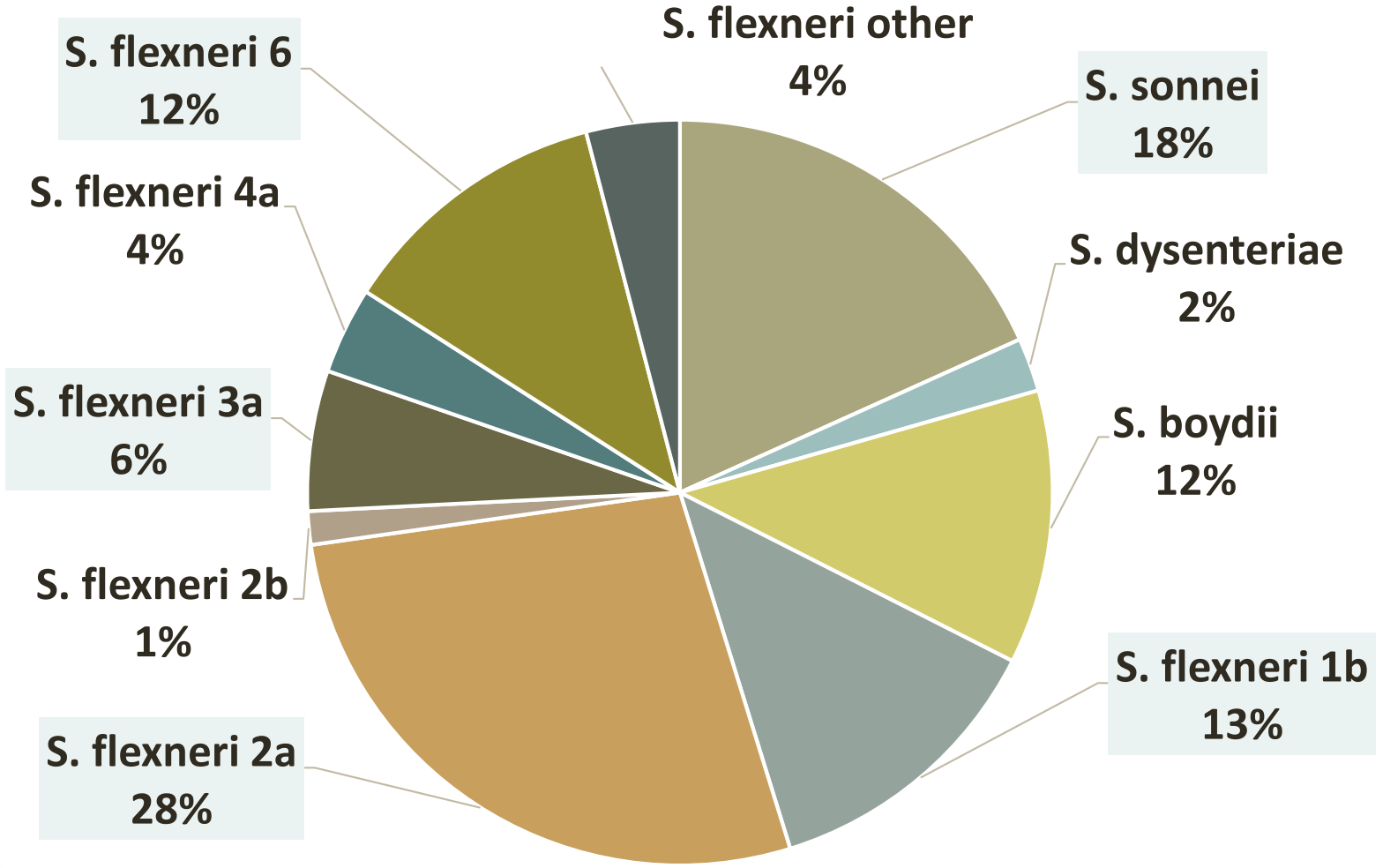
Shigella heterotypic immunity

- Protection against serogroups and serotypes not contained in a vaccine will be important to examine as a secondary endpoint (heterotypic protection)
  - If cross-protection among *S flexneri* serotypes is observed, then a vaccine containing *S sonnei* and *S flexneri* 1b, 2a, 3a, and 6 O-antigens could provide coverage for up to **90%** of *Shigella* strains.



(Livio, 2014, *Clin. Inf. Dis.*; Noriega, 1999 *Infect. Immun*; Levine et al, 2007, *Nat. Rev. Micro*).

Shigella homotypic immunity: VIDA (3 sites in sub-Saharan Africa)



VIDA 2015-2018

A vaccine containing S. *sonnei*, *S. flex* 2a, 3a, 6, & 1b could provide direct protection against **77%** of *Shigella* isolates

(Kotloff unpublished)

What do we need to know for FVVA

- Disease burden
  - Incidence, pandemic potential, longterm effects, mortality
  - Target population
  - Universal or targeted
  - Preventable burden
- What do policy-makers need to know and what is the clearest message
- What does a *Shigella* vaccine need to look like? Protective efficacy, formulation, etc
- Which direct outcomes are most important to prevent: Symptomatic, asymptomatic, all shigellosis, mod-severe
- Which indirect outcomes are most important
  - Cost:benefit
  - PAR for diarrheal mortality
  - PAR for stunting
  - Equity
  - Hospitalization
  - Outbreak control
  - Antimicrobial resistance
    - Does vaccine reduce AMR
    - Does threat of highly resistant strains increase value of vaccine
  - Hospitalization
  - Outbreak control

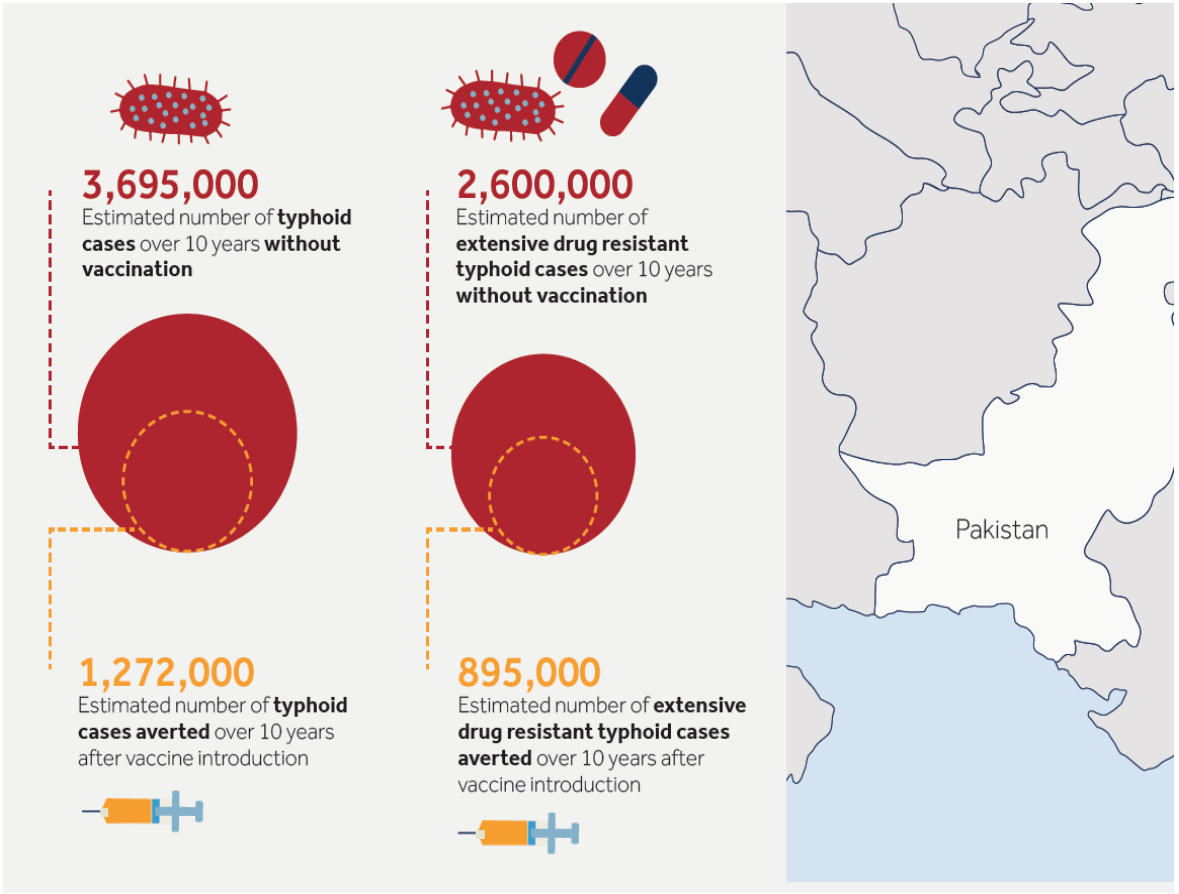

THANK YOU

AMR as an incentive for vaccine development and use

Mateusz Hasso-Agopsowicz (WHO, Geneva, Switzerland)

The Problem of AMR and the role of vaccines

- Global estimates suggest that drug-resistant infections result in **700,000 deaths per year**
- Could rise to **10 million annual deaths** by 2050
- Economical expenditure of **US$10 trillion** by 2050
- Mobilisation of efforts by WHO, UN, international organizations, member states, public health stakeholders to produce **a list of recommendations to combat AMR**
- **Vaccines** highlighted as having an **important** role in the process:
  - Vaccines prevent the infection and reduce carriage and transmission of AMR pathogen
  - Vaccines reduce the presence of clinical symptoms, reducing the pathogen associated antibiotic use



The role of WHO in vaccines and AMR

- Call from the AMR community to work on vaccines and AMR
- The aim of WHO is to highlight the role of vaccines and their impact against AMR
- To highlight priority activities around vaccines and AMR

Through:

- Creation of an action framework – or how to strengthen the role of vaccines in the fight against AMR
- Developing a value attribution framework to articulate the value of vaccine against AMR

All with input from an expert Working Group overseeing both processes

An action framework

Goal: a high level statement from WHO on the need to realise the full potential of vaccines in the fight against AMR

Strategic vision: For vaccines to contribute fully, sustainably and equitably to the prevention and control of antimicrobial resistance by preventing infections and reducing antimicrobial use.

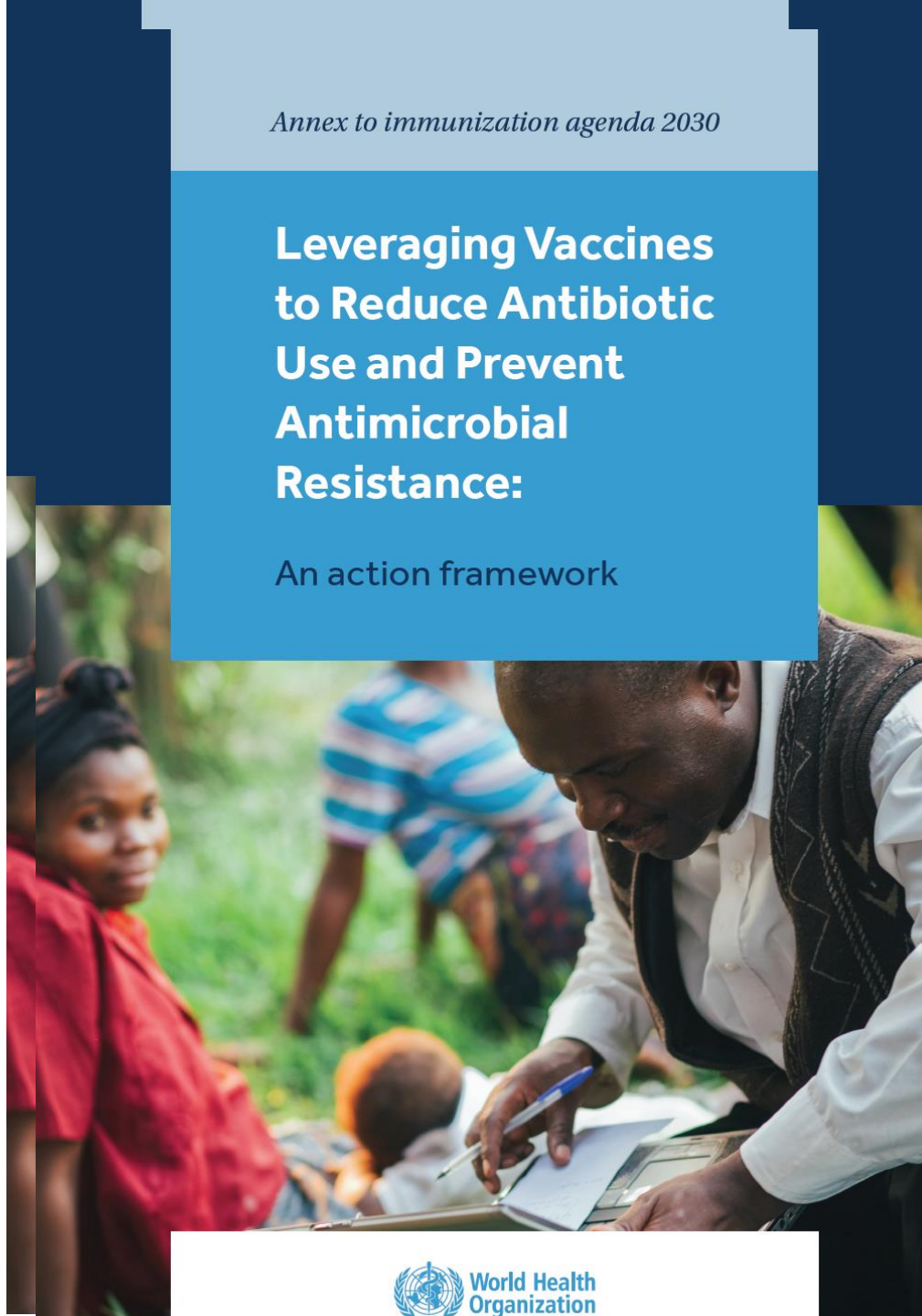
How: a technical document that outlines key actions for vaccines to be considered against AMR

- it builds on existing initiatives
- is presented in context of the role of infection prevention alongside other efforts
- has been developed through a consensual process with vaccines, AMR, industry, academia experts

Methodology: Focus on three activity areas:

1) expanding use of licensed vaccines to maximise impact on AMR
2) developing new vaccines that contribute to prevention and control of AMR
3) expanding knowledge of vaccine impact on AMR

Timeline: undergoing final approval



Value attribution framework for impact of vaccines against AMR

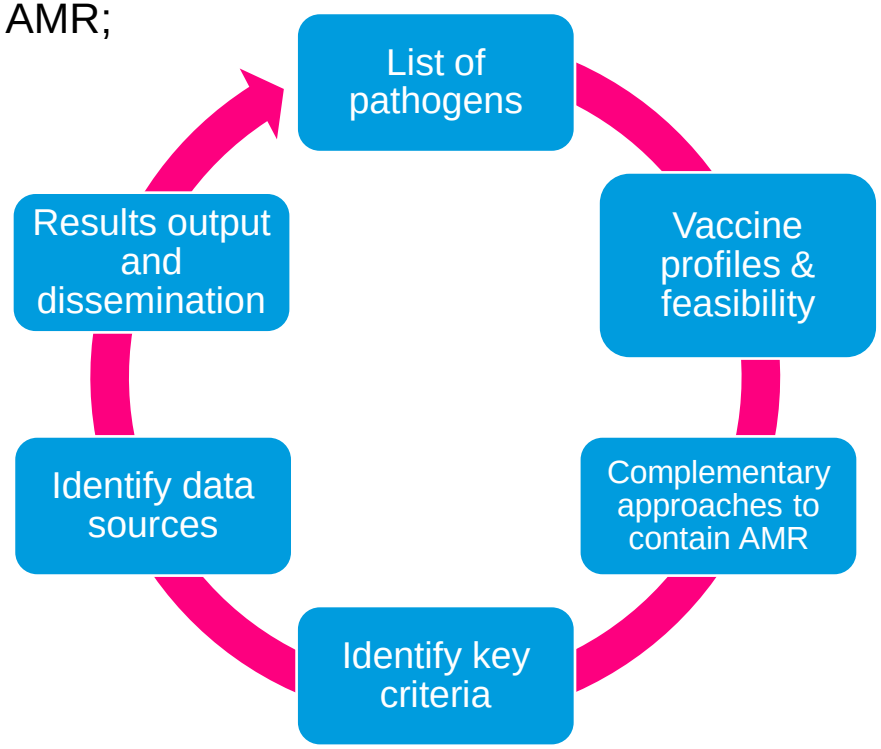
Goal: a semi-quantitative framework to articulate the value of vaccines for their impact on AMR

Strategic vision: the framework aims to:

1) Support prioritisation of decisions and investments about vaccine development and use;
2) Synthesise best available evidence for the impact of vaccines against AMR;
3) Highlight the AMR component of the full value of vaccines;
4) Highlight knowledge gaps;

Methodology: a framework that considers 30 pathogens and five key criteria:

1) Vaccine averted AMR health burden;
2) Vaccine averted AMR economic burden;
3) Vaccine averted antibiotic use;
4) Sense of urgency to develop approaches to contain AMR;
5) Vaccine impact on equity and social justice



Timeline: final results expected in November 2020, planned publication February 2021

Define vaccine profiles and their feasibility

Aim: to identify assumptions around vaccine characteristics and use cases to support aligned and systematic modelling estimates.

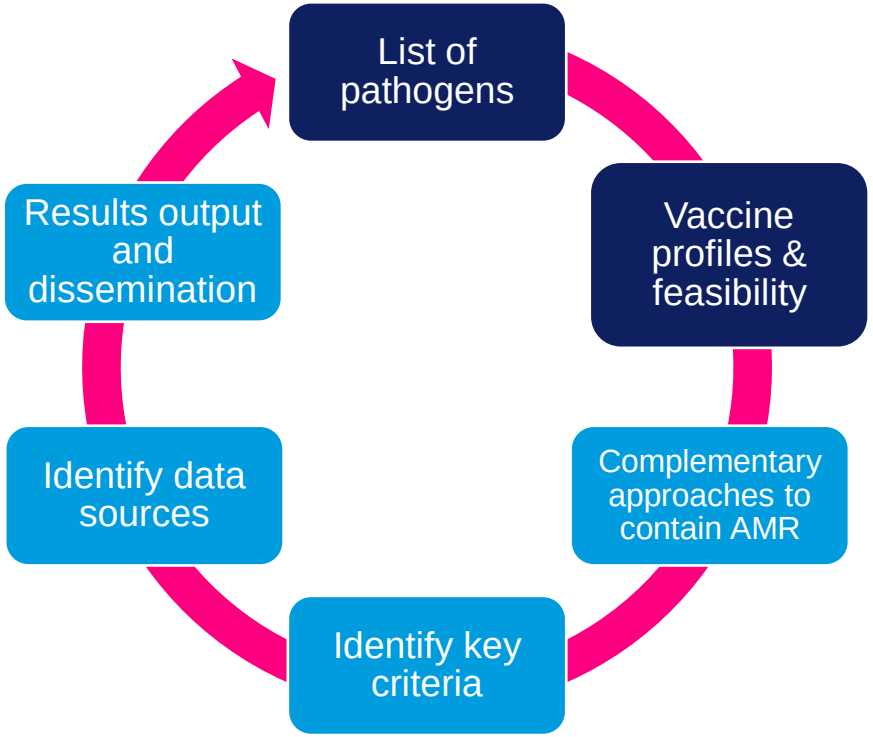
Developed by PATH and vaccine experts (Lou Bourgeois, Mark Riddle).

Vaccine profile 1: A vaccine against Shigella given to 90% of 6-12 months infants in Shigella endemic countries, with 4 years efficacy of 70% against severe shigella disease.

Biological feasibility: **MODERATE**
Product development feasibility: **MODERATE**
Access & Implementation feasibility: **MODERATE**

Vaccine profile 2: A vaccine against Shigella given to 90% of 6-12 months infants in Shigella endemic countries, with 1 year efficacy of 50% against severe shigella disease.

Biological feasibility: **MODERATE-HIGH**
Product development feasibility: **MODERATE-HIGH**
Access & Implementation feasibility: **LOW-MODERATE**



Vaccines in context of other approaches to contain AMR

Aim: to identify approaches in addition to vaccines to contain AMR

Developed by Lindsey Wu, LSHTM

Methodology:

- Literature reviews and expert consultations
- Categorising approaches under broad intervention categories
- Aligning and mapping complementary approaches to Pathogens in scope of VAF
- Summary of most relevant approaches for each pathogen (or group of pathogens)

Pathogen: Shigella	

Current standard of care	▪ First line drug therapy
	  • Trimethaprim-sulfamethoxazole, ampicillin
	▪ Second line drug therapy
	  • Azithromycin, cefixime, ceftriaxone
	▪ First line treatment varies depending on regional resistance patterns but is typically a course of treatment with fluoroquinolone. Although treatment duration varies; a three-day course is typical[119]

Suggested complementary approaches to contain AMR	

Antimicrobial stewardship	▪ Education for healthcare workers (align with WHO AWaRe antibiotic classifications)
	▪ Audit and feedback for healthcare staff
	▪ Restricted prescribing (e.g., formulary restrictions, automatic stop orders)
	▪ Improved prescribing practices
	  • Rotating use of antibiotics
	  • Dose optimisation
	  • De-escalation
	  • Delayed prescribing
	  • Duration by indication
	▪ Mass media campaigns and public education

Prevention of infection	▪ Improved food and water sanitation in the community ▪ Improved household and hand-hygiene in the community
Alternative treatments	Microbiome-based therapies
One Health	None

Criteria to define the value of vaccines against AMR

Criterion 1: Vaccine averted AMR health burden

Ramanan Laxminarayan, CDDEP

Outputs:

- Number of symptomatic AMR infections
- Number of symptomatic AMR infections averted by a vaccine
- Number of deaths due to an AMR pathogen
- Number of deaths due to an AMR pathogen averted by a vaccine

Criterion 2: Vaccine averted economic burden

Nichola Naylor & Mark Jit, LSHTM

Outputs:

- Productivity cost
- Excess healthcare cost
- Direct antibiotic cost
- GDP impact

Criterion 3: Vaccine averted antibiotic use

Nicholas Davies & Mark Jit, LSHTM

Outputs:

- Pathogen specific antibiotic use
- Vaccine averted antibiotic use

Timeline: results in November 2020

Criterion 4: Sense of urgency to develop approaches to contain AMR

WHO IVB & WHO AMR

Outputs:

- Measure of urgency to develop approaches to contain AMR

Timeline: results in August 2020

Criteria to define the value of vaccines against AMR

Criterion 5: Vaccine impact on equity and social justice (Maria Merritt, Sanjana Ravi, Michael DiStefano, Alexandra Ruth, JHU)

Social justice dimension	Pathogen-related impact	Vulnerable populations of concern
Agency	Impeded ability to work while ill, leading to lost wages	General, low-income populations
	Muscle weakness resulting from illness may make it difficult to independently complete tasks of daily living	General
	Fear of consuming well-liked foods due to risk of infection	General
	Long recovery time for children can potentially disrupt schooling and impede educational attainment, limiting future opportunities	Children
Association	Long recovery time for children can potentially disrupt schooling and social participation	Children
	Fear of being isolated from others while ill	General
	Fear of infecting others potentially leading to reduced social participation	General
Respect	In cases of individuals co-infected with HIV at risk of more serious infection and increased risk overall: Potential stigma associated with being infected where infection may imply stigmatized behaviors (e.g. MSM)	Hard-to-reach populations
	Potential stigma associated with lowered socioeconomic status due to lost wages from illness period; potentially reduced sense of self-worth stemming from inability to work	General
	Potential to seem “unclean” or unhygienic to others while ill	General

The potential impact and cost-effectiveness of a Shigella vaccine

Implications for a full public health value proposition

Farzana Muhib, MPH, MALD

Senior Program Officer, CVIA PATH

PATH

Objectives

- Review key elements and findings of Shigella impact and cost-effectiveness analysis
- Discuss the rationale for considering the relationship between stunting, cognition, learning and macroeconomic effects and their contribution to the full public health value proposition

Estimating the burden of Shigella

Variable	Annual burden	Sources/assumptions
Direct deaths from Shigella infections	49.4K deaths (36.4K-64.5K)	Used the mid-point estimates (IHME, MCEE 2015)
Shigella cases	111.2M cases (78.8M-149.4M)	Etiologic fraction of all diarrhea (GEMS, Adjusted for PCR)
Moderate to severe stunting cases due to Shigella	2,144K cases (728-3299K)	MSD associated with a shift in HAZ score of 0.082
Additional deaths from other infectious disease	13.2K deaths (4.6K-20.7K)	Population attributable risk for other infectious disease in stunted children (Black et al)

Source: Anderson et al 2019: Kotloff et al, 2012; Black et al 2008

The cost-effectiveness of Shigella vaccines in context

Vaccine	Results	Sources/assumptions
Shigella excluding deaths due to other infectious diseases and stunting	$3,114 ($2,117-$6,276)/DALY averted (2016$/DALY)	79 LLMIC*, vaccine efficacy of 60%, 3 doses and DTP3 coverage, $3.30 per dose
Shigella including deaths due to other infectious diseases and stunting	$2,513 ($1,708-$5,088)/DALY averted (2016$/DALY)	79 LLMIC*, vaccine efficacy of 60%, 3 doses and DTP3 coverage, $3.30 per dose
Rotavirus	$325/DALY averted (2015$/DALY)	73 “Gavi” countries, vaccine efficacy of 44-77% at 12 months, 2 or 3 doses, $0.85-$3.2 per dose
Malaria	$87 ($48-$244) averted (2013$/DALY)	P*f*PR$_{2-10}$ (3-60%), vaccine efficacy 43·9% (95% CI 39·7–47·8) over 32 months, 4 doses, $5 dollars per dose

Source: Anderson et al 2019:; Debellut et al 2019 Penny et al 2015

*Low- and lower middle-income countries

PATH

Implications of impact and cost effectiveness studies

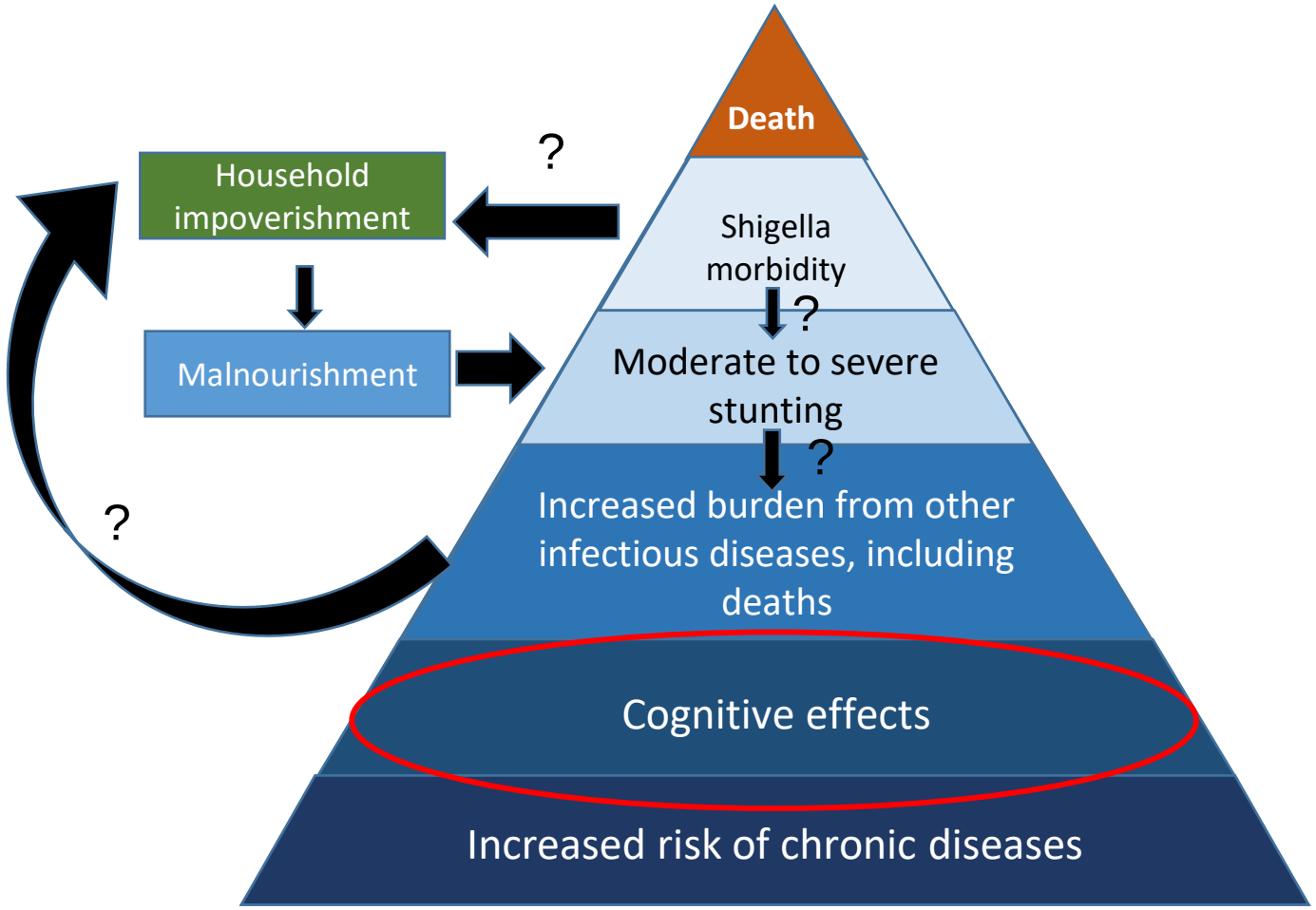
- Shigella mortality is lower than some other vaccine preventable diseases
- Vaccine cost-effectiveness is driven by number of deaths averted
- Simplistic comparisons (prior slide) show that shigella vaccine is less likely to be attractive compared to current vaccines from a standard impact and cost effectiveness perspective

- Why is Shigella different?
- Why should donors and countries be interested despite lower mortality?
- Need to understand the full public health value of a shigella vaccine to answer this question

PATH

What is the full value of a Shigella vaccine?

- Many interrelated effects that may be important
- Long-term sequelae and potential linkages to cognition and broader macroeconomic implications may be distinct features of Shigella
- Individual effects may be small, but macroeconomic effects can be broad



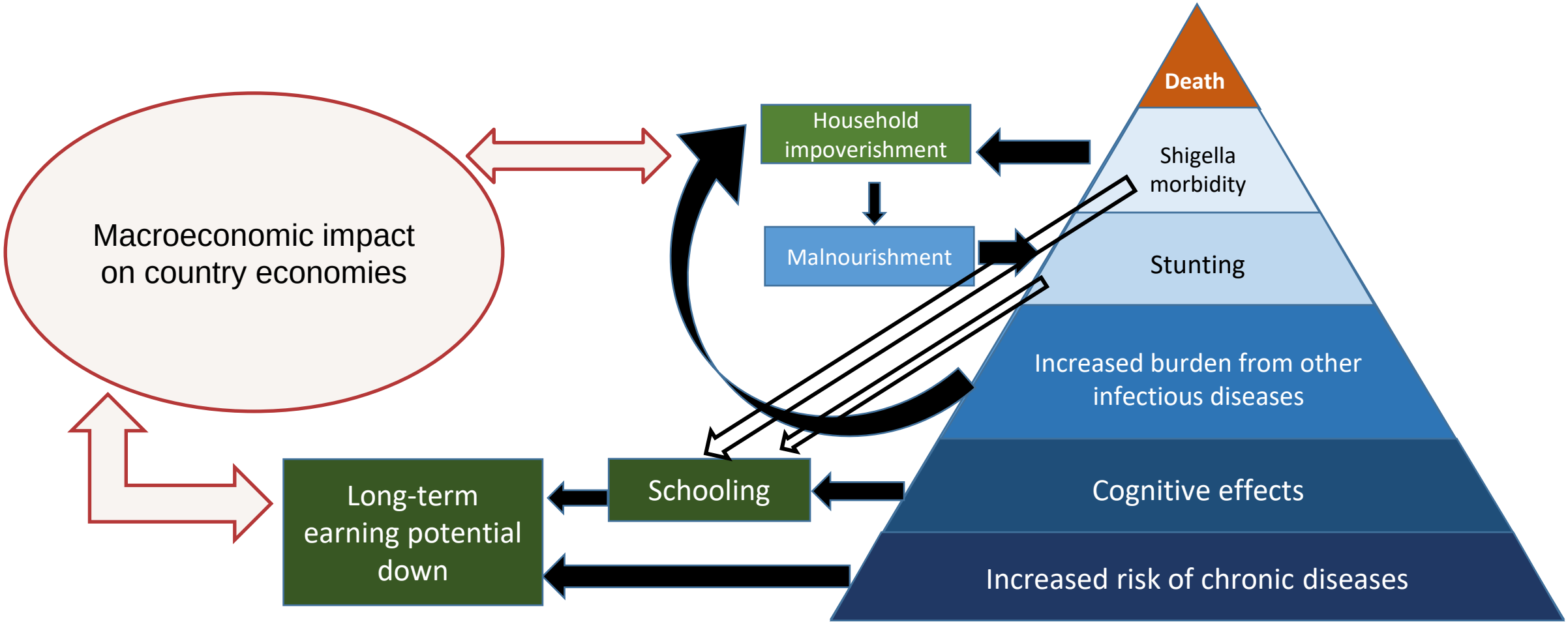
Source: Kotloff et al, 2012; Rheingans, R. et al., 2012; Victoria et al 2008; Black et al, 2008)

*Size of triangles do not necessarily correspond directly to size of burden

PATH

Macro-economic impact of Shigella infections

- Need to develop a framework to understand how various factors may impact economy, and the sources of uncertainty
- Two-way relationship between household impoverishment and long-term potential growth & macroeconomic impact



Source: Kotloff et al, 2012; Rheingans, R. et al., 2012; Victoria et al 2008: Black et al 2008;
*Size/shading of triangles and arrows do not necessarily correspond directly to size of burden/impact

PATH

Other considerations for Shigella vaccine impact and cost effectiveness

- Impoverishment
- Equity
- Malnutrition
- Influence on other infectious diseases
- Potential to be part of a combination vaccine

Summary

- Uncertain economic case for Shigella vaccine relative to some other vaccines
- Significant epidemiological and economic information gaps to understanding the full value of a Shigella vaccine
- Links between stunting, cognition, educational attainment and macroeconomic effects may be critical
    - Other factors that need exploration (e.g. equity, malnutrition)
- Need to build and populate a macroeconomic model that can use available data to understand both magnitude and uncertainty associated with different factors
- Once the magnitude and uncertainty is understood, we can prioritize research to fill these gaps

PATH

For more information contact:

Farzana Muhib, MPH, MALD

Senior Program Officer, Center for Vaccine Introduction & Access, PATH

fmuhib@path.org


PATH

World Health Organization

Questions for consideration

Q1: Burden of disease

- Assumes Shigella mortality burden alone will not be sufficient to drive development of, and policy recommendation for, a Shigella vaccine.
- In addition to revised assessments of the Shigella short term morbidity burden, suggestive data link Shigella infections to stunting, and prevention of stunting to economic and macroeconomic outcomes.

- Do you consider **a comprehensive analysis of the robustness and magnitude** of these associations, based on current data, to **be a critical part of a FVVA of Shigella**?
- Do you consider a macroeconomic assessment of a Shigella vaccine's impact on stunting, other long-term sequelae to be a timely and critical part of these FVVA?

Q2: Vaccine impact and cost effectiveness modelling

Assumes inclusion of direct and indirect effects due to stunting, AMR, and consideration of a combination vaccine, would provide more favourable cost effectiveness assessment

- What modifications, if any, to current cost effectiveness analyses should be included based on new data, or understanding of the disease, AMR impact or epidemiology?
- (When) should we model the incremental cost-effectiveness ratio for different vaccine combinations?

Q3: Understand end-user preferences and demand

- Assumes systematically assessing LMIC interest and priorities, as candidates progress along the product development continuum, is crucial to ‘pull’ Shigella vaccine development and help shape the vaccine attributes.
- Assumes this is a key part of a FVVA to de-risk and incentivize investment for manufacturers.

➢ How, and when, should we engage with / gather information on current national stakeholder and health care practitioner perceptions of Shigella burden and of a vaccine’s potential impact on diarrheal disease burden?