



Wisdom Begins With Wonder  
IPAC CANADA

# What's New in Number 2? Update on Diarrheal Disease from a Global Perspective

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BC Children's Hospital

Teleclass broadcast sponsored by



[www.webbertraining.com](http://www.webbertraining.com)

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# Disclosure

- Faculty: Dr. David Goldfarb
- Relationships with commercial interests:
  - Nothing to disclose
- Research funding from the Public Health Agency of Canada, CIHR, Grand Challenges Canada, CDC Foundation, Bill and Melinda Gates Foundation, IDRC, ArcticNet, and **investigator initiated grant from bioMerieux**

# Outline

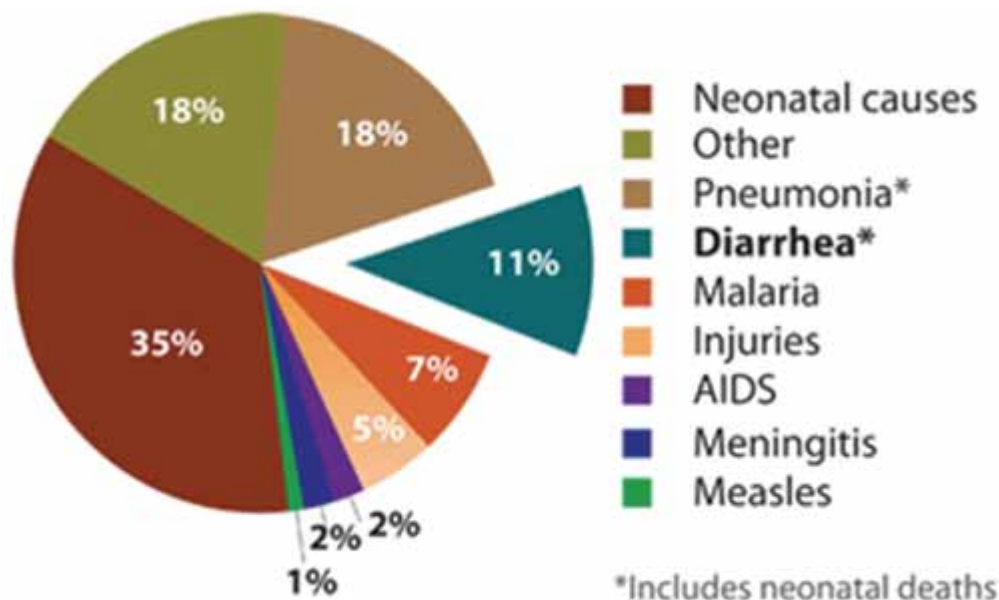
- Global Burden of childhood enteric infections
- New insights from enhanced diagnostic studies
- Examples of efforts to address childhood diarrheal disease

# Outline

- **Global burden of childhood enteric infections**
- New insights from enhanced diagnostic studies
- Examples of efforts to address childhood diarrheal disease

# Burden of diarrheal diseases

- Diarrhea kills **2,195 children** every day—more than AIDS, malaria, and measles combined

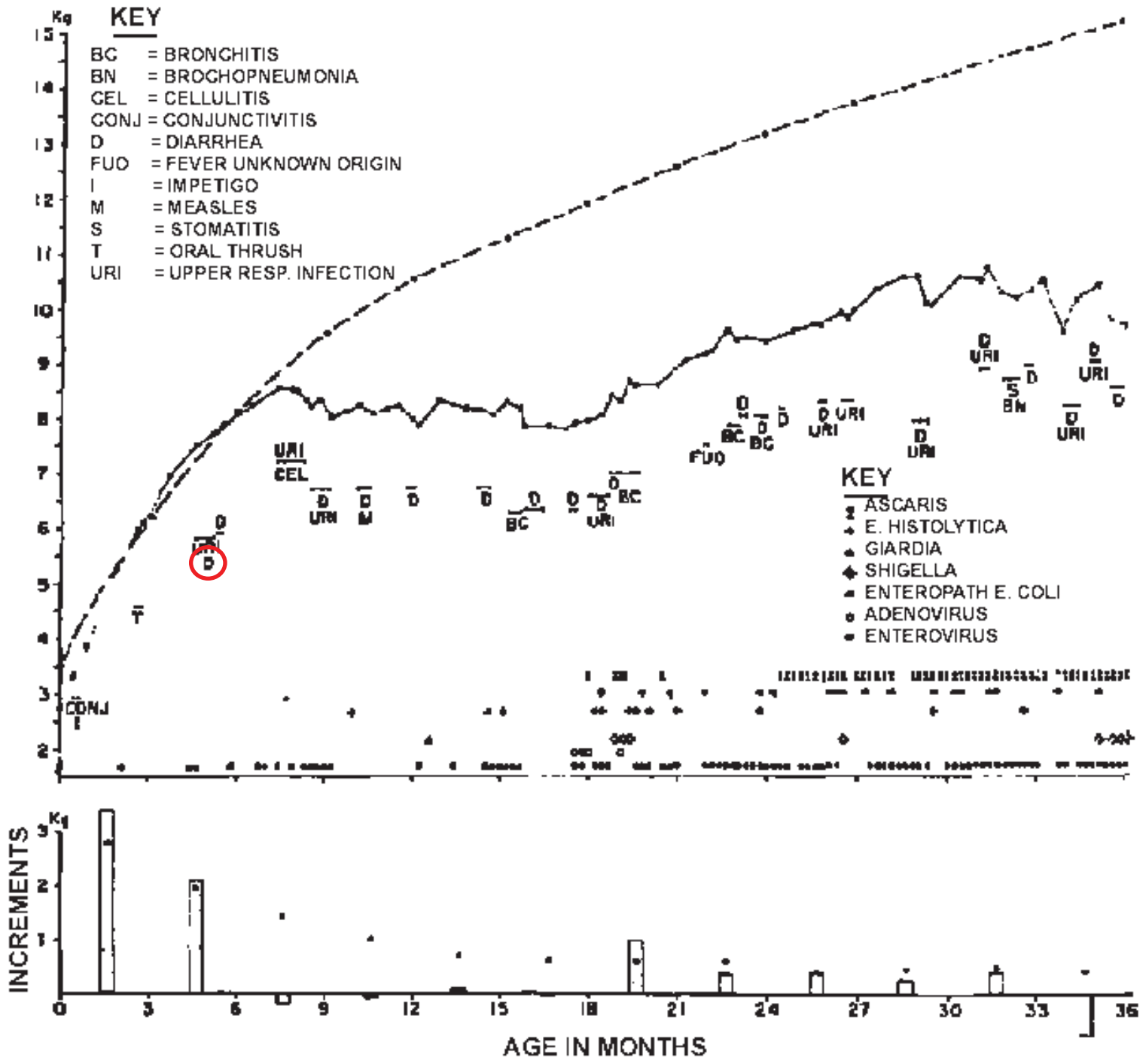


2<sup>nd</sup> leading cause of child death

# Burden Diarrheal Disease (cont'd)

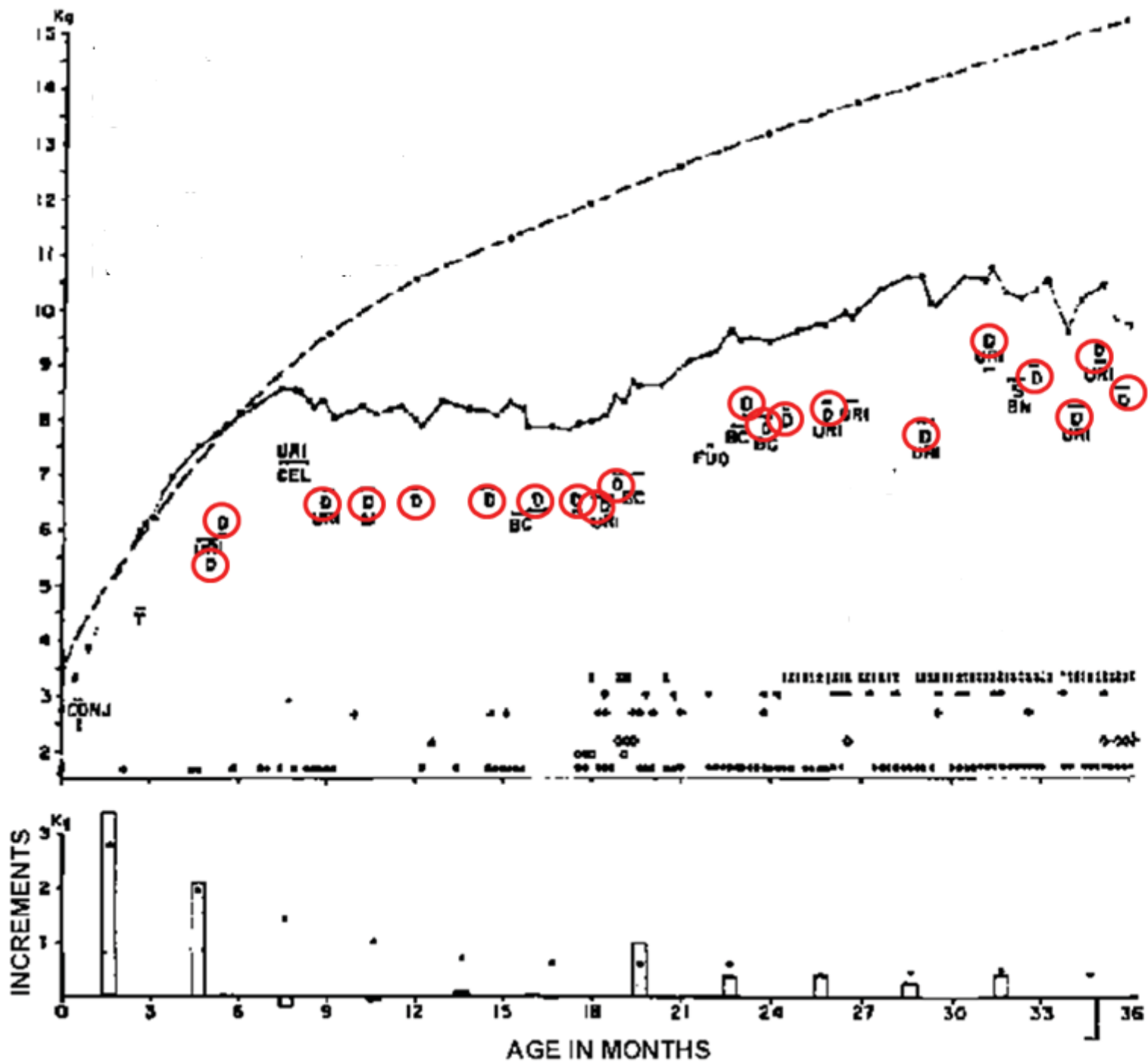
- What about the children that make it through these frequent episodes of diarrhea in childhood?





Mata L *et al.* 1971

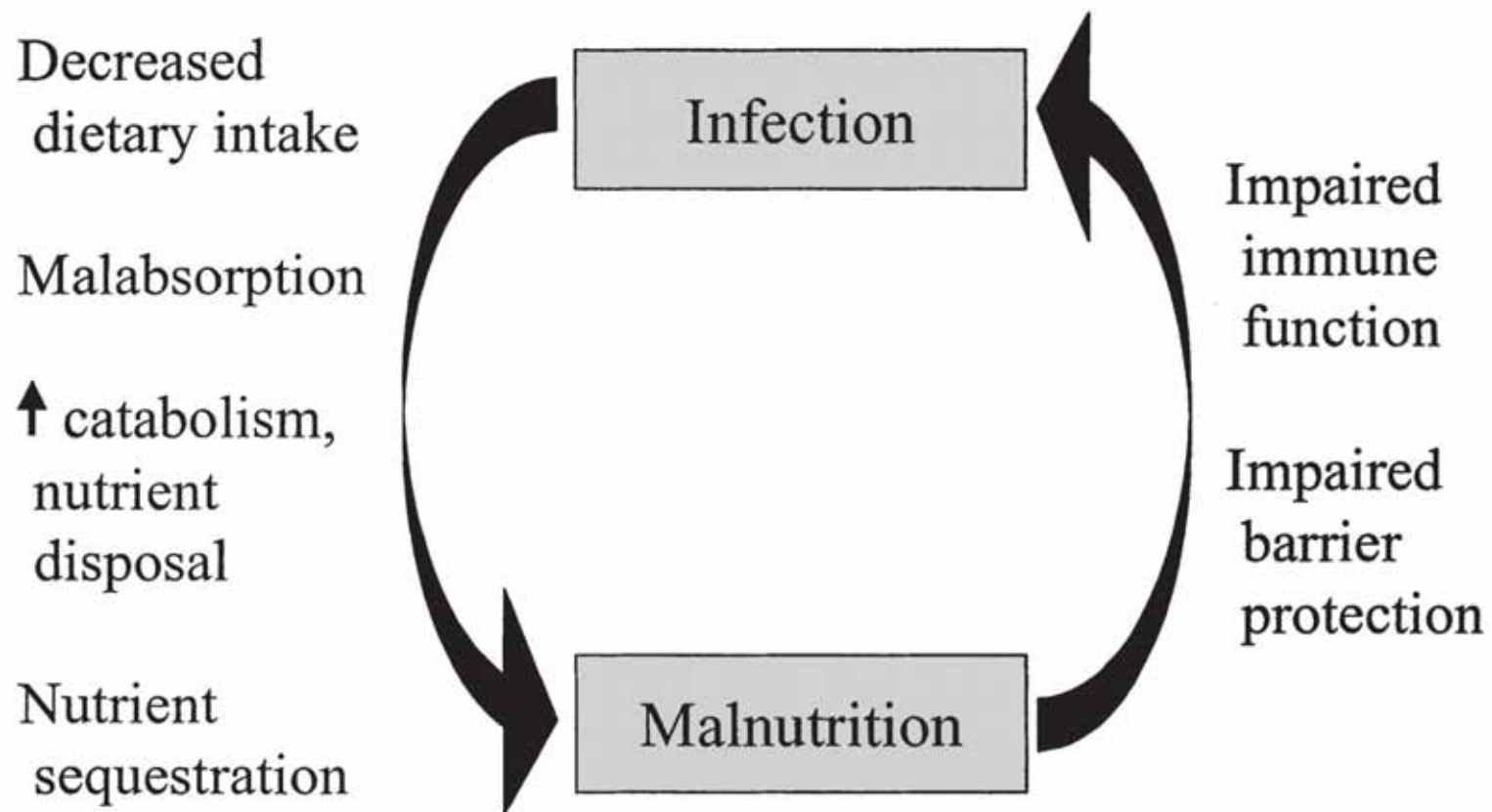




Mata L et al. 1971

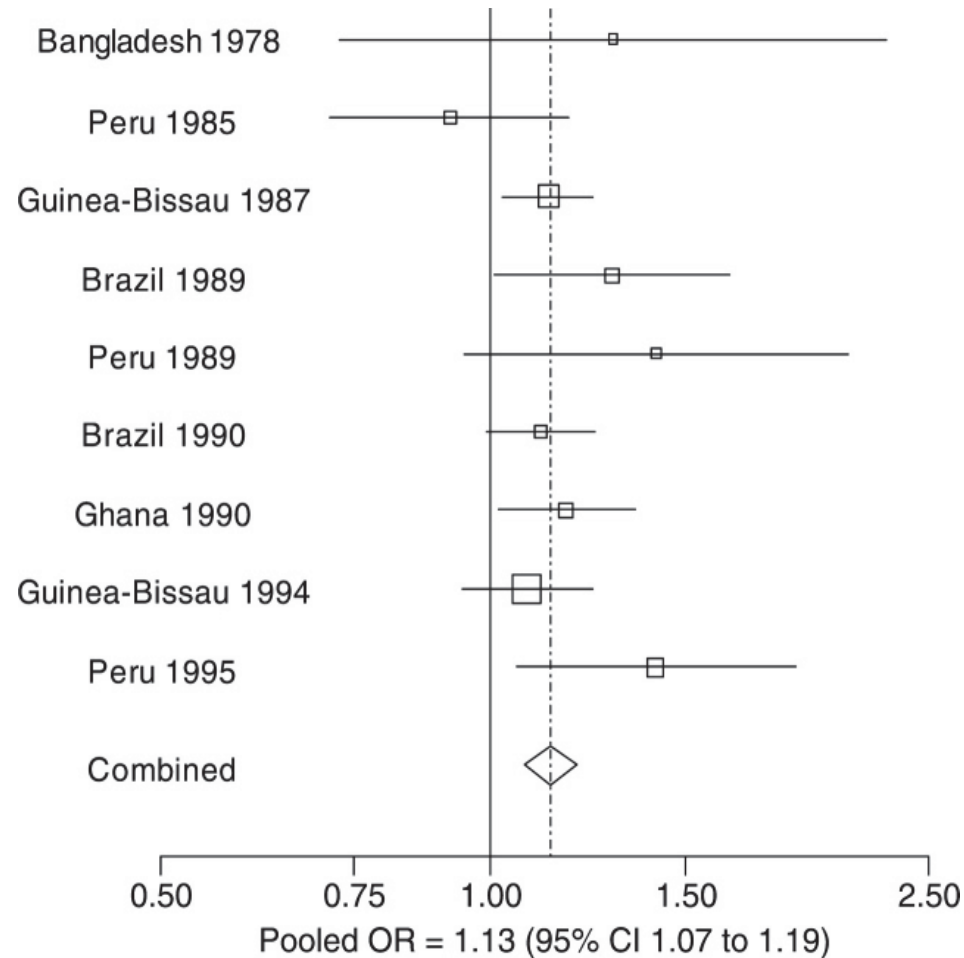
# Global burden of enteric infections

*synergy between malnutrition and infection*



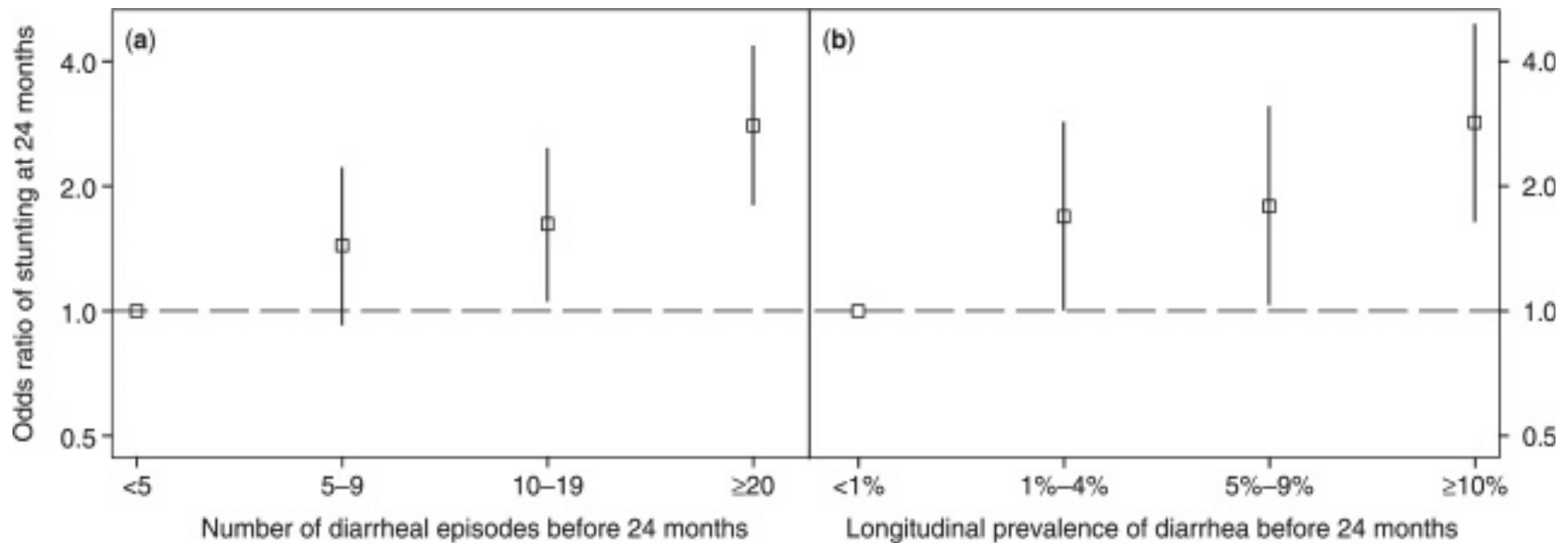
# Global burden of enteric infections

*early childhood diarrhea leads to stunting (HAZ <-2)*



# Global burden of enteric infections

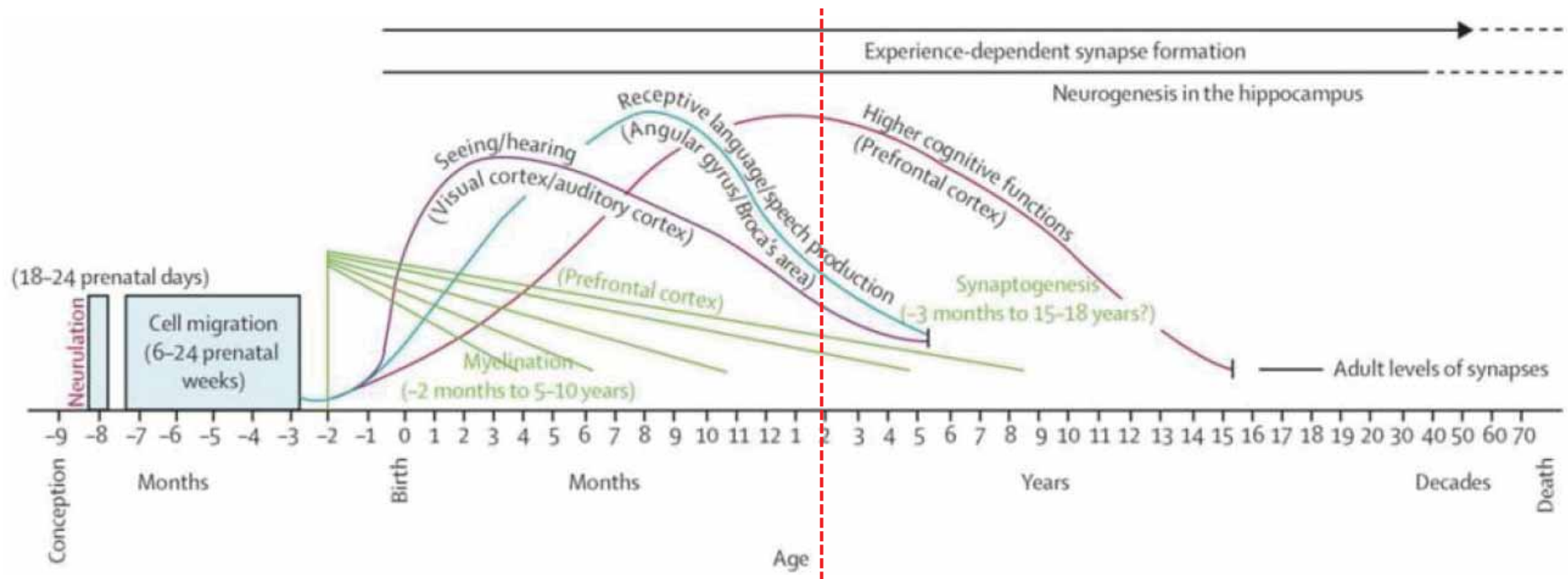
*early childhood diarrhea leads to stunting*



But does being a little shorter  
really matter?

# Global burden of enteric infections

*brain development is greatest before age 2*



# Global burden of enteric infections

## *stunting and cognitive outcomes*

Descriptive summary of follow-up studies showing associations between stunting in early childhood and later scores on cognitive tests and school outcomes

	Philippines	South Africa	Indonesia	Brazil <sup>*</sup>	Peru	Jamaica <sup>†</sup>	
	Cognitive score (8 years, n=2489)	Ravens Matrices <sup>120</sup> (7 years, n=603) <sup>‡</sup>	Reasoning and arithmetic (9 years, n=368)	Attained grades (18 years, n=2041)	WISC IQ <sup>119</sup> (9 years, n=72)	WAIS IQ <sup>‡118</sup> (17-18 years, n=165)	Reading and arithmetic <sup>‡</sup> (17-18 years)
Not stunted	56.4	0.17	11.2	8.1	92.3	0.38	0.40
Mildly stunted	53.8 (-0.21)	0.05 (-0.12)	10.3 (-0.26)	7.2 (-0.4)	89.8 (-0.20)		
Moderately or severely stunted	49.6 (-0.54)	-0.23 (-0.40)	9.7 (-0.43)	6.5 (-0.7)	79.2 (-1.05)	-0.55 (-0.93)	-0.60 (-1.00)

Data are mean (effect size as unadjusted difference from non-stunted children in z scores).

<sup>\*</sup> Males only.

<sup>†</sup> The sample comprised stunted (<-2 SD) children participating in an intervention trial and a non-stunted (>-1 SD) comparison group.

<sup>‡</sup> SD scores. WISC=Wechsler Intelligence Scale for Children. WAIS=Wechsler Adult Intelligence Scale.



# Evidence for lasting disability effects from early childhood diarrhea/enteric infections\*

## Growth shortfalls (esp. HAZ-2; 8.2cm by 7yo)

- **Crypto** Infections increase diarrhea morbidity and nutritional shortfalls to 18m [Agnew 98; Lima 00; Newman 99]
- **Crypto** infections  $\pm$  diarrhea = dec. wt gain @1m [Checkley 97]
- **Crypto** infections <6m/stunted = .95-1.05 cm deficits @1y [Checkley 98]
- EAaggEC infections + inflammation = growth shortfalls [Steiner 98]
- Diarrhea <2yo = 3.6cm stunted @7yo (8.2cm w helminths) [Moore 01; + Checkley et al, 08]

## Fitness impairment (=17% decr. work prod.)

- Albendazole = 7% inc. HST @4m [Stephenson 93]
- Diarrhea or **Crypto** <2yo = 4-8% dec. HST @4-7yo [Guerrant 99]
- 4.3% inc. HST = 16.6% inc. work prod. [Ndamba 93]

## Cognitive impairment (c. 10 IQ points)

- Diarrhea <2yo dec. WISC coding/digit @5-9yo [Guerrant 99]
- Diarrhea <2yo dec. TONI @6-10yo [Niehaus 02]
- Giardia or stunting = 4-10 pts dec. WISC-R @9yo [Berkman 02]

## School performance (c. 1 yr)

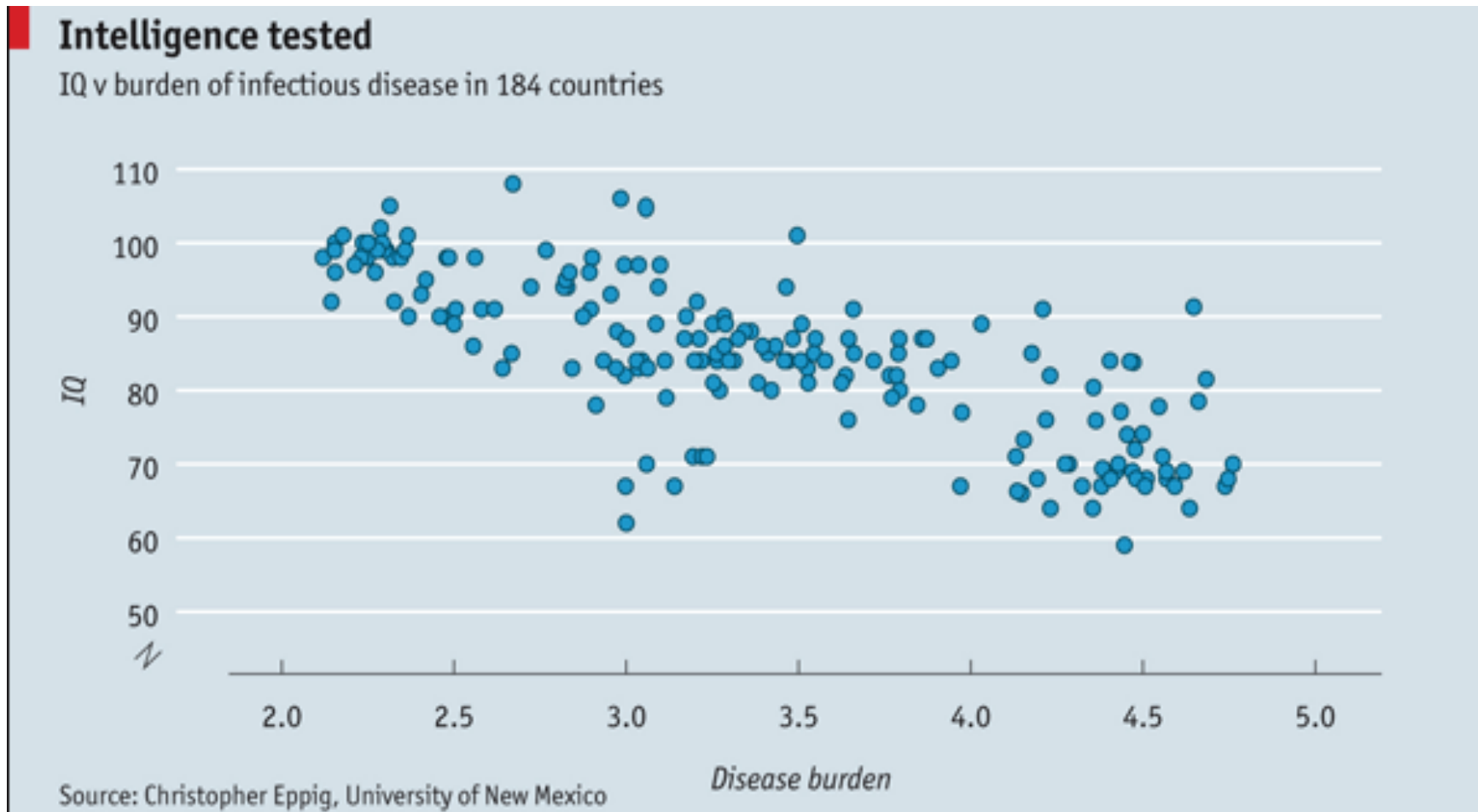
- Diarrhea <2yo = inc. AASS; AFG [Lorntz 06; Guerrant 02]

\* Petri et al JCI 118: 1277-1290, 2008; Guerrant et al Nutr Rev 66: 487-505, 2008.



# Global burden of enteric infections

*overall infections and cognitive development*





Review

# Early childhood diarrhoeal diseases and cognition: are we missing the rest of the iceberg?

**Jessica MacIntyre<sup>1</sup>, Jennifer McTaggart<sup>2</sup>, Richard L. Guerrant<sup>3</sup>, David M. Goldfarb<sup>\*4,5</sup>**

# Outline

- Global burden of childhood enteric infections
- **New insights from enhanced diagnostic studies**
- Examples of efforts to address childhood diarrheal disease





 Nanosphere

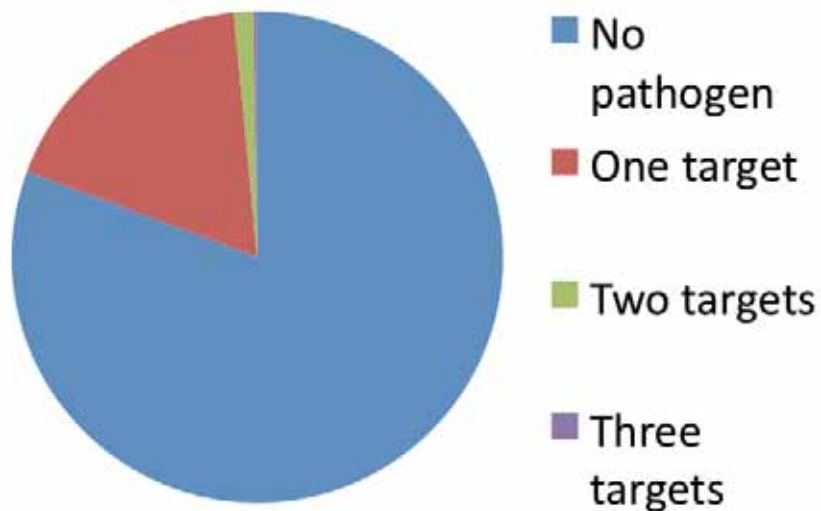
ENTERIC PATHOGENS TEST

Nanosphere's Verigene® Enteric Pathogens Test (EP) for the simultaneous detection and identification of genetic virulence markers.

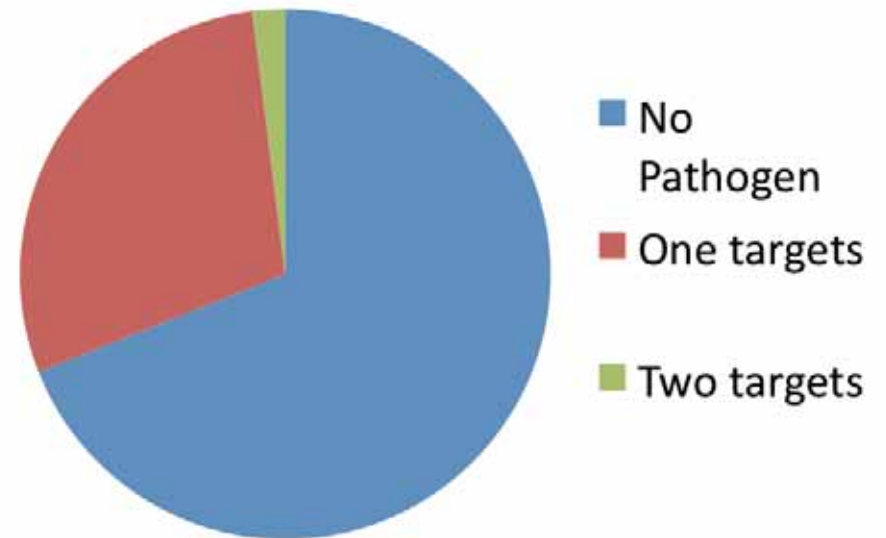


# xTAG GPP<sup>®</sup> Assay Used in Prospective Clinical Studies in Europe

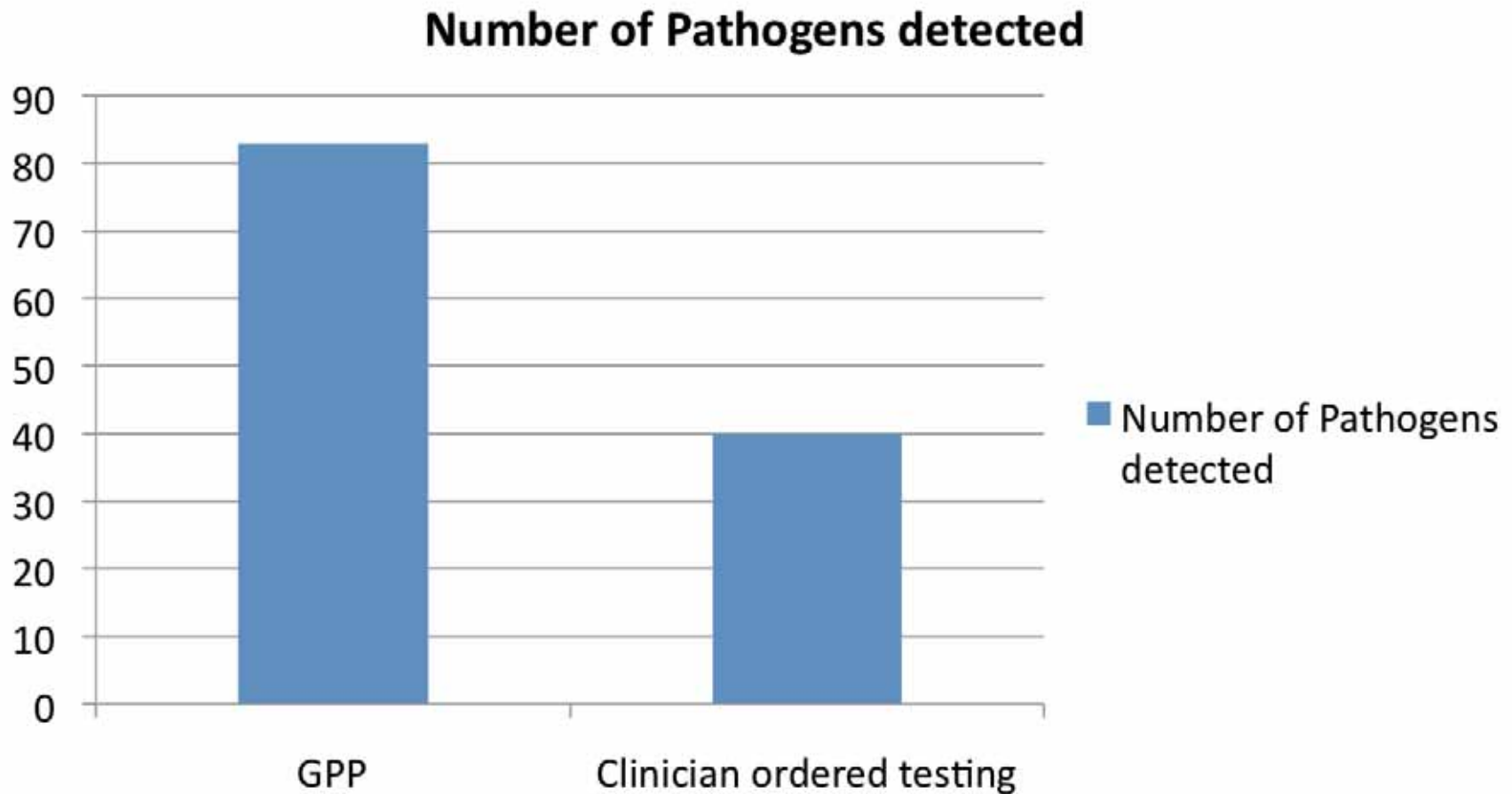
**Netherlands – 19% detection**



**Germany – 31% detection**



# Benefits of “Syndromic approach”



# Pediatric Oncology Population

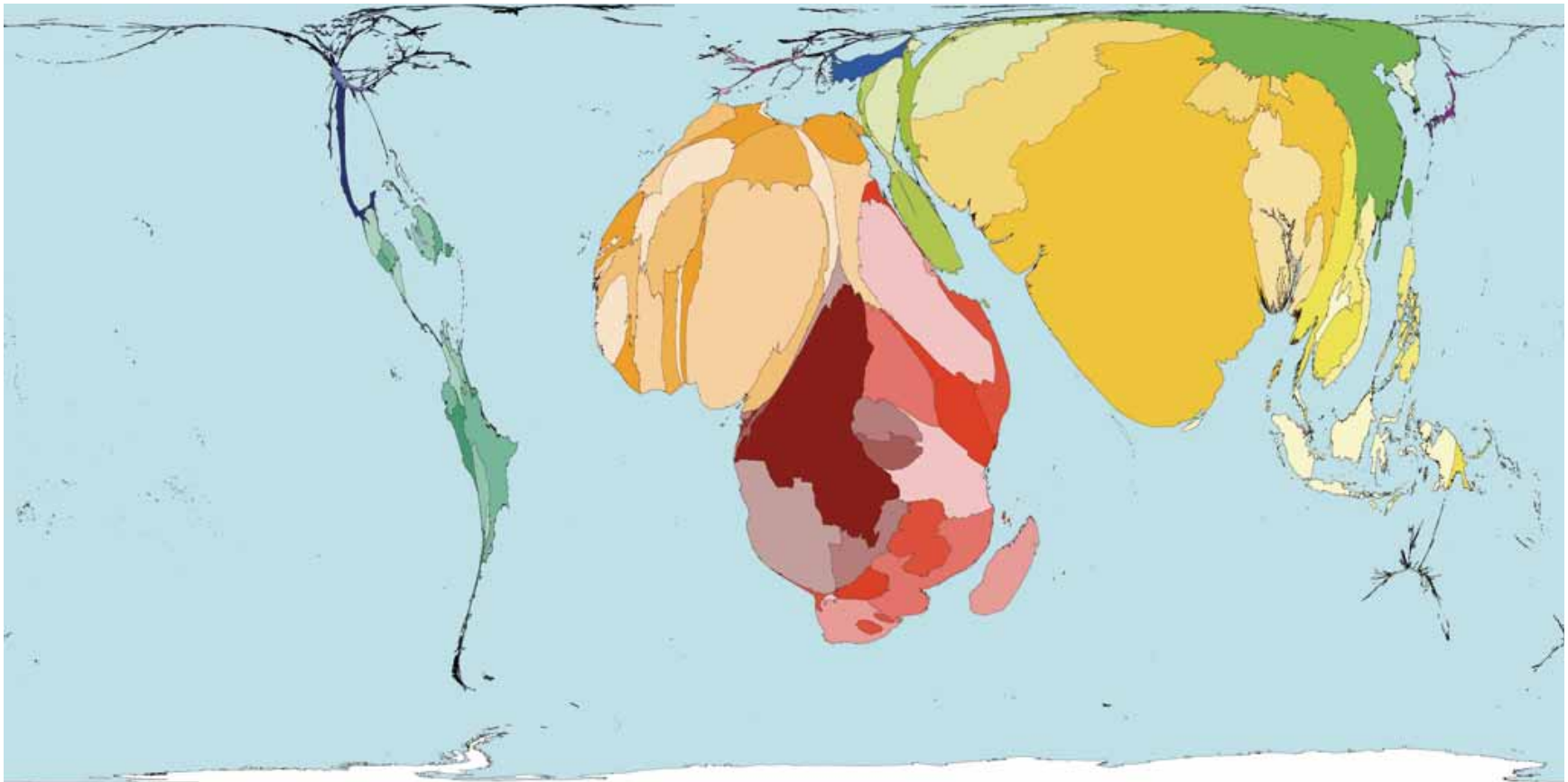
**Table 3** Overall Results for BioFire, Luminex, and In-House Testing

First episode per patient	BioFire	Luminex	In house*
Negative	105	100	152
Positive	94	99	47
Targets detected, <i>n</i> (%)			
1	80 (85.1)	80 (80.8)	46 (97.9)
2	12 (12.8)	11 (11.1)	1 (2.1)
3	2 (2.1)	7 (7.1)	0
4	0	1 (1)	0

\*Astrovirus, norovirus I and II, and sapovirus tested by PCR.



# What about high burden settings?



Diarrheal Deaths - 2002

<http://worldmapper.org/>

# Two Large Multi-centre Studies of childhood diarrheal disease

- **Global Enteric Multicentre Study (GEMS)**



- The Interactions of **Mal**nutrition & **Enteric** Infections: Consequences for Child Health and **Development** (MAL – ED)



BILL & MELINDA  
GATES *foundation*

# Global burden of enteric infections

*etiologic spectrum and impact*

## Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study

*Karen L Kotloff, James P Nataro, William C Blackwelder, Dilruba Nasrin, Tamer H Farag, Sandra Panchalingam, Yukun Wu, Samba O Sow, Dipika Sur, Robert F Breiman, Abu S G Faruque, Anita K M Zaidi, Debasish Saha, Pedro L Alonso, Boubou Tamboura, Doh Sanogo, Uma Onwuchekwa, Byomkesh Manna, Thandavarayan Ramamurthy, Suman Kanungo, John B Ochieng, Richard Omore, Joseph O Oundo, Anowar Hossain, Sumon K Das, Shahnawaz Ahmed, Shahida Qureshi, Farheen Quadri, Richard A Adegbola, Martin Antonio, M Jahangir Hossain, Adebayo Akinsola, Inacio Mandomando, Tacilta Nhampossa, Sozinho Acácio, Kousick Biswas, Ciara E O'Reilly, Eric D Mintz, Lynette Y Berkeley, Khitam Muhsen, Halvor Sommerfelt, Roy M Robins-Browne, Myron M Levine*

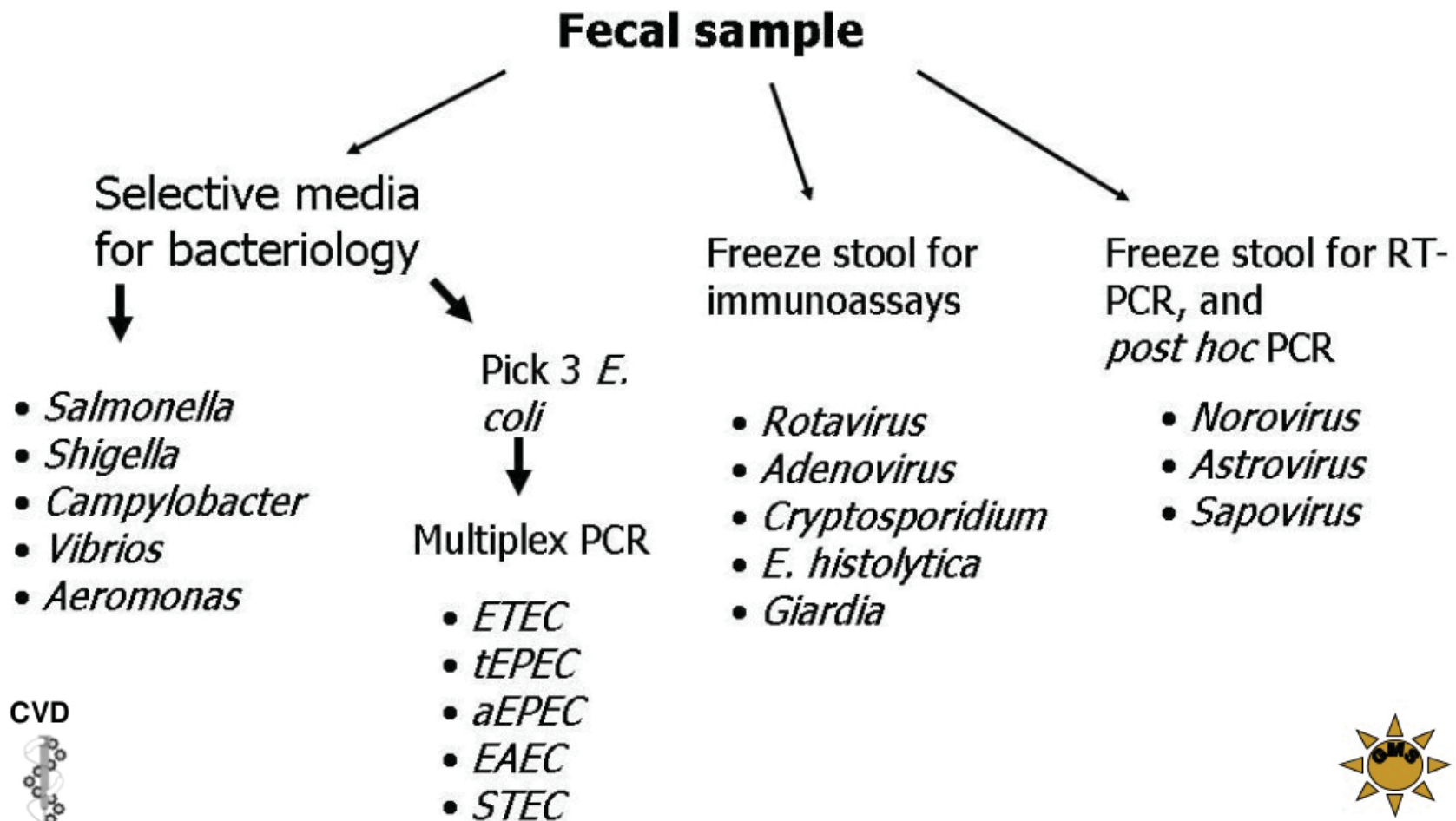
### Summary

**Background** Diarrhoeal diseases cause illness and death among children younger than 5 years in low-income countries. We designed the Global Enteric Multicenter Study (GEMS) to identify the aetiology and population-based burden of paediatric diarrhoeal disease in sub-Saharan Africa and south Asia.

**Methods** The GEMS is a 3-year, prospective, age-stratified, matched case-control study of moderate-to-severe diarrhoea in children aged 0–59 months residing in censused populations at four sites in Africa and three in Asia. We recruited

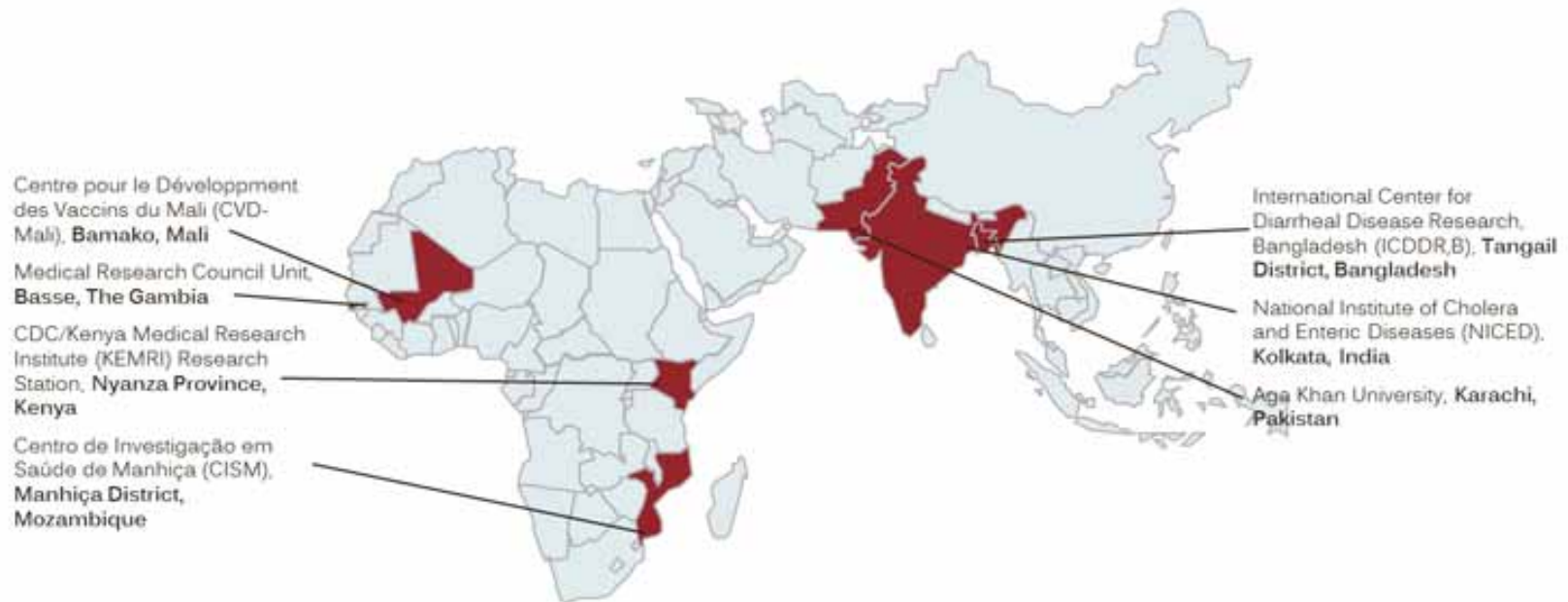
# Global Enteric Multicenter Study

## Microbiology work flow



# GEMS case control design

- Cases of mod to severe diarrhea = 9439
- Community controls = 13129



<http://medschool.umaryland.edu/GEMS/>



# Global Enteric Multicenter Study

**Pathogens (including *Giardia*) identified in stool specimens from cases and controls during the first 2 years of GEMS**

No. of pathogens identified	4 African sites		3 Asian sites	
	Cases (%)	Ctrls (%)	Cases (%)	Ctrls (%)
At least 1	79	71	83	70
At least 2	37	29	47	32
At least 3	10	7	16	10

# Attributable Fraction

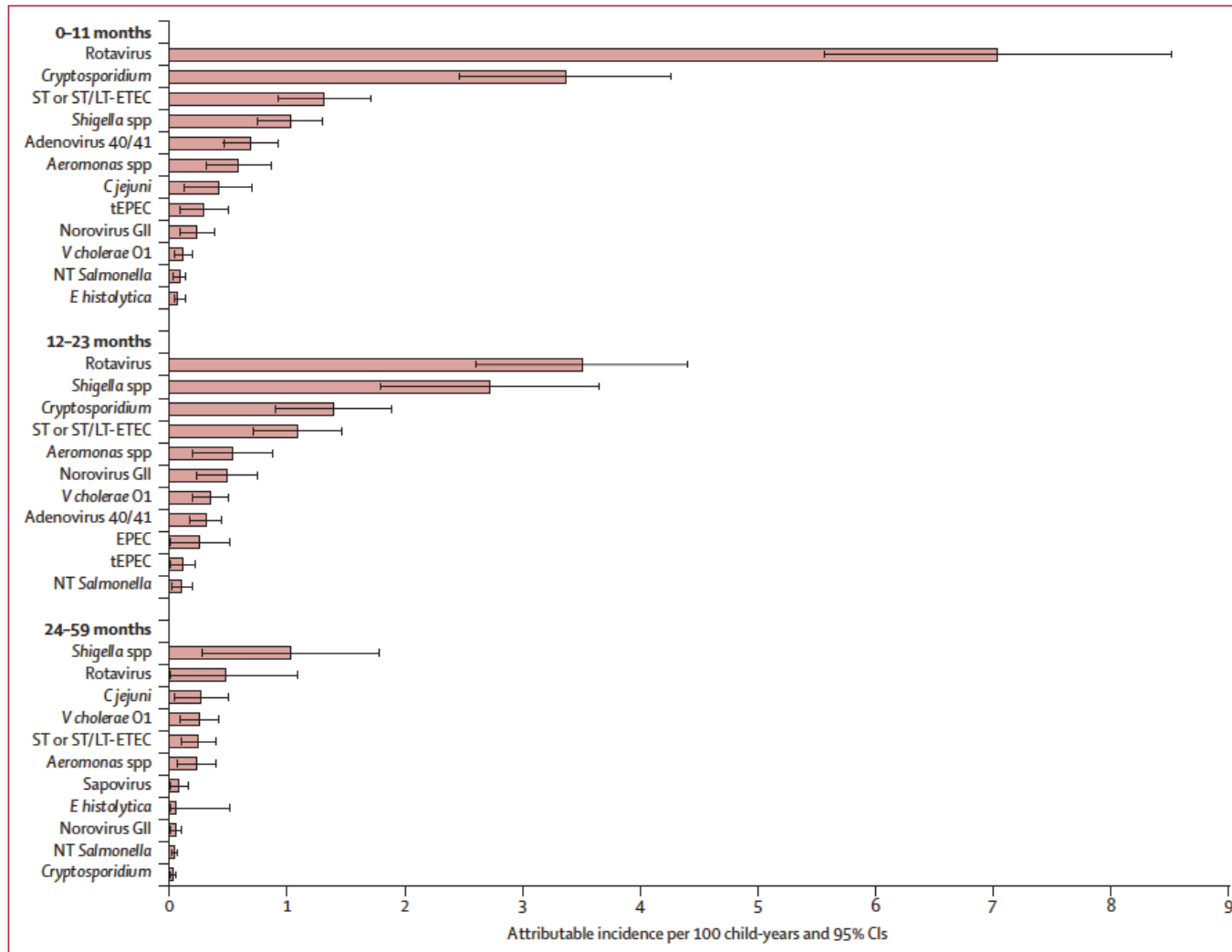


Figure 4: Attributable incidence of pathogen-specific moderate-to-severe diarrhoea per 100 child-years by age stratum, all sites combined

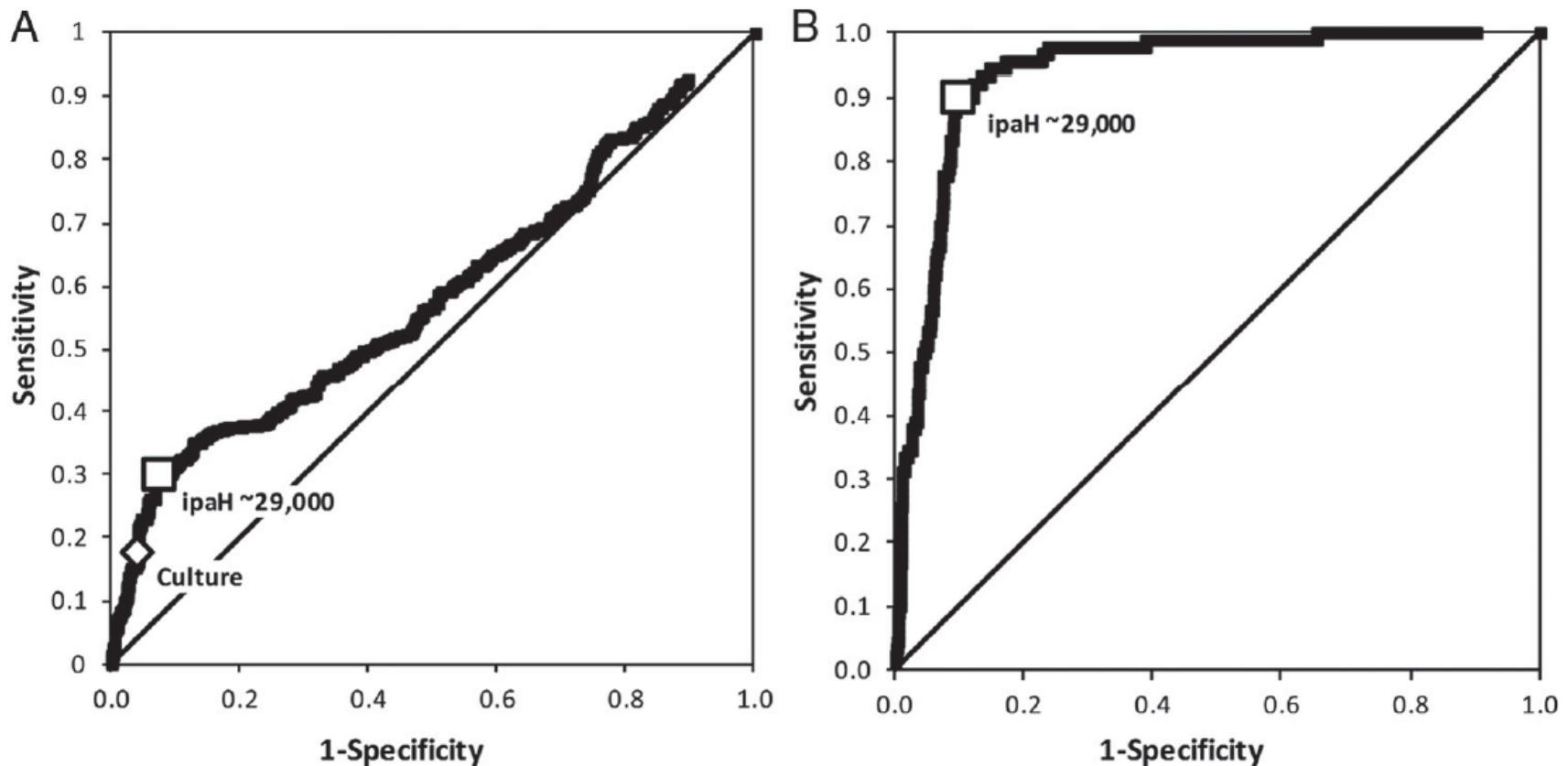
The bars show the incidence rates and the error bars show the 95% CIs.

# GEMS – main initial findings

- Odds of dying during follow-up were 8.5X higher in children with mod to severe diarrhea as compared with controls
- Case mortality at African sites as high as 7.5%!
- Interventions are needed to target:
  - rotavirus
  - *Shigella*
  - ST-EPEC
  - *Cryptosporidium*
  - Typical enteropathogenic *E coli*



# Culture estimated to have missed ~50% of *Shigella* cases in GEMS



Receiver operating characteristic (ROC) curves

# **BROAD MOLECULAR DIAGNOSTIC PANELS**

# xTAG GPP<sup>®</sup> assay - Targets

## Bacteria and bacterial toxins

- *Salmonella*
- *Shigella*
- *Campylobacter*
- *Clostridium difficile* Toxin A/B
- Enterotoxigenic *E. coli* (ETEC) LT/ST
- *E. coli* O157
- Shiga-like Toxin producing *E. coli* (STEC) stx 1/stx 2
- *Vibrio cholerae*
- *Yersinia enterocolitica*

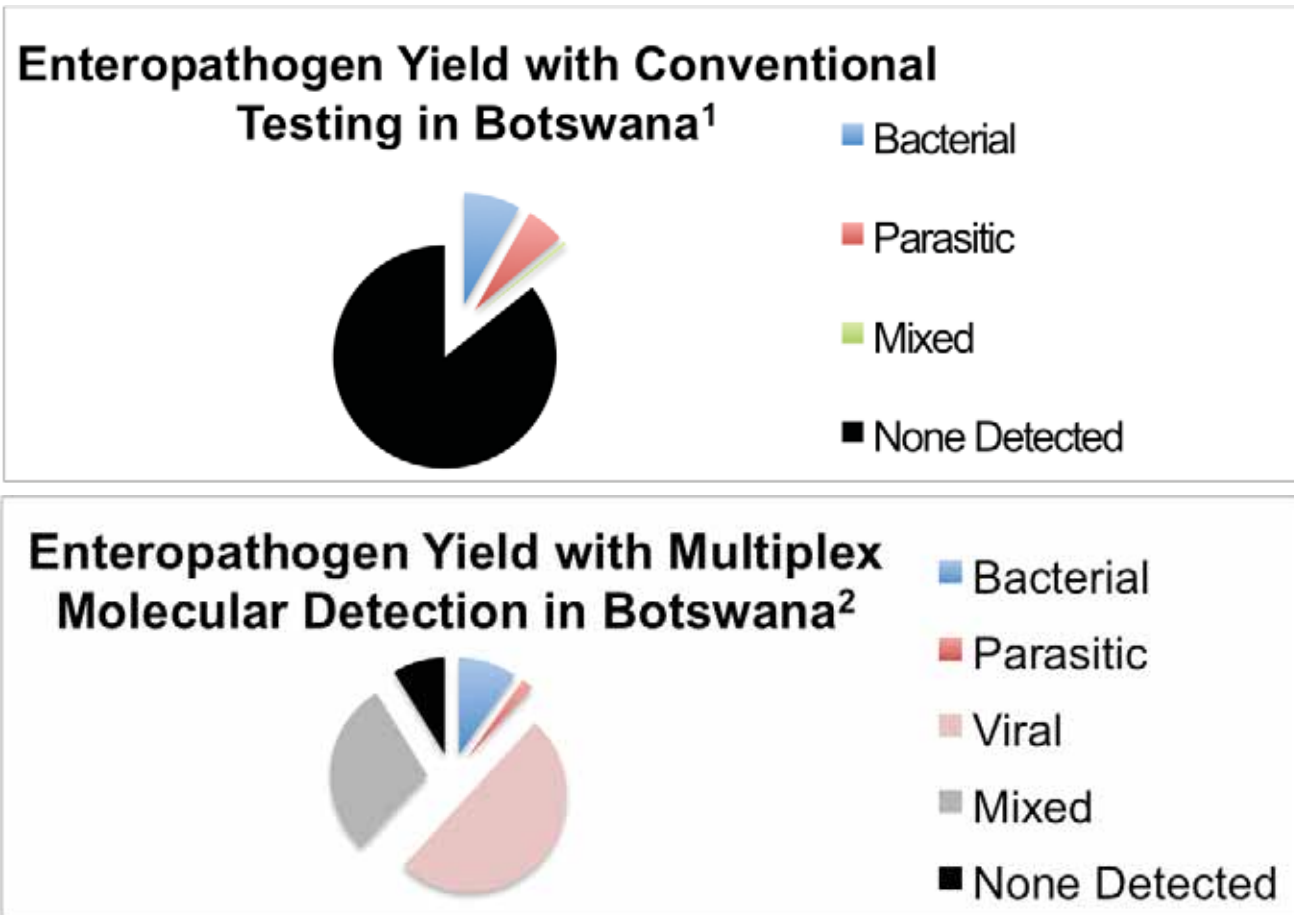
## Viruses

- Adenovirus 40/41
- Rotavirus A
- Norovirus GI/GII

## Parasites

- *Giardia*
- *Entamoeba histolytica*
- *Cryptosporidium*

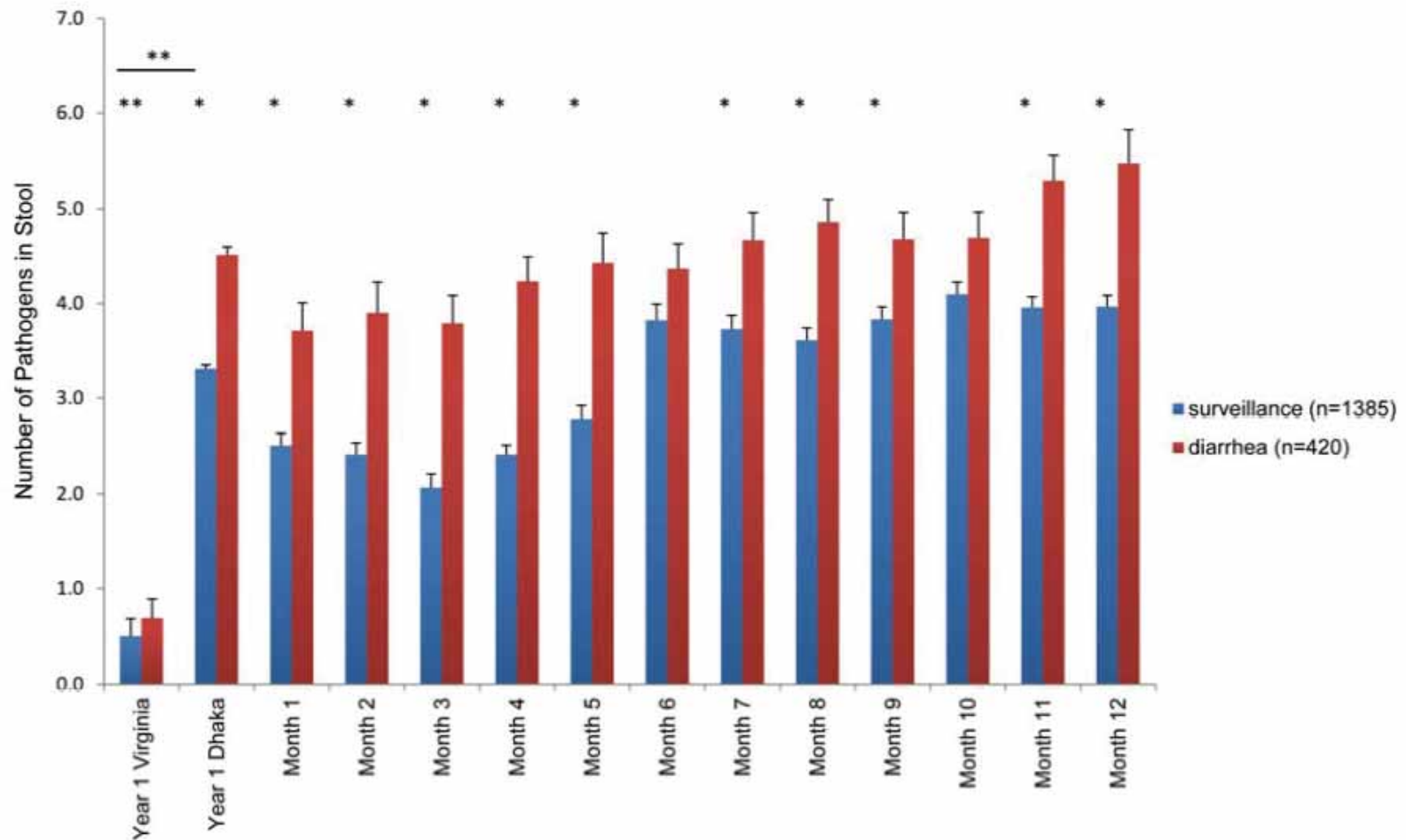
# Newer More Sensitive Techniques



1. Rowe J, et al. PLoS One. 2010 June 2;5(6):e10924.

2. Goldfarb DM et al. PAS. Boston 2012.

# 32 Pathogen Gene targets (Luminex)



# The Intestinal Pathobiome: Its Reality and Consequences Among Infants and Young Children in Resource-Limited Settings

Edward T. Ryan

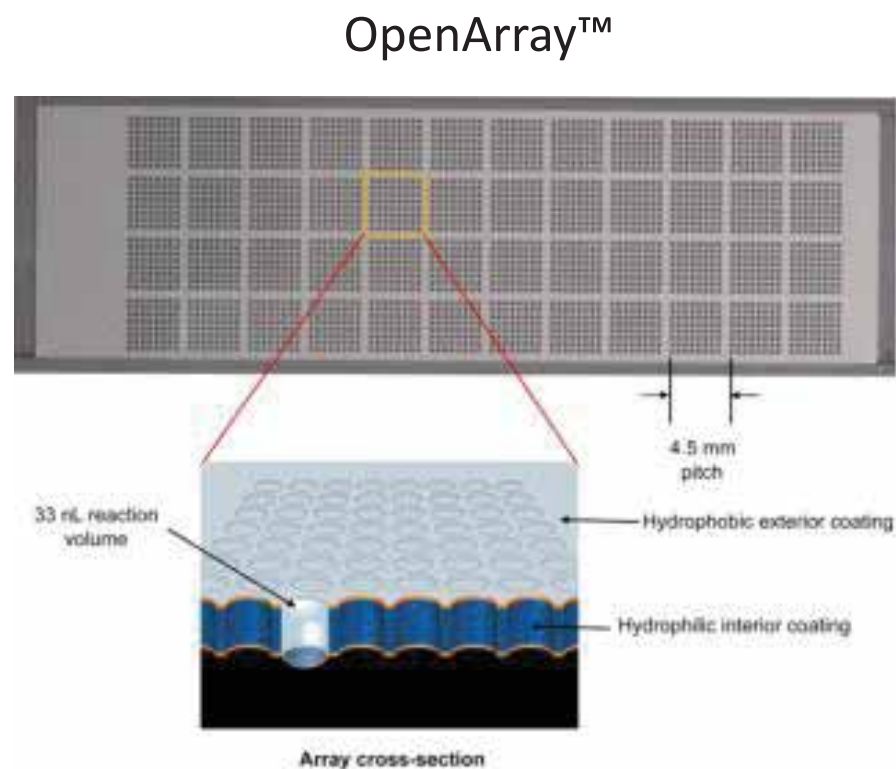
- Mean of 4.3 pathogen targets in “healthy” controls
- Concept of “pathogen excess”

# Nunavut – another high burden setting



# Enteric panels for public health surveillance

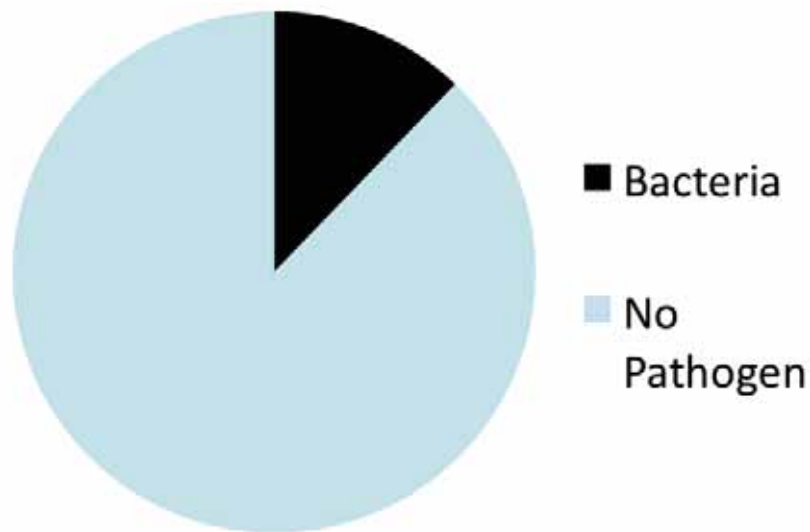
- As part of National Enteric Surveillance Program (NESP) in 2012 Nunavut had only reported
  - 2 Campylobacter
  - 8 Salmonella
  - 1 E. coli O157



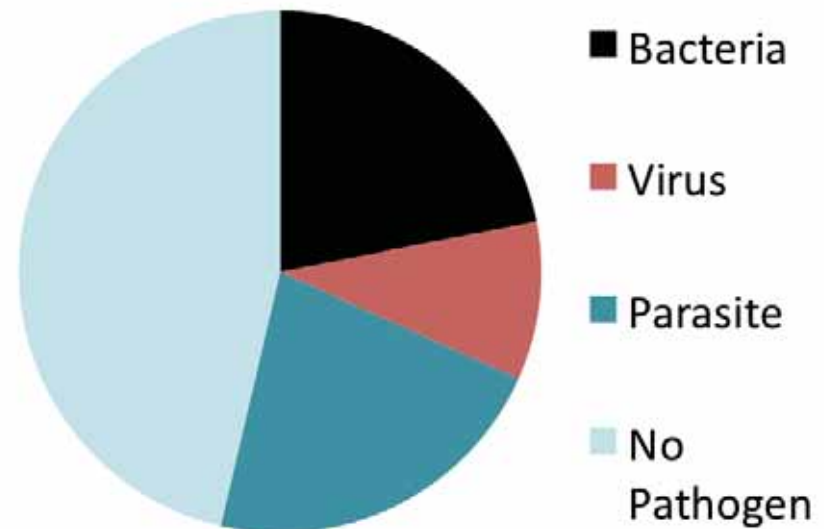


# PCR Detection of Enteric Pathogens – clinical samples submitted to Iqaluit hospital (QGH)

## Clinical Testing



## Real time PCR



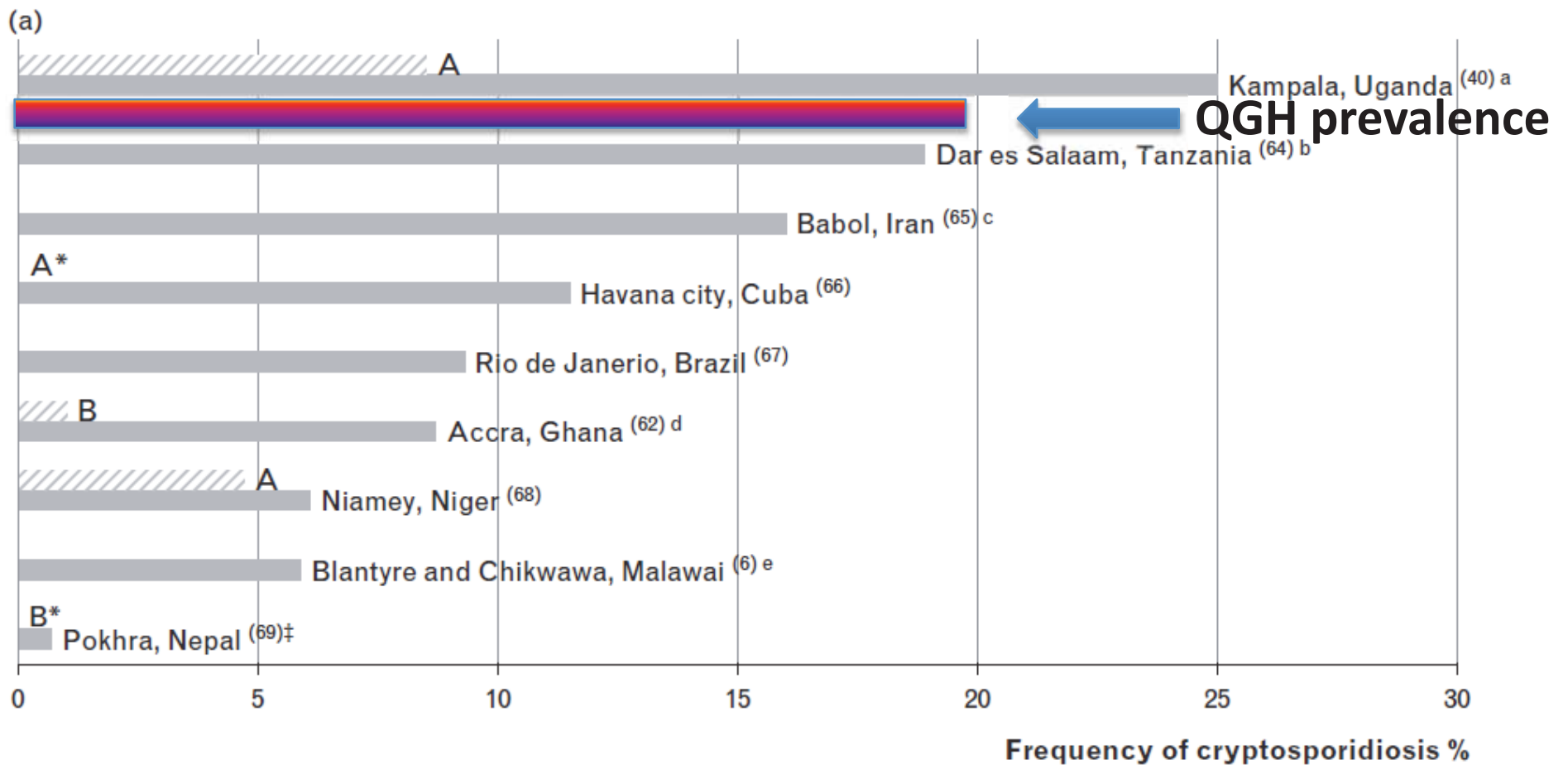
# Novel Diagnostics - Public Health

*old specimens, new tools*

*Table II.* Nanolitre real-time RT-PCR panel results on the detection of food- and water-borne microbial agents in northern communities

Microorganism	Nanolitre PCR positives (N = 86) (%)
Bacteria	
<i>Campylobacter</i> spp.	6 (7.0)
<i>Salmonella</i> spp.	6 (7.0)
<i>Clostridium difficile</i> with toxin B detected	5 (5.8)
<i>Shigella</i> spp.	1 (1.1)
Parasites	
<i>Cryptosporidium</i> spp.	17 (19.8)
<i>Giardia</i> spp.	1 (1.1)
Viruses	
Astroviruses	4 (4.6)
Noroviruses groups 2	3 (3.5)
Rotaviruses	1 (1.1)

# How common is Cryptosporidium in Iqaluit compared to rest of world?

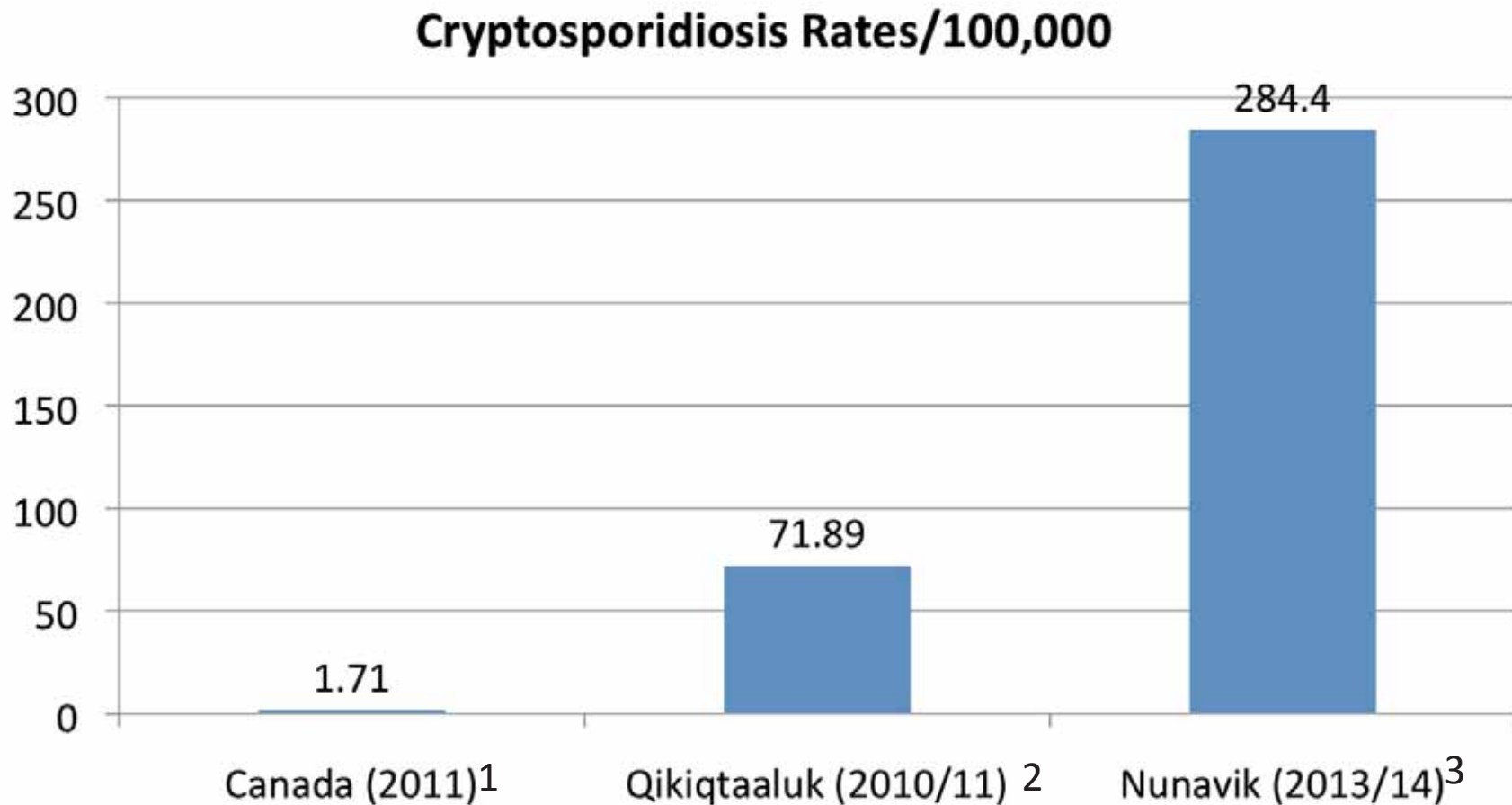


# Cryptosporidium – discovery new kid on the map



Slide courtesy Dr. Cedric Yansouni McGill University

# Cryptosporidium is a big problem in the Arctic!



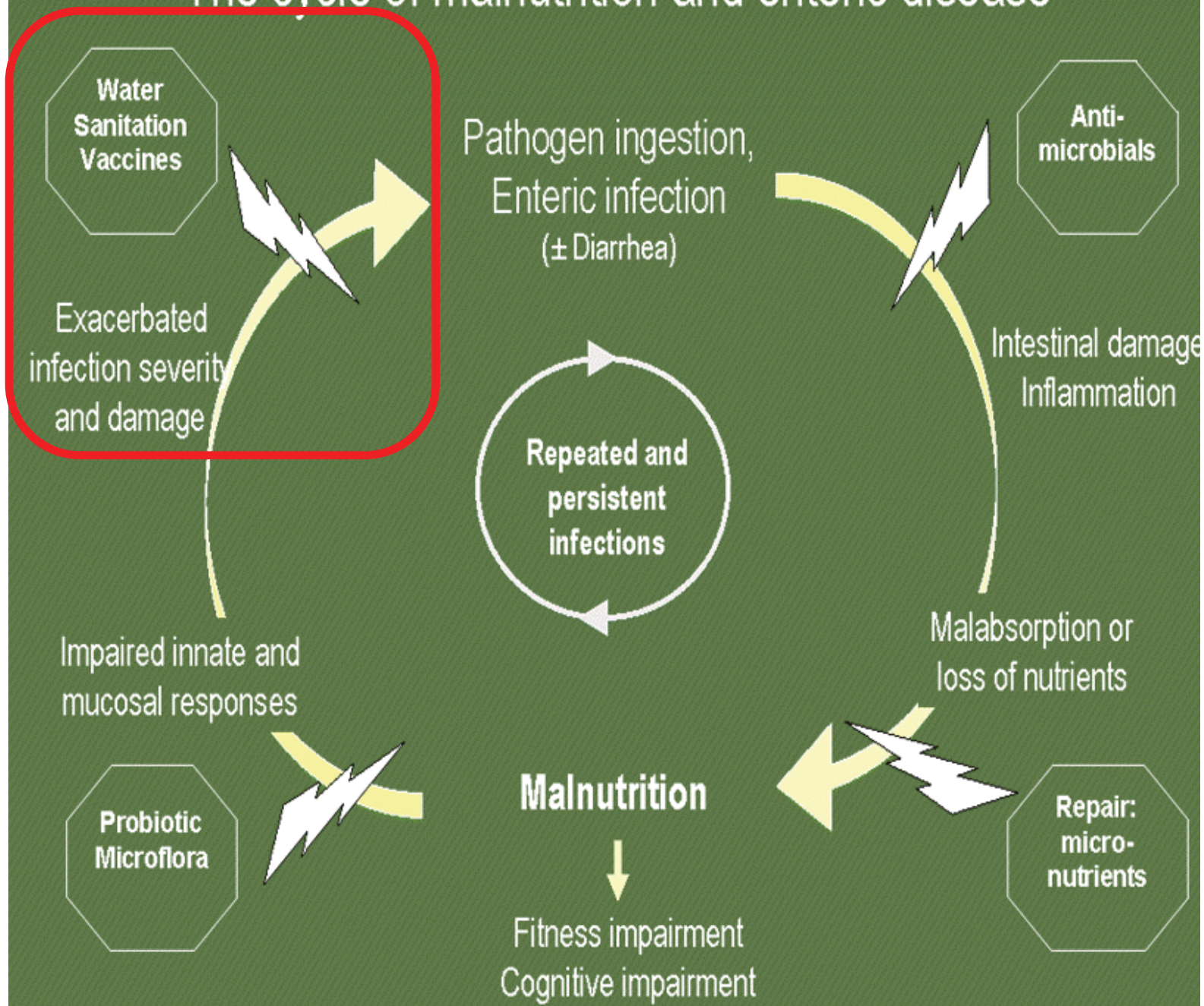
1. Canadian Notifiable Disease Surveillance System (CNDSS) 2011
2. Goldfarb DM et al; Int J Circumpolar Health. 2013;72:19903.
3. Thivierge K et al.; PLoS Negl Trop Dis. 2016 Apr 8;10(4):e0004534.

# Outline

- Global burden of childhood enteric infections
- New insights from enhanced diagnostic studies
- **Examples of efforts to address childhood diarrheal disease**



# The cycle of malnutrition and enteric disease





# Rotavirus is the leading cause of severe gastroenteritis worldwide

Among children <5 years:

- **453,000 deaths**
- 37% of deaths attributable to diarrhea
- 5% of all under 5 yr old deaths
  
- 40% of hospitalizations for diarrhea in Africa

# Rotavirus vaccination

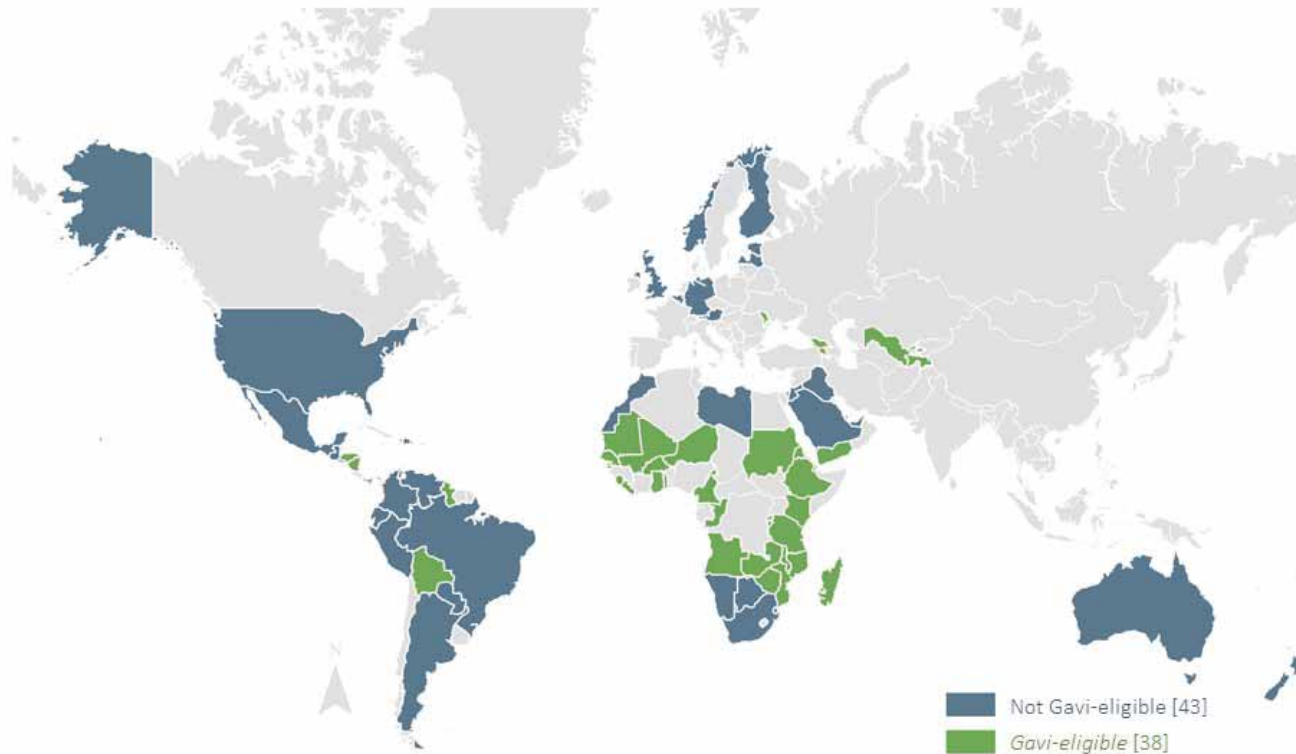


**WHO Recommends Global Use of Rotavirus Vaccines**  
*Decision Could Help Protect Millions of Children in Africa and Asia  
from Lethal Diarrheal Disease*

- Americas and Europe – 2006
- Africa and Asia - 2009

# Scale-up of rotavirus vaccine

81 countries\* have introduced RV nationally

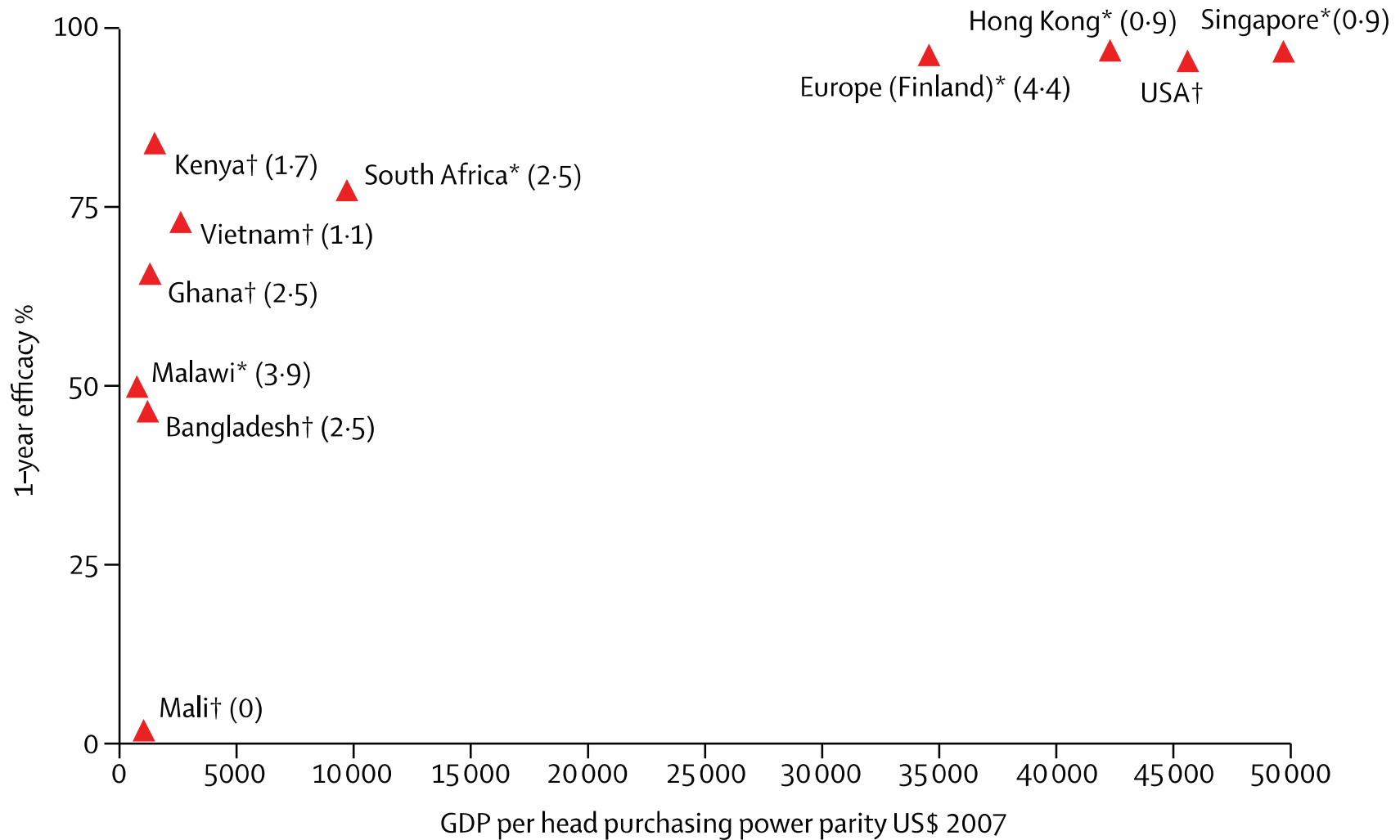


\*As of May 1, 2016  
RV = rotavirus vaccine



[http://sites.path.org/rotavirusvaccine/files/2016/05/PATH-Worldwide-Rotavirus-Vaccine-Introduction-Map-EN-2016.05.01\\_blank.jpg](http://sites.path.org/rotavirusvaccine/files/2016/05/PATH-Worldwide-Rotavirus-Vaccine-Introduction-Map-EN-2016.05.01_blank.jpg)

# Vaccine efficacy and GDP



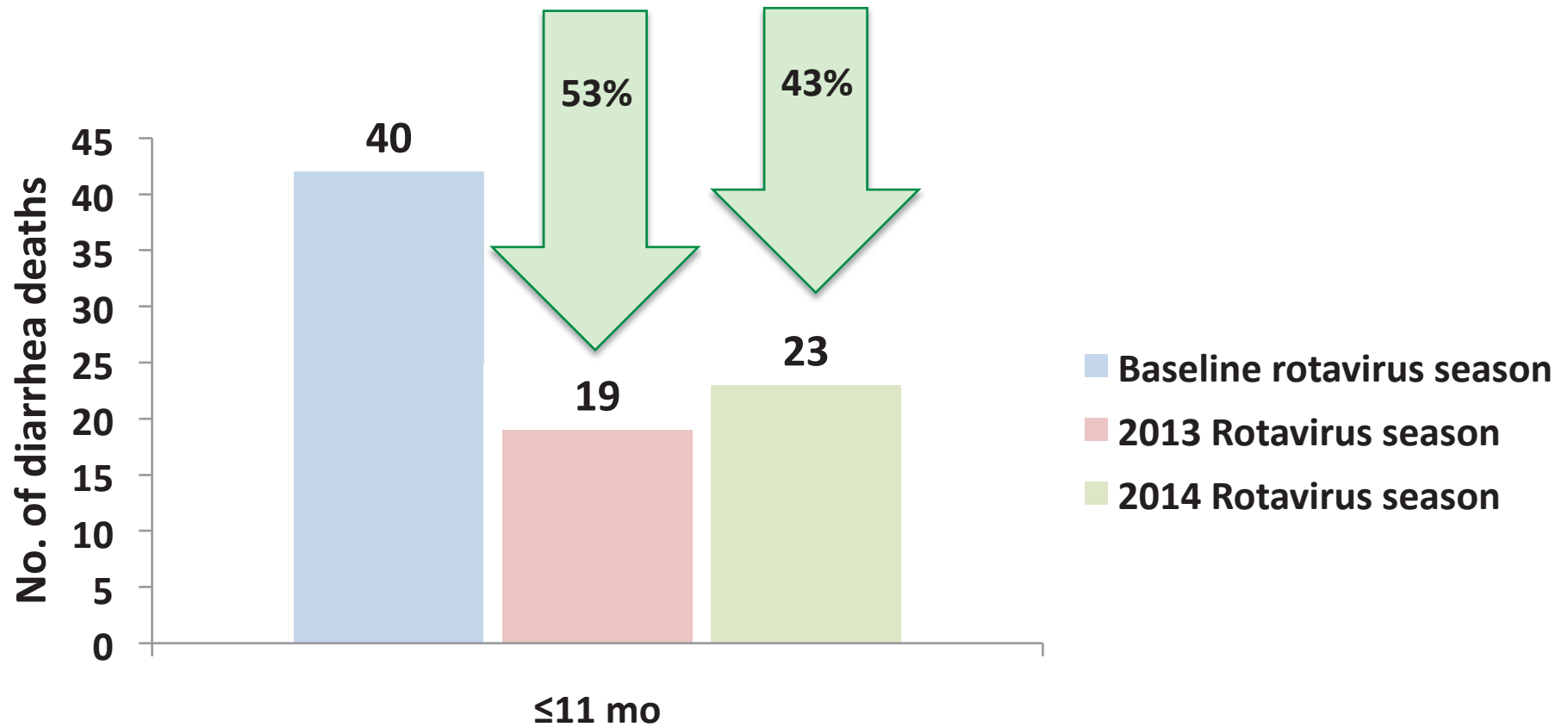
# Botswana RV Vaccine Impact Study

- **Botswana among first African countries to introduce RV vaccine in 2012**
- **High in hospital gastroenteritis mortality**

Pediatr Infect Dis J. 2013 May;32(5):570-2

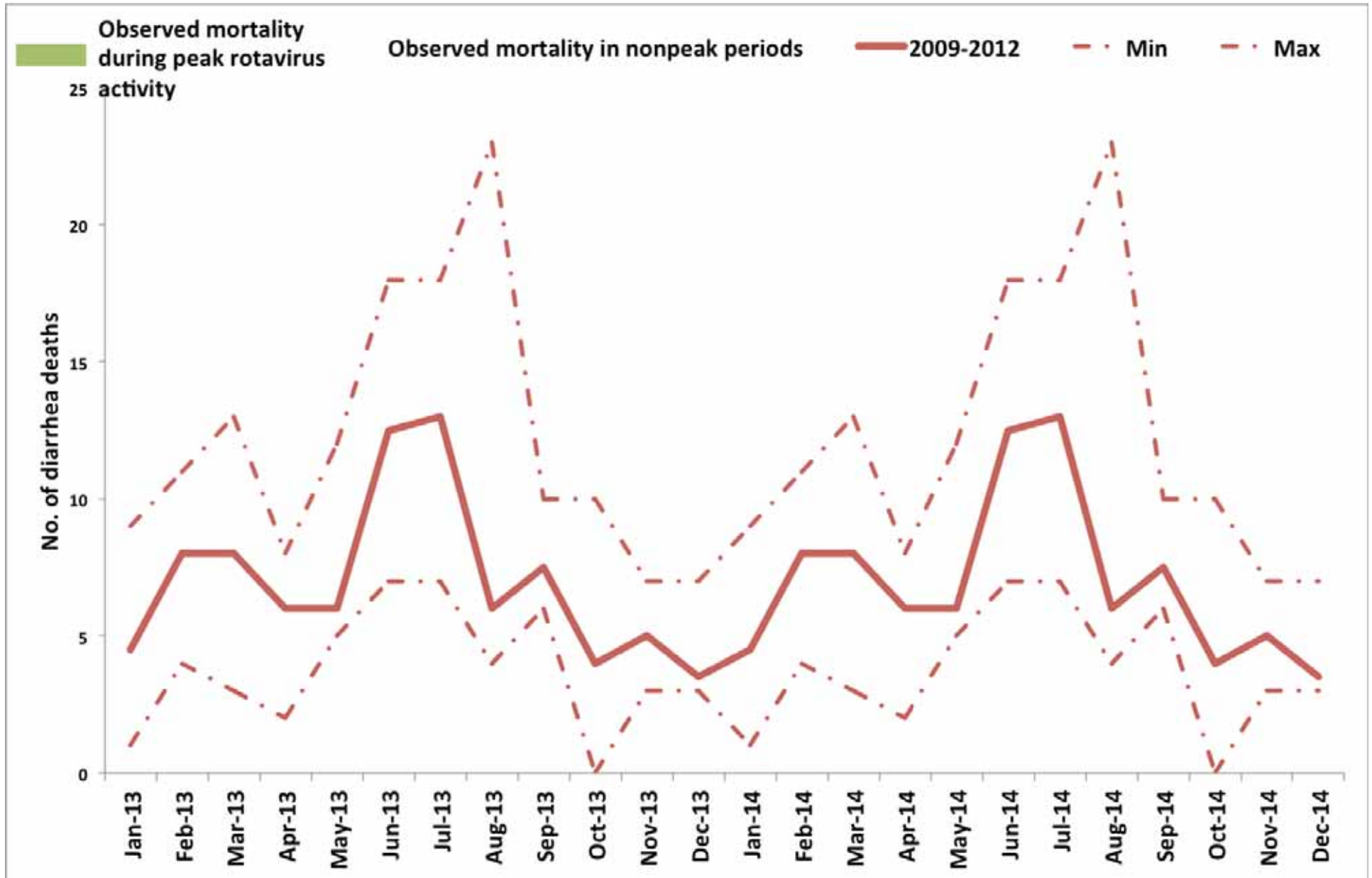


# Rotavirus season deaths



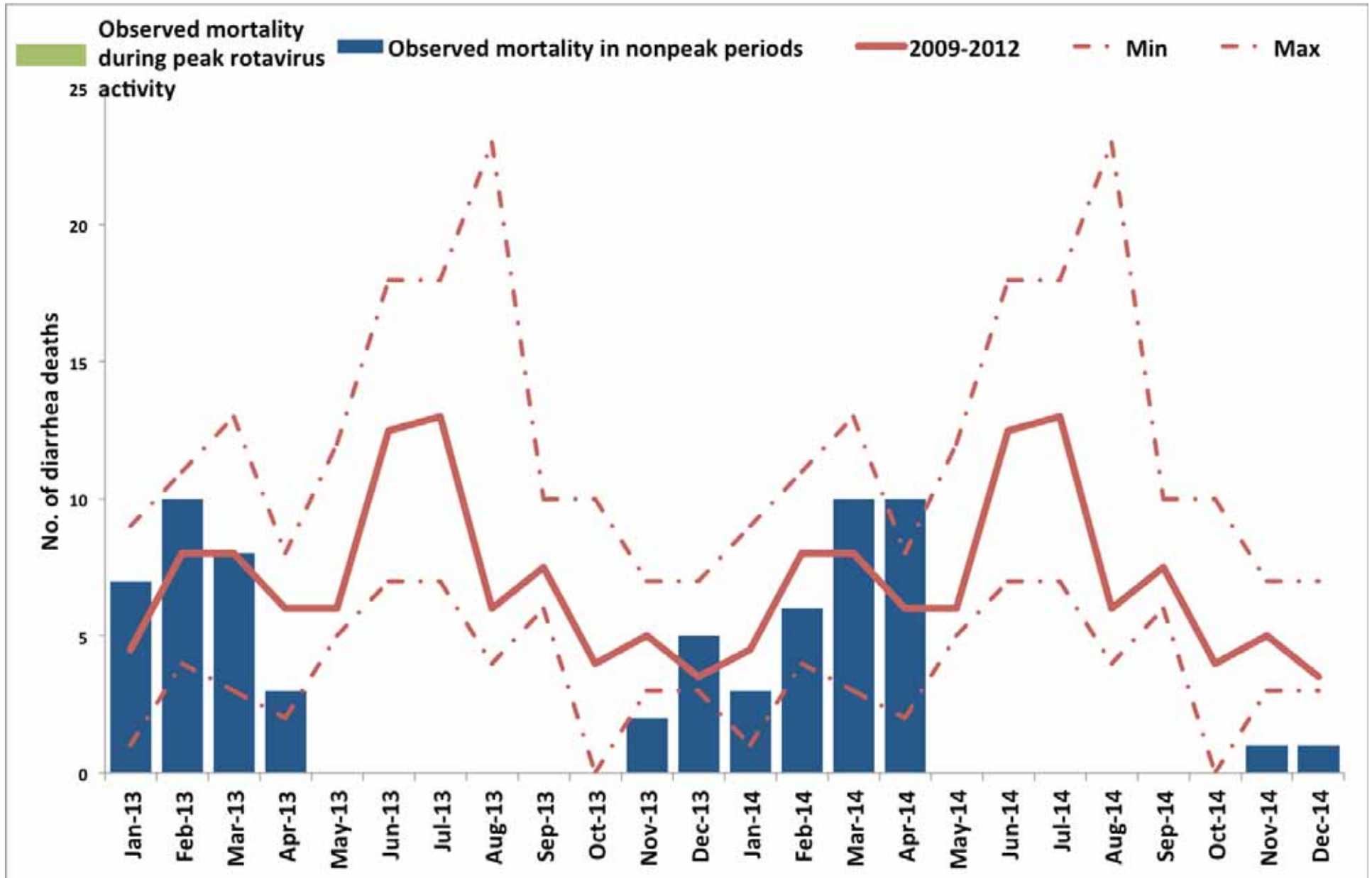
Rotavirus season = May to October

# Deaths

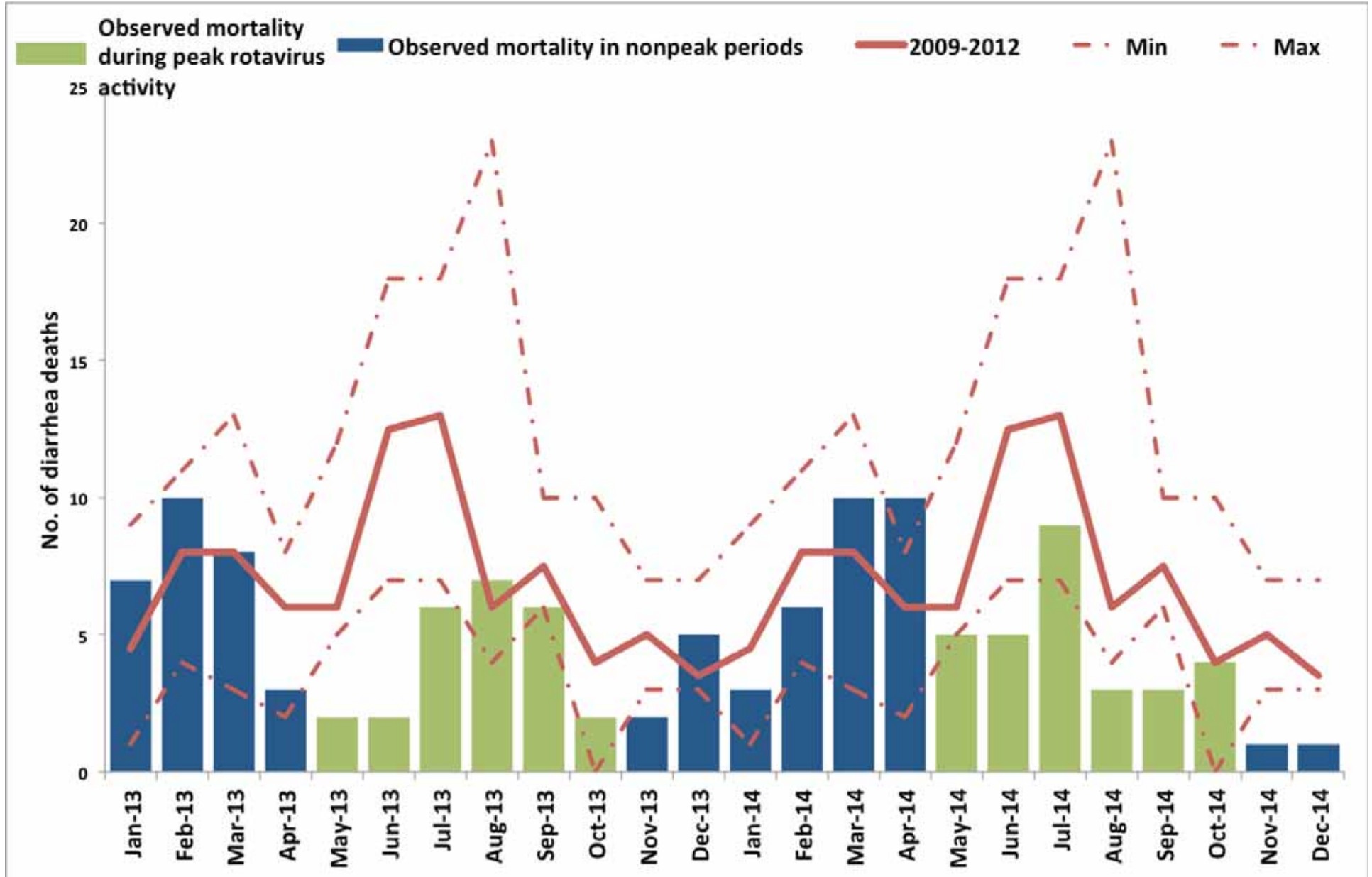




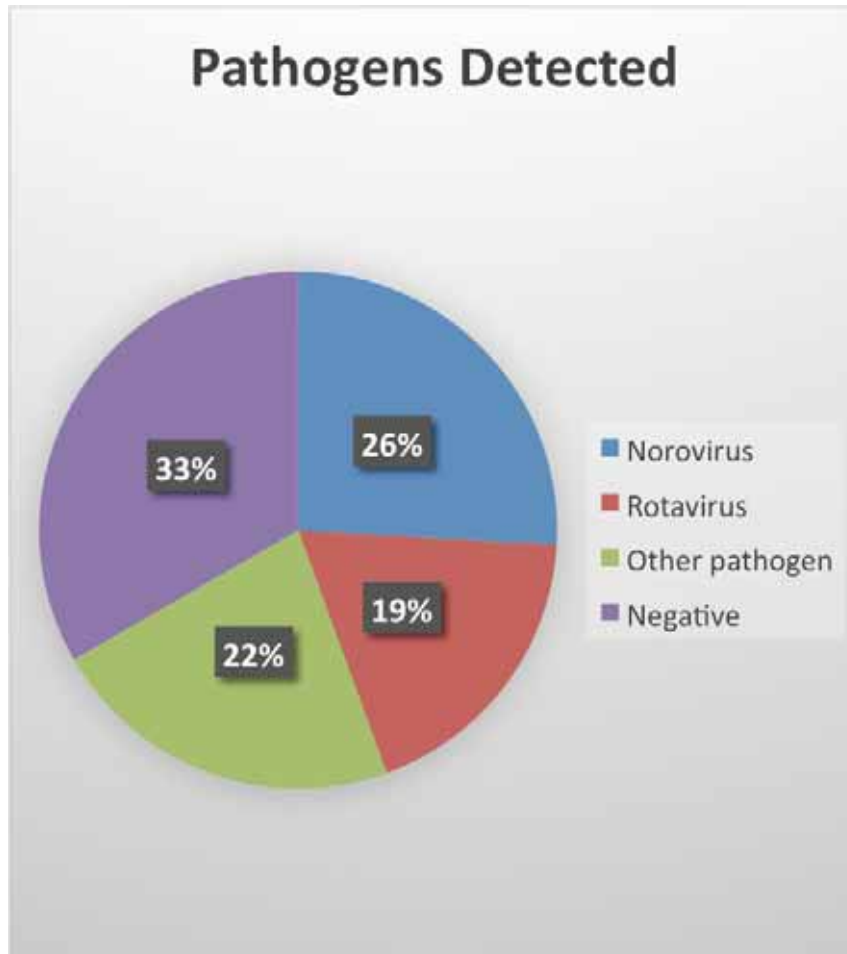
# Deaths



# Deaths



# Hospital Acquired GE in Botswana



- **4/32 (12%) in-hospital mortality at one site**
- **Rotavirus 2<sup>nd</sup> leading pathogen @ 19%**

# 'WaSH' interventions



## **SAFE WATER/ ADEQUATE SANITATION**

Treat water before use and  
dispose of waste safely



## **IMPROVED HYGIENE**

Wash hands when appropriate

<http://www.cdc.gov/healthywater/global/diarrhea-burden.html>

# WaSH Interventions

Two major trials ongoing

- WASH Benefits Bangladesh
- WASH Benefits Kenya
- Sanitation Hygiene Infant Nutrition Efficacy trial**  
- Zimbabwe





# SHINE Trial Design

## Sanitation/Hygiene

1. VIP latrine
2. 2 Tippy Taps



3. POU Water treatment

4. Clean area for eating and play

5. Behavior Change!

## Nutrition & Sanitation/Hygiene

## Nutrition

- 20 g Nutributter daily provided for infants (6-18 mo)



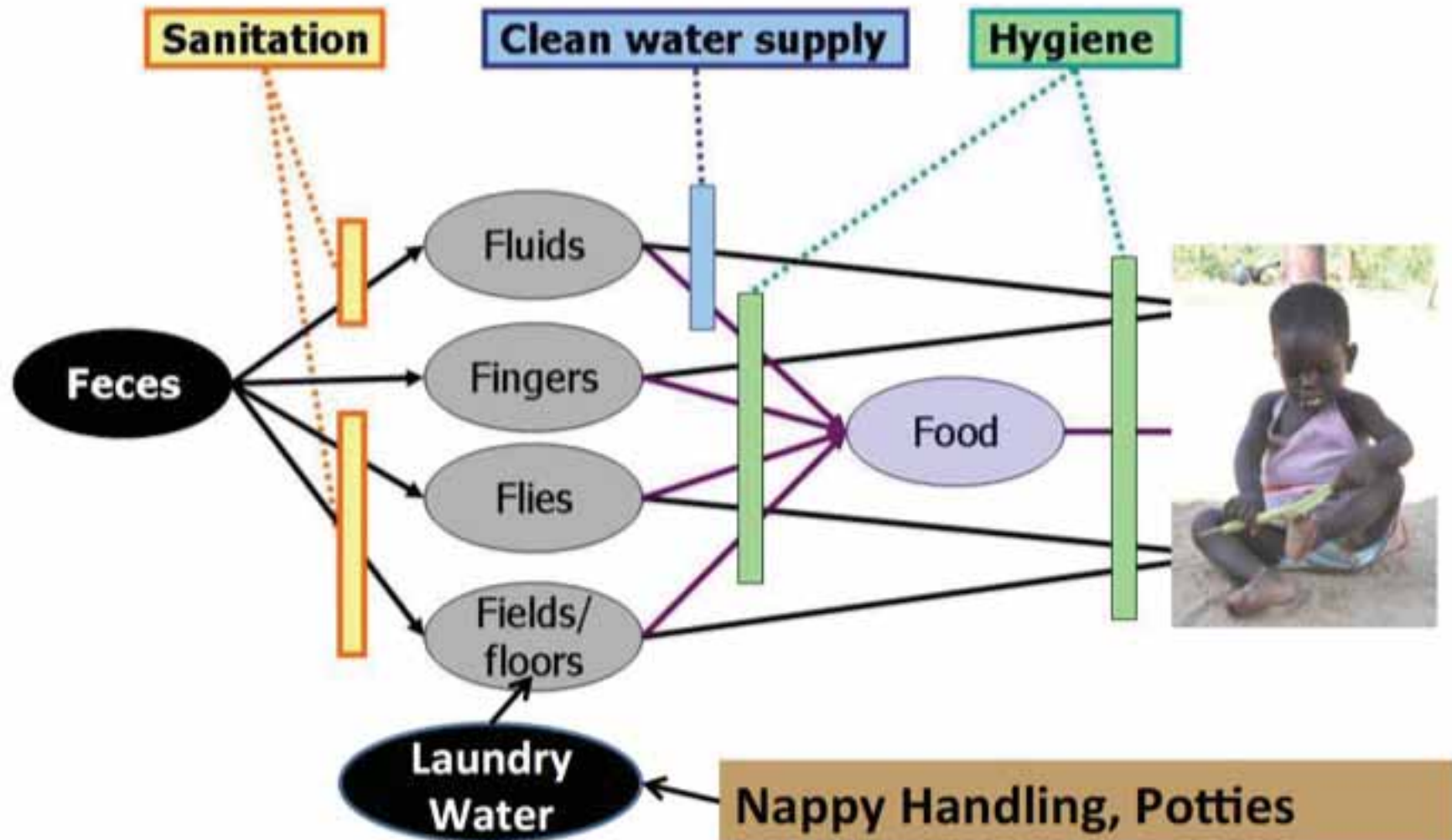
- Behavior Change! optimal use of local foods for complementary feeding

## Standard Care

Strengthened early antenatal care and Exclusive Breastfeeding



# Routes of fecal disease transmission and protective barriers *for babies!*





- Infant's own fingers most frequently mouthed
- 38 times in 6 hours
- 75% of the time visibly dirty

- Frequent ingestion of soil, chicken feces and stones



# Causes of intestinal damage in rural Zimbabwean infants

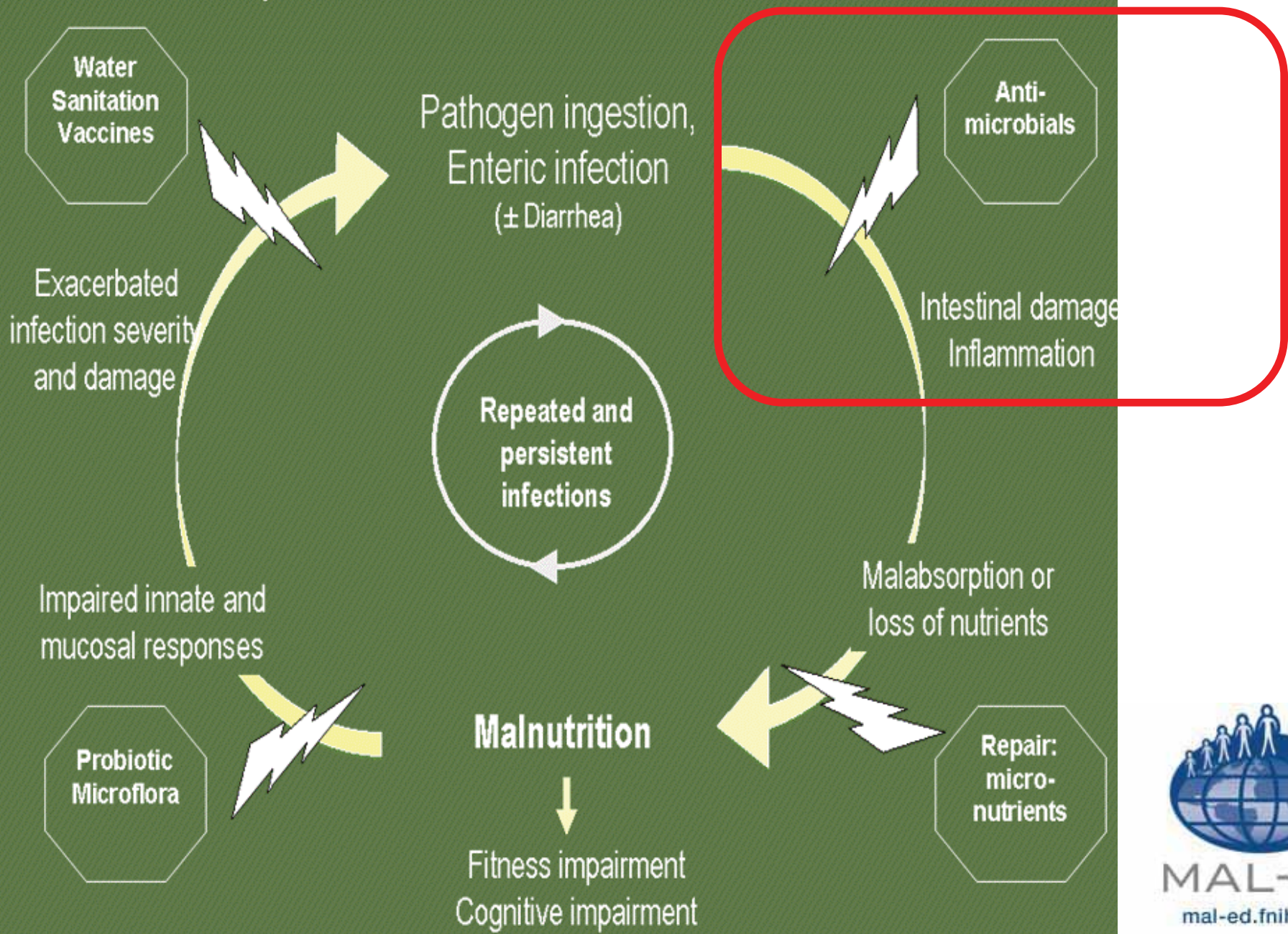
	% houses with E coli + sample	Mean E Coli cfu/g	Mean E Coli "per serving size" cfu/g
Infant food	0%	0	0
Drinking water	54%	2	<b>800</b>
Wet shaded soil	60-80%	69	<b>2,100</b>
Chicken feces	100%	10,000,000	<b>10,000,000</b>

# Protective play area





# The cycle of malnutrition and enteric disease



# “Nicole”

- Has kwashiokor (edematous malnutrition) and admitted with acute diarrhea
- Has a ~ **1/4 chance of dying<sup>1</sup>** during this admission

# “Nicole”

- What can we do to ensure that she has the best outcome possible?
  - Survival
  - Long-term growth and development

# Management of diarrhoea

- oral rehydration therapy key to preventing mortality
- zinc therapy reduces diarrhoea persistence in children > 6 months
- is there anything else?



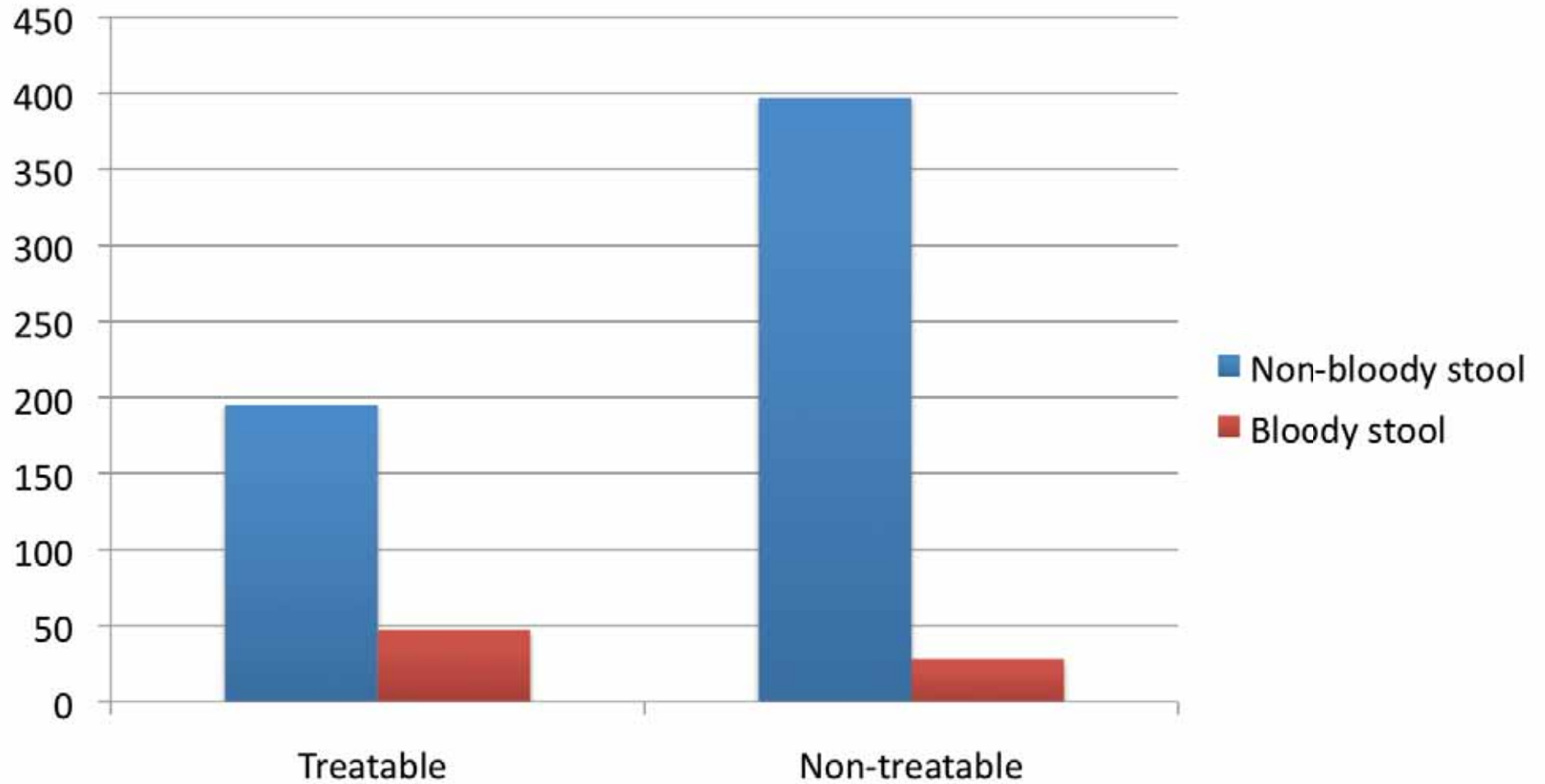
# Specific therapy

- majority of acute gastroenteritis presumed to be viral
  - WHO recommends treatment with antibiotics only for bloody dysentery
- is this assumption true in LMICs?

# Botswana 2011-2013

- n=671 children admitted to hospital with gastroenteritis
- median age 8.3 months, 11% severe acute malnutrition
- 26 deaths (case-fatality rate 3.9%)

# Indicator of treatable infection?



# Blood in stools

- presence of *Campylobacter/Shigella/* enterotoxigenic *E. coli* in stool associated with death (risk ratio 2.61, 95% CI 1.22-5.58)
  - magnitude of effect unchanged after stratifying by presence of blood in stools

# Measuring Impact of Diarrheal Diagnostics



BioFire™ - rapid pathogen detection

Immediate sample collection



**Point of Care Diagnostics for  
Diarrheal Disease**

# Study design

- experimental arms:
  1. rapid testing + treatment (if indicated) + probiotic
  2. rapid testing + treatment (if indicated) + placebo
  3. delayed testing + probiotic
  4. delayed testing + placebo
- probiotic: *Lactobacillus reuteri*  $5 \times 10^8$  cfu/mL daily x 60 days



# Interventions

- all participants treated as per standard of care (fluid resuscitation, zinc) + enteric specimens obtained
- rapid-testing groups
  - stool testing results available same-day
  - *Shigella/Campylobacter*/ETEC/EPEC: azithromycin
  - *Cryptosporidium*: nitazoxanide
- delayed-testing groups
  - swabs batched and run after the trial

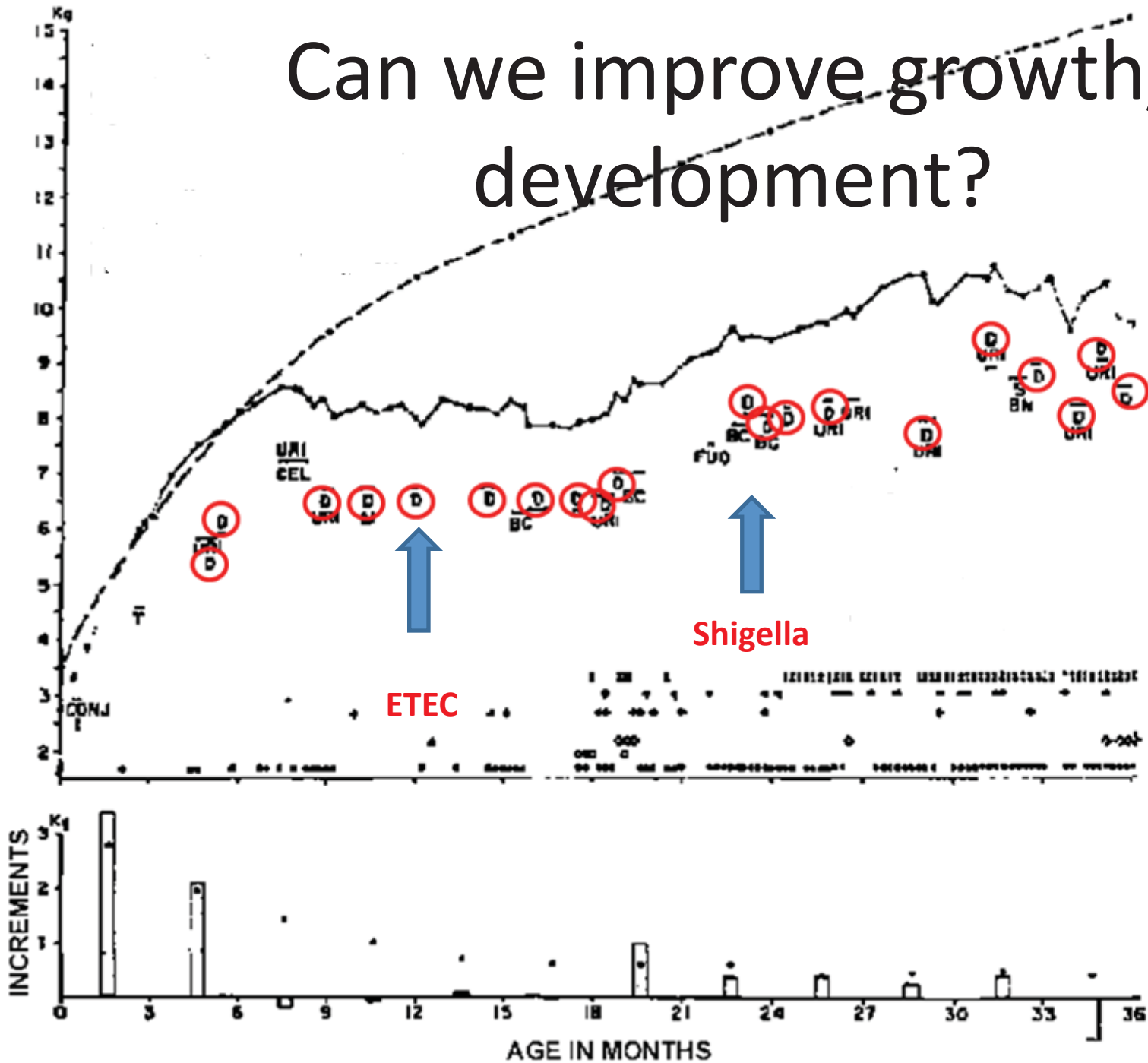
# Results – Pilot Study (n=73)

group	OR of recurrence of diarrhoea by 60 days (95% CI)	<i>p</i>
Delayed testing + placebo	(ref)	
Rapid testing + placebo	0.45 (0.12 to 1.79)	0.26
Delayed testing + <i>L. reuteri</i>	0.10 (0.01 to 0.93)	0.04
Rapid testing + <i>L. reuteri</i>	0.07 (0.01 to 0.61)	0.02

# Results – Pilot Study (n=73)

group	difference in HAZ @ 60 d adjusted for baseline (95% CI)	<i>p</i>
Delayed testing + placebo	(ref)	
Rapid testing + placebo	+ 0.33 (-0.24 to 0.89)	NS
Delayed testing + <i>L. reuteri</i>	+ 0.51 (-0.08 to 1.11)	NS
Rapid testing + <i>L. reuteri</i>	+ 0.61 (0.09 to 1.13)	0.02

# Can we improve growth/development?



Mata L et al. 1971



“Nicole” in follow up with her  
mother



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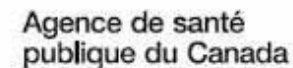
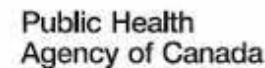
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