BC CHILDREN'S HOSPITAL
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What's New in Number Two?:

An update on pediatric acute gastroenteritis

David Goldfarb

BC Children's Hospital/UBC

March 2nd, 2017

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

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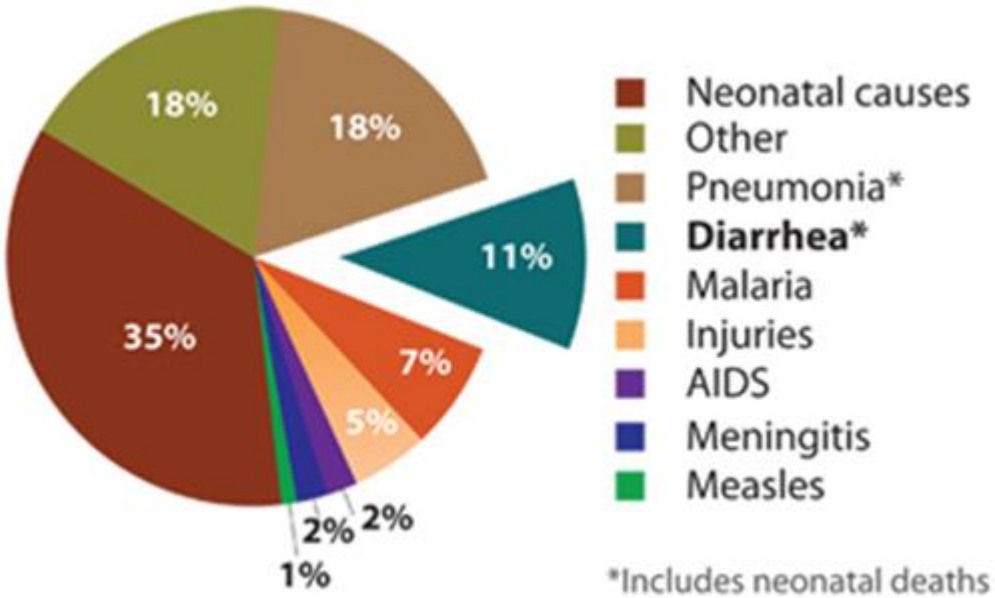
- Global burden of childhood enteric infections
- New insights from enhanced diagnostic studies
- Examples of efforts to address childhood diarrheal disease

Burden of diarrheal diseases

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



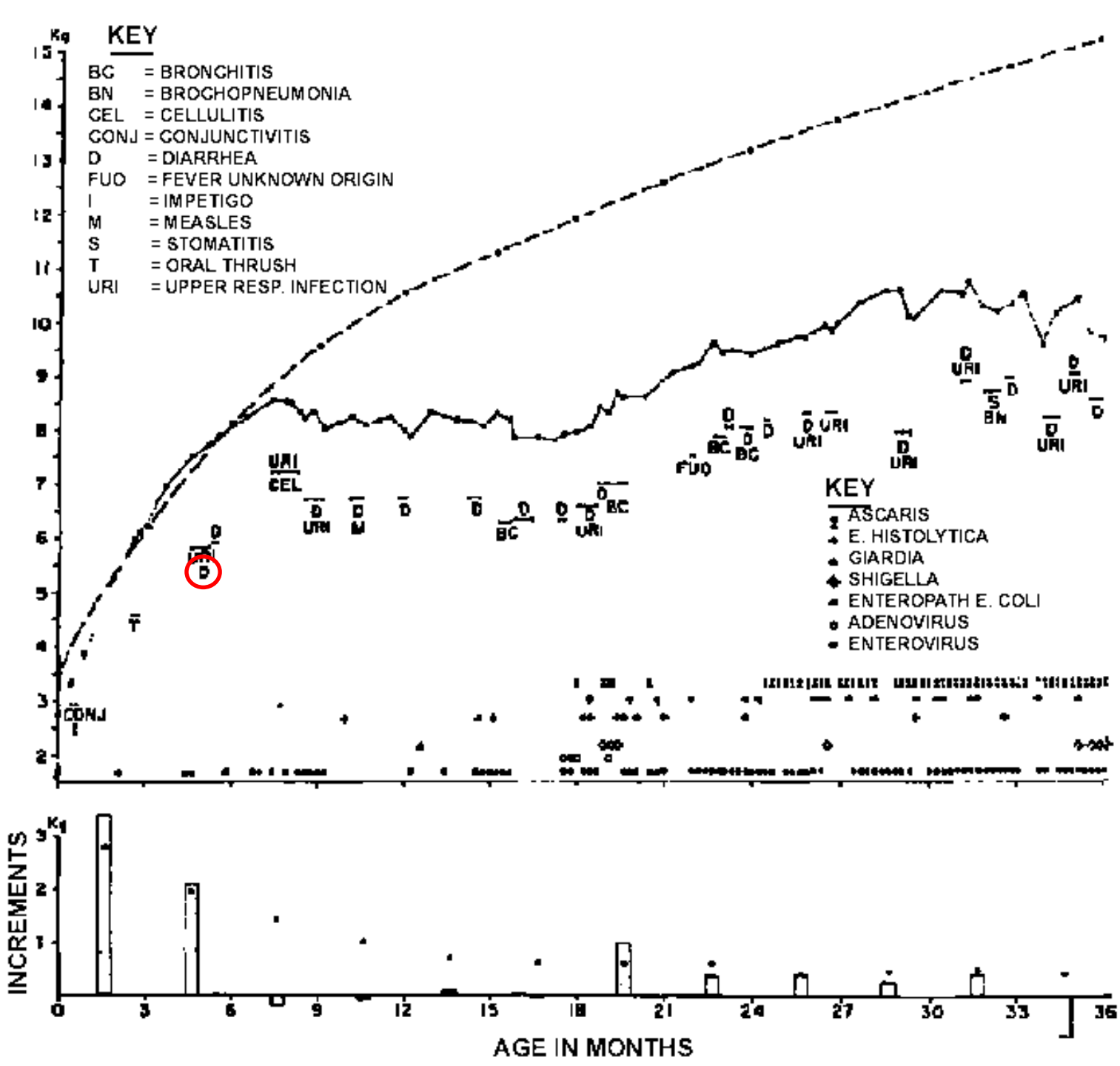
2nd leading cause of child death

Liu L *et al*, Lancet. 2012;379(9832):2151-61

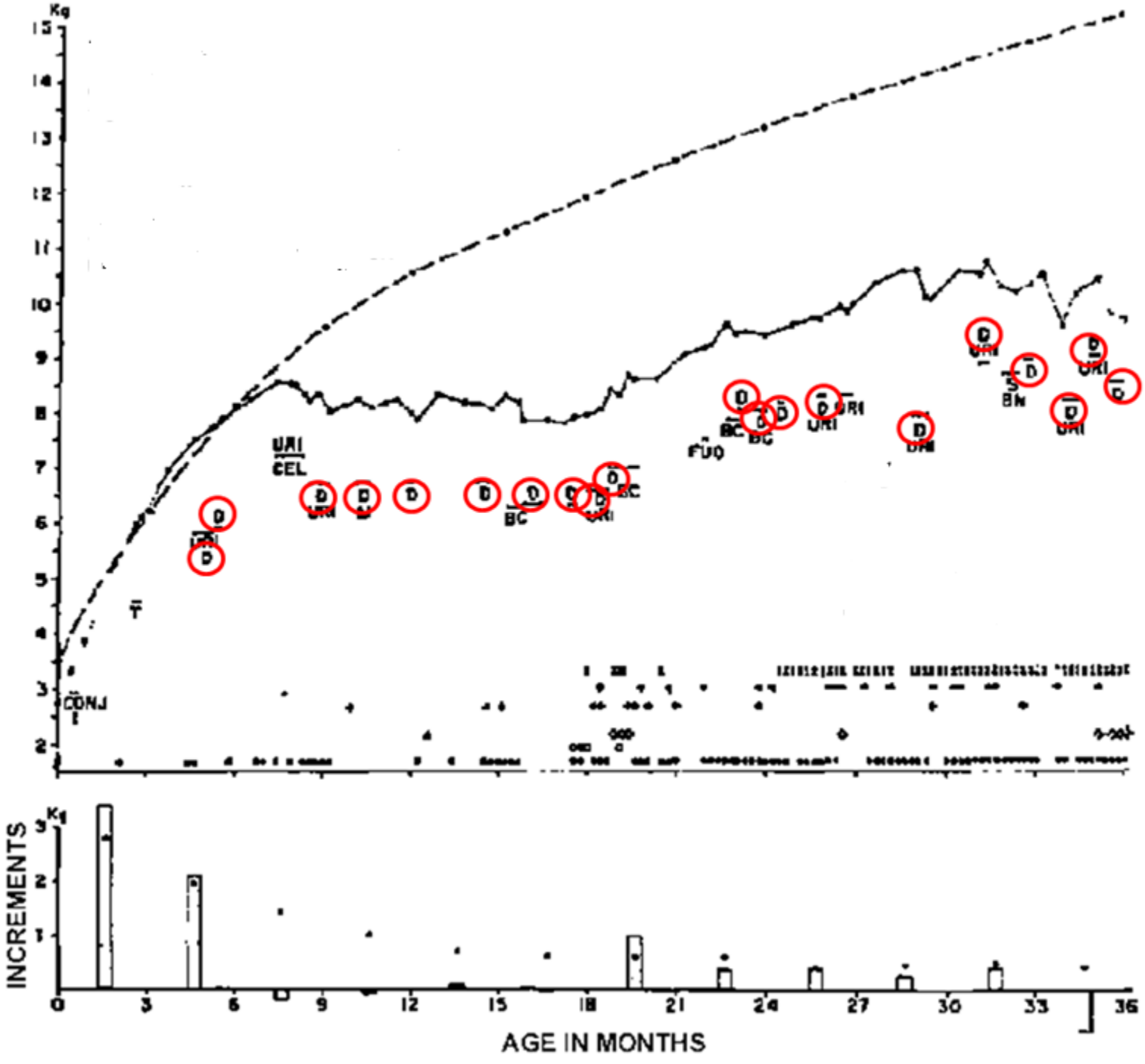
Burden Diarrheal Disease (cont'd)

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


Saturday



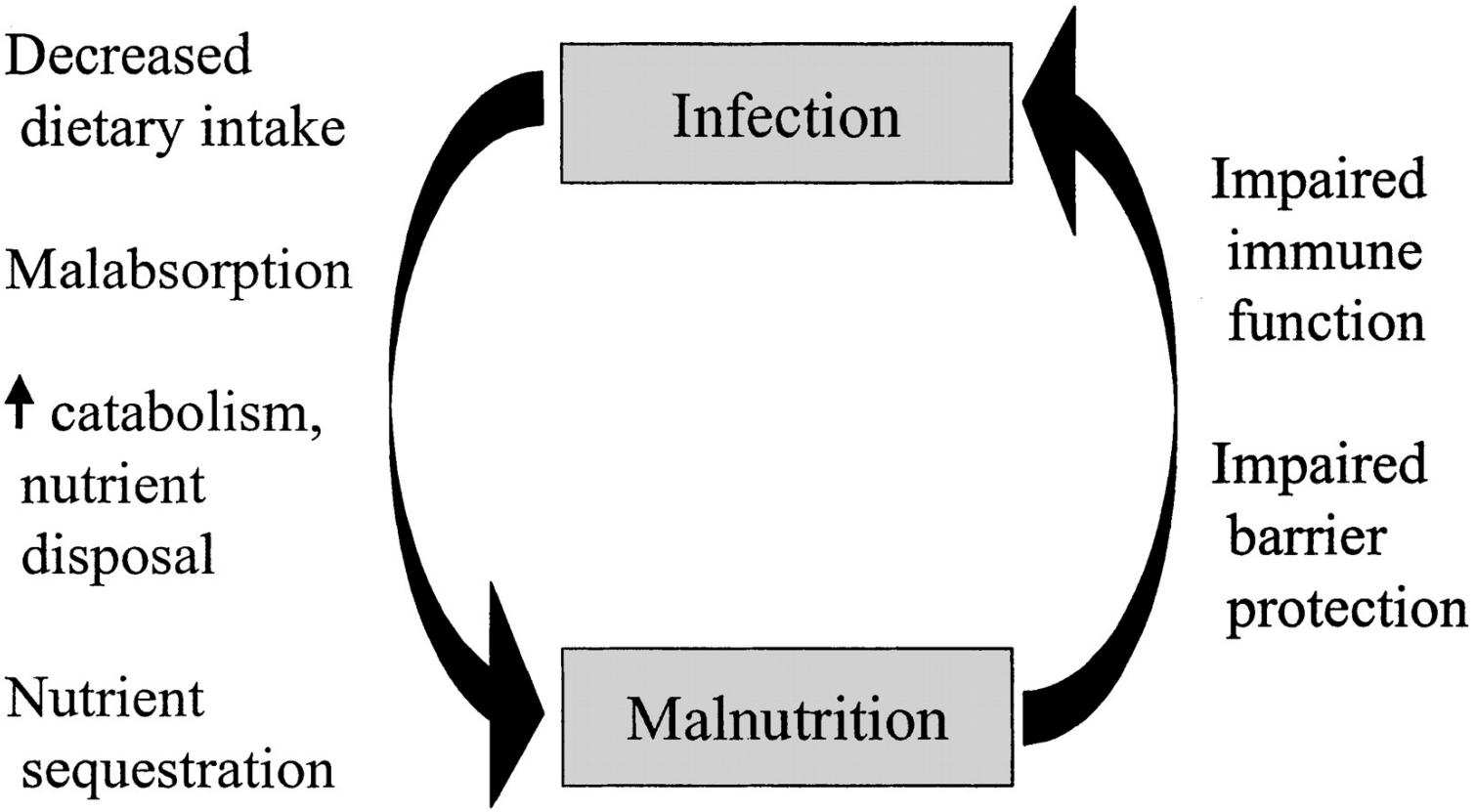
Mata L *et al.* 1971



Mata L et al. 1971

Global burden of enteric infections

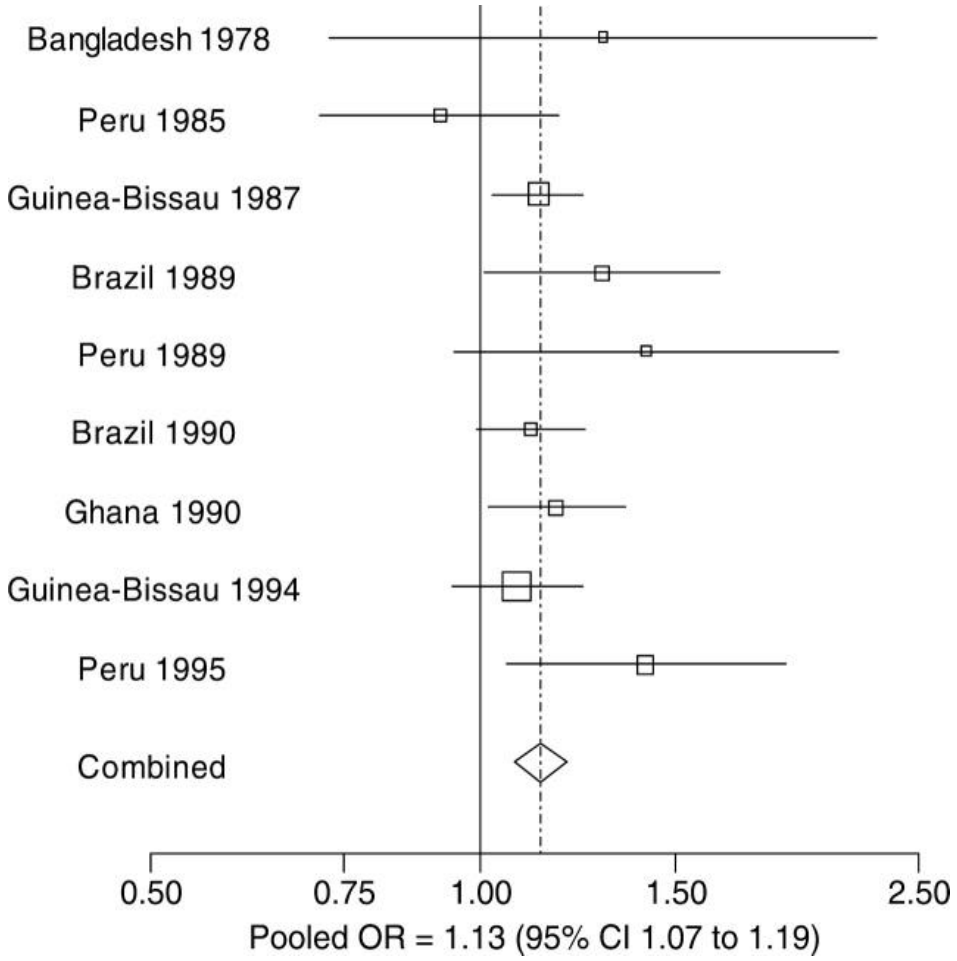
synergy between malnutrition and infection



Brown K H, J. Nutr. 2003

Global burden of enteric infections

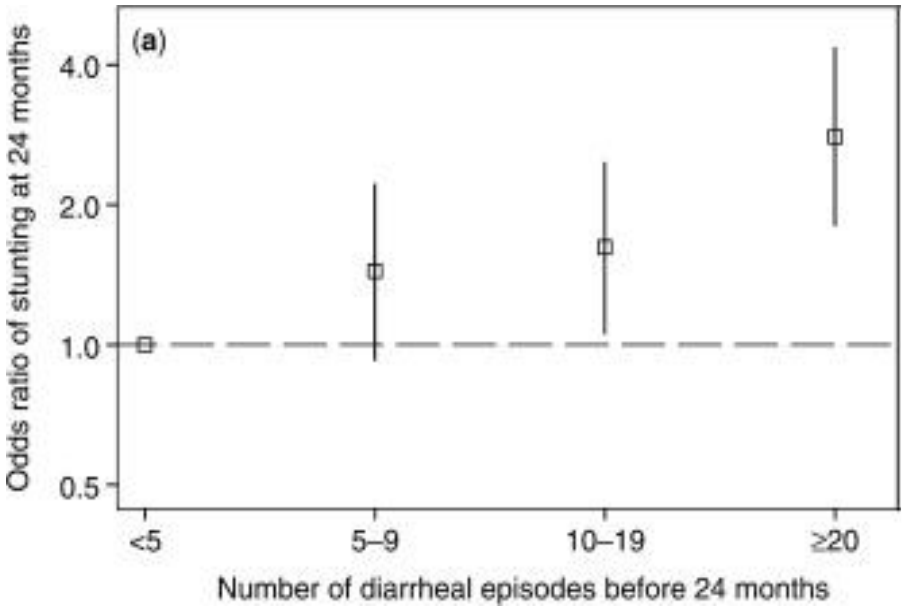
early childhood diarrhea leads to stunting (HAZ <-2)



Checkley W *et al.* Int J Epi, 2008

Global burden of enteric infections

early childhood diarrhea leads to stunting

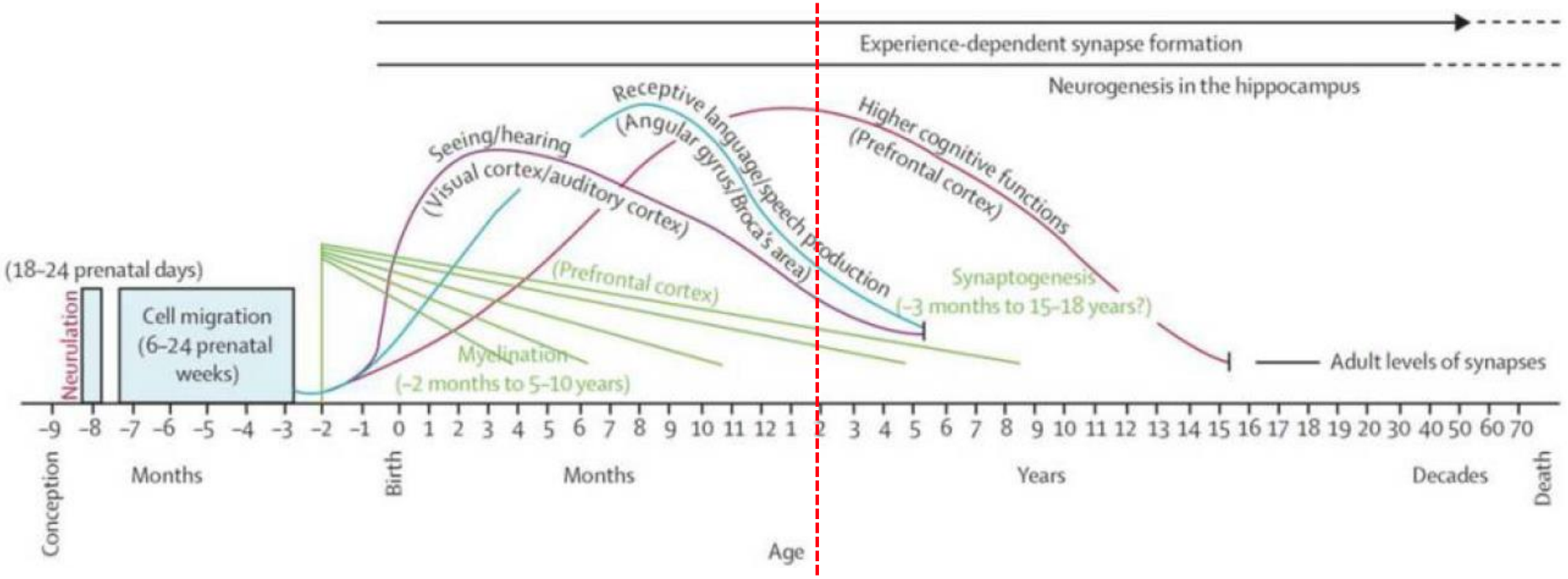


Checkley W *et al.* Int J Epi, 2008

But does being a little shorter really matter?

Global burden of enteric infections

brain development is greatest before age 2



Thompson RA, Nelson CA. Am Psychol. 2001;56:5–15

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*	Peru	Jamaica†	
	Cognitive score (8 years, n=2489)	Ravens Matrices[120] (7 years, n=603)‡	Reasoning and arithmetic (9 years, n=368)	Attained grades (18 years, n=2041)	WISC IQ[119] (9 years, n=72)	WAIS IQ‡[118] (17–18 years, n=165)	Reading and arithmetic‡ (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).

*Males only.

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

‡SD scores. WISC=Wechsler Intelligence Scale for Children. WAIS=Wechsler Adult Intelligence Scale.

Grantham-McGregor S *et al*. Lancet. 2007;369:61.

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 ±diarrhea = dec. wt gain @1m [Checkley 97]
- Crypto infections <6m/stunted = .95-1.05 cm deficits @1y [Checkley 98]
- EAggEC infections + inflammation = growth shortfalls [Steiner 98]
- Diarrrhea<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)

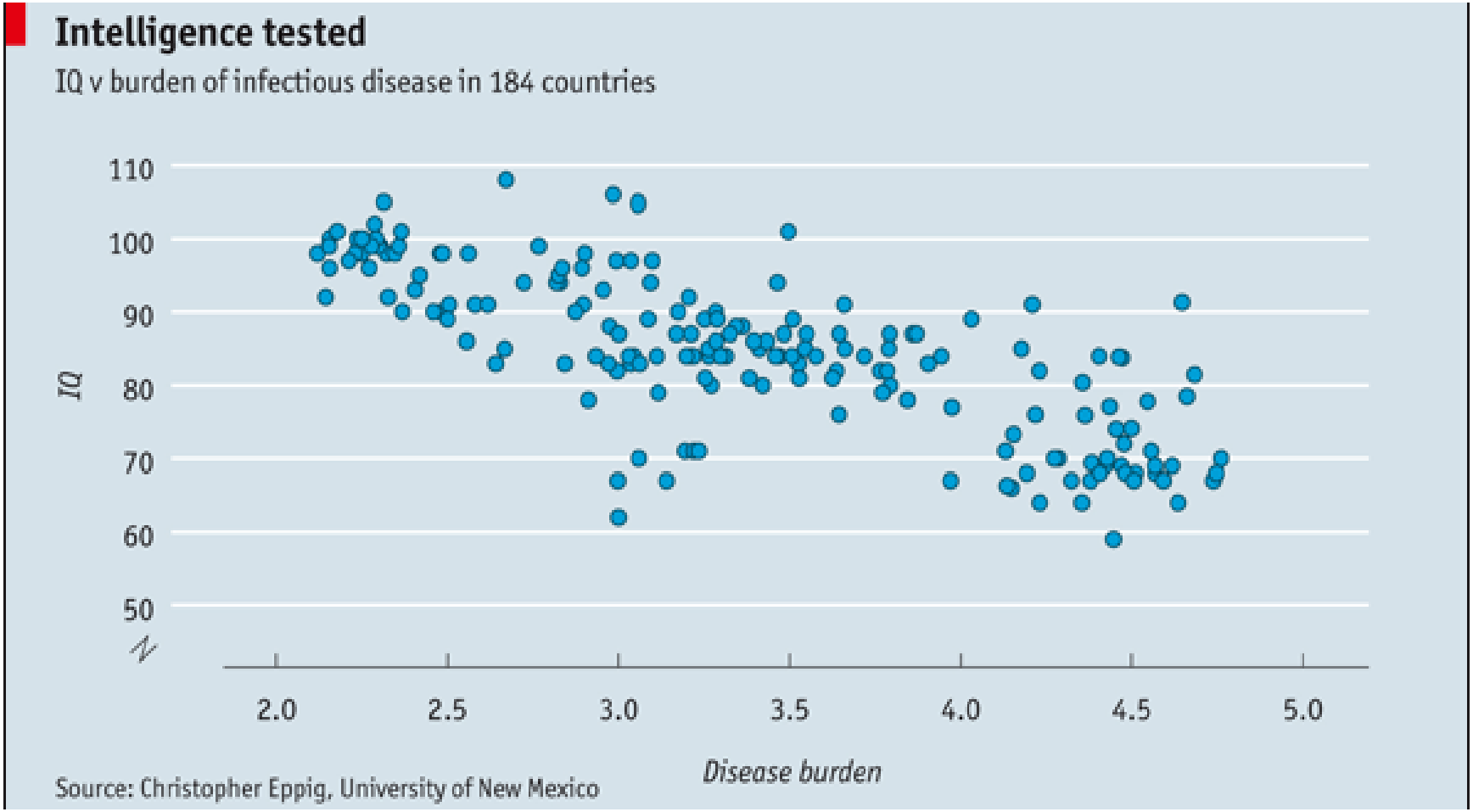
- Diarrhea <2yo = inc. AASS; AFG [Lorntz 06; Guerrant 02]

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

From: Guerrant R, Ped Acad Soc Mtg, April 30 2012

Global burden of enteric infections

overall infections and cognitive development



Eppig C et al. Proc Biol Sci, 2010

Image from* The Economist *July1, 2010


Panasonic
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Carrier

Review

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

Jessica MacIntyre[1], Jennifer McTaggart[2], Richard L. Guerrant[3], David M. Goldfarb*[4,5]

Outline

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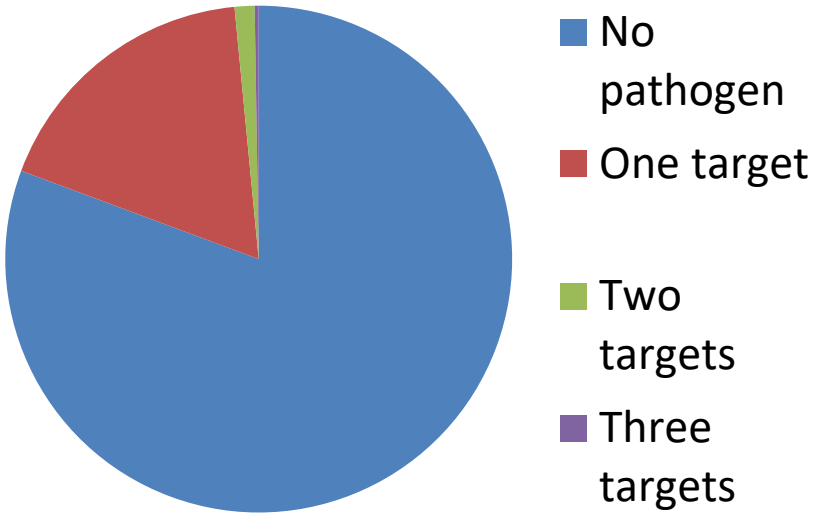
- Examples of efforts to address childhood diarrheal disease

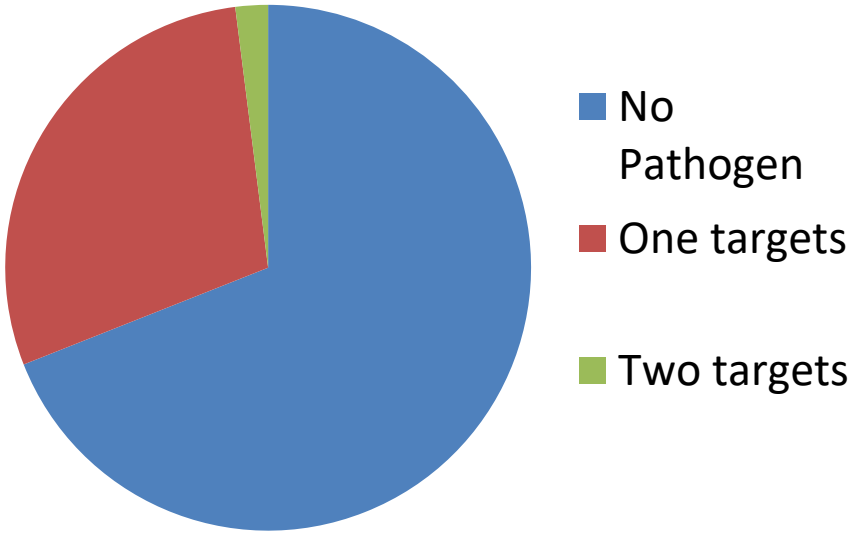

Nanosphere
ENTERIC PATHOGENS TEST
Nanosphere's Verigene® Enteric Pathogens Test (EP) for the simultaneous detection and identification of genetic virulence markers.
EP
NEW
PANEL
The most comprehensive FDA-cleared GI test on the market
Learn More
FilmArray™

xTAG GPP ® Assay Used in Prospective Clinical Studies in Europe

Netherlands – 19% detection



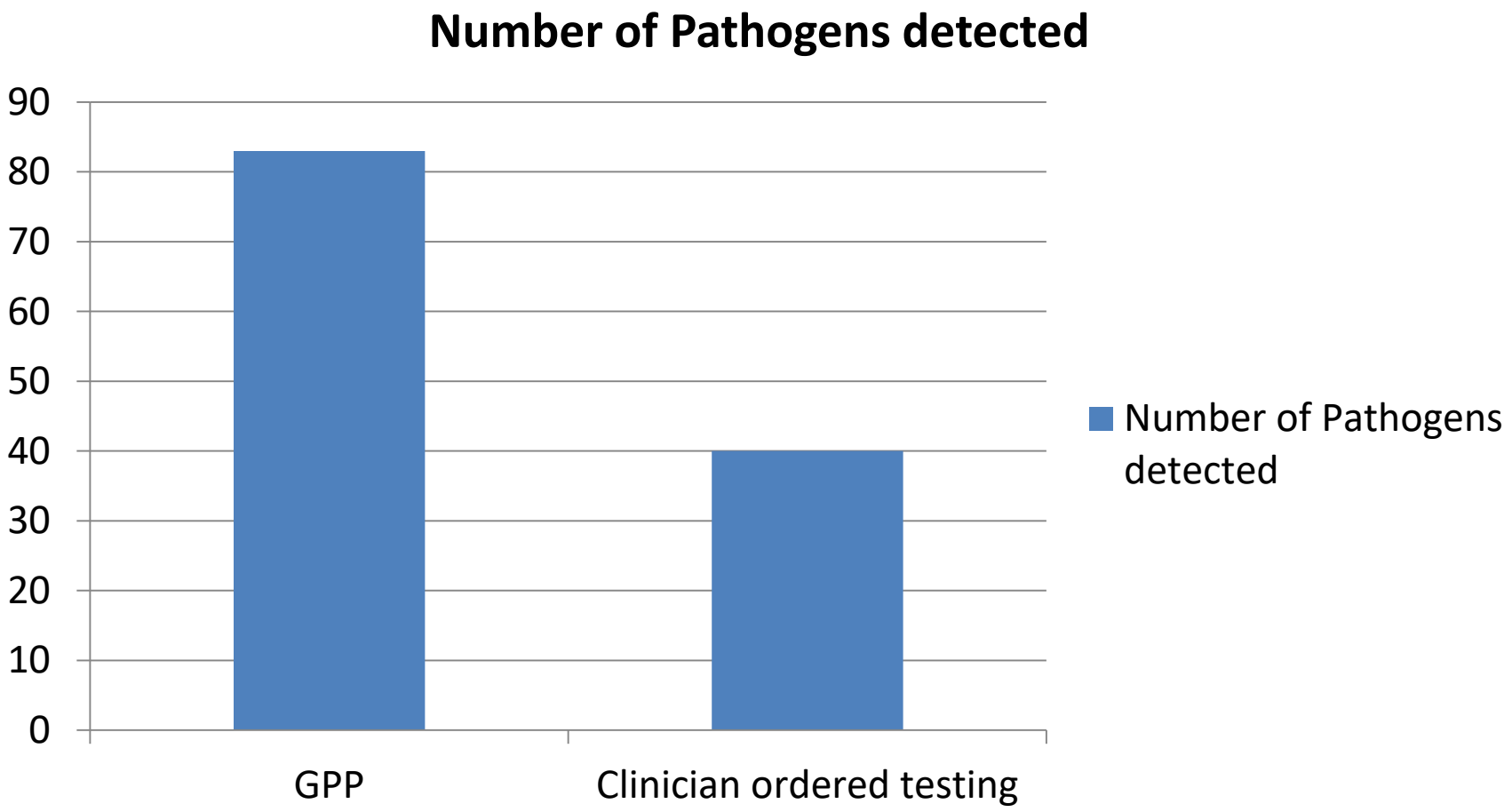
Germany – 31% detection



Wessels E *et al.* Clin Micro Inf 2013

Malecki M *et al.* ESCV 2011

Benefits of “Syndromic approach”



Wessels E *et al.* Clin Microbiol Infect 2014; 20: O182–O187

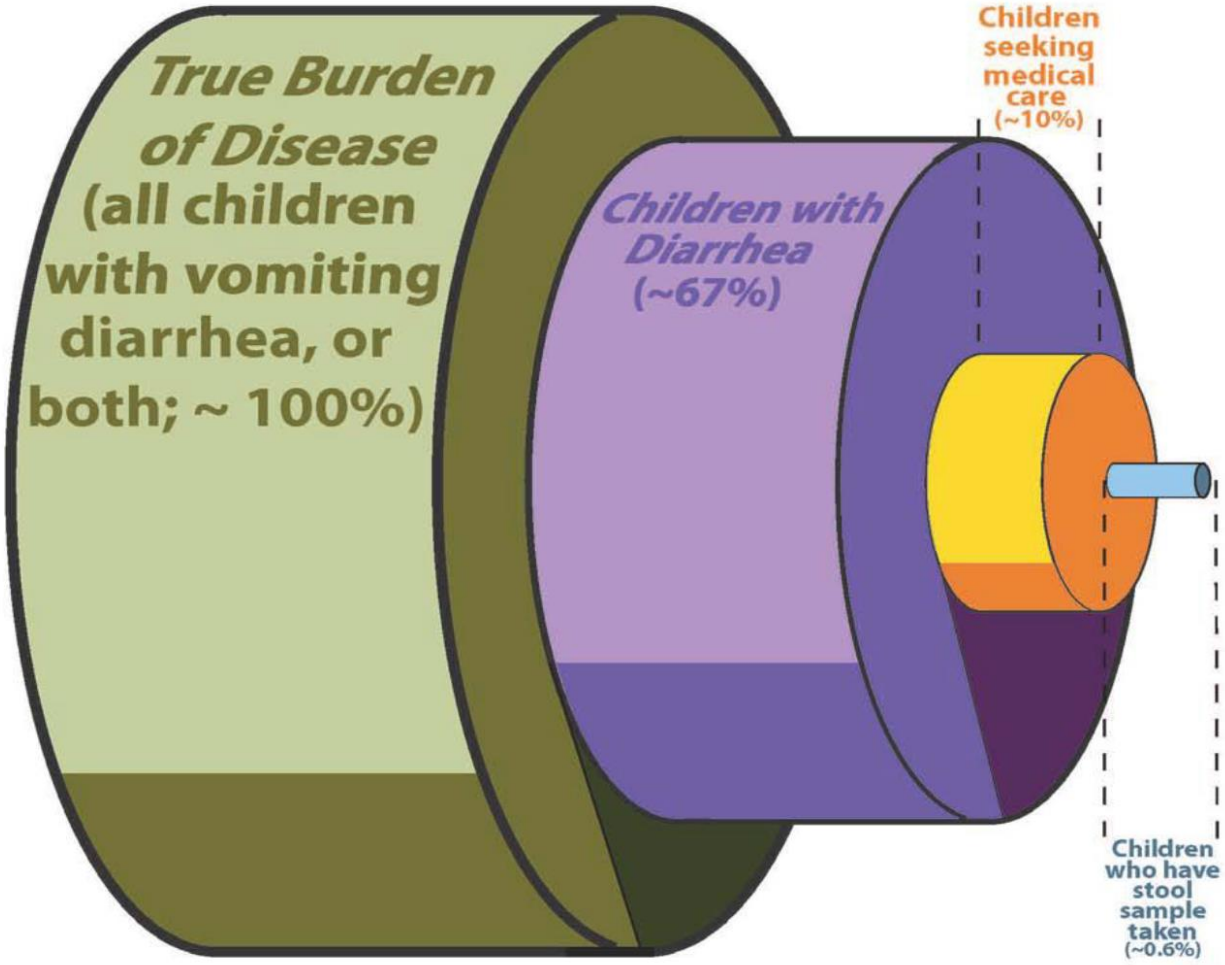
Pediatric Oncology Population

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, *n* (%)			
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.

J Mol Diagn. 2015 Nov;17(6):715-21


True Burden of Disease
(all children with vomiting diarrhea, or both; ~ 100%)
Children with Diarrhea
(~67%)
Children seeking medical care
(~10%)
Children who have stool sample taken
(~0.6%)

Global Burden of Disease Study 2013

Lancet 2015; 386: 743–800

	Cases in 1990 (×1000)	Cases in 2013 (×1000)	Percentage change	Age-standardised rate in 1990 (per 100 000)	Age-standardised rate in 2013 (per 100 000)	Percentage change
Upper respiratory infections	13 557 038 (13 317 034 to 13 806 346)	18 770 589 (18 479 508 to 19 048 703)	38·26* (35·33 to 41·60)	243 621·2 (239 383·6 to 248 019·3)	259 491·0 (255 547·1 to 263 318·4)	6·48* (4·20 to 8·95)
Diarrhoeal disease episodes	2 920 208 (2 866 614 to 2 968 429)	2 711 253 (2 666 452 to 2 761 161)	−7·29* (−9·55 to −4·91)	46 265·7 (45 440·7 to 47 003·5)	37 467·6 (36 858·2 to 38 151·9)	−19·07* (−20·98 to −17·09)
Other exposure to mechanical forces	349 533 (334 775 to 367 702)	381 968 (364 953 to 401 105)	9·28* (6·86 to 11·52)	6049·4 (5797·0 to 6369·6)	5092·8 (4866·9 to 5355·1)	−15·81* (−17·57 to −14·16)
Acute otitis media	339 485 (332 992 to 345 80	324 720 (318 445 to	−4·44* (−7·03 to −1·88)	5292·2 (5194·9 to	4480·9 (4394·0 to 4566·7)	−15·34* (−17·58 to −13·09)
Clinical episodes of malaria	172 (107 73 279 19					1* 9 to −5·93)
Lower respiratory infections	164 (162 19 167 30					3* 7 to −21·86)
Chickenpox and herpes zoster	128 (126 377 to 129 582)	(138 706 to 140 700)	(7·73 to 10·73)	(1970·9 to 2015·0)	(1920·8 to 1950·4)	9* (−4·00 to −1·54)
Hepatitis B	137 639 (133 533 to 143 049)	129 191 (124 907 to 132 890)	−6·22* (−9·67 to −2·53)	2644·5 (2562·1 to 2753·9)	1779·2 (1721·7 to 1830·2)	−32·74* (−35·29 to −29·95)

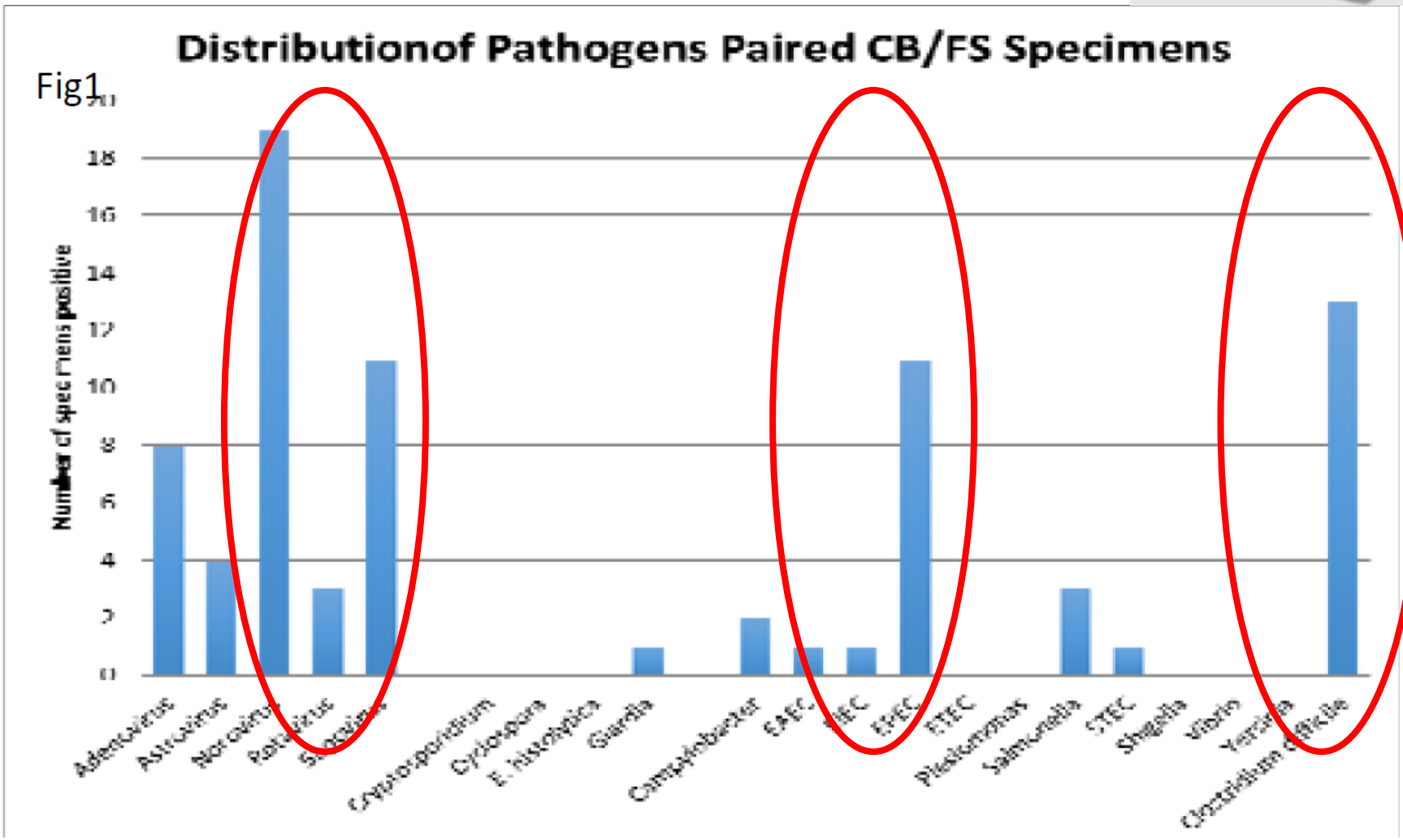
Gastroenteritis disease burden estimation is based on diarrheal disease only

GI IMPACT Study

The Diarrhea Study

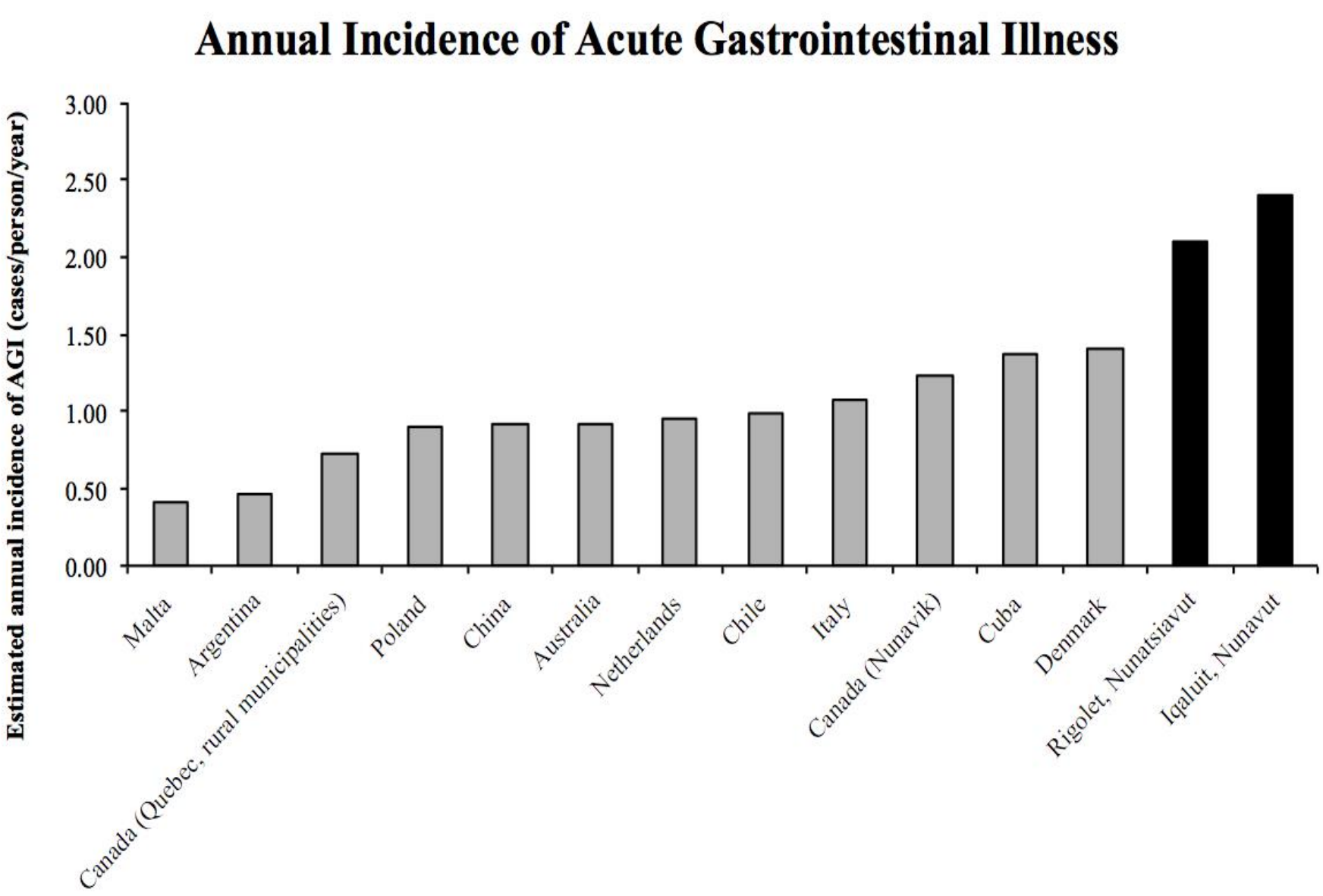
Fig1

Distributionof Pathogens Paired CB/FS Specimens



Chapin K *et al*. Clin Viro Symp April 2016

Nunavut – a high burden setting

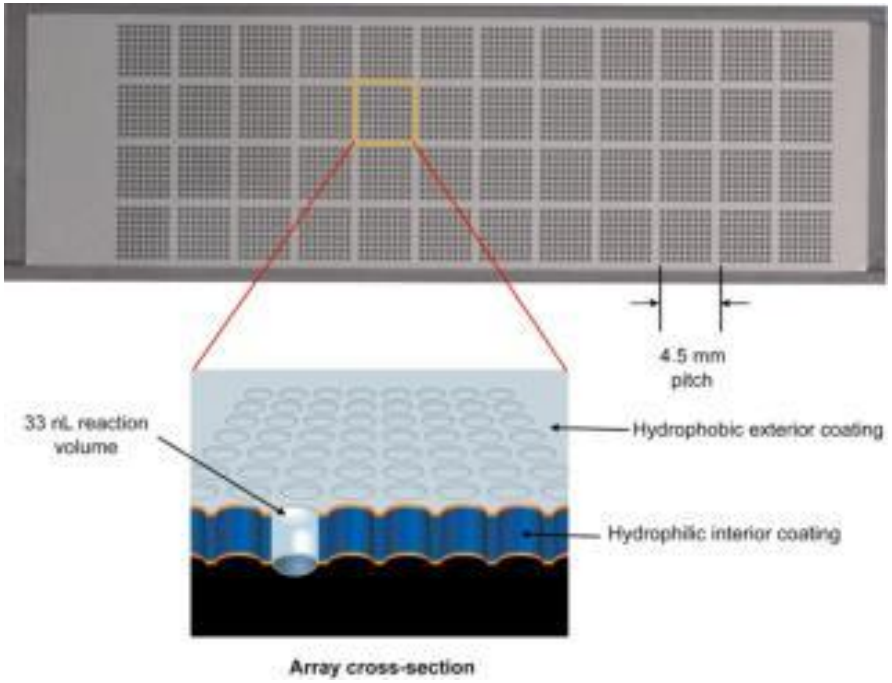


Harper et al., 2015

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

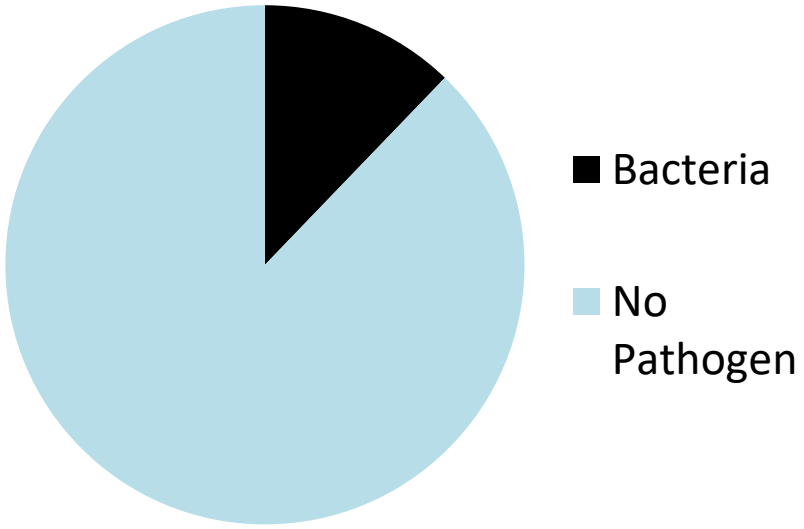
OpenArray™



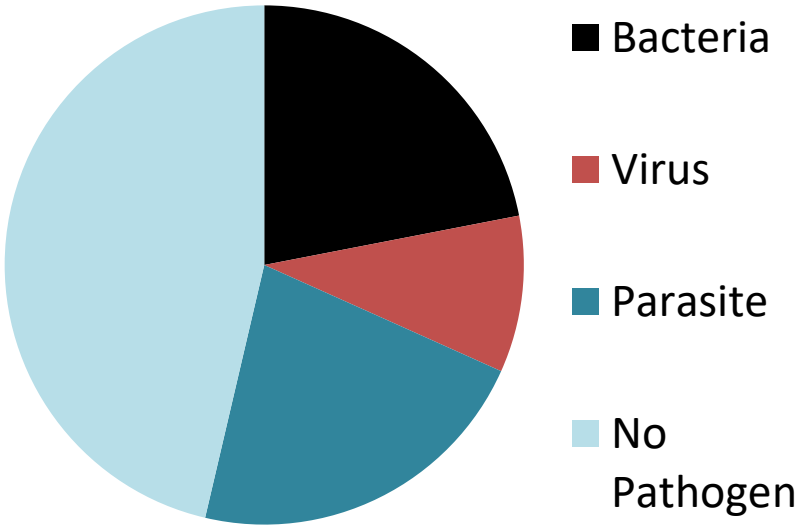
Source: http://publications.gc.ca/collections/collection_2014/aspc-phac/HP37-15-2012-eng.pdf

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

Clinical Testing



Real time PCR



CIHR IRSC

Goldfarb DM et al; Int J Circumpolar Health. 2013;72:19903.

Novel Diagnostics - Public Health

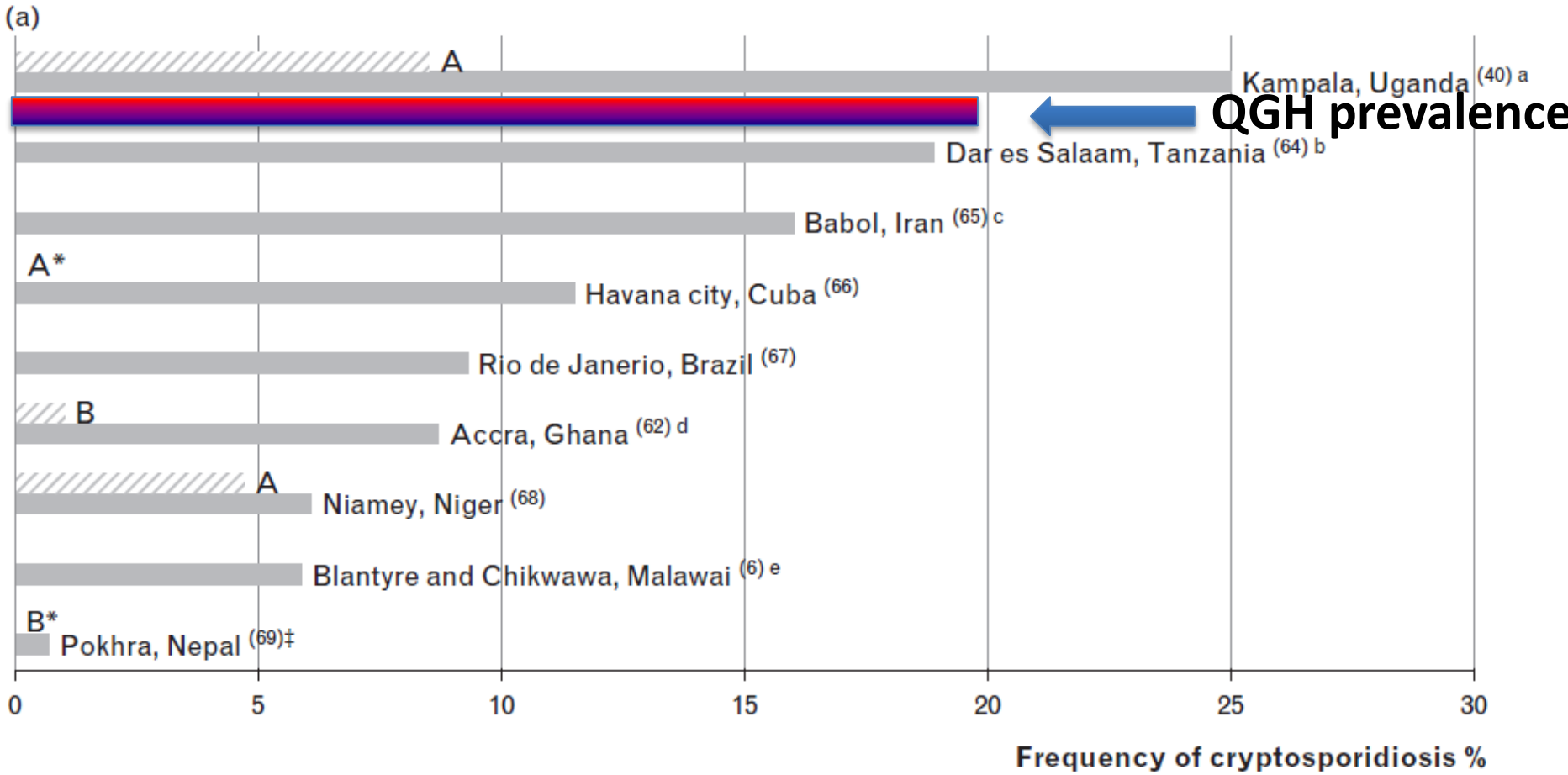
old specimens, new tools

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	
Campylobacter spp.	6 (7.0)
Salmonella spp.	6 (7.0)
Clostridium difficile with toxin B detected	5 (5.8)
Shigella spp.	1 (1.1)
Parasites	
Cryptosporidium spp.	17 (19.8)
Giardia spp.	1 (1.1)
Viruses	
Astroviruses	4 (4.6)
Noroviruses groups 2	3 (3.5)
Rotaviruses	1 (1.1)

Goldfarb et al; **Int J Circumpolar Health. 2013;72:19903.**

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

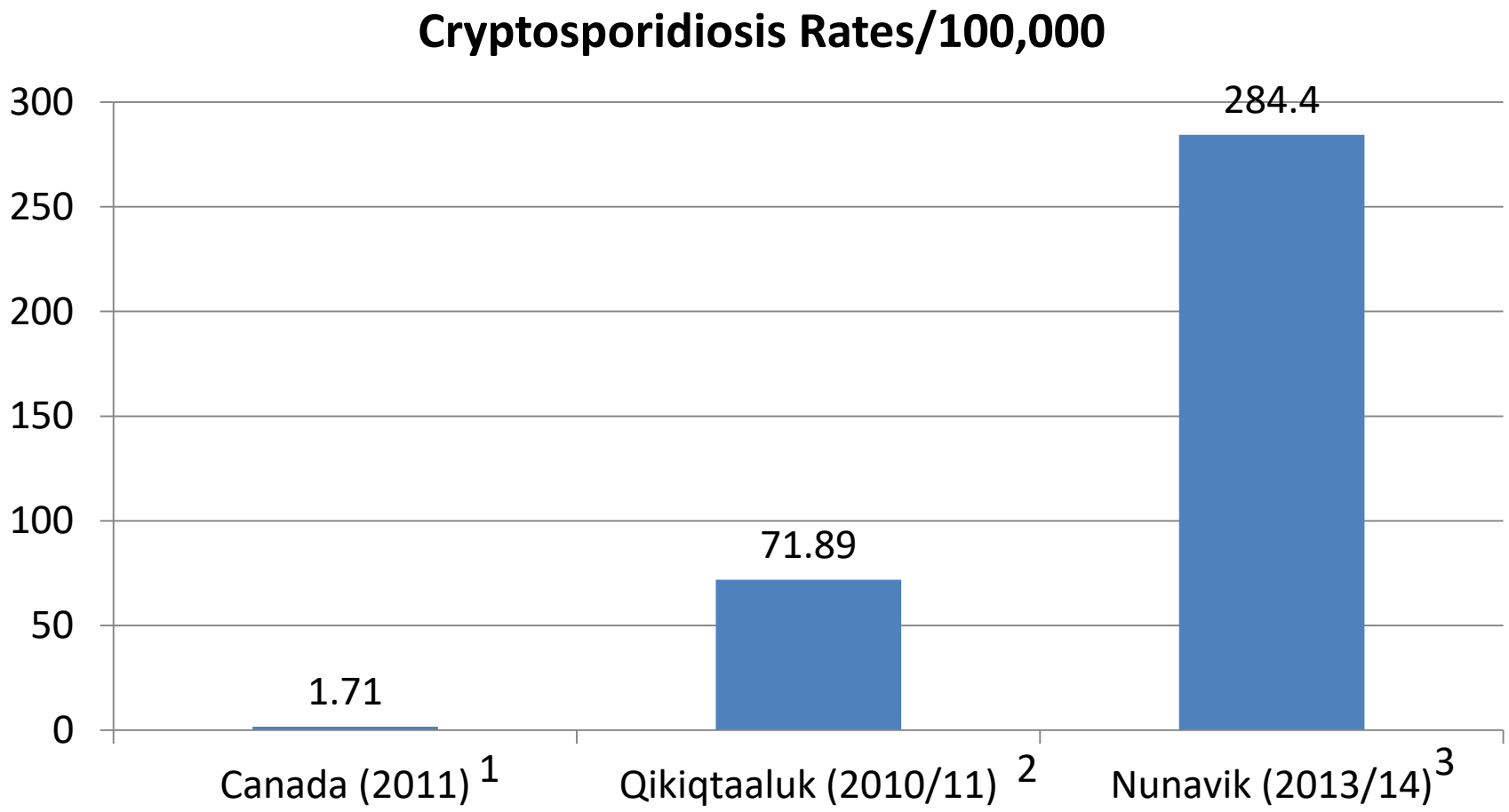


Shirley DT et al., Curr Opin Infect Dis 2012, 25:555–563

Cryptosporidium – discovery new kid on the map

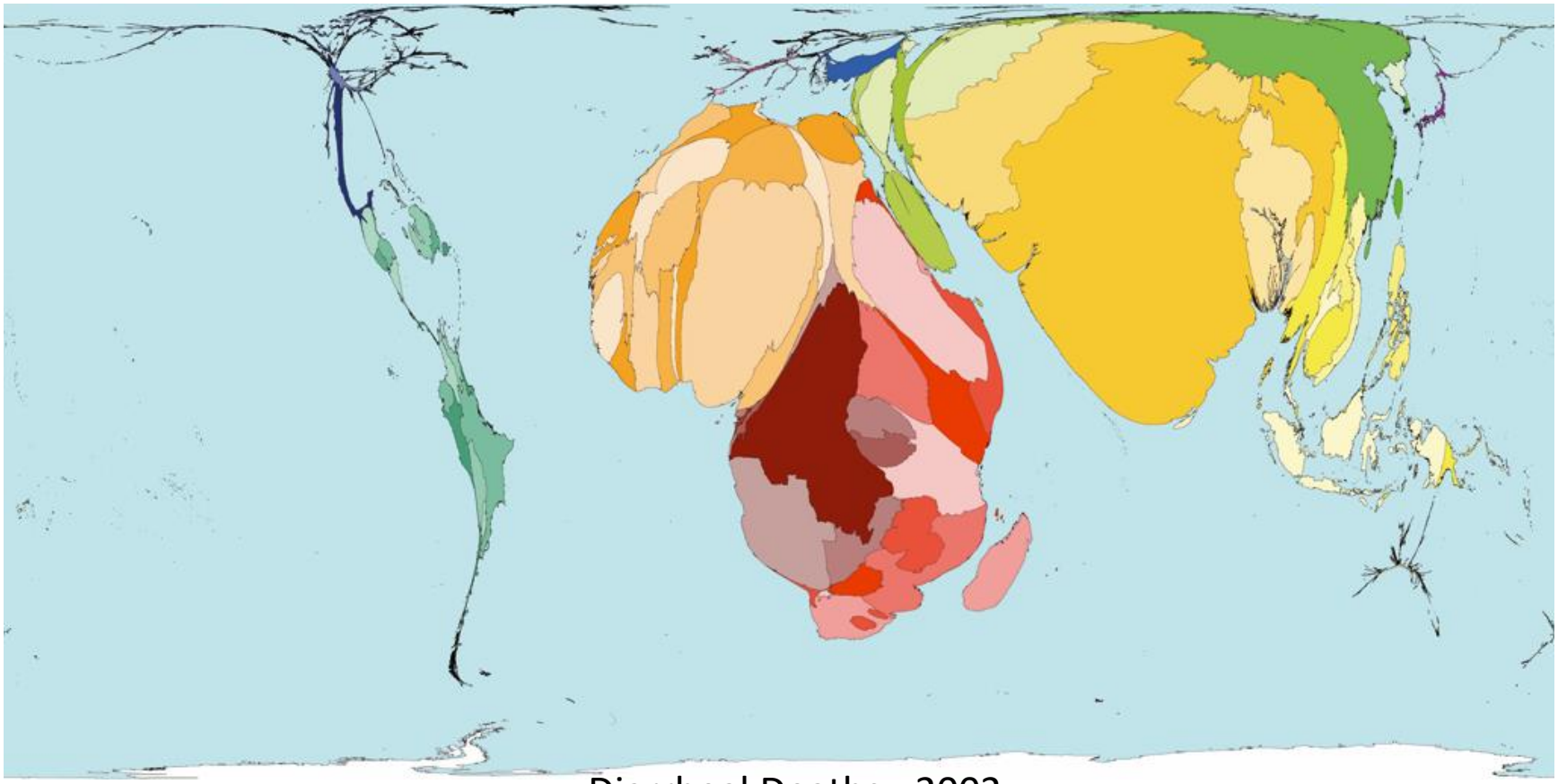
Slide courtesy Dr. Cedric Yansouni McGill University

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.

What about other high burden settings?



Diarrheal Deaths - 2002

http://worldmapper.org/

Two Large Multi-centre Studies of childhood diarrheal disease

- **G**lobal **E**nteric **M**ulticentre **S**tudy (GEMS)

- The Interactions of **Mal**nutrition & **E**nteric Infections: Consequences for Child Health and **D**evelopment (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

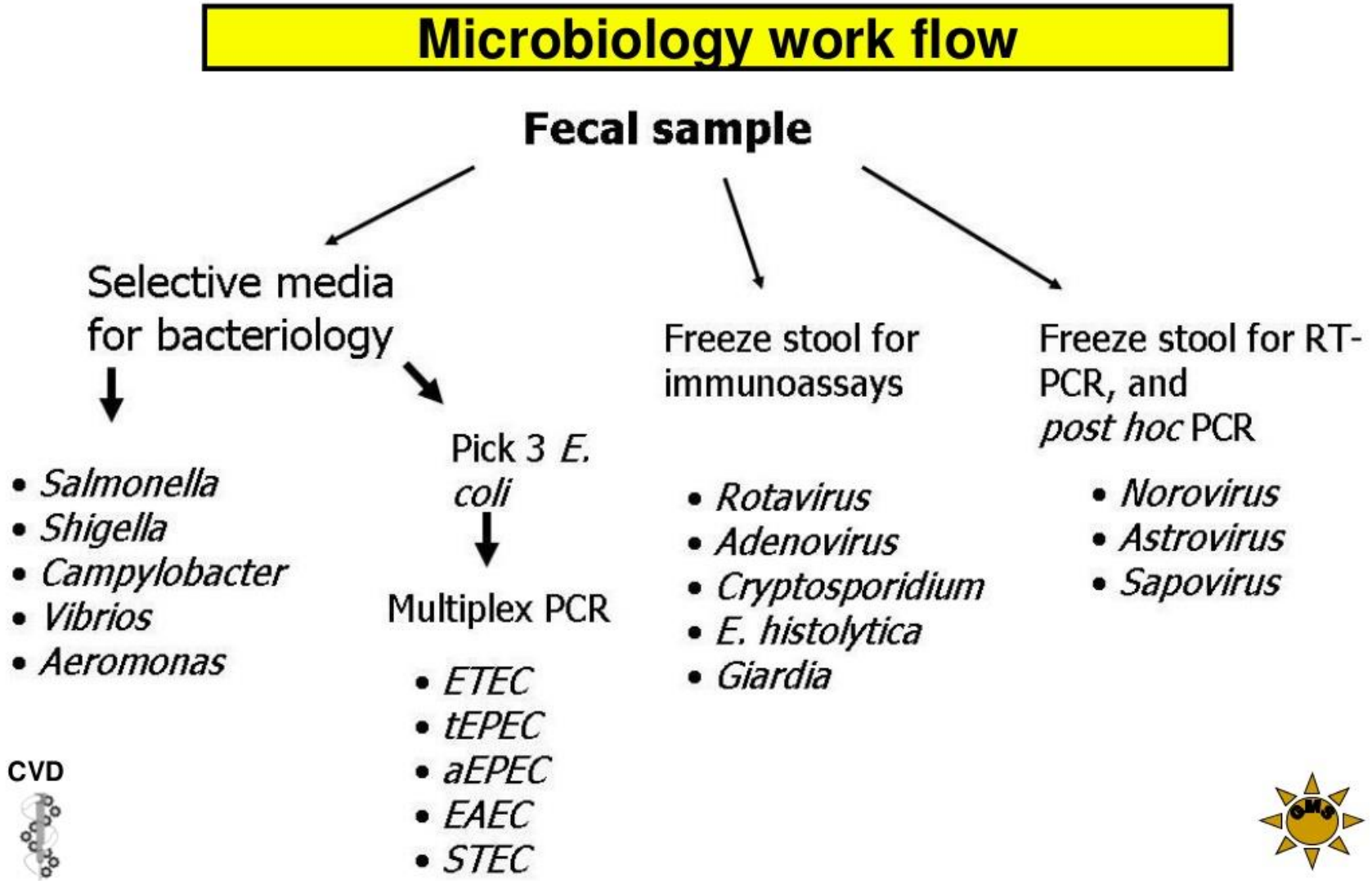
Summary

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

Kotloff KL et al. Lancet 2013; 382: 209–22

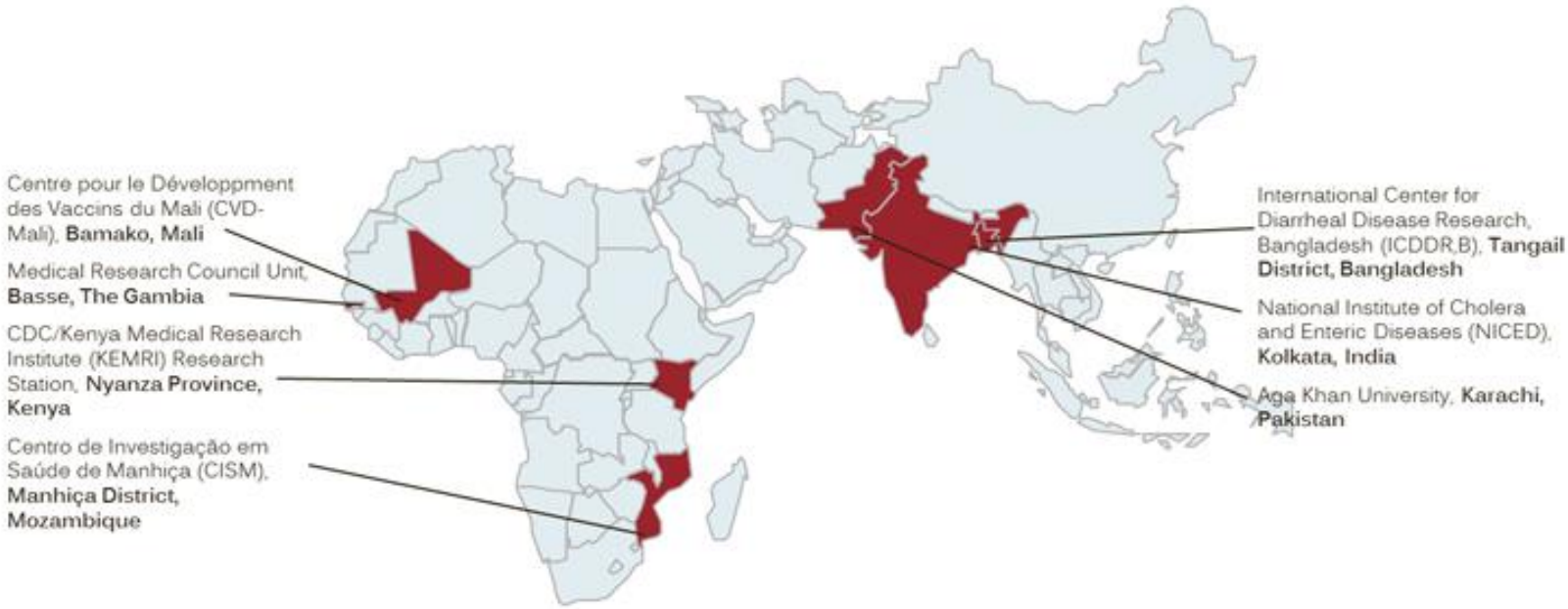
Global Enteric Multicenter Study



M. Levine, Ped Acad Soc Mtg, Boston, 2012

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

M. Levine, Ped. Acad. Soc., Boston, 2012

Attributable Fraction

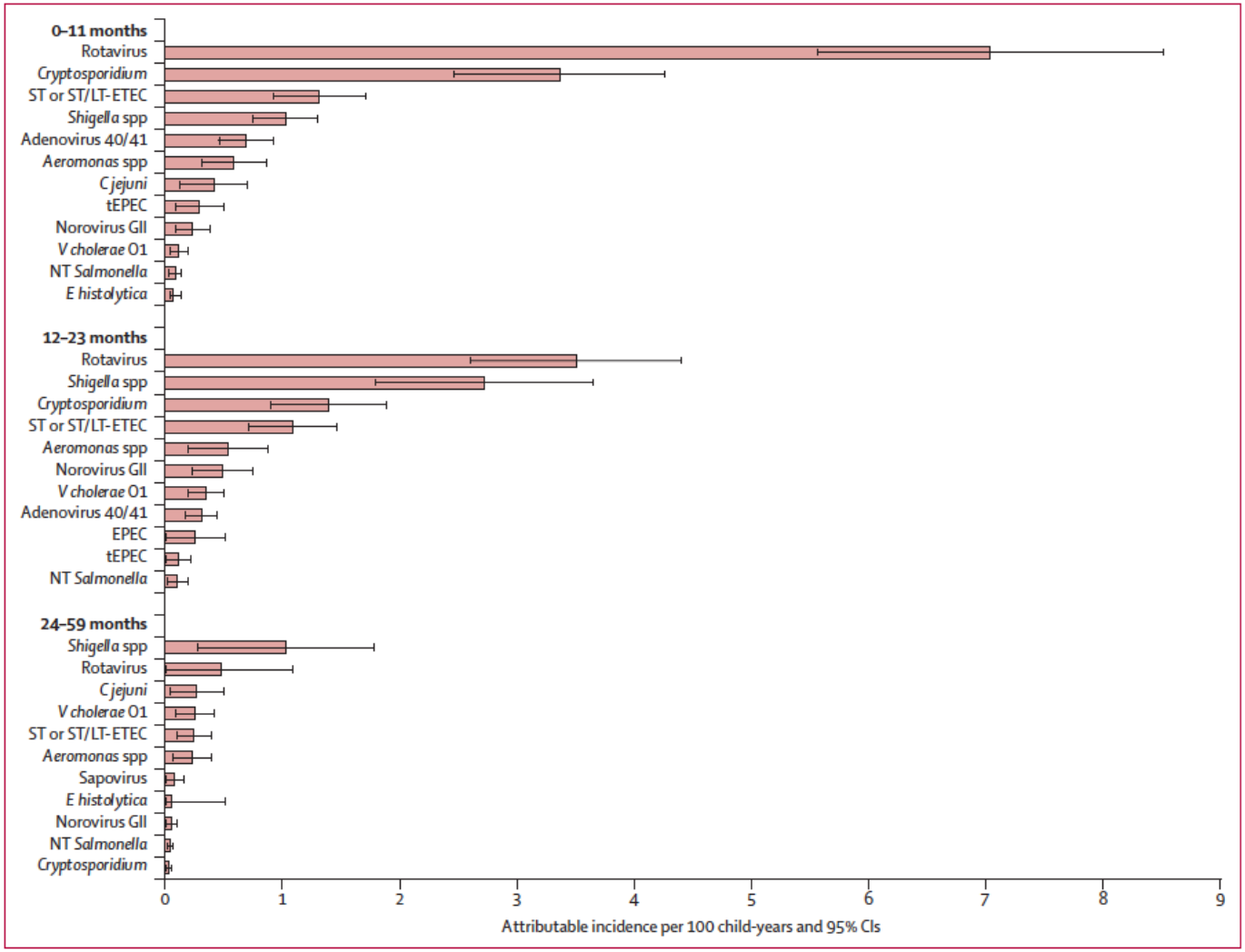
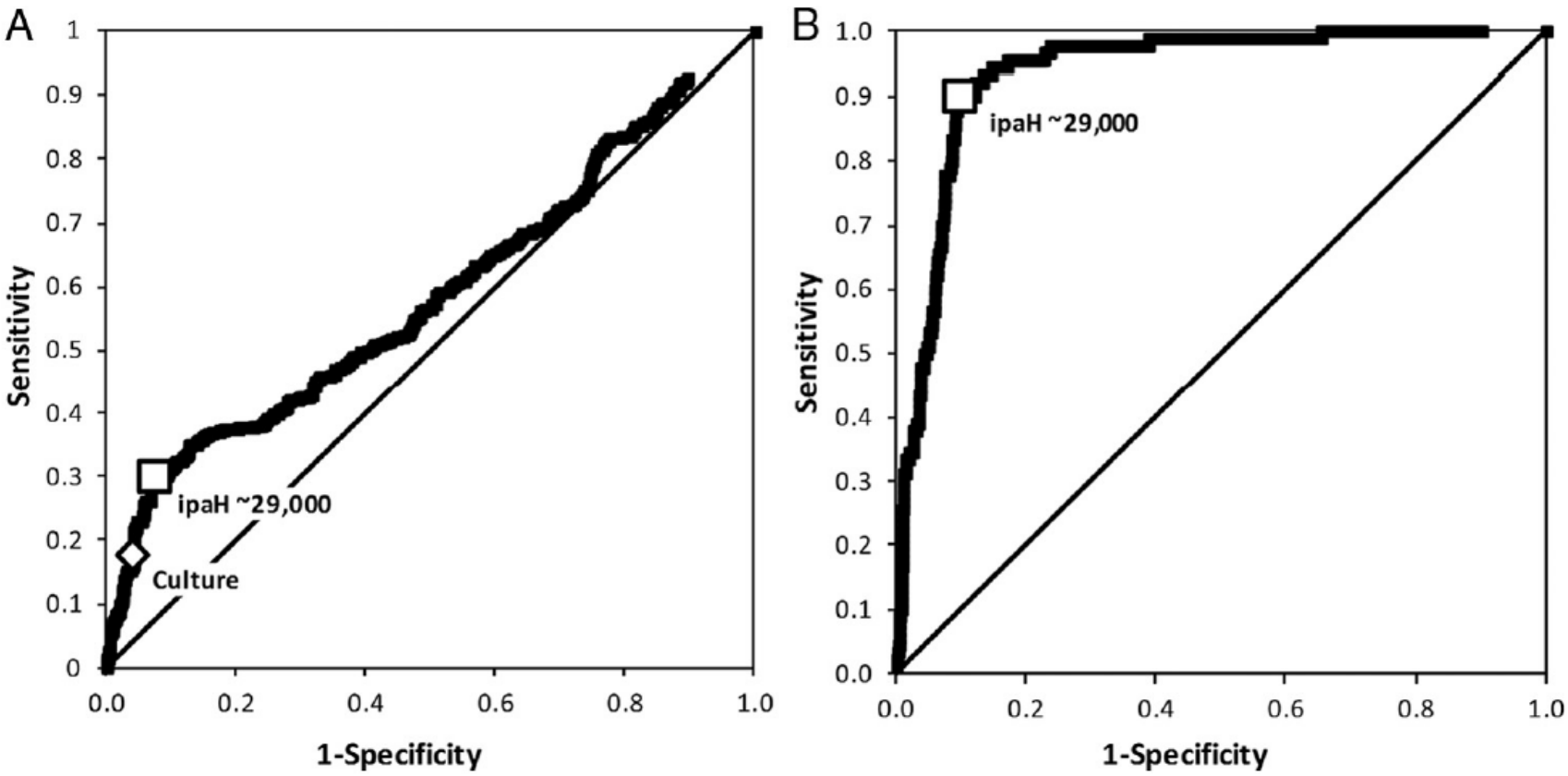


Figure 4: **Attributable incidence of pathogen-specific moderate-to-severe diarrhoea per 100 child-years by age stratum, all sites combined**
The bars show the incidence rates and the error bars show the 95% CIs.

Kotloff KL et al. Lancet 2013; 382: 209–22

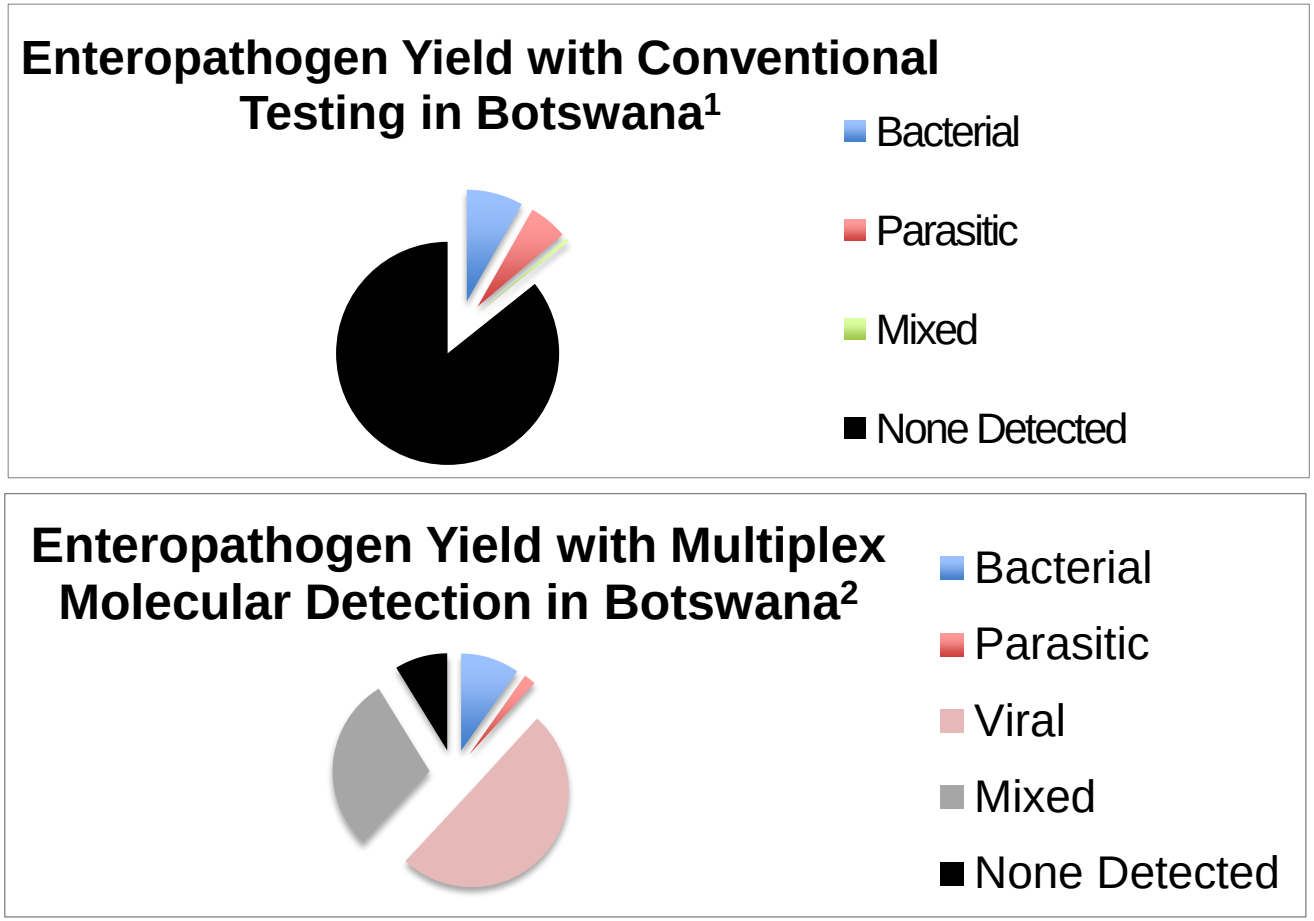
Culture estimated to have missed ~50% of *Shigella* cases in GEMS



Receiver operating characteristic (ROC) curves

Lindsay B et al. J. Clin. Microbiol. 2013, 51(6):1740.

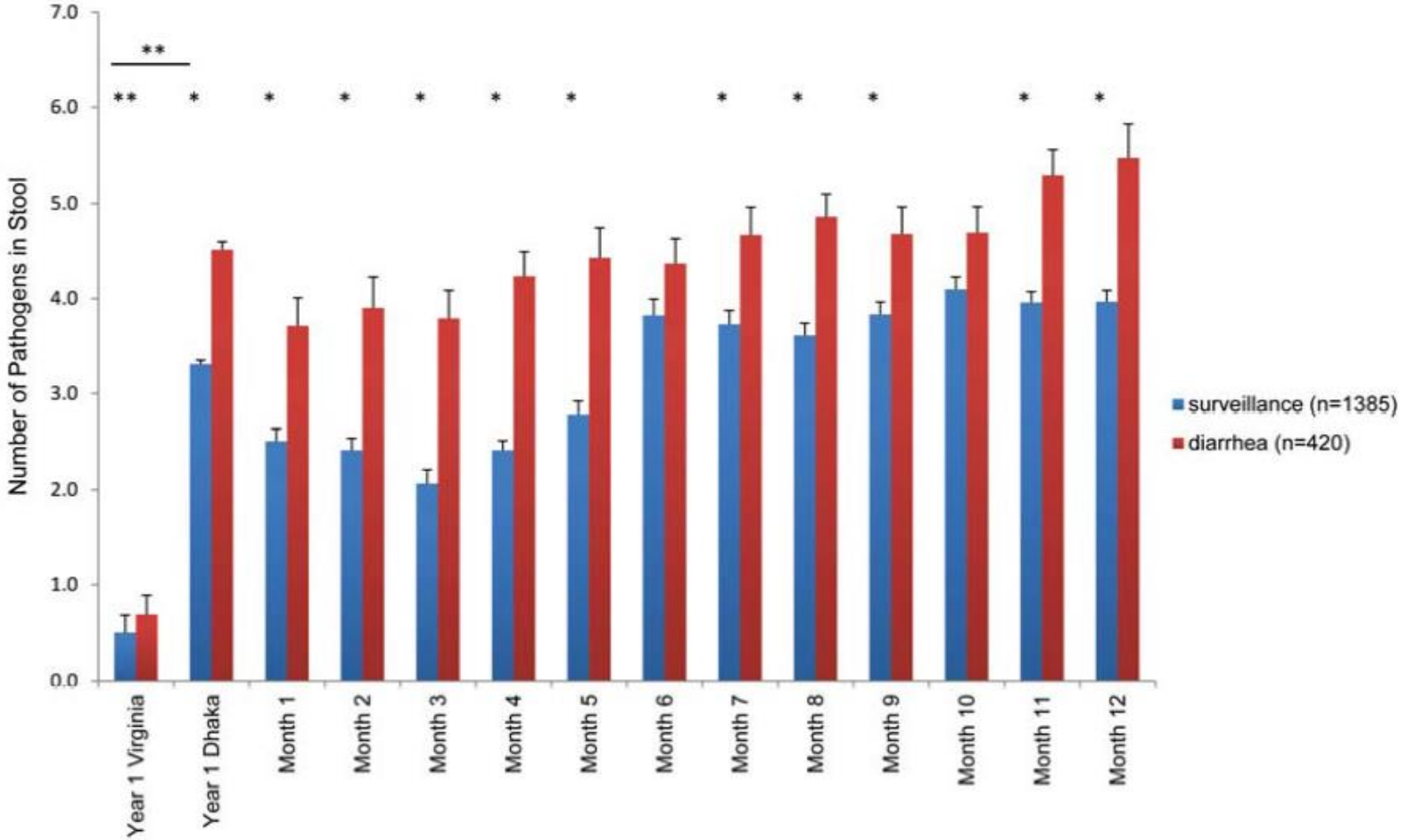
Newer More Sensitive Techniques



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)



MAL-ED
mal-ed.fnih.org

Taniuchi M *et al*. J Inf Dis. 2013;208:1794–802

Conventional testing vs. "Multiplex" molecular testing

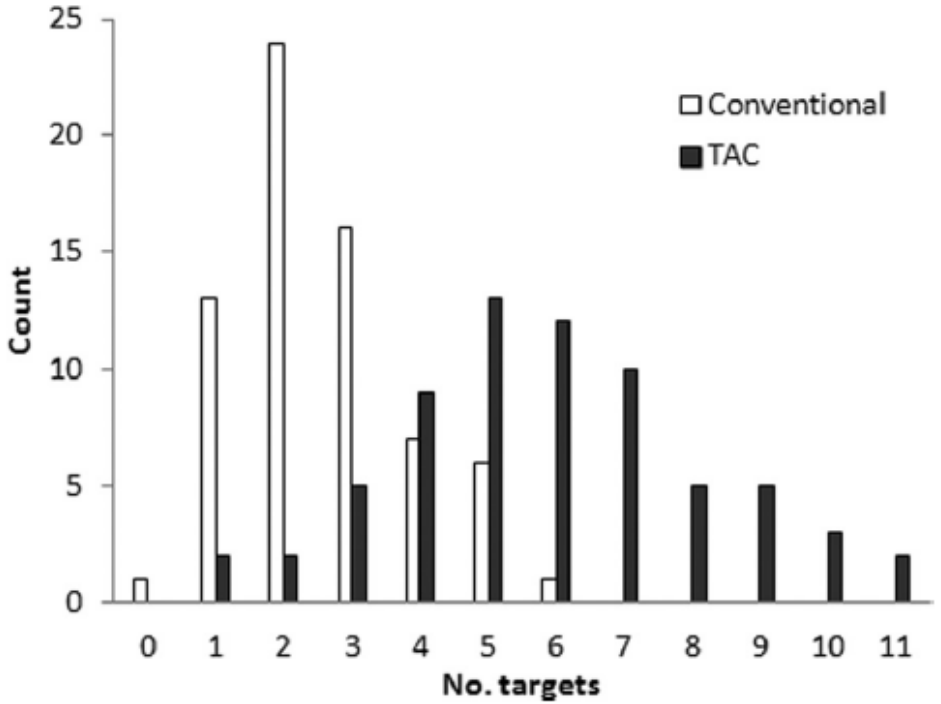
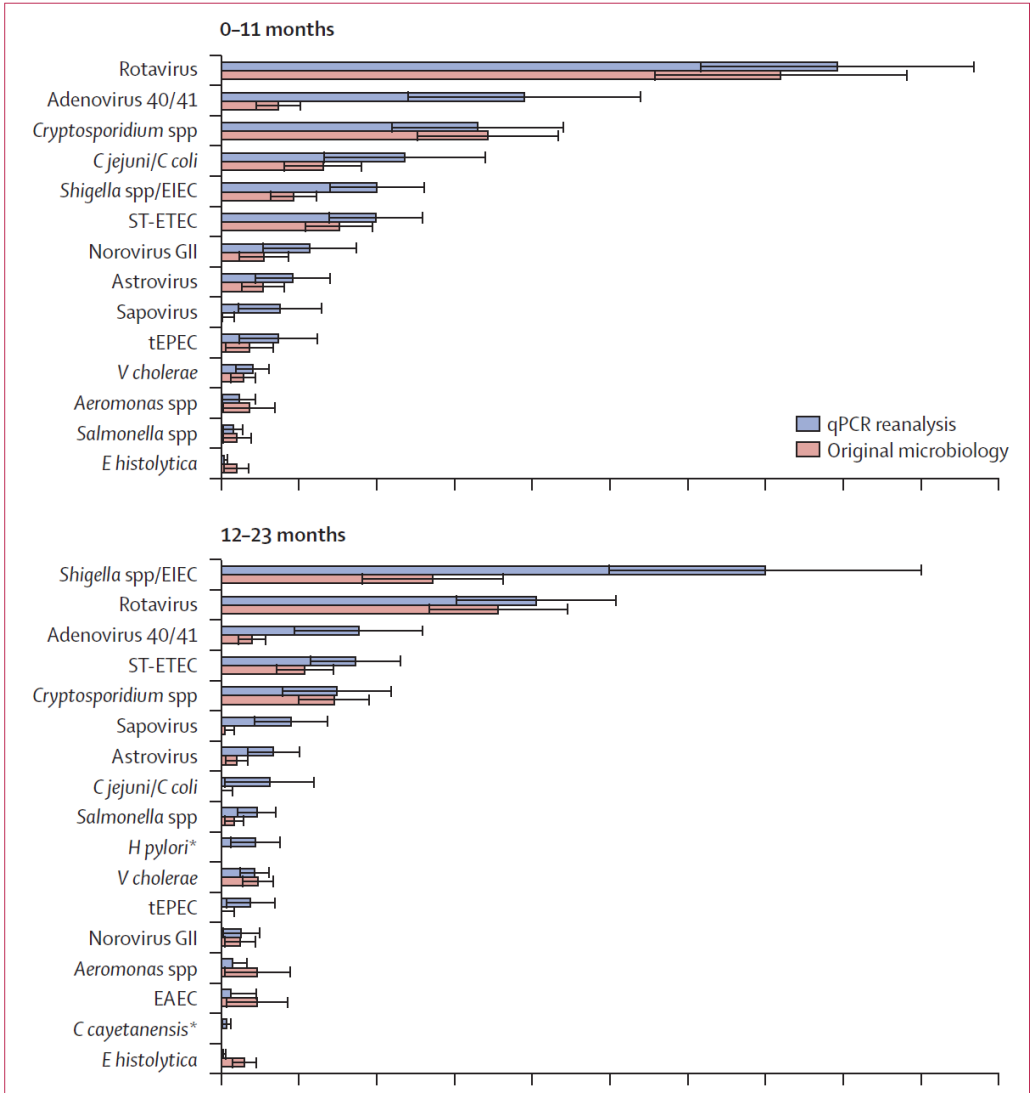


FIG 4 Numbers of mixed infections detected with TAC versus conventional methods for 16 pathogens on samples from Tanzania (medians; $P < 0.001$).

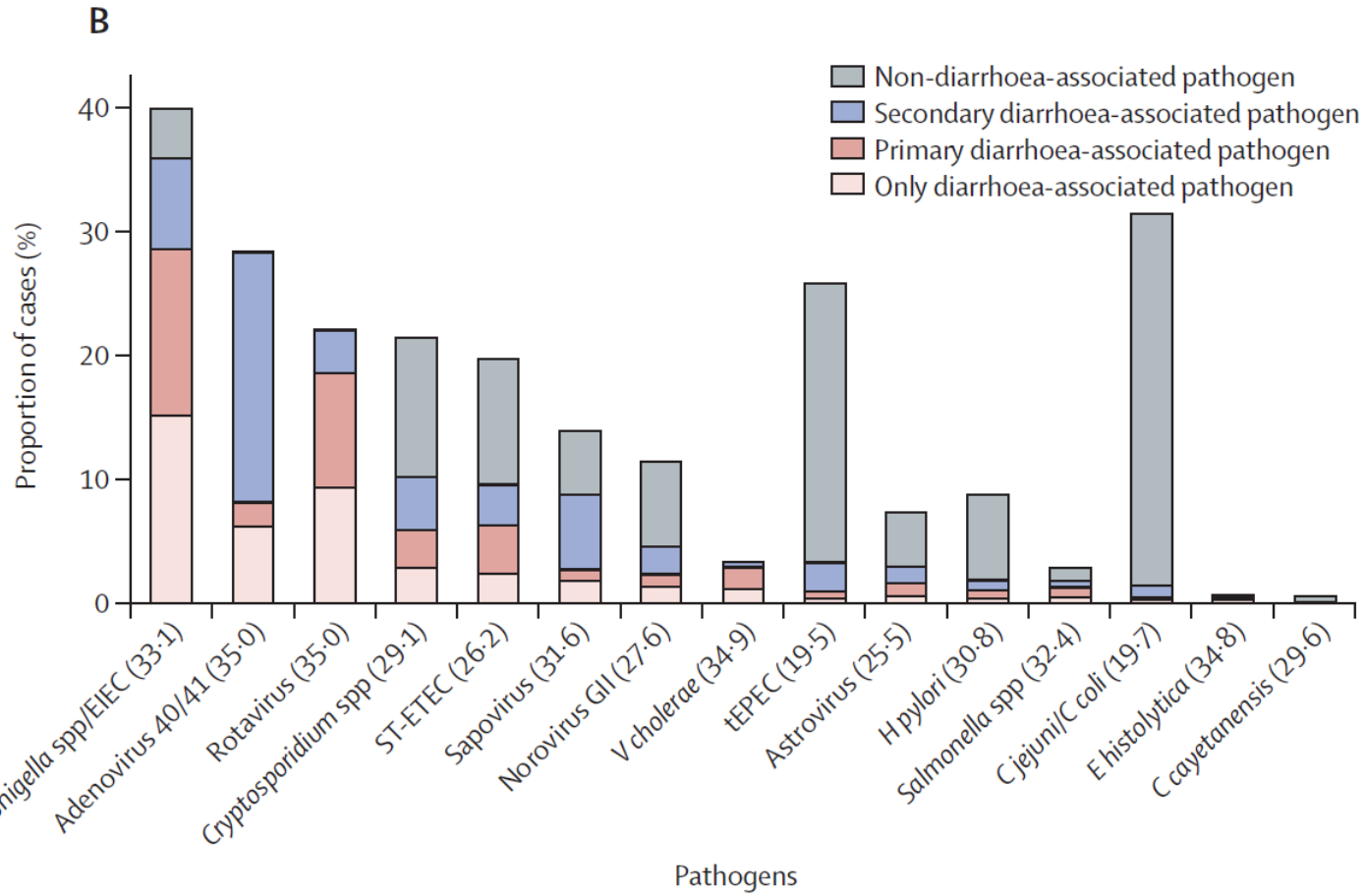
Liu J *et al.*, J. Clin. Microbiol. 2013, 51(2):472.

qPCR re-analysis of GEMS samples



Liu J *et al*. Lancet 2016

qPCR re-analysis changed a lot!



Liu J *et al*. Lancet 2016

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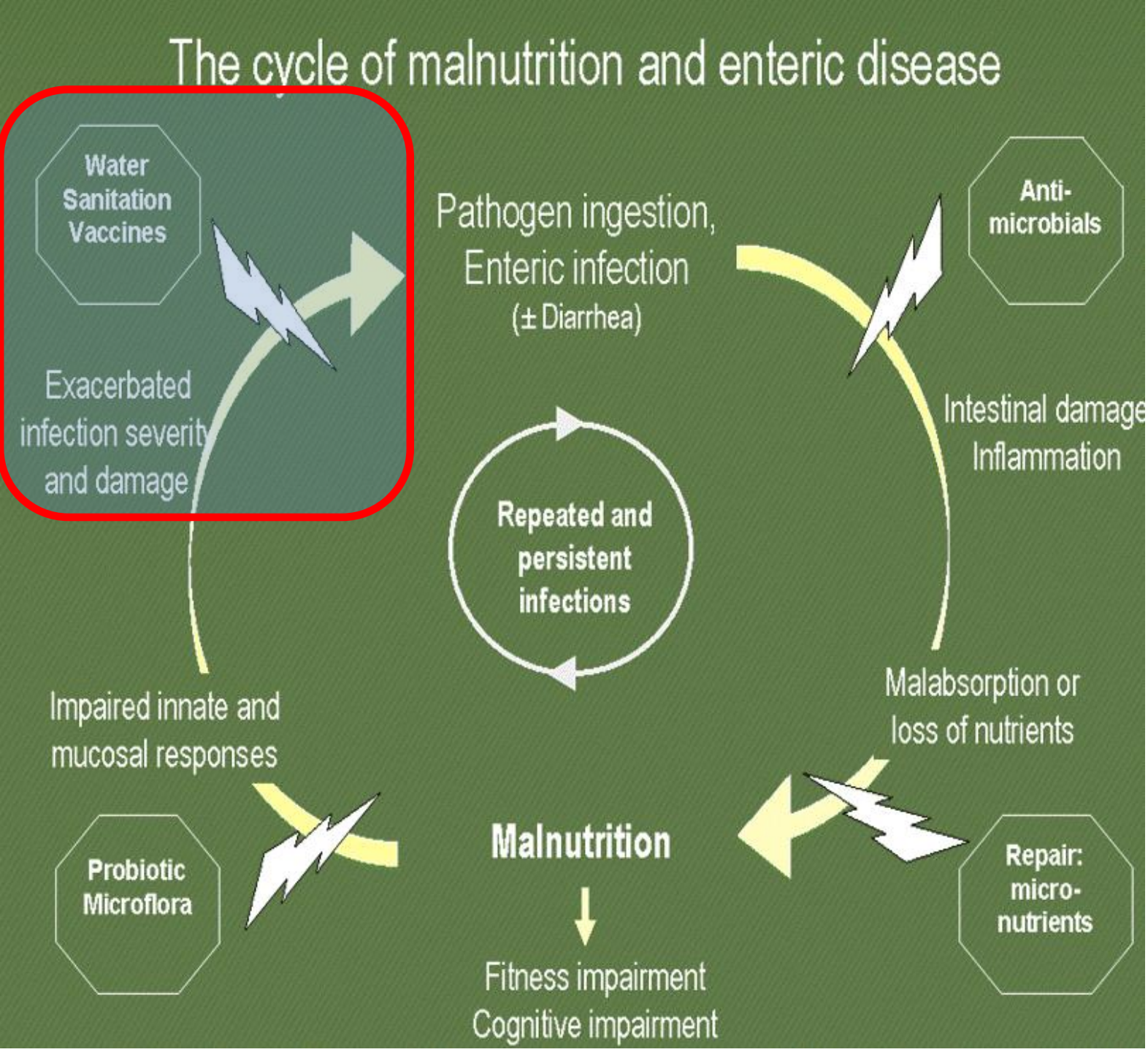
- New insights from enhanced diagnostic studies
- Examples of efforts to address childhood diarrheal disease



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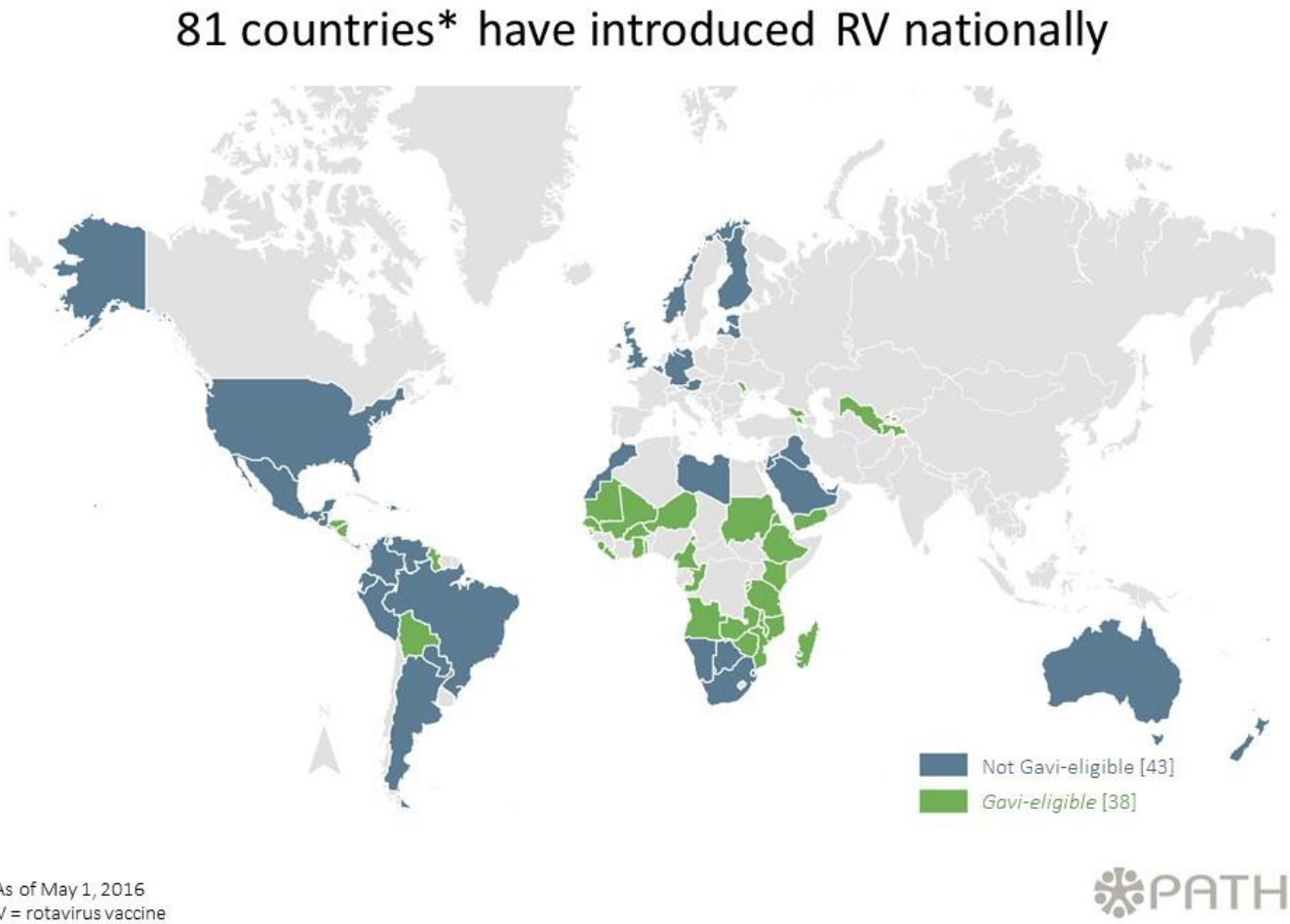
Rotavirus vaccination

WHO Recommends Global Use of Rotavirus Vaccines

Decision Could Help Protect Millions of Children in Africa and Asia from Lethal Diarrheal Disease

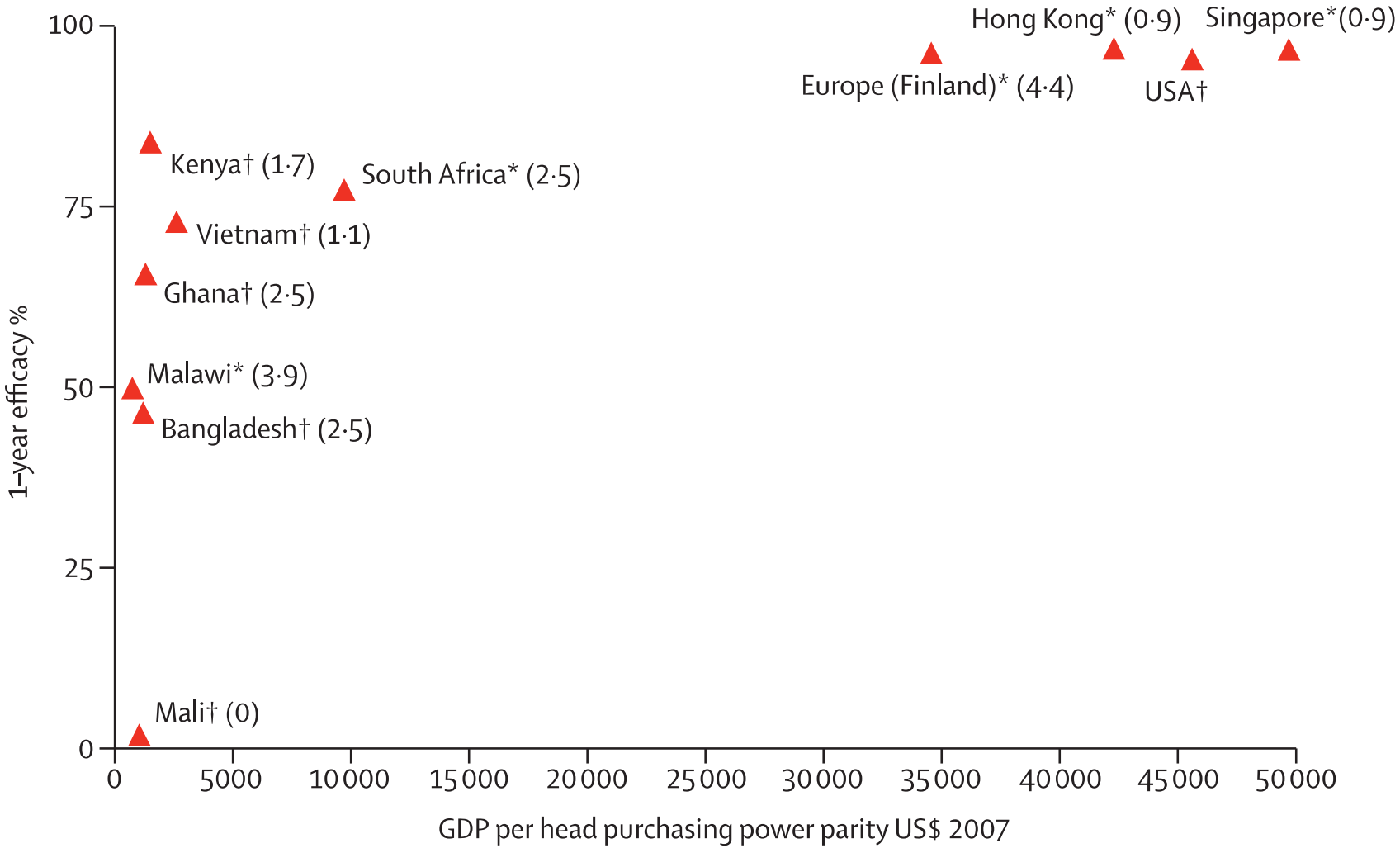
- Americas and Europe – 2006
- Africa and Asia - 2009

Scale-up of rotavirus vaccine



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

Vaccine efficacy and GDP



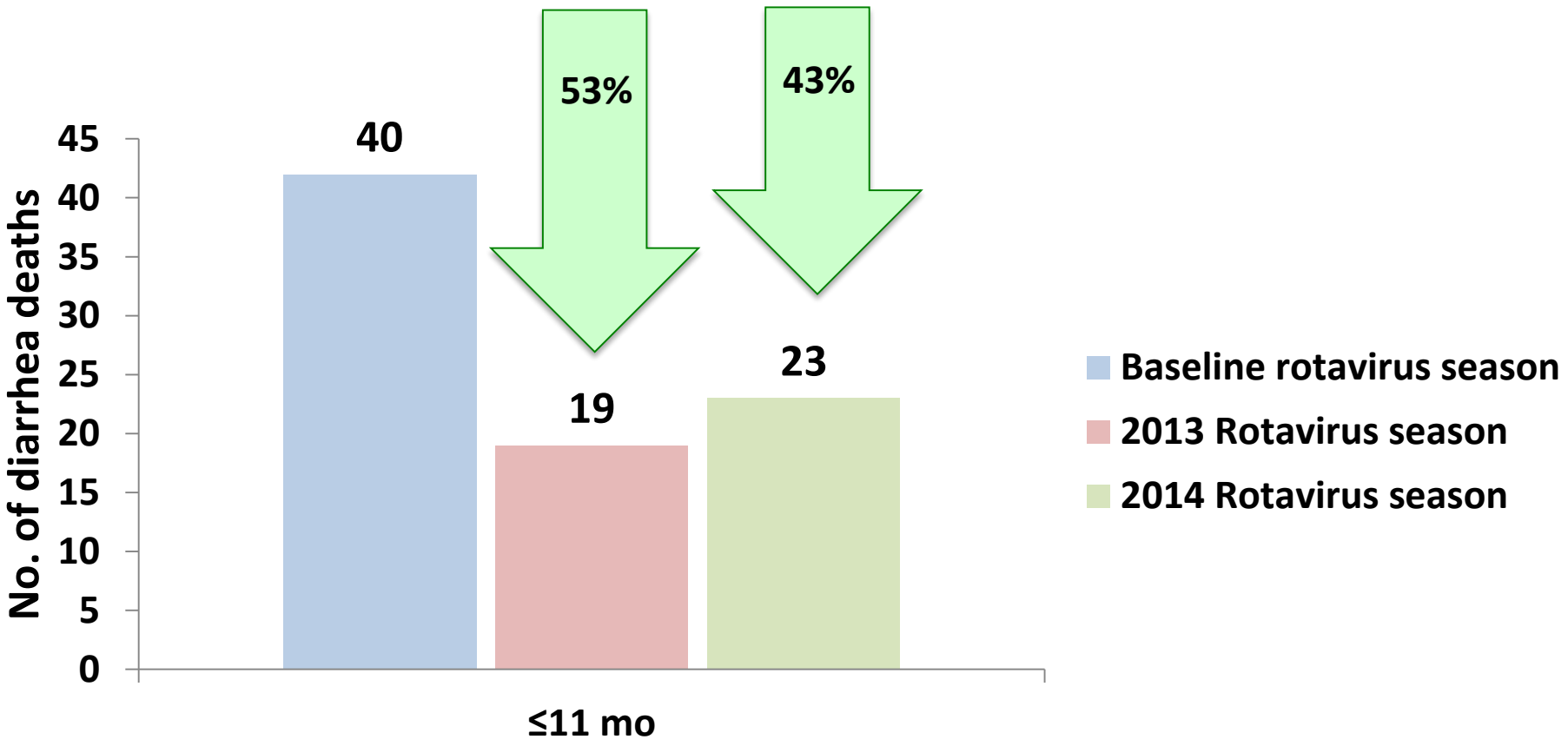
Nelson et al., *Lancet*, 2010

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

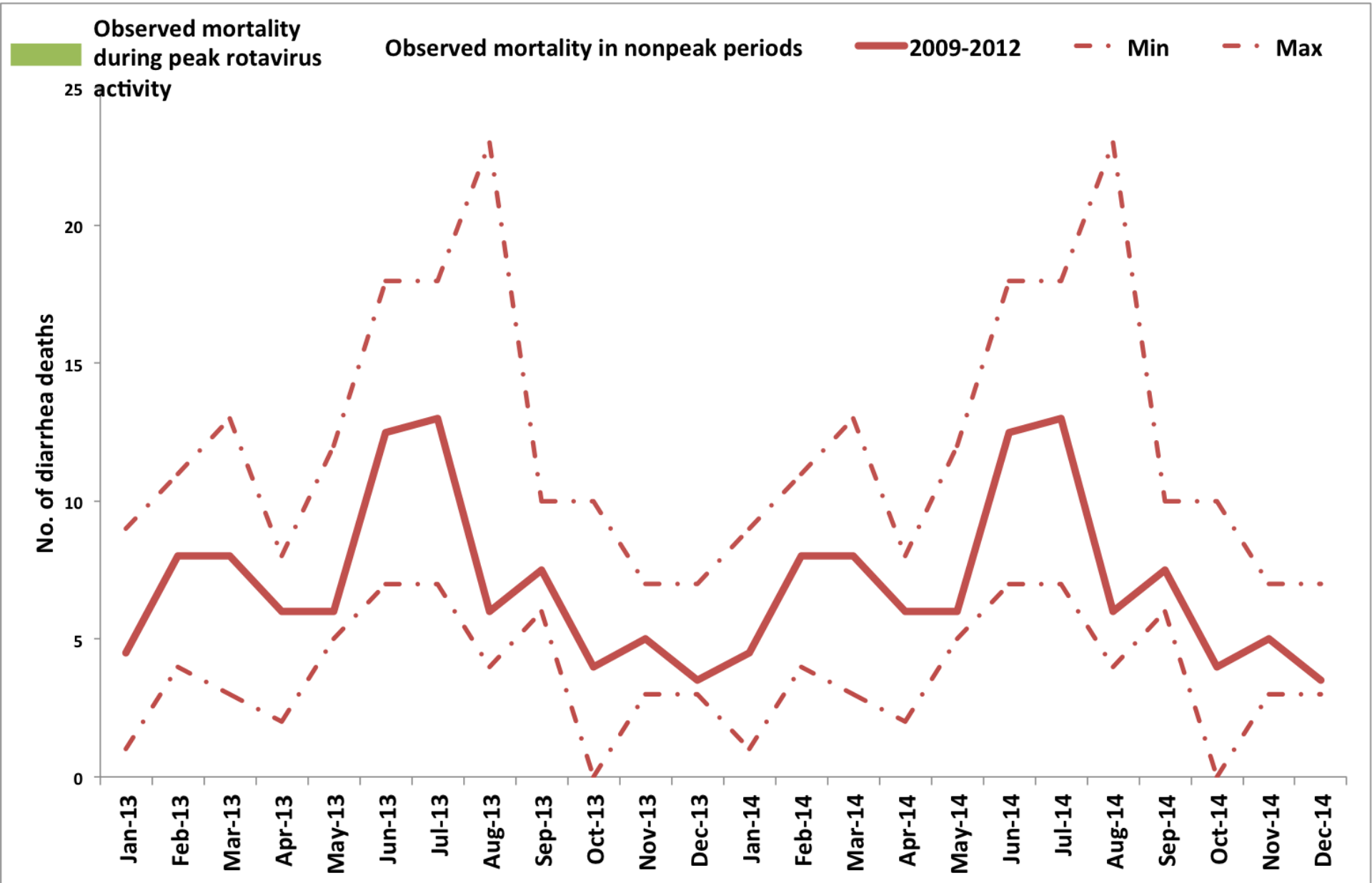
Rotavirus season deaths



Rotavirus season = May to October

Clin Infect Dis. (2016) 62 (suppl 2): S168-S174.

Deaths


Observed mortality during peak rotavirus activity
Observed mortality in nonpeak periods
2009-2012
Min
Max
No. of diarrhea deaths
25
20
15
10
5
0
Jan-13
Feb-13
Mar-13
Apr-13
May-13
Jun-13
Jul-13
Aug-13
Sep-13
Oct-13
Nov-13
Dec-13
Jan-14
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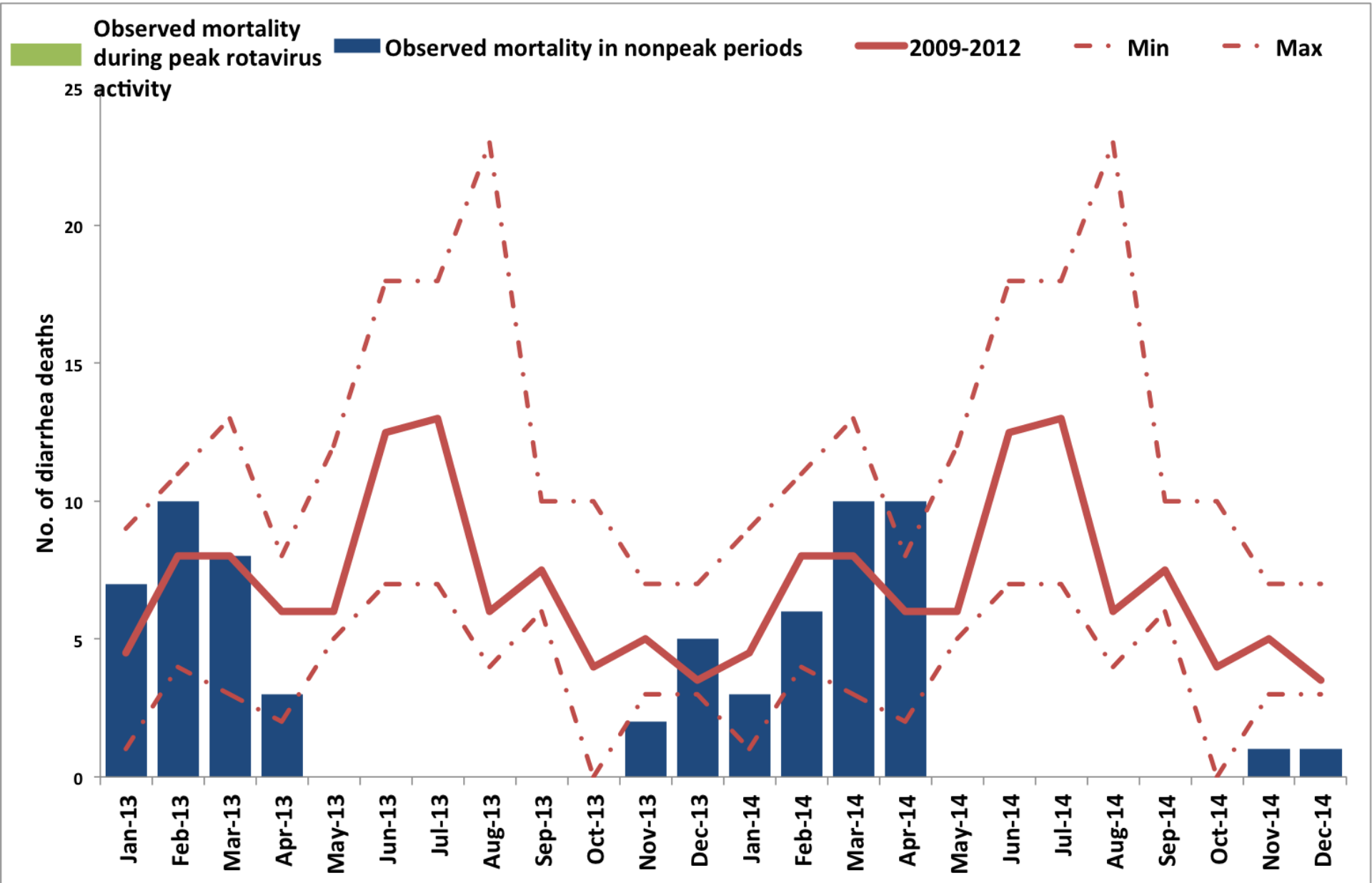
Oct-14
Nov-14
Dec-14

Deaths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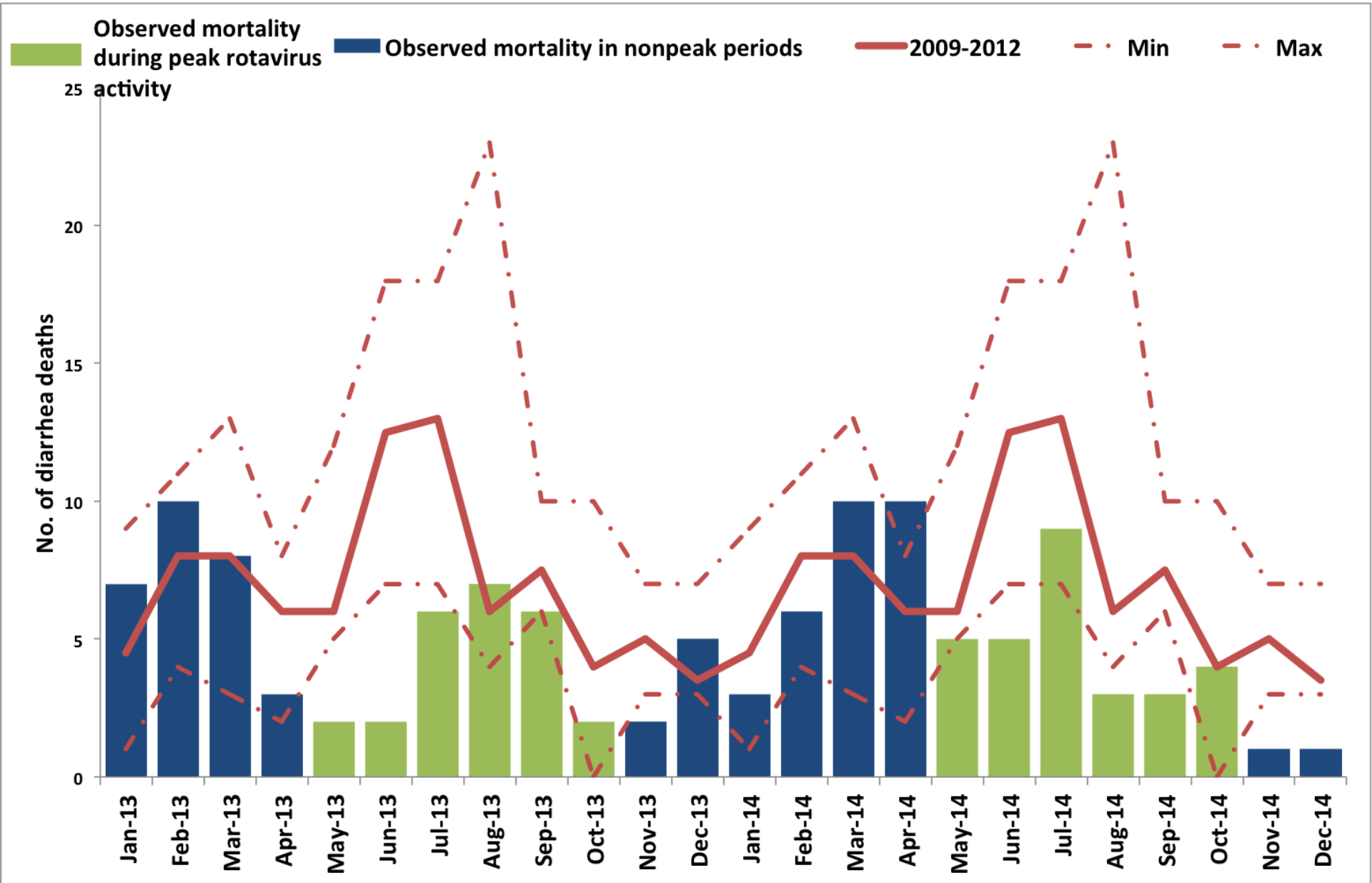
Nov-14
Dec-14

Deaths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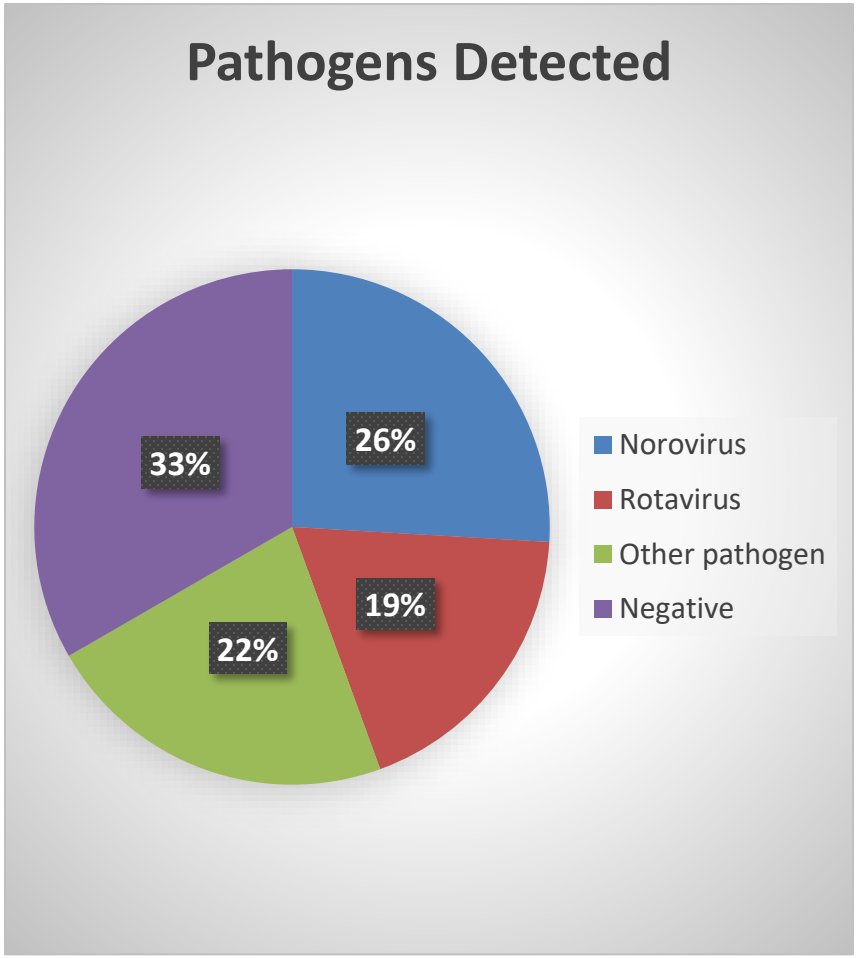
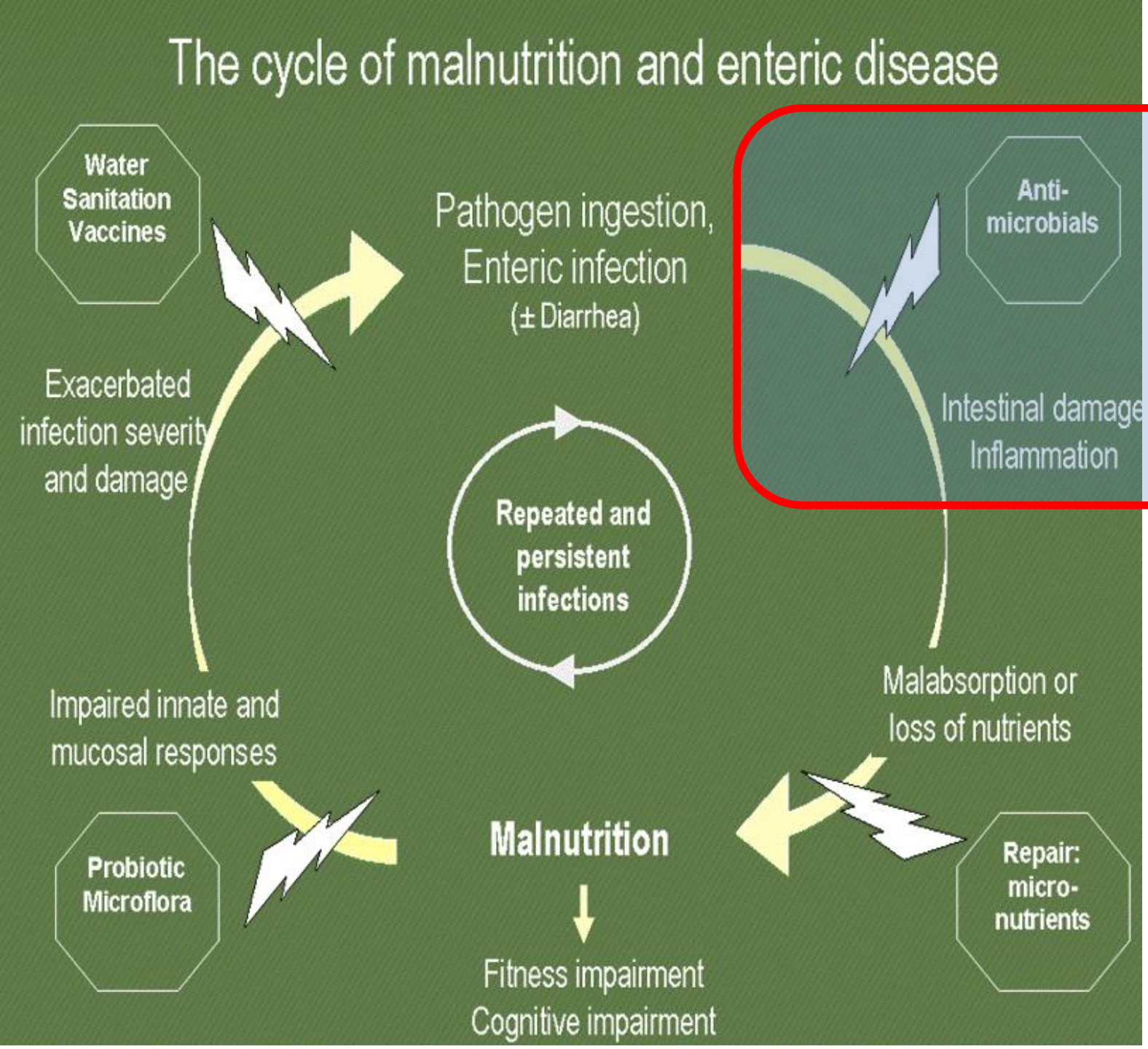
Dec-14

Hospital Acquired GE in Botswana



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

Welch H *et al.* Ped Acad Soc Mtg Vancouver 2014



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“Nicole”

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

Photos used with permission

1. Pernica JM *et al*., JPIDS, 2016

“Nicole”

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

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%)

Pernica JM *et al.* J Pediatr Infect Dis Soc 2016

Measuring Impact of Diarrheal Diagnostics

Grand Challenges Canada
Grands Défis Canada

BIOMÉRIEUX

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* $5x10^8$ cfu/mL daily x 60 days

Results – Pilot Study (n=73)

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

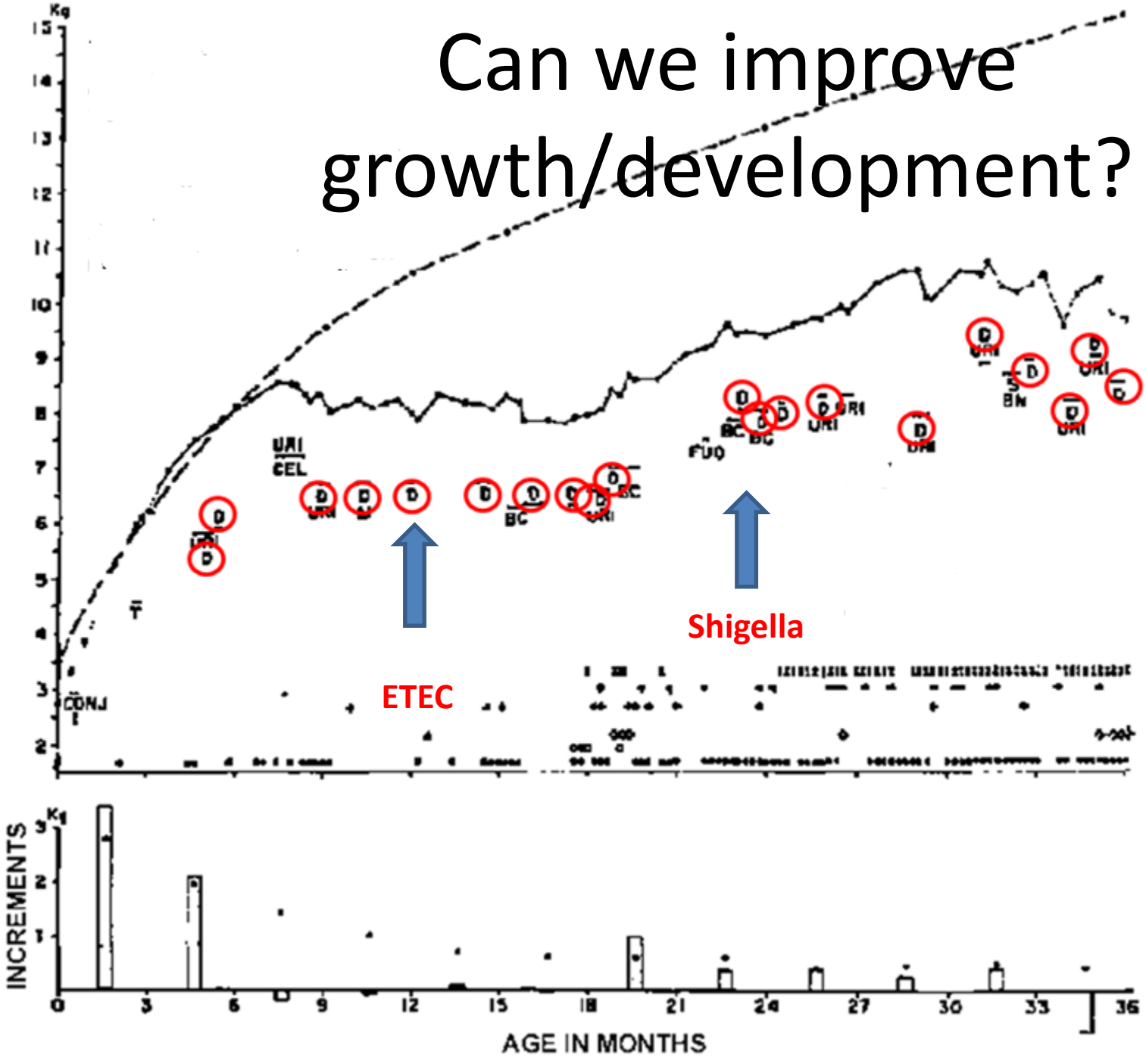
Pernica JM *et al.* under review

Results – Pilot Study (n=73)

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

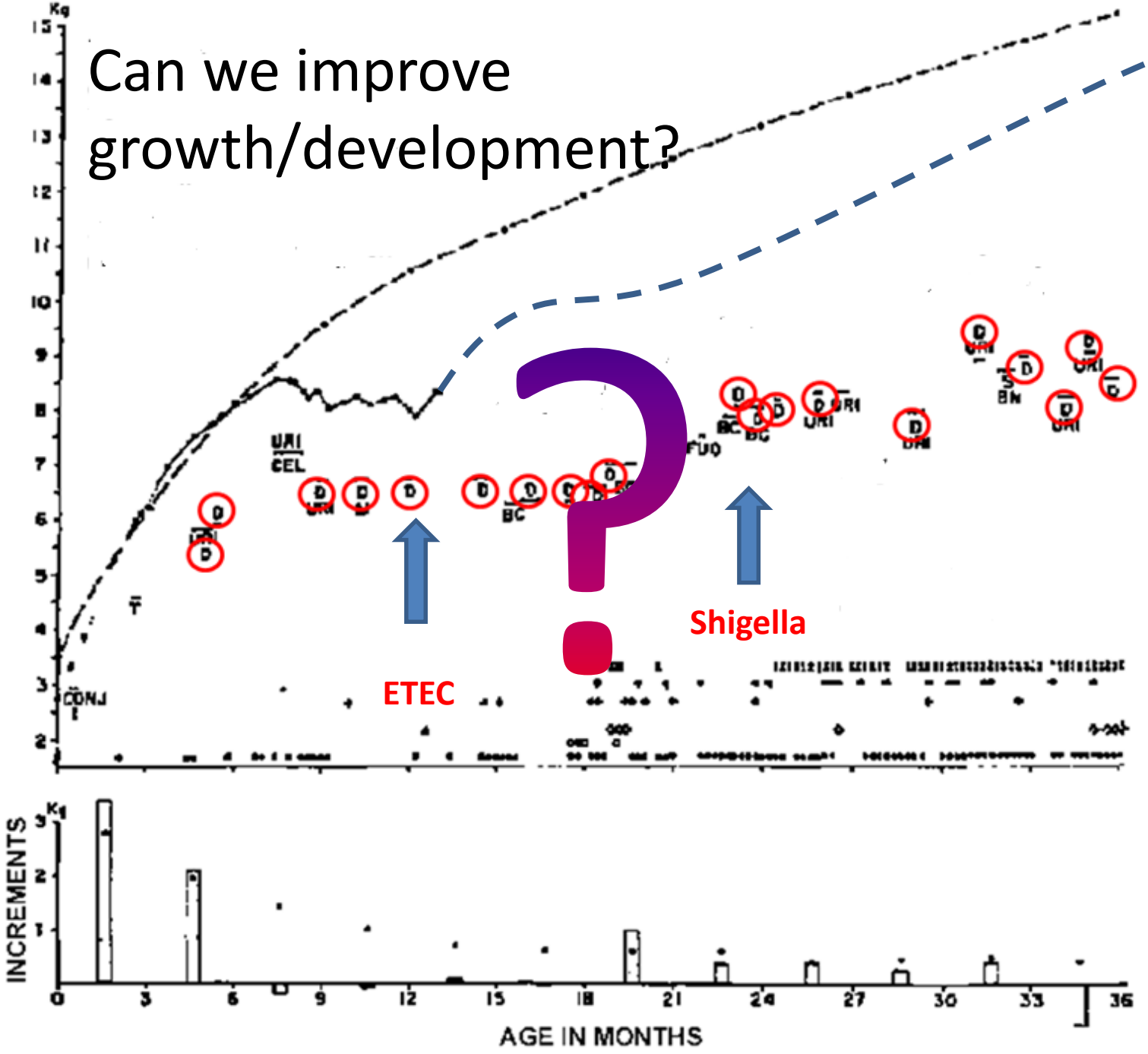
Pernica JM *et al.* under review

Can we improve growth/development?



Mata L et al. 1971

Can we improve growth/development?



Mata L et al. 1971

“Nicole” in follow up with her mother

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PATH

CIHR IRSC

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Bill & Melinda Gates foundation

Thank you!