

What's New in Number 2? Update on Diarrheal Disease from a Global Perspective
Dr. David Goldfarb, BC Children's Hospital
Broadcast live from the 2016 IPAC-Canada Conference



Wisdom Begins With Wonder
IPAC CANADA

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

David Goldfarb MD FRCP(C)
BC Children's Hospital

Teleclass broadcast sponsored by



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May 17, 2016

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**

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Outline

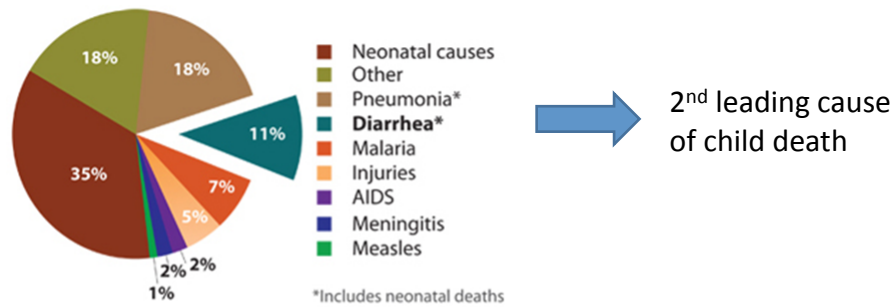
- Global Burden of childhood enteric infections
- New insights from enhanced diagnostic studies
- Examples of efforts to address childhood diarrheal disease

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

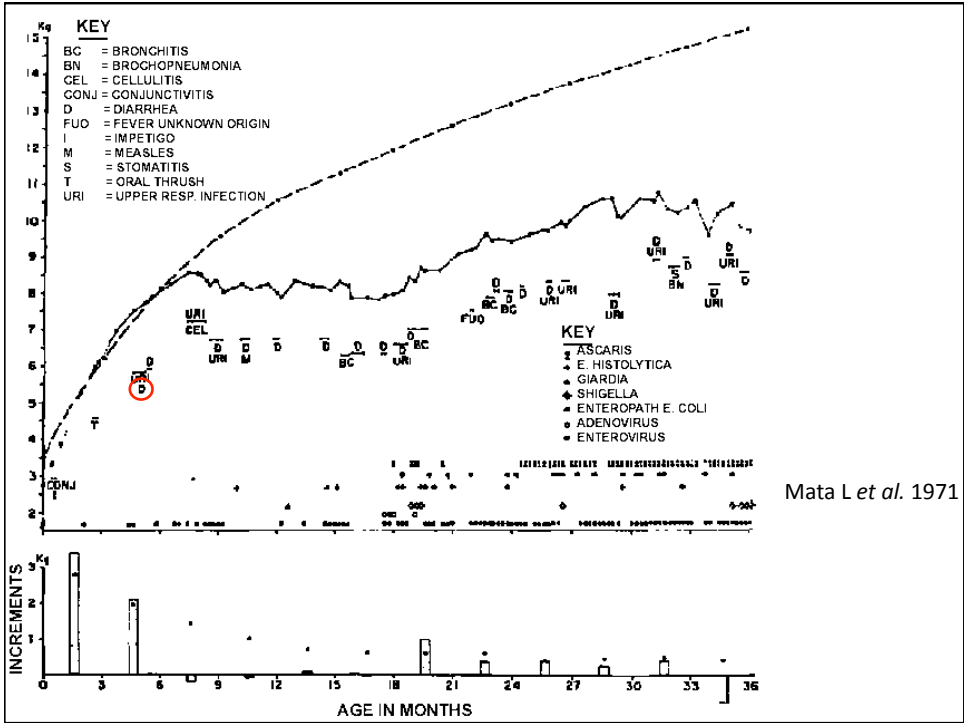


Liu L *et al*, Lancet. 2012;379(9832):2151-61

Burden Diarrheal Disease (cont'd)

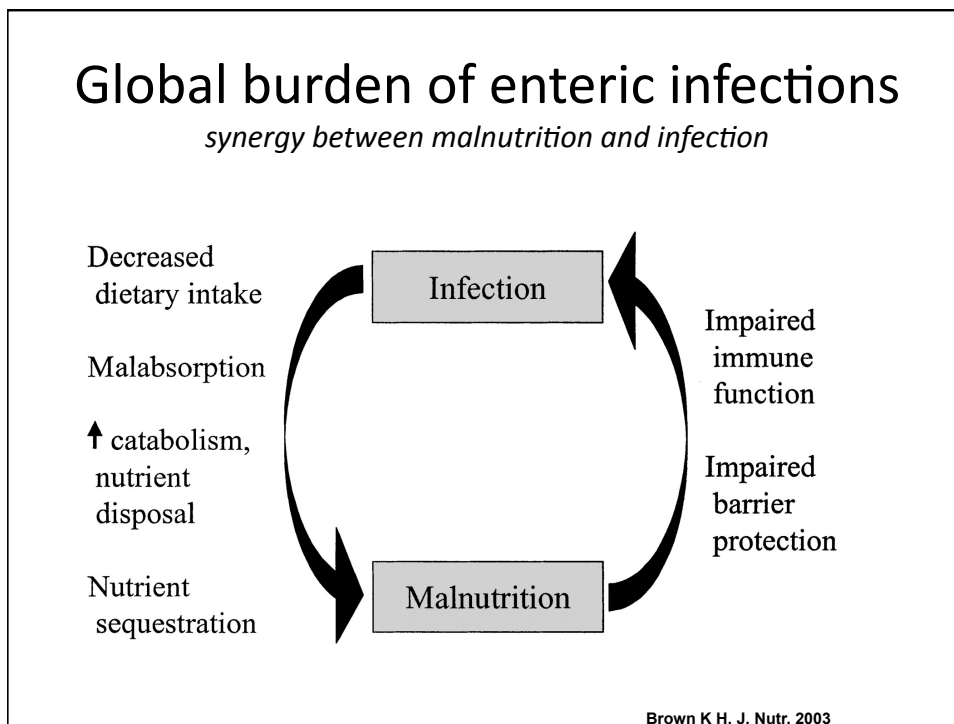
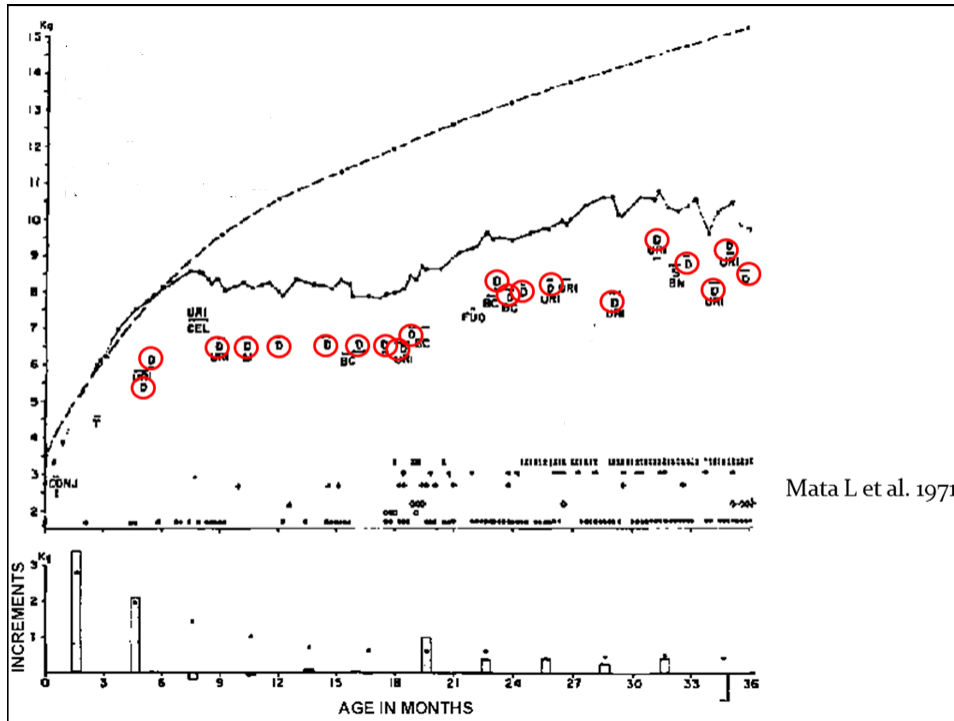
- What about the children that make it through these frequent episodes of diarrhea in childhood?

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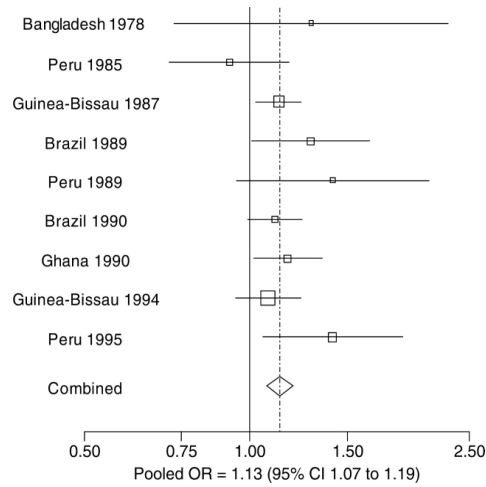


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Global burden of enteric infections

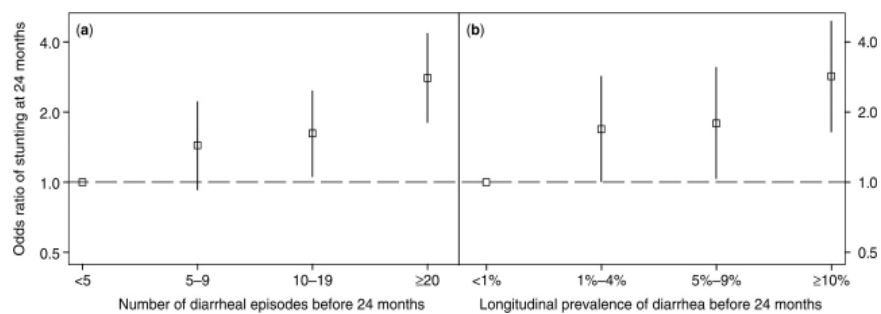
early childhood diarrhea leads to stunting (HAZ <-2)



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

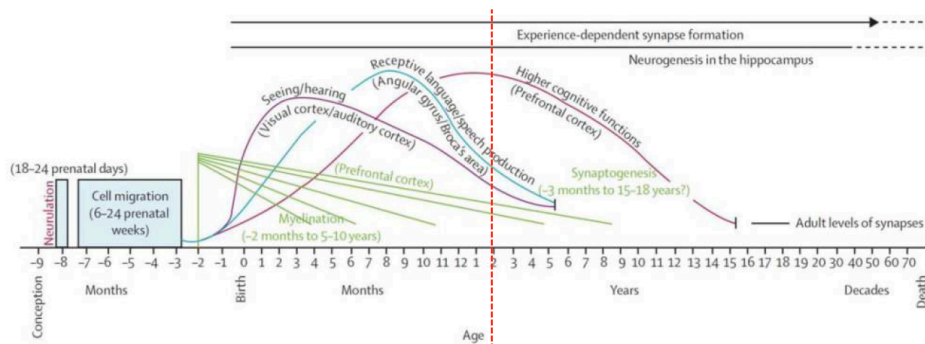
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But does being a little shorter
really matter?

Global burden of enteric infections

brain development is greatest before age 2



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

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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) and Reading and arithmetic [‡] (17-18 years) |
| Not stunted | 56.4 | 0.17 | 11.2 | 8.1 | 92.3 | 0.38 |
| Mildly stunted | 53.8 (-0.21) | 0.05 (-0.12) | 10.3 (-0.26) | 7.2 (-0.4) | 89.8 (-0.20) | 0.40 |
| 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]
- 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.

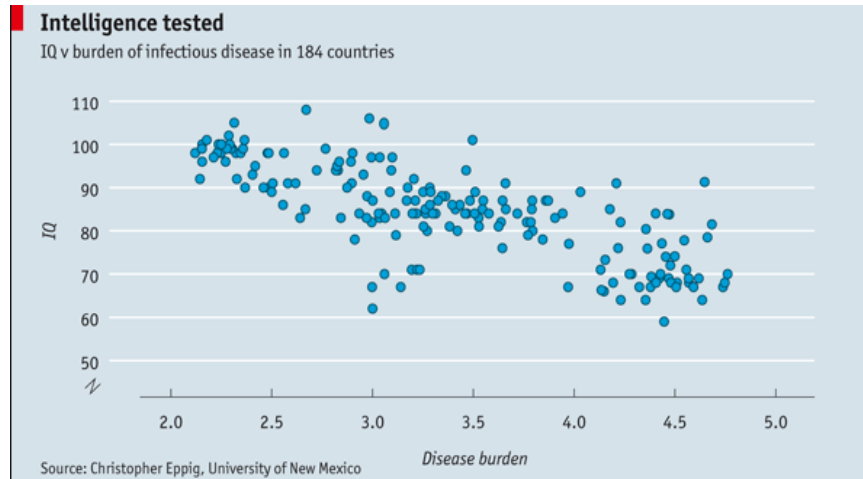
From: Guerrant R, Ped Acad Soc Mtg, April 30 2012

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Global burden of enteric infections

overall infections and cognitive development



Eppig C et al. Proc Biol Sci, 2010
Image from The Economist July1, 2010



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Review

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

Jessica MacIntyre¹, Jennifer McTaggart², Richard L. Guerrant³, David M. Goldfarb^{*4,5}

Outline

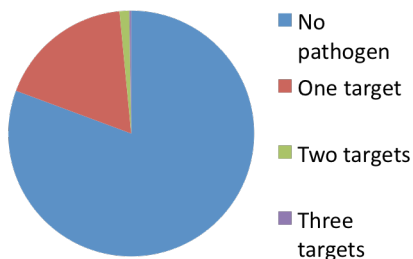
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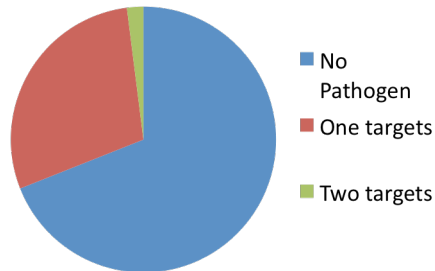
xTAG GPP[®] Assay Used in Prospective Clinical Studies in Europe

Netherlands – 19% detection



Wessels E *et al.* Clin Micro Inf 2013

Germany – 31% detection

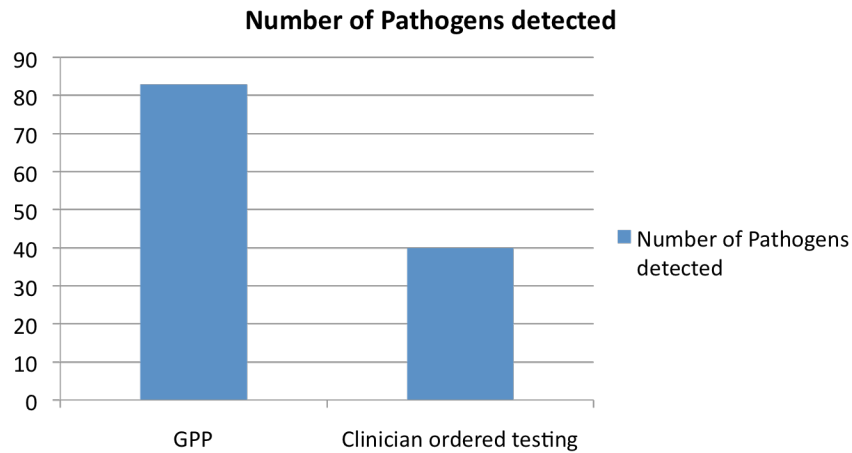


Malecki M *et al.* ESCV 2011

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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, <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 |

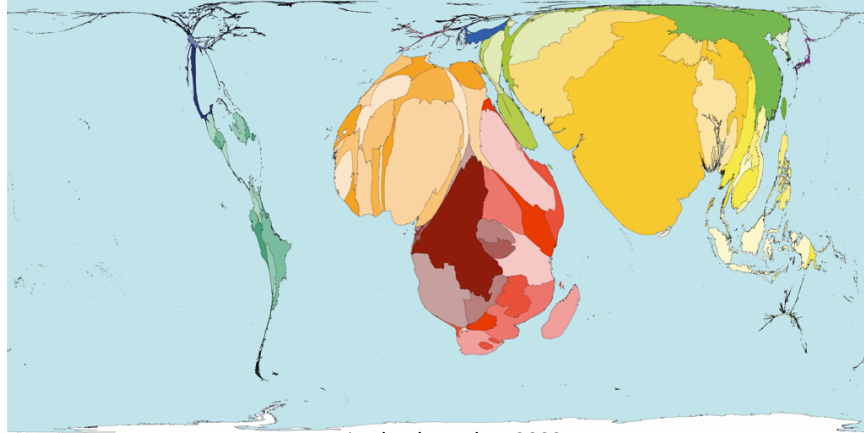
*Astrovirus, norovirus I and II, and sapovirus tested by PCR.

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

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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*

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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, Shah Nawaz 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

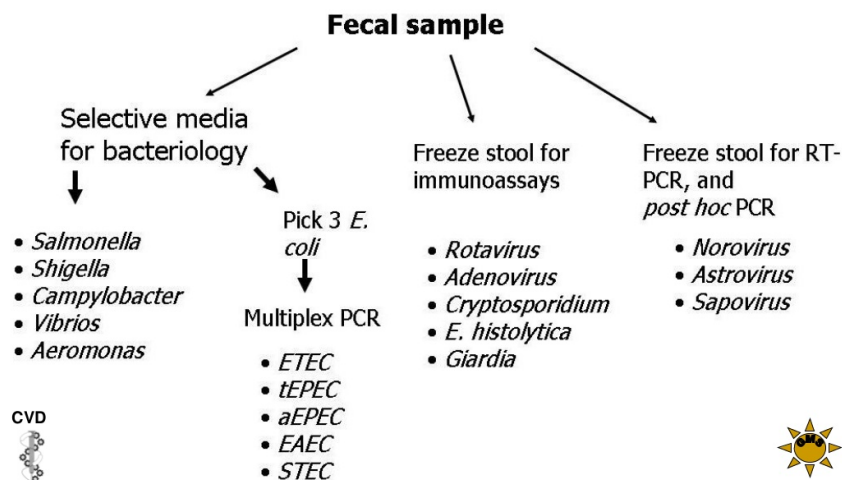
Background Diarrhoeal diseases cause illness and death among children younger than 5 years in low-income countries. We designed the Global Enteric Multicenter Study (GEMS) to identify the aetiology and population-based burden of paediatric diarrhoeal disease in sub-Saharan Africa and south Asia.

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

Microbiology work flow



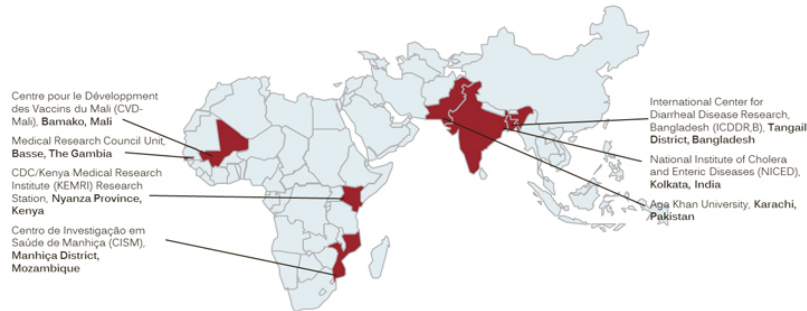
M. Levine, Ped Acad Soc Mtg, Boston, 2012

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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

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Attributable Fraction

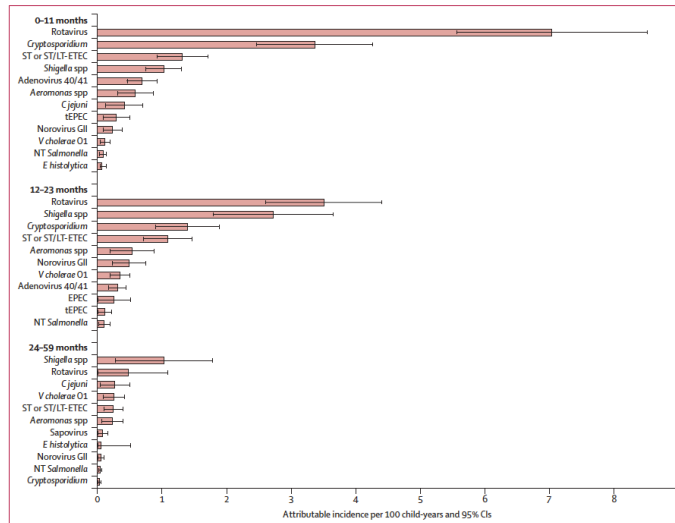


Figure 4: Attributable incidence of pathogen-specific moderate-to-severe diarrhoea per 100 child-years by age stratum, all sites combined. The bars show the incidence rates and the error bars show the 95% CIs.

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

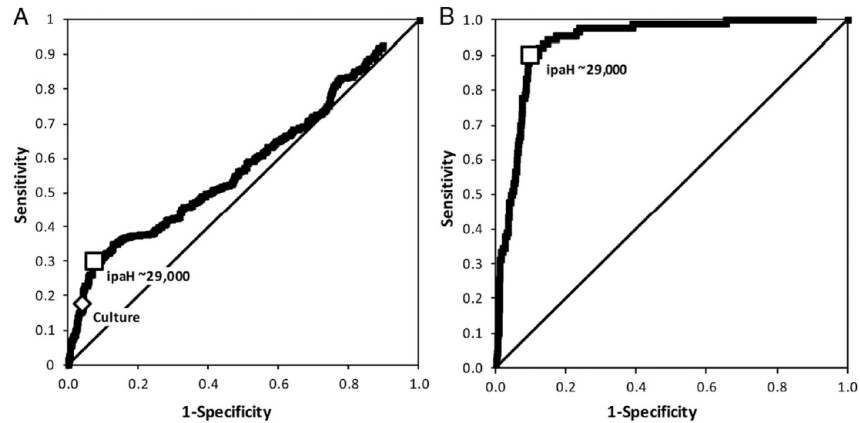
GEMS – main initial findings

- 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*

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

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



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

**BROAD MOLECULAR DIAGNOSTIC
PANELS**

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xTAG GPP® assay - Targets

Bacteria and bacterial toxins

- *Salmonella*
- *Shigella*
- *Campylobacter*
- *Clostridium difficile* Toxin A/B
- Enterotoxigenic *E. coli* (EPEC) 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*

<http://www.luminexcorp.com/Products/Assays/ClinicalDiagnostics/xTAGGPP/index.htm>

Newer More Sensitive Techniques

Enteropathogen Yield with Conventional Testing in Botswana¹



Enteropathogen Yield with Multiplex Molecular Detection in Botswana²



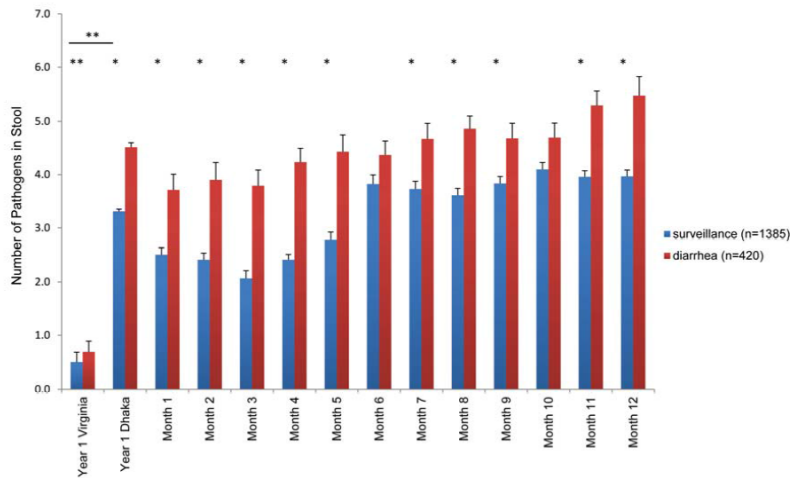
1. Rowe J, et al. PLoS One. 2010 June 2;5(6):e10924.

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

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32 Pathogen Gene targets (Luminex)



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

EDITORIAL COMMENTARY

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

Edward T. Ryan

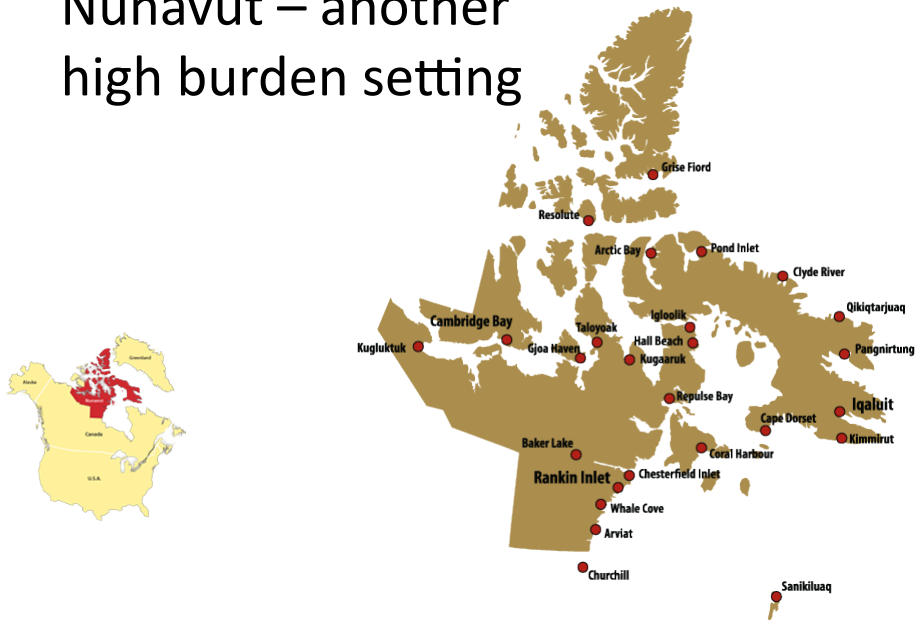
- Mean of 4.3 pathogen targets in “healthy” controls
- Concept of “pathogen excess”

Ryan ET J Infect Dis. 2013 Dec 1;208(11):1732-3.

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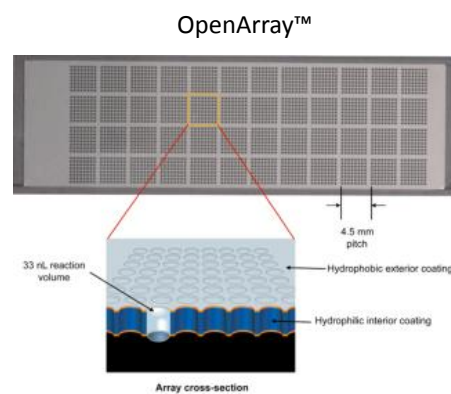
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Nunavut – another high burden setting



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

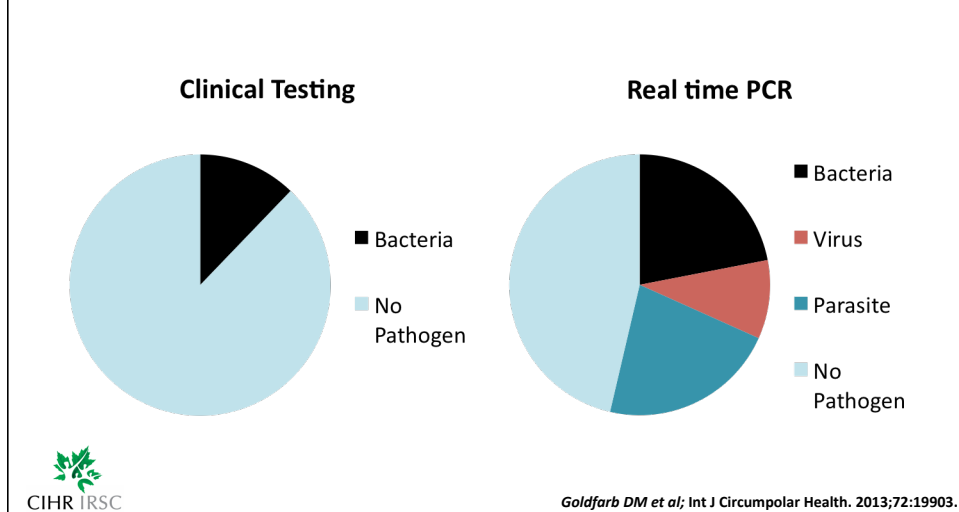


Source: http://publications.gc.ca/collections/collection_2014/aspc-phac/HP37-15-2012-eng.pdf

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



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

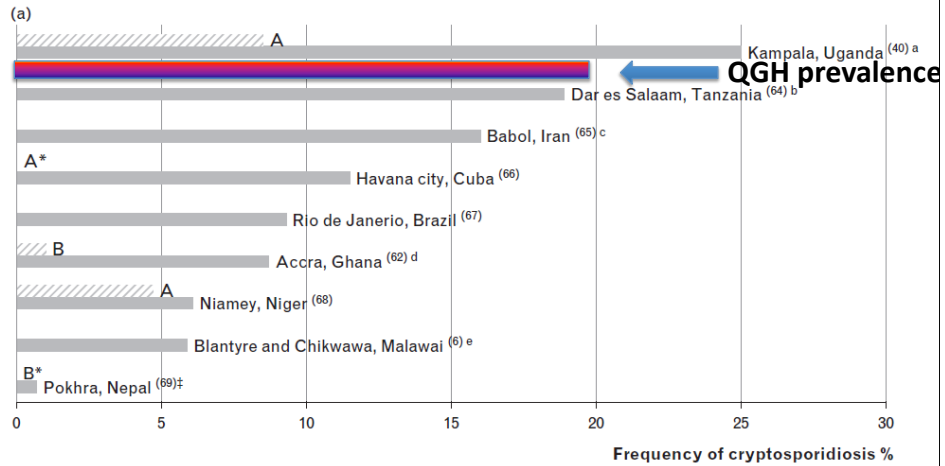
| Microorganism | Nanolitre PCR positives (N = 86) (%) |
|--|---|
| Bacteria | |
| <i>Campylobacter</i> spp. | 6 (7.0) |
| <i>Salmonella</i> spp. | 6 (7.0) |
| <i>Clostridium difficile</i> with toxin B detected | 5 (5.8) |
| <i>Shigella</i> spp. | 1 (1.1) |
| Parasites | |
| <i>Cryptosporidium</i> spp. | 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) |

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

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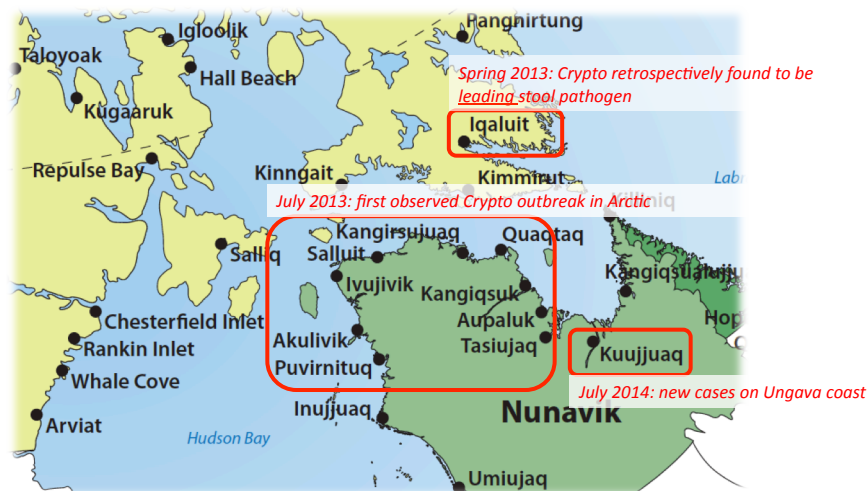
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How common is Cryptosporidium in Iqaluit compared to rest of world?



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

Cryptosporidium – discovery
 new kid on the map

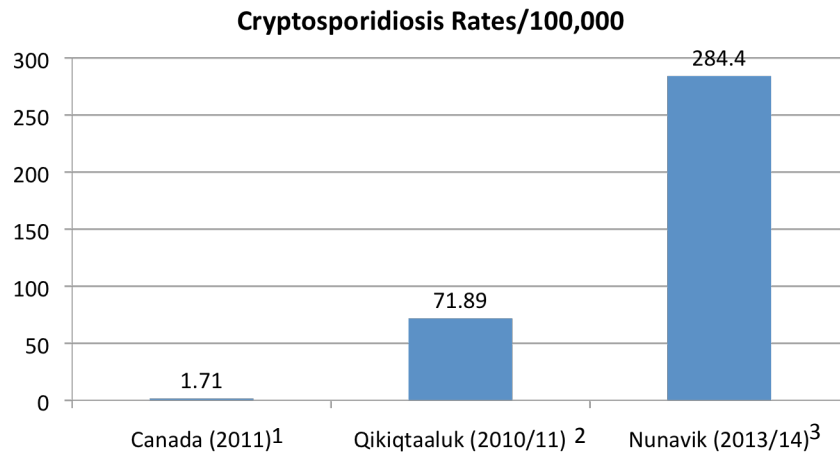


Slide courtesy Dr. Cedric Yansouni McGill University

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Cryptosporidium is a big problem in the Arctic!

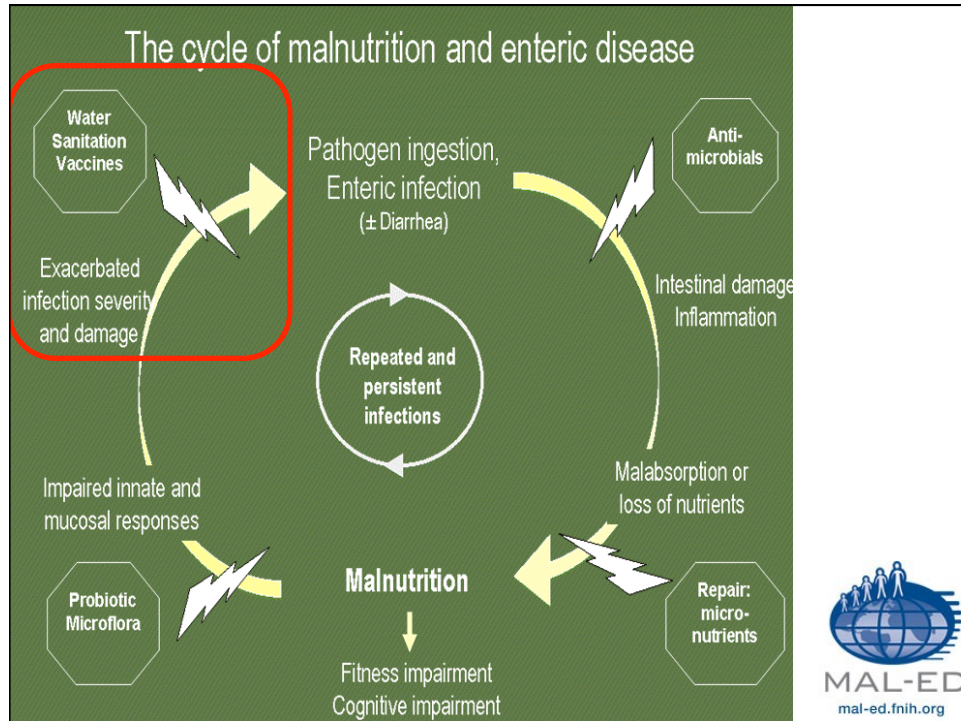


1. Canadian Notifiable Disease Surveillance System (CNDSS) 2011
2. Goldfarb DM et al; Int J Circumpolar Health. 2013;72:19903.
3. Thivierge K et al.; PLoS Negl Trop Dis. 2016 Apr 8;10(4):e0004534.

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

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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

Tate J et al., *Lancet Inf Dis*, 2012
Mwenda J et al., *PIDJ*, 2014

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Rotavirus vaccination



World Health
Organization

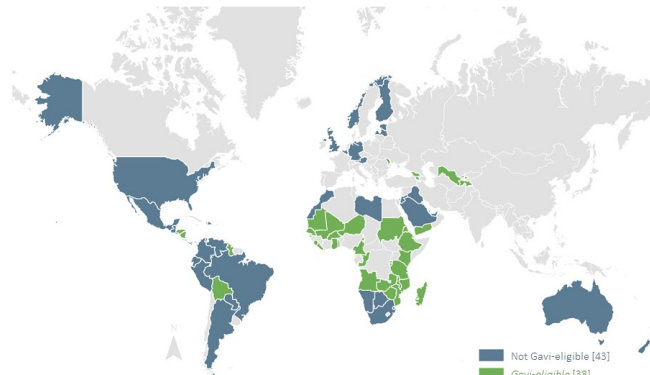


WHO Recommends Global Use of Rotavirus Vaccines
*Decision Could Help Protect Millions of Children in Africa and Asia
from Lethal Diarrheal Disease*

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

Scale-up of rotavirus vaccine

81 countries* have introduced RV nationally



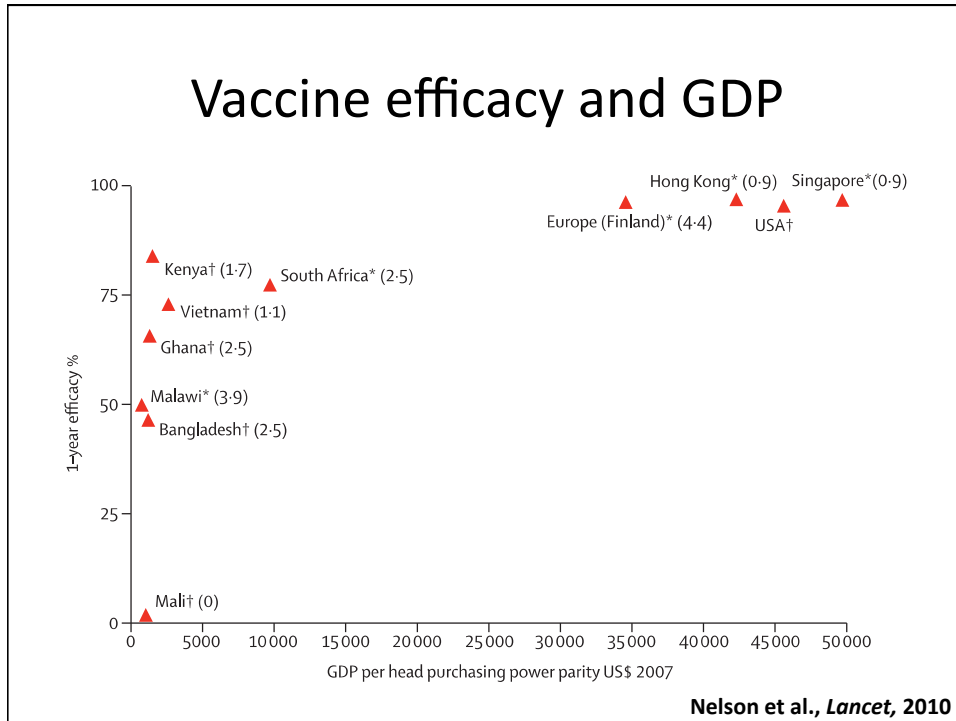
*As of May 1, 2016
RV = rotavirus vaccine



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

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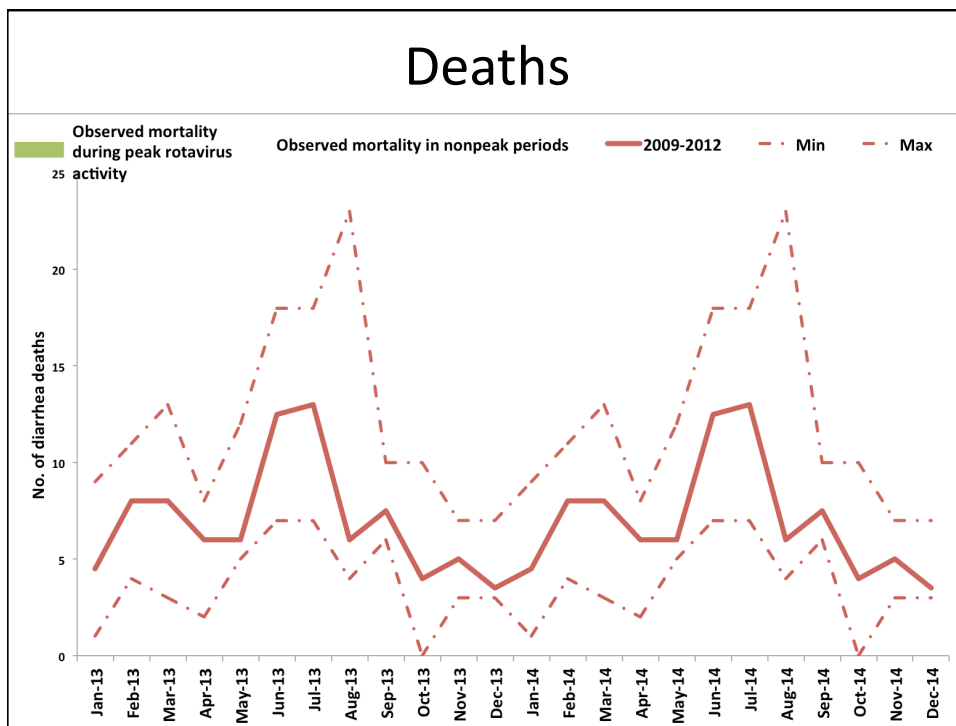
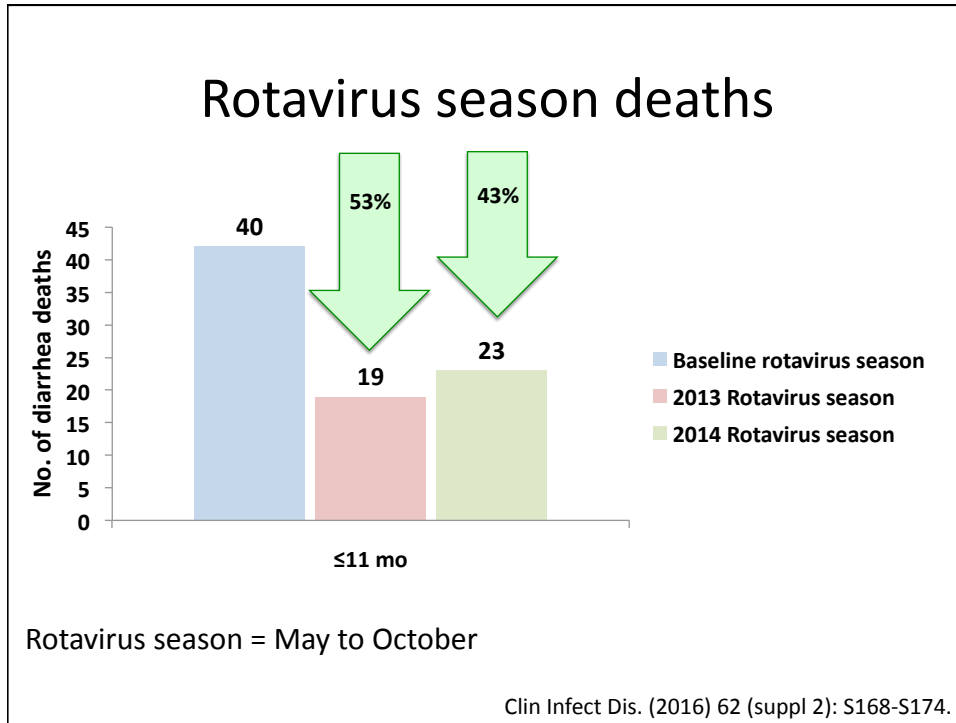
Botswana RV Vaccine Impact Study

- **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

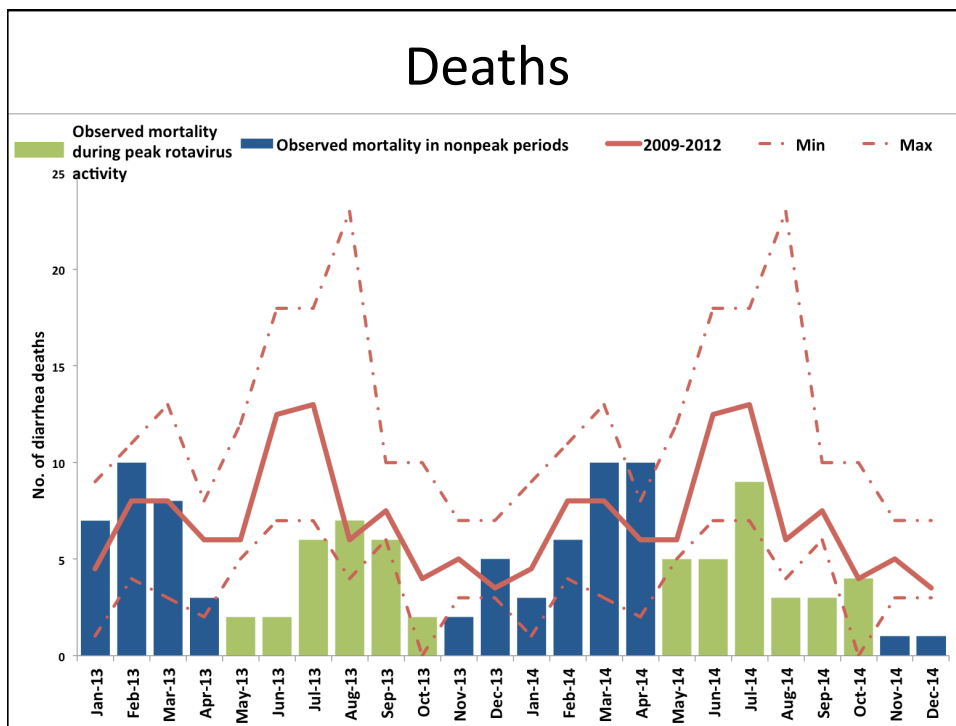
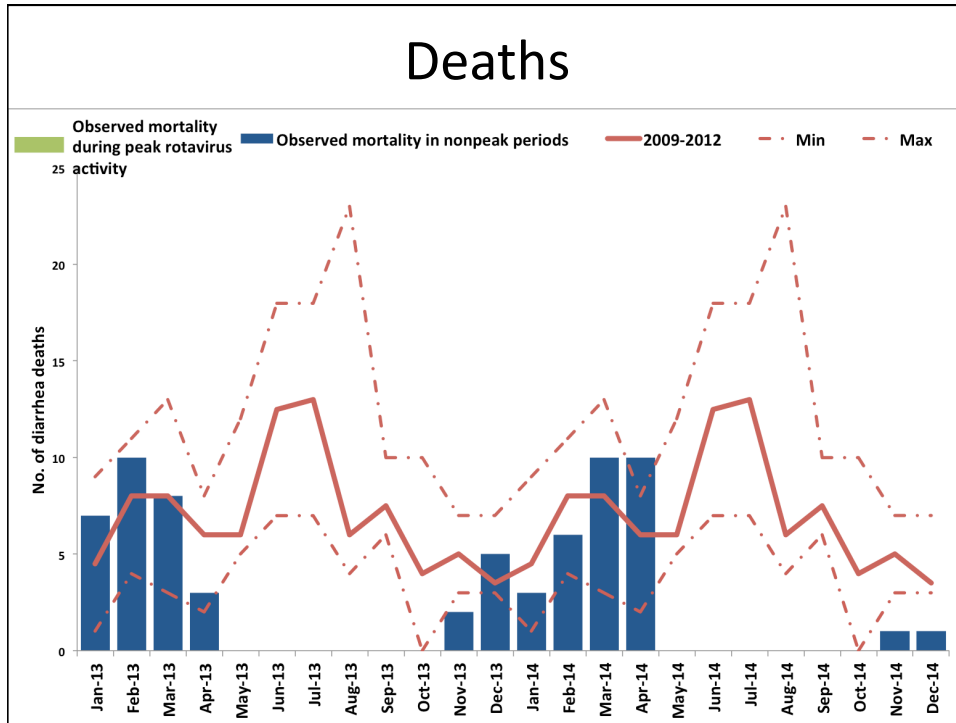
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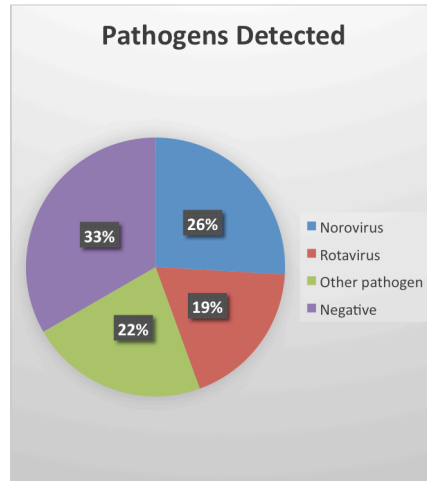
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Hospital Acquired GE in Botswana



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

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

'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>

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WaSH Interventions

Two major trials ongoing

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



SHINE Trial Design

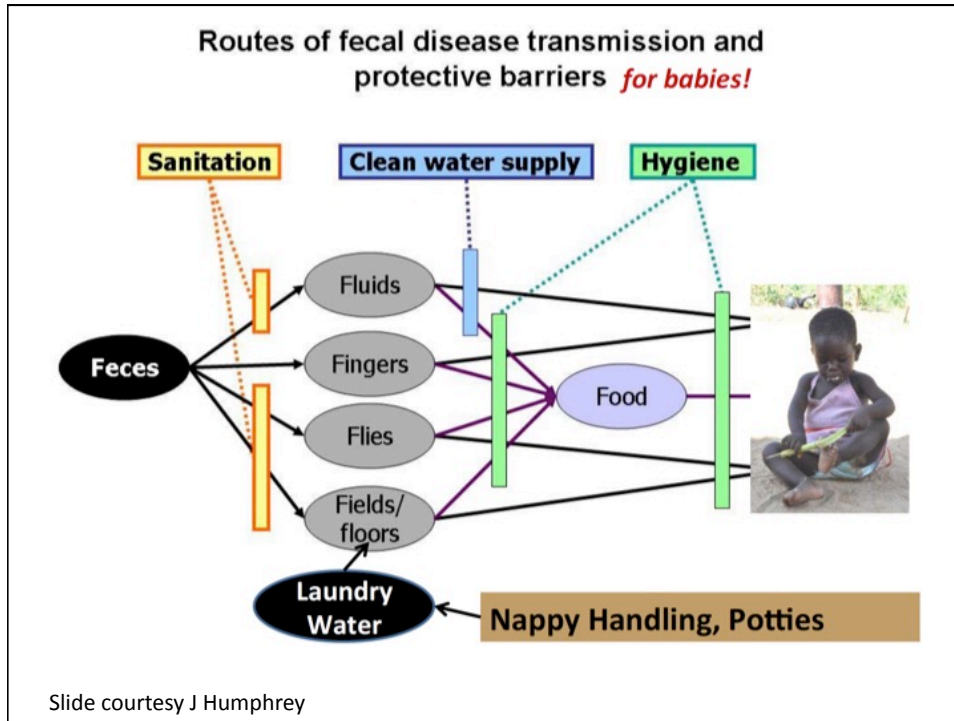
| | |
|---|--|
| <p><u>Sanitation/Hygiene</u></p> <ol style="list-style-type: none"> 1. VIP latrine 2. Tippy Taps   <ol style="list-style-type: none"> 3. POU Water treatment 4. Clean area for eating and play 5. Behavior Change! | <p><u>Nutrition</u></p> <ul style="list-style-type: none"> • 20 g Nutributter daily provided for infants (6-18 mo)  <ul style="list-style-type: none"> • Behavior Change! optimal use of local foods for complementary feeding |
| <p><u>Nutrition & Sanitation/Hygiene</u></p> | <p>Standard Care Strengthened early antenatal care and Exclusive Breastfeeding</p> |



Clinical Inf Dis 2015;61(S7):S685-702

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- 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

Slide courtesy J Humphrey Am J Trop Med Hyg. 2013 Oct;89(4):709-16.

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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 | 800 |
| Wet shaded soil | 60-80% | 69 | 2,100 |
| Chicken feces | 100% | 10,000,000 | 10,000,000 |

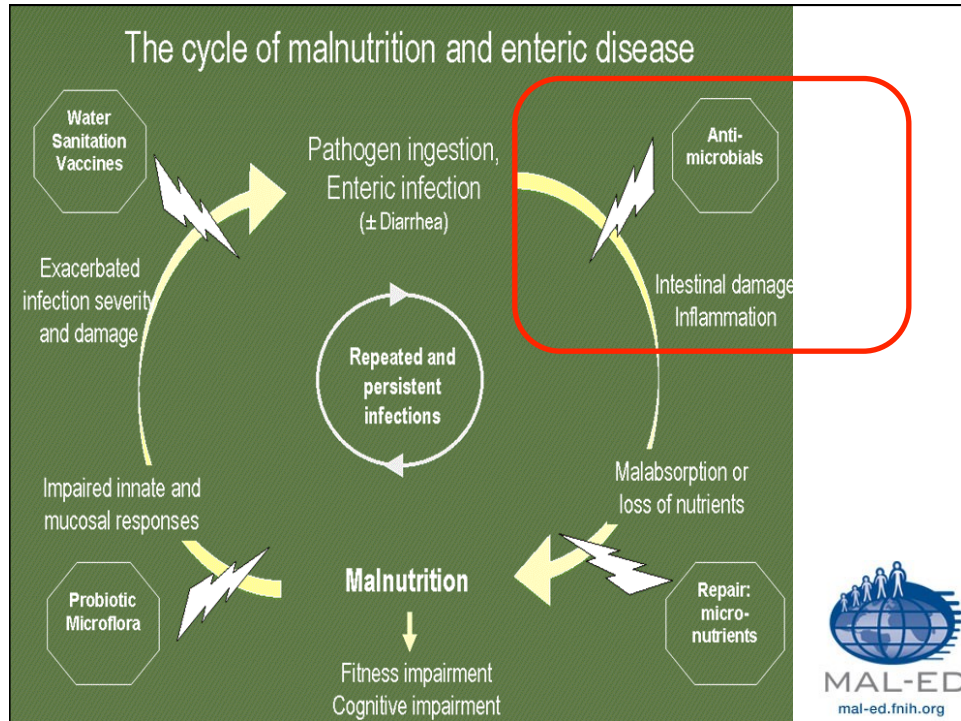
Am J Trop Med Hyg. 2013 Oct;89(4):709-16.

Protective play area



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“Nicole”

- Has kwashiorkor (edematous malnutrition) and admitted with acute diarrhea
- Has a ~ **1/4 chance of dying¹** during this admission

1. Pernica JM *et al.*, JPIDS, in press

“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

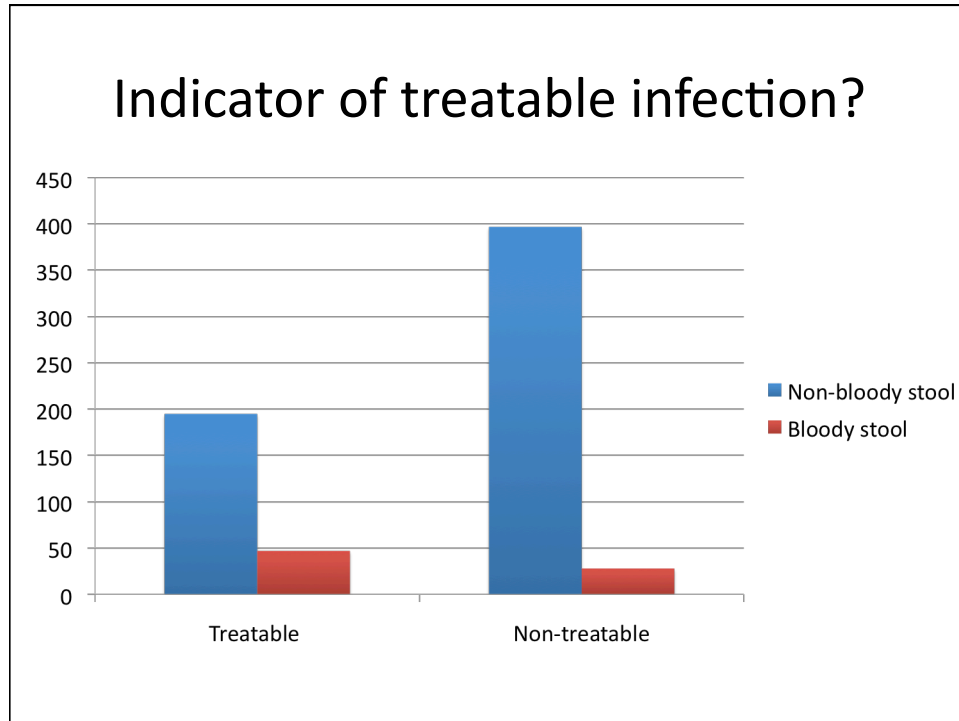
- majority of acute gastroenteritis presumed to be viral
 - WHO recommends treatment with antibiotics only for bloody dysentery
- is this assumption true in LMICs?

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%)

Pernica JM *et al.* J Pediatr Infect Dis Soc (in press)

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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

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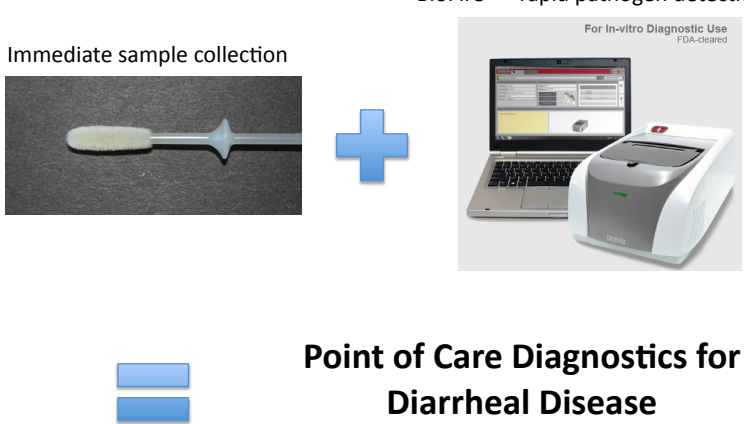
Measuring Impact of Diarrheal Diagnostics

Grand Challenges Canada
Grands Défis Canada

BIO-MÉRIEUX

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* 5×10^8 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 |

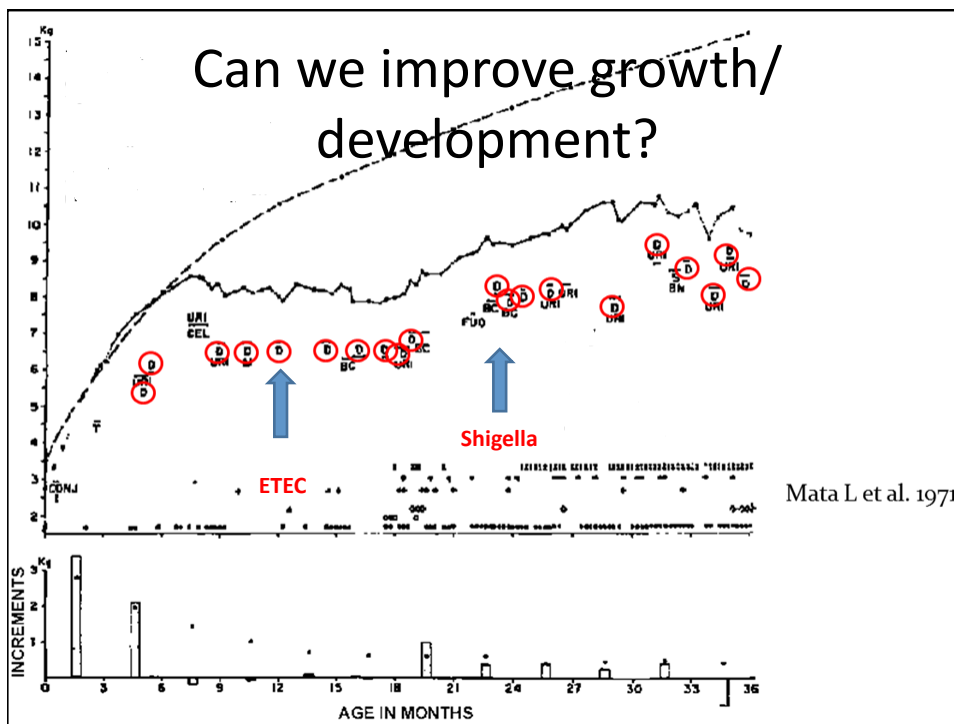
Pernica JM *et al.* IDWeek San Diego 2015

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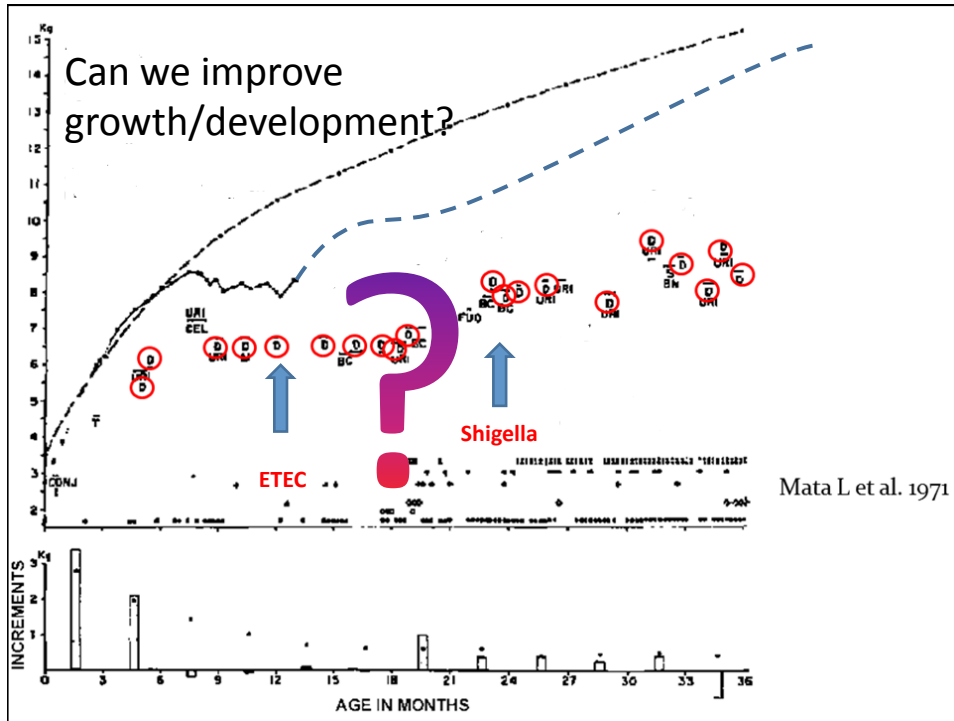
| group | difference in HAZ @ 60 d adjusted for baseline (95% CI) | p |
|-------------------------------------|---|------|
| Delayed testing + placebo | (ref) | |
| Rapid testing + placebo | + 0.33 (-0.24 to 0.89) | NS |
| Delayed testing + <i>L. reuteri</i> | + 0.51 (-0.08 to 1.11) | NS |
| Rapid testing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

Pernica JM et al. IDWeek San Diego 2015



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“Nicole” in follow up with her mother

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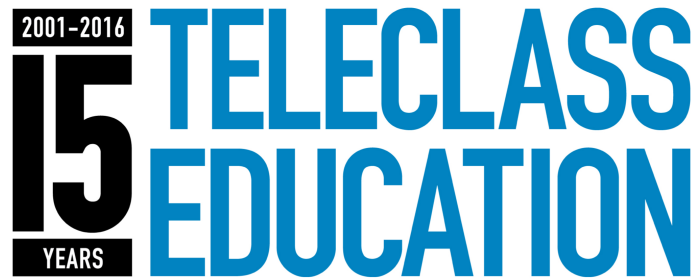
Agence de santé
publique du Canada

Thank you!



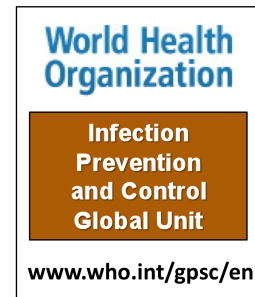
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