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

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

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

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Disclosure

• Faculty: Dr. David Goldfarb
• Relationships with commercial interests:
  – Nothing to disclose
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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

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Burden of diarrheal diseases

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


2nd 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?
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Global burden of enteric infections

synergy between malnutrition and infection

- Decreased dietary intake
- Malabsorption
- ↑ catabolism, nutrient disposal
- Nutrient sequestration

Infection

- Impaired immune function
- Impaired barrier protection

Malnutrition

Global burden of enteric infections
early childhood diarrhea leads to stunting (HAZ <-2)


Global burden of enteric infections
early childhood diarrhea leads to stunting


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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*

<table>
<thead>
<tr>
<th>Country</th>
<th>Cognitive score (8 years, n=48)</th>
<th>Ravens Matrix (47 years, n=403)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Philippines</td>
<td>5.17 (0.7)</td>
<td>11.2 (0.7)</td>
</tr>
<tr>
<td>South Africa</td>
<td>0.95 (0.12)</td>
<td>12.9 (0.56)</td>
</tr>
<tr>
<td>Indonesia</td>
<td>1.02 (0.4)</td>
<td>0.72 (0.4)</td>
</tr>
<tr>
<td>Brazil</td>
<td>5.1 (0.7)</td>
<td>9.23 (0.18)</td>
</tr>
<tr>
<td>Peru</td>
<td>0.0 (0.0)</td>
<td>8.9 (0.19)</td>
</tr>
<tr>
<td>Jamaica</td>
<td>0.00 (0.0)</td>
<td>0.40 (0.0)</td>
</tr>
</tbody>
</table>

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

1. Data only.
2. Sample comprised stunted (≤−2 SD) children participating in a randomized intervention trial and a non-stunted (≥−1 SD) comparison group.
3. 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; 8.2 cm by 7yo)

- *Cryptosporidiosis* infections increase diarrhea morbidity and nutritional shortfalls to 18m
- [Agnew 98; Lima 00; Newman 99]

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

- Albendazole 7% incr. HST @4m
- [Stephenson 93]

- Diarrhea or *Cryptosporidiosis* <2yo = 4-8% incr. HST @4-7yo
- [Guerrant 99]

- 4.3% incr. HST = 16.6% incr. work prod.
- [Ndamba 93]

**Cognitive impairment** (c. 10 IQ points)

- Diarrhea <2yo decr. WISC counting digits @5-9yo
- [Guerrant 90]

- Diarrhea <2yo decr. TONI-5-10yo
- [Niehaus 02]

- Giardia or stunting ≤4-10 pts decr. WISC-R @9yo
- [Berkman 02]

**School performance** (c. 1 yr)

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

---

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

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Global burden of enteric infections

*overall infections and cognitive development*

![Graph showing the relationship between disease burden and IQ](source)

*Image from The Economist, July 1, 2010*

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Review
Early childhood diarrhoeal diseases and cognition: are we missing the rest of the iceberg?
Jessica MacIntyre, Jennifer McTaggart, Richard L. Guerrant, David M. Goldfarb

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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xTAG GPP ® Assay Used in Prospective Clinical Studies in Europe

Netherlands – 19% detection
- No pathogen
- One target
- Two targets
- Three targets

Germany – 31% detection
- No Pathogen
- One targets
- Two targets

Wessels E et al. Clin Micro Inf 2013
Malecki M et al. ESCV 2011

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Benefits of “Syndromic approach”

![Bar chart showing number of pathogens detected between GPP and Clinician ordered testing.]


Pediatric Oncology Population

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Overall Results for BioFire, Luminex, and In-House Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>First episode per patient</td>
<td>BioFire</td>
</tr>
<tr>
<td>Negative</td>
<td>105</td>
</tr>
<tr>
<td>Positive</td>
<td>94</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Targets detected, n (%)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 (85.1)</td>
<td>80 (80.8)</td>
<td>46 (97.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 (12.8)</td>
<td>11 (11.1)</td>
<td>1 (2.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (2.1)</td>
<td>7 (7.1)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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?

**Two Large Multi-centre Studies of childhood diarrheal disease**

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

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

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Global burden of enteric infections

etiological spectrum and impact

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


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 etiology 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 census populations at four sites in Africa and three in Asia. We recruited

Global Enteric Multicenter Study

Microbiology work flow

Fecal sample

Selective media for bacteriology

Salmonella
Shigella
Campylobacter
Vibrios
Aeromonas

Pick 3 E. coli
Multiplex PCR
ETEC
IEPEC
aEPEC
EAEC
STEC

Freeze stool for inmmunoassays

Rotavirus
Adenovirus
Cryptosporidium
E. histolytica
Giardia

Freeze stool for RT-PCR, and post hoc PCR

Norovirus
Astrovirus
Sapovirus

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

Global Enteric Multicenter Study

<table>
<thead>
<tr>
<th>Pathogens (including Giardia) identified in stool specimens from cases and controls during the first 2 years of GEMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of pathogens identified</td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>Cases (%)</td>
</tr>
<tr>
<td>Cases (%)</td>
</tr>
<tr>
<td>At least 1</td>
</tr>
<tr>
<td>At least 2</td>
</tr>
<tr>
<td>At least 3</td>
</tr>
</tbody>
</table>


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Attributable Fraction

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-ETEC
  – Cryptosporidium
  – Typical enteropathogenic E coli

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

Receiver operating characteristic (ROC) curves


BROAD MOLECULAR DIAGNOSTIC PANELS

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### xTAG GPP® assay - Targets

<table>
<thead>
<tr>
<th>Bacteria and bacterial toxins</th>
<th>Viruses</th>
<th>Parasites</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <em>Salmonella</em></td>
<td>• Adenovirus 40/41</td>
<td>• <em>Giardia</em></td>
</tr>
<tr>
<td>• <em>Shigella</em></td>
<td>• Rotavirus A</td>
<td>• <em>Entamoeba histolytica</em></td>
</tr>
<tr>
<td>• <em>Campylobacter</em></td>
<td>• <em>Norovirus</em> GI/GII</td>
<td>• <em>Cryptosporidium</em></td>
</tr>
<tr>
<td>• <em>Clostridium difficile</em> Toxin A/B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Enterotoxigenic <em>E. coli</em> (ETEC) LT/ST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• <em>E. coli</em> O157</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Shiga-like Toxin producing <em>E. coli</em> (STEC) stx 1/stx 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• <em>Vibrio cholerae</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• <em>Yersinia enterocolitica</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

### Newer More Sensitive Techniques

<table>
<thead>
<tr>
<th>Enteropathogen Yield with Conventional Testing in Botswana¹</th>
<th>Enteropathogen Yield with Multiplex Molecular Detection in Botswana²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial</td>
<td>Bacterial</td>
</tr>
<tr>
<td>Parasitic</td>
<td>Parasitic</td>
</tr>
<tr>
<td>Mixed</td>
<td>Viral</td>
</tr>
<tr>
<td>None Detected</td>
<td>Mixed</td>
</tr>
</tbody>
</table>


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32 Pathogen Gene targets (Luminex)

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

EDITORIAL COMMENTARY

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

Edward T. Ryan

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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


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

Clinical Testing
- Bacteria
- No Pathogen

Real time PCR
- Bacteria
- Virus
- Parasite
- No Pathogen

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

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

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

Cryptosporidium – discovery new kid on the map

*Spring 2013: Crypto retrospectively found to be leading stool pathogen

*July 2013: first observed Crypto outbreak in Arctic

*July 2014: new cases on Ungava coast

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Cryptosporidium is a big problem in the Arctic!

1. Canadian Notifiable Disease Surveillance System (CNDSS) 2011

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• 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

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

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

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Vaccine efficacy and GDP

![Graph showing vaccine efficacy and GDP relationship]

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

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Rotavirus season deaths

<table>
<thead>
<tr>
<th>Season</th>
<th>Deaths</th>
<th>% Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>19</td>
<td>53%</td>
</tr>
<tr>
<td>2014</td>
<td>23</td>
<td>43%</td>
</tr>
</tbody>
</table>

Rotavirus season = May to October


Deaths

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Deaths

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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

<table>
<thead>
<tr>
<th>Sanitation/Hygiene</th>
<th>Nutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. VIP latrine</td>
<td>• 20 g Nutributter daily provided for infants (6-18 mo)</td>
</tr>
<tr>
<td>2. 2 Tippy Taps</td>
<td>• Behavior Change! optimal use of local foods for complementary feeding</td>
</tr>
<tr>
<td>3. POU Water treatment</td>
<td></td>
</tr>
<tr>
<td>4. Clean area for eating and play</td>
<td></td>
</tr>
<tr>
<td>5. Behavior Change!</td>
<td></td>
</tr>
<tr>
<td>Nutrition &amp; Sanitation/Hygiene</td>
<td>Standard Care</td>
</tr>
<tr>
<td></td>
<td>Strengthened early antenatal care and Exclusive Breastfeeding</td>
</tr>
</tbody>
</table>

Clinical Inf Dis 2015;61(S7):S685–702
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Slide courtesy J Humphrey

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Causes of intestinal damage in rural Zimbabwean infants

<table>
<thead>
<tr>
<th></th>
<th>% houses with E coli + sample</th>
<th>Mean E Coli cfu/g</th>
<th>Mean E Coli “per serving size” cfu/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant food</td>
<td>0%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Drinking water</td>
<td>54%</td>
<td>2</td>
<td>800</td>
</tr>
<tr>
<td>Wet shaded soil</td>
<td>60-80%</td>
<td>69</td>
<td>2,100</td>
</tr>
<tr>
<td>Chicken feces</td>
<td>100%</td>
<td>10,000,000</td>
<td>10,000,000</td>
</tr>
</tbody>
</table>


Protective play area

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The cycle of malnutrition and enteric disease

Pathogen ingestion, Enteric infection (± Diarrhea)

- Water Sanitation Vaccines
- Exacerbated infection severity and damage
- Impaired innate and mucosal responses
- Malnutrition
  - Fitness impairment
  - Cognitive impairment

Anti-microbials
- Intestinal damage
- Inflammation
- Malabsorption or loss of nutrients
- Repair micro-nutrients

Water Sanitation Vaccines

“Nicole”

- Has kwashiokor (edematous malnutrition) and admitted with acute diarrhea
- Has a \(~ \frac{1}{4} \text{ chance of dying}\) during this admission

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

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"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%)

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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

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Measuring Impact of Diarrheal Diagnostics

Immediate sample collection + BioFire™ - rapid pathogen detection

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
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)

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

Pernica JM *et al.* IDWeek San Diego 2015
Results – Pilot Study (n=73)

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

Pernica JM et al. IDWeek San Diego 2015

Can we improve growth/development?

Mata L et al. 1971

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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

Can we improve growth/development?

“Nicole” in follow up with her mother

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