Enteric infections in low-and middle-income countries-from research to prevention and the clinic

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The Gastrointestinal Tract

- Unique organ—both inside the body and a surface
- Lined with epithelial cells that must absorb and secrete
- Epithelium maintains the barrier that protects from microbial pathogens and mutagens/toxins
- Barrier consists of the intact mucosal surface and a large population of resident immune cells
Outline

• Enteric infections and diarrhoeal disease
• Patterns of disease
• Global burden of disease
• Research to prevention
• Research to treatment
• What does the future hold?
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The burden of enteric disease is not limited to diarrhoeal disease alone

- Enteric infections can result in
  - local (e.g. rotavirus, soil-transmitted helminths)
  - systemic disease (e.g. typhoid), or
  - disease in remote locations (hepatitis viruses)
- Enteric infections contribute to intestinal damage resulting in
  - Malnutrition and growth failure
  - Delayed cognitive development
  - Infections in the first 2 years of life can lead to a 8 cm growth shortfall and 10 point lower IQ at 7-9 years

Diarrhoea is a problem worldwide

- The amount of diarrhoeal water in a day equals the water over Victoria Falls in 1 min.
- It has been estimated that in any given 24 hr period, 200 million people on earth have gastroenteritis
Diarrhoea due to infections is more common than diarrhoea not due to infections, but it is important to remember that there are many non-infectious causes of diarrhoea which include:

- Antibiotics
- High blood pressure medications
- Cancer drugs
- Crohn’s disease
- Colitis
- Diabetes, thyroid and other endocrine diseases
- Food additives (sorbitol, fructose, and others)
- Food allergies
- Previous surgery or radiation of the abdomen or gastrointestinal tract
- Tumors
- Reduced blood flow to the intestine
- Heredity--certain diseases occur more often in related family members
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Infectious diarrhoea occurs in recognisable epidemiologic patterns

• **Diarrhoea in the immunocompetent adult**
  – Sporadic diarrhoea (*person-to-person*)
  – Diarrhoea in community outbreaks (*usually food or waterborne*)
  – Diarrhoea in closed communities (e.g. hospitals, nursing homes, cruise ships, *most often person-to-person or fomites*)
  – Traveller’s diarrhoea (*food or waterborne*)

• **Diarrhoea in the immunocompromised adult**
Causes of acute infectious diarrhoea in the immunocompetent

• >400 causes identified for infectious diarrhoea
• Criteria for identifying a pathogen as causally associated are
  – Identification more frequently in patients with diarrhoea than in controls
  – Immune response to specific agent
  – Beginning and end of illness correspond to onset and cessation of shedding
• In most sporadic cases, testing is rare and treatment is empirical
Sporadic or endemic diarrhoea

- Noroviruses, *Salmonella, Campylobacter, Shigella, Aeromonas, E. coli*, Group A rotaviruses, astroviruses, adenoviruses, *Cryptosporidium, Giardia*
- Acute watery diarrhoea, can be associated with vomiting and abdominal pain
- **Viral infections** more associated with vomiting and low grade fever
- **Bacterial infections** more associated with higher grade fever and dysentery
- **Parasitic infections** may resemble wither viral or bacterial infections, abdominal pain is common
- **Malabsorption** if prolonged

The Global Enterics Multi-Site Study

- 7 countries in Asia and Africa
- Children under 5 with moderate to severe diarrhoea
- Case-control design
- Best available tools identified rotavirus, Cryptosporidium, Shigella and ETEC
- Re-analysed by qPCR

Liu et al, Lancet 2016
Epidemic diarrhoea or community outbreaks

• Noroviruses, Sapoviruses, group B rotavirus, astroviruses, adenoviruses, Shigella, Vibrio cholerae, Cryptosporidium
  – Toxin mediated diarrhoea requires a large infectious dose
  – Intracellular pathogens require a small infectious dose
Outbreaks of diarrhoeal disease-cholera reports during 6 months of 2017
Travellers’ diarrhoea

- Domestic travellers-similar to causes of sporadic diarrhoea
- International travellers
  - *Campylobacter, Salmonella* (non-typhoidal and typhoidal) ETEC, EAEC, *Shigella*
  - *Giardia*
  - Noroviruses, astroviruses
Outline

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• **Global burden of disease**
• Research to prevention
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• What does the future hold?
Diarhoeal diseases

- DALYs, all ages
- 3.12% (2.63%–3.93%)
- -4.6% annual change

IHME, 2016
Diarhoeal diseases

- Deaths, all ages
- 3.03% (2.27% to 4.3%)
- -3.12% annual change

IHME, 2016
Diarhoeal diseases

• Deaths, <5 years
• 8.92% (7.95% to 9.94%)
• -5.01% annual change

IHME, 2016
Diarhoeal diseases

- DALYs, <5 years
- 8.74% (7.95% to 9.73%)
- -4.89% annual change

IHME, 2016
Diarhoeal diseases in low SDI

- Deaths, <5 years 10.2% (8.92% to 11.49%)
- -5.04% annual change

IHME, 2016
Food borne disease-annual estimates

- 1 in 10 people
- 330 million life years lost
- 420,000 deaths, one-third in children, mainly in Africa and South Asia
- About 50% due to 31 hazards
- Norovirus, Campylobacter, non-typhoidal salmonellae, *Salmonella Typhi*, *Taenia solium*, hepatitis A virus, and aflatoxin

WHO, 2015
Typhoid burden

• Typhoid continues to be a substantial public health threat that disproportionately impacts children and marginalized populations in much of Asia and sub-Saharan Africa.

• The burden of typhoid is underestimated due to challenges in surveillance and available diagnostics.
  – Current estimate is nearly 12 million cases and more than 128,000 deaths each year.

Mogasale, Lancet Glob Health, 2014
A triple threat from typhoid

• **Urbanization**: Rapid urbanization is leading to overcrowded populations in cities across Asia and sub-Saharan Africa—outdated, inadequate, or unsafe sanitation systems

• **Climate change**: Higher likelihood for natural disasters to occur.
  – During droughts, shallow water sources are more likely to be contaminated with typhoid; flooding can overwhelm sewage systems.

• **Drug resistance**: Drug- and multidrug-resistant strains of typhoid are spreading and becoming more difficult to treat.
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Studying complex interactions

- Enteropathogen carriage
- Diarrhoea

- WASH/Behaviours
- Cognition
- Immunity
- Enteropathy
- Nutrition
- Growth

- WASH/Behaviours
- Cognition
- Immunity
- Enteropathy
- Nutrition
- Growth
Water, sanitation and hygiene

CDC 2006, WHO 2018
Study area: Chinnallapuram, Ramnaickapalayam, Kaspa and Vasanthapuram
What can WASH interventions do in a challenging setting? Time to first cryptosporidial infection

Sarkar et al, CID 2013
WASH interventions-Bangladesh

- Cluster randomized trial with seven groups. 1382 women as controls; 698 to water; 696 to sanitation; 688 to handwashing; 702 to water, sanitation, and handwashing; 699 to nutrition; and 686 to water, sanitation, handwashing, and nutrition.
- Diarrhoea prevalence modestly reduced in all groups except water.
- Nutrient supplementation and counselling modestly improved linear growth, but there was no benefit to the integration of water, sanitation, and handwashing with nutrition.

Luby et al, Lancet Glob Health 2018
WASH intervention-Kenya

- 1919 women as controls; 938 to passive control; 904 to water; 892 to sanitation; 917 to handwashing; 912 to combined water, sanitation, and handwashing; 843 to nutrition; and 921 to combined water, sanitation, handwashing, and nutrition
- No reduction in childhood diarrhoea or improvement in growth
- Counselling and supplementation in the nutrition group and combined water, sanitation, handwashing, and nutrition interventions led to small growth benefits, but there was no advantage to integrating water, sanitation, and handwashing with nutrition.

Null et al, Lancet Glob Health 2018
Prevention

- Water, sanitation and hygiene
- Vaccines
Enteric vaccines

- Poliovirus vaccine (live attenuated and inactivated)
- Cholera vaccine (live and killed)
- Typhoid vaccine (killed, live and polysaccharide)
- Rotavirus vaccine (live attenuated)
- Vaccines in development
  - Enterotoxigenic *Escherichia coli*
  - Enterohaemorrhagic *E. coli*
  - *Shigella*
  - Non-typhoidal salmonellae
  - Norovirus
  - *Campylobacter*
  - *Helicobacter pylori*
Factors that lower inoculum
- Transplacental maternal antibodies
- Breast milk antibodies
- Stomach acid/proteases

Factors that affect antibody response
- Co-administration of other vaccines
- Nutrition
- Environmental enteropathy/microbiota
- Micronutrient deficiency
- Early and constant exposure to other gut pathogens
- Host genetics
Effect of Rotavirus Vaccination on Death from Childhood Diarrhea in Mexico

Richardson et al, NEJM 2010
Figure. Monthly Acute Gastroenteritis and Rotavirus-Coded Hospitalization Rates Among Children Younger Than 5 Years in 24 States During January 2000 Through December 2012

Leshem, JAMA 2015: 313, 2282-84
### Age-specific rotavirus hospitalization rate reduction and vaccine coverage, USA

<table>
<thead>
<tr>
<th>Age</th>
<th>Decline in rotavirus hospitalization rate (2008 vs. 2006)</th>
<th>Rotavirus vaccine coverage in 2008 (&gt;=1 dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year</td>
<td>66%</td>
<td>56%</td>
</tr>
<tr>
<td>1 -&lt; 2 years</td>
<td>95%</td>
<td>44%</td>
</tr>
<tr>
<td>2 -&lt; 3 years</td>
<td>85%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

*This age cohort was ineligible to receive rotavirus vaccine*

**Herd Protection?**
Impact on rotavirus and all-cause gastroenteritis hospitalizations in children, El Salvador

70-80% reduction in rotavirus hospitalizations children < 5 years

De Palma, BMJ, 2010
Herd protection: Reduction in rotavirus among UNVACCINATED age groups in El Salvador

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<thead>
<tr>
<th>Age</th>
<th>Decline in rotavirus hospitalization rate (2008 vs. 2006)</th>
<th>Rotavirus vaccine coverage in 2008 (&gt;=1 dose)</th>
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</thead>
<tbody>
<tr>
<td>&lt; 1 year</td>
<td>84% (80 to 88)</td>
<td>76%</td>
</tr>
<tr>
<td>1 year</td>
<td>86% (82 to 89)</td>
<td>84%</td>
</tr>
<tr>
<td>2 years</td>
<td>65% (50 to 75)</td>
<td>0</td>
</tr>
<tr>
<td>3 years</td>
<td>41% (-7 to 68)</td>
<td>0</td>
</tr>
<tr>
<td>4 years</td>
<td>68% (29 to 85)</td>
<td>0</td>
</tr>
</tbody>
</table>

These age cohorts were ineligible to receive rotavirus vaccine

Yen et al, PIDJ 2011
<table>
<thead>
<tr>
<th>Setting</th>
<th>Vaccine</th>
<th>Schedule</th>
<th>1st yr efficacy</th>
<th>2nd yr efficacy</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latin America</td>
<td>RV1</td>
<td>2, 4 months</td>
<td>83% (67-92)</td>
<td>79% (66-87)</td>
<td>81% (71-87)</td>
</tr>
<tr>
<td>Europe</td>
<td>RV1</td>
<td>3, 5 months</td>
<td>96% (90-99)</td>
<td>86% (76-92)</td>
<td>90% (85-94)</td>
</tr>
<tr>
<td>Asia (HIC)</td>
<td>RV1</td>
<td>3, 5 months</td>
<td></td>
<td>96% (85-100)</td>
<td></td>
</tr>
<tr>
<td>USA, Finland</td>
<td>RV5</td>
<td>2, 4, 6 months</td>
<td>98% (88-100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Africa</td>
<td>RV1</td>
<td>10, 14 weeks</td>
<td>72% (40-8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Africa</td>
<td>RV1</td>
<td>6, 10, 14 wks</td>
<td>82% (55-94)</td>
<td></td>
<td>85% (35-98)</td>
</tr>
<tr>
<td>Malawi</td>
<td>RV1</td>
<td>10, 14 wks</td>
<td>49% (11-72)</td>
<td>3% (-101-53)</td>
<td>34% (-2-58)</td>
</tr>
<tr>
<td>Malawi</td>
<td>RV1</td>
<td>6, 10, 14 wks</td>
<td>50% (11-72)</td>
<td>33% (-49-71)</td>
<td>42% (9-64)</td>
</tr>
<tr>
<td>Africa (Ghana, Kenya, Mali)</td>
<td>RV5</td>
<td>6, 10, 14 wks</td>
<td>64% (40-79)</td>
<td>20% (-16-44)</td>
<td>39% (19-55)</td>
</tr>
<tr>
<td>Ghana</td>
<td>RV5</td>
<td>6, 10, 14 wks</td>
<td>65% (36-82)</td>
<td>29% (-65-71)</td>
<td>56% (28-73)</td>
</tr>
<tr>
<td>Kenya</td>
<td>RV5</td>
<td>6, 10, 14 wks</td>
<td>83% (26-98)</td>
<td>-55% (-1753-82)</td>
<td>64% (-6-90)</td>
</tr>
<tr>
<td>Mali</td>
<td>RV5</td>
<td>6, 10, 14 wks</td>
<td>1% (-432-82)</td>
<td>19% (-23-47)</td>
<td>18% (-23-45)</td>
</tr>
<tr>
<td>Asia (Vietnam, Bangladesh)</td>
<td>RV5</td>
<td>6, 10, 14 wks</td>
<td>51% (13-73)</td>
<td>46% (1-71)</td>
<td>48% (22-66)</td>
</tr>
<tr>
<td>Vietnam</td>
<td>RV5</td>
<td>6, 10, 14 wks</td>
<td>72% (-45-97)</td>
<td>65% (-48-94)</td>
<td>64% (8-91)</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>RV5</td>
<td>6, 10, 14 wks</td>
<td>46% (-1-72)</td>
<td>39% (-18-70)</td>
<td>43% (10-64)</td>
</tr>
</tbody>
</table>
### Rotavirus vaccine effectiveness in age-eligible children in Malawi

<table>
<thead>
<tr>
<th></th>
<th>Rotavirus positive</th>
<th>Test negative controls</th>
<th>Community controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=90</td>
<td>N=197</td>
<td>N=288</td>
</tr>
<tr>
<td></td>
<td>Vaccine effectiveness (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children with Vesikari $\geq11$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age in months</td>
<td>8 (0-16)</td>
<td>9 (0-17)</td>
<td></td>
</tr>
<tr>
<td>0 doses</td>
<td>13 (14%)</td>
<td>10 (5%)</td>
<td>19 (7%)</td>
</tr>
<tr>
<td></td>
<td>reference</td>
<td></td>
<td>reference</td>
</tr>
<tr>
<td>2 doses</td>
<td>69 (77%)</td>
<td>195 (89%)</td>
<td>239 (83%)</td>
</tr>
<tr>
<td></td>
<td>68% (22-87%)</td>
<td></td>
<td>68% (23-86%)</td>
</tr>
<tr>
<td>At least 1 dose</td>
<td>77 (89%)</td>
<td>208 (95%)</td>
<td>269 (91%)</td>
</tr>
<tr>
<td></td>
<td>69% (25-87%)</td>
<td></td>
<td>68% (37-83%)</td>
</tr>
</tbody>
</table>
Follow-up of Rotavirus Vaccine Effectiveness in Malawi


<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Cases/Controls</th>
<th>2-dose vaccine effectiveness % (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>241/692</td>
<td>58.3 (20.2, 78.2)</td>
<td>0.008</td>
</tr>
<tr>
<td>&lt;12 mo</td>
<td>167/467</td>
<td>70.6 (33.6, 87.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>12-23 mo</td>
<td>71/201</td>
<td>31.7 (-140.6, 80.6)</td>
<td>0.552</td>
</tr>
<tr>
<td>&gt;23 mo</td>
<td>73/225</td>
<td>28.8 (-147.5, 79.5)</td>
<td>0.594</td>
</tr>
<tr>
<td>HIV unexposed</td>
<td>191/554</td>
<td>60.5 (13.3, 82.0)</td>
<td>0.021</td>
</tr>
<tr>
<td>HIV exposed, uninfected</td>
<td>48/126</td>
<td>42.2 (-106.9, 83.8)</td>
<td>0.400</td>
</tr>
<tr>
<td>Well nourished</td>
<td>74/183</td>
<td>78.1 (5.6, 94.9)</td>
<td>0.042</td>
</tr>
<tr>
<td>Stunted</td>
<td>53/152</td>
<td>27.8 (-99.5, 73.9)</td>
<td>0.320</td>
</tr>
</tbody>
</table>
Vaccines work

- But oral vaccines work less well in countries that need them the most
- Many questions remain
  - Herd effect in developing countries
  - Combinations of different types of vaccines
  - Booster requirements
  - Correlates of protection
  - Interactions with OPV/other viruses/microbiota
  - Intussusception
  - Seizures and extra-intestinal effects
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The causes of diarrhoea—but how often do we know?

- 7 countries in Asia and Africa
- Children under 5 with moderate to severe diarrhoea
- Case-control design
- Best available tools identified rotavirus, Cryptosporidium, Shigella and ETEC
- Re-analysed by qPCR

Liu et al, Lancet 2016
## Diagnostics and Antibiotics

<table>
<thead>
<tr>
<th>Diagnostic</th>
<th>Cost of 1 test</th>
<th>Antibiotic</th>
<th>Cost of course in India</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanging drop</td>
<td>1 $</td>
<td>Ciprofloxacin</td>
<td>0.70 $</td>
</tr>
<tr>
<td>Culture</td>
<td>6 $ without AST</td>
<td>Azithromycin</td>
<td>0.90 $</td>
</tr>
<tr>
<td>Molecular testing</td>
<td>12 $ for 1 target</td>
<td>Cephalexin</td>
<td>1 $</td>
</tr>
<tr>
<td>TAC card</td>
<td>70 $ for 44 targets</td>
<td>Cefpodoxime</td>
<td>10 $</td>
</tr>
</tbody>
</table>

Diagnostics are least available in the parts of the world that need them the most.
Treatment

• Standard of care
  – Rehydration, rehydration, rehydration (oral and IV)
  – Zinc in developing countries
  – Anti-secretory agents
  – Nitazoxanide
  – Anti-emetics, anti-motility agents only in adults
  – Specific treatment in the elderly and immunocompromised and for cholera, dysentery and C. difficile

• What is new or emerging?
  – New ORS (complex carbohydrates/resistant starch)
  – Single heavy chain antibodies
  – Probiotics
  – Faecal transplants/microbiome modification
Single heavy chain antibodies

Significant reduction in rate of stool output in boys with rotavirus gastroenteritis in Bangladesh

Transgenic rice expressing the neutralizing variable domain of a rotavirus-specific llama heavy-chain antibody fragment (MucoRice-ARP1) worked in mice

Sarker et al. Gastroenterol 2013
Tokuhara et al, JCI 2013
Oral rehydration therapy using resistant starch

Probiotics

- *Saccharomyces boulardii, Lactobacillus rhamnosus GG, Lactobacillus reuteri*
- Systematic reviews show a role in prevention of antibiotic associated diarrhoea and *C. difficile*
- But performance is probiotic dependent and gut function is rarely assessed

- RCT with LGG in children with rotaviral and cryptosporidial acute gastroenteritis
- Impaired intestinal permeability reduced in both infections with supplementation
- Immune response measured as serum antibodies increased in children with rotavirus acute gastroenteritis

Mantegazza et al, Pharmacol Res 2018
Sindhu et al, CID 2014
Faecal transplants

- Approved for *C. difficile* in developed countries
- Microbiome studies from Bangladesh, Malawi, India, Pakistan and Ghana demonstrate differences in flora in i) stunted children, ii) vaccine non-responders
- More to come....
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What does the future hold?

- Food and water safety in all parts of the world
- New vaccines for prevention of enteric infections
- Understanding pathways to long term damage and points of intervention in LMICs
  - New data from the MALED study indicates Shigella, Giardia, EAEC and Campylobacter carriage impact growth
- Understanding the role of the microbiome in absorptive, immune and barrier function
- New systems to better understand intestinal structure and function (capsule endoscopy and biopsy, enteroid/organoid culture)
Summary

• The epidemiology and burden of acute enteric infectious disease is changing
• New tools permit better understanding of infection, disease and long term consequences
• Oral vaccines do not work well in poorer countries
• New technologies are needed for better understanding, diagnostics, treatment and prevention
• There is much to be done!
Thank you