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

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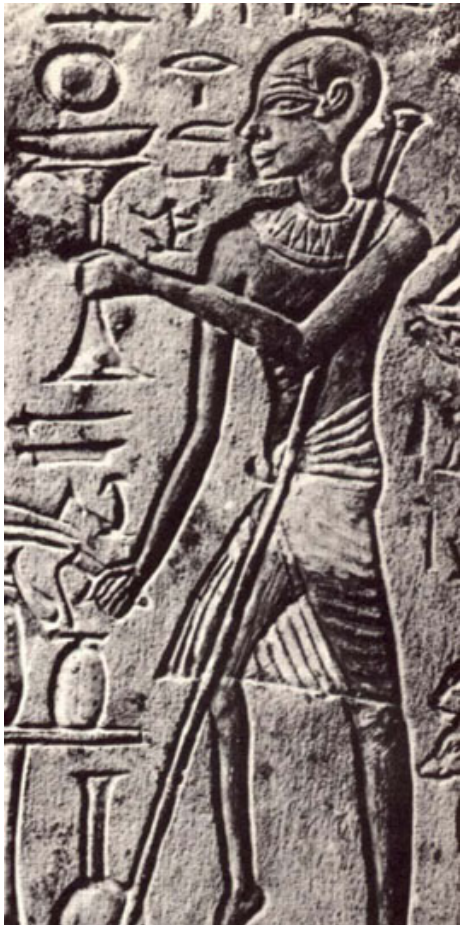

The Gastrointestinal Tract

- 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-transmittted 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

Guerrant et al. Nat Rev Gastroenterol Hepatol, 2013

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

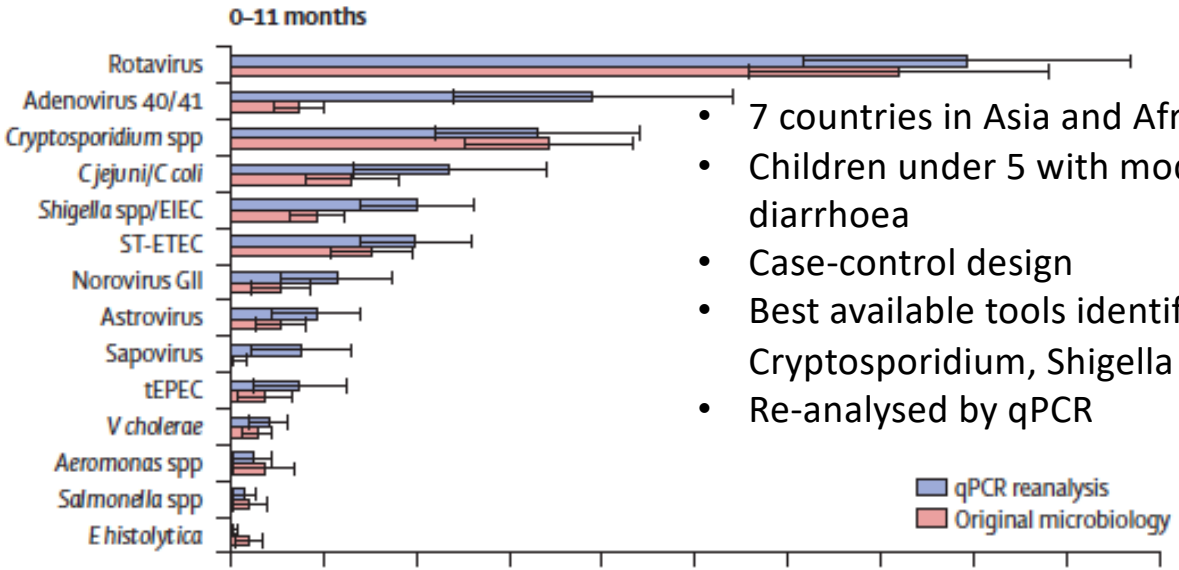
- >400 causes identified for infectious diarrhoea
- Criteria for identifying a pathogen as causally associated are
  - Identification more frequently in patients with diarrhoea than in controls
  - Immune response to specific agent
  - Beginning and end of illness correspond to onset and cessation of 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

DuPont. N Engl J Med. 2014

The Global Enterics Multi-Site Study



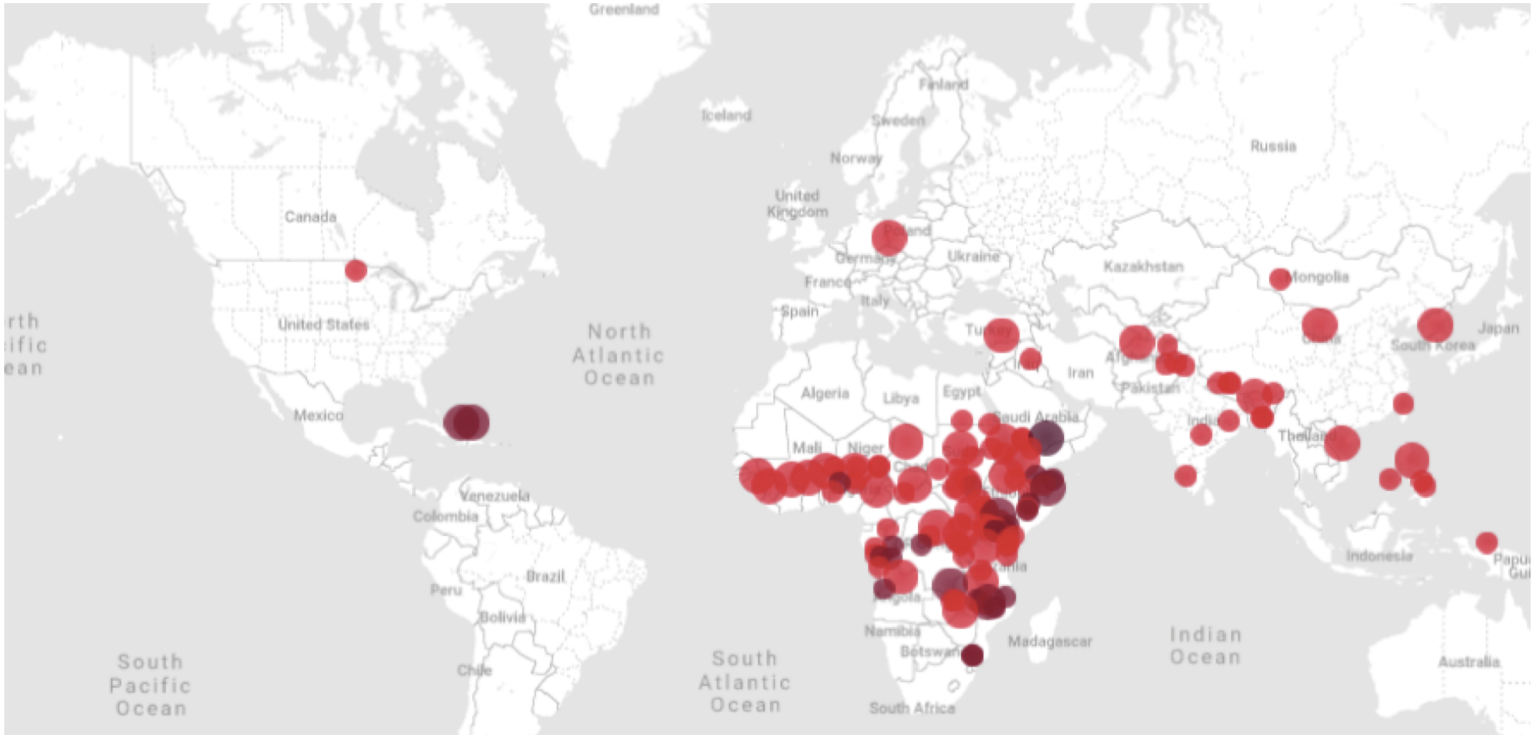
- 7 countries in Asia and Africa
- Children under 5 with moderate to severe diarrhoea
- Case-control design
- Best available tools identified rotavirus, Cryptosporidium, Shigella and ETEC
- Re-analysed by qPCR

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

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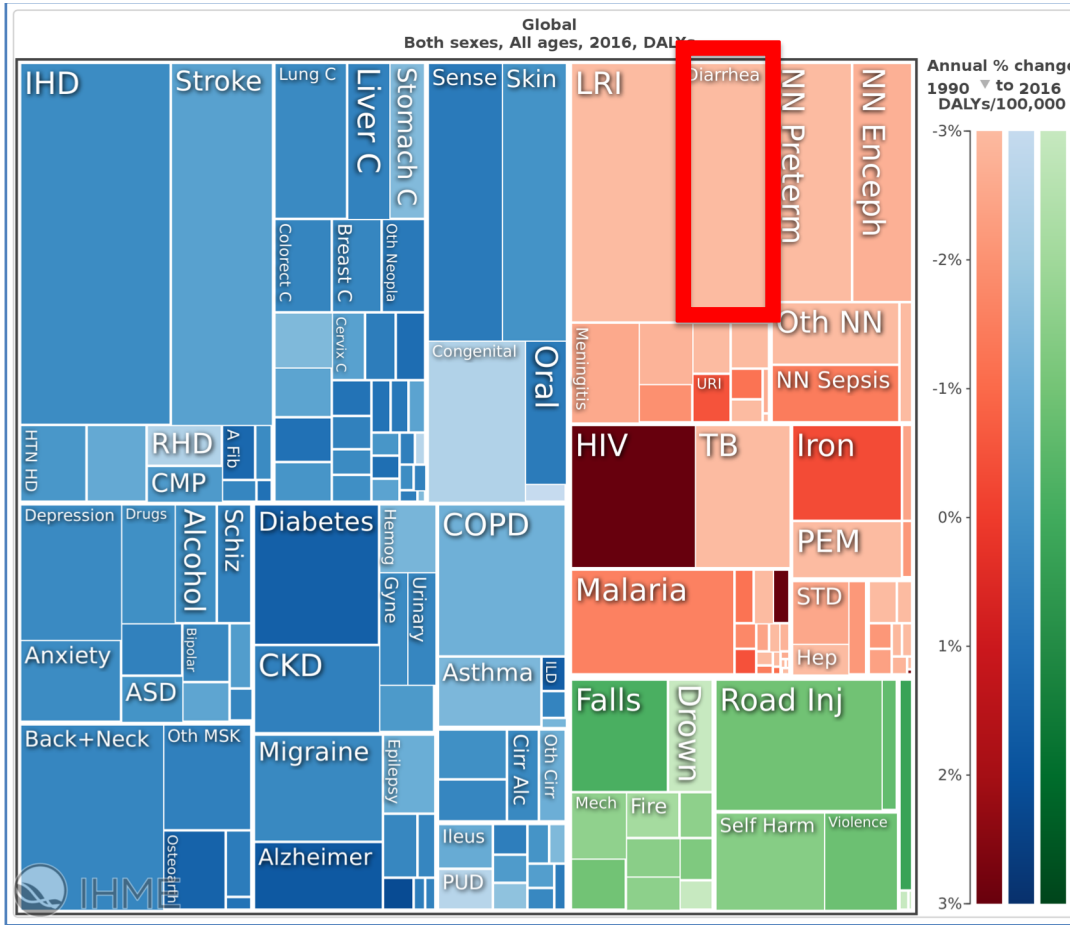
Diarhoeal diseases

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

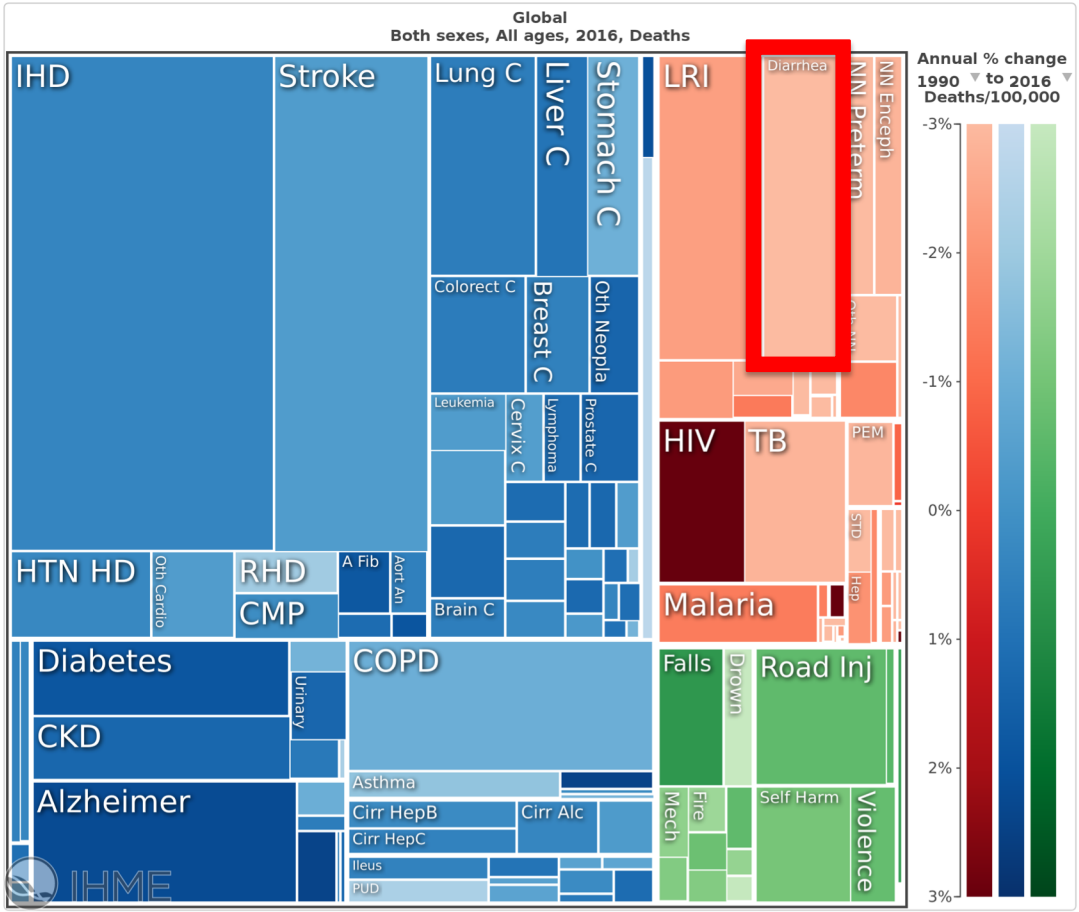
IHME, 2016



Diarhoeal diseases

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

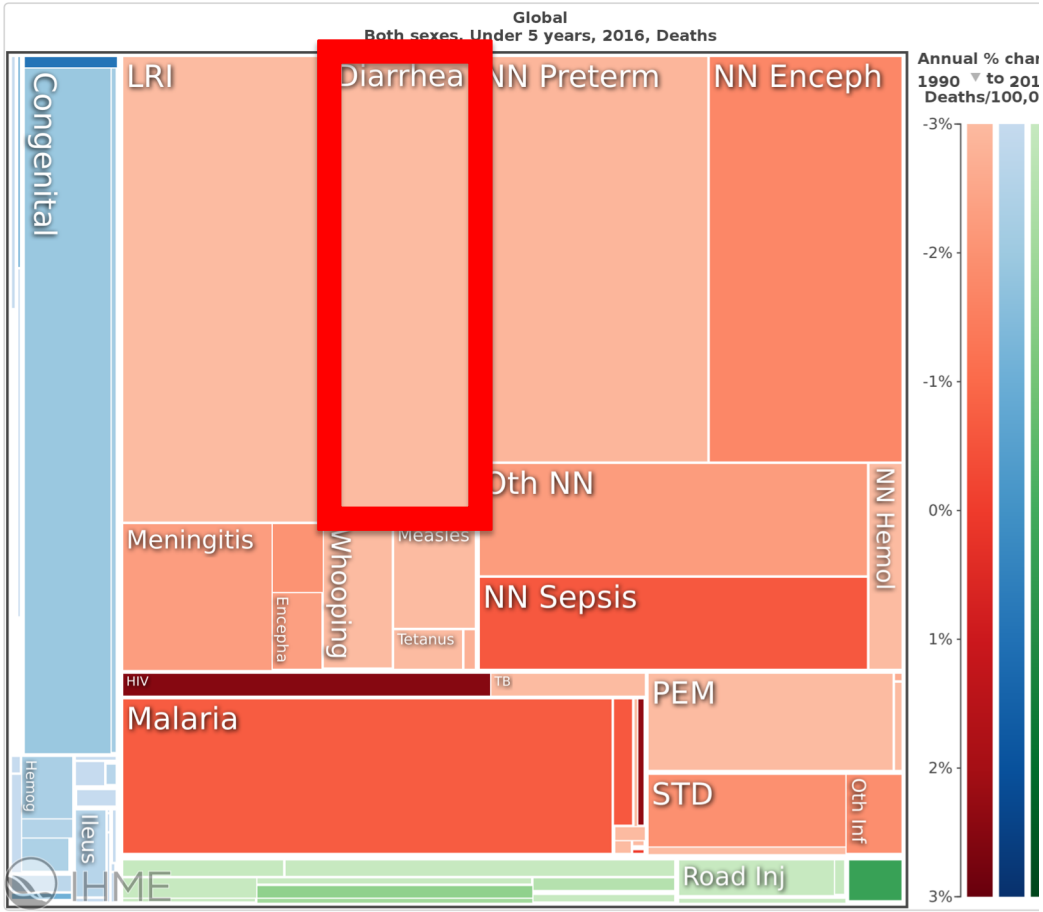
IHME, 2016



Diarhoeal diseases

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

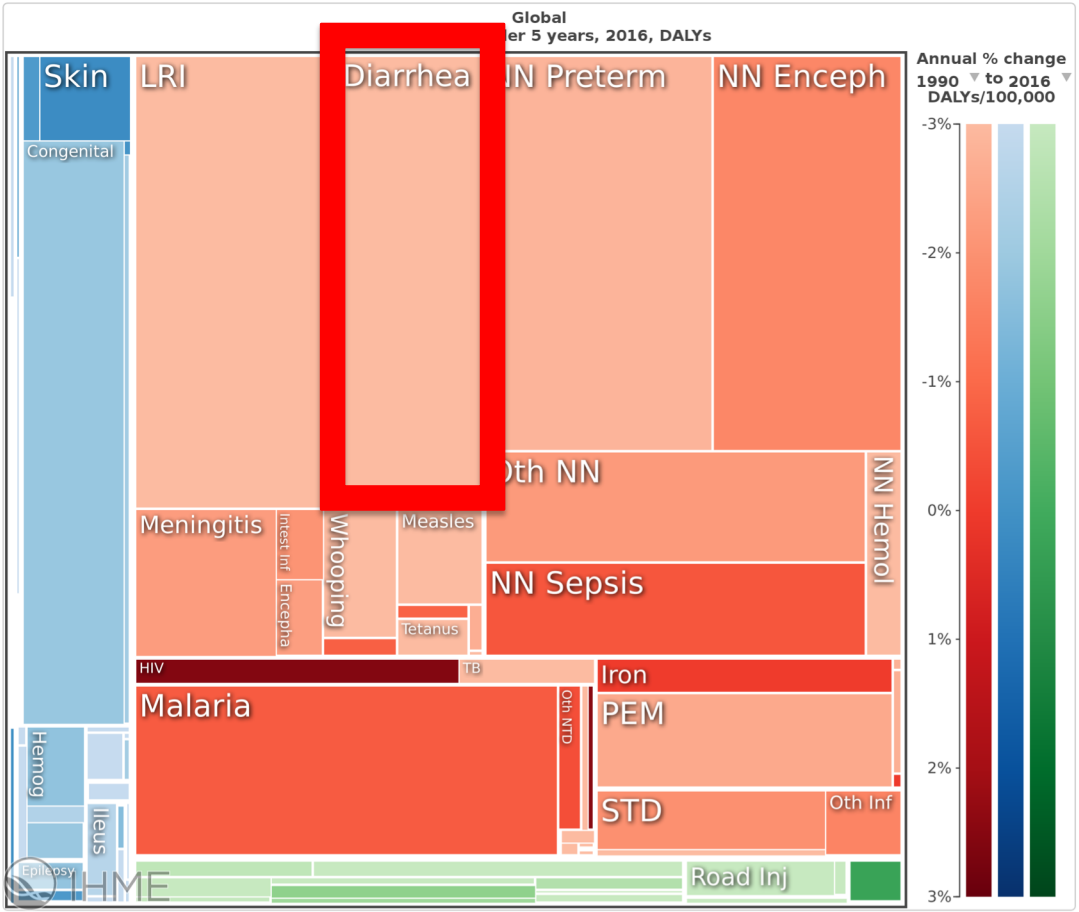
IHME, 2016



Diarhoeal diseases

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

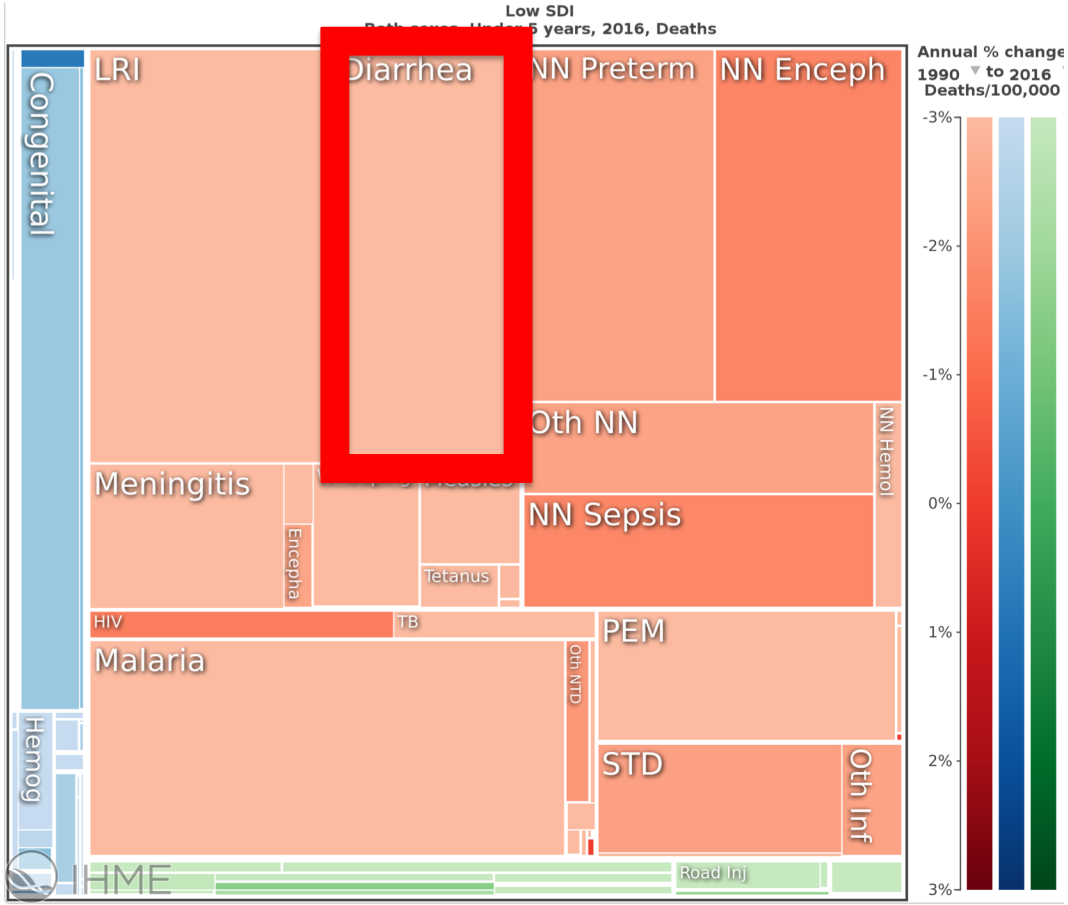
IHME, 2016



Diarhoeal diseases in low SDI

- Deaths, <5 years 10. 2% (8.92% to 11.49%)
- -5.04% annual change

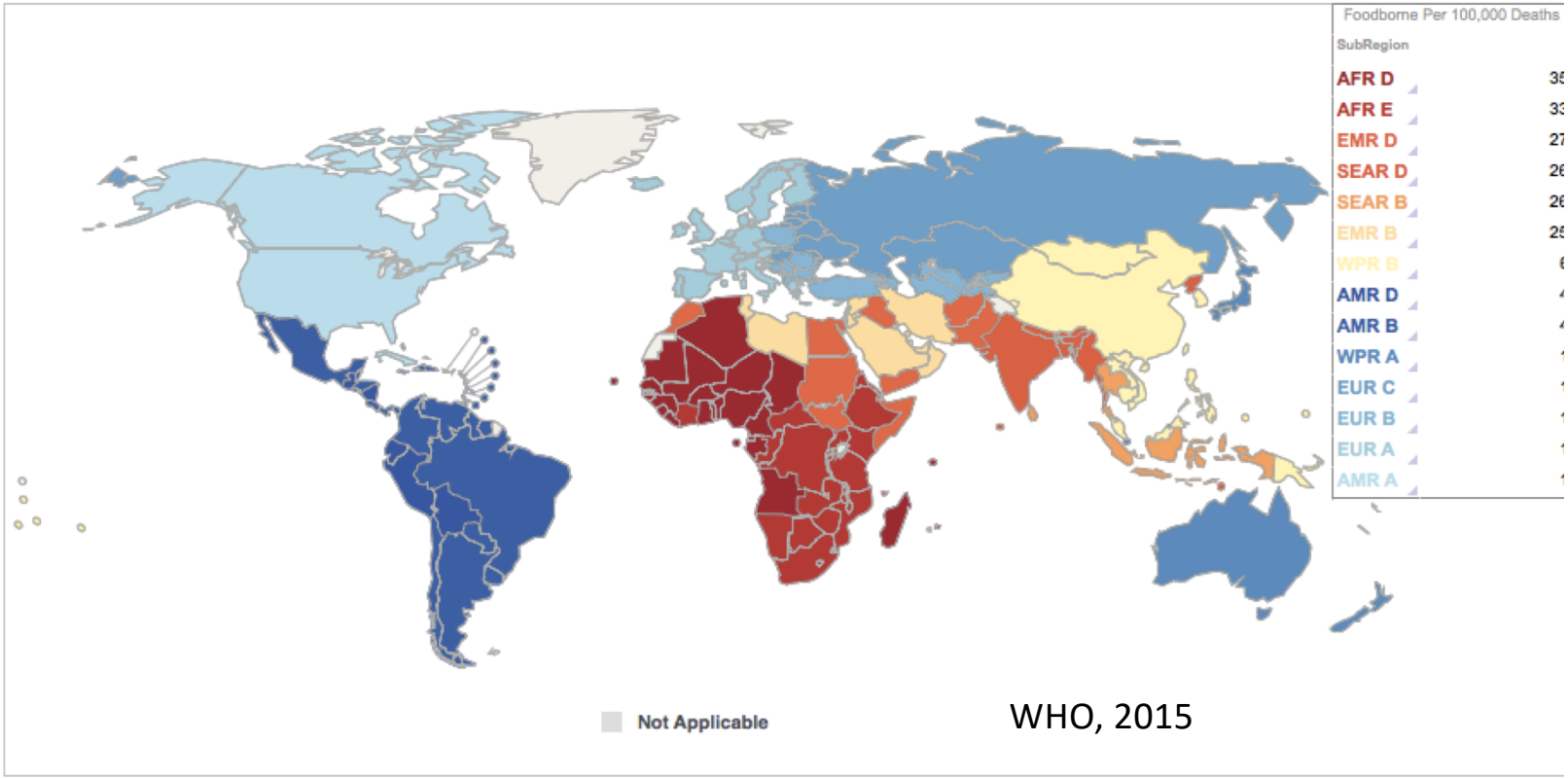
IHME, 2016



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


Foodborne Per 100,000 Deaths
SubRegion
AFR D 35
AFR E 33
EMR D 27
SEAR D 26
SEAR B 26
EMR B 25
WPR B 6
AMR D 4
AMR B 4
WPR A 1
EUR C 1
EUR B 1
EUR A 1
AMR A 1
Not Applicable

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.

PATH/Monique Berlier.

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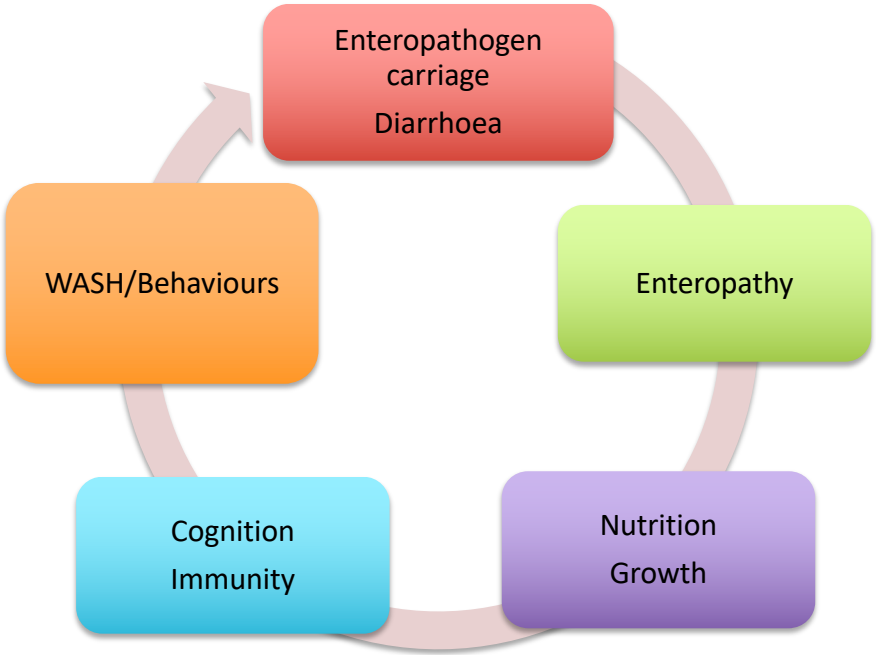
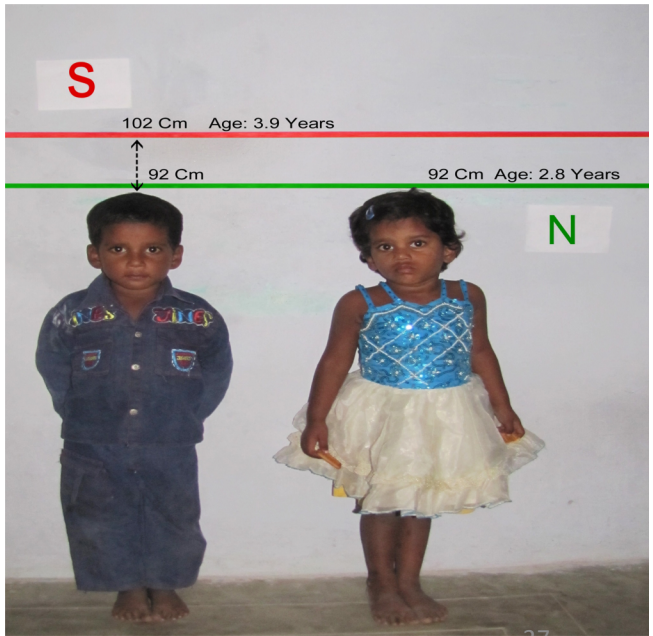
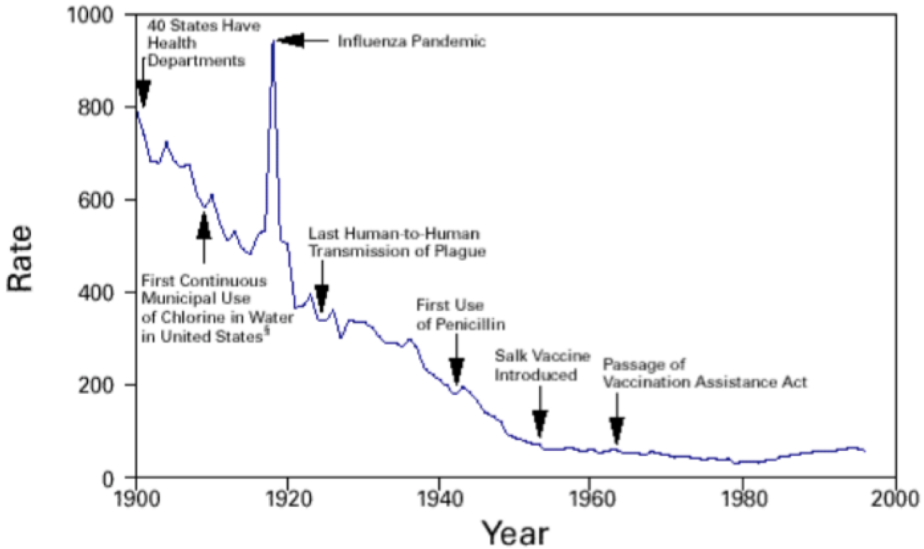
Studying complex interactions





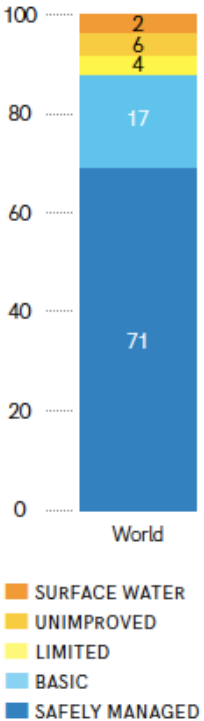
Water, sanitation and hygiene

FIGURE 1. Crude death rate* for infectious diseases — United States, 1900–1996†

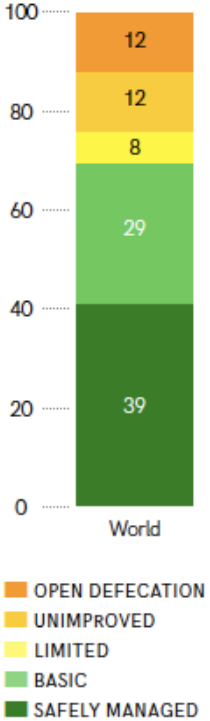


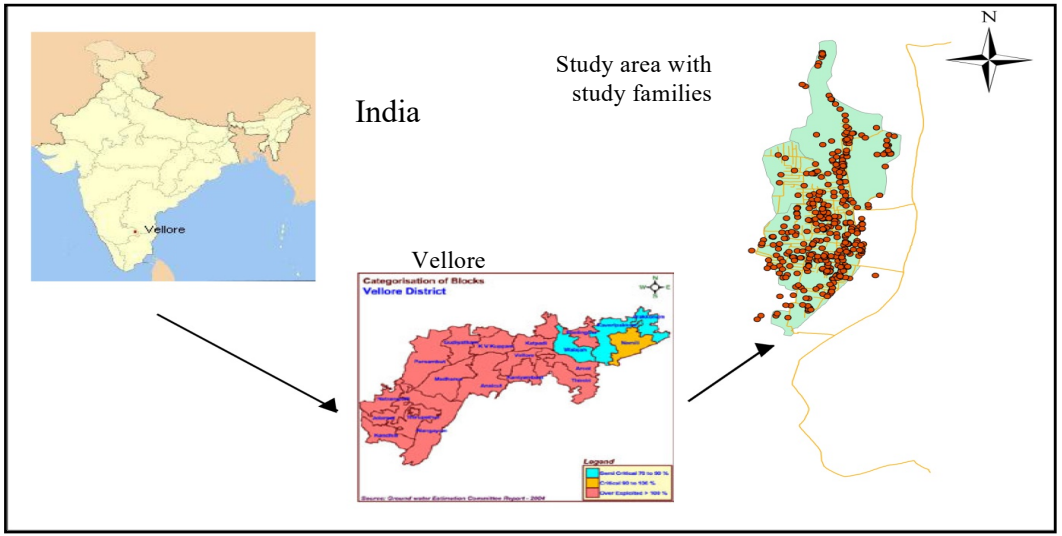
CDC 2006, WHO 2018

7 out of 10 people used safely managed drinking water services in 2015



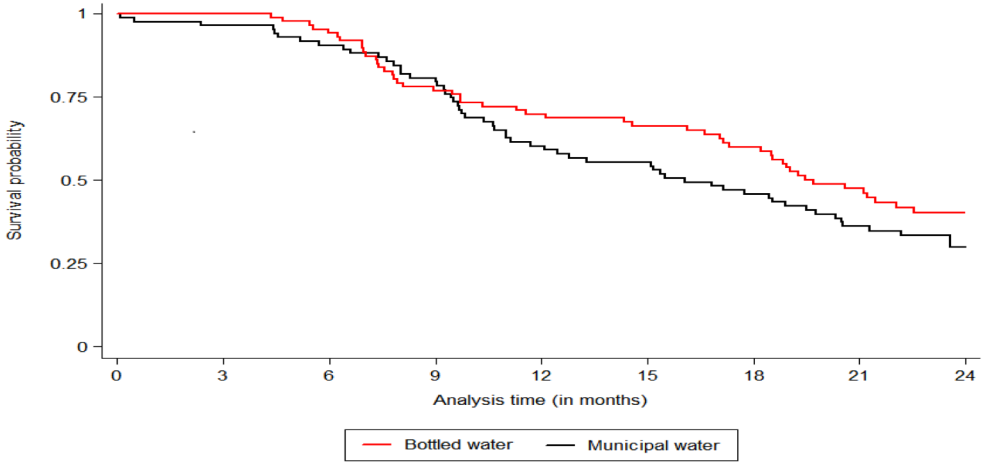
Two out of five people used safely managed sanitation services in 2015





Study area: Chinnallapuram, Ramnaickapalayam, Kaspa and Vasanthapuram

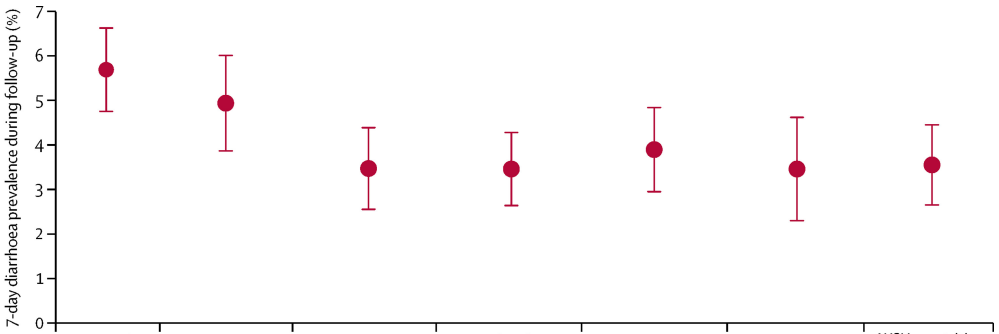
What can WASH interventions do in a challenging setting? Time to first cryptosporidial infection



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.

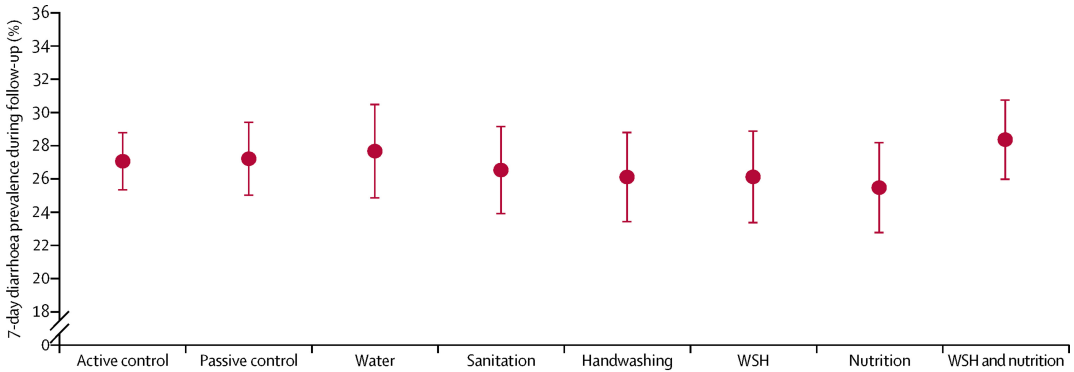


Prevalence ratio (95% CI)	Control	Water	Sanitation	Handwashing	WSH	Nutrition	WSH + nutrition
Intervention *vs* control	ref	0·89 (0·70–1·13)	0·61 (0·46–0·81)	0·60 (0·45–0·80)	0·69 (0·53–0·90)	0·64 (0·49–0·85)	0·62 (0·47–0·81)
WSH *vs* water		ref			0·77 (0·57–1·04)		
WSH *vs* sanitation			ref		1·13 (0·80–1·58)		
WSH *vs* handwashing				ref	1·07 (0·77–1·51)		

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.

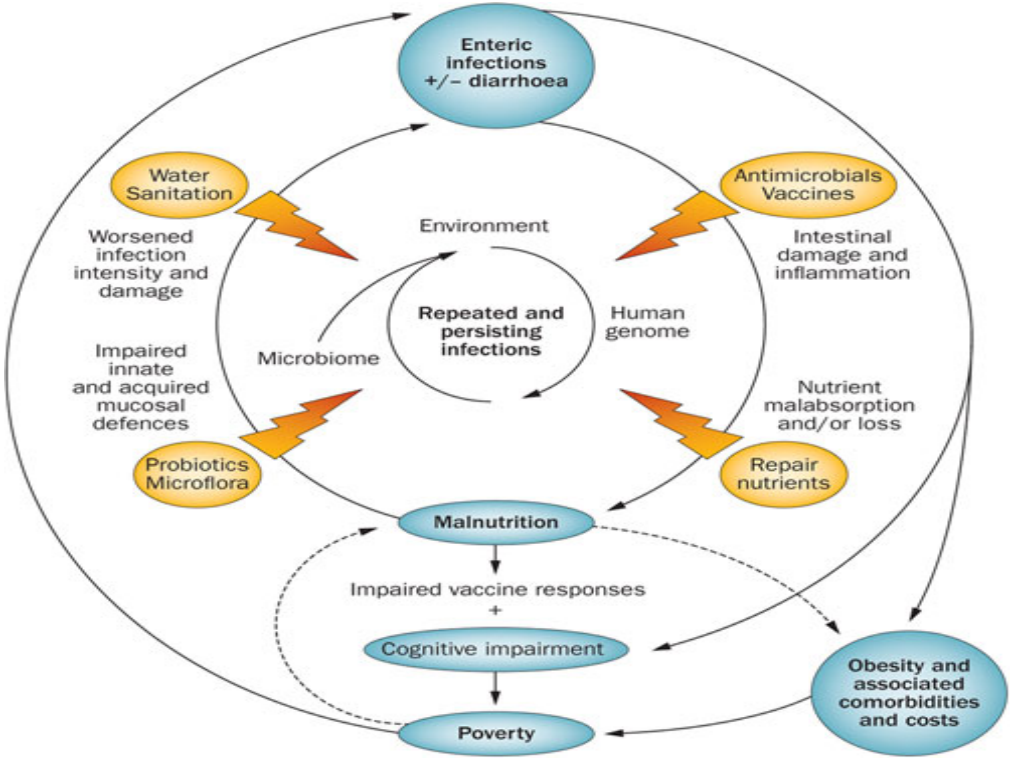


Prevelence ratio (95% CI)								
Intervention *vs* control	ref	1·00 (0·90–1·11)	1·02 (0·92–1·14)	0·99 (0·88–1·10)	0·98 (0·87–1·09)	0·96 (0·86–1·07)	0·96 (0·86–1·08)	1·05 (0·94–1·16)
WSH *vs* water			ref			0·94 (0·83–1·07)		
WSH *vs* sanitation				ref		0·99 (0·87–1·13)		
WSH *vs* handwashing					ref	1·01 (0·89–1·16)		

Null et al, Lancet Glob Health 2018

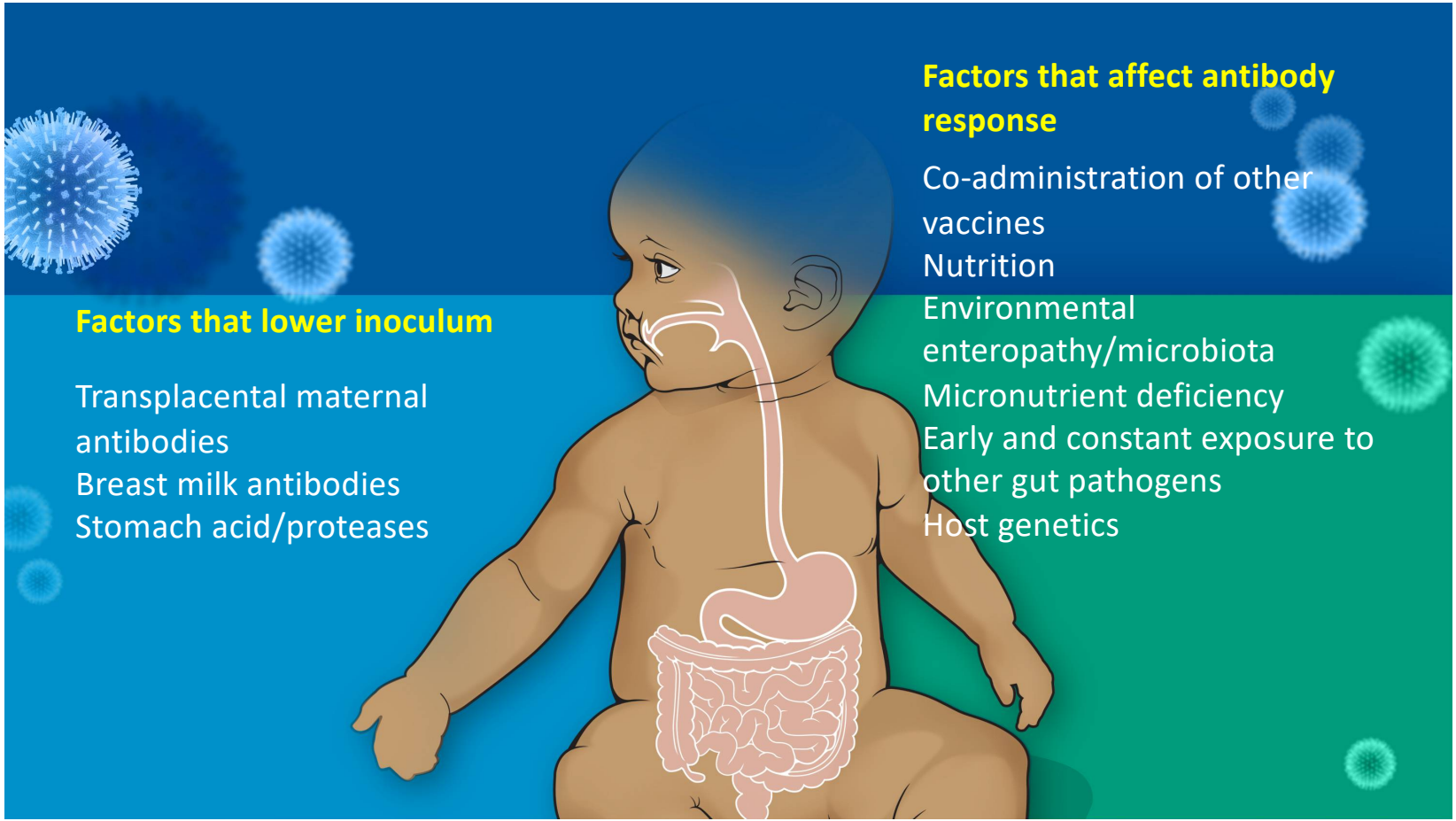
Prevention

- Water, sanitation and hygiene
- Vaccines



Enteric vaccines

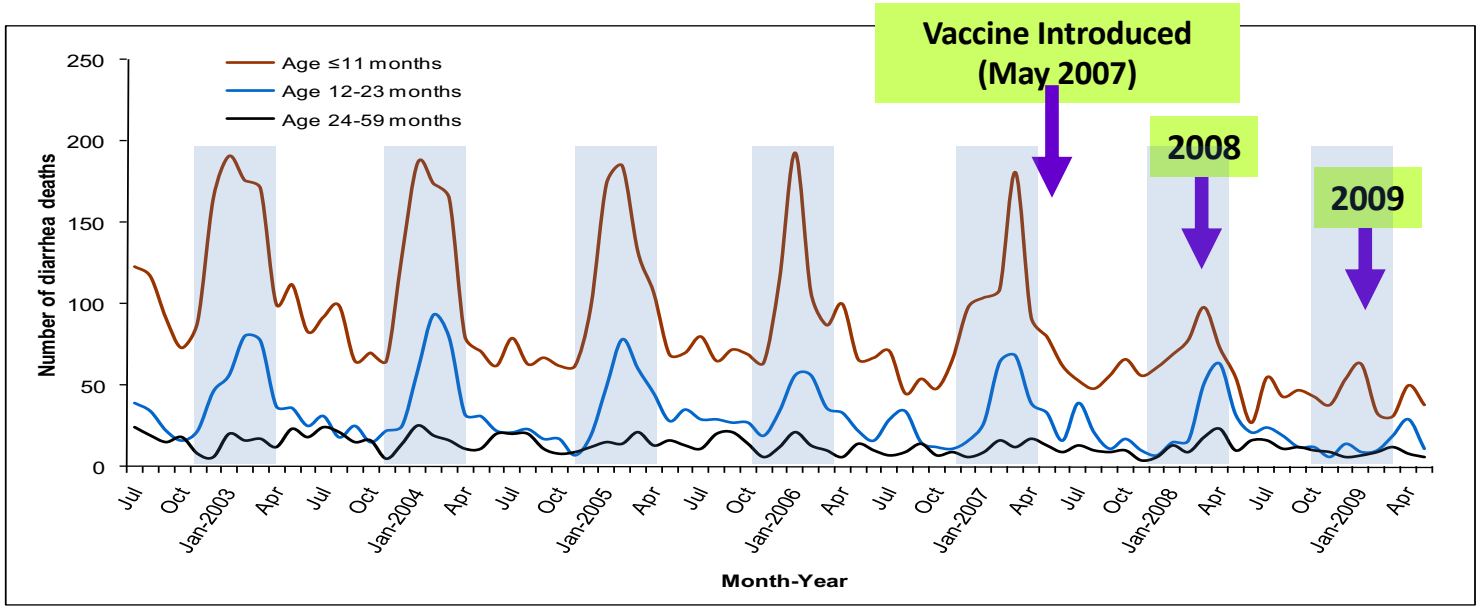
- Poliovirus vaccine (live attenuated and inactivated)
- Cholera vaccine (live and killed)
- Typhoid vaccine (killed, live and polysaccharide)
- Rotavirus vaccine (live attenuated)
- Vaccines in development
  - Enterotoxigenic *Escherichia coli*
  - Enterohaemorrhagic *E. coli*
  - *Shigella*
  - Non-typhoidal salmonellae
  - Norovirus
  - Campylobacter
  - *Helicobacter pylori*


Factors that affect antibody response
Co-administration of other vaccines
Nutrition
Environmental enteropathy/microbiota
Micronutrient deficiency
Early and constant exposure to other gut pathogens
Host genetics
Factors that lower inoculum
Transplacental maternal antibodies
Breast milk antibodies
Stomach acid/proteases

The NEW ENGLAND JOURNAL of MEDICINE

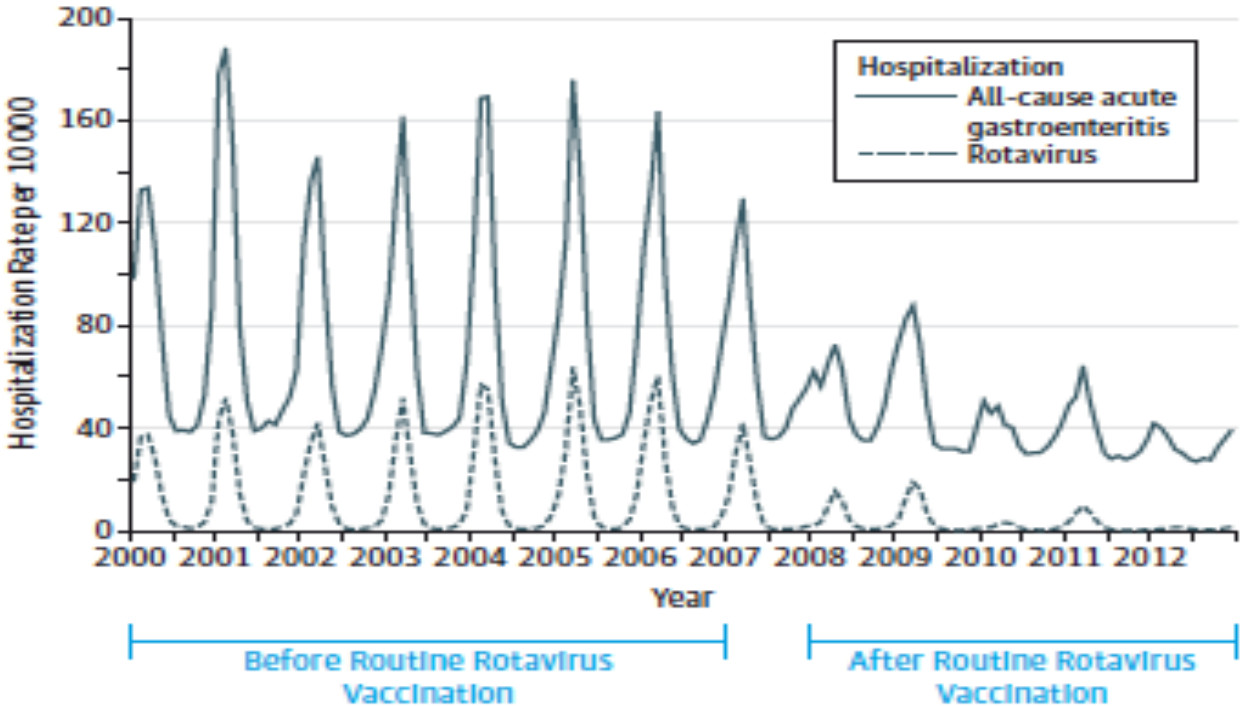
ORIGINAL ARTICLE

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

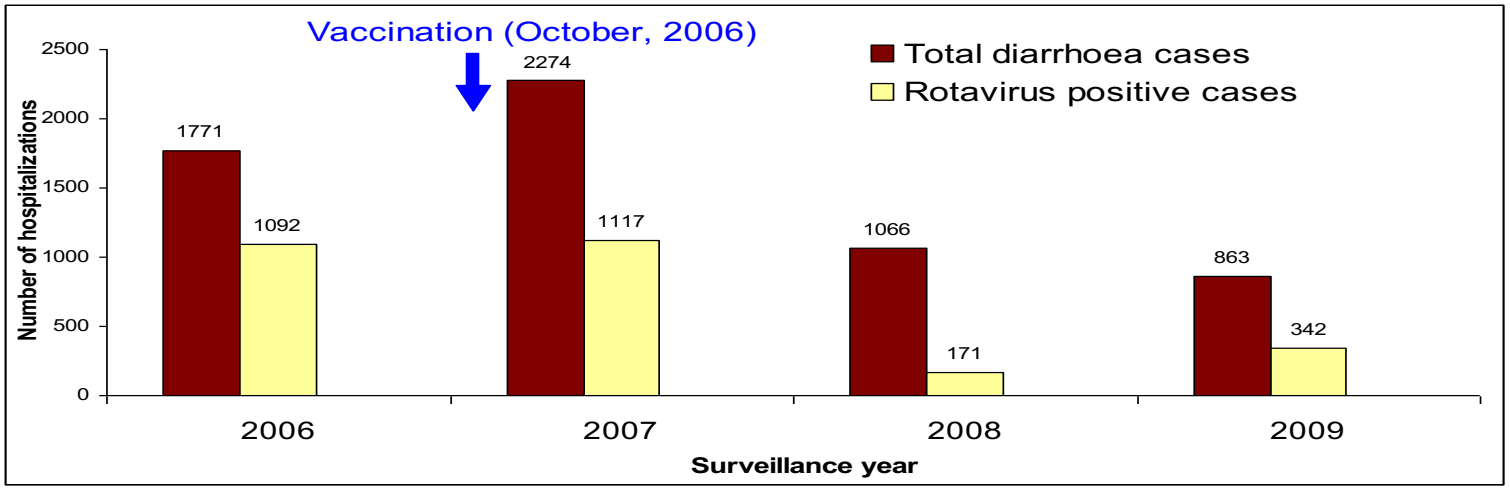
Age	Decline in rotavirus hospitalization rate (2008 vs. 2006)	Rotavirus vaccine coverage in 2008 (>=1 dose)
< 1 year	66%	56%
1 -< 2 years	95%	44%
2 -< 3 years	85%	<1%

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

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

These age cohorts were ineligible to receive rotavirus vaccine

Yen et al, PIDJ 2011

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

Rotavirus vaccine effectiveness in age-eligible children in Malawi

	Rotavirus positive	Test negative controls		Community controls	
Children with Vesikari ≥11	N=90	N=197	Vaccine effectiveness (95% CI)	N=288	Vaccine effectiveness (95% CI)
Median age in months	8 (0-16)	9 (0-17)			
0 doses	13 (14%)	10 (5%)	reference	19 (7%)	reference
2 doses	69 (77%)	195 (89%)	68% (22-87%)	239 (83%)	68% (23-86%)
At least 1 dose	77 (89%)	208 (95%)	69% (25-87%)	269 (91%)	68% (37-83%)

Follow-up of Rotavirus Vaccine Effectiveness in Malawi

Bar-Zeev et al. Clin Infect Dis 2016

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

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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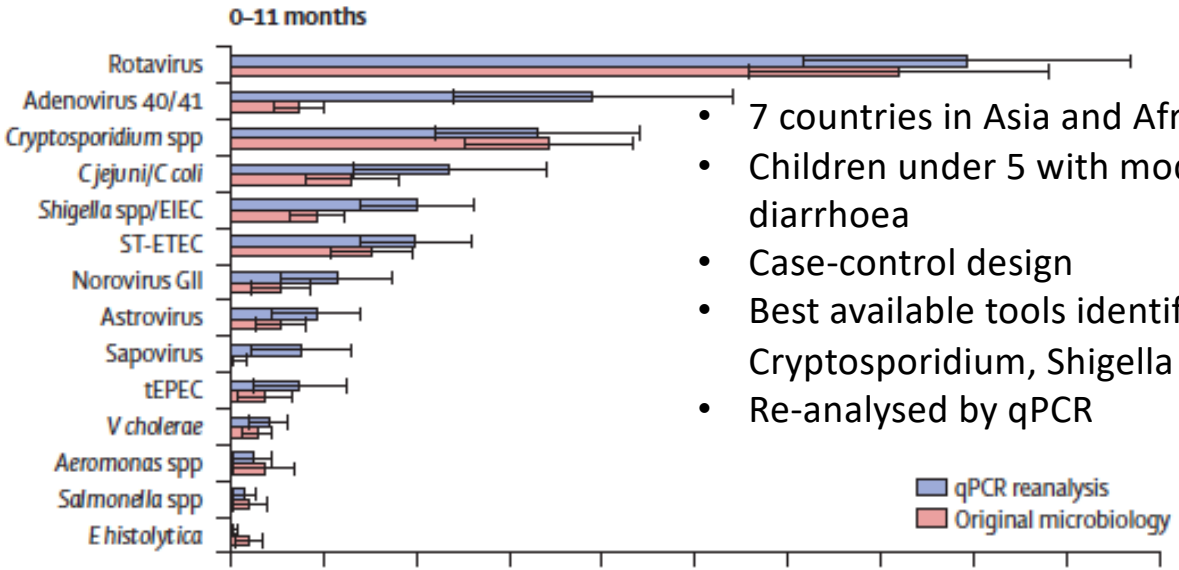
The causes of diarrhoea-but how often do we know?

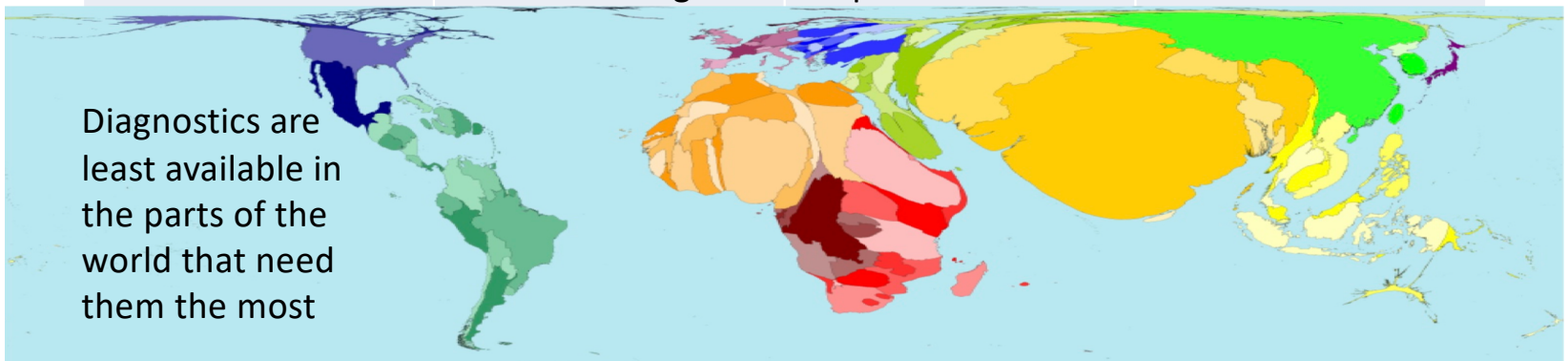


- 7 countries in Asia and Africa
- Children under 5 with moderate to severe diarrhoea
- Case-control design
- Best available tools identified rotavirus, Cryptosporidium, Shigella and ETEC
- Re-analysed by qPCR

Liu et al, Lancet 2016

Diagnostics and Antibiotics

Diagnostic	Cost of 1 test	Antibiotic	Cost of course in India
Hanging drop	1 $	Ciprofloxacin	0.70 $
Culture	6 $ without AST	Azithromycin	0.90 $
Molecular testing	12 $ for 1 target	Cephalexin	1 $
TAC card	70 $ for 44 targets	Cefpodoxime	10 $

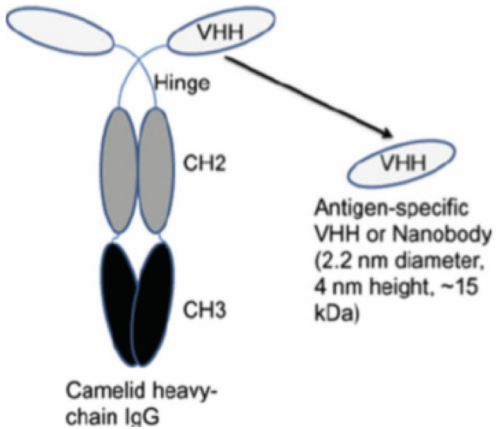


Diagnostics are least available in the parts of the world that need them the most

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

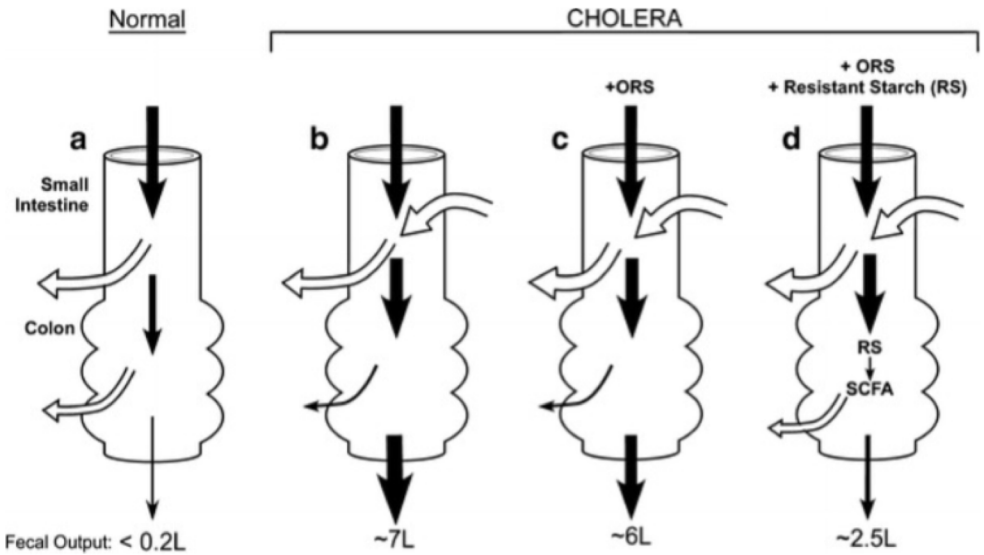


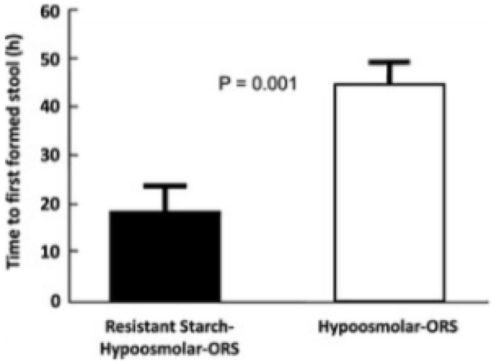
Significant reduction in rate of stool output in boys with rotavirus gastroenteritis in Bangladesh

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





Binder et al. Curr Gastroenterol Rep 2014

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

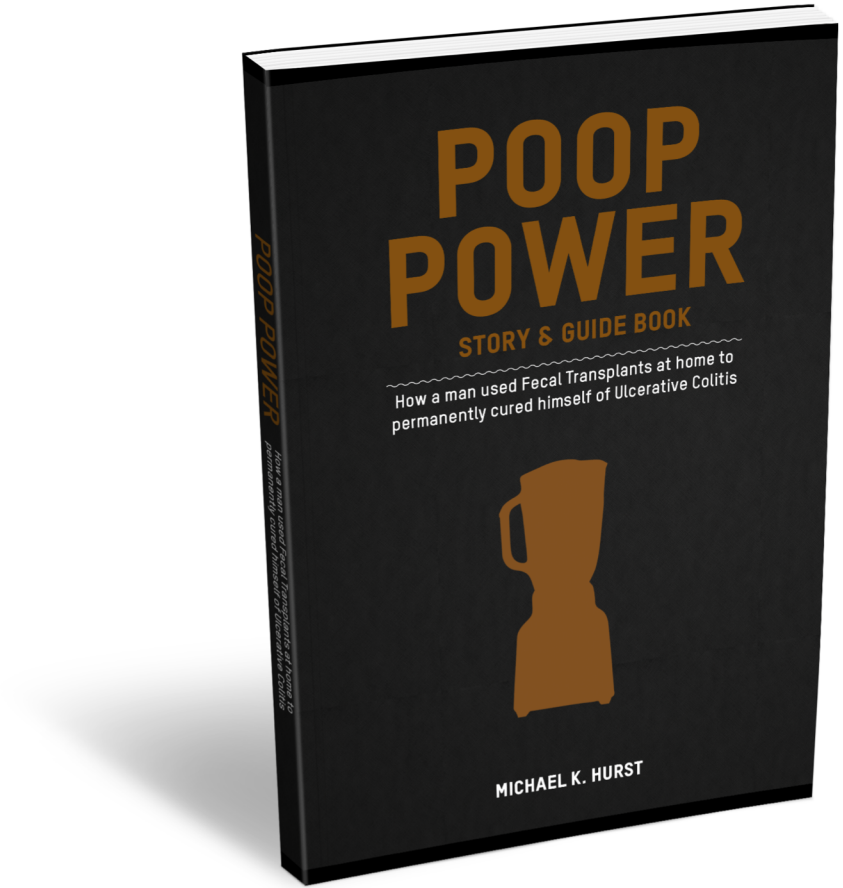
Mantegazza et al, Pharmacol Res 2018

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 flc in i) stunted children, ii) vaccir non-responders

- More to come….

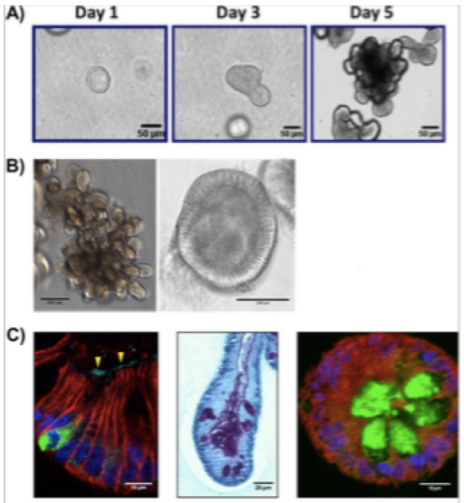


Outline

- Enteric infections and diarrhoeal disease
- Patterns of disease
- Global burden of disease
- Research to prevention
- Research to treatment
- What does the future hold?

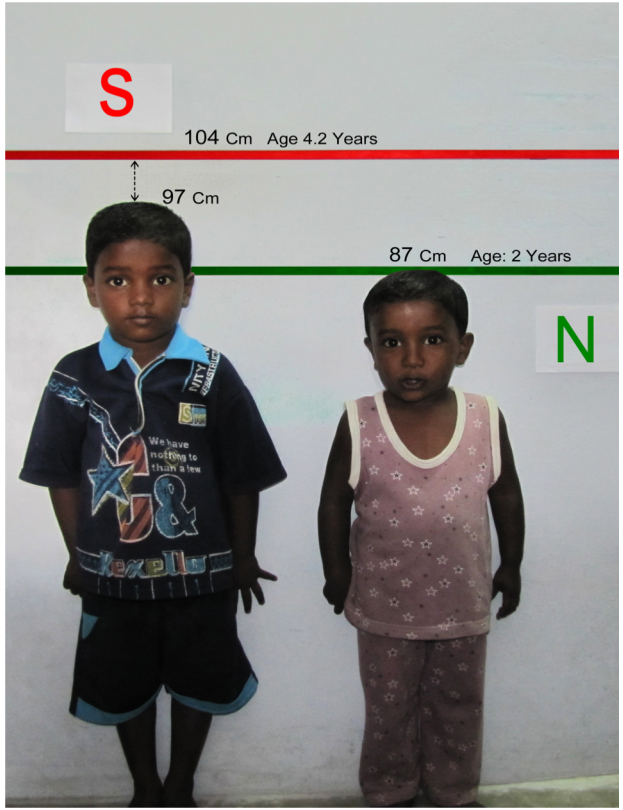
What does the future hold?

- 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