Epidemiology & Systemic Effects of Diarrhea

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PIDSP @ 25: Forging Ahead in Pediatric Infectious Diseases
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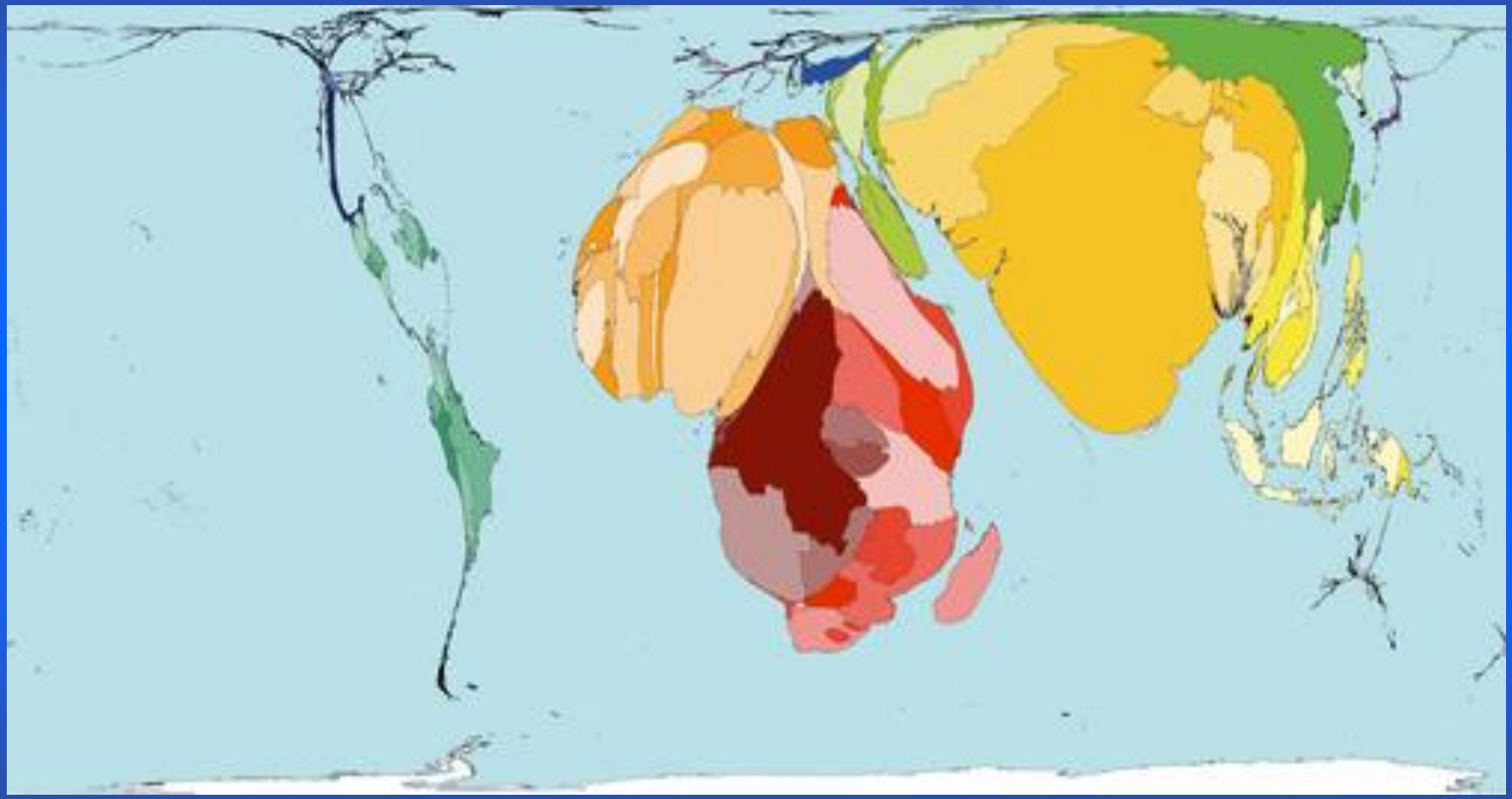
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Today's Discussion:

- Results from **GEMS**: "Global Enteric Multicentre Study"
  - Causes and patterns of severe diarrheal illnesses in children
- Results from **MAL-ED**: "The Malnutrition & Enteric Disease Study"
  - New findings relating enteric disease to child growth and cognitive development
- Pathogen-specific Systemic Effects:
  - Rotavirus – antigenemia & seizures

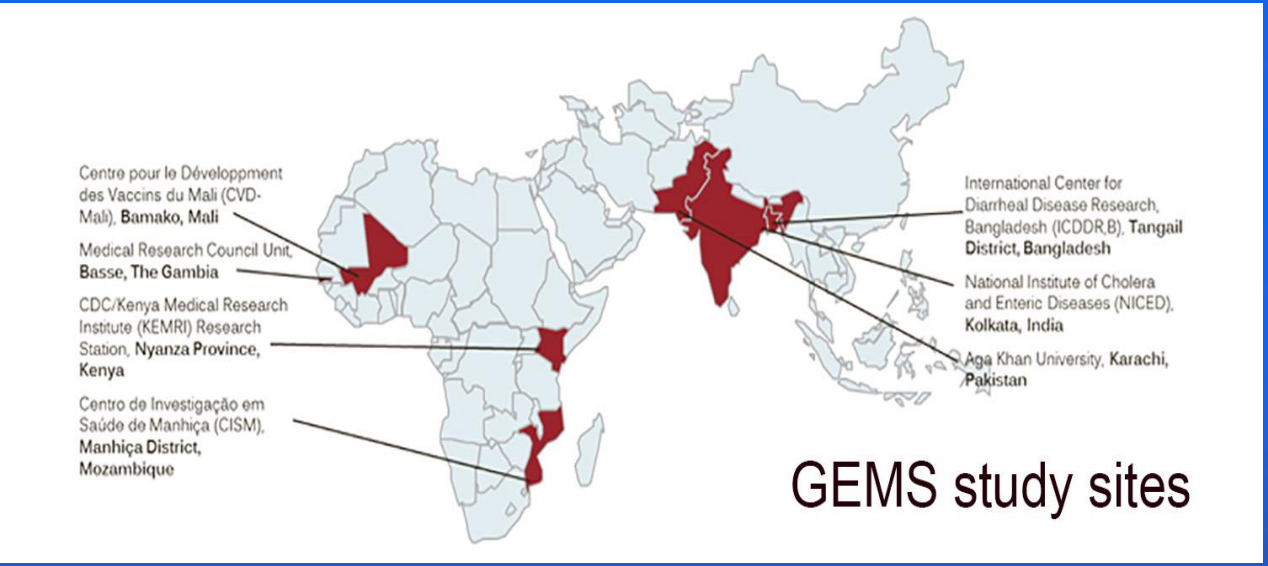
What if the world was re-sized in proportion to diarrheal deaths?



Source: http://worldmapper.org

GEMS: Global Enteric Multicentre Study

- Population-based case-control study of acute, medically attended moderate-to-severe diarrhea
- Children <5 years old living in 7 Sub-Saharan Africa & South Asian countries



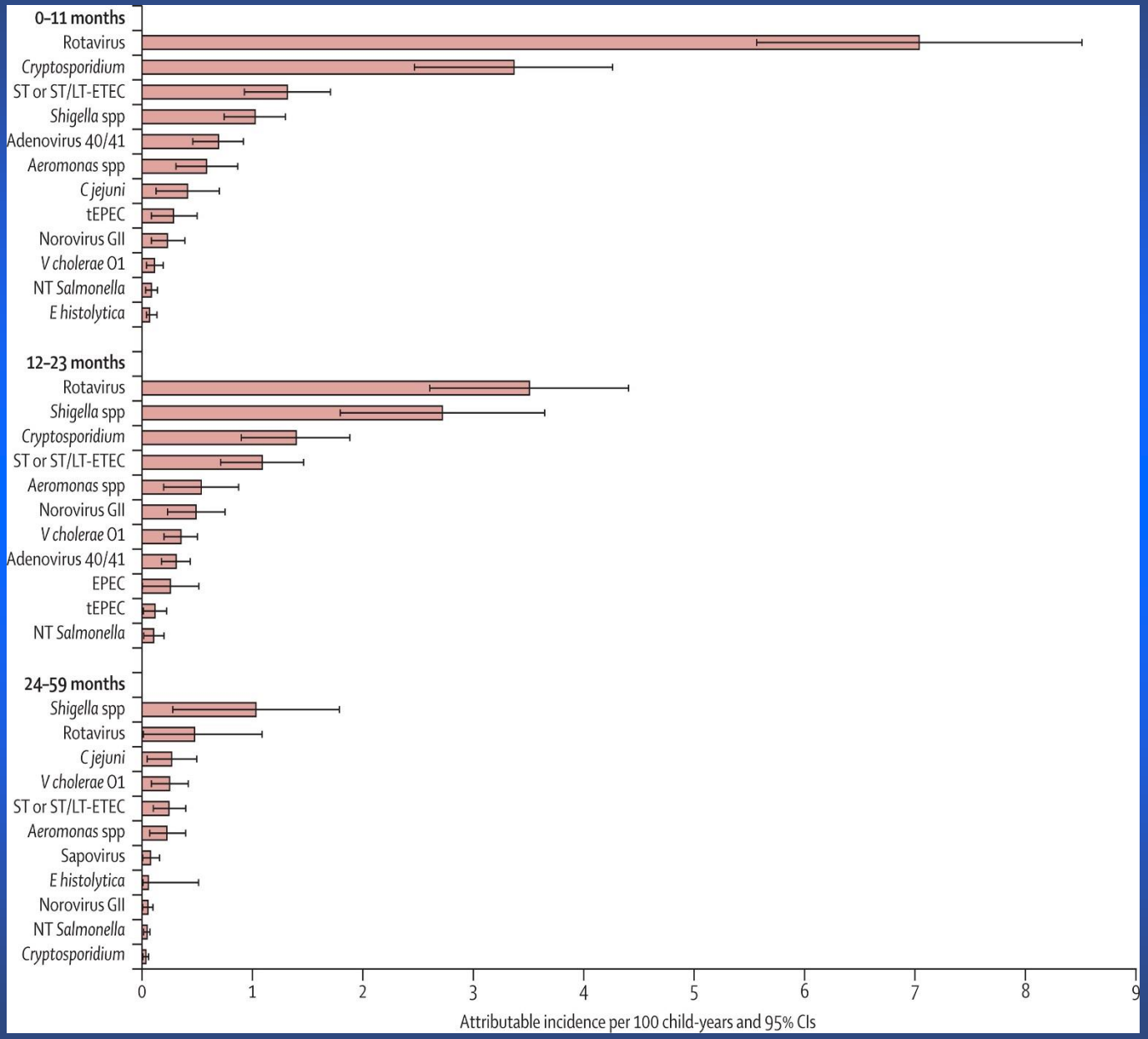
- 7 low socioeconomic regions
- Systematic diarrhea surveillance with follow-up 2-3 months later

GEMS: Most common severe diarrhea pathogens

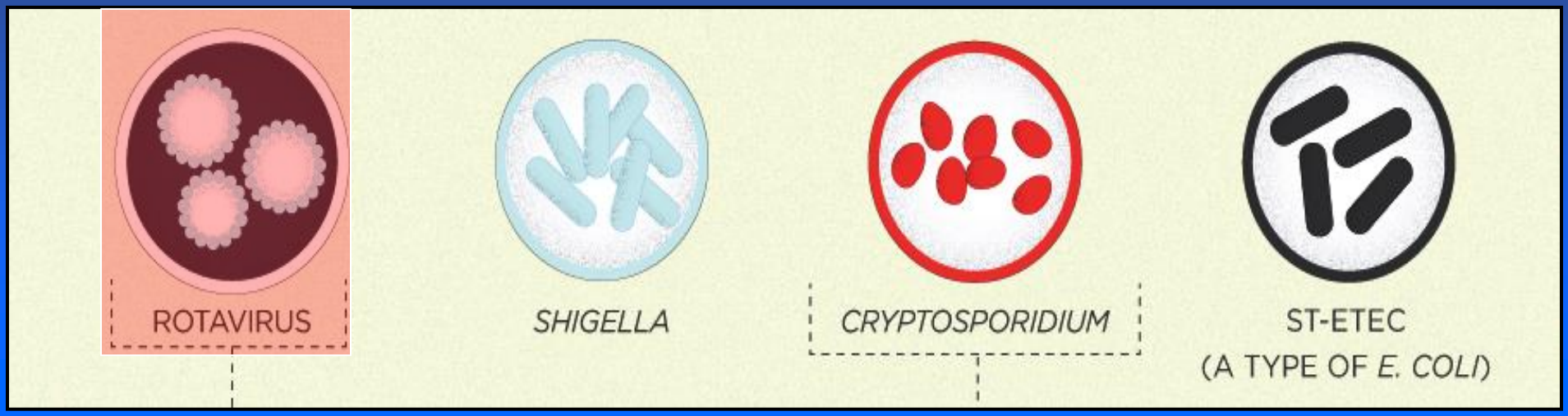
Infants:
Rotavirus
Cryptosporidium
ETEC

1 year olds:
Rotavirus
Shigella
Cryptosporidium

2-5 year olds:
Shigella
Rotavirus
C. *jejuni*



GEMS: Global Enteric Multicentre Study



Pathogens causing the majority of moderate-to-severe diarrhea in children under age 5

Rotavirus: *universally the leading cause of diarrhea in infants and 1-2 year olds; twice the disease burden as any other diarrheal pathogen; greatest cause of childhood diarrheal mortality worldwide; vaccine has been introduced in 93 countries to date*

Kotloff, et al. *Lancet*, 2013

Improvements in sanitation are associated with lowered risk of bacterial/parasitic enteric infections (**but are not associated with viral enteric etiologies**)

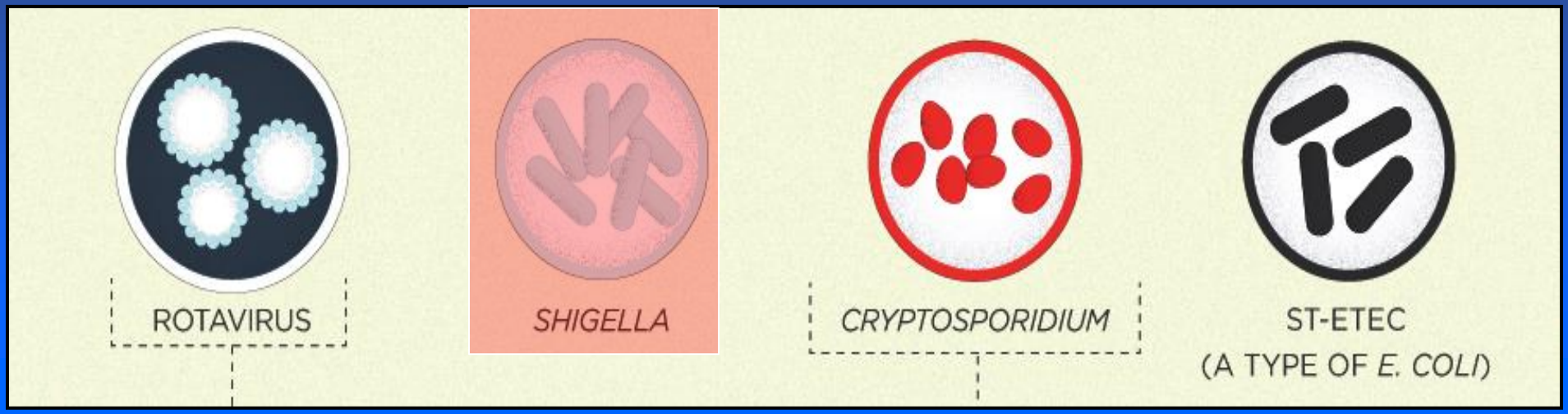
"…improvements in sanitation and hygiene… may have disproportionately reduced the bacterial and parasitic causes of diarrhea (which are mainly transmitted through contaminated food and water), but may have had less of an impact on rotavirus diarrhea (which is largely spread person-to-person), resulting in an increase in the proportion of diarrhea attributable to rotavirus."

Satter, et al. *Vaccine* 2017
Berendes, et al. *Trop Med Int Health* 2017

"Rotavirus vaccines should be included in all national immunization programmes and considered a priority, particularly in countries with high rotavirus gastroenteritis-associated fatality rates, such as in south and south-eastern Asia and sub-Saharan Africa."

Rotavirus Vaccines: WHO Position Paper, 2013

GEMS: Global Enteric Multicentre Study

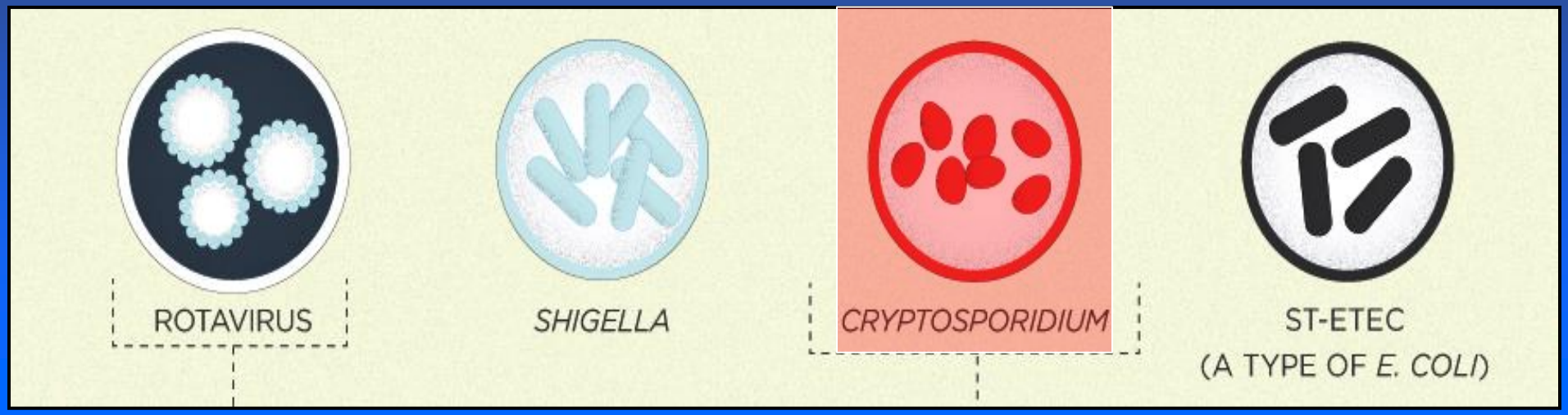


Pathogens causing the majority of moderate-to-severe diarrhea in children under age 5

Shigella: *causes 64% of bloody dysentery but also 13% of watery diarrhea; S. flexneri causes most endemic disease; incidence increases with age, with highest levels in 2-5 year olds; association with poor sanitation/hygiene*

Kotloff, et al. *Lancet*, 2013

GEMS: Global Enteric Multicentre Study

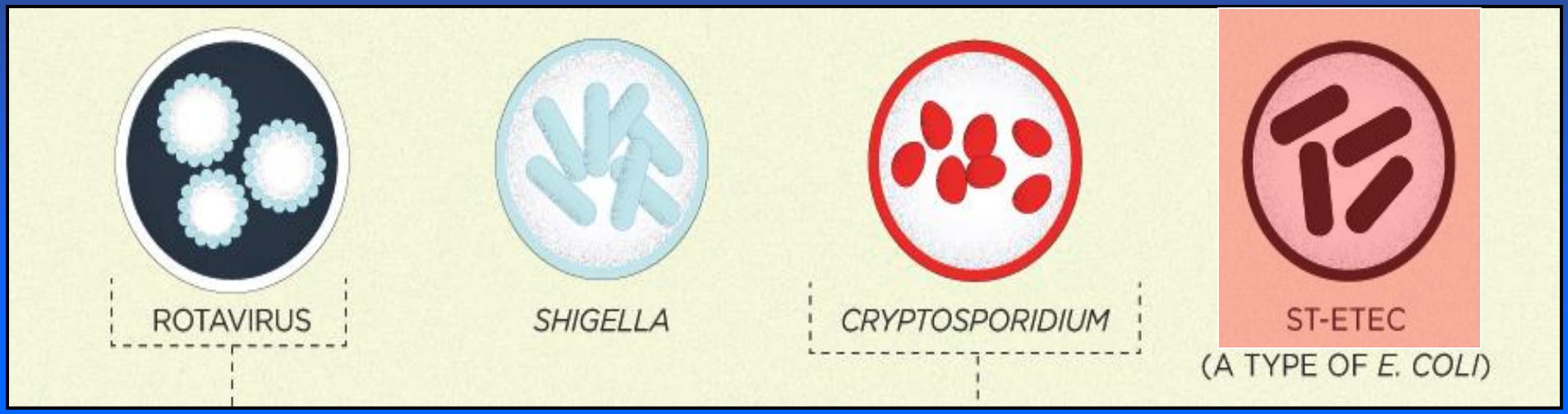


Pathogens causing the majority of moderate-to-severe diarrhea in children under age 5

Cryptosporidium: *protozoan infection; unexpected finding: second highest incidence among infants regardless of HIV status; among 1-2 year olds it was associated with a significantly higher risk of death 2-3 months following infection*

Kotloff, et al. *Lancet*, 2013

GEMS: Global Enteric Multicentre Study

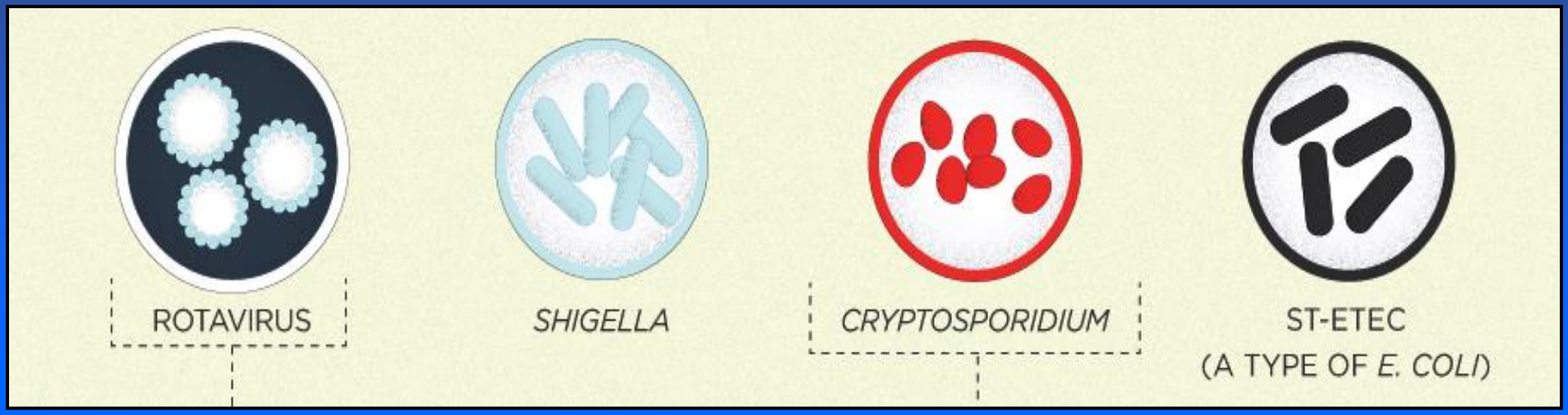


Pathogens causing the majority of moderate-to-severe diarrhea in children under age 5

ETEC producing heat-stable toxin: *causes watery diarrhea and a cholera-like severe diarrhea; vaccine being developed*

Kotloff, et al. *Lancet*, 2013

GEMS: Global Enteric Multicentre Study



Giardia: *found more often in controls rather than diarrheal cases; may actually interfere with pathogenic mechanisms of other pathogens*

Norovirus: *high incidence (esp. in first 2 years of life), and associated with growth faltering; However, attributable fraction in GEMS diminished by a.) large numbers of asymptomatic carriage/shedding, b.) geographic variation in incidence, c.) methods excluded vomit-only cases, and d.) typically shorter illness; vaccines are in clinical trials*

Kotloff, et al. *Lancet*, 2013

GEMS found that severe gastroenteritis episodes were associated with a

8.5X higher risk of death

from any cause within 2 months

Kotloff, et al. *Lancet* 2013

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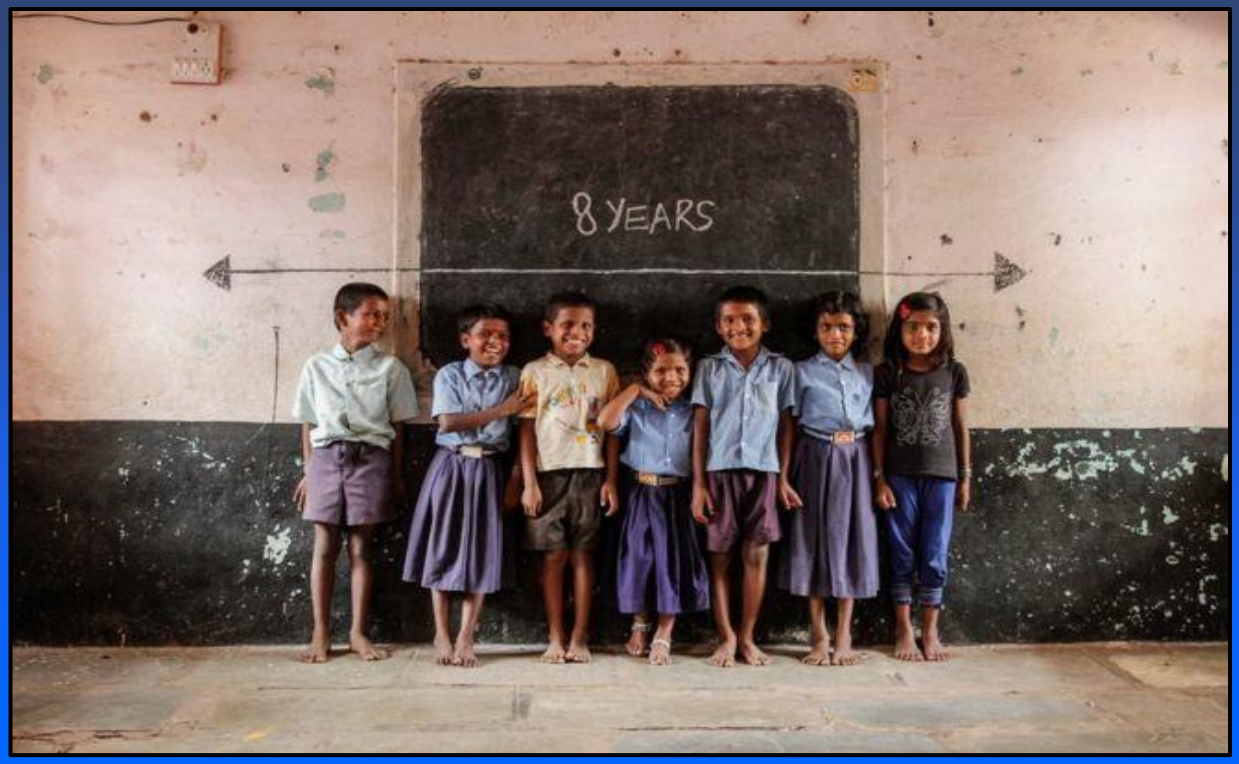
MAL-ED: The Malnutrition & Enteric Disease Study

- longitudinal community-based study of children <2 years old with sampling during healthy and acute diarrheal episodes
- Low- and middle-income countries across Africa, Asia, & South America
- Community cases
- Cohort serially followed



Diarrhea is a significant contributor to malnutrition and stunting among children of lower socio-economic status

Guerrant, et al. *Nature Reviews* 2013

Diarrhea significantly increased the likelihood of stunting in an analysis of 9 African, South American, and Asian countries

Checkley, et al. *Intern J Epidemiol* 2008

- MAL-ED: Length for Age most impacted by diarrheal pathogens (i.e., stunting rather than wasting)
- Deficits accumulated due to incomplete recoveries from repeated insults (including nutritional factors and re-infection), even absent diarrhea

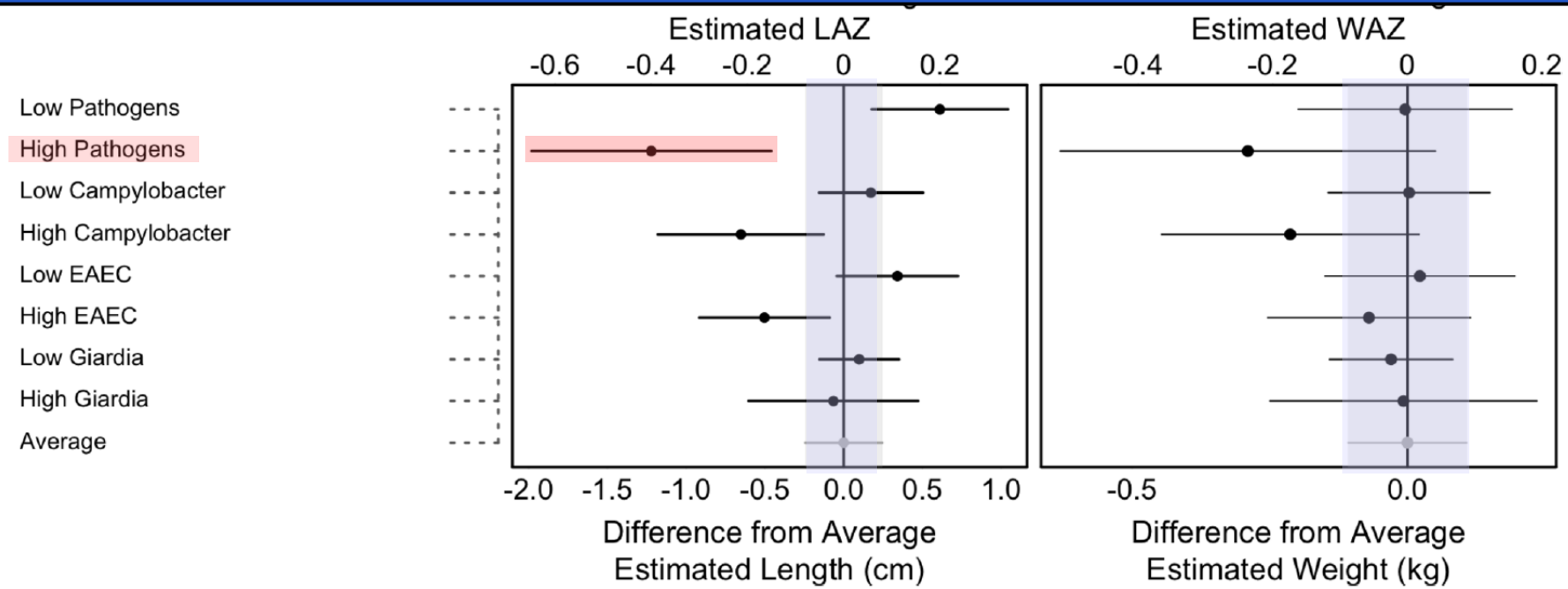


Figure 2 The predicted difference in length (bottom axis) and LAZ (top axis) (left) and weight (bottom axis) and WAZ (top axis) (right) at 24 months based on scenarios that change individual factors potentially affecting growth velocity adjusting for the mean of all factors. The absolute length and weight were converted to z-scores for length-for age (LAZ) and weight-for-age (WAZ) using the WHO Growth Standards.[17] The high and low scenarios are based on presence or absence of the named pathogen in at least one surveillance stool in each period while holding all other variables at their mean level. The pathogens represented here are the top three pathogens by prevalence (*Campylobacter*, EAEC and *Giardia*). Horizontal lines indicate the 95% CI around the mean differences. The grey vertical bars indicate the 95% CI around the average estimate (which has 0 difference from itself). Sites: BGD, Bangladesh (Dhaka); INV, India (Vellore); NEB, Nepal (Bhaktapur); BRF, Brazil (Fortaleza) PEL, Peru (Loreto); SAV, South Africa (Venda); TZH, Tanzania (Haydom). EAEC, enteroaggregative *Escherichia coli*.

MAL-ED: The Malnutrition & Enteric Disease Study

"Higher enteropathogen burdens in non-diarrhea stools, as well as lower energy and protein density of complementary foods, were found to be associated with poorer growth in children with accumulated impacts on weight and length at 24 months."

PREVAIL maternal-infant cohort subjects, used with consent 2017

Caulfield, et al. *BMJ Global Health* 2017

MAL-ED: The Malnutrition & Enteric Disease Study

" EAEC subclinical infection with any other pathogen was negatively associated with delta weight-for-length ($P<0.05$) and weight-for-age ($P>0.05$) z scores between 0 and 6 months."

Lima, et al. *J Peds Gastro Nutr* 2018

MAL-ED: The Malnutrition & Enteric Disease Study

- Children in settings of undernutrition and enteric disease are at risk for insufficient brain growth, as well as linear growth
- Measurements of head circumference were most predictive of cognitive scores at age 2

Scharf, et al. *Matern Child Nut* 2018

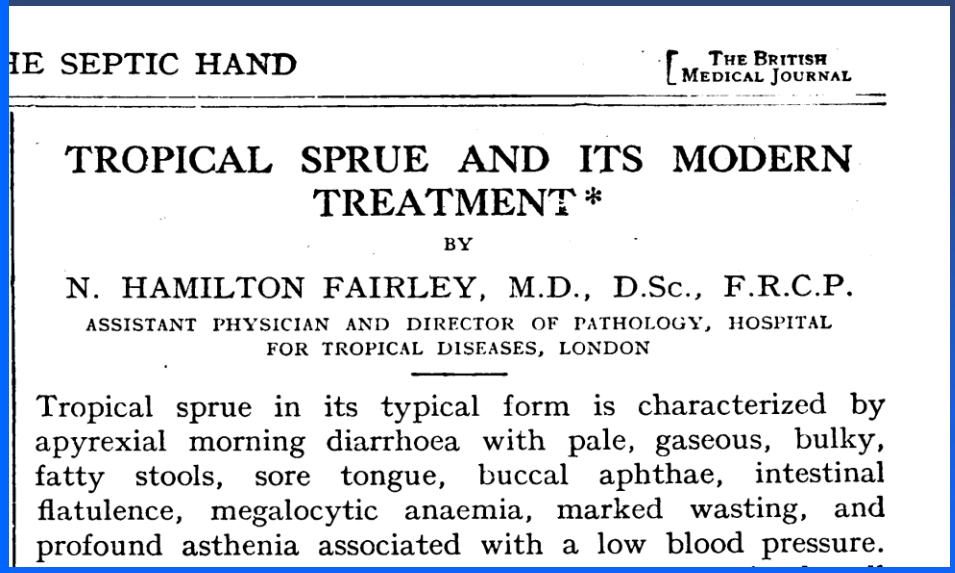
Growth faltering during early childhood is associated with:

- increased risk of illness and death
- fewer years of schooling
- lower earning potential

Undernutrition arises from dietary inadequacies and high enteric illness burden, related to (*and further causing*) poor socioeconomic & environmental situations

Olofin, et al. *PLoS One*, 2013
Black, et al. *Lancet* 2008
Hoddinott, et al. *Am J Clin Nutr* 2013

"Tropical Sprue"
c. 1934



HE SEPTIC HAND — THE BRITISH MEDICAL JOURNAL

TROPICAL SPRUE AND ITS MODERN TREATMENT*

BY

N. HAMILTON FAIRLEY, M.D., D.Sc., F.R.C.P.
ASSISTANT PHYSICIAN AND DIRECTOR OF PATHOLOGY, HOSPITAL FOR TROPICAL DISEASES, LONDON

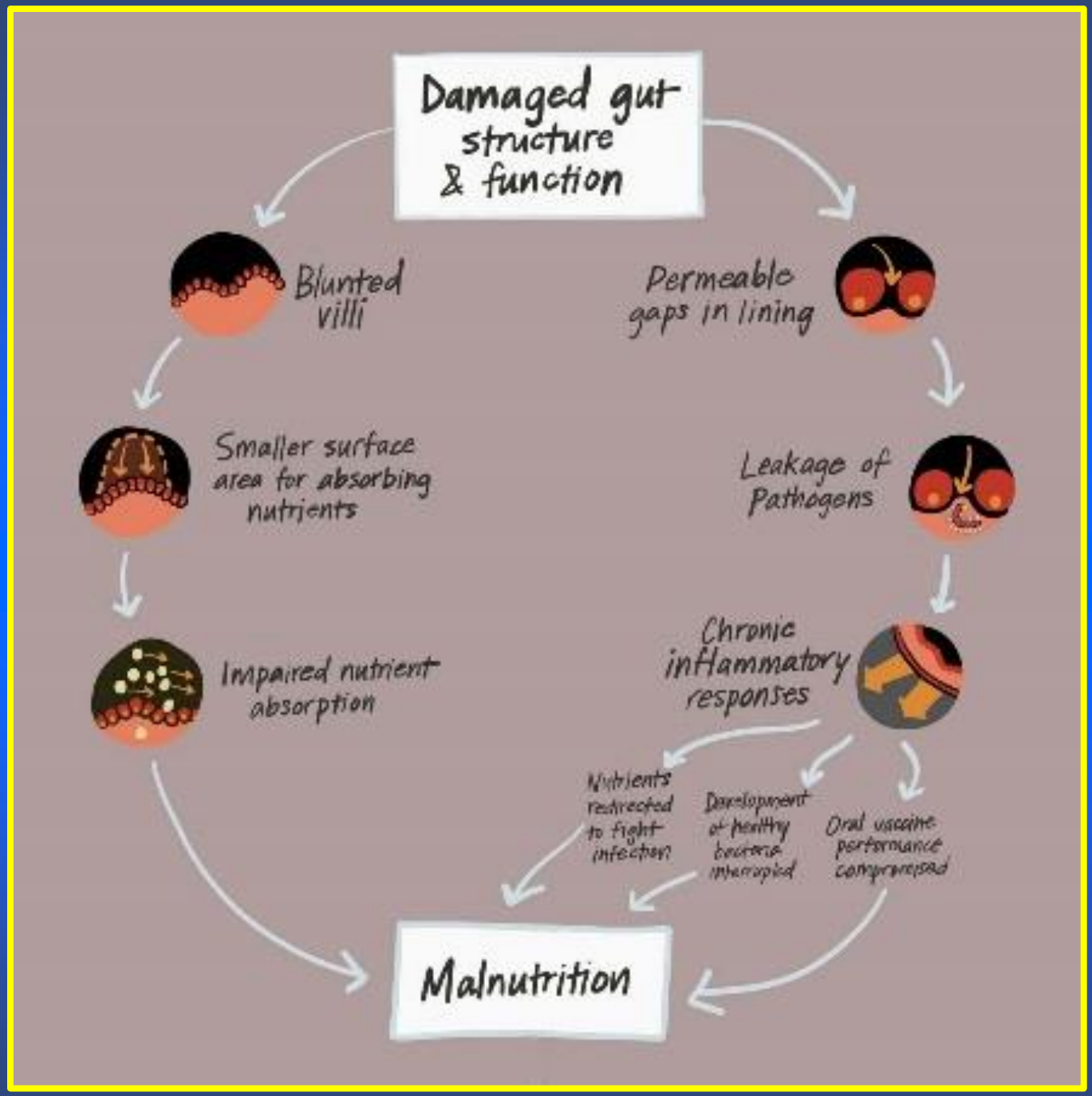
Tropical sprue in its typical form is characterized by apyrexial morning diarrhoea with pale, gaseous, bulky, fatty stools, sore tongue, buccal aphthae, intestinal flatulence, megalocytic anaemia, marked wasting, and profound asthenia associated with a low blood pressure.

Aetiological Considerations

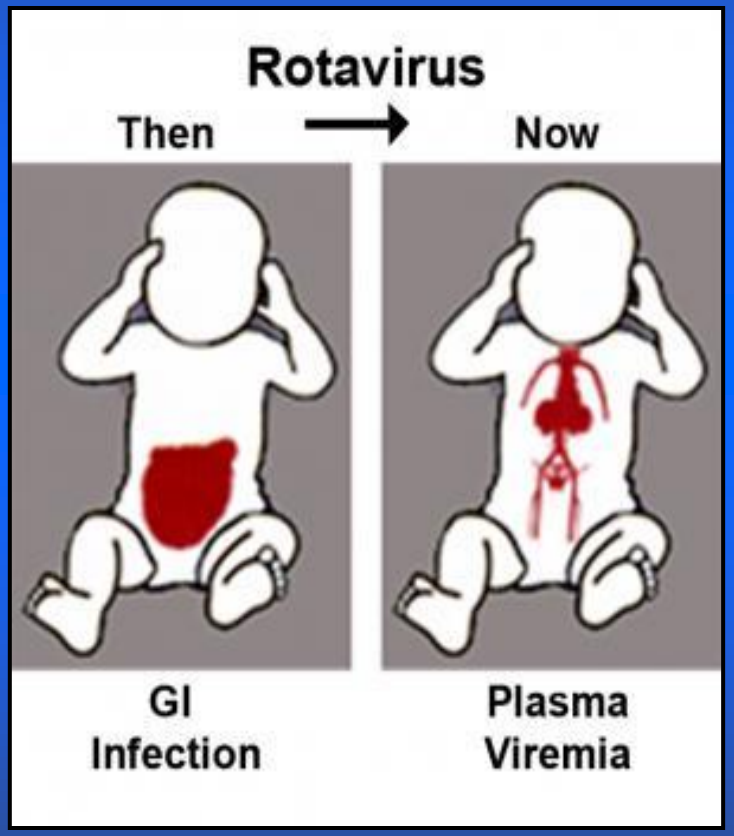
Sprue generally affects adult Europeans or those of mixed European stock after some years of residence in an endemic area: it may directly follow hill diarrhoea, as emphasized by Rogers (1921), and is not infrequently preceded by a history of dysentery or chronic malaria

"…characterized by apyrexial morning diarrhea…"

"…after some years of residence in an endemic area…"



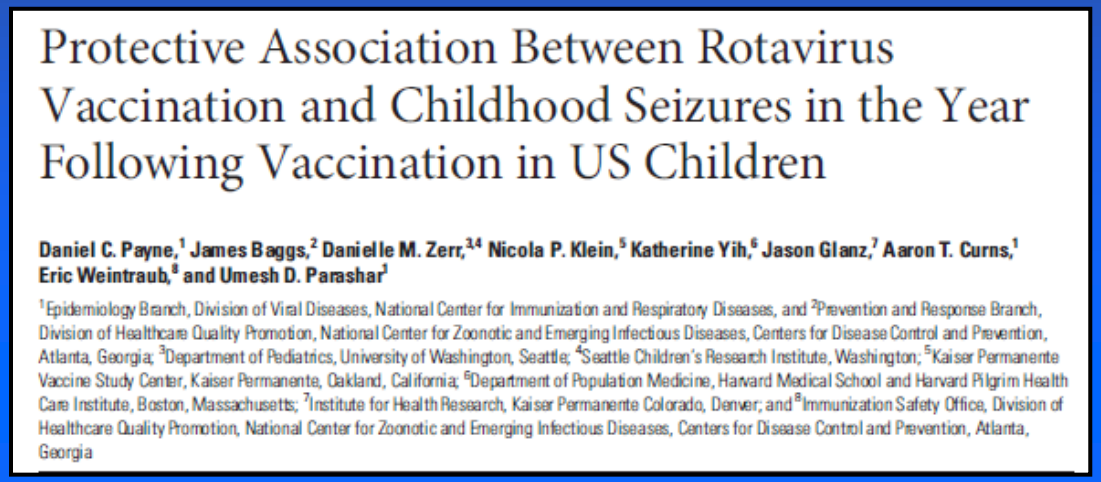
Rotavirus gastroenteritis: A systemic infection



- Most children hospitalized with rotavirus are viremic, indicating extra-intestinal involvement
- Rotavirus antigenemia observed in 61-90% of infected children
- RV-antigenemia has been observed to be associated with increased severity (fever and vomiting)
- Breastfed infants have been shown to have reduced risk of RV-antigenemia in some settings

Blutt, et al. *PLoS Medicine* 2007
Hemming, et al. *Pediatr Infect Dis J* 2014
Das, et al. *PLoS One* 2016

Rotavirus vaccine could avoid systemic complications from rotavirus infections (e.g. seizures)



Protective Association Between Rotavirus Vaccination and Childhood Seizures in the Year Following Vaccination in US Children

Daniel C. Payne,[1] James Baggs,[2] Danielle M. Zerr,[3,4] Nicola P. Klein,[5] Katherine Yih,[6] Jason Glanz,[7] Aaron T. Curns,[1] Eric Weintraub,[8] and Umesh D. Parashar[1]

[1]Epidemiology Branch, Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, and [2]Prevention and Response Branch, Division of Healthcare Quality Promotion, National Center for Zoonotic and Emerging Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; [3]Department of Pediatrics, University of Washington, Seattle; [4]Seattle Children's Research Institute, Washington; [5]Kaiser Permanente Vaccine Study Center, Kaiser Permanente, Oakland, California; [6]Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts; [7]Institute for Health Research, Kaiser Permanente Colorado, Denver; and [8]Immunization Safety Office, Division of Healthcare Quality Promotion, National Center for Zoonotic and Emerging Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Payne DC, et al. *Clin Infect Dis* 2013

Rotavirus vaccination was associated with a 20% reduction in risk of seizures requiring hospitalization/ED care compared with unvaccinated children during the year following vaccination

Australia: 36-38% reduction in ED/hosp. febrile seizures up to 2 years post-vaccination
(Sheridan SL, et al. *JPIDS* 2016)

Spain: 16-34% reductions in hospitalized seizures post-vaccination
(Pardo-Seco J, et al. *PIDJ* 2015)

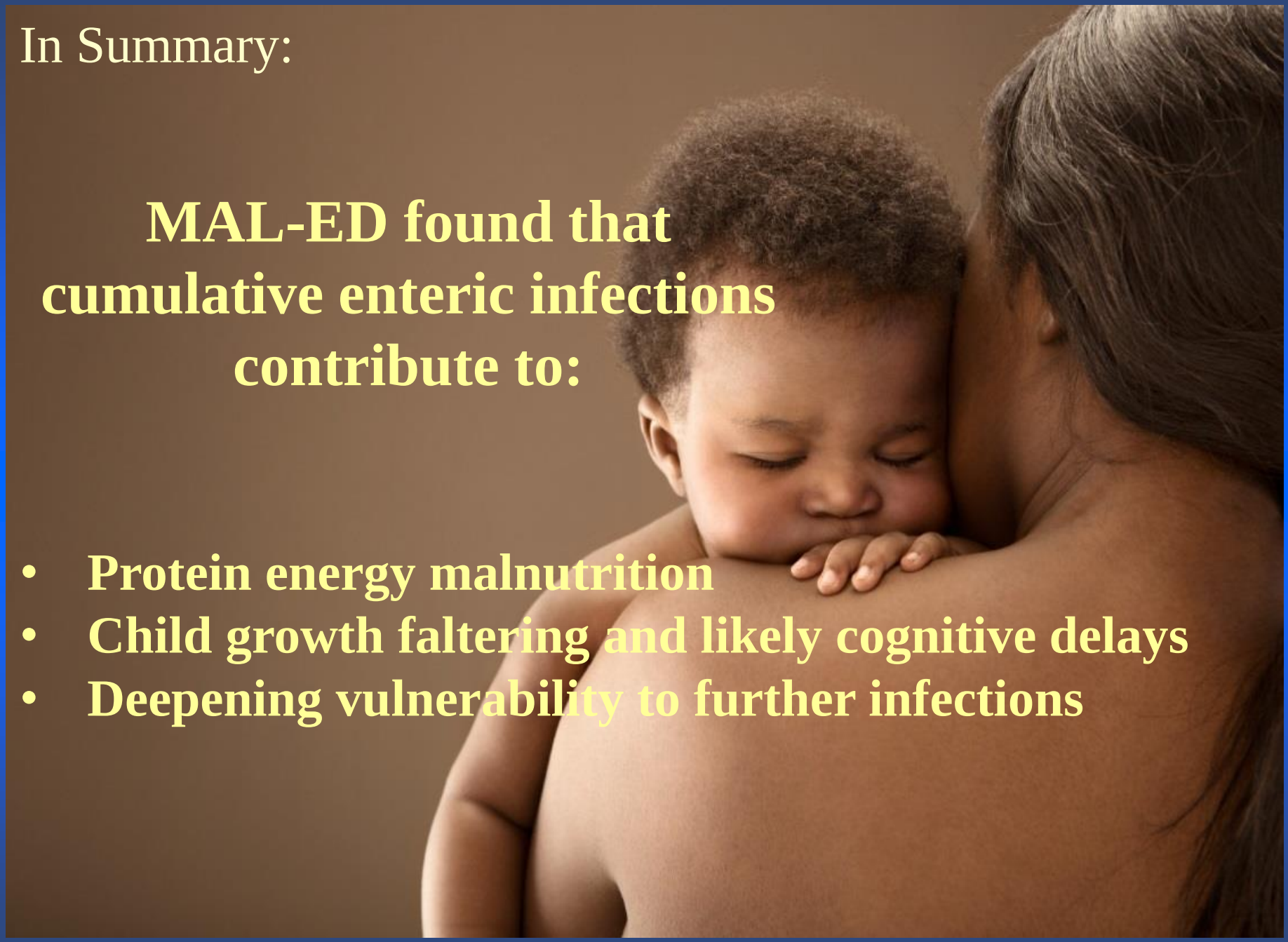
In Summary:

GEMS found the most prevalent, severe childhood enteric diseases include:

- **Rotavirus**
- **Shigella**
- **Cryptosporidium**
- **ST-ETEC**

And, severe diarrhea episodes were associated with a 8.5X higher risk of death from any cause within 2 months

In Summary:



MAL-ED found that cumulative enteric infections contribute to:

- **Protein energy malnutrition**
- **Child growth faltering and likely cognitive delays**
- **Deepening vulnerability to further infections**

In Summary:

Rotavirus gastroenteritis is associated with antigenemia and can be considered a systemic infection

Rotavirus vaccination may avert pediatric seizures, in addition to the well-documented prevention of severe acute gastroenteritis

Schlaudecker, et al. *Curr Opin Infect Dis* 2011

Thank you!

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PREVAIL maternal-infant cohort subjects, used with consent 2017

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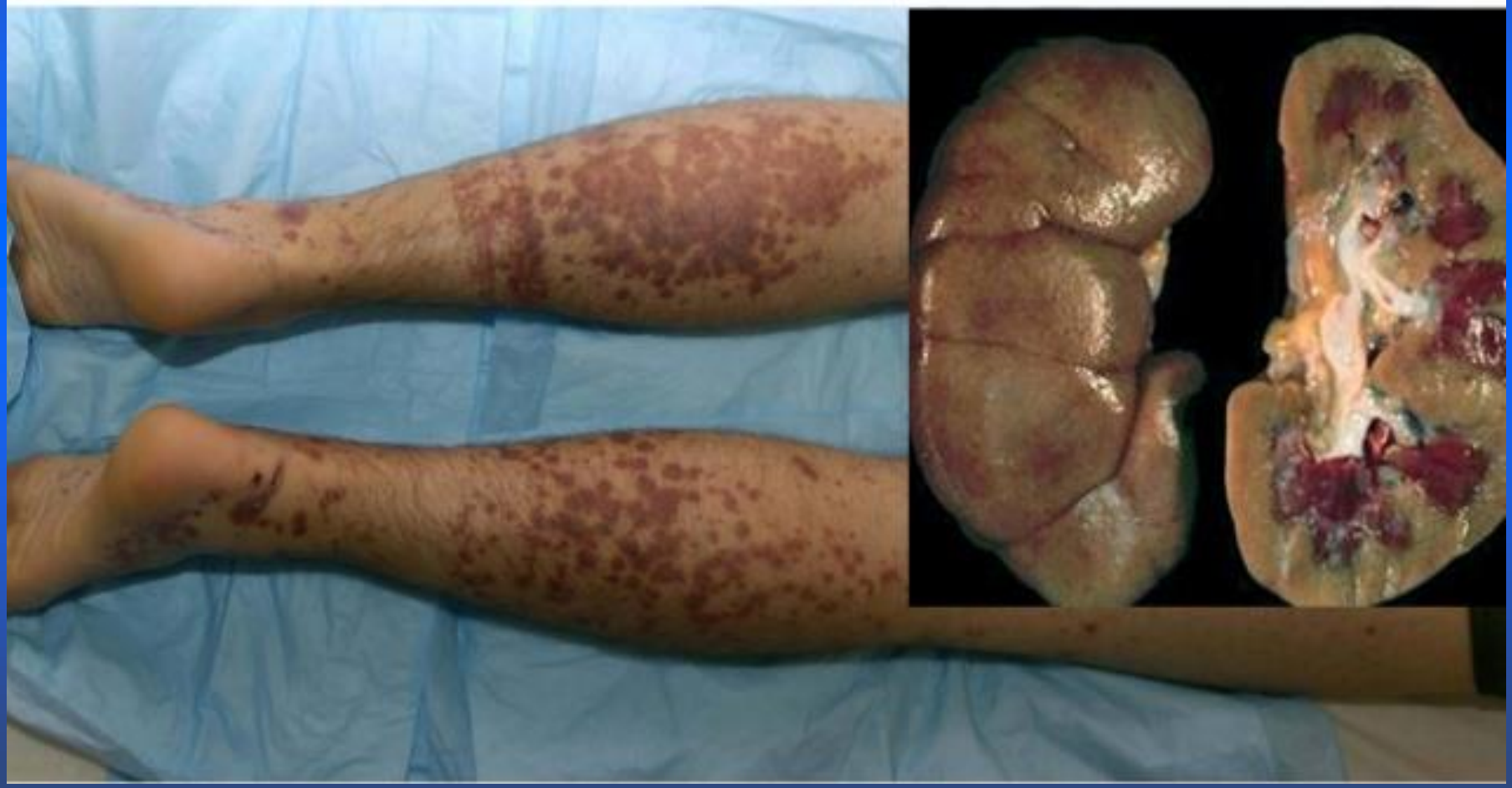
Hemolytic uremic syndrome(HUS)



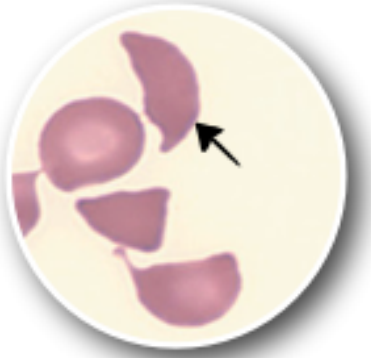
Hemolytic Uremic Syndrome (HUS)

Most common cause of acute renal failure in children

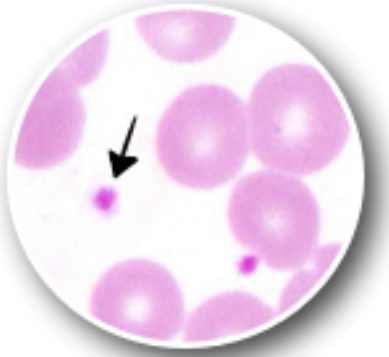
E. coli H7:0157

Shiga-like toxin (Verotoxin)

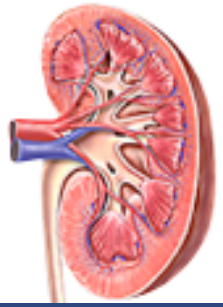
Abdominal Pain
Bloody Diarrhea
Fever
Seizures
Lethargy



Microangiopathic hemolytic anemia (schistocytes)



Thrombocytopenia



Renal Insufficiency

Treatment

- Mainly supportive
- Dialysis
- No Antibiotics
- Plasmapharesis/IVIG

CLINICAL FEATURES

- The commonest clinical presentation of HUS is :
  - ✓ Acute pallor
  - ✓ Oliguria
  - ✓ Diarrhea or dysentery
- It occurs commonly in children between 1-5 years of age
- HUS develops about 5-10 days after onset of diarrhea

Table 16. Summary of Pediatric (<18 Years) Post-diarrheal Hemolytic Uremic Syndrome (HUS) Cases—FoodNet, 2014

	n/N	(%)
Pediatric post-diarrheal HUS cases	61	(100.0)
DEMOGRAPHICS		
Female	36/61	(59.0)
Age group		
<5 years	32/61	(52.5)
5–14 years	27/61	(44.3)
15–17 years	2/61	(3.3)
OUTCOME		
Hospitalization, median days (range)	13 (1–368)	n/a
Death	2/61	(3.3)
SEASONALITY		
Illness onset that began June–September	30/61	(49.2)
STEC CASE CLASSIFICATION*		
Confirmed†	42/61	(68.9)
Probable‡	9/61	(14.8)
Suspected§	10/61	(16.4)
HUS among children <5 yrs with confirmed STEC O157 infection	22/98	(22.4)

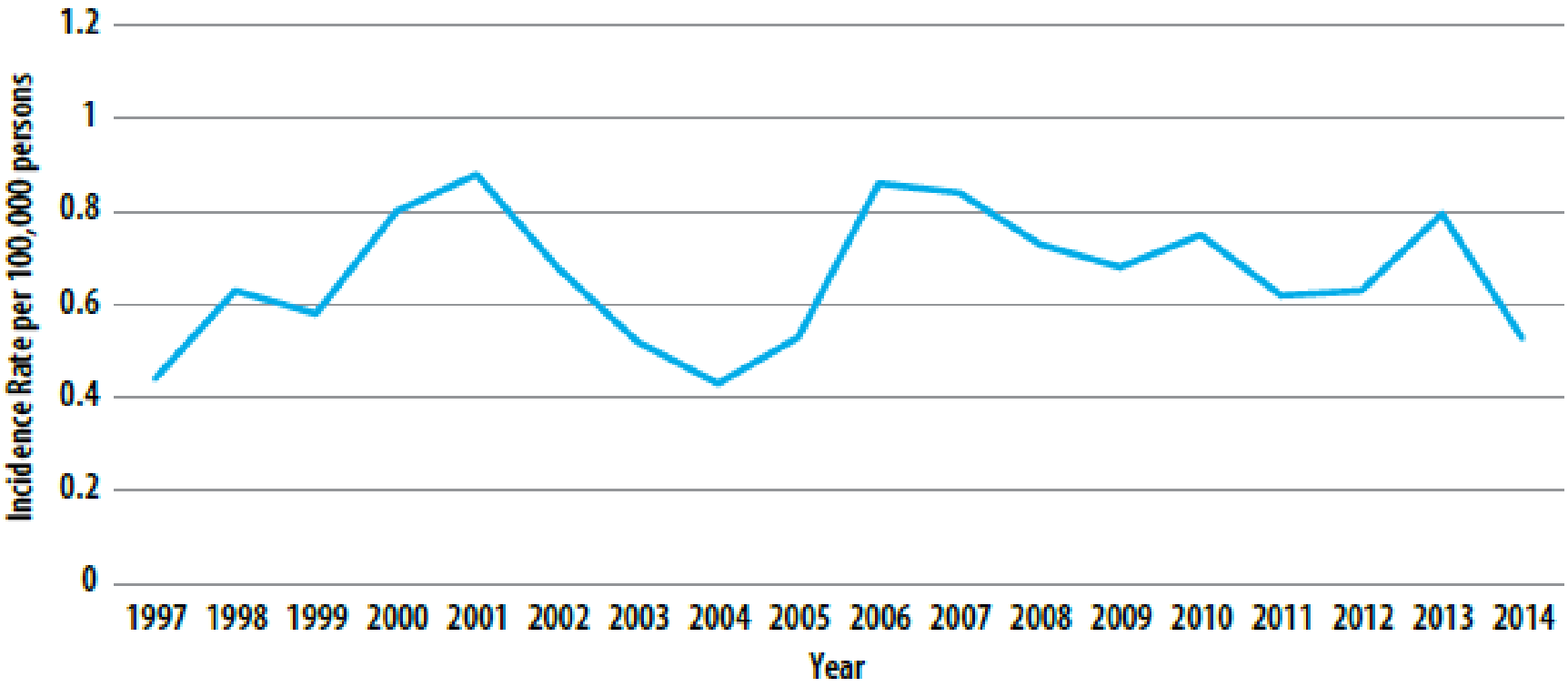
* Case classification based on 2014 CSTE case definition of Shiga toxin-producing *Escherichia coli* (STEC): https://wwwn.cdc.gov/nndss/conditions/shiga-toxin-producing-escherichia-coli/case-definition/2014/

† Isolation of E.coli with Shiga toxin production or the presence of Shiga toxin genes, or isolation of *E.coli* O157 that produces the H7 antigen. O Serogroups were O157 (37 patients), O121 (2), O111(1), both O157 and O45 (1), and undetermined (1). Six cases also had elevated antibody titer to E.coli O157 or O111.

‡ Isolation of *E.coli* O157 without H7 antigen or Shiga toxin production (0 patients) or an elevated antibody titer to *E.coli* O157 or O111 without isolation of STEC (9). We did not collect information necessary to classify HUS cases based on epidemiologic relationship to a confirmed or probable case.

§ Identification of Shiga toxin without the isolation of STEC (1 patient) or a pediatric post-diarrheal HUS case without sufficient laboratory evidence for STEC (9).

Figure 4. Incidence of Pediatric Post-diarrheal Hemolytic Uremic Syndrome (HUS)—FoodNet, 1997–2014



•The incidence of confirmed or CIDT-positive infections per 100,000 was highest for *Campylobacter* and *Salmonella*, which is consistent with previous years.
•The number of CIDT-positive reports is increasing. The number of *Campylobacter*, *Salmonella*, *Shigella*, *Vibrio*, and *Yersinia* infections diagnosed by CIDT alone increased 114% in 2016 compared with the 2013–2015 average.
•Although CIDTs can provide timely information for clinical management of foodborne infections and are easier for laboratories to do, increasing use of CIDTs affects interpretation of public health surveillance data and our ability to monitor progress toward achieving prevention goals. It is difficult to interpret whether these are true changes in incidence or whether the change is in part or completely due to changes in diagnostic testing practices and procedures.
•Trends for some pathogens may be more affected than others by changes in use of CIDTs. *Listeria* infections, for which CIDTs have not previously been available, and cases of HUS, which do not rely on CIDT, did not change significantly in 2016 compared with the previous three years.
•Recent changes in diagnostic practices also challenge our ability to find outbreaks and monitor disease trends. Some information about the bacteria causing infections, such as subtype and antimicrobial susceptibility, can be obtained only if a CIDT-positive specimen is also cultured. FoodNet is gathering additional information to better understand the effect of CIDT on surveillance.

Pros
CIDTs are faster and easier to use than the traditional method (culture) for detecting bacteria. (Culturing is a method that helps an organism multiply so that scientists can isolate it and then do tests on it, such as determining if it is resistant to antibiotics.)
Cons
CIDTs do not provide an isolate, which contains the organism that caused the illness. Isolates are vital to answering important questions, such as: *Is the organism a particularly virulent strain? Is it likely to respond to antibiotics? Has it recently been found in others who are sick, suggesting an outbreak?*

To maintain public health surveillance of foodborne and other bacterial enteric diseases and to preserve the quality of clinical decision making, it will be necessary to:
Enhance surveillance methods to capture information on the type and brand of CIDTs that clinical labs are using, so investigators can examine the lab results critically
Examine the criteria for diagnosing a case of enteric infection (called a case definition) to inform evidence-based best practices and clinical guidelines
Encourage and implement reflex culturing at clinical laboratories or submission of culture-ready specimens to public health laboratories
Develop culture-independent methods to identify characteristics of disease-causing bacteria, such as serotype, antimicrobial resistance, and virulence.

MAL-ED: The Malnutrition & Enteric Disease Study

"Exclusive breastfeeding 0-6 months was protective against diarrhea (0-2 months: RR 0.39, 95% CI 0.32, 0.49; 3-5 months: RR 0.83, 95% CI 0.75, 0.93) and ARI (3-5 months: RR 0.81, 95% CI 0.68, 0.98)."

"Children with recent illness who were exclusively breastfed were half as likely as those not exclusively breastfed to experience diarrhea in the first 3 months of life."

Richard, et al. *Am J Trop Med Hyg* 2018

Economic burden of rotavirus

Treating rotavirus diarrhea is expensive for families and countries

Uganda

Inpatient admission for one episode of severe rotavirus diarrhea costs **10%** of the average family's monthly income

Bangladesh

Treating one episode of rotavirus diarrhea can amount to **85%** of the average family's monthly income

Malaysia

Rotavirus hospitalization costs more than **25%** of the average family's monthly income

Slide courtesy of ROTA Council
Images courtesy of Photoshare: © 2009 Jessica Alderman, © 2014 SPRING Project, © 2014 Aji Styawan
Sigei C, et al., Vaccine. 2015;33 Suppl 1:A109-18; icddr,b. Preliminary analysis, Protocol# 14009; Chai PL, WS. Vaccine. 2009;27(5):F112-F115