Diarrhoeal disease: a major challenge to global health

BSc Global Health
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Key messages

Diarrhoeal disease is a major cause of death

Common pathogens include : viruses (rotavirus), bacteria (shigella, salmonella) and protozoa

Some pathogens are now amenable to vaccination

Broader interventions improving water supply can reduce the incidence of diarrhoeal disease but are not universally implemented

ORS saves lives as part of ICMI, but uptake still limited

Climate change is likely to influence diarrhoeal disease

Burden of disease

Global Burden of Diarrhoeal disease and MDG4

Current estimates that 8.8 million deaths under age of 5 in 2008

A large proportion of mortality in under 5s globally is due to infectious diseases (68%)

Hence targeting infectious diseases, and particularly diarrhoeal disease, is a major part of achieving MDG4 (to reduce under 5 mortality by 2/3)

Source: Black et al Lancet 2010

Global Burden of Diarrhoeal disease and MDG4

	Estimated number (UR; millions)
Neonates aged 0–27 days	
Preterm birth complications	1·033 (0·717–1·216)
Birth asphyxia	0·814 (0·563–0·997)
Sepsis	0·521 (0·356–0·735)
Other	0·409 (0·318–0·883)
Pneumonia*	0·386 (0·264–0·545)
Congenital abnormalities†	0·272 (0·205–0·384)
Diarrhoea‡	0·079 (0·057–0·211)
Tetanus	0·059 (0·032–0·083)
Children aged 1–59 months	
Diarrhoea‡	1·257 (0·774–1·886)
Pneumonia*	1·189 (0·789–1·415)
Other infections	0·753 (0·479–2·830)
Malaria	0·732 (0·601–0·851)
Other non-communicable diseases	0·228 (0·143–0·606)
Injury	0·279 (0·174–0·738)
AIDS§	0·201 (0·186–0·215)
Pertussis¶	0·195 (·—·)
Meningitis	0·164 (0·110–0·728)
Measles	0·118 (0·075–0·180)
Congenital abnormalities†	0·104 (0·078–0·160)

Uncertainty range (UR) is defined as the 2·5–97·5 centile. ·—·data unavailable. *Estimated number of deaths in children younger than 5 years overall is 1·575 million (UR 1·046 million–1·874 million). †Estimated number of deaths in children younger than 5 years overall is 0·376 million (UR 0·283 million–0·580 million). ‡Estimated number of deaths in children younger than 5 years overall is 1·336 million (UR 0·822 million–2·004 million). §Uncertainty range is based on UNAIDS' estimated lower and upper bounds for deaths in children younger than 15 years. ¶Crowcroft and colleagues'[20] sensitivity analysis presents extreme upper and lower values for various inputs.

Table 1: Estimated numbers of deaths by cause in 2008

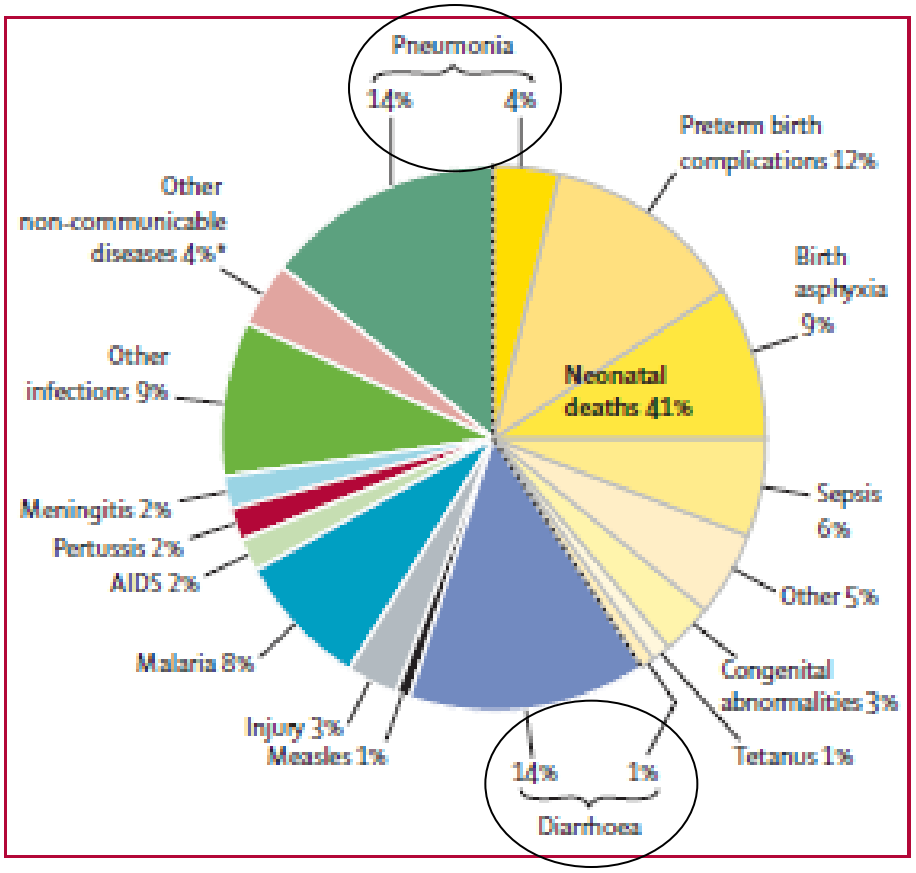
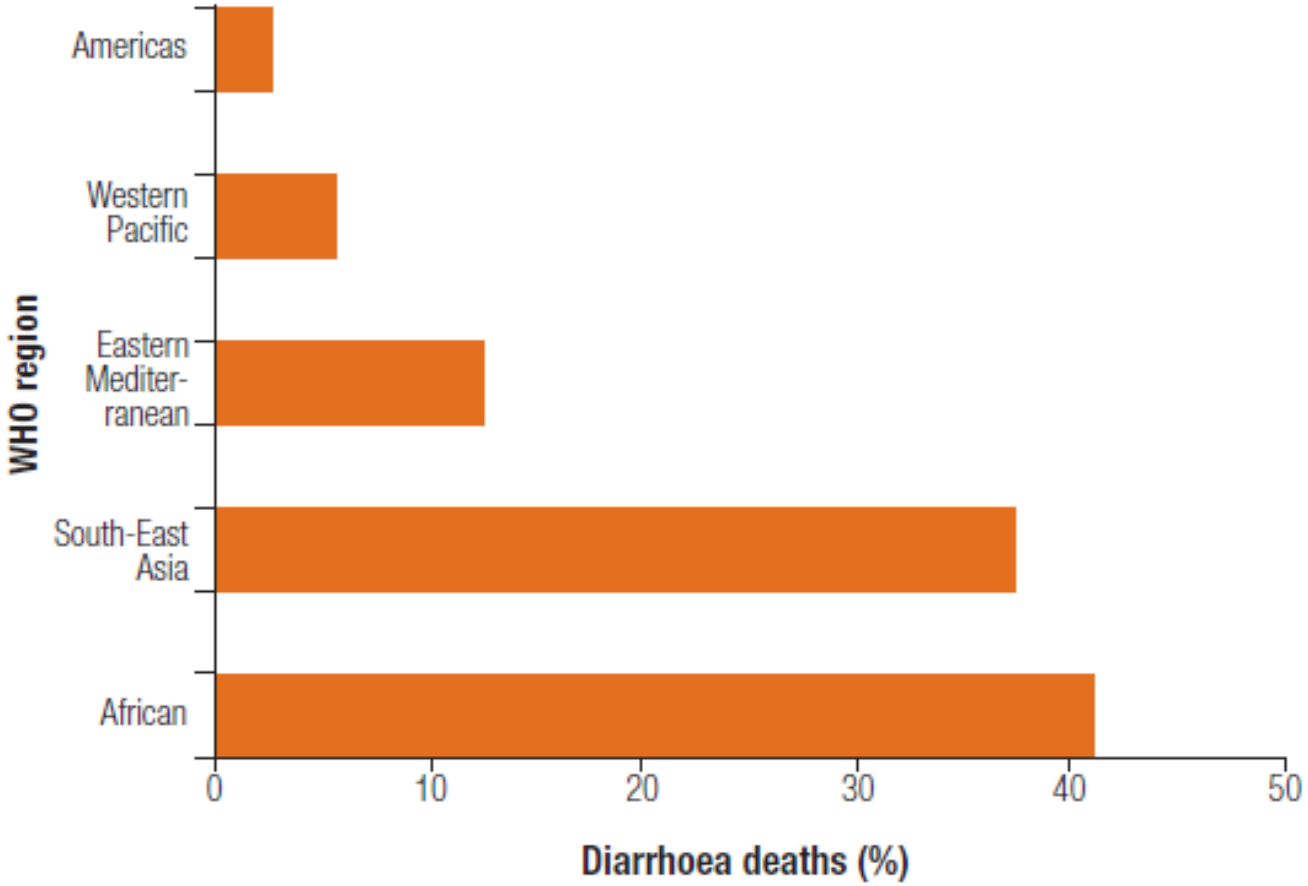


Figure 4: Global causes of child deaths
Data are separated into deaths of neonates aged 0–27 days and children aged 1–59 months. Causes that led to less than 1% of deaths are not presented.
*Includes data for congenital abnormalities.

Source: Black et al Lancet 2010

Distribution of diarrhoeal deaths by WHO region



Boschi-Pinto Bull WHO 08

Estimated proportion of under 5 mortality due to diarrhoeal disease

WHO region	Mortality stratum[a]	Average of diarrhoea-proportional mortality (%)	Estimated diarrhoea deaths (thousands)	Uncertainty ranges (thousands)
African (AFR)	D	17.8	402	346–455
	E	17.5	365	315–413
Americas (AMR)	B	13.3	35	30–40
	D	14.9	14	12–16
Eastern Mediterranean (EMR)	B	13.4	12	10–14
	D	16.9	221	190–250
South-East Asia (SEAR)	B	22.3	44	34–53
	D	24.5	651	500–793
Western Pacific (WPR)	B	13.8	105	90–118
World		**18.7**	**1870**	**1558–2193**

[a] WHO subregions are defined on the basis of levels of child and adult mortality: A, very low child and very low adult mortality; B, low child and low adult mortality; C, low child and high adult mortality; D, high child and high adult mortality; E, high child and very high adult mortality.

Deaths due to diarrhoea per 100,000 children younger than 5 years

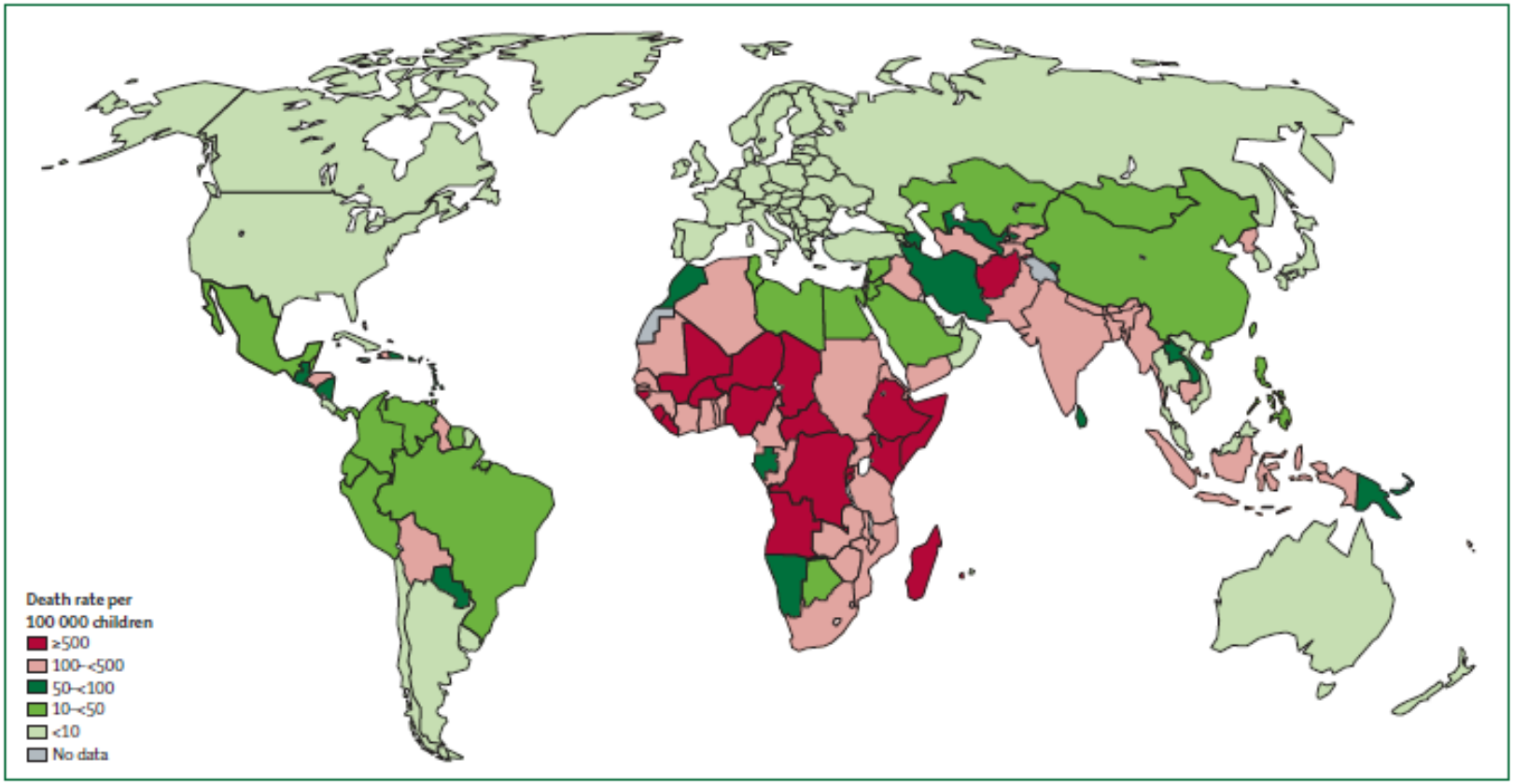


Figure 1: **Deaths due to diarrhoea per 100 000 children younger than 5 years**
Data from reference 1..

Santosham et al LID 10

ICMI (WHO)

- Classifies diarrhoea (watery, persistent, dysenteric)
- Classify dehydration

Type diarrhoea	% all childhood diarrhoea	%all childhood deaths due to diarrhoea	% deaths preventable by standard case management
Acute Watery	80	50	100
Dysentery	10	15	80
Persistent	10	35	80
Total	100	100	90

- Intervention bundle includes ORS, vitamin A, zinc supplements

Causes of disease

Pathogens causing diarrhoeal disease

ACUTE

- Bacteria
  - Shigella
  - Salmonellae
  - Vibrio cholerae
  - E Coli
  - Campylobacter
- Viral
  - Rotavirus
  - Hepatitis A,E
  - SMRVs (Norwalk)
- Protozoa
  - Entamoeba histolytica

CHRONIC (> 2weeks)

- Giardia
- Amoebiasis
- Tropical sprue
- Non-infective
- Malignancy
- UC
- Coeliac
- Lactase deficiency
- Drugs

Shigellosis

Small gram negative rods
40 serotypes
4 groups

Group A	*S dysenteriae*
Group B	*S flexneri*
Group C	*S boydii*
Group D	*S sonnei*

Typically low infecting dose
(cf salmonellae)

- Incubation 3 – 4 days
- Prodrome - fever
- Diarrhoea for 1 week (1 day to 1 month)
- Can be severe – “dysentery”
- Complications include:

  bacteraemia, septicaemia, pneumonia, keratoconjunctivitis, arthrirtis, Reiter’s syndrome in HLAB27+ individuals

Shigella and dysenteric diarrhoea

Major cause of dysenteric diarrhoea

Kotloff et al (1999) Bull WHO

Estimated 1.1 million deaths p.a.
61% are in those under age 5
S. flexeneri most common in developing countries
S. sonnei most common in industrialised countries

Dysenteric diarrhoea responds less well to ORT and risk of death with dysenteric vs watery diarrhoea 2-7x

Cholera

- Contaminated water / food
- Pandemic in developing world with epidemics
- Toxin mediated from 01 & 0139 serotypes of *Vibrio cholerae*
- Incubation 3 – 4 days
- Mild to severe
- Profuse watery stool – “rice water”
- Shock
- Not fever
- Diagnosis
  - Comma-shaped darting bacteria
  - Slide agglutination for 01 & 0139 serotypes
  - Antibody detection

Viral diarrhoeal disease

Organisms

- Rotavirus
- Enteric adenoviruses
- Caliciviruses
- Small round viruses
- Small round structured viruses (SRSVs) (Norwalk)
- Coronaviruses (Hep A & E)

Rotavirus

- Commonest viral gastroenteritis in children
- Important cause of mortality in developing world
- About 40% of hospitalisations with diarrhoea in SSA are with rotavirus
- Incubation 24 hours
- Lasts 2 – 4 days

Interventions to treat disease

UNICEF/WHO Package of interventions

Treatment

- Fluids including ORS
- Zinc

Prevention

- Promotion of breast feeding with Vit A supplements
- Promotion of handwashing
- Vaccination for rotavirus and measles
- Improved water supply and quality
- Improved community sanitation

ORS

	Original oral rehydration solution[8]	Low osmolarity oral rehydration solution[7]
Glucose	111	75
Sodium	90	75
Chloride	80	65
Potassium	20	20
Citrate	30	10
Total osmolarity (mOsm/L)	331	245

Data are mmol/L unless otherwise stated.

Table: Composition of original and low-osmolarity WHO oral rehydration solution

20% reduction in stool output
30% reduction in vomiting
40% reduction in need for unscheduled IV treatment

Low osmolality ORS now recommended

From Santosham et al LID 10

Evidence for impact of ORS solutions?

Egypt

- Between 1980 and 1991 Decline of 76% in diarrhoeal death rate in absence of change in diarrhoeal incidence and more modest reduction in non-diarrhoeal deaths

Brazil

- Between 1980 and 1990 under 5 mortality due to diarrhoea fell by 67% whilst non-diarrhoeal mortality fell by 32%

Formulation changed in 2002 with aim of improving outcome

Zinc: evidence for impact

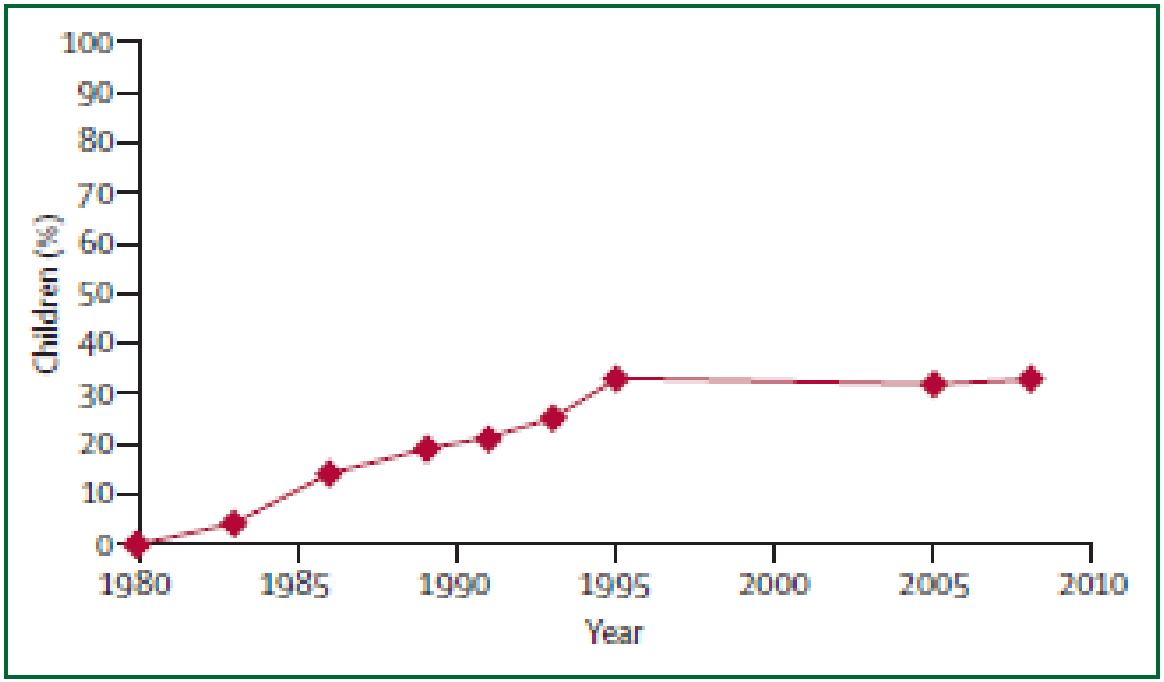
- Reduces duration of episodes of both acute and chronic diarrhoea

- Reduces risk of recurrence in next 2-3 months

- When introduced to community programmes, increased uptake of ORS

- Overall approximately 50% reduction in mortality

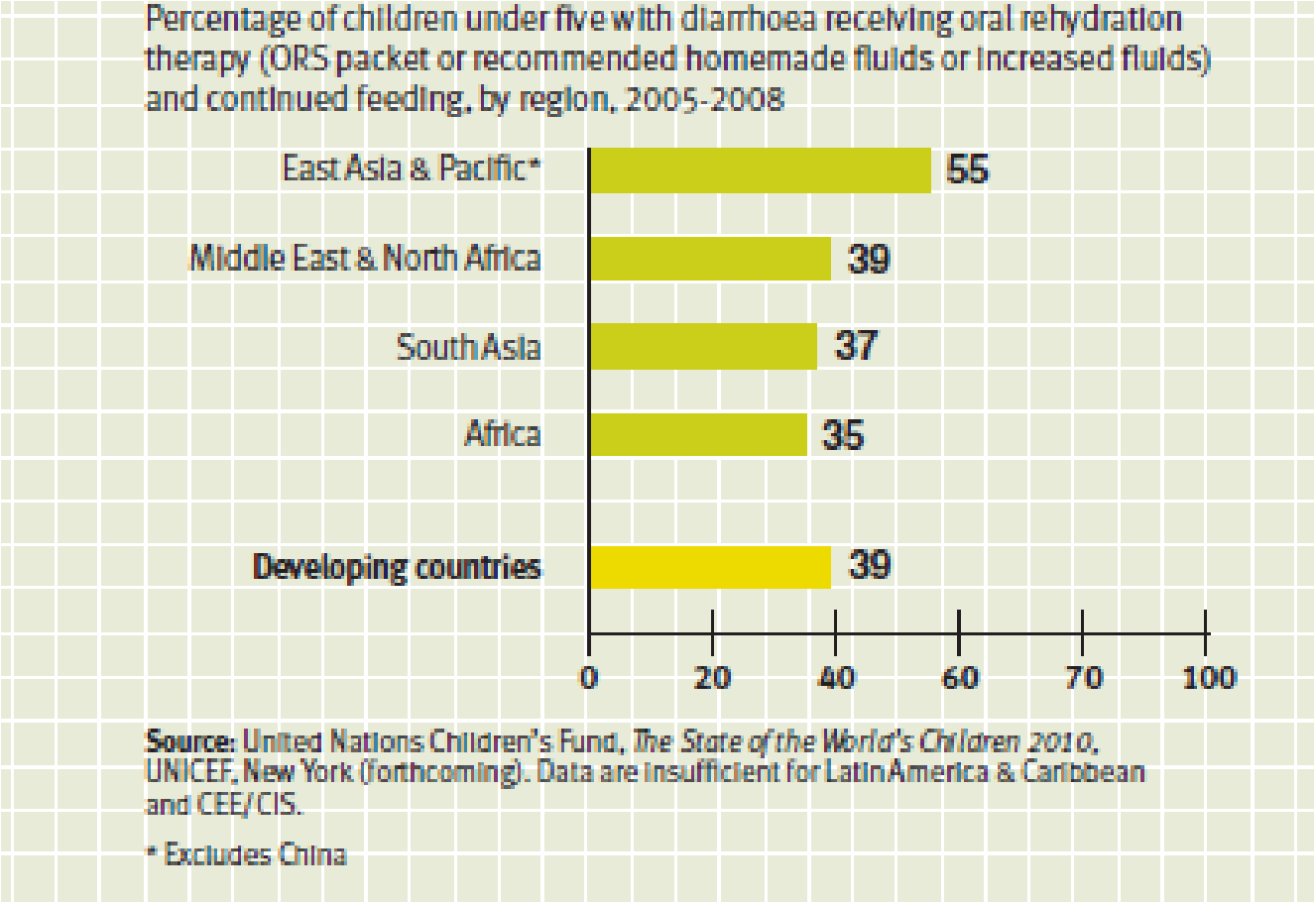
Oral rehydration solution: uptake



% children under 5 with diarrhoeal disease who receive ORS

From Santosham et al LID 10

ORS



Source: UNAIDS 2011

Oral rehydration solution: uptake

Possibly hampered by introduction in to ICMI

Less specific funding

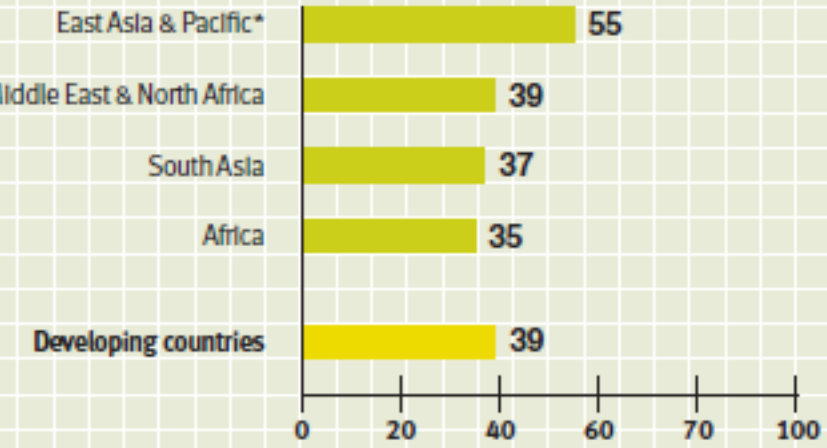
Changes to definition of what was considered acceptable fluid schedule

Similarly, challenges to zinc use

- often not procured, or given in package of care
- lack of awareness of its potential benefits

From Santosham et al LID 10

Percentage of children under five with diarrhoea receiving oral rehydration therapy (ORS packet or recommended homemade fluids or increased fluids) and continued feeding, by region, 2005-2008



Source: United Nations Children's Fund, *The State of the World's Children 2010*, UNICEF, New York (forthcoming). Data are insufficient for Latin America & Caribbean and CEE/CIS.

* Excludes China

Improving the product to increase uptake

Better flavours (no longer a concern that might od with newer Formulations

More convenient packaging/dosing, bundling with zinc

Better distribution (e.g. schools, community workers)

Interventions to prevent disease

Interventions to reduce diarrhoeal disease

Vaccination

Breast feeding

Water provision and water quality

Hygiene and Sanitation

Rotavirus vaccination

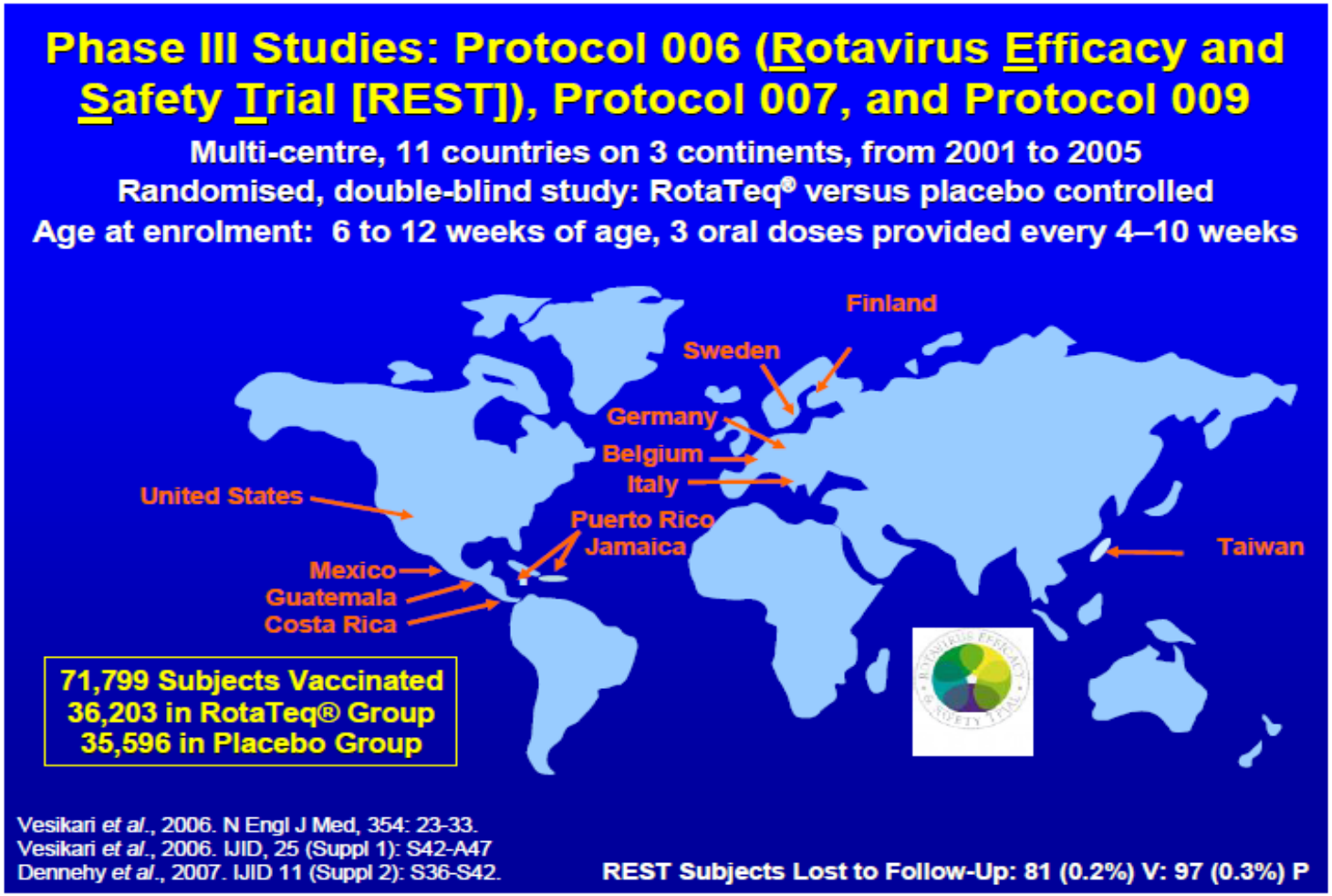
Characteristics of RotaTeq®

- Oral pentavalent vaccine suspended in a liquid buffer/stabilizer.
- Administered directly from tube.
- 3-dose regimen that integrates into pre-established immunization schedules:
  - First dose age 6 to 12 weeks
  - Subsequent doses at 1 to 2 month intervals
- Concomitant use: DTaP, DTwP, Hep B, Hib, IPV, Prevnar [1,2], OPV [3], Hexavalent (T-3Q08) [4], Meningococcal C conjugate (T-3Q08) [5]
- Contains 5 human-bovine reassortants:
  - G serotypes - human G1, G2, G3, G4, and bovine G6
  - P serotypes – human P1A[8] and bovine P7[5]

1 Vesikari *et al*., 2006. N Engl J Med, 354: 23-33.
2 Rodriguez et al., 2007. PIDJ, 26: 221-227
3 Ciarlet et al., PIDJ, in press.
4 Ciarlet et al., submitted PIDJ
5 Results to be presented at EAP, Oct 2008.

Source : Ciarlet , Merck

Rotavirus vaccination: landmark study



Source : Ciarlet , Merck

Rotavirus vaccination: landmark study

	Phase II		Phase III	
Study Protocol Composition; subject number	002 G1-3,P1A (n = 370)[1]	005 G1-4,P1A (n = 499)[2]	REST 006 G1-4,P1A (n=4,512)[3]	007 G1-4,P1A (n=1,115)[4]
Severe RGE % Efficacy (95% CI)	100% (44-100)	100% (35-100)	98% (88-100)	100% (13-100)
Any RGE % Efficacy (95% CI)	75% (50-88)	74% (38-91)	74% (67-80)	73% (51-86)

Efficacy measured from 14 days after the third dose.

RGE cases with score >16/24 by Clark severity scale based on the intensity and duration of symptoms (fever, vomiting, diarrhoea, and behavioural changes).

1. Clark *et al.*, 2004. J Pediatr, 144: 184-190.
2. Vesikari *et al.*, 2006. Vaccine, 24: 4821-4829.
3. Vesikari *et al.*, 2006. N Engl J Med, 354: 23-33.
4. Block *et al.*, 2007. Pediatrics, 119: 11-18.

Source : Ciarlet , Merck

Rotavirus vaccination

2006 WHO: advocated use of licensed rotavirus vaccine in Europe and Americas

Greater efficacy data needed from regions of greatest burden, particularly SSA and SE Asia

Two recent papers published on efficacy

Rotavirus vaccination: Efficacy in Africa

Armah et al 2010

Design: Multicentre placebo controlled trial (Ghana, Kenya, Mali)

Subjects: 5468 infants randomised 1:1 vaccine (3 doses)/placebo

HIV positive not excluded, given with EPI schedule

Primary endpoint: severe GE (Vesikari >=11) 14 days after final dose

Source : Armah et al 2010

Rotavirus vaccination

	Pentavalent rotavirus vaccine			Placebo			Vaccine efficacy, % (95% CI)	Rate reduction* (95% CI)
	Cases (n)	Person-years	Incidence*	Cases (n)	Person-years	Incidence*		
Entire study period (14 days after third dose to end of follow-up)†								
Overall	79	2610·6	3·0	129	2585·9	5·0	39·3% (19·1 to 54·7)‡	2·0 (0·9 to 3·1)
Ghana	26	1074·1	2·4	57	1048·8	5·4	55·5% (28·0 to 73·1)	3·0 (1·4 to 4·8)
Kenya	5	505·6	1·0	14	510·4	2·7	63·9% (−5·9 to 89·8)	1·8 (0·1 to 3·7)
Mali	48	1031·0	4·7	58	1026·6	5·6	17·6% (−22·9 to 45·0)	1·0 (−1·0 to 3·0)
First year of life (14 days after third dose to age 365 days)								
Overall	21	1420·0	1·5	58	1402·5	4·1	64·2% (40·2 to 79·4)	2·7 (1·5 to 4·0)
Ghana	15	558·0	2·7	42	547·6	7·7	65·0% (35·5 to 81·9)	5·0 (2·4 to 7·9)
Kenya	2	300·7	0·7	12	299·1	4·0	83·4% (25·5 to 98·2)	3·3 (1·1 to 6·4)
Mali	4	561·2	0·7	4	555·8	0·7	1·0% (−431·7 to 81·6)	0·0 (−1·2 to 1·2)
Second year of life (age 366–730 days)								
Overall	57	1305·9	4·4	70	1289·1	5·4	19·6% (−15·7 to 44·4)	1·1 (−0·6 to 2·8)
Ghana	11	584·5	1·9	15	562·9	2·7	29·4% (−64·6 to 70·7)	0·8 (−1·0 to 2·7)
Kenya	3	219·4	1·4	2	226·3	0·9	−54·7% (−1752·7 to 82·3)	−0·5 (−3·2 to 2·0)
Mali	43	502·1	8·6	53	499·9	10·6	19·2% (−23·1 to 47·3)	2·0 (−1·8 to 6·0)

Per-protocol analyses excluded participants who received fewer than three doses, incorrectly received vaccine and placebo, had no follow-up, or had laboratory-confirmed naturally occurring rotavirus before the start of the efficacy follow-up period. Participants whose classification could not be established because of incomplete clinical or laboratory data or with stool samples obtained out of day range were not assessed. *Per 100 person-years. †There was follow-up beyond the second year of life, although no cases were reported. Two participants (one in the vaccine group and one in the placebo group) in Mali had severe rotavirus gastroenteritis after day 366 of life that were counted as cases in the analysis of the entire study follow-up period but not in the analysis within the second year of life. This exclusion was because participants had laboratory-confirmed naturally occurring rotavirus 14 days after third dose, but before the second year of life. Cases were excluded if they had laboratory-confirmed naturally occurring rotavirus before the start of the efficacy follow-up period. For the entire study follow-up period analysis, the term before was defined as any time up to 14 days after third dose; for the within the second year of life analysis, before was any time up to day 366. ‡p=0·0003 for efficacy greater than 0%.

Table 3: **Efficacy of the pentavalent rotavirus vaccine for prevention of severe rotavirus gastroenteritis (Vesikari score ≥11) in Africa by country and follow-up period**

Source : Armah et al 2010

Rotavirus vaccination: Efficacy in Asia

Zaman et al 2010

Design: Multicentre placebo controlled trial (Bangladesh,Vietnam)

Subjects: 2036 infants randomised 1:1 vaccine (3 doses)/placebo

Primary endpoint: severe GE (Vesikari >=11) 14 days after final dose

Source : Zaman et al 2010

Rotavirus vaccination: Efficacy in Asia

	Pentavalent rotavirus vaccine			Placebo			Vaccine efficacy, % (95% CI)	Rate reduction* (95% CI)
	Cases (n)	Person-years	Incidence*	Cases (n)	Person-years	Incidence*		
Entire study period (14 days after third dose to end of follow-up)†								
Overall	38	1197·3	3·2	71	1156·9	6·1	48·3% (22·3 to 66·1)‡	3·0 (1·2 to 4·8)
Bangladesh	33	712·1	4·6	56	692·1	8·1	42·7% (10·4 to 63·9)	3·5 (0·8 to 6·2)
Vietnam	5	485·2	1·0	15	464·7	3·2	63·9% (7·6 to 90·9)	2·2 (0·4 to 4·4)
First year of life (14 days after third dose to age 365 days)								
Overall	19	605·9	3·1	38	594·3	6·4	51·0% (12·8 to 73·3)	3·3 (0·8 to 5·9)
Bangladesh	17	345·6	4·9	31	342·4	9·1	45·7% (−1·2 to 71·8)	4·1 (0·2 to 8·4)
Vietnam	2	260·3	0·8	7	251·9	2·8	72·3% (−45·2 to 97·2)	2·0 (−0·4 to 5·1)
Second year of life (age 366–730 days)								
Overall	19	586·4	3·2	33	555·6	5·9	45·5% (1·2 to 70·7)	2·7 (0·2 to 5·4)
Bangladesh	16	355·7	4·5	25	337·5	7·4	39·3% (−18·3 to 69·7)	2·9 (−0·7 to 6·9)
Vietnam	3	230·7	1·3	8	218·1	3·7	64·6 %(−47·7 to 93·9)	2·4 (−0·6 to 6·1)

Per-protocol analyses excluded participants who received fewer than three doses, incorrectly received vaccine and placebo, had no follow-up, or had laboratory-confirmed naturally occurring rotavirus before the start of the efficacy follow-up period. Participants whose classification could not be established because of incomplete clinical or laboratory data or with stool samples obtained out of day range were not assessed. *Per 100 person-years. †There was follow-up beyond the second year of life, although no cases were reported. ‡p=0·0005 for efficacy greater than 0%.

Table 3: **Efficacy of the pentavalent rotavirus vaccine for prevention of severe rotavirus gastroenteritis (Vesikari score ≥11) in Asia by country and follow-up period**

Source : Zaman et al 2010

Scale up

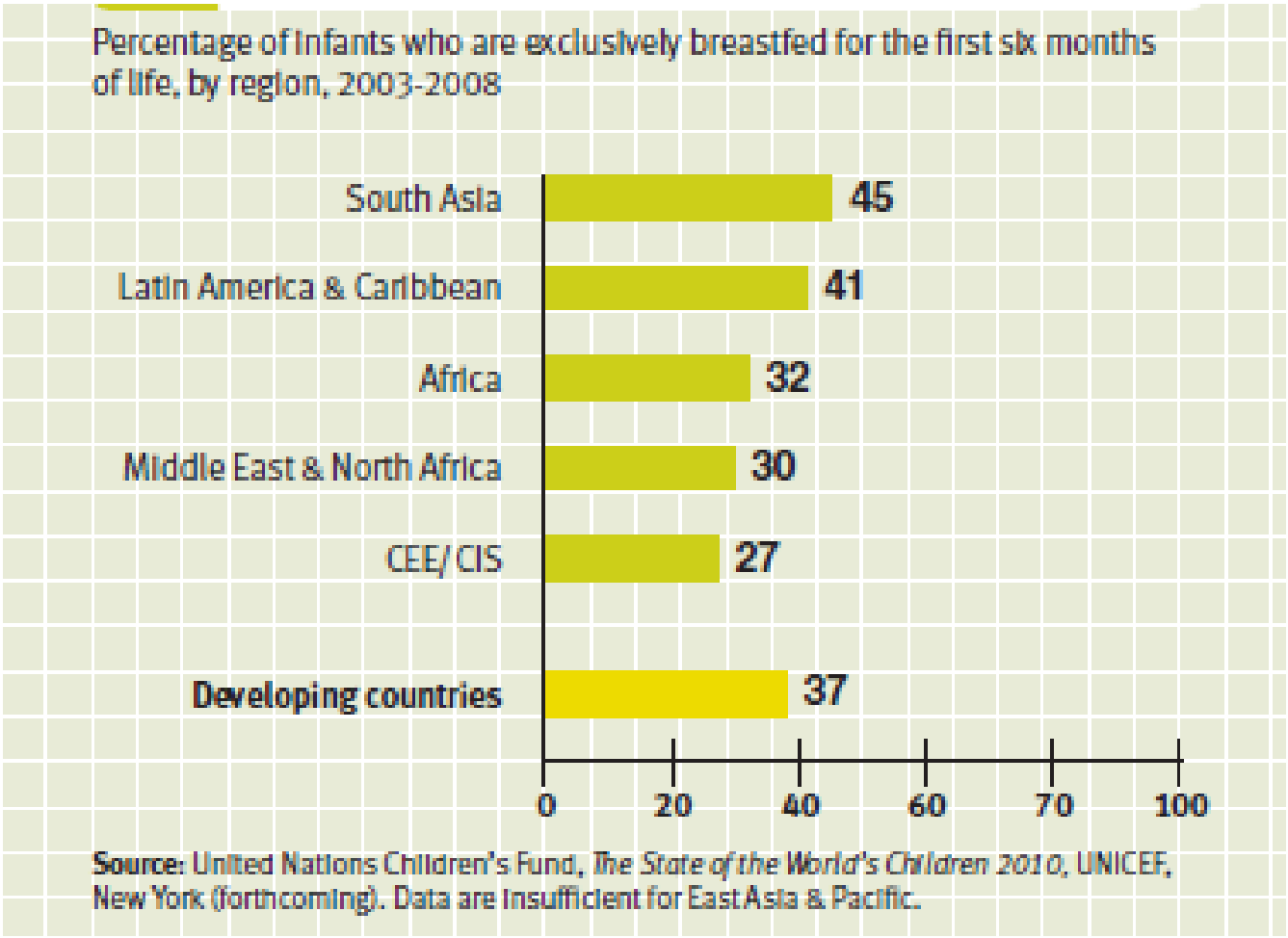
Desire to scale up vaccination

Needs innovations in cold chain supply

Concerns that it might jeapordise EPI

Source : Zaman et al 2010

Breastfeeding



Source: UNAIDS 2011

Other Interventions to reduce diarrhoeal disease

Water

- Improved provision of water or water supply at either household or community level
- Water quality – removal of microbes

Hygiene

- Hygiene and Health education and promotion (e.g.handwashing)
- Advice on handling pets

Sanitation

- Different methods of excreta disposal (particularly latrines)

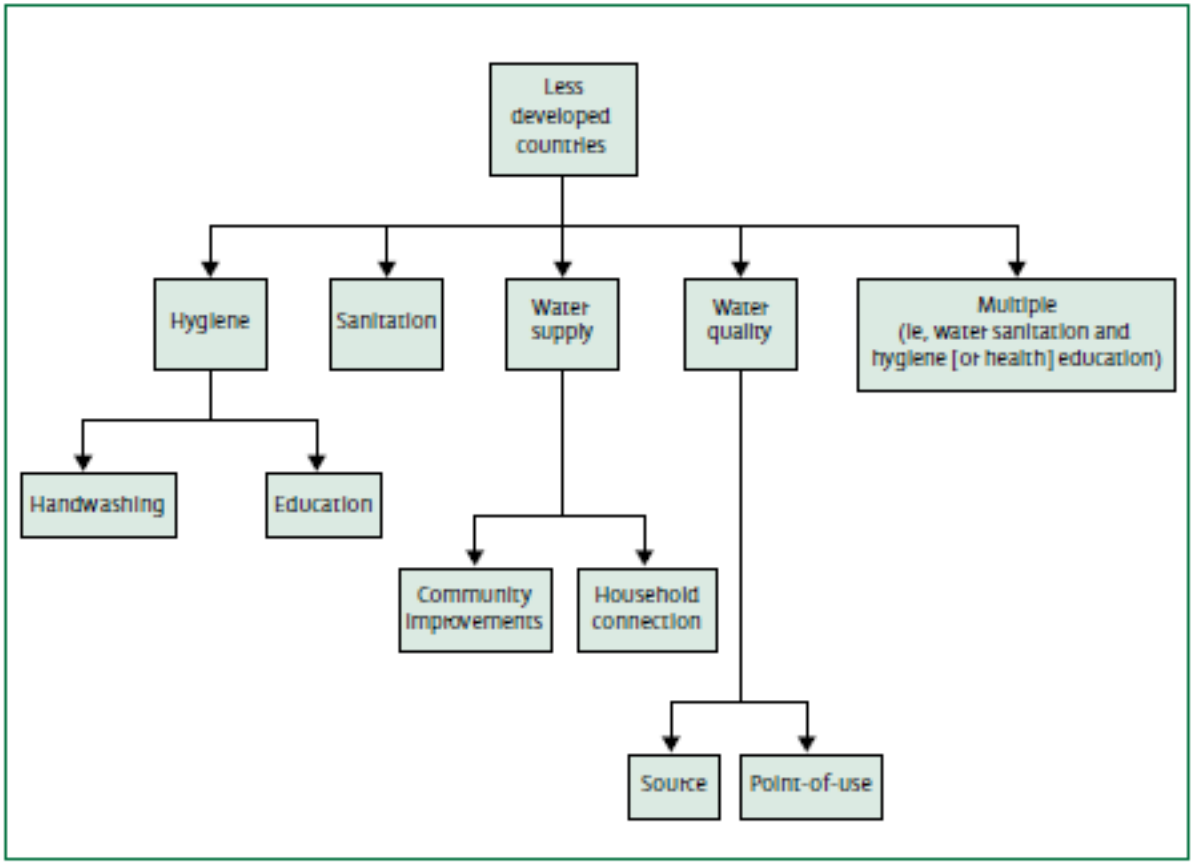


Figure 1: Intervention stratification

Fewtrell et al LID 2005

Water Supply Interventions

Zeng-sui et al Bull WHO (1989)

Setting: Rural China
Methodology: Case/control study
Period: June-October 1983
Subjects: 10290 intervention group, 9397 controls
Intervention: DWTW (deep well tap water)
Outcome measure: Enteric infectious diseases

Water Supply Interventions

Zeng-sui et al Bull WHO (1989)

Table 2: **Incidence of enteric infectious disease (EID) in the study and control regions, 1 June–31 October 1983**

	EID				
	Viral hepatitis A	Cholera	AWD[a]	Dysentery	Total
Study region:					
No. of cases	26	1	1816	83	1926
Incidence (per 1000)	2.5	0.1	176.5	8.1	187.2
Control region:					
No. of cases	88	8	2685	84	2865
Incidence (per 1000)	9.4	0.9	285.7	8.9	304.9
% reduction in study region	73.0	88.2	38.2	—	38.6
Statistical significance[b]	<0.001	0.02	<0.001	>0.05	<0.001

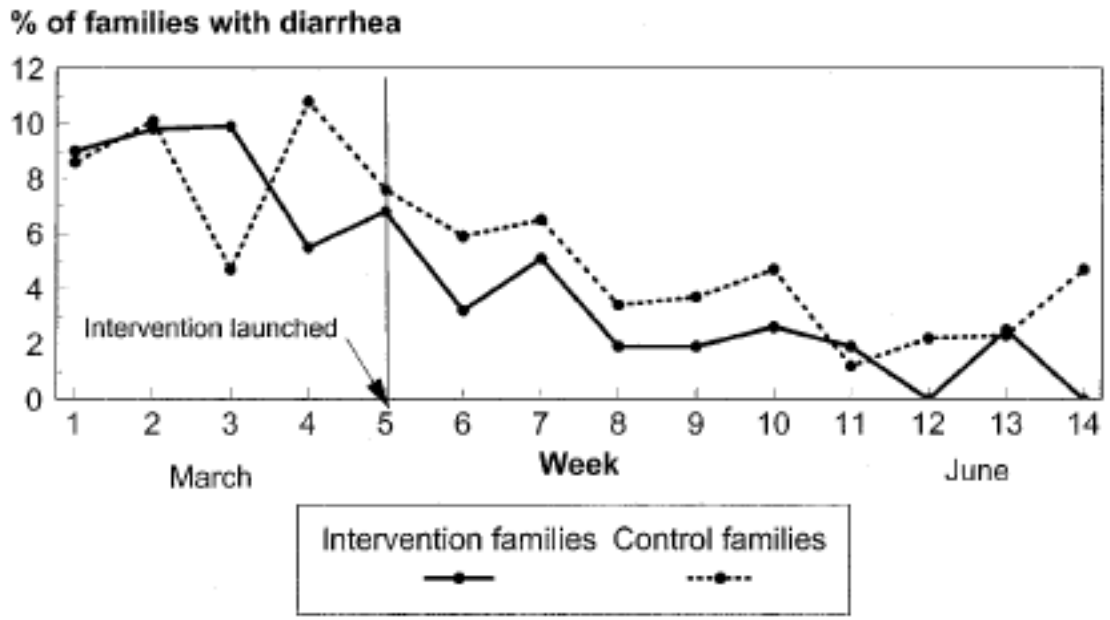
Water Quality Interventions

Quick et al (2002)

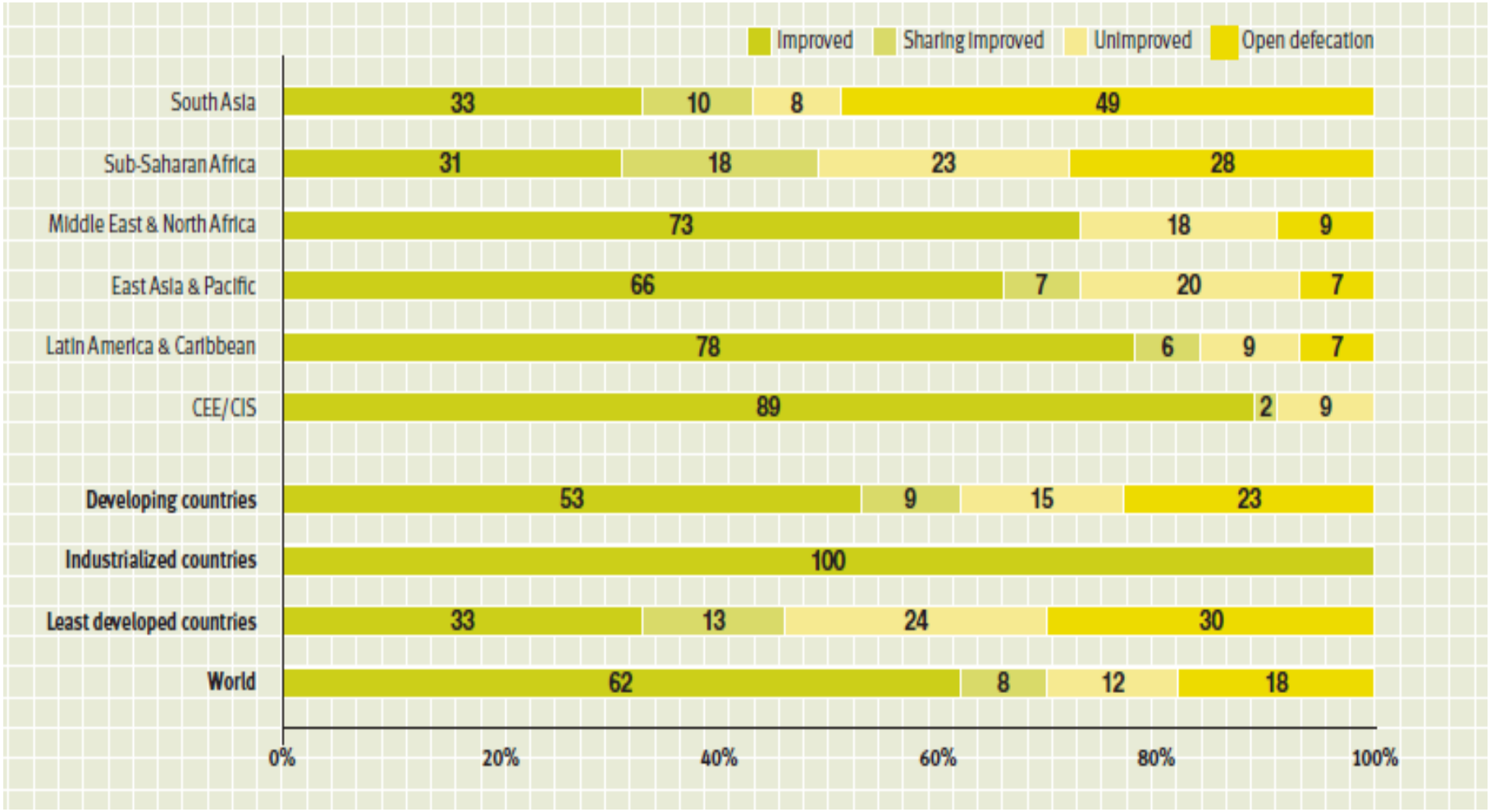
Setting: Periurban (Kitwe, Zambia)
Methodology: Case-control household intervention
Period: April-June 1999
Subjects: 260 households (1584 persons)
Intervention: (1) point of use sterilisation with hypochlorite, (2) durable plastic storage bottles, (3) community education
Outcome measure: Episodes of diarrhoea

Limitations: non-randomised, field site contaminated by local enterprise

Water Quality Interventions



Sanitation remains a major global issue



Comparison of interventions

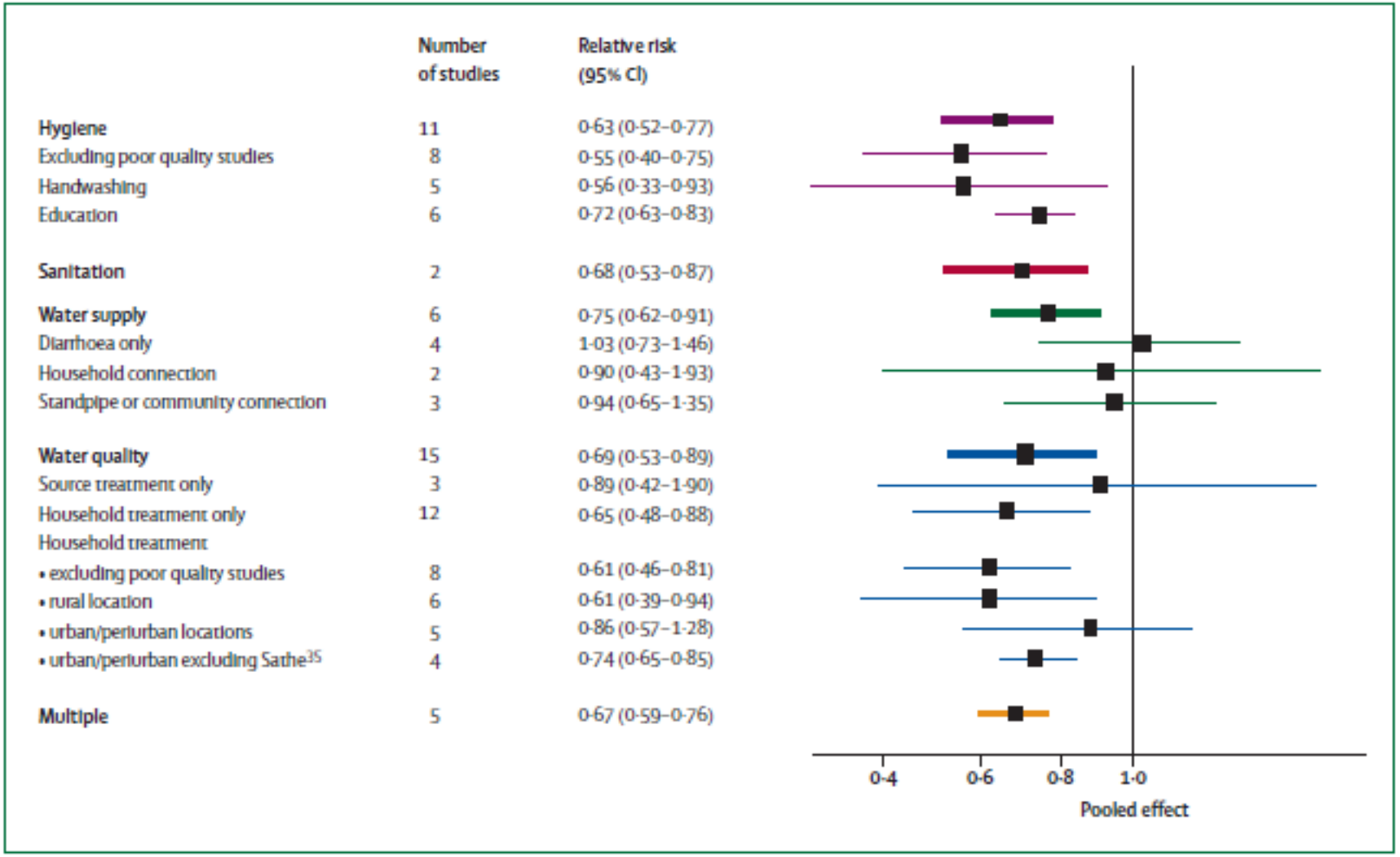


Figure 3: Summary of meta-analysis results

Fewtrell et al LID 2005

Climate change and diarrhoeal disease

Climate change and diarrhoeal disease

Factors potentially associated with diarrhoeal disease

- Weather; short terms trends in temperature and rainfall

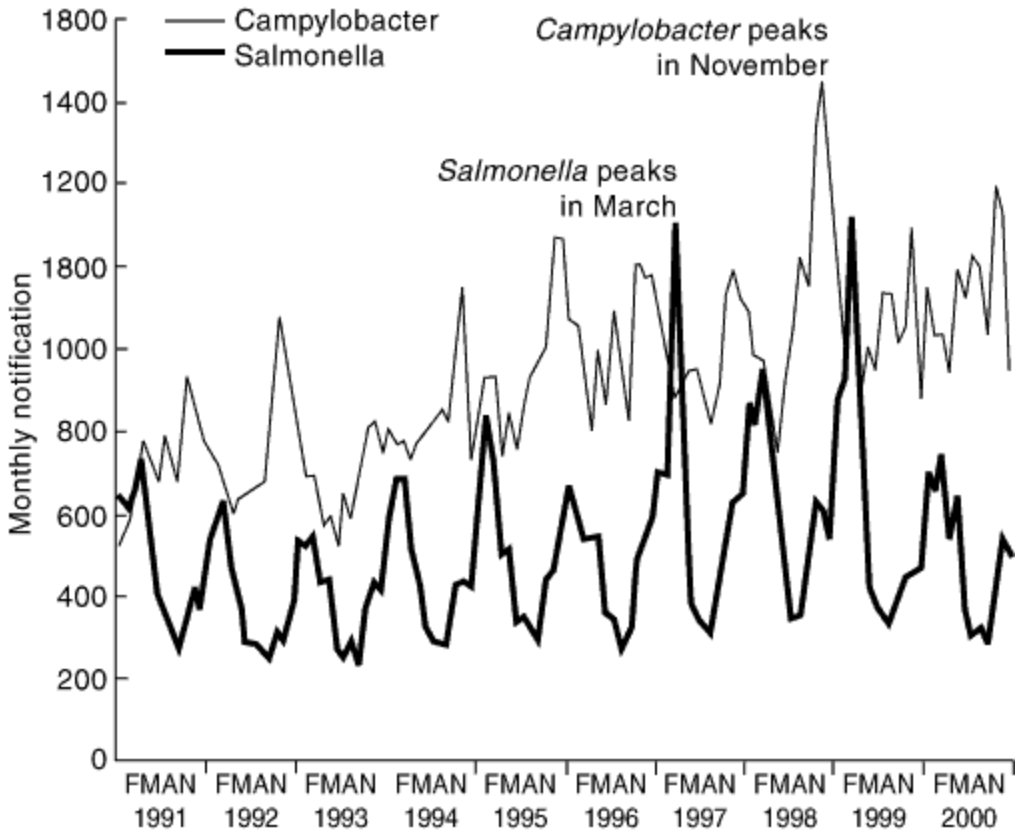
Methods: time-series analysis; weather exposure and outcome usually at one location

Use: early warning systems

- Climate; longer terms trends in climate

Methods: cross-sectional analysis,use of mean values over longer time periods; multilocational

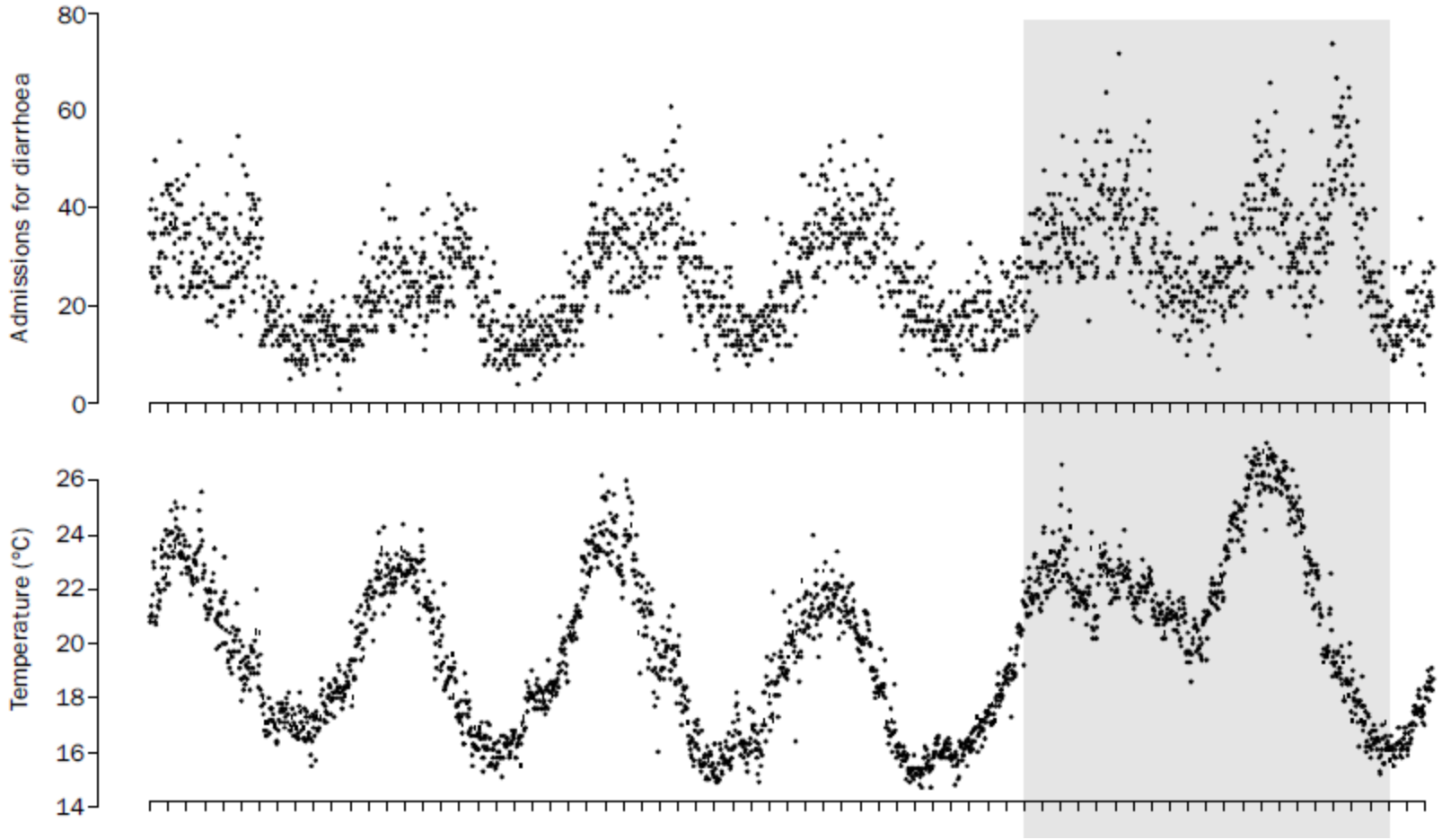
Use: Infrastructure planning



Imperial College London

Source : HPA

Short term association (El Nino, Peru)



Checkley Lancet 2000

Longer term association

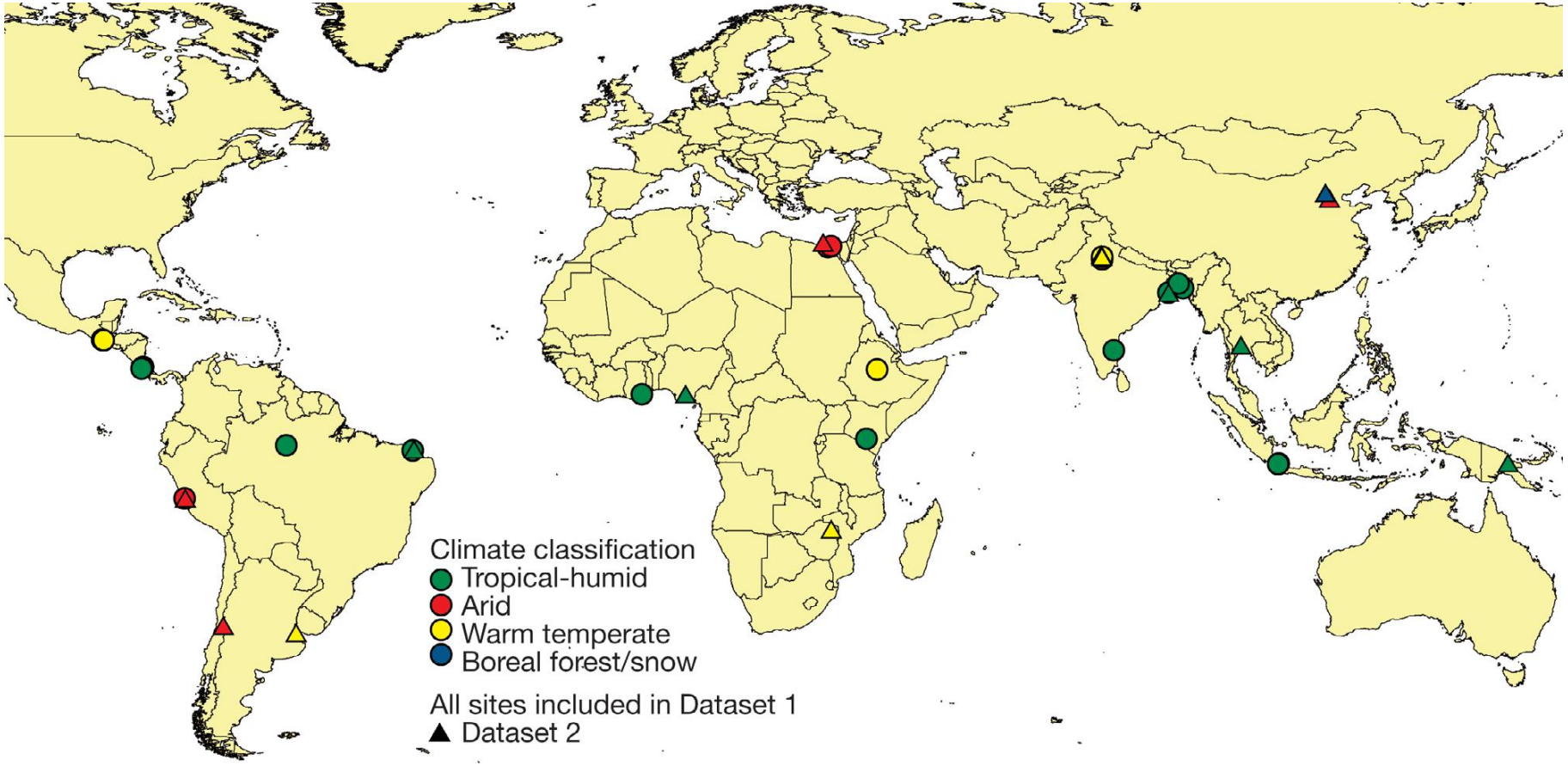
Methods: Global cross-sectional multi site study

Primary outcome: Age-specific all cause diarrhoeal morbidity in children under 5 years old

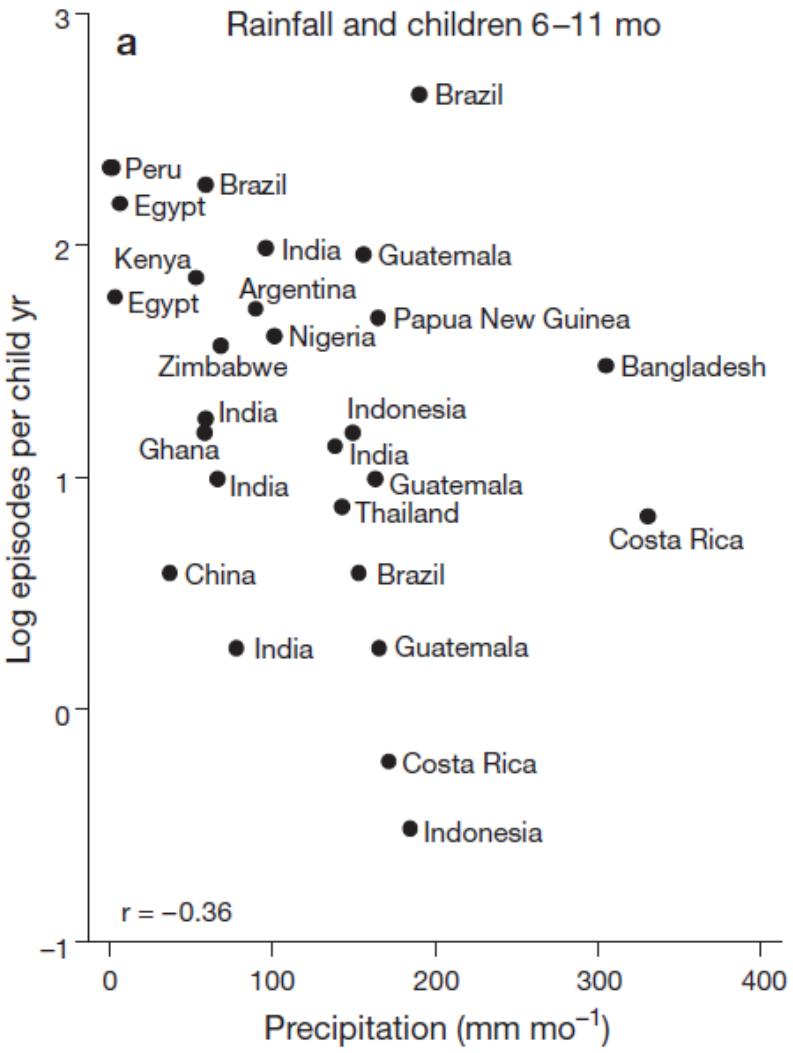
Exposures: mean monthly rainfall, mean temperature and climate type

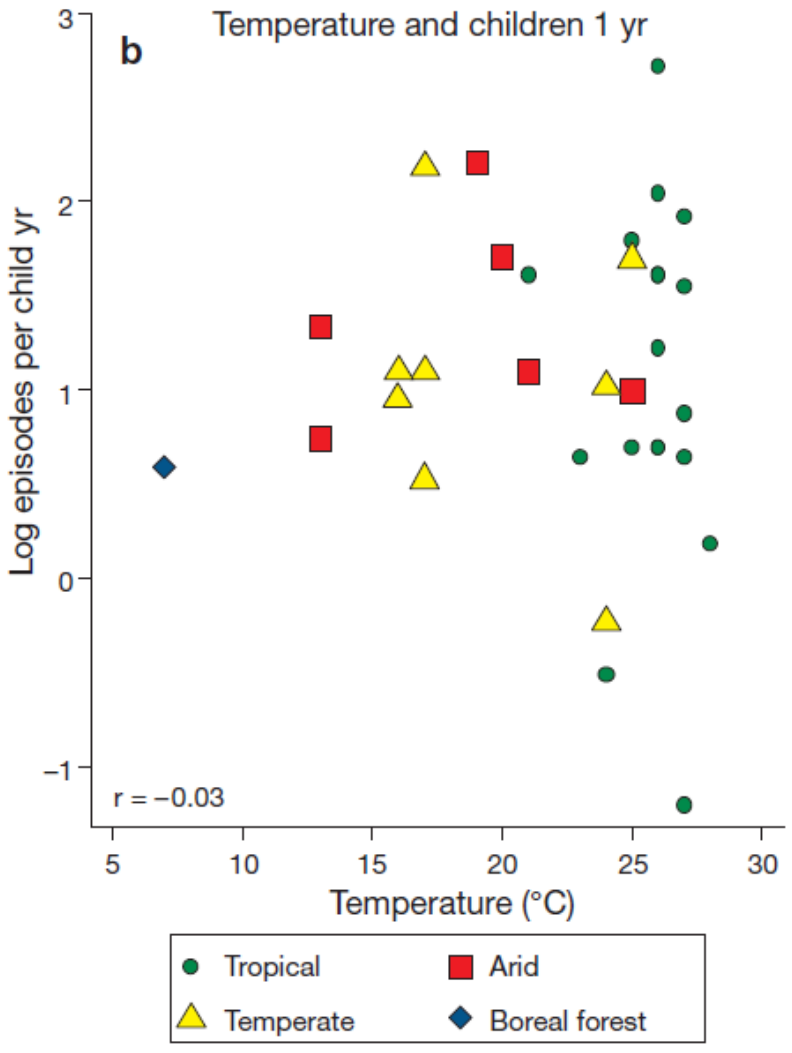
Lloyd et al 2007

Study sites and climate type



Outcomes


a
Rainfall and children 6–11 mo
Log episodes per child yr
Precipitation (mm mo^{-1})
r = −0.36
Brazil
Peru
Brazil
Egypt
India
Guatemala
Kenya
Argentina
Egypt
Papua New Guinea
Nigeria
Zimbabwe
Bangladesh
India
Indonesia
Ghana
India
India
Guatemala
Thailand
Costa Rica
China
Brazil
India
Guatemala
Costa Rica
Indonesia


b
Temperature and children 1 yr
Log episodes per child yr
Temperature (°C)
r = −0.03
Tropical
Arid
Temperate
Boreal forest

Concluded that

Studies of short term association between rainfall and diarrhoeal illness are inconclusive

Negative association between rainfall and diarrhoeal disease, possibly due to increased water scarcity

Didn’t see an impact of mean temperature

Suggested reading:

Diarrhoea: why children are still dying and what can be done (UNICEF/WHO 2010)

Bridging the gap from knowledge to delivery in the control of diarrhoea (Isanaka, Bull WHO 2012)

Questions