

Diarrhoeal disease: a major challenge to global health

BSc Global Health
18th October, 2011

Graham Cooke

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

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)

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'19 sensitivity analysis presents extreme upper and lower values for various inputs.

Table 1: Estimated numbers of deaths by cause in 2008

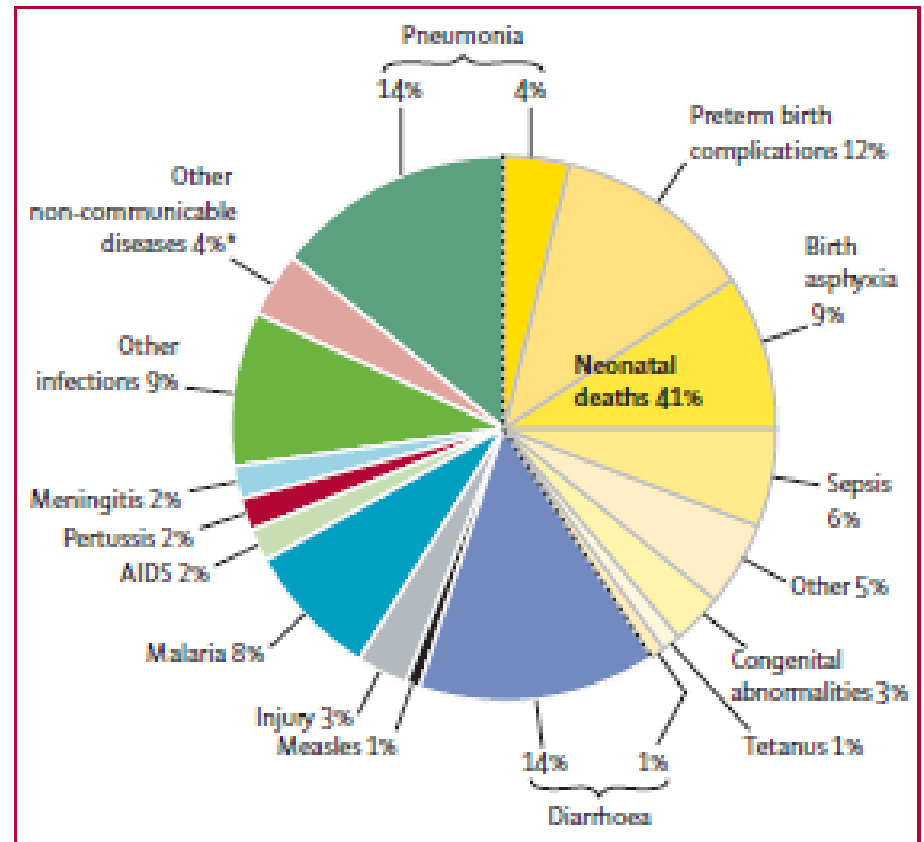
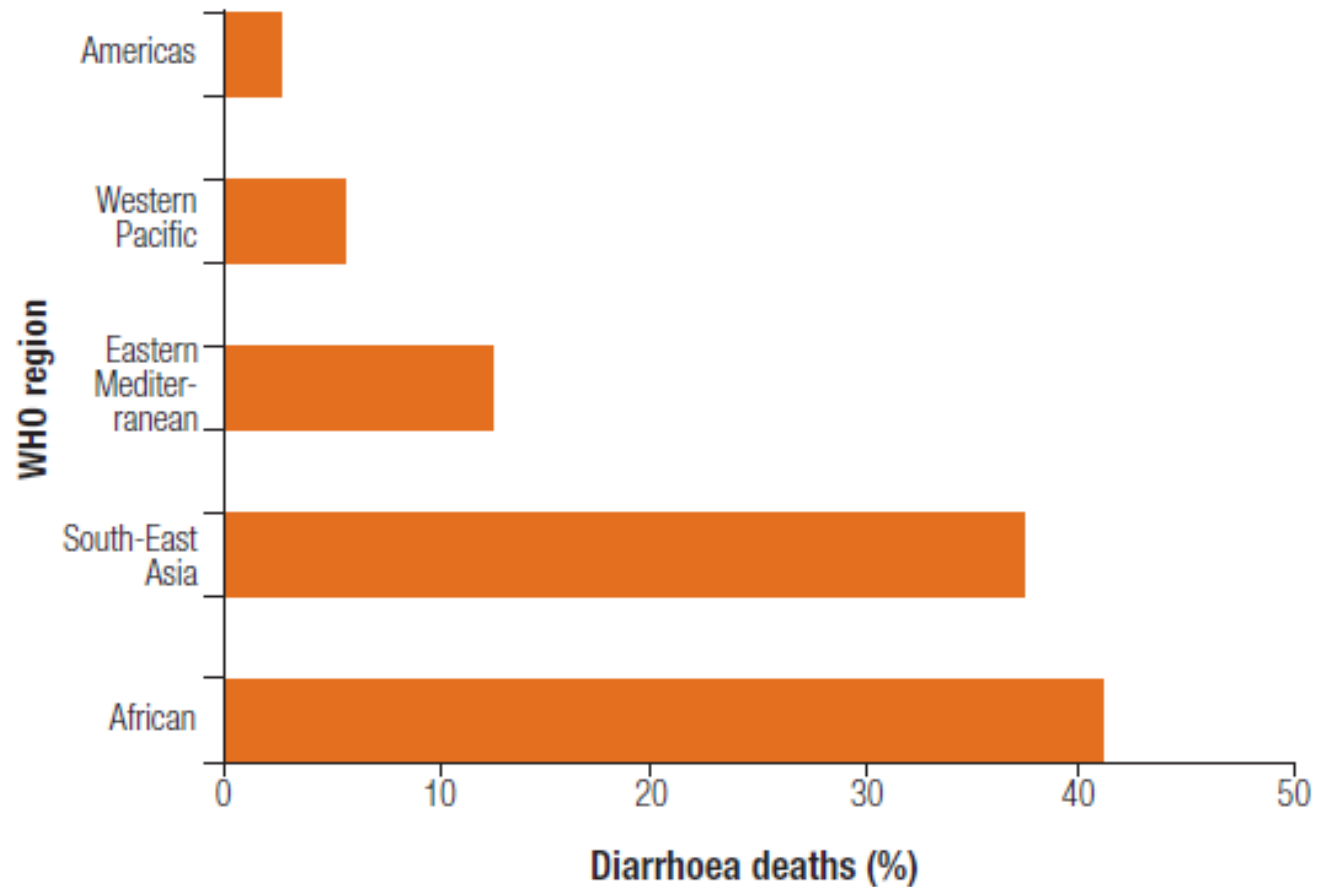


Figure 4: Global causes of child deaths

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.

Distribution of diarrhoeal deaths by WHO region



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 Mediter-ranean (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

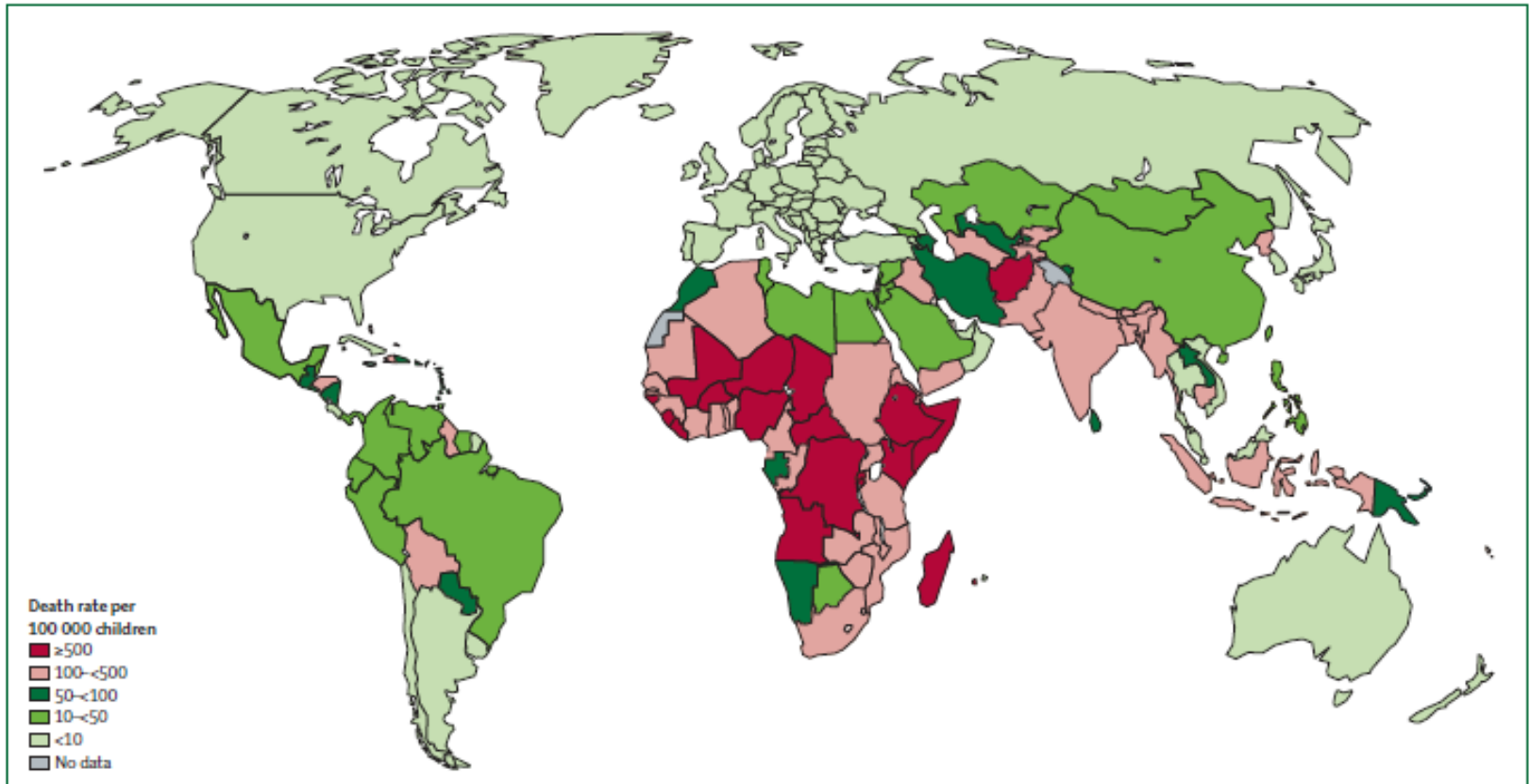


Figure 1: Deaths due to diarrhoea per 100 000 children younger than 5 years
Data from reference 1..

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, arthrititis,
 - 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. flexneri 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

Shigella and dysenteric diarrhoea

Table 5. Annual numbers of diarrhoea episodes and of *Shigella* episodes among older children and adults living in developing countries

	Age group			Total
	5–14 years	15–59 years	≥ 60 years	
Population	1 010 985 000	2 646 608 000	329 450 000	3 987 043 000
No. of diarrhoeal episodes per person per year ^a	0.65	0.50	0.69	NA ^b
Total number of diarrhoeal episodes	657 140 250	1 323 304 000	227 320 500	2 207 764 750
Annual number of diarrhoeal episodes:				
Reaching a treatment facility ^c	13 142 805	26 466 080	4 546 410	44 155 295
Remaining in domicile	643 997 445	1 296 837 920	222 774 090	2 163 609 455
Estimated % of diarrhoeal episodes attributed to <i>Shigella</i> :				
Reaching a treatment facility ^d	13.5	15.6	18.5	NA
Remaining in domicile ^e	2.0	2.0	2.0	NA
Annual number of <i>Shigella</i> diarrhoea episodes:				
Reaching a treatment facility	1 774 280	4 128 710	841 085	6 744 075
Remaining in domicile	12 879 950	25 936 760	4 455 480	43 272 190
Total	14 654 230	30 065 470	5 296 565	50 016 265

Shigella in children

Table 3. Proportion of diarrhoeal episodes in which *Shigella* was detected among children aged 1–4 years in three surveillance settings

Domicile				Outpatient treatment centre				Hospital			
Country	Years	Setting	No. of <i>Shigella</i> episodes/ total episodes	Country	Years	Setting	No. of <i>Shigella</i> episodes/ total episodes	Country	Years	Setting	No. of <i>Shigella</i> episodes/ total episodes
Chile (ref. 32)	1986–89	Urban	106/966 (11.0) ^a	Chile (ref. 32)	1986–89	Urban	138/1050 (13.0)	Chile (ref. 32)	1986–89	Urban	21/65 (32.0)
Bangladesh (ref. 51)	1978–79	Rural	68/364 (18.7)	Nigeria (ref. 43)	1984–85	Rural	121/826 (15.0)	Philippines (ref. 49)	1983–84	Urban	110/1152 (10.0)
Thailand (ref. 40)	1988–89	Urban	13/181 (7.2)	Bangladesh (ref. 46) ^b	1975–84	Rural	285/740 (39.0)	India (ref. 48)	1985–88	Urban	170/740 (23.0)
Egypt (ref. 41)	1981–83	Rural	35/636 (5.5)	Bangladesh (ref. 42)	1983–84	Rural	73/523 (14.0)	Islamic Republic of Iran (ref. 50)	1986–87	Urban	13/170 (8.0)
				Bangladesh (ref. 44) ^b	1979–80	Urban	379/1310 (29.0)				
				China, India, Mexico, Pakistan (ref. 98) ^b	1982–85	Urban	230/1004 (29.0)				
Median %			9.1				22.0				16.5

^a Figures in parentheses are percentages.

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

General supportive measures

ORS and zinc

Specific treatments; antibiotics

ORS

	Original oral rehydration solution ⁶	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

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

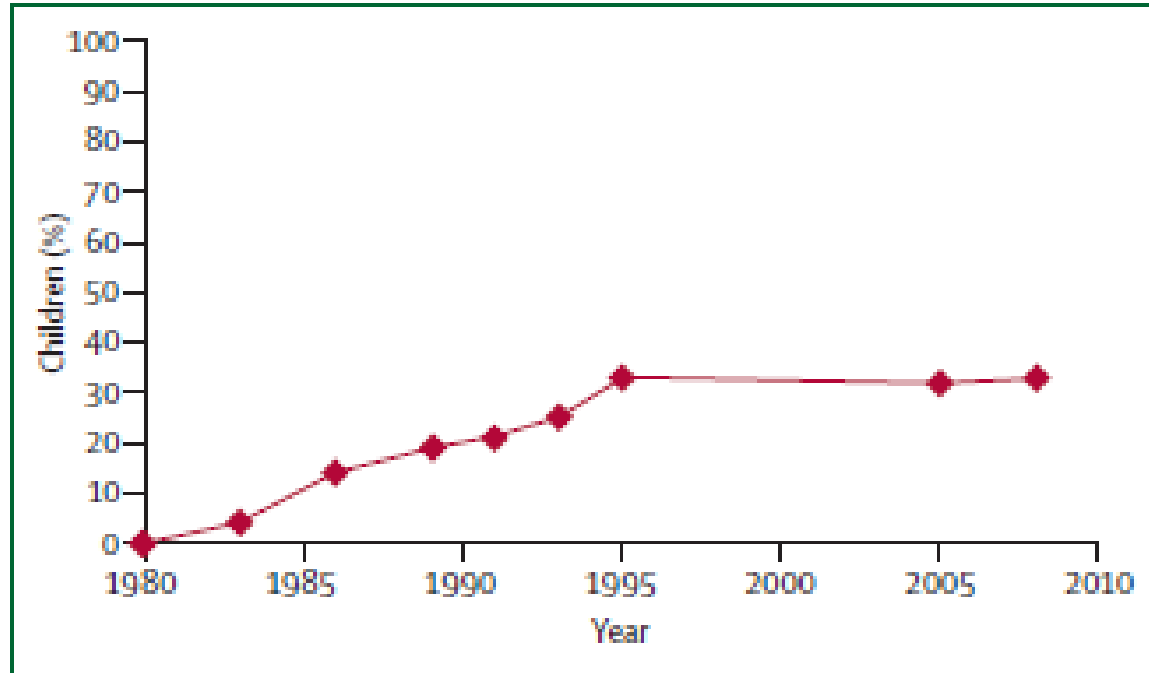
- Between 1980 and 1990 under 5 mortality due to diarrhoea fell by 67% whilst non-diarrhoeal mortality fell by 32%

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

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

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.



Rotavirus vaccination: landmark study

Phase III Studies: Protocol 006 (Rotavirus Efficacy and Safety Trial [REST]), Protocol 007, and Protocol 009

Multi-centre, 11 countries on 3 continents, from 2001 to 2005

Randomised, double-blind study: RotaTeq® versus placebo controlled

Age at enrolment: 6 to 12 weeks of age, 3 oral doses provided every 4–10 weeks



71,799 Subjects Vaccinated
36,203 in RotaTeq® Group
35,596 in Placebo Group

Vesikari *et al.*, 2006. *N Engl J Med*, 354: 23-33.
Vesikari *et al.*, 2006. *IJID*, 25 (Suppl 1): S42-A47
Dennehy *et al.*, 2007. *IJID* 11 (Suppl 2): S36-S42.

REST Subjects Lost to Follow-Up: 81 (0.2%) V: 97 (0.3%) P

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.

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

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% (-175.2 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

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

Rotavirus vaccination: Efficacy in Asia

	Pentavalent rotavirus vaccine			Placebo			Vaccine efficacy, % (95% CI)	Rate reduction* (95% CI)
	Cases (n)	Person-years	Incidence ^a	Cases (n)	Person-years	Incidence ^a		
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. ^aPer 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

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)

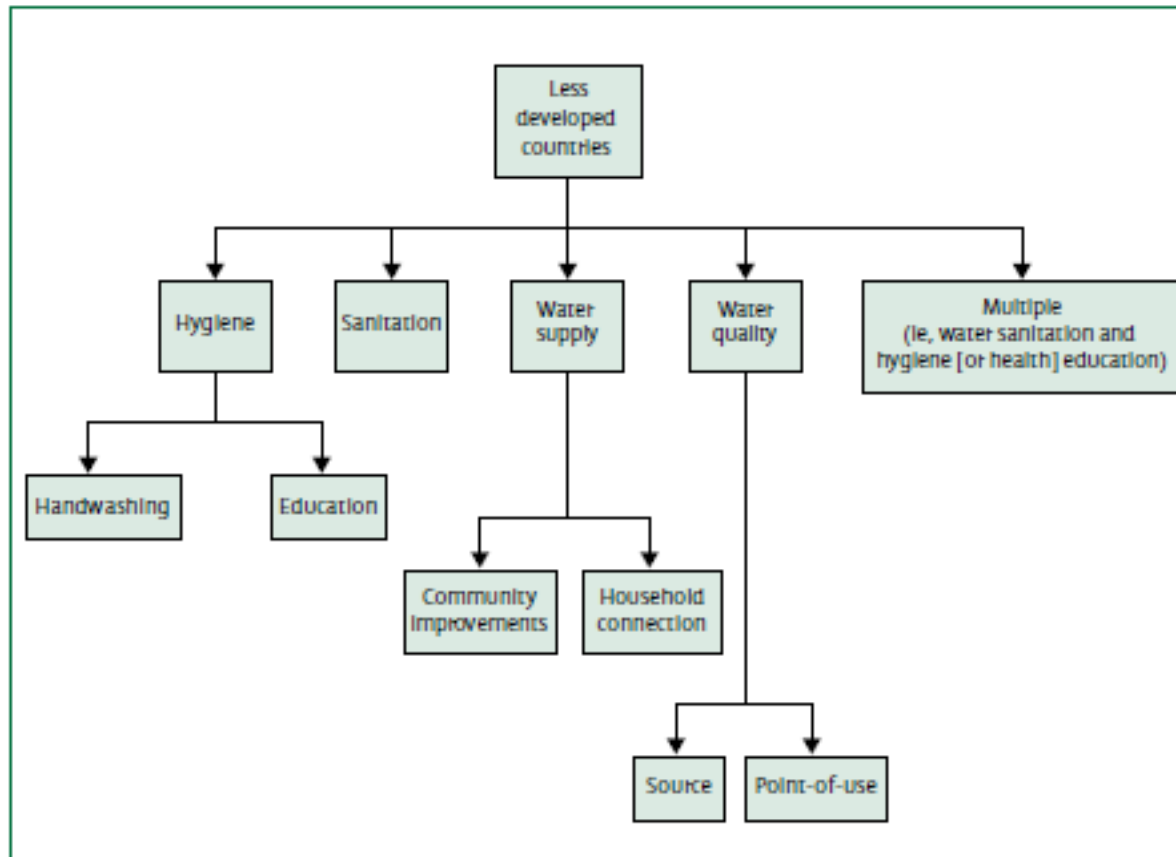


Figure 1: Intervention stratification

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				Total
	Viral hepatitis A	Cholera	AWD ^a	Dysentery	
<i>Study region:</i>					
No. of cases	26	1	1816	83	1926
Incidence (per 1000)	2.5	0.1	176.5	8.1	187.2
<i>Control region:</i>					
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

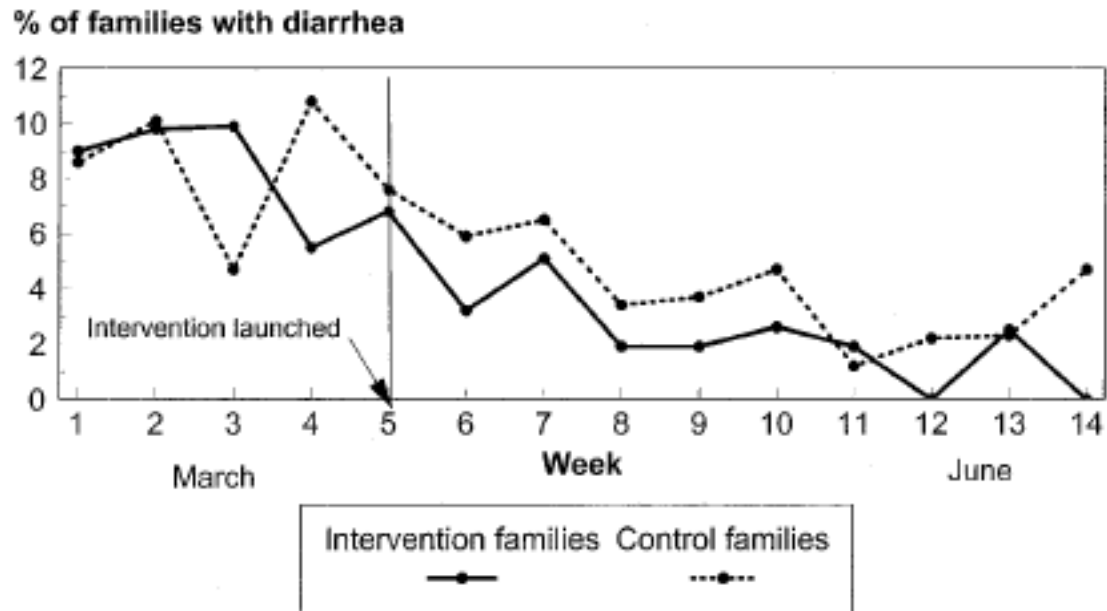
Subjects: 260 households (1584 persons)

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



Comparison of interventions

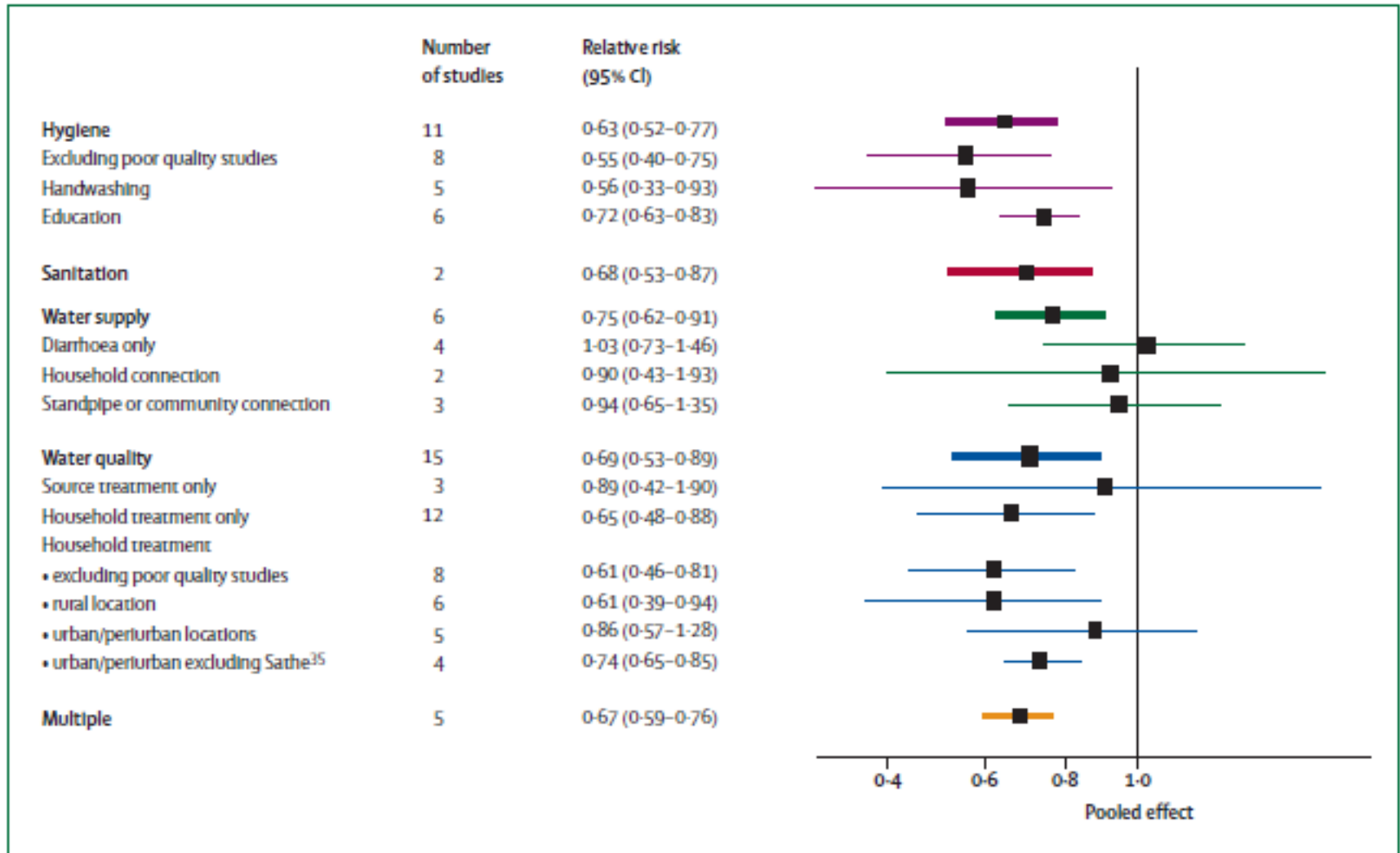


Figure 3: Summary of meta-analysis results

Climate change and diarrhoeal disease

Climate change and diarrhoeal disease

Factors potentially associated with diarrhoeal disease

- Weather; short terms trends in temperature and rainfall

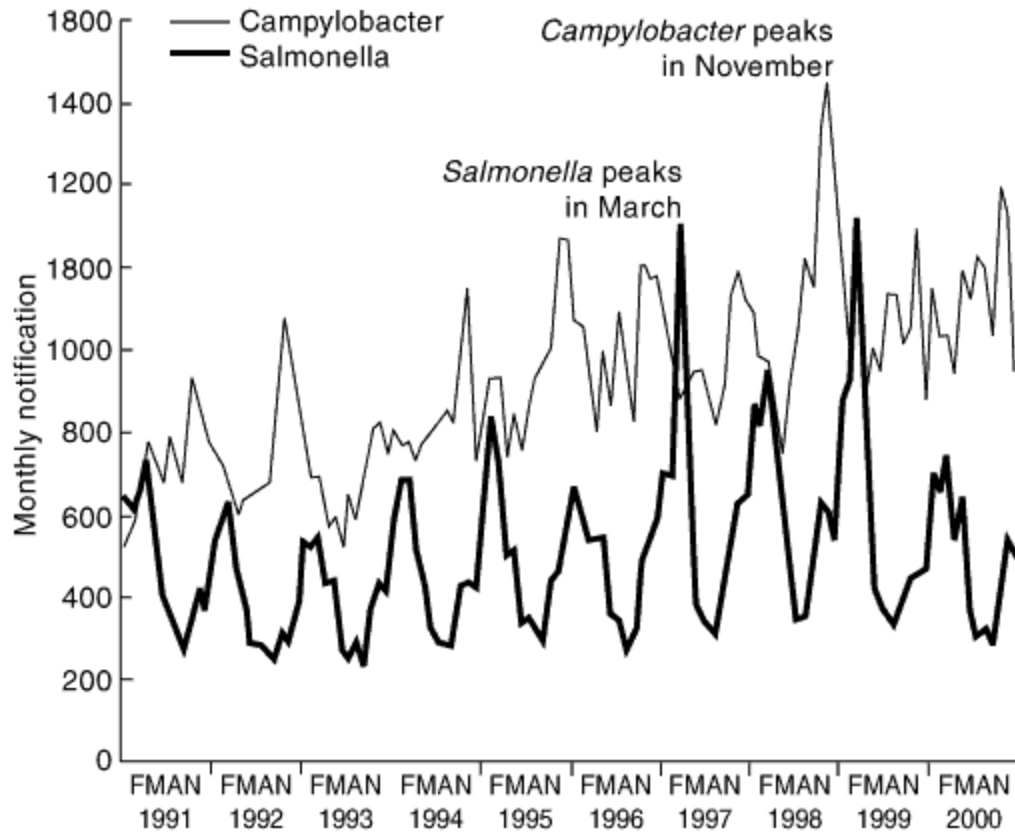
Methods: time-series analysis; weather exposure and outcome usually at one location

Use: early warning systems

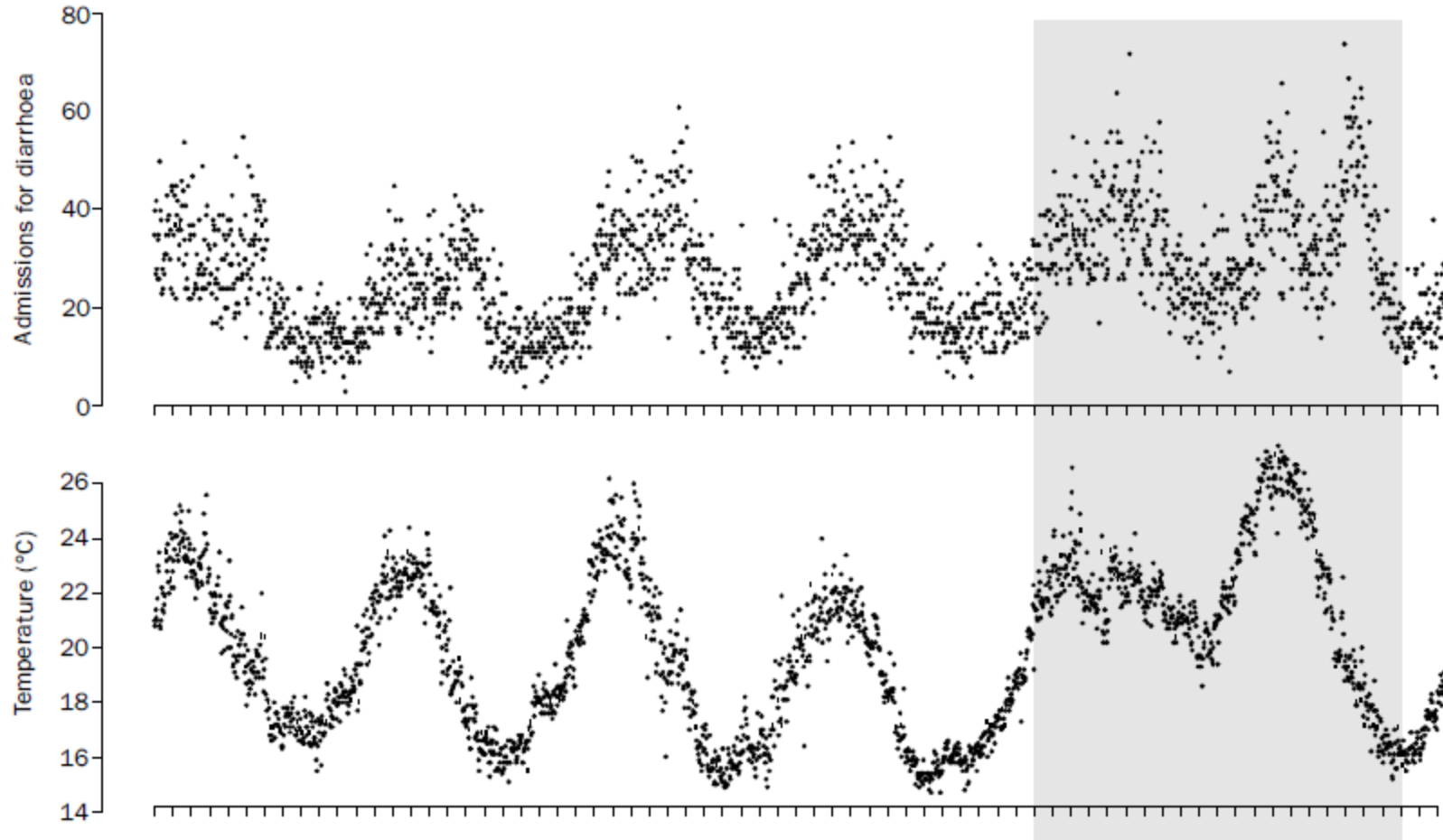
- Climate; longer terms trends in climate

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

Use: Infrastructure planning



Short term association (El Nino, Peru)



Longer term association

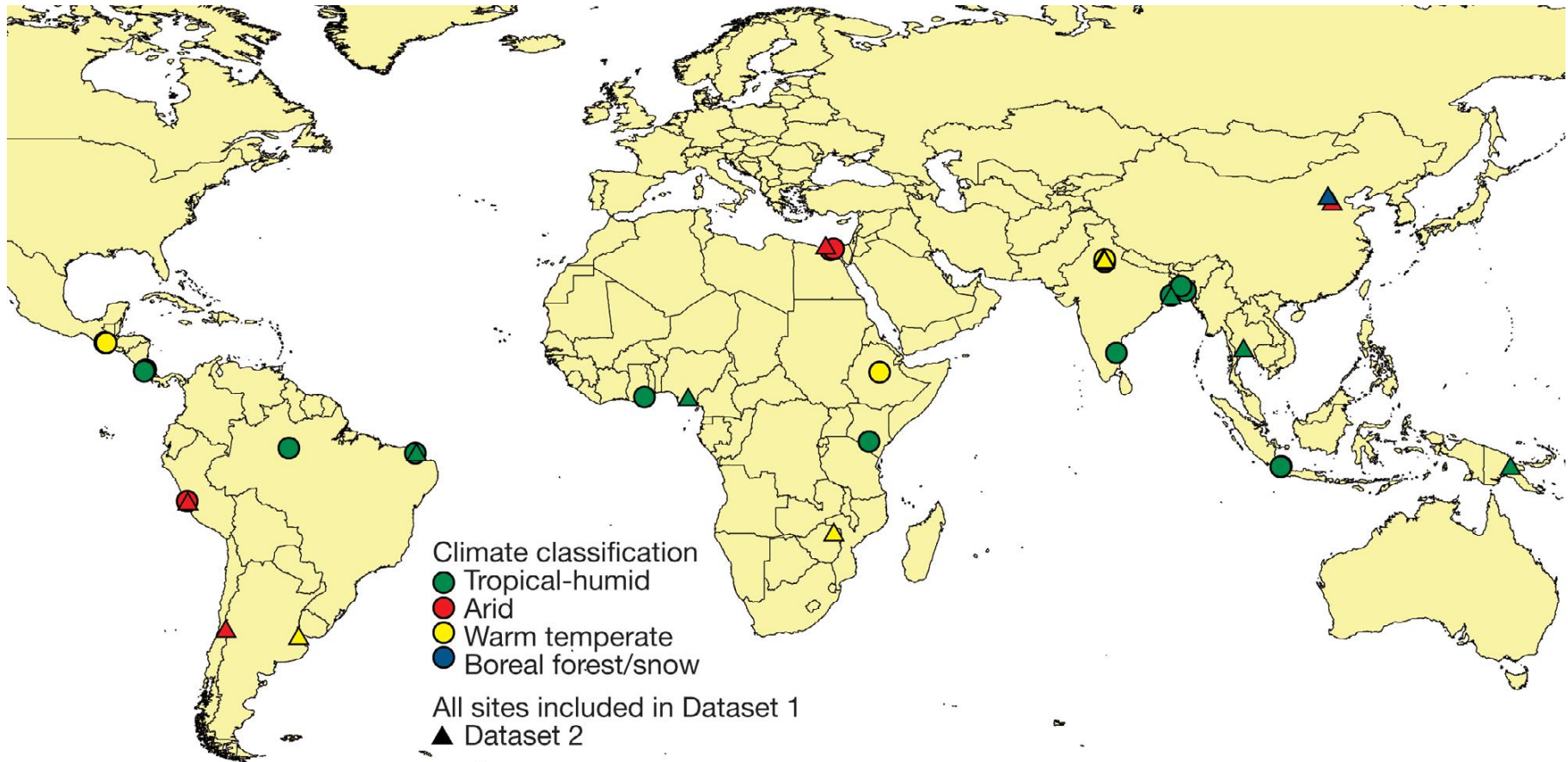
Methods: Global cross-sectional multi site study

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

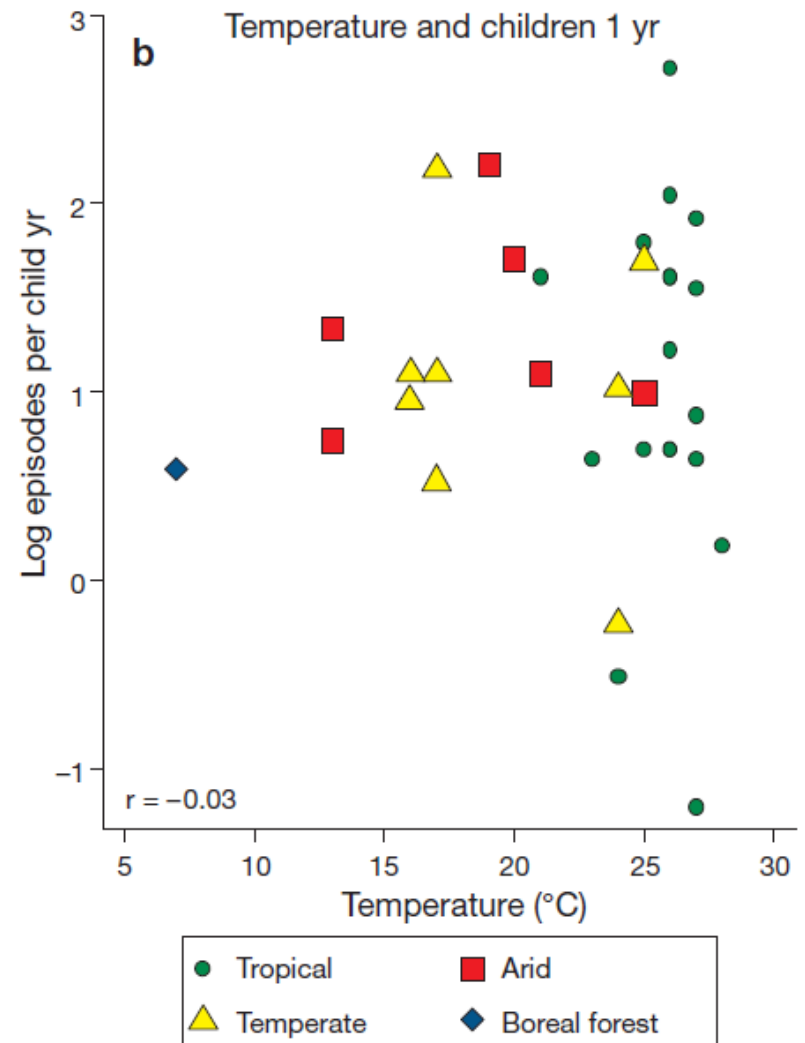
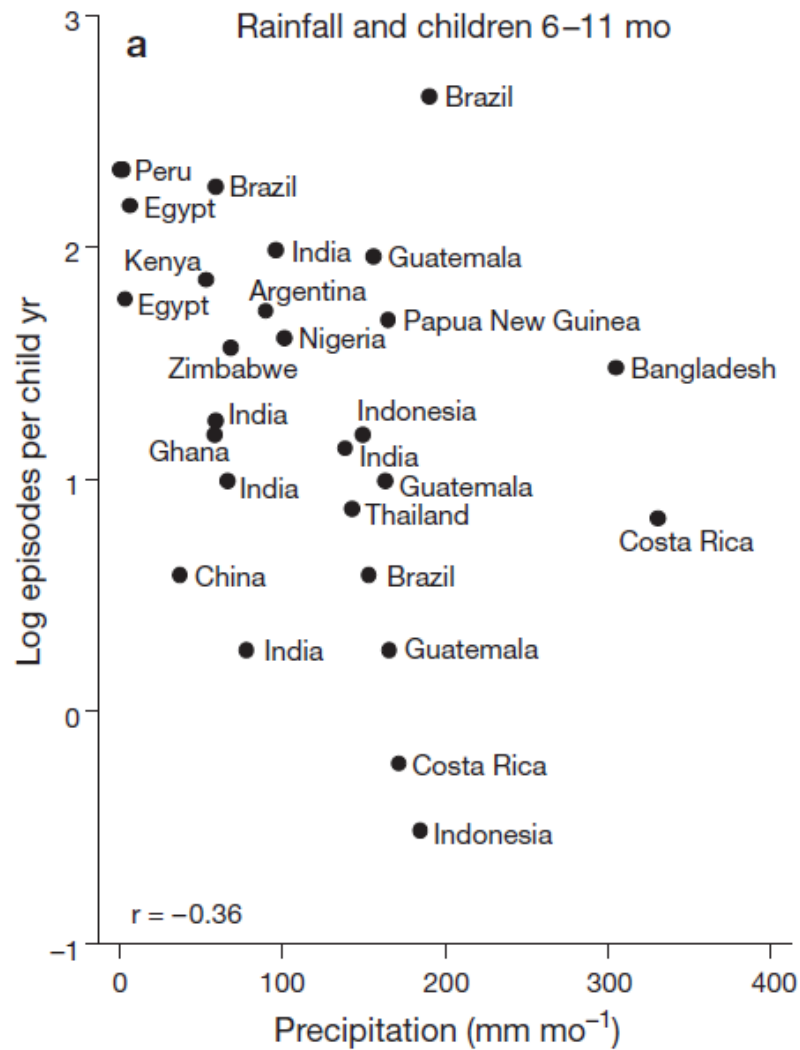
Exposures: mean monthly rainfall, mean temperature and climate type

Lloyd et al 2007

Study sites and climate type



Outcomes



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

Questions