CASI Nand and Jeet Khemka Distinguished Lectures 2024
Building Global Health Research from India for the World

Outline

- Foundational medical education
- The needs of context specific research-Enteric infections
- Cholera and oral rehydration
- Growth and development
- Polio vaccination
- Rotavirus vaccines
- Conclusion

On a timescale of centuries, the teaching of medicine has not changed very much

SEARO Regional Publications No. 18

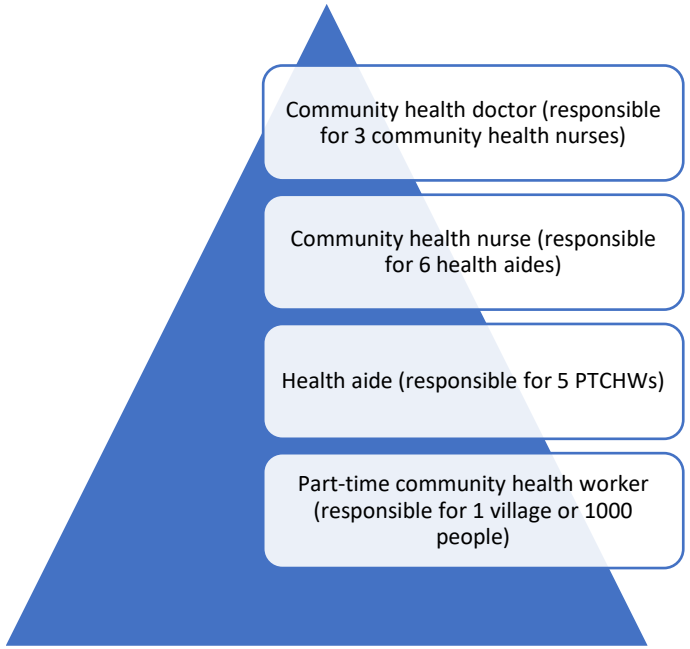
REORIENTATION OF
MEDICAL EDUCATION

Goal, Strategies and Targets

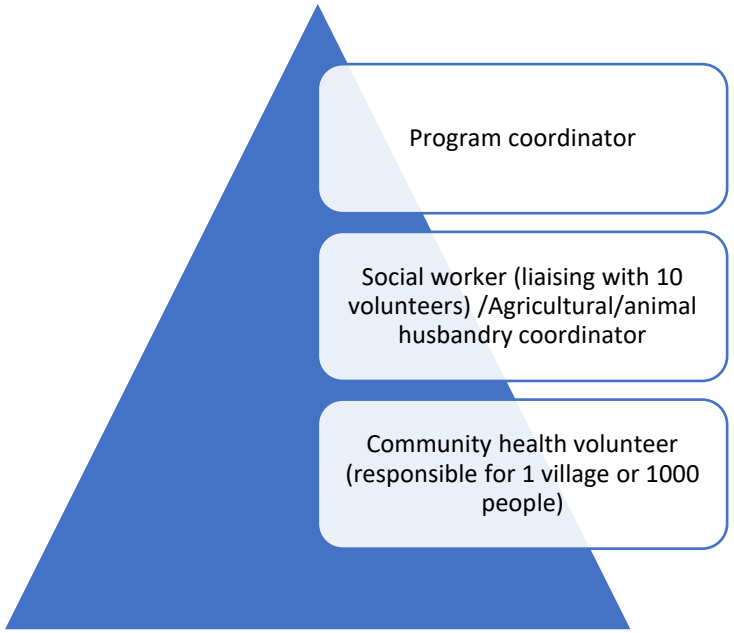
"notwithstanding the attainment of high standards of medical education, a large majority of doctors are not trained and equipped to meet the needs of the community in the matter of preventive, promotive and curative health care services, particularly for the rural areas;..... that the training continues to be hospital-based, thus making the trainee doctor dependent on sophisticated aids and diagnostic services and giving him very little exposure to rural conditions." It therefore "emphasised that doctors produced by medical institutions should be as close to the community as possible and be trained to be able to work in real life situations obtaining in rural communities."

(WHO SEA Regional Committee Resolution No. SEA/RC.29;R.9, 1976)

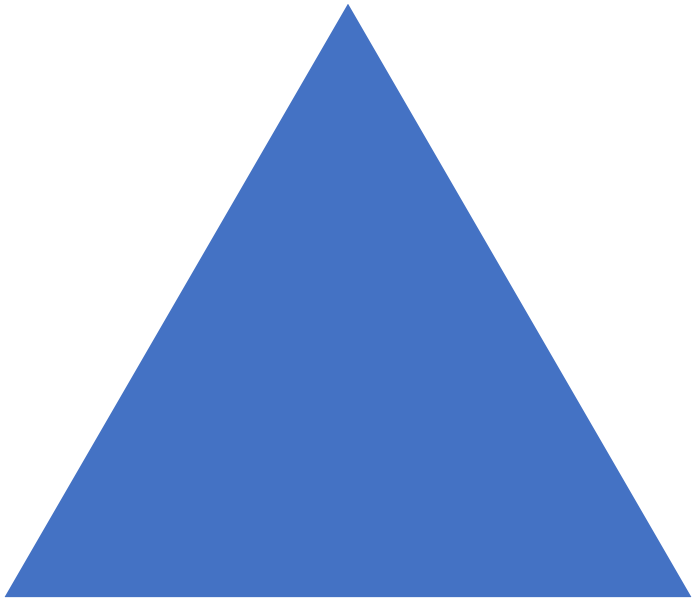
Three models of community care



Community health and development
80 bed hospital
Focus on maternal and child health, data to drive decisions
Computerised in 1986, GIS mapped from 2000
Women's economic empowerment



Rural Unit for Health and Social Affairs
60 bed hospital
Community volunteers for referral
Agriculture, animal husbandry, technical training



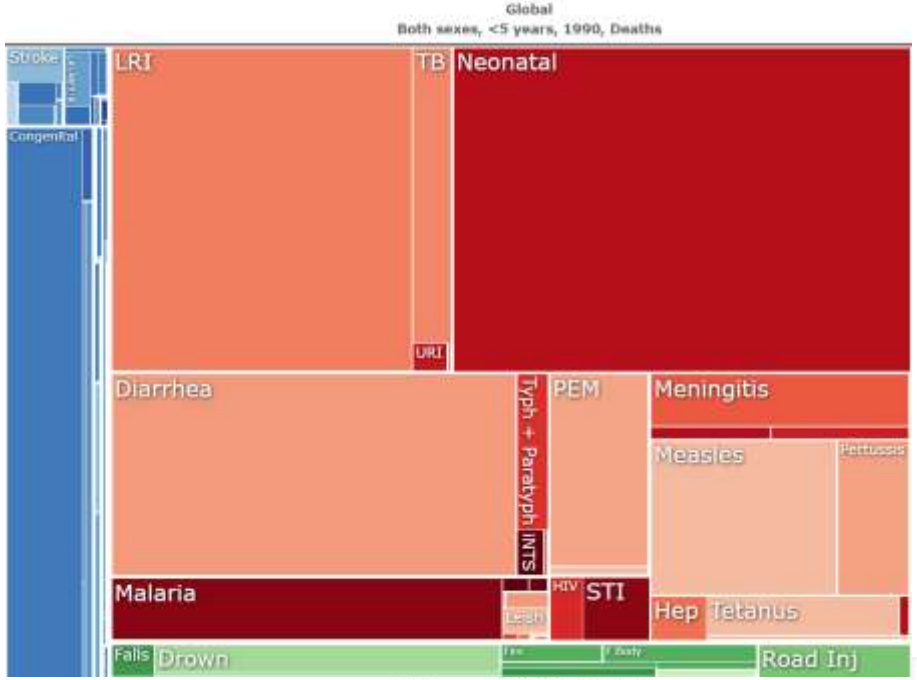
Support for government infrastructure
Primary health centre-posting doctors when needed
Technical advice

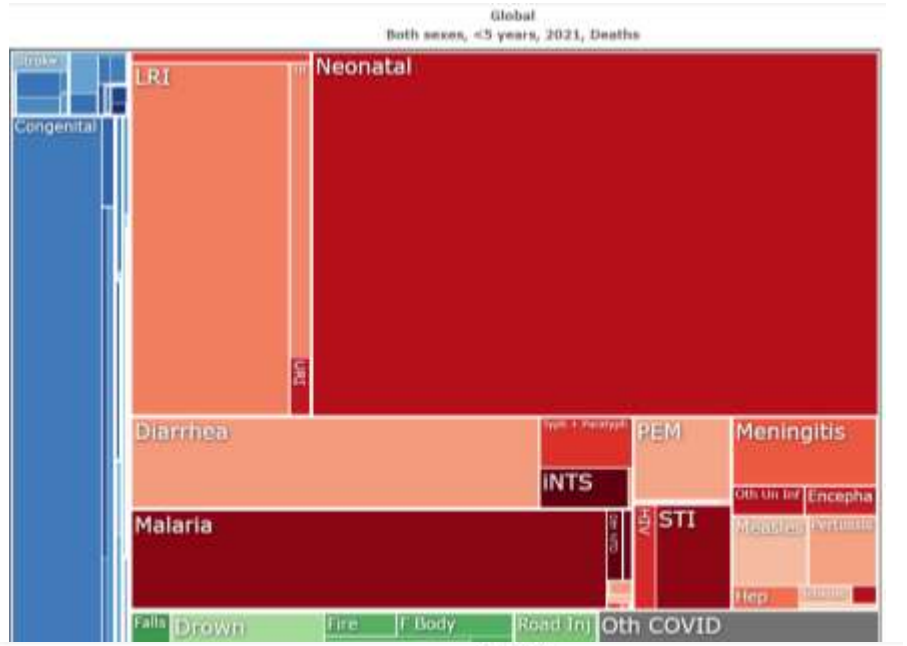

TMR 767

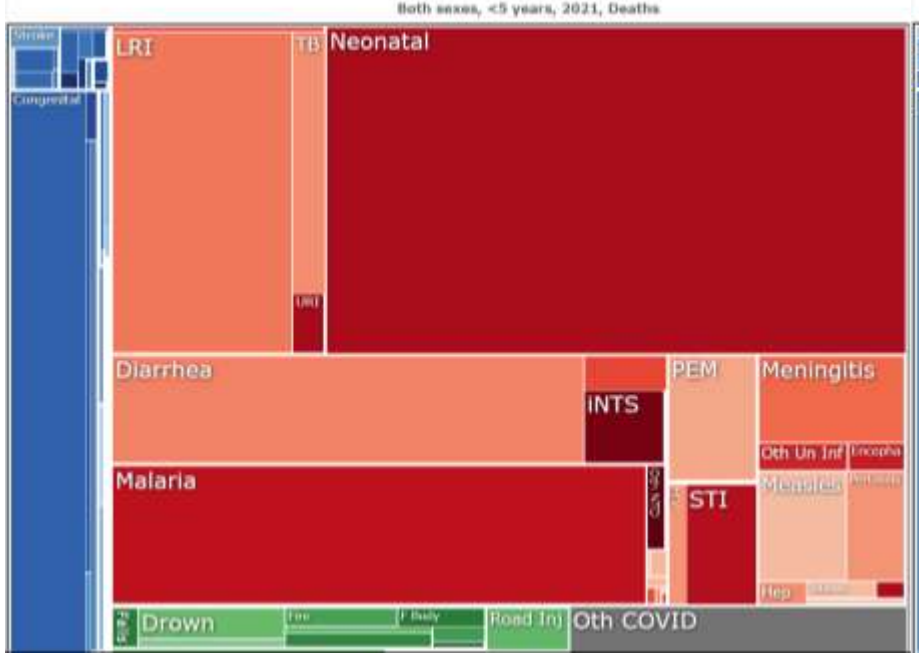

ne of the Villages
EPPAMPET
AGRAVARAM
KANIKANIYAN
SATHUPALAY
DHARMAVARA
504
265

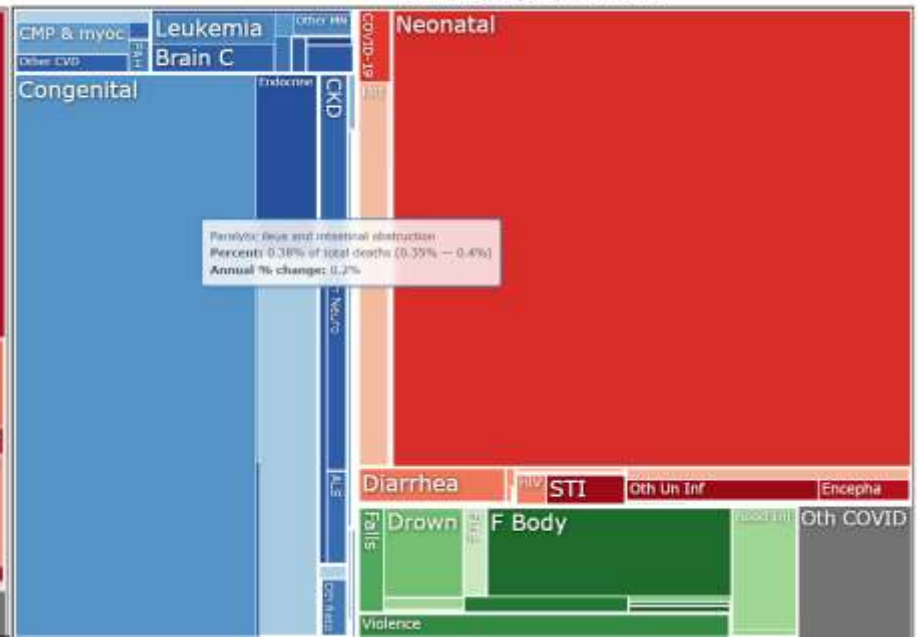
Community health teaching

The burden of common illnesses



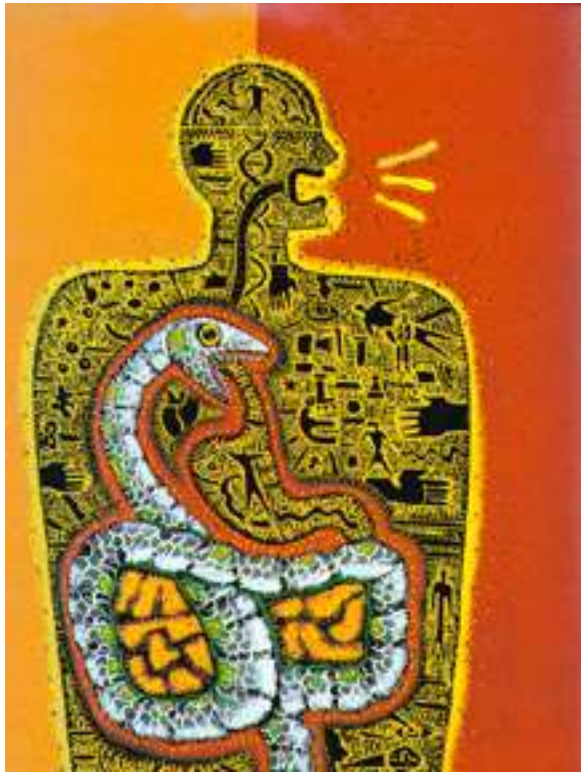


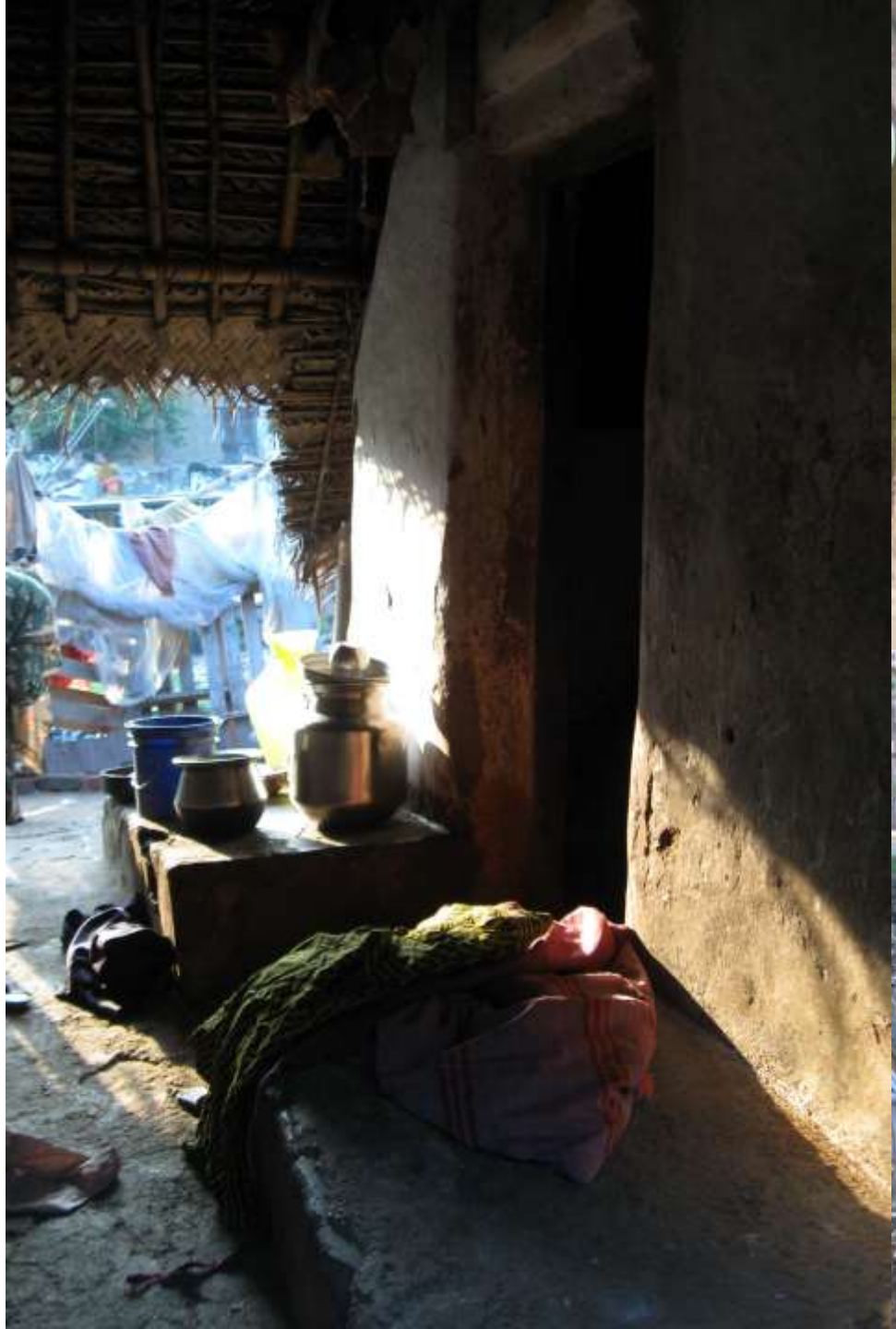




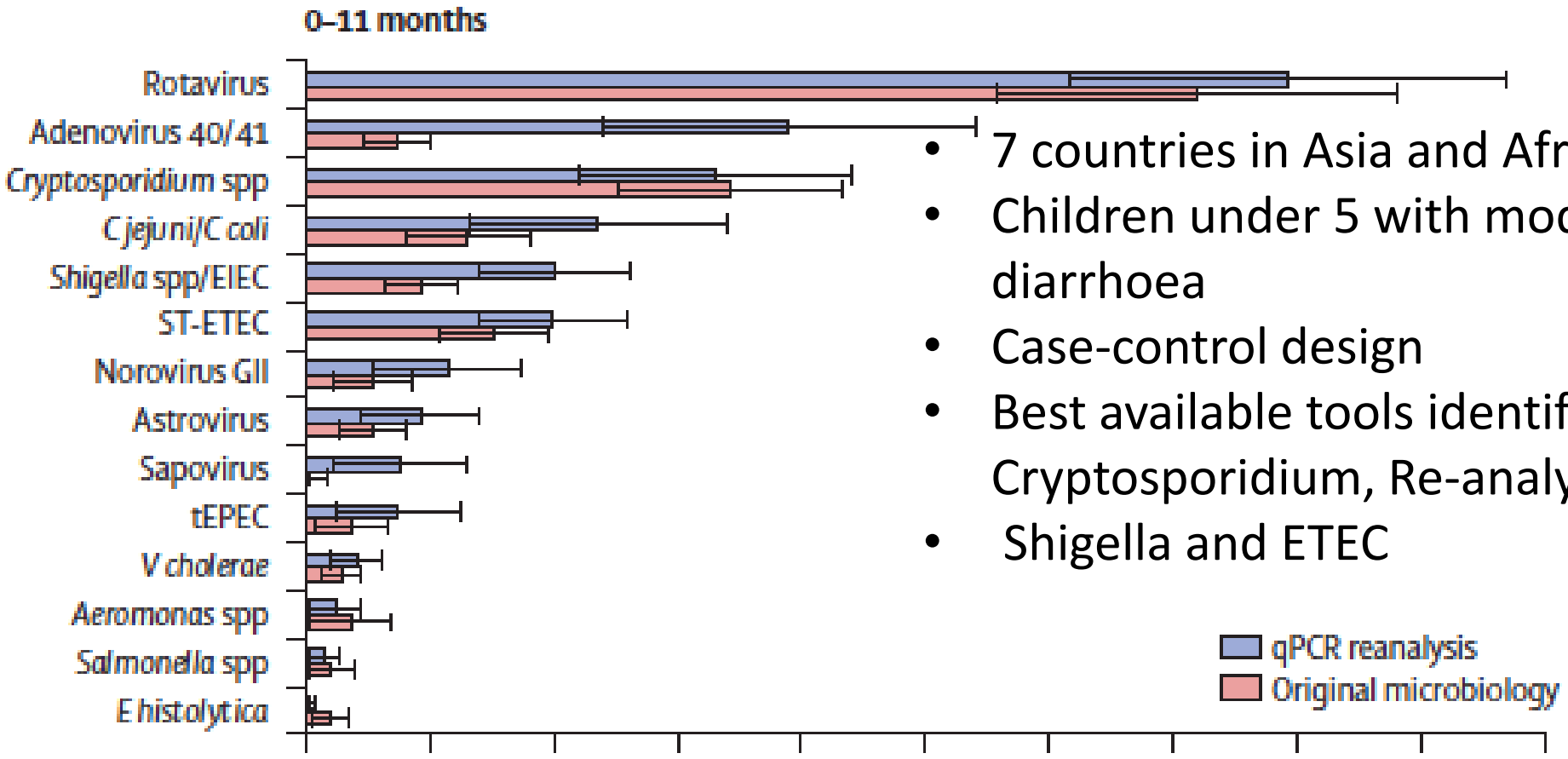
The gastrointestinal tract

- 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





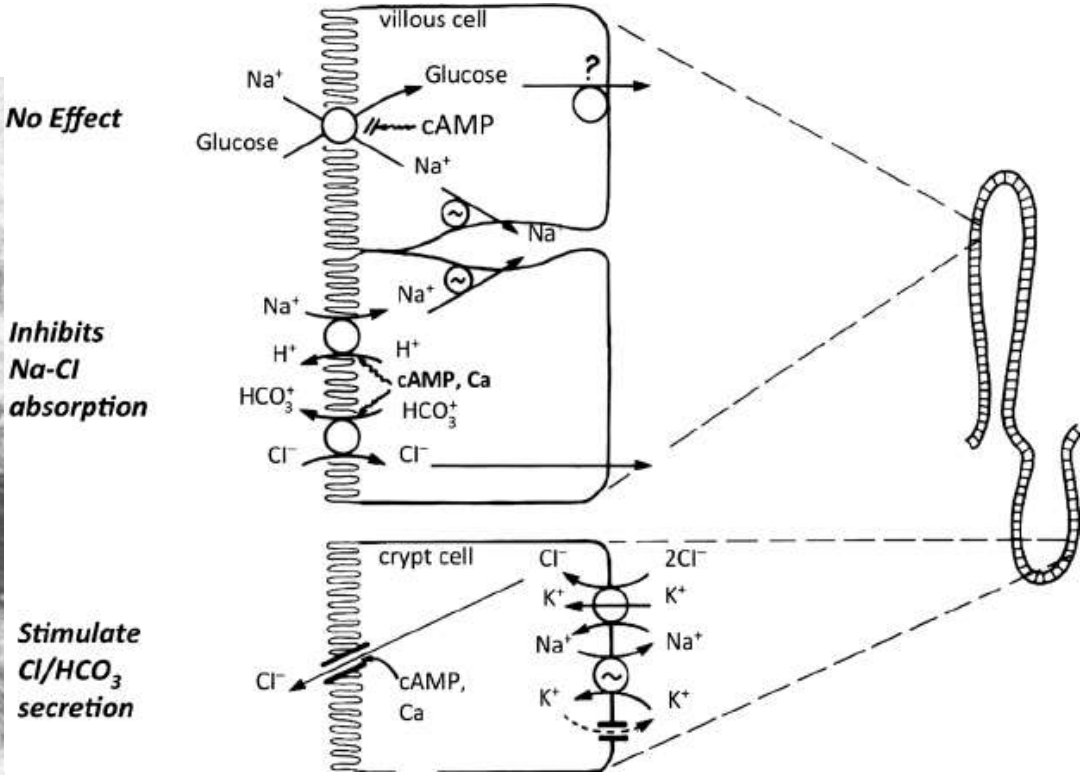
Diarrhea can be caused by many pathogens- but how often do we know what the cause is?



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

Liu et al, Lancet 2016

Cholera toxin and the basis of ORS



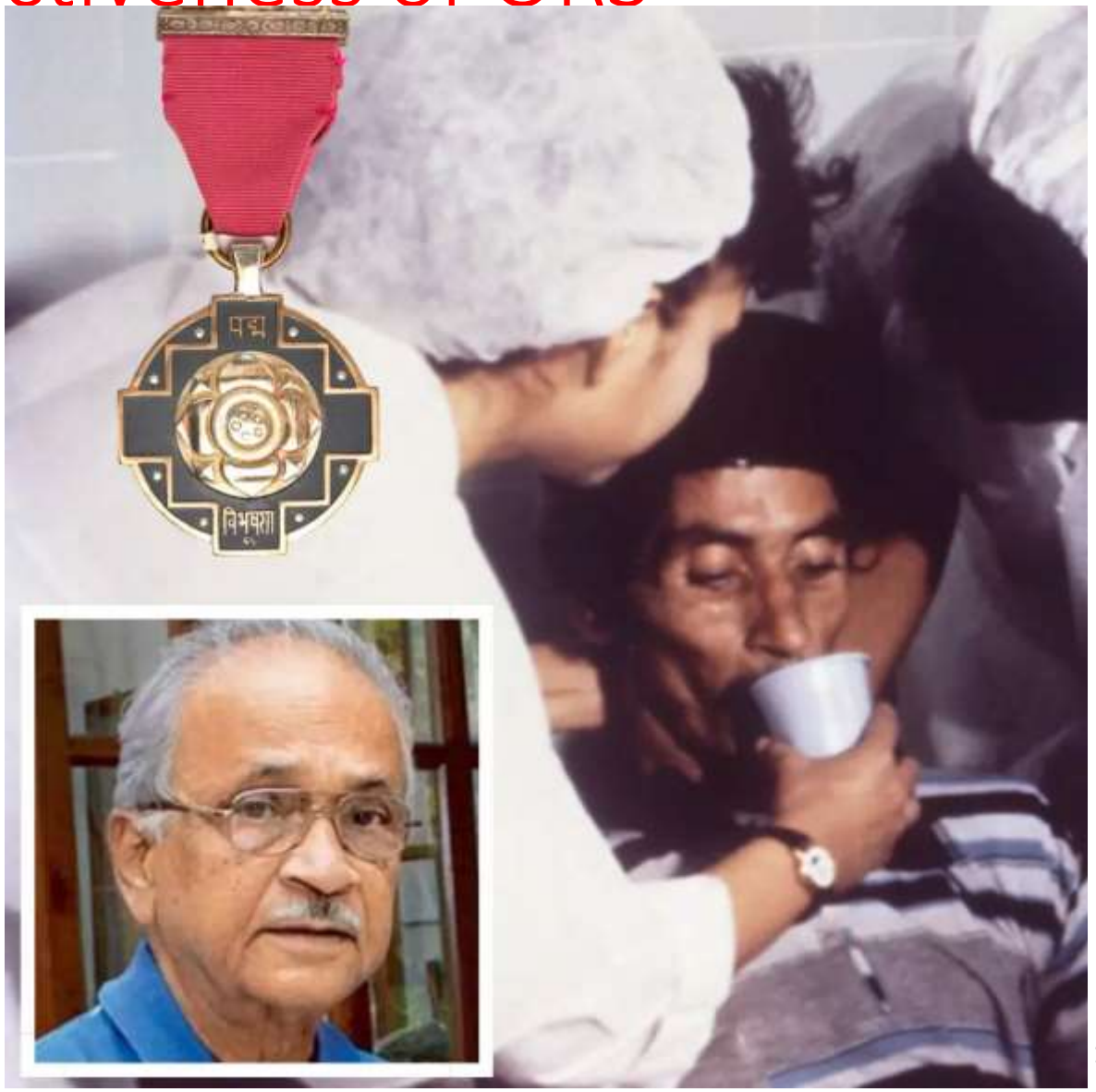
Glucose absorption in the mammalian small intestine needs luminal Na, and Na absorption is enhanced by the presence of luminal glucose. SGLT1 is the intestinal glucose-Na transporter

Cholera enterotoxin activates adenylate cyclase resulting in an increase in cyclic AMP in intestinal epithelial cells which stimulates active Cl secretion and inhibits electroneutral Na-Cl absorption

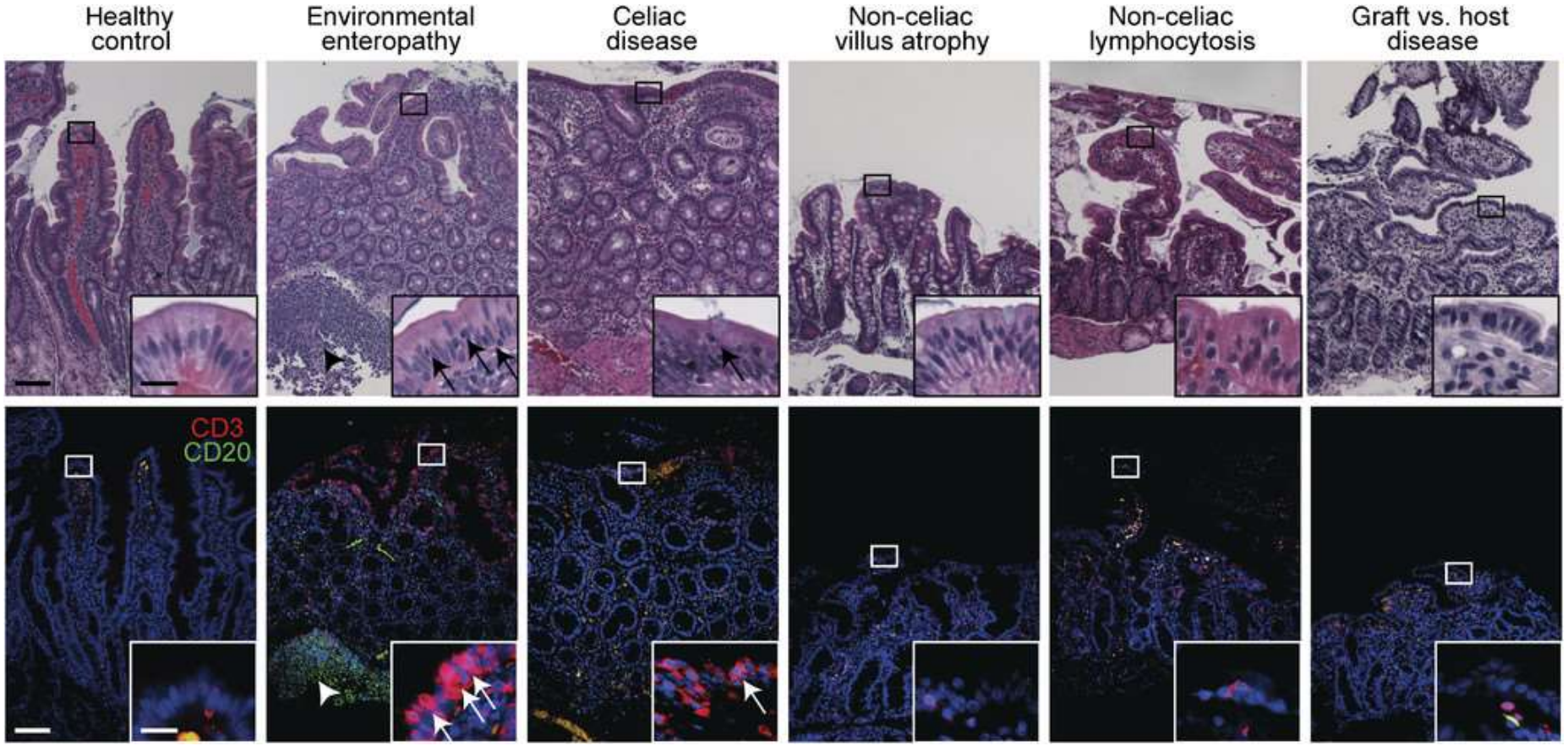
Cholera enterotoxin did not inhibit glucose- stimulated Na and thus fluid absorption

The physiological basis of ORS rests on the demonstration that absorptive and secretory processes in the mammalian small intestine are separate and independent.

1971- Dilip Mahalanabis proves effectiveness of ORS



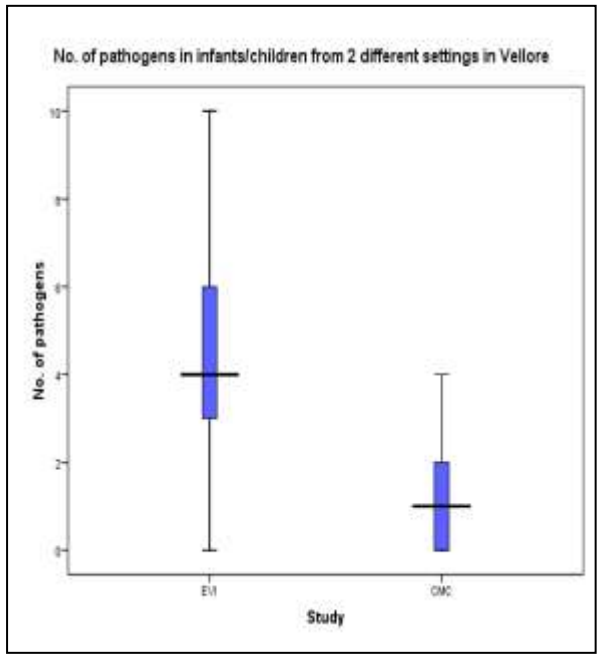
Acute and chronic damage



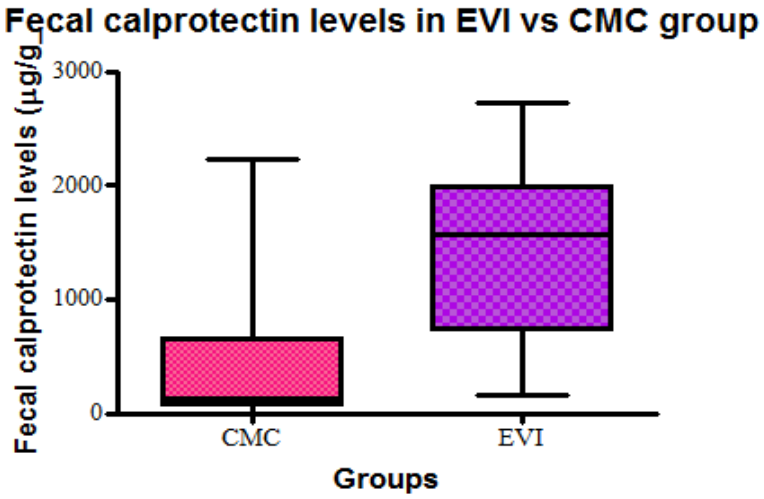
Duodenal histology and immunohistochemistry in environmental enteropathy (EE). Representative hematoxylin and eosin (H&E) (top) and immunofluorescence (bottom) images of matched fields for each subject group are shown. Immunofluorescence shows T-cell marker CD3 (red), B-cell marker CD20 (green), and a DNA stain (blue). Boxed areas on low magnification images designate the area shown in the inset. Arrows in the immunofluorescence images designate T cells. The arrowhead in the immunofluorescence image of the EE case indicates a lymphoid aggregate. Scale: low magnification images, bar = 100 µm; insets, bar = 20 µm. The H&E fields shown are of the same regions shown in the immunofluorescence images. These were selected to best demonstrate the immune infiltrates. In the cases of EE and GVHD, well-oriented crypt–villus units were not present in the most illustrative immunostained regions.

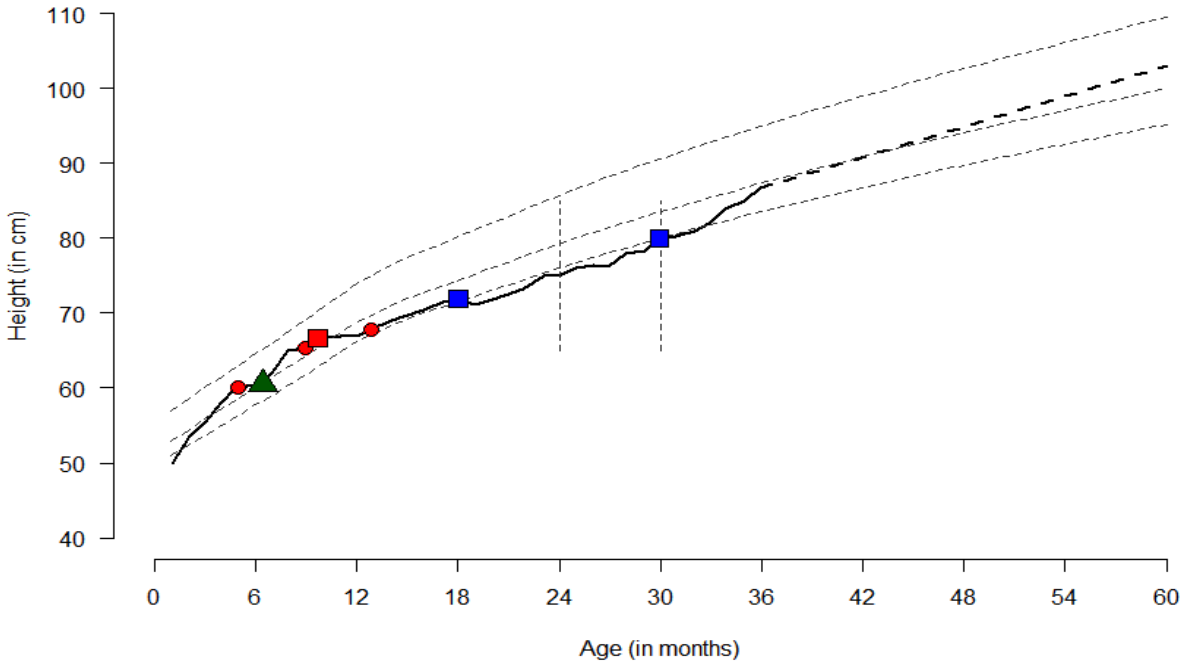
Syed, Yeruva, Hermann et al, 2018

Enteropathogen presence in asymptomatic infants from upper & lower socio-economic strata in Vellore

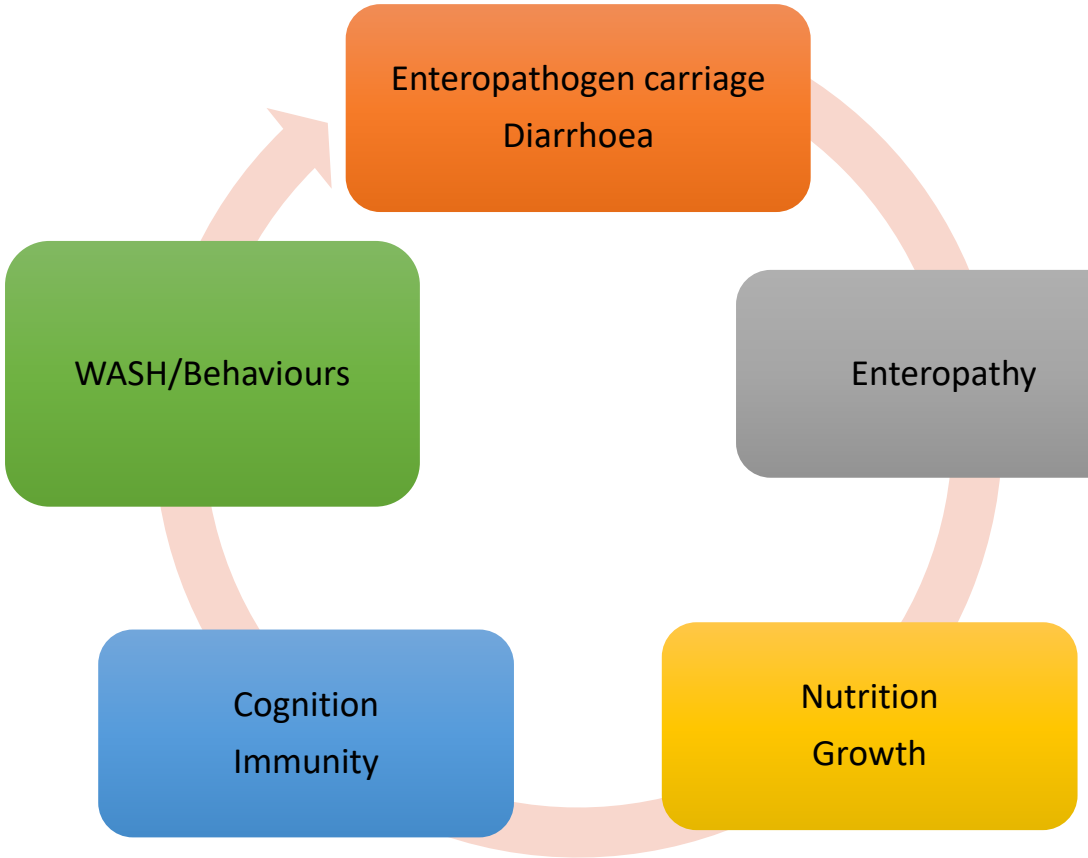


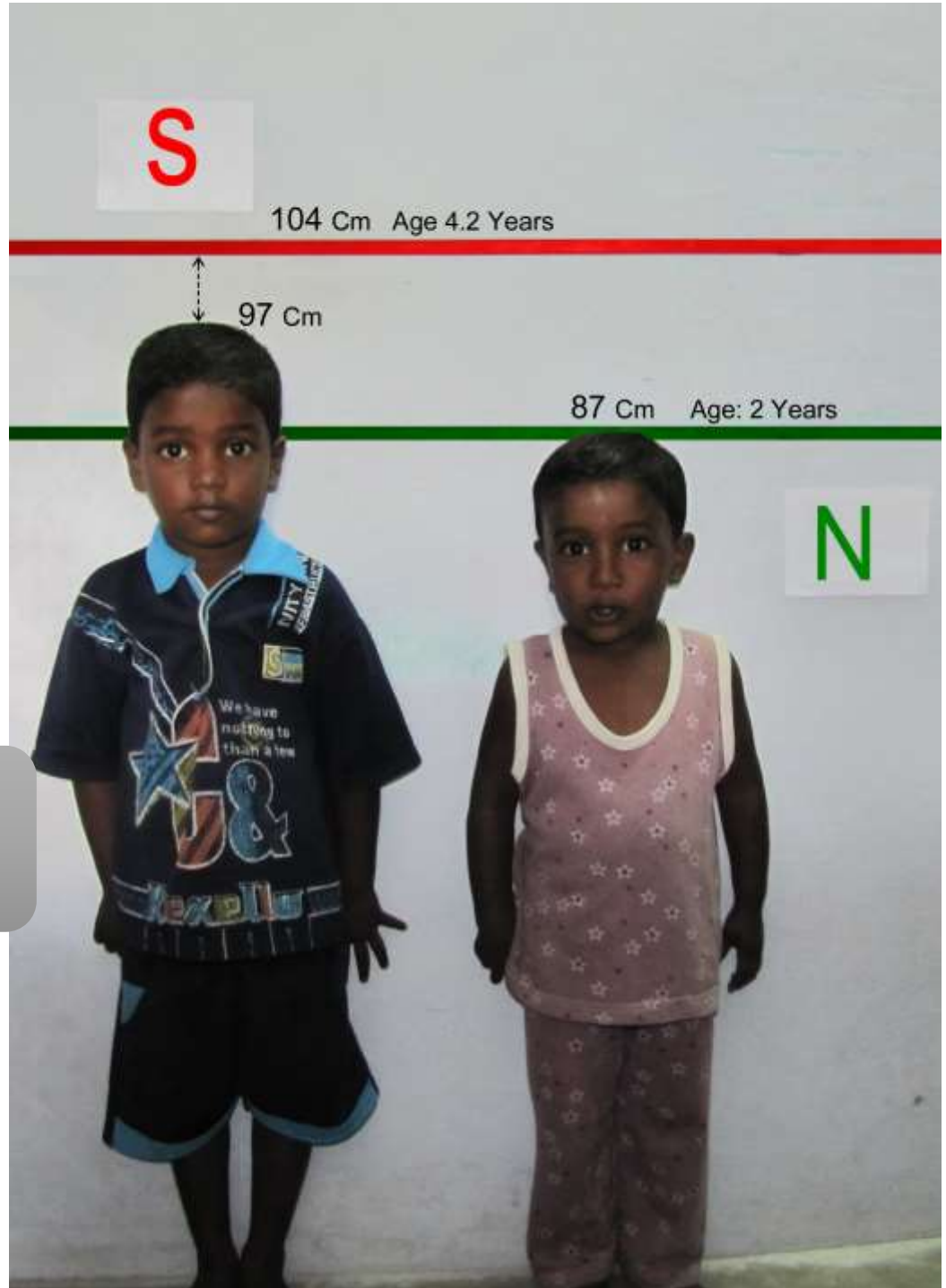
Enteropathogens	EVI infants (lower SES)	Infants/ Children from CMC (upper SES)
Mean no. of pathogens	4.25 (4.03-4.46)	1.22 (0.84-1.6)
Median no.	4	1
Range	10 (10-0)	4 (4-0)
IQR	3	2

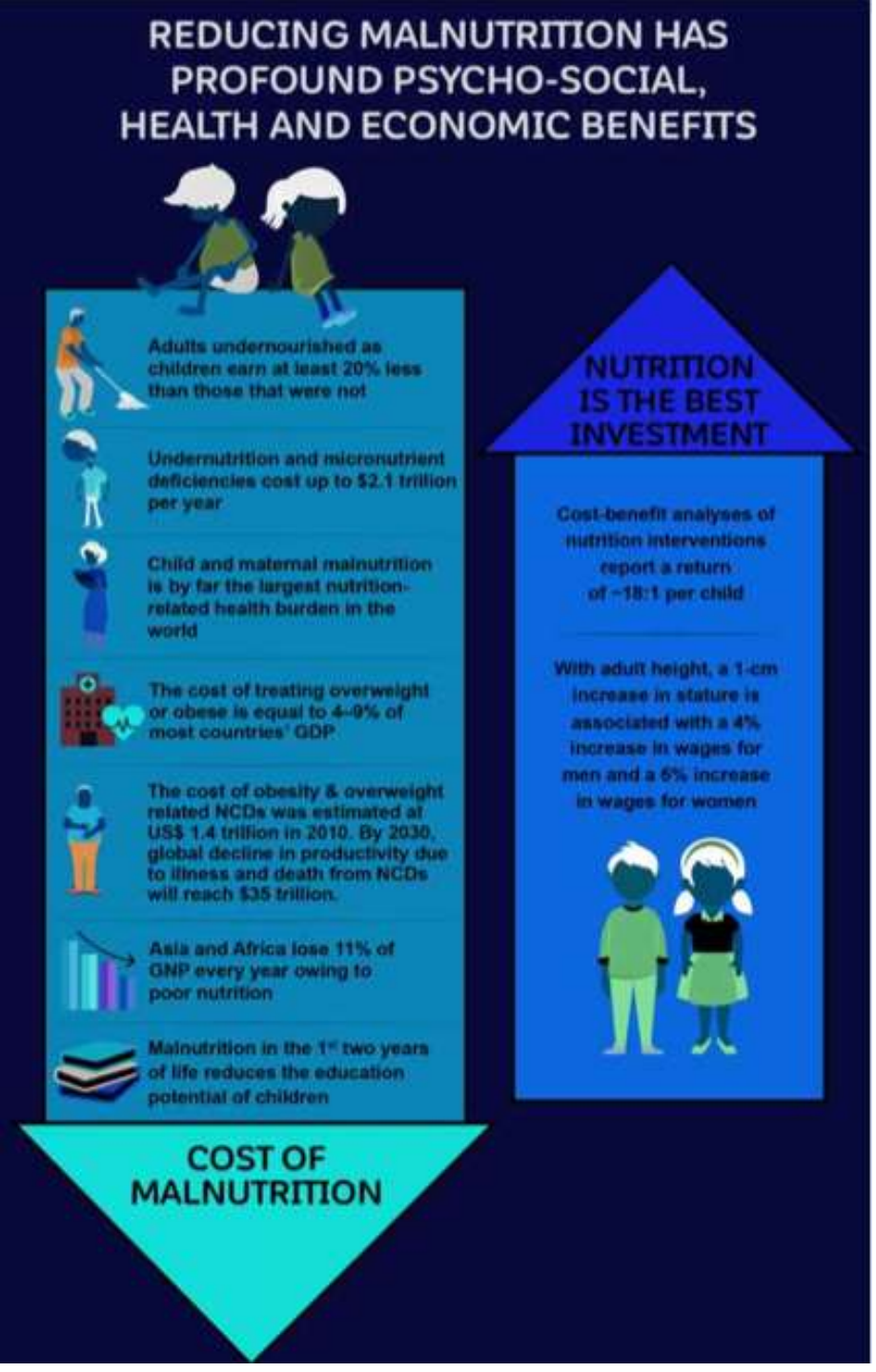




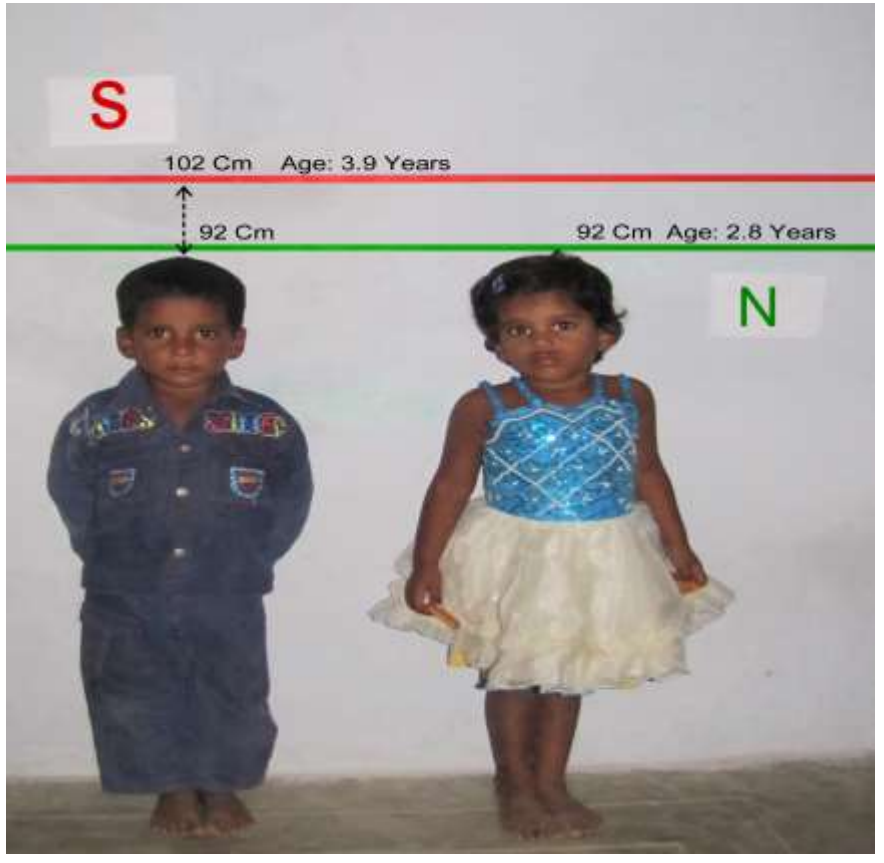
- Overall, children in urban slums in southern India have 30% stunting
- Median IQ in our slums is 89
- Persistently stunted children have significantly lower IQs than children who have never been stunted



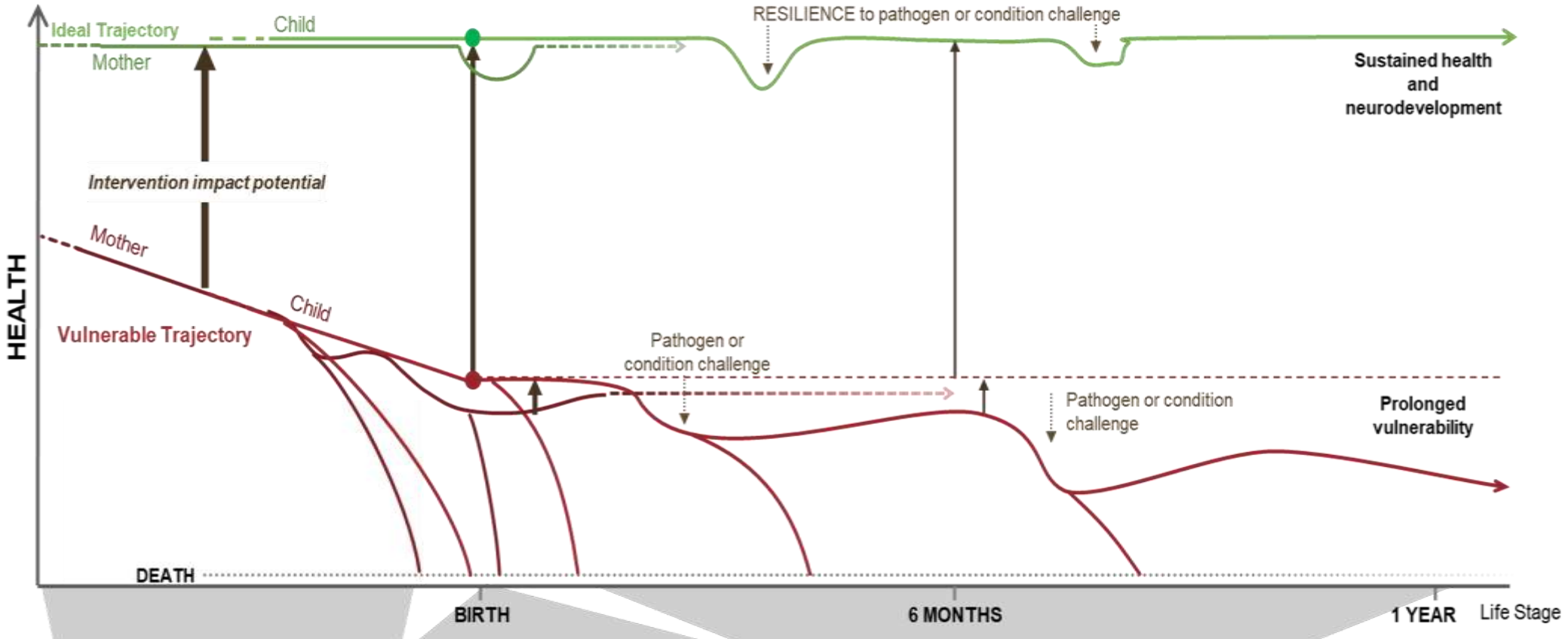




A poor start defines the future, and calories alone are not enough



Growth & Resilience lens to support optimal growth and development



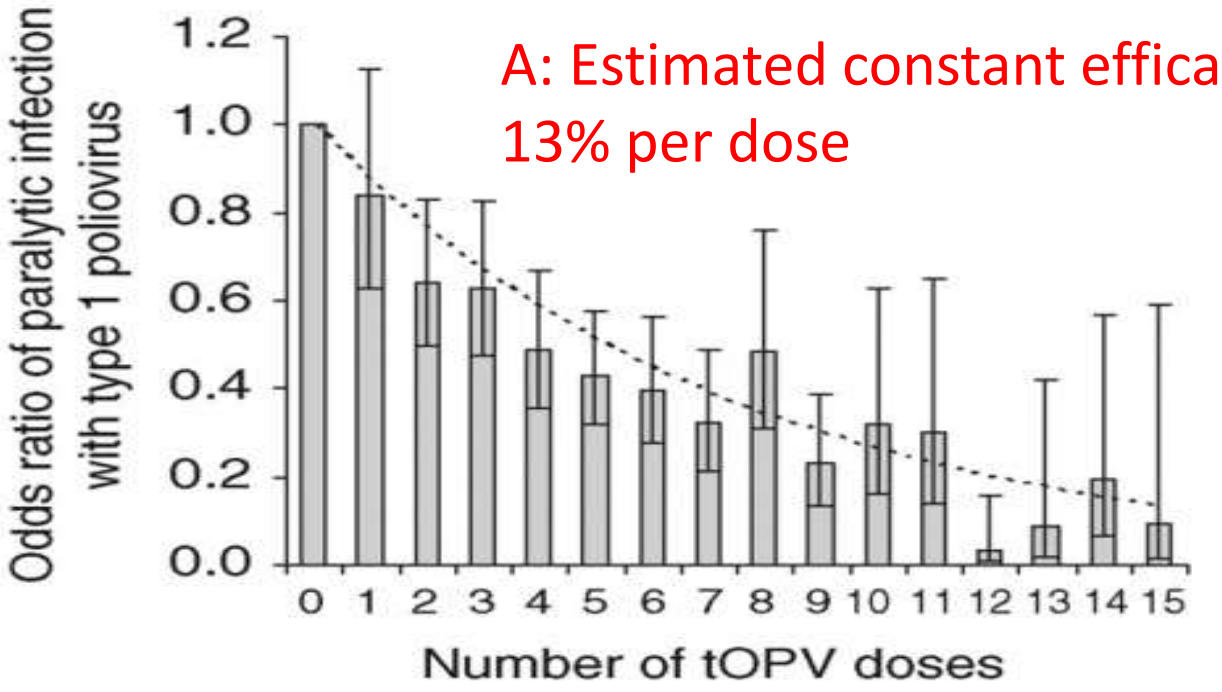
Prioritized adverse outcomes by life stage

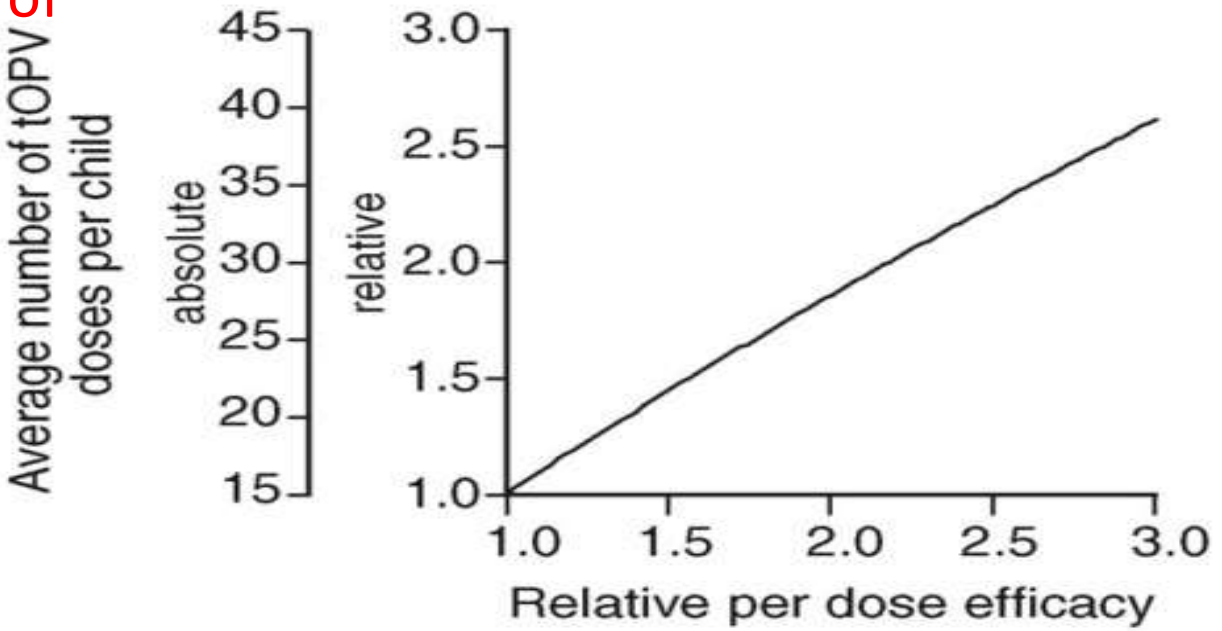
PREGNANCY	PERINATAL PERIOD	INFANCY
• Anemia • Undernutrition (maternal underweight, inadequate gestational weight gain, micronutrient deficiency) • Pre-eclampsia	• *Maternal:* postpartum hemorrhage, postpartum anemia, pre-eclampsia/ eclampsia, sepsis, mortality • *Neonatal:* stillbirth, preterm, LBW, RDS, sepsis, hypoxic ischemic encephalopathy, mortality	• Underweight, wasting, stunting, mortality • Sub-optimal neurodevelopment

Chronic gut damage has other consequences-Oral polio vaccines

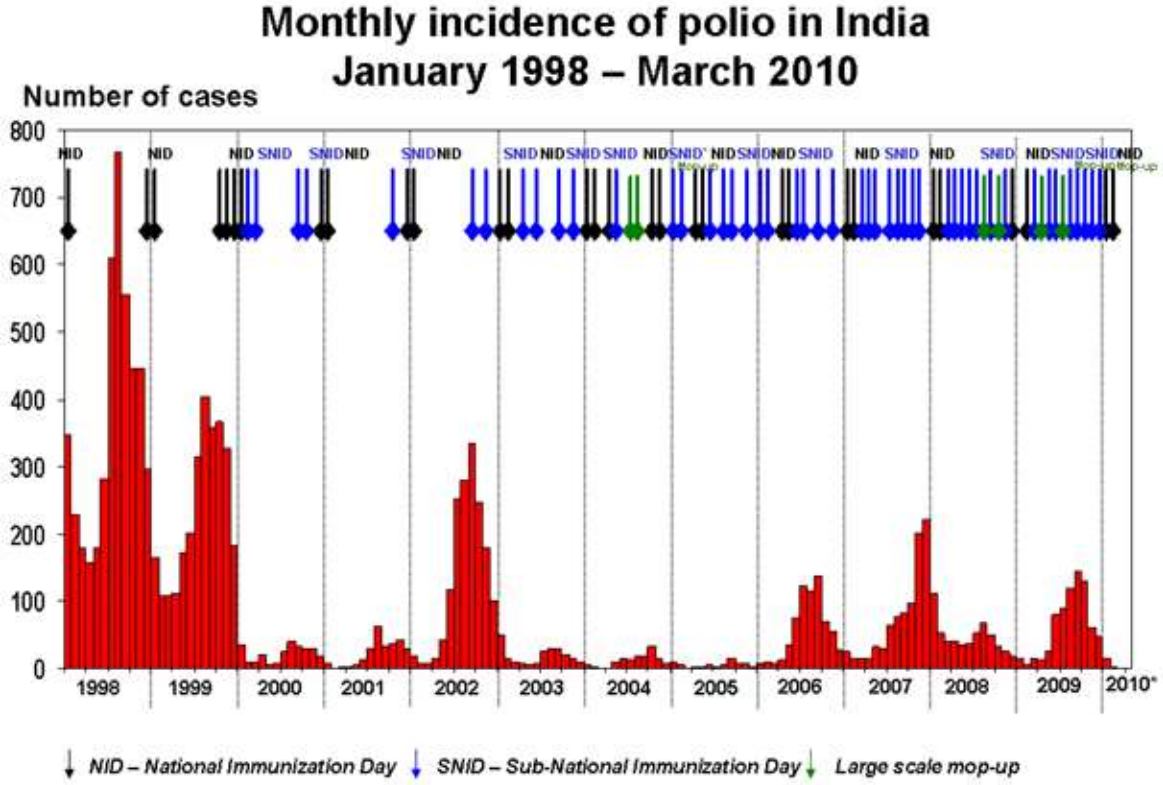
Sero-conversion	1 dose	2 doses	3 doses	Reference
USA	39,84,71	92,100, 96	97,100,100	Mcbean et al, 1988
Developing countries			73, 90, 70	Patriarca et al, 1991

A: Estimated constant efficacy of 13% per dose





Polio



* data as on 7 May 2010

Rukhsar Khatoon was unvaccinated when she developed paralysis in January 2011

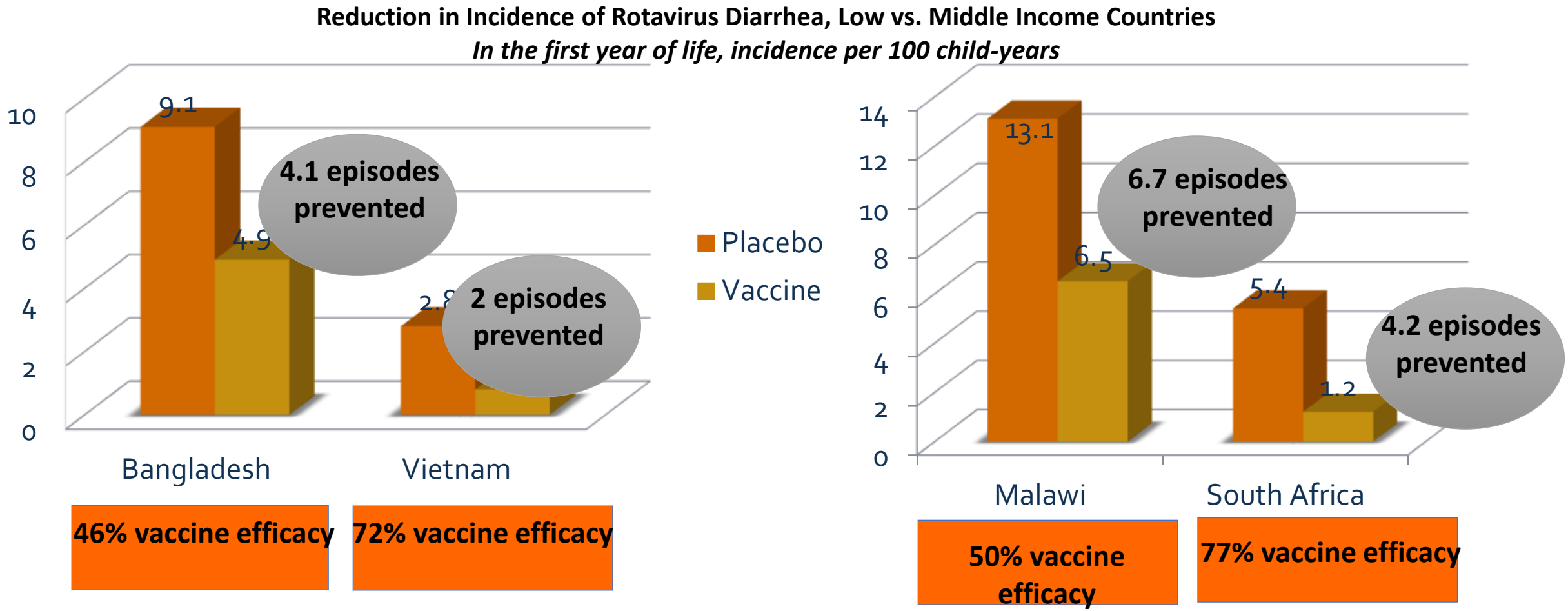
Polio is gone from India, but not Pakistan and Afghanistan or countries with circulating vaccine derived virus

- Vaccine trials in Vellore, population approx. 2 million
- North Arcot OPV coverage 85-90%, efficacy 66%
- Tiruvannamalai IPV coverage 75-80%, efficacy 92%
  - (John et al, 1992)

Performance of oral vaccines in lower income settings

Type	Disease	Vaccine	Protection
Live, attenuated	Typhoid	S. typhi (Ty21a)	96% in Egypt, 67% in Chile, 52% in Indonesia
	Cholera	V. cholerae (CVD103-HgR)	80-90% in volunteers, 14% efficacy in Indonesia
	Polio	Attenuated polioviruses (Sabin; multiple)	60-90%, PV3 lowest
	Rotavirus	Attenuated monovalent virus (Rotarix, Rotavac, Rotavin)	50-65% in Africa (Rotarix) 55% in India (Rotavac)
	Rotavirus	Human-bovine reassortant viruses (RotaTeq)	40-48% over one season in Africa and Asia
Inactivated	Cholera	V.cholerae + CTB (Dukoral)	85% over 6/12, 58% at 2 years in Bangladesh
	Cholera	Shanchol (bivalent O1/O139)	37-42% 1 dose in Bangladesh, 69% 2 doses in Odisha

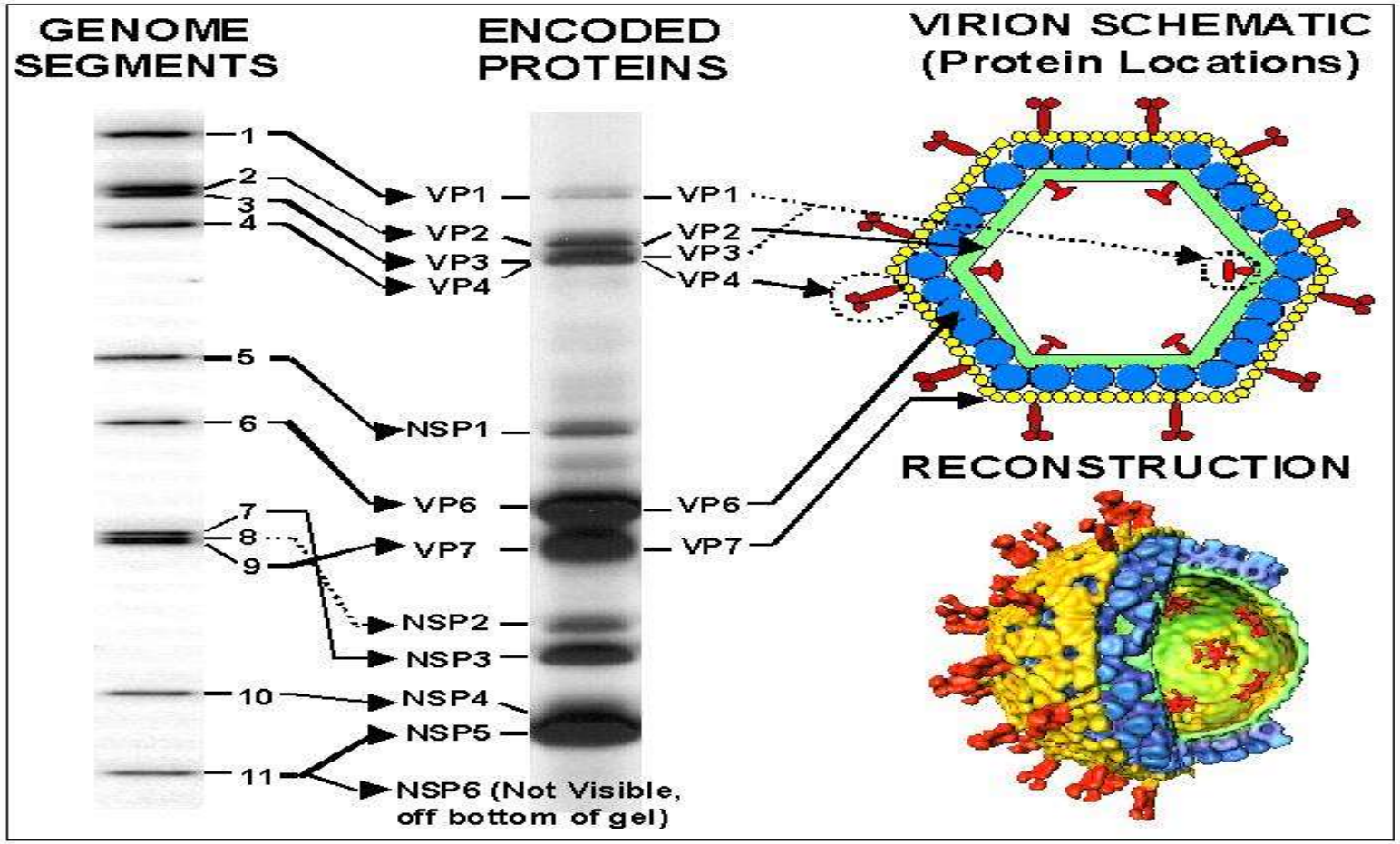
What does lower efficacy in developing countries mean?



Zaman et al, Lancet 2010

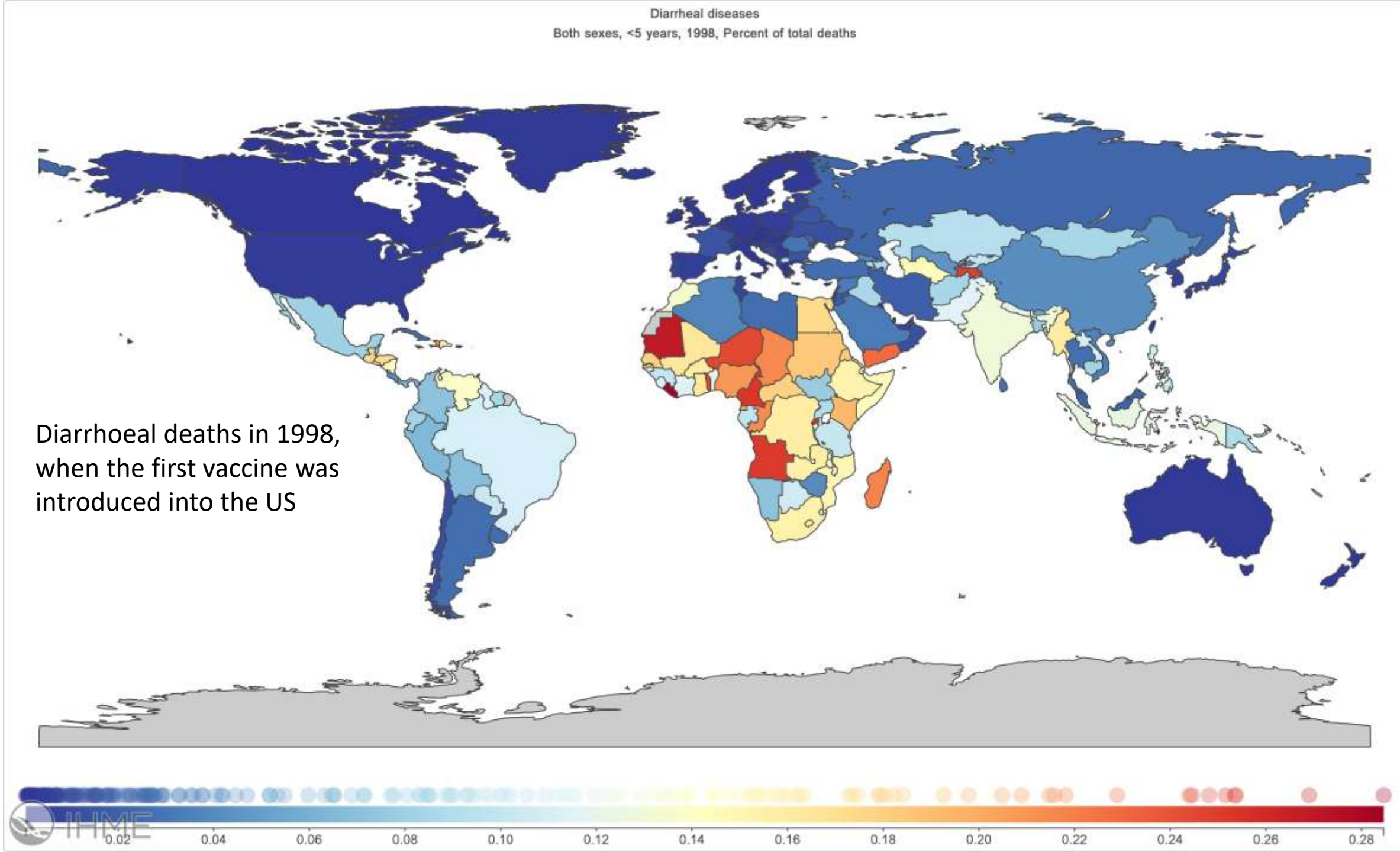
Madhi et al, NEJM 2010

Group A rotaviruses are the most common cause of dehydrating gastroenteritis in children

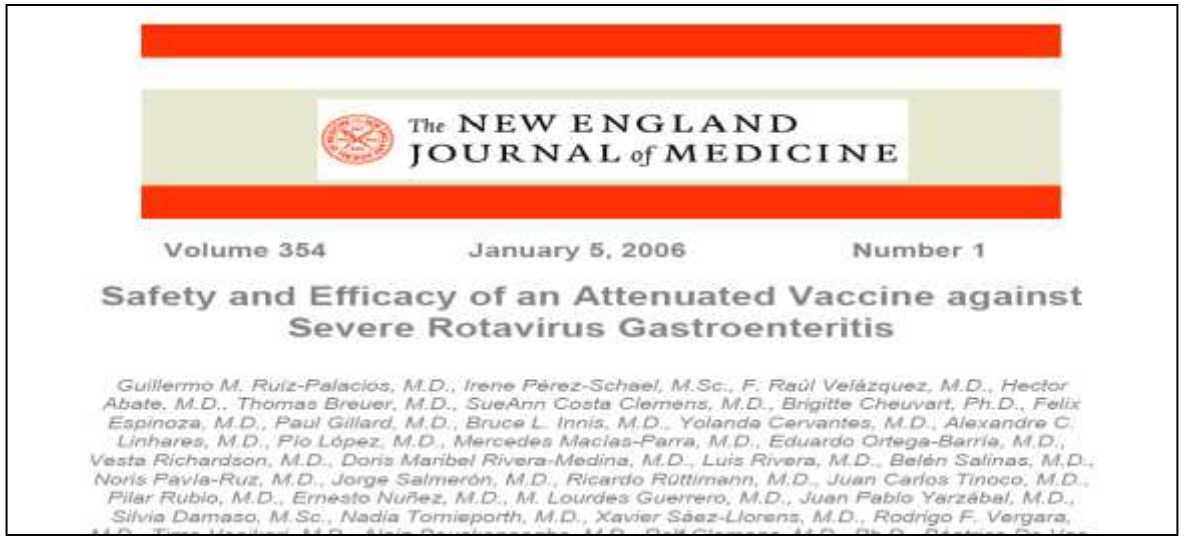


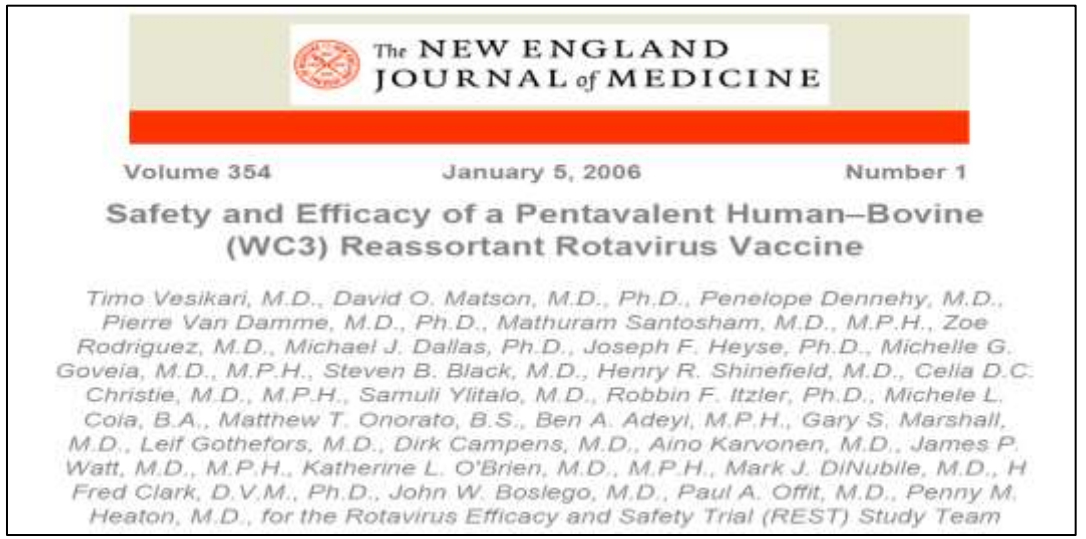
Rotavirus is democratic, and hygiene delays but does not prevent infection

- Rotavirus cannot be treated with antibiotics or other drugs
- Prompt **treatment with oral rehydration therapy (ORT) can be effective** in treating mild infections
- But many of **the world's poorest children do not have access to ORT**, despite the fact that it is effective and inexpensive
- **IV fluids may be required** if ORT is not administered, given too late or dehydration is too severe
- **Rotavirus prevention by vaccination is key to improving child survival**


Diarrheal diseases
Both sexes, <5 years, 1998, Percent of total deaths
Diarrhoeal deaths in 1998, when the first vaccine was introduced into the US
IHME
0.02
0.04
0.06
0.08
0.10
0.12
0.14
0.16
0.18
0.20
0.22
0.24
0.26
0.28

Two new rotavirus vaccines licensed in 2006





- Trials of 60-70,000 infants
- Specifically designed to assess risk of intussusception similar to Rotashield
- Cost 200 US$ for the course
- Introduced in India in 2008 in the private market-cost Rs. 1800 or Rs. 1200 per dose

Vesikari et al and Ruiz-Palacios et al, NEJM 2006

Efficacy against hospitalized rotavirus gastroenteritis

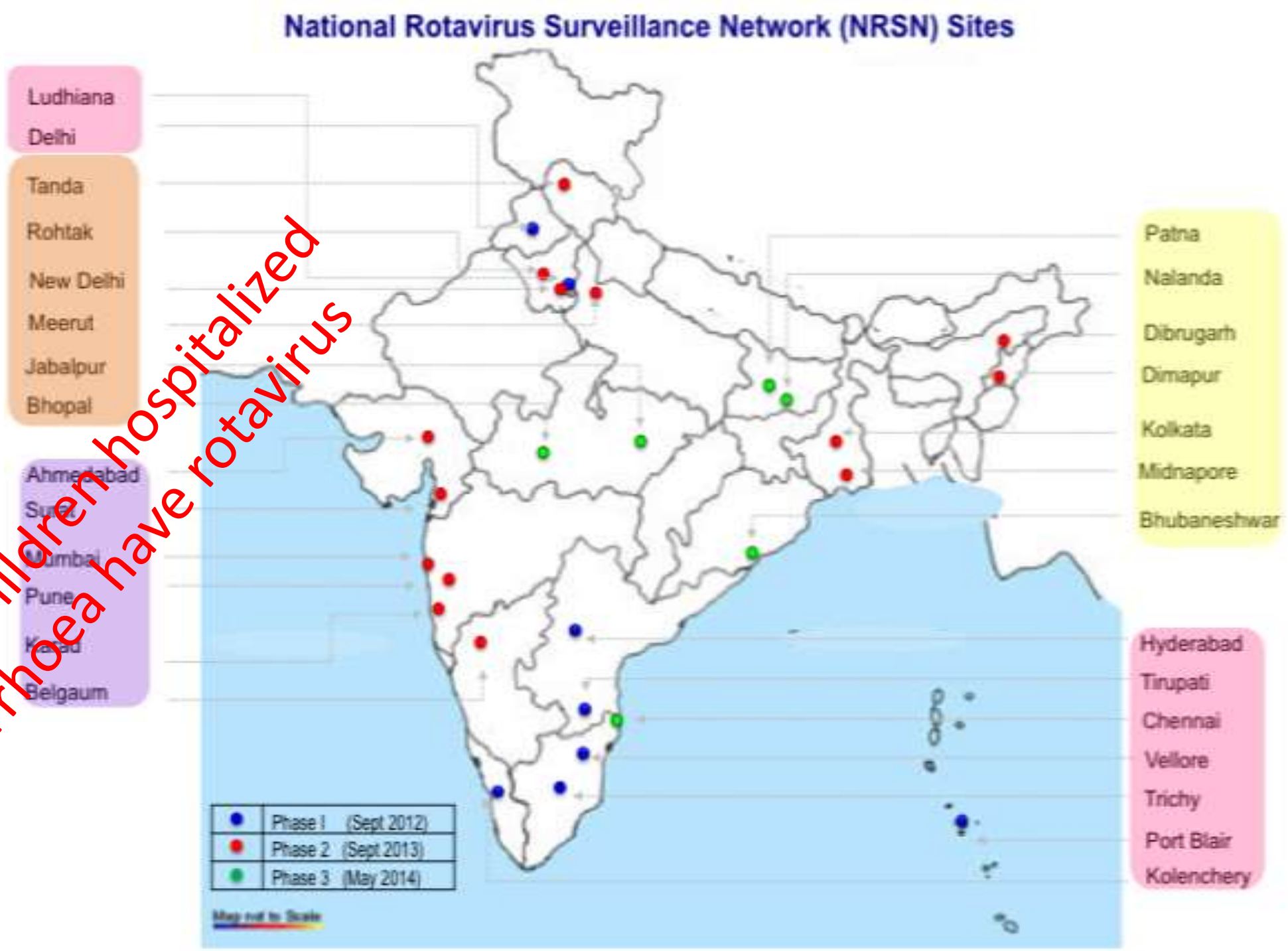
	Vaccine	Placebo	% efficacy	95% CI
Rotarix	9/9009	59/8858	85	69.6, 93.5
Rotateq	6/28646	144/28488	95.8	90.5, 98.2

Human G1P[8], monovalent, 2 doses

Bovine-human reassortant, G1-G4, P[8] pentavalent, 3 doses

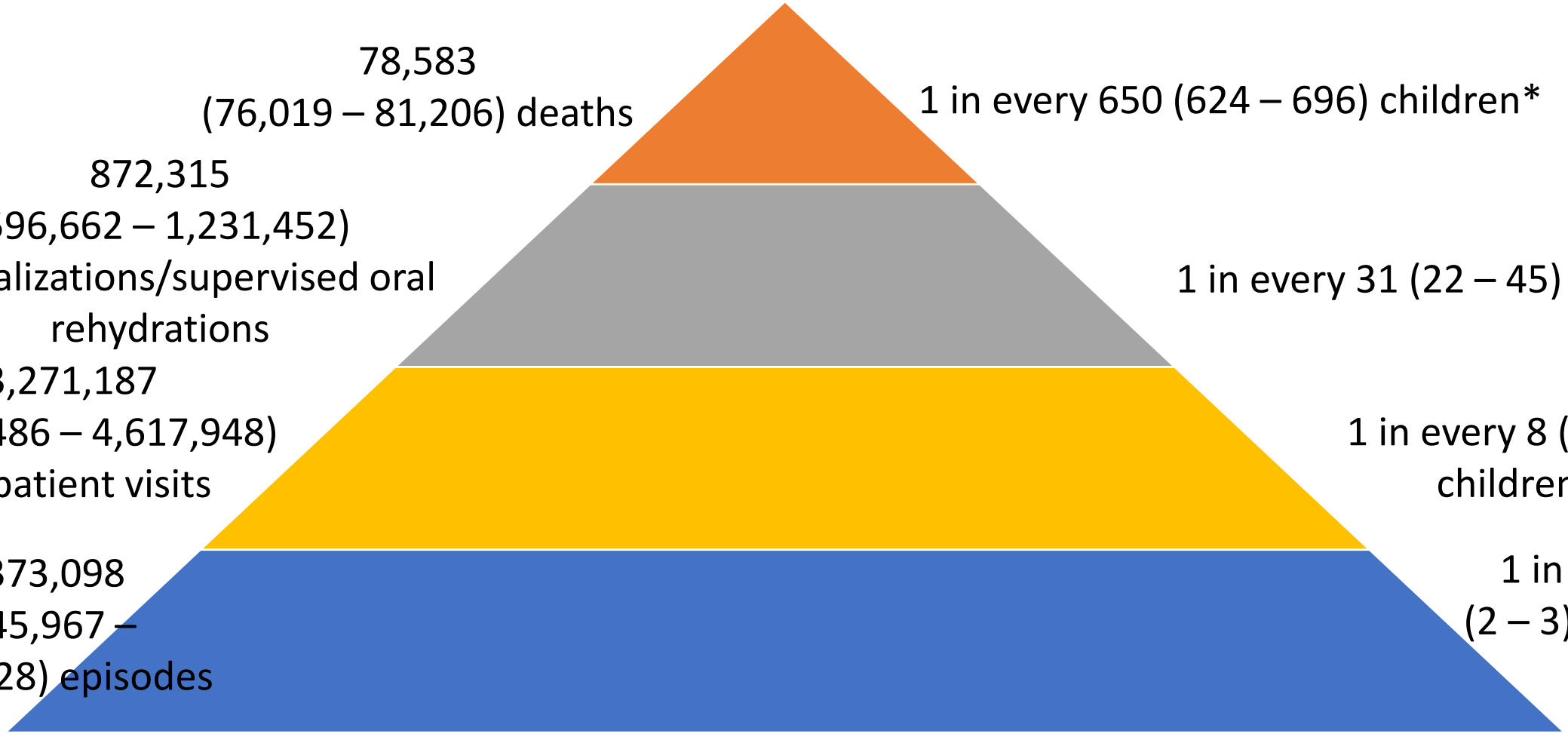
Ruiz-Palacios et al NEJM. 2006 Vesikari et al NEJM. 2006

National Rotavirus Surveillance - coordinated activities from 2005



37% of all children hospitalized with diarrhoea have rotavirus

Estimates of disease burden in India



* Estimates based on 2011 birth cohort of 27,098,000 children (UNICEF India Statistics)

Given our disease burden, we needed a vaccine.

- But which vaccine?
- Will it work?
- Can we afford it?

- Rotashield was produced under a licence from the National Institutes of Health
- India and the US had an Indo-US Vaccine Action Plan since 1987, that supported rotavirus vaccine development

The first Indian neonatal strain

- In 1985, an “outbreak” of asymptomatic rotavirus infections was observed in the newborn unit of the All India Institute of Medical Sciences (AIIMS)
- 50% for newborns hospitalized for 3 days and 75% for newborns hospitalized for a full week
- All asymptomatic
- All 11 gene segments of the neonatal strains appeared to be identical on the basis of the results of electrophoresis
- Persisted for several years in the newborn unit

The Indo-US Vaccine Action Program

- Supported strain characterization in the US and India
- Early clinical studies in the US
- 1999, licensed to Bharat Biotech
- Early clinical studies repeated in India

- But by the time the vaccine was ready for phase 3, multinational vaccines were licensed in India

Phase 3 study

Study sites: Delhi, Pune and Vellore

Sample size: 6800

Vaccine 32 (2014) 4708–4712

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

WHO report

Placebo use in vaccine trials: Recommendations of a WHO expert panel

Annette Rid[a,*], Abha Saxena[b], Abdhullah H. Baqui[c], Anant Bhan[d], Julie Bines[e], Marie-Charlotte Bouesseau[f], Arthur Caplan[g], James Colgrove[h], Ames Dhai[i], Rita Gomez-Diaz[j], Shane K. Green[k], Gagandeep Kang[l], Rosanna Lagos[m], Patricia Loh[n], Alex John London[o], Kim Mulholland[p], Pieter Neels[q], Punee Pitisuttithum[r], Samba Cor Sarr[s], Michael Selgelid[t], Mark Sheehan[u], Peter G. Smith[v]

Placebo controls may be acceptable even when an efficacious vaccine exists, in the following four possible situations:

When developing a locally affordable vaccine

When evaluating the local safety and efficacy of an existing vaccine

When testing a new vaccine when an existing vaccine is not considered appropriate locally

When determining the local burden of disease

Conducting the phase 3 trial

- Mobile phones given to families: Study contact numbers pre-fed
- Weekly contacts made through home visits or phones; at least one face to face contact per month
- Illnesses managed by study team
- Physicians available round the clock. Home visits made by physician at any time, if requested
- All costs covered by study team

Efficacy of Rotavac

	Number of Cases			
Disease Severity	RVV (N=4354)	Placebo (N=2187)	% Efficacy	95% CI
Severe	93	102	**55.1**	39.9, 66.4
Hospitalized	92	102	**55.6**	40.5, 66.8

No intussusception during 1, 2 or 4 week windows following any dose of vaccine

Licensed by the Indian regulatory authorities in 2014
1 US$ a dose for public markets

Bhandari et al. Lancet 2014

Why only 55% efficacy?

Protection against rotavirus diarrhoea

Outcome and no. of previous infections	No. of episodes	Incidence per 100 child months	Unadjusted relative risk (95% CI)	Adjusted efficacy (95% CI)
Mild diarrhoea				
0	84	3.13		
1	70	1.76	0.56 (0.41 – 0.77)	44 (23 – 59)
2	32	0.91	0.29 (0.19 – 0.44)	72 (58 – 81)
3	15	0.70	0.23 (0.13 – 0.39)	79 (64 – 88)
Moderate to severe diarrhoea				
0	17	0.63		
1	21	0.53	0.83 (0.44 – 1.58)	18 (-57 – 57)
2	10	0.28	0.45 (0.21 – 0.98)	57 (6 - 80)
3	3	0.14	0.22 (0.07 – 0.76)	79 (29 - 94)

Gladstone et al, NEJM, 2011

In March and April 2016, India introduced the indigenous rotavirus vaccine for 9% of the birth cohort

In 2017, an additional 4 states introduced vaccine

In 2018, UP

In 2019, all of India

The second Indian rotavirus vaccine

- Multivalent bovine-human reassortant vaccine developed by NIH, USA
- Bovine rotavirus tetravalent (BRV-TV) vaccine incorporates four reassortant viruses with a VP7 gene of either a G1, G2, G3, or G4 human serotype and 10 genes from the bovine rotavirus UK strain
- NIAID conducted phase1 studies of the individual vaccine components, as well as phase 1 and 2 studies of a quadrivalent version of the vaccine in the US and in Finland
- Licensed to Serum Institute of India (SII) in 2005

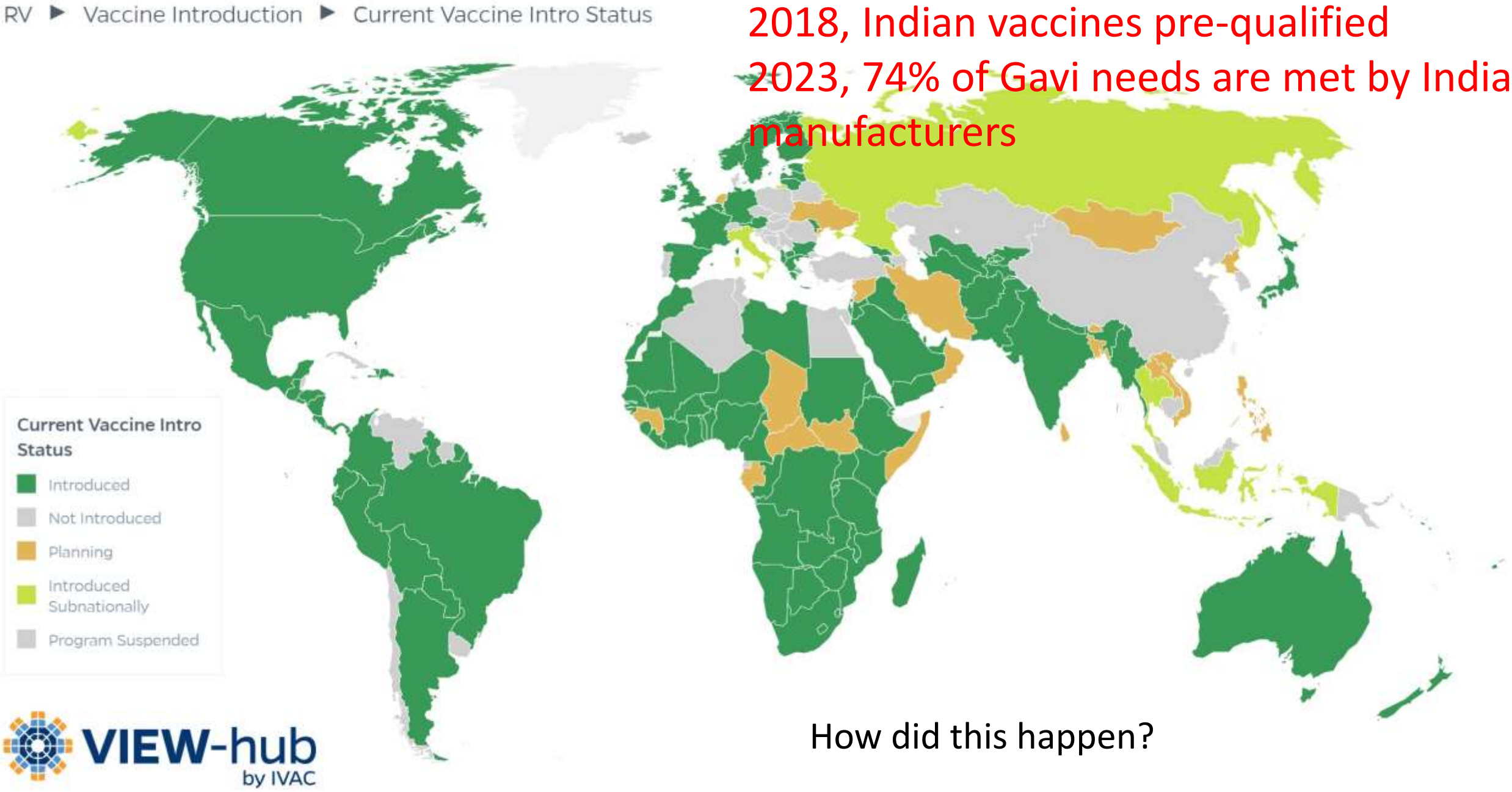
How a new Indian-made vaccine could slow rotavirus death march

Serum Institute of India's BRV-PV vaccine has shown 66.7% efficacy in trials in Africa. Crucially for poor countries, the new rotavirus vaccine requires no refrigeration

Indian Express, 31 March 2017

67% efficacy in Niger
42% efficacy in India

Isanaka et al, NEJM, 2017

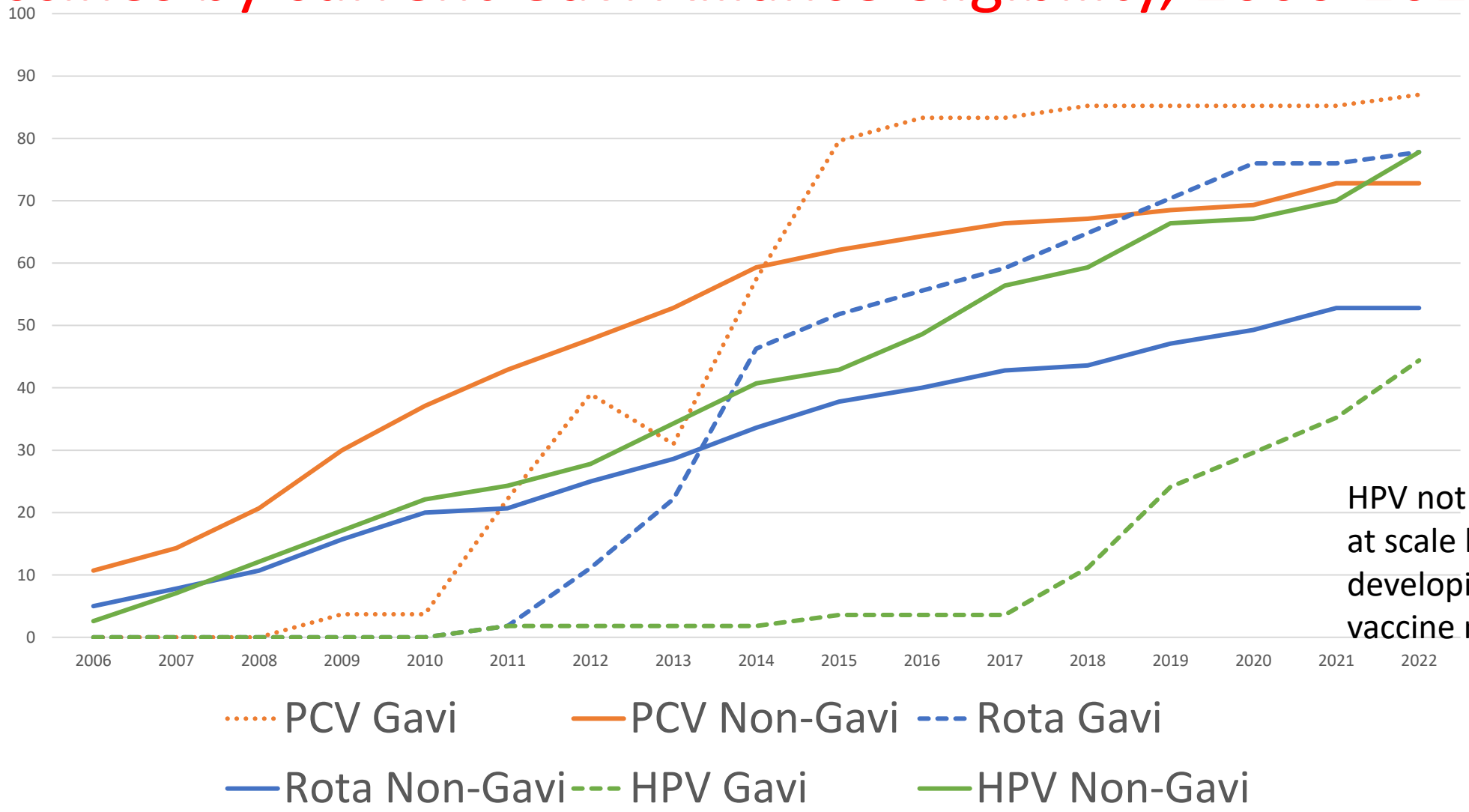


2018, Indian vaccines pre-qualified

2023, 74% of Gavi needs are met by Indian manufacturers

How did this happen?

Percentage of countries that have introduced new vaccines by current Gavi Alliance eligibility, 2006-2022

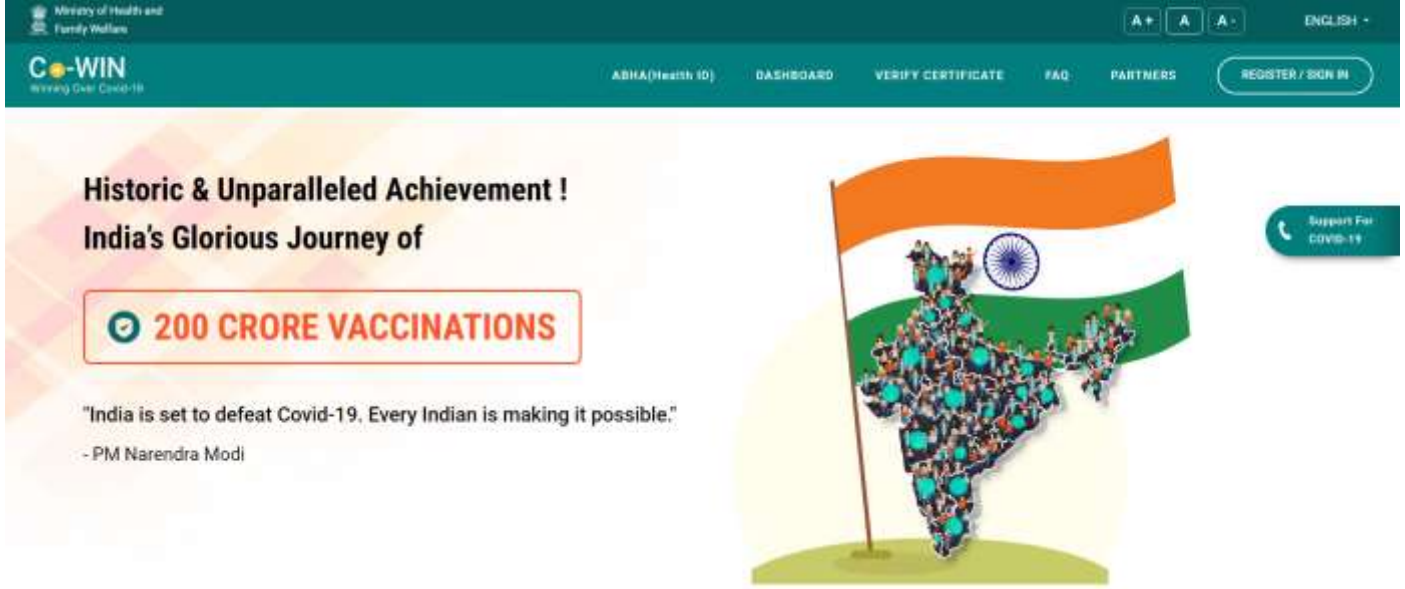


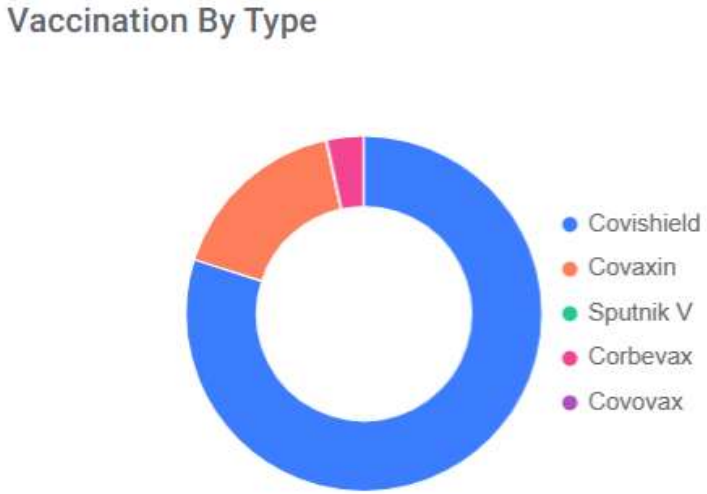
HPV not yet provided at scale by a developing country vaccine manufacturer

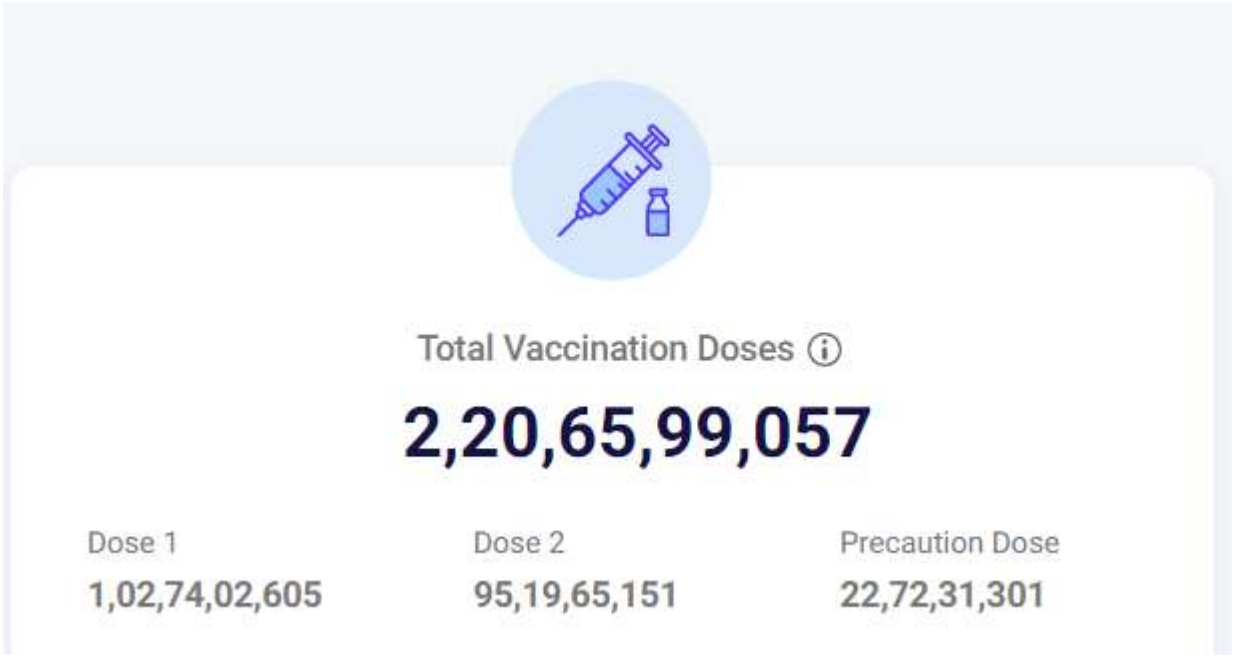
India’s place in the world of vaccines pre-COVID-19

- >60% of vaccines procured by the GAVI Alliance
- 40% of global vaccine manufacture by doses
- 2-3% of global valuation

- What happened with COVID-19?







India imported no vaccines

India was the only country to have supported the making of vaccines on all platforms

Outline

- Foundational medical education
- The needs of context specific research-Enteric infections
- Cholera and oral rehydration
- Growth and development
- Polio vaccination
- Rotavirus vaccines
- Conclusion

Coming full circle-enabling continuum across levels of care

Village/Urban Ward

Population Enumeration/line listing
Outreach Services/Community level care
Community Based Risk Assessment
Awareness Generation – health education
Counselling: Lifestyle changes; treatment compliance
Post Discharge home care

First Level Care, including screening
Use of Point of Care Diagnostics
Medicine Dispensation
Record keeping
Tele-consultation with the Medical Officer
Referral to PHC for confirmation/ complication

SHC-HWC

CHC/SDH/DH

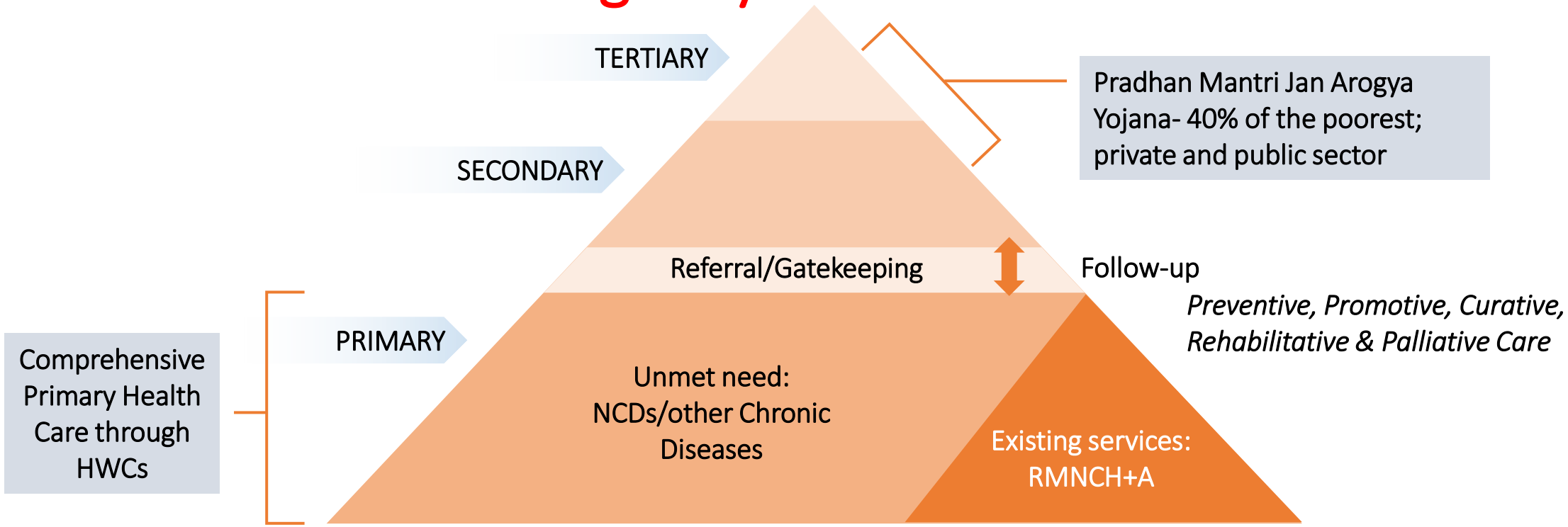
Hando ver and follow up at Home and HWC

Advanced diagnostics
Complication assessment
Hospitalization
Tertiary linkage/PMJAY

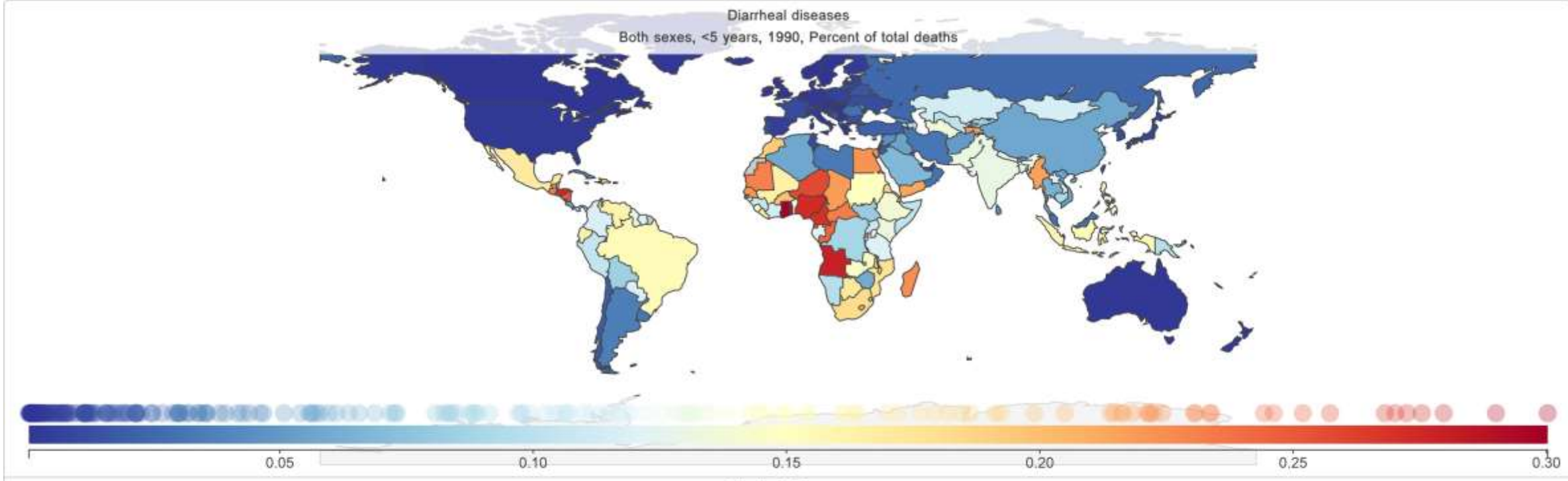
Diagnosis for NCDs
Prescription and Treatment Plan
Gate Keeping role for out patient and inpatient referral / PMJAY
Teleconsultation with specialists

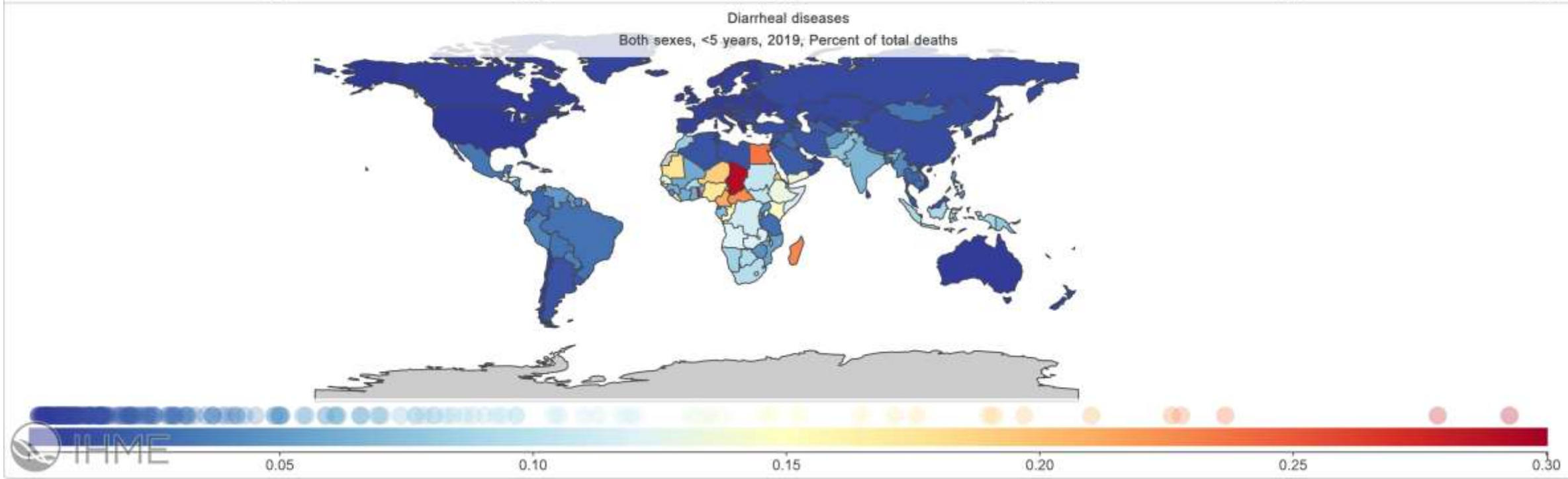
PHC-HWC

Universal Health Coverage: Ayushman Bharat



CONTINUUM OF CARE – Health and Wellness Centres/PMJAY


Diarrheal diseases
Both sexes, <5 years, 1990, Percent of total deaths
0.05
0.10
0.15
0.20
0.25
0.30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IHME


WILLIAMS
RESEARCH
BUILDING


MR. SNOWMAN


WOMEN'S HOSTEL