

Rotavirus Vaccines for Children in Developing Countries: Results of Clinical Trials

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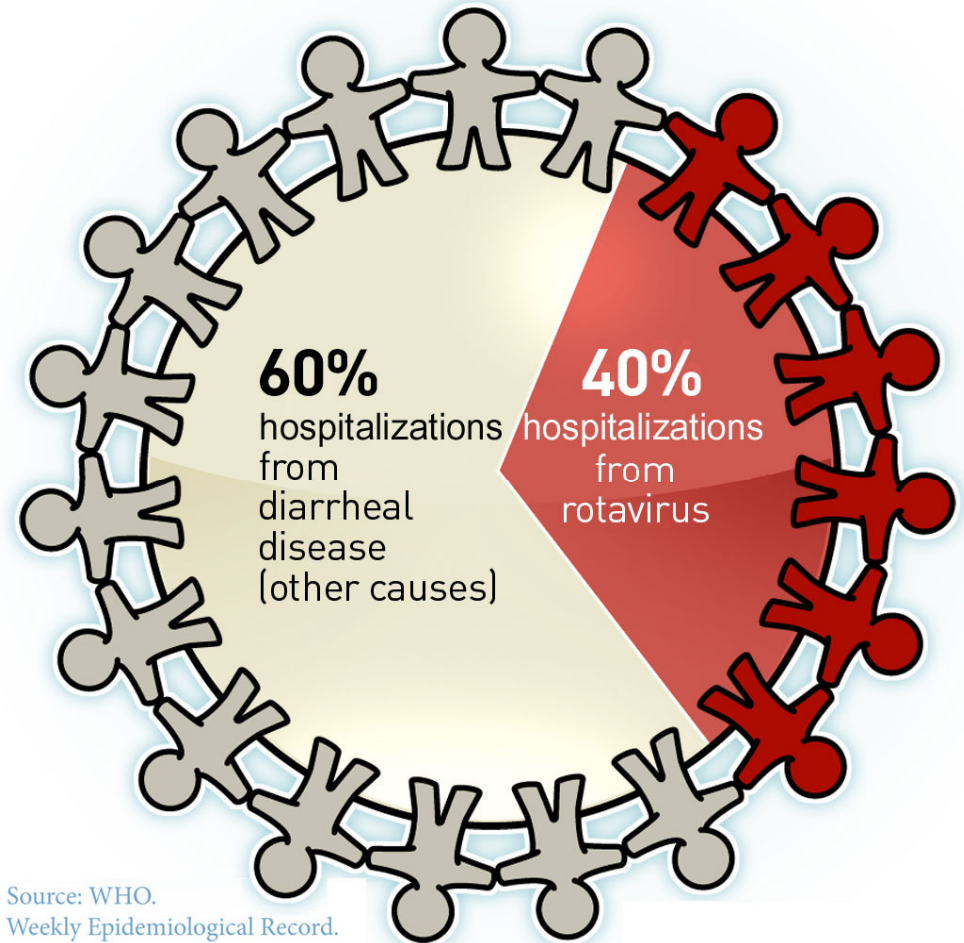


Rotavirus is the most common cause of severe, dehydrating diarrhea among children worldwide

Each year it causes:

- 111 million cases
- 25 million outpatient visits
- 2 million hospitalizations
- Over 500,000 deaths

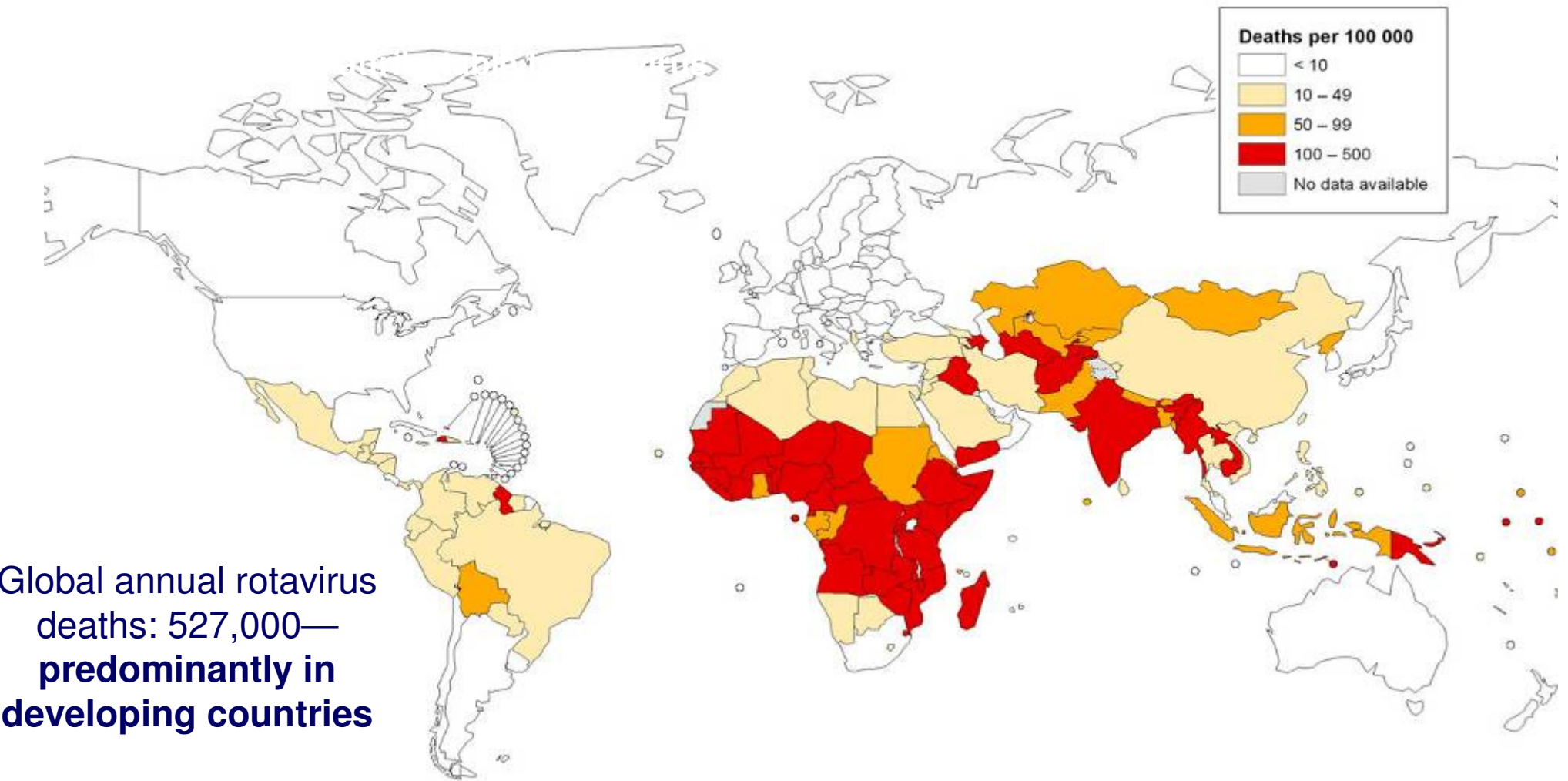
Global surveillance shows that 40% of diarrheal hospitalizations in young children are due to rotavirus



Source: WHO.
Weekly Epidemiological Record.
2008;83(47).



Asia and Africa carry the greatest rotavirus disease burden



Currently available rotavirus vaccines

	Rotarix® (GSK Bio)	RotaTeq® (Merck)
Origin	Human monovalent	Bovine pentavalent
Strain	G1, P[8]	G1, G2, G3, G4, P[8] & G6P[7]
Vaccine course	2 doses - oral	3 doses - oral
Pivotal Phase III trial	n=63,225 (20,169 for efficacy) Latin America and Finland	n=70,301 (5,673 for efficacy) Latin America, US and Finland
Efficacy vs rotavirus GE	85% - 100% vs severe rota GE	98% vs severe rota GE
Efficacy vs all-cause severe GE	42% hospitalization for severe GE of any cause	59% hospitalization for diarrhea of any cause
Intussusception risk	No association observed	No association observed

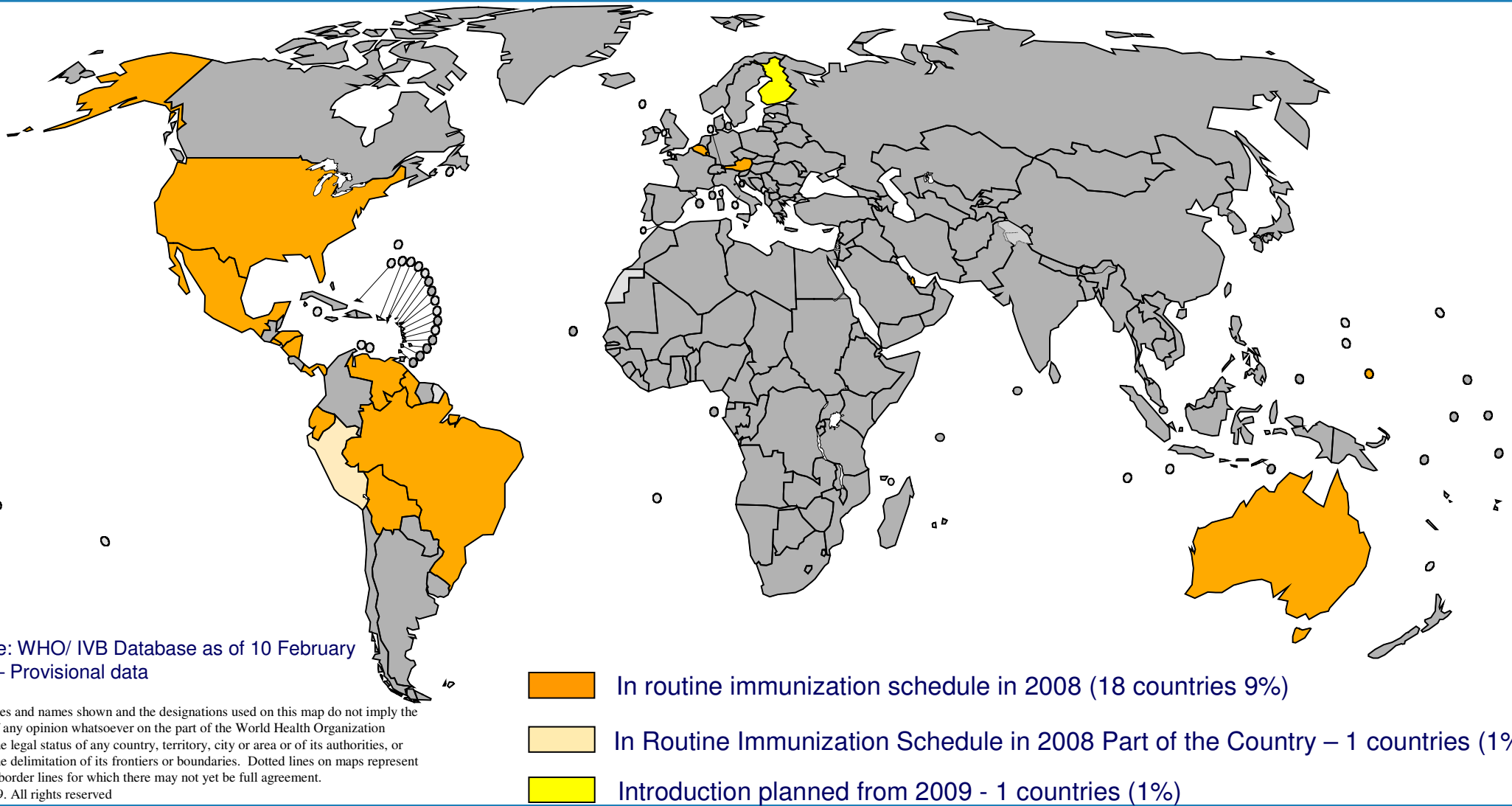


Background on rotavirus vaccine recommendations

- November 2005
 - SAGE recommended *"inclusion of rotavirus vaccination into the national immunization programmes of regions and countries where vaccine efficacy data suggest a significant public health impact..."*
 - Because of concerns that *"live oral vaccines may not be fully effective in protecting the poorest children in developing countries,"* SAGE noted *"the need for urgently generating efficacy data in Asia and Africa, where the disease burden is very high."*

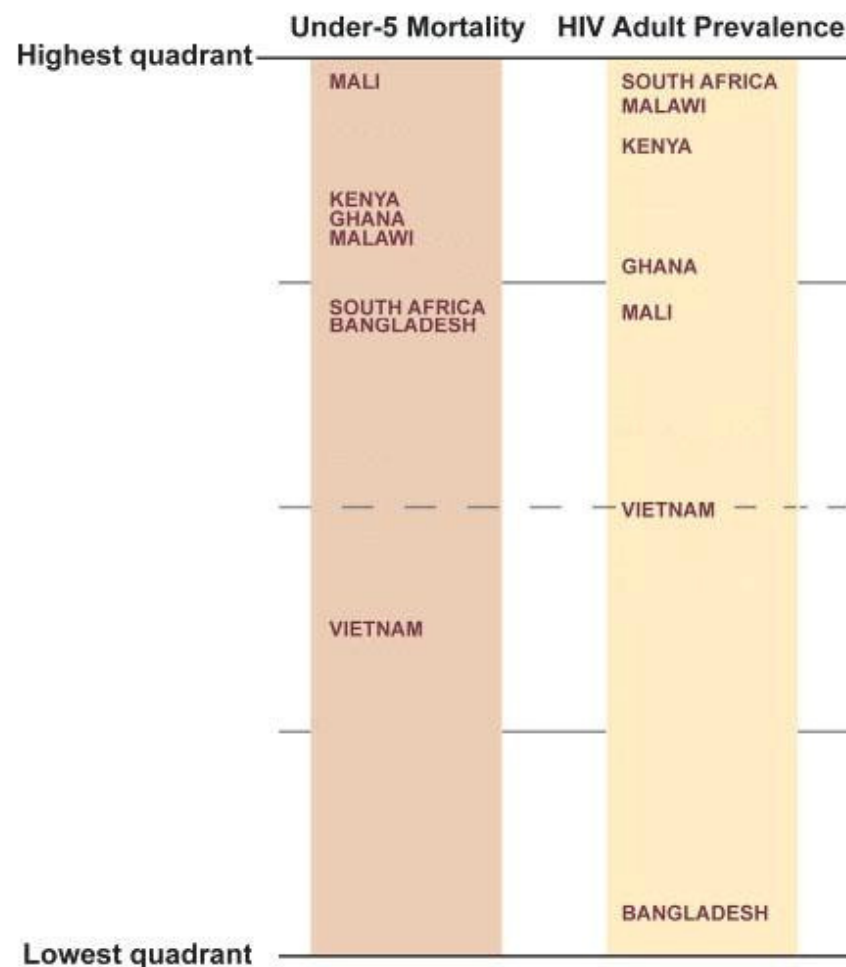


Status of global rotavirus vaccines introduction, 2008

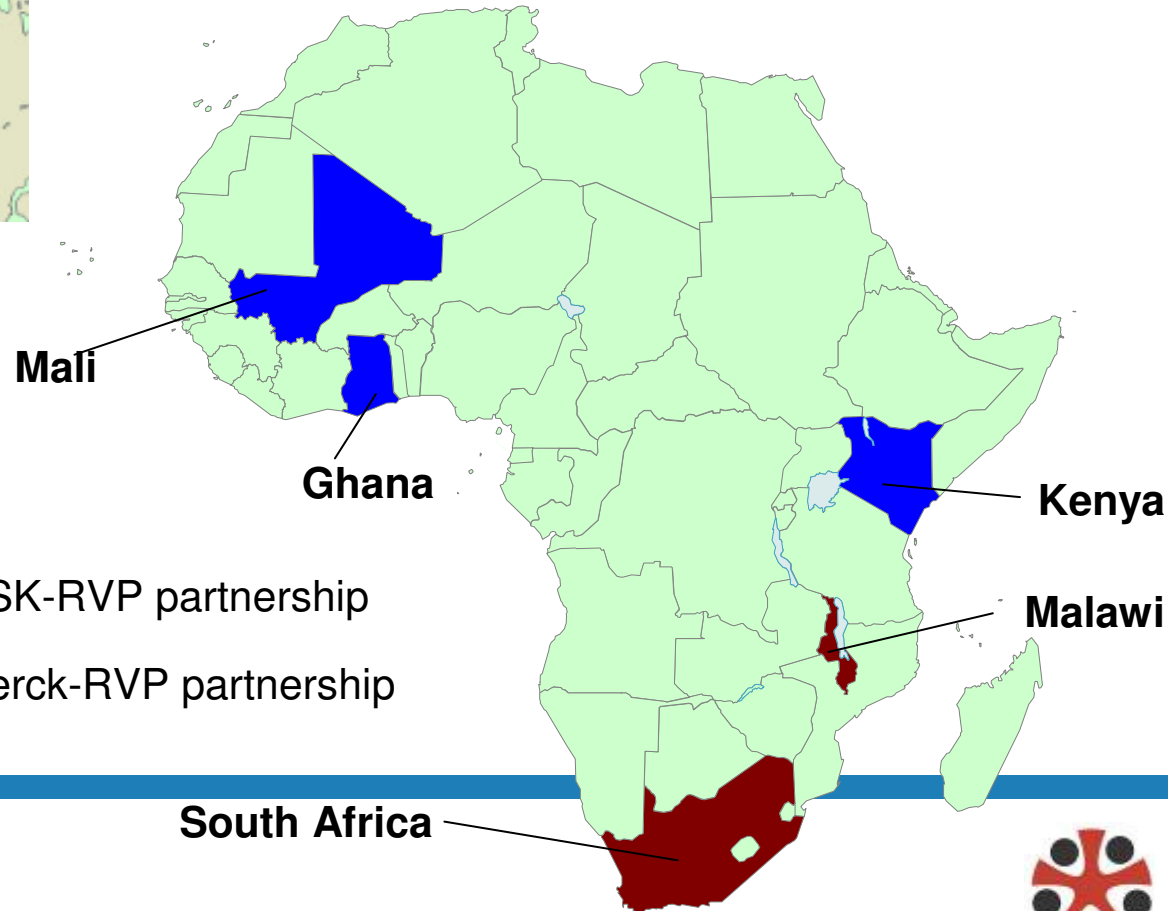


Clinical trials of rotavirus vaccines in Africa and Asia

- From 2005-2009 - 3 RCT that included over 12,000 children at sites in 7 countries
- Nearly all children followed through the first year of life and majority followed into the second year of life



Rotavirus vaccine study sites



GSK-RVP Phase III efficacy trial in Africa

- Phase III, RCT of efficacy, safety, and immunogenicity
 - 2 or 3 doses of live, attenuated human monovalent vaccine (Rotarix™, GSK)
 - South Africa (PI: Dr. Mari Kirsten)
 - Malawi (PI: Dr. Nigel Cunliffe)
- Trial began October 2005
- 4941 children enrolled
- Subject follow-up completed in January 2009



Methods – Study design

Treatment group	Dose1 (6 wks)	Dose2 (10 wks)	Dose3 (14 wks)
3 doses	Rotarix™	Rotarix™	Rotarix™
2 doses	placebo	Rotarix™	Rotarix™
Placebo	placebo	placebo	placebo

- Routine EPI vaccines, including oral polio vaccine (OPV), co-administered
- HIV-positive infants not excluded
- Breastfeeding not restricted



Methods - continued

- **Gastroenteritis:** Diarrhea (3 or more looser-than-normal stool/24 hours) with or without vomiting.
- **Active, weekly surveillance**
- **Severity:** Score ≥ 11 on 20-point Vesikari scale.
- **Confirmation:** Stools analyzed for rotavirus by ELISA (Rotaclone™).
 - Rotavirus positive samples tested by RT-PCR based method, followed by reverse hybridization assay to determine the G and P types.



Primary Outcome

Infants with at least one episode of severe rotavirus gastroenteritis during the period from 2 weeks post-last dose until one year of age were counted as the primary outcome in the *Rotarix*-pooled and placebo groups.



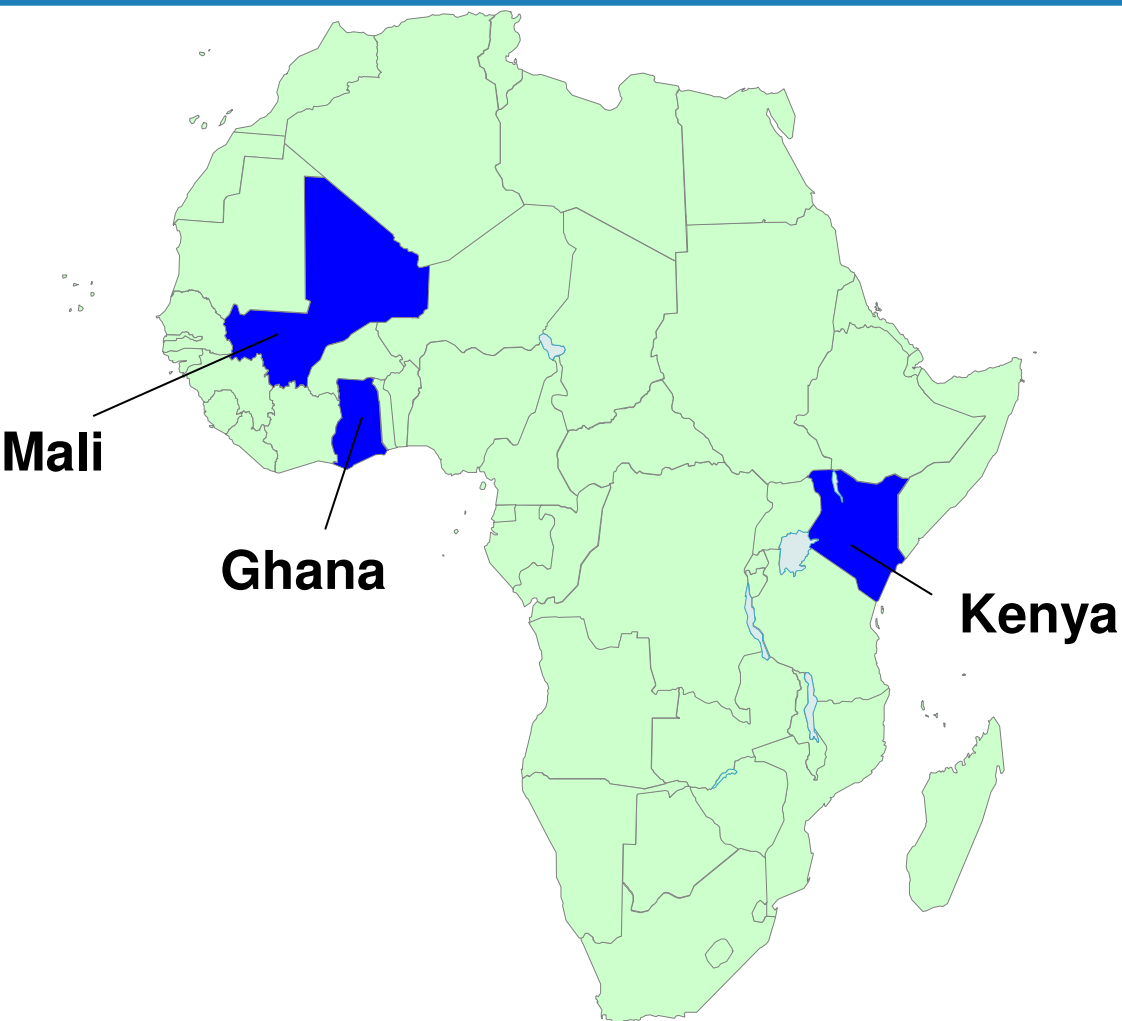
Primary Outcome

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Severe Rotavirus GE	Pooled Vaccine		Placebo		Efficacy (%)	95% CI
	# Cases	%	# Cases	%		
	56	1.9	70	4.9	61.2	44, 73



RotaTeq[®]: Phase III Study of Efficacy, Safety, and Immunogenicity



Ghana (PI: Dr. George Armah)

Site: rural Navrongo DSS

Kenya (PI: Dr. Rob Breiman)

Site: rural Kisumu DSS

Mali (PI: Dr. Samba Sow)

Site: urban Bamako



Methods – Study design

- **Double-blind, placebo-controlled trial of RotaTeq®**
- **3 doses given at ~6, 10, 14 weeks of age**, with routine EPI vaccines, including oral polio vaccine (OPV), when possible
- **No exclusions for HIV** (voluntary counselling and testing offered to all subjects at Kenya site)
- **No restriction on breastfeeding**
- **Primary outcome:** Severe rotavirus gastroenteritis (RVGE) caused by any rotavirus serotype 14 days following the third dose until end of study follow-up
- **Primary analysis:** pooled three African countries



Methods – Outcome Measures

- **Gastroenteritis:** diarrhea (3 or more looser-than-normal stools within 24 hours) and/or vomiting
- **Clinical Data Collection:**
 - Symptom data solicited from parents upon presentation to healthcare center
 - Clinical data then collected prospectively by physicians
- **Severity:** Score ≥ 11 on 20-point Vesikari scale
- **Confirmation:** Stools collected and analyzed for rotavirus by standard EIA format.
 - Rotavirus positive samples tested by RT-PCR based method for wildtype determination, as well as to determine the G and P genotypes



Details of Trial of RotaTeq® in Africa

- Enrollment began April 28, 2007
- 5,468 infants vaccinated
- Follow-up completed March 31, 2009
 - Nearly all children through at least one year of age
 - Majority of children through second year of life
- No safety concerns identified by the Data Safety Monitoring Board (DSMB)



RotaTeq[®]: Phase III Study of Efficacy, Safety, and Immunogenicity



Bangladesh (PI: Dr. K. Zaman)

Site: rural Matlab HDSS

Vietnam (PI: Dr. Duc Anh)

Site: urban and periurban Nha Trang DSS



Details of Trial of RotaTeq® in Asia

- Study design: protocol identical to clinical trial of RotaTeq® in Africa
- First efficacy trial in GAVI-eligible countries in Asia
- Enrollment began March 29, 2007
- 2,036 infants vaccinated
- Follow-up completed March 31, 2009
- No safety concerns identified by the Data Safety Monitoring Board (DSMB)



Further improving the impact of rotavirus vaccines

- Clinical trial data and early introduction experience can help us understand how to improve impact of these vaccines
 - OPV and maternal antibody effects on immunogenicity
 - Optimal dosing regimen and schedule
 - Effect of co-infections
 - Correlate of protection
- Indirect effects of these vaccines may be substantial



SAGE recommends the inclusion of rotavirus vaccination of infants into all national immunization programs

2009, 84, 213–236

No. 23



World Health
Organization

Organisation mondiale de la Santé

Weekly epidemiological record Relevé épidémiologique hebdomadaire

5 JUNE 2009, 84th YEAR / 5 JUIN 2009, 84^e ANNÉE

No. 23, 2009, 84, 213–236

<http://www.who.int/wer>

Rotavirus vaccination

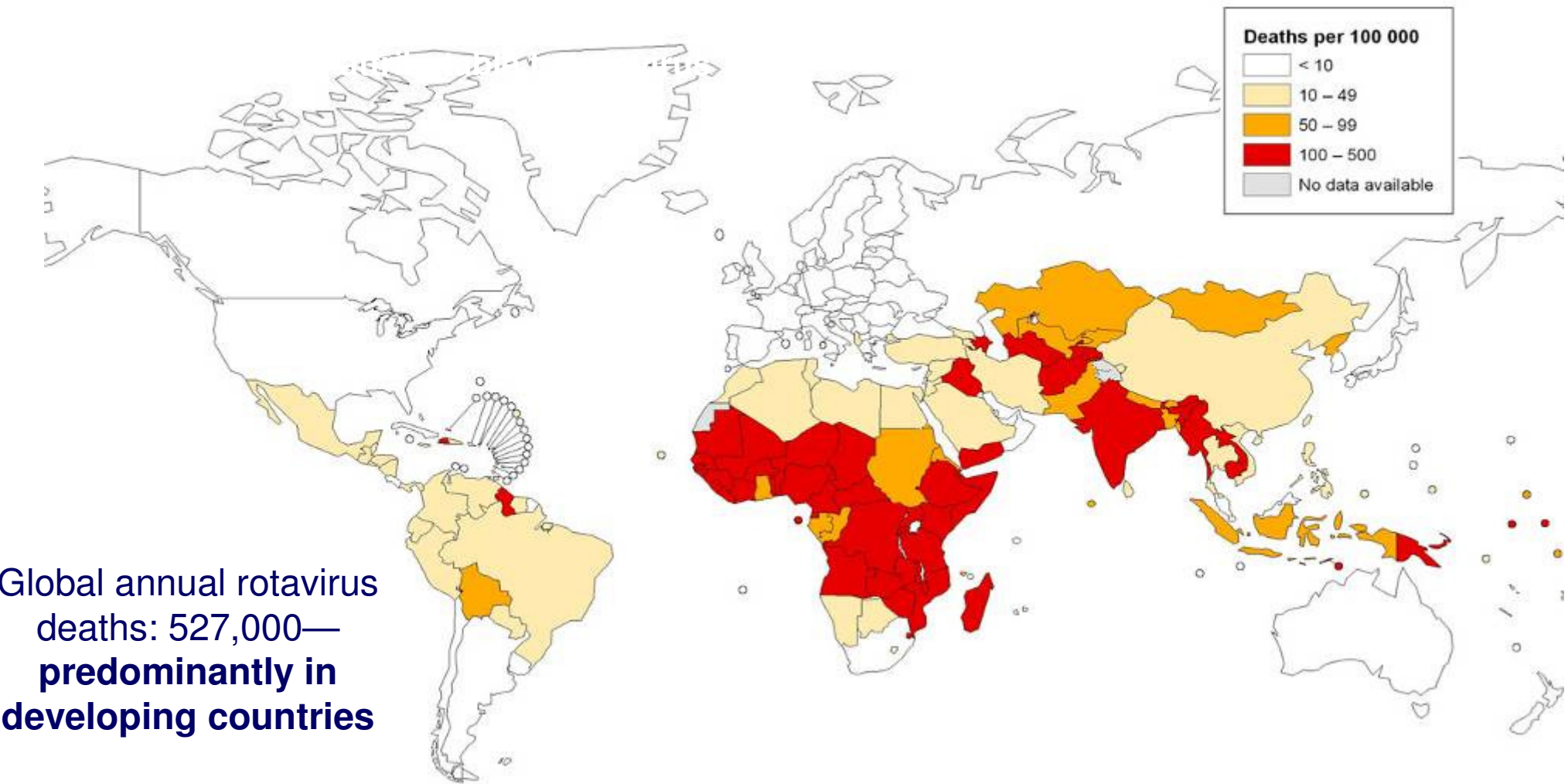
Data from trials in Latin America, Europe and the United States of 2 oral, live, attenuated rotavirus vaccines, Rotarix (GlaxoSmithKline) and RotaTeq (Merck & Co., Inc.) were reviewed by SAGE in 2005.⁸ Noting the variable efficacy of live, oral vaccines in different populations, SAGE considered that the introduction of vaccines would be appropriate only in regions where successful phase III efficacy trials had been conducted. SAGE therefore recommended that rotavirus vaccines be included in national immunization programmes in countries where data on vaccine efficacy suggest a significant public health impact; SAGE also noted the need to urgently generate such data in Africa and Asia.

Vaccination antirotavirus

En 2005, le SAGE a examiné les données d'essais cliniques menés en Amérique latine, en Europe et aux États Unis concernant 2 vaccins antirotavirus vivants atténués pour voie orale, le Rotarix (GlaxoSmithKline) et le RotaTeq (Merck & Co. Inc.).⁸ Notant que l'efficacité des vaccins vivants pour voie orale variait selon les populations, le SAGE a estimé judicieux de les adopter seulement dans les Régions où des essais d'efficacité de phase III avaient été effectués avec succès. Il a par conséquent recommandé que les vaccins antirotavirus soient inclus dans les programmes de vaccination nationaux des pays où les données sur l'efficacité des vaccins semblent indiquer qu'ils ont des répercussions importantes en santé publique; il a par ailleurs noté qu'il était urgent d'obtenir des données de ce type en Afrique et en Asie.



From 1999 – 2009: Over 5 million children died from rotavirus disease



2010– 2019: Over x million child deaths prevented by rotavirus vaccines?

