Rotavirus Vaccines: Global Progress with Introduction into National Immunization Programmes and Lessons Learnt

Duncan Steele, Robin Biellik, Kathy Neuzil

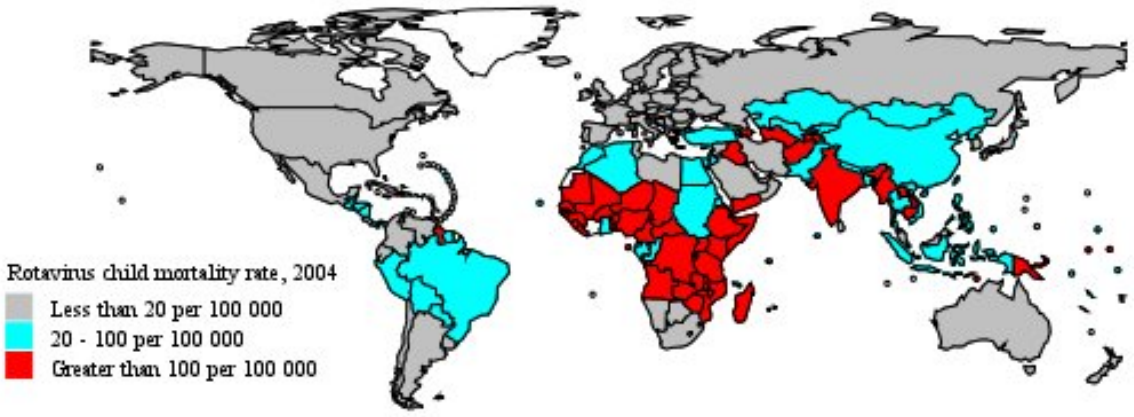
Rotavirus Vaccine Programme, PATH

Outline of presentation

- Status of global recommendations for rotavirus vaccines
- Status and Impact of pre-qualification of rotavirus vaccines
- Status of vaccine introduction in routine childhood immunizations schedules
- Lessons learnt with early introducing countries

Rotavirus: Global Burden of Illness

- Major cause worldwide of severe dehydrating gastroenteritis
- ~ 527,000 deaths per year
- >90% occur in poorest countries
- Several million hospitalizations per year
- Billions of $ in medical and indirect costs associated
- Sanitation and other diarrheal disease control efforts have limited effect



IVR, WHO 2007

GSK Rotarix™ - human, live, attenuated, oral Rotavirus Vaccine

- Lyophilized vaccine reconstituted with $CaCO_3$ buffer
  - human G1P8 strain
  - cross-protective of multiple strains
  - high efficacy and safety, no interference with OPV or other vaccines
  - 2-doses, given <24 weeks of age
- Current presentation:
  - mono-dose, 1 ml/dose
  - +2ºC to +8ºC, must not freeze
  - non-standard handling
  - large per-dose volume
  - VVM on UNICEF-supplied vaccine
  - WHO prequalified Jan 2007

New presentation from 2009:
All-liquid formulation (1.5 ml dose)
EMEA approved

Merck RotaTeq® - human-bovine reassortant, live, attenuated, oral, Rotavirus Vaccine

- Liquid vaccine, 5 human-bovine reassortant strains:
  - G serotypes - human G1, G2, G3 and G4; bovine G6
  - cross-protective of multiple strains
  - high efficacy and safety, no interference with OPV or other vaccines
  - 3-doses, given <32 weeks of age
- Current presentation:
  - mono-dose, 2 ml/dose
  - +2ºC to +8ºC storage
  - administered like OPV,
  - large per-dose volume
  - VVM to be developed
  - WHO prequalified: October 2008

Rotarix® vaccine efficacy: results of phase 3 studies

	Vaccine N=9,009	Placebo N=8,858	Efficacy (95% CI)
Against severe RV gastroenteritis	12	77	85 (72-92)
Against hospitalized RV gastroenteritis	9	59	85 (70-94)
Against any severe gastroenteritis	183	300	40 (28-56)
Against any hospitalized gastroenteritis	145	246	42 (29-53)
Against G1 infection	3	36	92 (74-98)
Against G3/G4/G9* infections	4	31	87 (64-97)
Against G2* infections	6	10	41 (<0-82)

Source: Ruiz-Palacios et al., NEJM 354:11-22; 2006

RotaTeq® vaccine efficacy: results of phase 3 studies

	Vaccine N=2,834	Placebo N=2,839	Efficacy (95% CI)
Against severe RV gastroenteritis	1	51	98 (88-100)
Against hospitalized or out-patient RV gastroenteritis	19	329	95 (91-97)
Against any RV gastroenteritis	82	315	74 (67-80)
Against G1 infection	72	286	75 (67-81)
Against G2 infections	6	17	63 (3-88)
Against G3 infections	1	6	83 (<0-100)
Against G4 infections	3	6	48 (<0-92)
Against G9* infections	1	3	65 (<0-99)

Source: Vesikari et al., NEJM 354:23-33; 2006

WHO Current Stance on Rotavirus Vaccines

1. **SAGE** recommendations for phased regional introduction in certain regions, but not a global recommendation

   Will review efficacy data from GSK-RVP in Africa in April 2009

2. Status of WHO **pre-qualification** of the rotavirus vaccines contains a caveat on the indication of the use of the vaccine

3. **Global Advisory Committee on Vaccine Safety**.

   Considered intussusception and recommended that post-marketing surveillance for safety is required.

   Considered Kawasaki disease and decided that there is no cause for concern with no evidence of association demonstrated.

4. **WHO Rotavirus Vaccine Position Paper** on the use of rotavirus vaccines, includes a restriction on the ages when the vaccines can be used

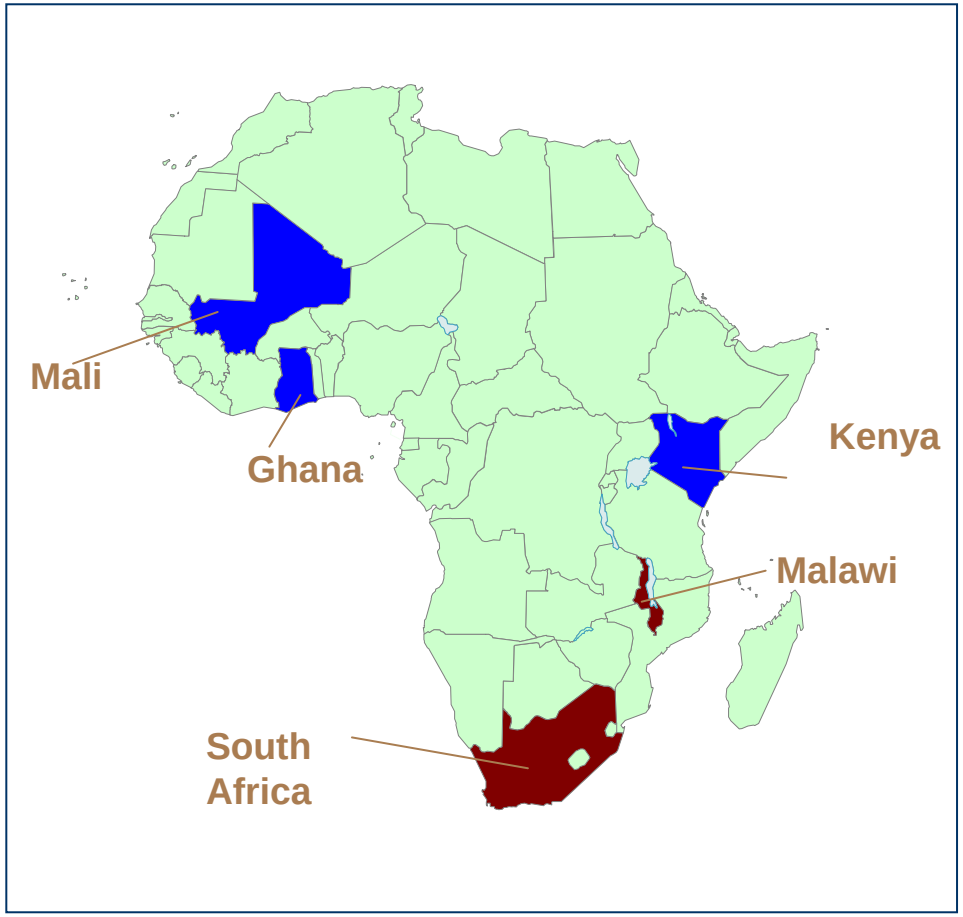
WER 2006; 82:8; WER 2006; 82:11; WER 2007; 82:256-7; WER 2007; 82:285-96

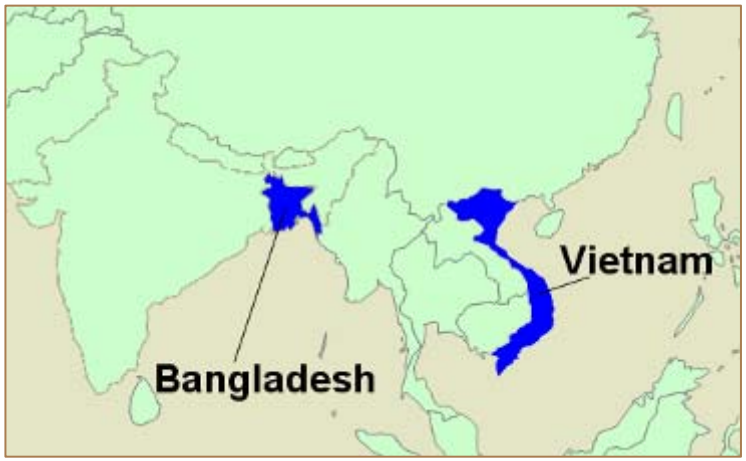
WHO Position Paper* - recommendations to countries

1. Include rotavirus vaccine in immunization programmes where vaccine efficacy data suggest significant public health benefit.
2. Conduct vaccine efficacy studies in Africa and Asia.
3. Conduct rotavirus surveillance rotavirus to assess the impact of rotavirus vaccine in reducing disease.
4. Conduct rotavirus strain characterization to assess strain distribution pre- and post-vaccine introduction.
5. Ensure that rotavirus vaccine is not administered above the recommended maximum ages.
6. Conduct post-marketing safety surveillance of rotavirus vaccine to confirm lack of safety problems observed in clinical trails.
7. Study and consider vaccine cost-effectiveness, affordability and financial sustainability.
8. Prepare carefully for vaccine introduction, particularly cold chain capacity, health worker training, IEC, etc.

Weekly Epidemiological Record, 10 August 2007

Phase III clinical trials: Sites in Africa and Asia





- GSK-RVP partnership
- Merck-RVP partnership

SAGE conclusions and recommendations (Nov 2008)

SAGE received an update on rotavirus vaccine introduction and surveillance and preliminary data on the Rotarix efficacy trials in Malawi & South Africa.

Rotavirus vaccines do not interfere with the immune response to OPV vaccines and vice versa. A preliminary analysis of the study in Malawi and South Africa demonstrated that Rotarix significantly reduced severe rotavirus gastroenteritis, even in settings with many challenges.

Requested a detailed report of the Rotarix trials in Africa and other pertinent information – this ***"may warrant global recommendations to be considered by SAGE in its April 2009 meeting".***

WER 9 January 2009; 84: 13-14

Status of rotavirus vaccine pre-qualification and the impact on global introduction in EPI

Pre-qualification of Rotavirus Vaccines

Rotarix* is WHO pre-qualified for procurement by the UN agencies

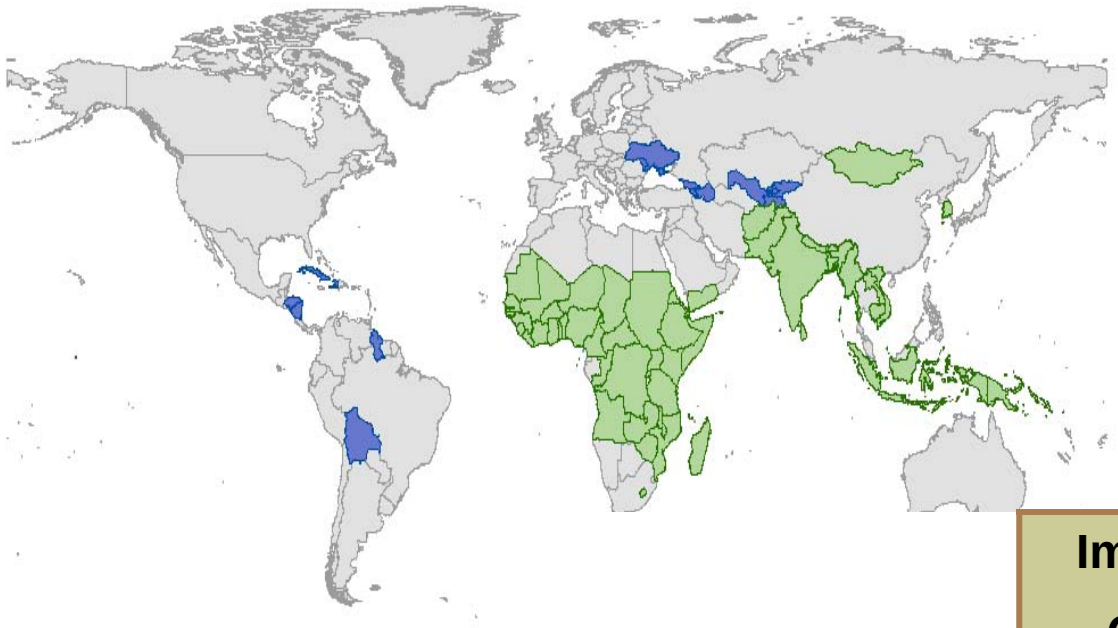
RotaTeq# is WHO pre-qualified for procurement by the UN agencies

**The approved indication for the use of this vaccine does not yet extend to all countries of the world and that additional evidence of safety and efficacy is being generated to support use of the vaccine in Africa and Asia*

Vaccine introduction strategy for GAVI-eligible countries

- GAVI Board decision (2006), based on SAGE recommendation and WHO position paper: targeting regions in 2 phases:
  - 1st phase: subsidized vaccine approved for immediate support in American and European regions where clinical trials were conducted
  - 2nd phase: SAGE to review current recommendation in April 2009
- Successful applications for rotavirus vaccine:
  - Bolivia and Honduras (introduced 2008), Guyana (2009)
- Impact studies in progress:
  - Nicaragua -- Merck vaccine
  - Honduras – GSK vaccine
  - Bangladesh – GSK vaccine

GAVI and Rotavirus Vaccines



SAGE Recommendation and GAVI support;

low mortality

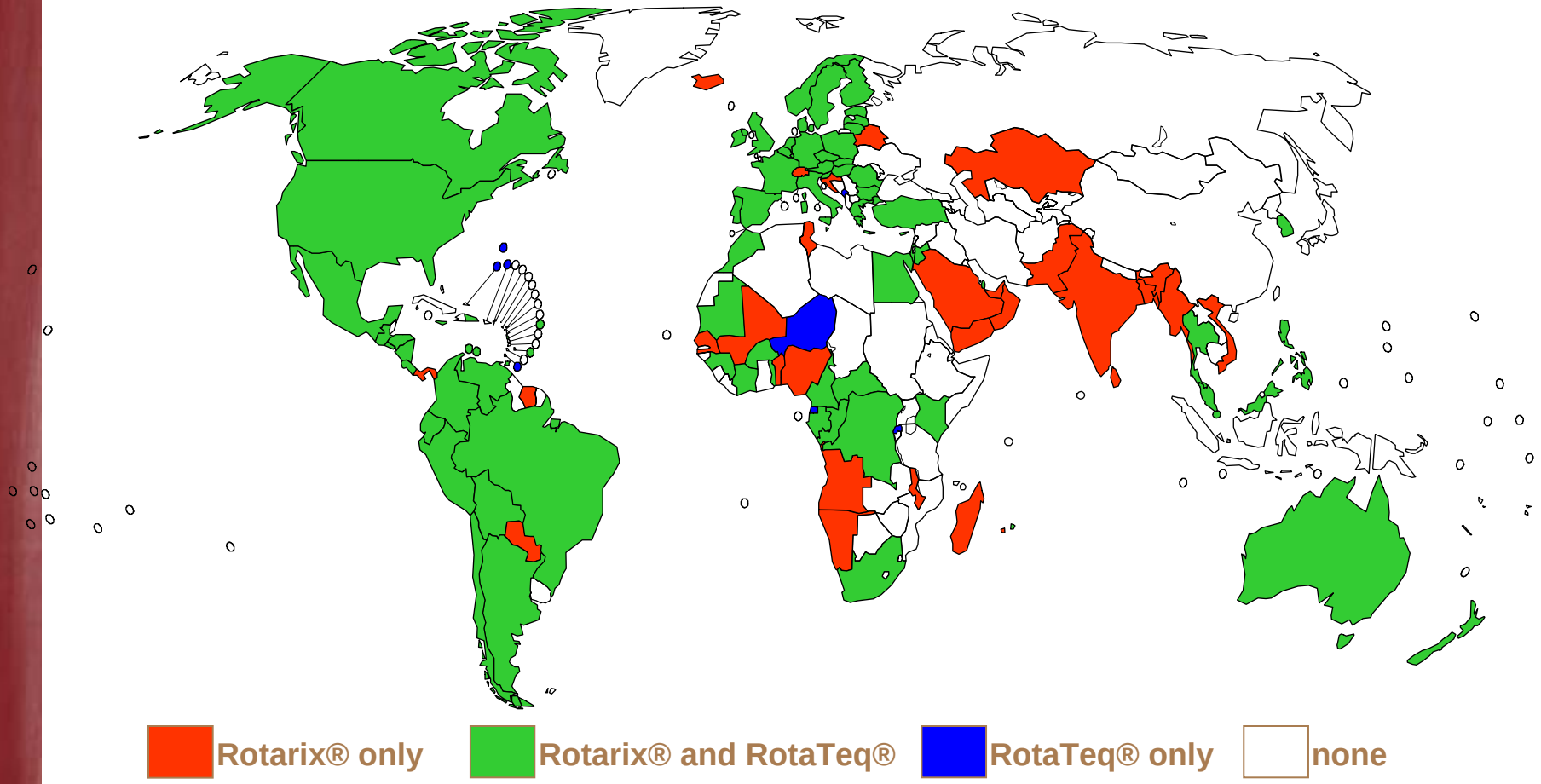
No SAGE Recommendation or GAVI support;

high mortality

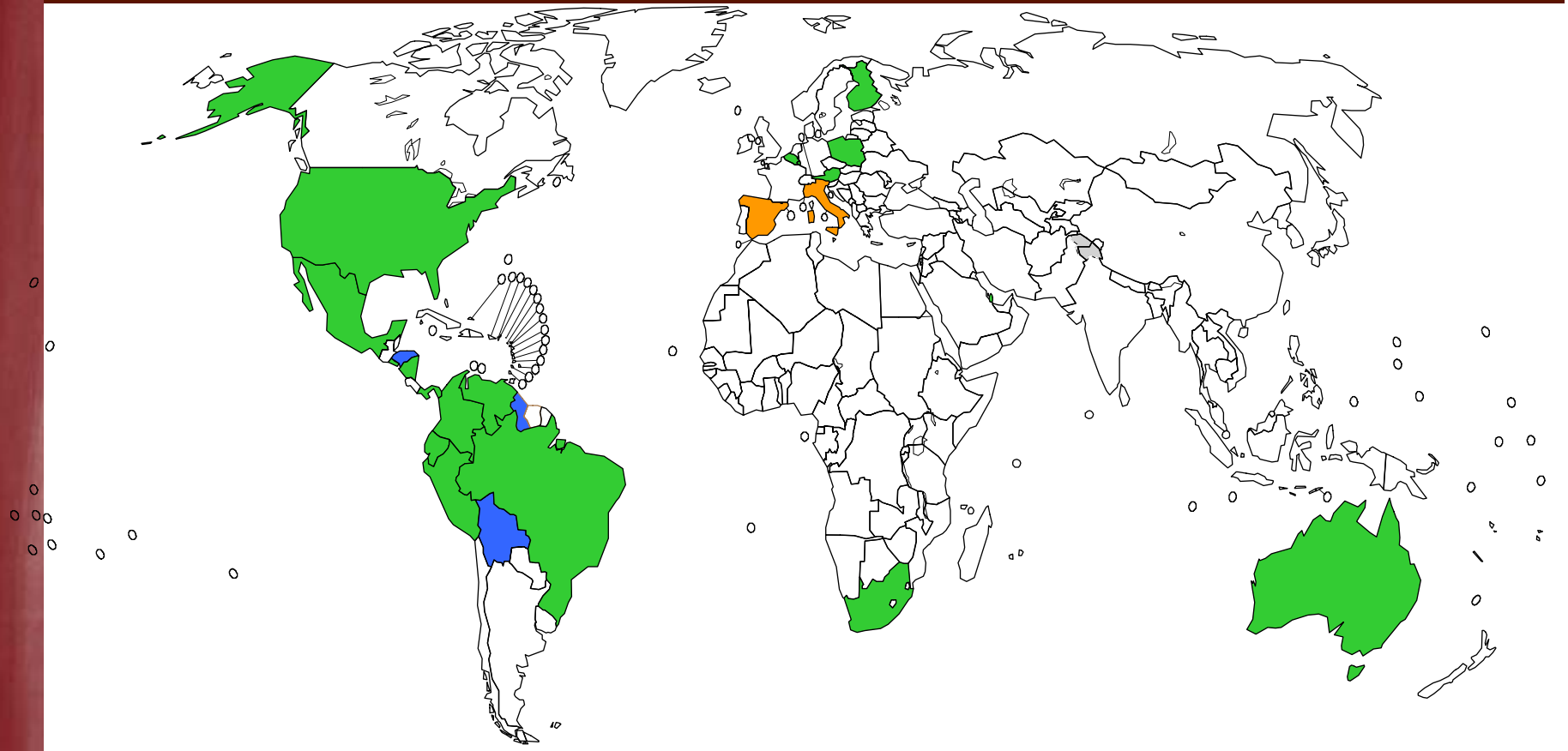
	Impact One	Impact Two
Start Vaccine Adoption	2007	2010
Geographic Focus	L. America, E. Europe	Asia, Africa
Available Vaccines at start of Impact phase	Rotarix®	Rotarix® RotaTeq®

Status of rotavirus vaccine introduction in routine childhood immunization schedules

Global status of Rotavirus vaccine licensure, November 2008

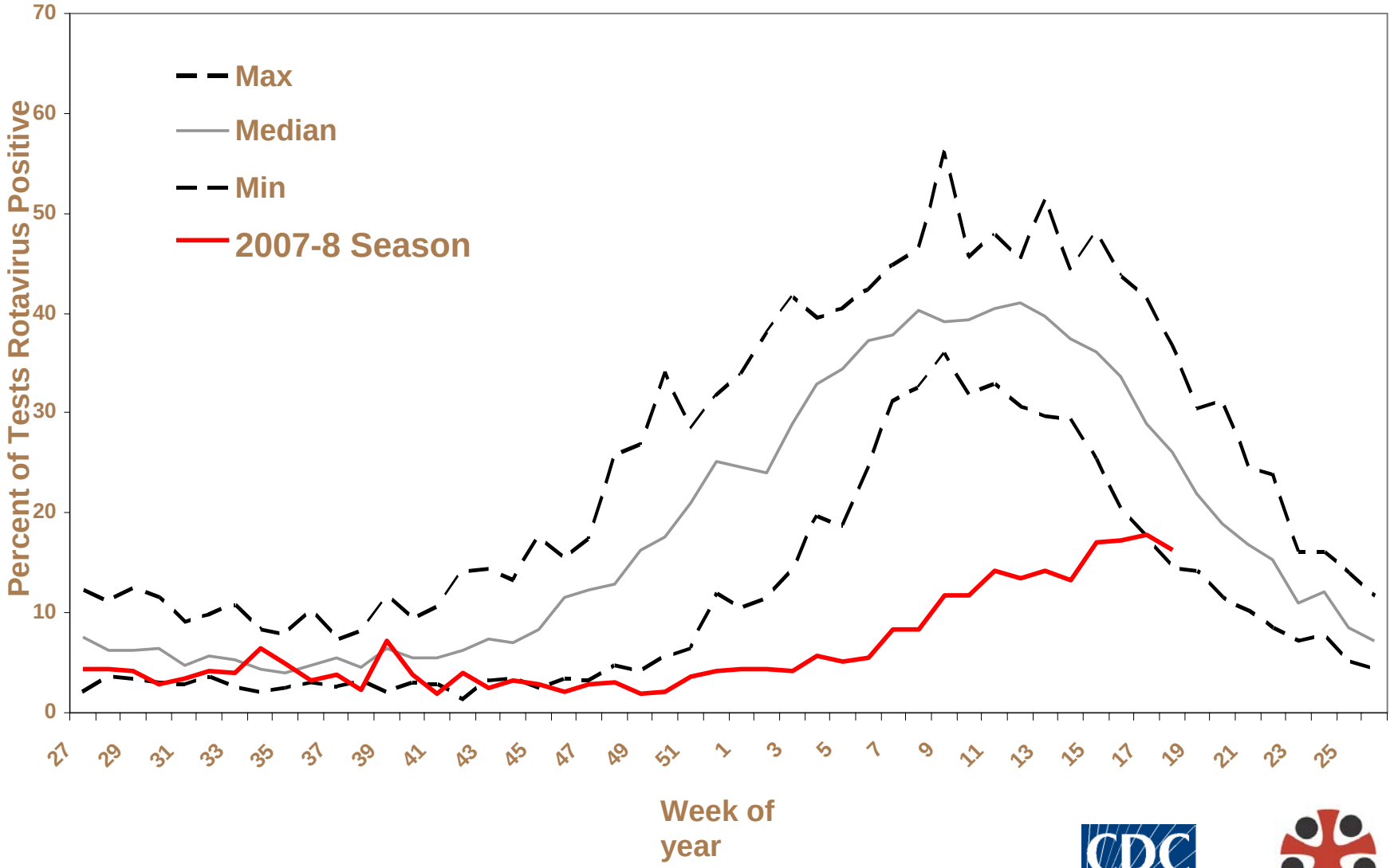


Status of public-sector Rotavirus vaccine introduction, 2008*



*as of end November 2008

Proportion of rotavirus positive tests from NREVSS labs, 1991-2006, compared with 2007-2008, by week of year, USA



Source: Panozzo C et al. MMWR 2008

SAVIC Symposium, Johannesburg. February 2009

Lessons Learnt with Rotavirus Vaccines

Operational issues associated with introducing Rotavirus vaccine

- Vaccination schedule, cards, registers modified
- Vaccine management and logistics planned:
  - forecasting supply
  - cold chain capacity
  - transport requirements
  - waste disposal
- Social mobilization, IEC for health workers and public
- Health worker training and supervision
- Roll-out:
  - phasing-in
  - post-introduction monitoring:
    - vaccination coverage, drop-out, wastage
    - adverse events, especially intussusception
  - impact evaluation

Lessons learned from Rotavirus Vaccine Introduction in Latin America

- Increased cold chain volume requirement:
  - Additional refrigerators
  - Additional transport volume
  - Increased frequency of vaccine deliveries
- Attention to training and supervision on vaccine handling, to avoid incorrect administration:
  - Incidents where GSK vaccine has been administered IM
  - Incidents where Merck vaccine has been administered like OPV drops
- Attention to punctuality of attendance to avoid passing maximum age to receive last dose:
  - GSK 1st dose not to be given >12 weeks, 2nd dose not to be given >24 weeks
  - Merck 3rd dose not to be given >32 weeks (>8 months in USA)

D'Oliveira et al. Expert Rev Vaccines 2008

Per-dose cold chain capacity requirements

Lyophilized Rotarix™ box of 25 single-dose vials, diluent inside cold chain

111 cc/dose

Lyophilized Rotarix™ box of 25 single-dose vials, diluent outside cold chain

11 cc/dose

Liquid Rotarix™ box of 50 single-dose vials

17 cc/dose

Liquid RotaTeq® box of 50 single-dose vials

85 cc/dose

[to be reduced by ~40% in next 2 years]

Correct administration

- Rotavirus vaccine must not be injected! Programmatic errors have been reported
- Large vaccine volume requires full insertion of vial tip into infant's mouth
- Contact with infant's mouth contaminates vial, complicates development of multi-dose vials

Summary

- Rotavirus vaccines are being successfully introduced in many countries in the Americas and Europe
- Efficacy data is being generated in multiple countries in Africa and Asia, including those with high mortality, low socio-economic, high co-morbidity and other infections
- SAGE recommendation for global introduction is likely in 2009
- GAVI Board approval for vaccine subsidy support is likely.
- Anticipated that this will lead to many more countries introducing rotavirus vaccines
- Some challenges remain for rotavirus vaccine introduction