Rotavirus Epidemiology and Prospects for Immunization in South Africa

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Rotavirus Introduction

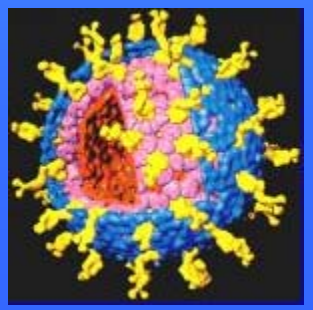
- Rotavirus is ubiquitous - 95% of children worldwide infected by 1–3y of age[1]
- “Democratic virus” – sanitation/clean water not reduced infection, prevalence of infection in Peru = USA
- The younger the child, the higher the risk of severe disease, hospitalization or death[2]
- Rotavirus accounts for approximately one third of cases of severe vomiting and diarrhoea requiring hospitalization[1]

[1]Parashar et al, Emerg Infect Dis 1998 4(4) 561–570; Bresee et al, 1999

[2]Linhares and Bresee, Pan Amer J Public Health 2000 8(5) 305–330

Burden of Disease Studies in Africa

- Guinea Bissau[1]
  - 3.4 rotavirus deaths/1000 infants per year
  - 145 000 rotavirus-related deaths in Africa
- Sub-Saharan Africa[2]
  - 110-155 000 rotavirus- related deaths per year
- Country-specific mortality[3,4]
  - Nigeria 80-90 deaths per day
  - Cameroon 50-60 deaths per day
  - South Africa 10-12 deaths per day



[1]Mølbak *et al*, Vaccine 2000 19:393-5 [2]Miller & McCann, Health Econ 2000 9:19-35
[3]Parashar *et al*, Emerg Infect Dis 2003 [4]Steele *et al*, Vaccine 2003 21:354-360; Afr Health Sc J 2002 9:103-7

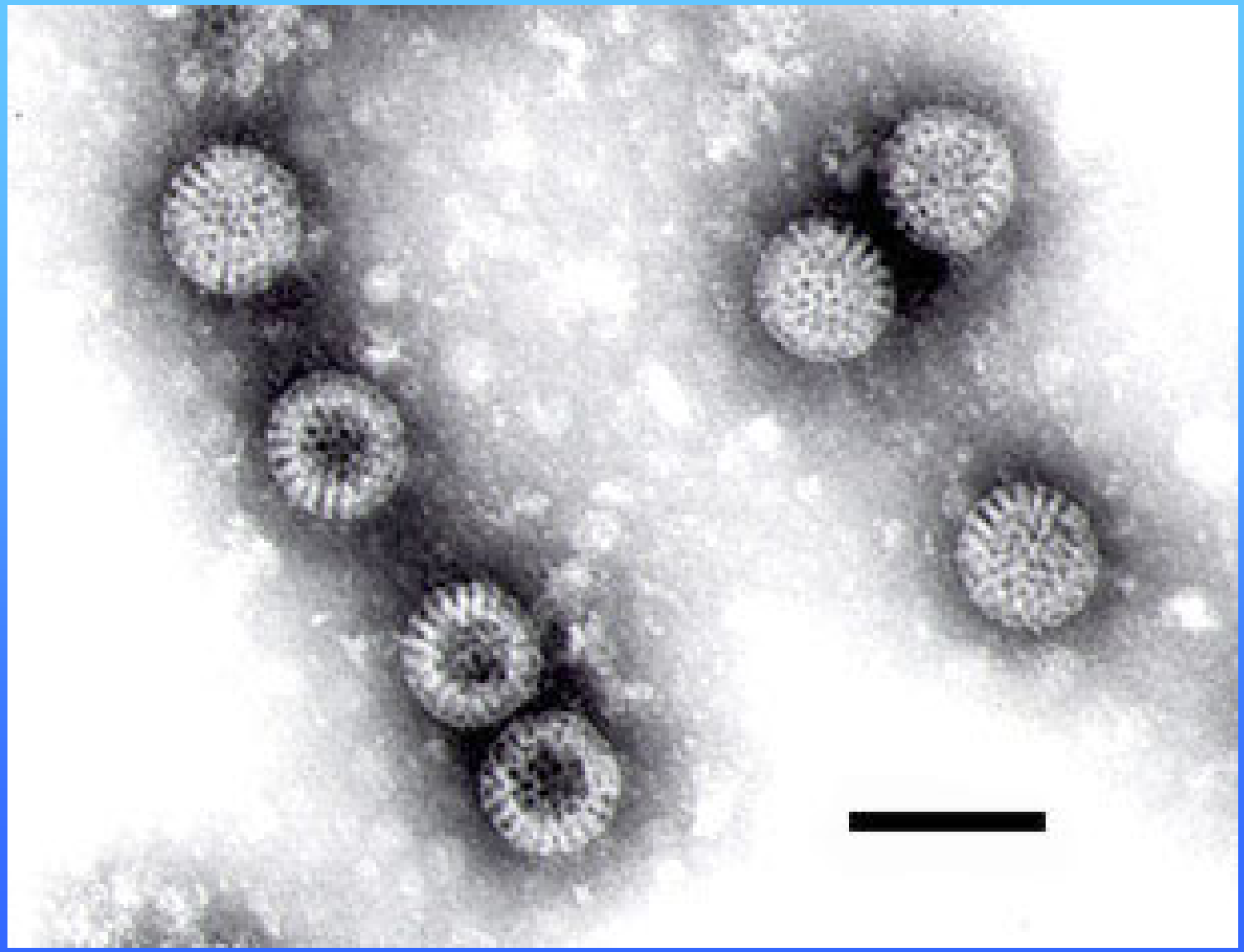
Global Need for Rotavirus Vaccines

- **Birth cohort** — **135 million / year**
- **Under 5 mortality** — **12,2 million / year**
- **Diarrhoreal deaths** — **2.8 million / year**
- **Rotavirus deaths** — **~500 000 / year**

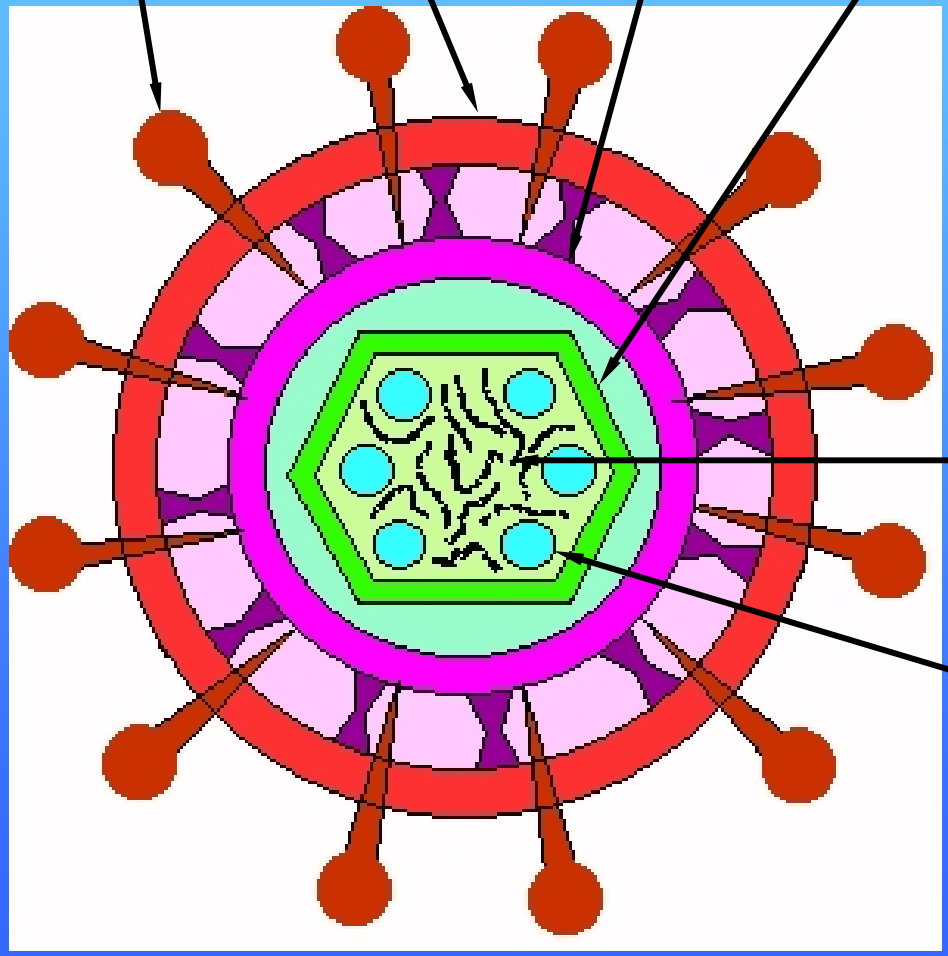
- **85% of these occur in developing countries**
- **Approximately 1 death per minute globally**

Global priority for rotavirus vaccines

The Rotavirus Particle



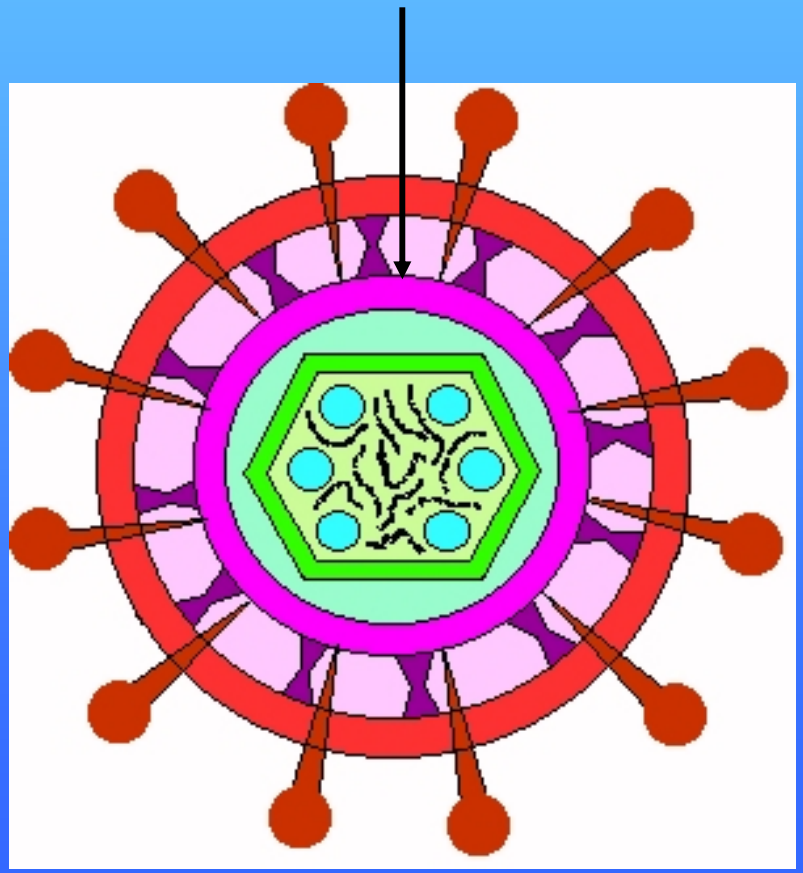
Rotavirus Structure



VP6 or Group Specificity

VP6 or inner capsid protein – specifies group

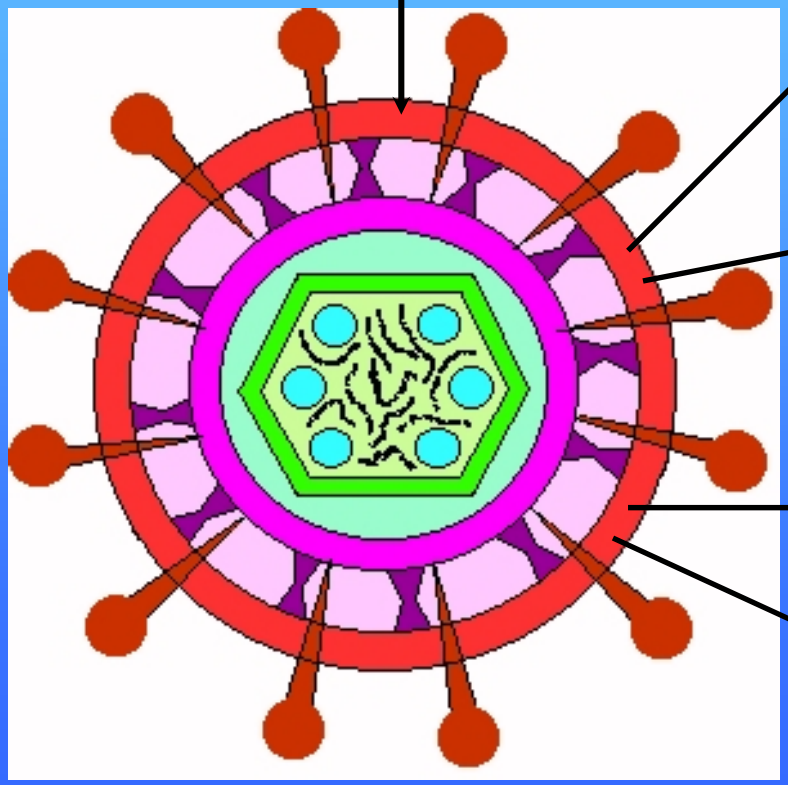
Plays key role in the organization of the virion



- Currently seven rotavirus Groups (A-G) defined
- Group A rotaviruses are responsible for majority of infections in children

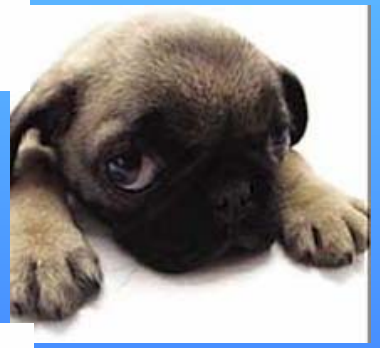
VP7 or G serotypes

VP7 Outer Capsid Protein – G serotype



G1

G2



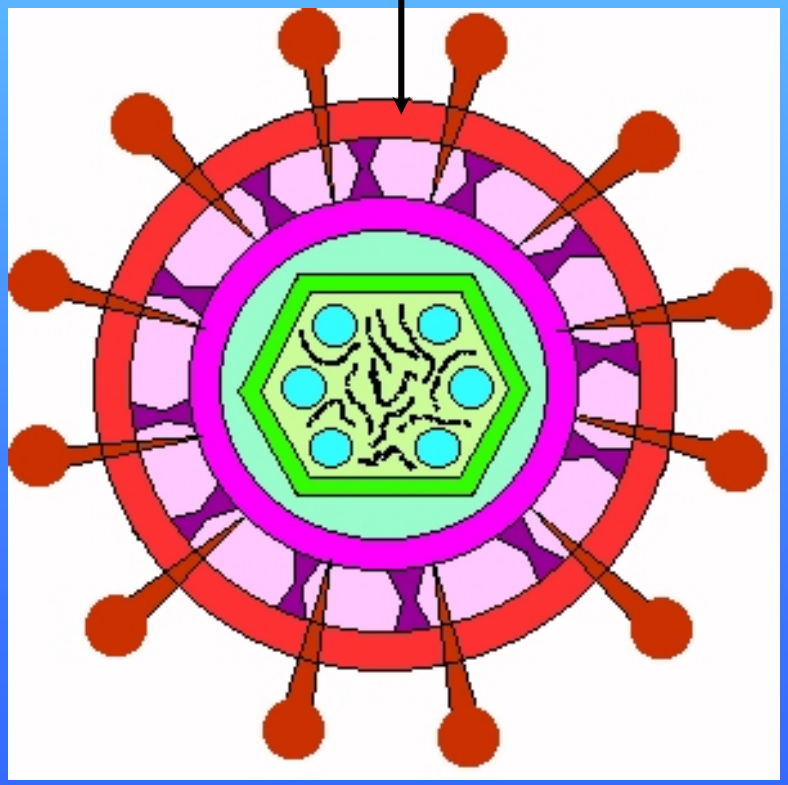
G3

G4

VP7 or G serotypes

VP7 Outer Capsid Protein – G serotype

Major neutralization protein

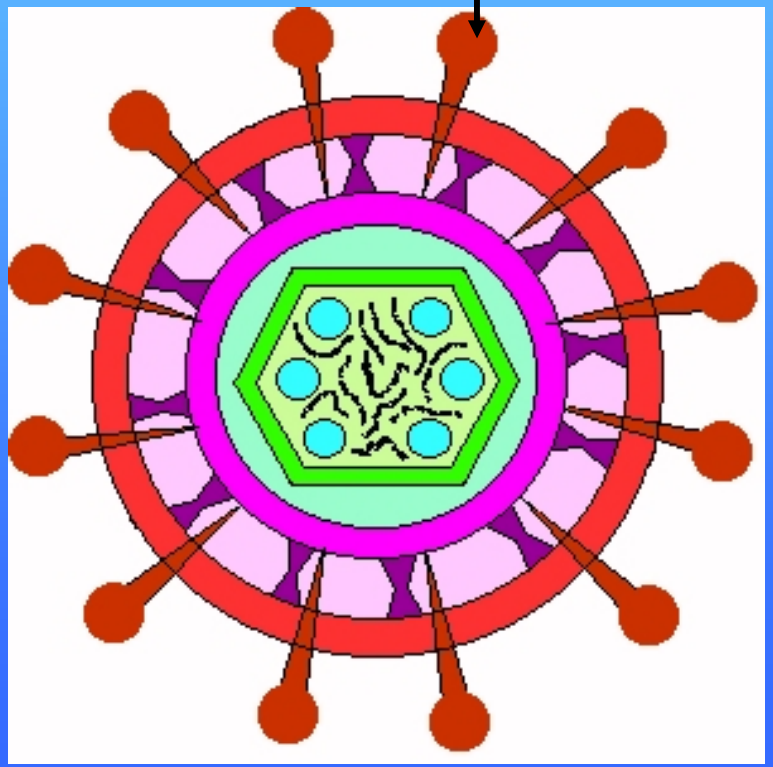


- Currently 15 G serotypes are defined for Group A rotaviruses.
- Serotypes G1-G4 thought to be most important globally
- New serotypes are emerging globally i.e. G8, G9, G10 and G12

VP4 or P genotypes

VP4 Outer Spike Protein – P genotypes

Neutralization protein, cell attachment and protease-enhanced infectivity, virulence, haemagglutination



- Currently 25 P genotypes are defined for Group A rotaviruses
- P types P[8] and P[4] thought to be globally important
- P[6] originally associated with neonatal infections

Rotavirus Vaccines

- Multi-national Candidates

  - Rotarix™ - GSK Biologicals
  - RotaTeq™ - Merck Research

Both live, attenuated oral vaccines

Rotarix™

- Human monovalent G1P[8] – relies on heterotypic immunity
- Given in two doses with regular EPI schedule
- No interference with OPV, DTPa, DTPw, HepB, Hib, pneumo

Rotarix™

- Finland – 2 doses 10^5 ffu[1]
  - Efficacy against any RV GE 69%
  - Efficacy against severe RV GE 90%
- Venezuela, Brazil and Mexico – 2 doses varied viral concentrations[2]
  - Efficacy against any RV GE 56-73%
  - Efficacy against severe RV GE 68-87%

[1]Vesikari, ICAAC, San Diego, 2002

[2]Perez-Schael, ICAAC, San Diego, 2002; Ruiz Palacios, WSPID, Santiago, 2002

Rotarix™

- Latin America (11 countries) and Finland
- Vaccinated >63 000 children 6-14 weeks
- Followed ~20 000 for efficacy
  - Efficacy against any RV GE 65%
  - Efficacy against severe RV GE 77%
- Ongoing trials in South Africa – safety in HIV-positive babies and Phase III efficacy

Vesikari, ESPID, Valencia, 2005

Valasques, ESPID, Valencia, 2005

RotaTeq™

- Bovine–human pentavalent G1, G2, G3, G4 and P[8] – relies on homotypic immunity
- Given in three doses with regular EPI schedule
- No interference with OPV, DTPa, DTPw, HepB, Hib, pneumo

RotaTeq™

- Finland – 3 doses at varied viral concentrations 10^4, 10^5, 10^6 ffu
  - Efficacy against any RV GE 59-77%
  - Efficacy against severe RV GE >95%

Vesikari *et al*, IDSA, Chicago, 2002

Vesikari, ESPID, Prague, 2004

RotaTeq™

- USA, Europe (5 countries) and Latin America (5 countries)
- Vaccinated >72 000 children 6-14 weeks
- Followed ~6 000 for efficacy (US & EU)
  - Efficacy against any RV GE 74%
  - Efficacy against severe RV GE 98%
- Clinical trials planned in Africa and Asia

Vesikari, ESPID, Valencia, 2004

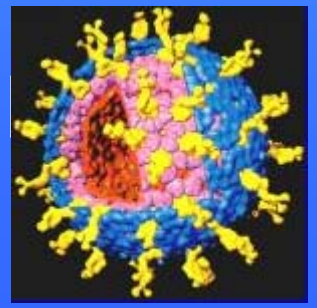
Dennehy, ESPID, Valencia, 2004

Alternatives to Vaccination

- Sanitation - has not worked
- Nutrition - recovery good
  - does not reduce incidence
- Breast feeding - less diarrhoea overall
  - may postpone RV onset
- ORS therapy - given too late in infection
  - not been universally used

Rotavirus Vaccines in South Africa

- Rotavirus vaccines soon to be registered in South Africa by MCC
- BOD data from George Mukhari and Brits Hospitals to be completed by end 2006 and published
- Efficacy trial (Rota037) with Rotarix™ to be finished by early 2007
- Safety of Rotarix™ in HIV-positive babies trial (Rota022) to be finished end 2006



Current Challenges for Rotavirus Vaccines

- Efficacy – will these live, oral vaccines work equally well in children living under disadvantaged conditions
  - OPV, oral cholera and rotavirus (RIT, WC3)
- Cost – How can we plan for high costs initially and how can we affect decreased costs soon?
  - Hepatitis B
- Supply – How can we affect technology transfer to emerging manufacturers to supply the vaccine?
- How do we get an efficacious rotavirus vaccine to the children who need it most in South Africa and Africa?

Rotavirus vaccines are no longer vaccines of the future, but will be used in routine EPI schedules in other regions with the next year

What is needed for Africa?