
**UGANDA NATIONAL ACADEMY OF SCIENCES**

# Rotavirus Vaccine Switch Technical Report

## Ratified Recommendation to the Ministry of Health – Uganda

By

Uganda National Immunisation Technical Advisory Group

9/8/2022

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# ROTAVIRUS VACCINE SWITCH 2022

## Executive Summary

Rotavirus is a common cause of diarrhea, diarrhea related admissions, and diarrhea- related deaths worldwide. Rotavirus ranks highest among the top 5 causes of death, accounting for 40% of diarrhea cases among children in Uganda.

Uganda introduced a vaccine against rotavirus (2 oral doses of Rotarix- monovalent) in 2018, This resulted in a significant annual reduction in the reported diarrhea cases in under fours by approximately 136,000 cases by 2020. However, the trend in cases stagnated between 2020 and 2021.

Before the introduction of a rotavirus vaccine (Rotarix) in Uganda, a study was conducted to assess the circulating rotavirus genotypes in Uganda. The most common genotypes detected were G1P[8] G9P[8] G2P[4], G9P[6], G8P[4], and G12P[6] plus some Mixed G or P types and partially typed either G or P types. After vaccine introduction, the main circulating genotypes are G1, G2, G3, G4, G9, and G12.

Between 2018 and 2019, WHO prequalified two new rotavirus vaccine products (Rotavac [Monovalent vaccine originating from human rotavirus G9P[11] and ROTASIIL [pentavalent vaccine with 5 attenuated bovine-human attenuated strains: G1, G2, G3, G4, & G9]).

The Ministry of Health decided to switch from Rotarix to Rotasill, with the argument that since it contains antigens against the genotypes currently circulating in the country, it may provide superior protection against rotavirus in Uganda than the monovalent Rotarix. The Ministry then consulted the UNITAG to provide an evidence-informed review of this assumption and decision.

UNITAG conducted an in-depth review of literature, including the WHO 2021 Position paper on Rotavirus vaccines, published systematic reviews, meta-analyses, and reports from clinical trials conducted in Africa and other high mortality countries in Latin America. They examined the efficacy and effectiveness data of the monovalent and pentavalent vaccines against vaccine and non-vaccine strains. They also had a presentation from a rotavirus expert from the WHO Africa Regional Office to share experiences of the performance of the different vaccines across the region.

The evidence showed that both monovalent and pentavalent rotavirus vaccines offer **comparable protection** against homotypic and heterotypic virus strains. Through cross-protection, both vaccine types elicit protection against genotypes not contained within the vaccines. In other words, none of the vaccines is better than the other.

**Recommendation:** The Ministry of Health should not switch rotavirus vaccine products premised on better addressing the circulating rotavirus strains, as all WHO prequalified rotavirus vaccines provide comparable protection against heterologous strains.

# ROTAVIRUS VACCINE SWITCH 2022

## Background

Rotavirus is a common cause of diarrhea, diarrhea-related admissions, and diarrhea-related deaths worldwide. Rotavirus ranks highest among the top 5 causes of death, accounting for 40% of diarrhea cases among children in Uganda. Every year, an estimated 10,637 children under 5 years of age die due to Rotavirus diarrhea[1].

Uganda introduced a vaccine against rotavirus (Rotarix) in June 2018 with support from GAVI, WHO, UNICEF, and Clinton Health Access Initiative (CHAI)[1].

As of the date of this report, there are four vaccines against Rotavirus prequalified by WHO: RotaTeq (in 2008), Rotarix (in 2009), Rotavac (Frozen – in 2018, Liquid -in 2021), and Rotasiil (Lyophilized – in 2018, Thermo-stabilized and liquid – 2020). All four vaccines have been assessed and shown to have comparative and acceptable results for safety and efficacy. Although rotavirus vaccines have reported a lower efficacy in low-income countries with higher burdens of disease compared to high-income low burden settings, they have resulted in substantial reductions in diarrheal disease and mortality and are cost-effective.

The four WHO-approved rotavirus vaccine products occur in different presentations. With the addition of new vaccines to the market, countries reviewing their vaccine product choices need to re-examine the vaccination impact for decision-making.

On the 9th of August 2022, the Ministry of Health requested the UNITAG, through its Chair, to review the rotavirus vaccine product selection to best align with the circulating rotavirus genotypes in the country (Appendix 1).

This document describes the four rotavirus vaccines prequalified by WHO, and reviews published literature on the efficacy and effectiveness of the monovalent and pentavalent vaccines against homotypic and heterotypic rotavirus genotypes.

[1] Ministry of Health, 2019. https://www.health.go.ug/2019/12/02/uganda-rolls-out-rotavirus-vaccine-into-the-routine-immunization-schedule/.

# ROTAVIRUS VACCINE SWITCH 2022

WHO Prequalified Rotavirus Vaccine characteristics:

| Characteristic | RotaTeq (Merck) | Rotarix (GSK) | Rotavac (Bharat Biotech) | ROTASIIL (Serum Institute) |
|---|---|---|---|---|
| **Type[2] (All are live attenuated)** | Pentavalent vaccine containing 5 reasortant rotaviruses (G1, G2, G3, G4, and P[8]) developed from human and bovine parent rotavirus strains | Monovalent vaccine originating from GIP[8] strain isolated from a case of infantile gastroenteritis | Monovalent vaccine originating from human rotavirus G9P[11] isolated from asymptomatic neonates with I rotavirus bovine gene and 10 human genes | Pentavalent vaccine with 5 attenuated bovine-human attenuated strains G1, G2, G3, G4, & G9 |
| **Presentation[2]** | Liquid in 1 dose squeezable plastic tube with twist-off cap | Lyophilized reconstituted in 1 dose squeezable plastic tube or strip of 5 single dose plastic tubes | Frozen liquid vaccine in glass vials with droppers, in 1, 5 or 10 doses | Liquid 1 & 2 dose vial or Freeze-dried powder (1 or 2 dose vials) that are reconstituted with a 2.5ml or 5 ml buffered diluent of citrated Sodium bicarbonate |
| **Dosage[2]** | 3 oral doses (@2.5 mls) given 4-10 wks apart, starting at 6-12 wks, to be completed by 32 wks | 2 oral doses (@1.5 mls) given 4 wks apart starting at 6 weeks, to be given before 16 wks and completed by 24 wks | 3 oral doses (@5mls) given 4wks apart starting at 6 wks and completed by 32 wks | 3 oral doses(@2.5mls) given 4 wks apart starting at 6 wks. Series should be completed during 1st year of life |

**Table 1 WHO prequalified Rotavirus Vaccine Characteristics**

[2] WHO Position Paper July 2021 No. 28, 2021, 96, 301-320

# Uganda Specific Considerations

## EPIDEMIOLOGY OF ROTAVIRUS IN UGANDA

Before introduction of a rotavirus vaccine (Rotarix) in Uganda, a study was conducted to assess to assess the circulating rotavirus genotypes in Uganda. To determine the prevalence of severe rotavirus infection in children admitted with acute diarrhea attending Mulago National Referral Hospital in Uganda, active sentinel surveillance was conducted from July 2006 to December 2012. The surveillance found that Rotavirus infections occurred throughout the year. During the surveillance period (2006-2012), a total of 354 positive stool samples were subjected to reverse transcription polymerase chain reaction and genotyping assays. The most common genotypes detected were G1P[8] (16.1%) and G9P[8] (15.3%), followed by G2P[4] (7.6%), G9P[6] (7.1%), G8P[4] (6.5%) and G12P[6](5.6%). Mixed G or P types (17.9%) and partially typed either G or P types (10.7%) were common[3].

Following the introduction of the Rotarix vaccine in 2018, a reduction in reported diarrhea cases was observed as shown in Figure 1.

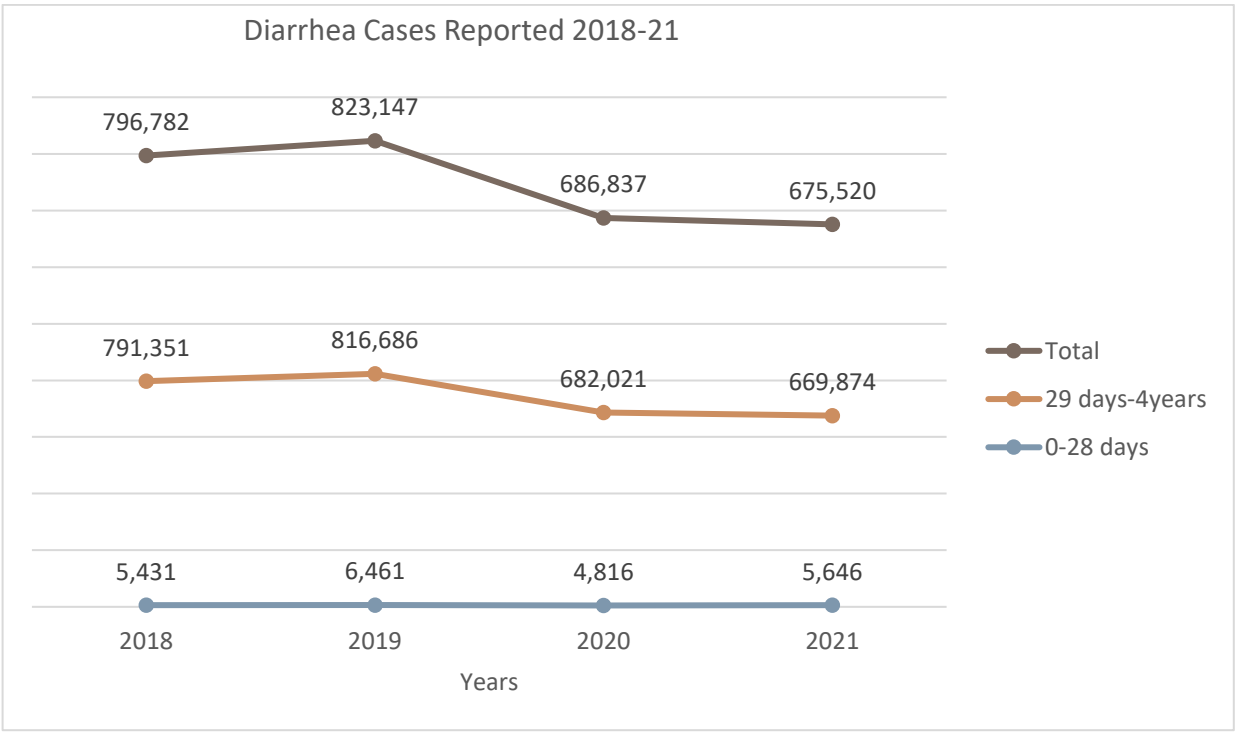


**Figure 1: Diarrhea cases in Uganda 2018-2021**

Source. Ministry of Health 2022. Presentation to UNITAG meeting Aug 2022

[3] Odiit A, Mulindwa A, Nalumansi E, Mphahlele MJ, Seheri LM, Mwenda JM, Kisakye A. Rotavirus prevalence and genotypes among children younger than 5 years with acute diarrhea at Mulago National Referral Hospital, Kampala, Uganda. Pediatr Infect Dis J. 2014 Jan;33 Suppl 1:S41-4. doi: 10.1097/INF.0000000000000070. PMID: 24343612.

The diversity of rotavirus genotypes may have profound consequences for successful vaccine execution if strains are not targeted by current vaccines. Continuous monitoring of the rotavirus genotypes circulating before and after the implementation of the vaccine is therefore important for the determination of the potential effectiveness and the need to change the vaccine[4].

The trend in rotavirus genotypes circulating in Uganda 2007 - 2022 is shown in Figure 2.

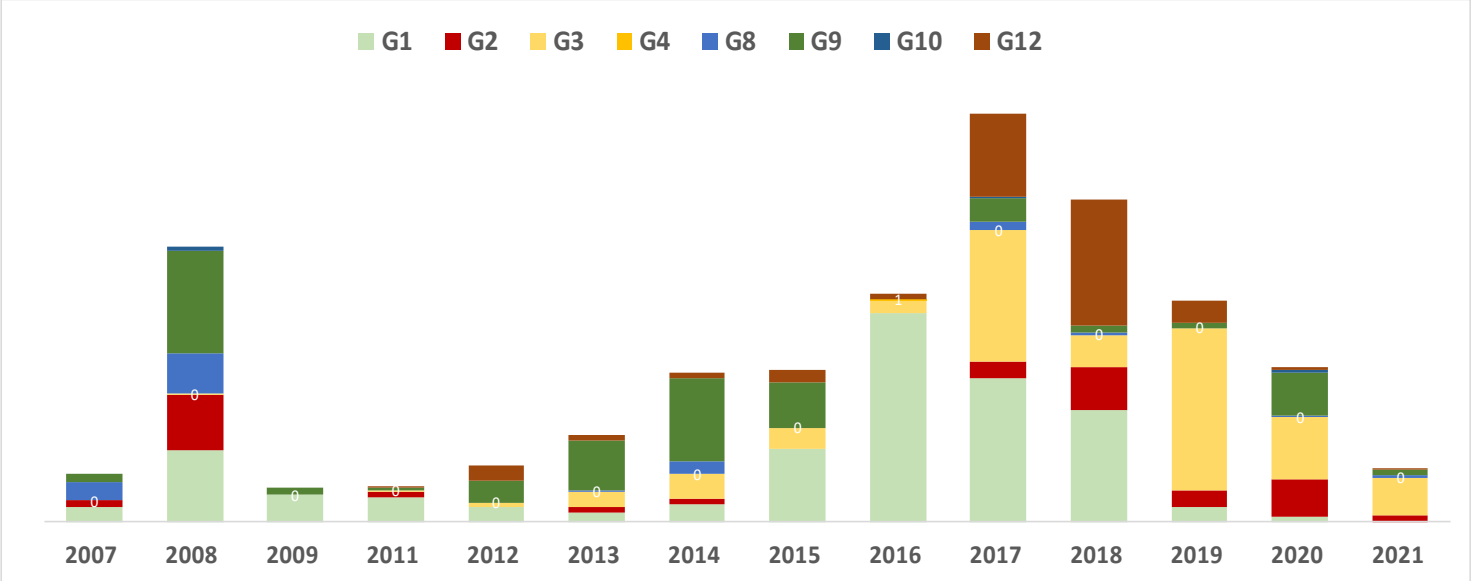


**Figure 2: circulating rotavirus genotypes in Uganda 2007-2021**

Source: WHO Uganda 2020. Courtesy of Dr Annet Kisakye.

[4] Kirkwood D. Carl. 2010. Genetic and antigenic diversity of human rotaviruses: potential impact on vaccination programs. Htpps://doi.org/10.1086/653548

# Summary of Evidence.

1. **Mechanisms of protection of monovalent and pentavalent rotavirus vaccine against circulating rotavirus strains**

The mechanisms of protection against rotavirus after vaccination are not fully understood. This has resulted in the adoption of different approaches to the development of broadly protective vaccines. The Pentavalent vaccine is based on the concept that genotype-specific neutralizing antibodies against the rotaviral outer capsid proteins VP7 and VP4 are the primary determinants of protection and thus include VP7 and VP4 components of the major human rotavirus genotypes. The monovalent vaccine, on the other hand, is based on the theory that protective immune response could be stimulated by B- or T-cell epitopes present on any rotaviral protein, and these epitopes may be conserved among different rotavirus VP7 and VP4 genotypes[5].

2. **Efficacy of Monovalent Rotarix vaccine against different heterogenous vaccine genotypes in high mortality settings.**

a) In an African clinical trial of Rotarix conducted in Malawi and South Africa[6], a great diversity of circulating rotavirus strains was observed, with the G1P[8] vaccine-type strains accounting for 57% of strains detected in South Africa and only 13% of strains in Malawi. The vaccine demonstrated a good efficacy against a range of G types—efficacy against G1, G12, and G8 types of 64, 52, and 64%, respectively—as well as a range of circulating P types—efficacy against P[8], P[4], and P[6] of 59, 71, and 55%, respectively.

b) A 2012 study reviewed the efficacy of Rotarix against circulating rotavirus stains among African infants[7]. Overall, 4939 infants were vaccinated and 4417 (pooled *Rotarix™* = 2974; placebo = 1443) were included in the per-protocol efficacy cohort. G1 wild-type was detected in 23 (1.6%) severe rotavirus gastroenteritis episodes from the placebo group. This was followed in order of detection by G12 (15 [1%] in placebo) and G8 types (15 [1%] in placebo). Vaccine efficacy against G1 wild-type, G12 and G8 types were 64.1% (95% CI: 29.9%; 82%), 51.5% (95% CI:-6.5%; 77.9%) and 64.4% (95% CI: 17.1%; 85.2%), respectively. Genotype P[8] was the predominant circulating P

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[5] *Richard L. Ward, H. Fred Clark, Paul A. Offit, Influence of Potential Protective Mechanisms on the Development of Live Rotavirus Vaccines, The Journal of Infectious Diseases, Volume 202, Issue Supplement_1, September 2010, Pages S72–S79, https://doi.org/10.1086/653549*

[6] Madhi SA, Cunliffe NA, Steele D, Witte D, Kirsten M, Louw C, Ngwira B, Victor JC, Gillard PH, Cheuvart BB, Han HH, Neuzil KM. Effect of human rotavirus vaccine on severe diarrhea in African infants. N Engl J Med. 2010 Jan 28;362(4):289-98. doi: 10.1056/NEJMoa0904797. PMID: 20107214.

[7] Steele, A.D., Neuzil, K.M., Cunliffe, N.A. et al. Human rotavirus vaccine Rotarix™ provides protection against diverse circulating rotavirus strains in African infants: a randomized controlled trial. BMC Infect Dis 12, 213 (2012). https://doi.org/10.1186/1471-2334-12-213

type and was detected in 38 (2.6%) severe rotavirus gastroenteritis cases in the placebo group. The remaining circulating P types comprised of P[4] (20 [1.4%] in placebo) and P[6] (13 [0.9%] in placebo). Vaccine efficacy against P[8] was 59.1% (95% CI: 32.8%; 75.3%), P[4] was 70.9% (95% CI: 37.5%; 87.0%) and P[6] was 55.2% (95% CI: -6.5%; 81.3%).

c) In a meta-analysis conducted by Keating GM in 2006[8], in a placebo-controlled Phase 3 trial conducted in Latin America and Finland, the efficacy of RIX4414 against severe rotavirus gastroenteritis showed 85% in healthy infants, with efficacy against hospitalization for severe rotavirus gastroenteritis of 85%. RIX4414 provided cross-protection against non-G1 serotypes containing the P[8] antigen. Moreover, in this trial, RIX4414 had a protective efficacy against severe gastroenteritis of any cause of 40%, with efficacy against hospitalization because of severe gastroenteritis of any cause of 42%.

d) In a randomized, placebo-controlled trial in Latin American infants[9], multiple rotavirus serotypes [G1 (50%), G9 (40%), G2, G3, and G4] were identified from gastroenteritis stools (enzyme-linked immunosorbent assay and reverse transcription-polymerase chain reaction) during the study period. For severe gastroenteritis caused by G9 serotypes, the protection after vaccination with ROTARIX reached 77% (95% CI 18-96%) in the vaccinated group, providing proof of concept that the monovalent G1P1A P[8] human rotavirus vaccine elicits cross-protection against the G9 strain.

e) In a randomized, double-blind, placebo-controlled, phase 3 trial[10], conducted in 11 Latin American Countries And Finland, assessing the efficacy and safety of Rotarix, the efficacy of the vaccine against strains sharing only the P[8] antigen (G3P[8], G4P[8], and G9P[8]) was 87.3 percent (P<0.001). The type G2P[4] rotavirus, which does not share either the G or the P antigen with the vaccine strain, was detected in specimens from five infants in the vaccine group and nine in the placebo group, for efficacy of 41.0 percent (P=0.30).

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[8] *Keating, G.M. Rotavirus Vaccine RIX4414 (Rotarix™). Pediatr-Drugs **8**, 389–395 (2006).* https://doi.org/10.2165/00148581-200608060-00006

[9] Salinas B, Pérez Schael I, Linhares AC, Ruiz Palacios GM, Guerrero ML, Yarzábal JP, Cervantes Y, Costa Clemens S, Damaso S, Hardt K, De Vos B. Evaluation of safety, immunogenicity and efficacy of an attenuated rotavirus vaccine, RIX4414: A randomized, placebo-controlled trial in Latin American infants. Pediatr Infect Dis J. 2005 Sep;24(9):807-16. DOI:10.1097/01.inf.0000178294.13954.a1. PMID: 16148848.

[10] Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, Abate H, Breuer T, Clemens SC, Cheuvart B, Espinoza F, Gillard P, Innis BL, Cervantes Y, Linhares AC, López P, Macías-Parra M, Ortega-Barría E, Richardson V, Rivera-Medina DM, Rivera L, Salinas B, Pavía-Ruz N, Salmerón J, Rüttimann R, Tinoco JC, Rubio P, Nuñez E, Guerrero ML, Yarzábal JP, Damaso S, Tornieporth N, Sáez-Llorens X, Vergara RF, Vesikari T, Bouckenooghe A, Clemens R, De Vos B, O'Ryan M; Human Rotavirus Vaccine Study Group. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med. 2006 Jan 5;354(1):11-22. doi: 10.1056/NEJMoa052434. PMID: 16394298.

f) A 2021 Systematic review and meta-analysis[11] found that in 2 low-income countries, RV1 VE was 80% (95% CI: 50–92) against homotypic strains, and 1 low-income study estimated an RV1 VE of 35% (95% CI: –135 to 82) against heterotypic strains.

**3. Efficacy of Pentavalent Rotasiil vaccine, against different heterogenous vaccine genotypes in high mortality settings**

a) A double-blind, placebo-controlled randomized phase III event-driven trial[12] was conducted in Madarounfa, Niger, to assess the efficacy and safety of Rotasiil against SRVGE in healthy infants up to 24 months of age. In addition to the common G1, 7 other G types (G2, G3, G4, G8, G9, G10, and G12) and 4 P types (P[4], P[6], P[8], and P[10]) were observed in circulation; 74.7% of cases were vaccine type. G2 was the most prevalent G type and constituted 37.8% of strains among all cases of rotavirus gastroenteritis, followed by genotypes G12 (18.9%) and G1 (15.7%). There was, however, a shift in G type predominance over time (Fig 4; Table D in S2 Table). G2 was the predominant G type during the first peak of the first rotavirus season (detected in 95.9% of stools tested from October to December 2015), whereas in the second peak of the first rotavirus season, G1 gained predominance and there was a marked increase in G12 and G9. In the second year of the study, G1 and G12 dominated the first rotavirus season, while G3 and G9 dominated the second rotavirus season. Rotasiil provided significant protection against SRVGE caused by rotavirus **serotypes contained in the vaccine** (1.57 and 3.99 cases per 100 person-years for vaccine and placebo, respectively: **vaccine efficacy 60.7%,** 95% CI 44.1% to 72.3%), as well as rotavirus **serotypes not contained in the vaccine** (0.32 and 0.40 cases per 100 person-years for vaccine and placebo, respectively, **vaccine efficacy 20.9%,** 95% CI –90.9% to 67.2%.

[11] Cates JE, Amin AB, Tate JE, Lopman B, Parashar U. Do Rotavirus Strains Affect Vaccine Effectiveness? A Systematic Review and Meta-analysis. Pediatr Infect Dis J. 2021 Dec 1;40(12):1135-1143. doi: 10.1097/INF.0000000000003286. PMID: 34870393; PMCID: PMC8966741.

[12] Isanaka S, Langendorf C, McNeal MM, Meyer N, Plikaytis B, Garba S, et al. (2021) Rotavirus vaccine efficacy up to 2 years of age and against diverse circulating rotavirus strains in Niger: Extended follow-up of a randomized controlled trial. PLoS Med 18(7): e1003655.
https://doi.org/10.1371/journal.pmed.1003655

4. **Strain diversity over time:**
   Strain diversity can be cyclical in human populations, with dominant strains emerging every 3–4 years[13], but strains are known to have important geographical differences and to evolve over time with natural molecular evolution.[14], [15]

5. **Efficacy of Rotarix and ROTASIIL against rotavirus in high mortality settings**

A 2021 Cochrane systematic review[16] found that in high-mortality countries, **Rotarix prevented 58% of severe rotavirus diarrhea cases** (15,882 participants, 4 trials; high-certainty evidence), **and 27% of severe all-cause diarrhea cases** (5639 participants, 2 trials; high-certainty evidence). Among children vaccinated and followed up for two years In high-mortality countries, **Rotasiil prevented 44% of severe rotavirus diarrhea cases** (11,008 participants, 2 trials; high-certainty evidence), **and resulted in little to no difference in severe all-cause diarrhea cases** (11,008 participants, 2 trials; high-certainty evidence).

## UNITAG Conclusions and Recommendations:

Based on the evidence:

**Conclusion:** Both monovalent and pentavalent rotavirus vaccines offer **comparable protection** against homotypic and heterotypic virus strains. Through cross-protection, both vaccine types elicit protection against serotypes not contained within the vaccines. In other words, none of the vaccines is better than the other.

**Recommendation:** The Ministry of Health should not switch rotavirus vaccine products premised on better addressing the circulating rotavirus strains, as all WHO prequalified rotavirus vaccines provide comparable protection against heterologous strains.

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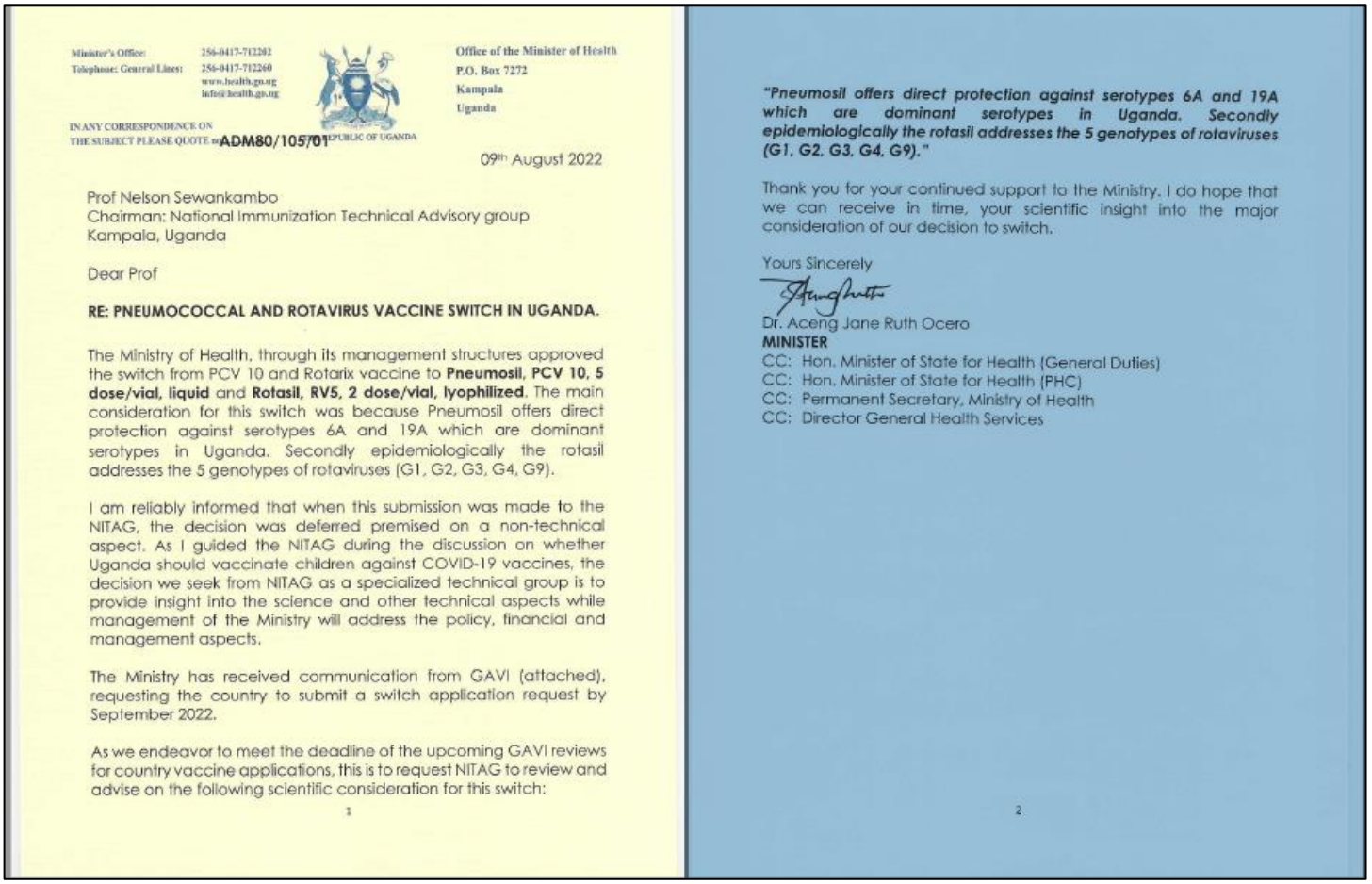
[13] Steele AD. Antigenic and genetic characterization of serotype G2 human rotavirus strains from South Africa from 1984 to 1998. J Med Virol. 2004; 72(2):320–7. https://doi.org/10.1002/jmv. 10571 PMID: 14695677

[14] Stacy Todd, Nicola A. Page, A. Duncan Steele, Ina Peenze, Nigel A. Cunliffe, Rotavirus Strain Types Circulating in Africa: Review of Studies Published during 1997–2006, *The Journal of Infectious Diseases*, Volume 202, Issue Supplement_1, September 2010, Pages S34–S42, https://doi.org/10.1086/653555

[15] Vizzi E, Piñeros OA, Oropeza MD, Naranjo L, Suárez JA, Fernández R, Zambrano JL, Celis A, Liprandi F. Human rotavirus strains circulating in Venezuela after vaccine introduction: predominance of G2P[4] and reemergence of G1P[8]. Virol J. 2017 Mar 21;14(1):58. doi: 10.1186/s12985-017-0721-9. PMID: 28320411; PMCID: PMC5359893.

[16] Bergman H, Henschke N, Hungerford D, Pitan F, Ndwandwe D, Cunliffe N, Soares-Weiser K. Vaccines for preventing rotavirus diarrhoea: vaccines in use. Cochrane Database of Systematic Reviews 2021, Issue 11. Art. No.: CD008521. DOI: 10.1002/14651858.CD008521.pub6. Accessed 26 August 2022.

# Appendix 1: Request letter to UNITAG from the Ministry of Health



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IN ANY CORRESPONDENCE ON THE SUBJECT PLEASE QUOTE NO. ADM80/105/01

REPUBLIC OF UGANDA

09th August 2022

Prof Nelson Sewankambo
Chairman: National Immunization Technical Advisory group
Kampala, Uganda

Dear Prof

**RE: PNEUMOCOCCAL AND ROTAVIRUS VACCINE SWITCH IN UGANDA.**

The Ministry of Health, through its management structures approved the switch from PCV 10 and Rotarix vaccine to **Pneumosil, PCV 10, 5 dose/vial, liquid** and **Rotasil, RV5, 2 dose/vial, lyophilized**. The main consideration for this switch was because Pneumosil offers direct protection against serotypes 6A and 19A which are dominant serotypes in Uganda. Secondly epidemiologically the rotasil addresses the 5 genotypes of rotaviruses (G1, G2, G3, G4, G9).

I am reliably informed that when this submission was made to the NITAG, the decision was deferred premised on a non-technical aspect. As I guided the NITAG during the discussion on whether Uganda should vaccinate children against COVID-19 vaccines, the decision we seek from NITAG as a specialized technical group is to provide insight into the science and other technical aspects while management of the Ministry will address the policy, financial and management aspects.

The Ministry has received communication from GAVI (attached), requesting the country to submit a switch application request by September 2022.

As we endeavor to meet the deadline of the upcoming GAVI reviews for country vaccine applications, this is to request NITAG to review and advise on the following scientific consideration for this switch:

1

***"Pneumosil offers direct protection against serotypes 6A and 19A which are dominant serotypes in Uganda. Secondly epidemiologically the rotasil addresses the 5 genotypes of rotaviruses (G1, G2, G3, G4, G9)."***

Thank you for your continued support to the Ministry. I do hope that we can receive in time, your scientific insight into the major consideration of our decision to switch.

Yours Sincerely

Dr. Aceng Jane Ruth Ocero
**MINISTER**
CC: Hon. Minister of State for Health (General Duties)
CC: Hon. Minister of State for Health (PHC)
CC: Permanent Secretary, Ministry of Health
CC: Director General Health Services

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