UGANDA NATIONAL ACADEMY OF SCIENCES

Advisory on switching PCV products from PCV10 – Synflorix to PCV10 - Pneumosil in Uganda's routine immunization schedule

Ratified Recommendation to the Ministry of Health – Uganda

By

UGANDA NATIONAL IMMUNISATION TECHNICAL ADVISORY GROUP (UNITAG)

SEPTEMBER 08, 2022

Table of Contents

EXECUTIVE SUMMARY

The Ministry of Health requested the Uganda National Technical Advisory group (UNITAG) to review and advise on the Ministry's scientific consideration (*"Pneumosil offers direct protection against serotypes 6A and 19A which are dominant serotypes in Uganda"*) to switch PCV products from the currently used PCV10 - Synflorix® to PCV 10 - Pneumosil, 5 dose/ vial, liquid:

In response to this request, UNITAG's working group on Pneumonia vaccines adopted a specific research question that was utilized to analyze available evidence regarding whether PCV10 – Pneumosil offers superior protection compared to PCV10 – Synflorix and PCV13 – Prevenar in high disease burden countries including those with high seroprevalence of 6A and 19A. Since epidemiological data on circulating serotypes in Uganda from 2011 to 2021 indicated that serotypes 6A, 19A, and 23F continue to circulate in the country following the introduction of PCV10- Synflorix in 2014, the working group developed a recommendation framework that took into account all WHO prequalified PCVs, infants aged 6 weeks up to 2 years in high disease burden countries, and vaccine efficacy/ effectiveness against serotypes 6A and 19A as the outcome.

Evidence showed that all of the capsular antigens included in PCV10 products are also included in the PCV13 product. However, while PCV13 - Prevenar and PCV10 - Pneumosil contain capsular antigens from serotypes 6A and 19A that are not contained in PCV10 – Synflorix, there is evidence that PCV10-Synflorix offers cross-protection against the two serotypes. In addition, the three vaccines contain non-toxic protein carriers, also found in other existing conjugated vaccines in the EPI. Similarly, all the three PCVs were licensed and prequalified (PQ) based on their immunogenicity hence being comparable. In particular, while Prevenar and Synflorix PQ based on their non-inferiority to PCV7 (no longer on the market), Pneumosil was licensed, and PQ based on its non-inferiority to Prevenar and Synflorix that had already received their PQ. Generally, evidence showed that all three PCVs have a comparable safety profile, are efficacious against the circulating serotypes in Uganda and can safely be co-administered with other vaccines in EPI.

Based on the available evidence, UNITAG concluded that all the three WHO prequalified PCVs have comparable safety, efficacy, immunogenicity, and impact on IPD and pneumonia. In addition, the committee concluded that although Pneumosil and Prevenar induce direct antibody response to serotypes 6A and 19A, Synflorix also induces cross-protection against these serotypes.

UNITAG thus recommends that the Ministry of Health should not switch PCV products premised on the vaccine's serotype constitution as their protective effects against various pneumococcal serotypes are comparable across all three PCV products.

INTRODUCTION

On August 09, 2022, the Minister of Health informed the NITAG that the Ministry of Health, through its management structures approved the switch from PCV10 - Synflorix® to PCV 10 - Pneumosil, 5 dose/ vial, liquid[1]. According to the letter, the main consideration for this switch was that **Pneumosil offers direct protection against serotypes 6A and 19A which are dominant serotypes in Uganda.** The Minister therefore requested the NITAG to review and advise on the following scientific consideration for this switch: *"Pneumosil offers direct protection against serotypes 6A and 19A which are dominant serotypes in Uganda"*.

This technical document summarizes current technical information including the epidemiologic and biologic evidence surrounding performance, effectiveness on all WHO prequalified pneumococcal conjugate vaccine (PCV) products to facilitate NITAG's informed conclusions and recommendations to the Ministry of Health on its plan to switch PCV antigens.

i) Research Question

Does PCV10 – Pneumosil offer superior protection compared to PCV10 – Synflorix and PCV13 – Prevenar in high disease burden countries including those with high seroprevalence of 6A and 19A?

ii) PICO Framework

Population: infants aged 6 weeks up to 2 years in high disease burden countries
Intervention: Vaccination with PCV10 – Pneumosil
Comparator: Vaccination with PCV10 – Synflorix and PCV13 – Prevenar
Outcome: Vaccine efficacy/ effectiveness against serotypes 6A and 19A

CONTEXT AND BACKGROUND

i) Burden of disease

Pneumonia is the leading cause of under-5 mortality beyond the neonatal period worldwide, and the leading cause of all under-5 mortality in sub-Saharan Africa. With *Streptococcus pneumoniae* being the most common cause of pneumonia-associated morbidity and mortality, more than 300,000 children die from pneumococcal pneumonia, meningitis, and other invasive pneumococcal diseases (IPDs) each year[2].

The burden of invasive pneumococcal disease (IPD) falls disproportionately on young children, especially those in low-income countries, and persons at high risk of infection because of underlying medical conditions such as HIV or sickle cell disease. Of the estimated 5.83 million deaths among children < 5 years of age globally in 2015, 294 000 (uncertainty range [UR], 192 000–366 000) were estimated to be caused by pneumococcal infections (WHO, 2019).

In April 2013, Uganda officially introduced the 10-valent PCV (PCV10 - Synflorix®) throughout the national childhood immunization programs and was later rolled out countrywide in 2014 to

[1] Ministry of Health Request to the NITAG regarding PCV antigen switch (ADM80/105/01)
[2] Wahl B, O'Brien KL, Greenbaum A, et al. Burden of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000–15. *Lancet Glob Health* 2018; **6:** e744–57.

protect children from pneumonia[3]. Citing emerging evidence on the new and recently WHO pre-qualified PCV10 - Pneumosil suggesting that the vaccine has a comparable safety profile, wider spectrum and better thermostability, the Ministry of Health (MoH) noted that this vaccine could help on further reduction in morbidity and mortality comparable to the vaccine in current use.

ii) Pneumococcal disease and serotype (ST) epidemiology

In the absence of PCV use, pneumococcal disease is the leading vaccine preventable cause of mortality of infancy and childhood. PCVs contain only a limited number of the more than 96 pneumococcal serotypes, and that immunity to one serotype does not necessarily confer immunity to others (i.e., there is limited cross-protection among serotypes, and always within a serogroup). However, since only a small subset of these serotypes are responsible for the vast majority of disease and deaths, they were targeted for inclusion in PCVs to represent those found across all epidemiologic settings[4]. 13 serotypes: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F & 23F are responsible for about 80%-90% of antibiotic-resistant pneumococcal strains in most parts of the world[5].

The figure below shows surveillance data on circulating serotypes in Uganda from 2011 to 2021:

Serotype	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Grand Total
1	1	23	16		1	1						42
3			1		1							2
4		2				1	1					4
5		5	6	1	4							16
8						1						1
14		2	3	2	2							9
12F/12A/12B/44/46	1	2	3		4		2	1				13
15A/15F		1			1				1			3
16F				3	2							5
18A/18B/18C/18F			1		1	1		1				4
19A		2						1	1	1		5
19F			4	3	2		1					10
22F		1										1
23A					1					2		3
23F		1	9		2	3	1	2	1	2		21
25F/25A/38		1										1
6A/6B	2	3	11	3	5	1	3	1	1			30
6A/B										2		2
6B		2	1									3
7F/7A		1										1
9V/9A		3										3
Non PCV 13 serotype	1	9	11	7	6	12	6	1	2	3		58
Non PCV13 Serotype										2		2
Other, specify			1									1
Unable to type - low DNA concentration (high Ct)		19	28	5	4	2	3	2		1		64
Grand Total	5	77	95	24	36	22	17	9	6	13		304

Source: WHO Uganda Office as of August 17, 2022

Before the introduction of pneumococcal vaccination in Uganda in 2014, serotypes 1, 5, 6A, 14, 12F, 23F were the most dominant. However, following the introduction of PCV10- Synflorix, serotypes 6A, 19A, and 23F remained the most dominant serotypes circulating in the country.

[3] Ministry of Heath website: Introduction of Pneumococcal vaccine in Uganda

[4] Johnson HL, Deloria-Knoll M, Levine OS, et al. Systematic evaluation of serotypes causing invasive pneumococcal disease among children under five: the pneumococcal global serotype project. *PLoS Med* 2010; **7:** e1000348.

[5]Invasive pneumococcal disease in young children before licensure of 13-valent pneumococcal conjugate vaccine - United States, 2007. Centers for Disease Control and Prevention (CDC) https://pubmed.ncbi.nlm.nih.gov/20224541/ *MMWR Morb Mortal Wkly Rep.* 2010;59:253–257.

SUMMARY OF EVIDENCE ON PNEUMOCOCCAL CONJUGATE VACCINES

Three polysaccharide-protein conjugate vaccines are prequalified by the World Health Organization (WHO) for use in infants and children and have been on the market since 2009. These include the 10-valent (PCV10) – Synflorix manufactured by GlaxoSmithKline, Belgium; the 13-valent (PCV13) – Prenevar manufactured by Pfizer; and the recently (December 2019) WHO pre-qualified 10-valent (PCV10) - Pneumosil manufactured by the Serum Institute of India[6].

i) Capsular antigens contained in the WHO prequalified PCVs

In considering the biological characteristics of the three prequalified PCV products, the key difference is the number and selection of the different capsular antigens from 13 serotypes (STs) of *S. pneumoniae* as indicated in the table below:

Table 1: Biological characteristics of available pneumococcal conjugate vaccines

Product	Carrier protein(s)	Conjugation method & Preservative	Pneumococcal Serotype (ST)													
			1	3	4	5	6A	6B	6C	7F	9V	14	18C	19A	19F	23F
PCV-10[GSK] Synflorix®	Protein D (PD), tetanus toxoid (TT), diphtheria toxoid (DT)	*Conjugation:* CDAP* *Preservative:* 1-dose vial – none 2-dose vial – none 4-dose vial – 2-phenoxyethanol														
PCV-10[SII] PNEUMOSIL®	CRM197	*Conjugation:* CDAP* *Preservative:* 1 dose vial – none 5 dose vial – thimerosal														
PCV-13 Prevnar®	CRM197	*Conjugation:* Reductive amination *Preservative:* 1-dose vial – none 4-dose vial – 2-phenoxyethanol														

* CDAP: 1-cyano-4-dimethylaminopyridinium tetrafluoroborate

ST included in vaccine	
ST not included in vaccine	
ST not included in vaccine but some evidence of cross-protection	
ST3	included in PCV-13 but no conclusive evidence for protection

Source: WHO Considerations for PCV product choice https://www.who.int/publications/i/item/considerations-for-pneumococcal-conjugate-vaccine-(pcv)-product-choice

All of the capsular antigens included in PCV10 products are also included in the PCV13 product. However, the two PCV10 products differ in terms of STs 4, 6A, 18C and 19A. While PCV10 – Synflorix contains antigens from STs 4 and 18C which are not included in PCV10 – Pneumosil, Pneumosil contains antigens from STs 6A and 19A which are not included in Synflorix. However, there is evidence of cross-protection by 6B for 6A and by 19F for 19A for PCV10 – Synflorix[7] as demonstrated in the vaccine performance section below. Nonetheless, all the three products are

[6] Gavi-supported PCV profiles to support country decision making. July 2020. https://www.gavi.org/sites/default/files/document/2020/Gavi-PCV-vaccines-profiles-july-2020.pdf

[7] PCV Product Assessment, April 2017. Published by Johns Hopkins University, International Vaccine Access Center. https://www.jhsph.edu/ivac/resources/pcv-product-assessment/

comparable in terms of their theoretical cumulative coverage within Africa, Asia, and LAC with PCV10 - Pneumosil (71%), PCV10 – Synflorix (66%) and PCV13 – Prevenar (76%)[8].

ii) Carrier Protein

Differences in carrier proteins, conjugation method, and preservatives used for each product are also shown in the table above. PCV13 – Prevenar and PCV10-Pneumosil use CRM197 protein as the protein carrier for each of the 13-serotypes. CRM197 is a non-toxic protein derived from Corynebacterium diphtheriae. This is the same carrier protein found in several Haemophilus influenzae type B (Hib)-conjugate vaccines. However, PCV10 - Synflorix uses protein D (derived from NTHi) as the carrier for eight of the STs while one ST (type 18C) are conjugated to tetanus toxoid and another (type 19F) is conjugated to diphtheria toxoid protein.

iii) Therapeutic indications

PCV10 - Synflorix and PCV13 – Prevenar were licensed and pre-qualified on the basis of immunogenicity non-inferiority to PCV7, which was licensed on the basis of demonstrated efficacy against invasive pneumococcal disease (IPD). Since the time of licensure both PCV10 – Synflorix and PCV13 - Prevenar have gained approval for indications beyond prevention of IPD. The WHO prequalification approved PCV10 - Synflorix for IPD, pneumococcal pneumonia, and otitis media, with labelling by the EMA and WHO PQ that includes the prevention of STs 19A[9]. PCV13 – Prevenar was approved for IPD, pneumococcal pneumonia, and otitis media caused by the 13 STs in the vaccine[10].

PCV10- Pneumosil was WHO pre-qualified based on its composition which is specially tailored to the prevailing serotype prevalence of S. pneumoniae in India which witnesses an estimated 71% of pneumonia deaths and 57% of severe pneumonia cases annually, and other regions of the world[11].

iv) Safety Profile

The safety profiles of both PCV10 (Synflorix) and PCV13 (Prenevar) were reviewed as part of the WHO prequalification process and by the Global Advisory Committee on Vaccine Safety (GACVS)[12]. Both products have accrued extensive post-marketing safety surveillance data, and both are assessed as having excellent safety profiles.

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[8] Johnson HL, Deloria-Knoll M, Levine OS, Stoszek SK, Freimanis Hance L, Reithinger R, Muenz LR, O' Brien KL. Systematic evaluation of serotypes causing invasive pneumococcal disease among children under five: the pneumococcal global serotype project. PLoS Med Internet. 2010;7(10.eng):e1000348. doi:10.1371/journal. pmed.1000348.

[9] Prequalification, W.H.O., *Pneumococcal (conjugate) Synflorix Product Insert*, Prequalification, Editor. 2010, World Health Organization: Geneva, Switzerland.

[10] Prequalification, W.H.O., *Pneumococcal (conjugate) Prevenar 13 Multidose Vial Prequalification Product Insert* Prequalification, Editor. 2016, World Health Organization: Geneva, Switzerland.

[11] https://www.lshtm.ac.uk/research/units/mrc-gambia/news/323506/pneumosil-vaccine-safe-use-part-routine-epi-vaccines

[12] Organization, W.H., Global Advisory Committee on Vaccine Safety, 29–30 November 2006: Safety of pneumococcal conjugate vaccine. Weekly epidemiological record, 2007. 3(82): p. 17-24.

Clinical findings from PCV10 – Pneumosil indicate that the vaccine can safely and effectively be administered concomitantly with diphtheria, tetanus, whole-cell pertussis, Haemophilus influenzae type b, inactivated or oral poliomyelitis, rotavirus, hepatitis B, measles and rubella and yellow fever vaccines[13][14]. Particularly, a phase 3, randomized, double-blind, non-inferiority trial assessing immunogenicity and safety of a novel PCV10-Pneumosil in healthy infants in The Gambia that was reviewed during the WHO prequalification process found that the product was well tolerated, with a comparable safety profile to the other prequalified PCVs, and can be co-administered with routine EPI vaccines [15].

The multi-site Phase 3 trial enrolled 448 infants and used a 3 + 0 schedule of PCV10-Pneumosil met all primary and secondary objectives demonstrating acceptable safety and tolerability and eliciting immune responses comparable to *Prevnar 13* and *Synflorix* for all 10 serotypes[16].

v) Performance and impact

a) Vaccine Efficacy/ Effectiveness (VE)

- A cluster randomized double-blind trial of PCV10 **(**Synflorix) in Finland demonstrated a 92% (95%CI 58–100) efficacy for vaccine type (VT) IPD using a 2+1 schedule among children <19-month-old[17].
- A PCV product assessment report published by Johns Hopkins University, International Vaccine Access Center in 2017 cited four case-control studies conducted in a setting of 3-dose schedule found that the VE of PCV10 (Synflorix) against VT IPD ranged from 77 to 97% for children receiving >1 dose[18].
- The same report cited five case-control studies conducted in a setting of 3-dose national schedule evaluating the VE of PCV13 against vaccine-type IPD found that VE ranged from 64 to 86% for children receiving >1 doses in three studies with 2+1 national schedule (Dominican Republic, UK, and Canada).

[13] Clinical Study Report PCV-10-003. A Phase 3, Randomized, Double-Blind Study to Evaluate the Immunogenicity, Safety and Tolerability of Serum Institute of India's 10-valent Pneumococcal Conjugate Vaccine (PNEUMOSIL®) in Healthy Indian Infants. Serum Institute of India Pvt. Ltd. 24 June 2020.

[14] WHO., Public Assessment Summary Report: Pneumococcal Conjugate Vaccine, (Adsorbed, 10-valent), Serum Institute of India Pvt. Ltd

[15] Clarke E, Bashorun A, Adigweme I et al. Immunogenicity and safety of a novel ten-valent pneumococcal conjugate vaccine in healthy infants in The Gambia: a phase 3, randomised, double-blind, non-inferiority trial. Lancet Infectious Diseases. 2021. https://doi.org/10.1016/S1473-3099(20)30735-0

[16] Mark R. Alderson, Vistasp Sethna, Lauren C. Newhouse, Steve Lamola & Rajeev Dhere (2021) Development strategy and lessons learned for a 10-valent pneumococcal conjugate vaccine (*PNEUMOSIL®*), Human Vaccines & Immunotherapeutics, 17:8, 2670-2677, DOI: 10.1080/21645515.2021.1874219

[17] Palmu, et al., *Effectiveness of the ten-valent pneumococcal Haemophilus influenzae protein D conjugate vaccine (PHiD-CV10) against invasive pneumococcal disease: A cluster randomised trial.* The Lancet, 2013. **381**(9862): p. 214-222.

[18] PCV Product Assessment, April 2017. Published by Johns Hopkins University, International Vaccine Access Center. https://www.jhsph.edu/ivac/resources/pcv-product-assessment/

- PCV10 (Pneumosil) efficacy data is not available but efficacy is expected to be equivalent to PCV13 (Prenevar) and PCV10 (Synflorix) based on immunogenicity data showing non-inferiority[19].

b) VE against ST 6A and 19A[20]

- Evidence from three case-control studies evaluating VE of PCV13 (Prevenar) against individual STs found that VE of >1 dose against type 19A IPD was 74% (Canada) and ranged from 67 to 94% for >2 doses (UK and South Africa). One study (UK) reported 98% VE against type 6A. PCV13 may have an additional benefit in settings where disease attributable to serotype 19A or serotype 6C is significant[21].
- Evidence from four case-control studies evaluating VE of PCV10 (Synflorix) against individual STs found that the VE of >1 dose against type 19A IPD ranged from 61 to 82%, although the estimates were not statistically significant in studies from Netherlands and Brazil (indirect cohort method). The VE of PCV10 (Synflorix) against ST 6A IPD was measured only in one study (Brazil), with non-significant VE of 8% and 15%, respectively[22].
- Both PCV10 (Synflorix) and PCV13 (Prevenar) have substantial impacts against pneumonia, vaccine-type IPD and NP carriage.
- Evidence from a study by Clarke et al (2021) found PCV10 (Pneumosil) to stimulate strong immune responses for ST 6A and 19A in phase 3 trials, with its immunogenicity being non-inferior to that of PCV10 (Synflorix). However, disease impact data is not yet available[23].

CONCLUSIONS

- All three WHO prequalified PCVs have comparable safety, efficacy, immunogenicity, impact on IPD and pneumonia.
- Both Pneumosil and Prevenar induce direct antibody response to serotype 6A and 19A which are dominant in Uganda. Although Synflorix does not contain antigens from serotypes 6A and 19A, there is evidence of cross-protection for serotypes 6A and 19A following PCV10 – Synflorix vaccination.

[19] WHO., Considerations for Pneumococcal Conjugate Vaccines product choice, 2021

[20] PCV Product Assessment, April 2017. Published by Johns Hopkins University, International Vaccine Access Center. https://www.jhsph.edu/ivac/resources/pcv-product-assessment/

[21] Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019 https://apps.who.int/iris/bitstream/handle/10665/310968/WER9408.pdf?ua=1

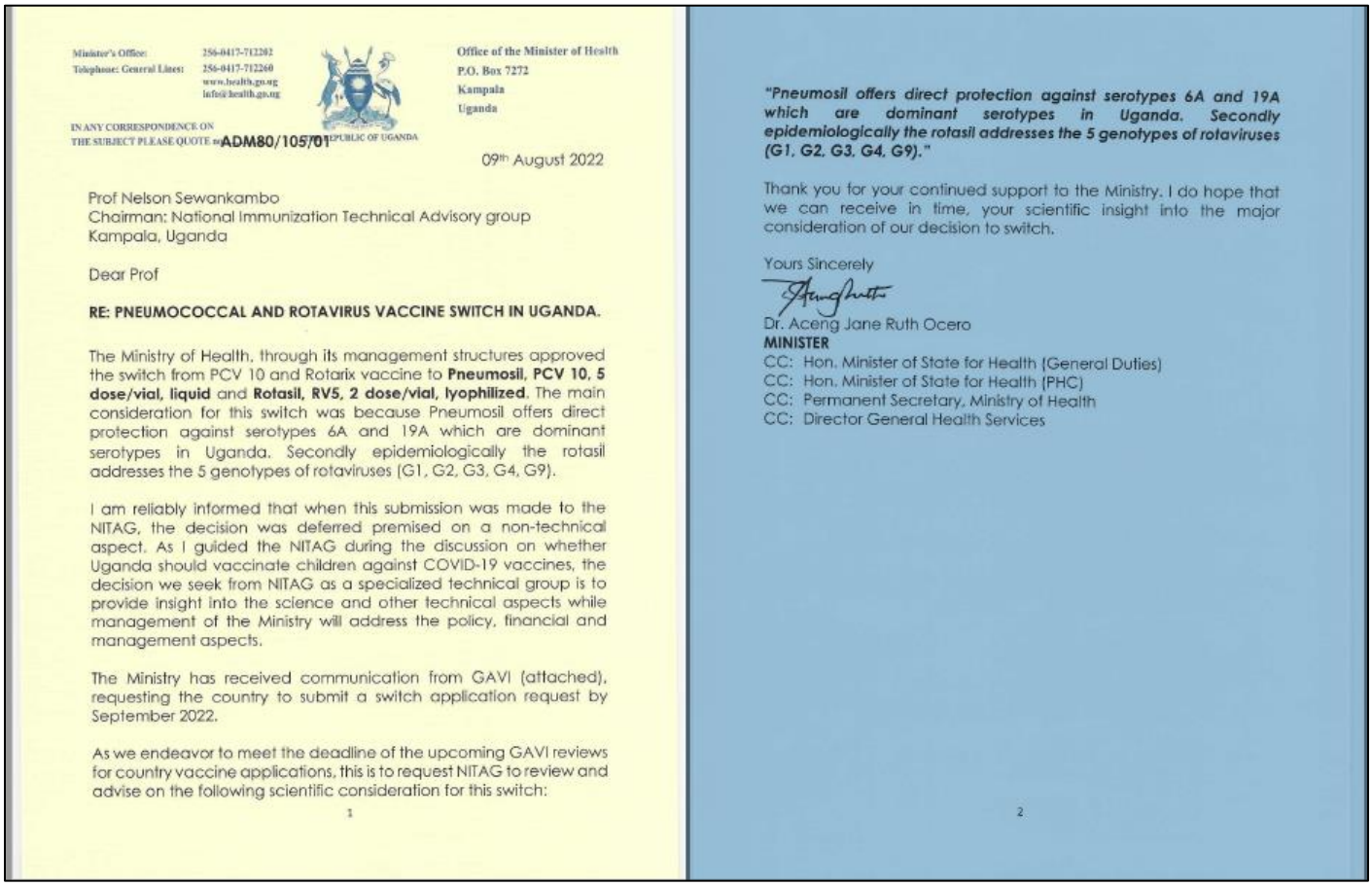
[22] Verani, J.R., C.M. Domingues, and J.C. Moraes, *Indirect cohort analysis of 10-valent pneumococcal conjugate vaccine effectiveness against vaccine-type and vaccine-related invasive pneumococcal disease.* Vaccine, 2015. **33**(46): p. 6145-8.

[23]Clarke E, Bashorun A, Adigweme I et al. Immunogenicity and safety of a novel ten-valent pneumococcal conjugate vaccine in healthy infants in The Gambia: a phase 3, randomised, double-blind, non-inferiority trial. Lancet Infectious Diseases. 2021. https://doi.org/10.1016/S1473-3099(20)30735-0

RECOMMENDATION

Based on the available evidence UNITAG thus recommends that the Ministry of Health should not switch PCV products premised on the vaccine's serotype constitution as their protective effects against various pneumococcal serotypes are comparable across all three PCV products.

Appendix 1: Ministry of Health Advisory request to UNITAG.



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

REPUBLIC OF UGANDA

Office of the Minister of Health
P.O. Box 7272
Kampala
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

2