COMPILATION OF THE UGANDA NATIONAL IMMUNISATION TECHNICAL ADVISORY GROUP REPORTS FOR THE PERIOD 2023-2025

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Report of UNITAG on HPV dose optimization in Uganda

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1. Executive summary.

On 5th April 2023, the Ministry of Health, through the Director General Health services, requested the Uganda National Immunisation Technical Advisory Group (UNITAG) to review the available evidence in support of a switch to a single dose Human Papilloma Virus (HPV) vaccination schedule (see request letter in Annex 1). This was in line with a 2022 Strategic Advisory Group of Experts (SAGE) recommendation for countries to consider a switch to a single dose schedule as emerging evidence showed that it conferred comparable protection as two and three doses, against HPV, which causes cervical cancer. Ministry of Health highlighted a challenge of low second dose coverage in its implementation of HPV vaccination.

UNITAG using a systematic Evidence to Recommendation framework, reviewed relevant contextual evidence for Uganda to develop conclusions and recommendations.

The analysis showed that HPV virus (particularly serotypes 16 and 18) caused cervical cancer is the most common cancer affecting women in Uganda, with national incidence averages three times the global levels. This public health problem is further aggravated by low community awareness levels for preventive tools such as screening to enable early detection and treatment, health system challenges with administering and completing timely treatment, leading to high numbers of avoidable morbidities and mortalities (7,000 cases and 6600 deaths) annually.

Efficacy and effectiveness data from ongoing randomized control trials in Kenya, Tanzania, Costa Rica and India showed that for immuno-competent girls and women, the protective effect from a single dose of HPV vaccine is non-inferior to that conferred by two or three doses, for at least four years; albeit with four times lower antibody concentrations. Immuno-bridging studies and modelling projections have shown that the protection conferred by a single dose of the vaccine persists for at least ten years.

Economic and financial analyses conducted in Uganda and modeling studies similarly showed that switching to a single dose of HPV would half the financial cost of a fully immunized girl and was more effective, requiring less vaccine doses to achieve similar results in number of cases averted and lives saved. This corresponded to modelling results which showed that with comparable coverage (70% +) and no waning, forty years after vaccine introduction, a single dose averted comparable cases of cervical cancer as two doses at half the upfront cost.

Regarding acceptability of the single does among vaccine recipients, a nested qualitative study in Tanzania among trial participants found that girls preferred a single dose, in order to avoid pain associated with a second jab, whereas caregivers deferred to decision on number of doses to the medical team trusting them to provide what was protective to their daughters. Other reasons given for single dose preference was less logistical requirements with no need for a second visit, and ethical considerations to avail the vaccine to more people that need it.

The switch to a single dose with the aim of reaching more girls with the HPV vaccine aligns with the National Cervical Cancer Strategic plan to reduce the incidence, prevalence and mortality from cervical cancer among Ugandan women for the period 2018 – 2023.

Having considered the contextual evidence, UNITAG thus concludes:

1. Cervical cancer, mainly caused by HPV, is a public health problem in Uganda. The available prevention and treatment options, such as early detection through screening and ablative or incision treatments are currently not being optimally utilized due to a combination of low community awareness and health system constraints.

2. HPV vaccination program in Uganda has been partially successful, with high coverage rates for the first dose, but low completion rates for the second dose.
3. There is interim efficacy data from settings in low and middle income countries that show that a single dose of Cervarix and Gardasil HPV vaccines provide comparable protection as two or three doses in immuno-competent girls and women for at least four years.
4. Switching from a two dose to a one dose schedule for HPV vaccine in immuno-competent recipients offers significant financial benefits in terms of costs saved per fully immunized child.
5. A switch from two doses to one dose of HPV vaccine is anticipated to reduce logistical costs associated with tracking targets for follow up doses and return visits, limiting it to only immuno-compromised recipients.

Based on the foregoing evidence and conclusions, UNITAG thus recommends:

1. For Immuno-competent girls aged 9-14 years in Uganda, there is sufficient scientific evidence to support the provision of one dose of Cervarix or Gardasil HPV vaccine, as the efficacy is comparable to that from two doses and is sufficient to provide protection against HPV disease. The shift from two doses to one dose would also be cost-saving and cost-effective for the country.
2. Immuno-compromised girls, including those who are HIV positive, should continue to receive three, if not at feasible, at least two doses of HPV vaccine. The second and third doses should be administered at the care clinics.

1 Introduction

On 5th April 2023, the Ministry of Health, through the Director General Health services, requested the UNITAG to review the available evidence in support of a switch to a single dose Human Papilloma Virus (HPV) vaccination schedule (see request letter in Annex 1). This was in line with a 2022 Strategic Advisory Group of Experts (SAGE) recommendation to the WHO Director General for countries to consider a switch to a single dose schedule as emerging evidence showed that it conferred comparable protection as two and three doses, against HPV, which causes cervical cancer. Ministry of Health highlighted a challenge of low second coverage in its implementation of HPV vaccination.

The WHO has in the past made similar off-label recommendations for change of vaccine dosage following updated evidence. An example is with Yellow fever vaccine, which was licensed in 1965 with a recommendation for a booster dose every ten years, based on limited data. Following new studies that showed persistence of the neutralizing antibodies several decades after vaccination, and using this as a proxy for efficacy, the WHO recommendation was updated in 2003 to one vaccine for lifelong protection.[1]

2 Background

2.1 Human Papilloma Virus (HPV) Disease[2]

HPV is mainly transmitted through sexual contact and most people are infected with HPV shortly after the onset of sexual activity. More than 90% of them clear the infection eventually. HPV cervical infection results in cervical morphological lesions ranging from normalcy (cytologically normal women) to different stages of precancerous lesions –Cervical Intraepithelial Neoplasia (CIN-1, CIN-2, CIN-3/CIS) and invasive cervical cancer. **HPV causes virtually 100% of cervical cancer cases**, and an underestimation of HPV prevalence in cervical cancer is most likely due to the limitations of study methodologies. **Worldwide, HPV16 and 18 (the two vaccine-preventable types) contribute to over 70% of all cervical cancer cases**, between 41% and 67% of high-grade cervical lesions and 16-32% of low-grade cervical lesions. HPV is also responsible for other diseases such as recurrent juvenile respiratory papillomatosis and genital warts, both mainly caused by HPV types 6 and 11.

Comprehensive cervical cancer control includes primary prevention (vaccination against HPV), secondary prevention (screening and treatment of pre-cancerous lesions), tertiary prevention (diagnosis and treatment of invasive cervical cancer) and palliative care. Cervical cancer can be cured if diagnosed at an early stage and treated promptly.

2.2 HPV burden coverage and trends[3]

2.2.1 Global burden of HPV related cancers and disease

Cancer of the cervix uteri is the 4th most common cancer among women worldwide, with an estimated 604,127 new cases and 341,831 deaths in 2020. Worldwide, mortality rates of cervical cancer are substantially lower than incidence with a ratio of mortality to incidence to 57% (GLOBOCAN 2020). **Worldwide, HPV16 and 18 (the two vaccine-preventable types) contribute to**

[1] WHO 2013. Background paper on Yellow Fever vaccine. SAGE Working Group. https://cdn.who.int/media/docs/default-source/immunization/position_paper_documents/yellow-fever/1-background-paper-yellow-fever-vaccines.pdf?sfvrsn=b8ed58a9_2

[2] WHO 2022. Cervical Cancer Fact sheet. https://www.who.int/news-room/fact-sheets/detail/cervical-cancer

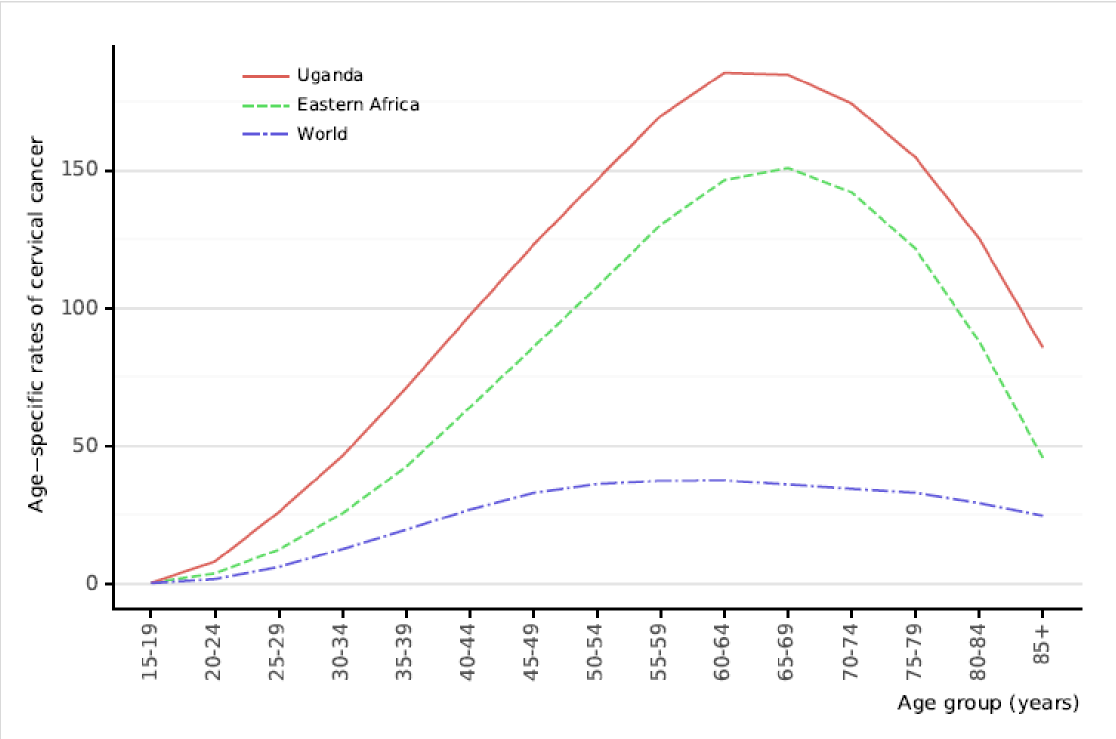
[3] Bruni L, Albero G, Serrano B, Mena M, Collado JJ, Gómez D, Muñoz J, Bosch FX, de Sanjosé S. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in Uganda. Summary Report 10 March 2023. [Accessed Sept 2023]

over 70% of all cervical cancer cases, between 41% and 67% of high-grade cervical lesions and 16-32% of low-grade cervical lesions. After HPV16/18, the **six most common HPV types are the same in all world regions, namely 31, 33, 35, 45, 52 and 58; these account for an additional 20% of cervical cancers worldwide** (Clifford G, Vaccine 2006;24(S3):26)
In November 2020, the Cervical Cancer Elimination Initiative (CCEI) was launched; an ambitious global strategy to eliminate cervical cancer as a public health problem, with the ultimate aim of reducing cervical cancer incidence to fewer than four women per 100,000 women-years worldwide.

2.2.2 Burden of HPV disease in Uganda

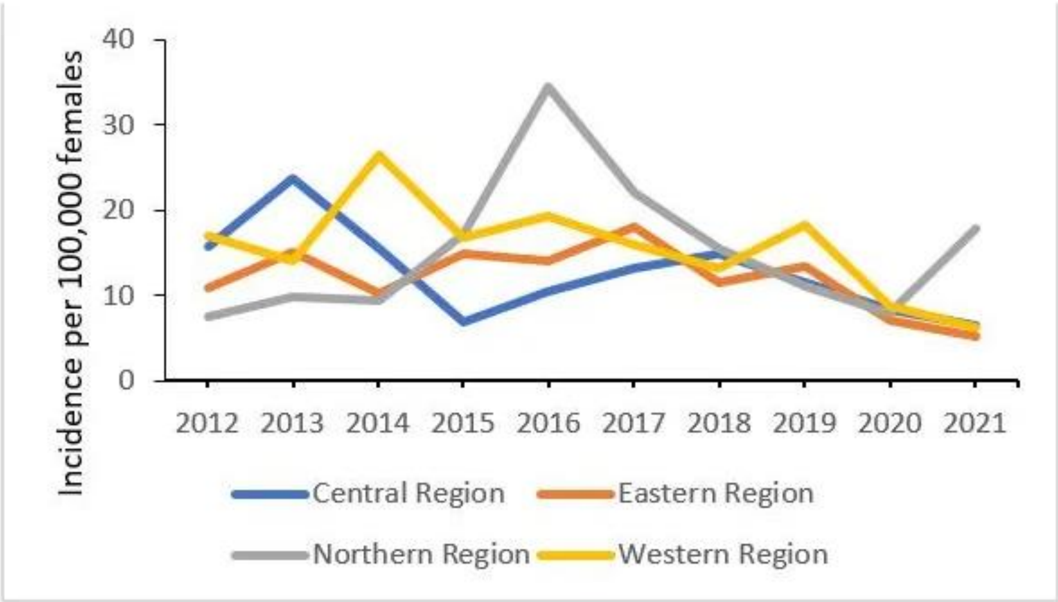
About 6,959 new cervical cancer cases are diagnosed annually in Uganda (estimations for 2020). **Cervical cancer ranks* as the 1st leading cause of female cancer in Uganda. Cervical cancer is the number one most common female cancer in women aged 15 to 44 years in Uganda.**

Age specific incidence of cervical cancer in Uganda compared to regional and global figures



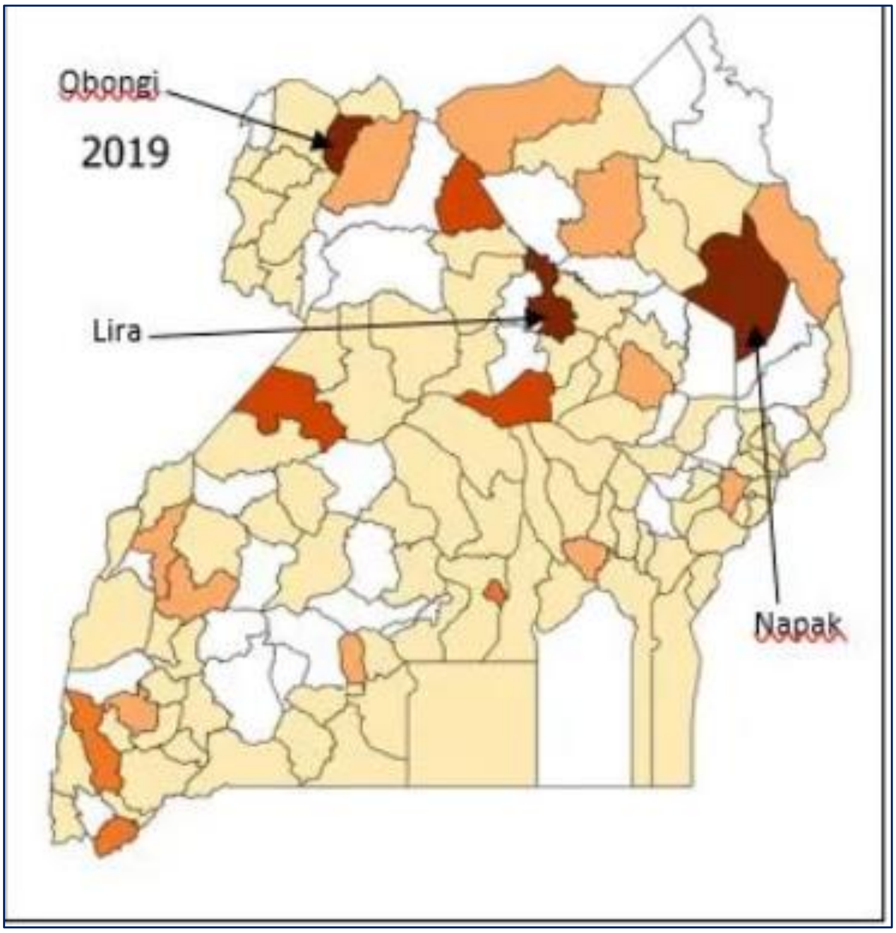
2.2.3 Cervical cancer incidence by region in Uganda (2012-2021)

The northern and north eastern parts of Uganda have registered higher cases of cervical cancer, with Lira, Obongi and Napak districts reporting the highest cases.



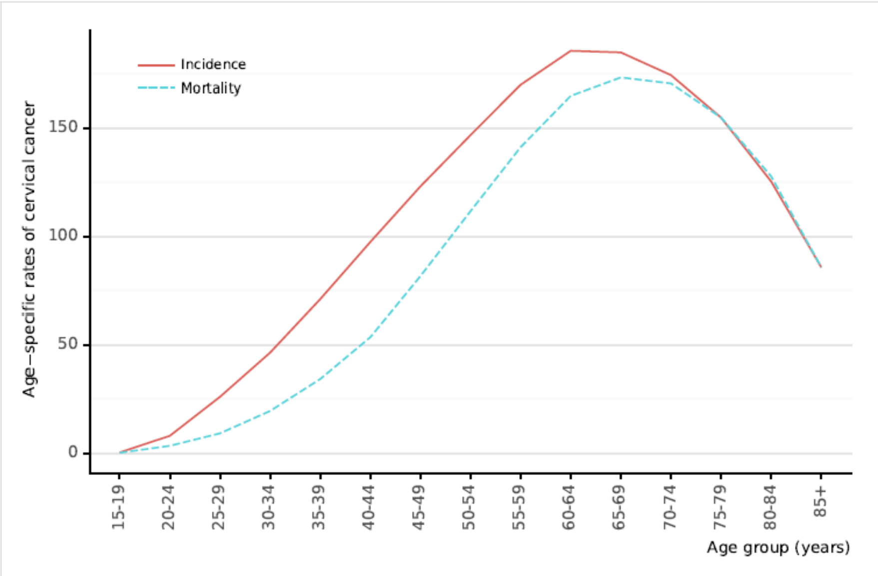
Source: Nampera et. al 2023. Uganda National Public Health Institute. Spatial and temporal trends of cervical cancer in Uganda. 2012-2021) Analysis of Surveillance Data. https://uniph.go.ug/spatial-and-temporal-trends-of-cervical-cancer-uganda-2012-2021-analysis-of-surveillance-data/

Spatial distribution of cervical cancer cases in Uganda, 2019.



Source: Source: Nampera et. al 2023. Uganda National Public Health Institute. Spatial and temporal trends of cervical cancer in Uganda. 2012-2021) Analysis of Surveillance Data. https://uniph.go.ug/spatial-and-temporal-trends-of-cervical-cancer-uganda-2012-2021-analysis-of-surveillance-data/

2.2.4 Comparison of age-specific cervical cancer incidence and mortality rates in Uganda (estimates for 2020)



Data accessed on 27 Jan 2021

Prevalence of other HPV infections and disease in Uganda

Disease/ infection	Annual new infections (nos.)		Annual Mortality (nos.)	
	Men	Women	Men	Women
Anal Cancer	70	43	51	31
Vulva Cancer	-	122	-	73
Vaginal Cancer	-	38	-	23
Penile Cancer	345		165	
Oro-pharyngeal cancer	79	13	53	9
Oral cavity cancer	264	122	169	78
Laryngeal cancer	186	50	120	34

Prevalence of HPV 16 /18 by cytology in Uganda

	Normal cytology	Cervical Cancer	Anal cancer
% HPV 16/18	3.6	57.0 (38/19)	58/11.8

2.3 Risk groups for HPV infection in Uganda:

2.3.1 High risk sexually active young people

Almost 14% of Ugandan adolescents is sexually active by age 15 (15.5% of the girls and 12.2% of the boys)[4] and over 50% by age 18[5]. When sexually active, around 15% of the young Ugandans aged 15–19 years, ever used a condom. Of those aged 15–24 years who ever had sex, 28% used a condom at

[4] UNAIDS: Global report. UNAIDS report on the global AIDS epidemic 2010. 2010, Geneva, Switzerland, Available at: http://www.unaids.org/globalreport/documents/20101123_GlobalReport_full_en.pdf
[5] Uganda Bureau of Statistics, & ORC Macro. MEASURE/DHS+ (Programme). (2007). *Uganda Demographic and Health Survey, 2006*. Uganda Bureau of Statistics.

first sex, with a slight difference between boys (29%) and girls (27%). By the age of 19, approximately 50% of all Ugandan women have had their first child[6].

2.3.2 HIV Positive Immuno-compromised

Banura et. al., 2011[7] conducted a systematic review on the burden of HPV among HIV infected persons in Uganda. **Among HIV negative adult women, the prevalence of HR-HPV infections ranged from 10.2% to 40.0% compared to 37.0% to 100.0% among HIV positive women**. Among HIV positive young women aged below 25 years, the prevalence of High Risk-HPV genotypes ranged from 41.6% to 75.0% compared to 23.7% to 67.1% among HIV negative women. Multiple infections with non-vaccine HR-HPV genotypes were frequent in both HIV positive and HIV negative women. **Among uncircumcised adult HIV positive males, HR-HPV prevalence ranged from 55.3% to 76.6% compared to 38.6% to 47.6% in HIV negative males.** Incident and multiple HR-HPV infections were frequent in HIV positive males. Being uncircumcised was the main risk factor for both prevalent and incident HPV infection.

2.3.3 Burden of HIV infection among Adolescent girls and young women in Uganda.

The Uganda National Institute of Public Health analysed routine HIV testing data from 2017 to 2021 for adolescent girls and young women reported through the District Health Information System 2 and from 600 clinical sites that test for HIV recency in Uganda.

According to the Ministry of Education and Sports Education Abstract of 2017[8], a total of 34,546 (**16,752 male and 17,794 female) pupils have HIV/AIDS**, a proportion of **0.35% to the total enrolment in primary schools.**

HIV positivity rate among young girls and adolescent women 2017-2021

Age Category	Total Tested	Tested Positive	HIV positivity rate (%)	95% Confidence Interval
10-14	732,433	5,972	0.82	(0.80-0.84)
15-19	3,204,505	45,381	1.42	(1.40-1.43)
20-24	4,596,054	117,280	2.55	(2.54-2.57)

Geographically, four districts had persistently high prevalence rates (>4%) among this population group: Mbarara, Rwampala, Sheema and Kalangala.

Spatial distribution of five year HIV positivity rate among adolescent girls and Young Women (10-24 years) in Uganda, 2017 – 2021.

[6] Rijsdijk, L.E., Bos, A.E., Lie, R. *et al.* Correlates of delayed sexual intercourse and condom use among adolescents in Uganda: a cross-sectional study. *BMC Public Health* **12**, 817 (2012). https://doi.org/10.1186/1471-2458-12-817

[7] Banura C, Mirembe FM, Katahoire AR, Namujju PB, Mbonye AK, Wabwire FM. Epidemiology of HPV genotypes in Uganda and the role of the current preventive vaccines: A systematic review. Infect Agent Cancer. 2011 Jul 12;6(1):11. doi: 10.1186/1750-9378-6-11. PMID: 21749691; PMCID: PMC3163594.

[8] Ministry of Education and Sports 2019. Education Abstract 2017. https://www.education.go.ug/wp-content/uploads/2019/08/Abstract-2017.pdf

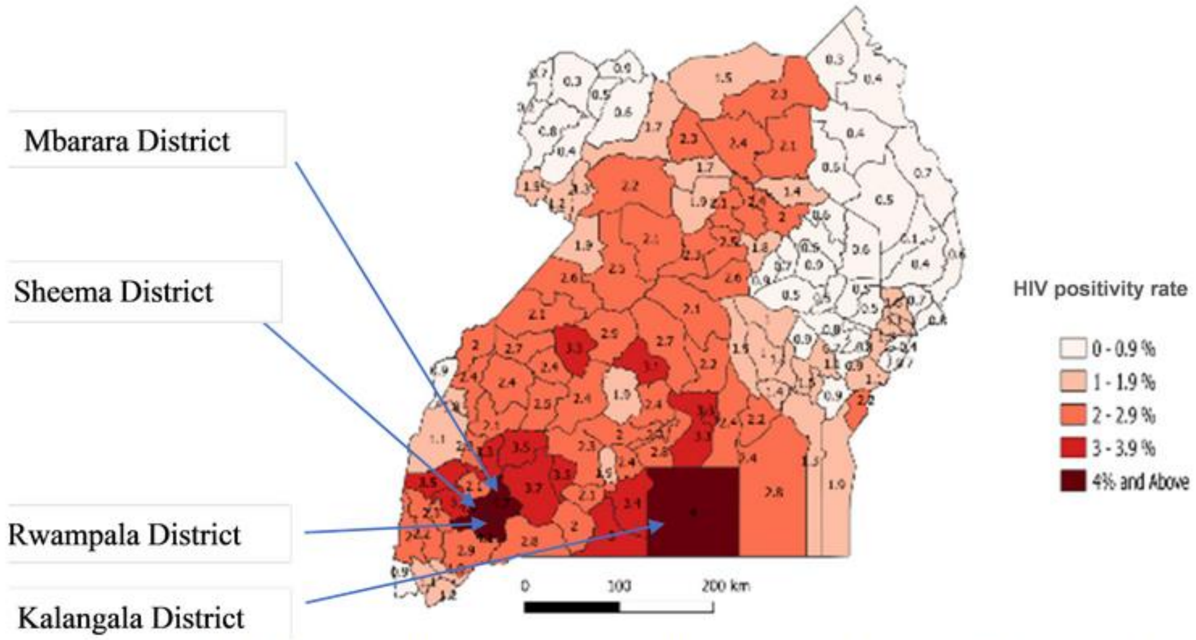


Figure 3: Spatial distribution of five-year HIV positivity rate among Adolescent Girls and Young Women 10-24 years, Uganda, 2017-2021

2.4 Strategies for cervical cancer prevention and care in Uganda.

In 2020, WHO launched a global strategy to eliminate cervical cancer as a public health problem. In order to achieve this, countries have to meet the 90-70-90 target:

1. 70% of women screened using a high-performance test by 35 years of age and again by 45 years of age
2. 90% of women identified with cervical disease are treated:
   - 90% of women with pre-cancer treated
   - 90% of women with invasive cancer managed
3. 90% of girls fully vaccinated with HPV vaccine by 15 years of age

Uganda's National Cervical Cancer Prevention and Control Strategic Plan 2018 aims to reduce the incidence, prevalence and mortality from cervical cancer among Ugandan women for the period 2018 – 2023.It proposed the following targets:

1. Increase screening rates of pre-cancer among women aged 25-49 years from 10% to 50%
2. Increase treatment rates of pre-cancer lesions among women aged 25-49 years by 80%
3. A 100% HPV1 and HPV2 vaccination to all eligible girls/women.

As of 2021, there was a 378% increase in screening for cervical cancer compared to the 2018 levels.[9] Despite this progress, Uganda's national screening program faces considerable implementation gaps. In practice, screening in Uganda is erratic and absent in many regions[10]. Unfortunately, there is very limited (or no) public funding for such programs which suffer from acute donor-dependency. Uptake of screening services that do exist are negatively impacted by limited access to facilities, compounded by the costs associated with services, travel, and wait times. There is also a shortage of trained screening providers. This explains the low **lifetime screening rate of between 4.8% and 0%**.[10]

[9] Nampera et. al 2023. Uganda National Public Health Institute. Spatial and temporal trends of cervical cancer in Uganda. 2012-2021) Analysis of Surveillance Data. https://uniph.go.ug/spatial-and-temporal-trends-of-cervical-cancer-uganda-2012-2021-analysis-of-surveillance-data/

[10] Auma et al 2023. Task-shifting for point-of-care cervical cancer prevention in low- and middle-income countries: a case study from Uganda. Frontiers for Public Health. Vol.11. doi 10.3389/fpubh.2023.1105559 https://www.frontiersin.org/articles/10.3389/fpubh.2023.1105559

Wanyenze et. al., 2017[11] found that only **33% of HIV positive women attending clinical care had been screened** for cervical cancer despite their high risk profile.

The Uganda Cancer Institute (UCI) is the main center for cancer care in the country with an 80-bed capacity receiving about 6,000 cases every year.[12] Based on the Kyadondo Cancer Registry, **more than 80% of women with cervical cancer referred to the UCI present with stage III or higher disease**. **70–80% of women who present to the UCI are infected with the human immunodeficiency virus (HIV)**. Surgery, radiotherapy, and chemotherapy as well as palliative care services were all available in Uganda for the treatment of invasive cervical cancer. However, there are persistent challenges with infrastructure, shortage of equipment and supplies and inadequate trained health care workers.[12] Additionally, there is low adherence to treatment, with one 2023 study of patients at the Uganda Cancer Institute showing a 12% adherence rate.[13]

3 HPV vaccines

3.1 Global HPV vaccination recommendations

Prophylactic HPV vaccines have now been in use for 15 years, during which time **they have been demonstrated to have an excellent safety profile in population use and very high efficacy against targeted type HPV infection and HPV-related diseases including cervical cancer**. **WHO has recommended their use in pre-adolescent girls for the prevention of cervical cancer since 2003, initially using the originally trialled three dose schedule and, from 2014, in a two dose schedule (based on immune-bridging data) for those aged under 15 at dose one[14]**. A two dose schedule was recommended with a minimum interval of six months. However, **HPV vaccine supply has been insufficient to meet demand since 2018.**

Basing on updated evidence from trials and immune-bridging data, off label vaccine dose optimization recommendations on the use of HPV vaccines were issued by the WHO Strategic Advisory Group of Experts (SAGE) on Immunization at its meeting in April 2022, and subsequently endorsed by WHO[15]:

i. A single dose schedule can be used in girls and boys aged 9-20 years
ii. Individuals known to be immune-compromised or HIV-infected (regardless of age or antiretroviral therapy status) should receive at least two HPV vaccine doses (minimum 6 months interval) and, where possible, three doses.

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[11] Rhoda K. Wanyenze, John Baptist Bwanika, Jolly Beyeza-Kashesya, Shaban Mugerwa, Jim Arinaitwe, Joseph K. B. Matovu, Violet Gwokyalya, Dickson Kasozi, Justine Bukenya & Fred Makumbi (2017) Uptake and correlates of cervical cancer screening among HIV-infected women attending HIV care in Uganda, Global Health Action, 10:1, DOI: 10.1080/16549716.2017.1380361

[12] Nakisige C, Schwartz M, Ndira AO.(2017) Cervical cancer screening and treatment in Uganda. Gynecol Oncol Rep. 2017 Feb 3;20:37-40. doi: 10.1016/j.gore.2017.01.009. PMID: 28275695; PMCID: PMC5331149.

[13] Najjemba, J.I., Ndagire, R., Mulamira, P. et al. Treatment compliance among adult cervical cancer patients receiving care at Uganda cancer institute, Uganda: a retrospective data review. BMC Cancer 23, 631 (2023). https://doi.org/10.1186/s12885-023-11145-1.
https://bmccancer.biomedcentral.com/articles/10.1186/s12885-023-11145-1#citeas

[14] WHO 2013. Immunogenicity of 2 vs 3 doses of HPV vaccination in immuno-competent girls. https://cdn.who.int/media/docs/default-source/immunization/position_paper_documents/human-papillomavirus-(hpv)/hpv-grad-immunogenicity-2vs3-immunocompetent.pdf?sfvrsn=63892fdb_2

[15] WHO 2022. Human Papilloma vaccines. Position paper (updated March 2022). https://www.who.int/publications/i/item/who-wer9750-645-672

3.2 Global HPV vaccine demand and supply forecast[16].

Global HPV vaccine supply

Currently, five HPV vaccines have received marketing authorisation and/or WHO prequalification:

1. GSK's Bivalent Cervarix® with proprietary AS04 adjuvant,
2. Innovax's Bivalent Cecolin® with aluminium-containing adjuvant,
3. Biotechnology's Bivalent Walvax with aluminium-containing adjuvant
4. Merck's Quadrivalent (HPV4) vaccine: Gardasil® with aluminium-containing adjuvant
5. Merck's Nonavalent (HPV9) vaccine: Gardasil 9® with aluminium-containing adjuvant

All HPV vaccines contain virus like particles (VLPs) against high-risk HPV types 16 and 18; the nonavalent vaccine also contains VLPs against high-risk HPV types 31, 33, 45, 52 and 58; and the quadrivalent and nonavalent vaccines contain VLPs to protect against anogenital warts causally related to HPV types 6 and 11.

Among fully vaccinated, baseline HPV-naïve women, the bivalent vaccine has shown statistically significant cross-protective efficacy, although with wide confidence intervals, against 6-month and 12-month persistent cervical infections and CIN2+ only consistently for HPV 31 and 45, with the highest effect observed for HPV 31 (range 64.6% [95% CI: 27.6 to 83.9] to 79.1% [97.7% CI: 27.6 to 95.9] for 6-month persistent infection; maximal follow-up 4.7 years). No cross-protection was shown in extended follow-up. The quadrivalent vaccine efficacy for HPV 31 is 46.2% [15.3-66.4]; follow-up: 3.6 years. Similarly, observational studies found consistently significant effectiveness only against HPV 31 and 45 with both vaccines[17].

Two quadrivalent HPV vaccines are currently in Phase 3 clinical development: one from Serum Institute of India and one from the China National Biotec Group (CNBG). All use aluminium-containing adjuvants and are likely to be licensed with an indication for girls 9–14 years old for two- and/or three-dose schedules.

Vaccine demand vs. supply

A global demand forecast for HPV vaccine has been developed for the 10-year period 2022–2031[16] based on historical procurement data and the latest available requests[16] A WHO projection forecasted an increase in available supply over the medium term (4–6 years, range 2–4X), from the ~80M doses that were expected to be available in 2022[16].

The base-case scenario of the forecast was developed based on the current WHO-recommended two-dose schedule for girls under 15 years of age. Starting from 2022, global supply is expected to be sufficient to meet base demand for a two-dose routine program targeting girls, inclusive of MACs campaigns. The supply–demand balance is expected to steadily improve from 2023 to 2024. After 2025, HPV vaccine supply is expected to significantly exceed demand even in the most pessimistic supply scenarios.

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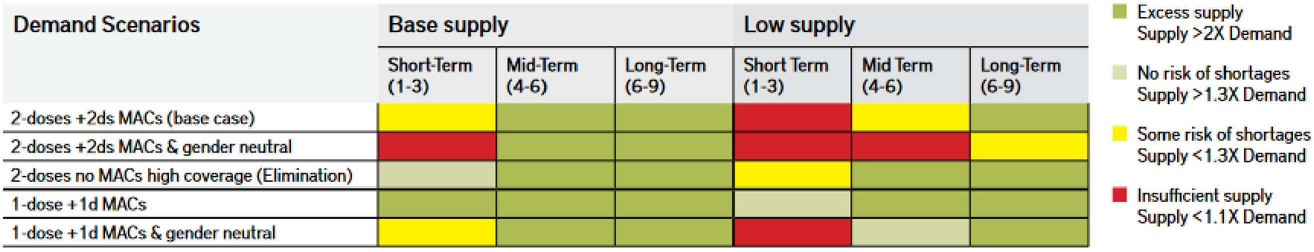
[16] WHO and Market Information for Access to Vaccines, March 2022. Global Market Study HPV. https://cdn.who.int/media/docs/default-source/immunization/mi4a/who-mi4a-global-market-study-hpv.pdf?sfvrsn=649561b3_1&download=true

[17] Brown DR, Joura EA, Yen GP, Kothari S, Luxembourg A, Saah A, Walia A, Perez G, Khoury H, Badgley D, Stanley M. Systematic literature review of cross-protective effect of HPV vaccines based on data from randomized clinical trials and real-world evidence. Vaccine. 2021 Apr 15;39(16):2224-2236. doi: 10.1016/j.vaccine.2020.11.076. Epub 2021 Mar 18. PMID: 33744051.



1d: one dose; 2ds: two doses; MACs: multi-age cohorts.

20 In this scenario, boys' vaccination is not expanded further to countries other than the ones that already have them in place.

21 Low supply scenario based on more conservative assumptions concerning manufacturing capacity increases and success in clinical development.

22 One-dose-only scenarios assume that supply is available solely from suppliers that have supporting data for a single-dose schedule.

3.3 Potential impact of one dose strategy on vaccine demand and supply

In this context, the potential adoption of a one-dose schedule would further improve the supply–demand balance in the short term, allowing accelerated implementation of MAC campaigns and more flexibility on product choice. In the medium and long term, the implementation of a one-dose schedule by a large number of countries could (i) either allow for a more generalized adoption of boys and/or older cohorts vaccination strategies or (ii) lead to a rapid reduction in programmatic dose requirements[16]. The latter, coupled with the fact that not all products have data available supporting the switch to one dose or boys vaccination, could impact the sustainability of the HPV market for vaccine manufacturers, including through price changes and/or market exits. Transition to a one-dose schedule would therefore require careful management, including through generation of evidence for single-dose efficacy for all products.

3.4 Vaccine Price

The reported price per dose of HPV vaccines shows a tiered structure by procurement method and income group **with UNICEF Supply Division (SD)**/Gavi and the PAHO (Pan American Health Organization) Revolving Fund (RF) paying the lowest prices, **at US$ 4.50** and US$ 9.98, respectively. The UNICEF SD/Gavi price for **GSK's HPV2 product increased to US$ 5.18** starting in 2022, and the price for **Merck's HPV4 will continue at US$ 4.50 until 2025**. Contracted price for **Innovax starting in 2022 is $2.90 per dose** though no country is yet to procure the vaccine. The **self-procuring** MICs' median price for HPV2 is **more than twice the Gavi price** and slightly higher than the PAHO price. Generally, GSK's HPV2 product is lower priced, ranging from US$ 11.17 to US$ 12.53, compared with **Merck's HPV4 product, which ranges from US$ 13.81 to US$ 64.16** for self-procuring MICs[16].

	USD			**UGX (USD *3730)**		
	Unicef/Gavi	PAHO	Self-Procuring	Unicef/Gavi	PAHO	Self-Procuring
HPV2- gsk (16/18)	5.18	10.2-11.4	14.14	19,321.4	38,046 - 42,522	52,742.2
HPV2 – Innovax (16/18)	2.9	2.9	2.9	10,817	10,817	10,817
HPV4 – Merck (6/11/16/18)	4.50		13.5 – 26.7	16,785		50,355 - 99,591
HPV 9 _Merck*			268.02			999,714.6

HPV Vaccine prices for 2023. Sources: UNICEF supply division (2022) https://www.unicef.org/supply/media/11776/file/HPV-vaccine-prices.pdf and *Merck webpage https://www.gardasil9.com/adults/cost/

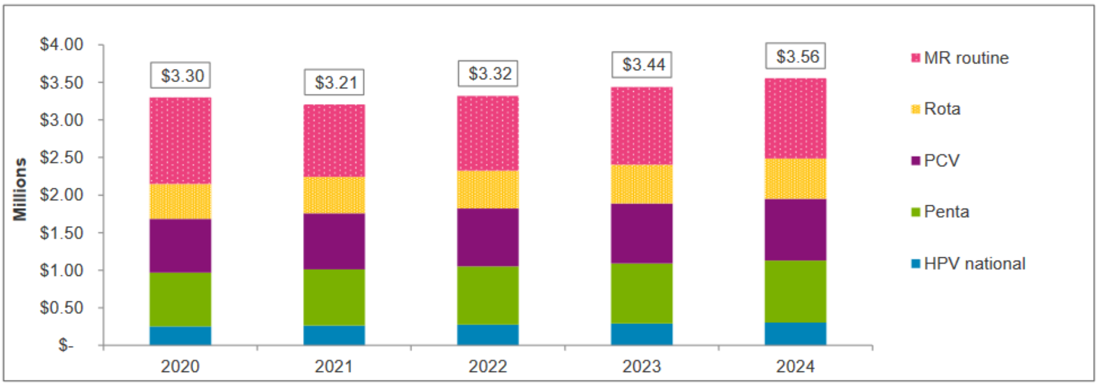
3.4.1 Funding for HPV Vaccines

HPV vaccines are listed among Gavi funded antigens for low and medium income countries, of which Uganda is among. In December 2022, the Gavi board made a decision to provide **additional** funding for HPV vaccines support to help countries and partners reach more girls with this life-saving vaccine than ever[18]. This includes **US$ 40 million to optimise health systems strengthening** investments focused on effective delivery of the HPV vaccine. Gavi will dedicate **US$ 15 million to establish a learning agenda** to support the integration of the HPV vaccination programme into routine immunisation and primary health care in lower- and middle-income countries. Gavi will also offer **support to countries to optimise the 2022 WHO Strategic Advisory Group of Experts on Immunization (SAGE) one-dose recommendation**.

3.4.2 HPV co-financing costs and projections for Uganda 2020-2024

In 2019, Uganda spent $ 156,000 in co-financing HPV vaccine out of the total $3,134,500 co-financing expenditure, accounting for 4.98%. HPV vaccines are projected to cost $303,855 in 2024 (see figure below).[19]

Co-financing projections for 2020 - 2024



	2020	2021	2022	2023	2024
HPV national	$ 251,407	$ 263,772	$ 276,832	$ 290,200	$ 303,855
Penta	$ 715,997	$ 747,030	$ 772,434	$ 798,236	$ 824,381
PCV	$ 715,997	$ 747,030	$ 772,434	$ 798,236	$ 824,381
Rota	$ 465,228	$ 485,163	$ 501,477	$ 518,041	$ 534,821
MR routine	$ 1,150,244	$ 962,703	$ 997,562	$ 1,033,020	$ 1,069,006
Total	**$ 3,298,872**	**$ 3,205,697**	**$ 3,320,739**	**$ 3,437,733**	**$ 3,556,444**

3.5 HPV Vaccine delivery in Uganda

In 2008, Uganda carried out a demonstration project for HPV vaccination in Nakasongola and Ibanda districts and the project ended with impressive results. Later in 2012, twelve additional districts were piloted to make a total of fourteen, implementing the HPV vaccination program supported by the Global Alliance for Vaccines and Immunization (GAVI), World Health Organization, UNICEF, and MSD. In November 2015, Uganda introduced HPV vaccine in its immunization schedule in all districts. HPV vaccine was introduced as a routine vaccine to be delivered during every static and outreach immunization sessions but intensified through Integrated Child Health Days during the months of April and October where health workers conduct school-based outreaches. In Uganda girls ages 10–14 years are eligible for vaccination. Catch-up vaccination is recommended for girls

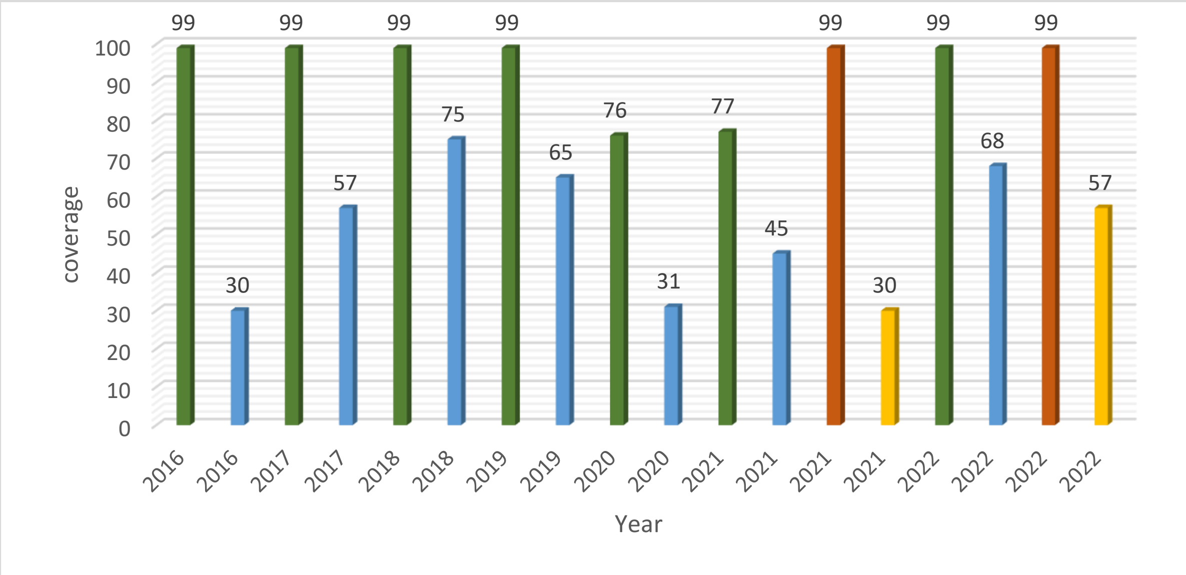
[18] Gavi the vaccine alliance, 2023. Press release. Immunisation partners outline ambitious plan to protect millions of girls in lower- and middle-income countries against cervical cancer. https://apigateway.agilitypr.com/distributions/history/5175d58e-cea7-4180-abfe-7a6c2edfc9bb

[19] Gavi 2019. Uganda. Key information on co-financing. https://www.gavi.org/sites/default/files/document/co-financing-information-sheet-ugandapdf.pdf

older than 14 years, provided they have not yet become sexually active.[20] Currently the vaccine is given in a two dose schedule, at least six months apart

3.6 HPV vaccination coverage trends in Uganda

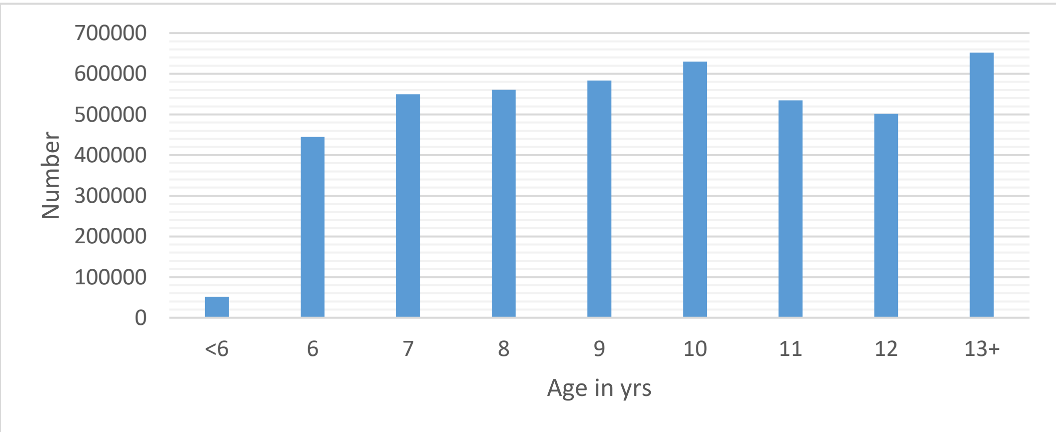
3.6.1 HPV coverage by dose



	Target population who received the first dose of HPV vaccine in the reporting year
	Target population who received the last dose of HPV vaccine in the reporting year
	Population turning 15 in the reporting year that received any time between age 9- 14 at least one dose of HPV vaccine
	Population turning 15 in the reporting year that received any time between age 9- 14 the full recommended schedule of HPV vaccine

Author generated figure. Source data: UNICEF 2023. Immunisation. Immunisation data. Build your own dataset. Human Papilloma Virus (HPV) Immunisation coverage estimates, July 2023. https://data.unicef.org/topic/child-health/immunization/#

Girl child enrollment in school by age in 2017



Author generated figure. Source data from Ministry of Education and Sports 2019. Education Abstract 2017. https://www.education.go.ug/wp-content/uploads/2019/08/Abstract-2017.pdf

[20] Minstry of Health, 2010. Strategic plan for cervical cancer prevention and control in Uganda 2010–2014. https://www.iccp-portal.org/system/files/plans/PATH_Uganda_cxca_strat_plan_2010-2014.pdf

3.7 Causes of low completion rates for HPV vaccine in Uganda

A 2022 mixed methods study was conducted in Mulago National Referral hospital adolescent clinic[21] covered 288 girls; 201(69.8%) girls completed 2 doses of HPV vaccine, while 87(30.2%) girls received only one dose of HPV vaccine. Findings showed **that Knowledge about HPV infection and HPV vaccine** benefits, **positive peer influence and healthcare worker recommendation** to get vaccinated at health facility level **positively influenced timely completion of HPV vaccine**. Among **barriers to completion** of HPV vaccine identified were: **inadequate information about HPV infection** and HPV vaccine**, concerns about HPV vaccine efficacy and safety**, **unclear communication with adolescents/caregivers from healthcare workers** and -**stock out of the HPV vaccine**.

A 2020 analysis by Kamulegeya John[22] indicated that **health service delivery challenges are one of the greatest barriers to HPV vaccination**, specifically **the lack of capacity to track and distribute reminders to eligible patients**, **low ability to effectively mobilize communities and commodity logistic challenges**. **Health care providers** do not strongly recommend the vaccine, are **not effectively educating their patients** about it, are not outlining its **vaccination schedule**, and are not urging families to start and then complete the vaccination in time. This analysis is consistent with findings by Kisakye et. al., 2018[23] study among adolescents in Lira district: Out of the 460 respondents interviewed, 49.6%, (228/460) had not received any dose of HPV vaccine, 18.0% (83/460) had received one dose, 14.8% (68/460) had received two doses, and 17.6% (81/460) had completed all the three doses. 0ut of the 232 respondents who had initiated on the vaccine, 180 (77.6%) had received it from school. **Most** of the adolescents **who had received one dose** of the HPV vaccine were aware of the HPV vaccine but **did not know the right doses and intervals between the doses**. Similarly, a 2020 qualitative study by Nabirye et.al.[24], among girls aged 9-15 years in Mbale district found that 49% (200/407) had initiated the vaccination, of these, adolescents that had initiated the HPV vaccine, only 13.8% (56/407) had received both doses and thus completed the vaccination**. Lack of awareness was the main reason given by 45%** (182/348) of the adolescents that had received one dose or none of the vaccine. While some respondents mentioned that they were not aware about the HPV vaccine, some **were not aware of the number of doses that they must receive** and others were **not aware of the schedule** or interval of the vaccines. In this study, the **major barriers to service delivery** from the key informant interviews included: **low financing**, **myths about the vaccine, unclear communication** on the target for the vaccine's coverage and **transport challenges to reach the adolescents in the community.** Rujumba et al. 2021[25] additionally

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[21] Patrick, L., Bakeera-Kitaka, S., Rujumba, J., & Malande, O. O. (2022). Encouraging improvement in HPV vaccination coverage among adolescent girls in Kampala, Uganda. *PLOS ONE*, *17*(6), e0269655. https://doi.org/10.1371/journal.pone.0269655

[22] John Kamulegeya. Uganda National Institute of Public Health (2020). Uptake of Human Papilloma Vaccination in Uganda, Barriers and Opportunities: A Policy Brief. https://uniph.go.ug/wp-content/uploads/2021/05/6-LB18Jan2021-John-Kamulegeya_HPV.pdf

[23] *Esther Kisaakye et al. Level and factors associated with uptake of Human papillomavirus infection vaccine among female adolescents in Lira District, Uganda. Pan African Medical Journal. 2018;31:184. [**doi:** 10.11604/pamj.2018.31.184.14801]*

[24] Nabirye, J., Okwi, L.A., Nuwematsiko, R. *et al.* Health system factors influencing uptake of Human Papilloma Virus (HPV) vaccine among adolescent girls 9-15 years in Mbale District, Uganda. *BMC Public Health* **20**, 171 (2020). https://doi.org/10.1186/s12889-020-8302-z

[25] Rujumba J, Akugizibwe M, Basta NE, Banura C (2021) Why don't adolescent girls in a rural Uganda district initiate or complete routine 2-dose HPV vaccine series: Perspectives of adolescent girls, their caregivers, healthcare workers, community health workers and teachers. PLoS ONE 16(6): e0253735. https://doi.org/10.1371/journal.pone.0253735

identified challenges of **vaccine stock outs**, **poor cold chain capacity**, **over stretched health-workforce**, **mistrust in government intentions**, **safety concerns and poor social mobilisation**.

Nakyita et. al., 2023[26] reiterated the **importance of health-worker endorsement**, having found that found that school girls aged 9–14 years in Lira City northern Uganda, who received a recommendation for HPV vaccination from health workers had nine odds of receiving the HPV vaccine compared to their counterparts. The study also found **that school girls who were exposed to outreach clinics** were having four odds of receiving HPV vaccine compared to their counterparts. Similarly, Kisaakye et. al., 2018[27] found that there was a **47% higher prevalence of uptake of HPV vaccine among adolescents who reported that HPV vaccine community outreaches** were conducted in their residences compared to those who reported that the outreaches were not conducted in their residences.

4 Considerations for switch to single dose HPV schedule

Proponents of the off-label single-dose HPV vaccination option, based on evidence that it provides comparable and high levels of individual protection, argue that:

1. A single-dose HPV vaccination schedule could **simplify delivery for key stakeholders**, **lower costs**, and/**or create new programme opportunities with the resources saved**. However, countries **should also consider the ability of the HPV programme to reach specific population subgroups, such as immune-compromised persons** who are currently recommended to receive a multi-dose schedule based on the existing data.
2. A single dose likely to be more efficient from a public health perspective **(fewer doses per cervical cancer case prevented), less resource-intensive, and easier to implement than a multi-dose schedule**.
3. However, there are also other key **programmatic aspects** and risks to consider e.g., how the introduction of **or switch to a single-dose schedule will be perceived by the key stakeholders** and how **trust in the immunization programme** might change. Another consideration is the impact on equity (e.g., how a single-dose strategy could impact the **programme's potential to vaccinate hard-to-reach populations, and whether the HPV programme will have the capacity to reach immune-compromised girls with a multi-dose schedule**).

4.1 Evidence for Cost effectiveness, and cost saving by switching from two dose to single dose HPV schedule

4.1.1 Cost savings and cost-effectiveness from single dose

A 2023 costing study conducted by PATH analysed the 2019 HPV vaccination program activities and cost categories for 66 health facilities in 22 districts in Uganda. The study focused on financial (direct financial expenditures) and opportunity costs (costs for use of existing resources) and combined to

[26] Nakayita, R.M., Benyumiza, D., Nekesa, C. *et al.* Factors associated with uptake of human papilloma virus vaccine among school girls aged 9–14 years in Lira City northern Uganda: a cross-sectional study. *BMC Women's Health* **23**, 362 (2023). https://doi.org/10.1186/s12905-023-02511-z

[27] *Esther Kisaakye et al. Level and factors associated with uptake of Human papillomavirus infection vaccine among female adolescents in Lira District, Uganda. Pan African Medical Journal. 2018;31:184. [**doi**: 10.11604/pamj.2018.31.184.14801]*

derive economic costs (financial + opportunity costs). Results showed that switching to a single dose cut the costs per fully immunized child by half (see table below).

		2 dose	I dose	Comments
Mean costs per dose	Financial	$3.32	$3.94	Cost per dose go up under a 1-dose scenario, as the numerator (activities and therefore costs) are decreasing less significantly than the denominator (number of doses delivered).
	Economic	$7.58	$7.90	
Mean costs per fully vaccinated child	Financial	$ 6.64	$3.94	Financial costs per fully vaccinated child decrease while economic costs per fully vaccinated child go down.
	Economic	$15.16	$7.90	

Financial and economic cost variations for 2 dose and I dose HPV schedules in Uganda.
Source. PATH 2023. HPV Vaccine Cost of Delivery and Operational Context Study. Uganda results

These findings are consistent with results from a modeling study by Burger et. al., 2018[28] which found that forty years after initiating routine vaccination and depending on assumptions of vaccine waning, **one-dose HPV vaccination with equivalent coverage (70%) averted 15–16% of cervical cancer cases versus 21% with two-dose vaccination but required only half the upfront economic investment**. Vaccination with **two doses had an attractive cost-effectiveness profile except if one-dose vaccination enabled higher coverage (90% vs. 70%) and efficacy did not wane.** (Note this study did not consider program costs for increasing coverage nor explicitly considered issues of HIV co-infection).

4.1.2 Cost effectiveness of adding boys to the immunization program.

Models using the evidence on the effectiveness of a 1-dose schedule on the primary target showed **that under the assumption of at least 20 years' protection, adding a second dose was not cost-effective.**[29,30]

Focusing on women and girls who are most vulnerable to HPV-associated cancers is an economically viable strategy in limited-resource settings. Gender-neutral vaccination is economically beneficial and it provides increased protection for everyone (Ng et al., 2018). Nonetheless, in limited resource settings, this approach may not be viable. Gavi subsidizes HPV vaccines for females only, focusing on cervical cancer prevention (Gavi, 2020). As such, even though it would be beneficial to vaccinate boys, the current evidence does not suggest this will be a sustainable approach for lower income countries[31].Adding boys to an already successful girls-only programme has a low cost-effectiveness, as males have high protection through herd immunity.[32]

[28] Emily A. Burger, Nicole G. Campos, Stephen Sy, Catherine Regan, Jane J. Kim (2018). Health and economic benefits of single-dose HPV vaccination in a Gavi-eligible country, Vaccine, Volume 36, Issue 32, Part A, 2018, Pages 4823-4829, ISSN 0264-410X, https://doi.org/10.1016/j.vaccine.2018.04.061.

[29] 9 Prem K et al. Global impact and cost-effectiveness of one-dose versus two-dose human papillomavirus vaccination schedules: a comparative modelling analysis. Submitted for publication. (Preprint: https://www.medrxiv.org/content/10.1101/202
1.02.08.21251186v2, accessed August 2022)

[30] . Jit M, Laprise JF, Choi YH, Brisson M. Fewer than three doses of HPV vaccine. The Lancet Oncology. 2015;16(9). Available from: https://doi.org/10.1016/s1470-2045(15)00229-6

[31] Akumbom, A. M., Lee, J. J., Reynolds, N. R., Thayer, W., Wang, J., & Slade, E. (2022). Cost and effectiveness of HPV vaccine delivery strategies: A systematic review. Preventive Medicine Reports, 26. https://doi.org/10.1016/j.pmedr.2022.101734

[32] Datta, S., Pink, J., Medley, G.F. et al. Assessing the cost-effectiveness of HPV vaccination strategies for adolescent girls and boys in the UK. BMC Infect Dis 19, 552 (2019). https://doi.org/10.1186/s12879-019-4108-y

4.2 Vaccine efficacy, effectiveness, immunogenicity and duration of protection of two vs.one dose HPV schedule

Waheed ae al., 2023[33] have summarized the considerations and outputs from the completed and ongoing trials.

4.2.1 Vaccine mode of operation

HPV vaccines induce a type-specific neutralising antibodies (NAb) response directed to the L1 loop regions exposed on the HPV capsid surface. Anti-L1 antibodies can reach the cervix via transudation from the systemic circulation and are postulated to be the primary mechanism of protection against HPV infection[34]. Evidence supports the conclusion that long lived plasma cells (LLPCs) that continuously produce antigen-specific antibodies, are the key immune effectors that underlie the strong type-restricted protection induced by the HPV vaccines. This results in exceptionally strong, consistent, and durable antibody responses to the HPV vaccines**. In healthy young women, sero-conversion rates are virtually 100%**, and, **after a relatively steep 10-fold drop in titer over the first two years, IgG titers plateau or decline very slowly, stabilizing at levels that are substantially higher than the antibody titers induced by natural infection**. This pattern of antibody response is observed **even after a single dose** of vaccine, with stable geometric **mean IgG binding and *in vitro* neutralizng titers that are about 4-fold lower than the plateau titers measured after three doses**[35].

4.2.2 Impact of HIV on sero-conversion and duration of protection

Sero-conversion rates and geometric mean titers elicited by vaccination are lower in People Living with HIV (PLH) compared to immuno-competent participants, especially in individuals with CD4 counts below 200 cells/mm^3 and a detectable viral load. Although waning humoral immunity for HPV seems to be more rapid in this population, there is **evidence that suggests that sero-positivity lasts at least 2-4 years following vaccination**[36]. Tan et al., 2018[37] modeled vaccine efficacy for **single dose HPV among HIV imuno-compromised women in South Africa, and showed that the strategy resulted in similar reductions in HIV + and HIV- populations in different scenarios of coverage and waning of protection.** An ongoing study in South Africa is analyzing HPV one and two-dose Population Effectiveness (HOPE) among adolescent girls with a sub-population of HIV girls. An impact survey has been conducted and one dose analysis is in progress[33].

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[33]Dur-e-Nayab Waheed, F. Ricardo Burdier, Carina Eklund, Iacopo Baussano, Filipe Colaço Mariz, Laura Téblick, Nelly Mugo, Deborah Watson-Jones, Margaret Stanley, Marc Baay, Alex Vorsters,2023. An update on one-dose HPV vaccine studies, immunobridging and humoral immune responses – A meeting report, Preventive Medicine Reports, Volume 35, 2023, 102368, ISSN 2211-3355,https://doi.org/10.1016/j.pmedr.2023.102368. (https://www.sciencedirect.com/science/article/pii/S2211335523002590)

[34] Mariani, L., Venuti, A. HPV vaccine: an overview of immune response, clinical protection, and new approaches for the future. *J Transl Med* **8**, 105 (2010). https://doi.org/10.1186/1479-5876-8-105

[35] Schiller J, Lowy D. Explanations for the high potency of HPV prophylactic vaccines. Vaccine . 2018;36(32 Pt A):4768 4773. doi : 10.1016/j.vaccine.2017.12.079.

[36] Losada C, Samaha H, Scherer EM, Kazzi B, Khalil L, Ofotokun I, Rouphael N. Efficacy and Durability of Immune Response after Receipt of HPV Vaccines in People Living with HIV. Vaccines (Basel). 2023 Jun 5;11(6):1067. doi: 10.3390/vaccines11061067. PMID: 37376456; PMCID: PMC10301114.

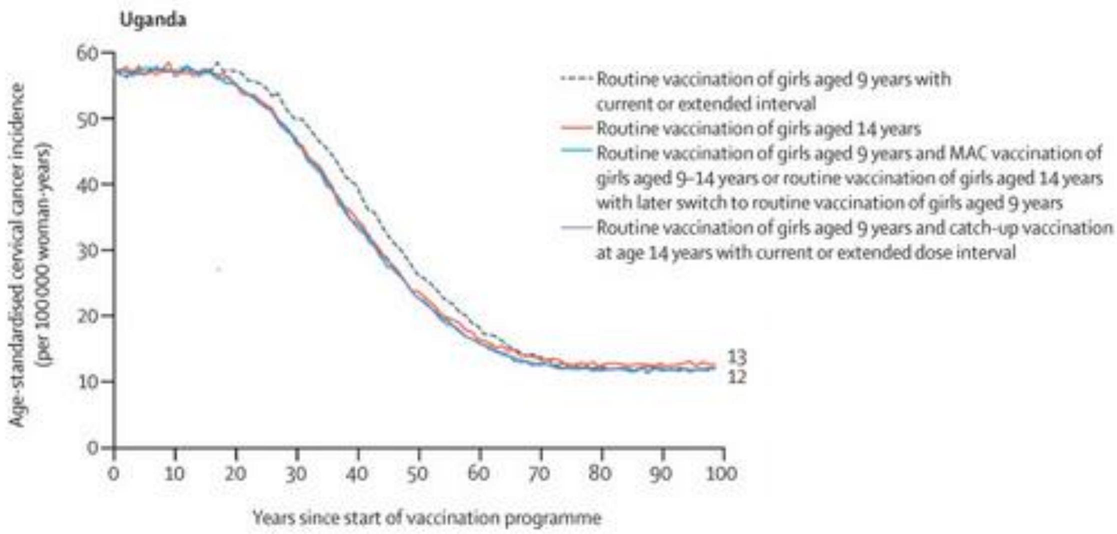
[37] Tan N, Sharma M, Winer R, Galloway D, Rees H, Barnabas RV. Model-estimated effectiveness of single dose 9-valent HPV vaccination for HIV-positive and HIV-negative females in South Africa. Vaccine. 2018 Aug 6;36(32 Pt A):4830-4836. doi: 10.1016/j.vaccine.2018.02.023. Epub 2018 Jun 8. PMID: 29891348; PMCID: PMC6508597.

4.2.3 Impact of delayed second dose on efficacy and efficiency outcome

Modelling studies[38] show that extending the gap between the doses by up to five years (when the dose at age 14 years is given to girls irrespective of vaccination status and assuming high vaccination coverage), resulted in a substantially greater reduction in cervical cancer incidence compared with the current two-dose schedule (reductions in cervical cancer incidence of 86–93% assuming 70% coverage). Efficiency of the extended schedule was greater than the two-dose schedule, even with a drop in vaccination coverage. This is because an extended schedule would provide the opportunity to vaccinate a greater number of girls with at least one dose and therefore increase the population-level impact of HPV vaccination.

4.2.4 Imapct of age at vaccination on efficacy and efficiency outcomes

Drolet et. al., 2021[39] found that **routine vaccination of girls aged 9 years with a 5-year extended interval between doses combined with a catch-up programme for girls aged 14 years was predicted to provide the same accelerated benefits and long-term population-level effectiveness as multiple age-cohort vaccination of girls aged 9–14 years in the first year** of the programme, but with fewer vaccine doses required in the short term and lower NNVs (number of doses needed to prevent one case of cervical cancer - as a measure of efficiency) and Incremental Cost Effectiveness Rations (ICERs).



Predicted population-level impact of different two-dose HPV vaccination strategies targeting girls aged 9–14 years

This study further showed that the long-term population-level effectiveness of routine vaccination of girls aged 14 years would be 3–4% percentage points lower than routine vaccination of girls aged 9 years in countries such as Nigeria and India, which have a relatively high proportion of girls aged 14 years who are sexually active (15–25%).

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[38] Bénard, É., Drolet, M., Laprise, J., Jit, M., Prem, K., Boily, M., & Brisson, M. (2023). Potential benefit of extended dose schedules of human papillomavirus vaccination in the context of scarce resources and COVID-19 disruptions in low-income and middle-income countries: A mathematical modelling analysis. The Lancet Global Health, 11(1), e48-e58. https://doi.org/10.1016/S2214-109X(22)00475-2

[39] Drolet, M., Laprise, J., Martin, D., Jit, M., Bénard, É., Gingras, G., Boily, M., Alary, M., Baussano, I., Hutubessy, R., & Brisson, M. (2021). Optimal human papillomavirus vaccination strategies to prevent cervical cancer in low-income and middle-income countries in the context of limited resources: A mathematical modelling analysis. The Lancet Infectious Diseases, 21(11), 1598-1610. https://doi.org/10.1016/S1473-3099(20)30860-4

Vaccination strategies that included boys or older women were substantially less efficient and cost effective than vaccination strategies that included girls aged 9-18 years only. Strategies that involved vaccinating boys were the least efficient and cost-effective, with number of doses required to prevent one case of cancer being six to eight times higher than when vaccinating girls and women up to age 25 years.

4.2.5 Impact of single dose on efficacy, effectiveness and efficiency

In **Kenya**, a 36 months prospective, double blind, randomized, controlled trial of single dose HPV vaccination, studied girls and women aged 15-20 years old receiving Cervarix or Gadasil 9 or a control Meningococcal vaccine analysed efficacy of single dose vaccination (2vHPV or 9vHPV) in preventing incident persistent (defined as vaccine type specific HPV detected at two consecutive time points no less than 4 months apart), HPV 16/18 infections compared to delayed vaccination, and efficacy of single dose 9vHPV in preventing incident persistent HPV 16/18/31/33/45/52/58 infections compared to delayed vaccination. **After 18 months** the single dose was found to **highly effective in preventing incident persistent oncogenic HPV infection** (see table below).[40]

The efficacy levels were similar to those after multi-dose schedules.

	No. of mITT	No. of events	Incidence/100 woman years	VE (%)	VE 95% CI
Delayed vaccination n=757	473	36	6.83	Referent	
Single dose Cervarix N=760	489	1	0.17	97.5	81.6; 99.7
Single dose Gadasil 9 N=758	496	1	0.17	97.5	81.7; 99.7

mITT sero-negative at baseline and HPV-DNA negative at baseline and month 3 for types analysed.
mITT – modified intention to treat

Nonavalent VE for HPV 16/18/31/33/45/52/58 was 88.9% (95% CI, 68.5 to 96.1; P<0.0001).

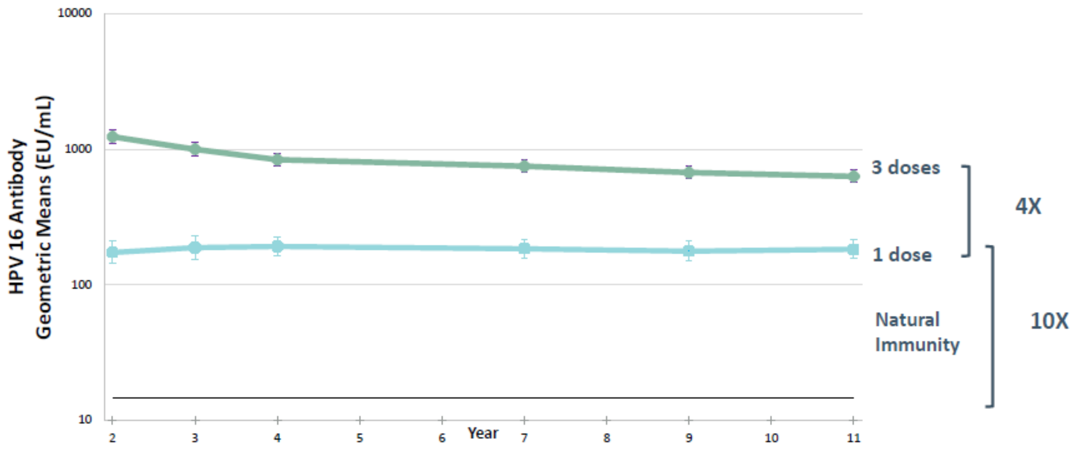
4.2.5.1 Durability of protection after single dose.

Review of two RCT studies; A ten year follow up in **India** following up after an RCT was discontinued having provided 1, 2, and 3 doses of Gardasil to females aged 10-18 years, and one in **Costa Rica** reviewing efficacy of 1, 2, and 3 doses in preventing persistent infection after **9 and 11 years**.
A longitudinal cohort study of the India trial showed that after ten years, single dose efficacy was comparable to multi-dose efficacy (see table below)[41]

	Sample size	No of events	Crude attack rates %	Adjusted VE point estimate	Adjusted VE 95% CI
Unvaccinated	1260	32	2.54	Referent	
Single dose	2135	1	0.05	95.4	85.0; 99.9
2 dose (0.6)	1452	1	0.07	93.1	77.3;99.8
3 dose	1460	1	0.07	93.3	77.5; 99.7

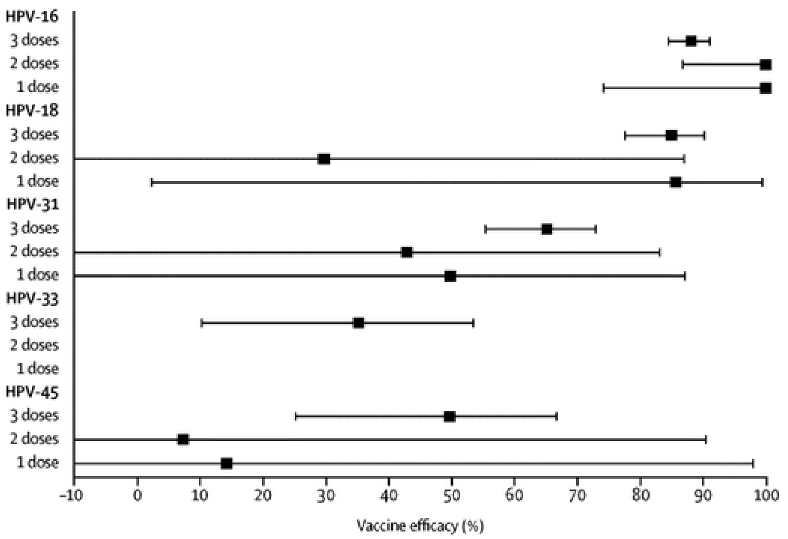
[40] Barnabas R, Brown E, Onono M, et al., 2022 Efficacy of Single-Dose HPV Vaccination among Young African. NEJM Evidence. 2022. doi : 10.1056/EVIDoa2100056.
[41] Basu P, Malvi SG, Joshi S, et al. Vaccine efficacy against persistent human papillomavirus (HPV) 16/18 infection at 10 years af ter one, ¿o, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre , prospective, cohort study [published correction appears in Lancet Oncol. 2022 Jan;23(1):e16]. Lancet Oncology . 2021;22(11):1518 1529. doi:10.1016/S1470 2045(21)00453 8 .

A Costa Rica trial[42] analysed efficacy of Cervarix among women aged 18-25 through long term follow up for prevalent infections and immunogenicity at Y7, 9 & 11 post vaccination. **An analysis of Geometric Mean Titres (GMTs) 11 (eleven) years after vaccination showed stable antibody levels for single dose recipients, ten times higher than natural immunity, and three time lower than the 3 dose schedule**



Stable antibody levels for HPV-16 and HPV-18 antibodies up to 11 years post-vaccination several times above natural immunity

Kreimer et al 2015[43] assessed vaccine efficacy against incident HPV-16/18 infection in the modified total vaccinated cohort (22 327 received three doses, 1185 two doses, 543 one dose) using data from the Costa Rica trial as well as data from a trial conducted in Finland analyzing efficacy of different schedules based on baseline status. They found that the **single dose schedule conferred sterilising immunity (defined as protection not only against clinical disease, but also infection) for most HPV-16/18 exposures up to four years post vaccination, similar to 2 and 3 doses** (see figure below).



Vaccine efficacy for individual HPV types by dose, for incident HPV infections that were detected one time that persisted for more than 12 months.

[42] Kreimer AR, Sampson JN, Porras C, et al. Evaluation of Durability of a Single Dose of the Bivalent HPV Vaccine: The CVT Trial. Journal of the National Cancer Institute. 2020;112(10):1038 1046. doi:10.1093/ jnci /djaa011

[43] Kreimer AR,Struyf F, Del Rosario Raymundo MR, et al. Efficacy of fewer than three doses of an HPV 16/18 AS04 adjuvanted vaccine: combined analysi s of data from the Costa Rica Vaccine and PATRICIA Trials. Lancet Oncol .2015;16(7):775 786. doi: 10.1016/S1470 2045(15)00047 9 .

A Dose Reduction Immunobridging and Safety Study (DoRIS) in Tanzania[44] aimed to determine whether HPV16 and HPV18 antibody GMCs at 24 months in girls who received one dose in DoRIS were non-inferior to those of one-dose historical cohorts in the CVT and IARC India studies. The secondary immuno-bridging objective was to determine whether HPV16 and HPV18 sero-positivity was non-inferior at 24 months. The study found that **for a single dose of HPV vaccine in girls aged aged 9–14 years, immune responses at 24 months in girls in Tanzania were non-inferior to those in study populations aged 18–25 years in Costa Rica and 10–18 years in India who received one dose and in whom one-dose efficacy against persistent HPV infection has been reported**. (see fig below).

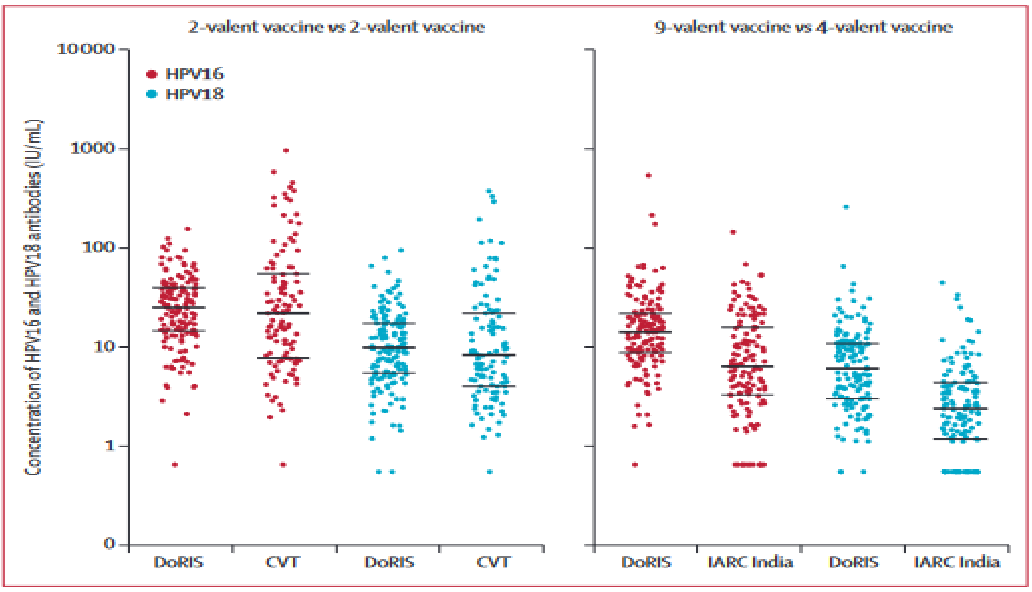


Figure: **Distribution of HPV16 and HPV18 antibody concentrations at 24 months after a single dose of HPV vaccine, by study group (total vaccinated cohort)**
Each datapoint represents a single individual and the line through the datapoints indicates the median concentration, with IQR shown by error bars. CVT=Costa Rica Vaccine trial. DoRIS=Dose Reduction Immunobridging and Safety Study. HPV=human papillomavirus. IARC=Institutional Agency for Research on Cancer.

Modeling studies by Prem et. al., 2023[45] showed that the difference in population benefits of the one-dose versus two-dose vaccination schedule is small if one dose confers ≥ 30 years of protection or lifelong protection but at 80% VE (see fig below).

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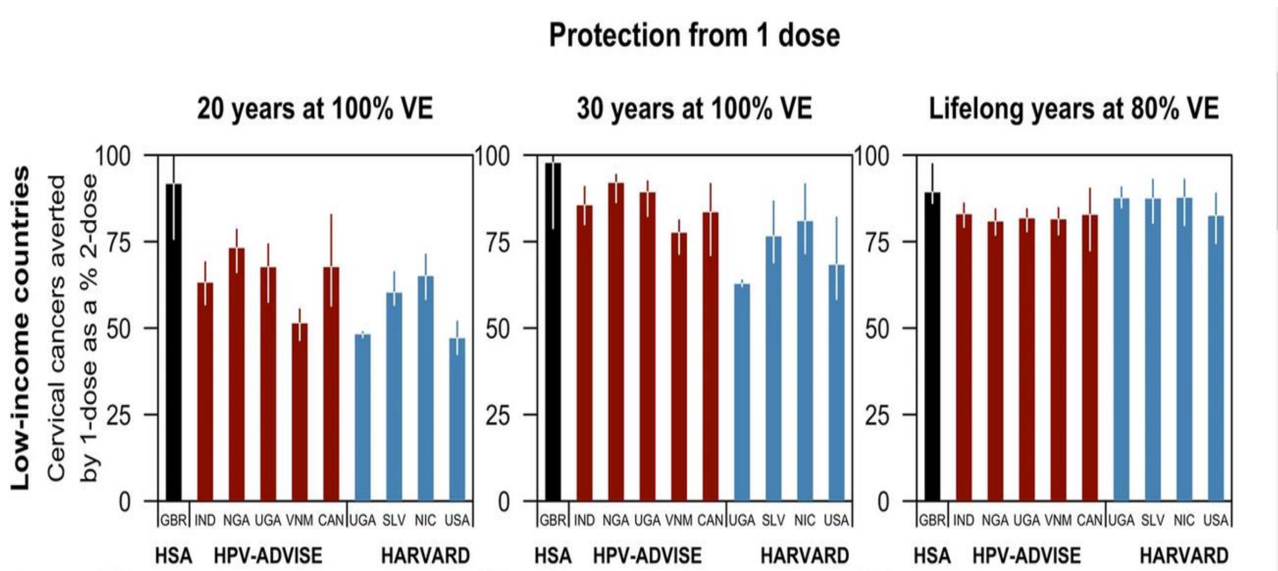
[44]Baisley et.al., 2022. Comparing one dose of HPV vaccine in girls aged 9–14 years in Tanzania (DoRIS) with one dose of HPV vaccine in historical cohorts: an immunobridging analysis of a randomized controlled trial https://www.thelancet.com/action/showPdf?pii=S2214-109X%2822%2900306-0
[45] Prem, K., Choi, Y.H., Bénard, É. *et al.* Global impact and cost-effectiveness of one-dose versus two-dose human papillomavirus vaccination schedules: a comparative modelling analysis. *BMC Med* **21**, 313 (2023). https://doi.org/10.1186/s12916-023-02988-3



4.3 Stakeholder perceptions on switch from two dose to single dose HPV

In Sub Saharan Africa, 23 countries had HPV vaccination programs as of October 2022 (see table below). Of these, only one (Cabo Verde) has achieved 2nd dose coverage of 90%.

Table 50: HPV vaccination policies in Africa

Country	Sex	Programme	Introduction year	Year of estimation of HPV vaccination coverage	HPV coverage – first dose (%)	HPV coverage – last dose (%)
Botswana	Female	Introduced	2015	2021	22	-
Cabo Verde	Female	Introduced	2021	2021	-	90
Cameroon	Female	Introduced	2020	2021	5	20
Cameroon	Male	Introduced	2020	2021	-	-
Côte d'Ivoire	Female	Introduced	2019	2021	41	34
Ethiopia	Female	Introduced	2018	2021	75	86
Gambia	Female	Introduced	2019	2021	30	34
Kenya	Female	Introduced	2019	2021	44	29
Liberia	Female	Introduced	2019	2021	30	43
Libya	Female	Introduced	2013	2021	-	-
Malawi	Female	Introduced	2019	2021	12	14
Mauritania	Female	Introduced	2021	2021	-	39
Mauritania	Male	Introduced	2021	2021	-	-
Mauritius	Female	Introduced	2016	2021	55	78
Mozambique	Female	Introduced	2021	2021	-	57
Rwanda	Female	Introduced	2011	2021	73	78
Senegal	Female	Introduced	2018	2021	21	39
Seychelles	Female	Introduced	2014	2021	39	84
South Africa	Female	Introduced	2014	2021	34	37
Uganda	Female	Introduced	2015	2021	44	75
United Republic of Tanzania	Female	Introduced	2018	2021	57	73
Zambia	Female	Introduced	2019	2021	33	45
Zimbabwe	Female	Introduced	2018	2021	40	67

Data accessed on 24 Oct 2022

Source: HPV information Center, 2023. Human Papilloma Virus and related diseases report. AFRICA. Posted March 2023. https://hpvcentre.net/statistics/reports/XFX.pdf?t=1693919242236

The following African countries have made the decision for a single dose HPV vaccine schedule: Burkina Faso, Cameroon, Cabo Verde, Cote d'Ivoire, Ethiopia, Lesotho, Malawi, Mozambique, Mali, Nigeria, Sierra Leone, Tanzania, Togo and Zambia.[46]

A few published global reports outline stakeholder concerns on switch from two doses to one dose.

In 2022, the UK Joint Committee on Vaccination and Immunisation (JCVI) conducted a 6 week stakeholder consultation on the switch from two to one dose HPV and the following concerns were raised:

Concern	Response
The decision was taken too early **as the evidence is incomplete with no evidence of duration of protection beyond 12 years**	*There is strong trial and non-trial evidence that that 1 dose protection was comparable to that from 2 doses, and that the long duration of protection already seen is associated with a level of antibody that is steady and it was not biologically plausible that the anti-body level would suddenly fall in the next few years after being sustained for more than ten years. The one dose antibody is associated with high efficacy against persistent infection of HPV vaccine types.*
The prime boost paradigm was being broken; that a prime and boost are required for this vaccine type	*The HPV vaccine like particles (VLP) is a very rigid and stable structure providing a sustained presentation to the immune system.*
Heavy reliance on models and the uncertainties associated with that.	*There are ongoing trials from which data is forthcoming. Should the evidence show that one dose protection was waning in the next ten years (at which time more than 20 years of follow up would be available. Switching back to 2 dose routine vaccination could mitigate losses in cervical cancer prevention. The committee would undertake ongoing review of the program which would pick up any new data that indicated a change was required, many years before waning was translated into an increased risk.*
One dose has the potential to lead to a drop in coverage and widen health inequities	*Efforts should be made to vaccinate anyone missed out in the first round. Resources freed up from reduced vaccinations should be re-directed to interventions that strengthen program delivery, increase coverage rates and reduce inequalities.* *A strong monitoring program for impact, coverage and inequalities should be maintained, as well as a strong surveillance package to monitor the incidence and prevalence of high risk HPV in the population.*

[46] Cathy Ndiaye (cndiaye@path.org), Personal Communication on September 27, 2023. UNITAG meeting proceedings.

The 12th HPV Prevention and Control meeting[47] was held on June 2–3, 2022, in Antwerp, Belgium also provided an opportunity for stakeholder to debate the potential concerns with the switch to one dose. The following were highlighted:

Concern	Response
One-dose HPV vaccine performance being subject to the difference in background HPV prevalence in the settings where these trials were carried out.	*Although the efficacy follow-up in KEN SHE is relatively short (18 months) and the antibody levels in participants receiving two or three-dose schedules is considerably higher across studies, there are suggestions that immune responses will be stable over time as presented from the African setting study (DoRIS) in Tanzania. Moreover, in all presented trials measuring one dose schedule, immunogenicity reports minimal HPV 16/18 antibody decay after plateau. Similar observations were presented in Costa Rica and India, where 10 years of follow-up has been done. DoRIS data presented during the meeting showed stable immune response at 3 years after a single dose of HPV vaccine. This may suggest that regardless of the number of doses administered, there is a stable long-lived plasma cells niche produced which continue to generate antibodies. Results from the HOPE study are expected to provide insight on the impact and effectiveness of one-dose HPV vaccination schedule at a wider level.*
Levels of protection elicited by one-dose HPV vaccination were raised as a point of concern, specifically with uncertainties of reduced dose schedules to allow type-replacement of oncogenic genotypes	*For type replacement to take place there needs to be competition, which is not seen at a lesion level. Although multiple infections can be found, lesions are known to be driven by only one genotype. Furthermore, characterisation of humoral responses following HPV vaccination have not shown results suggesting type replacement, in the contrary, the responses have suggested to be more cross-protective than expected.*
The impact of HPV vaccine–induced protection among people who will acquire HIV after being vaccinated with one dose **HPV vaccination**	*Results from the HOPE study, measuring the community-wide impact of one-dose HPV vaccination, are likely to provide further insight given the high prevalence of HIV in South Africa.*

A nested qualitative study within the DORIS trial in Tanzania[48] asked for **participant's and caregiver's opinions regarding the number of doses given.** Most girls **indicated preference for one dose so as to avoid pain from multiple jabs**, while most **caregivers' indicated that they trusted the**

[47] Dur-e-Nayab Waheed, F. Ricardo Burdier, Carina Eklund, Iacopo Baussano, Filipe Colaço Mariz, Laura Téblick, Nelly Mugo, Deborah Watson-Jones, Margaret Stanley, Marc Baay, Alex Vorsters. An update on one-dose HPV vaccine studies, immunobridging and humoral immune responses – A meeting report, Preventive Medicine Reports, Volume 35, 2023, 102368, ISSN 2211-3355, https://doi.org/10.1016/j.pmedr.2023.102368.
[48] K.R. Mitchell, T. Erio, H.S. Whitworth, G. Marwerwe, J. Changalucha, K. Baisley, C.J. Lacey, R. Hayes, S. de SanJosé, D. Watson-Jones.2021. Does the number of doses matter? A qualitative study of HPV vaccination acceptability nested in a dose reduction trial in Tanzania, Tumour Virus Research, Volume 12, 2021, 200217, ISSN 2666-6790, https://doi.org/10.1016/j.tvr.2021.200217.

doctors/scientist's recommendation for what would be most protective/efficacious for their children. Other reasons given **for preference of single dose was convenience due to reduced number of visits, and societal benefit through making the vaccine available to more people**. The study noted a **tendency among a few parents/guardians to equate a higher number of doses with greater protection.** Any national vaccination program switching to a lower dose will need to consider how to address this belief. The study concluded that switching to a single-dose vaccine would not pose major acceptability issues among those pre-disposed to vaccine uptake.

5 UNITAG conclusions

Having considered the contextual evidence, UNITAG thus concludes:

1. Cervical cancer, mainly caused by HPV, is a public health problem in Uganda. The available prevention and treatment options, such as early detection through screening and ablative or incision treatments are currently not being optimally utilized due to a combination of low community awareness and health system constraints.
2. HPV vaccination program in Uganda has been partially successful, with high coverage rates for the first dose, but low completion rates for the second dose.
3. There is interim efficacy data from settings in low and middle income countries that show that a single dose of Cervarix and Gardasil HPV vaccines provide comparable protection as two or three doses in immuno-competent girls and women for at least four years.
4. Switching from a two dose to a one dose schedule for HPV vaccine in immuno-competent recipients offers significant financial benefits in terms of costs saved per fully immunized child.
5. A switch from two doses to one dose of HPV vaccine is anticipated to reduce logistical costs associated with tracking targets for follow up doses and return visits, limiting it to only immuno-compromised recipients.

6 UNITAG recommendations

Based on the foregoing evidence and conclusions, UNITAG thus recommends:

1. For Immuno-competent girls aged 9-14 years in Uganda, there is sufficient scientific evidence to support the provision of one dose of Cervarix or Gardasil HPV vaccine, as the efficacy is comparable to that from two doses and is sufficient to provide protection against HPV disease. The shift from two doses to one dose would also be cost-saving and cost-effective for the country.
2. Immuno-compromised girls, including those who are HIV positive, should continue to receive three, if not at feasible, at least two doses of HPV vaccine. The second and third doses should be administered at the care clinics.

Annex: Letter from Ministry of Health to UNITAG on HPV dose optimisation

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IN ANY CORRESPONDENCE ON THIS SUBJECT PLEASE QUOTE NO. ADM: 05/509/20

Ministry of Health
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KAMPALA
UGANDA

5th April, 2023

The chairperson,
Uganda National Immunization Technical Advisory Group (UNITAG)
KAMPALA

REQUEST TO NITAG TO REVIEW THE EXISTING EVIDENCE IN SUPPORT OF THE SWITCH TO A SINGLE DOSE HPV VACCINE IN LINE WITH THE SAGE RECOMMENDATION

In April 2022, the convening of the WHO Strategic Advisory Group of Experts on Immunization (SAGE) evaluated the evidence that has been emerging over past years that single-dose schedules for Human Papillomavirus (HPV) Vaccine provide comparable efficacy to the two or three-dose regimens. SAGE's review concluded that a single-dose HPV **vaccine** delivers solid protection against HPV, the virus that causes cervical cancer.

More than 95% of cervical cancer is caused by sexually transmitted HPV, which is the fourth most common type of cancer in women globally with 90% of these women living in low and middle-income countries. This is often referred to as the 'silent killer' and almost entirely preventable, cervical cancer is a disease of inequity of access.

The option for a single dose of the vaccine is less costly, less resource intensive and easier to administer. It facilitates implementing catch-up campaigns for multiple age groups, reduces the challenges linked to tracing girls for their second dose and allows for financial and human resources to be redirected to other health priorities.

SAGE recommends updating dose schedules for HPV as follows:

- **One or two-dose schedule** for the primary target of girls aged **9-14**
- **One or two-dose schedule** for young women aged **15-20**
- **Two doses** with a 6-month interval for women **older than 21**.
- **Three doses** for the immunocompromised individuals, including those with HIV.

Report of Uganda National Immunization Technical Advisory Group (UNITAG) on TCV Introduction into Routine Immunization in Uganda

November 2023

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EXECUTIVE SUMMARY

Typhoid is a severe and life-threatening enteric fever caused by the bacterium *Salmonella Typhi* (*S.Typhi*) spread through water or food contaminated with faecal matter. Typhoid symptoms include prolonged high fever, fatigue, headache, nausea, abdominal pain, and constipation or diarrhoea. Some patients may have a rash. Severe disease is characterized by febrile illness and, in very severe cases, gastrointestinal bleeding, altered mental state, intestinal perforation, and can potentially lead to death. Typhoid symptoms are common to many infections, hence typhoid is often mistaken for other diseases such as malaria, pneumonia, dengue, or influenza.

The global burden of typhoid is likely underestimated due to limitations with typhoid surveillance and diagnostic challenges. Typhoid can be confirmed through a blood test. In Uganda, definitive diagnostic tests for typhoid fever, such as blood culture, are usually unavailable, unaffordable, or inconsistently applied. Instead, typhoid fever diagnosis and surveillance often rely on clinical judgment or widal tests, which have poor sensitivity and specificity. The burden of typhoid is likely underestimated due to limitations with typhoid surveillance and diagnostic challenges. Studies have estimated that typhoid may be responsible for more than 3 million cases and 33,000 deaths annually in the Africa region, with children under 5 year the most affected (27% of typhoid fever episodes are estimated to occur in children 0-4 years; including 29.7% of typhoid fever episodes in the <2 year age). No long term epidemiology figures are available for typhoid in Uganda. However, three large outbreaks have been recorded over the past 15 years: Two outbreaks in 2007 and 2009-2012 both in Kasese district, resulted in a combined 1900 infections, with over 800 cases of intestinal perforations and 47 fatalities. The most recent outbreak was in Kampala in 2015, with 10,230 people infected. While recent data shows decreasing incidence of typhoid, between 2010 and mid-2023, annual recorded episodes of typhoid in children under four years ranged between 5,125 and 10,214, with annual deaths ranging between 42 -288 children.

Typhoid can be treated with antibiotics. However, antimicrobial resistance is common with likelihood of more complicated and expensive treatment options required in the most affected regions. A 2021 survey in Uganda showed that Salmonella had a resistance profile of 24% against ciprofloxacin, 17% against ceftriaxone, and 4 % against imipemen. Multi-drug resistant (MDR) typhoid, which is not susceptible to chloramphenicol, ampicillin, cotrimoxazole, fluoroquinolones and third-generation cephalosporins, makes treatment increasingly difficult. Increasing cases of drug-resistant (XDR) typhoid, raise concerns about untreatable typhoid in the future.
Typhoid Intestinal Perforations require emergency surgical interventions.

Two polysaccharide typhoid vaccines have been used for many years in older children and adults at risk of typhoid, including travelers. These vaccines do not provide long-lasting immunity (requiring repeat or booster doses every three years) and are not approved for children younger than 2 years old. Advancements in typhoid vaccine research have resulted in development of typhoid conjugate vaccines (TCV) which have longer-lasting immunity (up to 4 years) than the older polysaccharide vaccines and can be given as a single dose to children from the age of 6 months .In March 2018, WHO recommended that typhoid endemic countries – and countries with high rates of drug-resistant typhoid introduce prequalified typhoid conjugate vaccines (TCV) via catch-up vaccination campaigns for children up to 15 years of age, followed by incorporating TCV into routine immunization programs as a single dose for infants and children older than 6 months of age. Currently, two WHO-prequalified TCV products are available for children older than 6 months. TCV can also be co-administered with measles-rubella and yellow fever vaccines at 9 months of age; co-administration of measles-rubella and meningococcal A vaccines at 15 months of age was found to be safe. More than 56 million children have been vaccinated during Typhoid Conjugate Vaccine campaigns to date. Pakistan's Sindh Province in November 2019. Liberia, Zimbabwe, Nepal, and Malawi have recently introduced Typhoid Conjugate Vaccine through campaigns and routine childhood immunizations. Social studies in the African region on acceptability show that populations, especially those that have experienced a typhoid outbreak are generally accepting of the typhoid conjugate vaccines.

Gavi provides support for the nationwide introduction of TCV into the routine immunization schedule through vaccine co-financing, and a targeted one-time catch-up immunization campaign children aged 9 months to 15 years based on local typhoid epidemiology. Modeled analysis predicts that TCV is likely to be cost-effective in countries with high typhoid incidence, high cost of typhoid treatment, and /or high death rates from typhoid. Modelling studies showed that Uganda was predicted to experience a 72.39% reduction in typhoid cases in the 10 years after introducing TCV in routine immunization at 9 months of age, plus a catch-up campaign up to 15 years old.

Having carefully analyzed the evidence above, the UNITAG thus concludes:

i. Uganda is a typhoid endemic country, with the most vulnerable population groups – children under five years living in crowded areas with poor sanitation facilities - most exposed to the risk of infection. The equity challenge is compounded by the same low income group being less likely to afford high quality typhoid diagnostic services, expensive antibiotic treatment options in the event of antibiotic resistance, or access to surgical treatment, in case of severe complications such as intestinal perforations.

ii. Typhoid conjugate vaccines are safe and immunogenic when administered as a single dose to children and adults aged between 6 months and 45 years of age. Vaccine administration possess no significant logistical challenges as vaccine is thermo-stable under temperatures 2-8 ^{0}C, can be safely co-administered with vaccines given as a single dose to children at 9 months of age such as Measles-Rubella, Meningitis, and Yellow Fever vaccines, and has a legacy of community acceptability in the African region.

iii. Introduction of the typhoid conjugate vaccine in Uganda's routine immunization program, starting with a catch up campaign targeting children aged 9 months to 15 years would be cost effective. Campaigns could be offset through a Gavi campaign grant and a Gavi co-financing grant could heavily subsidise the vaccine cost for the routine program.

Based on the above conclusion, the UNITAG thus recommends:

i. The Typhoid Conjugate vaccine be introduced in Uganda's routine immunization program as a single dose given to children aged 9 months, beginning with a nationwide catchup campaign targeting children aged 9 months to 15 years. This will reduce health inequity, address antimicrobial resistance, and reduce occurrence of typhoid disease outbreaks in Uganda.

BACKGROUND

On June 30, 2022, the Ministry of Health, through the Director General of Health Services, requested the UNITAG's guidance on the introduction of Typhoid Conjugate Vaccine (TCV) as part of the routine infant immunization schedule to control Uganda's typhoid burden, particularly the alarming rates of drug-resistant typhoid.

In March 2018, WHO recommended the introduction of prequalified Typhoid Conjugate Vaccines (TCV) in typhoid-endemic countries through routine immunization programs as a **single dose for infants and children over 6 months of age**, accompanied by catch-up vaccination campaigns for children **up to 15 years of age,** where feasible. In this regard, the Ministry of Health (MoH) requested the Uganda National Immunization Technical Advisory Group (UNITAG) for guidance on the introduction of TCV as part of the routine infant immunization schedule to control Uganda's typhoid burden, particularly the alarming rates of drug-resistant typhoid.

A. INTRODUCTION

Typhoid is a severe and life-threatening enteric fever caused by the bacterium *Salmonella Typhi* (*S.* Typhi) spread through ingesting contaminated water or food with faecal matter. The disease is characterized by febrile illness and, in severe cases, gastrointestinal bleeding, altered mental state, intestinal perforation, and death (WHO 2018).With symptoms common to many infections, typhoid may often be mistaken for other diseases such as malaria, pneumonia, dengue, or influenza, and if left untreated, it can cause a variety of short- and long-term complications[1].

An estimated 11–20 million people get sick from typhoid every year, and between 128,000 and 161,000 people die from typhoid globally, with poor communities and vulnerable groups, including children in Asia and sub-Saharan Africa (SSA), being at the highest risk[2]. Complications such as septic shock, gastrointestinal haemorrhage, or intestinal perforation can arise when typhoid fever goes untreated or is improperly treated, resulting in an estimated 1%–4% fatality with and 10%–20% without treatment[34]. While antibiotics are vital to the treatment of typhoid, antibiotic-resistant pathogens have become increasingly prevalent[5].

Take on Typhoid underscores improved water quality, sanitation, and hygiene (WASH) as the major ways to break the typhoid transmission cycle in the long term. However, current trends of drug resistance, urbanization associated with overcrowded populations, inadequate water and sanitation systems, and climate change have the potential to heighten the global burden of typhoid[6].

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[1] Typhoid fact sheet, June 2020 https://www.coalitionagainsttyphoid.org/wp-content/uploads/2020/07/Typhoid-fact-sheet_June-2020.pdf.
[2] WHO: Typhoid Disease https://www.who.int/health-topics/typhoid#tab=tab_1 Accessed on 15 September 2022
[3] Marchello, C.S., Birkhold, M. and Crump, J.A., 2020. Complications and mortality of typhoid fever: a global systematic review and meta-analysis. *Journal of Infection*, *81*(6), pp.902-910.
[4] Crump, J.A., Luby, S.P. and Mintz, E.D., 2004. The global burden of typhoid fever. *Bulletin of the World Health Organization*, *82*(5), pp.346-353.
[5] Klemm, E.J., et al. 2018. Emergence of an extensively drug-resistant Salmonella enterica serovar Typhi clone harboring a promiscuous plasmid encoding resistance to fluoroquinolones and third-generation cephalosporins. *MBio*, *9*(1), pp.e00105-18.
[6] PATH Typhoid fever: A past, present, and future threat, June 04, 2018 https://www.path.org/articles/typhoid-fever-past-present-and-future-threat/ Accessed on 10 September 2022

Hence, WHO recommends typhoid vaccination as a control strategy, emphasizing that until investments in improving WASH can be made in all countries, vaccination is an important and effective way to prevent the disease[7].

Table 1: PICO framework for TCV introduction in Uganda's routine immunization program

Broad Question: Should TCV be introduced into Uganda's routine immunization schedule?	
Specific "PICO" Question: Should a single dose of TCV be recommended for routine use in infants and children between 6 months to 15 years of age in Uganda?	
Population	– Infants and children from 6 months of age to 15 years
Intervention	– (i) TCV to all infants at 9 months of age in EPI routine delivery
	(ii) A one-off TCV campaign to all children 9 months to 15 years of age.
Comparator	- (i) Antibiotic treatment (typhoid intervention in place without vaccination)
	(ii) Surgical Interventions for the poorly or untreated typhoid and sometimes death
	(iii) Intensify WASH programs
Outcome	– typhoid fever (blood culture-confirmed), antimicrobial resistance, mortality

B. SUMMARY OF EVIDENCE CONSIDERED

1. DISEASE CONSIDERATIONS

i. Global and Regional Burden of Typhoid Disease

i) Typhoid fever

Typhoid fever is a substantial public health issue that disproportionately affects children and low-income populations in Asia and sub-Saharan Africa (SSA). In 2019, typhoid fever was responsible for more than 9 million infections, 110,000 attributable deaths, and 8 million disability-adjusted life years (DALYs) globally with an estimated 12.1% of the global cases in SSA[8]. Due to improvements in water and sanitation infrastructure, typhoid fever has mostly been eliminated in high-income countries[9].

A systematic review by Kim et al (2019) found that the largest number of outbreaks between 1989 and 2018 occurred in WHO African region[10]. Results showed that at **least one episode of culture-confirmed typhoid fever was reported in 42 of 57 African countries during 1900–2018** and the number of reports on typhoid fever had increased over time in Africa and highly heterogeneous between countries over time. This study also found that typhoid fever outbreaks were reported in 15 countries, with their frequency and size increasing over time. Indeed, the African region has

[7] WHO position paper, Typhoid vaccines, March 2018

[8] Institute for Health Metrics and Evaluation (IHME). Global Burden of Disease Study. The Lancet. 2020 Oct 17;396(10258):1129–306.

[9] Phillips, M.T., et al., 2020. Changes in historical typhoid transmission across 16 US cities, 1889-1931: Quantifying the impact of investments in water and sewer infrastructures. *PLoS neglected tropical diseases*, *14*(3), p.e0008048.

[10] Kim, J.H., et al., 2019. A systematic review of typhoid fever occurrence in Africa. *Clinical Infectious Diseases*, *69*(Supplement_6), pp.S492-S498.

suffered one of the largest typhoid outbreaks globally over the years as indicated in a systematic review by Appiah et al., 2020[11]. Specifically, of the 25 countries that reported outbreaks during this period, 12 (25%) were from the African region with reported typhoid cases as indicated in the table below. The study further showed a longer median duration of outbreaks caused by multi-drug resistant (MDR) strains (148 days versus 34 days for susceptible strains), although this difference was not statistically significant.

Table 2: Locations in the WHO African region where typhoid outbreaks were recorded 2004-2018

Table 1
Characteristics of included publications (*n* = 47)

WHO region, ref no.	Outbreak year(s)	Location	Incidence proportion	Number of cases	Number (%) hospitalized	Number (%) of complications	Number of deaths (case fatality ratio)
African							
83	2004–2005	Kinshasa, DRC	–	144	144	41 (28) IPs	64 (44)
52	2007–2009	Kasese, Uganda	–	577	289 (57)	249 (43) IPs	47 (9)
38	2009	Malawi–Mozambique	–	303	81 (27)	40 (13)	11 (4)
34	2009–2012	Kasese, Uganda	0.1%	1,341	–	568 (6)	–
50	2010–2012	Lusaka, Zambia	–	2,040	–	–	–
84	2011–2012	Kikwit, DRC	0.6%	1,430	–	71 (5)	17 (1.5)
85	2011–2012	Harare, Zimbabwe	–	3,795	–	–	–
53	2014–2015	Moyale, Kenya	–	317	–	–	2 (0.05)
49	2015	Kampala, Uganda	0.9%	10,230	–	–	–
86	2016	Tigray, Ethiopia	–	98	–	–	1
57	2016–2017	Harare, Zimbabwe	–	860	–	–	4 (0.5)
59	2017–2018	Harare, Zimbabwe	–	3,378	–	–	–

Source: Appiah, G.D., et al. 2020. Typhoid outbreaks, 1989–2018: implications for prevention and control. The American journal of tropical medicine and hygiene, 102(6), p.1296.

However, typhoid burden in the region is believed to have been long **underestimated largely due to limitations with typhoid surveillance and diagnostic challenges**. Several studies have estimated typhoid fever as being responsible for more than 3 million cases and 33,000 deaths annually in the region[12]. A systematic review and meta-analysis of global typhoid fever incidence by Marchello et al., (2019) identified variation in the criteria for collecting a blood culture, and among multiplier studies, identified a lack of standardization for the types of multipliers being

[11] Appiah, G.D., et al. 2020. Typhoid outbreaks, 1989–2018: implications for prevention and control. *The American journal of tropical medicine and hygiene*, *102*(6), p.1296.
[12] Ajibola, O., et al., 2018. Typhoid fever diagnosis in endemic countries: a clog in the wheel of progress? *Medicina*, *54*(2), p.23.

used to estimate incidence[13]. In addition, a systematic review by Mogasale et al., (2014) identified adjusting for risk-factor and updated diagnostic test correction as drivers of differences between the current estimate and past estimates. They estimated less typhoid cases and deaths in LMICs after adjusting for water-related risk than when unadjusted for risk[14]. It should be noted that typhoid fever is confirmed by isolation of *Salmonella* Typhi from bone marrow, blood, or another site in a patient with compatible illness[15]. However, blood culture diagnosis, which is mostly used in the region was found to have a sensitivity as low as 40%[16]. Overall, more recent studies reported lower typhoid incidence compared to years prior to 2000.

Furthermore, evidence on invasive salmonella disease incidence in SSA shows that typhoid fever and invasive non-typhoidal salmonella (Ints) disease are major causes of invasive bacterial febrile illness in the sampled locations, most commonly affecting children in both low and high population density settings[17]. This standardized, multicountry surveillance study between 2010 and 2014 found that Salmonella typi accounted for 33% or more of all bacterial pathogens at nine sites. The adjusted incidence rate of Ints and typhoid fever was typically higher in individuals younger than 15 years old than in those aged 15 years or older with MDR *Salmonella* Typhi isolated in Ghana, Kenya, and Tanzania, and MDR Ints isolated in Burkina Faso, Ghana, Kenya, and Guinea-Bissau. Given that typhoid symptoms are similar to many other diseases, including malaria, pneumonia, influenza, and other febrile illnesses, it is often misdiagnosed demonstrating the need for more accurate and rapid diagnostic tests.

In 2016, WHO set up an Enteric Fever (EF) Surveillance Pilot Initiative in four countries India, Bangladesh, Uganda, and Ghana. In Uganda 991 patients were enrolled in the Enteric Fever Surveillance, 585 males (59.3%) and 401 females (40.7%) with 6 cases with no gender recorded. The results indicate a modest burden of enteric fever and invasive non-typhoidal Salmonellosis in children under 15 years of age, with Salmonella Enterica Serovars including Salmonella Typi identified in children (0.6% for Salmonella Typi and 1.0% for other Serovars of Salmonella Enterica.)[18].

ii) Drug resistant typhoid

Antibiotic resistance is an emerging **public health threat worldwide**. WHO recommends chloramphenicol, ampicillin and cotrimoxazole (trimethoprim-sulfamethoxazole), fluoroquinolones, third generation cephalosporines (ceftriaxone, cefixime) and azithromycin for

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[13] Marchello, C.S., Hong, C.Y. and Crump, J.A., 2019. Global typhoid fever incidence: a systematic review and meta-analysis. *Clinical Infectious Diseases*, *68*(Supplement_2), pp.S105-S116.
[14] Mogasale, V., et al., 2014. Burden of typhoid fever in low-income and middle-income countries: a systematic, literature-based update with risk-factor adjustment. *The Lancet Global Health*, *2*(10), pp. e570-e580.
[15] Wain J., Hosoglu S. 2008: The laboratory diagnosis of enteric fever, J Infect Dev Ctries, 2008, vol. 2 (pg. 421-5)
[16] Gilman R, et al., 1975. Relative efficacy of blood, urine, rectal swab, bone-marrow, and rose-spot cultures for recovery of Salmonella typhi in typhoid fever, Lancet, 1975, vol. 305 (pg. 1211-3)
[17] Marks, F., et al., 2017. Incidence of invasive salmonella disease in sub-Saharan Africa: a multicentre population-based surveillance study. *The Lancet Global Health*, *5*(3), pp.e310-e323.
[18] Saha, S., Islam, M., Uddin, M. J., Saha, S., Das, R. C., Baqui, A. H., ... & Saha, S. K. (2017). Integration of enteric fever surveillance into the WHO-coordinated Invasive Bacterial-Vaccine Preventable Diseases (IB-VPD) platform: A low cost approach to track an increasingly important disease. PLoS neglected tropical diseases, 11(10), e0005999.

the treatment of enteric fever[19]. Although typically treated with antibiotics, increasing MDR typhoid strains (defined as resistance to three first-line antibiotics used to treat typhoid—chloramphenicol, ampicillin, and cotrimoxazole)[20], have been reported globally[21]. Resistance to antibiotic treatment has been seen since the 1970s, and evidence shows that drug resistance continues to spread. A systematic review by Park et al (2018) assessing phylogeography and incidence of MDR typhoid fever in SSA revealed that 129/249 (52%) of all genome sequenced S. Typhi isolates between 2008 and 2015 in eleven (11) SSA countries were MDR (resistant to ampicillin, chloramphenicol, and co-trimoxazole)[22]. A separate study in 9 sites in 6 African countries also reported MDR typhoid isolated in Kenya (79%) and Tanzania (89%)[23]. In Malawi, 92% of isolates analyzed between 2016 and 2018 were identified as MDR[24].

With decades of indiscriminate antibiotic usage, MDR has since evolved to more recently, extensively drug-resistant (XDR) typhoid (defined as typhoid strains resistant to five classes of antibiotics: chloramphenicol, ampicillin, cotrimoxazole, fluoroquinolones, and third generation cephalosporins)[25]. In November 2016, the first ever recorded outbreak of extensively drug resistant typhoid fever (XDR-TF), characterized by almost all known antibiotics against the disease (ampicillin, trimethoprim/sulfamethoxazole, chloramphenicol, fluoroquinolones, and ceftriaxone) was discovered in Pakistan[26]. Since then, sporadic cases of XDR-TF have been reported globally, thus raising the fear of antibiotic failure at a global level[27]. Thus, the increased frequency of reported typhoid outbreaks and the presence of drug-resistant typhoid call for controlling efforts of the disease such as vaccines and improved hygiene practices.

Findings from a model by Walker, et al. (2023) assessing the global risk of typhoid outbreaks caused by extensively drug resistant *Salmonella Typhi*, using data from the International Air Travel Association (IATA) looking at air travelers that flew from Pakistan to 200 countries in 2019 found that of the ten most popular country destinations for international flights from Pakistan, seven are

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[19] WHO. Vaccines and Biologicals. Background document: The diagnosis, treatment and prevention of typhoid fever. Geneva: 2003.

[20] Zaki, S.A. and Karande, S., 2011. Multidrug-resistant typhoid fever: a review. *The Journal of Infection in Developing Countries*, *5*(05), pp.324-337.

[21] Zakir, M., et al., 2021. Emerging Trends of Multidrug-Resistant (MDR) and Extensively Drug-Resistant (XDR) Salmonella Typhi in a Tertiary Care Hospital of Lahore, Pakistan. *Microorganisms*, *9*(12), p.2484.

[22] Park., et al., 2018. The phylogeography and incidence of multi-drug resistant typhoid fever in sub-Saharan Africa. *Nature communications*, *9*(1), pp.1-10.

[23] Al-Emran, et al., 2016. A multicountry molecular analysis of Salmonella enterica serovar Typhi with reduced susceptibility to ciprofloxacin in sub-Saharan Africa. *Clinical Infectious Diseases*, *62*(suppl_1), pp.S42-S46.

[24] Meiring, J.E., et al., 2021. Burden of enteric fever at three urban sites in Africa and Asia: a multicentre population-based study. *The Lancet Global Health*, *9*(12), pp.e1688-e1696.

[25] Akram, J., et al., 2020. Extensively drug-resistant (XDR) typhoid: evolution, prevention, and its management. *BioMed Research International*, *2020*.

[26] Rasheed, M.K., Hasan, S.S. and Ahmed, S.I., 2019. Extensively drug-resistant typhoid fever in Pakistan. *The Lancet Infectious Diseases*, *19*(3), pp.242-243.

[27] Browne, A.J., et al., 2020. Drug-resistant enteric fever worldwide, 1990 to 2018: a systematic review and meta-analysis. *BMC medicine*, *18*(1), pp.1-22.

known to have imported at least one case of XDR *Salmonella Typhi*. Uganda was listed among the top ten typhoid endemic countries at most risk of importing XDR typhoid from Pakistan.[28]

iii) Typhoid complications

Typhoid intestinal perforations (TIP) is a serious complication from undiagnosed and/or untreated typhoid that causes mortality and morbidity. TIP cases face long hospital stays and are associated with the need for safe surgical procedures that may not be available in some facilities. It should also be noted that many of the surgeries are costly and lead to nutritional deficiencies and other complications. TIP is observed in an estimated 0.8% to 39% of untreated or improperly treated cases globally, occurring more often in children, with increased mortality rates when compared to adults [29]. Although evidence shows that TIP related mortality rates in some endemic areas have decreased from 30-60% in the 60s and 70s to between 3-13% in the 90s[30], data specific to TIP in children living in SSA are limited. A systematic review by Birkhold et al. (2020) assessing morbidity and mortality of TIP among children in SSA between 1995–2019 found that current estimates of mortality related to TIP among children in SSA remain unacceptably high [28]. The review highlighted that slight progress had been made in reducing TIP-associated mortality over the past 50 years in SSA with mortality rates ranging from 4.6% to 75% between 1984 to 2018. From the data available since 2000, 79% of the reported mortality rates were between 10% and 30%. Although these numbers show consistent decline, they are still unacceptably high.

iv) Risk factors of typhoid fever

The risk of transmission of typhoid fever is increased in populations that lack access to safe water and adequate sanitation, and in the context of poor hygiene among food handlers. Available evidence shows that there are diverse risk factors for typhoid fever in different settings.

A case-control study by Gauld et al., (2020) assessing domestic river water use and risk of typhoid fever in Blantyre, Malawi found that use of river water for cooking and cleaning was highly associated with risk of typhoid fever (OR, 4.6; 95% CI, 1.7–12.5)[31]. Additional risk factors from this study included protective effects of soap in the household (OR, 0.6; 95% CI, .4–.98) and >1 water source used in the previous 3 weeks (OR, 3.2; 95% CI, 1.6–6.2). Attendance at school or other daycare was also identified as a risk factor (OR, 2.7; 95% CI, 1.4–5.3) and was associated with the highest attributable risk (51.3%).

Additionally, a systematic review and meta-analysis of observational studies by Mogasale et al (2018), estimating typhoid fever risk associated with lack of access to safe water from 1990 to

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[28] Walker, J., Chaguza, C., Grubaugh, N. D., Carey, M., Baker, S., Khan, K. ... & Pitzer, V. E. (2023). Assessing the global risk of typhoid outbreaks caused by extensively drug resistant Salmonella Typhi. Nature Communications, 14(1), 6502.

[29] Contini S. 2017. Typhoid intestinal perforation in developing countries: Still unavoidable deaths? *World J Gastroenterol.* 2017; 23:1925–1931. doi: 10.3748/wjg. v23.i11.1925.

[30] Birkhold, M., et al., 2020. Morbidity and mortality of typhoid intestinal perforation among children in sub-Saharan Africa 1995–2019: a scoping review. *World journal of surgery*, *44*(9), pp.2892-2902.

[31] Gauld, J.S., et al., 2020. Domestic river water use and risk of typhoid fever: results from a case-control study in Blantyre, Malawi. *Clinical Infectious Diseases*, *70*(7), pp.1278-1284.

2013, found that the odds of typhoid fever among those exposed to unimproved water as per WHO-UNICEF's definition or microbiologically unsafe water ranged from 1.06 to 9.26 with case weighted mean of 2.44 (95% CI: 1.65–3.59). Additional the study identified street vendors and food handlers as a significant risk factor for typhoid. The Data reviewed from several countries identify the consumption of street beverages and food as a high-risk activity for typhoid. Besides water-related risk, the studies also identified other risk factors related to socioeconomic aspects, the current climate changes including the increased occurrence of floods, migration, type of food consumption, knowledge and awareness about typhoid fever, and hygiene practices hence the need to consider additional interventions such as vaccination[32]**.**

In Uganda, a geographically weighted regression study of typhoid incidences by Ismail et al., (2021) revealed that; poor hand-washing practice, excessive rainfall, and poor drainage (floods effect) were responsible for the spatial variability of typhoid disease locally ($P<0.05$)[33]. Specifically, rainfall, floods, urbanization level, and household size were revealed to have a positive and significant influence on the occurrence of the disease ($P<0.05$). Results showed that average household size yielded a positive significant relationship with typhoid disease ($P<0.05$) and excessive rainfall was responsible for most typhoid disease occurrences in the Eastern and Southwestern parts of the country.

Bottom line messages

- a) **The burden of typhoid is likely underestimated due to limitations with typhoid surveillance and diagnostic challenges. Studies have estimated that typhoid may be responsible for more than 3 million cases and 33,000 deaths annually in the Africa region.**
- b) **Typhoid is typically treated with antibiotics, yet increasing MDR typhoid strains (defined as resistance to three first-line antibiotics used to treat typhoid—chloramphenicol, ampicillin, and cotrimoxazole), have been reported globally and continue to spread.**
- c) **Further evolution of MDR has resulted in extensively drug-resistant (XDR) typhoid (defined as typhoid strains resistant to five classes of antibiotics: chloramphenicol, ampicillin, cotrimoxazole, fluoroquinolones, and third generation cephalosporins). Increasing rates of XDR drive concerns about untreatable typhoid in the future.**
- d) **Typhoid intestinal perforation (TIP) is a serious complication resulting from undiagnosed and/or untreated typhoid that causes mortality and morbidity. Patients with TIP face long hospital stays and often undergo surgical procedures that may not be available in some facilities.**
- e) **The risk of transmission of typhoid fever is increased in populations that lack access to safe water and adequate sanitation, and in the context of poor hygiene among food handlers. Specifically, rainfall, floods, urbanization level and household size were**

[32] Mogasale, V.V., et al., 2018. Estimating typhoid fever risk associated with lack of access to safe water: a systematic literature review. Journal of environmental and public health, 2018.

[33] Ismail, K., et al., 2021. Spatial Variability of Typhoid Disease Incidences in Uganda Using Geographically Weighted Regression Approach. *International Journal of Health Economics and Policy*, *6*(2), p.56.

revealed to have positive and significant influence on the occurrence of the disease in Uganda.

ii. Typhoid fever burden in Uganda

The typhoid burden in Uganda remains high (>100 cases per 100,000 person years). The latest global burden of disease analysis estimates that Uganda had 41,734 typhoid cases (101 cases per 100,000 population) and 635 typhoid deaths in 2019. More than half of the cases and deaths (57% and 69% respectively) were among children under 15 years of age.[34]

Table 3: Typhoid Burden in Uganda for the period 2020-2023

Typhoid Fever	**2020**	**2021**	**2022**	**2023**
Typhoid Fever (Cases) 0-4 Years	6,760	7,948	10,214	5,125
Typhoid Fever (Deaths) 0-4Years	288	114	105	42
Typhoid Fever (Cases) 5-9Years	43,373	43,283	56,738	29,017
Typhoid Fever (Deaths) 5-9Years	42	63	102	31
Typhoid Fever 10-19Years Cases	40,429	51,258	51,424	26,462
Typhoid Fever 20+Years Cases	122,872	131,215	131,849	68,273
Grand Total	**213,764**	**233,881**	**250,432**	**128,950**

*Source: Ministry of Health (*Data Source: 108- HF07a, b, Data Source 105-EP15, Data under 1 year is not available, Years 2019 and below were very complicated to obtain, Deaths are not reported for ages 10 years and above).

i) History of typhoid outbreaks in Uganda

Uganda has experienced three major outbreaks in the last 15 years. A systematic review of reports on typhoid outbreaks from 1989 to 2018 by Appiah et al (2020)[35] details the three outbreaks in Uganda as detailed below:

From December 2007 to July 2009, Uganda experienced the first outbreak in Kasese district with 577 cases. Of these, 289 (57%) were hospitalized, 249 (43%) had intestinal perforations, and 47 were deaths with a case fatality ratio of 9**.** A report by Neil, et al (2012) on the 2008-2009 typhoid fever outbreak in Uganda reported that Kasese district hospitals encountered several patients with

[34] Institute for Health Metrics and Evaluation (IHME). Global Burden of Disease Study. The Lancet. 2020 Oct 17;396(10258):1129–306.

[35] Appiah, G.D., et al. 2020. Typhoid outbreaks, 1989–2018: implications for prevention and control. *The American journal of tropical medicine and hygiene*, *102*(6), p.1296.

TIP and an undiagnosed febrile illness[36]. Of the 11 (8%) suspected TIP cases who sought care at a health facility, 9 were hospitalized and 3 died, most of whom (52%) were persons aged between 5-19 years. The study estimated typhoid fever incidence in the community at 8,092 cases per 100,000 persons (estimated annual incidence rates ranged from 5,609 to 10,906 suspected cases per 100 000 persons). According to the report, only 1 of 3 hospitals in Kasese district had any microbiological culture capacity. It should be noted that since typhoid fever clinically resembles other febrile illnesses (eg, malaria), it is easily misdiagnosed without laboratory confirmation, likely resulting in unrecognized outbreaks and underestimation of incidence. In fact, this study reported that individuals with TIP were significantly more likely to report having taken antimicrobial (80% vs. 43%, P 5 .04) and antimalarial medications (85% vs. 52%, P 5 .03). The report further noted that although outbreak control measures were undertaken, the number of new cases (suspected and confirmed) with complications of TIP continued to rise.

The second outbreak of typhoid fever in Uganda was also recorded in Kasese from 2009 to 2012 where a total of 1,341 cases were reported, including 568 (6%) TIPs, and a 0.1% incidence proportion**.** Molecular and epidemiological evidence from a study by Walters et al (2014) suggests that during the prolonged outbreak, typhoid spread from Kasese to Bundibugyo with a prevalence of MDR strains[37]. According to this study, a total of 1,042 cases were identified among Kasese and Bundibugyo residents between August 2009 to December 2011 with TIP reported for 507 (82%) and 59 (20%) of Kasese and Bundibugyo cases, respectively. In addition, antimicrobial susceptibility was assessed for 18 isolates, among which, 15 (83%) were MDR, compared to 5% of 2009 isolates. Chloramphenicol was the only antibiotic specifically associated with TIP hence related to the widespread chloramphenicol resistance among the outbreak strains. The study recommended that lasting interventions, such as typhoid vaccination and improvements in drinking water infrastructure, should be considered to minimize the risk of prolonged outbreaks in the future.

In 2015, Uganda reported its third typhoid outbreak in Kampala city, with a total of 10,230 cases at an incidence proportion of 0.9%. The high disease burden was measured from suspected cases and incidence due to typhoid outbreaks. A study by Kabwama et al (2017) investigating the large and persistent outbreak of typhoid fever in Kampala from January 2015 to June 2015 found that 56 (15%) of blood samples collected from 364 patients yielded S. enterica ser. Typhi (S. Typhi) with 88 TIP cases identified. Similarly, environmental investigations revealed water and juice samples sold on the streets exhibiting evidence of fecal contamination[38]. The study estimated that the outbreak may have started earlier than January 2015 given that routine clinical and laboratory surveillance systems for typhoid fever were not in place before the investigation started in

[36] Neil et al., 2012. A Large Outbreak of Typhoid Fever Associated With a High Rate of Intestinal Perforation in Kasese District, Uganda, 2008–2009, *Clinical Infectious Diseases*, Volume 54, Issue 8, 15 April 2012, Pages 1091–1099, https://doi.org/10.1093/cid/cis025

[37] Walters, M.S., et al., 2014. Shifts in geographic distribution and antimicrobial resistance during a prolonged typhoid fever outbreak—Bundibugyo and Kasese Districts, Uganda, 2009–2011. *PLoS Neglected Tropical Diseases*, *8*(3), p.e2726.

[38] Kabwama S. N., et al., 2017. "A large and persistent outbreak of typhoid fever caused by consuming contaminated water and street-vended beverages: Kampala, Uganda, January – June 2015." BMC Public Health17 (1): 23.

February 2015. Indeed, a study by Atuyambe et al (2020) assessing the spread of typhoid fever in Kampala City, Uganda, confirmed that inadequate disease surveillance and delay in diagnosis and treatment of cases were the main factors that led to this outbreak[39].

Just like in many other LMICs, definitive diagnostic tests for typhoid fever, such as blood culture are usually unavailable, unaffordable, or inconsistently applied in Uganda. Instead, typhoid fever diagnosis and surveillance often rely on clinical judgment or Widal test, which has poor sensitivity and specificity[40]. As such, an evaluation of typhoid over diagnosis and reporting in Uganda by Kusiima et al. (2016) confirmed that of the 1,025 extracted records of patients treated for typhoid in Nakaseke district, 19% (192) had a positive Widal test as the supporting laboratory evidence against 81.2% that were clinical diagnoses[41]. The study also reported that none of the facilities in the district were able to conduct blood culture and sensitivity tests; hence all suspected typhoid diagnoses in the district were based on clinical symptoms and high typhoid O titers (antigen O > 160).

ii) Typhoid burden in Ugandan children

Typhoid burden in Uganda **weighs heavily on children,** including those who are school aged. Laboratory culture samples reviewed by PATH at the Central Public Health Laboratories (CPHL), Mulago National Referral Hospital, and Arua Regional Referral Hospital between 2015 and 2021 as illustrated in the figure below show that 204 of 237 typhoid culture samples had ages documented[42]. Of those with ages documented, 140 (69%) were children younger than 15 years old. It should be noted that school-going children falling ill translates into children missing school, and parents/ guardians missing work to care for the sick children.

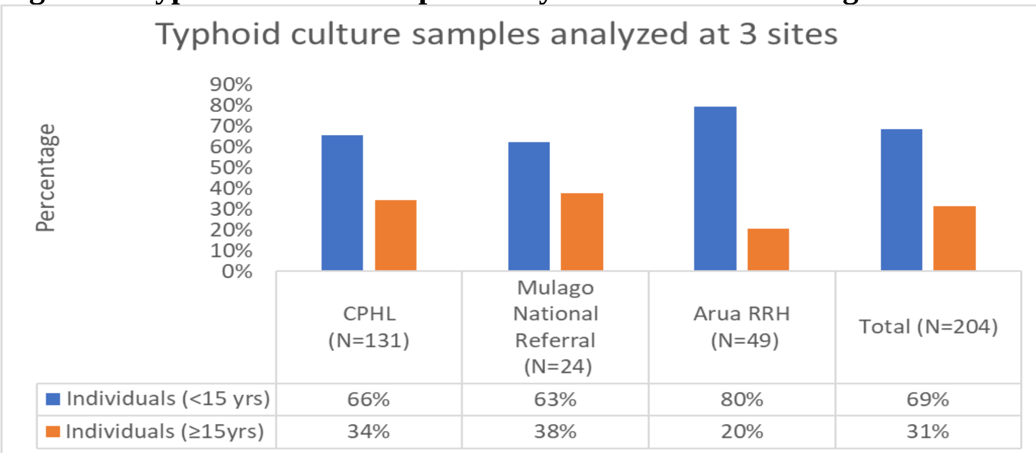
[39] Atuyambe, L., Atusingwize, E. and Kayemba, C.N., 2020. "The Underground Water Sources were Contaminated" A Qualitative Assessment of the Spread of Typhoid Fever in Kampala City, Uganda.

[40] Keddy KH, Sooka A, Letsoalo ME, Hoyland G, Chaignat CL, Morrissey AB, et al. Sensitivity and specificity of typhoid fever rapid antibody tests for laboratory diagnosis at two sub-Saharan African sites. Bull World Health Organ. 2011;89(9):640–7.

[41] Kusiima, J., Ikoona, E., Kadobera, D., & Ario, A. R. Typhoid over diagnosis and reporting in Nakaseke District, Uganda, 2016. Abstract in the 10th International Conference on Typhoid & Other Invasive Salmonelloses. April 4–6, 2017 Kampala Uganda

[42] A presentation to UNITAG Working Group on Typhoid burden in Uganda by the PATH Consultant gathering Typhoid data in Uganda on June 15,2023

Figure 1: Typhoid culture samples analyzed at the 3 sites in Uganda from 2015 to 2021



Source: Presentation slide on Typhoid burden in Uganda by PATH on June 15, 2023

iii) Incidence and prevalence of typhoid fever and its complications in Uganda

Over 80% of Ugandan districts are endemic for typhoid, largely attributable to a lack of reliable disease surveillance support. A retrospective study by Mirembe et al., (2019) revealed a total of 210,204 cases reported in this period with an incidence rate of approx. 160 cases per 100,000 persons at national level and 60 cases per 100,000 persons per year at district level, predominantly in urban areas[43]. The study utilized national and district level data from 2013 to 2016 assessing temporal, spatial and household dynamics of typhoid fever in Uganda and found that Bwera sub-county in Kasese district had the highest incidence rate, followed by Kisinga, Kitholhu and Nyakiyumbu sub-counties. While the study established that the outbreaks were preceded by precipitation, flooding and displacement of people, it also identified areas with high incidence of typhoid fever to have had high environmental contamination with limited water treatment. The S. Typhi isolated during the study were found to be resistant to more antibiotics than isolates obtained from Kasese district in 2009.

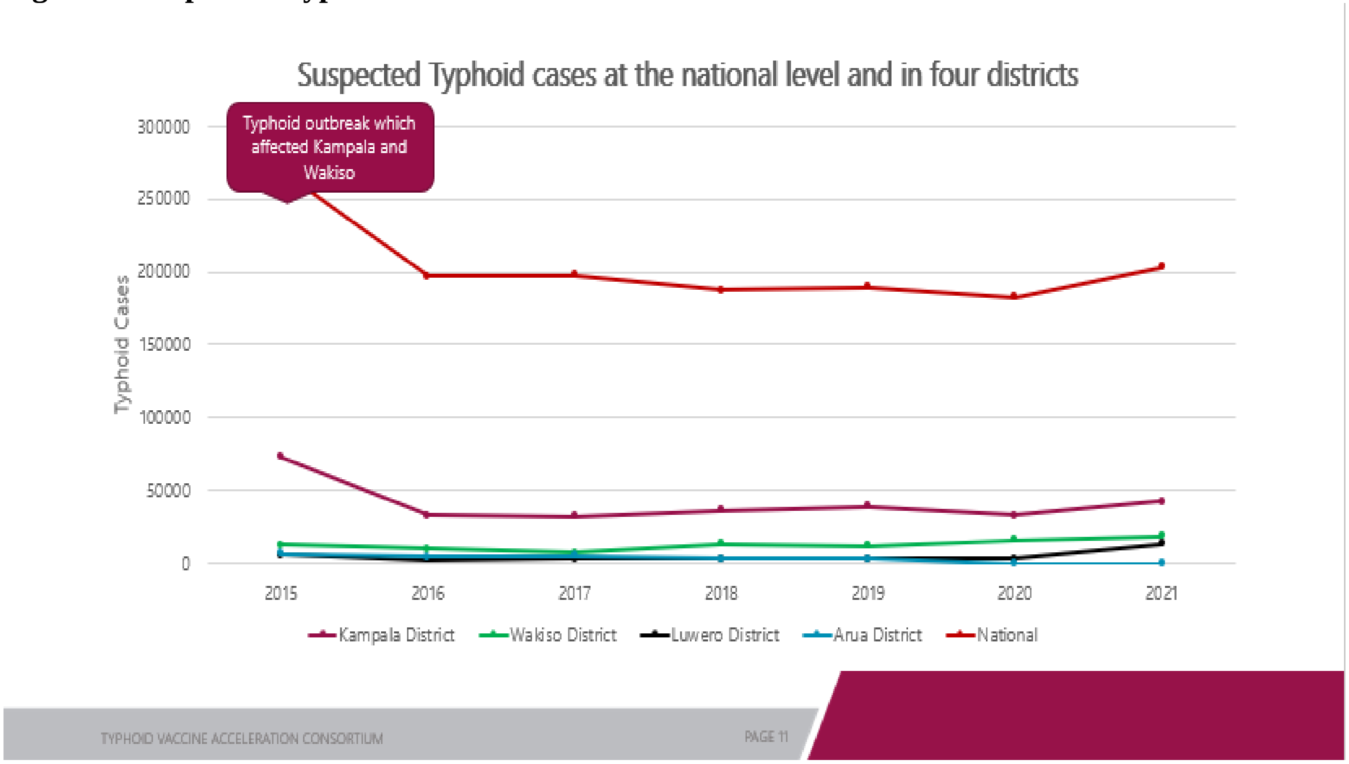
Similarly, an assessment of spatio-temporal trends and distribution patterns of typhoid disease in Uganda from 2012 to 2017 by Ismail et al. (2020) found spatio clusters for both years in the central region, followed by western and eastern regions, with the northern region having the least disease[44]. The study identified rainy seasons and poor drainage systems as the main risk factors for the disease. This coincides with evidence from the PATH report on typhoid burden in Uganda following a review of the district health information system (DHIS2) data that showed an increase in suspected typhoid cases by more than 100% in Luwero, 87% in Wakiso and 29% in Kampala

[43] Mirembe, B.B., Mazeri, S., Callaby, R., Nyakarahuka, L., Kankya, C. and Muwonge, A., 2019. Temporal, spatial and household dynamics of Typhoid fever in Kasese district, Uganda. *Plos one*, *14*(4), p.e0214650.

[44] Ismail, K., et al., 2020. Spatio-temporal trends and distribution patterns of typhoid disease in Uganda from 2012 to 2017. *Geospatial health*, *15*(2).

districts, though declined by 95% in Arua district between 2016 and 2021[45] as shown in the figure below.

Figure 2: Suspected Typhoid cases at the national level and in four districts 2015 and 2021



Source: Presentation slide on Typhoid burden in Uganda by PATH on June 15, 2023

In addition, findings from the PATH evaluation of typhoid burden in Uganda showed an overall increase in TIP cases in 2021. According to the data, there was a noted increase of TIP cases in Arua (26%) and Kiruddu Hospital (10-fold increase) between 2020 and 2021. The report further showed a double of TIP cases in Bishop Ceazer Memorial Hospital during this time. Increased TIP cases indicate severe typhoid presentation (in advanced stages) and may signal a higher typhoid burden**.** Likewise, the report highlighted health system challenges contributing to the typhoid burden in Uganda. According to the report, informal interviews with health workers in one facility revealed that they refer surgical cases to a private facility due to inadequate infrastructure**.** The respondents reported that not all referrals could access services at the private facility due to cost limitations. It was also emphasized that <u>none</u> of the facilities performed culture tests for TIP cases.

Further to note, evidence from an assessment of modifiable risk factors for TIP for the period 2013-2015 by Bulage et al. (2015) estimated the risk of TIP at 6.6 per 1,000 suspected typhoid infections (68/10,230) with a case-fatality rate of 10% (7/68)[46]. The study established that, of the 45 cases that sought treatment for the infection, only 42% (19/45) sought treatment 4–9 days after

[45] A presentation to UNITAG Working Group on Typhoid burden in Uganda by the PATH Consultant gathering Typhoid data in Uganda on August 12, 2022

[46] Bulage, L., et al., 2017. Modifiable risk factors for typhoid intestinal perforations during a large outbreak of typhoid fever, Kampala Uganda, 2015. *BMC Infectious Diseases*, *17*(1), pp.1-7.

illness onset (OR_{adj} = 2.2, 95%CI = 0.83–5.8), while 29% (13/45) sought treatment ≥10 days after onset (OR_{adj} = 11, 95%CI = 1.9–61). Moreover, 68% (96/141) of the cases that had received treatment got it before being treated at the treatment centre (OR_{adj} = 9.0, 95%CI = 1.1–78). Hence, the study concluded that delay in seeking treatment increased the risk of TIPs.

iv) Drug-resistant typhoid in Uganda

Similar to global and regional findings, evidence from several studies shows **increasing MDR in Uganda**. An AMR bulletin (July to September 2021) by the Uganda National One Health Platform (UNOHP) reporting Ministry of Health data from selected surveillance sites for the period between October 2018 and December 2020 indicated that different commonly used antibiotics such as Ciprofloxacin and Cefoxitin are experiencing **high degrees of resistance**[47] as shown in the figure 4. In addition, evidence from several studies details the extent of drug-resistant typhoid in Uganda over the years, as summarized in the table 4.

Figure 3: Resistance Profiles from selected surveillance sites

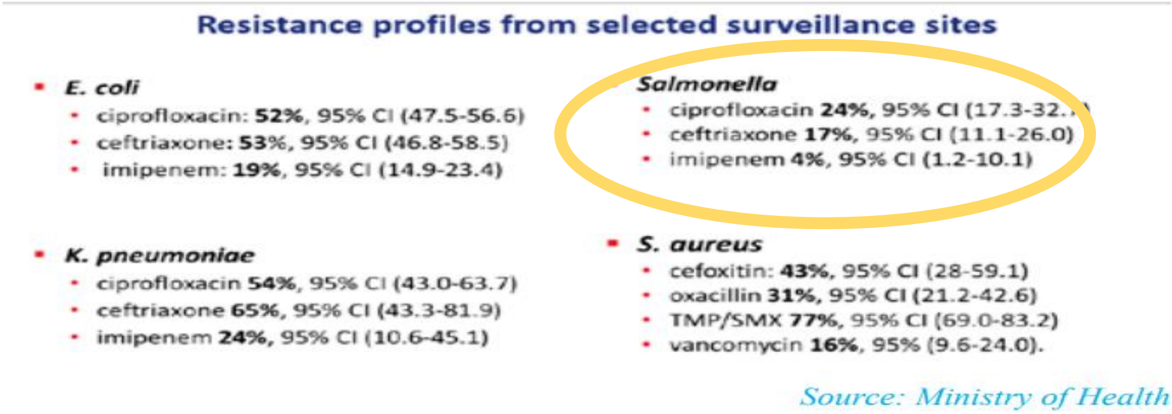


Table 4: Extent of drug-resistant typhoid in Uganda 2012-2017

First Author	Year	location	Period of study	No.of Salmonella typhi isolates	No. of confirmed MDR (%)	Resistance identified
Neil 34*	2012	Kasese	2008-2009	21	16 (76%)	ampicillin, streptomycin, sulfisoxazole, tetracycline, and cotrimoxazole, but were susceptible to chloramphenicol
Walters 35*	2014	Kasese, Bundibugyo	2009-2011	18	15 (83%)	Chloramphenicol
Kabwama 36*	2017	Kampala	Jan-Jun 2015	30	5	ampicillin, chloramphenicol, streptomycin, sulfisoxazole, nalidixic acid, trimethoprim/ sulfamethoxazole with intermediate interpretation to ciprofloxacin)

[47] Uganda National One Health Platform: Anti-Microbial Resistance: AMR Bulletin Volume 01, July-September 2021. file:///C:/Users/UNAS/Downloads/AMR%20Bulletin%20Volume%20One%20(1).pdf

					12	nalidixic acid with intermediate interpretation to ciprofloxacin.
Nakintu[48]	2017	Makerere University Clinical Microbiology Lab	Aug 2012 – Jul 2016	24	16	ampicillin,cotrimazole, chloramphenicol, nalidixic acid
Kajumbula	2018	Mulago N.R.H	Jun 2013 – Oct 2014	5 typhoidal	3	>3 different antimicrobial classes
				12 non-typhoidal	6	
Appiah[49]	2021	Apac, Jinja, Kabale, Mubende, Tororo	2016-2019	14	10 (71%)	decreased susceptibility to ciprofloxacin

This evidence coincides with the global and regional findings on the increasing risk of MDR. It should be noted that **resistance to first-line and alternative drugs poses challenges such as narrowing spectrum antibiotic classes, altered empiric therapy regimens, and the use of agents with reduced efficacy and increased toxicity**[50].

v) Economic burden of typhoid

Typhoid likely imposes an economic burden in Uganda. A cost effectiveness study conducted in Kabale district reported a mean outpatient cost of US$34 per case of typhoid and US$76 for hospitalized patients[51].Similarly in another study conducted in Kasese, Uganda using ViCPS during the 2008-2011 epidemic outbreak of typhoid found the cost of outpatient visit was US$4.30, while the case costs for hospitalized patients was US $58.10 for individuals without Intestinal perforation (IP) and US$155.60 for patients with intestinal perforations**.** In a similar study conducted in Pemba Zanzibar in Tanzania reported an average cost per typhoid episode of US$154.47[52]. Data from a costing cohort study estimating the economic burden of typhoid in children and adults in Blantyre, Malawi, showed that typhoid fever caused significant direct non-medical expenses and income loss that were catastrophic for a large proportion of households

[48] Robinah Christine Nakintu, Henry Kyobe Bosa, Daniel K. Bulwadda, Paul Katongole, Christine Najjuka, Henry Kajumbula. Earliest Evidence of Multidrug Antibiotic Resistant Non-Typhoidal Salmonella Spp. (Ints) In Uganda: Abstract in the 10th International Conference on Typhoid & Other Invasive Salmonelloses. April 4–6, 2017 Kampala Uganda

[49] Appiah, G.D., et al., 2021. Salmonella Bloodstream Infections in Hospitalized Children with Acute Febrile Illness-Uganda, 2016-2019. *The American Journal of Tropical Medicine and Hygiene*.

[50] Fair RJ, Tor Y. Antibiotics and bacterial resistance in the 21st century. Perspect Medicine Chem. 2014 Aug 28;6:25-64. doi: 10.4137/PMC.S14459. PMID: 25232278; PMCID: PMC4159373.

[51] Odulusi D,2018.Cost Effectiveness Analysis of Typhoid Fever Vaccination in an Endemic District of Kabale,Uganda

[52]Riewpaiboon A., et al., (2014). Cost of illness due to typhoid fever in Pemba, Zanzibar, East Africa. Journal of Health, Population and Nutrition. 2014;32(3):377-385

despite accessible free medical care[53]. The study recruited 109 participants, including 44 (40%) admitted inpatients, 65 (60%) outpatients at a mean age of 14 years (SD 11.6), with 58% younger than 15 years. The study established significant costs to the health care provider, including mean cost of **inpatient healthcare at $296.52** (225.79, 367.25) and mean cost of outpatient healthcare at **$39.67** (33.96, 45.39). In 48 (44%) households considered, total costs of illness exceeded 40% of reported monthly non-food expenditure rendering them catastrophic costs. However, the study relied on self-reported income and expenditure.

Bottom line message:

- **f) Typhoid burden in Uganda remains high. The country has experienced three major outbreaks in the last 15 years. Typhoid fever clinically resembles other febrile illnesses (eg, malaria), meaning it is easily misdiagnosed without laboratory confirmation, likely resulting in inappropriate treatment recommendations, unrecognized outbreaks, and underestimation of incidence.**
- **g) In Uganda, definitive diagnostic tests for typhoid fever, such as blood culture, are usually unavailable, unaffordable, or inconsistently applied. Instead, typhoid fever diagnosis and surveillance often rely on clinical judgment or Widal test, which has poor sensitivity and specificity.**
- **h) Typhoid burden in Uganda weighs heavily on children, including school-aged children. Laboratory culture samples collected between 2015 and 2021 show that of 204 typhoid culture samples that had ages documented, 140 (69%) were children younger than 15 years old.**
- **i) Typhoid likely imposes an economic burden in Uganda. Results from a cost effectiveness analysis conducted in Kabale reported a mean outpatient cost of $34 per case of typhoid and $76 for hospitalized patients. Analyses from Malawi found that the inpatient healthcare costs $296.52(225.79, 367.25) for a typhoid case and mean cost of outpatient healthcare costs $39.67.**

iii. Typhoid fever prevention and control measures in Uganda

Typhoid risk is higher in populations that lack access to safe water and adequate sanitation. Safe water, sanitation, and hygiene (WASH) interventions are critical to preventing the spread of typhoid[54]. A study by Atuyambe et al. (2020) assessing the spread of typhoid fever in Kampala City, Uganda, established that in addition to the prolonged dry season, inadequate disease surveillance and delay in diagnosis and treatment of cases, poor personal and food hygiene, contaminated water sources, consumption of unsafe beverages were the main factors that led to

[53] Limani, F., et al., 2021. Estimating the economic burden of typhoid in children and adults in Blantyre, Malawi: a costing cohort study (Unpublished). Accessible at https://assets.researchsquare.com/files/rs-1214074/v1/6ba67f9a-dda6-43c6-9bff-c7f6f1b9bb44.pdf?c=1641563956

[54] WHO: Key facts on Typhoid: https://www.who.int/news-room/fact-sheets/detail/typhoid#:~:text=Key%20facts,die%20from%20it%20every%20year. Accessed on 20 September 2022

the outbreak in 2015[55]. Incidentally, evidence from several other studies assessing the three major outbreaks in Uganda coincides with the findings above, as summarized in the table below:

Table 5: Status of WASH in sites with Typhoid outbreaks in Uganda 2014-2020

First Author	Year	Location	Period	WASH status
Ismail	2020	Uganda	2012-2017	Poor drainage
Mirembe 41*	2019	Kasese, Bundibugyo	2013-2016	Drinking water in both districts was fecally contaminated and the likely vehicle for the outbreaks.
Kabwama 36*	2017	Kampala	Jan-Jun 2015	Water and juice samples sold on the streets exhibited evidence of faecal contamination.
Murphy[56]	2017	Kampala	2015-2016	Salmonella spp. was detected in samples from two unprotected springs; one protected spring, and one refilled water bottle, suggestive of the fact that unregulated vended water and groundwater represented a risk for typhoid transmission.
Oguttu[57]	2017	Kampala	Jan 2015	heavy fecal contamination in locally made drinks and underground water
Walters 35*	2014	Kasese and Bundibugyo	2009-2011	E. coli detected in all the water samples: 6 drinking water taps and 2 surface water sources in Kasese; 2 drinking water taps and 1 surface water source in Bundibugyo.

It should be noted that Uganda faces enormous gaps between communities regarding sanitation and the prevention of typhoid spread. Uganda National Household survey revealed that up to 21% of households did not have access to improved sources of drinking water[58]. According to the survey, households in urban settings are more likely (92.3%) to have improved water sources than rural households (74.9%). However, 72.2% of urban households pay for water, compared to 31.4% in rural settings. This means that water costs may influence households to seek less expensive, unimproved water sources, thereby increasing their risk of contracting typhoid.

In addition, the Annual Heath Sector Performance Report 2020/21 shows a 72:1 pupil toilet stance ratio compared to the standard of 45:1 for day schools and 25:1 for boarding schools. Likewise, hand washing coverage at schools was measured at 57%, which puts schools at risk of typhoid transmission**.** The report further showed that 7% of households in Uganda used unimproved or no toilet facilities, including 35% of households in the severely affected Peace and Recovery Development Plan (PRDP) districts, which are mainly affected by conflicts or the spillover effects of conflict (including refugee settlements).

[55] Atuyambe, L., Atusingwize, E. and Kayemba, C.N., 2020. "The Underground Water Sources were Contaminated" A Qualitative Assessment of the Spread of Typhoid Fever in Kampala City, Uganda.

[56] Murphy, J.L., et al., 2017. Environmental survey of drinking water sources in Kampala, Uganda, during a typhoid fever outbreak. *Applied and Environmental Microbiology*, *83*(23), pp.e01706-17.

*Already referenced above

[57] David Oguttu. Typhoid Outbreak Caused by Drinks Made from Contaminated Underground Water Sources in Kampala, Uganda, January-March, 2015. Abstract in the 10th International Conference on Typhoid & Other Invasive Salmonelloses. April 4–6, 2017 Kampala Uganda

[58] Uganda Bureau of Statistics (UBOS): Uganda National Household Survey (UNHS) 2019/ 2020

Sampled Wash Data from major surveys in Uganda

Findings from the UNHS 2019/2020 report indicate urban households have improved sources of drinking water(91.3%) compared to three-quarters of the households in rural areas(75%). Among the sub–regions nearly all households in Kampala had the highest percentage of households that used improved drinking water sources (99%) while Ankole had the lowest. There were minimal variations in the percentage of households using improved sources in the 2016/2017 and 2019/2020 survey reports.[59]

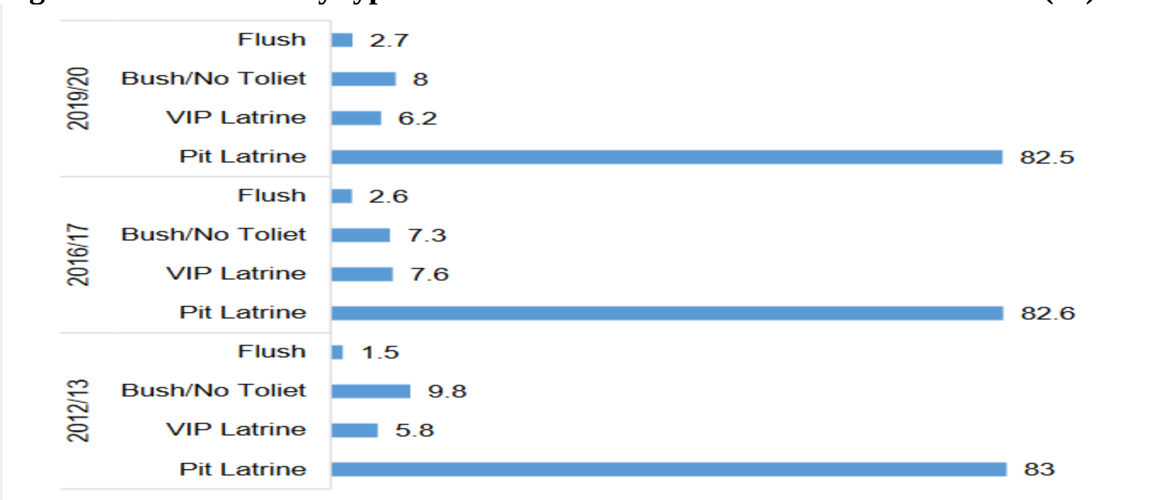
Table 6: Distribution of Households by Drinking water source and selected background characteristics UNHS Survey Results

Characteristic	2016/17 Water source			2019/20 Water source		
	Improved	Unimproved	Total	Improved	Unimproved	Total
Sex of Head						
Male	78.9	21.1	100	77.5	22.5	100
Female	82.0	18.0	100	80.1	19.9	100
Residence						
Rural	74.9	25.1	100	75.3	24.7	100
Urban	92.3	7.7	100	91.3	8.7	100
Sub-Region						
Kampala	96.4	3.6	100	98.8	1.2	100
Buganda South	75.5	24.5	100	72.9	27.1	100
Buganda North	75.5	24.5	100	75.1	24.9	100
Busoga	93.4	6.6	100	92.7	7.3	100
Bukedi	90.4	9.6	100	95.7	4.3	100
Elgon	84.1	15.9	100	86.2	13.8	100
Teso	90.1	9.9	100	95.7	4.3	100
Karamoja	92	8	100	83.6	16.4	100
Lango	86.3	13.7	100	91.1	8.9	100
Acholi	74.5	25.5	100	80.9	19.1	100
West Nile	83.3	16.7	100	87	13	100
Bunyoro	77	23	100	72.4	27.6	100
Tooro	62.5	37.5	100	60.5	39.5	100
Ankole	61.9	38.1	100	54.6	45.4	100
Kigezi	75.1	24.9	100	59.8	40.2	100

Source Uganda National Household Survey Report 2019/2020

59 *Already referenced*

Figure 4: Households by type of toilet facilities used from 2012-13 to 2019/20(%)



Source Uganda National Household Survey Report 2019/2020

The proportion of households that used pit latrines remained the same between 2012/13 and 2019/20(83%). There was a slight decrease in the percentage of households that used VIP latrines from 8% in 2016/17 to 6.2% in 2019/20. There was minimal change in the proportion of households that used bushes/did not use any type of toilet facility between the two surveys (2016/17&2019/20).

Table 7: PMA 2021 Survey Results: Use of Sanitation Facilities

Facility type estimates		Urban	Rural	National
	Improved	66.9	29.9	36.0
	Sewer connection	3.6	0.2	0.8
	Septic tanks	6.6	0.2	1.3
	Other	56.6	29.5	34.0
	Open defecation	0.7	6.7	5.7

Table 8: PMA 2020: Use of Sanitation Facilities

Facility type estimates		Urban	Rural	National
	Improved	68.6	26.7	35.7
	Sewer connection	3.6	0.1	0.8
	Septic tanks	5.2	0.7	1.6
	Other	59.8	26.0	33.3
	Open defecation	3.3	9.0	7.8

Source: Joint Monitoring Programme for Water supply, sanitation and hygiene

Findings from the Performance Monitoring for Action (PMA) 2021 survey results indicate 66.9% of urban areas had improved facility type and the rural areas with 29.9%, and a national average of 36.0%. Facilities with a sewer connection in urban areas were 6.6%, with rural areas standing at 0.2%, and a national average of 1.3%. Overall there was a reduction in open defecation from a national average of 7.8% in 2020 to 5.7% in 2021. There were minimal variations in survey results for 2020 and 2021.

Table 9: Access to drinking water using Population Figures

Time period	Population(1000s) Source UN Population Division	Improved water	At least basic(improved within 30 mins)	Limited (improved> 30mins	Unimproved water	Surface water
2020	44405	82.3	56.0	26.3	12.4	5.3
2021	45854	83.3	57.6	25.6	11.9	4.9
2022	47250	84.2	59.3	24.9	11.3	4.5

Source: Joint Monitoring Programme for Water supply, sanitation and hygiene

Bottom line messages:

j) **Typhoid risk is higher in populations that lack access to safe water and adequate sanitation. Safe water, sanitation, and hygiene (WASH) interventions are critical to preventing the spread of typhoid.**

k) **The prolonged dry season, inadequate disease surveillance, and delays in diagnosis and treatment of cases, poor personal and food hygiene, contaminated water sources, and consumption of unsafe beverages were the main factors that led to the outbreak in 2015 in Uganda.**

l) **Hand washing coverage at schools was measured at 57% in Uganda, which puts schools at risk of typhoid transmission.**

iv. Current status of typhoid surveillance in Uganda

Findings from a survey on typhoid burden in Uganda by PATH, 2022, emphasized the challenges associated with diagnostics and documenting typhoid data[60]. First, the available data collection tools provided limited options to document culture result outcomes. As a result, health workers broadly group ‘typhoid’ among other diseases or record typhoid under causes of illness. It was also noted that most facilities' access to blood cultures was limited, thereby leaving health workers to depend on clinical diagnosis. In addition, the survey revealed a limited capacity to conduct blood culture and sensitivity analysis at most health facilities. The report showed that among the available culture samples evaluated, 45% were not serotyped. This limits the opportunity to localize or determine the actual cause of an outbreak. The report further highlighted gaps in the national surveillance infrastructure, revealing that while refugee settlements are at risk of typhoid outbreaks, minimal data is collected on typhoid due to the limited laboratory and clinical structures in these settlements. As an alternative, most refugee camps were found to depend on the host community health care centres, which are mainly lower health facilities with ongoing challenges with typhoid diagnosis.

Bottom line messages:

m) **Available data collection tools provide limited options to document culture result outcomes; health workers broadly group ‘typhoid’ among other diseases or record typhoid under causes of illness, again contributing to the underestimation of burden.**

[60] Typhoid burden in Uganda: A presentation by PATH to UNITAG Working Group on Typhoid, June 15,2023

n) **Refugee settlements are at risk of typhoid outbreaks, yet minimal data is collected on typhoid due to the limited laboratory and clinical structures in these settlements. Alternatively, many refugee camps depend on the host community health care centres, often lower health facilities that already face challenges with typhoid diagnosis**.

2. VACCINE CONSIDERATIONS

A. Polysaccharide vaccines

Currently, there are three typhoid vaccines licensed for use and are globally available**: a parenteral typhoid conjugate vaccine (TCV) prequalified in 2017**; **parenteral unconjugated Vi capsular polysaccharide** (ViPS) prequalified and recommended for use in individuals >2 years of age; and an oral, live attenuated Ty21a vaccine, though not WHO prequalified but is recommended for use in individuals aged >**6 years of age**[61].

In 2008, WHO recommended the use of Ty21a and ViPS for the control of typhoid in typhoid endemic and epidemic settings. However, since none of the two vaccines are suitable for children younger than two years, they have not been eligible for Gavi support[62]. According to the WHO position paper on Typhoid vaccines (March 2018), uptake of these vaccines in typhoid-endemic countries has been low. Ty21a vaccine requires numerous (three/ four) doses and is licensed for adults and children aged six years and older. Similarly, ViPS vaccine has short-lived protection**,** requiring a booster dose every two to three years. As a result, these hindrances have prevented their inclusion in routine childhood vaccination programs[63].

B. Typhoid Conjugate Vaccines (TCV)

WHO recently prequalified two newer generation Vi-tetanus toxoid conjugate vaccines (TCV) i.e., TYPBAR TCV manufactured by Bharat Biotech International, India is WHO-prequalified in 2017; and TYPHIBEV manufactured by Biological Evans (BE) Limited, India, prequalified in 2020. The new generation of TCV overcomes many limitations that impended uptake of earlier vaccines through increased efficacy, suitability for children under the age of two years, and their easier inclusion in routine immunization programs[64]. Unlike Ty21a and ViPS vaccines, TCV has the potential to protect children under two years of age because it induces a T cell-dependent immune response (more robust responses involving high avidity antibodies and immunologic memory) in young children[65]. TCVs were licensed based on their safety and their ability to offer strong

[61] WHO Health Product Policy https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/vaccine-standardization/typhoid-fever Accessed on 15 September 2022

[62] Gavi: Typhoid vaccine, https://www.gavi.org/types-support/vaccine-support/typhoid, Accessed on 16 September 2022.

[63] Shakya, M., Neuzil, K.M. and Pollard, A.J., 2021. Prospects of future typhoid and paratyphoid vaccines in endemic countries. *The Journal of Infectious Diseases*, *224*(Supplement_7), pp.S770-S774.

[64] WHO. Typhoid vaccines: WHO position paper – March 2018. Weekly Epidemiological Record. 2018 Mar 30;93(13):153–72. Available from: https://www.who.int/publications/i/item/typhoid-vaccines-who-position-paper-march-2018

[65] SAGE Background Paper on Typhoid Vaccines for SAGE Meeting (October 2017)

protection after a single dose and are suitable for children 6 months of age and older, allowing for delivery through routine childhood immunization programs.

In 2018, WHO recommended introducing TCV in typhoid-endemic settings while noting that expanded use of TCV through routine immunization has the potential to reduce the need for antibiotics, slow further emergence of drug-resistant typhoid strains, and save lives.

Bottom line message

- **o) TCV can be included in routine EPI schedules as it can be given to children older than 6 months of age. TCV has the potential to prevent disease, reduce the need for antibiotics, and slow further drug resistance evolutions.**
- **p) TCV Vaccines are funded by Gavi in line with the country funding mechanism**

C. TCV performance in non-endemic settings

D. TCV performance in non-endemic settings

i) TCV immunogenicity and safety profile

Safety study in India

Typbar-TCV was licensed on the basis of its immunogenicity and safety demonstrated in a phase 3 study in an endemic setting. A double-blind, randomized controlled trial (RCT) and an open-label trial (OLT) in India assessed the safety and immunogenicity of Typbar-TCV in healthy subjects aged 2-45 years and healthy infants 6-23 months of age respectively and found that Typbar-TCV induced multiple immunoglobulin G (IgG) subclasses and strong booster responses in all ages with no vaccine-attributable severe adverse events observed[66]. Typbar-TCV in infants 6-23 years was highly immunogenic with a seroconversion (SCN) rate of 98% and geometric mean titre (GMT) of 1937 [95% CI, 1785–2103] 42 days after vaccination. Two years after vaccination, OLT, the infants achieved GMT of 48 (95% CI, 42–55) and GMAI of 57% as shown in the table below. The OLT that represented the first use of Typbar-TCV in young children <2 years of age concluded that the single-dose Typbar-TCV is well tolerated and induces robust and long-lasting serum anti-Vi IgG across age groups.

[66] Mohan, V.K., et al., 2015. Safety and immunogenicity of a Vi polysaccharide–tetanus toxoid conjugate vaccine (Typbar-TCV) in healthy infants, children, and adults in typhoid endemic areas: a multicenter, 2-cohort, open-label, double-blind, randomized controlled phase 3 study. *Clinical Infectious Diseases*, *61*(3), pp.393-402.

Table 10: GMT and rise of anti-Vi serum IgG enzyme-linked immunosorbent assay titres in the TCV RCT and OLT in India

Study design	Intervention	42 days after vaccination		2 years after vaccination	
		SCN	GMT (95% CI)	GMT	GMAI (95% CI)
Double-blind, RCT (n=644 healthy children and adults aged 2-45 years)	Single dose Typbar TCV	97%	1293	82%	60%
	Vi-polysaccharide Typbar	93%	411	46%	46%
OLT (n=327 healthy infants aged 6-23 months)	Single dose Typbar TCV	98%	1937	48%	57%

ii) TCV efficacy profile

Efficacy study in Oxford, UK

In addition to the immunogenicity studies in India, controlled human infection studies in adults in the United Kingdom provided evidence for the efficacy of TCV that informed the SAGE recommendation. A single-centre, randomized controlled, phase 2b study using an established outpatient-based human typhoid infection model found that TCV is a highly immunogenic vaccine that significantly reduces typhoid fever cases when assessed using a stringent controlled model of typhoid infection[67]. Participants (aged between 18 and 60 years) who received a single dose of TCV showed a vaccine efficacy of 54·6% (95% CI 26·8–71·8) and 100% SCN with significantly higher GMTs detected 1-month post-vaccination compared to 52·0% (23·2–70·0) efficacy and 88.6% SCN in participants that received ViPS. Although four serious adverse events (SAE) were reported during the study, none were related to vaccination (one in the TCV group and three in the ViPS group). The study concluded that TCV use has the potential to reduce both the burden of typhoid fever and associated health inequality.

Likewise, the first study to estimate the efficacy of a TCV from field data by Voysey et al. (2018) found TCV seroefficacy to be 85% (95% CI, 80%–88%)[68]. Using data obtained from the efficacy study above (only compared TCV with ViPS in 2–45-year-olds), and an additional OLT administering TCV to children aged 6–23 months, the study found seroincidence to be lower in participants randomized to TCV rather than ViPS during the 2-year post vaccination period. The study also found no difference in seroincidence for TCV between the two age groups as summarized in the tables below thus concluded that Typbar TCV substantially reduces the number of serologically defined clinical or subclinical infections in infants, children, and adults.

[67] Jin C, Gibani MM, Moore M, et al. Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of Salmonella Typhi: a randomized controlled, phase 2b trial. Lancet2017; 390:2472–80.
[68] Voysey, M. and Pollard, A.J., 2018. Seroefficacy of Vi polysaccharide–tetanus toxoid typhoid conjugate vaccine (Typbar TCV). *Clinical Infectious Diseases*, *67*(1), pp.18-24.

Table 11: Baseline characteristics of participants included in the study by randomized vaccine group

Baseline x-tic	Age group	N=387	Day 42 Vi IgG, GMT (95% CI)
TCV (RCT)	2-45 years	155 (47%)	1092.5 (931.2–1281.7)
TCV (OLT)	6-23 months	103 (34%)	1874.1 (1592.0–2206.3)
ViPS (RCT)	2-45 Years	129 (42%)	446.6 (358.8–555.8)

Table 12: Sero-incidence and RR of presumed typhoid infection

Age group	**Sero-incidence**			**Relative risk (95% CI)**	
	TCV (RCT)	TCV (OLT)	ViPS (RCT)	TCV vs ViPS	TCV: RCT vs OLT
All ages	21(13.5)	13(12.6)	47 (36.4)	0.372 (.235-.588)	1.073 (.563-2.046)
Children aged 2-15 years	13/108 (12.0)		25/88 (28.4)	0.424231-.778)	

Bottom line message

q) **A study in India was the first use of Typbar-TCV in young children <2 years of age and concluded that the single-dose Typbar-TCV is well tolerated and induces robust and long-lasting serum anti-Vi IgG across age groups.**
r) **Typbar TCV is shown to substantially reduce the number of serologically defined clinical or subclinical typhoid infections in infants, children, and adults.**

E. TCV performance in endemic settings

Results from three efficacy studies in Malawi, Nepal, and Bangladesh, conducted by the Typhoid Vaccine Acceleration Consortium (TyVAC**) indicate that Typbar TCV is safe, immunogenic, and efficacious at preventing blood culture-confirmed typhoid fever in children 9 months and older in African and Asian settings** as detailed below:

i) Phase 3 RCT in Nepal[69]

A phase 3, RCT in 9-month- to 16-year-old children vaccinated with TCV in Lalitpur, Nepal found that a single dose of TCV was associated with a reduction of 81.6% in the incidence of typhoid fever among the children aged between 9 months and 16 years of age. When the analysis was restricted to the WHO clinical diagnosis of typhoid fever, those presenting with at least 3 days of fever, the efficacy estimate increased to 85.1%. From the 10,005 participants who received the TCV, only 7 (79 cases per 100,000 person-years) had a blood culture–confirmed typhoid fever compared to 38 (428 cases per 100,000 person-years) of the 10,014 participants that received the capsular group A meningococcal conjugate (MenA) vaccine. The protective efficacy of TCV was 81.6% (95% CI, 58.8 to 91.8; P<0.001) with 99% SCN compared to 2% SCN in the MenA vaccine group. The study also found TCV to be immunogenic, eliciting an antibody response a month after vaccination. Although only one SAE was deemed to be a vaccine-related fever without any

[69] Shakya, M., et al., 2019. Phase 3 efficacy analysis of a typhoid conjugate vaccine trial in Nepal. *New England Journal of Medicine*, *381*(23), pp.2209-2218.

alternative diagnosis, reported adverse events indicated an acceptable safety profile that was comparable to that of MenA - another widely used conjugate vaccine.

Final results of the phase 3 RCT after 2 years were in keeping with the interim results. The participant-masked and observer-masked individually randomized trial in Lalitpur, Nepal, in which 20,019 children aged 9 months to younger than 16 years were randomly assigned in a 1:1 ratio to receive a single dose of Typbar TCV, or MenA and followed up for 2 years found the protective efficacy of TCV against blood culture-confirmed typhoid fever to be 79·0% (95% CI 61·9–88·5; p<0·0001) with no evidence of waning protection over a 2-year-period[70]. The incidence of typhoid fever was 72 (95% CI 38–123) cases per 100,000 person-years (PYs) in the TCV group and 342 (95% CI 262–438) cases per 100,000 person-years in the MenA group. Adverse events occurring within the first 7 days post-vaccination were reported previously.

Table 13: Adverse events occurring within the first 7 days post-vaccination

	Interim results (2017-2018)				**After 2 years (2019-2020)**	
Intervention	**Blood culture confirmed Typhoid fever**	**Efficacy (95% CI)**	**SCN**	**GMTs on day 28 (ELISA units/ mL)**	**Efficacy (95% CI)**	**Typhoid incidence (cases)**
TCV (n=10,005)	**7**(79/100,000 PYs)	81.6%	99%	2038	79.0%	72/100,000PYs
MenA (n=10,014)	38(428/100,000 PYs)		2%	7.0		342/100,000PYs

ii) A Phase 3, Double-blind RCT in Malawi[71]

Similar vaccine efficacy was observed in Malawi, with an efficacy estimate of 80.7% (intention-to-treat population) and 83.7% (per protocol population) against blood culture-confirmed typhoid fever among children 9 months through 12 years of age, after 18 months of study follow-up. A single-center, phase 3, double-blind, individually randomized, active-controlled trial in Blantyre, Malawi assessed TCV efficacy in children aged between 9 months and 12 years of age and found that administration of TCV resulted in a lower incidence of blood culture–confirmed typhoid fever than the control vaccine (MenA) after 2 years of follow-up. Of the 14,069 children that received TCV, only 12 (46.9 cases per 100,000 person-years) children had a blood culture–confirmed typhoid fever compared to 62 (243.2 cases per 100,000 person-years) of the 14,061 in the MenA group. Overall, TCV efficacy was 80.7% (95% CI, 64.2 to 89.6) in the intention-to-treat analysis and 83.7% (95% CI, 68.1 to 91.6) in the per-protocol analysis. Although a total of 130 SAEs (most common being respiratory tract infection, gastroenteritis, and malaria) occurred in the first 6 months after vaccination (52 I n the TCV group and 78 in the MenA group), including 6 deaths (all in the MenA group), no SAEs were considered to be vaccine related.

[70] Shakya, M., et al., 2021. Efficacy of typhoid conjugate vaccine in Nepal: final results of a phase 3, randomized, controlled trial. *The Lancet Global Health*, *9*(11), pp.e1561-e1568.
[71] Patel PD, Patel P, Liang Y, et al. Safety and efficacy of typhoid conjugate vaccine in Malawian children. N Engl J Med2021; 385:1104–15. doi:10.1056/NEJMoa2035916 Google ScholarWorldCat

Data from ongoing follow-up in Malawi show TCV prevents blood culture-confirmed typhoid for more than 4 years among children between the ages 9months and 12 years, proving that TCV offers safe and durable protection in the longer term[72].

Figure 5:Kaplan-Meier estimates of the cumulative Incidence of blood culture positive typhoid fever beginning on the vaccination day 0 in the Intention-to-treat population by Vaccine Group

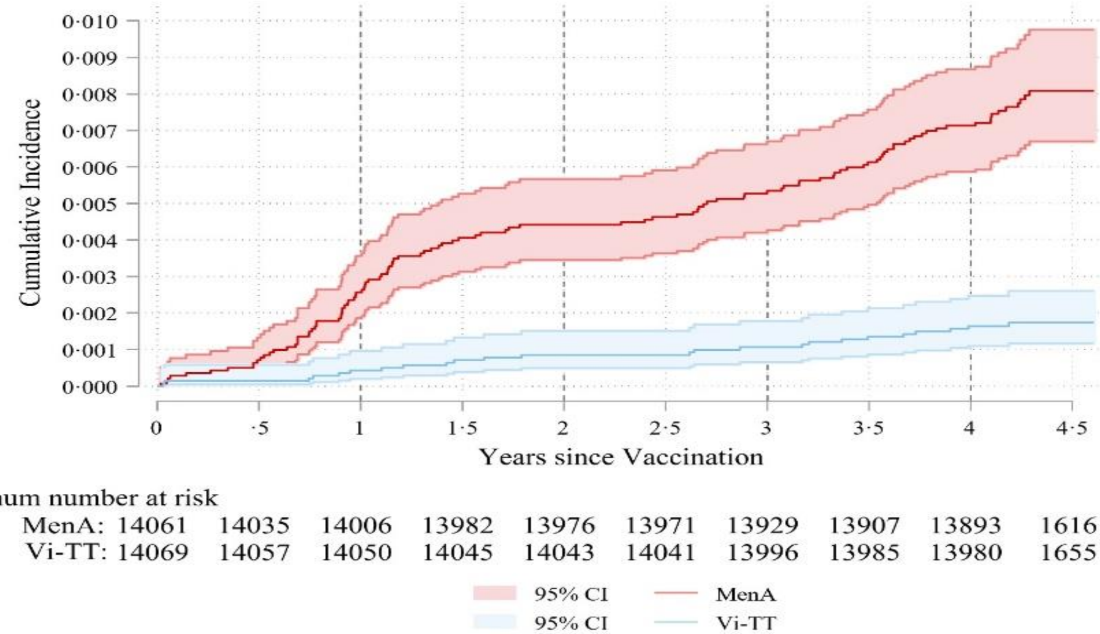


Figure 3: Kaplan-Meier estimates of the cumulative incidence of blood culture positive typhoid fever beginning on the vaccination day 0 in the intention-to-treat population by vaccine group. Maximum number of participants at risk is shown below the graph. CI = confidence interval; MenA = meningococcal capsular group A conjugate vaccine; Vi-TT = Vi polysaccharide tetanus toxoid typhoid conjugate vaccine.

iii) Phase 3 cluster randomized trial in Bangladesh[73]

A participant-masked and observer-masked cluster-randomized trial in Dhaka, Bangladesh assessing the protection of TCV against typhoid fever in children aged between 9 months and less than 16 years found that a single dose of TCV provided 85% protection (97·5% CI 76 to 91, p<0·0001) against typhoid fever. 61,756 children from 150 clusters were randomly assigned to receive TCV (41,344) or the control vaccine (20,412 -Japanese encephalitis (JE) vaccine). The study established that the total vaccine protection was consistent in different age groups, including children vaccinated at ages < 2 years (81%; 95% CI 39 to 94, p=0·0052). Following vaccination of the two groups of children with either vaccine, the study found that the incidence of typhoid fever (cases per 100,000 person-years) was lower (96) in TCV vaccines than in JE (635) vaccines, and the vaccines were well tolerated with no SAEs judged to be vaccine-related.

Similarly, a cluster –Randomized Trial in Dhaka, Bangladesh assessing the Prevention of Typhoid by Vi Conjugate Vaccine and Achievable Improvements in Household Water, Sanitation, and Hygiene among 61,654 urban Bangladesh children aged 9 months to <16 years were randomized

[72]

[73] Qadri F, Khanam F, Liu X, et al. 2021. Protection by vaccination of children against typhoid fever with a Vi-tetanus toxoid conjugate vaccine in urban Bangladesh: a cluster-randomized trial. Lancet2021; 398:675–84.

to Vi-tetanus toxoid TCV or Japanese encephalitis (JE), existing household WASH status was assessed at baseline as Better or Not Better using previously validated criteria. The adjusted reduced risk of typhoid among all residents living in the clusters assigned to TCV was 55%; 95%CI, 43%-65%; P<.001), and that of living in Better WASH households, regardless of the cluster, 37%(95% CI24%-48%; P<.0001.The highest risk of typhoid was observed in persons living in households with Not Better WASH in the JE clusters. In comparison, those living in households with Better WASH in the TCV cluster had an adjusted reduced risk of 71%(95%% CI,59%-80%;P<.001.The findings support a concerted approach to typhoid elimination through vaccination using safe and effective TCVs with the implementation of achievable WASH improvements in high-risk communities. The combination of TCV and living in a Better WASH household still reflected only a 70% reduction in relation to the absence of both.[74]

iv) A safety and immunogenic non-inferiority study on TYPHIBEV - TCV

TYPHIBEV manufactured by Biological Evans (BE) Limited, India, was prequalified by WHO in 2020. Results from a multicenter, single-blind, randomized, phase 2/3 clinical study conducted in India assessing the safety and immunogenic non-inferiority TYPHIBEV compared to Typbar-TCV demonstrated that the immune response profile of TYPHIBEV is comparable[75]. 622 healthy subjects aged ≥6 months to <64 years were enrolled in the study at 9 sites in India and were randomized 1:1 to receive a single 0.5 mL dose of either TYPHIBEV or Typbar TCV. Findings show that across all age groups, TYPHIBEV was non-inferior to Typbar-TCV in terms of antibody response (immunogenicity) and safety on days 0 and 42 after vaccination. All adverse events were mild or moderate with no difference in adverse events between the two vaccine groups. While efficacy and effectiveness data on TYPHIBEV is not yet available, these non-inferiority data were sufficient for WHO to prequalify TYPHIBEV.

[74] Tadesse, B. T., Khanam, F., Ahmmed, F., Im, J., Islam, M. T., Kim, D. R., Kang, S. S. Y., Liu, X., Chowdhury, F., Ahmed, T., Binte Aziz, A., Hoque, M., Park, J., Pak, G., Zaman, K., Khan, A. I., Pollard, A. J., Kim, J. H., Marks, F., Qadri, F., … Clemens, J. D. (2022). Prevention of Typhoid by Vi Conjugate Vaccine and Achievable Improvements in Household Water, Sanitation, and Hygiene: Evidence From a Cluster-Randomized Trial in Dhaka, Bangladesh. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America, 75(10), 1681–1687. https://doi.org/10.1093/cid/ciac289

[75] Thuluva, et al., 2022. "A multicenter, single-blind, randomized, phase-2/3 study to evaluate immunogenicity and safety of a single intramuscular dose of biological E's Vi-capsular polysaccharide-CRM197 conjugate typhoid vaccine (TyphiBEVTM) in healthy infants, children, and adults in comparison with a licensed comparator." *Human Vaccines & Immunotherapeutics* (2022): 1-11.

Table 14: TyVAC studies that provided data on safety, immunogenicity, and efficacy of Typbar TCV in endemic settings to inform country-level decision-making

Country	Design	Control vaccine	Ages	Study period Participant follow-up	Number vaccinated
Nepal	Individually-randomized efficacy	Meningitis A	9 months – 16 years	Nov 2017 – Jan 2020 2 years	20,019
Malawi	Individually-randomized efficacy	Meningitis A	9 months – 12 years	Feb 2018 – Sept 2021 3 years	28,130
Bangladesh	Cluster-randomized	Japanese encephalitis	9 months – 16 years	Apr 2018 – May 2020 2 years	67,395

Source: Slide from a TCV presentation by TyVAC to UNITAG working Group on Typhoid on 15 June, 2023.

Findings from other studies on the reactogenicity, safety and immunogenicity of TCV are consistent with the findings above. Evidence from a nested sub-study of a double-blind RCT by Nampota-Nkomba, et al. (2022) assessing TCV in Malawi shows that TCV is safe and immunogenic up to 730–1035 days in Malawian children aged 9 months to 12 years with no known immunosuppression or chronic health conditions, including HIV or severe malnutrition as summarized in the table below[76]. The sub study design nested within a phase 3 double blind, parallel design randomized Controlled Trial of TCV in Children randomly assigned (1:1) to received TCV or control Meningococcal Serogroup A conjugate Vaccine. Results from the trial indicate 305 participants in the TCV group and 297 participants in the MCV-A group were vaccinated. Among TCV reciepients ,anti-vi IgG geometric mean titres increased more than 500 times from 4.2 ELISA units(EU)Ml(95% Cl 4.0-4.4) at baseline to 2383.7 EU/mL(2087.2-22.3 at day 28,then decreased to 48.0 EU/mL (39.9-57.8) at day 730-1035 remaining more than 11 times higher than the baseline.

Among the MCV-A reciepients,anti-Vi I Gg titres remained unchanged:4.3 EU/ml(4.0-4.5) 730-1035 day.TCV and MCV-A recipients had similar solicited local 3% of 304,95% Cl 1.3-5.1 and three[1%] of 293,0.4-3.0) and systemic(27%[9%] of 304,6.2-12.6 and 27[9%] of 304,6.2-12.6 and 27[9%] of 293,6.4-13.1) reactogenicity

Table 15: Immunosuppression or chronic health conditions, including HIV or severe malnutrition

Age Group	Intervention/ control	Seroconversion - GMTs (EU/mL)		
		Day 0	Day 28	day 730-2387
9 months - 12 years	TCV (n=320)	4.2	2383.7	48
	MenA (n=311)	4.3	4.4	4.6

[76] Nampota-Nkomba, N., et al., 2022. Safety and immunogenicity of a typhoid conjugate vaccine among children aged 9 months to 12 years in Malawi: a nested substudy of a double-blind, randomized controlled trial. *The Lancet Global Health*, *10*(9), pp.e1326-e1335.

Also, results from a phase 3, double-blind trial by Patel et al. (2021) in Malawi assessing TCV efficacy in Malawian children 9 months to 12 years of age show that administration of Vi-TCV resulted in a lower incidence (12/ 14,065) of blood culture–confirmed typhoid fever than the MenA vaccine (62/14,065) with an overall efficacy of 80.7% (95% [CI], 64.2 to 89.6) in the intention-to-treat analysis and 83.7% (95% CI, 68.1 to 91.6) in the per-protocol analysis[77]. Although 130 SAEs occurred in the first 6 months after vaccination (52 in the Vi-TCV group and 78 in the MenA group), including 6 deaths (all in the MenA group) none were related to vaccination.

Table 16: Typhoid conjugate vaccine (TCV) provides strong protection in Africa and Asia

Typhoid conjugate vaccine (TCV) provides strong protection in Africa *and* Asia

Location	Nepal		Malawi		Bangladesh	
Number of participants	20,019		27,882		61,567	
Ages of participants	9 months to <16 years		9 months to <12 years		9 months to <16 years	
Study design	**Randomized 1:1** *TCV or meningococcal A (MenA) vaccine*		**Randomized 1:1** *TCV or MenA vaccine*		**Cluster* randomized 1:1** *TCV or Japanese encephalitis (JE) vaccine*	
Length of follow-up	24 months		48-54 months		18 months	
Blood-culture confirmed typhoid cases	TCV: 13	Meningococcal A: 62	TCV: 24	MenA: 110	TCV: 29	JE: 192
Vaccine efficacy	TCV prevents 78-85% of typhoid cases in children in Africa and Asia.					
Vaccine safety	Meets safety standards ✓		Meets safety standards ✓		Meets safety standards ✓	

*In cluster randomized trials, groups of participants (known as clusters) are randomized as opposed to individual participants being randomized.

Source: Slide from a TCV presentation by TyVAC to UNITAG working Group on Typhoid on 15 June, 2023.

v) TCV Contraindications, adverse effects

WHO recommends that TCV should not be administered in case of allergic reactions to any component of the vaccine. Specifically, WHO recommends that vaccination with TCV should be postponed in the event of severe acute febrile illness as minor infections are not contraindications. In the case of adverse events, vaccination with TCV may cause mild reactions at the injection site (pain, redness at the injection site), fever, headache, and myalgia (muscle pain) as evidenced in the safety and tolerability studies above, and rarely may cause anaphylactic reactions. Thus, WHO further recommends that if administered simultaneously with other vaccines, different syringes should be used on different injection sites.

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[77] Patel, P.D., et al., 2021. Safety and efficacy of a typhoid conjugate vaccine in Malawian children. *New England Journal of Medicine*, *385*(12), pp.1104-1115.

vi) TCV performance when co-administered with other vaccines at 9 months of age in RI

Results from Burkina Faso on co-administration of Typbar - TCV with yellow fever (YF) and measles-rubella (MR) vaccines at 9 months of age, and group A meningococcal conjugate vaccine (MenA) at 15 months old showed comparable TCV antibody responses in the countries where efficacy has been demonstrated. For all vaccines tested in the double-blind RCT, antibody responses were similar in the groups receiving concomitant TCV as compared to the group not receiving TCV[78]. The vaccinations were well-tolerated with no SAEs deemed related to vaccination (fever, irritability and any other systemic reactions). The study concluded that TCV can be safely co-administered at 15 months with MenA without interference.

Another randomized, double-blind, and controlled, phase 2 trial in Ouagadougou, Burkina Faso found that TCV can be safely co-administered with MR and YF vaccines to children at the 9-month vaccination visit[79]. Children aged 9–11 months were randomly vaccinated with TCV (49 children) or control vaccine (inactivated polio vaccine - 51 children) with routine MR and YF vaccines administered for both groups. The study found that anti-body responses increased significantly in the TCV recipients and remained relatively unchanged for the IPV group on day 28 post-vaccination, as shown in the figure below. Thus, the study concluded that a single dose of TCV demonstrated a robust antibody response in infants at 9 months of age.

Table 17: TCV Co-Administered with other vaccines

Group N=150	Intervention (all given routine MR)	Seroconversion - GMTs		AEs and SAEs	
		Day 0	Day 28	28 days	6 months
1(n=48)	TCV+IPV+MenA 28 days later	5.0 (4.0–6.3)	2754.1 (1537.3–4934.1)	61.2%	2.0%
2(n=50)	TCV+MenA	4.7 (3.7–5.8)	3707.3 (2632.0–5222.0)	64.0%	8.0%
3(n=51)	MenA+IPV	4.8 (3.8–6.2)	5.3 (4.1–6.9)	68.6%	5.9%

Sero conversion are comparable when co-administered with IPV, MenA and same applies to AEs

[78] Sirima, S.B., et al., 2021. Safety and immunogenicity of co-administration of meningococcal type A and measles–rubella vaccines with typhoid conjugate vaccine in children aged 15–23 months in Burkina Faso. *International Journal of Infectious Diseases*, *102*, pp.517-523.

[79] Sirima, S.B., et al., 2021. Safety and immunogenicity of Vi-typhoid conjugate vaccine co-administration with routine 9-month vaccination in Burkina Faso: A randomized controlled phase 2 trial. *International Journal of Infectious Diseases*, *108*, pp.465-472.

Table 18: Anti-Vi IgG antibody immunogenicity before vaccination (day 0) and 28 days after vaccination

	Group 1: TCV (N = 49)	Group 2: IPV (N = 51)
Seroconversion[a] (%, 95% CI)	43/49 (87·8%, 75·2–95·4)	4/50[b] (8·0%, 2·2–19·2)
Day 0 geometric mean titer (95% CI)	8·9 (5·9–13·6)	8·5 (5·6–12·7)
Day 28 geometric mean titer (95% CI)	1203·7 (747·1–1939·5)	8·9[b] (6·1–13·1)

Following routine MR and YF vaccines administration in the same study, anti-YF antibody titers for both groups increased significantly post-vaccination with 70% of participants in the TCV group being seropositive for anti-YF antibodies at the 500 mIU/mL threshold. Similarly, the anti-measles and rubella antibody GMTs for both groups significantly increased post-vaccination as shown in the image below. Almost 90% of participants in both TCV and IPV groups were seropositive for anti-measles and for anti-rubella antibodies. While the study found that anti-tetanus IgG antibody titers for both groups were above the threshold for short-term immunity post-vaccination, 98% (48/49) of TCV participants were above the threshold for long-term immunity post-vaccination. Hence study concluded that TCV did not interfere with YF or MR immunogenicity in the study population.

Table 19: Anti-measles and anti-rubella IgG and YF neutralizing antibody immunogenicity before vaccination (day 0) and 28 days after vaccination.

	N	Yellow fever			Measles			Rubella		
		GMT (95% CI)	Seropositivity[a] n	Seropositivity[a] % (95% CI)	GMT (95% CI)	Seropositivity[a] n	Seropositivity[a] % (95% CI)	GMT (95% CI)	Seropositivity[a] n	Seropositivity[a] % (95% CI)
Day 0										
Group 1: TCV	49	45·0 (45·0–45·0)	0	0·0 (0·0–7·3)	3·4 (3·0–3·8)	0	0·0 (0·0–7·3)	1·2 (0·8–1·8)	4	8·2 (2·3–19·6)
Group 2: IPV	50	45·8 (44·2–47·5)	0	0·0 (0·0–7·1)	4·1 (3·1–5·4)	1	2·0 (0·1–10·7)	2·0 (1·3–3·1)	8	16·0 (7·2–29·1)
p-Value[b]		0·32		NA	0·20		1·00	0·10		0·36
Day 28										
Group 1: TCV	46	815·5 (527·1–1261·6)	32	69·6 (54·3–82·3)	442·5 (314·9–566·8)	41	89·1 (76·4–96·4)	25·3 (19·3–33·3)	40	87·0 (73·7–95·1)
Group 2: IPV	48	688·5 (455·1–1041·5)	31	64·6 (49·5–77·8)	396·8 (307·6–511·8)	42	87·5 (74·8–95·3)	25·5 (19·4–33·5)	42	87·5 (74·8–95·3)
p-Value[b]		0·57		0·66	0·75		1·00	0·97		1·00

n = number of participants, N = total number, GMT = geometric mean titer, CI = confidence intervals, NA = not applicable, IU = international units.

The study also assessed the safety and reactogenicity profile of TCV and found that only 4 infants that received TCV (8·2%) experienced fever and irritability in the 7 days after vaccination, which was less than the observed rate of 18% for IPV recipients, and consistent with the safety profile in the 15-month-olds in Burkina Faso. As IPV is a well-accepted vaccine routinely administered to infants as young as six weeks of age, the finding that TCV was better tolerated than IPV bodies well for TCV acceptance among caregivers and healthcare practitioners**.**

vii) Indirect protection for those that may not be able to get vaccinated with TCV

There is considerable evidence that TCV offers **indirect protection among the unvaccinated**. Results from the cluster-randomized trial assessing protection of children against typhoid fever with a TCV vaccine in urban Bangladesh showed that TCV offered indirect vaccine protection (i.e., herd immunity) though not statistically significant **(19%; 95% CI −12 to 41, p=0·20)**.

In addition, a mathematical model evaluating the potential direct and indirect effects of vaccination on the projected typhoid incidence over time predicted **TCV vaccination to confer substantial**

indirect protection, particularly at coverage levels exceeding 40–50%[80]. The model was fit to data on culture-confirmed cases of typhoid fever from Vellore, India ranging from 2000-2012 and validated against the results of cluster randomized vaccine trials. A variety of school-based vaccination strategies were evaluated, including routine TCV vaccination at 9 months old, with and without a catch-up campaign among 9-month to 15-year-olds which predicted typhoid vaccination using **TCV to lead to short-term indirect protection and a decrease in typhoid incidence,** although unlikely to lead to elimination. The level of indirect protection was found to depend on assumptions about the role of chronic carriers, hence recommending future research.

viii) Duration of protection accorded by TCV when given to infants 6 months to 2 years of age and the need for booster doses

A study by Vadrevu, et al. (2021) found that antibody responses to Typbar-TCV vaccine in children < 2 years of age showed higher prevalence of persisting SCN at most time points with the gap widening by 7th year, though not statistically significant (except 3rd year)[81]. More boosted children exhibited higher persistent SCN at 5 years and 7 years post-primary vaccination compared to unboosted children. The study concluded that to extend protection, administering a booster of Typbar-TCV to children approx. 5 years after their primary dose, i.e., coinciding with school entry, may be advisable. However, currently, WHO does not recommend a booster dose.

Table 20: Duration of protection accorded by TCV when given to infants 6 months to 2 years of age and the need for booster doses

	GMTs post primary vaccination with TCV				Persistent SCN (>4-fold above baseline	
	On day 762	3 years	5 years	7 years	5 years	7 years
Boosted children (n=86)	Increased significantly	32-fold over baseline	14-fold over baseline	10-fold over baseline	84% (72/86)	71% (61/86)
Unboosted children (n=25)		21-fold over baseline	8-fold over baseline	5-fold over baseline	72% (18/25)	44% (11/25)

Bottom line messages

- **s) Results from three efficacy studies in Bangladesh, Malawi, and Nepal show that Typbar TCV prevented 85%, 84%, and 79%, respectively, of typhoid cases in children. Typbar TCV is proven safe, immunogenic, and efficacious at preventing blood culture-confirmed typhoid fever.**
- **t) Data from Malawi show that a single dose of TCV offers safe and durable protection.**
- **u) TCVs are safe and protective across diverse settings in Africa and Asia.**

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[80] Pitzer, V.E., et al., 2014. Predicting the impact of vaccination on the transmission dynamics of typhoid in South Asia: a mathematical modeling study. *PLoS neglected tropical diseases*, *8*(1), p.e2642.

[81] Vadrevu, K.M., et al., 2021. Persisting antibody responses to Vi polysaccharide–tetanus toxoid conjugate (Typbar TCV®) vaccine up to 7 years following primary vaccination of children< 2 years of age with, or without, a booster vaccination. *Vaccine*, *39*(45), pp.6682-6690.

v) **Results from a Phase 2/3 study conducted in India demonstrated that the immune response profile of TYPHIBEV is comparable to Typbar TCV.**
w) **Co-administration with measles-rubella and yellow fever vaccines at 9 months of age and co-administration of measles-rubella and meningococcal A vaccines at 15 months of age was found to be safe.**
x) **WHO does not currently recommend a booster dose.**

3. ECONOMIC CONSIDERATIONS

i. Impact and cost-effectiveness of TCV on typhoid burden

Several studies have shown that TCV **vaccination averts a considerable number of cases and deaths.** A study by Cook et al., (2008) evaluated the cost-effectiveness of TCV vaccination against typhoid in four sites, including Kolkata (India), Karachi (Pakistan), North Jakarta (Indonesia), and Hue (Vietnam) , and estimated that a vaccination program targeting all children (2–14.9) would prevent 456 typhoid cases in India, 158 in Pakistan, and 258 in Indonesia. Similarly, 4.6, 1.6, and 2.6 deaths and 126, 44, and 72 (DALYs) were estimated to be averted over 3 years in the 3 countries respectively[82]. A net social costs of US$160 and US$549, per DALY would be averted in the 3 countries respectively. Results showed that these programs would be considered cost-effective under a wide range of assumptions. The study, however, estimated that community-based vaccination programs that also target adults were less cost-effective because incidence was lower in adults than children but were also likely to be "very cost-effective". Similarly, a program targeting school-aged children in Hue, Vietnam would prevent 21 of 84 cases per year, avert 6 DALYs, and not be cost-effective (US$3779 per DALY averted) because of the low typhoid incidence there.

Models available on the 'Take on Typhoid' website predicted that TCV is likely to be cost-effective in countries with high typhoid incidence, high cost of typhoid treatment, and/or high death rates from typhoid, hence has the potential to significantly reduce typhoid burden[83]. In particular, Uganda was predicted to experience a 72.39% reduction in typhoid cases in the 10 years after introducing TCV in RI at 9 months of age, plus a catch-up campaign up to 15 years; 54.7% reduction in typhoid cases following RI plus catch-up up to 5 years; and 38.56% reduction in typhoid cases in RI only. Similarly, it was predicted that introducing TCV vaccination in Uganda, a Gavi eligible country would be cost-effective (the preferred option over no vaccination) if one year of life in perfect health is valued to be worth at least $300 (in USD2016) i.e., lowest cost per disability adjusted life year (DALY) averted at which vaccination is more cost-effective than no vaccination.

Furthermore, findings from several models indicate that RI of infants with TCV plus catch-up vaccination of older cohorts provides additional benefits towards an accelerated and sustained decline in typhoid fever incidence, compared with RI alone. A modeling study by Pitzer, et al. (2014) predicted RI with TCV at 9 months of age to generally prevent the most cases per course

[82] Cook, J., et al (2008). Typhoid Economics Study Group, 2008. The cost-effectiveness of typhoid Vi vaccination programs: calculations for four urban sites in four Asian countries. *Vaccine*, *26*(50), pp.6305-6316.
[83] World Overview: TCV Impact and Cost-Effectiveness. https://www.coalitionagainsttyphoid.org/resource-tools/cost-effectiveness/world-overview/#tab-1 [Accessed on October 05, 2022]

compared to the other typhoid vaccines[84]. Different vaccination strategies were evaluated, including a one-time campaign among school-aged children (6–15 years old), RI at school entry (6 years old), and RI at school entry plus a one-time catch-up campaign among 6–15-year-olds for TCV, Ty21a and ViPS. Assuming an initial TCV efficacy of 95.6% and a duration of 19.2 years based on a comparison between the predicted direct effect (i.e., reduction in the cumulative incidence among vaccinated versus unvaccinated individuals) and the waning of protection observed during trials, modeled results showed that typhoid incidence would decline by 36–42% over 20 years following introduction of TCV depending on the age at vaccination as shown in the figure below. Since TCV aims to provide immunity from a younger age, the study explored the potential impact of RI at 9 months old, with and without a catch-up campaign among 9-month to 15-year-olds and found that routine vaccination with TCV at 9 months of age generally prevented the most cases per course compared to all other vaccination strategies.

Table 21: Cumulative number of typhoid cases prevented per 1,000 vaccine courses when vaccination is introduced with 80% coverage

Vaccination scenario			Number of years post-introduction			
Vaccine	**Age at routine vaccination**	**Age range of campaign**	**1 year**	**5 years**	**10 years**	**20 years**
One-time campaign						
Ty21a		6–15 y	3.2	15.5	24.9	32.1
ViPS		6–15 y	4.6	14.2	13.0	8.9
ViCV		6–15 y	5.3	23.8	35.2	33.8
ViCV		9 m–15 y	4.6	21.4	34.5	35.7
Routine vaccination						
Ty21a	6 y		2.1	11.7	19.0	27.6
ViPS	6 y		3.7	12.1	13.8	11.2
ViPS	6, 9, 12 y		2.7	8.8	11.1	13.7
ViCV	6 y		4.2	19.9	29.8	38.1
ViCV	9 m		5.0	22.6	33.2	41.9
Routine vaccination + catch-up campaign						
Ty21a	6 y	6–15 y	3.0	12.9	20.1	28.2
ViPS	6 y	6–15 y	4.3	12.5	13.3	10.6
ViPS	6, 9, 12 y	6–15 y	3.7	9.2	11.4	14.1
ViCV	6 y	6–15 y	4.9	19.3	28.6	36.5
ViCV	9 m	9 m–15 y	4.4	17.9	27.8	37.0
ViCV	9 m, 6 y, 12 y	9 m–15 y	5.1	15.2	20.0	23.7

doi:10.1371/journal.pntd.0002642.t002

Pitzer VE, Bowles CC, Baker S, Kang G, Balaji V, et al. (2014) Predicting the Impact of Vaccination on the Transmission Dynamics of Typhoid in South Asia: A Mathematical Modeling Study. PLOS Neglected Tropical Diseases 8(1): e2642. https://doi.org/10.1371/journal.pntd.0002642
https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0002642

The model also predicted that a mass TCV vaccination campaign (targeting all age groups) followed by RI of 9-month, 6 - and 12-year-olds should lead to a >85% reduction in typhoid

[84] Pitzer, V.E., et al., 2014. Predicting the impact of vaccination on the transmission dynamics of typhoid in South Asia: a mathematical modeling study. *PLoS neglected tropical diseases*, *8*(1), p.e2642.

incidence at 80% coverage, though unlikely to eliminate typhoid. The overall effectiveness over the first 10 years following vaccine introduction for coverage was predicted to exceed the population direct effect for all coverage levels (0–100%). The model further predicted that administering TCV at 9 months of age would increase the overall effectiveness for all scenarios, suggesting a considerable benefit could be derived from vaccinating infants.

Another modelling study by Lo et al (2018) using a dynamic transmission model compared strategies and thresholds for TCV against typhoid fever and predicted that while RI of infants through EPI would be cost-effective in moderate incidence settings (an annual incidence of >50 cases/100,000 (95% CI, 40–75 cases) at USD $2 per dose, RI plus school-based catch-up campaigns would be ideal in higher incidence settings (>110/100,000 person-years)[85].

Similarly, Bilcke et al., (2019) predicted that RI with TCV plus an extended catch-up to under 15 years would avert the most cases of typhoid fever over 10 years, representing a 58% (95% PI 15–43) decrease in incidence in Gavi-eligible countries[86] as detailed below.

Table 22: Vaccination Strategy and Incidence Reduction

Vaccination strategy	Incidence reduction	No. of cases averted (million) globally
RI at 9 months alone	30%	33 M (16-59 M)
RI + catch-up campaign to 5 years	43%	47 M (22-73 M)
RI + catch-up campaign to 15 years	58%	63 M (31-94 M)

Antillón et al. (2019) estimated that TCV is likely to be **cost-effective in countries with high incidence, high cost of treatment, and/or high death rates from typhoid**[87]. Findings from the assessment of four strategies, including no vaccination, RI at 9 months, and RI at 9 months with catch-up campaigns to either age 5 years or 15 years for each of the 54 countries eligible for Gavi support showed that RI plus a catch-up campaign up-to-15 years of age was the most cost-effective strategy in the majority (38 of 54) countries analyzed. This strategy assumed a willingness to pay (WTP) value of at least US$200 per DALY averted, or assuming a WTP value of at least 25% of each country's gross domestic product (GDP) per capita per DALY averted, at a vaccine price of $1·50 per dose (but excluding Gavi's contribution according to each country's transition phase). This vaccination strategy was also optimal in; 48 countries assuming a WTP of at least $500 per DALY averted; 51 countries with assumed WTP values of at least $1000; 47 countries assuming a WTP value of at least 50% of GDP per capita per DALY averted; and 49 countries assuming a minimum of 100%. It was established that vaccination was likely to be cost-effective in countries with >300 typhoid cases per 100 000 person-years**.** Uncertainty about the probability of hospital admission (and typhoid incidence and mortality) greatly influenced the optimal strategy.

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[85] Lo, N.C., et al., 2018. Comparison of strategies and incidence thresholds for Vi conjugate vaccines against typhoid fever: a cost-effectiveness modeling study. *The Journal of infectious diseases*, *218*(suppl_4), pp.S232-S242.
[86] Bilcke, J., et al., 2019. Cost-effectiveness of routine and campaign use of typhoid Vi-conjugate vaccine in Gavi-eligible countries: a modelling study. *The Lancet Infectious Diseases*, *19*(7), pp.728-739.
[87] Antillón, M., Bilcke, J., Paltiel, A.D. and Pitzer, V.E., 2017. Cost-effectiveness analysis of typhoid conjugate vaccines in five endemic low-and middle-income settings. *Vaccine*, *35*(27), pp.3506-3514.

Another modeling study by Phillips et al. (2023) using a stochastic model of typhoid transmission fitted to data from Queen Elizabeth Hospital in Blantyre, Malawi, from **January 1996 to February 2015, used to evaluate the cost-effectiveness of vaccination strategies over 10-year time** horizon in three scenarios (1) when an outbreak is likely to occur; (2) when an outbreak is unlikely to occur within the next ten years; and (3) when an outbreak has already occurred and is unlikely to occur again, three vaccination strategies were compared to the **status quo of no vaccination:(a)preventive routine vaccination at 9 months of age;(b)preventive routine vaccination plus a catch-up campaign to 15 years of age; and(c)reactive vaccination with a catch-up campaign to age 15(for scenario 1**). With the assumption that an outbreak occurs within 10 years, the various vaccination strategies would prevent a median of 15-60% of disability-adjusted life years (DALYs). **Reactive vaccination was** the preferred strategy for WTP values of **$0-300 per DALY** averted. For WTP **values >$300, the introduction of preventive routine TCV immunization with a catch-up campaign was the preferred strategy**. **Routine vaccination with a catch-up campaign was cost-effective for WTP values above $890 per DALY averted if no outbreak occurs and >$140 per DALY averted if implemented after the outbreak** has already occurred. The findings suggest that **TCV introduction was cost-effective** compared to no vaccination for all WTP Values above $0.Reactive vaccination (with a 1 month delay in implementation) was cost saving, with estimated total costs averted of $17,147(95% CrI:-3500-$65,080) per 100,000 people. Reactive vaccination was preferred for a WTP range of $0-$300.[88]

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[88] Phillips, M.T., Antillon, M., Bilcke, J. *et al.* Cost-effectiveness analysis of typhoid conjugate vaccines in an outbreak setting: a modeling study. *BMC Infect Dis* **23**, 143 (2023). https://doi.org/10.1186/s12879-023-08105-2

Table 23: Expected cost-effectiveness of Vaccination strategies

From: Cost-effectiveness analysis of typhoid conjugate vaccines in an outbreak setting: a modeling study

Strategy	Expected net costs per 100,000 people in 2020 USD	Expected total DALYs per 100,000 people	Expected incremental costs per 100,000 people versus next best non-dominated alternative	Expected DALYs averted per 100,000 people versus next best non-dominated alternative	ICER versus next best non-dominated alternative ($ per DALY averted)
Scenario 1: When an outbreak occurs over the 10-year time horizon					
Reactive vaccination (routine + campaign)	$111,213	383	–	–	–
No vaccination (base case)	$128,360	689	–	–	Dominated
Preventative vaccination (routine + campaign)	$131,749	316	$20,536	67	307
Preventative vaccination (routine only)	$154,148	472	–	–	Dominated
Scenario 2: When no outbreak occurs (pre-outbreak incidence)					
No vaccination (base case)	$5893	35	–	–	–
Preventive vaccination (routine only)	$26,704	22	–	–	Dominated
Preventative vaccination (routine + campaign)	$27,109	11	$21,216	24	902
Scenario 3: When an outbreak has already occurred (post-outbreak incidence)					
No vaccination (base case)	$7242	577	–	–	–
Preventive vaccination (routine + campaign)	$49,406	295	$42,164	282	150
Preventative vaccination (routine only)	$51,717	372	–	–	Dominated

Expected total net costs, total disability-adjusted life-years (DALYs), incremental costs, DALYs averted, and incremental cost-effectiveness ratios (ICERs) per 100,000 people are shown for each strategy over the 10-year time horizon when (1) an outbreak occurs over the 10-year time horizon (randomized timing; Scenario 1), (2) an outbreak does not occur (i.e. assuming the pre-outbreak incidence; Scenario 2), and (3) an outbreak has already occurred and another one is unlikely (i.e. assuming the post-outbreak incidence; Scenario 3). Strategies are sorted from lowest to highest expected total costs per 100,000 individuals. All costs and DALYs are discounted at a rate of 3% per year. Dominated strategies do not form part of the cost-effectiveness frontier, i.e. no WTP value exists for which a dominated strategy is preferred in terms of cost-effectiveness

ii. The cost-effectiveness of TCV on drug-resistant typhoid

A recent modelling study by Birgen et al., (2022) estimating the effect of vaccination on antimicrobial-resistant (AMR) typhoid fever in 73 countries supported by Gavi predicted that the introduction of RI with TCV at age 9 months plus a catch-up campaign up to age 15 years would avert 46–74% of all typhoid fever cases in 73 countries over 10 years[89]. Specifically, the predicted number of typhoid cases, deaths, and DALYs averted over 10 years following the introduction of RI with TCV, plus a catch-up campaign in Uganda, are summarized in the table below.

[89] Birger, et al0., 2022. Estimating the effect of vaccination on antimicrobial-resistant typhoid fever in 73 countries supported by Gavi: a mathematical modelling study. *The Lancet Infectious Diseases*, *22*(5), pp.679-691.

Table 24: The cost-effectiveness of TCV on drug-resistant typhoid

Country	Baseline total typhoid cases (thousands)	Baseline total typhoid deaths	Baseline total typhoid DALYs (thousands)	Total cases averted (thousands)	Total deaths averted	Total DALYs averted (thousands)	% of typhoid cases averted
Uganda	532 (434-641)	2331 (124-34593)	116 (8-1654)	375 (193-518)	1670 (90-24335)	86 (6-1234)	74% (42-88%)

Vaccination was predicted to reduce the relative prevalence of AMR typhoid fever by 16% (95% CI, 0–49). TCV introduction with a catch-up campaign was predicted to avert 42·5 million (95% PI 24·8–62·8 million) cases and 506,000 (95% CI 187 000–1·9 million) deaths caused by fluoroquinolone non-susceptibility typhoid fever, and 21·2 million (95% PI 16·4–26·5 million) cases and 342,000 (95% PI 135 000–1·5 million) deaths from MDR typhoid fever over 10 years following introduction. Similarly, the predicted number of AMR typhoid cases, deaths, and DALYs averted over 10 years following the introduction of RI with TCV plus a catch-up campaign up to age 15 years in Uganda are summarized in the table below. Thus, the model indicated the benefits of prioritizing TCV introduction for countries with a high avertable burden of AMR typhoid fever.

Table 25: Introduction of RI with TCV plus a catch-up campaign up to age 15 years in Uganda (all typhoid cases)

Country	Baseline total AMR cases (thousands)	Baseline total AMR deaths	Baseline total AMR DALYs (thousands)	Total AMR cases averted (thousands)	Total AMR deaths averted	Total AMR DALYs averted (thousands)	% of typhoid cases averted
Uganda	356 (242-490)	1884 (82-34077)	91 (4-1635)	273 (154-399)	1410 (60-25100)	71 (5-1240)	74% (42-88%)

Bottom line message:

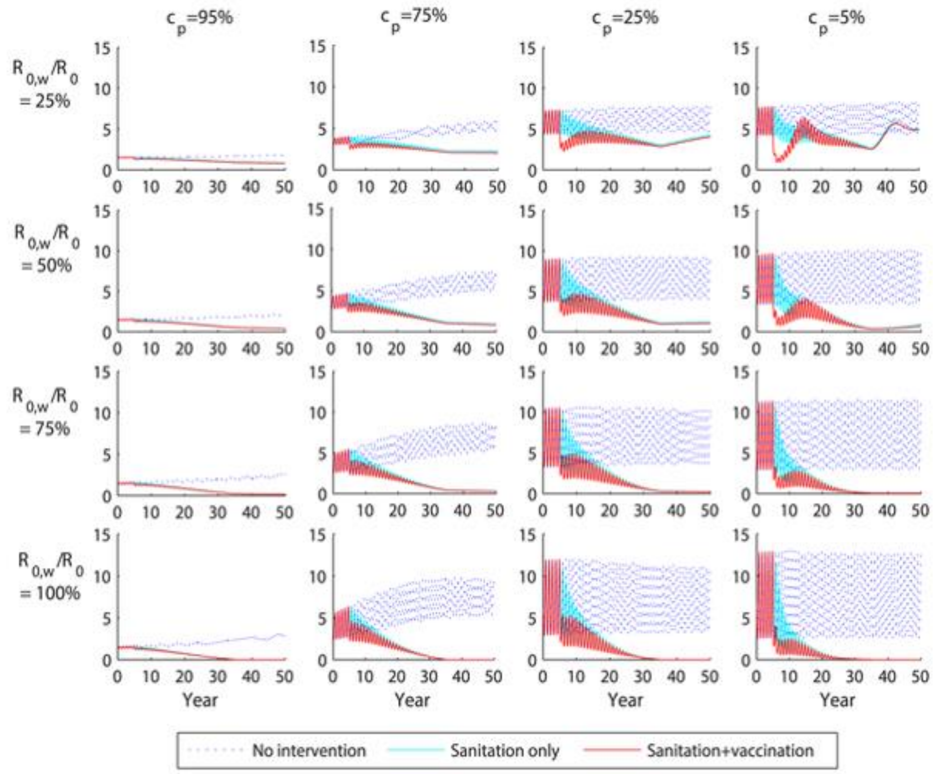
- y) **Modeled analysis predicts that TCV is likely to be cost-effective in countries with high typhoid incidence, high cost of typhoid treatment, and/or high death rates from typhoid.**
- z) **Uganda was predicted to experience a 72.39% reduction in typhoid cases in the 10 years after introducing TCV in RI at 9 months of age, plus a catch-up campaign up to 15 years old.**
- aa) **Several models indicate that RI of infants with TCV plus catch-up vaccination of older cohorts provides additional benefits towards an accelerated and sustained decline in typhoid fever incidence, compared with RI alone.**
- bb) **The model further predicted that administering TCV at 9 months of age would lead to an increase in the overall effectiveness for all scenarios, suggesting a considerable benefit could be derived from vaccinating infants.**

cc) **In the 10 years following the introduction of RI with TCV plus a catch-up campaign up to age 15 years in Uganda, drug-resistant typhoid cases are expected to decrease by 74%, and more than 1,400 related deaths will be averted.**

iii. Cost-effectiveness of a TCV vaccination program against typhoid fever in relation to other interventions in place

Findings from a study by Pitzer, et al. (2014) predicting the impact of vaccination on the transmission dynamics of typhoid in South Asia **show that combining vaccination with ongoing improvements in sanitation is expected to lead to a sustained decline in typhoid incidence** under most scenarios and could potentially lead to elimination as shown in the figure below. The study explored the potential impact of improvements in water quality and sanitation, with and without vaccination, under a variety of assumptions about the proportion of transmission due to carriers and the proportion of transmission that is water-borne (and therefore potentially reduced through such broad-scale interventions). Findings showed **that when improvements in water quality/sanitation were modelled together with vaccination, most of the model-predicted decline in incidence came from the impact of sanitation.** Hence, the model predicted that vaccination helps speed up the reduction in incidence when carriers are less important and offers additional benefit over sanitation alone in the long run when water-borne transmission is less important.

Figure 6: Combined impact of sanitation and vaccination on the projected weekly incidence of typhoid



Pitzer VE, Bowles CC, Baker S, Kang G, Balaji V, et al. (2014) Predicting the Impact of Vaccination on the Transmission Dynamics of Typhoid in South Asia: A Mathematical Modeling Study. PLOS Neglected Tropical Diseases 8(1): e2642. https://doi.org/10.1371/journal.pntd.0002642
https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0002642

Bottom line message:

dd) **A recent model predicts that combining TCV with ongoing improvements in sanitation is expected to lead to a sustained decline in typhoid incidence under most scenarios and could potentially lead to elimination.**

iv. The cost-benefit of TCV introduction in RI Vs. no vaccine for typhoid disease

Immunization is a priority intervention with **potential economic benefits beyond just health benefits**. Results from a systematic literature review by Ozawa, et al. (2012) aimed at documenting available evidence on the economic benefits of vaccines in LMICs from 2000 to 2010 show that vaccination in LMICs brings important economic benefits including greater future wage-earning capacity and cost savings from averting disease outbreaks[90]. The review also identified evidence that **vaccinations provide long-term and societal economic benefits such as morbidity-related productivity gains, averted catastrophic health expenditures, growth in**

[90] Ozawa, S., et al., 2012. Cost-effectiveness and economic benefits of vaccines in low-and middle-income countries: a systematic review. *Vaccine*, *31*(1), pp.96-108.

gross domestic product (GDP), and economic implications of demographic changes resulting from vaccination.

While vaccines are considered to be a cost-effective public health intervention, implementation has become increasingly challenging. An analysis of the cost-benefit of typhoid fever immunization programmes in India by Poulos et al. (2004) illustrating why typhoid vaccination programmes may often appear to be unattractive to public-health officials who adopt a public budgetary perspective, concluded that under many plausible sets of assumptions, public-sector expenditure on typhoid vaccination does not yield comparable public-sector cost savings[91]. The findings showed that while there are many situations in which different vaccination programmes will make economic sense, public-health officials should adopt a societal perspective on the economic benefits of vaccination. This statement was found to be true especially when public decision-makers recognized that (a) blood culture-positive cases underestimate the incidence of typhoid fever and (b) avoided costs of illness represent a significant underestimate of the actual economic benefits to individuals of vaccination.

Bottom line message:

ee) **Vaccination in LMICs brings important economic benefits, including greater future wage-earning capacity and cost savings from averting disease outbreaks. Evidence shows that vaccinations provide long-term and societal economic benefits such as morbidity-related productivity gains, averting catastrophic health expenditures, growth in gross domestic product (GDP), and economic implications of demographic changes resulting from vaccination.**

4. OPERATIONAL CONSIDERATIONS

i. Vaccine availability

WHO has prequalified two TCVs from different manufacturers so far. As of May 2022, data from UNICEF product menu on Gavi-supported vaccine products that UNICEF procures on behalf of countries shows that TCV supply exceeds demand from 2022 to 2025. https://www.unicef.org/supply/media/13181/file/Gavi-product-menu-May-2022.pdf

In line with WHO recommendations, Gavi provides support for nationwide introduction of TCV into the routine immunization schedule through vaccine co-financing and, depending on the country context, a targeted one-time catch-up immunization of up to 15 years of age based on local typhoid epidemiology[92]. According to the information on the Gavi website, Gavi funds the vaccine

[91] Poulos, C., et al., 2004. A cost-benefit analysis of typhoid fever immunization programmes in an Indian urban slum community. *Journal of Health, Population and Nutrition*, pp.311-321.

[92] Gavi Typhoid vaccine. https://www.gavi.org/types-support/vaccine-support/typhoid#:~:text=appropriate%20immunisation%20strategies.-,Gavi%20support,based%20on%20local%20typhoid%20epidemiology [Accessed on 05 October 2022]

itself, injection supplies and a grant to cover introduction costs. Support for TCV was Board-approved in late 2017, and the application window opened mid-2018.

ii. The current price per TCV dose

The direct TCV vaccine cost at Gavi price (both Typbar and TYPHIBEV) is currently **$1.39 per dose**. Direct vaccine cost includes **only the cost of the vaccine and does not include any associated costs**, including but not limited to freight, cold-chain costs, administrative costs, customs clearance and wastage or cost derived from the vaccine delivery. https://www.gavi.org/sites/default/files/document/support/TCV-Vaccine-Profiles.pdf

Similarly, data from UNICEF product menu on Gavi-supported vaccine products as of May 2022 shows the projected weighted average TCV price per dose at $1.07 in 2022, $1.39 in 2023 and 2024, and pending tender in 2025, as shown in the table below:

Table 26: The projected weighted average TCV price per dose at $1.07 in 2022, $1.39 in 2023 and 2024, and pending tender in 2025

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PRODUCT MENU FOR VACCINES SUPPLIED BY UNICEF FOR GAVI, THE VACCINE ALLIANCE

Vaccine	Form	Presentation	Number of awarded manufactures	Storage space (cm³/dose)		VVM	Product availability				Projected Weighted Average Price per Dose			
				Vaccine	Diluent		2022	2023	2024	2025	2022	2023	2024	2025
TCV	Liquid	5 ds	1	2.9	-	VVM30 Yes	Supply exceeds demand	Supply exceeds demand	Supply exceeds demand	Supply exceeds demand	$1.07	$1.39	$1.39	Pending Tender

Notes on general product availability:

- Supply exceeds current demand.
- Limited supply. Requires planning to ensure adequate supply.
- Very limited supply.
- No established demand. Availability needs to be determined based on needs.

Source: https://www.unicef.org/supply/documents/typhoid-conjugate-vaccine-tcv-price-data

iii. The cost per fully immunized child in Uganda

PATH estimated the government cost per child vaccinated at **$0.48 if TCV is introduced in a nationwide campaign followed by RI targeting children aged 1 to <15 years**[93].The estimates assumed that Gavi would fully finance the procurement cost of the vaccine, and injection supplies and provide an operational grant support of $0.65 per targeted child for the campaign.

This estimate assumed that for the routine, the government would be responsible for an average co-financing of **$0.20 per dose** during the period, injection supplies, and introduction/recurrent costs (Gavi covers remaining procurement costs) between 2023-2027. This estimate also assumed that if the country introduced TCV in 2023, **Gavi would provide a vaccine introduction grant** of **$0.80 per child** in the birth cohort to cover for introduction activities. It should be noted that Uganda is classified as an initial self-financing (ISF) for the next five years according to Gavi's

[93] PATH: TyVAC cost data presentation to the UNITAG working group on typhoid on August 12, 2022.

latest country co-financing fact sheet (LICs with gross net income per capita below US$ 995 in 2019 were classified as "initial self-financing).

PATH also calculated that should TCV be introduced in **RI only, the government would incur a cost of $1.38 per child** vaccinated as demonstrated in Table 27.

Table 27: Summary cost estimates, 2023-2027

Scenarios	Number of children vaccinated	Total vaccine program costs (procurement + delivery)	Total Gavi contribution	Country cost	Government cost per child vaccinated
Scenario 1: nationwide campaign (1 – <15-year-olds) and nationwide RI	25.5M	$66.2M	$54.0M	$12.2 M	$0.48
Scenario 2: nationwide RI only	7.6M	$22.9M	$12.4M	$10.5 M	$1.38

TYPHOID VACCINE ACCELERATION CONSORTIUM PAGE 24

Source: PATH: TyVAC cost data presentation to the UNITAG working group on typhoid on June 15, 2023.

The evaluation assumed that vaccine and supplies price (UNICEF cost per unit: vaccine at$1.39; syringes at $0.04; and safety boxes at $0.58 per -100 syringes per box) remain constant from 2023-2027, vaccine co-financing status to stay constant during period, and no shipping, handling, and insurance costs were included. It was also noted that all costs used in this analysis are subject to fluctuations and that the costs **noted above should be viewed as estimates that are impacted by many factors and subsequently may change.**

iv. The estimated cost of introducing TCV to infants in Uganda

PATH analyzed two vaccine introduction scenarios in Uganda- RI only and Campaign plus RI - and estimated costs associated with the vaccine introduction in the country as summarized in the tables below.

Table 28: Scenario 1: Nationwide routine only (9-months-olds)

Vaccinated children and doses needed	2023	2024-2027	Total
Target population	1,658,827	6,771,420	8,430,246
Total children vaccinated	1,492,944	6,094,278	7,587,221
Total vaccine doses required	2,129,640	7,181,345	9,310,986
Costs (US$)			
Total Vaccine procurement cost	2,960,200	9,982,070	12,942,270
Total injection supplies procurement costs	78,706	309,803	388,508
Total procurement cost	3,038,906	10,291,873	13,330,778
Country vaccine co-financing amount	425,928	1,436,269	1,862,197
Total country procurement cost	504,634	1,746,072	2,250,705
VIG received from Gavi	1,327,061	0	1,327,061
Recurrent costs (non-vaccine)	1,881,109	7,678,790	9,559,899
Total country cost	1,058,682	9,424,861	10,483,543

Source: PATH: TyVAC cost data presentation to the UNITAG working group on typhoid on June 15, 2023.

The estimates show that if Uganda is to introduce TCV via RI only, 7.6 million children would be vaccinated from 2023 to 2027 at an estimated country cost of approx. $10.5 million. Routine delivery costs were based on financial cost per dose in Zambia, and incremental costs per dose for PCV inflation were adjusted to $1.26 (2022 USD)[94]. However, it was noted that the cost estimates were based on existing literature and data, not detailed costing analyses.

Table 29: Scenario 2: Nationwide campaign (1 – <15-year-olds) and nationwide RI for 9-months-olds

Vaccinated children and doses required	Campaign	Routine		Total
	2023	2023	2024-2027	2023-2027
Target population	19,924,959	1,658,827	6,771,420	28,355,205
Total children vaccinated	17,932,463	1,492,944	6,094,278	25,519,684
Total vaccine doses required	19,924,959	2,129,640	7,181,345	29,235,944
Costs (US$)	Campaign	Routine		
Total vaccine only procurement cost	27,695,692	2,960,200	9,982,070	40,637,963
Total injection supplies procurement costs	912,564	78,706	309,803	1,301,072
Total procurement cost	28,608,256	3,038,906	10,291,873	41,939,035
Country vaccine co-financing amount	0	425,928	1,436,269	1,862,197
Total country procurement cost	0	504,634	1,746,072	2,250,705
Gavi operational grant/VIG received	12,951,223	1,327,061	0	14,278,284
Immunization delivery costs (non-vaccine)	14,704,619	1,881,109	7,678,790	24,264,518
Total country costs	1,753,396	1,058,682	9,424,861	12,236,939

On the other hand, the cost of introducing TCV via a nationwide campaign targeting approximately 19.9 million children aged 1 to <15 years in Uganda was estimated to be roughly USD$1.8M, on the assumption that the campaign starts in 2023 targeting to vaccinate a total of 17.9M children <15 years of age (19.9M doses) at a 90% coverage and 10% wastage rate with no buffer stock included. Campaign delivery costs were based on the incremental financial cost of oral cholera

[94] Guthrie, T., et al., 2016. *Costing and financing analyses of routine immunization in Uganda*. Technical report. http://www. Immunization costing. org, accessed July.

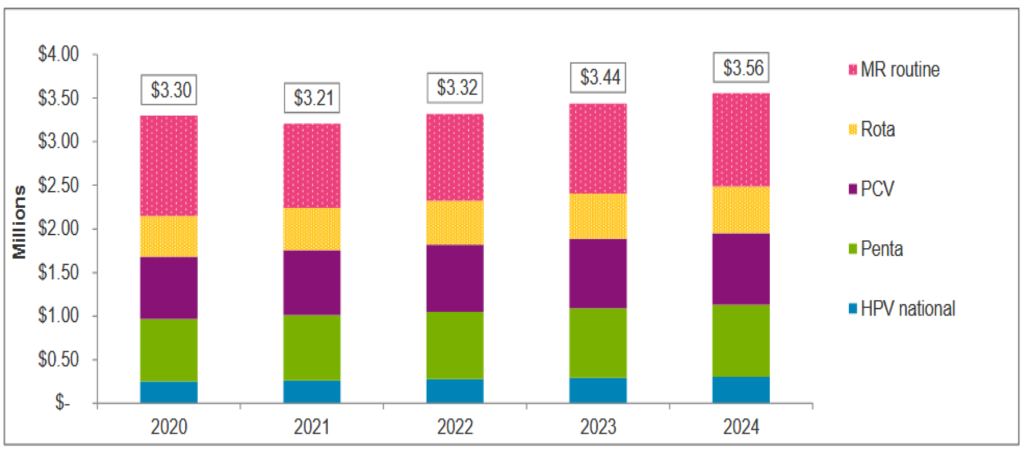
vaccine campaign in Ethiopia[95]. The cost per dose inflation was adjusted to $0.82 (2022 USD) including introduction and operational costs.

The estimates further show that if the country is to introduce TCV via a nationwide campaign and RI targeting the same age group, 25.5 million children would be vaccinated from 2023 to 2027 at an estimated total country cost of approx. USD$12.2 million.

The key difference between the two scenarios is that the campaign scenario is likely to have immediate impact on typhoid disease burden while benefits of RI accrue over time. Moreover, vaccinating a larger cohort via campaign lowers the cost per fully immunized child due to Gavi campaign support. In addition, including a campaign mode allows for the opportunity to receive operational grant to offset introduction costs for the RI program.

Table 30:Co-Financing Projections for 2020-2024[96]

Co-financing projections for 2020 - 2024



	2020	2021	2022	2023	2024
HPV national	$ 251,407	$ 263,772	$ 276,832	$ 290,200	$ 303,855
Penta	$ 715,997	$ 747,030	$ 772,434	$ 798,236	$ 824,381
PCV	$ 715,997	$ 747,030	$ 772,434	$ 798,236	$ 824,381
Rota	$ 465,228	$ 485,163	$ 501,477	$ 518,041	$ 534,821
MR routine	$ 1,150,244	$ 962,703	$ 997,562	$ 1,033,020	$ 1,069,006
Total	**$ 3,298,872**	**$ 3,205,697**	**$ 3,320,739**	**$ 3,437,733**	**$ 3,556,444**

[95] Immunization Costing Action Network (ICAN): A systematic review of immunization delivery cost in low-and middle-income countries. https://static1.squarespace.com/static/556deb8ee4b08a534b8360e7/t/5e4e9418dbed0d592f94d8bf/1582208033613/1.+ICAN+Summary+Report_29January20.pdf

[96] https://www.gavi.org/sites/default/files/document/co-financing-information-sheet-ugandapdf.pdf

Table 31: Projection of TCV Program Cost

	2025	2026	2027	2028	2029
Immunized children	22,883,562	1,808,861	1,843,286	1,877,711	1,912,136
Cost of vaccines and supplies[97]	$599,782	$519,319	$529,169	$539,018	$548,868
Immunization delivery cost[98]	$2,722,517	$2,279,165	$2,322,541	$2,365,915	$2,409,292
Total cost to government	**$3,322,299**	**$2,798,484**	**$2,851,710**	**$2,904,933**	**$2,958,160**

TCV program assumptions include TCV introduction in 2025, starting with a campaign followed by the start of routine immunization targeting 23,454,583 individuals aged 1 to 15 years with an anticipated coverage of 90% for both the campaign and routine immunization.

Table 32: Projection of Co-Financing for TCV

	2025	2026	2027	2028	2029
Co-financing for TCV doses (US$)	Routine: $506,237 Campaign: $0	Routine: $427,336	Routine: $435,436	Routine: $443,535	Routine: $451,636

The cost assumptions for co-financing projections for TCV include vaccine and injection supplies (syringes and safety boxes)provided for free by Gavi. During the routine immunization, the vaccine costs $0.20 co-financing per dose,$0.04 per syringe, and $0.58 per safety box. However, the shipping and handling costs have not been accounted for. The immunization delivery cost during the campaign is $0.82 per dose delivered and $1.26 per dose delivered. Additionally, the Gavi support during the campaign, the operational grant support equals $0.65 per targeted child, and the vaccine introduction grant equals $0.80 per child in the birth cohort.

v. The potential wastage rate of administering TCV to children at 9 months of age

Typhoid conjugate vaccines are available in 5-dose/vial presentation with an indicative wastage rate of 10% in routine settings. However, according to PATH estimates, this rate was estimated to further reduce in a campaign scenario. In addition, Gavi estimates the 2022 wastage adjusted vaccine cost per fully immunized person to be $1.19[99].

Bottom line messages:

[97] Cost of vaccine and supplies = co-financing for routine vaccines + safety boxes cost for routine + Syringes cost for routine

[98] Immunization delivery cost = (cost per dose X number of doses delivered) + (cost per dose X number of doses delivered) – Vaccine Introduction Grant – Campaign Operational Grant Support

[99] https://www.gavi.org/sites/default/files/document/support/TCV-Vaccine-Profiles.pdf

- **ff) Gavi will provide support for nationwide introduction of TCV into the routine immunization schedule through vaccine co-financing and a targeted one-time catch-up immunization of up to 15 years of age based on local typhoid epidemiology.**
- **gg) The direct TCV vaccine cost at Gavi price (both Typbar and TYPHIBEV) is currently $1.39 per dose. (Direct vaccine cost includes only the cost of the vaccine and does not include any associated costs).**
- **hh) The estimated government cost per child vaccinated is $0.48 if TCV is introduced in a nationwide campaign followed by RI targeting children aged 1 to <15 years.**
- **ii) Estimates show that if Uganda introduces TCV via a nationwide campaign (1 to <15-year-olds) and RI targeting 9 month olds, 25.5 million children would be vaccinated from 2023 to 2027 at an estimated total country cost of about USD $12.2 million.**
- **jj) The co-financing cost for vaccines will be lower than $500,000per year. Vaccines for use in the campaign will be provided free of charge by Gavi.**

5. HEALTH POLICY AND PROGRAMMATIC CONSIDERATIONS

i. TCV characteristics

While most characteristics for the two TCVs are similar, they mainly differ in composition and shelf life. Product information for vaccines and cold chain equipment shows that Typbar-TCV is a purified Vi-Capsular Polysaccharide of S. Typhi strain Ty2 conjugated to tetanus toxoid carrier protein in isotonic saline; TYPHIBEV is a Vi polysaccharide obtained from genetically modified Citrobacter freundii sensu lato 3056 and conjugated to CRM197[100]. Also, Typbar has a longer shelf life of 36 months while TYPHIBEV has a shelf life of 24 months.

As detailed in Annex 2, below is a summary of some of the TCV characteristics that similar:.

1. Both are recommended for storage under normal temperature of +2°C to +8°C.
2. Both have a vaccine vial monitor (VVM30)

In summary, the detailed TCV characteristics indicate that addition of TCV into the existing EPI systems would be easy and less constraining in regard to vaccine storage and administration.

ii. Proportion of children between 6 months and 2 years reached through UNEPI

Data from MoH as of October 04, 2022, shows that the program targets approximately 4.3% of 1,901,151 surviving infants aged 0 to 11 months for; MR1 at 9 months, MR2 at 18 months; YF at 9 months for vaccination; vitamin A at 6months; and deworming at 1 year as shown in the figure below:

[100] Gavi, The Vaccine Alliance. Product information for vaccines and cold chain equipment. Available from: https://www.gavi.org/sites/default/files/document/support/TCV-Vaccine-Profiles.pdf [Accessed 14 September 2022].

Figure 7: Proportion of children between 6 months and 2 years reached through UNEPI

Population Category targeted	Target Proportion	Target Population
0 – 11 months *(Live Births)*	4.85%	2,144,321
0 – 11 months *(Surviving Infants)*	4.30%	1,901,151
6months-59 months *Vitamin "A"*	16.20%	7,162,474
1year – 14 years *Deworming*	49.30%	21,796,911
WCBA 15 – 49 years *TT Immunization*	23%	10,168,944
Girls 10 years *HPV Immunization*	1.53%	680,878
Pregnant women *TT Immunization*	5%	2,210,640
Non pregnant women *TT Immunization*	18%	7,958,304

Source: MoH data from the UNEPI M&E specialist accessed on October 7, 2022

iii. Coverage and timeliness of other vaccines administered at 9 months of age in Uganda

MoH coverage data as of October 04, 2022, showed that access to measles vaccine administered at 9 months of age has improved over the last 4 years from 80% in financial year 2019/2020 to >90% in 2020/2021 and 91% in 2021/2022, hence indicating good access to children aged 9 months of age. This means that introducing TCV in the program would be feasible and would have a high coverage.

Figure 8: Coverage of other vaccines administered at 9 months of age in Uganda 2018 - 2022

Antigen	2018-2019	2019-2020	2020-2021	2021-2022
BCG	88%	79%	83%	**85%**
DPT1	103%	92%	97%	**98%**
DPT2	95%	87%	91%	**92%**
DPT3	93%	85%	91%	**92%**
IPV	88%	73%	90%	**91%**
Measles	87%	80%	90%	**91%**
PCV 1	100%	92%	97%	**99%**
PCV 2	94%	87%	91%	**93%**
PCV 3	92%	85%	91%	**93%**
Polio 0	74%	72%	77%	**79%**
Polio 1	103%	98%	97%	**98%**
Polio 2	94%	97%	91%	**93%**
Polio 3	92%	84%	91%	**93%**
Rotavirus 1	96%	90%	94%	**94%**
Rotavirus 2	88%	84%	87%	**86%**
HPV1	115%	95%	96%	**105%**
HPV2	65%	38%	56%	**56%**
TT2+_Preg Women	75%	58%	64%	**58%**
TT2+_Non Preg Women	6%	3%	5%	**3%**

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Source: MoH -UNEPI performance data to UNITAG as of October 04, 2022

Table 33:Uganda Routine Immunization Schedule 2023

Routine Immunization NEW Schedule

Vaccine/ Antigen	Dosage	Doses	Min. Interval per dosage	Min. Age at Start	Mode of Administration	Site of Administration	Storage Temperature (°C)	Remarks
BCG	0.05ml up to 11/12 0.1ml after 11/12	1	N/A	At birth or first contact after birth	Intra dermal	Rt. Upper arm	+2 to +8 °C	Only use diluent provided
DPT-HepB-Hib	0.5 ml	3	4 weeks	At 6 wks or first contact after 6 weeks	IM	Lt thigh upper outer aspect	+2 to +8 °C	Do not freeze
Hep B birth dose	o.5	1	None	At birth or within 24 Hours after birth up to 7 days	IM	Intramuscular, Outer Upper Aspect of Left Thigh	+2 to +8 °C	Do not freeze
OPV	2 drops	3	4 weeks	At birth or after 6 wks	Oral	mouth	+2 to +8 °C	It is not altered by freezing
IPV	0.5 ML	2	8 Weeks	6 Weeks	IM	Intramuscular, right upper thigh	+2^{0}C to +8^{0}C	DO NOT FREEZE
Rotavirus vaccine	1.5 ml	2	4 Weeks	6 Weeks	Oral	Mouth	+2 to +8 °C	Do not freeze
Yellow Fever	0.5	1	None	9 Months	IM	Intramuscular, Upper right Arm	+2 to +8 °C	It is not altered by freezing
Measles- Rubella	0.5ml	2	9 Months	9 months	Subcutaneous (SC)	Lt Upper Arm	+2 to +8 °C	Only use diluent provided
PCV	0.5ml	3	4 weeks	At 6 wks or after 6 weeks	IM	Rt. Thigh upper outer aspect	+2 to +8 °C	Do not freeze
HPV	0.5ml	2	6 months	10 year old girls in school and in the community	IM	Upper arm	+2 to +8 °C	Do not freeze
Tetanus Toxiod diphtheria(Td)	0.5ml	5	Td1- First contact with WCBA, Td2 dose after 4 weeks, Td3 Dose after 6 months , Td 4 dose after I year, Td 5 dose after 1 year.	First contact with pregnant or women of child bearing age (15-49 years)	IM	Upper arm	+2 to +8 °C	Do not freeze

Source: MoH -UNEPI performance data to UNITAG as of October 04, 2022

i. Impact on human, technical, logistics and financial resources if TCV is introduced in the immunization program in Uganda

TCV introduction in the immunization program may have minimal impact on the existing human, technical and logistical resources. Since TCV can be safely co-administered with MR which, according to MoH coverage data as of October 04, 2022, shows good access, its introduction will not require additional human resources. However, human resource training on a new vaccine introduction may be required, although several administration characteristics, including mode of administration (intramuscular) and storage temperature (+2°C to +8°C) are similar to most of the existing vaccine characteristics already in the program, as shown in the table below. Likewise, there may be a need to update the immunization card and the monitoring and evaluation (M&E) tools to include the new vaccine, all of which are supported by Gavi as new vaccine introduction costs.

ii. AEFI monitoring of vaccines administered at 9 months of age

Uganda has an **AEFI surveillance system** that was established to rapidly detect and respond on time to AEFI, identify, correct and prevent immunization errors related reactions, facilitate AEFI causality assessment, recognize clustering or unusually high rates of AEFI (even if considered mild), identify signals of unknown vaccine reactions and generate new hypotheses, and effectively communicate with parents, the community, media and other stake holders, to create awareness on AEFIs[101]. The system structure allows for both monthly routine reporting as well as efficient and immediate reporting and investigation of severe and serious AEFI. As such, the program is currently administering measles and rubella vaccine to children aged 9 months in the program whose AEFIs are being monitored and investigated.

Considering TCV and MR have comparable SAEs as shown in the TCV safety and tolerability when co-administered with MR evidence, TCV AEFIs will be easy monitor and report as the program would leverage on the existing AEFI monitoring structures for MR. However, health workers would benefit from refresher trainings on AEFIs following TCV introduction.

iii. The perception of the community on typhoid disease, AMR and having an additional vaccine administered at 9 months

A qualitative study by Atuyambe et al. (2020) assessing the spread of typhoid fever in Kampala city found that although majority of the participants were aware of the signs and symptoms of typhoid, there were knowledge gaps in the community's understanding of typhoid fever[102]. The study explored community understanding of typhoid to identify risk factors that propagated the 2015 typhoid outbreak in Kampala and the surrounding districts. Findings from participants revealed a few misconceptions about typhoid, including the perception that typhoid was an airborne disease caused by fog and affecting only specific nationals. In this regard, the study reported that most participants derived their knowledge on typhoid symptoms from observing typhoid patients, health education from the various communication channels, and lived experiences by recovering patients. The participants, including community leaders, health care providers in health facilities, health managers at district and national levels, officials in relevant government departments both at national and subnational levels and select typhoid patients, were engaged through focus group discussions (FGDs), in-depth interviews (IDIs) with select typhoid patients from health units and key informant interviews (KIIs).

In addition, the study further assessed participants' understanding of typhoid prevention, and the results show that most participants understood the strategies for preventing typhoid fever. Participants identified key short and long-term strategies for preventing typhoid, including community sensitization on improving personal, food and water hygiene both at workplaces and homes; vaccination of populations at risk against typhoid; promotion of good hygiene practices; ensuring aggressive improvements in access to sustainable safe water and sanitation in order to prevent further spread of typhoid in urban areas; an innovative and functional Health Management

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[101] Guidelines-for-Adverse-Events-Following-Immunization-AEFI, 2012, accessed via https://www.nda.or.ug/wp-content/uploads/2022/02/Guidlines-for-Adverse-Events-Following-Immunisation-AEFI.pdf

[102] Atuyambe, L., Atusingwize, E. and Kayemba, C.N., 2020. "The Underground Water Sources were Contaminated" A Qualitative Assessment of the Spread of Typhoid Fever in Kampala City, Uganda.

Information System (HMIS) to prevent typhoid outbreak by providing early warning information to detect possible epidemics; and a well-coordinated multi-disciplinary outbreak response team; proper resource mobilization at national, district and village levels. As quoted in the report, a national-level KI stressed that *"if all health facilities submitted accurate real-time data, appropriate time trend-analysis could be used for early detection of typhoid outbreak through defined alert thresholds"*.

Similarly, a community health survey by Karen et al. (2012) assessing the large outbreak of typhoid fever associated with a high rate of intestinal perforation in Kasese district, Uganda (2008–2009) found that majority of the community members were willing to use a vaccine to protect their families from typhoid fever. Findings from this community survey in 4 sub-counties (Bugoye, Kitswamba, Kyabarungira, and Maliba) within the most severely affected health sub-district (Busongora North) in Kasese district show that of 315 heads of households surveyed, 311 (99%) were willing to take a typhoid vaccine if it were offered at no cost, whereas 295 (95%) of 312 reported willingness to pay a fee for the vaccine[103].

Similarly, findings from Malawi also showed that affected communities understood typhoid and its prevention strategies. A study by Blum et al. (2014) investigating the acceptability of typhoid vaccine during a typhoid fever outbreak in Neno District, Malawi, found that respondents considered typhoid fever as an 'extremely dangerous' disease because of its rapid spread, the debilitating conditions it produced, the number of related fatalities, and the perception that it was highly contagious, although skeptical about the effectiveness of WASH interventions. Hence, the perceived severity of typhoid and fear of exposure, uncertainty about the effectiveness of WASH measures, and widespread belief in the efficacy of vaccines in preventing disease resulted in an overwhelming interest in receiving typhoid vaccine during an outbreak[104].

Overwhelmingly, most researched community members are aware of typhoid, its impact and related complications and are ready to accept a Typhoid vaccine, which is a favorable consideration.

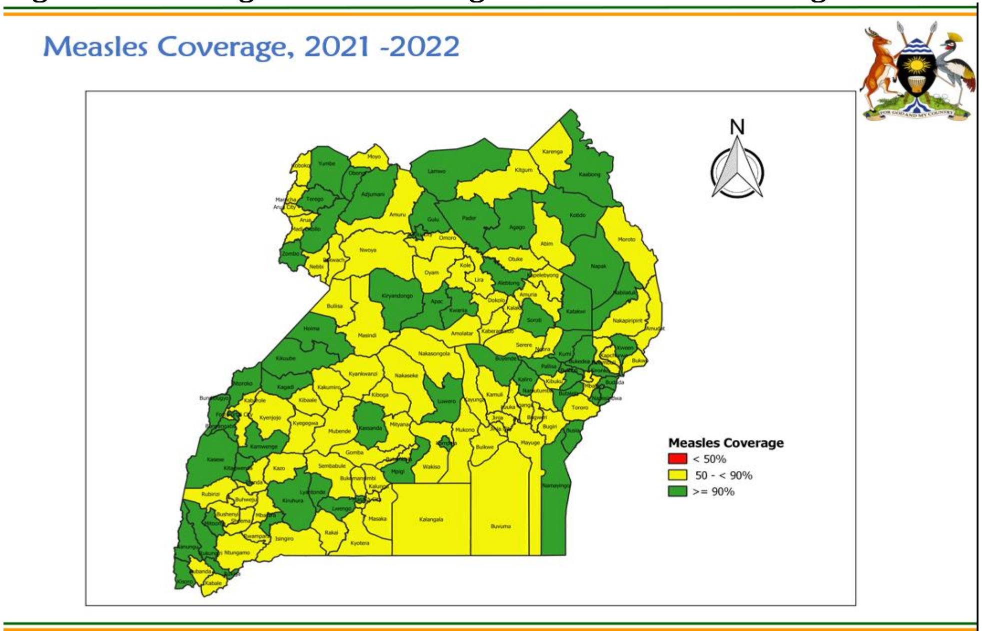
iv. The performance of vaccines given at 9 months in underserved/hard-to-reach communities in Uganda

According to MoH, the HMIS – tool used to track vaccine coverage - does not disaggregate access data by community category, save for refugees whose data is included among the nationals' data. However, available measles coverage data as of October 04, 2022, shows poor access (<90%) among island districts, including Kalangala at 73.3%, Buvuma at 79.9%, and Buikwe at 82.6% as shown in the map below.

[103] Karen P. Neil, et al., 2012. A Large Outbreak of Typhoid Fever Associated With a High Rate of Intestinal Perforation in Kasese District, Uganda, 2008–2009, *Clinical Infectious Diseases*, Volume 54, Issue 8, 15 April 2012, Pages 1091–1099, https://doi.org/10.1093/cid/cis025

[104] Blum, L.S. et al., 2014. Formative investigation of acceptability of typhoid vaccine during a typhoid fever outbreak in Neno District, Malawi. *The American Journal of Tropical Medicine and Hygiene*, *91*(4), p.729.

Figure 9: Showing Measles coverage for FY 2021/2022 in Uganda



Source: MoH -UNEPI performance data to UNITAG as of October 04, 2022

Bottom line messages:

- kk) **While most characteristics for the two TCVs are similar, they mainly differ in composition and shelf life**.
- ll) **Vaccine coverage data as of October 2022 showed that access to measles vaccine administered at 9 months of age has improved during the last 4 years from 80% in FY2019/2020 to 91% in FY2021/2022. This is a strong indicator for accessing children aged 9 months, which means TCV introduction would be feasible and likely have high coverage.**
- mm) **Since TCV can be safely co-administered with MR, which, according to MoH coverage data, shows good access, its introduction will not require additional human resources.TCV campaigns offer an opportune time to identify zero-dose and under-immunized children.**
- nn) **A recent qualitative study found that most participants were aware of typhoid's signs and symptoms, yet there were knowledge gaps and misconceptions about typhoid, including the perception that typhoid was an airborne disease caused by fog. Most participants, however, understood the strategies for preventing typhoid fever, including vaccination of at-risk populations; promotion of good hygiene practices; ensuring aggressive improvements in access to sustainable safe water and sanitation to prevent the further spread of typhoid in urban areas.**

6. OTHER CONSIDERATIONS

a) TCV Introduction in other endemic countries

Pakistan, Liberia, Zimbabwe, Nepal and Malawi recently introduced TCV through campaigns and routine childhood immunizations, providing protection for this vulnerable population. Based on the WHO SAGE recommendations for TCV introduction, Gavi announced support for TCVs in November 2017 and allocated $85 million of funding support for Gavi-eligible countries.

In early 2019, as a response to a typhoid fever outbreak, the Zimbabwe Ministry of Health carried out an emergency mass TCV campaign through the WHO and subsidized with Gavi funding. This was the first programmatic use of TCV in Africa and resulted in decreased typhoid cases[105].

In November 2019, Pakistan became the first country to introduce TCV into its routine immunization schedule, a decision driven by an XDR typhoid outbreak. Pakistan used a phased approach to ultimately vaccinate approx. 23 million children with TCV. Nearly 30 million children were vaccinated in campaigns in Sindh and Punjab provinces. Results from the outbreak response in Pakistan show TCV was 95% effective against blood-culture-confirmed typhoid fever and 97% effective again XDR typhoid fever[106].

Liberia was the first African country to introduce TCV in a non-outbreak setting, starting with a week-long campaign in April 2021 for children aged 9 months to younger than 15 years, followed by integration into the country's routine immunization program.

In May 2021, Zimbabwe began its large national TCV campaign, aiming to vaccinate 6.2 million children aged 9 months to younger than 15 years. Following this campaign, through their EPI, TCV will be available for administration alongside the measles vaccine for all 9-month-old infants[107].

Nepal introduced TCV in April 2022, beginning with a 3-week campaign to reach 7 million children aged 15 months to 15 years old at 50,000 vaccination sites across the country[108]. Nepal, the fourth country to introduce TCV is a typhoid-endemic country estimated to have one of the highest typhoid burden globally with increasing rates of drug-resistant typhoid [109].

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[105] Olaru ID, Mtapuri-Zinyowera S, Feasey N, Ferrand RA, Kranzer K. Typhoid Vi-conjugate vaccine for outbreak control in Zimbabwe. Lancet Infect Dis2019; 19:930.
[106] Yousafzai MT, Karim S, Qureshi S, et al., 2021. Effectiveness of typhoid conjugate vaccine against culture-confirmed Salmonella enterica serotype Typhi in an extensively drug-resistant outbreak setting of Hyderabad, Pakistan: a cohort study. Lancet Glob Health2021; 9:e1154–62.
[107] Oberman E. Typhoid conjugate vaccine arrives in Zimbabwe,2021. https://www.coalitionagainsttyphoid.org/typhoid-conjugate-vaccine-arrives-in-zimbabwe /. Accessed 23 September 2022.
[108] Coalition against Typhoid: Take on Typhoid Newsletter June 2022. https://www.coalitionagainsttyphoid.org/take-on-typhoid-newsletter-june-2022/ [Accessed on 01 October 2022].
[109] UNICEF. Nepal introduces typhoid vaccine into routine immunisation across the country. https://www.unicef.org/nepal/press-releases/nepal-introduces-typhoid-vaccine-routine-immunisation-across-country [Accessed on 01 October 2022]

TCV campaigns present an opportunity to identify zero-dose and under-immunized children. A recent case study from Nepal, based on the 2022 TCV introduction, highlights how children who presented for TCV can be screened for previous vaccines and referred for follow up vaccinations. In Nepal, micro planning prioritized low coverage or hard-to-reach communities and health workers were trained to identify and refer zero dose children[110].

Malawi conducted an intergrated TCV campaign in May 2023, offering Bopv and MR, as well as Vitamin A supplementation alongside TCV.More than 7 million children were reached with TCV in the week-long campaign[111].

Table 34: Gavi-supported TCV introductions as at 2023

Country	Introduction Strategy	Age	Rationale
Pakistan	Nationwide (phased) campaign; transition to routine immunization (RI) following campaign.	Campaign: 9 month to younger-than-15 years RI: 9 months	National epidemiological data; ecological conditions that promote typhoid transmission.
Liberia	Nationwide campaign; transition to RI following campaign.	Campaign: 9 months to younger-than-15 years RI: 9 months	Neighboring country, regional, and global data to project local burden and risk
Zimbabwe	Nationwide campaign (integrated with HPV & IPV); transition to RI following campaign.	Campaign: 9 months to younger-than-15 years RI: 9 months	High disease burden nationwide, esp. in younger age groups. Leverage 9 months co-administration with MR. Easier to reach children at 9 months vs. 18 or 24 months.
Nepal	Nationwide campaign; transition to RI following campaign,	Campaign: 15 months to younger-than-15 years RI: 15 months	National burden data; vaccine coverage/acceptance data; increase update of TCV + MCV2; crowded 9-month RI visit.

TYPHOID VACCINE ACCELERATION CONSORTIUM PAGE 19

Source: PATH: TyVAC Presentation on TCV to UNITAG's Typhoid Working Group on June 15, 2023.

110 https://zdlh.gavi.org/

111 https://www.coalitionagainsttyphoid.org/scenes-from-malawi/Accessed 14 November 2023

Bottom line messages:

- **oo) Pakistan began introduction of TCV in Sindh Province in November 2019. Pakistan completed its phased introduction in October 2022, reaching more than 30 million children in campaigns. TCV is now available nationwide in routine immunization.**
- **pp) Liberia and Zimbabwe introduced TCV into their routine childhood immunization programs in 2021. Liberia vaccinated more than 1.5 million children and Zimbabwe aimed to vaccinate more than 6 million children during the introduction campaigns. Nepal introduced TCV into its routine childhood immunization program in 2022 and aimed to vaccinate more than 7.5 million children during its introduction campaign. Malawi conducted an integrated TCV campaign in May 2023, reaching more than 7 million children.**
- **qq) More than 56 million children have been vaccinated during TCV campaigns to date.**

C. UNITAG CONCLUSIONS

Having carefully analyzed the evidence above, the UNITAG thus concludes:

1. Uganda is a typhoid-endemic country, with children under five being the most disproportionately affected. Persons with poor sanitation facilities are most at risk for the infection. In Uganda, definitive diagnostic tests for typhoid fever such as blood culture are usually unavailable, unaffordable, or inconsistently applied. Typhoid diagnosis and surveillance often rely on clinical judgment or the Widal test which has poor sensitivity and specificity.
2. Typhoid Intestinal Perforations (TIP) is a serious complication resulting from poorly or untreated typhoid. These cases require long hospital stays and need surgical procedures that are costly and unavailable in most lower health facilities.
3. Typhoid is typically treated with antibiotics, however increasing cases of Multi-Drug Resistant typhoid strains have been reported globally with resistance to three first-line antibiotics (chloramphenicol, ampicillin, cotrimoxazole). Multi-drug resistance has evolved to more extensively drug-resistant typhoid (XDR) and Uganda is among the top ten at-risk countries.
4. Typhoid Conjugate Vaccines are safe and immunogenic when administered as a single dose to children aged 9 months to 15 years of age. TCVs can be safely co-administered with other vaccines at 9 months of age such as Measles Rubella, Meningitis, and Yellow Fever Vaccine. Data from Malawi show that a single dose of TCV offers safe and durable protection up to 4 years.
5. Vaccination with TCV alongside investment in water, sanitation, and hygiene will drastically reduce typhoid cases in the country.
6. Establishment of baseline surveillance for the prevalence of typhoid Fever in Uganda be conducted to enable Impact Analysis post TCV introduction

D. UNITAG'S RECOMMENDATIONS

1. The UNITAG recommends the introduction of Typhoid Conjugate Vaccine in Uganda's routine immunization schedule as a single dose at 9 months, starting with a catch-up

campaign targeting 9 months to 15 years. This will reduce health inequity, address antimicrobial resistance, and reduce the occurrence of typhoid outbreaks. Having a catch-up campaign reaches a larger cohort and presents an opportunity to advocate for better WASH facilities which are critical in typhoid prevention.

E. OTHER CONSIDERATIONS

Roll-out options:

1. Full country introduction

A full country introduction poses the least logistical challenges. There are opportunities to administer one dose of TCV at 9 months of age with MCV1, -18 months of age with MCV2, recognizing that in many places the appreciable burden of typhoid fever starts to appear at 12 months of age.

2. Other Typhoid prevention and treatment strategies.

ANNEXES

1. MoH Request for guidance to NITAG

Telephone: General Lines: 256 – 417 – 712260
Permanent Secretary's Office: 256 – 417 – 712221
E-mail: ps@health.go.ug
Website: www.health.go.ug

THE REPUBLIC OF UGANDA

Ministry of Health
P. O. Box 7272
Plot 6, Lourdel Road,
Wandegeya
KAMPALA,
UGANDA

IN ANY CORRESPONDENCE ON
THIS SUBJECT PLEASE QUOTE NO. ADM:105/309/18

30th June 2022

The Chairperson
NITAG

Dear Sir,

REQUEST FOR NITAG's GUIDANCE AND RECOMMENDATION ON THE INTRODUCTION OF RTSS/AS01 MALARIA VACCINE AND TYPHOID CONJUGATE VACCINE

On behalf of the Ministry of Health and Uganda National Expanded Program on Immunization (UNEPI), I write to request for NITAG's guidance on the introduction of the RTSS vaccine as part of the currently recommended Malaria Control interventions to reduce under-five child mortality in Uganda. It is estimated that Uganda contributes 5.4% to the global burden of malaria, making it the third highest malaria burdened country, it also contributes 30,900 (3.5%) estimated deaths. (World Malaria Report, 2021).

The Ministry of Health (MOH) has followed with keen interest the developments around the RTSS/AS01. In 2021, WHO prequalified RTSS and in the same year, Gavi included RTSS in the Gavi supported vaccines list. In May 2022, Uganda expressed interest to introduce the malaria vaccine RTSS/AS01, including participation in the planning workshops/meetings to prepare the application package as part of the September 2022 process.

I similarly request NITAG's guidance on the introduction of Typhoid Conjugate Vaccine (TCV) as part of the routine infant immunization schedule to control Uganda's typhoid burden, particularly the alarming rates of drug-resistant Typhoid. WHO has prequalified two TCVs—Typbar TCV® and TYPHIBEV®. Gavi, the Vaccine Alliance, provides financial support for eligible countries to introduce TCV into their routine immunization programs.

Uganda is a typhoid endemic country, facing more than 41,700 cases of typhoid annually (2019). This is likely an underestimate due to the challenges and limitations with blood culture diagnosis. Typhoid recovery can be long and difficult, placing a high health toll and economic burden on Uganda's families and health system. Drug-resistant typhoid strains are a growing problem in Uganda. During the 2015 outbreak in Kampala, which caused more than 10,000 suspected cases of typhoid, one analysis found that 22.7% of isolates had multidrug resistance genes, and all showed reduced susceptibility to ciprofloxacin. As drug-resistant typhoid becomes more common, it will become more difficult to treat and force the use of more expensive and less readily-available treatment options. TCV can protect against transmission of drug resistant typhoid.

Uganda's immunization program is among the most successful government interventions in reducing child mortality. The country has consistently maintained high coverage rates with a vaccination coverage for tracer vaccines for 2021 at 91% for DPT3, 90% for MR1 and 90% for IPV. Adding the RTSS/AS01 and TCV will further strengthen the program and protection of our children.

I therefore write to request NITAG's guidance on the introduction the malaria vaccine RTSS/AS01 and TCV.

Yours sincerely,

Dr. Daniel J. Kyabayinze
FOR: DIRECTOR GENERAL HEALTH SERVICES

CC: Hon. Minister of Health
CC: Hon. Minister of State for Health –General Duties
CC: Hon. Minister of State for Health-Primary Health Care
CC: Permanent Secretary
CC: Director Health Services-Public Health
CC: Commissioner Health Services-NDC

ON THE Gavi MENU

The vaccines listed below are currently offered by Gavi and listed in the country application portal.

Vaccine group[1]	Typhoid Conjugate Vaccine	
Vaccine type[1]	Vi Capsular Polysaccharide-Tetanus Toxoid Conjugate Vaccine	
Serotypes[1]	Ty2 Salmonella Typhi	Vi polysaccharide produced from *Citrobacter freundii sensu lato* 3056 (Vi)
Presentation (doses per container, primary container type, pharmaceutical form)[1]	**TCV, 5 dose/vial, liquid**	
Product availability 2022[2]	supply exceeds demand	
Routine and/or campaign	routine and campaign	
WHO recommended vaccine schedule[3]	Single dose for infants and children over 6 months of age (suggested at 9 months or 15-18 months of age) and if possible, one-time single dose catch-up vaccination of children up to 15 years of age	
Estimated 2022 price per dose (USD)[4]	$1.07	
Doses per fully immunised person	1	
2022 price per fully immunised person (USD) [4]	$1.07	
Indicative wastage rate[4]	10%	
2022 wastage adjusted price per fully immunised person (USD)[4]	$1.19	
Manufacturer[1]	Bharat Biotech International	Biological Evans Limited
Vaccine trade name[1]	TYPBAR TCV	TYPHIBEV
Country of manufacture[1]	India	
National regulatory agency[1]	CDSCO (India)	
WHO PQ-date[1]	22/12/2017	04/12/2020
Administration[1]	intramuscular	
Secondary packaging[1]	Carton of 36 vials (180 doses) Dimensions: 11x11x4.5 cm	Carton of 48 vials (240 doses) Dimensions: 4.5 x 10.8 x 14.5
Shelf-life[1]	36 months at 2-8°C	24 months at 2-8°C
Cold chain volume per dose (cm^3)[1]	2.9 cm^3	
Vaccine vial monitor type[1]	Type 30	
Handling open vials[1]	WHO recommends that opened vials of this vaccine should be discarded 6 hours after opening or at the end of the immunization session, whichever comes first[6]	
Controlled Temperature Chain (CTC)[1]	n/a	
WHO PQ link[1]	https://extranet.who.int/pqweb/content/typbar-tcv-0	https://extranet.who.int/pqweb/content/typhibev%C2%AE-0
Remarks WHO[1]	n/a	
Notes	n/a	
Vaccine price commitments	n/a	

1 Source: WHO PQ webpage: WHO updates these webpages as new information on products becomes available. Please refer to these pages (WHO PQ link) for the most up-to-date information. For presentations no

2 Source: UNICEF PRODUCT MENU FOR VACCINES SUPPLIED BY UNICEF FOR GAVI, THE VACCINE ALLIANCE (https://www.unicef.org/supply/media/10501/file/Gavi-product-Menu-Dec-2021.pdf)

3 Source: WHO position paper: http://www.who.int/immunization/documents/positionpapers/en/

4 Source: Gavi Secretariat, see definitions tab for details

5 Source: Review of WHO vaccine wastage rate tool, 2021

6 Open vial policy currently under review by WHO PQ with consideration to change to: WHO recommends that vials may be used up to 28 days after opening, provided that the product is appropriately handled and s

World Health Organization

Comparison table of WHO prequalified typhoid conjugate vaccines (TCVs)

Characteristics	*Typbar TCV® (Bharat)*	*TYPHIBEV® (Biological E)*
Composition	*Salmonella* Typhi Vi polysaccharide conjugated to tetanus toxoid	Vi polysaccharide prepared from *Citrobacter freundii sensu lato*[a] conjugated to CRM *(1–3)*.
Immunogenicity	Single dose *Typbar TCV* elicited a protective immune response[b] among children and adults aged 6 months to 45 years *(2, 5–7)*.	Clinical trial immunogenicity data establish non-inferiority to *Typbar TCV*. Among individuals ≥6 months to <64 years of age, 95.59% had protective immune response *(8)*.[b]
WHO prequalification	December 2017	December 2020
WHO recommendation for programmatic use *(2)*	• WHO recommends TCV as a single dose (0.5 mL) for individuals ≥6 months to ≤45 years of age in typhoid-endemic regions. • WHO encourages routine programmatic administration of TCV at 9 months of age, or in the second year of life. Catch-up vaccination up to 15 years of age is recommended when feasible and supported by epidemiological data.	
Comparability of products	Based on non-inferiority data, these vaccines are expected to have similar performance despite difference in the conjugation protein.	
Efficacy/effectiveness (Blood-culture confirmed typhoid fever in endemic settings)	**Efficacy** Nepal: 79.1% (95% CI, 62.0%, 88.5%), 9 months–16 years of age, 2 years follow-up *(5)*. Malawi: 80.7% (95% CI: 64.2%, 89.6%), 9 months–12 years of age, 18–24 months follow-up *(6)*. **Effectiveness** India: 80.2% (95% CI: 53.2%, 91.6%), 9 months–14 years of age *(9)*.	Efficacy/effectiveness data are not yet available.
Coadministration	• TCV is recommended for routine programmatic use at the same time as other vaccine visits at 9 months of age or in the second year of life *(2)*. • Available data on *Typbar TCV* co-administration with measles-containing vaccines *(2)* and meningococcal conjugate serogroup A vaccine *(7)* show no evidence of interference with the immune response to either *Typbar TCV* or the coadministered antigen. • Coadministration data for *TYPHIBEV* are not yet available.	
Safety	Based on a comprehensive review of clinical data by WHO SAGE *(2)*,a review by the Global Advisory Committee on Vaccine Safety *(3)* and safety surveillance after routine introduction in India *(10)*, *Typbar TCV* has a favourable safety profile with no safety signals.	Based on clinical trial data *(8)*, *TYPHIBEV* has an acceptable safety profile with no safety signals to date. The Global Advisory Committee on Vaccine Safety is expected to review the data in the future.

[a]Vi polysaccharide from *Citrobacter freundii* is structurally similar and immunologically indistinguishable to Vi from *S.* Typhi *(1)*.
[b]No internationally agreed correlate or surrogate of protection has been identified for Vi conjugate vaccines *(4)*.

Appendix: Gavi Detailed Product Profiles for typhoid conjugate vaccines: https://www.gavi.org/about/market-shaping/detailed-product-profiles/

Sciences for Prosperity

COMBINED MALARIA REPORTS

Uganda National Academy of Sciences

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Sciences for Prosperity

July 11, 2023

The Director General Health Services
Ministry of Health
Uganda

REF: ADM 105/309/15

Dear Sir,

RE: GUIDANCE AND ADVICE ON PROPOSED INTRODUCTION RTS,S MALARIA VACCINE IN UGANDA'S ROUTINE IMMUNISATION PROGRAM

Uganda National Immunisation Technical Advisory Group (UNITAG) assures you of its highest compliments.
Reference is made to your letter to the UNITAG Chair dated June 30, 2022, in which you requested the committee to review relevant evidence and provide guidance and advice on the proposal to introduce the RTS,S/AS10 Malaria vaccine in Uganda's routine immunization schedule.

UNITAG has reviewed the evidence relevant to the burden of malaria disease in Uganda, the potential benefits and harms of the proposed interventions, the values and preferences of the target beneficiaries and their caregivers, the resource requirements of the intervention, equity, acceptability and feasibility of the proposed roll out plan and has come to the conclusion that the proposed interventions' benefits outweigh undesirable consequences in Uganda's context. Malaria continues to be a disease of public health concern particularly among children under 5 years. The proposed vaccine provided moderate protection against disease and significantly reduces the burden of clinical malaria on Uganda's health care system. The side effects of the vaccine are generally mild and the vaccine is considered to be safe for most children. UNITAG acknowledges the need for continued monitoring and evaluation of the impact of the vaccine on the malaria burden in Uganda, as well as any adverse events following immunization.

UNITAG recommends that RTS,S/AS01 should be provided at a minimum of 4 doses to reduce malaria disease burden in children from 5to 17 months of age in Uganda, starting with the highest burden districts.

The details of the evidence considerations and judgments of UNITAG are provided in the Evidence to Recommendation framework, and background evidence documents, as attached.

Sincerely,

Harriet Mayanja Kizza, (Prof)
CHAIRPERSON, UNITAG

PICO Question	Should RTS,S malaria vaccine be introduced in Uganda's EPI for children aged 5- 17 months starting with the highest burden areas? **Population** — *Children aged 5-17 months in Uganda* **Intervention** — *Vaccination with four doses of RTS,S starting at 5-17 months of age* **Comparator** — *Current malaria prevention strategies without vaccine* **Outcome** — *Decreased incidence and severity of malaria cases*
Background	The National Malaria Control Program (NMCP) has put in place the following programs to fight malaria: Long-lasting insecticidal nets (LLIN) distribution through Mass Campaigns and 10% in ante-natal facilities, distribution of Artemisinin-based Combination Therapy (ACT), Integrated Community Case management (iCCM), Indoor Residual Spraying (IRS), and Intermittent Preventive Treatment of malaria in pregnancy (IPTp) using Sulfadoxine-Pyrimethamine (SP)[1]. Despite these efforts, Uganda's achievements on epidemiological impact had stalled in 2022 as total malaria incidence had increased from 246/1000 in 2019 to 306/1000 persons per year in 2022, a 24.4% increase. The total malaria inpatient incidence increased from 16/1000 in 2019 to 17.1/1000 persons per year in 2022, a 6.9% increase while the total malaria-related death rate remained stable (from 6.3/100,000 to 6.4/100,000). The Uganda Malaria Reduction & Elimination Strategic Plan (UMRESP) 2021-2025 has a goal of reducing malaria infection and morbidity by 50% and malaria-related mortality by 75% of 2019 levels by 2025. [2] In March 2022, the World Health Organisation (WHO) recommended the wider use of the RTS,S/AS01 vaccine for the reduction of malaria morbidity and mortality in children living in areas of moderate to high malaria transmission[i3]. This followed the evaluation of the WHO-coordinated Malaria Vaccine Implementation Programme (MVIP), and additional results from 7 year clinical trials providing additional data since 2015[4].

[1] Ministry of Health, 2011. Uganda National Malaria Control policy, 2011.
[2] Ministry of Health, 2022. National Malaria Control Division Newsletter. Vol. 3. Edition 2. Issue 1. October-December 2022.
[3] WHO 2022. Malaria Vaccine RTS,S position paper, updated Mach 2022. https://www.who.int/publications/i/item/who-wer9709-61%E2%80%9380
[4] WHO Malaria Vaccine Implementation Programme (MVIP) Programme Advisory Group (PAG), 2021. Full Evidence Report on the RTS,S/AS01 Malaria Vaccine. Background Paper. https://cdn.who.int/media/docs/default-source/immunization/mvip/full-evidence-report-on-the-rtss-as01-malaria-vaccine-for-sage-mpag-%28sept2021%29.pdf

DOMAINS	CRITERIA	EVIDENCE	JUDGEMENT	ADDITIONAL INFORMATION
1. Problem	Is the problem of public health importance?	Malaria is **endemic in approximately 95% of the country**, affecting over 90% of the population. Up to **70% of outpatient cases and over 50% of inpatient admissions in the under-fives are malaria cases**. It is responsible for a specific death rate among this age group of 37/1000 and 18/1000 live births in high and low malaria endemic areas respectively or a **total of 70,000–110,000 child health deaths annually**[5]. Malaria accounts for **25% of all-cause mortality** among children **under five[6].** **Under-fives** account for approximately **10% of all malaria deaths** in Uganda[7]. Kamaya et. al., 2015[8] studied the incidence rate of malaria in children in 3 sites in Uganda. They found that he incidence of malaria was 0.43 episodes per person-years (PPY) in Walukuba, 1.43 episodes PPY in Kihihi, and 2.81 episodes PPY in Nagongera. Incidence of malaria is highest in the Karamoja, West Nile and Busoga regions of the country. **9% of children under 5 tested positive** for malaria by microscopy[9]. **Anemia due to malaria** was the **leading cause of blood transfusion requirement** among patients, accounting for **38.8%** of all transfusion cases[10].	Yes	

[5] Gertrude N. Kiwanuka. 2003. J Vect Borne Dis 40, March–June 2003, pp 16–19. Malaria morbidity and mortality in Uganda. http://www.mrcindia.org/journal/issues/401016.pdf

[6] Ministry of Health, 2014. Uganda Malaria Reduction Strategic Plan 2014-2020, Ministry of Health. 2016. Malaria bulletin 2016

[7] Health Management Information System, 2022

[8] Kamya MR, Arinaitwe E, Wanzira H, Katureebe A, Barusya C, Kigozi SP, Kilama M, Tatem AJ, Rosenthal PJ, Drakeley C, Lindsay SW, Staedke SG, Smith DL, Greenhouse B, Dorsey G. Malaria transmission, infection, and disease at three sites with varied transmission intensity in Uganda: implications for malaria control. Am J Trop Med Hyg. 2015 May;92(5):903-12. doi: 10.4269/ajtmh.14-0312. Epub 2015 Mar 16. PMID: 25778501; PMCID: PMC4426576.

[9] Ministry of Health 2019. 2018-2019 Malaria Indicator Survey

[10] Natukunda B, Schonewille H, Smit Sibinga CT. Assessment of the clinical transfusion practice at a regional referral hospital in Uganda. Transfus Med. 2010 Jun;20(3):134-9. doi: 10.1111/j.1365-3148.2010.00992.x. Epub 2010 Feb 1. PMID: 20136779.

		Current malaria control strategies have limitations: non-adherence to LLIN resulted in increased prevalence of malaria[11] malaria incidence in under-fives reached epidemic levels six months after the cessation of IRS[12], an indigenous emergence and spread of clinical artemisinin resistance was identified in Northern Uganda[13] Ugandan **households spend $7.58/month on childhood malaria treatment**, accounting for 4.3% of their average income per febrile episode[14]. Annual mean total **provider cost** of outpatient visits for malaria ranges between $1,608 and $14,535. Inpatient mean total provider cost for malaria was $ 15,395[15]		
2. Benefits & harms of the options	Are desirable anticipated effects large? Are undesirable anticipated effects small? Balance between benefits and harms. What is the quality of evidence for critical outcomes?	Results from phase 3 clinical trials showed that among 5-7 months old children, in the 12 months following administration of the first **3 doses**, vaccine **efficacy against clinical malaria** (uncomplicated and non-severe) **was 51%** (95% CI 47–55) and against **severe malaria was 45%**. In children who received **a fourth dose** 18 months after the third dose, vaccine **efficacy against clinical malaria was 39%**, and against **severe malaria 29%.** Over the same period of 12 months, the **vaccine reduced severe malarial anemia by 61% and the need for blood transfusions by 29%**. Vaccine	Are desirable effects large? Efficacy of intervention-moderate Effectiveness of intervention-moderate	It should also be noted that, in areas of moderate to high transmission, the period of highest risk for severe malaria is during the first few years of life, when the vaccine provides greatest protection.

[11] Rek J, Musiime A, Zedi M, Otto G, Kyagamba P, Asiimwe Rwatooro J, et al. (2020) Non-adherence to long-lasting insecticide treated bed net use following successful malaria control in Tororo, Uganda. PLoS ONE 15(12): e0243303. https://doi.org/10.1371/journal.pone.0243303

[12] Okullo, A.E., Matovu, J.K.B., Ario, A.R. *et al.* Malaria incidence among children less than 5 years during and after cessation of indoor residual spraying in Northern Uganda. *Malar J* **16**, 319 (2017). https://doi.org/10.1186/s12936-017-1966-x

[13] Mpimbaza, A., Sserwanga, A., Rutazaana, D. et al. Changing malaria fever test positivity among paediatric admissions to Tororo district hospital, Uganda 2012–2019. Malar J 19, 416 (2020). https://doi.org/10.1186/s12936-020-03490-4

[14] El-Houderi A, Constantin J, Castelnuovo E, Sauboin C. Economic and Resource Use Associated With Management of Malaria in Children Aged <5 Years in Sub-Saharan Africa: A Systematic Literature Review. MDM Policy & Practice. 2019;4(2). doi:10.1177/2381468319893986

[15] Batura, N., Kasteng, F., Condoane, J. et al. Costs of treating childhood malaria, diarrhoea and pneumonia in rural Mozambique and Uganda. Malar J 21, 239 (2022). https://doi.org/10.1186/s12936-022-04254-y

		efficacy against malaria-related hospitalization was 37% during a 4-year follow-up period[16]. In a follow up study, **vaccine efficacy against severe malaria was sustained;** vaccine efficacy against severe malaria during **the 6-year or 7-year post-vaccination period in children who had received a booster dose was 36·7%** in the older age group (5–7 years) and **Vaccine Efficacy uncomplicated malaria during the full follow-up period was 23·7%[17],[18].** Data on the effectiveness of RTS,S were generated through evaluation of the pilot phased introductions via the routine immunization systems in parts of Ghana, Kenya and Malawi. Pooled data across the 3 countries showed that hospitalization with severe malaria among children eligible for at least 3 doses of vaccine was reduced by 29% (rate ratio 0.71 (95% CI 0.55–0.93), and hospitalization with malarial parasitaemia or antigenaemia was reduced by 21% (95% CI 7–32)[3] From the pilot studies, the incidence rate ratio of severe malaria in children eligible for three doses of RTS,S was 0.78 (95% CI 0.55, 1.09)[4] In clinical studies, the most serious adverse reaction associated with RTS,S was febrile seizures (within 7 days post-vaccination) (0.1%). This effect was transient, and all affected children recovered after 7 days. The most reported adverse reactions were	Are undesirable effects small? very small	

[16] RTS,S Clinical Trials Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. Lancet. 2015 Jul 4;386(9988):31-45. doi: 10.1016/S0140-6736(15)60721-8. Epub 2015 Apr 23. Erratum in: Lancet. 2015 Jul 4;386(9988):30. PMID: 25913272; PMCID: PMC5626001.

[17] Olotu A, Fegan G, Wambua J, Nyangweso G, Leach A, Lievens M, Kaslow DC, Njuguna P, Marsh K, Bejon P. Seven-Year Efficacy of RTS,S/AS01 Malaria Vaccine among Young African Children. N Engl J Med. 2016 Jun 30;374(26):2519-29. doi: 10.1056/NEJMoa1515257. PMID: 27355532; PMCID: PMC4962898. https://www.nejm.org/doi/full/10.1056/nejmoa1515257

[18] Halidou Tinto, Walter Otieno, Samwel Gesase, Hermann Sorgho, Lucas Otieno, Edwin Liheluka, Innocent Valéa, Valentine Sing'oei, Anangisye Malabeja, Daniel Valia, Anne Wangwe, Emilia Gvozdenovic, Yolanda Guerra Mendoza, Erik Jongert, Marc Lievens, François Roman, Lode Schuerman, John Lusingu. Long-term incidence of severe malaria following RTS,S/AS01 vaccination in children and infants in Africa: an open-label 3-year extension study of a phase 3 randomised controlled trial,The Lancet Infectious Diseases, Volume 19, Issue 8, 2019, Pages 821-832, ISSN 1473-3099, https://doi.org/10.1016/S1473-3099(19)30300-7.

		fever (27%), irritability (14%) and injection site reactions such as pain (16%) and swelling (7%) [19]The safety profiles were similar for HIV infected, pre-term and malnourished babies.[20] The incidence of serious adverse events over the entire study period in children receiving RTS,S/AS01 with (24.2%) or without (25.3%) a booster dose was similar to that in the control group (28.4%)[21]. Three safety signals were identified in the Phase 3 trials, which were unexplained: an excess of meningitis and cerebral malaria cases in vaccine recipients (rate ratio of 10.5:1), an excess (rate ratio 2.15:1) and, among girls, excess all-cause mortality (rate ratio 2.0), These safety signals were further analyzed in the larger pilot studies done in Malawi, Ghana, and Kenya and shown to have no linkage to RTS,S[4].	Overall quality of evidence for critical outcomes Effectiveness-high Safety- high	Safety data from the pilots eliminated any links between RTS,S and the three safety signals from phase 3 trials
3. Values & preferences	Does the target population feel the desirable effects are large relative to the undesirable effects?	In a cross-sectional study of mothers in Nigeria, almost all respondents (98%; 177 of 180) indicated that they would allow their child to be immunized with malaria vaccine. 99% (179 of 180) of respondents were willing to bring their child four times to receive the vaccine and 98% (176/180) would accept malaria vaccination for their child even if given by injection. [22]	Yes	Families with experience of severe malaria, and those that have information on RTS,S are more likely to value the vaccine.

[19] European Medicines Agency. Mosquirix: Opinion on medicine for use outside EU. https://www.ema.europa.eu/en/opinion-medicine-use-outside-EU/human/mosquirix

[20] Otieno L, Guerra Mendoza Y, Adjei S, Agbenyega T, Agnandji ST, Aide P, Akoo P, Ansong D, Asante KP, Berkley JA, Gesase S, Hamel MJ, Hoffman I, Kaali S, Kamthunzi P, Kariuki S, Kremsner P, Lanaspa M, Lell B, Lievens M, Lusingu J, Malabeja A, Masoud NS, Mtoro AT, Njuguna P, Ofori-Anyinam O, Otieno GA, Otieno W, Owusu-Agyei S, Schuerman L, Sorgho H, Tanner M, Tinto H, Valea I, Vandoolaeghe P, Sacarlal J, Oneko M. Safety and immunogenicity of the RTS,S/AS01 malaria vaccine in infants and children identified as HIV-infected during a randomized trial in sub-Saharan Africa. Vaccine. 2020 Jan 22;38(4):897-906. doi: 10.1016/j.vaccine.2019.10.077. Epub 2019 Nov 7. PMID: 31708182; PMCID: PMC7613311.

[21] Guerra Mendoza Y, Garric E, Leach A, et al. Safety profile of the RTS, S/AS01 malaria vaccine in infants and children: additional data from a phase III randomized controlled trial in sub-Saharan Africa. Hum Vaccin Immunother. 2019;15(10):2386–98. https://doi.org/10.1080/21645515.2019.1586040

[22] Tolulope O. Musa-Booth, Blessing E. Enobun, Adewumi J. Agbomola, Clive J. Shiff medRxiv 2020.12.03.20242784; doi: https://doi.org/10.1101/2020.12.03.20242784. Now published in Annals of African Medical Research doi: 10.4081/aamr.2021.128

		Families that had a history of malaria infections, lived in urban areas, wealthy, had knowledge about malaria control were more accepting of the vaccine[23]		
4. Resource use	Are the resources required small? What is the cost-effectiveness?	Assuming a $5 price per dose, a 6-9 months schedule and routine administration strategy, for Uganda, **the financial cost of introduction per surviving infant was $0.76; recurrent cost per dose administered was $7.08; total financial cost per fully vaccinated child was $22.86, total economic cost per fully vaccinated child (FVC) $24.80**, total **procurement costs were $18,322,750**, making a total **financial cost of $19,388,822** and a total **economic cost of $21,037,518**[24]. The RTS,S/AS01 malaria vaccine will cost EUR 9.30 (USD 9.09) per dose for supply during 2023-2025[25]. The RTS,S vaccine is available on the GAVI support portfolio[26] and under the Gavi co-financing requirements, would cost the country $0.2 per dose in co-financing[27], (Seo et. al., 2015[28] used a Markov model simulated malaria progression in a hypothetical Malawian birth cohort, to **compare cost effectiveness of RTS,S Vaccine compared to LLINs and no intervention**. From a societal perspective the vaccine strategy was dominant. RTS,S **averted 0.11 more DALYs than LLINs and 0.372**	Resources are not small, although Gavi will absorb most of the cost. The investment is cost effective.	Plans for Government of Uganda (GoU) to gradually absorb the full cost of the vaccine should be developed at the country graduate from Gavi support. Introduction of other effective malaria vaccines currently in the pipeline following WHO prequalification is anticipated to drive down the cost of malaria vaccines in the future.

[23] Yohannes Wagnew, Tsega Hagos, Berhanemeskel Weldegerima & Ayal Debie (2021) Willingness to Pay for Childhood Malaria Vaccine Among Caregivers of Under-Five Children in Northwest Ethiopia, ClinicoEconomics and Outcomes Research, 13:, 165-174, DOI: 10.2147/CEOR.S299050

[24] Katya Galactionova, Melanie Bertram, Jeremy Lauer, Fabrizio Tediosi. Costing RTS,S introduction in Burkina Faso, Ghana, Kenya, Senegal, Tanzania, and Uganda: A generalizable approach drawing on publicly available data, Vaccine, Volume 33, Issue 48, 2015, Pages 6710-6718, ISSN 0264-410X, https://doi.org/10.1016/j.vaccine.2015.10.079

[25] UNICEF Supply Division, Aug 2022. Malaria Vaccine: Questions and Answers on Vaccine Supply, Price and Market Shaping. https://www.unicef.org/supply/media/13396/file/Malaria-Vaccine-Supply-Price-Market-Questions-Answers-August2022.pdf

[26] Gavi the Vaccine Alliance. Gavi Board approves funding to support malaria vaccine roll-out in Sub Saharan Africa. https://www.gavi.org/news/media-room/gavi-board-approves-funding-support-malaria-vaccine-roll-out-sub-saharan-africa

[27] UNICEF 2023. Malaria Vaccine: Questions and Answers on Vaccine Supply, Price, and Market Shaping February 2023. https://www.unicef.org/supply/media/15726/file/Malaria-Vaccine-Questions-and-Answers-on-Supply-Price-and-Market-Shaping-February-2023.pdf

[28] Seo, M.K., Baker, P. & Ngo, K.NL. Cost-effectiveness analysis of vaccinating children in Malawi with RTS,S vaccines in comparison with long-lasting insecticide-treated nets. *Malar J* **13**, 66 (2014). https://doi.org/10.1186/1475-2875-13-66

[redacted]		**more DALYs than the no intervention strategy per person, while costing $10.04 less than LLINs and $59.74 less than no intervention**. From a health service perspective **the vaccine's ICER was $145.03 per DALY averted, and thus can be considered very cost-effective**. The results were robust to changes in all variables except the vaccine and LLINs' duration of efficacy. **Vaccines remained cost-effective even at the lowest assumed efficacy levels of 49.6% (mild malaria) and 14.2% (severe malaria), and the highest price of $15.** Penny et. al., 2015[29] used mathematical models to calculate cost-effectiveness of RTS,S using the 3 dose schedule and the 3+1 dose schedule. Their findings indicated that in regions with a Parasite Prevalence (*Pf*PR$_{2-10}$) of 10–65%, RTS,S/AS01 is predicted to avert a median of 93 940 clinical cases and 394 deaths for the three-dose schedule, or 116 480 clinical cases and 484 deaths for the four-dose schedule, per 100 000 fully vaccinated children. The funding for the malaria vaccine introduction will come from GAVI, which has committed US$ 176,527.36 for 627,183 and 829,863 doses in 2014 and 2025 doses respectively. In the first phase, the co-financing from GoU will be US$ 291,409.		

[29] Melissa A Penny, Robert Verity, Caitlin A Bever, Christophe Sauboin, Katya Galactionova, Stefan Flasche, Michael T White, Edward A Wenger, Nicolas Van de Velde, Peter Pemberton-Ross, Jamie T Griffin, Thomas A Smith, Philip A Eckhoff, Farzana Muhib, Mark Jit, Azra C Ghani.2015. Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models. Lancet 2016; 387: 367–75. DOI:https://doi.org/10.1016/S0140-6736(15)00725-4

5. Equity	What would be the impact on health inequities?	The introduction of the malaria vaccine in Ghana expanded the uptake of at least one malaria preventive intervention from 67% of children to 92%, with 54% benefiting from both interventions. In Kenya, reported ITN use was very high, at 92%, malaria vaccine coverage was 79% and among children who did not sleep under an ITN the prior night, 69% received the first malaria vaccine dose. The addition of the malaria vaccine resulted in 97% of children accessing at least one malaria preventive intervention, with 73% of children benefiting from both interventions[4].	Varies	Prioritising areas with the highest burden at the sub-national level ensures the vaccine reaches those in most need. For those that receive the vaccine, it reduces inequities for access to malaria prevention tools. The lack of sufficient supply introduces inequities for regions not covered.
6. Acceptability	Which option is acceptable to key stakeholders? To the target population?	Aremu at. al., 2022[30] conducted a cross-sectional survey and found that 67.6% of Ugandan respondents were aware of the malaria vaccine. GeoPoll in collaboration with PATH conducted an SMS mobile phone-based survey in February 2022[31]; 81% of parents in the study say they intend to take their child to get the malaria vaccine if it is available. Convenience does not appear to be an obstacle.	Intervention	The combination of current interventions with the vaccine results in greater impact than either the vaccine or the alternative control strategies alone.

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[30] Aremu TO, Singhal C, Ajibola OA, Agyin-Frimpong E, Appiah-Num Safo AA, Ihekoronye MR, Nabirye SE, Okoro ON. Assessing Public Awareness of the Malaria Vaccine in Sub-Saharan Africa. Tropical Medicine and Infectious Disease. 2022; 7(9):215. https://doi.org/10.3390/tropicalmed7090215

[31] Fran Bodine, 2022. GeoPoll Reports: Parent Perceptions of the Malaria Vaccine in sub-Saharan Africa. https://www.geopoll.com/blog/malaria-vaccine-parent-perceptions/

<table>
<tr>
<td>7. Feasibility</td>
<td>Is the intervention feasible to implement?</td>
<td colspan="3">Uganda has adopted 6 months, 7 months and 8 months for the first three doses maintaining a minimum interval of 4 weeks. The 1st dose will be given from 6 months and capped at 1 year. At 6 months of age, the dose shall be integrating with vitamin A, while completing the initial 3 doses at 8 months of age will allow for catching missed opportunities that will turn up for MR1 at 9 months. The 4th dose will be given at 18 months of age to coincide with Measles Rubella second dose.[32]</td>
<td>Yes</td>
<td>The MVIP studies show that the coverage of RTS,S is similar to that of other vaccines in routine EPI. Dropout rates for 4th dose is around 30%.</td>
</tr>
<tr>
<td colspan="2">Balance of consequences</td>
<td>~~Undesirable consequences clearly outweigh desirable consequences in most settings~~</td>
<td>~~Undesirable consequences probably outweigh desirable consequences in most settings~~</td>
<td>~~The balance between desirable and undesirable consequences is closely balanced in most settings or is uncertain~~</td>
<td>~~Desirable consequences probably outweigh undesirable consequences in most settings~~</td>
<td>Desirable consequences clearly outweigh undesirable consequences in most settings</td>
</tr>
<tr>
<td colspan="2">Type of recommendation</td>
<td>We recommend the intervention</td>
<td colspan="2">~~We suggest considering the intervention~~
~~o Only in the context of rigorous research~~
~~o Only with targeted monitoring and evaluation~~
~~o Only in specific contexts or specific (sub)populations~~</td>
<td>~~We recommend the comparison~~</td>
<td>~~We recommend against the intervention and the comparison~~</td>
</tr>
<tr>
<td colspan="2">Recommendation (text)</td>
<td colspan="5">UNITAG recommends that RTS,S/AS01 should be provided at a minimum of 4 doses to reduce malaria disease burden in children from 5 months of age in Uganda, starting with the highest burden districts. The RTS,S/AS01 vaccine has an acceptable safety profile, and its introduction results in a significant reduction in severe malaria, and reduces the incidences of hospitalization with clinical malaria, the need for blood transfusion and saves household expenditure on health care.</td>
</tr>
<tr>
<td colspan="2">Implementation considerations</td>
<td colspan="5">i. Integration of the RTS,S vaccine in a comprehensive malaria control package of proven interventions is essential, including LLINs and chemoprevention where appropriate and according to the national malaria strategy.</td>
</tr>
</table>

[32] MoH 2022. Malaria Vaccine Strategy and Implementation plan.

	ii. The EPI Health communication program should develop a clear plan to mitigate mis and dis-information, and likely politicization of the phased roll out strategy, through adequate community engagement. iii. Special effort to be made to ensure completion of the fourth dose in order to maximise the benefits from RTS,S vaccination. iv. Lessons learned from COVID-19 roll out to increase acceptability and efficiency in vaccine roll out, including timely disbursement of funds, should be implemented. v. As a vaccine that requires reconstitution before administration, health worker training should emphasize safe handling techniques to avoid possible contamination.
Monitoring and evaluation	i. Routine monitoring for adverse events during the introduction and roll-out of malaria vaccines should be embedded into the national pharmacovigilance system. ii. A mixed methods strategy of Monitoring and Evaluation should be employed, specifically including qualitative aspects looking at issues such as acceptance and community perspectives.
Research priorities	Vaccine impact studies on malaria incidence and severity should be carried out, as well as impact on hospitalization, healthcare costs, and under five mortality.

Confirmation and Signature

I attest that the foregoing is the consensus recommendation of the Uganda National Immunisation Technical Advisory Group, regarding the introduction of RTS,S/ASO1 malaria vaccine in Uganda's routine immunization schedule

………………………………………………………… Date 11th July 2023

Prof Harriet Mayanja Kizza
Chairperson
UNITAG

UNITAG RTS,S BACKGROUND EVIDENCE

Contents

Introduction

1. Malaria Disease

Malaria is an acute febrile illness caused by Plasmodium parasites, which are spread to people through the bites of infected female *Anopheles* mosquitoes. There are 5 parasite species that cause malaria in humans, and 2 of these species – *P. falciparum and P. vivax* – pose the greatest threat. P. falciparum is the deadliest malaria parasite and the most prevalent on the African continent. The first symptoms – fever, headache and chills – usually appear 10–15 days after the infective mosquito bite and may be mild and difficult to recognize as malaria. Left untreated, P. falciparum malaria can progress to severe illness. The manifestations of severe malaria include severe anaemia, coma, respiratory distress, circulatory shock, hypoglycaemia, kidney failure and pulmonary oedema and death within a period of 24 hours[1].

The socio-economic impact of malaria includes out-of-pocket expenditure for consultation fees, drugs, transport and subsistence at a distant health facility. These costs are estimated to be between USD 0.41 and USD 3.88 per person per month (equivalent to USD 1.88 and USD 26 per household)[4].

2. Global and Regional Malaria Burden

According to the World Malaria report 2021[2], globally, there were an estimated **241 million malaria cases in 2020** in 85 malaria-endemic countries, increasing from **227 million in 2019**, with most of this increase coming from countries in the WHO African Region. Twenty-nine countries accounted for 96% of malaria cases globally, and six countries – Nigeria (27%), the Democratic Republic of the Congo (12%), **Uganda (5%),** Mozambique (4%), Angola (3.4%) and Burkina Faso (3.4%) – accounted for about 55% of all cases globally.

Globally, **malaria deaths** reduced steadily over the period 2000–2019, from **896 000 in 2000** to **562 000 in 2015** and to **558 000 in 2019**. **In 2020**, malaria deaths increased by 12% compared with 2019, to an **estimated 627 000**. The **malaria mortality rate** (i.e. deaths per 100 000 population at risk) halved from about **30 in 2000** to **15 in 2015** and then continued to decrease but at a slower rate, falling to **13 in 2019**. **In 2020**, the mortality rate increased again, to **15**. **Six countries** – Nigeria (27%), the Democratic Republic of the Congo (12%), **Uganda (5%),** Mozambique (4%), Angola (3%) and Burkina Faso (3%) – accounted for just over **half of all malaria deaths** globally in 2020.

WHO has set a global target to reduce malaria mortality deaths globally by 90% by 2030 compared to 2015 figures (Figure 1)

[1] WHO. 2022. Malaria Fact Sheet. https://www.who.int/news-room/fact-sheets/detail/malaria
[2] World malaria report 2021. Geneva: World Health Organization; 2021. Licence:
CC BY-NC-SA 3.0 IGO. https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2021

GOALS	MILESTONES		TARGETS
	2020	2025	2030
1. Reduce malaria mortality rates globally compared with 2015	At least 40%	At least 75%	At least 90%
2. Reduce malaria case incidence globally compared with 2015	At least 40%	At least 75%	At least 90%
3. Eliminate malaria from countries in which malaria was transmitted in 2015	At least 10 countries	At least 20 countries	At least 35 countries
4. Prevent re-establishment of malaria in all countries that are malaria-free	Re-establishment prevented	Re-establishment prevented	Re-establishment prevented

Figure 1 Goals, milestones and targets for the Global technical strategy for malaria 2016-2030

Malaria in Africa

According to the 2021 World Malaria report[2], the WHO African Region continues to shoulder the heaviest burden of malaria. Globally in 2020, the Region accounted for **95% of all malaria cases** (228 million); **96% of all malaria deaths (602 000**). **80% of all malaria deaths** in the Region were among **children under the age of 5**. **In 2020**, **increases in the mortality rate** of between **5% and 25%** were seen in eight countries: Angola, the Democratic Republic of the Congo, Guinea-Bissau, Liberia, Namibia, Nigeria, South Sudan, and **Uganda**.

In 2019 malaria was the second most common cause of death constituting (8.3%) of mortality amongst refugees (in the 20 HIS reporting countries in 2019). In 2021, malaria was the second most common cause of morbidity among refugees in the 20 countries reporting through the health information system. The top 5 morbidities were: upper respiratory tract infections (22.7%), malaria (18.7%), lower respiratory tract infections (7.5%), NCDs (5.4%), and watery diarrhoea (4.9%)[3].

[3]UNHCR, Africa, 2022. Guidance note on malaria programmes in refugee operations. https://www.unhcr.org/afr/protection/health/53ba5cca9/guidance-note-malaria-programmes-refugee-operations.html?query=malaria

Summary of evidence:

Burden of disease

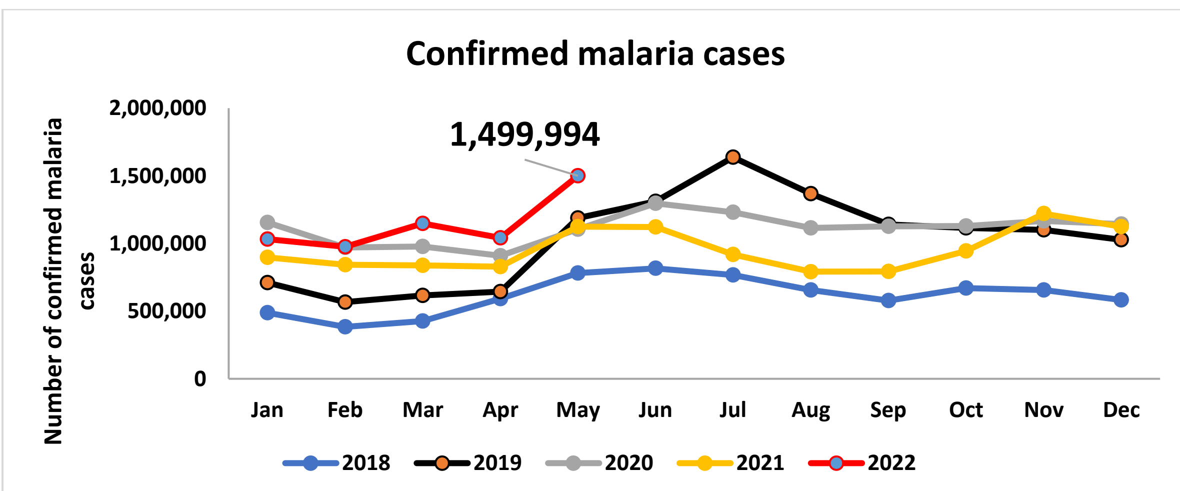
3. Malaria in Uganda

Malaria is **endemic in approximately 95% of the country**, affecting over 90% of the population. The remaining 5% of the country consists of unstable and epidemic-prone transmission areas in the highlands of the south- and mid-west, along the eastern border with Rwanda, and the north-eastern border with Sudan[4]. Malaria accounts for 27% of all hospital deaths in Uganda[5].

According to the **2018-2019** Uganda Malaria Indicator Survey[6], overall, **9% of children under 5 tested positive** for malaria by microscopy. Malaria in children was **most common in Karamoja, where 1 in 3** (34%) children tested positive for malaria, while less than 1% of children tested positive for malaria in Kampala and Kigezi. Among children under 5 **in refugee settlements, 13% tested positive for malaria**.

The most common malaria parasite is ***Plasmodium falciparum***. The most common malaria vectors are *Anopheles gambiae s.l.* and *Anopheles funestus*. *A. gambiae* is the dominant species in most places, while *A. funestus* is generally found at higher altitudes and during the short dry seasons[4].

Figure 1 shows the monthly **trends in malaria cases, admissions, and deaths** in Uganda from 2018-2022.



[4] Ministry of Health, 2014. Uganda Malaria Reduction Strategic Plan 2014-2020
[5] Ministry of Health. 2016. Malaria bulletin 2016. https://www.health.go.ug/cause/malaria-bulletin-2016/
[6] https://dhsprogram.com/pubs/pdf/ATR21/ATR21.pdf

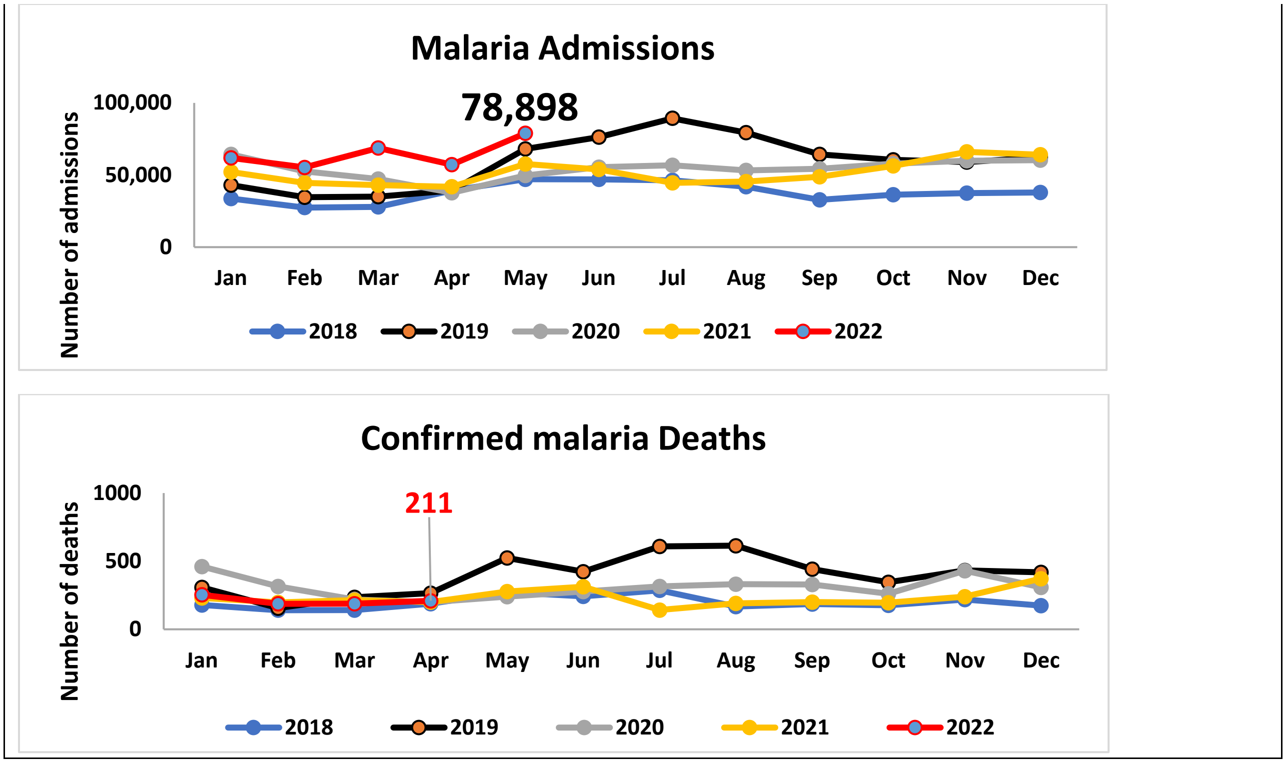


Figure 2 Trends in malaria cases, admissions, and deaths in Uganda 2018-2022. Source: Ministry of Health, 2022.

4. Prevalence of malaria among different age groups in Uganda.

One-third of all malaria **cases** in Uganda are **children under 5 years** (Figure 3). Up to 70% of outpatient cases and over 50% of inpatient admissions in the under-fives are malaria cases. It is responsible for a specific death rate among this age group of 37/1000 and 18/1000 live births in high and low malaria endemic areas respectively or a total of 70,000–110,000 child health deaths annually[7]. Malaria accounts for **25% of all-cause mortality** among children **under five[7]**.

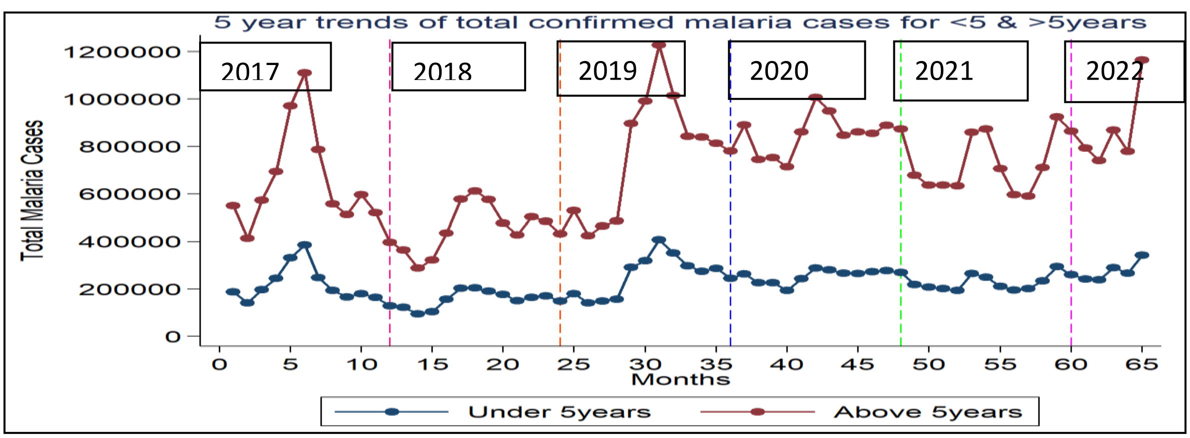


Figure 3: 5-year trends of total confirmed malaria cases for under five and over five years in Uganda 2017-2022

[7] Gertrude N. Kiwanuka. 2003. J Vect Borne Dis 40, March–June 2003, pp 16–19. Malaria morbidity and mortality in Uganda. http://www.mrcindia.org/journal/issues/401016.pdf

Source: Ministry of Health, Uganda. 2022

Under-fives account for approximately **10% of all malaria deaths** in Uganda (Figure 4).

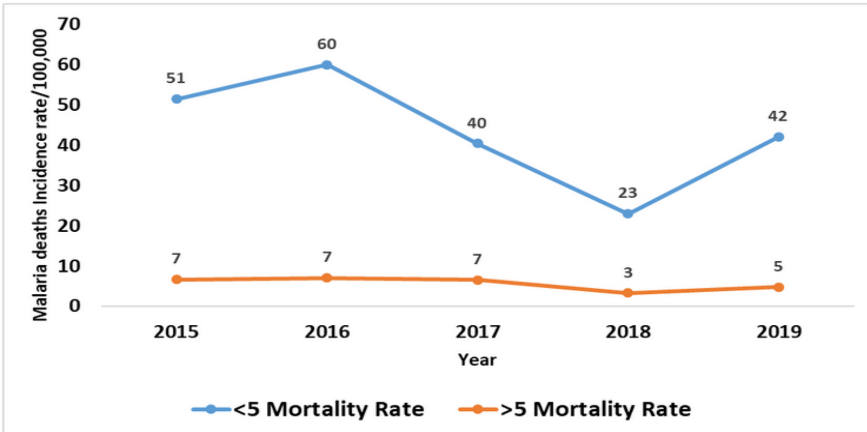


Figure 2: Incidence of malaria deaths by age group, Uganda, 2015-2019

Figure 4: Incidence of malaria deaths by age group in Uganda, 2015-2019[8]

Geographical distribution of malaria in Uganda

Incidence of malaria is highest in the Karamoja, West Nile and Busoga regions of the country (Figure 5 and Figure 6)

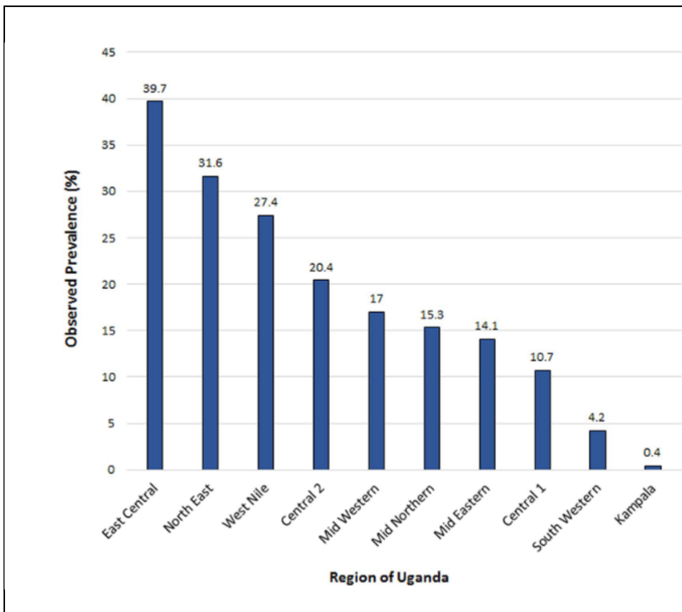


Figure 5 Observed prevalence of malaria among sampled children in different regions in Uganda[9]*.*
Source: Roberts and Matthews, 2015

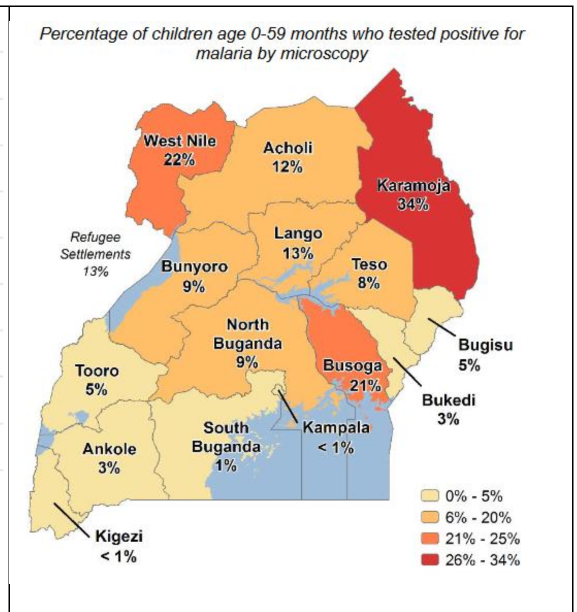


Figure 6: Regional prevalence of malaria in under-fives in Uganda.
Source: Malaria Indicator survey 2019.

[8] Source: Oumo et al. 2022. Trends and distribution of malaria deaths among the general population, Uganda, 2015-2019. Uganda National Institute of Public Health Bulleting, Volume 6, Issue 3. July-Sept 2021. https://uniph.go.ug/trends-and-distribution-of-malaria-deaths-among-the-general-population-uganda-2015-2019/

[9] Roberts and Matthews Malar J (2016) 15:246. DOI 10.1186/s12936-016-1290-x. https://malariajournal.biomedcentral.com/counter/pdf/10.1186/s12936-016-1290-x.pdf

5. Malaria epidemics and upsurges in Uganda.

Uganda has experienced upsurges of malaria in the recent past. Kitgum district experienced an epidemic between the years 2015 and 2016; the malaria burden rose above the established normal channels. At its peak the number of malaria cases attending Kitgum General Hospital was over 20 times above the normal channels. The total number of cases per 1000 population increased from 7 in 2014 to 113 in 2015 and 114 in 2016 (p value for trend < 0.0001). Similarly, test positivity rate increased from 10.5% to 54.6% between 2014 and 2016 (p value for trend < 0.0001). This trend was also observed for malaria attributable hospitalizations, and malaria in pregnancy. The malaria upsurge occurred in conjunction with a general decline in the use and application of malaria control interventions.[10]

6. Clinical epidemiology of severe malaria among Ugandan children.

Oluput-Olupot et. al. 2020 conducted a prospective descriptive study to determine the prevalence, clinical spectrum, and outcome of severe *Plasmodium falciparum* malaria at Mbale Regional Referral Hospital in Eastern Uganda. 662 children ranging from 2 months to 12 years were analysed. Respiratory distress was the most common severity feature (554; 83.7%), while 365/585 (62.4%) had hyperparasitaemia, 177/662 (26.7%) had clinical jaundice, 169 (25.5%) had severe anaemia, 134/660 (20.2%) had hyperlactataemia (lactate ≥ 5 mmol/L), 93 (14.0%) had passed dark red or black urine, 52 (7.9%) had impaired consciousness and 49/662 (7.4%) had hypoxaemia (oxygen saturations < 90%). In-hospital mortality was 63/662 (9.5%) overall but was higher in children with either cerebral malaria (33.3%) or severe anaemia (19.5%). Factors that were independently associated with mortality on multivariate analysis included severe anaemia [odds ratio (OR) 5.36; 2.16–1.32; $P = 0.0002$], hyperlactataemia (OR 3.66; 1.72–7.80; $P = 0.001$), hypoxaemia (OR) 3.64 (95% CI 1.39–9.52; $P = 0.008$), and hepatomegaly (OR 2.29; 1.29–4.06; $P = 0.004$). [11]

7. *Implications of malaria infection in under-fives on the health care systems in Uganda i.e. on short and long-term use of health care services?*

From MoH data, in 2020 there were 8,066,227 new Out-Patient Department (OPD) cases of under-five malaria, 402,421 re-attendances, 589,292 admissions, and 5,166 deaths.
From published literature, in 2017, malaria accounted for **27-34 percent of outpatient** visits and **19-30 percent of inpatient** admissions[12]. According to Mpimbaza et. al. 2020[13], the overall malaria **hospitalisation incidence rate** (IR) was **7.3 (95% CI 7.0, 7.7) per 1000 children aged 1 month to 14 years per annum**, with variations from 0.3-20.3 in the lowest and highest transmission rate catchments

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[10] Ogwang et. al., 2018. Acta Trop. 2018 The 2015–2016 malaria epidemic in Northern Uganda; What are the implications for malaria control interventions? December 01; 188: 27–33. oi:10.1016/j.actatropica.2018.08.023
[11] Olupot-Olupot, P., Engoru, C., Nteziyaremye, J. *et al.* The clinical spectrum of severe childhood malaria in Eastern Uganda. *Malar J* **19**, 322 (2020). https://doi.org/10.1186/s12936-020-03390-7
[12] President's Malaria Initiative Uganda. Operational plan FY 2019. https://d1u4sg1s9ptc4z.cloudfront.net/uploads/2021/03/fy-2019-uganda-malaria-operational-plan.pdf
[13] Mpimbaza A, Walemwa R, Kapisi J, Sserwanga A, Namuganga JF, Kisambira Y, Tagoola A, Nanteza JF, Rutazaana D, Staedke SG, Dorsey G, Opigo J, Kamau A, Snow RW. The age-specific incidence of hospitalized paediatric malaria in Uganda. BMC Infect Dis. 2020 Jul 13;20(1):503. doi: 10.1186/s12879-020-05215-z. PMID: 32660434; PMCID: PMC7359223.

respectively. **73.6% of all malaria admissions were aged less than 5 years**. Of all hospitalised cases**, 7.3% had severe anemia**, with 1.8% cases of **unconsciousness**, and 3.2% cases of **respiratory distress**.

8. Effectiveness of other prevention measures in place at controlling malaria transmission in children under five?

The Uganda Malaria Reduction Strategic Plan 2014-2020 set out the following measures to control malaria transmission: **integrated vector management** (IVM) and rapid and sustained scale-up of **Long Lasting Insecticide-treated Nets** (LLINs), **Indoor Residual Spraying** (IRS), intensifying **environmental management** and **larviciding** where feasible; scaling up **diagnosis** using microscopy and **Rapid Diagnostic Tests** (RDTs) and **treatment with effective anti-malarial drugs**.

The **National Malaria Control Program** has put in place the following programs to fight malaria: **LLINs distribution through Mass Campaigns** and 10% in ante-natal facilities, distribution of Artemisinin-based Combination Therapy **(ACT**), Integrated Community Case management (**iCCM**), Indoor Residual Spraying **IRS**, and **Intermittent Preventive Treatment of malaria in pregnancy (IPTp)** using Sulfa-doxine-Pyremethamine (SP)[14].

Despite these efforts, Uganda's achievements on epidemiological impact had stalled in 2022 as total malaria incidence had increased from 246/1000 in 2019 to 306/1000 persons per year in 2022, a 24.4% increase. The total malaria inpatient incidence increased from 16/1000 in 2019 to 17.1/1000 persons per year in 2022, a 6.9% increase while the total malaria-related death rate remained stable (from 6.3/100,000 to 6.4/100,000).[15]

The Uganda Malaria Reduction & Elimination Strategic Plan (UMRESP) 2021-2025 has a goal of reducing malaria infection and morbidity by 50% and malaria-related mortality by 75% of 2019 levels by 2025.

9. Long Lasting Insecticide-treated Nets (LLINs)

In **2013**, Uganda conducted its **first mass LLIN distribution campaign**, where over **20 million nets** were distributed free-of-charge to all registered households country-wide, to over 41 million registered individuals, with the objective of achieving universal coverage (one net to every two people). The **2014 Uganda malaria indicator survey (MIS)** showed that **79 % of the household population had access** to an LLIN (measured by the proportion of the population that could sleep under an LLIN if each LLIN in the household were used by up to two people) within their household and yet only **69 % of these households slept under it**. A secondary analysis of the MIS data showed that **83.12 % of children under 5 years slept under an LLIN**[16]. Households with more children under 5 years and women of child-bearing age (15–45 years) were significantly associated with using an LLIN.

[14] Ministry of Health, 2011. Uganda National Malaria Control policy, 2011.
[15] Ministry of Health, 2022. National Malaria Control Division Newsletter. Vol. 3. Edition 2. Issue 1. October-December 2022.
[16] Wanzira, H., Katamba, H. and Rubahika, D., 2016. Use of long-lasting insecticide-treated bed nets in a population with universal coverage following a mass distribution campaign in Uganda. *Malaria Journal*, *15*(1), pp.1-8.

A cross-sectional survey[17] was conducted in **2017 to assess the impact of the first LLIN distribution** campaign, and comparisons were made between the Malaria Indicator Surveys and the 2017 survey reported suggested that **parasite prevalence fell from 45.6 to 16.9% between 2009 and 2014–2015**, with significant decreases in all five regions of the country. However, **in 2017, parasite prevalence rose** to **21.4%.** Overall, **26.0% of children aged 2–10 years were positive for malaria parasitaemia** by microscopy. Parasitaemia varied widely across the country, ranging from **8.0% in the South-Western** region **to 53.1% in the East Central** region. Trends in parasite prevalence were thought to be attributable to **net attrition, poor LLIN coverage and use,** and the spread of **pyrethroid resistance.**

The second round of **campaigns was conducted from 2017-18**. Another study group conducted cross-sectional surveys at 6, 12, 18, and 25 months after LLIN distribution[18]: Study participants reported sleeping under a LLIN the previous night at 6 months (85·2%), 12 months (79·5%) 18 months (75·7%), but with a **notable decline at 25 months (60·2%).** Even lower results were observed in a 2019 survey[19] where only 39.5% of residents reported sleeping under a LLIN the previous night.

Musiime et. al., 2020[20] showed that **non-adherence to LLIN resulted in increased prevalence of malaria** in Tororo district despite previous successful interventions of LLIN distribution and Indoor Residual Spraying. When asked about recent experience with LLIN non-adherence, participants reported that they **simply forgot (35.2%)**, were **traveling (18.5%),** it was **too hot (16.8%)**, there were **no mosquitoes** (7.4%), and that there was **no malaria** (2.8%). Figure 7 shows changes in net use by age in Tororo district.

[17] Rugnao, S., Gonahasa, S., Maiteki-Sebuguzi, C. *et al.* LLIN Evaluation in Uganda Project (LLINEUP): factors associated with childhood parasitaemia and anaemia 3 years after a national long-lasting insecticidal net distribution campaign: a cross-sectional survey. *Malar J* **18**, 207 (2019). https://doi.org/10.1186/s12936-019-2838-3

[18] Maiteki-Sebuguzi, C., Gonahasa, S., Kamya, M.R., Katureebe, A., Bagala, I., Lynd, A., Mutungi, P., Kigozi, S.P., Opigo, J., Hemingway, J. and Dorsey, G., 2022. Effect of long-lasting insecticidal nets with and without piperonyl butoxide on malaria indicators in Uganda (LLINEUP): final results of a cluster-randomised trial embedded in a national distribution campaign. The Lancet Infectious Diseases.

[19] Gonahasa, S., Maiteki-Sebuguzi, C., Rugnao, S. *et al.* LLIN Evaluation in Uganda Project (LLINEUP): factors associated with ownership and use of long-lasting insecticidal nets in Uganda: a cross-sectional survey of 48 districts. *Malar J* **17**, 421 (2018). https://doi.org/10.1186/s12936-018-2571-3

[20] Okullo

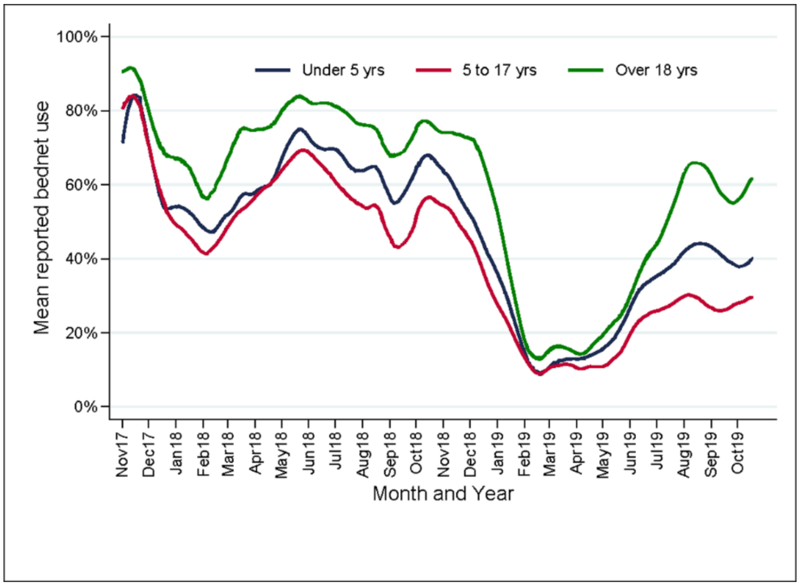

Figure 7 Changes in LLIN use over time stratified by age category in Tororo District[20].

10. Indoor Residual Spraying (IRS)

According to MoH 2021 data, IRS has been done in areas of **Teso, Lango and Busoga** since 2006, achieving an average coverage of 95%. Different studies have **analysed the impact of IRS on malaria prevalence**, with many showing **reductions soon after spraying but the effect wanes with time**. Tukei et. al. 2017[21] showed that following 5 rounds of spraying in the districts of Kitgum, Gulu and Apac using a mix of Alpha-Cypermethrin (round one-2009-10) and Bendiocarb (rounds 2-5, 2010-2011) with an average coverage of 95%, slide positivity rates dropped within a month of spraying, however, the **impact lasted only four months, and six months later results for under-fives were higher than before IRS** . Kigozi et. al.,2019[22] demonstrated that the level of decline in test positivity rates following IRS were dependent on the chemical used, with Apha Cypermethrin and Bendiocarb resulting in significantly sharper drops than DDT.

The main challenge observed with IRS is **lack of sustainability** due to its **reliance on external development partner funding**[23]. The total cost of rolling out IRS in the whole country was estimated to be between 106.7bn to 235bn UGX depending on the strategy employed[24]. In areas **where IRS was**

[21] Tukei, B.B., Beke, A. & Lamadrid-Figueroa, H. Assessing the effect of indoor residual spraying (IRS) on malaria morbidity in Northern Uganda: a before and after study. *Malar J* **16**, 4 (2017). https://doi.org/10.1186/s12936-016-1652-4

[22] Kigozi R, Baxi SM, Gasasira A, Sserwanga A, Kakeeto S, Nasr S, Rubahika D, Dissanayake G, Kamya MR, Filler S, Dorsey G. Indoor residual spraying of insecticide and malaria morbidity in a high transmission intensity area of Uganda. PLoS One. 2012;7(8):e42857. doi: 10.1371/journal.pone.0042857. Epub 2012 Aug 6. PMID: 22880123; PMCID: PMC3412792.

[23] Javier Burgos, 2020. SPEED Uganda- Government allocates 10 million USD to IRS malaria fight. https://europa.eu/capacity4dev/capacity-building-in-public-health-for-development/discussions/speed-uganda-government-allocates-10-million-usd-irs-fight-malaria

[24] Odokonyero Tonny, Ahabwe Gemma, Ssengooba Freddie, 2019. Financing indoor residual spraying for malaria Prevention in Uganda: options for cost minimization. ECONOMIC Policy Research Council (EPRC) Research Series No. 147.

discontinued, the impact was lost in a short time even when ITNs were distributed shortly before the spraying ceased. A time series study in Tororo district[25] where IRS AND LLIN campaigns were run concurrently, showed that during the 4–18 months after IRS was discontinued, there was a significant increase in the TPR, returning to baseline levels. TPRs began to rise 4 months after IRS was discontinued, reaching pre-IRS levels within 18 months. Okullo et. al 2017[26] found that in the five IRS districts, malaria **incidence in under-fives reached epidemic levels** (defined as an increase in incidence per month beyond one standard deviation above mean incidence of previous 5 years) **six months after the cessation of IRS** (Figure 8).

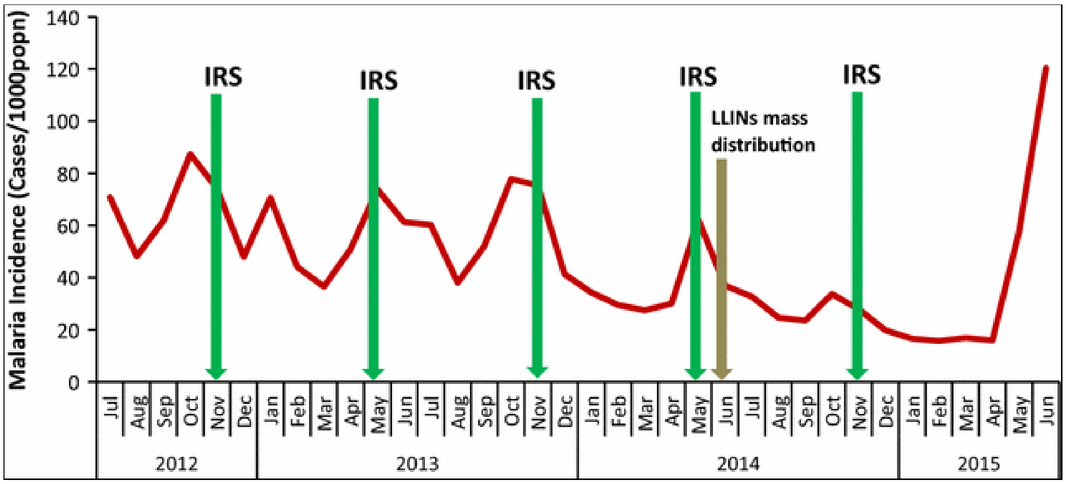

Figure 8: Malaria incidence among under-5 year-olds vis-à-vis control interventions in five districts that ended IRS in November 2014 for period July 2012 to June 2015.[26]

11. Environmental Management and Larviciding

Larval source management (LSM) is an additional malaria vector control intervention aimed at source reduction of all mosquitoes (malaria transmitting and biting nuisances).Uganda's larvicide program aims to spray at least 90% of potential breeding sites in the epidemic districts of Kigezi region and at least 80% of potential breeding sites in ten epidemic districts of Northern Uganda[27]. A large-scale larviciding trial was conducted in Tumba-Kamuli, Lwabyata Sub-County, Nakasongola District, between October 2017 and March 2018. A larvicide called Sun Activated Formulation Extract (SAFE) was applied in a model demonstrating sustainable community-led malaria control. The population of both aquatic and adult stages of Anopheline and Culicine mosquitoes was reduced. Analysis of variance showed a significant difference ($P \geq 0.05$) in the treatment and control sites. Likewise, malaria cases showed reducing trends by

[25] Houderi

[26] Okullo, A.E., Matovu, J.K.B., Ario, A.R. *et al.* Malaria incidence among children less than 5 years during and after cessation of indoor residual spraying in Northern Uganda. *Malar J* **16**, 319 (2017). https://doi.org/10.1186/s12936-017-1966-x

[27] Charles Ntege, National Malaria Control Program, 2020. Status of larval source management implementation in Uganda. Vector Control Working Group 15th Annul General Meeting. Movenpick Hotel and Casino. Geneva Switzerland. https://endmalaria.org/sites/default/files/u224/3_Charles%20Ntege.pdf

the end of the study period (y = -149.9x + 659.5; R^2 = 0.67502), suggesting that larviciding could substantially contribute to malaria reduction[28].

12. Artemisinin-based Combination Therapy (ACT)

In 2004, the country switched **the first line drugs** from CQ+SP to **artemether-lumefantrine (AL)**, a WHO-recommended **artemisinin-based combination therapy** (ACT), for **uncomplicated malaria** in response to growing CQ+SP resistance. Since 2005, Uganda's **second-line drug** has been **dihydroartemisnin-piperaquine** (DHA/PPQ). For **severe malaria**, **quinine IV** is used as an alternative to **injectable artesunate**[29]. A 14-month trial to evaluate the **efficacy of ACTs in children aged 4 to 5 years** in high transmission Tororo district showed **excellent performance** with the prevalence of parasitaemia on days 1, 2, and 3 following initiation of therapy was **67.6, 5.6 and 0% in those treated with AL**, and **52.2, 5.7 and 0.3% in those treated with DP**[30]. Byakika-Kibwika et. al., 2017[31] **evaluated** the 42-day parasitological treatment out-comes and safety of ACT (**severe malaria treatment** with **intravenous artesunate (AS)** or **intravenous quinine (QNN) followed by oral artemisinin based combination therapy**) in children attending Tororo District Hospital in Eastern Uganda and found that the median and interquartile range for number of **days from baseline to parasite clearance was significantly lower among participants who received intravenous AS**. Overall, **63.3%** (178/281) of the participants had **unadjusted parasitological treatment failure** over the 42-day follow-up period. Molecular genotyping to distinguish re-infection from recrudescence showed **majority 93 (73.2%) had re-infection and 34 (26.8%) had recrudescence**. The 42 days **risk of recrudescence did not differ with ACT administered**.

Another challenge identified regarding this intervention was **poor adherence to Integrated Malaria Management (IMM) Guidelines for testing and treating**. A study looking at IMM adherence in lakeshore facilities of Kaliro and Buyende districts found that 65.5% of the patients presenting with fevers were recommended for malaria (laboratory) testing. Regarding adherence to prescription guidelines, **64.5%** of the patients **received artemisinin combination therapy (ACT)** drug prescription. On the other hand, **18.6% of those who tested negative received an ACT** drug/prescription and **10.1% tested positive but did not receive an ACT drug or prescription**. **Overall adherence to IMM guidelines was only 3.1%**[32]**.** A similar study conducted in the **Busoga sub-region** found that over **95% of those the tested positive for malaria were prescribed AL**. Overall **adherence was high at 86.9%** , though only **50.7% among those**

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[28] MESA track, 2019. Field piloting of mosquito larviciding in Lwabyata sub-county, Nakasongola district, for malaria control in Uganda https://mesamalaria.org/mesa-track/field-piloting-mosquito-larviciding-lwabyata-sub-county-nakasongola-district-malaria

[29] National Malaria Control Programme, KEMRI-Wellcome Research Trust and LSHTM (2018). Uganda: A Profile of Malaria Control and Epidemiology. Uganda Ministry of Health.

[30] Muhindo, M.K., Kakuru, A., Jagannathan, P. *et al.* Early parasite clearance following artemisinin-based combination therapy among Ugandan children with uncomplicated *Plasmodium falciparum* malaria. *Malar J* **13**, 32 (2014). https://doi.org/10.1186/1475-2875-13-32

[31] Byakika-Kibwika, P., Achan, J., Lamorde, M. et al. Intravenous artesunate plus Artemisnin based Combination Therapy (ACT) or intravenous quinine plus ACT for treatment of severe malaria in Ugandan children: a randomized controlled clinical trial. BMC Infect Dis 17, 794 (2017). https://doi.org/10.1186/s12879-017-2924-5

[32] Kaula, H., Kiconco, S. & Nuñez, L. Cross-sectional study on the adherence to malaria guidelines in lakeshore facilities of Buyende and Kaliro districts, Uganda. *Malar J* **17**, 432 (2018). https://doi.org/10.1186/s12936-018-2577-x

treated at PFPs[33]. Additionally, an indigenous emergence and spread of clinical **artemisinin resistance was identified in Northern Uganda** following a review of treatment outcomes from 2017 through 2019[34].

13. Integrated Community Case management (iCCM)

In 2010, Uganda introduced a more comprehensive scheme that built upon the country's Village Health Team (VHT) strategy to deliver iCCM, which is the treatment of uncomplicated childhood illness (pneumonia, diarrhoea and malaria) by Community Health Workers (CHWs) and referral of complicated cases. iCCM is hosted by the Department of Child Health and is implemented at HC I level[29]. Through iCCM, CHWs test children under five for malaria using an RDT and treat positive cases of uncomplicated malaria with ACTs. CHWs also offer LLINs and intermittent preventive treatment of malaria during pregnancy. As per 2020 DHIS 2 data analysis, 14.5% of malaria cases are managed in the community, with ICCM implementation in 70 districts across the country.

14. Cost of Malaria Treatment

The socioeconomic impact of malaria includes out-of-pocket expenditures for consultation fees, drugs, and transport to and subsistence at a distant health facility. According to MoH, treatment costs are estimated to be between USD 0.41 and USD 3.88 per person per month (equivalent to USD 1.88 and USD 26 per household)[35].
A systematic review by Houderi et. al., 2019[36] found that Ugandan households spend $7.58/month on childhood malaria treatment, accounting for 4.3% of their average income per febrile episode.
Batura et al 2022[37] estimated the costs of treating childhood (under 5 years) diarrhea, malaria, pneumonia in rural Uganda. The highest unit cost for outpatient visits for malaria treatment ranged between $0.8 to 1.2. The highest unit cost for inpatient admissions was for malaria ($19.6).
The annual mean total provider cost of outpatient visits for malaria ranged between $1608 and $14,535. Inpatient mean total provider cost for malaria was 15,395 compared to 3033 for pneumonia. Overall, the cost of treating malaria (whether complicated or uncomplicated) was the highest amongst the three illnesses, irrespective of the level of facility under consideration.

[33] Mpimbaza A, Babikako H, Rutazanna D, Karamagi C, Ndeezi G, Katahoire A, Opigo J, Snow RW, Kalyango JN. Adherence to malaria management guidelines by health care workers in the Busoga sub-region, eastern Uganda. Malar J. 2022 Jan 25;21(1):25. doi: 10.1186/s12936-022-04048-2. PMID: 35078479; PMCID: PMC8788114.
[34] Balikagala, Betty, Naoyuki Fukuda, Mie Ikeda, Osbert T. Katuro, Shin-Ichiro Tachibana, Masato Yamauchi, Walter Opio et al. "Evidence of artemisinin-resistant malaria in Africa." New England Journal of Medicine 385, no. 13 (2021): 1163-1171.
[35] Ministry of Health. National Malaria Control Program. 2022. https://www.health.go.ug/programs/national-malaria-control-program/
[36] El-Houderi A, Constantin J, Castelnuovo E, Sauboin C. Economic and Resource Use Associated With Management of Malaria in Children Aged <5 Years in Sub-Saharan Africa: A Systematic Literature Review. MDM Policy & Practice. 2019;4(2). doi:10.1177/2381468319893986
[37] Batura, N., Kasteng, F., Condoane, J. et al. Costs of treating childhood malaria, diarrhoea and pneumonia in rural Mozambique and Uganda. Malar J 21, 239 (2022). https://doi.org/10.1186/s12936-022-04254-y

15. Impact of combination of therapies for malaria elimination

Kamya et. al., 2020[38], **measured the impact of malaria control interventions** on young children in Tororo, Uganda, a historically high-transmission area. Data were pooled from children aged 0.5–2 years. Interventions included individually assigned **chemoprevention**, repeated rounds of indoor residual spraying **(IRS)** of insecticide, long-lasting insecticidal nets (**LLINs**), and treatment for symptomatic malaria with **artemisinin-based combination therapy**. Malaria incidence was measured using passive surveillance and parasite prevalence by microscopy and molecular methods at regular intervals. In the absence of chemoprevention and IRS (reference group), malaria incidence was 4.94 episodes per person year and parasite prevalence 47.3%. Compared with the reference group, implementation of **IRS was associated with a 97.6% decrease in the incidence of malaria and a 96.0% decrease in parasite prevalence**. In children who were not receiving chemoprevention, the first four rounds of **IRS were associated with a relative reduction in the prevalence of 82.2%**, and this **increased to 96.0% during the fifth and sixth rounds**. In contrast to the results from the incidence and microscopic prevalence analyses, **adding chemoprevention with DP given every 12weeks** was associated with additional reductions in the prevalence of microscopic and submicroscopic parasitemia as compared with IRS alone (**relative reduction of 93.6%**). Addition of **DP given every 4weeks** was associated with almost complete protection against microscopic or submicroscopic parasitemia (**protective efficacy 98.9%).** This study concluded that in a historically high–malaria burden area of Uganda, **a combination of LLINs, effective case management, IRS, and chemoprevention was associated with almost complete elimination of malaria in young children**.

Vaccine and Immunisation Characteristics

16. RTS,S Vaccine description and mode of operation

RTS,S is RTS,S/AS01 is a monovalent pre-erythrocytic recombinant protein vaccine that comprises *P. falciparum* circumsporozoite protein (CSP) regions known to induce humoral (R region) and cellular (T region) immune responses, covalently linked to the hepatitis B virus surface antigen (S). RTS,S/AS01 elicits humoral and cellular immunity against the circumsporozoite protein amply expressed on the sporozoite surface, thereby limiting the ability of P. falciparum to infect, mature and multiply in the liver. RTS,S is presented in a powder form with a liquid adjuvant, which is mixed to form a suspension for injection[39].

17. Vaccine presentation, cold chain logistics and requirements

RTS,S vaccine presentation is a 2-dose vial of lyophilized (freeze-dried powder) RTS,S antigen clipped to a 2-dose vial of liquid AS01 adjuvant suspension to be used for reconstitution.

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[38] Kamya MR, Kakuru A, Muhindo M, Arinaitwe E, Nankabirwa JI, Rek J, Bigira V, Kapisi J, Wanzira H, Achan J, Natureeba P, Gasasira A, Havlir D, Jagannathan P, Rosenthal PJ, Rodriguez-Barraquer I, Dorsey G. The Impact of Control Interventions on Malaria Burden in Young Children in a Historically High-Transmission District of Uganda: A Pooled Analysis of Cohort Studies from 2007 to 2018. Am J Trop Med Hyg. 2020 Aug;103(2):785-792. doi: 10.4269/ajtmh.20-0100. Epub 2020 May 14. PMID: 32431280; PMCID: PMC7410449.

[39] European Medicines Agency. Mosquirix: Opinion on medicine for use outside EU. https://www.ema.europa.eu/en/opinion-medicine-use-outside-EU/human/mosquirix

The vaccine requires storage at 2-8°C. It should not be frozen. There is a VVM on the side of diluent ASO1 vial. In line with WHO's multi-dose vial policy (MDVP)16, because there is no preservative, once reconstituted the RTS,S vaccine must be discarded after six hours, or at the end of the session, whichever comes first. The pack is a 100-vial pack (17.8cm x 14.7cm x 3.7cm). The cold chain volume for RTS,S vaccine is 9.7 cc/dose. As such, the cold chain storage requirement for RTS,S vaccine (4 doses), when compared to other new vaccines, is equivalent to the two-dose Rota vaccine i.e. approximately 35 cc/child[40]. Shelf-life is 3 years[39].

18. ***Vaccine dosage and administration***

WHO recommends that the first dose of vaccine be administered to children living in moderate to high transmission areas from 5 months of age. The vaccine should be administered in a 3-dose primary schedule (minimum interval of 4 weeks between doses), with a fourth dose provided approximately 12–18 months after the third dose to prolong the duration of protection[47]. At its March 2023 meeting, WHO SAGE made a recommendation to allow for flexibility in the immunization schedule and to reduce the minimum interval between the doses 3 and 4 to 6 months to optimize impact[41].

Countries may consider providing the RTS,S/AS01 vaccine seasonally, with a 5-dose strategy, in areas with highly seasonal malaria or with perennial malaria transmission with seasonal peaks[47]. The vaccine is injected intramuscularly in the deltoid muscle.

Vaccine safety.

19. **Safety profile of RTS,S vaccine compared to other vaccines administered in children 5+ months e.g. MR, Men A?**

In clinical studies, the most serious adverse reaction associated with RTS,S was febrile seizures (within 7 days post-vaccination) (0.1%).This effect was transient, and all affected children recovered after 7 days. The most commonly reported adverse reactions were fever (27%), irritability (14%) and injection site reactions such as pain (16%) and swelling (7%)[42].

Three safety signals were identified in the Phase 3 trials, which were unexplained: an excess of meningitis cases in vaccine recipients (rate ratio of 10.5:1), an excess of cerebral malaria cases (rate ratio

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[40] WHO, 2015. Background Paper: Programmatic Options for Implementation of Malaria RTS,S Vaccination Schedule for Young Children. https://terrance.who.int/mediacentre/data/sage/SAGE_Docs_Ppt_Oct2015/7_session_malaria/Oct2015_session7_JTEG_Programmatic_Options%20_malarai_vaccine.pdf

[41] Highlights from the Meeting of the Strategic Advisory Group of Experts (SAGE) on Immunization 20-22 March 2023 https://cdn.who.int/media/docs/default-source/immunization/sage/2023/march-2023/sage_march_2023_meeting_highlights.pdf?sfvrsn=a8e5be9_4

[42] RTS,S Clinical Trials Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. Lancet. 2015 Jul 4;386(9988):31-45. doi: 10.1016/S0140-6736(15)60721-8. Epub 2015 Apr 23. Erratum in: Lancet. 2015 Jul 4;386(9988):30. PMID: 25913272; PMCID: PMC5626001.

2.15:1) and, among girls, excess all-cause mortality (rate ratio 2.0), with a mortality ratio (RTS,S/AS01: control) that was 2.6 fold greater among girls than for boys[43].

These safety signals were further analysed in the bigger pilot studies done in Malawi, Ghana, and Kenya. A total of 4,311 suspected cases of meningitis were investigated. Of the patients with probable or confirmed meningitis in vaccine-eligible age groups from implementation areas, 41% (11/27) had received RTS,S/AS01 vaccine, compared to 53% (2491/4672) of all other hospital admissions in this age group from implementation areas (odds ratio, adjusted for country and age, 0.73 (95%CI 0.31,1.71). *There was therefore no evidence that the introduction of the malaria vaccine led to an increase in the incidence of hospital admission with meningitis*[43].

Regarding cerebral malaria, the incidence rate ratio comparing rates of admission to hospital with cerebral malaria (with the broader case definition) in implementation areas relative to comparison areas, among children eligible for the malaria vaccine, was 0.96 (95%CI 0.61, 1.52). Of the patients with cerebral malaria in vaccine-eligible age groups from implementation areas, 47% (23/49) had received RTS,S/AS01 vaccine, compared to 53% (2479/4650) of all other admissions in this age group from implementation areas. *Therefore, there was no evidence that introduction of the malaria vaccine led to an increase in the incidence of hospital admission with cerebral malaria*[43].

20. Risk factors that can predispose to RTS,S vaccine adverse events in children 5+ months. Contraindications for RTS,S vaccine

Looking at special interest groups, Otieno et. al., 2020[44] studied the safety of the vaccine among HIV positive children. Of 15459 children enrolled in the trial, at least 1953 were tested for HIV and 153 were confirmed as HIV-infected. Thirty (28.6%) RTS,S/AS01-vaccinated and 12 (25.0%) comparator-vaccinated HIV-infected participants experienced an SAE within 30 days after any of the first 3 vaccine doses. Most were HIV and opportunistic infections, with no apparent imbalances between groups. Two SAEs (both febrile convulsions reported for the same child in the 5–17 months age category) were considered related to vaccination.

The safety profile of RTS,S in preterm infants and malnourished children (i.e. low weight-for-age) was generally similar to that in the overall study populations. SAE incidences in preterm infants were 19.7% in the RTS,S and 11.0% in the control group[45]. The vaccine must not be used in children who have had a hypersensitivity (allergic) reaction to a previous dose of RTS,S or to a hepatitis B vaccine[45].

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[43] WHO Malaria Vaccine Implementation Programme (MVIP) Programme Advisory Group (PAG), 2021. Full Evidence Report on the RTS,S/AS01 Malaria Vaccine. Background Paper. https://cdn.who.int/media/docs/default-source/immunization/mvip/full-evidence-report-on-the-rtss-as01-malaria-vaccine-for-sage-mpag-%28sept2021%29.pdf

[44] Otieno L, Guerra Mendoza Y, Adjei S, Agbenyega T, Agnandji ST, Aide P, Akoo P, Ansong D, Asante KP, Berkley JA, Gesase S, Hamel MJ, Hoffman I, Kaali S, Kamthunzi P, Kariuki S, Kremsner P, Lanaspa M, Lell B, Lievens M, Lusingu J, Malabeja A, Masoud NS, Mtoro AT, Njuguna P, Ofori-Anyinam O, Otieno GA, Otieno W, Owusu-Agyei S, Schuerman L, Sorgho H, Tanner M, Tinto H, Valea I, Vandoolaeghe P, Sacarlal J, Oneko M. Safety and immunogenicity of the RTS,S/AS01 malaria vaccine in infants and children identified as HIV-infected during a randomized trial in sub-Saharan Africa. Vaccine. 2020 Jan 22;38(4):897-906. doi: 10.1016/j.vaccine.2019.10.077. Epub 2019 Nov 7. PMID: 31708182; PMCID: PMC7613311.

21. Impact on safety by co-administration of RTS,S with other EPI vaccines

An in-depth safety analysis study from the phase III trial data[45] compared safety of RTS,S with EPI vaccines. Subjects were randomized to one of three groups: three doses of RTS,S/AS01 at months 0, 1, 2 and a booster dose at month 20; three doses of RTS,S/AS01 and a dose of control vaccine [meningococcal sero-group C conjugate vaccine (Menjugate®)] at month 20; three doses of control vaccines [Menjugate® for infants and rabies vaccine (VeroRab®) for children] at months 0, 1, 2, and a control vaccine (Menjugate® in both age categories) at month 20 . Infants received RTS,S/AS01 concomitantly with the Expanded Programme on Immunization (EPI) vaccines. The incidence of serious AEs over the entire study period in children receiving RTS,S/AS01 with (24.2%) or without (25.3%) a booster dose was similar to that in the control group (28.4%).

In a Ghanaian study[46], where RTS,S was co-administered with Measles Rubella, and Yellow Fever vaccines there was no imbalance in the reporting of SAEs between groups (6.1%, 5.1% and 9.1% of children in the RTS,S co-administered, RTS,S alone and Control groups, respectively)

Vaccine Efficacy

22. Efficacy of the RTS,S vaccine in reducing the risk of malaria infection, severe malaria, and malaria-attributed death, when given in three, and four-dose -schedules in children 5+ months?

Results from phase 3 trials showed that among 5-7 months old children, in the 12 months following administration of the first 3 doses, vaccine efficacy against clinical malaria (uncomplicated and non-severe) was 51% (95% CI 47–55) and against severe malaria was 45%. In children who received a fourth dose 18 months after the third dose, vaccine efficacy against clinical malaria was 39%, and against severe malaria 29%. Over the same period, the vaccine reduced severe malarial anemia by 61% and the need for musiimes by 29%. Vaccine efficacy against malaria-related hospitalization was 37% during a 4-year follow-up period[47]. RTS,S vaccine efficacy is comparable with that of BCG vaccine which has a 50% protective effect against tuberculosis infection and 70% protective effect against death from TB[48].

The number of clinical malaria cases averted during the same period was 1,363 per 1000 among children who received 3 vaccine doses, and 1,774 per 1000 among those given 4 vaccine doses. The largest numbers of cases averted per 1000 vaccinees were at sites with the greatest disease burden, reaching more than 6500 cases averted per1000 children vaccinated with 3 doses[47].

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[45] Guerra Mendoza Y, Garric E, Leach A, et al. Safety profile of the RTS, S/AS01 malaria vaccine in infants and children: additional data from a phase III randomized controlled trial in sub-Saharan Africa. Hum Vaccin Immunother. 2019;15(10):2386–98. https://doi.org/10.1080/21645515.2019.1586040

[46] Asante, Kwaku Poku, Daniel Ansong, Seyram Kaali, Samuel Adjei, Marc Lievens, Lydia Nana Badu, Prince Agyapong Darko et al. "Immunogenicity and safety of the RTS, S/AS01 malaria vaccine co-administered with measles, rubella and yellow fever vaccines in Ghanaian children: A phase IIIb, multi-center, non-inferiority, randomized, open, controlled trial." Vaccine 38, no. 18 (2020): 3411-3421.

[47] WHO, Malaria Vaccine Position Paper, March 2022. Weekly Epidemiological Record No 9, 2022, 97, 61–80 https://www.who.int/publications-detail-redirect/who-wer9709-61%E2%80%9380

[48]Colditz GA, Brewer TF, Berkey CS, et al. Efficacy of BCG Vaccine in the Prevention of Tuberculosis: Meta-analysis of the Published Literature. JAMA. 1994;271(9):698–702. doi:10.1001/jama.1994.03510330076038

23. Duration of protection

Vaccine efficacy in the first 6 months following completion of the initial 3 doses was 68%; efficacy waned over time. Six months after the fourth dose, vaccine efficacy was 43%; thus, although the fourth dose extended the period of protection, it did not restore efficacy to the level seen after the initial vaccine series[47]. Olutu et. al., 2016[49], in a 7 year follow up study among the intention to treat population found that efficacy waned over time, with negative effects for the high exposure cohort starting in year 6 (Figure 9). Another 7 year follow up study by Tinto et. al., 2019[50], found that in the 5-17 months old age category, 95·5% of children in the four-dose group and 82·8% of children in the three-dose groups had anti-circumsporozoite antibody concentrations of 1·9 EU/mL or more at the cross-sectional assessment in 2016 (Figure 9). Vaccine efficacy against severe malaria was sustained; vaccine efficacy against severe malaria during the 6-year or 7-year post-vaccination period in children who had received a booster dose was 36·7% in the older age group (5–7 years) and VE uncomplicated malaria during the full follow-up period was 23·7%. In the centre with the highest transmission, a statistically significant increase in the incidence of clinical malaria was measured for older children during the extension period (vaccine efficacy −30·3%.)

Severe malaria during the three-year follow-up period. In the older age category, the overall incidences of severe malaria per person year at risk were 0.004 (95% CI 0 to 0.33) in **the 4-dose group**, **0.007** (0.001 to 0.052) in the **3-dose group**, **and 0.009** (0.001 to 0.066) in **the control group** . In older children, vaccine efficacies against severe malaria over the entire follow-up period of 6-7 years in older children were 36.7% (14.6 to 53.1) for the 4-dose group and 10.1% (-18.1 to 31.6) for the 3- dose group.[51] Participants were also followed **for incidence of clinical malaria, and no additional benefit of vaccination was seen during the extended three-year follow-up period**. In the older children, the overall vaccine **efficacy against clinical malaria during the entire 6–7-year period remained positive**; **23.7% (15.9-30.7) for the 4-dose group and 19.1% (10.8-26.7) for the 3-dose group**. In one **site with intense seasonal transmission** (Nanoro), there were **more episodes of clinical malaria among vaccine recipients** during the extended follow-up than in the control group; in the 4-dose group the vaccine efficacy against clinical malaria was –30.3% (-59.5 to –6.4), and in the 3-dose group it was –26.0% (-56.0 to –6.4). Nonetheless**, in Nanoro there was still overall (6–7-year period) benefit of vaccination**, with a vaccine efficacy against clinical malaria of 13.8% (3.3 to 23.1) for the 4-dose group and 7.2% (-4.2 to 17.5) for the 3-dose group.[51]

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[49] Olotu A, Fegan G, Wambua J, Nyangweso G, Leach A, Lievens M, Kaslow DC, Njuguna P, Marsh K, Bejon P. Seven-Year Efficacy of RTS,S/AS01 Malaria Vaccine among Young African Children. N Engl J Med. 2016 Jun 30;374(26):2519-29. doi: 10.1056/NEJMoa1515257. PMID: 27355532; PMCID: PMC4962898. https://www.nejm.org/doi/full/10.1056/nejmoa1515257

[50] Halidou Tinto, Walter Otieno, Samwel Gesase, Hermann Sorgho, Lucas Otieno, Edwin Liheluka, Innocent Valéa, Valentine Sing'oei, Anangisye Malabeja, Daniel Valia, Anne Wangwe, Emilia Gvozdenovic, Yolanda Guerra Mendoza, Erik Jongert, Marc Lievens, François Roman, Lode Schuerman, John Lusingu. Long-term incidence of severe malaria following RTS,S/AS01 vaccination in children and infants in Africa: an open-label 3-year extension study of a phase 3 randomised controlled trial,The Lancet Infectious Diseases, Volume 19, Issue 8, 2019, Pages 821-832, ISSN 1473-3099, https://doi.org/10.1016/S1473-3099(19)30300-7.

51 RTS,S/AS01 SAGE/MPAG Working Group. SAGE Meeting October 2021. Full evidence report on the RTS,S/AS01 malaria vaccine

24. *Is there a rebound effect in children vaccinated with RTS,S ?*

Analyzing data from the Olutu[49] and Tinto[50] studies, as well as a Tanzania study following a year of Seasonal Malaria Chemoprevention (SMC), Dicko and Greenwood[52] argued that **longer periods of protection might be followed by a substantial, although short-lasting, increase in susceptibility to clinical malaria, but in all cases the benefits of protection exceeded those of the subsequent period of enhanced risk.** A study among infants receiving RTS,S in Malawi, Ghana, and Gabon[53] similarly **observed a rebound effect among children receiving 3 doses particularly in high transmission settings**. Over time, malaria incidence decreased in the control group and increased in the vaccine group. Three-dose efficacy in the lowest-transmission-intensity group decreased from 88.2% to 15.0% over 4.5 years, compared with 81.6% to −27.7% in the highest-transmission-intensity group.

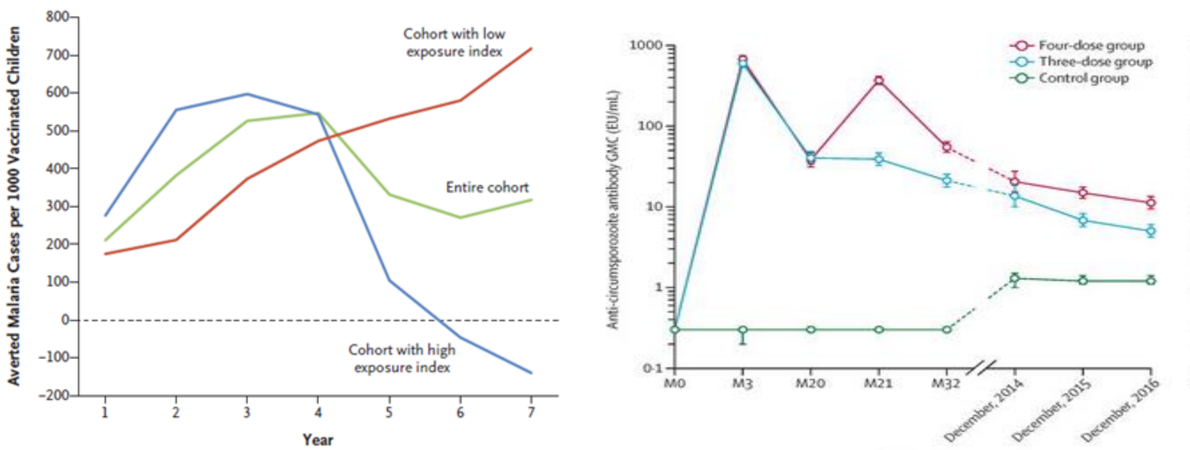

Figure 9 Left: Malaria Cases Averted during Follow-up in the Intention-to-treat Population (Olutu study). Right: Anti-circumsporozoite-repeat region antibody kinetics (evolution of antibody geometric mean concentrations over time)

25. *Impact on efficacy when RTS,S vaccine is co-administered with other EPI vaccines*

In a phase 3b, open-label, controlled study[46] 709 Ghanaian children were randomized (1:1:1) to receive RTS,S/AS01 at 6, 7.5 and 9 months of age, and **YF and MR vaccines** at 9 or 10.5 months of age (RTS,S co-ad and RTS,S alone groups, respectively). The third group received YF and MR vaccines at 9 months of age and will receive RTS,S/AS01 at 10.5, 11.5 and 12.5 months of age (Control group). All children received Vitamin A at 6 months of age. Non-inferiority of immune responses to the vaccine antigens was evaluated 1 month following co-administration *versus* RTS,S/AS01 or EPI vaccines (YF and MR vaccines) alone. Regarding impact on efficacy of RTS,S vaccine, one month after the third dose of RTS,S/AS01, the results showed 100% anti-HBs antibody sero-protection rates in both groups. **Anti-HBs antibody response was non-inferior in the RTS,S co-ad group compared to the RTS,S alone group**.

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[52] Alassane Dicko and Brian Greenwood, 2019. Malaria Vaccination and rebound malaria. https://doi.org/10.1016/S1473-3099(19)30282-8. The Lancet. Volume 19, ISSUE 8, P790-791, August 01, 2019
[53] Griffin J Bell, Varun Goel, Paulin Essone, David Dosoo, Bright Adu, Benedicta Ayiedu Mensah, Stephaney Gyaase, Kenneth Wiru, Fabrice Mougeni, Musah Osei, Pamela Minsoko, Cyrus Sinai, Karamoko Niaré, Jonathan J Juliano, Michael Hudgens, Anita Ghansah, Portia Kamthunzi, Tisungane Mvalo, Selidji Todagbe Agnandji, Jeffrey A Bailey, Kwaku Poku Asante, Michael Emch, Malaria Transmission Intensity Likely Modifies RTS, S/AS01 Efficacy Due to a Rebound Effect in Ghana, Malawi, and Gabon, *The Journal of Infectious Diseases*, 2022;, jiac322, https://doi.org/10.1093/infdis/jiac322

Regarding impact on efficacy of measles, rubella and yellow fever vaccines; one month post-vaccination, seropositivity rates were 96.1% and 98.2% against measles, 99.5% and 100% against rubella, and 98.1% and 98.6% against YF in the RTS,S co-ad and the control groups, respectively.

Economic and Operational Considerations: Vaccine related costs and resource use

26. The current cost of RTS,S vaccine available to the Uganda EPI

The RTS,S/AS01 malaria vaccine will cost EUR 9.30 (USD 9.09) per dose for supply during 2023-2025[54]. The RTS,S vaccine is available on the GAVI support portfolio[55] and under the Gavi co-financing requirements, would cost the country $0.2 per dose in co-financing[56].

Gavi approved in December 2022 an exceptional and time-limited co-financing modality for malaria vaccines, which would be reviewed no later than end-2027[57].

- This exceptional co-financing modality would entail a country contribution of USD 0.20 per dose for initial self-financing countries.
- For preparatory transitioning countries, their co-financing of USD 0.20 per dose in the first year would increase by 15 per cent a year.
- For countries in an accelerated transition phase, their contribution would be 20 per cent of the price in the first year of introduction and will increase by 10 per cent annually. In addition, they will be eligible for eight years of Gavi support irrespective of when during their accelerated transition phase they apply.

27. Total cost (direct and indirect) of administering RTS,S per fully immunised child?

Galactionova et. al., 2015[58], used publicly available data from CMYP, UNICEF, and WHO-CHOICE, to estimate the cost of RTS,S introduction in five African countries including Uganda. Assuming a $5 price per dose, a 6-9 months schedule and routine administration strategy, for Uganda, **the financial cost of introduction per surviving infant was $0.76; recurrent cost per dose administered was $7.08; total financial cost per fully vaccinated child was $22.86, total economic cost per FVC $24.80**, total **procurement costs were $18,322,750**, making a total **financial cost of $19,388,822** and a total **economic cost of $21,037,518**. The study computed the share of annual economic cost of RTS,S immunisation as follows: vaccination 40%, storage 20%, transport 10%, introduction 10%, supervision 9%, EIC 2%, monitoring 2%, training 0%.

[54] UNICEF Supply Division, Aug 2022. Malaria Vaccine: Questions and Answers on Vaccine Supply, Price and Market Shaping. https://www.unicef.org/supply/media/13396/file/Malaria-Vaccine-Supply-Price-Market-Questions-Answers-August2022.pdf

[55] Gavi the Vaccine Alliance. Gavi Board approves funding to support malaria vaccine roll-out in Sub Saharan Africa. https://www.gavi.org/news/media-room/gavi-board-approves-funding-support-malaria-vaccine-roll-out-sub-saharan-africa

[56] Gavi the Vaccinae Alliance, July 2022. Co-financing policy. https://www.gavi.org/programmes-impact/programmatic-policies/co-financing-policy

[57] UNICEF 2023. Malaria Vaccine: Questions and Answers on Vaccine Supply, Price, and Market Shaping February 2023. https://www.unicef.org/supply/media/15726/file/Malaria-Vaccine-Questions-and-Answers-on-Supply-Price-and-Market-Shaping-February-2023.pdf

[58] Katya Galactionova, Melanie Bertram, Jeremy Lauer, Fabrizio Tediosi. Costing RTS,S introduction in Burkina Faso, Ghana, Kenya, Senegal, Tanzania, and Uganda: A generalizable approach drawing on publicly available data, Vaccine, Volume 33, Issue 48, 2015, Pages 6710-6718, ISSN 0264-410X, https://doi.org/10.1016/j.vaccine.2015.10.079.

Comparatively, Baral et. al., 2021[59] calculated the RTS,S Vaccination costs for the three pilot countries: Malawi, Kenya, and Ghana. All the activities identified for costing were grouped into key components of the vaccination program, including vaccine procurement (included costs of purchasing vaccine and injection supplies), micro-planning, training, communications, social mobilization, cold chain expansion, service delivery, supervision, and monitoring of vaccine delivery. **The cost of delivering a dose of vaccine, excluding procurement add-on costs, was estimated to be $0.24** in Malawi, **$0.90 in Ghana, and $0.71 in Kenya**. The **financial cost per FVC was estimated to be $13.69 in Malawi, $12.49 in Ghana, and $12.66** in Kenya.

28. *Estimated cost of outreach programs to provide RTS,S vaccines outside of Health Facilities*

A 2019 exploratory study[60] aimed to estimate the costs of implementing RTS,S in Burkina Faso, Ghana, Kenya, Mozambique, and Tanzania assumed the **four vaccine doses were either all delivered at health facilities or the fourth dose was delivered in an outreach setting**. The cost estimations included the purchase prices of the vaccine and vaccine supplies (syringes, cotton, alcohol, and safety boxes), wastage, cold chain storage/distribution, administration of the vaccine, management, training, and social mobilization. The costs per FVC ranged from US$25 (Burkina Faso) to US$37 (Kenya) assuming a vaccine price of US$5 per dose. Across countries, recurrent costs represented the largest share dominated by vaccines ($5 per dose) (including wastage) and supply costs. **Delivering the fourth dose in outreach settings raised the costs, mostly fuel, per FVC by less than US$1 regardless of the country**.

29. **Cost effectiveness of introducing RTS,S in routine EPI**

Seo et. al., 2015[61] used a Markov model simulated malaria progression in a hypothetical Malawian birth cohort, to **compare cost effectiveness of RTS,S Vaccine compared to LLINs and no intervention**. From a societal perspective the vaccine strategy was dominant. RTS,S **averted 0.11 more DALYs than LLINs and 0.372 more DALYs than the no intervention strategy per person, while costing $10.04 less than LLINs and $59.74 less than no intervention**. From a health service perspective **the vaccine's ICER was $145.03 per DALY averted, and thus can be considered very cost-effective**. The results were robust to changes in all variables except the vaccine and LLINs' duration of efficacy. **Vaccines remained cost-effective even at the lowest assumed efficacy levels of 49.6% (mild malaria) and 14.2% (severe malaria), and the highest price of $15**. However, from a societal perspective, if the vaccine duration efficacy was set below 2.69 years or the LLIN duration of efficacy was greater than 4.24 years then LLINs became the more cost-effective strategy.

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[59] Baral R, Levin A, Odero C, Pecenka C, Tabu C, Mwendo E, et al. (2021) Costs of continuing RTS,S/ASO1E malaria vaccination in the three malaria vaccine pilot implementation countries. PLoS ONE 16(1): e0244995. https://doi.org/10.1371/journal.pone.0244995

[60] Sicuri E, Yaya Bocoum F, Nonvignon J, et al. The Costs of Implementing Vaccination With the RTS,S Malaria Vaccine in Five Sub-Saharan African Countries. MDM Policy & Practice. 2019;4(2). doi:10.1177/2381468319896280

[61] Seo, M.K., Baker, P. & Ngo, K.NL. Cost-effectiveness analysis of vaccinating children in Malawi with RTS,S vaccines in comparison with long-lasting insecticide-treated nets. *Malar J* **13**, 66 (2014). https://doi.org/10.1186/1475-2875-13-66

Penny et. al., 2015[62] used mathematical models to calculate cost-effectiveness of RTS,S using the 3 dose schedule and the 3+1 dose schedule. Their findings indicated that in regions with a Parasite Prevalence (*Pf*PR$_{2-10}$) of 10–65%, RTS,S/AS01 is predicted to avert a median of 93 940 clinical cases and 394 deaths for the three-dose schedule, or 116 480 clinical cases and 484 deaths for the four-dose schedule, per 100 000 fully vaccinated children. A positive impact was also predicted at a *Pf*PR$_{2-10}$ of 5–10%, but there is little impact at a prevalence of lower than 3%. **At $5 per dose and a *Pf*PR$_{2-10}$ of 10–65%, they estimated a median incremental cost-effectiveness ratio compared with current interventions of $30 per clinical case averted and $80 per DALY averted for the three-dose schedule, and of $25 and $87, respectively, for the four-dose schedule.**

Diawara et. al., 2022[63] assessed cost of RTS,S, vaccine introduction in a seasonal malaria setting. They found that at an assumed vaccine price of US $5 per dose, the economic cost per dose administered ranges between $7.73 and $8.68 (mass campaign), $7.04 and $7.38 (routine EPI) and $7.26 and $7.93 (mixed delivery). Excluding commodities, the cost ranges between $1.17 and $2.12 (mass campaign), $0.48 and $0.82 (routine EPI) and $0.70 and $1.37 (mixed delivery). The financial non-commodity cost per dose administered ranges between $0.99 and $1.99 (mass campaign), $0.39 and $0.76 (routine EPI) and $0.58 and $1.28 (mixed delivery). Excluding commodity costs, service delivery is the main cost driver under the mass campaign scenario, accounting for 36% to 55% of the financial cost. Service delivery accounts for 2%–8% and 12%–23% of the total financial cost under routine EPI and mixed delivery scenarios, respectively.

30. **Cost-effectiveness of introducing RTS,S in highest burden districts vs the entire country**

At an **African continental level**, Hogal et.al., 2020[64], used mathematical modelling to **compare cost effectiveness of introducing RTS,S countrywide versus at sub-national levels** considering anticipated supply shortages. Assuming that the vaccine could be **introduced at the subnational** (admin-1) level rather than countrywide **resulted in a greater estimated health impact, with 4.1 million clinical cases /17,000 deaths averted under a 20 million dose constraint, 5.3 million clinical cases 24,000 averted under a 30 million dose constraint, and 7.8 million clinical cases /41,000 deaths averted under a 60 million dose constraint** in the "Realistic vaccine coverage" (RTS,S coverage = DPT3). These **represent a 37%, 23%, and 18% increase, respectively, in clinical cases averted compared to the country-level introductions**.

[62] Melissa A Penny, Robert Verity, Caitlin A Bever, Christophe Sauboin, Katya Galactionova, Stefan Flasche, Michael T White, Edward A Wenger, Nicolas Van de Velde, Peter Pemberton-Ross, Jamie T Griffin, Thomas A Smith, Philip A Eckhoff, Farzana Muhib, Mark Jit, Azra C Ghani.2015. Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models. Lancet 2016; 387: 367–75. DOI:https://doi.org/10.1016/S0140-6736(15)00725-4

[63] Diawara H, Bocoum FY ,Dicko A, et al. Cost of introducing and delivering malaria vaccine (RTS,S/AS01 E) in areas of seasonal malaria transmission, Mali and Burkina Faso. BMJ Global Health 2023;8:e011316. doi:10.1136/bmjgh-2022-01131

[64] Hogan AB, Winskill P, Ghani AC (2020) Estimated impact of RTS,S/AS01 malaria vaccine allocation strategies in sub-Saharan Africa: A modelling study. PLoS Med 17(11): e1003377. https://doi.org/10.1371/journal.pmed.1003377

Winskill et. al. 2019[65] used incremental cost effectiveness ratios to show that when resources are limited, the prioritization of the use of available tools can help to maximize the impact of available finances, reducing malaria morbidity and mortality in a cost-effective manner. It was **more cost effective to roll out RTS,S vaccine incrementally, while initially prioritizing LLINs and treatment** (Figure 10). The vaccine was introduced later than for other interventions because of the limited age groups the vaccine provides protection to combine with the relatively high costs (at an assumed cost per dose of $5). It is, therefore, **apparent that focusing resources on achieving good levels of vector control and treatment coverage would be the priority before investing in vaccination**.

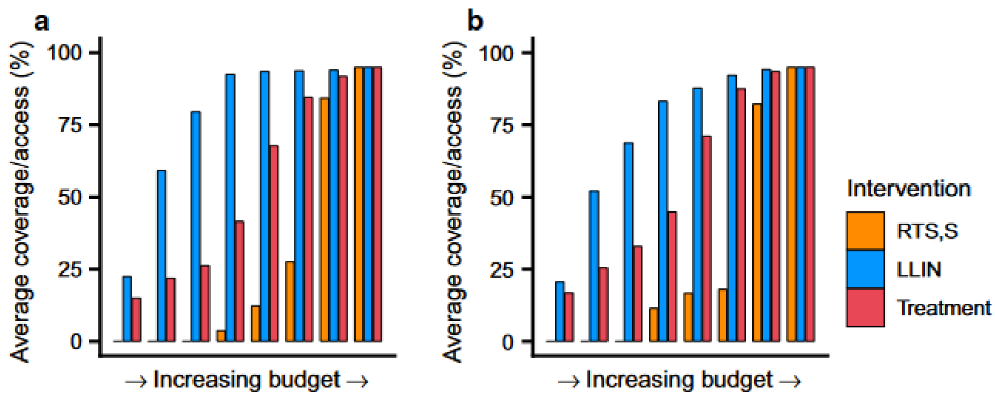

Fig. 4 Cost-effective prioritization of LLINs, treatment and the RTS,S vaccine. The average cost-effective scale-up of access to LLINs (blue bars), coverage of treatment (red bars) and the RTS,S vaccine (orange bars) for **a** medium (baseline $PfPr_{2\text{-}10}$: 30%) and **b** high (baseline $PfPr_{2\text{-}10}$: 60%) perennial transmission settings

Figure 10 Cost effective prioritisation of LLINs, Treatment and RTS,S vaccine.

31. The projected global supply of RTS,S Vaccine

Over the **2023-2025 period**, GSK, the developer and manufacturer, expects to **produce approximately 18 million doses in total, with 4 million doses being available for supply from late 2023**. GSK plans to increase supply availability to **6 million doses in 2024**, and **8 million doses in 2025**. UNICEF expects malaria vaccine supply constraints to continue for the next two to five years. UNICEF anticipates that the market will have sufficient malaria vaccine supply to meet expected demand sometime between 2026 and 2028.[54]

Health Policy and Programmatic Issues

Feasibility

Uganda has adopted 6 months, 7 months and 8 months for the first three doses maintaining a minimum interval of 4 weeks. The 1st dose will be given from 6 months and capped at 1 year. At 6 months we shall be integrating with vitamin A, while completing the initial 3 doses at 8 months will allow for catching missed opportunities that will turn up for MR1 at 9 months. The 4th dose will be given at 18 months of age to coincide with MR2.[66]

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[65] Winskill, Peter, Patrick G. Walker, Richard E. Cibulskis, and Azra C. Ghani. "Prioritizing the scale-up of interventions for malaria control and elimination." *Malaria journal* 18, no. 1 (2019): 1-11.
[66] MoH 2022. The Malaria Vacccine strategy and implementation plan.

This proposed schedule provides a vaccination window in the first year of life unique for RTS,S, and thus offers an opportunity to monitor for effectiveness and any safety concerns without potential interruptions from the effects of other vaccines. The phased introduction also provides a classic "intervention" and "control" comparison scenario, considering some parts of the country will have the vaccine, while others will not.

32. *Coverage of vaccines given in the second year of life, e.g. Measles Rubella second dose?*

Uganda plans to introduce its first second year of life vaccine, MR2, in November 2022, therefore no data exists on coverage on this platform. However, preliminary data from the pilot studies indicated **that drop off rates between RTS,S dose 3 and dose 4 have been around 19-30%[67].**

In the Pilot countries the vaccine is administered as below

Child Age / Vaccine/1	Birth	6 wks	10 wks	14 wks	5 mo	6 mo	7 mo	9 mo	12 mo	18 mo	22 mo	24 mo
BCG	1											
Oral polio	0	1	2	3								
DTP-HepB-Hib (penta)		1	2	3								
Pneumococcal conj.		1	2	3								
Rotavirus		1	2									
Inactivated Polio				1								
Meningococcal A conj.										1		
Measles-Rubella								1		2		
Yellow Fever								1				
RTS,S in Ghana						1	2	3				4
RTS,S in Kenya						1	2	3				4
RTS,S in Malawi					1	2	3				4	
Vitamin A						1			2	3		4
Growth Monitoring	●	●	●	●	●	●	●	●	●	●	●	●
Deworming												●

Table 1: Integration of RTS,S/AS01 malaria vaccine into the childhood immunization schedule

33. ***Impact of increased vaccinations workload on health worker morale***

Increase in workload during the COVID-19 vaccination campaigns resulted in complaints from health workers regarding poor facilitation in terms of allowances for meals. [68] This is consistent with findings by Hagopian et. al., 2009[69], where nurses surveyed cited compensation as their most important motivator (2.9 on a scale of 1-3) in the workplace. Health workers in the trial countries raised the concern of

[67] WHO, 2021. RTS,S/AS01 SAGE/MPAG Working Group. *Full evidence report on the RTS,S/AS01 malaria vaccine. https://terrance.who.int/mediacentre/data/sage/SAGE_eYB_Oct2021.pdf*

[68] The Daily Monitor. 5 Oct 2021. Uganda: Nurses raise alarm over vaccination allowances. https://allafrica.com/stories/202110051122.html

[69] Amy Hagopian, Anneke Zuyderduin, Naomi Kyobutungi, and Fatu Yumkella, 2009. Job Satisfaction and morale In the Ugandan Health Workforce. Health Affairs, Vol.28 no. Supplement 1. https://doi.org/10.1377/hlthaff.28.5.w863

increased workload due to additional vaccination contacts when RTS,S was added to the routine schedule.[67]

34. *Capacity for AEFI monitoring of vaccines administered in the country*

The National Drug Authority is the body mandated to monitor for AEFIs in Uganda. NDA houses the National Pharmacovigilance center, which is supported by regional pharmacovigilance centers at regional referral hospitals. AEFIs are monitored through a passive surveillance system where vaccine recipients or their caregivers report any AEFIs to the health facility, where the health-worker fills in a special form. All AEFIs identified in any week or month are be reported through the existing disease surveillance systems (Weekly and Monthly HMIS reports) and then submitted to the national level using the current reporting system for HMIS. They are also line listed and reported to UNEPI. Non serious AEFIs are to be reported within 15 days. Serious Adverse Events should be reported within 24 hours. There is an independent National AEFI committee in place that supports the causality assessments for serious AEFIs[70].
Other reporting platforms include: a toll-free telephone line, a web-based database called *vigiflow* available at regional centers, a med-safe mobile app, and an online reporting platform.
Kjungu et. al., 2021[71] compared an active AEFI reporting strategy for Measles Rubella and Polio vaccine campaigns by following up vaccine recipients through village health teams, parents and teachers in Iganga and Mayuge districts and found that it had a reporting rate of 3.9% compared with the national passive surveillance of 0.005%.

35. Perception of the community on malaria vaccine

Aremu at. al., 2022[72] conducted a cross-sectional survey with the aim of assessing the level of public awareness of the malaria vaccine among residents of sub-Saharan African countries, specifically Uganda, Ghana, and Nigeria. This study found that 67.6% of Ugandan respondents were aware of the malaria vaccine but there was a significant association between the awareness of the malaria vaccine and a place of residence for Uganda.
To explore parents' perceptions of the new malaria vaccine, GeoPoll in collaboration with PATH conducted an SMS mobile phone-based survey in February 2022 in several high-burden malaria countries: three from the original vaccine trial (Ghana, Kenya, and Malawi), as well as Nigeria, the Democratic Republic of the Congo (DRC), Uganda, and Mozambique73. From this poll 43% of Ugandans had heard of the malaria vaccine, compared to 52% in Kenya and 39% in DRC. Despite relatively low awareness of the new vaccine at this stage, demand is fairly high. Overall, 81% of parents in our study say they intend to take their child to get the malaria vaccine if it is available. Convenience does not

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[70] National Drug Authority. 2019. Guidelines on detecting and reporting adverse drug reactions in Uganda. Doc. No. DPS/GDL/013. https://www.nda.or.ug/wp-content/uploads/2022/02/GUIDELINES-detecting-and-reporting-ADR.pdf
[71] Kajungu, Dan, Victoria Nambasa, Michael Muhoozi, Joan Tusabe, Beate Kampmann, and Jim Todd. 2021. "Using Population-Based Structures to Actively Monitor AEFIs during a Mass Immunization Campaign—A Case of Measles–Rubella and Polio Vaccines" *Vaccines* 9, no. 11: 1293. https://doi.org/10.3390/vaccines9111293
[72] Aremu TO, Singhal C, Ajibola OA, Agyin-Frimpong E, Appiah-Num Safo AA, Ihekoronye MR, Nabirye SE, Okoro ON. Assessing Public Awareness of the Malaria Vaccine in Sub-Saharan Africa. Tropical Medicine and Infectious Disease. 2022; 7(9):215. https://doi.org/10.3390/tropicalmed7090215
[73] Fran Bodine, 2022. GeoPoll Reports: Parent Perceptions of the Malaria Vaccine in sub-Saharan Africa. https://www.geopoll.com/blog/malaria-vaccine-parent-perceptions/

appear to be an obstacle. Across countries, 93% of parents say they would make an extra visit to a health center to get their child immunized if required. Only 3% of respondents say they do not intend to take their child to get the malaria vaccine and would not make an extra visit to do it if required. Their justification is distributed between, "my children are protected from malaria already" (36%), "I don't know enough about the vaccine" (36%), and "my children get enough vaccines already" (27%).

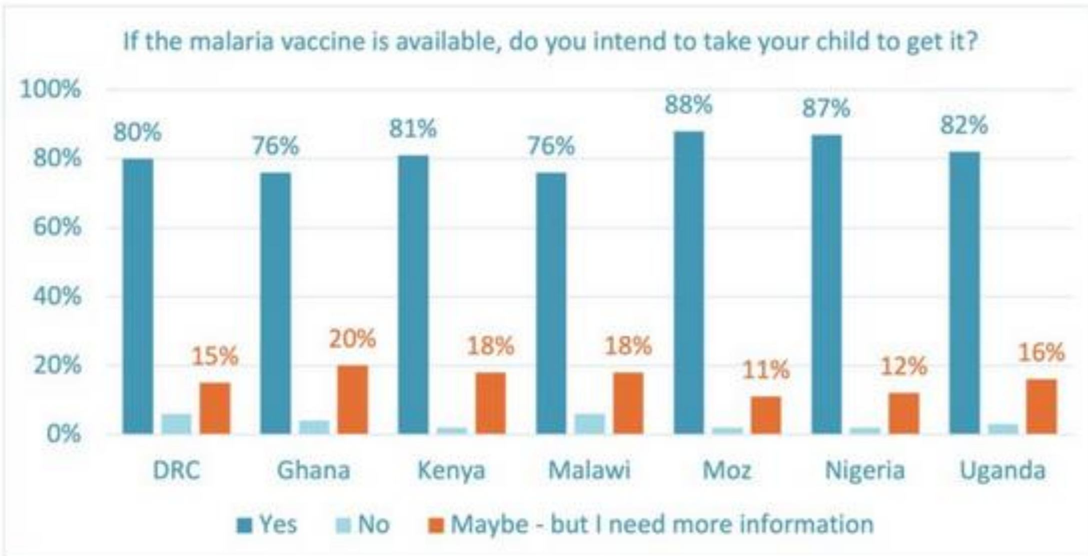

Figure 11: Outcomes of Community perception poll on malaria vaccine in seven African countries[73]

A study conducted in parts of South Eastern Nigeria[74] found that awareness of malaria as a public health problem was high (89.8%), but awareness about a prospective malaria vaccine was not high (48.2%). Up to 88.2% of respondents showed positive perception towards the vaccine, of which 65.2% had strong positive perception. The study found high level of intent to comply with the prospective malaria vaccine among the study group (95.6% positive). Significant association was established between caregivers perception and intent to comply with the prospective malaria vaccine ($\chi^2 = 144.52$; $p < 0.0001$)
These positive perception findings tally with those of the systematic review conducted by Dimalla et. al.,[75] in 2018, where 8 studies were reviewed and found that there was an overall positive acceptance towards the new malaria vaccine (n = 6/8studies), with a mean acceptance rate of 86.1% (95% CI: 62.0–110.2, n = 2). The main challenges to vaccine receptivity were: inadequate community engagement due to lack of information about the vaccine (n = 6), fear of the vaccine's side effects (n = 5), inefficient delivery of vaccination services to children (n = 4), and sub-optimal quality of the health services (n = 3).

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[74] Chukwuocha, U.M., Okorie, P.C., Iwuoha, G.N. *et al.* Awareness, perceptions and intent to comply with the prospective malaria vaccine in parts of South Eastern Nigeria. *Malar J* **17**, 187 (2018). https://doi.org/10.1186/s12936-018-2335-0
[75] Dimala CA, Kika BT, Kadia BM, Blencowe H (2018) Current challenges and proposed solutions to the effective implementation of the RTS, S/AS01 Malaria Vaccine Program in sub-Saharan Africa: A systematic review. PLoS ONE 13(12): e0209744. https://doi.org/10.1371/journal.pone.0209744

Studies on community perceptions about Malaria vaccines in Kenya, Ghana and Mozambique showed that when deciding whether or not to have their children vaccinated, and the decision often is influenced by a network of people, including community leaders and health workers[76],[77], [78].
In Kenya, concerns around affordability of a new vaccine surfaced in many parent discussions. Even though there is no charge for vaccines in Kenya, participants discussed affordability within the context of expenses related to clinic visits, for example, transportation to and from health facilities and unofficial charges for services at clinics.

In a cross sectional study conducted in Abuja, Nigeria to assess knowledge, attitude and willingness to accept the RTS,S malaria vaccine among mothers, 91% of mothers (163/180) had positive attitude to malaria vaccine and 98% (176/180) were willing to allow their child(ren) to be immunized with RTS,S despite the efficacy of the vaccine, route of administration and number of doses. Almost all respondents (98%; 177 of 180) would allow their child to be immunized with malaria vaccine, 99% (179 of 180) of respondents are willing to bring their child four times to receive the vaccine and 98% (176/180) would accept malaria vaccination for their child even if given by injection [79]

A community-based cross-sectional study was conducted to assess the willingness to pay (WTP) for childhood malaria vaccine and associated factors among caregivers of under-five children in one district in Ethiopia[80]. Overall, 60.6% (95% CI: 56.60, 64.40%) of caregivers of under-five children were WTP for the childhood malaria vaccine at a price of US$ 23.11 per full doses. Urban residence (AOR=1.78, 95% CI: 1.04, 3.04), educational status (AOR=3.27; 95% CI: 1.07, 9.94) and vaccination experience for children (AOR= 2.12; 95% CI: 1.29, 3.48) were positively associated with the WTP. WTP for the vaccine was higher among rich households (AOR=3.15; 95% CI: 1.90, 5.22), caregivers who had the previous history of malaria attack (AOR=2.62; 95% CI: 1.68, 4.08), households with fewer members (AOR=1.59; 95% CI: 1.06, 2.40), and families more knowledgeable about malaria prevention and control.

A Ghanaian study[81]that looked at the drivers and hindrances for nationwide implementation of RTS,S vaccine found that the disease burden of malaria deaths in Ghana, the efficacy of the vaccine, stakeholder involvement and evidence for the feasibility of vaccine delivery generated by the consortium of researchers (body of researchers) that can track the implementation were the driving forces to scale up the vaccine into a routine health system. On the other hand, the needed logistics, funding, administration of the four-dose vaccine and follow-up were identified as potential barriers. The most

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[76] Febir, L.G., Asante, K.P., Dzorgbo, DB.S. *et al.* Community perceptions of a malaria vaccine in the Kintampo districts of Ghana. *Malar J* **12**, 156 (2013). https://doi.org/10.1186/1475-2875-12-156
[77] Bingham, A., Gaspar, F., Lancaster, K. *et al.* Community perceptions of malaria and vaccines in two districts of Mozambique. *Malar J* **11**, 394 (2012). https://doi.org/10.1186/1475-2875-11-394
[78] Ojakaa DI, Ofware P, Machira YW, Yamo E, Collymore Y, Ba-Nguz A, Vansadia P, Bingham A. Community perceptions of malaria and vaccines in the South Coast and Busia regions of Kenya. Malar J. 2011 May 30;10:147. doi: 10.1186/1475-2875-10-147. PMID: 21624117; PMCID: PMC3120733.
[79] Tolulope O. Musa-Booth, Blessing E. Enobun, Adewumi J. Agbomola, Clive J. Shiff medRxiv 2020.12.03.20242784; doi: https://doi.org/10.1101/2020.12.03.20242784. Now published in Annals of African Medical Research doi: 10.4081/aamr.2021.128
[80] Yohannes Wagnew, Tsega Hagos, Berhanemeskel Weldegerima & Ayal Debie (2021) Willingness to Pay for Childhood Malaria Vaccine Among Caregivers of Under-Five Children in Northwest Ethiopia, ClinicoEconomics and Outcomes Research, 13:, 165-174, DOI: 10.2147/CEOR.S299050
[81] Omolola Oyinkan Adeshina and others, Barriers and facilitators to nationwide implementation of the malaria vaccine in Ghana, *Health Policy and Planning*, Volume 38, Issue 1, January 2023, Pages 28–37, https://doi.org/10.1093/heapol/czac077

influential force collectively highlighted by the respondents was the disease burden, and the most influential barrier was the logistics of delivering the vaccine.

36. The impact of RTS,S vaccines on the health-seeking behavior among the communities for fevers

Meñaca et. al 2014,[82] following a qualitataive study in two districts in Ghana concluded that a malaria vaccine would not affect the use of other preventive measures, as many participants saw vaccines as only reducing the severity of disease and never providing complete protection. Secondly, community members were already combining different preventive methods–mainly bed nets and hygienic measures–because no single measure was seen as totally efficacious.
Results from the RTS,S pilot studies[43] also showed that in all countries, there was no impact on the use of ITNs in children following the introduction of the malaria vaccine when comparing the implementation versus the comparison areas, and no impact on health seeking behaviour. Seeking treatment for fever, getting a diagnostic test, or receiving antimalarials for treatment was comparable between baseline and midline survey in Ghana, Malawi, and Kenya, and between implementation and comparison areas.

37. Equity considerations: Improved access to malaria control interventions[43]:

Data from the household surveys (reflecting the first 18-20 months of vaccine introduction) show that the availability of the malaria vaccine expanded the reach of malaria preventive interventions to vulnerable children. In Ghana 69% of children reportedly slept under an ITN the night prior to the survey and 77% had received a first dose of RTS,S/AS01. Among children who did not sleep under an ITN, 72% received a first dose of the malaria vaccine. The introduction of the malaria vaccine expanded the percentage of children accessing at least one malaria prevention measure – an ITN or the malaria vaccine -with coverage increasing from 69% to 91%, while 55% of children benefitted from both an ITN and the vaccine. Similar results were observed in Malawi, where ITN use was 67%, vaccine coverage was 79%, and among the children who did not sleep under an ITN, 75% were vaccinated with the malaria vaccine. The introduction of the malaria vaccine expanded the uptake of at least one malaria preventive intervention from 67% of children to 92%, with 54% benefiting from both interventions. In Kenya, reported ITN use was very high, at 92%, malaria vaccine coverage was 79% and among children who did not sleep under an ITN the prior night, 69% received the first malaria vaccine dose. The addition of the malaria vaccine resulted in 97% of children accessing at least one malaria preventive intervention, with 73% of children benefiting from both interventions.

38. Progress with other Malaria vaccine candidates

The most progressive malaria vaccine candidate currently is the R21/Matrix-M. A double-blind phase 1/2b randomised controlled trial was done in children aged 5–17 months in Nanoro, Burkina Faso. Group 1 received 5 µg R21/25 µg Matrix-M, group 2 received 5 µg R21/50 µg Matrix-M, and group 3, the control group, received the Rabivax-S rabies vaccine. 3-dose primary series with 0,1,2 M dosing; dose

[82] Meñaca A, Tagbor H, Adjei R, Bart-Plange C, Collymore Y, Ba-Nguz A, et al. (2014) Factors Likely to Affect Community Acceptance of a Malaria Vaccine in Two Districts of Ghana: A Qualitative Study. PLoS ONE 9(10): e109707. https://doi.org/10.1371/journal.pone.0109707

dose-4 given 12 months after dose dose-3. Vaccine efficacy according to the primary case definition from 14 days following booster vaccination to 12 months was 70% (95% CI 59–78; p<0·0001) in group 1 and 80% (72–85; p<0·0001) in group 2. Further adjustment for use of seasonal malaria chemoprevention (at least one monthly course of three doses) resulted in a vaccine efficacy of 81% (95% CI 74–87; p<0·0001) in group 2. Participants received a booster dose before the second malaria season, approximately 12 months following the primary series of vaccinations. Cox regression analysis showed a vaccine efficacy of 66% (95% CI 55–74; p<0·0001) for group 1 and 75% (66–81; p<0·0001) for group 2[83].

Multi -centre Phase 3 trials began January 2021, evaluating efficacy of 5µg R21 / 50 µg Matrix M. Sites include: Bougouni, , Mali and Nanoro , Burkina Faso (for seasonal adminstarion); Dande, Burkina Faso (highly seasonal transmission - low or low/moderate/), Kilifi, Kenya (low transmission), Bagamoyo, Tanzania (low transmission) for age based administraytion. No assessment of vaccine efficacy or duration in areas of high perennial transmission.[84]

Next steps:

- SAGE/MPAG WG will next review the data when 18-month follow -up is complete for the seasonal administration sites, and 12-month follow -up is complete for the “standard” or age age-based administration sites.
- Global Advisory Committee on Vaccine Safety (GACVS) will conduct a safety review for R21/ MatrixM . Anticipate review in May 2023
- WHO Prequalification (PQ) screening underway. Per ordinary processes, 9 9-12 months required for PQ review after acceptance of dossier.

39. Experience from other countries:

13 countries have submitted malaria vaccine funding applications to Gavi on 17 January 2023:
Benin, Burkina Faso, Burundi, Cameroon, Chad, DR Congo, Ghana, Liberia, Mozambique, Niger, Sierra Leone, Sudan, and Uganda.[85]

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[83] Datoo et. al., 2022. Efficacy and immunogenicity of R21/Matrix-M vaccine against clinical malaria after 2 years' follow-up in children in Burkina Faso: a phase 1/2b randomised controlled trial. Lancet Infect Dis 2022; 22: 1728–36. https://doi.org/10.1016/S1473-3099(22)00442-X

[84] Who SAGE March 2023 meeting. Malaria Slide deck

[85] Gavi , 2023. Dr Stephen Sosler, Head, Vaccines Program. Gavi Malaria Vaccine Programme update Workshop on implementation strategies for RTS,S malaria vaccine in countries with areas of highly seasonal transmission. https://tdr.who.int/docs/librariesprovider10/rtss-workshop/05_stephensosler_update-on-gavi-malaria-vaccine-programme_seasonal-malaria-ws_23-january-2023_vfinal.pdf?sfvrsn=5b3732f9_11

Statistical outcomes from Pilot study

40. Impact data[86]

Outcome	No. of events in eligible age groups[1] Implementing	Comparison	Rate ratio (95%CI)	% impact[2] (95% confidence interval)
Hospital admission with severe malaria[3]	418	689	0.70 (0.54, 0.92)	30% (8.0%,46%)
Hospital admission with severe malaria[4]	324	549	0.65 (0.49, 0.86)	35% (14%,51%)
Mortality due to all causes excluding injuries[5]	1421	1443	0.93 (0.84,1.03)	7.0% (-3.0%,16%)
Hospital admission for any cause[6]	3340	3678	0.92 (0.83, 1.03)	8.0% (-3.0%,17%)
Hospital admission with a positive malaria test	1119	1606	0.79 (0.68, 0.93)	21% (7.0%,32%)
Hospital admission with severe malaria anaemia	131	153	0.78 (0.55, 1.09)	22% (-9.0%,45%)

1: Number of cases by area are given for the age-eligible population. Rate ratios were estimated by comparing the ratio of events in eligible to non-eligible children in implementation areas, with the corresponding ratio in comparison areas (Annex 1).
2: percentage reduction in incidence associated with introduction of the RTS,S/AS01 vaccine, among the age group of children eligible to have received three doses of the vaccine.
3: Severe malaria definition: *P. falciparum* infection detected by RDT microscopy AND one or more of the following: a) impaired consciousness (Glasgow coma score<11, Blantyre coma score<3, or assessed as P or U on the AVPU score and CSF findings not consistent with probable or confirmed meningitis; b) multiple of atypical convulsions (more than two episodes within 24 hours or prolonged (>15minutes), or focal) and CSF findings not consistent with probable or confirmed meningitis; c) respiratory distress (manifested as chest indrawing or deep breathing); d) severe malaria anaemia (haemoglobin concentration <5g/dL or haematocrit <15%).
4: Severe malaria, defined as above, but excluding cases if they had impaired consciousness or convulsions but had not had an LP performed to exclude meningitis, and they did not fulfil other criteria for severe malaria (severe anaemia or respiratory distress).
5: Death due to any cause excluding injury (InterVA code 12).
6: A stay in hospital/inpatient facility for at least one night, (and patients who were admitted but died before an overnight stay was completed).

86 Paul Milligan and Kerryn Moore, Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine. Statistical report on the results of the RTS,S/AS01 Malaria Vaccine Pilot Evaluation 24 months after the vaccine was introduced (September 2021, v1.2)

41. Safety data:Comparison with safety signals from phase 3 trials[86]

Outcome	Rate ratio in the phase 3 trial[2] (95%CI)	Rate ratio of the phase 3 trial, adjusted for MVIP coverage[3] (95%CI)	Rate ratio in the MVIP (95%CI)	z	p-value
Meningitis	10.5 (1.41,78.0)	3.92 (1.22,12.6)	0.81 (0.43, 1.55)	2.31	0.0207
Cerebral malaria[4]	2.15 (1.1,4.3)	1.60 (1.05,2.43)	0.77 (0.44, 1.35)	2.06	0.0397
Cerebral malaria[5]		1.60 (1.05,2.43)	0.96 (0.61, 1.52)	1.62	0.1049
Mortality ratio[6]	2.61 (1.29,5.26)	1.83 (1.17,2.85)	1.08 (0.93, 1.25)	2.19	0.0285

1: If the safety signals observed in the phase 3 trial occurred in the MVIP, the magnitude of the effect we would observe would be smaller than in the phase 3 trial, since not all children will have received the vaccine. Any effects would be further diluted if there was contamination due to some children in comparison areas, or children in non-eligible age groups, receiving the vaccine. We used estimates of coverage and timing of malaria vaccine doses from the household surveys in each country to estimate the person time in vaccinated children as a proportion of total person time, and the degree of contamination. These estimates were used to calculate the expected effect in each country, if the safety signals in the phase 3 trial had occurred in the pilot. The average of these effects for each outcome is shown in column 2, and compared with the observed rate ratio from the MVIP (column 3) using a z-test. For each safety outcome, the observed rate ratio in the MVIP was inconsistent with the signal in the phase 3 trial. The hypothesis that the signal observed in the phase 3 trial occurred in the MVIP, given the degree of dilution that was estimated, was rejected ($p<0.05$), except when the broader case definition for cerebral malaria was used (including cases in whom lumbar puncture had not been performed), when the p-value was 0.1049.

2: Rate ratio in the phase 3 trial comparing the combined vaccine groups (R3R and R3R) with the control group, from month 0 to study end.

3: In each country the expected rate ratio for each safety outcome, if the safety signal from the phase 3 were to have occurred in the MVIP, was estimated as $R'=[(Rc+1-c)/(Rd+1-d)]/[(Rf+1-f)/(Rg+1-g)]$, where R is the rate ratio in the phase 3 trial, c is the proportion of vaccinated person time in implementation areas in eligible age groups, d the proportion in comparison areas in eligible age groups, and f and g are the corresponding values in non-eligible groups, for that country. The average across the three countries was calculated as $\exp[\Sigma w_i \log(R_i')]$, where the weights wi are the normalised weights used to obtain the pooled estimate of the rate ratio (column 3) for that outcome (as detailed in Annex 1), so that the comparison is based on the same relative weightings of the three countries. The estimates used were c=0.611 in Malawi, 0.690 in Ghana and 0.668 in Kenya (Figure 3); the corresponding proportions in comparison areas were d=0.016, 0.056, 0.087, and in non-eligible age groups in implementation areas, f=0.016 in Malawi and 0.027 in Ghana and Kenya. We (conservatively) assumed g=0 in each country.

4: Cerebral malaria, MVIP cases in which lumbar puncture had been performed to exclude cases with probable meningitis.

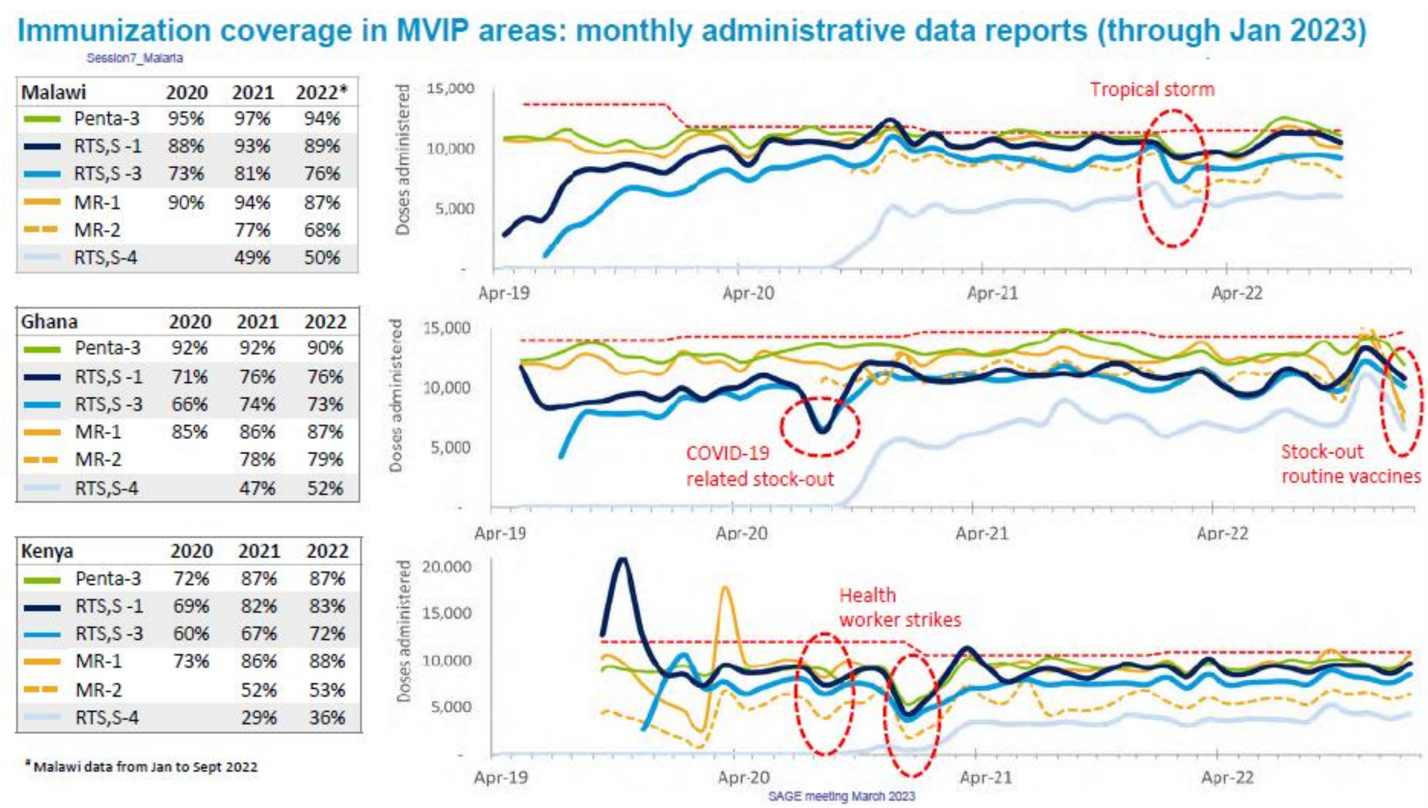
5: Cerebral malaria, using, for MVIP, a case definition broadened to include cases in which lumbar puncture had not been performed.

6: The mortality ratio, in the phase 3 trial, was defined as the ratio of the mortality rate between vaccine recipients and controls, for girls, relative to that for boys.

42. Acceptability data[51]

RTS,S/AS01 vaccine uptake from household surveys of children aged 12-23 months

	Ghana	Kenya	Malawi
Month of survey	November 2020	May – July 2021	March 2021
Period when children surveyed were due to have received their first dose of RTS,S/AS01	Jun 2019 – May 2020	Dec 2019-Jan 2021	Sep 2019 – Aug 2020
No. with home-based record of vaccination (HBR)/no. surveyed (%)	1082/1179 (91.8%)	1395/1438 (98.0%)	1082/1184 (91.4%)
Coverage of 1st dose by HBR (by HBR or recall)	79.7% (75.2%)	79.5% (78.6%)	74.1% (72.5%)
Coverage of 3rd dose by HBR (by HBR or recall)	71.2% (67.0%)	65.5% (62.3%)	65.2% (62.3%)
median age of receiving dose 3	9.7 months	9.0 months	8.5 months
90th percentile of age at dose 3	13 months	11.0 months	13 months
% received RTSS-1 in comparison areas by HBR	6.1%	10.2%	1.9%
% received RTSS-1 in older age groups in implementation areas, by HBR	1.1%	Not surveyed	1.9%



Source: WHO SAGE March 2023, Malaria slide deck

Fourth dose

The first children who were 7 months of age at the start of the programme in Ghana in May 2019 were age eligible (24 months) for the fourth dose in October 2020. Therefore, as of June 2021, there had been approximately 9 months of fourth dose administration. During this period, approximately 70% of all age-eligible children who received dose 3 have returned for dose 4 (i.e., a **drop-out rate of approximately 30%**).

43. Vaccine effectiveness with and without chemo-prevention[87]

Table 1. Incidence of Uncomplicated Clinical Malaria (Modified Intention-to-Treat Population).*

Variable	Person-yr at Risk	Events	Incidence (95% CI)	Protective Efficacy, Vaccine Alone or Combination vs. Chemoprevention (95% CI)	Protective Efficacy, Combination vs. Vaccine Alone (95% CI)
		no.	*no. of events/1000 person-yr at risk*		
Burkina Faso and Mali					
Chemoprevention alone	5449.9	1661	304.8 (290.5 to 319.8)	Reference	
Vaccine alone	5535.7	1540	278.2 (264.6 to 292.4)	7.9 (−1.0 to 16.0)	Reference
Combination	5508.0	624	113.3 (104.7 to 122.5)	62.8 (58.4 to 66.8)	59.6 (54.7 to 64.0)
Burkina Faso					
Chemoprevention alone	2602.9	1028	394.9 (371.5 to 419.8)	Reference	
Vaccine alone	2550.9	998	391.2 (367.7 to 416.3)	1.1 (−10.1 to 11.1)	Reference
Combination	2602.3	401	154.1 (139.7 to 169.9)	61.1 (55.4 to 66.1)	60.7 (55.0 to 65.7)
Mali					
Chemoprevention alone	2847.0	633	222.3 (205.7 to 240.4)	Reference	
Vaccine alone	2984.8	542	181.6 (166.9 to 197.5)	18.6 (3.4 to 31.3)	Reference
Combination	2905.7	223	76.7 (67.3 to 87.5)	65.6 (57.9 to 71.9)	57.8 (47.9 to 65.8)
Year 1					
Chemoprevention alone	1794.3	309	172.2 (154.0 to 192.5)	Reference	
Vaccine alone	1816.8	318	175.0 (156.8 to 195.4)	−1.7 (−21.4 to 14.8)	Reference
Combination	1802.3	88	48.8 (39.6 to 60.2)	71.7 (63.8 to 77.8)	72.1 (64.4 to 78.2)
Year 2					
Chemoprevention alone	1868.5	705	377.3 (350.5 to 406.2)	Reference	
Vaccine alone	1903.4	647	339.9 (314.7 to 367.1)	10.1 (−1.9 to 20.6)	Reference
Combination	1894.4	264	139.4 (123.5 to 157.2)	63.2 (56.8 to 68.6)	59.1 (51.9 to 65.1)
Year 3					
Chemoprevention alone	1787.1	647	362.0 (335.2 to 391.0)	Reference	
Vaccine alone	1815.5	575	316.7 (291.9 to 343.7)	12.7 (0.9 to 23.1)	Reference
Combination	1811.3	272	150.2 (133.3 to 169.1)	58.6 (51.5 to 64.6)	52.6 (44.2 to 59.7)

The modified intention-to-treat population included all eligible children whose parents or guardians provided consent and who received a first dose of trial vaccine or vaccine placebo. Children received chemoprevention (chemoprevention-alone group), RTS,S/AS01E (vaccine alone group), or chemoprevention and RTS,S/AS01E (combination group). The protective efficacy was calculated as (1 − hazard ratio) × 100. CI denotes confidence interval.

[87] Chandramohan et al, 2021. Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention. DOI: 10.1056/NEJMoa2026330

44. Incidence of severe secondary outcomes comparing vaccine, chemoprevention, and combination

Table 2. Incidence of Secondary Severe Outcomes According to Trial Group (Modified Intention-to-Treat Population).*

Outcome and Group	Events	Incidence (95% CI)	Protective Efficacy, Vaccine Alone or Combination vs. Chemoprevention (95% CI)	Protective Efficacy, Combination vs. Vaccine Alone (95% CI)
	no.	*no. of events/1000 person-yr at risk*		
Hospitalizations				
Any reason, excluding external causes and surgery				
Chemoprevention alone	60	11.0 (8.6 to 14.2)	Reference	
Vaccine alone	73	13.2 (10.5 to 16.6)	−22.3 (−74.4 to 14.3)	Reference
Combination	49	8.9 (6.7 to 11.8)	18.7 (−19.4 to 44.7)	33.5 (3.0 to 54.5)
All cases of malaria				
Chemoprevention alone	49	9.0 (6.8 to 11.9)	Reference	
Vaccine alone	54	9.8 (7.5 to 12.7)	−11.0 (−65.8 to 25.7)	Reference
Combination	28	5.1 (3.5 to 7.4)	43.2 (7.7 to 65.0)	48.8 (17.1 to 68.4)
Severe malaria†				
Chemoprevention alone	37	6.8 (4.9 to 9.4)	Reference	
Vaccine alone	37	6.7 (4.8 to 9.2)	−0.4 (−60.2 to 37.1)	Reference
Combination	11	2.0 (1.1 to 3.6)	70.5 (41.9 to 85.0)	70.6 (42.3 to 85.0)
Cerebral malaria†				
Chemoprevention alone	0	0	Reference	
Vaccine alone	4	0.7 (0.3 to 1.9)	—	Reference
Combination	1	0.2 (0.0 to 1.3)	—	74.6 (−128.0 to 97.2)
Severe malarial anemia†				
Chemoprevention alone	31	5.7 (4.0 to 8.1)	Reference	
Vaccine alone	25	4.5 (3.1 to 6.7)	18.4 (−39.3 to 52.2)	Reference
Combination	10	1.8 (1.0 to 3.4)	67.9 (34.1 to 84.3)	60.6 (18.3 to 81.0)
Blood transfusion				
Chemoprevention alone	23	4.2 (2.8 to 6.4)	Reference	
Vaccine alone	21	3.8 (2.5 to 5.8)	8.3 (−67.6 to 49.8)	Reference
Combination	8	1.5 (0.7 to 2.9)	65.4 (22.9 to 84.5)	62.3 (14.1 to 83.4)
Deaths				
All, including external causes and surgery				
Chemoprevention alone	32	5.9 (4.2 to 8.3)	Reference	
Vaccine alone	27	4.9 (3.3 to 7.1)	15.9 (−40.3 to 49.6)	Reference
Combination	15	2.7 (1.6 to 4.5)	53.4 (14.0 to 74.8)	44.6 (−4.1 to 70.5)
All, excluding external causes and surgery				
Chemoprevention alone	25	4.6 (3.1 to 6.8)	Reference	
Vaccine alone	22	4.0 (2.6 to 6.0)	12.1 (−55.7 to 50.4)	Reference
Combination	12	2.2 (1.2 to 3.8)	52.3 (5.0 to 76.0)	45.7 (−9.6 to 73.1)
Malaria				
Chemoprevention alone	11	2.0 (1.1 to 3.6)	Reference	
Vaccine alone	12	2.2 (1.2 to 3.8)	−9.5 (−148.3 to 51.7)	Reference
Combination	3	0.5 (0.2 to 1.7)	72.9 (2.9 to 92.4)	75.3 (12.5 to 93.0)

45. Prevalence of outcomes comparing vaccine, chemoprevention, and combination

Table 3. Prevalence of Outcomes at Weekly Surveys and at Surveys Conducted at the End of Each Malaria Transmission Season.*

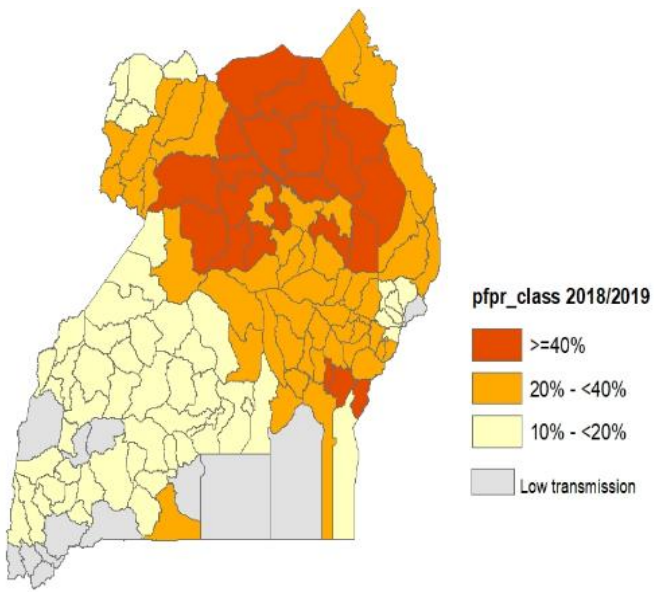
Variable	Children	Prevalence Ratio, Vaccine Alone or Combination vs. Chemoprevention (95% CI)	Prevalence Ratio, Combination vs. Vaccine Alone (95% CI)
	no./total no. (%)		
***Plasmodium falciparum* infection at weekly surveys**			
2017			
Chemoprevention	17/637 (2.7)	Reference	
Vaccine alone	36/627 (5.7)	2.20 (1.26–3.85)	Reference
Combination	8/648 (1.2)	0.47 (0.21–1.08)	0.21 (0.10–0.46)
2018			
Chemoprevention	46/666 (6.9)	Reference	
Vaccine alone	39/677 (5.8)	0.81 (0.55–1.21)	Reference
Combination	23/685 (3.4)	0.48 (0.30–0.78)	0.59 (0.36–0.97)
2019			
Chemoprevention	26/491 (5.3)	Reference	
Vaccine alone	34/505 (6.7)	1.25 (0.77–2.04)	Reference
Combination	11/518 (2.1)	0.39 (0.19–0.77)	0.31 (0.16–0.60)
***P. falciparum* infection at end-of-season surveys**			
2017			
Chemoprevention	29/1708 (1.7)	Reference	
Vaccine alone	100/1741 (5.7)	3.46 (2.30–5.19)	Reference
Combination	13/1718 (0.8)	0.45 (0.24–0.87)	0.13 (0.07–0.23)
2018			
Chemoprevention	225/1651 (13.6)	Reference	
Vaccine alone	210/1717 (12.2)	0.92 (0.78–1.08)	Reference
Combination	111/1695 (6.6)	0.48 (0.39–0.59)	0.52 (0.42–0.65)
2019			
Chemoprevention	219/1619 (13.5)	Reference	
Vaccine alone	213/1649 (12.9)	0.98 (0.83–1.17)	Reference
Combination	92/1641 (5.6)	0.42 (0.33–0.53)	0.43 (0.34–0.54)
Hemoglobin level <7 g/dl at end-of-season surveys			
2017			
Chemoprevention	21/1710 (1.2)	Reference	
Vaccine alone	28/1742 (1.6)	1.33 (0.76–2.33)	Reference
Combination	18/1719 (1.0)	0.86 (0.46–1.61)	0.65 (0.36–1.17)
2018			
Chemoprevention	38/1655 (2.3)	Reference	
Vaccine alone	40/1717 (2.3)	1.03 (0.67–1.59)	Reference
Combination	12/1695 (0.7)	0.31 (0.16–0.59)	0.30 (0.16–0.57)

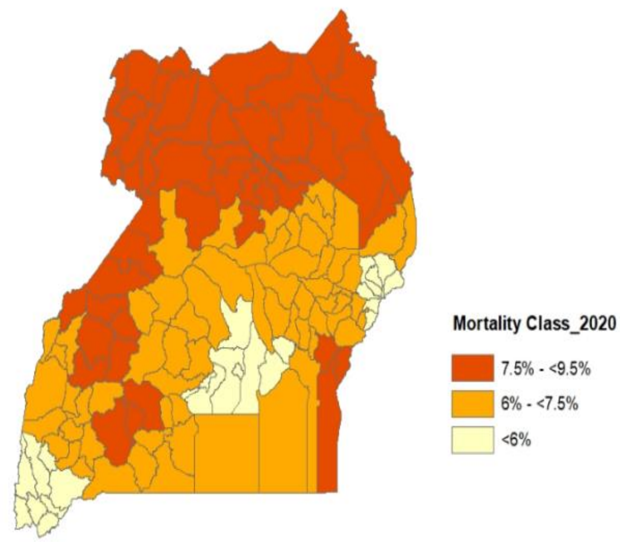
46. Phased roll out plan for Uganda[88]

As the initial vaccine supply outstrips demand, the introduction of the Malaria vaccine will be guided by WHO allocation framework and the Gavi criteria based on malaria prevalence and all-cause under 5 mortality. Using the P. P. falciparum prevalence rate (PfPR), the country was divided into 4 categories:

i. Those above 40% (High transmission),
ii. 20%-40% (High to moderate),
iii. 10%-<20%(Moderate)
iv. and <20% (low transmission),

The All cause under 5 mortality criteria divided the country into 3; high burden (7.5% and above), medium burden (6%<7.5%) and low burden (<6%) as illustrated in the two maps below:



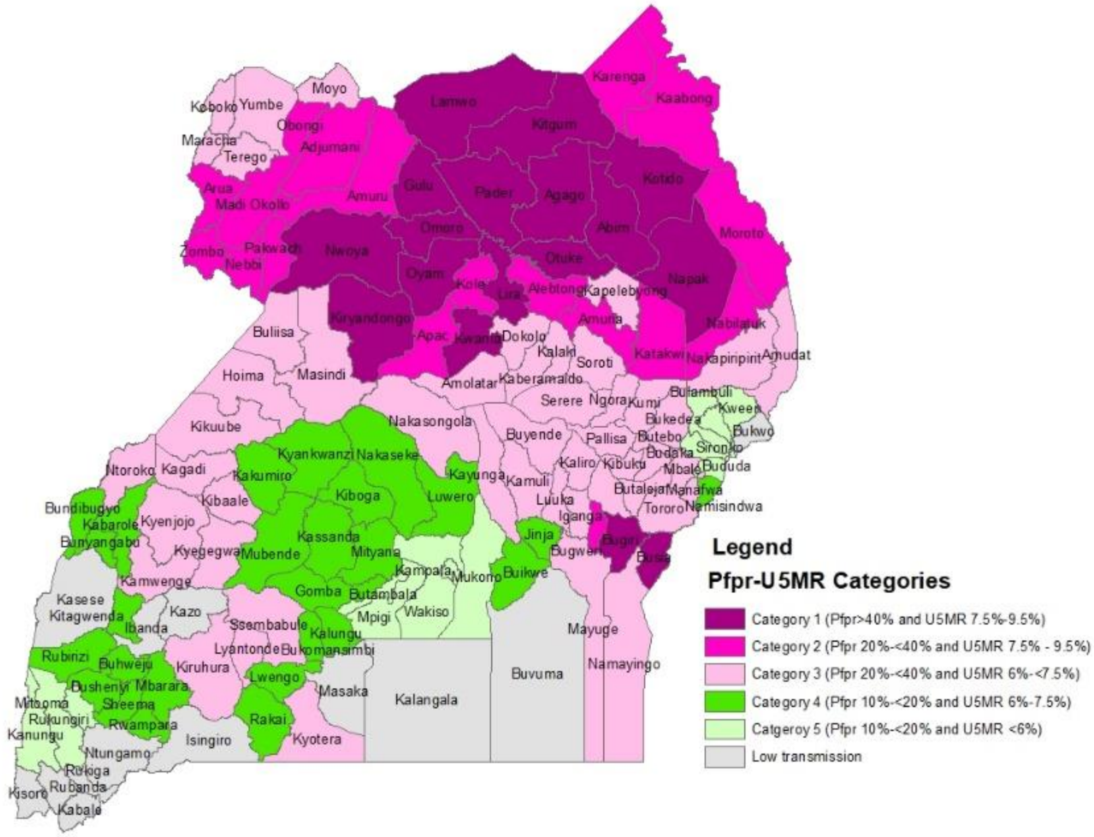


Superimposing the P. Falciparum map over the all cause under 5 motality provided the five categories that subdivieded the country indicating prirotiy need for the malaria vaccine as follows:

i. Areas with Malaria PF prevalence of > 40% and all cause under 5 mortality of 7.5% - 9.5%.
ii. Areas with Malaria PF prevalence of 20- <40% and all cause under 5 mortality of 7.5% - 9.5%.
iii. Areas with Malaria PF prevalence of 20- <40% and all cause under 5 mortality of 6% - < 7.5%.
iv. Areas with Malaria PF prevalence of 10- <20% and all cause under 5 mortality of 6% - < 7.5%.
v. Areas with Malaria PF prevalence of 10- <20% and all cause under 5 mortality of< 6%.

[88] Minstry of Health, 2023. Malaria Vaccine Roll out Strategy

The map below shows the classification for RTS,S Malaria vaccine prioritization for Uganda.



The 19 districts to be prioritized in Category one are as below:

District and City	Birth Cohort_2024	District and City	Birth Cohort_2024
Abim	5,798	Kwania	11,615
Agago	12,362	Lamwo	8,180
Bugiri	20,479	Lira and Lira City	23,891
Busia	17,106	Napak	7707
Gulu and Gulu City	16,979	Nwoya	9,282
Kiryandongo	18,599	Omoro	9,370
Kitgum	9,420	Otuke	7,437
Kotido	8734	Oyam	22,420
		Pader	8,781

Report of the Uganda National Immunisation Technical Advisory Group (UNITAG) on Vaccine Introduction of R21 Matrix-M for the Control of Malaria in Uganda.

1. Background

In October 2021, the World Health Organization (WHO) recommended the first malaria vaccine, RTS,S/AS01, for the prevention of *Plasmodium falciparum (P. falciparum)* malaria in children living in regions with moderate to high transmission, as defined by WHO.

In response to a request from the Ministry of Health, the Uganda National Immunisation Technical Advisory Group (UNITAG) issued a recommendation in July 2023 for the introduction of RTS,S malaria vaccine in Uganda's routine immunization schedule for the reduction of incidence and severity of malaria disease among children in Uganda. Due to global supply limitations of RTS,S, the vaccine was to be rolled out using a phased approach prioritizing areas of highest risk for malaria infection. Under its co-financing arrangement, Gavi approved the supply of 1.45 million doses of RTS,S vaccine to Uganda for 2024-2025.

The WHO Strategic Advisory Group of Experts (SAGE), at their September 2023 meeting, approved a second malaria vaccine, R21/Matrix M, for use in malaria endemic countries. The R21/Matrix-M vaccine aims to reduce clinical malaria due to *P. falciparum* in infants and young children. Similar to RTS,S, R21/Matrix-M generates immunity against the *P. falciparum* pre-erythrocytic circumsporozoite protein (CSP). Their recommendation followed review of evidence from a doubleblind, randomized, controlled Phase 3 trial that began in late April 2021 to assess the safety and protective efficacy of R21/Matrix-M against clinical malaria caused by P. falciparum in children 5–36 months of age at first vaccination using a seasonal vaccination strategy, whereby the primary series and dose 4 given 12 months after dose 3 are given just prior to the malaria transmission season in Nanoro, Burkina Faso, and Bougouni, Mali, (areas of highly seasonal transmission), or using an agebased 4-dose ("standard") vaccine strategy (also referred to in the trial as a "standard" strategy), in Bagamoyo, Tanzania, and Kilifi, Kenya, (areas of low/moderate perennial transmission) and Dandé, Burkina Faso, (an area of highly seasonal moderate transmission).

Subsequently, the Ministry of Health requested UNITAG to review the evidence on R21/Matrix M vaccine and provide guidance on the optimal malaria vaccine product for Uganda. (Annex 1)

2. Introduction

UNITAG adopted the standard NITAG Evidence to Recommendation (EtR) framework to analyze the comparative evidence of the two malaria vaccines, RTS,S and a R21/Matrix M) in the context of Uganda's health system. Criteria covered included, the Problem (disease burden and transmission patterns), benefits and harms of the two vaccines (composition, mode of work, efficacy, effectiveness, and safety), resource use (vaccine cost, cold chain requirements), Equity, Feasibility (scheduling, co-administration), values and preferences, and acceptability. (Annex 2).

The UNITAG adopted the research question and PICO framework as outlined below:

Research Question: Should Uganda switch from RTS, S to R21 for the control of malaria in Uganda?

Population	*Children aged 5+ months in Uganda*
Intervention	*Vaccination with four doses of R 21 starting at 5-17 months of age*
Comparators	*Vaccination with four doses of RTS,S starting at 5-17 months of age Other malaria control interventions without a vaccine*
Outcome	*Decreased incidence and severity of malaria cases, hospitalization due to malaria*

3. Review of Evidence

i. Burden of disease and transmission patterns:

Malaria is endemic in over 95% of Uganda, with a parasite prevalence of 42% among children under 5 years of age. Over 98% of infections are caused by *Plasmodium falciparum*. Malaria transmission is perennial, with two annual peaks following the two rainy seasons (March–May and August–October)[1]. Malaria accounts for 25% of all-cause mortality among children under five.[2]

Uganda is divided into 15 health regions including Acholi, Ankole, Bugisu, Bukedi, Bunyoro, Busoga, Kampala, Karamoja, Kigezi, Lango, North Central, Teso, Tooro and West Nile. Regions of West Nile and Acholi have a high transmission intensity with malaria incidence above 450 cases/1000 population. Lango, Karamoja, Teso, Bukedi and Busoga regions have medium transmission intensity (malaria incidence between 251-450 cases/1000 populations). Low transmission intensity regions with malaria incidence between 101-250 cases/1000 populations include: South central, North Central, Kampala, Ankole, Tooro and Bunyoro regions. Kigezi region has a very low malaria transmission intensity with malaria incidence between 0-100 cases/1000 populations[3].

---

[1] Kamya MR, Arinaitwe E, Wanzira H, Katureebe A, Barusya C, Kigozi SP, Kilama M, Tatem AJ, Rosenthal PJ, Drakeley C, Lindsay SW, Staedke SG, Smith DL, Greenhouse B, Dorsey G. Malaria transmission, infection, and disease at three sites with varied transmission intensity in Uganda: implications for malaria control. Am J Trop Med Hyg. 2015 May;92(5):90312. doi: 10.4269/ajtmh.14-0312. Epub 2015 Mar 16. PMID: 25778501; PMCID: PMC4426576.

[2] (Ministry of Health, 2014. Uganda Malaria Reduction Strategic Plan 2014-2020, Ministry of Health. 2016. Malaria bulletin 2016.)

[3] Zalwango et. al 2023. Uganda National Institute of Public Health Trends and distribution of severe malaria cases Uganda 2017-2021. Analysis of HMIS data. https://uniph.go.ug/trends-and-distribution-of-severe-malaria-caseshttps://uniph.go.ug/trends-and-distribution-of-severe-malaria-cases-uganda-2017-2021-analysis-of-health-management-information-system-data/uganda-2017-2021-analysis-of-health-management-information-system-data/

ii. Benefits and Harms

a) Vaccine technical specifications

The R21/Matrix-M vaccine aims to reduce clinical malaria caused by *P. falciparum* in infants and young children. Similar to RTS,S, R21 targets generation of immunity to the central repeat region of tandemly repeated NANP sequences in the *P. falciparum* pre-erythrocytic circumsporozoite protein (CSP). CSP plays a key role in sporozoite development and hepatocyte invasion.

R21 is a virus-like particle of about 23 nm in diameter and is comprised of a fusion protein of the central repeats and C-terminus of CSP to the N-terminus of the hepatitis B surface antigen (hBsAg). These repeats contain many copies of the four amino acid sequence NANP. The R21 fusion protein is similar to that in RTS,S, but the latter includes unfused hBsAg molecules, while R21 does not contain unfused hBsAg molecules.R21/Matrix-M malaria vaccine, manufactured by the Serum Institute of India Pvt Ltd (SIIPL), is formulated with the saponin-based adjuvant Matrix-M, which is manufactured by Novavax AB.

HBsAg nano particle – fusion above and in table unclear to me

Table 1 Comparison of R21, and RTS,S vaccines

Characteristic	RTS,S/AS01	R21/Matrix-M
Platform	hBsAg nanoparticle	hBsAg nanoparticle
Target	CSP	CSP
Yeast used for production	*Saccharomyces cerevisiae*	*Hansenula polymorpha*
Ratio of CSP fusion protein to unfused hBsAg	1:4	1:0
Adjuvant	AS01 (saponin extract)	Matrix-M (saponin extract)
Primary series	3 doses, 1 month apart	3 doses, 1 month apart
Dose 4	12–18 months following dose 3, but flexibility allowed to reduce interval below 12 months	12 months following dose 3
Dose 5	12 months after dose 4	Optional dose 5, data from Phase 3 trial not yet available

Please see attached Evidence to Recommendation table for a more detailed comparative evidence review by criteria.

4. UNITAG conclusion

While RTS,S and R 21 vaccines have not been directly compared under the same circumstances, similarities in their composition and efficacy data for the two vaccines against clinical malaria in settings of seasonal low medium and high transmission settings suggests that their impact on malaria control is comparable. However, there is no clinical trial evidence that R21 is efficacious in perennial high transmission settings, such as those found in Northern Uganda and West Nile areas where the risk of contracting malaria is highest. Statistically significant data on the impact of the vaccine against severe malaria, hospitalization and death is lacking, as well as peer reviewed evidence of R 21 vaccine safety in HIV positive infants. The committee could not find scientific evidence on the impact of R21 when co-administered with other EPI vaccines. The assumption that data from RTS,S is applicable to R21 is plausible, but not scientifically definitive.

Currently the RTS,S price per dose is nearly 3 times that of R21. As a Gavi eligible country in the initial self- financing phase, in the near term (5-10 years), the co-financing cost of the two vaccines is comparable. Expressed concerns about future costs of the vaccine in the medium to long term as Uganda graduates from Gavi financing are currently speculative. Various market shaping interventions are currently underway meaning factors affecting vaccine price are subject to change over time.

Concerns about inconveniences to the immunization program due to future need for vaccine product switches because of global supply shortages are similarly speculative as there is currently no strong evidence for security of long-term supply of either vaccine.

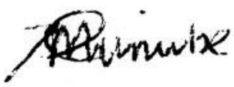
The programmatic ease of use of the single vial (one or two doses) ready to use presentation of R21 compared to the two vial presentation of RTS,S that requires reconstitution needs to be weighed against the intense post market pharmacovigilance surveillance, monitoring and evaluation and research needs accompanying the introduction of R21 due to its evidence gaps and lack of long term data.

UNITAG thus concludes that there is currently insufficient scientific basis to support the introduction of R21 in Uganda's routine immunisation program.

5. UNITAG Recommendation.

As more scientific evidence on R21 becomes publicly available, the question on the scientific evidence base for its introduction in Uganda's routine immunisation schedule for the control of malaria should be revisited at a future time.

Singed



………………………………………………………………………… Date………..15th December 2023……………………….

Dr Deogratias Munube

Co-Chair

Uganda National Immunization Technical Advisory Group

Uganda National Academy of Sciences

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April 12, 2024

The Director General Health Services
Ministry of Health
Uganda
REF: ADM 105/309/15

Dear Sir,

RE: REVIEW OF NEW EVIDENCE ON R21 MALARIA VACCINE

Uganda National Immunisation Technical Advisory Group (UNITAG) assures you of its highest compliments.
Reference is made to your letter to the UNITAG Chair dated February 19, 2024, in which you requested the committee to review updated evidence on R21 malaria vaccine.

UNITAG has reviewed the evidence relevant updated evidence and publications that have become available since its last review in early December of 2023 and come to the conclusion **that that there is sufficient evidence that the desirable consequences clearly outweigh undesirable consequences in most settings** for the introduction of R21 vaccine in Uganda's EPI program.

Based on the reviewed evidence and the above conclusion, UNITAG thus recommends that:

1. **Four doses of R21 malaria vaccine be introduced in Uganda's routine EPI program for children starting at 5-17 months of age.**

2. **UNITAG continue to review updated evidence** on the malaria vaccines as it becomes available, and provides relevant guidance to the Ministry of Health.

The details of the evidence considerations and judgments of UNITAG are provided in the detailed updated report document, and Evidence to recommendation framework as attached.

Sincerely,

Harriet Mayanja Kizza, Prof
CHAIRPERSON, UNITAG

CC Hon Minister of Health
CC Permanent Secretary
CC Director Public Health

OFFICE OF THE DIRECTOR GENERAL HEALTH SERVICES
16 APR 2024
P. O. BOX 7272, KAMPALA

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April 12, 2024

UNITAG Updated Report on R21 Malaria Vaccine

The UNITAG reviewed updated evidence on the R21 malaria vaccine at its sitting on April 4, 2024. Having found the following:

1. The R21 Malaria vaccine was **prequalified by WHO** on 19th December 20231
2. There is now **sufficient malaria vaccine supply to meet demand**, rendering the previous **WHO allocation framework un-necessary**2.
3. **Gavi has approved the 2 dose vial presentation of R21** and revised the criteria for allocation of malaria vaccine to areas with moderate to high *P.falciparum* prevalence. **Gavi has approved Uganda to receive the R21 vaccine in October 2024.**[2]
4. Additional evidence of **mathematical modelling data3 showing that R21 has similar immunogenicity as RTS,S** and further lending credibility to the assumption that the vaccine is expected to perform as well as RTS,S vaccine in areas of low, medium and high malaria prevalence of *P. falciparum* prevalence and both seasonal and malaria transmission scenarios.
5. Additional evidence on R21 vaccine **safety data showing that the vaccine trials among HIV positive** infants in Uganda and **among infants where the vaccine was co-administered with other EPI routine vaccines** in Mali have registered **no safety signals over a 12 month** study period4.

UNITAG **thus concluded that there is sufficient evidence that the desirable consequences clearly outweigh undesirable consequences in most settings** for the introduction of R21 vaccine in Uganda's EPI program.

UNITAG thus **recommends that four doses of R21 malaria vaccine be introduced in Uganda's routine EPI program for children starting at 5-17 months of age.**

UNITAG further recommends that the **UNITAG continue to review updated evidence** on the malaria vaccines as it becomes available.

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1 **WHO Press release:** https://www.who.int/news/item/21-12-2023-who-prequalifies-a-second-malaria-vaccine-a-significant-milestone-in-prevention-of-the-disease

2 **Personal Comms. Dr Mary J Hammel**. WHO Immunisations, Vaccines and Biologicals Dept. **15 March 2024**.

3 **Schmit, N.,** Topazian, H. M., Natama, H. M., Bellamy, D., Traoré, O., Somé, M. A., Rouamba, T., Tahita, M. C., Bonko, M. D. A., Sourabié, A., Sorgho, H., Stockdale, L., Provstgaard-Morys, S., Aboagye, J., Woods, D., Rapi, K., Datoo, M. S., Lopez, F. R., Charles, G. D., . . . Winskill, P. **(2024)**. The public health impact and cost-effectiveness of the R21/Matrix-M malaria vaccine: A mathematical modelling study. *The Lancet Infectious Diseases*. https://doi.org/10.1016/S1473-3099(23)00816-2.

4 **Datoo, M. S.**, Dicko, A., Tinto, H., Ouédraogo, J., Hamaluba, M., Olotu, A., Beaumont, E., Ramos Lopez, F., Natama, H. M., Weston, S., Chemba, M., Compaore, Y. D., Issiaka, D., Salou, D., Some, A. M., Omenda, S., Lawrie, A., Bejon, P., Rao, H., . . . Valea, I. **(2024)**. Safety and efficacy of malaria vaccine candidate R21/Matrix-M in African children: A multicentre, double-blind, randomised, phase 3 trial. *The Lancet*, *403*(10426), 533-544. https://doi.org/10.1016/S0140-6736(23)02511-4

Signed... Date...............................

Harriet Mayanja Kizza (Prof), Chair

Research Question: Should Uganda switch from RTS, S to R21 for the control of Malaria in Uganda?

Population	*Children aged 5+ months in Uganda*
Intervention	*Vaccination with four doses of R 21 starting at 5-17 months of age*
Comparators	*Vaccination with four doses of RTS,S starting at 5-17 months of age* *Other malaria control interventions without a vaccine*
Outcome	*Decreased incidence and severity of malaria cases, and hospitalization*

Criteria			**UNITAG comments**
1. Problem	National Incidence	Regional Incidence	
Malaria incidence and transmission intensity in Uganda	Malaria is **endemic in approximately 95% of the country**, affecting over 90% of the population. The remaining 5% of the country consists of unstable and epidemic-prone transmission areas in the highlands of the south- and mid-west, along the eastern border with Rwanda, and the north-eastern border with Sudan[1]. Malaria accounts for 27% of all hospital deaths in Uganda[2]. Malaria accounts for 19,600 deaths annually in Uganda.	Uganda is divided into 15 health regions including Acholi, Ankole, Bugisu, Bukedi, Bunyoro, Busoga, Kampala, Karamoja, Kigezi, Lango, North Central, Teso, Tooro and West Nile. Regions of West Nile and Acholi have a high transmission intensity with malaria incidence above 450 cases/1000 population. Lango, Karamoja, Teso, Bukedi and Busoga regions have medium transmission intensity (malaria incidence between 251-450 cases/1000 populations). Low transmission intensity regions with malaria incidence between 101-250 cases/1000 population include: South central, North Central, Kampala, Ankole, Tooro and Bunyoro regions. Kigezi region has a very low malaria transmission intensity with malaria incidence between 0-100 cases/1000 population[3].	Malaria transmission in Uganda is mostly perennial and intensity ranges from high, medium, and low.

[1] Ministry of Health, 2014. Uganda Malaria Reduction Strategic Plan 2014-2020
[2]Ministry of Health. 2016. Malaria bulletin 2016. https://www.health.go.ug/cause/malaria-bulletin-2016/
[3] Zalwango et. al 2023. Uganda National Institute of Public Health Trends and distribution of severe malaria cases Uganda 2017-2021. Analysis of HMIS data. https://uniph.go.ug/trends-and-distribution-of-severe-malaria-cases-uganda-2017-2021-analysis-of-health-management-information-system-data/

		RTS,S	R 21	Comments
	WHO prequalification status	WHO prequalified	WHO prequalified on 19/12/2023[4]	**Both vaccine products are WHO prequalified**
	Duration of vaccine trials and follow up	Duration of follow up to 7years	Duration of follow up is 18 months	**For R21, relatively short-term information only is currently available Updated information expected summer of 2024[5]**
1.	**Benefits and Harms**	*Ref. UNITAG recommendation on RTS,S issued June 2023*	*Ref: Background paper Full evidence report on the R21/Matrix-M™ malaria vaccine. WHO SAGE Sept 2023*	
a)	**Composition and mode of work**	RTS,S is RTS,S/AS01 is a monovalent pre-erythrocytic recombinant protein vaccine that comprises *P. falciparum* circumsporozoite protein (CSP) regions known to induce humoral (R region) and cellular (T region) immune responses, covalently linked to the hepatitis B virus surface antigen (S). RTS,S/AS01 elicits humoral and cellular immunity against the circumsporozoite protein amply expressed on the sporozoite surface, thereby limiting the ability of P. falciparum to infect, mature and multiply in the liver. Dosage: 4 doses: 3 monthly doses from 5 months of age and a 4th dose provided after 1 year to prolong protection. 5th dose may be considered where there is a significant malaria risk remaining in children a year after receiving dose 4.	R21 is a virus-like particle and is comprised of a fusion protein of the central repeats and C-terminus of CSP to the N-terminus of the hepatitis B surface antigen (hBsAg). These repeats contain many copies of the four amino acid sequence NANP. The R21 fusion protein is similar to that in RTS,S, but the latter includes unfused hBsAg molecules, while R21 does not contain unfused hBsAg molecules. R21/Matrix-M malaria vaccine, manufactured by the Serum Institute of India Pvt Ltd (SIIPL), is formulated with the saponin-based adjuvant Matrix-M, which is manufactured by Novavax AB. Similar to RTS,S, R21 targets generation of immunity to *P. falciparum* pre-erythrocytic circumsporozoite protein (CSP).	Given the similarity of the vaccines and that RTS, S has had substantial impact in areas of high, moderate, and low transmission, it is likely that R21 will also be efficacious in all malaria endemic settings.

[4] **WHO Press release:** https://www.who.int/news/item/21-12-2023-who-prequalifies-a-second-malaria-vaccine-a-significant-milestone-in-prevention-of-the-disease
[5] Personal Comms. Dr Mary J Hammel. WHO Immunisations, Vaccines and Biologicals Dept. 14 March 2024.

		Same dosing as RTS,S	
b) Efficacy	In the pivotal Phase 3 trial, vaccine efficacy against clinical malaria in 5-17 month old children in settings of seasonal malaria transmission in Burkina Faso and Mali was 67.6% in the 6 months following the third dose. Based on the Phase 3 trial results over 4 years of follow-up, among children 5-17 months of age at the time of first vaccination who were given a fourth dose 18 months after the primary series, RTS,S/AS01 was noted to be immunogenic, and to have moderate protective efficacy against clinical malaria (39%), severe malaria (31.5%), and malaria-related hospitalizations (37.2%). • Vaccine efficacy was reasonably high over the first 6 months following completion of the initial 3 monthly doses (67.6%) but waned over time to essentially zero in the last six-month interval at trial's end, which occurred a median of 48 months after the 3rd dose. At six months following the 4th dose, vaccine efficacy was 42.9%.	Pooled **efficacy against all episodes of clinical malaria (in sites of low to moderate transmission)** for children aged 5-18 months 14 months after 1st dose was **75% when using seasonal administration and 66% when using standard administration**. **There were very few episodes of severe malaria during the trial, hence low statistical power for analysis.** At **seasonal** sites, among all age children (5–36 months at first vaccine dose) through 18 months of follow-up, **VE against severe malaria was estimated at 50%, with confidence intervals that included zero.** •At **standard sites**, through 12 months of follow-up, there **was a slightly higher rate of severe malaria cases in the R21/Matrix-M arm (7 cases) compared to the control arm (3 cases)**. Confidence intervals were wide. Few cases of severe malaria were observed in the trial, and the power to	Although the vaccines have not been assessed and compared to a head situation, separate clinical data shows that to both vaccines have relatively comparable efficacy in settings of seasonal and perennial malaria transmission. Given the similarity of the vaccines and that RTS,S has had substantial impact in areas of high, moderate and low transmission, it is likely that R21 will also be efficacious in all malaria endemic settings. Additional modelling data[6] supports the conclusion that R21 is likely to be as efficacious as RTS,S in all malaria transmission settings

[6] Schmit, N., Topazian, H. M., Natama, H. M., Bellamy, D., Traoré, O., Somé, M. A., Rouamba, T., Tahita, M. C., Bonko, M. D. A., Sourabié, A., Sorgho, H., Stockdale, L., Provstgaard-Morys, S., Aboagye, J., Woods, D., Rapi, K., Datoo, M. S., Lopez, F. R., Charles, G. D., . . . Winskill, P. (2024). The public health impact and cost-effectiveness of the R21/Matrix-M malaria vaccine: A mathematical modelling study. *The Lancet Infectious Diseases*. https://doi.org/10.1016/S1473-3099(23)00816-2

	In a follow up study, vaccine efficacy against severe malaria during **the 6-year or 7-year post-vaccination period in children who had received a booster dose was 36·7%** in the older age group (5–17 months) and **Vaccine Efficacy against uncomplicated malaria during the full follow-up period was 23·7%.**	assess significant VE against severe malaria was insufficient. At seasonal sites, among all age children (5–36 months at first vaccine dose) through18 months of follow-up, 16 cases of malaria hospitalization were recorded, with 8 occurring inthe R21/Matrix-M and 8 in the control arm, resulting in estimates of VE against malaria hospitalization of 50% (95% CI: -32 to 81), noting wide confidence intervals. At standard sites, during 12 months follow-up post dose 3, there were 9 cases of malaria hospitalization in theR21/Matrix-M arm and 4 cases in the control arm, resulting in estimates of VE against malaria hospitalization of -8% (95% CI: -250 to 67), again noting the wide confidence intervals. • No VE estimates against all-cause mortality were statistically significant by site or when stratified by age group at which the first vaccine dose was given.	
c) Duration of protection	Vaccine efficacy in the first 6 months following completion of the initial 3 doses was 68%; efficacy waned over time. Six months after the fourth dose, vaccine efficacy was 43%; thus, although the fourth dose extended the period of protection, it did not restore efficacy to the level seen after the initial vaccine series[7].	At seasonal sites among children of all ages, VE (according to mPP1 population) point estimates remained high for the first 6 months following dose 3 (81% during months 1–3 and 74% during months 4–6), then dropped significantly during months 7–9 (44%), but increased again in months 10–12 (prior to dose 4) to 67% (95% CIs	Both vaccines display a waning of protection after 3 doses, with a booster effect after the fourth dose. Long term data for 3 dose and 4 dose recipients of R21 vaccine were not available at the time, but expected to be similar to that of RTS,S. vaccine[6].

[7] WHO, Malaria Vaccine Position Paper, March 2022. Weekly Epidemiological Record No 9, 2022, 97, 61–80 https://www.who.int/publications-detail-redirect/who-wer9709-61%E2%80%9380

	Vaccine efficacies against severe malaria over the entire follow-up period of 6-7 years in older children were 36.7% (14.6 to 53.1) for the 4-dose group and 10.1% (-18.1 to 31.6) for the 3- dose group[8].	are provided in Table 17). The overall decrease in VE at seasonal sites during months 7–9 was driven largely by a decrease in VE in Nanoro to 42% (95% CI: 16–61). This was due to a large reduction in events during the low transmission season. After dose 4, protective efficacy was maintained during the 6 months post dose 4 follow-up, with point estimates of 70% (13–15 months) and 69% (16–18 months). At standard sites among children of all ages, VE point estimates declined slowly over time (test for trend was not conducted), with point estimates decreasing from 79%, during 1–3 months post dose 3, to 68% during 4–6 months, 64% during 7–9 months, and 63% during 10–12 months .	
d) Effectiveness (Under real life settings)	Pooled effectiveness data across the 3 countries showed **that hospitalization with severe malaria among children eligible for at least 3 doses of vaccine was reduced by 29%** (rate ratio 0.71 (95% CI 0.55–0.93), and hospitalization with malarial parasitaemia or antigenaemia was reduced by 21% (95% CI 7–32) (WHO position paper, 2022)	Published data not available.	R21 long term effectiveness is unknown. Extrapolations based on RTS,S data expect similar effectiveness values. Plausibility based on similarities in vaccine components and modelling data[6.]
e) Safety	In clinical studies, the most serious adverse reaction associated with RTS,S was febrile seizures (within 7 days post-vaccination) (0.1%). This effect was transient, and all affected children recovered after 7 days. The most commonly reported adverse reactions	Overall, in the Phase 3 trial, as of 31 March 2023, frequency of Severe Adverse Events was balanced between the study arms[9]. Six SAEs were considered related to vaccination (all febrile convulsions – 5 in	Both vaccines have a comparable AEFI profile among healthy infants. Febrile convulsions are a side effect with both vaccines, which resolves within a week.

8 8 RTS,S/AS01 SAGE/MPAG Working Group. SAGE Meeting October 2021. Full evidence report on the RTS,S/AS01 malaria vaccine

	were fever (27%), irritability (14%) and injection site reactions such as pain (16%) and swelling (7%) (European Medicines Agency, 2015, who Position Paper 2022). The safety profiles were similar for HIV infected, pre-term and malnourished babies (Otieno et. al., 2020.)	the R21/Matrix-M vaccine arm and 1 in the rabies vaccine arm); all resolved without sequelae. In a Phase 1b trial (VAC092 – NCT05385510) 100 HIV-positive (WHO HIV stage 1 or 2 disease) Ugandan children aged 5—36 months have been enrolled to receive R21/Matrix-M vaccine to assess safety and immunogenicity. Immunizations with R21/Matrix-M began in mid-January 2023. Another group (*n* = 150) has been enrolled to assess the safety and immunogenicity of co-administration of R21/Matrix-M administered as a third dose at approximately 9 months of age with yellow fever and measles-rubella vaccines. Vaccinations began in early 2023; and results show no safety concerns after 12 months[9] . This study also assessed the co-administration of R21/Matrix-M with pentavalent (diphtheria, tetanus, pertussis, hepatitis B and *Haemophilus influenzae* type b), rotavirus, pneumococcal, and oral polio vaccines (OPV) at 6, 10 and 14 weeks of age (*n* = 30); children l also received inactivated	. Vaccine safety trial among HIV infected infants in Uganda shows no safety concerns to date[9] Vaccine safety trials in Mali looking at safety of co-administering R21 with EPI vaccines in Mali shows no safety concerns to date[9]

[9] Datoo, M. S., Dicko, A., Tinto, H., Ouédraogo, J., Hamaluba, M., Olotu, A., Beaumont, E., Ramos Lopez, F., Natama, H. M., Weston, S., Chemba, M., Compaore, Y. D., Issiaka, D., Salou, D., Some, A. M., Omenda, S., Lawrie, A., Bejon, P., Rao, H., . . . Valea, I. (2024). Safety and efficacy of malaria vaccine candidate R21/Matrix-M in African children: A multicentre, double-blind, randomised, phase 3 trial. *The Lancet*, *403*(10426), 533-544. https://doi.org/10.1016/S0140-6736(23)02511-4

		polio vaccine (IPV) 2 weeks following dose 3 of R21/Matrix-M.	
2. Resource Use		*Ref. WHO presentation to UNITAG 27/11/2023*	
a) Vaccine cost per dose	The RTS,S/AS01 malaria vaccine will cost EUR 9.30 (USD 9.09) per dose for supply during 2023-2025[10]. The RTS,S vaccine is available on the GAVI support portfolio[11] and under the Gavi co-financing requirements, would cost the country $0.2 per dose in co-financing. With the GSK transfer of production of RTS,S/AS01 to Bharat Biotec India Limited and the potential entry of R21/Matrix-M into the market, the average price per dose is expected to decrease over time, and supply volumes are predicted to improve.	The initial price of R21/Matrix-M vaccine has been announced at US$ 3.90 per dose. The R21 vaccine is available on the GAVI support portfolio and would cost the country $0.2 per dose in co-financing.	No difference in co-financing cost to country in the next 5-10 years, as Uganda is under the initial self-financing Gavi grant category. The current vaccine cost of R21 is about one third that of the RTS,S. The future cost of the two vaccines in the next 5 to10 years when Uganda is envisaged to begin its Gavi transition phase and increasingly meet its own vaccine costs is hard to predict as it is subject to very many variables.
b) Cold chain space requirements	RTS,S vaccine presentation is a 2-dose vial of lyophilized (freeze-dried powder) RTS,S antigen clipped to a 2-dose vial of liquid AS01 adjuvant suspension to be used for reconstitution. The vaccine requires storage at 2-8°C. Shelf-life is 3 years. There is a VVM on the side of diluent ASO1 vial. There is no preservative, once reconstituted the RTS,S vaccine must be discarded after six hours, or at the end of the session, whichever comes first.	R21/Matrix-M is available in ready to use liquid formulation in a single-vial and two dose vial vaccine presentation. Shelf-life of 24 months at 2–8 °C. Gavi supports the 2 dose vial presentation only. Each vial has a VVM. Cold chain space requirement is 7.03 cc/dose (in secondary packaging)	R21 two dose-vial presentation requires no reconstitution, thus simplifying delivery, reducing the need for ancillary supplies. Cold chain Storage requirements are higher with RTS,S by about 2.6 cc per dose

[10] UNICEF Supply Division, Aug 2022. Malaria Vaccine: Questions and Answers on Vaccine Supply, Price and Market Shaping. https://www.unicef.org/supply/media/13396/file/Malaria-Vaccine-Supply-Price-Market-Questions-Answers-August2022.pdf

[11] Gavi the Vaccine Alliance. Gavi Board approves funding to support malaria vaccine roll-out in Sub Saharan Africa. https://www.gavi.org/news/media-room/gavi-board-approves-funding-support-malaria-vaccine-roll-out-sub-saharan-africa

	The cold chain volume for RTS,S vaccine is 9.7 cc/dose[12].	MoH assessment shows sufficient national level cold chain space, and a deficit of 7,000 litres sub-nationally, with plans to fill this gap in the next two years.	
3. Equity			
What would be the impact on health inequities?	RTS,S vaccine is currently available on the GAVI portfolio for areas with moderate to high prevalence (*P. falciparum* parasite prevalence greater than 10% **or** an annual incidence greater than 250 per 1000 [WHO guidelines for malaria, 16 October 2023]") starting January 2024.	Based on current estimated demand from countries, and subject to approximately four (4) months production lead time from confirmed order Uganda has been approved by Gavi to receive R21[5.] Vaccine roll out is expected in areas of high and medium prevalence in October, 2024	. The framework for allocation of limited supplies that was previously required due to low vaccine supply no longer applies.[5] Regions with low malaria prevalence will have to wait for the GAVI 6.0 strategy decision, expected in 2026.
4. Vaccine supply[13]	Over the 2023-2025 period, GSK, the developer and manufacturer, expects to produce approximately 18 million doses in total, with 4 million doses being available for supply from late 2023. Expected availability for 2024 is 6 million doses, and 8 million doses in 2025. UNICEF has secured access to these volumes through a supply agreement established between the parties. Working towards increasing production volumes, with a plan to produce 15 million doses annually from 2026 through 2028.	Following the WHO recommendation for the R21/Matrix-M vaccine, and through a recently executed conditional supply agreement, UNICEF secured access to R21/Matrix-M.. Based on current estimated demand from countries, and subject to approximately four (4) months production lead time from confirmed order, UNICEF expects sufficient supply availability to meet countries' needs in 2024 and beyond as per WHO recommendations.	. The availability of two WHO recommended and pre-qualified vaccines is expected to result in sufficient supply to meet demand starting in 2024.

[12] WHO, 2015. Background Paper: Programmatic Options for Implementation of Malaria RTS,S Vaccination Schedule for Young Children. https://terrance.who.int/mediacentre/data/sage/SAGE_Docs_Ppt_Oct2015/7_session_malaria/Oct2015_session7_JTEG_Programmatic_Options%20_malarai_vaccine.pdf

[13] Unicef Supply division October 2023.Malaria Vaccines. Questions and Answers on Supply, Price and market shaping. https://www.unicef.org/supply/media/19456/file/Malaria%20-%20Vaccine%20-%20QA%20-%20October%202023%20-%20English%20.pdf

	To ensure long-term sustainable supply, accessibility, and affordability of RTS,S/AS01 vaccine, GSK, Bharat Biotech (BBIL), and PATH announced in January 2021 the signing of a technology transfer agreement which is expected to be completed by 2028. The technology transfer to BBIL is the pathway towards increased supply of RTS,S/AS01, as UNICEF expects BBIL to have a greater antigen manufacturing capacity than GSK (i.e., greater than 15 million doses per year). GSK confirmed it will double the production of its AS01 adjuvant for use in the RTS,S/AS01 malaria vaccine to enable increased production capacity at BBIL. GSK's commitment to supply the AS01 adjuvant currently extends until the end of 2042.		
5. Feasibility	Non-inferiority of immune responses to the vaccine antigens was evaluated 1 month following co-administration *versus* RTS,S/AS01 or EPI vaccines (YF and MR vaccines) alone. Regarding impact on efficacy of RTS,S vaccine, one month after the third dose of RTS,S/AS01, the results showed 100% anti-HBs antibody sero-protection rates in both groups. Uganda has adopted 6 months, 7 months and 8 months for the first three doses maintaining a minimum interval of 4 weeks. The 1st dose will be given from 6 months and capped at 1 year. The 4th dose will be given at 18 months of age to coincide with MR2. The vaccine requires reconstitution before administration.	Proposed schedule similar to RTS,S The ready to use liquid vaccine is packaged in a 2 dose vail. WHO recommends that opened vials of this vaccine should be discarded 6 hours after opening or at the end of the immunization session, whichever comes first.	Schedules for both RTS,S and R21 are similar and feasible to implement within the current routine immunisation schedule. R21 may be easier for the health-workers to use, as it requires no reconstitution.

	WHO recommends that opened vials of this vaccine should be discarded 6 hours after opening or at the end of the immunization session, whichever comes first.		

<table>
<tr><td>Balance of consequences</td><td>Desirable consequences clearly outweigh undesirable consequences in most settings</td></tr>
<tr><td>Type of recommendation</td><td>We recommend the intervention</td></tr>
<tr><td>Recommendation (text)</td><td>UNITAG recommends the introduction of R21 malaria vaccine in Uganda’s routine immunisation program.</td></tr>
<tr><td>Implementation considerations</td><td>Gavi supports the roll out of the vaccine in all regions with moderate to high malaria prevalence.</td></tr>
<tr><td>Monitoring and evaluation</td><td rowspan="2">The SAGE/MPAG recommendation on R21 identified the following high priority areas for Monitoring and evaluation as well as research:
i. Immunological co-administration studies with other relevant infant vaccines such as pneumococcal conjugate vaccines, rotavirus, pentavalent vaccines (DTP-HepB-Hib), IPV, typhoid conjugate vaccine, meningococcal vaccine, hexavalent (DTwP-HepB-IPV-Hib)vaccine, measles vaccine, and observational studies for the occurrence of febrile seizures
ii. Post-licensure evaluation studies should be conducted on vaccine effectiveness in high perennial transmission settings, which are not represented in the Phase 3 trial
iii. Monitoring for risk of malaria rebound and collecting further data on severe malaria and mortality as part of the ongoing Phase 3 trial and 4 years of follow-up (already planned by the developer)</td></tr>
<tr><td>Research priorities</td></tr>
</table>

Sciences for Prosperity

COMBINED MPOX REPORTS

Uganda National Academy of Sciences

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Sciences for Prosperity

September 09, 2024

The Director General Health Services
Ministry of Health
Uganda
REF: ADM 105/309/15

Dear Sir,

RE: RESPONSE TO REQUEST FOR NITAG GUIDANCE AND RECOMMENDATION ON THE MPOX VACCINE

Uganda National Immunisation Technical Advisory Group (UNITAG) assures you of its highest compliments.

Reference is made to your letter to the UNITAG Chair dated July26, 2024, in which you requested the committee to review relevant evidence and provide guidance on the Mpox vaccine for high risk population groups in Uganda.

The UNITAG has reviewed the available evidence on Mpox vaccines viz-a-vis the country's disease and health system context and concluded that there is sufficient scientific evidence on which to base a recommendation for a targeted introduction of two vaccines, MVA BN and LC 16, for populations at highest risk of contracting the disease and or severe outcomes or death.

The UNITAG will continue to review more scientific evidence on Mpox vaccines as it becomes publicly available, and also closely observe the country's evolving disease situation and provide periodic updates to this recommendation as necessary.

A detailed report and Annex table highlighting the UNITAG's judgment on the various aspects related to Mpox vaccine introduction are attached for your consideration.

Sincerely,

Dr. Deogratias Munube
CO-CHAIRPERSON, UNITAG

09 SEP 2024

EtR Framework

PICO Questions	1. Should Uganda introduce a vaccine against Mpox for high-risk populations to halt Mpox transmission? 2. Which populations are at the highest risk of contracting Mpox, and suffering severe effects or death? 3. Which Vaccines should Uganda use to prevent an outbreak Mpox in Uganda? 4. What mode of introduction should be used? WHO EUL or Research?			
Background				
DOMAINS	CRITERIA	JUDGEMENTS	EVIDENCE	ADDITIONAL INFORMATION
1. Problem	Is the problem of public health importance?	Yes, considering the Africa CDC and WHO declarations, and meeting the WHO Mpox outbreak. (2+ confirmed cases) Uganda is at risk of bigger outbreaks due to proximity to DRC, and inadequate capacity to diagnose and to identify exposure accurately.	a) Mpox (monkeypox) is a **zoonotic infectious disease** caused by the monkeypox virus (Orthopoxvirus). **Mpox spreads through contact with infected individuals, animals, and contaminated materials. Animal-to-human transmission of mpox occurs from infected animals to humans** from bites or scratches, or during activities such as hunting or eating animals. The **animal reservoir** of the monkeypox virus remains **unknown**.[1] There are two known clades; clade I, previously known as the Congo Basin clade; and clade II, previously called the West African clade[1.] The common symptoms of Mpox include skin rash or mucosal lesions which can last 2–4 weeks accompanied by fever, headache, muscle aches, back pain, low energy, and swollen lymph nodes Most cases are self-limiting.[1]. **Severe mpox** can include larger, more widespread lesions (especially in the mouth, eyes and genitals), conditions such as **inflammation of the heart, brain or other organs**, or **secondary bacterial infections** of the skin or blood and lung infections[1]. b) **Sexual contact** is the most commonly reported mode of **human to human transmission: 83.8%**[2]. Other transmission routes are	Africa CDC declared Mpox a Public Health Emergency of Continental Security on August 13, 2024. On 14th August 2024, WHO declared Mpox a Public Health Emergency of International Concern

[1] WHO 2024. Mpox Factsheet. https://www.who.int/news-room/fact-sheets/detail/mpox

[2] Pinto, P., Costa, M. A., Gonçalves, M. F., Rodrigues, A. G., & Lisboa, C. (2023). Mpox person-to-person transmission—where have we got so far? a systematic review. *Viruses*, *15*(5), 1074.

			respiratory particles, and sharing the same household surfaces. Incubation period is 7-14 days. **Persons with immune suppression** (such as those with advanced/untreated HIV) are **at higher risk of developing severe mpox** or dying2. Globally, 96.4% (87,189 of 90,410 cases) of confirmed cases with available data are male, with a median age of 34 years[2]. c) **Lab confirmation is by testing skin lesion materials by PCR and treatment is with supportive care**. Mpox is treated with supportive care for symptoms such as pain and fever, skin care, prevention of secondary infections and treatment of co-infections[1]. d) As of Aug 2024, the Africa CDC reported **2,863 confirmed cases and 517 deaths in the region, primarily in the Democratic Republic of Congo (DRC) with a case fatality of 3%.** Suspected cases across the continent have surged past 17,000, a significant increase from 7,146 cases in 2022 and 14,957 cases in 2023[2]. e) In DRC **children under 15 years** of age represent the **most reported** mpox cases[2]. f) **As of 04 Sept, 2024, ten confirmed cases of Mpox in Uganda**, distributed **across all geographical regions** (Kasese, Mayuge, Kampala, Wakiso and Amuru districts). 6 of them are men, 3 are HIV+, 1 pregnant mother, and 1 child under 15 years. 3 cases, one confirmed and two suspected having severe effects. No deaths have been registered.[3] g) Apart from the **first 2 cases with Clade 1b linked to DRC**, the **transmission chains of other cases are unknown**. Contact tracing is suboptimal. Limited lab testing facilities and inaccuracies in diagnosis are some of the response challenges. The epidemic response plan is currently unfunded[3]. h) **High risk populations in Uganda** have been profiled as follows: i. *Transmission risk*: *extremely high* - Health care workers or other caretakers who manage cases and samples, Sexual contacts of confirmed case of Mpox disease/ *very high*- Sex workers, Persons with multiple sex partners of cases, Family or other social contacts	

[3] MoH, 2024. Mpox Status Update to Strategic Committee.

			of a confirmed case/ *high* - Travelers from epicenters established MPOX community ii. *Severe or fatal outcomes risk- extremely high*: PLWHA with poorly controlled, viremia, Pregnant women, - Children < 5yrs/ *very high*: Persons on Immuno-suppresive treatments, Persons with congenital or chronic disease that affects T cell function e.g congenital T cell deficiency syndromes, Leukemia, Diabetes Mellitus, etc.	
2. Benefits & harms of the options	Are desirable anticipated effects large? Are undesirable anticipated effects small? Balance between benefits and harms. What is the quality of evidence for critical outcomes?	Are desirable effects large? **MVA BN** Efficacy of intervention- High Overall quality of evidence for critical outcomes Efficacy- high for adults, moderate for children Safety- high for adults, moderate for children	Mpox vaccines are developed in formulations based on the vaccinia virus, which offer some cross-protection for the immune response to orthopox viruses. At present, WHO has not prequalified or Emergency Use listed any mpox vaccines but recommends use of MVA-BN 93rd generation non replicating) or LC16 vaccines (3rd generation minimally replicating, or the ACAM2000 vaccine (2nd generation replicating) when the others are not available[4]. **MVA-BN** (non-replicating- subcutaneous or intradermal injection/liquid, frozen or freeze dried). Third generation vaccine. Licensed in USA (vs. Mpox 2019) for use in adult populations. Emergency authorization in USA for under 18 yrs[4]. **Vaccine Efficacy** MVA-BN induces strong cellular activity (CTL) as well as humoral (antibody) immune response and has demonstrated an ability to stimulate a response even in individuals with pre-existing immunity against vaccinia.1 and 2 doses of MVA-BN were highly effective at preventing Mpox with a VE for 1 dose was 76% (95%CI 64–88%) and 82% (95%CI 72–92%) for 2 doses. Additionally, MVA-BN vaccination may also have some benefit in preventing hospitalization with a VE of 67% (95%CI 55–78%).[5]	Vaccination is recommended for high-risk groups, including healthcare workers, individuals with multiple sexual partners, men who have sex with men, and contacts of persons with mpox and sex workers[4]. Clinical features and outcomes of repeat infection and infection after complete vaccination appear to be less clinically severe[12]

[4] WHO 2022. Vaccines and Immunisation for Monkey POX. Interim guidance.

[5] Pischel, L., Martini, B. A., Yu, N., Cacesse, D., Tracy, M., Kharbanda, K., Ahmed, N., Patel, K. M., Grimshaw, A. A., Malik, A. A., Goshua, G., & Omer, S. B. (2024). Vaccine effectiveness of 3rd generation mpox vaccines against mpox and disease severity: A systematic review and meta-analysis. *Vaccine*. https://doi.org/10.1016/j.vaccine.2024.06.021

[12] Hazra A, Zucker J, Bell E, Flores J, Gordon L, Mitjà O, Suñer C, Lemaignen A, Jamard S, Nozza S, Nori AV, Pérez-Barragán E, Rodríguez-Aldama JC, Blanco JL, Delaugerre C, Turner D, Fuertes I, Leiro V, Walmsley SL, Orkin CM; SHARE-NET writing group. Mpox in people with past infection or a complete vaccination course: a global case series. Lancet Infect Dis. 2024 Jan;24(1):57-64. doi: 10.1016/S1473-3099(23)00492-9. Epub 2023 Sep 4. PMID: 37678309.

			Fractional dosing: In immuno-competent adult individuals, MVA-BN administration at 1/5th (0.1 Ml) of the standard sub cutaneous dose was found to be immunologically non-inferior compared to the standard sub-cutaneous dose for a period of six months[6]. **Duration of protection**: it is estimated that antibody titers after two doses of MVA-BN vaccination (with 28-day interval) remain above or equal to the peak GMT of one dose for **81 days** (CI:72–93) and above historically vaccinated cohorts for 102 days (CI: 74–173). Analysis predicts **vaccination with one dose of MVA-BN** will have an **effectiveness of 64.8% (CI:47.8–76.9) at two years post-vaccination**. A **two-dose regimen** on a 4-week schedule is anticipated to still **provide 71.8% (CI:58–80.8) effectiveness from mpox infection at two years.** Extrapolating antibody decay beyond the available time series predicts the level **of long-term effectiveness from 1- and 2-dose** MVA-BN vaccination (with 28-day spacing) after 10 years will be **59.2% (CI: 38.7–74.2) and 66.6% (CI:48.8–78.2),** respectively[7]. **Safety**: Besides general disorders and **administration-site conditions** (57%) the most common adverse events within 29 days after MVA vaccination were **headache** (16**%), myalgia** (14%), and **lymphadenopathy** (9%). **No Serious Adverse Events** were observed[8]. MVA-BN is well tolerated with similar immunogenicity and the rates of adverse events in persons with HIV[9]. In children, a study in England testing blood samples and using an online questionnaire for AEFI monitoring, targeting 87 children, median age was 5 years (IQR 5–9), where Seven (8%) of 87 children provided a first blood sample a median of 6 weeks after vaccination and five at a median of 15 weeks (14–15). All children had poxvirus IgG antibodies	

[6] Schnyder JL, De Pijper CA, Garcia Garrido HM, Daams JG, Goorhuis A, Stijnis C, et al. Fractional dose of intradermal compared to intramuscular and subcutaneous vaccination - A systematic review and meta-analysis. Travel Med Infect Dis. 2020 Sep-Oct;37:101868. doi: 10.1016/j.tmaid.2020.101868.

[7] Berry, M.T., Khan, S.R., Schlub, T.E. *et al.* Predicting vaccine effectiveness for mpox. *Nat Commun* **15**, 3856 (2024). https://doi.org/10.1038/s41467-024-48180-w

[8] Pittman PR, Hahn M, Lee HS, Koca C, Samy N, Schmidt D, Hornung J, Weidenthaler H, Heery CR, Meyer TPH, Silbernagl G, Maclennan J, Chaplin P. Phase 3 Efficacy Trial of Modified Vaccinia Ankara as a Vaccine against Smallpox. N Engl J Med. 2019 Nov 14;381(20):1897-1908. doi: 10.1056/NEJMoa1817307. PMID: 31722150.

[9] O'Shea, J. (2022). Interim guidance for prevention and treatment of monkeypox in persons with HIV infection—United States, August 2022. *MMWR. Morbidity and Mortality Weekly Report*, *71*

			with titres well above the assay cutoff of OD_{450nm} 0·1926 with mean absorbances of 1·380 at six weeks and 0·9826 at 15 weeks post-vaccination. Regarding AEFIs, 16 (36%) reported no symptoms, 18 (40%) reported local reaction only, and 11 (24%) reported systemic symptoms with or without local reactions. The study concluded that a single dose of MVA–BN for post-exposure prophylaxis was well-tolerated in children and induced robust antibody and cellular immune responses up to 15 weeks after vaccination[10] In the 2022 US outbreak, children as young as 4 months were vaccinated with MVA BN as PEP after a known exposure, with no serious AEFIs registered after administering over 1600 doses[11].	
		LC 16 Efficacy of intervention- moderate Efficacy of intervention- high, for adults Overall quality of evidence for critical outcomes Efficacy- moderate for adults Safety- moderate	**LC16-** minimally replicating freeze dried vaccine licensed in Japan (vs. mpax 2022) for use in all ages including infants. LC16m8 is inoculated singly and intradermally using a bifurcated needle and multiple-puncture technique. **Efficacy and safety**: No clinical trial efficacy data for LC16 specifically against Mpox is available. However, several studies on the efficacy and safety of the LC16 vaccine confirmed the induction of neutralizing antibodies against MPXV**, and no serious adverse events related to the LC16 vaccine were observed**. A study in Japan with 3000+ participants reported that **sero-conversion or an effective booster response among the individuals with take was elicited in 37 of 41 (90.2% [95% CI, 81.2%-99.3%]) vaccinia-naive participants and in 93 of 155 (60.0% [95% CI, 52.3%-67.7%]) previously vaccinated participants**. One case of allergic dermatitis and another of erythema multiforme, both of which	

[10] Ladhani SN, Dowell AC, Jones S, Hicks B, Rowe C, Begum J, Wailblinger D, Wright J, Owens S, Pickering A, Shilltoe B, McMaster P, Whittaker E, Zuo J, Powell A, Amirthalingam G, Mandal S, Lopez-Bernal J, Ramsay ME, Kissane N, Bell M, Watson H, Ho D, Hallis B, Otter A, Moss P, Cohen J. Early evaluation of the safety, reactogenicity, and immune response after a single dose of modified vaccinia Ankara-Bavaria Nordic vaccine against mpox in children: a national outbreak response. Lancet Infect Dis. 2023 Sep;23(9):1042-1050. doi: 10.1016/S1473-3099(23)00270-0. Epub 2023 Jun 16. PMID: 37336224.

[11] US CDC, 2024. Clinical Considerations for Mpox in Children and Adolescents in the U.S. https://www.cdc.gov/poxvirus/mpox/clinicians/pediatric.html

			were mild and self-limited, were suspected to be caused by vaccination. No severe adverse events were observed.[13] A 2024 report of a multicenter, randomized, open-label trial where **1006 high risk adults** of median age was 41 years were vaccinated with LC16; 99.7% were male and 34.4% had human immunodeficiency virus (HIV). **No mpox cases occurred**, precluding VE calculations. **Serious adverse events (SAE) were observed in 0.6% (HIV-infected) and 0.5% (uninfected) of patients**. One participant without HIV reported pulmonary embolism and deep vein thrombosis as causally undeniable SAE. Local skin reactions (97%); systemic reactions: 64% were reported[14].	
		ACAM2000 Efficacy of intervention- moderate Overall quality of evidence for critical outcomes Efficacy- low Safety- low	ACAM2000- No human efficacy data against mpox available but has shown efficacy against mpox in animal challenge study. Antibody-mediated depletion of B cells, but not CD4+ or CD8+ T cells, abrogated vaccine-induced protection from a lethal intravenous challenge with monkeypox virus. In addition, passive transfer of human vaccinia-neutralizing antibodies protected nonimmunized macaques from severe disease. [15] Severe and long-term side effects like myopericarditis have been reported to be found in approximately every 20 individuals out of 100,000 ACAM2000 vaccine recipients.[32] Duration of protection is unknown, though reported case of full blown disease eight years after vaccination in the US[16].	

[13] Saito T, Fujii T, Kanatani Y, Saijo M, Morikawa S, Yokote H, Takeuchi T, Kuwabara N. Clinical and immunological response to attenuated tissue-cultured smallpox vaccine LC16m8. JAMA. 2009 Mar 11;301(10):1025-33. doi: 10.1001/jama.2009.289. PMID: 19278946.

[14] Okumura, Nobumasa & Morino, Eriko & Nomoto, Hidetoshi & Yanagi, Mashiho & Takahashi, Kozue & Iwasaki, Haruka & Uemura, Yukari & Shimizu, Yosuke & Mizushima, Daisuke & Fukushima, Kazuaki & Kinai, Ei & Shiojiri, Daisuke & Itoda, Ichiro & Onoe, Yasuhiko & Kobori, Yoshitomo & Nakamura, Fukumi & Tokita, Daisuke & Sugiura, Wataru & Ohmagari, Norio & Ujiie, Mugen. (2024). Safety and Effectiveness of LC16m8 for Pre-Exposure Prophylaxis against mpox in a High-Risk Population: An Open-Label Randomized Trial. 10.1101/2024.06.06.24308551.

[15] Edghill-Smith, Y., Golding, H., Manischewitz, J., King, L. R., Scott, D., Bray, M., … Franchini, G. (2005). *Smallpox vaccine–induced antibodies are necessary and sufficient for protection against monkeypox virus. Nature Medicine, 11(7), 740–747.* doi:10.1038/nm1261

[16] Turner, M., Mandia, J., Keltner, C., Haynes, R., Faestel, P., & Mease, L. (2022). Monkeypox in Patient Immunized with ACAM2000 Smallpox Vaccine During 2022 Outbreak. Emerging Infectious Diseases, 28(11), 2336-2338. https://doi.org/10.3201/eid2811.221215

3. Values & preferences	Does the target population feel the desirable effects are large relative to the undesirable effects?	Target population preferences are mixed, with low acceptance in cases with little information about the disease and vaccines. Fear of vaccines is driven by inadequate research information and serious adverse events.	An online survey was run among **HCW and community members in Saudi Arabia** to **assess participants' MPOX and monkeypox virus (MPV) knowledge** in terms of transmission, vaccination, isolation precautions, and their attitudes toward seeking more information among HCW and community groups. Both groups **showed a decent attitude in terms of seeking more MPOX knowledge**, which correlated positively with their worry about and awareness of the disease. These observations are **mostly as a consequence of the ongoing COVID-19 pandemic**, which encouraged the public and HCW to acquire more information about any novel emerging disease[17]. A **cross-sectional observation study among high risk population** in Italy showed that most respondents got their information about Mpox from, televisions, newspapers, and social media, and few from health workers. While most respondents expressed fear of contracting the disease and acknowledged their risk behavior, **when asked if they would accept a vaccine to prevent the disease, more than a third (46;32%) of respondents expressed hesitation or complete refusal to be vaccinated**[18]. A **descriptive cross-sectional study in Cameroon**, showed that while local populations in rural villages facing instability were at high risk of Mpox, due to high game meat consumption rates, **significant knowledge gaps were noted**. out of the 398 participants from the Southwest and Littoral recruited in this study, **196(49.2%) participants reported that fear can cause them to hesitate or deny the vaccine, while 92 (23.1%) participants reported that mpox can be treated traditionally in their culture**[19].	

[17] Temsah, H., Aljamaan, F., Alenezi, S., Abouammoh, N., Alhasan, K., Dasuqi, S. A., Alhaboob, A., Hamad, M. A., Halwani, R., Alrabiaah, A., Alsubaie, S., Alshahrani, F. S., AlZamil, F., Memish, Z. A., Barry, M., & Al-Tawfiq, J. A. (2022). Monkeypox Disease (MPOX) Perceptions among Healthcare Workers versus General Population during the First Month of the WHO Alert: Cross-Sectional Survey in Saudi Arabia. *Vaccines*, *10*(12). https://doi.org/10.3390/vaccines10122071

[18] Crosato, V., Formenti, B., Gulletta, M. et al. Perception and Awareness about Monkeypox and Vaccination Acceptance in an At-Risk Population in Brescia, Italy: An Investigative Survey. AIDS Behav 28, 1594–1600 (2024). https://doi.org/10.1007/s10461-024-04271-9

[19] Tambo et al., 2024. Assessment of risk perception and determinants of mpox for strengthening community engagement in local populations in Cameroon https://doi.org/10.1101/2024.03.20.24304629. Pre-print.

			The findings were similar in Nigeria, despite the country contributing 60% of confirmed mpox infection in Africa, analysis study findings revealed **significant knowledge gaps and a very low level of public awareness about mpox**. Key areas of limited knowledge included the disease's **route of transmission, as well as its prevention and treatment**[20]. Drawing from the **Uganda COVID-19 vaccine experience health-worker perceptions**, common **reasons for not wanting a COVID-19 vaccine were concerns that the vaccines were new (*n* = 75/107; 70.1%) and fear of side effects** (*n* = 74/107; 69.2%)[21].	
4. Resource use	Are the resources required small? What is the cost-effectiveness?	The vaccine purchase price is very high. Option for subsidized costs in donations, and research trial.	Market **price for MVA-BN is $100 per dose**[22]. The manufacturer, Bavarian Nordic, has **ample production capacity to supply Africa with some two million Mpox doses by the end of this year, and another eight million doses by end 2025**[22]. **Africa CDC estimates that currently a requirement of at least 10 million doses**, based on estimates from countries that have prepared vaccination plans[23]. The WHO has issued an invitation to manufacturers to submit applications for EUL listing. Gavi has announced it has accelerated engagement with manufacturers for potential direct procurement of mpox vaccines to support the response to the outbreak, which would follow an Emergency Use Listing by the WHO. Another route to getting vaccines to the African countries that need them is through donated vaccine doses. Several countries in the global	

[20] Bakare et.al., 2024 Assessment of the Level of Awareness, Knowledge, and Risk Perception of Community Members About Mpox Infection in Nigeria.

[21] Whitworth, H. S., Kitonsa, J., Kasonia, K., Tindanbil, D., Kafeero, P., Bangura, J., Nije, Y., Teta, D. T., Greenwood, B., Kavunga-Membo, H., Leigh, B., Ruzagira, E., Gallagher, K. E., & Watson-Jones, D. (2022). COVID-19 Vaccine Acceptability Among Healthcare Facility Workers in Sierra Leone, the Democratic Republic of Congo and Uganda: A Multi-Centre Cross-Sectional Survey. *International Journal of Public Health*, *67*. https://doi.org/10.3389/ijph.2022.1605113

[22] Ellaine Ruth Fletcher, Health Policy Watch 2024. https://healthpolicy-watch.news/mpox-vaccine-manufacturing-in-africa-unlikely-donations-are-most-likely-supply-channel-says-bavarian-nordic-official/

			north have stockpiles of smallpox vaccines that could be made available to support the mpox effort.[23] European Commission's Health Emergency Preparedness and Response Authority (HERA) will contribute with 175,420 doses of MVA-BN vaccine to Africa, while Bavarian Nordic has committed an additional 40,000 doses. These vaccines will be distributed by Africa CDC based on regional needs and an established vaccine strategy.[24] Uganda has been allocated 2000 doses of MVA_BN[25] Uganda has also been selected to participate in the the first cluster randomized control trial to assess the potential to vaccinate high-risk individuals post mpox exposure with MVA-BN® vaccine. The trial will target 1680 participants in Uganda[26] An ethical framework to prioritize high burden countries and high risk populations has been proposed.[27]	
5. Equity	What would be the impact on health inequities?	Diversion of resources (HR and funds) to mpox vaccination may negatively impact the routine immunisation program.	The global labelling of mpox as a disease that primarily affects MSM had implications for how MSM sought care in a country where same-sex relations are criminalised and stigmatised. The vulnerability of people who are immuno-compromised, e.g. because of HIV, was noted.[28] The target population is outside the usual target population for UNEPI.	
6. Acceptability	Which option is acceptable to	Gavi/UNICEF likely to supply MVA BN	Gavi/UNICEF can only purchase vaccines that are authorized by WHO.	

[23] Gavi 2024 website. https://www.gavi.org/vaccineswork/will-vaccines-help-stop-mpox-outbreak-africa
[24] European Commission website. Aug 2024. https://health.ec.europa.eu/latest-updates/mpox-hera-donate-over-215000-vaccine-doses-africa-cdc-amid-urgent-outbreak-2024-08-14_en
[25] MOH, personal communication, 2024.
[26] SMART Vaccines Trail investigators, 2024. Personal Communication. Dr Keith Kakame
[27] Schaefer, G. O., Emanuel, E. J., Atuire, C. A., Leland, R., Persad, G., Richardson, H. S., & Saenz, C. (2023). Equitable global allocation of monkeypox vaccines. *Vaccine*, *41*(48), 7084-7088. https://doi.org/10.1016/j.vaccine.2023.07.021

[28] https://www.socialscienceinaction.org/resources/roundtable-report-discussion-on-mpox-in-drc-and-social-science-considerations-for-operational-response/

	key stakeholders? To the target population?	in future as it has applied for EUL. HCW prefer vaccines with clear scientific evidence of Efficacy and Safety, MVa BN has the most advanced information. MoH prefers vaccines with easier storage requirements and application procedures that are familiar for the vaccinators – MVA BN method of syringe and needle seems most compatible	WHO recommends non replicating (MVA-BN) and minimally replicating vaccines (LC16) over replicating vaccines(ACAM2000) NDA registration process requires that the vaccine have authorization from countries with Stringent Drug Regulatory Authority, or who recommendation and Manufacturing Authorisation for pharmaceutical production[29]. HCWs prefer pre-mixed vaccines that can be administered with standard needle and syringe and stored at 2-80C or room temperature. MVA-BN can be stored at 2-8 ^{o}C for 8 weeks or frozen at -20 ^{o}C until expiry[30]. LC16 – requires reconstitution. Before dissolution can be stored at 2-8 ^{o}C for 2 years and for 4 weeks at room temperature. After dissolution, use within 24 hrs if stored at room temp, or within one month if at 2-8 ^{o}C . Sensitive to sunlight and rapidly inactivated. Requires bifurcated needle to make 15 small pokes[31]. Persons to be immunised prefer single-dose injections with minimal side effects. MVA-BN, 2 doses 4 weeks apart. In different clinical trials of the vaccine injection site, reactions like redness, firmness/tightening, pain, induration, itching, sore throat, myalgia, headache, chills, and nausea have been reported[32] LC16. Single dose. Shock and anaphylaxis can occur following vaccination. Other side effects include swelling of axillary lymph nodes, fever, febrile convulsions and post-vaccination auto inoculation.[31]	

[29] National Drug Authority, 2019. Guidelines for registration of human vaccines https://www.nda.or.ug/wp-content/uploads/2022/02/NDA-Guidelines-on-registration-of-Vaccines.pdf

[30] Bavarian Nordic 2022. Vaccine package insert. https://aspr.hhs.gov/SNS/Documents/MVA-BN-Information-Ltr-Effective-14June2022.pdf

[31] National Center for Global Health and Medicine, Immunization Support Center, 2024. Freeze-dried Smallpox Vaccine Prepared in Cell Culture LC16 “KMB” Vaccination Procedure Guidelines

[32] Sah, R., Paul, D., Mohanty, A., Shah, A., Mohanasundaram, A. S., & Padhi, B. K. (2023). Monkeypox (Mpox) vaccines and their side effects: The other side of the coin. *International Journal of Surgery (London, England)*, *109*(2), 215-217. https://doi.org/10.1097/JS9.0000000000000142

			ACAM2000- Severe and long-term side effects like myopericarditis have been reported to be found in approximately every 20 individuals out of 100,000 ACAM2000 vaccine recipients[32]. Donations of vaccines. List of Pledges: https://www.thinkglobalhealth.org/article/mpox-vaccine-tracker-millions-pledged-millions-still-be-delivered	
7. Feasibility	Is the intervention feasible to implement?	Moderate ease of implementation, though target population may be difficult to locate.	Previous experience with Ebola and Covid 19 Vaccination, epidemic response pillars in place for example, risk communication, surveillance, etc HIV and STI healthcare clinics available	
Balance of consequences		~~Undesirable consequences clearly outweigh desirable consequences in most settings~~ Undesirable consequences probably outweigh desirable consequences in most settings		
Type of recommendation		We suggest considering the intervention o in the context of rigorous research o with targeted monitoring and evaluation o in specific contexts or specific (sub)populations		
Recommendations		Introduce targeted mpox vaccination, starting with the most at risk populations, using MVA_BN vaccine, through the Research and Donation routes. For cases in which numbers at highest risk of infection exceed vaccine supply, there might be benefit in prioritizing delivery of first doses and fractional doses. We do not recommend the use of ACAM2000 vaccines		
Implementation considerations		Mpox vaccination should be done within the full package of public health response measures such as proper surveillance, contact tracing, rapid diagnosis, and isolation and care of patients		

	Mpox vaccine response should consider combining efforts with other health programmes, including epidemiological disease surveillance, sexual health services, HIV/STI testing, prevention and care supported by risk communication and community engagement, and primary health care, and other clinical services
Research priorities	1. Further study of the protection offered by Mpox vaccines against monkeypox infection, disease and transmission (in pre-exposure and post-exposure vaccination scenarios), 2. Understanding how the impact of previous orthopox infection or vaccination impacts the protection offered by Mpox 3. Real-world evidence on the vaccine effectiveness of Mpox vaccines against monkeypox when used as a single SC dose, with extended intervals, and/or in combination with fractional intradermal dosing. 4. Additional studies to further inform on the safety of Mpox vaccines vaccine including both clinical trials and post-market safety surveillance. 5. Further studies to assess vaccine efficacy/effectiveness and safety of Mpox vaccine in priority populations, including people who are pregnant or breastfeeding, children <18 years of age, and people who are immunocompromised. 6. Further study into the epidemiology of the disease to better understand the modes of transmission, the disease presentation, and to identify the populations at highest risk for severe disease in order to inform and optimize disease prevention strategies. 7. Further study into the optimal immunization strategies for outbreak control (e.g., ring vaccinations, population groups at medium/low risk of infection). 8. Further study into the optimal immunization strategies to reach and enhance vaccine acceptance and uptake in populations at highest risk of infection.

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Jan 28th, 2025

The Director General Health Services,
Ministry of Health, Uganda.

REF: ADM 105/309/15

Dear Sir,

RE: INTERIM GUIDANCE ON VACCINE DOSAGE OF MPOX VACCINE IN OUTBREAK SETTING WITH LIMITED SUPPLY IN UGANDA

Uganda National Immunisation Technical Advisory Group (UNITAG) assures you of its highest compliments.

Reference is made to your letter to the UNITAG Chair dated July 26, 2024, in which you requested the committee to review relevant evidence and provide guidance on vaccination using Mpox vaccines to interrupt human-to-human transmission in Uganda. Reference is also made to guidance from UNITAG on this topic submitted to the Ministry of Health dated September 9^{th}, 2024, in which the use of two Mpox vaccines (MVA_BN and LC 16) was recommended for populations at highest risk of contracting the disease or suffering severe outcomes or death.

As was our commitment, UNITAG has reviewed updated evidence on vaccine effectiveness and efficacy, the disease epidemiology in the country, and available vaccine supply and came to the following conclusions:

1. Human to human transmission of Mpox disease continues to spread in Uganda, mainly in urban epicentres, with a total of 2,209 confirmed cases and 13 deaths as of 22 January, 2025. The disease trajectory is projected to continue growing in the short to medium term, and to become endemic in the long term.
2. Mpox vaccine supply is still below demand, with 10,000 doses in the country and expected 100,000 doses in the future.
3. There is now sufficient efficacy and effectiveness data to show that a single dose confers acceptable levels of protection against Mpox disease. One full dose (0.5 mL) of MVA_BN vaccine administered subcuteaneously is estimated to provide a vaccine effectiveness of 76% (95%CI 64 -88%). See attached Evidence Table.

Based on the reviewed evidence and the above conclusions, and considering the WHO recommendation for "off-label" use of a single dose or intradermal fractional dosing of MVA-BN in supply-constrained outbreak situations[1], UNITAG thus recommends in the interim:

1. Persons at highest risk of infection with Mpox vaccine be offered **<u>at least one</u>** dose of MVA BN vaccine (0.5 mL) administered subcutaneously, to interrupt human to human transmission of the disease in Uganda. In the future when vaccine supply is sufficient to cover the high risk populations, a second dose can be offered to those that received a single dose of the vaccine.

2. Ongoing studies be conducted to:

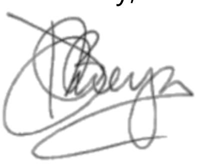
a) Evaluate acceptability and vaccine perception among the targeted high-risk groups before and after vaccination. This will help with vaccine demand forecasting and minimize vaccine wastage.

b) Review the available disaggregated data to estimate the rate of spread of Mpox among schoolgoing persons between September and December 2024, in order to estimate the level of risk in school settings.

c) Assess vaccine efficacy, effectiveness and safety across the different risk groups, including studies on re-infection following natural infection in vaccinated individuals

3. Vaccination be done in combination with other public health interventions such as risk communication, personal hygiene e.g. hand washing, and minimizing human contact.

Sincerely,



Assoc. Prof. David Meya, PhD, FRCP

Chair, UNITAG Mpox Working Group

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[1] WER No 34, 2024, 99, 429–456

Research question: Does a single dose of MVA-BN vaccine offer protection against MPOX infection in high risk populations during an outbreak?

Evidence summary

Reference	Type of study	Efficacy results
1. Hatch et al 2013 Assessment of the protective effect of Imvamune and Acam2000 vaccines against aerosolized monkeypox virus in cynomolgus macaques. J Virol. 2013 PMID: 23658452; PMCID: PMC3700201	Animal challenge study	Neutralizing antibodies with **a single dose of Imvamune** were **13 U/ml**, compared **69 U/ml** for 2 doses, 6 days prior to challenge **Clinical presentation:** **Clinical signs** were 3 times in the control, compared to 2 in 1 dose, and 1 in 2 doses. **Onset of lesions** was on day 9 in the 1 dose vs day 6 in 2 dose. **Resolutions of lesions** was within 5 days for both 1 and 2 doses. **Survival %** was 0 for control, 67% for 1 dose and 100% for 2 doses.
2. Pischel, et. al. (2024). Vaccine effectiveness of 3rd generation mpox vaccines against mpox and disease severity: A systematic review and meta-analysis. Vaccine, 42(25), 126053. https://doi.org/10.1016/j.vaccine.2024.06.021	A systematic review on 1 dose of MVA-BN across 12 studies. Majority of study population men 18–49 years and included HIV+ individuals. Real world observational studies from outbreak of clade 2b in Europe.	**Vaccine effectiveness (VE)** for **a single** subcutaneously-administered **dose of MVA-BN at 76%** (95%CI 64–88%) across 13 studies VS 82**%** (95%CI 72–92%) across 6 studies in meta- analysis
3. Bertran et. al. 2023. Effectiveness of one dose of MVA-BN smallpox vaccine against mpox in England using the casecoverage method: an observational study. Lancet Infect Dis. 2023 Jul;23(7):828-835. doi: 10.1016/S1473-3099(23)00057-9. Epub 2023 Mar 13. PMID: 36924787.	Case-coverage study, mpox cases in England were sent questionnaires collecting information on demographics, vaccination history, symptoms, and sexual orientation.	The estimated vaccine effectiveness against symptomatic mpox at least 14 days after a single dose was **78% (95% CI 54 to 89)** ranging from 71 to 85 in sensitivity analyses.
4. Hernando, et. al.(2024). Effectiveness of Modified Vaccinia Ankara-Bavaria Nordic Vaccination in a Population at High Risk of Mpox: A Spanish Cohort Study. *Clinical Infectious Diseases*, *78*(2), 476-483. https://doi.org/10.1093/cid/ciad645	National retrospective cohort study between 12 July and 12 December 2022. Effectiveness assessment of 1 dose of MVA-BN vaccine as pre-exposure prophylaxis against mpox virus (MPXV) infection in persons on HIVPrEP.	Mpox cumulative incidence was **5.6 per 1000 (25 cases) in unvaccinated and 3.5 per 1000 (18 cases) in vaccinated**. No effect was found during days 0–6 post-vaccination (VE, −38.3; 95% confidence interval [CI], −332.7 to 46.4), but VE was 65% at ≥7 days (95% CI, 22.9 to 88.0) and **79% at ≥14 days (95% CI, 33.3 to 100.0) postvaccination.**

5. Ilchmann et. al., 2023. One- and Two-Dose Vaccinations With Modified Vaccinia Ankara-	Randomised control trial. Participants naive to smallpox vaccination randomized to 1 dose MVA-	Neutralizing antibody (nAb) geometric mean titers (GMTs) increased from 1.1 (baseline, both naive groups) to 7.2 and 7.5 (week 4, 1×MVA and

Bavarian Nordic Induce Durable B-Cell Memory Responses Comparable to Replicating Smallpox Vaccines. J Infect Dis. 2023 May 12;227(10):12031213. doi: 10.1093/infdis/jiac455.	BN. 2 doses MVA-BN or placebo Participants 1 dose group received an MVA-BN booster 2 years later.	2×MVA, respectively), and further to 45.6 (week 6, 2×MVA after second vaccination).
6. Berry et. al.,(2024). Predicting vaccine effectiveness for mpox. *Nature Communications*, *15*(1), 1-11. https://doi.org/10.1038/s 41467-024-48180-w	Systematic search and metaanalysis to test whether vaccinia-binding ELISA endpoint titer is predictive of vaccine effectiveness against mpox. they aggregated data on vacciniaspecific ELISA endpoint titers AND analyzed the kinetics of antibody decay over time to predict the duration of protection afforded by 1, 2 or 3 doses of vaccination. Aggregating the available data, they used a Bayesian hierarchical model to obtain bestestimates of the effectiveness.	Best-estimates of the effectiveness for historic first-generation vaccines (73.6%, CI:49.0−85.8%), one dose of MVA-BN (73.6%, CI:50.2−83.5%) and two doses of MVA-BN (81.8% CI:65.0−89.1%). Following the approach used in COVID-19, **they found evidence of a significant positive association between antibody titers and effectiveness** (Odds Ratio: 0.49 (CI 0.21−0.79) for each 10-fold change in vaccinia-binding, p < 0.001). **Duration of protection:** They estimated that **antibody titers after two doses of MVA-BN vaccination (with 28-day interval) remain above or equal to the peak GMT of one dose for 81 days** (CI:72−93) and **above historically vaccinated cohorts for 102 days** (CI: 74−173). **By delaying the second dose to two years**, **antibody titers remain above the one-dose peak for 13.2 years** (CI:7.5−48.3 years).
7. Navarro et. al, 2024; Effectiveness of modified vaccinia Ankara-Bavarian Nordic vaccine against mpox infection: emulation of a target trial. BMJ. 2024 Sep 11;386:e078243. doi: 10.1136/bmj-2023078243.	Study targeted aged ≥18 years with a history of being tested for syphilis and a laboratory confirmed bacterial (STI). Outcome measure was vaccine effectiveness ((1-hazard ratio)×100) of one dose of subcutaneously administered MVA-BN against laboratory confirmed mpox infection.	A total of 71 mpox infections were diagnosed, with 0.09 per 1000 person days (95% confidence interval (CI) 0.05 to 0.13) in the vaccinated group and 0.20 per 1000 person days (0.15 to 0.27) in the unvaccinated group over the study period of 153 days. **Estimated vaccine effectiveness of one dose of MVA-BN against mpox infection was 58% (95% CI 31% to 75%).**

8. Ladhani et. al., 2023 Early evaluation of the safety, reactogenicity, and immune response after a single dose of modified vaccinia Ankara-Bavaria Nordic vaccine against mpox in children: a national outbreak response. Lancet Infect Dis. 2023 Sep;23(9):10421050. doi: 10.1016/S14733099(23)00270-0.	This is an assessment of children receiving MVA-BN for post-exposure prophylaxis in response to a national mpox outbreak in England. All children receiving MVA-BN were asked to complete a postvaccination questionnaire online and provide a blood sample 1 month and 3 months after vaccination.	87 children had one MVA-BN dose and none developed any serious adverse events or developed mpox disease after vaccination. All children had poxvirus IgG antibodies with titres well above the assay cutoff of OD_{450nm} 0·1926 with mean absorbances of 1·380 at six weeks and 0·9826 at 15 weeks post-vaccination.

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02 SEP 2025
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September 1st, 2025

The Director General Health Services
Ministry of Health
Uganda
REF: CDC/085/600/03

Dear Sir,

RE: USE OF FRACTIONATED DOSING MPOX VACCINE MVA BN IN AN OUTBREAK SETTING WITH LIMITED SUPPLY IN UGANDA

Uganda National Immunisation Technical Advisory Group (UNITAG) assures you of its highest compliments.

Reference is made to your letter to the UNITAG Chair dated June 26, 2025, in which you requested the committee to review relevant evidence and provide guidance on use of fractionated doses of MVA-BN vaccine, as a dose sparing strategy in an outbreak setting with limited supply.

This report serves as an addendum to the guidance from UNITAG on Mpox vaccines submitted to the Ministry of Health dated September 9th, 2024.

UNITAG has reviewed updated evidence on vaccine effectiveness and efficacy, the disease epidemiology in the country, and available vaccine supply and came to conclusions and recommendations:

Conclusions:

i. Fractional dose, (0.1 mL) of MVA_BN, is non inferior in terms of effectiveness, to the single dose delivered subcutaneously. Fractional dosing has an acceptable safety profile with less occurrence of injection site reactions compared to intradermal, including local pain, swelling, and redness, though fainting episodes are more common.

ii. As at August 2025, the projected demand for mpox vaccines (estimated at 1.35-2.5 million people) far outstrips the supply (estimated 151,400 doses). By making the most of available supply, fractional dosing, where each 0.5ml vial could potentially vaccinate 5 people, maximizes available doses.

iii. With the price of mpox vaccination as high as $65 per dose, the financial burden on global health funders is significant. Fractional dosing could reduce these costs substantially, making it a more feasible option for widespread vaccination campaigns, without significantly compromising the effectiveness or safety of the vaccine.

Recommendation on fractional dosing using MVA_BN:
Uganda should implement a single fractional dose strategy for mpox vaccination of high-risk population groups aged 1-50 years, as an off-label use in an outbreak setting with limited vaccine supply.

Additionally, UNITAG recommends that the following research and implementation needs be considered in rolling out the fractional MVA_BN vaccination:

i. There is currently insufficient data on fractional dosing's effectiveness in certain key populations, such as children and individuals living with HIV. Additionally, there are no established correlates of protection against mpox, meaning we do not fully understand how well mpox virus-neutralizing antibodies protect against disease or transmission. This uncertainty complicates public health decision making.
   Research studies to generate evidence on these are greatly encouraged.
ii. Fractional dose administration necessitates specialized needles and syringes, as well as additional training for healthcare workers to ensure proper administration. Vaccinators should also be well educated on possible side effects such as fainting and proper handling of such cases.
iii. Local reactions to ID injections can leave visible marks at the injection site, potentially increasing the stigma for vaccinated individuals. This is a particularly important consideration in communities where vaccine-related stigma may already be a barrier to uptake. The decision of injection site should take this into consideration.

UNITAG commits to continued engagement with the Ministry of Health in addressing this outbreak, by keeping up with the evolving scientific evidence on Mpox vaccines and providing relevant guidance as needed.

Sincerely,

Harriet Mayanja-Kizza (Prof.)

UNITAG Chair

Addendum two to UNITAG Recommendation on use of Mpox vaccine in Uganda

Executive summary

Uganda National Immunisation Technical Advisory Group (UNITAG) reviewed updated evidence and developed two new broad recommendations on the mpox vaccination response regarding:

1. Use of Mpox vaccine in children under 12 years
2. Use of fractional dose of MVA_BN vaccine

A. On use of MVA_BN vaccine in children at risk of contracting the Mpox vaccine, based on the available evidence, UNITAG concluded that:

i. Whilst young adults are the most affected age group with the 20–40-year-olds most impacted, children under 12 years comprise approximately 10% of mpox cases and they need to be protected at the earliest.

ii. Limited data available points to a reassuring safety profile of MVA-BN in children, with local reactions such as pain and swelling at the injection site, which self-resolve, as the frequent reported side effects. Systemic reaction included fever, fatigue, and headache, which were short lived. No Severe Adverse Events (SAEs) were reported. Final outcomes from Uganda and DRC trials, when ready, should be used to further guide the vaccination of children.

iii. Immunogenicity is expected to be satisfactory considering data from UK where a single dose of MVA–BN for post-exposure prophylaxis induced robust antibody and cellular immune responses up to 15 weeks after vaccination. Data on vaccination of children with other vaccines using MVA backbone such as the Ebola vaccine, and data collected in adolescents that supported the European Medicines Agency approval in this age.

Recommendation on vaccinating children

While the current Mpox vaccination strategy targets at highest risk adult population groups in order to interrupt transmission, **children aged 1 to 18 years, identified to be at high risk of contracting mpox, e.g. those living in households with targeted high-risk adult individuals, should also be protected through off label vaccination with MVA_BN**.

B. On use of fractional dose of MVA_BN vaccine based on the available evidence, UNITAG concluded that:

i. Fractional dose, (0.1 mL) of MVA_BN, is non inferior in terms of effectiveness, to the single dose delivered subcutaneously. Fractional dosing has an acceptable safety profile with less occurrence of injection site reactions compared to intradermal,

including local pain, swelling, and redness, though fainting episodes are more common.

ii. As at August 2025, the projected demand for mpox vaccines (estimated at 1.35-2.5 million people) far outstrips the supply (estimated 151,400 doses). By making the most of available supply, fractional dosing, where each 0.5ml vial could potentially vaccinate 5 people, maximizes available doses.

iii. With the price of mpox vaccination as high as $65 per dose, the financial burden on global health funders is significant. Fractional dosing could reduce these costs substantially, making it a more feasible option for widespread vaccination campaigns, without significantly compromising the effectiveness or safety of the vaccine.

Recommendation on fractional dosing: **Uganda should implement a single fractional dose strategy for mpox MVA_BN vaccination of high-risk population groups aged 1-50 years, as an off-label use in an outbreak setting with limited vaccine supply.**

Background

Noting that the National Drug Authority in Uganda approved MVA_BN for emergency use for those aged 12 years and above, and following updates in scientific information and the evolving epidemiology of the Mpox outbreak in Uganda; the Uganda National Immunisation Technical Advisory Group (UNITAG) reviewed updated evidence and developed two new broad recommendations on the mpox vaccination response regarding:

3. Us of Mpox vaccine in children under 12 years
4. Use of fractional dose of MVA_BN vaccine

1. Use of Mpox vaccine in children under 12 years old

a) Mpox in children in Uganda

According to the Ministry of Health's Mpox Outbreak Situation Report of July 8, 2025[1], of the 7,043 age recorded cases of Mpox, 323 are children aged, 0-4 years, 307 aged 5-9 years, and 198 aged 10-14 years.

b) Global and National recommendations for use of Mpox vaccine in Children

Currently Uganda is using the non-replicating MVA_BN vaccine.

i. While MVA-BN is currently not authorized for use in under 12 years of age (with exception of DRC EUA), it may be used off-label[2] (evidence informed use that is different from what is indicated on the manufactures label) in infants and children as per WHO SAGE recommendations[3].

ii. Reassured by data from UK Health Security Agency from single dose post-exposure prophylaxis in 87 children aged birth to 16 years (median 5 years) from real world use during 2022-2023 mpox outbreak in Europe[4] and taking into account the limited options for prevention of mpox in the pediatric population, and the safety data of MVA-based vaccines in different age groups, the European Medicines Agency's Emergency Task Force recommended that MVA_BN could be used for the prevention of mpox in children below 12 years of age at risk of mpox disease during the international public health emergency[5] (Reference Number: EMA/528419/2024)

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[1]WHO Afro, 2025. Mpox Outbreak in Uganda, Situation report, July 08, 2025. https://www.afro.who.int/countries/uganda/publication/mpox-outbreak-uganda-situation-update-8-july-2025

[2] WHO 2025. Off label Use: Explanatory note for countries. https://www.who.int/publications/m/item/off-label-vaccine-use--explanatory-note-for-countries

[3] WHO 2024. MVA-BN (Modified Vaccinia Ankara – Bavarian Nordic) smallpox and mpox vaccine: interim guidance, 27 November 2024. https://iris.who.int/handle/10665/379882

[4] Shamez N Ladhani et. al., 2023. Early evaluation of the safety, reactogenicity, and immune response after a single dose of modified vaccinia Ankara–Bavaria Nordic vaccine against mpox in children: a national outbreak response. Lancet Infect Dis 2023; 23: 1042–50. https://doi.org/10.1016/S1473-3099(23)00270-0

[5] European Medicines Agency website, 2025. Mpox. https://www.ema.europa.eu/en/human-regulatory-overview/public-health-threats/mpox

c) *Efficacy and safety of MVA-BN in children*

A systematic review conducted by Yale University identified one observational study, that studied 62 individuals aged < 18 years (range: 4 months to 17 years) who received at least one dose of MVA-BN (38). AEs occurred in ten vaccinees after the first dose (N=57) and five vaccinees after the second dose (N=24). Most AEs included injection site reactions such as pain, erythema, swelling, and induration. Systemic symptoms included fever, fatigue, and headache. No SAEs were reported[6].

A different study[7] evaluated the safety and immunogenicity of a single dose of MVA-BN administered to children undergoing post-exposure vaccination in England. In 2022, a total of 87 children were administered a single dose of MVA-BN, and a subsequent questionnaire was completed by 45 participants. The median age of participants was 5 years (IQR 5-9). No SAE or cases of mpox were reported following vaccination. Out of the surveyed group, 18 children (40%) experienced local reactions such as pain and swelling at the injection site, while 24% reported systemic symptoms, either independently or in conjunction with local reactions. A single dose of MVA–BN for post-exposure prophylaxis induced robust antibody and cellular immune responses up to 15 weeks after vaccination.

A phase 2 randomized, open-label trial in adolescents aged 12 to 17 (n=314) is currently ongoing in the US[8]. The trial compares immunogenicity and safety of MVA-BN in adolescents to adults aged 18 to 50 years (n=135). A mid-stage study in the United States to evaluate the safety and immune response generated by two doses of MVA-BN in adolescents aged 12-17 years, comparing outcomes to those in adults aged 18-50 years. In a planned interim analysis, study investigators measured antibody levels two weeks after the second dose (study day 43) and monitored safety through 180 days after the second dose (study day 210). The analysis showed that the MVA-BN vaccine generated antibody levels in adolescents equivalent to those observed in adults at day 43 and found that the vaccine was well tolerated through study day 210. The overall frequency of adverse events was comparable between the study groups. Reports of dizziness were more common in adolescents than adults, but similar to the frequency of dizziness reported when other vaccines are administered in adolescents.

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[6] WHO, 2024. Background document for the SAGE March 2024 session on mpox vaccines and immunization. https://cdn.who.int/media/docs/default-source/immunization/sage/vpp-background-documents/mpox/mpox_background_paper_sage_march_2024.pdf?sfvrsn=88884143_1

[7] Ladhani SN, et. al., 2023. Early evaluation of the safety, reactogenicity, and immune response after a single dose of modified vaccinia Ankara-Bavaria Nordic vaccine against mpox in children: a national outbreak response. Lancet Infect Dis. 2023 Sep;23(9):1042-1050. doi: 10.1016/S1473-3099(23)00270-0.

[8] National Institutes of Health, 2024. Mpox vaccine is safe and generates a robust antibody response in adolescents. https://www.nih.gov/news-events/news-releases/mpox-vaccine-safe-generates-robust-antibody-response-adolescents

d) Experience with other similar vaccines

While MVA-BN has not been specifically studied in clinical trials in children, the same non-replicating Modified Vaccinia Ankara virus as platform is used as a platform for other vaccines including MVA-filo (marketed as Mvabea™) against Ebola virus disease (EVD). This EVD vaccine is approved in the European Union for adults and children aged one year and older[9].

Mvabea data from clinical trial EBL2005 in Guinea and Sierra Leone, which included 75 infants from 4 to 11 months of age. Safety profile in infants was similar to that observed in children from 1 to 18 years[10].

In all key studies, Imvanex and Mvabea were administered subcutaneously, at same dose and posology in adults and in pediatric populations.

d) *Liability concerns for off label use*

In case of unexpected Severe Adverse Event, Bavarian Nordic, the manufacturer of MVA-BN, has issued a product liability insurance related to the MVA-BN vaccine shipments to the African continent[11], which requires the National Regulatory Authorities to include the age groups in the Emergency Use Authorisation document. If no age group is specified, BN will assess on case-by-case basis whether product liability insurance applies to age groups that are not indicated on the product label.

If/when a claim for product liability is submitted to BN, there will be a process where BN's Insurance Team, together with the insurance company, will need to establish whether a claim is eligible for coverage. Certain information will need to be provided to BN and its insurance company for this assessment to be made. Timely assessment of a product liability claim therefore depends a lot on the quality of the information provided and how fast this can be provided.

e) UNITAG Conclusions:

i. Whilst young adults are the most affected age group with the 20–40-year-olds most impacted, children under 12 years comprise approximately 10% of mpox cases and they need to be protected at the earliest.

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[9] Johnson and Johnson. Zabdeno and Mvabea Ebla vaccine product label. https://ec.europa.eu/health/documents/community-register/2025/20250328165434/anx_165434_en.pdf

[10] Muhammed O Afolabi et. al., 2022. Safety and immunogenicity of the two-dose heterologous Ad26.ZEBOV and MVA-BN-Filo Ebola vaccine regimen in children in Sierra Leone: a randomised, double-blind, controlled trial, The Lancet Infectious Diseases, Volume 22, Issue 1, 2022, Pages 110-122, ISSN 1473-3099, https://doi.org/10.1016/S1473-3099(21)00128-6.

[11] WHO 2025. Multi-country external situation report no. 51 published 29 April 2025, page 19. https://cdn.who.int/media/docs/default-source/documents/emergencies/multi-country-outbreak-of-mpox--external-situation-report--51.pdf?sfvrsn=be407586_1

ii. Limited data available points to a reassuring safety profile of MVA-BN in children. Final outcomes from Uganda and DRC trials, when ready, should be used to further guide the vaccination of children.

iii. Immunogenicity is expected to be satisfactory considering data from UK, data with other vaccines using MVA backbone, and data collected in adolescents that supported the approval in this age group in the European Union.

f) Recommendation on vaccinating children

While the current Mpox vaccination strategy targets at highest risk adult population groups in order to interrupt transmission, **children aged 1 to 18 years, identified to be at high risk of contracting mpox, e.g. those living in households with targeted high-risk adult individuals, should also be protected through off label vaccination with MVA_BN**.

2. Use of fractional dose of MVA_BN vaccine

WHO has previously recommended the "off-label[2]" use of a single full dose of MVA-BN vaccine (0.5mL/dose) administered subcutaneously or fractional dosing (0.1mL/dose) administered intradermally in supply-constrained outbreak situation. One full dose of MVA-BN vaccine is 0.5 mL suspension provided in a single-dose vial. A fractional dose (0.1 mL) is a reduced dose of the same vaccine, equivalent to one-fifth of the usual dose (each single-dose vial provides 4-5 fractional doses). As the volume of the given dose is smaller, a fractional dose will be administered intradermally (given just below the top layer of the skin) using a 0.1 mL auto disable (AD) syringe with a shorter needle (10-13 mm).

a) Mpox vaccine supply situation

In November 2024, the Access and Allocation Mechanism (AAM) for mpox allocated an initial 899, 000 vaccine doses for 9 countries across the African region that are hit hard by the current mpox surge[12]. The largest number of doses – 85% of the allocation – were to the Democratic Republic of the Congo, as the hardest hit country. Uganda has received 209,060 doses of mpox vaccine, and so far, utilized 109,400 in 10 districts.

Over 5.85 million vaccine doses were expected to be available to the Mpox Vaccines AAM by the end of 2024, including the nearly 900 000 allocated doses. The supply includes contributions from multiple nations and organizations, including 1.85 million dose donations of MVA-BN from the European Union, United States, and Canada, 500 000 doses of MVA-BN from Gavi utilizing the First Response Fund, 500 000 doses procured through UNICEF, as well as a further 3 million doses of the LC16 vaccine from Japan.

[12] UNICEF 2024. Joint press release Africa CDC, CEPI, Gavi, UNICEF, WHO. Vaccine doses allocated to nine African countries hardest hit by mpox surge. https://www.unicef.org/press-releases/vaccine-doses-allocated-nine-african-countries-hardest-hit-mpox-surge

As of 31 July 2025, Uganda had been allocated an additional 42,420 doses of MVA BN donation from the United States of America, with the African CDC recommending that the country adopt a dose sparing strategy of utilizing the limited number of available and highly expensive vaccines[13].

The cost of the key mpox vaccine called MVA-BN, produced by Bavarian Nordic, has raised serious concerns about accessibility. UNICEF negotiated a price of up to $65 per dose from Bavarian Nordic[14].

b) Mpox vaccine demand situation

Uganda is applying a pro-active vaccination model by targeting Mpox hot spots especially with crowded communities. Key populations include: sex workers, men having sex with men, Long distance drivers (track drivers) and Fisher folks. Target age group is 12 – 50 years

Uganda has so far received 209,060 doses of MVA-BN vaccine, and utilized 109,400 in 10 districts. One dose has been administered as per UNITAG recommendation. The uptake has been high 100%.

MoH plans to vaccinate long distance drivers and hosting communities. People with co-morbidities and HIV will be targeted next.

The geographical areas to be targeted are those reporting the highest attack rates as outlined in the following table:

District	Total cases	Population	Attack rate/10,000
Masaka City	223	103,829	21.5
Kalangala	65	74,411	8.7
Lyantonde	113	136,900	8.3
Mukono	227	757,500	3.0
Kyotera	70	286,000	2.6
Total		**1,358,640**	

[13] CDC Africa special briefing on Mpox and other health emergencies July 31, 2025. https://www.youtube.com/watch?v=fB0uDbvMjLw

[14] UNICEF 2025. Price for Mpox Vaccine, Barvarian Nordic. https://www.unicef.org/supply/media/23226/file/Mpox-vaccine-prices-11032025.pdf

Using Uganda Bureau of statistics population projection figures, the MoH has come up with estimated vaccine demand projections as outlined in the following table:

S.no	Category	UBOS Total Popn 2024	2025 projection (2.9%)	Target Population 12 – 50yrs. (53.2%)	Total target popn	Total Mpox vaccine (WF= 1.05) at 100% coverage	Total Mpox vaccine (WF= 1.05) at 80% coverage	2 doses
1	PLWHIV	1,468,973	1,894,976	1,008,127	1,008,127	1,018,712	814,970	1,629,940
2	CSW	133,126	171,732	91,362	91,362	92,321	73,857	147,713
3	Long distance drivers	80,000	80,000	42,560	42,560	43,007	34,406	68,811
4	MSM	224,937	231,235	123,017	123,017	124,309	99,447	198,894
5	Health workers	156,078	160,449	85,359	85,359	86,255	69,004	138,008
6	Security forces	91,811	94,382	50,211	50,211	50,738	40,591	81,181
7	Commute r taxi drivers	35,000	35,000	18,620	18,620	18,816	15,052	30,105
8	Boda-boda riders	1,198,131	1,231,679	655,253	655,253	662,133	529,707	1,059,413
9	Fisher Folks	1,239,446	1,274,151	677,848	677,848	684,966	547,972	1,095,945
Sum		**4,627,502**	**5,173,603**	**2,752,357**	**2,752,357**	**2,781,256**	**2,225,005**	**4,450,010**

c) *Efficacy of MVA-BN fractional dose*

i. Efficacy in the general population

In a study to assess reactogenicity following MVA_BN using different modes of application, after second vaccination Day (42–208 days later), geometric mean of peak neutralization titers were 87.8, 49.5 and 59.5 for the Lyophilized-SC, Liquid-SC and fractional Liquid-ID groups, respectively[15], and the maximum number of responders based on peak titer in each group was 142/145 (97.9%), 142/149 (95.3%) and 138/146 (94.5%), respectively. At 180 days after the second vaccination, geometric mean neutralization titers declined to 11.7, 10.2 and 10.4 with only 54.3%,

[15] Sharon E. Frey, et. al., 2015. Comparison of lyophilized versus liquid modified vaccinia Ankara (MVA) formulations and subcutaneous versus intradermal routes of administration in healthy vaccinia-naïve subjects, Vaccine, Volume 33, Issue 39, 015, Pages 5225-5234, ISSN 0264-410X, https://doi.org/10.1016/j.vaccine.2015.06.075.

39.2% and 35.2% of subjects remaining seropositive for the Lyophilized-SC, Liquid-SC and Liquid-ID groups, respectively. Both the Lyophilized-SC and Liquid-ID groups were considered non-inferior (primary objective) to the Liquid-SC group.

ii. Efficacy of fractional dose in children:
No studies conducted in children specifically for mpox, though other vaccines are routinely safely given to children intradermally such as IPV and BCG.

iii. Efficacy of fractional dose in immunocompromised populations
While no studies have yet assessed the immunogenicity or vaccine effectiveness of intradermal fractional dosing in this population, in immunocompetent individuals: one intradermal fractional dosing has demonstrated immunogenicity and effectiveness equivalent to or greater than a single full subcutaneous dose. Higher responses have been observed when two intradermal fractional or two subcutaneous full doses are administered.
WHO recommends that countries may therefore consider administering one fractional dose or two fractional doses aiming for higher effectiveness to enhance protection to immunocompromised persons taking into account national recommendations and programmatic considerations[16].

iv. When comparing efficacy of two versus one fractional dose, an unpublished US CDC studied provided the following evidence:

Route of administration	**Subcutaneous**		**Intradermal**	
Number of doses	Two full doses	One full dose	Two fractional doses	One fractional dose
Vaccine effectiveness	• **82%** (95% CI 78-88) based on a systematic review of 9 studies • **87%** (95% CI 68-95) based on US CDC unpublished data	• **75%** (95% CI 66-85) based systematic review of 15 studies • **71%** (95% CI 53-83) based on US CDC unpublished data	**91%** (95% CI 78-97) based on US CDC unpublished data	**75%** (95% CI 55-86) based on US CDC unpublished data

A 2022 modelling study[17] comparing the effectiveness of mpox vaccine fractional dosing against full dose strategy suggests that dose-sparing strategies would outperform full-dose vaccination provided that the fractional dose retains at least 60% effectiveness of the full dose.

[16] WHO 2025. Frequently Asked Questions (FAQ) on use of fractional dosing with intradermal administration of mpox MVA-BN vaccine in the context of vaccine supply-constrained outbreak response.

[17] Dimitrov D, Adamson B, Matrajt L. Evaluation of mpox vaccine dose-sparing strategies. PNAS Nexus. 2023 Mar 28;2(5):pgad095. doi: 10.1093/pnasnexus/pgad095. PMID: 37152676; PMCID: PMC10154907.

c) Safety of MVA BN fractional dose

The following table summarizes the results from safety studies of fractional dose intradermal administration of MVA_BN compared to subcutaneous administration.

Year	Location	Simple size	Design	Results
2015[1]	US	524	ID fractional vs subcutaneous, 2 doses 28 days apart	ID vaccination site displayed erythema/induration (>30 mm), however it did not result in different functional outcomes (e.g. performing routine activities)
2023[2]	Australia	13,306	ID fractional vs subcutaneous; vaccine safety surveillance system, survey on AE 0 to 7 days after vaccination.	Adverse events were highest after the first dose of intradermal vaccination (53%) and lowest after the second dose of subcutaneous vaccination (31%). The most common reported reactions included local redness, itching, and swelling for intradermal vaccination, and local pain, swelling, and redness for subcutaneous vaccination
2024[3]	Italy	718	ID fractional vs subcutaneous, 2 doses 28 days apart	Systemic adverse events were more frequently observed after intradermal vaccination compared to subcutaneous (59.1% vs. 45.8%), as were local adverse events (94.4% vs. 80.0%).
2024[4]	Global	9,585 AEFI reported	BN global safety database, proportion of syncope following ID administration (78.7%) compared to subcutaneous (16.9%)	Intradermal administration is likely associated with more common fainting episodes

Source: 1. Comparison of lyophilized versus liquid modified vaccinia Ankara (MVA) formulations and subcutaneous versus intradermal routes of administration in healthy vaccinia-naïve subjects - PubMed https://pubmed.ncbi.nlm.nih.gov/26143613/

2. Short-term Adverse Events Following Immunization With Modified Vaccinia Ankara-Bavarian Nordic (MVA-BN) Vaccine for Mpox https://pmc.ncbi.nlm.nih.gov/articles/PMC10282881/

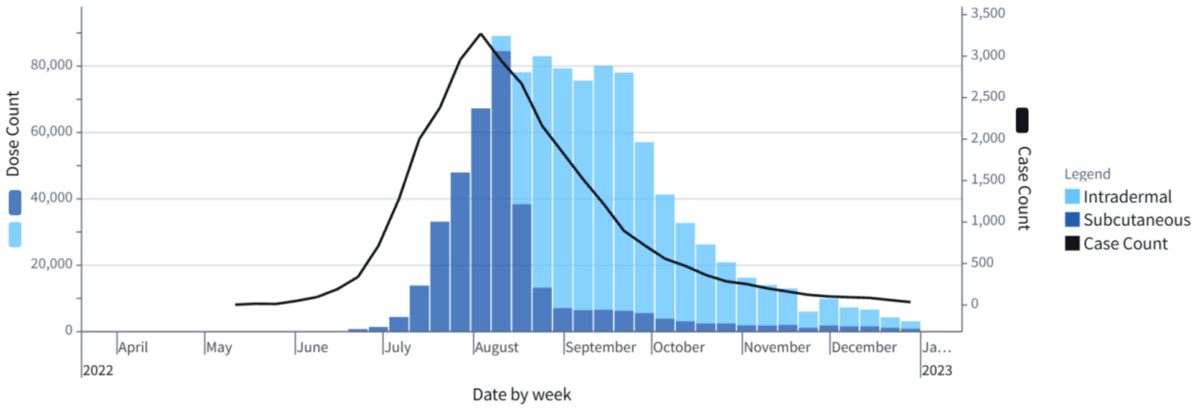
3. Reactogenicity and Immunogenicity Against MPXV of the Intradermal Administration of Modified Vaccinia Ankara Compared to the Standard Subcutaneous Route https://pubmed.ncbi.nlm.nih.gov/39852811/

4. Real-world safety data for MVA-BN: Increased frequency of syncope following intradermal administration for immunization against mpox disease https://pubmed.ncbi.nlm.nih.gov/38839518/

Note: Increased rates of local reactions are expected with all intradermal vaccinations, which subside over time.

d) Impact of fractional dose on the outbreak trajectory

In 2022, FDA issued an Emergency Use Authorization (EUA) for Jynneos, a brand of MVA-BN, to allow healthcare providers to administer the vaccine intradermally for individuals 18 years of age and older who are determined to be at high risk for mpox infection. This allowed to increase the number of doses administered and showed a corresponding reduction in reported cases, as shown in the following figure:



Source: US CDC unpublished data[18].

e) Logistical considerations for introducing fractional dosing

Intradermal vaccine administration uses a short needle to inject a 0.1 mL dose of the MVA BN mpox vaccine into the space between the two outer layers (epidermis and dermis) of the skin. The injection ancillaries required include AD syringes with needles in the range of 26G-27G and a 10-13 mm length, along with AD syringe safety boxes to ensure safe disposal. AD syringes are dose volume specific, and the 0.1 ml size usually requires placing a specific order and a distribution planning. A number of 0.1 ml AD syringes are listed in the WHO catalogue and can be procured either through UNICEF or via self-procurement. The indicative lead time for the production and air shipment of 0.1 ml AD syringes is approximately two months from the date of order placement.

The intradermal injection technique requires specialized training and only providers who have undertaken this training can administer vaccines using this technique. Currently, other vaccines that are administered intradermally include BCG, rabies and hepatitis B vaccines.

f) UNITAG conclusions

i. Fractional dose, (0.1 mL) of MVA_BN, is non inferior in terms of effectiveness, to the single dose delivered subcutaneously. Fractional dosing has an acceptable safety profile with less occurrence of injection site reactions compared to intradermal, including local pain, swelling, and redness, though fainting episodes are more common.

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[18] WHO 2025. Frequently Asked Questions (FAQ) on use of fractional dosing with intradermal administration of mpox MVA-BN vaccine in the context of vaccine supply-constrained outbreak response

ii. As at August 2025, the projected demand for mpox vaccines (estimated at 1.35-2.5 million people) far outstrips the supply (estimated 151,400 doses). By making the most of available supply, fractional dosing, where each 0.5ml vial could potentially vaccinate 5 people, maximizes available doses.
iii. With the price of mpox vaccination as high as $65 per dose, the financial burden on global health funders is significant. Fractional dosing could reduce these costs substantially, making it a more feasible option for widespread vaccination campaigns, without significantly compromising the effectiveness or safety of the vaccine.

g. UNITAG recommendation

Uganda should implement a single fractional dose strategy for mpox vaccination of high-risk population groups aged 1-50 years, as an off-label use in an outbreak setting with limited vaccine supply.

g) Research and implementation considerations

i. There is currently insufficient data on fractional dosing's effectiveness in certain key populations, such as children and individuals living with HIV. Additionally, there are no established correlates of protection against mpox, meaning we do not fully understand how well mpox virus-neutralizing antibodies protect against disease or transmission. This uncertainty complicates public health decision making. Research studies to generate evidence on these are greatly encouraged.
ii. Fractional dose administration necessitates specialized needles and syringes, as well as additional training for healthcare workers to ensure proper administration. Vaccinators should also be well educated on possible side effects such as fainting and proper handling of such cases.
iii. Local reactions to ID injections can leave visible marks at the injection site, potentially increasing the stigma for vaccinated individuals. This is a particularly important consideration in communities where vaccine-related stigma may already be a barrier to uptake. The decision of injection site should take this into consideration.

Report of UNITAG on pneumonia prevalence and PCV coverage in Uganda, June 2024-July 2025

1 EXECUTIVE SUMMARY

The Ministry of Health (MoH) requested for guidance from the Uganda National Immunisation Technical Advisory Group (UNITAG) on the rising number of pneumonia cases in the country despite high PCV coverage. Specifically, UNITAG was tasked to address:

i. The potential causes of the persistent burden of pneumonia despite high PCV coverage
ii. The possible need for changes in vaccine product, schedule, or strategy
iii. Any other evidence -based recommendations that could enhance the prevention of pneumococcal disease in Uganda

The UNITAG members analyzed the HMIS data on pneumonia morbidity and mortality in the different districts by age group over the past twelve months, reviewed statistics for PCV coverage and measles cases in the same period, and analyzed relevant published literature on PCV vaccines, the experience of other countries with similar and varying PCV programs, and data on other potential pneumonia causes including RSV and measles cases-known to have a comorbidity with pneumonia.

The UNITAG findings indicate that:

a) The PCV 10 vaccine, introduced in 2014, is effective against vaccine serotypes in the country. The available data shows no vaccine type or non-vaccine type pneumonia serotypes circulating in the country since 2011. There is no data to justify a change to a higher valent vaccine.
b) The increase in pneumonia cases is predominantly affecting the under four-year-olds, indicating no shift in affected age groups to the older populations, and hence no justification for introduction of a booster dose.
c) The conclusion is that the increase in pneumonia cases may have other causes, such as viruses. While no Uganda specific data exists for Respiratory Syncytial Virus (RSV) prevalence in under four-year-olds other than in neonates, literature from other countries suggest it is becoming a leading cause of pneumonia in under fours where PCV coverage is high.
d) Another suspected cause may be linked to the ongoing measles outbreak in the country. Pneumonia is a known comorbidity associated with severe measles infections. Many of the districts reporting increased measles cases are also reporting increased pneumonia cases. There is a planned Measles Rubella vaccination campaign to respond to the outbreak.

The UNITAG therefore recommends

1) The MoH should continue to invest in strengthening PCV coverage, to at least 90% in each district. The strategy to use a PCV 10 product in a 3+0 schedule should be maintained.
2) MoH should enhance serotyping and periodic nasopharyngeal carriage surveys to ascertain the maximum vaccine effectiveness and monitor *Strep pneumonae* serotypes
3) MoH should ensure high coverage, at least 95%, for the upcoming measles rubella vaccination campaign, and continue to monitor pneumonia trends (maintaining the same definition for consistency) after the campaign to check for a cross-effect.
4) As many of the affected measles-pneumonia cases are under 9 months old, research on possible earlier vaccination should be conducted to inform a possible earlier measles vaccination age.

2 BACKGROUND

Despite high pneumococcal conjugate vaccine (PCV) coverage, data captured in the District Health Information Software (DHIS)2 shows an increase in morbidity and mortality attributable to pneumonia, particularly among children under five years of age.

The Ministry of Health requested the Uganda National Immunisation Technical Advisory Group (UNITAG) to conduct a review of the scientific evidence and epidemiological data on pneumococcal disease in Uganda, and specifically guide on:

1. Potential causes of persistent burden of pneumonia despite high PCV coverage
2. The possible need for changes in vaccine schedule, product or strategy
3. Any other evidence-based recommendations that could enhance the prevention and control of pneumococcal disease in Uganda.

3 METHODOLOGY

In order to systematically analyze all relevant evidence, the UNITAG developed a research strategy, breaking down the specific question into research questions that would generate the data required to provide an informed response.

Evidence was collected from national databases such as Health Monitoring and Information Software (HMIS)2, records from national sentinel sites, relevant published and grey literature, Ministry of Health reports, as well as personal communication from in service personnel.

Based on the available evidence, the committee drew some conclusions, and made recommendations for action and further research.

Uganda's Pneumonia trends and PCV analysis evidence table

Broad question	Specific Questions	Evidence	Conclusions
v. **The Potential causes of the persistent burden of pneumonia despite high PCV coverage**	What are the trends in bacterial and non- bacterial caused pneumonia over the last 12 months?	The aetiology of pneumonia cases is not routinely assessed. A 2010-2020 retrospective analysis study[1] in Kigezi, Busoga and Tororo regions found that most prevalent pneumococcal aetiological serotype was S. pneumoniae at 15% compared to *H. influenzae* at 0.05%.	There is insufficient evidence to support a conclusion on whether increases in pneumonia cases are due to bacterial or viral causes of pneumonia.
	What is the definition of pneumonia used by MoH?	Pneumonia is defined as presence cough and/or difficulty in breathing with fast breathing and/or chest indrawing[2]	Pneumonia is defined by clinical classification with no confirmatory testing
	What are the trends of severe pneumonia (resulting in hospitalization) over the last 12 months?	In the different districts, the period Jun 2024 – Jun 2025 For 0-4 yrs average was 62,429, ranging from 57,368 to 66,127 cases For 5+ yrs, average was 12,4847, ranging from 114,726 to 132,256 cases. There is an observable increase by approximately 2,000 cases in the 0-4 years age group between February 2025 and April 2025. (Annex 1)	Seasons of spikes in severe cases month to month particularly among the 0-4 age-group
	What are the trending serotypes of pneumonia pre and post vaccine introduction?	PCV was rolled out nationally in 2014. There is no surveillance system for pneumonia serotypes in the country, but meningococcal surveillance through analysis of spinal fluid at sentinel sites shows pneumonia serotype prevalence from 2014-2021: more prevalent	Despite the absence of active pneumonia surveillance, no detection of any serotype in suspected meningitis samples since 2021 seems to

[1] Antony I, Rubaihayo J, Atuhe I, Mujawimana A, Ndungutse D (2022) Burden of Pneumococcal Disease: An 8-Year Retrospective Analysis of Local Surveillance Data from Three Regions in Uganda (2012-2020). J Vaccines Res Vaccine 8: 21.

[2] *World Health Organisation, 2022. Pneumonia in Children, factsheet. https://www.who.int/news-room/fact-sheets/detail/pneumonia*

		serotypes are 1, 6A/6B, 23F and 5. No pneumonia serotypes were detected since 2021 (Figure 2)[3] All of the most prevalent serotypes are vaccine types for Pneumosil and Synflorix vaccines except for 6A/6B found in Pneumosil but not in Synflorix vaccine. Serotype 3, found only in PCV13, was detected in only 2 isolates (Annex 2)	suggest that the current PCV vaccination strategy is working well, covering the prevailing serotypes.
	What are the geographical variabilities in pneumonia morbidity and mortality over the last 12 months? Is there a linkage between morbidity/ mortality and PCV coverage?	The geographical areas with high pneumonia morbidity and mortality over the past year include refugee hosting districts like Kiryandongo and Kasese, South western border districts including Kisoro, Kabale and Bundibugyo, West-Nile districts including Arua and Nebbi, central Northern districts including Lira, Pader, the Karamoja area including Kotido, Moroto, down to the Eastern districts of Mbale, Tororo, and the central districts including Kampala, Wakiso, Luwero. The districts reporting lowest PCV coverage include: Sheema, Nakasongola, Soroti, Bulisa, Mabarara City, Gulu and Moyo. (Annex 3) This trend is consistent with another study's findings. Wanyana et. al., 2025[4] found that after the official roll-out of PCV-10 in Uganda in 2014, there was a ≥ 40% reduction in pneumonia cases admitted, mortality, and case-fatality rates among	There is no clear correlation between PCV coverage and increase in severe pneumonia cases. Many of the districts reporting high rates of severe pneumonia are also reporting over 90% PCV3 coverage.

[3] Source -Dr. Helen Aanyu, Mulago National Referral Hospital

[4] Wanyana MW, Migisha R, King P, Bulage L, Kwesiga B, Kadobera D, Ario AR, Harris JR. Long-term impact of 10-valent pneumococcal conjugate vaccine among children <5 years, Uganda, 2014-2021. PLOS Glob Public Health. 2025 Jan 6;5(1):e0002980. doi: 10.1371/journal.pgph.0002980. PMID: 39761235; PMCID: PMC11703042.

			children <5 years over the next 8 years. Both the proportion of pneumonia cases admitted and pneumonia mortality rates among children <5 years were higher in the Northern Region than in the Western, Eastern, and Central Regions.	
	Broad Conclusions	The high burden of pneumonia may not be related to PCV failure. There is need to investigate other causes such as viral causes including RSV, or linkage to current measles outbreak as pneumonia is known to have high co-morbidity with measles.		
	Recommendations	a) MoH should enhance serotyping and periodic nasopharyngeal carriage surveys to ascertain the maximum vaccine effectiveness and monitor *Spn* serotypes b) Strengthen RSV research beyond infant period to >1 Year olds c) MoH should improve routine immunization for PCV in all districts to at least 90% to ensure herd immunity.		
v.	**The possible need for changes in vaccine product, schedule, or strategy**	What is the current PCV product, sero-groups, dosage and strategy?	Since the introduction of the vaccine in 2014, MoH provides 3 doses of synflorix vaccine at 6, 10 and 14 weeks provided through the routine EPI. There are plans to switch to the cheaper pneumosil vaccine product.	The current strategy seems effective as there are no vaccine type serotypes detected since 2011, and the infants are still the most affected age group -hence no justification for changes in schedule.
		What are the trending serotypes of pneumonia pre and post vaccine introduction in Uganda?	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. (Annex 4 and 5)	The planned switch to pneumosil vaccine PCV10 product is expected to directly protect against serotypes 6A and 19A

	Any relevant WHO or SAGE recommendations with regards to products, dosage and schedule?	WHO recommends[5] 3 primary doses (the 3p+0 schedule) starting as early as 6 weeks of age, or, as an alternative, 2 primary doses by the age of 6 months plus a booster dose at 9 - 15 months of age (the 2p + 1 schedule) The sage recommendations states that both PCV10 and PCV13 have substantial impact against pneumonia, vaccine-type IPD and NP carriage. There is at present insufficient evidence of a difference in the net impact of the 2 products on overall disease burden. PCV13 may have an additional benefit in settings where disease attributable to ST19A or ST6C is significant. The choice of product to be used in a country should be based on programmatic characteristics, vaccine supply, vaccine price, the local and regional prevalence of vaccine serotypes and antimicrobial resistance patterns.	
	What are the current vaccine management processes for PCV?	A liquid vaccine packaged as a single dose vial stored at 2-8^{o}C, not frozen, and protected from heat and sunlight.	Vial has Vaccine Vial Monitor (VVM) that minimizes use of impotent vaccines
	What is the immunization uptake of PCV 10? Coverage or the last 2 years? Disaggregated by district	WUENIC administrative coverage[6] for PCV3 in 2023 was 91%. According to the Jan-Dec 2024 Quarterly immunization reports, 108/145 reporting districts had a PCV 3 percentage coverage of 90+	74% of districts achieved coverage required for herd immunity

[5] WHO 2025. Weekly epidemiological record. Meeting of the Strategic Advisory Group of Experts on Immunization, March 2025: conclusions and recommendations. https://iris.who.int/bitstream/handle/10665/381603/WER10023-eng-fre.pdf

[6] WHO/UNICEF, 2024. Uganda: WHO and UNICEF estimates of immunization coverage: 2023 revision dn.who.int/media/docs/default-source/country-profiles/immunization/2024-country-profiles/immunization-2024-uga.pdf?sfvrsn=f323c824_3&download=true

	What are the prices for the various PCV products approved by WHO?	In 2025, UNICEF market report reports[7]: PCV 13 priced at USD 3.0 to Gavi and USD 14.8-25 for middle income countries (MICs) Synflorix PCV 10 4-dose vial priced at USD 2.9 to Gavi Pnuemosil PCV 10 5-dose vial at USD 2.0 to Gavi and USD 2.9- 4.0 for MICs Pneumosil PCV 10 1-dose vial at USD2.9 to Gavi and USD 7.o to MICs	Moving to PCV 13 would increase the buyer's vaccine cost without clear epidemiological justification
Conclusions	• PCV roll-out has had a significant positive impact on pneumonia infection in Uganda. • There is no evidence to justify a change in the current PCV schedule from a 3+0 to a 2+1 as the data does not show a shift of the disease to an older age group. • Product change to PCV 13 would need updated serotype prevalence data, particularly evidence of increase in serotypes not included in PCV 10, i.e. serotypes 3 and 18C. • The planned change from Synflorix to Pneumosil is expected to directly target serotype 19A		
Recommendation	The MoH should continue to invest in strengthening PCV coverage, to at least 90% in each district		
vi. Any other evidence -based recommendations that could enhance the prevention of pneumococcal disease in Uganda	Other country experiences, with similar, and varying vaccination and disease trends?	In Kenya PCV10, delivered at 6, 10, and 14 weeks of age was introduced in Kenya in January, 2011. Among children younger than 5 years, the annual incidence of VT-IPD declined from 60·8 per 100 000 in the pre-vaccine era to 3·2 per 100 000 in the post-vaccine era representing a reduction of 92% (95% CI 78–97; adjusted for year). The incidence of non-VT IPD did not increase following introduction of PCV10 (IRR 1·31; 95% CI 0·65–2·64)[8]. A multi-country study in low income and low middle income settings with widespread uptake of Hib vaccine and PCV, viruses, especially RSV, were the	PCV 10 vaccines are effective in reducing vaccine serotype pneumonia, and cases due to vaccine failures are not common. Viruses, including RSV, are possible causes of increasing IPD cases in Uganda.

[7] UNICEF 2025. Pneumococcal Conjugate Vaccine price data. https://www.unicef.org/supply/documents/pneumococcal-conjugate-vaccine-pcv-price-data
[8] Hammit et. l., 2019. Effect of ten-valent pneumococcal conjugate vaccine on invasive pneumococcal disease and nasopharyngeal carriage in Kenya: a longitudinal surveillance study. The Lancet. doi: 10.1016/S0140-6736(18)33005-8

		predominant cause of pneumonia requiring hospital admission in children younger than 5 years at all sites.[9] In countries with a high uptake of PCVs, approximately 8% of the IPD cases observed in children ≤5 years of age, and 13% of IPD cases observed in children ≤17 years of age, are due to vaccine breakthrough or failure[10]. Cases of vaccine failure are mostly caused by serotypes that are more virulent or resistant to antibiotics (3 and 19A)[10]. Between January 2000 and April 2016, Oligbu et al.[11] identified serotypes 19F and 6B as being responsible for more than two-thirds of cases of vaccine failure in countries with established PCV programs. In Botswana, five years after roll out of PCV13, colonization by vaccine serotypes steadily declined. Despite high national vaccine uptake, the proportion of colonizing strains that were PCV-13 serotypes remained high (25%) five years after vaccine introduction.[12]Also, an increase in	In other cases, increased cases pf pneumonia have been attributed to non-vaccine serotypes of *S. pneumonae*.

[9] The Pneumonia Etiology Research for Child Health (PERCH) Study Group. www.thelancet.com Published online June 27, 2019 http://dx.doi.org/10.1016/S0140-6736(19)30721-4

[10] Feemster, K.; Weaver, J.; Buchwald, U.; Banniettis, N.; Cox, K.S.; McIntosh, E.D.; Spoulou, V. Pneumococcal Vaccine Breakthrough and Failure in Infants and Children: A Narrative Review. Vaccines 2023, 11, 1750. https://doi.org/10.3390/vaccines11121750

[11] Oligbu G, Hsia Y, Folgori L, Collins S, Ladhani S. Pneumococcal conjugate vaccine failure in children: A systematic review of the literature. Vaccine. 2016 Dec 7;34(50):6126-6132. doi: 10.1016/j.vaccine.2016.10.050. Epub 2016 Nov 9. PMID: 27838066.

[12] Patel SM, Shaik-Dasthagirisaheb YB, Congdon M, Young RR, Patel MZ, Mazhani T, Boiditswe S, Leburu T, Lechiile K, Arscott-Mills T, Steenhoff AP, Feemster KA, Shah SS, Cunningham CK, Pelton SI, Kelly MS. Evolution of pneumococcal serotype epidemiology in Botswana following introduction of 13-valent pneumococcal conjugate vaccine. PLoS One. 2022 Jan 5;17(1):e0262225. doi: 10.1371/journal.pone.0262225. PMID: 34986196; PMCID: PMC8730465.

		colonization by non-vaccine serotypes 21 and 23B, which have been associated with invasive pneumococcal disease and antibiotic resistance, was observed. A study in the Gambia[13] indicated a 47% increase in pneumococcal pneumonia due to non-vaccine serotypes 3 years following PCV13 introduction.	
	What are the trends of RSV related pneumonia in children in Uganda over the last 12 months?	As part of the neonatal sepsis study at Kawempe and Mulago Hospitals[14], 2563 babies had a naso-pharyngeal swab collected and processed using a multiplex real-time PCR assay. 115 (6.1%) were positive**: RSV in 44.5%**. Other viruses detected include Rhinovirus, Influenza A and B.	High prevalence of RSV in neonates in Uganda, though the prevalence in infants under 4 years is unknown.
	Vaccination trends in special groups e.g. Sickle cell anemia over the last 2 years?	MoH offers no booster PCV doses for special populations. The WHO position paper states that HIV-positive infants and pre-term neonates who have received their 3 primary vaccine doses before 12 months of age may benefit from a booster dose in the second year of life[15].	The pneumonia cases data does not indicate that immunocompromised children comprise majority of cases
	Trend relationship between measles and pneumonia cases in Uganda? By district? Over the last 12 months?	HMIS data shows that over the last 12 months, some districts reporting high cases of measles are also reporting high numbers of pneumonia cases e.g. Kampala. Wakiso, Kasese, Napak, and Moroto.	

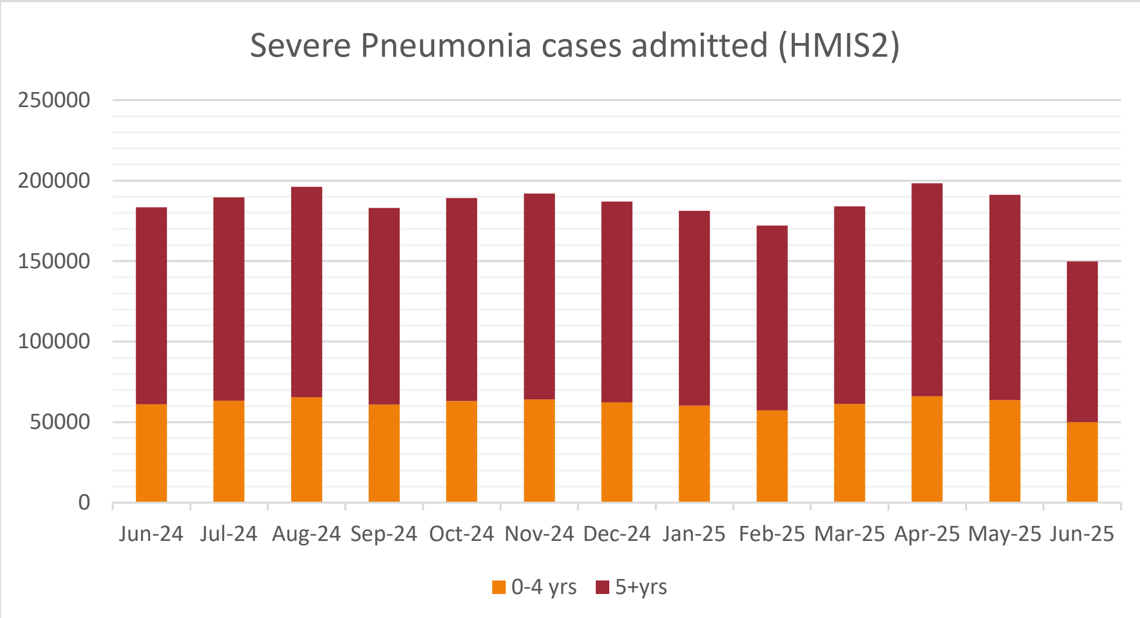
[13] Mackenzie GA, et. al, 2016. Effect of the introduction of pneumococcal conjugate vaccination on invasive pneumococcal disease in The Gambia: a population-based surveillance study. Lancet Infect Dis. 2016 Jun;16(6):703-711. doi: 10.1016/S1473-3099(16)00054-2. Epub 2016 Feb 18. PMID: 26897105; PMCID: PMC4909992.
[14] Makarere University John Hopkins University Collaboration 2024. RSV cases among neonates at Kawempe Regional Referral Hospital.
[15] WHO 2019. Pneumococcal Congugate Vaccines in infants and children under five years of age. WHO Position paper. https://iris.who.int/bitstream/handle/10665/310968/WER9408.pdf?sequence=1

		At Mulago National referral hospital, seven in ten of admitted measles cases also report co-morbidity with pneumonia.[16] Many of the cases are under 9 months, which is the age for measles 1 vaccination	
Conclusion	There seems to be a correlation between an increase in measles cases with an increase in pneumonia cases in the country. Pneumonia is a common comorbidity in severe measles cases.		
Recommendations	a) MoH should ensure high coverage, at least 95%, for the upcoming measles rubella vaccination campaign b) Explore evidence to support lower age vaccination for measles to six months as many affected are under 9 months. c) Pneumonia surveillance should be continued after the MR campaign to check for trend changes. DHIS2 case-based definition should be retained for consistency.		

[16] Dr Lucy Amaniyo - Head, infectious diseases ward, Mulago National Referral Hospital, personal communication.

Annexes: Figures and tables

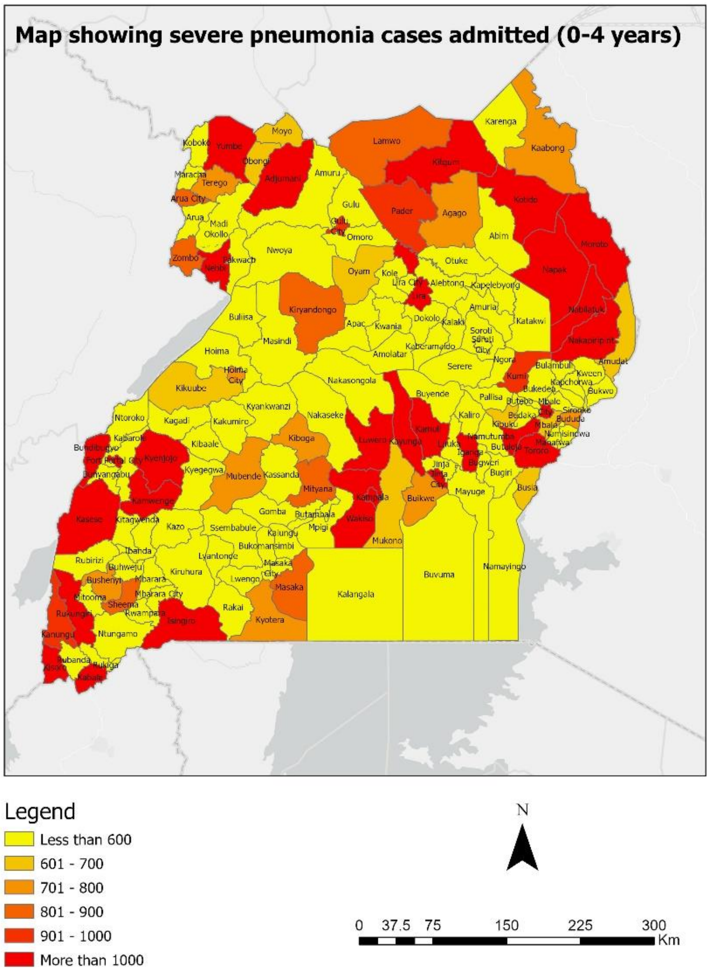
1. Severe pneumonia cases admitted by age-group HMIS2



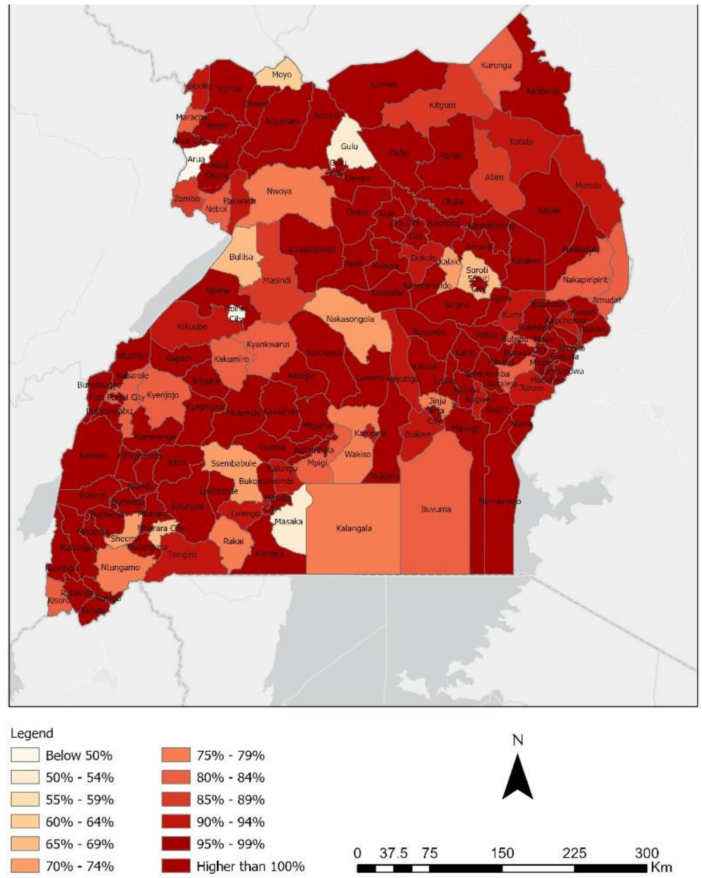
2. Pneumonia serotype prevalence 2014-2021

Sero types	**1**	**3**	**4**	**5**	**19A**	**19F**	**23F**	**6A/6B**	**6A/B**	**6B**	**7F/7A**	**9V/9A**
Total isolates 2011 - 2021	42	2	4	16	5	10	21	30	2	3	1	3
Vaccine type	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	y
PCV-10GSK Synflorix	Y		Y	Y		Y	Y			Y	Y	Y
PCV-10SII PNEUMOSIL	Y			Y	Y	Y	Y	Y	Y	Y	Y	Y
PCV-13 Prevnar	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

3. Maps showing Severe pneumonia cases admitted 0-4 years (DHIS2) and PCV3 coverage by district in 2025



Map showing PCV3 Coverage by district



4. PCV circulating serotypes before and after vaccine introduction

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

5. Biological characteristics of available Pneumococcal conjugate vaccines

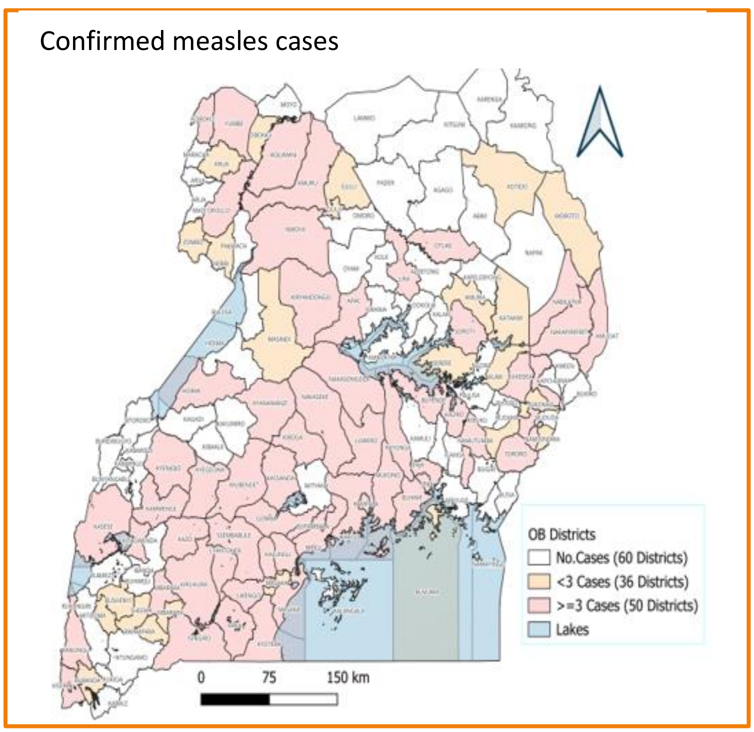
Product	Carrier protein(s)	Conjugation method & Preservative	Pneumococcal Serotype (ST) 1	3	4	5	6A	6B	6C	7F	9V	14	18C	19A	19F	23F
PCV-10[GSK] Synflorix®	Protein D (PD), tetanus toxoid (TT), diphtheria toxoid (DT)	*Conjugation:* CDAP* *Preservative:* 1-dose vial – none 2-dose vial – none 4-dose vial – 2-phenoxyethanol	ST included in vaccine	ST not included in vaccine	ST included in vaccine	ST included in vaccine	ST not included in vaccine but some evidence of cross-protection	ST included in vaccine	ST not included in vaccine	ST included in vaccine	ST included in vaccine	ST included in vaccine	ST included in vaccine	ST not included in vaccine	ST included in vaccine	ST included in vaccine
PCV-10[SII] PNEUMOSIL®	CRM197	*Conjugation:* CDAP* *Preservative:* 1 dose vial – none 5 dose vial – thimerosal	ST included in vaccine	ST not included in vaccine	ST not included in vaccine	ST included in vaccine	ST included in vaccine	ST included in vaccine	ST not included in vaccine	ST included in vaccine	ST included in vaccine	ST included in vaccine	ST not included in vaccine	ST included in vaccine	ST included in vaccine	ST included in vaccine
PCV-13 Prevnar®	CRM197	*Conjugation:* Reductive amination *Preservative:* 1-dose vial – none 4-dose vial – 2-phenoxyethanol	ST included in vaccine	ST3 included in PCV-13 but no conclusive evidence for protection	ST included in vaccine	ST included in vaccine	ST included in vaccine	ST included in vaccine	ST not included in vaccine but some evidence of cross-protection	ST included in vaccine	ST included in vaccine	ST included in vaccine	ST included in vaccine	ST included in vaccine	ST included in vaccine	ST included in vaccine

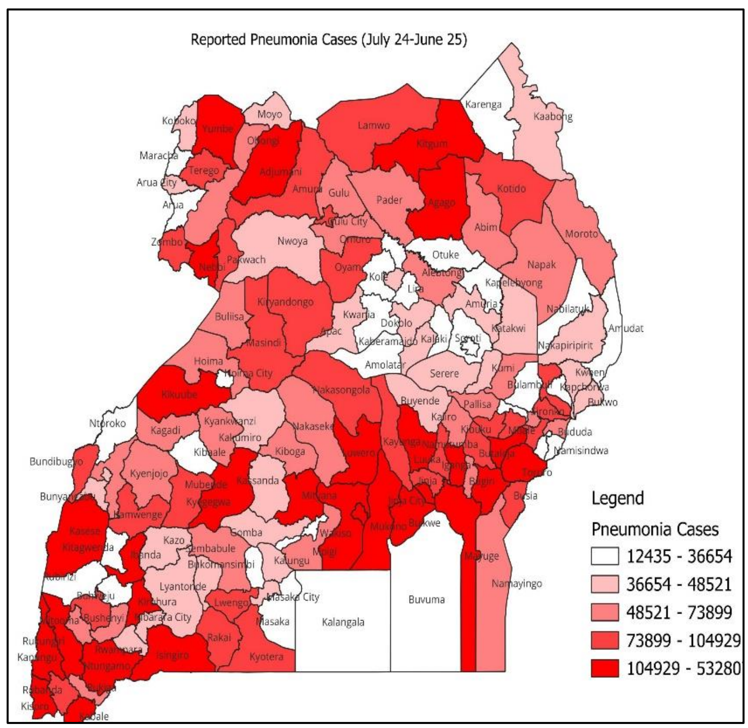
* CDAP: 1-cyano-4-dimethylaminopyridinium tetrafluoroborate

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

6. Measles and pneumonia cases by district June 2024-June 2025





Source: Measles DHIS2 data, pneumonia HMIS2 data

Sciences for Prosperity

Report of the Uganda National Immunization Technical Advisory Group on Preventive Vaccination against Ebola Virus Disease

November 2025

Executive Summary

Ebola Virus Disease (EVD) is a severe and often fatal hemorrhagic fever caused by viruses of the *Orthoebolavirus* genus, primarily caused by the Zaire, Sudan, and Bundibugyo strains. The disease is spread through direct contact with the blood, secretions, organs or other bodily fluids of an infected person. Since 2000, Uganda has registered eight outbreaks of EVD (six due to E. Sudan, 1 E. Bundibugyo, and one E. Zaire), accounting for 366 cumulative deaths, with a case fatality rate ranging between 25 to 100%. The 2019 E. Zaire outbreak was a spillover from the Democratic Republic of Conge where frequent outbreaks are known to occur, with the latest outbreak reported in 2025.

The Strategic Advisory Group of Experts (SAGE) updated its guidance on Ebola vaccination in May 2024, and recommended preventive vaccination in countries at risk of EVD, those with a history of outbreaks, or located in neighboring regions, having assessed their transmission risk based on outbreak epidemiology and local evidence. Each country was advised to identify priority areas and target populations for preventive vaccination. Vaccines would be supplied from a Global emergency stockpile of 500,000 doses of EVERBO vaccine managed by the International Coordinating Group, which makes available vials nearing their expiry date.

As Uganda falls under the risk categories identified by SAGE, the Ministry of Health requested the Uganda National Immunization Technical Advisory Group (UNITAG) to provide scientific guidance on the strategic use of the Ebola vaccines in Uganda. Specifically, the Ministry sought advice on:

i. the feasibility of preventive Ebola vaccination,
ii. identification of priority groups and
iii. preparedness to access the global vaccine stockpile.

The UNITAG reviewed contextual evidence including the history of EVD in Uganda, an Ebola outbreak risk analysis, the efficacy, safety, feasibility and acceptability of available Ebola vaccines, and lessons learned from two previous rounds of preventive EVD vaccination. UNITAG reviewed two vaccines against Ebola Zaire: VSVΔG-ZEBOV-GP (ERVEBO®, Merck & Co) – a single-dose vaccine demonstrating 100% efficacy in field trials and an immune response lasting at least five years, and Ad26.ZEBOV, recommended for use in outbreak settings; and MVA-BN-Filo (Johnson & Johnson) – a two-dose regimen given 56 days apart, shown to induce strong immune responses in adults and children but lacking direct human efficacy data. UNITAG noted that there is currently no licensed vaccine against the Sudan Ebola virus, however the Uganda Virus Research Institute (UVRI) and other partners initiated a clinical trial of the rVSV-SUDV candidate vaccine in 2025.

UNITAG conclusions:

i. While Uganda has experienced mostly Sudan Ebola virus outbreaks, the threat of the Zaire Ebola virus strain remains, due to potential cross-border spillovers from the Democratic Republic of Congo.
ii. The most at-risk groups for contracting the Ebola virus include frontline health workers, responders, border district populations with Democratic Republic of Congo, and security forces operating in and near the Democratic Republic of Congo. Kampala district is also considered as high risk due to its large urban and migrant population, and sizeable refugee population.
iii. The two licensed and prequalified Zaire Ebola virus vaccines ERVEBO® (Merck), and MVA-BN-Filo(J&J) are safe and efficacious for use in preventive vaccination campaigns of individuals aged 12 months and older. The single dose EVERBO vaccine is logistically easier to implement over the two dose J& J vaccine due to high drop-out rates observed in previous preventive campaigns. EVERBO is also readily available through the Global stockpile, and through Gavi, comes with support for operational costs.

UNITAG Recommendations:

i. Uganda should conduct preventive vaccination campaigns against EVD in the high-risk population groups including frontline health workers, responders, security personnel operating in or near border districts with the Democratic Republic of Congo (DRC), and populations in districts along the Uganda–DRC border.
ii. The high priority groups for EVD preventive vaccination include; frontline health workers, responders, border district populations with Democratic Republic of Congo, and security forces operating in and near the Democratic Republic of Congo. Kampala district is considered among the high-risk areas due to its large urban and dynamic population, and sizeable urban refugee population.
iii. The use of ERVEBO® over Ad26.ZEBOV, MVA-BN-Filo vaccines is preferable due to its single-dose regimen, higher efficacy, and availability through the global stockpile. The ERVEBO® vaccine is approved by the National Drug Authority.
iv. Uganda should formally request the International Coordinating Group to provide for an in-country Ebola vaccine stockpile, which would be used for preventive vaccination and can be quickly transitioned to ring vaccination in the event of an outbreak.
v. Ministry of Health through the National Medical Stores and health subdistricts should ensure proper cold-chain infrastructure and stock management, to minimize Ebola Vaccine wastage.
vi. Ministry of Health should prepare clear protocols for preventive Ebola vaccination campaigns. The Department of Health Education, Promotion, and Communication should strengthen engagements with stakeholders on the advantages of preventive Ebola vaccination to support its uptake, the surveillance pillar should be vigilant to detect any cases of EVD early, and the pharmacovigilance pillar should be strengthened to detect and respond to any adverse events following vaccination and thus boost vaccine confidence.

UNITAG will continue to review new evidence from the Sudan Ebola virus vaccine trials and update its recommendations accordingly as more data becomes available.

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1.0 Background

On June 26, 2025, the Ministry of Health, through the Director General of Health Services, requested UNITAG's guidance on the strategic application of Ebola Viral Disease (EVD) vaccines. Specifically, the Ministry of Health sought advice on:

i. The feasibility and appropriateness of preventive EVD vaccination in Uganda
ii. Priority groups and settings that should be considered.
iii. Recommendations for preparedness to access the global vaccine stockpile.

On May 7, 2024, the Strategic Advisory Group of Experts (SAGE) held an extraordinary meeting to update its guidance on Ebola vaccination, replacing the recommendations issued in May 2019. SAGE advised that countries at risk of Ebola Virus Disease (EVD), those with a history of outbreaks or located in neighboring regions should assess their transmission risk based on outbreak epidemiology and local evidence. Each country should then identify priority areas and target populations for preventive vaccination.

In order to comprehensively provide scientific guidance to the Ministry of Health on Ebola, the UNITAG Ebola working group was constituted. The working group comprised of core members, liaison members, Ex-officials and a co-opted expert on Ebola. The Ebola working group adopted the Evidence to Recommendation framework, in addition to the PICO framework below, to guide the extensive review and compilation of Ebola literature that supported the drafting of conclusions and recommendations.

Table 1: Pico Framework

Broad Policy Question: Should Uganda conduct preventive campaigns of the Ebola vaccine for high-risk populations?
Specific PICO Question: Should Uganda introduce preventive campaigns with Ebola vaccines for frontline workers and populations in border districts against EVD to increase resilience of health system and reduce outbreak numbers in vaccinated groups?
Population-Frontline workers including health care workers, responders, people in high-risk districts with Democratic Republic of Congo
Intervention-Preventive campaigns
Comparator- i. No preventive vaccination ii. Ring vaccination outbreak response iii. Therapeutics for infected persons
Outcome- Reduce number of infections during outbreaks, ensure resilient healthcare system in case of outbreaks

1. Introduction

Ebola virus disease (EVD) is a severe hemorrhagic fever caused by viruses of the genus Orthoebolavirus (EBOV) and is transmitted through direct or indirect contact with blood, body fluids, or secretions (stool, saliva, semen) of infected individuals[1].

There are three different viruses known to cause large Ebola disease outbreaks; the Zaire Ebola virus, Sudan Ebola virus and Bundibugyo Ebola virus. The Ebola viral disease is usually difficult to distinguish from other infectious diseases because the symptoms at early stage of the disease are similar to those of other infectious diseases and hemorrhagic fevers. The disease is characterized by sudden fever, fatigue, muscle pain, headache, sore throat, and usually followed by vomiting, diarrhea, abdominal pain. However, some patients have internal/external bleeding (blood in vomit& faeces, bleeding from nose, gums and vagina[2].Since its discovery in 1976, most Ebola outbreaks have occurred in sub-Saharan Africa. The largest outbreak took place in West Africa between 2014 and 2016, leading to over 28,600 cases and 11,300 deaths[3].

Table 2: History of Ebola Outbreaks in Uganda (2000-2025)

District/Year	Cases	Deaths	Case Fatality rate (CFR)	Strain
Gulu, Masindi, Mbarara (2000)	425	224	53%	Sudan Ebola virus[4],[5]
Bundibugyo (2007-2008)	149	37	25%	Bundibugyo Ebola virus[6]
Luwero (2011)	1	1	100%	Sudan Ebola virus[7]
Luwero (2012)	7	4	57%	Sudan Ebola virus[8]
Kibaale (2012)	24	17	71%	Sudan Ebola virus[9]
Kasese (2019)	4	4	100%	Zaire Ebola virus[10]
Mubende &Multiple districts (2022)	164	77	47%	Sudan Ebola virus[11]
Kampala, Ntoroko, Wakiso (2025)	12	2	29%	Sudan Ebola virus[12]

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[1] https://www.who.int/health-topics/ebola
[2] WHO 2025, Ebola Fact Sheet; https://www.who.int/news-room/fact-sheets/detail/ebola-disease
[3] https://www.cdc.gov/ebola/outbreaks/index.html
[4] Okware, S. I., Omaswa, F. G., Zaramba, S., Opio, A., Lutwama, J. J., Kamugisha, J., ... & Lamunu, M. (2002). An outbreak of Ebola in Uganda. *Tropical Medicine & International Health*, *7*(12), 1068-1075
[5] Okware, S. (2016). Managing Ebola in low-resource settings: experiences from Uganda. In *Ebola*. IntechOpen
[6] Towner, J. S., Sealy, T. K., Khristova, M. L., Albariño, C. G., Conlan, S., Reeder, S. A., ... & Nichol, S. T. (2008). Newly discovered ebola virus associated with hemorrhagic fever outbreak in Uganda. *PLoS pathogens*, *4*(11), e1000212.
[7] Okware, S. (2016). Managing Ebola in low-resource settings: experiences from Uganda. In *Ebola*. IntechOpen
[8] Already referenced
[9] Okware, S. (2016). Managing Ebola in low-resource settings: experiences from Uganda. In *Ebola*. IntechOpen
[10] Nyakarahuka, L., Mulei, S., Whitmer, S., Jackson, K., Tumusiime, A., Schuh, A., ... & 'Kasese EVD Outbreak Response Team'. (2022). First laboratory confirmation and sequencing of Zaire ebolavirus in Uganda following two independent introductions of cases from the 10th Ebola Outbreak in the Democratic Republic of the Congo, June 2019. *PLoS neglected tropical diseases*, *16*(2), e0010205
[11] Aceng, J. R., Bosa, H. K., Kamara, N., Atwine, D., Mwebesa, H., Nyika, H., ... & Ouma, A. O. (2023). Continental concerted efforts to control the seventh outbreak of Ebola Virus disease in Uganda: The first 90 days of the response. *Journal of public health in Africa*, *14*(9), 2735.
[12] https://www.who.int/emergencies/disease-outbreak-news/item/2025-DON566

Table 3: Ebola Outbreaks in the DRC (2000-2025)

Year	District/Health Zone	Deaths	Cases	Case-Fatality rate (CFR)	Strain
2007	Kasaï-Occidental — Luebo & Mweka	187	264	70.8%	Zaire ebolavirus
2008–2009	Kasaï-Occidental — Mweka & Luebo	15	32	46.9%	Zaire ebolavirus
2014	Équateur — Boende area	49	69	71.0%	Zaire ebolavirus
2017	Bas-Uélé — Likati health zone	4	8	50.0%	Zaire ebolavirus
May–Jul 2018	Équateur — Bikoro (Bikoro cluster)	33	54	61.1%	Zaire ebolavirus
Aug 2018 – Jun 2020	North Kivu, Ituri, South Kivu (large Kivu epidemic)	2,287	3,470	65.9%	Zaire ebolavirus
Jun–Nov 2020	Équateur — Mbandaka (2020 Équateur outbreak)	55	130	42.3%	Zaire ebolavirus
Feb–May 2021	North Kivu — Biena health zone	6	12	50.0%	Zaire ebolavirus
Oct–Dec 2021	North Kivu — Beni health zone	9	11	81.8%	Zaire ebolavirus
Apr–Jul 2022	Équateur — Mbandaka (Apr–Jul 2022 cluster)	5	5	100.0%	Zaire ebolavirus
Aug–Sep 2022	North Kivu — Beni (single confirmed case)	1	1	100.0%	Zaire ebolavirus
Sep 2025 (declared 4 Sep 2025)	Kasai Province — Bulape & Mweka health zones	45	64	70.3%	Zaire ebolavirus (ongoing / situation report numbers as of Oct 12, 2025)
History of Ebola Outbreaks in South Sudan					
1976	Nzara, Maridi, Tembura, Juba (then southern Sudan)	284	151	53%	Sudan ebolavirus (SUDV)
1979	Nzara and Maridi, southern Sudan	34	22	~ 65%	Sudan ebolavirus (SUDV)
2004	Yambio county, Western Equatoria, South Sudan	17	7	~ 41%	Sudan ebolavirus

2. Vaccine Considerations

As at November 2025, two Zaire Ebola vaccines are licensed and prequalified by the World Health Organization. The rVSVΔG-ZEBOV-GP (Ervebo®, Merck & Co) is a fully liquid, single-dose recombinant vesicular stomatitis virus vaccine expressing Ebola virus glycoprotein (Zaire ebolavirus) targeting Zaire ebolavirus indicated for individuals ≥1 year administered intramuscularly. It offers high flexibility in outbreak response, requires no revaccination within 6 months, and may be boosted after 6 months for high-risk groups.

Ad26.ZEBOV, MVA-BN-Filo (Johnson & Johnson two-dose regimen) consists of Ad26.ZEBOV (adenovirus vector) and MVA-BN-Filo (modified vaccinia Ankara vector) targeting Zaire ebolavirus and other filoviruses. Both are liquid formulations, indicated for individuals >1 year, with two 0.5 mL doses given 56 days apart.

There is currently no licensed vaccine for the Sudan Ebola virus, which has caused most of the Ebola outbreaks in Uganda. However, in 2025, Uganda launched a clinical trial of the IAVI rVSV-SUDV vaccine, led by the Uganda Virus Research Institute in collaboration with other partner organizations.

3. Efficacy, Effectiveness and safety of the Ebola Vaccines

i. rVSVΔG-ZEBOV-GP vaccine (Ervebo, Merck &Co)

Results from an open-label, cluster-randomized ring vaccination trial conducted in Guinea, West Africa, demonstrated a vaccine efficacy of **100% (95% CI: 74.7–100.0; p=0.0036)** among adults aged 18 years and older who were not pregnant, breastfeeding, or severely ill. No new Ebola Virus Disease (EVD) cases were reported among vaccinated individuals 6 days post vaccination.

At the cluster level, the estimated vaccine effectiveness was 75.1% (95% CI: –7.1 to 94.2; p=0.1791) when including all eligible adults, and 76.3% (95% CI: –15.5 to 95.1; p=0.3351) when including all individuals, regardless of eligibility for vaccination[13].Similarly, results from a retrospective test-negative analysis estimating the vaccine effectiveness of rVSV-ZEBOV vaccination against Ebola virus disease during the 2018-2020 epidemic in the Democractic Republic of Congo found **vaccine effectiveness 10 days or more post-vaccination at 84**% **(95% CI: 70–92)**, confirming strong protection against Ebola virus disease. Out of 26,438 individuals**,** 1,273 (4.8%) were Ebola virus disease cases and 25,165 (95.2%) were controls. Among them, 3.1% of cases and 5.1% of controls had been vaccinated with rVSV-ZEBOV at least 10 days before symptom onset[14].

A study by Huttner et.al. (2023) assessed the 5-year durability of immune responses to the rVSV-ZEBOV (Ervebo®) Ebola vaccine among adults in Switzerland and Gabon over a five-year period. Results showed that **Ebola glycoprotein specific IgG antibodies persisted in**

[13] Henao-Restrepo, A. M., Longini, I. M., Egger, M., Dean, N. E., Edmunds, W. J., Camacho, A., ... & Røttingen, J. A. (2015). Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomized trial. *The Lancet*, *386*(9996), 857-866.

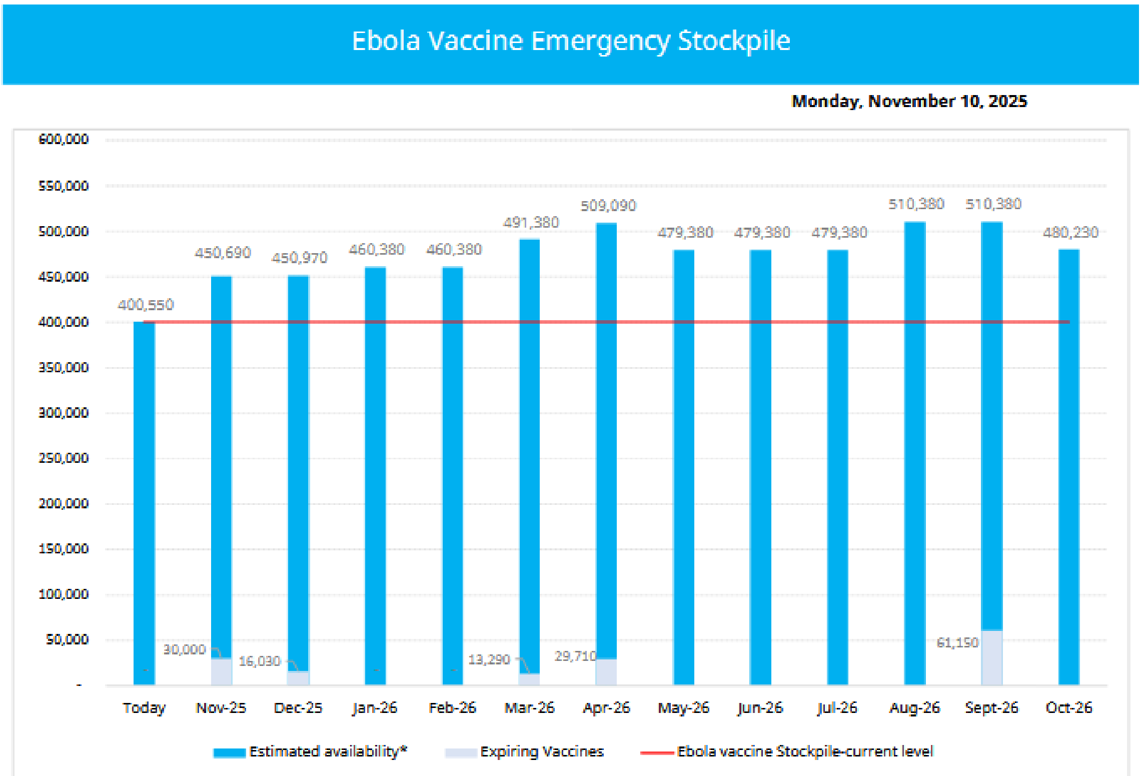
[14] Meakin, S., Nsio, J., Camacho, A., Kitenge, R., Coulborn, R. M., Gignoux, E., ... & Ahuka-Mundeke, S. (2024). Effectiveness of rVSV-ZEBOV vaccination during the 2018–20 Ebola virus disease epidemic in the Democratic Republic of the Congo: a retrospective test-negative study. *The Lancet Infectious Diseases*, *24*(12), 1357-1365

100% of the participants, showing no decline in titres between 1 and 5 years after vaccination. **The findings indicate that a single dose of rVSV-ZEBOV induces durable and strong immune responses lasting at least five years**, however, further research is needed to determine the exact duration of actual clinical protection[15].
The single-dose Ervebo vaccine has a favorable safety profile, with serious vaccine-related adverse events being rare. However, common side effects include injection site pain, headache, fever, muscle pain, and fatigue. The safety and effectiveness of Ervebo have not yet been evaluated in immunocompromised individuals[16].There is limited data on the use of Ervebo during pregnancy, however, **a clinical trial in Sierra Leone found no significant differences in pregnancy loss or birth defects between vaccinated and unvaccinated women**. Similarly, there is no data on the use of Ervebo among lactating mothers however, the World Health Organization recommends using Ervebo in pregnant and breastfeeding women only during active Ebola outbreaks when the risk of exposure is high[17].

On the issue of vaccine availability, in 2021 a global ERVEBO vaccine stockpile was created under the International Coordinating Group (ICG) to ensure equitable and timely access during Ebola outbreaks. The stockpile, maintained at 500,000 doses, is supported by Gavi and is primarily intended for outbreak response. The International Coordinating Group has approved targeted preventive vaccination for high-risk groups such as health care and frontline workers. The World Health Organization notes that Ervebo is currently the only vaccine available in the global stockpile. The UNICEF cost of Ervebo list price is about $98.60 per dose[18].However, during the 2021 Ebola outbreak in Guinea, WHO coordinated access to ERVEBO at approximately $12-$16 per dose for African countries significantly below commercial rates.

[15] Huttner, A., Agnandji, S. T., Engler, O., Hooer, J. W., Kwilas, S., Ricks, K., ... & Vianello, E. (2023). Antibody responses to recombinant vesicular stomatitis virus-Zaire Ebolavirus vaccination for Ebola virus disease across doses and continents: 5-year durability. Clinical Microbiology and Infection, 29(12), 1587-1594
[16] https://www.merck.com/news/u-s-fda-approves-mercks-ervebo-ebola-zaire-vaccine-live-for-use-in-children-12-months-of-age-and-older/
[17] https://www.cdc.gov/ebola/hcp/vaccines/index.html
[18]

Table 4 Ervebo Vaccine Emergency Stockpile



Expiry date	Qty available (doses)
27 Nov 2025	30,000
4 Dec 2025	16,030
6 Mar 2026	380
27 Mar 2026	12,910
11 Apr 2026	29,710
4 Sept 2026	30,360
11 Sept 2026	30,790
4 Dec 2026	25,890
15 Apr 2027	30,620
22 Apr 2027	28,330
17 Jun 2027	30,400
19 Aug 2027	30,380
7 Oct 2027	29,590
21 Oct 2027	16,190
26 Apr 2028	31,820
5 May 2028	27,150
Total current availability	**400,550**

on about Ebola vaccine in the Stockpile			
Presentation	**Cold Chain volume**	**WHO PQ**	**Shipment**
1 dose vial	16.42	Yes	US$ 0.85

Source: UNICEF, Nov. 2025. https://www.unicef.org/supply/media/24281/file/Ebola-Stockpile-Availability-Report-10-11-25.pdf

ii. Ad26.ZEBOV, MVA-BN-Filo (Johnson & Johnson two-dose regimen)

Ad26.ZEBOV, MVA-BN-Filo (Johnson & Johnson two-dose regimen) consists of Ad26.ZEBOV (adenovirus vector), and MVA-BN-Filo (modified vaccinia Ankara vector) targeting Zaire ebolavirus and other filoviruses. Both are liquid formulations, indicated for individuals >1 year, with two 0.5 mL doses given 56 days apart. The vaccine is administered intramuscularly[19]. There are currently no studies evaluating the efficacy of the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen in humans. However, the European Medicines Agency (EMA) has authorized its use under exceptional circumstances.

Immunobridging studies have demonstrated that Ad26.ZEBOV, MVA-BN-Filo triggers an immune response that can provide protection against Ebola virus disease. Data from 764 vaccinated healthy adults across five clinical studies were analyzed to estimate the mean predicted survival probability using a logistic regression model based on Ebola virus glycoprotein antibody responses in vaccinated non-human primates (NHPs) and their survival after Ebola. The primary immunobridging analysis evaluated the lower limit of the CI against predefined success criterion of 20% and passed with mean predicted survival probability of 53.4% (95% CI: 36.7–67.4). While this method infers the vaccine's protective effect in humans, the estimated survival probability does not directly represent vaccine efficacy[20]. Similarly, another study by Roozendaal et al.(2020) evaluated the protective effect of the two-dose Ebola vaccine regimen Ad26.ZEBOV, MVA-BN-Filo by linking immune responses in humans to survival outcomes in non-human primates (NHPs) findings showed the Ad26.ZEBOV, MVA-BN-Filo regimen given eight weeks apart provided complete protection (25 of 25 NHPs, 100%), while shorter dosing intervals (six or four weeks) resulted in partial protection (80% and 57% survival, respectively. Using this animal-derived logistic model, antibody data from human phase I trials were analyzed. The mean predicted survival probability in humans was 47.8% (95% CI: 24.1–66.3%), later refined to 53.4% (95% CI: 36.7–67.4%) in an updated 2022 analysis. Although this probability does not directly represent vaccine efficacy, it indicates that the vaccine is likely to confer protection in humans[21].

a. Children and Adolescents

Results from a Phase II randomized controlled trial involving 131 adolescents (12 to 17 years old) and 132 children (4 to 11 years old) conducted in 7 sites in 4 African countries: Burkina Faso (Bobo-Dioulasso and Banfora), Côte d'Ivoire (Abidjan and Toupah/Ousrou), Kenya (Nairobi), and Uganda (Masaka and Kampala), were randomized 5:1 to receive study vaccines or placebo. Vaccine groups received intramuscular injections of Ad26.ZEBOV (5×10^{10} viral particles) and MVA-BN-Filo (1×10^{8} infectious units) 28 or 56 days apart; placebo recipients received saline. The study findings indicate twenty-one days post-MVA-BN-Filo vaccination,

[19] https://www.ema.europa.eu/en/documents/product-information/zabdeno-epar-product-information_en.pdf
[20] Bockstal, V., Leyssen, M., Heerwegh, D., Spiessens, B., Robinson, C., Stoop, J. N., ... & Van Hoof, J. (2022). Non-human primate to human immunobridging demonstrates a protective effect of Ad26. ZEBOV, MVA-BN-Filo vaccine against Ebola. npj Vaccines, 7(1), 156.
[21] Roozendaal, R., Hendriks, J., van Effelterre, T., Spiessens, B., Dekking, L., Solforosi, L., ... & Callendret, B. (2020). Nonhuman primate to human immunobridging to infer the protective effect of an Ebola virus vaccine candidate. npj Vaccines, 5(1), 112.

binding antibody responses against EBOV GP were observed in 100% of vaccinees (106 adolescents, 104 children). Geometric mean concentrations tended to be higher after the 56-day interval (adolescents 13,532 ELISA units [EU]/mL, children 17,388 EU/mL) than the 28-day interval (adolescents 6,993 EU/mL, children 8,007 EU/mL). Humoral responses persisted at least up to Day 365. No vaccine-related SAEs were reported; solicited AEs were mostly mild/moderate[22].Similarly, results from a Phase 3 trial (DRC-EB-001) of the **Ad26.ZEBOV, MVA-BN-Filo Ebola vaccine** conducted in Goma, DRC among children and adults, during the 2018–2020 Ebola outbreak found that **antibody levels (GMC)** were already detectable across all groups,217 EU/mL in adults, 378 EU/mL in adolescents, and 558 EU/mL in children indicating persistent immunity from the first dose. After receiving the delayed second dose, the antibody levels rose sharply: **22,194 EU/mL in adults**, **37,896 EU/mL in adolescents**, and **34,652 EU/mL in children**. The study found that participants who received the delayed second dose developed stronger immune responses than those vaccinated on the standard 56-day schedule in previous trials. The findings indicate that **Ad26.ZEBOV, MVA-BN-Filo regimen is highly immunogenic across all age groups** and that **longer intervals between doses may enhance antibody responses** without compromising vaccine effectiveness. The study aimed to assess antibody responses across different age groups who received the two-dose regimen originally planned 56days apart however due to interruptions caused by the COVID-19 pandemic, some participants received the second dose much later than the scheduled date[23].

Table 5: Ad26.ZEBOV, MVA-BN-Filo use in Different Age Groups

Table 2. Ebola virus glycoprotein-specific binding antibody concentrations.

Immunogenicity Analysis Population	Adults (18+ Years)	Adolescents (12–17 Years)	Children (4–11 Years)
Participants with paired samples, n (total = 133)	49	32	52
Pre-dose 2 GMC (95% CI)	217 (157; 301)	378 (281; 510)	558 (471; 661)
21 days post-dose 2 GMC (95% CI)	22,194 (16,726; 29,449)	37,896 (29,985; 47,893)	34,652 (27,906; 43,028)
GMC fold change * between time points	102	100	62

Data are number of paired samples (n), geometric mean concentration, and 95% confidence interval (GMC, 95% CI). * Fold change = GMC at 21 days post-dose 2/GMC at pre-dose 2.

Results from a randomized double blind controlled trial at three sites in Kambia district, Sierra Leone among 576 healthy children and adolescents in three age cohorts 1-3 years,4-11 years and

[22] Anywaine, Z., Barry, H., Anzala, O., Mutua, G., Sirima, S. B., Eholie, S., ... & EBL2002 Study group. (2022). Safety and immunogenicity of 2-dose heterologous Ad26. ZEBOV, MVA-BN-Filo Ebola vaccination in children and adolescents in Africa: A randomised, placebo-controlled, multicentre Phase II clinical trial. *PLoS medicine*, *19*(1), e1003865.

[23] Choi, E. M. L., Kasonia, K., Kavunga-Membo, H., Mukadi-Bamuleka, D., Soumah, A., Mossoko, Z., ... & Toure, O. (2024). *Immunogenicity of an Extended Dose Interval for the Ad26. ZEBOV, MVA-BN-Filo Ebola Vaccine Regimen in Adults and Children in the Democratic Republic of the Congo. Vaccines 2024, 12, 828*.

12-17 years were assigned to receive Ad26.ZEBOV as the first dose and MVA-BN-Filo as the second dose (on day 57), or a control vaccine (MenACWY + placebo).The findings indicate the vaccine induced strong antibody responses in nearly all participants(98-99% sero response, at 21 days post second dose, Ebola virus glycoprotein-specific antibody concentrations (GMCs) were:12–17 years: 9,929 EU/mL (95% CI 8,172–12,064);4–11 years: 10,212 EU/mL (95% CI 8,419–12,388);1–3 years: 22,568 EU/mL (95% CI 18,426–27,642),highest antibody levels were observed in the youngest cohort(1-3years).

In terms of safety, the vaccine was well tolerated across all age groups, the most common local AE was injection site pain up to 21% in 4-11 years group and the most frequent systemic AEs were headache in older cohorts and fever among the 1-3 years cohort[24].

b. Adults Populations

Results from a study assessing the safety and immunogenicity of the two dose Ebola vaccine regimen, consisting of Ad26.ZEBOV and MVA-BN-Filo, have showed to have high antibody responses in healthcare providers and frontliners in the Democratic Republic of Congo. The findings showed the vaccine was well tolerated with no vaccine-related adverse events reported,21 days after the second dose, an EBOV glycoprotein-specific binding antibody response was observed in 95.2% of the participants[25].

Results from a Phase 3, double-blind, placebo-controlled trial evaluating the lot-to-lot consistency**,** immunogenicity**,** and safety of the Ad26.ZEBOV, MVA-BN-Filo among medically stable men or women aged 18–50 years, without known prior exposure to Ebolavirus at seven sites in the United States. The study participants were randomized to receive the two-dose vaccine (Ad26.ZEBOV on Day 1 and MVA-BN-Filo on Day 57) from one of three consecutively manufactured lots, or placebo. An additional group received a **booster dose** of Ad26.ZEBOV or placebo four months after the second dose. The findings indicate at day 21 post dose two,99.5% (419/421) of participants achieved a >2.5-fold increase in Ebola glycoprotein (GP)–binding antibodies, even after a single dose, by 56 days post dose one, 96.7% (445/460) had significant antibody rises. In the booster cohort, GMCs increased 9-fold by Day 7 and 11.8-fold by Day 21 post-booster, showing strong immune responses. The vaccine was tolerated, with no safety concerns or serious vaccine related adverse events reported. Overall, **Ad26.ZEBOV, MVA-BN-Filo Ebola vaccine** demonstrated **consistent immunogenicity** and good **safety**. With nearly all recipients developed strong antibody responses, including those that received the booster dose[26].

[24] Afolabi, M. O., Ishola, D., Manno, D., Keshinro, B., Bockstal, V., Rogers, B., ... & Ishola, D. (2022). Safety and immunogenicity of the two-dose heterologous Ad26. ZEBOV and MVA-BN-Filo Ebola vaccine regimen in children in Sierra Leone: a randomised, double-blind, controlled trial. *The Lancet Infectious Diseases*, *22*(1), 110-122.
[25] Larivière, Y., Garcia-Fogeda, I., Zola Matuvanga, T., Isekah Osang'ir, B., Milolo, S., Meta, R., ... & Van Damme, P. (2024). Safety and immunogenicity of the heterologous 2-dose Ad26. ZEBOV, MVA-BN-Filo vaccine regimen in health care providers and frontliners of the Democratic Republic of the Congo. The Journal of infectious diseases, 229(4), 1068-1076.
[26] Goldstein, N., McLean, C., Gaddah, A., Doua, J., Keshinro, B., Bus-Jacobs, L., ... & Douoguih, M. (2024). Lot-to-lot consistency, immunogenicity, and safety of the Ad26. ZEBOV, MVA-BN-Filo Ebola virus vaccine regimen: a phase 3, randomized, double-blind, placebo-controlled trial. *Human Vaccines & Immunotherapeutics*, *20*(1), 2327747.

Vaccine supply of **Ad26.ZEBOV, MVA-BN-Filo Ebola vaccine** has been affected by production challenges, as Johnson & Johnson has stopped manufacturing the vaccine. However, there are plans to **transfer the production technology to another manufacturer** to ensure continued supply.UNICEF doesnot list a sticker price for the vaccine however, in 2023 the Ministry of Health secured a 5 year supply of the **Ad26.ZEBOV, MVA-BN-Filo Ebola vaccine at $21 per two dose regimen in 2023[27].**

Table 6: Comparison of the rVSVΔG-ZEBOV-GP (Ervebo®, Merck & Co) and Ad26.ZEBOV and MVA-BN-Filo vaccine regimen

	rVSV-ZEBOV (ERVEBO)	Ad26.ZEBOV/MVA-BN-Filo (Zabdeno/Mvabea)
Regulatory status	Licensed by US FDA, EMA, WHO PQ >500,000 vaccinated globally	Licensed by EMA based on the animal rule, WHO PQ >300,000 vaccinated globally
Indication	≥1 years, single dose SAGE recommends off label use for pregnant and lactating women if part of risk group	≥1 years, 2 doses 56 days apart *Additional dose of Ad26.ZEBOV should be considered for individuals at imminent risk of exposure >4 months ago
Administration	1-mL single dose vial Intramuscular (IM) administration	One dose (0.5 mL) zabdeno, one dose (0.5 mL) mvabea IM administration
Efficacy and effectiveness	Efficacy study phase III. Ca suffit :100% (95% CI: 68.9–100.0) Field effectiveness in DRC: 97.5%, 95% CI [95.8 – 98.5%]	Efficacy inferred through animal model (expected to be >53% based survival with lethal dose and correlation with immunogenicity studies in humans)
Durability	Unknown; Immunogenicity studies up to 5 years	Unknown; Immunogenicity studies up to 5 years
Safety	Live virus, sore arm, fatigue, fever, muscle aches Contraindication: Severe allergic reaction (e.g., anaphylaxis) to any component of ERVEBO®	Similar safety profile
Storage	<-60°C; once thawed can be stored for up to 14 days at 2°C to 8°C. Cannot be refrozen, at room temp (up to 25°C) vaccine should be discarded after 4 hours	Transport at-25°C to -15°C and store for a single period of up to 20 months or 2°C to 8°C for a single period of up to 8 months

Source: WHO Presentation to the Ebola Working Group on August 7, 2025

[27] https://pmarketresearch.com/hc/ebola-virus-vaccine-market/?utm_source=

Table 7: Targeted Health Care Worker Population for Ebola Vaccination

Coverage by Targeted HCW population in district per microplan					
Health Sub-region/ Special Category	**District/Division**	**Total (HCW) Popn Microplan**	**Vaccine allocated**	**Coverage (Phase-1 (Zabdeno®)**	**Coverage Phase-2 (Mvabea®)**
West Nile	Adjumani	518	335	65%	55%
	Arua City	1,230	796	46%	21%
	Obongi	1,010	653	65%	34%
	Yumbe	791	591	75%	40%
Bunyoro	Kagadi	600	388	65%	34%
	Kyegegwa	1,310	842	39%	28%
Tooro	Fort-Portal City	1,400	906	60%	25%
	Bundibugyo	1,355	877	34%	9%
	Ntoroko	530	343	62%	19%
	Kasese	2,910	1,882	34%	9%
Kigezi	Kanungu	510	330	65%	36%
	Kisoro	1,027	664	57%	32%
Central	Mubende	853	552	65%	34%
	Luweero	1,415	915	65%	63%
	Sub total	**15,459**	**10,074**	**52%**	**28%**

Source: Ministry of Health

5. **Ebola Regimen Vaccination Consumption in Targeted regions-In country Experience**

The Ministry of Health (MoH), working through the Infectious Diseases Institute (IDI) as its implementing partner, launched a targeted preventive Ebola vaccination campaign using the WHO-prequalified two-dose regimen (Zabdeno® followed by Mvabea®). The efforts focused on vaccinating high-risk individuals including frontline health workers, refugees, immigration officers, and traditional healers or birth attendants in 14 high risk districts.

Table 8: Ebola Regimen Vaccination Consumption in Targeted regions-In country Experience

Region	District/Division	Allocation	[illegible]		[illegible]	
			Consumption	Coverage	Consumption	Coverage
West Nile	Adjumani	335	335	100%	284	85%
	Arua City	796	567	71%	253	45%
	Obongi	653	653	100%	345	53%
	Yumbe	591	591	100%	317	54%
Bunyoro	Kagadi	388	388	100%	204	70%
	Kyegegwa	842	507	60%	361	86%
Tooro	Fort-Portal City	906	836	92%	356	57%
	Bundibugyo	877	459	52%	121	26%
	Ntoroko	343	330	96%	103	31%
	Kasese	1,882	979	52%	276	29%
Kigezi	Kanungu	330	330	100%	185	56%
	Kisoro	664	590	89%	327	55%
Central	Mubende	552	552	100%	290	52%
	Luweero	915	915	100%	888	97%
Sub-total Districts		**10,074**	**8032**	80%	**4,310**	53%
UPS	Uganda Prisons	2,000	1,960	98%	1,586	81%
UPDF	MTN DIV (Fort Portal)	2,000	2,000	100%	2,070	100%
	2 DIV (Mbarara)	3,000	3,000	100%	3,074	100%
	4 DIV (Gulu & Arua)	3,000	2,850	95%	3,069	95%
	5 DIV (Acholi)	3,000	3,000	100%	3,000	100%
	FAD (Masindi&Bulisa)	2,000	2,000	100%	3,480	100%
SubTotal (Forces)		**15,000**	**14,810**	99%	16,279	97%
OVERALL TOTAL		**25,074**	**22,842**	91%	**20,589**	69%

Summary

- Phase 1 began on September 23,2024
- 22,842 out of 25,074 allocated Johnson and Johnson doses were administered achieving over 91% coverage
- 25,000 doses of the WHO prequalified two dose JNJ Ebola vaccine regimen (Zabdeno® (Ad26.ZEBOV) and Mvabea® (MVA-BN-Filo)donated to the government of Uganda
- A total of 50,124 doses (25,062 Zabdeno® and 25,062 Mvabea®) were distributed across 14 civilian districts and special populations (Uganda Prisons and UPDF).
- High performance districts include: Adjumani, Yumbe, Luwero, UPDF &Uganda Prisons (97-100%)
- Low performance districts: Kasese and Bundibugyo (52% coverage)
- Redistribution of doses:502 doses reallocated to Kampala &Mbale to optimize utilization.

Table 9: Health Workers Vaccination with the two-dose Ebola regimen in Targeted Districts

Health Sub-region	District	Healthcare workers targeted (Microplan)	Vaccine allocated	Coverage (Phase-1 (Zabdeno®)	Coverage Phase-2 (Mvabea®)
West Nile	Adjumani	518	335	65%	55%
	Arua City	1,230	796	46%	21%
	Obongi	1,010	653	65%	34%
	Yumbe	791	591	75%	40%
Bunyoro	Kagadi	600	388	65%	34%
	Kyegegwa	1,310	842	39%	28%
Tooro	Fort-Portal City	1,400	906	60%	25%
	Bundibugyo	1,355	877	34%	9%
	Ntoroko	530	343	62%	19%
	Kasese	2,910	1,882	34%	9%
Kigezi	Kanungu	510	330	65%	36%
	Kisoro	1,027	664	57%	32%
Central	Mubende	853	552	65%	34%
	Luweero	1,415	915	65%	63%
Total		15,459	10,074	52%	28%

Summary

- A total of 15,459 healthcare workers were targeted across 14 districts.
- Overall coverage: 52% for Phase 1 (Zabdeno®) and 28% for Phase 2 (Mvabea®), indicating significant attrition between doses.

Regional performance:

- West Nile (Adjumani, Obongi, Yumbe): High Phase 1 uptake (65–75%) with a moderate decline in Phase 2 (34–55%).
- Bunyoro & Tooro: Moderate Phase 1 coverage (34–65%) but sharp declines in Phase 2 (9–34%), especially in Bundibugyo and Kasese.
- Kigezi: Moderate performance with Phase 1 uptake (57–65%) and Phase 2 coverage (32–36%).
- Central (Mubende, Luweero): Consistent Phase 1 uptake (65%), with Luweero showing the best second-dose retention (63%).

Table 10: Preventive Vaccination in Kampala and Mbale

Health Facility	Feb 2025		April 2025		May 2025	
	1st dose	2nd dose	1st dose	2nd dose	1st dose	2nd dose
Kiruddu hospital	30	00	65	00	00	15
Kisenyi h/c IV	5	00	00	00	00	05
Mulago NRH	25	00	00	00	00	16
Kawempe NRH	0	00	26	00	00	00
Mbale	0	00	312	129	00	00
Total	60	00	403	129	00	36
Total number of Health workers Vaccinated=568; female=345;223males						

Summary

- 1st Dose: ZABDENO (Batch No. 23E011-01):403 doses dispatched (0 wastage) and all doses utilised.
- 2nd Dose: MVABEA (Batch No. 23E09-02):200 doses dispatched (0 wastage, 129 doses utilized and 71 doses left

To implement targeted preventive vaccination of willing high-risk individuals, including healthcare workers in Kampala and Mbale, using the Johnson & Johnson (J&J) Ebola vaccine within 72 hours of outbreak declaration.

Lessons Learnt from the In-country Ebola Vaccination

i. It is critical that the surveillance teams coordinate well with the vaccination teams to allow for systematic identification of contacts and vaccination.
ii. An existing vaccination response plan or approved protocol and a standby stock of vaccines are critical for timely resource mapping, preparation and execution of the response.
iii. An existing response plan/protocol allows for vaccination in line with standard procedures and support of the investigators.
iv. The engagement and visibility of leadership are key to the implementation of the EVD vaccination. These key leaders' involvement creates and maintains a supportive environment for health workers and contacts who are volunteering to receive the vaccine as they are trusted and believed to bring only what is good for the community.
v. Coordinating meetings to facilitate the flow of communication between the UNEPI program and the communities including partners increases the population's understanding of the EVD vaccine benefits.
vi. Use of a comprehensive engagement and vaccination movement plans increases uptake of the vaccine and gives a clear direction of the response.

vii. Vaccination of health workers on the vaccination teams builds trust among other high-risk recipients.

6. Cost Effectiveness of Ebola Vaccination

Results from a dynamic transmission model assessing the cost-effectiveness of an Ebola vaccine package which included the vaccine, storage, maintenance, and administration across four affected countries (the Democratic Republic of Congo, Liberia, Sierra Leone, and Uganda) showed that **Uganda's vaccination program was the most cost-effective**. At a willingness-to-pay (WTP) threshold of $**175 per disability-adjusted life year (DALY) averted**, Uganda achieved an **Incremental Cost-Effectiveness Ratio (ICER)** of **$73.43 per DALY averted**. Uganda also had the **highest value-based price (VBP) ceiling** for the vaccine, reflecting both its higher GDP per capita and superior cost-effectiveness compared to the other countries. The corresponding ICERs were **$94.44/DALY averted** for the Democratic Republic of Congo, **$101.63/DALY averted** for Liberia, and **$666.38/DALY averted** for Sierra Leone. The vaccine demonstrated a **99.99% probability of being cost-effective** in Uganda at the same threshold[28].

7. UNITAG Conclusions

Having reviewed and analyzed the foregoing evidence, the UNITAG thus concluded:

i. While Uganda has experienced mostly Sudan Ebola virus outbreaks, the threat of the Zaire Ebola virus strain remains, due to potential cross-border spillovers from the Democratic Republic of Congo.
ii. The most at-risk groups for contracting the Ebola virus include frontline health workers, responders, border district populations with Democratic Republic of Congo, and security forces operating in and near the Democratic Republic of Congo. Kampala district is also considered as high risk due to its large urban and migrant population, and sizeable refugee population.
iii. The two licensed and prequalified Zaire Ebola virus vaccines ERVEBO® (Merck), and MVA-BN-Filo(J&J) are safe and efficacious for use in preventive vaccination campaigns of individuals aged 12 months and older. The single dose EVERBO vaccine is logistically easier to implement over the two dose J& J vaccine due to high drop-out rates observed in previous preventive campaigns. EVERBO is also readily available through the Global stockpile, and through Gavi, comes with support for operational costs.

8. UNITAG Recommendations:

i. Uganda should conduct preventive vaccination campaigns against EVD in the high-risk population groups including frontline health workers, responders, security personnel operating in or near border districts with the Democratic Republic of Congo (DRC), and populations in districts along the Uganda–DRC border.
ii. The high priority groups for EVD preventive vaccination include; frontline health workers, responders, border district populations with Democratic Republic of Congo,

[28] https://pubmed.ncbi.nlm.nih.gov/35748085/

and security forces operating in and near the Democratic Republic of Congo. Kampala district is considered among the high-risk areas due to its large urban and dynamic population, and sizeable urban refugee population.

iii. The use of ERVEBO® over Ad26.ZEBOV, MVA-BN-Filo vaccines is preferable due to its single-dose regimen, higher efficacy, and availability through the global stockpile The ERVEBO® vaccine is approved by the National Drug Authority.

iv. Uganda should formally request the International Coordinating Group to provide for an in-country Ebola vaccine stockpile, which would be used for preventive vaccination and can be quickly transitioned to ring vaccination in the event of an outbreak.

v. Ministry of Health through the National Medical Stores and health subdistricts should ensure proper cold-chain infrastructure and stock management, to minimize Ebola Vaccine wastage.

vi. Ministry of Health should prepare clear protocols for preventive Ebola vaccination campaigns. The Department of Health Education, Promotion, and Communication should strengthen engagements with stakeholders on the advantages of preventive Ebola vaccination to support its uptake, the surveillance pillar should be vigilant to detect any cases of EVD early, and the pharmacovigilance pillar should be strengthened to detect and respond to any adverse events following vaccination and thus boost vaccine confidence.

vii. UNITAG will continue to review new evidence from the Sudan Ebola virus vaccine trials and update its recommendations accordingly as more data becomes available.

Sciences for Prosperity

Uganda National Immunization Technical Advisory Group (UNITAG) Recommendation Report on New Vaccines Prioritisation 2025-2030

July 2025

Contents

Acronyms

AEFIs – Adverse Events Following Immunisation

AMR – Antimicrobial Resistance

CFR – Case Fatality Rate

DALYs – Disability Adjusted Life Years

DTP – Diphtheria, Tetanus & Pertussis

EPI – Expanded Programme on Immunisation

GMTs – Geometric Mean Titre

IMD – Invasive Meningococcal Disease

IPV – Inactivated Polio Vaccine

KAP – Knowledge, Attitudes & Practices

MMCV – Multivalent Meningococcal Conjugate Vaccine

MDR –Multidrug resistance

NITAG – National Immunization Technical Advisory Group

NVI – New Vaccine Introduction

OCV – Oral Cholera Vaccine

PCR – Polymerase Chain Reaction

RDT – Rapid Diagnostic Test

TCV – Typhoid Conjugate Vaccine

UNICEF – United Nations Children Fund

UNITAG – Uganda National Immunisation Technical Advisory Group

VE – Vaccine Effectiveness

WHO – World Health Organization

XDR – Extensively Drug Resistance

Executive Summary

The Ministry of Health requested the Uganda National Immunization Technical Advisory Group (UNITAG) to provide guidance on prioritization and sequencing for new vaccine introductions into the expanded program on immunization in the five years (2025-2030) basing on the prevailing disease epidemiology and socio-economic conditions in the country.

For the exercise, UNITAG adopted the New Vaccine Introduction Prioritization and Sequencing Framework, which leverages a simple, evidence-based and comprehensive approach based on a pre-hierarchized list of potential criteria. The framework follows a three-phase implementation process 1) the framework adaptation where candidate vaccines for consideration are selected, 2) assessment, prioritization and sequencing where using evidence, the candidate vaccines are analyzed based on their importance and feasibility of introduction. 3) recommendation- based on programmatic constraints and other uncertainties, two introduction scenarios are considered, and introduction & sequencing proposals are developed.

Based on the members knowledge and experience of the Global vaccines and Ugandan contexts, UNITAG selected six candidate vaccines from the WHO Global Priority list of vaccines, and these were: Hexavalent (Pentavalent + IPV), Meningitis multivalent (Men ACYWX), Seasonal influenza, Typhoid conjugate, Cholera (seasonal campaign), and DPT booster vaccines.

Evidence was collated and analyzed for each vaccine regarding a) its importance – (disease burden, vaccine impact, ethical, legal and social considerations and the economic impacts), and b) the feasibility of its introduction – (costs and available funding, markets and supply, access target population, human resource and cold chain requirements). Through a system of scoring and weighted averages, vaccines were ranked by order of importance. A review of programmatic constraints and uncertainties, including a growing financial burden of cofinancing costs, a stretched human resource, and several planned vaccination campaigns within the considered time period, guided the development of two sequencing scenarios for vaccine introduction:

a) *Scenario one: primary:* assumes MMCV doses available for introduction in Uganda, Ability to introduce MMCV directly (instead of MenA first) and confirmed burden of disease of Typhoid in Uganda

1. Hexavalent (2026-2028)
2. Meningitis multivalent (2026-2028)
3. DTP Booster (2027-2031+)
4. Typhoid Conjugate vaccine (2029-2030+)

a) *Scenario two: alternative:* assumes MMCV not available for direct introduction and MMCV doses available for switch at some future time

1. Hexavalent (2026-2028)
2. Meningitis A (2026-2028)
3. DTP Booster (2027-2031+)
4. Meningitis multivalent (switch) (2029-2030+)

The committee made the following recommendations for future research that would support new vaccine introduction decision making:

i. Hexavalent - need for qualitative social studies on community perceptions about the new vaccine.
ii. Seasonal influenza - need to assess the burden of disease among infants and children
iii. Typhoid - need to assess true burden of disease through blood culture testing, including data from private health facilities.
iv. Phase 4 Post marketing studies following new vaccine introductions to study immune responses and duration of protection.
v. Cost benefit studies of new vaccines

Regarding follow-up actions, the committee recommended that:

i. the scenarios proposed and any relevant new information should be reassessed in two years' time (2027) unless GAVI replenishment strongly impact the funding scenarios, then these should be reassessed earlier.
ii. the NITAG re-conduct the full prioritization and sequencing exercise for a new future timeframe in 5 years (2030)

Introduction

At its annual stakeholder's meeting held on December 15, 2023 at Kampala Serena Hotel, UNITAG members engaged with representatives from Ministry of Health, and immunization agencies to identify advisory needs for the coming year. The Ministry of Health requested for advice on prioritization of new vaccines to be introduced into the immunization schedule. The rationale was that with many new vaccines being prequalified by WHO, and considering the country's resource constraints, an evidence- informed approach would help the Ministry of Health to select and sequence the new vaccine introduction process considering both the local epidemiological context, and the prevailing social-economic environment.

Methodology

With support from WHO Africa office, consultants from Development Catalysts consultancy firm were hired to support members of the UNITAG in the New Vaccines Prioritization exercise. They facilitated the UNITAG members in using a New Vaccine Introduction (NVI) prioritization and sequencing framework.

The NVI Prioritization and Sequencing Framework is a proven NITAG-driven framework supporting the prioritization of new vaccine introductions. It leverages a simple, evidence-based and comprehensive approach to support the preparation of NVI sequencing scenarios based on a pre-hierarchized list of potential criteria. It was developed in alignment with existing tools (such as the Evidence to Recommendation framework) to ensure the consistency of the process.

Having a Prioritization and Sequencing framework for new vaccine introduction serves a number of purposes, such as to:

1. provide an evidence-based vaccine prioritization to inform and balance the political agenda.
2. inform the national immunization strategy and roadmap while integrating the programmatic considerations to ensure feasibility.
3. kick-start financial discussions to anticipate funding constraints and dependances.
4. clarify data gaps and mandate new studies to ensure future decisions rely on up-to-date evidence.
5. send market signals to donors and suppliers to ensure availability at the time of introduction.

The framework follows a three-phase implementation process (Figure 1): 1) the framework adaptation where candidate vaccines for consideration are selected, 2) Assessment, prioritization and sequencing where using evidence, the candidate vaccines are analyzed based on their importance and feasibility of introduction. The vaccines were then ranked based on their position on the grid. 3) Recommendation phase where, based on programmatic constraints and other uncertainties, two introduction scenarios are considered and recommendations are made.

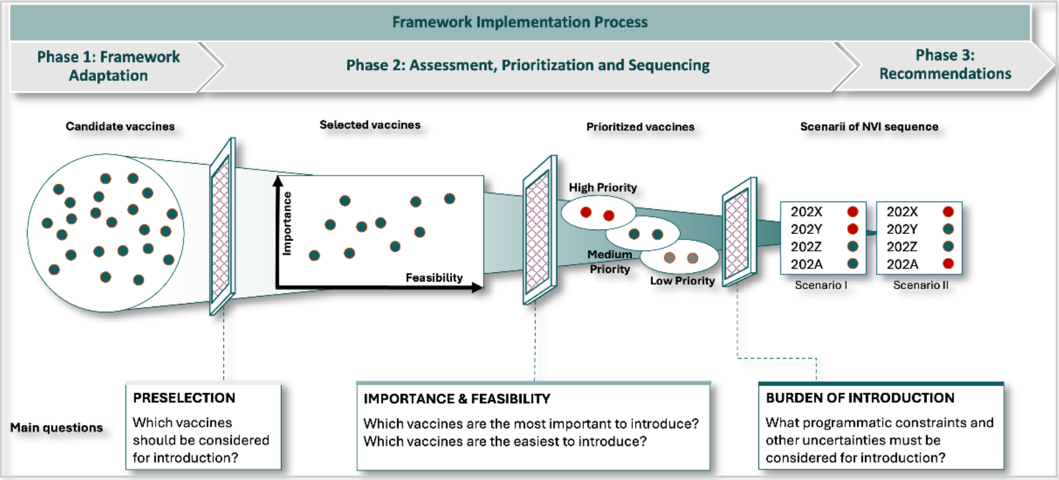


Figure 1 NVI prioritisation recommendation framework

In terms of the actual process, the activity was conducted in three phases (Figure 2)

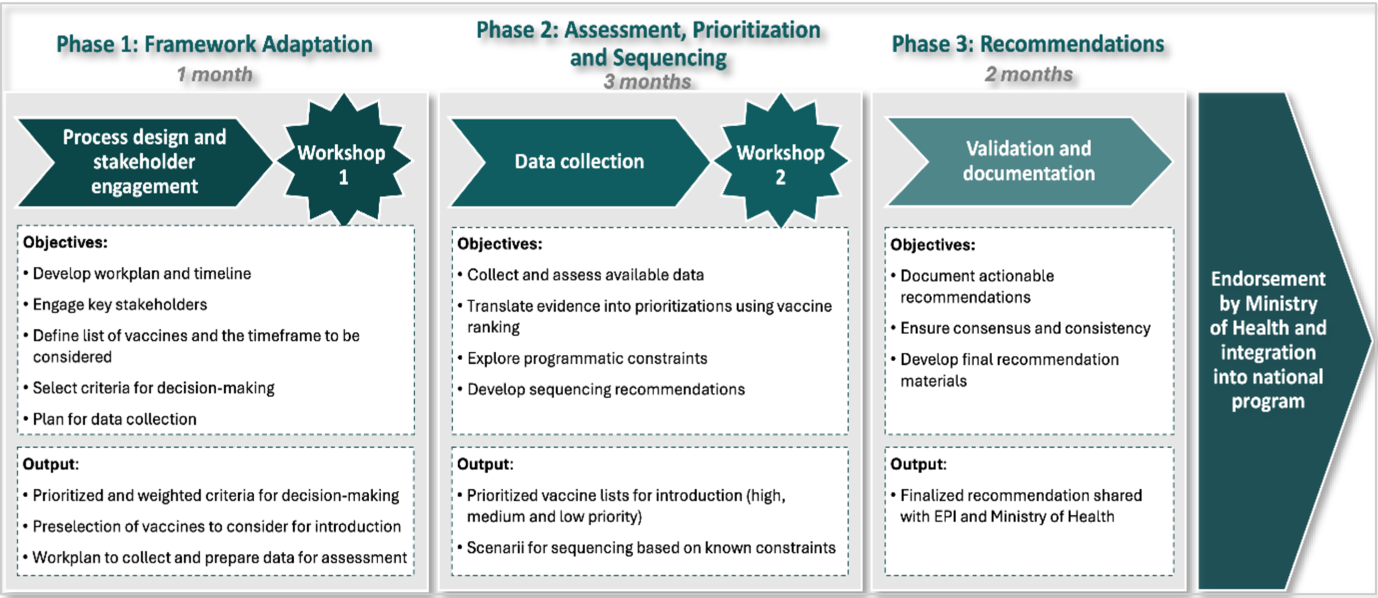


Figure 2: NVI PS three phase process undertaken by UNITAG

The first workshop was held on October 27,2024 where UNITAG members defined the methodological scope by selecting 6 vaccines and 18 criteria over a 5-year timeframe (2026-2031). The six pre-selected vaccines were picked from the World Health Organization vaccine prequalification priority list 2024-2026, basing on the UNITAG members' knowledge of Uganda's vaccine preventable disease and immunization contexts. The selected vaccines were; Meningitis

Multivalent (Men ACWXY), Seasonal Influenza, Cholera, Typhoid conjugate, Hexavalent (pentavalent + IPV), and DTP (booster doses).

Members were then presented with a detailed list of seventy-one (71) criteria based on WHO guidance on considerations for new vaccine introduction, each broken down into its indicators. To simplify the work process, UNITAG members selected eighteen (8) most relevant criteria and these were classified as Essential with a weight of 2.0, Important with a weight of 1.5 and other with a weight of 1.0.

UNITAG members were divided into four thematic working groups, based on their area of expertise. Each group selected one to three indicators for each of the criteria assigned to them. The thematic working groups were;

i. Burden of Disease
ii. Impact of the Vaccine
iii. Ethical, Legal and Social
iv. Economics

The selected criteria for Burden of disease and impact of vaccine by category and their relevant indicators are summarized in Table 1.

Table 1: Criteria and their categorization as used in the NVI PS process

Criteria	Classification	Weight	Indicators
1. Incidence	Essential	2.0	1. Number of new cases per year (last 3-5 years)
2. Mortality and lethality	Essential	2.0	1. Number of deaths from the disease per year (# deaths) 2. Case fatality ratio (number of deaths / numbers of new cases) (in %)
3. Cost of the disease to the health system	Important	1.5	1. Cost of hospitalization (in USD or local currency) 2. Diagnostic Testing Costs (in USD or local currency)
4. Effectiveness of the vaccine	Essential	2.0	1. Reduction in disease incidence in the general population (in %) 2. Reduction in disease incidence in risk population (in %) 3. Reduction in disease severity in risk population (in %) 4. Reduction in mortality in the risk population
5. Impact on resistance to antibiotics	Other	1.0	1. Impact of the vaccine on resistance (yes/no) 2. Type of Resistance (MDR, XDR)
6. Disability Adjusted Life Years (DALYs)	Important	1.5	1. Expected impacts of immunization 2. Cost per DALY averted

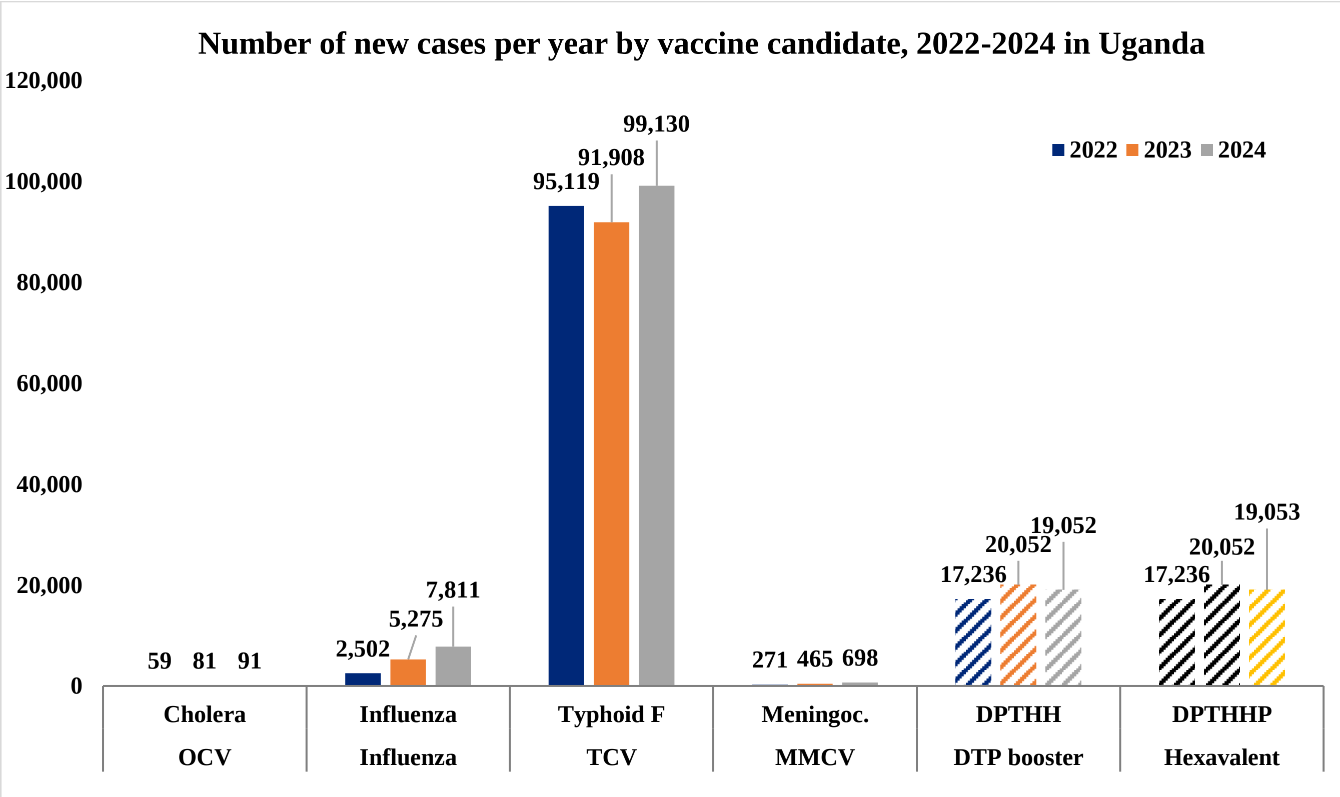
Criteria	Classification	Weight	Indicators
7. Equity of vaccination	Other	1.0	1. Does the vaccine target an underserved population group(yes/no)
8. Contribution to goals	Important	1.5	1. How does the Vaccine contribute to national goals? High/Medium/low

The Secretariat then conducted a review of literature, as guided by the selected indicators, compiled relevant evidence. Working group members reviewed and summarized the information and presented to the full committee to guide the prioritization process.

Summary of evidence

A. Burden of disease

1. Disease Incidence



Hexavalent & DTP booster data:

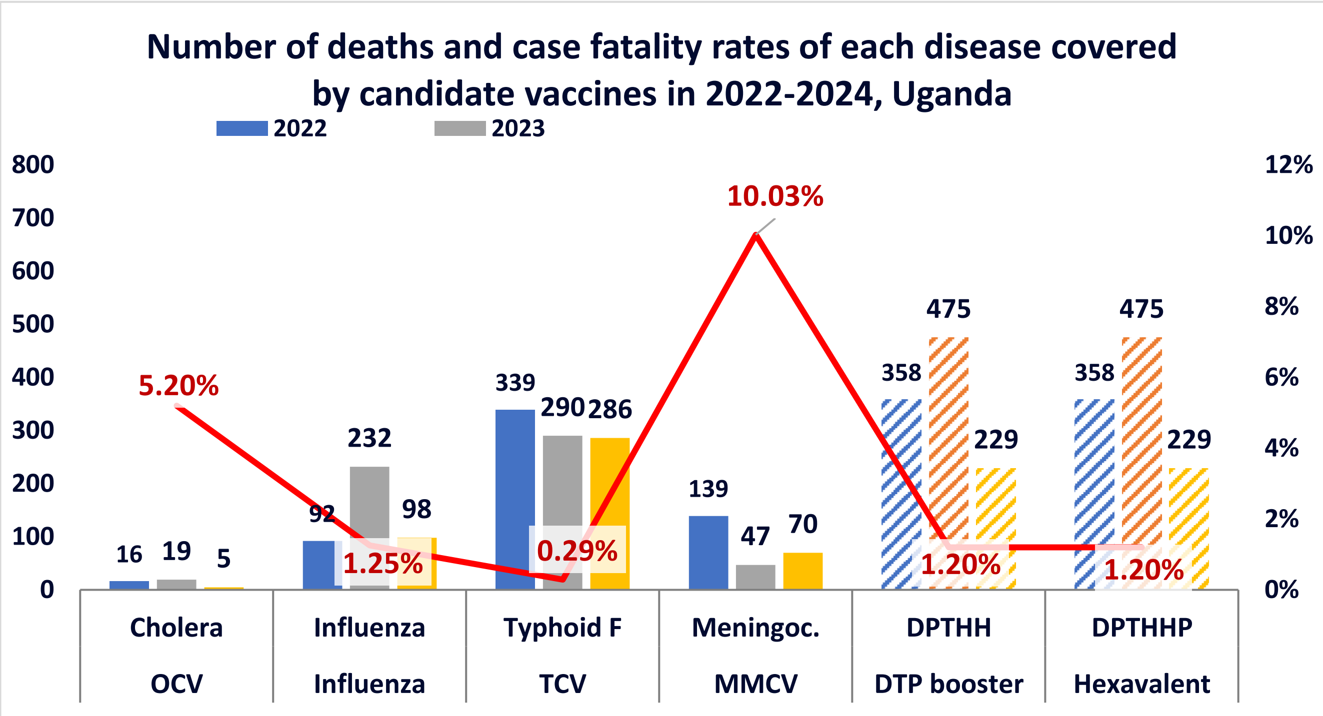
- Diphtheria: 78 in 2022; 71 in 2023; 40 in 2024
- Polio: 1 case in 2024
- Tetanus: 4044 in 2022; 1914 in 2023; 2485 in 2024
- Hepatitis B: 13114 in 2022; 18067 in 2023; 16527 in 2024
- No cases of Haemophilius Influenza B and Pertussis from 2022; however, the WHO/UNICEF Joint reporting form indicated 382 pertussis cases in Uganda in 2021

Sources: Ugandan Ministry of Health, Bwire et.al, (2013), WHO External Situation Report, Uganda Virus Research Institute National Influenza Centre (UVRI-NIC), WHO UNICEF Joint reporting form on Immunization

Comments

- Cholera: MoH data in line with WHO reports, but underestimated compared to 2013 article (11 000 cases per year). Majority of cases occur within fishing communities and on the DRC/South Sudan/Kenya borders + Kampala slums
- Influenza: during peak flu season, prevalence estimated to be between 10% and 13% of the population, much higher than estimated here
- Typhoid: MoH data in line with WHO-UNICEF JRF; many cases reported in the capital city. Caveat: testing is not systematic to confirm S. Typhi
- Meningitis: Karamoja region most affected; incidence higher for children < 5yo; most recent data show prevalence of Serogroups C and A

2. Mortality and Lethality



Hexavalent & DTP booster data:

- Diphtheria : 16 in 2022; 96 in 2023; 8 in 2024
- Polio: no death in 2024
- Tetanus: 100 in 2022; 208 in 2023; 78 in 2024
- Hepatitis B: 242 in 2022; 171 in 2023; 143 in 2024
- No deaths of Haemophilius Influenza B and Pertussis from 2022

Sources:Ugandan Ministry of Health, Bwire et.al, (2013),WHO External Situation Report, WHO Global Cholera Dashboard, Uganda Virus Research Institute National Influenza Centre (UVRI-NIC), WHO UNICEF Joint reporting form on Immunization; Santaniello-Newton et.al,2000;Busuulwa,(2010); Quealee C, et al. 2025

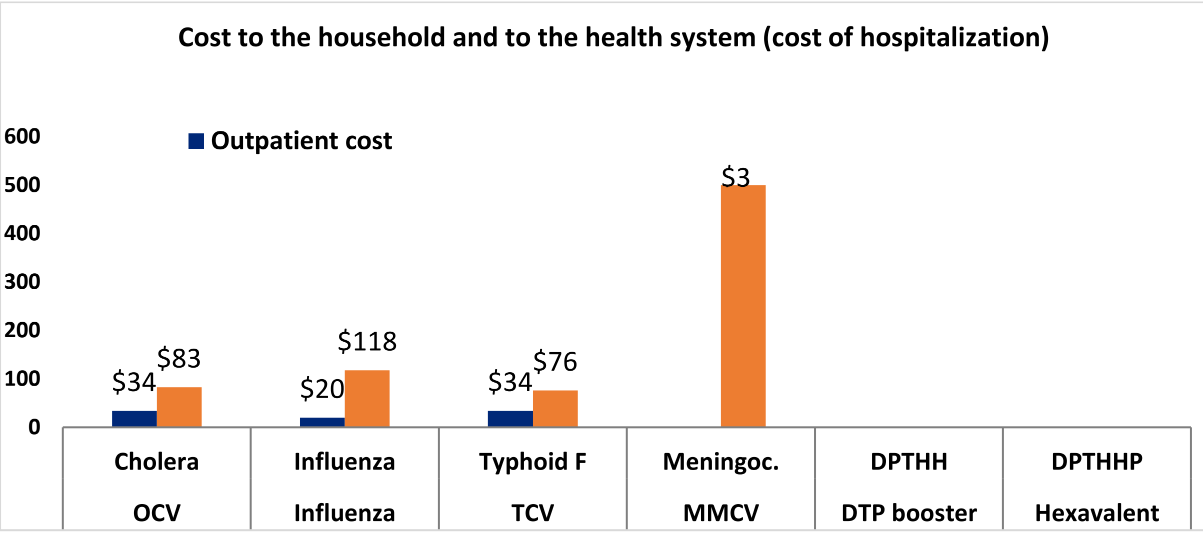
Comments

- Cholera: MoH data states no death in 2024 vs. 5 in the WHO ESR (CFR: 5.2%)
- Influenza: CFR likely to be overestimated (denominator- cases - probably higher)
- Typhoid: CFR likely to be underestimated; a study of typhoid intestinal perforations (TIP) found that TIP remains a major contributor to morbidity and mortality rates, with a mortality rate of 35%
- Meningitis: studies indicate a CFR between 6.6% and 60%

B. Impact of the vaccine

3. Cost of disease to the health system-

a) cost of hospitalization



Hexavalent & DTP booster data:

- Hepatitis B: around **$150** ($163.59 in Arua and $145.76 in Koboko)
- Polio: cost of hospitalization of polio differs by region-low-income countries-**$700** (Zimmemann 2020)
- Tetanus: study from Korea found that median total healthcare cost per patient was $18,011
- Diptheria ICU patient in SouthAfrica costs ZAR 22,870-26,954 app USD 1,251.41-1,474.51 CU

Sources: Riewpaiboon, A., Piatti, M., Ley, B., Deen, J., Thriemer, K., Von Seidlein, L., ... & Typhoid Economic Study Group. (2014).; Emukule, G. O., Ndegwa, L. K., Washington, M. L., Paget, J. W., Duque, J., Chaves, S. S., ... & Mott, J. A. (2019).; Chala, T. K., Lemma, T. D., Godana, K. T., Arefayine, M. B., Abdissa, A., & Gudina, E. K. (2022)Bae et.al,(2021); Salman, O., Procter, S. R., McGregor, C., Paul, P., Hutubessy, R., Lawn, J. E., & Jit, M. (2020), 39(1), 35-40;Ejalu, D. L., Mutyoba, J. N., Wandera, C., Seremba, E., Kambugu, A., Muganzi, A., ... & Ocama, P. (2022); Figuereo et.al(2024); Mogasale et al,(2021); Tembo et.al,(2019), Emukule et al,(2019); Limani et al., 2022

Comments

- Cholera: data from modelling study in Somalia, direct / indirect costs is app. 50%/50%; other study in Zambia estimate the cost of hospitalization around US$14.49–US$18.03 and up to US$17.66–US$35.16 patients > 15yo
- Influenza: data from Kenya, slight variations per age
- Typhoid: data from Malawi showed inpatients cost between $93.85-$296.52 & $19.05-$39.65 for outpatients; similar study in Pemba Zanzibar reported an average cost per typhoid episode of US$154.47
- Meningitis: data from study in Ethiopia Jimma University Medical Centre; most other studies state very high costs (up to $56k) but have been conducted in the US
- DTP Booster/Hexavalent: data from Uganda for Hepatitis B; study for Tetanus is from Korea

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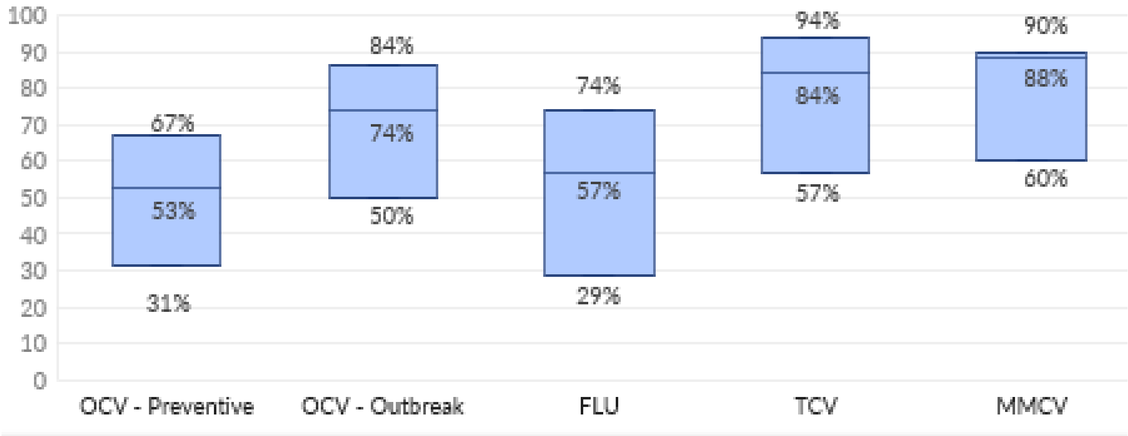
3b. Cost of disease to the health system- b) cost of testing

	OCV	Influenza	TCV	MMCV	DTP Booster	Hexavalent
Free testing	Free in government hospitals and lower health facility for the RDTs.	Influenza testing (RDT) is free in referral and national referral health facilities in Uganda.	Free in government facilities	Free testing in referral hospitals	HepB testing free in most hospitals	Free polio testing at UVRI
Paying testing	Depending on the test: 25,000-50,000 UGX (7-15 USD)	Testing in private hospital, estimated at 100,000 UGX ($25-$30 USD) per test PCR Tests: the cost of rapid influenza diagnostic test is approximately is 20 USD each RT-PCR test cost 90 USD	Widal Test costs between 5,000 to 8,000 UGX (1.4 to 2.2 USD) but less reliable Blood Culture (more reliable but limited to larger hospitals or private facilities) is 20,000 to 50,000 UGX ($5-$13 USD),	Blood culture cost ranges from 35,000 to 50,000 UGX (10 to 15 USD) Minimal testing: 6.17 USD / patient Stepwise testing: 9.72 USD Comprehensive testing: 32 USD / patient	Diphtheria diagnosis (swab cultures or PCR tests) typically ranges from 35,000 to 50,000 UGX (10 to 15 USD) Pertussis Diagnosis: Pertussis PCR tests or serology tests cost UGX 165,000 (45 USD) Hepatitis B: RDTs are cheap (3000-5000 UGX – 1-1.4USD); General Diagnostic cost from 10000 to 50000 UGX (2.8-15USD); prospective study is approximately 80 USD	Same as for DTP booster

Source: Personal staff communication and enquiry responses from various hospitals around Kampala in April 2025.

4. Vaccine effectiveness

a) in reducing disease incidence in the general population by percentage



Hexavalent (primary series)	DTP Booster
• Diphtheria: 97% (95% CI: 94.3–98.4) • Pertussis: 96.2% (95% CI: 86.5–98.9) • Hib: 90.4% (95% CI: 70.6–96.8) • HepB: 95% with seroprotective titres • of anti-HBs antibodies, 1 month following completion • Tetanus: seroprotective **antibodies between 92.5% and 100%**	• Diphtheria: 97% (95% confidence interval: 94.3–98.4). • Pertussis: 100% VE with 4 and 5 booster doses • Polio:94.3% & 100% (2) ,97.9% & 100% (3) after dose 3 • Hib: 100% VE for full immunization • HepB:93.1% and 98.3% had anti-HBs antibodies ≥10 mIU/ml after booster 97.7% and 100% Tetanus: Efficacy of 100%(CDC)

Sources: Sialubanje et al,(2022), Malembaka et,al (2024), Katz et.al,2016; Gao et.al,(2024), Lightowler et.al,2022, Haidara et al., 2023, Im et et Al., 2020; Bisgard et al., 2000 ; Calvo et al., 2024; Kalies et al., 2008; Mallet, E., Belohradsky, B. H., Lagos, R., Gothefors, L., Camier, P., Carrière, J. P., ... & Hexavalent Vaccine Trial Study Group. (2004); Yousafzai et.al, 2021,Baldo et.al,2014

Comments

- Cholera: study in DRC for preventive context and one-dose, waning immunity after 2 years (44.7% vs. 52.7%); study in Zambia for post outbreak context, one dose: 81.0%
- Influenza: effectiveness differs based on population and influenza strain; study in Kenya (2010-12) VE against RT-PCR confirmed symptomatic influenza of IIV3 in children aged 6 months to 10 months; wanes over time; consistent with study in south China
- TCV: case-control study in Zimbabwe, VE against community controls for individuals 6mo to 15yo; VE against facility controls is lower (75%); study conducted in Pakistan found that vaccine effectiveness was 95% (93–96) against culture-confirmed S Typhi, and 97% (95–98) against XDR S Typhi
- Meningitis: two studies (India & Mali/Gambia) show M5CV has a higher sero-response rate than MenACWY-D ; effectiveness to be non-inferior; study used for effectiveness is from Korea (no study in Africa)

4b. Vaccine effectiveness in reducing disease incidence in the risk populations

Vulnerable group	OCV	Influenza	TCV	MMCV	DTP Booster	Hexavalent
Pregnant women	**Overall, no significant increase in pregnancy loss, neonatal mortality, or malformations among those exposed to the vaccine compared to those not exposed** Adjusted relative risk for pregnancy loss among those exposed to oral cholera vaccine was 1.24 (95% CI 0.64–2.43; p=0.52) compared with those not exposed to the vaccine. The neonatal mortality rate was 11·78 (95% CI 5·92–23·46) per 1000 livebirths for infants whose mothers were exposed	Lower risk of getting laboratory confirmed influenza (LCI) (Relative risk [RR] 0.3, 95% confidence interval [CI] 0.26–0.35) and influenza -like illness (ILI) (RR 0.15, 95% CI 0.06–0.36).	*No study among pregnant women*	No specific study Recommendation from WHO that pregnant and lactating women should receive MMCV if they are in the age range targeted by mass preventive campaigns based on evidence from Men A	In Peru infants born to mothers who received the Tdap vaccine during pregnancy had an 81% reduced risk of pertussis	*N/A*

	to oral cholera vaccine versus 8·91 (4·02–19·77) per 1000 livebirths for infants whose mothers were not exposed to the vaccine (crude relative risk 1·32, 95% CI 0·46–3·84; p=0·60).					
Children	Reactive vaccination in Cameroon: cholera cases dropped from about 10.5 to 9.3 cases per week at the regional level In Haiti culture-confirmed cholera was significantly less frequent in vaccine recipients (18/52,357) compared with unvaccinated cases (370/17,643), P value < 0.001	Fully vaccinated children 61.79%; partially vaccinated 33.91%; influenza VE was high in CHN less than 5 years old 61.71% as well as in CHN 6–17 years old 54.37%	TCV is effective against drug resistant strains of S*almonella typi*, which is crucial in regions facing antimicrobial resistance In India a campaign in Mumbai showed 56% reduction in typhoid cases among vaccinated communities compared to unvaccinated area (95% confidence interval [CI], 25% to 74%; P = .002)	VE was 79% (49% to 91%) at <1 year 69% (44% to 83%) at 1 to <3 years, and 61% (25% to 79%) at 3 to <8 years VE was 77% (57% to 88%) against serogroup C and 51% (1% to 76%) against serogroup Y	Among children in US VE exceeded 75% in children aged 5-9years and that more than 65% of children remained immune to pertussis 5 years after the last DTaP dose	VE against pertussis as high as 91.8% after the second dose. In Netherlands VE against invasive Hib was 92·8% (95% CI 88·7–95·4), VE highest in children aged 1-2 years at disease onset (97·1–99·0%) and was lowest in children aged 3–4 years at disease onset (60·7–82·3%; p=0·0008).
Immuno-depressed (e.g. HIV)	78% protective in a high HIV prevalence setting in Mozambique	Among high-risk adults 18-64years vaccination prevented 78% of deaths (95% CI, 39%-92%), 87% of hospitalizations (95% CI, 39%-97%), and 26% of GP visits (95% CI, 7%-47%).	TCVs are safe and immunogenic in HIV - exposed uninfected children. Anti-Vi geometric mean titers (GMT) increased significantly from 4.1 to 4.6 ELISA units (EU)/mL at baseline to 2572.0 - 4117.6 EU/mL on day 28 post-vaccination	WHO recommends that all persons with these medical conditions or living with HIV infection are at increased risk for meningococcal disease and should receive Men5CV	Tdap vaccination rates among adults with chronic respiratory conditions found that vaccination rates were suboptimal, but higher in individuals with asthma compared	Among HIV-exposed infected and HIV-exposed uninfected infants vaccine given as a 6, 10, 14 weeks primary series with a toddler booster at 15–18 months of age, in each group, primary series and booster immune sero-protection rates were strong, and pre-booster antibody persistence was

					to the general population	good, although anti-HBs ≥10 mIU/mL in Group A was 78.6% post-primary series, 58.3% pre-booster, and 75.0% post-booster
Elderly	*No study for persons 60 years and above*	CDC report, those over 65 years were 28% less likely to be hospitalized with flu	Participants (aged between 18 and 60 years) who received a single dose of TCV showed vaccine efficacy of 54•6% (95% CI 26•8–71•8) and 100% SCN with significantly higher GMTs detected 1-month post-vaccination compared to 52•0% (23•2–70•0) efficacy and 88.6% SCN in participants that received ViPS.	Latin America and the Caribbean: A review of literature of 32 studies found that the effectiveness of meningococcal conjugate vaccines in reducing disease incidence ranges from 66% to 100% across different age groups (inferred from MCV)	*N/A*	*N/A*

Sources: Ali et.al,2021 Qadri et.al,2018; Quach et.al,2020; Juscamayta-López et al., 2023; Amani et.al,2021; Kalligeros et.al,2020; Nampota-Nkomba et.al,2023; Domenech de Celles et.al,2019; Koen et.al.2021; Sévère et.al,2016;Jeuland et.al,(2010); Hak et.,(2005); Naeger et al., 2023; Jin et.al,2017; Oliveira et,al 2018; WHO position paper on Typhoid

4c. Vaccine effectiveness in reducing disease severity

	OCV	Influenza	TCV	MMCV	DTP Booster	Hexavalent
Impact on disease severity	Retrospective study in South Sudan found that patients who received two doses of the oral cholera vaccine were 4.5 less likely to develop severe disease than unvaccinated patients (adjusted odds ratio OR:0.22;95 Confidence Interval, Cl:0.11-0.44). 2 doses of Shanchol in India had reduced severe dehydrating cholera in India by VE 63% (*RR 0.37, 95% CI 0.28 to 0.50*) at 6 months and 50% at two years *(RR 0.50, 95% CI 0.42 to 0.60)*	Flu vaccine reduced the risk of hospitalization by 37%, vaccinated persons aged 18-64 years were 47% less likely to be hospitalized with flue, those over 65 years were 28% less likely to be hospitalized with flu In the US during 2017-2018 influenza season vaccination prevented 7.1 million illnesses, 3.7 million medical, 109,000 hospitalizations, and 8000 deaths; vaccination prevented 10% of expected hospitalizations, and 41% among young children (6 months–4 years)	In Malawi among 9months and 12years children TCV resulted in lower incidence of blood culture confirmed typhoid fever than the control Men A after 2 years of follow up	Systematic review found that MMCV is effective in preventing IMD caused by several serogroups, with overall vaccine effectiveness (VE) of about 69% for however VE wanes overtime.	CDC report indicates the vaccines reduce the risk and severity of diphtheria and tetanus infections to nearly zero. However, for pertussis, vaccinated individuals who still contract the disease often experience milder symptoms compared to unvaccinated individuals	Vaxelis showed protective antibody levels against diphtheria (100%), tetanus (100%), pertussis, hepatitis B (98%), polio (100%), and Hib (98%) one month after completing the three-dose primary vaccination schedule

Sources: Bekolo et.al,2016; Saif-Ur-Rahman et al,2024; Nichol et.al,2007; Rolfes et.al,2019; Naeger et al., 2023, Patel et.al,2021, Mcmillan et.al,2021

4d. Vaccine effectiveness in reducing mortality

	OCV	Influenza	TCV	MMCV	DTP Booster	Hexavalent
Impact on mortality	Results from a modelling study showed that a single-dose reactive campaign could have prevented 70,584 cases in Zimbabwe, 78,317, Haiti, and 2,826 cases in Conakry, Guinea	In US Vaccinated individuals over 80 years old had a lower mortality rate compared to unvaccinated peers (20.9% vs. 23.9%) (OR = 0.84 [0.75–0.93], p = 0.001). after adjusting for comorbidities Effectiveness study conducted among the elderly in the US found that vaccination was associated with 48% reduction in the risk of death (adjusted odds ratio, 0.52; 95% CI, 0.50 to 0.55). The study used data pooled from 18 cohorts of elderly persons between 1990-2000 in the US	Results from a modeling study estimating the effect of vaccination on AMR predicted that TCV introduction with a catch-up campaign was predicted to avert 506,000 (95% CI 187 000–1•9 million) deaths caused by fluoroquinolone non-susceptibility typhoid fever and 342,000 (95% PI 135 000–1•5 million) deaths from MDR typhoid fever over 10 years following introduction	Results from 9 countries in SSA between 2010 and 2015 showed a 58% decline in suspected meningitis and a greater than 99% decline in laboratory-confirmed meningitis after mass vaccination campaigns with MenAfrivac	Studies from Ghana and Tanzania showed that DTP vaccination is associated with reduced mortality. Receiving a DTP vaccination was associated with a decreased risk of death (Ghana aHR: 0.39, 95% CI: 0.26–0.59; Tanzania aHR: 0.19, 95% CI: 0.16–0.22) showing 61% reduction in mortality. (Quinn et.al,2022)	A WHO report indicated the Hexavalent vaccine can prevent the death of some 2 to 3 million of children suffering from diphtheria, tetanus, pertussis and rubella in the world (Not specific to country)

Sources: Walzer et.al,2020; Nichol et.al,2007); Birger et al., (2022); Quinn et.al,2022; https://www.afro.who.int/news/hexavalent-vaccine-less-injections-and-more-protection-babies, Bella et.al,2019

4e. Vaccine effectiveness in reducing transmission for the general population

	OCV	Influenza	TCV	MMCV	DTP Booster	Hexavalent
Reduction in transmission for the general populations	50% coverage was sufficient to stop transmission (model from Bangladesh) Incidence among placebo recipients was 7.0 cases per 1,000 population in the lowest-coverage quintile (< 28%) versus 1.47 cases per 1,000 population in the highest quintile (> 51%)	The overall estimated VE for preventing secondary infection among household contacts in US was 21.0% (95% CI,1.4% to 36.7%) and varied by type Estimated VE against Influenza A was 5.0%(95% CI,22.3% to 26.3%) and 56.4%(95% CI,30.1% to 72.8%) against Influenza B	Routine vaccination predicted to reduce symptomatic cases by 10–46 % over a 10-year time horizon under an optimistic scenario (95 % initial vaccine efficacy and 19-year mean duration of protection), and by 2–16 % under a pessimistic scenario (82 % initial efficacy and 6-year mean protection)	A systematic review by showed lower carriage among vaccinated people may reduce transmission to non-vaccinated individuals to provide herd protection against IMD. Results demonstrated that serogroup A carriage was completely eliminated up to 13 months postvaccination	Tdap vaccination during pregnancy safe and results in high concentrations of pertussis antibodies in infants, providing protection against pertussis in the first months of life In West Java, Indonesia found that increasing diphtheria booster vaccination coverage from 64.84% to 75.15% was predicted to reduce diphtheria transmission by controlling the basic reproduction number (R0) from 1.17 to below 1	Indirect impact Systematic review studies have demonstrated high sero-protection/ seroconversion rates against most antigens included in hexavalent vaccines. Post-booster indicated these rates were at or above 88.9% against all antigens, thereby reducing the risk of transmission

Sources: Burrows H, et al. Comparison of model predictions of typhoid conjugate vaccine public health impact and cost-effectiveness. Vaccine. 2023, Grijalva, C. G., Nguyen, H. Q., Zhu, Y., Mellis, A. M., McGonigle, T., Meece, J. K., ... & Rolfes, M. A. (2024). Estimated effectiveness of influenza vaccines in preventing secondary infections in households; Wierzba ,2019; Balmer et.al,2018; Munoz et al., 2014; Fauzi et al., 2024; Ozen et.al,2024

5. Impact on resistance to antibiotics

	OCV	Influenza	TCV	MMCV	DTP Booster	Hexavalent
Type of resistance	Multi Drug Resistance, Intermediate resistance	None	MDR, XDR	MDR	*No drug resistance*	*No drug resistance*
Impact of the vaccine on resistance	YES In Kasese: 100% resistance to Ampicillin and over 50% were resistant to trimethoprim/Sulfamethoxazole Results from 3 outbreaks in Uganda 2014-2016 found that the 10 sequenced strains all showed genotypic resistance to streptomycin, aminoglycosides, fosfomycin, fluoroquinolones, sulphonamides, trimethoprim, chloramphenicol/florfenicol, and tetracyclines	YES 10-percentage point increase in the influenza vaccination rate was associated with a 6.5% decrease in antibiotic use (most significant in children (0–18 years) and the elderly (65+ years)) – (USA)	YES Strong efficacy against Salmonella Typhi irrespective of antimicrobial resistance TCVs could prevent 28,700 drug-resistance-associated deaths each year in children younger than 15years Increased use of TCVs in high burden countries could prevent 45Mn doses of antibiotics, US$2.3Bnin productivity losses, and US$117Mn in hospital costs annually An infant TCV program with a CU campaign could prevent ~53.5Mn cases of drug-resistant typhoid fever in 73 LMICs countries over 10 years	YES Despite vaccination efforts, antimicrobial resistance remains a significant challenge for treating bacterial infections like meningitis. Multidrug-resistant pathogens continue to emerge and spread globally.	NO	NO
Grading	**Medium**	**Low**	**High**	**Medium**	**N/A**	**N/A**

Sources: Abdulrahim, A., & Adesola, R. O. (2022);Das, B., Verma, J., Kumar, P., Ghosh, A., & Ramamurthy, T. (2020);Klugman, K. P., & Madhi, S. A. (1999);Abdelkader, M. M., Aboshanab, K. M., El-Ashry, M. A., & Aboulwafa, M. M. (2017) Dixit, S. M., Johura, F. T., Manandhar, S., Sadique, A., Rajbhandari, R. M., Mannan, S. B., ... & Alam, M. (2014);Das, S., Choudhry, S., Saha, R., Ramachandran, V. G., Kaur, K., & Sarkar, B. L. (2011);Murhekar, M., Dutta, S., Ropa, B., Dagina, R., Posanai, E., & Rosewell, A. (2013); Iramiot, J. S., Rwego, I. B., Kansiime, C., & Asiimwe, B. B. (2019); Aruhomukama, D., Sserwadda, I., & Mboowa, G. (2019);Shah, M. M., Bundi, M., Kathiiko, C., Guyo, S., Galata, A., Miringu, G., ... & Yoshida, L. M. (2023);Lewnard JA, et al. (2024);Estimating the impact of vaccines in reducing antimicrobial resistance and antibiotic use: Technical report. Geneva: World Health Organization;

6. Disability adjusted life years (DALYs)

	OCV	Influenza	TCV	MMCV	DTP Booster	Hexavalent
Expected impacts of immunization	Geographic targeting based on historical burden could avert 828,971 cases (34.0%) in sub-Saharan Africa.	Vaccinating children 6–23 months once per year had the highest net monetary benefit (INMB: $872).	RI at 9 months + catch-up up to 15 years could avert 46–74% of typhoid cases over 10y in 73 GAVI countries	Vaccine could prevent 63 IMD cases, 17 cases with long-term sequelae, and 6 IMD-related deaths, full protection against all five serogroups	UNICEF projection: DTP boosters could prevent ~106,000 deaths from 2021–2035 Introducing the EC booster alone is projected to avert 4,470 DALYs per year from 2025 to 2039 (tetanus and pertussis-related) and up to 7,700 DALYs for three boosters (EC+A+C)	Economic assessment in Peru: budgetary impact was reduced to 8.7%.
Cost per DALY averted	$1,843 Per DALY averted for the most logistically feasible strategy	$442 to $1,573 of Incremental cost-effectiveness ratio (ICER) per DALY averted (varies per age group	$95–789 of ICER per DALY averted (ICER) for RI with or without a catch-up campaign	$96.36 Per DALY averted by MenAfrivac	$3,151 per QALY gained	Main impact is the increased coverage of IPV 2, with marginal impact on DALY

Sources: Dawa, J., Emukule et al. (2020) ;Lee, E. C. et al. (2019); Cho et al,2020;https://millionssaved.cgdev.org/case-studies/eliminating-meningitis-across-africas-meningitis-belt;Versteeg, J. W., Jamet, N., & Redekop, K. (2023).;Kirigia, J. M., & Mwabu, G. M. (2018); Schley, K., Presa, J. V., Snow, V., Cane, A. D., Peyrani, P., Farkouh, R., ... & Caro, J. J. (2023, November). 1146. Cost-effectiveness of the Pentavalent Meningococcal Vaccine (MenABCWY): A steady-state cohort modelling approach. In *Open Forum Infectious Diseases* (Vol. 10, No. Suppl 2, pp. ofad500-987); Burrows et.al,2022

7. Equity of vaccination

		OCV	Influenza	TCV	MMCV	DTP Booster	Hexavalent
Does the vaccine target an underserved population group (yes/no)	*Gender*	NO	YES Pregnant women	NO	NO	YES Boys who were not previously targeted	NO
	Age	NO	YES Children under five, elderly especially those with co-morbidities	NO	NO	NO	NO
	Other	NO	YES Health workers	NO	YES Special populations including immuno-compromised, HIV infected persons and laboratory personnel	NO	NO
	Economic	YES Populations in poor resource settings with limited clean water, sanitation and hygiene	NO	YES Populations that lack access to safe water and adequate sanitation	NO	NO	YES Can reduce zero-dose from poor households (limited access to RI) limiting number of injections
Expected impact on equity		**High**	**Medium**	**Medium to High**	**Medium**	**Low**	**Low**

8. Contribution to national / regional / global goals

	OCV	Influenza	TCV	MMCV	DTP Booster	Hexavalent
Contribution to national goals	National Integrated Comprehensive Cholera Control Plan for 2017-2022 which aimed to reduce Cholera cases by 50% by 2022	In line with NIS 2024-2028	In line with NIS 2024-2028	No specific goal, but integral to achieving Uganda's national health goals	In line with NIS 2024-2028 Ensures sustained Maternal and neonatal tetanus elimination status Hepatitis elimination	In line with NIS 2024-2028 Ensures sustained Maternal and neonatal tetanus elimination status Hepatitis elimination
Contribution to global goals	Yes, contributes to global cholera elimination targets (Uganda part of the 20 countries with elimination target by 2030)	Global Influenza Strategy for 2019-2030	In line with the Global Policy for typhoid (focus on drug resistance)	Global Roadmap for Defeating Meningitis by 2030	Global Pertussis Initiative WHO global hepatitis strategy to reduce new infections by 90% and deaths by 65% between 2016 and 2030	Global Polio elimination strategy 2022-2026 Global Pertussis Initiative WHO global hepatitis strategy to reduce new infections by 90% and deaths by 65% between 2016 and 2030

Sources: Mahmood, K., Pelkowski, S., Atherly, D., Sitrin, R., & Donnelly, J. J. (2013. (https://www.afro.who.int/news/uganda-targets-over-1600000-persons-cholera-vaccination-campaign),https://www.preventionweb.net/publication/uganda-national-integrated-comprehensive-cholera-prevention-and-control-plan-fiscal;https://www.afro.who.int/news/uganda-vaccinates-against-meningitis-type-39-high-risk-districts;https://www.path.org/our-impact/media-center/multivalent-meningococcal-meningitis-vaccine-from-serum-institute-of-india-achieves-who-;https://www.meningitis.org/blogs/new-vaccine-could-end-meningitis-epidemics-africa;https://library.health.go.ug/sites/default/files/resources/NATIONAL%20IMMUNISATION%20STRATEGY%20(NIS)%202024-2028.pdf;https://www.coalitionagainsttyphoid.org/wp-content/uploads/2023/11/Uganda-TCV-Fact-Sheet-Sept-2023.pdf;https://www.gavi.org/news/media-room/gavi-expands-portfolio-introduces-new-vaccine-programmes;https://afenet.net/health-and-economic-impact-of-introducing-dtp-booster-doses-in-uganda-generating-country-specific-evidence/;;https://www.who.int/initiatives/defeating-meningitis-by-2030;

Vaccine ranking by importance

UNITAG members reviewed the importance evidence collated, and were requested to individually rank the six selected vaccines in order of importance after reviewing evidence for each criterion; 1 being the highest rank and 6 being the lowest. The average from the members' scores for each vaccine per criterion was then calculated and a position assigned (1-6). Finally, the average ranking with weighting for importance for each vaccine was calculated and the vaccines ranked. The outcomes were as summarized below:

Vaccine	1. Disease Incidence	2. Mortality and lethality	3. Cost of the disease to the health system	4. Effectiveness of the vaccine	5. Impact on resistance to antibiotics	6. Disability Adjusted Life Years (DALYs)	7. Equity of vaccination	8. Contribution to goals	Average ranking with weighting for importance
Meningitis Multivalent	3	1	1	1	4	6	4	2	2,7
Hexavalent	2	5	3	1	3	4	2	1	3,2
Typhoid	1	3	2	4	1	3	4	4	3,3
Cholera	6	2	6	5	1	4	1	6	3,7
DTP Booster	4	6	5	1	5	1	6	3	3,8
Influenza	5	4	3	6	6	2	2	4	4,4

C. Feasibility criteria assessment

The next stage was to assess the feasibility of introduction of each vaccine into the routine immunization schedule. The members had identified 8 feasibility criteria, including 4 essential criteria, 3 important criteria and 1 other criteria. This group of evidence was compiled and summarized by two working groups:

i. Ethical, Legal and Social

ii. Economics

Selected feasibility criteria, their classification, weight, and selected indicators

Criteria	Classification	Weight	Indicators
9. Safety/risk at individual level	Essential	2.0	1. List of mild AEFIs with corresponding occurrence in the vaccinated population per 100,000 2. List of moderate AEFIs with corresponding occurrence in vaccinated per 100,000 3. List of severe AEFIs with corresponding occurrence in the vaccinated population per 100,000
10. Ethical, reputational and social issues	Important	1.5	1. Existence of ethical, reputation or social barrier affecting acceptability of the vaccine(yes/no) 2. Knowledge of the vaccine (KAP studies)
11. Accessibility of the target population	Other	1.0	1. Easiness to reach the population based on introduction strategy (routine vs. Campaign or outreach)
12. Direct costs	Essential	2.0	1. Estimated annual cost of vaccines (in USD or local currency) 2. Estimated annual cost of materials (syringes, waste-box in USD or local currency)
13. Sustainability of the market availability	Important	1.5	1. Expected number of new suppliers beyond the selected time period
14. Availability & sustainability of funding	Essential	2.0	1. Estimated total cost of the Program (In USD or local currency) 2. For Gavi eligible countries, Expected co-funding from the government (in USD/Per dose)
15. Availability of cold chain equipment at all levels	Essential	1.0	1. Net additional cold chain volume required for the vaccine at central, hub and district level. 2. Availability of cold chain volume at central hub and district level 3. Current occupation of cold chain at central, hub and district level 4. Projected expansion over the 5 years 5. Occupation of pentavalent and IPV at central, hub and district level
16. Expected Impact of on human resources	Important	1.5	1. Is the target population already reached by existing immunization programs(yes/no) 2. Number of additional contacts required for target population (#) 3. Impact of introduction on workload (in time per health personnel)

9. Safety/Risk at individual level – AEFIs

	OCV	Influenza	TCV	MMCV	DTP Booster	Hexavalent
Mild to moderate AEFIs (incidence and nature)	In Hoima, 5.6% reported an AEFI, Abdominal pain, diarrhoea, fever, nausea and headache. Results from Lebanon: fever (39.13%), diarrhea (30.43%), and vomiting (30.43%) In IDP camps in Borno Nigeria: fever (50%,34%), headache (17% &22%), diarrhea (17%21%) during the first and second rounds of vaccination.	Mild pain at the injection site (60-80% of recipients, fever, (2–10%), malaise, headache, myalgia (muscle pain) and fatigue In Afghanistan among health workers: Pain at the injection site (53%) Swelling (29%) Redness (28%) Fever within the first 3 days (40%), body pain (39%) and headache (26%)	Fever, Pain, swelling (1-10%) of vaccines in any age group	Pain, headache swelling & redness / erythema Fever and vomiting (Malian toddlers' study)	Fever, irritability (40-75%); drowsiness (33-62%); loss of appetite (20-35%); vomiting (6_13%)	Injection site pain, fever, drowsiness, loss of appetite
Severe AEFIs *(incidence and nature)*	None	Anaphylaxis, and cardiac arrest reported. Guillain-Barré syndrome (GBS) with an annual incidence of 10–20 cases per million adults.	No severe adverse events reported	No severe AEFIs across all the clinical trials	None	None

Sources: Bwire et.al, (2020), Zeitoun et.al., (2024), Influenza-WHO position paper, Van-Balveren et.al,2014 &De Lusignan et.al,2022; Ngwa et.al,2020,Mofleh et.al,2012;Typhoid-WHO position paper; MMCV: Haidara et.al,2023;Kulkarni et.al,2024;Chen et.,al,2024; Hexavalent: Marshall et.al,2015;Zepp et.al,2024;Izadi et.al,2022

10. Ethical, reputational and social issues

10a) Ethical, reputational and social issues – affecting acceptability

	OCV	Influenza	TCV	MMCV	DTP Booster	Hexavalent
Existence of ethical, reputation or social barrier affecting acceptability of the vaccine	OCV already used during outbreaks in specific locations Study evaluating the OCV in Hoima noted that most people were willing to take the vaccine DRC: vaccine refusal was associated with a lack of confidence in the vaccine's safety, 29% of unvaccinated adults reported it was unlikely they would accept OCV	Resistance to new vaccines given it's targeting the elderly and other vulnerable populations Quality assessment in Kenya: potential misconceptions about the disease and perception that influenza is not serious (esp. vs. potential side effects of the vaccine)	In Malawi the perceived severity of typhoid, uncertainty about the effectiveness of WASH (water, sanitation, and hygiene) measures, and widespread belief in the efficacy of vaccines greatly influenced uptake during the outbreak.	As of 2025, Uganda is using Men A during campaigns Potential concerns may arise from vaccinated people with Men A and whether there is need to get Men5 given it provides protection against 5 serogroups.	Vaccine hesitancy given its targeting adolescents, misconceptions about vaccines that target this age group	Vaccine hesitancy for new vaccines however - advantageous because it reduces the number of injections and burden on parents and care givers-multiple visits Parental acceptance, willingness to pay, and factors influencing these aspects, such as education & disease knowledge affect acceptance of the vaccine

	OCV	Influenza	TCV	MMCV	DTP Booster	Hexavalent
Knowledge and awareness	In Hoima, individuals with primary education or higher more knowledgeable about OCV than those without formal education. Health workers had high knowledge of cholera control (93%), but 29% lacked training on managing vaccine side effects In Zimbabwe and Tanzania, knowledge about cholera and prevention was high (86.9% and 97.4%) In Nigeria, 88.2% of respondents aware of OCV, mainly through radio, but many did not fully understand its safety and administration	In four counties (Nairobi, Mombasa, Marsabit, and Siaya) found that 72.8% pregnant women had heard of influenza. Among those aware of influenza, 78.1% believed that vaccination would protect them during pregnancy.	>80% of Uganda's districts are endemic for typhoid fever attributable to lack of reliable knowledge to support disease surveillance In Soroti, Uganda, patients aged 15-45 years recognized fever, headache, and abdominal pain as symptoms of typhoid fever In Nigeria, only 31.1% of participants were aware of the typhoid vaccine, while in Zimbabwe, post-vaccination campaigns led to high acceptance of TCVs in urban areas.	In Uganda, study among nurses and healthcare providers in rural Uganda found that only 50% knew about CM transmission. 74% of participants last received education on CM during their didactic training, highlighting gaps in continued professional learning. 25% of healthcare providers disclosed they never educate patients about CM due to time constraints, and 30% cited lack of knowledge as a barrier. In Burkina Faso, 84.5% were aware of the vaccine,	Among adult travelers in Singapore,38% did not know mode of transmission for pertussis,83% had never heard of pertussis vaccine for adults – indicating poor knowledge of pertussis Only 7% of Thai adults and 26.3% of medical personnel were aware of the necessity of TD booster doses.	In Northern and Central Uganda, only 36% of pregnant women had adequate HBV knowledge In Kasangati, Uganda, 61% had poor knowledge of Hepatitis B vaccine dosing. In Mbale, Uganda, 58.8% had moderate knowledge of HBV and its vaccine In China, 74.87% of parents accepted the hexavalent vaccine, with acceptance influenced by education, knowledge, and perceived costs.

	OCV	Influenza	TCV	MMCV	DTP Booster	Hexavalent
KAP	While knowledge and acceptance of OCV are generally high, vaccine uptake is hindered by logistical issues, misinformation, and cultural beliefs. Effective community engagement and education are essential for improving vaccination coverage	While awareness of influenza and its vaccine is high among pregnant women, misconceptions, perceived side effects, and administrative barriers influence vaccine uptake—especially for children.	While awareness of typhoid fever and TCV varies across countries, misconceptions, skepticism about preventive measures, and low vaccine awareness hinder uptake. Post-campaign efforts in Zimbabwe improves acceptance.	Limited knowledge among healthcare providers on cryptococcal meningitis affects patient education.	Vaccine awareness is driven by the first three doses. However, dropout from the first to third dose is driven by misinformation, long waiting times, and hidden costs	While high awareness exists in some cases (e.g., polio in Nigeria, HBV screening in Uganda), misinformation and hesitancy remain challenges. Impact on time available to nurses can be used for pedagogical activities

Sources: Bwire et al., 2020, Maigoro et al., 2025, Merten et.al,(2013), Orimbo et al., 2020, (Teshome et al., 2018), Awahd et.al,2014, Link et al. (2023) , (Otieno et.al,2022) Mustapha & Harrison, 2018, Liku et.al,2024,Kamya et.al,2022; Nyoja et.al,2021, Bennett et.al,2018;Blum et.al,2014; Rosso et.al,2019), Mueller et.al,2021, Ozen et.al,2024, AI Bashir et.al,2023,(Wilder-Smith et.al,2017);Mercogliano et al.,2023;Donnan et al,2013;Ismail et al.,2021

10 b) Ethical, reputational and social issues – Perception & Attitudes						
	OCV	**Influenza**	**TCV**	**MMCV**	**DTP Booster**	**Hexavalent**
Perception & Attitude	In Katanga, DRC, 97% of respondents accepted OCV if offered for free, and most correctly identified cholera causes In Kenya, younger and more educated individuals were more likely to follow vaccination schedules In Nigeria, attitudes were mixed—53.2% believed OCV was unsafe for ill persons, and only 54% received the vaccine. Misconceptions about OCV safety and who should receive it influenced uptake, with 60.5% failing to complete the second dose due to lack of understanding	68.3% of pregnant women felt it was safe to receive the influenza vaccine while pregnant. 83.7% of pregnant women were willing to receive the vaccine if given the opportunity. More than 95% of respondents agreed that maternal vaccines are important for their health In Kenya, perception that influenza is not a serious disease	In Malawi, respondents were willing to accept the TCV due to the perceived severity of the disease. In Uganda, there was skepticism about the effectiveness of WASH interventions in preventing typhoid fever. In Malawi, despite the distribution of water treatment products, only 34% of households reported treating their drinking water.	The new multivalent vaccine, targeting multiple serogroups, is anticipated to enhance preventive measures against emerging strains, yet public acceptance remains crucial.	In Tz, both rural and urban infants experienced delays in DTP vaccination, with maternal education being a significant determinant. In Southern Italy 34.47% of healthcare workers received the Tdap booster, with attitudes influenced by their professional roles and years of experience. -need for targeted strategies to improve uptake	In Sironko, Uganda, fear of side effects (47%) was a key barrier to HBV vaccination. In Nigeria, 51% feared adverse effects from administering more than four polio vaccine doses. In Mbale, Uganda, 29.6% would vaccinate if given the opportunity, and 56.3% preferred government health facilities. In China, willingness to pay for the hexavalent vaccine increased when financial barriers were removed.

Sources: Bwire et al., 2020, Maigoro et al., 2025, Merten et.al,(2013), Orimbo et al., 2020, (Teshome et al., 2018), Awahd et.al, 2014, Link et al. (2023), (Otieno et.al,2022) Mustapha & Harrison, 2018, Liku et.al,2024,Kamya et.al,2022;Mustapha &Harrison,2018;Bennett et.al,2018;Blum et.al,2014; Rosso et.al,2019), Mueller et.al,2021, Ozen et.al,2024, AI Bashir et.al,2023, Wilder-Smith et.al,2007;Mercogliano et al.,2023;Donnan et al,2013;Ismail et al.,2021.

10 c) Ethical, reputational and social issues – Norms

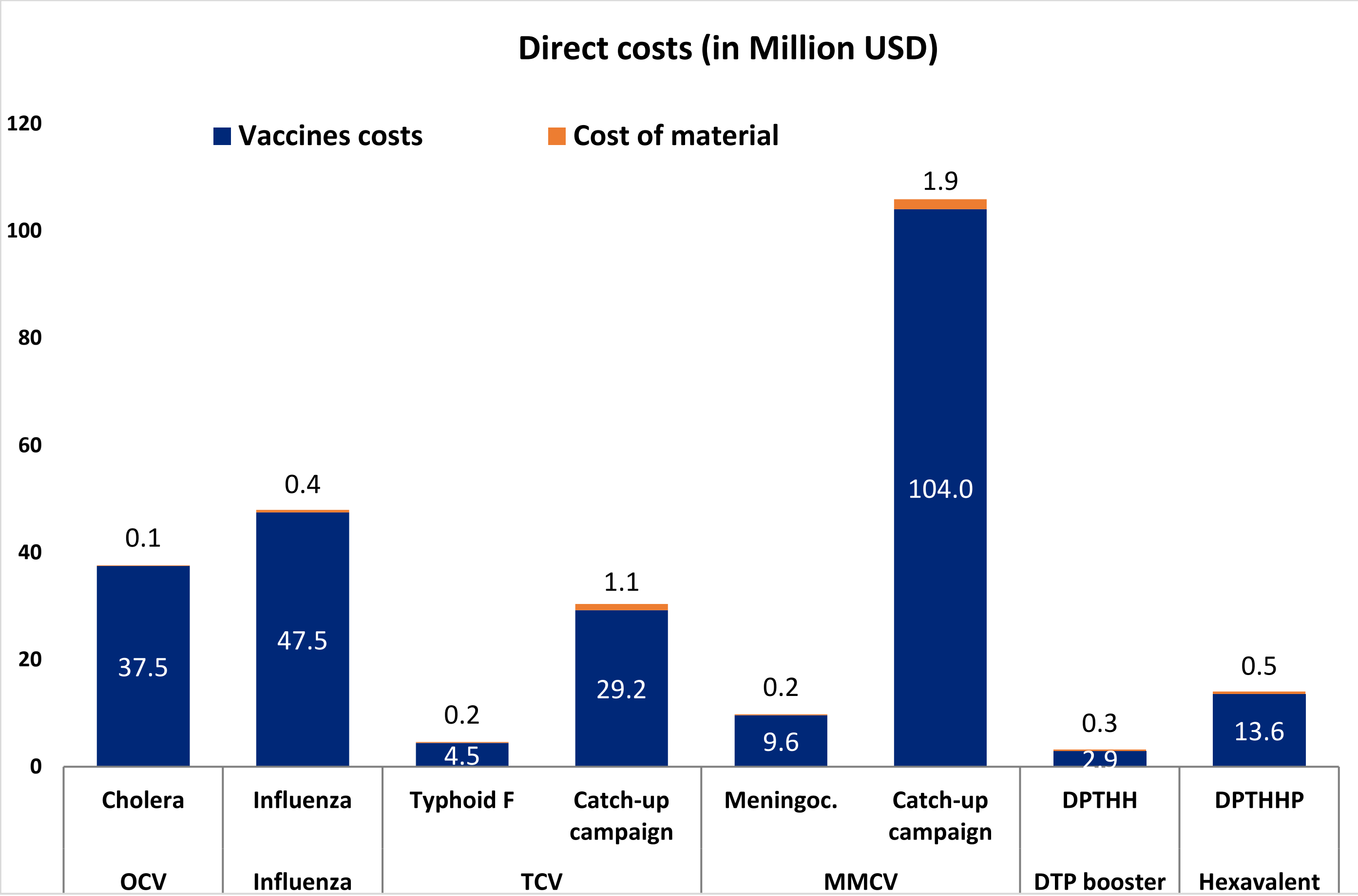
	OCV	Influenza	TCV	MMCV	DTP Booster	Hexavalent
Norms	In Cameroon, cultural beliefs influenced perceptions of cholera, with some attributing it to spiritual causes, which acted as a barrier to vaccine acceptance Social and cultural factors affected vaccine uptake, such as beliefs in spiritual causes of cholera in Cameroon	The willingness to receive the influenza vaccine was strongly associated with the belief in its protective effect [OR 3.87; 95% CI 1.56,9.59] and its perceived safety [OR 5.32; 95% CI 2.35,12.01]; In Kenya; also, bad perception of side effects	Poor sanitation and limited access to water are primary transmission routes leading to a high disease burden. Vaccine hesitancy remains a barrier, necessitating community engagement and effective communication strategies	Community engagement and education can enhance vaccine uptake of meningitis vaccine. Cultural practices and local understanding play a significant role in shaping perceptions of meningitis risk and prevention	DTP1 coverage is 96%, dropout rate from 1st to third dose is 17.3% attributed to misinformation, long waiting times and hidden costs deter parents from completing the vaccination schedule.	In Malaysia-Nurses indicated that the time saved by using a fully liquid hexavalent vaccine during the immunization process might be used to carry out additional tasks, such as teaching and enlightening the parents and answering any of their queries about vaccination. Hexavalent would decrease patient overcrowding in the mother and child healthcare unit and consequently alleviate the nurse's workload. Results from Turkey parents had a positive perception toward the fully liquid hexavalent vaccine's potential ability to reduce their child's pain and discomfort, and less transportation expenses

Sources: Bwire et al., 2020, Maigoro et al., 2025, Merten et.al,(2013), Orimbo et al., 2020, (Teshome et al., 2018), Awahd et.al,2014, Link et al. (2023) , (Otieno et.al,2022) Mustapha & Harrison, 2018, Liku et.al,2024,Kamya et.al,2022;Mustapha &Harrison,2018;Bennett et.al,2018;Blum et.al,2014; Rosso et.al,2019), Mueller et.al,2021, Ozen et.al,2024, AI Bashir et.al,2023, .(Wilder-Smith et.al,2007), Otieno et al., 2022;Carey et.al.,2019 & Steele et al.,2020;Kariuki&Onsare,2024)

11. Accessibility of the target population						
	OCV	Influenza	TCV	MMCV	DTP Booster	Hexavalent
Accessibility	Children under 2 years can be reached through RI Scorecard to identify districts for targeted vaccination. Previously coverage administered in 16 hotspot districts, in 2018 36 of 146 had a case Previous OCV Coverage rates of 87% in Adjumani district and 83% for the first dose in a South Sudanese refugee camp. OCV Campaigns conducted in Hoima, Buliisa, Packwach, Nebbi, Kasese, Ntoroko, Zombo, Moyo, Busia, Namayingo, and Arua	Children under-five can be accessed through RI during the 2nd year of life. 99% of pregnant women aged 15-49 years received ANC from a skilled provider for those who had a livebirth in the past 2 years before survey Elderly not currently targeted (require targeted outreach)	Children aged 9months can be reached through RI TCV can be Co-administered with MR, Yellow Fever.	Children 9-18months can be reached through RI. Can be co-administered with measles, rubella, yellow fever vaccines No specific accessibility difficulty related to high-risk districts High risk regions Karamoja West-Nile, Bunyoro Acholi, Lango and Teso.	12-23months through RI Preschool booster 4-7 (can be accessed through school system Adolescent booster (9-15) through school system	Children can be accessed through RI, taking into consideration the differences between urban and rural areas Switch = accessibility is the same as the current DTP target

Sources: Bwire et.al,2023; Dorlencourt et al., 1999; UDHS,2022;https://reliefweb.int/report/Uganda/ministry-health-set-roll-out-cholera-vaccine-ocv

12. Direct cost of the vaccines and consumable material



Comments

- Caveat: these are absolute costs, not necessarily costs paid by the country given most of these vaccines are at least partially funded by GAVI
- Meningitis: cost is for MMCV; for Men A, cost of vaccines is roughly one third of the displayed costs
- Hexavalent: cost is incremental vs. 3 doses of Penta + 2 doses of IPV
- Cholera: assumed targeting 15% of the population (top 20 districts with cholera cases)
- Coverage assumptions are 98% for Hexa, 50% for influenza and 90% for all other vaccines
- Target populations and number of doses follow WHO and GAVI recommendations. For influenza, target is limited to pregnant women, 6mo-5yo children and 65+ elderly

Sources: GAVI detailed product profiles, EPI logistics (SMT), WHO RI guidelines, Uganda Bureau of Statistics

13. Sustainability of the market availability

	OCV	Influenza	TCV	MMCV	DTP booster	Hexavalent
No of suppliers (UNICEF)	1	0 (UNICEF) 6 (WHO)	2	1 (MMCV) 1 (Men A)	4 (Penta) 3 (DTP) 4 (Td)	1
No of countries supplied by UNICEF	20 (2021)	0	5 (2022)	N/A	25 (2023) *May be more today*	1 (2024) 54 (Agreement)
Overall availability assessment in the future	*Supply needs planning and is currently not sufficient*	*Supply exceeds demand and likely to continue exceeding demand*	*Supply exceeds demand. Supply for catch-up campaigns need planning*	*Supply needs planning but likely to require prioritization between countries*	*Supply exceeds demand (Td & DTP)* *Supply needs planning (Penta)*	*Supply needs planning*
Comments	2026-2030 Supply is expected to increase and begin to meet both emergency and preventive demand over time Eubiologics Co., Ltd (Republic of Korea)	Several companies supply seasonal influenza vaccines. Key suppliers include GlaxoSmithKline (GSK), Seqirus, and Sanofi Pasteur.	Bharat Biotech International (India) Biological E (India)	Serum Institute of India Pvt. Ltd. Product will be available in 2025 Currently, emergency stockpiles by UNICEF.	Serum Institute of India, Bio Farma, BE vaccines, etc	Gavi eligible countries for hexavalent support and a Gavi countries not eligible for hexavalent support and MICs.

Sources: GAVI detailed product profiles, WHO Mi4A, Unicef supply and demand updates

14. Availability and sustainability of funding

	OCV	Influenza	TCV	MMCV	DTP Booster	Hexavalent
GAVI eligibility	✓ *(Campaign only)*	✗	✓	✓ *(MenACV only[1])*	✓	✓
Available grants	OPS, RDT	*No*	VIG, OPS	VIG, OPS	One-time VIG	Switch, VIG *(no 2YL booster)*
Country, co-financing per dose (amount in USD)	Fully covered by Gavi for preventive campaigns		$0.20	$0.20	$0.20[3]	$0.20[4]
Actual vaccines cost of introducing the programme with GAVI funding	$0 M	$47.9 M	$0.64 M	$0.64 M	$1.0 M	0.4 M
Amount of add. Grants	OPS: $0.65 USD per dose		VIG: $0.80 / FVC or $100,000 OPS: full funding of CU campaign	VIG: $0.80 / FVC or $100,000 OPS: full funding of CU campaign	VIG: $0.80 / FVC or $100,000	VIG: $0.80 / FVC or $100,000

1. For countries which have not introduced Meningitis vaccine yet; switch to MMCV only offered to countries having introduced MenACV

2. For OCV it is preventive campaign not routine immunization; 3. For 2YL dose only, full government financing for Td doses as long as price is below $0.20;

Sources: GAVI, Detailed Product Profiles (DPPs) for WHO prequalified vaccines. Baral R, et al. Cost of delivering childhood RSV prevention interventions to the health system in Kenya: a prospective analysis; BMJ Open. Gavi, Vaccine funding guidelines, June 2024

15. Availability of cold chain equipment

	Cholera (OCV)	Influenza	TCV	Meningitis Multivalent	DTP Booster	Hexavalent
Cold chain volume requirement per dose	11 cm3	10.5 cm3	2.9 cm3	8.64 cm3	2.11-2.9 cm3	2.11 cm3
Total cold chain volume requirement	164 882 L	85 498 L	9 296 L (RI) + 61 001 L (CU)	27 710 L (RI) + 299 809 L (CU)	11 230 L	- 8 533 L
Required cold chain space at central storage (as % of available space)	18.8%	9.8%	7.0% 1.1%	34.3% 3.2%	1.3%	-1.0%
Required cold chain space at SP level (as % of available space)	53.2%	27.6%	19.7% 3.0%	96.8% 8.9%	3.6%	-2.8%

■ Routine Immunization ▨ Catch-up campaigns

Sources: GAVI, Detailed Product Profiles (DPPs) for WHO prequalified vaccines. EPI team

Comments

- Hexavalent: introduction allows to save cold chain space thanks to the reduction of total volume (4 doses of hexa instead of 3 doses of penta and 2 doses of IPV)
- Meningitis: space is for MMCV; for Men A, volume of vaccines is roughly 50% lower than the displayed volume
- Available total space: Central level: 875 300 L , SP level : 309 834 L, LD level : 128 167 L

16. Impact on human resources

	Cholera (OCV)	Influenza	TCV	MMCV	DTP Booster	Hexavalent
Is the target population already reached by existing immunization programs (yes/no)?	No	No	Yes	Yes, for routine immunization	Yes	Yes
Number of additional contacts required for target population (#)	Two	One	One	One	Three	Four vs five before (-1 contact)
Impact of introduction on workload (Personnel time in minutes per fully immunized person)	6	No data (but likely to be 5 to 20m)	7.5	7.5	22.5	30 vs 37.5 before (-7.5 saved time)
Expected requirements in terms of training for the existing personnel	Required (2-3 days of training)	Required (2-3 days of training)	Required (2-3 days of training)	Required (2-3 days of training)	Limited training	Required (2-3 days of training)

Sources: GAVI, Detailed Product Profiles (DPPs) for WHO prequalified vaccines. EPI team. Boniol M et al. Estimating the health workforce requirements and costing to reach 70% COVID-19 vaccination coverage by mid-2022: a modelling study and global estimates, BMJ Open 2022.

Vaccines ranking by feasibility

UNITAG members reviewed the feasibility evidence collated, and were requested to individually rank the six selected vaccines in order of importance after reviewing evidence for each criterion; 1 being the highest rank and 6 being the lowest. The average from the members' scores for each vaccine per criterion was then calculated and a position assigned (1-6). Finally, the average ranking with weighting for importance for each vaccine was calculated and the vaccines ranked. The outcomes were as summarized below

Vaccine	Safety/risk at individual level	Ethical, reputation and social issues	Accessibility of the target population	Direct costs	Sustainability of the market availability	Availability & sustainability of funding	Availability of cold chain equipment at all levels	Expected Impact of on human resources	**Average ranking with weighting for Feasibility**
Hexavalent	1	1	1	3	3	1	1	1	2.2
DTP Booster	3	3	2	1	1	5	2	5	3.2
Typhoid	4	6	4	2	2	3	2	2	3.4
Meningitis Multivalent	2	2	3	4	5	4	4	3	3.5
Cholera	5	3	4	5	6	2	6	4	3.8
Influenza	6	5	6	6	4	6	5	6	4.9

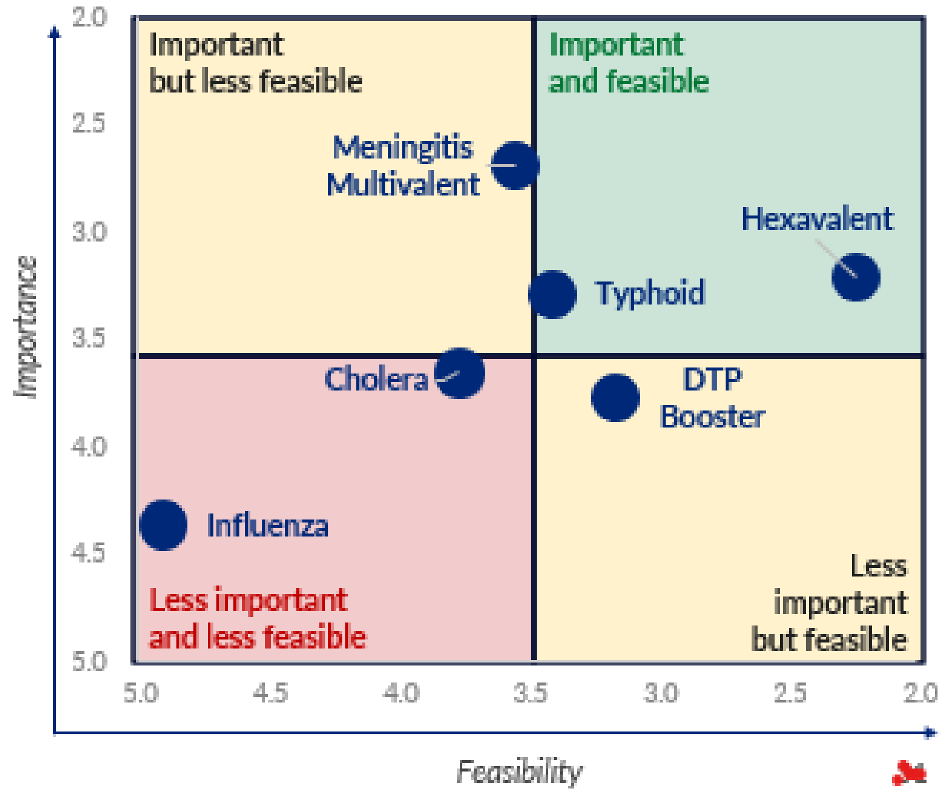
D. Vaccine prioritization based on importance and feasibility

The total weighted average for each vaccine was calculated, and the six vaccines were than plotted on a strategic x-y grid to place them in their relevant quadrats as shown in the following figures. Vaccines in the important and feasible quadrant were graded as of highest priority, those in the less important and less feasible quadrant ranked as the least priority vaccines.

Average weighted ranking for each vaccine

Vaccine	Ranking importance	Ranking Feasibility	Combined ranking
Meningitis Multivalent	2.7	3.5	3.2
Hexavalent	3.2	2.2	2.6
Typhoid	3.3	3.4	3.4
Cholera	3.7	3.8	3.7
DTP Booster	3.8	3.2	3.4
Influenza	4.4	4.9	4.7

Vaccine placement on x-y grid by quadrant



Following a review of the scores and a discussion among the UNITAG members, the recommended order of vaccine priorities from highest to lowest was: Hexavalent, Meningitis multivalent, DTP boosters, typhoid, cholera and influenza vaccines.

E: Vaccine sequencing

The final step was to propose the time periods for vaccine introduction, and to generate scenarios based on anticipated constraints and uncertainties.

Review of vaccine specific constraints and uncertainties

This involved reviewing the vaccine specific constraints and uncertainties for the six candidates, to assess any challenges that might be faced by the EPI in their introduction and roll out.

i. All vaccines- uncertainties on future sustainable funding, including duration of GAVI support.
ii. Meningitis Multivalent Containing Vaccines - It was noted that GAVI had a condition that countries could only qualify for Meningitis Multivalent Containing vaccines after they introduced Meningitis A vaccines in their routine vaccination programs. Uganda has only introduced Meningitis A vaccines in the highest burden districts. The availability of supply for a full country roll out of MMCV was also uncertain.
iii. DTP boosters – Uganda is still exploring different scenarios regarding vaccine products and schedules for the DTP booster vaccines
iv. Typhoid vaccine – uncetainites remained regarding the true burden of typhoid in Uganda with a requirement for more documentation on blood-culture confirmed cases and circulating strains.

Review of UNEPI specific constraints and uncertainties

The Uganda National Expanded program identified the following constraints that may affect new vaccine introductions over the next five years:

i. Competing programs (HIV/Malaria/Tb) with immunization for limited resources. The Gavi co financing budget stands at 10Mn USD, and growing.
ii. Limited capacity/ resources to manage/oversee implementation as the program has grown significantly (from six to fourteen antigens)
iii. Data management constraints –efforts to transition to electronic repository, unfortunately no alignment with top management at the time.
iv. Cold chain Significant costs covered by WB / GAVI right now
v. Human Resource challenges – more vaccines increase workload of healthcare workers who already have many of primary Health Care duties
vi. Coverage for newer vaccines is not as high as targeted with the program struggling to get health care workers onboard, especially with data requirements.
vii. Upcoming vaccination campaigns – the many upcoming campaigns resulting in health-worker and community fatigue; these include: Mpox, Ebola, Polio, tallow fever and measles-rubella vaccination campaigns.
viii. Upcoming general elections in early 2026, that creates a political charged environment

Recommendations and Scenarios for new vaccine introduction

Scenario one: primary

Assumptions:

b) MMCV doses available for introduction in Uganda
c) Ability to introduce MMCV directly (instead of MenA first)
d) Confirmed burden of disease of TCV

Based on the above assumptions, the committee recommends the following order of introduction (earliest year of introduction- latest year of introduction):

1. Hexavalent (2026-2028)
2. Meningitis multivalent (2026-2028)
3. DTP Booster (2027-2031+)
4. Typhoid Conjugate vaccine (2029-2030+)

Scenario two: alternative

Assumptions:

b) MMCV not available for direct introduction
c) MMCV doses available for switch at the time

Based on the above assumptions, the committee recommends the following alternative order of introduction:

1. Hexavalent (2026-2028)
2. Meningitis A (2026-2028)
3. DTP Booster (2027-2031+)
4. Meningitis multivalent (switch) (2029-2030+)

Research recommendations

The committee made the following recommendations for future research that would support new vaccine introduction decision making:

vi. Hexavalent - need for qualitative social studies on community perceptions about the new vaccine.
vii. Seasonal influenza - need to assess the burden of disease among infants and children
viii. Typhoid - need to assess true burden of disease through blood culture testing, including data from private health facilities.
ix. Phase 4 Post marketing studies following new vaccine introductions to study immune responses and duration of protection.
x. Cost benefit studies of new vaccines

Regarding follow-up actions, the committee recommended that:

iii. the scenarios proposed and any relevant new information should be reassessed in two years' time (2027) unless GAVI replenishment strongly impact the funding scenarios, then these should be reassessed earlier.
iv. the NITAG re-conduct the full prioritization and sequencing exercise for a new future timeframe in 5 years (2030)

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Criteria 1:0: Incidence of Disease

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Criteria 8:0: Feasibility

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