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Key Factors to Consider When Introducing a New Vaccine in Low-Income Settings: Lessons from Malawi Expanded Program on Immunization

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Abstract

Introduction: As new vaccines become available, countries must assess the relevance to introduce them into their vaccination schedules. Malawi has recently introduced several new vaccines and plans to introduce more. This study was conducted to identify key factors that need to be considered when deciding to introduce a new vaccine and current challenges faced by low and middle income countries using Malawi as an example. Methodology: The study employed a desk review approach, examining published literature from various sources such as PubMed, Medline, and Google Scholar. Policy documents from organizations like the World Health Organization, GAVI the Alliance, and the Ministry of Health for Malawi were also included. A total of 99 articles and documents on new vaccine introduction, challenges of immunization, policy documents in immunization and health systems strengthening were included. The review focused on addressing five key areas critical to new vaccine introduction namely: the need for a vaccine, availability of the vaccine, safety and effectiveness of the vaccine, demand for the vaccine, and the prudent use of public or private funds. Results: Malawi considered the burden of cervical cancer and the significance of malaria in the country when introducing the HPV and malaria vaccines. The country opted for vaccines that can be handled by the cold chain capacity and available human resources. Despite that malaria vaccine and Typhoid Conjugate Vaccine trials were done in country, there are limited vaccine safety and efficacy trials conducted in

Malawi, leading to a reliance on WHO-prequalified vaccines. Demand for newly introduced vaccines varied, with high demand for Oral Cholera Vaccine during a cholera outbreak, while demand for COVID-19 vaccines decreased over time. Although cost-effectiveness studies were limited in the country, 2 studies indicated that Typhoid Conjugate Vaccine and malaria vaccine would be cost effective. All these have been implemented despite having challenges like lack of accurate surveillance data, inadequate cold chain capacity, limited safety and efficacy vaccine clinical trials, political influence, and limited funding. Conclusion: Despite several challenges Malawi set a good example of the careful considerations required before introducing a new vaccine. The process involves data review, priority setting, precise planning, and consultation with stakeholders. Low-income countries should invest in vaccine safety, efficacy, and cost-effectiveness trials.

Keywords

Vaccine, Introduction, Implementation, Expanded Program on Immunization, Low-Income, Stakeholders

1. Introduction

Africa and other Low and Middle (LMICs) Income settings are facing a significant problem with infectious diseases, leading to high morbidity and mortality. Tuberculosis, HIV, malaria, cholera, cervical cancer, continue to be significant causes of morbidity and mortality in these settings. For instance tuberculosis caused 2.5 million infections and 417,000 deaths in 2016, accounting for a quarter of the global burden [1]. 214 million cases and 627,000 deaths due to malaria were recorded in 2020, 95% of which occurred in Africa [2]. 570,000 cases of cervical cancer identified in 2018, and 80% of those occurred in LMICs and associated with Human Papilloma Virus (HPV) [3] [4].

The advancement in vaccine development and manufacturing technology means more vaccines against previously uncurable infectious diseases will be available [5]-[7]. As more vaccines become available and receive marketing authorization, countries will need to consider adding them to their vaccine programs. In Africa, new vaccines such as Ebola vaccine, Oral Cholera Vaccine, HPV vaccine and malaria vaccine have been introduced in the couple of years [8]-[10].

However, introducing new vaccines in LMICs countries requires careful planning and coordination to overcome challenges such as inadequate funds, vaccine hesitancy, and regulatory requirements. The COVID-19 pandemic highlighted gaps in vaccine introduction and provided unique challenges, requiring sustained and congruous efforts from politicians, civil society organizations, and the public [11]-[18]. LIMCs need to find innovative ways to deal with these challenges and optimize new opportunities to sustain the availability and demand for new vaccines while meeting regulatory and post-marketing surveil-

lance requirements. This is especially important with the emergence of relatively newly approved vaccines such as HPV, malaria vaccine, Tyhoid Conjugate Vaccine (TCV), and OCV, which are being planned to be scaled up.

The purpose of this review is to describe the process of introducing new vaccines by addressing key questions that must be carefully considered. The study uses lessons learned from Malawi to understand the key areas to consider when introducing a new vaccine in Africa. Despite being a small country, Malawi has successfully introduced a number of new vaccines recently and plans to introduce more vaccines into her routine immunization schedule. Malawi shares similar characteristics with most African countries and other LMICs in terms of disease burden, population structure, and strength of health systems [19] [20].

Specifically, this review aimed at describing five key questions that must be considered when planning new vaccine introduction in National Expanded Program on Immunization; and to review existing challenges and opportunities for new vaccine introduction in Malawi and other LMICs.

2. Methodology

The study involved a review of literature on health systems, vaccine introduction guidelines, disease burden, challenges, and opportunities for new vaccine introduction in Malawi and Africa. The review focused on five key considerations when developing a new vaccine program which are: the need for a vaccine, availability of the vaccine, safety and effectiveness of the vaccine, demand for the vaccine, and the prudent use of funds.

The literature search aimed to describe key questions for introducing a new vaccine, using Malawi as an example. The study also aimed to identify challenges and areas for improvement in vaccine introduction, and reviewed current policy documents in Malawi, including those for newly introduced and upcoming vaccines.

2.1. Search Strategy

An extensive database search was performed using Pubmed, Medline, and Science Direct among others. Further, published articles and reports on government and international organizations websites such as GAVI, WHO, UNICEF, PATH, World Bank were included. The key terms and phrases used include new vaccine introduction; new vaccine program challenges and opportunities; building new vaccine programs; and these were blended with Low- and Middle-Income settings, Malawi, or Sub-Saharan Africa. Articles or documents that discussed new vaccine introduction or challenges in immunization in LMICs were included. Additionally, articles on health systems strengthening that included building new vaccine programs, documents on immunization related policy and funding were included. Articles or documents focusing on monitoring and evaluation of established immunization programs; those purely focused on developed countries; and those on health systems strengthening that did not include immunization were excluded. A three-step search strategy was used: firstly, a crude

initial search done; then extensive search done to identify key terms and words; and finally, search of reference lists and bibliographies for any other relevant articles. All literature was thoroughly scrutinized to check relevance with regards to the extent to which it is aiding to answer the five questions shown above (see Figure 1).

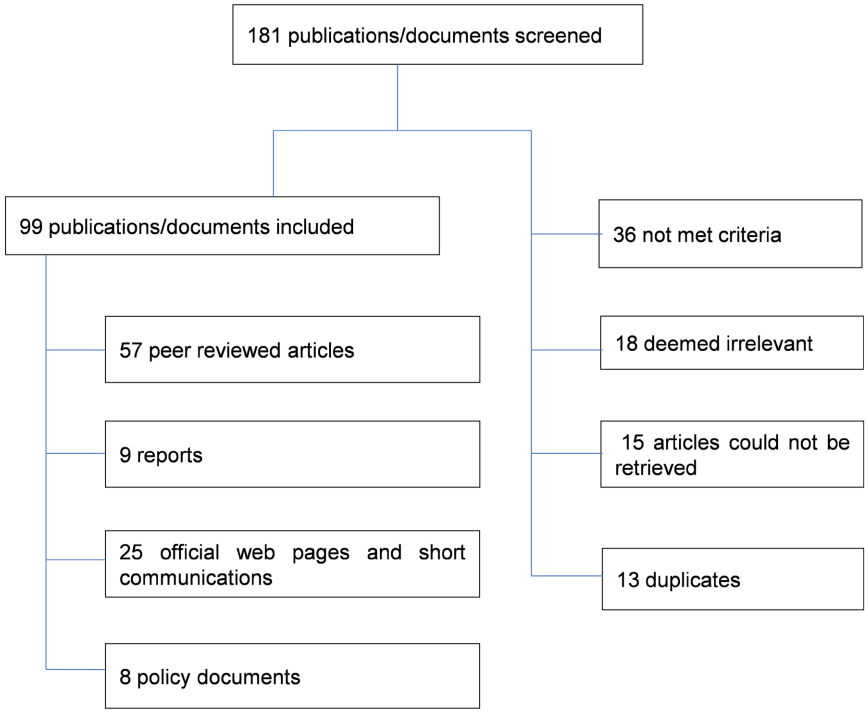

Figure 1. Flow chart shows the literature selection, inclusion and exclusion process.

2.2. Data Collection

The data collection process involved perusing through numerous articles and documents, reports, and short communications. Specifically, the authors extracted textual and where relevant graphical data from the documents and articles that were considered relevant to the key questions that were being considered.

2.3. Data Analysis

The data analysis mainly involved reading text and aggregating the findings to come to one conclusion with regards to the five key questions. The main objective was to bring key points of one question together. Hence, it required reading and re-reading to comprehend the meaning of the written content and make summaries that precisely mirror the original thoughts. This has been presented as text narrative, figures, and tables.

2.4. Ethical Consideration

The study was a desk review which involved usage of freely public documents

and published articles. Therefore, there was no need for to obtain ethical clearance from ethical boards. However, note that all figures and graphs have been acknowledged from the source.

3. Results

3.1. Country Profile

3.1.1. Demography

Malawi is a landlocked country in Southern Africa, bordered by Tanzania, Zambia, and Mozambique (see **Figure 2**). It has a population of 20.4 million and a young population, with 64% under the age of 15 as of 2021 [21]-[23]. Development partners provide a significant amount of funding for the health sector in Malawi, with the government only funding 25% of the health sector budget in the 2017/2018 fiscal year.

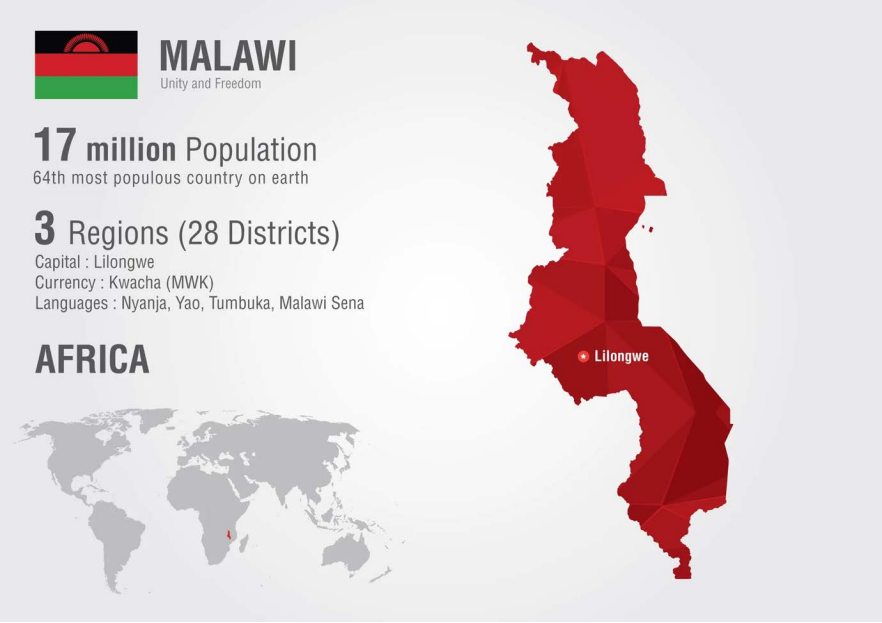

Figure 2. Map of Malawi [24].

3.1.2. Expanded Program on Immunization in Malawi

The Expanded Program on Immunization in Malawi is under Directorate of Preventive Health Services of the Ministry of Health and is managed by the EPI manager and deputy EPI manager. Vaccines are administered by community health care workers called Health Surveillance Assistants (HSAs) through static and outreach clinics [20].

Malawi has introduced several vaccines to its EPI schedule, including Td, HPV, MR, IPV, Measles Second dose, and COVID-19 vaccines. There are plans to introduce more vaccines such as RTS,S/A01, TCV, IPV second dose, and nOPV due to the recent increase in cVDPVs (see revised Malawi EPI schedule **Table 1**). The country has used bOPV and OCV to respond to recent outbreaks of WPV1 and cholera [20] [25] [26].

Table 1. Updated immunization schedule for Malawi (April 2023).

Age	Vaccine
At birth	BCG
0 - 14 days	OPV
At 6 weeks	OPV1, Rota 1, DPT-HepB-Hib1, PCV1
At 10 weeks	OPV2, Rota 2, DPT-HepB-Hib2, PCV2
At 14 weeks	OPV3, DPT-HpB-Hib3, PCV3 IPV
At 5 months	MV1
At 6 months	MV2
At 7 months	MV3
At 6 - 11 months	Vitamin A
At 9 - 11 months	MR1, TCV
15 - 23 months	MR2
22 - 36 months	MV4
At 12 - 59 months	Vitamin A
First contact (10-year old girls)	HPV1
6 months after HPV1	HPV2
First contact (15 - 45 years and pregnant women)	Td1
4 weeks after Td1	Td2
6 months after Td2	Td3
1 year after Td3	Td4
1 year after Td4	Td5
Within 2 weeks of delivery for postnatal mothers	Vitamin A

Now let us see how Malawi considered the five key questions using examples from a few recently introduced or pipeline vaccines (see **Table 2**) [27].

3.2. Is There a Need for a Vaccine?

This question considers whether there is a significant burden of the target disease to warrant the introduction of a new vaccine.

What is the impact of this disease on mortality and morbidity? In Malawi, cervical cancer is the most common cancer among women, with the highest incidence of all new cancer cases reported by the WHO in 2020 in the world. Cervical cancer accounted for 23% of all cancer-related deaths in the country and had a 5-year prevalence of 72 cases per 100,000 women population. The significant morbidity and mortality caused by cervical cancer in Malawi makes it is an important disease to address through vaccination, and the country introduced the HPV vaccine in 2019 [28] [29].

Is this a disease of public health importance and would it be politically prioritized for vaccination? In developing countries, there are limited resources and

multiple competing interests, so diseases that are more visible and have clear detrimental effects are more likely to be prioritized by policy makers [8]. Malaria is a disease of public health importance in Malawi, with approximately 4 million people diagnosed with the disease yearly [30]-[32]. Malawi has been listed as one of the top 15 countries with a huge burden of malaria, and policy makers in Malawi opted to pilot roll out the RTS,S/A01 vaccine in high transmission areas of Plasmodium Falciparum after WHO recommended its widespread use [33]-[37]. The decision to introduce the vaccine in Malawi was influenced by the public health importance of malaria.

Does controlling this disease help achieve national, regional, and international priorities? Policy makers may consider vaccines recommended by WHO or those likely to be supplied by procurement agencies like UNICEF or GAVI. Vaccines that align with set priorities such as the Global Vaccine Action Plan or Immunization Agenda 2030 may also be considered. For example, Malawi has sustained efforts to eradicate polio through the introduction of IPV in 2018 and plans to introduce nOPV2 to achieve regional and global targets [25] [38] [39]. Similarly, controlling malaria in Malawi is a priority, and the introduction of the RTS,S/A01 vaccine is seen as a contributory effort to reduce morbidity and mortality in line with national and global plans [19] [31] [40].

Does the disease to which the vaccine wants to be introduced for disproportionately affect marginalized and poor communities? Such kind of a vaccine would likely be prioritized. In developing countries, access to health services is often limited, particularly for groups such as women and girls due to poverty, social stigma, and geographic barriers. Specifically, in Malawi, many women with cervical cancer come from rural areas and present to healthcare facilities with advanced disease, usually too late for curative treatment [41]-[45]. The introduction of an HPV vaccine could significantly improve the livelihoods of these women by increasing access to preventative care. Experience has shown that vaccines are more likely to reach marginalized and poor communities than routine curative services [20] [42].

Final aspect to consider is programmatic complexities and practicality of alternative preventive, curative, and control measures compared to vaccination. BCG vaccine has been shown to prevent TB in young children but is not effective in adults [46] [47]. Despite this, BCG vaccination may be a better alternative for preventing TB in children due to practicality, cost, and feasibility compared to treating TB with the 6-month regimen. However, the majority of people who harbor and transmit TB infection are adults, and therefore vaccines targeting adolescents and adults are being developed and may be considered by policy makers if they add positive value to the control of TB [48]-[50]. Policy makers may consider introducing TB vaccines in Malawi and beyond if they are effective and feasible.

3.3. Is There a Vaccine Available for This Disease?

The question discusses various factors about the vaccine that need to be consid-

ered when making decisions about vaccines, such as their characteristics, formulation, required doses, packaging, and sensitivity to heat and freezing. Policy makers need to evaluate whether a vaccine is suitable for their cold chain systems, human resource capacity, funding, and ability to sustain demand. For example, the number of doses required for full immunization can impact storage, cold chain, and supply needs, as well as demand due to the need for multiple visits. Overall, these factors need to be carefully considered to ensure successful implementation of a vaccine program [27].

The majority of antigens in Malawi's vaccination schedule have good coverage above 80%, but DPT and OPV require three doses with the third dose being the indicator for full immunization [51]. The new RTS,S/A01 malaria vaccine requires four visits, which may pose challenges to achieving full coverage [20] [36] [37]. However, most antigens in the schedule do not require multiple visits, and they are synchronized to minimize the need for separate visits. Jensen and Jensen vaccine has become preferable in Malawi's EPI program due to its single dose primary vaccination requirement, reducing loss follow-ups [5] [27] [52]-[54]. The number of doses needed for full immunization is an important factor to consider when introducing new vaccines.

In Malawi's EPI, most antigens are polyvalent, but among the newly introduced ones, only the MR vaccine is polyvalent. The other newly introduced vaccines, such as COVID-19 vaccines, OCV, nOPV, IPV, are monovalent [20]. Additionally, most of the newly introduced vaccines are in liquid formulation, except for the RTS,S/A01 vaccine, which is lyophilized and comes with an adjuvanated diluent attached to the antigen. This vaccine is light and freeze-sensitive, and reconstitution errors are rare in Malawi. However, it is still important to emphasize the adjuvant-containing diluent during RTS,S/A01 training to minimize errors [27] [55] [56].

During the polio outbreak in Malawi, the bOPV vaccine, which is resistant to heat, was used in the Supplementary Immunization Activities (SIA) response. This was necessary because the vaccine had to travel long distances in cooler boxes during the summer. In contrast, IPV, which was introduced in Malawi a few years earlier to help achieve the GPEI goal of eradicating polio, is heat-sensitive and challenging to use in outreach and campaign settings [20]. Currently, there is an influx of freezing-sensitive vaccines like the RTS,S/A01 malaria vaccine and COVID-19 vaccines, which must be considered when deciding which vaccines to introduce in the EPI program [27]. In Malawi, the Astrazeneca vaccine was chosen over Moderna, primarily because Moderna requires extreme cold handling environment, which Malawi's cold chain capacity cannot handle [57].

In Malawi, most vaccines come in multi-dose vials due to the unreliable and inadequate cold chain capacity of the country. This allows for more children to be vaccinated with minimal cold chain requirements. However, in some cases, healthcare workers have missed opportunities to vaccinate children because they feel it is a waste to open a full vial for just one child. The volume of the contain-

ers is also important when assessing cold chain capacity [20] [27].

The availability and supply of vaccines are crucial factors to consider when introducing new vaccines. New vaccines are often produced by only a few manufacturers, making them expensive and limiting supply to developing countries. Policy makers need to forecast future supply trends of vaccines. COVID-19 vaccines showed an example of this, with the first five vaccines in short supply due to high demand from developed countries. This put developing countries at a disadvantage until the COVID-19 Vaccine Global Access Facility (COVAX) was established. Malawi started vaccinating four months after developed nations due to limited vaccine supply [58]-[61].

3.4. Is the Available Vaccine Safe and Effective?

Before introducing a new vaccine, policy makers must consider its safety, efficacy, effectiveness, and quality. The vaccine must have an acceptable safety profile based on clinical trials and post-marketing surveillance data from either in country studies or other settings that have used the vaccine. Adverse events following immunization must be carefully considered as they impact demand for the vaccine. With newer vaccines using new technology, safety records may be limited, and post-marketing surveillance data is necessary. WHO provides fact sheets on safety information for different vaccines that are frequently updated [11] [12] [58]. Overall, safety information must be reviewed carefully to ensure that the benefits of the vaccine outweigh its risks.

Clinical trials are required to demonstrate safety, and efficacy of a vaccine before it can be authorized for marketing. However, these trials are conducted under ideal conditions on healthy individuals, and the vaccine's efficacy may vary across different populations due to factors such as age, co-infections, and nutrition status [11]. Therefore, it is important to include these factors in mathematical models when estimating the vaccine's efficacy in a particular population. Additionally, it is crucial to consider data from various sources and whether the clinical trials were conducted in a setting similar to the country where the vaccine will be used [62]-[65].

Malawi has limited vaccine clinical trials to generate safety and efficacy data for new vaccines. As a result, the country mainly relies on WHO recommendations on safety and efficacy or data from other countries, including post-marketing data, to introduce new vaccines [27]. However, Malawi was one of the three African countries that participated in the RTS,S/A01 clinical trials, which evaluated the safety, efficacy, and effectiveness of a vaccine. This participation gave Malawi an advantage and allowed policy makers to review local data and make recommendations to the EPI program in conjunction with WHO recommendations [36] [37] [62]-[64].

3.5. Are There Sufficient People to Be Vaccinated?

When deciding whether to introduce a vaccine, it is important to evaluate the

target population to ensure resources are used optimally. Factors to consider include whether there are enough people to benefit from the vaccine [27]. For example, if a vaccine is introduced for adults, policymakers need to ensure that the older population is adequate to warrant the undertaking compared to vaccinating infants only [29] [66]. In resource-limited countries, it is important to decide whether to introduce a vaccine to a marginalized group or the general population, and whether the marginalized populations are in sufficient proportions to offer significant benefits compared to alternatives [65] [67].

In Malawi, policymakers responded to a cholera outbreak by prioritizing the distribution of the oral cholera vaccine in districts that were severely affected, based on available data on the target population at highest risk [26] [68]. Similarly, the COVID-19 vaccine was implemented in the country with a focus on prioritizing those at highest risk of severe disease, such as healthcare workers and individuals with comorbidities. In both cases, policymakers ensured that there was an adequate target population to receive the vaccines [69] [70].

The HPV vaccine has low uptake in Malawi due to rumors of conspiracy, fears of infertility, and unwillingness of parents to consent to their children getting the vaccine [51]. The same applies to the COVID-19 vaccine, where vaccine hesitancy has been a problem in Malawi [51]. However, demand and acceptability for other routine childhood vaccines are excellent [71]. During the SIA, the coverage for bOPV has been consistently above 100%. Similarly, demand for the RTS,S/A01 vaccine was high in the implementing districts and facilities during the demonstration phase, which has been a basis for the planned roll out to other districts in the future [27] [65] [71] [72].

Table 2. Examples on how Malawi considered the five key questions using a few antigens.

Key question	Vaccine	Examples from Malawi
Is there a need for the vaccine?	HPV vaccine and cervical cancer	• High incidence rates of cervical cancer in Malawi (37% of all new cancer cases. • Contribute 23% of all cancer related deaths. • 5-year prevalence of 72/100,000 women population. • Disproportionately affects women with poor access to health services.
	nOPV, IPV, bOPV and polio	• GPEI goals to eradicate WPV1. • GPEI goals to eradicate cVDPVs.
	TB vaccines and TB	• TB disease is more difficult to treat, requires 6month regimen. • BCG vaccine protects children from Tb disease. • Prospective TB vaccine for adults if efficacious would be preferable in comparison to treat with medication.
	RTS,S/A01 vaccine and malaria	• Malaria registering about 4 millions cases yearly. • Top five cause of under-five deaths in Malawi. • Most of the population aware of the disease. • Commonest case for OPD visits. • It falls in the national priorities (Malawi National Malaria Control Program).

Continued

Is the vaccine there?	Polio vaccine	• IPV single dose, extremely sensitive to heat and light, liquid vaccine comes in a multidose vial.
	MR	• MR 2 doses, sensitive to heat, liquid vaccine, comes in a multidose vial.
	COVID-19	• COVID-19 o Moderna stringent cold chain requirements. o Astrazenneca 2 doses, liquid, multidose vials. o J and J single dose, liquid multidose vials. o Pfizer 2 dose, liquid formulation, multidose vials. • COVID-19 vaccines only available in the country 4 months after developed countries had started vaccination.
	RTS,S/A01	RTS,S/A01 vaccine 4 doses (lyophilized vaccine with adjuvinated diluent).
	HPV	HPV 2 doses, sensitive to freezing, liquid with aluminum adjuvant, multidose vial.
Is the vaccine safe, efficacious, and effective?	IPV, OPV, HPV	• Most vaccines already have safety profiles, efficacy studies and effectiveness studies done elsewhere. • Depend on WHO pre-qualified vaccines and safety information sheets. • Local reports of AEFIs as part of post-marketing surveillance.
	COVID-19 vaccines	• New vaccines (with no long safety profiles) necessitated intensified efforts to report AEFIs. • Local efficacy and effectiveness studies underway to generate local data.
	RTS,S/A01 vaccines	• Local studies done as part pilot implementation. • Acceptable safety profile in the local safety studies. • Recommended by WHO SAGE as an efficacious vaccine in high transmission areas worldwide.
Are there people to be vaccinated?	OCV	• Cholera outbreak (ongoing) provided enough people to get the introduced vaccine on an emergency response basis.
	RTS,S/A01	• High demand for the vaccine in the pilot phase. • Now being extended to the comparator areas. • Plans underway to extend to other districts in the future dependent on other factors.
	COVID-19	• Early in the pandemic, vaccine prioritized to HCWs, travelers, those with comorbidities and other high-risk groups. • Low coverage due to lack of demand and hesitancy. • New strategies being employed (vaccinate my village campaigns, etc).
	HPV	• Adequate population to be vaccinated. • Started as pilot project in 2013 in Rumphi and Zomba to learn about acceptability and demand. • Low coverage due to vaccine hesitancy. • Now new strategies being employed (working with education sector and communities), educating parents to improve coverage.
	bOPV	Different strategies used to generate demand • SMS messages on phones. • Posters (IEC) on public places include health facilities, churches, markets, etc. • Community leadership engagements meetings. • Launch with high profile people from ministry and media house coverage. • Volunteers to visit house to house to mobilize guardians for the vaccines. • Setting up AEFI rapid response teams.

Continued

Is it good use of public or personal funds?	MR, PCV, Rota	• Malawi benefits from GAVI new vaccine introduction grant. • GAVI funds the measles component and Malawi government funds the rubella component for 5 years since introduction. • PCV13 and Rota increased vaccine budget by 175%. • Need of sourcing funds for sustainability purposes.
	TCV	Limani F, et al, 2021: • Outpatient costs on were 20$ (95%CI: 4.38 - 33.71) and 40$ (95%CI: 33.93 - 45.39) and inpatient were 93$ (95%CI: 68.87 - 118.84 and 296$ (95%CI: 225.79 - 367.25) on households and health system respectively. • Introducing TCV vaccine is cost-effective.
	RTS,S/A01	Ndeketa *et al*.: • Vaccine veered USD115 and USD109 for the health system and society, lower than GDP per capita of USD398.6. • 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. • Based on this model the study concluded that RTS,S/A01 would be highly cost effective.
	Cost effectiveness studies	• Limited cost-effectiveness studies in the country. • Dependence on studies from elsewhere and WHO recommendations.

3.6. Would It Be Prudent of Personal, Public or Donor Funds?

The costs associated with introducing a new vaccine are an important consideration and can be funded by public funds, private funds, or donors. These costs include activities such as social mobilization, cold chain expansion, health worker training, disease surveillance, waste management, delivery strategy revision, health record book revision, program monitoring and evaluation, and adverse event surveillance and management. It is important to consider all of these costs when determining if a new vaccine can be added to the schedule [27].

Key considerations include:

- If the new vaccine and its operational costs are affordable to an extent that the system will be able to sustain the antigens in a long-term plan.
- Potential funding gap if the new vaccine is in-fact introduced into the routine schedule as well as impact on national budget.
- If the new antigens are cost effective if compared against known cost-effectiveness thresholds and other vaccines or health interventions.

Cost effectiveness studies look at the value for money. Is adding this vaccine into the routine immunization a good value for money to achieve the targeted results such as reduction in mortality or hospitalization [27]? Cost effectiveness analyses are necessary to decide:

- If the new vaccine should be phased or universal.
- Introduce the vaccine only or blended with other interventions to target the disease.

LMICs, including Malawi, lack cost-effectiveness studies to make informed

policy decisions based on local situations. When considering introducing the malaria vaccine, one cost-effectiveness study that calculated the incremental cost-effectiveness ratio (ICER) per disability-adjusted life year (DALY) averted by vaccination and compared it to Malawi's mean GDP per capita. The study found that the RTS,S/AS01 malaria vaccine would be highly cost-effective, with an ICER lower than Malawi's GDP per capita, and could avert a significant number of clinical cases and deaths per 100,000 fully vaccinated children [27] [73]. Similarly, a study conducted in Malawi showed that typhoid infection is associated with high costs for both outpatient and inpatient care. Outpatient costs were 20$ (95%CI: 4.38 - 33.71) and 40$ (95%CI: 33.93 - 45.39); and inpatient costs were 93$ (95%CI: 68.87 - 118.84 and 296$ (95%CI: 225.79 - 367.25) on households and health system respectively. The study concluded that despite medical care being free in Malawi, a vaccine would likely be cost-effective with regards typhoid associated costs [74] [75].

4. Discussion

This study aimed at discussing key factors for consideration when introducing new vaccine and challenges encountered by LMICs using Malawi as a case study. Particularly, the focus was on the need for a vaccine, if a vaccine is available, safety and efficacy of the vaccines, demand for the vaccine and if introducing that vaccine would be cost effective.

On the need for a vaccine the key question to answer is if there is indeed a significant disease burden warranting a new vaccine introduction. It has been demonstrated that there was a need to introduce vaccines for HPV, malaria, polio, and other diseases in Malawi by considering the disease burden, public importance of the disease, how they align with national and regional priorities as well as how they can change lives of the disadvantaged ones [4] [25] [28] [42]-[44] [76]. However, it is important to note that these decisions need local data, and some countries may struggle to get accurate estimates on disease burden. For example, Malawi collects mortality data through death registries based at the facility. Of course, it may not capture all cases because the complimentary community-based mechanism of capturing all deaths is not optimal. However, with the introduction of death certification from the National Registration Bureau, it is expected that this will improve the accuracy of the hospital-based data and eventually be able to capture all causes of mortality [77]. Further, all information on diseases is entered on registries based at the facility which is then transferred onto digital system called Digital Health Information System (DHIS2) [51]. To supplement this, every four years Malawi conducts a cross sectional demographic survey which contains information on important diseases [30]. One other line of thought would be to conduct a needs assessment targeting the policy makers, public health officials and public representatives to assess opinions and readiness for vaccine introduction. Nonetheless, Malawi diligently answered this question and demonstrated the need to introduce HPV, IPV, nOPV,

bOPV, RTS,S/A01 vaccines [12] [27]. Suffice to emphasize the importance of strengthening quality public health surveillance systems to be able to obtain accurate disease burden data.

Availability of vaccines is quite critical. Malawi made different choices of vaccines with regards to this. Explicitly, it can be observed on how different vaccines were chosen with different doses, cold chain requirements (Moderna vs Astrazeneca), formulation and availability of the vaccine. Another aspect is how Malawi opted to start with a phased approach for COVID-19, HPV and RTS,S/A01 vaccines due to supply constraints. This was a prudent approach until a health market develops. A health market is one where vaccine supplies are produced by multiple manufacturers making vaccine products affordable and in constant supply [78]-[80]. Key to development of a healthy market is technology transfer from market authorization holders to high quality producers from LMIC producers who often have large production capacities and low production costs which consequently results in low prices on the vaccine market for the antigen [27] [81] [82]. In cases, where the country feels it is still necessary to introduce the vaccine despite the limited supplies, one option would be to use a different vaccine till the vaccine of choice becomes available. Nonetheless, this approach would mean extra costs if the alternative vaccine requires additional trainings or stock management costs [27]. This is in complete agreement with what WHO recommends [27]. The policy makers took into consideration the cold chain capacity, the expertise of the human resource, dosing schedules and vaccine characteristics [20]. This is extremely important to ensure that vaccines can reach undeserved and marginalized communities, ensuring fair access to vaccines and addressing disparities in vaccine uptake. This demonstrates the understanding that the policy makers in Malawi have and know what is best for their country and indeed are a good example.

Now going to safety and efficacy of the introduced vaccines, due to limited vaccine clinical trials in Malawi and other African countries, usually policy makers depend on WHO recommendations and at times data from other countries that have used the vaccine for quite some time [83] [84]. This has been common with most of the old vaccines that have been introduced. For example, introduction of the RTS,S/A01 vaccine was based on review of local safety data and recommendation from the WHO SAGE [37] [55] [62]-[64] [85]. However, the influx of new vaccines, like COVID-19 vaccines, that do not have a long safety profile in the developed world poses a special challenge to Malawi and other developing countries. Unfortunately, most developing countries do not have well matured pharmacovigilance systems that can conduct optimal safety post-marketing surveillance [86]-[89]. For this reason, when COVID-19 vaccination campaign started, the Malawi National Pharmacovigilance Centre based at Kamuzu University of Health Sciences (KUHES) had put deliberate effort to ensure that all safety signals for these vaccines are collected, reported, and investigated if need be. Similarly, in terms of vaccine efficacy and effectiveness, apart from following recommendations from WHO, European Medicines Agency

(EMA) as well as other regulatory bodies, Malawi through its academic and research institutions is conducting COVID-19 efficacy and effectiveness studies to generate local data as there is much to learn from these vaccines despite its emergency roll out [90] [91]. Hence, policy changes and recommendations may be expected in the future once these studies are concluded and the data critically reviewed.

On demand for the vaccine, the key question to be addressed is if there is a population to receive the vaccine and the target population is willing to get the vaccine. OCV in Malawi targeted those in the cholera affected districts. Similarly, COVID-19 was prioritized to health workers and those with comorbidities early in the response in Malawi. In addition, different strategies have been employed by the country to create a demand for different newly introduced vaccines. The low uptake of COVID-19 vaccines would be because no Knowledge, Attitudes, Beliefs, and Practices (KABP) studies were done. Probably, because they were introduced in an emergency mode. Only one KABP and one vaccine hesitancy studies were conducted between 2015 and 2020 for HPV [20]. KABP studies help to inform communication strategy about the targeted disease, the vaccine, and immunization in general. The design for the study will vary depending on the vaccine, target population, age groups among other things. Hence, they can range from focus group discussions, in-depth interviews, key informant interviews, to systemic surveys in the community. The objective is to identify gaps in knowledge, beliefs, perceptions, misconceptions, and concerns about the vaccine. Further, amongst the health care workers, it can help to correct any inaccurate perceptions concerning parents' attitudes and beliefs towards the vaccine. In addition, it will bring out any critical issues that may significantly affect acceptability of the vaccine such as anti-vaccination groups [27]. Moreover, it may bring to light other social and cultural factors influencing vaccine acceptance which can be used to inform strategies such as community engagement, trust-building and addressing cultural beliefs and practices. Regardless of this, Malawi has demonstrated apt comprehension on how the issue of target population and demand generation needs to be considered during vaccine introduction. This speaks volumes with regards to the level of maturity for the EPI program of Malawi. However, there still a need for support to consider doing KABP studies for all non-emergency vaccines that need to be introduced or those in the pipelines.

The last item is value for money. Is it worth investing in this vaccine? Will the returns outweigh the costs that will be incurred in the program? This is answered through cost-effectiveness studies. Sadly, cost-effectiveness studies require special expertise and resources which most countries may not have especially in Africa and other LMICs. Cost-effectiveness studies are challenging, time consuming and usually it may be extremely hard to get estimates on costs per child and model the impact of the vaccines. Furthermore, the technical capacity to run cost-effectiveness models may be lacking in most settings. Therefore, these studies are lacking in most African and other LMICs. In fact, as indicated above,

for Malawi only 2 cost-effectiveness studies were found to have been done before wider roll out of a vaccine (that on RTS,S/A01 and TCV) [72] [73]. This poses as a serious challenge if a vaccine is being introduced but has no cost effectiveness studies done elsewhere. Another option is to do cost-effectiveness studies while the program is already running but most countries do not prioritize this neither do they have the capacity or the resources. Hence, there is a need for in-country research institutions to seriously consider investing in cost-effectiveness studies so that local policy can be adjusted using local evidence [92].

Malawi is eligible for Global Vaccine Alliance Initiative (now called GAVI the Alliance) funding. For new vaccine introduction in the past, Malawi has benefited from the GAVI vaccine introduction grant [93]. GAVI supports procurement of new vaccines and vaccine introduction [93] [94]. However, Malawi and other countries that benefit from this grant need to look into the long-term sustainability after vaccine introduction. There is need to strategize on long-term financing, capacity building and domestic resource mobilization such as local partnerships. Hence, there would be a need to mobilize resources after expiring of the five years to continue providing the vaccine. As described above, new vaccine introduction can indeed increase costs for EPI program [19] [20] [95]. Hence, the need to continuously mobilize resources.

5. Conclusion

Malawi had a need to introduce HPV, RTS,S/A01, IPV and nOPV. Vaccine characteristics are taken into consideration considering the cold chain capacity, technical expertise of service providers, availability of specific vaccines and vaccine characteristics. Due to limited vaccine safety and efficacy trials in Malawi, the country mainly depends on WHO-prequalified vaccines or data from other countries. Most of the vaccines have a population ready to receive and benefit from the vaccines such as RTSS, HPV others. However, the coming in of new vaccines and rumours requires efforts generate demand for the new vaccines such as COVID-19 vaccines. TCV and RTSS have been shown to be cost-effective. Nonetheless the country has limited cost-effectiveness studies. Additionally, the country is heavily dependent on GAVI and other development partners for sustainability of newly introduced vaccines.

Strengths

This study comprehensively reviewed available evidence in new vaccine introduction in low resource setting. Malawi is a typical example of such a setting and that adds to the generalizability of the findings in other similar settings. The rigorous methodology employed has helped to minimize bias, identify existing gaps. and increase transparency and reproducibility of the study.

Limitations

The study did not look at decision making processes, implementation of new vaccine, as well as monitoring and evaluation of new vaccine programs. Further,

it would have been of more added value if opinions of policy makers and partners (such as MAITAG, UNICEF, WHO, EPI, MoH) were included in form of interviews to get a better understanding from the experts. Additionally other literature included in the review like reports and short communications could be less reliable as they are not peer reviewed. Further studies are needed to explore this topic in the direction suggested above.

Recommendations

LMICs countries should strengthen their post-marketing surveillance systems especially with introduction of new vaccines with short safety profiles. Additionally, countries should create an enabling environment for research (such as user-friendly ethical approval and regulatory application processes) for attract vaccine clinical trials and cost-effectiveness studies. Furthermore, countries should build capacity and set research priorities for research institutions to prioritize vaccine efficacy, effectiveness cost-effectiveness studies so that decisions are based on local data. As an extension to that, countries should consider conducting KABP and vaccine hesitancy studies more especially for vaccines that are completely new. Further, they must prioritize community leadership engagement and work with different sectors such as education to create a demand for vaccines. Lastly, countries must look beyond new vaccine introduction and be sure to form long-lasting partnerships that will last beyond the new vaccine introduction period to ensure sustainability. These may include domestic resource mobilization and formation of partnerships. This will help to mobilize resources and forecast the needed extra support to avoid disruptions of vaccination program due to funding.

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Conflicts of Interest

At the writing of the article Boston Zimba was working for World Health Organization Malawi Country Office as Immunization Technical Officer. The rest of the authors have no interest to declare.

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