

A narrative review of strategies to improve childhood vaccination coverage in Low- and Middle-Income Countries

Improvement of Childhood Vaccination Coverage

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Abstract

Background: Childhood vaccination is a fundamental human right and a core component of successful primary care. It has positive benefits on population health as it reduces the burden and costs associated with infectious diseases.

Main Body: Despite the immense benefits of childhood vaccination, vaccine coverage remains poor in many Low- and Middle-Income Countries (LMICs) due to several barriers. Examples of these barriers include parental misperceptions about vaccine safety, poor vaccine distribution networks and insufficient funding for childhood vaccination programs. It is therefore necessary to design suitable and effective strategies to overcome these barriers.

Conclusion: This narrative review article discusses effective strategies to improve vaccine coverage in Low- and Middle-Income Countries (LMICs).

Keywords: Childhood vaccination, Strategies, Low and Middle-Income Countries, Vaccination Coverage

Background

Vaccination has positive benefits on population health as it reduces the burden and costs of infectious diseases on the population and the health system (1). It is estimated that the return on investment for vaccination is about \$44 for every dollar invested (2). Despite the social and economic benefits of vaccination, it is observed that vaccine coverage in many Low- and Middle-Income Countries (LMICs) is low (3). For example, 1 in 5 African children and 1 in 4 South American children, fail to receive all the recommended

childhood vaccinations, and this results in considerable morbidity and mortality from vaccine-preventable diseases (1, 3). Similarly, 58% of global deaths due to vaccine-preventable diseases occur in Africa in children less than 5 years of age (4). The occurrence of the COVID-19 pandemic has exacerbated the problem of poor vaccine coverage in LMICs (5). In 2019 before the pandemic, about 19 million children under the age of 1 year failed to receive routine childhood vaccines and by 2021 this figure had risen to about 25 million children under the age of 1 year (5). The

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COVID-19 pandemic also adversely affected vaccine uptake among zero-dose children (i.e. children who have never received routine childhood vaccination) as an estimated 18 million zero-dose children failed to receive routine childhood vaccination in 2021 (5). This accounts for the highest figure of poor vaccine uptake in zero-dose children since 2005 (5).

It has therefore become imperative to improve childhood vaccine coverage in low- and middle-income countries (6). However, efforts to improve vaccine coverage must identify barriers to the successful implementation of vaccination programs (7, 8). A clear knowledge of these barriers will help in designing strategies to improve vaccine coverage in Low- and Middle-Income Countries (9). In this review, barriers to childhood vaccination coverage are identified and strategies to overcome these barriers are discussed.

Main Text

What is Vaccination?

A vaccine is defined as an “immunobiological substance used for active immunization by introducing into the body a live modified (attenuated), or killed (inactivated) infectious organism or its toxin. The vaccine is capable of stimulating an immune response by the host, who is thus rendered resistant to infection” (10). The term vaccination refers to the administration (such as by injections) of a vaccine to prevent a disease (11).

Types of Vaccines

Live Attenuated Vaccines

Attenuated vaccines comprise live, whole bacterial cells or virus particles whose virulence in the human host has been diminished or attenuated while still retaining the ability to provoke an immune response (11, 12, 13, 14, 15, 16, 17). A variety of methods may be used to produce attenuated vaccines (13). For example, a live virus can be passed through several series of cell cultures or animal embryos such as chick embryos (13, 18, 19). With each passage through a chick embryo, the virulence of the virus is weakened. However, the virus still retains the ability to provoke an immune response (13). Examples of live vaccines include oral polio and yellow fever vaccines. A major advantage of live vaccines is that they provide long-term immunity (11, 12, 13, 14, 15, 16, 17, 18). However, a major concern regarding the use of live vaccines is their potential capacity to

mutate and become capable of causing disease (13). For example, mutations have occurred with the oral polio vaccine leading to cases of paralytic polio (13, 20, 21, 22, 23).

Killed or Inactivated Vaccines

Killed or inactivated vaccines are made by using several methods (such as heat or chemicals such as formalin) to kill the pathogen. The pathogen therefore loses its ability to replicate but still retains its ability to stimulate an immunogenic reaction (11, 12, 13, 14, 15, 16, 17, 18, 24, 25). Since these vaccines are killed, they cannot mutate (13). However, they provide shorter protection compared to live vaccines; therefore, booster doses are required to maintain effective immunity. Examples of killed or inactivated vaccines include the inactivated polio vaccine and the injectable seasonal influenza vaccine (13).

Toxoids

Toxoid vaccines are bacterial toxins which have been rendered non-toxic through chemical treatment but still possess the capacity to provoke an immune response. Toxoids are important in toxin-mediated diseases e.g. tetanus (13, 17). Examples of toxoids include tetanus toxoid and diphtheria toxoid (13, 26).

Subunit and Conjugate Vaccines

Subunit vaccines comprise only components or antigens of the pathogen. Examples of subunit vaccines include the acellular pertussis vaccine and the shot form of the influenza vaccine (11, 12, 13, 14, 15, 16, 17, 18, 27, 28). To improve the effectiveness of the immune response, some subunit vaccines may be combined with an adjuvant (e.g. a protein antigen) to form a conjugate vaccine (29, 30, 31, 32). An example of a conjugate vaccine is the Haemophilus influenza type b (Hib) conjugate vaccine (33).

Recombinant vaccines are subunit vaccines which are genetically engineered and involve the insertion of a gene coding for a vaccine protein into another virus (27). The vaccine protein is subsequently created when the carrier virus undergoes reproduction (32, 34). An example of a

recombinant vaccine is the Hepatitis B vaccine (35).

Viral vector vaccines

Viral vector vaccines use a non-pathogenic virus to deliver to the host cells the genetic code or instructions required to produce antigens to a pathogenic virus and subsequently trigger an immune response against the pathogenic virus. The immune response produced by viral vector vaccines is usually strong and only one dose of the vaccine is required to develop immunity (11, 12, 13, 14, 15, 16, 17, 18, 27, 32, 36, 37). Examples include the Ebola vaccine, and COVID-19 vaccines (AstraZeneca and Johnson & Johnson) (15, 38, 39).

mRNA Vaccines

These vaccines are pieces of mRNA enveloped in a lipid sapphire which corresponds to a viral protein. When the vaccine is administered, the body's immune cells pick up the vaccine particles and reveal the mRNA. The mRNA subsequently gives the immune cells a code or signal to create proteins similar to the proteins found on the pathogenic virus (such as the "spike" protein on the coronavirus' surface). Subsequently, these proteins are released by the host's immune cells to other immune cells, and this triggers an immune response involving antibody production and activation of specialized cells to find and kill the viruses bearing these proteins (e.g. spike protein) and other infected host cells (11, 12, 13, 14, 15, 16, 17, 18, 27, 40, 41). Examples of mRNA vaccines include the COVID-19 vaccines (Pfizer and Moderna) (42).

Barriers to Childhood Vaccine Coverage in Low-And Middle-Income Countries

Several barriers result in low childhood vaccine coverage in LMICs. These barriers include:

Parental Barriers

Parental barriers are factors which are peculiar to parents or guardians and hinder parents or guardians from taking their children or wards for vaccination (43, 44, 45). Examples of these barriers include illiteracy, a misperception by parents that vaccines will harm their children, poor knowledge of childhood vaccination schedules and

lack of funds to commute to vaccine delivery centres (43, 44, 45, 46). For example, a study conducted in Ethiopia revealed that many mothers were unaware of the appropriate age to commence childhood vaccination (47).

Maternal education is also a significant influencer of childhood vaccination uptake in many LMICs. Several studies have shown a close association between maternal education and a positive attitude toward childhood vaccination (6, 47, 48, 49, 50, 51). For example, a systematic review showed that vaccine uptake was better in children whose mothers were educated (49). Sadly, in many LMICs such as in Africa, female education is hindered by socio-cultural values that promote early marriages and pregnancies (8, 52, 53).

Some studies have shown that some parents or caregivers may prefer certain modes of childhood vaccine delivery. For example, a study done in Sokoto State, North-West Nigeria, showed that some mothers preferred vaccine campaign programs to facility-based delivery of childhood vaccinations because, in vaccine campaign programs, the vaccines were brought to them at home, compared to facility-based delivery programs where they had to commute to the vaccine delivery centre (54).

Health System Barriers

Health system barriers are major barriers to effective childhood vaccination especially in LMICs with weak and poorly funded health systems. Examples of these barriers include poor storage facilities for vaccines, inadequate infrastructures to maintain the cold chain, poor vaccine distribution and delivery systems, inadequate manpower, and long distances between vaccine delivery centres and target communities (43, 55, 56, 57, 58, 59, 60). In addition, poorly coordinated vaccination services in vaccination centres may result in unduly long waiting times for vaccine recipients, disrupted vaccine schedules and missed opportunities (43). Also, the poor attitude of personnel in vaccine delivery centres may deter many mothers or caregivers from bringing their children to initiate or complete their vaccination schedules (55, 56, 57).

Infrastructural Barriers

These refer to barriers outside the health sector which can impinge on the effectiveness of vaccination programs. Examples of these barriers include poor road networks, inefficient or irregular power supply, and poor communication facilities (60, 61, 62, 63). For example, consistent and timely delivery of childhood vaccines to remote rural

vaccine centres is often hindered by bad road networks (61).

Political Barriers

Political barriers include poor commitment by LMIC governments to invest in improved vaccine coverage, and a lack of multi-sectoral collaboration (e.g. improved power supply, improved road and transportation systems and ensuring that other relevant sectors of the economy collaborate) to ensure the success of vaccination programs (43, 63). In addition, many LMIC governments rely on foreign aid or donor organizations to fund or provide childhood vaccine services. While foreign or donor aid makes it possible for LMICs to acquire childhood vaccines, it is however not a sustainable model for financing childhood vaccination. For example, childhood vaccine delivery services in some LMICs have been disrupted when donors stopped providing funds (8, 63).

Political Instability

Closely related to political barriers is political instability. Political instability includes wars, crises and outbreaks of violence that may interrupt existing vaccine delivery services. For example, the war in Ethiopia has disrupted childhood vaccination programs. When compared to the period before the conflict (8, 64, 65, 66, 67). In addition, the destruction of infrastructure and health facilities, and the loss of skilled vaccine delivery health workers (due to death, war injuries or flight) make it difficult to easily restore disrupted childhood vaccine services (8, 68, 69).

Disease-Specific Barriers and Challenges

While the above-mentioned barriers are common to childhood vaccination, certain barriers are peculiar to some vaccine-preventable diseases. Measles is a vaccine-preventable disease. However, major barriers to measles vaccination are the inability to maintain the cold chain in areas with poor power supply; poor storage facilities; vaccine stock outs and vaccine hesitancy from communities due to misinformation about the vaccine (43, 54, 70, 71, 72). Sadly, this has led to outbreaks (73, 74). Outbreaks of measles reflect inadequate childhood vaccine coverage and defective health systems. In contrast, high measles vaccine coverage indicates strong immunization programs (70).

A major challenge with the Oral Polio Vaccine (OPV) is the emerging problem of circulating vaccine-derived polioviruses (cVDPVs) (75). These cVDPVs are virulent mutants of weakened polio viruses which have been excreted or

defecated into the environment by recently vaccinated children (75). Open defecation and inadequate management of human waste are predominant problems in LMICs with poor Water, Sanitation and Hygiene (WASH) facilities (76). In such countries, individuals may unknowingly consume food or water which has been contaminated by the excreted polio vaccine virus. In poorly vaccinated communities, ingestion of virus vaccine-contaminated food or water results in uninterrupted circulation of the virus among susceptible children and possible outbreaks of polio (75).

In addition, the immune response to OPV is further reduced by co-existing conditions (such as diarrhoea, concurrent infection with other enteroviruses and chronic malnutrition) which may be pervasive in some LMICs (77, 78, 79). Therefore, more OPV doses are required to achieve protective immunity and reduce poliovirus transmission among children living in such communities (80, 81). The above-mentioned challenges are not associated with the Injectable Polio Vaccine (IPV) which is used in high-income countries and confers excellent mucosal immunity in vaccinated children. However, its high cost makes it unaffordable in many LMICs (82).

Diphtheria is another vaccine-preventable disease. However, outbreaks have recently occurred in Nigeria due to poor vaccine coverage, vaccine hesitancy and pathogen dynamics resulting in the emergence of virulent and antimicrobial-resistant strains (83, 84, 85, 86, 87, 88).

A major challenge with the Bacillus Calmette–Guérin (BCG) vaccine for Tuberculosis is the restricted vaccine opening policy due to multi-dose vials and limited time of use. For example in some vaccination centres, unless a certain number of children are available, the vaccine vial is not opened for vaccination. Children and their parents or caregivers are therefore told to return for the BCG vaccination at a future date when more children are expected to be present for vaccination. Some parents may not return, particularly if they reside a considerable distance from the vaccine centre, or they lack funds for public transportation (89, 90).

Strategies to Improve Childhood Vaccine Coverage in Low- And Middle-Income Countries

Political commitment, adequate funding and innovative strategies and products will be required to improve vaccine uptake and coverage in LMICs. In addition, LMIC governments must commit increased funding for infrastructure; services; increased training of health workers on vaccination;

surveillance for vaccine-preventable diseases; equipment to improve and maintain effective cold chains in remote areas; and the strengthening of national health systems. Childhood vaccination programs should be expanded to include more vaccines. If LMIC governments lack the required funds, then it is advisable to seek funding from donor agencies or engage the private sector through public-private partnerships (63, 91, 92, 93). Innovative strategies and products which are tailored to meet local needs are also required to improve vaccine uptake and coverage. An example is the Vaccine Innovation Prioritization Strategy (VIPS) which is geared towards developing innovative approaches to address immunization barriers and achieve immunization coverage in LMICs (94). The Vaccine Innovation Prioritization Strategy (VIPS) is an alliance made up of the World Health Organization (WHO), The United Nations Children's Fund (UNICEF), Bill and Melinda Gates Foundation, Program for Appropriate Technology in Health (PATH) and the Global Alliance for Vaccines and Immunisation (GAVI) (94). In this regard, VIPS has prioritized 3 vaccine product innovations (among 24) with the greatest potential to achieve equity, improve immunization systems and focused investments. These three innovations are microarray patches, heat-stable controlled temperature chain liquid formulations, and barcoding on primary containers (94). Microarray patches are a form of intradermal delivery technology for vaccinations. They do not require the use of needles and can improve safety during administration, reduce the need for cold chains, enable easier storage and transport and remove the risks of needle waste. Since they are single-dose, they also reduce missed vaccination opportunities (which occur when vaccination staff, are reluctant to open a multi-dose vial for a single individual. Heat-stable controlled temperature chain liquid formulations are vaccine formulations that are sufficiently heat-stable to be kept in a controlled temperature chain. Therefore, they help to overcome the challenge of maintaining a cold chain or thermostability of vaccines (94). The inability to maintain cold chains is a major barrier to vaccine uptake and coverage in LMICs (43). However, by obviating the need for cold chains, they improve the possibility of accessing remote and underserved communities in LMICs (94). Barcodes on primary packaging will increase accuracy in tracking and tracing vaccines especially when they are removed from their secondary packaging at lower levels of distribution. They (i.e. barcodes) will also support the eventual transition to electronic record keeping, in line with

the objectives of advancing digital health in Primary Health Care. Barcodes on primary packaging are seen as highly valuable in terms of tracking inventory and immunization coverage (94). Individually, some of the partners in VIPS and other global agencies have also learnt about their strengths in efforts to improve childhood vaccination in LMICs.

The World Health Organization (WHO) has launched the "Immunization Agenda 2030: A Global Strategy to Leave No One Behind" (70). The agenda seeks to guarantee access to the required vaccines for everyone (irrespective of age, gender, geographic location, race, socio-economic status etc.); ensure that current achievements in vaccination are not lost; foster recovery from the disruptions caused by the COVID-19 pandemic to vaccine coverage globally and improve vaccine coverage globally. The strategy is founded on four core principles and seven strategic priorities. The four principles include: People-centred: The thrust of this principle is to ensure that the design, management and service delivery of vaccinations respond to the needs of target populations and are inclusive i.e. devoid of barriers such as age, gender, geographic, cultural or socio-economic barriers (70).

Partnership-based

This principle emphasizes the need for multi-sectoral collaborations in efforts to improve vaccine coverage. Multi-sectoral collaborations possess the capacity to achieve more impact and better outcomes in vaccine delivery programs (70).

Country-owned

Immunization programs should be context-specific and essentially take into consideration the geo-political, economic and socio-cultural dynamics of target populations or countries. In other words what applies in one LMIC may not apply in another due to differences in political dynamics, cultures and values (70).

Data-guided

The essence of comprehensive, high-quality data cannot be over-emphasized. Data provides a basis for decision-making, evaluation and quality improvement (70).

The above principles are applied across the agenda's seven strategic priorities. The strategic priorities are designed to complement the Sustainable Development Goals (SDGs). The first strategic priority (i.e. immunization programmes for primary health care and universal health coverage) is focused on achieving Universal Health Coverage

by completely integrating vaccination programs with primary healthcare. The second priority (commitment and demand) strives for increased political and financial commitment, particularly by LMIC governments and vaccination agencies, to improve vaccination coverage. This priority also advocates for increased support and demand for vaccination services by target communities. The third priority (coverage and equity) seeks to ensure equitable coverage of vaccination services to all, particularly to vulnerable populations such as children, the elderly, internally displaced individuals and refugees. The fourth priority (life course and integration) is geared towards providing sustained vaccination services to individuals throughout life. The fifth priority (outbreaks and emergencies) aims to curb outbreaks of vaccine-preventable diseases, and at the same time, ensure sustained delivery of vaccines during periods of instability such as wars and natural disasters. The sixth priority (supply and sustainability) is focused on increased national funding and donor aid for vaccination services. This priority also seeks to improve timely access to vaccines in all countries through efficient supply and delivery systems. The seventh priority (research and innovation) targets more research and development efforts for new and effective vaccines (70).

Another global organization which has made a strong commitment to improving childhood vaccination is The United Nations Children's Fund (UNICEF). This commitment is spelt out in the UNICEF Immunization Roadmap 2022–2030. The roadmap is an update of the UNICEF Immunization Roadmap 2018–2030, which was first launched in September 2019. The update became necessary in light of COVID-19-related disruptions to childhood vaccination programs globally. To overcome the challenges posed by the COVID-19 disruptions to childhood vaccination programmes, the UNICEF Immunization Roadmap 2022–2030 has incorporated five strategic shifts into its framework. The first strategic shift (zero-dose agenda) is focused on providing full vaccination services to zero-dose children, especially children in remote rural areas or conflict zones. The second strategic shift (immunization as a strong foundation for primary health care) seeks to integrate childhood immunization services with existing primary healthcare services and programs such as polio eradication programs. The third strategic shift (innovative evidence-based approaches to social and behavioural change) is geared towards deploying evidence-based behavioural science approaches to develop positive attitudes, values

and behaviour towards childhood vaccination in target communities. The fourth strategic shift (supporting immunization in middle-income countries) aims at improved funding for middle-income countries to scale up childhood vaccination services. The fifth strategic shift (strengthening readiness and response in humanitarian settings) is an effort by UNICEF to incorporate the lessons and insights learnt from the global disruption of childhood vaccination services during the COVID-19 pandemic, into policies to forestall future disruptions to childhood vaccination services (95). The Global Alliance for Vaccines and Immunisation (GAVI) is a private-public partnership founded in 2000 by the Bill and Melinda Gates Foundation and key partners (WHO, UNICEF, and the World Bank), to improve the introduction and coverage of new and underused vaccines to children in the world's poorest countries (91, 96, 97). The efforts of GAVI have led to the uptake of hepatitis B, Hib, yellow fever, pneumococcus, rotavirus, inactivated polio, and HPV vaccines in the world's poorest countries (91). Country eligibility for GAVI support is based on a threshold determined by a nation's Gross National Income (GNI) per capita over the preceding 3 years (91). For example, in 2011, only countries with a GNI below US\$1500 were eligible for GAVI support for the introduction of new or underused vaccines, as well as for health systems strengthening funds for vaccine delivery infrastructure (91, 98). However, the requirements for eligibility have been modified to accommodate pertinent realities such as the fact that many unimmunized children live in middle-income countries with per capita GNI above US\$1500; while internal displacements, war and political instability have increased the number of children living in difficult-to-reach, crisis and war-torn zones (91). In this regard, GAVI has introduced a 5-year-strategy, GAVI 2021-2025 (GAVI 5.0) which seeks to ensure equitable childhood vaccine coverage in alignment with the Sustainable Development Goals (SDGs) and the strategic priorities of the Immunisation Agenda 2030 (IA2030) (91, 99, 100). Regarding specific diseases, several initiatives have also emerged. For example, the Global Polio Eradication Initiative is a public-private partnership led by national governments with six partners – the World Health Organization (WHO), Rotary International, the US Centers for Disease Control and Prevention (CDC), the United Nations Children's Fund (UNICEF), Bill & Melinda Gates Foundation and GAVI (101). Its goal is to eradicate polio worldwide (101). The initiative has recently launched the Polio Eradication Strategy 2022–2026 which seeks to reposition the battle against

polio to meet current challenges such as the vaccine delivery disruptions caused by the COVID-19 Pandemic (102). The strategy seeks to improve political commitment to fight polio; improve vaccine acceptance through community engagement; foster integration with existing health services; empower frontline workers by equipping them with the required knowledge, attitude, skills, supplies, facilities and where necessary, security cover to perform their duties; and improve surveillance efforts to improve outbreak detection and response (102).

Similarly, the Measles & Rubella Partnership (M&RP) seeks to achieve a world devoid of measles and rubella by supporting countries to improve vaccine coverage of measles, rubella and other vaccines; provide the necessary funding and technical support for quality supplementary campaigns, outbreak responses and investigations; recommend and support solutions to strengthen immunization delivery; and support a global laboratory network for measles and rubella (103). The Measles & Rubella Partnership (M&RP) is led by the American Red Cross, the Bill & Melinda Gates Foundation, GAVI, the Vaccine Alliance, the United Nations Foundation, the U.S. Centers for Disease Control and Prevention, UNICEF and the World Health Organization (103). Other innovative strategies include using drones to deliver vaccines to remote populations and rural areas (63, 104, 105, 106).

In addition to innovation, it is appropriate to conduct research (e.g. implementation research) on how to improve vaccine coverage among underserved populations. Also, research will help to identify managerial, systems, socio-cultural, financial, and communications bottlenecks which hinder vaccine uptake and coverage in LMICs (70).

Increasing public awareness about the benefits and safety of vaccination will also improve vaccine uptake (63, 107). Suggested approaches to increase public awareness will include community engagement, deploying digital and electronic media (e.g. radio, television, social media handles etc.), regular immunization outreach programs and maternal (as well as paternal) education on the importance of vaccination (63, 70, 107). Finally, adequate and regular training and capacity building are required to improve the knowledge and skills of primary care workers about vaccination (63, 70).

Conclusion

Vaccination is a fundamental human right and a public health investment to create a safer, healthier and more prosperous world. However, many communities in low- and middle-income countries

still lack access to effective vaccination services resulting in considerable childhood morbidity and mortality. Effective strategies and multi-sectoral collaboration are required to surmount the barriers that hinder vaccine coverage in low- and middle-income countries (70). The time to act is now.

List of Abbreviations

BCG:	Bacillus Calmette–Guérin
COVID-19:	coronavirus disease 2019
cVDPVs:	circulating vaccine-derived polioviruses
GAVI:	Global Alliance for Vaccines and Immunisation
GNI:	Gross National Income
Hib:	Haemophilus influenzae type b
HPV:	Human Papilloma Virus
IA2030:	Immunisation Agenda 2030
IPV:	Injectable Polio Vaccine
M&RP:	Measles and Rubella Partnership
mRNA:	messenger Ribonucleic Acid
LMIC:	Low- and Middle-Income Countries
OPV:	Oral Polio Vaccine
PATH:	Program for Appropriate Technology in Health
SDG:	Sustainable Development Goals
UNICEF:	United Nations Children’s Fund
VIPS:	Vaccine Innovation Prioritization Strategy
WASH:	Water, Sanitation and Hygiene
WHO:	World Health Organization

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication

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Availability of data and materials

The articles used in this study are publicly available.

Competing interests

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Authors' contributions

Oll conceptualized, designed the study, and drafted the manuscript.

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