African Journal of Pharmaceutical Research & Development

Vol. 12 No.1; pp. 001-014 (2020)

ROLE OF VACCINES IN PREVENTION OF DISEASES: A REVIEW

ILO CAJETAN ELOCHUKWU, ONYEKA OKORO, PRINCE UNEKWE*, ERIC IRINMWINUWA

Department of Pharmacology and Therapeutics, Faculty of Medicine, College of Health Sciences, Nnamdi Azikiwe University Awka, Nnewi- Campus, Nnewi.

SUMMARY

Vaccines have remained one of the enviable tools available to man in the emerging and re-emerging warfare with pathogens. Vaccines have proven to be effective in immunology and immuno-pharmacology because some diseases which affect human being can now be prevented. Strict adherence to vaccination schedule reduces morbidity and a nation with reduced morbidity and mortality can as well be free of some diseases. Ignorance and poor resources in some countries like Nigeria have continued to hamper the progress in vaccination. The warfare therefore remains a continuum.

KEYWORDS: **Vaccines; Immunity; Antibodies; Antigen disease.**

INTRODUCTION

Vaccine

A vaccine is a biological preparation that provide active acquired immunity to a particular disease-causing microorganism and is often made from weakened or killed forms of the microbe, it's toxins or one of its surface proteins [1]. A product that stimulates a person's immune system to produce immunity to a specific disease, protecting the person from that disease is known as vaccine. Vaccines are usually administered through injections, but can also be administered by mouth or sprayed into the nose [2]. The agent stimulates the body's immune system to recognize the organism as foreign, destroy it and "remembers" it, so that the immune system can more easily recognize and destroy any of the microorganisms that it later encounters [3]. The administration of vaccines is referred to as vaccination. There is overwhelming scientific consensus that vaccines are a very safe and effective way to fight and eradicate infectious diseases [1]. Limitations to their effectiveness nevertheless exist. Sometimes, protection fails because the host's immune system simply does not respond adequately or at all. Lack of response commonly results from clinical factors such as diabetes, steroid use, HIV infection, or age [2]. It also might fail for genetic reasons if the host's immune system includes no strains of B cells that can generate antibodies suited to reacting effectively and binding to the antigens associated with the pathogen. [2] Vaccination is the most effective method of preventing infectious diseases [1]. Widespread immunity due to vaccination is largely responsible for the world wide eradication of smallpox and the restriction of diseases such as polio, measles and tetanus from many parts of the world [4, 5]. Vaccination is the process of administering a vaccine, ie, a biological substance intended to stimulate a recipient's immune system to produce antibodies or to undergo other changes that provide future protection against specific infectious diseases. Vaccination is considered the most successful and cost-effective medical intervention ever introduced [6], and it may be prepared from live modified organisms, inactivated or killed organisms, extracted cellular fractions, toxoids or combination of these forms [7]

***Corresponding author:** Princeunekwe@yahoo.com; +2348037077065*

Modern technology has continued to provide state of the act preparations such as subunit vaccines and recombinant vaccines to stem the tide of rampaging virulent organisms [7]. The mutation and multiple antigenic natures of some of these organisms like plasmodium and human immune deficiency virus have however continued to limit a breakthrough in their vaccination [8].

Type of vaccines

Vaccines may be classified as;

(a) Inactivated vaccine

Some vaccines contain inactivated, but previously virulent, micro-organism that has been destroyed with chemicals, heat, radiation and antibiotics, examples are influenza, cholera, bubonic plaque, polio hepatitis A and rabies vaccines [9,10].

(b) Attenuated vaccine

Some vaccines contain live attenuated microorganism, many of these are active viruses that have been cultivated under conditions that disable their virulent properties or that use closely related but less dangerous organisms to produce a broad immune response. Altogether most attenuated vaccines are viral, some are bacterial in nature, examples include the viral diseases, yellow fever, measles, rubella and mumps, and the bacterial disease typhoid [11, 12, 13].

(c) Toxoid

Toxoid vaccines are made from inactivated toxic compounds that cause illness rather than the microorganism. Examples are tetanus and diphtheria vaccines [14,15]

(d) Protein subunit

Rather than introducing an inactivated or attenuated microorganism to an immune system, a fragment of it can create an immune response. Example include the subunit vaccine against Hepatitis B virus that is composed of only the surface proteins of the virus [16, 15]

(e) Conjugate

Certain bacteria have polysaccharide outer coats that are poorly immunogenic. By linking these outer coats to proteins, the immune system can be led to recognize the polysaccharide as if it is a protein antigen This approach is used in the Haemophilus influenza type B vaccine [17,15].

(f) Valence

Vaccines may be monovalent also called univalent, or multivalent. A monovalent vaccine is designed to immunize against a single antigen or single microorganism. A multivalent vaccine is designed to immunize against two or more strains of the same microorganism, or against two or more microorganisms [18,15].

Mechanism of action of vaccine

Vaccines help to confer immunity by imitating an infection. This type of infection, however, almost never causes illness, but it does cause the immune system to produce T-lymphocytes and once the imitation infection fades, the body is left with a supply of “memory” T-lymphocytes, as well as B-lymphocytes that will remember how to fight that disease in the future [19]. Vaccines also act by conferring immunity to the particular disease by indexing the development of antibodies. There are basically two types of immunity, viz, innate immunity and acquired immunity. Innate immunity develops after actual exposure to the disease organism. Acquired immunity develops after exposure to vaccine action. Acquired immunity may be active or passive immunity. Active immunity is that immunity that develops following exposure to antigenic stimuli, while passive immunity develops after direct injection of antibodies in the form of either sera or immunoglobulin, inside the body [20].

Limitations of vaccines

Many management factors can limit the effectiveness of vaccination. These include nutrition, environmental conditions, exposure to disease and vaccination administration. Protein, energy, minerals and vitamins are all required to develop and maintain a strong immune system [21]. Specific vitamins and minerals associated with optimal immune function include vitamin A, vitamin E, selenium, copper and zinc [22].

Harsh or stressful environmental conditions can have significant detrimental effects on immune functions in addition, crowding and poor sanitation increase the exposure to infectious agents which can overcome even high level of immunity [23]. Two very

common causes of vaccine failure are inappropriate storage and administration [24].

Challenges of vaccination

The challenges which are not insurmountable including wrong attitude and mal-orientation of health workers, poor political commitment, and poor global donor interest in routine immunization [25]. In Nigeria, the National Programme on Immunization (NPI) suffers recurrent setbacks due to many factors including ethnicity and religious beliefs [26].

Prospects of vaccination

The end to malaria infection is insight as the first malaria vaccine candidate to reach phase 3 of clinical testing found to partially protect children against the disease up to four years after vaccination, is available [27].

Benefits of vaccines in health care

(i) Disease eradication

Unless an environmental reservoir exists, an eradicated pathogen cannot re-emerge, unless accidentally or malevolently reintroduced by humans, allowing vaccination or other preventive measures to be discontinued. While eradication may be an ideal goal for an immunization programme, to date only smallpox has been eradicated, allowing discontinuation of routine smallpox immunization globally. Potentially, other infectious diseases with no extra human reservoir can be eradicated provided an effective vaccine and specific diagnostic tests are available. Eradication requires high levels of population immunity in all regions of the world over a prolonged period with adequate surveillance in place. The next disease targeted for eradication is polio, which is still a global challenge. Altogether high coverage with oral polio vaccine (OPV) has eliminated type 2 poliovirus globally, while transmission of type 1 and 3 continues in limited areas in a few countries [28]. Over the years, vaccines have prevented countless cases of disease and disability, and have saved millions of lives. For example, polio, which caused approximately 50,000 cases each year in the U.S., was one of the most dreaded childhood diseases of the 20th century. But through successful vaccination programmes around the world, polio is almost eradicated from the world [29].

(ii) Disease elimination

Disease can be eliminated locally without global eradication of the causative microorganism. In four of six WHO regions, substantial progress has been made in measles eliminations. Transmission no longer occurs indigenously and importation does not result in sustained spread of the virus. Key to this achievement is more than 95% population immunity through a two-dose vaccination regimen. Combined measles, mumps and rubella (MMR) vaccine could also eliminate and eventually eradicate rubella and mumps. Already, elimination of measles from the Americas, and measles, mumps and rubella in Finland has been achieved, providing proof in principle of feasibility of their ultimate global eradication. It may also be possible to eliminate Haemophilus influenzae type b (Hib) disease through well implemented national programmes, as experience in the West. Some diseases that once injured or killed thousands of children, have been eliminated completely and others are close to extinction– primarily due to safe and effective vaccines. Polio is one example of the great impact that vaccines have had in the United States. Polio was once America's most-feared disease, causing death and paralysis across the country, but today, thanks to vaccination, there are no reports of polio in the United States [30]. Local elimination does not remove the danger of reintroduction. For instance, Botswana was polio free since 1991, but re-imported type 1 poliovirus from Nigeria in 2004, also in the United States of America (USA) measles was reintroduced in Indiana in 2005 by a traveler from Romania [31].

(iii) Control of mortality, morbidity and complications

Efficacious vaccines protect individuals if administered before exposure. Pre-exposure vaccination of infants with several antigens is the cornerstone of successful immunization programmes against a cluster of childhood diseases. Vaccine efficacy against invasive Hib disease of more than 90% was demonstrated in European, Native American, Chilean and African children in large clinical studies in the 1990s [30]. Some vaccine preventable diseases can result in prolonged disabilities and can take a financial toll because of lost time at work, medical bills or long-term disability care [30].

In the United Kingdom, no infant given three doses developed Hib disease in the short term (boosters

may be required for long-term protection), and post marketing studies have confirmed the high effectiveness of vaccination of infants against Hib in Germany and Pertussis in Sweden. Many vaccines can also protect when administered after exposure - examples are rabies, hepatitis B, hepatitis A, measles and varicella [32].

Studies [33] estimated that vaccines annually prevent almost 6 million deaths worldwide. In the United State of America, there has been a 99% decrease in incidence for the nine diseases for which vaccines have been recommended, accompanied by a similar decline in mortality and disease sequelae [33]. Complications such as congenital rubella syndrome, liver cirrhosis and cancer caused by chronic hepatitis B infection or neurological lesions secondary to measles or mumps can have a greater long-term impact than the acute disease. Up to 40% of children who survive meningitis due to Hib may have life-long neurological defects.

In field trials, mortality and morbidity reductions were seen for pneumococcal disease in sub-Saharan Africa and rotavirus in Latin America. Specific vaccines have also been used to protect those in greatest need of protection against infectious diseases, such as pregnant women, cancer patients and the immunocompromised [29,33].

(iv) Mitigation of disease severity

Disease may occur in previously vaccinated individuals. Such breakthroughs are either primary - due to vaccine failure - or secondary. In such cases, the disease is usually milder than in the non-vaccinated. In a German efficacy study of a cellular pertussis vaccine, vaccinated individuals who developed whooping cough has a significantly shorter duration of chronic cough than controls [34]. Such findings were confirmed in Senegal [34]. Varicella breakthroughs exhibit little fever, fewer skin lesions and fewer complications than unvaccinated cases. Milder disease in vaccines was also reported for rotavirus vaccine [34].

(v) Prevention of infection

Many vaccines are primarily intended to prevent diseases and do not necessarily protect against infections. Some vaccines protect against infection as well. Hepatitis A vaccine has been shown to be equally efficacious (over 90% protection) against symptomatic disease and asymptomatic infections. Complete prevention of persistent vaccine-type infection has been demonstrated for human papilomavirus ((HPV) vaccine. Such protection is referred to as "sterilizing immunity". Sterilizing immunity may wane in the long term, but protection against disease usually persists because immune memory minimizes the consequences of infection. [35, 29]

(vi) Protection of the unvaccinated population

Efficacious vaccines not only protect the immunized, but can also reduce disease among non-immunized individuals in the community through "indirect effects" or herd protection". Hib vaccine coverage of less than 70% in the Gambia was sufficient to eliminate Hib disease, with similar findings seen in Navajo populations [36]. Another example of herd protection is a measles outbreak among preschool-age children in the USA in which the attack rate decreased faster than coverage increased [36]. Herd protection may also be conferred by vaccines against diarrhea diseases, as has been demonstrated for oral cholera vaccines [36, 37]. "Herd protection" of the unvaccinated occurs when a sufficient proportion of the group is immunized. The decline of disease incidence is greater than the proportion of individuals immunized because vaccination reduces the spread of an infectious agent by reducing the amount and/or duration of pathogen shedding by vaccines, retarding transmission. Herd protection as observed with OPV involves the additional mechanism of "contact immunization" vaccine viruses infect more individuals than those administered vaccine.

The coverage rate necessary to stop transmission depends on the basic reproduction number (R 0), defined as the average number of transmissions expected from a single primary case introduced into a totally susceptible population [36]. Diseases with high R 0 (e.g measles) require higher coverage to attain herd protection than a disease with a lower R 0 (e.g rubella, polio and Hib), Because of herd protection, some diseases can be eliminated without 100% immunization coverage [36].

Source drying is a related concept to herd protection. If a particular subgroup is identified as the reservoir of infection, targeted vaccination will decrease disease in the whole population. In North Queensland, Australia, there was a high incidence of hepatitis A in the indigenous population. Vaccination of indigenous toddlers, with catch-up up to the sixth birthday, had a rapid and dramatic impact in eliminating the disease in the indigenous population and in the much larger non-indigenous population (who were not vaccinated) across the whole of Queensland [36]. Similar approaches have been

very successfully applied in several other larger settings, including Israel and the United State of America [36].The success of source drying justifies vaccination of special occupational groups, such as food handlers, to control typhoid and hepatitis A. Pertussis vaccine boosters for close contacts (such as parents, grandparents, nannies, siblings and baby unit nurses), who are the most common sources of transmission to infants protect those too young to be given primary vaccination with a surrounding "pertussis-free cocoon" [8].

(vii) Prevention of related diseases and cancer

Vaccines will also protect against diseases related to the targeted disease. For example, in Finland, and the United States of America, influenza vaccination has been found protective for acute otitis media in children, with a vaccine efficacy of more than 30% [38]. Measles vaccination protects against multiple complications such as dysentery, bacterial pneumonia, keratomalacia and malnutrition [37]. An entero-toxic *Escherichia coli* vaccine demonstrated protection against diarrhea due to Salmonella enteric [37].

Infective agents cause several cancers. Chronic hepatitis B infection leads to liver cancer. Vaccination against such pathogens should prevent the associated cancer as already observed for hepatocellular carcinoma in Taiwan, China [9]. These results could be replicated in Africa. Reduction of the incidence of cervical cancer is expected with the use of HPV vaccines against serotypes 16 and 18, responsible for over 70% of the global cervical cancer burden, as reduction in precancerous lesions has been demonstrated in vaccines [9]. When patients receive a vaccination for certain diseases, they will also be protected from cancers associated with them. For example, getting a vaccine for hepatitis B can protect people from developing liver cancer and the HPV vaccine reduces the risk of getting cervical cancer.[37]

(viii) Societal and other benefits

(a) Health-care and other savings for society

Immunization programmes require funding for infrastructure (e.g cold-chain maintenance), purchase of vaccines and adequate staffing. However, the mortality and morbidity prevented translates into long-term cost savings and potential economic growth. Globally, the savings from vaccines were estimated to be of the order of tens of billions of US dollars savings [38, 29].

Malaria (for which there are currently several promising vaccines in development) costs sub-Saharan Africa US$ 100 billion worth of lost annual gross domestic product (GDP) [38]. Savings are enhanced if several antigens are delivered in a single vaccine. Combination vaccines bring the added benefit of better compliance, coverage, and injection safety. Introduction of a new antigen is facilitated with combination vaccines, ensuring early high coverage by maintaining previous immunization schedules, without compromising (and sometimes improving) immunogenicity and reactogenicity [9].

When taking into account indirect costs, savings are higher for common diseases with lower mortality and morbidity (such as varicella) than for more severe diseases (such as polio). Indirect costs, such as lost productivity (as well as direct medical costs) have been emphasized by eminent health economists in assessing the full value of vaccination. Immunization programmes, compared to other common public health interventions such as wearing seat-belts and chlorination of drinking water, are a good investment and more cost effective than, for example, advice on smoking cessation. Cost savings will be achieved with the new live-attenuated rotavirus and conjugated pneumococcal vaccines, as well as wider use of hepatitis B and Hib vaccines [38].

(b) Prevention of development of antibiotic resistance

By reducing the need for antibiotics, vaccines may reduce the prevalence and hinder the development of resistant strains. Vaccination directly reduces the incidence of sensitive and resistant infections. It also reduces both appropriate and inappropriate use of antimicrobials by reducing overall disease incidence, including infections caused by susceptible pathogens and by viruses (such as influenza) that are often inappropriately treated with antibiotics. This reduced antimicrobial use further diminishes pressure toward resistance among bystander members of the normal human flora. [39] Introduction of a conjugate pneumococcal vaccine for infants in the USA in 2000 saw a 57% decline in invasive disease caused by penicillin resistant strains and a 59% decline in strains resistant to multiple antibiotics by 2004 across a broad age spectrum: 81% among children under 2 years of age and 49% among persons aged 65 years and older [9]. Vaccines against typhoid can prevent primary

infection and the spread of antibiotic-sensitive as well as multidrug-resistant strains. The development of new vaccines against infectious pathogens where antibiotic resistance is a global threat (e.g. Staphylococcus aureus) is viewed as a better long-term option to control the problem of increasing resistance [9].

(c) Extending life expectancy

Vaccines can increase life expectancy by protecting against disease. Elderly individuals given influenza vaccine in the USA had approximately 20% Chance less of suffering cardiovascular and cerebrovascular disease and 50% lower risk of mortality from all cause compared to their unvaccinated counterparts [39]. In Sweden, administration of polysaccharide pneumococcal vaccine and inactivated influenza vaccine significantly reduced the risk of in-hospital mortality for pneumonia and cardiac failure among elderly persons, with an additive effect when both vaccines had been administered [38,29].

(d) Safe travel and mortality

With global rise in air travel, there is an increased risk of exposure to infectious diseases. Travelers transmit and disseminate disease, as has been observed in the case of polio, ebola, and in the dispersal of meningococcal strains by returning pilgrims from Saudi Arabia. In the case of Muslim Hajj (the largest annual human gathering in the world) local authorities require meningococcal ACWY vaccination and recommend various other vaccinations, such as influenza and hepatitis B, [8]. In our global economy, people are travelling to foreign countries more than ever before. This makes vaccinations extremely important, as foreign travel can put people at risk for a number of different illnesses around the globe [37]. The most common vaccine-preventable disease among travelers are influenza and hepatitis A. Other vaccines to consider for travel include rabies, hepatitis B, cholera, yellow fever, Japanese encephalitis, and measles. Many vaccines can be given in flexible accelerated schedules to ensure early protection. Thus, travelers seeking health advice, even within a few weeks of departure, can travel without vaccine-preventable health risk to themselves and others [8].

(viii) Other public health benefits

In developing countries, vaccination programmes are cornerstone of primary health-care services. The infrastructure and personnel required for an effective and sustainable immunization programme gives opportunities for better primary health- care services, particularly in the critical perinatal and early infancy period [1].

(a) Promoting economic growth

Poor health has been shown to stunt economic growth while good health can promote social development and economic growth. Health is fundamental to economic growth for developing countries and vaccination form the bedrock of their public health programmes. A healthy population is a strong population, and countries where vaccinations are prevalent tend to have stronger economies. [37] The annual return on investment in vaccination has been calculated to be in range of 12% to 18%, but the economic benefits of improved health continue to be largely underestimated [1].

(b) Enhancing equity

The burden of infectious, including vaccine-preventable disease falls disproportionately on the disadvantaged. Vaccines have clear benefit for the disadvantaged. Pneumococcal immunization programmes in the United States of America have at least removed racial and socioeconomic disparities in invasive pneumococcal disease incidence, while in Bangladesh, measles vaccination has enhanced equity between high-and-low socioeconomic groups [18].World Health Organization's Global Vaccine Action Plan 2011–2020 listed equity as one of its six guiding principles, limited evidence assessing the distribution of health benefits of vaccines by socioeconomic strata exists. [40].

(c) Promoting peace

There were at least seven United Nations Children Fund (UNICEF) vaccine-mediated ceasefires during civil conflicts. These conflicts were in diverse part of the world, from Liberia to Afghanistan, where even warring factions saw the benefit of immunization programmes. People were fighting in a terrible war. In November, each fighting side agreed to stop fighting for one week. For seven days there was peace. Both sides had agreed to peace because each side had the same important goal. They wanted health workers to give Afghani children vaccines [41]. During protracted conflict it is possible to ensure that vaccination coverage remains high. This is seen in Sri Lanka, where despite unrest for at least two decades coverage in 2005 for both three doses of diphtheria- tetanus- pertusis vaccine and one dose

of measles vaccine was 99%. The high cost effectiveness and multiple benefits of relatively modest resource investments in immunization contrast starkly with profligate global military expenditures, currently over US$ 1 trillion annually [18].

Status of malaria vaccine development

The complexity of the malaria parasite makes development of a malaria vaccine a very difficult task. Recent progress has been made with the completion of a Phase 3 trial of the RTS,S/AS01 candidate vaccine and review by the European Medicines Agency and WHO. There is currently no commercially available malaria vaccine. Over 20 other vaccine constructs are currently being evaluated in clinical trials or are in advanced preclinical development (Table 1).

The malaria vaccine candidate RTS,S/AS01

RTS,S/AS01 is the most advanced vaccine candidate against the most deadly form of human malaria, *Plasmodium falciparum*. A Phase 3 trial with 15 460 children in seven countries in sub-Saharan Africa (Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and the United Republic of Tanzania) began in May 2009 and has now been completed. There were two age categories in the trial:

(a) children aged 5-17 months at first dose receiving the RTS,S/AS01 vaccine or a comparator vaccine; and
(b) children aged 6-14 weeks at first dose who receive the RTS,S/AS01 vaccine or a comparator vaccine in co-administration with the pentavalent vaccine from the routine immunization schedule.

All children received 3 doses of the vaccine at 1 month intervals. The role of a fourth dose 20 months after the first dose was also evaluated. After review of the study data, the European Medicines Agency issued a positive Scientific Opinion about the risk-benefit balance, upon agreement with the manufacturing company about further research plans as part of Phase 4 evaluation. WHO, upon review of the data, recommended pilot implementation studies to be conducted for further evaluation of implementability of a four dose schedule in children aged 5-17 months at first dose and further evaluation of the risk/benefit profile. A comprehensive WHO Q&A gives further information on the RTS,S/AS01 malaria vaccine implementation programme (MVIP)[43].

Antimalaria vaccines are classified into the following, which includes: pre-erythrocytic stage vaccine, Blood stage vaccine, Transmission-blocking vaccines (TBVs).

Origins of the ebola vaccine

Though the deadly 2014 Ebola outbreak is credited for prompting researchers to create an effective vaccine against the disease, scientists have been working for decades to develop protection from Ebola. According to the *New York Times*, scientists have pursued several ultimately unsuccessful efforts at creating a vaccine since the disease emerged in the former Zaire in 1976. Despite over 1,500 Ebola-related deaths and reports of the devastating symptoms, Ebola vaccination developments stalled time and time again. In fact, by 2005, a group of North American researchers had developed and tested a vaccine that proved completely effective against Ebola in monkeys. Though the scientists suggested a five-year timeline for human testing and product licensing, developments stopped shortly after the initial announcement. Sometimes, the relative rarity of a disease works against it. In this case, because Ebola was considered somewhat rare and its outbreaks relatively limited, neither effort nor funding pushed for the release of the Ebola vaccine.

Ebola outbreak prompts renewed vaccination testing

Until 2014, the Ebola virus had killed an average of fewer than 50 people per year. When the outbreak began to spread in West Africa, however, the number of both reported cases and deaths quickly skyrocketed. As the nearly 30,000 reported cases spread to five African countries and the United States, researchers revisited earlier Ebola research and restarted long-delayed tests and trials. As the *New York Times* reports, the vaccine featured in these tests was the one originally developed by the Public Health Agency of Canada and the United States Army in 2005.

Table 1: Current malaria vaccines under preclinical development or in clinical trials

Parasite stage	Vaccine classification	Current status
Pre-erythrocytic stage		
PfSPZ vaccine	Whole organism (radiation attenuation)	Phase II
GAP vaccines	Whole organism (genetic attenuation)	Phase I
RTS,S	Subunit	Phase IV
CVac	Whole organism (chemical attenuation)	Phase I
Blood stage		
Chemically attenuated parasites	Whole organism	Preclinical
AMA1-RON2	Subunit	Preclinical
PfRH5	Subunit	Phase I
Mosquito stage (TBVs)		
Pfs25	Subunit	Phase I
Pfs230	Subunit	Phase I
Pfs47	Subunit	Preclinical

[44].

Table 2: Putative ebola vaccines

Vaccine	Associated organisations	Status
Chimp adenovirus 3 vectored glycoprotein (cAd3-EBO Z)	GSK & NIAID	Phase III Feb. 2016 [50]
rVSV vectored glycoprotein (VSV-EBOV)	Newlink Genetics & Merck	*in use* [51]
Human adenovirus 5 vectored 2014 glycoprotein insert (Ad5-EBOV)	BIT & CanSino	Phase I complete [52]
Adenovirus 26 vectored glycoprotein / MVA-BN (Ad26.ZEBOV/MVA-BN)	Johnson & Johnson	Phase I complete April, 2016 [53]
HPIV-3 vectored glycoprotein	Ministry of Health (Russia)	Phase I planned 54)
Rabies vectored glycoprotein	Thomas Jefferson University & NIAID	Non-human primate challenge complete [55]
Purified glycoprotein	Protein Sciences	NHP challenge initiated [56]
Ebola ΔVP30 H2O2 treated	University of Wisconsin	Non-human primate challenge complete [57]

According to the *WHO*, vaccination trials took place in Guinea's coastal Basse-Guinée region and included more than 11,000 test subjects, nearly 6,000 of whom received the test vaccine. When testing began in 2015, this area was still experiencing a moderate level of new Ebola cases. To select test subjects, WHO-led researchers monitored the area for new Ebola cases. When one emerged, researchers identified people who had been in close contact with the afflicted patients or their clothing within three weeks prior to diagnosis. On average, these groups numbered about 80 people, with 117 total groups, or rings. Researchers then randomized the rings, with some subjects receiving the vaccine right away or after a three-week delay. Though only adults over 18 received the vaccination at first, positive preliminary results led researchers to administer the vaccine immediately to all subjects over 6 years old. Among those who received the test vaccine, none contracted Ebola 10 or more days afterward. In contrast, 23 people who did not receive t he test vaccine reported cases of Ebola within the same time frame. These results suggest that the vaccine is completely effective against Ebola. Ultimately, the trials reported no long-term effects from the Ebola vaccine. According to *WHO*, about half of the subjects reported mild symptoms like headaches and fatigue, but these dissipated quickly. Just one anaphylaxis reaction emerged from the study, but the subject did not have long-term effects.

Next steps for the Ebola vaccine

Though testing started and finished during the Ebola outbreak in West Africa, lengthy regulatory and licensing processes mean that the vaccine was not available to patients afflicted at that time. However, continued developments mean that the Ebola vaccine may soon be available (Table 2). In the past, limited funding prevented the development process from moving forward, but $5 million in funding from Gavi, the Vaccine Alliance, suggests an optimistic conclusion to the testing process. This funding is designed to help Merck procure the vaccine once WHO approves and recommends it, and Merck has agreed to make 300,000 doses available for emergency use. The pharmaceutical company has also committed to moving forward with the vaccine licensing process by the end of 2017. In addition, further research may be required to provide even more robust Ebola vaccine options. While the vaccine currently under development targets the most common strain of Ebola, five subtypes of the disease exist. The *New York Times* reports that the current vaccine is not effective against all five subtypes, and a comprehensive vaccine based on the existing model would likely cause unacceptable side effects. While the vaccine offers an effective solution now, it may not ultimately eradicate Ebola [44-48].

Ebola vaccination saving lives but challenges remain

More than 111 000 people have been vaccinated in the DRC since the outbreak was declared in August 2018. However, despite the use of a highly efficacious vaccine, the number of new cases continues to rise, in part due to repeated incidents of violence affecting the ability of response teams to immediately identify and create vaccination rings around all people at risk of contracting Ebola [57].

Human immunodeficiency virus (HIV)

Since 1987, hundreds of vaccine candidates have been clinically tested as HIV-1 vaccines (Table 3). However, to date only six HIV-1 vaccine efficacy trials have been completed. Most vaccines work through elicitation of protective antibody responses. Initial vaccine candidates were based on Env glycoproteins and tested in preclinical NHP studies [58], as well as in human safety and immunogenicity trials [60]. Such studies provided critical evidence that Env-based vaccines could be safely administered and were immunogenic in humans and NHPs. Yet, studies in NHPs soon identified a significant flaw in early recombinant Env vaccines. Although the elicited immune responses were protective against homologous challenge infections, they were not protective against heterologous challenge [60]. In 1999, the randomized, double blind, placebo-controlled efficacy trial of AIDSVAX B/E (VAX003) was initiated and involved the enrollment of 2546 injection drug user (IDU) cohort in Thailand. The AIDSVAX B/E vaccine contained two recombinant gp120 HIV Env antigens from a CXCR4 lab-adapted clade B strain and a CCR5 primary subtype CRF01_AE isolate adjuvanted in alum [61]. Despite induction of anti-gp120 antibodies, VAX003 did not provide any protection from infection, with 8.3% in the placebo and 8.4% in the vaccine arm becoming infected [61]. In VAX003, vaccine efficacy was estimated at 0.1%. Another Env-based efficacy

Table 3: Recent and ongoing HIV clinical trials.

Trial ID	Vaccine Description	Category	Phase	Duration
NCT01084343	Virosome (IRIV) expressing lipidated gp41 peptide	Virosome based	I	2009.11–2010.09
RV305	ALVAC-HIV (vCP1521) and/or AIDSVAX gp120 B/E late boost	RV144-related	II	2012.04–2017.05
RV306	ALVAC-HIV (vCP1521) prime, ALVAC-HIV/AIDSVAX gp120 B/E boost	RV144-related	II	2013.09–2017.11
RV328	AIDSVAX gp120 B/E prime and boost	RV144-related	II	2014.07–2018.12
HVTN100	ALVAC-HIV (vCP2438) prime, ALVAC-HIV (vCP2438)/bivalent clade C gp120/MF59 boost	RV144-related	I/II	2015.01–2017.01
HVTN702	ALVAC-HIV (vCP2438) prime, ALVAC-HIV (vCP2438)/bivalent clade C gp120/MF59 boost	RV144-related	IIb/III	2016.10–2021.07
X001	CN54gp140 with GLA-AF	Env immunogens	I	2013.10–2015.11
CR104488/HIV-V-A003/IPCAVD008	Trimeric gp140 with/without aluminum phosphate	Env immunogens	I	2014.12–2016.04
FLSC-001	Full length single chain gp120-CD4 complex vaccine	Env immunogens	I	2015.11–2018.07
CR100965/HIV-V-A002/IPCAVD006	MVA Mosaic HIV in individuals with/without prior Ad26.ENVA.01	Mosaic vaccine	I	2014.09–2015.11
CR106152/HIV-V-A004/IPCAVD009	Ad26 Mosaic HIV prime, Ad26 Mosaic HIV or MVA Mosaic (*env* or *gag-pol*) and/or clade C gp140/aluminum phosphate boost	Mosaic vaccine	I/II	2014.12–2019.04
CR108152/VAC89220HPX2004	Ad26 Mosaic HIV or Ad26 Mosaic4 HIV prime (*env* or *gag-pol*), clade C gp140/aluminum phosphate and Ad26 Mosaic HIV or Ad26 Mosaic4 HIV boost	Mosaic vaccine	II	2016.07–2018.09
CR108068/VAC89220HPX1002	Ad26 Mosaic HIV (*env* or *gag-pol*) with clade C gp140/aluminum phosphate prime and boost	Mosaic vaccine	I	2016.03–2019.01
HVTN 090/NCT01438606	VSV-Indiana HIV *gag* vaccine	Replicating vectors	I	2011.10–2013.01
NCT01989533	Ad4-mgag and Ad4-*env*C150	Replicating vectors	I	2013.11–2020.02
HVTN 110	Ad4-mgag and/or Ad4-*env*C150 prime, AIDSVAX gp120 B/E/aluminum hydroxide boost	Replicating vectors	I	2015.03–2017.02
rcAd001/IAVI R001	RcAd26.Mosaic1.HIV-*env*	Replicating vectors	I	2015.01–2016.06
HVTN076/NCT00955006	VRC-HIVDNA-016-00-VP prime (clade B *gag*, *pol*, *nef*, clade ABC *env*) VRC-	DNA-based	I	2011.05–2013.09

Trial ID	Vaccine Description	Category	Phase	Duration
	HIVADV014-00-VP boost (clade B *gag-pol* and clade ABC *env*)			
HVTN 087	HIV-MAG vaccine with/without IL-12 pDNA adjuvant electroporation prime, VSV HIV *gag* boost	DNA-based	I	2012.05–2014.09
CRO2059	HIV DNA (CN54ENV/ZM6GPN) prime, MVA-/CN54rgp140/GLA-AF adjuvant boost	DNA based	I	2014–2016
HVTN 092	DNA-HIV-PT123 prime with/without NYVAC-HIV-PT1 and NYVAC-HIV-PT4 Boost	DNA-based	I	2013.04–2014.09
HIV-CORE 004/IAVI N004	Ad35-GRIN/MVA.HIVconsv with/without pSG2. HIVconsv DNA with/without electroporation	DNA-based	I/II	2014.03–2015.08
HVTN 106	DNA Nat-B *env* or DNA CON-S *env* or DNA Mosaic *env* prime, MVA-CMDR boost	DNA-based	I	2015.01–2020.09
HVTN 098	PENNVAX®-GP HIV-1 DNA (*gag*, *pol*, *env*) vaccine with electroporation with/without IL-12 DNA adjuvant	DNA-based	I	2015.04–2016.08
CUTHIVAC002	HIV DNA-C CN54*env* prime with and without electroporation, CN54gp140 boost	DNA-based	I	2015.11–2017.04
VRI01	LIPO-5 or MVA HIV-B LIPO-5 or MVA HIV-B or GTU-Multi HIV B prime and LIPO-5 or MVA HIV-B boost	Lipopeptides	I/II	2014.03–2016.03

Some of the current ongoing and recently completed human clinical trials are shown. Note: This is not a complete list. Ad = Adenovirus; CN = Chinese; CUTHIVAC = Cutaneous and Mucosal HIV Vaccination; Env = viral envelope; FLSC = full-length single chain; GLA-AF = glucopyranosyl lipid adjuvant–aqueous formulation; GP = glycoprotein; HVTN = HIV Vaccine Trials Network; IAVI = International AIDS Vaccine Initiative; IPCAVD = Integrated Preclinical/Clinical AIDS Vaccine Development Program; MVA = modified vaccinia virus Ankara; NCT = National Clinical Trials identifier; vCP = canarypox vector; VRC = Vaccine Research Centre (USA); VRI = Vaccine Research Institute.

trial named VAX004 was a randomized, double blind, test of AIDSVAX B/B. This formulation was the first phase 3, placebo-controlled efficacy study against HIV acquisition and contained subtype B recombinant gp120 in alum. VAX004 was administered to 5403 men who have sex with men (MSM) and women at high risk of infection in North America and the Netherlands [63]. Despite inducing neutralizing and CD4 blocking antibody in all vaccines, HIV seroconversion rates were 6.7% in the vaccine arm and 7% in the placebo arm, with overall vaccine efficacy estimated at 6% [63]. In short, despite being immunogenic, VAX003 and VAX004 recombinant Env-based vaccines failed to demonstrate any level of protection from infection. In contrast to the previous disappointing Env-based efficacy trials, the STEP (HIV Vaccine Trials Network 502, HVTN502) and Phambili (HVTN503) trials were designed to elicit cellular immune responses.[63].

The STEP study was a phase II, double-blind, randomized, placebo-controlled trial using the MRKAd5 HIV-1 Gag/Pol/Nef vaccine in high-risk of infection, HIV-1 seronegative women and MSM [65]. This multicenter trial enrolled 3000 individuals with study sites in North America, the Caribbean, South America, and Australia [64]. The closely related phase II Phambili trial involved MRKAd5 clade B Gag/Pol/Nef administered to 801 of a scheduled 3000 heterosexual men and women in South Africa [64]. Although both vaccines were immunogenic and well tolerated, an exploratory multivariate interim analysis from the STEP trial revealed an alarming increased incidence of HIV-1 acquisition in male vaccinees versus placebo recipients who had adenoviral seropositivity, the STEP trial MRKAd5 HIV-1 Gag/Pol/Nef also failed (Genetic impact of vaccination on breakthrough HIV-1 sequences from the STEP trial[65].

CONCLUSIONS

The benefits of vaccination extend beyond prevention of specific diseases in individuals. They enable a rich, multifaceted harvest for societies and nations. Vaccination makes good economic sense, and meets the need to care for the weakest members of societies. Reducing global child mortality by facilitating universal access to safe vaccine of proven efficacy is a moral obligation for the international community as it is a human right for every individual to have opportunity to a healthier and fuller life. Achievements of the Millennium Development Goal (two-third reduction in 1990 under-5 child mortality by 2015) will be greatly advanced by, and unlikely to be achieved without, expanded and timely global access to key life-saving immunization such as measles, Hib rotavirus and pneumococcal vaccines. A comprehensive vaccination programme is a cornerstone of good public health and will reduce inequities and poverty.

REFERENCES

1. CDC frame work for preventing infectious disease, 2011.
2. National Center for Immunization and Respiratory Diseases 2018.
3. WHO. Vaccine safety basis. Proceedings of the National Academy of Science of the United States of America 9(34), 2015: 12313-12319.
4. WHO. Global Vaccine Action Plan 2012. 20111-2020 Geneva.
5. Nieburg P & Mclaren NM. Role of vaccines and immunization programs in Global Disease Control. Washington D.C. Center for strategic and international studies; *A report of the CSIS Global Health Policy Center*. 2015.
6. Berkeley S. improving access to vaccine through tiered piercing. Lancet 383, 2018: :2256-2267.
7. Tagbo BN, Uleanya ND, Nwokoye IC, Omotowo IB. Mother's knowledge, perception and practice of immunization in Enugu, *Nigeria Journal of Pediatric* 39, 2013, 90-96.
8. Abdulraheem IS, Onajole AF, Jimohaag, Oladipo AK, Reasons for incomplete vaccination and factors for missed opportunities among rural Nigeria Children. *Journal of Public Health Epidermiology 93,* 2011*;* 194-203.
9. Shapiro CG, Kendrick P, Grace E. Pertussis vaccines emerging infectious; *Journal of medicine,* 339(4), 2010; 209-215.
10. "Types of Vaccines". Archived from the original on 2017. Retrieved October 19, 2017.
11. Pliaka V, Kyriakopoulou D, Markoulatos P. Risk associated with the use of live attenuated vaccine poliovirus strain and the strategies for control and eradication of paralytic poliomyelitis. *Expert review of Vaccine*, 5, 2012; 609-623.
12. Rappouli R. Vaccine science, health and longevity. *Proceedings of the National Academy of Science of the United State of America*, 111 (34), 2014; 12282.
13. Sinha JK, Bhattacharya S. A Text Book of Immunology (Google Book Preview). Academic Publishers.2014. p. 318. ISBN 978-81-89781-09-5. Retrieved 2014-01-09.

14. Oyston P & Robinson K. The current challenges for vaccine development. *Journal of Medical Microbiology* 61, 2012; 889-894.
15. Different Types of Vaccines | History of Vaccines". www.historyofvaccines.org. Retrieved 2019-05-03.
16. Low N. Efficacy of tetravalent dengue vaccine in children in Latin America. *The new England Journal of Medicine.* 312, 2015: 113-123.
17. Bonten MJM. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *The New England Journal of Medicine.* 372, 2015; 14-25.
18. Edwards KM, Decker MD. Pertusis vaccine, 6th Edition Elsevier, 2013; Philadephia pp 427-482.
19. www.cdc.gov/vaccines/conversations, 2018.
20. Singa JK, Bhattaehaya S. A text book of immunology.2016; Academic publishers, p 318.
21. Neighmund, Patti. Adapting vaccines for our aging immune system, Morning edition (NPR). 2010.
22. Bello RH, Obok E, Olabode HOK. Sero-prevalence and risk factors associated with hepatitis B surface antigen. *Public Health Epidemiology*, 3, 2016;444-453.
23. Pediatric Association of Nigeria. recommended routine immunization schedule for Nigeria Children. *Nigeria Journal of Pediatrics,* 39(4), 2012; 152-158.
24. Australian Academy of Science. The science of immunization Question and Answers Canberra: Cosmos media limited, pp 1-19. 2012.
25. Tagbo BN. Achieving polio eradication in Nigeria; prospects and challenges, Nigeria *Journal of Pediatrics,* 40(1), 2017; 15-23.
26. Endurance A. Ophori , Musa Y. Tula , Azuka V. Azih1, Rachel O and Precious E. Current Trends of Immunization in Nigeria: Prospect and Challenges. *Tropical Medicine and Health,* 42 (2), 2014: 67–75.
27. Alley O. Four-year Efficacy of RTS, S/ASOIE and its interaction with malaria exposure. *The New England Journal of Medicine,* 368, 2018;11-20.
28. Folb PI, Bernastokwa E, Chen R, Clemens J, Dodoo AN, Ellenberg SS. A global perspective on vaccine safety and public health: The global advisory committee on vaccine safety. *American Journal on Public Health,* 94, 2019: 1926-2276.
29. Every Child By Two / Vaccinate Your Family 2019.
30. (http://www.cdc.gov/vaccines 2018).
31. Muller CP, Kremer JR, Best JM, Durado I, Triki H, Reef S. World Health Organization Steering Committee for Measles and Rubella. Reducing global disease burden of measles and rubella: *Vaccine,* 25, 2016:1-9.
32. Peltola H, Davidkin I, Paunio M, Valle M, Leinikki P, Heinonen OP. Mumps and rubella elimination from Finland. *Journal American Medical Association,* 284, 2019: 2643-2647.
33. Ehret J. The global value of vaccination. *Vaccine,* 21, 2013: 596-600.
34. Preziosi M-P, Halloran ME. Effect of pertussis vaccination on disease: vaccine efficacy in reducing clinical severity. *Clinical Infection Disease,* 37 2013: 772-779.
35. Kallen KJ. A novel, descriptive vaccination technology; self-adjuvant Active vaccines. *Human Vaccines and Immunotherapeutics,.* 9(10), 2018; 2263- 2276.
36. Ali M, Emch M, Seidlen L, Yunus M, Sack D, Rao M. Herd immunity conferred by killed oral cholera vaccines in Bangladesh. *Lancet,* 366, 2019: 44-9.
37. Marijoyce IN, Communicable Disease Emergency Response Branch of the California Department of Public Health as an Ebola Returning Traveler Epidemiologist, 2019.
38. Maclannan CA & Saul A. Vaccine against poverty. *Proceedings of The National Academy of Science of United State of America,* 111, 2014*;* 12307-12312.
39. Kennedy DA, Read AF Why the evolution of vaccine resistance is less of a concern than evolution of drug resistance*. Proceedings of The National Academy of Science of United State of America,* 115, *2018:*12878–12886.
40. Angela Y. Chang C, Riumallo-Herl NA. Perales The Equity, Impact Vaccines May Have on Averting Deaths and Medical Impoverishment In Developing Countries. Health Affairs 37, No. 2, 2018.
41. (www.radioenglish.net. 2018).
42. www.who.int.>immunization>research>development>malaria>en
43. Camila HC, Justin YA, Doritchamou, Irfan Z, and Patrick ED. Advances in malaria vaccine development: report from the 2017 malaria vaccine symposium 2017;10.1038/s41541-017-0035-3.
44. http://www.who.int/features/2017/ebola-guinea-photos/en/

45. http://www.who.int/mediacentre/news/releases/2016/ebola-vaccine-results/en/
46. https://www.nytimes.com/2016/12/22/health/ebola-vaccine.html
47. https://www.nytimes.com/2014/10/24/health/without-lucrative-market-potential-ebola-vaccine-was-shelved-for-years.html
48. https://www.nature.com/news/ebola-vaccine-approved-for-use-in-ongoing-outbreak-1.22024
49. Pavot V. "Ebola virus vaccines: Where do we stand?". *Clinical Immunology,* 173, 2016: 44–49.
50. WHO coordinating vaccination of contacts to contain Ebola flare-up in Guinea". *World Health Organization.* 2016.
51. Hu FC, Hou LH, Li JX, Wu SP, Liu P, Zhang GR. "Safety and immunogenicity of a novel recombinant adenovirus type-5 vector-based Ebola vaccine in healthy adults in China: preliminary report of a randomised, double-blind, placebo-controlled, phase 1 trial". *Lancet*. 385 (9984), 2015: 2272–2279.
52. Clinical trial number NCT02313077 for "A Safety and Immunogenicity Study of Heterologous Prime-Boost Ebola Vaccine Regimens in Healthy Participants" at ClinicalTrials.gov
53. Ebola vaccines, therapies, and diagnostics". World Health Organization *(WHO). 6 July 2015. Retrieved 10 September 2015*.
54. Blaney JE, Marzi A, Willet M, Papaneri AB, Wirblich C, Feldmann F. "Antibody quality and protection from lethal Ebola virus challenge in nonhuman primates immunized with rabies virus based bivalent vaccine". PLoS Pathogens. 9 (5), 2015: e1003389.
55. CT lab hopes to stop spread of Ebola". *3 March 2015. Retrieved 10 September 2015.*
56. Marzi A, Halfmann P, Hill-Batorski L, Feldmann F, Shupert WL, Neumann G. "Vaccines. An Ebola whole-virus vaccine is protective in nonhuman primates". Science, 348 (6233), 2015; 439–442.
57. www.who.int/news-room/detail/07-05-2019-who-adapts-ebola-vaccination-strategy-in-the-democratic-republic-of-the-congo-to-account-for-insecurity-and-community-feedback
58. Berman PW, Murthy KK, Wrin T, Vennari JC, Cobb EK, Eastman DJ, Champe M, Nakamura GR, Davison D, Powell MF. Protection of MN-rgp120-immunized chimpanzees from heterologous infection with a primary isolate of human immunodeficiency virus type 1. *Journal of Infectious Disease,* 173, 1996:52–59.
59. Pitisuttithum P, Nitayaphan S, Thongcharoen P, Khamboonruang C, Kim J, de Souza M, Chuenchitra T, Garner RP, Thapinta D, Polonis V. Safety and immunogenicity of combinations of recombinant subtype E and B human immunodeficiency virus type 1 envelope glycoprotein 120 vaccines in healthy Thai adults. *Journal of Infectious Disease,* 188, 2003;219–227.
60. Stott EJ, Almond N, Kent K, Walker B, Hull R, Rose J, Silvera P, Sangster R, Corcoran T, Lines J. Evaluation of a candidate human immunodeficiency virus type 1 (HIV-1) vaccine in macaques: Effect of vaccination with HIV-1 gp120 on subsequent challenge with heterologous simian immunodeficiency virus-HIV-1 chimeric virus. Part 3. *Journal of General Virology*, 79, 1998:423–432.
61. Pitisuttithum P, Gilbert P, Gurwith M, Heyward W, Martin M, van Griensven F, Hu D, Tappero JW, Choopanya K, Bangkok Vaccine Evaluation G. Randomized, double-blind, placebo-controlled efficacy trial of a bivalent recombinant glycoprotein 120 HIV-1 vaccine among injection drug users in Bangkok, Thailand. *Journal of Infectious Disease*, 194, 2006:1661–1671.
62. Flynn N.M., Forthal D.N., Harro C.D., Judson F.N., Mayer K.H., Para M.F., rgp120 HIV Vaccine Study Group Placebo-controlled phase 3 trial of a recombinant glycoprotein 120 vaccine to prevent HIV-1 infection. *Journal of Infectious Disease*, 191, 2005: 654–665.
63. Buchbinder SP, Mehrotra DV, Duerr A, Fitzgerald DW, Mogg R, Li D, Gilbert PB, Lama JR, Marmor M, Del Rio C. Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): A double-blind, randomised, placebo-controlled, test-of-concept trial. *Lancet.* 372, 2008:1881–1893.
64. Gray GE, Allen M, Moodie Z, Churchyard G, Bekker LG, Nchabeleng M, Mlisana K, Metch B, de Bruyn G, Latka MH. Safety and efficacy of the HVTN 503/Phambili study of a clade-B- based HIV-1 vaccine in South Africa: A double- blind, randomised, placebo-controlled test-of- concept phase 2b study. *Lancet Infectious Disease,* 11, 2011: 507–515.