IAVI VACCINE LITERACY LIBRARY

2022

iavi

Translating **science** into **global** health impact

About IAVI

IAVI is a non-profit scientific research organization dedicated to addressing urgent, unmet global health challenges including HIV, tuberculosis, and emerging infectious diseases. Its mission is to translate scientific discoveries into affordable, globally accessible public health solutions.

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As of April 2022

Abbreviations

AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
APC	Antigen-presenting cell
BCG	Bacillus of Calmette and Guerin
CAB	Community advisory board
CBO	Community-based organisation
CD	Cluster of differentiation
CDC	Centers for Disease Control and Prevention
CEPI	Coalition for Epidemic Preparedness Innovations
COVID-19	Coronavirus Disease 2019
CRF	Circulating recombinant forms
CTL	Cytotoxic T lymphocyte
DNA	Deoxyribonucleic acid
DOT	Directly observed therapy
EMA	European Medicines Agency
ERC	Ethics Review Committee
FDA	U.S. Food and Drug Administration
GCLP	Good Clinical Laboratory Practice
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IGRA	Interferon-gamma release assays
IRB	Institutional Review Board
LASV	Lassa virus
LMIC	Low- to middle-income countries
LTBI	Latent tuberculosis infecton
MDR-TB	Multidrug-resistant tuberculosis
M.tb	Mycobacterium tuberculosis
NAT	Nucleic acid test
NGO	Non-governmental organisation
NK	Natural killer cells
NP	Nucleoprotein
NRA	National Regulatory Authority
POD	Prevention of disease
POI	Prevention of infection
POR	Prevention of reinfection
RNA	Ribonucleic acid
SAE	Serious adverse event
SAHPRA	South African Health Products Regulatory Authority
TB	Tuberculosis
TPP	Target product profile
TST	Tuberculin skin test
UNAIDS	Joint United Nations Programme on HIV/AIDS
VISP	Vaccine-induced seropositivity
VL	Viral load
VMMC	Voluntary medical male circumcision
WHO	World Health Organization
XDR-TB	Extensively drug-resistant TB

Introduction

The **IAVI Vaccine Literacy Library** contains basic information about HIV, TB, and Lassa virus vaccines, explained in simple language and in a user-friendly format. The text is divided into eight modules covering a range of topics, from basic science and clinical trials to social and ethical issues related to vaccine development and testing, as well as future access to and use of vaccines. The resource also includes a list of abbreviations used and a glossary with definitions of key terms.

Audience

The **IAVI Vaccine Literacy Library** is targeted to a broad range of stakeholders involved in HIV, TB, and Lassa virus vaccine-related work. While all the modules can be adapted for use at the local community level, they are generally written for individuals who provide education and information related to HIV, TB and Lassa virus.

Use of the IAVI Vaccine Literacy Library

The **IAVI Vaccine Literacy Library** is meant for use by individuals and organisations that are providing education and information related to HIV, TB and Lassa virus vaccine research and development.

Groups that may use this material include, but are not limited to:

- Clinical vaccine trial site staff.
- Non-Governmental Organisation (NGO) staff, to incorporate vaccine messages into their existing work.
- Medical professionals or institutions, to provide vaccine information to patients or to incorporate into advocacy efforts.
- Health Centres, to provide clients with vaccine information.
- Academic or religious leaders, to provide information and/or informed advice.
- Community Advisory Boards.

The **IAVI Vaccine Literacy Library** is designed for multiple uses to serve a variety of needs. For certain audiences, it may be used as reference information, such as background reading for training workshops. It can also be used as a reference document to develop educational materials or tools, or to incorporate vaccine information into existing tools, such as:

- Fact sheets on specific vaccine topics.
- Brochures to be given to potential vaccine trial participants.
- Informational videos to be shown in community settings.
- Street plays to be performed in community settings.
- Radio programmes.

The **IAVI Vaccine Literacy Library** can also be used directly for recruitment of trial participants or may be used to engage communities or national-level stakeholders to build understanding of and support for clinical trials and an eventual vaccine.

Using and Navigating the Core Content

The **IAVI Vaccine Literacy Library** is divided into eight modules covering a range of topics, from basic science and clinical trials to social and ethical issues related to vaccine development and testing, as well as future access and use.

Each module can be read and used as a standalone document.

Certain issues or concepts are covered in more than one module. These "cross-cutting issues" are cross referenced to other modules in capitalised text. All scientific and technical terms are defined in a comprehensive glossary that provides definitions for technical and scientific terms and expressions.

Acknowledgement of IAVI and Materials Review

As described, the **IAVI Vaccine Literacy Library** is designed primarily as a reference on HIV, TB, and Lassa virus vaccines that can be used to develop or adapt materials or messages.

If IAVI has not been involved in production of materials or tools based on the **IAVI Vaccine Literacy Library**, no review by IAVI is required. IAVI does request that appropriate acknowledgement of the **IAVI Vaccine Literacy Library** be given, but the IAVI logo should not be used.

IAVI requests that it be notified of any tools or materials produced, in order that they be added to the **IAVI Vaccine Resource Library**, which is a public resource serving the entire HIV, TB, and Lassa virus-vaccine field. Proper credit will be given for all resources included in the **IAVI Vaccine Literacy Library**.

Disclaimer

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How to Cite the IAVI Vaccine Literacy Library

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MODULE 4:
INTRODUCTION TO VACCINES

MODULE 4

INTRODUCTION TO VACCINES

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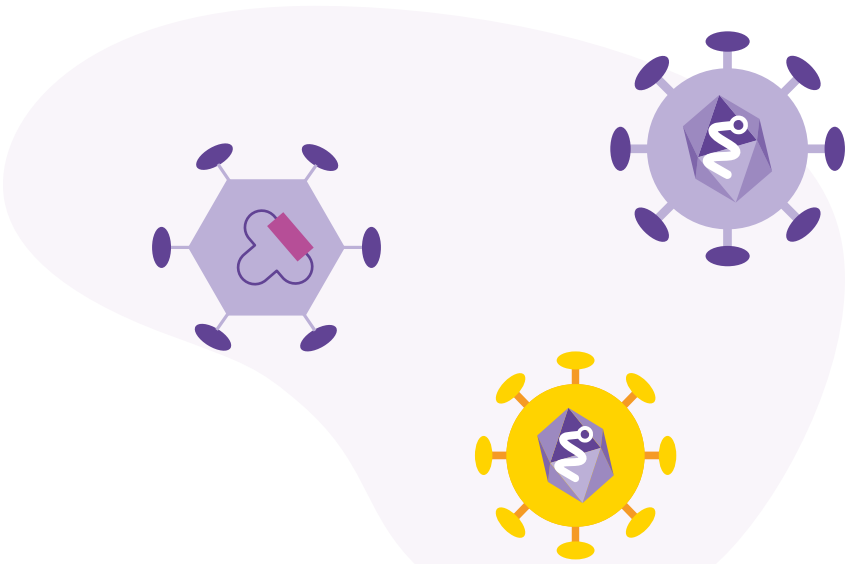


Summary Points

- Vaccines work and save lives.
- Vaccines 'teach' the immune system how to defend itself against a disease-causing agent, known as a pathogen.
- Vaccine efficacy refers to how well a vaccine protects against disease or infection when it is tested in a large trial in humans; vaccine effectiveness refers to how well a vaccine reduces the risk of infection once it is used in the overall population.
- No existing vaccine works in all people all the time. It is possible for a vaccine to be less than 100% effective and therefore it will not eliminate the risk of infection. However, this vaccine may still be beneficial in reducing the burden of an epidemic at population level.
- Traditionally, vaccines are used to prevent illness. Therapeutic vaccines are also being developed that can help fight disease after infection has taken hold.

1. Key Definitions and Concepts of Vaccinology

1.1 What is a Vaccine?

A vaccine is a biological product that is introduced into the body to trigger an immune response to prevent infection or to control a disease caused by a virus, bacteria, or parasite (these are called 'pathogens').

A vaccine 'teaches' the body how to defend itself against a pathogen. It can contain all or a part of the pathogen, produced synthetically, or derived from the pathogen and known as an 'antigen.' Vaccines can be introduced into the body by different ways, such as injection into the muscle (intramuscular); into or under the skin (intradermal or subcutaneous); application to the skin (transdermal); application to the inside of the nose (nasal); or by being swallowed (oral).

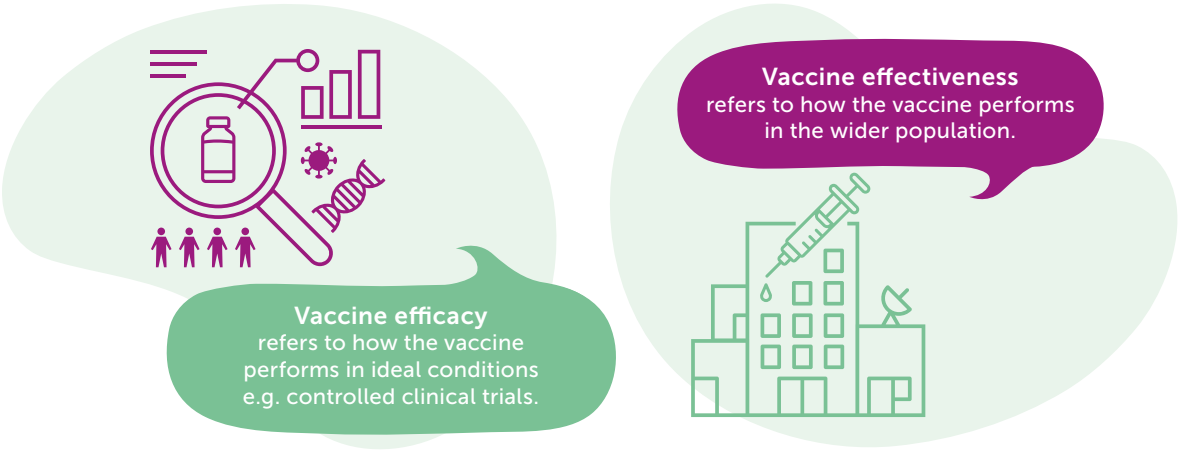
Vaccines have been successfully used for decades to prevent many diseases in humans (and in animals). A few well-known examples are polio, tetanus, and measles vaccines, but there are many others. Each vaccine is designed to protect against a specific disease, but can be combined into one jab with other vaccines, for example the vaccine for diphtheria, pertussis (whooping cough), and tetanus (called DTP). In some cases, the immune response triggered by a vaccine can also target a pathogen not specifically targeted by the vaccine itself; this is called cross-reactivity. A vaccine can then offer protection against a related pathogen; this is called cross-protection.

Every available vaccine has gone through animal and human testing to prove that it is safe and effective for use in humans. For more information on how vaccines are tested, see **MODULE 5**.

1.2 Adjuvants

A vaccine typically contains only a small part of the pathogen it is designed to fight. To ensure a strong immune response is triggered, an adjuvant can be added to the vaccine to increase the body's immune response. Like vaccines, adjuvants are tested in clinical trials for safety and efficacy.

1.3 Efficacy and Effectiveness

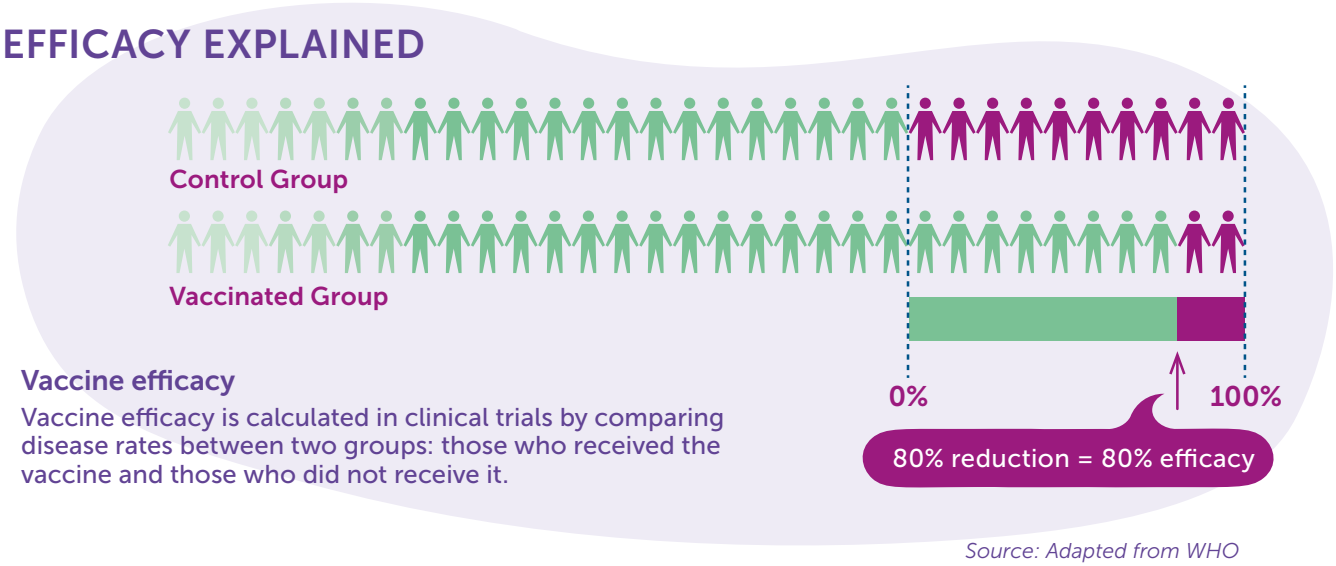


Source: Adapted from WHO

1.3.1 Efficacy

A vaccine's efficacy refers to the rate of protection from infection and/or disease under optimal clinical trial conditions.

Efficacy is measured in a Phase IIb or Phase III clinical trial and is calculated by comparing the number of people who got the vaccine and developed the 'outcome of interest' (usually disease or infection) to the number of people who did not get the vaccine (usually a Control group, or dummy vaccine) and developed the same 'outcome of interest' over a period of time.

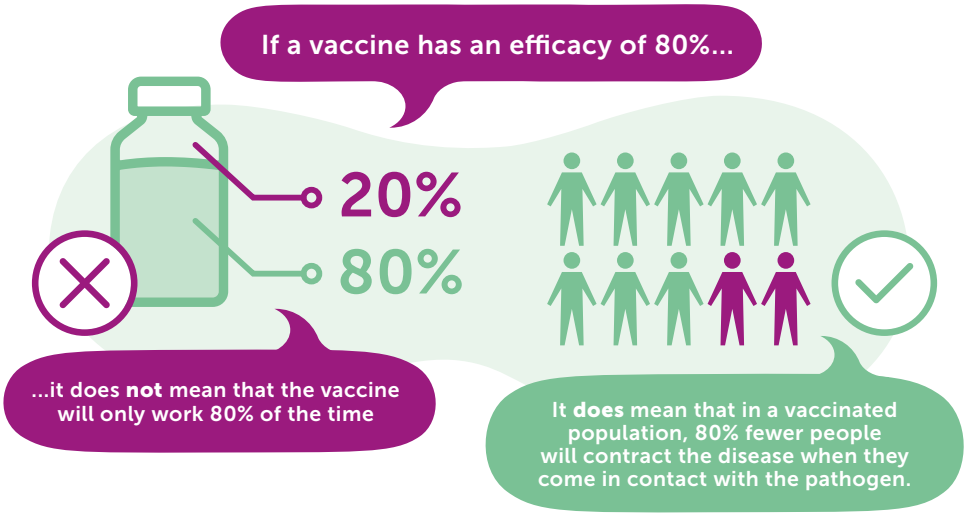


Source: Adapted from WHO

If there is less infection or disease in the vaccine group, the vaccine is said to have efficacy or to be efficacious. This process is not a simple calculation and requires the use of statistical methods to ensure the result observed did not happen just by chance.

No vaccine is 100% protective. Some vaccines, like the hepatitis B vaccine, have an efficacy of over 95% if all three doses are given, and this protection can last for up to 10 years. Some vaccines do not protect as many people against disease but may still be able to stop a disease from spreading.

People who are vaccinated may also be less likely to pass on the infectious pathogen to others, so protection can be greater for the group. This is described as herd immunity (see **1.3.3**).



After a vaccine has been proven to work in a clinical trial, it is still important to find out how well it works when given to people of different ages, people whose immune systems are not strong, and people with chronic diseases, malnutrition, etc. It also is important to find out how long the protection lasts.

1.3.2 Effectiveness

Effectiveness describes how well the vaccine works at reducing the number of infections or disease progression in the general population when used in the real world. This depends on the efficacy as defined in clinical trials and characteristics of the population in which the vaccine is used, including how many people get vaccinated, as well as whether they complete their full series of vaccinations.

1.3.3 Herd Immunity

It is important for all eligible people to receive vaccines that are licensed and available in their communities. When many people in a community are vaccinated against a disease, even those who are not vaccinated in that community may also get some protection because of a phenomenon called herd immunity.

If enough people in the community are vaccinated, there is less chance of the infection spreading from person to person, and unvaccinated individuals may be less likely to get infected because there is a lower risk of exposure. For example, measles and rubella vaccines protect vaccinated people and also cut down on spread of the disease to people who are not infected. However, if too many people choose not to be vaccinated, the community will not acquire 'herd immunity.'

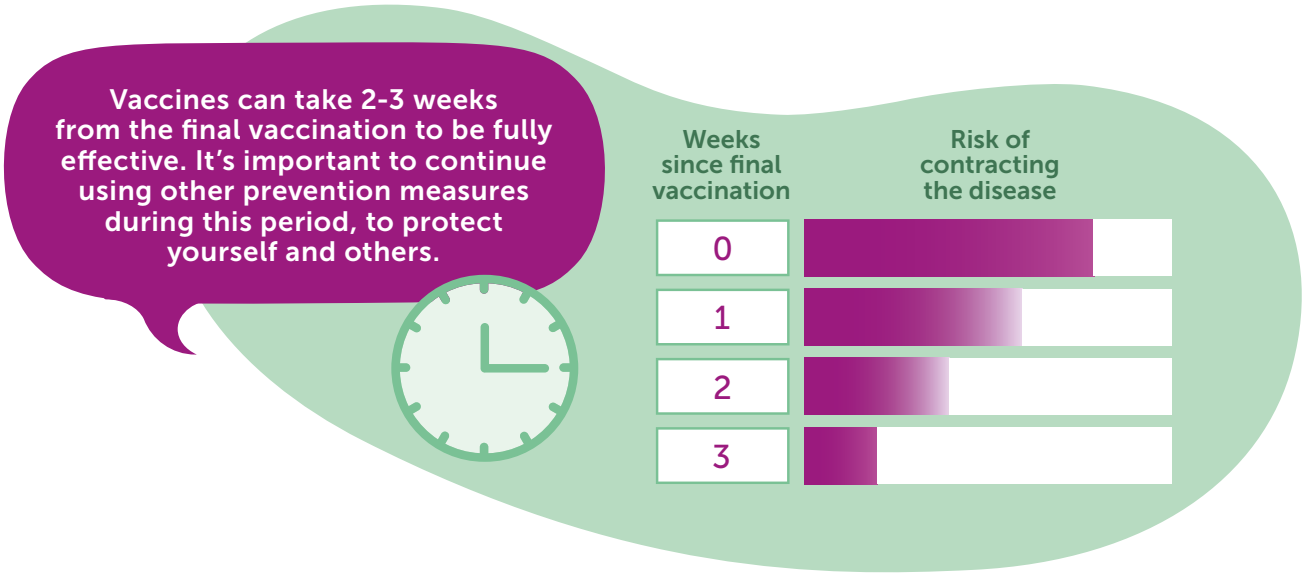
Source: Adapted from WHO

2. How Vaccines Work

The following steps outline how a preventive vaccine protects an individual from infection or disease (for a more complete explanation see **MODULE 3**):

1. Vaccines typically introduce a small piece of the pathogen or a non-harmful version of it, called the antigen, into the body. The immune system mounts an adaptive immune response against the antigen by making antibodies (humoral immunity), killer cells (cellular immunity), or both.
2. B cells and T cells of the immune system cooperate in the immune response.
3. Antibodies, produced by B cells, attach to the pathogen (binding and neutralising antibodies) rendering it harmless and preventing it from infecting more cells.
4. Some T cells help with the production of antibodies. Some T cells ('killer' T cells) attack and kill cells that have been infected with the pathogen.
5. The immune system also makes memory B cells and memory T cells. When the pathogen is encountered, the immune system is primed and immediately recognises and remembers it and mounts a much larger and quicker response than it would have if the person had never received the vaccine. This process is called 'immune memory.'

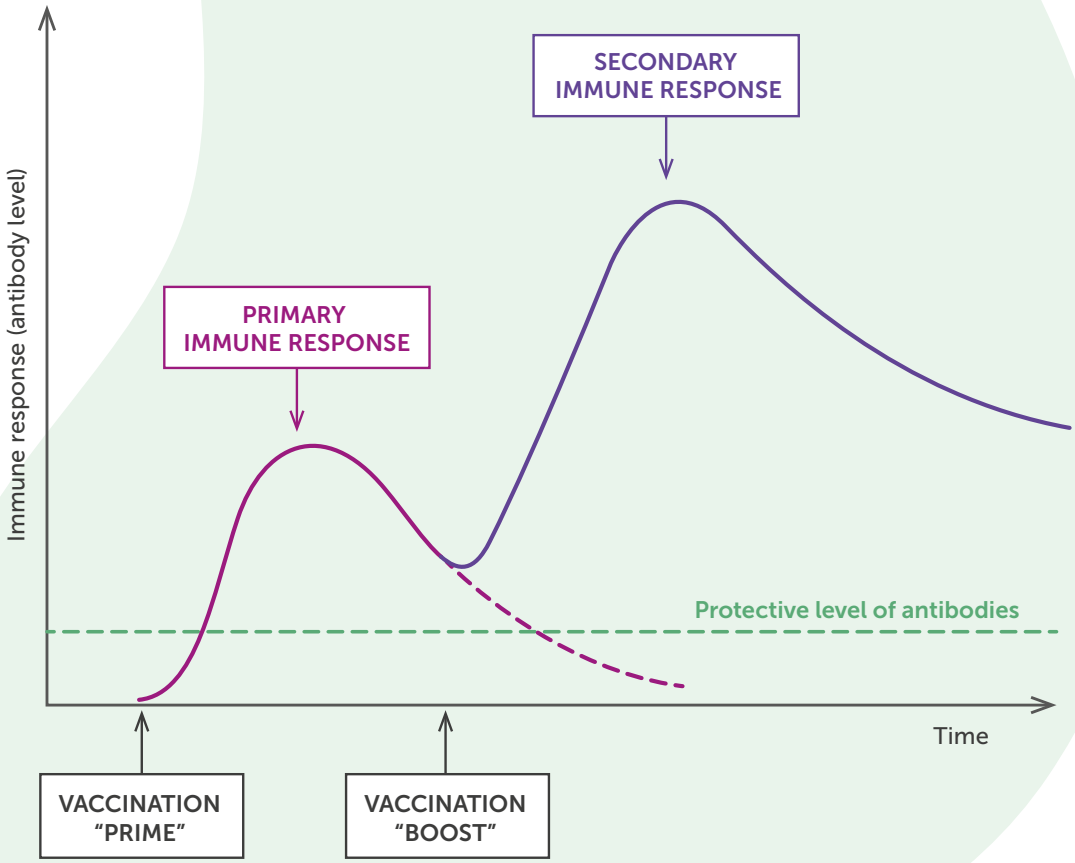
It takes time for the body to mount an effective immune response. Some vaccines require multiple doses to be given over a period of time. The first dose typically only provides partial protection, the second dose ('booster') increases that protection and further doses may be needed on a regular basis to maintain the immune response.



Source: Adapted from WHO

‘Prime-boost’

A series of immunisations meant to ‘prime’ or prepare the immune system with the first vaccination and ‘boost’ the immune response with the next vaccination(s). The same or different types of vaccine may be used for the prime and boost.



Most vaccines aim to prevent infection by a pathogen. However, vaccines can also prevent the development and progression of a disease. In some cases, for example COVID-19 vaccines and the BCG vaccine, they can reduce both the risk of infection and the severity of the disease. Vaccines that reduce the severity of the disease are especially important in the control of epidemics, as we have seen with COVID-19.

Traditional vaccines are preventive vaccines. They are intended for people who have not yet been infected and prepare the immune system to respond in case of future exposure to the pathogen. Common examples include polio, measles, hepatitis B, and tetanus vaccines. All vaccines currently available throughout the world are preventive vaccines, although a few can work if given immediately after exposure (such as a rabies vaccine given right after a dog bite or a tetanus 'booster' vaccine given after an injury provided that the patient has been vaccinated before and has immune memory).

Scientists believe that another way a vaccine might work would be to start an immune response after a person has been infected; this would be called a therapeutic, or 'treatment,' vaccine.

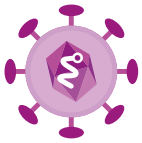
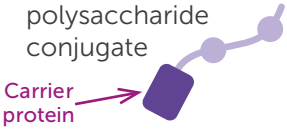
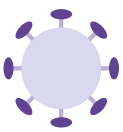
Characteristics of an ideal preventive vaccine

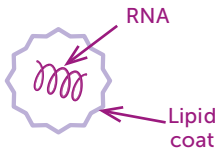
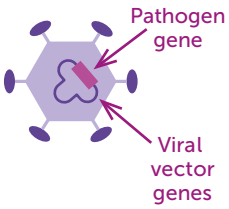
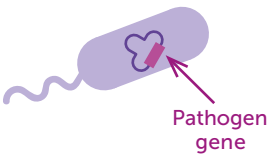
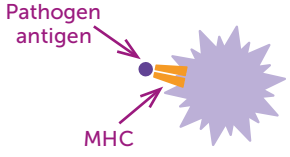
- **Safe** – does not cause any serious side effects.
- **Efficacious** – people who are vaccinated have significantly lower risk of infections or disease.
- **Available** – should be able to be produced in large quantities and be deliverable to everyone who needs it.
- **Effective** – must decrease the incidence of the disease in the general population.
- **Durable** – can last for a long time in various conditions or environments.
- **Accessible** – should effectively reach the populations in need quickly and easily.
- **Affordable** – should be affordable by governments or individuals who need it most.

3. Vaccine Platforms

There are many different types of vaccines, based on how they can produce immune responses.

It is important to distinguish between traditional 'live attenuated' vaccines (see **BOX**) from those that contain only components of a pathogen or 'whole-killed' vaccines. New vaccines developed over the past few decades include viral vectors, nucleic acid-based RNA and DNA vaccines, and virus-like particles.

Types of vaccines		Licensed vaccines using this technology	First introduced
Whole-killed/Whole-inactivated vaccines			
	Uses the entire pathogen to stimulate an immune response. Pathogen is killed or is made inactive so that it cannot cause infection.	Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies	1896 (typhoid)
Live-attenuated vaccines			
	Use a weakened, harmless form of the pathogen. Introduction of the weakened pathogen into a human will mimic true infection without causing disease and will enable the body to produce an immune response.	Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster	1798 (smallpox)
Subunit vaccines (purified protein, recombinant protein, polysaccharide, peptide)			
Subunit vaccines 	Most subunit vaccines contain a piece of the pathogen, for example one of its proteins. The subunit acts as the foreign antigen, which will start the immune response. Certain subunit vaccines are made from smaller pieces of proteins called peptides.	Pertussis, influenza, hepatitis B, meningococcal, penumococcal, typhoid, hepatitis A	1970 (anthrax)
Protein-polysaccharide conjugate 		Haemophilus influenzae type B, meningococcal, penumococcal, typhoid	1987 (H. influenzae type B)
Toxoid 		Diphtheria, tetanus	1923 (diphtheria)
Virus-like particle 		Human papillomavirus	1986 (hepatitis B)

Type of vaccine		Licensed vaccines using this technology	First introduced
Nucleic acid vaccines			
DNA vaccines 	Use copies of single or multiple genes from the pathogen. Genes enter human cells and use the cell's machinery to produce some protein(s) of the pathogen encoded by the gene(s). When the protein is produced, the immune system sees it as a foreign or harmful antigen and produces an immune response.	SARS-CoV-2	2020 (SARS-CoV-2)
RNA vaccines 	RNA contains instructions for the cells to make protein(s). RNA is introduced into the cell using a lipid vesicle and uses the cell machinery to produce some protein(s) of the pathogen. When the protein is produced, the immune system sees it as a foreign or harmful antigen and produces an immune response. RNA technology allows vaccines to be developed in a much shorter period than before.	SARS-CoV-2	2020 (SARS-CoV-2)
Recombinant vector vaccines			
Viral vectored 	Use the same strategy as DNA vaccines, but the genes are carried by a harmless or a very weakened bacterium or virus, called a vector. Genes are inserted into the DNA of the vector, carrying the genes into the human cell. Once in the human cell, genes produce protein(s) to which the body responds.	Ebola, SARS-CoV-2	2019 (Ebola) 2020 (SARS-CoV-2)
Bacterial vectored 		Experimental	
Antigen-presenting cell			
		Experimental	

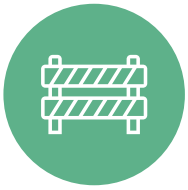
4. Challenges in Developing Vaccines

Vaccine development faces numerous challenges, both biological and technological, but also financial, due to the cost of conducting complex research in difficult environments and with limited resources, as well as social and political hurdles. Research can be lengthy and costly for a number of reasons:

- The pathogen may be complex and diverse (e.g., HIV).
- Immune responses are still poorly understood.
- Animal models are limited and may not perfectly match the human model.
- Large clinical trials are needed to show results.
- Little engagement from the pharmaceutical industry.

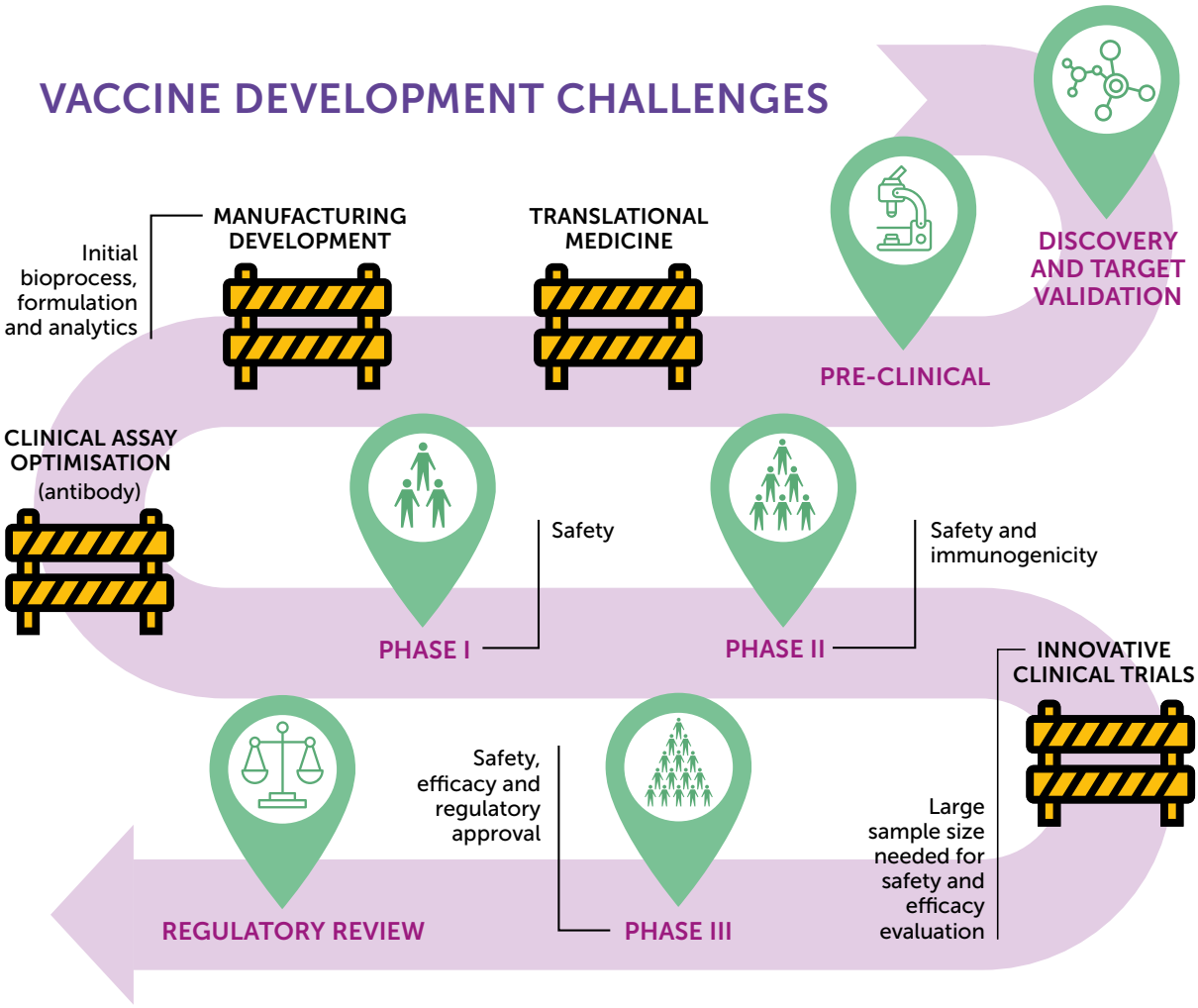
These challenges are often compounded by the fact that infectious diseases often occur in countries with limited ability to purchase vaccines should they become available, making the pharmaceutical industry wary of not being able to recover the costs of research and development.

Emerging pandemics, such as COVID-19, may redefine the strategies and approaches for vaccine development by increasing investment in research, building better collaboration between vaccine scientists and improving new platforms for vaccine design.



Vaccine development challenges

ALL VACCINES	UNIQUE TO TB AND HIV VACCINES
Manufacturing-bioprocess, formulation, and analytical development	Complex life cycle of target pathogen(s) make antigen(s) selection difficult
Optimisation of clinical immunologic assays	Protective immune response unclear
Large clinical trials required to evaluate safety in healthy individuals	Poor memory responses with rapidly waning efficacy
	Regulatory, Ethical Committee, and clinical trial infrastructure limitations for large studies involving novel technologies
	Insufficient financial resources for development
	No/limited high-income country markets



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5. HIV Vaccine Research and Development

5.1 A Brief History

As of 2022, no HIV vaccine has been proven efficacious in clinical trials. Many vaccine candidates are in various stages of research, development, and testing.

Since clinical trials started in 1987, over 30 different HIV vaccine candidates have been tested in over 70 clinical trials around the world. Only one vaccine tested between 2003 and 2009 in the RV144 'Thai trial' has shown some limited efficacy in preventing HIV. As of 2022, this encouraging result has not been reproduced.

In the early years of HIV vaccine research, most vaccines were developed for subtype B vaccines, the subtype now most common in North America and Europe.

Since the mid to late 1990s, more emphasis has been placed on the creation of vaccines for LMICs, focusing on subtypes common in Central and South America, Africa, and Asia.

Experts agree that many different types of vaccines will need to be tested in different regions of the world before an HIV vaccine will be approved and licensed.

HIV VACCINE TIMELINE

1984

HIV was identified as the cause of AIDS. United States Health and Human Services Secretary Margaret Heckler declared that an HIV vaccine would be ready for testing within two years.

1987

The first HIV vaccine clinical trial opened at the National Institutes of Health (NIH) Clinical Center in Bethesda, Maryland. This Phase I trial enrolled 138 healthy, HIV-negative participants. The gp160 subunit vaccine showed no serious adverse effects.

1998

The first large-scale HIV vaccine trial began. VaxGen initiated a Phase III trial of AIDSVAX (VAX004) in North America and the Netherlands involving more than 5,400 participants.

1999

NIAID began the first African preventive HIV vaccine trial in Uganda.

2000

NIAID formed the HIV Vaccine Trials Network (HVTN), an international network of clinical sites dedicated to developing a preventive HIV vaccine by testing and evaluating candidate vaccines in all phases of clinical trials.

2003

The United States and Royal Thai governments jointly initiated RV144, a Phase III trial to evaluate a novel HIV vaccine strategy commonly referred to as 'prime-boost.'

2004

VaxGen candidates failed to confer protection against HIV in Phase III trials.

The STEP study, also known as the HVTN 502 study, was launched. The clinical trial evaluated the safety and efficacy of an investigational Adenovirus 5 vectored HIV vaccine in populations at high risk of HIV infection.

2007

NIAID halted the Phase II STEP study.

The HVTN 503 (Phambili) study designed to evaluate the safety and preliminary efficacy of the same HIV candidate vaccine tested in the HVTN 502 STEP study, was launched in South Africa in January, and stopped in September following the discontinuation of the STEP study.

2009

The Phase II HVTN 505 study was initiated to evaluate a 'prime-boost' vaccine regimen developed by the VRC.

Results of the Phase III Thai Trial (RV144) revealed that the vaccine combination demonstrated a modest preventive effect in humans. The trial, which enrolled more than 16,000 participants, was the first, and to date only, large clinical study to demonstrate efficacy for an investigational HIV vaccine.

2010

VRC scientists identified two potent antibodies that neutralise most strains of HIV in the laboratory (VRC01 and VRC02).

The Pox-Protein Public-Private Partnership (P5), an international collaborative team committed to building on the modest success of RV144, was formed.

2016

NIAID launched the AMP Studies to test whether intravenous infusions of the antibody VRC01 are safe, tolerable, and effective at preventing HIV infection. The trials were also designed to answer fundamental scientific questions for HIV prevention and vaccine research.

HVTN 702, part of the P5 research endeavour, launched to test whether a new version of the RV144 HIV vaccine candidate safely prevents HIV infection among adults in South Africa.

The European Union's Horizon 2020 Research and Innovation Programme launched the European HIV Vaccine Alliance and European AIDS Vaccine Initiative. These five-year programmes bring together a multidisciplinary approach to vaccine development at EU level.

2017

NIAID and partners launched Imbokodo or HVTN 705/HPX2008, a Phase IIb proof-of-concept study evaluating the safety and efficacy of an experimental regimen based on a 'mosaic' vaccine designed to induce immune responses against a wide variety of global HIV strains.

2019

The Mosaico (HPX3002/HVTN 706) Phase III HIV vaccine efficacy trial is launched by a public-private partnership. The study will enroll 3,800 HIV-negative men and transgender people, aged 18 to 60, who have sex with men and/or transgender people.

2020

The Phase IIb HIV vaccine clinical trial known as UHAMBO (NIAID/HVTN 702) that was following in the steps of the RV144 trial, was stopped as the experimental vaccine did not prevent HIV infection in a population of sexually active women and men at high risk of acquiring HIV.

PrEPVacc, an African-led European-supported HIV prevention Phase IIb study is launched in East and Southern Africa. For the first time, a study is combining evaluation of experimental HIV vaccines and pre-exposure prophylaxis (PrEP) at the same time.

2021

The Phase IIb HIV vaccine clinical trial known as Imbokodo (HVTN 705/HPX2008) was stopped as data showed the investigational HIV vaccine regimen did not prevent HIV infection in a population of young women in sub-Saharan Africa at high risk of acquiring HIV.

IAVI and Scripps announced the results of a new vaccine concept based on the eOD-GT8 60mer. In this Phase I proof of principle the vaccine candidate stimulates the human immune system and generates broadly neutralising antibodies against known sites of vulnerability on the virus.

2022

Moderna announced human trials of the candidate mRNA-1644 in partnership with IAVI and Scripps Research. The vaccine candidate is based on the same mRNA platform as Moderna's successful COVID-19 vaccine.

5.2 HIV Vaccine Research and Development

Most HIV vaccines in development are preventive vaccines (although some work is being done on the development of therapeutic vaccines).

Many of the proven ways for making vaccines produce a strong immune response because the whole pathogen, either in killed or attenuated (weakened) form, is used in the vaccine. This strategy has not been applied when developing an HIV vaccine for use in humans. If a vaccine were made from a whole virus, it would be very hard for scientists to be absolutely sure that the vaccine could not cause HIV infection. Likewise, a 'killed HIV' vaccine would be difficult to produce in large quantities.

Early types of HIV vaccines contained only copies of parts of HIV, made in a laboratory. These vaccines contain synthetic structural materials like proteins or peptides. The HIV envelope glycoprotein has been the target of many vaccine candidates, but it can vary extensively, making designing a vaccine difficult.

Nowadays, vaccines contain genetic material that resembles pieces of the HIV genome. Genetic material is chosen because it produces proteins that should trigger the immune system to develop a response to HIV if it enters the body. These vaccines cannot cause HIV infection since no part of HIV is used directly in a vaccine.

In contrast to COVID-19 vaccines that were supported by significant government and private investment and global collaboration, traditional vaccine development takes several decades to reach final stage testing. Much has been learned from COVID-19 vaccine development that may enable scientists to develop products more efficiently. However, it is important to keep in mind that vaccines for more complex diseases like HIV may still take a long time to develop.

A preventive HIV vaccine could work in one of two ways:

- Blocking infection, so the vaccinated person does not aquire HIV in the future.
- Modifying the course of HIV infection so that even if it were not successful in preventing HIV aquisition, the vaccinated person would have a mild course of disease and AIDS would develop more slowly or not at all.

Because of these challenges, scientists and their collaborators are pursuing innovative strategies to design vaccines capable of activating both arms of the adaptive immune response — antibodies and T cells — simultaneously to induce durable immunity against HIV.

B-cell immunogens

Since 2009 the identification of potent broadly neutralising antibodies (bnAbs) from large cohorts of people living with HIV, new and improved HIV vaccine candidates carrying immunogens have been designed to stimulate B cells of the immune system to generate these antibodies against the virus and are in clinical trials. This approach is referred to as structure-based vaccine design.

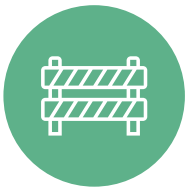
The other scientific development fuelling the design of immunogens to induce bnAbs was obtaining a clearer understanding of the structure of HIV's outermost protein known as HIV Envelope, which is the target of all bnAbs. For decades scientists were held back by their inability to capture the precise structure of this protein, but technological advances have allowed them to both stabilise and understand HIV Envelope in unprecedented detail.

Researchers are developing and testing engineered vaccine immunogens that are meant to look like the actual structure of the HIV envelope. These are so-called native-like trimers and are being evaluated in clinical trials.

The goal of the immunogen design work is to refine and improve these vaccine candidates until they can induce bnAbs that can protect against HIV infection.

T-cell immunogens

Some of the most promising T-cell immunogens in development are specifically designed to address the global diversity of HIV. So-called conserved HIV immunogens combine portions of the virus (referred to as viral 'epitopes') that are consistent across most of the genetically distinct variants of HIV currently in circulation.



5.3 HIV Vaccine Development Challenges

There are numerous scientific challenges to developing an HIV vaccine. The unprecedented genetic variability of the virus, its ability to quickly establish a persistent lifelong infection, and the fact that not a single person has cleared HIV on their own are just some of the obstacles researchers face in trying to understand how to induce protective immunity against the virus.

In addition, there is a lack of appropriate animal models available to test vaccine candidates before they are allowed to be tested in humans. Unlike many other diseases, we also don't have biological markers to tell us if someone is protected or not – these are known as 'immune correlates of protection.' These would be levels of antibodies or other immune cells such as killer T cells. It is not impossible to develop a vaccine in this situation, but it is more challenging.

Recent advances in HIV prevention such as PrEP (pre-exposure prophylaxis), means it is becoming more challenging to conduct efficacy trials with a control group. Indeed, research investigators should, at a minimum, ensure that study participants have access to the package of prevention methods recommended by the WHO, which includes effective HIV prevention like PrEP. However, these may reduce the risk of HIV acquisition in the study (compared to the real world where the best prevention is not always available) and make it more difficult to show that a new method is better than existing methods. It also increases the number of participants required to conduct the study and therefore its cost. New clinical study designs are being developed to replace the placebo group in efficacy trials.

For up-to-date information on HIV vaccine trials go to:

- TAG: *https://www.treatmentactiongroup.org/resources/pipeline-report/2021-pipeline-report*
- AVAC: *https://www.avac.org/infographic/vaccine-pipeline*
- IAVI: *https://www.iavi.org/our-science/pipeline*

6. TB Vaccine Research and Development

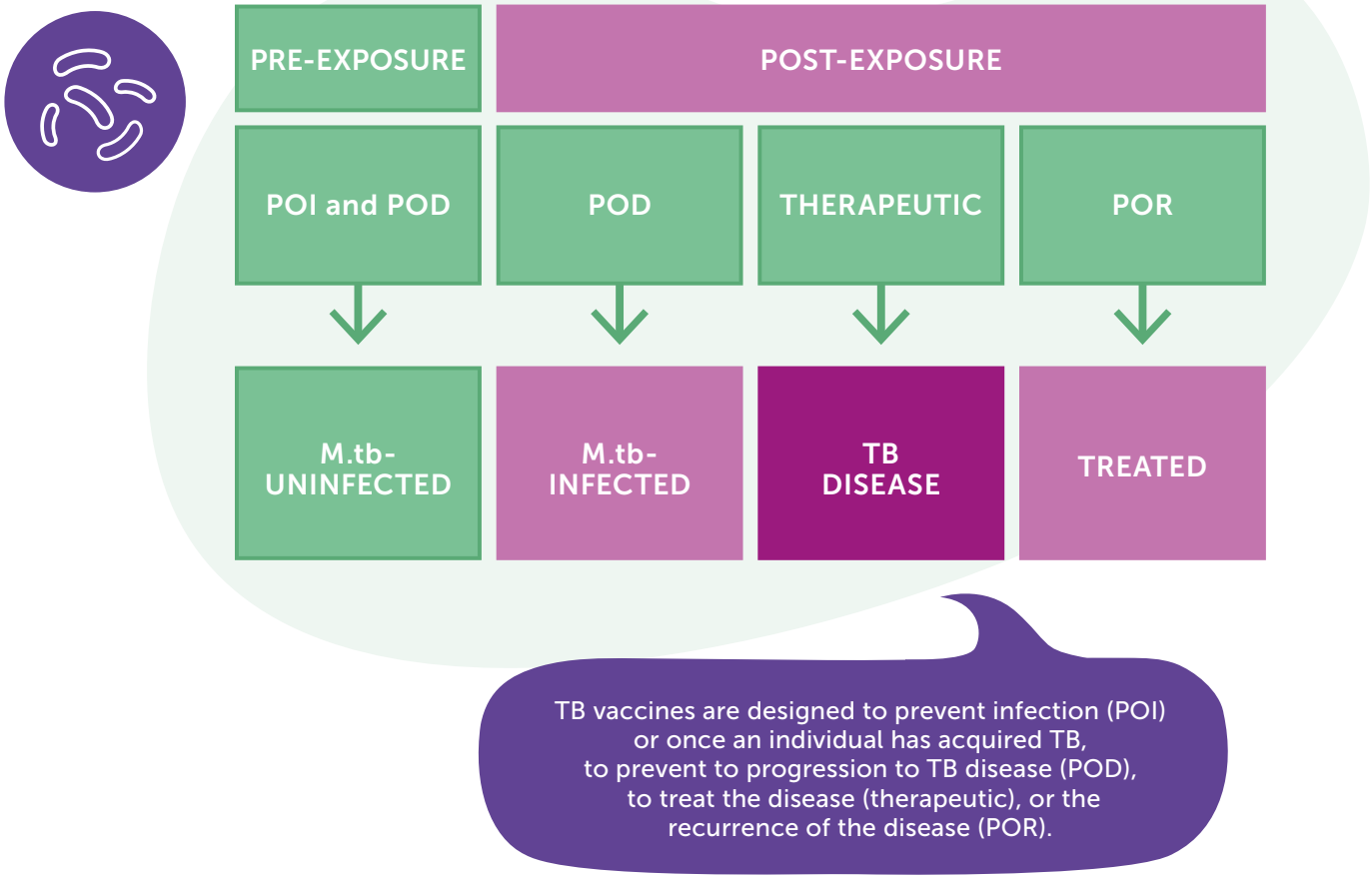
6.1 A Brief History

The development of a TB vaccine has been challenging for many reasons. The world still relies on the BCG vaccine to prevent severe disease in infants and young children, but the vaccine offers variable and mostly poor protection against lung disease in adolescents and adults.

The BCG vaccine was developed in 1921 and it is the only licensed vaccine to prevent the development of active TB disease. The mechanisms by which it works are not completely understood and its efficacy against pulmonary TB in adults has been reported to between 0–80%.

Mycobacterium tuberculosis (M.tb) can cause different forms of tuberculosis from asymptomatic latent infection to TB with clinical manifestations (see **MODULE 2**). For this reason, vaccine development focuses either on:

- Prophylactic vaccines that prevent infection (POI).
- Post exposure vaccines that prevent progression from latent TB infection to active disease (POD).
- Vaccines administered to be therapeutic in individuals with clinical disease in combination with treatment or after treatment to prevent recurrence of disease (POR).



6.2 TB Vaccine Research and Development

The main goal of current vaccination research is to help prevent active TB disease from developing in people who cannot contain the infection on their own. With TB being mostly spread by adolescents and adults with active pulmonary TB disease, the development of a new vaccine largely focuses on vaccines that are designed for these age groups.

The WHO has published a Target Product Profile (TPP) that should guide researchers in their effort to develop a vaccine. A range of TB vaccine candidates with different designs and that work in different ways is currently being evaluated in clinical trials. These include whole live attenuated and inactivated vaccines, adjuvanted protein subunits, viral vectored vaccines. In addition, revaccination in adults after receiving BCG in childhood is under consideration in specific settings and populations.

In 2019, the results of a Phase IIb vaccine trial to prevent active pulmonary tuberculosis disease were published. The vaccine efficacy was 49.7%, which means that active disease was prevented in almost half of the population participating in the study. Further studies of this vaccine are planned.

These and other significant trial results suggest new effective TB vaccines can be developed and there are ongoing efforts across the TB research community to broaden the diversity of immune responses triggered by vaccines through innovative and emerging platforms, such as nucleic acid vector approaches, antibody mediated protection, recombinant BCG, and improved protein-adjuvant combinations (see **Section 3: Vaccine platforms**).

6.3 Challenges of TB Vaccine Development

TB vaccine R&D has been chronically underfunded in relation to the impact of TB upon global health, even though it causes more deaths than HIV and malaria combined.

The design of TB vaccines is also challenging. Animal models to test vaccine candidates before they are administered to humans are imperfect and limited. In clinical trials, new vaccines against TB are compared to BCG, a partially effective vaccine. Furthermore, knowledge is lacking about 'immune correlates of protection' (biological markers such as a sufficient level of antibodies or other immune cells) to indicate if a person is protected against infection.

The emergence of drug-resistant TB is a further challenge to vaccine development, as an efficacious vaccine should work just as well against drug-sensitive and drug-resistant strains.

Despite these challenges, development of a better TB vaccine remains a possibility.

For up-to-date information of TB vaccine trial see:

- TAG: *https://www.treatmentactiongroup.org/resources/pipeline-report/2021-pipeline-report*
- IAVI: *https://www.iavi.org/our-science/pipeline*
- TBVI: *https://www.tbvi.eu/what-we-do/pipeline-of-vaccines*
- Accelerating research and development of new vaccines against tuberculosis: a global roadmap - Lancet Infect Dis 2022. Published Online February 28, 2022: *https://doi.org/10.1016/ S1473-3099(21)00810-0*

FIND OUT MORE...

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- WHO Preferred Product Characteristics for New Tuberculosis Vaccines: *https://apps.who.int/iris/bitstream/handle/10665/273089/WHO-IVB-18.06-eng.pdf?*

7. Lassa Virus Vaccine Research and Development

7.1 A Brief History

There is currently no vaccine approved to prevent Lassa fever although several candidates are advancing towards clinical trials.

The first vaccine to show any promise against Lassa virus was described in 1987. This candidate vaccine was tested in animals only and was based on a recombinant vaccinia virus (the virus used to create the smallpox vaccine) and contained one of the Lassa virus proteins.

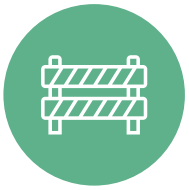
Other vaccines have been developed using other virus vectors with various success in animal models. There have been very few studies of Lassa virus vaccine candidates in humans.

7.2 Lassa Virus Vaccine Research and Development

The WHO has published a Target Product Profile (TPP) for Lassa virus vaccine that provides guidance to researchers in their effort to develop a vaccine.

The Coalition for Epidemic Preparedness Innovations (CEPI), an alliance formed in 2017 to support and finance vaccine development for the prevention of infectious disease epidemics, is supporting the development of six Lassa virus vaccine candidates based on DNA or recombinant vectors. Three of these have entered Phase I trials in humans as of 2022.

IAVI is researching a vaccine known as 'recombinant vesicular stomatitis virus LASV expressing the GPC protein.' This is among the leading candidates developed so far.



7.3 Challenges of Lassa Virus Vaccine Development

There are numerous scientific challenges to developing a Lassa virus vaccine, which is considered a neglected disease and receives limited research funding. There are considerable variations between strains of Lassa virus and there are limitations with current animal models. Despite being carried by rodents, the infection differs between humans and rodents. Non-human models most closely replicate Lassa fever, but these have not yet been extensively used to develop a Lassa virus vaccine. Unknown 'correlates of protection' (see above) for Lassa Fever have also impeded the development of a vaccine.

FIND OUT MORE...

- Current research for a vaccine against Lassa haemorrhagic fever virus: *https://www.dovepress.com/current-research-for-a-vaccine-against-lassa-hemorrhagic-fever-virus-peer-reviewed-fulltext-article-DDDT*
- Purushotham J, Lambe T, Gilbert SC. Vaccine platforms for the prevention of Lassa fever. Immunol Lett. Nov;215:1-11 (2019)
- WHO Target Product Profile for Lassa virus Vaccine: *https://www.who.int/blueprint/priority-diseases/key-action/LassaVirusVaccineTPP.PDF*
- The Coalition for Epidemic Preparedness Innovations (CEPI): *https://cepi.net*

Glossary

A

Acquired immunity: immunity that develops during a person's lifetime.

Adjuvant: a substance added to its formulation to enhance or modify the immune response to the components of the vaccine.

Adverse event: an unexpected medical problem experienced by an individual in a clinical trial. The term is used whether the effect can be attributed to the vaccine under study or something else happening during the study.

Adverse reaction (also known as adverse event or side effect): in a clinical trial, an unwanted effect detected in participants and attributed to the study vaccine.

AIDS (acquired immunodeficiency syndrome): the most advanced stage of HIV infection, characterised by a deterioration of the immune system and a susceptibility to a range of opportunistic infections and cancers.

Antibody: a protein found in the blood or bodily fluids that binds, neutralises, and helps destroy pathogens (e.g., bacteria, viruses) or toxins. Antibodies are also known as immunoglobulins. Each antibody binds specifically to the antigen that stimulated its production.

Antibody-mediated immunity: immunity that results from the activity of antibodies. Also called humoral immunity.

Antigen: any substance that stimulates the immune system to trigger an immune response.

Antigen-presenting cell (APC): B cell, macrophage, dendritic cell or other cells that ingest and process pathogens such as bacteria and viruses. An APC displays fragments of the pathogen on its surface to attract and activate the cells of the immune system that respond specifically to that antigen (see also dendritic cell; macrophage).

Antiretrovirals: drugs that reduce the ability of HIV or other types of viruses to multiply in the body.

Apoptosis: cellular suicide. A possible mechanism used by HIV to destroy cells of the immune system. HIV may cause apoptosis in both HIV-infected and HIV-uninfected immune system cells. Also known as programmed cell death.

Arm: a group of participants in a clinical trial, all of whom receive the same treatment, intervention, or placebo.

Attenuated: weakened. Attenuated viruses are often used as vaccines because they can no longer produce disease but still stimulate a strong immune response, similar to that caused by the natural virus.

B

B lymphocyte (B cell): one of the two major classes of lymphocytes, B lymphocytes are white blood cells of the immune system that are derived from the bone marrow and spleen. B cells develop into plasma cells, which produce antibodies.

Baseline: the time point in a study just before initiation of an intervention (for example vaccination). Measurements taken at later time points may be compared with those taken at baseline to determine if the intervention makes a difference.

B

Binding antibody: an antibody that attaches to part of a pathogen. Binding antibodies may or may not lead to the killing of the pathogen.

Blinded study: a clinical trial in which participants are unaware as to whether they are in the experimental or control arm of the study. See also double-blind study.

Booster: a vaccine dose given after the first dose to increase the immune response to the vaccine antigen(s). A booster may be given shortly after the first dose or much later. The vaccine given as the booster dose may or may not be the same as the primary vaccine. See also prime-boost.

Breakthrough infection: an infection that occurs during a vaccine trial conducted to prevent that infection. Such an infection is caused by exposure to the infectious agent and may occur before or after the vaccine has taken effect or all doses have been given.

C

CD: abbreviation for 'cluster of differentiation,' referring to molecules at the surface of cells that are used to identify immune cells, for example, CD4+ T cells.

CD4+ T lymphocyte: cell of the immune system that carries a molecule on its surface known as 'cluster of differentiation 4' (CD4). These cells are the primary targets of HIV. Also known as helper T cells, CD4+ T cells help orchestrate the immune response, including antibody responses as well as CTL responses (see also T cell).

CD8+ T lymphocyte: cell of the immune system that carries a molecule on its surface known as 'cluster of differentiation 8' (CD8) (see also cytotoxic T lymphocyte (CTL); T cell).

Cell-mediated immunity (cellular immune response): the immune response coordinated by T cells. This branch of the immune system targets cells infected with microorganisms such as viruses, fungi, and certain bacteria.

Challenge: in vaccine research and development, the deliberate exposure of an immunised animal to the infectious agent. Challenge experiments are never done in human HIV vaccine research.

Circulating recombinant forms (CRFs): HIV made of different subtypes of the virus that have recombined.

Clade: a group of related viruses classified according to their degree of genetic similarity. Also called a subtype or strain.

Cohort: groups of individuals who share one or more characteristics in a research study and who are followed over time. For example, a vaccine trial might include two cohorts, a group at low risk for HIV and a group at higher risk for HIV.

Complement proteins: blood proteins that play an important role in the immune response. Generally, complement proteins amplify the effects of antibodies and inflammation.

Control arm: in vaccine clinical trials, the group of participants that is not given the experimental intervention. The control arm can be given an intervention that is considered effective (the standard of prevention), a placebo, or no intervention. The control group is compared with one or more groups of participants given experimental vaccines to measure any effects of the vaccines tested as well as to measure differences in safety.

C

Core: the section of a virus that contains the genetic information and other proteins needed for a virus to replicate.

Correlates of immunity (correlates of protection): the immune responses a vaccine or natural immunity need to trigger to protect an individual from a certain infection.

Cytokine: a hormone-like protein produced by white blood cells that acts as a messenger between cells. Cytokines can stimulate or inhibit the growth and activity of various immune cells. Cytokines are essential for a coordinated immune response and can also be used as immunologic adjuvants. HIV replication is regulated by a delicate balance among cytokines.

Cytotoxic T lymphocyte (CTL): a type of immune system cell that can destroy cancer cells and cells infected with viruses, fungi, or certain bacteria. Also known as killer T cells.

D

Deletion (genetic): elimination of a gene or portion of a gene. Genetic deletion can occur naturally or in the laboratory.

Dendritic cell: antigen-presenting cell with thread-like tentacles (called dendrites) used to surround antigen, which they present to T cells.

DNA (deoxyribonucleic acid): the double-stranded, helical molecular chain found within the nucleus of each cell. DNA carries the genetic information that encodes proteins and enables cells to reproduce and perform their functions.

Dose-ranging study: a clinical trial in which two or more doses (starting at a lower dose and proceeding to higher doses) of a vaccine are tested against each other to determine which dose works best and has acceptable side effects.

Dose-response relationship: the relationship between the dose of a vaccine and an immune or physiologic response. In vaccine research, a dose-response effect means that as the dose of the vaccine increases, so does the level of the immune response.

Double-blind study: a type of clinical trial in which neither the participants nor the research team know which intervention a specific participant is receiving. This helps prevent bias or expectations from influencing the results of the study.

Data and Safety Monitoring Board (DSMB): a committee of independent clinical research experts who review data while a clinical trial is in progress. The DSMB ensures that participants are not exposed to undue (unacceptable) risk and looks for any differences in effectiveness between the experimental and control groups. The DSMB may review the data in such a way that they know which group received the vaccine and which group did not. This group may also recommend that a trial be modified or stopped if there are safety concerns or if the trial objectives have been achieved or will not be achieved. See futility.

E

Effectiveness: the measurement of how well a vaccine works to reduce infection or disease in the overall population when used in the 'real world.'

Efficacy: the measurement of how well a vaccine works at producing a desired clinical effect in optimal conditions, that is, in clinical trials.

ELISA (enzyme-linked immunoabsorbent assay): a laboratory test to detect the presence of antibodies in the blood or other body fluid.

E

Endpoint: an outcome or event used to objectively measure the effect of a drug or other intervention being studied in a clinical trial. Common endpoints include infection, severe toxicity, relief of symptoms, and improvements in quality of life.

Envelope: outer surface of a virus, also called the coat. Not all viruses have an envelope.

Enzyme: a protein produced by cells to trigger a specific chemical reaction. Enzymes are generally named by adding the ending '-ase' to the name of the substance on which the enzyme acts (for example, the HIV reverse transcriptase converts HIV RNA into viral DNA)

Epidemic: a widespread outbreak of a disease in a large number of individuals over a particular period of time either in a given area or among a specific group of people.

Epidemiology: the study of the characteristics, frequency, and distribution of diseases in human populations.

Epitope: a specific part of an antigen that stimulates specific immune responses.

Experimental arm: in a clinical trial, the group of participants given the intervention being studied. Outcomes in the experimental arm are compared with those in the control arm to determine any differences, for example, in safety and effectiveness.

F

Functional antibody: an antibody that binds to an antigen and has an effect that can be demonstrated in laboratory tests. For example, neutralising antibodies are functional antibodies that inactivate HIV or prevent it from infecting other cells.

Futility: the inability of a clinical trial to achieve its objectives. A clinical trial can be stopped when an interim analysis of the results by the DSMB suggests that it is unlikely to achieve its objective and stopping it can save resources and time that could be used on more promising research.

G

Genetic engineering: the laboratory technique of recombining genes to produce proteins used for drugs and vaccines.

Genome: the complete genetic material of an organism, including all its genes. The genomes of viruses can exist as DNA or RNA.

Glycoprotein (gp): A protein that is coated with carbohydrates (sugars).

H

Healthy participant: someone with no known significant health conditions who participates in research to test a new drug, device, or intervention. Also known as 'Clinical Research Participant.'

Helper T cell: T-cell lymphocyte bearing the CD4 marker. Helper T cells regulate the functions of other cells of the immune response.

Herd immunity: protection from an infectious disease happening when a significant percentage of a population is immune to the infection either through vaccination or immunity developed through previous infection.

Host: a plant or animal harbouring another organism.

Humoral immunity: see antibody-mediated immunity.

Hypothesis: a proposed explanation made based on limited evidence as a starting point for further investigation.

I

Immune complex: an antigen bound to its specific antibody.

Immune deficiency: a breakdown or inability of certain parts of the immune system to function, thus making a person susceptible to diseases that they would not ordinarily develop.

Immunisation: the process of inducing immunity by administering a vaccine.

Immunity: protection provided by the immune system to a specific disease. Immunity may be innate or acquired, partial or complete, specific or nonspecific, long-lasting, or temporary.

Immunocompetent: capable of developing an immune response; possessing a normal immune system.

Immunogen: a substance capable of provoking an immune response. Also called an antigen.

Immunogenicity: the ability of an antigen or vaccine to stimulate immune responses.

Immunoglobulin: a general term for antibody immunotherapy: a treatment that stimulates or modifies the body's immune response.

in vitro: an artificial environment outside a living organism (e.g., in a laboratory) used for the conduct of experimental research.

in vivo: research performed with a living organism, e.g., human or animal studies.

Incidence: the number of individuals who develop a specific disease or experience a specific health-related event during a particular period of time (such as a month or year).

Inclusion/exclusion criteria: factors used to determine whether a person is eligible (inclusion criteria) or not eligible (exclusion criteria) to participate in a clinical trial. Eligibility criteria may include disease type and stage, other medical conditions, previous treatment history, age, and gender.

Informed consent: a process between a person and a researcher to ensure that the person understands all relevant facts associated with their participation in a clinical trial. Participants into a clinical trial are required to sign an informed consent form before joining a clinical trial to show that they understand the risks and benefits of participating in the research. Informed consent includes the right to leave a clinical trial at any point during the study.

Innate immunity: immunity that is present at birth and lasts a person's entire life. Innate immunity is the first response of the body's immune system to a harmful foreign substance or pathogen.

Institutional Review Board (IRB): a committee of medical professionals, statisticians, community advocates, and others that reviews clinical trial protocols before they can be initiated. IRBs ensure that the trial is scientifically sound, ethical, and that the rights and safety of participants are adequately protected.

K

Key populations: groups of people such as sex workers, people who use drugs, prisoners, transgender people, and men who have sex with men that are at higher risk of HIV or TB, in part due to discrimination and social exclusion.

L

Latent TB infection (LTBI): a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of active TB.

Live-vector vaccine: a vaccine in which a live pathogen is weakened (attenuated) through chemical or physical processes to produce an immune response without causing the severe effects of the disease.

Lymphadenopathy: enlargement of the lymph nodes in response to regional infection or inflammation.

Lymphocyte: a type of white blood cell primarily responsible for immune responses. Present in the blood, lymph, and lymphoid tissues. See also B cell and T cell.

Lymphoid tissue: the part of the body that plays an important role in the immune response and helps protect it from infection and pathogens. Lymphoid tissue is present throughout the body and includes the lymph nodes, spleen, tonsils, adenoids, and other organs.

Lymphomas: types of cancer that begin in the lymphatic system.

M

Macrophage: a large cell of the immune system that can ingest pathogens. Macrophages stimulate other immune cells by presenting them with small pieces of the pathogen. Macrophages also can harbour large quantities of HIV without being killed, acting as reservoirs of the virus.

Memory cell: a subset of T cells and B cells that help the body defend itself against disease by remembering prior exposure to specific pathogens. They can proliferate (recognise the antigen and divide) more readily when the immune system re-encounters the same pathogen.

Monoclonal antibody: a custom-made, identical antibody that recognises only one epitope.

Monocyte: a type of immune cell that is made in the bone marrow and travels through the blood to tissues in the body where it becomes a macrophage or a dendritic cell.

Monovalent vaccine: a vaccine that contains only one antigen.

Mucosal immunity: immune response pertaining to mucous membranes. Mucosal immunity relies on immune cells and antibodies present in the linings of the reproductive tract, gastrointestinal tract, and other moist surfaces of the body exposed to the outside world.

N

Natural killer cell (NK cell): a type of immune cell that can kill tumour cells or cells infected with a virus or bacteria. An NK cell is a type of white blood cell. NK cells are 'natural' killers because they do not need to recognise a specific antigen to attack and kill their target.

Neutralising antibody: an antibody that prevents a virus from infecting a cell in the body, usually by blocking receptors on the cell or the virus itself.

Nosocomial: an infection acquired or occurring in a hospital.

Nucleic acid: an important class of macromolecules found in all cells and viruses. Nucleic acids play an important role in how genetic information is stored and used.

Nucleic acid test (NAT): a laboratory test to detect the genetic material of a microorganism. The viral load (HIV RNA) test is a type of nucleic acid test.

O

Off-label use: the legal use of a prescription drug to treat a disease or condition for which the drug has not already been approved by the regulatory authority.

Open-label trial: a type of clinical study in which both the researchers and the participants are aware of the drug or treatment being given.

Opportunistic infection: an illness caused by an organism that usually does not cause disease in a person with a healthy immune system.

P

Pandemic: An epidemic occurring over a very wide area (several countries or continents) and usually affecting a large proportion of the population.

Parenteral: administered into the bloodstream or by injection.

Pathogen: organisms (e.g., bacteria, viruses, parasites, and fungi) that cause disease in human beings.

Pathogenesis: the origin and development of a disease. More specifically, the way a microbe (bacteria, virus, etc.) causes a disease.

Peptide: a short compound formed by linking two or more amino acids. Peptides that contain many amino acids are called polypeptides or proteins.

Phase I clinical trial: The first step in testing a new vaccine in humans. A Phase I clinical trial tests the safety, side effects, best dose, and timing of a new vaccine.

Phase II clinical trial: These trials measure safety and immunogenicity in a larger group (50–3000) of participants. Here the goal is also to find the best dose and regimen. Phase II trials may last up to two years or longer.

Phase III vaccine trial: A large study that tests the safety and how well a new vaccine works compared with a standard treatment.

Placebo: An inactive substance or other intervention that looks the same as, and is given the same way as, the vaccine being tested.

Plasma: The clear, yellowish, fluid part of the blood that carries the blood cells.

Preclinical: research often using animals to find out if a drug, procedure, or treatment is likely to be useful. Preclinical studies take place before any testing in humans is done.

Prevalence: the total number of individuals in a population who have a disease or health condition at a specific point in time, usually expressed as a percentage of the population.

Prime-boost: in HIV vaccine research, administration of one type of vaccine, such as a live-vector vaccine, followed by or together with a second type of vaccine, such as a recombinant subunit vaccine. The intent of this combination regimen is to induce different types of immune responses and enhance the overall immune response, a result that may not occur if only one type of vaccine were to be given for all doses.

Priming: the first dose of a vaccine given to induce a particular immune response, followed by or together with a second dose of vaccine. The intent of priming is to induce certain immune responses that will be enhanced by the booster dose(s).

Prophylaxis: the prevention of disease.

Protocol: the detailed plan for a clinical trial that states the trial's rationale, purpose, vaccine dosage, routes of administration, length of study, eligibility criteria and other aspects of trial design.

R

Randomised trial: a study in which participants are assigned by chance to one of two or more intervention arms or regimens. Randomisation minimises the differences among groups by equally distributing people with particular characteristics among all the trial arms.

Reactogenicity: physical reactions that occur soon after vaccination and are a physical manifestation of the inflammatory response to vaccination.

Reagent: any chemical used in a laboratory test or experiment.

Receptor: a molecule on the surface of a cell that can recognise and bind to other molecules such as antigens, antibodies.

Recombinant DNA technology: the technique by which genetic material from one organism is inserted into a cell to mass produce proteins.

Regulatory gene: genes that regulate the replication of pathogens.

Reservoir: HIV-infected cells that are not actively producing HIV.

Retrovirus: viruses that carry their genetic material in the form of RNA rather than DNA and have the enzyme reverse transcriptase that can transcribe it into DNA. In turn, this DNA will be used to create viral RNA in the infected cells.

Reverse transcriptase: the enzyme found in retroviruses that enables them to direct a cell to make DNA from their viral RNA.

RNA (ribonucleic acid): one of two types of nucleic acid made by cells. RNA contains information that has been copied from DNA (the other type of nucleic acid). Many forms of RNA have functions related to making proteins.

S

Seroconversion: the production of antibodies against a particular antigen in the blood of a person who did not have the antibodies before. When people develop antibodies, they 'seroconvert' from antibody-negative to antibody-positive (see also VISP).

Serostatus: the state of either having or not having detectable antibodies against a specific antigen, as measured by a blood test (serologic test).

Serum: the clear, yellowish liquid part of blood that remains after clotting. Serum is used for various laboratory tests.

Simian-Human Immunodeficiency Virus (SHIV): a genetically engineered hybrid virus with a human virus envelope and a simian virus core.

Side effect: see adverse reaction.

Simian Immunodeficiency Virus (SIV): a diverse group of viruses that naturally infect a wide range of African monkeys. This infection generally does not result in immunodeficiency in African monkeys, but Asian or Indian rhesus macaques will develop simian AIDS (SAIDS).

Statistical significance: a mathematical measure of difference between groups in a clinical study. The difference is said to be statistically significant if it is greater than what might be expected to happen by chance alone.

Sterilising immunity: an immune response that completely prevents the establishment of an infection.

Strain: a specific version of virus of bacteria. Many diseases, including HIV and Lassa fever virus have multiple strains.

S

Stratification: separation of a study cohort into subgroups or strata according to specific characteristics.

Subtype: a subgroup of genetically related HIV-1 viruses. Also called a clade.

Subunit vaccine: a vaccine that contains only part of the virus or other pathogen which have been specially selected for their ability to stimulate immune cells.

Surrogate marker: substitute measure of a clinical or biological endpoint. For example, CD4 count is a surrogate marker of disease progression.

T

T cell: a type of white blood cell critical to the immune response. Among these are CD4 T cells and CD8 T cells.

Therapeutic HIV vaccine: a vaccine designed to boost the immune response against HIV in a person living with the virus to slow the progression of HIV infection or delay the onset of AIDS.

V

Vaccine: a substance administered to trigger an immune response against a particular disease to prevent an infection.

Vector: a bacteria or virus that does not cause disease in humans and is used in genetically engineered vaccines to transport genes coding for antigens into the body to induce an immune response.

Viral Load (VL): the amount of HIV in a sample of blood. Viral load is reported as the number of HIV RNA copies per millilitre of blood.

Viremia: the presence of virus in the bloodstream.

Virion: a mature infectious virus particle that exists outside of a cell.

Virus: a microorganism that infects cells and may cause disease. To reproduce, a virus must infect a cell and direct its cellular machinery to produce new viruses.

Vaccine-Induced HIV Seropositivity (VISP): antibody induced by vaccination and that can confound the interpretation of HIV diagnostics tests. VISP may have implications in the everyday life of clinical trial participants (for example access to insurance, employment, or immigration).

W

Western blot: a laboratory test to detect antibodies to specific components of a virus such as HIV in the blood.

Window period: the period of time from exposure to HIV to when the body produces enough HIV antibodies to be detected by standard HIV tests.

RESOURCES

- NIH glossary of HIV/AIDS-related terms: *https://clinicalinfo.hiv.gov/en/glossary*
- CDC Vaccines and immunisation glossary: *https://www.cdc.gov/vaccines/terms/glossary.html*

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