IAVI VACCINE LITERACY LIBRARY

2022

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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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Lead Consultants: Roger Tatoud and Rebekah Webb.

Design and Illustration: Anthea Duce.

Requests for permission and inquiries should be directed to:

IAVI
Email: info@iavi.org
Website: iavi.org
Tel: +1.212.847.1111
125 Broad Street, 9th floor
New York, NY 10004

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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 5:
WHAT IS A VACCINE CLINICAL TRIAL?

MODULE 5

WHAT IS A VACCINE CLINICAL TRIAL?

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» Summary Points

- A clinical trial is a type of research that studies new medicines, treatments, medical devices, or prevention tools to evaluate their effect on human health.
- All new vaccines must be thoroughly researched and tested in the laboratory and in animals before they are tested on people.
- To receive approval for human testing, researchers must first show data demonstrating that the intervention is unlikely to harm people and likely to be effective.
- The inclusion of diverse populations in clinical trials is important to provide evidence that the new vaccine will be safe and effective in the full range of people likely to use it.

1. Introduction: What is a Clinical Trial?

A clinical trial is a type of research that studies new medicines, treatments, medical devices or prevention tools to evaluate their effect on human health. This module is focused on preventive vaccine trials, but the basic principles apply in all clinical trials.

While undergoing testing, vaccines are referred to as 'candidate' vaccines. Vaccine clinical trials evaluate whether candidate vaccines are safe and effective at preventing or controlling infections and diseases.

A sequential series of trials are required to determine whether the candidate vaccine is both safe and efficacious. Without this information, new vaccines and medicines cannot be licensed for use.

2. Key Definitions in Vaccine Clinical Trials

2.1 Safety

Clinical trials are used to establish that the candidate vaccine does not cause serious reactions or side effects that would prevent its use. These are technically known as adverse events (AE) and they can be mild, moderate, severe or serious (see **BOX**). If adverse events are mild, these are considered acceptable. Serious reactions to vaccines and long-term side effects are very rare.

Common reactions or side effects that are expected for vaccines include fever, headache, tiredness, or body aches. They usually last only a few days. Rare (1 in 1,000,000) or uncommon (1 in 1,000) side effects can only be seen after many people have received the vaccine. Thus, safety information is actively collected in all studies. Even after a vaccine has been approved for use, safety is monitored by the reporting of side effects through central data collection systems.

Most vaccine candidates are injected into the muscle of the upper arm. This can cause soreness in the arm, and some can cause mild fever or tiredness initially, but long-term side effects are very rare. Any general side effects or illnesses that might be related to the vaccine are carefully studied in clinical trials to determine whether the vaccine is safe enough to be moved on to further trials and eventually licensed for use.

One of the most important tasks of researchers is to assess whether an adverse event is related to the vaccine being tested or not. Some adverse events are expected reactions, or side effects, caused by the vaccine. These usually only last a few days and include pain, redness, or swelling at the site of injection or systemic symptoms like fever, headache, tiredness, or body pains.

Adverse events explained

Adverse event (AE) – any unfavourable event or physical condition that an individual experiences during participation in a clinical trial; the event may be sudden or may develop over time. The unfavourable event may or may not be caused by the candidate vaccine.

Serious adverse event (SAE) – an event that causes death, is life-threatening, requires hospitalisation, produces significant disability, or produces congenital abnormality (birth defect) in a child of a vaccinated person. SAEs may or may not be caused by the candidate vaccine.

What does 'safety' mean in the context of a vaccine trial?

The term 'safety,' as used in clinical trials, means that researchers are looking to make sure the vaccine does not cause side effects in a significant number of people or to a significant or severe degree in any person. Safety means that the vaccine itself is not harmful.

Testing for safety does not mean testing to see if the vaccine causes infection. Before a vaccine goes into clinical trials, researchers already know that there is no chance it will cause infection in humans (see **MODULE 3**).

Finally, people may think safety means safe from the infection that the vaccine is designed to protect against. People who join a clinical trial should never count on the candidate vaccine protecting them. All participants should continue to practice forms of risk-reduction and not rely on what they receive in a trial to protect them.

2.2 Dose, Regimen, and Route of Immunisation

Clinical trials make it possible to define how much of the vaccine to give (the dose), how often to give it, and how far apart the doses should be given (the regimen).

Trials can also explore the best route for the vaccine to be given, 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).

2.3 Immunogenicity

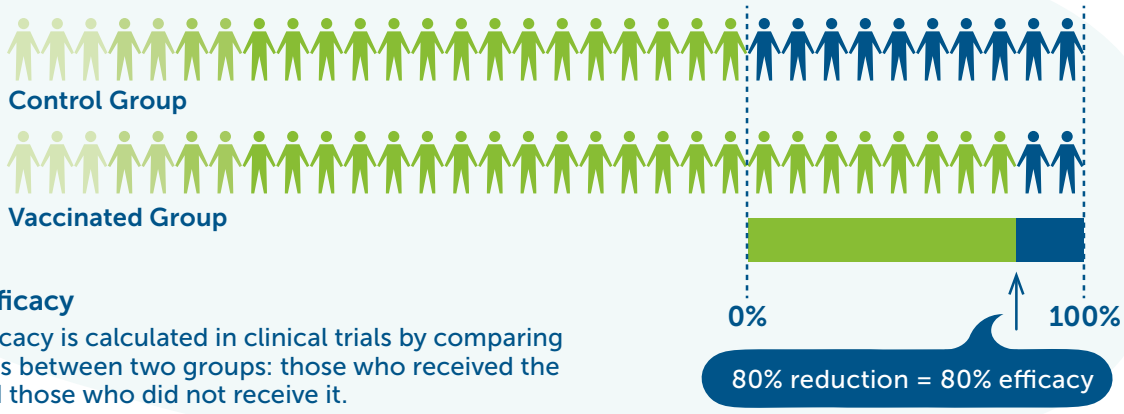
Clinical trials measure the ability, strength, and type of immune responses. These immune responses are measured through laboratory tests on samples of participants' blood, or other body fluids and sometimes body tissue (for example, lymph node or bone marrow sample).

2.4 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) to the number of people who did not get the vaccine (usually a placebo, or dummy vaccine) and developed the same outcome over a period of time.

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

EFFICACY EXPLAINED



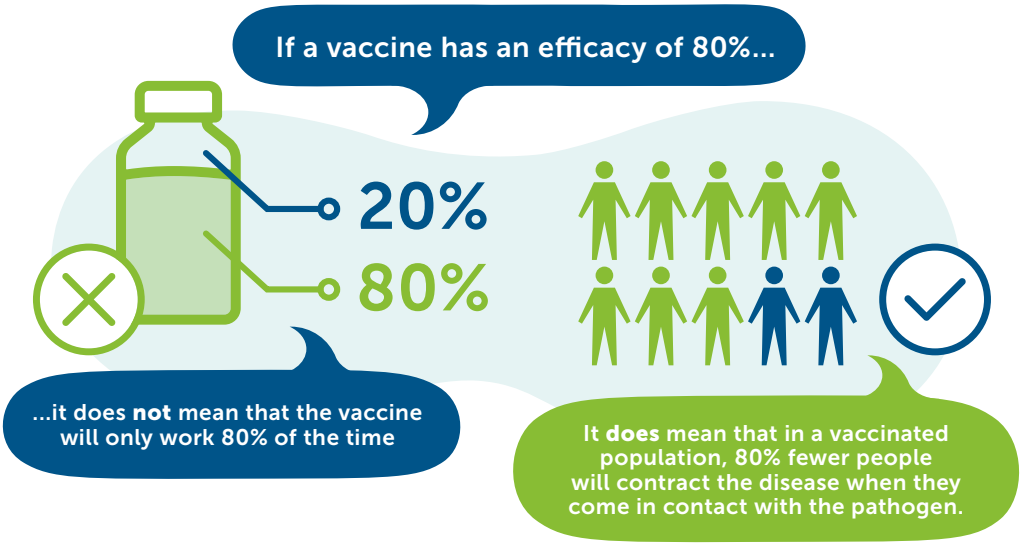
Vaccine efficacy

Vaccine efficacy is calculated in clinical trials by comparing disease rates between two groups: those who received the vaccine and those who did not receive it.

Source: Adapted from WHO

No vaccine is 100% protective. Some vaccines, like the Hepatitis B vaccine, have an efficacy of over 95% if all three injections are received, 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 epidemics.

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.



Source: Adapted from WHO

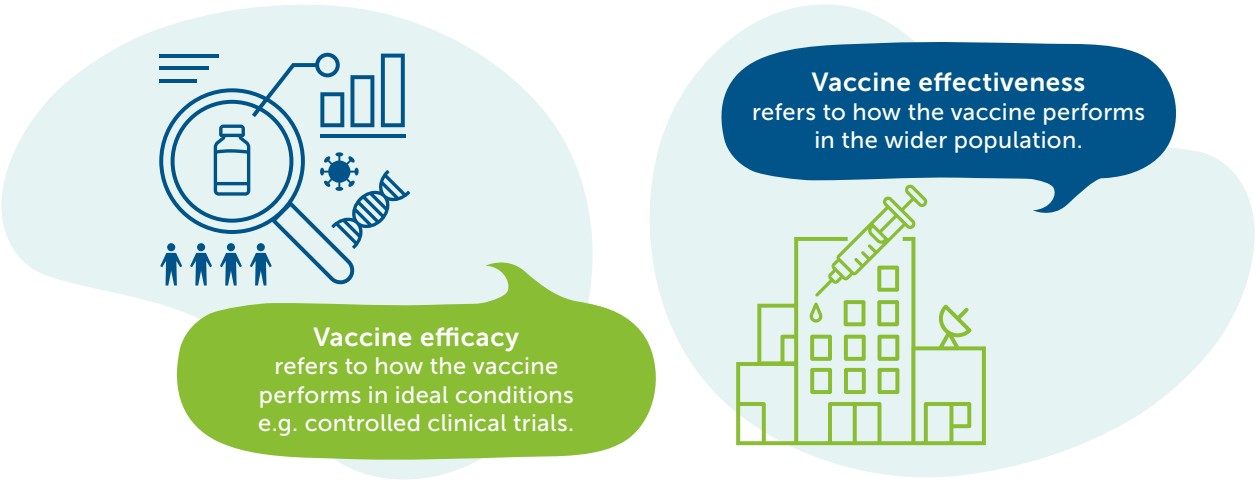
After a vaccine has been proven to work, it is still important to find out how well it works when given to people of different ages, people whose immune systems are not strong, and people with chronic diseases, malnutrition, etc. It also is important to find out how long the protection lasts.

2.5 Effectiveness

One thing that clinical trials cannot tell us is how well the vaccine reduces disease when it is used in a real-life setting (i.e., not in a clinical trial). The term 'effectiveness' is used to describe how well the vaccine works at reducing infection or disease in the overall population when it is rolled out.

Effectiveness in the population depends on many factors: the efficacy as defined in clinical trials, and the characteristics of the population in which the vaccine is used, including how many people get vaccinated, as well as whether they take their full series of vaccinations.

Effectiveness can be measured through additional studies conducted after a vaccine has been through clinical trials and is licensed and being used in the general population (see section on Phase IV studies, below).



2.6 Sample Size and 'Power'

The likelihood that a clinical study detects a difference in efficacy between the test groups and the control group in a particular setting is called the 'power.' Power depends on the incidence of a disease in a setting. Power and incidence will determine the sample size, that is the number of participants to enrol in a study to detect the predetermined difference.

If the incidence of a disease is high in the community where the vaccine candidate is tested, the number of people needed in the clinical trial will be low. The study can be 'powered' at different levels of efficacy, based on the incidence in the population where the vaccine is tested.

3. Clinical Trial Methods

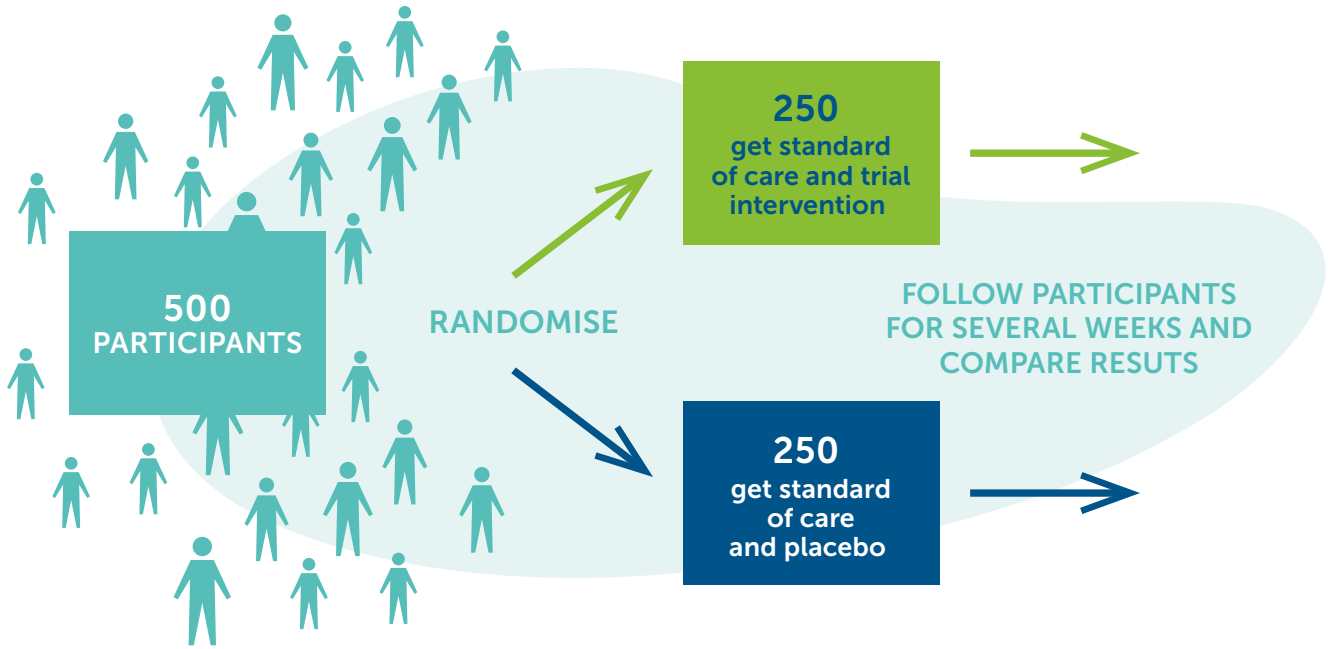
Clinical trials use established and regulated scientific methods to remove as much bias and human error as possible. This ensures the results of testing can be trusted, and protects individuals from harm. To do this, they use a range of methods, including placebos, controls, blinding, and randomisation.

3.1 Control Group in a Trial

Many (but not all) vaccine trials involve a control group using a placebo, which is a harmless, inactive substance. Sometimes this is called a 'dummy' or a 'blank.' The placebo is given to one group of participants, while the candidate vaccine is given to another group. The group receiving the placebo is usually called the control group. Safety, immunogenicity, and efficacy of the candidate vaccine are determined by comparing observations in the control versus the vaccine group.

A placebo is not always used. Sometimes a candidate vaccine might be compared with an existing vaccine that is known to be effective, for example the BCG vaccine for TB. In this case, the control group would receive the existing vaccine. In the case of HIV, recent advances in HIV prevention such as PrEP (pre-exposure prophylaxis), means it is becoming more challenging to conduct efficacy trials with a placebo 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.

USE OF A CONTROL GROUP IN A TRIAL

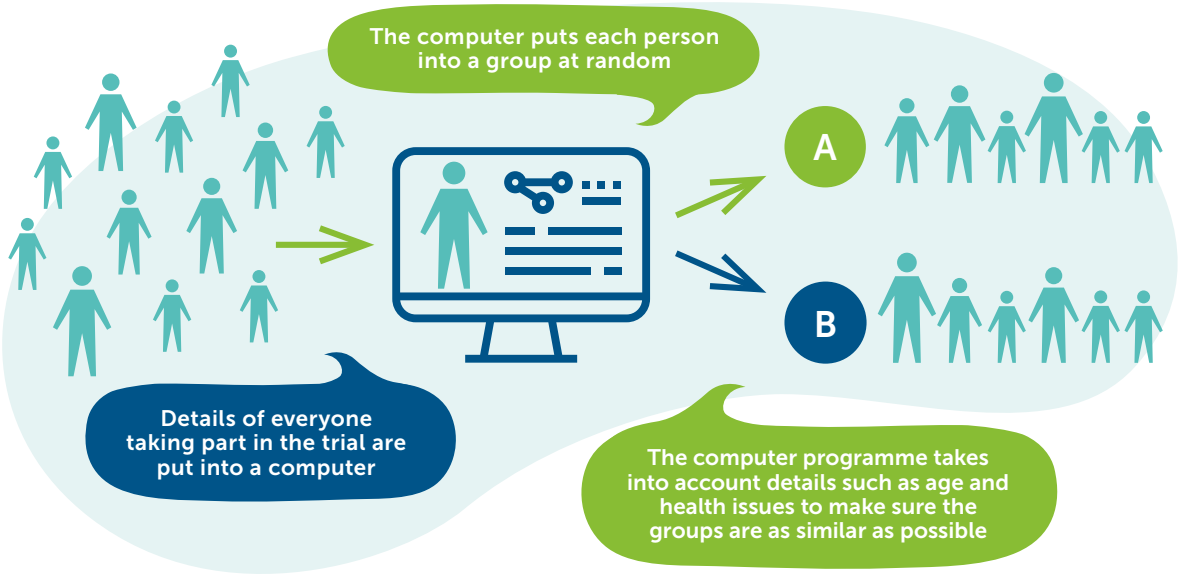


3.2 Randomisation

Participants in a trial are assigned to the vaccine and control groups by chance or by random selection, sometimes using a computer. Neither the researchers nor the participants can decide which study group each participant will go into. This process is known as randomisation.

Randomisation is the best way to make sure that the different testing groups do not have different characteristics that would affect the outcome of the study. If researchers or participants could choose which group to go into, the groups may be unfairly divided and may be not alike enough to compare, for example if there were more women than men in one group than in the other. If the groups are not comparable, the effects of the vaccine cannot be measured rigorously.

RANDOMISATION



3.3. Blinding

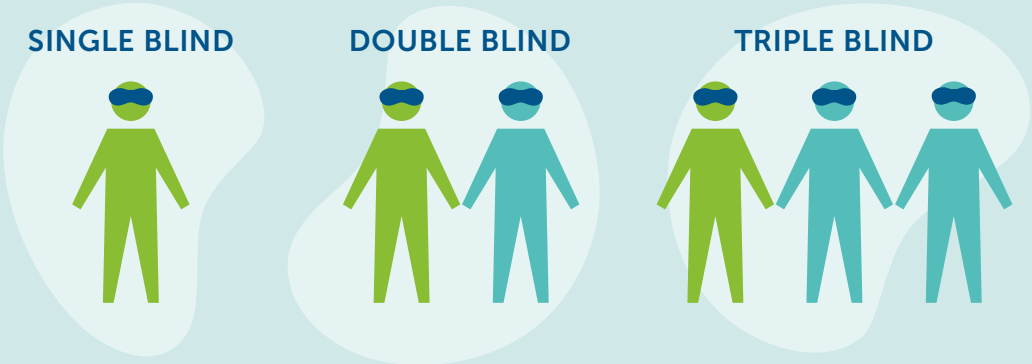
Blinding refers to the fact that the participants do not know whether they have received the candidate vaccine or the placebo; therefore, they are 'blind' to what they have received in the trial. This is also sometimes called 'masking.' The purpose of blinding is to make sure that side effects are not interpreted differently according to whether someone has received the vaccine or placebo and to make sure that participants do not change their behaviour or what they report (for example, side effects) according to whether they received vaccine or placebo.

In many trials, neither the researchers nor the participants know who is getting the vaccine. This is called double-blinding. Double-blinding ensures that researchers are not biased, or unfairly influenced, by knowing what the participant has received. If researchers know whether the participant received the vaccine or the placebo, they may over- or under-report side effects. The individuals responsible for randomisation (generally statisticians, but never anyone on the clinical trial staff) keep the information in a secure location until the end of the study. Most clinical trials are double-blinded.

After the trial is complete and all data have been collected and analysed, researchers 'unblind' the study to see which participants received the vaccine and which received the placebo. Once the trial is unblinded, the participants are also told what they received. In some special cases researchers may have to see whether the participant was in the vaccine or placebo group before the trial is complete. This 'unblinding' is very rare, especially in vaccine trials, for several reasons, but mainly because serious reactions to vaccines are very rare.

Blinding

- Having a blind trial helps prevent any bias.
- Relevant groups who may or may not have knowledge of treatment assignments:
  - **Single blind trial:** Participants do not know what intervention they are given.
  - **Double blind trial:** Investigators and participants do not know what intervention is given to whom.
  - **Triple blind trial:** Investigators, participants, and statisticians do not know what intervention is given to whom.



4. Clinical Trial Phases

All new vaccines and drugs must be thoroughly researched and tested in the laboratory and in animals (known as preclinical studies) before they are tested on people. To receive approval for human testing, researchers must first show data demonstrating that the candidate vaccine is unlikely to harm people *and* likely to be effective.

A series of carefully conducted trials is the gold-standard method to determine if a new vaccine protects people from infection or disease. This series involves three or more phases and several trials before a vaccine can be approved by public health regulatory authorities and thereafter licensed and distributed for targeted or general use.

The whole process, including all phases of testing, can take 10 years or more. In the case of COVID-19 vaccines, significant global government and private collaboration and investment was able to reduce this timeframe by testing multiple candidate vaccines simultaneously rather than sequentially as well as minimising the time lapse between clinical trial phases. Unfortunately, vaccines for more complex diseases like HIV may still take a long time.

A vaccine must be proven safe and efficacious before it can be approved for licensure by public health regulatory agencies, licensed, and distributed to the community.

4.1 Phase I

These trials are the first tests in humans of a candidate vaccine. They measure safety and immunogenicity in a small group (20–60) of participants who do not have the disease being studied. Several Phase I trials may be conducted to obtain this information, possibly involving different routes of injection, vaccine doses, and populations. If a vaccine is found to be 'immunogenic,' this means that immune responses have been observed in participants' blood or body tissue after they receive the vaccine. Further studies are needed to establish whether this immune response will protect a person against infection or disease. Phase I trials typically last 12–18 months.

4.2 Phase II

These trials also measure safety and immunogenicity but in a larger group (50–3,000) 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.

In some cases, a larger group of participants that represent the population at risk for the disease is asked to join a trial; or different dosages are studied to find the best dose with minimal side effects. These trials are known as Phase IIb trials. These trials can provide important data about safety of the vaccine and may give some information about whether the vaccine works or has efficacy.

4.3 Phase III

Phase III trials continue to evaluate the safety and measure efficacy of the vaccine in a much larger number of people (estimates range from 2,000 to over 20,000, depending on the number of infections per year in the population) who are at significant risk of infection.

Immunogenicity may be measured in some or all participants to ensure that the vaccine is inducing the same immune response it did in previous smaller trials. This is particularly important if the vaccine is from a different manufacturing batch than the one tested in earlier phases. Phase III trials can last for several (3–5) years.

Why it is important to also conduct clinical trials in low- and middle-income countries

It is important to test vaccines in the regions where they are most likely to be used — including LMICs — to ensure that they are suitable for use in those settings. Testing vaccines in these countries will also provide the evidence needed to speed up approval and access where vaccines are needed most.

1. Ensuring the vaccine is safe and effective for the populations that need it most

It is important to test vaccines in different areas of the world because the genetic make-up and health status of individuals may affect how a vaccine works. By conducting large-scale trials in settings where the disease is common, researchers can learn more about any side effects in any given specific population. In the case of HIV for example, it is important to know that the vaccine can protect against the specific type of HIV that the population encounters in their part of the world. Some subtypes of HIV are more common in certain regions than in others (see **MODULE 4** for further information). Differences between these subtypes (as well as differences within them) and high levels of co-infections may affect how well a vaccine works in a particular area.

2. Measuring efficacy can only be done where the disease is common

After a vaccine has been tested for safety, it needs to be tested in places where the disease is very common to see if it effectively prevents disease where it is most needed. For infectious diseases such as HIV, TB, and Lassa, this means testing vaccines in countries with high incidence rates. For example, Lassa fever is predominantly found in West Africa. Outside of this region, there is so little Lassa virus infection and disease that a Phase II or III clinical trial would not be feasible.

3. Ensuring that it is appropriate to local conditions

Conducting clinical trials in-country may demonstrate that the vaccine can be delivered effectively in the local conditions. For example, if the vaccine requires maintaining a cold chain for transportation, the trial can explore how that would work in tropical settings. Researchers can also ascertain how best to introduce the vaccine in a particular population if it is shown to be effective.

4. Facilitating national regulatory approval

   Historically, vaccines have taken up to 20 years from approval and licensure to reach low- and middle-income countries, where they are most needed. For example, while a vaccine against hepatitis B virus has been available since 1981, coverage of the vaccine dose at birth in 2019 was only 43% globally and only 6% in the WHO African Region.

   Many governments ask to see data from trials conducted in their own regions to licence new vaccines for use. Conducting Phase III trials in the countries that are hardest hit provides the relevant data to support local vaccine approval by the national regulatory authorities and can mean that they reach those that need the vaccine sooner.

5. Raising awareness and preparing communities

   The process of conducting a clinical trial will help increase knowledge and awareness of vaccine research among key stakeholders and communities, which will help ready communities for a vaccine when one is available.

4.4 Further Studies

Pilot Projects and Acceptability Studies

Pilot and pre-introductory projects can be designed to learn more about an intervention and can happen while the regulatory approval process is underway. These projects are usually relatively small, and they may look at different strategies for delivering or communicating about the intervention and other issues.

Groups of people who were not originally included in early trials, such as children, adolescents, the elderly, and people who have weaker immune systems (immunocompromised), may be included in these further studies to ensure that the performance of the vaccine is adequate in these groups.

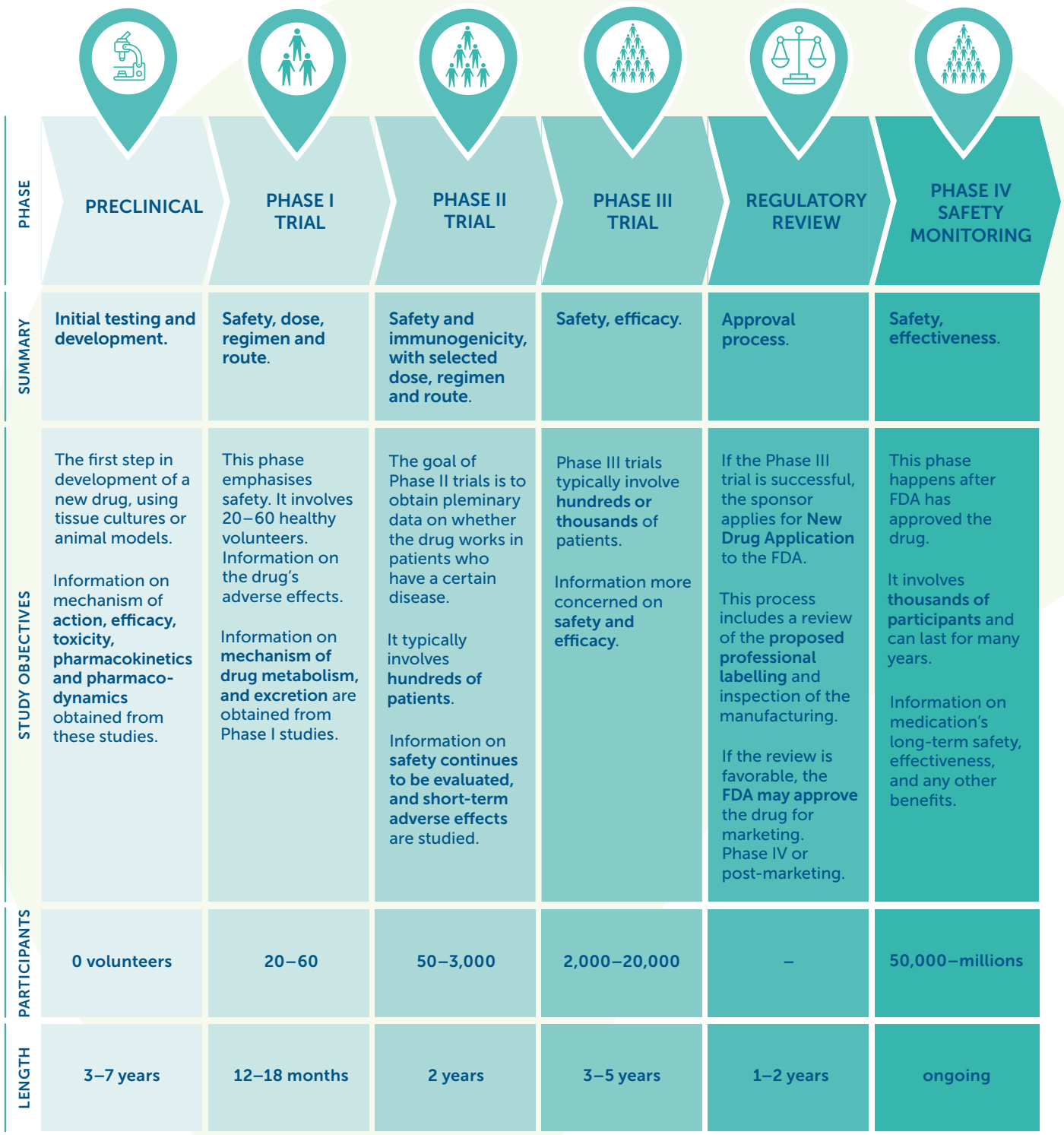
Phase IV

One type of Phase IV study, called an 'expanded access' study, is usually conducted during the interval between the end of the efficacy trial and regulatory approval of the vaccine. This allows for the collection of safety data in a larger population of people as well as access to the candidate vaccine before it is fully approved and licensed.

Phase IV studies may also look at the safety and effectiveness of the vaccine after it is licensed and in use by large populations. These studies examine how the vaccine performs under real-life conditions, as opposed to the controlled conditions of a clinical trial. These studies are sometimes called post-marketing surveillance studies or field studies.

In all cases, the primary aims of these studies are to collect further safety data and data on rare adverse events.

PHASES OF CLINICAL TRIALS



PHASE	PRECLINICAL	PHASE I TRIAL	PHASE II TRIAL	PHASE III TRIAL	REGULATORY REVIEW	PHASE IV SAFETY MONITORING
SUMMARY	**Initial testing and development.**	**Safety, dose, regimen and route.**	**Safety and immunogenicity, with selected dose, regimen and route.**	**Safety, efficacy.**	**Approval process.**	**Safety, effectiveness.**
STUDY OBJECTIVES	The first step in development of a new drug, using tissue cultures or animal models. Information on mechanism of **action, efficacy, toxicity, pharmacokinetics and pharmaco-dynamics** obtained from these studies.	This phase emphasises safety. It involves 20–60 healthy volunteers. Information on the drug's adverse effects. Information on **mechanism of drug metabolism, and excretion** are obtained from Phase I studies.	The goal of Phase II trials is to obtain pleminary data on whether the drug works in patients who have a certain disease. It typically involves **hundreds of patients.** Information on **safety continues to be evaluated, and short-term adverse effects** are studied.	Phase III trials typically involve **hundreds or thousands** of patients. Information more concerned on **safety and efficacy.**	If the Phase III trial is successful, the sponsor applies for **New Drug Application** to the FDA. This process includes a review of the **proposed professional labelling** and inspection of the manufacturing. If the review is favorable, the **FDA may approve** the drug for marketing. Phase IV or post-marketing.	This phase happens after FDA has approved the drug. It involves **thousands of participants** and can last for many years. Information on medication's long-term safety, effectiveness, and any other benefits.
PARTICIPANTS	**0 volunteers**	**20–60**	**50–3,000**	**2,000–20,000**	**–**	**50,000–millions**
LENGTH	**3–7 years**	**12–18 months**	**2 years**	**3–5 years**	**1–2 years**	**ongoing**

5. Participation in Vaccine Trials

Participation in a vaccine clinical trial is usually a major commitment. A typical trial involves many visits to the clinical research centre to receive medical evaluation, counselling, laboratory tests, and injections. While it can be a lengthy and involved process, it can also be a rewarding experience.

Participation in any clinical trial is always voluntary. Enrolment can only occur after a thorough process to obtain informed consent. Participants' health, welfare, and human rights are strictly protected by international and national guidelines and consultation with community advisory boards (CABs). For more information see **MODULE 6**.

Eligibility criteria determine who can participate in clinical trials. The inclusion of diverse populations in clinical trials is important to provide evidence that the vaccine will be safe and effective in the full range of people likely to use it. It is increasingly recognised that the inclusion of populations such as adolescents, children, and even pregnant and breastfeeding women is very important.

Importance of including women in clinical trials

The number of women participating in trials has historically been lower than the number of men. This is due to a range of factors including mistrust of clinical research, the requirement to be on contraception for a specified period during the study, childcare responsibilities, and/or cultural or social expectations.

It is important for adequate numbers of women to be involved in vaccine trials to be able to differentiate the effect of the vaccine on men and women. It is possible that the vaccine will work differently in men and women due to differences in anatomy and biology.

Without participation of women in the trial, regulatory authorities may decide that there is not enough information to approve the vaccine for both women and men.

Before an individual can be enrolled onto a trial, they must meet the trial eligibility criteria. These are not the same in each trial and are specified in the trial protocol. There are both inclusion and exclusion criteria.

Inclusion criteria specify the characteristics required for study entry, such as general health status, ability to provide informed consent, specific biological characteristics, or stage of the disease in the case of TB vaccines (see **MODULE 2**).

Exclusion criteria specify the characteristics that disqualify people from participation. They often include factors such as having other health conditions at the same time (such as diabetes or heart disease).

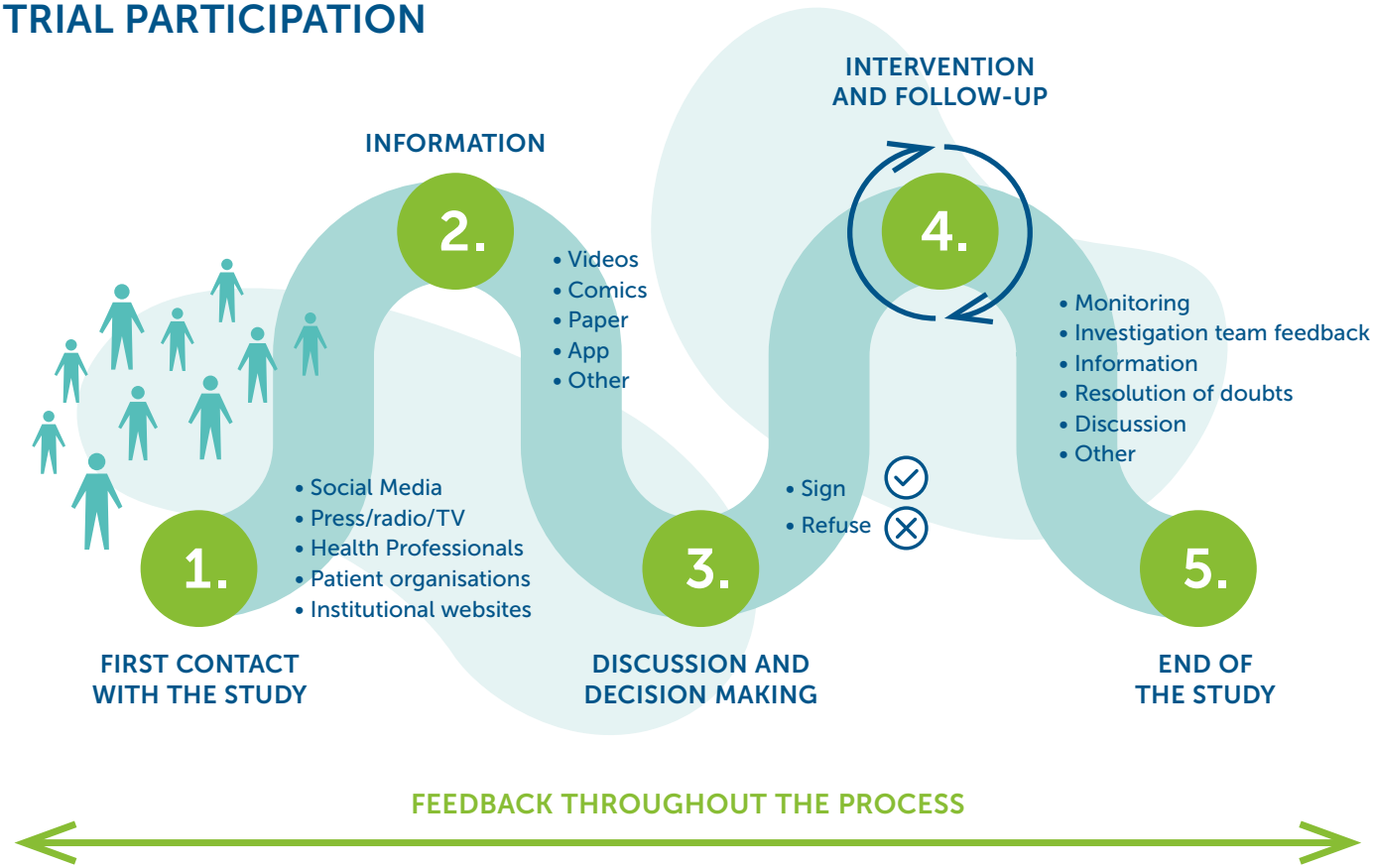
Prevention trials only enrol participants who are not already living with the infection or disease that the vaccine is trying to prevent. However, some trials do need participants who have had the disease when they look at preventing disease progression (for example TB). In general, participants must also not be enrolled unless they are:

- Able to fully understand the trial and willing to give informed consent.
- Willing to stay in the study for the amount of time required, generally up to 18 months for Phase I/Phase II trials and several years for Phase III trials.

The decision about whether to participate in a trial can only be made by the individual — it is unethical for anyone (family members, trial staff, and any other person) to pressure someone into participating.

All participants should be counselled on disease prevention and risk-reduction. No participant should participate in a trial and believe they will be protected. As part of the study, they may be receiving a placebo, and it is not known if the candidate vaccine will provide protection.

TRIAL PARTICIPATION



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- International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Copyright ICH Secretariat, Geneva, Switzerland. Online version: *https://www.ich.org*
- Clinical Research Resources: *http://www.clinicalresearchresources.com*
- National Institutes of Health website on clinical trials: *http://www.clinicaltrials.gov/ct/info/resources.*
- World Health Organization: *https://www.who.int/health-topics/clinical-trials*
- Evaluating inclusion and exclusion criteria in clinical trials public workshops: workshop report, FDA: *https://www.fda.gov/media/134754/download*

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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