

IAVI VACCINE LITERACY LIBRARY

2022



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.

Acknowledgements

IAVI would like to acknowledge the contribution of Doreen Asio, Monica Bagaya, Vincent Basajja, Kundai Chinyenze, William Dekker, Evanson Gichuru, Nyokabi Jacinta, Sarah Joseph, Dagna Laufer, Sharon Lipesa, Shelly Malhotra, Miliswa Magongo, Blossom Makhubalo, Roselyn Malogo, John Mdluli, Ireen Mosweu, Juliet Mpendo, Gaudensia Mutua, Vincent Muturi-Kioi, Conwell Mwakoi, Jauhara Nanyondo, Gertrude Nanyonjo, Jacinta Nyakobi, Faith Ochieng, Fred Otieno, Daisy Ouya, Gayle Patenaude, Hilda Phiri, Lewis Schrager, Nicole Sender, Elana Van Brakel, Anja Van der Westhuizen, Kelvin Vollenhoven, Jeffery Walimbwa, Mathias Wambuzi for reviewing the content of the **IAVI Vaccine Literacy Library**.

Lead Consultants: Roger Tatoud and Rebekah Webb.

Design and Illustration: Anthea Duce.

© International AIDS Vaccine Initiative, Inc. 2022

All information in this document may be reproduced or copied without permission, provided IAVI is acknowledged as the source. However, reproduction of substantial portions of the manual, or any use of the material other than for education or non-commercial purposes, requires explicit, prior authorization in writing.

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

The text of the **IAVI Vaccine Literacy Library** may be found online at www.iavi.org/news-resources/iavi-vaccine-literacy-library

IAVI gratefully acknowledges the generous support provided by the following major funders



Biomedical Advanced Research and Development Authority (BARDA) | Foundation for the National Institutes of Health | National Institute of Allergy and Infectious Diseases | amfAR, The Foundation for AIDS Research | Broadway Cares/Equity Fights AIDS | Cancer Research UK | The City of New York, Economic Development Corporation | Congressionally Directed Medical Research Program (DoD) | GSK | The Hearst Foundations | Keith Haring Foundation | Merck & Co., Inc., Kenilworth, NJ, USA (known as MSD outside the USA and Canada)

And many other generous individuals and partners around the world

As of April 2022

Contents

Abbreviations	7
Introduction	8
MODULE 1: VACCINES AND THE GLOBAL RESPONSE TO INFECTIOUS DISEASES	10
1. Global Health and Emerging Epidemics	12
2. Why Vaccines Are Needed	13
3. The HIV Epidemic	15
4. The TB Epidemic	16
5. Endemic Lassa Fever in West Africa	17
MODULE 2: INTRODUCTION TO HIV, TUBERCULOSIS, AND LASSA FEVER	20
1. HIV	22
1.1 A Brief History	22
1.2 Human Immunodeficiency Virus	22
1.3 HIV Life Cycle	24
1.4 Diagnosis	26
1.5 Disease Progression	26
1.6 Prevention and Treatment	28
2. Tuberculosis	31
2.1 A Brief History	31
2.2 Mycobacterium Tuberculosis (M.tb)	31
2.3 Diagnosis	32
2.4 Disease Progression	33
2.5 Prevention and Treatment	34
3. Lassa Fever	36
3.1 A Brief History	36
3.2 Lassa Virus	36
3.3 Diagnosis	37
3.4 Disease Progression	37
3.5 Prevention and Treatment	38





MODULE 3: THE IMMUNE SYSTEM 39

Summary Points	41
1. Introduction	41
2. The Immune System: Key Concepts	42
2.1 The Immune Response	42
2.2 Organs of the Immune Systems	42
2.3 Cells of the Immune Systems	43
2.4 The Humoral Immune Response	45
2.5 The Cellular Immune Response	46
3. HIV and the Immune System	47
4. TB and the Immune System	48
5. Lassa Fever and the Immune System	49

MODULE 4: INTRODUCTION TO VACCINES 50

Summary Points	52
1. Key Definitions and Concepts of Vaccinology	52
1.1 What is a Vaccine?	52
1.2 Adjuvants	52
1.3 Efficacy and Effectiveness	53
2. How Vaccines Work	55
3. Vaccine Platforms	58
4. Challenges in Developing Vaccines	60
5. HIV Vaccine Research and Development	62
5.1 A Brief History	62
5.2 HIV Vaccine Research and Development	64
5.3 HIV Vaccine Development Challenges	65
6. TB Vaccine Research and Development	66
6.1 A Brief History	66
6.2 TB Vaccine Research and Development	67
6.3 Challenges of TB Vaccine Development	67
7. Lassa Fever Vaccine Research and Development	69
7.1 A Brief History	69
7.2 Lassa Vaccine Research and Development	69
7.3 Challenges of Lassa Vaccine Development	69





MODULE 5: WHAT IS A VACCINE CLINICAL TRIAL? 70

Summary Points	72
1. Introduction: What is a Clinical Trial?	72
2. Key Definitions in Clinical Trials	73
2.1 Safety	73
2.2 Dose, Regimen and Route of Immunisation	74
2.3 Immunogenicity	74
2.4 Efficacy	75
2.5 Effectiveness	76
2.6 Sample Size and 'Power'	76
3. Clinical Trial Methods	77
3.1 Control Group in a Trial	77
3.2 Randomisation	78
3.3 Blinding	78
4. Clinical Trial Phases	80
4.1 Phase I	80
4.2 Phase II	80
4.3 Phase III	81
4.4 Further Studies	82
5. Participation in Vaccine Trials	84

MODULE 6: THE ETHICS AND REGULATION OF CLINICAL TRIALS 87

Summary Points	89
1. Introduction:	89
2. Principles of Ethical Research	90
2.1 Value	90
2.2 Scientific Validity	91
2.3 Fair Participant Selection	91
2.4 Favourable Risk/Benefit Ratio	91
2.5 Independent Review	93
2.6 Trial Guidelines	95
2.7 Informed Consent	97
2.8 Respect for Participants	100
3. Community Outreach	101





MODULE 7: PREPARING FOR FUTURE ACCESS 102

Summary Points	104
1. Introduction	104
2. Barriers to Vaccine Roll Out	106
2.1 Global Funding, Finance Mechanisms, and Pricing	106
2.2 Regulatory Approval and Licensure	108
2.3 Manufacturing Capacity	109
2.4 Operational Research	109
2.5 Delivery and Roll Out	109
3. Barriers to Vaccine Acceptance and Use	110
3.1 Acceptability	110
3.2 Vaccine Hesitancy	110
3.3 Efficacy	111
3.4 Product Characteristics	111
3.5 Stigma and Risk Perception	111

MODULE 8: GUIDANCE FOR TRAINERS 112

1. Introduction	114
2. Target Audience	114
3. How to Use this Manual	115
4. Using the Slides	115
5. How to Plan a Training or Presentation	115
6. Selecting the Content	116
7. Answering Difficult Questions	117
8. How to Conduct a Refresher Training	117
9. Acknowledgement of IAVI and Materials Review	118

Glossary	119
----------	-----



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 infection
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

WHAT IS THE
VACCINE LITERACY
LIBRARY?

Where can I learn
about vaccines and
clinical trials?

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

IAVI assumes no responsibility or liability for any errors or omissions in the content of the **IAVI Vaccine Literacy Library**. The information contained in this Resource Library is provided on an ‘as is’ basis with no guarantees of completeness, accuracy, usefulness, or timeliness.

How to Cite the IAVI Vaccine Literacy Library

IAVI Vaccine Literacy Library, IAVI, New York, USA, 2022.

MODULE 1: VACCINES AND THE GLOBAL RESPONSE TO INFECTIOUS DISEASES



MODULE 1

VACCINES AND THE GLOBAL RESPONSE TO INFECTIOUS DISEASES

CONTENTS 11

1. Global Health and Emerging Epidemics	12
2. Why Vaccines Are Needed	13
Vaccines save lives	13
Vaccines protect the most vulnerable	13
Vaccines are cost-effective	14
Vaccines end epidemics	14
Vaccines protect health systems	14
3. The HIV Epidemic	15
4. The TB Epidemic	16
5. Endemic Lassa Fever in West Africa	17



1. Global Health and Emerging Epidemics

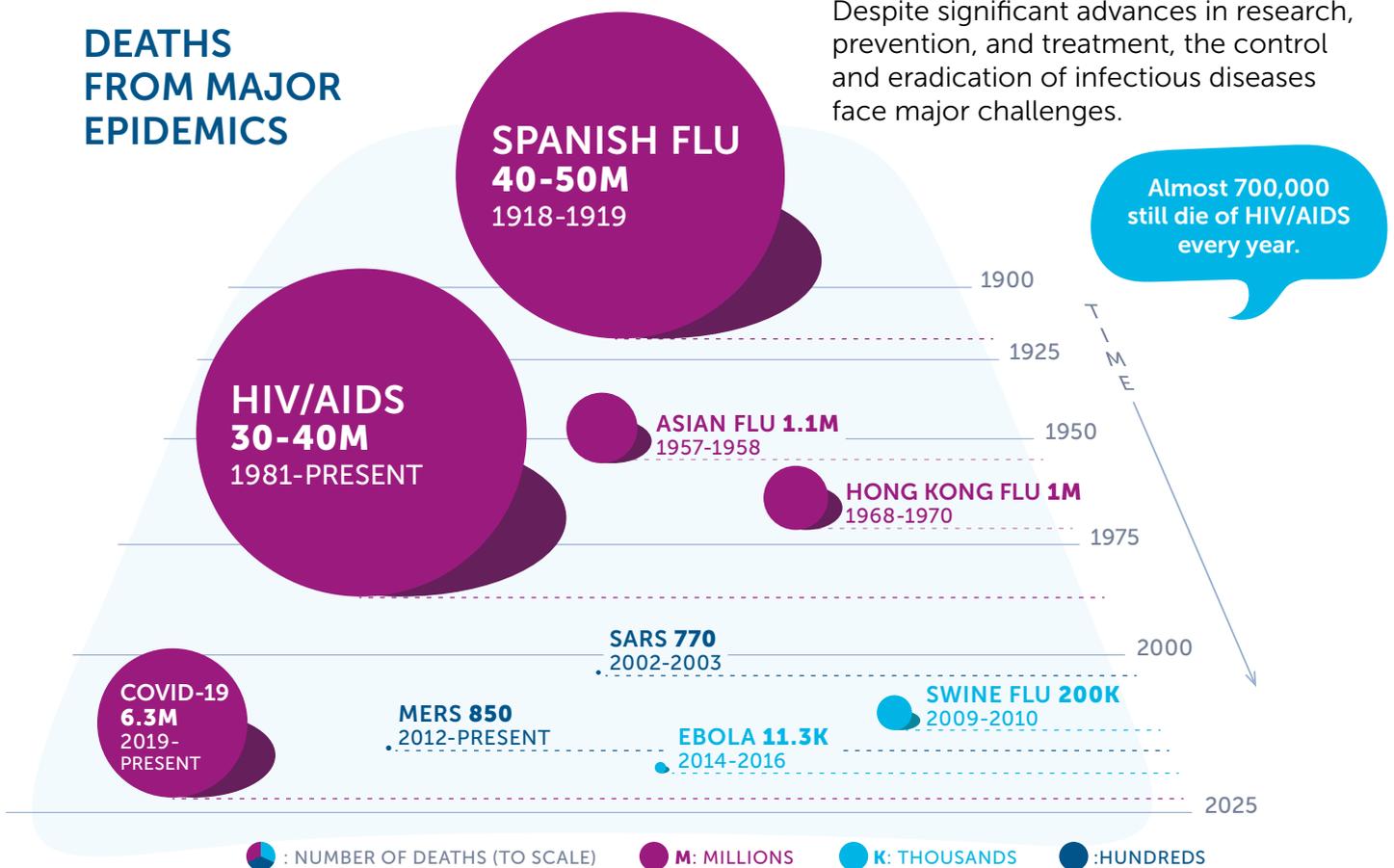
Infectious diseases are global killers. Every year, millions of people around the world are affected by HIV/AIDS, TB, malaria, and other diseases caused by organisms such as bacteria, viruses, fungi or parasites. COVID-19 has taught us the danger of new, emerging epidemics that have the power to bring our world to a standstill.

Children are among those most affected. According to the World Health Organization, infectious diseases are leading causes of death for children under five.

Low-income countries bear the highest burden. Six of the top 10 causes of death in low-income countries are communicable diseases. Together, these diseases are a significant threat to human life, sustainable development, and the global economy.

Despite significant advances in research, prevention, and treatment, the control and eradication of infectious diseases face major challenges.

DEATHS FROM MAJOR EPIDEMICS



Epidemic, Pandemic, and Endemic

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.

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

Endemic: When a disease occurs frequently and at a predictable rate in a specific location or population.

2. Why Vaccines Are Needed

Vaccines are one of the most effective health interventions that we have to prevent the spread of infectious diseases and their associated economic and social impact. Vaccines are also central to the management of infectious disease outbreaks and one of the best ways to prevent epidemics and pandemics. Vaccines work by preparing a person's immune system (the body's natural defences) to recognise and defend itself against a specific disease. No epidemics have been successfully brought under control without the use of vaccines.



Vaccines save lives

Vaccination prevents 2–3 million deaths every year from diseases like diphtheria, tetanus, pertussis, influenza, measles, and severe diarrhoea caused by Rotavirus. Infectious diseases circulating today – including HIV and tuberculosis – continue to have unacceptably high death rates, despite huge advances in prevention and effective treatment. Emerging and re-emerging diseases have the potential to evolve into pandemics.

All too often, disease prevention strategies rely on people changing their behaviour. While behaviour change has an important role to play, it is unlikely to be effective by itself to prevent infection or further transmission in communities. Vaccines are a crucial tool in controlling the spread of infectious diseases together with addressing long-term structural factors such as poverty, poor housing, and inadequate sanitation that put people at increased risk of certain infectious diseases.

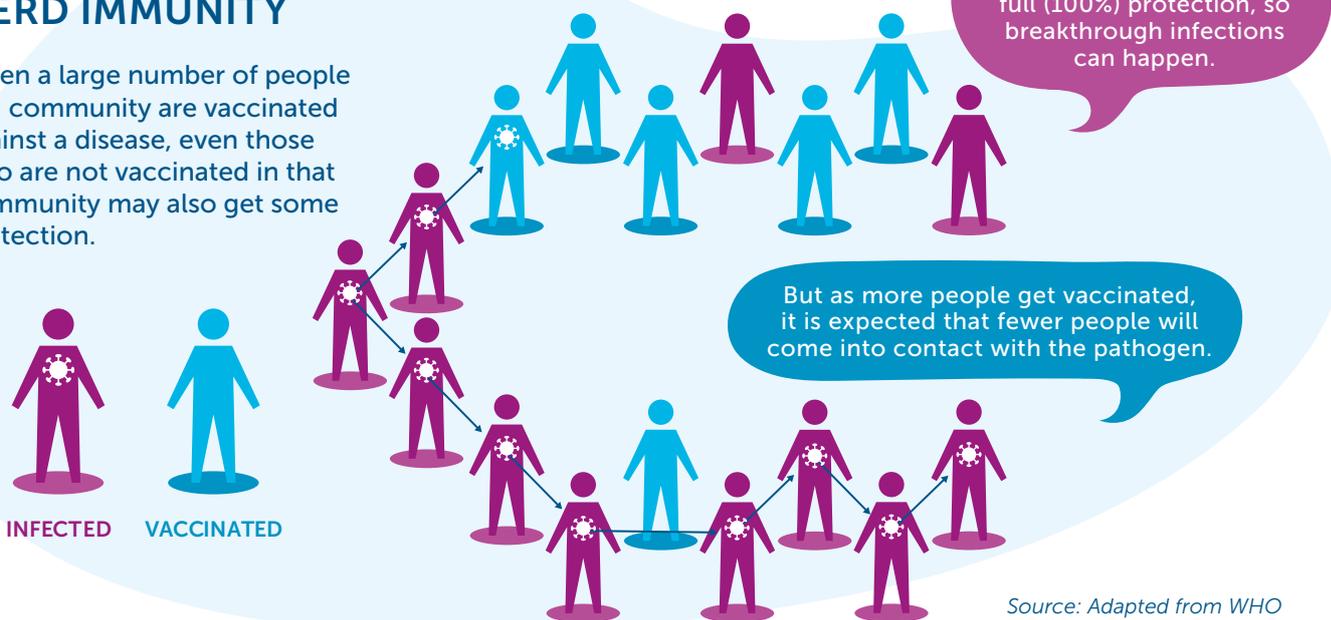


Vaccines protect the most vulnerable

By providing protection from disease at an individual level and stopping its spread in the community, vaccines can protect highly vulnerable people from severe illness and death. These include the very young and the very old, as well as people with suppressed immune systems, such as people living with cancer or HIV. Without a vaccine, these people are more likely to die from their infection.

VACCINE-INDUCED HERD IMMUNITY

When a large number of people in a community are vaccinated against a disease, even those who are not vaccinated in that community may also get some protection.



Source: Adapted from WHO



Vaccines are cost-effective

Immunisation, one of the most cost-effective health interventions, provides savings to the health system by reducing the number of people who need treatment and lifetime care, as well as lost wages and lost productivity. Gavi, the Vaccine Alliance has estimated that every dollar invested in vaccination saves US\$16 in health care costs (in 2016). Since 2000, Gavi has helped lower-income countries to prevent more than 15 million future deaths through its support for routine immunisation programmes and vaccination.



Vaccines end epidemics

Vaccines play a critical role in the prevention and control of disease outbreaks and in promoting global health. Without a vaccine, it is nearly impossible to bring any epidemic or pandemic to an end. Infectious diseases can spread rapidly through a community, and through the ease of today's international travel, reach every part of the world. Border controls, quarantine, lockdowns, self-isolation, and social distancing measures can all play a role but have a huge negative impact on society and the economy and these strategies have been shown to be politically unsustainable as long-term strategies in all but the most extreme cases.

Without vaccination, we are unlikely to see an end to the big killers such as HIV, TB, and other major infectious diseases.



Vaccines protect health systems

Without immunisation, epidemics and pandemics can easily overwhelm health systems. Even when treatment exists, the rate at which people can be treated is often limiting. In addition, health professionals looking after the sick can be at risk of infection themselves.

While treatment itself can be a form of prevention (such as is the case with TB and HIV), it often needs to be long-term and brings its own challenges. These include stigma, the burden of taking pills daily, side effects, and the possibility of viral resistance in the case of non-compliance. Vaccines offer considerable advantages over treatment in that they trigger the body's own immune system to do the work. Although additional vaccine shots are sometimes needed to provide lasting protection, immunisation remains efficient, durable, and is likely to have fewer side effects than the infectious disease itself.

Incidence and Prevalence

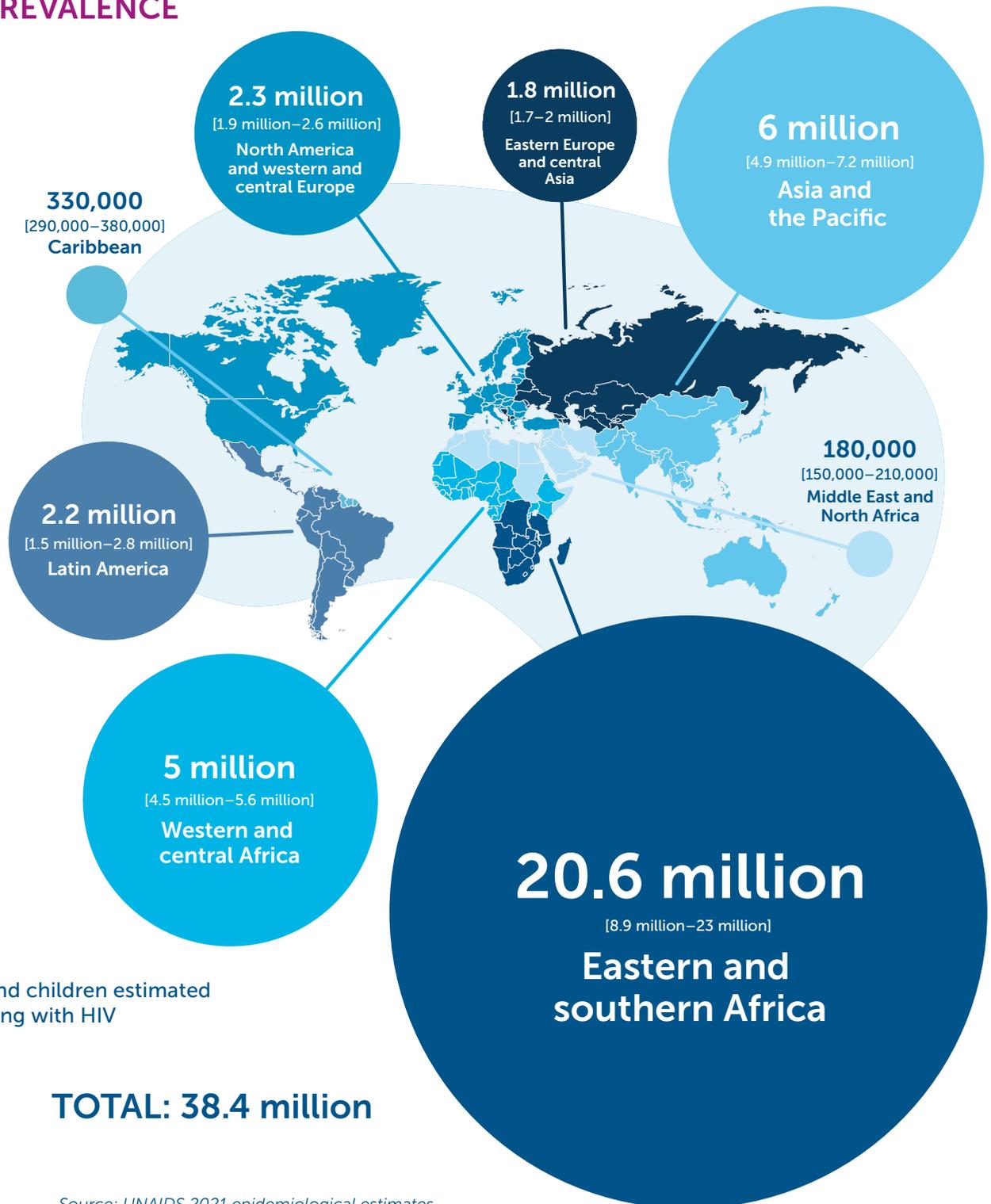
Prevalence refers to the total number of individuals in a population who have a disease or health condition (e.g., infection) at a specific period of time, usually expressed as a percentage of the population.

Incidence refers to the number of individuals who develop a specific disease or experience a specific health-related event (e.g., infection) during a particular time period (such as a month or year).

3. The HIV Epidemic

HIV is one of the worst epidemics the world has ever seen. The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates globally 38.4 million adults and 1.7 million children were living with HIV at the end of 2021. Over half of all people living with HIV are women and girls.

HIV PREVALENCE



Adults and children estimated to be living with HIV 2021

Source: UNAIDS 2021 epidemiological estimates

One and a half million new infections and 650,000 deaths occurred in 2021 alone. This brings the cumulative number of people living with HIV worldwide to over 84 million since the beginning of the epidemic.

The effects of the HIV epidemic globally are devastating. An estimated 90% of the people living with HIV are in low- and middle-income countries (LMICs), where the resources to undertake prevention efforts and to provide care can be limited.

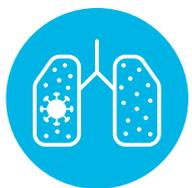
Sub-Saharan Africa is the region most affected:

- Home to nearly two thirds of the people (25 million) living with HIV in the world.
- AIDS is a leading cause of death in the region.
- Women and girls accounted for 63% of all new HIV infections in the region in 2021. Young women aged 15–24 years are twice as likely to be living with HIV than men. Six in seven new HIV infections among adolescents aged 15–19 years are among girls. Approximately 4,900 adolescent girls and young women aged 15–24 years acquired HIV every week in 2021.
- Half of all new HIV infections in this region are among key populations (see **MODULE 6**).

4. The TB Epidemic

Before the COVID-19 pandemic, TB was the leading infectious disease killer worldwide. Found in every country in the world, TB kills 1.5 million people each year. Over 95% of cases and deaths are in low- and middle-income countries (LMICs).

Close to one-quarter of the world’s population (approximately 2 billion people) have been infected with *Mycobacterium tuberculosis* (*M.tb*), the bacteria that causes TB; 5–10% of these people (100–200 million people) will develop active TB disease over their lifetimes. Although anyone can develop TB, the risk is much higher among people living with HIV, and people with other risk factors including undernourishment, diabetes, alcoholism, and smoking. Although most cases of active TB disease occur in adolescents and adults, and in men more than women, 1.2 million children also get sick with TB each year.



Most cases of TB are treatable and curable. The spread of drug-resistant *M.tb* strains, however, is making treatment more difficult, with an increasing proportion of treatment failure and TB-related death. This is particularly true in LMICs. Extensively drug-resistant TB (XDR-TB), caused by strains of *M.tb* resistant to most anti-tuberculosis drugs leads to TB that is very difficult and expensive to treat, with a high treatment failure rate. XDR-TB has now been identified in over 131 countries.

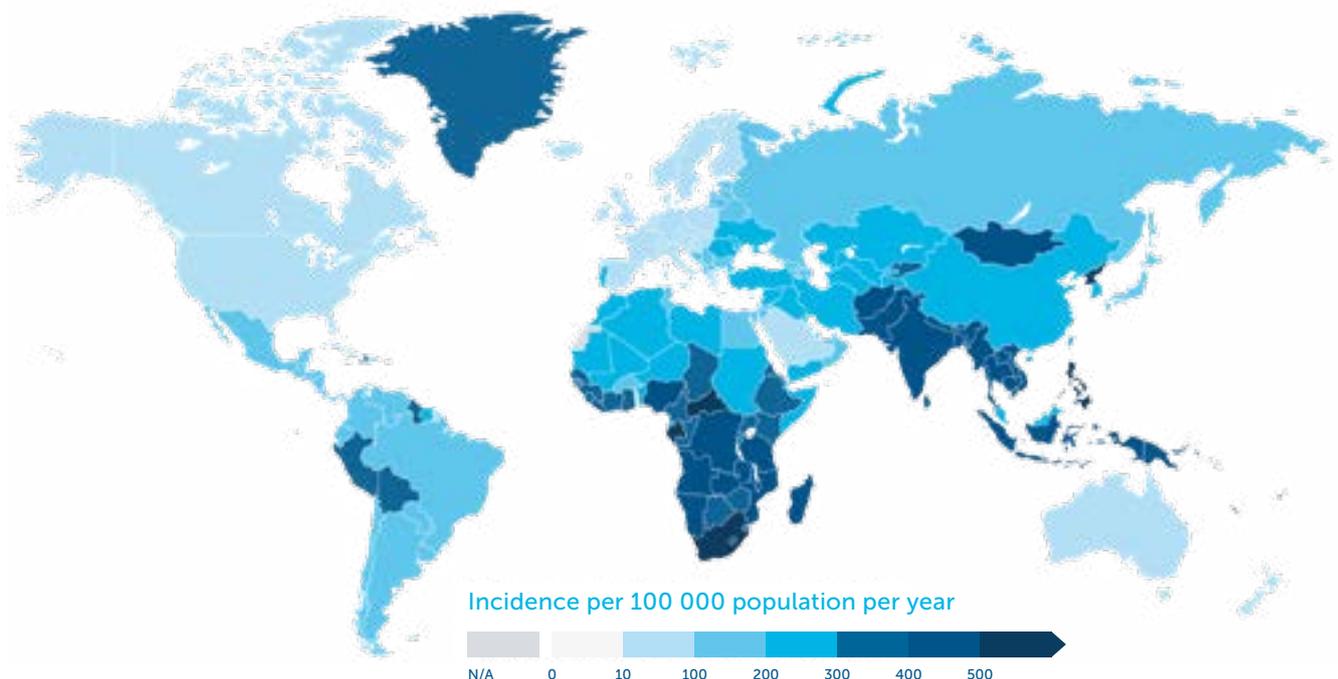
Because of TB, people can typically face costs or suffer income loss equivalent on average to more than 50% of their income.

30 countries account for 86% of all estimated cases worldwide. Most of these countries are found in Asia and include India, China, Indonesia, and the Philippines. 43% of all TB cases occur in South-East Asia.

Africa accounts for a quarter of all TB cases and deaths globally, with Nigeria and South Africa the countries with highest incidence in the region.

TB INCIDENCE

Estimated TB incidence rates | 2020



5. Endemic Lassa Fever in West Africa

Lassa fever is an acute viral illness endemic in some parts of West Africa, causing significant outbreaks of disease each year. There are an estimated 100,000–300,000 cases and 5,000 related deaths each year.

A poorly understood disease that is challenging to diagnose and treat, Lassa fever is particularly dangerous to pregnant women and small children. It increases the risk of death in the third trimester of pregnancy by more than 30% and the risk of miscarriage by 90%. It is also a significant cause of child hospitalisation in some areas. Neurological problems have also been described, including various degrees of deafness, which occur in approximately one-third of infections, and in many cases hearing loss is permanent.

The WHO has identified Lassa fever as one of the top emerging pathogens likely to cause severe outbreaks in the near future.



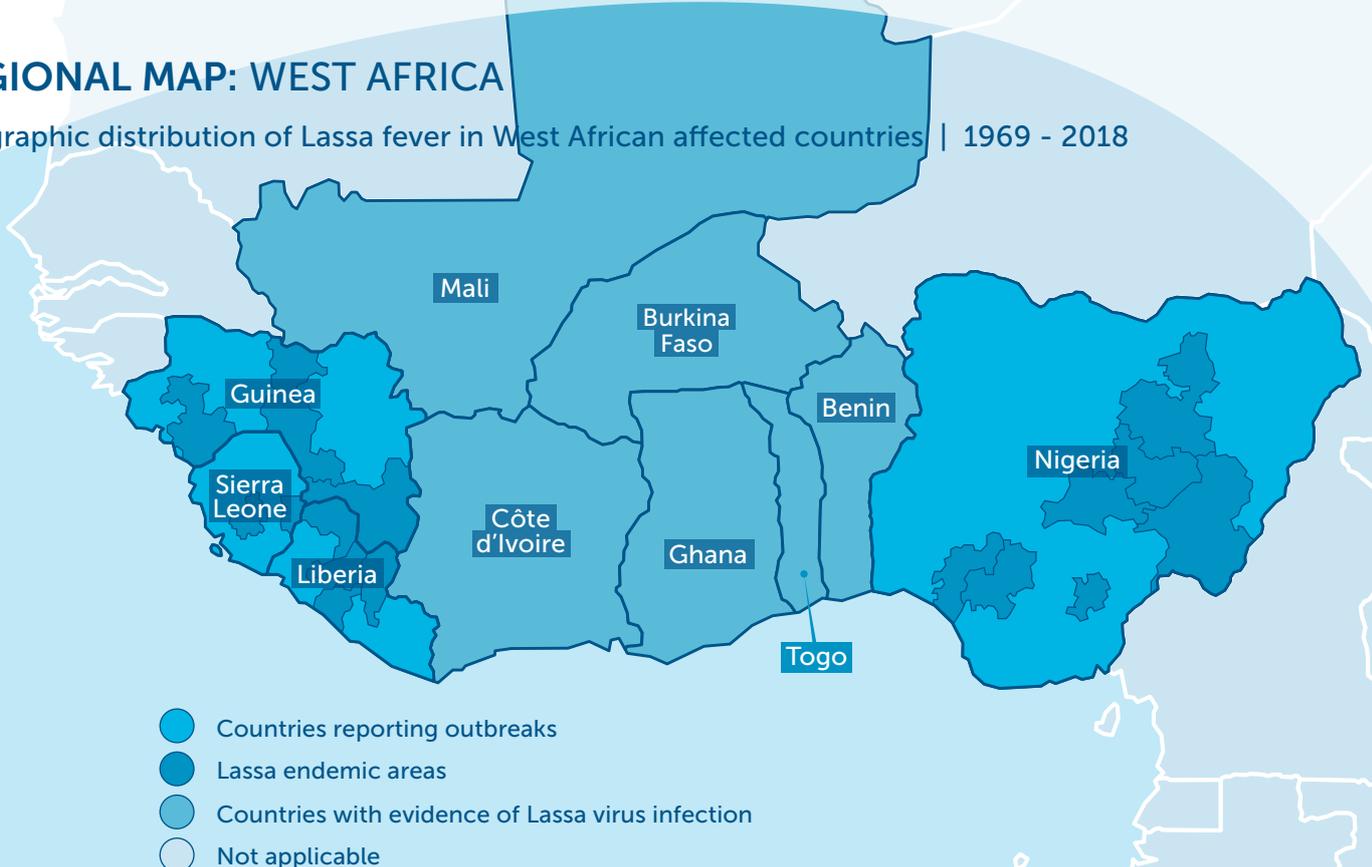
Lassa fever is endemic in parts of West Africa including Guinea, Liberia, Nigeria, and Sierra Leone. The worst outbreaks of Lassa fever have been in Nigeria and Liberia. In 2018, Nigeria had the worst epidemic of Lassa fever ever recorded, spreading across 18 states. Overall, there were an estimated 1,400 infections and 135 deaths. Another outbreak the following year led to 167 deaths.

The disease is less common in neighbouring countries such as the Central African Republic, Mali, and Senegal. Cases have been reported in Côte d'Ivoire, Benin, Burkina Faso, Ghana, the Democratic Republic of the Congo, and Togo.

Outside of West Africa the disease is rarely seen — a few cases have been reported in Europe in individuals who have travelled from endemic countries.

REGIONAL MAP: WEST AFRICA

Geographic distribution of Lassa fever in West African affected countries | 1969 - 2018





FIND OUT MORE...

- UNAIDS Report 2021:
<https://www.unaids.org/en/resources/documents/2021/2021-World-AIDS-Day-report>
- WHO Global TB Report 2021:
<https://www.who.int/teams/global-tuberculosis-programme/tb-reports>
- CDC: <https://www.cdc.gov/vhf/lassa/index.html>
- TB Alliance: <https://www.tballiance.org>
- Excler, J.L., Saville, M., Berkley, S. et al. Vaccine development for emerging infectious diseases. *Nat Med* 27, 591–600 (2021).
- Baker, R.E., Mahmud, A.S., Miller, I.F. et al. Infectious disease in an era of global change. *Nat Rev Microbiol* 20, 193–205 (2022).

MODULE 2: INTRODUCTION TO HIV, TUBERCULOSIS, AND LASSA FEVER

WHY ARE WE STILL
TALKING ABOUT
THESE DISEASES?

Which countries
are worst affected?



MODULE 2

INTRODUCTION TO HIV, TUBERCULOSIS, AND LASSA FEVER

CONTENTS	21
1. HIV	22
1.1 A Brief History	22
1.2 Human Immunodeficiency Virus	22
1.3 HIV Life Cycle	24
1.4 Diagnosis	26
1.5 Disease Progression	26
1.6 Prevention and Treatment	28
2. Tuberculosis	31
2.1 A Brief History	31
2.2 Mycobacterium Tuberculosis (M.tb)	31
2.3 Diagnosis	32
2.4 Disease Progression	33
2.5 Prevention and Treatment	34
3. Lassa Fever	36
3.1 A Brief History	36
3.2 Lassa Virus	36
3.3 Diagnosis	37
3.4 Disease Progression	37
3.5 Prevention and Treatment	38



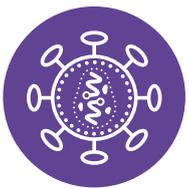
1. HIV

1.1 A Brief History

The origin of the human immunodeficiency virus (HIV) has been extensively researched and it is accepted that the infection spread from non-human primates to humans in Africa sometime in the early 20th century. The virus did not come to widespread public attention until 1981 when an unexplained illness was reported in men who have sex with men in the USA, now known as acquired immune deficiency syndrome (AIDS).

Within two years, in 1983, the virus that causes AIDS was discovered by two teams of researchers based in France and the USA who were awarded the Nobel Prize in Medicine in 2008. Since then, HIV and AIDS have been extensively studied leading to significant progress in diagnosis, prevention, and treatment.

Despite these worldwide efforts, HIV remains a major global public health issue, having claimed 40 million lives since it was first reported (see **MODULE 1** for more information).

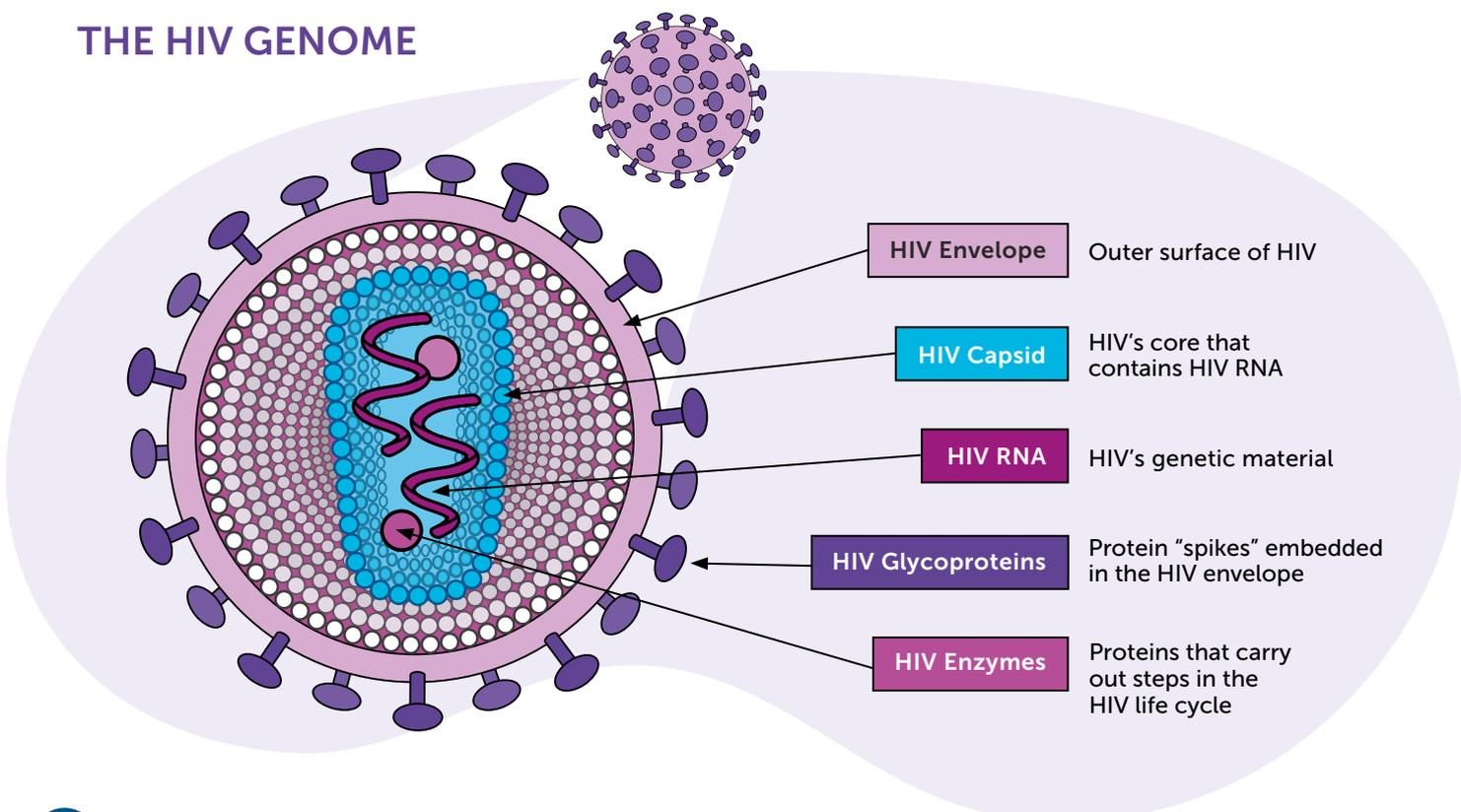


1.2 Human Immunodeficiency Virus

HIV is a retrovirus — this type of virus leads to multi-organ disease characterised by long incubation periods and long-lasting (persistent) infection. The HIV genome, which is made of RNA, contains nine genes that encode 15 viral proteins including structural proteins, enzymes, and envelope glycoproteins.

There are two types of HIV: HIV-1 and HIV-2. HIV-1 is responsible for most infections worldwide, whilst HIV-2 is less infectious, takes longer to cause AIDS and is mostly confined to West Africa and countries with links to West Africa.

THE HIV GENOME

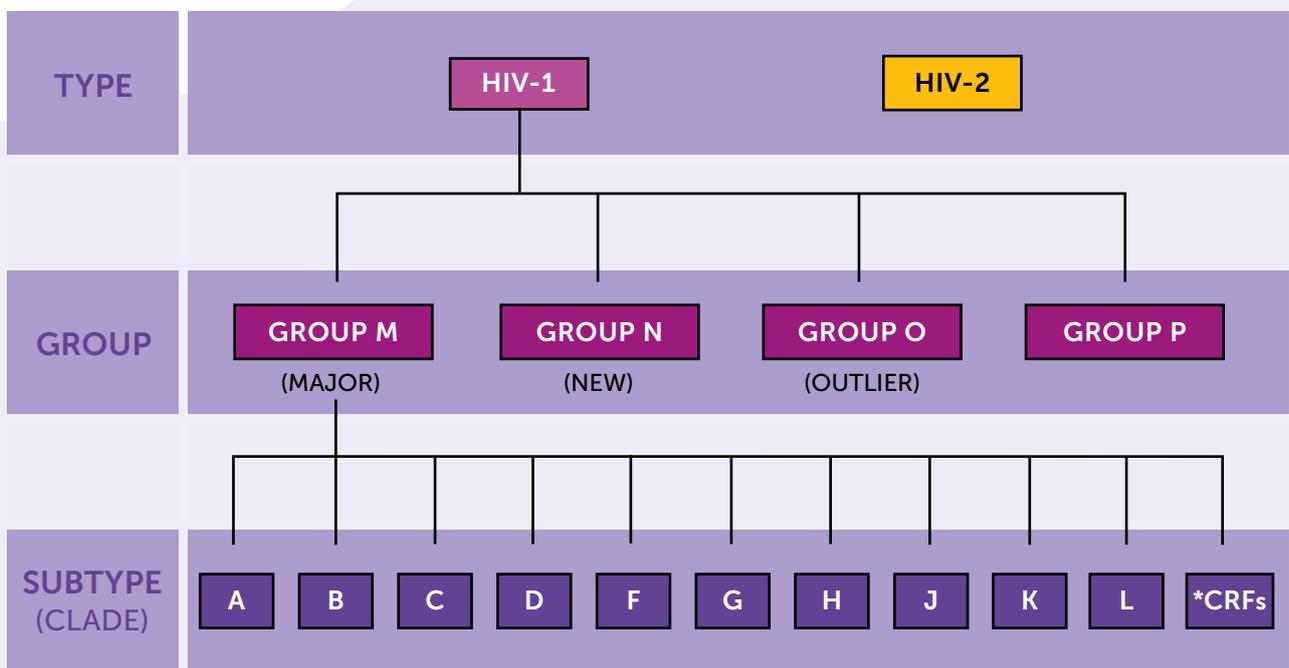


MODULE 2

HIV-1 can be classified in four groups, with group M being the group responsible for the global HIV epidemic. Within group M, there are 10 distinct subtypes of viruses called clades, and hybrid viruses known as circulating recombinant forms (CRFs). The wide diversity of types of HIV makes prevention and treatment challenging.

HIV-1 GROUPS AND SUBTYPES

There are two types of HIV: HIV-1 and HIV-2. HIV-1 can be classified in four groups: M, N, O, and P with M being the group responsible for the global HIV epidemic. Within group M, there are 10 distinct subtypes, or clades, of viruses (A, B, C, D, F, G, H, J, K and L), and hybrid viruses known as circulating recombinant forms, CRFs.



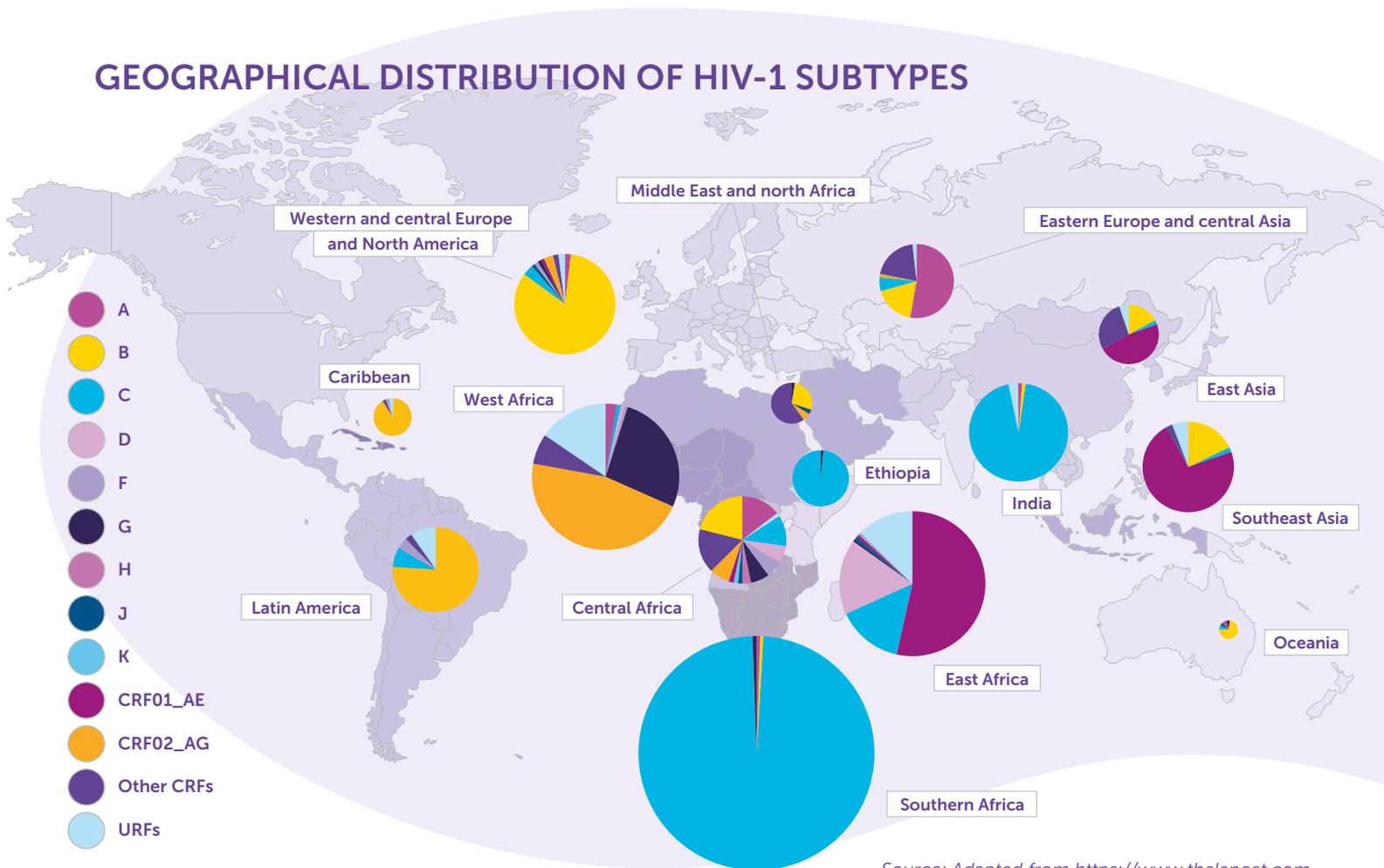
*CRFs = Circulating Recombinant Forms

HIV-1 Group M is the strain that is responsible for 90% of the global HIV pandemic.

Within group M, there are 10 distinct subtypes, or clades, of viruses (A, B, C, D, F, G, H, J, K and L).

The greatest diversity of HIV subtypes is found in Central Africa where the virus originated. Virus subtypes are distributed to varying degrees across different regions of the world. Subtype C is responsible for almost half of all HIV-1 infections worldwide. Subtype B is most common in the Americas, Western Europe, and Australasia. Virus diversity plays an important role in vaccine design and vaccine efficacy (see **MODULE 4**).

GEOGRAPHICAL DISTRIBUTION OF HIV-1 SUBTYPES



Source: Adapted from <https://www.thelancet.com>

1.3 HIV Life Cycle

HIV infection occurs via direct contact with the bodily fluids from a person with HIV with a detectable viral load. People with HIV who take HIV medicine consistently and do not have a detectable viral load have effectively no risk of sexually transmitting HIV to their HIV-negative partners (this is known as U=U, Undetectable = Untransmissible).

The bodily fluids involved in HIV transmission are:

- Blood
- Semen and pre-seminal fluid
- Rectal fluids
- Vaginal fluids
- Breast milk

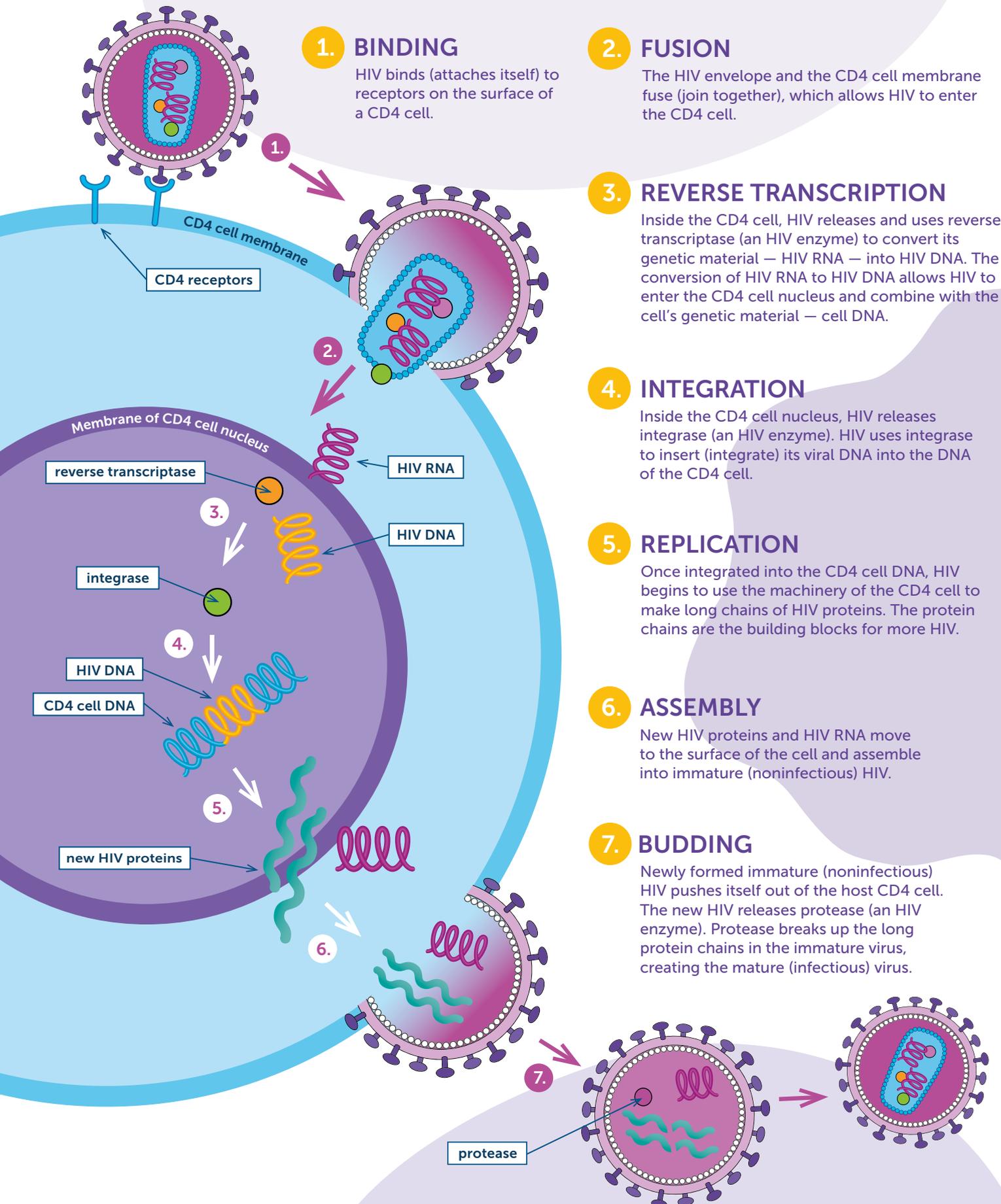
Ways HIV is not transmitted: sharing dishes; saliva; tears; sweat; shaking hands.

HIV enters cells using a 'lock and key' mechanism. Spikes on its outer surface (envelope glycoprotein) lock onto receptors on the cell's surface. The most frequent target cells for HIV infection are immune cells known as CD4+ T-cell lymphocytes.

After entering a cell, HIV RNA is transcribed into DNA by an enzyme called reverse transcriptase. HIV viral DNA can then be part of the genome of the host where it can hide in a dormant state for several years, creating a 'reservoir' of infected cells.

Once in the cell, the virus takes advantage of the cell machinery to produce viral RNA and other different viral components. The viral RNA is then packaged into mature 'virions' that are released by infected cells, killing the cells in the process.

THE HIV LIFE CYCLE





1.4 Diagnosis

Many people with HIV do not have symptoms at first and are unaware of their infection status until much later. The incubation period, the time from exposure to the virus to when the first symptoms develop, can last several years. The most common way to diagnose an HIV infection is through a blood or saliva test.

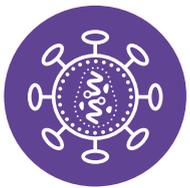
There are three types of HIV tests available:

- Nucleic acid tests (NAT) that can detect HIV RNA in the blood.
- Antigen/antibody tests to detect parts of the virus, for example the viral capsid protein along with antibodies generated in response to the infection.
- Tests to detect antibodies generated by the body in response to the infection.

Antigen and/or antibody HIV tests can be performed with blood or saliva samples (oral test).

HIV testing can be performed by professionals in various settings (hospitals, local clinics, community health organisations) and by people using self-sampling or self-testing. In self-sampling the individual takes their own blood sample and sends it to a laboratory for testing; the results are returned a few days later. With self-testing, the individual collects a sample of saliva, then performs, and interprets the test themselves.

Tests work differently depending on the type of test and when it is carried out. HIV tests have a 'window period' between exposure to the virus and when a test can detect the infection. Laboratory tests are the most sensitive and the most accurate. No single test can provide a full HIV diagnosis and all positive tests require confirmation, while negative tests require regular testing.



1.5 Disease progression

Without treatment, HIV infection progresses in three stages, worsening over time: acute HIV infection, chronic HIV infection, and AIDS.

Acute Infection

During the first few weeks of the infection, HIV multiplies rapidly and spreads through the body. The amount of virus in the blood (viral load) increases exponentially and quickly becomes detectable. The body responds with an 'adaptive' immune response that involves two kinds of responses (these are described in detail in **MODULE 3**). When the first antibodies are produced and detectable this is called seroconversion. This phase may or may not be accompanied by symptoms. Some people may develop fever, generalised enlarged lymph nodes, a non-specific rash, muscle pain, and/or malaise. Others have a short flu-like illness called "seroconversion illness." People are most infectious during this phase.

Chronic Infection

During chronic infection, also called asymptomatic infection, HIV multiplies less rapidly, and HIV viral load decreases. This phase can last several years during which infected individuals show no symptoms or health problems. However, HIV continues to affect the immune system and other systems in the body. During this phase, viral load and CD4 counts indicate how well the body is responding to the infection.

CD4 Count and Viral Load

- CD4 cells are white blood cells of the immune system that fulfil various functions, notably they help coordinate the immune response by stimulating other cells of the immune system. A normal CD4 count ranges from 500 to 1,400 cells per cubic millimetre of blood. HIV weakens the immune system by destroying CD4 cells. The CD4 count is the most important indicator of immune function and the strongest predictor of HIV progression.
- **Viral load (VL)** measures the quantity of HIV in the blood and refers to the number of HIV RNA copies per millilitre of blood.

Over time, the virus rapidly changes and escapes the body's immune response. As the CD4 count decreases, the immune system becomes weaker, and symptomatic infections, such as severe bacterial and viral infections like chicken pox and tuberculosis, can start to occur. Further opportunistic infections, illnesses that the immune system can usually fight, such as fungal diseases begin to occur.

AIDS

In absence of treatment, the HIV infection develops into AIDS, the most advanced stage of the disease. AIDS (acquired immune deficiency syndrome) describes a number of potentially life-threatening infections and illnesses that happen when the immune system has been severely damaged by HIV. AIDS is characterised by a range of illnesses including cancers such as Kaposi sarcoma, certain lymphomas, invasive cervical cancers, and other infectious diseases. People diagnosed with AIDS have a very high viral load and can transmit HIV to others very easily. Without treatment, people with AIDS typically live for only about three years.

Elite Controllers

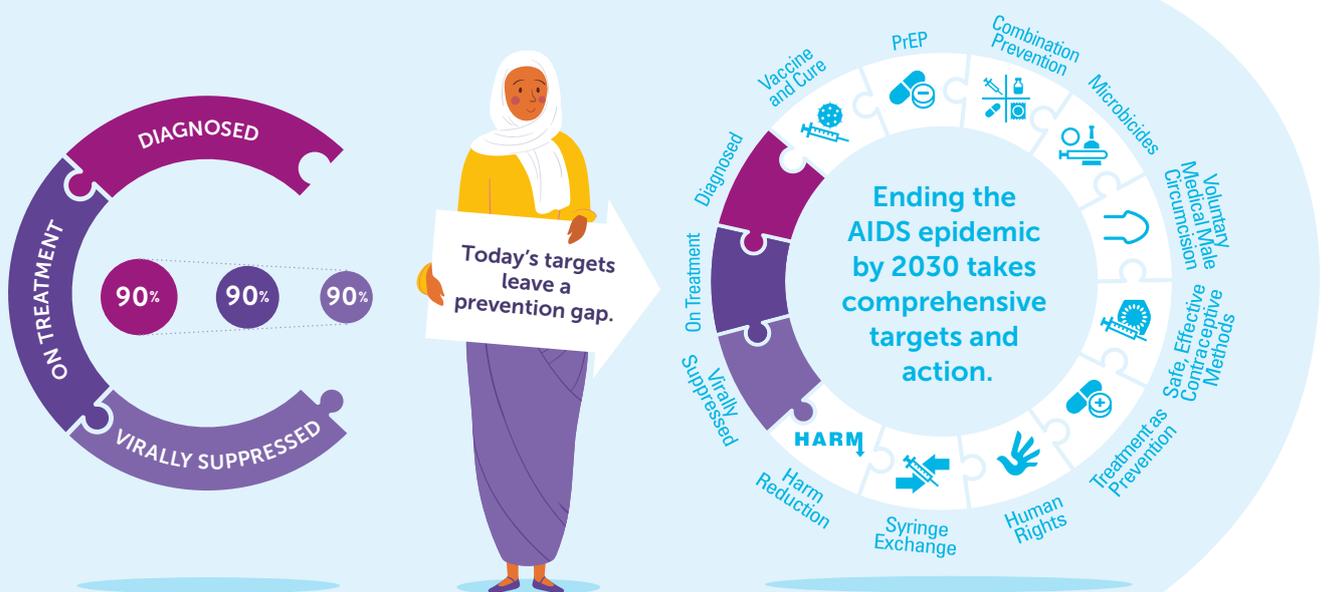
Elite controllers are people who naturally control HIV without antiretroviral therapy (ART). The study of their immune system and immune responses provides new information and directions for prevention, treatment, and cure research.

1.6 Prevention and Treatment

Today several prevention options are available to avert HIV acquisition in various settings and for different transmission routes including:

- Male and female condom use.
- Testing and counselling for HIV and STIs.
- Voluntary medical male circumcision (VMMC).
- Antiretroviral drugs (ARVs) for prevention, also known as PrEP (pre-exposure prophylaxis) or post-exposure prophylaxis (PEP).
- Harm reduction for people who use drugs.
- Elimination of mother-to-child transmission (MTCT) of HIV.
- Treatment of people living with HIV to prevent further transmission.

MIND THE GAP



Source: Adapted from AVAC Report 2014/15: Prevention on the Line www.avac.org/report2014-15/graphics

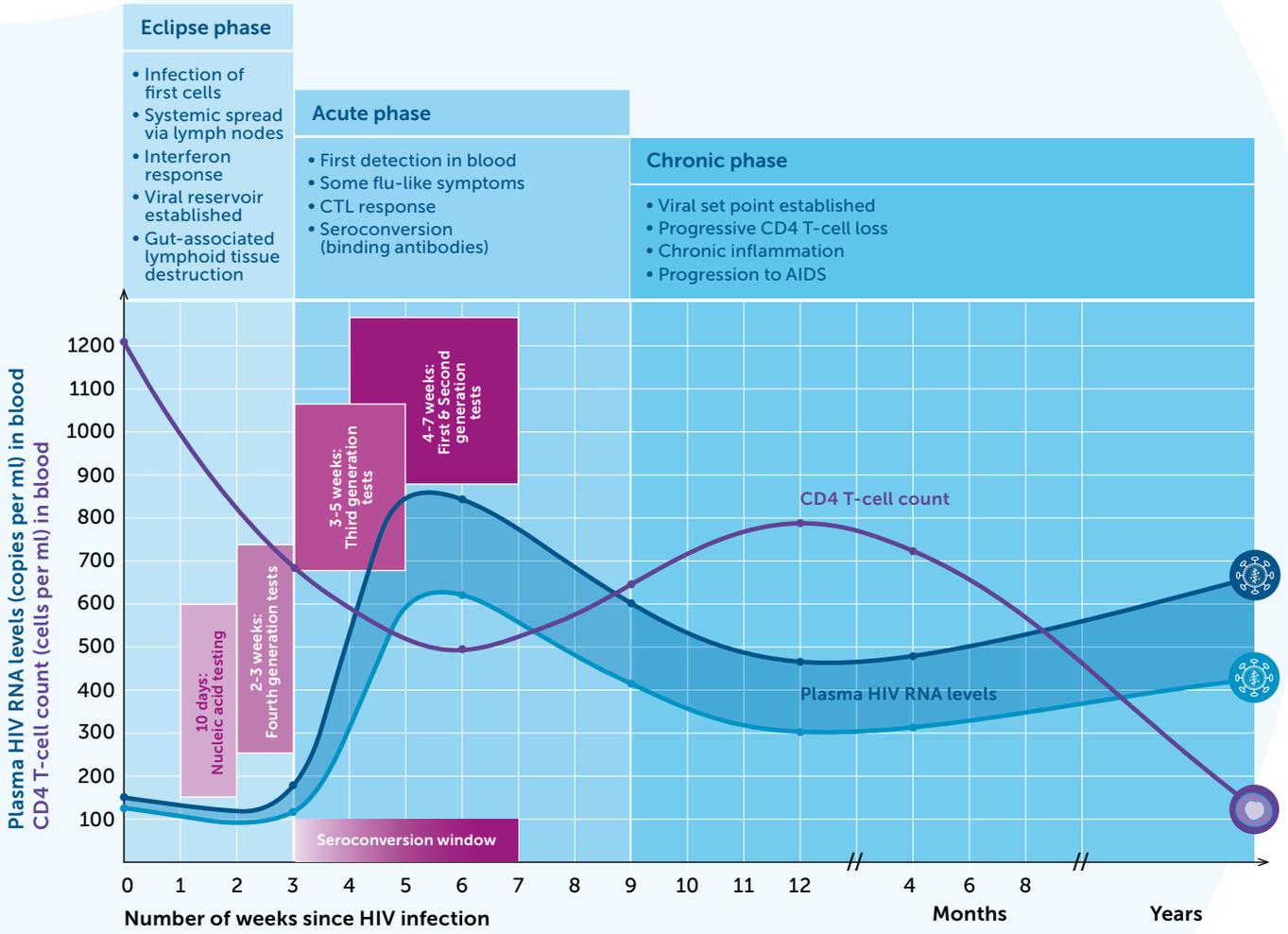
There is no cure for HIV and treatment requires taking a combination of ARVs that reduce the amount of virus in the body. There are now more than 30 ARVs that can be used in first-, second-, and third-line therapy. Treatment requires a combination of at least two different drugs that can be made into one pill that must be taken daily for life. New long-acting drugs are being developed that will not require taking pills daily.

Resistance to treatment can occur, especially when people are not taking treatment as prescribed. This can lead to people needing to change to a different drug regimen, which can be more difficult to take.

People living with HIV on treatment lead healthy, productive lives. Effective treatment also prevents the transmission of HIV from mother to child, and someone who is on antiretroviral therapy and has an undetectable viral load will not pass HIV to their sexual partners.

HIV PROGRESSION

- KEY:**
- CD4 T-cell count (cells per ml) in blood
 - Plasma HIV RNA levels (copies per ml) in blood (higher set point)
 - Plasma HIV RNA levels (copies per ml) in blood (lower set point)
 - HIV testing window period



HIV Testing Window Period

10 days: HIV virus detectable in the blood by HIV-1 RNA PCR
Nucleic acid test: Might not detect HIV-2 infection

2-3 weeks: Fourth generation tests
• IgG and IgM and P24 antibodies become detectable
• Recommended as an initial diagnostic test for HIV infection

3-5 weeks: IgG and IgM detectable by third generation tests
• Same technology as 4th generation assay, but less sensitive
• Assay is being phased out

4-7 weeks: IgG antibodies detectable by first & second generation tests
• 1st gen.: HIV-1 western blot test & HIV-1 immunofluorescence assay
• 2nd gen.: Can differentiate HIV-1 from HIV-2 infection

Point of Infection with HIV

During this time tests cannot detect HIV infection



FIND OUT MORE...

- Centers for Disease Control and Prevention: <https://www.cdc.gov/hiv/default.html>
- World Health Organization: <https://www.who.int/health-topics/hiv-aids>
- AVERT: <https://www.avert.org/professionals/hiv-science/overview>
- Deeks, S., Overbaugh, J., Phillips, A. et al. HIV infection. Nat Rev Dis Primers 1, 15035 (2015): <https://doi.org/10.1038/nrdp.2015.35>

2. Tuberculosis

2.1 A Brief History

Tuberculosis (TB) has affected humans for thousands of years. It is caused by *Mycobacterium tuberculosis* (*M.tb*) a bacteria discovered in 1882 by Dr Robert Koch who was awarded the Nobel Prize of Medicine in 1905 for this discovery.

Over two billion people are infected with *M.tb* worldwide, but only 5–10% will develop tuberculosis during their lifetime. Although anyone can develop TB, the risk is much higher among people living with HIV, as well as people with other risk factors including undernourishment, diabetes, alcoholism, and smoking. Although most cases of active TB disease occur in adolescents and adults, and in men more than women, 1.2 million children also get sick with TB each year.

Before the COVID-19 pandemic, TB was the leading infectious disease killer worldwide and the leading infectious cause of death among people living with HIV. TB remains a major cause of morbidity and mortality, primarily in low- and middle-income countries.

TB is treatable and curable. However, multidrug-resistant TB (MDR-TB) can develop when the TB bacteria become resistant to the ordinary drugs used to treat the disease. This occurs for various reasons:

- TB drugs are not prescribed or taken as prescribed.
- Routine TB treatment is not completed.
- Routine TB treatment is stopped and restarted.

A person can also be exposed to someone already infected with MDR-TB. MDR-TB has a huge impact on the cost of treatment and is a public health crisis and a health security threat.

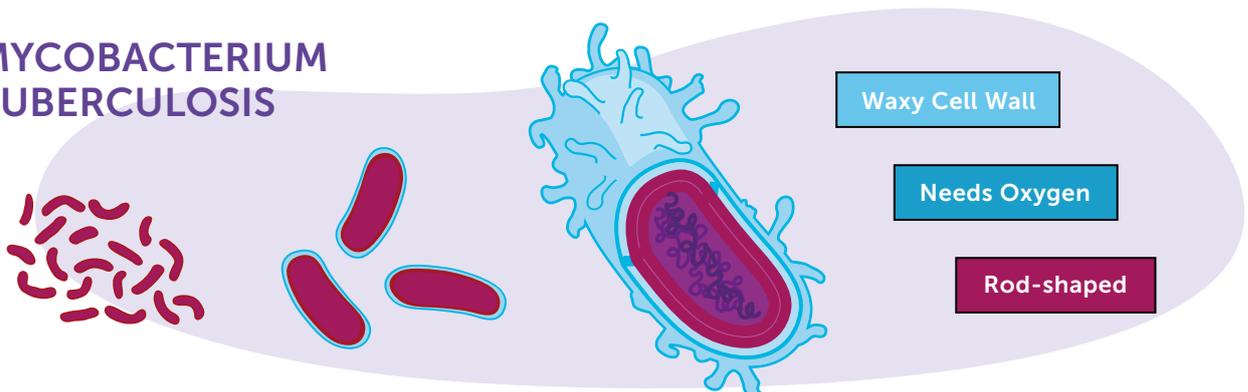


2.2 Mycobacterium tuberculosis (M.tb)

M.tuberculosis is a member of the Mycobacterium family, which includes other bacteria that can be responsible for diseases in humans. Able to survive for several weeks in a dormant state, it grows slowly compared to other bacteria and has unique features that makes it difficult to diagnose, treat, and to develop a vaccine against it. The organism is also able to survive and evolve within its human host.

M.tb is not highly infectious compared to other bacteria and viruses. It spreads primarily through the air from individuals with active pulmonary TB when they speak, cough, spit, or sing.

MYCOBACTERIUM TUBERCULOSIS



2.3 Diagnosis

TB presents in people in two forms, active and latent TB. The symptoms of a TB infection are diverse depending on where the bacteria are in the body. M.tb most often affects the lungs, causing pulmonary TB. Common signs and symptoms include coughing with sputum (phlegm) and blood at times, chest pain, weakness, weight loss, fever, and night sweats. A person with latent TB disease may have no symptoms. It is important to screen for TB when individuals experience common signs for TB.

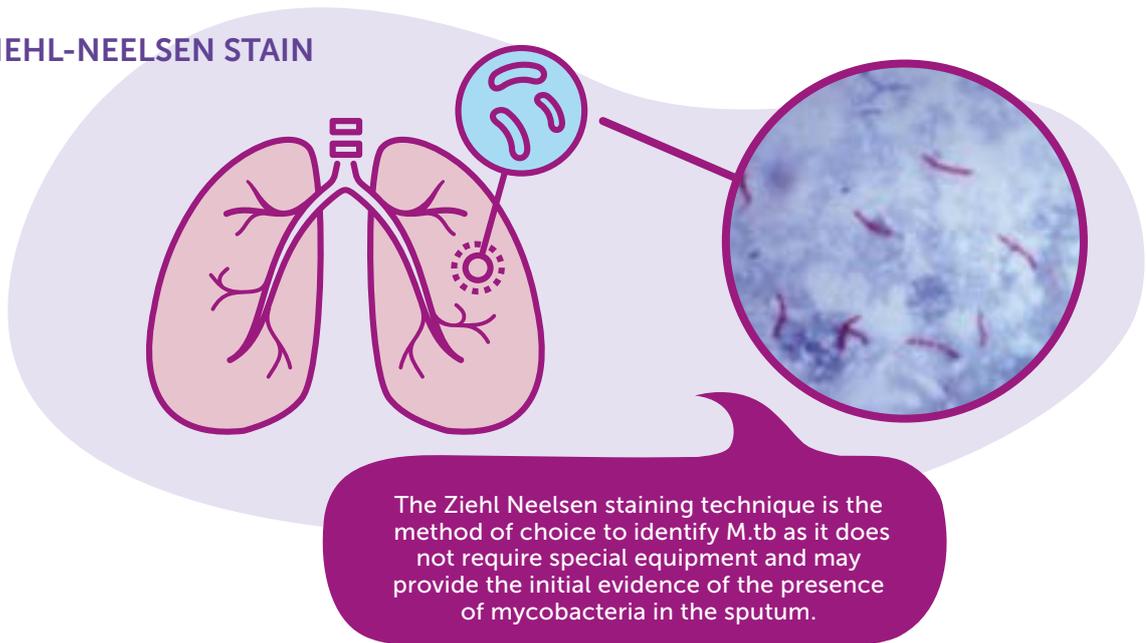


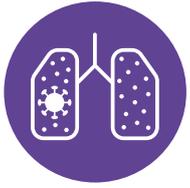
Diagnosing TB requires a clinical examination and confirmatory diagnostic tests. In some cases, diagnostic tests are also used to determine if a person has a latent TB infection or the TB disease. Tuberculosis is very difficult to diagnose in children as it can be difficult to distinguish from other respiratory diseases that cause fever.

Diagnostic tests for TB include-

- Mantoux tuberculin skin test (TST) can be performed in the clinic and tells if a person has been infected with M.tb, but not whether the person has latent TB infection or has progressed to TB disease.
- Interferon Gamma Release Assay (IGRA), a blood test performed in a laboratory to assess a person’s immune system reaction to M.tb. Additional tests are needed to determine whether the person has latent TB infection or TB disease.
- Imaging techniques (mainly chest X-ray, Positron emission tomography-computed tomography).
- In a laboratory, by visualising the bacteria in phlegm smear with a microscope using special staining techniques (the Ziehl-Neelsen staining).
- In a laboratory, by detecting components of M.tb in the sputum using rapid molecular tests. These tests can also be used to detect if an infecting strain of M.tb is resistant to rifampin, an important drug used in treating active TB.
- M.tb antigen detection in a laboratory, especially for people living with HIV.
- Growing the bacteria in a laboratory from sputum samples. This is considered as the most accurate test but takes up to eight weeks to provide results.

ZIEHL-NEELEN STAIN





2.4 Disease Progression

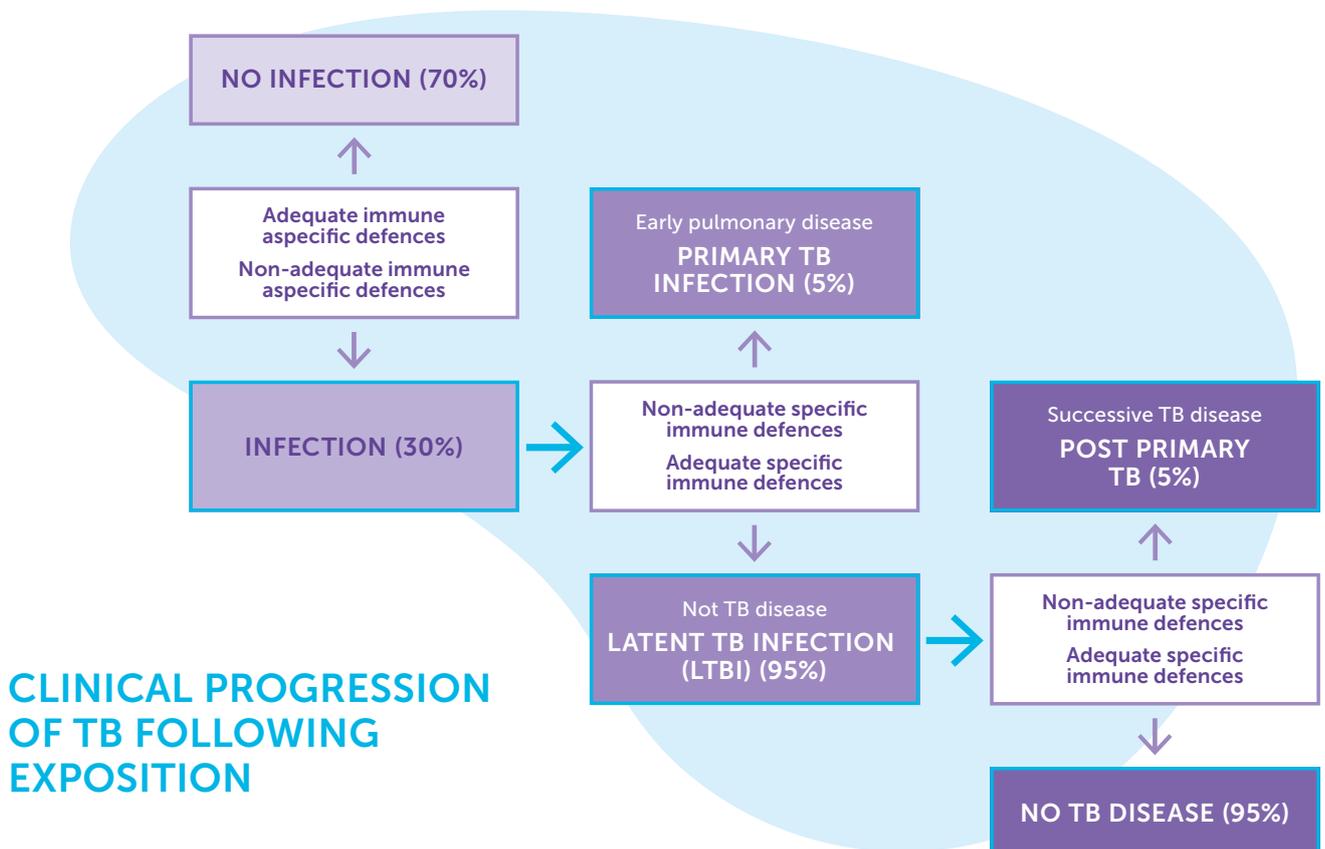
M.tb enters the lungs via inhalation and infects lung macrophages, lung-based scavenger cells that normally ingest and destroy the infecting bacteria. M.tb can prevent its destruction in the macrophages and can survive in these cells where they multiply, infect other cells, and eventually establish new infections in other areas, most commonly the upper parts of the lungs.

If the body can control the infection at this point, and no symptoms develop, the person is said to have latent TB infection (LTBI). People with LTBI are not infectious, but the bacteria can become active, multiply and progress from LTBI to TB disease depending on the person’s immunity and comorbidities (for example HIV).

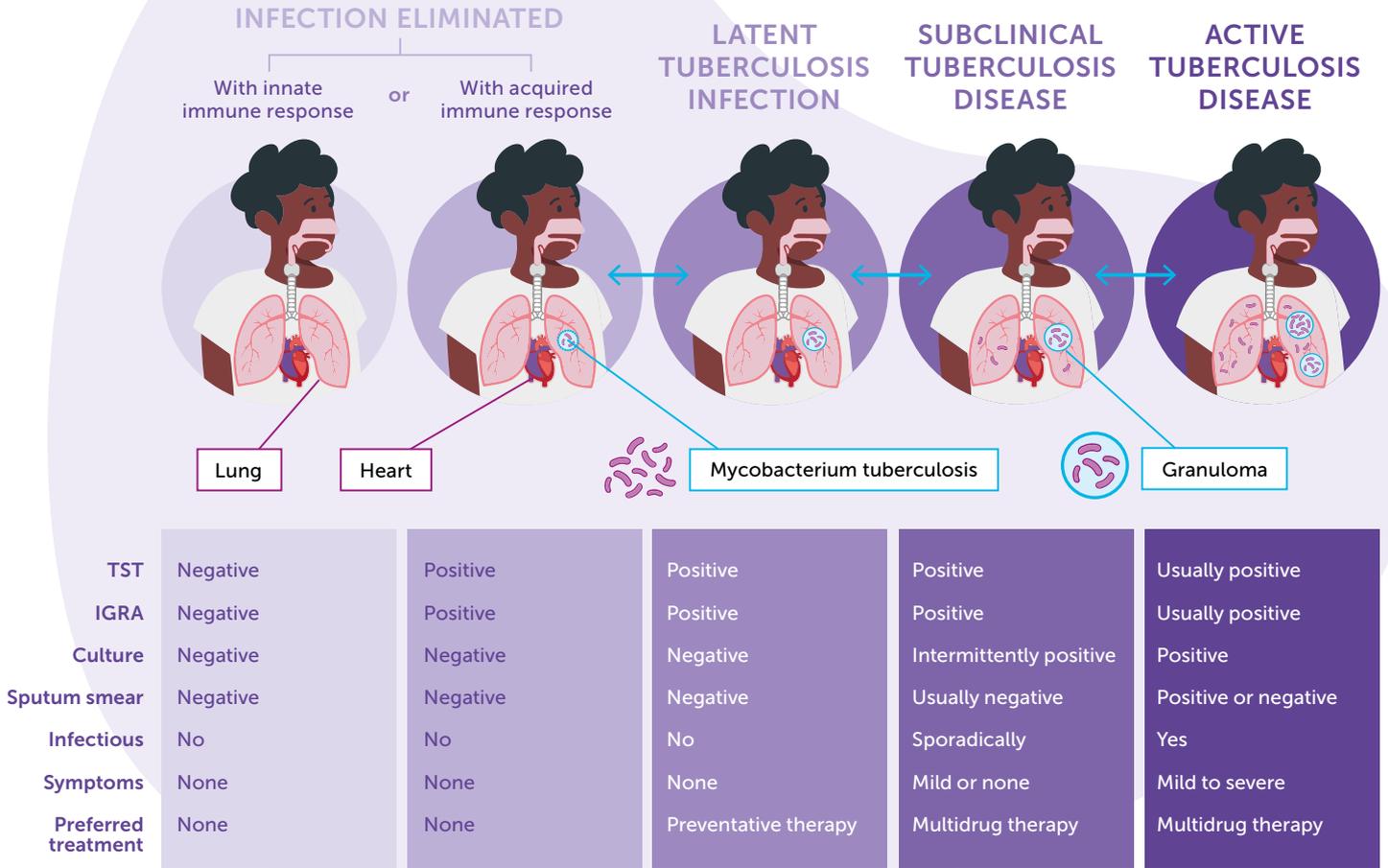
Approximately 5% of all persons infected with M.tb develop active TB disease within the first 18–24 months following initial infection. Another 5% will develop TB at some time later in life. The other 90% of persons infected with M.tb maintain the infection in a latent stage for the rest of their lives (LTBI); an unknown percentage of these M.tb-infected individuals may eradicate the organism completely.

Active TB disease can develop in the lung, or the bacteria may disseminate further in the body and reach other organs and cause active TB in other organs, including the brain and the kidneys. Individuals who have active TB disease are symptomatic and infectious.

- **TB disease:** after infection, the bacteria persist in the body in an active state. The individual shows a variety of symptoms and can infect others.
- **TB latent infection:** the bacterium lives in the person’s body without making them sick. People are not infectious, but the bacterium can become active, multiply and trigger TB disease.



TB CLINICAL PROGRESSION



Source: Adapted from <https://www.nature.com/articles/nrdp201676>



2.5 Prevention and Treatment

TB is preventable. Prevention involves both preventing infection and preventing latent TB infection from progressing to TB disease. Important strategies to prevent initial M.tb infection include:

- Avoidance as much as possible of crowded, poorly ventilated spaces in areas where TB disease is endemic (e.g., minibuses, crowded trains, factories, classrooms, camps for displaced persons, barracks for migrant workers).
- Reducing crowding and improving ventilation in locations such as these.
- Active case finding, early diagnosis and treatment; community education and awareness; and the development of vaccines capable of preventing TB disease, particularly in adolescents and adults.
- Early diagnosis and implementation of effective drug treatment of new TB cases is a critically important strategy in preventing the spread of M.tb.
- Emphasising the importance of screening when symptoms are experienced.



The Bacillus of Calmette and Guerin (BCG) is the only vaccine currently available against TB. It was first used in 1921 and is made from a weakened form of *Mycobacterium bovis*, responsible for TB in cattle. BCG vaccination offers variable levels of protection and prevents severe forms of TB in children. It has not been able to prevent the epidemic of global M.tb infection and TB disease and there is currently no vaccine that is effective in preventing TB disease in adolescents and adults, who are responsible for most M.tb transmission.

Not everyone infected with TB bacteria becomes sick. Without treatment however, latent TB infection can progress to TB disease, and result in death. TB infection and active TB disease are treated with different combinations of drugs and different duration of treatment. Drug-sensitive TB is curable with a four- to six-month course of currently available TB treatment. MDR-TB is also treatable, but with a much longer course of multiple drugs that can cause many side-effects.



Standard treatment for TB disease is based on first-line antimicrobials (isoniazid, rifampicin, pyrazinamide, and ethambutol). Resistance to treatment can occur and second-line antimicrobials are then needed, usually administered for up to 20 months based on level of resistance and previous treatment received and may involve daily injections for six months. If treatment fails, extensively drug-resistant TB (XDR-TB) can develop. Treatment of XDR-TB is lengthier, more complex, and more expensive. In resource-limited settings, XDR-TB is extremely difficult to treat, and at times impossible to treat.

There are several treatment regimens recommended for LBTI, and to avoid the development of drug resistant TB, Directly Observed Therapy (DOT) can be used with people who are at high risk for TB disease and who are either taking an intermittent regimen or who may have difficulty with taking treatment regularly.

Drug interactions should be considered when treating people who are also living with HIV.



FIND OUT MORE...

- World Health Organization: <https://www.who.int/health-topics/tuberculosis>
- Centers for Disease Control and Prevention: <https://www.cdc.gov/tb/default.htm>
- Medscape: <https://emedicine.medscape.com/article/230802-overview>
- TB Alliance: <https://www.tballiance.org/>
- TB Vaccine Initiative: <https://www.tbvi.eu/>
- Pai, M., Behr, M., Dowdy, D. et al. Tuberculosis. *Nat Rev Dis Primers* 2, 16076 (2016).

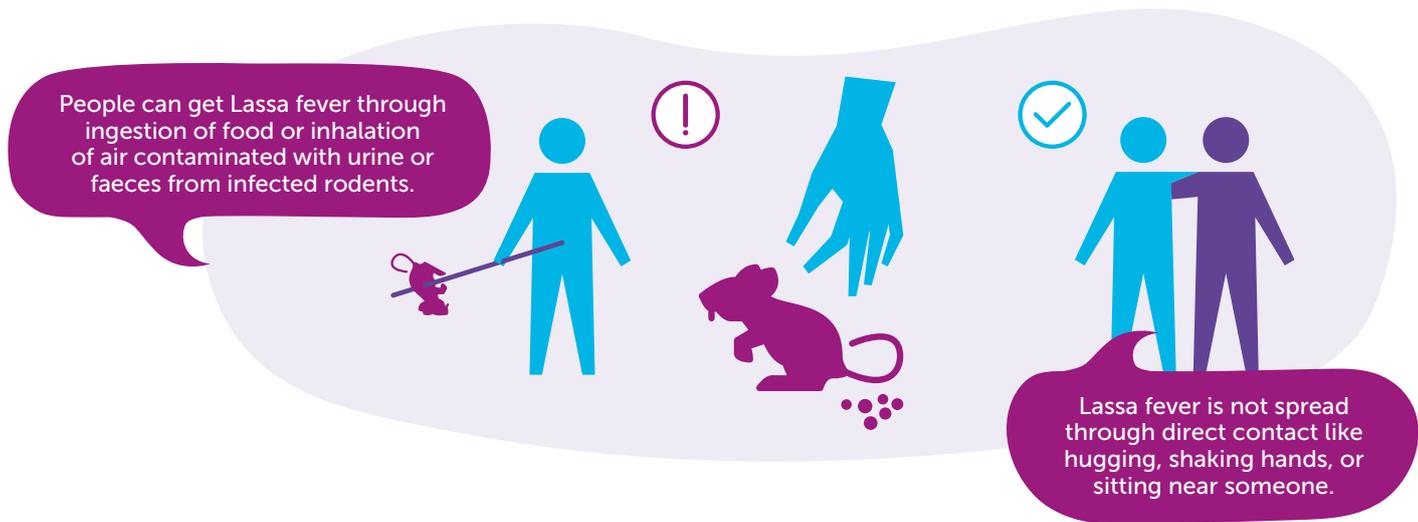
3. Lassa Fever Virus

3.1 A Brief History

Lassa haemorrhagic fever (Lassa fever) was first described in the 1950s. The virus responsible for the disease, Lassa mammarenavirus (LASV), was identified in 1969 after the death of two missionary nurses in the town of Lassa in Nigeria. The disease is spread by rats and mice that live in large numbers in West Africa where the disease is endemic.

People can get Lassa fever through ingestion of food or inhalation of air contaminated with urine or faeces from infected rodents. Person-to-person transmission may occur after exposure to Lassa virus in the blood, tissue, secretions, or excretions of a Lassa-infected individual, often in health care settings where protective equipment is not available or medical equipment is contaminated. Lassa fever is not spread through direct contact (like hugging, shaking hands, or sitting near someone) but sexual transmission has been reported.

Nearly 60 million people are estimated to be at risk of infection. The proportion of people who die from a confirmed Lassa fever infection is estimated at 1% but among patients who are hospitalised with severe Lassa fever, the fatality rate is estimated at around 15%. The World Health Organization (WHO) has listed Lassa as a high priority pathogen for the development of new prevention and treatment options.



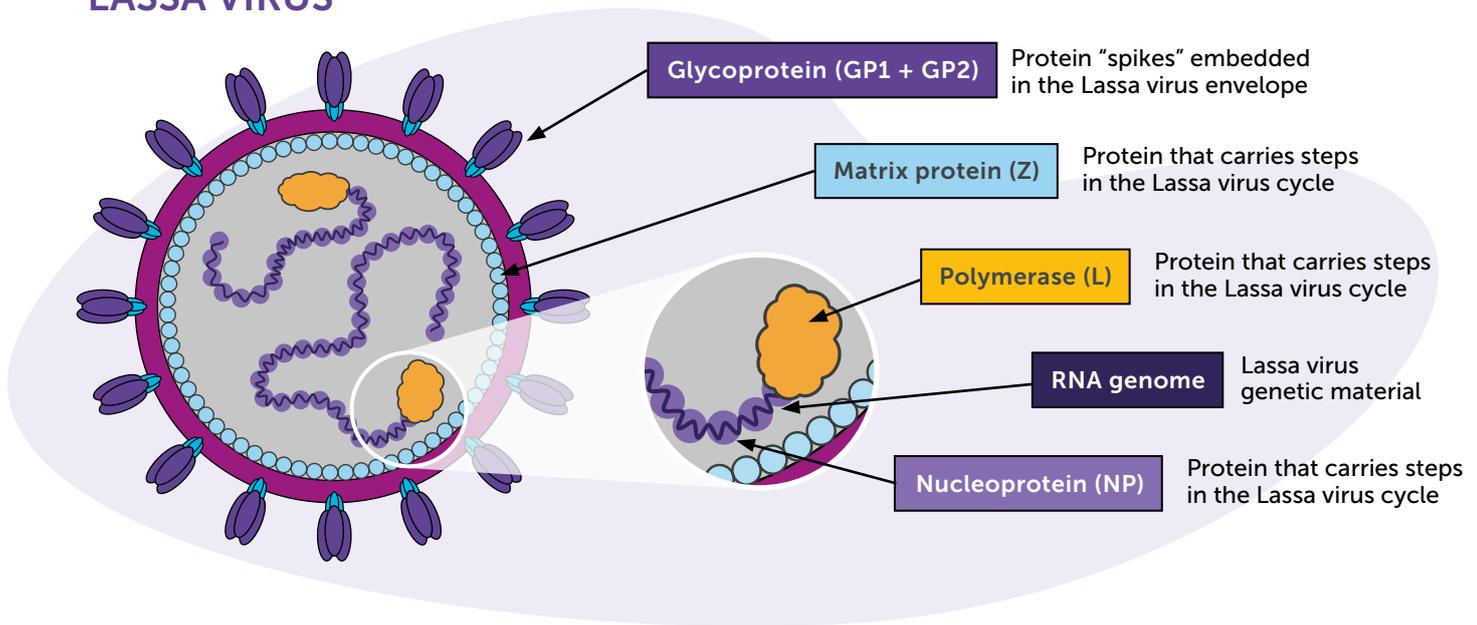
3.2 The Lassa Virus

LASV is a retrovirus, generally spread by rodents that act as the virus' natural reservoir. The LASV genome is made of two single-strand RNA that contains genes for four viral proteins including structural proteins, enzymes, and envelope glycoproteins.

There are six types of LASV identified so far with different geographic localisation. The Josiah strain from Sierra Leone is the most studied and is widely used in vaccine research.

Little is known about the replication and life cycle of the Lassa virus. The virus enters human cells using its envelope glycoprotein and a receptor present at the surface of human cells. Once in the cell, the viral genome is replicated in the cytoplasm using the cell machinery to produce new viral RNA and the different viral components. Viral RNA is then packaged into mature virions that bud out of the infected cells.

LASSA VIRUS



3.3 Diagnosis

Clinical diagnosis of Lassa fever is often difficult due to the variety of non-specific symptoms, many of which are like those observed with other viral haemorrhagic fever such as Ebola.

Definitive diagnosis requires testing only available in specialised laboratories using the following tests:

- Nucleic acid tests (NAT) that detect RNA from the virus in the blood.
- Tests to detect antibodies generated by the body in response to the infection.
- Antigenic tests to detect parts of the virus.
- Virus isolation by cell culture.

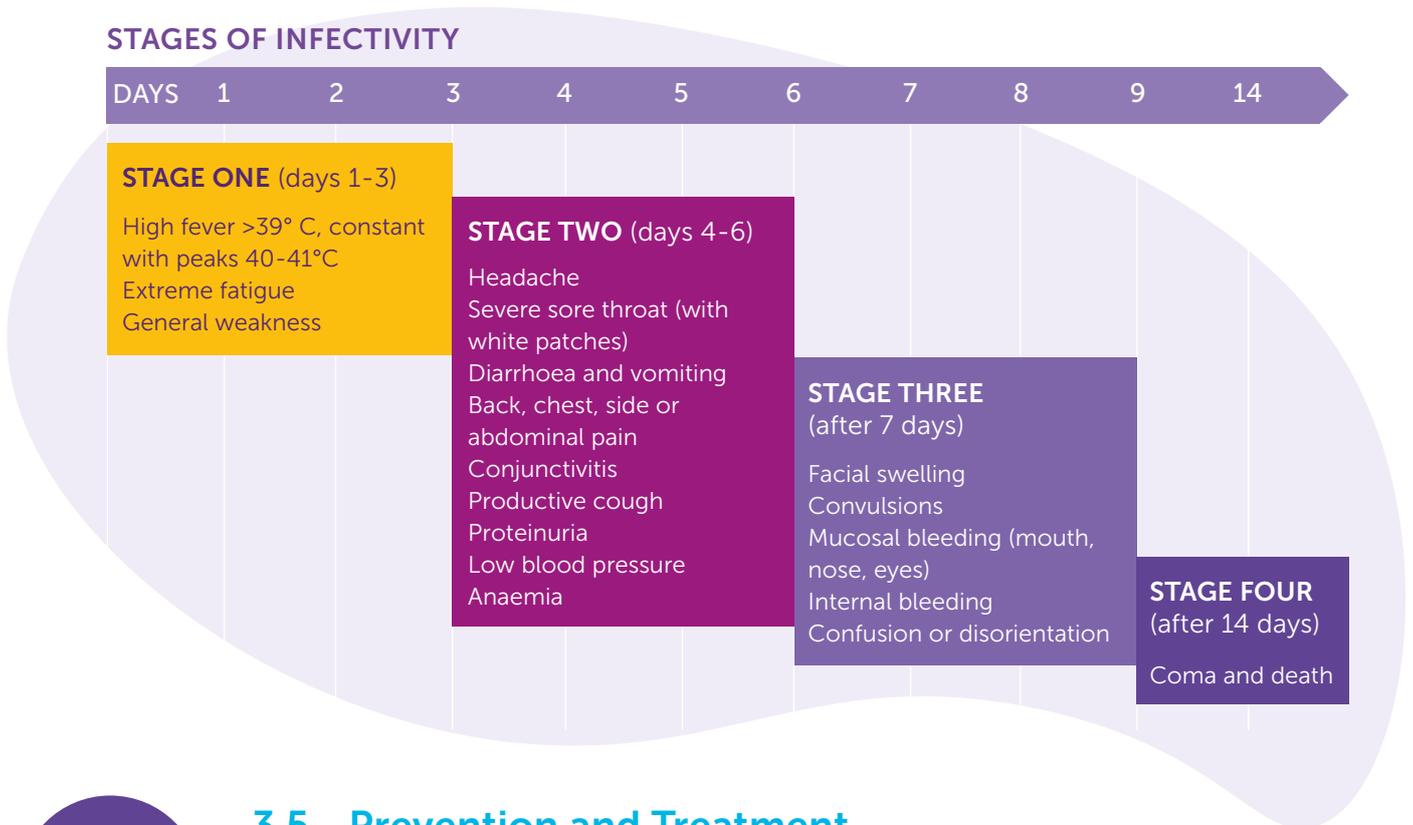
3.4 Disease Progression

Lassa fever is an acute viral haemorrhagic fever that is often mild or has no observable symptoms for most of the infections (approximately 80%). Symptoms include slight fever, general malaise and weakness, and headache.

However, for 20% of infected individuals, severe illnesses are observed including bleeding (in gums, eyes, or nose, for example), respiratory distress, repeated vomiting, facial swelling, pain in the chest, back, and abdomen, and shock. Death may occur within two weeks after symptoms start due to multi-organ failure and although 1% case fatality has been reported, there is considerable uncertainty around this estimate with some believing that this is an underestimate. Various degrees of deafness have been seen to occur in 25% of recovered patients with hearing returning in half the cases after 1–3 months.

Lassa fever is especially severe in pregnant women, with an increased maternal mortality in the third trimester (greater than 30%) and spontaneous abortion with an estimated 90% mortality in foetuses of infected pregnant mothers. Lassa is also a significant cause of child hospitalisations in some areas of West Africa.

TIMELINE OF LASSA FEVER DISEASE FROM SYMPTOM ONSET



3.5 Prevention and Treatment

Community education in areas affected is an important part of the control and prevention of Lassa fever. Prevention relies on good ‘community hygiene’ to prevent rodents from entering homes and good public health practice to prevent transmission in health-care settings.

There is currently no approved treatment for Lassa fever. Off-label use of ribavirin, an antiviral medication used to treat chronic hepatitis C, fluid replacement, and dialysis are used for the treatment of severe Lassa fever.

Several treatments are under investigation including the antiviral favipiravir, plasma from convalescent people that contain antibodies against the virus, and a human monoclonal antibody cocktail that have shown some efficacy in preclinical research and a potential for use in clinical settings.



FIND OUT MORE...

- Centers for Disease Control and Prevention: <https://www.cdc.gov/vhf/lassa/index.html>
- World Health Organization: <https://www.who.int/health-topics/lassa-fever>
- Purushotham J, Lambe T, Gilbert SC. Vaccine platforms for the prevention of Lassa fever. *Immunology Letter* 215:1-11, (2019).

MODULE 3: THE IMMUNE SYSTEM

How does my body
protect me from
infection?

HOW DOES THE
IMMUNE SYSTEM
WORK?

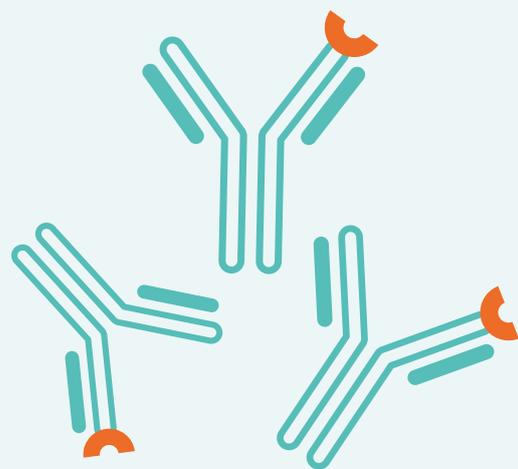


MODULE 3

THE IMMUNE SYSTEM

CONTENTS 40

Summary Points	41
1. Introduction	41
2. The Immune System: Key Concepts	42
2.1 The Immune Response	42
2.2 Organs of the Immune Systems	42
2.3 Cells of the Immune Systems	43
2.4 The Humoral Immune Response	45
2.5 The Cellular Immune Response	46
3. HIV and the Immune System	47
4. TB and the Immune System	48
5. Lassa Fever and the Immune System	49



» Summary Points



- The immune system is the set of organs, tissues, and cells that defend the body against infections and diseases.
- It is very sophisticated and is designed to recognise common pathogens that enter the body, such as viruses, bacteria, or parasites.
- The immune system develops defence responses to invading organisms and usually will 'remember' and respond more rapidly during future encounters.
- Some pathogens such as HIV can disrupt or evade immune responses.

1. Introduction

The immune system is a complex system of organs, tissues, cells, and processes that has evolved to protect us from diseases. The immune system enables the body to recognise anything that is different from itself (i.e., 'foreign') and that is potentially harmful. The immune system creates defences against these invaders, which are called pathogens. Our immune system is divided into two broad categories: 'innate immunity' and 'acquired immunity.'

Innate immune defences are the first to respond to any pathogen. These defences are not specific to one pathogen. This arm of the immune system cannot usually be 'taught' to respond better by a vaccine. Innate immunity is often not enough to get rid of pathogens as the first line of defence and a second line of defence kicks in.

Acquired immunity is the second line of defence of the body. These defences are activated only after our immune system has 'seen' and 'recognised' a pathogen. Acquired immunity is typically directed towards a single, specific pathogen. The acquired immune responses are those involved in the function of a vaccine.

This module describes acquired immunity. There are two branches or 'arms' of the acquired immune system (see **BOX** and **DIAGRAM**):



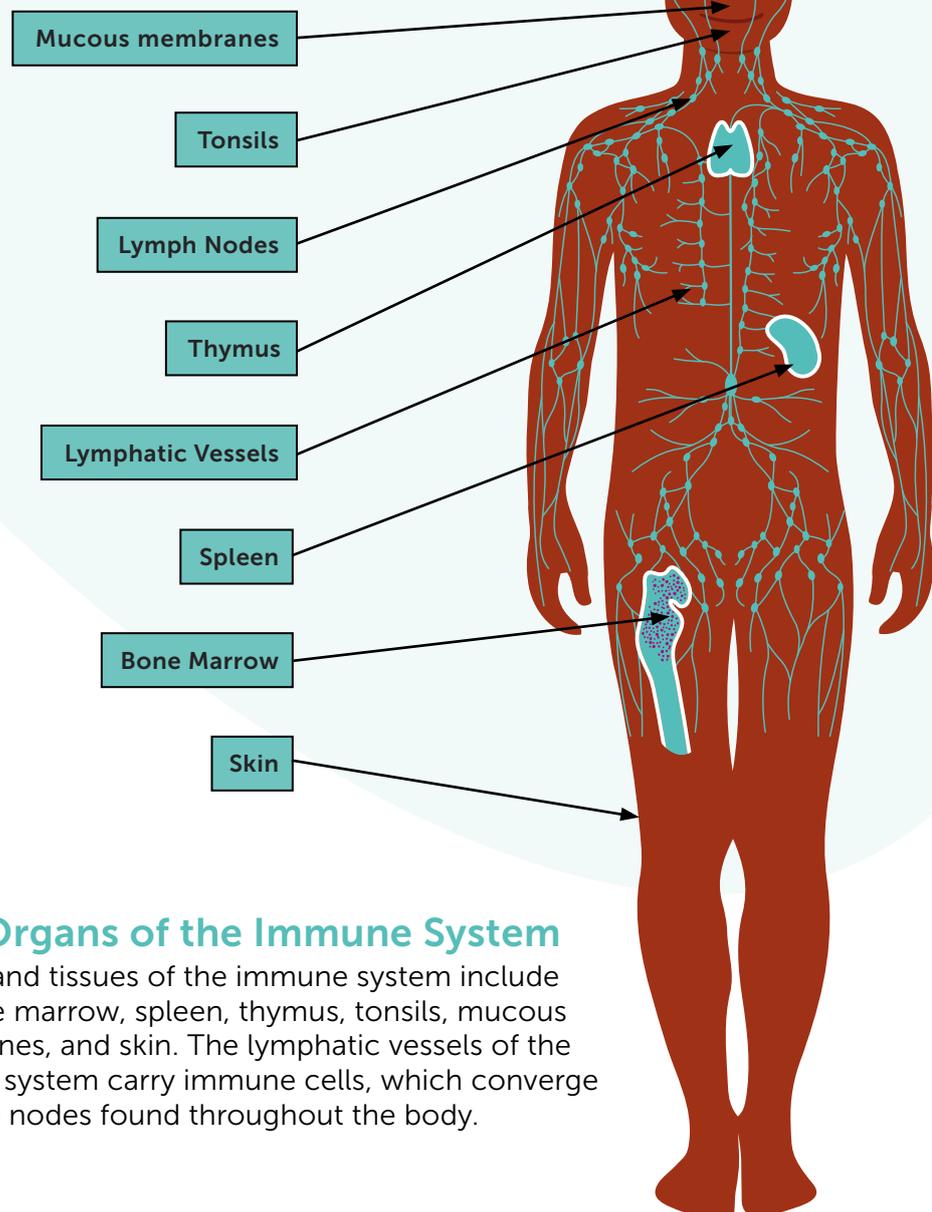
- **Cell-mediated or cellular immune response** – the immune response coordinated by 'T cells' which targets cells that have been infected with a pathogen.
- **Antibody-mediated or humoral immune response** – includes antibodies and 'B-cell' responses.

2. The Immune System: Key Concepts

2.1 The Immune Response

The immune response is a collection of activities from the immune system to defend the body against bacteria, viruses, or other substances that the body recognises as foreign and harmful. When a pathogen enters the body, the immune system's first responders (macrophages and dendritic cells) detect and ingest the invader, package some of its components or pieces (called antigens) and present these on their outer surfaces, so that other immune cells (lymphocytes) can 'see' the pathogen and respond appropriately to it.

ORGANS OF THE IMMUNE SYSTEM

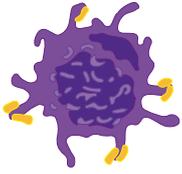


2.2 Organs of the Immune System

Organs and tissues of the immune system include the bone marrow, spleen, thymus, tonsils, mucous membranes, and skin. The lymphatic vessels of the immune system carry immune cells, which converge in lymph nodes found throughout the body.

2.3 Cells of the Immune Systems

The immune system comprises many cells located in different organs. Each plays a role in recognising pathogens and mounting a response.



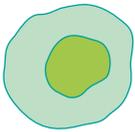
Macrophages/Dendritic cells/Phagocytes

These cells look out for pathogens. When they encounter a pathogen, they ingest and process it and 'alert' other immune cells of its presence.

Antigen-presenting cells (APCs)

APCs engulf and process the antigens to present them on their own outer surface in a way that can be 'seen' by other immune cells called lymphocytes. This process activates the lymphocytes to function. Immune cells that act as APCs include:

- B cells
- Macrophages
- Dendritic cells

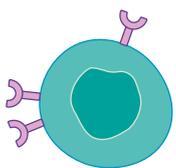


Lymphocytes

Lymphocytes are white blood cells. When the APCs present antigens to the lymphocytes they respond against the pathogen associated with the antigens. The two most important types of lymphocytes are T cells and B cells.

B-Cell receptors and T-Cell receptors

B-cell receptors and T-cell receptors are key proteins responsible for specific antigen recognition in acquired immunity. They are found at the surface of the T and B cells of the immune system, and they can recognise antigens or part of the antigens presented by the APCs. There is a vast diversity of B- and T-cell receptors allowing the human immune system to recognise a very large number of pathogens.



T cells

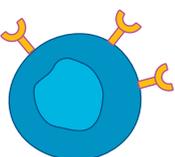
T cells can recognise a pathogen or a virus-infected cell presented by the antigen presenting cells (APCs). They release substances that cause inflammation (cytokines), and they can kill abnormal or virus-infected cells. There are two types of T cells: CD4+ lymphocytes and CD8+ lymphocytes.

- CD4+ cells

The main function of these T cells is to recognise antigens presented by the APCs and to help coordinate the specific immune response against that antigen. Therefore, they are also called 'helper T cells.'

- CD8+ cells

These T cells kill cells or slow down activity of cells that have been infected with the pathogen. They are also called cytotoxic T lymphocytes (CTLs) or 'killer T cells.' They do this through 'cytotoxic' activity, a process that kills the infected cells.



B Cells

B cells can recognise and target pathogens that have entered the body. B cells can evolve into plasma B cells that produce antibodies specifically designed to recognise and attach to circulating pathogens and antigens.

CELLS OF THE ACQUIRED IMMUNE SYSTEM

ANTIGEN PRESENTING CELLS (APCs)
e.g., macrophages

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

Macrophage ingests the pathogen (Phagocytosis)

Pathogen is broken down into components inside the macrophage

Macrophage presents components of the pathogen to a lymphocyte

B cell receptor protein

T cell receptor protein recognises the pathogen's component

B CELL

T CELL

PROLIFERATION

MEMORY B CELL

PLASMA CELL

HELPER T CELL

CYTOTOXIC T CELL

Memory cells can later induce the secondary immune response upon renewed contact with the same pathogen

Plasma cells produce specific antibodies

ANTIBODY SECRETION

INFECTED CELL

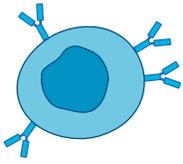
KILLING OF INFECTED CELL

Cytotoxic T cell destroys infected body cell

Antigen antibody complexes

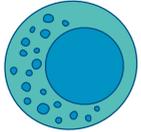
Macrophages ingest and digest

ANTIGEN ELIMINATION



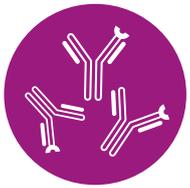
Memory B cells and memory T cells

Helper T cells, killer T cells and plasma B cells form responses to many infections, such as HIV, tuberculosis, or malaria. Once the individual has recovered from the infection, a small population of memory T cells and memory B cells remains. These cells can quickly restart a response if the pathogen ever returns. Memory cells 'remember' the pathogen and are prepared to start an appropriate response more quickly and more vigorously the next time the body encounters the same pathogen.



Natural killer (NK) cells

Natural killer (NK) cells are a type of lymphocyte that contain enzymes that can kill other cells, especially tumour cells and cells infected by viruses.



2.4 The Humoral Immune Response

The humoral response is the arm of the immune system mediated by B cells through the production of antibodies.

Antibody

Also called immunoglobulins, antibodies are proteins produced by plasma B cells in response to an antigen. They can be found in bodily fluids such as plasma, serum, tears, saliva, and cervical fluids. An antibody is specifically designed to attach to part of the pathogen, called an antigen.

When antibodies lock or bind to antigens on the surface of the pathogen, they coat the pathogen, making it inactive and marking it so that other immune cells can kill it. Antibodies can also prevent viruses from getting into cells, which is where they must be to reproduce. There are different types of antibodies.

Binding antibody

Binding antibodies are usually produced in large quantities following a bacterial or viral infection. They can recognise and bind to parts of a foreign body but cannot directly prevent infections or destroy the pathogen. They require the involvement of other immune mechanisms to destroy the foreign agent. A common way of diagnosing infections is to test for the presence of these antibodies in biological fluids. Binding antibodies are also called non-neutralising antibodies.

Neutralising antibody

Neutralising antibodies react with an infectious agent, usually a virus, and destroy or inhibit its ability to enter a cell (infectiveness) and virulence (ability to multiply).

Broadly neutralising antibody (bnAbs)

Viruses can evade the immune response and in particular the humoral response through a variety of mechanisms. Viral DNA can mutate quickly allowing viruses to escape recognition by both humoral and cellular immune responses. However, as a virus evolves, the immune response also evolves in tandem and can adapt by developing bnAbs. These antibodies are more efficient because they can recognise a wide range of viruses even if they are different from the virus that initially infected the individual. This evolution of both the virus and the immune system is a complex and lengthy process which is not necessarily inevitable and requires other cells of the immune responses.

2.5 The Cellular Immune Response

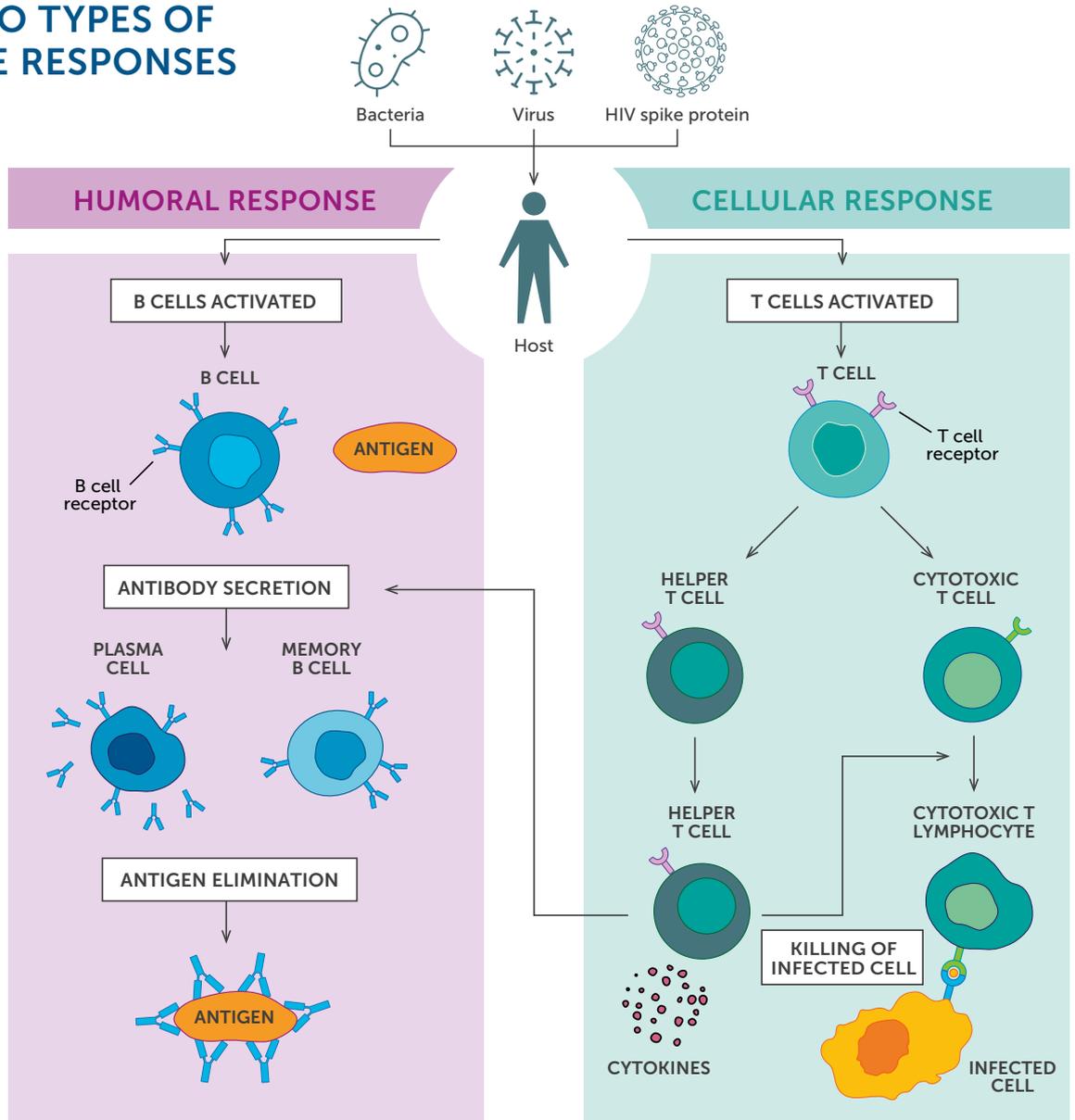
The cellular response is the arm of the immune response mediated by cells from the immune system and the production of cytokines. Cytokines are proteins that act as messengers between cells to regulate and coordinate the immune responses.

Cellular immunity is most effective in destroying virus-infected cells, and bacteria within cells. Cellular immunity works by activating antigen-specific cytotoxic T lymphocytes (CTLs), macrophages and natural killer cells that can destroy cells displaying foreign antigens on their surface.

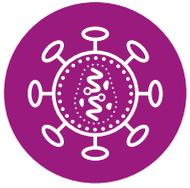
Cells involved in the cellular immune response produce a variety of cytokines that influence the function of other cells involved in acquired immune responses and innate immune responses.

The cellular immune response is also responsible for the development of CD4+ and CD8+ memory cells. These memory cells can persist for the remainder of a person's life and lead to a rapid response if the body is exposed again to the same pathogen.

THE TWO TYPES OF IMMUNE RESPONSES



3. HIV and the Immune System



At first, the immune system mounts a defence that can help people living with HIV to remain healthy for some years after acquiring HIV. Eventually HIV overcomes these defences, allowing infections and diseases to take hold, and ultimately causing death.

HIV preferentially infects the cells of the immune system, killing them and therefore making it difficult for the body to fight against the virus and other pathogens. When someone has had HIV for some time, their immune system weakens, and they may get ill from pathogens that would not normally cause disease in a person not infected with HIV. These are called opportunistic infections. Pneumocystis pneumonia (a fungal disease) and thrush are examples of common opportunistic infections. Other infectious diseases may be more serious in people living with HIV, such as tuberculosis or genital herpes.

HIV has many ways of avoiding the immune system. Starting with transmission, HIV interacts with various immune cells such as dendritic cells, macrophages, APCs, and lymphocytes. HIV uses these cells to make more copies of itself, killing them in the process.

HIV also kills the CD4+ cells that help plasma B cells to make antibodies and direct CD8+ T-cell responses, both of which are important to fight HIV. The lower the number of CD4+ cells, the more difficult it is for the body to fight pathogens. Another weapon that HIV can use is its viral diversity, which is a major challenge for the immune system. HIV can change some of its parts to avoid detection. This process is sometimes referred to as 'immune evasion.'

The virus can also hide its surface envelope glycoprotein by coating it with sugar molecules and therefore making it difficult for the cells of the immune system to see and to mount a response against the virus. In this way the virus can escape antibodies and cellular responses. Although the body can adapt and develop bnAbs, these are rare and ultimately fail to prevent the disease from progressing because other parts of the immune system are too weak.

Finally, another way for the virus to escape from the body's immune response is where HIV viral DNA hides in the genome in a dormant state without multiplying, in a 'reservoir' of infected cells.

4. TB and the Immune System

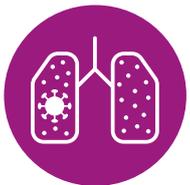


The interaction between the immune system and *M.tb*, the pathogen responsible for tuberculosis (TB), are complex and lead to either clearance of the bacteria, latent TB infection, or TB disease (see **MODULE 2**).

- Macrophages and CD4+ T lymphocytes play a central role in the immune responses to *M.tb* that can use multiple strategies to escape the immune system.
- *M.tb* can prevent the activation of pathogen destruction systems within macrophages where it can hide, reproduce slowly, and modify the cell to its advantage.
- *M.tb* can affect the function of dendritic cells by altering the production of various cytokines involved in the immune responses and the suppression of T lymphocyte activity.
- *M.tb* can also interfere with the interactions between the different cells of the immune system and hamper their ability to work together and kill or constrain the organism.

Following infection of the cells of the lung by *M.tb*, a complex, localised and well-coordinated immune response keeps the pathogen under control, preventing transmission in 90% of infected individuals and resulting in latent TB infection (LTBI). The granuloma is made of many cells involved in the immune responses and aims at keeping the pathogen contained and under control. *M.tb* trapped in a dormant state within a granuloma is a characteristic of latent *M.tb* infection (LTBI).

Macrophages, CD4+ T lymphocytes and the formation of the granuloma are believed to be central to the immune defence against *M.tb*. The development of the granuloma is the ancestral mechanism of defence against *M.tb* and a defining feature of TB disease.



LTBI progresses into active TB disease when the balance between host immune responses and *M.tb* counter-response in the granuloma is broken. *M.tb* can escape the granuloma leading to the individual developing TB disease and becoming capable of transmitting the infection. This shift can be triggered by *M.tb* virulence factors, molecules that help the bacteria to colonise the host at the cellular level.

M.tb represents a classic example of an organism that has evolved with the human species over thousands of years, developing a remarkable ability to take advantage of what otherwise would be an appropriate immune response against it and using this immune response to successfully propagate itself, leading to its spread and the infection of more than 25% of humanity with *M.tb* across most areas of the globe.

5. Lassa Fever and the Immune System



The immune response to natural Lassa virus infection has yet to be fully explained by scientists. Knowledge and understanding are hampered by several factors including the need to handle the virus in a special high safety laboratory. Outbreaks are typically sporadic, with the annual peak of cases usually observed during the dry season (December–April), and often in remote locations, where laboratory infrastructure is limited. However, it appears that Lassa virus infection results in immunosuppression enabling the Lassa virus to evade and undermine effective immune responses.

The Lassa virus specifically targets antigen-presenting cells (APCs), dendritic cells, and macrophages. Infected cells can produce large quantities of viruses without being killed and the virus prevents them performing their function of presenting antigens to other cells of the immune system.

Temporary reduction in the number of CD4+ and CD8+ T cells, NK cells and B cells have been observed in the early stage of the disease. The Lassa virus can also reduce and alter the production of cytokines involved in the immune responses.

The Lassa nucleoprotein (NP) can hold back the ability of both arms of the immune system to respond to the infection. Despite being strong, the antibody response to the virus does not seem to impact the progression of the disease and neutralising antibodies are produced in small amounts.

Cellular immune responses may play a crucial role in the progression and outcome of the disease as these responses are strongest in those that recover well, albeit with limited data. Unfortunately, the Lassa virus seems to be able to interfere with T-cell activation as well as destroying the lymphoid organs in which these cells reside.



FIND OUT MORE...

- **Essential Medical Immunology:** <http://www.roitt.com>
- **ClinicalInfoHIV.gov:** <https://clinicalinfo.hiv.gov/en/glossary>
- **British Society for Immunology:** <https://www.immunology.org/public-information>
- **de Martino M, Lodi L, Galli L and Chiappini E, Immune Response to Mycobacterium tuberculosis: A Narrative Review. Front. Pediatr. 7:350 (2019)**
- **Prescott JB, Marzi A, Safronetz D, Robertson SJ, Feldmann H, Best SM. Immunobiology of Ebola and Lassa virus infections. Nat Rev Immunol. 17(3):195-207 (2017)**

MODULE 4: INTRODUCTION TO VACCINES

HOW DO
VACCINES
WORK?

Should I be worried
about side effects?



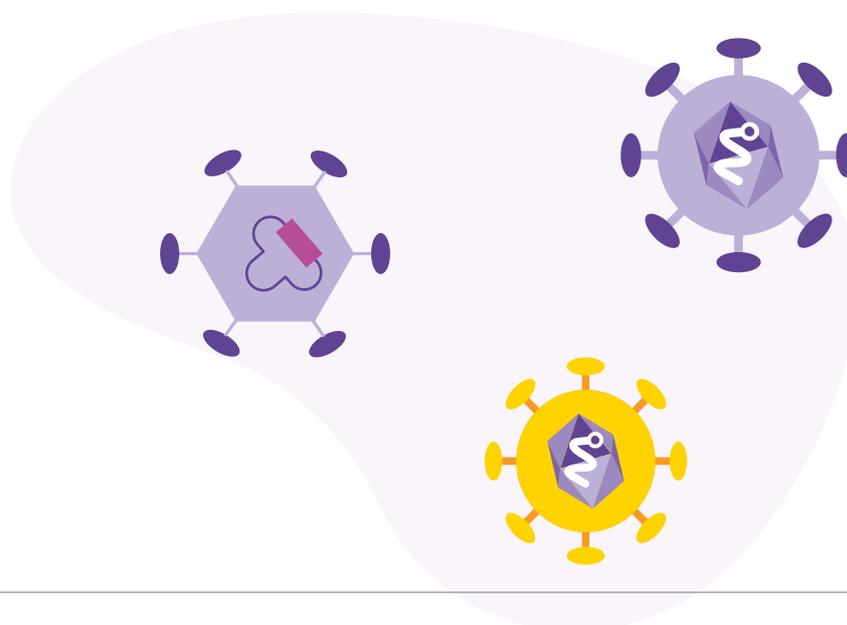
MODULE 4

INTRODUCTION TO VACCINES

CONTENTS

51

Summary Points	52
1. Key Definitions and Concepts of Vaccinology	52
1.1 What is a Vaccine?	52
1.2 Adjuvants	52
1.3 Efficacy and Effectiveness	53
2. How Vaccines Work	55
3. Vaccine Platforms	58
4. Challenges in Developing Vaccines	60
5. HIV Vaccine Research and Development	62
5.1 A Brief History	62
5.2 HIV Vaccine Research and Development	64
5.3 HIV Vaccine Development Challenges	65
6. TB Vaccine Research and Development	66
6.1 A Brief History	66
6.2 TB Vaccine Research and Development	67
6.3 Challenges of TB Vaccine Development	67
7. Lassa Virus Vaccine Research and Development	69
7.1 A Brief History	69
7.2 Lassa Virus Vaccine Research and Development	69
7.3 Challenges of Lassa Virus Vaccine Development	69





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 (intra-dermal or subcutaneous); application to the skin (transdermal); application to the inside of the nose (nasal); or by being swallowed (oral).

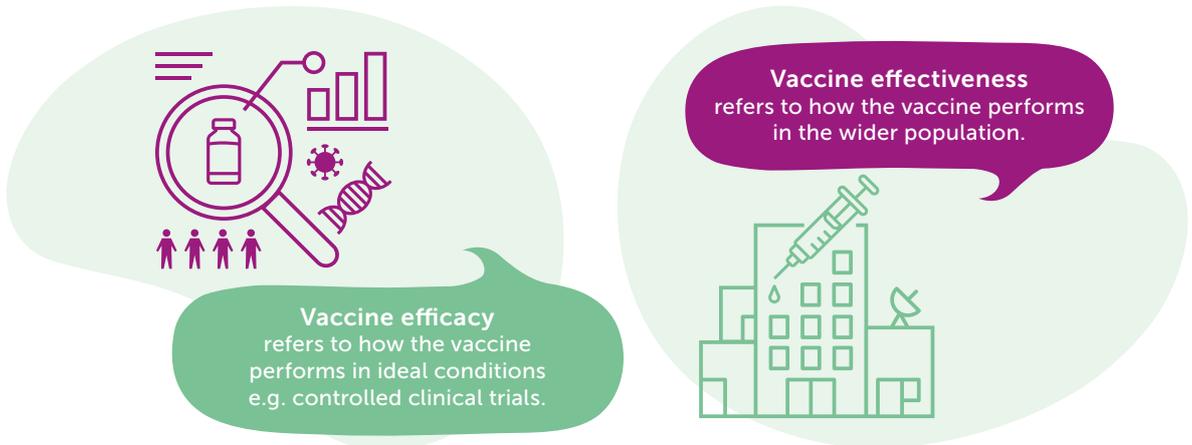
Vaccines have been successfully used for decades to prevent many diseases in humans (and in animals). A few well-known examples are polio, tetanus, and measles vaccines, but there are many others. Each vaccine is designed to protect against a specific disease, but can be combined into one jab with other 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



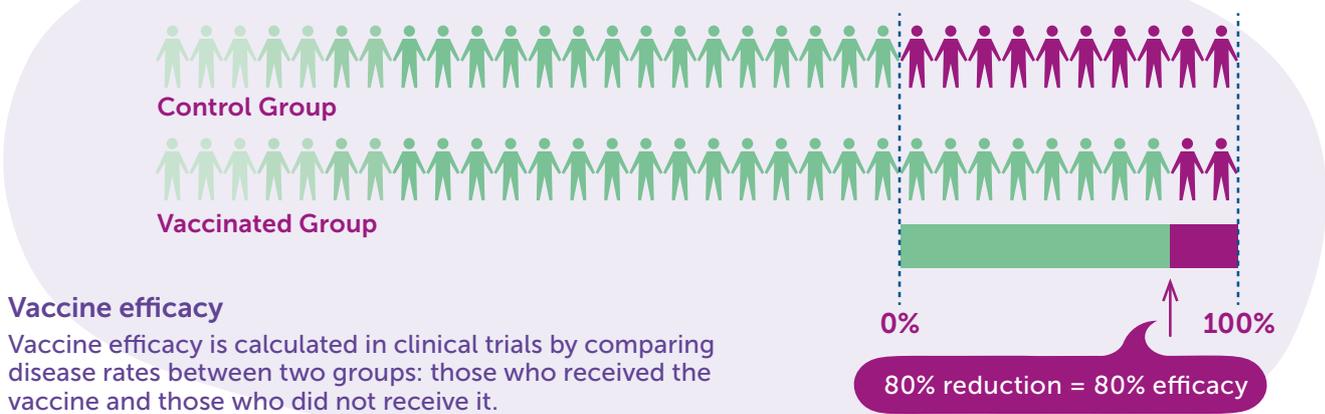
Source: Adapted from WHO

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.

EFFICACY EXPLAINED

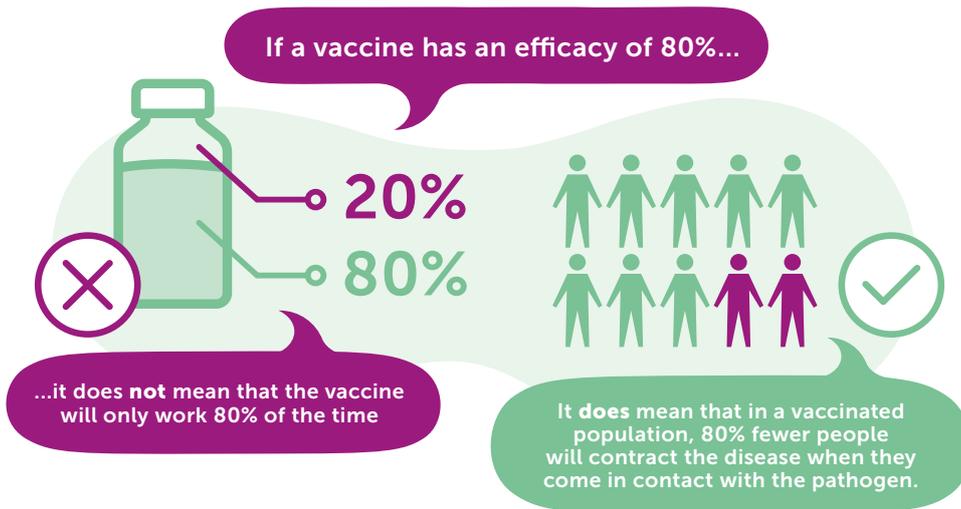


Source: Adapted from WHO

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.

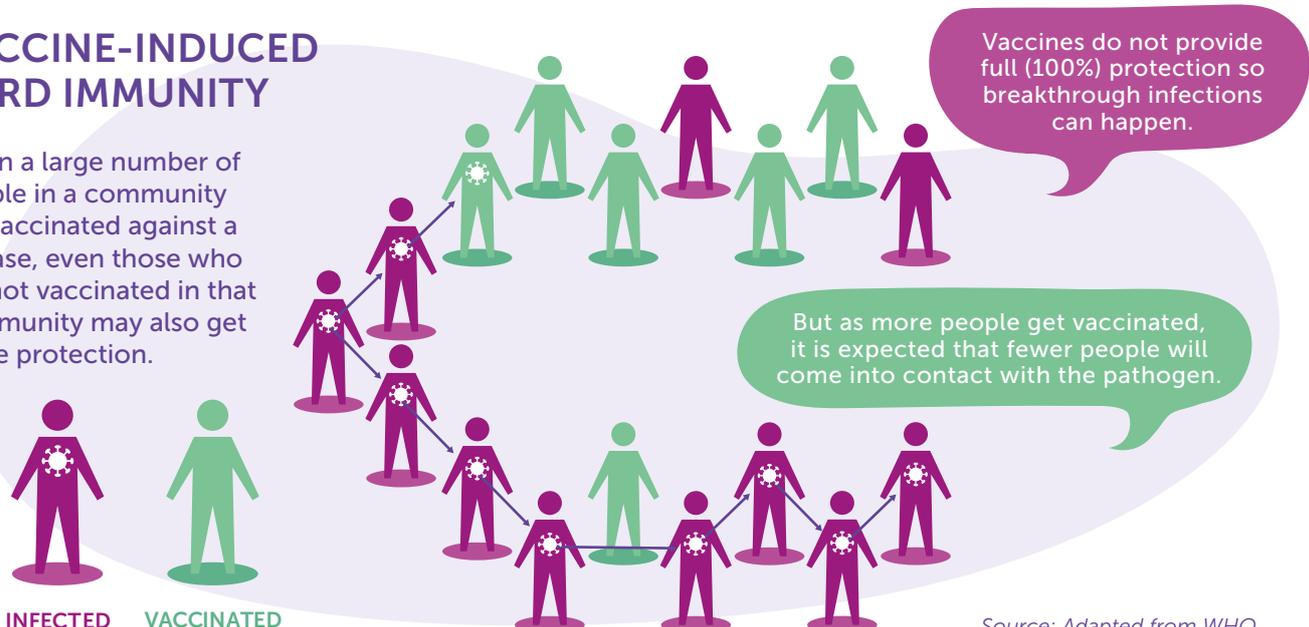
1.3.3 Herd Immunity

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.'

VACCINE-INDUCED HERD IMMUNITY

When a large number of people in a community are vaccinated against a disease, even those who are not vaccinated in that community may also get some protection.

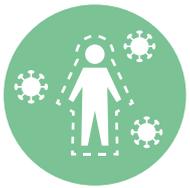


Source: Adapted from WHO

2. How Vaccines Work

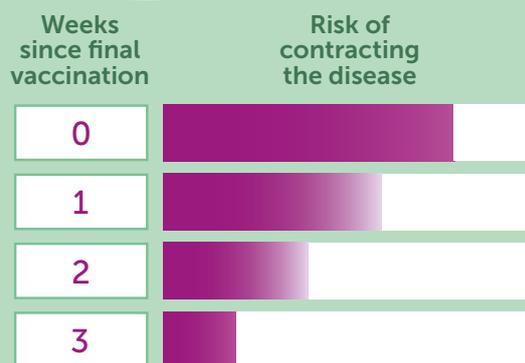
The following steps outline how a preventive vaccine protects an individual from infection or disease (for a more complete explanation see **MODULE 3**):

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.

Vaccines can take 2-3 weeks from the final vaccination to be fully effective. It's important to continue using other prevention measures during this period, to protect yourself and others.

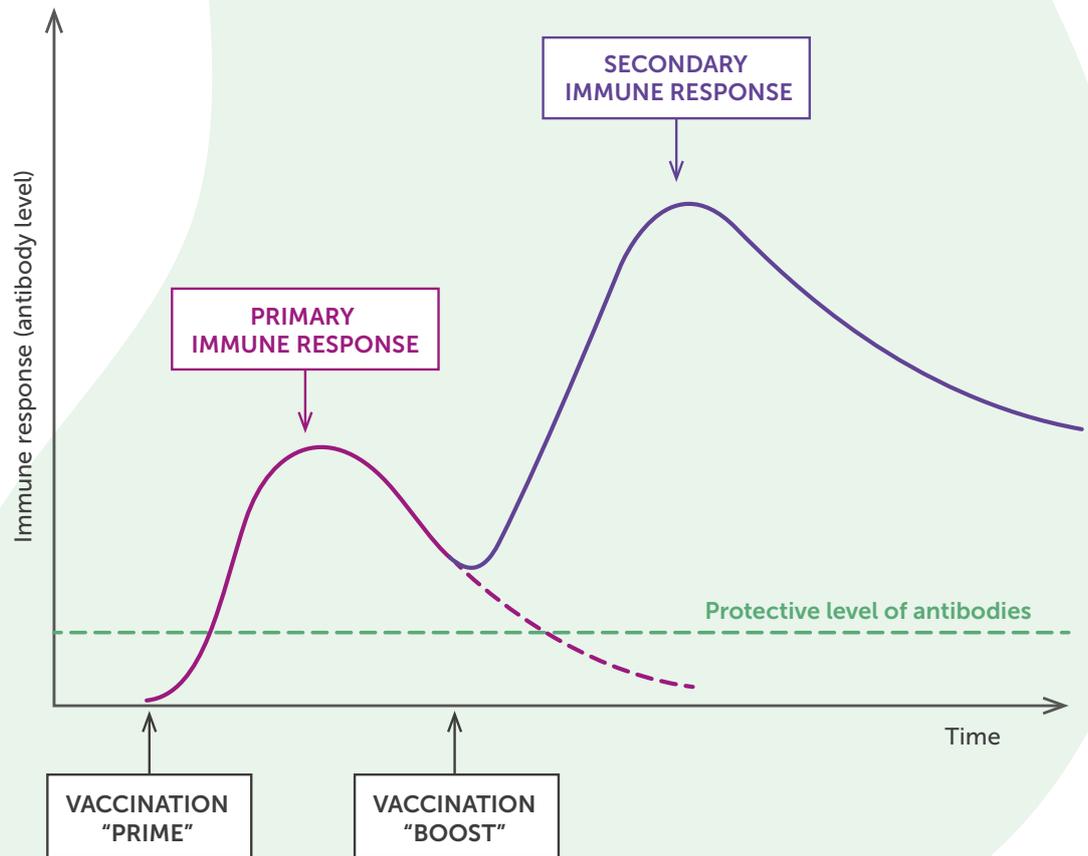


Source: Adapted from WHO



'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

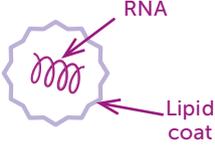
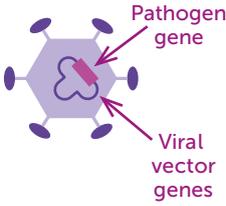
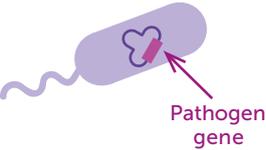
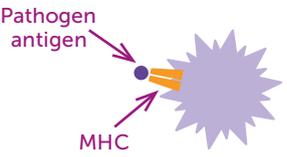


There are many different types of vaccines, based on how they can produce immune responses.

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			
	<p>Uses the entire pathogen to stimulate an immune response.</p> <p>Pathogen is killed or is made inactive so that it cannot cause infection.</p>	<p>Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies</p>	<p>1896 (typhoid)</p>
Live-attenuated vaccines			
	<p>Use a weakened, harmless form of the pathogen.</p> <p>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.</p>	<p>Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster</p>	<p>1798 (smallpox)</p>
Subunit vaccines (purified protein, recombinant protein, polysaccharide, peptide)			
<p>Subunit vaccines</p> 	<p>Most subunit vaccines contain a piece of the pathogen, for example one of its proteins.</p> <p>The subunit acts as the foreign antigen, which will start the immune response.</p>	<p>Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A</p>	<p>1970 (anthrax)</p>
<p>Protein-polysaccharide conjugate</p> 	<p>Certain subunit vaccines are made from smaller pieces of proteins called peptides.</p>	<p>Haemophilus influenzae type B, meningococcal, pneumococcal, typhoid</p>	<p>1987 (H. influenzae type B)</p>
<p>Toxoid</p> 		<p>Diphtheria, tetanus</p>	<p>1923 (diphtheria)</p>
<p>Virus-like particle</p> 		<p>Human papillomavirus</p>	<p>1986 (hepatitis B)</p>

MODULE 4

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

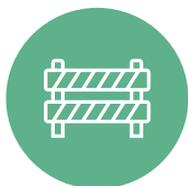
4. Challenges in Developing Vaccines

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:

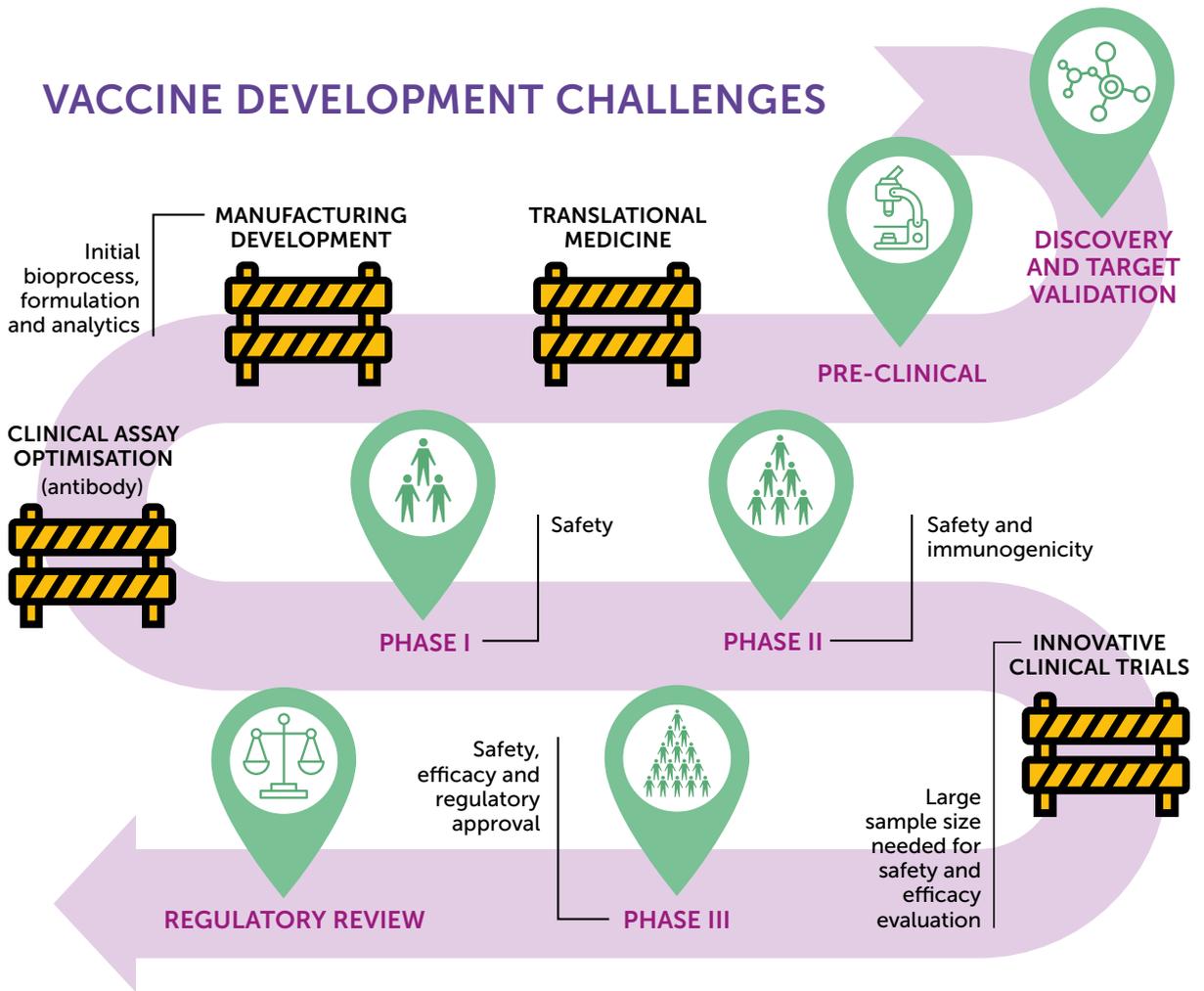
- The pathogen may be complex and diverse (e.g., HIV).
- Immune responses are still poorly understood.
- Animal models are limited and may not perfectly match the human model.
- Large clinical trials are needed to show results.
- Little engagement from the pharmaceutical industry.

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.



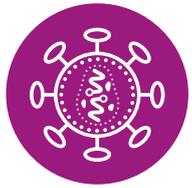
Vaccine development challenges	
ALL VACCINES	UNIQUE TO TB AND HIV VACCINES
Manufacturing-bioprocess, formulation, and analytical development	Complex life cycle of target pathogen(s) make antigen(s) selection difficult
Optimisation of clinical immunologic assays	Protective immune response unclear
Large 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



FIND OUT MORE...

- Pollard, A.J., Bijker, E.M. A guide to vaccinology: from basic principles to new developments. *Nat Rev Immunol* 21, 83–100 (2021).
- Sobia, P.; Archary, D. Preventive HIV Vaccines-Leveraging on Lessons from the Past to Pave the Way Forward. *Vaccines*, 9, 1001 (2021).
- Heaton PM Challenges of Developing Novel Vaccines with Particular Global Health Importance. *Front. Immunol.* 11:517290 (2020).
- Rodrigues CMC and Plotkin SA Impact of Vaccines; Health, Economic and Social Perspectives. *Front. Microbiol.* 11:1526 (2020).

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.

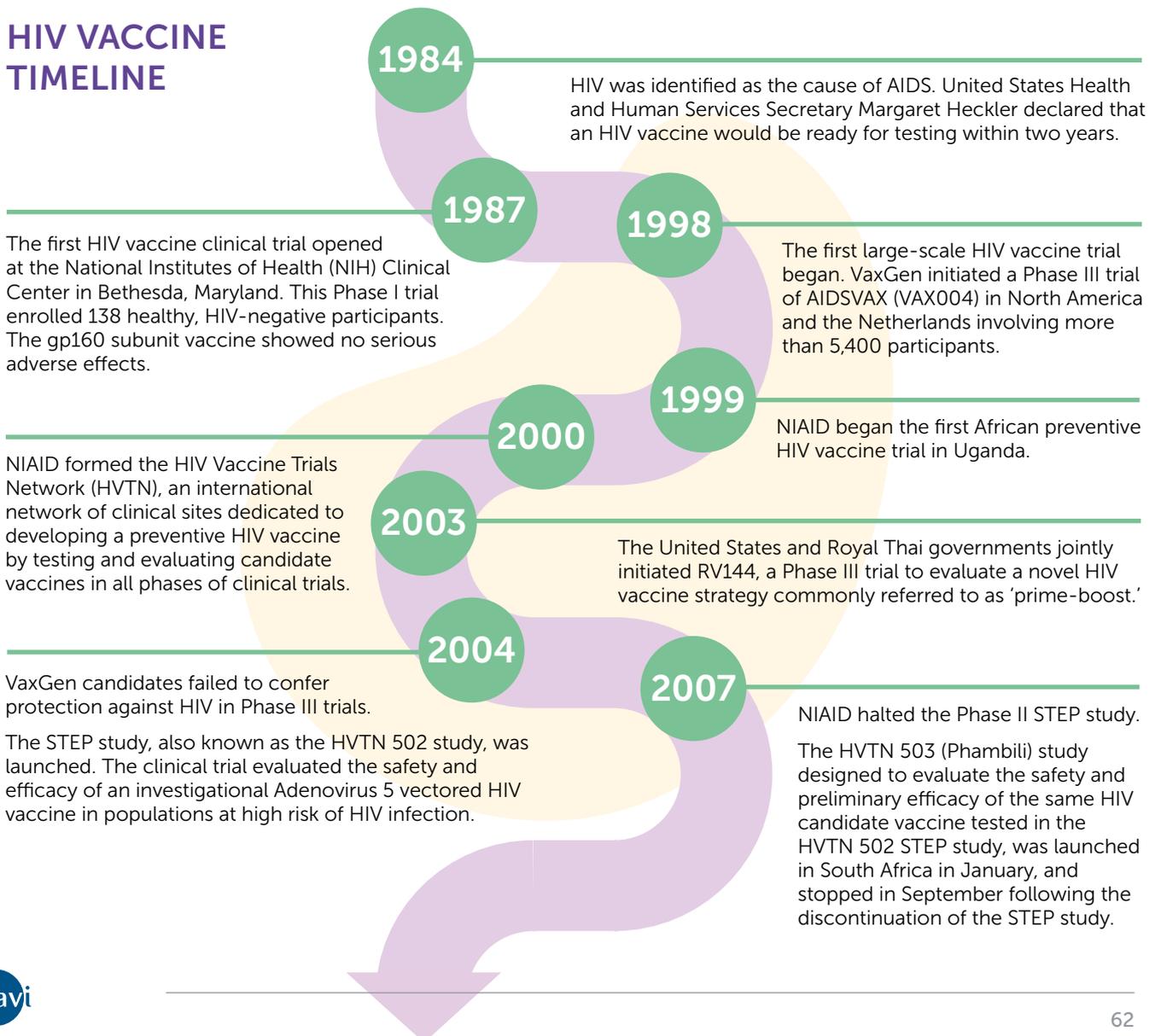
Since clinical trials started in 1987, over 30 different HIV vaccine candidates have been tested in over 70 clinical trials around the world. Only one vaccine tested between 2003 and 2009 in the RV144 ‘Thai trial’ has shown some limited efficacy in preventing HIV. As of 2022, this encouraging result 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



MODULE 4

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.

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.

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.



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 acquire HIV in the future.
- Modifying the course of HIV infection so that even if it were not successful in preventing HIV acquisition, 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.

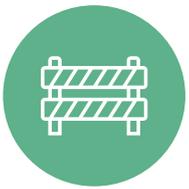
The other scientific development fuelling the design of immunogens to induce bnAbs was obtaining a clearer understanding of the structure of HIV's outermost protein known as HIV Envelope, which is the target of all bnAbs. For decades scientists were held back by their inability to capture the precise 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

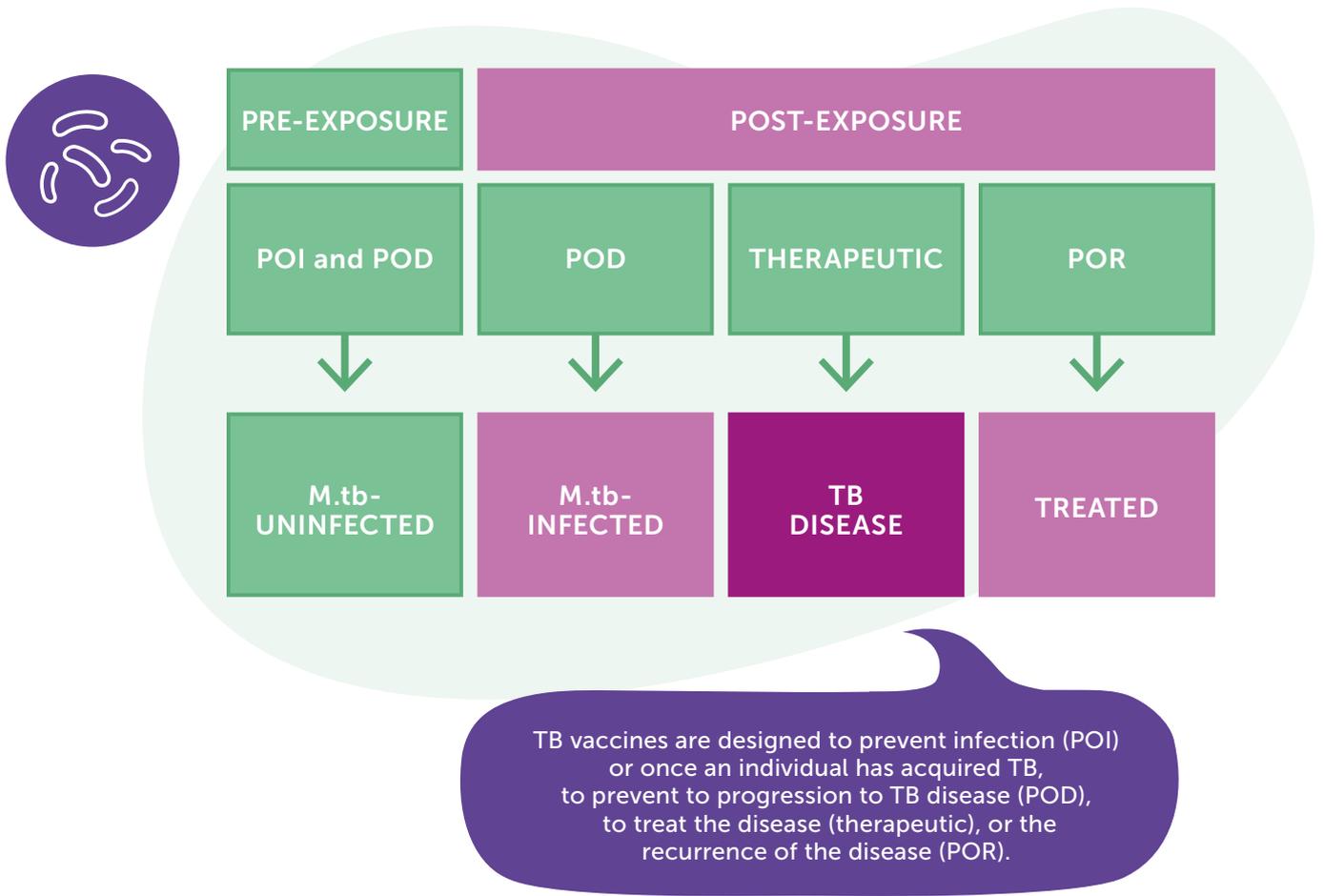
6.1 A Brief History

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](https://doi.org/10.1016/S1473-3099(21)00810-0)



FIND OUT MORE...

- Hatherill M, White RG and Hawn TR Clinical Development of New TB Vaccines: Recent Advances and Next Steps. *Front. Microbiol.* 10:3154 (2020).
- Andersen, P., Scriba, T.J. Moving tuberculosis vaccines from theory to practice. *Nat Rev Immunol* 19, 550–562 (2019).
- Elizabeth M. MacDonald and Angelo A. Izzo. Tuberculosis Vaccine Development – Its History and Future Directions, *Tuberculosis - Expanding Knowledge*, Wellman Ribon, IntechOpen (2015). Available from: <https://www.intechopen.com/chapters/47940>
- 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.

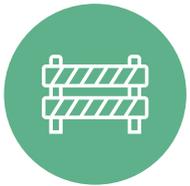
IAVI is researching a vaccine known as 'recombinant vesicular stomatitis virus LASV expressing the GPC protein.' This is among the leading candidates developed so far.

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>



MODULE 5: WHAT IS A VACCINE CLINICAL TRIAL?

How do clinical
trials work?

WHY DO THEY TAKE
PLACE IN DEVELOPING
COUNTRIES?



MODULE 5

WHAT IS A VACCINE CLINICAL TRIAL?

CONTENTS

71

Summary Points	72
1. Introduction: What is a Clinical Trial?	72
2. Key Definitions in Clinical Trials	73
2.1 Safety	73
2.2 Dose, Regimen and Route of Immunisation	74
2.3 Immunogenicity	74
2.4 Efficacy	75
2.5 Effectiveness	76
2.6 Sample Size and 'Power'	76
3. Clinical Trial Methods	77
3.1 Control Group in a Trial	77
3.2 Randomisation	78
3.3 Blinding	78
4. Clinical Trial Phases	80
4.1 Phase I	80
4.2 Phase II	80
4.3 Phase III	81
4.4 Further Studies	82
5. Participation in Vaccine Trials	84





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 (intra-dermal or subcutaneous); application to the skin (transdermal); application to the inside of the nose (nasal); or by being swallowed (oral).

2.3 Immunogenicity

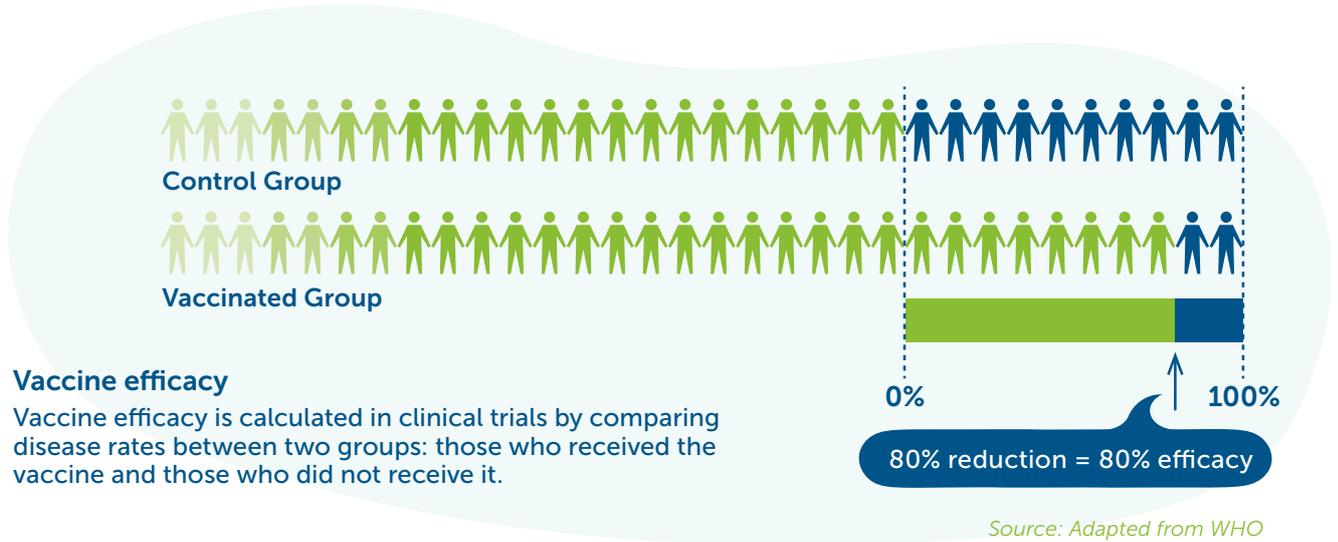
Clinical trials measure the ability, strength, and type of immune responses. These immune responses are measured through laboratory tests on samples of participants' blood, or other body fluids and sometimes body tissue (for example, lymph node or bone marrow sample).

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.

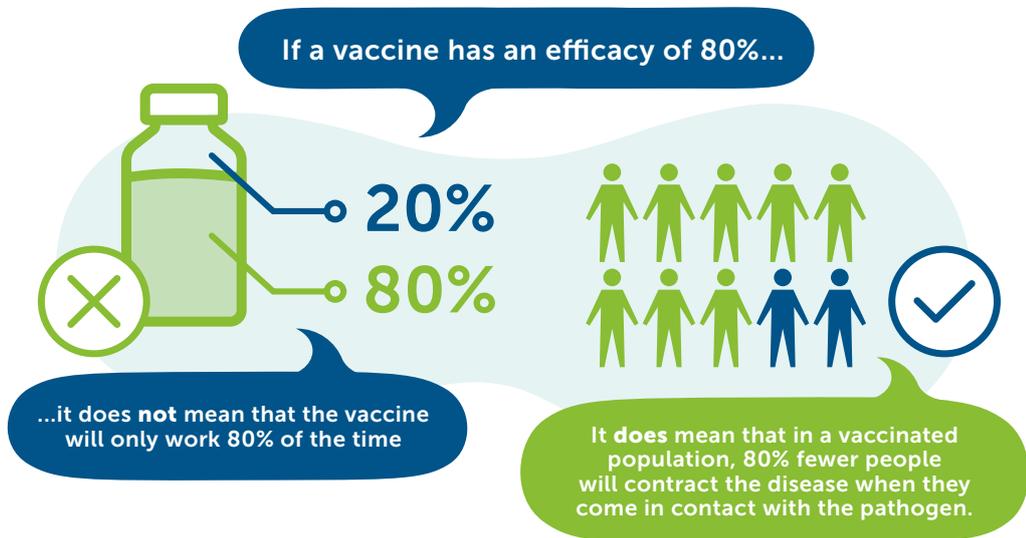
If the vaccine group has less infection or disease, the vaccine is said to have efficacy or to be efficacious. This is not a simple calculation and requires the use of statistical methods to ensure the result observed did not happen just by chance.

EFFICACY EXPLAINED



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.



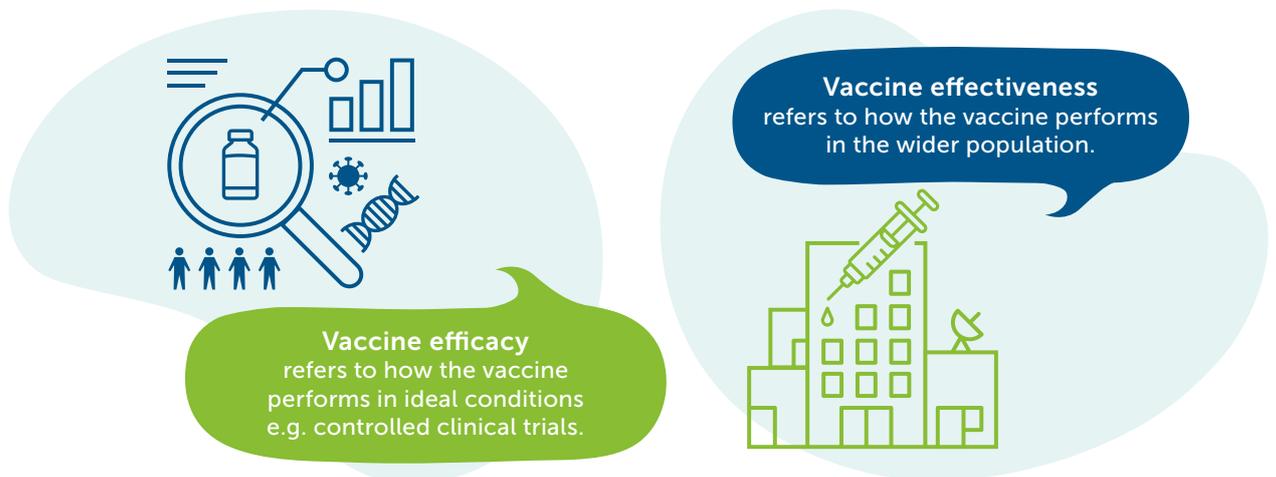
After a vaccine has been proven to work, it is still important to find out how well it works when given to people of different ages, people whose immune systems are not strong, and people with chronic diseases, malnutrition, etc. It also is important to find out how long the protection lasts.

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

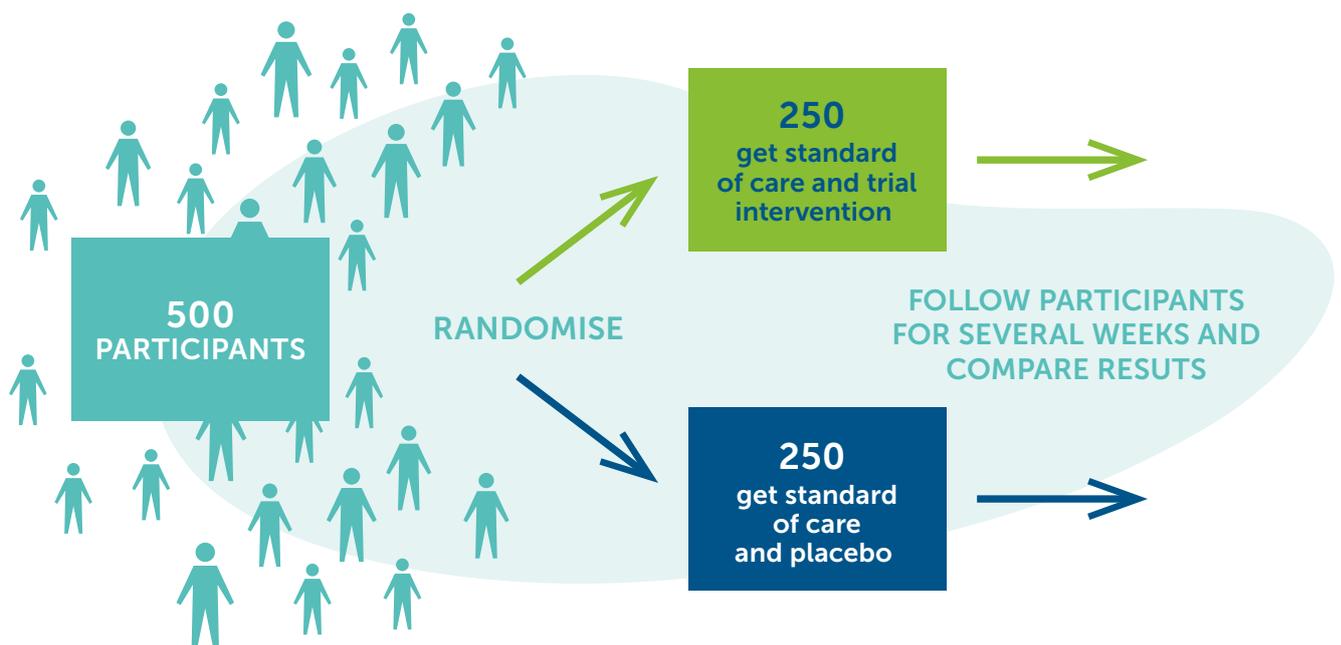
Clinical trials use established and regulated scientific methods to remove as much bias and human error as possible. This ensures the results of testing can be trusted, and protects individuals from harm. To do this, they use a range of methods, including placebos, controls, blinding, and randomisation.

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

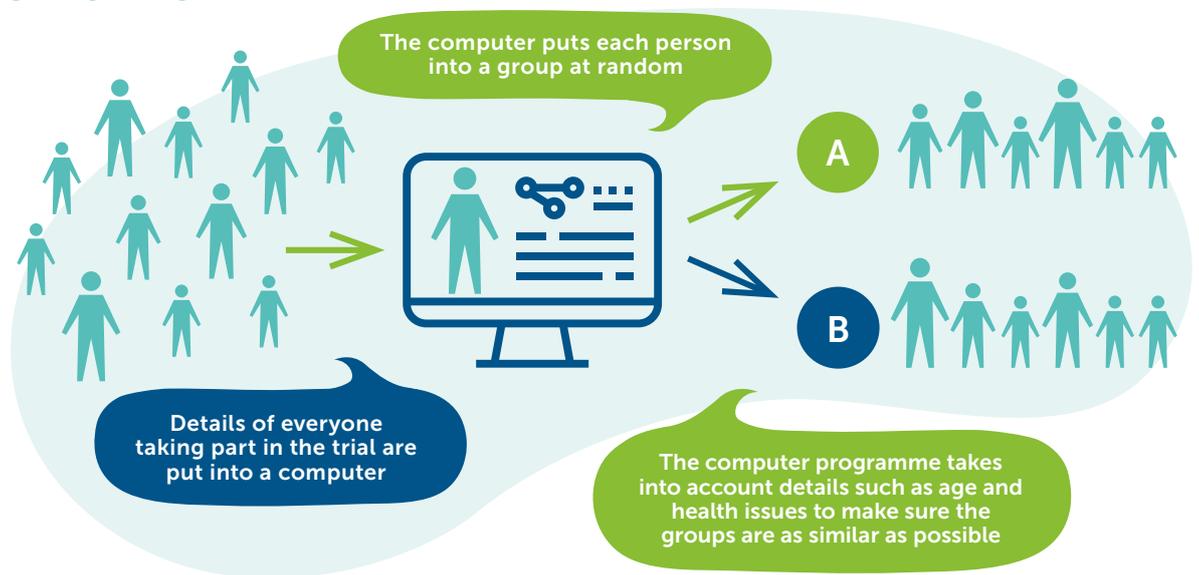


3.2 Randomisation

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.

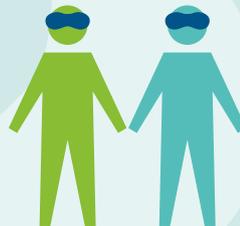
Blinding

- 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.

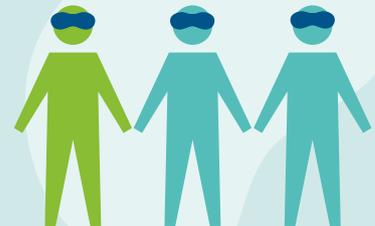
SINGLE BLIND



DOUBLE BLIND



TRIPLE BLIND



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	<p>The first step in development of a new drug, using tissue cultures or animal models.</p> <p>Information on mechanism of action, efficacy, toxicity, pharmacokinetics and pharmacodynamics obtained from these studies.</p>	<p>This phase emphasises safety. It involves 20–60 healthy volunteers. Information on the drug's adverse effects.</p> <p>Information on mechanism of drug metabolism, and excretion are obtained from Phase I studies.</p>	<p>The goal of Phase II trials is to obtain preliminary data on whether the drug works in patients who have a certain disease.</p> <p>It typically involves hundreds of patients.</p> <p>Information on safety continues to be evaluated, and short-term adverse effects are studied.</p>	<p>Phase III trials typically involve hundreds or thousands of patients.</p> <p>Information more concerned on safety and efficacy.</p>	<p>If the Phase III trial is successful, the sponsor applies for New Drug Application to the FDA.</p> <p>This process includes a review of the proposed professional labelling and inspection of the manufacturing.</p> <p>If the review is favorable, the FDA may approve the drug for marketing. Phase IV or post-marketing.</p>	<p>This phase happens after FDA has approved the drug.</p> <p>It involves thousands of participants and can last for many years.</p> <p>Information on medication's long-term safety, effectiveness, and any other benefits.</p>
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).

MODULE 5



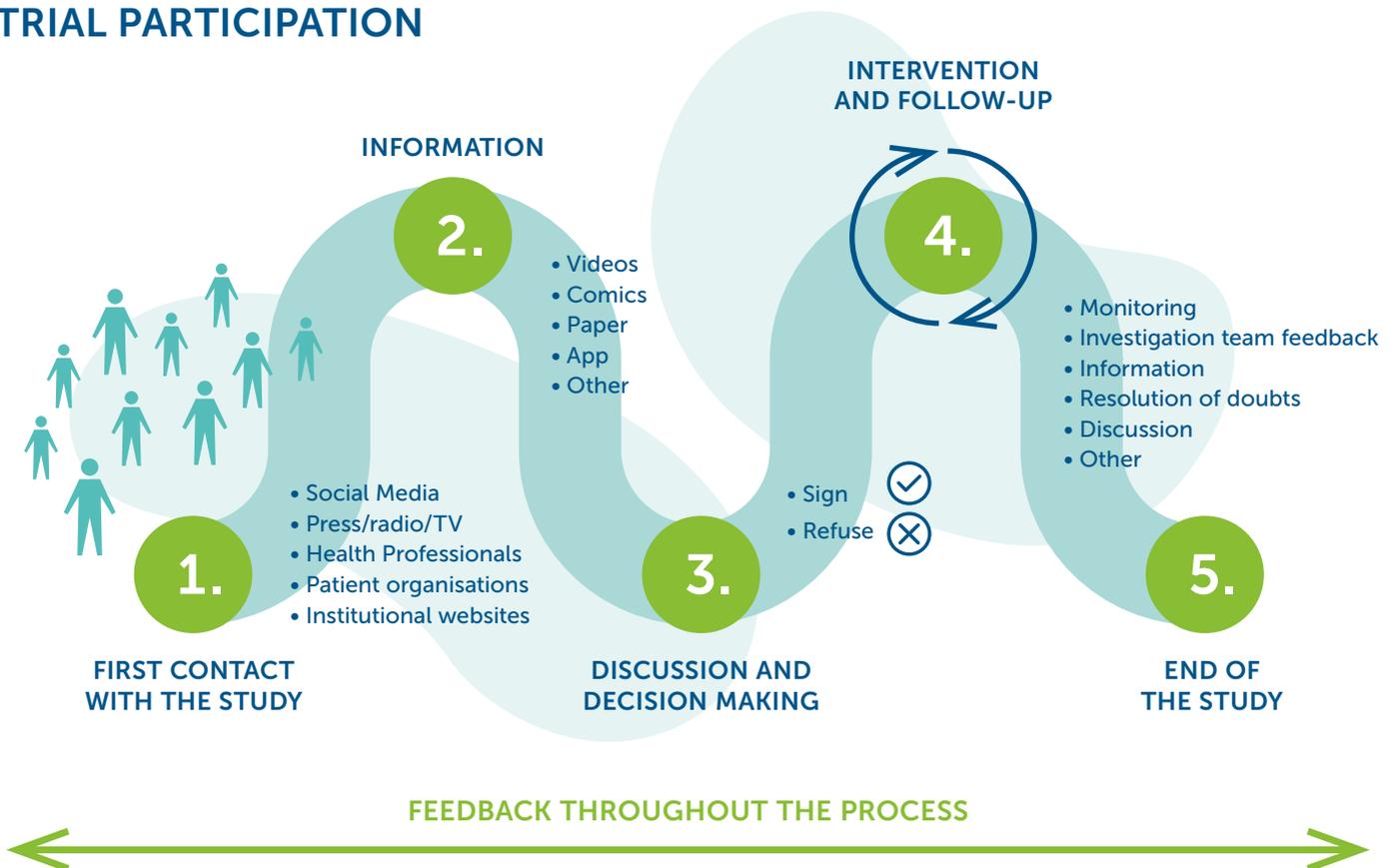
Prevention trials only enrol participants who are not already living with the infection or disease that the vaccine is trying to prevent. However, some trials do need participants who have had the disease when they look at preventing disease progression (for example TB). In general, participants must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





FIND OUT MORE...

- 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>

MODULE 6: THE ETHICS AND REGULATION OF CLINICAL TRIALS

How do we
know that trials
are safe?

ARE WE BEING USED
AS GUINEA PIGS?



MODULE 6

THE ETHICS AND REGULATION OF CLINICAL TRIALS

CONTENTS

88

Summary Points	89
1. Introduction	89
2. Principles of Ethical Research	90
2.1 Value	90
2.2 Scientific Validity	91
2.3 Fair Participant Selection	91
2.4 Favourable Risk/Benefit Ratio	91
2.5 Independent Review	93
Review by Regulatory Authority	93
Review by an Independent Ethics Review Committee	93
Local Ethics Committees	94
Data and Safety Monitoring during Clinical Research	94
Data Safety Monitoring Boards	94
Protocol Safety Review Teams (PSRTs)	94
Community Advisory Boards (CABs)	94
2.6 Trial Guidelines	95
International Council for Harmonisation (ICH)	95
Good Clinical Practice (GCP)	95
Good Participatory Practice (GPP)	96
Specific Guidance	96
2.7 Informed Consent	97
Informed Consent and Specific Populations	98
Vulnerable Populations	98
Women	99
Adolescents	99
2.8 Respect for Participants	100
Welfare	100
Confidentiality	100
3. Community Outreach	101





Summary Points

- All clinical trials are carefully evaluated before they can start to make sure that they are scientifically and ethically sound, and most importantly, safe for participants.
- Independent review committees and regulatory authorities at local and international level conduct additional reviews as a trial is carried out to ensure they meet ethical standards and have the power to stop a trial at any time.
- All vaccine trials follow the same set of international ethical guidelines to ensure that each participant's health, dignity, and well-being are protected.
- Obtaining each participant's informed consent to participate in a trial is essential to ethical research; the purpose is to ensure that participants fully understand essential information about the trial and that they are not unfairly influenced to participate.

1. Introduction



All medical research is governed by principles of ethics. The same legal and ethical standards that are used for regular medical practice also apply to clinical trials, no matter in which country they are conducted. Additional consideration is given for the protection of clinical trial participants.

All vaccine trials follow the same set of international ethical guidelines to ensure that each participant's health, dignity, and well-being are protected. It is the duty of researchers to make sure that local standards of health and human rights of participants are also upheld.

Every clinical research project or study involving humans must go through a standard review process. This includes a review of both the product or vaccine to be tested, and the plan for how the study will be done, known as the protocol. The purpose of the review is to ensure first and foremost that the product is safe for testing in humans and that there are strong reasons for the specific study. Studies that do not enhance or advance our knowledge of human health would be considered unethical and not permitted.

2. Principles of Ethical Research

Researchers and ethical authorities work to ensure that research is conducted according to high ethical standards.

Seven primary principles form a basis for ethical conduct of clinical trials. These are principles for all types of clinical research and are applied to vaccine trials (see **BOX**).



The Seven Primary Principles of Ethical Research

1. **Value** – should answer a question that will enhance health or provide useful knowledge in the health field (see also **MODULE 1**).
2. **Validity** – should have an appropriate, careful, practical design and methodology (see also **MODULE 5**).
3. **Fair participant selection** – participants should be selected in a fair manner, based on scientifically and ethically sound factors (see also **MODULE 5 – Participation**).
4. **Favourable risk/benefit ratio** – risks of participating should be kept to a minimum and should be justified by benefits of participating and of knowledge gained by the study.
5. **Independent review** – independent ethical and regulatory committees must review and give approval for the study.
6. **Informed consent** – every participant must understand the process, risks, and benefits of trial participation so she or he can make an educated and independent decision to participate.
7. **Respect for participants** – rights and welfare of participants must be protected throughout the entire trial, conclusion, and afterwards (follow-up).

2.1 Value

Every clinical trial or research study is designed to answer a specific question. Answering certain questions will have significant value for society or for people with a particular illness, now or in the future.

An answer to the research question should be important or valuable enough to justify asking people to accept some risk or inconvenience for others. Answers to the research question should contribute to scientific understanding of health or improve our ways of preventing, treating, or caring for people with a given disease or condition.

Clinical trials can only be justified if society will gain useful knowledge from the research.

MODULE 1 sets out the reasons why vaccine clinical trials for infectious diseases such as HIV, TB, and Lassa fever are vitally important.

2.2 Scientific Validity

Once it has been established that the clinical trial is answering a valuable research question, it should be designed in a way that will get an ‘understandable answer.’

This includes considering whether the question researchers are asking is answerable, whether the research methods are valid and feasible, and whether the study is designed with a clear scientific objective and using accepted principles, methods, and reliable practices.

Invalid research is unethical because it is a waste of resources and exposes people to risk for no purpose.

See **MODULE 5** for a more detailed explanation of the methods and best practices that clinical trials use to ensure they deliver clear answers.



2.3 Fair Participant Selection

In order to answer the research question, scientists must consider who the study needs to include. The primary basis for recruiting and enrolling groups and individuals should be the scientific goals of the study – not vulnerability, privilege, or other factors unrelated to the purposes of the study.

Consistent with the scientific purpose, people should be chosen in a way that minimises risks and enhances benefits to individuals and society. Groups and individuals who accept the risks and burdens of research should be in a position to enjoy its benefits, and those who may benefit should share some of the risks and burdens.

Specific groups or individuals (for example, women or children) should not be excluded from the opportunity to participate in research without a good scientific reason or a particular susceptibility to risk.

This is further explored in **MODULE 5**.

2.4 Favourable Risk/Benefit Ratio

Participating in any clinical trial involves both risks and benefits. There will always be uncertainty about these, especially in the early trial stages. At the same time, participants may benefit from receiving health services that may not be otherwise available in that location, although the purpose of clinical trials is not to provide health services. These are important ethical considerations.

When researchers plan a study, they must make sure that the risks and benefits of participation have been thought through. If the relative balance of risks and benefits is not reasonable, the trial will not be seen as fair. If there are many risks, it is unfair to ask people to participate. On the other hand, if the standard of care within the trial is higher than outside the trial, people may participate for the wrong reasons and the study may be considered coercive.

When someone is deciding whether or not to participate in a trial, that person must fully understand the risks and benefits involved to make an informed choice of whether he or she feels that the benefits outweigh the risks of participation.

An ethical review board determines the balance of risks and benefits. Every study plan, or protocol, must be reviewed by such a board before the trial is approved.



Examples of Risks and Benefits in HIV Prevention Trials

Examples of risks include:

- Physical side effects of the candidate vaccine, such as a sore arm, headache or fever, and possible serious adverse events (SAEs).
- Social risks such as stigma or discrimination that may be associated with participating in a vaccine trial.
- False sense of protection from the vaccine, which may cause participants to be less careful about exposure to HIV, or risk behaviour.
- False-positive HIV antibody tests (in a person who received vaccine but does not have HIV); the risk of this happening and the time it might last are as yet unknown (see **BOX VISP**).
- Participants may not be able to donate blood during or after the trial, if they have antibodies that cause their blood to falsely test positive for HIV.

Benefits vary from place to place and person to person. Some potential benefits that have been cited include the following:

- Rewarding feeling of being involved in the clinical trial team — some participants report feeling that the staff becomes a ‘family’ or the study clinic, a place of comfort.
- Rewarding feeling of contributing to important medical research.
- Better understanding of HIV and how to avoid becoming infected.
- Receiving medical attention — although this must NOT be confused with standard health care, it may be attention an individual would not receive otherwise; for example, HIV counselling and testing, routine blood analysis/ monitoring.

Also known as vaccine-induced seropositivity (VISP)

False positive tests in HIV vaccine clinical trials

One of the potential risks of participating in a vaccine trial is testing ‘antibody positive’ for HIV, due to what is known as **vaccine-induced seropositivity (VISP)**. Many diagnostic tests use antibodies to diagnose infection, but they are unable to tell if those antibodies are from a vaccine or from natural exposure to disease.

For example, a participant in an HIV vaccine trial may falsely test HIV positive after the trial because of antibodies stimulated by the vaccine, even though the participant is not actually HIV positive.

This is particularly a risk for young people, as a false positive result may present potential barriers to pursuing college education, military service, seeking employment, getting married, and obtaining health insurance.

False positivity may or may not happen depending on the way the vaccine is designed, and if it does happen, it is not certain how long it will last. If this does happen, there are other tests that can easily be done to establish true infection (see **MODULE 3**) and the trial should provide documentation to enable the participant to explain false positivity, for example for insurance, travel, or blood donation purposes.



2.5 Independent Review

Before a trial can be conducted anywhere in the world, it must go through a scientific and ethics review.

All clinical trials are conducted according to a carefully controlled protocol, a detailed description, or guidelines, for how the trial will be carried out. All protocols must be carried out according to strict international standards, such as guidelines set by the International Council for Harmonisation (ICH) on Good Clinical Practices (GCP) and Good Clinical Laboratory Practices (GCLP).

Before any protocol can begin, it must be reviewed and approved by an ethics committee and relevant regulatory committees at the national level. Both national and international authorities that are independent of trial researchers and sponsors conduct ongoing monitoring of research projects to ensure that they meet ethical standards.

Review by Regulatory Authority

A National Regulatory Authority (NRA) generally reviews the information about the product (for example, the candidate drug or vaccine) as a whole, as well as the protocol that explains how a particular study of the product will be done. The NRA is ultimately responsible for approval of the specific study and approving and licensing the product for use in that country.

NRA approval is for clinical trials in the country itself, and if a study is done in more than one country, an NRA from each country must give approval. A report of the progress and results of the trial is sent regularly to the NRA.

Regulatory Authorities are not the same as Independent Ethics Committees, that focus solely on how the clinical trial is conducted.



Review by an Independent Ethics Review Committee

Before any candidate vaccine is tested in people, independent ethics committees (IECs), also called ethics review committees (ERCs) or institutional review boards (IRBs) from the institutions where the clinical trial will be conducted must review specific documents and approve the trial. This review process is designed to ensure the safety, human rights, and wellbeing of the participants involved in the trial.

The names of these review committees can differ from country to country (and even within the same country may differ from institution to institution), but they are all set up in a similar way and abide by the same set of principles.

After the IEC reviews the protocol and all trial-related documents (including recruitment advertisements and community education materials), they may make suggestions and recommend or require changes. The committee will document its recommendations to the site's Principal Investigator (PI), who will then communicate the recommendations or requirements to the sponsor. Trial sponsors and PIs may respond to concerns in writing. If required changes are made to the protocol or other documents, they need to be resubmitted for approval. A trial can begin only after all of the committees have given their final written and dated approval. More than one ethics committee may need to approve a protocol if different groups are involved.

After a vaccine trial begins, committees receive regular reports, including safety data summaries, notification of serious adverse events according to their requirements, and new information on the vaccine that allows them to monitor the safe and ethical conduct of the trial. In particular, committees make sure the investigator and sponsor are fulfilling their obligations to participants. These committees also have the power to stop the trial if there are any concerns for safety or if the trial is not being conducted ethically.



Local Ethics Committees

To ensure that trials are conducted according to ethical standards, a locally based ethics committee must review the proposed trial protocol, informed consent, and other study-related materials. The ethics committee may be called an ethics review committee (ERC) or an institutional review board (IRB). The main purpose of these committees is to ensure the safety and respect of human rights of trial participants and the ethical conduct of the trial.

These committees are made up of scientists, ethicists, community members, and other experts who are independent of the trial sponsors and investigators and are trained in evaluating research proposals. Ethics review committees should also include individuals with gender expertise to ensure that gender issues are considered during the review of the informed consent process and that decision-making is truly informed and voluntary.

This combination of people provides an unbiased, fair, and well-rounded evaluation of the study proposal. In addition to the ethics review, the ERC, IRB, or a related committee usually also conducts a science review.

Data and Safety Monitoring during Clinical Research

Participant's safety during clinical research is constantly monitored by internal and external monitoring boards.

Protocol Safety Review Teams (PSRTs)

The PSRT is an internal review committee that consists of the study principal investigators, and medical and other representatives of the study sponsor. The PSRT conducts day-to-day reviews (typically by conference call) of the safety data reports generated on a regular basis during the study. The PSRT also meet by conference call as needed to discuss any potential safety concerns. Not all studies include a PSRT.

Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) or Independent Data Monitoring Committee (IDMC) is a multidisciplinary group of independent experts made of physicians from relevant medical specialties and biostatisticians. The DSMB may include other experts such as bioethicists, epidemiologists, and basic scientists. The DSMB conducts interim monitoring of the data from research activities as they arise to ensure the continuing safety of research participants, relevance of the study question, appropriateness of the study, and integrity of the accumulating data.



Community Advisory Boards (CABs)

Community Advisory Boards (CABs) are composed of leaders and other individuals representing various parts of the community, such as religious groups, schools or universities, media and non-governmental or community-based organisations, who review protocols and the informed consent documents, and help educate and inform the rest of the community.

Although CABs often provide feedback on research protocols, this is not considered official approval. Such groups often provide valuable insight that helps improve the trial process and are therefore important for a successful trial.

Often a senior scientist or medical professional and/or another member of the trial staff attends CAB meetings with some regularity, which is a sign of the CAB's significance in the trial process.

CAB members may take a very active role in planning for and undertaking vaccine trials. Some examples of their activities include the following:

- General community outreach and education.
- Support for participant recruitment by disseminating information about the trial.
- Providing feedback to the study team on trial protocols, including criteria for participation, informed consent forms and processes, and participant recruitment and retention.
- Keeping track of community views and concerns about the trial including rumours and misinformation related to the trial.
- Advising investigators regarding potential participants' perspectives about the trial.
- Providing a safeguard (in addition to institutional ethics review committee) for participants' rights.
- Representation at important national, regional, and international meetings and conferences.

Most researchers acknowledge that for a trial to be successful, it is important to obtain general support from the communities that will be involved in the research. As the CAB acts as a liaison between the researchers and the community, researchers may hold consultations with CABs about an upcoming trial.

2.6 Trial Guidelines

All review committees follow internationally agreed-upon guidelines that provide detailed definitions of the requirements for ethical research. These guidelines create uniform ethical and scientific standards for all trials with human participants, wherever they take place.

International Council for Harmonisation (ICH)

The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) brings together regulatory authorities and the pharmaceutical industry to discuss scientific and technical aspects of pharmaceuticals and develop ICH guidelines. ICH's mission is to achieve greater harmonisation worldwide to ensure that safe, effective, and high-quality medicines are developed, registered, and maintained in the most resource efficient manner whilst meeting high standards.

Good Clinical Practice (GCP)

Good clinical practice is an international quality standard based on the ICH. The official guidelines for GCP were established by the U.S. Food and Drug Administration (FDA), in agreement with the ICH. The purpose of the guidelines is to establish standards for designing, conducting, recording, and reporting clinical trials. These guidelines establish the requirements needed for effective review and approval of proposed clinical studies.



Good Participatory Practice (GPP)

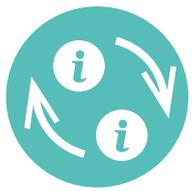
Good Participatory Practice (GPP) guidelines provide clinical trial funders, sponsors, and implementers with systematic guidance on how to effectively engage with all stakeholders in the design and conduct of vaccine biomedical research. Guidelines also exist for emerging infectious diseases.

Specific Guidance

HIV vaccine research involves unique additional ethical issues. The Joint United Nations Programme on HIV/AIDS (UNAIDS) has helped to address them by issuing an official ethics guidance document, found in the resources section below.

ETHICS AND SCIENTIFIC ADVISORY COMMITTEES

	REGULATORY	SCIENTIFIC	ETHICS
Focus of information reviewed	Package for review includes all relevant information about the product, including all previous tests (preclinical and clinical) done on the product and how it will be tested in humans, including protocol for testing the product, and the Investigator’s Brochure.	Scientific committee review ensures that the trial is asking legitimate scientific questions and that the study is well designed to answer these questions. NOTE: Scientific review may be carried out by an ethics committee.	Package for review includes all relevant information about the protocol, focusing on one study of the product to be conducted at a specific institution. Some also include review of the product, usually based on the Investigator’s Brochure.
Level of committee	Country/national, appointed by government; sometimes regional.	Institution/university or country/national.	Institution/university in most cases; national in some cases.
Materials reviewed	Product specific materials – entire package of information on preclinical and clinical testing of the product, its safety and its biological effects and rationale for specific details of testing; trial-specific materials (such as the protocol) are also reviewed.	Product- and trial-specific materials.	Trial-specific materials – study protocol, including the informed consent, advertisements for study recruitment, informed consent document.
Examples	U.S. Food and Drug Administration (FDA); National Council of Science and Technology of Government of Kenya.	Institutional Review Board (IRB) at an academic institution involved in the trial.	Kenyatta National Hospital Ethical and Research Committee – a joint committee between the University of Nairobi and Kenyatta National Hospital.

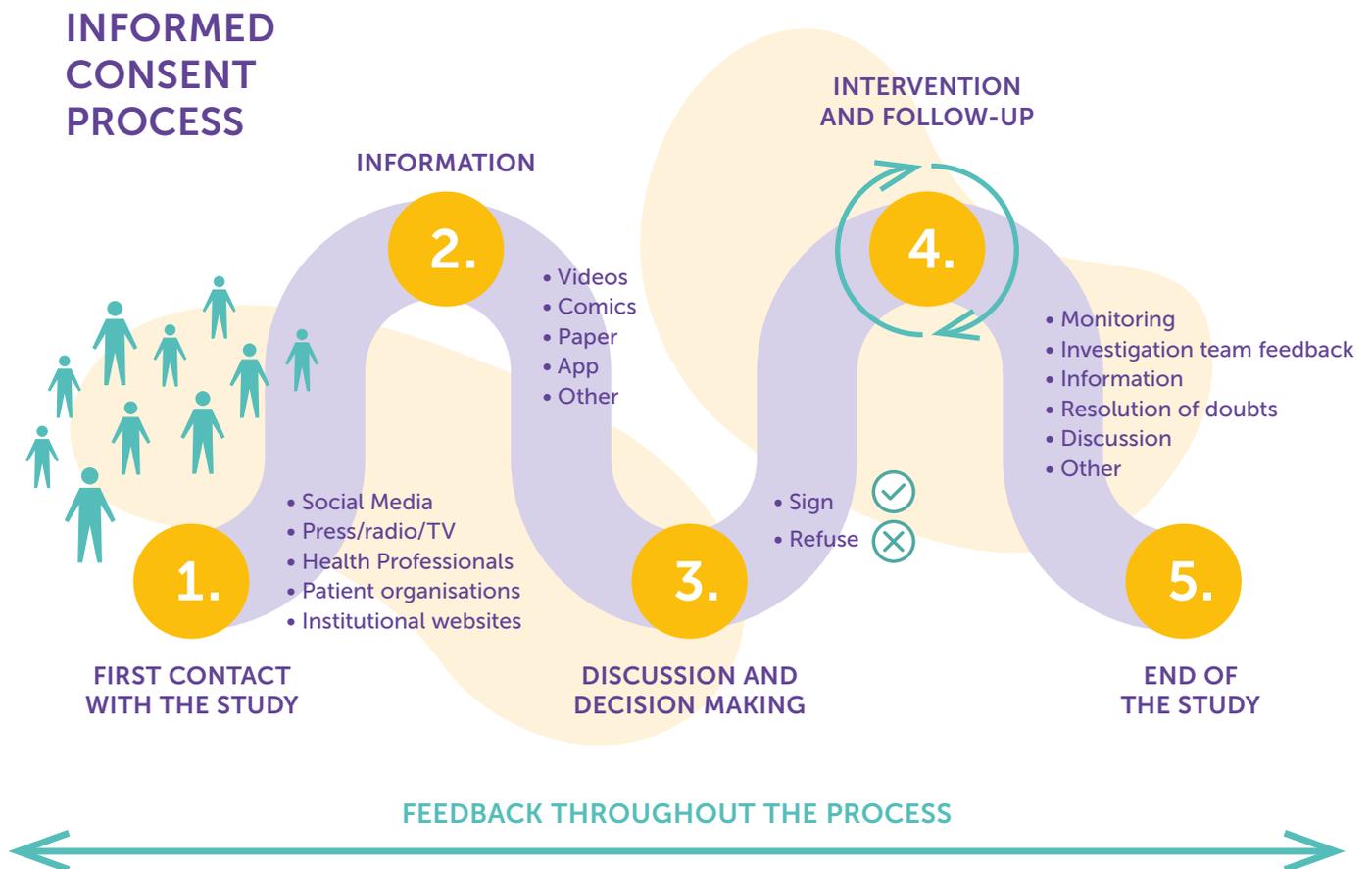


2.7 Informed Consent

Informed consent is not a one-off event but is 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 enrolled in 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.

Researchers cannot rely on this document alone to ensure that the individual truly understands the trial. Obtaining true informed consent involves a process of delivering information about the trial, making sure people understand the information and ensuring that the participant makes his or her own decision to participate. Community education is an important part of this process of education and dialogue between researchers, communities, and potential participants.

Obtaining true informed consent can be a challenge in communities that are not familiar with medical research or with vaccines, and in populations or individuals that may be vulnerable to pressures from others. This means that potential participants must fully understand key aspects of trial participation, including the potential risks and benefits (see below), before they sign the informed consent form. In many trial sites, this involves two levels of outreach, one to the broader community and one to the individual.



Although informed consent is not the only factor in ensuring the ethical conduct of a trial, it is a key factor. The researchers must explain to participants many important facts about the trial, including its purpose, the vaccine that will be tested, the number of clinical visits required, and possible benefits and risks. Participants also need to know that they have the right to not participate or to withdraw at any time. Importantly, researchers must be sure that the participant's decision is free from inducement or coercion of any kind. This should be clearly presented in the informed consent document (see **BOX**).



The Informed Consent Document

The informed consent is the document signed by anyone who decides to participate in a trial that indicates his or her understanding of, and agreement to, the following:

1. Why the research is being done.
2. What researchers want to accomplish and who is responsible for the trial.
3. What will be done during the trial and for how long.
4. What risks are involved.
5. What is expected of trial participants.
6. What, if any, benefits can be expected from the trial.
7. The system in place for care and support of participants.
8. What other interventions are available.
9. The participant's right to leave the trial at any time.

Informed Consent and Specific Populations

Communicating the complete information and ensuring understanding can be complex and difficult, particularly for vulnerable groups, as well as women and adolescents in specific situations.

As part of the process of ensuring informed consent, the community at large should be provided with information about the trial. This process helps to create an environment that will help enable women, adolescents, and other vulnerable people to participate in trials. Giving informed consent and participating, however, is ultimately the individual's decision.

Vulnerable Populations

Specific measures should be taken to support and protect people who are, or who may be, limited in their ability to participate voluntarily or provide informed consent. This can include prisoners, and those who have limited literacy or low levels of education.

It is also important to consider that the populations who are recruited to clinical trials may be stigmatised, discriminated against, and criminalised in the country in which the research is taking place, such as people living with HIV, men who have sex with men, transgender people, sex workers, and people who use drugs.

Information must be presented in language that all participants understand, in a way that prepares people to fully understand their rights, risks, and benefits and in an environment that supports independent decision-making. All participants should fully understand the information provided before they sign an informed consent form.

Women

In some contexts, women may be vulnerable to unfair influence and coercion from husbands, family, community members, and healthcare providers to sign consent forms. Many women may want to discuss potential participation with important people in their lives, including husbands, partners, and fathers. It is important for these women to have the opportunity to consult with whomever they wish, but they should know that this is not required for informed consent.

To participate in a trial, only the woman's personal, individual informed consent is required. As explained below, her confidentiality is always protected if she wants to participate but does not want to inform others, for example a male partner.

Adolescents

It is important to include young people in vaccine clinical research for a number of reasons.

The optimal age for vaccination may be before puberty, and data on how vaccines work in young people are usually required by regulatory authorities to be sure of safety. Young people, especially young women, are also among the highest risk group for several sexually transmitted infections, including HIV.

However, in most countries, young people under the age of 18 are legal 'minors' and therefore usually unable to give consent for participation in clinical research without parental permission. Parents may be reluctant to give consent due to stigma, and young people may be unwilling to ask. Patient confidentiality about sexual history and reproductive health may conflict with the local expectations around the age of consent. Adolescents may not fully understand their personal risk, posing challenges for informed consent as well as prevention counselling during the trial.

It is vitally important that additional regulatory and ethical safeguards are put in place to protect adolescents, but equally vaccine trial sites need to be youth-friendly and cater specifically to their unique needs.





2.8 Respect for Participants

Protection of trial participants is a human rights issue and has become a defining factor in the conduct of all vaccine trials.

Participants do a service for researchers and for medical science in general and it is the duty of researchers to make sure participants are taken care of. Participating in a trial involves certain risks that a person may not encounter in normal daily life, as discussed above. Individuals should be treated with respect from the time they are approached for possible participation — even if they refuse enrolment in a study — throughout their participation and after their participation ends. This includes informing participants and the community about what was learned from the research by sharing the results.

Welfare

Researchers should take measures to protect the safety, human rights and welfare of participants, and to prevent discrimination or prejudice. For example, they may take professional development courses on stigma in health care and other settings, or on culturally appropriate care and language. Staff in the trial sites should be educated about stigma and discrimination around key populations, gender, human rights and health care, and gender-based violence. Staff should know how to identify participants affected by these issues and be familiar with the resources available or services to refer them to.

When monitoring participants' welfare, the study team must be able to ensure appropriate treatment and support if they experience adverse reactions or change in clinical status. Participants must be informed of any new information that emerges, which might change their assessment of the risks and benefits of participating. Researchers must respect their right to change their mind, to decide that the research does not match their interests, and to withdraw without penalty.

Confidentiality

The study team must keep all information about participants confidential. Information collected about the participant during the trial should not be disclosed to anyone except study staff without the consent of the participant.

If a participant sees a doctor who is not involved in the trial for a medical problem, it is helpful to let the doctor know that he or she is participating in the trial, so the doctor can do a better job of treating the individual. However, the participant must provide that information themselves; the study team will not give the doctor information unless requested by the participant.

While confidentiality is critical for all trial participants, women may be particularly vulnerable if confidentiality is broken, as disclosure of participation in trials itself may lead to stigma, discrimination, and violence. This is particularly relevant to HIV vaccine trials: If a woman is known to be participating in such a trial, people may assume she is engaging in risky behaviour or that she is protecting herself from the risky behaviour of her partner. Similarly, there is considerable potential for stigma and discrimination against vulnerable and other marginalised populations. All trial staff must be trained in handling confidentiality in a diversity- and gender-sensitive manner.

3. Community Outreach



Outreach to the broader community extends beyond the scope of trial recruitment. It involves informing the leaders in a community well in advance of the trial as an important channel for building understanding and support among the community at large. Having leaders who are informed and supportive of the trial will also minimise stigma that may be attached to community members who participate or who even ask for information about the trial.

Most vaccine trial sites have active community advisory boards (CABs) that are an important form of outreach to the broader community, although alternative community advisory mechanisms may also exist. These groups act as liaisons between the trial researchers and the community, and they help to tailor and deliver the proper information to potential participants.

For outreach to the individual, a trial site will sometimes offer general information sessions, where anyone interested can learn about vaccine research. There may also be one-on-one counselling sessions where potential participants learn about the trial in more detail. Finally, some studies require that before signing the informed consent, potential participants complete a questionnaire to test comprehension.



FIND OUT MORE...

- International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Copyright ICH Secretariat, Geneva, Switzerland. Online version: <https://www.ich.org>
- Good Participatory Practice Guidelines 2nd edition (June 2011): <https://www.avac.org/resource/good-participatory-practice-guidelines-biomedical-hiv-prevention-trials-second-edition>
- Science, theory, and practice of engaged research: Good Participatory Practice and beyond JIAS, (2018): https://www.avac.org/sites/default/files/resource-files/JIAS_Vol21-S7.pdf
- Good Participatory Practice for TB vaccine research: <https://www.avac.org/resource/good-participatory-practice-guidelines-tb-vaccine-research-2017>
- Ethical considerations in HIV prevention trials: https://www.unaids.org/sites/default/files/media_asset/ethical-considerations-hiv-prevention-trials_en.pdf
- WMA Declaration of Helsinki – ethical principles for medical research involving human subjects: <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>
- Research Fairness Initiative: <https://rfi.cohred.org>
- TRUST Equitable Research Partnerships: <http://trust-project.eu>

MODULE 7: PREPARING FOR FUTURE ACCESS

When will we
have an HIV
vaccine?

HOW MUCH
WILL IT COST?

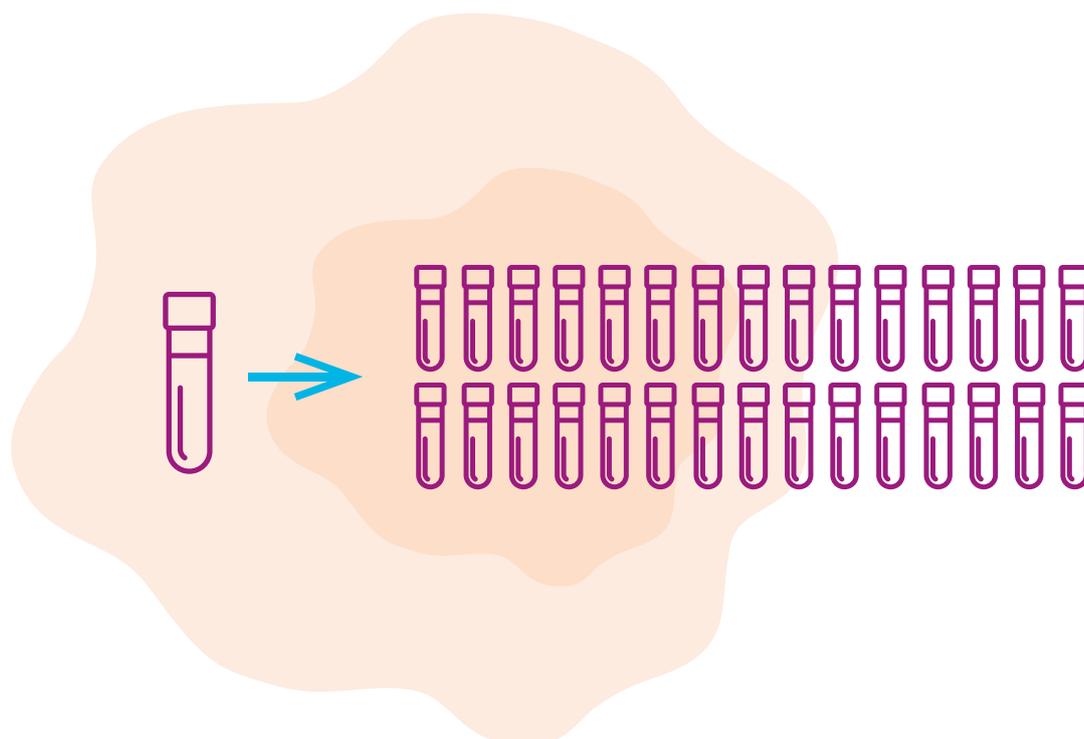


MODULE 7

PREPARING FOR FUTURE ACCESS

CONTENTS 103

Summary Points	104
1. Introduction	104
2. Barriers to Vaccine Roll Out	106
2.1 Global Funding, Finance Mechanisms, and Pricing	106
2.2 Regulatory Approval and Licensure	108
2.3 Manufacturing Capacity	109
2.4 Operational Research	109
2.5 Delivery and Roll Out	109
3. Barriers to Vaccine Acceptance and Use	110
3.1 Vaccine Hesitancy	110
3.2 Efficacy	110
3.3 Characteristics	111
3.4 Stigma and Risk Perception	111



» Summary Points

- Making a vaccine available to the world requires much more than proving that it is safe and efficacious in clinical trials.
- There are many barriers that can prevent wide uptake and use of vaccines, including lack of funding, regulatory hurdles, manufacturing capacity, supply chain issues, affordability, and acceptability.
- Reluctance or refusal to be vaccinated (vaccine hesitancy) may be influenced by a complex mix of historical, political, social, and behavioural factors.

1. Introduction



The COVID-19 pandemic has shown that making a vaccine available to the world requires much more than proving that it is safe and efficacious in clinical trials.

Potential barriers to immediate and equitable access relate to regulatory capacity for licensure, delays in pursuing licensure in high prevalence settings, limited manufacturing capacity, ability to match demand and supply, sensible delivery systems, affordable pricing, and financing.

Even where these challenges are overcome, there can be low uptake of vaccines due to acceptability factors such as vaccine hesitancy, risk perception, stigma, and/or the social and political context.

Addressing the potential barriers to access during vaccine development and clinical trials can potentially make access faster once licensure has been achieved.

Vaccine development challenges

ALL VACCINES

Manufacturing-bioprocess, formulation, and analytical development

Optimisation of clinical immunologic assays

Large clinical trials required to evaluate safety in healthy individuals

UNIQUE TO TB AND HIV VACCINES

Complex life cycle of target pathogen(s) make antigen(s) selection difficult

Protective immune response unclear

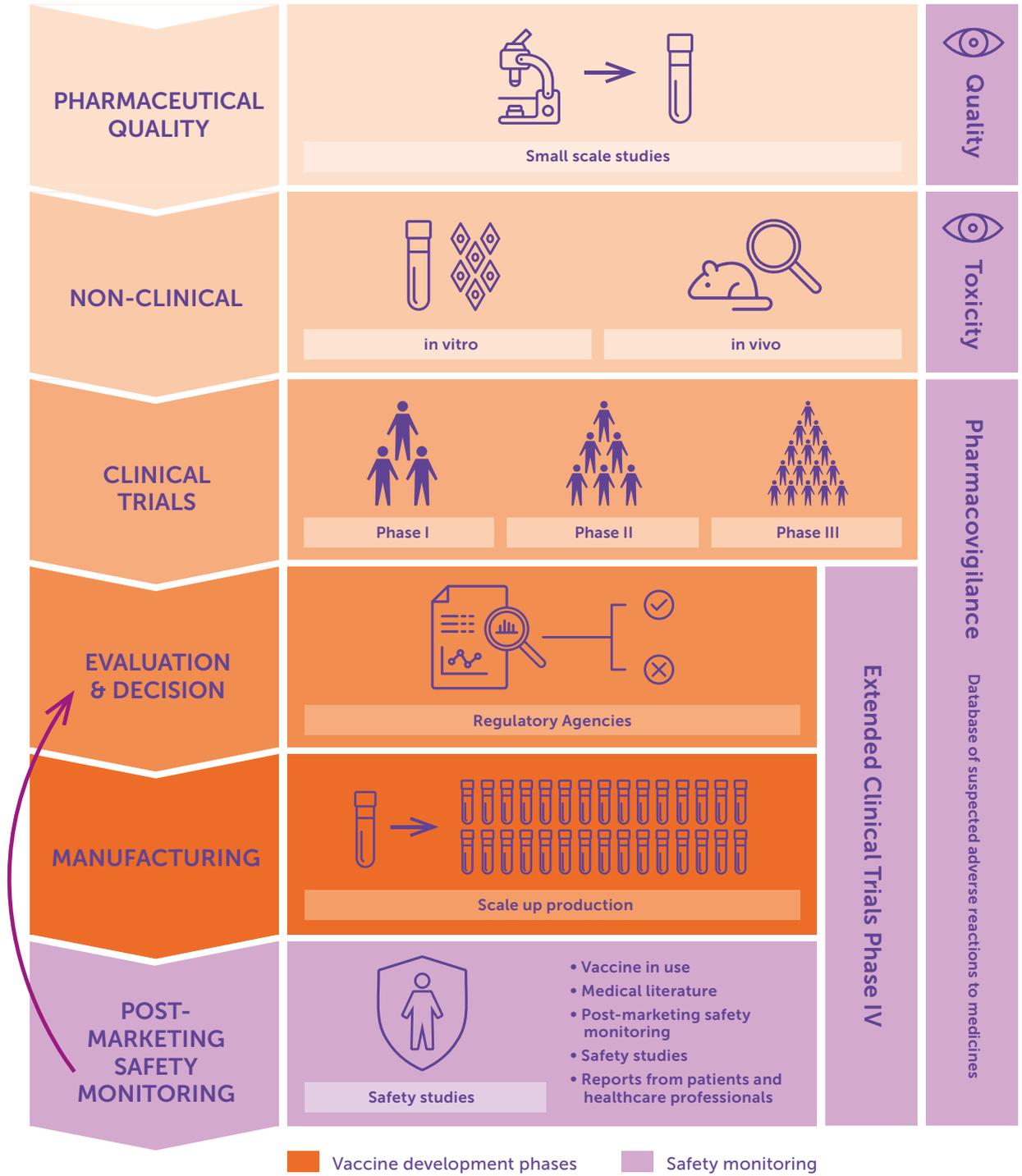
Poor memory responses with rapidly waning efficacy

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

VACCINE DEVELOPMENT PHASES



2. Barriers to Vaccine Roll Out



2.1 Global Funding, Finance Mechanisms, and Pricing

Billions of dollars are needed to purchase and deliver vaccines globally. Most of this funding must come from national governments, especially in wealthy countries, as well as multinational funding bodies like Gavi, the Vaccine Alliance (Gavi), the Global Fund, and organisations like the World Bank.

Financial mechanisms must be set up to ensure that there are sufficient funds in place to purchase and deliver vaccines as soon as a product is licensed.

In addition, vaccines must be affordably priced, particularly when they have been developed with public funds. The pricing of vaccines is driven by a combination of factors but is ultimately set by the manufacturer. Some vaccines are more expensive than others to develop or produce due to their ingredients or mechanism of action.

It is possible to make vaccines available on a not-for-profit basis or have 'tiered pricing' structures to support affordability in low- and middle-income countries. The diagram below shows how COVID-19 vaccines, for example, compare in terms of price per dose.

Fifty-seven countries, many of which have high HIV prevalence, are currently eligible for financial support through Gavi for vaccine procurement. Integration of new vaccines into Gavi's Vaccine Investment Strategy, which is updated every five years, will be important for ensuring access in these low- and lower-middle income countries.

For vaccines that are procured directly from companies, the actual price that a government pays for a vaccine is negotiated with the company that produces the vaccine, depending on the number of doses ordered and the urgency of the need. A vaccine that is needed globally may be cheaper to purchase than one that is only needed in a handful of countries. Prices negotiated between vaccine makers and governments are not always made publicly available. Procuring through pooled procurement platforms, such as UNICEF or the Pan-American Health Organization (PAHO), can allow countries to access lower pricing.

Avoiding vaccine nationalism: the COVAX example

During the COVID-19 pandemic, many governments signed 'bilateral' agreements with vaccine manufacturers to supply their own populations with vaccines ahead of them becoming available for other countries.

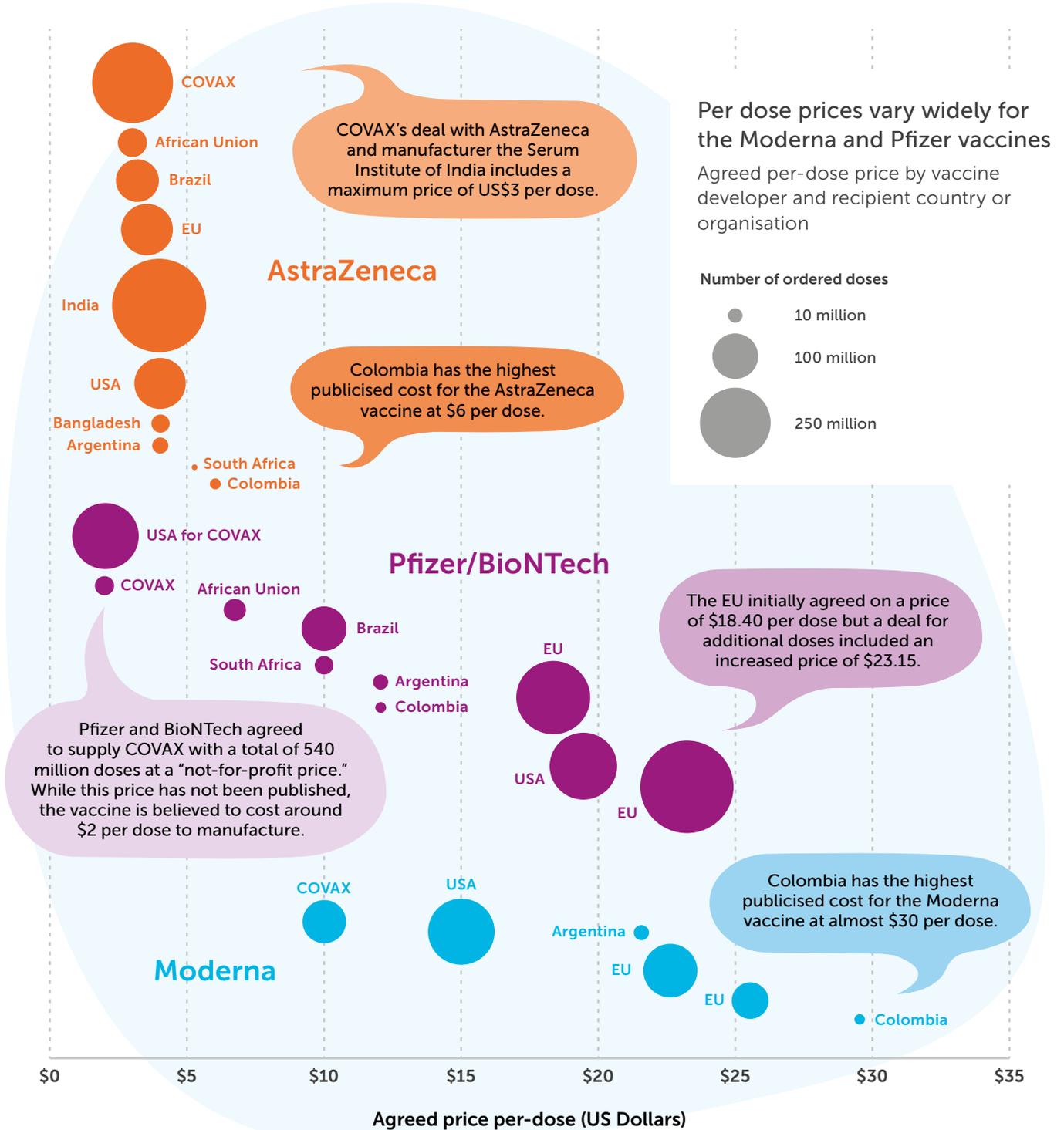
To counter this vaccine nationalism, WHO, Gavi and other global partners set up COVAX as the vaccines arm of the Access to COVID-19 Tools (ACT)-Accelerator, a ground-breaking global collaboration to accelerate development, production, and equitable access to COVID-19 tests, treatments, and vaccines.

COVAX devised centralised procurement mechanisms that enable countries to buy COVID-19 vaccines irrespective of their income status at tiered pricing levels and based on agreed upon allocation principles.

To help guarantee sufficient funding, other mechanisms for purchase and delivery can be put into place including, for example, 'advance market commitments' from funders. If such commitments are made, governments will likely be more willing and able to create systems for delivery.

Ensuring demand may also encourage investment by pharmaceutical and biotech firms who may be reluctant to invest in developing a product that might only have a small profit.

AN EXAMPLE OF VACCINE PRICING: COVID VACCINES



Source: <https://www.pharmaceutical-technology.com/analysis/covid-19-vaccine-pricing-varies-country-company>



2.2 Regulatory Approval and Licensure

In order to make a vaccine available in a country it must first be licensed or approved by national regulatory authorities.

Where there is a lack of regulatory expertise and capacity, countries can look to prior approval by established regulatory agencies, such as the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA). Alternatively, there are mechanisms that specifically focus on evaluating medicines intended for markets outside of the U.S. and the EU, including the EU-Medicines for all or 'EU-M4all' procedure and the WHO collaborative procedure for accelerated registration. By leveraging assessment and inspection outputs already produced by WHO prequalification, and thereby eliminating duplicative regulatory work, it speeds up in-country registration of quality-assured products and contributes to their wider availability.

Regulatory capacity in Africa has increased over time with the introduction of the African Medicines Agency and other initiatives in a growing effort to harmonise regulatory processes across the continent.

The **African Medicines Agency (AMA)** aims to establish common standards and regulations for the region, and coordinates joint reviews of clinical trial applications for vaccines.

The **East African Community's Medicines Regulatory Harmonisation** initiative supports a joint regional assessment process that harmonises technical documents, combines inspections and review processes, and accelerates approvals among member states.

The **African Vaccine Regulatory Forum (AVAREF)** assists national regulatory authorities, ethics committees, and sponsors to achieve consensus on ethical and regulatory questions surrounding the research and development of medical products in Africa. Its primary aim is to improve access to medical products across the continent by reducing review and approval times for clinical trial applications, while also optimising quality of regulatory processes.

The **South African Health Products Regulatory Authority (SAHPRA)** regulates all health products in the country through monitoring, evaluation, investigation, inspection, and registration. This includes clinical trials, complementary medicines, medical devices, and diagnostics.

Approval of a new product requires review of a detailed record that presents the safety and efficacy of the vaccine. Since the approval process and the type of data needed for approval may vary between countries, vaccine developers may be required to prepare and submit multiple applications for approval. It is important to work with regulatory authorities when designing the clinical trials to ensure that the trial will provide the necessary data to support eventual licensure. AVAREF can provide a platform for early engagement with regulators on clinical trial design.

Working with the appropriate authorities in advance may prevent unnecessary delays and assure a smoother approval process. Efforts to better coordinate and standardise regulatory processes across regions and internationally may facilitate approval.

Finally, even after vaccines have been licensed, they may not be rolled out until and unless global and national policy recommendations support their use.

2.3 Manufacturing Capacity

Manufacturing any new vaccine entails two costly elements: building large-scale manufacturing facilities and developing biological processes ('bioprocesses') to produce large quantities of the vaccine. Manufacturing vaccines is largely carried out by the private (pharmaceutical) sector.

Depending on the amount of financing available, it can take years to build sufficient capacity for manufacturing, so work should begin well in advance of vaccine availability. Advance market commitments can reduce the risk for companies when considering this.

Policy action and advocacy are needed at both the global and local level to create additional incentives for large pharmaceuticals to work on scale-up for manufacturing or to transfer their technology to other companies to do this work. Technology transfer to enable scaling up manufacturing by additional companies is often held back by issues of intellectual property.

Approaches such as voluntary licensing and early technology transfer to manufacturers with strong commercial reach in high prevalence settings could help support the scale-up of manufacturing.



2.4 Operational Research

Before making a vaccine available, a range of studies can look at how to introduce and deliver a new vaccine, including how to add it to existing prevention or other health programs. This operational research can answer questions about which vaccine delivery systems are best and how to sustain and improve on these programs as access to the new intervention expands during the rollout (program implementation) process.

2.5 Delivery and Roll Out

Vaccines for infants and children are usually integrated within newborn medical care and the school system. Unlike childhood vaccinations, the new vaccines for HIV and TB may first be available for adults who may be difficult to reach through traditional vaccine delivery systems.

Efforts to reach those who would most benefit from a vaccine may be difficult in certain settings and for certain infections. In some cases, it will be necessary to establish a 'cold-chain' to keep the vaccine at the right temperature.

Strategies for vaccine delivery should be planned ahead and placed within the broader public health agenda. They should also be compatible with existing national vaccine programmes. Important lessons can be gathered from the experience of rolling out adult and adolescent vaccines as part of the COVID-19 response.

A delivery strategy should address:

- Transportation.
- Storage facilities.
- Storage conditions.
- Appropriate venues for delivering vaccines (e.g., clinics, community settings).
- Education and social marketing appropriate to specific populations.
- Human resources.
- Linkages to the wider health system.

3. Barriers to Vaccine Acceptance and Use



What makes a vaccine acceptable or not to people can depend on many factors, including:

- Actual or perceived efficacy.
- The immunisation schedule or regimen (number and timing of doses).
- Characteristics, such as method of delivery.
- Cost-effectiveness.
- Stigma and risk-perception (whether people believe they are at risk of an infection).

The acceptability of a new vaccine is important on various levels. If it is acceptable to policymakers and other influential people, they may be more willing to approve and licence the vaccine, introduce the vaccine in-country, and integrate it as part of the national health programme.

If it is acceptable to the medical community and health organisations, they may be more willing to support and promote use of the vaccine. And if it is acceptable to individuals and communities, they may be more willing to be vaccinated. Acceptability therefore affects accessibility and uptake of a vaccine.

In addition, to make sure that vaccines are accepted, supported, and used by the public, education campaigns should build knowledge among communities and societies about the characteristics, advantages, risks, and limitations of vaccines.



3.1 Vaccine Hesitancy

As we have seen with COVID-19 vaccination roll out, fears, myths, and rumours about the vaccine have a negative impact on how many people come forward to be vaccinated. The reluctance or refusal to be vaccinated may be influenced by a complex mix of historical, political, social, and behavioural factors. Some common concerns include:

- Worry that the vaccine may cause infection.
- Concern that any illness following vaccination is due to the vaccine.
- Fear that the vaccine could cause sterility.
- Misinformation spread by social networks.
- Fear that the vaccine was developed too quickly.
- Concern that long-term side effects could appear in years to come.

In 2019, WHO listed vaccine hesitancy among the 'Top 10' threats to global health, citing its potential to undermine global efforts to eradicate polio, eliminate measles, and contain certain cancers. Knowledge of vaccines and their potential benefit will have an impact on whether governments make vaccines a public health priority. It is important that advocates, community groups, and vaccine developers increase awareness and support among government officials to help ensure vaccine access.

3.2 Efficacy

The higher the efficacy of a vaccine, the more likely it is to be acceptable to individuals, public health providers, and governments. The first HIV vaccines to be licensed and made available to the public may be of low-to-moderate efficacy in comparison to some vaccines that are available for the prevention of other diseases.

Policymakers must weigh up vaccine effectiveness against its cost compared with other interventions. It is therefore critically important that stakeholders at all levels understand the benefits of a partially efficacious vaccine. Even a vaccine with relatively low efficacy would have a significant impact on the epidemic in high incidence countries if given to a large segment of the population. Epidemiological impact modelling of vaccines at varying efficacy levels can provide useful information on the potential impact of vaccines to inform local, national, and global decisions.

3.3 Product Characteristics

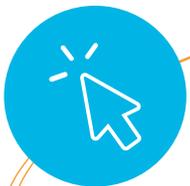
The characteristics of any vaccine product are strong determinants of its acceptability to the end user. A vaccine that requires one or two doses may be more acceptable than a vaccine that requires multiple doses if the infection is perceived as more serious; an oral vaccine might be more acceptable than an injected vaccine for some people. Research is needed, both early in vaccine development and in preparation for introduction, to understand the attributes, clinical trial designs, dosing schedules, packaging, presentation, and delivery approaches that will be most acceptable to eventual providers and users. These are important to inform Target Product Profiles (see **MODULE 4**) and planning for eventual access.

3.4 Stigma and Risk Perception

As with other interventions, both stigma and perceived risk are likely to affect access to and use of vaccines.

Stigma can affect how people evaluate their risk of infection (this is known as risk perception). People often believe that only certain stigmatised groups (e.g., people who are homeless, or who engage in sex work or drug use) are at risk from disease. Even if people do understand their risk of exposure and the benefits of vaccination, they might fear that they will be stigmatised or judged to be high risk if they come forward for vaccination.

In the case of vaccines for HIV and other sexually transmitted infections, women in particular might fear that they will be accused of unfaithfulness, and they might experience violence from or abandonment by partners. These issues need to be addressed within vaccine delivery plans and by working closely with communities and individuals.



FIND OUT MORE...

- **Evolving access pathways for long-acting HIV prevention products (2021):** <https://www.iavi.org/phocadownload/Access-pathways-for-long-acting-HIV-prevention-products.pdf>
- **Advocates guide to COVID-19 vaccine access:** <https://www.avac.org/resource/advocate's-guide-covid-19-vaccine-access>
- **Vaccine misinformation management field guide:** <https://vaccinemisinformation.guide>
- **Vaccine nationalism:** <https://gh.bmj.com/content/6/10/e006305>

MODULE 8: GUIDANCE FOR TRAINERS

HOW DO I
ANSWER DIFFICULT
QUESTIONS?

How do I put together
a training session?



MODULE 8

GUIDANCE FOR TRAINERS

CONTENTS	113
1. Introduction	114
2. Target Audience	114
3. How to Use this Manual	115
4. Using the Slides	115
5. How to Plan a Training or Presentation	115
6. Selecting the Content	116
Introduction to HIV, TB, and Lassa Fever Vaccine Research	116
Introduction to Vaccines (HIV, TB, and Lassa)	116
Disease-Specific Trainings	116
Introduction to Vaccine Clinical Trials	116
Adapting Training Materials for Different Audiences	116
7. Answering Difficult Questions	117
8. How to Conduct a Refresher Training	117
9. Acknowledgement of IAVI and Materials Review	118



1. Introduction

This **IAVI Vaccine Literacy Library** is a core reference text that provides simple explanations about key aspects of vaccine development and clinical trials. It has been designed to help members of the vaccine research field fill any gaps in their knowledge, and to conduct training workshops for relevant audiences about a range of issues related to vaccine development.

The aim of this manual is to:

- Build vaccine clinical trial literacy among communities where research is conducted.
- Support literacy and understanding among NGO partners and communities.
- Serve as a reference tool for training various stakeholders, including the media, policymakers and new staff working in clinical trial settings.

2. Target Audience



The target audience for the manual includes:

- Community liaison officers and community engagement staff who deliver trainings and presentations to the community.
- Clinical trial staff as needed, for example as part of their induction training.

The target audience for the slides for each module is the community in which the research is being conducted, including:

- Communities and civil society groups and networks in countries and regions where trials are being conducted.
- Non-Governmental Organisation (NGO) staff that advocate and support clinical trials particularly in settings where access to information may be limited.
- Community Advisory Board (CAB) members, and other community members who conduct outreach around clinical trials, (e.g., peer leader network members).
- Clinical trial centre staff, particularly those who are not directly involved in vaccine work.
- Health care professionals or institutions that conduct clinical trials or provide information to potential study participants.
- Key media representatives in relevant countries who may cover stories on vaccine development.
- Other community leaders such as religious or academic leaders.

3. How to Use this Manual

The manual consists of seven content modules. Each module has a table of contents at the beginning, with a set of summary points.

The glossary contains definitions of all the scientific and technical terms used in the manual.

At the end of each module is a key references section.

TIP!

It is important to read and understand the content of each module, perhaps with a member of your clinical trial staff, before delivering a training session.

4. Using the Slides

Each module has an accompanying set of slides that can be used in presentations with community audiences. These slides incorporate the summary points, diagrams, and illustrations from each module.

5. How to Plan a Training or Presentation



The most important thing to do when planning a training session is to think about your audience and the key information that they need to take home with them.

1. Who is being trained? Consider what level of knowledge your audience already has about the subject. Are they potential trial participants or already working in the field? Have they received any other training on vaccines or clinical trials?
2. Who should co-facilitate the session? Is it important to have someone from the community co-present or co-host? Will the audience be more receptive to a medical professional? It is often useful to have an expert to serve as a resource for any questions that may be asked, such as a trial coordinator, nurse from the trial site staff, or a local expert from an ethics review board.
3. How long is the training? In some contexts, a multi-day training is not feasible. Community audiences usually have limited time and will need shorter sessions, perhaps scheduled over a number of weeks. Consider carefully the amount of information that your audience can take in over the time you have.
4. What equipment will be needed? Will you use a laptop and projector, or work from handouts only? Do you need flipcharts and markers?

TIP!

Remember to allow plenty of time for questions from the audience. Be clear whether you want people to ask questions as they arise, or to save them for a Q&A part of the training.

6. Selecting the Content

The manual has been structured to allow modules to be presented individually or grouped together to suit the needs of the audience. The content of some modules overlaps so that you can deliver modules separately if you wish. This flexible format allows trainers to design their own tailored sessions based on the specific needs of the audience.

Trainers should also consider adapting sessions based on the cultural context of trainees. Sessions have been developed with generic content, and where possible, trainers may choose to include culturally-relevant examples, metaphors, or stories as a way to make the subject matter more relevant to trainees.

Introduction to HIV, TB, and Lassa Fever Vaccine Research

This training would include all seven content modules (97 slides) and follow the order of the modules as set out in the manual. The session could be delivered in half a day with a coffee break and time for questions or extended into a whole day if time allows.

Introduction to Vaccines (HIV, TB, and Lassa)

For audiences outside of clinical trial settings, this shorter training would include Modules 1-4 and Module 6 (70 slides).

Disease-Specific Trainings

In contexts where research only focuses on one disease, this training would draw only the specific content from all seven modules and could be delivered in 2 hours including time for questions.

Introduction to Vaccine Clinical Trials

For audiences that already know about how vaccines work, you can exclude Modules 2, 3, and 4 and focus on Modules 5 and 6. This training would take 1.5–2 hours including time for questions.

Adapting Training Materials for Different Audiences

The slides have been designed so that you can print them out as handouts. Ideally, you would print one slide per page so that any diagrams and illustrations can be clearly read. Depending on your audience you may also want to use the resources listed at the end of each module to supplement your handout materials.

TIP!

When drawing up your training agenda, remember to build in time for introductions and setting ground rules, coffee/tea breaks, wrapping up, and evaluation. Ground rules may include things such as returning from breaks on time, not interrupting others, and turning mobile phones off while the workshop is in session.

7. Answering Difficult Questions

There are a number of questions that are frequently asked by the community at any presentation on vaccine research. These include questions about vaccine safety, the ethics of clinical trials and how human rights are protected, for example:



- Can vaccines cause illness?
- How do we know vaccines are safe?
- Do the vaccines used in clinical trials protect you?
- Why are vaccines tested on people in developing countries?
- Why are vaccines tested on babies and young children?
- Will our community have access to the vaccine if it is effective?

With vaccine hesitancy growing around the world, it is important to take these questions seriously and prepare how to answer them. You may be challenged by people in the community who feel their rights have been neglected in the past, or who are tired of being the subject of research. It is recommended to always begin presentations to the community with a focus on how collaboration between communities and researchers can solve long-standing problems caused by disease and ill-health.

Each module has been written with the frequently asked questions on vaccines and clinical trials in mind, and Module 6 addresses many of these in detail. The summary points from Modules 1 and 5 are also useful in this context.

TIP!

If you are not sure how to answer a question, make a note of it and tell your audience you will find out and feed back to them after the training session.

8. How to Conduct a Refresher Training

In contexts where research is ongoing over a number of years, for example at a Phase III trial site, it will be useful to hold refresher training for key stakeholders each year. To do this you can use the summary points slides and a few illustrations, rather than the complete set of slides. Rather than going through the script line by line, you can ask the audience what they remember from the previous training. A refresher training can be shorter and conducted in a two-hour session if needed.

9. 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 educational and advocacy 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 acknowledgment 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 Literacy 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**.

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 immunosorbent 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.



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.



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 or bacteria. Many diseases, including HIV and Lassa fever virus have multiple strains.

GLOSSARY

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>

