Virology of Measles

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Conference of Measles Re-Emergence in Iran
1 Jun, 2025
SBMU

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Measles: A Deep Dive into the Virus

Measles remains a highly contagious viral disease with a significant global health impact. Despite the availability of effective vaccines, outbreaks continue to occur worldwide. This presentation offers an exploration of measles virology, covering its history, viral structure, replication, transmission, and the ongoing efforts to control and eradicate the disease. By understanding the virus in depth, we can appreciate the scientific progress made and the challenges that still lie ahead.

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History of Measles

Back to ancient times

The earliest known description of measles was recorded in the 9th century by the Persian physician Rhazes.

- Called "Moretum“

As a distinct illness

In the 16th century that the disease was formally recognized as a distinct illness, when the Italian physician Giovanni Filippo described an outbreak of a highly contagious fever with a rash.

Defining the clinical features

In 1757, the English physician Francis Home published a seminal work on the clinical features of measles, describing the characteristic rash, fever, and cough associated with the disease.

By the 19th century, measles had become a widespread and highly contagious, with outbreaks occurring throughout Europe and North America. During this time, physicians and researchers began to develop new techniques for diagnosing and studying the disease.

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Measles; Virus Isolation & Vaccine

MeV isolation

The measles virus was first isolated in 1954 by John F. Enders and Thomas C. Peebles in the United States. This was long after the development of modern virology and laboratory techniques.

Development of Measles Vaccines

The development of effective vaccines for measles has been a major public health achievement with vaccines helping to significantly reduce the incidence and severity of the disease worldwide.

First measles vaccine

Developed in the 1960s by the American virologist John Enders, who used a weakened form of the virus to produce an attenuated vaccine that was highly effective at preventing measles.

Over the next few decades, several other types of measles vaccine, including inactivated and subunit vaccines, were developed.

Measles Virus Classification: Taxonomy

Phylum	***Negarnaviricota***
	• established in 2019 by the International Committee on Taxonomy of Viruses (ICTV) for negative-sense RNA viruses that can be connected evolutionarily through the possession of virally encoded RNA-directed RNA polymerases (RdRps)
Order	***Mononegavirales***
Family	***Paramyxoviridae***
Subfamily	***Orthoparamyxovirinae***
Genus	***Morbillivirus***
	• includes several other significant pathogens affecting animals and humans.
Species	***Measles morbillivirus***
Virus	**Measles virus (MeV)**

Kuhn et al. Arch Virol. 2021 December; 166(12): 3513–3566. (available in PMC 2022 December 01.)

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Measles Virus Structure: A Closer Look

Virus Composition

The measles virus is approximately 150-300 nm in diameter and has a spherical shape

- **Enveloped with lipid membrane**
- **Nucleocapsid encapsulating the RNA genome**
- **Key surface glycoproteins: Hemagglutinin and Fusion proteins**

Surface Proteins Role

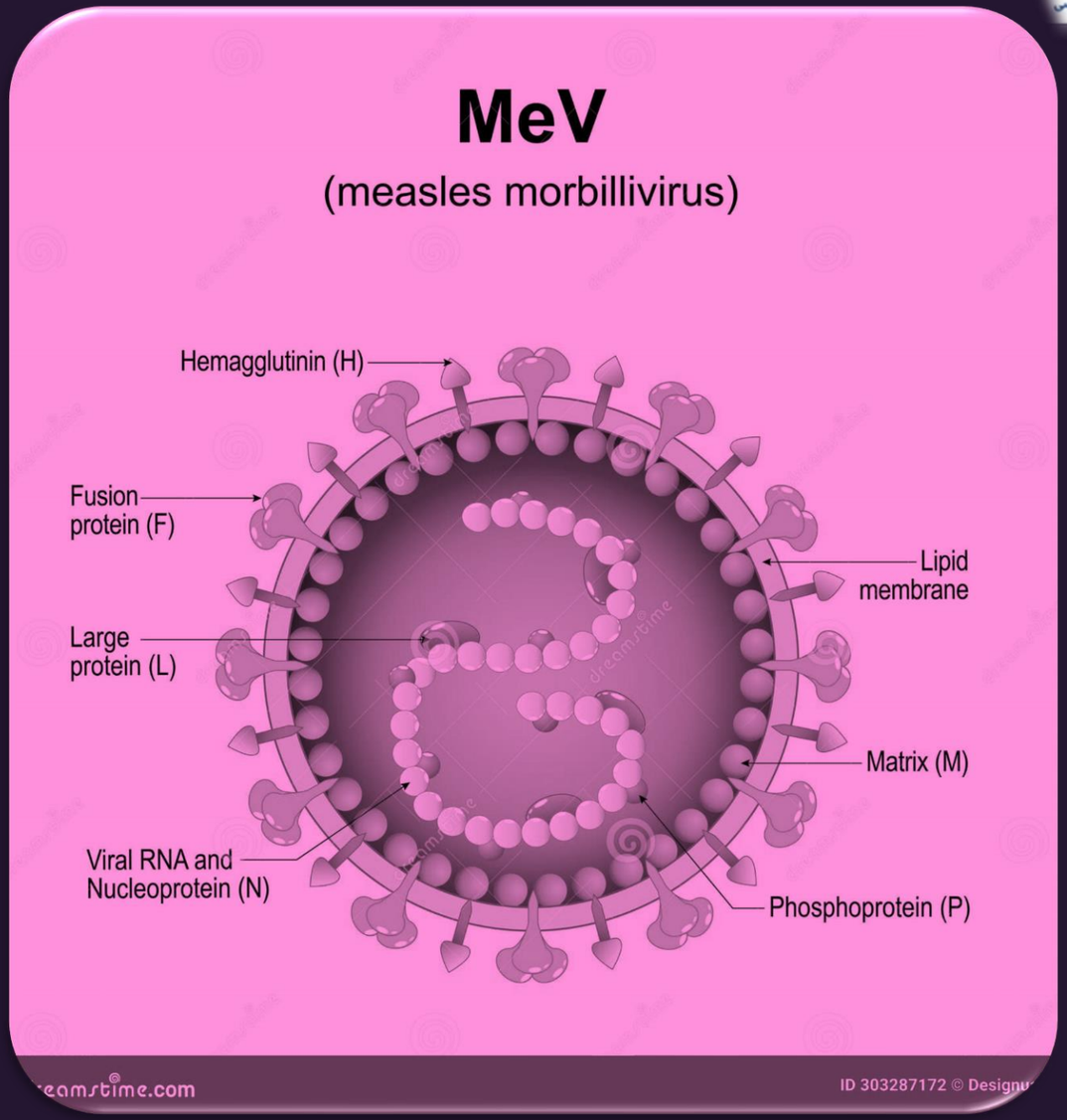
Hemagglutinin (H) facilitates viral attachment to host cells, while Fusion (F) protein mediates membrane fusion for entry.

These proteins are prime targets for neutralizing antibodies and vaccine design.

nucleocapsid core

made up of the viral RNA genome, which is tightly bound to the nucleoprotein (N protein) and is associated with the viral polymerase complex.

The RNA genome is approximately 15,894 nucleotides in length and encodes six structural proteins (N, P, M, F, H, and L) and two nonstructural proteins (V and C).



Int. J. Path. Res., vol. 12, no. 4, pp. 1-10, 2023;

Measles Virus Structure

N protein

plays a critical role in viral RNA packaging and replication

- binds to the viral RNA genome and forms a ribonucleoprotein (RNP) complex, which is essential for viral transcription and replication

P protein

interacts with the N protein and forms a complex with the viral RNA polymerase, which is responsible for viral transcription and Replication.

M protein

a transmembrane protein that interacts with the viral envelope and nucleocapsid core.

- plays a critical role in viral assembly and budding by facilitating the transport of viral components to the plasma membrane and coordinating viral assembly at the plasma membrane.

Surface Proteins Role

Hemagglutinin (H) facilitates viral attachment to host cells

- a viral attachment protein that binds to host cell receptors, initiating viral attachment and entry.
- The H protein interacts with the F protein and is responsible for the specificity of the viral attachment to host cells.

while Fusion (F) protein is a class I viral fusion protein that mediates viral entry into host cells.

- It interacts with the host cell receptor and undergoes conformational changes that facilitate viral fusion with the host cell membrane, leading to viral entry into the cytoplasm.

These proteins (F&H) are prime targets for neutralizing antibodies and vaccine design.

L protein

The L protein is the viral RNA polymerase, which is responsible for viral transcription and replication. It interacts with the P protein and forms a complex with the viral RNA genome, which is essential for viral RNA synthesis.

Encyclopedia of Virology. 3rd ed. Oxford: Elsevier. 2018; 129-135.

Measles Virus Replication Cycle: Step-by-Step

1

Attachment

H protein binds to receptors on the host cell surface.

- CD150 (also known as SLAM), Nectin-4, and CD46, which are expressed on immune, Epithelial, and various other cell types.

2

Fusion and Entry

F protein triggers merging of viral and cellular membranes, releasing RNA into cytoplasm.

- must be activated by cleavage to its fusion-active form by host proteases, such as furin into two subunits, F1 and F2

3

Replication & Transcription

Viral RNA-dependent RNA polymerase synthesizes mRNA and replicates genome.

- The viral C protein interacts with the host RNA helicase DDX3 to modulate RNA synthesis and promote viral replication.

4

Assembly & Release

New viral particles assemble and bud from host cell, ready to infect others.

- The viral V protein also plays a role in virion release by interacting with host cell factors that regulate the cellular trafficking and secretion of viral particles.

- Microbiology and Molecular Biology Review. 2021;21-25.
- Viruses. 2019;11(3):282.
- Journal of Clinical Investigation. 2021;115(7):1688- 1698.
- National Structure of Molecular Biology. 2019;18(5):135-41.
- Procedings of National Academy of Science U S A. 2017; 104(28):11537-11542.

Measles Transmission: Modes and Risk Factors

Modes of Transmission

Measles is highly contagious and is transmitted through respiratory droplets when an infected person coughs or sneezes. The virus can survive in the air or on surfaces for up to two hours, making it highly transmissible in crowded settings

Measles is most infectious in the period from four days before to four days after the appearance of the rash, but it can be transmitted from a person with measles for up to seven days before and after the onset of rash

Measles is a disease of humans, and there are no animal reservoirs. The virus is transmitted only from person to person, and there is no evidence of airborne spread over long distances or transmission through food or water

Risk Factors

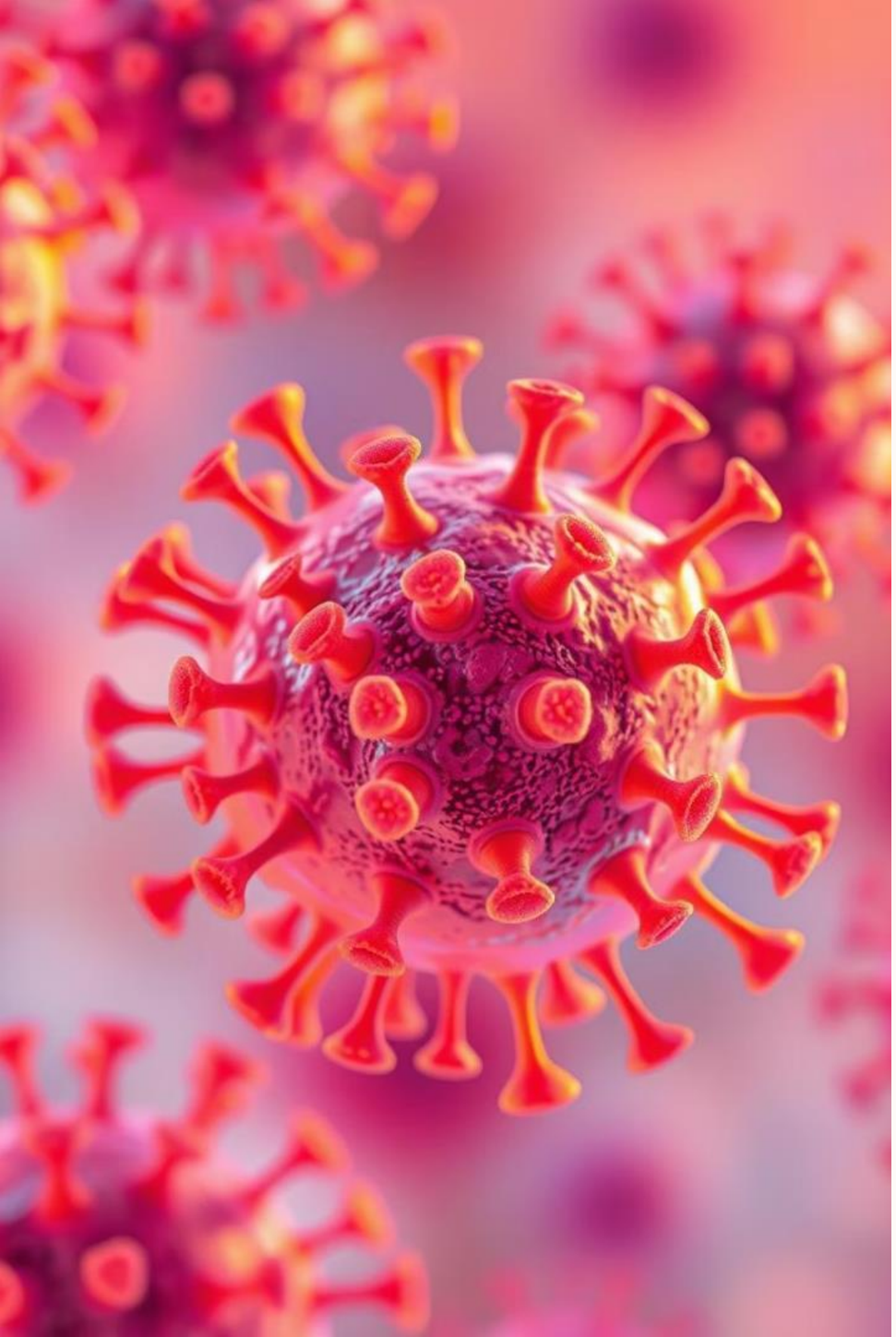
Anyone who is not immune to measles and comes into contact with the virus is at risk of infection.

Transmission is highly efficient, with an R0 of 12-18, demanding high herd immunity for control.

MMR vaccine provides long-lasting protection against measles

- Low vaccination coverage
- Lack of access to healthcare, which can delay diagnosis and treatment
- Travel to areas with ongoing measles outbreaks
- Close contact in Crowded living conditions, such as refugee camps or slums
- Poor nutrition (especially vitamin A deficiency) which can weaken the immune system
- Immunocompromising conditions or treatments, which can increase the risk of severe disease and complications.

https://www.cdc.gov/measles/about/transmission.html



Measles Virus Pathogenesis

This presentation explores the intricate pathogenesis of the measles virus, a highly contagious pathogen responsible for significant morbidity and mortality worldwide.

The key stages of infection are from viral entry to clinical impact, and how the virus evades the immune system. Understanding these mechanisms is crucial for developing effective prevention strategies and improving patient outcomes.

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How Measles Invades Cells

After initial infection, the virus disseminates systemically, causing immune suppression and characteristic symptoms.

Complications can include pneumonia, encephalitis, and increased vulnerability to other infections.

Virus dissemination

The pathogenesis of MeV begins with the entry of the virus into the host's respiratory tract through inhalation of infectious droplets.

MeV initially infects epithelial cells of the respiratory tract, where it replicates and spreads to regional lymph nodes

MeV targets dendritic cells and macrophages, which facilitate viral dissemination to other organs

- Current Opinions on Virology. 2018;2(3):248- 255.
- Breast Cancer Research. 2018;20(1):70.
- Journal of Virology. 2019;89(9):5236-5250.

Immune suppression

During the early phase of infection, MeV suppresses the host's innate immune response by inhibiting interferon production and reducing the expression of major histocompatibility complex (MHC) class I and II molecules.

This allows the virus to evade detection and clearance by the host's immune system.

- As the infection progresses, MeV induces a strong T cell response, leading to the production of pro-inflammatory cytokines such as interferon gamma, tumor necrosis factor-alpha, and interleukin-6.
- These cytokines promote the **recruitment** of additional immune cells to the site of infection and contribute to the development of the characteristic measles rash.

Medical Microbiology and Immunology. 2020;199(4):227- 237.

- In addition to its effects on the immune system, MeV also has direct cytopathic effects on infected cells. Me induces syncytia formation, in which infected cells fuse together to form multinucleated giant cells.
- This process can lead to tissue damage and contribute to the development of MeV-associated complications such as encephalitis.

Immune Evasion: Tricks the Virus Uses to Hide

to Hide

The measles virus has evolved several strategies to evade the host immune response, including inhibition of IFN production, suppression of antigen presentation, and modulation of cytokine signaling

Interference with Interferon Response

The virus inhibits production of interferons, key antiviral signaling molecules, impairing the body's early defense and allowing unchecked replication.

- Measles virus infection can inhibit the production of type I IFNs by infected cells, reducing the activation of antiviral signaling pathways and the expression of ISGs

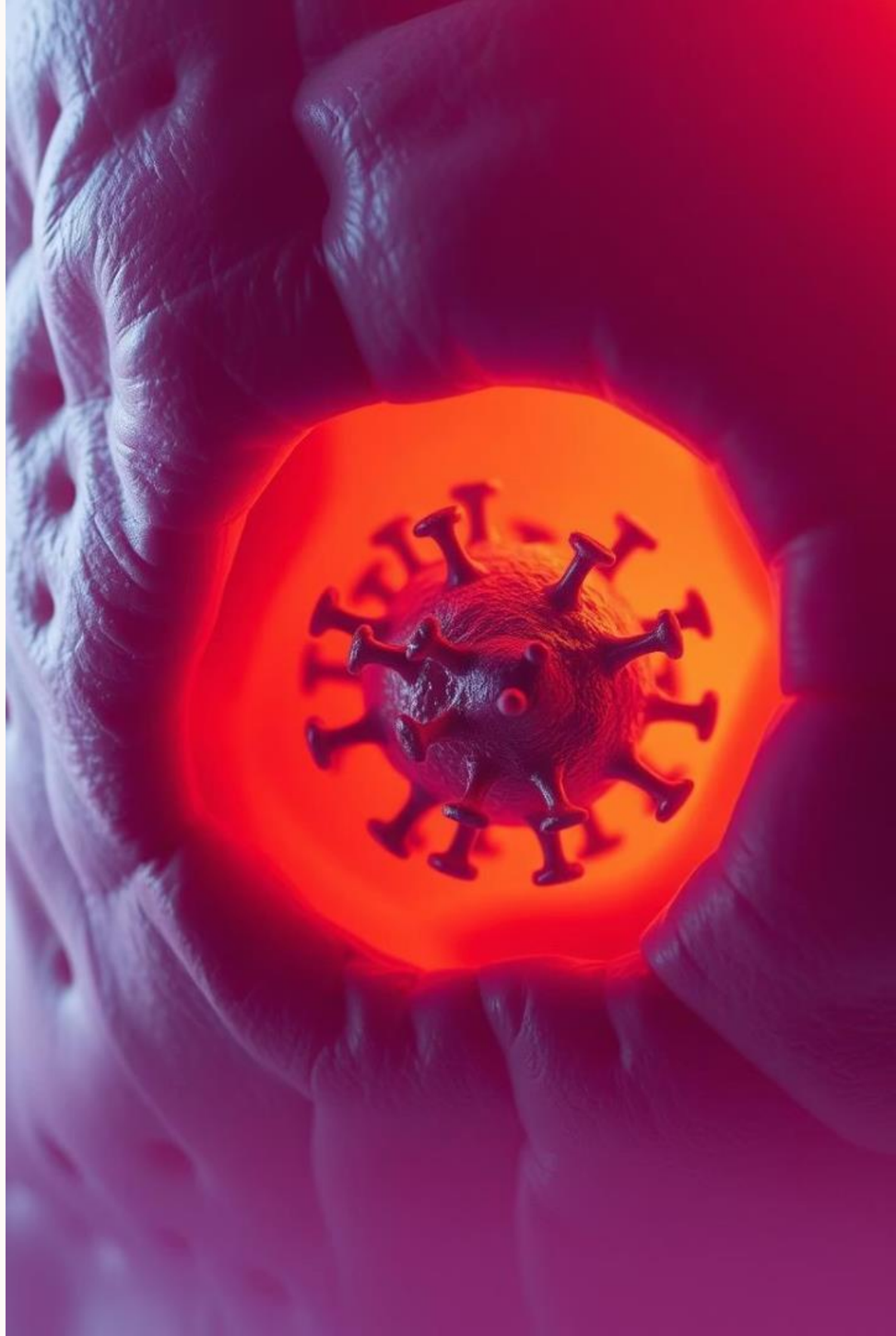
Suppression of T-Cell Activation

Measles virus disrupts activation of T cells, weakening adaptive immune response and delaying viral clearance.

- Measles virus can also modulate cytokine signaling by inhibiting the production of pro-inflammatory cytokines and promoting the production of anti-inflammatory cytokines, which can limit the recruitment and activation of immune cells

Immune Amnesia

Notably, measles can erase established immune memory, increasing susceptibility to other infections long after recovery.



Pathological Findings: What Measles Does to Tissues

Respiratory Tract Damage

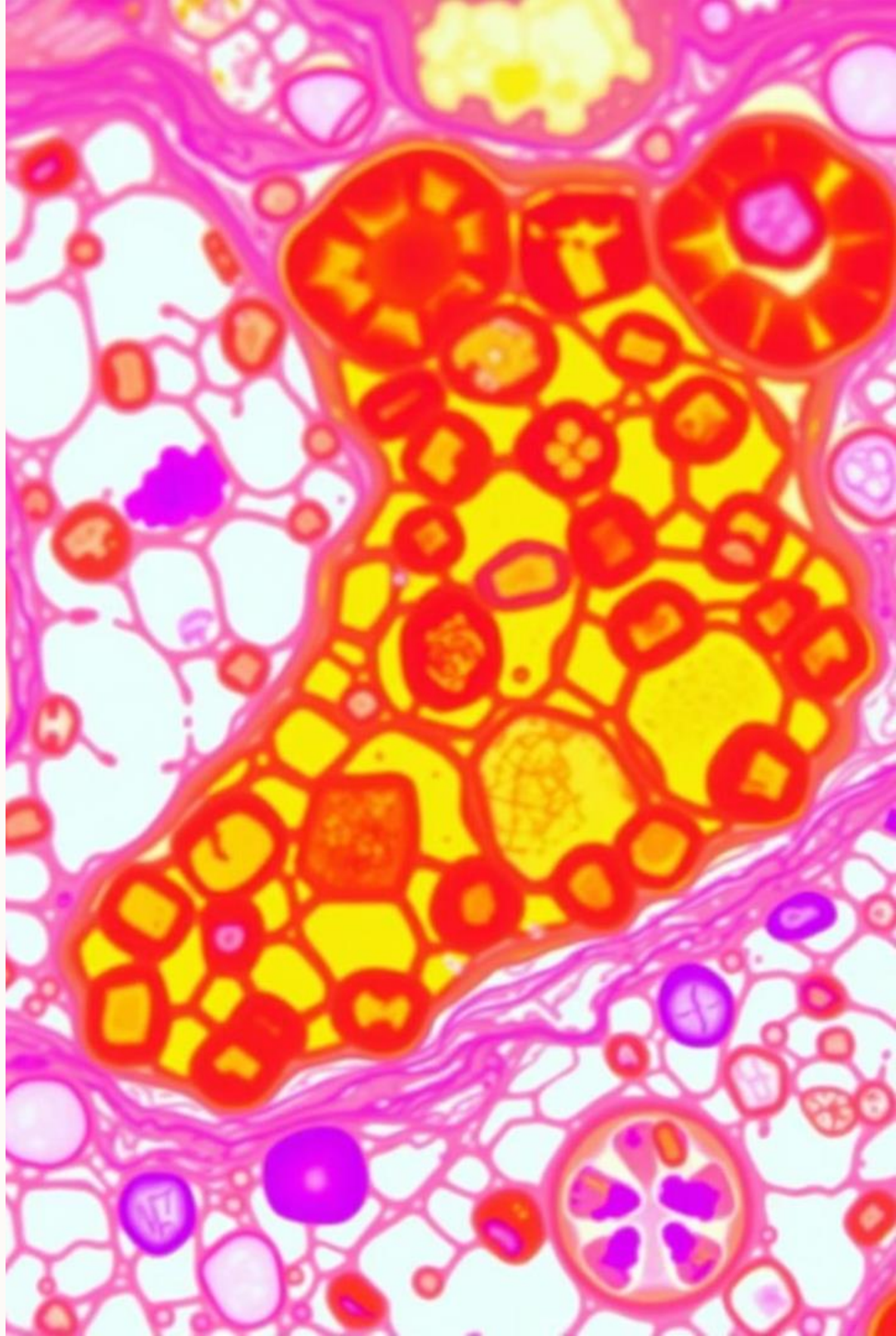
Infected epithelium shows cell fusion forming giant multinucleated cells (syncytia) and inflammation, leading to respiratory distress.

Lymphoid Tissue Suppression

The virus induces depletion of lymphocytes, causing immunosuppression and secondary infection risk.

Skin Changes

Rash corresponds to immune response in dermal vessels accompanied by viral presence in skin cells.



The Measles Immune Response: A Dual Defense

This presentation will explore the intricate mechanisms by which the human immune system combats the measles virus.

Measles is an acute viral infection typically characterized by a fever, cough, coryza, and conjunctivitis, followed by a maculopapular rash.

The measles virus primarily infects the respiratory tract and spreads to the regional lymph nodes, infecting immune cells, including dendritic and T cells.

We will delve into the immediate, non-specific innate responses and the highly targeted, long-lasting adaptive immunity that protects us from this formidable pathogen. Understanding these processes is crucial for appreciating the power of vaccination.

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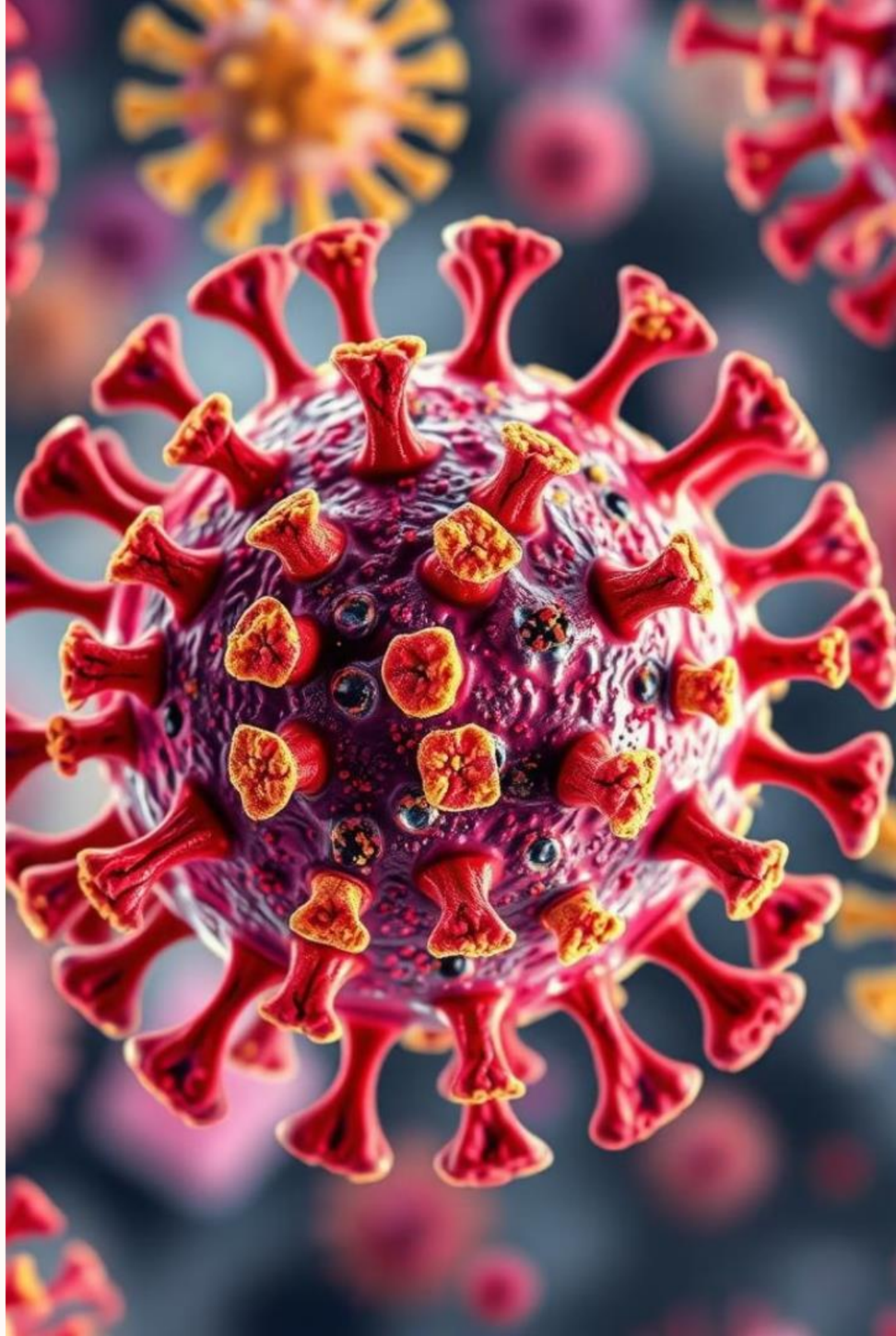


Vaccine. 2017;35(9): 1262-1267.

Innate Immune Response: Interferons and NK Cells

Interferon Production

Upon viral infection, infected cells rapidly produce interferons (IFNs), which activate antiviral signaling pathways and induce the expression of hundreds of interferon-stimulated genes (ISGs). These signaling proteins alert neighboring cells, causing an antiviral state that inhibits viral replication and spread.

Direct Viral Inhibition

IFNs directly interfere with viral protein synthesis and assembly, effectively slowing down the viral life cycle and limiting the initial burst of infection.

NK Cell Activation

Natural Killer (NK) cells, a type of lymphocyte, are crucial in the early response. They are activated by IFNs and directly kill virus-infected cells without prior sensitization, preventing further viral dissemination.

The innate immune system provides the body's first line of defense against the measles virus. This rapid response is crucial for controlling the initial infection before the adaptive immune system fully mobilizes. Interferons and NK cells work in concert to limit viral spread and minimize tissue damage in the early stages of the disease.

Current Opinions on Virology. 2018;2(3):248- 255.

Dendritic Cells: Antigen Presentation and T Cell Activation

Antigen Uptake

Dendritic cells, specialized antigen-presenting cells, engulf measles virus particles or infected cell debris at the site of infection.

Antigen Processing

Inside the dendritic cell, the measles antigens are processed into smaller peptide fragments, which are then loaded onto MHC (Major Histocompatibility Complex) molecules.

Migration to Lymph Nodes

The activated dendritic cells migrate to draining lymph nodes, where they encounter naive T cells, presenting the processed measles antigens to them.

T Cell Activation

This antigen presentation, along with co-stimulatory signals, leads to the activation and proliferation of measles-specific T cells, initiating the adaptive immune response.

Dendritic cells act as critical bridges between the innate and adaptive immune systems. Their ability to capture, process, and present viral antigens is fundamental for initiating a specific and powerful adaptive immune response against the measles virus.

Adaptive Immune Response: B Cell Activation and Antibody Production Production

B Cell Activation

Measles virus particles directly bind to specific receptors on naive B cells, leading to their initial activation. Helper T cells (activated by dendritic cells) also provide crucial co-stimulation.

Clonal Expansion

Activated B cells undergo rapid proliferation, generating many identical copies, or clones, of themselves, all specific to measles antigens.

Differentiation into Plasma Cells

Most of these B cells differentiate into plasma cells, which are antibody-producing factories. They secrete large quantities of measles-specific antibodies.

Antibody Function

These antibodies neutralize the measles virus by blocking its ability to infect cells, mark infected cells for destruction by other immune cells, and prevent viral spread within the body.

The humoral arm of the adaptive immune response, mediated by B cells and antibodies, is essential for clearing the measles virus from the bloodstream and preventing it from infecting new cells. This targeted antibody production provides crucial protection against the circulating virus.

T Cell Response: Cytotoxic T Cells and Viral Clearance

Recognition of Infected Cells

Cytotoxic T lymphocytes (CTLs), also known as killer T cells, recognize and bind to measles virus antigens presented on the surface of infected cells via MHC class I molecules.

Direct Killing Mechanism

Upon recognition, CTLs release cytotoxic granules containing perforin and granzymes. Perforin creates pores in the target cell membrane, allowing granzymes to enter and induce apoptosis (programmed cell death), effectively eliminating the infected cell.

Viral Clearance

By destroying infected cells, CTLs prevent further viral replication and assembly, thereby clearing the virus from the body and contributing significantly to recovery from measles infection.

While antibodies target extracellular virus, cytotoxic T cells are crucial for eliminating cells that have already been infected. This cellular arm of the adaptive immune response is vital for truly eradicating the measles virus from the body and preventing chronic infection.

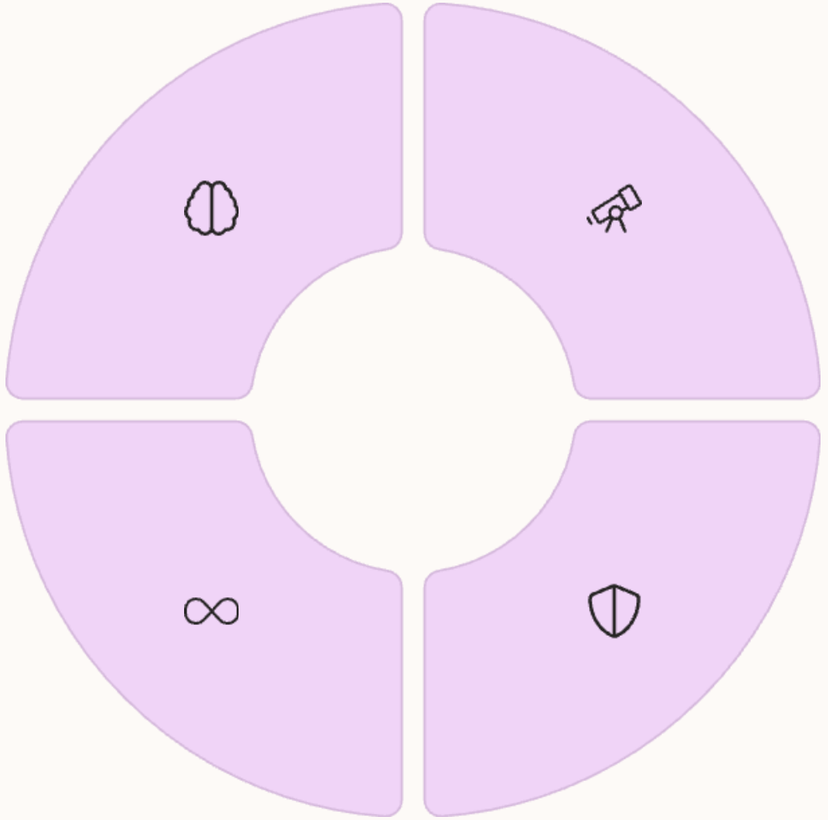
Immune Memory: Long-Term Protection After Measles

Memory B Cells

A subset of activated B cells differentiates into long-lived memory B cells. These cells circulate in the body and rapidly transform into plasma cells upon re-exposure to measles.

Lifelong Immunity

Natural measles infection typically confers lifelong immunity, a testament to the robust and enduring nature of immune memory generated by both B and T cells.



Memory T Cells

Similarly, memory T cells persist after the initial infection. These cells are poised to quickly proliferate and differentiate into effector T cells upon subsequent encounter with the measles virus.

Enhanced Secondary Response

Upon re-exposure, the immune system mounts a faster, stronger, and more effective response due to the presence of these memory cells, often preventing any symptoms of disease.

One of the most remarkable features of adaptive immunity is the establishment of immune memory. This critical component ensures that once an individual has recovered from measles, their immune system is armed and ready to prevent future infections, offering lifelong protection.

Clinical Implications: Vaccination and Herd Immunity

Individual Protection

Measles vaccination safely mimics natural infection, inducing both antibody and T cell memory, providing robust individual protection against the virus without the risks of the disease.

Herd Immunity

When a critical percentage of a population is vaccinated, it creates "herd immunity." This indirect protection prevents the spread of measles to vulnerable individuals who cannot be vaccinated.

Disease Eradication

High vaccination rates are essential for controlling and ultimately eradicating measles globally, as demonstrated by the near elimination of the disease in many regions.

Understanding the measles immune response underscores the profound importance of vaccination. Vaccines leverage the body's natural defense mechanisms to create a protective memory without the suffering and risks of the actual disease. This not only safeguards individuals but also contributes to the collective health of the community through herd immunity, aiming for global eradication.

Measles Genotypes: Understanding Diversity

Clade Definition

Clades are major lineage groups within the measles virus that share distinct genetic characteristics, reflecting evolutionary relationships.

There are several clades labeled A through H, which represent the global genetic diversity of the virus.

Genotype Classification

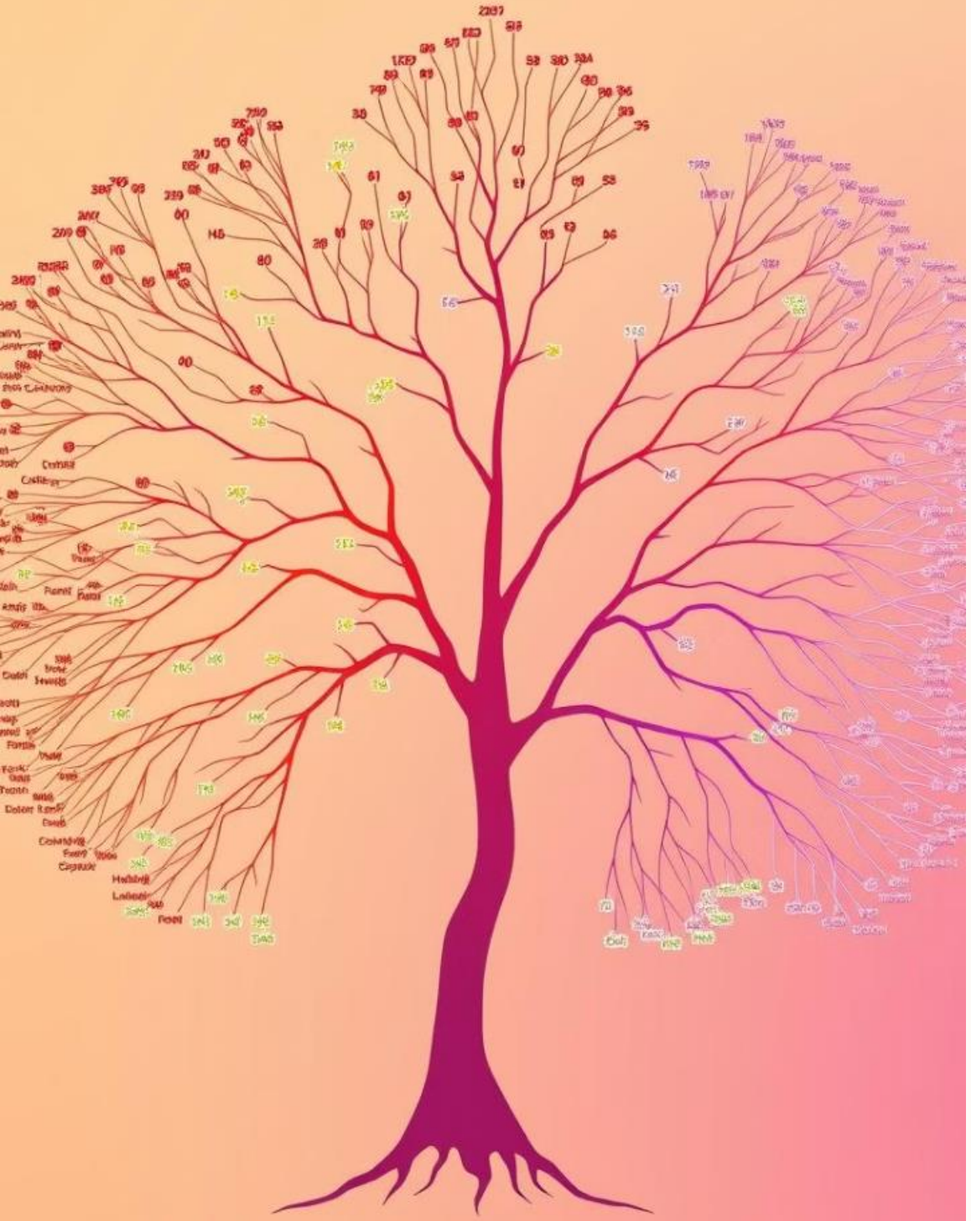
Currently, 24 measles virus genotypes are recognized, grouped based on nucleoprotein gene variations.

Global Distribution

Different genotypes predominate in various regions, providing clues about transmission patterns.

Epidemiological Use

Genotyping assists in outbreak source tracing and monitoring vaccination impact.



Measles Virus Genotypes: Identification and Significance Significance

Genotype Characterization

Genotyping distinguishes closely related virus variants within clades, supporting precise epidemiological investigations.

Tracking Spread

Genotypes help monitor virus importation and local transmission patterns, crucial for elimination campaigns.

Vaccine Impact

Monitoring genotypes can identify vaccine escape mutants or changes in virus evolution over time.

Laboratory Diagnosis of Measles: Genotyping Methods

Method	Description	Application
RT-PCR	Reverse transcription PCR amplifies viral RNA for detection and sequencing.	Initial diagnosis and genotype identification.
Sequencing	Sanger or Next-generation sequencing used for detailed genotype and clade assignment.	Molecular epidemiology and surveillance.
Phylogenetic Analysis	Computational comparison of sequences to map viral evolution.	Outbreak source tracking and confirmation.

Global Measles Elimination Efforts: Genotype Surveillance

1

Genotype Monitoring

Continuous global genotyping efforts support WHO goals to interrupt measles transmission worldwide.

2

Outbreak Containment

Quick identification of genotypes helps target vaccination and containment measures efficiently.

3

Data Sharing

Collaborative platforms enable real-time genotype data exchange among countries and labs.

4

Impact Assessment

Genotype tracking evaluates progress of elimination campaigns and guides resource allocation.

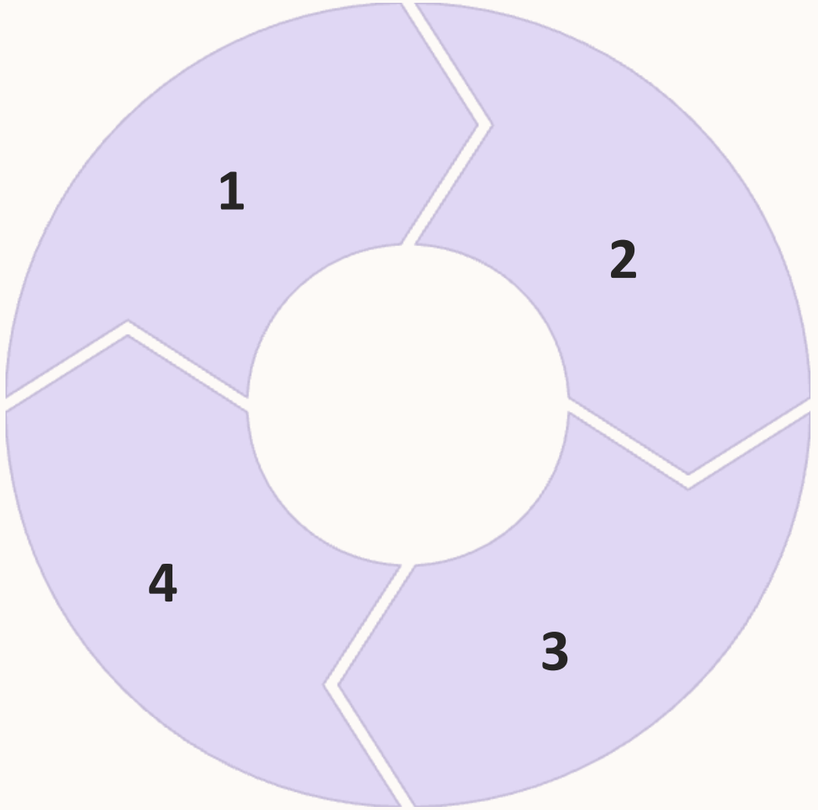
Future Directions: Research and Public Health Implications

Enhanced Genomic Surveillance

Integration of whole-genome sequencing will refine understanding of viral evolution and transmission.

Global Collaboration

Strengthening international partnerships will ensure rapid detection and containment of outbreaks.



Vaccine Improvements

Research into vaccine efficacy against emerging genotypes is vital to sustain elimination efforts.

Public Health Strategies

Data-driven responses will optimize vaccination campaigns and resource distribution globally.

Measles Epidemiology: Global Distribution and Trends

1 Endemic Areas

Measles remains endemic in parts of Africa and Asia where vaccination coverage is incomplete.

2 Outbreak Trends

Periodic outbreaks occur worldwide due to vaccine hesitancy, conflict zones, and healthcare disruptions, threatening herd immunity.

3 Surveillance Importance

Ongoing surveillance and rapid response are critical to detecting cases early and controlling spread efficiently.

Measles Eradication Efforts: Global Initiatives

1 — **WHO Strategy**

Focus on increasing vaccination coverage and surveillance to interrupt transmission.

2 — **Mass Vaccination Campaigns**

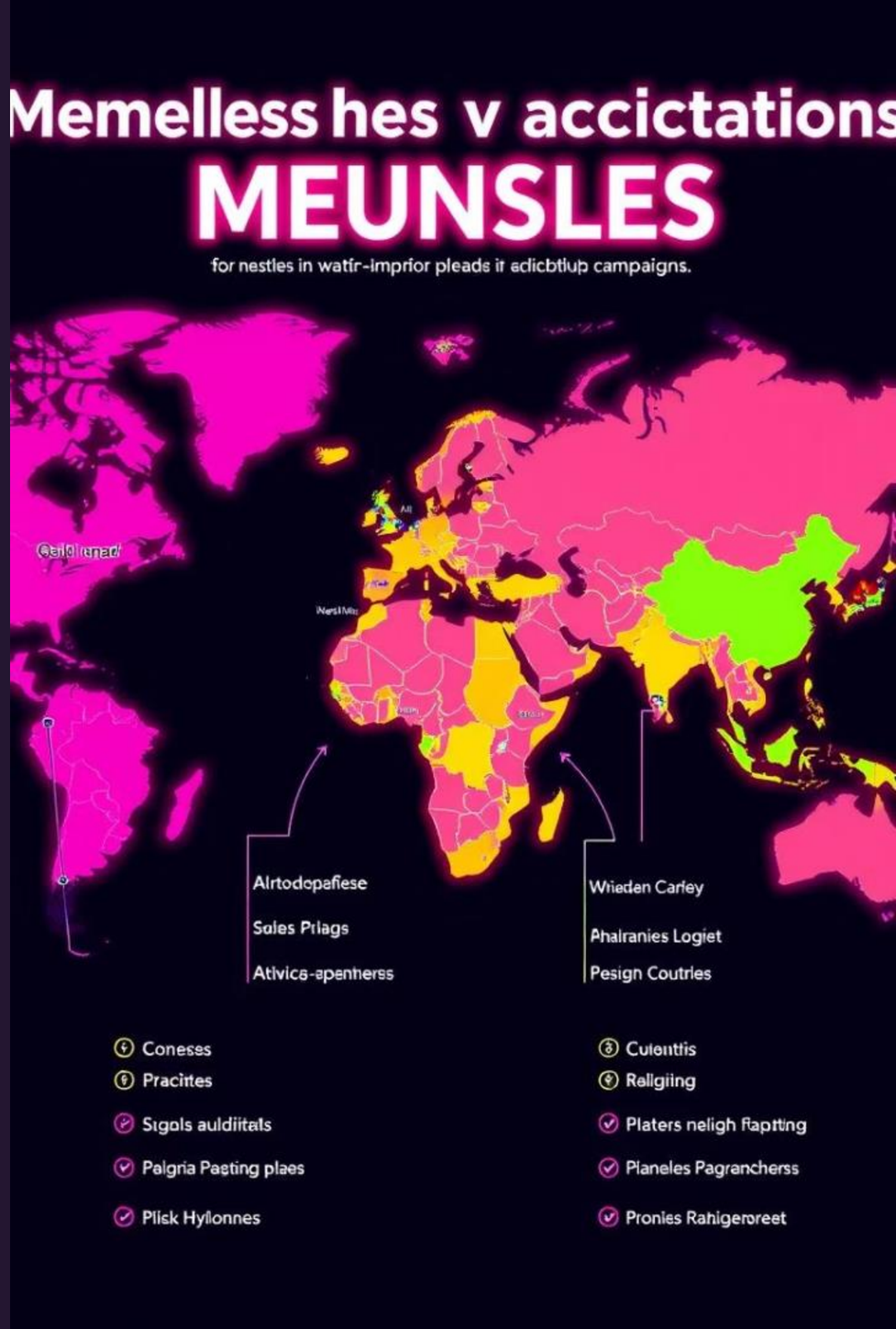
Supplementary immunization activities reduce immunity gaps in vulnerable populations.

3 — **Challenges**

Vaccine hesitancy, conflict zones, and logistics limit progress in some regions.

4 — **Progress**

Significant reductions in cases and deaths have been achieved globally since 2000.



Measles Eradication: Challenges and Prospects

1

Access Barriers

Remote regions, political instability, and conflict hinder vaccine delivery and surveillance.

2

Vaccine Hesitancy

Misinformation and cultural beliefs reduce vaccination rates, complicating eradication efforts.

3

Global Initiatives

WHO and partner organizations focus on improving coverage, outbreak response, and strengthening health systems for lasting control.

The Future of Measles Research and Control

Innovative Vaccines

Development of thermostable, needle-free vaccines to improve accessibility and compliance worldwide.

Enhanced Surveillance

Utilizing genomic sequencing and digital tools to detect and respond rapidly to outbreaks.

Global Collaboration

Coordinated efforts must continue to achieve the goal of measles eradication in the coming decades.

I appreciate your patience …

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