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Between the Past and the Modern Era

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شكر و عرفان

الى اساتذتي الذين يسرو لي الطريق و لو بكلمة فيما مضى..

الى كل عامل في المدرسة و الاقامة كان ليا معينا مبتسما يوما..

شكرا من القلب

الاهداء

رجوت كريما قد وثقت بصنعه .. و ما كان من يرجو الكريم يخيب
أنا لم أنل ما نلت إلا بالذي .. فطر السماء و سخر الأسباب
ٱلاهي لا يطيب الليل إلا بشكرك .. و لا يطيب النهار إلا بطاعتك
ولا تطيب اللحظات إلا بذكرك ..ولا تطيب الآخرة إلا بعفوك
ولا تطيب الجنة إلا برؤيتك..
الله جل جلاله
إلى من بلغ الرسالة و ادى الأمانة و نصح الأمة إلى **نبي الرحمة سيدنا محمد صلى الله عليه وسلم**
إلى كل من مات لتحيا أرضه في **فلسطين الأبية**
إلى ملاكي في الحياة.. إلى قدوتي في الاجتهاد الى من افنت سنينها تعلمني ..الى عنوان التضحية و الارادة، إلى التي منحتني طعما للحياة، إلى الملجأ الحنون مهما طالت بي السنون إلى **أمي الغالية** ***سواعدي جميلة..***
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إلى مجموعتي no risk no fun المحبة **ماريهان و جهينة..**
الى من جاورتني و كانت الملجأ الى الروح الطيبة جيهان..
الى أخي و صديقي من جمعتني به المدرسة بحلوها و مرها من كان خير الصديق أخي رائد..
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إلى رفيقاتي المخلصات في الحياة مؤنساتي **هبة أماني أميمة شهلة**
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وصلنا لنهاية البداية و ماهي إلا بداية جديدة لقصة أخرى و عالم مختلف..
{و آخر دعواهم أن الحمدلله رب العالمين}

Figures list:

Tables list

Abbreviations:

- **AAPC** (Antigen Presenting Cell)
- **Bcell** (B lymphocyte)
- **BL** (Memory B cell)
- **CALT** (Cutaneous-associated lymphoid tissue)
- **DNA** (Deoxyribonucleic acid)
- **Eos** (Eosinophil)
- **Ig** (Immunoglobulin)
- **IgA** (Immunoglobulin A)
- **IgG** (Immunoglobulin G)
- **IgM** (Immunoglobulin M)
- **MALT** (Mucosa-associated lymphoid tissue)
- **MHC** (Major histocompatibility complex) [Table 1] (not mentioned in this chapter but relevant to APCs)
- **NK cell** (Natural killer cell)
- **RNA** (Ribonucleic acid)
- **T cell** (T lymphocyte)
- **Th cell** (Helper T cell)
- **Tc cell** (Cytotoxic T cell)
- **Tregs** (Regulatory T cells)
- **CDC** (Centers for Disease Control and Prevention) [2]
- **WHO** (World Health Organization) [5]
- **MMR** (Measles, Mumps, and Rubella) [11]
- **Hib** (Haemophilus influenzae type b) [11]
- **PCV** (pneumococcal conjugate vaccine) [11]
- **PPSV** (pneumococcal polysaccharide vaccine) [11]
- **IPV** (inactivated poliovirus vaccine) [11]
- **OPV** (oral poliovirus vaccine)
- **DTP** (diphtheria and tetanus toxoids and pertussis vaccine)
- **DTaP** (diphtheria and tetanus toxoids and acellular pertussis vaccine)
- **Td** (tetanus and diphtheria toxoids)
- **Tdap** (tetanus and diphtheria toxoids and acellular pertussis vaccine)

- **MenACWY** (quadrivalent meningococcal conjugate vaccine)
- **variolation** [obsolete method of immunizing patients against smallpox]
- **US** (United States)
- **OBRR** (Office of Bioresearch and Review) [within the U.S. Department of Health and Human Services]
- **DoD** (Department of Defense) [of the United States]

Key words:
Vaccinology,Virology,Immunology, Public Health,Variolation, Jennerian Vaccination.

Abstract
Vaccines are one of the most important forms of primary public health prevention. Nowadays, modern technologies provide many opportunities to prevent infectious diseases by vaccination. However, vaccines are still missing for a number of diseases like malaria, tuberculosis and AIDS, that are still major causes of morbidity and mortality. Therefore, the development of effective vaccines towards those diseases, as well as the improvement of efficacy and safety of existing vaccines, is needed. We use a large-n cross-country regression framework to evaluate the effect of social media and online foreign disinformation campaigns on vaccination rates and attitudes towards vaccine safety. We found that social media usage is highly predictive of the belief that vaccinations are unsafe; with such beliefs mounting as more organisation occurs on social media. In addition, there is a substantial relationship between foreign dis information campaigns and declining vaccination coverage over time.

الملخص

تعتبر اللقاحات واحدة من أهم أشكال الوقاية الأولية للصحة العامة. في الوقت الحاضر، تتيح التقنيات الحديثة العديد من الفرص للوقاية من الأمراض المعدية عن طريق التطعيم. ومع ذلك، لا تزال اللقاحات مفقودة لعدد من الأمراض مثل الملاريا والسل والإيدز، والتي لا تزال من الأسباب الرئيسية للوفاة والمرض. لذلك، هناك حاجة إلى تطوير لقاحات فعالة ضد هذه الأمراض، وكذلك تحسين فعالية وسلامة اللقاحات الموجودة. نستخدم إطار عمل الانحدار عبر البلدان الكبير n لتقييم تأثير وسائل التواصل الاجتماعي وحملات التضليل الأجنبية عبر الإنترنت على معدلات التطعيم والمواقف تجاه سلامة اللقاح. وجدنا أن استخدام وسائل التواصل الاجتماعي له قوة تنبؤية عالية بالاعتقاد بأن اللقاحات غير آمنة؛ حيث تزداد مثل هذه المعتقدات مع زيادة التنظيم على وسائل التواصل الاجتماعي. بالإضافة إلى ذلك، هناك علاقة جوهرية بين حملات التضليل الأجنبية وتراجع تغطية التطعيم بمرور الوقت.

Résumé

Les vaccins constituent l'une des formes les plus importantes de prévention primaire en santé publique. De nos jours, les technologies modernes offrent de nombreuses possibilités de prévenir les maladies infectieuses par la vaccination. Cependant, il n'existe toujours pas de vaccins pour un certain nombre de maladies comme le paludisme, la tuberculose et le sida, qui restent des causes majeures de morbidité et de mortalité. Par conséquent, il est nécessaire de développer des vaccins efficaces contre ces maladies, ainsi que d'améliorer l'efficacité et la sécurité des vaccins existants. Nous utilisons un cadre de régression multi-pays à grand effectif (n) pour évaluer l'effet des médias sociaux et des campagnes de désinformation étrangères en ligne sur les taux de vaccination et les attitudes à l'égard de la sécurité des vaccins. Nous avons constaté que l'utilisation des médias sociaux est fortement prédictive de la croyance selon laquelle les vaccinations ne sont pas sûres, ces croyances augmentant à mesure que l'organisation sur les médias sociaux se renforce. En outre, il existe une relation substantielle entre les campagnes de désinformation étrangères et la baisse de la couverture vaccinale au fil du temps.

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General Introduction

Introduction:

Vaccines: A Legacy of Triumph and a Promise for the Future
For millennia, humanity has coexisted with a microscopic enemy – viruses. These insidious invaders, invisible to the naked eye, have caused widespread devastation, shaping the course of history. However, a beacon of hope emerged in the form of vaccines, a testament to human ingenuity in the face of adversity. This dissertation delves into the intricate dance between our body's defenses and these viral foes, culminating in the remarkable story of vaccine development.

Chapter 1 sets the stage by exploring the marvels of the human immune system. We will unveil its intricate architecture – the elegant interplay between cells and molecules that form the body's fortress against infection. We will then turn our attention to viruses, these cunning hijackers of cellular machinery, understanding their unique biology and the havoc they wreak.

Chapter 2 takes center stage, delving deep into the science of vaccines. Here, we will dissect the diverse arsenal in our fight against viruses – weakened or inactivated viruses, cleverly disguised antigens, and the ingenious messenger RNA technology. This chapter will equip you with a profound understanding of how vaccines train our immune system to recognize and defeat specific viral threats.

Finally, Chapter 3 embarks on a historical voyage of discovery. We will trace the remarkable story of vaccine development, from the daring practices of variolation in ancient times to the cutting-edge technologies that drive vaccine design today. This chapter will illuminate the scientific triumphs and challenges that have shaped the field of vaccinology, highlighting the continuous evolution in the face of emerging and re-emerging viral threats.

Through this comprehensive exploration, this dissertation bridges the gap between the past, present, and future of vaccines. By appreciating the intricacies of both the immune system and viruses, alongside the science and history of vaccine development, we gain a deeper understanding of their transformative impact on public health and the boundless potential they hold in safeguarding future generations.

___Chapter01___ Immune system and viruses

1. Immune system

A. overview of the immune system

A.1.LYMPHOID ORGANS

The immune system is a complex network of organs and tissues, each with specialized functions. These are majorly classified into primary and secondary lymphoid organs also referred to as central and peripheral lymphoid organs respectively.

A.1.1.Primary Lymphoid Organs

Primary lymphoid organs (bone marrow and thymus) nurture lymphocyte development. Here, they mature, gaining immune power and eliminating self-recognizing cells. Though not yet antigen-experienced, these naïve lymphocytes emerge ready to join the fight in secondary organs.

A.1.1.1 Bone marrow:

Central to blood cell production, this crucial tissue houses stem cells differentiating into diverse lineages. B cells mature here, undergoing selection and becoming antibody-producing powerhouses. Fat gradually replaces marrow with age. Notably, B cell maturation sites differ across species: birds (bursa of Fabricius), sheep/cattle (fetal spleen, then Peyer's patches).

A.1.1.2Thymus:

Near heart, grows till puberty, then shrinks. Crucial for early T cell maturation, it selects, regulates (thymosin), and releases mature T cells to peripheral organs. Cortex houses densely packed maturing T cells, while medulla boasts Hassall's corpuscles. Finally, matured T cells migrate for activation.

A.1.2. Secondary Lymphoid Organs

Secondary lymphoid organs monitor fluids for invaders. Here, lymphocytes meet their targets, sparking immune response. Throngs of activated lymphocytes then swarm the battlefield. Examples include spleen, lymph nodes, and mucosa-linked outposts.

A.1.2.1 Lymph Node:

Bean-shaped lymph nodes filter pathogens from lymph. Inside, B cell clusters in follicles grapple with antigens, while T cells in the Para cortex stand ready. Macrophages capture foes and present them, triggering lymphocyte activation and antibody production. Armed cells and antibody-rich lymph then flow out, ready to neutralize threats.

A.1.2.2 Spleen:

Blood-borne invaders meet their match in the spleen, a master of antibody production and cellular cleanup. Red pulp, a vascular maze, traps and disposes of worn-out blood cells. White pulp, rich in lymphocytes, orchestrates immune battle against antigens via T cells and antibody-churning plasma cells. This dual function makes the spleen a crucial frontline in the body's defense.

A.12.3 MALT:

Beyond organized organs, immune outposts (MALT) guard mucosal frontiers like gut, airways, and skin. Intraepithelial warriors (T cells) and M cells work together: M cells capture invaders, while T cells orchestrate defense and B cells churn out IgA antibodies to neutralize threats. Similar sentinels guard the skin (CALT), ensuring constant vigilance against external foes.**(1)**

A.2 Immune system cells:

Table 1: immune system cells (2)

Cells	General Description
Antigen presenting cell (APC)	Cells, such as macrophages, dendritic cells and B cells that can process protein antigens into peptides.
Basophil	A basophil is a type of phagocytic immune cell that has granules. Inflammation causes basophils to release histamine during allergic reactions.
B lymphocyte	A B lymphocyte is a type of white blood cell that develops in the bone marrow and makes antibodies.
Memory B cell	B cells that are long lived and remember past antigen exposure.
Plasma B cell	Activated B cells that produce antibodies. Only one type of antibody is produced per plasma B cell.
Dendritic cell	Dendritic cells are antigen-presenting cells (APCs). Antigen is combined with major histocompatibility complex and presented on a dendritic cell to active T and B lymphocytes.
Eosinophil	An eosinophil is a type of immune cell (leukocyte, or white blood cell). They help fight infection or cause inflammation.
Granulocyte	Granulocytes (including eosinophil, neutrophils and basophils) are a type of white blood cell that releases toxic materials, such as antimicrobial agents, enzymes, nitrogen oxides and others, during an

	attack from a pathogen.
Natural killer (NK) cell	The primary effector cell of innate immunity; the first responders of the immune system. They interact with signals from other cells (activating and inhibitory).
T lymphocyte (also called T cell)	Type of white blood cell that is involved with the immune system. T lymphocytes mature in the thymus.
Cytotoxic T cell	Cytotoxic T cells are the primary effector cells of adaptive immunity. Activated cytotoxic T cells can migrate through blood vessel walls and non-lymphoid tissues. They can also travel across the blood brain barrier.Cytotoxic T cells are activated by cytokines. They can attach to cancer cells and kill them.
Memory T cell	Derived from activated cytotoxic T cells, memory T cells are long-lived and antigen-experienced. One memory T cell can produce multiple cytotoxic T cells. After activated cytotoxic T cells attack the pathogen, the memory T cells hang around to mitigate any recurrence.
Helper T cell	Helper T cells secrete cytokines that help B cells differentiate into plasma cells. These cells also help to activate cytotoxic T cells and macrophages.
Regulatory T cell	Regulatory T cells (or Tregs) help to suppress the immune system.
Lymphocyte	Lymphocytes are immune cells found in the blood and lymph tissue. T and B lymphocytes are the two main types.
Macrophage	Macrophages are large white blood cells that reside in tissues that specialize in engulfing and digesting cellular debris, pathogens and other foreign substances in the body.
Mast cell	Mast cells release histamine and help to get rid of allergens.
Monocyte	Large white blood cells that reside in the blood stream that specialize in engulfing and digesting cellular debris, pathogens and other foreign

	substances in the body. Monocytes become macrophages.
Myeloid-derived suppressor cells	When immature myeloid cells cannot differentiate into mature myeloid cells, due to conditions like cancer, expansion of myeloid-derived suppressor cells occurs, and the T-cell response can be suppressed.
Neutrophil	A type of white blood cell, granulocyte, and phagocyte that aids in fighting infection. Neutrophils kill pathogens by ingesting them.
Phagocytes	Phagocytes eat up pathogens by attaching to and wrapping around the pathogen to engulf it. Once the pathogen is trapped inside the phagocyte, it is in a compartment called a phagosome. The phagosome will then merge with a lysosome or granule to form a phagolysosome, where the pathogen is killed by toxic materials, such as antimicrobial agents, enzymes, nitrogen oxides or other proteins.

A.2.1 Cytokines:

Table 2: cytokines

(cytokine)			
IL-1	Macrophage, lymphocytes, endothelium, fibroblasts, astrocytes	T-cells, B-cells macrophage, endothelium, tissue cells	Lymphocyte activation, leukocyte-endothelial adhesion, fever, regulates sleep
IL-2	T-cells	T-cells	T-cell growth factor
IL-3	T-cells	Bone marrow cells	Stimulates bone marrow growth
IL-4	T-cells	B- and T-cells	B-cell growth factor
IL-5	T-cells	B-cells	B-cell growth factor
IL-6	T- and B-cells, macrophages, fibroblasts	B-cells and hepatocytes	B-cell differentiation and synthesis of acute phase reactants
IL-7	Lymphocytes	B- and T-cells	Stimulates proliferation of immature cells
IL-8	T-cells, macrophages	Granulocytes, endothelium	Stimulates the activity of neutrophils, acts as chemotaxin, inhibitor of endothelial cell-leukocyte adhesion
IL-9	T-cells	T-cell	T-cell and mast cell growth enhancement
IL-10	T-cells	Macrophage	Suppresses the development of T-cell subpopulations (TH_1) by inhibition of macrophage IL-12 production
IL-11	Bone marrow stromal cells	Hepatocyte	Induces synthesis of acute phase proteins
IL-12	Macrophage	T-cells	Enhances the B-cells expression of IFN-γ during T-cell activation; also stimulates a lymphocyte subpopulation (NK cells)

A.3 Immune system types

A.3.1 Innate immunity:

Non-specific defenses of the body against infections present since birth is known as the innate immune response. Constituting the initial defense line, the innate immune system mounts a broad, non-specific response against any foreign molecule or antigen, regardless of the particular pathogen involved. Also, it is immediately functional to fight against the broad range of pathogens and does not require prior exposure to the pathogens. **(1)**

A.3.2 Adaptive immunity:

The second major branch of the immune system is the adaptive immune system. It is activated via signals from the innate immune system and by binding of antigens to receptors on antigen presenting cells (APCs) which are lymphocytes in the adaptive immune system. It takes longer to activate upon encounter with a ‘new’ pathogen. Upon activation, it’s response exhibits increased specificity compared to the innate immune response. Additionally, because the adaptive immune system has memoryat the next encounter with the same pathogen, the immune response is much more rapid and robust. Broadly speaking, the adaptive immune system can be divided into two parts, the humoral (B cells and antibodies) and the cell-mediated (T cells and macrophages) pathways. B and T lymphocytes originate within the bone marrow and undergo maturation through a process of proliferation, receptor gene expression, and rigorous receptor selection. **(3)**

B.Immune system responses:

The primary and secondary antibody responses to protein antigens differ both qualitatively and quantitatively.

B.1 Primary Response

First-time antigen exposure awakens naive B cells. They transform into antibody factories and enduring memory guards. Antibodies surge swiftly, plateauing before their gradual retreat. This primary defense paves the way for a quicker, mightier second act. Memory whispers the pathogen's secrets, amplifying the future response.

B.2 Secondary Response

Upon secondary antigen exposure, pre-existing memory B cells (BL) from the primary response rapidly mount a stronger, faster, and more sustained antibody response.

IgM and IgG isotypes are produced in both types of response, primary and secondary; however, in the primary response, IgM is the main Ig and the production of IgG is lower and occurs later. In the secondary response, IgG is the predominant immunoglobulin. In both responses, the serum levels of IgM decrease rapidly, so that after one or two weeks, there is a marked decrease, whereas the production of IgG is persistent. It is noteworthy the fact that the very sensitive immunoenzymatic tests can register low or residual levels of IgM for months, in some cases. **(4)**

2. VIRUSES

2.1. **General:**

Viruses are tiny biological entities that lack a cellular structure and do not possess all the properties generally attributed to living beings. They can only reproduce inside living cells, making them obligate intracellular parasites. For this reason, they are most often pathogenic. Viruses are similar to living things because they are made up of the molecules that are characteristic of them, and they have genetic material that allows them to reproduce and evolve. Mature viruses, as they exist outside cells, are called virions or viral particles. They constitute the form of dissemination and the infectious form of these entities. **(5)**

2.2. Definition:

The word "virus" comes from the Latin word "virus," which means "poison." A virus is a biological entity that is incapable of reproducing on its own. It requires a host cell, of which it uses the constituents to multiply, hence the name "obligatory cellular parasite."

- A microorganism consisting essentially of a nucleic acid (genetic material) surrounded by a protein shell.
- Viruses are important because they are responsible for a variety of diseases, from the flu to polio to AIDS. Virology is the branch of microbiology that studies viruses.

- Viruses exist in two forms:

1. **Intracellular:** Inside the host cell (prokaryotic or eukaryotic), the viral genetic material replicates and commands the synthesis of specifically viral proteins.
2. **Extracellular:** Isolated, exhibiting no vital activity or virion.

- **Virion:**
  The virion is the free viral particle in the extracellular environment that is infectious, has no metabolism of its own, no replication capacity, and no autonomous activity**. (6)**

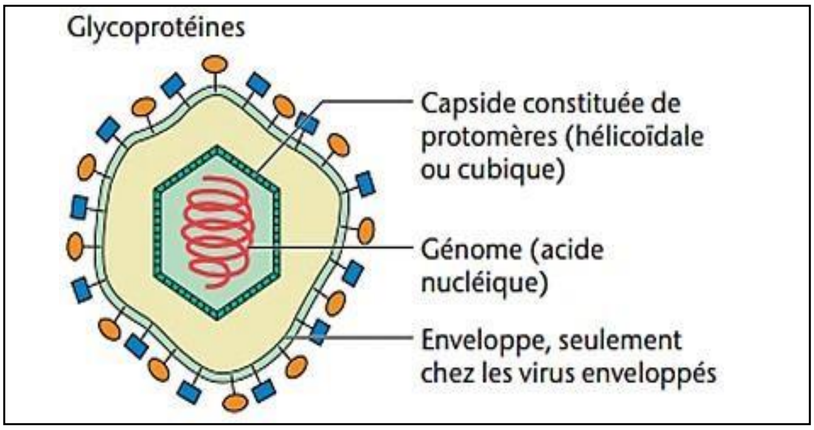

Figure 1: Virus Structure

2.3. Morphological Specificities of Viruses:

- Viruses measure between 20 and 300 nanometers and are 100 times smaller than a bacterium.
- Every viral particle is made up of at least two constant and obligatory elements, a genome and a capsid, and an inconstant element, the envelope.
- The nucleic acid and capsid together are called the nucleocapsid and can have helical, icosahedral, or complex symmetry.
- The shape of the capsid is the basis for the different morphologies of viruses.

2.4. **Components of Viruses:**

There is a great morphological diversity among viruses, but they are all composed of constant and inconstant elements that classify them into two types:

- **Naked viruses:** do not have an envelope (Figure 01), such as the poliovirus (Pico virus).

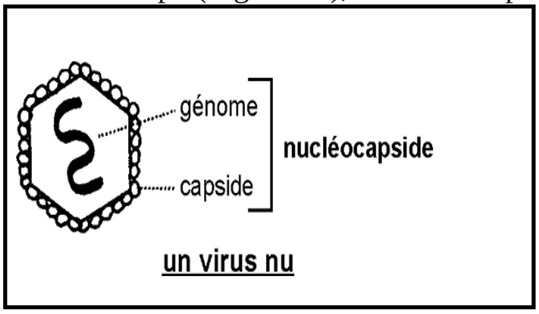

Figure 2: Diagram Illustrating the Organization of Non-Enveloped Viruses

- **Enveloped viruses:** have an envelope (Figure 02), such as the influenza virus (Orthomyxoviridae) and the HIV virus (Retroviridae).**(5)**

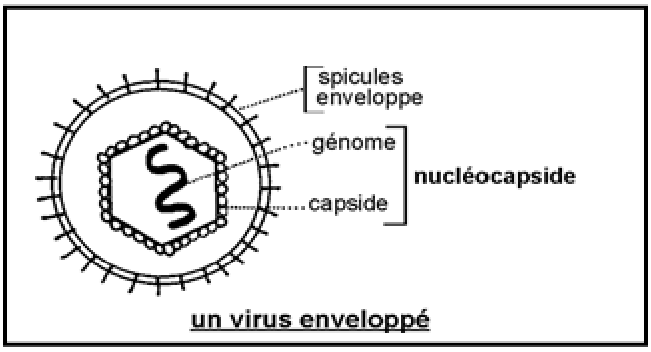

Figure 3: Diagram Illustrating the Organization of Enveloped Viruses

Table 3: virus's components

Components	Description	Diagram illustrating
Constant elements of viruses		
Viral genome	• The carrier of the virus's genetic information. • Its size varies from 5 to 280 K bases and thus codes for 3 to more than 100 different proteins (structural and non-structural). • It can be DNA or RNA and can be circular or linear, single-stranded or double-stranded.	
Viral capsid	• A compact structure of protein nature, which surrounds the viral genome. • Resistant and very stable, it protects it from various aggressions of the external environment or the cytoplasmic environment of the host cell. • In naked viruses, it also plays a role in their attachment to the surface of host cells. • Due to the reduced coding capacities of viral genomes, capsids are formed by the assembly of a single or a small number of protein subunits. • Based on the type of assembly, 3 main categories of capsids are distinguished:	

<table>
<tr>
<td></td>
<td>a. Icosahedral capsid with cubic symmetry:
The capsid has the shape of an icosahedron, made up of equilateral triangles with 20 faces, 30 edges, and 12 vertices.
The protein subunits of the capsid assemble into capsomers formed: either from 5 subunits or pentons located at the vertices of the icosahedron.
or from 6 units or hexons forming the faces and edges.</td>
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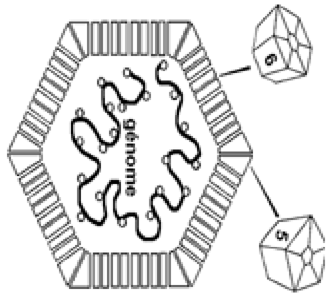
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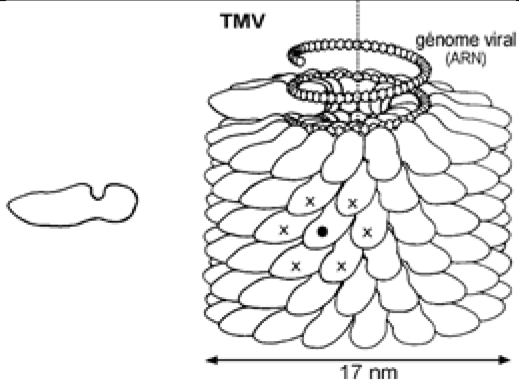
<td></td>
<td>b.Helical symmetry capsid:
The protein subunits assemble to form a helix that constitutes a rigid tube in which the viral nucleic acid is embedded</td>
<td>
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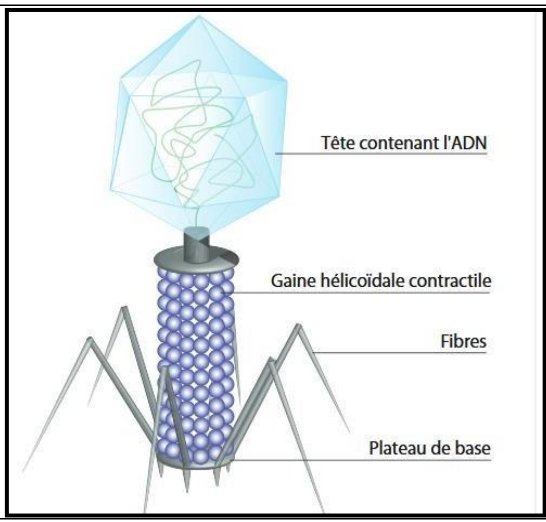
<td>c. Complex symmetry capsid:
For some viruses, the symmetry of the capsid cannot be determined and we then speak of complex symmetry.
A number of viruses elaborate their capsid in a way that does not correspond to helical or icosahedral standards.
Like bacteriophages which show a binary structure, involving both helical and icosahedral elements</td>
<td>
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<tr>
<td colspan="3">Inconstant elements of viruses</td>
</tr>
</table>

Viral envelope	• Or peplos (Greek word meaning mantle), is a glycolipid-protein structure that surrounds the viral capsid, for enveloped viruses. • It is made up of a double lipid layer derived from the budding of the virus through one of the membranes of the infected cell (nuclear membrane, cytoplasmic membrane, endoplasmic reticulum or Golgi apparatus). • On the viral envelope we find:Spicules	
Spicules	• Which are glycoproteins of viral origin anchored on the external face of the lipid layer. • They play a very important role in enveloped viruses because they are used to attach the virus to the surface of the host cell.	

Note: For some viruses, there is a matrix which is an additional viral protein layer that lines the inner face of the envelope**. (5)**

2.5. Virus Classification:

The Lwoff, Horne, and Tournier Classification:

Viruses are classified according to three essential criteria:

1. **The nature of the genetic material:**

- Viruses specific to eukaryotes with RNA (single-stranded or double-stranded) or DNA (single-stranded or double-stranded).
- Viruses specific to prokaryotes called bacteriophages.

2. **The type of symmetry of the capsid:**Helical or cubic.
3. **The naked or enveloped nature of the capsid.**

A. RNA Viruses:

RNA viruses can be classified into four main groups:

- **Double-stranded RNA viruses.**
- **Single-stranded RNA viruses (- strand):** These viruses are helical in symmetry and the RNA is translated indirectly into proteins. Example: Paramyxovirus (mumps, measles).
- **Single-stranded RNA viruses (+ strand):** These viruses are icosahedral and naked, and the RNA is directly translated into proteins, without prior transcription. Example: Picovirus (poliomyelitis, foot-and-mouth disease).
- **Retroviruses:** The single-stranded RNA is transcribed into DNA by an enzyme, reverse transcriptase. Example: HIV.

B. DNA Viruses:

- Single-stranded or double-stranded.**(2)**

Table 4: rna/dna classification

nucleic acid nature	capsid symmetry	presence or absence of the envelope	example
RNA	Helical	wrapped	Mumps, flu
		naked	tobacco mosaic
	Cubic(icosahedral)	wrapped	HIV, Yellow fever
		naked	Hepatitis A
DNA	Helical	wrapped	**Vaccine**
		naked	Polyoma
	Cubic	wrapped	Herpes, Rubella
		naked	Hepatitis B, Chickenpox

(6)

The classification of viruses into major families is based upon a few simple criteria. These include:

- The type of nucleic acid in the genome;

- The number of nucleic acid strands and their polarity;

- The type of nucleic acid in the genome;

- The number of nucleic acid strands and their polarity;

2.6. **Stages of the Viral Replication Cycle**

Table 5: Stages of the Viral Replication Cycle (7)

Stages of the Viral Replication Cycle	Description
1. Attachment	The attachment of virions requires the interaction between a viral ligand and a cellular receptor. A cell with 10,000 to 500,000 receptors can therefore be infected simultaneously by more than one virion. Some viruses are able to attach to different receptors. Others require two receptors present on the same cell (a receptor and a co-receptor). **A. The Cellular Receptor** The presence of cellular receptors defines the host range, i.e. the animal species or species that are sensitive, as well as the tissue or tissues that the virus can infect. The host range can be: • **Wide** when a virus uses ubiquitous receptors, present on cells of different animal species. • **Narrow** if the receptors are specific to a single species. **B. The Viral Ligand** • When the virus is naked, it is a particular conformation of the capsid proteins.

	• When the virus is enveloped, it is the spikes of the envelope.
Penetration	Several mechanisms are possible, depending on whether the virus is naked or enveloped: **A. Fusion of the envelope with the plasma membrane** This mechanism is specific to enveloped viruses, since it involves the fusion properties of the spikes: The fusion of the envelope with the plasma membrane introduces the nucleocapsid into the cytoplasm. **B. Endocytosis of the virion (Receptor-mediated endocytosis)** The cytoplasmic membrane provides a vehicle for entry. When a ligand binds to its receptor, it is endocytosed at specialized regions of the membrane that are lined with clathrin. **C. Naked viruses** The binding of the virus and the acidification of the vesicle gradually dissociate the capsid. Some viral proteins can then induce the lysis of the endosome membrane and the "core" of the virus attaches near a nuclear pore. **D. Direct penetration of the genome through a membrane pore** The process is rare. It is used by Picornaviruses in two steps: • Binding to the cellular receptor destabilizes the capsid, allowing the insertion of certain hydrophobic viral proteins that form a channel, either in the cytoplasmic membrane or in the membrane of an endosome; The genome uses this channel and enters the cytoplasm directly
3. Uncoating	To express itself, the viral genome must be released from the capsid. Cellular or viral proteases are involved in this step, which is still poorly understood for most viruses. For Reoviruses, uncoating is partial of the double capsid, only the outer capsid is dissociated. The genome remains in the capsid and the messenger RNAs pass into the cytoplasm through pores located at the vertices of the virion
4. Transport of the genome to the nucleus and the eclipse phase	This step is mandatory for most DNA viruses and some RNA viruses whose cycle includes a nuclear step. • A motor protein (dynein) linked to the microtubules of the cellular cytoskeleton, takes up the nucleocapsid and transports it to the vicinity of the nuclear membrane. • If the genome is released into the cytosol, it associates with cellular and/or viral proteins before being taken up by dynein. At least one of the proteins allows the binding of cellular factors responsible for ensuring the import of the nucleoprotein complex into the nucleus through a nuclear pore. Once uncoating is complete, there are no more virions, they seem to have disappeared; the eclipse phase begins.
	A. Eclipse phase The eclipse phase corresponds to viral multiplication. It is often accompanied by an inhibition of cellular functions. Multiplication takes place in two steps: • Replication of the genome; • Transcription of the new genomes.

	A1. DNA viruses. **A2. RNA viruses: The process differs depending on the nature of the genomic RNA**
	B. Circulation of structural proteins: Once synthesized, the structural proteins are brought to the cellular regions where the new virions are assembled: **B1. Capside proteins.** **B2. Envelope proteins.** **B3. Matrix protéine**.
5. Assembly	This is the end of the eclipse period which began with uncoating. The capsid proteins assemble around the new genomes, or form a procapsid permeable to the genomic nucleic acid. The targeting of envelope and matrix proteins is oriented: either towards the apical pole or towards the basolateral pole.
6. Release	Assembled virions leave the cell in two ways: **A. Lysis of the cell (naked viruses):** The release of naked viruses depends on cell lysis.
	B. Budding (enveloped viruses): Budding of enveloped viruses occurs at the level of modified membranes following specific interactions between the nucleocapsid and envelope proteins. The release of virions continues for a long time, before the cell dies.

___Chapter02___

Vaccines

Chapter 2: Vaccines

1. Introduction

Infectious diseases have always been scourge for humans. They are
Responsible for approximately 25% of global mortality, especially in children younger than five years. Nowadays, modern technologies provide many opportunities to prevent infectious diseases by vaccination. Vaccination mainly capitalizes the immune system's ability to respond rapidly to microorganisms upon a second encounter. Large-scale and comprehensive national immunization programs, and the considerable successes that were achieved in the eradication of smallpox and the reduction of polio, measles, pertussis, tetanus and meningitis, were among the most notable achievements of the 20th century. Unfortunately, vaccines are still missing for a number of diseases like malaria, tuberculosis and AIDS, that are still major causes of morbidity and mortality. Moreover, some of the existing vaccines do not induce complete protection. Therefore, the development of effective vaccines towards those diseases, as well as the improvement of efficacy and safety of existing vaccines is needed. **(8)**

2. Background

Along with the central idea of public health and preventative care, the CDC reminds parents and providers that it is far better to prevent a disease before it occurs rather than treating it after it infects someone (2018). As one of the most important forms of primary public health prevention, vaccines have prevented millions of cases of diseases and saved many more lives. As defined by the CDC (2017), immunity is the human body's defense against disease with "defenders" in cells, glands, organs, and fluids. These defenders identify foreign invaders, called antigens, and produce fighter proteins called antibodies to fight them. When an antigen is introduced to the body for the first time, the body recognizes that it is not itself and begins to create antibodies to fight this foreign substance. This process often takes time so one can still get sick. Upon any subsequent exposure to this same antigen, the body "remembers" it and activates the immune system to create a faster response of antibodies. This process of preventing disease is called immunity.
There are two divisions of immunity: acquired and innate. Innate immunity includes non-specific mechanisms of defense that come into play almost immediately when an antigen is encountered. Innate immunity mechanisms include barriers like skin, chemicals in the bloodstream, and generalized immune system cells. Adaptive immunity is the more specific response, where the immune system creates a customized plan to prevent against a certain

disease. There are four methods of acquired immunity, whether it is active or passive and natural or artificial. Passive natural immunity is acquired through breast milk while a fetus is in the placenta whereas passive artificial is a “quick fix” by a fabricated antibody injection which breaks down after use. Active natural immunity is acquired through getting a disease. This is the result if one is not vaccinated against the antigen. Active artificial immunity creates immunological memory so the body can better fight the antigen if it encounters it subsequently. This is the type of immunity acquired in the field of vaccinations. **(6)**

3. History of vaccines

Immunization against smallpox, a process known as variolation started more than 1000 years ago in India and China. However, in 1789, Edward Jenner developed the first scientific smallpox vaccine, which controlled this fatal disease. Jenner’s work with cowpox vaccination is widely recognized as the foundation of modern vaccinology because it’s the first scientific attempt to control an infectious disease with non-disease leading vaccination other than transmitting the disease. **(9)**

Jenner inoculated and protected an eight year old boy against smallpox using pus collected from the hand of a milkmaid infected with cowpox. Since then, the development and global use of vaccines against a variety of infectious agents is arguably one of the greatest medical achievements. Vaccination is often considered to be the most effective and economical method of preventing infectious diseases. **(10)**

Figure 4: first vaccine against smallpox

4. The aim of vaccination

The aim of vaccination is to induce a protective immune response to the targeted pathogen without the risk of acquiring the disease and its potential complications.

5. Definition of Vaccines

Vaccination is one of the most important discoveries in medicine. It is generally accepted that, outside of clean water, nothing has had a more significant impact on reducing mortality and population growth. From the first voluntary immunizations, several centuries ago, to Jenner and Pasteur, who gave birth to vaccination and vaccines, to the present day with the development of several vaccines, the principles of vaccination have been developed. Thus, more than a dozen major infectious diseases have been controlled in most parts of the world. But only smallpox has been eradicated to date thanks to the global vaccination campaigns of the World Health Organization (WHO). Other infectious diseases have retreated, have been eliminated in certain regions of the world, and could be eradicated in the coming years. However, there are still many challenges posed by the complexity of certain infectious diseases such as tuberculosis, malaria, or infection with the human immunodeficiency virus (HIV), as well as by the emergence or re-emergence of new infectious agents.

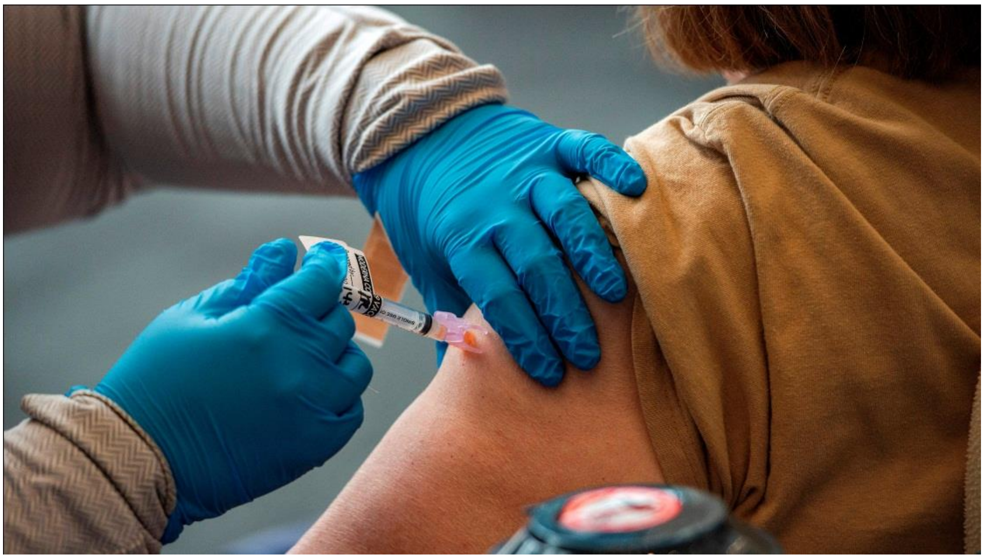


Figure 5: Taking vaccine

6. The principle of vaccination

The principle of vaccination is to induce a durable and effective protection against a pathogenic agent (mainly bacteria or viruses) responsible for an infectious disease, and this without causing clinical symptoms or side effects. Thus, vaccines are antigenic preparations that can induce an active immune response in an individual that can prevent the onset of the disease or attenuate its clinical manifestations. This individual protection, based on the ability of the immune system to recognize, memorize, and optimize the immune response, specific to an antigen upon a second encounter with it, allows, when a sufficiently large proportion of the population is vaccinated, a collective protection that makes vaccination successful and that is important to promote. **(11)**

7. Characteristics of an ideal vaccine:

Table 6: characteristics of an ideal vaccine(1)

Characteristics	Description
It should stimulate a strong, protective and long lasting immune Response.	The key to lasting vaccine protection lies in the ability to induce strong and lasting T and B cell memory. This involves recalling previous exposures to antigens and mounting enhanced responses. Some infections and vaccines provide enduring immunity. Research is being done to identify the cells responsible for this memory and protection, which may help in vaccine development.
It should induce the right sort of immune responses.	Current vaccines induce immune responses through antibodies, but for diseases like malaria, tuberculosis, and HIV, cellular immune responses are important for protection. Understanding these responses is crucial for developing successful vaccines.
It should show an impeccable safety profile in all populations,including young infants, elderly and immunocompromised subjects.	Vaccination success is hindered by public reluctance to accept even minor side effects, leading to outbreaks like the pertussis epidemic in Great Britain during the 1970s. Reports linking vaccinations to asthma, Crohn's disease, and autism have been refuted in follow-up studies. Developing effective vaccines with minimal side effects is a challenge.
A single dose of vaccine should confer robust, long-lived immunity.	Only a fewlive vaccines have achieved this goal. In contrast to the results with live vaccines, ithas been difficult to promote long-lived immunity with a single dose of non-living Antigen vaccines. One goal of vaccine development is to rectify this using new Adjuvants and antigen delivery systems.
It should be affordable by the population at which they are aimed and should be formulated to resist high and low temperatures to facilitate distribution	Efficient vaccine production is crucial for affordability and availability. 'Glassification' technology using sugars makes vaccines stable in extreme temperatures, benefiting developing countries.

8. How vaccines work

Vaccines, like natural infections, act by initiating an innate immune response, which in turn activates an antigen-specific adaptive immune response. Innate immunity is the first line of defense against pathogens that have entered the body. It is established within a few hours but is not specific for a particular pathogen and has no memory. Adaptive immunity provides a second line of defense, generally at a later stage of infection, characterized by an extraordinarily diverse set of lymphocytes and antibodies able to recognize and eliminate virtually all known pathogens. Each pathogen (or vaccine) expresses (or contains) antigens that induce cell-mediated immunity by activating highly specific subsets of T lymphocytes and humoral immunity by stimulating B lymphocytes to produce specific antibodies. After elimination of the pathogen, the adaptive immune system generally establishes immunological memory. This immunological memory – the basis of long-term protection and the goal of vaccination – is characterized by the persistence of antibodies and the generation of memory cells that can rapidly reactivate upon subsequent exposure to the same pathogen. **(12)**

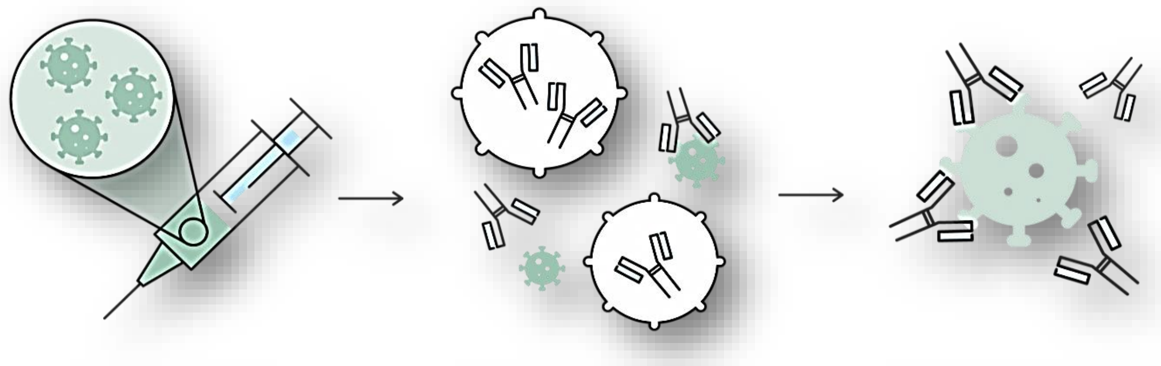


Figure 6: Diagram Illustrating the Organization of Enveloped Viruses

9. Types of vaccines:

Table 7: types of vaccines (15)

Vaccine type	Description	Examples	First introduced
Whole-cell inactivated vaccines	These vaccines contain an inactivated version of a virus or bacteria. The viruses in these vaccines are inactivated or split, and bacteria are killed.	Hepatitis A, polio, influenza, rabies, Japanese encephalitis (JEspect)	
Protein subunit vaccines	These vaccines contain specific isolated proteins from viral or bacterial pathogens that stimulate an immune response	Pertussis (whooping cough), Novavax COVID-19 vaccine (Nuvaxovid)	1970 (anthrax)
Recombinant vaccines	These vaccines are engineered by inserting a small piece of the virus or bacterium into cells used to manufacture the vaccine.	Hepatitis B, HPV, meningococcal B	
Polysaccharide and conjugate vaccines	Polysaccharide vaccines include only the sugar (carbohydrate) molecules found on the outside of some bacteria. Conjugate vaccines are those where the polysaccharide is attached (conjugated) to another protein that creates a stronger immune response. Diphtheria and tetanus toxoids are common conjugate proteins	Haemophilus influenzae type B, meningococcal ACWY, pneumococcal conjugate vaccine, pneumococcal polysaccharide vaccine	1987 (H. influenzae type b)

	used in vaccines.		
Nucleic acid-based vaccines (mRNA vaccines)	These vaccines use genetic material (either DNA or RNA) from the virus or bacterium to stimulate an immune response. The DNA or RNA provides the instructions for making a specific protein (the antigen). When a person is vaccinated, the DNA or RNA starts producing antigens, which are detected by the immune system, triggering an immune response. The DNA or RNA from the vaccine breaks down quickly in the body.	Pfizer COVID-19 vaccine (Comirnaty), Moderna COVID-19 vaccine (Spikevax)	2020 (SARS-CoV-2)
Viral vector vaccines	These vaccines include an unrelated harmless virus (a vector) that is engineered to deliver the genetic code of the vaccine antigens to the cells in the body, which then produce protein antigens to stimulate an immune response.	AstraZeneca COVID-19 vaccine (Vaxzevria)	
Toxoid vaccines	These vaccines contain weakened versions of toxins (poisons) produced by certain bacteria. These weakened toxins (called toxoids) trigger the immune system to generate a response against the toxin.	diphtheria tetanus	1923 (diphtheria)

10. Vaccine components:

Table 8: vaccine components (16)

Component	What they are	Examples
Adjuvants	These are substances added to improve the immune response to vaccines. By enhancing the immune response, they reduce the amount of antigen required and reduce the number of vaccine doses required to provide protection. Substances used as adjuvants are also commonly found in household and food products like tap water, infant formula, and consumer products like antacids, deodorants and cosmetics.	Aluminium hydroxide, aluminium phosphate, potassium aluminium sulphate (alum), MF59/squalene (oil and water mix)
Conjugate proteins	These are proteins that are attached (conjugated) to the antigen to create a stronger immune response to the vaccine, reducing the number of vaccine doses required to provide protection.	Diphtheria and tetanus toxoid
Stabilisers	These substances help keep the vaccine stable and maintain vaccine effectiveness by stopping chemical reactions occurring in the vaccine, and preventing components from separating from each other or sticking to the	Sugars (lactose and sucrose), glycine, monosodium glutamate (MSG), albumin (human or bovine), gelatin (bovine or

	vaccine vial during transportation and storage. Stabilisers used in vaccines are commonly found in food products like cheese, tomatoes, vegemite and confectionary items (like marshmallows and gummy bears).	porcine)
Preservatives and antibiotics	These substances prevent vaccines from losing their potency, and prevent fungal and bacterial contamination of vaccines after they are opened. Most single-dose vaccine vials do not contain preservatives because they are only used once and there is minimal chances of contamination. Preservatives are mostly used in vaccines supplied in multidose vials. Preservatives and antibiotics are used in household products like cosmetic products, green tea, antiseptics and eye drops.	Thiomersal (with ethylmercury), phenoxyethanol, phenol, antibiotics (neomycin, polymyxin, gentamicin)
Buffers	These substances prevent changes in the pH (acidity) of the vaccine. These substances are found in common items like food additives, laundry detergents and medicines. The most commonly used buffer substance, sodium chloride, is table salt.	Monopotassium phosphate, sodium borate, sodium chloride, disodium adipate, succinic acid, sodium hydroxide and hydrochloric acid (which react together to form water and salt), histidine, trometamol
Surfactants or emulsifiers	These substances help particles remain suspended in liquid, preventing them from settling and clumping. Surfactants and emulsifiers are commonly used in household items like shampoos, toothpastes, fabric softeners, and as food additives. A commonly used surfactant in vaccines, polysorbate 80, is made from sorbitol (sugar alcohol) and oleic acid (a natural omega-9 fatty acid), and is a common food additive in foods like ice cream. Food items usually contain a much greater amount of polysorbate 80 than vaccines do.	Polysorbate 80, sorbitan trioleate (made from oleic acid), sorbitol
Diluents	Diluents are liquids used to dilute vaccines to the proper concentration immediately before they are administered.	Sterile water, saline
Solvents	These are substances that dissolve another substance to create a solution. The most common solvent used in vaccine manufacture is water.	Water, ethanol
Residuals and other trace components	These are the leftover ingredients used to manufacture or produce individual vaccines. They are typically present in minute quantities, and the components present depend on the process used to produce the vaccine. Trace components that are typically found in vaccines are also usually consumed in a	Formaldehyde, egg proteins, yeast

	person's diet, such as in fruits, vegetables, eggs and bread.	
Latex	Latex is used in the packaging of some vaccines. This may be a risk for people who have a severe allergy to latex. People who have a less severe latex allergy are usually not at risk from latex in vaccine packaging.	Latex bung

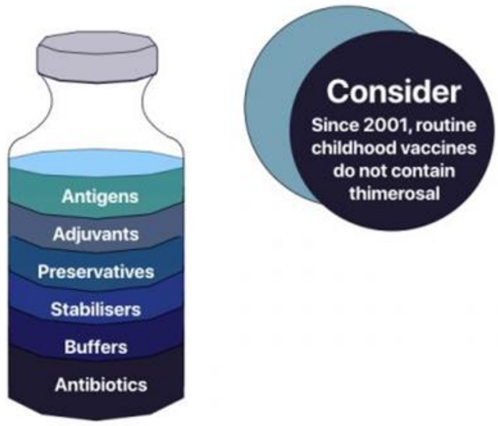


Figure 7: vaccine components

11. Vaccine requirements according to applicant age for civil surgeons:(14)

Table 9: vaccine requirements according to applicant age for civil surgeons

Vaccines byapplicant age	Birth-1month	2-11months	12months-6years	7-10years	11-17years	18-64 years	≥65 years
DTP/DTaP/DT	NO	YES			**No**		
Td/Tdap	NO			Sometimes *	**S,substitute1-timedoseofTdapforTdbooster;thenboostwithTdorTdapevery10years**		
Polio(IPV/OPV)	NO	YES				**NO**	
leasles, Mumps,andRubella	NO		YES,ifbornin1957orlater				**NO**
Rotavirus***	NO	YES Six weeks toEightmonths	**NO**				
Hib	NO	YES 2through59monthsold			**NO**		
HepatitisA	NO		YES 12monthsthrough18years old			**NO**	
Hepatitis B	YES,through 59 yearsold					**NO**	
Meningococcal(MenACWY)	NO				Yes 11through18yearsold	**NO**	
Varicella	NO		**YES**				
Pneumococcal	NO	9monthsold(administerPCV)		NO		**One dosePCV15 followedby PPSV23 or onedosePCV20**	
Influenza	NO,iflessthansixmonthsold			**YES,≥6months (annuallywhenfluvaccineisavailableincountryofexam)**			
COVID-19	**NO,iflessthansixmonthsold**			**YES,≥6months SeeCOVID-19sectionforadditionalinformation**			

DTP=pediatric formulation diphtheria and tetanus toxoids and pertussis vaccine; **DTaP**=pediatric formulation diphtheria and tetanus toxoids andacellular pertussis vaccine; **DT**=pediatric formulation diphtheria and tetanus toxoids; **Td**=adult formulation tetanus and diphtheria toxoids;**Tdap**=adolescent and adult formulation tetanus and diphtheria toxoids and acellular pertussis vaccine (*Children 7-10 years old sometimes need a doseof Tdap depending on their vaccine history.
IPV=inactivatedpoliovirusvaccine(killed);**OPV**=oralpoliovirusvaccine(live);**Hib**=*Haemophilusinfluenzae*typebconjugatevaccine; **MenACWY**=quadravalent meningococcal conjugate vaccine;

PCV=pneumococcal conjugate vaccine; **PPSV=**pneumococcal polysaccharidevaccine.***Rotavirusvaccinationshouldnotbeinitiatedforinfants aged15weeks 0daysorolder.ThistabledescribesvaccinerequirementsforU.S.immigrantvisaandstatusadjustmentapplicantsanddoesnotincluderecommendationsforotherclinicalpurposes.

12. Vaccines Importance:

To become immune to a disease, one must get the corresponding vaccine. There are currently 27 vaccine-preventable illnesses. Getting vaccinated not only helps the individual person, but their community as a whole through the concept of herd immunity. Herd immunity is the process by which a population is protected against or becomes immune to a disease. This works by stopping the transmission of the germ between people. This way, even those who do not or are medically unable to receive the immunization, will be protected. This medical phenomenon is most important for children since they are most at risk for contracting serious illnesses.

Because of herd immunity, diseases like polio have been eradicated in the United States. Polio was declared eradicated in the U.S. in 1979, but this is not the case for the entire globe. In 2014, the WHO stated that four of its six regions were polio-free but that still leaves ⅓ of the globe where polio is still endemic. Developing and lower-income countries face a daily fight against these illnesses, making it more important than ever to spread the success of vaccines to other countries. Herd immunity is beneficial, and a lack of it is detrimental to a population as it puts every member at risk. **(13)**

13. The Current State of Vaccination Worldwide:

Significant progress has been made worldwide with vaccine coverage. Global measles mortality has declined by 73% (WHO, 2017) and modern technologies are making vaccines more efficient and accessible, especially those considered in the childhood schedule. Still, that estimated 19.4 million infants are unprotected against these diseases. Over 60% these children live in the following 10 nations, making it timelier than ever to create plans to increase coverage: Angola, Brazil, the Democratic Republic of the Congo, Ethiopia, India, Indonesia, Nigeria, Pakistan, the Philippines and Vietnam (CDC, 2018). The main goal of the GVAP in these developing nations is to increase access to immunization, but the plan covers all 194 member countries. The anti-vaccination movement is more the focus in the developed regions, especially the United States and Europe. **(13)**

__Chapter03__

Vaccines Development

1. Vaccines: Past, Present, and Future
1.1. History of immunization:

Variolation offered some protection but wasn't perfect. It occasionally caused serious illness and even death. This led to the search for a safer and more reliable method.

By the 18th century, scientists observed that cowpox, a milder disease in cows, seemed to protect milkmaids from smallpox. In 1796, Edward Jenner conducted his famous experiment, demonstrating that inoculation with cowpox could effectively prevent smallpox.

Jenner's discovery marked a turning point. It showed that immunity could be acquired through a weakened or related virus, paving the way for the development of safer vaccines.

The success with smallpox vaccination spurred efforts to combat other infectious diseases. In the late 19th century, Louis Pasteur developed a vaccine for rabies, followed by advancements in diphtheria and tetanus antitoxins.

However, concerns arose about the quality and safety of these early vaccines. Uneven production methods sometimes resulted in ineffective or even harmful products.

This led to the creation of regulations and oversight. The Virus-Toxin Act of 1902 established a system for licensing vaccine manufacturers and ensuring product quality.

These advancements in vaccine development, production, and regulation have had a profound impact on public health. Vaccines have dramatically reduced or even eradicated diseases like smallpox, polio, and measles.

(Variolation, obsolete method of immunizing patients against smallpox by infecting them with substance from the pustules of patients with a mild form of the disease (variola minor).)

1.2. The present:

In the US, twelve companies, two state labs, and a university produce vaccines. There are vaccines for twenty diseases, with some combinations available. Seven are recommended for all children, while others target specific high-risk groups.

The future of vaccines is bright. Vaccines for chickenpox and rotavirus are close to approval, with research ongoing for hepatitis A, herpes, cytomegalovirus, and more. Vaccines for respiratory, intestinal, and parasitic illnesses are also being explored.

Unlike early vaccines developed through trial and error, modern ones leverage advancements in science. This knowledge of how germs infect us and how our bodies fight them allows us to target specific weaknesses in infectious organisms.

These developments offer exciting possibilities. We can potentially prevent a wider range of diseases and address new needs arising from changes in lifestyle, hygiene, and medicine. New medical practices can create populations susceptible to infections, and vaccines can offer them crucial protection.

1.3. Development of Vaccines and Recommendations for Vaccine Use:

Developing a vaccine is a complex, joint effort by public and private sectors. After assessing the disease's burden, cost-effectiveness, and priority ranking, researchers delve into the causative organism.

They identify the organism, understand how it causes disease, and pinpoint the components responsible for illness and immunity. Crucially, they determine if reliable methods exist to produce the organism for study and vaccine creation.

Several questions depend on the organism's nature. For bacterial vaccines, can immunity-inducing parts be separated from harmful elements? For viral vaccines, can the immune-producing antigen be extracted or incorporated into another organism? For live vaccines, can the organism's virulence be reduced and stably maintained?

An animal model to evaluate the vaccine's safety, potency, and potential protection is typically developed. Reliable laboratory tests to assess these qualities in humans are also crucial.

Throughout this process, there's ongoing communication between government agencies, scientists, and manufacturers. Conferences are held to exchange ideas and coordinate efforts.

After this groundwork, promising vaccines may proceed to human trials in three phases with increasing numbers of participants. Rigorous institutional review boards ensure the protection of human subjects before any trials begin.

Phase 3 trials, typically involving hundreds or thousands of participants from diverse backgrounds, are designed to definitively assess the vaccine's safety and effectiveness.

If all data is satisfactory, a license application is submitted for review of production, testing, and clinical evaluation records. The product itself undergoes lab testing, and the manufacturing facilities are inspected.

An advisory committee also reviews the product before a license can be granted. Even after licensure, the OBRR monitors vaccine safety by encouraging manufacturers to report adverse events.

Recommendations for vaccine use come from advisory groups and ensure consistency between vaccine labeling and recommendations.

The Department of the Army oversees vaccine development for military personnel against uncommon threats. Recommendations for these vaccines are developed by a separate board.

The entire process is complex and time-consuming but safeguards the safety and effectiveness of marketed vaccines. As new technologies emerge, like genetically engineered vaccines, the regulatory landscape may become even more intricate.

1.4. The future:

The future of vaccines is bright due to new technologies and a better understanding of immunity. This will lead to vaccines for diseases like malaria and diarrheal diseases that cause significant illness and death worldwide.

Many current vaccines contain unnecessary materials that may cause side effects. Research is underway to develop vaccines that are more effective, safer, and cheaper by using only the specific antigens that trigger immunity.

These improved vaccines could significantly increase vaccination rates around the world, especially in developing countries. Vaccination is crucial for global health as diseases can easily spread across borders.

New vaccine development is focused on genetic engineering to identify and produce the specific antigens that induce immunity. Scientists are working to determine the precise structure of these antigens and then synthesize them.

One approach is recombinant DNA technology, where the gene for the antigen is inserted into another organism, such as yeast, that can then produce large amounts of the antigen for the vaccine. This method is being used to develop a vaccine for hepatitis B.

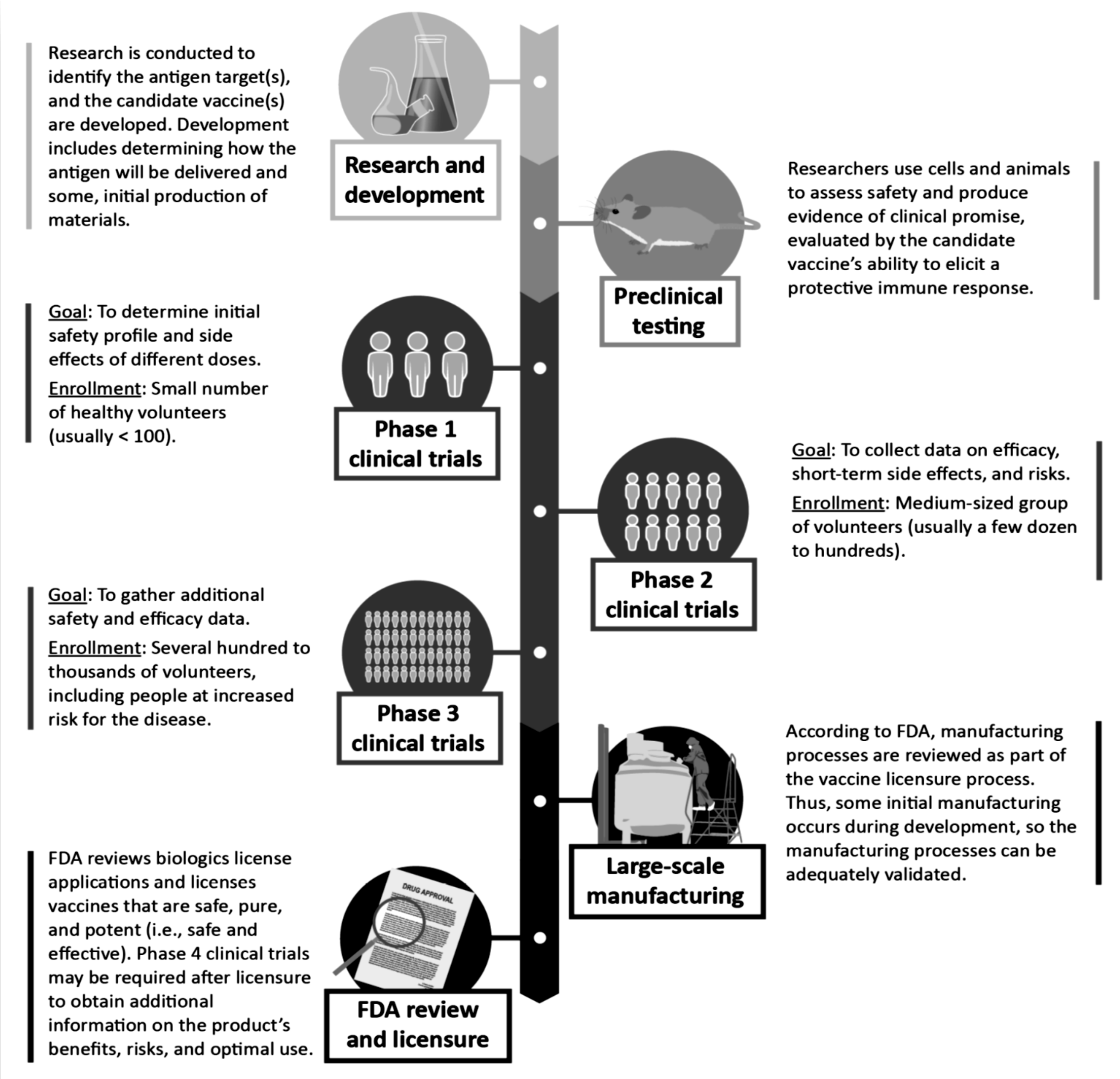
Another approach is polypeptide synthesis, where the amino acid sequence of the antigen is used to create a synthetic version. While these synthetic antigens are less effective than natural ones currently, researchers believe this will improve. Synthetic antigens are expected to be safer and cheaper to produce.

A third approach is using weakened or attenuated live pathogens, like the one used in the polio vaccine. The challenge with this approach is ensuring the virus stays weakened and doesn't revert to a harmful form. Researchers are looking at ways to genetically modify viruses to prevent this from happening.

The most promising new approach is the development of anti-idiotype antibodies. These antibodies mimic the antigen and can induce an immune response. This could theoretically lead to vaccines with no viral components at all. However, there are still technical and safety questions that need to be resolved.

Overall, these new technologies hold great promise for the development of new and improved vaccines. However, the same challenges that hinder traditional vaccine development, such as cost and regulatory hurdles, will also need to be addressed to bring these new vaccines to the public**. (17)**

2.Traditional vaccine development process:



Source: GAO analysis of information from the Food and Drug Administration (FDA) and literature. | GAO-22-104371

Figure 8: Traditional vaccine development process(18)

Note: The steps shown in the timeline are not drawn to scale, and the specific development steps for a given vaccine may vary. For example, the federal government accelerated this process for the development of a COVID-19 vaccine under the HHS-DOD COVID-19 Countermeasures Acceleration Group (formerly known as Operation Warp Speed) by overlapping certain phases to speed up the process so the vaccines could be used as quickly as possible to control the pandemic. No trial phases were skipped.

3.Vaccine Innovations:

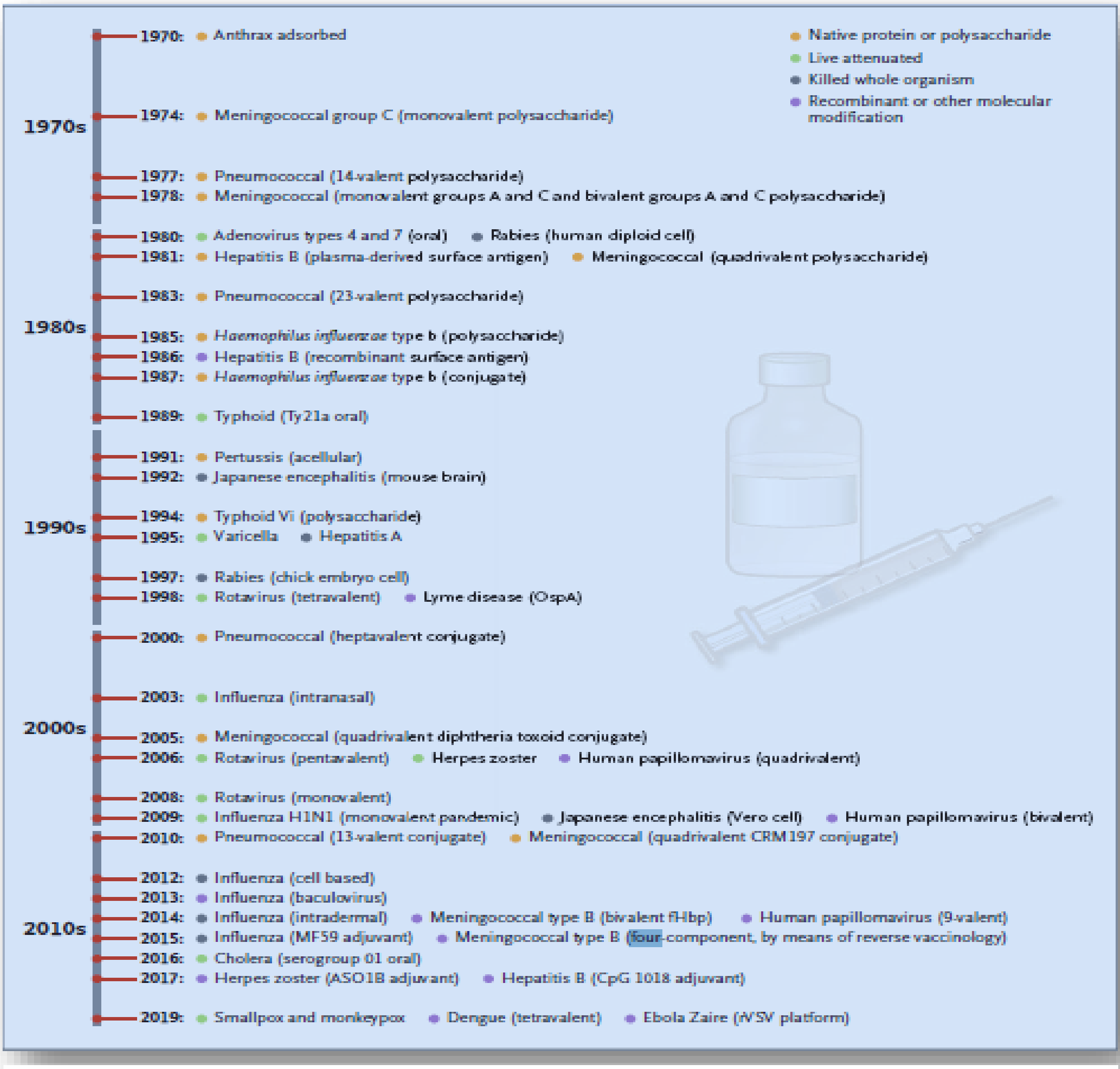


Figure 9: vaccine innovation **(19)**

4.Vaccine Hesitancy:

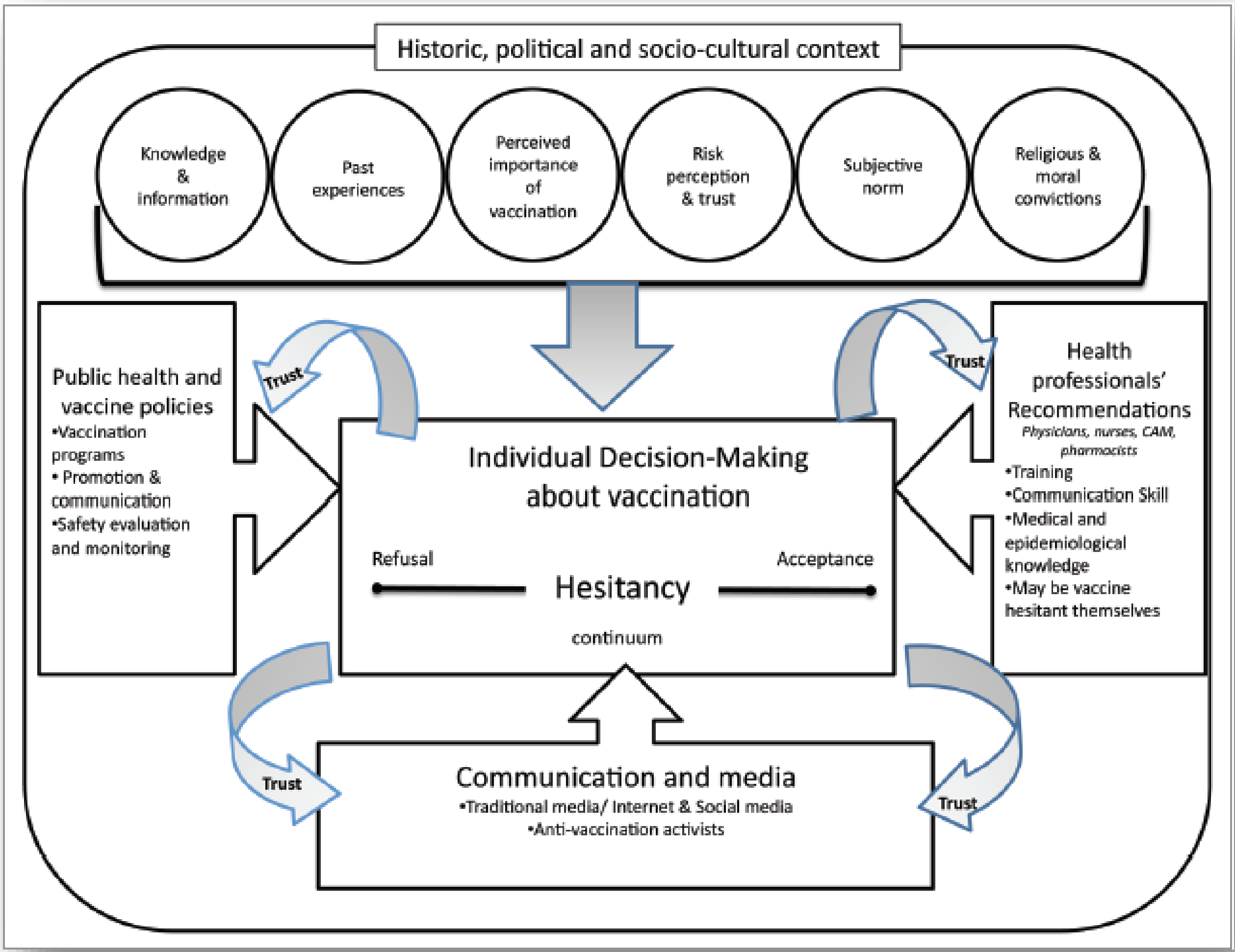


Figure 10: a conceptual model of Vaccine Hesitancy (20)

Note: a conceptual model of Vaccine Hesitancy. Adapted from the Schema summary of discussions held during the Workshop on the cultural and religious roots of vaccine hesitancy: Explanations and implications for the Canadian healthcare.

5.Social media and vaccine hesitancy:

Background Understanding the threat posed by anti-vaccination efforts on social media is critically important with the forth coming need for worldwide COVID-19 vaccination programs. We globally evaluate the effect of social media and online foreign disinformation campaigns on vaccination rates and attitudes towards vaccine safety. Methods we use a large-n cross-country regression framework to evaluate the effect of social media on vaccine hesitancy globally. To do so, we operationalize social media usage in two dimensions: the use of it by the public to organize action (using Digital Society Project indicators), and the level of negatively oriented discourse about vaccines on social media (using a data set of all geocoded tweets in the world from 2018-2019). In addition, we measure the level of foreign-sourced coordinated disinformation operations on social media in each country (using Digital Society Project indicators). The outcome of vaccine hesitancy is measured in two ways. First, we use polls of what proportion of the public per country feels vaccines are unsafe (using well come Global Monitor indicators for 137 countries). Second, we use annual data of actual vaccination rates from the WHO for 166 countries. Results We found the use of social media to organize offline action to be highly predictive of the belief that vaccinations are unsafe, with such beliefs mounting as more organisation occurs on social media. In addition, the prevalence of foreign disinformation is highly statistically and substantively significant in predicting a drop in mean vaccination coverage over time. A 1-point shift upwards in the 5-point disinformation scale is associated with a 2-percentage point drop in mean vaccination coverage year over year. We also found support for the connection of foreign disinformation with negative social media activity about vaccination. The substantive effect of foreign disinformation is to increase the number of negative vaccine tweets by 15% for the median country. Conclusion There is a significant relationship between organisation on social media and public doubts of vaccine safety. In addition, there is a substantial relationship between foreign disinformation campaigns and declining vaccination coverage. **(21)**

5.1. Relationship between disbelief in vaccine safety and use of social media to organise offline action:

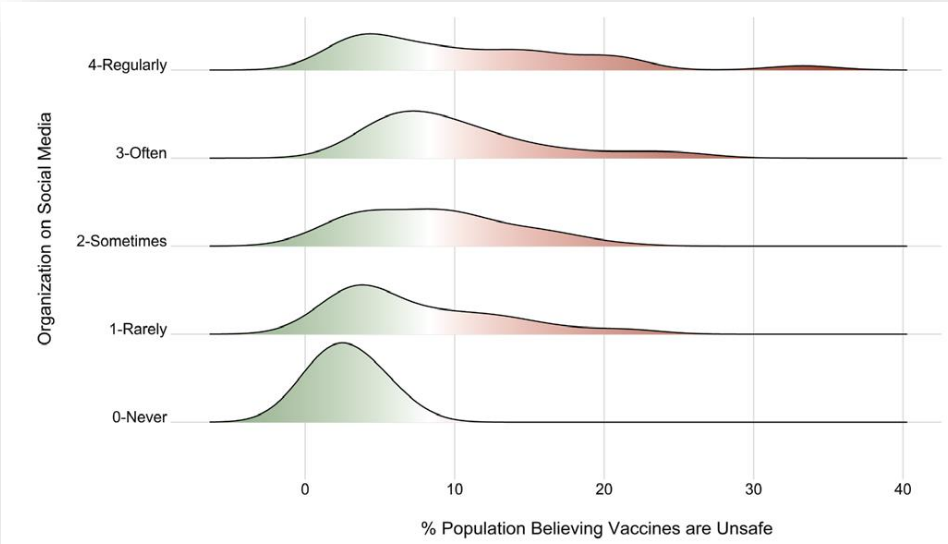


Figure 11: relationship between disbelief in vaccine safety and use of social media to organise offline action (21)

General Conclusion

Conclusion:

A Legacy of Protection, a Future of Promise
This dissertation has traversed a fascinating landscape – the intricate workings of the immune system, the cunning nature of viruses, and the remarkable journey of vaccine development. Throughout this exploration, one overarching theme has emerged: vaccines stand as a testament to human ingenuity in the face of adversity.

From the early, daring practices of variolation to the sophisticated technologies driving contemporary research, vaccines have fundamentally altered the course of public health. By harnessing our understanding of the immune system and viral biology, we have developed a powerful arsenal against infectious diseases that once ravaged entire populations.

Looking towards the future, the field of vaccinology pulsates with promise. New platforms, such as mRNA vaccines, offer unprecedented speed and versatility in vaccine design. Ongoing research into universal vaccines holds the potential to provide broad-spectrum protection against a multitude of pathogens. However, challenges remain. Vaccine hesitancy, misinformation, and the ever-evolving nature of viruses all demand continued vigilance and research efforts.

The story of vaccines is a narrative of triumph, resilience, and the enduring human spirit. By bridging the gap between the past and present, this dissertation underscores the critical role vaccines play in safeguarding global health. As we move forward, continued scientific exploration and unwavering public health initiatives remain paramount in ensuring that vaccines continue to serve as a powerful shield against infectious diseases, protecting not only the present generation but also the generations to come.

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