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VACCINE DEVELOPMENT CHALLENGES IN 21ST CENTURY

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ABSTRACT

In the last century, vaccination has been the most effective medical intervention to reduce death and morbidity caused by infectious diseases. It is believed that vaccines save at least 2–3 million lives per year worldwide. Smallpox has been eradicated and polio has almost disappeared worldwide through global vaccine campaigns. Most of the viral and bacterial infections that traditionally affected children have been drastically reduced thanks to national immunization programs in developed countries. However, many diseases are not yet preventable by vaccination, and vaccines have not been fully exploited for target populations such as elderly and pregnant women. This review focuses on the state of the art of recent clinical trials of vaccines for major unmet medical needs such as HIV, malaria, TB, and cancer. In addition, we describe the innovative technologies currently used in vaccine research and development including adjuvant, vectors, nucleic acid vaccines, and structure-based antigen design. The hope is that thanks to these technologies, more diseases will be addressed in the 21st century by novel preventative and therapeutic vaccines.

KEYWORDS: Edward Jenner's, Immune system, Antisera, Vaccine Development, Vaccinology, Antibody.

INTRODUCTION

A preparation that is used to stimulate the body's immune response against diseases.

Vaccines are usually administered through needle injections, but some can be administered by mouth or sprayed into the nose.

Vaccination has played a crucial role in preventing diseases ever since **Edward Jenner's** discovery of the smallpox vaccine in the late 18th century. Vaccination could also provide an enticing alternative therapy against diseases such as cancers and substance abuse. However, the efficacy of these vaccines is limited by the disease complexity and the lack of a more complete understanding of protective immunity in these medical conditions. The healthcare environment of the 21st century is markedly different from the 1940–50s' when vaccines were first introduced for routine use in universal immunization programs.[1]

Vaccination has played a crucial role in preventing diseases ever since Edward Jenner's discovery of the smallpox vaccine in the late 18th century. Despite the successes of vaccines in preventing and managing various diseases, there are still considerable hurdles to overcome in the fields of vaccine development and distribution. Diseases like influenza, HIV, and tuberculosis, which are widespread and have significant impact, present ongoing challenges in achieving effective immunization strategies. The emergence and re-emergence of viruses further underscore the urgent need for accelerated vaccine research and approval processes to rapidly respond to outbreaks, as seen in the recent global COVID-19 pandemic caused by the SARS-CoV-2 virus, causing immense loss of life and severe economic repercussions. Various vaccines were swiftly developed and subjected to rigorous clinical trials. Notably, mRNA-based vaccines have shown exceptional promise owing to their synthetic composition and sequence-flexible manufacturing, allowing for rapid and adaptable vaccine creation and production. The traditional methods to produce a vaccine, such as live attenuated and inactivated vaccines or protein subunit vaccines have their advantages and disadvantages, which have been extensively reviewed elsewhere. Briefly, live attenuated vaccines present the risk of reversion to a highly pathogenic form while inactivated vaccines may not be sufficiently immunogenic or in some cases can lead to enhanced disease pathology. Other fundamental challenges toward successful vaccination include the ever-changing and highly divergent nature of some viruses that allow for the potential to escape vaccine coverage, pre-existing immunity of the vaccinated populations, and pre-existing medical conditions that can prevent vaccines from being fully effective and safe.[2]

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disease complexity and the lack of a more complete understanding of protective immunity in these medical conditions. The relative contribution and balance of the different arms of host immunity, i.e., antibodies and cell-mediated responses, toward protection without adverse effects remains a challenging issue that needs to be addressed for individual disease.[3]

ADVANTAGES AND DISADVANTAGES OF VACCINE DEVELOPMENT

ADVANTAGES

- Induce humeral and cellular response.
- Both MHC I and MHC II Presentation.
- Ability to polarize T cell help for type 1 or type 2.
- Immune response only to chosen antigens.
- Native structure of protein.
- Structure and post translational modification of antigen like in natural infection.
- Stability during storage and shipping.
- Simplicityof formulation and preparation.
- Fast to produce and modify.
- Safety – Without infective agent.
- Easy to development and production.
- Relatively inexpensive.[4]

DISADVANTAGES

- Lower efficiency in large animals and humans than small animals models.
- Necessity for increasing response – enhancers,chemical or physical modifications.
- Necessity for repeated or multiple doses.
- No mass application methods for animals.
- Lower immunogenicity than inactivated vaccine.
- Limited to protein antigens.
- Atypical posttranslational modifications of bacterial and parasite antigens.
- (Negligible) threat of autoimmune reactions or integration of DNA into host genome.[4]

OBJECTIVES

- The goal of a vaccine is to prime the immune response so the immune memory can facilitate a rapid response to adequately control the pathogen on natural infection and prevent disease manifestation.

- This article reviews the main elements that provide for the development of safe and effective vaccines.[5]

NEED OF VACCINE DEVELOPMENT

- Vaccines have a long history of successfully protecting people and communities against infectious diseases.
- Vaccination has improved the quality of life for many, and serious diseases like smallpox have been eliminated.
- As vaccine technology advances, researchers can develop better and safer vaccines.

IMMUNOLOGY BEHIND VACCINE DEVELOPMENT

- Even though this article is about vaccine development, however, we need to know about immunology to know about vaccines.
- Immunology is the study of the immune system of one individual's body and functions of the immune system and also its disorder.[6]
- Antibodies are proteins that are released by our body's immune system to break down or neutralize the toxins released by the disease causing microorganism or pathogen Antigens are foreign substances which cause the production of antibody.
- So, antibodies are disease-specific, which implies that only a type of antibody works against a specific type of antigen.
- For example, Measles antibody only protects from measles disease and will have no other effects on mumps or rabies disease.[7]
- Immunity is classified into two.

1. ACTIVE and
2. PASSIVE**.**

STAGES OF VACCINE DEVELOPMENT

- A vaccine is a preparation that protects by forming antibodies and by boosting the immunity against the infection or disease.
- It is prepared from the weakened or killed version of the causative agent of disease it is administered to induce immunity.
- Vaccination is a process by which immunity to a pathogen is elicited (meaning that one who has taken the vaccine have been developed antibodies against the pathogen and now is immune).

- Nowadays vaccines are being developed with genetic engineering, it lets not cause any infection while it enters the body.
- So, the stages involved in vaccine production are to identify the strains for vaccine production as follows.[8]

Figure 1: -Stages of Vaccine Development.

Stage1: The Exploratory Stage (Takes usually 2-4 Years).

This is where laboratory testing is conducted to identify an antigen (a substance capable of stimulating an immune response to help the body develop antibodies).

A variety of compounds, including virus-like spores, weakened viruses or bacteria, weakened bacterial toxins, or other substances originating from pathogens, can be made up of antigens.

Stage 2: Pre-Clinical (Takes usually 1-2 years)

Different experiments are conducted on cells, tissues, and animals at this level. This decides the efficacy of the vaccine, how to administer the vaccine, the patient's effective dosage, and how effectively it contributes to an immune reaction (immunogenicity).

These experiments are conducted to guarantee that testing the vaccine in humans is genuinely safe and to check that it cannot cause significant harm to patients. Not all vaccines make it to the clinical level after testing.

Stage 3: Clinical Development

After a vaccine has been approved to progress to the clinical stage, it is safe for human testing. This process can be broken down into three sub-phases, namely Phase I, Phase II, and Phase III.[9]

Phase I (Takes usually 2 years)

The first phase usually entails the vaccine being administered to about 20-80 volunteers. The aim is to assess the vaccine's efficacy, side effects, sufficient dosing, and immune response. The aim is to check if the vaccine is performing as expected. The question to be answered is: did the vaccine prevent the disease, and did it produce antibodies?

Phase II (Take usually 2-3 Years)

The vaccine will proceed to Phase II if the answer to the question in phase I is positive. A wide group (usually hundreds) of volunteers are included in this phase. Volunteers are randomly chosen to obtain either the new vaccine or a placebo (saline solution, a vaccine for another illness, or some other substance).

The aim is to begin tracking the efficacy of the vaccine, the doses of the vaccine, the duration of the immunization, and the delivery mode of the vaccine. The method of administration could be oral, subcutaneous, intramuscular, intradermal, or intranasal.

Phase III Stages (Takes usually 5-10 Years)

Like phase II, this third phase will involve a larger group of people, usually tens of thousands of volunteers. The volunteers are randomly assigned to the experimental or placebo group. The primary purpose is to test the vaccine's efficacy and safety in a much greater group of individuals, especially in the population for which the vaccine is intended. In a larger group of individuals, it is possible to detect a rare side effect than in a smaller group.

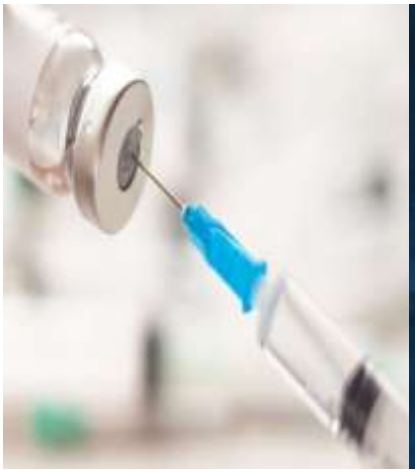

Figure 2:- Injectable vaccine. **Figure 3:-Additional phases of vaccine development.**

Stage 4: Approval

The sponsor of the vaccine follows an approval process after a vaccine has successfully passed phase III trials. The vaccine is approved by the governing authority only if it is safe and reliable, and the benefits outweigh the risks it may pose to the patients.

Stage 5: Pharmacovigilance

Once the vaccine is available to the public, the vaccine manufacturer continues to monitor the vaccine's efficacy to avoid any adverse events. To ensure that the vaccine is healthy for the public, the governing authority will also monitor the entire production process.[10]

CURRENT CHALLENGES FACING VACCINE DEVELOPMENT EFFORTS

The creation of new vaccines is a slow, Systematic. Expensive and laborious process that requires coordination between scientists, physician & public health officials.[11] Industry and vaccine developers and society.[12] These shareholders must work together n order for us to overcome the listed challenges in order to successfully development safe and effective vaccines that see widespread use.[13]

- High (and increasing) costs for vaccine development (-$700 millons - $1 billion).
- Vaccine hesitancy.
- More stringent safety requirements.
- Societal expectations of 100% efficacy.[14]
- Need to maintain cold - chain for vaccines.
- Increasing requirements for single dose efficacy.
- Need for rapid response to global outbreaks.

- Limited number of vaccine manufacturers.[15]
- Product development time (typically --10 years).
- Current pathogen require more complicated vaccines.
- Low efficacy of some licensed vaccines.
- Business models prioritize vaccines by market potential not by public health need.
- Aging world population that respond poorly to most vaccines (Immunosenescence).
- Limited number of approved and acceptable adjuvants.[16]
- Concurrent health problems in developing world that compromise immune response (nutrition, co-infection).
- Incomplete or inadequate understanding of biology, pathogenesis, and /or immunology of emerging pathogens.
- Inability to properly attenuate pathogens OR risk of reversion to wild type organism.[17]
- Humoral immune responses do not always correlate with protection.
- Inappropriate / harmful immune response (formalin-inactivated RSV products) or enhanced disease upon re-infection (Dengue).
- Inadequate durability of immune response (ex- Peruses).[18]

CHANGES IN VACCINE DEVELOPMENT

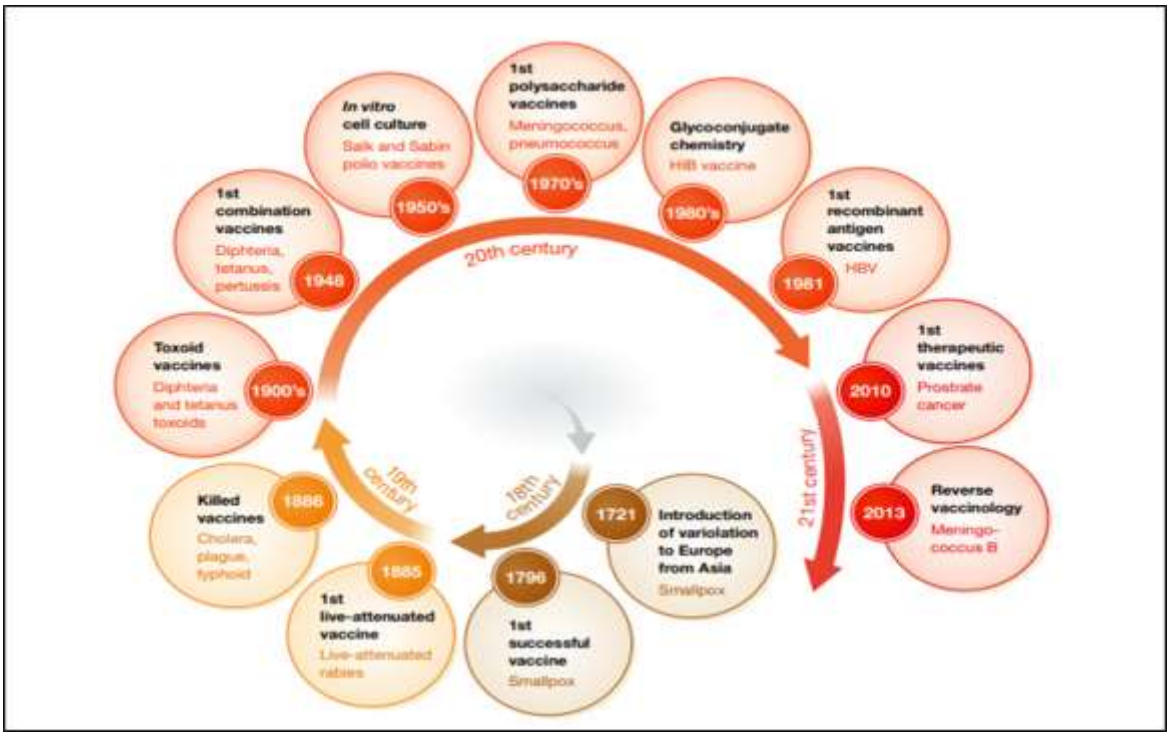

Figure No 4:- Changes of vaccine development up to 21st century.

FROM 18th CENTURY → TOWARDS 21ST CENTURY[19]

Table No 1:- Changes of vaccine development.

18th CENTURY	
17963	Edward Jenner develops and documents first vaccine for smallpox.[20]
19th CENTURY	
1884-1885	First vaccine for cholera by Jaime Ferran y Claus .
1885	First vaccine for rabies by Louis Pasteur and Emilee Roux.
1890	First vaccine for tetanus (serum antitoxin) by Emil von Behring
1896	Vaccine for typhoid fever by Almroth Edward Wright, Richard Pfeiffer, and Wilhelm Kolle.
1897	First vaccine for bubonic plague by Waldemar Haffkine.[21]
20th CENTURY	
1923	First vaccine for diphtheria by Gaston Ramon, Emil von Behring and Kitasato Shibasaburo.
1924	First vaccine for scarlet fever by George F. Dick and Gladys Dick.
1924	First inactive vaccine for tetanus (tetanus toxoid, TT) by Gaston Ramon, C. Zoeller, P. Descombey.
1926	First vaccine for pertussis (whooping cough) by Leila Denmark.
1932	First vaccine for yellow fever by Max Theiler and Jean Laigret.
1937	First vaccine for influenza by Anatol Smorodintsev.
1937	First vaccine for typhus by Rudolf Weigl, Ludwik Fleck and Hans Zinsser.
1940	First vaccine for anthrax.
1941	First vaccine for tick-borne encephalitis.
1952	First intravenous vaccine for polio.
1954	First vaccine for Japanese encephalitis.
1957	First vaccine for adenovirus-4 and 7.
1962	First oral vaccine for polio.
1963	First vaccine for measles.
1967	First vaccine for mumps.
1970	First vaccine for rubella.
1977	First vaccine for pneumonia (Streptococcus pneumoniae).
1978	First vaccine for meningitis (Neisseria meningitidis).
1980	Smallpox declared eradicated worldwide due to vaccination efforts.
1981	First vaccine for hepatitis B (first vaccine to target a cause of cancer).
1984	First vaccine for chicken pox.
1985	First vaccine for Haemophilus influenzae type b (HiB).
1989	First vaccine for Q fever.
1990	First vaccine for hantavirus hemorrhagic fever with renal syndrome.
1991	First vaccine for hepatitis A.
1998	First vaccine for Lyme disease.
1998	First vaccine for rotavirus.[22]

21st CENTURY	
2000	First pneumococcal conjugate vaccine approved in the U.S. (PCV7 or Prevnar).
2003	First nasal influenza vaccine approved in U.S. (Flu Mist).
2003	First vaccine for Argentine hemorrhagic fever.
2006	First vaccine for human papillomavirus (which is a cause of cervical cancer).
2006	First herpes zoster vaccine for shingles.
2011	First vaccine for non-small-cell lung carcinoma (comprises 85% of lung cancer cases).
2012	First vaccine for hepatitis E.
2012	First quadrivalent (4-strain) influenza vaccine.
2013	First vaccine for enterovirus 71, one cause of hand, foot, and mouth disease.
2015	First vaccine for malaria.
2015	First vaccine for dengue fever.
2019	First vaccine for Ebola approved.
2020	First vaccine for COVID-19.
2023	First respiratory syncytial virus vaccine.
2023	First vaccine for Chikungunya.[23]

APPLICATION OF VACCINE

- It uses your body's natural defenses to build resistance to specific infections and makes your immune system stronger.
- Vaccines help your body in learning how to protect it from viruses.
- It makes your immune system stronger that helps your body in fighting from those viruses due to which very little amount of those viruses attacks the body which automatically get killed after arriving inside the body.[24]
- It is used to induce long term humeral as well as cell-mediated immune response against disease-causing pathogens.
- Vaccines help in developing immunity against specific diseases.
- It initiates a primary immune response, generating memory cells without making a person ill. Later, if the same or very similar pathogens attack, a specific memory cell already exists. They recognize the antigen and evoke secondary immune response producing large numbers of antibodies that quickly overpower the invaders.[25]
- The immune system is strongest in adulthood that means infants; children and elderly are particularly susceptible to a dangerous infection. Vaccines strengthen their immune system and bypass this risk.
- The use of vaccines has been effective in developing resistance of infection of microorganisms that cause cholera, diphtheria, measles, mumps, whooping cough, rabies, smallpox, tetanus, typhoid, yellow fever and poliomyelitis.
- Vaccines can be a key tool in managing threat or pandemic situations such as Covid-19 caused by a corona virus.[26]

CONCLUSION

Vaccine development in the twenty-first century is enabled by increasingly sophisticated genetic and high-dimensional assays, aided by bioinformatics approaches. This has allowed unprecedented resolution, at the whole-systems level, of how innate, adaptive, and cellular immune responses are generated, interact, and are maintained after vaccination. These technologies are being further leveraged in understanding adverse (aberrant) vaccine responses and the durability of immunity to vaccines, which represent areas of intense investigation due to their importance to human health.

Taken together, genetic technologies and approaches have led to a new era of genetic design of vaccines and have provided solutions to the barriers currently impeding progress in this area.

Genetic approaches have enabled the identification of relationships/networks between individual genetic variants and specific aspects of vaccine-induced innate, adaptive, or cellular immune responses. The promise of vaccinomics is to identify specific immune response profiles that may serve as signatures or biomarkers that accurately predict vaccine immunogenicity, efficacy, and/or safety. Furthermore, it has the potential to identify genetic variants or antigens that lead to newer and safer vaccine candidates.

We believe that the development of very large and detailed genotype :phenotype databases will eventually lead to a new model of personalized vaccine practice (i.e., the delivery of the right vaccine to the right person at the right time) that utilizes genetic and immune signatures to do the following: develop new vaccine candidates; predict the need for a vaccine and the dose needed to induce protective immunity; and to predict whether a significant adverse effect is likely to occur—in other words, personalized vaccinology. Yet, barriers remain. Issues of high costs for genetic-based assays, including the cost of analysis and the complexity of such data exist, as well as inertia on the part of current vaccine developers conspiring to delay the full use of these rapidly advancing new paradigms.

Funders of research must realize not only the promise of such vaccine development approaches but also the costs. For example, the standard allowable budget for the most common NIH research funding mechanism in the USA, the R01, has not changed in the past 30 years despite massive advances in science and the cost of experiments and statistical analysis over this time period.

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