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CURRENT CHALLENGES IN VACCINE DEVELOPMENT

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Abstract:

One of the most successful therapeutic strategies to prevent or control various diseases is by "vaccination" protocol The terms "vaccine" and "vaccinology" came into use soon after Edward Jenner discovered the smallpox vaccine. Jenner called the smallpox vaccine "variola vaccinae." For his contribution, Jenner is often referred to as the "Father of Vaccinology" (though this epithet is sometimes also used for Louis Pasteur). The word "vaccine" originated from vacca, a Latin term for the cow. The credit for the first use of the term "vaccine" goes to Swiss physician Louis Odier (1748-1817), and the terms "vaccination" and "to vaccinate" were first used by Richard Dunning (1710- 1797)

A vaccine is a biological preparation that can be used to safely induce an immune response that confers protection against infection and/or disease on subsequent exposure to a pathogen.

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INTRODUCTION:

One of the most successful therapeutic strategies to prevent or control various diseases is by "vaccination" protocol The terms "vaccine" and "vaccinology" came into use soon after Edward Jenner discovered the smallpox vaccine. Jenner called the smallpox vaccine "variola vaccinae." For his contribution, Jenner is often referred to as the "Father of Vaccinology" (though this epithet is sometimes also used for Louis Pasteur). The word "vaccine" originated from vacca, a Latin term for the cow. The credit for the first use of the term "vaccine" goes to Swiss physician Louis Odier (1748-1817), and the terms "vaccination" and "to vaccinate" were first used by Richard Dunning (1710- 1797) [1].

A vaccine is a biological preparation that can be used to safely induce an immune response that confers protection against infection and/or disease on subsequent exposure to a pathogen. A vaccine typically containsan agent that resembles a disease-causing microorganism and is often made from weakened or killed forms ofthe microbe, its toxins or one of its surface proteins. This agent stimulates the body immune system to recognize the agent as foreign, destroy it, and keep a record of it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters. Protection conferred by a vaccine is measured in clinical trials that relate immune responses to the vaccine antigen to clinical end points (such as prevention of infection, a reduction in disease severity or a decreased rate of hospitalization). Finding an immune response that correlates with protection can accelerate the development of and access to new vaccines.

Vaccines are generally classified as live or non-live (sometimes loosely referred to as 'inactivated') to distinguish those vaccines that contain attenuated replicating strains of the relevant pathogenic organism fromthose that contain only components of a pathogen or killed whole organisms. In addition to the 'traditional' live and non-live vaccines, several other platforms have been developed over the past few decades, includingviral vectors, nucleic acid-based RNA and DNA vaccines, and virus-like particles. The distinction between live and non-live vaccines is important. The former may have the potential to replicate in an uncontrolled manner in immunocompromised individuals (for example, children with some primary immunodeficiencies, or individuals with HIV infection or those receiving immunosuppressive drugs), leading to some restrictions to their use. By contrast, non-live vaccines pose no risk to immunocompromised. Individuals.

Live vaccines are developed so that, in an immunocompetent host, they replicate sufficient strong immune response, but not so much as to cause significant disease manifestations (for example, the vaccines for measles, mumps, rubella and rotavirus, oral polio vaccine.

The antigenic component of non-live vaccines can be killed whole organisms (for example, whole-cell pertussis vaccine and inactivated polio vaccine), purified proteins from the organism (for example, acellular pertussis vaccine), recombinant proteins (for example, hepatitis B virus (HBV) vaccine) or polysaccharides (for example, the pneumococcal vaccine against S. pneumoniae). Toxoid vaccines (for example, for tetanus and diphtheria) are formaldehyde-inactivated protein toxins that have been purified from the pathogen. Non-live vaccines are often combined with an adjuvant to improve their ability to induce an immune response (immunogenicity). There are only a few adjuvants that are used routinely in licensed vaccines.Vaccines contain other components that function as preservatives, emulsifiers (such as polysorbate 80) or stabilizers (for example, gelatine or sorbitol).Various products used in the manufacture of vaccines could theoretically also be carried over to the final product and are included as potential trace components of a vaccine, including antibiotics, egg or yeast proteins, latex, formaldehyde and/or gluteraldehyde and acidity regulators (such as potassium or sodium salts). Except in the case of allergy to any of these components, there is no evidence of risk to human health from these trace components of some vaccines. (1).

1.TYPES OF VACCINES

There are seven types of vaccines –

1. Live attenuated (weakened or inactivated) :

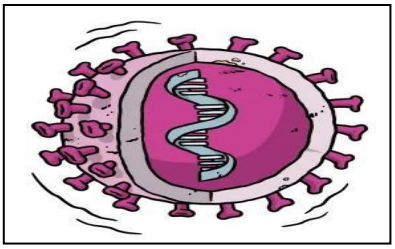


Figure No.1: Live attenuated (weakened or inactivated)

Live-attenuated vaccines are the first type of vaccines developed, and they have successfully eradicated smallpox in 1798, almost eradicated poliomyelitis, and contribute to control the worldwide cases of measles while being less effective for chronic infections. The live attenuated vaccine containing strain Yersinia pestisEV is used for plague immunization [2,3]. Advantage is, after administration, live vaccines may replicate in the host similar to their pathogenic counterparts. This confronts the host with a larger and more sustained dose of antigen, which means that few and low doses are required. In general, the vaccines give long-lasting humoral and cell-mediated immunity. Furthermore, these viruses are sensitive to storage conditions and demand a well-kept cold chain. Licensed vaccines using this technology are Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster [4,5]

2. Killed whole organism:

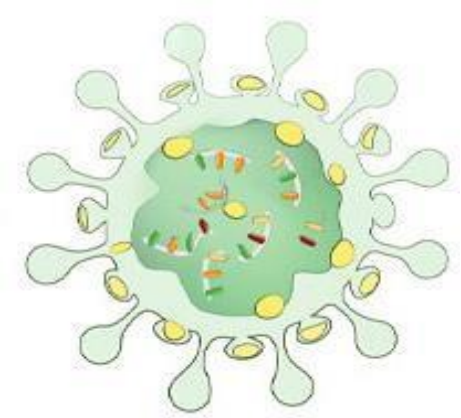


Figure No.2: Killed whole organism

Killed (inactivated) Vaccines are prepared when safe live vaccine is not available. Some vaccines contain killed, but previously virulent, micro-organisms that have been destroyed with chemicals, heat, radioactivity or antibiotics. Inactivating means to destroy the ability of the virus to replicate in the human body while keeping all the antigens present in the viral structure. A variety in the immune response according to the sourceof the antigen, the need for adjuvants, and the lower efficacy are the downsides of this class of vaccines. Licensed vaccines using this technology are Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies. This type of vaccine was first introduced in year 1896 for (typhoid) [6,7].

3. Toxoid :

Figure No.3: Toxoid

The third class of vaccines in order of discovery is toxoids [8]. This vaccine prevents the disease resulting from the toxins released by a virus into the body. Since the toxic substances administered are weak they are unable to cause the illness, while the immune system which encounters this toxoid vaccine, becomes able to repel the natural toxin. Toxoid vaccines are prepared from the toxins secreted from bacteria (e.g., tetanus anddiphtheria). It is a mature technology, and vaccines for tetanus and diphtheria are commonly administered worldwide. It was first introduced in 1923 (diphtheria) [9]

4. Subunit :

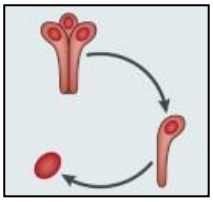


Figure No.4: Subunit

Subunit vaccines are composed by protein immunogens, or antigens, usually produced through recombinant technologies. Examples include the subunit vaccine against Hepatitis B virus that is composed of only the surface proteins of the virus (previously extracted from the blood serum of chronically infected patients, but now produced by recombination of the viral genes into yeast), the virus-like particle (VLP) vaccine against human papillomavirus (HPV) that is composed of the viral major capsid protein, and the hemagglutinin and neuraminidase subunits of the influenza virus. They show an excellent safety profile and can be modified to change properties facilitating the development of stable formulations. However, the downside is their limited immunogenicity when compared with live attenuated vaccines. Thereby,

they often require the formulation together with adjuvants, to increase their efficacy [10,11]. Other licensed vaccines using this technology are Pertussis, influenza, meningococcal, pneumococcal, typhoid, hepatitis A. It was first introduced in 1970 for (anthrax) [12].

5. Protein – Polysaccharide Conjugate :

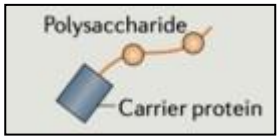


Figure No.5: Protein – Polysaccharide Conjugate

Streptococcus pneumoniae (pneumococcus) is accountable for approximately 800,000 deaths of children under five annually, followed by Haemophilus influenzae type b (Hib) and Neisseria meningitidis (meningococcus). Polysaccharide vaccines against these bacteria are available since 1980s, but these are not effective in infants and children who are the common targets. Therefore, protein-conjugate polysaccharide vaccines were developed [13]. These all are encapsulated bacteria, the capsule being composed of polysaccharide. Destruction of the polysaccharide capsule which is the determinant of virulence in these bacteria is essential to protect against them. Normally, the capsule is destroyed by the complement system of the host along with antibodies produced by the B lymphocytes [14]. The capsular polysaccharide is presented directly to the B cell surface and not through the antigen-presenting cells (APC), the CD4+ T-cells are not stimulated, resulting in a weak proliferation of B cells to produce IgM and IgG2 without formation of memorycells [15].

6. Viral vectored :

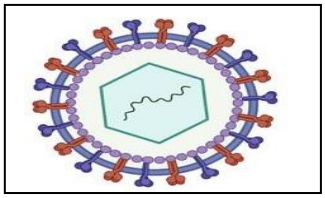


Figure No.6: Viral vectored

Recombinant viral vectors have been used to deliver antigens from specific pathogens. The first viral vector expressing a foreign gene was created from the SV40 virus in 1972 [16,17]; since then, a variety of other viruses, including adenoviruses, poxviruses, herpesviruses, vesicular stomatitis virus, and lentiviruses, have been engineered into vaccine vectors to stimulate immune responses against the proteins generated from the encoded transgenes. Additionally, viral vectors can induce high immunogenicity without the use of an adjuvant, as well as long lasting immune responses—in some cases after just a single dose. Furthermore, viral vectors can be engineered to deliver vaccine antigens to specific cells or tissues. Additionally, the presence of the antigen on the surface of the vector particles or inside the virion can also contribute to the induction of an immune response [18,19]. Although intramuscular injection is the most common route of immunization to induce systemic immunity, viral vector vaccines can also be administered intranasally, orally, intradermally and via aerosol. Viral vectors have been used in both pre-clinical and clinical trials as vaccines against a variety of infectious diseases, such as HIV, Malaria, Ebola, and more recently, SARS-CoV-2 [20,21].

7. Nucleic acid vaccine :

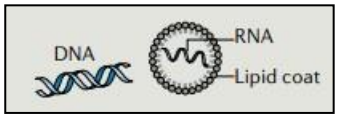


Figure No.7: Nucleic acid vaccine

It has now been three decades since Felgner and colleagues published that nucleic acid constructs, i.e., both plasmid DNA and mRNA could be directly injected in vivo into mice resulting in the encoded protein made in situ. Immunization with nucleic acid vaccines involves the administration of genetic material, plasmid DNA or messenger RNA, encoding the desired antigen. The challenges for use of nucleic acids as a means of producing therapeutic proteins in vivo included both targeting the correct tissue and having therapeutic levels of the protein made [22,23]. The DNA vaccines were shown to be capable of generating protective neutralizing antibodies and both helper T cells and Cytolytic T Lymphocytes (CTLS). The T cell help was predominantly of the Th1 phenotype for directly injected DNA. The improvement of immunogenicity and the easy efficient delivery of NA vaccines provide several rationales for NA vaccination of companion and production animals against classical and emerging veterinary virus diseases, as well as new zoonotic viruses [24].

In recent years, there seems to be an increased frequency of emerging virus outbreaks among humans. Most of these novel viruses are zoonotic RNA viruses with high mutation potential emerging from wild animals. This is a consequence of increased contact with wild animals and their

viruses. This cross-species infection iseither directly or after virus amplification and super-spreading events in flocks of humans of flocks of production animals. Examples of this are the 2003 Sars-CoV from bats and mammals, the 2009 swine influenza from pigs, the 2012 Mers-Cov from bats and camels [25,26], the 2014 world's largest Ebola outbreak from bats in Central or West Africa [27], the 2015 Zika virus from mosquitoes and monkeys [28], and the 2019 Sars-CoV-2/Covid-19 with a possible origin from bats [29,30].

3. VACCINE DEVELOPMENT

To meet society's need for safe and efficacious vaccines, the clinical vaccine development process has been refined for more than a century. Vaccine development involves the process of taking a new antigen or immunogen identified in the research process and developing this substance into a final vaccine that can be evaluated through preclinical and clinical studies to determine the safety and efficacy of the resultant vaccine. During initial process, the product's components, in-process materials, final product specifications, and manufacturing process are defined. The manufacturing scale used during development is usually significantly smaller than that used in the final manufacturing process [31]. Vaccine-specific developmental plan should beclearly established to ensure the sufficient and successful development before clinical evaluation. This includes the following contents:

1) Identification of the target population (mostly healthy people with particular demographic characteristics) and their sociocultural factors.
2) Risk assessment of the target disease and the vaccine itself.
3) Understanding of the incidence of the target disease and environmental factors.
4) Identification of the dose and route of administration.
5) Plans to induce herd immunity.
6) Regulatory strategies.

The clinical evaluation of a vaccine typically comprises three phases and the entire process takes 10-15 yearsapprox [32].

Preclinical Studies –The development begins with basic research to identify the virus responsible for the
diseases and, if possible, the antigen(s) that elicit a protective immune response. In addition, attempts are made to determine which immune responses are protective (antibodies, T cells, for example). in the laboratory. In cases where an animal model is available, candidate vaccines can be tested for protectionafter challenge with virulent virus. Finally, toxicity data are collected. The preclinical stage ends with the establishment of a production process [33].

In Human Studies –

Phase I and, sometimes, Phase II clinical trial vaccines are typically produced in product development, but it is usually anticipated that at least one of the three or more consistency lots used for Phase III clinical trials will be manufactured at full-scale production volume. The product manufactured during the development phase is manufactured according to current GMP [34]. After the preclinical studies have come to a satisfactory end, the vaccine is tested in humans (or animals for veterinary vaccines). 'First-in human' studies and all other clinical studies are subject to strict rules to protect study participants and ensure quality. Clinical trials in humans are classified into three phases: phase I, phase II and phase III [35].

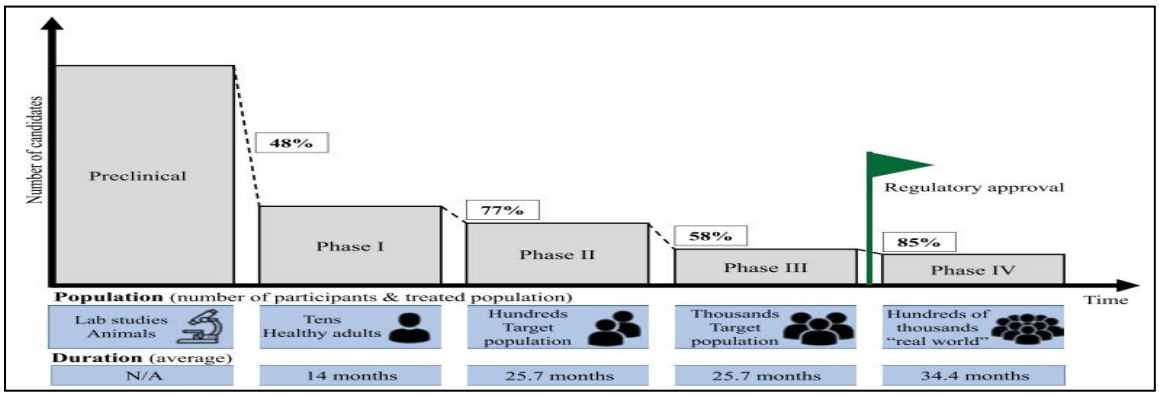
Phase I : In these phase human studies of the acceptable safety and reactogenicity of a vaccine candidate are achieved. In this phase, safety and tolerability are evaluated at both the local and systemic levels as the primary endpoint. Dose ranging and/or repeated-dose studies are often performed [36,37]. The statistical analysis is generally descriptive and exploratory in nature because the trials involve only small numbers of participants (20-80 healthy adults), and thus sufficient information needed for confirmatory tests cannot be obtained. In the 'first-in-human' setting, more attention should be given to live attenuated vaccines because the risks tend to be higher than those of killed vaccines [38].

Phase II : These studies involve larger numbers of persons belonging to the target population with the aim of getting preliminary information about efficacy, usually immunogenicity and additional safety data. Theses purposes are often achieved by separating clinical trials into 'Phase IIA' and 'Phase IIB.' In designing these clinical trials, multiple variables associated with the host immune response are considered. Determinants of clinically applicable vaccine regimens are also included, such as the dose and number of doses, sequence/interval between doses, and route of administration. Together, phase I and II trials should give sufficient confidence that a vaccine is efficacious and safe.

Phase III : The final step in the clinical evaluation before product license is the 'Phase III' trial. This stage is intended to provide a pivotal conclusion

needed for marketing approval, and the efficacy and safety of formulation(s) of the immunologically active component(s) must be assessed in the large-scale target population [39]. Depending on the prevalence of the disease these studies may require 10,000 or more participants. After the completion of the phase III studies, all results are summarized in a dossier. This dossier also includes data on a consistent manufacturing process and assays to monitor the production and its end products and in consideration of the modern vaccination strategy—administration of multiple vaccines at the same time—interaction and/or interference with other vaccines are evaluated routinely. Then this information obtained during the developmental processes mentioned above are summarized and filed for submission to the regulatory authorities. After the regulatory authorities have decided that the vaccine is safe and effective, it is licensed and can be released to the market [40]. The WHO and each regulatory authority have their own guidelines to ensure the quality of the information provided [41].

Phase IV : Even though a vaccine may be licensed, the safety information provided for licensure is regardedas insufficient, because at that point, only a few thousand people have likely been exposed to the vaccine. Thus, many vaccines undergo post-licensure ('Phase IV') studies. For example Phase IV studies revealed that a rotavirus vaccine caused intussusception in one or two cases per 10,000 infants vaccinated. This vaccine waswithdrawn from the market. Newer rotavirus vaccines are 10-fold safer, but not completely without AEFI [42].



FigureNO.8: Vaccine development phases

4. COMBINATION VACCINES

The development of combination vaccines for protection against multiple diseases began with the combination of individual diphtheria, tetanus, and pertussis (DTP) vaccines into a single product; this combined vaccine was first used to vaccinate infants and children in 1948 [43]. Since oral immunization is not possible for most available vaccines, the strategy to mix individual vaccines in order to limit the number of injections has been common practice since many decades. Under the current immunization schedule, an infant could receive as many as 6 injections at a single visit. Some parents believe this to be an excessive number of injections and some choose to defer some vaccines to a later visit or decline them altogether [44,45,46]. With combination vaccines, the number of injections could be reduced by 2 or more per visit, which may decrease vaccine refusal and increase immunization coverage [47,48]. Improved immunization coverage benefits the entire community, as vaccine-preventable diseases are less likely to circulate and cause infection. Another benefit of combining vaccine products is the simplification of immunization delivery. Simplifying the vaccination schedule means that children receive fewer injections and require fewer visits to a health care provider to acquire immunity to important diseases. Reducing injections by combining vaccines reduces trauma to the infant and has been found to lead to higher rates of compliance with complex vaccination schedules [49,50].

Potential advantages of combination vaccines:

i. Fewer injections.
ii. Reduced trauma to the infant
iii. Higher rates of compliance with complex vaccination schedules
iv. Better vaccine coverage [51]
v. Timely vaccination – vaccination schedule completed on time[51]
vi. Reduced administration costs

vii. Lower storage space requirements
viii. Allows incorporation of new vaccines into immunization schedules [52]

Combination vaccines also have drawbacks. Depending on the combination vaccine and immunization schedule used, they may result in the administration of extra doses of antigen. This can occur when 3 doses of DTaP-HepB-IPV are given on schedule at 2, 4, and 6 months, in addition to the hepatitis B dose recommended at birth [53]. In addition, some combination vaccines are associated with higher rates of minor adverse events, such as fever [54,55]. Another recent concern about combination vaccines is the hypothesis that the measles, mumps and rubella vaccines, administered together as MMR, could be associated with an increased risk of developing autism or inflammatory bowel disease [56,57].

4.1 Measles And Rubella

The control of measles and congenital rubella in developing countries is an important program. Vaccination coverage against measles in children must be extraordinarily high to prevent the virus from spreading, and it must also be high against rubella to prevent a paradoxical increase in the susceptibility of women because of decreased exposure to natural infection. Mass vaccination by injection is difficult and risky in some settings. Years ago, Albert Sabin showed that aerosol administration of measles vaccine is feasible, and during the development of RA 27/3 rubella vaccine, we showed that its administration by nose drops, no less than injection, resulted in successful vaccination. Recently, Mexican researchers led by Sepulveda-Amor and Valdespino Gomez have administered a combined measles-rubella vaccine to the children by means of a simple aerosol apparatus and have succeeded in immunizing against both infections in 190% of cases [58]. This opens the way to simpler mass vaccination campaigns and to the simultaneous control of both measles and congenital rubella syndrome.

5. SAFETY AND SIDE EFFECTS OF VACCINE

Despite the public impression that vaccines are associated with specific safety concerns, the existing data indicate that vaccines are remarkably safe as interventions to defend human health. Common side effects, particularly those associated with the early innate immune response to vaccines, are carefully documentedin clinical trials. Although rare side effects might not be identified in clinical trials, vaccine development is tightly controlled and robust post-marketing surveillance systems are in place in many countries, whichaim to pick these up if they do occur [59].

A recent example can be used to highlight vaccine safety and to illustrate how the vaccine community responded to an apparent problem with a marketed product. In 1998, a live, oral rotavirus vaccine was introduced onto the market for immunization of infants, but a year later this product was withdrawn because of an association with intussusception, a rare but serious obstruction of the intestine. Before licensure, only five cases of intussusception were reported in 10,000 vaccine recipients versus one case in4633 placebo recipients [60].

Again, several approaches have been developed that have the potential to produce safer vaccines. The use of the genomic information that is available on important microorganisms and the approach termed ‘reverse vaccinology’ enables the identification of novel recombinant antigens that have the potential to be excellent vaccine candidates [61]. Overall, the increasing use of postlicensure safety studies (often called Phase IV studies) for new vaccine products will ensure that safety issues that arise even at low levelswill be identified quickly.

5.1 Common side effects

Licensure of a new vaccine normally requires safety studies involving from 3,000 to tens of thousands ofindividuals. Thus, common side effects are very well known and are published by the regulator at the time of licensure. Common side effects of many vaccines include injection site pain, redness and swelling and some systemic symptoms such as fever, malaise and headache [62]. All of these side effects, which occur in the first 1–2days following vaccination, reflect the inflammatory and immune responses that lead to the successful development of vaccine-induced protection. Local adverse reactions that generally start within a few hours of the injection and are usually mild and self-limiting. Although these are often referred to as ‘hypersensitivity reactions [63]. Although these side effects are self-limiting and relatively mild and are trivial in comparison with the high morbidity and mortality of the diseases from which the vaccines protect they can be very worrying for parents and their importance is often underestimated by clinicians who are counselling families about immunization.

5.2 Immunodeficiency and vaccination

Primary immunodeficiency is generally inherited and includes conditions defined by the absence or quantitative deficiency of cellular or humoral components of immunity (e.g. X-linked agammaglobulinaemia). Secondary

immunodeficiency is generally acquired and is defined by loss or qualitative deficiency in cellular or humoral immune components as a result of a disease process or its treatment (e.g. HIV infection) [64].

Before vaccination of a patient who is immunodeficient, consideration must be taken of whether the vaccine is inactivated or live. All inactivated vaccines can be administered safely to people with altered immunocompetence, and the usual doses and schedules are recommended; however, the effectiveness of the vaccine might be suboptimal. People with any of most forms of altered immunocompetence should not receive live vaccines, and those with severe cell-mediated immunodeficiency should not receive live attenuated viral or bacterial vaccines [65].

6. VACCINATION

Modern vaccines provide high levels of protection against an increasing number of diseases and the symptoms, disability and death that may occur. At the same time, serious reactions to vaccines are rare. The devastating effects of these diseases are no longer so evident, public attention is focused on the side-effects of vaccination. In some instances, concerns about the safety of certain vaccines have led to downturns in vaccination rates and outbreaks of disease [66]. Some people believe that vaccine-preventable diseases have been almost entirely eliminated and that the risk for exposure to infectious disease is minimal; therefore, they conclude that no vaccination programme is needed. The public may receive mixed, often confusing messages that leave them feeling ambivalent about vaccination.

Schedule of vaccination:

For most vaccines that are used in the first year of life, 3–4 doses are administered by 12 months of age. Conventionally, in human vaccinology, 'priming' doses are all those administered at less than 6 months of age and the 'booster' dose is given at 9–12 months of age. So, for example, the standard WHO schedule for diphtheria–tetanus–pertussis-containing vaccines consists of 3 priming doses at 6, 10 and 14 weeks of age with no booster. This schedule was selected to provide early protection before levels of maternal antibody had waned (maternal antibody has a half-life of around 30–40 days) [67].

7. VACCINOLOGY

Vaccinology combines the principles of microbiology, immunology, epidemiology, public health, and pharmacy, amongst other. Developing vaccines is central to the control of infectious diseases of animals and new vaccines have the potential to reduce antibiotic use, prevent losses in livestock production and protect people from zoonotic infections. The International Veterinary Vaccinology Network is a multidisciplinary vaccinology research and development community that addresses the challenges impeding vaccine discovery, evaluation and delivery and that help the control of priority livestock and zoonotic diseases in low-and-middle income countries (LMICs). It aims to help international researchers collaborate in addressing the challenges of vaccine development for major livestock and zoonotic diseases affecting agriculture in LMICs. This includes all species of agricultural importance in LMICs with an emphasis on molecular and cellular biology work relevant to vaccine development. The network brings together partners from academia, industry and other sectors. [68]

7.1 Current Challenges in Vaccinology

The COVID19 pandemic has focused minds as rarely before on the vital contribution of vaccines to modern life. In addition to issues related to antigen identification, vaccine adjuvants, vectors and formulations, knowledge is increasing on how a range of factors including age, sex, comorbidities, and the microbiome can impact on responses to vaccines. Even before the current SARS-CoV-2 pandemic, there have been a number of endemic and emerging viral pathogens for which vaccines still are urgently required. Norovirus, among the most common causes of outbreaks of acute gastroenteritis and sporadic acute diarrhoea episodes and the current status of vaccine development against the virus. The Arboviruses, Chikungunya, and Zika virus transmitted by Aedes mosquitoes are of increasing concern due to more widespread prevalence globally.

In addition to emerging pathogen threats for which no vaccines currently exist, antimicrobial resistance is a global emergency "In terms of magnitude, the economic impact of AMR is estimated to be comparable to thatof climate global change in 2030.

8. COVID 19 VACCINE

World Health Organization (WHO's) official definition of COVID-19 is that it is a viral disease caused by a new coronavirus. It was first reported on the 31st of December 2019 in the Wuhan Province of China. First recognized in the mid-1960s, COVID-19 belongs to a larger family of respiratory viruses called Coronaviridae and affects both humans and animals and are also known to cause severe respiratory infections such as severe

acute respiratory syndrome (SARS-CoV), middle east respiratory syndrome (MERS-CoV), and now globally famous novel coronavirus severe acute respiratory syndrome (SARS-Cov-2) and the disease is named as COVID-19 by WHO. As of 1 May 2021, there have been 152 661 445 confirmed cases of COVID-19 and 3 202 256 deaths globally.

The disease infects the upper respiratory and gastrointestinal tract of birds and mammals. Owing to its slow mutation, the virus poses a treatment and control challenge. It manifests anywhere between 2 and 14 days of infection with the virus prevailing even after 27 days in some cases and has an average incubation period of
5.2 days. The disease has an average mortality duration of 6-24 days depending on prevailing clinical conditions of patients, their health, and age as well. Common infection symptoms include respiratory complications, high fever, dry cough, sore throat, sneezing, muscle pain, and fatigue.

The emergence of the pandemic led to the race to discover a vaccine to achieve herd immunity and curtail the damaging effects of COVID-19. On 31 December 2020, the Pfizer COVID-19 vaccine (BNT162b2) was issued for emergency use listing by WHO. This was followed by the AstraZeneca/Oxford COVID-19 vaccine, manufactured by the Serum Institute of India and SKBio on 15 February 2021, and most recently, on 12 March 2021, the Ad26.COV2.S, developed by Janssen (Johnson & Johnson) and Moderna on 30 April [69].

8.1 Types of COVID-19 vaccines

There are 138 vaccine candidates (among them, 21 are approved worldwide for emergency use) in the pipeline for COVID-19 as of 13 August 2021, and their mode of action relies on the immune response to its integral parts (DNA, RNA, or protein) [70,71]. The spike proteins (S protein) found on the surface of the SARS-CoV- 2 is the central antigenic phenomenon by which the virus particle initiates its pathogenesis [72]. There are mainly five types of vaccine candidate developed and being used for vaccination, including the whole virus (live attenuated and inactivated), viral vector (replicating and non-replicating), protein subunit, nucleic acid (DNA and RNA), and virus-like particles (VLPs) vaccines.

8.1.1 COVID-19 inactivated vaccines –

Inactivated vaccines are produced by inactivating the in vitro cultured viruses using chemical reagents. The vaccine can maintain the integrity of virus particles as immunogens [73,74]. The seventh-generation virus, BJ- P-0207, was selected as the original strain of the COVID-19 inactivated vaccine and then β-propiolactone was used to inactivate the virus. An advantage of inactivated vaccines is using the entire virus as an immunogen. Compared with vaccines based on the SARS-CoV2 S protein or partial protein fragments, such as RBD, inactivated vaccines can induce a wider range of antibodies against more epitopes [75,76].

8.1.2 COVID-19 live attenuated vaccines-

Live attenuated vaccines are based on the virus obtained by reverse genetics or adaptation to reduce virulence and are used as non-pathogenic or weakly pathogenic antigens. Currently, the main manufacturing processes include codon pair deoptimization (CPD) and virulence gene knockout. It is reported that the CPD-based methods to modify SARS-CoV-2 genes genetically. In their studies, amino acid (aa) 283 deletion was introduced into the S protein, and the furin site was also deleted to attenuate the virulence of the virus but retain its replication ability [77,78].

8.1.3 COVID-19 Viral vector vaccine-

Viral vector vaccines use the host cells' translation machinery to produce antigens rather than having antigens by themselves. In this regard, modified viruses (vector) are used to deliver antigen encoding genes; in the caseof SARS-CoV-2, the gene encodes the surface spike proteins found on the virus is delivered into human cells by other modified viruses. There are two main types of them, such as replicating and non-replicating viral vector vaccines. After cell entry, replicating viral vector vaccines produce whole viral particles in the host cells and generate the vaccine antigen (SARS-CoV-2 spike protein). On the contrary, non-replicating viral vector vaccines do not produce whole virus particles in the host cells but could generate only the vaccine antigen. Currently available viral vector vaccines for SARS-CoV-2 are mainly non-replicating types [79].

8.1.4 COVID-19 protein subunit vaccine –

The protein subunit vaccines contain purified antigenic parts of the desired virus rather than a whole virus to trigger an immune response. There are mainly two types of them such as polysaccharide and conjugate vaccines. The polysaccharide vaccines contain polysaccharides from the viral cell wall, and the conjugate subunit vaccines tie on a polysaccharide chain with a carrier protein to boost the immune response [80].

8.1.5 COVID-19 DNA vaccines –

DNA vaccines are based on viral antigens encoded

by a recombinant plasmid. Viral proteins or polypeptides are produced by transcription and translation processes in host cells. d the DNA encoding SARS CoV-2 S protein into the pWRG skeleton plasmid by cloning the gene with optimized human codons, and this skeletonplasmid was used to produce a DNA vaccine against hantavirus [81,82]. There is no COVID-19 DNA vaccineauthorized by the WHO for emergency use.

8.1.6 COVID-19 mRNA vaccines –

mRNA vaccines are based on mRNA encapsulated by vectors (usually lipid nanoparticles), viral proteins, or polypeptides produced during the translation process in the host cells. The mechanism of mRNA vaccine- induced immunity is similar to that of the DNA vaccines. Both BNT162b1 and BNT162b2 vaccines transmit the genetic information of the antigen rather than the antigen itself, so they only need to synthesize the corresponding RNA of viral proteins, improving the production speed. In addition, mRNA vaccines can induce strong Th1 cell responses and GC B-cell responses and simultaneously produce long-lived plasma cells and memory cells, continuously eliciting SARS-CoV-2 neutralizing antibodies [83,84,85].

8.1.7 COVID-19 VLP vaccines –

The virus-like particles (VLPs) vaccines have protein multimers imitating the constituents of the original virus, which have no genetic material and thus are non-infectious. These synthetic particles can consolidate more than one type of protein responsible for forming protein chimeras known as cVLPs. VLPs stimulate B and T cell mediated immune responses by antigen-presenting cells. The particles also produce CD8 T cell responses, which facilitate the destruction of the viruses. The immune system recognizes VLPs as original viruses; thus, they can help boost immune responses [86,87,88]. VLP vaccines do not contain viral genomes, and plant- based VLP vaccines have the potential of oral delivery vaccines [89].

8.2 Hopes and challenges

At this moment, the Delta and Alpha variants of SARS CoV-2 are a matter of discussion worldwide for their profound infectivity. The vaccines we are using now were designed based on the earlier variants of SARS- CoV2, but scientists believe they should still work maybe with less effectiveness. However, studies data suggest that the BNT162b2 vaccine is effective against the new variants, although slightly less efficiently. Theefficacy of the ChAdOx1 nCoV-19 vaccine against the Beta variant is not up to the mark but gives sound protection against the Alpha variant. Moreover, the mRNA-1273 vaccine showed more effectiveness against the Beta variant with a weaker and shorter-lived immune response [90,91]. More vaccines are getting approval with time, and governments and other organizations should take proper initiatives to produce required vaccine doses. Some issues have already arisen, including failure in delivery within the promised date, supply chain breakdown, and substantial global inequality in vaccine access, which is termed ‘‘vaccine apartheid’’ (50-40). Conversely, though COVID-19 vaccines are becoming available day by day, different studies reported that many people are in dilemma whether they and their family members should take the vaccines or not. In this era of social media, different kinds of fake news are reported related to the vaccines’ safety, and this news is spreading hastily, which is mainly responsible for the vaccine hesitation and anti-vax movement among the people [92].

9. SOME CURRENT ISSUES IN VACCINOLOGY

One of the most important aspects of vaccinology in the 21st century is the extension of the target population by the development of new vaccines against emerging infections, tumors, and chronic diseases. Ultimately, the goal of modern vaccination may be expressed as to prevent or to cure as many diseases with vaccination as possible. Another focus is to improve the efficacy and safety of vaccines even further beyond the overwhelming successes of vaccines in the past several centuries. The most important keyword from the efficacy viewpoint is ‘adjuvant’. Because they facilitate the immune response to vaccination in older people. Most of the currently licensed adjuvanted vaccine products target influenza [93].

Vaccine development faces a number of challenges, developing vaccines to combat current and future pathogens will require to overcome challenges and recent developments in genomic technologies may providethe solutions (94).

So, some of these barriers to vaccine development are :An incomplete understanding of how immunity develops.

a) Host and pathogen genetic variability.
b) Problems related to vaccine safety.
c) Environmental and geographic factors.

Understanding of how immunity develops	Host variability	Pathogen variability	Vaccine safety	Environmental and geographic factors
Poor immunogenicity	Inter-individual variability	Pathogen diversity	Adverse events	Poor nutrition
No correlates of protection	Non-responder populations	Hypervariable viruses	Vaccine hesitancy	Co-infection
Lack of animal models	Sex, age, race, ethnicity	Complex biology	Autoimmunity	Pollution

In response to the challenges posed by these barriers, improvements in genomic techniques, new vaccine- design methods, such as reverse vaccinology (which uses genetic sequence information to identify immunogenic antigens), have enabled the high-throughput screening of vaccine candidates with greater confidence in their safety profiles. The characteristics of vaccine recipients are also considered, and there is much focus on developing ways to personalize vaccination, which is termed 'vaccinomics' (which aims to understand genomic and systems-level data to elucidate the basis of inter-individual variations in immune responses) [95,96]. and structure-based vaccine design have been developed to take advantage of high- dimensional tools and techniques and generate novel data that can be leveraged to create new vaccine products[97,98]. In the past decade, new vaccines, including the licensed Meningococcus B vaccine, have been designed and developed using such genomics-based approaches [99,100].

10. FUTURE VACCINE DEVELOPMENT

To date the development of a new vaccine has been a long process that typically takes anywhere from 10 to 15 years. There are several important diseases for which new vaccines are needed to reduce morbidity and mortality globally. Major line of development of new vaccines is to combat hospital-acquired infections, particularly with antibiotic-resistant Gram-positive bacteria (such as Staphylococcus aureus) that are associated with wound infections and intravenous catheters and various Gram-negative organisms (such as Klebsiella spp. and Pseudomonas aeruginosa). Progress has been slow in this field and an important consideration will be targeting products to the at-risk patient groups before hospital admission or surgery [101]. Perhaps the largest area of growth for vaccine development is for older adults, with few products aimed specifically at this population currently. With the population of older adults set to increase substantially (the proportion of the population who are more than 60 years of age is expected to increase from 12% to 22% by 2050 [102], prevention of infection in this population should be a public health priority.

11. CONCLUSION:

Immunization protects populations from diseases that previously claimed the lives of millions of individuals each year, mostly children. Despite the outstanding success of vaccination in protecting the health of our children, there are important knowledge gaps and challenges to be addressed. An incomplete understanding of immune mechanisms of protection and the lack of solutions to overcome antigenic variability have hampered the design of effective vaccines against major diseases such as HIV/AIDS and TB. Huge efforts have resultedin the licensure of a partially effective vaccine against malaria, but more effective vaccines will be needed to defeat this disease. Moreover, it is becoming clear that variation in host response is an important factor to take into account. New technologies and analytical methods will aid the delineation of the complex immune mechanisms involved, and this knowledge will be important to design effective vaccines for the future. There are still many infectious diseases and other diseases (e.g., cancer) against which no effective vaccine exists. Although modern vaccines – like other biopharmaceuticals – are expensive, calculations may indicate cost-effectiveness for vaccination against many of these diseases. In addition, the growing resistance to the existing arsenal of antibiotics increases the need to develop vaccines against common bacterial infections. It is expectedthat novel vaccines against

several of these diseases will become available.

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