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ADVANCEMENT, EXPLORATION AND OUTLOOK OF THE BURGEONED COVID 19 VACCINE – AN OVERARCHING RECAPITULATION

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ABSTRACT: The new Covid-19 virus has reported deaths of around 1 million within about half a year. It has also led to high financial and social crises worldwide. Recent research has been performed to identify suitable treatment procedures. Steps have been taken to develop complicated, costly, and time-consuming vaccines. Viruses are highly potential to develop into perilous diseases. Over 165 vaccines were developed, and 45 are under clinical trials. The cost to manufacture and internationally deploy an efficacious COVID-19 vaccine will be vast, and the process will be at risk of politicization. Even though few countries may deploy COVID-19 vaccines based on the safety and immunogenicity information alone, vaccine development aims to obtain direct proof of vaccine efficacy for protection against SARS-CoV-2 infection. In this review, we have focused on the latest developments in COVID-19 and have sought to resolve the process and present development efforts of the vaccine in progress. Furthermore focused on the potential strategies in optimizing the COVID-19 vaccine.

INTRODUCTION: A novel SARS-CoV-2 inflicting COVID-19 has spilled over and disseminated quickly across the globe within the first half of 2020, inflicting a worldwide pandemic. The medical and scientific people are mounting severe actions to limit these pandemics and succeeding waves of viral spread through the development of preventative COVID-19 vaccines [1]. Infrastructure ready that could churn out vaccines for use in the global population quickly and effectively, potentially stopping an emerging virus in its tracks [2].

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From the cost, production, safety and efficacy, many factors are in play that decide how helpful a vaccine under development is. More than that, vaccines generally take a lot of time to develop, passing through large-scale clinical trials, meeting safety standards and getting necessary approvals before being pushed out for public use [3].

Significant measures are being implemented to develop a safe and effective COVID-19 vaccine. Various types of vaccines are previously enrolled in clinical testing, like vector, inactivated, and nucleic acid-based vaccines [4]. This article focuses on the latest developments in COVID-19 and has tried to address the process and current development efforts of vaccine in progress with potential strategies adopted to optimize the vaccine.

Vaccine: An Overview: Developing a new vaccine is a complicated and time-consuming process; they

vary from developing standard medicines. Usually, the period for the development of a new vaccine is 12-15 years [5]. The novel coronavirus is an enveloped, single-stranded positive-sense RNA virus with much of the complexity on the surface and within the genome. The genome is quite simple and has no difficulty. The way it assaults and gathers immune cells to possibly activate the entire immune reaction to harm the person's own body tissue. **Fig. 1** Envelope (E), membrane (M), nucleocapsid (N) and spike (S) are its four structural proteins while its genome comprises 29,891 nucleotides, which encode the 12 putative open reading frames responsible for the synthesis of viral structural and non-structural proteins **Table 1** [6-9]. The name coronavirus is derived from Latin corona, meaning crown or wreath [10]. Due to the characteristic appearance of virions by electron microscopy on the surface of the virus, creating an image reminiscent of a crown or of a solar corona, coronavirus has acquired its name. SARS-CoV-2 viruses evolved into two major types (L and S types) with the S type being the more ancient version of SARS-CoV-2. L type was shown to be more aggressive than the S type and more prevalent in the early stages of the outbreak in Wuhan, the frequency of the L type decreased after early January 2020 possibly due to human intervention [11, 12].

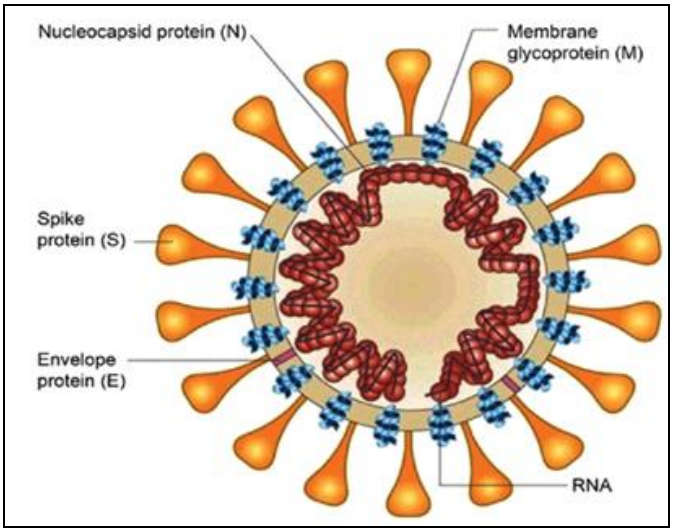

FIG. 1: STRUCTURE OF CORONAVIRUS

TABLE 1: CORONAVIRUS STRUCTURAL PROTEIN AND ITS FUNCTION

Structural protein	Function of Protein
Envelope protein (E)	Interacts with M to form envelope (E)
Membrane protein (M)	Central Organizer of CoV assembly and determine the shape of the viral envelope
Nucleocapsid protein (N)	Binds with the RNA genome to make up nucleocapsid
Spike protein (S)	Helps in entry to host cell by binding with host cell receptors
Non-structural protein	Implicated in inhibiting host mRNA synthesis, nuclear export of viral mRNA, and translation of viral proteins

Current Sars-Cov-2 Vaccine Platforms: Many vaccine development platforms against the coronavirus, including viral vectors, live attenuated virus, subunit vaccines, inactivated virus, protein vaccines and recombinant DNA [13, 14].

Live Attenuated Vaccines: Utilize an altered live SARS-CoV-2 virus with less virulence. This method can induce a short and robust immune reaction, however may be risky for immune suppressed people.

Viral-Vector-Based Vaccines: Use of a viral backbone to initiate a SARS-CoV-2 gene into the host cell. This method can improve immune-genericity without an adjuvant to assist a robust cytotoxic response to remove infected virus cells.

Recombinant Protein-Based Vaccines: Utilization of SARS-CoV-2 proteins to provoke an immune reaction in the host cell. Generally utilized in fusion with an adjuvant for enhanced immunogenicity.

DNA Vaccines: Usage of plasmid DNA to explicit antigens of SARS-CoV-2 for effective implementation into the host. As of now, there are no authorized DNA vaccines for humans.

mRNA Vaccines: Encodes a COVID antigen and utilizes a system including a liposome for transferring into the host cell. There are presently no authorized mRNA vaccines for humans.

Virus-Like Particles (VLPs): Virus-like particles made by the viral structural constituent with self-assembling nature into the nanostructure. VLPs mimics the structure of the complete virus. VLPs may trigger the innate immune response through pathogen recognition receptors. VLPs depict

progressed subunit vaccine with greater immunogenicity because it includes the virus's structural protein. VLPs must have a non-replicative and non-infectious property due to loss in the genomic components. VLPs allow the development of safer and cheaper vaccine candidates [15].

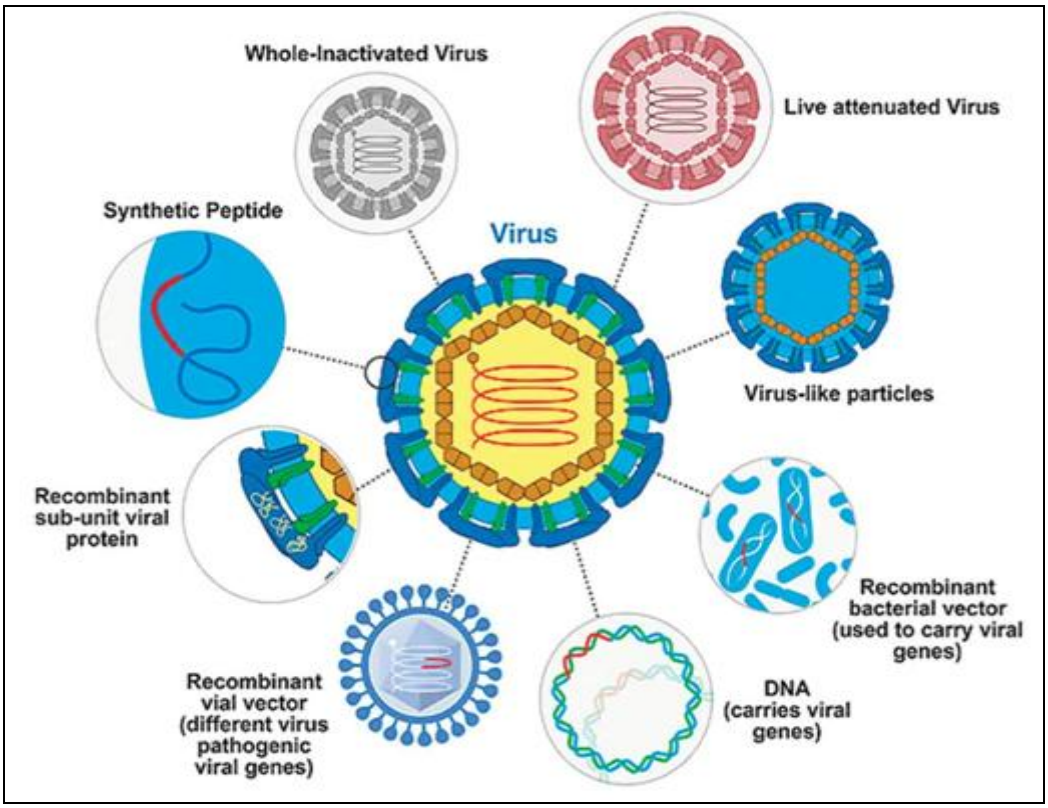

FIG. 2: REPRESENTS THE STRATEGY OF VACCINE TYPES FOR VACCINE DEVELOPMENT

The Vaccine Testing Process:
The Vaccine Development Process consists of [16]:

- Exploratory stage
- Pre-clinical trial
- Clinical trial
- Regulatory review and approval process
- Manufacturing of vaccine
- Quality control (QC)

A Clinical trial involves a three-step process. Fewer individuals receive the trial vaccine in the Phase I clinical trial. During Phase II clinical trial, the testing is extended and vaccines are administered to individuals with characteristics of physical health condition, and age is equal for whom the current vaccine is intended. In the Phase III clinical trial, the new vaccine is administered to thousands of individuals and assessment of safety and efficacy. Numerous vaccines enter into the Phase IV formal study, continuing testing later the vaccine is approved and licensed [17].

Pre-clinical Testing: Vaccine is administered to monkeys, rats and mice to discern either it has to generate an immune response or not.

Phase I: Vaccine are given to a very limited number of individuals to test their safety and dosage in addition, to verify whether the vaccine produces immunity to the system.

Phase II: Vaccine are administered to hundreds of individuals to confirm whether the vaccine acts diversely in them. These Phase II trials additionally evaluate the vaccine's ability and safety to stimulate the immune system.

Phase III: Vaccines are administered to thousands of individuals to perceive how many of them infected, in relation to volunteers who received a placebo.

Phase III trials determine whether the vaccine protects against the coronavirus infection. Furthermore, Phase III trials reveal proof of comparatively rare side effects that can be lost in previous research [18].

Approval: Regulation bodies in each country evaluate the clinical trial results and determine whether to approve the vaccine. During the pandemic, a new vaccine might be eligible for emergency use authorization before receiving proper approval. The researchers regularly check the vaccine's safety and efficacy after the vaccine's approval.

Combined Phases: An alternative approach to expedite the development of new vaccines in combined phases. Few COVID-19 vaccines are presently in Phase 1/2 clinical trials [19].

Current Treatment Strategies for Covid-19: A summary of vaccine types, advantages, and disadvantages with examples is shown below in **Table 2** [20].

TABLE 2: VACCINE CLASSIFICATION

Type	Active Component	Advantage	Disadvantage	Vaccine Example
Live, attenuated	Pathogen responsible for replication	Lifetime protection, Strong and long-lasting immune response against disease.	Risk of disease	Tuberculosis, smallpox, MMR, yellow fever, chickenpox
Inactivated	Pathogen chemical or heat treated to prevent replication	No risk of disease	Lesser immune response.	Hepatitis A, Flu, Rabies, Polio
VLP	Outer coat of virus	No risk of disease	-	Cervical cancer, Hepatitis B, Malaria
Subunit (protein, conjugate, polysaccharide and toxoid)	Portions of a pathogen	No chance of disease	Booster shot usually required	HPV, meningococcal disease, whooping cough, diphtheria, Hepatitis B shingles, tetanus, pneumococcal disease
DNA vaccine	Expression or plasmid vector	Rapidly produce, no chance of disease	Lack of data	Veterinary medicine
Recombinant vector vaccine	Non-pathogenic bacteria or virus as a carrier of immunogen of interest	Reusable for different antigens, no chance of disease	Existing or development of immunity to vector	Not yet approved
mRNA vaccine	RNA that encodes a disease-specific pathogen protein	Rapidly produced, no chance of disease.	Effectiveness and side effects are unknown	Not yet approved

A summary of 11 COVID-19 vaccines are approved worldwide in **Table 1**. A summary of 42 Vaccine candidates under clinical development were given in **Table 2** with type, stage, developers, and Clinical trial registrations updated from COVID-19 tracker [21, 22].

Potential Strategies to Optimize Vaccines:

1. Antigen design
2. Adjuvants
3. Several promising delivery approaches

Antigen design: The identity of immunodominant T- and B-cell epitopes provokes and protects immune system responses within the host cell, which is important for powerful vaccine design. COVID-19 strains shared 79% identification with SARS-CoV on the complete genome level, numerous latest researches predicting a sequence of T-cell and B-cell epitopes from the SARS-CoV-2, primarily depend on the scientifically determined SARS-CoV epitopes [23].

Many of the epitopes are similar to that of the SARS-CoV-2 proteins like T-cell epitopes, six discontinuous B epitopes and forty-nine liner B epitopes and most of the epitopes had been acquired from the N- or S protein.[24] Comparing the epitopes detected through homology with the epitopes detected by epitope predictions, identify twelve SARS-CoV-2 T-cell epitopes, 2 confor-mational B epitope and 3 linear B-cell epitopes as a

target for SARS-CoV-2 immune recognition [25]. By the in-depth immunoinformatics method, identified twenty-five immunodominant epitopes from SARS-CoV-2 proteins, eight epitopes within the N protein, four epitopes within the M protein and thirteen epitopes in the S protein [26]. Optimally designed vaccines goal to maximize immunogenicity to protein domain that plays an important function in protective immunity even as excluding unnecessary protein domain which could purpose autoimmunity or maybe greater infectivity [27]. The post-fusion confirmation might also reveal the non-neutralizing epitopes and disturb the host cell immunity [28].

Consequently, reducing the range of the post-fusion S2 trimers might improve the efficacy of vaccines, which mandates further investigation [29]. Moreover, structural antigen design carries out a huge function in vaccine efficacy. The S protein alternative denoted as Hexa Proembeds 4 useful proline substitutes and two proline substitutes within the S2 subunit, therefore increasing protein yields and stability [30].

Adjuvants: Another manner of enhancing coronavirus vaccines is via adding adjuvants to the vaccine formulations. Adjuvants can enhance the immunity of the co-injected vaccine antigens, polarize the immune system reaction against the suitable reaction, and enhance the human immune response. Numerous adjuvants are used to develop vaccines, like MF59, aluminum, and the adjuvant system series [31].

Alum-based adjuvants have been the primary adjuvants utilized in licensed human vaccines. Nevertheless, they are the most extensively used due to their wide-spectrum capacity to reinforce immune responses and their tremendous safety track record [32, 33]. In confined coronavirus vaccine research, it has been recommended that neutralizing antibodies towards the spike protein is probably mechanistically correlated with immune protection [34]. The emulsion adjuvants MF59 and AS03 have already been utilized in licensed human vaccines to enhance the immunogenicity of the antigens [35]. Compared with alum which lacks the functionality to mediate cell-mediated immunity [36], MF59 and AS03 can elicit greater balanced immunity, probably through enhancing antigen uptake, recruiting immune cells, and promoting the migration of activated antigen-presenting cells [37, 38]. Toll-like receptors (TLRs), a class of pattern-recognition receptors, are essential to pathogen recognition. This allows for the fast activation of innate immunity and powerful adaptive immunity. TLR agonists have been substantially studied as vaccine adjuvants [39]. CpG, Poly I: C, glucopyranosyl lipid A (GLA) and resiquimod (R848) are agonists for TLR9, TLR3, TLR4 and TLR7/8, respectively. These adjuvants have been evaluated in candidate vaccines for SARS-CoV [40].

Several Promising Delivery Approaches: To ensure vaccines activate responses, this is essential to engage powerful strategies to supply antigens to the host. A gene gun is a sensible approach to providing DNA and RNA [41]. Preceding research described the transport of DNA to DCs through gene gun towards the viral infection [42]. Furthermore, electroporation expanded the self-amplifying RNA and cellular intake of DNA, inflicting elevated immune response [43].

Dendritic cells are skilled APCs of the immune response system and vaccines targeting the dendritic cells may support antigen illustration and enhance the immune system responses [44]. The Dendritic cell target on the protein that especially bound to the surface molecule. This should provide the ability to improve the immunogenicity and the antiviral property of DNA vaccines [45, 46].

In addition to the preceding techniques, potential transport will be carried out by administering the mixture of nucleic acids with compounds including lipids and polymers. Over the fast few years, LNPs have become an attractive transport approach in the vaccine development process. The LNPs commonly consist of 4 lipid components [47]. The ionizable amino lipid substantially benefits the transport of encapsulated nucleic acid and encourages its endosomal discharge later LNP endocytosis [48].

CONCLUSION: This review article is focused on the present vaccine strategies of numerous pathogenic viruses to enhance vaccine safety and efficacy towards SARS-CoV-2. Utilizing an appropriate transport system is important for vaccine efficacy. Deciding which approach

operates best based on several causes, including the types of COVID-19 vaccines and their administration routes. Moreover, adjuvants must be mixed with the numerous forms of vaccines to improve immunity; thereby, choosing suitable adjuvants is essential for developing COVID-19 vaccines. Up to now, various research had stated the immune reactions produced by SARS-CoV-2 vaccine candidates. Additional clinical trials might evaluate the new vaccines' safety and efficacy and find effective methods to optimize the vaccines.

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