ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 15, Issue 12, 2022

Online - 2455-3891
Print - 0974-2441

Review Article

COVID-19 VACCINES: TARGETS, PRE-CLINICAL STUDIES, MECHANISMS OF ACTION, ADRS, AND ROLLOUT IN INDIA – A JOURNEY SO FAR

DEVESH D GOSAVI, CHETA N SHINDE

Department of Pharmacology, Mahatma Gandhi Institute of Medical Sciences, Sewagram, Maharashtra, India. Email: chetashinde@gmail.com

Received: 28 July 2022, Revised and Accepted: 17 September 2022

ABSTRACT

Coronavirus disease 2019 pandemic has been posing a serious threat to global public health till date. This calls for the development of effective treatment protocols, and most importantly, vaccines against the pathogen. Keeping these requirements in mind, we have pooled together, across broad domains of research, accounts on the leading efforts in the development of various vaccine candidates. It is apparent from our review of various studies that the efficacy of seemingly different techniques applied together, collaborative efforts coupled with rapid, timely dissemination of results has been the key behind successful vaccine development. The availability of curated databases has also been of great advantage. Furthermore, we have summarized in this article, the side effects of the various vaccines. We hope that this review will appeal the researchers and students as well as recent entrants in these research domains and the various studies described herein will inspire and be helpful for the advancement of public health.

Keywords: COVID vaccines, Adverse effects of COVID vaccines.

 DOI: http://dx.doi.org/10.22159/ajpcr.2022v15i12.46003. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Coronavirus disease 2019 (COVID-19) pandemic has posed a serious threat to global public health. This outbreak has imposed a great challenge on global research community, government sectors, and various industries to develop therapies and diagnostic tools as well as vaccines against SARS CoV2. We expect this review article to provide a detailed account on the efforts in COVID-19 vaccine development and the journey of research and progress so far. Furthermore, various approaches for the development of vaccines and the current scenario worldwide as well as in India have been highlighted and key points from the previous studies have been summarized.

TARGETS FOR VACCINE DEVELOPMENT

Various innovative approaches were undertaken by researchers toward determining potential vaccine candidates to prevent COVID 19, few of them are discussed in this section.

A study was planned to determine the sequence variation, structural, and antigenic divergence of S glycoprotein, demonstrated novel Cytotoxic T-Lymphocytes (CTL) epitopes. This study by Kumar *et al*. revealed similar antigenic sites in both COVID-19 and SARS coronavirus thus suggesting the scope of SARS associated peptide-based vaccine for the prevention of COVID-19 [1].

NOVEL DECOY CELLULAR VACCINE STRATEGY [2] (FIG. 1)

Novel decoy cellular vaccine strategy (modifying cells to express viral markers to elicit protective immunity responses) has been chosen by Ji *et al.* [2] On the surface of K562 human myelogenous leukemia cells, engineered Spike-1 proteins were expressed. Introduction of expression constructs into the cellular genome allowing for stable expression of the transgene was done. The stable-modified K562 clones were selected and profiled for Spike-1 expression as well as overall immunogenic potency. Irradiated cells were formulated as vaccine product [2].

REVERSE VACCINOLOGY-*IN SILICO* STUDY

Bioinformatics approach was employed in another study to design and introduce a novel multi-epitope vaccine against 2019-nCoV. This vaccine candidate had the potential to trigger both CD4 and CD8 T-cell

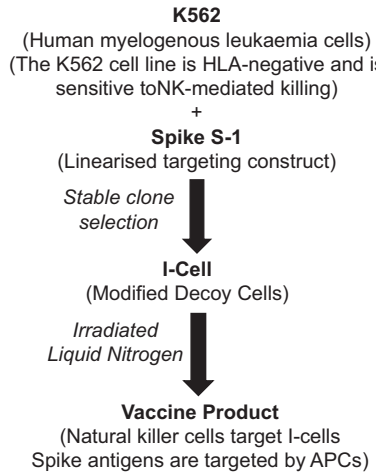

Fig. 1: Targeted expression of SARS-CoV-2 Spike immunogen and resulting I-cell vaccine candidate [2]. (Ji *et al*. Medicine in drug discovery 5 (2020) 100026)

immune responses and was investigated for its biological activities by *in-silico* evaluation [3].

For the prediction of the potential immunogenic B and T-cell epitopes, three known antigenic proteins (Nucleocapsid, ORF3a, and Membrane protein- NOM) from the virus were selected, analyzed and then validated using bioinformatic tools.

Based on this *in silico* analysis conducted by Enayatkhani *et al*. [3], a multi-epitope vaccine candidate (NOM) with five rich-epitopes domain was constructed including highly scored T and B-cell epitopes. The best 3D predicted model was applied for docking studies with Toll-like receptor 4 (TLR4) and HLA-A_11:01. Molecular dynamics (MD) simulation was then used to evaluate the stability of the designed fusion protein with TLR4 and HLA-A_11:01 receptors [3].

The computational method was employed for identification of potential cross protective epitope between COVID-19 virus and SARS virus in

another study. A highly similar epitope was thus identified between the 2019-nCoV and SARS virus, in the region of the binding site of the S proteins to the human angiotensin-converting enzyme 2 (ACE2) receptor, in this study by Qiu *et al*. [4].

RECEPTOR-BINDING DOMAIN (RBD) RECOMBINANT PROTEIN

Tai *et al*. [5] identified the RBD in SARS-CoV-2 S protein and found that the RBD protein bound strongly to human and bat ACE2 receptors. Appreciablygreater binding affinity to ACE2 receptor was exhibited by SARS-CoV-2 RBD than SARS-CoV RBD and could block the binding and, hence, attachment of SARS-CoV-2 RBD and SARS-CoV RBD to ACE2-expressing cells, thus inhibiting their infection to host cells. SARS-CoV RBD-specific antibodies could cross react with SARS-CoV-2 RBD protein, and SARS-CoV RBD-induced antisera could cross-neutralize SARS-CoV-2. Thus, suggesting the potential to develop SARS-CoV RBD-based vaccines for prevention of SARS-CoV-2 and SARS-CoV infection [5].

The similar approach has been advocated by Chen *et al*. [6] who considered RBD219- N1 (an yeast expressed potential vaccine candidate against SARS COV) as a heterologous vaccine against SARS-CoV-2 [6].

COVIDep

First-of-its-kind web-based platform, COVIDep has been developed by Enayatkhani *et al*. [3]. This platform pools genetic data for SARS-CoV-2 and immunological data for the 2003 SARS virus, to identify B-cell and T-cell epitopes to serve as vaccine target recommendations for SARS-CoV-2 [7].

IMMUNOINFORMATICS

A prolific approach of immunoinformatics was taken in a study by Barua and Bose [8]. They identified significant CTL and B cell epitopes in the 2019-nCoV surface glycoprotein. Using MD simulations, interactions between identified CTL epitopes and their corresponding major histocompatibility complex (MHC) Class I supertype representatives were studied. They identified five CTL epitopes, three sequential B cell epitopes, and five discontinuous B cell epitopes in the viral surface glycoprotein. Furthermore, it was observed during simulations that the CTL epitopes were binding MHC Class I peptide – binding grooves through multiple contacts. This binding was through continuous hydrogen bonds and salt bridge anchors, indicating their potential in generating immune responses [8].

ANTIBODY DEPENDENT ENHANCEMENT

The phenomenon of antibody dependent enhancement (ADE) has been studied in a review by Iwasaki and Yang [9]. ADE occurs when therapeutically administered antibodies exacerbate the existing pathology by enabling infection of immune cells by the invading virus, promoting inflammation, down regulation of anti-inflammatory factors such as IL-10, and tissue injury caused due to anomalous activation of the immune system. The dangers associated with hyper-inflammation and immune dysregulation in the context of SARS-CoV-2 infections have been addressed in details in the same review.

The authors outline several possible contributing factors toward ADE, including antibody specificity, choice of target epitope, affinity, subtype (IgM or IgG), dosage, and patient status [9].

An approach based on comparing the human and viral proteomes to search for pentapeptide sequences unique to the SARS-CoV-2 was proposed by Lucchese [10], as these would be expected to have high immunogenicity as well as specificity [10].

PRE-CLINICAL STUDIES, SARS-COV-2 INFECTION IN ANIMAL MODELS VERSUS IN HUMANS [11]

An international panel was assembled by the World Health Organization (WHO) in February 2020 to develop animal models for COVID-19 to accelerate the testing of vaccines and therapeutic agents.

The current literature on animal models for COVID as well as studies generated by the WHO-COM group, summarized as follows, may serve to facilitate further preclinical analysis of vaccines and therapeutic agents.

The experiments inferred that infection with SARS CoV2 in various animal models were characterized by fever, nasal discharge in humans, ferrets, and hamsters additionally labored breathing in hamsters.

Virus replication was predominant in both upper and lower respiratory tract in mice, ferrets, and non-human primates but only in the upper respiratory tract in mink, cats, and bats.

Pneumonia with bilateral lung involvement manifested in humans, hamsters, and non-human primates whereas ground glass opacities were evident in humans and hamsters. Signs like focal edema and inflammation were observed in humans and hamsters along with ferrets. Acute Respiratory Distress Syndrome was apparent only in humans.

Transmission, as the studies have revealed, was seen only among humans, hamsters, ferrets, cats, and bats. Seroconversion, neutralization of antibody titers, t cell immunity, and pro-inflammatory cytokines-mediated response were seen in humans, mice, and non-human primates. Ferrets demonstrated the same immune responses except pro-inflammatory cytokines release. Hamsters responded with seroconversion and neutralization of antibodies. Only seroconversion was seen in bats.

PRE-CLINICAL ALTERNATIVES

The existing cell culture and animal studies have been facing many limitations. These limitations have served as stimulus for the development of alternative cell-based *in vitro* models that better mimic the complex structures and functions of living organs. Considerable advances have been made in this area as a result of the application of microsystem engineering for studies with cultured cells [12].

Recent developments such as organ on chips may complement, or even represent alternatives to, some animal models and cell culture systems. They are efficient in providing greater physiological relevance and mimicry of human organ-specific responses [13-15]. It has been postulated that organ on chip technology could help to reduce the high failure rate in current drug and vaccine development where many drugs and vaccines that are found to be safe and effective in laboratory animals, fail when they enter human clinical trials [16,17]. Furthermore, successful organ chips could thus help to reverse the increasing cost and attrition rates in clinical trials.

The organs-on-chips are potential alternatives to conventional cell culture models and animal testing for pharmaceutical and toxicology applications. In the "Organs-on-Chips", living cells are cultured within microfluidic devices that have been micro engineered to reconstitute tissue arrangements observed in living organs to study physiology in an organ-specific context and to develop specialized *in vitro* disease models [12].

Lung organoids are derived from embryonic and induced pluripotent stem cells. These contain both lung epithelium and mesoderm and, together with cell lines derived from human fetal lung, have the potential to provide important information about human lung development as well as COVID-19 disease [18].

When infection with SARS-CoV-2 was induced, micro-engineered organs-on-chips and lung organoids showed the key hallmarks of the cytopathology and inflammatory responses in human airways. They have served to facilitate the study of human disease pathogenesis, test candidate COVID-19 therapeutic agents, vaccines, and expedite drug repurposing [19].

The exponential rise in the number of cases of COVID 19 warranted urgent measures to limit spread of the same. In the record-breaking short span of time, therapeutic trials were conducted all over the world so in India. Hence, we discuss here two important vaccines in Indian context.

COVAXIN AND COVISHIELD [20]

Covaxin

Covaxin was developed by Bharat Biotech, India, and the Indian Council of Medical Research. This purified inactivated whole virion vaccine is developed by β-propiolactone inactivation of Indian strain of the novel coronavirus. Covaxin was isolated by the Indian National Institute of Virology. It was propagated in Vero CCL-81 cells.

Composition of Covaxin includes inactivated Coronavirus, Aluminium Hydroxide Gel, TLR 7/8 Agonist, 2 Phenoxyethanol, and Phosphate Buffered Saline [21].

There are two types of adjuvants used in Covaxin thus the two versions of the vaccine. An alum-adjuvanted version of the vaccine candidate was found to significantly reduce or nullify- Viral loads and bronchoalveolar affection (in rhesus macaques challenged with SARS-CoV-2; 14 days after receiving the second dose of the vaccine candidate). This finding was confirmed by viral load measurement in bronchoalveolar lavage fluid, nasal swab, throat swab, and lung tissues at 7-day post-infection in the immunized animals.

Alum mainly induces NALP3-inflammasome, while imidazoquinolinone is a TLR 7 and 8 agonist. Significant potentiation of the immunogenicity of the vaccine was found with the combination of alum and imidazoquinolinone.

On December 15, a preprint of a Phase 1 clinical trial of BBV152 was released. Adverse effects were found to be mild or moderate with an incidence rate between 10 and 20% and pain at the injection site being the most common reported event.

To evaluate efficacy, safety and immunogenicity of this candidate a Phase 3 randomized, double-blind, and clinical study began on October 23 in India.

On January 3, 2021, India granted an emergency use authorization (EUA) to BBV152 although participants were still recruited for the candidates' Phase 3 safety and efficacy trials.

AZD1222 (AstraZeneca/Oxford University) [22,23].

Oxford University and AstraZeneca were one of the first to begin clinical trials with its viral vectored vaccine – CoviShield. They were the only one to use debilitated chimpanzee adenovirus (ChAdOx1). Thus, they evaded the issue of pre-existing immunity against the vector as very few -if any- humans would have had a previous contact with a simian virus.

The ChAdOx1 vector wasso engineered that it codifies for the wild-type SARS-CoV-2 Spike protein. Rhesus macaques were immunized with AZD1222 and then challenged with SARS-CoV-2 strain nCoV-WA1-2020. Results showed both cellular and humoral responses that reduced viral load in the lower respiratory tract of the vaccinated animal.

Composition of CoviShield includes inactivated adenovirus with segments of Coronavirus, Aluminum Hydroxide Gel, L Histidine, L-Histidine Hydrochloride Monohydrate, Magnesium Chloride Hexahydrate, Polysorbate 80, Ethanol, Sucrose, Sodium Chloride, and Disodium Edetate Dihydrate (EDTA).

On July 20, 2020, the first results of a Phase 1 and 2 were reported. It was a single-blinded, randomized, multicenter and control study and it included 1090 healthy adult volunteers aged 18–55 years.

Phase 3 efficacy and safety trials with the two-dose regimen are being carried out in more than 30,000 individuals in the U.S., India, Brazil, Russia, and South Africa. The Phase 3 study was focused on COVID-19 prevention and reactogenicity and tolerance profile of the candidate.

The safety profile of the vaccine was found to be very good with a few and less intense adverse effects. These few percentages of adverse effects were frequent in older population with inadequate doses and these events declined after the second dose.

AstraZeneca supported by Oxford University, submitted the complete interim Phase 3 safety and efficacy to several regulators including the UK, European medicines agency (EMA), and Brazil for revision and emergency use approval of their candidate.

India granted an EUA to AZD1222 on January 3, 2021, while on January 4, the first vaccinations with AZD1222 began at Oxford's Churchill Hospital.

INDIA: JOURNEY SO FAR

On January 16, 2021, India began administration of COVID-19 vaccines. India has administered over 1.57 billion doses overall, as of January 16, 2022, including first, second and precautionary (booster) doses of the currently approved vaccines [21,24]. In India, 89% of the eligible population has received at least one shot, and 64% of the eligible population is fully vaccinated [25].

CoviShield and Covaxin were initially approved in India. Followed by approval of the SputnikV (manufactured under license by Dr. Reddy's Laboratories, with additional production from Serum Institute of India) in September [26,27], Moderna vaccines, Johnson and Johnson vaccine, and ZyCoV-D (a vaccine locally developed by Zydus Cadila) (Moderna, Johnson and Johnson, and Zydus Cadila are not yet under distribution – Zydus Cadila is the only vaccine which has been approved for children above 12 years) and other vaccine candidates undergoing local clinical trials.

On January 01, 2021, emergency use of CoviShield was approved by the Drug Controller General of India (DCGI) [28-30]. On January 2, the DCGI also granted an interim EUA to Covaxin [31]. As the vaccine had not then completed Phase 3 clinical trials, this approval was met with some concern [32]. Due to this status, those receiving Covaxin were required to sign a consent form [33], while some states chose to relegate Covaxin to a "buffer stock" and primarily distribute CoviShield.

India started giving booster shots from January 10, 2022, to health and frontline workers and those over 60 with comorbidities or other health problems.

Vaccinations began for children between 15 and 18 years from January 3, 2022. Among healthcare and frontline workers and those aged 60 and above with comorbidities, prioritization, and sequencing is based on completion of 9 months or 39 weeks from the date of the second dose as of January 10, 2022, the government said in its guidelines.

Covaxin is the only COVID vaccine available for children between 15 and 18 [34].

SCENARIO IN THE WORLD ACCORDING TO THE WHO

Forty-four vaccines are in Phase 1, 64 vaccines in Phase 2, 65 vaccines in Phase 3, and 33 vaccines have been approved so far whereas eight vaccines no longer progressing (Tables 1 and 2, Fig. 2)

SIDE EFFECTS OF VARIOUS VACCINES [41-43]

According to the Centres for Disease Control and Prevention (CDC) [44] and the WHO [45], common side effects of a COVID-19 vaccine include:

- A fever
- Fatigue

Table 1: WHO approved vaccines in use [35]

S. No.	Vaccine	Manufactured by	Type
1	Novavax: NVX-CoV2373	The serum Institute of India	Protein subunit
2	Covovax (Novavax formulation)	The serum Institute of India	Protein subunit
3	Moderna: mRNA-1273 (Spikevax)	Takeda (TAK-919)	RNA
4	Pfizer/BioNTech: BNT162b2 (Tozinameran, Comirnaty)	The German biotechnology company BioNTech	RNA
5	Janssen (Johnson and Johnson): Ad26.COV2. S (Ad26COVS1, JNJ-78436735)	Janssen vaccines in Leiden, Netherlands, and its Belgian parent company Janssen pharmaceuticals, a subsidiary of American company Johnson and Johnson.	Non-replicating viral vector
6	Oxford/AstraZeneca: AZD1222 (Vaxzervria, ChAdO×1 nCoV-19)	The oxford university, UK and British-Swedish company Astrazeneca	Non-replicating viral vector
7	CoviShield (Oxford/AstraZeneca formulation)	Serum Institute of India	Non-replicating viral vector
8	Covaxin (BBV152)	Bharat biotech	Inactivated
9	BBIBP-CorV (Vero Cells, Covilo)	Sinopharm (Beijing)	Inactivated
10	Sinovac: CoronaVac	Sinovac (Beijing)	Inactivated

Table 2: ICMR approved vaccines for use in INDIA [35-37]

S. No.	Vaccine	Manufactured by	Type	Schedule
1	Covaxin	The Serum Institute of India	Inactivated	2 Doses IM 4 weeks apart
2	Covishield	The Serum Institute of India	Non-replicating viral vector	2 Doses IM 84 days apart
3	ZyCoV-D	Cadila Healthcare, India	DNA	3 Doses 28 days apart
4	Sputnik V	Dr. Reddy's laboratories Limited India, Gamaleya Research Institute, Russia	Viral vector	The first dose (based on Ad26) is administered on the 1st day, and the second dose (based on Ad5)- on the 21st day to boost immune response. Both doses are administered into the deltoid muscle.
5	Biological E's novel CoViD-19 vaccine (Corbevax, BECOV2D)	Texas children's hospital center for vaccine development and Baylor college of medicine in Houston, Texas and Dynavax technologies based in Emeryville California. it is licensed to Indian biopharmaceutical firm biological e. limited (Bioe) for development and production	Protein subunit	intramuscularly in a two-dose schedule (0, 28D)
6	BBV154 - intranasal vaccine	Bharat biotech	Adenoviral vector based	
7	COVOVAX [SARS-CoV-2 recombinant spike protein nanoparticle vaccine (SARS-CoV-2 rS) with Matrix-M1adjuvant]	Serum Institute of India Private Limited	Protein based	
8	mRNA based vaccine (HGCO19)	Gennova Biopharmaceuticals Limited, Pune	mRNA	
9	Janssen (Johnson and Johnson): Ad26.COV2. S (Ad26COVS1, JNJ-78436735)	Janssen vaccines in Leiden, Netherlands, and its Belgian parent company Janssen pharmaceuticals, a subsidiary of American company Johnson and Johnson.	Non-replicating viral vector	Single dose emergency

- Headaches
- Body aches
- Chills
- Nausea.

Side effects experienced around the injection site includes swelling, pain, redness, an itchy rash, and other mild forms of irritation.

There have been new concerns, recently, about serious side effects of COVID-19 vaccines. There is currently not enough conclusive evidence to link these effects to specific vaccines thus these effects may be coincidental. Precautionary measures have been taken by regulatory agencies to investigate these safety concerns.

PFIZER-BIONTECH AND MODERNA

With the Pfizer-BioNTech and Moderna vaccines people have reported similar, common side effects as mentioned above after the second doses of each.

FDA states that few people experienced myocarditis or pericarditis after their vaccine, symptoms began within a few days following receipt of the second dose.

JANSSEN (JOHNSON AND JOHNSON)

The Janssen vaccine has also been found to cause common vaccine side effects.

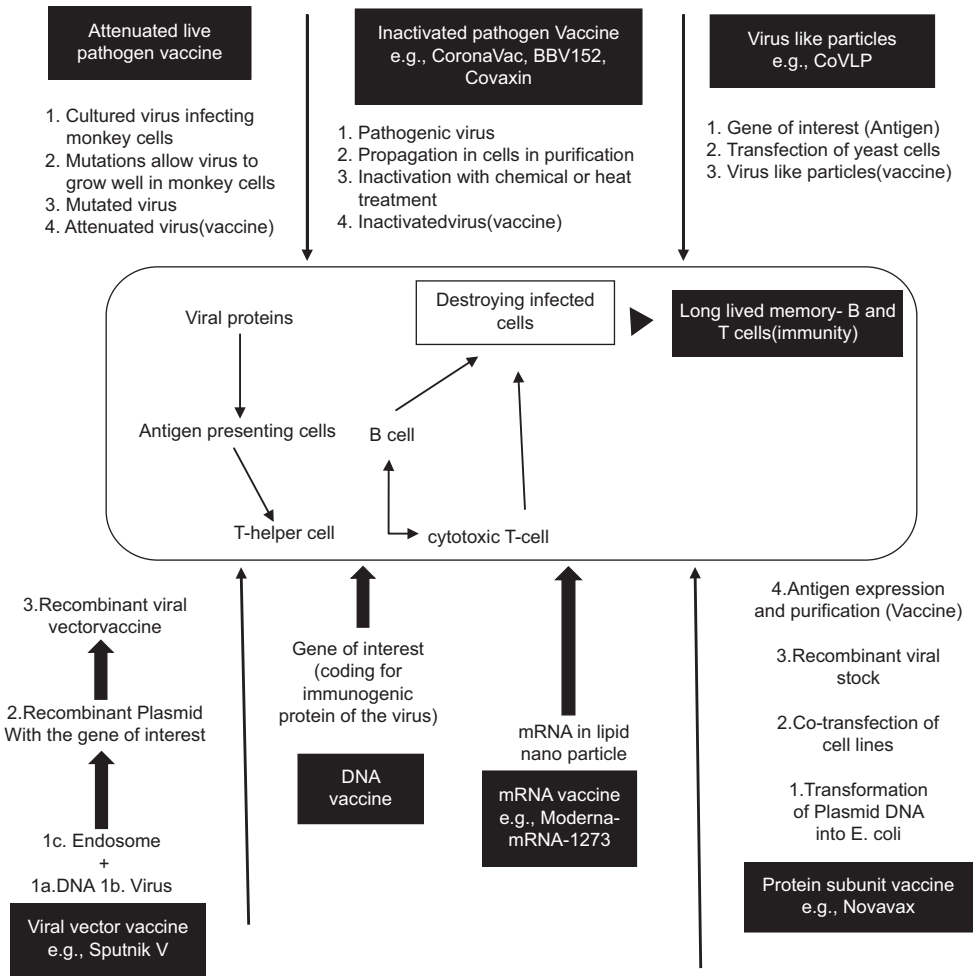

Fig. 2: Mechanisms by which various vaccines act [38-40]

Following reports [46] of cases of thrombosis with thrombocytopenia syndrome (TTS), the CDC and the FDA briefly recommended [47] pausing the distribution of the Janssen COVID-19 vaccine in April 2021.

The two federal agencies lifted the recommended pause, after conducting a safety review, concluding that the vaccine's "known and potential benefits outweigh its known and potential risks in individuals 18 years of age and older" and that the risk of TTS after vaccination was "very low."

As of July 12, 2021, the FDA [48] has added a warning that some people who receive the Johnson and Johnson vaccine might develop Guillain-Barré syndrome [49]. For this reason, on July 9, 2021, the EMA [50] recommended adding a warning to the vaccine's label to reflect this potential risk. The agency also noted that it is not yet fully confirmed that this vaccine is directly responsible for the development of this disorder in those who experienced it.

OXFORD-ASTRAZENECA AND SERUM INSTITUTE OF INDIA

Incidents of blood clots have been reported by EMA and Danish Health Authority in people who received the Oxford-AstraZeneca vaccine.

Of the 5 million people who received this vaccine, there have been 30 reported cases [51] of blood clots, as of March 2021. One case in Denmark was fatal.

On April 7, 2021, the EMA [52] concluded that the Oxford-AstraZeneca vaccine should carry a warning of TTS as a very rare side effect.

Multiple countries, including Denmark, Norway, Germany, and France, initially paused the distribution [53] of the Oxford-AstraZeneca COVID-19 vaccine as a precautionary response to initial reports of blood clots. On April 14, 2021, Denmark decided [54] to stop the distribution of this vaccine entirely.

On April 15, the Norwegian Institute of Public Health recommended [47] stopping the distribution of both the Oxford-AstraZeneca and Janssen vaccines in the country, due to the risk of blood clots.

Both Germany [55] and France [56] have resumed administering the Oxford-AstraZeneca COVID-19 vaccine. However, the distribution may eventually halt altogether, as the European union has not renewed [57] its order of Oxford-AstraZeneca vaccine doses beyond June 2021.

India had not reported [52] any incidents of blood clotting related to CoviShield as of March 2021 and currently has no plans to discontinue its distribution.

To ensure that there are no causal links, drug regulatory agencies in India are still closely examining the data.

NOVAVAX [58]

Side effects of Nuvaxovid are usually not serious and the most common ones include pain or tenderness at the injection site, tiredness, headaches, muscle, or joint pain and generally feeling unwell.

CONCLUSION

Researchers came up with various targets for vaccine development and stood the test of time in the pandemic era. Furthermore, organ vhip-

based assays seem to be the promising alternatives that may provide rapid pre-clinical evaluation, accessibility to study virus-induced diseases in real-time, and at high resolution. They can open new paths to study viral pathogenesis in a human-relevant environment and may eventually enable development of novel therapeutics and vaccines.

CoviShield and Covaxin have remained the choice of vaccines in India and have proved to be effective reducing morbidity and mortality considerably.

Very few and mild side effects were mostly reported and the ones with life-threatening side effects were banned and association of moderate ones was mostly not proven.

Applying established facts and knowledge of closely related species such as the SARS CoV has played a major role when there was a limited time available for the research on new variant. The key features which hastened the whole process of vaccine development as it is apparent from the review of various studies are the efficacy of seemingly different techniques applied together, collaborative efforts coupled with rapid, and timely dissemination of results. The availability of curated databases has also been of great advantage. We conclude our narrative with the hope that this review will appeal the researchers, students as well as recententrants in these research domains and the various studies described herein will inspire and be helpful for the advancement of public health.

CONTRIBUTIONS OF AUTHORS

Both authors have contributed equally.

CONFLICTS OF INTERESTS

There are no conflicts of interest to declare. There is no financial interest to report. We certify that this submission is an original work and is not under review at any other journal.

FUNDING

We received no financial support for the research, authorship, and publication of this article.

REFERENCES

1. Kumar S, Maurya VK, Prasad AK, Bhatt ML, Saxena SK. Structural, glycosylation and antigenic variation between 2019 novel coronavirus (2019-nCoV) and SARS coronavirus (SARS-CoV). Virusdisease 2020;31:13-21. doi: 10.1007/s13337-020-00571-5, PMID 32206694
2. Ji H, Yan Y, Ding B, Guo W, Brunswick M, Niethammer A, *et al*. Novel decoy cellular vaccine strategy utilizing transgenic antigen-expressing cells as immune presenter and adjuvant in vaccine prototype against SARS-CoV-2 virus. Med Drug Discov 2020;5:100026. doi: 10.1016/j.medidd.2020.100026, PMID 32289117
3. Enayatkhani M, Hasaniazad M, Faezi S, Gouklani H, Davoodian P, Ahmadi N, *et al*. Reverse vaccinology approach to design a novel multi-epitope vaccine candidate against COVID-19: An *in silico* study. J Biomol Struct Dyn 2021;39:2857-72. doi: 10.1080/07391102.2020.1756411, PMID 32295479
4. Qiu T, Mao T, Wang Y, Zhou M, Qiu J, Wang J, *et al*. Identification of potential cross-protective epitope between a new type of coronavirus (2019-nCoV) and severe acute respiratory syndrome virus. J Genet Genomics 2020;47:115-7. doi: 10.1016/j.jgg.2020.01.003, PMID 32171450
5. Tai W, He L, Zhang X, Pu J, Voronin D, Jiang S, *et al*. Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: Implication for development of RBD protein as a viral attachment inhibitor and vaccine. Cell Mol Immunol 2020;17:613-20. doi: 10.1038/s41423-020-0400-4, PMID 32203189
6. Chen WH, Hotez PJ, Bottazzi ME. Potential for developing a SARS-CoV receptor-binding domain (RBD) recombinant protein as a heterologous human vaccine against coronavirus infectious disease (COVID)-19. Hum Vaccin Immunother 2020;16:1239-42. doi: 10.1080/21645515.2020.1740560, PMID 32298218
7. Ahmed SF, Quadeer AA, McKay MR. COVIDep: A web-based platform for real-time reporting of vaccine target recommendations for SARS-CoV-2. Nat Protoc 2020;15:2141-2. doi: 10.1038/s41596-020-0358-9, PMID 32555466
8. Baruah V, Bose S. Immunoinformatics-aided identification of T cell and B cell epitopes in the surface glycoprotein of 2019-nCoV. J Med Virol 2020;92:495-500. doi: 10.1002/jmv.25698, PMID 32022276
9. Iwasaki A, Yang Y. The potential danger of suboptimal antibody responses in COVID-19. Nat Rev Immunol 2020;20:339-41. doi: 10.1038/s41577-020-0321-6, PMID 32317716
10. Lucchese G. Epitopes for a 2019-nCoV vaccine. Cell Mol Immunol 2020;17:539-40. doi: 10.1038/s41423-020-0377-z, PMID 32094505
11. Muñoz-Fontela C, Dowling WE, Funnell SG, Gsell PS, Riveros-Balta AX, Albrecht RA, *et al*. Animal models for COVID-19. Nature 2020;586:509-15. doi: 10.1038/s41586-020-2787-6, PMID 32967005
12. Huh D, Torisawa YS, Hamilton GA, Kim HJ, Ingber DE. Microengineered physiological biomimicry: Organs-on-chips. Lab Chip 2012;12:2156-64. doi: 10.1039/c2lc40089h, PMID 22555377
13. Ramani S, Crawford SE, Blutt SE, Estes MK. Human organoid cultures: Transformative new tools for human virus studies. Curr Opin Virol 2018;29:79-86. doi: 10.1016/j.coviro.2018.04.001, PMID 29656244
14. Rosellini A, Freer G, Quaranta P, Dovere V, Menichini M, Maggi F, *et al*. Enhanced *in vitro* virus expression using 3-dimensional cell culture spheroids for infection. J Virol Methods 2019;265:99-104. doi: 10.1016/j.jviromet.2018.12.017, PMID 30582939
15. He B, Chen G, Zeng Y. Three-dimensional cell culture models for investigating human viruses. Virol Sin 2016;31:363-79. doi: 10.1007/s12250-016-3889-z, PMID 27822716
16. Safronetz D, Geisbert TW, Feldmann H. Animal models for highly pathogenic emerging viruses. Curr Opin Virol 2013;3:205-9. doi: 10.1016/j.coviro.2013.01.001, PMID 23403208
17. Mestas J, Hughes CC. Of mice and not men: Differences between mouse and human immunology. J Immunol 2004;172:2731-8. doi: 10.4049/jimmunol.172.5.2731, PMID 14978070
18. Barkauskas CE, Chung MI, Fioret B, Gao X, Katsura H, Hogan BL. Lung organoids: Current uses and future promise. Development 2017;144:986-97. doi: 10.1242/dev.140103, PMID 28292845
19. Si L, Bai H, Rodas M, Cao W, Oh CY, Jiang A, *et al*. Human organ chip-enabled pipeline to rapidly repurpose therapeutics during viral pandemics. bioRxiv 2020;02115:212-41.
20. Ella R, Vadrevu KM, Jogdand H, Prasad S, Reddy S, Sarangi V, *et al*. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: A double-blind, randomised, phase 1 trial. Lancet Infect Dis 2021;21:637-46. doi: 10.1016/S1473-3099(20)30942-7, PMID 33485468
21. Available from: https://www.mohfw.home
22. Willis DB, Goorha R, Chinchar VG. Macromolecular synthesis in cells infected by frog virus 3. Curr Top Microbiol Immunol 1985;116:77-106. doi: 10.1007/978-3-642-70280-8_5, PMID 3893912
23. Shanmugam S, Venugopal P, Sriram DK, George M. Evaluation of adenoviral vector-based vaccines for prevention of COVID-19-an overview. Asian J Pharm Clin Res 2022;15:6-16. doi: 10.22159/ajpcr.2022.v15i7.44261
24. Covid-19 Vaccination in India-vaccinate India. Available from: https://www.vaccinate-india.in/dashboard [Last accessed on 2022 Feb 11].
25. CoWIN Dashboard. Available from: https://www.dashboard.cowin.gov.in/[Last accessed on 2022 Feb 11].
26. Serum Institute gets DCGI's nod to Manufacture Covid Vaccine Sputnik V in India: Report. Available from: https://www.livemint.com/news/india/serum-institute-gets-dcgi-s-nod-to-manufacture-covid-vaccine-sputnik-v-in-india-report-11622818500423.html [Last accessed on 2022 Feb 11].
27. RDIF and Serum Institute of India, the World's Largest Vaccine Manufacturer by volume, to Start Production of Sputnik Vaccine at Company's Facilities in September [press release]; 13.07.2021 Russian Direct Investment Fund. Available from: https://www.rdif.ru/Eng_fullNews/6934/[Last accessed on 2022 Feb 11].
28. Coronavirus: India Approves Vaccines from Bharat Biotech and Oxford/Astra Zeneca-BBC News. Available from: https://www.bbc.com/news/world-asia-india-55520658 [Last accessed on 2022 Feb 11].
29. Delhi Reportedly Halts Astra Zeneca Covid Vaccine Exports as Cases Soar India. The Guardian. Available from: https://www.theguardian.com/world/2021/mar/24/delhi-reportedly-halts-astrazeneca-covid-vaccine-exports-as-cases-soar [Last accessed on 2022 Feb 11].
30. Covid Vaccine: Why did EU take Astra Zeneca to Court?-BBC News. Available from: https://www.bbc.com/news/56483766 [Last accessed on 2022 Feb 11].
31. Expert Panel Clears Bharat Biotech's Covaxin amid UK Virus Strain:

What you Need to Know Available from: https://www.news18.com/news/india/expert-panel-clears-bharat-biotechs-covaxin-amid-uk-virus-strain-what-you-need-to-know-3240500.html [Last accessed on 2022 Feb 11].
32. Coronavirus Vaccine Dilemma-to Take or not to Take Covaxin-the Hindu. Available from: https://www.thehindu.com/sci-tech/health/vaccine-dilemma-to-take-or-not-to-take-covaxin/article33577223.ece [Last accessed on 2022 Feb 11].
33. Coronavirus Covaxin Recipients Asked to Sign Consent Form on 'Clinical Trial Mode'-the Hindu. Available from: https://www.thehindu.com/news/national/coronavirus-bharat-biotech-to-pay-compensation-if-covaxin-vaccine-causes-side-effects/article33587377.ece [Last accessed on 2022 Feb 11].
34. Covid Vaccination for Children in India: Children between 15-18 Years can Register on CoWin from Jan 1, on-site from Jan 3 India news-times of India. Available from: https://www.timesofindia.indiatimes.com/india/covid-vaccination-children-between-15-18-years-can-register-on-cowin-from-jan-1-on-site-from-jan-3/articleshow/88531760.cms [Last accessed on 2022 Feb 13].
35. World Health Organization. COVID19 Vaccine Tracker. Geneva: World Health Organization. Available from: https://covid19.trackvaccines.org/agency/who/[Last accessed on 2022 Feb 13].
36. Ella R, Reddy S, Blackwelder W, Potdar V, Yadav P, Sarangi V, *et al*. Efficacy, safety, and lot-to-lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): Interim results of a randomised, double-blind, controlled, phase 3 trial. Lancet 2021;398:2173-84. doi: 10.1016/S0140-6736(21)02000-6, PMID 34774196
37. Vaccine Information. New Delhi: Indian Council of Medical Research-COVID-19 Vaccine. Available from: https://www.vaccine.icmr.org.in/covid-19-vaccine [Last accessed on 2022 Feb 13].
38. Misra SK, Pathak K, Pathak D, Yadav R. Current updates on Covid-19 vaccines. Asian J Pharm Clin Res 2021;14:17-23. doi: 10.22159/ajpcr.2021.v14i5.41061
39. Kyriakidis NC, López-Cortés A, González EV, Grimaldos AB, Prado EO. SARS-CoV-2 vaccines strategies: A comprehensive review of phase 3 candidates. NPJ Vaccines 2021;6:28.
40. Arya SC, Agarwal N. Apropos risks associated with the use of live-attenuated vaccine poliovirus strains and the strategies for control and eradication of paralytic poliomyelitis. Expert Rev Vaccines 2012;11:1291. doi: 10.1586/erv.12.110, PMID 23249227
41. What are the Side Effects of COVID-19 Vaccines, and Should you Worry? Available from: https://www.medicalnewstoday.com/articles/global-covid-19-vaccine-summary-side-effects#Potential-side-effects-per-vaccine [Last accessed on 2022 Feb 16].
42. Hasselbach L, Voß A. Thrombotic thrombocytopenic purpura after COVID-19 vaccination: A case report. Arch Clin Biomed Res 2021;5:737-41. doi: 10.26502/acbr.50170198
43. Nyayakar S, Srinivasan R, Archana L, Nithyanandan S. A cross-sectional study on acceptance and post-vaccination symptoms of Covid-19 vaccination in India. Asian J Pharm Clin Res 2022;15:107-10. doi: 10.22159/ajpcr.2022.v15i1.43158
44. Centers for Disease Control and Prevention. Possible Side Effects after Getting a COVID-19 vaccine. CDC. Georgia, United States: Centers for Disease Control and Prevention.
45. Coronavirus Disease (COVID-19): Vaccines Safety. Available from: https://www.who.int/news-room/questions-and-answers/item/coronavirus-disease-(covid-19)-vaccines-safety [Last accessed on 2022 Feb 17].
46. Shimabukuro T. Thrombosis with Thrombocytopenia Syndrome (TTS) following Janssen COVID-19 Vaccine Advisory Committee on Immunization PrSactices (ACIP). CDC COVID-19 Vaccine Task Force Vaccine Safety Team. Atlanta, Georgia: Advisory Committee on Immunization Practices; 2021.
47. Norway should exclude J&J, Astra Zeneca from vaccine scheme-panel. Reuters. Available from: https://www.reuters.com/world/europe/norway-should-exclude-jj-astrazeneca-covid-vaccination-scheme-says-commission-2021-05-10/[Last accessed on 2022 Feb 17].
48. Flaherty L. Department of health and human services. J Emerg Nurs 2000;26:242-6. doi: 10.1016/S0099-1767(00)90099-0.
49. Guillain-Barré syndrome: Symptoms, Causes, Diagnosis, and Treatment. Available from: https://www.medicalnewstoday.com/articles/167892 [Last accessed on 2022 Feb 17].
50. Meeting Highlights from the Pharmacovigilance Risk Assessment Committee (PRAC). South Amsterdam: European Medicines Agency. Available from: https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-5-8-july-2021 [Last accessed on 2022 Feb 17].
51. COVID-19 Vaccine Astra Zeneca: PRAC Investigating Cases of Thromboembolic events-vaccine's Benefits Currently Still Outweigh risks-Update. South Amsterdam: European Medicines Agency. Available from: https://www.ema.europa.eu/en/news/covid-19-vaccine-astrazeneca-prac-investigating-cases-thromboembolic-events-vaccines-benefits [Last accessed on 2022 Feb 17].
52. Astra Zeneca's COVID-19 vaccine: EMA Finds Possible Link to Very Rare Cases of Unusual Blood Clots with Low Blood Platelets. South Amsterdam: European Medicines Agency. Available from: https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood [Last accessed on 2022 Feb 17].
53. Oxford-Astra Zeneca: EU says 'No Indication' Vaccine Linked to Clots-BBC News. Available from: https://www.bbc.com/news/world-europe-56357760 [Last accessed on 2022 Feb 17].
54. In world first, Denmark ditches Astra Zeneca's COVID-19 shot. Reuters. Available from: https://www.reuters.com/world/europe/world-first-denmark-ditches-astrazenecas-covid-19-shot-2021-04-14/[Last accessed on 2022 Feb 17].
55. Britain. Germany in role reversal on Astra Zeneca vaccine risks. Available from: https://www.reuters.com/world/europe/third-wave-pandemic-appears-be-broken-german-health-minister-2021-05-07/ [Last accessed on 2022 Feb 17].
56. I don't want that. Reuters. France Struggles to Pitch AstraZeneca Vaccine. Available from: https://www.reuters.com/world/europe/i-dont-want-that-france-struggles-pitch-astrazeneca-vaccine-2021-04-19 [Last accessed on 2022 Feb 17].
57. EU has not Ordered Astra Zeneca Vaccines Beyond June-commissioner. Canary Wharf, London: Reuters. Available from: https://www.reuters.com/world/europe/eus-breton-eu-did-not-renew-astrazeneca-covid-19-vaccine-order-after-june-2021-05-09 [Last accessed on 2022 Feb 17].
58. Heath PT, Galiza EP, Baxter DN, Boffito M, Browne D, Burns F, *et al*. Safety and efficacy of NVX-CoV2373 Covid-19 vaccine. N Engl J Med 2021;385:1172-83. doi: 10.1056/NEJMoa2107659, PMID 34192426