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NARRATIVE REVIEW

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An update on vaccine status and the role of nanomedicine against SARS-CoV-2: A narrative review

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Abstract

Background and Aims: Coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2 novel coronavirus, is a highly communicable disease that gave rise to the ongoing pandemic. Despite prompt action across many laboratories in many countries, effective management of this disease is still out of reach. The focus of this review is to describe various vaccination approaches and nanomedicine-based delivery systems against COVID-19.

Methods: The articles included in this study were searched and added from different electronic databases, including PubMed, Scopus, Cochrane, Embase, and preprint databases.

Results: Mass immunization with vaccines is currently at the forefront of COVID-19 infection control. Such vaccines are live attenuated vaccines, inactivated vaccines, nucleic acid-based vaccines, protein subunit vaccines, viral-vector vaccines, and virus-like particle platforms. However, many promising avenues are currently being explored in laboratory and clinical settings, including treatment options, prevention, diagnosis, and management of the disease. Soft nanoparticles like lipid nanoparticles (solid lipid nanoparticles (SLNPs), liposomes, nanostructured lipid carriers, nanoemulsions, and protein nanoparticles play an essential role in nanomedicine. Because of their unique and excellent properties, nanomedicines have potential applications in treating COVID-19 disease.

Conclusions: This review work provides an overview of the therapeutic aspects of COVID-19, including vaccination and the role of nanomedicines in the diagnosis, treatment, and prevention of COVID-19.

KEYWORDS

COVID-19, nanomedicine, nanoparticle, SARS-CoV-2, vaccine

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1 | INTRODUCTION

Coronaviruses are positive-sense single-strand RNA (+ssRNA) viruses belonging to the family *Coronaviridae*.[1,2] They got their name from the halo, the spike proteins studded on their outer surface resembling a crown.[1,3] Basically, coronavirus causes mild to severe respiratory illness in human beings as well as a variety of illnesses in animals.[4,5] The human coronaviruses first came to light in the 1960s as a cause of the common cold, approximately 30 kb (27–32 kb) in genomic size.[5] In the last two decades, coronaviruses have been issued as epidemic and pandemic threats in the world.[6] As a fatal respiratory infection, Severe Acute Respiratory Syndrome (SARS-CoV) emerged in 2002 and 2003 in the Guangdong province, China and Middle East Respiratory Syndrome (MERS-CoV) emerged in 2012 in the Middle Eastern countries.[4,6] In addition, the third zoonotic human coronavirus, named novel coronavirus (2019-nCoV), subsequently issued a pandemic that the World had not seen before late 2019.[7] It is also introduced as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2) because this virus is genetically related to SARS-CoV, which was the reason behind SARS outbreak of 2003.[8] SARS-CoV-2 has a homologous genome sequence with SARS-CoV and MERS-CoV, 77.5% and 50%, respectively.[3,9] In general, they contain various components in their structure, including spike (S) glycoprotein, nucleocapsid (N) protein, membrane (M) protein, and envelope (E) protein that contributes to its pathogenesis. The binding of the S protein to the angiotensin-converting enzyme 2 (ACE2) receptor facilitates viral fusion, enabling the virus to enter host cells.[10,11]

Initially, a cluster of pneumonia patients of the unidentified cause was linked to the seafood and wet animal wholesale market located in Wuhan, a city in Hubei Province, China.[10] As a matter of fact, the symptoms were found to be identical to the patients with SARS-CoV and MERS-CoV; for instance, fever, cough with chest pain, and in worst cases, difficulty in breathing and bilateral pulmonary infiltration.[10,12] The World Health Organisation (WHO) named the disease COVID-19 in December 2019.[13] This virus spreads rapidly throughout the world,[14] caused by an aerial person-to-person transmission by either virion suspended on large droplets via coughs, sneezes and even talks or fine aerosols expelled from the respiratory tract of the affected person.[15] It is a highly infectious virus with multiple mutations.[16] The COVID-19 disease is still spreading continuously. So, vaccination can be a suitable option to stop millions of deaths, like eradicating smallpox and rinderpest, by effective and universal vaccination.[17]

In terms of ending up the pandemic, hundreds of vaccine candidates are in the pipeline for COVID-19 disease.[18] Traditional vaccine development takes many years and even decades, but due to the previously gained knowledge and experience from related viruses, the world was able to develop COVID-19 vaccines in a successful way,[19] and at the same time, nanomedicine added a new dimension to deal with the diagnosis, treatment, and prevention of COVID-19.[20] According to the definition of the European Science Foundation (ESF), nanomedicine is the science and technology associated with the diagnosis, treatment, and prevention of disease by applying molecular knowledge of the body.[21,22] The approximate size of nanomedicine is around 100–200 nm with hydrophilic surface modification.[23] Multiple nanotechnology method-based strategies are ongoing for COVID-19, for example, nanomedicine-dependent mRNA vaccines, Pfizer-BioNTech (BNT162b2), and Moderna (mRNA-1273) are under the authorization of emergency use, leading the most significant role in COVID-19 disease,[24] nanoparticles (NPs) in diagnosis have potential applications in quick, sensitive and accurate results in COVID-19 detection due to the efficient interaction with biomolecules (protein, DNA) and even impregnation of metallic NPs as like Ag-NPs in various protective materials including masks, medical devices, gloves could be helpful in the prevention of viral spread.[20] Therefore, nanomedicine is like a rational key factor or like a rescue from the COVID-19 pandemic.

The focus of this review is to describe various vaccination approaches against the novel coronavirus, including both conventional and innovative approaches, including but not limited to nanomedicine-based delivery systems, gene delivery, viral carriers and so forth.

2 | METHODS

The articles included in this study were searched and added from different electronic databases, including PubMed, Scopus, Cochrane, Embase, and preprint databases. The authors have tried to collect all available data related to the concept of the study (COVID-19 vaccination and nanomedicine) without any language or region-specific barriers. However, the authors have also tried to remove some articles from the reference list that have been retracted already. The authors are not liable for any future concern related to retracted articles. As the data on COVID-19 is rapidly updating, the authors recommend using the latest available data for future works on this theme.

3 | CURRENT THEMES COVID-19 VACCINES

In the race of developing enough safe and effective COVID-19 vaccines, in words of WHO onNovember 18, 2022, 175 vaccine candidates are in human clinical trials and more than 199 candidates in preclinical trials all over the world which are from live attenuated vaccines, nucleic acid-based vaccines, inactivated vaccines, protein subunit vaccines, viral-vector vaccines, and virus-like particles platforms.[18]

3.1 | Whole-virus vaccines

Two types of whole-pathogen vaccine are commonly distinguished: Live-attenuated vaccines (LAV) and inactivated vaccines.[25]

3.1.1 | LAV

LAV use live pathogens with reduced virulence, which can grow and replicate without causing disease.[26] They introduce a mild infection, that is, the natural infection, and provide a strong, long-lasting immune response against the disease.[25] However, live vaccines are not suitable for people whose immune system is weak.[25]

An example of an existing live-attenuated vaccine is Bacillus Calmette-Guerin (BCG) is still the only vaccine highly effective in preventing Tuberculosis (TB) in humans resulting in a significant reduction in the number of deaths.[27] The WHO and International Union against Tuberculosis and Lung Disease suggest that the substrain of BCG may be the future vaccine.[27] This vaccine can offer a powerful specific and nonspecific immune response though it is still unknown whether it can offer potent protection against COVID-19 or not.[28]

3.1.2 | Inactivated vaccine

The inactivated vaccine uses inactivated versions of viruses or other pathogens using chemicals, UV light and heat to produce an immune response.[29] Although the immune response is weaker than live vaccines and needs several booster doses, it is safe, especially for immunocompromised persons.[29]

CoronaVac from Sinovac (China) is an example of inactivated vaccine.[30] It is a two-dose vaccine adjuvanted with aluminum hydroxide currently in phase IV trial.[19,31,32] In this vaccine, SARS-CoV-2 is deactivated by beta-propiolactone.[19] A recent study demonstrated that the host cells of the participants vaccinated with CoronaVac defenced through the immune system by targeting spike protein and nucleoprotein, where the fever was relatively low compared to other RNA vaccines, DNA vaccines, and viral vector vaccines.[30] Application of mRNA-based or vector-based vaccines for heterologous boosting after primary CoronaVac vaccination may cause to the recovery of high COVID-19 protective antibody concentrations quickly.[33]

Valneva's Vero-cell-based VLA2001 is a highly purified inactivated vaccine against COVID-19,[34] transitioned into a phase III trial (NCT04864561). It contains an inactivated version of the whole virus, SARS-CoV-2, with a high-density of S protein with the combination of cytosine phosphate-guanine (CpG 1018) and aluminum hydroxide as adjuvants in expecting to induce a strong immune response[35] by triggering the production of antibodies. On April 6, 2021, Valneva reported positive phase I/II data in which VLA2001 was well tolerated in participants with no safety concerns identified.[35] Data showed that VLA2001 could neutralize the initial SARS-CoV-2 virus along with the variants Omicron and Delta (https://www.nihr.ac.uk/news/nihr-supported-valneva-covid-vaccine-trial-reports-positive-results/28969).

China-based Sinopharm developed BBIBP-CorV, a two-dose inactivated vaccine, which underwent into phase IV trial.[32,36] It showed good immunogenicity in phase I/II trials of randomized, double-blinded, placebo-controlled.[37] A recent study uncovered a lower prevalence of adverse reactions of the Sinopharm vaccine in contrast to Pfizer and AstraZeneca vaccines.[36]

Bharat Biotech and the Indian Council of Medical Research and the National Institute of Virology jointly developed COVAXIN, which is composed of the inactivated whole virion (SARSCoV-2), produced with two adjuvants Algel and Algel-IMDG.[38] The advantages and limitations of different types of vaccines with their target portions for COVID-19 are shown in Table 1.[25,31,39]

3.2 | Protein subunit vaccine

Protein subunit vaccine is composed of one or more fragments of actual viral protein as antigens to trigger immune response.[40,41] They are manufactured easily using recombinant DNA technology and contain well-defined compositions.[41,42] Although live attenuated or killed (inactivated) vaccines have gained success in several diseases like polio, they are not always effective and have some issues.[42] But protein subunit vaccines are attractive vaccine candidates and gained enough interest in recent years.[42] They are inherently safe and do not induce injection site pain.[42] However, the vaccines require additional support of an adjuvant in amplifying immune response due to low immunogenicity.[40,41] Many protein subunit vaccine candidates have participated in clinical phase trials using S protein and its fragments, like S1, S2, RBD, and nucleocapsid protein, as a main target antigen for COVID-19.[41]

Novavax (USA) offered NVX-CoX2373 is a protein-based nanoparticle vaccine with saponin-based Matrix M1 adjuvant.[43] In the preclinical study, NVX-CoV2373 induced antibodies responsible for blocking the spike protein to bind with receptors and provided protection against COVID-19.[44] It was well-tolerated with robust antibody response in phase I/II trial.[44] Follow-up with the phase III clinical trial of NVXCoV2373 has shown 89.7% efficacy against SARS-CoV-2.[45]

Clover Biopharmaceuticals in China designed SCB-2019 as a vaccine candidate for COVID-19.[46] This vaccine contains a stabilized trimeric form of S protein (S-Trimer) formulated with either ASO3 or CpG/Alum as adjuvants.[46] Phase 1 data shows the vaccine is well-tolerated as well as has a strong immune response in younger and older age groups and this result preferred the vaccine to move into phase 2/3 trial.[46,47]

3.3 | Nucleic acid vaccine

This vaccine can be DNA or RNA. To trigger an immune response, this category of vaccine utilizes genetic material derived from a pathogen.[18]

3.3.1 | DNA vaccine

Inovio Pharmaceuticals is working on a DNA vaccine candidate (INO-4800) that encodes the S-protein of SARS-CoV-2.[48] In the

TABLE 1 Advantages and limitations of different types of vaccines with their target portions for COVID-19.[25,31,39]

Vaccine type	Targets	Advantages	Limitations
Live attenuated	Whole virus	– Provide strong and long-term immune response – Single dose administration is often enough – Cost effective	– Often induce higher reactogenicity cold storage condition is required – Can lead to transient immunosuppression in healthy person – Not suitable for people with weak immune system
Inactivated	Whole virus	– More stable than other platforms – Good safety profile as no live virus is present – Easy to transport and storage condition is not as critical	– Less immunogenic than a live vaccine – Requiring booster dose thus increases costs – Use of adjuvants can lead to unwanted inflammation
Protein subunit	S protein	– Cannot induce infection – Safe for immunosuppressed patients – Have fewer side effects – Do not induce injection site pain	– May require adjuvants – Weak immunogenic – Cannot mimic the size of the native pathogen like
DNA-based	S protein	– Fast production capacity – Safe, well tolerated and reusable – Can be stored at room temperature	– High production and development cost – Require specific delivery devices and equipment – Genome integrational risk resulting in insertional mutagenesis – No vaccines licensed for humans
mRNA-based	S protein	– Fast production capacitySafe and nonintegrating – Reusable and highly immunogenic	– Necessary to store at cooler temperatures – In vivo vaccine delivery
VLP-based	S protein	– Self-adjuvant properties capable of inducing strong immune responses – Safe because it does not induce infection	– Higher doses are required for administration – Challenges to producing with good immunogenicity
Viral vector	S protein	– Less infectious and reusable – Fast production capacity – Provide both cellular and humoral immune responses	– Pre-existing immunity against vector may misdirect immune response – Possibility of adverse reaction

phase 1 trial, INO-4800 was safe and well tolerable and at the same time and 100% of vaccinated participants showed immunogenicity by expressing either or both humoral or cellular immune responses.[48] Phase II/III clinical trial is underway (NCT04642638).

3.3.2 | mRNA vaccines

Pfizer and BioNTech collaborated and took two immunogens, BNT162b1, the receptor-binding domain (RBD), and BNT162b2, the full-length S protein in a preliminary clinical trial.[49] BNT162b2 was found to be safer than BNT162b1, especially in aged adults and thus, BNT162b2 was entered into phase II/III clinical trial.[49] Phase 3 clinical trial has shown 95% efficacy of Pfizer/BioNTech BNT162b2, an excellent result for mRNA vaccines against SARS-CoV-2 and just need two shots 21 days apart for this efficacy.[50]

Moderna's mRNA-1273, also a two-dose vaccine based on stabilized mRNA of the viral spike protein (mRNA-1273) is given 28 days apart.[51] Phase I clinical trial of this has demonstrated that the mRNA-1273 vaccine induced immune responses against SARS-CoV-2 in all subjects with no identifiable safety concern that set the vaccine to enter into the stage of II/III trials.[52] The mRNA-1273 vaccine candidate passed in the phase 3 trial consisting of 30,420 participants with 185 cases at high risk for COVID-19, giving 94.1% effectiveness in preventing COVID-19 without identifiable safety concerns.[53]

These two mRNA vaccines have been developed using lipid nanoparticles (LNPs) and due to the presence of PEG in the formulation, both of them have side effects such as injection site pain, fever, muscle or joint pain, chills, fatigue, headache, as well as allergic reaction in some patients.[51] Both of them are currently transitioning into phase IV trial.[32]

CVnCOV is also an mRNA vaccine candidate produced by the German company CureVac.[54] A study provides evidence that CVnCOV is safe and potent for the protection of SARS-CoV-2.[55] A study of randomized observer-blinded, placebo-controlled phase IIb/III showed this vaccine had 70.7% overall efficacy in moderate-to-severe and 77.2% in participants aged 18–60, and it had a good safety profile in phase II randomized study.[56]

In addition, Globe Biotech Ltd from Bangladesh is working on a nucleocapsid-modified mRNA vaccine that encodes the S protein that is BANCOVID. The vaccine is based on the D614G variant, which is 10 times more infectious than the D614 genotype. The vaccine is encapsulated by lipid nanoparticles (LNP). A study indicated that the in vivo administration of the vaccine was safe and exhibited a consistent and stable immune response, both at the cellular and humoral levels, effectively neutralizing infection caused by the S protein.[57]

3.4 | Viral vector-based vaccines

Viral vector vaccine is produced by a gene of interest and inserted with the sequence of coding of the target virus, and its goal is to provide an immune response against the target antigen.[31]

3.4.1 | Nonreplicating viral vector vaccines

ChAdOx1 nCoV-19 or AZD1222 (sold under the names Covishield, Vaxzevria etc.), a chimpanzee adenovirus vaccine against SARS-CoV-2 offered by AstraZeneca and Oxford Vaccine Group (UK-Sweden).[58] There are two shots to be administrated 4 weeks apart.[59] A phase I/II study of single-blind, randomized controlled trial in five trial sites in the UK showed that AstraZeneca candidate was safe, tolerable, and immunogenic.[60] Local and systemic reactogenicity like fever, injection site pain, headache, muscle ache, and malaise were common factors in participants reduced by acetaminophen.[60] So, there was no such serious adverse effect. Interim analysis of Phase II/III trial had found that AstraZeneca was 70.4% effective after two shots and 64.1% protective after at least one standard shot against COVID-19 disease with on safety concern.[61] Another analysis of the Phase III trial of the vaccine ensured 79% effectiveness in preventing symptomatic COVID-19 disease.[59] This vaccine was re-checked 2 days later, and the efficacy was around 76% indeed.[62] Now in the phase IV trial.[32]

The major European nations tentatively suspend Oxford-AstraZeneca vaccine due to the issue of its thromboembolic effects.[54,62] There is no justification and proper evidence for the ban, however.[54] An evaluation of safety data of more than 10 million records provides evidence of no identification of blood clots at any batch, gender, defined age group or in any specific country.[54]

Based on adenovirus, Janssen Pharmaceutical Companies of Johnson & Johnson developed a single-shot vaccine candidate Ad26.COV2-S/JNJ-78436735 shows 66% efficacy against COVID-19 and US Food and Drug Administration (US-FDA) has approved this J&J vaccine for Emergency use.[63–65] Phase IV is underway.[32]

Nevertheless, the distributions of J&J vaccine faced a temporary pause by the US regulator because the blood clot problem was issued in six cases out of seven million dose administrations after reports of a blood clot in vaccinated people. The symptoms occurred 6–13 days after vaccination in all six women aged between 18 and 48. According to a newspaper article, both AstraZeneca and J&J vaccine has the same problem though; the reason is yet to be found, but something might have something to do with the adenoviral vector EDTA and in these vaccine formulations, they are likely causing this problem.[66,67]

Ad5-nCoV is another single-dose nonreplicating viral vector vaccine currently transitioned into phase IV.[32] It had an efficacy of 57.5% against symptomatic.[68]

3.4.2 | Replicating viral vector vaccine

Initially produced in Russia, Sputnik V is a two-component adenoviral-based vaccine where serotypes 5 and 26 of adenovirus are used.[58,69] In phase I/II trial, this vaccine showed a good safety profile and as well as produced a strong cellular and humoral immune response.[70] Recently, an interim analysis of a randomized controlled phase 3 trial in Russia, published in the *Lancet*, examined the safety and efficacy of a COVID-19 vaccine based on rAd26 and rAd5 vectors in a heterologous prime-boost regimen. The study demonstrated that the vaccine exhibited a high efficacy of 91.61% against SARS-CoV-2.[70]

3.5 | Virus like-particle vaccine

Plant-based COVID-19 vaccine candidate of Medicago Inc co-administered with GSK's pandemic adjuvant uses coronavirus like-particles (CoVLP) now in phase III. Two shots of 3.75 μg are given 21 days apart (https://www.medicago.com/en/media-room/medicago-and-gsk-start-phase-3-trial-of-adjuvanted-COVID-19-vaccine-candidate/).

Table 2 shows the overview of COVID-19 vaccine candidates.

4 | EFFECTIVENESS OF COVID-19 VACCINES AGAINST NEW VARIANTS

All the currently developing COVID-19 vaccines are mainly focused on the original, unstable D614 forms of S protein.[92] D614G mutation of S protein emerged early in this pandemic is not an obstacle for this vaccine development.[93] However, recently different variants of SARS-CoV-2 have raised concern on the efficacy of emergency-authorized vaccines.

In September 2020, B.1.1.7 (Alpha) variant contained several mutations of S protein, including the most significant spike N501Y mutation flowed out in Southeast England.[94] It is also referred to as 501Y.V1.[94] This variant rapidly spread throughout the UK along with other countries.[95] A recent analysis suggested that sera samples from the vaccinated individuals of Pfizer vaccine or Moderna vaccine have identical neutralizing activities against Alpha variant as compared with wild type.[94] Emary et al.[96] run a study and provide evidence that the AstraZeneca vaccine has reduced neutralizing activity against Alpha variant than non-Alpha variant in vitro and this vaccine is efficacious against Alpha variant. Novavax, a protein-based vaccine, has approximately 86% efficacy against this variant.[97]

The B.1.351 (Beta) variant of coronavirus was identified in late 2020 in South Africa,[95] and since then, this variant has shown a dominant character.[14] The variant contains N501Y mutation in the S protein like UK variant.[95] An investigation reported that sera samples from people vaccinated with Pfizer vaccine or Moderna vaccine might not have comparable efficacy to this variant when compared

TABLE 2 An overview of COVID-19 vaccine candidates.

Vaccine candidate	Mechanism	Primary MFR (country of origin)	Status	Shot	Route	Efficacy (%)	Storage condition	Reg. no./Reference
CoronaVac	Inactivated vaccine	Sinovac (China)	Phase IV	Two shots 14 days apart	IM	51	2–8°C	[19, 32, 58, 71–73]
VLA2001	Inactivated vaccine	Valneva; UK National Institute for Health Research (UK)	Phase III	Two shots 28 days apart	IM	_	2–8°C	(NCT04864561)[74]
BBIBP-CorV	Inactivated vaccine	Sinopharm (China)	Phase IV	Two shots	IM	79.34	2–8°C	[18, 32, 75, 76]
COVAXIN (BBV152)	Inactivated vaccine	Bharat Biotech (India)	Phase III	Two shots 28 days apart	IM	81	2–8°C	[18, 77–79]
NVX-CoV2373	Protein- subunit vaccine	Novavax (USA)	Phase III/IV	Two shots	IM	89.7	2–8°C	[45, 58, 72, 80, 81]
SCB-2019	Protein subunit vaccine	Clover Biopharmaceuticals (China)	Phase II/III	Two shots	IM	_	_	(NCT04672395)[46]
INO-4800	DNA vaccine	Inovio Pharmaceuticals (USA)	Phase II/III	Two shots	ID	_	_	(NCT04642638)[18]
BNT162b2	mRNA vaccine	Pfizer; BioNTech; Forsun (USA)	Phase IV	Two shots 21 days apart plus one booster shot after 6 months	IM	95	−70°C	[32, 58, 82–85]
mRNA-1273	mRNA vaccine	Moderna (USA)	Phase IV	Two shots 28 days apart plus one booster shot after 6 months	IM	94.1	−20°C	[32, 58, 82, 83, 85, 86]
CVnCOV	mRNA vaccine	CureVac (Germany)	Phase IIb/III	Two shots	IM	_	_	NCT04652102[87]
AZD1222	Nonreplicating viral vector vaccine	Oxford University; AstraZeneca (UK)	Phase IV	Two shots 28 days apart	IM	76	2–8°C	[32, 62, 85, 88, 89]
Ad26.COV2.S/JNJ-78436735	Nonreplicating viral vector vaccine	Johnson & Johnson (USA; Belgium)	Phase IV	Single shot plus one booster shot after 2 months	IM	66	2–8°C	[32, 63, 82, 85, 89, 90]
Sputnik V	Replicating viral vector vaccine	Gamaleya Research Institute (Russia)	Phase III	Two shots 21 days Apart	IM	92	−18°C or 2–8°C	[58, 61, 69, 89, 91]

with the wild type.[94] In a recent analysis, two shots of the AstraZeneca vaccine had no efficacy with the South African variant to prevent COVID-19.[98] In contrast, Novavax vaccines have 60% efficacy against this variant.[97]

In early January 2021, Brazil experienced a new SARS-CoV-2 variant P.1 (Gamma),[99] from a local B. 1. 1.28 clade.[100] P.1 is also called N501Y.V3.[100] Basically, It was 1st detected in four travelers returning from the Amazon state, and by this, the second wave flowed out in Brazil.[100] A recent analysis suggests that after administration of the second shot, CoronaVac has 42% efficacy in the real-world setting of excessive P.1 transmission and vaccine effectiveness will be less among adults ≥70 years of age.[99]

Recently, the major concern regarding vaccination against COVID-19 has been raised for the novel variants (Delta and Omicron) of SARS-CoV-2. The Delta variant of SARS-CoV-2 first emerged in mid-April 2021 in the United Kingdom, which rapidly caused a spike in COVID-19 cases and hospitalization around various parts of the world. While the Delta variant has higher transmissibility, it is not due to vaccine inefficiency but a higher viral load.[101,102] The difference in vaccine effectiveness after two doses was negligible between the Alpha and the Delta variants.[103]

A current study demonstrates that two doses of Pfizer vaccine have 87.9% efficacy against symptomatic disease caused by B.1.617.2 (Delta) variant, while two shots of AstraZeneca vaccine show 59.8% efficacy.[104]

B.1.1.529 (Omicron), one more variant first came up in Botswana and South Africa, has been designated by WHO as a variant of concern.[105] Early reports showed the Omicron variant is highly transmissible and has high vaccine escape due to frequent mutations in the S protein receptor-binding domain and S2 fusion domain; however, fully vaccinated individuals showed higher protection against severe COVID-19 infection.[106,107] Reported data from South Africa on >11,000 subjects (aged 19–59 years) showed that omicron variant had a lower percentage of hospital admission and less clinical severity compared to the early SARS-CoV-2 variants.[108] The authority of J&J vaccine said that this vaccine has a critical tool in fighting this pandemic, that is, it has the ability to provide protection from different variants across countries.[64]

5 | NEXT-GENERATION COVID-19 VACCINES

Although multiple approved first-generation vaccines made tremendous progress in COVID-19 disease, still, many challenges are remaining as like further increasing efficacy, sufficient vaccine distribution, fighting against different variants.[109] So, the development of second-generation vaccines may be a better option to overcome these gaps and lessen ongoing global spread by focusing on the limitation of first-generation vaccines. The second-generation vaccines are targeting the new variants as well as old ones.

CureVac and GlaxoSmithKline (GSK) are working on a second-generation vaccine for COVID-19. It is designed with a new mRNA backbone that does not conform to CureVac's first-generation CVnCoV candidate.[110] In a preclinical study, two shots of CVnCoV were given to some rats, and they induced strong neutralizing antibodies for SARS-CoV-2 at all dose levels.[109] Sera from these vaccinated animals revealed cross-neutralization activity against the variants that was originated in the UK (B.1.1.7), Denmark (B.1.1.298), and South Africa (B.1.351).[109] This preclinical study suggests that CV2CoV is able to generate a strong immune response against COVID-19 disease and tackle future challenges of this pandemic, allowing this vaccine for further clinical development.[109,110]

CoVepiT is another second-generation COVID-19 vaccine of OSE Immunotherapeutics (France).[111] It is like a peptide-based, multitarget and multivariant vaccine. Its aim is to induce CD8+Tcell-mediated immune response by targeting 11 SARS-CoV-2 virus proteins, such as S protein, M protein and several nonstructural proteins, to cover all initial and novel SARS-Cov-2 variants and strains.[111]

Sanofi Pasteur and GSK vaccine targeting original D614 virus as we as B.1.351 variant. Phase III pending (https://www.sanofi.com/en/media-room/press-releases/2021/2021-05-27-07-30-00-2236989).

6 | ROLE OF NANOMEDICINE IN COVID-19

Current applications of nanomedicine span across a multitude of fields, such as drug delivery, vaccine development, diagnostic (both in vivo and ex vivo), therapeutic, and theragnostic purposes.[21,112] Soft nanoparticles like lipid NPs (solid lipid nanoparticles (SLNPs), liposomes, nanostructured lipid carriers), nanoemulsions, and protein nanoparticles play an effective role in the nanomedicine platform.[113] Because of their unique and excellent properties, nanomedicines have potential applications in treating cardiovascular diseases, neurological diseases, inflammatory diseases, and even cancer.[113,114] The metal nanoparticles, including gold (Au), zinc (Zn), silver (Ag), and titanium (Ti), have proven their ability against various types of viruses like influenza virus,[115] hepatitis B virus,[116] HIV-1,[117] respiratory syncytial virus, zika virus monkeypox virus.[113] The specialty of these metal nanoparticles is to block viral attachment on the surface of cell and cause inhibition of viral internalization.[113] Multiple vaccine products and potential candidates are utilizing nanoparticles to facilitate the vaccine delivery at the targeted area and to protect its cargo while traveling to the site of action. The mRNA-based vaccine candidates are packaged this way.[118] The pros and cons of few nanoparticles are described in Table 3.

6.1 | Nanoformulations in the diagnosis of COVID-19

COVID-19 diagnosis is performed by following up on epidemiological history, auxiliary examinations and clinical manifestations, including nucleic acid testing, computed tomography (CT) scans, blood

TABLE 3 Pros and cons of some nanoparticles.

Nanoparticles	Pros	Cons
Liposomes[119,120]	– Biocompatible and biodegradable – Drug loading capacity is high – Able to modify the physical and chemical properties of drugs	– Manufacturing cost is high – Less stable – More complex than conventional items
Solid-lipid NPs (SLNPs)[121]	– Biocompatible and biodegradable – Large-scale production is easy to do	– Low drug loading capacity – Possible to have drug expulsions
Gold NPs (AuNPs)[122,123]	– Highly biocompatible – Less toxic in nature	– Manufacturing cost is high – Limited availability in the markets
Silver NPs (AgNPs)[124,125]	– Have adjustable size and shape – Density of surface ligand attachment is high	– Expensive and toxic
Dendrimer NPs[120,126,127]	– Biodegradable – Highly soluble – Structural and chemical homogeneity is high	– Manufacturing cost is high – Nonspecific toxicity is high

culture.[128] However, sometimes they have a few limitations as time-consuming, low sensitivity, and lack of specificity due to being a conventional method.[129] Metal nanoparticles (Ag, Au, Cu), magnetic nanoparticles (iron oxide), and quantum dots (Pb, Cu, Ga, Zn, Hg) are synthesized in varying sizes ranging from 2 to 60 nm and used for finding out if the patient has a specific disease or not caused by several viruses as like MERS, SARS, IBV, and H5N1. During this pandemic, this nanoparticles-based diagnosis system provided rapid and selective detection.[129]

Nano biosensor can selectively detect any kind of analyte that is usually made by optical and electrical properties containing nano-materials with biological or synthetic molecules.[130] Since the main purpose of nano diagnosis is to enhance the rapid detection and efficacy,[131] the use of thiol-modified antisense oligonucleotides-capped gold nanoparticles (AuNPs), for example, is a good example of COVID-19 nano diagnosis.[132]

Here are some reports on nano diagnosis for COVID-19 that are introduced:

- Mertens et al.[133] reported a silver (Ag) Respi-Strip diagnostic assay for nano diagnosis of COVID-19, which is able to work within 15 min for detection.
- The dual-functional plasmonic system has fast and effective diagnostic capabilities for SARS-CoV-2 detection.[134]
- Bai and colleagues conducted a study based on the inductive magnetic NP sensor-dependent microfluidic chip oil detection method. According to this study, inductive oil detection sensors with magnetic nanoparticles has great advantages on high detection accuracy.[135]
- Wen and colleagues worked on the lateral flow immunoassay strip to quickly detect the IgG antibody against the coronavirus. This method is economical, more efficient, and easier than other techniques, such as the implementation of isolation and Enzyme-Linked Immunosorbent assay (ELISA).[136]
- Huang and colleagues developed a colloidal Au NP-dependent lateral-flow assay for quick diagnosis and on-site detection of IgM antibodies for coronavirus. This method ensured a low-cost, less time-consuming, effective, and easily operative diagnostic process.[137]

Furthermore, the optoelectric-magnetic biosystems based on immune-sensing and geno-sensing have the ability to detect SARS-CoV-2 efficiently.[138]

6.2 | Nanomedicine-based treatment of COVID-19

Nanomaterials can provide a powerful solution to neutralize the coronavirus infection. The utilization of nanoparticles has significant potential in terms of developing updated treatment strategies for COVID-19.[139] Based on the published literature, using nanomaterials like liposomes, polymeric and lipid nanoparticles and so forth, offer a number of solutions for safe and effective COVID-19 treatment, reducing drug toxicity, improvement of physicochemical properties, enabling drug encapsulation, and targeting the specific binding site.[130,140] Evidence shows that nanoparticles function as potential tools for modulating the immune system that activates the immune activity against viruses. For instance, the modification of graphene oxide with amino groups altered the signaling mechanism of STAT1/IRF1 interferons in T lymphocytes which further induced chemoattractant expression.[139]

A report by Zhang and colleagues described two types of cellular nanosponges, namely, human pulmonary epithelial type II nanosponges and human macrophage nanosponges. These nanosponges attract SARS-CoV-2 viruses and capture them, resulting in the neutralization and disabling of SARS-CoV-2 viruses. As a result, they report nanosponges as an effective countermeasure to coronavirus.[141]

Chitosan nanoparticle has been widely used in various medical fields, such as treating cancer, pulmonary diseases, gastrointestinal diseases, and carrying drugs to the brain because of their biodegradability, biocompatibility, and nontoxic nature.[142] Besides, chitosan NP has already shown its effectiveness in inducing protective immunity against several infectious diseases.[143] In addition, chitosan-based-NPs are useful for the pulmonary delivery of

drugs. Thus, chitosan NPs can be a possible alternative to treating COVID-19 disease.[143]

In another study, McKay and colleagues developed a self-amplifying RNA that encodes the S protein of SARS-CoV-2. This RNA is packaged in a lipid nanoparticle, facilitating the generation of significant levels of neutralizing antibodies. This lipid nanoparticle could be used for the development of novel vaccines and the assessment of immunogenicity that will be useful in developing nanomaterial-based vaccines.[144]

Some research suggests that the use of nano-decoys can inhibit the replication of SARS-CoV-2 and neutralize inflammatory cytokines like GM-CSF and IL-6. Consequently, employing Cell-Derived Vesicles as a treatment method could serve as a promising alternative against SARS-CoV-2.[145]

Nitric oxide (NO) has shown potential in inhibiting the replication of SARS-CoV.[146] Given that SARS-CoV-2 primarily targets endothelial cells, which are a significant source of NO synthesis, delivering NO-based nanoparticles may offer a response to this viral assault on endothelial cells.[147] Therefore, NO nanoparticles could be considered as a viable option for treating COVID-19.

Iron oxide (FeO) nanoparticles have been approved by the US-FDA for treating anemia, and some studies have reported their potential antiviral activity. Abo-Zeid and colleagues conducted a molecular docking study to evaluate the interaction between IONPs and the S protein receptor of SARS-CoV-2, which is necessary for binding to host cells. They recommended the clinical trial of FDA-approved IONPs for treating COVID-19 based on their potential to induce conformational changes in viral proteins and thus inactivate SARS-CoV-2.[148]

6.3 | Nano-formulations in the prevention of COVID-19

As SARS-CoV-2 can be persistent for 3 h in aerosolized form and more than 9 days at 30°C, WHO recommends maintaining personal hygiene, wearing a mask, and cleaning up surfaces with disinfectant. In this situation, nanotechnology-based formulations open up new avenues.[149]

Experts have developed disinfectants formulated with silver NPs and titanium oxide and used for building cleaning. This disinfectant acts as a penitential disinfectant by oxidation reaction by utilizing light indeed. NPs-based disinfectants have several challenges in reaching the market, for example, production cost, toxicity, scalability and so forth, although they have various advantages.[149] Silver nanoparticles (Ag-NPs) based sanitizers have possible applications against the virus.[150] The antiviral effect of this nanoparticle has already been proven. It helps to damage the structure of virus. The job of impregnation of Ag-NPs in face masks and air filters is to inactivate SARS-CoV-2.[145] Influenza viruses can be inactivated when exposed to a mask containing CuO-NPs. A recent study demonstrated that the SARS-CoV-2 virus is inactivated on the surface by copper-filled materials. Hence, CuO with NPs has a suitable strategy in deactivating the SARS-CoV-2 viruses in the outward environment.[145] Additionally, various nanoparticle-based cloths not only trap SARS-CoV-2 but also successfully eradicate them.[138]

The use of gold nanoparticles in vaccine development can be an effective alternative for COVID-19 disease as these can easily produce an immune response by accessory cells.[145]

LNPs have a significant role in Covid-19 as vaccine candidates, and they proved their success in the nervous system by developing Paticiran (Onpattro), an RNAi-based treatment.[151] Many pharmaceutical companies are working on a nanomaterial-based vaccine to fight against SARS-CoV-2.[152]

For example:

- Novavax, Inc. has designed NVX-CoV2373 by conjugating the spike protein of SARS-CoV-2 on the virus-like nanoparticle's surface[43] for delivery to the host body.[153]
- Moderna and BioNTech/Pfizer have encapsulated their mRNA vaccine in lipid NPs.[50,53]
- Janssen Pharmaceuticals has developed a recombinant vaccine using AdVac® in which adenovirus vectors are combined with PER.C6®, a human cell line.[152]

Besides, more NPs-based vaccines are now under development, aiming to fix this pandemic. It can be considered that nano-based vaccines will be a better option for the prevention of this disease than conventional vaccines due to their quicker, safer, and more effective natures.[152]

7 | CONCLUSIONS AND FUTURE PERSPECTIVES

Due to the electric inception of vaccinations against SARS-CoV-2, the pandemic scenario has shifted radically, with countries opening their borders and enterprises. While new variants of the virus are ever emerging due to various mutations, fully vaccinated individuals so far have shown great resiliency against the infection. Works on the overall management of COVID-19 may be missing until now; research works on several vaccines and medications are well underway. Based on the evidence and discussions, nano-based vaccines and medicines may provide better outcomes for diagnosing and preventing COVID-19 than the available conventional vaccines because of their faster, safer, and more effective features. However, the potential side effects of nanotechnology-based vaccines or medicines should be carefully investigated. Besides, further studies are warranted to accelerate the outcomes of nanomaterial-based therapeutics. Moreover, the inclusion of advanced technologies such as computational analysis or artificial intelligence could significantly fasten the discovery and development of high-performance nanomedicine to combat SARS-CoV-2.

AUTHOR CONTRIBUTIONS

Rabeya Tajnur: Data curation; formal analysis; methodology; visualization; writing—original draft. **Refaya Rezwan**: Conceptualization; methodology; validation; writing—original draft; writing—review & editing. **Abdul Aziz**: Validation; visualization; writing—review & editing. **Mohammad Safiqul Islam**: Supervision; writing—review & editing.

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CONFLICT OF INTEREST STATEMENT

Mohammad Safiqul Islam is an Editorial Board member of Health Science Reports and a co-author of this article. To minimize bias, they were excluded from all editorial decision-making related to the acceptance of this article for publication. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its Supporting Information.

TRANSPARENCY STATEMENT

The lead author Mohammad Safiqul Islam affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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