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REVIEW ARTICLE

Comparing the immunogenicity of mRNA and non-mRNA COVID-19 vaccines: A scoping review

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ABSTRACT

For the past five years, the Coronavirus disease (2019 COVID-19) has spread alarmingly, challenging the economy and public health. The COVID-19 mRNA vaccines, such as Pfizer-BioNTech's BNT162 and Moderna's mRNA-1273, were developed in a short space of time and were the first mRNA vaccines approved by the United States Food and Drug Administration (US FDA) for Emergency Use Authorization (EUA). In phase II trials, the BNT16b2 vaccine was reported to have 91.3% efficacy against COVID-19, while the mRNA-1273 vaccine showed a slightly higher (94.1%) efficacy against COVID-19 in phase III trials. Both mRNA vaccines are reported to be safe and effective against COVID-19 and have an acceptable adverse event profile. The analysis from this scoping review suggests that the efficacy of the mRNA vaccines was superior to non-mRNA vaccines, which is based on the vaccine efficacy (VE) and antibody response analysis. Further analysis of the mRNA vaccines showed that the Moderna (mRNA-1273) vaccine had higher efficacy compared to the BioNTech, Pfizer (BNT1262b) vaccine. However, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) appears to undergo frequent mutations in its spike protein gene, posing substantial public health concerns as even fully vaccinated individuals can succumb to the newer variants of the COVID-19 virus, warranting further investigation.

1. INTRODUCTION

In late 2019, the coronavirus disease-2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first discovered in Wuhan, China [1]. The virus spread internationally at an alarming pace, challenging public health, and causing severe economic and societal disruptions. The virus outbreak was declared a public health emergency of international concern by the World Health Organization (WHO) on 30 January 2020 and was subsequently declared a global pandemic on 11 March 2020 [2]. The virus is transmitted human-to-human via inhalation of respiratory droplets from coughing and sneezing COVID-19-positive patients [3]. The viral infection caused mild to moderate symptoms in approximately 80% of the patients, while 20% experienced acute symptoms such as sepsis, acute respiratory distress syndrome, severe pneumonia, and death [4]. As of February 2022, the WHO has recorded 428 million confirmed cases of COVID-19, including approximately 5.9 million deaths [5]. To limit the spread of the COVID-19 pandemic, the WHO proposed some Public Health and Social Measures (PHSM)

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guidelines such as wearing face masks, adapting or closing schools and businesses, imposing restrictions on gathering, limiting domestic movements and international travelling [6]. Besides these preventative measures, vaccination was considered a crucial way to stop the spread of COVID-19.

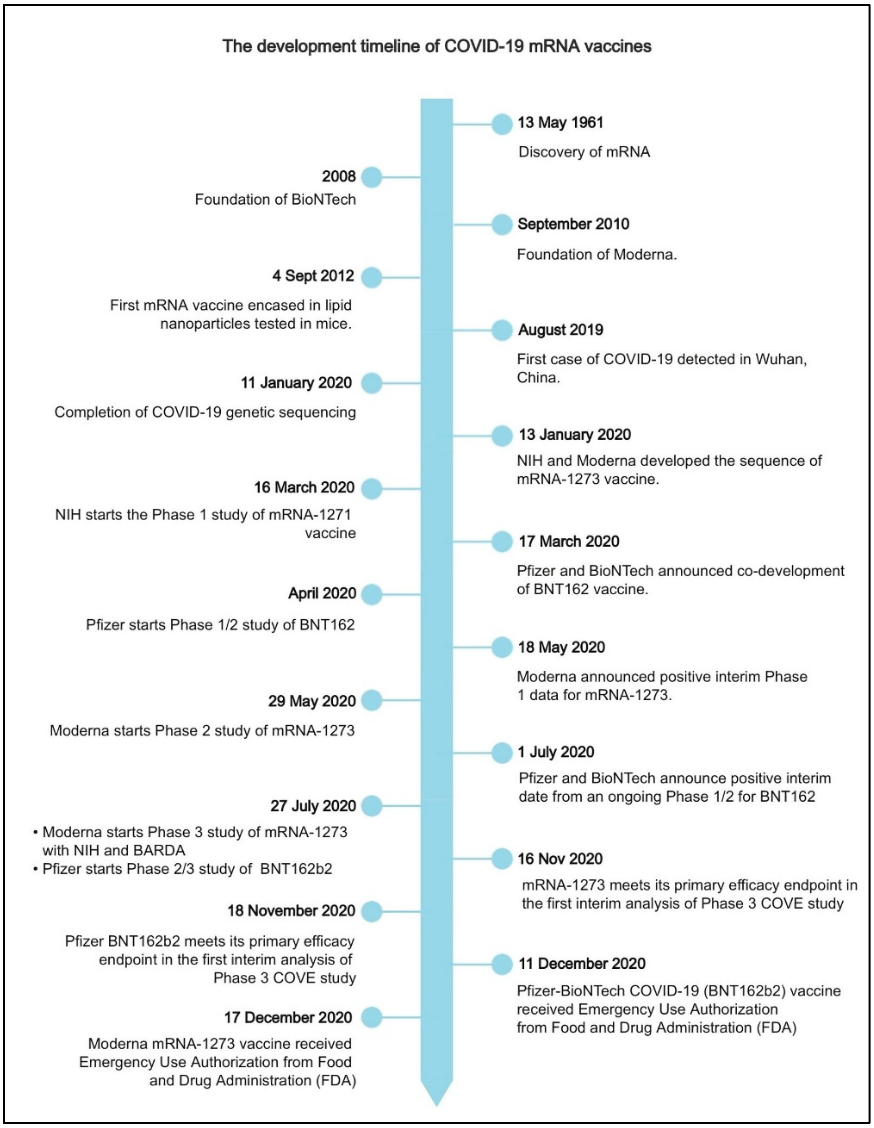

Fig.1 Timeline for the development of COVID-19 mRNA vaccines

Various COVID-19 vaccines were developed using several platforms such as the mRNA vaccine, DNA vaccine, attenuated virus vaccine, inactivated virus vaccine, and adenovirus vector vaccine. Major pharmaceutical companies like Pfizer and Moderna have developed mRNA vaccines against COVID-19 in record time (Figure 1), making mRNA COVID-19 vaccine the first mRNA vaccine authorized to be used in humans, marking the beginning of a new era in vaccine development. The mRNA vaccines became new players in human vaccines developed using a newly authorized platform, which have the edge over the traditional approaches in a pandemic situation. The COVID-19 mRNA vaccines were developed based on the genetic sequence coding for the spike protein of the SARS-Cov-2 virus, which can be rapidly produced in a laboratory setting compared to inactivated-virus vaccines that require bioreactor culture [7]. In addition, the mRNA vaccines elicited robust immune responses while maintaining cost-effective, rapid, large-scale production.

This paper assesses the development of the COVID-19 mRNA vaccines, their mechanism of action, the efficacy of the vaccines, the obstacles faced in developing mRNA vaccines, the side effects reported post-vaccination and the research gaps in COVID-19 mRNA vaccines. Additionally, we also carried out a scoping review aimed to review research articles to compare the efficacy of mRNA and non-mRNA COVID-19 vaccines.

2. REVIEW

2.1 History of the development of mRNA vaccine

Since the discovery of mRNA, research in this field has grown exponentially, ultimately leading to the development of RNA-base vaccines [8]. In the early phase, the research on mRNA is impeded by poor cellular uptake of naked mRNA. In 1978, the challenge was overcome by the development of lipid-based formulations, where rabbit globin mRNA introduced to mouse lymphocytes have been translated successfully [9]. Following closely in that year, protein expression from human epithelial carcinoma cells (HEp-2) was successfully stimulated by Iiposomally-encapsulated mRNA [10]. Subsequently, the efficiency of RNA transfection was further improved by incorporating synthetic cationic lipid in liposome [11].

The discovery of deoxyribonucleic acid (DNA)-dependent RNA polymerase enzymes enables in-vitro mRNA transcription (IVT) based on DNA templates. This led to the first transcription of specific mRNA using a template in 1984 [12]. mRNA was not used as a vaccine until 1993, where liposome-encapsulated mRNA was applied in preclinical study [13]. mRNA vaccines were tested against infectious disease such as influenza and rabies by Phase I clinical trials in 2017 [14, 15]. To overcome the potential toxicity of liposomes, mRNA is delivered using ionizable lipid nanoparticles (LNPs) [16, 17]. LNPs also serve as potent vaccine adjuvant and significantly improve the delivery efficacy [18].

The combination of modified mRNAs and LNPs serves as the current foundation of the mRNA vaccine [19]. This platform has been well-proven to elicit optimal immune response, this is contributed by the synergy between LNPs and modified mRNA which improve vaccine safety and efficacy [18]. During the COVID-19 outbreak, the nucleoside-modified mRNA-LNP vaccine platform is applied by Pfizer-BioNTech and Moderna for their vaccine development [20].

2.2 Development and efficacy of COVID-19 mRNA vaccines

Within a year, Pfizer and Moderna had developed their mRNA vaccines, and the WHO and the Food and Drug Administration (FDA), USA, authorized these vaccines for emergency use (Table 1) [21, 22]. The mRNA vaccine platform has been proven to be time-effective as these vaccines can be produced rapidly, an essential feature in a pandemic scenario like the COVID-19 pandemic. In addition, the mRNA vaccine platform allows flexible vaccine design and, most importantly, the mRNA vaccines are deemed to be safe as the mRNA is eliminated in the host body naturally and does not integrate into the host genome. The study of the Pfizer BNT162 vaccine was determined based on pooled data from phase I and II/III studies, 26 observational vaccine effectiveness studies, and two post-authorization vaccine safety monitoring systems, i.e. 1) the vaccine adverse events reporting system (VAERS) and 2) the vaccine safety datalink (VSD). The Pfizer BNT162 vaccine had an efficacy of 94.3% in the prevention of COVID-19–associated hospitalization; 89.3% in preventing asymptomatic SARS-CoV-2 infection; and 96.1% in the prevention of COVID-19–associated death [23]. A Phase III study using the Moderna mRNA-1273 vaccine achieved an efficacy of 93.2% in preventing COVID-19, 98.2% in preventing severe COVID-19, and 63.0% against asymptomatic COVID-19 [24].

Table 1. Information of COVID-19 mRNA vaccines

Vaccines	Developer	Dose	Schedule	Efficacy	References
Moderna mRNA -1273	Moderna, National Institute of Allergy and Infectious Diseases (NIAID)	2 (50 µg, 0.5 mL)	Day 0 + 28	Phase III 94.1%	[8]
Pfizer BNT162b2 /Comirnaty	Pfizer/BioNTec h, Fosun Pharma	2 (30 µg, 0.3 mL)	Day 0 + 21	Phase II/III 91.3%	[9]

2.3 Vaccination and host immune system

Vaccination is a simple and effective way to provide immunity against harmful diseases. It stimulates pathogenic exposure, activating our immune system to generate effector cells and antibodies against specific infectious agents. The human immune system consists of leucocytes, lymphoid organs and tissues, soluble factors and various molecules/proteins that work together to help the body fight pathogens and to develop long term protection against infectious agents. In general, the human immune system has two main arms, i.e., innate, and adaptive immune systems that protect the human body against various infectious agents and cancer. The innate arm has an important role in preventing entry and containing any breach by pathogens. The leucocytes involved in innate immune response [e.g., neutrophils, eosinophils, natural killer (NK) cells, dendritic cells (DC), macrophages, and mast cells] can respond rapidly to pathogens [25], but these cells cannot provide long-lasting immunity [25]. In the adaptive immune system, the lymphocytes (T- and B-cells) possess cell surface receptors that enable specific antigen recognition. Upon activation by specific antigens, these lymphocytes will undergo clonal expansion and differentiate into effector and long-lived memory cells that are specific for the targeted pathogen [25, 26]. The T-cells are responsible for coordinating the immune responses and killing infected cells, whereas the activated B-cells differentiate into plasma cells that produce antigen-specific antibodies The adaptive immune system requires a longer response time compared to the innate immune system, and proper activation of the adaptive arm will produce long-lived memory B- and T-cells, which can provide a faster and stronger immune response when faced with reinfection [25]. This is the principle used in vaccination, which means that vaccinations can be used to generate immunological memory that can help to defend the host against future infections by vaccine-specific pathogens.

2.4 How do mRNA vaccines work?

Coronavirus is an enveloped RNA virus with four structural proteins, namely: envelope (E), membrane (M), nucleocapsid (N), and spike (S) proteins [25]. The S-protein is the primary surface protein of the SARS-CoV-2 virus is responsible for infection of human cells as these proteins allow viral attachment, fusion, and entry into target human cells [27-29]. The receptor for the S-protein of SARS-CoV 2 is the angiotensin-converting enzyme 2 (ACE 2) receptor found on host cells [28]. The receptor-binding domain (RBD) located in the S1 subunit initiates viral attachment to the host cell by binding to the ACE 2 receptors on host cells. The S2 subunit induces significant structural rearrangement, which allows the fusion of the

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viral and host membranes [27, 28]. Therefore, the viral S-protein of the SARS-CoV 2 virus was the main target for developing vaccines, host antibodies, and entry inhibitors.

In the development of the mRNA vaccine, the mRNA that codes for the S-protein of SARS-CoV 2 was encapsulated in lipid nanoparticles (NPs) as these NPs enable uptake of mRNA into host cells [30]. Once the vaccine is injected intramuscularly, the encapsulated mRNA enters the muscle cells, and translation of the mRNA will be initiated to produce the S-protein (Fig. 2) [27]. The peptides presented on the major histocompatibility complex (MHC) class II (MHC II) proteins can activate CD4+ T-lymphocytes, also known as T-helper (Th) cells [27]; while peptides presented on MHC class I (MHC I) proteins can activate the CD8+ T-cells, also known as the cytotoxic T-lymphocytes (CTL) [27]. The activated CD4+ T-cells will produce cytokines that stimulate activation of antigen-specific B-lymphocytes, inducing them to differentiate into plasma cells, which produce S-protein-specific antibodies and memory cells. The S-protein-specific antibodies can be used as defence mechanisms against the antigen [27]. In addition, the T-cell receptor (TCR) of the activated CD8+ T-cells can recognize virus-infected cells through the S-protein peptides expressed on the surface of some host cells [25, 26].

The S-protein produced from the mRNA vaccines can also directly activate antigen-specific B-lymphocytes, which will induce these cells to differentiate into plasma cells that produce IgM class antibodies against various epitopes on the S-protein. However, for memory cells to develop, it is crucial that the Th cells are also activated as the interactions between the T- and B-cells are crucial for development of memory cells as well as producing antibodies of different isotypes, in particular IgG [27, 28]. The plasma cells will secrete large amounts of antibodies against the S-protein, while the memory B cells serve as long term immunological memory against future detection of S-protein [25].

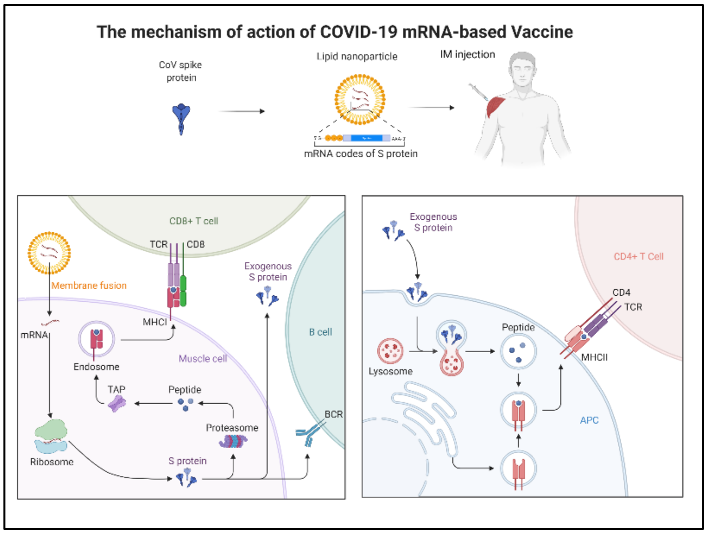

Fig.2 The mechanism of action of COVID-19 mRNA vaccines

Source: Corbett et al (2020)

2.5 Adverse effects of mRNA vaccines

Several post-vaccination adverse effects were reported with the two COVID-19 mRNA vaccines, i.e., Pfizer BNT162 and Moderna mRNA-1273. Some common post-vaccination symptoms include allergy, pain and swelling at the injection site, fatigue, fever, headache, nausea, itching, joint pain, chills, and vomiting [31, 32]. Both vaccines appear to induce rare side effects such as myocarditis and anaphylactic shock [31, 32]. Long term post-vaccination studies should be carried out to monitor the safety and effectiveness of the

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vaccines post-vaccination. In addition, similar monitoring should be observed with booster doses and heterologous vaccinations.

2.6 Emerging variants of concern

The SARS-CoV-2 virus appears to undergo mutations over time, producing newer viral strains circulating in the community. Some of the newly emerging virus strains pose serious concerns to the community, while some are relatively harmless. Some of the variants of concern (VOC) include the Alpha (B.1.1.7), Beta (B.1.351), Delta (B.1.17.2) and Omicron (B.1.1.529) variants [33-35]. These VOC have mutations in the spike protein's receptor-binding domain (RBD) and have increased viral transmission. These mutations can potentially affect the molecular, antigen and serology tests for COVID-19 and the vaccine effectiveness against the virus. In a study conducted in South Africa, vaccination with the Pfizer BNT162b2 had an efficacy of 70% and 93% against COVID-19 hospitalization during the omicron and delta dominant period [33].

Individuals vaccinated with the Moderna mRNA-1273 or Pfizer BNT162b2 vaccine had 27±17 times lower plasma neutralization potency against the omicron S-protein compared to the original (Wuhan-hu-1) variant [36]. These findings indicate a reduction in vaccine effectiveness against the new emerging variants. Therefore, the vaccines must be constantly tested against the emerging virus strains and, in some cases, be redesigned to adapt to the emerging virus strains. The recent authorization of booster dosage and heterologous vaccination reported enhancement of protection from the primary vaccination dosage, which is essential to defend against the mutated variants [37, 38].

A scoping review was undertaken to compare the immunogenicity of mRNA and non-mRNA vaccines against the COVID-19 virus.

3. MATERIALS AND METHODS

This scoping review followed the Arksey and O’Malley’s five-stage framework, which includes, Stage 1: identifying the research question, Stage 2: identifying relevant studies, stage 3: Study selection, Stage 4: charting the data and lastly, Stage 5: collating, summarizing, and reporting the results [39].

3.1 Research question

The research question of this scoping review was “Do mRNA COVID-19 vaccines have higher immunogenicity compared to non- mRNA COVID-19 vaccines?”

3.2 Identification of relevant studies

A PICO template with was used to identify and develop the description that would fit each category for this study (Table 2), which was used to develop search terms that were used to search for relevant original research articles in the five databases, which were Ovid MEDLINE, Cochrane, PubMed, Scopus and Web-of-Science (WOS). The search was limited to research articles published in the last one year (2021 to 2022) as there was a huge number of research papers on this topic as COVID-19 is a heavily researched area presently. The research papers identified from the five databases were imported into EndNote X9, where duplicate papers from the different databases were removed.

Table 2. PICO template used to develop search terms

PICO Terms		Description
P	Patient/Problem	COVID-19 pandemic
I	Intervention	COVID-19 mRNA vaccines
C	Comparison	COVID-19 non-mRNA vaccines
O	Outcome	Higher antibody response and improved efficacy

Source: Tan et al (2026)

3.3 Study selection

The articles were then exported to an online software Covidence, for further de-duplication and screening steps. Covidence is an online software that can be used to carry out systematic review-based research. In the initial screening step, the title and abstract of the selected articles were screened based on the exclusion and inclusion criteria of this study (Table 3). Then, full-text review based on the exclusion and inclusion criteria of this study was performed. In both these screening steps, each research article was reviewed independently by two researchers, and any arising conflicts were resolved by a third independent researcher. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) chart (Fig. 3) was used to show the details of these screening and selection steps.

Table 3. Exclusion and inclusion criteria of this study

Inclusion criteria	Exclusion criteria
• Studies comparing the efficacy of COVID-19 mRNA vaccines in humans. • Studies conducting a trial on non-mRNA vaccines. • Studies that are in English. • Studies that are conducted in adults (above 18 years old).	• Studies comparing the efficacy of the COVID-19 vaccines in pregnant women, lactating women and in children (below 18 years old). • Studies that tested the efficacy of vaccines in animals. • Studies that are conducted as a review, opinion papers and systematic reviews. • Non-English language papers.

Source: Tan et al (2026)

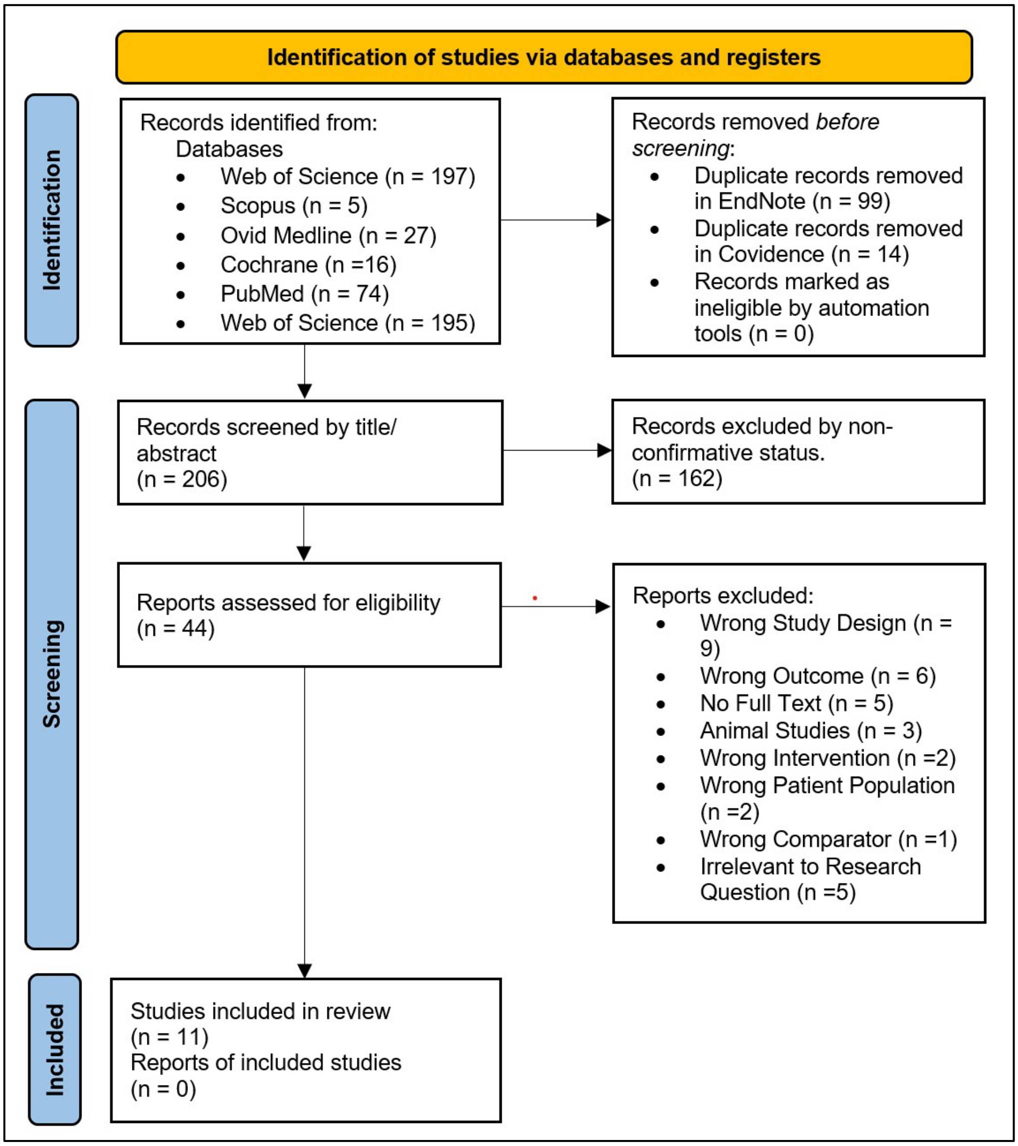

Fig.3 PRISMA chart showing the details of screening and selection of research articles

Source: Tan et al (2026)

3.4 Data charting and analysis

Each article that was included for the final analysis was read and the relevant data was gathered in an organized way using a template generated on an Excel sheet. The data were critically analysed. After data extraction was completed, analysing the data was next. Each article that was extracted was then analysed to achieve a common conclusion. The therapeutic outcomes were analysed and divided based on (i) vaccine efficacy, (ii) antibody response and (iii) neutralizing capacity.

4. RESULTS

4.1 Selection of research articles

The initial search identified 319 publications, which was reduced to 220 studies once the duplicate records were removed using a function in the EndNote X9 software. A second round of removing duplicates was performed once these articles were imported into Covidence, where the total number of eligible papers dropped to 206 articles. Screening these 206 articles initially based on title and abstract reduced the number of papers to 44 articles (Fig. 3). Then, the 44 articles were subjected to full-text review, which eliminated 33 articles, yielding 11 articles. In both cases, screening and selection were performed based on the exclusion and inclusion criteria of this study (Table 3) and their relevance to the research question. In addition, the broad reasons for rejecting research articles during the full-text review are provided for each article (Fig. 3). Following this, relevant data were extracted from the 11 research articles that were included in this study (Table 4), which was then used for analysis.

4.2 Information on research article

Of the 11 research articles shortlisted for this study, four (36%) were published in the year 2021; five (46%) were published in 2022, while the remaining two were published in 2023 (Fig. 4a).

Three research approaches were used in the nine studies i.e. (i) observational studies (18%; n=2); (ii) cohort studies (73%; n=8); and (iii) prospective study (9%; n=1) (Fig. 4b). The nine research articles were classified into three regions of studies (Fig. 4c), eight studies from Europe (73%), two studies from North America (18%), and a study from Asia (9%). In addition, eight studies compared the efficacy of mRNA vaccines with viral vector vaccines, one study compared the efficacy of mRNA vaccines to the inactivated vaccines while two studies compared the efficacy of mRNA vaccine to both viral vector vaccine and inactivated virus vaccine (Fig. 4d).

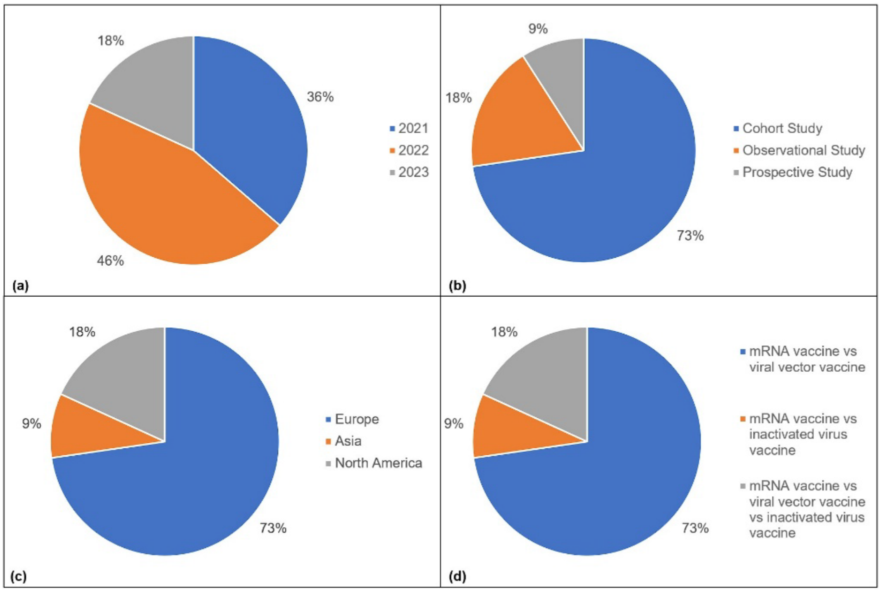

Fig. 4 Analysis of the short-listed research articles (a) type of studies included in the scoping review; (b) region in the world where the studies included in the scoping review were conducted; (c) the types of vaccine intervention used in the studies included in this scoping review

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Table 4 Summary of data extracted from studies comparing immune response parameters of mRNA and non-mRNA COVID-19 vaccinations

	Author (s)	Region	Vaccine Type	Vaccine Name	Groups	Number	Number of doses	Duration between doses	Vaccine Efficacy	Binding antibody responses	Neutralizing antibody
1	Braeye *et al*., 2021	Europe	mRNA	mRNA-1273	mRNA-1273	652	2	3-5 weeks	85% (95% CI 80–90)	NA	NA
				BNT162b2	BNT162b2	7275	2	3-5 weeks	74% (95% CI 72–76)		
			Viral vector	ChadOx1	ChadOx1	55	2	12 weeks	53% (95% CI 12–84)		
				Ad26.CoV2.S	Ad26.CoV2.S	74	1	NA	61% (95% CI 29–84)		
2	Vitek *et al*., 2022	Europe	mRNA	BNT162b2 +mRNA-1273	mRNA-Age group 18-49	8	2	NA	18-49: 92% (85-96%)	NA	NA
					mRNA-Age group 50-64 age group	22	2		50-64: 93% (90-96%)		
					mRNA-Age group ≥ 65	243	2		≥ 65: 79% (75-82%)		
			Viral vector	ChAdOx1CoV-19 + Ad26.CoV2-S	Viral vector- Age group 18-49	19	2		18-49: 76% (62-85%)		
					Viral vector-Age group 50-64	39	2		50-64: 82% (75-87%)		
					Viral vector-Age group ≥ 65	36	2		≥ 65: 61% (46-72%)		
3	Paris *et al*., 2021	Europe	mRNA	mRNA-1273	mRNA-1273	Partially vaccinated 262; Fully vaccinated 464	2	3-4 weeks	Partially vaccinated = 38.2% (6.3-59.2%)	NA	NA
				BNT162b2	BNT162b2	Partially vaccinated 246; Fully	2	3-4 weeks	Partially vaccinated = 49.2% (19.1-68.1%); Fully		

						vaccinated 685			vaccinated = 94.6% (61.0-99.2%)		
			Viral vector	ChadOx1	ChadOx1	Partially vaccinated 776; Fully vaccinated 1	2	12 weeks	Partially vaccinated= 86.2% (76.5-91.0%)		
4	Poukkaa *et al*., 2021	Europe	mRNA	BNT162b2 + mRNA-1273	BNT162b2 + mRNA-1273	315413	2	3-4 weeks	VE against infection= 82% (95% CI 79–85%); 91–180 days after the second dose= 62% (95% CI 55–68%)	NA	NA
			Viral vector	ChAdOx1	ChAdOx1	14760	2	12 weeks	VE against infection= 89% (73–95%); 91–180 days after the second dose= 63% (-166–95%)		
5	Self *et al*., 2021	North America	mRNA	mRNA-1273	mRNA-1273	476	2	4 weeks	Full surveillance period= 93% (91-95%); 14–120 days after full vaccination =93% (90-95%); >120 days after full vaccination 92% (87-96%)	Anti-RBD IgG level (median = 4,333; interquartile range [IQR] = 3,134–7,197; geometric mean = 4,274; 95% CI = 3,393–	Anti-spike IgG level (median = 3,236; IQR = 2,125–4,975, geometric mean = 3,059; 95% CI = 2,479–3,774 BAU/mL)

										5,384 BAU/mL)	
				BNT162b2	BNT162b2	738	2	3 weeks	Full surveillance period= 88% (85-91%); 14–120 days after full vaccination= 91% (88–93%); >120 days after full vaccination 77% (67–84%)	Anti-RBD level (median = 3,217; IQR = 2,048–4,668; geometric mean = 2,950; 95% CI = 2,325–3,742 BAU/mL) (p = 0.033)	Anti-spike IgG level (median = 2,983; IQR = 1,954–4,059; geometric mean = 2,444; 95% CI = 1,936–3,085 BAU/mL) (p = 0.217)
			Viral vector	Ad26.CoV2.S	Ad26.CoV2.S	113	1	NA	Full surveillance period=71% (56–81%); >28 days after full vaccination=68 % (49–80%)	Anti-RBD level (median = 57; IQR = 26–94; geometric mean = 51; 95% CI = 30–90 BAU/mL) (p<0.001)	Anti-spike IgG level (median = 59; IQR = 30–104; geometric mean = 56; 95% CI = 32–97 BAU/mL) (p<0.001)
6	Goldblatt *et al*., 2022	Europe	mRNA	mRNA-1273	mRNA-1273	19/19	1/2	27(26–28)	NA	Anti-spike IgG, Geometric mean concentrations (GMC) against wild-type 5530 (4007–7633), alpha	NA

								3890(2791–5421) or delta 1957(1426–2686) variants
		BNT162b2	BNT162b2	36/51	1/2	21(20–60)		IgG GMC against wild-type 2667 (2077–3425), alpha 1801 (1390–2332) or delta 1061 (811–1387) variants
	Viral vector	ChadOx1	ChadOx1	28/21	1/2	66 (33–79)		IgG GMC against wild-type 196 (141–273), alpha 108 (76–154) or delta 52 (35–77) variants
		Ad26.CoV2.S	Ad26.CoV2.S	25/NA	1/2	NA		IgG GMC against wild-type virus 61 (37–101), alpha 37 (22–62) or delta 32 (35–77) variants

7	Kwok *et al*., 2022	Asia	mRNA	BNT162b2	BNT162b2	BNT162b2, 0 month after vaccination = 140	2	NA	NA	ELISA positive IgG against RBD,% (≥ 0.5)= 100 (97.4-100)	Surrogate virus neutralisation test (sVNT) % of positives (≥ 30%)=98.6 (94.9-99.8)
						BNT162b2, 1 month after vaccination = 188	2			ELISA % of positives(≥ 0.5)= 99.5 (97.1-100)	(sVNT) % of positives (≥ 30%)=100 (98.1-100)
						BNT162b2, 2 month after vaccination = 121	2			ELISA % of positives(≥ 0.5)= 100 (97.0-100)	(sVNT) % of positives (≥ 30%)=100 (97.0-100)
						BNT162b2, 3 month after vaccination = 83	2			ELISA % of positives(≥ 0.5)= 100 (95.7-100)	(sVNT) % of positives (≥ 30%)=100 (95.7-100)
						BNT162b2, 4 month after vaccination = 35	2			ELISA % of positives(≥ 0.5)= 97.1 (85.1-99.9)	(sVNT) % of positives (≥ 30%)=97.1 (85.1-99.9)
						BNT162b2, 5 month after vaccination = 23	2			ELISA % of positives(≥ 0.5)= 100 (85.2-100)	(sVNT) % of positives (≥ 30%)=100 (85.1-100)
						BNT162b2, 6 month after	2			ELISA % of positives(≥	(sVNT) % of positives (≥

				vaccination = 3				0.5)= 100 (29.2-100)	30%)=100 (29.2-100)
	Inactivated virus	Cvac	257	Cvac, 0 month after vaccination = 57	2			ELISA % of positives(≥ 0.5)= 93 (83.0-98.1)	(sVNT) % of positives (≥ 30%)=96.5 (87.9-99.6)
				Cvac, 1 month after vaccination = 81	2			ELISA % of positives(≥ 0.5)= 85.2 (75.6-92.1)	(sVNT) % of positives (≥ 30%)=77.8 (67.2-86.3)
				Cvac, 2 month after vaccination = 48	2			ELISA % of positives(≥ 0.5)= 79.2 (65-89.5)	(sVNT) % of positives (≥ 30%)=75(60 .4-86.4)
				Cvac, 3 month after vaccination = 23	2			ELISA % of positives(≥ 0.5)= 47.8 (26.8-69.4)	(sVNT) % of positives (≥ 30%)=60.9 (38.5- 80.5)
				Cvac, 4 month after vaccination = 19	2			ELISA % of positives (≥ 0.5)= 26.3 (9.1- 51.2)	(sVNT) % of positives (≥ 30%)= 21.1 (6.1- 45.6)
				Cvac, 5 month after vaccination = 17	2			ELISA % of positives (≥ 0.5)= 47.1 (23- 72.2)	(sVNT) % of positives (≥ 30%)= 23.5 (6.8- 49.9)

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						Cvac, 6 month after vaccination = 12	2			ELISA % of positives(≥ 0.5)= 41.7 (15.2-72.3)	(sVNT) % of positives (≥ 30%)= 16.7 (2.1-48.8)
8	Ukey *et al*., 2022	North America	mRNA	mRNA-1273 + BNT162b2	mRNA - 1273 + BNT162b2	16	2	NA	NA	Estimates of the mean difference in each measurement between mRNA and J&J: Anti-RBD IgG titers 519.9 (169.1, 870.8), NT50 99.1 (47.9, 150.3), RBD+ (%B cells) 0.036 (− 0.084, 0.156), IFNγ (pg/ml) 35.7	NA
			Viral vector	Ad26.CoV2.S	Ad26.CoV2 .S	17	2	NA			

9	Terpos *et al*., 2022	Europe	mRNA	BNT162b2	BNT162b2	83	2	3 weeks	1 Month after second vaccination: 95.2% 3 Month after second vaccination: 91.25% 6 Month after second vaccination: 75.3%	NA
			Viral vector	ChAdOx1	ChAdOx1	199	2	12 weeks	1 Month after second vaccination: 81.6% 3 Month after second vaccination: 63.09% 6 Month after second vaccination: 59.4%	

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10	Böröcz *et al*., 2023	Europe	mRNA	BNT162b2	BNT162b2	106	2	NA		Anti-SARS-CoV-2 spike IgG Sero-Positivity Ratio= 95.88%; Anti-SARS-CoV-2 IgA Sero-Positivity Ratio= 65.38%
			Viral vector	ChadOx1, Sputnik V	ChadOx1, Sputnik V	77	2			87.67%; 45.21%
			Inactivated virus	BBIP	BBIP	34	2			69.23%; 22.58%
11	Csoma, *et al*., 2023	Europe	mRNA	BNT162b2	BNT162b2	50	2		Total SARS-CoV-2 S-specific antibody (S-Ab) titer: 993 BAU/mL	Anti-SARS-CoV-2 Neutralizing Antibody, Snibe assay: 1.59 µg/mL; Medcaptain test: 31.82 AU/mL
			Viral vector	ChadOx1, Sputnik V	ChadOx1, Sputnik V	50	2		237 BAU/mL	0.50 µg/mL; 12.25 AU/mL
			Inactivated virus	BIBP	BIBP	50	2		139 BAU/mL	0.41 µg/mL; 8.97 AU/mL

NA: not applicable; mRNA: mRNA vaccine; Ad26.CoV2.S: Janssen viral vector; BNT162b2: Pfizer-BioNtech mRNA vaccine; ChAdOx1: Astra-Zeneca viral vector vaccine; Cvac: CoronaVac inactivated virus vaccine; mRNA-1273: Moderna mRNA vaccine; Sputnik V : Gamaleya Center viral vector vaccine; BIBP: Sinopharm inactivated virus vaccine

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4.3 Comparison of immune response parameters

Majority of the studies reported higher vaccine efficacy in mRNA vaccination regimen compared to non-mRNA vaccinations (viral vector vaccine, inactivated vaccine). Similarly, mRNA vaccination also displayed superior immunogenicity in eliciting production of IgG, IgA and neutralizing antibodies (Table 5).

Table 5. Comparing immune response parameters from mRNA vaccination versus non-mRNA vaccination regime

Immune response parameter	Total studies	Number of studies showing higher immune parameters with mRNA vaccination regime [n(%)]	References
Vaccine efficacy	6	4 (67%)	[42-47]
Anti-Spike IgG antibodies	4	4 (100%)	[40, 41, 48, 45]
Anti-RBD IgG antibodies	3	3 (100%)	[49, 45, 50]
Anti-Spike IgA antibodies	1	1 (100%)	[40]
Neutralizing antibodies	2	2 (100%)	[41, 49]

4.4 Vaccine efficacy

Six studies (Table 5) measured the therapeutic outcomes based on vaccine efficacy (VE) [42-47]. In most studies (67%) of this review, mRNA vaccination displayed higher VE compared to non-mRNA counterparts. Contrastingly, in the study comparing the efficacy of partial vaccination by Paris et al., mRNA vaccines displayed lower VE (mRNA-1273: 38.2%; BNT162b2: 49.2%) than viral vector vaccination (ChadOx1: 86.2%). However, the cohort that received full dosage of BNT162b2 mRNA vaccine reported the highest VE (94.6%) in the study, suggesting the need of full vaccination, particularly for mRNA vaccination [43]. In a cohort study, two dosage of homologous mRNA vaccination (mRNA-1273+BNT162b2) were reported have lower VE than two dosage of ChAdOx1 vaccine, although the differences are not meaningful (mRNA: 82%; ChAdOx1: 89%).

4.5 Anti-SARS-CoV-2 IgG and IgA Antibody Levels

Three studies that compared (anti-RBD, spike) IgG antibody levels from individuals who were fully vaccinated with either mRNA or viral vector vaccines [48, 45, 50]. The results show that all the COVID-19 vaccines passed this threshold. The mRNA vaccines produced substantially higher IgG antibody compared to viral vector vaccines [48, 45, 50]. In addition, it was also noted that the mRNA-1273 (Moderna) vaccine produced the highest antibody response compared to the other vaccines.

The mRNA vaccine regimen is compared to viral vector and inactivated virus vaccines in two cohort studies by Böröcz et al., and Csoma et al., Both studies reported mRNA (BNT162b2) to elicit the highest

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production of antibodies (anti-spike IgG, IgA), followed by viral vector vaccine (ChadOx1, Sputnik V), while inactivated virus vaccine (BBIP) has the lowest antibody response.

One study compared antibody responses between BNT162b2 vaccinated and CoronaVac vaccinated cohorts over a period of 6-months. Majority of BNT162b2-vaccinated group have higher levels of antibody responses compared to the CoronaVac group. In addition, the antibody response appears to be stable for BNT162b2 vaccinated group throughout 6-months post-vaccination while CoronaVac vaccinated group drastically dropped at four-months after vaccination [49].

4.6 Neutralizing antibodies

In a cohort study conducted by Csoma et al., mRNA (BNT162b2) vaccinated group were reported to produce the highest neutralizing antibody level at 31.82 AU/mL compared to viral vector vaccinated group (ChadOx1, 12.25 AU/mL), and inactivated virus vaccinated group (BIBP, 8.97 AU/mL).

Similarly in the study conducted by Kwok et al., BNT162b2 vaccinated cohort displayed stable prolonged neutralizing antibody production (sVNT % of positives [≥ 30%]) post-vaccination (0 month after vaccination = 98.6%; 6 months after vaccination= 100%). While CoronaVac vaccinated cohort exhibited substantial waning (0 month after vaccination = 96.5%; 6 months after vaccination= 16.7%).
This suggests mRNA vaccines can provide strong and long-lasting immunity compared to viral vector vaccine and inactivated virus vaccine.

5. DISCUSSION

The concept of mRNA Vaccine have been in development to be since the early 21st century. The mechanism of the mRNA vaccine is through introducing the mRNA that corresponds to a viral protein. In general, the vaccine ends up providing the recipient's cells to construct the protein. This process leads to initiate an immune response against the protein. Furthering into the process, inducing an immune response will proceeds to the beginning of antibody production [51]. As this is a new vaccine production, there have been concerns regarding the harmful side effects that this vaccine might cause. The common side effects that are associated with the administration includes local side effects such as fever, pain at site of injection and redness and swelling [51]. A study by Oster ME et al., showed that myocarditis was identified as a rare but severe adverse effect after Covid-19 mRNA vaccination. There was an increased risk in adolescent males and young men particularly after the second dose of the vaccination [52]. The long-term side effects should be explored to ensure proper prevention and treatment can be taken into consideration.

Viral vector vaccines were commonly compared in this review to mRNA Vaccines as it is widely used in many different countries. Viral vector vaccines consist of a genetic modified virus, and it exhibits foreign antigen using the host translational machinery [53]. The common side effects that are exhibited are systemic side effects such as headache, fever, and fatigue. Most of these side effects depletes after 1-3 days of vaccination which is promising [54]. However, the ChAdOx1 nCoV-19 have been associated with thrombosis and thrombocytopenia [55]. It was noted that in the study approximately five patients previously healthy) were associated with this rare side effect after 10 days receiving the first dose of AstraZeneca. They were aged between 32-54 years old. This side effect was found in other studies particularly in the younger age group, proving further safety of this vaccine needs to be investigated.

Inactivated vaccines have been effectively used for many years against Polio, Hepatitis A and Rabies. The mechanism of the vaccine is initiated by chemical neutralization of the virus, cultivated using Vero cell lines in conditional medium [53]. CoronaVac has been approved to use in China and has Emergency Use Authorization (EUA) in multiple countries such as Brazil and Malaysia. This vaccine has been associated with a lower vaccine efficacy compared to other in multiple studies. However, on the bright side this vaccine is associated with higher safety recognition due to its property of being an inactivated vaccine.

This scoping review aims to explore the efficacy of mRNA vaccines to non-mRNA Vaccines. According to the studies included, the efficacy of the mRNA Vaccination deemed to be more superior compared to non-mRNA Vaccines based on the analysis of VE and overall antibody response. Further analysing of information showed that, Moderna (mRNA-1273) had a better general efficacy compared to BioNTech, Pfizer (BNT1262b). Nevertheless, both mRNA Vaccines have proofed to be efficacious and beneficial to combat the pandemic, Covid-19. Despite that, the vaccines can be resistant to different variants which complicates the situation. In a study, comparing VE of one dose versus two dose mRNA Vaccine (mRNA-1273, Moderna) with different variants of concern (VOC) of the COVID-19 virus concluded that the mRNA vaccines were efficacious when two-doses were administered instead of one dose, suggests the significance of receiving full vaccination [56]. For instance, the VE against Delta variant was 86.7%, significantly lower compared to efficacy against Alpha Variant (98.4%). This is important to note as SARS-CoV2 is a virus that will continue replicating and the efficacy of the vaccine now will not remain the same as more variants come into play. More research should be conducted as more variants develop to ensure a better understanding is entailed from this situation.

Another aspect that was noted through this review were, certain studies compared the efficacy of the vaccines based on the age groups. Girgic VM et al., compared the Vaccine Efficacy of the mRNA Vaccines (BioNTech, Pfizer (BNT1262b), Moderna (mRNA-1273) to Viral Vector Vaccines (Oxford, AstraZeneca (ChAdOx1), Johnson & Johnson (Ad26.CoV2.S)) based on three categories of age group being 18-49, 50-64 and ≥ 65 years. The study showed the efficacy of mRNA vaccine being more efficacious in all three age groups compared to the viral vector vaccines. However, vaccine efficacy of both mRNA and viral vector vaccines depleted in the age group of ≥ 65 years old [47]. This can also be proved in the study by Collier DA et al., that showed the serum neutralization and antibody response of IgA and IgG after the first dose of Pfizer vaccine were lower in the older individuals (>80 years) [57]. This indicates that antibody response is lower in the older age group compared to the younger age group which is crucial as the older generation is more susceptible to the disease of Covid-19 even if they have gotten their full vaccination.

Elderly people (≥ 65 years) who got either mRNA vaccine 6 months ago or more showed a substantial reduction of Vaccine Efficacy to 43% [47]. This proves the need of a booster to ensure proper protection against Covid-19 particularly in the older age group. Many countries are urging the citizens for their need of booster to ensure the waning of the antibody response would not put their lives in danger and lead to hospitalisation and death. Interestingly, the intervals between the doses of the vaccines have also been shown to modify the efficacy of vaccines. A study shows that an interval of at least six weeks between the administration of two doses of mRNA Vaccine increased the neutralising antibodies [58]. This shows the importance of spacing the doses to ensure better overall efficacy can be achieved. However, certain countries reduced the interval at the beginning of the pandemic to ensure herd immunity was achieved at a faster rate due to the situation being out of hand. All in all, this review shows the importance of research to ensure information stays up-to-date and more guidelines can be created to ensure a safer and protected community.

5.1 Future challenges and research gaps of COVID-19 mRNA vaccines

Recently, the FDA USA authorized booster doses of the COVID-19 vaccines and heterologous vaccination regimes to restore or enhance the protection provided by the primary vaccination [59]. Due to the constant mutation of the SARS-CoV-2 virus, vaccines may require regular evaluation and updating to accommodate mutated viral strains. Moreover, the newer or better COVID-19 vaccines, booster dosage strategies and heterologous vaccination regimes were developed and authorized for emergency use in record time. However, the long-term safety of the vaccines, particularly in immunocompromised individuals, should be closely monitored. Currently, most studies of COVID-19 mRNA vaccines prioritize neutralizing antibodies, additional parameters of vaccine immune response such as T- and B-cell responses should be carried out to provide better insight into the effect of these vaccines on the SARS-CoV-2 virus.

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5.2 Advantages of mRNA vaccines

mRNA vaccines, such as Moderna mRNA-1273 and Pfizer-BioNTech BNT162b2, offer several distinct advantages compared to the inactivated virus vaccine and viral vector vaccine.

One of the most crucial advantages offered by the mRNA vaccine platform is its short development time. Both Moderna and Pfizer have successfully developed their respective mRNA against SARS-CoV 2 and were authorized to use in a short time [21, 22]. This is contributed by the flexibility in manufacturing mRNA vaccine [60]. Upon acquisition of the sequence of the antigen, the mRNA can be synthesized, enabling rapid large-scaled production at a lower cost [60]. This nature of mRNA vaccine also allows rapid adaptation against virus mutation by adapting the mRNA sequence against the mutated variant accordingly [61].

Additionally, mRNA vaccine can eliminate the risk of infection compared to the inactivated virus vaccine. Inactivated virus vaccine utilizes whole virus particles that has been killed, which have a small chance for incomplete inactivation that can poses as a safety concern [62]. In contrast, since mRNA vaccines do not use any live virus, the risk of infection can be eliminated [63].

Lastly, mRNA vaccine has demonstrated a stronger immune response and higher vaccine efficacy than the inactivated virus vaccine. Inactivated virus vaccines present the virus in a non-replicating form [62]. Although they stimulate both humoral (antibody-mediated) and cellular (T cell-mediated) immunity, they may not closely replicate the natural infection compared to the mRNA vaccines, which influence the strength and specificity of the immune response [64]. mRNA vaccines are encoded to produce a specific antigen protein (such as the spike protein of SARS-CoV-2), this contributes to a robust and highly specific activation of antibody-producing B-cells and T-cells and against the virus [65].

In comparison, inactivated vaccines from Sinovac and Sinopharm have been applied widely and are effective vaccines, they generally are more time-consuming to be developed and to scale up for production as biosafety level 3 is required for production of inactivated virus vaccines [62]. They are also based on a more traditional vaccine platform, which can be a bottleneck when rapid adaptation to new variants is required.

These vaccines have played important roles in combating the COVID-19 pandemic, with mRNA vaccines standing out for their rapid development, high efficacy, and adaptability to emerging variants.

5.3 Disadvantages of mRNA vaccine

While mRNA vaccines have displayed remarkable efficacy and have been crucial against the spread of COVID-19 infection, there are a few disadvantages associated with the mRNA vaccine platform.

mRNA vaccines, such as Moderna mRNA-1273 and Pfizer-BioNTech BNT162b2, require ultra-cold storage temperatures (-20°C for Moderna and -80°C to -60°C for Pfizer-BioNTech) for long-term storage up to 6 months [66]. This stringent requirement can be logistically challenging, particularly in regions with limited access to specialized storage facilities or in tropical countries. Once mRNA vaccines are removed from ultra-cold storage, the shelf life and stability of the vaccines are reduced significantly (6 month in ultra-cold storage; up to 30 days in 4°C) [66].

Currently, mRNA COVID-19 vaccines from Pfizer-BioNTech and Moderna have a cost disadvantage compared to inactivated virus vaccines [67]. The higher cost of mRNA vaccines can be attributed by higher upfront research and development cost, and production cost as the mRNA vaccine platform is novel and have a complex manufacturing process. In addition, the distribution cost of the mRNA vaccine is higher due to the requirement of ultra-low temperature for cold chain.

mRNA vaccines are reported to have a higher potential for reactogenicity compared to inactivated virus vaccines [63]. Studies have shown a higher rate of short-term side effects such as fatigue, fever and muscle pain after vaccination compared to inactivated virus vaccines [31, 32]. The novel implementation of mRNA technology into COVID-19 vaccines received some negative public perceptions. The hesitancy toward the mRNA vaccine mainly circles the safety concern of the mRNA vaccination [63]. While mRNA

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vaccines have shown excellent efficacy and flexibility, especially against evolving variants of SARS-CoV-2, they need to overcome some challenges such as logistic, cost, and public perception to expand their impact and accessibility.

6. CONCLUSION

Although vaccines are not the panacea for COVID-19, it is the key to controlling the pandemic's spread and minimizing the adverse effects caused by SAR-CoV-2 infections. A good candidate COVID-19 vaccine should be safe, reliable, induce long-lasting immunity and be widely available. The ability of COVID-19 mRNA vaccines to be designed and be mass-produced in a short time while prompting robust immune response against SAR-CoV-2 is truly remarkable, which indicates the success of the mRNA vaccine platform. However, vaccine-related adverse effects and the long-term effectiveness of mRNA vaccines should be closely monitored to evaluate the safety of the vaccines and facilitate the design of a better mRNA vaccine in the future.

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8. CONFLICT OF INTEREST

Authors declare none.

8. AUTHORS' CONTRIBUTION

Kang Wei Tan, Ashwini Mahendran, and Samantha Khoo Si Mei conducted the review and drafted the manuscript. Saatheeyavaane Bhuvanendran, and Ammu Kutty Radhakrishnan provided critical input towards its content. Kang Wei Tan revised the manuscript.

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