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Original Article

Immunogenicity of a single dose mRNA vaccine in SARS-CoV-2 exposed subjects: A systematic review

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ABSTRACT

The novel coronavirus is quickly spreading and mutating, putting the public's health and lifestyle in shambles. The development and approval of mRNA vaccines came as a breakthrough. The breadth of immune response after a single-dose vaccination in the already infected population is discovered for understanding the hybrid immunity and side effects associated with the second dose. Administering a single-dose vaccine to the seropositive population can spare the doses for the population at higher risk. Methods: PubMed, Web of Science, Google scholar, medRxiv, and the Cochrane library were explored to extract the original data on the efficacy of single-dose mRNA vaccines in seropositive subjects. The Cochrane risk of bias tool was used to assess the risk of bias in the studies. Results: Six studies evaluating the immunogenicity of single-dose mRNA vaccines were incorporated along with some observational studies and literature. These studies present promising evidence for administering only single-dose mRNA vaccines in seropositive subjects, providing biphasic immune responses of greater breadth and duration. Limitations: Most studies had a small sample size, did not correlate the results with higher age groups, with potential risk factors, or with the percentage of individuals who contracted breakthrough infections. Conclusions: A single-dose mRNA vaccine can be immunogenic and protective enough for an already seropositive population by increasing the number of spike protein-specific memory B-cells. Vaccination schedules based on existing anti-body titers in such individuals can spare doses for vulnerable groups, especially when there is limited production and supply of vaccines worldwide.

Keywords:: Immunity, SARS-CoV-2, Vaccination, COVID-19, mRNA.

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INTRODUCTION

The SARS-CoV-2 virus is mutating quickly, and the emerging mutant variants carry high transmissibility. So far, over 227 million global cases have been reported, including 4.6 million deaths until September 2021 [1]. During the raging pandemic, the development and approval of potential mRNA vaccines served the purpose of protecting the population at a greater risk of being infected, like health care workers. Interestingly, the majority of the population recovers after seeking no specific medical treatment. The real-world data from the USA, UK, China, and India provides a promising piece of evidence that the individuals who were infected, recovered, and were never vaccinated, had retained antibody titers even 7 months post-infection [2]. However, these antibodies may not be able to neutralize the emerging variants of concern, highlighting the importance of vaccines. The scope of immunity generated after natural infection when combined with that generated by vaccines has extensively been studied and the results are encouraging [3]. The correlation with the severity of past infection, population characteristics, and effective dosage regimen needs to be studied further to vaccinate the population based on the evidence, keeping the priority population at the top and leading ahead of the pandemic [4].

2. SARS-CoV-2 specific immunity

Lab findings have shown poor cross-reactivity between the antibodies produced in response to SARS-CoV-2 and previous strains of the human Corona-virus (SARS-CoV-1 of 2003) [5].

2.1 Natural immunity versus vaccine-induced immunity

According to the serosurveillance analysis and immunoassay data, the vaccine-induced immune response is more homogeneous, and it reinforces the defense mechanisms that were already in place. Upon contracting infection, most individuals start producing antigen-specific antibodies, showing peak titers within a month, which gradually fade away after accompanying an acute immune response [6]. This results in a significant reduction in serum neutralizing antibody levels, but the memory B and T-cell responses take the work for protection against breakthrough infections [7]. But what about reinfection with a mutated version of SARS-CoV-2 type (Figure 1)? In this case, the protection provided by artificially induced active immunity proves to be superior.

The mRNA vaccines have been reported to generate an immune response against emerging variants of the virus [8]. The in vitro neutralization of viral spike-protein by antibodies generated by these vaccines suggests that these antibodies target a broader extent of places in the receptor-binding domain (RBD) of viral spike-protein when the same effect is compared with natural infection [9,10]. Such a response may be due to the presentation of viral protein in an altered conformation by a vaccine along with the adjuvant. Thus, naturally acquired immunity through infection has the potential for immune evasion against SARS-CoV-2 variants [11].

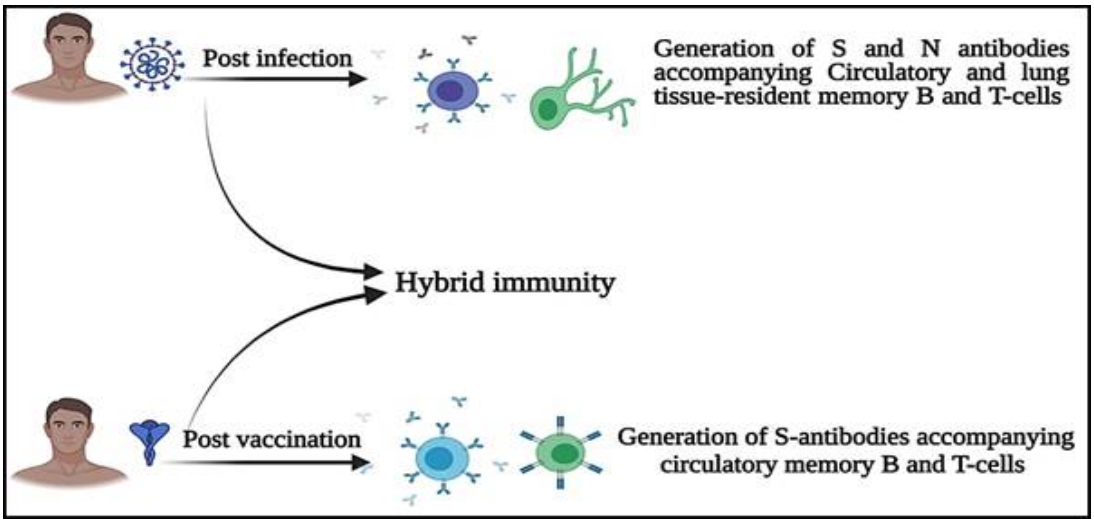

Figure 1. Comparison of the immune response elicited post infection and post vaccination

Another factor responsible for the supremacy of vaccine-induced immunity could be the site of exposure to the antigen. The administration of the vaccine in the deltoid muscle (along with potent adjuvants) optimizes the immunogenicity where the antigen-presenting cells have a better chance of activating the helper T-cells and further proliferation of plasma B-cells to produce antigen-specific circulating IgG antibodies [4].

Taking natural immunity into consideration, the alveolar-macrophages present the viral antigen to CD4+ T-cells, leading to the activation of B-cells. The antibodies thus formed are secretory IgA and circulating IgG. The lungs' tissue-resident CD4+ and CD8+ T-cells limit future re-infections while the presence of secretory IgA antibodies in the airways reduces viral replication and transmission [12]. However, such a response is variable across different population demographics. mRNA vaccines produce homogeneous immune responses across a diverse population demographic and have the potential to achieve herd immunity [13].

2.2 Hybrid immunity

The findings from a study conducted at Chongqing Medical University, China revealed that most of the individuals who recover from COVID-19, develop antibodies after acute infection [4]. The neutralizing character of these antibodies needs to be studied further. The antibodies generated after primary infection may last for about 12 months, providing enough protection for these individuals, followed by a gradual decrease in serum antibody titers [14].

The major concern that remains here is the reinfection with variants of concern (B.1.351 and B.1.617.2). The neutralizing ability of mRNA vaccines has seen a small reduction against emerging variants. So, what if the immunity induced by natural infection and the one induced by vaccination were combined? This gives an insight into the concept of hybrid immunity, where the body's natural primary immune response works in synergy with the secondary immune response, induced by the vaccine, resulting in the robust production of neutralizing antibodies [15]. The recall of diverse and superior memory B-cells that stockpile the immunological variants like an encoding library results in the production of neutralizing antibodies against variants of concern [4]. Thus, hybrid immunity can provide protection of greater breadth than that provided by vaccination alone, suggesting the administration of a single-dose mRNA vaccine to the previously-infected and recovered subjects.

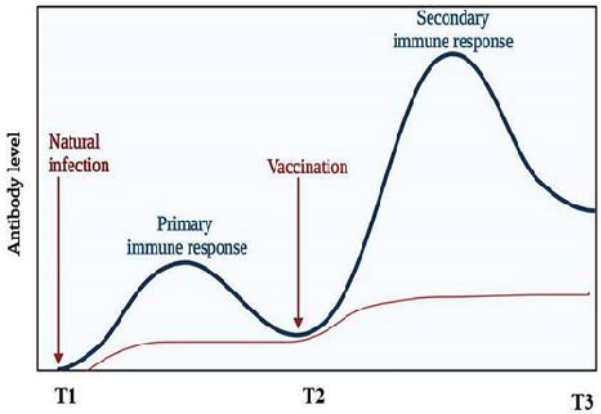

Figure 2. Overview of Hybrid immunity

The red line represents memory B-cells. The blue line represents serum antibody levels. T1: At the time of infection T2: 6 months following infection T3: 12 months following infection.

The natural infection triggers the immune response, slow and gradual in onset, producing IgM antibodies as the primary response followed

by IgG, which sustains in serum for a modest period. Upon vaccinating the previously infected individuals, the antibody and T-cell response are seen to be much superior, referred to as a secondary immune response, having greater breadth and perpetuity.

METHODOLOGY

PRISMA guidelines and recommendations were followed to address systematic study. For the identification and inclusion of relevant records from databases, the PRISMA flow chart was used as shown in Figure 3.

3.1 Search strategy

The databases like PubMed, Scopus, Google Scholar, bioRxiv, medRxiv, Web of Science were used to obtain published records, by using the following search terms: vaccination, SARS-CoV-2, mRNA, Pfizer, Long-term aspects of immunity, antibody titers, single-dose vaccination, COVID-19, immunization, memory B-cell response in COVID-19, and observational studies on mRNA vaccination.

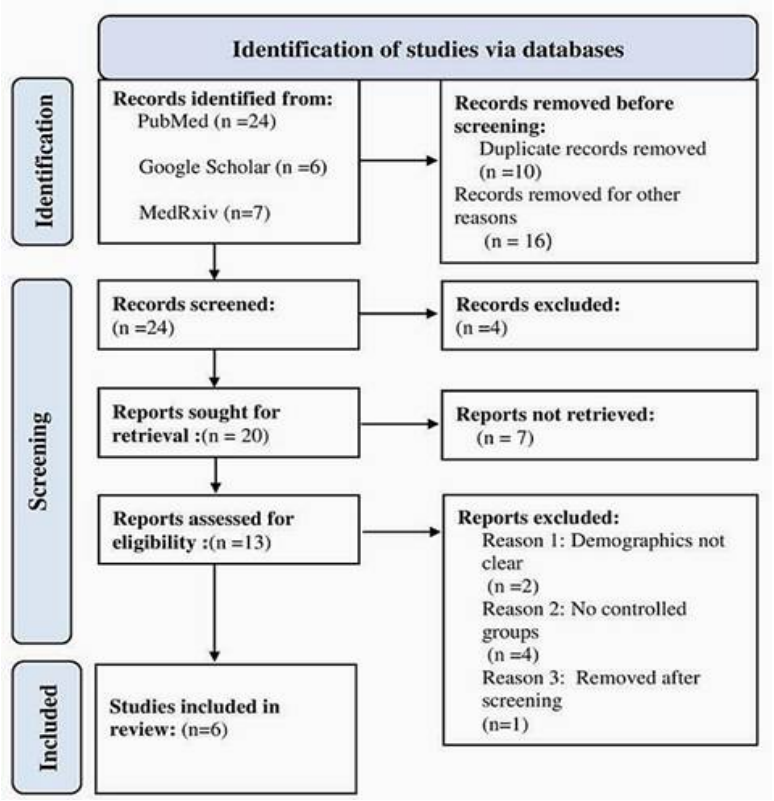

Figure 3. Flow chart of the studies selected for systematic review as per PRISMA guidelines.

3.2 Inclusion and exclusion criteria

The published literature was assessed till September, 2021. The bibliography of the research articles was manually searched to assess further relevant articles. The articles, including the original data, type of vaccine used, characteristics of participants, and the pattern of study, were assessed in full text and considered for inclusion and analysis. Studies with no control groups, no specifications of participants, and articles like letters to the editors, supplementary, and commentaries were excluded.

3.3 Data extraction

After removing irrelevant, duplicate, and biased publications, the following information was extracted from selected publications: date of publication; study design; vaccine type; mean age groups; immunoassay data; serum antibody-titers; number of subjects; statistical and clinical outcome.

4. Systematic analysis and qualitative synthesis

An independent review was done and study characteristics (number of participants, mean age of participants, type of study, and outcomes) are summarised in tabulated form in Table 1.

5. The risk of bias assessment

Taking the study pattern and population characteristics into consideration, risk assessment was done using the Cochrane risk of bias tool (Figure. 4). The numbers of participants in most of the studies were small, including multiple case series or case reports. In the case-control studies, results could be biased by not considering the comorbid conditions and non-uniform time range in which the sampling was done. In the cohort studies, the study confounding carried the risk of bias.

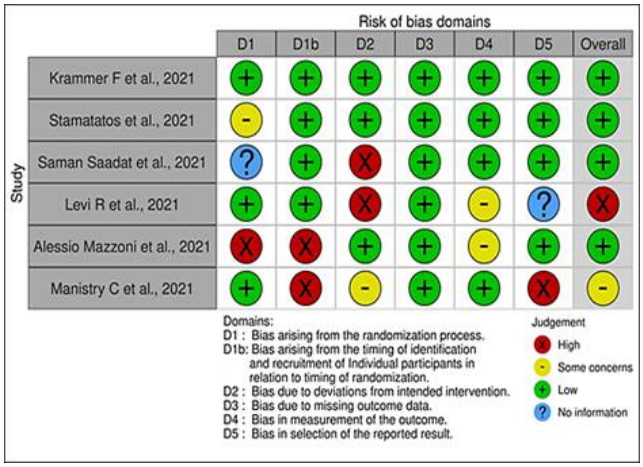

Figure 4. Risk of bias assessment done by Cochrane risk of bias assessment tool.

Table 1. Data representing the characteristics of the study and outcomes (Result part contined)

Study	Design	Number of participants	Age (mean)	Vaccine Type	Place of study	P value	Findings
Krammer F et al., 2021	Cohort study	n=110 (67-seronegative; 43-seropositive)	40 years	mRNA-(Pfizer; Moderna)	USA	P<0.001	Single-dose vaccination in seropositive subjects produced rapid and uniform antibody titers (10-45X to seronegative subjects; response to the second dose was observed to be less significant (Ab titers increase by a factor of 3 only)
Stamatatos et al.2021	Cohort study	n=28 (13-seronegative; 15-seropositive)	49 years	mRNA-(Pfizer; Moderna)	USA	P<0.001	Neutralizing Ab titers after a single-dose vaccination of seropositive subjects found to be ~100X than the infection alone(Ab titre after infection produced non-nAbs against B.1.351 variant, while post-vaccination Ab titre had neutralizing response towards B.1.1351 variant)
Samansaadat et al.2021	Case control study	n=59 (17-seronegative; 42 seropositive)	56 years	mRNA-(Pfizer; Moderna)	USA	P<0.01	Median reciprocal half-maximal binding titres were higher in both symptomatic and non-symptomatic previously infected subjects after single-dose vaccination, while the same response was heterogeneous in seronegative subjects)
Levi R et al.2021	Case control study	n=127 (67- seronegative; 57-seropositive)	40 years	mRNA-(Pfizer; Moderna)	Italy	P<0.05	Serum nAb level was directly correlated with severity of symptoms,a single-dose vaccine induced robust anti-S1/2 Ab response in the previously infected subjects
Alessio mazzoni et al., 2021	Cohort study	n=22 (11-seronegative; 11-seropositive)	47 years	mRNA-(Pfizer; Moderna)	Italy	P<0.01	The frequency of IgG titers and spike-specific B-cells were higher in the previously infected individuals after single-dose vaccination, which significantly reduced after second dose administration.
Manistry C, et al., 2021	Case control study	n=51 (27- seronegative; 24-seropositive)	42 years	mRNA-(Pfizer; Moderna)	UK	P<0.001	The seropositive subjects produced anti-S IgG antibodies 140 folds after first dose of vaccine compared with the IgG titres produced by naïves

RESULTS

Out of the 40 articles accessed for systematic review, 6 observational studies were selected, of which 3 were cohort studies and 3 were case-control studies. The administration of single-dose mRNA vaccines to previously infected and recovered subjects generates a robust immune response with greater breadth and longer duration. The immunogenicity of the second dose in such individuals has shown no significant add-on benefits. The qualitative synthesis of these studies is presented in Table 1, while the clinical outcomes of these observational studies are discussed separately.

DISCUSSION

Looking into the 3 pillars of adaptive immunity—the B-cells, CD4+ T-cells, and CD8+ T-cells play a pivotal role in regulating the breadth and perpetuity of immune response, either through natural infection or induced by the vaccine [16]. In the case of natural infection, cohort studies suggest that the serum antibody titers can be

detected up to 8 months after the infection, though T cell mechanisms remain in action for a longer period [17]. But as far as the aspect of viral mutations is considered, upon reinfection, the body's natural immune system may become susceptible to evasion against mutants of concern [18].

Even the efficacy of mRNA vaccines has seen a three-fold reduction in terms of producing neutralizing antibodies against the Delta variant, which has been studied to be robust against the ancestral strains (though double dose vaccination still provides excellent protection against hospitalization and a reduction in mortality). So when the body's natural immune response is combined or synergized with that induced by the vaccine, this results in enhanced immunogenicity compared with the immunogenicity of the vaccine alone or the immunogenicity after the infection alone, providing superior protection against future reinfection with mutant strains [17].

7.1 Role of memory B cells in cross variant neutralization

Stamatatos et al., 2021 reported that the reason behind the increased breadth of the immune response in the previously infected subjects after vaccination was the memory B and T-cells. Upon infection, the activated memory B-cells stockpile the immunological memory, out of which a significant proportion of those memory B-cells encode spike specific antibodies, which are efficient in neutralizing the variants of concern [6].

When a single-dose of mRNA vaccine (Pfizer-BNT162b2) was administered to the previously infected individuals, the recall of diverse memory B-cells (CD4+ T-cell dependant instruction by T-follicular helper cells) was observed. The result was the production of cross-variant neutralizing antibodies [19].

Memory B-cells were increased by 5–10 folds, which were observed only in the hybridized group. The reinfection with mutated strains in such individuals won't result in immune escape because mutations in T-cell epitopes are not supposed to occur, which gives promising insight toward the long term retention of immunity [4].

Finally, Stamatatos et al., 2021 reported in their study on 28 participants (15 previously infected) that the immunogenicity against cross variants after single-dose vaccination in SARS-CoV-2 exposed subjects was more robust than the immunogenicity produced by the second-dose of vaccine in those individuals who were never infected.

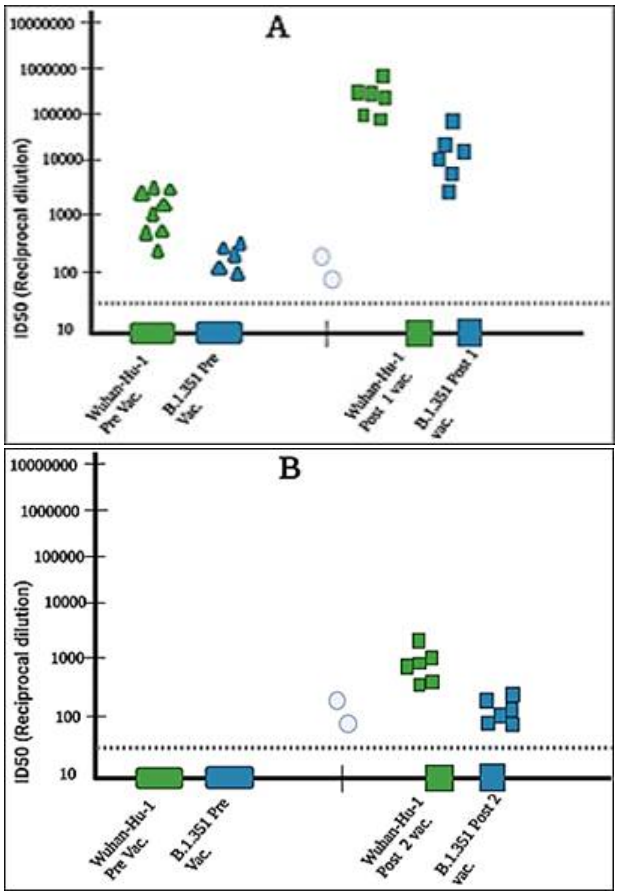

Figure 5. Single-dose mRNA vaccine boosted the immune response in seropositive subjects

A. Serum antibody titers of seropositive and vaccinated subjects upon dilution resulting in 50% neutralization against SARS-CoV-2 variants.

B. Serum antibody titers of naïve and 2 dose vaccinated subjects upon dilution resulting in 50% neutralization against SARS-CoV-2 variants.

*Antibody titers before vaccination shown in triangle and post vaccination shown in square. The previously infected subjects found seronegative shown as open circles. Dashed lines mark off the lowest serum dilutions tested. [As per Stamatatos et al., 2021]

Further, the neutralizing titers against B.1.351 after a single dose of vaccine in subjects who were

previously infected with a non-B.1.351 variant were found to be 25-X higher than titers produced by vaccine alone and 100-X higher than after infection alone. The response was heterogeneous and less potent in non-infected subjects, giving insights for administration of double-dose vaccine in such individuals only [17].

7.2 Immunogenicity of the second dose

The findings from observational studies present promising evidence that single-dose mRNA vaccines produce an immune response of high breadth, both in terms of neutralizing antibody titers and B-cell response, and that skipping or delaying the second dose can be considered for such individuals [17].

Krammer F et al., 2021 in their observational study, including 110 participants, out of which 67 were previously infected and recovered, while 43, were naïve. The average age of participants enrolled was 40 years. They received mRNA vaccines (Pfizer-BNT162b2 and mRNA-1273) either due to their choice or availability. The blood samples were extracted from participants on base-line (day 0) and repeated sampling up to 27 days, with intervals of 4 days. (Figure 6.) A two-step ELISA was used for measuring SARS-CoV-2 spike IgG antibodies [20].

Krammer F et al., 2021 reported that antibody titers in naïve individuals were lower in concentration and the overall response was variable during the sampling and testing period. The previously infected and recovered subjects, upon vaccination, produced uniform, rapid, and at least 10-45 times higher IgG titers than those produced by naïve individuals. Upon administration of the second-dose of vaccine to naïve individuals, the antibody titers were boosted by a factor of 3, whereas no significant increase in IgG titers was reported in the previously infected, recovered, and one-dose vaccinated subjects [20].

A. High antibody titers reported in previously seropositive subjects after single-dose vaccination with no significant increase after second dose.

B. More systemic side effects reported in previously seropositive subjects after vaccination, frequency was comparatively lower in naïve individuals. [As per Krammer F et. al.,2021]

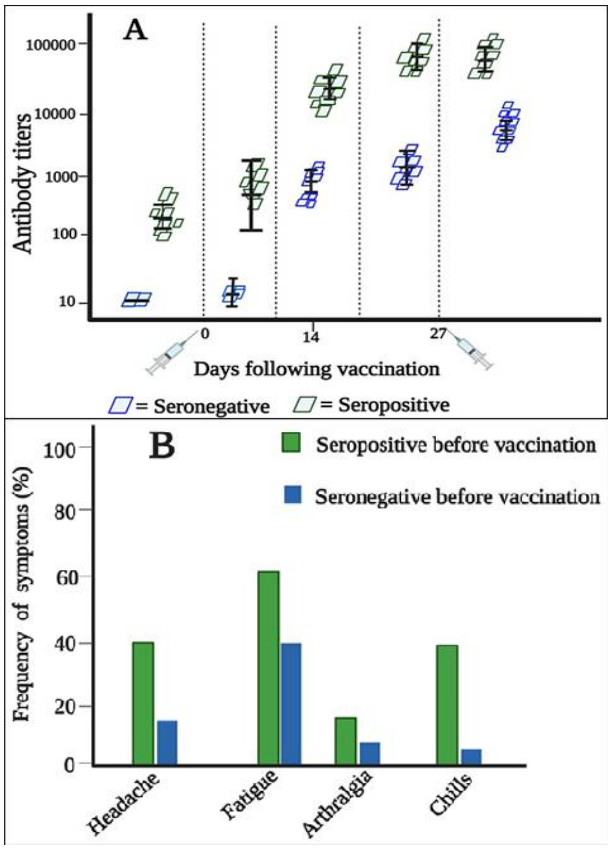

Figure 6. Immunogenicity of mRNA vaccines in seropositive and seronegative subjects

Further, Krammer F et al., 2021 also conducted a study on 230 participants to correlate the side effects associated with the administration of the first and second dose, where they reported more frequent systemic side effects (fatigue, fever, muscle pain, chills, and joint pain) in the previously infected and vaccinated groups than in the naïve and vaccinated group. Thus, if the immunogenicity of a single-dose vaccine is efficacious enough in previously seropositive subjects with no significant boosterim after the second dose, skipping or delaying the second dose will limit the side effects associated with boosterism in such individuals [20].

7.3 IgG titers in correlation with severity of past infection

During initial serosurveillance studies, it was observed that the individuals who were infected with SARS-CoV-2 and were asymptomatic or had mild sore throat like symptoms, the IgG titers in such individuals were present in less concentration and the B-Cells lack spike protein specificity [21]. This clearly indicates that these individuals were not protected well enough

against future re-infections [22].

The following reasons can be assigned to this observation: more efficient mucosal immunity (mediated by IgA); less viral load in the respiratory tract, thus leading to immune escape. In their study on 127 participants, Levi et al., 2021 observed that the IgG titers after infection with SARS-CoV-2 were higher in those subjects who experienced gastro-intestinal disturbances, generalized myalgia, anosmia/dysgeusia, and fever during infection. Upon recovery, when these individuals were given the first dose of mRNA vaccine, the antibody response was more rapid and robust in terms of IgG titers (in the sample taken on the 14th day following the first dose) compared with the antibody response in the infected but asymptomatic subjects [23].

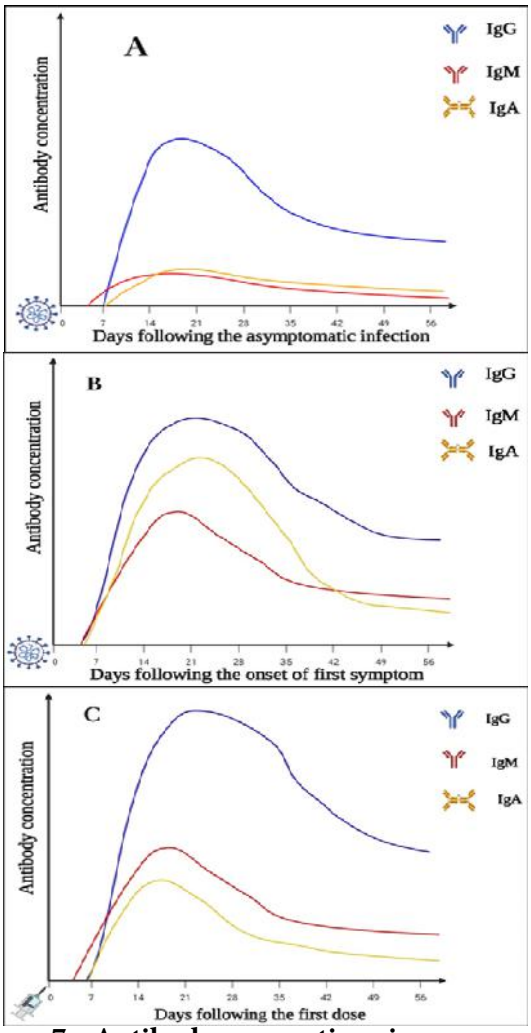

Figure 7. Antibody generation in response to infection and vaccination

A. The IgG antibodies dominate, followed by IgA and IgM after asymptomatic infection.

B. High breadth of IgG followed by IgM and IgA in symptomatic infection.

C. The overall response boosted by single-dose of mRNA vaccine.

Although the antibody response was delayed until 28 days following the first dose, both the subjects (infected but symptomatic and infected but asymptomatic) had the same frequency of IgG titers. Roltgen et al., 2021 in their cohort study reported that in the individuals with a previous history of infection with mild to moderate symptoms, their serum antibody titers had more titers of IgG followed by IgA and IgM. In contrast, the naïve individuals upon vaccination, produced a much higher amount of IgG, while the levels of IgM and IgA were observed to be significantly lower. Thus, the correlation between the severity of past infection and antibody response on the first and second dose needs to be studied further, taking age, sex, ethnicity, and comorbid conditions into consideration [5].

7.4 Immune exhaustion associated with the administration of the second dose

After vaccination, the memory B cell response to SARS-CoV-2 can be variable in naïve individuals and in seropositive individuals [23]. As the previously-infected and recovered subjects have a significant number of SARS-CoV-2 specific memory B-cells, only a single dose vaccine can be efficacious enough for the recall of immune memory, leading to the generation of diversified memory B cells in the lymphoid germinal center [24].

In the case of naïve individuals, a dosage regimen of two shots has been studied to boost the immune response and B-cell memory against ancestral and mutant strains [25]. The effect of second dose vaccine in the previously infected and recovered subjects need to be studied on larger population, to investigate if the breakthrough infections occurring in such population may be due to blunting of the immune response post 2 dose vaccination.

Levi et al., 2021, in their observational study on 127 participants, observed that in 4 participants who were previously symptomatic COVID-19 positive, the antibody response (after administration of the

second dose) was reduced. Such a response was not reported in the individuals who decided not to take their second dose.

Another observational study reported by Alessio M et al., 2021 evaluated the frequency of SARS-CoV-2 spike-protein specific B-cells using flow cytometry. The increase in the frequency of spike-protein specific B-cells was observed in previously infected, recovered, and one-dose vaccinated subjects up to 21 days following the vaccination. Moreover, the serum antibody titers were on the higher side in COVID-19 exposed, recovered, and one-dose vaccinated subjects within 28 days, while the response was variable in naïve individuals, especially for the neutralizing character of IgG antibodies [26].

After the administration of second dose in SARS-CoV-2 exposed individuals, the frequency of spike-protein specific B-cells drastically reduced. The Naïve individuals had an increased frequency of spike-protein specific B-cells after the administration of a second dose [26].

although the efficacy in terms of reducing hospitalizations and preventing the development of severe disease is still maintained at > 90%. As a result, developing an enduring immune response becomes an important step toward achieving herd immunity [27].If we look into the long-term aspects of an immune response, the memory B-cells stand tall on the ground [28]. The findings of a case-control study conducted by Turner et al. in 2021 suggest that memory B-cells can be the best predictors of long term immunity against SARS-CoV-2, apart from the protection provided by circulating antibodies.

Turner et al., 2021, in their study on 19 participants who were previously infected, reported that their bone marrow aspirates had SARS-CoV-2 spike specific memory B-cells, after 7 months following the infection [29]. This promising study clearly points toward the administration of a single dose to such convalescent individuals to further potentiate their immune response with dominance of IgG class switching, leading to the production of diversified memory B-cells [29].

8. Long-term aspects of SARS-CoV-2 specific immunity

8.1 After infection and recovery from SARS-CoV-2

Since the cases of breakthrough infections started rising due to emerging mutant strains of SARS-CoV-2, the efficacy of mRNA vaccines has come under the spotlight for further studies and screening [32]. The efficacy of the mRNA vaccine in terms of reducing symptomatic infections has been reduced by 7 fold against the Delta variant (B.1.617.2) compared with the efficacy against the ancestral strain.

Although the efficacy in terms of reducing hospitalizations and preventing the development of severe disease is still maintained at > 90%. As a result, developing an enduring immune response becomes an important step toward achieving herd immunity [32].If we look into the long term aspects of an immune response, the memory B-cells stand tall on the ground [28]. The findings of a case-control study conducted by Turner et al. in 2021 suggest that memory B-cells can be the best predictors of long term immunity against SARS-CoV-2, apart from the protection provided by circulating antibodies.

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8.2 Post vaccination

The observational study conducted by Turner et al., 2021 produced a qualitative scenario regarding the presence of memory B-cells in convalescent individuals (previously infected and recovered), but didn't calculate the number of memory B-cells present after a specified period post-infection.

Just like the serum antibody titers decline gradually following an acute immune response, the level of circulating memory B-cells too falls significantly. However, the response may be variable in different groups depending on age, comorbid conditions, ethnicity, etc. [30]. Wang Z et al., 2021 counted the levels of circulating memory B-cells by flow cytometry and reported that in the previously-

infected and recovered subjects, the number of memory B-cells declined by 1.35 folds after 12 months of previous exposure when compared with the number of memory B-cells present after 6 months of infection. The administration of a single-dose mRNA vaccine to such individuals increased the number of circulating memory B-cells by 8.6 folds [31].

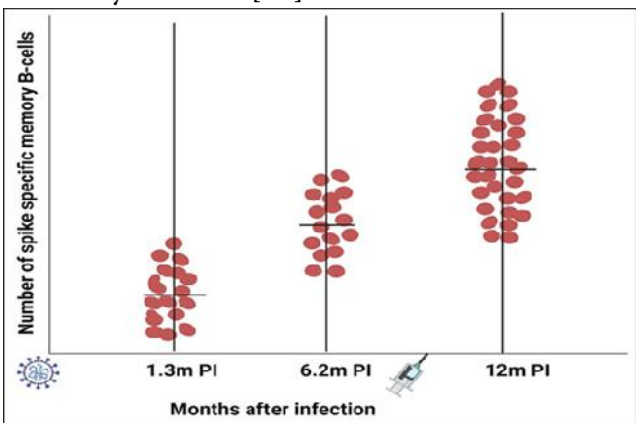

Figure 8. The number of spike-specific memory B-cells increased after single-dose vaccination in previously infected and recovered subjects.

Administration of mRNA vaccine 12 months post infection (PI) increased spike specific memory B-cells by 8.6 folds. [As per Wang Z et al., 2021]

In fact, the administration of the vaccine after recovery from infection increased the number of memory B-cells specific to the receptor-binding domain of the spike-protein of SARS-CoV-2. Upon vaccination, the neutralizing character of anti-RBD IgG antibodies increased significantly, the reason being the stimulation of additional plasma cells towards differentiation from the memory B-cell compartment. The biphasic immune response (antibodies and memory B-cells) in vaccinated individuals can provide long term protection against the mutant strains [33].

8.3 Clonal expansion and somatic hypermutation

After an acute immune response (post recovery from infection), the number of circulating memory B-cells reaches a plateau phase and ceases to differentiate further [34]. Upon reinfection, these memory B-cells undergo extrafollicular clonal expansion, proliferating into plasmablasts of antibody producing plasma cells, generating a quick response to deal with the virus.

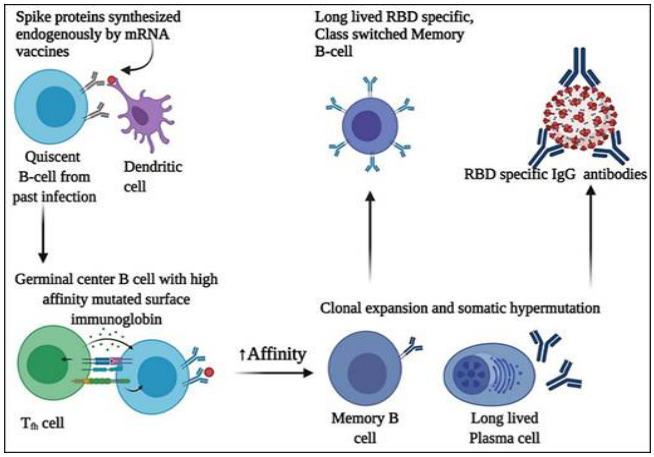

Figure 9. Mechanism of somatic hypermutation and affinity maturation after single-dose vaccination in previously infected and recovered subjects.

Moreover, in the previously infected and recovered subjects, these naïve B-cells has been observed to undergo T-follicular helper cell mediated B-cell activation and differentiation into plasma cells by a magnitude of 1.5 orders after first dose vaccination. The memory B-cells undergo somatic hypermutation in their variable region genes, leading to affinity maturation and clonal expansion [35].

Upon vaccinating these convalescent individuals, the generation of diversified memory B-cells highly specific to the receptor-binding domain of the spike-protein results in immunogenicity of greater breadth and duration against the emerging variants of concern [36]. These studies provide a promising piece of evidence for the generation of biphasic responses (neutralising antibody titers and memory B-cell responses post single-dose vaccination) generated by mRNA vaccines as a correlate for protection against infections and mortality in the future [36].

CONCLUSION

A single-dose mRNA vaccine (Pfizer-BNT162b2 and mRNA-1273) can provide immunity of high breadth in the population with previous exposure to SARS-CoV-2. In fact, some of the studies even reported the presence of spike-protein specific antibodies till 7-8 months post infection and further increased post single-dose vaccination [12]. Thus, increasing the gap between two doses should be considered in such individuals while retaining the protection and limiting the side effects associated with boosterism.

Though the sample sizes of these studies were small, seeing the encouraging evidence, studies on larger sample sizes should be conducted, considering the vital characteristics like age of participants, ethnicity, percentage with comorbid conditions, the percentage reduction in breakthrough infections and hospitalizations post single-dose vaccination. The single-dose efficacy of other authorized vaccine candidates should also be studied on larger samples of SARS-CoV-2 exposed subjects. This review strongly lays out promising evidence for the same.

More data is expected for the second dose of boosterism if it really provides added benefits to the population with already high IgG titers. By liberalization of COVID-19 antibody tests, several doses can be spared by skipping or delaying the vaccination for people already seropositive, thus prioritizing the population at higher risk. This becomes more important for countries with limited production and supply of doses. The aim is to vaccinate as many people as possible to attain herd immunity and lead ahead of the pandemic.

Acknowledgments : The figures used in the review were created with Biorender.com

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