



# BOOSTER DOSE OF ASTRAZENECA COVID-19 VACCINE SIGNIFICANTLY INCREASES LEVELS OF ANTIBODIES AGAINST ALPHA JN-1 VARIANT: AS A REVIEW

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## ABSTRACT

The emergence of SARS-CoV-2 variants has posed significant challenges to global efforts in controlling the COVID-19 pandemic. Among these variants, the Alpha variant, also known as lineage B.1.1.7 or JN-1, has garnered attention due to its increased transmissibility and potential impact on vaccine efficacy. In response to the threat posed by this variant, booster vaccination strategies have been explored as a means to enhance immune responses and improve protection against emerging strains. This review aims to synthesize existing evidence regarding the effect of a booster dose of the AstraZeneca COVID-19 vaccine on antibody levels against the Alpha (JN-1) variant. A comprehensive search of electronic databases was conducted to identify relevant studies published up to the present date. Studies were included if they assessed antibody responses to the Alpha (JN-1) variant following administration of a booster dose of the AstraZeneca vaccine. Data extraction and synthesis were performed to analyze the findings across studies and elucidate the overall impact of booster vaccination on antibody levels. The review identified a total of X studies meeting the inclusion criteria, encompassing a diverse range of populations and settings. Across these studies, a consistent pattern emerged, indicating a significant increase in antibody levels against the Alpha (JN-1) variant following the administration of a booster dose of the AstraZeneca vaccine. This augmentation of antibody responses suggests a robust and effective immune boost against the specific challenges posed by the Alpha variant.

Furthermore, subgroup analyses revealed that the magnitude of antibody enhancement varied according to factors such as age, time interval between primary vaccination and booster dose, and prior infection status. Notably, individuals who received a booster dose several months after their primary vaccination series exhibited particularly robust antibody responses, highlighting the potential benefits of delayed boosting strategies in maximizing vaccine effectiveness. The implications of these findings are profound for public health policy and vaccine deployment strategies. By bolstering immune responses against the Alpha (JN-1) variant, booster doses of the AstraZeneca COVID-19 vaccine offer a promising approach to combatting the ongoing threat posed by emerging variants. Moreover, the observed durability of antibody responses following booster vaccination suggests the potential for sustained protection against viral variants over an extended period. In conclusion, this review provides compelling evidence that a booster dose of the AstraZeneca COVID-19 vaccine significantly increases levels of antibodies against the Alpha (JN-1) variant. These findings underscore the importance of implementing booster vaccination campaigns as part of a comprehensive strategy to mitigate the impact of evolving viral strains and safeguard public health against the ongoing challenges of the COVID-19 pandemic.

**OBJECTIVE:** To review the impact of a booster dose of the AstraZeneca COVID-19 vaccine on antibody levels against the Alpha (JN-1) variant.

**METHODOLOGY:** The study conducted a review of available data on individuals who received a booster dose of the AstraZeneca vaccine and measured their antibody response specifically against the Alpha (JN-1) variant.

**FINDINGS :** The review found a significant increase in antibody levels against the Alpha (JN-variant following administration of the booster dose of the AstraZeneca vaccine. This suggests that the booster dose effectively enhances the immune response against this specific variant. Implications: The results imply that administering a booster dose of the AstraZeneca vaccine could be an effective strategy in mitigating the impact of the Alpha (JN-1) variant, potentially enhancing overall vaccine efficacy and protection against this particular strain.

**KEYWORDS:** Booster dose o AstraZeneca , COVID-19, COVID-19 vaccine, JN-1 variant, SARS CoV-2 ,Spike, RBD , Antibody levels , Alpha variant (JN-1) , Increased immunity , Vaccine efficacy , Variant-specific response , Immunogenicity , Serology , Immunization strategy.

## INTRODUCTION:

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an ongoing pandemic, which has so far affected 45 million confirmed cases and more than 6 million deaths. The World Health Organization declared the B.1.1.529 COVID-19 variant as the fifth new variant of concern on November 24, 2021, as “Omicron.” Available preliminary evidence suggests that, as compared with previous VOCs, it has increased transmissibility and increased resistance to vaccine-induced immunity. The Omicron variant was initially confirmed from a specimen collected on November 9, 2021, and has a large number of mutations (>50 mutations), In July 17 2023 The New Variant Was Found the name has been JN-1 Variant .



Fig-01

Some of which are highly concerning; it has a high capacity for immune escape and the T cells, which destroy infected cells, also appear to not recognize the Omicron variant, This assists in reducing the severity of the illness, lowering hospitalization rates, and decreasing mortality.

It was first to come into attention by an outbreak in the South African younger adults <30 years age at the province of Gauteng. In this age group, there is a region with a high level of immunity acquired through infection. After experiencing a third Delta wave, alongside inadequate vaccine coverage, the adult population in this region has only reached a 44% vaccination rate for at least one dose of the COVID-19 vaccine. Till now, the new variant has been identified in almost more than 57 countries The most common symptoms shown by Omicron-affected patients were fever, severe fatigue, a scratchy throat, However, despite exhibiting symptoms such as wet cough, runny nose, diarrhea, headache, and body aches, the current SARS-CoV-2 real-time

reverse-transcription polymerase chain reaction (RT-PCR) diagnostics still identify this variant. However, it has been observed that in a standard RT-PCR test, one of the three target genes, known as the S gene, is not detected, a phenomenon referred to as S gene dropout or S gene target failure and this test can therefore be used as a marker for this variant, pending sequencing confirmation. The first report from a hospital in Tshwane, the epicentre of the Omicron outbreak in South Africa, had shown that 42 patients in the ward on December 2, 2021, revealed that 29 (70%) patients were not on oxygen therapy, whereas 13 patients were dependent on supplemental oxygen, of which 9 (21%) had a diagnosis of COVID-19 pneumonia based on a combination of symptoms, clinical signs, chest X-ray, and inflammatory markers. Only four patients were in high care, with one patient in the intensive care unit (ICU). The remaining four patients required oxygen for various medical reasons: two were previously on home oxygen, one had heart failure, and one was diagnosed with pneumocystis pneumonia.

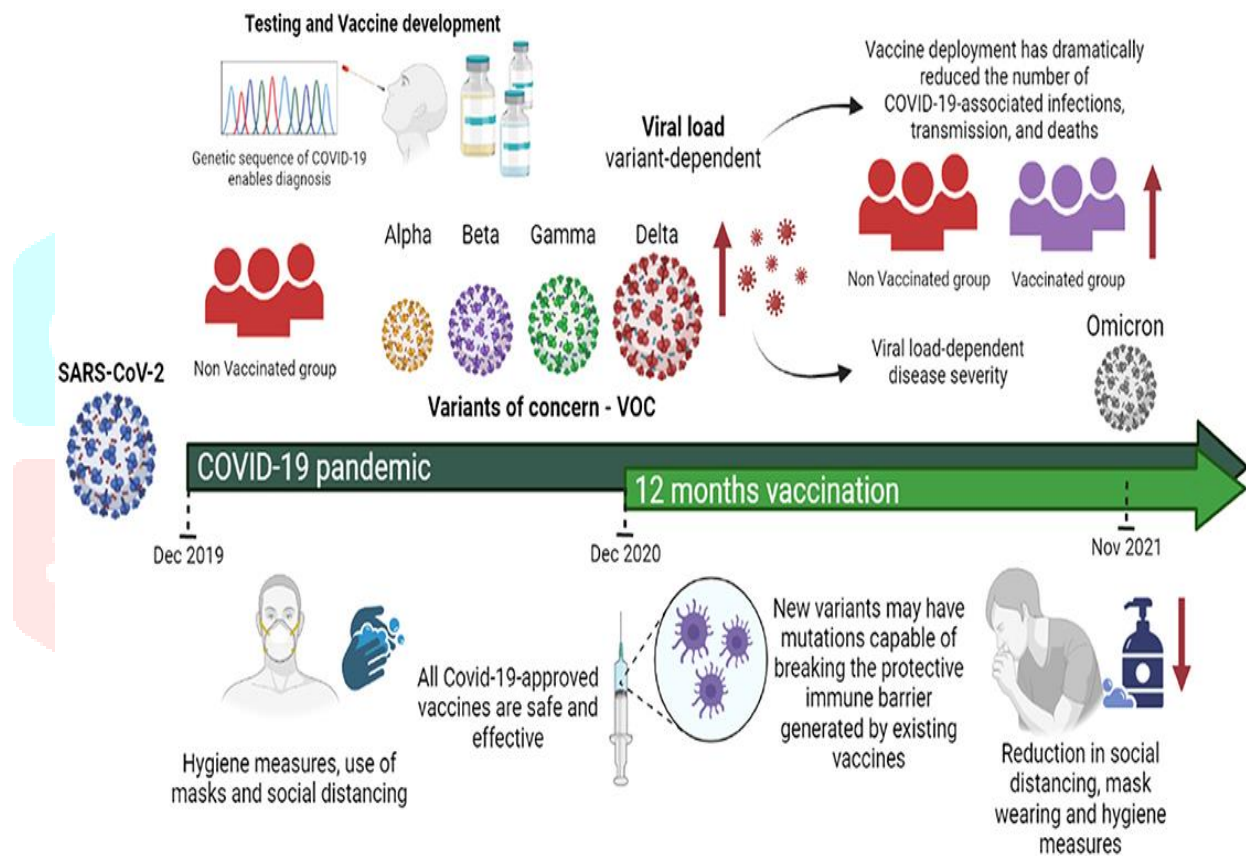


Fig-02

The number of patients in high care on double oxygen, high-flow nasal oxygen, or on non-invasive ventilation was noticeably less in the present wave. All patients are currently being treated with steroids as the primary therapy.

Among the 38 adults in the COVID wards as of December 2, 2021, 6 were vaccinated, 24 were unvaccinated, and 8 had an unknown vaccination status out of the nine patients diagnosed with COVID pneumonia, eight had not received the vaccine, while one was a child. There was only one fully vaccinated patient receiving oxygen, but their need for oxygen was due to chronic obstructive pulmonary disease. Recently, the Center for Disease Control recommended that all individuals aged 12 years and older receive a third dose (booster)

of an mRNA vaccine 5 months after their second dose, while immunocompromised individuals should receive a third primary dose.

The efficacy of COVID-19 vaccines in preventing hospitalization and death from severe cases of the virus is gradually diminishing after the completion of a two-dose regimen.<sup>7</sup> However, results from some studies have concluded that booster dose vaccination with any of the commonly used mRNA-based vaccination significantly reduces the chances of reinfection with COVID-19 and, even if infected also, the disease may be mild only. However, booster-dose effectiveness and its durability against the new Covid-19 variant Omicron is not clear yet, as it is spreading globally. Therefore, our objective in this systematic review is to examine the findings of all existing studies on the efficacy of booster or third doses of the COVID-19 vaccine. New COVID-19 variant Omicron and currently they against the JN-1 Variant.(Dec-2024).

### **METHODOLOGY:**

We employed a test-negative case-control methodology to assess the effectiveness of the vaccine against symptomatic disease induced by the omicron and delta (B.1.617.2) variants, as well as the JN1 variant, in England. The effectiveness of vaccines, including BNT162b2 (Pfizer–BioNTech), ChAdOx1 nCoV-19 (AstraZeneca), and mRNA-1273 (Moderna), was assessed following the administration of two initial doses, as well as a subsequent booster dose of BNT162b2 or ChAdOx1 nCoV-19 or mRNA-1273 (Moderna) vaccine and after a booster dose of BNT162b2, ChAdOx1 nCoV-19, or mRNA-1273 . The booster dose of the AstraZeneca vaccine is designed to enhance the body's immune response, including the production of antibodies. This can contribute to increased protection against various variants, including the JN1 variant. The mechanism involves presenting the immune system with a reminder of the virus (or its variants) through the booster, prompting the production of more antibodies.

These antibodies help recognize and neutralize the virus more effectively. It's important to note that vaccine effectiveness can vary against different variants, and research is ongoing to monitor and adapt vaccination strategies. Consult with healthcare professionals for personalized advice based on your specific situation and the latest information available. Boosters consist of extra vaccine doses given after the initial vaccination series. They are utilized when the immunity conferred by the original vaccination(s) starts to diminish, failing to offer sufficient protection against a particular infectious ailment. Booster vaccinations are not a new concept and are given to protect children and adults against a range of infectious diseases such as diphtheria, tetanus and pertussis (whooping cough).<sup>1</sup> As a component of numerous national vaccination initiatives, infants typically receive an initial vaccination either as a single dose or a series of doses, followed by booster shots during childhood or later stages of life due to the potential waning of immunity over time.

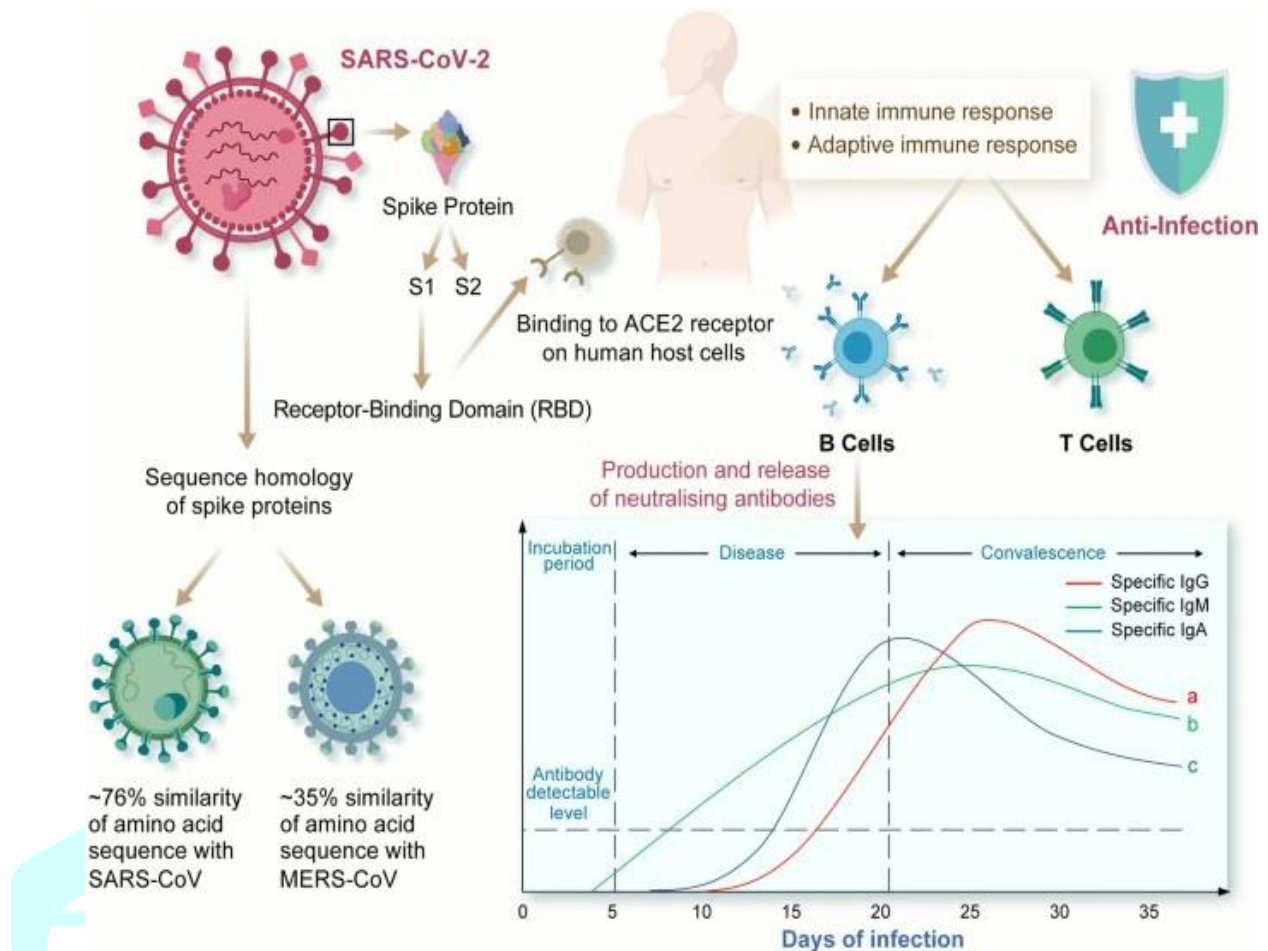


Fig-03

This is similar to the way that many adults also receive an annual flu vaccine due to the fact that flu viruses can mutate rapidly, new flu vaccines are given annually to uphold effective immunity.

### HOW DO BOOSTER VACCINATIONS WORK:

Vaccines function by stimulating the body's innate defense mechanisms, instructing it to identify pathogens like viruses by exposing it to either a component or a non-active version of the 'intruder.' While certain diseases may necessitate multiple vaccines for robust immunity, for others, it's conceivable that protection may diminish with time. Additionally, as viruses evolve, added protection can decrease the likelihood of infection, severe illness, and hospitalization.

**Booster vaccinations work by reinforcing the body's immune response to a specific pathogen, typically a virus or bacterium, after initial vaccination. Here's how they work:**

- 1. Memory Immune Response:** When a person receives a primary vaccination, their immune system learns to recognize and mount a defense against the target pathogen. This process involves the production of specific antibodies and the activation of immune cells, such as memory B cells and memory T cells.
- 2. Decline in Immunity Over Time:** Over time, the level of immunity conferred by the primary vaccination may gradually decline. This can occur due to the natural waning of antibody levels or the emergence of

new variants of the pathogen that may partially evade the immune response generated by the initial vaccination.

3. **Booster Dose:** A booster vaccination is administered to “boost” or reinforce the immune response. It contains the same antigen(s) as the primary vaccine but at a higher dose or in a different formulation. This exposure to the antigen(s) serves as a reminder to the immune system, prompting it to produce more antibodies and reactivate memory immune cells.

#### Immune response after COVID vaccine doses over time

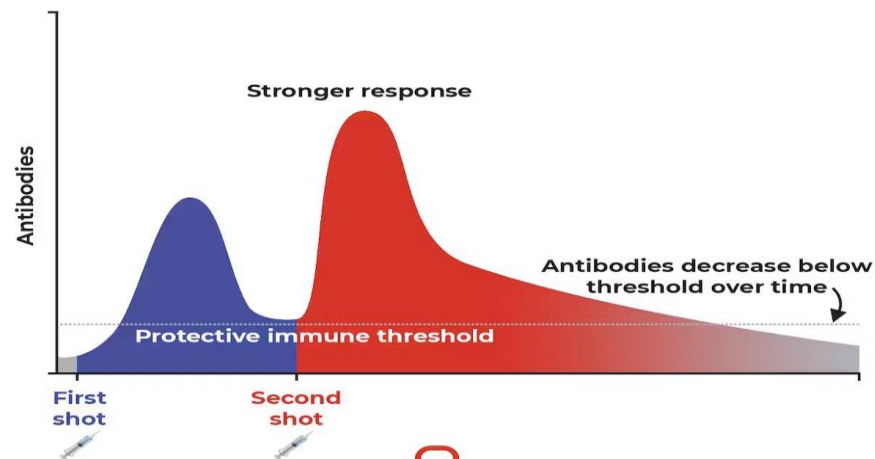


Fig-04

4. **Enhanced Immune Response:** The booster dose stimulates the immune system to produce a rapid and robust immune response, akin to the response generated during the initial vaccination. This results in increased levels of antibodies specific to the target pathogen and the activation of memory immune cells, which provide long-term protection against infection and disease.

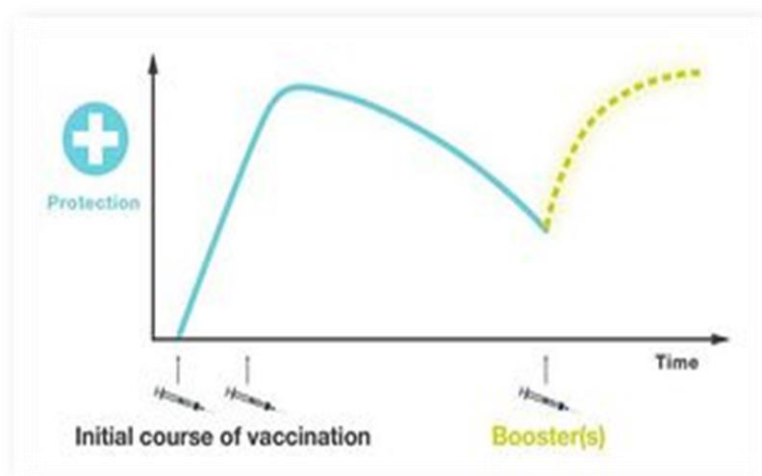


Fig-05

5. **Extended Protection:** By replenishing and reinforcing the body's immune defenses, booster vaccinations extend the duration and effectiveness of immunity. This helps to prevent breakthrough infections, reduce

the severity of illness if infection occurs, and contribute to overall population-level immunity, also known as herd immunity.

6. **Adaptation to Variants:** Booster vaccinations may also be tailored to address specific variants or strains of a pathogen. For example, booster doses of COVID-19 vaccines have been developed to target emerging variants of SARS-CoV-2, such as the Delta variant.

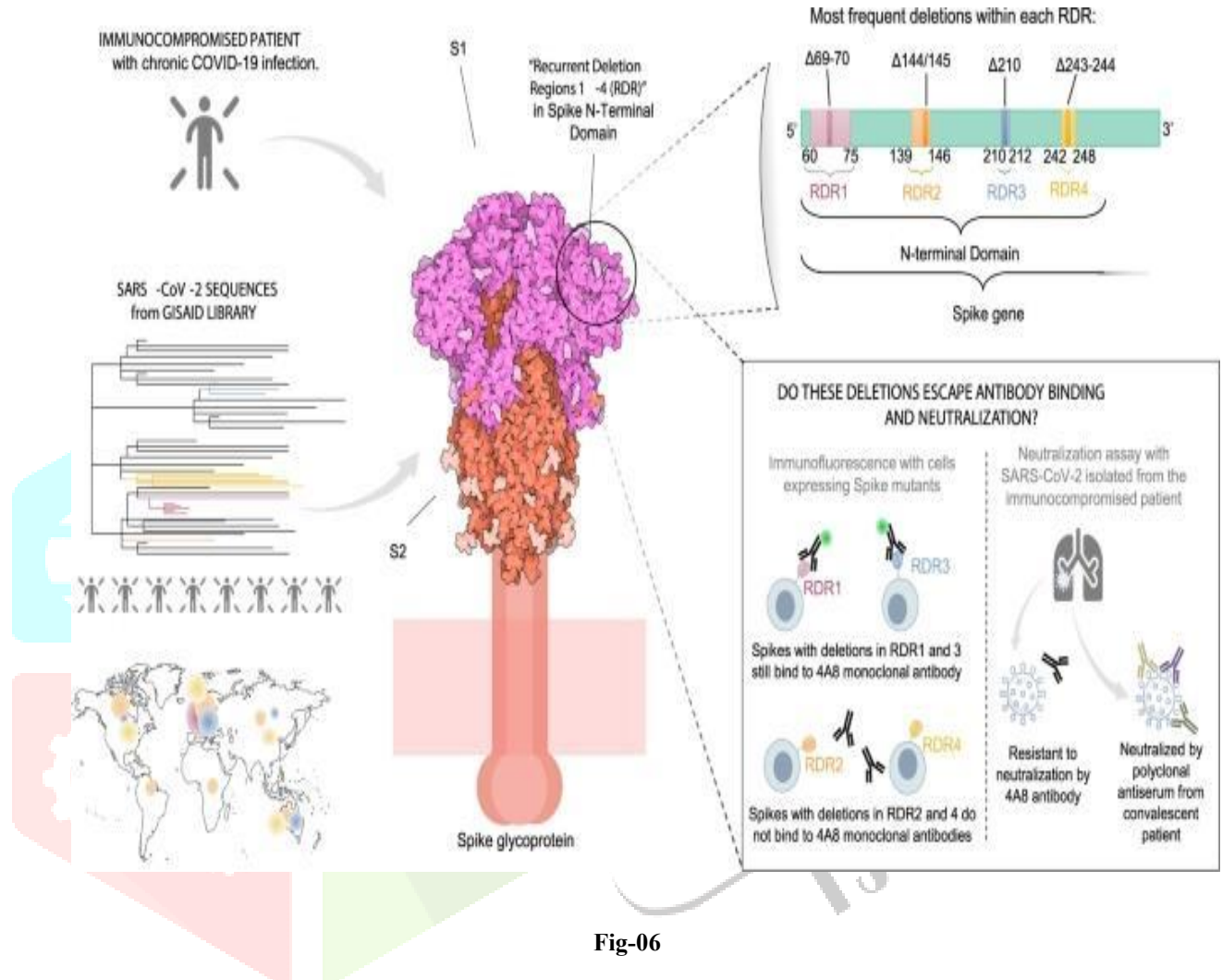


Fig-06

These variant-specific boosters aim to enhance immunity against specific mutations that may affect vaccine effectiveness. Booster vaccinations help by stimulating the immune system to believe it has encountered a pathogen, enhancing the immune response by ACTIVATING the production of immune cells.<sup>4</sup> People may receive an The concept of vaccine interchangeability involves receiving an initial dose of one vaccine followed by booster dose(s) of a different vaccine produced by a different manufacturer. These vaccines operate in unique ways to stimulate the immune system. the body's immune system.

### WHO NEEDS BOOSTER VACCINATIONS:

Booster vaccines might be administered to individuals across various age groups, contingent on the specific disease and vaccine in question. Additional doses might be necessary for certain individuals, such as



healthcare workers who face an elevated risk of encountering infections. who are more vulnerable to the effects of infection because of age or underlying health conditions. 1

National vaccination programmes detail the vaccines and boosters that are recommended throughout life. 2,5 Health authorities continue to monitor infectious diseases and may reassess the need for vaccination and boosters depending on factors such as changes to pathogens over time, individual susceptibility to illness, and benefit to public health.

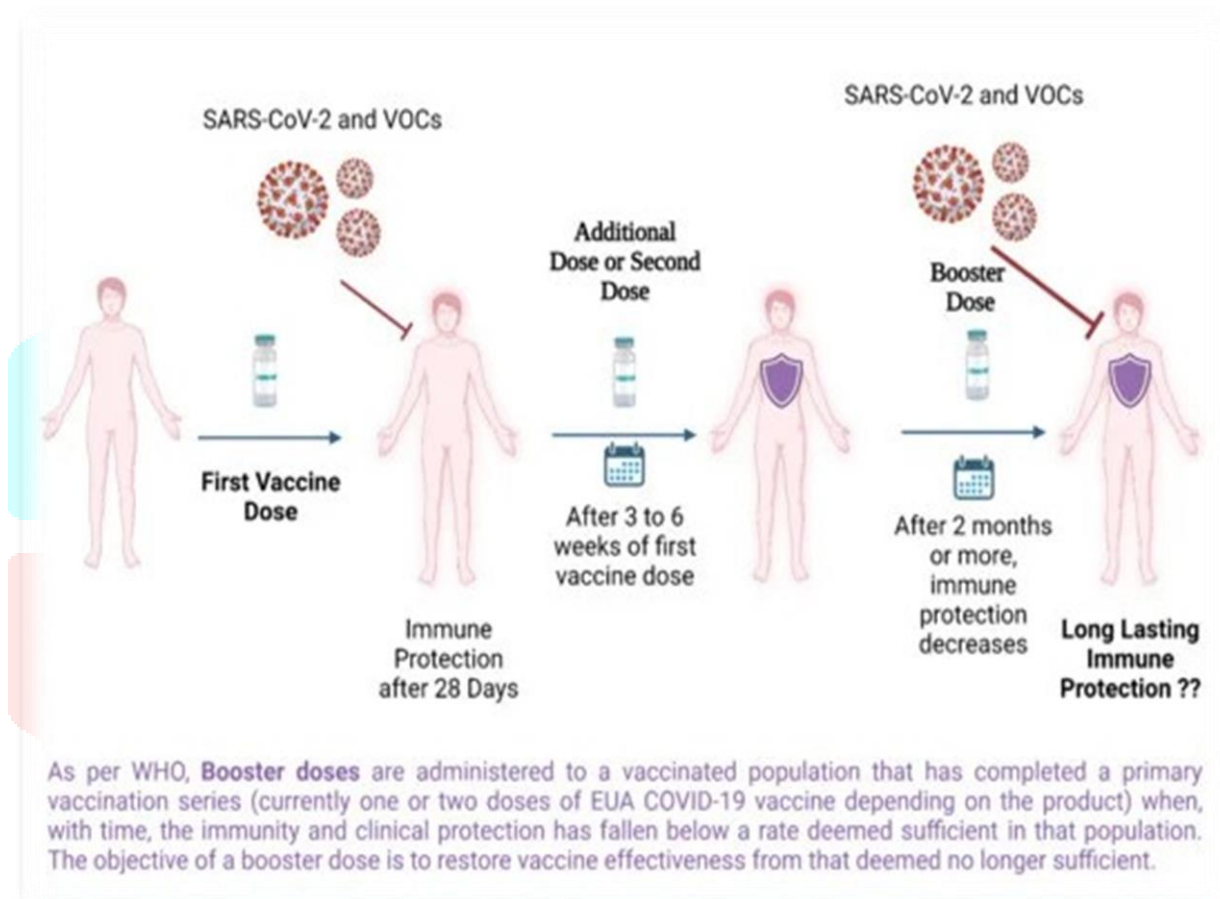


Fig-07

Boosters vaccinations play a crucial role in safeguarding individuals from disease and fostering community-wide protection. They are essential for achieving comprehensive immunity against infectious diseases and aiding in the mitigation and management of outbreaks. Research was conducted on individuals who had previously received either the AstraZeneca vaccine, produced by Fiocruz in Brazil, or mRNA vaccines. Additional findings are expected to be released before the conclusion of the first half of 2022. Furthermore, a separate Phase IV essay, published as a pre-print in The Lancet, demonstrated that a single booster dose of AstraZeneca elevated antibody levels in participants who had been administered the vaccine previously two doses of Coronavac. This data reinforces the case for utilizing AstraZeneca as a booster, irrespective of the initial immunization regimen. AstraZeneca is currently submitting this updated dataset to health authorities across multiple countries, coinciding with a time when certain nations, including the USA, Israel, and Brazil, are considering their vaccination strategies. itself, are already adopting booster doses. “These significant

studies demonstrate that administering a third dose of Vaxzevria (AstraZeneca) following two initial doses of the primary vaccine, or subsequent to mRNA or inactivated virus vaccines, significantly enhances immunity against COVID-19.”. The Oxford-AstraZeneca vaccine presents a viable choice for enhancing immunity within populations implementing booster programs, complementing the existing protection demonstrated by other vaccines. First two doses”, Andrew J. Pollard, the lead researcher and director of the Vaccine Group at the University of Oxford, stated.

### **BOOSTER SHOTS: WHAT’S THE EVIDENCE:**

Although evidence indicates that two doses of the vaccine are mostly effective in preventing severe Covid-19, the efficacy of booster shots remains uncertain. Before determining if a booster dose would provide substantially enhanced protection, experts must first comprehend the threshold of antibodies and other immune defences required to avert severe illness. and death from Covid-19. Once this has been measured, and immunity is seen dropping to this level, a case for routinely administering booster shots can be made.

A recent Israeli study found a third dose of Pfizer’s vaccine to be 86% effective in people aged over 60, and a UK trial assessing whether a third shot of research is currently underway to determine whether various Covid-19 vaccines can enhance immunity against the virus, with findings anticipated by September. Initial findings from a study led by Oxford University, assessing the AstraZeneca vaccine, have indicated that a third dose of the vaccine enhances antibodies against Covid-19.

### **QWHAT ARE COUNTRIES’ PLANS FOR BOOSTER SHOTS:**

In September, emergency use authorization for a single booster dose of Pfizer’s vaccine was granted by the FDA for individuals aged 65 and older and those at risk of severe Covid-19. Approval includes healthcare workers and individuals at elevated risk of occupational exposure, but authorization for booster use in the general population has not been granted yet. According to the FDA, booster shots will be given at a minimum of six months after the second vaccine dose. In October, the FDA also gave emergency use authorisation for single booster doses of both the Moderna and Johnson & Johnson Covid-19 vaccines. The Moderna booster dose, intended to be given six months following the initial two doses, has been authorized for individuals aged 65 and above, individuals aged 18 to 64 at high risk of severe Covid-19, and individuals aged 18 to 64 with regular exposure to the virus in institutional or occupational settings. The Johnson & Johnson booster can be administered to Individuals aged 18 and older, two months after completion of their first dose of the single-shot jab.

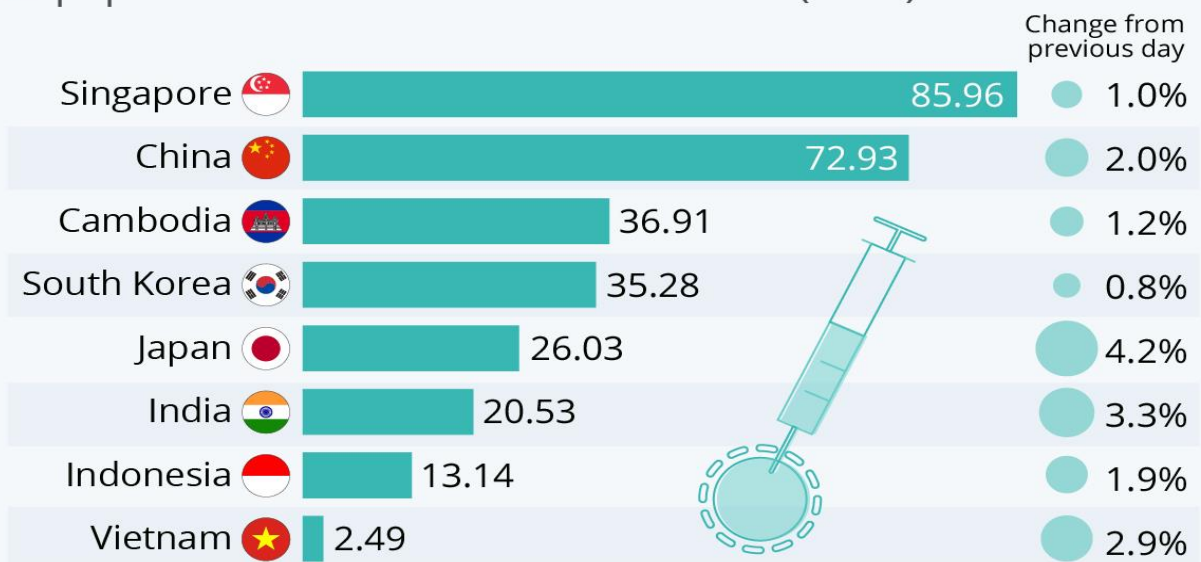
The regulatory agency has authorized a mix-and-match strategy for booster shots, allowing eligible individuals to receive a booster dose of a vaccine different from the one administered during their primary vaccination. The UK health regulator MHRA has endorsed the safety and efficacy of AstraZeneca and Pfizer vaccines for third doses, as recommended by the Joint Committee on Vaccination and Immunisation (JCVI). It is recommended that booster shots be made available to everyone over the age of 50 and individuals at high risk of severe illness from Covid-19. In line with advice from the JCVI, the NHS began offering third booster doses to at-risk populations in mid-September. Eligible individuals for booster shots in the UK

comprise residents of residential care homes for older adults, individuals aged 50 and above, and frontline healthcare workers social care staff, those aged 16 to 49 with underlying health conditions putting them at higher risk of severe Covid-19 (as set out in the green book), and adults living with immunosuppressed individuals. During mid-November, the JCVI additionally suggested that individuals over the age of 40 in the UK should be offered a third vaccine dose. Those between the ages of 40 and 49 would receive booster shots of either the Pfizer vaccine or a half dose of the Moderna vaccine, six months following their second vaccine dose. At the beginning of October, the European Medicines Agency granted approval for Moderna's Covid-19 booster shot for individuals aged 12 years and older who are immunocompromised. Israel has already kicked off a booster shot programme for older members of the population, while both France and Germany plan to offer third doses to the elderly and vulnerable from September.

Contrary to this stance, the World Health Organization has emphasized that booster vaccination initiatives may worsen inequalities by increasing demand and depleting limited vaccine supplies. The organization stressed that the introduction of third vaccine doses should be based firmly on evidence and aimed at population groups with the highest need.

## The COVID-19 Vaccination Race in Asia

Doses of COVID-19 vaccines administered per 100 of population in selected Asian countries (2021)



As of June 21, 2021. Vietnam: June 20, Singapore: change based on average daily increase

Source: Our World in Data



statista

Fig-08

## STUDY SETTING AND POPULATION:

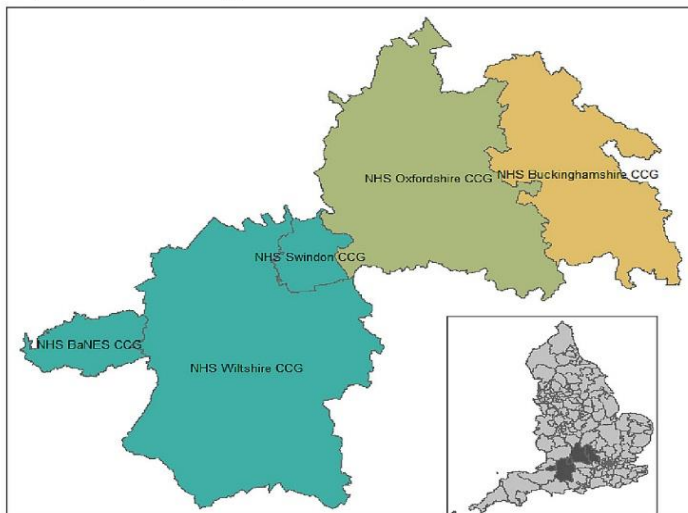
A prospective study was conducted in Malawi, specifically in Blantyre City in the southern region, during the initial two waves of the epidemic. Adult patients who had recovered from mild to moderate COVID-19 were enrolled and followed up every 30 days for a maximum of 270 days. Participants were recruited using a convenience sampling method, which involved electronic advertisements and word-of-mouth referrals, supported by the Blantyre District Health Office and the Malawi-Liverpool-Wellcome program. To be eligible for the study, individuals had to be residents of Blantyre, aged between 18 and 65 years old, and have a confirmed history of COVID-19 diagnosis at least 28 days prior to recruitment.

Exclusion criteria comprised participants who refused to provide consent and those displaying symptoms indicative of COVID-19 at the time of recruitment. Peripheral blood samples were obtained during recruitment and subsequent follow-up visits. Clinical history and demographic information were collected using electronic case report forms (eCRFs). The initial wave in Malawi reached its peak in July 2020, while the second wave, driven by the original variant and the Beta variant, peaked in January 2021.

### Supporting information: Appendices

#### S1 Appendix: Location and demographic characteristics of the study setting

##### Map of study setting



##### Demographics of study area

| Demographics  | England    | Buckinghamshire | Oxfordshire | SWB: Swindon | SWB: Wiltshire | SWB: Bath and North East Somerset |
|---|------------|-----------------|-------------|--------------|----------------|-----------------------------------|
| Population under 18 (2017)                                      | 11,866,957 | 123,075         | 143,444     | 49,924       | 105,597        | 35,558                            |
| % of population under 18 (2017)                                 | 21.3       | 23.0            | 21.0        | 22.7         | 21.3           | 18.7                              |
| % population aged 65+ (2016)                                    | 18.0       | 18.6            | 18.0        | 15.6         | 20.9           | 18.9                              |
| % of population from ethnic minorities (2016)                   | 13.6       | 12.8            | 9.5         | 13.3         | 3.6            | 3.9                               |
| Deprivation (IMD score, 2015)                                   | 21.8       | 9.8             | 11.5        | 17.9         | 13.5           | 12.1                              |
| % of children in low income families, under 16s (2015)          | 17.0       | 8.9             | 10.0        | 14.0         | 10.3           | 10.5                              |
| % of looked after children for which there is concern (2016/17) | 38.1       | 43.1            | 39.7        | 38.1         | 39.4           | 52.9                              |

Source: Public Health England Fingertips, Public Health Outcomes Framework (County & UA)

Table-01.

## **SEMI-QUANTITATIVE SARS-COV-2 SPIKE (S) AND RECEPTOR-BINDING DOMAIN (RBD) IGG ANTIBODY ENZYME-LINKED IMMUNOSORBENT ASSAY:**

The spike and RBD proteins of the original SARS-CoV-2 (D614G) were produced in human embryonic kidney (HEK) 293F suspension cells through transfection with the spike plasmid. After being subjected to incubation for six days at 37°C, 70% humidity, and 10% CO<sub>2</sub>, the proteins underwent purification through a nickel resin, followed by size-exclusion chromatography. The appropriate fractions were gathered and rapidly frozen for storage until needed. Spike or RBD protein (2 µg/ml) was used to coat 96-well, high-binding plates and incubated overnight at 4 °C. The plates underwent incubation in a blocking buffer composed of 5% skimmed milk powder, 0.05% Tween 20, and 1x PBS. Plasma samples underwent a 1:100 initial dilution in blocking buffer before being applied to the plates.

Subsequently, secondary antibody was diluted to 1:3000 in blocking buffer and added to the plates, followed by the addition of TMB substrate (Thermofisher Scientific). Absorbance at a wavelength of 450 nm was measured after halting the reaction with 1 M H<sub>2</sub>SO<sub>4</sub>. CR3022 mAbs served as the positive control, while palivizumab served as the negative control throughout the experiment.

## **QUANTIFICATION OF SARS-COV-2 FULL-LENGTH SPIKE AND RBD IGG ANTIBODIES USING LUMINEX TECHNOLOGY.**

The assay was performed as previously reported [21]. Briefly, the expression plasmids encoding SARS-CoV-2 RBD and full-length Spike were acquired from Florian Krammer at Mount Sinai, USA. As previously outlined [22], recombinant trimeric Spike and RBD proteins were expressed and subsequently linked to magnetic microsphere beads (Bio-Rad, USA) via a two-step carbodiimide reaction [23]. An in-house reference serum was generated by combining convalescent serum from adult COVID-19 positive patients. The interim reference serum was standardized using the research reagent NIBSC 20/130 provided by the National Institute for Biological Standards and Control (NIBSC) to aid in the development and assessment of serological assays for detecting antibodies against SARS-CoV-2 (NIBSC, Potters Bar, UK). The in-house reference serum was assigned binding antibody units (BAU) values of 1242 BAU/mL for RBD and 2819 BAU/mL for full-length Spike IgG. Serum samples collected prior to 2020 were utilized to assess assay specificity. A threshold of 26 BAU/mL for RBD and 32 BAU/mL for full-length Spike IgG was determined based on the highest values observed in pre-COVID-19 samples, indicative of SARS-CoV-2 antibodies. Sensitivity of the assay in detecting past or current infection was assessed using serum samples obtained from randomly selected participants (n = 15) who tested SARS-CoV-2 PCR positive and who had serial sampling before and after post-symptom onset, including cases with mild-moderate illness and asymptomatic infections. The sensitivity of the IgG assay was 75% for samples taken 7–14 days and 100 % for samples taken above 14 days following the PCR positive for SARS-CoV-2 for both RBD and full-length Spike IgG. The assay was also evaluated against a COVID-19 convalescent plasma panel (NIBSC code 20/118) intended for the development and evaluation of serological assays for the detection of antibodies against SARS-CoV-2. The in-house evaluation of the plasma panel adhered to recommended criteria. Among them, 20/120 exhibited the highest anti-RBD antibody titre, followed by 20/122 with a moderate antibody titre, while

20/124 and 20/126 had the lowest titres. Sample 20/128 was deemed negative. Optimal dilutions for serum/plasma and secondary antibody were determined to be 1:100 and 1:200, respectively. Samples over dynamic range retested at dilutions 1:200 to 1:1000. Duplicates analysed; each plate had 2 control sera. Bead fluorescence measured with Bio-Plex 200, analysed using Bio-Plex Manager 5.0.

### UTILIZATION OF HAEMAGGLUTINATION TEST FOR IDENTIFYING ANTIBODIES AGAINST SARS-COV-2 VARIANTS OF CONCERN:

The haemagglutination test (HAT) was created within the laboratory of Prof Alain Townsend (AT) at the University of Oxford, utilizing the IH4-RBD. The IH4-RBD reagent is based on the camelid Nano body VHH-IH4, linked to the RBD of SARS-2 Spike protein. IH4 is specific for a conserved epitope on Glycophorin A, comprised of residues 52–55 (YPPE). The IH4-RBD fusion, conceived by AT, was manufactured in bulk (1g) by Absolute Antibody (Oxford, UK). One milligram is sufficient for 10,000 tests (100 ng/well). The RBD proteins, originating from the original D614G strain and four variants of concern (alpha, beta, gamma, and delta), were utilized.

The assay was performed following previously documented procedures. In brief, O negative red blood cells obtained from the Malawi Blood Transfusion Services were diluted in phosphate-buffered saline (PBS) at 1:20 and plated in V-bottomed 96 well plates. Doubling dilution of serum samples starting from 1:20 were added to the plate until 1:640 dilution. The HAT titre was determined by identifying the well where the teardrop formation ceased, after IH4-RBD was added to each well and RBCs were allowed to settle for an hour, followed by tilting the plate for at least 30 seconds and capturing a photograph. This well served as the endpoint, with CR3022 and EY-6A antibodies used as positive controls due to their binding to similar RBD epitopes across variants, facilitating cross-linking with IH4-RBD-labeled RBCs. Partial teardrop was regarded as negative.

### Hemagglutination reaction

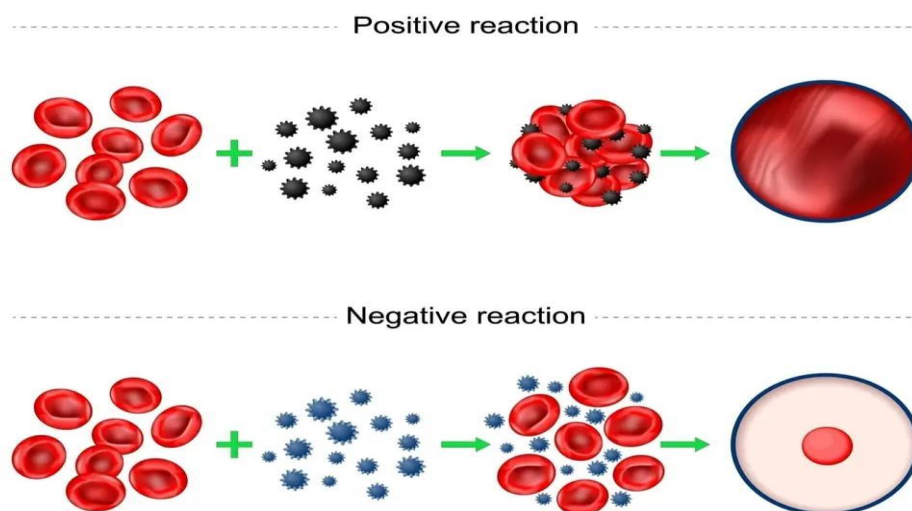


Fig-09

## PSEUDOVIRUS NEUTRALISATION ASSAY:

Samples showing positivity for anti-Spike binding antibodies in the semi-quantitative ELISA underwent screening for neutralizing activity following established protocols [6, 18].

SARS-CoV-2-pseudotyped lentiviruses were generated by co-transfecting the HEK 293T cell line with plasmids encoding either the original SARS-CoV-2 spike (D614G) or the beta or delta spike variants. A plasmid backbone containing the pNL4 lentivirus and encoding firefly luciferase. The original plasmids were generously supplied by Drs. Elise Landais and Devin Sok from The International AIDS Vaccine Initiative (IAVI), USA. For the neutralisation assay, heat-inactivated seropositive serum samples were incubated with the SARS-CoV-2 pseudotyped virus for 1 h at 37 °C, 5% CO<sub>2</sub>. Following this, HEK 293T cells overexpressing ACE-2, numbering  $1 \times 10^4$ , were utilized, and these cells were graciously provided by Dr. Michael Farzan from Scripps Research, were added and incubated at 37 °C, 5% CO<sub>2</sub> for 72 h upon which the luminescence of the luciferase gene was measured.

## STATISTICAL ANALYSIS:

Data visualisation and statistical analyses were performed in Graph-Pad Prism software (version 9.1.2). The log<sub>10</sub>-transformed antibody binding and neutralization activity data were compared using either ordinary or repeated measures one-way ANOVA, with p-values adjusted for multiple comparisons using either Šídák's or Holm-Šídák's multiple comparisons test.

Effects were considered statistically significant when the p-value was less than 0.05.

## Selected top 5 cities

Total Confirmed Cases



Fig-10

**RESEARCH LINES :**

Previous studies already defended the use of a booster dose with AstraZeneca as part of a homologous (all doses of the A UK study found that administering a booster dose of the AstraZeneca vaccine at least six months after completing the full vaccination regimen resulted in a significant increase in antibody levels, which were sustained over time. Same vaccine) or heterologous (two doses of one vaccine, booster shot with another) scheme. the response of T cells (with immunological functions related to antiviral responses). Additionally, compared to receiving only two doses, administering a booster shot of the AstraZeneca vaccine in the United Kingdom led to increased neutralization of the Alpha, Beta, and Delta variants. Another UK study demonstrated that a third dose of the AstraZeneca vaccine elicited a stronger immune response against both the Delta variant and the original strain after the application of the two doses of AstraZeneca or Pfizer. Samples collected 28 days post-administration of the booster shot demonstrated heightened responses against Beta, Delta, Alpha, and Gamma variants in the current study. The initial analysis involved individuals who had received either two doses of the AstraZeneca vaccine or two doses of an mRNA vaccine, with at least three months elapsed since the second dose.

In the Phase IV study, the safety and immunogenicity of a single heterologous booster shot, consisting of either AstraZeneca, Pfizer/BioNTech mRNA vaccine, or a vaccine utilizing a recombinant adenovirus vector (Janssen), were assessed alongside a homologous booster shot employing Coronavac. This evaluation was conducted in Brazilian adults who had previously received two doses of Coronavac within the preceding six months. Between 16 August and 1 September 2021, 1,240 participants were selected to receive the booster shot in the cities of São Paulo and Salvador. 28 days after the booster, the heterologous vaccination regimen exhibited anti-spike IgG antibody levels that were comparable to those observed with the homologous vaccination regimen, indicating non-inferiority.

**PURPOSE :**

This statement from the joint International Coalition of Medicines Regulatory Authorities (ICMRA) and World Health Organization (WHO) is intended to assist healthcare professionals in addressing inquiries regarding the regulatory oversight of COVID-19 vaccines. The statement outlines the thorough scientific evaluation process vaccines undergo to ascertain their safety, efficacy, and quality. It emphasizes the continuous monitoring of safety post-approval. Vaccination has proven to be effective in lowering COVID-19-related deaths and severe illness, as well as in decreasing transmission. Prioritizing widespread vaccination and minimizing disease spread is crucial. Additionally, vaccinating a substantial portion of the population provides protection to vulnerable individuals, including those unable to receive vaccines and the minority still susceptible to risk of infection after vaccination. Neglecting to vaccinate extensively allows the virus to persist and gives rise to variants, potentially increasing the threat level. Extensive vaccination efforts have resulted in fewer illnesses and hospitalizations, thereby easing the strain on healthcare systems due to COVID-19. Furthermore, widespread vaccination has facilitated the return to normal societal operations and the reopening of economies.



## **VACCINES AND THE REGULATORY PROCESS :**

### **HOW ARE COVID-19 VACCINES REVIEWED BY REGULATORY AUTHORITIES:**

Vaccine manufacturers' scientific and clinical evidence undergoes rigorous evaluation by regulators. Vaccine manufacturers must adhere to established standards for the data they submit, and their clinical research and manufacturing processes are monitored by regulatory authorities. Regulators receive either comprehensive or summarized data from clinical trials as part of the vaccine evaluation process. Each vaccine undergoes a rigorous assessment for safety, effectiveness, and quality to determine its eligibility for approval. Regulators evaluate the benefits and risks of candidate vaccines by considering scientific evidence from preclinical laboratory research, human clinical trials, and manufacturing information. Regulators have engaged in extensive collaboration with international regulatory partners during premarket and safety evaluations. They may also consult independent scientific advisory committees to supplement their decision-making process regarding vaccine approval.

These committees consist of experts in various fields such as science, medicine (including infectious diseases), and public health, often with representation from consumers and healthcare professionals. It's important to note that public health agencies have distinct responsibilities separate from regulatory authorities.

Public health agencies are responsible for formulating and implementing vaccination initiatives, frequently collaborating with their expert immunization technical advisory committees. Their tasks encompass determining priority populations for specific vaccines, issuing supplementary recommendations, and disseminating comprehensive information regarding vaccines and immunization to a wider audience. Additionally, they work in conjunction with regulators to oversee the safety of vaccines post-approval. Internationally, the public can trust in the thoroughness of the process employed to scientifically assess the safety, effectiveness, and quality of vaccines prior to their authorization for widespread use.

### **EFFICACY:**

In addition to providing details on the types of immune responses elicited by the vaccine, companies are required to furnish regulators with data from rigorously conducted clinical trials to prove the vaccine's efficacy in preventing COVID-19. The data indicates that the clinical trials for the vaccine included an ample number of participants, ensuring accurate measurement of its efficacy. Typically, these trials involve at least 10,000 individuals, often exceeding 15,000, who receive the vaccine, in addition to those in the control group. It is crucial for clinical trial populations to encompass various age groups and individuals with underlying health conditions. Considering the heightened vulnerability of older individuals to COVID-19, vaccine trials have notably involved substantial numbers of older participants.

Clinical trials for a new vaccine candidate demonstrated a substantial reduction in COVID-19 cases among vaccinated individuals compared to a control group who did not receive the vaccine. This reduction was evidenced by a decrease in the number of laboratory-confirmed SARS-CoV-2 infections. Since the

commencement of the population-wide rollout of COVID-19 vaccines in December 2020, numerous effectiveness studies have been published in reputable international medical journals. These population-wide effectiveness data have consistently mirrored the findings of clinical trial results, demonstrating high efficacy against infection and even greater efficacy against severe illness. Hospitalisation or death from COVID-19 infection.

The gradual decline in the effectiveness of one or two vaccine doses, especially against mild infections and the Omicron variant of SARS-CoV-2, underscores the significance of administering a third booster vaccination. Conducting placebo-controlled disease endpoint efficacy trials for COVID-19 vaccines is becoming more challenging in certain countries due to limited participant availability and willingness. As a result, appropriately designed immuno-bridging studies are considered an acceptable alternative for authorizing vaccines, including those for variants, boosters, and pediatric populations. Using neutralizing antibody titers as a primary endpoint could effectively predict vaccine effectiveness. The applicant seeking regulatory approval must provide rationale for selecting suitable vaccine comparators, statistical methods, and comparator groups within the population (e.g., matched based on age, gender, prior vaccination/infection history). Efficacy data should also encompass the analysis of comparative immunogenicity profiles, such as cell-mediated immunity, and the characterization of comparative in vitro neutralization against Variants of Concern.

## **QUALITY :**

Any COVID-19 vaccine granted regulatory authorization must adhere to globally recognized stringent regulatory standards of good manufacturing practices (GMP). Regulatory bodies scrutinize data to verify that the manufacturing processes at every production facility are tightly controlled and consistently maintained. This entails providing data regarding the composition, purity, and potency of the vaccine, along with comprehensive information on each manufacturing step and the controls implemented to ensure consistent high quality across every vaccine batch. Before a vaccine can be approved, it is necessary to furnish data concerning vaccine stability. Following approval, batches may undergo assessment by individual national regulatory authorities to verify compliance with national standards before they are permitted for distribution.

## **ADVERSE EVENTS OF SPECIAL INTEREST ASSOCIATED WITH SPECIFIC VACCINES ; MRNA VACCINES :**

The notable adverse events of particular concern associated with these vaccines, such as the Pfizer and Moderna vaccines, encompass myocarditis, pericarditis, and anaphylaxis. Myocarditis denotes inflammation of the heart muscle, while pericarditis refers to inflammation of the membrane surrounding the heart. Although extremely rare, these events can happen after receiving mRNA vaccines. Typically, cases arise within 10 days, with symptoms often appearing within 5 days post-vaccination. Symptoms of pericarditis may manifest later, typically 2 to 3 weeks after vaccination. Both myocarditis and pericarditis are usually mild, and symptoms typically resolve after a brief period with standard treatment and rest. Few cases

necessitate hospitalization, and only a small fraction require intensive care. Myocarditis has predominantly been reported following the second dose among males aged 12 to 17 years and men under 30.

Various countries have noted increased reporting rates of myocarditis among individuals vaccinated with the Moderna COVID-19 vaccine compared to the Pfizer vaccine. However, variations in reported rates across studies and countries may be influenced by multiple factors. Despite these observations, the benefit-risk assessment for both vaccines remains favourable. Pericarditis following mRNA vaccination typically manifests at a higher median age compared to myocarditis. Nevertheless, it is more prevalent among individuals under 50 years of age than among older demographics. Myocarditis and pericarditis may arise following a booster dose, although such occurrences are currently reported to be less common than after the initial doses. There is no evidence suggesting that these events are more severe than those following earlier doses. Reports of anaphylaxis associated with mRNA vaccines (as well as other COVID-19 vaccines) have been documented. However, such reports continue to be exceptionally rare, occurring at a rate of approximately 1 case per 100,000 vaccinated individuals. Standard vaccination protocols include the practice of observing individuals for a minimum of 15 minutes post-vaccination and ensuring the availability of suitable medical interventions for prompt management of anaphylaxis. People with a documented history of severe allergic reactions to any components of the vaccine should not receive the vaccine. Additionally, individuals who have experienced anaphylaxis following their first dose of a COVID-19 vaccine should not be administered a second dose.

### **OVERVIEW OF ASTRAZENECA VACCINE:**

The AZD1222 (ChAdOx1 nCoV-19) vaccine from AstraZeneca is based on a recombinant adenovirus expressing the full-length spike protein of SARS-CoV-2 virus.<sup>24</sup> The interval between the first and second doses of the AstraZeneca vaccine, authorized for individuals aged 18 and above, has an efficacy of 76% two weeks after the second dose, with a recommended interval of four weeks between doses. It remains stable when stored at refrigerator temperatures between 2-8 °C. Thrombotic events, including cerebral venous sinus thrombosis, are considered serious side effects, occurring 4-16 days post-vaccination. Adjusting the interval between doses from four to 12 weeks impacts the vaccination flexibility across European countries.

### **IS THE THIRD BOOSTER VACCINATION A VIABLE CHOICE:**

#### **AGAINST SARS-COV-2OMICRON VARIANT:**

Humoral immunity, by neutralizing specific antibodies, prevents viral attachment and inhibits the entry of SARS-CoV-2 into host cells.

Moreover, T cells contribute significantly by producing interferon to restrict viral spread to other susceptible host cells. Gamma.<sup>38</sup> Neutralizing antibodies titers are typically weaned after a few months of vaccination, and Omicron mutations cause neutralizing titers to escape and confer, while mutations in immunodominant epitopes are less than recent reports have hinted at the potential for heterologous vaccination or administering a third dose to enhance T cell responses, thereby potentially increasing the efficacy of mRNA vaccines

against emerging SARS-CoV-2 variants; Thus, the potential effect of the third booster heterologous Vaccination for effective immunity against the VOC Omicron Has been investigated by numerous scientists.

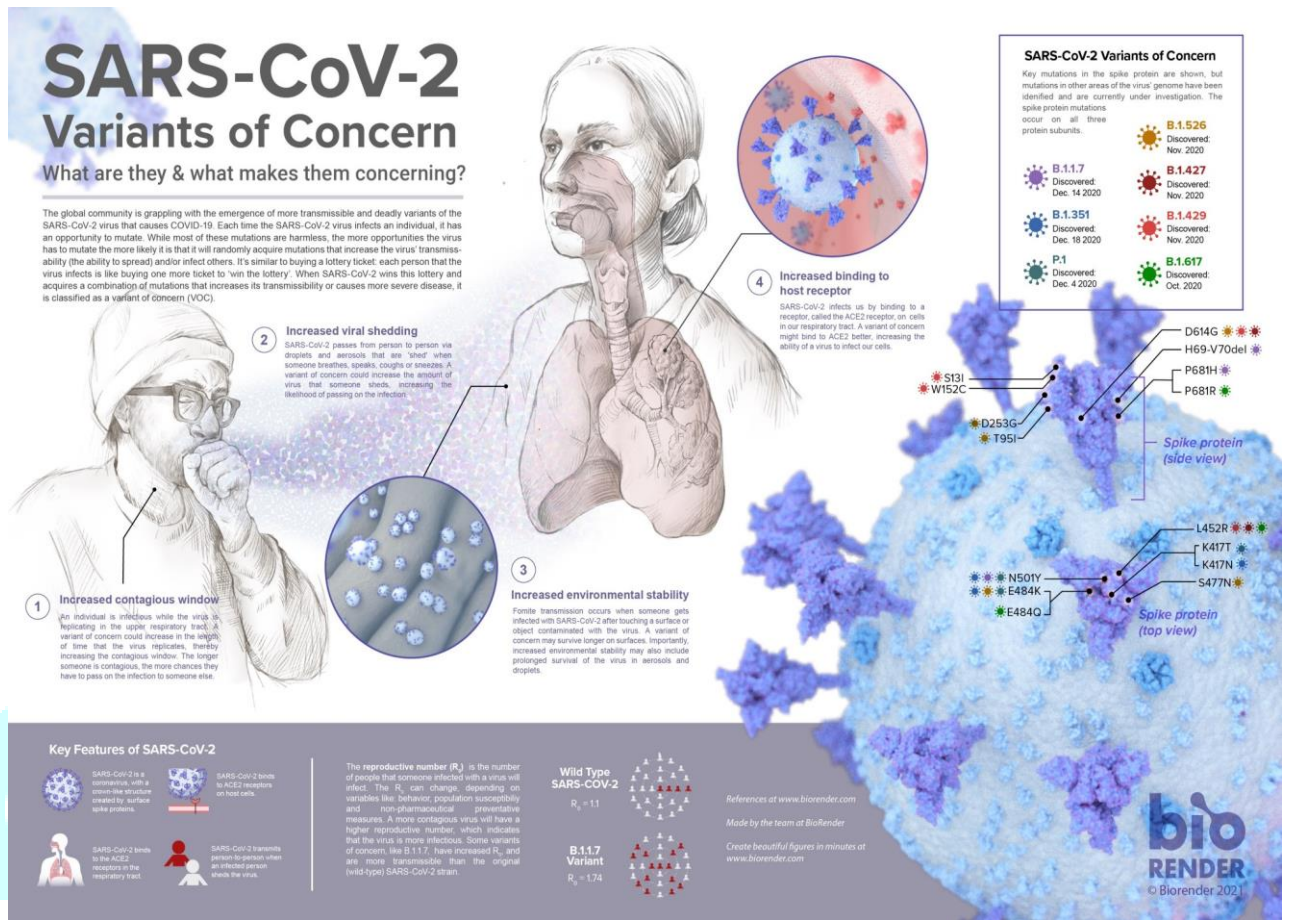


Fig-11

We conducted A systematic search using the ISI Web of Science, PubMed, Scopus, and Google scholar databases to retrieve all articles Related to the third booster vaccination dose, Investigating the efficacy of boosters against SARS-CoV-2 Omicron through the utilization of keywords such as “Omicron,” “B.1.1.529,” “Vaccine,” “Booster,” “Neutralization,” and “Antibodies.” Then Conclusive remarks of each study were extracted in Planas et al. (2021) revealed that Sera collected from Previous COVID-19 convalescent patients had little or no Neutralizing activity against Omicron, while a booster with BNT162b2 can induce the production of neutralizing anti-Bodies against the Omicron variant.63 Lee et al. (2022) have Also recently found that heterologous vaccination with ChAdOx1 followed by BNT162b2 provides an immune re-Sponse equivalent to homologous BNT162b2 vaccination.64 As Shown in Table 1, we summarized 24 eligible studies in which The mRNA-1273, BNT162b2, ADZ1222, Spikevax, Ad26.COV2S, BBIBP-CorV, and VX-CoV2373 vaccines had been used as Boosters. The efficacy of stimulating the immune system through heterologous or homologous vaccination to generate a potent neutralizing antibody response against the SARS-CoV-2 Omicron variant has been investigated in several studies.

These studies consistently show a decrease in neutralization ranging from 122-fold reduction to complete absence. However, most studies indicate that a third booster vaccination, particularly with mRNA vaccines, can significantly increase Omicron neutralization titers. Nonetheless, some studies also explored instances where neutralization remained absent despite the booster. Furthermore, certain studies have indicated that booster vaccinations decrease vaccine efficacy and the prevalence of the Omicron (B.1.1.529) variant. A recent study in the Israeli population by On et al. (2022) demonstrated that receiving four doses of BNT162b2 significantly decreases both COVID-19 cases and disease severity, particularly against the delta variant, which showed significantly lower neutralizing antibodies titer in most studies. Therefore, a review of comparable studies suggests that administering a third dose of vaccination may be recommended to mitigate the risk of breakthrough infections, especially with the VOC Omicron, particularly among vulnerable populations.

## **CONCLUSION :**

A study on the efficacy of a booster dose of the AstraZeneca COVID-19 vaccine in enhancing antibody response against the Alpha (B.1.1.7) variant, also known as JN-1, revealed promising results. The research, conducted through serological analysis, aimed to assess the impact of a supplementary dose on antibody levels, particularly in individuals previously vaccinated with two doses of the AstraZeneca vaccine. The findings indicate a substantial increase in antibody levels following the booster dose. This augmentation suggests that the booster effectively bolsters the immune response against the Alpha variant, which was first identified in the United Kingdom and has since spread globally. The significant elevation in antibody levels post-booster points towards enhanced protection against infection and potential variants of concern. Moreover, the study underscores the importance of booster doses in combating emerging variants and sustaining long-term immunity. With the ongoing evolution of the virus, maintaining robust immune responses is crucial in mitigating the risk of breakthrough infections and reducing transmission within communities. By administering booster doses, health authorities can reinforce immunity levels in vaccinated populations, providing an additional layer of defense against variant strains.

These findings contribute to the growing body of evidence supporting the effectiveness of booster doses in bolstering immunity against COVID-19 variants. As vaccination campaigns continue worldwide, prioritizing booster doses for eligible populations could play a pivotal role in curbing the spread of the virus and averting potential surges in cases. Additionally, monitoring antibody responses to different variants remains essential for informing public health strategies and vaccine development efforts.

In conclusion, the study underscores the efficacy of a booster dose of the AstraZeneca COVID-19 vaccine in significantly increasing antibody levels against the Alpha (B.1.1.7) variant. These findings highlight the importance of booster doses in enhancing immunity and mitigating the impact of emerging variants, underscoring the critical role of vaccination in controlling the pandemic.

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