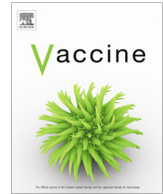




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Evaluating correlates of protection for mix-match vaccine against COVID-19 VOCs with potential of evading immunity



Sih-Han Liao^{a,b,c,1}, Wei-Jung Chang^{c,1}, Chen-Yang Hsu^{c,d}, Amy Ming-Fang Yen^e, Ting-Yu Lin^c, Sam Li-Sheng Chen^e, Tony Hsiu-Hsi Chen^{c,*}

^a Department of Medicine, National Taiwan University Cancer Center, Taipei, Taiwan

^b Division of Gastroenterology and Hepatology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

^c Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan

^d Daichung Hospital, Miaoli, Taiwan

^e School of Oral Hygiene, College of Oral Medicine, Taipei Medical University, Taipei, Taiwan

ARTICLE INFO

Article history:

Received 5 January 2022

Received in revised form 2 October 2022

Accepted 7 October 2022

Available online 17 October 2022

Keywords:

Mix-match

Correlate of protection

Variant of concern

COVID-19

ABSTRACT

Background: In the face of rapid emerging variants of concern (VOCs) with potential of evading immunity from Beta to Omicron and uneven distribution of different vaccine brands, a mix-match strategy has been considered to enhance immunity. However, whether increasing immunogenicity using such a mix-match can lead to high clinical efficacy, particularly when facing Omicron pandemic, still remains elusive without using the traditional phase 3 trial. The aim of this study is to demonstrate how to evaluate correlates of protection (CoP) of the mix-match vaccination.

Methods: Data on neutralizing antibody (NtAb) titers and clinical efficacy against Wuhan or D614G strains of homologous ChAdOx1 nCov-19 or mRNA-1273 and heterologous vaccination were extracted from previous studies for demonstration. The reductions in NtAb titers of homologous vaccination against Beta, Delta, and Omicron variants were obtained from literatures. A Bayesian inversion method was used to derive CoP from homologous to mix-match vaccine.

Findings

The predicted efficacy of ChAdOx1 nCov-19 and mRNA-1273 for Wuhan or D614G strains was 93 % (89 %–97 %). Given 8 ~ 11-fold, 2 ~ 5.5-fold, and 32.5 ~ 36-fold reduction of NtAb for Beta, Delta, and Omicron variants compared with D614G, the corresponding predictive efficacy of the mix-match ranged from 75.63 % to 73.87 %, 84.87 % to 81.25 %, and 0.067 % to 0.059 %, respectively.

Interpretations

While ChAdOx1 nCov-19 and mRNA-1273 used for demonstrating how to timely evaluate CoP for the mix-match vaccine still provides clinical efficacy against Beta and Delta VOCs but it appears ineffective for Omicron variants, which highlights the urgent need for next generation vaccine against Omicron variant.

© 2022 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

1. Introduction

While SARS-CoV-2 variants have evolved from the wild type/D614G to a series of variant of concerns (VOCs), including Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617) and Omicron (B.1.1.529) during COVID-19 pandemic the effectiveness of the first generation vaccine has been challenged. To tackle this issue, the mix-match vaccination is proposed as a potential strat-

egy to booster effectiveness in the face of new VOCs. Several clinical trials have been conducted to examine whether the mix-match vaccination has higher immunogenicity than the administration of homologous vaccine. The enhanced immune response had been noted in ChAdOx1 nCov-19 (AZD1222) combined with BNT162b2 vaccination compared with a single dose of ChAdOx1 nCov-19 [1]. The similar findings on the facilitation of immune response were further observed in the UK mix-match trial on eight groups randomly allocated to 4- or 12-week interval of combining ChAdOx1 nCov-19 with BNT162b2 [2] and also the similar two mix-match trials targeting healthcare workers and the elderly people in Germany [3,4]. The higher immunogenicity on ChAdOx1 nCov-19 in combination with mRNA1273 was also noted in the mix-match trial in Sweden [5]. Despite these studies focusing on the

* Corresponding author at: Institute of Epidemiology and Prevention Medicine, College of Public Health, National Taiwan University, Room 533, No. 17, Xu-Zhou Road, Taipei 100, Taiwan.

E-mail address: chenlin@ntu.edu.tw (T. Hsiu-Hsi Chen).

¹ Sih-Han Liao and Wei-Jung Chang contributed equally to this article.

enhancement of immune response using the mix-match vaccination, whether the good performance of immunogenicity as a result of mix-match can also lead to high clinical efficacy still remain elusive without translating the enhanced immunogenicity into clinical efficacy based on the traditional phase 3 trial. However, it is very difficult to have timeliness of conducting a phase 3 randomized controlled trial for directly proving the clinical efficacy of the mix-match vaccination in the face of emerging SARS-CoV-2 variants. The alternative is to elucidate the immune correlate of protection (CoP) from vaccination and to predict the effect of SARS-CoV-2 variants on the changes in immunity timely. Two previous studies have already provided good methodology for immunobridging between immunological response and clinical efficacy, the aforementioned two studies need either convalescent cohorts as reference or comprehensive data of case and non-case with vaccination [6,7]. From the viewpoint of immunology and the neutralizing activities revealed by bench studies, the mixed-match strategy may provide a solution to cope with the resurgence of COVID-19 pandemic as a result of the emergence of VOCs, particularly in the era of Omicron pandemic.

Evaluating correlates of protection for mix-match vaccine against COVID-19 is also meaningful for setting up the benchmark for those countries facing the issue of delivery. Although many vaccines based on different mechanisms to elicit immune response against COVID-19 have been developed [8], the delivery and the distribution of vaccines in most countries were more challenging than those of high-income countries like Israel where the administration of BNT162b2 (Pfizer-BioNTech) has been swiftly adopted as a nationwide mass vaccination program since December 2020 immediately after the introduction of mRNA vaccine [9]. While it is true that boosting with an mRNA vaccine might increase effectiveness many countries having supply chain issue to administer a homologous second dose are exactly the same countries whether infrastructure is inadequate to maintain the cold chain needed to ensure that the mRNA vaccines remain effective. Therefore, even if heterologous boosting is effective, it may not be practical in many countries. In addition to solving the feasibility of cold chain, setting up the benchmark for the mix-match vaccination not perturbed by the cold chain issue is also important.

It should be noted that the evidence of immunogenicity related to immune protection from heterologous vaccination has barely been addressed because of two thorny issues. Unlike the immunobridging study on the CoP for the homologous vaccine that have convalescent cohorts as reference or comprehensive data of case and non-case, it is very difficult for heterologous vaccination to have such a reference group. A new methodology for the immunobridging study on the CoP for heterologous vaccination is therefore required.

The aim of this study was to evaluate the clinical efficacy of the mix-match vaccination can be predicted by the immunological response elicited from each homologous vaccine with available information on the corresponding clinical efficacy accrued from the phase 3 randomized controlled trial on the homologous vaccine based on the new developed Bayesian reasoning method dispensing with information on convalescent cohorts as reference or comprehensive data of case and non-case with vaccination. The proposed methodology and application were demonstrated by using the mix-match of ChAdOx1 nCov-19 and mRNA1273.

2. Materials and methods

2.1. Study framework

As the objective of this study is to develop the methodology for evaluating clinical efficacy of the mix-match vaccination dispensing with the conduction of a phase 3 randomized controlled trial

it is important to propose the study framework for delineating how and what kind of information selected from literature are required. Fig. 1 shows the study flowchart for predicting clinical efficacy of mix-match vaccination with vaccine A (first dose) and vaccine M (second dose). The first required information is neutralizing antibody titer (NtAb) from phase 1/2 trial of each homologous vaccine. The ratio of clinical efficacy regarding protection from COVID-19 infection between vaccine A and vaccine M ($P(NtAb_M)/P(NtAb_A)$) is derived. Clinical efficacy of protecting COVID-19 infection from the respective phase 3 trials of each homologous vaccine is therefore used to determine the cut-off of the mix-match antibody titer ($NtAb_{MM-A}$). Finally, the clinical efficacy of protection from infection for the heterogeneous vaccination can be predicted. Based on Fig. 1, information required has to have available information on NtAb titer from phase 1/2 trial and also consecutive data on clinical efficacy from phase 3 trial of each homologous vaccine. Although our proposed methodology can be applied to any mix-match vaccination if information is available performing systematic review for meta-analysis is beyond the scope of the current study. We therefore selected the mix-match vaccination with AZD1222 and mRNA1273 as our illustration.

2.2. Bayesian COP for evaluating clinical efficacy of the mix-match vaccination

To achieve the goal of predicting clinical efficacy of the mix-match vaccination, we developed a step-by-step Bayesian algorithm in commensuration with the study framework of Fig. 1. The detailed methodology of Bayesian inversion for the derivation of CoP is depicted in the **Appendix**.

2.3. Distribution of dispersion-rescaled neutralizing antibody titer

The ratio of clinical protection achieved by mRNA1273 ($P(PE_M | NtAb_M)$) and ChAdOx1 nCov-19 ($P(PF_A | \text{titer of } NtAb_A)$) (see **(A-5)** in **Appendix**) is that of the probability of NtAb titers conferred by two vaccines. This probability ratio can be estimated by using the likelihood ratio (LR_{M-A}) derived from the probability density function of NtAb titers written as follows.

$$LR_{M-A} = \frac{P(NtAb_M)}{P(NtAb_A)} = \frac{dF(NtAb_M)}{dF(NtAb_A)} = \frac{\frac{1}{\sigma_M} e^{-\frac{1}{2} \left(\frac{X-\mu_M}{\sigma_M} \right)^2}}{\frac{1}{\sigma_A} e^{-\frac{1}{2} \left(\frac{X-\mu_A}{\sigma_A} \right)^2}}, \quad (1)$$

where σ_M and σ_A are both unit in dispersion-rescaled distribution of NtAb titer and X represents the dispersion-rescaled titer of NtAb. Note that LR_{M-A} can be interpreted as Bayes factor by which the prior risk ratio of escaping from COVID-19 without vaccination can be updated to the condition after vaccination.

2.4. Predicting protective efficacy conferred by the mix-match vaccine

In the expression (A-5), the ratio of clinical efficacy conferred by mRNA1273 and ChAdOx1 nCov-19 can be derived from the results of published literature [10,11]. Calibrated by this figure, the value of LR^{M-A} and the corresponding cut-off (c) of dispersion-rescaled titer can be determined due to a monotonic likelihood ratio. On the basis of this cut-off value, the LR of mix-match vaccination to ChAdOx1 nCov-19 (LR_{MM-A}) can be derived by using (1) as follows.

$$LR_{MM-A} = \frac{P(NtAb_{MM})}{P(NtAb_A)} = \frac{dF(NtAb_{MM})}{dF(NtAb_A)} = \frac{\frac{1}{\sigma_{MM}} e^{-\frac{1}{2} \left(\frac{c-\mu_{MM}}{\sigma_{MM}} \right)^2}}{\frac{1}{\sigma_A} e^{-\frac{1}{2} \left(\frac{c-\mu_A}{\sigma_A} \right)^2}}. \quad (2)$$

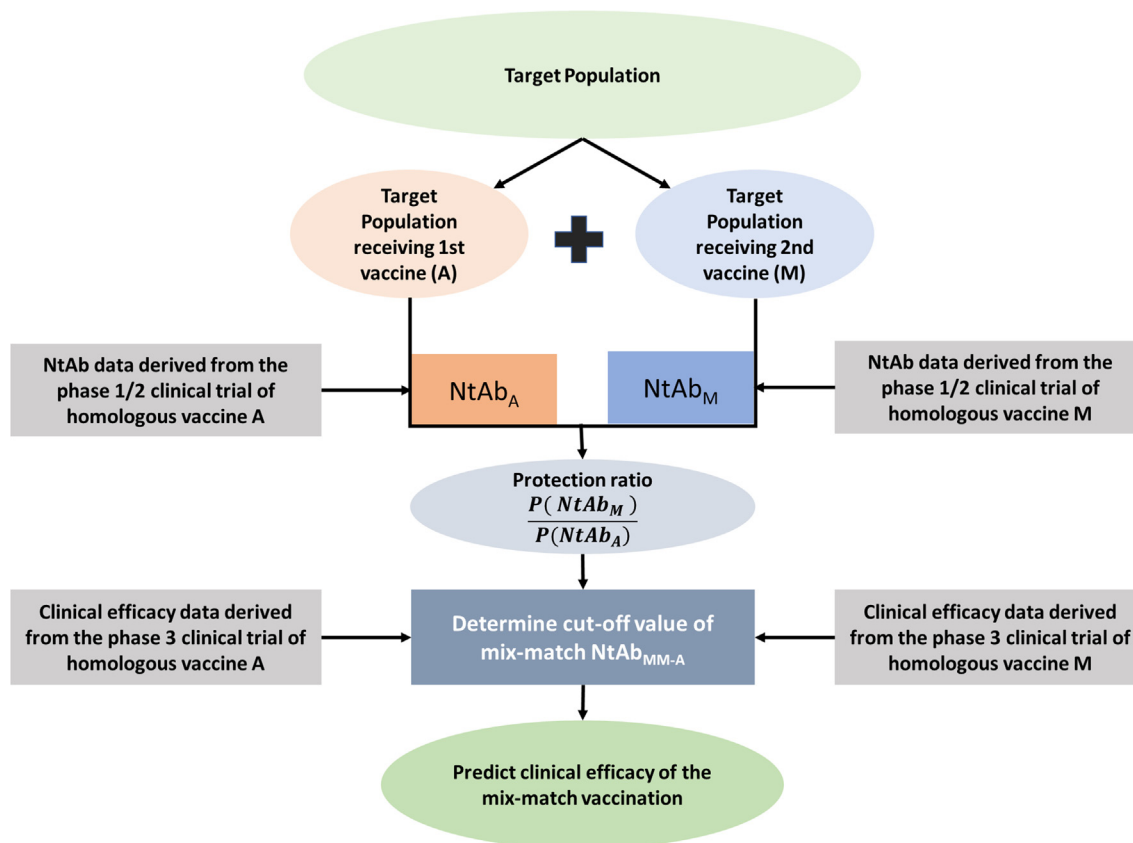


Fig. 1. Study Framework.

The protective efficacy (PE) of mix-match vaccination given the NtAb titer induced by vaccination can thus be derived by the product of $P(PE | NtAb_A)$ and Bayes factor, LR_{MM-A} .

First, we used the mean and standard deviation of NtAb titers from the phase 1/2 clinical trials of homologous ChAdOx1 nCov-19 [12] and mRNA1273 [13] to find a cut-off which can be linked to clinical protection ratio between two vaccines as shown in phase 3 clinical trials [10,11]. Second, the NtAb titers changed from study to study because of different techniques. Thus, most of the previous studies need the titers of convalescent individuals to have a fair comparison [6,7]. The statistical procedure of determining the cut-off of applying to the mix-match vaccination is illustrated in Fig. 2.

3. Results

3.1. Data sources

3.1.1. Homologous vaccination studies

Two studies were used to assess the neutralizing antibody (NtAb) and the subsequent clinical efficacies associated with homologous vaccination strategy. The NtAb titer was obtained from a phase 1/2, single-blind, randomized controlled trial with a total of 1,077 participants enrolled. Among these participants, 543 persons received two doses of ChAdOx1 nCov-19. The neutralizing activity was evaluated by using an assay with lentivirus-based SARS CoV-2 pseudovirus particles expressing spike protein on the surface and reported as the 50% inhibitory dilution (ID₅₀). The ID₅₀ against Wuhan strain was 162.90 (standard deviation [SD], 61.20, Table 1) at 28 days after the boost dose [12]. Another analysis comprised data from four blinded, randomized, controlled

trials conducted in the UK, Brazil, and South Africa with a total of 23,848 participants enrolled. The interim analysis of the four phase 3 clinical included 11,636 participants. Among these participants, total 4,440 persons received two standard doses and 1,367 persons received a low dose followed by a standard dose. Comparing with the participants in the control group, the overall vaccine efficacy against the occurrence of symptomatic COVID-19 was 70.4% (95% confidence interval [CI], 54.8%–80.6%) [10].

The NtAb titers of mRNA1273 was extracted from a phase 1, dose-escalation, open-label trial with a total 45 healthy adults aged 18 to 55 years, who received two vaccinations in a dose of 25 µg, 100 µg, and 250 µg. There were 15 participants in each group. The neutralizing activity was assessed by a pseudotyped lentivirus reporter single-round-of-infection neutralization assay. The ID₅₀ against D614G variant was 231.80 (SD, 41.53, Table 1) at 28 days after the boost dose in the dose of 100 µg group [13]. Another phase 3 randomized, observer-blinded, placebo-controlled trial was conducted in the United States and enrolled 30,420 participants, who were randomly assigned in a 1:1 ratio to either vaccine or placebo group. Finally, a total of 14,134 and 14,073 participants in the corresponding vaccine and control groups were included in the per-protocol analysis. The clinical efficacy of vaccine to prevent the occurrence of symptomatic COVID-19 was 94.1% (95% CI, 89.3%–96.8%) [11].

3.1.2. Heterologous vaccination study

A total of 88 health care workers received one dose of ChAdOx1 nCov-19. Among these participants, 37 chose a homologous boost with ChAdOx1 nCov-19 and the other 51 chose a heterologous boost with mRNA1273 9 to 12 weeks later. The ID₅₀ against original Swedish isolate in the heterologous groups at 30 days after the boost was 1000.00 (SD, 248.73, Table 1) [5].

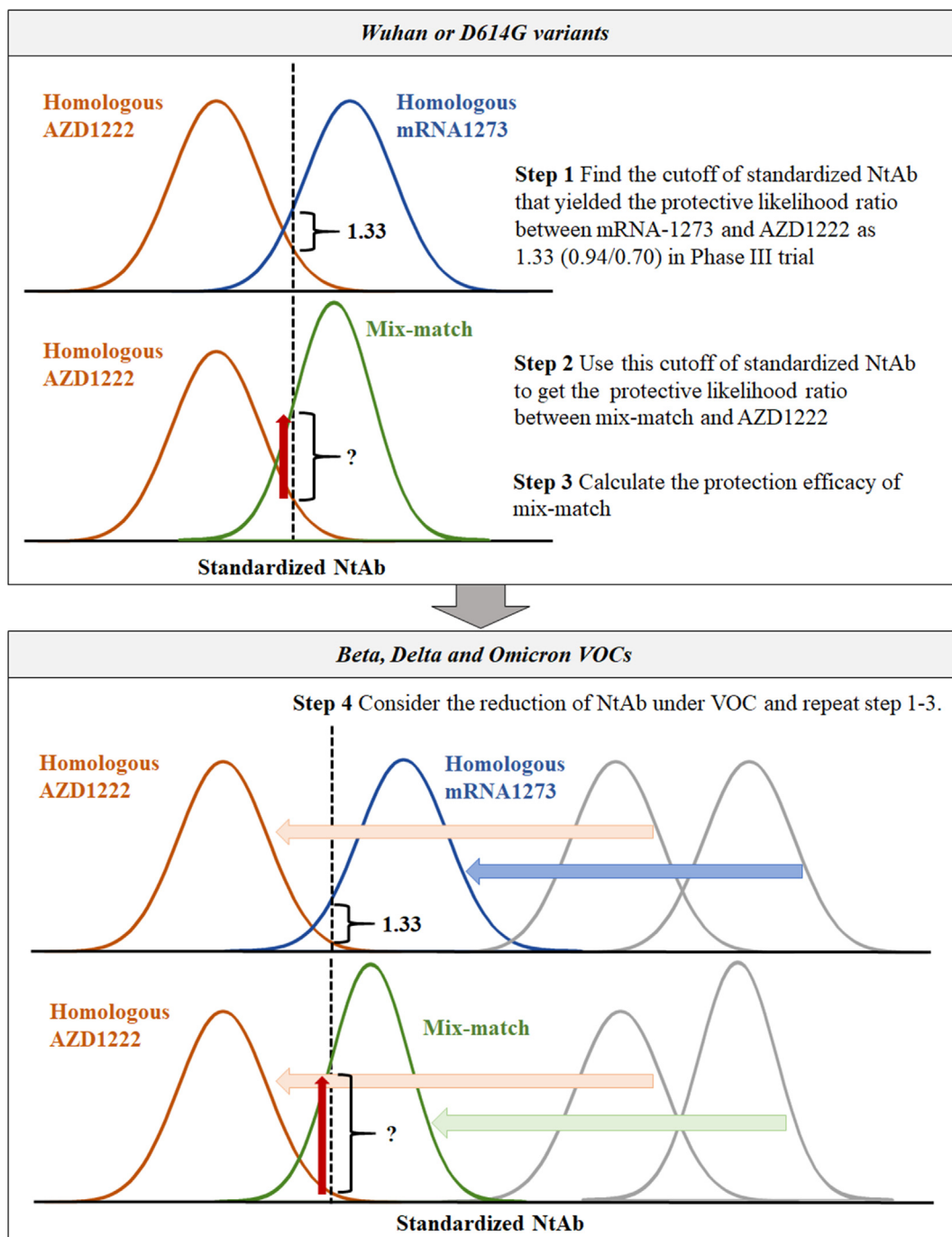


Fig. 2. Statistical procedure of determining the cut-off of the mix-match vaccination.

3.1.3. Impact of VOC on neutralizing antibody titer

A multicenter, double-blind, randomized, controlled trial was conducted in South Africa and a total of 2,021 participants with 1,010 receiving ChAdOx1 nCov-19 and 1,011 receiving placebo. Greater resistance to Beta variant in serum specimens obtained from the vaccine group was proved by using the live-virus neutralization assays. Comparing with the 50 % plaque reduction neutralization titer against B.1.1.117, the NtAb titer against beta variant had a 11-fold reduction [14]. Another phase 1 clinical trial of mRNA1273 was conducted in the United States with serum samples obtained from 12 participants receiving two immunizations with mRNA1273. Comparing the immunogenicity against D614G

strain, the neutralizing activity against beta variant reported an 8.6-fold reduction [15].

According to COVID-19 Weekly Epidemiological Update from World Health Organization, the neutralization activity against Delta variant reported an approximate 4-fold reduction for ChAdOx1 nCov-19 and found about 2 to 3-fold reduction (we took 3.13-fold reduction in this study by derivation from the aforementioned data) for mRNA1273 [16]. In contrast to Beta and Delta variants, Omicron variant was found to have dramatic reduction of NtAb titer, around 33-fold for ChAdOx1 nCov-19 and 36-fold for mRNA1273 [17].

Table 1
NtAb titers extracted from Phase 2 trials of vaccines.

	NtAb		Standardized NtAb		Ref
	Mean	SD	Mean*		
Wuhan or D614G variant					
Homologous AZD1222	162.90	61.20	2.66		Folegatti, et al
Homologous mRNA1273	231.80	41.53	5.58		Jackson, et al
Mix-match	1000.00	248.73	4.02		Normark, et al.
B.1.351 (Beta) VOC					
Homologous AZD1222	14.81	61.20	0.24		Madhi, et al
Homologous mRNA1273	26.95	41.53	0.65		Wang, et al
B.1.671 (Delta) VOC					
Homologous AZD1222	40.73	61.20	0.67		WHO Weekly Report
Homologous mRNA1273	74.13	41.53	1.79		WHO Weekly Report
B.1.1.529 (Omicron) VOC					
Homologous AZD1222	4.53	61.20	0.07		Cameroni, et al.
Homologous mRNA1273	7.02	41.53	0.17		Cameroni, et al.

* SD equals to 1.

3.2. Standardized (Dispersion-rescaled) neutralizing antibody

Fig. 3 (a) shows the unstandardized distribution of NtAb for homologous ChAdOx1 nCov-19, and homologous mRNA1273. As indicated in the method section, we re-scaled the distribution of NtAb for each type of vaccine, including homologous ChAdOx1 nCov-19, homologous mRNA1273, and the mix-match of both vaccines as shown in the upper panel of Table 1 for Wuhan or D614G. After dispersion-rescaled transformation, the standardized mean titer for the mix-match was slightly lower than that for homologous mRNA1273 but approximately 1.51-fold compared with homologous ChAdOx1 nCov-19 (Fig. 3 (b)). The middle panel and lower panel of Table 1 also shows the corresponding standardized mean titer for Beta, Delta and Omicron variants (Fig. 4 (a)-(c)).

3.3. Cut-off selection

Fig. 3 (b) and Table 2 show the protective likelihood ratio between mRNA1273 and ChAdOx1 nCov-19 following the expression (1). When the selected cut-off goes left further, the protective likelihood ratio becomes lower and vice versa. Note that the protective likelihood ratio as shown in the final column of Table 2 was computed by the ratio of two probability density function (see the second and the third column of Table 2) following the expression (1). Recall that the optimal cut-off between the distribution of NtAb for both vaccines was in the light of the empirical results of Phase 3 trial on clinical efficacy of reducing symptomatic COVID-19 cases 93 % for mRNA1273 and 70 % for ChAdOx1 nCov-19, yielding 1.33 (0.94/0.70) protective likelihood ratio. Table 2 shows that it corresponds to the optimal cut-off of 4.22 (equivalent to 0.12 and 0.16 of the probability density for homologous ChAdOx1 nCov-19 and mRNA1273, respectively).

Table 3 shows the corresponding detailed information for homologous ChAdOx1 nCov-19 and mix-match. The application of 4.22 cut-off obtained from above gives 5.68 protective likelihood ratio between the mix-match and homologous ChAdOx1 nCov-19. The predicted protection effect of the mix-match for Wuhan or D614G was 93 % (89 %-97 %) with small variation when the cut-off is lowered to 4.00 or raised to 4.50 (Table 3).

3.4. Correlates of protection (CoP) for mix-match vaccines against COVID-19 VOCs

Table 4 shows the alteration of cut-off on NtAb due to the administration of both homologous ChAdOx1 nCov-19 and mRNA1273 to prevent infection from Beta, Delta and Omicron VOCs based on the same protective likelihood ratio. The cut-off

for Wuhan or D614G was changed from 4.22 to 1.14, 1.48 and 3.14 for Beta, Delta, Omicron variants, respectively.

Based on the alteration of the cut-off of the baseline group ChAdOx1 nCov-19 from 4.22 to 1.14 attributed to Beta VOC relative to Wuhan or D614G, the corresponding probability density value for ChAdOx1 nCov-19 given the altered cut-off and 0.24 obtained from Table 1 in the face of Beta VOC was 0.27 (Table 4). The corresponding probability density figure for Beta VOC given a series of different degrees of reduction using 4.2 mean titer of NtAb of the mix-match for Wuhan or D614G obtained from Table 1, ranged from 0.32 to 0.35 as shown in the upper panel of Table 5. Table 5 also shows protective likelihood ratios for mix-match of combining ChAdOx1 nCov-19 and mRNA1273 against Beta. Based on these positive likelihood ratios, the corresponding predictive protective efficacy for the mix-match can be estimated with the range from 75.63 % to 73.87 % given 8–11-fold reduction of NtAb. The similar procedure was also applied to Delta and Omicron VOCs and the corresponding figures are shown in the middle and low panel of Table 5. The corresponding predictive efficacy for the mix-match strategy ranged from 84.87 % to 81.25 % given 2–5.5-fold reduction of NtAb for Delta and from 0.067 % to 0.059 % for Omicron given 32.5–36-fold reduction of NtAb.

4. Discussion

4.1. Rational for using mix-match vaccine strategy

By using a Bayesian reasoning method dispensing with information on convalescent cohorts as reference or comprehensive data of case and non-case with vaccination as used in previous studies on predicting CoP for various kinds of vaccine [6,7], the link between NtAb titer and the clinical efficacy of the mix-match can be predicted dispensing with the conduction of a phase 3 randomized controlled trial on the mix-match vaccination. Here, ChAdOx1 nCov-19 and mRNA1273 against VOCs has been demonstrated. These findings show that the NtAb titer of the mix-match vaccine was lower than that of homologous mRNA1263 but higher than that of ChAdOx1 nCov-19. The corresponding clinical efficacy against Beta, Delta, and Omicron was from 73.87 % to 75.63 %, 81.25 % to 84.87 %, and 0.059 % to 0.067 % given the magnitude of reduction, respectively. By contrast, the predicted efficacy given 9.65-fold reduction of NtAb observed from the original mix-match study for Beta was 74.55 %. Note that our result is compatible with the main finding of the original mix-match study [5].

The second reason for evaluating clinical efficacy of the mix-match vaccination is related to the delivery and the distribution of mRNA with the cold chain issue as mentioned earlier. The most effective intervention to end the pandemic of COVID-19 was based on

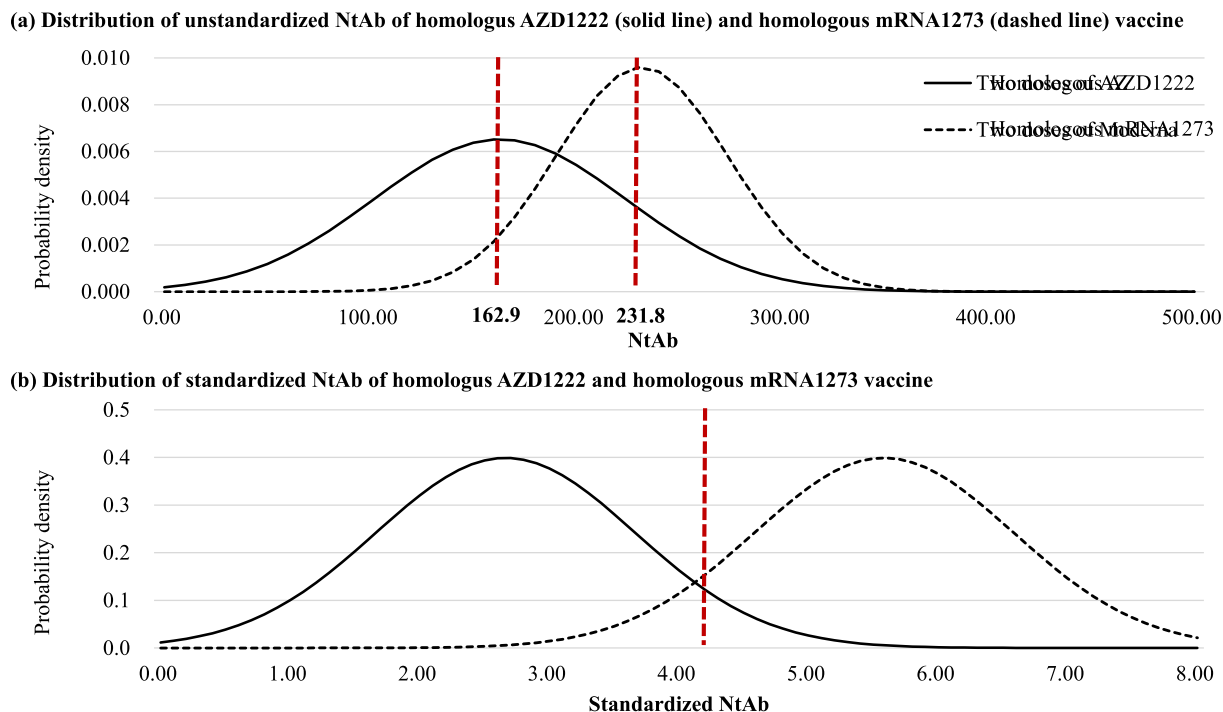


Fig. 3. Distributions of unstandardized NtAb (a) and standardized NtAb (b).

population-wide mass vaccination to achieve herd immunity as soon as possible. To this end, a nationwide mass vaccination program with BNT162b2 (Pfizer-BioNTech) mRNA COVID-19 vaccine has been initiated in Israel since December 2020. Then, the epidemic has gradually slowed down and they moved to lifting of restrictions in June 2021 [9]. In addition to BNT162b2, a series of different vaccine brands were introduced, including the other mRNA1273, vector-based vaccine (ChAdOx1 nCov-19 and Ad26.COV2.S (Johnson & Johnson/Janssen)), recombinant nanoparticle spike protein such as NVX-CoV2373 (Novavax), and inactivated-virus vaccines such as BBIBP-CorV (Sinopharm) and CoronaVac (Sinovac) [8,18].

Although many vaccines based on different mechanisms to elicit immune response against COVID-19 have been developed and rolled out, the distribution of vaccines around the world was still not evenly distributed. Up to date, Africa had only less than 10 % vaccination rate in comparison with over 60 % in Europe and North America. The disparity in vaccination rate still also exists within region. Production and delivery of various vaccine brands as mentioned above has also complicated this situation. This is particularly important for the country with the issue of cold chain on mRNA. In addition to tackle the feasibility of cold chain, it is necessary to set up the benchmark for the mix-match vaccination not affected by the cold chain issue. This has raised the necessity for the mix-match strategy. In addition to all the aspects of production, delivery, and administration, as the effectiveness of vaccines against SARS-CoV-2 VOCs, such as Alpha, Beta, Gamma, and Delta was notably reduced, using the mix-match strategy to enhance immunity is an expedient method. However, it is impractical to verify the effectiveness of mix-match vaccines against VOCs via the traditional phase 3 randomized controlled trial because the emerging VOCs such as Omicron and its spread is so rapid.

4.2. Current evidence on immunogenicity and effectiveness for the mix-match strategy

In Spain, CombiVacS trial enrolled a total of 676 individuals aged 18–60 years, who were randomly assigned to the prime dose of ChAdOx1 nCov-19 followed by the boost dose of BNT162b2 and a single

dose of ChAdOx1 nCov-19. The geometric mean titers of the interventional group were significantly higher for receptor-binding domain (RBD) protein and trimeric spike protein IgG than those of the control group [1]. In UK, Com-COV trial with 830 adults aged older than 50 years enrolled and randomized across eight groups to receive ChAdOx1 nCov-19-ChAdOx1 nCov-19, ChAdOx1 nCov-19-BNT162b2, BNT162b2- BNT162b2 and BNT162b2-ChAdOx1 nCov-19, administered at 4- or 12-week intervals. The geometric mean concentrations of both anti-spike IgG and T cell response were higher than those of homologous group with ChAdOx1 nCov-19 [2]. One study enrolled healthcare workers in Germany, with 174 receiving homologous BNT162b2, 38 receiving homologous ChAdOx1 nCov-19, and 104 receiving heterologous ChAdOx1 nCov-19-BNT162b2. The SARS-CoV2-specific IgG and T-cell responses of the heterologous group after the boost immunization were higher than those of the homologous groups with either BNT162b2 or ChAdOx1 nCov-19. Although the aforementioned differences were not statistically significant, but the geometric mean of 50 % inhibitory dose against alpha and beta variants were highest in the participants of heterologous group [3]. Another study in Germany enrolled individuals older than 60 years with the first dose of ChAdOx1 nCov-19 vaccination followed by the boost dose of homologous ChAdOx1 nCov-19 or heterologous BNT162b2 vaccine by their own choice. The heterologous group induced significantly higher titer of NtAb against not only Wuhan strain but also other VOCs like Alpha, Beta, and Gamma variants [4]. The other study was conducted in Sweden to compare the NtAb titers of homologous ChAdOx1 nCov-19 vaccination and heterologous ChAdOx1 nCov-19- mRNA1273. The NtAb titer against both original Swedish isolate and Beta variants was significantly higher in the heterologous group than that of the homologous group [5]. Most of the aforementioned studies merely quantify the difference of NtAb titers between mix-match and homologous groups. However, the link between NtAb titer and the correlate of protection should be elucidated. It is the main purpose of our study.

The effectiveness of heterologous ChAdOx1 nCov-19-mRNA1273 has been reported as 79 % (95 % confidence interval [CI], 62 %–88 %) through a nationwide cohort study in Sweden which included 16,402 vaccinated and 10,984 unvaccinated individuals. The estimate

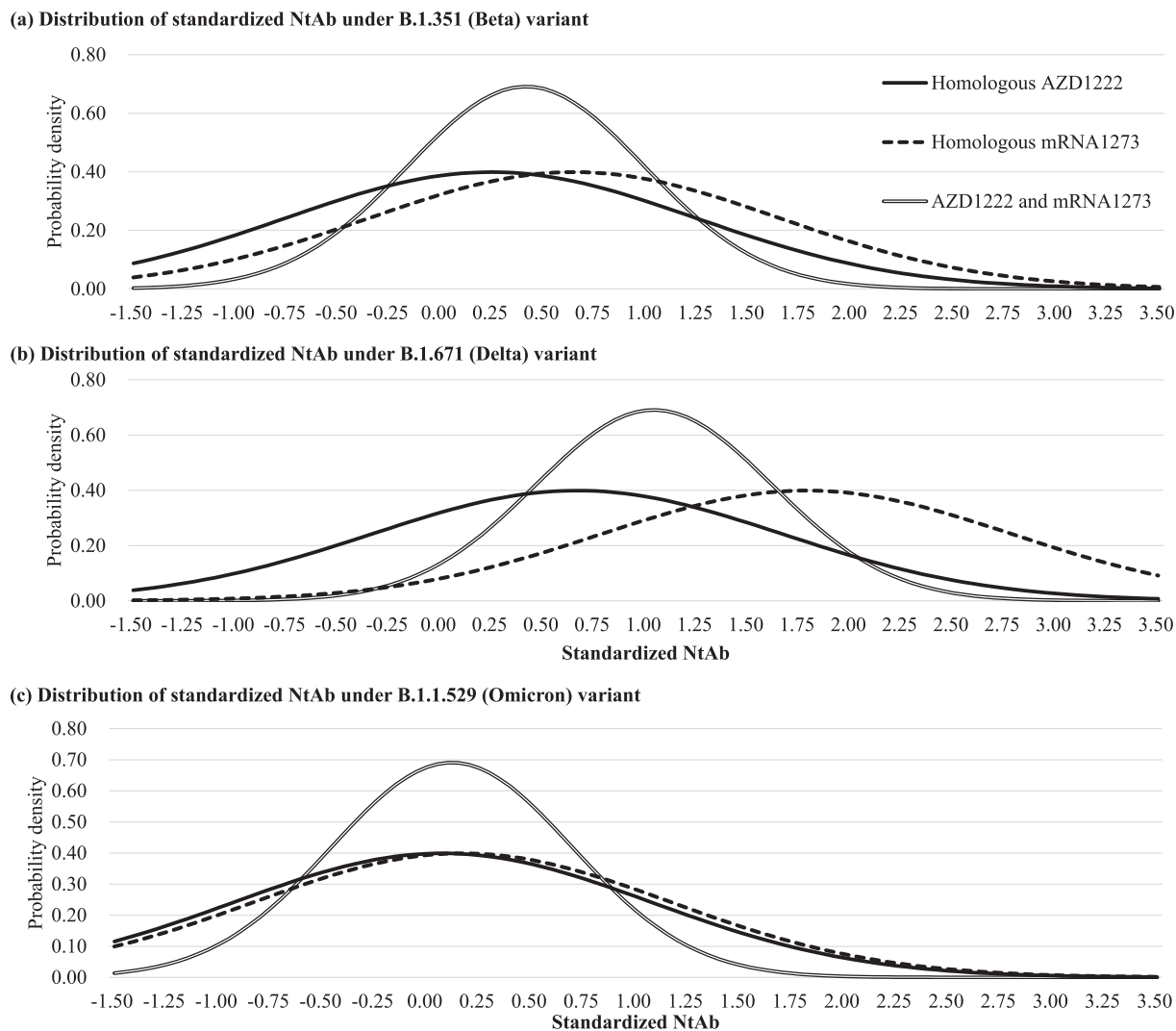


Fig. 4. Distributions of standardized NtAb under different VOCs (a) B.1.351 (Beta) (b) B.1.671 (Delta) (c) B.1.1.529 (Omicron).

Table 2
Protection ratio between homologous AZD1222 and mRNA-1273 given a cutoff of standardized NtAb.

Standardized NtAb	Probability density given a cutoff of standardized NtAb		Protection ratio
	Homologous AZD1222	Homologous mRNA-1273	
4.000	0.16	0.11	0.70
4.100	0.14	0.13	0.94
4.123	0.14	0.14	1.00
4.200	0.12	0.15	1.26
4.220	0.12	0.16	1.33
4.300	0.10	0.18	1.68
4.400	0.09	0.20	2.25
4.500	0.07	0.22	3.02

from Swedish study is very close to our estimate ranged from 81.25 % to 84.87 % under Delta VOC [19]. The validity of using CoP to prove clinical efficacy has also been demonstrated in a randomized controlled trial for homologous mRNA vaccination [20].

4.3. The methodology for immunobridging

Furthermore, to identify the immune correlate of protection from vaccination and predict the effect of VOCs on the changes

in immunity will be reflected in clinical outcomes should be timely and precise to accelerate the development of vaccine strategies and the deployment of vaccine. One study analyzed the relationship between neutralization levels and the observed protection from symptomatic SARS-CoV-2 infection by using the data from seven different vaccines with the respective convalescent cohorts as a reference group under the framework of logistic method [6]. The other study derived a weighted generalized additive model to predict the absolute risk of SARS-CoV-2 infection by using the data of infected and non-infected participants vaccinated with ChAdOx1 nCov-19 [7]. However, the aforementioned two studies needed either convalescent cohorts as reference or comprehensive data of case and non-case with vaccination. These analyzing methods were time-consuming and impractical in the current situation with the rapid evolution of SARS-CoV-2 variants. The information on convalescent cohorts as reference or comprehensive data of case and non-case with vaccination is not necessary to estimate the CoP of mix-match vaccine by using our Bayesian reasoning method. More importantly, with more and more vaccines entering the market, this methodology can be applied to efficiently determine what potential mix-matching of products would likely produce the best efficacy before a clinical trial. However, our methodology for predicting CoP would not replace Phase 2–3 trial but only strengthening immunobridging and providing the guid-

Table 3

Protection ratio between mix-match vaccine (AZD1222 and mRNA-1273) and homologous AZD1222 and predicted protection of mix-match vaccine given a cutoff of standardized NtAb.

Standardized NtAb	Probability density given a cutoff of standardized NtAb		Protection ratio	Predicted protection, % (95 % Confidence Interval)
	Homologous AZD1222	Mix-match		
4.000	0.16	0.68	4.19	0.91 (0.85, 0.96)
4.100	0.14	0.69	4.87	0.92 (0.87, 0.96)
4.123	0.14	0.69	5.03	0.92 (0.88, 0.96)
4.200	0.12	0.68	5.55	0.93 (0.89, 0.97)
4.220	0.12	0.67	5.68	0.93 (0.89, 0.97)
4.300	0.10	0.65	6.20	0.94 (0.90, 0.97)
4.400	0.09	0.60	6.78	0.94 (0.91, 0.97)
4.500	0.07	0.54	7.27	0.94 (0.91, 0.97)

Table 4

Protection ratio between homologous AZD1222 and mRNA-1273 given a cutoff of standardized NtAb under different VOCs.

Standardized NtAb	Probability density given a cutoff of standardized NtAb		Protection ratio
	Homologous AZD1222	Homologous mRNA-1273	
Wuhan or D614G variant			
4.22	0.12	0.16	1.33
B.1.351 (Beta) VOC			
1.14	0.27	0.35	1.33
B.1.671 (Delta) VOC			
1.48	0.29	0.38	1.33
B.1.1.529 (Omicron) VOC			
3.14	0.0036	0.0048	1.33

Table 5

Predicted protection of mixed vaccine (AZD1222 and mRNA-1273) for different fold reduction of NtAb given a cutoff for Beta VOC.

Fold reduction	Standardized NtAb	Probability density	Protection ratio	Predicted protection, % (95 % Confidence Interval)
B.1.351 (Beta) VOC				
8	0.50	0.35	1.31	75.63 (63.84, 86.00)
9	0.45	0.34	1.26	74.93 (62.96, 85.53)
9.65	0.42	0.33	1.23	74.55 (62.47, 85.27)
10	0.40	0.33	1.22	74.36 (62.23, 85.15)
11	0.37	0.32	1.19	73.87 (61.62, 84.82)
B.1.671 (Delta) VOC				
2	2.01	0.69	2.56	84.87 (76.76, 92.20)
2.5	1.61	0.67	2.50	84.56 (76.33, 92.02)
3.5	1.15	0.61	2.28	83.33 (74.61, 91.31)
4.5	0.89	0.57	2.10	82.18 (73.04, 90.65)
5.5	0.73	0.53	1.97	81.25 (71.77, 90.10)
B.1.1.529 (Omicron) VOC				
32.5	0.124	0.0000082	0.00066	0.067 (0.003,0.011)
33	0.122	0.0000080	0.00065	0.065 (0.003,0.011)
34	0.118	0.0000078	0.00063	0.063 (0.003,0.010)
35	0.115	0.0000075	0.00061	0.061 (0.003,0.010)
36	0.112	0.0000073	0.00059	0.059 (0.003,0.010)

ance for Phase 3 trial, if new mix-match strategy is considered on sample size determination and a surrogate endpoint for CoP.

By using the proposed immunobridging approach, the comparison of clinical efficacy between the mix-match vaccination with the homologous vaccine can be attained [21,22], however this is the purpose of this study. Following the spirit of CoP on immunobridging studies as the previous mix-match trial [1–5] has demonstrated the heterologous vaccination had higher immunogenicity than the homologous vaccine. This implies the mix-match can attain a higher clinical efficacy than the homologous vaccine. If this is not true it is very difficult to apply these immunobridging studies to compete the EUA in the face of emerging variants. Otherwise, one need to do a phase 3 randomized trial on the comparison between the mix-match vaccination and the homologous vaccine, which is not infeasible when facing the new variants.

There are some inevitable limitations in this study. First, we estimate CoP via the NtAb titers, which is related to B cell immunity. Vaccine-induced T cell-mediated immunity is not investigated in this study. Second, immunity waning could not be evaluated in this study. The exact duration of mix-match vaccine against VOCs is still elusive. Third, heterogeneity across studies is one of potential factors affecting the results should be considered in the future.

In conclusion, we developed a very useful means for CoP targeting at the mix-match vaccine type with timeliness of dispensing with the conduction of a phase 3 trial on the mix-match vaccination. The finding and methodology can be applied to evaluating CoP for any kind of the mix-match vaccine against VOCs. Here, we demonstrate the mix-match of ChAdOx1 nCov-19 and mRNA1273 vaccine still provides clinical efficacy against Beta

and Delta VOCs but it appears ineffective for Omicron variants. These findings highlight the urgent need for next generation vaccine against emerging variant such as Omicron.

Funding

This work was supported by Ministry of Science and Technology, Taiwan (MOST 109-2327-B-002-009). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

CRedit authorship contribution statement

Sih-Han Liao: Data curation, Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Wei-Jung Chang:** Data curation, Formal analysis, Methodology, Visualization, Writing – original draft. **Chen-Yang Hsu:** Investigation, Methodology. **Amy Ming-Fang Yen:** Supervision, Validation. **Ting-Yu Lin:** Methodology, Validation. **Sam Li-Sheng Chen:** Conceptualization. **Tony Hsiu-Hsi Chen:** Conceptualization, Resources, Supervision, Writing – review & editing.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We thank Dr. Alexandra Hogan for very helpful advices and comments for evaluating CoP based on immunobridging.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2022.10.011>.

References

- [1] Borobia AM, Carcas AJ, Pérez-Olmeda M, Castaño L, Bertran MJ, García-Pérez J, et al. Immunogenicity and reactogenicity of BNT162b2 booster in ChAdOx1-S-primed participants (CombiVacS): a multicentre, open-label, randomised, controlled, phase 2 trial. *Lancet* 2021;398(10295):121–30.
- [2] Liu X, Shaw RH, Stuart ASV, Greenland M, Aley PK, Andrews NJ, et al. Safety and immunogenicity of heterologous versus homologous prime-boost schedules with an adenoviral vectored and mRNA COVID-19 vaccine (Com-COV): a single-blind, randomised, non-inferiority trial. *Lancet* 2021;398(10303):856–69.
- [3] Hillus D, Schwarz T, Tober-Lau P, et al. Safety, reactogenicity, and immunogenicity of homologous and heterologous prime-boost immunisation with ChAdOx1 nCoV-19 and BNT162b2: a prospective cohort study. *Lancet Respir Med* 2021.
- [4] Barros-Martins J, Hammerschmidt SI, Cossmann A, Odak I, Stankov MV, Morillas Ramos G, et al. Immune responses against SARS-CoV-2 variants after heterologous and homologous ChAdOx1 nCoV-19/BNT162b2 vaccination. *Nat Med* 2021;27(9):1525–9.
- [5] Normark J, Vikström L, Gwon Y-D, Persson I-L, Edin A, Björnell T, et al. Heterologous ChAdOx1 nCoV-19 and mRNA-1273 Vaccination. *N Engl J Med* 2021;385(11):1049–51.
- [6] Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med* 2021;27(7):1205–11.
- [7] Feng S, Phillips DJ, White T, et al. Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. *Nat Med* 2021.
- [8] Azevedo TCPd, Freitas Pvd, Cunha PHPd, Moreira EAP, Rocha TJM, Barbosa FT, et al. Efficacy and landscape of Covid-19 vaccines: a review article. *Rev Assoc Med Bras* 1992;67(3):474–8.
- [9] Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med* 2021;384(15):1412–23.
- [10] Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021;397(10269):99–111.
- [11] Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021;384(5):403–16.
- [12] Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet* 2020;396(10249):467–78.
- [13] Jackson LA, Anderson EJ, Roupael NG, Roberts PC, Makhene M, Coler RN, et al. An mRNA vaccine against SARS-CoV-2 - preliminary report. *N Engl J Med* 2020;383(20):1920–31.
- [14] Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 vaccine against the B.1.351 variant. *N Engl J Med* 2021;384(20):1885–98.
- [15] Wang P, Nair MS, Liu L, Iketani S, Luo Y, Guo Y, et al. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. *Nature* 2021;593(7857):130–5.
- [16] World Health Organization. COVID-19 weekly epidemiological update, edition 47, 6 July 2021. Geneva: World Health Organization; 2021 2021-07-06.
- [17] Cameroni E, Saliba C, Bowen JE, et al. Broadly neutralizing antibodies overcome SARS-CoV-2 Omicron antigenic shift. *bioRxiv*. 2021 Dec 14:2021.12.12.472269. doi: 10.1101/2021.12.12.472269. PMID: 34931194; PMCID: PMC8687478.
- [18] Heath PT, Galiza EP, Baxter DN, Boffito M, Browne D, Burns F, et al. Safety and efficacy of NVX-CoV2373 Covid-19 vaccine. *N Engl J Med* 2021;385(13):1172–83.
- [19] Nordström P, Ballin M, Nordström A. Effectiveness of heterologous ChAdOx1 nCoV-19 and mRNA prime-boost vaccination against symptomatic Covid-19 infection in Sweden: a nationwide cohort study. *Lancet Reg Health Eur* 2021;11:100249.
- [20] Stuart ASV, Shaw RH, Liu X, Greenland M, Aley PK, Andrews NJ, et al. Immunogenicity, safety, and reactogenicity of heterologous COVID-19 primary vaccination incorporating mRNA, viral-vector, and protein-adjuvant vaccines in the UK (Com-COV2): a single-blind, randomised, phase 2, non-inferiority trial. *Lancet* 2022;399(10319):36–49.
- [21] Gilbert PB, Montefiori DC, McDermott A, et al. Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy trial. *Science* 2022;375:43–50.
- [22] Earle KA, Ambrosino DM, Fiore-Gartland A, Goldblatt D, Gilbert PB, Siber GR, et al. Evidence for antibody as a protective correlate for COVID-19 vaccines. *Vaccine* 2021;39(32):4423–8.