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SARS-Cov-2 vaccination strategies in hospitalized recovered COVID-19 patients: a randomized clinical trial (VATICO Trial)

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The impact on immunogenicity and efficacy of SARS-CoV-2 vaccination in people with prior COVID-19 could differ depending on timing of vaccination and number of doses. The VATICO study randomized 66 hospitalized recovered COVID-19 individuals to receive either immediate or deferred vaccination, with one or two doses of mRNA SARS-CoV-2 vaccines. We measured binding and neutralizing antibodies against SARS-CoV-2 at enrollment and longitudinally. Median (IQR) time from SARS-CoV-2 infection to first vaccination was 68 (53–75) days in the immediate group, and 151 (137–173) days in the deferred group. At week 48, timing or number of vaccine doses did not influence the change in antibody levels relative to baseline. Adherence to the assigned vaccine regimen was lower in the deferred group, particularly in participants receiving two doses. Although the study ultimately lacked adequate power to draw firm conclusions, these results suggest possible benefits of prompt vaccination after recovery from COVID-19.

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The development of safe and effective vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of Coronavirus Disease 2019 (COVID-19), was critical in reducing morbidity and mortality associated with COVID-19 worldwide[1,2]. Pfizer-BioNTech 162b2 and Moderna mRNA-1273 were amongst the first COVID-19 vaccines to be approved for emergency use, based on extensive clinical trials that demonstrated their safety and effectiveness in people without prior COVID-19[2,3]. Although both vaccines were initially approved as a two-dose regimen, several factors led to the consideration of a one-dose strategy, particularly for individuals previously infected with SARS-CoV-2. These factors included early vaccine supply shortages and the urgency to respond swiftly to the pandemic. The rationale supporting vaccination with one dose instead of two in people with prior COVID-19 was based on observations of induction of viral-specific neutralizing antibodies and T-cell responses generating immunological memory after natural infection with SARS-CoV-2 (natural immunity)[4]. In fact, higher neutralization activity and antibodies targeting SARS-CoV-2 proteins were observed in individuals after severe COVID-19 when compared to responses in people with mild disease[5]. The possibility that SARS-CoV-2 infection could stimulate the immune system, with a single dose of vaccine after COVID-19 being sufficient to elicit strong and durable specific immune responses,was proposed by several observational studies[6–12]. These studies showed similar or even higher antibody responses in individuals with prior COVID-19 who received a single dose of mRNA vaccine (hybrid immunity) compared to those without prior SARS-Cov-2 infection who received two doses of vaccine (vaccinal immunity). However, comparative studies specifically assessing whether one dose of mRNA vaccine provides similar protective efficacy and long-term immunity than two doses in people recovered from COVID-19 are lacking. Today, conducting studies to answer this question is challenging due to the high seroprevalence of COVID-19 and the current vaccination rates among general populations.

The optimal timing for vaccination after recent SARS-CoV-2 infection is not well established. Deferring vaccination after natural infection may lead to a more robust immune response, since the immune system has more time to mature, and prior non-randomized studies have shown that a longer interval between COVID-19 and vaccination could enhance the immune response[9,13]. Additionally, although supported by little evidence, the theoretical concern that pre-existing natural immunity could contribute to increased frequency and severity of adverse reactions to COVID-19 vaccines could also support delaying vaccination in people with recent COVID-19[3].

The recent use of SARS-CoV-2 neutralizing monoclonal antibodies (NMAb) as a treatment for COVID-19 raised concerns about potential interference with vaccine efficacy by blocking key immune-recognized epitopes, raising the question of whether vaccination should be delayed in NMAb recipients[14–16].

Understanding the dynamics of humoral immunity in response to SARS-CoV-2 infection and to vaccination is crucial to better guide the optimal timing and dosing schemes in vaccination programs. This is especially the case for people who have recovered from SARS-CoV-2 infection and who have received therapy with NMAb, a group that was excluded from pivotal clinical vaccine trials. Therefore, we aimed to compare the effects on humoral immune responses of one versus two doses of mRNA SARS-Cov-2 vaccines, as well as early versus deferred administration after recovery from severe SARS-Cov-2 infection, in previously hospitalized COVID-19 patients participating in the TICO/ACTIV-3 (Therapeutics for Inpatients with COVID-19) clinical trial (clinicaltrials.gov ID NCT04501978). TICO/ACTIV-3 served as a platform for conducting randomized, placebo-controlled clinical trials to assess the safety and efficacy of various investigational agents against SARS-CoV-2, including the NMAb Tixagevimab/Cilgavimab and Ensovibep[17–19]. Figure 1A shows the timeline from participation in TICO to enrollment in VATICO.

Results

The VATICO study initially planned to enroll 640 participants with a primary analysis based on the subgroup of participants who received a placebo in the TICO trial, which was the source of participants for VATICO. However, due to the end of the TICO trial, the study ultimately concluded with 66 participants and the primary analysis was amended to include all participants, regardless of their TICO assignment. Participants were included across 19 sites in 4 countries: Switzerland (4), Spain (14), Uganda (20) and the US (28), from August 2021 through January 2022.

After inclusion, participants were randomized 1:1 to receive vaccines at study entry (immediate vaccination group, n = 34) or 12 weeks thereafter (deferred vaccination group, n = 32). Within the immediate vaccination group, 16 individuals were randomized to receive one dose of vaccine (I1), and 18 to receive two doses of vaccine four weeks apart (I2). Similarly, within the deferred vaccination arm, 16 participants were randomized to receive one dose of vaccine (D1), and 16 two vaccine doses four weeks apart (D2). Figure 1B shows the study design, and Fig. 2 summarizes participants' disposition during the study.

Baseline clinical characteristics

Table 1 summarizes the main demographic and clinical characteristics of the study population. Noteworthy, neither the TICO trial nor the VATICO trial excluded individuals with immunocompromising conditions, and

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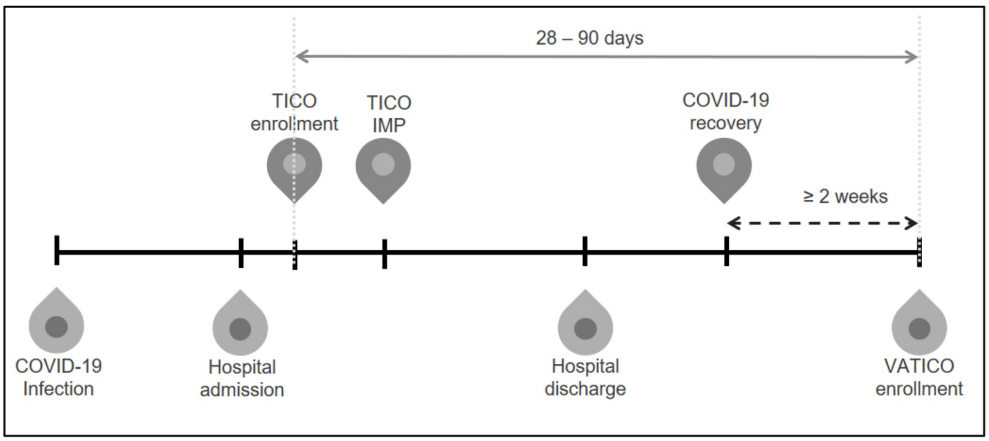

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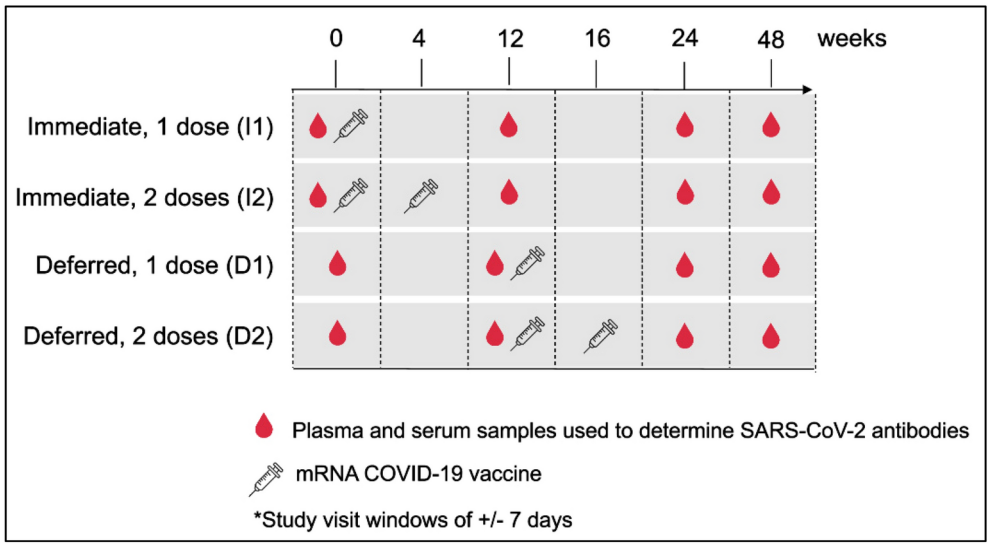

Fig. 1. Study design. (**A**) Timeline from participation in TICO to enrollment in VATICO. (**B**) Diagram of study visits. TICO IMP: TICO Investigational Medical Product (Tixagevimab/Cilgavimab and Ensovibep or Placebo).

those with such conditions or taking immunosuppressive medications may have been included in numbers too small to significantly impact the analysis. Seventeen (26%) participants had already been vaccinated against SARS-Cov-2 before TICO randomization, with slightly lower rates of prior vaccination in the immediate than the deferred group (21% versus 31%), and in the two-dose than the one-dose group (15% versus 38%). Medical conditions were present in 27 (41%) participants, mainly hypertension in 19 (29%) or diabetes in 10 (15%). The severity of COVID-19 in terms of oxygen requirement, duration of symptoms, and time to recovery was similar across groups, like the numbers of participants who received active treatment (Tixagevimab/cilgavimab or Ensovibep) versus placebo in TICO. Median (IQR) time from COVID infection to first vaccination was 68 days (53–75) in the immediate group, and 151 days (137–173) in the deferred group, and median (IQR) time from NMAb/placebo administration in TICO to first vaccination was 63 days (46–70) in the immediate group, and 145 days (131–165) in the deferred group.

Antibody results

At study entry, more than 90% of participants were positive for IgG antibodies directed against SARS-CoV-2 nucleocapsid protein (anti-N Ab) and neutralizing antibodies against SARS-CoV-2 spike protein (anti-S neutralizing Ab), with median (IQR) neutralizing activity of 97.0% (95.0–98.0). There were no differences between immediate or deferred vaccination or between the one-dose and the two-dose groups (Table 2). Overall, median (IQR) anti-S Ab concentration at study entry was 51,124 (12,848–221,724) pg/mL. Aligned with lower rates of prior SARS-CoV-2 vaccination, individuals allocated to immediate vaccination showed lower anti-S Ab

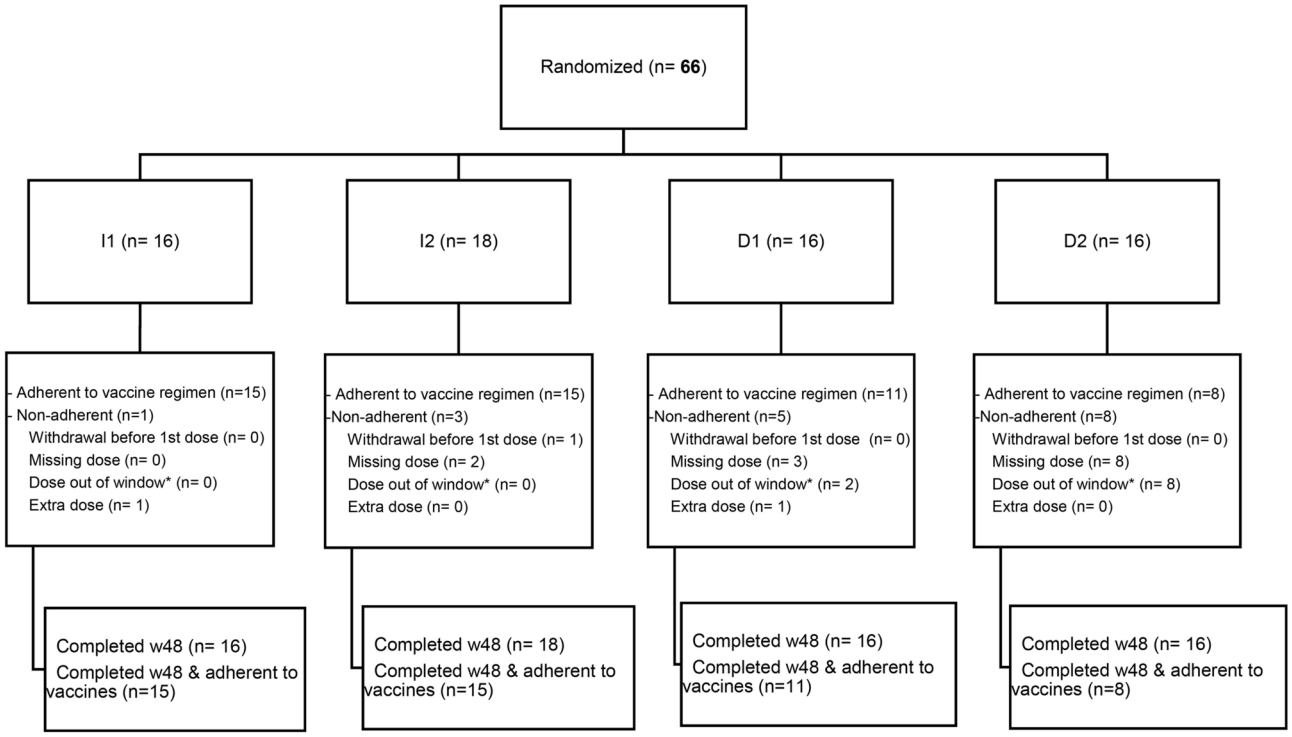

Fig. 2. Consolidated Standards of Reporting Trials (CONSORT) flow diagram for the trial. *Out of window of ± 7 days of the per-protocol scheduled visit.

levels than those allocated to the deferred group (42,944 versus 81,992 pg/mL). Similarly, anti-S Ab levels were lower in participants allocated to receive two doses of vaccine than in those allocated to receive one dose of vaccine (40,845 versus 66,857 pg/mL).

Anti-S Ab levels increased after vaccination in all study groups (Fig. 3). Geometric mean ratios for the relative change from baseline at weeks 12, 24 and 48 in anti-S Ab titers for the immediate versus deferred strategy, and for the one- versus two-dose strategy, were estimated. At week 12, participants allocated to the deferred group (before they received their first vaccination) had lower median anti-S Ab and ratios from baseline compared to the immediate group. However, at weeks 24 and 48 immediate and deferred groups had similar median anti-S Ab levels (Fig. 3A). Because the immediate group had lower anti-S Ab levels at baseline, the concentration ratio relative to baseline was higher at 24 and 48 weeks in the immediate group than in the deferred group. However, there was no statistically significant evidence that timing of vaccination influenced the change in antibody concentrations relative to baseline at 48 weeks (GMR 1.71, 95% CI 0.73 to 3.97, $p = 0.21$; Fig. 4).

Regarding vaccination with one or with two-doses of vaccine, concentrations of anti-S Ab and ratios from baseline were lower in the one-dose group than in the two-dose group through the study, although at week 48 these differences were not statistically significant (Fig. 3B). At week 48, median (IQR) ratio in anti-S Ab titers from baseline was 0.6 (0.3–7.9) in the one-dose group and 2.8 (0.6–20.8) in the two dose-group. However, there was no statistically significant evidence that the assigned number of doses had an effect on the change in antibody concentration relative to baseline at 48 weeks (GMR 0.68, 95% CI 0.29 to 1.59, $p = 0.37$; Fig. 5).

As shown in Table 2, the proportion of participants with > fourfold increase from baseline to week 48 in anti-S Ab levels was 48% and 29% in the immediate and in the deferred group, respectively ($p = 0.25$), and 36% and 42% in the one-dose and in the two-dose group, respectively ($p = 0.95$).

There was not statistically significant evidence of heterogeneity by baseline or clinical characteristics, or prior administration of SARS-CoV-2 NMAb within TICO in the effect of timing (Fig. 4) or number of doses (Fig. 5) on the antibody response to mRNA vaccines. Antibody levels at TICO baseline may modify the effect of one versus two vaccine doses (interaction $p < 0.01$). However, the estimated effects, 95% confidence intervals, and p-values within subgroups, and p-values for the interaction between treatment group and subgroup should be interpreted with caution as these are not adjusted for multiple comparisons and have low power.

Adverse events

Overall, 89 doses of SARS-CoV-2 vaccines were administered during the study; 85 (95.5%) doses were Pfizer BNT162b2 vaccine, and 4 (4.5%) doses were Moderna mRNA-1273 vaccine. There were two serious adverse events (SAEs) during the study and neither considered to be vaccine-related. One participant who has been allocated to the I1 group died five weeks after enrollment from preexisting cancer. The other SAE occurred in one participant assigned to the D2 group who required hospital admission due to recurrent COVID-19 at week 12, before receiving the first dose of the vaccine.

	I1 group n = 16	I2 group n = 18	D1 group n = 16	D2 group n = 16
Age at TICO enrollment [Years, (median, IQR)]	51 (35, 64)	43 (38, 57)	53 (45, 60)	44 (37, 59)
≧ 65 years (n, %)	4 (25)	3 (17)	3 (19)	1 (6)
Sex, Male (n, %)	8 (50)	12 (67)	10 (63)	8 (50)
Race/Ethnicity (n, %)				
Black	8 (50)	8 (44)	7 (44)	9 (56)
White	5 (31)	5 (28)	5 (31)	4 (25)
Hispanic	3 (19)	4 (22)	3 (19)	3 (19)
Asian	0 (0)	0 (0)	1 (6)	0 (0)
Other	0 (0)	1 (6)	0 (0)	0 (0)
Medical conditions (n, %)	9 (56)	6 (33)	6 (38)	6 (38)
Hypertension	7 (44)	4 (22)	5 (31)	3 (19)
Diabetes requiring medication	4 (25)	1 (6)	3 (19)	2 (13)
Asthma	1 (6)	1 (6)	0 (0)	1 (6)
COPD	0 (0)	1 (6)	0 (0)	1 (6)
HIV or other immune suppression	1 (6)	1 (6)	0 (0)	0 (0)
Heart Failure	(0)	1 (6)	0 (0)	0 (0)
Hepatic impairment	0 (0)	0 (0)	1 (6)	0 (0)
Malignancy	1 (6)	0 (0)	0 (0)	0 (0)
Renal impairment	1 (6)	0 (0)	0 (0)	0 (0)
BMI > 30 k/m^2 (n, %)	9 (56)	7 (39)	7 (44)	5 (31)
COVID-19 vaccination status before TICO (n, %)				
Not vaccinated	11 (69)	16 (89)	9 (56)	13 (81)
One dose	2 (13)	1 (6)	5 (31)	1 (6)
Two doses	3 (19)	1 (6)	2 (13)	2 (13)
Days from COVID-19 symptoms to TICO enrollment (median, IQR)	7 (3, 10)	8 (6, 9)	8 (7, 11)	8 (6, 10)
Maximum supplemental O2 requirement during TICO (n, %)				
None	10 (29)	5 (16)	9 (28)	6 (18)
< 4 L/min	8 (24)	8 (25)	5 (16)	11 (32)
≥ 4 L/min	16 (47)	19 (59)	18 (56)	17 (49)
Days from COVID-19 infection to first vaccination (median, IQR)	60 (51, 72)	70 (59, 76)	151 (134, 173)	151 (137, 168)
Days from TICO enrollment to recovery (median, IQR)	20 (19, 23)	21 (19, 24)	21 (19, 25)	19 (19, 30)
Received NMAb within TICO (n, %)	7 (44)	11 (61)	8 (50)	9 (56)
Days from TICO enrollment and NMAb/placebo administration to first vaccination (median, IQR)	58 (42, 69)	64 (52, 70)	145 (130, 165)	145 (131, 163)

Table 1. Demographic and clinical characteristics of the study population at study entry. I1, Immediate one dose; I2, Immediate two doses; D1, Deferred one dose; D2, Deferred two doses. COPD, Chronic obstructive pulmonary disease. BMI, Body Mass Index. NMAb, Neutralizing Monoclonal Antibodies.

Overall, 10 participants (15.2%) tested positive for SARS-CoV-2 at least once after their baseline study visit. Evidence of recurrent COVID-19 during the study occurred only in one participant allocated to the I2 group (5.6%), compared with three participants (18.8%) allocated to each of the other three study groups (I1, D1 and D2).

Adherence to the vaccination regimen

Table 3 shows the proportion of participants who were adherent to the vaccination regimen among individuals allocated to immediate or to deferred vaccination and to receive one or two vaccine doses. Overall, 49 (74%) of participants were adherent to their assigned vaccination schedule during the study. Among the 17 non-adherent participants, reasons for non-adherence included: missing the first dose in 7 (41%); receiving the first dose outside a 7-day window of the per-protocol scheduled visit in 7 (41%); missing the second dose in 6 (35%); and receiving the second dose outside the 7-day window visit in 3 (18%) participants. One participant allocated to the I2 group withdrew from the study before first vaccination. In addition, 2 individuals assigned to one-dose regimen received an additional dose during the study. Furthermore, 7 (11%) participants received extra vaccinations out of the study that were reported during TICO follow-up (3 in the I1 group, 1 in the I2 group, and 3 in the D2 group).

Adherence was statistically significantly higher among participants allocated to immediate versus deferred vaccination (88% vs 59%, $p = 0.0015$), whereas there was no statistically significant difference in adherence between participants allocated to one versus two vaccine doses (81% versus 68%, $p = 0.27$). The first vaccine

	Immediate n = 34	Deferred n = 32	One dose n = 32	Two doses n = 34
Anti-S IgG concentration (pg/mL) Median (IQR)				
Available data at BL/W12/W24/W48	32/29/31/27	29/30/28/27	30/29/30/26	31/30/29/28
Baseline	42,944 (11,641–205,993)	81,992 (15,805–268,464)	66,857 (11,634–221,724)	40,845 (12,848–268,464)
12 weeks	332,482 (105,657–701,712)	54,020 (21,372–134,978)	72,912 (29,001–207,222)	253,811 (50,845–701,712)
24 weeks	177,969 (41,719–370,373)	256,597 (58,687–621,416)	61,889 (30,666–244,600)	370,373 (196,418–629,936)
48 weeks	119,336 (37,425–360,684)	120,016 (37,440–245,659)	90,087 (37,425–217,819)	152,651 (47,370–311,719)
Ratio anti-S IgG from baseline Median (IQR)				
12 weeks	7.7 (1.2–52.5)	0.4 (0.3–2.3)	1.1 (0.3–3.2)	2.9 (0.4–18.0)
24 weeks	3.4 (0.7–25.2)	1.3 (0.5–5.0)	0.8 (0.4–3.7)	4.5 (1.3–34.9)
48 weeks	3.8 (0.6–20.8)	0.6 (0.3–8.6)	0.6 (0.3–7.9)	2.8 (0.6–20.8)
≥ fourfold increase in anti-S IgG from baseline N (%)				
12 weeks	15 (53.6)	4 (14.8)	6 (22.2)	13 (46.4)
24 weeks	11 (36.7)	9 (34.6)	6 (21.4)	14 (50.0)
48 weeks	13 (48.1)	7 (29.2)	9 (36.0)	11 (42.3)
Anti-S neutralizing Ab positive N (%)				
Available data at BL/W12/W24/W48	32/29/31/27	29/30/28/27	30/29/30/26	31/30/29/28
Baseline	32 (94)	28 (88)	30 (94)	30 (88)
12 weeks	29 (85)	28 (88)	29 (91)	28 (82)
24 weeks	31 (91)	27 (84)	30 (94)	28 (82)
48 weeks	27 (79)	26 (81)	26 (81)	27 (79)
% binding inhibition Median (IQR)				
Available data at BL/W12/W24/W48	32/29/31/27	29/30/28/27	30/29/30/26	31/30/29/28
Baseline	97.0 (95.5–98.0)	97.0 (94.0–98.0)	97.0 (94.0–98.0)	97.0 (95.0–98.0)
12 weeks	98.0 (97.0–98.0)	97.0 (96.0–98.0)	97.0 (97.0–98.0)	97.5 (97.0–98.0)
24 weeks	98.0 (97.0–98.0)	98.0 (98.0–98.0)	98.0 (97.0–98.0)	98.0 (98.0–98.0)
48 weeks	98.0 (97.0–98.0)	98.0 (97.0–98.0)	98.0 (97.0–98.0)	98.0 (97.0–98.0)

Table 2. Antibody results during the study. BL, baseline; W12, week 12; W24, week 24; W48, week 48.

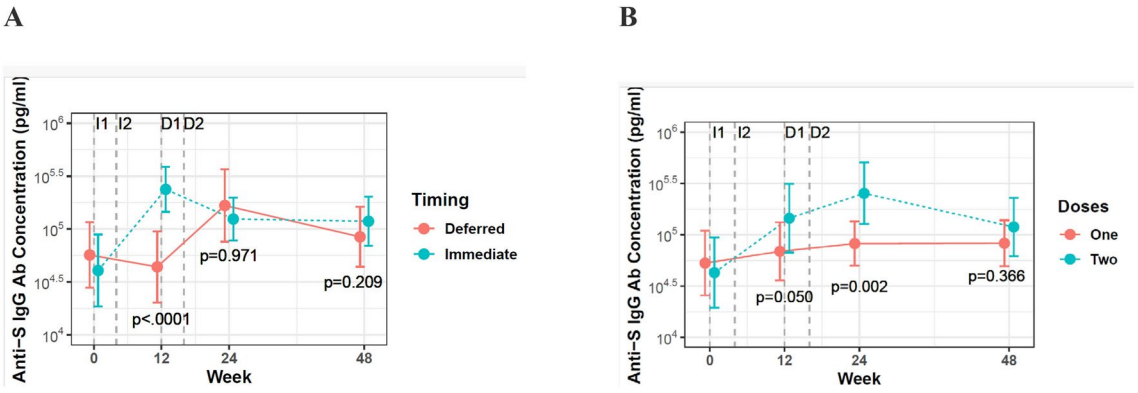

Fig. 3. Anti-S IgG antibody levels in plasma during the study (means and 95% confidence intervals). (**A**) Immediate (blue) vs. deferred (red) vaccination. (**B**) One-dose (red) vs. two-dose (blue). The vertical grey dashed lines indicate the timing of vaccine administration for each group.

dose was missed in 1 (3%) participant allocated to immediate vaccination, compared to 6 (19%) participants allocated to deferred vaccination. The second vaccination was missed in 1 (6%) participant allocated to the I2 group, compared with 5 (31%) participants allocated to the D2 group. Rates of adherence to the assigned vaccine regimen were especially low among participants allocated to D2 group, with 8 (50%) participants being non-adherent to the deferred two dose regimen.

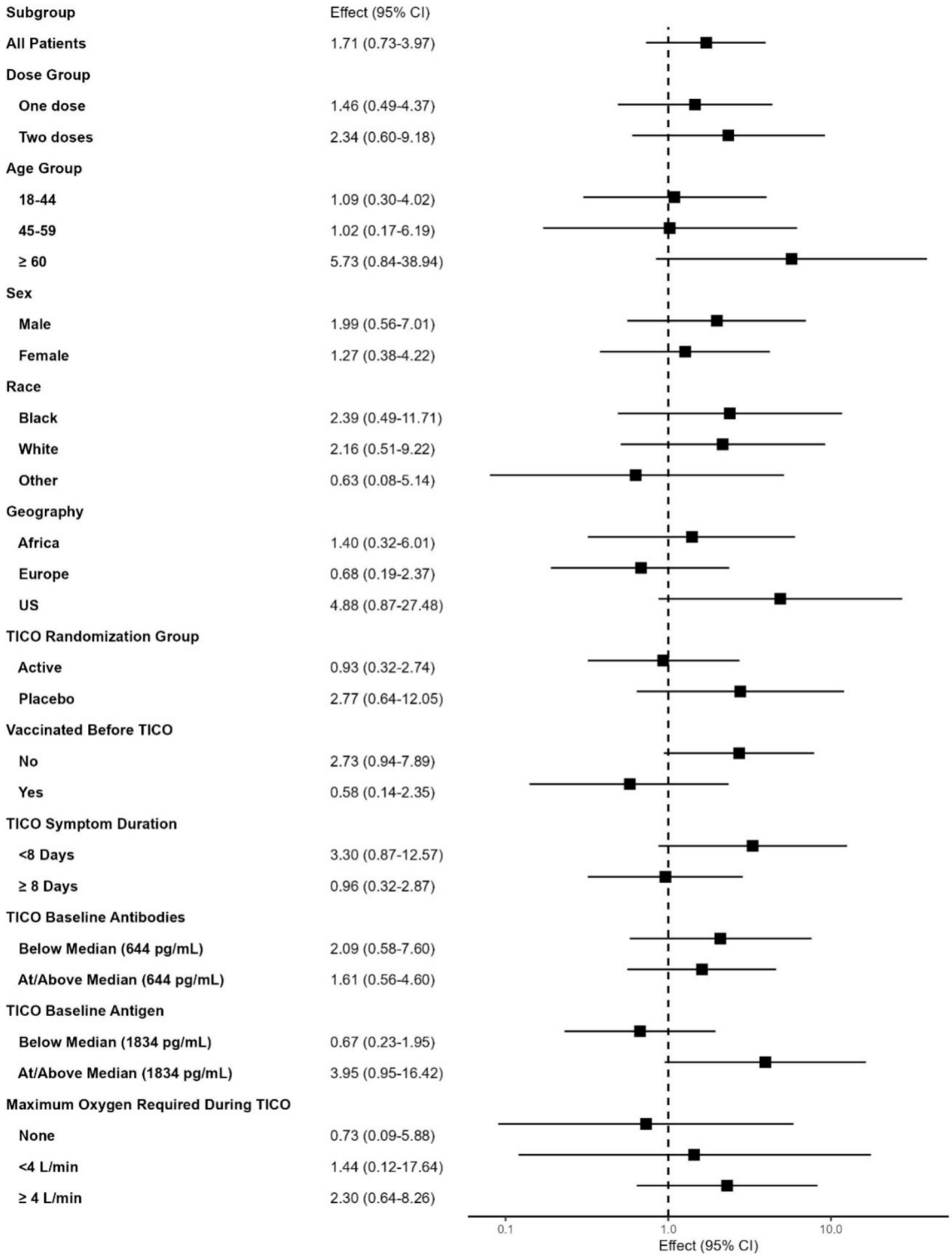

Fig. 4. Effect and 95% confidence interval for vaccination timing on anti-S IgG Ab levels at week 48 reported overall and by subgroup as a geometric mean ratio (GMR) comparing immediate versus deferred vaccination. An effect > 1 indicates a higher 48-week antibody level with immediate vaccination. Effect estimates reflect adjustments for anti-S IgG Ab levels at baseline and the other factorial randomization, i.e. one-dose versus two-dose vaccination. TICO randomization group ACTIVE: NMAb (Tixagevimab/Cilgavimab or Enzovibep). TICO symptom duration: days from COVID symptoms onset to TICO enrollment.

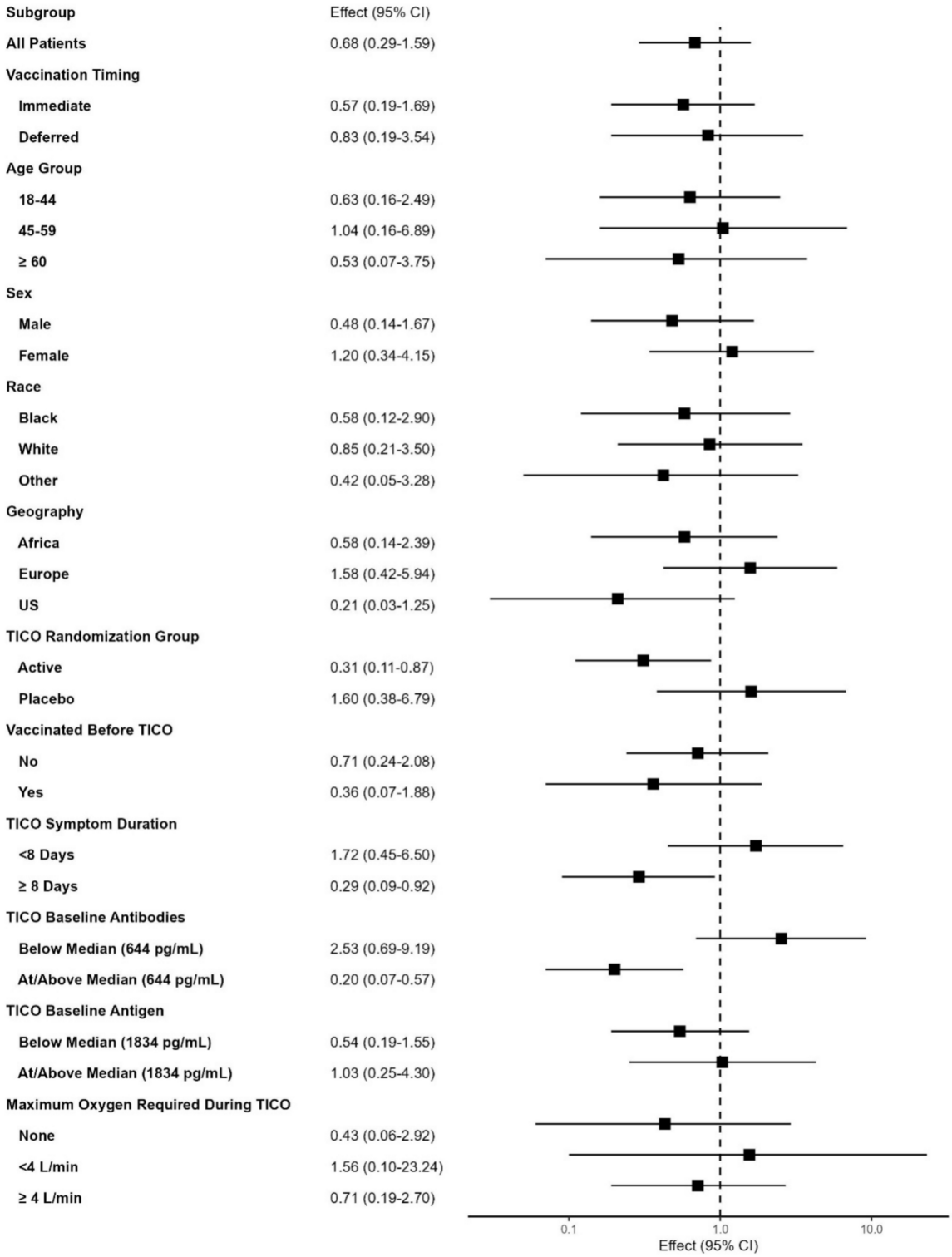

Fig. 5. Effect and 95% confidence interval for number of vaccination doses on anti-S IgG Ab levels at week 48 reported overall and by subgroup as a geometric mean ratio (GMR) comparing one versus two doses. An effect > 1 indicates higher 48-week antibody level with one dose than with two doses. Effect estimates reflect adjustments for anti-S IgG Ab levels at baseline and the other factorial randomization, i.e. immediate versus deferred vaccination. TICO randomization group ACTIVE: NMAb (Tixagevimab/Cilgavimab or Enzovibep). TICO symptom duration: days from COVID symptoms onset to TICO enrollment.

	Immediate	Deferred	Total
One dose	15 (94%)	11 (69%)	26 (81%)
Two doses	15 (83%)	8 (50%)	23 (68%)
Total	30 (88%)	19 (59%)	

Table 3. Adherence to the assigned vaccination regimen in participants allocated to the immediate versus the deferred vaccination group or to the one-dose versus the two-dose vaccination group. Results are expressed as n (%).

A sensitivity analysis restricted to participants who were adherent to their assigned vaccination regimen did not result in statistically significant evidence that the timing of vaccination or the number of doses had an effect on the change in antibody concentration relative to baseline at 48 weeks (immediate versus deferred vaccination GMR 1.16, 95% CI 0.49 to 2.74, $p = 0.73$; one versus two doses GMR 0.73, 95% CI 0.31 to 1.73, $p = 0.46$).

Discussion

Our study was unable to clearly determine whether, following recovery from severe COVID-19, the humoral response to mRNA SARS-CoV-2 vaccines can be influenced by the timing of vaccination or the number of doses administered. Despite being designed with sufficient statistical power to meet its planned objectives, the study did not enroll the original sample size, and was closed after only 66 participants recruited. This early closure was primarily due to the termination of enrollment in the TICO protocol, the source of VATICO participants. The multinational scope of the trial was a notable strength, offering a diverse representation across different region. However, it also introduced the logistical challenge in accesing to mRNA vaccines at non-US sites where they were less available. In addition, rising vaccine skepticism in the US further complicated recruitment efforts[20]. The small sample size, combined with disbalances at baseline, evolving variants and changing population immunity, makes it difficult to draw definitive conclusions. Thus, our findings should be validated in larger, more diverse cohorts in future studies.

In most early clinical trials designed to assess the efficacy and safety of COVID-19 vaccines, prior history of symptomatic and/or confirmed SARS-CoV-2 infection was an exclusion criterion. Consequently, there is limited information on immunogenicity of COVID-19 vaccines following SARS-CoV-2 infection, and it comes mostly from observational studies[2,3,21]. Similarly, data on the immune response to COVID-19 vaccines after the administration of NMAb against SARS-CoV-2 are limited.

The concern about the optimal timing of vaccination and number of doses after COVID-19 recovery has been examined in several observational studies. The majority of these studies compared immunogenicity induced after one dose of vaccine in individuals with prior SARS-CoV-2 infection (hybrid immunity) versus a two-dose regimen in individuals without previous infection (vaccinal immunity)[9,21]. Here we observed that vaccination within 2 months or within 5 months after severe COVID-19 presented comparable and persistent anti-S levels, without differences between administration of one or two vaccine doses. Our results show an increase in the anti-S Ab levels soon after each vaccine dose was administered, regardless of baseline anti-S IgG levels, but waning over time, and reaching similar levels at week 48 among all the study groups. These findings are in agreement with results from prior observational studies showing that people with prior SARS-CoV-2 infection who were vaccinated with BNT162b2 (Pfizer–BioNTech) mRNA developed similar antibody responses after a single vaccine dose compared to SARS-CoV-2 infection-naive individuals after two-dose vaccination course[6,9,21]. Therefore, although prior SARS-CoV-2 infection may enhance immune responses after one vaccine dose, the impact on long-term immunity appears to be slight[6,22]. Another cohort study suggested that longer intervals between natural infection and vaccination could enhance neutralizing antibodies levels and postulated that the immune system matures over time following exposure[12]. Despìte several limitations discussed below, the present study does not support this hypothesis, as we did not observe a significant effect of the interval between infection and vaccination in anti-S Ab levels when comparing the immediate and deferred vaccination groups.

In addition to timing of vaccination and number of doses, little is known about how prior administration of NMAb can influence the immune response to COVID-19 vaccines. It was suggested that pre-existing high–affinity antibodies, such as NMAb used to treat COVID-19, could hinder immune responses leading to vaccine failure[14], but this hypothesis was not confirmed by other authors[15]. In our study, we observed comparable immune responses between individuals who had recently received Tixagevimab/cilgavimab and Ensovibep or placebo in the TICO trial. However, our study is limited in detecting modest differences due to the small number of participants in the study.

Pre-existing natural immunity from recent SARS-Cov-2 infection was hypothesized to increase frequency and severity of adverse reactions related to COVID-19 vaccines, supporting deferral of vaccination in people recovering from COVID-19. However, Ciccimarra et al. reported a lack of influence of the time between COVID-19 disease and subsequent vaccination and the development of major adverse events related to the vaccine[23]. In our study, only two serious adverse events (SAEs) were reported. One of these was a new severe COVID-19 in the deferred group while awaiting to receive the first vaccine, raising the question of whether this could be considered a related adverse event due to the delay in vaccination. However, the study lacks the statistical power to effectively evaluate whether the timing or number of doses affects safety.

Importantly, our results show that deferring vaccination after COVID-19 was associated with lower adherence to the vaccine regimen, resulting in higher probability of missing vaccine doses when compared with the early vaccination strategy. Notably, the only serious recurrent COVID-19 requiring hospital admission happened in a

participant allocated to the deferred group, while was awaiting the start of the assigned vaccine regimen. Better adherence to vaccination regimen among participants allocated to early vaccination may be influenced by positive attitudes towards COVID-19 vaccine immediately after being discharged for COVID-19 hospitalization[24]. This point, together with the absence of any influence of vaccination timing on immunogenicity or vaccine safety profiles, supports a recommendation to vaccinate all individuals as soon as possible after recovery from a COVID-19. Although early vaccination may offer advantages in terms of adherence and protection against severe disease, the limited number of reinfections in our study prevented a meaningful statistical analysis of the relationship between antibody titers and reinfection. Nevertheless, the association between antibody titers and protection against COVID-19 has been well documented in the literature, demonstrating a correlation between higher antibody levels and reduced risk of infection or severe disease[25,26]. Early vaccination can help prevent recurrent infections, optimize patient retention, and reduce missed opportunities for vaccination. The Centers for Disease Control and Prevention (CDC) currently suggests considering delaying a COVID-19 vaccine dose by 3 months from symptom onset or a positive test in people with SARS-CoV-2 infection, based on improved immune response to vaccination and a low risk of reinfection in the months following infection[27]. However, they also emphasize that individual factors, such as the risk of severe COVID-19, should be taken into account when determining whether to delay vaccination after infection. In our study, which included a population of hospitalized patients with severe COVID-19, immediate or deferred vaccination after recovery resulted in similar humoral responses. This finding, together with lower adherence observed in the deferred group and the case of recurrent severe COVID-19 suggest that early vaccination should be prioritized after recovery.

The main limitation of this study was its reduced sample size, which precludes drawing firm conslusions from our results. With the number of participants included, we had enough statistical power to detect fourfold differences in anti-S Ab levels between study arms, but not smaller ones. Additionally, as we did not have sufficient statistical power to conduct meaningful comparisons between all four study groups individually, we opted to report the marginal results (i.e., immediate vs. deferred and one dose vs. two doses) aiming to provide a more robust analysis within the context of our study's power. Beside the limited sample size of VATICO, the high rates of non-adherence to the assigned vaccine regimen could be considered a potential limitation. However, supplementary analyses that included only participants who adhered to their assigned vaccine regimen yielded similar results. Moreover, the lack of adherence in the deferred group may reflect real-world vaccination patterns, underscoring the study's relevance. Finally, it is important to keep in mind that most data generated in this study primarily pertain to Pfizer BNT162b2 vaccine, and we do not have sufficient data to draw meaningful conclusions regarding the Moderna mRNA-1273 vaccine.

It is not clear whether we can extrapolate our findings to the current population, characterized by a high prevalence of vaccination, booster doses and exposure to SARS-CoV-2 variants of concern beyond the original Wuhan variant. Our results were obtained using the original mRNA vaccines, which were not adapted to the circulating variants during the study period, primarily the Delta variant of concern, as indicated by GISAID (www.gisaid.org). It is important to note that protection against infection is influenced not only by the vaccine-induced immune response but also by the specific variants of SARS-CoV-2[28]. These variants are evolving rapidly, potentially exceeding the development of adapted vaccines. However, emerging data suggest that adapted vaccines may confer a slight benefit against certain variants[9].

Conclusion

In conclusion, our study was limited in recruitment but contributes to the evolving understanding of COVID-19 vaccination strategies after severe SARS-CoV-2 infection.

While long-term humoral immune response might be independent of the timing or number of vaccine doses after recovery from COVID-19, early vaccination had better vaccine regimen adherence and may thus be beneficial for maximizing immunization coverage and preventing reinfections.

Methods

Study design and population

Vaccination Strategies for Recovered Hospitalized Patients with COVID-19 (VATICO) was a phase 4, open-label, randomized clinical trial to compare humoral responses to mRNA COVID-19 vaccines in hospitalized COVID-19 recovered individuals participating in the TICO/ACTIV-3 clinical trial. Participants were recruited from August 2021 to January 2022, and were allocated to receive immediate versus deferred vaccination, with one versus two doses of vaccines. TICO (Therapeutics for Inpatients with COVID-19) was a platform for conducting randomized, blinded, placebo-controlled trials to evaluate the safety and efficacy of multiple investigational agents aimed at modifying the host immune response to SARS-CoV-2 infection, or at enhancing viral control to limit disease progression, including the use of NMAb directed against SARS-CoV-2[19,29].

To be included in VATICO participants had to have received TICO agent/placebo within 28 and 90 days prior and had to experience sustained recovery (i.e. participant had returned to their premorbid living facility, or a facility with an equivalent level of care) for at least 2 consecutive weeks before screening (Fig. 1A). COVID-vaccination prior inclusion in TICO was allowed, but not after TICO inclusion.

After inclusion into VATICO, participants were randomized to one of the four study arms reflecting a 2×2 factorial for the timing and number of doses of mRNA SARS-CoV-2 vaccines (Fig. 1B). The four study arms were as follows: Group I1: one dose administered immediately after randomization; Group I2: two doses with the first administered immediately after randomization and the second 4 weeks later; Group D1: one dose administered 12 weeks after randomization; Group D2: two doses administered 12 and 16 weeks after randomization. COVID-19 vaccines used in the study were Moderna mRNA-1273 (100 μg as intramuscular injection) or Pfizer

BNT162b2 (30 µg as intramuscular injection). Vaccine administration was facilitated either directly through the study or via local pharmacy or established public vaccination programs.

Besides vaccination visits, follow-up visits were performed at weeks 0, 12, 24 and 48 after enrollment (Fig. 1B). At each visit, blood samples were obtained, and serum and plasma samples were stored at -70ºC at a central repository until analysis.

The primary objective of the study was to test the difference in response to mRNA vaccines in the form of plasma anti-S Ab levels from baseline to week 48 among participants vaccinated early versus deferred and with one versus two doses.

Secondary objectives included: (1) To estimate the percentage of participants with > fourfold differences in anti-S Ab levels from baseline to week 48; (2) To explore whether host characteristics (i.e., age, race, geographical location of care, ethnicity, history of immunosuppression, body mass index (BMI), co-morbidities, co-medication), the course of prior COVID-19 (i.e. severity and duration of infection until recovery, use of immunosuppressive agents, etc.), type of vaccine (Moderna or Pfizer), interval between enrollment in TICO and this protocol, prior allocation to an active versus placebo arm in TICO, and baseline immune status may affect humoral responses to SARS-CoV-2 vaccination; (3) To explore whether the timing of vaccination (immediate versus deferred), and the number of doses affects the safety and tolerability of mRNA vaccines; (4) To evaluate the reasons for non-adherence to the assigned vaccination schedule.

Laboratory assessments

Levels of plasma anti-S Ab, anti-N Ab, and anti-S Ab neutralizing activity were determined centrally, blinded to treatment group. Titers of anti-S Ab were determined by the Simoa^{tm} SARS-CoV-2 Spike IgG Advantage Kit (Quanterix^{tm}), with a lower limit of detection of 0.015 ng/ml (https://www.quanterix.com/simoa-assay-kits/sars-cov-2-spike-igg/).

The titers of anti-N Ab was determined using the BioRad Platelia SARS-CoV-2 Total Ab assay (BioRad). The assay results were reported as signal-to-cutoff ratio (S/C ratio), defined as the specimen optical density divided by that of the control. An S/C ratio above 1 was considered positive.

The titers of anti-S Ab neutralizing activity was evaluated using the GenScript SARS-CoV-2 cPass Surrogate Virus Neutralization assay (GenScript). Titers were expressed as percentage of viral inhibition, and a positive result was defined as 30% viral inhibition or more.

Adherence to the assigned vaccination regimen

Participants were considered adherent to their assigned vaccination schedule when they received the number of doses assigned to their study group, and vaccines were administered within a 2-week window of the scheduled visit, as pre-specified in the study protocol.

Ethics statement

Before inclusion, all participants signed an informed consent that had been approved centrally, by the Advarra Institutional Review Board (IRB) on June 15, 2021 (Advarra, Columbia, MD, USA), as well as by each participating site´s local IRB and the Ethics Committee. The study was conducted in accordance with the principles of the Helsinki Declaration and local personal data protection law (LOPD 15/1999). It was submitted on 16/07/2021 and registered on 20/07/2021 (first posted date), at the Clinical Trials Register (study code: INSIGHT – 016. VATICO; NCT04969250, 20/07/2021; EudraCT number: 2021-003386-35).

Statistical analysis

Baseline clinical characteristics were expressed using summary statistics, including means and standard deviations (SD) or medians and interquartile range (IQR) for the continuous variables, and counts and percentages for the categorical variables.

Levels of anti-S Ab at baseline, and at weeks 12, 24, and 48 in each study group were summarized using means and 95% confidence intervals and displayed as a line graph.

Analysis of the primary efficacy endpoint was performed as intention to treat, including all randomized participants in their assigned arm. Additionally, a per-protocol analysis only including participants who adhered to their assigned vaccination regimen was performed.

For the comparison of anti-S Ab levels at week 48, titers were log10 transformed and evaluated with analysis of covariance (ANCOVA) that included indicators for assigned timing (immediate versus deferred) and number of doses (one versus two) as well as an adjustment for the anti-S Ab levels prior to randomization into VATICO. ANCOVA coefficients were anti-logged to provide estimates and confidence intervals for the geometric mean ratio (GMR) of anti-S Ab levels at week 48 comparing immediate versus deferred and one versus two vaccination strategies. A GMR of one indicates there is no difference between the two groups being compared. An interaction test was also carried out between the timing and number of doses factors to evaluate whether one factor modifies the other's effect.

The percentage of participants with a > fourfold increase in anti-S Ab levels from baseline to week 48 was compared between study groups using Cochrane Mantel–Haenszel tests.

The planned sample size was 640 participants, which was chosen to provide 80% power to detect a GMR of 1.5 in antibody levels at 48 weeks between the dose groups and between the timing groups among persons assigned to a placebo in TICO. However, on 21 February 2022 enrollment to VATICO closed with 66 participants of which 35 had received an investigational agent in TICO and 31 had received a placebo. This closure followed the end of enrollment to the TICO master protocol on 27 December 2021. The end of enrollment in TICO, which was the source of participants for VATICO, coupled with low enrollment in the US and an inability to obtain the Moderna mRNA-1273 or Pfizer BNT162b2 vaccine to provide to sites outside of the US had hampered

enrollment into VATICO. However, the sample size for the VATICO trial of 66 participants still provided 94% power to detect a GMR of 4.0 in antibody levels at 48 weeks between the dose groups (i.e., one versus two doses) and between the timing groups (i.e., immediate versus deferred).

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

Data is provided within this manuscript. Additional de-identified data will be freely available for download via https://public-data.ccbr.umn.edu/. Additional data from this study are available from the corresponding authors upon request.

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S.S. drafted the manuscript as writing group lead. S.B., clinical trial execution, drafted the manuscript as writing group lead. A.J.R, clinical trial execution and writing group lead. T.A.M. and M.S., statistical analysis and prepare figures. B.M., R.P., A.M., F.K., D.K., M.K.J., J.L., M.G.N., N.S., E.M., D.L.B., T.H., I.K., C.K., H.M., J.K., K.K., P.C.T, clinical trial execution and revised the manuscript. J.H., A.L.M, laboratory analysis. A.S., D.D.M., protocol writing team, clinical trial execution and revised the manuscript. A.G.B., previous London INSIGHT ICC (International Coordinating Center) Lead, V.J.D., VA INSIGHT ICC Lead, D.C.F., PETAL lead, A.C.G, CTSN ICC lead, E.S.H, NIH DCR ICC lead, V.L.K., Washington INSIGHT ICC lead, G.V.M., SYD ICC lead, S.L.P, current London ICC lead, H.C.L, NIAID lead, C.R., SDMC lead, A.G., revised the manuscript, J.D.L., VATICO PI, INSIGHT Copenhagen ICC lead, protocol team and writing group. J.M., writing group lead, clinical trial execution. S.S. and S.B. contributed equally to this work and shared first authorship. J.D.L. and J.M. contributed equally to this work and share last authorship. All authors read and approved the final manuscript.

Declarations

Competing interests

B.M., reports consultancy, advisory and/or speaker fees from AELIX Therapeutics, Gilead Sciences, AbbVie, Janssen, ViiV and MSD. R.P., has served on advisory boards for Gilead Sciences Inc., Pfizer Inc., Roche Therapeutics, MSD, GSK, ViiV Healthcare, Eli Lilly and Company, Astra Zeneca, Exevir, PharmaMar and Atea Pharmaceuticals Inc. He has had research grants paid to his institution by MSD, ViiV Healthcare, Gilead Sciences, and PharmaMar. M.K.J., has received research funding directed to her institution from Gilead Sciences, AbbVie, and Laurent. D.L.B., received money for advisory boards, lectures and travel grants paid to himself from the companies Gilead, MSD, ViiV and Pfizer. K.K., has received research funding from NIH, Astra Zeneca, Pfizer, Abbott, Romark, MSD, and Novartis and has served on advisory boards for the Burroughs Wellcome Fund, ParaFRAP, and the Sanford Guide. P.C.T., has received a grant support from Merck which was paid to her institution. G.V.M., have served on advisory board for Astra Zeneca. A.G., is named as an inventor on a patent covering a promoter construct used in ChAdOx1-vectored vaccines, including ChAdOx1 nCoV-19 vaccine, and has received royalty income through the University of Oxford's from sales of Astra Zeneca vaccines and its sublicensees under the University's revenue sharing policy whith potential benefits in the future. AG has also collaborated with Moderna and Novavax through her organization on commercial vaccine projects, which provided funding directly to the trials and the organization but not to her personally. J.M., has received research funding, consultancy fees and lecture sponsorships from and have served on advisory boards for MSD, Gilead Sciences, ViiV Healthcare, and Johnson & Johnson. The other authors declare non-financial competing interests.

Additional information

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Clinical Sites by Country

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