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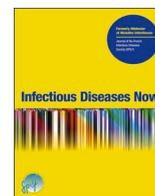
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Original article



Incidence of COVID-19 mRNA vaccine symptomatic breakthrough infections during Omicron circulation in adults with or without infection prior to vaccination[☆]

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ABSTRACT

Objectives: COVID-19 vaccine breakthrough infections were frequently reported during circulation of the Omicron variant. The ANRS|MIE CoviCompareP study investigated these infections in adults vaccinated and boosted with BNT162b2 [Pfizer-BioNTech] and with/without SARS-CoV-2 infection before vaccination.

Methods: In the first half of 2021, healthy adults (aged 18–45, 65–74 and 75 or older) received either one dose of BNT162b2 (n = 120) if they had a documented history of SARS-CoV-2 infection at least five months previously, or two doses (n = 147) if they had no history confirmed by negative serological tests. A first booster dose was administered at least 6 months after the primary vaccination, and a second booster dose, if any, was reported in the database. Neutralizing antibodies (NAbs) against the European (D614G) strain and the Omicron BA.1 variant were assessed up to 28 days after the first booster dose. A case-control analysis was performed for the 252 participants who were followed up in 2022, during the Omicron waves.

[☆] These data were partially presented at the 33rd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) 15–18 April 2023.

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Results: From January to October 2022, 78/252 (31%) had a documented symptomatic breakthrough infection after full vaccination: 21/117 (18%) in those who had been infected before vaccination vs. 57/135 (42%) in those who had not. In a multivariate logistic regression model, factors associated with a lower risk of breakthrough infection were older age, a higher number of booster doses, and higher levels of Omicron BA.1 NAb titers in adults with infection before vaccination, but not in those without prior infection.

Conclusion: Our results highlight the need to consider immune markers of protection in association with infection and vaccination history.

1. Introduction

The evolution of SARS-CoV-2 has led to the emergence of several variants with modified transmissibility and immune-evasive properties. While immunity due to SARS-CoV-2 infection or vaccination has generally provided protection against the severe outcomes of COVID-19 caused by the different variants [1–3], it has had limited impact on infection by the recently emerged and highly immune-evasive Omicron variants [4,5]. Breakthrough infections in fully vaccinated individuals have raised questions about the determinants of vaccine failure and the underlying immunological mechanisms [6–9].

In France, circulation of Omicron variants was detected from December 2021 onward and rapidly increased despite screening, contact tracing efforts and intensification of the booster vaccination campaign. The objective of our study was to investigate the vaccine breakthrough infections that occurred after vaccination among participants in the ANRS|MIE CoviCompareP comparative trial assessing the immunogenicity and safety of the BNT162b2 [Pfizer|BioNTech] vaccine in younger versus older adults [10,11]. The study was performed from January to October 2022, a period characterized by predominant circulation of the BA.1 and BA.2 sublineages of the Omicron variant, although the Delta variant was still present, albeit to a lesser extent, in early 2022.

Differences in immunological markers of protection [12,13], namely, the levels of neutralizing antibodies against the ancestral strain and the Omicron BA.1 variant, between vaccinated individuals infected during dominant circulation of Omicron and uninfected controls were assessed. Overall, the role of SARS-CoV-2 infection in 2020 before the first vaccine dose was evaluated [14–17] likely modulated the effect of neutralizing antibodies in subsequent breakthrough infections.

2. Methods

2.1. Participants

Participants were healthy adults or those with a stable medical condition (defined as an illness that had not required a change in

treatment or hospitalization due to worsening of the illness in the three months prior to registration, nor any significant change expected in the foreseeable future) included in the ANRS002S CoviCompareP trial (ClinicalTrials.gov NCT04824638). CoviCompareP is a nationwide open phase II trial aimed at evaluating the immunogenicity and safety of the COVID-19 mRNA BNT162b2 [Pfizer|BioNTech] vaccine in young (18–45 years old) and elderly (65–74, 75 or older) participants, either those not infected prior to vaccination (NPI) confirmed by negative serological tests and who received one dose on Day 1 (D1) and on D29, or those with previous biologically confirmed SARS-CoV-2 infection (positive RT-PCR or antigenic test) dating back to more than 5 months before (PI) and who received only one dose on D1 (Fig. 1). The trial started in March 2021. An additional dose (or booster) of BNT162b2 vaccine was administered to trial participants approximately eight months later (from mid-October 2021). Later, in 2022, a second mRNA booster vaccination according to age and risk group could be administered in accordance with French recommendations and was reported in the trial database.

2.2. Design and event of interest in the ancillary study

To analyze breakthrough infections that occurred in the CoviCompareP study during dominant Omicron circulation, a case-control analysis was performed on vaccinated participants who were not infected in 2021 and were still being monitored in 2022. Breakthrough cases involved participants with symptomatic biologically confirmed SARS-CoV-2 infection (positive RT-PCR or antigen test) between January and October 2022. Controls were participants with no symptomatic infection between January and October 2022. Cases were defined as symptomatic breakthrough infections at least 7 days after booster doses or after primary vaccination. Mild COVID-19 disease was defined by infection with various symptoms, such as fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, loss of taste and smell, asthenia and rhinorrhea. In addition to these symptoms, moderate severity was defined by evidence of lower respiratory tract disease (with oxygen saturation higher than 94 %). Severe disease

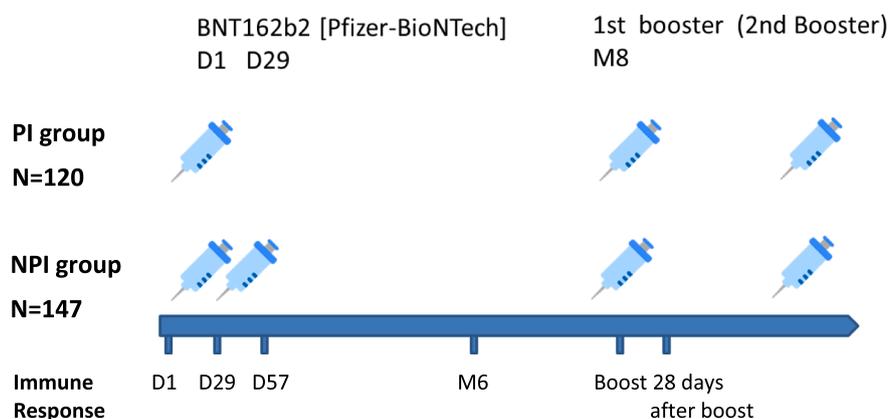


Fig. 1. ANRS002S CoviCompareP Study design. National (France) open phase II trial assessing immunogenicity and safety of COVID-19 mRNA BNT162b2 [Pfizer|BioNTech] vaccine in young (aged 18–45) and elderly (65–74, 75 or older) healthy participants, previously infected (PI) at least 5 months prior to vaccination or not previously infected (NPI). Set-up of mRNA vaccine boosters for different age and risk groups according to the French recommendations.

was defined as more severe lower respiratory tract disease (typically oxygen saturation below 94 %) [18].

2.3. Immunogenicity assessments

Serum samples were tested for neutralizing antibodies (NAbs) against the European B.1 (D614G) SARS-CoV-2 strain and the Omicron BA.1 variant at D1, D29, D57, and M6 after the primo-vaccination (one or two doses, respectively, in participants infected or not before vaccination), the day of the first booster and 28 days after, by the micro-neutralization method as described elsewhere [11,19]. In brief, the test used clinical strains of SARS-CoV-2 (0.5 TCID₅₀/μL of serum dilution) and TMPRSS2-expressing VeroE6 cells. It relied on cytopathic effect (CPE) detection at five days post-infection, and positive sero-neutralization was defined as an NAb titer ≥ 20 .

Pseudo-neutralization for the original Wuhan strain and the Omicron BA.1 variant was likewise tested at D1, D29, D57 and M6. This test [20,21] measured neutralization of lentiviral pseudo-types carrying the SARS-CoV-2 Spike protein and expressing a luciferase reporter after 60–72 h of transduction in 293T-ACE2 cells. Luciferase activity was related to the signal obtained with negative sera. Positive pseudo-neutralization was defined as a pseudo-neutralizing antibody titer (pNAb) ≥ 10 .

Two neutralization assays were carried out to globally confirm the antibody results. Pseudo-neutralization was a less time-consuming assay and did not require a Biosafety Level 3 laboratory. In these data, all antibodies were measured prior to the reported breakthrough infections. If an infection occurred, the antibody measurement schedule for that individual was interrupted.

2.4. Statistical analysis

We first drew the cumulative curve of cases by status of infection prior to vaccination. We investigated differences between cases and controls for pre-vaccination characteristics, vaccine regimens, and SARS-CoV-2 antibody titers (European B.1 (D614G) for NAb and Wuhan for pNAb, Omicron BA.1 variant for both) at different time points following vaccination, separately in participants infected prior to vaccination (PI) or not (NPI). Vaccine regimens (before infection) were categorized as 1) primary vaccination only, *i.e.*, two doses for the NPI group and one dose for the PI group, 2) primary vaccination plus one booster and 3) primary vaccination plus two boosters. Categorical data are presented as frequency counts and percentages, and continuous variables are presented as medians and interquartile ranges (and ranges for some data). Percentages were compared by Fisher's test, and antibody titers were compared by the Wilcoxon test.

Univariate logistic regression models were applied to study the crude association between breakthrough infection and prior infection status, age group (aged 18–45, 65–74, 75 or over), sex at birth, comorbidities at inclusion, vaccine regimens and the most recent NAb titers (log₂ transformed). A multivariate logistic regression model was built to examine the association between breakthrough infection and prior infection status, adjusted for age group, vaccine regimen and the most recent Omicron NAb titer. We tested an interaction term between the NAb titer and a prior infection. The cutoff date for analysis was November 18, 2022. Statistical analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC).

3. Results

3.1. Breakthrough infections

In the CoviCompareP trial, 267 participants were vaccinated in 2021 (N = 147 not previously infected (NPI), N = 120 previously infected (PI)). Ten participants developed biologically confirmed SARS-CoV-2 infections in 2021 (all in the NPI group), four others were lost to

follow-up early in 2021, and one participant died in 2021 (NPI group). Excluding these participants, the analysis included 252 participants still followed in 2022 (117/120 from the PI group and 135/147 from the NPI group).

During the period of predominant Omicron BA.1 circulation between January and October 2022, 78 participants (30.9 %) reported a symptomatic breakthrough infection, which was significantly more frequent in not previously infected than in previously infected participants: 42.2 % (57/135), 95 % confidence interval (CI) = (33.8, 51.0 %) and 17.9 % (21/117), 95 % CI = (11.5, 26.1 %), respectively ($p < 0.0001$) (Fig. 2). By age groups, the symptomatic breakthrough infections in NPI and PI participants were 56.8 % (25/44) and 27.1 % (27/48), 42.3 % (22/52) and 14.3 % (7/49), 25.6 % (10/39) and 5 % (1/20) in those aged 18–45, 65–74, 75 or over respectively, with highly significant differences for the two younger groups (18–45 and 65–74) with $p < 0.01$, but not significant for older patients ($p = 0.12$). Within the NPI group, the distribution of clinical forms was 50 (88 %) mild, 7 (12 %) moderate and 0 severe cases, similar to the PI group, with 17 (81 %) mild, 4 (19 %) moderate and 0 severe cases.

Comparing participant characteristics (Table 1), breakthrough infections were significantly more frequent among younger participants in the NPI group, and the same trend was observed in the PI group. As all but six participants had received at least one booster dose, this difference between age groups was not associated with first booster vaccination. The association with the absence of comorbidities was nearly significant in the NPI group. The proportion of participants with at least one comorbidity increased with age in both groups ($p < 0.0001$): for the NPI group, 11 % of those aged 18–75, 56 % of those aged 65–74 years, 64 % of those aged 75 and over, and for the PI group, 12.5 %, 49 %, and 70 %, respectively (Table 2). In conjunction with the first waves of Omicron, breakthrough infections were mostly reported after the first booster dose, 91 % and 76 % in the NPI and PI groups, respectively, within a median delay of 4–5 months after the last vaccine dose (range: 3–4 weeks to 10 months in both groups). Calendar dates of vaccination (first and last doses) were similar in patients with breakthrough infections and in controls. For the PI group, there was no significant association between severity of the previous infection and occurrence of a breakthrough infection.

Regarding age groups (Table 2), subjects from the two oldest groups received their most recent vaccination a few weeks before the younger

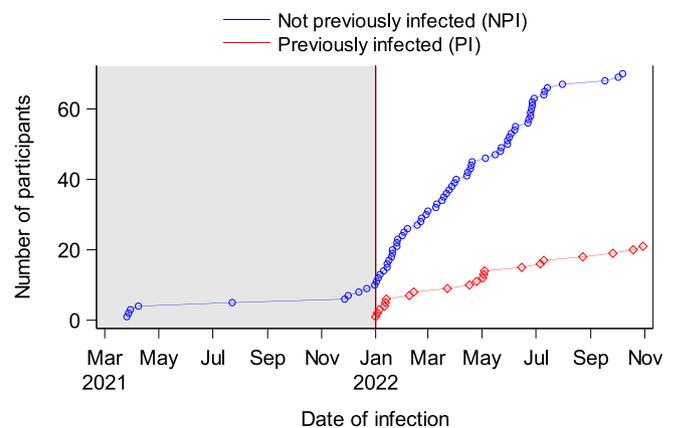


Fig. 2. Cumulative curve of SARS-CoV-2 infections among the two groups of the ANRS002S CoviCompareP trial since March 2021 at the start of vaccinations. The blue curve corresponds to participants without previous SARS-CoV-2 infection (NPI) and the red curve corresponds to participants with previous SARS-CoV-2 infection before vaccination (PI). The date of infection (X-axis) is the date of first symptoms (confirmed by positive test) or the date of positive test. Ten participants infected in 2021 were not included in the ancillary study. From January 2022, the Omicron variants were dominant.

Table 1

Characteristics of the ANRS002S CoviCompareP participants by SARS-CoV-2 infection prior to vaccination status and comparisons between symptomatic breakthrough infection status during Omicron-dominant circulation.

| | Not previously infected (NPI; N = 135) | | | Previously infected (PI; N = 117) | | |
|---|---|-------------------------------|----------------------|--------------------------------------|-------------------------------|----------------------|
| | Breakthrough infection | | P-value ³ | Breakthrough infection | | P-value ³ |
| | No (N = 78) | Yes (N = 57) | | No (N = 96) | Yes (N = 21) | |
| Age group, n (%) | | | 0.017 | | | 0.076 |
| 18–45 years old | 19 (24.4) | 25 (43.9) | | 35 (36.5) | 13 (61.9) | |
| 65–74 years old | 30 (38.5) | 22 (38.6) | | 42 (43.8) | 7 (33.3) | |
| 75 or older | 29 (37.2) | 10 (17.5) | | 19 (19.8) | 1 (4.8) | |
| Sex at birth, n (%) | | | 0.73 | | | 0.47 |
| Male | 40 (51.3) | 27 (47.4) | | 52 (54.2) | 9 (42.9) | |
| Female | 38 (48.7) | 30 (52.6) | | 44 (45.8) | 12 (57.1) | |
| Comorbidities ¹ , n (%) | | | 0.053 | | | 0.21 |
| At least one | 40 (51.3) | 19 (33.3) | | 39 (40.6) | 5 (23.8) | |
| None | 38 (48.7) | 38 (66.7) | | 57 (59.4) | 16 (76.2) | |
| Vaccine regimen ² , n (%) | | | <0.0001 | | | 0.0076 |
| 1 Booster | 53 (67.9) | 52 (91.2) | | 68 (70.8) | 16 (76.2) | |
| 2 Boosters | 25 (32.1) | 3 (5.3) | | 27 (28.1) | 2 (9.5) | |
| Primary vaccination | 0 (0.0) | 2 (3.5) | | 1 (1.0) | 3 (14.3) | |
| First Covid-19 vaccine date | | | | | | |
| Median (IQR) | 24MAR21 (16MAR21, 30MAR21) | 25MAR21 (18MAR21, 31MAR21) | | 13APR21 (29MAR21, 19APR21) | 06APR21 (25MAR21, 20APR21) | |
| Most recent Covid-19 vaccine date | | | | | | |
| Median (IQR) | 07DEC21 (17NOV21, 14JUN22) | 26NOV21 (16NOV21, 16DEC21) | | 20DEC21 (25NOV21, 22JUN22) | 09DEC21 (19NOV21, 16DEC21) | |
| Range | 29OCT21, 14OCT22 | 22APR21, 01JUL22 | | 07APR21, 04NOV22 | 22MAR21, 29JUN22 | |
| Days between infection and most recent dose | | | | | | |
| Median (IQR) | | 126 (70, 172) | | | 146 (65, 219) | |
| Range | | 21, 319 | | | 33, 318 | |
| Previous SARS-CoV-2 infection severity, n (%) | | | | | | 0.32 |
| Asymptomatic | | | | 17 (17.7) | 6 (28.6) | |
| Moderate | | | | 43 (44.8) | 10 (47.6) | |
| Severe | | | | 36 (37.5) | 5 (23.8) | |

From January 2022 to October 2022, the Omicron variants were dominant.

¹ Comorbidities: Arterial hypertension (n = 59), Hypercholesterolemia (39), Cancer (15), Diabetes (15), Coronary artery disease (10), COPD and/or respiratory failure (7), Chronic renal failure (5), Stroke (4), Auto-inflammatory/autoimmune diseases (4), Heart failure (3), Hematological diseases (2), Chronic liver diseases (2).

² Vaccine regimen: Primary vaccination is one mRNA BNT162b2 vaccine dose for previously infected (PI) and two mRNA BNT162b2 doses for not previously infected participants (NPI) at least 14 days before breakthrough infection; one booster or two boosters are primary vaccination plus first or second mRNA booster doses at least seven days before breakthrough infection.

³ Fisher Exact or Wilcoxon p-value; IQR: interquartile range.

participants, but with no statistically significant difference in terms of time to breakthrough infection. Participants aged 75 and over were vaccinated with a second booster dose (25.6 % and 35 % in the NPI and PI groups, respectively) in similar proportions to those aged 65–74 years (34.6 % and 40.8 % in the NPI and PI groups). Notably, no young participant in the NPI group and only two young participants in the PI group had received two booster doses. The vaccination campaign with bivalent vaccines was launched in France on October 14, 2022, and four controls only (one in NPI, three in PI) were probably boosted with a bivalent vaccine.

3.2. Neutralizing antibodies

A graphical summary with boxplots of the neutralization and pseudo-neutralization results showed similar results for the two assays (Fig. 3)

and, more specifically, six months after the first dose (M6), the Spearman correlation coefficient between European B.1 (D614G) neutralizing Ab and Wuhan pseudo-neutralizing Ab titers was 0.74 ($p < 0.0001$). By both techniques, the levels of antibodies to Omicron BA.1 did not increase after primary vaccination in participants with no prior infection. In contrast, in participants infected before vaccination, antibody levels, particularly against Omicron BA.1, increased after primary vaccination. They were lower in those who had a breakthrough infection than in those who did not, with statistically significant differences one and six months after primary vaccination and one month after booster (Fig. 3) based on all time points before the breakthrough. Ages were used to obtain graphs, which showed similar results across different age groups, even though differences between breakthrough infections and non-breakthrough infections were more difficult to assess (Fig. S1).

To study the relationship between neutralizing antibodies and

Table 2

Comorbidities, vaccination regimen and most recent vaccine dose date of ANRS002S CoviCompareP participants by SARS-CoV-2 infection status prior to vaccination and comparisons between age groups.

| | Not previously infected (NPI; N = 135) | | | P-value | Previously infected (PI; N = 117) | | | P-value |
|---|--|----------------------------------|----------------------------------|----------------------|-----------------------------------|----------------------------------|----------------------------------|----------------------|
| | 18–45 years (N = 44) | 65–74 years (N = 52) | 75 or older (N = 39) | | 18–45 years (N = 48) | 65–74 years (N = 49) | 75 or older (N = 20) | |
| Comorbidities, n (%) | | | | <0.0001 ¹ | | | | <0.0001 ¹ |
| At least one | 5 (11.4) | 29 (55.8) | 25 (64.1) | | 6 (12.5) | 24 (49.0) | 14 (70.0) | |
| None | 39 (88.6) | 23 (44.2) | 14 (35.9) | | 42 (87.5) | 25 (51.0) | 6 (30.0) | |
| Vaccine regimen, n (%) | | | | <0.0001 ¹ | | | | <0.0001 ¹ |
| 1 Booster | 42 (95.5) | 34 (65.4) | 29 (74.4) | | 43 (89.6) | 28 (57.1) | 13 (65.0) | |
| 2 Boosters | 0 (0.0) | 18 (34.6) | 10 (25.6) | | 2 (4.2) | 20 (40.8) | 7 (35.0) | |
| Primary vaccination | 2 (4.5) | 0 (0.0) | 0 (0.0) | | 3 (6.3) | 1 (2.0) | 0 (0.0) | |
| Most recent Covid-19 vaccine date | | | | | | | | |
| Median (IQR) | 13DEC21 (20NOV21, 27DEC21) | 22NOV21 (15NOV21, 17JUN22) | 25NOV21 (16NOV21, 22MAR22) | | 21DEC21 (02DEC21, 06JAN22) | 09DEC21 (19NOV21, 07JUL22) | 01DEC21 (16NOV21, 22JUN22) | |
| Range | 22APR21, 12JAN22 | 02NOV21, 14OCT22 | 29OCT21, 04AUG22 | | 22MAR21, 19OCT22 | 07APR21, 01SEP22 | 05NOV21, 04NOV22 | |
| Days between infection and most recent dose | | | | 0.31 ² | | | | 0.88 ² |
| N infected | 25 | 22 | 10 | | 13 | 7 | 1 | |
| Median (IQR) | 102 (62, 166) | 128 (70, 167) | 164.5 (112, 212) | | 122 (60, 255) | 146 (112, 219) | 165 | |
| Range | 29, 257 | 21, 237 | 61, 319 | | 33, 296 | 56, 318 | 165 | |

¹ Chi p-value; ²Kruskal-Wallis p-value; IQR: inter-quartile range.

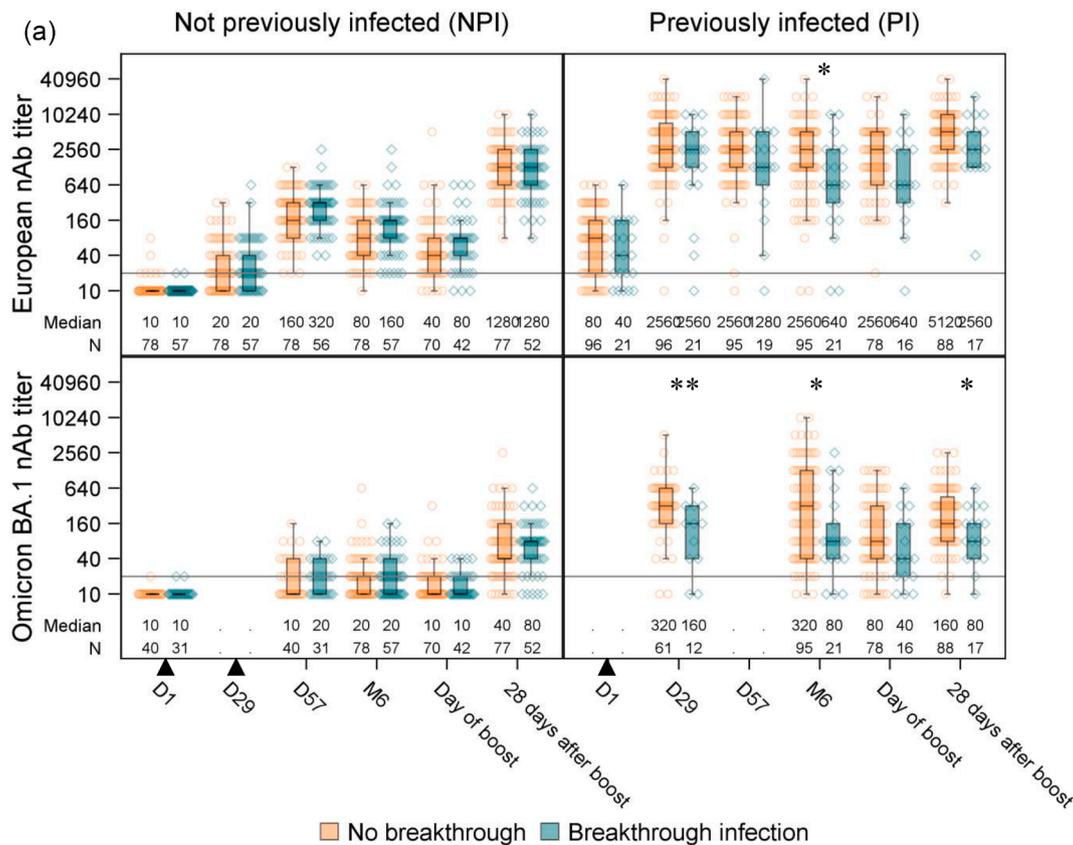


Fig. 3. (a) Neutralizing antibody titers against the European B.1 (D614G) strain and Omicron BA.1 variant. (b) Pseudo-neutralizing antibody titers against Wuhan strain and Omicron BA.1 variant in “not previously infected” (NPI) and “previously infected” (PI). N is the number of participants evaluated at each timepoint and Median is their median titer. ▲ show vaccination timepoints. Grey lines represent positivity thresholds. ** Wilcoxon P < 0.01, * Wilcoxon P < 0.05.

infection, the cumulative percentage of breakthrough infections was plotted according to the most recent level of the European B.1 (D614G) strain (Fig. 4a) or Omicron BA.1 NAB titer (Fig. 4b). The curve between

antibody levels and observed percentages of breakthrough infection was steep in previously infected and less steep in not previously infected participants, especially for the Omicron BA.1 variant. Breakthrough

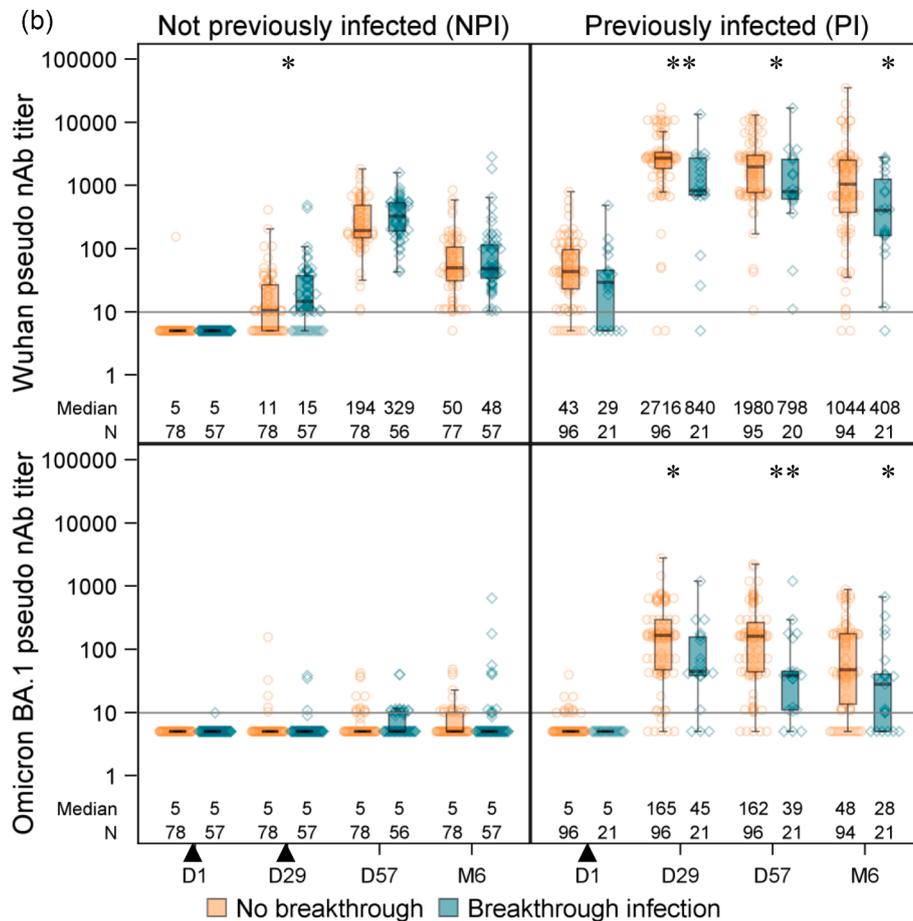


Fig. 3. (continued).

infections were notably less frequent in the PI group than the NPI group when the NAb titers were high. The most recent NAb titers for controls and cases were evaluated at similar visits, generally 28 days after the first booster (all in all 234/252, 93 %) and at similar calendar dates (September 2021 to February 2022). Taken as a whole, antibody levels against the European B.1 (D614G) strain were higher than those against the Omicron BA.1 variant, and among previously infected individuals, they were significantly lower in those with breakthrough infection (Table 3).

Using logistic regressions (Table 4), unadjusted analyses showed that younger age, absence of comorbidities, no infection before vaccination, vaccine regimen, and the most recent NAb titers for both the European B.1 (D614G) and Omicron BA.1 variants were associated with breakthrough infection. As the European B.1 (D614G) and Omicron BA.1 variant titers were correlated (Spearman correlation = 0.64), we chose to enter the Omicron BA.1 titer into the multivariate model. This model also included an interaction between prior infection status and Omicron BA.1 NAb titer. In this model, participants aged 75 or older still had reduced odds of breakthrough infection (OR = 0.37, $p = 0.026$), whereas this was not the case for those aged 65–74 years (OR = 1) compared to those aged 18–45 years (Fig. 5a). Participants who received two boosters had reduced odds of breakthrough infection (OR = 0.17, $p = 0.001$) compared to those who had received one booster. Those who received no booster had increased odds of breakthrough infection (OR = 13.7, $p = 0.047$) compared to those who had received one booster. The interaction term between prior infection and NAb titer was statistically significant ($p = 0.011$): in the previously infected group, higher NAb titers were associated with decreased odds of breakthrough infection (OR = 0.60 per log₂ increase in NAb titer, $p = 0.002$), which was not the case for participants who were not previously infected (OR = 1.03, $p =$

0.83). Predicted probabilities (Fig. 5b) more extensively illustrate the results of this interaction based on the risk of infection: for low antibody levels (Omicron BA.1 NAb titer = 40), the two groups had similar odds of breakthrough infection (NPI vs. PI, OR = 1.84, 95 % CI = (0.80–4.24)), while for higher antibody levels (Omicron BA.1 NAb titer = 160), PI participants were less likely than NPI participants to be infected during Omicron circulation (NPI vs. PI, OR = 9.42, 95 % CI = (3.28–27.1)). Graphically, the model is fully congruent with the data observed in Fig. 4b.

4. Discussion

The aim of this ancillary study of the ANRS002S CoviCompareP trial was to investigate symptomatic breakthrough infections during Omicron variant dominant circulation for participants vaccinated and boosted with the BNT162b2 mRNA vaccine. The cumulative incidence of breakthrough infections was 31 % in January–October 2022, while 98 % of participants had received a booster. Breakthrough infections were mostly of mild severity (86 %) and were more frequent in the group with no infection before vaccination (42 %) than in the group with infection before primary vaccination (18 %). These infections tended to occur in younger participants and those with no comorbidity, and they were less frequent in participants infected before vaccination with a higher previous number of boosters and with higher Omicron neutralizing and pseudo-neutralizing titers. In a multivariate analysis, factors associated with a lower risk of breakthrough infection were older age and a higher number of booster doses, and in participants infected before vaccination only, a higher most recent Omicron BA.1 NAb titer.

Consistent results were observed across all age groups. However, due to the smaller sample sizes resulting from dividing the total population

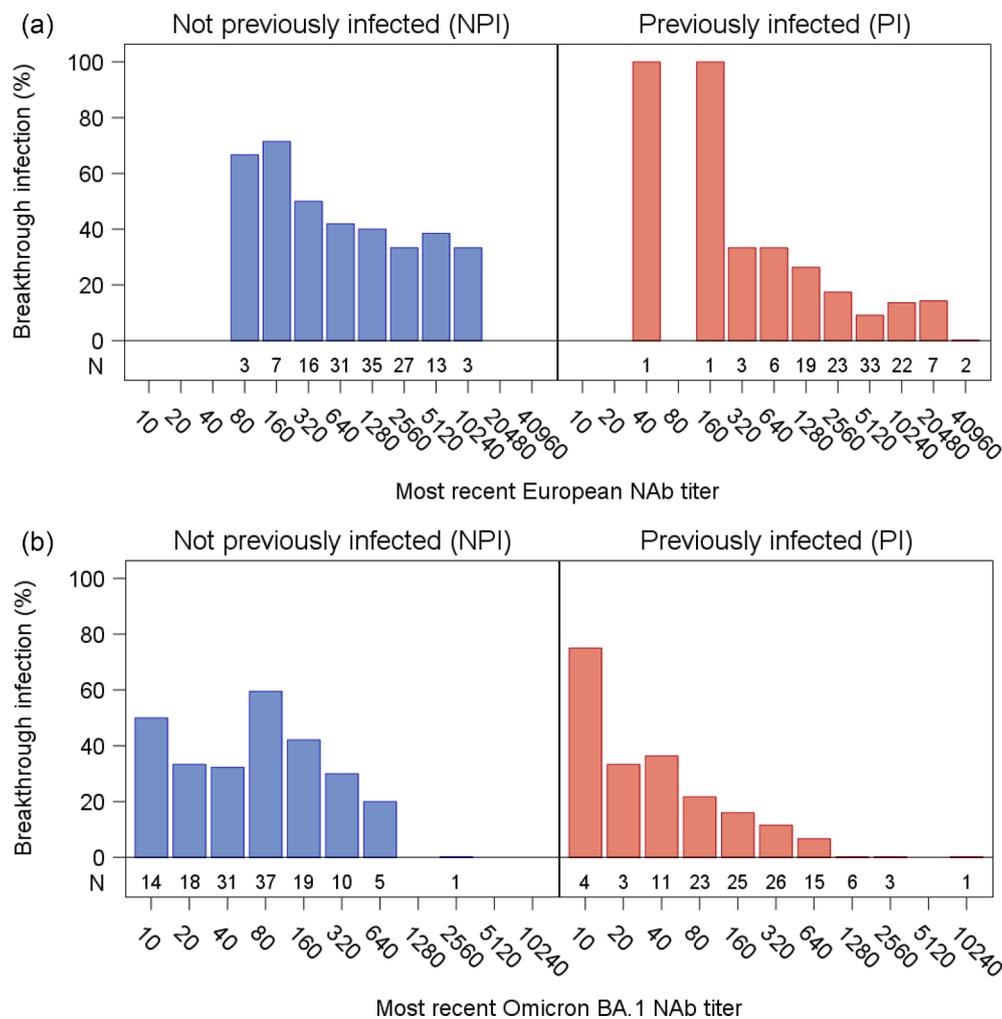


Fig. 4. Observed cumulative percentage of symptomatic infections during Omicron-dominant circulation by the level at most recent assessment of (a) European B.1 (D614G) strain NAb titer (b) Omicron BA.1 NAb titer. For each antibody titer, breakthrough infection (%) is the cumulative number of infections divided by N, the total number of participants shown on the graph. The most recent assessment for NPI group: 1 at M6, 5 at day of boost, 129 at 28 days after boost; for PI group: 10 at M6, 2 at day of boost, 105 at 28 days after boost.

by age, data analysis by age group was not performed in this study. Multivariate logistic regression was utilized to analyze all participants simultaneously and increase statistical power. Interaction between infection before vaccination and neutralizing antibodies could be accounted for and interpretation of the results required consideration of the combined effects of the predictors.

The youngest individuals (aged 18–45 years) were significantly more likely to have symptomatic infections during Omicron-dominant circulation. While this is likely due to intrafamilial and professional interactions identified as predictive factors for infection in the first waves [22,23], our study did not explore these exposures. Older participants (aged 75 or over) experienced significantly fewer symptomatic infections, although this difference was not related to the first booster in this population. Health recommendations regarding medical and nonmedical intervention measures have always been stronger for them, and older people may have taken individual preventive measures to limit their risk of infection. The trend toward fewer participants with comorbidities in the cases examined was probably related to age. A second mRNA booster vaccine was associated with less frequent breakthrough infections, even after adjustment for age, prior infection status and NAb titer. This is in line with publications in which a second booster partially protected against infection and, notably, severe infection, particularly in older individuals [24–28]. Participants were also less likely to receive a second booster if they were infected in 2022.

Neutralizing antibody titers have been found to be correlates of protection after two doses of the BNT162b2 [Pfizer|BioNTech] vaccine [12,13]. Our study focused on immune responses to the first booster, rather than to the primary vaccination with BNT162b2, which has more frequently been studied as a correlate of protection (CoP). To our knowledge, no large-scale studies have been published on booster doses of this vaccine. In some publications with limited data [29,30], none of the usual immune parameters, including NAb titers against the Omicron variant, predicted individual risk of infection. In line with these results, we found that the most recent Omicron BA.1 NAb titer was not associated with breakthrough infection in the group of participants not infected before vaccination, and that Omicron infection mainly occurs after the first booster dose for heterogeneous NABs. Neutralization and pseudo-neutralization techniques for anti-SARS-CoV-2 antibodies had similar results and correlated well in our study. Pseudo-neutralization is easier to develop and adapt to new variants without requiring new virus strains in the laboratory. Its safety also makes it easier to implement in hospital laboratories.

Recently, several studies and meta-analyses have shown that hybrid immunity (infection plus vaccination) provides the strongest protection against SARS-CoV-2 infection [14–16], especially against Omicron variant infection [17]. Primary infection reduces the risk of symptomatic reinfection and severe disease [31], although no differences in clinical presentation have been shown between primary infection and

Table 3

Description of most recent neutralizing antibody titers and comparisons between symptomatic breakthrough infection status during Omicron-dominant circulation in ANRS002S CoviCompareP participants.

| | Not previously infected (NPI; N = 135) | | P- value ² | Previously infected (PI; N = 117) | | P-value ² |
|---|---|----------------------------|----------------------------|--------------------------------------|-------------------|----------------------|
| | Breakthrough infection | | | Breakthrough infection | | |
| | No (N = 78) | Yes (N = 57) | | No (N = 96) | Yes (N = 21) | |
| Most recent NAb ¹ Visit, n (%) | | | | | | |
| 6 months after first vaccine dose (M6) | 1 (1.3) | 4 (7.0) | 8 (8.3) | 2 (9.5) | | |
| Day of boost | 0 (0.0) | 1 (1.8) | 0 (0.0) | 2 (9.5) | | |
| 28 days after boost | 77 (98.7) | 52 (91.2) | 88 (91.7) | 17 (81.0) | | |
| Date | | | | | | |
| Median (IQR) | 16DEC21 (13DEC21, 03JAN22) | 17DEC21 (13DEC21, 10JAN22) | 25DEC21 (14DEC21, 15JAN22) | 07JAN22 (17DEC21, 13JAN22) | | |
| Range | 14SEP21, 11FEB22 | 09SEP21, 08FEB22 | 27SEP21, 11FEB22 | 27SEP21, 08FEB22 | | |
| European B.1 (D614G) NAb titer | | | 0.089 | | | 0.018 |
| Median (IQR) | 1280 (640, 2560) | 1280 (320, 2560) | | 5120 (2560, 10240) | 2560 (1280, 5120) | |
| Omicron BA.1 NAb titer | | | 0.95 | | | <0.0001 |
| Median (IQR) | 40 (40, 160) | 80 (40, 80) | | 160 (80, 480) | 80 (40, 160) | |

¹ NAb: neutralizing antibody titer; ²Wilcoxon p-value; IQR: Interquartile range.

reinfection [32]. In our study, infection before vaccination also reduced the risk of reinfection, while prior disease severity was not associated with symptomatic breakthrough infection. Based on a limited sample size, we confirmed that NAb titers against the ancestral strain and the BA.1 variant were higher in participants with hybrid immunity than in those with vaccine-only immunity [16]. Finally, in participants with hybrid immunity (infection prior to vaccination) and one primary dose plus a booster, Omicron NAb titers correlated with protection against reinfection during Omicron BA.1- dominant circulation. This result warrants further investigation to assess whether other immune responses, such as cellular responses, are associated with reinfection. Our results underline the need to consider immune markers of protection with regard to infection and vaccination history.

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Table 4

Univariate and multivariate logistic regression analyses to predict symptomatic breakthrough infection during Omicron-dominant circulation in ANRS002S CoviCompareP participants.

| Characteristic | N | Breakthrough infection, n (%) | Unadjusted Odds Ratios (95% CI) | Adjusted Odds Ratios (95%CI) |
|--|------------|-------------------------------|---------------------------------|------------------------------|
| Sex at birth | | | | |
| Male | 128 | 36 (28.1) | ref | |
| Female | 124 | 42 (33.9) | 1.31 (0.77–2.24) | |
| Comorbidities | | | | |
| At least one | 103 | 24 (23.3) | ref | |
| None | 149 | 54 (36.2) | 1.87 (1.06–3.29) | |
| Age group | | | | |
| 18–45 years old | 92 | 38 (41.3) | ref | ref |
| 65–74 years old | 101 | 29 (28.7) | 0.57 (0.31–1.04) | 1.00 (0.49–2.03) |
| 75 or older | 59 | 11 (18.6) | 0.33 (0.15–0.71) | 0.37 (0.15–0.89) |
| Vaccine regimen¹ | | | | |
| 1 Booster | 189 | 68 (36.0) | ref | ref |
| 2 Boosters | 57 | 5 (8.8) | 0.17 (0.065–0.45) | 0.17 (0.059–0.49) |
| Primary vaccination | 6 | 5 (83.3) | 8.90 (1.02–77.73) | 13.73 (1.03–182.2) |
| Prior SARS-CoV-2 infection | | | | |
| Previously infected (PI) | 117 | 21 (17.9) | ref | |
| Not previously infected (NPI) | 135 | 57 (42.2) | 3.34 (1.87–5.99) | |
| European B.1 (D614G) NAb² titer (per log₂) | | | | |
| Omicron BA.1 NAb titer (per log ₂) | | | 0.72 (0.61–0.85) | – |
| Interaction between prior infection and Omicron BA.1 NAb titer | | | | |
| NPI vs. PI according to Omicron BA.1 NAb titer | Titer: 40 | | | 1.84 (0.80–4.24) |
| | Titer: 160 | | | 9.42 (3.28–27.1) |
| Omicron BA.1 NAb titer (per log ₂) within group of Prior infection | PI group | | | 0.60 (0.42–0.84) |
| | NPI group | | | 1.03 (0.81–1.30) |

¹ Vaccine regimen: Primary vaccination is one mRNA BNT162b2 vaccine dose for previously infected (PI) and two mRNA BNT162b2 doses for not previously infected participants (NPI) at least 14 days before breakthrough infection; one booster or two boosters are primary vaccination plus first or second mRNA booster doses at least seven days before breakthrough infection

² NAb: neutralizing antibody titer. N: total number of participants in the study; number of participants with breakthrough infection (%: n/N*100). Unadjusted odds ratio (OR) and 95 % Wald confidence interval (CI) by univariate logistic regression analyses. Adjusted OR (95 % CI) by multivariate regression model including age group, vaccine regimen, prior infection status, the most recent Omicron NAb titer and an interaction term between NAb titer and a prior

infection. An OR greater than 1 indicates an increased risk of infection with the presence of the characteristic or an increase in NAb titer.

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Author contributions

OL, ET, JDL, XdL, ML, CDu, LM, LN, SV, YK, CDe conceived and designed the study. ASL, ML, ZMV, JFN, RV, JK, PL, CSM, VC, SA, GM, CDe, MR, EN, RT recruited, monitored the study subjects and managed the study. LN, XdL, SV, MA carried out the laboratory data collection. CDu, RB, CDe, LM, ML, OL, ET, LN, XdL, SV analyzed and interpreted the data. CDu, ML, SV, XdL, ET, CDe, RB, LM, OL wrote and made major revisions to the manuscript. All authors reviewed and approved the final version of the manuscript.

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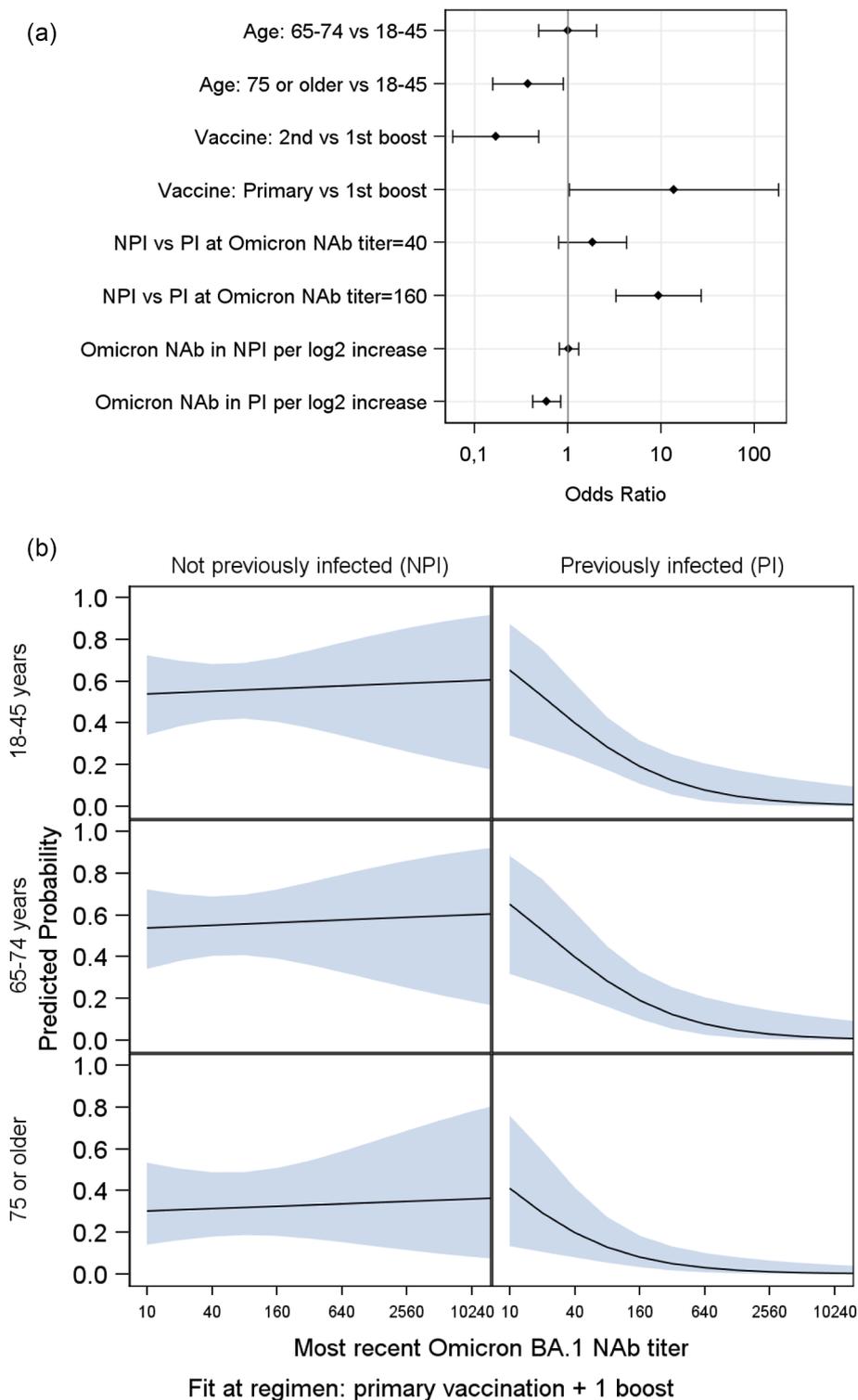


Fig. 5. Predictors of symptomatic breakthrough infection during Omicron-dominant circulation, (a) Odds ratios (with 95 % Wald confidence limits (CL)) in adjusted analysis (b) Predicted probabilities (with 95 % CL) by age group and infection status prior to vaccination according to the most recent Omicron BA.1 NAb titer. Estimates at vaccine regimen of one booster after primary vaccination (two doses for NPI, one dose for PI) and before breakthrough infection.

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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.

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Appendix A. Supplementary data

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