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Original article

SARS-CoV-2 neutralizing antibody response in vaccinated and non-vaccinated hospital healthcare workers with or without history of infection

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ABSTRACT

Between March 2021 and February 2022, SARS-CoV-2 neutralizing antibodies dynamics was investigated in a prospective observational study in 903 healthcare workers of a hospital in Switzerland. A surrogate neutralization assay measuring the competitive inhibition of the angiotensin converting enzyme 2 (ACE2) binding to the spike protein (S) of the SARS-CoV-2 wild type virus and to five variants of concern (Alpha, Beta, Gamma, Delta, Omicron) was used. We observed a broad distribution of neutralization activity among participants and substantial differences in neutralizing titers against variants. Participants were grouped based on combinations of vaccination status (1, 2 or 3 doses) and/or prior or subsequent SARS-CoV-2 infection/reinfection. Triple vaccination resulted in the highest neutralization response, as did double vaccination with prior or subsequent infection. Double vaccination without infection showed an intermediate neutralization response while SARS-CoV-2 infection in non-vaccinated participants resulted in poor neutralization response. After triple vaccination or double vaccination plus infection, additional vaccination and/or reinfection had no impact on neutralizing antibody titers over the observed period. These results strongly support the booster dose strategy, while additional booster doses within short time intervals might not improve immunization. However, dynamics of neutralizing antibodies titers needs to be monitored individually, over time and include newly emerging variants.

End of 2019, a new virus named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was reported in Wuhan City (China) which is responsible of the still ongoing pandemic of Coronavirus Disease 2019 (COVID-19). In March 2022, half a billion individuals have been infected worldwide and 2.5 billions have been vaccinated (WHO, 2022). In Switzerland, 2.5 millions infections were recorded and 70% of the population was vaccinated with two doses of mRNA vaccine (Pfizer-BioNTech or Moderna) while 42% received a third booster dose [1]. In addition, a vaccine dose was recommended to individuals who had been infected before vaccination. Re-infections post-vaccination were reported with a frequency of 1%–15% depending on the type of study and the viral variant under investigation [2–4]. Individuals with a positive SARS-CoV-2 serology can be categorized into three major groups: vaccinated without infection, convalescent after infection, vaccinated plus infection. These groups can be subdivided depending on the number of vaccination doses received and the timing of infection before or after vaccination.

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Serological investigations look for the presence of virus-specific antibodies as a marker of previous infection or vaccination [5]. However, these analyses do not assess whether the detected antibodies display a protective antiviral activity [6]. In SARS-CoV-2, the viral spike protein (S) is the primary target for neutralizing antibodies, which inhibit its binding to the host angiotensin-converting enzyme 2 (ACE2) receptor, the trigger of cell membrane fusion between the virus and the human cell [7–10]. As neutralizing antibodies play a key role for viral clearance, the quantification of their activity provides a good estimate of immune protection [11–13]. The gold standard for measuring SARS-CoV-2 neutralizing antibodies activity relies on quantification of the reduction of virus-induced cytopathic effects after infection of ACE2-expressing cells with live virus but simpler cell-free neutralization assays have been developed [14]. In the present study, we used a surrogate neutralization assay measuring the competitive inhibition of ACE2 binding to a trimeric S protein loaded on beads [15]. This method is quantitative, high throughput and allows the simultaneous evaluation of the neutralization activity targeting spike protein encoded by different SARS-CoV-2 variants of concern [16,17].

Here, we investigated at four time points, between March 2021 and February 2022, the dynamics of SARS-CoV-2 neutralizing antibodies against the original Wuhan wild type virus and five major variants of concern (Alpha, Beta, Gamma, Delta and Omicron BA.1). This prospective observational study was conducted in health-care workers at the "Ensemble Hospitalier de la Côte" (EHC), a public hospital in Morges, Western Switzerland with 1′800 employees, 240 acute beds and 85 post-acute beds. The objective of the investigation was to quantify the neutralization activity of anti-SARS-CoV-2 antibodies in seropositive participants according to their vaccination and convalescent status.

2. Materials and methods

2.1. Study design

A prospective observational study was proposed to all EHC employees, Morges, Switzerland (n = 1′800). Participants over 18 years old were included on a voluntary basis after written informed consent at one of the following study visits: March 2021, June 2021, September 2021, and February 2022. Volunteers had the opportunity to be recruited or drop out at any of the four visits.

2.2. Questionnaire

All participants filled in a questionnaire with demographic characteristics, history and date of positive SARS-CoV-2 RT-PCR or antigen (AG) tests as well as date of first, second and/or third vaccination (Supplementary File 1). Questionnaires were manually digitalized.

2.3. Serum sampling

Blood was obtained at the inclusion and follow-up visits (10 ml Monovette® without anticoagulant) and processed as previously described [18].

2.4. Serological method

The samples were analyzed with a standard serological test for IgG anti-Spike (anti-S) and IgG anti-Nucleocapsid (anti-N) SARS-CoV-2 antibodies using the Luminex® system [19] as previously described [18]. Samples with a positive serology were further investigated using a surrogate neutralization test [15]. Dilutions of serum samples in PBS were added to plate wells containing S proteins-coupled beads. Variant investigated include the sequence of the wild type Wuhan, Alpha, Beta, Gamma, Delta and Omicron BA.1. The positive control for 100% neutralization consisted of a cocktail of two neutralizing antibodies binding distinct epitopes on the SARS-CoV-2 Spike protein. In absence of neutralizing antibodies, a tagged ACE2-Fc can freely bind to the S protein and induce maximal fluorescence intensity (MFIs). Neutralizing antibodies bind to the S protein and compete with its binding to ACE2: this inhibition effect can be quantified by reduced fluorescence intensities. Results are presented as IC_{50} of the calculated inhibition curve. Neutralization responses were classified in four categories: <50: undetectable neutralizing activity, 50–100: low neutralizing activity, >100–150: moderate neutralizing activity, >150: strong neutralizing activity. All sera were processed at the Laboratory of Immunology and Allergy, Lausanne University Hospital (CHUV), Switzerland.

2.5. Group definition

Participants were grouped according to data extracted from questionnaires and serological results. In absence of a history of documented infection (positive RT-PCR or AG tests) volunteers with a positive anti-S SARS-CoV-2 serology prior to the first vaccination (n = 32) or with a positive anti-N serology (n = 58) were excluded from the group vaccinated only. As the date of infection was unknown they were not included in the group vaccination/infection. Time course representation, in convalescent subjects and in those vaccinated with two doses or three doses, t = 0 was defined as the date of the first positive RT-PCR or AG test, of the second or the third vaccination dose, respectively. The time interval in days elapsed between t = 0 and the date of the study visit is represented. For vaccinated individuals (two or three doses), the status of infection before or after vaccination was determined using respectively, the second or third vaccination date as reference. For participants vaccinated with a single dose, the date of the first dose was used. For participants with two reported SARS-CoV-2 infection episodes, the first date was used unless otherwise specified in the text.

2.6. Statistical analysis

All analyses were performed with R version 4.0.2. Local polynomial regression fitting was performed using stat_smooth method loess. Graphs were drawn with ggplot2. Median and interquartile ranges were used to describe continuous variables. Kruskal–Wallis test by rank was used to compare the different groups (pairwise.wilcox.test). The significance level was set with two-sided $p < 0.05$.

2.7. Ethics

The Cantonal Ethical Review Board for Human Research (CER-VD, Commission cantonale d'éthique de la recherche sur l'être humain) approved the study protocol and the participants' informed consent form (Authorization Nr 2020–02300).

3. Results

3.1. Demographics of study volunteers

A total of 903 volunteers participated to this prospective observational study, representing half of the 1′800 hospital employees. 191 participated to all four visits, 147 to three visits, 207 to

two visits and 358 to one visit for a total of 1977 sera. The majority of study participants were women (84%) and the median age was 43 years (IQR 33–52) (Fig. 1A and Fig. S1A). 74.5% of participants were vaccinated with two doses (or one dose if they had a previously documented infection). Half of them received a third (respectively second) booster dose. 39.6% of participants reported a history of SARS-CoV-2 infection documented by a positive RT-PCR or AG test. The majority of these infections occurred during the epidemic waves preceding the first vaccination campaign in March 2021 (Fig. 1A and B). At the first visit, 45.3% of volunteers had a positive SARS-CoV-2 serology, 75% at the second visit, 85% at the third and 94.8% at the last visit (Table S1). A positive anti-S serology

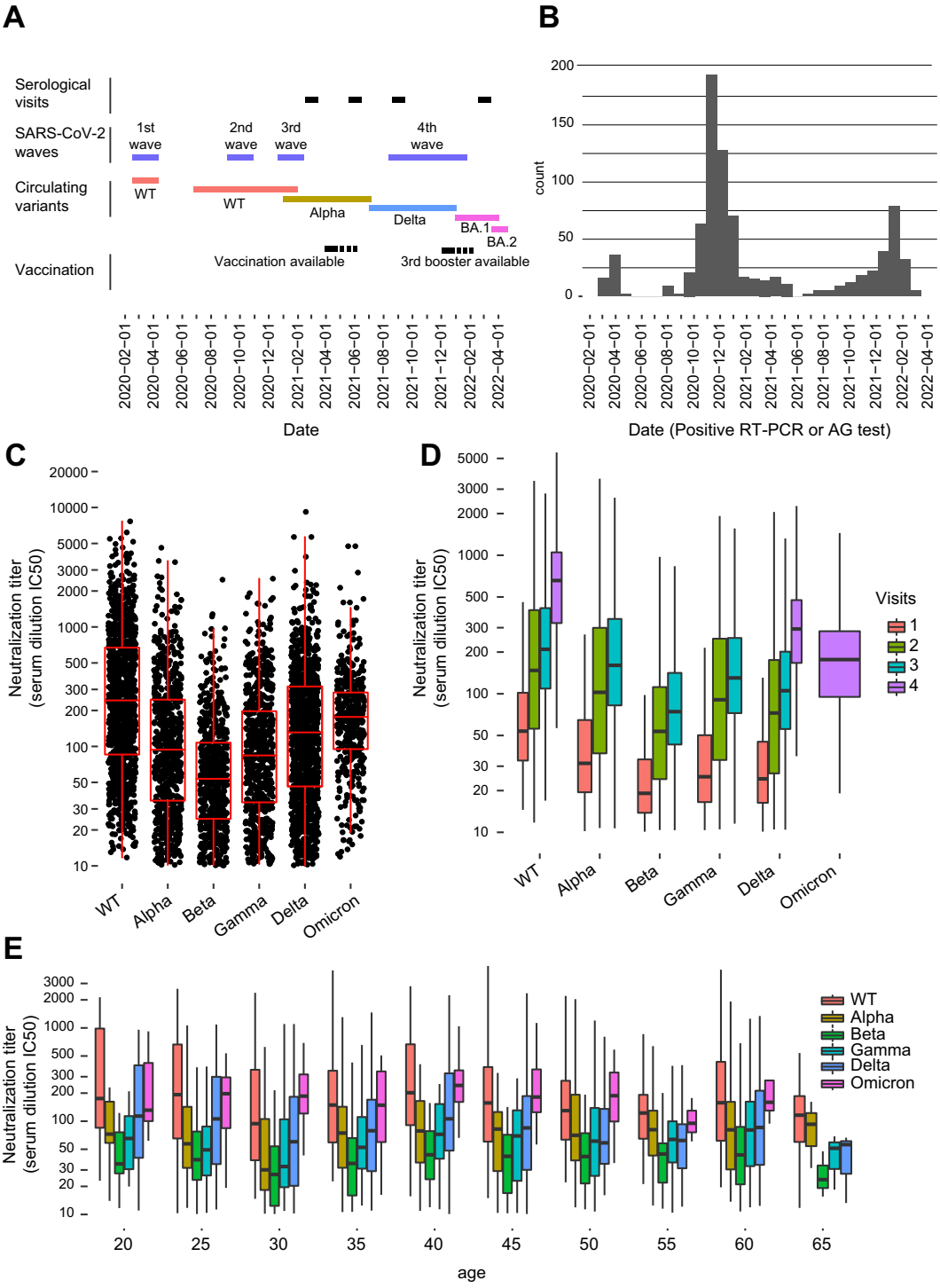

Fig. 1. **A.** Schematic representation of the study period: study visits, circulating SARS-CoV-2 variants, key epidemiological and immunization events. BA.1 and BA.2 are from the Omicron lineage. **B.** Positive SARS-CoV-2 RT-PCR and AG tests in volunteers throughout the study. **C.** Aggregate data of neutralizing antibodies titers against the Wuhan SARS-CoV-2 wild type and different variants (Alpha, Beta, Gamma, Delta, Omicron) throughout the study. **D.** Dynamics of neutralization response against the different variants at each of the four visits. Omicron was only investigated at the fourth visit, because it emerged after the third visit. Alpha, Beta and Gamma were only investigated at the first, second and third visit, as they disappeared at the time of the fourth visit. **E.** Age of volunteers versus neutralization response to the different variants.

was observed in both convalescent and vaccinated individuals, while the anti-N serology was only positive after a natural infection. Re-infections post-vaccination occurred in 15.9% of volunteers, almost exclusively with the Omicron BA.1 strain in December 2021–January 2022, prior to the last visit (Fig. S1B).

3.2. Neutralization activity across variants

The neutralization activity was investigated against the S protein of the Wuhan SARS-CoV-2 wild type and of the variants of concern Alpha, Beta, Gamma, Delta and Omicron. The neutralization assay was available at the time of the third study visit when variants Alpha, Beta and Gamma were circulating worldwide while Delta was emerging and Omicron was absent. Therefore, for the first, second and third visits, neutralization tests were performed on the SARS-CoV-2 wild type plus Alpha, Beta, and Gamma. At the fourth visit, Alpha, Beta and Gamma variants had disappeared while the Delta was being progressively replaced by Omicron (BA.1). Hence, neutralization tests were performed on the SARS-CoV-2 wild type plus Delta and Omicron. Overall, we observed a broad distribution of neutralization activity among participants indicating an important variability in inter-individual humoral immune responses and among viral variants (Fig. 1C). The Beta and Gamma variants escaped significantly the neutralizing activities of anti-S antibodies while the SARS-CoV-2 wild type showed the highest response to neutralizing antibodies (Fig. 1C). A progressive increase of neutralization titers was observed across the four visits mirroring the increasing number of volunteers who were vaccinated and/or reported an infection during the study period (Fig. 1D). The relative low increase in neutralization response between the second (June 2021) and third (September 2021) visit is likely linked to the absence of vaccination campaign and low prevalence of infections during the summer 2021 (Fig. 1B and D). We observed no significant difference in neutralizing activity among age groups (Fig. 1E).

3.3. Neutralization antibody titers in convalescent and vaccinated individuals

Participants with a positive serology (n = 773) were classified according to the vaccination status (one dose, two doses, or three doses) and/or the convalescent status (history of SARS-CoV-2 infection and reinfection documented by a positive RT-PCR or AG test) (Table 1). We first investigated the dynamics of the serological response in volunteers vaccinated with two or three doses without history of infection and in convalescent individuals without history of vaccination. These three groups displayed a simple immunization event (second vaccination, third vaccination or infection) that was used as reference time point to follow the dynamics of the neutralizing antibodies response. The date of the second or third vaccination and of the first positive RT-PCR or AG test was set as t = 0 for vaccinated and convalescent volunteers, respectively. The group of participants who were vaccinated with one single dose is not shown as most volunteers registered only for the second visit and then dropped out of the study. A local polynomial regression-fitting model was used to display an average neutralization response curve across variants and for each group. Convalescent participants showed the lowest neutralization activity after a three to four-month time interval following the reported infection (Fig. 2A–C). Vaccination with two doses without a history of infection resulted in a robust neutralization response that slowly decreased over a three to six-month time interval (Fig. 2D–F). The third booster dose of SARS-CoV-2 mRNA vaccine was followed by a rapid and significant increase in neutralization titers (Fig. 2G–I). As the booster dose was made available shortly before the last visit, the dynamic of antibody titers after the vaccination was not recorded. The increases in neutralization titers observed beyond 250 days after a documented infection or a second vaccination likely represent reinfections, that were in part asymptomatic (Fig. 2A–F). The highest neutralization response was observed after triple vaccination and an intermediate response after two vaccinations. An increase of neutralization titers was observed after a second infection in convalescent only individuals in whom the response was comparable to that observed after double vaccination (Fig. 3A). Although we observed substantial differences comparing the neutralization activities against the variants, the overall trends remained similar: convalescent individuals had the lowest neutralization response and a progressive increase of the neutralization activity was observed after double and triple vaccination (Fig. 3B–D and Fig. S2A-F).

3.4. Neutralization antibody titers in vaccinated individuals with documented COVID-19 infections

We investigated the different combinations of vaccinations (one, two, or three doses) with a documented SARS-CoV-2 infection occurring prior or post vaccination. A two-dose vaccination administered prior or after a natural infection (three immunization events) resulted in a neutralization response comparable to that obtained after a triple vaccination (three immunization events) (Fig. 4A–C). The same neutralization dynamics was observed against the SARS-CoV-2 wild type, Delta and Omicron variant, although with Omicron differences were less pronounced likely due to its ability to escape humoral response. Among the volunteers, 39 reported two COVID-19 episodes confirmed by positive RT-PCR or AG test more than 60 days apart. All were vaccinated with either two or three doses and were re-infected recently with the Omicron BA.1 variant. Four (2 vaccinations and 2 infections) or five (3 vaccinations and 2 infections) immunization events did not further boost the neutralization titers compared to those observed after three immunization events (3 vaccinations or 2 vaccinations and 1 infection) (Fig. 4A–C, Table S2). Of note, volunteers with two infections showed the lowest neutralization titers at the study visit preceding the second infection, which was in agreement with a higher probability of getting re-infected (Fig. S3A-B). The same variation trends were observed against all variants.

Table 1
Groups of volunteers according to their vaccination status (no, one, two or three vaccine doses) and/or convalescent status (no, one or two reported positive SARS-CoV-2 PCR or AG tests as a documentation of infection/reinfection). Number of volunteers/number of serological data throughout the study visits are reported. Of importance, volunteers could be included and drop out at any of the four study visits.

Immune status	One reported positive test	Two reported positive tests	No reported positive RT-PCR or AG tests	Total
Convalescent	89/139	6/15	96/118	
Vaccination 1 dose	30/75	10/22	57/75	
Vaccination 2 doses	68/172	17/48	183/296	
Vaccination 3 doses	82/227	6/19	129/255	
Total	269	39	465	773/1461

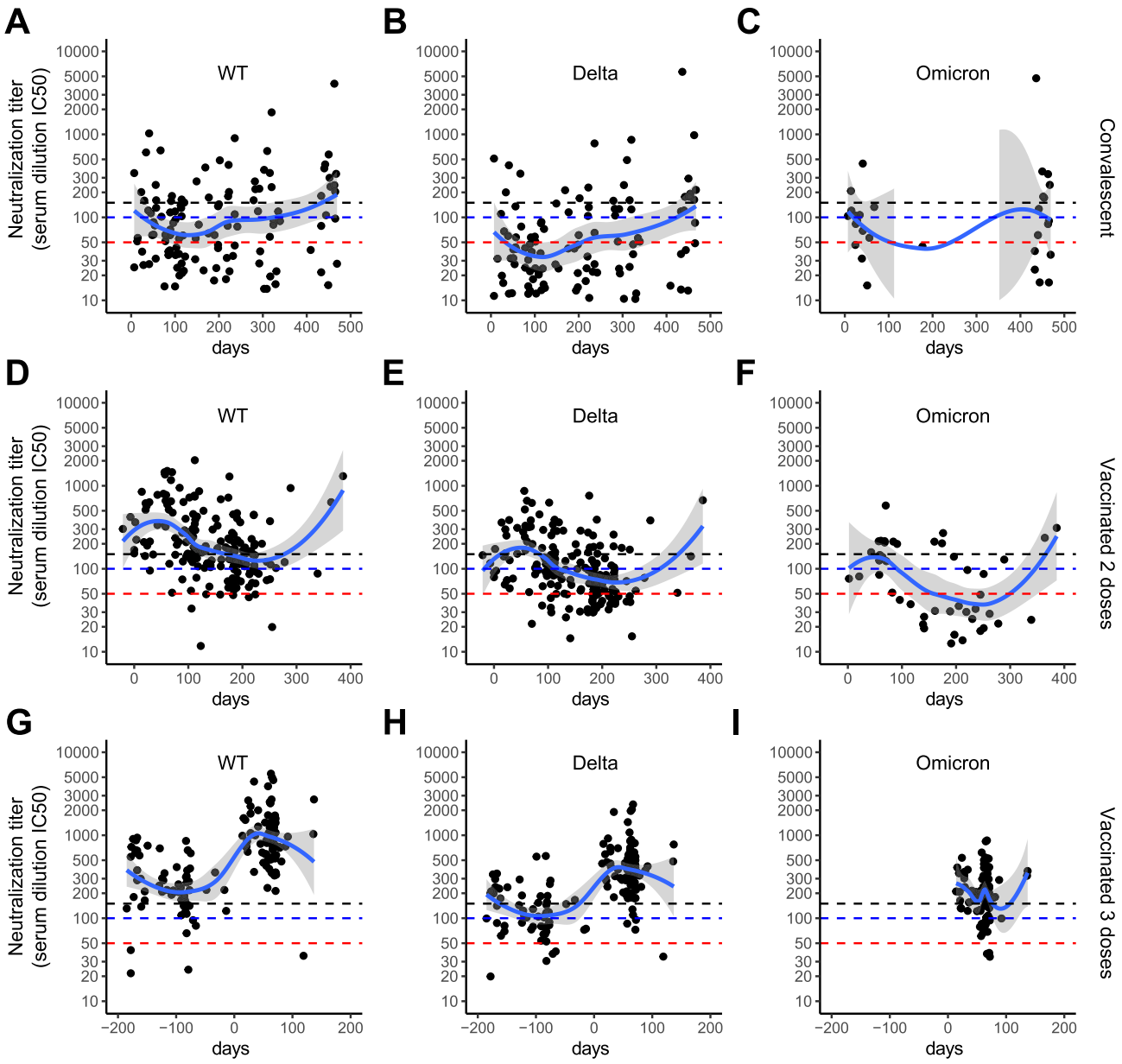

Fig. 2. Dynamics of neutralizing antibodies titers over time against the Wuhan SARS-CoV-2 wild type, Delta and Omicron variants. As Omicron was only investigated at the last visit, fewer points are represented. Dashed lines: < 50 (red): no neutralizing activity; 50–100 (blue): low neutralizing activity; 100–150 (black): moderate neutralizing activity; > 150: high neutralizing activity [24]. **A-C.** Convalescent non-vaccinated volunteers. Time 0 corresponds to the reported date of the first positive SARS-CoV-2 RT-PCR or AG test as documentation of infection. **D-F.** Volunteers vaccinated with two doses and without history of COVID-19. Time 0 corresponds to second vaccination date. **G-I.** Volunteers vaccinated with three doses and without history of COVID-19. Time 0 corresponds to the third vaccination date.

4. Discussion

In this one-year prospective observational study in 903 hospital employees, we observed important variations in neutralizing anti-SARS-CoV-2 antibodies activities in seropositive individual [13]. At the group level, overall trends in viral neutralization could be predicted based on the history of vaccination and/or infection. However, large inter-individual differences highlight the difficulty to accurately predict the level of protection and illustrate the value of individual assessments of neutralizing antibodies.

As reported in other studies [20,21], neutralization titers differed significantly against the tested SARS-CoV-2 variants. Antibodies showed the highest neutralizing activity against the Wuhan wild type virus related to its spike protein being used for the development of mRNA vaccines. In convalescent non-vaccinated individuals, mostly exposed to the Alpha, Delta and Omicron variants, the neutralization activity was highest against the Wuhan wild type virus; although after natural infection, a variant-specific increase in neutralization titers would be expected. This discrepant observation could suggest that immunity to variants is not solely due to neutralization antibodies against a mutated S-protein but also to a more complex interplay with the immune system.

Significant differences in neutralizing antibodies activity were also observed among the different groups based on history of vaccination (one dose, two doses, or three doses) and SARS-CoV-2 infection. We showed that individuals with a convalescent status had a significantly lower neutralization response compared to

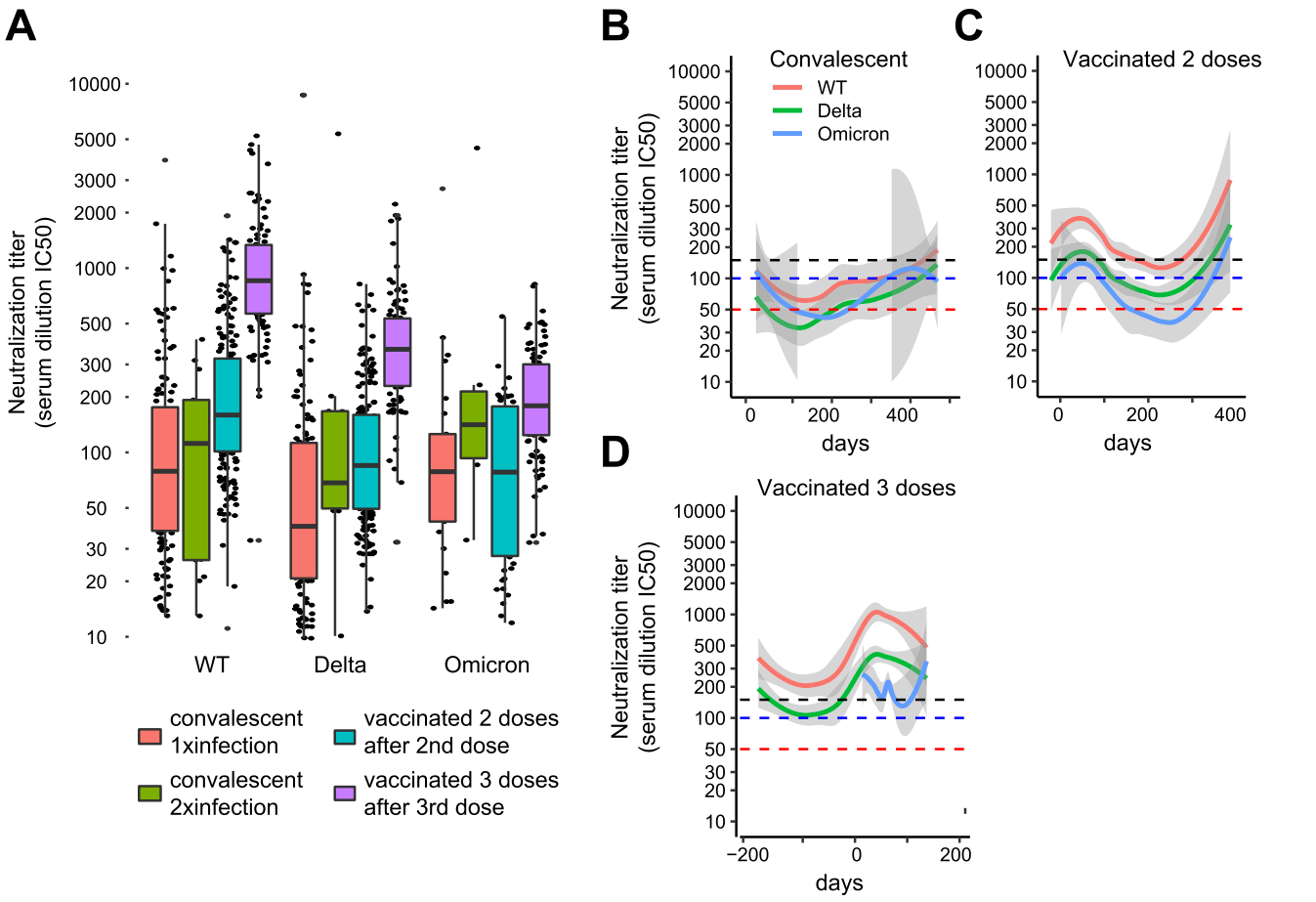

Fig. 3. A. Neutralizing antibodies titers against the Wuhan SARS-CoV-2 wild type, Delta and Omicron variants in convalescent individuals after the first or second infection and in vaccinated individuals after the second or third vaccination. Only the serological data after either the first or second infection and the second or third vaccination are shown in the graph. **B-D.** Neutralization response against the Wuhan SARS-CoV-2 wild type, Delta and Omicron variants in convalescent individuals and in individuals vaccinated with two or three doses.

vaccinated individuals [22,23]. SARS-CoV-2 antibody response after infection was previously shown to correlate with the severity of the disease [24–26]. In the present study, only volunteers with low to mild COVID-19 infections (only one volunteer reported a hospitalization) were investigated, which represents a good estimate of the immunization profile in the general population.

In individuals vaccinated with two doses, we observed significant neutralization titers followed by a progressive decrease beyond three months after the second dose. A third booster dose resulted in a significant rebound of neutralization activity. A similar boosted neutralization response was observed in individuals with SARS-CoV-2 breakthrough infection after two vaccine doses [27] and in convalescent individuals who received two vaccine doses after infection. These observations suggest that the sequential order of different immunological stimulations (vaccination followed by infection or *viceversa*) does not significantly impact the level of neutralization antibodies [28,29]. A maximal neutralization response was observed after three immunological stimuli (triple vaccination or double vaccination preceded or followed by infection) while double vaccinated or convalescent individuals showed significantly lower neutralization titers. After three immunization events, additional vaccination or reinfection had limited impact on the neutralization activity. This suggests that additional boosters (four or five immunization events) after reaching a neutralization antibodies titers plateau might be of limited value in the following three to six months period while the persistence of neutralization activity beyond this period remains to be investigated. Indeed, as a significant decrease in neutralizing antibody titers was observed over time in double vaccinated individuals, a similar decline might occur after three immunization events. In addition, significant differences might occur over time among triple vaccinated individuals and those with hybrid immunity (vaccination and natural infection). These heterologous immunization regimens can result in different long-term neutralization responses [28,30], as shown in a recent study showing that booster durability was longer in participants who had breakthrough infection [31]. Interestingly, we only observed reinfections in vaccinated individuals, but with more than 75% of volunteers being vaccinated the significance of this observation is unclear.

Among limitations of the present study, the used neutralization test is a proxy of the immune response measuring solely the antibodies activity on the interaction between the S protein and its ACE2 receptor *in vitro*. The complex interplay of humoral and cellular immune response to infection and/or vaccination was not investigated. While we observed no significant correlation between neutralizing antibody titers and age, other studies showed a consistent decrease of immunity in older individuals [26,32,33]. As the present investigation was restricted to working individuals younger than 65 years, we are unable to draw any conclusions on the duration of immunity in the elderly.

In conclusion, a triple vaccination or a natural infection prior or after a double vaccination result in a robust neutralization response

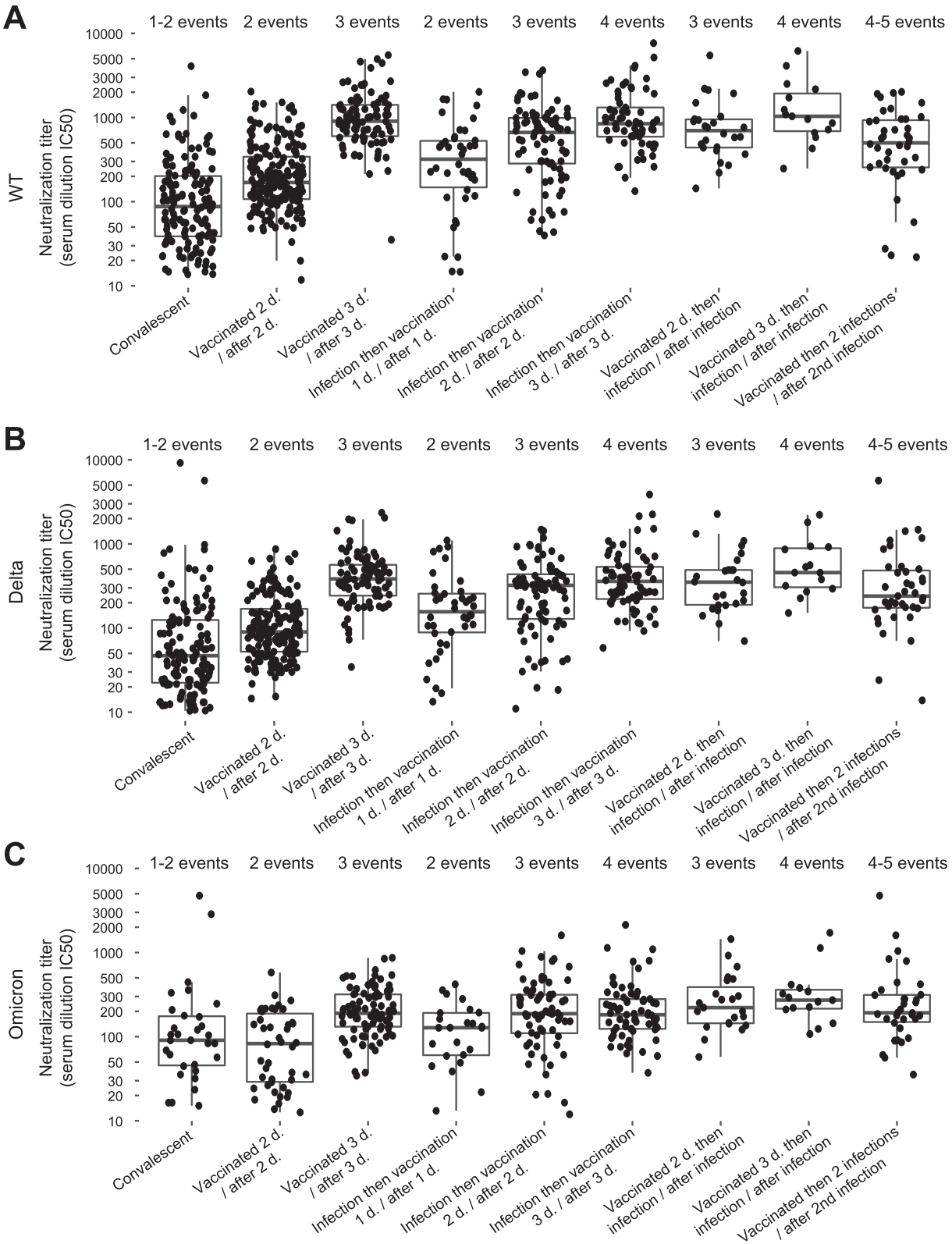

Fig. 4. Neutralization responses after different numbers of immunization events including infections and/or vaccinations. **A.** Wuhan SARS-CoV-2 wild type. **B.** Delta variant. **C.** Omicron variant.

strongly supporting a booster dose strategy. Although additional booster doses within three to six months after a third immunization event (infection or vaccination) might not boost immunity, the decline of neutralizing antibodies titers beyond this time window needs to be monitored on an individual basis by including new variants in neutralization assays. Yet the protection conferred by neutralizing antibodies against emerging variants is unpredictable: for example, immunity was shown to be strongly reduced against

the most recent Omicron BA.4 and BA.5 variants [4] and appears to more rapidly decline [34]. A booster vaccine dose integrating newly appearing variants might contribute to meet the complex challenge of maintaining an effective immunity over time.

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Declaration of competing interest

G. Greub is medical advisor of Resistell, a startup active in the development of a new instrument to faster antibiotic susceptibility results. G. Greub has a research agreement with Becton Dickinson (USA) and Resistell (Switzerland), both unrelated to the present work. The rest of the authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.micinf.2022.105077.

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