International Journal of Infectious Diseases 148 (2024) 107240

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Short Communication

SARS-CoV-2 Omicron XBB.1 variant outbreak in a defined cohort: an epidemiological investigation incorporating longitudinal assessment of humoral response

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ARTICLE INFO

Article history:
Received 28 July 2024
Revised 8 September 2024
Accepted 9 September 2024

Keywords:
COVID-19
Healthcare workers
Infection control
Virus neutralization

ABSTRACT

Background: We describe an epidemiological investigation of a SARS-CoV-2-XBB.1 outbreak among healthcare workers (HCWs) returning from a 5-days educational tour abroad.

Methods: We prospectively followed participants for symptoms and sampled blood for neutralization assays of four SARS-CoV-2 variants (wild type, XBB, EG.5.1, and BA.2.86) at 1, 3, and 6 months after their return. When available, samples from the 3 months preceding the outbreak were also tested. We compared geometric mean titers (GMT) of neutralizing antibodies of infected versus uninfected HCWs and febrile versus afebrile infected HCWs.

Results: Nineteen (10%) of 181 HCWs were infected, all had mild COVID-19, 90% (17/19) had symptoms, and 16% (3/19) reported fever. Infected individuals tended to have lower pre-exposure XBB-neutralizing antibody titers (GMT of 32 versus 107 ID50, $P = 0.248$). Neutralization against XBB and newer subvariants peaked at 3 months and was higher among infected individuals (GMT 702 versus 156 [$P < 0.001$], 558 versus 163 [$P = 0.001$], and 558 vs. 182 [$P = 0.002$], ID50 for XBB, EG.5.1., and BA.2.86, respectively). By six months, these differences were no longer observed. Fever was positively associated with XBB neutralization (GMT 3474 versus 485, ID50 $P = 0.005$).

Conclusions: Recently infected individuals are protected from reinfection with newer subvariants. However, protection is likely short lived.

Introduction

COVID-19 reinfection is frequent, and the burden on healthcare systems remains considerable [1]. SARS-CoV-2 Omicron subvariant XBB has rapidly spread since December 2022 [2]. While new variants continue to circulate, vaccinated healthcare workers (HCWs) are still susceptible to infection acquisition even in the postpandemic era [3]. Markedly, an outbreak among HCWs could reduce the ability to provide care and increase the risk of infection for vulnerable patients. Early detection of an outbreak can disrupt the chain of transmission through usage of surgical masks and avoidance of unnecessary gatherings of HCWs.

Here we report on an outbreak of Omicron XBB.1 subvariant SARS-CoV-2 infection, among a defined group of HCWs. We evaluated neutralizing antibody titers before and after exposure and analyzed their correlation with symptoms and effectiveness in neutralizing newer Omicron subvariants.

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https://doi.org/10.1016/j.ijid.2024.107240

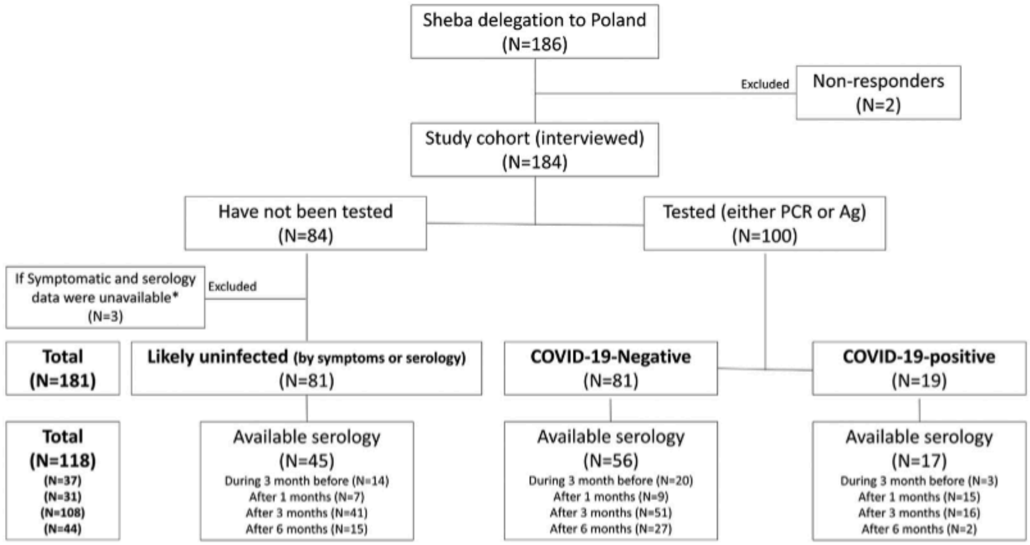

Figure 1. Study population. *Symptoms included cough and/or fever.

Materials and methods

In March 2023, Sheba Medical Center (SMC) launched a delegation of HCWs for a 5-days educational tour in Poland. Upon embarkation, all participants felt well and were symptom-free. On their return, a few symptomatic participating HCWs tested positive for SARS-CoV-2. SMC's Infection Control and Prevention Unit (ICPU) performed an epidemiological investigation and instructed all participating HCWs to perform SARS-CoV-2 tests (either PCR or rapid antigen test) as soon as possible and to repeat testing if fever or any respiratory symptom appeared. Delegation members were followed for 14 days, beginning at the date of the first positive case on March 31, 2023.

The current study was nested in the SMC HCWs cohort [4,5] (for further details, see supplemental material). Participating HCWs were invited for serology sampling at 1,3, and 6 months following the outbreak reference date. In this study, we assessed the humoral response to SARS-CoV-2 wild type (WT) virus as well as XBB and recent emerging variants and compared neutralizing antibody levels (measured in 50% inhibitory dilution [ID50]) of infected and uninfected HCWs before-and-after the outbreak (data collection and laboratory methods are detailed in the supplemental material).

Geometric mean titers (GMT) of neutralizing antibodies with 95% confidence intervals (CI) were estimated using the t-distribution for the log-transformed values. Comparisons by infection status (i.e., infected *vs* uninfected) and fever status (i.e., febrile vs. afebrile) during the acute illness were performed using the student's *t*-test on the log-transformed data. Analysis was carried out using IBM SPSS version 28 (Armonk, New York, USA) and GraphPad Prism 8.0.1. For all analyses, $P < 0.05$ was considered statistically significant.

Results

The delegation included 186 individuals, 181 (97%) of whom were included in this study. Their median age was 51 (IQR 13; range 18-76) years and 150 (83%) were women. A total of 19 HCWs were infected with SARS-CoV-2 XBB.1, reflecting an attack rate of at least 10% (19/181). Of those included, 118/181 (65%) provided blood samples for serological tests, before and/or after exposure, including 17 (89%) of the 19 infected individuals (Figure 1; further details on the study population are provided in the supplementary material).

Serological samples during the 3 months preceding the outbreak were available for 37 (31%) participants, only 3 (8%) of whom were infected during the outbreak. SARS-CoV-2 IgG levels during that period were similar between groups (GMT of 4134 vs. 3335 antibody binding units [BAU], for infected and uninfected HCWs, respectively, $P = 0.716$). While neutralization against the WT SARS-CoV-2 did not differ between the groups ($P = 0.794$), infected individuals had an average 3-fold lower XBB-neutralizing antibodies titers (GMT of 32 vs. 107 ID50, for infected and uninfected individuals, respectively), although this finding did not reach statistical significance ($P = 0.248$) (Figure S1, supplementary material).

At 3 months following the outbreak, infected individuals had significantly higher IgG levels (GMT 5739 *vs* 2130 BAU, $P < 0.001$) and neutralization against XBB (GMT 702 vs. 156 ID50, $P < 0.001$), EG.5.1 (GMT 558 vs. 163 ID50, $P = 0.001$), and BA.2.86 (GMT 558 vs. 182 ID50, $P = 0.002$) variants. Similarly, infected individuals had higher neutralization against the WT virus, though this finding was nonstatistically significant (GMT 4414 vs. 2829 ID50, $P = 0.074$). At six months following the outbreak, differences in SARS-CoV-2 IgG levels and neutralization between the groups became nonstatistically significant: IgG (GMT 2106 vs. 1764 BAU, $P = 0.781$), XBB (GMT 362 vs. 175 ID50, $P = 0.398$), EG.5.1 (GMT 362 vs. 158 ID50, $P = 0.441$), BA.2.86 (GMT 512 vs. 292 ID50, $P = 0.519$), and WT (GMT 2896 vs. 2550 ID50, $P = 0.837$) (Figure 2a & b).

Of the 19 infected individuals, 16 (84%) provided samples for serology at three months. Of these, 3 (19%) had febrile acute illness. These individuals had significantly increased neutralization against SARS-CoV-2 XBB (GMT 3474 vs. 485 ID50, $P = 0.005$), EG.5.1 (GMT 1626 vs. 436 ID50, $P = 0.030$), and BA.286 (GMT 1626 vs. 436 ID50, $P = 0.018$). They also had higher neutralization against the WT (GMT 7427 vs. 3915 ID50, $P = 0.194$) although these results were nonstatistically significant (Figure 2c).

Discussion

In this study we report an outbreak of SARS-CoV-2 XBB among a group of HCWs. The outbreak occurred outside the hospital setting, during a 5-day educational tour organized by the medical institute, yet we observed a non-negligible attack rate of at least 10%. Despite becoming endemic, SARS-CoV-2 remains highly transmissible and can still significantly impact the health workforce. This

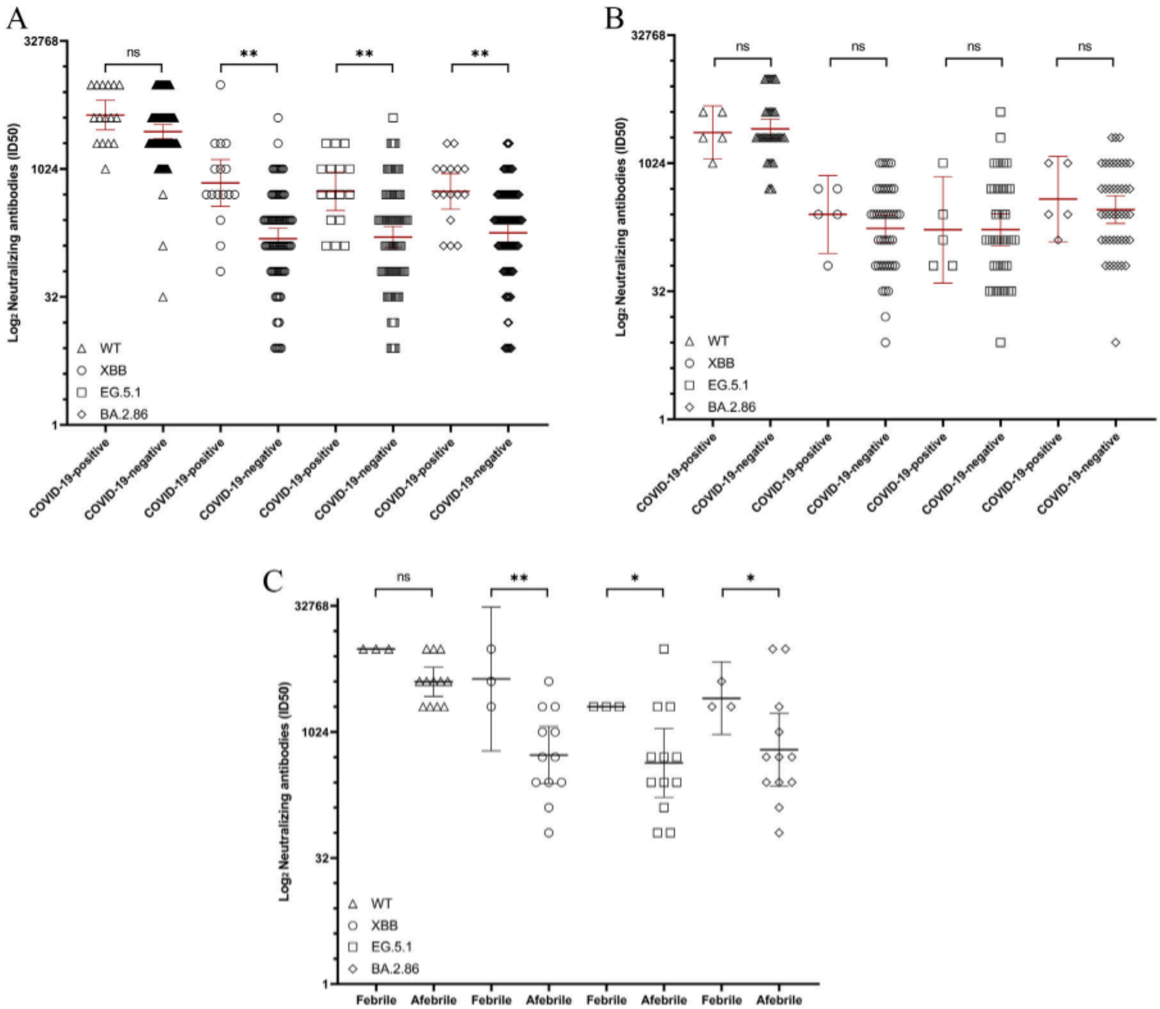

Figure 2. Neutralizing antibody levels at 3 and 6 months following the outbreak. WT, XBB, EG.5.1, and BA.2.86 neutralizing antibody levels (ID50) among COVID-19-infected and uninfected healthcare workers at 3 (panel A) and 6 (panel B) months and at 3 months among febrile and afebrile acutely infected healthcare workers (panel C). The bars indicate geometric mean titer ± 95% confidence interval. ID50 = 50% inhibitory dilution; ns = not significant; WT = wild type; ns = not significant; $**P < 0.01$, $*P < 0.05$.

supports the recommendation for healthcare facilities to maintain a precautionary approach regarding staff gatherings, particularly during times of increased incidence.

As expected, individuals with documented COVID-19 had significantly higher neutralizing antibody titers at 3 months following acute infection. High neutralizing antibody titers are well-established markers of protection [6]. Accordingly, a recently convalescent individual can be deemed unlikely to transmit COVID-19 to vulnerable patients. However, as COVID-19 immunity rapidly wanes, the period of low risk for reinfection is relatively short. Currently, neutralization assays provide the best marker of protection [7].

Here, we show that XBB-COVID-19-infected individuals had increased neutralization antibody titers against recently emerging variants (BA.2.86 and EG.5.1), suggesting cross-protection against newer subvariants consequent to an infection with the XBB variant. Accordingly, a recent exposure provides protection similar to that exerted by a booster dose [8]. This reinforces the recommendation that a recently infected individual can delay receipt of COVID-19 booster doses. Nevertheless, the infection-to-revaccination interval is currently unknown.

A particularly interesting finding of our study is the increased immune response among febrile COVID-19-infected HCWs. During earlier stages of the pandemic, febrile COVID-19 infection was associated with decreased risk for reinfection [9]. The association between febrile acute illness and higher neutralization titers found in our cohort implies that a febrile COVID-19 episode still provides improved protection against reinfection, even in the XBB-Omicron era, when the population is no longer naive to the virus [10].

The study is limited by the somewhat small sample size. Nonetheless, our main findings did reach statistical significance owing to the large effect sizes. Classification bias is another concern, as only 54% (100/184) of the cohort was tested for COVID-19. However, we systematically interviewed all exposed HCWs, and those who reported symptoms without being tested for COVID-19 were included only if before-after serological tests suggested that they were likely uninfected. Accordingly, we were able to ascertain that an individual was not infected, hence mitigating this bias. Nonetheless, misclassification of asymptomatic individuals is possible, as many participants used antigen testing, potentially having a lower sensitivity compared to PCR.

In conclusion, COVID-19-XBB-infected individuals had an improved postinfection neutralization against XBB and newer variants for an average of ~3 months, suggesting short-term protection. Fever during acute illness correlated with improved humoral response. Healthcare facilities may consider incorporating serial serological sampling as a tool for encouraging HCWs to adhere with vaccination recommendations and timing booster vaccines.

Declarations of competing interest

All authors report no conflicts of interest relevant to this article.

Funding source

This study was funded using Sheba Pandemic Preparedness Research Institute (SPRI) internal funds.

Ethical approval

The cohort study was approved by the Institutional Review Board at Sheba Medical Center. All participants provided their written consent to participate in the study.

Author contributions

Ili Margalit: Conceptualization, Formal analysis, Writing - original draft; **Yael Weiss–Ottolenghi:** Conceptualization, Investigation, Data curation, Writing - review & editing; **Einat Panet:** Conceptualization, Investigation, Data curation; **Victoria Indenbaum:** Investigation, Data curation; **Neta S. Zuckerman:** Investigation, Data curation; **Gili Joseph:** Conceptualization, Writing - review & editing; **Yovel Peretz:** Investigation, Data curation; **Noam Barda:** Writing - review & editing; **Yaniv Lustig:** Investigation, Writing - review & editing; **Gili Regev–Yochay:** Conceptualization, Supervision, Writing - review & editing. All authors contributed to the interpretation of the results and to the writing of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2024.107240.

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