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Letter to the Editor

Investigation of vaccine breakthrough infections by vaccination scheme during the Delta variant wave in France

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To the Editor,

As of 16 December 2021, 90% of the adult population in France was fully vaccinated with different vaccines [1]. During this vaccination campaign, vaccine breakthrough infections (VBIs) caused by the Delta variant and associated with a high viral load were reported [2]. Furthermore, the level and duration of humoral and cellular immune responses were shown to be different according to the vaccine used [3,4]. Herein, we describe demographic and virological characteristics of VBI in fully vaccinated individuals with five different vaccination schemes.

An observational study was conducted at the National Reference Center for Respiratory Viruses in Lyon, France, from April 2021 to August 2021. During this period, samples positive for SARS-CoV-2 in Biogroup community testing laboratories were retrieved for whole-genome sequencing. The inclusion criterion was a positive test in fully vaccinated individuals. Individuals were considered fully vaccinated 2 weeks after homologous vaccination with Pfizer-BioNTech (BNT162b2) or Moderna (mRNA-1273) vaccines, heterologous vaccination with AstraZeneca and Pfizer-BioNTech (ChadOx1/BNT162b2) vaccines, or single-dose vaccination with Johnson & Johnson (Ad26.COV2.S) or AstraZeneca (ChadOx1) vaccines. Continuous variables are presented as median with interquartile range (IQR) and compared using nonparametric Kruskal–Wallis tests. Proportions were compared using the χ^2 or Fisher's exact test, as appropriate. A p-value of <0.05 was regarded as statistically significant. Statistical analyses were conducted using R software, version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria).

A total of 1366 VBIs among patients who were fully vaccinated between February 2021 and July 2021 were included in this study. The number of VBIs reported in each age group followed the dynamics of SARS-CoV-2 infections in France, with a peak occurring in August (Fig. 1(a) and (b)). BNT162b2 was the most frequently reported vaccine (1083/1366, 79.3%), followed by ChadOx1 (128/1366, 9.4%) and mRNA-1273 (93/1366, 6.8%).

SARS-CoV-2 sequencing showed that the Delta variant represented 94.1% (1286/1366) of VBIs, whereas Alpha and Beta variants represented 4.5% (61/1366) and 0.6% (8/1366), respectively. During the epidemic peak in August, only 4 of 1048 (0.4%) VBI viruses belonged to non-Delta viruses, including two Mu viruses (lineage B.1.621, Fig. 1(a)). In addition to the S-gene mutations appearing in at least 75% of Delta variant sequences (https://outbreak.info/compare-lineages), additional receptor-binding domain (RBD) substitutions were noticed in 37 of 1286 (2.9%) Delta VBI viruses (32/1017 (3.1%), 3/118 (2.5%), and 2/90 (2.2%) for BNT162b2, ChadOx1 and mRNA-1273 groups, respectively). The most frequent were S:A520S ($n = 4$), S:G446V ($n = 4$), S:Y508H ($n = 4$), S:N354K ($n = 3$), S:V445F ($n = 3$), and S:V503F ($n = 3$), which were independently detected. Note that an amino-acid substitution at spike position 484 was identified in only one sequence (E484D). No significant differences were observed in

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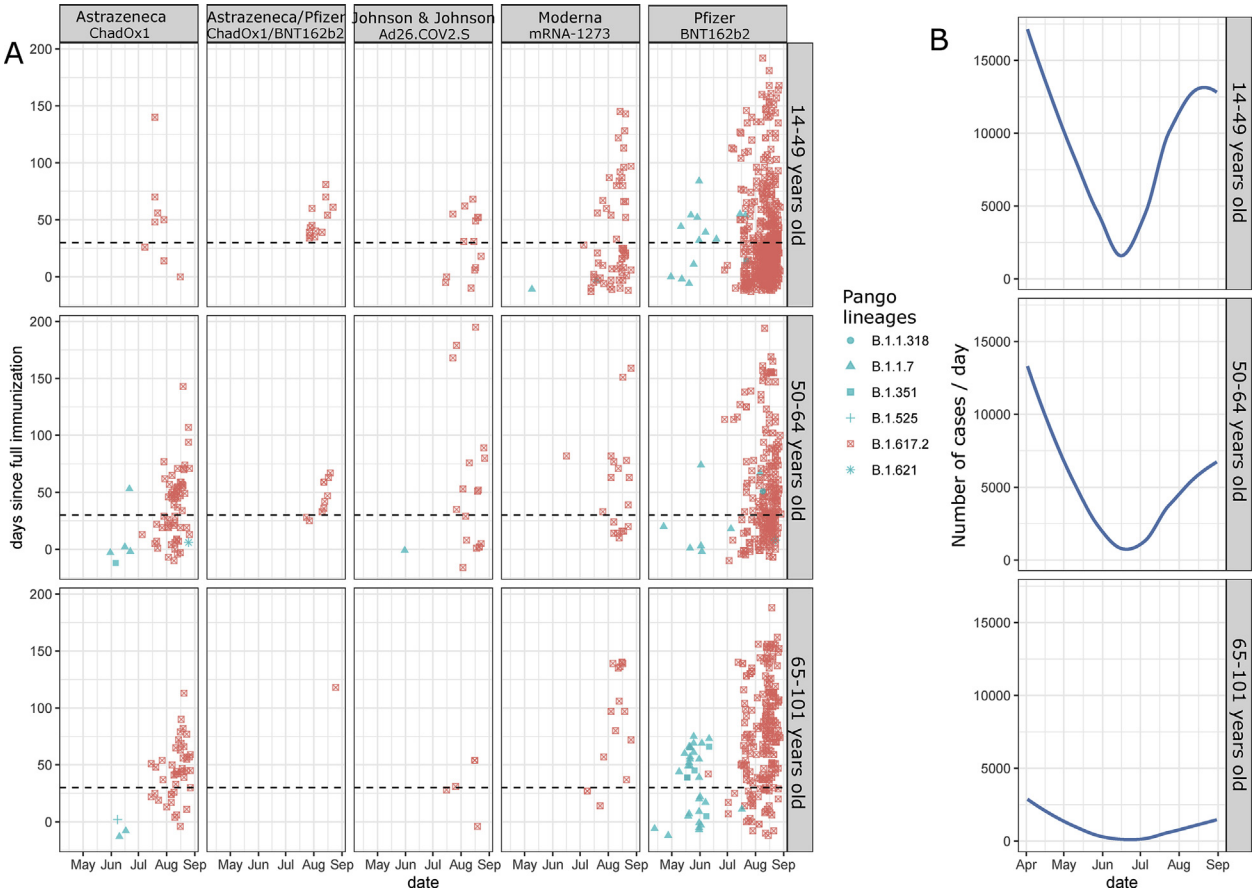

Fig. 1. Next-generation sequencing-confirmed vaccine breakthrough infections in fully vaccinated individuals, 12 April to 30 August 2021. (a) Vaccine breakthrough infections (VBIs) are represented by vaccine scheme and by age group. Each symbol represents a VBI case. The three age groups represented are 14–49 years, 50–64 years, and 65–101 years. The time since full vaccination is represented in the y-axis. The horizontal dotted lines indicate 1 month after full vaccination. VBI below these lines is defined as early VBI. Each Pango lineage determined through whole-genome sequencing is represented by a symbol. Lineage B.1.617.2 (Delta variant) is represented in red. (b) Estimation of the number of cases per day in France represented by age group. The estimation was determined by regression analysis (Loess method) based on national data [6]. The three age groups are 14–49 years, 50–64 years, and 65–101 years.

the RBD sequences or in other SARS-CoV-2 genomic regions according to the vaccination scheme.

The median age of individuals with Delta VBI significantly differed depending on the vaccination scheme, with a median of <50 years except for Ad26.COV2.S and ChadOx1 groups ($p < 0.001$). Delta VBIs were mainly symptomatic (mild symptoms) for all vaccination schemes (>69% of symptomatic infections for all groups); limited RT-PCR Ct-value differences at diagnosis were noted in symptomatic and asymptomatic Delta VBIs for the BNT162b2 group (17.7 (15.07–20.51) vs. 19.00 (16.00–23.00); $p = 0.004$). Interestingly, more than 75% of Delta VBIs occurred in patients who were infected within 3 months after full vaccination, regardless of the vaccination scheme. Furthermore, up to 50% of Delta VBIs were classified as early VBIs (infected <1 month after full vaccination) for BNT162b2, mRNA-1273, ChadOx1, and Ad26.COV2.S (Table S1). People aged 14–49 years were over-represented in early VBI compared to non-early VBI for BNT162b2 and mRNA-1273 (73.92% vs. 37.87% for BNT162b2 and 77.78% vs. 46.67% for mRNA-1273; $p < 0.05$; Fig. 1).

Our data showed that mild VBI detected in community laboratories during the spread of the Delta variant mainly occurred within 3 months after full vaccination for all vaccination schemes. Low Ct values and the presence of symptoms observed herein support a risk of transmission as previously noted in fully vaccinated health care workers infected by the Delta variant [5].

Importantly, additional RBD mutations, including immune-escape mutations, were identified in 2.9% of Delta VBIs, but those mutations were not associated with a specific vaccination scheme. These RBD mutations were found in 1.3% of the 17 018 other Delta viruses sequenced in our laboratory during the same period (June to August). This observation should be further explored using phylogeographic and phylodynamics approaches on a large sequence dataset including the vaccination and clinical status of all individuals.

The main limitations of this study are related to French vaccine policies, explaining the limited sample sizes for ChadOx1/BNT162b2 and Ad26.COV2.S groups and differences in vaccination date between age groups and vaccine types. Importantly, BNT162b2 was the most frequently used vaccine reported herein, which is consistent with the distribution of vaccine types administered in France during the study period. Furthermore, the full vaccination scheme with ChadOx1 or Ad26.COV2.S was recommended in patients aged >55 years. This explains the differences found herein between age and comorbidities according to vaccine scheme.

Nonetheless, our data emphasize a high prevalence of early Delta VBI in young patients that might be related to epidemiological factors (the peak of the Delta variant in France when a large part of the population was within 3 months after full vaccination) and social behaviour (relaxation of protective measures in patients, thinking that vaccination alone is sufficient to protect them from SARS-CoV-2 infection). The investigation of VBI should be reinforced in the context of the booster vaccination campaign.

Ethics statement

Ethics approval was obtained from the National Review Board for Biomedical Research (Comité de Protection des Personnes Centre-Ouest I, France; ID-RCB 2021-A01877-34), and the study was registered on ClinicalTrials.gov (NCT05060939).

Transparency declaration

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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Author contributions

AB, GD, and BS contributed equally to this work.

AB, GD, BL, FM conceived the study. AB, GD, BS, LJ managed the sample preparations and sequencing. BS performed bioinformatic analysis. LJ is the guarantor for the NGS data. JMG is the guarantor for clinical data and sample collection. AB was the main writer of the manuscript. All authors reviewed and approved the final version of the manuscript.

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Appendix

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.02.034.

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