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Letter to the editor

Assessment 2 months after the administration of a 3rd dose mRNA: a new variant-adapted vaccine is expected

Since the start of the pandemic, the virus has continued to adapt and new, more contagious variants have emerged. Despite massive vaccination efforts, the health situation remains worrying. The health policy pursued by many countries (and among the first, Israel) consisted in responding with a boost[1] of the same anti-SARS-CoV-2 vaccines developed from the native virus since no new variant-adapted version gained, to date, a marketing authorization. Among these, the mRNA-1273 vaccine (Moderna) showed 94.1% efficacy against the Wuhan reference strain. Different studies have already shown a loss of production of neutralizing antibodies with variants B.1.1.7, B.1.351, B.1.1.28.1 and B.1.617.2 after two mRNA-1273 doses[2] and the effectiveness against the last variant of concern, the B.1.1.529, remains largely unknown to date. We read with interest the study by Dimeglio et al, who proposed a threshold of protection according to neutralizing or binding antibody classes in a cohort of 8758 healthcare workers (HCWs) studied before the emergence of B.1.1.529.[3]

In our study, we followed a cohort of HCWs from the two first administrations of the mRNA-1273 vaccine in January 2021 until January 28th, 2022 corresponding to two months after the injection of a 3rd dose of mRNA (either mRNA-1273 or BNT162b2 (Pfizer-BioNTech)) to verify vaccine efficacy by analyzing cases of infection, to measure the immunogenicity induced by this 3rd dose and to evaluate the protection threshold proposed by Dimeglio et al. The characteristics of the population of HCWs studied have previously been described.[4]

In this letter, we compared all cases of infection observed in HCWs who received a third dose (D3) of mRNA vaccine with those who did not, describing the symptoms reported by the participants, the delay between the onset of infection and the last dose of vaccine administered (D2 or D3) and finally the variant concerned. Having a positive RT-qPCR result was the criterion chosen to consider a SARS-CoV-2 infection. In this event, an analysis of the variants was carried out using an RT-qPCR method targeting the characteristic mutations of the variants (Novaplex^{TM}, Seegene Technologies, Seoul, South Korea).

In parallel, participant serological follow-ups were carried out based on their initial antibody status at the time of vaccination (T0), on the vaccination schedule administered (only D2 versus D3) and whether they were infected or not. The quantitative analysis of the anti-trimeric spike protein specific IgG antibodies to SARS-CoV-2 was carried out using the LIAISON® SARS-CoV-2 TrimericS IgG kit (DiaSorin®, Saluggia, Italy) and calibrated with the first WHO International Standard Anti-SARS-CoV-2 Immunoglobulin.[5] The kinetics of SARS-CoV-2 IgG antibodies included 7 sampling timepoints: the day of the first and third injection (T0, T5); 2 weeks after the first, second and third injections (T1, T2, T6); 3 and 6 months (T3, T4) after the first injection. In the event of infection, an additional serological test was offered to participants 2 weeks after infection (TAI).

250 participants (200 seronegative and 50 seropositive at inclusion) were followed for 1 year. Among the seronegative, 69% (20/29) were infected after the administration of 2 doses (D2) of vaccine and 9% (16/171) after a 3rd dose (D3). Among the seropositive, only 1 participant was infected after D2 (1/5), and 4 (4/45) after D3.

Interestingly, the time to onset of infections in participants who received only 2 doses of vaccine (D2-infected) (n=21) occurred with a median time of [± 95% CI]: 259 [230 -268] days after administration of this 2nd dose, whereas in participants who received a third dose (D3-infected), it occurred earlier with a median time of [± 95% CI]: 36 [27-46] days after the boost (Figure 1B,1D) ($P<0.0001$; Mann-Whitney). These last observations should be interpreted cautiously and according to the variant epidemiology. Except for 2 participants infected at the beginning of January, the infections described in the D2-infected (08/11/21-01/10/22) mostly occurred when the B.1.617.2 variant was predominant in Belgium while all the ones described in the D3-infected occurred when the B.1.1.529 variant gained dominance (12/7/21-01/28/22). Variant analysis only possible for samples with Ct < 33 (n=15) confirmed the presence of the HV69/70 deletion (10/10), the N501Y (10/10) and the K417N (6/10) mutations pointing to the B.1.1.529 variant in D3-infected (10/10). The E484K mutation, pointing to the B.1.617.2 variant was found in D2-infected (5/5).

Ageusia (1/19; 5%) and anosmia (1/19; 5%) in D3-infected are much less frequent compared to D2-infected, respectively 67% (14/21) and 71% (15/21) ($P= 0.0003$ and $P= 0.0001$); chi-square) (Figure 2). Except for one participant infected with the B.1.617.2 variant and hospitalized in November 2021 for a pulmonary embolism, none of the other HCWs experienced severe symptoms.

D3 boosted the antibody production, especially in initially seronegative HCWs (Figure 1A,1B). All D3-infected participants had already reached an antibody peak value > 2080 BAU/mL before infection (Figure 1B). The protective threshold proposed at 1700 BAU/mL by Dimeglio et al does not seem to apply with B.1.1.529. Finally, among the participants, 19/216 received a 3rd dose of BNT162b2 and 197/216 mRNA-1273. No difference between these 2 vaccines, whether in terms of antibody boost generated or the frequency of occurrence of SARS-CoV-2 infection, was observed ($P= 0.83$; chi-square).

We report for the first time the immunogenicity induced by a third dose of mRNA-1273 vaccine in HCWs. These results are in line with those of the study by Saiag et al on a BNT162b2 boost in an older population of HCWs (median age of 67 instead of 48 years).[6] The second originality of our study lies in the rarity of ageusia and anosmia felt in D3-infected with B.1.1.529 compared to D2-infected with B.1.617.2. Indeed, few data compare the

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