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Effect of a SARS-CoV-2 booster vaccine dose on the immune response of adults with Down syndrome

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HIGHLIGHTS

Immune protection granted by COVID-19 vaccines wanes over time. Individuals with Down syndrome (DS) are considered an at-risk population for COVID-19 hospitalization and death. Our findings show that a booster COVID-19 vaccine dose promotes a renewed, effective cellular and humoral immune response in adults with DS, akin to the general population.

To the Editor:

Adults with Down syndrome are a high-risk population for hospitalization and death due to COVID-19, **and have been frequently compared to other immunocompromised populations, as recently reviewed by Marra et al. in this journal** [1,2]. Their worse prognosis has been attributed to a higher prevalence of comorbidities and to a congenital immune dysregulation, which impairs the generation of a protective immunity after vaccination [2]. Though adults with DS develop an effective immune response after receiving a two-dose regime of SARS-CoV-2 vaccination [3], SARS-COV-2-specific IgG titers wane over time, especially in adults over 40 years of age, and the duration of vaccine-elicited protection is unknown. A third vaccine dose (booster dose) has been recommended for adults with DS, but its impact on the immune response of this population has not been studied. Following an initial study on a cohort of adults with DS one to three (V1) and six (V2) months after a two-dose SARS-CoV-2 vaccination regime [3], we here describe the dynamic changes in the cellular and humoral responses of 41 DS patients after receiving a booster vaccine dose.

The description of the study population, determination of specific IgG, analysis of T cell response, ethical considerations and statistical analysis are detailed in *Supplementary material*. A total of 41 adults with DS and 20 age-matched, non-DS donors received a third booster SARS-CoV-2 vaccine dose 6.1 months (5-8) after completing the initial two-dose schedule. Evaluations occurred 66 days (55-98.5) and 77.5 days (72-105) after the administration of this third dose (DS and non-DS subjects respectively, Suppl. Table 1). T cell response showed a similar degree and specificity profile in both cohorts. This response was mainly CD4+ in both groups (95% in DS vs. 100% in non-DS donors, Fig. 1A), with a predominant Th1 specificity. However, the latter subpopulation was significantly higher in non-DS donors, particularly in those under 40 years ($p<0.05$, Fig. 1B). Comparable levels of SARS-CoV-2-specific circulating T follicular helper cells were also observed in both cohorts (Fig. 1C). All DS subjects developed specific anti-S IgG antibodies after the third dose of vaccine and reached similar titers than non-DS controls (Fig. 1D), though mean IgG titers were lower in individuals with DS over 40 years (Fig. 1D).

These results must be put in context against what was already known about the dynamics of the immune response after two doses of SARS-CoV-2 vaccination in DS [3-5]. Prior reports have observed that, after developing an adequate humoral response 1 to 3 months after vaccination, antibody titers decreased over time in adults with DS, especially among adults over 40 years, a subgroup of particular higher risk of COVID-19 infection and death[3-5]. This decline has been interpreted as reflecting “the risk of no longer being protected by the effects of vaccination at an earlier time than the general population” [5].

Unfortunately, prior studies by Valentini et al and Sali et al [4-5] did not address cellular immunity nor provided information after a booster dose. In our experience, adults with DS developed a milder, delayed cellular immune response to the initial two doses of vaccine compared to non-DS donors (73.21% adults with DS with specific CD4+ and 16.36% with specific CD8+ at 6 months compared to 100% CD4+ and 33.33% CD8+ specific response in controls at the same time point, ref. 3). After a booster dose, the percentage of CD4/CD8 positive DS individuals, their Th1 response and T-cell follicular helper populations

significantly improved compared to those evaluated 6 months after receiving the first two doses, a response which was comparable to that of non-DS donors.

Our study presents several limitations. Although we have been able to follow-up the same cohort of adults with DS since their vaccination, we have used different populations as controls over time. Because vaccine recommendations changed over time, a prolonged follow-up of healthy donors was not initially planned. However, this limitation only affects the comparison of non-DS results over time and does not weaken the conclusions about vaccine effectiveness in adults with DS.

In all, our present results show that, despite showing a relatively delayed T-cell response after vaccination, adults with DS showed a comparable response to that of non-DS donors after a booster dose, which was not the case 6 months after the initial 2-dose regime. It is our hope that these results may help overcome vaccination hesitancy in this population and further improve healthcare policy recommendations. Considering our findings, a standard, three dose SARS-CoV-2 vaccine schedule should be established for adults with DS.

AUTHOR CONTRIBUTIONS

Project coordination, original idea: AA, AGC, DRA. Subject recruitment and follow-up: GM, DRA. Database compilation: GM, AYC, LEP. Sample processing, collection preservation/storage: GM, AYC, LEP. Serological assays: AGC, AYC. Cellular immunity assays: LEP, AA. Statistical analysis: AGC, AA, DRA. Results evaluation, manuscript drafting and publication: All.

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CONFLICT OF INTERESTS STATEMENT: The authors have no conflicts of interest to disclose

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FIGURE LEGENDS

Figure 1. Immune response in Down syndrome patients after a third dose of SARS-CoV-2 vaccine. A., Pie charts indicate the percentages of SARS-CoV-2-specific CD4+ and CD8+ lymphocytes in non-DS and DS donors after third dose administration. **B.,** *Upper panels*, graphics show the percentage (mean+SD) of Th1 (*left*) and Th2 (*right*) CD4+ subsets in non-DS and DS donors. *Lower panels*, the percentage (mean+SD) of Th1 (*left*) and Th2 (*right*) CD4+ subsets in non-DS and DS donors under and over 40 years is shown. **C.,** Percentage of circulating CD4+CXCR5+ Tfh cells in non-DS and DS individuals. **D.,** *Left,* specific anti-SARS-CoV-2 S IgG titers (BAU/ml) in non-DS and DS donors; *right*, specific anti-SARS-CoV-2 S IgG titers (BAU/ml) in non-DS and DS < 40 and > 40 years. *p<0.01; ns, non-significant.

Figure 1