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Letter to the Editor

# Factor associated with SARS-CoV-2 vaccination serological efficacy in adolescents and adults with Down syndrome: Data from an international, collaborative initiative of the Trisomy 21 Research Society

*Dear Editor,*

Individuals with Down syndrome (DS) have been prioritized for vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in many Western countries due to their higher risk for hospitalization and mortality following infection.[1] In this sense, this population has been frequently compared to other immunocompromised patients, as recently reviewed by Marra et al. in this journal.[2] Disputing this evidence, Real de Asua et al. recently published in this journal how, despite an initially delayed T-cell response to vaccination, adults with DS showed a comparable cellular and humoral immune response to that of non-DS donors after three vaccine doses.[3] However, due to small sample size, this and other prior studies have had limited ability to analyze which factors could influence the serological efficacy of COVID-19 vaccines in this population.[4,5] Since the worse prognosis of individuals with DS and SARS-CoV-2 infection has been attributed to a higher prevalence of comorbidities and to a congenital immune dysregulation which could impair the generation of a protective immunity after vaccination,[6,7] understanding which factors affect their immune response is essential. Thus, we performed an analysis on a pooled multicenter cohort of vaccinated individuals with DS to evaluate whether and which comorbidities commonly associated with DS determined serological efficacy 6 months after 2 doses of COVID-19 vaccines. The description of the study population, determination of SARS-CoV-2 specific IgG, ethical considerations and statistical analysis are detailed in Supplementary materials.

We present data from 126 subjects with DS (mean age 36.1 ± 15.0 years, range 12–63 years, 68% male) followed at three European centers for DS (Table 1). The age distribution was similar among the centers with the exception of the Bambino Gesù Children's Hospital, which enrolled a younger cohort. Almost all subjects received two doses of BNT162b2, with the exception of 3 individuals (2.4%) who were vaccinated with mRNA-1273. Thirteen patients (10.3%) were known to have contracted COVID-19 before receiving vaccination. The distribution of comorbidities commonly associated with immunological dysregulation or poor COVID-19-related clinical outcomes was uneven across study sites. Of relevance, the distribution of inflammatory skin disorders, congenital heart diseases, differed significantly among sites (Table 1), the latter being present only in the two adult cohorts. To determine whether any of these comorbidities influenced serological efficacy 6 months after vaccination, and adjusting for potential confounders, a multiple linear regression was fitted including age, sex, and several clinical diagnoses (See *Statistical analysis* in Supplementary materials for details). In this model, age was the only variable significantly associated with vaccine efficacy, with older subjects presenting significantly lower antibody titers at V2 (correlation coefficient: −0.049 C.I. [−0.064 to −0.034], Supl. Fig. 1A and B). Importantly, this age-dependent trend was observed even among the cohort of adolescents with DS (Supl. Fig. 1B). On the other hand, no single, specific comorbidity was significantly associated with antibody response at V2 (Fig. 1 and Supl. Fig. 2).

This study included a wide cohort of adolescents and adults with DS, whose humoral response was measured 6 months after receiving two doses of mRNA-derived COVID-19 vaccines. Although many individuals presented a varied array of clinical comorbidities, ranging from congenital heart diseases to autoimmune disorders, none of these were associated with decreased serological efficacy. Indeed, age was the sole determinant of vaccine efficacy in this population.

Factors modifying immune response to vaccination in DS have been little explored. In a study by Valentini et al., no clinical comorbidity was linked to a lessened response to influenza vaccination in children with DS.[8] Similar results have been observed in adults with DS after influenza vaccination (Real de Asua et al., unpublished data). Present results are nonetheless highly relevant and reassuring for many individuals with DS and their families. The observed lack of impact in serological efficacy of many relevant and frequent conditions observed in DS, such as congenital heart disease, autoimmune disorders, epilepsy, or dementia, coupled with the prior results of Valentini et al., Sali et al., and Real de Asua et al. in this journal, can hopefully further the confidence about the effectiveness of these vaccines, regardless of potential coexisting comorbidities.

Our goal is not only to support and relieve patients and families, but also to help overcome vaccination hesitancy in this population and further improve current healthcare policies. Indeed, given the strong association observed between age and antibody titer decline throughout the age spectrum, and particularly in adults over 40, we believe our results lend further support to the present recommendation to administer consecutive vaccine doses in this age group.

Several aspects of our work warrant consideration. Though this is the largest sample to date of vaccinated individuals with DS, our sample size might have still been underpowered to detect the influence of specific comorbidities on serological efficacy. However, the width of all confidence intervals in the regression analysis was so broad that it seems unlikely that our conclusions may have changed with a bigger sample. Secondly, a longer follow-up of the study obstructive sleep apnea and Alzheimer's disease related-dementia

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**Table 1**
Clinical characteristics of the study sample by center.

| | Total | HULP | FPG | OPBG | *p* |
|---|---|---|---|---|---|
| | n = 126 | n = 48 | n = 41 | n = 37 | |
| Age | 36.1 (15.0) | 45.2 (10.8) | 41.7 (10.9) | 18.1 (4.7) | < 0.001 |
| Males | 68 (54%) | 22 (45.8%) | 23 (56.1%) | 23 (62.2%) | 0.308 |
| *Living situation* | | | | | < 0.001 |
| Family home | 100 (79.4%) | 36 (75%) | 27 (65.9%) | 37 (100%) | |
| Supervised group home | 15 (11.9%) | 1 (2.1%) | 14 (34.1%) | 0 (0%) | |
| Institutionalized | 11 (8.7%) | 11 (22.9%) | 0 (0%) | 0 (0%) | |
| *Degree of intellectual disability* | | | | | 0.002 |
| Mild | 63 (50%) | 34 (70.8%) | 18 (43.9%) | 11 (29.7%) | |
| Moderate | 37 (29.4%) | 12 (25%) | 11 (26.8%) | 14 (37.8%) | |
| Severe | 19 (15.1%) | 2 (4.2%) | 12 (29.3%) | 5 (13.5%) | |
| *NA* | 7 (5.6%) | 0 (0%) | 0 (0%) | 7 (18.9%) | |
| *Comorbidities* | | | | | |
| Skin Conditions | 42 (33.3%) | 30 (62.5%) | 12 (29.3%) | 0 (0%) | < 0.001 |
| Hypothyroidism | 66 (52.4%) | 27 (56.2%) | 19 (46.3%) | 20 (54.1%) | 0.628 |
| Gastrointestinal Disorders | 30 (23.8%) | 18 (37.5%) | 4 (9.8%) | 8 (21.6%) | 0.009 |
| Obesity | 32 (25.4%) | 16 (33.3%) | 7 (17.1%) | 9 (24.3%) | 0.21 |
| Diabetes | 3 (2.4%) | 1 (2.1%) | 2 (4.9%) | 0 (0%) | 0.364 |
| Obstructive Sleep Apnea | 33 (26.2%) | 16 (33.3%) | 2 (4.9%) | 15 (40.5%) | < 0.001 |
| Congenital Heart Disease | 46 (36.5%) | 8 (16.7%) | 17 (41.5%) | 21 (56.8%) | < 0.001 |
| Alzheimer Disease | 18 (14.3%) | 10 (20.8%) | 8 (19.5%) | 0 (0%) | 0.013 |
| Epilepsy | 4 (3.2%) | 3 (6.2%) | 1 (2.4%) | 0 (0%) | 0.251 |
| *Vaccine type* | | | | | 0.152 |
| BNT162b2 Comirnaty®, Pfizer/BioNTech | 122 (96.8%) | 44 (91.7%) | 41 (100%) | 37 (100%) | |
| mRNA-1273 Spikevax®, Moderna | 3 (2.4%) | 3 (6.2%) | 0 (0%) | 0 (0%) | |
| Vaxzevria®, Oxford/Astra Zeneca | 1 (0.8%) | 1 (2.1%) | 0 (0%) | 0 (0%) | |
| Diagnosis of COVID-19 before vaccination | 13 (10.3%) | 11 (22.9%) | 0 (0%) | 2 (5.4%) | < 0.001 |
| *Antibody titers (BAU/mL) (geometric means)* | | | | | |
| V1–1–3 months after 1st dose | 6.5 (1.4) | 6.2 (1.6) | 6.8 (1.1) | | 0.07 |
| V2–6 months after 2nd dose | 5.6 (1.4) | 5.0 (1.6) | 5.0 (0.9) | 6.8 (0.7) | < 0.001 |

Categorical data are described as frequencies (percentages).
Quantitative variables, as mean (SD).
Antibody titers are presented after logarithmic transformation as geometric mean and standard deviation factor.
HULP – Hospital Universitario La Princesa, Madrid, Spain.
FPG – Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy.
OPBG – Ospedale Pediatrico Bambino Gesù IRCCS, Rome, Italy.

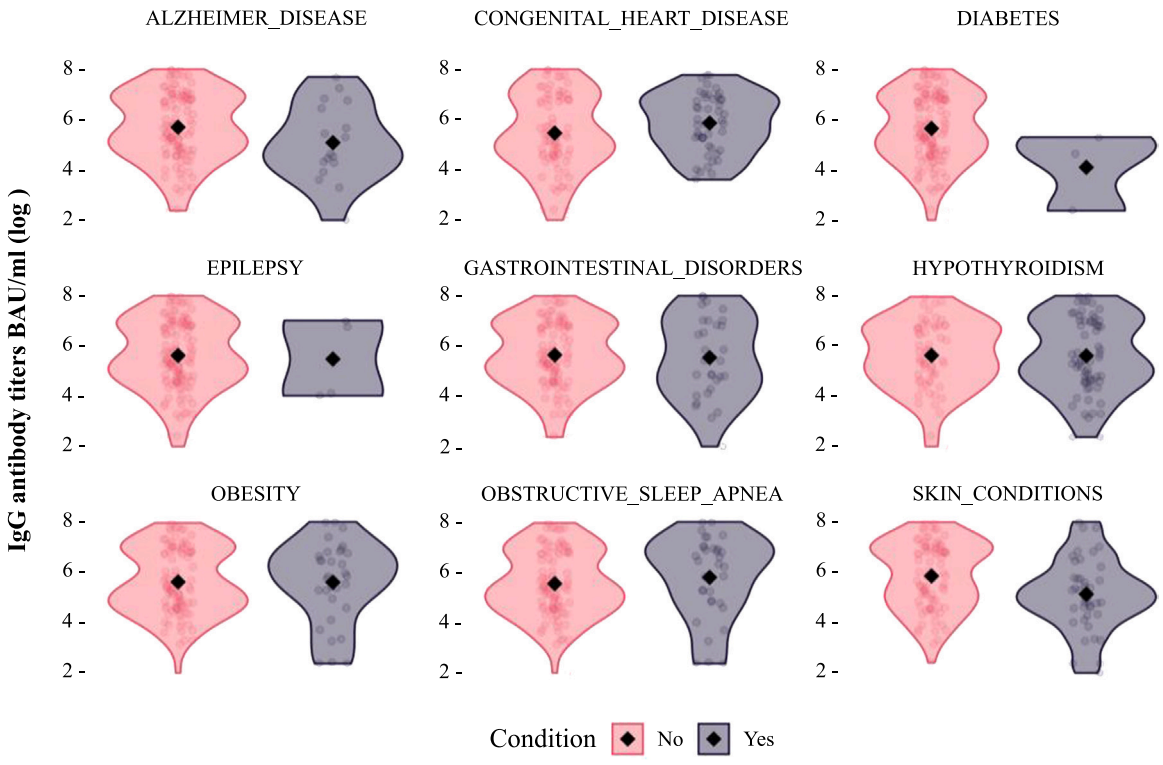


**Fig. 1.** Antibody titers in subjects with Down syndrome and controls stratified by clinical comorbidities. Violin plots of antibody titers by condition. Inside each violin plot, the geometric mean is depicted as a point.

subjects could have been desirable, but this was only available in one of the participating centers. Their results after a third vaccine dose have already been communicated in this *Journal*.[3]

In sum, in a wide cohort of individuals with DS spanning through all the age spectrum, age was the only variable linked to COVID-19 IgG antibody titers 6 months after vaccination. No other clinical comorbidity influenced vaccine efficacy in this population.

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## Conflict of interest statement

The authors have no conflict of interest to report.

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## Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2023.02.021.

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