Clinical Infectious Diseases

MAJOR ARTICLE

Development of an Effective Immune Response in Adults With Down Syndrome After Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Vaccination

Laura Esparcia-Pinedo,[1,a] Ayla Yarci-Carrión,[2,a] Gloria Mateo-Jiménez,[3] Noelia Ropero,[1] Laura Gómez-Cabañas,[4] Ángel Lancho-Sánchez,[4] Patricia Almendro-Vázquez,[5] Enrique Martín-Gayo,[1,6] Estela Paz-Artal,[5] Francisco Sanchez-Madrid,[1,6] Fernando Moldenhauer,[7] Ainhoa Gutiérrez-Cobos,[2,a] Diego Real de Asúa,[6,7,a] and Arantzazu Alfranca[1,6,a]

[1]Immunology Department, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa, Madrid, Spain; [2]Microbiology Department, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa, Madrid, Spain; [3]Fundación de Investigación Biomédica del Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa, Madrid, Spain; [4]Biobanco, Fundación de Investigación del Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa, Madrid, Spain; [5]Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), Madrid, Spain; [6]Department of Medicine, School of Medicine, Universidad Autónoma de Madrid, Madrid, Spain; and [7]Internal Medicine Department, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa, Madrid, Spain

Background. Immune dysregulation in individuals with Down syndrome (DS) leads to an increased risk for hospitalization and death due to coronavirus disease 2019 (COVID-19) and may impair the generation of protective immunity after vaccine administration.

Methods. The cellular and humoral responses of 55 individuals with DS who received a complete SARS-CoV-2 vaccination regime at 1 to 3 (visit [V 1]) and 6 (V2) months were characterized.

Results. SARS-CoV-2–reactive CD4+ and CD8+ T lymphocytes with a predominant Th1 phenotype were observed at V1 and increased at V2. Likewise, an increase in SARS-CoV-2–specific circulating Tfh (cTfh) cells and CD8+ CXCR5+ PD-1hi lymphocytes was already observed at V1 after vaccine administration. Specific immunoglobulin G (IgG) antibodies against SARS-CoV-2 S protein were detected in 96% and 98% of subjects at V1 and V2, respectively, although IgG titers decreased significantly between both time points.

Conclusions. Our findings show that DS individuals develop an effective immune response to usual regimes of SARS-CoV-2 vaccination.

Keywords. Down syndrome; COVID-19; SARS-CoV-2; vaccination; immune system.

The new coronavirus disease 2019 (COVID-19) has been a global health emergency since March 2020. Although COVID-19 entails no or mild symptoms in most individuals, several patient subgroups develop a severe form of the disease, leading to acute respiratory distress syndrome (ARDS) [1, 2]. Individuals with Down syndrome (DS), are particularly vulnerable to the disease, with a 4-fold increased risk for COVID-19–related hospitalization and a 3- to 10-fold increased risk for COVID-19–related mortality [3–5].

Although this increase can be partially attributed to a higher prevalence of comorbidities associated with a poorer COVID-19–related prognosis, such as obesity, congenital heart disease, or respiratory diseases [6, 7], the susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can be further explained by immune dysregulation. Patients with DS show higher levels of interferon (IFN)-stimulated genes, which explains their higher basal levels of IFN-α signaling and hypersensitivity to IFN stimulation [8]. Indeed, 4 subunits of IFN receptors are encoded on HSA21 (IFNAR1, IFNAR2, IFNGR2, and IL10RB), and an increase in IFNAR1 and IFNAR2 expression in different cell types from DS donors has been described [9]. Furthermore, the increased expression of transmembrane serine protease 2 (TMPRSS2), which primes the viral S protein for entry into host cells and is also encoded in HSA21, may facilitate the infection of target cells by SARS-CoV-2, whereas nod-like receptor family pyrin domain containing 3 (NLRP3) downregulation and increased interleukin (IL)-10 production could be involved in the higher risk of bacterial infectious complications in these patients [10, 11]. Individuals with DS have high basal levels of proinflammatory cytokines such as IL-2, IL-6, or tumor necrosis factor α (TNF-α), which may enhance the "cytokine storm" that underlies ARDS [11]. Although the overall effect of these alterations provides some proof for the worse outcomes following

Received 17 March 2022; editorial decision 08 July 2022; published online 23 July 2022

[a]L. E.-P., A. Y.-C., A. G.-C., D. R. d. A., and A. A. contributed equally to this manuscript.

Correspondence: A. Alfranca, Immunology Department, Hospital Universitario de La Princesa, Dieo de León 62, 28006 Madrid, Spain (mariaaranzazu.alfranca@salud.madrid.org).

Clinical Infectious Diseases®

https://doi.org/10.1093/cid/ciac590

SARS-CoV-2 infection, the net balance between all of these interplaying factors is far from clear.

This immune dysregulation may also impair the generation of protective immunity after vaccine administration in individuals. In fact, although people with DS usually develop protective antibody responses after vaccination, overall antibody levels tend to be lower and decline faster than in individuals without DS [12]. Due to their excess mortality risk and these concerns over vaccine protection, most countries have included adults with DS, especially those over 40 years, in prioritized vaccination groups [13–15]. However, data on the immune response elicited by SARS-CoV-2 vaccines in the DS population are lacking, and the degree of protection achieved is unknown. A thorough characterization of the humoral and cellular immunity mechanisms underlying the response of individuals with DS to COVID-19 vaccines is needed to appropriately tailor future vaccination campaigns for this population. Moreover, this knowledge may also shed light onto general immune mechanisms involved in the response to SARS-CoV-2, and in the development of postvaccination responses.

METHODS

Details on the study population, determination of specific immunoglobulin G (IgG) antibodies, analysis of T-cell response, and statistical analysis are provided in the Supplementary Methods.

Ethical Considerations

This project was approved by the Institutional Review Board (IRB) at La Princesa University Hospital (register number: 4386), meets international standards of data protection, and is in line with practice guidelines established in the Declaration of Helsinki.

RESULTS

T-Cell Response to SARS-CoV-2 Vaccination in Down Syndrome Donors

To assess immune response to SARS-CoV-2 vaccine in DS, we recruited 55 DS, 50 non-DS A, and 39 non-DS B donors, whose demographic and clinical characteristics are shown in Table 1. They were inoculated with 2 doses of a SARS-CoV-2 vaccine following the recommended schedule (Table 1), and both T-cell and antibody responses were analyzed before vaccine administration (V0) and 1–3 months (V1) and 6 months (V2) after the second vaccination. Fifty-one subjects with DS (93%), 50 non-DS A (100%), and 39 non-DS B (100%) donors were enrolled after having received at least 1 vaccination dose. To avoid any delay in official vaccination strategies, we admitted the use of biobank-stored samples (from earlier than February 2020) as baseline (V0) in 44 subjects with DS, 48 controls from non-DS cohort A, and none from cohort B. COVID-19 infection prior to vaccination occurred in 15 individuals with DS (27%), 2 non-DS individuals from cohort A (4%), and none from cohort B. Ten subjects with DS were living in the community when they acquired COVID-19 infection; the rest were institutionalized. Thirteen of these subjects had a biobank-stored sample

Table 1. Demographic and Clinical Characteristics of the Study Sample

		Controls	
	Down Syndrome (n = 55)	Cellular Immunity (A) (n = 50)	Controls Humoral Immunity (B) (n = 39)
Age, y	44 ± 10	44 ± 13	
(*P* = .8414)	44 ± 14		
(*P* = .3520)			
Sex (male)	25 (44%)	25 (50%)	9 (21%)
Living situation		N/A	
Family home	31 (55%)		
Supervised group home	1 (2%)		
Institutionalized	11 (20%)		
Degree of intellectual disability		N/A	
Mild	45 (80%)		
Moderate	9 (16%)		
Severe	2 (4%)		
Comorbidities[a]			
Skin conditions	36 (64%)	…	…
Hypothyroidism	29 (51%)	…	4 (10%)
Gastrointestinal disorders	21 (37.5%)	…	…
Obstructive sleep apnea	19 (34%)	…	…
Congenital heart disease	10 (18%)	…	…
Alzheimer disease	11 (20%)	…	…
Epilepsy	2 (4%)	…	…
Allergy	…	…	3 (7.6%)
HT	…	1 (2%)	2 (5%)
Obesity	…	1 (2%)	…
Diabetes mellitus	…	1 (2%)	…
Multiple sclerosis	…	…	1 (2.56%)
Glaucoma	…	…	1 (2.56%)
Vaccine type			
BNT162b2 (Comirnaty, Pfizer/BioNTech)	48 (86%)	50 (100%)	39 (100%)
mRNA-1273 (Spikevax, Moderna)	7 (12.5%)	…	…
ChAdOx1 (Vaxzevria, Oxford/AstraZeneca)	1 (1.5%)	…	…
Adverse reactions[b]		N/A	
To first vaccine dose	6 (11%)		
To second vaccine dose	6 (11%)		
Vaccinated in the past 12 mo[c]	10 (18%)	…	

Data are presented as n (%) unless otherwise indicated. Abbreviations: HT, hypertension; N/A, non-applicable; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Only comorbidities that have been linked to a worse prognosis of SARS-CoV-2 infection or to immune dysregulation are presented.

[b]Noted adverse reactions were all mild (involving either local pain, fever, or malaise, lasting <24 hours).

[c]Other than vaccination against SARS-CoV-2 (ie, influenza or pneumococcal vaccination).

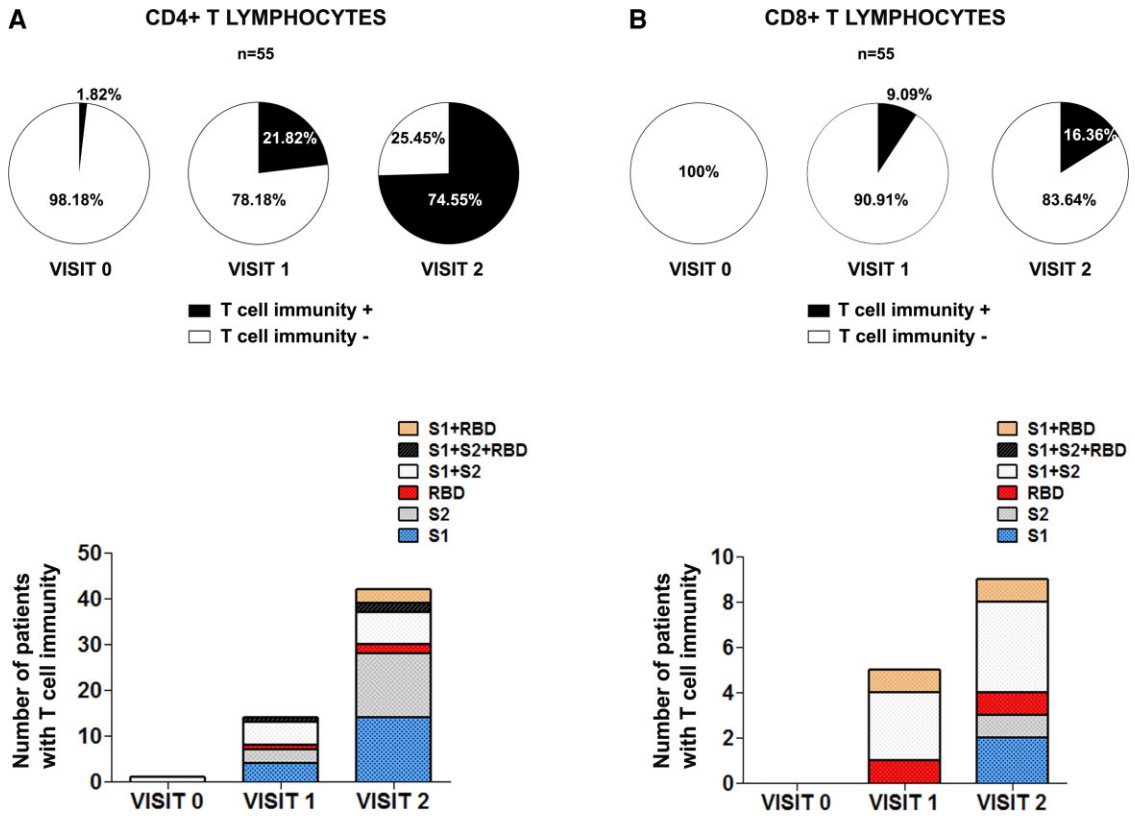

Figure 1. T-cell response in patients with DS after SARS-CoV-2 vaccination. SARS-CoV-2–specific CD4+ (*A*) and CD8+ (*B*) lymphocytes in patients with DS at visit 0, visit 1, and visit 2. *Upper panels*: pie charts indicate the percentage of patients with or without T-cell immunity against SARS-CoV-2 at each visit. *Lower panels*: number of patients with T-cell response against specific peptide pools at each visit. Abbreviations: DS, Down syndrome; RBD, receptor binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

extracted prior to February 2020 as the baseline determination. Median (interquartile range) time from the last dose of the recommended vaccination schedule to the first blood extraction (V1) was 62 (42–70) days for DS donors, 75 (43–84) days for non-DS A donors, and 98 (84–100) days for non-DS B donors. In the case of V2, median times were 159 days (150–172) for DS donors, 182 (173–190) for non-DS A donors, and 174 (161–183) for non-DS B donors.

To assess the percentage of responsive T cells, we used an activation-induced marker assay based on the detection of CD4+ OX40/CD137 double-positive and CD8+ CD69/CD137 double-positive cells after 24 hours in the presence of peptide pools from SARS-CoV-2 (NCAP, S1, S2, RBD domain, VME1, and Mpro proteins for V0 and S1, S2, and RBD domain for V1 and V2). We included a human actin-derived peptide pool as a negative control, and Staphylococcal enterotoxin B (SEB) as a positive control.

As shown in Figure 1 and Supplementary Table 1*A*, we found a predominant CD4+ response in DS donors (73.21% patients with specific CD4+ and 16.36% patients with specific CD8+ at V2), which was similar to that observed in non-DS individuals (100% with CD4+ and 33.33% with CD8+ specific response at the same time point) (Supplementary Table 1*B* and Supplementary Figure 2*A*). Of note, CD4+ activation against S1 and S2 was observed in 1 DS and 4 non-DS prepandemic samples from V0 (Figure 1*A* and Supplementary Figure 2*A*). We did not detect SARS-CoV-2–specific CD8+ lymphocytes in this baseline visit in any cohort (Figure 1*B* and Supplementary Figure 2*A*).

After vaccination, the percentage of individuals with DS with SARS-CoV-2–responsive T lymphocytes increased from 23.8% at V1 to 73.21% at V2 for CD4+, and from 8.93% at V1 to 16.36% at V2 for CD8+. We detected vaccine-elicited specific CD4+ and CD8+ directed against S1, S2, and RBD, with a similar pattern at V1 and V2 (Figure 1*A* and 1*B* and Supplementary Table 1*A*). Neither the existence of a previous SARS-CoV-2 infection in DS nor the recruitment date modified cellular immune responses to vaccination (Supplementary Figure 3*A* and 3*B*). Of note, all non-DS donors showed a specific CD4+ response at V1, while the percentage of specific CD8+ lymphocytes increased from 10% at V1 to 33.33% at V2 (Supplementary Table 1*B* and Supplementary Figure 2*A*).

SARS-CoV-2 mRNA vaccines promote a T-helper (Th) 1 (Th1) reaction in the general population [16]. Individuals

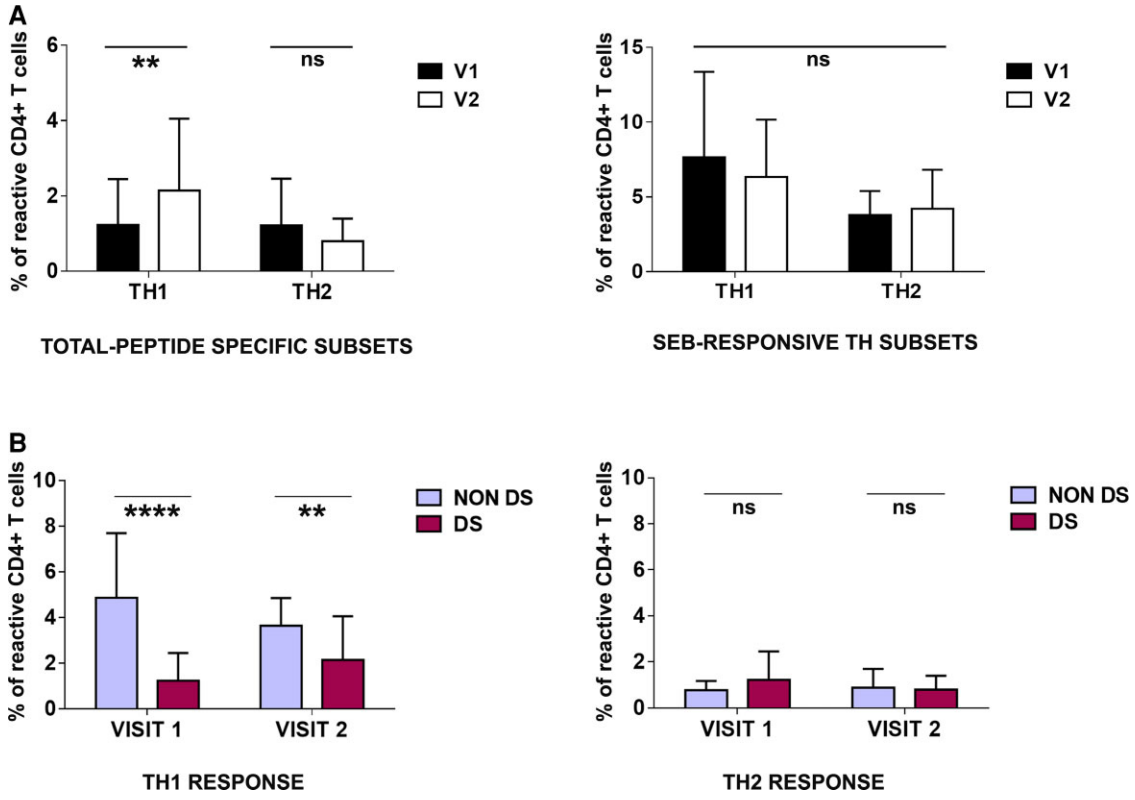

Figure 2. T-helper subsets in patients with DS after SARS-CoV-2 vaccination. *A* (*Left*), percentage of SARS-CoV-2–specific Th1 and Th2 CD4+ lymphocytes at visits 1 (V1) and 2 (V2); (*right*) percentage of SEB-activated Th1 and Th2 CD4+ cells at V1 and V2. *B*, Graphics show the percentage of Th1 (*left*) and Th2 (*right*) CD4+ subsets in non-DS and DS donors at visits 1 and 2. Mean + SD values are shown. $^{**}P < .01$; $^{****}P < .0001$. Abbreviations: DS, Down syndrome; ns, nonsignificant; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SEB, Staphylococcal enterotoxin B; SD, standard deviation; Th/TH, T-helper.

with DS present a higher Th1:Th2 ratio than euploid donors, a finding related to an increase in baseline IFN-γ levels [17]. We evaluated T-helper populations in SARS-CoV-2–specific CD4+ lymphocytes in DS donors, and found comparable percentages of Th1 and Th2 in V1. However, a significant increase in Th1 but not Th2 could be observed at V2 ($P < .01$). As a specificity control, we determined Th1 and Th2 distribution in SEB-stimulated CD4+ cells and found no significant differences between both subsets at either V1 or V2 (Figure 2*A*). A similar pattern was detected regardless of the peptide pool (S1 or S2) analyzed (Supplementary Figure 4*A*). The percentage of Th1-reactive CD4+ cells was significantly higher in non-DS individuals than in DS donors both at V1 and V2, whereas we found no significant differences in Th2 response at either visit (Figure 2*B*). In addition, there were no gender differences in Th1 and Th2 behavior, except for a significantly higher Th2 response at V1 in male DS donors (Supplementary Figure 4*B*). Notably, although a Th1 increase at V2 could be observed in all individuals with DS, it was higher in individuals aged 40 years and younger (Supplementary Figure 4*C*).

T-follicular helper cells (Tfh) constitute a specialized subset of CD4+ T cells that collaborates in the generation of high-affinity antibodies. In vaccinated DS donors, we found a SARS-CoV-2–specific circulating Tfh (cTfh) population with sustained levels between V1 and V2 (Figure 3*A*). We detected similar percentages of cTfh in non-DS donors at both V1 and V2 (Figure 3*B*). PD-1hi cTfh cells represent a subset of recently activated cTfh cells [18]. Accordingly, we detected SARS-CoV-2–specific CD4+ CXCR5+ PD-1hi cells at V1 in DS donors, whose levels were slightly reduced at V2 (Figure 3*A*). Likewise, in non-DS individuals we found a CD4+ CXCR5+ PD-1hi population whose levels at V2 were significantly higher than those of individuals with DS (Figure 3*B*).

A population of CD8+ CXCR5+ PD-1hi cells with Tfh-like properties has been recently identified [19]. We therefore investigated the presence of SARS-CoV-2–specific CD8+ CXCR5+ PD-1hi cells in vaccinated patients with DS and found that these cells were detectable at V1, and their levels significantly increased at V2 ($P < .01$) (Figure 3*C*). Because of the reduced number of non-DS donors with SARS-CoV-2–specific CD8+ lymphocytes at V1 (Supplementary Figure 2*B*), we could not analyze the behavior of the CD8+ CXCR5+ PD-1hi population in this cohort. Hence, our results show that SARS-CoV-2 vaccination efficiently induces the differentiation of specific

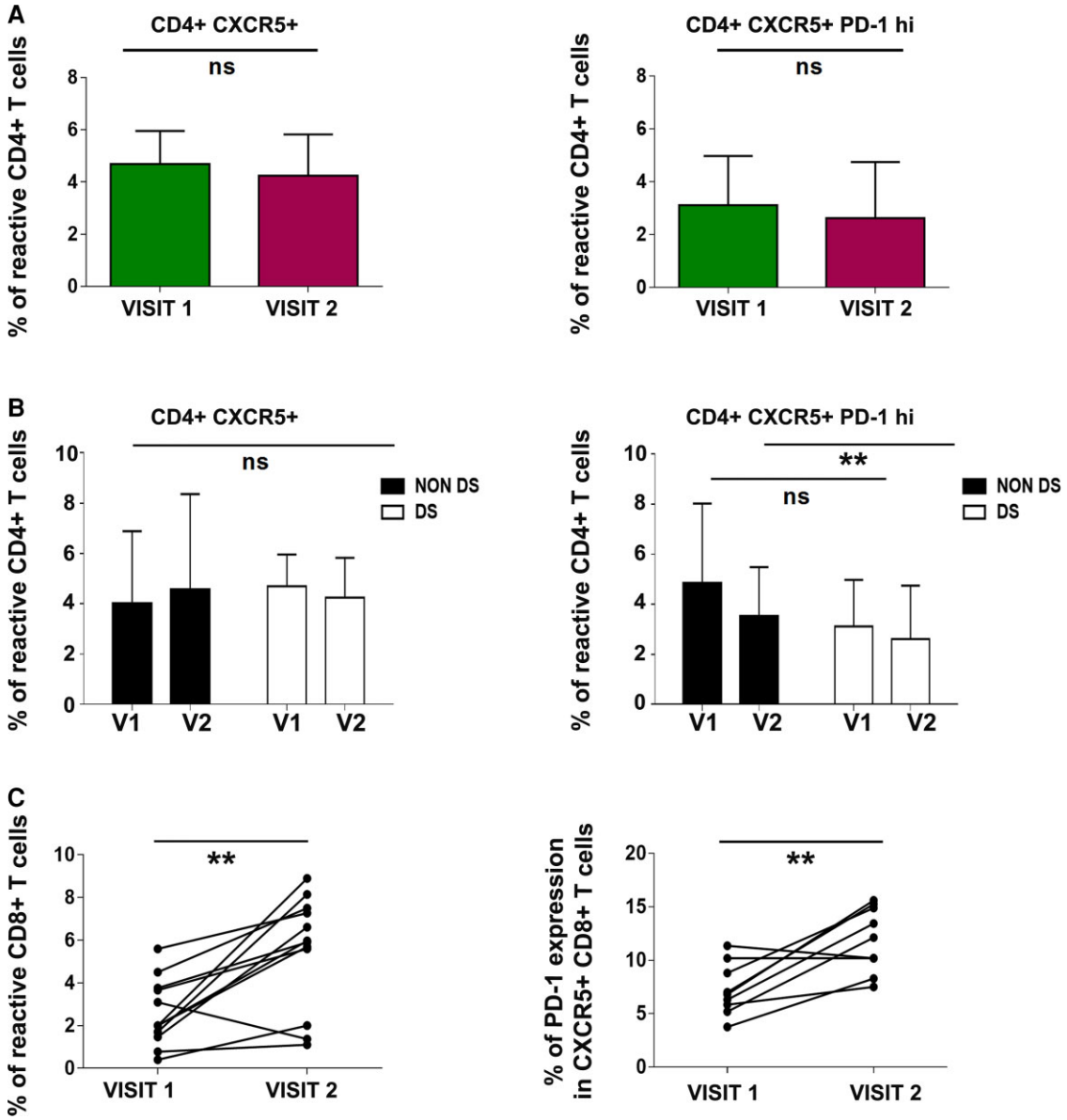

Figure 3. Circulating Tfh in patients with DS after SARS-CoV-2 vaccination. *A*, Graphics show the percentage of circulating CD4+ CXCR5+ (*left*) and CD4+ CXCR5+ PD-1hi (*right*) cells at visits 1 (V1) and 2 (V2). Mean + SD values are shown. *B*, Graphics show the percentage of CD4+ CXCR5+ (*left*) and CD4+ CXCR5+ PD-1high (PD-1hi) (*right*) cells at V1 and V2 in non-DS and DS donors. *C*, Graphics show the percentage of SARS-CoV-2–specific CD8+ CXCR5+ (*left*) and PD-1hi expression within the CD8+ CXCR5+ population (*right*) at V1 and V2 ($n = 11$). $^{**}P < .01$. Abbreviations: DS, Down syndrome; ns, nonsignificant; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; Tfh T-follicular helper cells.

populations in DS that may collaborate in an effective antibody response.

Humoral Response to SARS-CoV-2 Vaccination in Individuals With Down Syndrome

Individuals with DS exhibit alterations in B-lymphocyte maturation and function that may account for an impaired humoral response to vaccination. Therefore, we analyzed humoral response to SARS-CoV-2 vaccination in DS donors. No patients were positive for anti–SARS-CoV-2 IgG before vaccination; however, we found detectable titers of specific IgG in 96.4% of patients at V1 (median, 62 days). Two patients did not develop anti-S IgG antibodies at V1, one of whom showed detectable titers of IgG at V2 (median, 159 days). The percentage of positive donors was similar at V2, when detectable titers of specific IgG were observed in 98.1% of patients (2 patients with no data on humoral response at this time point) (Supplementary Figure 2*B* and Supplementary Table 2*A*). Likewise, in non-DS donors, we did not find humoral response in prepandemic samples. However, 97.4% of individuals showed detectable

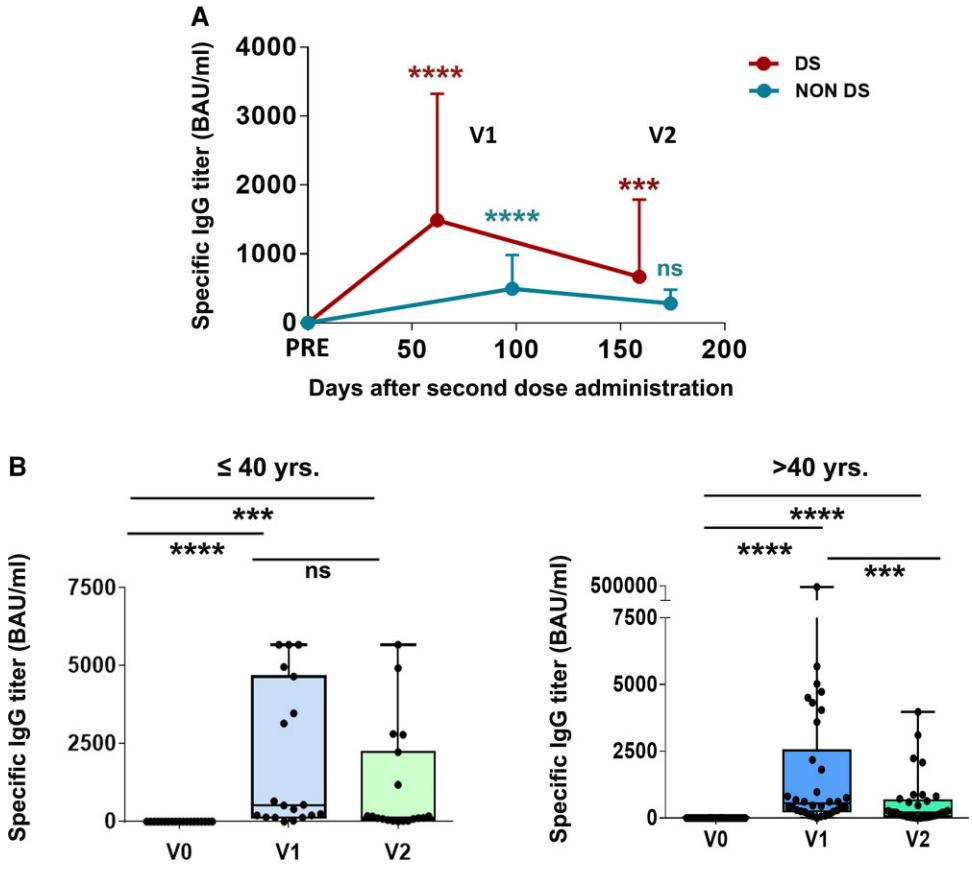

Figure 4. Humoral response in patients after SARS-CoV-2 vaccination. *A*, Specific anti–SARS-CoV-2 S IgG titers in patients with DS at visits 0 (PRE), 1 (V1), and 2 (V2), in DS and non-DS donors. Dots show median time for V1 and V2 in each cohort. *B*, Specific anti–SARS-CoV-2 S IgG titers at visits 0 (V0), 1 (V1), and 2 (V2) in patients with DS ≤40 years (*left*) or >40 years (*right*). ****$P < .0001$; ***$P < .001$. Abbreviations: BAU, binding antibody units; DS, Down syndrome; IgG, immunoglobulin G; ns, nonsignificant; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

antibody titers at V1 (median, 98 days), which reached 100% at V2 (median, 174 days) (Supplementary Table 2*B* and Supplementary Figure 2*B*).

A significant decrease in IgG titers was found in 92.6% of individuals with DS between both time points (Figure 4*A* and Supplementary Table 1*A*). Average specific IgG titers declined from 1520.84 binding antibody units (BAU)/mL at V1 to 780.88 BAU/mL at V2. This decrease was statistically significant in individuals older than 40 years but not in those younger than 40 years of age (Figure 4*B*). In addition, we did not find significant differences in specific IgG titers between genders in these patients (Supplementary Figure 4*D*). Similar to T-cell responses, IgG titers were analogous in COVID-19–convalescent and non-convalescent DS donors, and did not vary with the date of admission in the study (Supplementary Figure 3C). In non-DS individuals, we found an average IgG titer of 483.2 BAU/mL at V1, which decreased to 282.7 BAU/mL at V2. Our data indicate that individuals with DS develop a detectable humoral response after SARS-CoV-2 vaccination, comparable to that of healthy donors.

DISCUSSION

In the present study we investigated the immune response to SARS-CoV-2 vaccination in adults with DS. Our results provide evidence of the presence of SARS-CoV-2–reactive CD4+ and CD8+ T lymphocytes with a predominant Th1 phenotype at V1, which increases at V2. A sustained increase in SARS-CoV-2–specific cTfh cells was observed in these individuals 1–3 months after vaccine administration. Specific IgG antibodies against the SARS-CoV-2 S protein were detected at V1, but significantly decreased at V2.

We observed S1- and S2-responsive CD4+ cells in a single individual with DS at V0 (Figure 1*A*). Conversely, SARS-CoV-2 S-specific CD4+ lymphocytes have been frequently detected in healthy non-DS donors, and their presence is explained by a possible cross-reaction with pathogens that contain SARS-CoV-2 homologous sequences [20]. In addition, unlike in our DS donors, NCAP-specific CD4+ T cells have also been identified in healthy non-DS individuals [21], a finding that has been attributed to former exposure to SARS-CoV-2 [22]. Because most V0 samples in our study were collected

before the beginning of the pandemic, previous asymptomatic contact with SARS-CoV-2 can be reliably excluded. After vaccination, we detected CD4+-specific activation in a reduced percentage of individuals with DS at V1 (21.86%), which reached frequencies similar to non-DS donors at V2 (74.55%) (Figure 1 and Supplementary Figure 2*A*). Thus, CD4+ cell responses to SARS-CoV-2 vaccination seem to be delayed in comparison to non-DS donors, which usually reach a higher percentage of individuals with specific T-cell immunity within 4–7 weeks post–SARS-CoV-2 vaccination (Supplementary Figure 2*A* and reference [23]).

The Tfh-like CD8+ CXCR5+ PD-1hi subset has been recently reported to increase in acute immunization settings and collaborate in specific antibody response [24]. An increase in this population was found after SARS-CoV-2 vaccination in individuals with DS (Figure 3*B*), suggesting that this cell subset could also cooperate in antibody generation after vaccine administration, although the actual functional significance of this population remains to be determined.

A reduced frequency of switched memory B cells specific to vaccine antigens has been described in DS [25]. However, the degree of humoral response in individuals with DS is highly variable among different vaccines. Thus, influenza A/H1N1, pneumococcal capsular polysaccharide, or hepatitis B virus vaccination induce a partial antibody response [26, 27], while conjugated pneumococcal or hepatitis A virus vaccines elicit adequate antibody titers. We detected specific IgG antibodies against SARS-CoV-2 S in 96% and 98% of subjects at V1 and V2, respectively (Figure 4*A*), indicating that an effective humoral response was indeed elicited by SARS-CoV-2 vaccination in DS. These findings are in accordance with a recent report, which shows a proper antibody response in individuals with DS that declines over time with a rate similar to that of non-DS donors (reference [28] and Figure 4). Our results show an uncoupled humoral and cellular response in these patients, with antibody titers peaking already at V1 (Figure 4*A*), whereas CD4+ T-cell activation peaks at V2 (Figure 1). A dissociation between both arms of adaptive immunity has been described in euploid individuals infected with SARS-CoV-2, and the development of an overt antibody response is not always accompanied by detectable T-cell–specific activation [29, 30]. This phenomenon has been attributed, among other causes, to higher levels of IP-10, PD-1 expression, or an increased presence of apoptotic T lymphocytes [31]. It is possible that an increase in the production of IP-10 due to the intrinsic activation of the IFN pathway, or in the expression of lymphocyte PD-1 [32], could participate in the uncoupling of humoral and cellular responses to SARS-CoV-2 vaccine in DS.

These findings show that an immune adaptive response is achieved in individuals with DS 3 months after SARS-CoV-2 vaccination lasting, at least, up to 6 months after vaccination. The degree of protection conveyed by these vaccination-elicited immunological changes should nonetheless be carefully interpreted. Recent reports still show an increased hazard ratio for COVID-19 hospital admission (2.55-fold increase) and mortality rate (12.7-fold increase) in patients with DS, despite vaccination with 1 or 2 doses of either ChAdOx1 nCoV-19 (AstraZeneca) or BNT162b2 (Pfizer/BioNTech) [33]. It is likely that other mechanisms beyond viral infection, and probably related to the intrinsic proinflammatory status present in patients with DS, operate to lead to a worse outcome even in vaccinated individuals. Our findings support the generalization of current recommendations to promote booster doses in the DS population. Moreover, because we observed a more robust response to vaccination in individuals with DS younger than 40 years, we believe our results lend further support to the recommendation of prioritizing the administration of an additional vaccine booster dose preferably in adults with DS over 40 years.

Our study presents several additional limitations. It could be argued that the higher rates of institutionalization might have increased the COVID-19 exposure risk prior to vaccination. However, only a minority of prior COVID-19 infections were documented among institutionalized individuals in our sample. To further control for COVID-19 exposure prior to vaccination, an ideal control group would have included individuals with non–trisomy 21 intellectual disabilities. However, this would have been an extremely difficult population to recruit. Likewise, we acknowledge that the potential (deleterious) role played by certain comorbidities, such as obesity or cardiac disease, has not been explored. However, this does not weaken the robustness of our conclusion, that individuals with DS elicit good immune responses to COVID-19 vaccines despite their increased-risk phenotype.

Yet unexplored but interesting issues are whether and how long vaccine-elicited responses persist over time in these individuals. We are currently collecting samples to assess the evolution of humoral end cellular immunity up to 12 months after vaccination. Meanwhile, individuals with DS older than 40 years are already being administered a third dose of mRNA SARS-CoV-2 vaccine in Spain at the time of this publication. Analyzing the impact of this additional booster dose in their immune response will also be of great interest.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. Project coordination, original idea: A. A., A. G.-C., and D. R. d. A. Subject recruitment and follow-up: F. M. and D. R. d. A. Database compilation: G. M.-J., A. Y.-C., and L. E.-P. Sample processing, collection preservation/storage: G. M.-J., A. Y.-C., L. E.-P., N. R., and A. L.-S. Serological assays: A. G.-C. and A. Y.-C. Cellular

immunity assays: A. L.-S., L. E.-P., and N. R. Statistical analysis: A. G.-C., A. A., and D. R. d. A. Results evaluation, manuscript drafting and publication: all authors.

Financial support. This work was supported by grants to A. A. from the Fondo de Investigación Sanitaria del Instituto de Salud Carlos III, co-funded by the Fondo Europeo de Desarrollo Regional (FEDER) (FIS PI19/00549), and Sociedad Cooperativa de Viviendas Buen Suceso, S. Coop. Mad; to A. A. and F. S.-M. from the Fondo de Investigación Sanitaria del Instituto de Salud Carlos III, co-funded by the Fondo Europeo de Desarrollo Regional (FEDER) (CIBER Cardiovascular); to F. S.-M. from the Banco de Santander and CRUE (Fondos Supera COVID19); and from the Comunidad de Madrid (Ayuda Covid 2019 and Inmunovacter REACT-UE). D. R. d. A. was supported by the Fondo de Investigación Sanitaria del Instituto de Salud Carlos III (PI19/00634), co-funded by the Fondo Europeo de Desarrollo Regional (FEDER), A Way to Make Europe; and the Fondation Jérôme Lejeune (grant number 2021a-2069). F. M. is supported by the Fondation Jérôme Lejeune (grant number 2017b-1711). The Adult Down Syndrome Outpatient Unit at Hospital Universitario de La Princesa is grateful to Licenciado don Jesús Coronado Hinojosa for his financial support.

Potential conflicts of interest. E. P.-A. reports fees for Advisory Board participation from Pharmamar and AstraZeneca. D. R. d. A. reports grant number 19/00634 from Instituto Carlos III and grant number 2021A/2069 from Fondation Jerome Lejeune; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Universidad Complutense de Madrid (Título propio de experto en bioética clínica), Weill Cornell Medicine-Qatar (Division of Medical Ethics—several courses), Instituto Universitario de Investigación Ortega Y Gasset (Máster oficial en bioética clínica), Escuela Andaluza de Salud Pública (Curso Consultoría Ética Clínica [2022] y Máster en bioética [2021]), and Consejería de Salud, Comunidad De Madrid (Curso Consultoría Ética Clínica [November 2021]). All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med **2020**; 46:846–8.
2. Brodin P. Immune determinants of COVID-19 disease presentation and severity. Nat Med **2021**; 27:28–33.
3. Wadman M. People with down syndrome face high risk from coronavirus. Science **2020**; 370:1384–5.
4. Clift AK, Coupland CAC, Keogh RH, Hemingway H, Hippisley-Cox J. COVID-19 mortality risk in down syndrome: results from a cohort study of 8 million adults. Ann Intern Med **2021**; 174:572–6.
5. Hüls A, Costa ACS, Dierssen M, et al. Medical vulnerability of individuals with Down syndrome to severe COVID-19-data from the trisomy 21 research society and the UK ISARIC4C survey. EClinicalMedicine **2021**; 33:100769.
6. Perera B, Laugharne R, Henley W, et al. COVID-19 deaths in people with intellectual disability in the UK and Ireland: descriptive study. BJPsych Open **2020**; 6:e123.
7. de Asua D R, Mayer MA, Ortega MDC, et al. Comparison of COVID-19 and non-COVID-19 pneumonia in Down syndrome. J Clin Med **2021**; 10:3748.
8. Chung H, Green PHR, Wang TC, Kong XF. Interferon-driven immune dysregulation in Down syndrome: a review of the evidence. J Inflamm Res **2021**; 14: 5187–200.
9. Kong XF, Worley L, Rinchai D, et al. Three copies of four interferon receptor genes underlie a mild type I interferonopathy in Down syndrome. J Clin Immunol **2020**; 40:807–19.
10. De Toma I, Dierssen M. Network analysis of down syndrome and SARS-CoV-2 identifies risk and protective factors for COVID-19. Sci Rep **2021**; 11:1930.
11. Espinosa JM. Down syndrome and COVID-19: a perfect storm? Cell Rep Med **2020**; 1:100019.
12. Joshi AY, Abraham RS, Snyder MR, Boyce TG. Immune evaluation and vaccine responses in Down syndrome: evidence of immunodeficiency? Vaccine **2011**; 29:5040–6.
13. Hüls A, Costa ACS, Dierssen M, et al. An international survey on the impact of COVID-19 in individuals with Down syndrome. medRxiv, **2020**, preprint: not peer-reviewed. November 05, 2020.
14. SNS CI. Estrategia de vacunación frente a COVID-19 en España. Actualización 9 modificada. Grupo de Trabajo Técnico de Vacunación COVID-19, de la Ponencia de Programa y Registro de Vacunaciones. November 2021. Available at: https://www.sanidad.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/covid19/Actualizaciones_Estrategia_Vacunacion/docs/COVID-19_Actualizacion9_Modificada_EstrategiaVacunacion.pdf
15. National Health Service. Booster dose of the coronavirus (COVID-19) vaccine. November 2021. Available at: https://www.nhs.uk/conditions/coronavirus-covid-19/coronavirus-vaccination/coronavirus-booster-vaccine/
16. Sadarangani M, Marchant A, Kollmann TR. Immunological mechanisms of vaccine-induced protection against COVID-19 in humans. Nat Rev Immunol **2021**; 21:475–84.
17. Franciotta D, Verri A, Zardini E, et al. Interferon-gamma- and interleukin-4-producing T cells in down's syndrome. Neurosci Lett **2006**; 395:67–70.
18. Dan JM, Mateus J, Kato Y, et al. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science **2021**; 371:eabf4063.
19. Valentine KM, Hoyer KK. CXCR5+ CD8 T cells: protective or pathogenic? Front Immunol **2019**; 10:1322.
20. Woldemeskel BA, Kwaa AK, Garliss CC, Laeyendecker O, Ray SC, Blankson JN. Healthy donor T cell responses to common cold coronaviruses and SARS-CoV-2. J Clin Invest **2020**; 130:6631–8.
21. Mateus J, Grifoni A, Tarke A, et al. Selective and cross-reactive SARS-CoV-2 T cell epitopes in unexposed humans. Science **2020**; 370:89–94.
22. Sekine T, Perez-Potti A, Rivera-Ballesteros O, et al. Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19. Cell **2020**; 183:158–68, e14.
23. Esparcia-Pinedo L, Martínez-Fleta P, Ropero N, et al. CD4+ T cell immune specificity changes after vaccination in healthy and COVID-19 convalescent subjects. Front Immunol **2022**; 12:755891.
24. Tyllis TS, Fenix KA, Norton TS, et al. CXCR5. Front Immunol **2021**; 12:626199.
25. Valentini D, Marcellini V, Bianchi S, et al. Generation of switched memory B cells in response to vaccination in down syndrome children and their siblings. Vaccine **2015**; 33:6689–96.
26. Costa-Carvalho BT, Martinez RM, Dias AT, et al. Antibody response to pneumococcal capsular polysaccharide vaccine in Down syndrome patients. Braz J Med Biol Res **2006**; 39:1587–92.
27. Eijsvoogel NB, Hollegien MI, Bok VLA, et al. Declining antibody levels after hepatitis B vaccination in down syndrome: a need for booster vaccination? J Med Virol **2017**; 89:1682–5.
28. Diletta V, Nicola C, Vittorio S, et al. Safety and long-term immunogenicity of BNT162b2 vaccine in individuals with down syndrome. J Clin Med **2022**; 11:694.
29. Grifoni A, Weiskopf D, Ramirez SI, et al. Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. Cell **2020**; 181:1489–501, e15
30. Oja AE, Saris A, Ghandour CA, et al. Divergent SARS-CoV-2-specific T- and B-cell responses in severe but not mild COVID-19 patients. Eur J Immunol **2020**; 50:1998–2012.
31. Bonifacius A, Tischer-Zimmermann S, Dragon AC, et al. COVID-19 immune signatures reveal stable antiviral T cell function despite declining humoral responses. Immunity **2021**; 54:340–54.
32. Araya P, Waugh KA, Sullivan KD, et al. Trisomy 21 dysregulates T cell lineages toward an autoimmunity-prone state associated with interferon hyperactivity. Proc Natl Acad Sci USA **2019**;116:24231–41.
33. Hippisley-Cox J, Coupland CA, Mehta N, et al. Risk prediction of COVID-19 related death and hospital admission in adults after COVID-19 vaccination: national prospective cohort study. BMJ **2021**; 374:n2244.