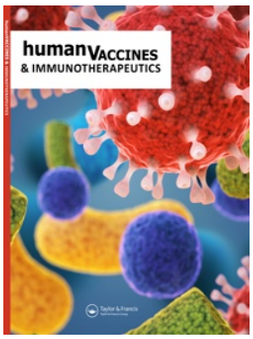

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Human Vaccines & Immunotherapeutics

ISSN: 2164-5515 (Print) 2164-554X (Online) Journal homepage: www.tandfonline.com/journals/khvi20

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To cite this article: Ludovica Soldateschi , Silvia Leoncini , Fabio Fiorino , Simone Lucchesi , Jacopo Polvere , Lidia Boasiako , Gabiria Pastore , Caterina Fazzi , Maria Altamura , Valeria Scandurra , Salvatore Grosso , Francesca Montagnani , Claudio De Felice , Annalisa Ciabattini & Donata Medaglini (2026) Unexpectedly competent immune response to SARS-CoV-2 vaccination in Rett syndrome, Human Vaccines & Immunotherapeutics, 22:1, 2612817, DOI: 10.1080/21645515.2026.2612817

To link to this article: https://doi.org/10.1080/21645515.2026.2612817

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HUMAN VACCINES & IMMUNOTHERAPEUTICS
2026, VOL. 22, NO. 1, 2612817
https://doi.org/10.1080/21645515.2026.2612817

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BRIEF REPORT

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Unexpectedly competent immune response to SARS-CoV-2 vaccination in Rett syndrome

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ABSTRACT

Rett syndrome (RTT) is a rare neurodevelopmental disorder of genetic origin characterized by chronic low-grade inflammation, immune imbalance, and frequently associated with compromised respiratory function. During the COVID-19 pandemic, individuals with RTT were classified as high-risk and invited to follow stringent vaccination protocols that included multiple booster doses. However, the immune response elicited by vaccination in this population has never been systematically investigated. Here, we provide the first characterization of spike-specific antibody and memory B cell responses in 23 RTT patients following two or three doses of SARS-CoV-2 mRNA vaccines. RTT patients developed spike-specific IgG levels comparable to those observed in healthy female controls (GMT 8476 [range 5120–20480] and 9213 [640–81920] after the first two vaccine doses, respectively). The frequencies and phenotype of spike-specific memory B cells were also similar between RTT and controls (mean frequency of 1.3 ± 0.6 and 1.6 ± 1.1, respectively) and these cells displayed functional reactivity upon antigenic stimulation *in vitro*. The assessment of vaccine-induced immunity in RTT addresses a critical knowledge gap by demonstrating the ability of these patients to develop an immune response to mRNA vaccination, thereby providing insights that may inform tailored vaccination strategies and improve understanding of immune competence in this rare disorder.

ARTICLE HISTORY
Received 29 October 2025
Revised 16 December 2025
Accepted 1 January 2026

KEYWORDS
Rett syndrome; SARS-CoV-2; COVID-19; vaccination; memory B cells

Introduction

In individuals with rare diseases, immune responses to infection and vaccination are often poorly characterized and may differ from those of the general population.[1] The COVID-19 pandemic (2020–2023) further underscored the need for optimized vaccination strategies in at-risk groups. Patients with rare diseases, immunocompromising conditions, or otherwise classified as clinically vulnerable were prioritized for early and booster-dose vaccination protocols during the rapid spread of the pandemic.[2] However, clinical studies conducted in real-world settings have shown that the immune response to SARS-CoV-2 vaccination can vary considerably across these vulnerable individuals.[3]

Rett syndrome is a rare neurodevelopmental disorder with a multisystemic involvement, mainly affecting females (~1:10.000–15.000 live births) and primarily caused by loss-of-function mutations in *MECP2* gene, a key transcriptional regulator involved in neurodevelopment, inflammation, and immunity.[4] Although RTT patients show a complex interplay of chronic low-grade inflammation, dysfunctional immune cells,

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/21645515.2026.2612817

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and dysregulated cytokines, which contribute to disease severity,[4] no immunodeficiency is reported. In the pandemic context, individuals with RTT were classified as high-risk and invited to follow vaccination protocols that included multiple booster doses. To note, data on vaccine immunogenicity in these patients are not available yet.

Considering the globally persistent circulation of SARS-CoV-2 variants and the compromised respiratory function in RTT patients,[5] understanding their response to SARS-CoV-2 vaccination is essential for tailored guidelines. To this aim, here we first report the Spike-specific immune response to SARS-CoV-2 vaccination in RTT patients followed under strict clinical monitoring.

Materials and methods

Study design

A total of 23 female patients with a clinical diagnosis of typical RTT and proven *MECP2* gene mutation were enrolled in the observational clinical study IMMUNO_RETT_CoVax. Patients were recruited at the Rett Syndrome National Reference Centre of the Azienda Ospedaliera Universitaria Senese, Siena, Italy. Patients with nonpathogenic *MECP2* mutations, presence of *MECP2* gene duplication, presence of mutations in other pathogenic genes for Rett-like syndromes (e.g. CDKL5, FOXG1) were excluded from the study. The study, performed in compliance with all relevant ethical regulations, was approved by Ethical Committee for Clinical Experimentation of Regione Toscana Area Vasta Sud Est (n.19672). A cohort of 23 female healthy individuals under 59 y of age, enrolled in the IMMUNO_CoV clinical study (n. 18869 by C.E.A.V.S.E), was included as healthy control (HC). RTT patients and HC were vaccinated with the SARS-CoV-2 mRNA BNT162b2 (Pfizer/BioNTech) vaccine two or three times. SARS-CoV-2 infection-related information was reported to the clinicians.

Plasma and peripheral blood mononuclear cells isolation

A single blood sample from each RTT patient was collected during routine visits, while multiple blood samples, provided before and after each vaccine dose, were collected from HC. Blood samples were collected and treated as previously described.[6] Isolated PBMCs were cryopreserved and stored in liquid nitrogen until used. Plasma samples were stored at −80°C.

Enzyme-linked immunosorbent assay and ACE2/RBD binding inhibition assay

Plasma samples were assessed by ELISA for spike-specific IgG, and by surrogate virus neutralization test (sVNT, cPass™ SARS-CoV-2 Neutralization Antibody Detection Kit, Genscript, Piscataway, NJ, USA) for detecting the ACE2/RBD binding inhibition activity, as previously described.[7] Recombinant SARS-CoV-2 full Spike protein (Sino Biological; 1 ug/ml protein) was used for coating wells in ELISA assay. Results of the ACE2/RBD inhibition assay are expressed as percentage inhibition = (1−sample OD value/negative control OD value) * 100. Inhibition values ≥30% are regarded as positive results.

Multiparametric flow cytometry

PBMCs were stained for flow cytometry analysis as previously described.[7] Recombinant biotinylated-RBD (BioLegend), tetramerized with fluorescently labeled SA-Allophycocyanin (APC), was used to identify antigen-specific B cells. Fluorescent antibodies used for staining are reported in Supplementary Table 1. Cells were acquired with SO LSRFortessa X20 flow cytometer (BD Biosciences). Data analysis was performed using FlowJo v10 (TreeStar, USA). Data preprocessing and FlowSOM (package v2.10.0) clustering analysis were performed as already described,[8,9] setting grid size to 8 × 8 and the parameter nClus = 15.

Memory B-cell ELISpot

Spike-specific IgG secreting memory B cells (MBC) were evaluated using the Human IgG Single-Color ELISpot Assay (CTL Europe GmbH, Germany), as previously described.[6] For each subject, antigen-specific IgG is reported as percentages of total MBC producing IgG.

Statistical analysis

To compare antibody titer trajectories between RTT and HC, titers were $\log_2$-transformed. A linear interpolation curve was generated using data from HC via the approxfun function (R v4.3.3, default parameters) and, subsequently, it was applied to the RTT dataset to evaluate its generalizability. Model performance was assessed using the coefficient of determination (R^2), mean squared error (MSE), and standard deviation (SD) for both the HC and RTT groups. Mann–Whitney test was used for assessing the statistical differences between Rett patients and HC and between vaccinated Rett patients infected and not infected and to compare the residuals obtained from the two fitted models. Data analyses were performed using GraphPad Prism v9 (GraphPad Software, USA) and R v4.3.3. Clinical data statistics were performed by using MedCalc Statistical Software v.19.0.7 (Ostend, Belgium).

Results

A total of 23 female RTT patients were enrolled in the prospective longitudinal study IMMUNO_RETT_CoVax. Demographics of RTT and sex-matched HC individuals are reported in Table 1. The two cohorts significantly differed for age (median value 25 [IQR 21.5–34] and 47 [IQR 35.25–52.75], respectively; $P < .0001$) but not for BMI (median value 20.30 [IQR 16.20–24.12] and 21.63 [IQR 19.47–24.70], respectively). Clinical characteristics of RTT patients, subdivided according to the number of mRNA BNT162b2 vaccine doses received and infection, are reported in Table 2. The overwhelming majority of RTT patients (95.6%) showed a typical clinical disease presentation, over one third (9/23) harbored pathogenetic *MECP2* early truncating, and about one quarter (6/23) missense mutations with remaining patients showing either gene deletions or late truncating. Clinical stages distribution was as follows: stage III (n = 9) and stage IV (n = 14).

A longitudinal curve of spike-specific IgG was generated in HC from baseline to 6 months after the third vaccine dose. Antibody titers from RTT patients were then overlaid on this reference curve (Figure 1A), showing comparable fit metrics ($R^2 = 0.70$ and 0.72, respectively). Residual comparison did not reveal significant differences between the two cohorts ($P = .227$). Spike-specific IgG geometric mean titers (GMT) measured after the second and the third vaccine doses were 8,476 (range 5,120–20,480) and 48,710 (range 20,480–81,920) in RTT patients, and 9,213 (range 640–81,920) and 72,982 (range 20,480–32,7680) in HC. RTT patients efficiently responded to SARS-CoV-2 infection, as observed by the increased levels of spike-specific IgG (GMT of 81,920 [range 10240–327680] and 94,101 [range 40,960–3,27,680], in RTT patients infected and vaccinated two or three times, respectively; Figure 1B; $P < .05$). Additionally, IgG antibodies from RTT patients and HC displayed comparable binding to the spike RBD and subsequent inhibition of its interaction with ACE2 (Figure 1C). The serological response detected in RTT patients is indicative of spike-specific plasma cells elicited by vaccination. Nevertheless, a critical goal of vaccination is the induction of memory B cells (MBC), capable of persisting for long time and rapidly reactivate and protect upon antigen re-exposure.

Table 1. Comparison of demographics between Rett syndrome patients and healthy controls.

Variables	RTT	HC	P-value
Age, years (IQR)	25 [21.50-34]	47 [35.25-52.75]	**<.0001**
BMI, kg/m^2 (IQR)	20.30 [16.20-24.12]	21.63 [19.47-24.70]	.2318

Bold values indicate statistical significance $p \leq 0.05$. BMI, body mass index; IQR interquartile range. Age reported as median value [IQR].

Table 2. Demographics and clinical characteristics of Rett syndrome patients.

	RTT patient categories					
Variables	K	V2	V2Inf	V3	V3Inf	P-value
N patients	4	11	4	4	4	
Age (yr)	9.5 [4.25 - 14.75]	26 [22 - 34]	28.5 [23.25 – 34.5]	25.5 [20 - 34]	17 [15.25 – 26.25]	**.0097**
Head circ. (z)	-0.7 ± 1.7	-3.0 ± 1.9	-1.5 ± 1.3	-3.4 ± 0.6	-2.9 ± 2.0	.238
BMI (z score)	0.5 ± 0.4	-0.7 ± 2.0	-1.1 ± 2.1	-0.04 ± 1.8	-1.5 ± 2	.598
Height (z)	-1.5 ± 2.2	-2.4 ± 1.3	-2.7 ± 0.9	-2.8 ± 1.0	-2.3 ± 1.5	.722
Body weight (z)	-0.147 [-1.5, 0.4]	-1.645 [-4, 0.2]	-2.370 [-4, -0.6]	-1.080 [-3.3, -0.2]	-2.190 [-3.2, -1.8]	.597
Disease severity						
RCSS	23.1 ± 12.4	22.6 ± 9.3	23.5 ± 5.3	23.8 ± 6.9	22.6 ± 4.7	.999
MBAS	61.75 [40 - 65.7]	60 [40 - 64.4]	62 [46 - 76]	49 [42.5 - 60.5]	57.75 [49.7 - 60.5]	.868
RSBQ	38 ± 17	39.1 ± 15.4	40 ± 9.1	48 ± 9.5	41 ± 6	.826
Disease stage						
II	1	0	0	0	0	.2076
III	2	6	0	1	2	
IV	1	5	4	3	2	
MECP2 genotype						
Early trunc.	1	4	0	1	3	.604
Late trunc.	0	2	1	1	0	
Missense	2	2	1	2	0	
Deletion	0	2	1	0	1	
RTT phenotype						
Classic (C)	3	10	4	4	4	.590
Non-Classic (NC)	1	1	0	0	0	
Other clinical conditions						
URTI	3	5	0	3	1	.144
UTI	1	1	1	3	0	.068
Atopy	2	2	0	1	0	.335
Food allergy	0	3	0	1	0	.438
Coeliac dis.	0	0	0	1	0	.201
PEG	0	1	0	0	0	.825
CMPI	1	0	0	1	0	.274
Autoimmunity	0	1	1	1	0	.625
Neutropenia	0	1	0	1	1	.625
IgA deficiency	1	0	0	1	0	.274
ASM	2	8	3	3	3	.917
Walking ability	2	6	0	1	2	.365
Breastfeeding	4	8	3	3	4	.626

K, unvaccinated and non-infected patients; V2, patients vaccinated with 2 doses; V2inf, patients infected and vaccinated with 2 doses; V3, patients vaccinated with 3 doses; V3inf, patients infected and vaccinated with 3 doses; Age is expressed as median value [IQR]; BMI, Body Mass Index; RCSS, Rett Clinical Severity Scale; MBAS, Motor Behaviour Assessment Scale; RSBQ, Rett Syndrome Behavioural Questionnaire; URTI, Upper Respiratory Tract Infection; UTI, Urinary Tract Infection; PEG, Percutaneous Endoscopic Gastrostomy; CMP, Cow Milk Protein Intolerance; ASM, Anti-Seizure Medication.

Circulating spike-specific MBCs were identified among total MBCs (live $CD19^+IgD^-$) as positive for biotinylated-RBD/streptavidin-APC tetramers (hereafter named RBD^+MBC; Figure 1D). A similar frequency of RBD^+MBCs was observed in RTT and HC individuals (mean frequency of 1.3 ± 0.6 and 1.6 ± 1.1, respectively; Figure 1E). Moreover, the clustering analysis of RBD^+MBCs, performed with FlowSOM algorithm, showed a similar profile between the two cohorts. Based on the expression of CD10, CD11c, CD20, CD21, CD27, CD38, IgD, IgM, IgG, IgA surface markers, 15 clusters of MBCs were identified (Figure 1F). These clusters were grouped into Ig-switched ($CD27^+IgD^-CD20^+$), Double Negative ($CD27^-IgD^-$), Ig-unswitched ($CD27^+IgD^+CD20^+$) MBCs, and plasmablasts ($CD27^-IgD^-CD20^-CD38^+$). When assessing RBD^+MBCs frequency within each cluster, most of them were included into the IgG^+ resting MBCs (cluster 6), in both RTT and HC cohorts (Figure 1F, right heatmap). Other RBD^+MBCs were present in the DN1 (cluster 2) and in the unswitched MBCs (cluster 12). The origin of the DN MBCs subset is still under debate: typically, DN1 MBCs ($CD27^-$ IgD^- $CD21^+$) are prevalent in healthy individuals, whereas DN2 MBCs ($CD27^-$ IgD^- $CD21^-$) originate in autoimmune disorders, chronic infections, and cancers.[7,10] As DN1 MBCs (cluster 2) and DN2 MBCs (cluster 4) did not differ significantly between the two cohorts, it is reasonable to conclude that individuals with RTT can generate a B cell response following

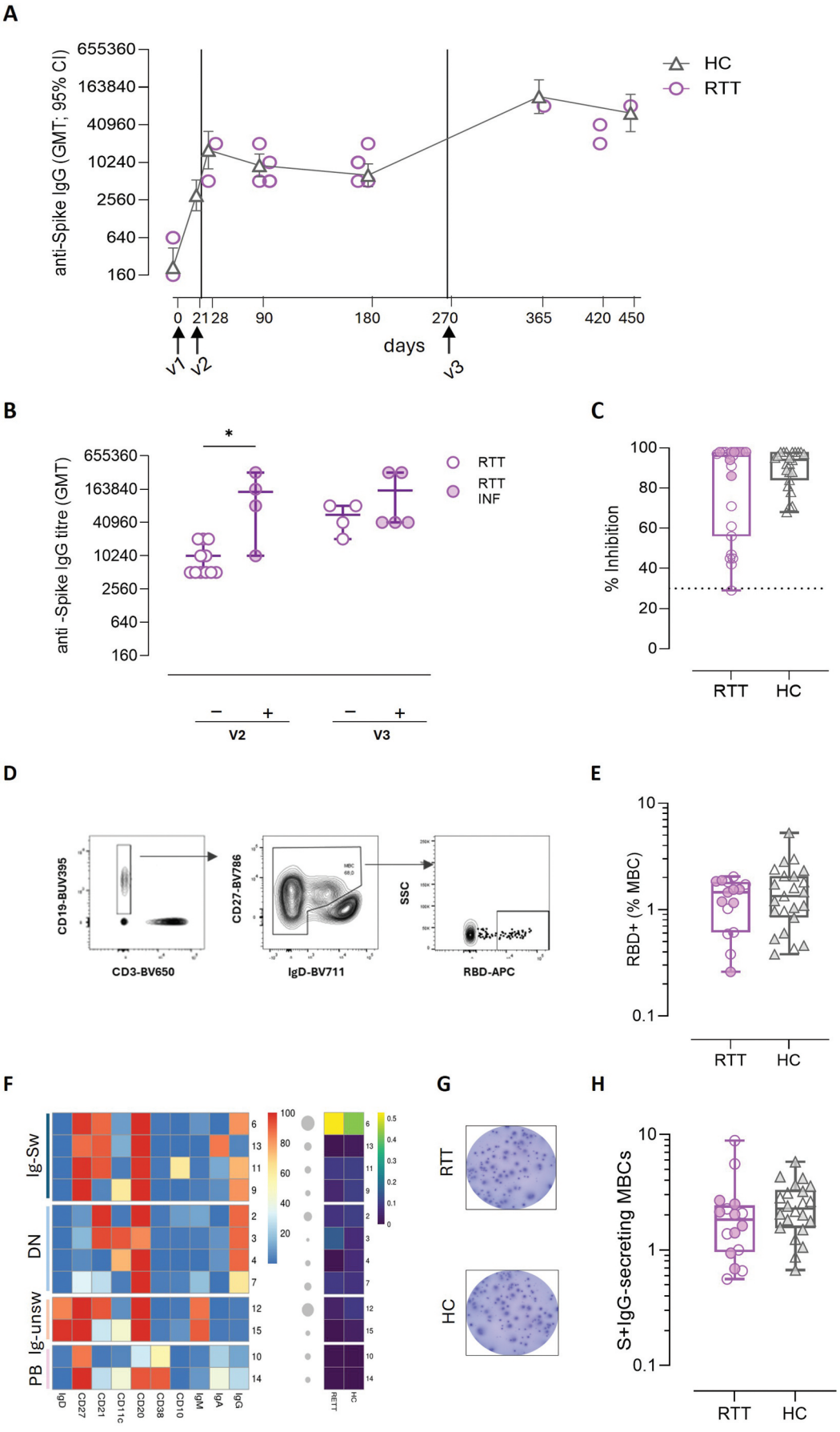

Figure 1. Spike-specific immune responses following SARS-CoV-2 vaccination in RTT and HC. (A) Longitudinal spike-specific IgG analysis from baseline (0) to 6 months post third dose (day 450) in HC with overlaid single values assessed in RTT patients. The first (v1, day 0), second (v2, day21) and third (v3, day270) vaccine dose administration is shown by arrows.

vaccination comparable to that of HC. Furthermore, circulating RBD^+ MBCs were capable of reactivating upon *in vitro* stimulation, showing a mean frequency of spike-specific IgG-secreting cells of 2.3 ± 2.1 and 2.5 ± 1.3 in people with RTT and HC, respectively, with no statistically significant differences (Figure 1G,H).

Discussion

In this work, we provide the first evidence of the immunogenicity of SARS-CoV-2 mRNA vaccines in patients with RTT, a rare disorder characterized by persistent subclinical inflammation. Given the frequent presence of a compromised respiratory function in RTT, clarifying the ability of these patients to respond to vaccination against a respiratory virus becomes essential for developing tailored clinical recommendations.

In this monocentric observational study, we show that RTT patients are able to develop an immune response comparable to that of HC, both in terms of spike-specific antibody levels and spike-specific memory B-cell generation, phenotype differentiation and functionality. This provides the first evidence that individuals with RTT can effectively respond to SARS-CoV-2 mRNA vaccination.

Studies performed in real-world settings among different high-risks categories have shown a great variability across clinically vulnerable individuals.[3] While patients with hematological malignancies or undergoing hemodialysis developed a slower and lower immune response,[11–13] people living with HIV or receiving stem cell transplantation developed an immune response more similar to healthy individuals.[3,7,9,14,15] Overall, these studies pointed out that factors such as the stage of disease, ongoing immunosuppressive treatments, and the combination of multiple therapies significantly influence the variability in immune response to vaccination.

Generalization of our findings is partially limited by the relatively small patient cohort, which reduces the statistical power of our analyses, as well as by variations in blood sample timing and differences in SARS-CoV-2 vaccination rates or timing, influenced by regional protocols or family vaccine hesitancy. Furthermore, the difference in median age between the RTT cohort and the healthy individuals should be taken into account, as it may represent a potential factor influencing the vaccine immune response.

Of note, considering the ongoing circulation of Omicron subvariants and the potential emergence of future pandemics, our findings provide valuable insights to inform vaccination strategies specifically tailored for these individuals affected by a rare and seriously debilitating syndrome and contribute to broadening the understanding of vaccination responses in neurodevelopmental disorders characterized by persistent subclinical inflammation.

Acknowledgments

We would like to thank all the volunteers who participated in the study.

Author contributions

CRediT: **Ludovica Soldateschi:** Investigation, Methodology, Visualization, Writing – original draft; **Silvia Leoncini:** Conceptualization, Data curation, Investigation, Methodology, Resources, Writing – review & editing; **Fabio Fiorino:** Investigation; **Simone Lucchesi:** Data curation, Formal analysis, Software; **Jacopo Polvere:** Investigation; **Lidia**

Figure 1. Continues. (B) Spike-specific IgG titres (GMT with range) detected in RTT patients vaccinated with two (v2) or three (v3) doses, with (+) or without (–) SARS-CoV-2 infection. (C) ACE2/RBD binding inhibition assay. The dotted line at 30% inhibition percentage, indicates the threshold of positivity of the assay. (D) RBD^+ MBCs gating strategy and (E) frequencies of RBD^+ MBC in RTT and HC following two and three vaccine doses in SARS-CoV-2 infected (filled symbols) or non-infected (open symbols) individuals. (F) FlowSOM clustering analysis performed on total MBCs (left heatmap), and RBD^+ MBCs (right heatmap). (G) Spike-specific IgG-secreting MBCs assessed by ELISpot assay and (H) their frequencies in RTT and HC. Data from SARS-CoV-2 infected individuals are shown as filled symbols. Statistical differences were assessed by Mann–Whitney test.

Boasiako: Conceptualization, Investigation, Resources; **Gabiria Pastore:** Investigation; **Caterina Fazzi:** Investigation, Resources; **Maria Altamura:** Investigation, Resources; **Valeria Scandurra:** Resources; **Salvatore Grosso:** Resources; **Francesca Montagnani:** Resources; **Claudio De Felice:** Conceptualization, Formal analysis, Investigation, Methodology, Resources, Writing – review & editing; **Annalisa Ciabattini:** Conceptualization, Formal analysis, Investigation, Methodology, Funding acquisition, Writing – original draft; **Donata Medaglini:** Conceptualization, Funding acquisition, Methodology, Resources, Writing – review & editing.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The work was supported by the Department of Medical Biotechnologies, the 2022 Research Support Plan (F-Cur), and the Open Access Fund, all from the University of Siena.

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Claudio De Felice, MD, is currently Advisory Scientific Board at the Pediatrics Unit of the University General Hospital in Siena, Italy. He has coordinated several International clinical research projects on Rett syndrome and *MeCP2*-mutated animal models. Furthermore, he has extensive longstanding experience on oxidative stress, rare genetic neurodevelopmental diseases, autism spectrum disorders, perinatal infections/inflammatory diseases, and intensive care neonatology. He has extensive and continued publication activity in peer-reviewed journals and he is currently Associate Editor and Editorial Board Member of several scientific Journals.

Annalisa Ciabattini, PhD, is Associate Professor of Microbiology at the University of Siena. She has extensive experience in vaccine immunology, spanning both pre-clinical and clinical studies. During the COVID-19 pandemic, she integrated advanced flow cytometry, computational modelling, and systems immunology to dissect the dynamics of B cell and antibody responses following mRNA vaccination and breakthrough infections in healthy and vulnerable individuals. Through longitudinal studies across individuals with different immunocompromising conditions, she has contributed to defining heterogeneity of vaccine-induced immune response across distinct conditions.

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