Long-term humoral and cellular SARS-CoV-2 vaccine-specific immune response in patients with primary antibody deficiencies

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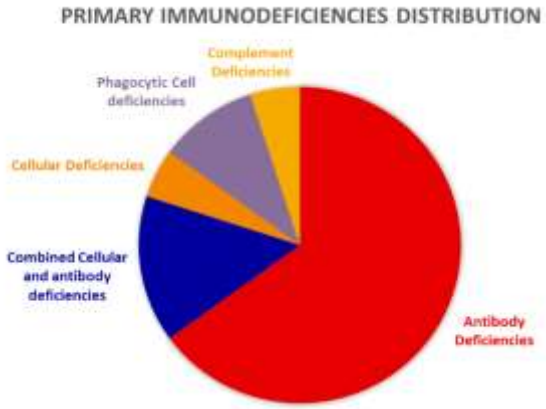
Latvian Council of Science project Nr.lzp-2020/1–0269

Background I

Inborn errors of immunity (IEI) are a group of nearly 500 rare diseases caused by genetic defects that result in the specific impairment of normal immune function.

Collective prevalence - 1:1000 to 1:5000.

The most common IEI are **predominantly antibody deficiencies** - selective IgA deficiency and common variable immunodeficiency (CVID).



Selective IgA deficiency

At least one of the following:
- increased susceptibility to infection
- autoimmune manifestations
- affected family member

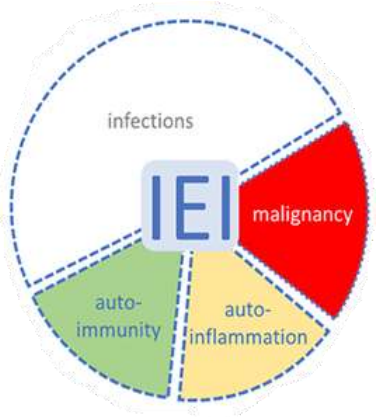
AND diagnosis after 4th year of life
AND undetectable serum IgA (when measured with nephelometry less than 0.07 g/L) but normal serum IgG and IgM (measured at least twice)
AND secondary causes of hypogammaglobulinemia have been excluded.
AND normal IgG antibody response to all vaccinations
AND Exclusion of T-cell defect

CVID

At least one of the following:
- increased susceptibility to infection
- autoimmune manifestations
- granulomatous disease
- unexplained polyclonal lymphoproliferation
- affected family member with antibody deficiency

AND marked decrease of IgG and marked decrease of IgA with or without low IgM levels (measured at least twice; <2SD of the normal levels for their age)
AND at least one of the following:
- poor antibody response to vaccines (and/or absent isohemagglutinins); ie, absence of protective levels despite vaccination where defined
- low switched memory B cells (<70% of age-related normal value)

AND secondary causes of hypogammaglobulinemia have been excluded (eg, infection, protein loss, medication, malignancy)
AND diagnosis is established after the fourth year of life (but symptoms may be present before)
AND no evidence of profound T-cell deficiency, defined as 2 of the following (y = years of life)
- CD4 numbers/microliter: 2-6 y < 300, 6-12 y < 250, >12 y < 200
- % naïve of CD4: 2-6 y < 25%, 6-16 y < 20%, >16 y < 10%



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Bousfiha, A., Jeddane, L., Picard, C. et al. Human Inborn Errors of Immunity: 2019 Update of the IUIS Phenotypical Classification. J Clin Immunol 40, 66–81 (2020). https://doi.org/10.1007/s10875-020-00758-x 2. Bomken S, van der Werff Ten Bosch J, Attarbaschi A, Bacon CM, Borkhardt A, Boztug K, Fischer U, Hauck F, Kuiper RP, Lammens T, Loeffen J, Neven B, Pan-Hammarström Q, Quinti I, Seidel MG, Warnatz K, Wehr C, Lankester AC, Gennery AR. Current Understanding and Future Research Priorities in Malignancy Associated With Inborn Errors of Immunity and DNA Repair Disorders: The Perspective of an Interdisciplinary Working Group. Front Immunol. 2018 Dec 12;9:2912. doi: 10.3389/fimmu.2018.02912.; https://www.cytognos.com/academy/primary-immunodeficiencies/description/; Seidel MG, Kindle G, Gathmann B, Quinti I, Buckland M, van Montfrans J, Scheible R, Rusch S, Gasteiger LM, Grimbacher B, Mahlaoui N, Ehl S; ESID Registry Working Party and collaborators. The European Society for Immunodeficiencies (ESID) Registry Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity. J Allergy Clin Immunol Pract. 2019 Jul-Aug;7(6):1763-1770. doi: 10.1016/j.jaip.2019.02.004. Epub 2019 Feb 15. PMID: 30776527

Background II

A **higher morbidity** and **mortality** from SARS-CoV-2 has been described and **vaccination** is the most effective form of prophylaxis in these patients.

The mechanisms of somatic mutation and selection in germinal centers that lead to differentiation of mature class-switched memory B cells and antibody secretion may be altered in patients with specific antibody deficiencies.

Assessment of cellular response specific for the SARS-CoV-2 antigen is important when evaluating vaccine-specific responses.

However, the **durability** of humoral and especially cellular **immune responses** in this specific group remains **to be clarified**.

The primary objective of this study was to **evaluate a longer-term SARS-CoV-2 spike-specific** humoral and cellular immune **response** in patients with primary antibody deficiencies compared to healthy controls of the same age.

The secondary objective was to **identify markers** that are **associated** with a **better** immune **response** after COVID-19 vaccination in the patient group.

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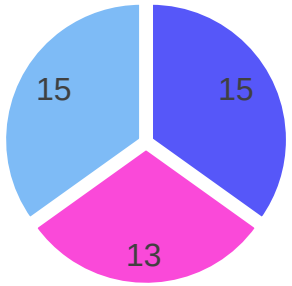
Shields AM, Burns SO, Savic S, Richter AG, Anantharachagan A, Arumugakani G, et al. COVID-19 in patients with primary and secondary immunodeficiency: The United Kingdom experience. J Allergy ClinImmunol 2021 Mar;147(3):870-875.e1. doi: 10.1016/j.jaci.2020.12.620. 2. Amodio D, Ruggiero A, Sgrulletti M, Pighi C, Cotugno N, Medri C, et al. Humoral and Cellular Response Following Vaccination With the BNT162b2 mRNA COVID-19 Vaccine in Patients Affected by Primary Immunodeficiencies. Front Immunol. Front Immunol. 2021 Oct 4;12:727850. doi: 10.3389/fimmu.2021.727850.

Methods I



Humoral response was evaluated using an ELISA assay that detects specific SARS-CoV-2 IgG antibodies against S1 domain of spike protein.

T cell response was detected by an IGRA assay QuantiFERON SARS-CoV-2, which measures CD4+ and CD8+ T cell immune responses to S1 and S2 antigen pools.

Methods II

Relevant clinical data on patients were obtained from patient electronic health records, including data on family history of IEI, treatment, history of SARS-CoV-2 vaccination and infection, confirmed by a PCR, clinical characteristics, including prior infections, bronchiectasias, autoimmunity, polyclonal benign lymphoproliferation, granulomatous disease, enteropathy and malignancy.

T and B cell subclass phenotyping was performed by flow cytometry to identify immunological correlates with the magnitude of SARS-CoV-2 vaccine-specific immune response:

B cell panel: naïve B cells (CD19+CD27−IgM+IgD+), marginal zone B cells (CD19+CD27+IgM++IgD+), switched memory B (CD19+CD27+IgM−IgD−), IgM-only memory B cells (CD19+CD27+IgM++IgD−), transitional B cells (CD19+IgD+CD27-IgM++CD38++), CD21low B cell (CD19+ IgM+,CD21-CD38-), plasmablasts (CD19+CD21+CD38+++IgM−), atypical memory B cells (CD19+CD21-CD27-IgD-);

T cell panel: CD3+CD4+CD27+CD45RA+ naïve T helper cells, CD3+CD4+CD27+CD45RA- central/transitory memory T helper cells, CD3+CD4+CD27-CD45RA- effector memory T helper cells, CD3+CD4+CD27-CD45RA+ terminally differentiated T helper cells, CD3+CD4+CD31+CD45RO- recent thymic emigrant T cells, CD3+CD8+CD27+CD45RA+ naïve T cytotoxic cells, CD3+CD8+CD27+CD45RA- central/transitory memory T cytotoxic cells, CD3+CD8+CD27-CD45RA- effector memory T cytotoxic cells, CD3+CD8+CD27-CD45RA+ terminally differentiated T cytotoxic cells, CD3+CD4+FOXP3+CD127dim T regulatory cells.

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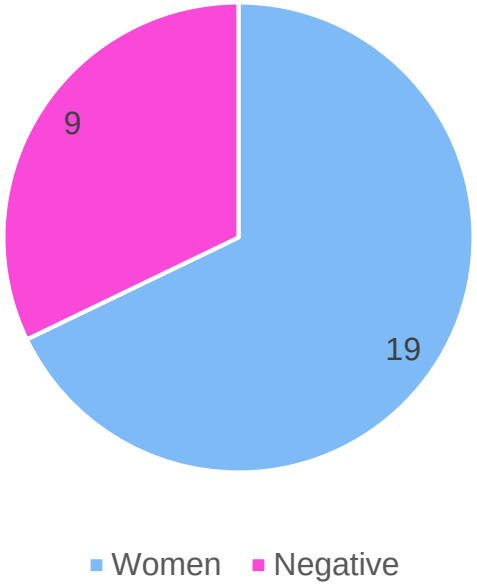
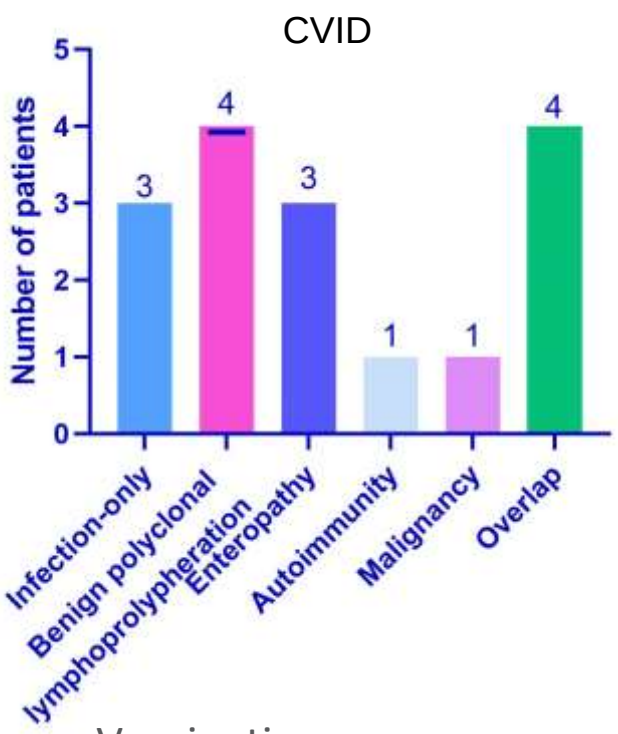
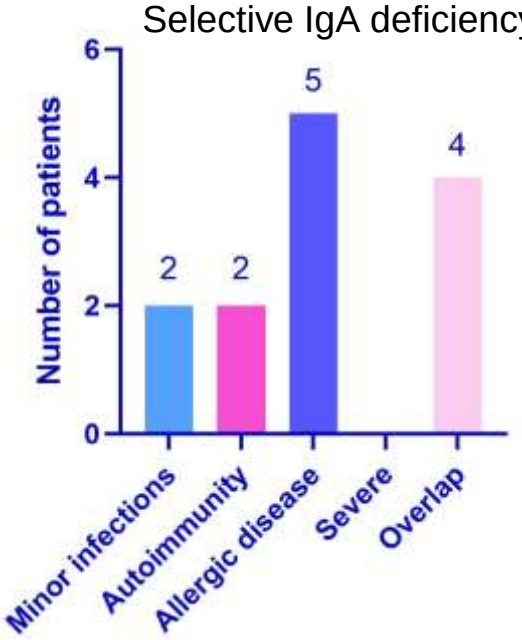
Results I







The median age was 38.5 (IQR=21) years

Vaccinations:

Pfizer BioNTechBNT162b2, N=18 (patients), N=12 (control)

Spikevax mRNA-1273, N=9 (patients), N=3 (control)

Jcovden Ad26.COV2, N=1 (patients), N=0 (controls)

The median time after vaccination was 173 (IQR=142) days, ranging from 25 to 345 days in the patient group and 215 days (IQR=201) in control group (p=0.156)

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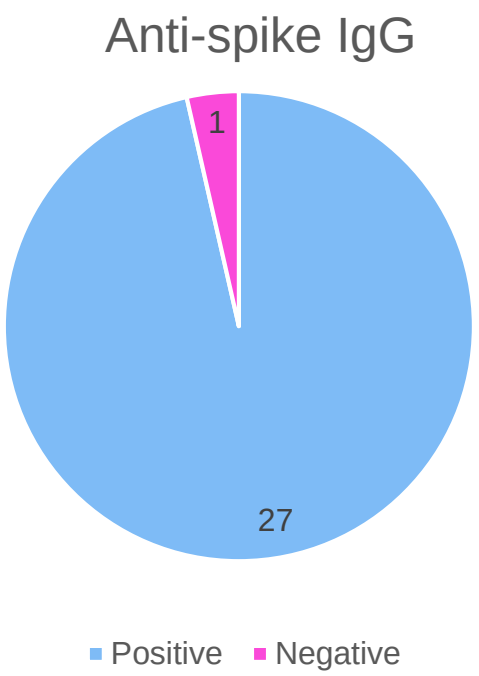
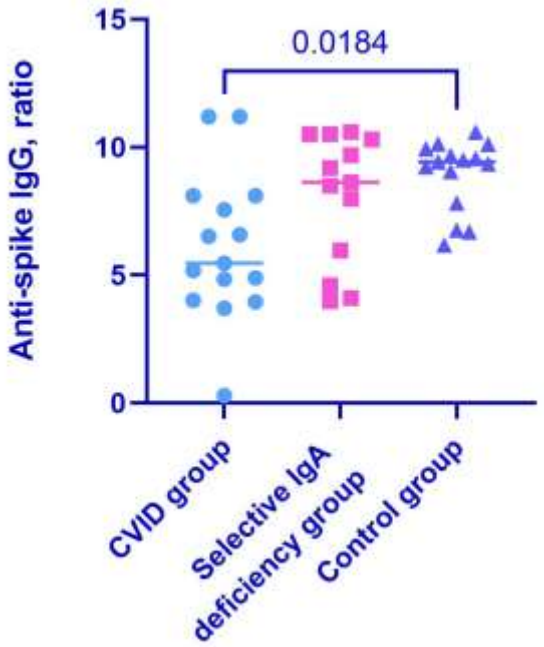
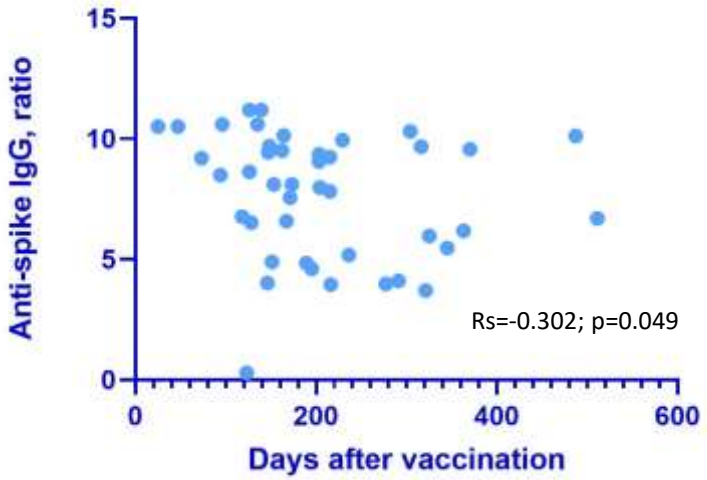
Results II







Group	Median anti-spike IgG level (IQR)
CVID	5.4720 (4.08)
Selective IgA deficiency	8.6260 (5.12)
Control group	9.4350 (2.13)

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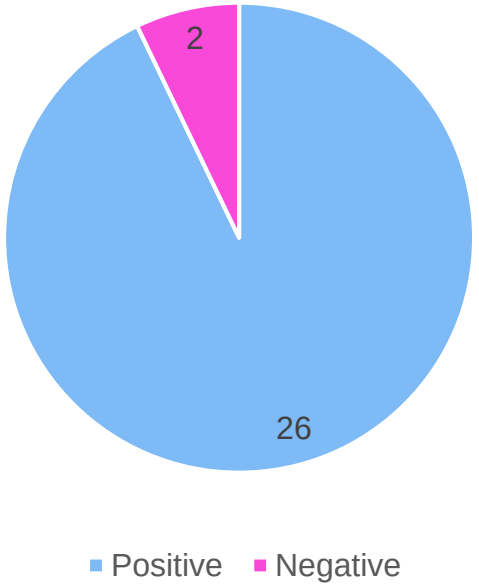
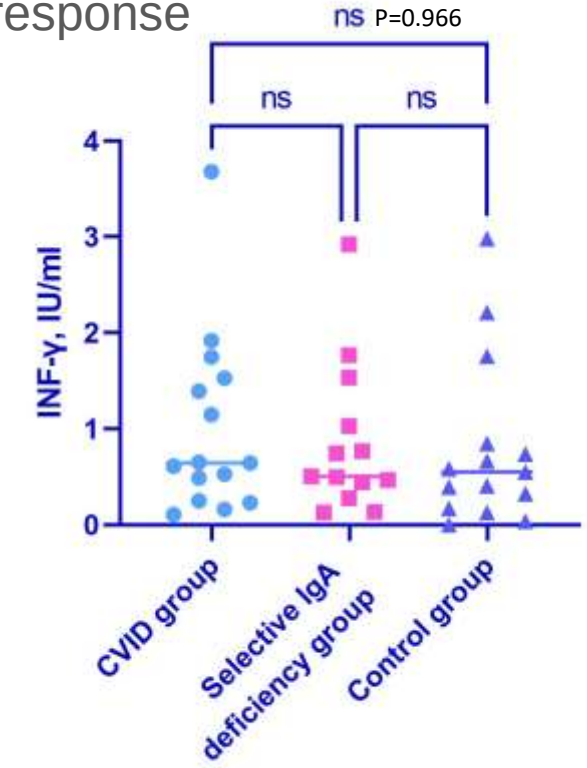
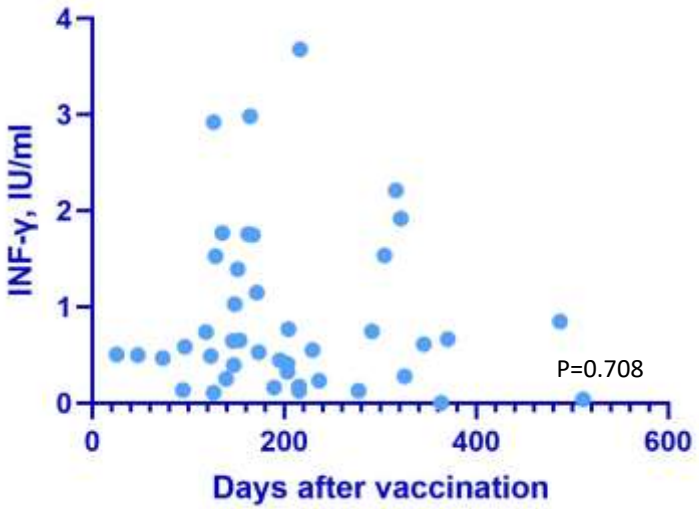
Results III

Anti-spike CD4+ and CD8+ response







Group	Median CD4+ and CD8+ cell response (INF-γ) to S1 and S2 pool specific proteins, IU/ml (IQR)
CVID	0.6451 (1.28)
Selective IgA deficiency	0.5052 (0 .92)
Control group	0.5503 (0.68)

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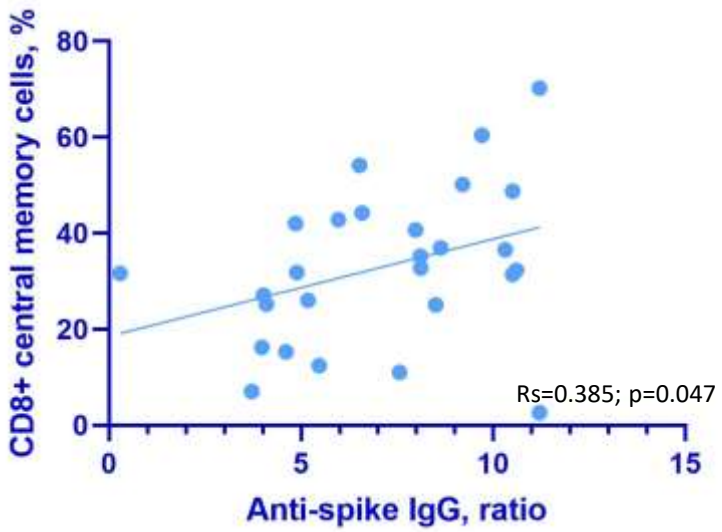
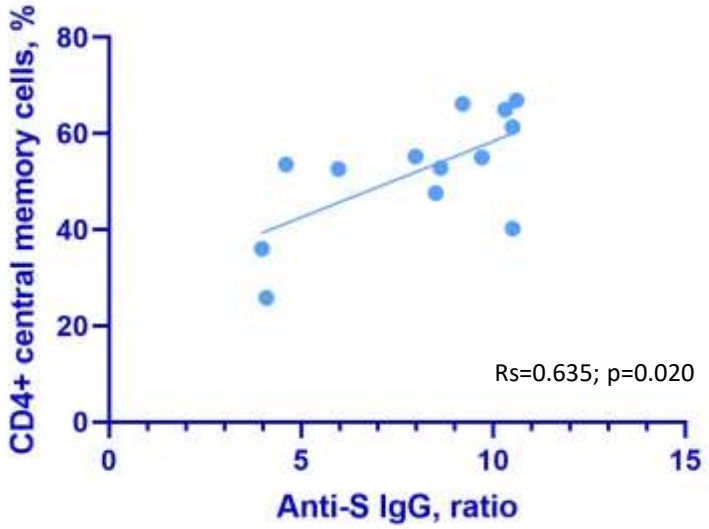
Results IV





Age did not significantly influence the extent of humoral or cellular response in any of groups.

No differences in humoral or T cell immune responses were found when dividing patients according to their clinical parameters or previous COVID-19.

No statistically significant differences were detected between SARS-CoV-2 specific cellular immune responses and T lymphocyte subtypes, nor between SARS-CoV-2 specific humoral or cellular immune responses and B lymphocyte subtypes.

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Conclusion

The results of this study indicate that markers of the sustained SARS-CoV-2 spike-specific humoral and cellular immune response **are detectable almost up to a year** after vaccination either in patients with primary antibody deficiencies as well as in healthy controls.

Despite on the significantly lower median levels of anti-spike IgG response in CVID patients than in healthy controls, the T cell response was unchanged in all studied groups.

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Thank you for attention!