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SARS-Cov-2 Vaccination in Patients with Inborn Errors of Immunity in Latvia: Immune Response and Reasons for Refusal of Recommended Vaccination

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Abbreviations used in the Thesis

BAFF	B-cell activating factor
CD	Cluster of Differentiation
COVID-19	Coronavirus Disease 2019
CXCL13	CXC Motif Chemokine Ligand 13
ESID	European Society for Immunodeficiencies
ICOS	Inducible Co-Stimulator
Ig	Immunoglobulin
IGRA	Interferon-γ Release Assay
IEI	Inborn Errors of Immunity
IL	Interleukin
IFN	Interferon
mRNA	Messenger Ribonucleic Acid
NFKB2	Nuclear Factor Kappa B Subunit 2
NK	Natural killer cells
NRAS	Neuroblastoma RAS Viral Oncogene Homolog
PAD	Predominantly Antibody Deficiency
CVID	Common Variable Immunodeficiency
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SIgAD	Selective IgA Deficiency
SCID	Severe Combined Immunodeficiency
SMAD7	Drosophila protein Mothers against decapentaplegic homolog 7
TGF-β1	Tumour Growth Factor β1
TFH	T Follicular Helper
TFR	T Follicular Regulatory cell
TNF-α	Tumour necrosis factor α
Treg	Regulatory T cell

Introduction

Inborn errors of immunity (IEI) are a heterogeneous group of rare diseases characterised by immune dysregulation (Bousfiha et al., 2020). Clinically, these conditions manifest through recurrent or unusual infections, autoimmunity, autoinflammatory syndromes, atopy, and/or malignancies (Poli et al., 2025). The diagnosis of IEI is based on clinical and laboratory criteria, as well as genetic testing results (Costagliola & Consolini, 2023). Treatment depends on the specific diagnosis and the severity of the immune defect and may include allogeneic hematopoietic stem cell transplantation, immunoglobulin replacement therapy, biological agents, prophylactic antibiotic use, other infection prevention strategies including vaccination, and management of complications (Fevang, 2023; Hanitsch et al., 2020). Vaccination is considered one of the most effective means of infection prevention. Vaccines are believed to work by inducing pathogen-specific immune responses that result in the production of protective antibodies and memory immune cells (Shoja Doost et al., 2024). However, in some types of IEI, this mechanism may be defective (Paris, 2023; Tangye et al., 2022).

The most common form of IEI in which vaccine-induced immune responses may be impaired is predominantly antibody deficiencies (PAD) (Poli et al., 2025). The most frequent PAD types are selective IgA deficiency (SIgAD) and common variable immunodeficiency (CVID). These disorders are clinically characterised by increased susceptibility to infections and non-infectious complications associated with immune dysregulation (Edwards et al., 2019). Both are associated with B-cell defects or functional impairments in other immune cell lineages, leading to reduced immunoglobulin production (Bagheri et al., 2023; Milito et al., 2021). In addition to low immunoglobulin levels common to all PAD patients, CVID diagnostic criteria also include impaired vaccine responses and/or reduced switched memory B-cell counts, indicating dysfunction of germinal centres in secondary lymphoid organs (Seidel et al.,

2019). Germinal centres are critical sites for class-switch recombination, somatic hypermutation, and antibody affinity maturation. In patients with CVID, these centres may be dysfunctional and disorganised (Schouwenburg van et al., 2022).

Several mechanisms may contribute to germinal centre dysfunction, including chronic infection, overexpression of the transcription factor T-bet, increased formation of CD21low memory B cells, CXCL13 dysregulation (a B cell chemoattractant), and impaired function of follicular helper T cells (TFH) and follicular regulatory T cells (TFR) (Gupta et al., 2022; Romberg et al., 2019; Yang et al., 2022). TFH cells, through secretion of interleukin (IL)-4 and IL-21, play a key role in the differentiation of B cells into antibody-producing plasma cells and memory B cells in germinal centre reactions (Baumjohann & Fazilleau, 2021), while TFR cells regulate TFH activity by controlling the immune synapse between B cells and TFH. Dysfunction of these cell types may also contribute to autoimmunity (Gupta et al., 2024; Padron & Hernandez-Trujillo, 2023).

B cell dysfunction may also affect T cell responses in PAD patients, as B cells can act as antigen-presenting cells and participate in T cell activation (Apostolidis et al., 2021). In addition to B cell impairment, PAD may involve disrupted coordination and regulation of the immune response, including defects in T cell signalling pathways and dysfunction of innate immune cells such as macrophages, dendritic cells, natural killer (NK) cells, and innate lymphoid cells. Dysregulation may also occur in the microenvironment of primary or secondary lymphoid organs (Fernando et al., 2021; Ho & Cunningham-Rundles, 2020; Le Saos-Patrinos et al., 2020; Martelius et al., 2023). These cellular dysregulations are reflected in altered cytokine profiles (Polito et al., 2019; Poto et al., 2023; Rodríguez-Ubreva et al., 2024). However, many aspects of PAD pathogenesis, particularly regarding non-infectious complications, remain unknown. Since the most common PAD types usually manifest in adulthood, one

of the hypothesised environmental factors that may influence disease onset and complications is impaired immune response to antigens, including viral antigens (Al-Hakim et al., 2024; Ameratunga et al., 2023; Strohmeier et al., 2023).

At the end of 2019, a novel virus – severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – was identified in China, causing pneumonia and rapidly spreading to pandemic levels (Zhou et al., 2020). The exposure of patients to SARS-CoV-2 antigen provided an opportunity to study how immune defects in PAD and other IEI patients influence the response to this novel pathogen (Quinti et al., 2022; Rodríguez-Ubreva et al., 2024).

Despite recommendations from relevant authorities that IEI patients should receive SARS-CoV-2 vaccination (ESID, 2022), some individuals with IEI declined the recommended vaccination. It is important to identify the most common concerns among these patients in order to address misconceptions and ensure that patients receive necessary immunization. Even in cases where protective antibody levels are not achieved, the SARS-CoV-2 vaccine may still be beneficial, as memory T cells can aid in infection control (Amodio et al., 2021). The role of T cells in COVID-19 protection is supported by evidence showing that patients with severe disease often lack virus-specific T cells, while those with milder illness typically exhibit early induction of functional SARS-CoV-2-specific T cells. Furthermore, asymptomatic individuals infected with SARS-CoV-2 may mount T cell responses in the absence of a detectable humoral response (Sahin et al., 2021; Sekine et al., 2020; Sette & Crotty, 2021; Tan et al., 2021).

This Doctoral Thesis consists of three main parts:

1 An analysis of IEI prevalence in the Latvian population (Prokofjeva et al., 2022);

2 Evaluation of SARS-CoV-2-specific immune responses in patients with PAD (Lucane, Slisere, Gersone, et al., 2023; Lucane, Slisere, Ozola, et al., 2023);

3 An analysis of the factors contributing to the refusal of recommended SARS-CoV-2 vaccination among patients with IEI (Lucane, Kursite, et al., 2023).

Aim of the Thesis

To describe the prevalence of inborn errors of immunity (IEI) in the Latvian population, to evaluate SARS-CoV-2 antigen-specific humoral and T-cell immune responses and their association with disease phenotype and severity in patients with predominantly antibody deficiencies (PAD), as well as to identify factors influencing the refusal of recommended SARS-CoV-2 vaccination among patients with IEI in Latvia.

Tasks of the Thesis

1 To collect and analyse data on patients with inborn errors of immunity (IEI) to determine their prevalence in the Latvian population.
2 To assess SARS-CoV-2-specific T-cell and antibody-mediated immune responses in the study group (CVID and SIgAD patients) and the control group; to evaluate differences between the groups and examine associations between SARS-CoV-2-specific immune responses and disease phenotype/severity in the study group.
3 To assess cytokine level changes following SARS-CoV-2 antigen stimulation in the study group (CVID and SIgAD patients) and the control group; to compare intergroup differences and assess the associations between cytokine levels and disease phenotype/severity in the study group.
4 To investigate the reasons for refusal of recommended SARS-CoV-2 vaccination among patients with IEI.

Hypotheses of the Thesis

1 Patients with CVID exhibit lower SARS-CoV-2-specific antibody levels, whereas their T-cell responses are comparable to those observed in SIgAD patients and healthy controls, while the cytokine secretion profile elicited by SARS-CoV-2 antigen stimulation differs between the groups and correlates with disease phenotype and severity.

2 In addition to the factors influencing vaccine refusal in the general population, patients with IEI express specific concerns related to their underlying condition and its treatment.

Novelty of the Thesis

The study initially focused on determining the prevalence of inborn errors of immunity (IEI) in the Latvian population. This was the first investigation to report prevalence estimates of IEI in Latvia. From the overall cohort of IEI patients, individuals with predominantly antibody deficiencies (PAD) were selected for the subsequent phases of the study. PAD represents a specific group of IEI characterised by impaired vaccine-induced immune responses and a high frequency of non-infectious complications.

In studies on SARS-CoV-2-specific immune memory in PAD patients, antibody levels have most commonly been used as surrogate markers (Abo-Helo et al., 2021; Bergman et al., 2021; Delmonte et al., 2021; Ponsford et al., 2022), whereas data on SARS-CoV-2-specific T-cell memory are limited. Notably, to date, no study has specifically analysed cellular immune responses to SARS-CoV-2 antigen in patients with selective IgA deficiency (SIgAD).

Given that environmental factors – including antigen exposure – may influence both PAD development and the onset of non-infectious complications (Rodríguez-Ubreva et al., 2024), exploring immune response differences to SARS-CoV-2 antigen in PAD patients may provide novel insights into disease

pathogenesis. Since cytokines play a key role in T cell survival and differentiation, characterization of cytokine secretion may reveal functionally relevant differences with clinical significance (Abyazi et al., 2022). Only a few studies have explored associations between clinical phenotypes and immunological parameters (e. g. immunoglobulin levels, T and B cell subpopulations, baseline cytokine concentrations) with immune responses to SARS-CoV-2 antigen. Moreover, most studies evaluating T cell responses to SARS-CoV-2 antigen have focused on IL-2 and/or IFN-γ secretion (Hagin et al., 2021; Pham et al., 2022; Leeuwen van et al., 2022). This was the first study to assess a broader spectrum of cytokines following whole blood stimulation with SARS-CoV-2 antigen in PAD patients.

As some IEI diagnoses are associated with reduced antibody responses to SARS-CoV-2 vaccination and initial vaccine trials excluded individuals with IEI, the lack of data in this specific population served as a reason for hesitation among some patients regarding vaccination. Therefore, studies on immune responses are essential in patients with rare immune system disorders (Aberumand et al., 2022). However, there are additional reasons for vaccine refusal. To date, only three studies have explored the reasons for SARS-CoV-2 vaccine refusal among patients with IEI (Aberumand et al., 2022; Pergent et al., 2023; Więsik-Szewczyk et al., 2022), and none of these employed a qualitative research design. By using a qualitative approach, it is possible to identify novel, IEI-specific factors influencing vaccine refusal that may not be captured through pre-formulated, multiple-choice surveys designed by researchers. These context-specific factors may differ significantly from those observed in the general population and warrant deeper investigation.

Discussion

1 Prevalence of Inborn Errors of Immunity in Latvian Population

In the first part of the study, data on patients diagnosed with inborn errors of immunity (IEI) in Latvia were obtained from medical records in order to estimate the prevalence of IEI in the Latvian population and to select patients for subsequent stages of the research. In Latvia, IEI patients are monitored at Pauls Stradiņš Clinical University Hospital and the Children's Clinical University Hospital, and data were collected from both institutions.

Over a 27-year period from 1994 to 2020, a total of 173 patients with IEI were diagnosed in Latvia. The point prevalence of IEI in Latvia in December 2020 was 7.1 per 100,000 inhabitants. According to the European Society for Immunodeficiencies (ESID) registry data, the overall prevalence of IEI in European countries ranges from 1.3 per 100,000 inhabitants in Poland to 8.85 per 100,000 inhabitants in Ireland (Bonilla et al., 2016; Ryan et al., 2022). It should be noted that the prevalence of IEI in Latvia was initially very low but has increased in recent years: from 0.08 cases per 100,000 inhabitants in 1994 and 1.1 per 100,000 in 2004 to 7.1 per 100,000 inhabitants in 2020. In 2004, the international "J Project" – an educational and clinical research collaboration in the field of immunodeficiencies, now involving 32 countries – was launched. The aim of the J Project is to raise awareness and improve early diagnosis and treatment of IEI. In Latvia, as well as in other Eastern and Central European countries, the project has contributed to better recognition and diagnosis of IEI, resulting in an increase in patient numbers (Abolhassani et al., 2022). IEI diagnostics have also improved due to the introduction of new diagnostic methods and greater availability of genetic testing.

In Latvia, the most frequently diagnosed IEI group is combined immunodeficiencies with syndromic features, whereas in many other countries, PAD predominate – from 20 % of all IEI cases in Iceland to 63 % in Italy (Lougaris et al., 2020; Ludviksson et al., 2014). In J Project countries, PAD accounted for 46.3 % of all IEI patients, with combined immunodeficiencies being the second most common type (14.3 %) (Abolhassani et al., 2022). In contrast, PAD in Latvia accounts for only 21 % of all IEI cases. The lower proportion of PAD may be explained by under-recognition of these disorders.

For the most severe forms of IEI, the incidence of severe combined immunodeficiency (SCID) in Latvia between 1994 and 2020 was 1 in 32,963 live births. Early detection of this condition is crucial, as it allows for immediate isolation and referral for allogeneic hematopoietic stem cell transplantation. Outcomes are better in children who undergo transplantation before 3.5 months of age, prior to developing severe infections (Thakar et al., 2023). Newborn screening for early diagnosis of SCID has been implemented in 17 European countries (Blom et al., 2024) and, since 2023, also in Latvia (Ministry of Health, 2023). Following the introduction of screening, SCID detection rates are expected to rise, as cases that would otherwise result in early death from infection prior to diagnosis can now be identified, suggesting that the true incidence may be higher (Ricci et al., 2024).

This is the first study on the prevalence of IEI in the Latvian population. The main strength of the study is the long observation period and the availability of data from all Latvian centres treating these rare diseases. A potential limitation is the absence of a national registry for IEI patients, the possibility of incomplete information in medical records, and the likelihood that some patients remain undiagnosed or have not been referred to an immunologist, which means that the prevalence of IEI in Latvia may be underestimated.

2 Immunological Response of PAD Patients to the SARS-CoV-2 Antigen

For the second part of the study, from all IEI patients diagnosed in Latvia, those with the most common PADs were selected. This part of the study included 47 participants: 17 patients with CVID, 15 patients with SIgAD, and 15 individuals from the control group. Relevant clinical data for CVID and SIgAD patients were obtained from medical records and questionnaires. The patients in our study and control group participants had received a homologous vaccination regimen with one of the following vaccines – Pfizer-BioNTech/BNT162b2 (two or three doses), Spikevax mRNA-1273 (two or three doses), or Jcovden Ad26. COV2 (one dose); 50 % of patients and 53 % of control group participants had received a booster dose at least 6 months after completion of the primary vaccination series. The mean time since the last vaccine dose was 173 days in the patient group and 215 days in the control group. In this part of the study, the humoral and T-cell immune responses to the SARS-CoV-2 antigen in PAD patients were assessed.

Blood samples from study participants were collected between April and July 2022. To assess the SARS-CoV-2-specific humoral response, SARS-CoV-2 spike protein S1 domain – specific IgG antibody levels were measured using an enzyme-linked immunosorbent assay (ELISA). To determine the T-cell response specific to the SARS-CoV-2 spike protein S1 and S2 domains, the interferon-γ (IFN-γ) release assay (IGRA) QuantiFERON SARS-CoV-2 was used, which measured IFN-γ increase after stimulation with SARS-CoV-2 peptide antigens. For the detection of cytokine changes before and after stimulation with SARS-CoV-2 spike protein antigens, xMAP Luminex technology was used. Differences in antibody levels, T-cell-derived IFN-γ, and other cytokines were assessed between the patient and control groups, and within

the patient group – also their association with clinical presentation and disease severity.

2.1 Humoral Response

Seroconversion, defined as an IgG antibody level specific to the SARS-CoV-2 spike protein exceeding the positivity threshold, was observed in 93 % of CVID patients and in all SIgAD patients and control group participants. In contrast, other studies have reported substantial variation in seropositivity rates among PAD patients, with rates ranging from 15 % to 100 % in adult populations (Abella et al., 2022; Amodio et al., 2021; Barmettler et al., 2022; Bergman et al., 2021; Delmonte et al., 2021; Göschl et al., 2022; Hagin et al., 2021; Lin et al., 2022; Oyaert et al., 2022; Pham et al., 2022; Pulvirenti et al., 2021; Salinas et al., 2021; Shields, Faustini, Hill, Al-Taei, Walder, et al., 2022a; Squire & Joshi, 2021; Steiner et al., 2023; A. M. Zhang et al., 2024). It should be noted, however, that many of these studies had relatively small sample sizes. In studies with larger CVID cohorts, seropositivity rates ranged from 66 % to 81 % (Shields, Faustini, Hill, Al-Taei, Tanner, et al., 2022; Leeuwen van et al., 2022). This broad variation may also be explained by differences in study methodologies and disease heterogeneity, prior COVID-19 infection history, differences in vaccination regimens, and the time elapsed since the last vaccine dose (Quinti et al., 2022; Steiner et al., 2023).

Although the majority of our study participants achieved specific antibody levels above the positivity threshold, SARS-CoV-2-specific antibody levels were lower in CVID patients compared with healthy controls and SIgAD patients. This finding aligns with other studies reporting both a lower initial SARS-CoV-2-specific antibody response and a more rapid decline in antibody levels after vaccination in CVID patients compared with other IEI patients or controls (Pino-Molina del et al., 2021; Shields, Faustini, Hill, Al-Taei, Tanner, et al., 2022; Leeuwen van et al., 2023). We did not assess neutralizing capacity;

however, in CVID, even quantitatively adequate antibody levels may be associated with reduced quality – lower avidity, impaired neutralizing capacity, and a restricted antibody repertoire (Nadesalingam et al., 2023; Pham et al., 2022; Shields, Faustini, Hill, Al-Taei, Walder, et al., 2022a; Steiner et al., 2023; Troelnikov et al., 2023). These findings have been attributed to impaired germinal center formation and memory B-cell development. For example, after Pfizer-BioNTech/BNT162b2 vaccination, CVID patients had reduced numbers of SARS-CoV-2-specific memory B cells compared with controls, and a higher proportion of atypical memory B cells, likely generated in extrafollicular rather than germinal center reactions, resulting in shorter antibody persistence (Salinas et al., 2021). Another study found reduced IgG1+ and CD11c+ memory B cells after primary mRNA vaccination in PAD patients, suggesting defects in B-cell receptor signaling and/or reduced T-cell help (Lin et al., 2022).

In our study, neither prior COVID-19 infection nor its severity was associated with SARS-CoV-2-specific antibody levels or seropositivity. However, at the time of the study in April 2022, the majority of patients (59 %) and controls (53 %) had already been exposed to SARS-CoV-2. The rarity of these diseases limited the sample size and thus the statistical power to detect significant associations. Previous studies have shown that PAD patients with prior COVID-19 infection had higher post-vaccination antibody levels than infection-naïve patients (Shields, Faustini, Hill, Al-Taei, Walder, et al., 2022), although other studies found no such association in IEI patients (Erra et al., 2022).

No differences were observed between vaccine types and SARS-CoV-2-specific antibody levels or seropositivity in our study. Similarly, the COV-AD study reported no difference in immunogenicity between several homologous vaccine regimens in PAD patients (Shields, Faustini, Hill, Al-Taei, Tanner, et al., 2022), whereas another study including various IEI patients found higher immunogenicity for Spikevax mRNA-1273 compared with other

vaccines (Sputnik V, Oxford-AstraZeneca ChAdOx1, Sinopharm/BIBP, Pfizer-BioNTech/BNT162b2) (Erra et al., 2022). All patients in our study received homologous regimens, while some studies reported higher seropositivity with heterologous regimens (e. g. Oxford-AstraZeneca ChAdOx1 primary series and Pfizer-BioNTech/BNT162b2 booster) (Kamar et al., 2021; Shields, Faustini, Hill, Al-Taei, Tanner, et al., 2022; Zimmerman et al., 2022). In our study, the number of vaccine doses was not associated with seropositivity or antibody levels, and our design did not allow assessment of antibody kinetics after each dose. However, other studies have shown that some CVID patients without seroconversion after the first mRNA dose developed positive antibody levels after additional doses, and avidity improved (Delmonte et al., 2021; Goda et al., 2022; Shin et al., 2022; Barmettler et al., 2022; Shields, Faustini, Hill, Al-Taei, Tanner, et al., 2022; Tandon et al., 2023; Zimmerman et al., 2022). This suggests that multiple vaccine doses are clinically beneficial, especially in high-risk PAD patients (A. M. Zhang et al., 2024). Another study found that revaccination corrected the IgG1 class-switching defect in PAD patients' memory B cells (Lin et al., 2022). However, other reports suggest that CVID patients without an initial response may not improve after a third or fourth mRNA dose (Nielsen et al., 2022; Leeuwen van et al., 2023). Overall, although many CVID patients produce detectable SARS-CoV-2-specific antibodies, some still fail to mount a sufficient immune response, which could theoretically be predicted based on baseline immune profiles and clinical features.

Previous reports have indicated that PAD patients with a history of autoimmunity or other non-infectious complications have a poorer response to vaccination (Durkee-Shock & Keller, 2022; Goda et al., 2022; Pulvirenti et al., 2021; Shin et al., 2022; Leeuwen van et al., 2023). However, some studies have found no association between immune response and clinical manifestations (Mizera et al., 2023; Steiner et al., 2023). In our study, no association was found

between SARS-CoV-2-specific IgG levels and clinical manifestations of the disease, although interpretation of these data should take into account the limited sample size, which reduced the ability to detect significant associations. Nevertheless, it should be noted that while the SARS-CoV-2 spike protein-specific IgG level did not directly correlate with clinical parameters in our study, we did find an association between cytokine levels produced by cells involved in antibody synthesis and the presence of autoantibodies in patient sera. This association will be discussed further in the Discussion section.

No statistically significant correlation was observed between SARS-CoV-2-specific antibody and T-cell responses in the CVID group. In contrast, in the SIgAD and control groups, a correlation was observed between SARS-CoV-2-specific antibodies and T-cell immunity, a trend also described in studies of healthy individuals – a positive correlation between the frequency of SARS-CoV-2 spike protein-specific T cells (CD4+ and CD8+) and IgG antibody levels early after vaccination, suggesting the parallel development of adaptive humoral and cellular immunity (Boppana et al., 2021; Sahin et al., 2021). In other studies, including PAD patients, however, specific antibody titers did not correlate with T-cell response (Göschl et al., 2022; Mizera et al., 2023). Regarding correlations between T-cell subpopulations and SARS-CoV-2-specific humoral response, our study found an association between humoral response and the number of central memory CD8+ cells, and specifically in the SIgAD group – also with the number of central memory CD4+ cells, similar to findings previously described in PAD patients (Rosenthal et al., 2023; Shin et al., 2022).

In our study, no association was found between SARS-CoV-2-specific antibody response and the number of B-cell subpopulations, a result similar to another study of early post-vaccination responses in IEI patients (Amodio et al., 2021). However, other studies have reported associations between post-vaccination SARS-CoV-2 humoral response and baseline IgG, IgA, total

B-cell counts, switched memory B cells, marginal zone-like B cells, regulatory B cells, or CD21low B-cell counts in PAD patients (Antolí et al., 2022; Barmettler et al., 2022; Gupta et al., 2024; Pham et al., 2022; Sauerwein et al., 2022; Shin et al., 2022). In our study, EUROclass phenotypes were also not associated with SARS-CoV-2-specific humoral response, and no other reports on this association in the context of SARS-CoV-2 vaccination are currently available.

It is important to note that interpretation of SARS-CoV-2-specific antibody levels in this and other studies may be influenced by the fact that CVID patients receive immunoglobulin replacement therapy. It is possible that immunoglobulin preparations contained specific antibodies to the SARS-CoV-2 antigen at the time of blood sampling in April 2022 (Babaha & Rezaei, 2020; Göschl et al., 2022). To minimize potential interference, blood samples in our study were collected before the next scheduled immunoglobulin infusion. The time from donor plasma collection to the distribution of a ready-to-use immunoglobulin product is usually up to one year (Zimmerman et al., 2022). In other studies, CVID patients without a SARS-CoV-2-specific humoral response after vaccination were also receiving IgG replacement therapy, making it unlikely that passive immunization from IgG therapy significantly influenced the results of SARS-CoV-2 antibody analysis (Arroyo-Sánchez et al., 2022; Nielsen et al., 2022; Pham et al., 2022; Sauerwein et al., 2022; Shin et al., 2022; Volk et al., 2022). A similar finding was observed in our study group: a patient receiving immunoglobulin replacement therapy – achieving normal serum IgG levels, confirming treatment adherence – had SARS-CoV-2-specific antibody titers below the reference interval positivity threshold. Furthermore, immunoglobulin replacement products tested in the first half of 2022 still had low antibody titers both against the SARS-CoV-2 spike protein and against

the receptor-binding domain (Farcet et al., 2022; Nielsen et al., 2022; Romero et al., 2022; Zimmerman et al., 2022).

2.2 T-cell response

CD8+ T cells play a crucial role in the antiviral response during acute infection, whereas B and CD4+ T cells are essential for preventing viral infection and ultimately clearing the virus (Wolf de et al., 2022). If a virus infects an immunocompetent person with acquired immunity to that virus, activated CD8+ cytotoxic T lymphocytes limit the spread of intracellular viral components by releasing granzymes and perforins, delivering apoptosis signals, and secreting immunostimulatory cytokines, including IFN-γ and TNF-α. In viral infections, the role of various CD4+ T-cell subpopulations is to coordinate and regulate antiviral immunity (Apostolidis et al., 2021; Piazza di et al., 2021).

In our study, a T-cell response to the SARS-CoV-2 antigen was detected in the majority of patients with CVID (93 %) and SIgAD (92 %), measured as an increase in IFN-γ synthesis following stimulation with SARS-CoV-2-specific antigens in the IGRA assay. In other studies, T-cell responses have been reported in 53 % to 90 % of patients with IEI (Amodio et al., 2021; Antolí et al., 2022; Delmonte et al., 2021; Gernez et al., 2022; Goda et al., 2022; Göschl et al., 2022; Hagin et al., 2021; Lin et al., 2022; Mizera et al., 2023; Oyaert et al., 2022; Salinas et al., 2021; Steiner et al., 2023).

In our work, no statistically significant differences in SARS-CoV-2-specific T-cell responses were observed between the PAD patient and control groups, consistent with findings from other studies (Abolhassani et al., 2022; Goda et al., 2022; Göschl et al., 2022; Gupta et al., 2024; Hagin et al., 2021; Murray et al., 2023; Pham et al., 2022; Leeuwen van et al., 2023). This aligns with disease pathogenesis, as PID patients primarily have impaired antibody production rather than peripheral T-cell function (Tangye et al., 2022). In several studies, T-cell responses in PID patients were even more pronounced compared to controls

(Ainsua-Enrich et al., 2022; Amodio et al., 2021; Delmonte et al., 2021), possibly due to compensatory T-cell function in patients with primary B-cell defects (Amodio et al., 2021).

However, PIDs are a heterogeneous group of disorders, and some studies have found that CVID patients have reduced T-cell responses compared to controls (Ainsua-Enrich et al., 2022; Antolí et al., 2022; Gupta et al., 2021; Sauerwein et al., 2022; Leeuwen van et al., 2023). For example, in a study assessing SARS-CoV-2 spike protein-specific cytotoxic T-cell activation, CVID patients had a lower number of spike-specific activated CD8+CD25+ T cells compared to controls, and this did not improve even after the third vaccine dose. Although the IFN-γ positivity threshold was reached as frequently in CVID patients as in controls, the absolute number of IFN-γ–secreting T cells was significantly lower in CVID patients (Ainsua-Enrich et al., 2022). Similarly, another small study found reduced numbers of SARS-CoV-2 spike-specific cytotoxic T cells (CD8+ CD107a+ granzyme B+ perforin+) in CVID patients compared to healthy controls or patients with X-linked agammaglobulinemia (Gupta et al., 2021). These conflicting results may reflect methodological differences and disease heterogeneity. Although most PID patients do not have primary T-cell defects, mild cellular immune impairments are possible in some cases. For example, in certain patients, an antibody production defect may be due not to a primary B-cell dysfunction, but to reduced T follicular helper cell support for B cells in the germinal centre reaction of secondary lymphoid organs (Amodio et al., 2021; Sepahi et al., 2024). Specific pathogenic gene variants related to CVID can also impair T-cell immune responses; for instance, pathogenic variants in NFKB1 disrupt the NF-κB signalling pathway – an essential transcription factor regulating antigen-specific immune responses – and may also cause excessive proinflammatory cytokine (IL-1β, TNF-α, IFN-γ) expression, potentially contributing to autoimmunity (Dieli-Crimi et al., 2018).

Although our study found no statistically significant link between clinical manifestations and T-cell responses, it is worth noting that the only CVID patient without a detectable T-cell response had three autoimmune diseases and a confirmed pathogenic NRAS variant on genetic testing. This patient showed no IFN-γ increase because the baseline serum IFN-γ level before antigen stimulation was similar to the post-stimulation levels seen in other samples. Previous reports have described enhanced type I IFN pathway activation in patients with NRAS pathogenic variants (Papa et al., 2021), but elevated type II IFN levels have not been reported. Immunosuppressive therapy may also account for reduced T-cell responses after vaccination. In our study, the only SIgAD patient without a positive T-cell response (low serum IFN-γ both before and after antigen stimulation) had rheumatoid arthritis and was receiving immunosuppressive therapy, including biologics. Previous studies have similarly reported poor T-cell responses in patients on immunosuppression (Liebers et al., 2022; Oyaert et al., 2022; Sleen van et al., 2023).

In our study, there were no differences in T-cell responses between recipients of different vaccines, consistent with other IEI studies (Arroyo-Sánchez et al., 2022; Erra et al., 2022; Shields, Faustini, Hill, Al-Taei, Walder, et al., 2022). We found no association between the magnitude of T-cell response and prior COVID-19 infection or disease severity. Data on this point are mixed – some studies have similar findings (Erra et al., 2022), while the COV-AD study found stronger T-cell responses in patients with prior COVID-19 compared to COVID-19-naïve PID patients (Shields et al., 2022).

In this study, no significant association was found between SARS-CoV-2-specific T-cell responses and T-cell subsets, as also reported in other studies (Antolí et al., 2022; Goda et al., 2022; Shields et al., 2022). Patients without a detectable T-cell response did not differ significantly in T-cell subset frequencies in our study or in others (Amodio et al., 2021). We also found no

significant correlation between SARS-CoV-2-specific T-cell responses and B-cell subsets, or total IgG, IgM, or IgA levels, consistent with prior reports (Goda et al., 2022; Shields et al., 2022). In our cohort, EUROclass phenotypes were not associated with T-cell responses, and no other reports addressing this point in the context of SARS-CoV-2 vaccination are available.

Differences in T-cell responses were not linked to clinical parameters, except in the SIgAD group, where patients with recurrent otitis had significantly lower T-cell responses compared to those without this infection. However, in other studies, as with absent SARS-CoV-2-specific antibody responses, absent T-cell responses were seen in patients with autoimmune diseases (Amodio et al., 2021; Hagin et al., 2021; Leeuwen van et al., 2022) and benign lymphoproliferation (Arroyo-Sánchez et al., 2022), although some studies did not find such associations (Goda et al., 2022). Interpretation of these data must take into account the sample size, which limited the ability to detect significant associations.

The method used to assess T-cell responses has limitations that must be considered: T-cell responses are complex and can activate various molecular pathways, resulting in different functional cytokine expression profiles. In this study, we used a commercially available IGRA assay to measure SARS-CoV-2-specific T-cell immunity, but methodological variability is high (e. g. assays based on cytokine secretion profiles, antigen-induced proliferative responses, expression of specific activation markers, delayed-type hypersensitivity skin tests, etc.), and no consensus exists on the single most accurate method for characterizing antigen-specific T-cell responses, which complicates comparison across studies (Barrios et al., 2022; Friedmann et al., 2020).

Overall, although our study did not find statistically significant differences in SARS-CoV-2-specific IFN-γ responses between CVID, SIgAD, and control groups,

this does not exclude the possibility that in some cases PID patients may have impairments in the secretion of other cytokines (Lin et al., 2022).

3 Cytokine Secretion Profile of PAD Patients after SARS-CoV-2 Antigen Stimulation

The results of this study revealed that PAD patients exhibited a statistically significant increase in IFN-γ, TNF-α, IL-1β, IL-10, IL-15, and IL-17A levels after whole blood stimulation with SARS-CoV-2 antigen, while IL-21, IL-4, and IL-6 levels did not increase. Conversely, TGF-β1 levels were lower after incubation with SARS-CoV-2 antigen compared to baseline. No differences were observed between groups (SIgAD, CVID, and control) in the dynamics of cytokine level changes, whereas in measurements without antigen incubation (cytokine baseline levels), several cytokine differences were noted: PAD patients had higher baseline IL-10 and IL-4 levels compared to controls. Previously, IL-4 signalling pathway disruptions have been associated with CVID severity (Taraldsrud et al., 2017). Another study reported that increases in cytokines IL-10, IL-12, IFN-γ, IL-6, IL-8, and IL-22 one month post SARS-CoV-2 vaccination were higher in CVID patients compared to pre-vaccination levels, while other cytokines (IL-1β, IL-4, IL-5, and TNF-α) did not show differential increases versus controls (Rosenthal et al., 2023).

As mentioned earlier, vaccinated PAD patients showed higher IFN-γ levels after SARS-CoV-2 antigen stimulation compared to unvaccinated patients who had recovered from COVID-19. In this study, no differences were found in other cytokine level changes after stimulation between vaccinated and unvaccinated patients, although a prior study in healthy individuals demonstrated that TNF-α responses to stimulation with SARS-CoV-2 peptide pools (spike, nucleocapsid, and membrane proteins) were significantly higher in vaccinated versus unvaccinated convalescent participants (Li et al., 2021). This discrepancy

may relate to differences in the peptide pools used for antigen stimulation and the relatively small sample size of this dissertation study.

Further, this work explored whether SARS-CoV-2-specific cytokine responses correlated with immunological and clinical phenotypes of PAD patients, including non-infectious complications. In this study, the presence of autoantibodies in PAD patient serum correlated with higher baseline IL-4 and TNF-α levels, as well as with an increase in IL-4 levels following SARS-CoV-2 antigen stimulation. IL-4 elevation also correlated with total IgG and IgM levels but not with SARS-CoV-2-specific IgG. Additionally, IL-21 increases post-stimulation correlated with CVID severity (as measured by a clinical severity scale that increases with both infectious and non-infectious complications). It is known that in germinal centres, TFH cells predominantly produce IL-21 and IL-4 to support B-cell survival, proliferation, and differentiation (Ueno, 2016). Deficiency of TFH-derived IL-4 results in inadequate B-cell help (Yusuf et al., 2010), and IL-21 defects associate with long-lived plasma cell abnormalities. In IL-21 receptor knockout mouse models (IL-21R-/-), initial germinal centre formation, immunoglobulin class switching, and virus-specific IgG responses were normal, but germinal centres dissipated earlier and long-lived plasma cell formation and sustained antibody levels were impaired (Rasheed et al., 2013). Other studies have linked IL-4 and IL-21 pathway defects in both CVID and SIgAD patients with increased prevalence of non-infectious complications, including autoimmunity (Desjardins et al., 2018; Ho & Cunningham-Rundles, 2020; Salzer et al., 2014; Singh et al., 2014; Yazdani et al., 2019).

Although a direct connection between COVID-19 and autoimmunity has not been established, multiple reports have described autoimmune disease development following COVID-19 infection (Banjongjit et al., 2024; Catriona & Paolo, 2022; Diao et al., 2020; Halpert & Shoenfeld, 2020; Kasperkiewicz &

Woodley, 2023; Kouranloo et al., 2023; Laxminarayana, 2022; Lyons-Weiler, 2020; Nabizadeh et al., 2022; Shoenfeld, 2020; Stathi et al., 2023; Y. Zhang et al., 2020). In immunocompetent COVID-19 patients, excessive plasmablast expansion associated with autoantibody production was observed. These plasmablasts developed under the influence of IL-4 and B-cell activating factor (BAFF), and two distinct memory B-cell populations with autoreactive features were identified (Schultheiß et al., 2021). Previous studies have also linked polymorphisms in IL-4 and IL-10 gene promoters with CVID development (Rezaei et al., 2010).

In this dissertation study, PAD patients with benign polyclonal lymphoproliferation – manifested as hepatomegaly, splenomegaly, and lymphadenopathy – showed a smaller increase in IL-10 levels after SARS-CoV-2 antigen stimulation compared to patients without these manifestations or controls. IL-10 is primarily produced by T cells, especially Tregs and TFH cells, as well as monocytes and regulatory B cells. It functions as an anti-inflammatory cytokine that can inhibit proinflammatory cytokine synthesis (Varzaneh et al., 2014). Previous studies linked splenomegaly with B-cell homeostasis dysregulation, including decreased switched memory B-cell numbers, indicative of germinal centre dysfunction (Wehr et al., 2008).

Interestingly, a 2024 study reported the first use of CD4+ T-cell inducible costimulator (ICOS) activation with vopratelimab in CVID treatment, which significantly increased total TFH and TFH2 cell counts and normalised IL-4, IL-10, and IL-21 secretion in vitro. Vopratelimab treatment also increased plasma cells, IgG+ B cells, decreased naïve and transitional B cells, and significantly increased IgG1 secretion in CVID patients. Remarkably, vopratelimab restored IgA secretion in vitro in several CVID patients with complete endogenous IgA deficiency in serum, supporting the clinical

importance of IL-4, IL-10, and IL-21 dysfunction in CVID pathogenesis (Sepahi et al., 2024).

In our study, alongside the aforementioned cytokine changes, a decrease in TGF-β1 levels after whole blood stimulation with SARS-CoV-2 antigen was observed, more pronounced in patients with lower SARS-CoV-2-specific IgG titers. TGF-β1's role in antibody synthesis mainly involves inducing Treg activity to suppress B cells (Strainic et al., 2013; Xu et al., 2016) and promoting class switching primarily to IgA1 and IgA2 antibodies (Ferreira-Gomes et al., 2021). Various cells, including most immune cells, can produce TGF-β1 in response to infection; it mainly acts as a regulator of immune cells such as Tregs, NK cells, and macrophages (Ramírez-Martínez et al., 2022). TGF-β1 is initially produced as a latent complex requiring activation, which can occur via multiple mechanisms including Treg-mediated pathways (Liénart et al., 2018). TGF-β1 can activate NF-κB, further regulating expression of cytokines such as IFN-γ, TNF-α, and IL-1β (Hamidi et al., 2021; Yan et al., 2022). In our PAD patient group, changes in TGF-β1 negatively correlated with IL-1β and TNF-α levels. A possible explanation for decreased TGF-β1 after SARS-CoV-2 stimulation is TNF-α and IL-1β-induced activation of SMAD7 (main signal transducers for receptors of TGF- β superfamily) expression, which inhibits TGF-β1 synthesis (Bitzer et al., 2000; Liang et al., 2024). Additionally, TNF-α levels were significantly higher in patients with low switched memory B-cell counts (EUROclass B+SmB−).

The study has several limitations. First, the sample size was limited due to the rarity of these diseases and the relatively small and imbalanced control group, reducing statistical power and the ability to detect significant associations. Second, the observational design and long post-immunization time window precluded evaluation of immune response dynamics. Third, SARS-CoV-2 infection history was assessed based on medical records and PCR tests rather

than anti-nucleocapsid antibody testing, potentially limiting the accuracy of hybrid immunity detection, especially in mild or asymptomatic infections. Fourth, SARS-CoV-2-specific memory B-cell evaluation and neutralizing antibody capacity were not included. In healthy patients after COVID-19, SARS-CoV-2-specific memory B-cell numbers tend to increase for several months post-infection (Dan et al., 2021). Lastly, whole blood antigen stimulation has limitations: T-cell responses are complex, activating various cell subsets and molecular pathways, producing diverse cytokine expression profiles. Moreover, only the SARS-CoV-2 spike protein antigen was used; nucleocapsid and membrane proteins were not included. IL-2 cytokine analysis was excluded due to technical reasons. Comparison with other studies is limited due to methodological differences.

4 Reasons for Refusal of Recommended SARS-CoV-2 Vaccination

As mentioned, the most common clinical manifestation of inborn errors of immunity (IEI) is increased susceptibility to infectious diseases, which might suggest that these patients would be especially interested in infection prevention measures. However, despite the fact that responsible institutions recommended SARS-CoV-2 vaccination for IEI patients (ESID, 2022), and multiple studies demonstrated vaccine safety specifically in this patient group and reported positive immune response markers after vaccination (Bergman et al., 2021; Milito et al., 2023), there were patients who refused vaccination against SARS-CoV-2.

This is the first study that used qualitative research methods to gain a broader understanding of the motivations underlying IEI patients' decisions to refuse vaccination. The dissertation concluded that patients' choices to refuse SARS-CoV-2 vaccination were influenced by several interrelated and reinforcing reasons. The main themes identified as reasons for refusal were: (1)

fear and uncertainty, (2) concerns about risks and perceived lack of benefits, (3) external influences from people around them, (4) distrust and unwillingness to comply, and (5) personal beliefs about vaccination and COVID-19.

4.1 Fear and Uncertainty

Several patients in the study reported fear of SARS-CoV-2 vaccination. Some could specify the reasons for their fear, while others described more vague fears not linked to rational considerations. Patients also felt unique due to their disease and felt that recommendations offered to the general population by public health specialists did not apply to them. Some participants emphasized feelings of confusion and uncertainty about what to consider truth versus myth. From a vaccine communication perspective, healthcare professionals play a crucial role in building trust, informing patients about the personal benefits of vaccination, and addressing these patients' specific concerns and misinformation regarding SARS-CoV-2 vaccines (Silver et al., 2022). Trust between doctors and patients is especially important; it has been shown that a personal recommendation from a healthcare provider positively influences vaccination decisions (Fernandes et al., 2021; Silver et al., 2022). These results also highlight the importance of ensuring physicians' and nurses' awareness about the efficacy and safety of SARS-CoV-2 vaccination in individuals with IEI (Pergent et al., 2023).

4.2 Risk and Benefit Assessment

A reduced perception of possible benefit combined with concerns about health deterioration after vaccination led some participants to consider the risks associated with vaccination greater than its potential benefits. Previous studies showed that IEI patients who refused vaccination most frequently expressed concerns that vaccination would not provide sufficient protection against COVID-19; followed by concerns about allergic reactions, unknown vaccine side effects, or possible disease exacerbation (Aberumand et al., 2022; Pergent

et al., 2023). In contrast, in the general population, the most commonly cited concerns relate directly to possible vaccine side effects. In our study, patients with antibody deficiency noted that a reason for refusal was their previous lack of antibody development after vaccinations for other vaccine-preventable diseases. Furthermore, although most people in this study group were convinced that COVID-19 is a severe disease, some patients perceived the potential threats posed by vaccines as more serious than the illness itself. A study in the Latvian general population revealed that subjectively perceived susceptibility to COVID-19 was not identified as a factor influencing SARS-CoV-2 vaccination behaviour (Šuriņa et al., 2021), unlike in other countries (Al-Amer et al., 2022).

4.3 External Influences

Narratives about negative health outcomes following SARS-CoV-2 vaccination are also present in the Latvian population (Šuriņa et al., 2021) and may affect IEI patients' attitudes toward vaccination. Some participants shared negative experiences from family members or close friends, others from more distant sources including healthcare workers and legislators. Several study participants admitted hearing these stories on social media platforms. Studies have also confirmed a connection between media discourse and willingness to vaccinate: in countries where social media discussions focus more on side effects or negative emotions related to SARS-CoV-2 vaccination, vaccine uptake rates are lower (Jun et al., 2022).

4.4 Distrust and Unwillingness to Comply – "Individual vs. System"

Previous studies showed that the majority of IEI patients' concerns were specifically related to the SARS-CoV-2 vaccine, and only 1.7–4.7 % expressed distrust of vaccines in general (Aberumand et al., 2022; Pergent et al., 2023). In our study, participants also expressed views on topics such as distrust of

the medical system or policy-makers. Many of these factors influencing vaccine hesitancy were also identified in the Latvian general population, so they are not unique to immunocompromised groups. Interestingly, another Latvian general population study found that trust in state institutions and fear of COVID-19 are key determinants of SARS-CoV-2 vaccination behaviour (Šuriņa et al., 2022). Trust in vaccination can be viewed at three levels: trust in the specific vaccine product (e. g. the SARS-CoV-2 vaccine and its developers), trust in the vaccine provider (e. g. healthcare workers), and faith in legislators (e. g. government and health system leadership) (Maciuszek et al., 2023; Prati, 2020). Our study data indicate that patients' perceptions of vaccine efficacy and safety are influenced by distrust at all three levels. Other studies confirm that distrust in state institutions directly affects the willingness of people to act according to recommendations, whereas trust and confidence in the state and healthcare system correlate with greater willingness to vaccinate against SARS-CoV-2 (Chan et al., 2020). Distrust of policymakers, combined with psychological and structural factors, is considered an important aspect shaping belief in conspiracy theories (Kim & Kim, 2020; Simione et al., 2021; Uscinski et al., 2020; Prooijen van, 2019). Some participants also reported feeling that vaccination was forced upon them and that their personal bodily autonomy was restricted, creating a stronger desire to resist SARS-CoV-2 vaccination; a similar tendency was observed in a study among Latvian healthcare workers (Lielsvagere-Endele et al., 2022). While mandatory vaccination may be effective in the short term, it can potentially provoke resistance and adverse attitudes toward vaccination in the long term (Bardosh et al., 2022).

4.5 Personal Beliefs about Vaccination and COVID-19

Negative personal experiences related to vaccination and mistaken beliefs were factors deterring IEI patients from vaccination in our study. Some erroneous beliefs were widespread vaccine myths, such as the idea that vaccines can

"overload" or "weaken" the immune system (Geoghegan et al., 2020). Others were specific to IEI patients, for example, the belief that vaccination is unnecessary if a patient receives immunoglobulin replacement therapy. This belief is incorrect and not consistent with ESID recommendations (ESID, 2022). Firstly, immunoglobulin preparation is a complex process lasting several months (up to about a year), so SARS-CoV-2-specific antibodies appear in these products with a delay (Jin et al., 2021; Pham et al., 2022). Secondly, even if a specific antibody response to vaccination is absent in a patient, T-cell immune responses may be normal and provide additional protection against SARS-CoV-2 infection (Amodio et al., 2021; Bergman et al., 2021; Li et al., 2021; Moss, 2022; Shields et al., 2022).

Hope that vaccines provide complete sterile immunity, combined with a tendency to assess vaccine effectiveness based not on empirical evidence but on a limited number of cases observed in close social circles, was an additional factor contributing to scepticism about vaccine efficacy. These misconceptions may be linked to insufficient health literacy among the Latvian population. Previous studies show that approximately 79 % of Latvian residents have weak health literacy competencies, which may contribute to widespread risky health behaviours, including vaccine refusal (Gatulytė et al., 2022). However, other studies show that education in the general population has less influence on vaccine hesitancy than trust in healthcare and science. This suggests that lack of knowledge may be less significant than public trust in healthcare and science (Rughiniș et al., 2022).

This part of the study has several limitations. First, interviews were conducted from April to August 2023, i. e., around the end of the pandemic situation in May 2023. Considering that vaccination initiatives were mainly carried out in 2021 and 2022, recall bias is possible. However, this timing also allowed exclusion of IEI patients who were willing to vaccinate. Second, some

specific IEI diagnosis groups may be underrepresented. Third, multiple models explaining vaccine hesitancy exist. In our study, the Health Belief Model was used to design interview questions. Other models exist, such as the 5C model, which considers confidence, complacency, constraints, calculation, and collective responsibility as factors influencing vaccine hesitancy (Gendler & Ofri, 2021). Our interview questions did not include constraints (e. g. physical or financial access), self-efficacy, or views on collective responsibility, as these were not predicted to be important in deterring immunodeficient patients from vaccination (Aberumand et al., 2022; Pergent et al., 2023; Więsik-Szewczyk et al., 2022). Nevertheless, the semi-structured interview format and open questions allowed participants to express any vaccination-related concerns. Also, vaccination was easily accessible through specialised vaccination centres or family doctor practices across Latvia and was provided free of charge, minimizing access-related concerns as factors influencing SARS-CoV-2 vaccination behaviour.

In conclusion, reasons for refusal of recommended SARS-CoV-2 vaccination among IEI patients in Latvia are multifaceted, involving political context as well as societal and individual psychological factors. While most reasons for vaccine hesitancy in this group mirror those in the general population, the data indicate that immunodeficient individuals have unique beliefs and concerns influencing their vaccination decisions.

Conclusions

1 The point prevalence of inborn errors of immunity (IEI) in Latvia in December 2020 was 7.1 per 100,000 inhabitants.

2 SARS-CoV-2-specific T-cell responses in patients with CVID and SIgAD did not differ significantly from those in the control group, whereas the humoral response in CVID patients was significantly lower compared to both SIgAD patients and healthy controls.

3 Humoral immune responses did not differ significantly between clinical phenotypes of PAD; however, post-stimulation changes in the levels of several cytokines (IL-4, IL-10, IL-21, TNF-α) showed a tendency toward association with clinical manifestations or phenotypes.

4 Among IEI patients, specific disease-related reasons for vaccine refusal were identified, including the belief that vaccination is contraindicated in immunodeficient individuals, and the perception that SARS-CoV-2 vaccination is unnecessary if receiving immunoglobulin replacement therapy.

Proposals

1 A lower proportion of predominantly antibody deficiencies (PAD) was observed among diagnosed IEI patients in Latvia. Continued efforts are needed to improve PAD recognition and diagnosis within the Latvian population by educating healthcare professionals who may be involved in the care of these patients.

2 SARS-CoV-2-specific T-cell responses in PAD patients did not differ from those in the control group, and the majority of patients also demonstrated a positive humoral response. SARS-CoV-2 vaccination should therefore be recommended for this patient group.

3 Healthcare professionals play a crucial role in building trust, communicating the personal benefits of vaccination, and addressing disease-specific concerns and misinformation regarding SARS-CoV-2 vaccines in this patient population.

List of publications, reports and patents on the topic of the Thesis

Publications:

1. Prokofjeva, T., Lucane, Z., Kovalova, Z., Kurjane, N. 2022. Inborn Errors of Immunity in Latvia: Analysis of Data from 1994 to 2020. *J Clin Immunol*. 24.02.2022. 42:876-879. doi: 10.1007/s10875-022-01229-1.

2. Lucane, Z., Freidenberga, D., Kurjane, N. 2021. Inborn error of immunity as the cause of recurrent pericarditis. *BMJ Case Rep*. 19.05.2021. 14:e241449. doi: 10.1136/bcr-2020-241449.

3. Lucane, Z., Davidsone, Z., Micule, I., Auzenbaha, M., Kurjane, N. 2022. A novel frameshift variant in the ADA2 gene of a patient with a neurological phenotype: a case report. *Pediatr Rheumatol Online J.* 17.12.2022. 20:118. doi: 10.1186/s12969-022-00781-9.

4. Lucane, Z., Slisere, B., Ozola, L., Rots, D., Papirte, S., Vilne, B., Gailite, L., Kurjane, N. 2023. Long-Term Immunological Memory of SARS-CoV-2 Is Present in Patients with Primary Antibody Deficiencies for up to a Year after Vaccination. *Vaccines (Basel)*. 03.02.2023. 11:354. doi: 10. 3390/vaccines11020354.

5. Lucane, Z., Slisere, B., Gersone, G., Papirte, S., Gailite, L., Tretjakovs, P., Kurjane, N. 2023. Cytokine Response Following SARS-CoV-2 Antigen Stimulation in Patients with Predominantly Antibody Deficiencies. *Viruses.* 10.05.2023. 15:1146. doi: 10.3390/v15051146.

6. Lucane, Z., Kursite, M., Sablinskis, K., Gailite, L., Kurjane, N. 2023. COVID-19 Vaccination Coverage and Factors Influencing Vaccine Hesitancy among Patients with Inborn Errors of Immunity in Latvia: A Mixed-Methods Study. *Vaccines (Basel)*. 25.10.2023. 11:1637. doi: 10.3390/vaccines11111637.

Reports and theses at international congresses and conferences:

1. Lucāne, Z. ; Šlisere, B. ; Nokalna-Spale, I. ; Krike, P. ; Gerula, N. ; Jaunalksne, I. ; Kurjāne, N. Serum B-cell Activating Factor (BAFF) Levels are Unrelated to SARS-CoV-2-Specific T cell and Spike-Specific Antibody Responses. 2025. Rīga Stradiņš University International Research Conference on Medical and Health Care Sciences *Knowledge for Use in Practice,* Abstract book, 26.–28.03.2025., 142.

2. Rozevska, M., Lucane, Z., Ozola, L., Nartiša, I., Gailite, L., Rots, D., Kurjane, N. 2023. Clinical and genetic diversity of PAD: what is hidden behind PAD? Rīga Stradiņš University Conference *Baltic Immunology Day*, 17.11.2023.

3. Nartisa, I., Gailite, L., Lucāne, Z., Neiburga, K. D., Ozola, L., Rozevska, M., Vilne, B., Rots, D., Kurjane, N. 2023. Molecular characterization of Inborn errors of immunity (or primary immunodeficiencies) using Genome sequencing – first findings of the Latvian Council of Science project. Rīga Stradiņš University Conference *Baltic Immunology Day*, 17.11.2023.

4. Lucāne, Z., Papirte, S., Gersone, G., Straupmane, D., Šlisere, B., Vilne, B., Gailīte, L., Tretjakovs, P. & Kurjāne, N. 2023. Cytokine Profile in Patients with Primary Antibody Deficiency in Response to SARS-CoV-2 Antigen. Rīga Stradiņš University Research week 2023: *Knowledge for Use in Practice*. In: *Medicina (Kaunas)*. 59, Suppl. 2, 359.

5. Nartisa, I., Gailīte, L., Lucāne, Z., Vilne, B., Rots, D., Kurjāne, N. 2023. First results of using genome sequencing in discovering the molecular cause of primary immunodeficiencies. Rīga Stradiņš University Research week 2023: *Knowledge for Use in Practice*. In: *Medicina (Kaunas)*. 59, Suppl. 2, 370.

6. Neiburga, K. D., Lucāne, Z., Nartisa, I., Rots, D., Gailite, L., Kisand, K., Pajusalu, S., Vilne, B., Kurjane, N. 2023. Opportunities of RNA-seq in the molecular diagnosis of primary immunodeficiencies. Rīga Stradiņš University Research week 2023: *Knowledge for Use in Practice*. In: *Medicina (Kaunas).* 59, Suppl. 2, 584.

7. Lucane, Z., Slisere, B., Ozola, L., Straupmane, D., Nartisa, I., Rots, D., Paprite, S., Gailite, L., Vilne, B., Kurjane, N. 2022. Long-term humoral and cellular SARS-CoV-2 vaccine specific immune response in patients with primary antibody deficiencies, International online conference *Vaccines and Vaccination During and Post Covid Pandemics.* Abstract book, 07.–09.12.2022, 53: 3rd Place Award Certificate.

8. Lucane, Z., Slisere, B., Ozola, L., Gerula, N., Jaunalksne, I., Straupmane, D., Kurjane, N. 2022. T Cell Response to SARS-CoV-2 in patients with Common Variable Immunodeficiency and Selective IgA deficiency, *20th biennial Meeting of the ESID*: Abstract book, 12.10.2022, PD550.

9. Lucane, Z. 2022. Primary antibody deficiency – a pediatric diagnosis? *3rd European Advanced School of Internal Medicine postgraduated course endorsed by EFIM*, 03.07.2022.

10. Lucāne, Z. 2022. Bieži slimojošs bērns un ģenētiskās testēšanas nozīme imūndeficīta diagnostikā. Klīniskā gadījuma demonstrācija. Rīgas Stradiņa universitātes konference *Primārie prevalējoši antivielu deficīti – dažādās sejas klīniskajā praksē*, 25.05.2022.

11. Lucane, Z., Prokofjeva, T., Ozola, L., Kurjane, L. 2022. Atopic and autoimmune manifestations in patients with selective IgA deficiency in Latvia. *80th International Scientific Conference of the University of Latvia*. In: *Medicina (Kaunas).* 2022, 58, Suppl. 1, 136.

12. Lucāne, Z. 2021. Perikardīts kā primārs imūndeficīts. Latvijas Ārstu biedrības starpdisciplinārā konference *Primāri imūndeficīti klīniskajā praksē – bērniem un pieaugušajiem. Klīnisko gadījumu analīze*, 24.04.2021.

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