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Innate immune response after BNT162b2 COVID-19 vaccination associates with reactogenicity

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ABSTRACT

Background: The innate immune response is important for the development of the specific adaptive immunity, however it may also be associated with reactogenicity after vaccination. We explore the association between innate responsiveness, reactogenicity, and antibody response after first COVID-19 vaccination.

Methods: We included 146 healthy Dutch individuals aged 12–59 who received their first BNT162b2 (Comirnaty, Pfizer) COVID-19 vaccination. Data on reactogenicity were collected for each individual through daily questionnaires from day 0–5 after vaccination. From 60 participants, serum (adults) and plasma (adolescents) samples were collected before and/or 2 ± 1 days after vaccination to measure cytokines/chemokines as markers for innate responsiveness. Each individual was categorised into innate low, intermediate and high responder based on above or below the median value for each analyte detected after vaccination. For 137 participants, serum was collected at day 28 after vaccination for Spike S1- and RBD-antibody concentration. The associations between reactogenicity and/or innate responsiveness and/or log-transformed antibody concentration were explored using logistic and linear regressions.

Results: Most participants (85 %) reported both local and systemic symptoms after vaccination. Two participants reported no symptoms. More than half (54 %) reported one or more moderate symptoms. Significantly higher levels of pro-inflammatory mediators CXCL9, CXCL10, CXCL11, IFNγ and CCL20 in adults, and CXCL9, CXCL10 and CXCL11 in adolescents, were found after vaccination. Participants who showed high innate immune responsiveness had higher odds (OR 6.0; 95 % CI 1.4–33) of experiencing one or more moderate symptoms. No association was found between innate responsiveness or having one or more moderate symptoms with Spike S1- or RBD-antibody concentration at day 28 after vaccination.

Conclusion: Our results suggest an association between the strength of the innate immune response and the severity of reactogenicity to SARS-CoV-2 vaccination. However, more research is needed to understand the relation between reactogenicity and immunogenicity of COVID-19 vaccines.

1. Introduction

The first Coronavirus Disease 2019 (COVID-19) vaccines were licensed globally in December 2020, following trials that demonstrated good efficacy and an acceptable safety profile [1–4]. The first COVID-19 vaccine, in the European Union, that was granted market authorisation by the European Medicines Agency was BNT162b2 (Comirnaty; BioNTech-Pfizer) [5].

BNT162b2, the first messenger RNA (mRNA) vaccine, contained nucleoside modified mRNA encoding the spike protein of SARS-CoV-2

Abbreviations: BAU, binding antibody units; COVID-19, Coronavirus Disease 2019; IFN, interferon; IL, interleukin; N, nucleoprotein; NK, natural killer; RBD, receptor binding domain.

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encapsulated in lipid nanoparticles [6]. Upon vaccination, the individual's cells transcribe the mRNA to produce the spike protein. The vaccine adjuvants and antigens are recognised by innate immune cells such as natural killer (NK) cells, monocytes, macrophages and dendritic cells, which orchestrate a local immune response by releasing chemokines and cytokines and recruiting other immune cells [7,8]. These inflammatory events may cause local and systemic symptoms (reactogenicity) shortly after vaccination. The activation of the innate response is important for the development of the adaptive immunity, leading to antibody production [9].

We hypothesised that the early immune responses initiated after vaccination might be crucial for underlying vaccine immunogenicity and reactogenicity. Previous studies have shown a correlation between early innate inflammatory mediators and the occurrence of reactogenicity after vaccination. For example, serum cytokines and chemokines, such as C-reactive protein, interleukin (IL)-6, interferon(IFN)-y and CXCL10, were correlated with systemic reactogenicity in individuals who received the AS01 adjuvanted hepatitis B vaccine [10,11]. Furthermore, an interferon signalling transcriptional profile correlated with local reactogenicity, such as redness and swelling, but only after a second MF-59 adjuvanted influenza vaccination in children [12]. These findings indicate a causal link between the innate immune response and reactogenicity early after vaccination.

Research on the relationship between BNT162b2 vaccine reactogenicity and immunogenicity are disparate. Coggins et al. did not find an association between reactogenicity and SARS-CoV-2-Spike specific antibody titers [13]. However, other studies have observed a positive correlation between reactogenicity, particularly after the second BNT162b2 vaccination, and the development of anti-Spike specific antibodies, but not with T cell responses [14–17]. Takano et al. demonstrated that a decreased number of NK cells and Dendritic cells after BNT162b2 vaccination correlated with neutralizing antibody responses and reactogenicity, with IFNγ-inducible chemokines playing a crucial role [18]. Graydon et al. showed that NK cell activation post-BNT162b2 vaccination may contribute to reactogenicity, but baseline NK cell numbers did not correlate with Spike-specific IgG levels one month after second vaccination [19]. These studies have in common that reactogenicity does not appear to be a prerequisite for the development of a protective immune response. This indicates that vaccine immunogenicity may influence reactogenicity but that the underlying immunological mechanisms are highly complex.

In our study, we examined whether there is an association between the innate immune response and reactogenicity in the first days after following BNT162b2 vaccination in Dutch adolescents and adults. Additionally, we explored whether there is an link between reactogenicity or innate immune responsiveness and the concentrations of Spike S1- or RBD-antibodies at day 28 post-vaccination.

2. Methods

2.1. Ethical statement

Studies were conducted in compliance with the European Statements for Good Clinical Practice and the Declaration of Helsinki of the World Medical Association, and Ethical approval was obtained through the Medical Research Ethics Committee Utrecht (NL76440.041.21, EudraCT: 2021–001357-31). All participants of 12 years and older provided written informed consent. Additionally, for participants of 12–16 years of age written informed consent for participation in this study was also provided by the participants' parents or legal guardians.

2.2. Study population

This study was performed within the IIVAC (Immune response Induced by Vaccination Against COVID-19) study, a prospective cohort study with participant inclusions between May 2021 and August 2022 with last follow-up in February 2024 and a total participant inclusion of 1459 individuals. The IIVAC study aims to monitor and evaluate the immune response induced by COVID-19 vaccines (primary vaccination series and boosters) through self-sampling finger pricks in healthy individuals aged 12–59 in the Netherlands [20]. Participants from the IIVAC study were approached from the general population via several Personal Records Database drawings; by participation in other studies by the Dutch National Institute of Public Health and the Environment (RIVM), if consented to be contacted for additional research; or by spontaneous applications from interested citizens. Participants with cancer, transplants, chronic kidney disease, Down syndrome, HIV, autoimmune diseases and/or any immune deficiency through disease or medication were excluded from participation. Participants received their COVID-19 vaccination by Public Health Services (GGD) through the regular national vaccination campaign: approximately 75 % of the first vaccinations in the Netherlands in 2021 were with BNT162b2 (Comirnaty, Pfizer) 30 μg/dose, given intra-muscular in the upper arm [21].

Our study population consists of a subset of the IIVAC study population. We included participants who received their first COVID-19 vaccination between May and October 2021. Blood samples to investigate the innate immune response were collected through venepuncture by a nurse during a home visit. Due to practical and logistical limitations only a subset of individuals recruited in the reactogenicity study provided blood samples. Blood samples and questionnaires were taken prior to COVID-19 vaccination and at fixed intervals after vaccination (see 'Sample acquisition and procession' and 'Reactogenicity data collection'). Innate immune response and reactogenicity were only measured after first COVID-19 vaccination.

2.3. Sample acquisition and processing

Serum (adults), plasma (adolescents), and PBMC (adults and adolescents) samples were collected before the first vaccination (T0) and at day 2 (± 1 day) after first vaccination (T1). At 28 days (± 2 days) after the first vaccination (T2) and before the second COVID-19 vaccination was given, serum was collected. Blood was collected via venepuncture in coagulation or heparin tubes by a research nurse during a home visit. Once received by the laboratory, coagulation tubes were stored overnight at 4 °C and heparin tubes at room temperature, next day serum was aliquoted from centrifuged (1800 ×*g* for 10 min) coagulation tubes (Vacuette 8 mL tubes, Greiner Bio-one) and plasma was collected from heparin tubes after centrifugation (700 ×*g* for 10 min). Serum and plasma samples were frozen at −80 °C until use. PBMCs were isolated from blood collected in heparin tubes using Lymphoprep (Progen) density gradient and frozen in FBS and 20 % DMSO and stored at −135 °C until use.

2.4. Cytokine and chemokine analysis

Cytokines and chemokines were measured in undiluted serum (adults, i.e. aged 18 years and older) and 1:1 in PBS diluted plasma (adolescents, i.e. 12–17 years old) using a multiplex bead-based assay (LEGENDplex Human Anti-virus Response and LEGENDplex HU Proinflammatory Chemokine Panel, BioLegend) to quantify IL-1β, IL-6, IL-10, IL-12p70, IFN-α2, IFN-β, IFN-λ1, IFN-λ2/3, IFNγ, TNF-α, GM-CSF, CXCL1, CXCL5, CXCL8, CXCL9, CXCL10, CXCL11, CCL3, CCL4, CCL11, CCL17, CCL20 and MCP-1. Data were acquired using FACSCanto (BD Biosciences) and analysed using the data analysis Software Suite for LEGENDplex from Biolegend.

2.5. Reactogenicity data collection

Participants were asked to fill in a questionnaire once on their demographics and on their reactogenicity symptoms starting on the day of their first COVID-19 vaccination (day 0) up and to 5 days after

vaccination (day 5). Questions were asked on the presence of local injection site symptoms (redness, swelling, pain, bruising, impaired arm mobility, hard disc) and systemic symptoms (fever, myalgia, joint pain, headache, malaise, fatigue). The severity of these symptoms were reported in the questionnaire as none, mild, moderate, or severe for most systemic symptoms and impaired arm mobility. Fever was measured in degrees Celsius, and local injection site symptoms were measured in millimetres. In addition, questions were asked whether medical care was obtained for their reactogenicity symptoms, such as a consultation with a general practitioner, hospitalisation, and whether antipyretic medication (paracetamol and nonsteroidal anti-inflammatory drugs) were used.

2.6. SARS-CoV-2 Multiplex Immunoassay

SARS-CoV-2 multiplex immunoassays were carried out to determine specific serum IgG levels towards SARS-CoV-2 nucleoprotein (N), Spike S1 and receptor binding domain (RBD) (Sino Biological, 40,591-V08H) as described previously [22]. In short, serum was incubated with antigen-coupled beads for 45 min in the dark, followed by a 30 min incubation with goat-anti-human IgG. Samples were incubated in SM01 (Surmodics) and washing steps after each incubation were carried out with PBS. Antibody binding to antigen-coupled beads was determined with FM3D (Luminex) and antibody levels were expressed as binding antibody units (BAU)/ml for S1 and RBD. Antibody data for the 12–17-year-old and adult participants in this study were published previously [23,24]. The threshold for seropositivity was set at 10.1 BAU/mL for Spike S1 and 14.3 BAU/mL for N, as previously standardized for the Wuhan (vaccine) strain against the NIBSC/WHO COVID-19 reference serum 20/136 [25].

2.7. Data analysis

2.7.1. Reactogenicity

For analysis we excluded participants who received a COVID-19 vaccination other than BNT162b2, who did not complete their reactogenicity diary up and to 5 days after COVID-19 vaccination, and/or who tested positive for COVID-19 in the 5 days post vaccination (Fig. 1). We assumed that participants who filled in one or more questions every day up and to day 5 completed their diary. We assumed that symptoms were not present at the time of filling in the questionnaire if no answer was given on a specific day for those symptoms but one or more other questions for that day were answered.

We used descriptive statistics for the participants' characteristics. We calculated the median time between the T0 sample and vaccination, and between the T0 and T1 sample in days, between vaccination and T1 sample in hours, and between vaccination and T2 in days.

We categorised the severity of reported local and systemic symptoms into none (Grade 0), mild (Grade 1), moderate (Grade 2) or severe (Grade 3), where possible, to be in line with the Food & Drug Administration Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials [26]. For example, mild symptoms were local symptoms such as redness up to 50 mm width, and systemic symptoms such as headache that did not require pain relieve medication; moderate symptoms were local symptoms such as redness up 50-100 mm width, and systemic symptoms such as headache that required non-narcotic pain relieve medication; and severe symptoms were local symptoms such as redness over 100 mm width, and systemic symptoms that required narcotic pain relieve or medical attention. The severity of reported symptoms was based on the maximum severity of a specific symptom reported by the participant during day 0–5. We then calculated the percentages of participants reporting local and systemic symptoms per symptom categorised into none, mild, moderate, or severe. To classify the overall severity of reactogenicity that participants experienced after COVID-19 vaccination, we categorised participants in those reporting no symptoms, only local, only systemic or both local and systemic symptoms. We additionally categorised participants in those reporting none or only mild symptoms, and those reporting one or more moderate symptom. Lastly, we categorised the participants according to the total number of symptoms reported: those who reported less than or the medium number (0–4 symptoms), and those who reported above the median number (5–11) of reported symptoms. We compared reactogenicity symptoms between participants who had T1 blood sample drawn and those who had not using Fisher's exact or Chi-squared test. All reactogenicity classifications were done before the association with innate immune response was explored. To determine whether age and sex were determinants for reactogenicity we used multivariable logistic regression analysis.

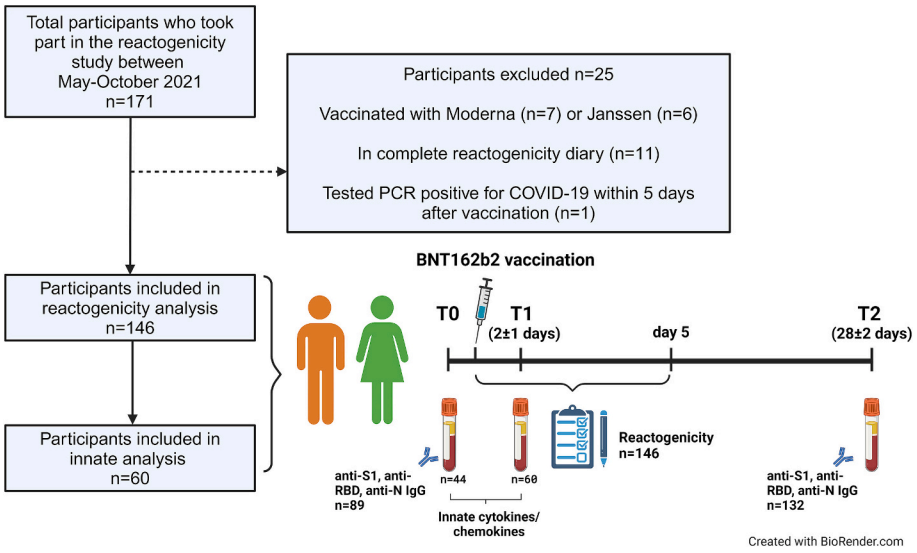

Fig. 1. Study flowchart and schematic layout. A total of 171 individuals were recruited from which 25 were excluded. A total of 146 individuals completely filled in the reactogenicity dairy up to day 5 post vaccination. Of these 146 participants, 89 and 132 individuals donated blood to determine their SARS-CoV-2 specific IgG levels pre (T0) and post (T2) vaccination, respectively. For innate analysis, 47 pre-vaccination and 60 post-vaccination (T1) samples were analysed for innate cytokines and chemokines.

2.7.2. Determination of innate immune responders after vaccination

The levels of cytokine and chemokines in serum and plasma early after vaccination vary depending on the type of sample and the time of sampling. To be able to assess the association between the innate immune response and reactogenicity we classified the participants as high, intermediate or low innate responders. To this end, we determined the median value per cytokine/chemokine of each group (adult or adolescent), and per classified sample time: before <48 h after vaccination, between 48 and 72, or after 72 h.

Each individual with a cytokine or chemokine value above median received a + 1 score, and below the median a 0 score. We used the sum of the scores to determine the overall innate responsiveness of each adult and adolescent and to categorise each individual into an innate response category. Innate responsiveness was defined using those cytokines and chemokines that showed a significant increase, or strong trend (CXCL9 in adults) after COVID-19 vaccination compared to pre-vaccination using Kruskal-Wallis test followed by Dunn's multiple comparison test using GraphPad PrismV9.5.1 software. Innate responsiveness classifications were done before the association with reactogenicity was explored.

2.7.3. Association between reactogenicity and innate immune response

We explored the association between the innate responsiveness and reactogenicity by creating a heatmap visualising the association (*p*-value) between each local and systemic reactogenicity symptom and the cytokines and chemokines. We calculated the corresponding p-value using the Fisher's Exact Test

We used logistic regression to assess the association between the innate immune responsiveness (low, intermediate, high) and three different reactogenicity severity classifications: firstly the type of reported symptoms categorised as none, only local, or only systemic symptoms and both local and systemic symptoms. Secondly, the number of symptoms reported during the 5 days post COVID-19 vaccination as: 0–4 and 5–11 symptoms. Lastly, the severity of reported symptoms categorised as: none or only mild symptoms and one or more moderate symptoms. No covariates were used in the model due to small sample size. Additionally, we used logistic regression to assess the association between the reactogenicity severity classification categorised as 1) none or only mild symptoms, and 2) one or more moderate symptoms with the separate cytokine and chemokines (IFNγ, CXCL9, CXCL11, CCL20, CXCL10).

2.7.4. Association between reactogenicity/innate responsiveness and antibody response

Among participants from whom reactogenicity data and antibody concentrations at day 28 after vaccination were available ($n = 120$), we investigated the association between reactogenicity (categorised as 1) none or only mild symptoms and 2) one or more moderate symptoms) and log-transformed Spike S1- and RBD-antibody concentration (BAU/ml) at day 28 after first COVID-19 vaccination using linear regression. Covariates in the model were age (categorised as 12–30, 31–40, and 41–59 years), and sex. Participants who were seropositive for SARS-CoV-2 Spike-S1 and/or N prior to vaccination, indicating infection with SARS-CoV-2, were excluded ($n = 8$) from analysis. In 54 participants the Spike-S1 and N seropositivity was not determined prior to vaccination. However, 50/54 participants tested negative for N-antibodies at day 28 and were thus assumed to be N-seronegative prior to vaccination. Participants from whom the N-seropositivity remained unknown ($N = 4$) were excluded from analysis.

Additionally, among participants from whom innate data and antibody concentrations at day 28 after vaccination were available ($n = 51$), we investigated the association between innate responsiveness (categorised as low, intermediate or high) and log-transformed Spike S1- and RBD-antibody concentration (BAU/ml) at day 28 after first COVID-19 vaccination using linear regression. No covariates were used in the model due to small sample numbers. Statistical analyses were performed in R version 4.4.0.

3. Results

3.1. Study population characteristics

In total 171 participants filled out the reactogenicity diary after their first COVID-19 vaccination between May and October 2021, of whom 25 were excluded for the analyses: 13 were vaccinated with a vaccine other than BNT162b2, 11 had an incomplete reactogenicity diary, and one participant tested positive for COVID-19 within 5 days after vaccination (Fig. 1). For 60 out of these 146 participants, blood samples were available at T1 (2 ± 1 days after vaccination) to measure innate cytokines and chemokines, which allowed to test the association between reactogenicity and innate immune response early after vaccination (Fig. 1).

Overall, the 146 participants had a mean age of 29 (range 12–59) years and more than half were females (84/146, 58 %). The 60 participants from whom blood samples were available in the first days after vaccination had a mean age of 28 (range 12–51) years, and most were females (37/60, 62 %). Pre-vaccination (T0) blood samples were taken a median of 3 (range 0–9) days before COVID-19 vaccination in 47/146 participants. Post-vaccination (T1) blood samples were taken from 60/146 participants a median of 51 (range 26–85) hours after COVID-19 vaccination (Table 1).

3.2. Reported reactogenicity

The majority of participants (135/146, 92 %) reported local symptoms in the first days after vaccination, of which pain (128/146, 87 %), impaired arm mobility (90/146, 62 %) and redness (29/146, 20 %) were most often reported. Systemic symptoms were also reported by a large number of participants (133/146, 91 %), of which myalgia (113/146, 77 %), fatigue (89/146, 61 %), and headache (57/146, 39 %) were most often reported. Only two (1 %) participants reported fever, and another two (1 %) participants visited the first aid station at the COVID-19 vaccination location shortly after vaccination. However, none of the participants needed extra medical care such as consultation with a general practitioner or hospital admission for their reactogenicity symptoms. Nineteen (13 %) participants used antipyretic medication for their symptoms (Table 2).

A combination of both local and systemic symptoms during the five

Table 1
Characteristics of all participants with reactogenicity data and the subgroup with T1 blood samples.

		All participants $n = 146$		Participants with T1 blood samples $n = 60$	
		n	%	n	%
Age	12–17	20	14	15	25
	18–30	64	44	16	27
	31–40	46	32	23	38
	41–49	8	5	4	7
	50+	8	5	2	3
Sex	Female	84	58	37	62
	Male	62	42	23	38
Time (days) between T0 sample and vaccination	median, min-max	3	(0–9)	3	0–9
Time (hours) between vaccination and T1 sample	median, min-max	NA	NA	51	26–85
Time (days) between T0 and T1 sample	median, min-max	NA	NA	5	1–12
Time (days) between vaccination and T2 sample	median, min-max	30	10–42	30	10–38

NA = Not applicable.

Table 2
Reported reactogenicity of all study participants and the subgroups with and without T1 blood samples taken.

		All participants n = 146		Participants with T1 blood samples n = 60		Participants without T1 blood samples *n* = 86		
Symptoms [a]		n	%	n	%	n	%	p-value
Any local symptoms	Yes	135	92	56	93	79	92	>0.99
Redness	None	117	80	52	87	65	76	0.14
	Mild (up to 50 mm)	29	20	6	10	21	24	
	Moderate (51–100 mm)	–	–	–	–	–	–	
Swelling	None	128	88	51	85	77	90	0.43
	Mild (up to 50 mm)	17	12	8	13	9	10	
	Moderate (51–100 mm)	1	1	1	2	–	–	
Local pain	None	18	12	5	8	13	15	0.21
	Mild	78	53	30	50	48	56	
	Moderate	50	34	25	42	25	29	
Impaired arm mobility	None	56	38	21	35	35	41	0.74
	Mild	68	47	30	50	38	44	
	Moderate	22	15	9	15	13	15	
Hard disc	None	119	82	46	77	73	85	0.28
	Mild (up to 50 mm)	27	18	14	23	13	15	
	Moderate (51–100 mm)	–	–	–	–	–	–	
Bruising	None	132	90	52	87	80	93	0.26
	Mild (up to 50 mm)	14	10	8	13	6	7	
	Moderate (51–100 mm)	–	–	–	–	–	–	
Any systemic symptoms	Yes	133	91	52	87	81	94	0.12
Fever	None (<38.0)	144	99	60	100	84	98	0.51
	Mild (38.0–38.4)	2	1	–	–	2	2	
	Moderate (38.5–38.9)	–	–	–	–	–	–	
	Severe (39+)	–	–	–	–	–	–	
Headache	None	89	61	39	65	50	58	0.67
	Mild	37	25	13	22	24	28	
	Moderate	20	14	8	13	12	14	
Myalgia	None	33	23	14	23	19	22	0.93
	Mild	73	50	29	48	44	51	
	Moderate	40	27	17	28	23	27	
Malaise	None	95	65	41	68	54	63	0.50
	Mild	42	29	17	28	25	29	
	Moderate	9	6	2	3	7	8	
Joint pain	None	131	90	55	92	76	88	0.9
	Mild	12	8	4	7	8	9	
	Moderate	3	2	1	1	2	2	
Fatigue	None	57	39	26	43	31	36	0.67
	Mild	53	36	20	33	33	38	
	Moderate	36	25	14	23	22	26	
Medical care	Consulted a GP	–	–	–	–	–	–	NA
	Visited the first aid station	2	1	2	3	–	–	0.17
	Hospitalisation	–	–	–	–	–	–	NA
	Antipyretic medication	19	13	8	13	11	13	0.92
Type of symptoms reported	None	2	1	2	3	–	–	0.17
	Local only	11	8	6	10	5	6	
	Systemic only	9	6	2	3	7	8	
	Both local and systemic	124	85	50	83	74	86	
Number of symptoms reported	0–4	77	53	30	50	47	5	0.58
	5–11	69	47	30	50	39	45	
Severity of symptoms	None or only mild	67	46	28	47	39	45	0.88
	One or more moderate	79	54	32	53	47	55	

NA = not applicable.
[a] Categorised, where possible, according to the Food & Drug Administration Toxicity Grading Scale for Healthy Adults and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials [26].

days post-COVID-19 vaccination was reported by 124/146 (85 %) participants. Eleven (8 %) participants reported only local and nine (6 %) only systemic symptoms. Sixty-seven out of 146 (46 %) participants reported none (two participants) or only mild symptoms, and 79/146 (54 %) reported one or more moderate symptoms. The number of symptoms reported varied from 0 to 11 with 77/146 (53 %) participants reporting 0–4 symptoms, and 69/146 (47 %) participants reported 5–11 symptoms within day 5 of their first COVID-19 vaccination. The subgroup of sixty participants who were included in our association analyses between reactogenicity and the innate immune response post-vaccination, reported similar reactogenicity compared to all participants (Table 2). In general, older participants and male participants reported less reactogenicity. A significant difference was only seen for male participants regarding local symptoms and the number of symptoms: male participants reported less often local symptoms (odds ratio (OR) 0.2, 95 % confidence interval (CI) 0.1–0.9) and less often 5–11 symptoms (OR 0.3, 95 % CI 0.1–0.6) compared to female participants (Table 3).

3.3. Innate immune response after vaccination

The early immune response after vaccination was characterised by measuring cytokines and chemokines in the first days (2 ± 1 days) after vaccination in serum or plasma. Adults showed significantly higher levels of serum CXCL9, CXCL10, CXCL11, IFNγ and CCL20 compared to pre-vaccination samples (**Supplemental Fig. 1 A**). In plasma samples

Table 3
Age and sex as potential determinants for reactogenicity in Dutch healthy adolescents and adults.

		Local symptoms	Systemic symptoms	Number of symptoms	One or more moderate				
		OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI
Age group [a]	12–30	Ref.		Ref.		Ref.		Ref.	
	31–40	1.7	0.4–12.0	0.3	0.1–1.0	0.6	0.3–1.3	0.4	0.2–0.9
	41–59	0.5	0.1–3.6	0.4	0.1–2.9	0.5	0.1–1.4	0.4	0.1–1.3
Sex [b]	Female	Ref.		Ref.		Ref.		Ref.	
	Male	0.2	0.1–0.9	1.5	0.4–5.8	0.4	0.2–0.7	0.6	0.3–1.1

[a] Age group 12–30 years $n = 84$, 31–40 years $n = 46$, 41–59 years $n = 16$; [b] Sex female n = 84, male $n = 62$.

from adolescents, we also detected significantly higher levels of CXCL9, CXCL10 and CXCL11 early after vaccination, but not IFNγ and CCL20 (**Supplemental Fig. 1B**). Sampling time after vaccination is an important factor in determining these early serum/plasma chemokines and cytokines. The levels of CXCL10, CXCL11, IFNγ and CCL20 were significantly higher in samples taken within 48 h after vaccination (Fig. 2A). In adults, the CXCL9 levels tended to be elevated in samples collected between 48 and 72 h after vaccination, whereas the CXCL10 levels were still significantly higher in samples collected >48 h and higher levels of CXCL11 were also measured between 48 and 72 h (Fig. 2A). In plasma from adolescents, CXCL9, CXCL10, and CXCL11 were all significantly higher in samples collected within 48 h after vaccination (Fig. 2B). These plasma chemokines were lower in samples collected >48 h, with CXCL11 levels still significantly higher between 48 and 72 h (Fig. 2B). IL-1β, IL-6, IL-10, IL-12p70, IFN-α2, IFN-β, IFN-λ1, IFN-λ2/3, TNF-α, GM-CSF, CXCL1, CXCL8, CCL3, CCL4, CCL5, CCL11, CCL17, and MCP-1 were not detected or significantly different pre- and post-vaccination (Supplemental Fig. 2).

Since the levels of detected chemokines and cytokines early after vaccination are dependent on the sample taken, serum (adults) or plasma (adolescents), and the time of sampling (<48, 48–72, or > 72 h), correlation analysis with reactogenicity would not yield enough power due to a low number of comparable participants. Therefore, we categorised individuals into high, intermediate and low innate responders by scoring their levels above or below median for each analyte detected in serum or plasma. Based on CXCL9, CXCL10, CXCL11, IFNγ, and CCL20 data we classified 12 adults as innate high responders, 21 as intermediate responders, and 12 as low responders (Fig. 3A). Among the adolescents 4 individuals were classified as innate high responders, 4 as intermediate, and 7 as low responders (Fig. 3B). Plotting the actual

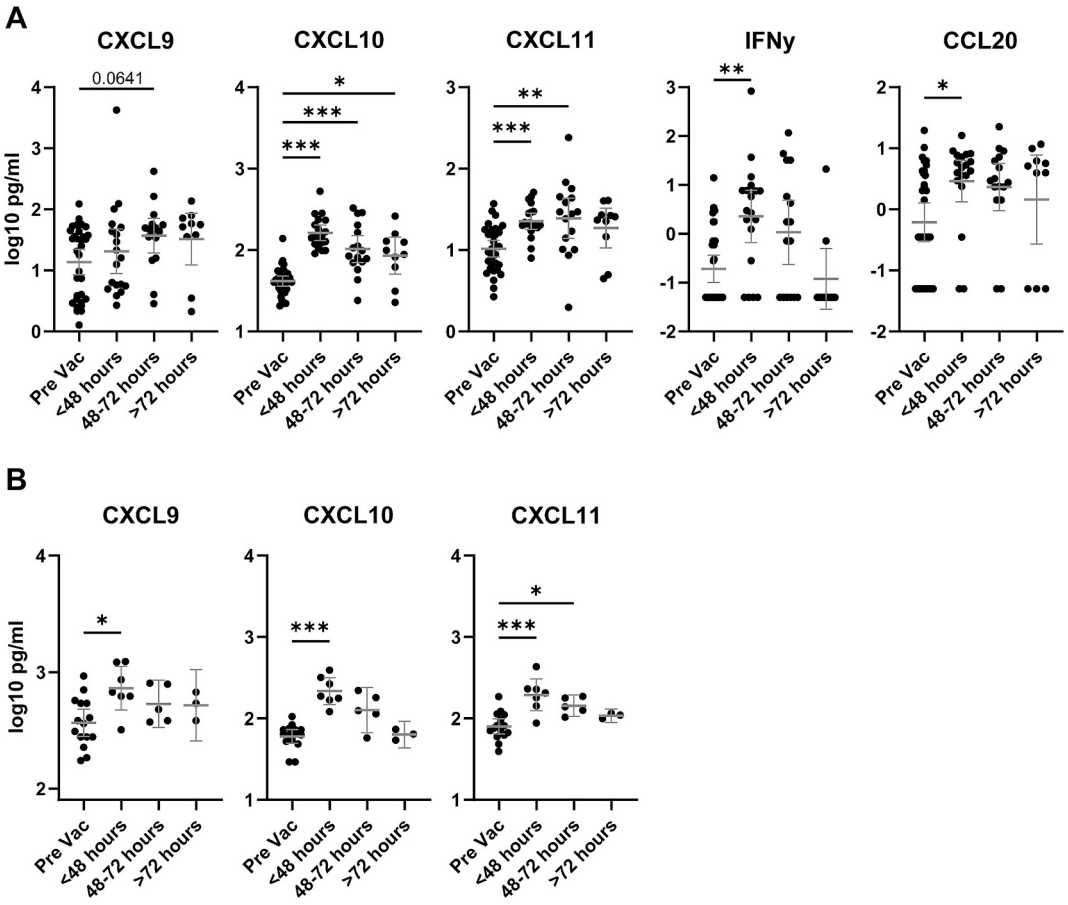

Fig. 2. Elevated cytokine and chemokines in the first days after vaccination. Levels of CXCL9, CXCL10, CXCL11, IFNγ, and CCL20 in serum from adults (A), and CXCL9, CXCL10, CXCL11 levels in plasma from adolescents (B). Serum and plasma samples were collected pre ($n = 32$ adults, $n = 15$ adolescents) and post vaccination <48 h, between 48 and 72, and > 72 h ($n = 20$, n = 15, $n = 10$ for adults, $n = 7$, $n = 5$, n = 3 for adolescents, respectively). Values are depicted as log10 pg/ml and bars indicate geometric mean ± 95% Confidence interval. Kruskal-Wallis test was used to compare post vaccination groups to pre-vaccination group, after which Dunn's multiple comparison test was executed *p-adj < 0.05, **p-adj < 0.01, ***p-adj < 0.001.

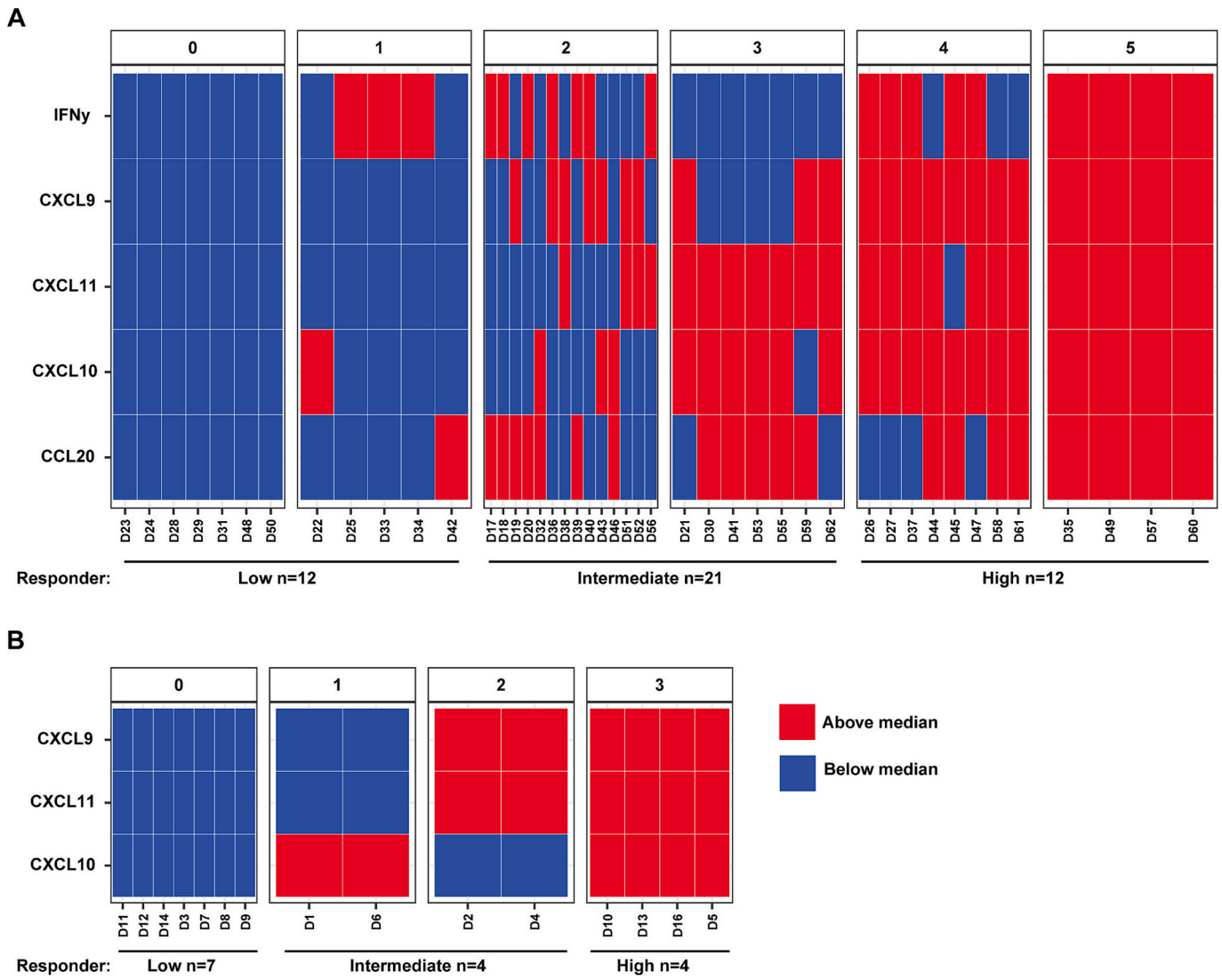

Fig. 3. Defining innate high, intermediate and low responders to COVID-19 vaccination. The median value for each detected cytokine/chemokine in each group (adult or adolescent), sampled before <48 h, between 48 and 72, or after 72 h was determined. Each individual with a cytokine/chemokine value above median received a + 1 score, and below the median a 0 score. The sum of the scores for all analytes was used to determine the overall innate responsiveness for each individual (D1–60) and is shown in bars on top of the heatmap for adults (**A**) and adolescent (**B**). Heatmap shows in red which individual who had a value above the median and in blue below the median per analyte (**A** + **B**). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

values for each analyte in each group of high, intermediate and low responders confirms their grouping independent of time of sampling for adults (**Supplemental Fig. 3A**) and adolescents (**Supplemental Fig. 3B**).

3.4. Association between reactogenicity and innate immune response

We determined the relation between reactogenicity and the innate immune response using regression analysis between innate responsiveness and the type of symptoms, number of symptoms and severity of reported reactogenicity. Participants who showed a high innate immune responsiveness had higher odds (OR 6.0; 95 % CI 1.4–33) of experiencing one or more moderate symptoms (Table 4). There was no significant association between the innate responsiveness and the number of reported symptoms or the type of reported symptoms (none, only local or systemic vs both local and systemic symptoms), although the OR pointed into the same direction as for severity (OR 3.0 and 5.4, respectively) (Table 4).

Next we investigated whether individual cytokine/chemokine responses underly the association between high innate responsiveness and experiencing one or more moderate symptoms. Grouping the individuals with above or below the median value per cytokine/chemokine, showed that having high IFNγ response was significantly associated with having higher odds experiencing (OR 6.0; 95 % CI 1.7–26) one or more moderate symptoms (Table 5). The CXCL9, CXCL10, CXCL11, or CCL20 responses were not associated with severity of reported reactogenicity.

High IFNγ showed the overall strongest association with local and systemic symptoms, albeit not statistically significant, compared to the other detected chemokines (Fig. 4). High CCL20 responses significantly associated with swelling ($p = 0.01$) from the local reactogenicity symptoms (Fig. 4A), and high IFNy levels significantly associated with systemic symptom malaise ($p = 0.03$, Fig. 4B). Overall, being an intermediate innate responder tended to associate more with local then with systemic symptoms, whereas for innate high responders it was the other way around with a stronger association with systemic symptoms (Fig. 4). Furthermore, experiencing headache was significantly associated with high innate responsiveness (Fig. 4B). Overall these data indicate a link

Table 4
The association between reported reactogenicity and innate immune response in Dutch healthy adolescents and adults.

		Innate response						Odds ratio		Odds ratio	
		Low N = 19		Intermediate N = 25		High N = 16		Intermediate – Low*	95 %CI	high – low*	95 %CI
		n	%	n	%	n	%				
Type of symptoms	None or only local or systemic	5	26	4	16	1	6	Ref.		Ref.	
	Both local and systemic	14	74	21	84	15	94	1.9	0.4–8.8	5.4	0.7–110
Number of symptoms	0–4	11	58	14	56	5	31	Ref.		Ref.	
	5–11	8	42	11	44	11	69	1.1	0.3–3.7	3.0	0.8–13
Severity of symptoms	None or only mild symptoms	11	58	14	56	3	19	Ref.		Ref.	
	One or more moderate symptom	8	42	11	44	13	88	1.1	0.3–3.7	6.0	1.4–33

* Logistic regression without covariates was used to determine associations.

between the early innate responses after vaccination and the experienced reactogenicity.

No association between reactogenicity and vaccine induced antibody response.

BNT162b2 vaccination induced Spike S1 specific antibody responses, 28 days post vaccination, in 131/132 individuals (**Supplemental Fig. 4**). No association was found between reporting one or more moderate reactogenicity symptoms and the Spike S1-antibody concentration at day-28 after first COVID-19 vaccination: geometric mean concentration ratio (GMC ratio) 1.2, 95 % CI 0.9–1.7. Adjusting for age and sex showed similar results (GMC ratio: 1.1, 95 % CI 0.8–1.5). No association was found either between reporting one or more moderate reactogenicity symptoms and the RBD-antibody concentration at day 28 after first vaccination: unadjusted GMC ratio 1.2 (95 % CI 0.8–1,7) with an adjusted GMC ratio 1.1 (95 % CI 0.7–1.5).

3.5. Innate responsiveness early after vaccination does not associate with Spike S1 specific antibody responses

Within our innate subgroup, the development of Spike S1 and RBD specific antibody 28 days after vaccination varied with levels ranging from 3.29 to 20,896.48 BAU/ml and 5.26 to 11,943.04 BAU/ml, respectively (**Supplemental Fig. 4**). We wondered whether the innate responsiveness after vaccination relates to the specific antibody development. However, no association was found between innate responsiveness and Spike S1 or RBD antibody concentration at day 28 after first COVID-19 vaccination. Participants with an intermediate innate responsiveness had an Spike S1-antibody GMC ratio of 0.7 (95 % CI 0.4–1.3) and participants with a high innate responsiveness had a GMC ratio of 1.1 (95 % CI 0.6–2.1) compared to participants with a low innate responsiveness. Similar results were found for RBD-antibody concentrations at day-28 after vaccination: participants with an intermediate responsiveness showed an RBD antibody GMC ratio of 0.9 (95 % CI 0.5–1.6) and participants with a high innate responsiveness a GMC ratio of 1.3 (95 % CI 0.7–2.7) compared to participants with a low innate responsiveness.

4. Discussion

We studied serum and plasma markers of the innate immune response, and their relation to reactogenicity early after the first BNT162b2 vaccination in Dutch adolescents and adults. Additionally we studied the relation between innate immune response and reactogenicity with the antibody concentration 28 days after first vaccination. We showed that individuals with a high innate immune response had higher odds of experiencing one or more moderate reactogenicity symptoms, compared to those with low innate responsiveness.

The innate immune response after BNT162b2 vaccination was characterised by elevated CXCL9, CXCL10, CXCL11 in both adolescents and adults, in the latter we also detected higher levels of IFN-y and CCL20. Adults with higher IFN-y levels had increased odds of experiencing one or more moderate symptoms. Interestingly, CXCL9, CXCL10, CXCL11 and CCL20 are all chemokines that are predominantly induced by IFN-y, which stresses the importance of IFN-y in orchestrating the early immune response after vaccination. CXCL9, CXCL10 and CXCL11 can be secreted by various cell types, i.e. monocytes, fibroblast and endothelial cells, and they all attract and bind to CXCR3 expressing cells, including plasmacytoid dendritic cells, NK cells, and effector memory CD4+ and CD8+ T cells [27]. CCL20 is most prominently expressed, but not limited to, by monocytic cells and attracts CCR6 expressing myeloid dendritic cells, CD4+ T cell subsets, and B cells [28]. The kinetics of IFN-y and the chemokines subsequently released, combined with our time of sampling, may explain why only IFN-y associated with severity of the symptoms.

Our results are in line with previous research showing elevated IFN-y, and CXCL10, serum and plasma after first BNT162b2 vaccination

Table 5
The association between reported reactogenicity and innate immune response per cytokine or chemokine in Dutch healthy adolescents and adults.

		None or only mild symptoms N = 28		One or more moderate symptoms N = 32		Odds ratio#	95 %CI
		n	%	N	%		
Interferon gamma (IFNγ)*	Below median	16	57	10	31	Ref.	
	Above median	4	14	15	47	6.0	1.7–26
Monokine induced by gamma interferon (CXCL9)	Below median	16	57	16	50	Ref.	
	Above median	12	43	16	50	1.3	0.5–3.8
Interferon-inducible T-cell alpha chemoattractant (CXCL11)	Below median	14	50	18	56	Ref	
	Above median	14	50	14	44	0.8	0.3–2.2
Macrophage inflammatory protein-3 alpha (CCL20)*	Below median	10	36	14	44	Ref.	
	Above median	10	36	11	34	0.8	0.2–2.7
Interferon gamma-induced protein 10 (CXCL10)	Below median	18	64	14	44	Ref.	
	Above median	10	36	18	56	2.3	0.8–6.7

*interferon gamma and CCL20 were not detected in the plasma samples from adolescents (n = 15); # Logistic regression without covariates was used to determine associations.

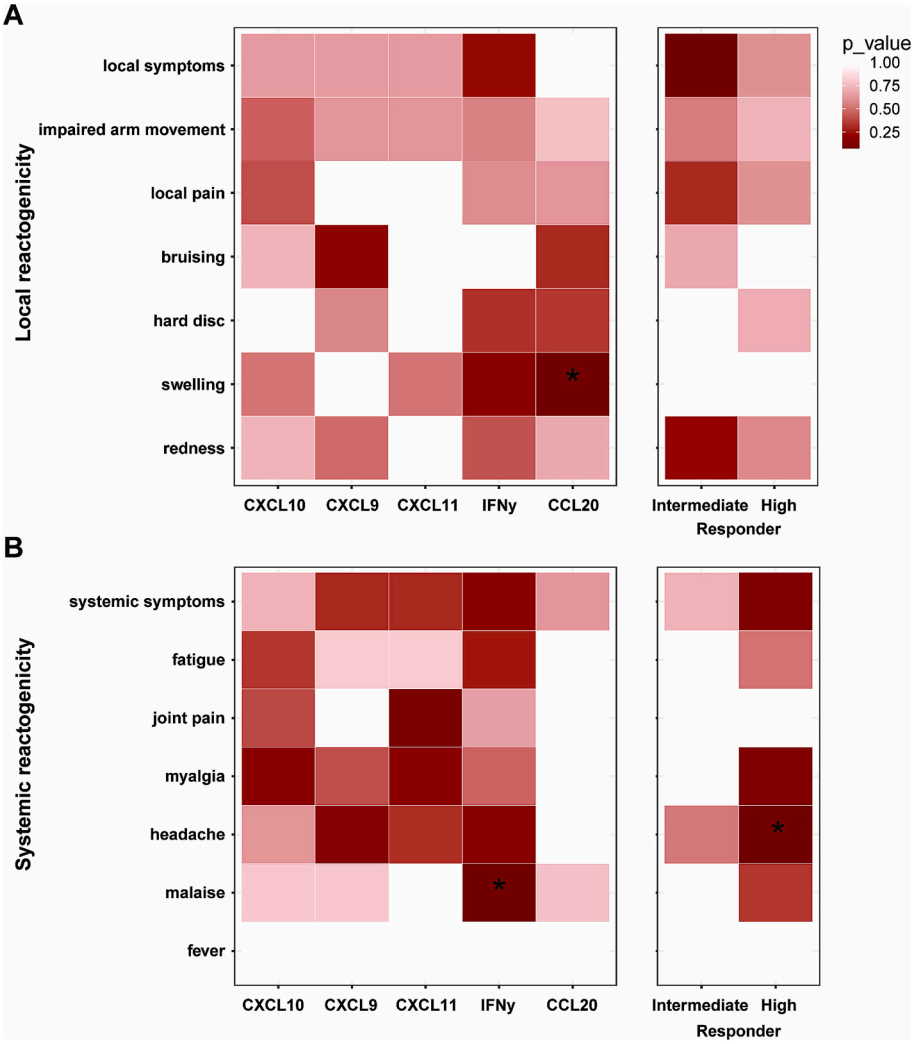

Fig. 4. Correlations between reactogenicity and the early innate immune response. Heatmap showing the correlation between the local (**A**) and systemic (**B**) reactogenicity symptoms and the cytokine/chemokines (above or below median) and the overall innate responder status (as defined in Fig. 3). Colour scale, from dark red to white, indicates low and high *p*-values, respectively. *$p < 0.05$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

[8,18,29]. These responses were even more pronounced following a second vaccination; however, our study was limited to only the first vaccination of the primary series. IFN-y levels induced by a second BNT162b2 vaccination were associated with systemic adverse events and the development of Spike S1 specific antibodies [18,29]. An association between BNT162b2 reactogenicity and the development of Spike S1/RBD specific antibodies has been described more often, but absence of symptoms does not exclude the development of a specific immune response [14–17,30]. Our reactogenicity and innate analysis was limited to the first vaccination, but we did identify a relation between high innate responders, and IFN-y levels in adults, and their reactogenicity. However, no associations were found between reactogenicity or innate responsiveness, and the development of Spike S1 or RBD specific antibodies.

In this study, the vast majority of participants reported reactogenicity within the first 5 days after primary COVID-19 vaccination. Most individuals reported both systemic and local symptoms, and only two participants reported no symptoms. Overall, females and younger individuals reported more often local and systemic symptoms. This is in line with previous studies describing more reactogenicity in this population [4,13,15,16,30–32]. In our study, the percentage of participants reportingreactogenicity symptoms after first COVID-19 vaccination was much higher (99 %) compared to another Dutch study (53 %) [32]. Seventy-seven percent of the participants experienced myalgia after vaccination, which is much higher compared to the 14–21 % in the initial BNT162b2 safety and efficacy study [4]. Furthermore, the symptoms local pain, swelling, headache, and fatigue were all slightly overrepresented in our study. Our study population consisted of younger and more female participants compared to other reactogenicity studies, possibly leading to more symptoms reported. In addition, participants were actively asked to report their symptoms daily, which may have resulted in more symptoms reported compared to when participants receive a questionnaire to fill in retrospectively.

Our study has several limitations including a relatively small sample size and the different sample types collected for adolescents (plasma) and adults (serum), which did not allow for direct comparison or grouping of the data or adjustment for age and sex in the analyses. Furthermore, samples were not collected within a short time window, but in the first days after vaccination ranging from 23 to 83 h. Although this time span after vaccination provided insights in kinetics of the measured cytokines and chemokines it did not allow direct correlation analysis with reactogenicity. Therefore, our innate responder categorisation was essential, but may not fully reflect the true high or low innate responders.

Overall, our data suggest an association between the strength of the innate immune response and the severity of reactogenicity early after

first COVID-19 vaccination, but both did not associate with SARS-CoV-2 specific antibody concentration after first vaccination. More research is needed to understand the relation between immunogenicity and reactogenicity of COVID-19 vaccination. Identifying the sources of the early induced cytokines and chemokines may help to comprehend the exact mechanisms underlying vaccine induced immunity and their relation to reactogenicity.

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CRediT authorship contribution statement

Catharina E. van Ewijk: Formal analysis, Writing – original draft. **Sara Suárez Hernández:** Formal analysis, Writing – original draft. **Ronald H.J. Jacobi:** Data curation. **Mirjam J. Knol:** Formal analysis, Supervision. **Susan J.M. Hahné:** Writing – review & editing. **Alienke J. Wijmenga-Monsuur:** Conceptualization, Project administration. **Mardi C. Boer:** Conceptualization, Project administration, Supervision. **Martijn D.B. van de Garde:** Data curation, Formal analysis, Supervision, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvacx.2024.100593.

Data availability

Data will be made available on request.

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