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COVID-19 vaccination, acceptance, safety, and side-effects in European patients with severe asthma

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Key Words:	COVID-19 vaccination, severe asthma, Vaccination hesitancy, VAX scale, side-effects
Abstract:	<p>Background: Vaccination is vital for achieving population immunity to SARS-CoV-2, but vaccination hesitancy presents a threat to achieving widespread immunity. Vaccine acceptance in chronic potentially immunosuppressed patients is largely unclear, especially in patients with asthma. The aim was to investigate the vaccination experience in people with severe asthma.</p> <p>Methods: Questionnaires about vaccination beliefs (including the Vaccination Attitudes EXamination (VAX) Scale, a measure of vaccination hesitancy-related beliefs), vaccination side-effects, asthma control and overall safety perceptions following COVID-19 vaccination were sent to patients with severe asthma in 12 European countries between May 2021 and June 2021.</p> <p>Results: 660 participants returned completed questionnaires (87.4% response rate). Of these, 88% stated that they had been, or intended to be, vaccinated, 9. 5% were undecided/hesitant, and 3% had refused vaccination. Patients who hesitated or refused vaccination had more negative beliefs towards vaccination. Most patients reported mild (48.2%) or no side effects (43.8 %). Patients reporting severe side effects (5.7%) had more negative beliefs. Most patients (88.8%) reported no change in asthma symptoms after vaccination, while 2.4% reported an improvement, 5.3% a slight and 1.2% a considerable deterioration. Almost all vaccinated (98%) patients would recommend vaccination to other severe asthma patients.</p> <p>Conclusions: Uptake of vaccination in patients with severe asthma in Europe was high, with a small minority refusing vaccination. Beliefs predicted vaccination behaviour and side effects. Vaccination had little impact on asthma control. Our findings in people with severe asthma support the broad message that COVID-19 vaccination is safe and well tolerated.</p>



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COVID-19 vaccination, acceptance, safety, and side-effects in European patients with severe asthma

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Take home message: Vaccination rate was high in patients with severe asthma. Half reported mild side effects, and < 6% severe side effects. Negative vaccination beliefs predicted severe side effects—no evidence of poorer asthma control post-vaccination.

Keywords: COVID-19 vaccination, Severe asthma, Vaccination hesitancy, VAX scale, side-effects.

Abstract

Background Vaccination is vital for achieving population immunity to SARS-CoV-2, but vaccination hesitancy presents a threat to achieving widespread immunity. Vaccine acceptance in chronic potentially immunosuppressed patients is largely unclear, especially in patients with asthma. The aim was to investigate the vaccination experience in people with severe asthma.

Methods Questionnaires about vaccination beliefs (including the Vaccination Attitudes EXamination (VAX) Scale, a measure of vaccination hesitancy-related beliefs), vaccination side-effects, asthma control and overall safety perceptions following COVID-19 vaccination were sent to patients with severe asthma in 12 European countries between May 2021 and June 2021.

Results 660 participants returned completed questionnaires (87.4% response rate). Of these, 88% stated that they had been, or intended to be, vaccinated, 9.5% were undecided/hesitant, and 3% had refused vaccination. Patients who hesitated or refused vaccination had more negative beliefs towards vaccination. Most patients reported mild (48.2%) or no side effects (43.8%). Patients reporting severe side effects (5.7%) had more negative beliefs. Most patients (88.8%) reported no change in asthma symptoms after vaccination, while 2.4% reported an improvement, 5.3% a slight and 1.2% a considerable deterioration. Almost all vaccinated (98%) patients would recommend vaccination to other severe asthma patients.

Conclusions Uptake of vaccination in patients with severe asthma in Europe was high, with a small minority refusing vaccination. Beliefs predicted vaccination behaviour and side effects. Vaccination had little impact on asthma control. Our findings in people with severe asthma support the broad message that COVID-19 vaccination is safe and well tolerated.

Introduction

Since the COVID-19 pandemic emerged in December 2019, around 769 million cases and > 6.9 million deaths were reported by week 32 of August 2023 [1]. Although population immunity can be achieved through infection, vaccination is a safer means of achieving this objective while reducing the societal and financial burden of COVID-19. Vaccination hesitancy, defined as the “delay in acceptance or refusal of vaccination despite the availability of vaccination services” [2], is a major threat to achieving herd immunity without too many casualties. Hesitancy is not a modern phenomenon and was a feature of the first vaccine for smallpox in the 1790s [3]. Vaccination hesitancy is a top global health threat [4], an annual problem for preventing seasonal influenza, and has presented challenges in previous pandemics, such as the 2009 H1N1 outbreak [5, 6]. During the COVID-19 pandemic, vaccination hesitancy has become a global health problem [7, 8], with an increasing number of studies revealing decreased vaccine acceptance with a pattern of doubts about vaccine safety and effectiveness, exacerbated by ubiquitous unsubstantiated scientific misinformation [9] and distrust of politicians [10].

Vaccination hesitancy is often related to fears about personal safety. The main concern is the fear of a severe allergic reaction as a side-effect of vaccination contributes to COVID-19 hesitancy among people with allergic diseases [11], even though that risk is extremely low. Concerns may also focus on potential future effects, and in COVID-19, these have been increased by a perception that the vaccine was developed more quickly than for previous vaccines and, therefore, may not have been rigorously tested [12]. Ideological concerns around profiteering by pharmaceutical companies and a general preference for natural immunity can also contribute to vaccine hesitancy, including in COVID-19 [6, 13]. A systematic review [8] of 60 worldwide studies conducted from February to December 2020 reported that vaccination acceptance rates varied between 24% and 97% in different populations. A further review and meta-analysis reported a similar range (28-93%) [14]. Overall, vaccination acceptance varies widely. A low vaccination intention was reported in healthcare personnel [15] as well as among vulnerable populations with a potentially decreased immune

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3 response, including HIV [16], cancer [17] and rheumatic diseases [18] in whom 38.4%, 28.3 % and
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5 35.5% respectively showed hesitancy to be vaccinated for one reason or another.
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8 Three to ten per cent of patients diagnosed with asthma experience severe disease [19], and
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10 these patients not only have many co-morbidities [20] but often need treatment with high doses of
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12 inhaled steroids or oral corticosteroids [21] and/or biological therapies [22]. In patients with severe
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14 asthma, a dominating endotype of immune dysregulation is driven by T2 high inflammation [23], with
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16 up to 80% having an allergic/atopic component. Underlying dysregulation of innate immunity can
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18 predispose individuals to viral infections [24]. Although asthma may be an independent risk factor for
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20 COVID-19 outcome, due to their co-morbidities, severe asthma patients are likely to experience more
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22 severe disease and worse longer-term outcomes [25-27]. Therefore, understanding or overcoming
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24 vaccine hesitancy in the population with severe asthma is particularly important. However, no studies
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26 to date have addressed this issue.
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30 The aims of the study were to: 1) determine the proportion and characteristics of people with
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32 severe asthma in Europe who report that they have either been or will be vaccinated, are unsure
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34 whether to get vaccinated or have decided not to be vaccinated against COVID-19; 2) examine the
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36 relationship between vaccination hesitancy beliefs and vaccination status, the relationship between
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38 vaccination hesitancy beliefs and perceived side-effects and perceived asthma symptom change
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40 following vaccination. 3) identify the extent to which patients who have received COVID-19
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42 vaccination feel safe following vaccination and whether they would recommend vaccination to other
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44 patients with severe asthma.
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48 Data were obtained using a survey involving patients with severe asthma from the 'Severe
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50 Heterogeneous Asthma Research Collaboration, Patient-centred' (SHARP) Clinical Research
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52 Collaboration (CRC). This collaboration is hosted by the European Respiratory Society (ERS) and
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54 engages a network of severe asthma experts and patients from clinical centres across 28 countries to
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56 promote Europe-wide, patient-centred severe asthma research [28].
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Methods

Design, survey development and patient population.

This was a cross-sectional study in which the survey was sent to patients with severe asthma within Europe from 5 May 2021 to 30 June 2021. The survey was developed iteratively by severe asthma experts (physicians and scientists), health psychologists, and patients. Members of the European Lung Foundation’s asthma Patient Advisory Group (PAG) had a central role, consistent with the international guidelines for patients reporting [29]. Professional translators translated the patient surveys into the native languages of the 12 participating European countries, and the translations were checked for medical accuracy by asthma specialists. Physicians were asked to recruit severe asthma patients for the survey as they came into their outpatient clinic to prevent selection bias using online and paper versions of the survey according to individual preference. The online survey was hosted by Survey Monkey (SurveyMonkey, Momentive Inc, USA). Paper versions of the survey were used if online versions were unavailable to patients, and results from these were transferred into the SurveyMonkey system by the local research team. All data collection was anonymous. Patients were eligible for inclusion if they had physician-diagnosed severe asthma and were under the care of a severe asthma clinic for at least six months prior to the onset of the COVID-19 pandemic.

Survey content

The survey consisted of 18 questions about demographics, asthma medication use, experience of COVID-19 infection, vaccination status and if the patient had been vaccinated, and type of vaccine received. Those already vaccinated were asked about side effects, whether they felt safer for being vaccinated and whether they would recommend vaccination to other patients with severe asthma. In addition, all patients were asked to complete the Vaccination Attitudes EXamination (VAX) Scale [30], a questionnaire which yields scores on four subscales representing beliefs that may underlie vaccination hesitancy: mistrust of vaccine benefit, worries about unforeseen future effects, concerns about commercial profiteering, and a preference for natural immunity. Participants

responded to questions on a 5-point scale whereby 1 = agree strongly and 5 = disagree strongly, and responses were averaged to obtain a score for each subscale. A higher score indicates a higher level of belief. The full survey is shown in the supplementary material.

Ethics

Approval for the study was obtained from the medical ethical board of the Amsterdam University Medical Center (W20_463 # 20.512) and the ethical boards of every individual country where there was a requirement for approval for survey-based studies. All patients provided digital or written informed consent for participation in this study.

Statistical analysis

Descriptive statistics or proportions of positive (Yes) responses were calculated for each question, as appropriate. Patients were grouped according to whether or not they had been, or intended to be, vaccinated, and we also examined the extent to which they reported vaccination hesitancy according to scores on the VAX questionnaire. Groups were compared using independent samples t-tests, Pearson's Chi-square or Analysis of variance (ANOVA) with post-hoc tests with Bonferroni adjustment for multiple comparisons. P values ≤ 0.05 were regarded as statistically significant. Statistical analyses were performed using IBM SPSS v.25 software (IBM Corp., Armonk, NY, USA).

Results

Patient demographics

In total, 798 surveys were sent through the SHARP network in twelve European countries, and 697 patients were recruited, giving a response rate of 87.34%. Thirty-seven surveys were incomplete and were removed from the sample, leaving 660 for analysis (Table 1). As the number of patients recruited from each country varied largely, no statistical comparisons between countries were possible. Vaccination rates for each country is presented in the supplement, TableS1. Thus we chose to address the whole population as one European population. The majority of patients were females (65%), over one-fifth (22%) were on daily oral corticosteroids, and more than half (64%) were receiving biological therapy for their asthma. Most (70%) had not had a COVID-19 infection, 12% reported a positive COVID-19 test, and only 22 (3%) reported hospitalisation due to COVID-19.

Table 1: Participant details by country.

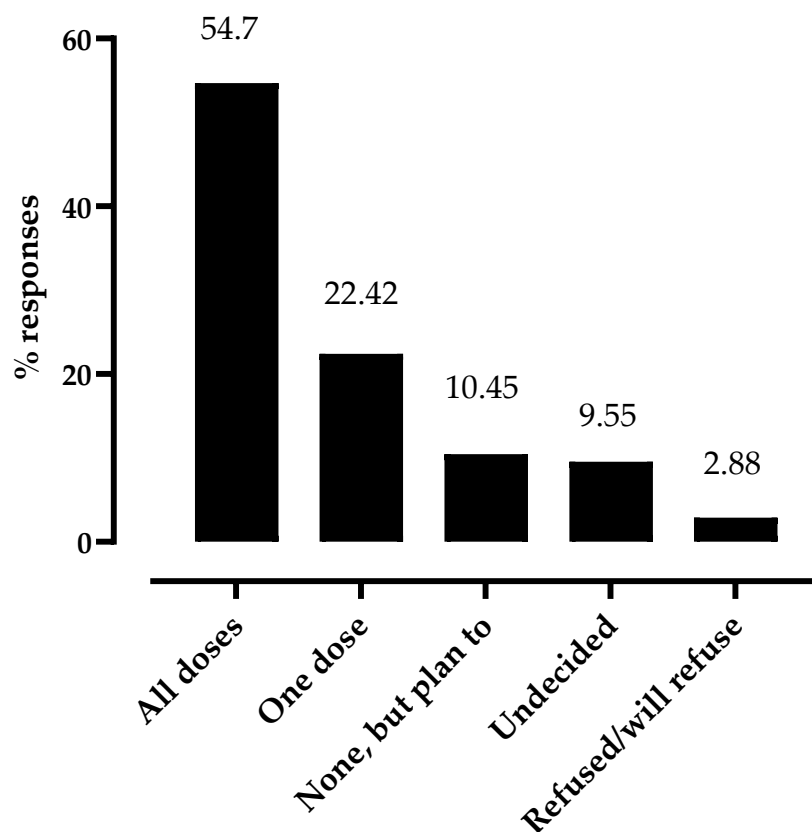
	n (% of total)	Age Mean (range)	Female n (%)	Daily Prednisolone n (%)	Biologics n (%)
Belgium	166 (25)	59 (21-86)	95 (57)	33 (20)	98 (59)
Estonia	43 (7)	57 (22-86)	32 (74)	11 (26)	21 (49)
France	1 (.15)	53 (53-53)	1 (100)	1 (100)	1 (100)
Greece	104 (16)	56 (18-80)	75 (72)	18 (17)	88 (85)
Hungary	73 (11)	57 (23-84)	49 (67)	12 (16)	47 (47)
Latvia	23 (3)	59 (42-81)	16 (70)	3 (3)	8 (35)
Lithuania	24 (4)	54 (31-78)	17 (71)	3 (3)	23 96)
Netherlands	62 (9)	54 (25-75)	35 (82)	14 (14)	53 (85)
Romania	11 (2)	56 (38-77)	9 (82)	1 (9)	10 (91)
Russian Federation	19 (3)	49 (30-70)	11 (58)	3 (16)	5 (26)
Serbia	92 (14)	53 (26-76)	57 (62)	38 (41)	45 (49)
United Kingdom	42 (6)	51 (28-73)	30 (71)	7 (16.7)	21 (50)
All patients	660 (100)	55 (18-86)	427 (65)	144 (22)	420 (64)

Footnote Table 1. Numbers and characteristics of participating patients per country. Data are presented as n (%) for each participating country.

COVID-19 vaccination status

Five-hundred and nine of 660 patients (77%) had already received at least one dose of vaccine at the time of the study, with a further 10.45% intending to be vaccinated, while 9.55% were still undecided and a smaller proportion (2.88%) had refused vaccination (Figure 1).

Figure 1: COVID-19 vaccination status in patients with severe asthma who completed the survey.



Footnote Figure 1. Graph showing patients with severe asthma reporting their vaccination status.

Data are presented as (%) of the total population who replied to the survey (n=660).

Of the 509 patients who had been vaccinated, 300 (59%) had received an mRNA-based vaccine, with the remainder receiving vector and protein subunit technology vaccines. We grouped patients into three categories according to their reported vaccination status: accepters (patients who are accepting vaccination; vaccinated/will be vaccinated), hesitant (undecided) and refusers (see Table 2 for patient characteristics). Patients accepting vaccination were significantly older than those in the other groups, $F(2, 653) = 5.08, p = 0.006, \eta^2 = 0.02$. Pearson’s Chi-square indicated that hesitators were most likely to have had a COVID-19 infection, $\chi^2(2) = 39.45, p < 0.001$, and the vaccine refusers were least likely to be on a biological treatment, $\chi^2(2) = 6.19, p = 0.05$. Refusers were also least likely compared to other categories to use daily prednisolone, although this difference did not reach significance ($p = 0.23$).

Title Table 2: Characteristics of vaccine refusers, hesitant and accepters.

	Refuser (n = 18)	Hesitant (n = 63)	Accepters (n = 575)
Age (M/SD)	51.28/8.71	51.68/13.37	56.53/13.14
Female	61%	76%	64%
Had COVID-19	17%	41%	12%
Daily Prednisolone	11%	29%	22%
Biologics for Asthma	44%	54%	65%

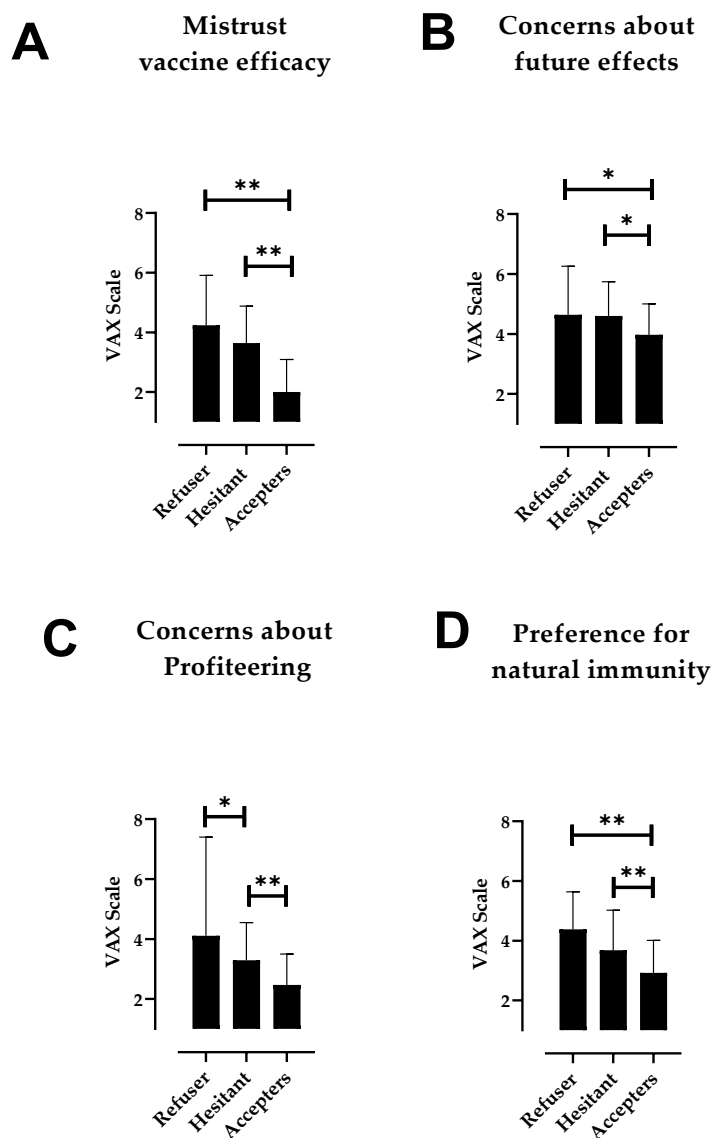
Footnote Table 2. Characteristics of patients according to their reported vaccination status. Patients are grouped as accepters of vaccination (vaccinated/will be vaccinated), hesitant (undecided) and refusers.

Vaccination hesitancy among patients with severe asthma

We then compared three categories of patients in terms of their vaccination beliefs, as indicated by VAX scores (Figure 2). ANOVA showed significant differences in all four beliefs as a function of vaccination status. Post-hoc tests with Bonferroni adjustment indicated that for mistrust, refusers and

hesitators scored similarly ($p=0.09$) but more highly than accepters (patients who had been vaccinated or planned to be) ($p < 0.001$). For concerns about future effects, refusers and hesitators scored very similarly ($p=0.99$) and more highly than accepters ($p < 0.04$). In terms of concerns about profiteering, refusers scored higher than hesitators ($p = .02$), who, in turn, reported more concerns than accepters ($p < 0.001$). Finally, the preference for natural immunity was similar in both hesitators and refusers ($p=0.19$) and higher than accepters ($p=0.001$).

Figure 2. Vaccination hesitancy between patients with severe asthma (VAX subscale scores), according to their vaccination status.



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Footnote Figure 2. Descriptive statistics for the VAX questionnaire by reported vaccination status for A) mistrust of vaccine benefit, B) concerns about future effects, C) concerns about profiteering, and D) about preference for natural immunity. Patients are grouped as ‘accepters’ of vaccination (vaccinated/will be vaccinated), ‘hesitant’ (undecided) and ‘refusers.’ Data show results of a 5-point scale whereby 1 = agree strongly and 5 = disagree strongly, and responses were averaged to obtain a score for each subscale. Significance for paired comparisons with Bonferroni post-hoc tests: * $p<0.05$, ** $p<0.001$.

Perceptions of vaccination safety, asthma symptoms and side effects

The 509 patients who had received at least one dose of a COVID-19 vaccine were presented with a final set of questions about their perception of vaccination side effects and effects on their asthma symptoms. These items required a Yes or No response. Most of the patients experienced mild or no side effects; notably, only 7% reported a need for any treatment for side effects (see Table 3). Markedly, the vast majority (89%) did not perceive a change in asthma symptoms following vaccination, with 12 patients (2%) reporting an improvement. Twenty-seven patients (5%) perceived that their asthma symptoms got slightly worse without needing any change in treatment, and only six (1%) patients reported that their asthma symptoms got worse and needed a treatment change. Little difference was observed as a function of the type of vaccine received.

Title Table 3: Perceptions of Vaccination side effects and effects on asthma symptoms.

	Yes responses n (%)	Type of vaccine n (%)	
		mRNA	Other
<i>Perceived side effects of vaccination</i>			
Severe Side-effects	29 (5.70)	13 (2.55)	16 (4.00)
Mild side-effects	245 (48.16)	154 (30.26)	91 (17.88)
No side-effects	223 (43.81)	128 (25.15)	95 (18.66)
Treatment sought for side-effects	35 (6.88)	6 (1.18)	7 (1.38)
<i>Perceived change in asthma symptoms following vaccination</i>			
No change in symptoms	452 (88.80)	265 (52.06)	187 (36.74)
Symptoms got better	12 (2.36)	6 (1.18)	6 (1.18)
Symptoms slightly worse, no change in treatment needed	27 (5.30)	18 (3.54)	9 (1.77)
Symptoms worse needed a change in treatment	6 (1.18)	6 (1.18)	0

Footnote Table 3. Perceptions following vaccination (count and % of Yes responses) by patients who had received at least one dose of vaccine (n = 509). Only 497 surveys had complete answers and were analysed. Percentages represent the proportion of Yes responses overall and in terms of the type of vaccine received.

We then considered whether general beliefs about vaccination (and, by implication, vaccination hesitancy) were related to the perception of side effects (Table 4). A comparison of the four VAX subscales regarding the level of reported side effects (none, mild, severe) revealed significant differences in all but the natural immunity subscale. In each case, there was no significant difference in scores between patients with no or mild side effects (p range 0.25 - 0.99), but those who reported severe side effects scored significantly higher on all three subscales ($p = 0.001$ in every case). We observed no significant differences in preference for natural immunity ($p > 0.50$).

Title Table 4: Vaccination hesitancy related beliefs (VAX subscale scores) for patients with severe asthma, according to their perception of vaccination side effects.

	N	Mistrust vaccine efficacy	Concerns about future effects	Concerns about profiteering	Preference for natural immunity
Severe side effects	29	2.34/0.82	4.42/1.18	3.14/1.19	3.08/1.08
Mild side effects	245	1.99/0.83	3.99/0.98	2.42/0.97	2.80/1.02
No side effects	221	1.85/0.80	3.82/1.04	2.41/1.01	2.87/1.11
Results of ANOVA		$F(2, 492) = 5.04, p = 0.01, \eta^2 = 0.02$	$F(2, 492) = 5.01, p = 0.01, \eta^2 = 0.02$	$F(2, 492) = 7.08, p = 0.001, \eta^2 = 0.03$	$F(2, 492) = 0.99, p = 0.37, \eta^2 = 0.004$

Footnote Table 4. VAX questionnaire scores (Mean/SD) and results of between group analysis of variance for patients who reported no, mild, or severe side effects following COVID-19 vaccination.

Overall evaluation of vaccination experience

Finally, we were interested in how vaccinated patients felt concerning their safety. Importantly, the vast majority of patients (90%) felt safer following vaccination. Virtually all (98%) would recommend vaccination to other severe asthma patients, irrespective of the vaccine type they received .

Discussion

This survey was conducted in twelve European countries between May and June 2021, about six months after COVID-19 vaccines were authorised and at a time when COVID-19 was prevalent, causing significant societal disruption and burden on the healthcare systems. Most severe asthma patients had positive behaviour or intentions to COVID-19 vaccination, with 88% of the participant sample already vaccinated or intending to be. Fewer than 3% of the respondents said they did not intend to be vaccinated, with the remaining 9% being undecided. Vaccinated patients were slightly older than the other two groups and were less likely to be on a biological treatment. Patients who reported more negative beliefs about vaccination were more likely to be undecided about vaccination or to deny it. Among the vaccinated, those with more negative beliefs were more likely to report severe side effects. Almost all patients who had received at least one vaccination dose (98%) stated that they would recommend vaccination to other patients with severe asthma.

Vaccination beliefs assessed through the VAX scale showed greater hesitancy for the refuser or undecided groups on all four VAX subscales: mistrust of vaccine efficacy, concerns about future effects, concerns about profiteering and preference for natural immunity. These results are broadly in line with those from general public samples. In terms of the subscales of the VAX, a recently published study reported concerns about future effects to be the most highly endorsed belief (Mean 3.32), followed by a preference for natural immunity (2.44), concerns about profiteering (2.17) and lastly mistrust of vaccine efficacy (1.97) [13]. Our survey showed a similar overall pattern.

General public samples often report higher levels of hesitancy than observed in the present study. In a large-scale general population study from the UK, with 32,361 adults, 14 % of the sample reported unwillingness to receive a vaccine, with a further 23% unsure/hesitant [31]. Some studies refer to patient groups that have reported high hesitancy rates. Notably, the severe asthmatic population sample in the current study showed more positive attitudes when compared to other

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chronic or malignant diseases and, generally, when comparing people from outside Europe. In HIV patients surveyed in India between January and February 2021, 38.4% reported being hesitant [16] [17]. Among cancer patients from Tunisia asked about COVID-19 vaccination acceptance between February and May 2021 (close chronically to the present study), 28.3% were refusers, and 21.2 % were undecided [17]. Similarly, a survey of 521 adults with chronic disease in Saudi Arabia found COVID-19 vaccine acceptance as low as 52% [32]. Intentions to be vaccinated may change over time. UK hesitancy rates in the general public have been reported to fall from over 25% prior to vaccine development to just 13% once the UK vaccination programme was underway [12]. During the first wave of the pandemic (April 2020), COVID-19 vaccination acceptance was examined in two French high-risk groups: patients above 65 years old and patients with chronic airway disease, asthma or COPD (N = 216; mean age of 43.8 years). In the second group, most relevant to the present context, vaccination acceptance was 85% [33].

This survey showed that vaccines were well tolerated. Of the 509 participants who had received at least one vaccine dose, the majority reported mild or no side effects. However, there was evidence of a nocebo effect: people with negative beliefs towards vaccination had more severe side effects. A minority of patients reported an improvement in asthma symptoms or reported a worsening of symptoms following vaccination. Severe asthma exhibits idiopathic variation in symptoms, so these results may be due to natural variation in asthma control, and the slightly larger number of patients experiencing mild worsening can be explained by a nocebo effect.

Our results are in accordance with an Italian study [34] that evaluated COVID-19 vaccination safety and its effect on asthma control in 253 patients with severe asthma. Fewer than 20% of patients reported side effects, and vaccination positively affected asthma symptoms and quality of life. Our present study corroborates these important findings with a larger and more diverse sample, including patients treated with biologics and oral corticosteroids (patients receiving >10 mg prednisolone were excluded from the Italian study). Furthermore, we examined the effects of mRNA and vector/protein

subunit technology vaccines, with no differences reported in perceptions of either side effects or changes in asthma symptoms. A recent meta-analysis of studies involving over 26 million vaccine recipients [34] reported a low prevalence of COVID-19 mRNA vaccine-associated anaphylaxis, with non-anaphylactic reactions occurring at a higher rate and being largely self-limited. This was the case in a study of patients with mastocytosis, a group with an increased risk of anaphylaxis where COVID-19 mRNA vaccination was well tolerated [35]. The low number of side effects reported in our study supports this conclusion. An important finding in our study is that perception of side effect severity is highest in patients with a general mistrust of vaccines, suggesting that perceptions may be influenced by psychological factors linked to negative expectations. The nocebo effect is recognised as a cause of side effect reporting for COVID-19 vaccination [36], but we provide evidence for the first time that side effect reporting is increased with negative beliefs about vaccination

Finally, this study has shown that 90% of severe asthma patients feel safe following vaccination, and 98% would recommend COVID-19 vaccination to other patients with severe asthma. The experience of vaccination in those patients who received the vaccine was positive.

The current recommendation on COVID-19 vaccination from the Centers for Disease Control and Prevention (CDC) is that everyone from the age of five should get one dose of an updated vaccine to protect against serious illness from COVID-19 [37]. However, COVID-19 booster vaccination represents a challenge as it rises up to 30% globally. [38]. Safety concerns and doubts about safety represent the main reasons [39, 40] which our paper shows are unwarranted.

Our study has some limitations. We cannot exclude the possibility that patients with strong vaccination refusal beliefs chose not to respond, thereby introducing an element of bias. Different vaccine availability between countries may have affected the results. In addition, we conducted no clinical evaluations, and our data, therefore, rely on self-reported perceptions, with their inherent limitations. However, patients with severe asthma tend to have accurate perceptions of their asthma and can be considered “experts by lived experience”. In addition, people react to their perceptions of

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events, be they accurate or not, so understanding perceptions can be as important as measuring biomedical data. This survey also does not have the power to compare attitudes towards vaccination between individual countries.

Then, most of our population is on biologics (64%), which may increase the relationship between health practitioners and patients, as presume a frequent and more close contact, i.e. frequent visits for injections. This relationship could have made it easier for patients to accept vaccinations. Opposite patients with severe asthma, not on biologics, may have less frequent visits and thus might not have the same acceptance of the COVID-19 vaccination. We address this risk in Table 2, where we found that the vaccine refusers were least likely to be on biological treatment. This finding points out the importance of developing regular contact and trust between health professionals and patients in agreement with earlier studies, where the lack of trust has been identified among the reasons for vaccination hesitancy [41].

Conclusions and future implications.

In our study, only 9% of patients with severe asthma remained undecided about the COVID-19 vaccine. This hesitant minority is important as still potentially persuadable. With this study, we provide evidence that might be able to persuade that hesitant minority. Firstly, COVID-19 vaccines are medically safe for people with severe asthma, with no evidence of adverse asthma-related side effects. Secondly, people with severe asthma feel safe after having vaccinations. Finally, 98% of patients who had received vaccination would recommend it to other asthma patients, sending a powerful message to patients with asthma and other chronic immune-related diseases who are hesitant about getting vaccinated. This message is valuable for convincing asthma patients and patients with other immune-related diseases, as well as other patients and healthy individuals, to receive a boost vaccine for COVID-19[[37] and overall our preparation for future pandemics [42].

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Tables

Table 1. Participant details by country.

	n (% of total)	Age Mean (range)	Female n (%)	Daily Prednisolone n (%)	Biologics n (%)
Belgium	166 (25)	59 (21-86)	95 (57)	33 (20)	98 (59)
Estonia	43 (7)	57 (22-86)	32 (74)	11 (26)	21 (49)
France	1 (.15)	53 (53-53)	1 (100)	1 (100)	1 (100)
Greece	104 (16)	56 (18-80)	75 (72)	18 (17)	88 (85)
Hungary	73 (11)	57 (23-84)	49 (67)	12 (16)	47 (47)
Latvia	23 (3)	59 (42-81)	16 (70)	3 (3)	8 (35)
Lithuania	24 (4)	54 (31-78)	17 (71)	3 (3)	23 (96)
Netherlands	62 (9)	54 (25-75)	35 (82)	14 (14)	53 (85)
Romania	11 (2)	56 (38-77)	9 (82)	1 (9)	10 (91)
Russian Federation	19 (3)	49 (30-70)	11 (58)	3 (16)	5 (26)
Serbia	92 (14)	53 (26-76)	57 (62)	38 (41)	45 (49)
United Kingdom	42 (6)	51 (28-73)	30 (71)	7 (16.7)	21 (50)
All patients	660 (100)	55 (18-86)	427 (65)	144 (22)	420 (64)

Footnote Table 1. Numbers and characteristics of participating patients per country. Data are presented as n (%) for each participating country.

Table 2. Characteristics of vaccine refusers, hesitant and accepters.

	Refuser (n = 18)	Hesitant (n = 63)	Accepters (n = 575)
Age (M/SD)	51.28/8.71	51.68/13.37	56.53/13.14
Female	61%	76%	64%
Had COVID-19	17%	41%	12%
Daily Prednisolone	11%	29%	22%
Biologics for Asthma	44%	54%	65%

Footnote Table 2. Characteristics of patients according to their reported vaccination status. Patients are grouped as accepters of vaccination (vaccinated/will be vaccinated), hesitant (undecided) and refusers.

Table 3. Perceptions of Vaccination side effects and effects on asthma symptoms.

	Yes responses n (%)	Type of vaccine n (%)	
		mRNA	Other
<i>Perceived side effects of vaccination</i>			
Severe Side-effects	29 (5.70)	13 (2.55)	16 (4.00)
Mild side-effects	245 (48.16)	154 (30.26)	91 (17.88)
No side-effects	223 (43.81)	128 (25.15)	95 (18.66)
Treatment sought for side-effects	35 (6.88)	6 (1.18)	7 (1.38)
<i>Perceived change in asthma symptoms following vaccination</i>			
No change in symptoms	452 (88.80)	265 (52.06)	187 (36.74)
Symptoms got better	12 (2.36)	6 (1.18)	6 (1.18)
Symptoms slightly worse, no change in treatment needed	27 (5.30)	18 (3.54)	9 (1.77)
Symptoms worse needed a change in treatment	6 (1.18)	6 (1.18)	0

Footnote Table 3. Perceptions following vaccination (count and % of Yes responses) by patients who had received at least one dose of vaccine (n = 509). Only 497 surveys had completed answers and were analysed. Percentages represent the proportion of Yes responses overall and in terms of the type of vaccine received.

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Title Table 4. Vaccination hesitancy related beliefs (VAX subscale scores) for patients with severe asthma, according to their perception of vaccination side-effects.

	N	Mistrust vaccine efficacy	Concerns about future effects	Concerns about profiteering	Preference for natural immunity
Severe side effects	29	2.34/0.82	4.42/1.18	3.14/1.19	3.08/1.08
Mild side effects	245	1.99/0.83	3.99/0.98	2.42/0.97	2.80/1.02
No side effects	221	1.85/0.80	3.82/1.04	2.41/1.01	2.87/1.11
Results of ANOVA		$F(2, 492) = 5.04, p = 0.01, \eta^2 = 0.02$	$F(2, 492) = 5.01, p = 0.01, \eta^2 = 0.02$	$F(2, 492) = 7.08, p = 0.001, \eta^2 = 0.03$	$F(2, 492) = 0.99, p = 0.37, \eta^2 = 0.004$

Footnote Table 4. VAX questionnaire scores (Mean/SD) and results of between group analysis of variance for patients who reported no, mild, or severe side effects following COVID-19 vaccination.

Figures legends

Figure 1. COVID-19 vaccination status in patients with severe asthma who completed the survey.

Footnote Figure 1. Graph showing patients with severe asthma reporting their vaccination status.

Data are presented as (%) of the total population who replied to the survey (n=660).

Figure 2. Vaccination hesitancy between patients with severe asthma (VAX subscale scores), according to their vaccination status.

Footnote Figure 2. Descriptive statistics for the VAX questionnaire by reported vaccination status for A) mistrust of vaccine benefit, B) concerns about future effects, C) concerns about profiteering, and D) about preference for natural immunity. Patients grouped as 'accepters' of vaccination (vaccinated/will be vaccinated), 'hesitant' (undecided) and 'refusers.' Data show results of a 5-point scale whereby 1 = agree strongly and 5 = disagree strongly, and responses were averaged to obtain a score for each subscale. Significance for paired comparisons with Bonferroni post-hoc tests: * $p < 0.05$, ** $p < 0.001$.

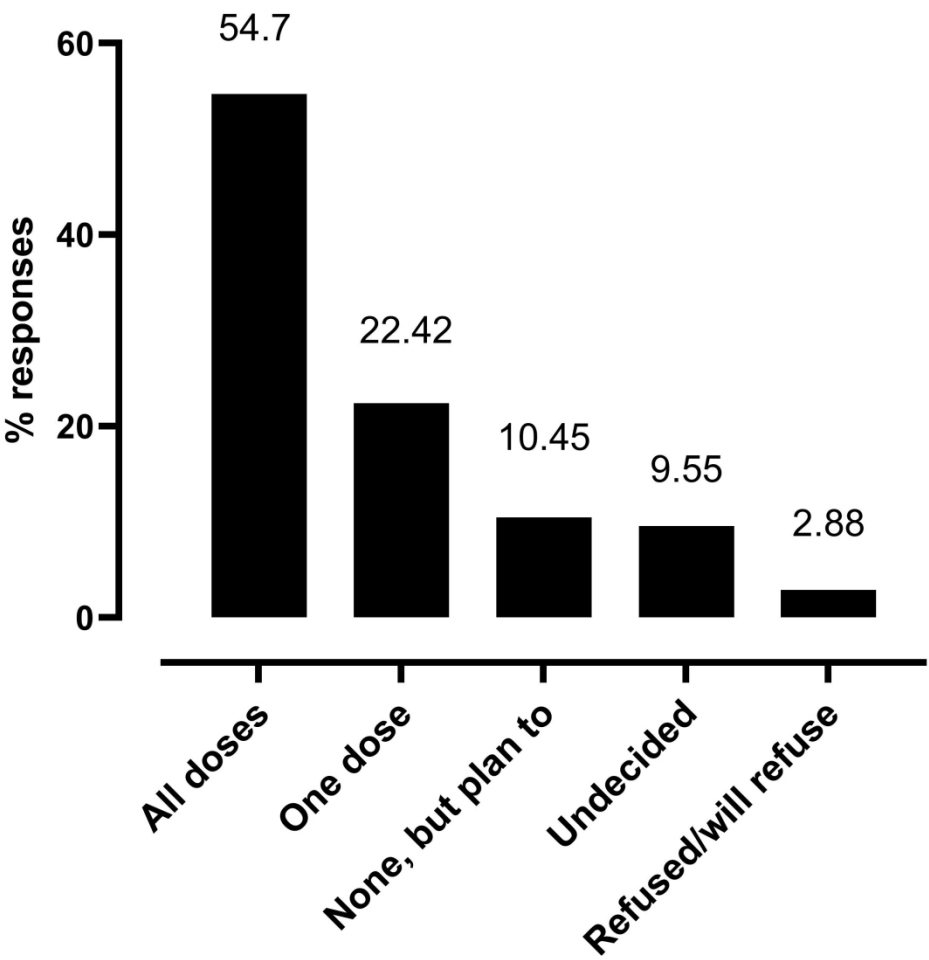


Figure 1. COVID-19 vaccination status in patients with severe asthma who complete the survey.

Footnote Figure 1. Graph showing patients with severe asthma reporting their vaccination status. Data are presented as (%) of the total population who replied to the survey (n=660).

112x114mm (600 x 600 DPI)

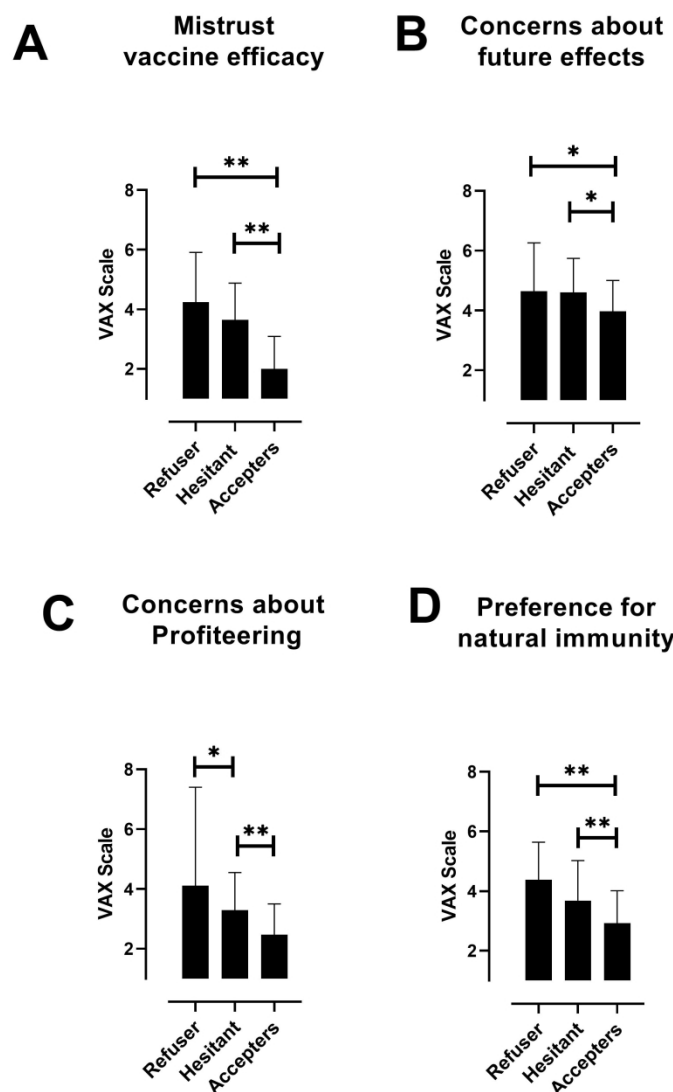


Figure 2. Vaccination hesitancy between patients with severe asthma (VAX subscale scores), according to their vaccination status.

Footnote Figure 2. Descriptive statistics for the VAX questionnaire by reported vaccination status for A) mistrust of vaccine benefit, B) concerns about future effects, C) concerns about profiteering, and D) about preference for natural immunity. Patients grouped as 'accepters' of vaccination (vaccinated/will be vaccinated), 'hesitant' (undecided) and 'refusers.' Data show results of a 5-point scale whereby 1 = agree strongly and 5 = disagree strongly, and responses were averaged to obtain a score for each subscale. Significance for paired comparisons with Bonferroni post-hoc tests: * $p < 0.05$, ** $p < 0.001$.

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COVID-19 vaccination, acceptance, safety, and side-effects in European patients with severe asthma

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Table S1 Title: Vaccination rates in each country.

	Patients n	Vaccination – all doses n (%)	Vaccination – one dose n (%)
Belgium	166	79 (48)	63 (38)
Estonia	43	18 (42)	8 (19)
France	1	0	0
Greece	104	61 (59)	17 (16)
Hungary	73	54 (74)	12 (16)
Latvia	23	3 (13)	8 (35)
Lithuania	24	14 (58)	5 (21)
Netherlands	62	29 (47)	26 (42)
Romania	11	5 (45)	0
Russian Federation	19	4 (21)	2 (11)
Serbia	92	52 (57)	7 (8)
United Kingdom	42	42 (100)	0
All patients	660	361(55)	148 (22)

Footnote Table S1. Vaccination rates (all doses and one dose) per country. Data are presented as n (%) for each participating country.

COVID-19 vaccination perception within patients with severe asthma in Europe.

A survey from the Severe Heterogeneous Asthma
Research Network – Patient centered (SHARP)



For Review Only

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Dear Sir or Madam,

The purpose of this survey is to understand what people with severe asthma think about the COVID-19 vaccination. This information will help improve care for patients with asthma. The questionnaire is anonymous (this means that you will not be asked to provide any personal details), and answers will be kept confidential (this means we will not share your specific answers with others but will combine all the responses when creating a report). The survey contains 19 questions and takes approximately 3 – 4 minutes to complete.

1. Do you agree to answer the following questions anonymously for scientific research?

- ☐ No, I don't agree, and will therefore not complete this survey.
- ☐ Yes, I agree

2. Which country do you live in?

.....

3. What is the year of your birth?

- ☐

4. Are you?

- ☐ Male
- ☐ Female
- ☐ Other/ Prefer not to say.

5. Do you think you had COVID-19?

(tick one)

- ☐ No
- ☐ Yes, but I was not diagnosed by a doctor and was not tested.
- ☐ Yes, I was diagnosed by a doctor but was not tested.
- ☐ Yes, I had a positive test result.
- ☐ Yes, I had a positive test result and was admitted to hospital.
- ☐ I don't know.

6. At the start of the coronavirus outbreak in Europe (February 2020) did you use asthma inhalers (relievers or preventers) every day?

- ☐ No
- ☐ Yes

- 1
2
3 7. At the start of the coronavirus outbreak in Europe (February 2020) did you take
4 prednisolone, (or similar i.e., cortisone or prednisone) tablets **every day**?
5 ☐ No
6
7 ☐ Yes
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11 8. At the start of the coronavirus outbreak in Europe did you have any biologic* injections
12 (or intravenous) for your asthma?
13 ☐ Not applicable, I did not have biologic injections.
14 ☐ Yes, I had biologic injections.
15
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18 * *Biologic injections for severe asthma include:*

19 *Xolair (omalizumab)*

20 *Nucala (mepolizumab,*

21 *Cinqaero (reslizumab)*

22 *Fasenra (benralizumab)*

23 *Dupixent (dupilumab)*

- 24
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28 9. Do you take medicines for diseases other than asthma ?
29 ☐ No
30 ☐ Yes

31 If yes, please tell us what:
32
33
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- 36
37 10. Have you been vaccinated against COVID-19?

38 *(tick one)*

- 39 ☐ Yes, I have had all the doses required.
40 ☐ Yes, I have one of the two doses required.
41 ☐ I have not but I plan to.
42 ☐ I have not yet received information from my health system/ doctor about
43 vaccination and will decide when I have this information.
44 ☐ I have not decided yet.
45 ☐ I have decided not to be vaccinated.
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- 51 11. If you have been vaccinated, please write the date of the first and (if relevant) the date
52 of the second dose.

- 53 • Date of the first vaccination dose
54 • Date of the second vaccination dose
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12. Which vaccine have you received?

- ☐ BioNTech/Pfizer vaccine
- ☐ Moderna vaccine
- ☐ Oxford/AstraZeneca vaccine
- ☐ Johnsson & Johnsson/Janssen vaccine
- ☐ Sputnik V (Gam-COVID-Vac) vaccine
- ☐ Shinopharm vaccine
- ☐ Other vaccine :.....

13. Please show to what extent you agree or disagree with the following statements about vaccinations, in general, using the following scale:

- 1: strongly agree
- 2: agree
- 3: slightly agree
- 4: slightly disagree
- 5: disagree
- 6: strongly disagree

- i. I feel safe after being vaccinated (.....)
- ii. I can rely on vaccines to stop serious infectious diseases (.....)
- iii. I feel protected after getting vaccinated (.....)
- iv. Although most vaccines appear to be safe, there may be problems that we have not yet discovered (.....)
- v. Vaccines can cause unforeseen problems in children (.....)
- vi. I worry about the unknown effects of vaccines in the future (.....)
- vii. Vaccines make a lot of money for pharmaceutical companies, but do not do much for regular people (.....)
- viii. Authorities promote vaccination for financial gain, not for people’s health (.....)
- ix. Vaccination programs are a big con (.....)
- x. Natural immunity lasts longer than a vaccination (.....)
- xi. Natural exposure to viruses and germs gives the safest protection (.....)
- xii. Being exposed to diseases naturally is safer for the immune system than being exposed through vaccination (.....)

14. Where did you get information about vaccination in general?

(tick all that apply)

- ☐ Social Media
- ☐ Friends and family
- ☐ News
- ☐ Government letter/email
- ☐ Doctor/other health professional
- ☐ Other.....

If you have had the COVID vaccine, answer the questions below. Answer ONLY if you have had the vaccine (one or more doses). Otherwise leave blank and finish.

15. Did you feel safer after the vaccination?

- ☐ No
☐ Yes

16. Would you recommend vaccination to other patients with asthma?

- ☐ No
☐ Yes

17. Did you have any side effects after you received the vaccine?

- ☐ No
☐ Yes, mild ones.
☐ Yes, more severe ones.

18. If yes did you seek medical treatment for the side-effects?

- ☐ No
☐ Yes

19. Did your asthma symptoms change after the vaccination?

- ☐ No
☐ Yes, it got better.
☐ Yes, it got slightly worse, but did not need a change in treatment.
☐ Yes, it got worse and needed a change in treatment.

Do you have any brief comments on the subject?

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Thank you!