# Cluster analysis reveals 3 main patterns of behavior towards SARS-CoV-2 vaccination in patients with autoimmune and inflammatory diseases

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**Key messages:**

- SARS-CoV-2 vaccine willingness is limited in patients with autoimmune or inflammatory rheumatic diseases.
- We identified significant behavioral differences between patients willing / unwilling to get vaccinated against SARS-CoV-2.
- This study may help improving communication with patients, in order to increase SARS-CoV-2 vaccine coverage.

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**Patient and public involvement**

Patients were not involved in the design of this study, however patient organizations were involved in its dissemination as well as in that of the study results to participants and to wider and relevant patient communities.

**Patient consent for publication**

The study was approved by the ethic review board of Strasbourg (#CE-2020-199) and informed consent was obtained from patients (via a dedicated question at the beginning of the online questionnaire).

**Data availability statement**

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

## ABSTRACT

### Introduction

Given the COVID19 pandemic, it is crucial to understand the underlying behavioral determinants of SARS-CoV-2 vaccine hesitancy in patients with autoimmune or inflammatory rheumatic diseases (AIIRD). We aimed to analyze patterns of behaviors regarding SARS-CoV-2 vaccination in AIIRD patients, as a mean to identify pragmatic actions to increase vaccine coverage in this population.

### Methods

Data of 1258 AIIRD patients were analyzed using univariate and multivariate logistic regression models, to identify variables associated independently with the willingness to get vaccinated against SARS-CoV-2. Subsets of patients showing similar behaviors towards SARS-CoV-2 vaccination were characterized using cluster analysis.

### Results

Hierarchical cluster analysis identified 3 distinct clusters of AIIRD patients. Three predominant patients' behavior towards SARS-COV-2 vaccination: 'voluntary', 'hesitant' and 'suspicious' were identified. While vaccine willingness was significantly different across the 3 clusters ($p<0.0001$), there was no difference regarding the fear to get COVID-19 ($p=0.11$), the presence of co-morbidities ($p=0.23$), the use of glucocorticoids ($p=0.21$) or the immunocompromised status ($p=0.63$). However, patients from cluster #3 ('suspicious') were significantly more concerned about vaccination, the use of a new vaccine technology, the lack of hindsight regarding COVID vaccination and potential financial links with pharmaceutical companies ($p<0.0001$ in all) than in the other 2 clusters.

### Discussion

Importantly, the differences between patients' behaviors are not related to the fear of getting COVID-19 or to any state of frailty, but point out to specific concerns about vaccination. This study may serve as a basis for improved communication, to increase COVID-19 vaccine coverage in AIIRD patients.

## Introduction

The SARS-CoV-2 vaccines will improve the general health situation secondary to the pandemic, by preventing future contaminations and consequently severe forms of COVID-19 [1]. The role of the rheumatologists, working together with the general practitioners as well as other specialists, is essential to increase SARS-CoV-2 vaccine coverage in patients with autoimmune or inflammatory rheumatic diseases (AIIRDs) [2,3] which could be at increased risk of severe form of COVID-19 [4,5]. We recently published the international VAXICOV study, which aim was to describe the expectations and potential concerns related to SARS-CoV-2 vaccination in AIIRD patients [2]. One of the main findings of VAXICOV was the limited willingness to get the SARS-CoV-2 vaccines from AIIRD patients. From a public health perspective, it is therefore crucial to understand the underlying determinants of vaccine hesitancy [6] in the context of the SARS-CoV-2 pandemic. The objective of this new study was to analyze the different types of patient behaviors regarding SARS-CoV-2 vaccination as well as their determinants, using a data-driven approach, in order to identify pragmatic means to impact positively those behaviors by the rheumatologist.

## Methods

### *Study design and dissemination*

The VAXICOV study consisted of an online questionnaire of 57 questions which addressed epidemiological, socio-demographic and therapeutic elements associated with expectations and potential concerns regarding SARS-CoV-2 vaccination. The online survey took place from December 12, 2020 to December 21, 2020. The questionnaire was translated from English into French and Spanish by native speakers. The detailed methods of the VAXICOV study and main findings have been already described [2].

### *Study participants and main study outcomes*

The study included patients with a self-reported diagnosis of AIIRDs. Main study outcomes included: demographical characteristics (age, prior chronic medical conditions, marital status, children, profession, income); experiences about COVID-19; history of vaccination against seasonal influenza and pneumococcus; intention to get vaccinated if a COVID-19 vaccine were available; vaccine hesitancy; and fears and expectations about COVID-19 vaccine. Participants rated their feelings about SARS-CoV-2 vaccination using 0 to 10 scales (0: Not at all in agreement; 10: fully agree). An "immunocompromised" status was defined as participants taking at least one immunosuppressant or glucocorticoids at a dose greater than 10 mg per day of prednisone-equivalent. The study was approved by the ethic review board of Strasbourg (#CE-2020-199).

### *Statistical analysis*

Continuous data are presented as medians and their 25th-75th percentile interquartile range (IQR) and categorical data as counts and percentages. Comparisons between independent groups were made using the Mann-Whitney test for continuous outcomes and the Chi-2 test (or Fisher's exact test when appropriate) for quantitative data.

Univariate and multivariate logistic regression models using a backward stepwise approach were built to identify variables associated independently with the willingness to get vaccinated against SARS-CoV-2 (selected as the dependent variable). All Likert statements with a p-value <0.10 in univariate analysis were included as independent variables in the multivariate logistic regression models. Subsets of patients showing similar specific perception about SARS-CoV-2 vaccination (based on the patient's answers to the 5 significant statements from the VAXICOV study, see results) were characterized using cluster analysis. Hierarchical cluster analysis using Ward's method was used as the principal clustering technique and the optimal number of clusters was determined using the gap/elbow method, and pre-specified in a k-means cluster analysis, and the agreement between the two clustering methods was calculated using Cohen's kappa. Principal component analysis was performed using data from the statements which remained significant in the stepwise multivariable model, using a color code according to the main clustering group for each patient. All tests were bilateral and p-values <0.05 were considered statistically significant. Statistical analyses were performed with the software JMP13 (SAS institute, Cary, NC, USA).

## Results

### *Patients characteristics*

The study included 1258 patients with AIIRDs (1138 [90.5%] women and 120 [9.5%] men; median age 50 [IQR: 40-61] years), from 56 countries. The most common inflammatory or autoimmune conditions (Table 1) were Systemic Lupus Erythematosus (n=492, 39.1%), spondyloarthritis (n=174, 13.8%), rheumatoid arthritis (n=157, 12.5%) and polymyalgia rheumatic/giant cell arteritis (n=144, 11.5%).

### *Main characteristics of the 3 clusters*

From the 14 statements assessed in VAXICOV, multivariate logistic regression models identified 5 statements independently associated with the willingness to get vaccinated against SARS-CoV-2 (#3-6-10-13-14, Table 2). Based on the patient's answers to these 5 significant statements, hierarchical cluster analysis identified 3 distinct clusters within the study population (labeled cluster #1, #2 and #3, Figure 1 A and B) regrouping 180, 688 and 390 patients, respectively. The detailed characteristics of

the 3 clusters are shown in table 3. The concordance with k-means clustering was high (Cohen's kappa: 0.76).

***Vaccine willingness across the 3 clusters***

Vaccine willingness was significantly different across the 3 clusters (Table 3): patients from cluster #1 were the most willing to get vaccinated (willing in 97.2%, unsure in 1.7% and would decline vaccination in 1.1%). Patients from cluster #2 were more hesitant (willing in 64.8%, unsure in 30.1%, would decline for 5.1%) while patients from cluster #3 were mostly opposed to getting vaccinated (willing in 15.6%, unsure in 49.7%, would decline for 34.6%). These patterns were similar if their doctor advised them to get vaccinated (Table 3). Importantly, the most trustworthy healthcare professional across the 3 clusters was the medical specialist (by 70.0% of patients in cluster #1, 70.9% in cluster #2, and 68.0% in cluster #3). However, 14.1% of patients from cluster #3 did not trust any healthcare professional (versus 0.6% and 4.9% in clusters #1 and #2 respectively, p<0.0001).

***Main predictors of cluster membership***

While vaccine willingness and hesitancy were significantly different across the 3 clusters (p<0.0001, Table 3), there was no difference regarding the fear to get COVID-19 (median score on the 0 to 10 Likert scale: 8 [6-10] for cluster #1, 8 [7-10] for cluster #2, and 8 [6-10] for cluster #3, p=0.11) or the fear to get a severe form of COVID-19 (Cluster #1: 9 [7-10], cluster #2: 9 [8-10], and cluster #3: 9 [6-10], p=0.11) (Table 4). Strikingly, patients from cluster #3 were significantly more concerned about vaccination in general (p<0.0001), though it was less important to get vaccinated (p<0.0001), were significantly more concerned about the use of a new vaccine technology (e.g., RNA vaccine) (p<0.0001), about the lack of hindsight regarding COVID vaccination (p<0.0001) as well as about potential financial links between governments and pharmaceutical companies (p<0.0001) than in the other 2 clusters (Table 4). Patients in clusters #2 and #3 were significantly more concerned that the vaccine would induce a flare of their disease than those in cluster #1 (p<0.0001). Detailed behavioral results across the 3 clusters are shown in table 4. The proportion of men was significantly higher in cluster #1 than in the 2 other clusters (18.9% in cluster #1 versus 8.7% in cluster #2 and 6.7% in cluster #3, p<0.0001). Patients in cluster #3 were significantly younger (median age: 46.5 [37-56] years) than those in cluster #1 (56.5 [41-67] years) and cluster #2 (51 [41-63] years), p<0.0001 (Table 3). Also, countries of origin (p<0.0001) and rheumatic diseases (p<0.0001) were statistically different between the 3 clusters. Importantly, there were no significant difference as to the presence of co-morbidities (p=0.23), the use of glucocorticoids (p=0.21) or the immunocompromised status (p=0.63) (Table 3).

## Discussion

Our results based on a cluster analysis of a large international sample of patients with autoimmune and inflammatory diseases enabled the identification of 3 distinct clusters of behavior towards SARS-COV-2 vaccination. Identifying those patients' behaviors can help tailoring the approach to be adopted by healthcare professionals and governments at the individual and collective level, in order to improve SARS-CoV-2 vaccination coverage. Based on the willingness to get vaccinated and the answers to the statements presented in tables 2 and 4, cluster #1 members can be seen as *voluntary,* cluster #2 members as *hesitant*, and cluster #3 members as *suspicious* towards SARS-CoV-2 vaccination.

Contrary to what might have been expected, willingness to get vaccinated was not statistically related to increased frailty, as evidenced by the lack of difference in terms of immunosuppression or associated comorbidities. Importantly, the fear of getting COVID19 was high among the 3 groups. While this does not mean it is an irrelevant factor for why someone would ultimately get vaccinated, the fear of getting COVID-19 or a severe form of SARS-CoV-2 infection was not statistically different across the 3 clusters therefore suggesting that there seems to be no relevance to use this element as an anchor to convince AIIRD patients to get vaccinated.

This study further highlighted important differences which may exist between countries regarding vaccine willingness (Table 3). This had already been shown in a worldwide study showing disparities in acceptance of COVID vaccination ranging from 90% in China to less than 55% in Russia [7]. Also, another important finding was the differences in age across the three clusters (Table 3). In the VAXICOV study, the willingness to get vaccinated increased significantly with age [2]. Similarly, COVID-19 vaccine hesitancy and refusal were both associated significantly to age in a previous study [8]. Interestingly, we point out that this is not explained by a difference in the fear of getting COVID-19 or severe COVID-19.

What differed the most between the 3 clusters were the concerns about vaccination *in general* or about *COVID-19 vaccines*, the lack of hindsight regarding the use of *new vaccine technologie*s (such as RNA vaccines) and the possible *financial links* with the pharmaceutical companies. Patients for whom giving the medical advice to get vaccinated would be the most effective were those from cluster #2 "hesitant" and #3 "suspicious" (Table 3). Accordingly and based on significant concerns identified in this study, the physician's attitude towards a reluctant patient with AIIRD should be to discuss the general principles behind vaccination, including its immunological basis, the main efficacy and safety data from the large phase 3 trials [9–12] and the general drug approval and licensing process in order to respond to the patients' fears on those possible points. This is an important point as it is the medical specialist who is the most trustworthy in all clusters.

Another issue in 'hesitant' or 'suspicious' patients was the potential induction of a flare by the SARS-CoV-2 vaccine. This point seems worth discussing with patients, and it is important to emphasize that the benefit-risk ratio likely favors vaccination. International registries will probably provide clarification for our patients in the near future.

This cluster analysis based on a large international sample of AIIRD patients enabled the identification of 3 main patterns of patients' behavior towards SARS-COV-2 vaccination: hesitant, voluntary and suspicious. Importantly, the differences between those behaviors are not related to the fear of getting COVID-19 or to any state of frailty such as immunodepression, but point out to concerns about available scientific data on vaccination, lack of hindsight and potential financial links with the pharmaceutical industry. Interestingly, these specific concerns about vaccination are also major factors related to non-adherence to chronic treatment in patients with inflammatory rheumatic diseases. This study may serve as a basis for improved communication by physicians and health agencies to increase the COVID-19 vaccine coverage in AIIRD patients both at the individual and population level.

**Table 1. Patients characteristics**

| **Parameters** | |
|---|---|
| **Number of patients** | 1258 |
| **Age (years)**, median [IQR25-75] | 50 [40-61] |
| **Female**, n (%) | 1138 (90.5%) |
| **Male, n (%)** | 120 (9.5%) |
| **Country**, n (%) | |
| UK | 345 (27.4%) |
| France | 313 (24.9%) |
| Chile | 123 (9.7%) |
| USA | 114 (9.1%) |
| Spain | 57 (4.5%) |
| Mexico | 53 (4.2%) |
| Argentina | 45 (3.6%) |
| Venezuela | 43 (3.4%) |
| Other* | 165 (13.1%) |
| **Rheumatic diagnosis**, n (%) | |
| Systemic lupus erythematosus | 492 (39.1%) |
| Spondyloarthritis | 174 (13.8%) |
| Rheumatoid arthritis | 157 (12.5%) |
| Giant cell arteritis / Polymyalgia rheumatica | 144 (11.5%) |
| Primary anti-phospholipid syndrome | 64 (5.1%) |
| Inflammatory myositis | 62 (4.9%) |
| Relapsing polychondritis | 45 (3.6%) |
| Other** | 120 (9.6%) |
| **Associated comorbidities**, n (%) | |
| Diabetes | 68 (5.4%) |
| Hypertension | 263 (20.9%) |
| Myocardial infarction, stroke, transient stroke | 58 (4.6%) |
| Respiratory disease (asthma, chronic bronchitis, emphysema, etc.) | 168 (13.4%) |
| Renal failure | 43 (3.4%) |
| Obesity (BMI > 30) | 227 (18.0%) |
| **At least one associated comorbidity**, n (%) | 582 (46.3%) |
| **Smoker**, n (%) | 1250 |
| Current | 126 (10.1%) |
| Past | 407 (32.6%) |
| Never | 717 (57.4%) |
| **Use of oral glucocorticoids**, n (%) | 547 (56.1%) |
| **Immunocompromised**[$], n (%) | 766 (60.9%) |

*Other countries: Algeria (n=1), Australia (n=10), Austria (n=1), Belgium (n=3), Bolivia (n=2), Brazil (n=1), Canada (n=18), Colombia (n=12), Costa Rica (n=3), Cuba (n=2), Denmark (n=1), Ecuador (n=4), El Salvador (n=3), Estonia (n=2), Finland (n=1), Germany (n=8), Gibraltar (n=1), Greece (n=1), Guatemala (n=2), Honduras (n=1), Iceland (n=7), India (n=7), Ireland (n=7), Israel (n=2), Italy (n=1), Jordan (n=1), Lebanon (n=1), Lithuania (n=2), Luxembourg (n=1), New Zealand (n=4), Nicaragua (n=2), Norway (n=2), Panama (n=2), Paraguay (n=2), Peru (n=27), Philippines (n=1), Poland (n=1), Portugal (n=1), Puerto Rico (n=3), Slovakia (n=2), Sweden (n=3), Switzerland (n=2), The Netherlands (n=3), Uruguay (n=6).

** Other rheumatic diagnosis: Behçet n=11, mixed connective tissue disease n=10, other type of vasculitis n=8, overlap n=23, undifferentiated connective tissue disease n=8, unknown n=7, sarcoidosis n=2, Sjögren's syndrome n=18, Systemic sclerosis n=16, other autoimmune or inflammatory diseases n=17.

[$] at least one immunosuppressant (except hydroxychloroquine/chloroquine and apremilast) or glucocorticoids at a dose greater than 10 mg per day of prednisone-equivalent

**Table 2. Association between the risk to decline SARS-CoV-2 vaccination and VAXICOV statements.**

| Statements | Proportions among those* | | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|---|
| | Willing to get vaccinated | Unwilling to get vaccinated | OR (95%CI) | p-values | OR (95%CI) | p-values |
| **#1: I am one of those people who never get sick/ill therefore vaccines are not useful in my case** | 4.2% | 19.8% | 1.44 (1.35-1.53) | <0.0001 | - | - |
| **#2: a COVID-19 vaccine may have DECREASED EFFICACY in my personal situation** | 23.9% | 30.3% | 1.15 (1.09-1.21) | <0.0001 | - | - |
| **#3: There is a lack of hindsight regarding new anti-COVID-19 vaccines** | 35.5% | 89.5% | 1.81 (1.65-2.02) | <0.0001 | 1.37 (1.23-1.54) | <0.0001 |
| **#4: There is a lack of hindsight regarding vaccines in general** | 21.0% | 59.3% | 1.37 (1.29-1.45) | <0.0001 | - | - |
| **#5: I will be careful if the anti-COVID-19 vaccines uses a technology that has never been used before (e.g., RNA vaccine)** | 35.9% | 77.3% | 1.50 (1.39-1.62) | <0.0001 | - | - |
| **#6: Maybe a COVID-19 vaccine can induce a flare of my auto-immune/inflammatory disease** | 39.6% | 80.8% | 1.60 (1.47-1.75) | <0.0001 | 1.17 (1.05-1.30) | <0.0001 |
| **#7: I am afraid of the pain of the injection, or to develop local reaction after the vaccination** | 12.3% | 32.6% | 1.20 (1.15-1.26) | <0.0001 | - | - |
| **#8: I am concerned about vaccination, in general** | 17.3% | 50.6% | 1.32 (1.25-1.39) | <0.0001 | - | - |
| **#9: I am concerned about the general management of this health crisis by governments** | 62.9% | 82.6% | 1.26 (1.17-1.36) | <0.0001 | - | - |
| **#10: I am afraid of potential side-effects induced by the COVID-19 vaccine** | 39.3% | 95.3% | 2.11 (1.86-2.43) | <0.0001 | 1.43 (1.24-1.68) | <0.0001 |
| **#11: a COVID-19 vaccine could induce a disease, such as a chronic disease, an infection or a cancer** | 12.0% | 66.3% | 1.59 (1.49-1.70) | <0.0001 | - | - |
| **#12: a COVID-19 vaccine could give me the COVID-19** | 7.2% | 43.6% | 1.46 (1.38-1.55) | <0.0001 | - | - |
| **#13: I think a COVID-19 vaccine is not needed in my case** | 3.7% | 32.0% | 1.76 (1.64-1.90) | <0.0001 | 1.43 (1.32-1.56) | <0.0001 |
| **#14: I think COVID-19 vaccination is mostly recommended because of the financial links between governments and pharmaceutical companies.** | 6.4% | 54.6% | 1.63 (1.54-1.74) | <0.0001 | 1.21 (1.12-1.31) | <0.0001 |

Odds Ratio (OR) and 95% Confidence Interval (95%CI) for the risk to decline SARS-CoV-2 vaccination versus to get vaccinated (as the reference category), in association with each statement. *Proportion of patients with a value ≥ 7 (on the 0-10 Likert scale) for each statement, according to the willing/unwilling status.

**Table 3. Comparisons of patients' characteristics and vaccine willingness according to the clusters**

| Subject groups | Cluster #1 *"Voluntary"* | Cluster #2 *"Hesitant"* | Cluster #3 *"Suspicious"* | p-value |
|---|---|---|---|---|
| **Number of patients**, n (%) | 180 | 688 | 390 | - |
| **Age (years)**, median [IQR25-75] | 56.5 [41-67] | 51 [41-63] | 46.5 [37-56] | **<0.0001** |
| **Female**, n (%) | 146 (81.1%) | 628 (91.3%) | 364 (93.3%) | **<0.0001** |
| **Male**, n (%) | 34 (18.9%) | 60 (8.7%) | 26 (6.7%) | |
| **Country**, n (%) | | | | **<0.0001** |
| UK | 71 (39.4%) | 215 (31.3%) | 41 (10.5%) | |
| France | 26 (14.4%) | 155 (22.5%) | 132 (33.9%) | |
| Chile | 9 (5.0%) | 55 (8.0%) | 59 (15.1%) | |
| USA | 28 (15.6%) | 63 (9.2%) | 23 (5.9%) | |
| Spain | 1 (0.6%) | 35 (5.1%) | 21 (5.4%) | |
| Mexico | 5 (2.8%) | 25 (3.6%) | 23 (5.9%) | |
| Argentina | 7 (3.9%) | 19 (2.8%) | 19 (4.9%) | |
| Venezuela | 0 | 20 (2.9%) | 23 (5.9%) | |
| Other* | 33 (18.3%) | 101 (14.6%) | 49 (12.6%) | |
| **Rheumatic diagnosis**, n (%) | | | | **<0.0001** |
| Systemic lupus erythematosus | 60 (33.3%) | 271 (39.4%) | 161 (41.3%) | |
| Spondyloarthritis | 14 (7.8%) | 94 (13.7%) | 66 (16.9%) | |
| Rheumatoid arthritis | 19 (10.6%) | 78 (11.3%) | 60 (15.4%) | |
| Giant cell arteritis / Polymyalgia rheumatica | 40 (22.2%) | 91 (13.2%) | 13 (3.3%) | |
| Primary anti-phospholipid syndrome | 4 (2.2%) | 41 (6.0%) | 7 (1.8%) | |
| Inflammatory myositis | 13 (7.2%) | 30 (13.2%) | 19 (4.9%) | |
| Relapsing polychondritis | 6 (3.3%) | 27 (3.9%) | 12 (3.1%) | |
| Other** | 24 (13.3%) | 56 (8.1%) | 52 (13.3%) | |
| **Associated comorbidities**, n (%) | | | | |
| Diabetes | 7 (3.9%) | 41 (6.0%) | 20 (5.1%) | 0.53 |
| Hypertension | 38 (21.1%) | 140 (20.4%) | 85 (21.8%) | 0.85 |
| Myocardial infarction, stroke, transient stroke | 6 (3.3%) | 38 (5.5%) | 14 (3.6%) | 0.24 |
| Respiratory disease (asthma, chronic bronchitis, emphysema, etc.) | 25 (13.9%) | 87 (12.7%) | 56 (14.4%) | 0.71 |
| Renal failure | 9 (5.0%) | 17 (2.5%) | 17 (4.4%) | 0.12 |
| Obesity (BMI > 30) | 33 (18.3%) | 111 (16.1%) | 83 (21.3%) | 0.11 |
| **At least one associated comorbidity**, n (%) | 83 (46.1%) | 305 (44.3%) | 194 (49.7%) | 0.23 |
| **Smoker**, n (%) | | | | **0.0009** |
| Current | 13 (7.3%) | 54 (7.9%) | 59 (15.2%) | |
| Past | 60 (33.7%) | 217 (31.7%) | 130 (33.5%) | |
| Never | 105 (59.0%) | 413 (60.4%) | 199 (51.3%) | |
| **Use of oral glucocorticoids**, n (%) | 90 (50%) | 299 (43.5%) | 158 (40.5%) | 0.21 |
| **Immunocompromised**[$], n (%) | 114 (63.3%) | 421 (61.2%) | 231 (59.2%) | 0.63 |
| **Willing to get vaccinated : Yes/uncertain/No**, % | 97.2/1.7/1.1 | 64.8/30.1/5.1 | 15.6/49.7/34.6 | **<0.0001** |
| **Willing to get vaccinated after medical advice : (Yes/uncertain/No)**, % | 98.9/0.6/0.6 | 72.8/24.3/2.9 | 28.7/48.2/23.1 | **<0.0001** |
| **Vaccine hesitancy**, n (%) | 15 (8.3%) | 166 (24.1%) | 176 (45.1%) | **<0.0001** |

P-values in bold remain statistically significant after Bonferroni correction for multiple testing.

**Table 4. Participants' behavior and willingness to get vaccinated against SARS-CoV-2 according to the clusters**

| Statements | Subject groups | | | p-value |
|---|---|---|---|---|
| | Cluster #1 *"Voluntary"* | Cluster #2 *"Hesitant"* | Cluster #3 *"Suspicious"* | |
| **#1: I am one of those people who never get sick/ill therefore vaccines are not useful in my case** | 0 [0-0] | 0 [0-2] | 3 [0-5] | **<.0001** |
| **#2: a COVID-19 vaccine may have DECREASED EFFICACY in my personal situation** | 1 [0-5] | 5 [1-7] | 5 [5-8] | **<.0001** |
| **#3: There is a lack of hindsight regarding new anti-COVID-19 vaccines** | 1.5 [0-3] | 6 [5-9] | 10 [8-10] | **<.0001** |
| **#4: There is a lack of hindsight regarding vaccines in general** | 0 [0-2] | 5 [1-6] | 8 [5-10] | **<.0001** |
| **#5: I will be careful if the anti-COVID-19 vaccines uses a technology that has never been used before (e.g., RNA vaccine)** | 2 [0-5] | 6 [4-8] | 9 [7-10] | **<.0001** |
| **#6: Maybe a COVID-19 vaccine can induce a flare of my auto-immune/inflammatory disease** | 3 [1-5] | 7 [5-9] | 9 [8-10] | **<.0001** |
| **#7: I am afraid of the pain of the injection, or to develop local reaction after the vaccination** | 0 | 1 [0-5] | 4 [1-8] | **<.0001** |
| **#8: I am concerned about vaccination, in general** | 0 [0-1] | 3 [0-6] | 7 [5-10] | **<.0001** |
| **#9: I am concerned about the general management of this health crisis by governments** | 6 [3-10] | 8 [5-10] | 10 [8-10] | **<.0001** |
| **#10: I am afraid of potential side-effects induced by the COVID-19 vaccine** | 1 [0-2] | 7 [5-9] | 10 [9-10] | **<.0001** |
| **#11: a COVID-19 vaccine could induce a disease, such as a chronic disease, an infection or a cancer** | 0 [0-1] | 5 [1-6] | 8 [6-10] | **<.0001** |
| **#12: a COVID-19 vaccine could give me the COVID-19** | 0 | 1 [0-5] | 6 [3-9] | **<.0001** |
| **#13: I think a COVID-19 vaccine is not needed in my case** | 0 | 0 [0-1] | 5 [2-7] | **<.0001** |
| **#14: I think COVID-19 vaccination is mostly recommended because of the financial links between governments and pharmaceutical companies.** | 0 | 0 [0-3] | 8 [5-10] | **<.0001** |
| **How important is it to get people vaccinated?** | 10 | 10 [9-10] | 9 [7-10] | **<.0001** |
| **How important is it to get YOU (personally) vaccinated?** | 10 | 10 [9-10] | 8 [6-10] | **<.0001** |
| **How suspicious are you about vaccination in general?** | 0 [0-1] | 3 [1-9] | 7 [3-9] | **<.0001** |
| **How afraid are you to get infected by the COVID19?** | 8 [6-10] | 8 [7-10] | 8 [6-10] | 0.11 |
| **How afraid are you to get a SEVERE COVID19 infection?** | 9 [7-10] | 9 [8-10] | 9 [6-10] | 0.11 |

Median [IQR]. P-values in bold remain significant after Bonferroni correction.

Answers were assessed on a 0 to 10 Likert scale.

**Figure 1 Cluster analysis**

**A. Hierarchical Ascending Clustering showing the 3 clusters**

Dendrogram showing the 3 clusters based on the patient's answers (color coded from green [lowest value] to red [highest value]) to the 5 significant statements (statements #3-6-10-13-14) from the VAXICOV study.

**B. Principal component analysis showing the 3 clusters**

Principal component analysis (3D plot) based on individual patient's answers to the 5 significant statements from the VAXICOV study, according to the three first principal components (labeled Prin 1, 2 and 3), and color-coded according to the 3 clusters (cluster #1: green cluster #2: red and cluster #3: blue).

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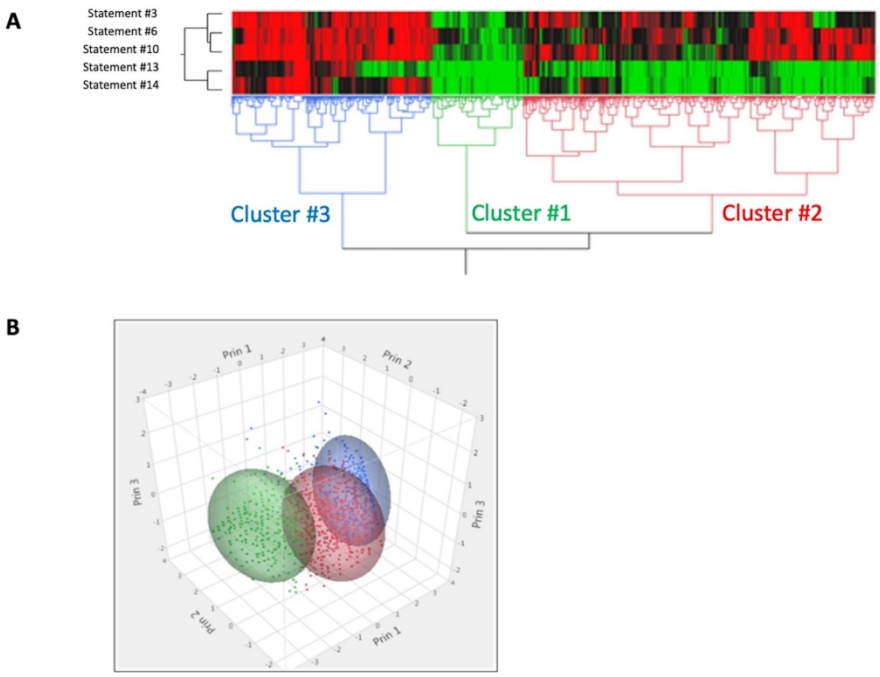


Figure 1 Cluster analysis. Panel A: Hierarchical Ascending Clustering showing the 3 clusters; Dendrogram showing the 3 clusters based on the patient's answers (color coded from green [lowest value] to red [highest value]) to the 5 significant statements (statements #3-6-10-13-14) from the VAXICOV study. Panel B: Principal component analysis showing the 3 clusters; Principal component analysis (3D plot) based on individual patient's answers to the 5 significant statements from the VAXICOV study, according to the three first principal components (labeled Prin 1, 2 and 3), and color-coded according to the 3 clusters (cluster #1: green cluster #2: red and cluster #3: blue).

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