COVID-19 vaccine hesitancy and acceptance among individuals with cancer, autoimmune diseases, and other serious comorbid conditions: A cross-sectional internet-based survey

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Richard Tsai[1] MS; John Hervey[1] BA; Kathleen Hoffman[1] PhD; Jessica Wood[1] MS; Jennifer Johnson[1] MS; Dana Deighton[1] BA; Donald Clermont[1] MPH; Brian Loew[1] BS; Stuart Goldberg[2] MD

[1]Inspire Arlington US
[2]Hackensack Meridian School of Medicine Nutley US

Corresponding Author:
Richard Tsai MS
Inspire
3101 Wilson Boulevard
Suite 220
Arlington
US

Abstract

Background: Individuals with comorbid conditions have been disproportionately affected by COVID-19. Since regulatory trials with COVID-19 vaccines excluded those with immunocompromising conditions, few patients with cancer and autoimmune diseases were enrolled. With limited vaccine safety data available vulnerable populations may have conflicted vaccine attitudes.

Objective: We sought to assess the prevalence and independent predictors of COVID-19 vaccine hesitancy and acceptance among individuals with serious comorbidities, and to assess self-reported side-effects among those who had received the vaccine.

Methods: We conducted a cross-sectional 55-item online survey, fielded January 15, 2021 through February 22, 2021, among a random sample of members of Inspire, an online health community of over 2.2 million individuals with comorbid conditions. Multivariable regression analysis was utilized to determine factors independently associated with vaccine hesitancy and acceptance.

Results: Of the 996,500 members of the Inspire health community who were invited to participate responses were received from 21,943 individuals (2.2%). Respondents resided in 123 countries (74% USA), had a median age range 56-65 years, were highly educated (60% holding college or post-graduate degrees), and had diverse political leanings. All respondents self-reported at least one co-morbidity, with 27% having cancer, 23% autoimmune diseases, and 38% chronic lung diseases. COVID-19 vaccine hesitancy was identified in 18.6%, with 2190 (10.3%) declaring that they would not, 742 (3.4%) stating that they probably would not, and 1028 (4.8%) not sure whether they would agree to be vaccinated. Hesitancy was expressed by 13.4% cancer patients, 19.4% with autoimmune diseases, and 17.8% with chronic lung diseases. Positive predictors of vaccine acceptance included routine influenza vaccination (odds ratio 1.53), trust in responsible vaccine development (odds ratio 14.04), residing in the USA (odds ratio 1.31) and never smoker status (odds ratio 1.06). Hesitancy was increased with a history of prior COVID-19 (odds ratio .86), conservative political leaning (odds ratio .93), younger age (odds ratio .83), and lower education level (odds ratio .90). One quarter (5501 participants) had received at least one COVID-19 vaccine injection and 1390 (6.2%) completed a two-dose series. Following the first injection, 69% self-reported local and 40% systemic reactions, which increased following the second injection to 76% and 67%, respectively.

Conclusions: In this survey of individuals with serious comorbid conditions significant vaccine hesitancy remains. Assumptions that the most vulnerable would automatically accept COVID-19 vaccination are erroneous and thus call for healthcare team members to initiate discussions focusing on the impact of the vaccine on an individual's underlying condition. Early self-reported side-effect experiences among those who have already been vaccinated, as expressed by our population, should be reassuring and might be utilized to alleviate vaccine fears. Healthcare related social media forums which rapidly disseminate accurate information about the COVID-19 vaccine may play an important role.

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COVID-19 vaccine hesitancy and acceptance among individuals with cancer, autoimmune diseases, and other serious comorbid conditions: A cross-sectional internet-based survey

Running Title: COVID-19 vaccine hesitancy and acceptance in vulnerable populations

Richard Tsai[1], John Hervey[1], Kathleen D Hoffman[1], Jessica Wood[1], Jennifer Johnson[1], Dana C. Deighton[1], Donald Clermont[1], Brian Loew[1], Stuart L Goldberg[2]

1. Inspire, Arlington VA

2. Hackensack Meridian School of Medicine, Nutley NJ

Corresponding Author

Richard Tsai

3101 Wilson Blvd, Suite 220

Arlington, VA 22201

Phone: 571-277-6340

Email: richard@inspire.com

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Introduction*:*

The rapid development of safe and effective vaccines against SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) may stem the global COVID-19 (coronavirus disease 2019) pandemic. However, vaccine hesitancy – the reluctance or refusal to vaccinate – has emerged as a major worldwide public health concern, especially as it may impair the ability to reach herd immunity status. [1-5] An IPOS poll for the World Economic Forum conducted in January 2021 of 15 countries reported vaccine acceptances ranging from 86% in Brazil to only 46% in Russia, with the United States ranking 12th (63% vaccine acceptance). [6] Over time COVID-19 vaccine acceptance has increased. Serial tracking polls by the Kaiser Family Foundation conducted in the United States reported that as of July 2021 70% of adults had either "received" or "will receive as soon as possible" the vaccine, up from 55% in February 2021, and 34% in early December 2020. [7,8] However, anti-vaccination sentiment remained constant over this timeframe with 14% stating that they would "definitely not get vaccinated" and 3% agreeing "only if required". [8] Although the more virulent coronavirus delta variant has increased the rapidity of vaccination uptake among individuals who were "waiting to see," only 2% of those who refused vaccines were influenced by its emergence. [8] Multiple studies have explored reasons for COVID-19 vaccine hesitancy, with vaccine-specific concerns (side-effects and efficacy), a need for more information, racial/ethnic biases, political views, general anti-vaccine attitudes or beliefs, and a lack of trust being most commonly cited. [4,5, 7-12]

Individuals with comorbid conditions have been disproportionately affected by COVID-19. A USA review of nearly a half-million commercially insured COVID-19 patients noted that although only 51.7% had pre-existing conditions, 83.3% of the COVID-19 related deaths occurred among those with comorbidities. The risk of dying from COVID-19 was strongly correlated with the number of comorbidities, nearly doubling with a single comorbid condition and increasing 8-fold with five or more conditions. [13] Persons with developmental disorders, congenital and acquired neurologic

disabilities, cancers (especially lung cancer, leukemia and lymphoma), sickle cell disease, chronic kidney disease, heart failure, and diabetes appear to be at a particularly high risk for COVID-19 related mortality. [13, 14] Hypertension, obesity, chronic lung diseases, and chronic liver diseases have also been associated with more severe COVID-19 disease. [15-18]

COVID-19 vaccine allocation policies have prioritized individuals with serious comorbidities. [19] However, since regulatory clinical trials with COVID-19 vaccines excluded those with immunocompromising conditions and those receiving immunosuppressive therapies, few patients with cancer and autoimmune diseases were enrolled. [20, 21] Thus, with limited vaccine safety and efficacy data available, but noting the increased mortality risk, patients with comorbidities may have conflicted COVID-19 vaccine attitudes. We therefore initiated an internet-based survey drawing from our international health oriented social network to explore issues surrounding COVID-19 vaccine hesitancy in these vulnerable populations. Additionally, we sought to explore early self-reported side-effect experiences among those who had already been vaccinated, as this might provide information useful to combating hesitancy.

Methods:

Study design and participants

Survey participants were recruited from Inspire (Arlington, VA, USA), an online health community of over 2.2 million individuals with comorbid conditions and their caregivers. Members anonymously engage with others with similar conditions through discussion posts and direct messaging. The community, with members residing in over 100 countries, represents over 3,600 comorbid conditions including cancer, autoimmune diseases, rare diseases and other chronic conditions.

When individuals join Inspire they are given the opportunity of opting in to receive invitations for research projects. For this study, email invitations were sent on a daily basis to a computer-generated random sample of members who had agreed to receive research survey requests. Prior to participating in this study, individuals completed a consent form (approved by WCG IRB, Puyallup WA, USA) that detailed the purpose of the research. Participants were able to withdraw at any time throughout the survey. Participants were not compensated. Duplicate responses were removed by review of unique tokens assigned to participants.

Measures

The survey consisted of 55 items, with initial responses leading to a potential increase of 8 additional follow-up questions. The survey was implemented using Alchemer, a web-based survey tool. Survey logic, programming, testing, and data validation were done via Alchemer. Items used to assess vaccine perception and hesitancy were adapted from PEW Research Center's American Trends Panel 2020 survey, with additional questions added and linguistic adjustments. [22] Demographic, health conditions, and treatment related questions were adapted from Inspire's standard question sets. Behavioral and political leaning questions were adapted and modified from the Kaiser Family Foundation's vaccine perception survey. [7] A dichotomous conservative political leaning variable was created from the multi-option political leaning question to include in logistic regression. This was done by grouping participants into either conservative political leaning or non-conservative political leaning.

Independent measures in the survey detailed demographics including age, education level, political leaning, ethnicity, income, residence (country of residence: if USA, state of residence), patient history of disease including specific disease, current treatment status if cancer patient, and gender. Dependent measures included plans to receive the vaccine, and attitudes and concerns toward the COVID-19 vaccines.

Interest in obtaining the vaccine was evaluated through the question, “Do you plan to get the COVID-19 vaccine when one is available?” This item was evaluated with options of “I already got it,’ ‘I’ve tried but have not been able to get it,’ ‘Definitely,’ ‘Probably,’ ‘Unsure,’ ‘Probably not,’ and ‘Definitely not.’ For the purposes of analysis subjects who responded as ‘definitely not’, ‘probably not’ and ‘unsure’ were consider to be “vaccine hesitant.” Subjects indicating the other responses, including those who had already received the COVID-19 vaccine, were considered to be “vaccine acceptant”.

Attitudes and concerns about the vaccine were elicited through the question, “What are your concerns about the vaccine? Check all that apply. ‘I do not believe I need it,’ ‘I do not think it was developed responsibly,’ ‘I do not trust the government has insured that the vaccines are safe and effective,’ ‘I do not trust vaccines in general,’ ‘I do not trust the COVID-19 vaccine in particular,’ ‘I am concerned that the COVID-19 vaccine is too new,’ ‘I want to see how others respond first,’ ‘Concerns over the role of politics in the development process,’ ‘It is too difficult to get vaccinated,’ ‘I am concerned with contracting the coronavirus from the vaccine’ ‘I am concerned about the side effects or discomfort,’ and ‘I have religious objections.’”

As concerns about side-effects may contribute to COVID-19 vaccine hesitancy, and since immunocompromised individuals were largely excluded from COVID-19 vaccine trials, we sought to obtain additional information about the experiences of individuals who had received the vaccine. Specifically, we included questions about the type of vaccine received and which (if any) side-effects were experienced. The list of reportable symptoms and effects from the vaccine included on the survey were adapted from the Pfizer/ BioNTech BNT162b2 mRNA COVID-19 Vaccine FDA Briefing Report. [23] Potential localized side-effects included pain at the injection site, swelling at the injection site, redness at the injection site, itching at the injection site and other. Potential

systemic side-effects included fever, chills, headache, joint pain, muscle/body aches, fatigue, nausea, vomiting, diarrhea, abdominal pain, rash and other.

Statistical Plan

Two-way cross tabulations were used to summarize sociodemographic variables, behavioral and public health belief variables, and comorbid disease variables across vaccine hesitancy. Pearson's Chi Square tests were performed to assess for statistical significance in difference between groups. Univariate logistic regressions were performed to assess independent relationship between several variables and the dichotomous vaccine acceptance variable.

Multivariate logistic regression was performed to assess the relationship between multiple predictor variables and the dichotomized vaccine acceptance variable. Two-sided design-based tests and an alpha level of 0.05 was used to evaluate statistical significance in all chi-squares, F-tests, and logistic regressions. No backward selection was used and all variables remained in the model, regardless of their significance level. All data management and analysis were conducted using IBM's SPSS Version 28.

Study Funding

This study was funded by Inspire which is responsible for the study design; the collection, analysis, and interpretation of the data; and the decision to approve publication of the finished manuscript.

Results:

Survey Respondent Demographics

Invitations to participate in this survey were sent to 996,500 members of the Inspire health

community between January 15, 2021 and February 22, 2021. Responses to the survey request were received from 21,943 individuals (2.2%) of which 17,115 completed the entire survey (1.7% of those invited and 78% of respondents). The median age range of respondents was 56-65 years which appeared older than the Inspire community median age range of 40-49 years. The survey respondents were mostly female (76%) similar to the general Inspire community (77%). There was minimal self-identification as belonging to a racial or ethnic minority within the respondent population.

Inspire's membership is made up of both individuals with declared illnesses and their caregivers. However, caregivers who wished to participate in this study separate from their loved ones were instructed to complete a separate survey based on their own attitudes and to document their own health status. All participants (100%) in this project indicated at least one comorbid condition. A cancer diagnosis was self-reported by 27% of participants, 23% had an autoimmune disease, and 38% were diagnosed with a chronic lung disease.

Respondents were highly educated with 60% holding college or post-graduate degrees. Political leanings were diverse, with 32% self-declaring liberal tendencies, 21% conservative, 24% independent and 23% preferring not to declare. Respondents lived in 123 countries, with 74% residing in the USA, 8% from Canada, 8% from the United Kingdom, 3% from Australia, and the remaining 6% in Europe, Central, South America and the Caribbean, the Middle East, the Russian Federation, Africa and the Far East.

COVID-19 Vaccine Hesitancy in the study cohort

Among the 21,294 individuals with cancer, autoimmune diseases, and other serious diseases who

responded to survey questions about their attitudes on vaccination, 10.3% indicated COVID-19 vaccine hesitancy including 2190 (10.3%) who declared that they would not receive the vaccine, 742 (3.4%) who stated that they would probably not, and 1028 (4.8%) who were not sure whether they would agree to be vaccinated. By contrast 5501 (25.0%) respondents reported that they had already received at least one COVID-19 vaccine injection by February 22, 2021. Of the USA participants 29% has already undergone vaccination. Among participants from other countries 688 had undergone vaccination including 68% of participants living in Israel, 27% in United Kingdom, 4% in Canada, and none in Australia. Additionally, 1462 (7%) had tried but had been unable to obtain the vaccine, 9223 (43%) definitely planned to undergo vaccination, and 1029 (5%) indicated that they probably would undergo vaccination, leading to an overall vaccine acceptance of 81%.

Factors independently associated with COVID-19 vaccine hesitancy

As shown in Table 1, multiple demographic factors by simple logistic regression were associated with vaccine hesitancy. Younger age was associated with increased vaccine hesitancy. In this survey of Inspire members with serious illnesses nearly two-thirds of respondents were greater than 55 years of age and in this subgroup only 14% were vaccine hesitant compared to 25% among those younger in age. Although few responded self-reported a non-white racial or ethnic category, those that did report were more likely to be vaccine hesitant. The Inspire respondent members were highly educated with 60% possessing a college degree; a cohort that had a vaccine prevalence of 13% compared to 23% among those with less formal education. Respondents had diverse political leanings, but those with more conservative political leanings were more likely to express vaccine hesitancy. Respondents living outside the USA (n=5243) were more likely to be vaccine hesitant (21.8%) compared to those from the USA (n=16,061; 17.5% hesitant).

Table 1: Vaccine Hesitancy by Age, Gender, Ethnicity, Education level and Political leanings

Among Individuals with Serious Comorbidities (N = 21,294) using Inspire between January 15, 2021 and February 22, 2021.

	COVID-19 Vaccine received, Definitely will, or Probably will receive the vaccine	**Definitely will not, Probably will not, or unsure about receiving the vaccine**
OVERALL N= 21294	**17334 (81.4%)**	**3960 (18.6%)**
Age n=20225		
<26 n=381 (2%)	289 (75.9%)	92 (24.1%)
26-35 n=1315 (6%)	928 (70.6%)	387 (29.4%)
36-45 n=2513 (12%)	1871 (74.5%)	642 (25.5%)
46-55 n=3309 (16%)	2541 (76.8%)	768 (23.2%)
56-65 n=5288 (26%)	4340 (81.1%)	948 (17.9%)
66-75 n=5591 (28%)	4961 (88.7%)	630 (11.3%)
75+ n=1828 (9%)	1649 (90.2%)	179 (9.8%)
Gender n=20592		
- male n= 4898 (14%)	4237 (84.6%)	752 (15.4%)
- female n= 14,910 (76%)	12802 (81.5%)	2894 (18.5%)
Race/ethnicity n=19465		

- White n=17354 (85%)	14487 (83.5%)	2867 (16.5%)
- Black or African American n=514 (2%)	391 (76.1%)	123 (23.9%)
- Hispanic or Latino n=614 (3%)	509 (82.9%)	105 (17.1%)
- Asian n=627 (3%)	520 (82.9%)	107 (17.1%)
-Hawaiian/Pacific Islander n=22 (.1%)	15 (67.2%)	7 (31.8%)
- Native American/Alaskan n=132 (.6%)	88 (66.7%)	44 (33.3%)
-Other n=479 (2%)	337 (70.4%)	142 (29.6%)
- Prefer not to answer n=706 (4%)	306 (43.4%)	400 (56.6%)
Education level n=17298		
- high school or less n=1640 (9%)	1246 (75.9%)	394 (24.1%)
- vocational & associates degree n=2546 (15%)	1955 (76.8%)	591 (23.2%)
- some college n=2914 (17%)	2302 (79%)	612 (21%)
- college degree n=4448 (26%)	3748 (84.3%)	700 (15.7%)
- post-graduate n=5927 (34%)	5054 (87.9%)	696 (12.1%)
Political leaning n=17967		
- liberal n=5683 (32%)	5401 (95.0%)	282 (5.0%)
- conservative n=3711 (21%)	2653 (71.5%)	1058 (28.5%)
- independent n=4357 (24%)	3520 (80.8%)	837 (19.2%)
- prefer not to answer n=4216 (23%)	3185 (75.5%)	1031 (24.5%)

Opinions about public health policy also shaped vaccine hesitancy attitudes. In our study population of individuals with severe illnesses 96% reported routinely wearing masks. Although a greater proportion of mask wearers reported vaccine acceptance than those who reported not wearing masks, 18.4% of mask wearers remained vaccine hesitant. Most (78%) respondents routinely received influenza vaccination; a cohort with a vaccination acceptance prevalence of 91.6% compared to the 45.9% acceptance prevalence among those who did not routinely receive influenza vaccines. Respondents who did not feel that the media reported scientific data accurately had a slightly higher prevalence of vaccine hesitancy (20.6%) compared to those that did believe media information was scientifically accurate (18.4%). Among those who responded “No” and “Probably not” to the question “do you trust the vaccine was developed responsibly?”, 98.4% and 91% reported being vaccine hesitant respectively. (Table 2)

Table 2: Vaccine Hesitancy by Mask wearing, Routine influenza vaccination, Belief in media coverage accuracy, and Trust in Responsible Development among Individuals with Serious Comorbidities (N = 21,294) using Inspire between January 15, 2021 and February 22, 2021.

“Do you plan to get the COVID-19 vaccine when one is available?	**“I already got it,’ ‘I’ve tried but have not been able to get it,’ ‘Definitely,’ ‘Probably’**	**‘Unsure,’ ‘Probably not,’ ‘Definitely not’**
Mask wearing n=19468		
-Always/ sometimes wears mask n=18736 (96%)	15292 (81.6%)	3444 (18.4%)
-Rarely/ Never wears a mask n=732 (4%)	557 (76.1%)	175 (23.9%)

Routine influenza vaccine n=20817		
-Usually gets a flu vaccine n=16269 (78%)	14905 (91.6%)	1364 (8.4%)
-No flu vaccine n=4548 (22%)	2083 (45.9%)	2462 (54.1%)
Media information scientifically accurate n=19459		
-Yes or generally yes n=10465 (54%)	8541 (81.6%)	1924 (18.4%)
-No or generally no n=3084(16%)	2449 (79.4%)	635 (20.6%)
-Mixed n=5910 (30%)	4852 (82.1%)	1058 (17.9%)
Do you trust the vaccine was developed responsibly n=20409		
-Yes n=12498	12292 (98.4%)	206 (1.6%)
-Probably so n=3900	3494 (89.6%)	406 (10.4%)
-Not sure n=1837	750 (40.8%)	1087 (59.2%)
-Probably not n=632	57 (9%)	575 (91%)
-No n=1537	25 (1.6%)	1512 (98.4%)

Nine percent of the survey respondents self-reported a prior history of COVID-19 infection and an additional 5% believed that they had experienced symptoms suggestive of COVID-19 without confirmation (or were unsure). Although current guidelines recommend vaccination despite prior infection, 34.7% of these individuals were vaccine hesitant. By contrast among the more than 17,000 respondents who claimed no prior exposure to SARS-CoV-2 only 15.8% were vaccine hesitant. (Table 3)

Table 3 Vaccine Hesitancy by Previous COVID-19 infection Among Individuals with Serious Comorbidities (N = 21,294) using Inspire between January 15, 2021 and February 22, 2021.

"Do you plan to get the COVID-19 vaccine when one is available?"	**"I already got it,' 'I've tried but have not been able to get it,' 'Definitely,' 'Probably'**	**'Unsure,' 'Probably not,' 'Definitely not'**
COVID-19 infection n=20451		
Had COVID-19 n=1906 (9%)	1209 (63.4%)	697 (36.6%)
Unsure if had COVID-19 n=1085 (5%)	743 (68.5%)	342 (31.5%)
Did not have COVID-19 n=17460 (85%)	14702 (84%)	2758 (15.8%)

Vaccine Hesitancy in specific high risk comorbid populations

Among the 5459 individuals with cancer, 731 (13.4%) indicated vaccine hesitancy, including 193 (11%) of those who were currently receiving treatment were vaccine hesitant as were 538 (13%) of those who had completed prior treatment. Those who were not being treated for cancer had a vaccine hesitancy proportion of 20.3%. The difference in vaccine hesitancy proportions between those being treated for cancer and those not being treated for cancer was statistically significant. Among the 4946 individuals with autoimmune diseases, 962 (19%) self-reported vaccine hesitancy compared to 18% of those not being treated for autoimmune diseases who reported vaccine hesitancy though the difference was not statistically significant. 17.8% of the 7544 respondents with chronic lung disease reported vaccine hesitancy compared to 19% of those not being treated for chronic lung disease, a difference which was statistically significant. Vaccine hesitancy was also expressed by

19.7% of those diagnosed as obese, 18% diagnosed with hypertension, and 19% of individuals living with Type 2 diabetes, though the difference of these proportions from the general population were not statistically significant. (Table 4)

Table 4: Vaccine Hesitancy Rates among Individuals with Serious Comorbidities (N = 21,294) using Inspire between January 15, 2021 and February 22, 2021.

"Do you plan to get the COVID-19 vaccine when one is available?"	**"I already got it,' 'I've tried but have not been able to get it,' 'Definitely,' 'Probably'**	**'Unsure,' 'Probably not,' 'Definitely not'**
Cancer n=19980		
-Yes in treatment n=1463 (7%)	1270 (88.8%)	193 (13.2%)
-Yes past treatment n=3996 (20%)	3458 (86.6%)	538 (13.4%)
-No Cancer n=14,521 (73%)	11567 (79.7%)	2954 (20.3%)
Autoimmune disease n=21294		
-Yes n=4946 (23%)	3984 (80.6%)	962 (19.4%)
-No n=16348 (77%)	13405 (82%)	2943 (18%)
Chronic lung disease n=21294		
-Yes n=7544 (35%)	6200 (82.2%)	1344 (17.8%)
-No n=13750 (65%)	11134 (81%)	2616 (19%)
Hypertension n=21294		
-Yes n=5358 (25%)	4395 (82%)	963 (18%)

-No n=15936 (75%)	13068 (81%)	2868 (18%)
Type 2 Diabetes n=21294		
-Yes n=1400 (7%)	1134 (81%)	266 (19%)
-No n=19894 (93%)	16353 (82.2%)	3541 (17.8%)
Obesity n=21294		
- Yes n=3041 (14%)	2443 (80.3%)	598 (19.7%)
-No n=18253 (86%)	14968 (82%)	3285 (18%)

Univariate logistic regression of COVID-19 vaccine acceptance

In univariate logistic regression, having received a routine influenza vaccine was associated with COVID-19 vaccine acceptance (OR: 1.24). Those who reported routinely receiving an influenza vaccine had 1.24 times the odds of being COVID-19 vaccine acceptant. Those who reported having trust that the COVID-19 vaccine was developed responsibly had 2.07 times the odds of being vaccine acceptant (OR: 2.07). Those who reported being previously infected with COVID-19 had 0.93 times the odds of being vaccine hesitant (OR: 0.93). Those who reported independent political leaning and liberal political leaning had 1.12 and 1.14 times the odds respectively of being vaccine acceptant when compared to those who reported conservative political learning. Respondents residing within the U.S. had 1.03 times the odds of reporting vaccine acceptance than those living outside the U.S. Those with an age higher than the median age of the study had 1.12 times the odds (or a 12% increase in odds) of reporting vaccine acceptance compared to those below the median age while those at the median age had 0.99 times the odds of being vaccine acceptant compared to those below the median age. Moreover, those with some college education had 1.03 times the odds of

being vaccine acceptant compared to those with a high school degree or less, while those with a four-year degree or beyond had 1.04 times the odds of being vaccine acceptant compared to those with a high school degree or less. Smoking status was not significantly associated with vaccine acceptance. Men had 0.98 times the odds of being vaccine acceptant than women. Those diagnosed with cancer had 1.03 times the odds of being vaccine acceptant compared to those not diagnosed with cancer and those who reported mask wearing had 1.02 times the odds of being vaccine acceptant.

Table 5: Univariate logistic regression of vaccine acceptance among Individuals with Serious Comorbidities (N = 21,294) using Inspire between January 15, 2021 and February 22, 2021

	Odds Ratio	95% Confidence Interval	P value
Routine Influenza vaccine	1.24	[1.23 - 1.25]	<.001
Trust in responsible development of COVID vaccine	2.07	[2.05 - 2.09]	<.001
Prior COVID infection	.93	[.92 -.94]	<.001
Political leaning			<.001
Conservative political leaning [reference]			
Independent	1.12	[1.01 – 1.03]	.003
Liberal leaning	1.14	[1.12 – 1.15]	<.001
Residence (US vs outside US)	1.03	[1.02 – 1.04]	<.001
Age			
Age below median [reference]			
Median age	.99	[.98 – .99]	<.001
Age above median	1.12	[1.11 – 1.13]	<.001

Education level			
High school and less [reference]			
Some college, associate's degree	1.03	[1.03 – 1.04]	<.001
College and beyond college	1.04	[1.02 - 1.06]	<.001
Smoking status	1.01	[1.00 – 1.02]	.174
Gender	.98	[.97 - .99]	.001
Cancer diagnosis	1.03	[1.02 -1.04]	.001
Mask wearing	1.02	[1.01 – 1.03]	<.001

Multivariate logistic regression models of COVID-19 vaccine acceptance

To understand the impact of these independent variables on vaccine acceptance, a multivariate logistic regression was performed to predict those who had received or planned to receive their vaccination by February 20, 2021. Overall, our model was a statistically significant predictor of vaccine acceptance, with an Adjusted R^2 of .525, meaning our model explained 52.5% of the variance in vaccine acceptance. Results of the multivariate logistic regression are shown in Table 6. The Pearson goodness-of-fit test yielded a $\chi 2$ (1474) of 1500.56 which was considered insignificant (P=.31). The Deviance goodness-of-fit test yielded a $\chi 2$ (1474) of 1374.86 was also considered insignificant (P=.97). These results suggest good model fit.

Factors associated with a vaccine acceptance after controlling for other covariates include routine influenza vaccination, political leaning, age (below median versus median range versus above median), country of residence (USA versus living outside the USA), prior COVID-19 infection, and trust in COVID-19 vaccine responsible development. Routine receipt of influenza vaccination

remained a positive predictor of COVID-19 vaccine acceptance after controlling for other covariates with an odds ratio of 1.08, meaning participants who reported regularly receiving the flu shot had 1.08 times the odds of being vaccine acceptant. Trust in responsible development of the vaccine was also a significant predictor of COVID-19 vaccine acceptance with an odds ratio of 1.86 meaning that those who reported having trust in the development of the vaccine had 1.86 times the odds of receiving it than those that reported not having trust in the development. Those residing in the U.S. (odds ratio 0.98) had 0.98 times the odds of accepting the vaccine than those living outside the U.S. Those who reported never smoking also had slightly greater odds of vaccine acceptance (odds ratio 1.01). By contrast, vaccine acceptance was decreased with a history of prior COVID-19 infection (odds ratio 0.97). After controlling for other variables, those reporting independent political leaning had 1.02 times the odds of being vaccine acceptant compared to those who reported conservative political leaning and those who reported liberal political learning had 1.02 times the odds of being vaccine acceptant than those who reported conservative political leaning. Age remained a statistically significant predictor of vaccine acceptance after controlling for other variables. Those with an age higher than the median age of the study had 1.02 times the odds of reporting vaccine acceptance compared to those below the median age while those at the median age had 1.01 times the odds of being vaccine acceptant compared to those below the median age. When controlling for other variables, gender was no longer a statistically significant predictor of vaccine acceptance. The same is true for education level, cancer diagnosis, and mask wearing.

Table 6: Multivariate logistic regression of vaccine acceptance among Individuals with Serious Comorbidities (N = 21,294) using Inspire between January 15, 2021 and February 22, 2021

	Odds Ratio	95% Confidence Interval	P value

Routine Influenza vaccine	1.08	[1.07 – 1.08]	<.001
Trust in responsible development of COVID vaccine	1.86	[1.84 – 1.88]	<.001
Prior COVID infection	.97	[.96 - .98]	<.001
Political leaning			<.001
Independent	1.02	[1.01 – 1.03]	<.001
Liberal	1.06	[1.05 – 1.07]	<.001
Residence (US vs outside US)	.98	[.98 – 99]	<.001
Age			
Medan age	1.01	[.99 – 1.02]	.074
Above median age	1.02	[1.01 – 1.03]	<.001
Education level			
Some College	1.00	[.99 – 1.01]	.561
College and graduate school	.99	[.98 – 1.01]	.676
Smoking status	1.01	[1.00 - 1.02]	.004
Gender	1.00	[.99 - 1.02]	..674
Cancer diagnosis	1.00	[.99 - 1.00]	.453
Mask wearing	.1	[.99 - 1.01]	.962

Concerns about Vaccines

Of the 3960 respondents who indicated COVID-19 vaccine hesitancy, apprehensions regarding the newness of the vaccine were the most commonly cited reason for hesitancy, expressed by 53% of hesitant respondents. Concerns about the safety of the vaccine and a general distrust of the development process (including governmental oversight) also were common. (Table 7)

Table 7: Concerns about the COVID-19 vaccine among the vaccine hesitant individuals (n=

3,960) using Inspire between January 15, 2021 and February 22, 2021.

What are your concerns about the vaccine? Check all that apply.			
	Overall n=3960	USA n=2817	Outside USA n=1143
I am concerned the COVD-19 vaccine is too new	2104 (53.1%)	1532 (54.4%)	572 (50.0%)
I do not trust the government has ensured that the vaccines are safe and effective	1900 (48.0%)	1365 (48.5%)	535 (46.8%)
I am concerned about side effects and discomfort	1738 (43.9%)	1219 (43.4%)	519 (45.5%)
I do not trust the COVID-19 vaccine in particular	1571 (39.7%)	1126 (40.0%)	445 (38.9%)
Concerns over the role of politics in the development process	1533 (38.7%)	1112 (39.4%)	421 (36.8%)
I want to see how others respond first	1319 (33.3%)	974 (34.6%)	345 (30.2%)
I do not think it was developed responsibly	1313 (33.2%)	922 (32.7%)	391 (34.2%)
I do not believe I need it	869 (22.0%)	589 (20.9%)	280 (24.5%)
I do not trust vaccines in general	832 (21.0%)	591 (21.0%)	292 (25.5%)
I have religious objections	331 (8.4%)	262 (9.3%)	69 (6.0%)
I am concerned with contracting the coronavirus from the vaccine	327 (8.3%)	221 (7.8%)	106 (9.3%)
It is too difficult to get vaccinated	86 (2.2%)	74 (2.6%)	12 (1.0%)

Early experience with COVID-19 vaccination in high-risk populations

As of the study cutoff, 5501 (25%) survey respondents had received at least one COVID-19 vaccination (Pfizer-BioNTech 48%, Moderna 47%, Oxford-Astra-Zeneca 1%, other/unknown <1%). A two-injection series was completed by 1390 (6.2%) of respondents. Following the first injection, 3796 (69%) self-reported experiencing local adverse events (AEs) and 2200 (40%) self-reported

systemic reactions. Pain at the injection site was the most commonly self-reported side-effect. Fatigue and myalgias were the most commonly self-reported systemic side-effects. Among those who had received two vaccine injections (n=1390), the frequencies of self-reported local and systemic reactions increased following the second injection to 77% (n=1070) and 67% (n=931), respectively. (Figures 1, 2).

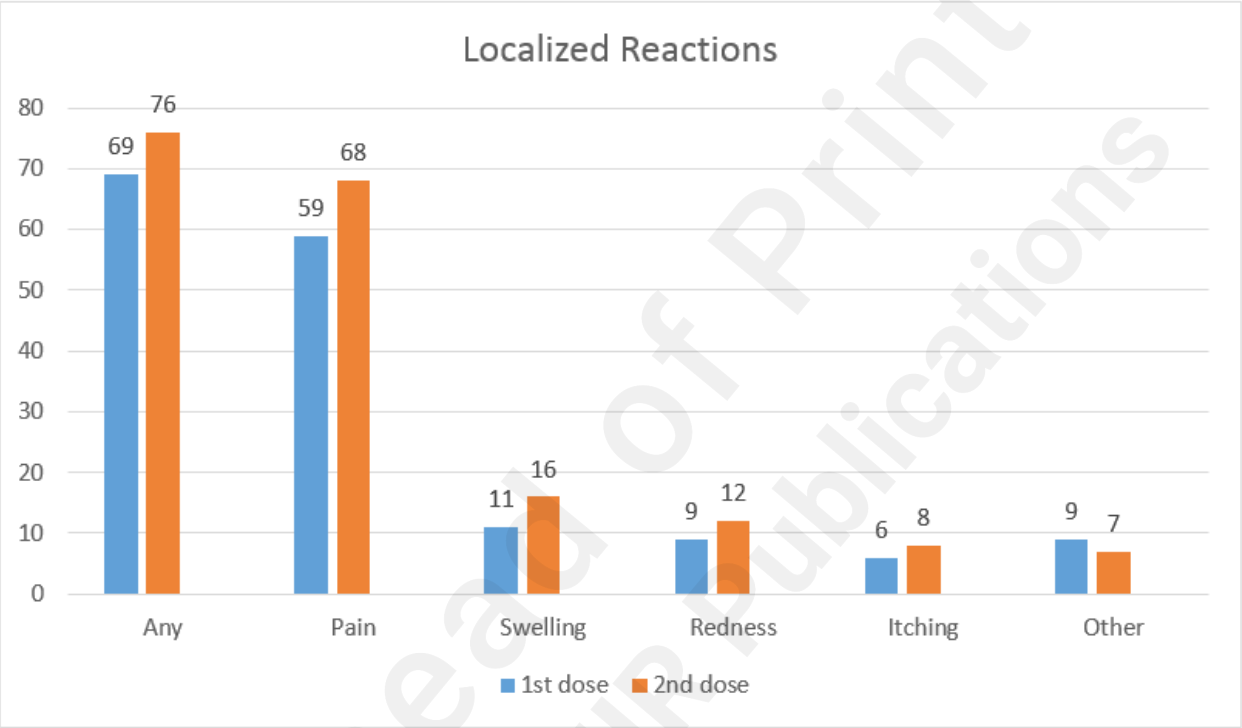

Figure 1. Self-reported localized reactions to COVID-19 vaccination among individuals with cancer, autoimmune diseases, other serious comorbidities and/or their caregivers. Responses were obtained from 5501 individuals who received an initial vaccine dose and 1390 individuals who completed a two-dose series. The online survey, which utilized reportable symptom options adapted from the Pfizer/ BioNTech BNT162b2 mRNA COVID-19 Vaccine FDA Briefing Report [23], was conducted between January 15, 2021 and February 22, 2021.

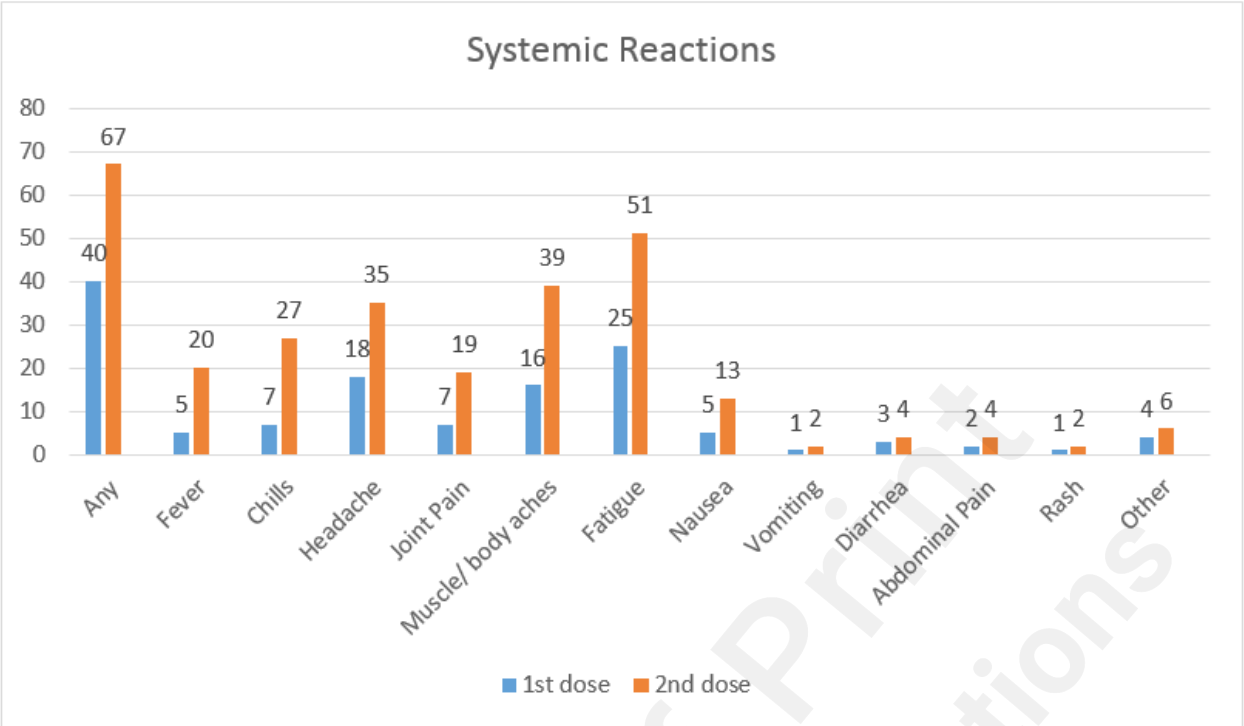

Figure 2. Self-reported systemic reactions to COVID-19 vaccination among individuals with cancer, autoimmune diseases, other serious comorbidities and/or their caregivers. Responses were obtained from 5501 individuals who received an initial vaccine dose and 1390 individuals who completed a two-dose series. The online survey, which utilized reportable symptom options adapted from the Pfizer/ BioNTech BNT162b2 mRNA COVID-19 Vaccine FDA Briefing Report [23], was conducted between January 15, 2021 and February 22, 2021.

Among respondents who had received a vaccination with the Pfizer-BioNTech (n=2640) and Moderna vaccines (n=2586) the initial injection led to overall self-reported localized side-effects among 65% and 75% respectively. Local reactions increased to 72% (n=480) and 85% (n=368) with the second booster Pfizer-BioNTech and Moderna injections, respectively. A more dramatic increase in self-reported systemic side-effects was noted with the second injection. with overall systemic effects rising from 37% to 62%, and 40% to 77%, with the Pfizer-BioNTech and Moderna vaccines, respectively.

Of the 5459 cancer patients who responded to the survey, 30% had received one injection and 6% completed both vaccine injections. In this cancer population, 65% self-reported local reactions and 34% systemic reactions to the first injection, with local reactions to the second occurring in 72% and 34% systemic reactions. The types of reactions mirrored the overall study population. Of the 5186 individuals with autoimmune disorders, 24% had received one vaccination and 6% had completed the series. In this immunocompromised population local reactions were described in 16% and systemic reactions in 41% with the first, and 78% local and 67% systemic with the second vaccine. Among the 1878 respondents with chronic lung diseases who received the vaccine, 67% self-reported local reactions and 40% systemic reactions to the first injection, with local reactions to the second occurring in 76% and 69% systemic reactions. Similar patterns were noted among respondents with obesity (1st dose 69% local and 43% systemic; 2nd dose 76% local and 75% systemic reactions), hypertension (1st dose 67% local and 39% systemic; 2nd dose 74% local and 66% systemic reactions), and individuals with Type 2 diabetes (1st dose 67% local and 42% systemic; 2nd dose 78% local and 79% systemic reactions).

Discussion

In this survey of nearly 22,000 individuals with serious comorbid conditions conducted shortly after vaccine regulatory approvals, eight in ten respondents reported a willingness to receive the COVID-19 vaccine. This high level of vaccine acceptance in a community of vulnerable individuals who regularly seeks medical information through participation in an online health forum compares favorably to reports in public opinion polls drawn from general populations taken at the same timeframe. [6,7] Additionally, as of late February 2021, 29% of USA participants in the survey stated that they had already received at least one COVID-19 vaccine injection, which compared favorably to the 18% adult USA national vaccination prevalence at that time. [24] Our survey thus appears to confirm a strong desire for protection against SARS-CoV-2 in vulnerable populations, although vaccine allocation prioritization may have also influenced these findings.

However, almost one in five respondents to our survey, all of whom harbored comorbidities, reported COVID-19 vaccine hesitancy. This was a similar hesitancy prevalence to general population polls at the time. [6, 7] Among patients with cancer, autoimmune diseases, and chronic lung diseases 13.4%, 19.4%, and 17.8% expressed hesitancy, respectively. This is very concerning given that individuals with cancer and other serious comorbidities have experienced an increased proportion of the mortality from the pandemic. [13-18] Furthermore, since our survey drew enrollment from a medically savvy population who participate in online health forums, we were surprised by these results. The lack of inclusion of immunocompromised individuals within regulatory clinical trials may have contributed to the safety concerns expressed by 43.9% of vaccine hesitant respondents. [20,21] However other factors, many of which were similar to concerns raised by the general public, were deemed important by our respondents. Thus, it appears that our study population fell into two polarizing cohorts: one group that was more eager to undergo vaccination as a consequence of co-existing illnesses and increased mortality risks, and a second group that was COVID-19 vaccine hesitant being influenced by broad social vaccine concerns.

We identified multiple factors that were independently associated with vaccine hesitancy. Lack of trust in COVID-19 vaccine development, including the rapidity and politicization of the process, were expressed by our comorbid cohort but are views not unique to our population. [12] Generalized distrust of vaccines and avoidance of influenza vaccines were additional broad concerns that transcend comorbid status. Conservative political leaning, lower education level, and younger age are also commonly cited in public opinion polls. [7,8, 10,11, 25] Individuals who had already contracted COVID-19 avoided vaccination, possibly believing natural immunity alone was protective. [26]

Few studies have specifically explored issues of COVID-19 vaccine hesitancy among patients with severe comorbid conditions and/or strategies to increase acceptance in high-risk populations. As these individuals already have ongoing healthcare contact, the potential influence of their physicians

should not be ignored. A Korean study noted that although only 61.8% of their cancer patients were initially willing to receive the COVID-19 vaccine, acceptance increased by 30% if their oncologist recommended it. [27] Similarly, a Tunisian study noted that a discussion about the impact of COVID-19 upon cancer treatments and outcomes was projected to have the single greatest impact on reducing hesitancy. [28] An online survey of 540 Mexican women with breast cancer also noted a 3-fold increase in likelihood of accepting vaccination following their oncologist's recommendation. [29] Unfortunately, the physician's recommendation does not always carry change opinions. Nearly 40% of French cancer patients who were vaccine hesitant did not feel that their oncologist was qualified to advise them on COVID-19 vaccination and instead preferred to rely on personal judgements. [30] Nonetheless, the specialist physician possesses unique insights into potential impacts of vaccination on the patient's underlying disease, a fear that must be allayed as expressed by a cohort of patients with autoimmune rheumatic disease. [31] A United Kingdom randomized trial demonstrated that emphasizing the personal benefits of vaccination reduced hesitancy to a greater extent than information about collective benefit. Where perception of risk from vaccines is most salient, which is likely among high-risk comorbid populations, decision making frequently becomes centered on the personal. [32]

Establishing trust in science and vaccine development is critical to reducing vaccine hesitancy. Despite our population having ongoing contact with healthcare system (by virtue of their underlying diseases) and routinely engaging in an online health-related forum, we noted that issues regarding trust were expressed by over 40% of vaccine hesitant respondents. A survey of nearly 6000 USA healthcare workers, older adults, frontline essential workers, other essential workers, and individuals with high-risk chronic condition conducted in early 2021 identified that lack of trust in the vaccine approval and development processes was the most important trust issue. Other domains of trust (in vaccine safety and efficacy, in healthcare providers, in sources of information, and generalized trust) were of lesser importance. [33] Similar results were noted in an online survey of over 1000 Italians

who responded that vaccine acceptance was driven by a trust in science, acceptance of prior vaccines, and an understanding that COVID-19 is more serious than influenza. [34]

The potential role of social media in combating the COVID-19 pandemic cannot not be underestimated. This study was sponsored by an online health community whose international membership shares medical information and personal experiences via hundreds of disease specific forums. Our motivation for designing the study was to increase our membership's knowledge and encourage discussions regarding COVID-19 vaccine experiences. The rapid enrollment of nearly 22,000 respondents with serious diseases over a 5-week time course, with additional thousands viewing the online results, attests to the potential influence of the world-wide web on health issues. An infodemiology study of over 650,000 "tweets" from November 2020, prior to the release of vaccines, identified that the main themes driving vaccine hesitancy were concerns of safety, efficacy, freedom, and mistrust in institutions (either the government or multinational corporations). [35] A qualitative coding methodologic review of anti-vaccine social media noted that the most frequent narratives centered on "corrupt elites" and rhetorics appealing to the vulnerability of children. [36] As rumors and conspiracy theories are common, tracking COVID-19 vaccine misinformation in real-time and engaging with social media to disseminate correct information can be an important safeguard against misinformation. [37] Healthcare related patient platforms, such as Inspire, where individuals with concerns can obtain understandable COVID-19 related medical information relevant to their other medical conditions should play an important role in decreasing vaccine hesitancy.

As noted in our survey, COVID-19 vaccine acceptance and hesitancy are a global issue. Respondents residing outside the USA were more likely to exhibit vaccine hesitancy, but the reasons for concerns about vaccination appeared similar. A systematic review of WHO Regions noted great variability in acceptance of the vaccine, with lowest rates in Hong Kong and the Democratic Republic of the Congo, two countries with recent political instability. By contrast China, Indonesia, and Malaysia all reported hesitancy prevalence below 10%, potentially a reflection of their early

experiences with SARS-CoV-2. Across Europe hesitancy varied greatly from 20% in the United Kingdom to almost 60% in Italy. [38] Other reports have indicated higher acceptance of vaccination in lower- and middle-income countries. [39, 40] As evidenced by the 123 nations represented in our respondent population, the internet represents a powerful potential tool for dissemination of information about COVID-19 vaccination across boundaries.

Limited data exists regarding the safety and effectiveness of COVID-19 vaccination among immunocompromised individuals (with the exception of individuals infected with Human Immunodeficiency Virus) (HIV) since they were excluded from the regulatory phase III trials. We therefore we expected safety concerns to dominate vaccine hesitancy concerns in our survey. [41] To address this we requested information about side-effect profiles among respondents who had undergone vaccination with the goal of sharing this information with our online membership in hopes that this would reduce vaccine hesitancy. Indeed, early experience with vaccinations, as self-reported by the over 5000 respondents who had already been vaccinated, should be reassuring to individuals with serious comorbidities. Side-effect profiles were similar to adverse event reports on the regulatory trials, although overall generally lower in frequency. [23, 42] Whether this is a reflection of the weaker immune status of our population or a result of differences in reporting styles (online survey versus research grade clinical trial monitoring) is unknown. However, an interesting finding was that the prevalence of self-reported systemic reactions to the initial vaccination appeared to be much lower than those reported in the clinical regulatory trials, but increased towards the general population results with the booster. This pattern of side-effect intensity (as a surrogate for immune responsiveness) suggests that booster vaccines may be required in immunocompromised individuals and/or that confirmation of antibody response may be necessary. Regardless, given the side-effect profiles noted in our survey the recommendations to vaccinate individuals with potential immune dysfunction despite a lack of clinical trial data appear justified, although future studies to document vaccine efficacy in these populations are needed.

We recognize several limitations to our study. The survey was conducted in January and February 2021, shortly after the release of the COVID-19 vaccine, and represents attitudes from a single timepoint. As additional information about the safety and efficacy of vaccination becomes available to our subjects, we expect that attitudes might change. Indeed, serial tracking polls conducted by the Kaiser Family Foundation have noted an increase in the acceptance of vaccination over time, although most of the changes in attitudes have occurred among the “wait and see” populations with little movement among the vaccine hesitant cohort. [8] Nonetheless, it is probable that our findings do not represent current opinions. Additionally, odds ratios determined by logistic regression do not approximate relative risk or prevalence ratios since the outcome variable of vaccine hesitancy was not rare in our study population. [43] Additionally, the Inspire community membership is 77% female with a median age of 40-49 years. Given the composition of Inspire’s community, survey respondents were not intended to represent a random sampling of the general population or any outside demographic. We also obtained a low (2.2%) response rate to our online survey, and thus our findings might not be representative of our membership population. It is possible that the most vocal opinions were overexpressed. We noted a dichotomous response with an increased cohort desiring vaccination (more than the general population) but also a significant vaccine hesitant cohort, with few respondents in the middle. It is interesting that our vaccine hesitancy prevalence and concerns mirrors that of general population opinion polls, indicating that vulnerable populations are susceptible to anti-vaccination social issues. Additionally, although we noted several factors that appeared to be associated with vaccine hesitancy or acceptance, a cause-and-effect relationship should not be inferred on the basis of our survey. Finally, we did not investigate methods to reduce vaccine hesitancy in this study but plan to add items to ongoing online surveys of our membership with this goal.

In summary, our online survey highlights a high level of acceptance of COVID-19 vaccines among vulnerable individuals. However, the finding that one in five remain vaccine hesitant is of concern and points to a need for additional efforts. Although governmental mandates or financial incentives are being considered, educational efforts must continue. [44, 45] Among individuals who have

serious comorbid diseases, and thus are already connected to the healthcare system, direct conversations by the medical specialist team about the impact of the COVID-19 vaccine has been demonstrated to reduce hesitancy and should be intensified. As demonstrated by our survey it cannot be assumed by physicians that the most medically vulnerable automatically accept vaccination. Disinformation about the COVID-19 vaccines is common on social media sites and fosters hesitancy. [46] Our intent is to share our study results with the 2+ million members of the Inspire health community, harnessing the Internet to increase vaccine acceptance by demonstrating tolerable vaccine side-effects among individuals with serious comorbid conditions. A website detailing the survey questions and updated daily with results is now available to the general public. [47]

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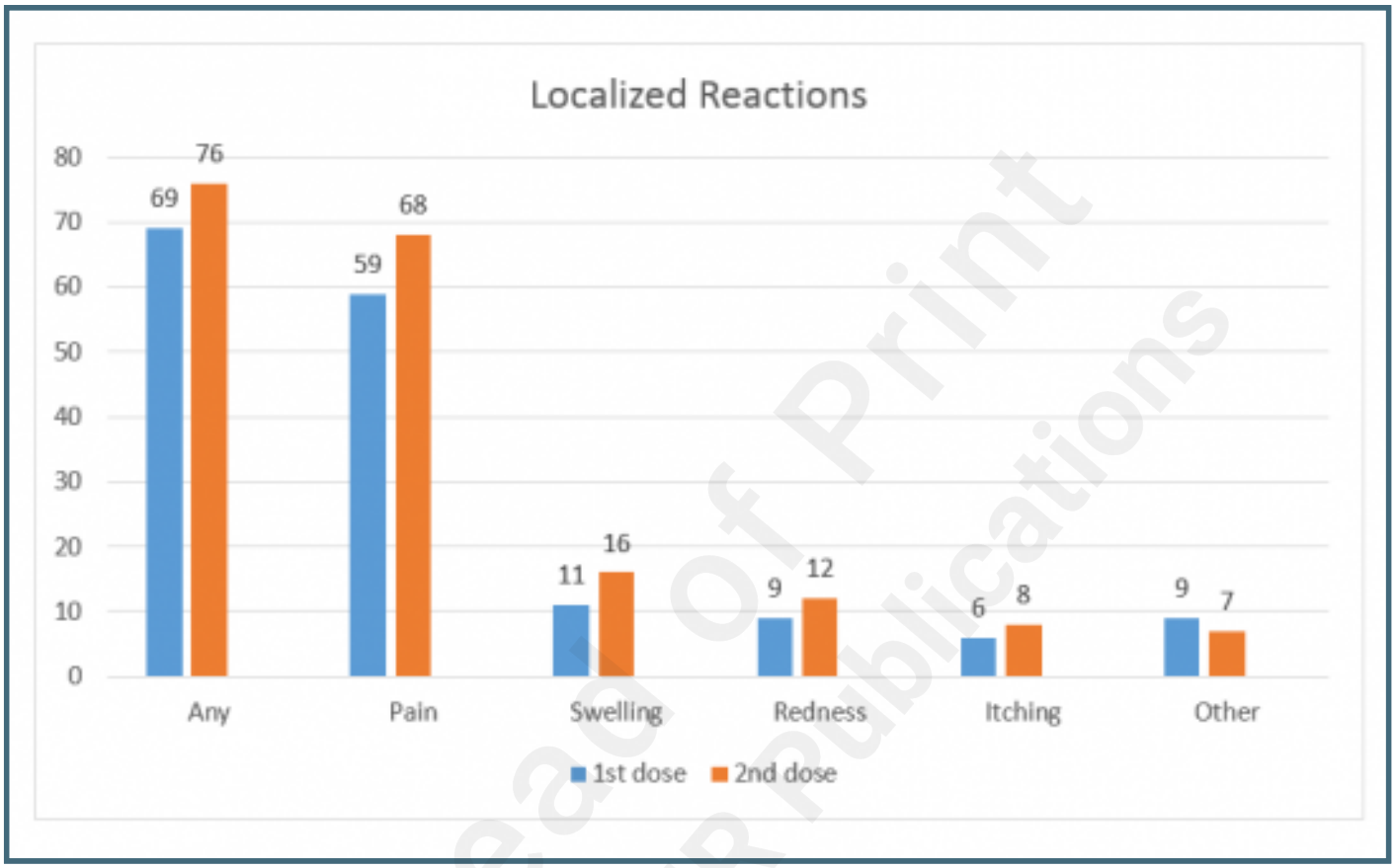
Supplementary Files

Figures

Self-reported localized reactions to COVID-19 vaccination among individuals with cancer, autoimmune diseases, other serious comorbidities and/or their caregivers. Responses were obtained from 5501 individuals who received an initial vaccine dose and 1390 individuals who completed a two-dose series. The online survey, which utilized reportable symptom options adapted from the Pfizer/ BioNTech BNT162b2 mRNA COVID-19 Vaccine FDA Briefing Report [23], was conducted between January 15, 2021 and February 22, 2021.



Self-reported systemic reactions to COVID-19 vaccination among individuals with cancer, autoimmune diseases, other serious comorbidities and/or their caregivers. Responses were obtained from 5501 individuals who received an initial vaccine dose and 1390 individuals who completed a two-dose series. The online survey, which utilized reportable symptom options adapted from the Pfizer/ BioNTech BNT162b2 mRNA COVID-19 Vaccine FDA Briefing Report [23], was conducted between January 15, 2021 and February 22, 2021.