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Improving immunization programmes uptake and addressing vaccine hesitancy

Edited by
Aida Bianco, Francesca Licata and Alessandra Casuccio

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Improving immunization programmes uptake and addressing vaccine hesitancy

Topic editors

Aida Bianco — University Magna Graecia of Catanzaro, Italy

Francesca Licata — University Magna Graecia of Catanzaro, Italy

Alessandra Casuccio — University of Palermo, Italy

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Short-Term Prognostic Factors in Hospitalized Herpes Zoster Patients and Its Associated Cerebro-Cardiovascular Events: A Nationwide Retrospective Cohort in Japan

Yuichi Ishikawa[1,2], *Kazuhisa Nakano*[1,3], *Kei Tokutsu*[4], *Shingo Nakayamada*[1], *Shinya Matsuda*[4], *Kiyohide Fushimi*[5] *and Yoshiya Tanaka*[1]*

[1] *The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan,* [2] *Sato Clinic, Ebisu, Shibuya-ku, Tokyo, Japan,* [3] *Department of Rheumatology, Kawasaki Medical School, Kurashiki, Japan,* [4] *Department of Preventive Medicine and Community Health, University of Occupational and Environmental Health, Kitakyushu, Japan,* [5] *Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School, Tokyo, Japan*

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Alessandra Casuccio, University of Palermo, Italy

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Antonino Tuttolomondo, University of Palermo, Italy

***Correspondence:**
Yoshiya Tanaka
tanaka@med.uoeh-u.ac.jp

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Background: Short-term mortality and incidence of cerebrovascular and cardiovascular events (C-CVE) during hospitalization of patients with severe herpes zoster (HZ) have not been sufficiently investigated. We aimed to investigate short-term prognosis and incidence of C-CVE associated with HZ in hospitalized patients.

Methods: This retrospective cohort study from April 2016 to March 2018 included HZ inpatient cases selected from the Diagnosis Procedure Combination database—a Japanese nationwide inpatient database. HZ and C-CVE were diagnosed based on the 10th revision of the International Classification of Diseases and Injuries codes. The definition of primary exposure was that treatments were initiated within 7 days of admission, and antivirals were administered for ≥7 days. Main Outcomes were in-hospital deaths and C-CVE onset after hospitalization.

Results: Among 16,811,501 in-hospital cases registered from 1,208 hospitals, 29,054 cases with HZ were enrolled. The median age was 71.0 years, 15,202 cases (52.3%) were female, and the HZ types were the central nervous system (n=9,034), disseminated (n=3,051), and ophthalmicus (n=1,069) types. There were 301 (1.0%) in-hospital deaths and 385 (1.3%) post-hospitalization onset of C-CVE. The 30-day in-hospital survival rates with or without underlying disease were 96.8% and 98.5%, respectively. Age ≥75 years (hazard ratio [HR], 2.18; 95% confidence interval [CI], 1.55–3.05), liver cirrhosis or hepatic failure (HR, 5.93; 95% CI, 2.16–16.27), chronic kidney disease (HR, 1.82; 95% CI, 1.24–2.68), heart failure (HR, 1.65; 95% CI, 1.22–2.24), and old cerebrovascular

events (HR, 1.92; 95% CI, 1.10–3.34) were associated with poor short-term prognosis. Age ≥75 years (odds ratio [OR], 1.70; 95% CI, 1.29–2.24), diabetes (OR, 1.50; 95% CI, 1.19–1.89), dyslipidemia (OR, 1.95; 95% CI, 1.51–2.51), hyperuricemia (OR, 1.63; 95% CI, 1.18–2.27), hypertension (OR, 1.76; 95% CI, 1.40–2.20), heart failure (OR, 1.84; 95% CI, 1.32–2.55), and glucocorticoid administration (OR, 1.59; 95% CI, 1.25–2.01) were associated with increased risks for in-hospital C-CVE onset.

Conclusions: The underlying diseases that could influence the short-term mortality of severe HZ were identified. Glucocorticoid is a possible risk factor for the in-hospital onset of C-CVE after severe HZ development.

Keywords: herpes zoster (HZ), cerebrovascular event, glucocorticoids, DPC (Diagnosis Procedure Combination), nationwide administrative database, cardiovascular event

INTRODUCTION

Herpes zoster (HZ) is an infection caused by the varicella-zoster virus (VZV). The risk of onset and severity increases in the elderly and in patients with underlying diseases that can lead to immunosuppression, such as connective tissue diseases (CTD) and malignancies (1–5). The incidence of HZ is increasing due to an aging society and the development of immunosuppressive therapy for autoimmune diseases, including CTD, and the occurrence of severe HZ may increase (6–8). Compared to other races, the incidence of HZ is higher in Japanese rheumatoid arthritis (RA) patients treated with a Janus kinase inhibitor (JAK-i), and the reasons have received attention (9, 10). Although it has been reported that mortality increases after the onset of HZ, the prognosis after the onset of HZ remains unclear due to substantial differences in survival rates among previous studies (11, 12). Moreover, information on the short-term prognosis of severe HZ and poor prognostic factors is limited. HZ is caused by various complications, including cerebrovascular and cardiovascular events (C-CVE) such as stroke and ischemic heart disease (IHD) (13). Reactivation of VZV can cause vasculitis, which can result in stroke and IHD (13, 14). The risk of developing C-CVE increases after HZ, and the risk of C-CVE may increase just after HZ onset (13, 15–18). There have been a few studies that have focused on patients hospitalized with severe HZ, which increases the incidence of death or C-CVE onset, and there is a paucity of studies that have examined short-term prognostic factors, the frequency of HZ-related C-CVE during hospitalization, and risk factors for developing C-CVE. Severe HZ increases the burden of medical costs for treating complications and sequelae (19), and the investigation of risk factors for severity and severe complications may be important public health information for taking preventive measures, including appropriate vaccination strategies against the onset and severe complications. We focused on patients with severe HZ that required hospitalization and investigated the short-term prognosis and prognostic factors and the incidence of C-CVE onset and risk factors of C-CVE onset after hospitalization for HZ treatment using the national administrative inpatient database in Japan.

MATERIALS AND METHODS

Study Design

This was a retrospective cohort study using the Diagnosis Procedure Combination (DPC) database which is a nationwide inpatient database in Japan.

Setting

Data were collected by the DPC research group, funded by the Ministry of Health, Labour, and Welfare, Japan. In the study period, 1,208 hospitals participated in the survey of the DPC research group and provided their data for research purpose (20). The database contains patient information and detailed procedures for the Japanese national insurance system (21, 22). Patient information recorded in the DPC database includes diagnosis based on the 10th revision of the International Classification of Diseases and Injuries (ICD-10) codes at the time of admission, comorbidities, and complications after admission. The DPC database also contains information on administered drugs, blood products used, and outcomes at discharge (23, 24).

Participant Selection

Cases were enrolled from April 1, 2016 to March 31, 2018. First, 41,499 in-hospital cases over 18 years old who have a diagnosis of HZ and treated with HZ-specific antivirals (acyclovir, famciclovir, valaciclovir, amenamevir, or vidarabine) for 7 days or more were extracted from the DPC database among a total of 16,811,501 inpatient cases from 1,208 hospitals in the DPC database. Second, of the 41,499 cases, 12,445 cases that did not start a specific antiviral treatment within 7 days after admission and did not have a diagnosis of HZ on admission were excluded. After the exclusion, there were a total of 29,054 cases diagnosed with HZ included in the study (**Figure 1**).

Definition of HZ and Underlying Diseases

The principal diagnosis of HZ was based on the ICD-10 code B02. The four types of HZ were classified as follows: central nervous system (CNS) (B02.0, B02.1), disseminated (B02.7), ophthalmicus (B02.3), and others (B02.8 and B02.9). It was expected that using the ICD-10 codes alone would identify patients who were not treated for HZ as well as those suspected with HZ who initiated treatment. To ensure

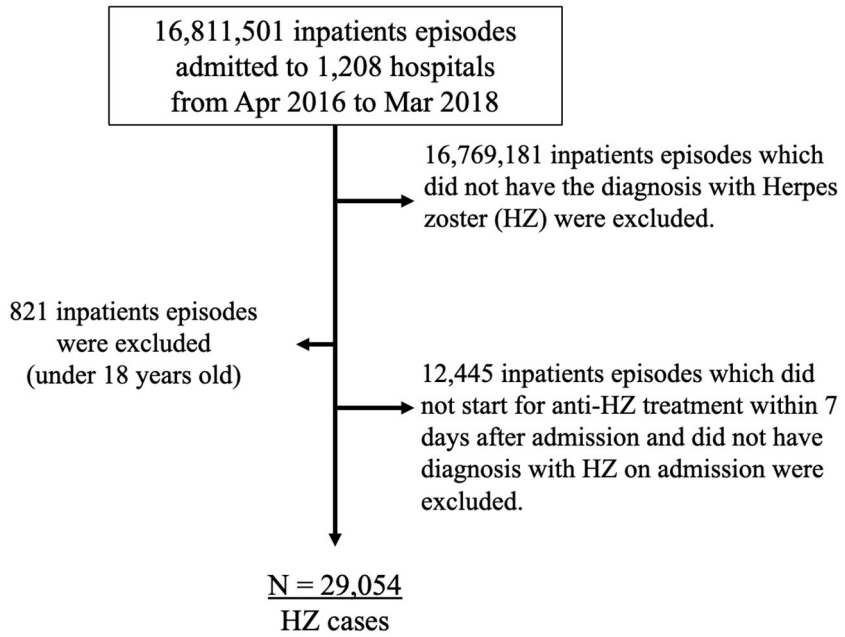

FIGURE 1 | Flowchart of eligible and ineligible participants. HZ, herpes zoster.

robust diagnosis, we enrolled cases who received HZ-specific antivirals for at least 7 days, the standard duration of HZ treatment (25, 26). The principal diagnosis of underlying diseases was recorded using the following ICD-10 codes: malignancies, C00–C98; solid cancer, C00–C80, C97; malignant lymphoma and hematopoietic malignancies, C81–C96; human immunodeficiency virus disease, B20–B24; immunodeficiencies, D80–D84; Transplanted organ and tissue status, Z94; disorders of the thyroid gland, E05.1, E06.3; diabetes mellitus (DM); E10–E14; dyslipidemia, E78; hyperuricemia, E79.0, M10; depressive disorder, F31–F34; demyelinating diseases, G35–G37; chronic obstructive pulmonary disease (COPD), J44; asthma, J45; interstitial lung disease (ILD), J84, J99.0, J99.1; hypertension (HT) and HT-related diseases, I10–I15; heart failure (HF), I11.0, I13.0, I50, I97.1; chronic ischemic heart disease (cIHD), I25; sequelae of cerebrovascular disease (CVD), I69; inflammatory bowel diseases, K50 and K51; autoimmune hepatitis, K75.4; cirrhosis and hepatic failure, K70.3, K70.4, K71.7, K72, K74; chronic viral hepatitis, B18; CTD, L40.5, M05–M07, M30–M35, M45, M94.1 (*M07.4–M07.6, M30.2, M30.3, M31.5, M33.0, M34.2, and M35.3–M35.7 were excluded), RA; M05–M06, M31.5 (*M06.1 was excluded); systemic vasculitis, M30, M31 (*M30.2, M30.3, M31.5 were excluded); systemic lupus erythematosus, M32; others, L40.5, M06.1, M07, M33–35, M94.1 (*M07.4–M07.6, M33.0, M34.2, and M35.3–M35.7 were excluded); chronic kidney disease (CKD), N18; glomerular diseases, N00, N01, N03–N05, and N08.

Study Outcomes

The primary outcome was overall in-hospital survival at 30 and 60 days after the initiation of treatment for HZ. The secondary outcome was in-hospital C-CVE onset after admission for HZ treatment. The diagnosis of C-CVE was based on the ICD-10 codes as follows: cerebrovascular diseases (I60–I67) and cardiovascular diseases (I20–I24). The definition of the secondary outcome was extracted from the post-hospitalization onset of secondary diseases recorded in the DPC database. The study also aimed to investigate the prognostic factors associated with in-hospital mortality and risk factors for C-CVE onset associated with HZ after admission.

Statistical Analysis

Categorical variables are presented as numbers (%), and continuous variables are presented as medians with interquartile ranges (IQR) or numbers with percentages (%). An independent sample, the Mann–Whitney test, was employed to evaluate non-normally distributed data for comparison between the two groups. Classification data number (percentage) were aggregated. Chi-square or Fisher's exact test was performed. The log-rank test was used to compare the survival rates among the groups. Univariable Cox regression analysis and logistic regression analysis were used to screen for potential confounders associated with in-hospital mortality and in-hospital C-CVE onset after admission for HZ treatment. Associations among covariates and risk of in-hospital mortality were evaluated using multivariable Cox proportional hazards regression analysis, and associations between covariates and risk of in-hospital C-CVE onset after admission for HZ treatment were evaluated using multivariable logistic regression analysis. Hazard ratios (HRs) and odds ratios (ORs) with 95% confidence intervals (CIs) were determined after adjusting for potential confounders. Multivariable Cox

TABLE 1 | Patient characteristics.

	N (%)
Total number of cases	29,054
Age	
Year, Median (IQR)	71 [61, 80]
18–64 (%)	9,103 (31.3)
65–74 (%)	8,095 (27.9)
75- (%)	11,856 (40.8)
Gender	
Male (%)	13,704 (47.2)
Female (%)	15,350 (52.8)
Smoking	
Brinkman index, Median (IQR)	0 [0, 50]
Smoking history (%)	6,489 (22.3)
Missing data	3,180 (10.9)
Body mass index (BMI)	
Median, IQR	17.8 [16.3, 19.5]
−18.4 (%)	16,724 (57.6)
18.5–24.9 (%)	10,989 (37.8)
25.0- (%)	142 (0.5)
Missing data	1,199 (4.1)
Length of hospital stay	
Days, Median (IQR)	9 [8, 13]
Types of herpes zoster	
Central nervous system (%)	9,034 (31.1)
Disseminated (%)	3,051 (10.5)
Ophthalmicus (%)	1,069 (3.7)
Others (%)	19,905 (68.5)
Underlying disease	
With underlying disease (%)	17,973 (61.9)
Without underlying disease (%)	11,081 (38.1)
Malignant diseases	
All malignancies (%)	6,882 (23.7)
Solid cancer (%)	2,283 (7.9)
Malignant lymphoma and hematopoietic malignancies (%)	4,804 (16.5)
Autoimmune diseases	
Connective tissue diseases (CTD) (%)	1,492 (5.1)
Rheumatoid arthritis (%)	757 (2.6)
Systemic lupus erythematosus (%)	280 (1.0)
Systemic vasculitis (%)	132 (0.5)
Other CTD (%)	426 (1.5)
Demyelinating diseases (%)	52 (0.2)
Immune disorder	
Human immunodeficiency virus infection (%)	75 (0.3)
Transplanted organ and tissue status (%)	281 (1.0)
Immunodeficiencies (%)	553 (1.9)
Gastrointestinal and liver diseases	
Inflammatory bowel diseases (%)	97 (0.3)
Autoimmune hepatitis (%)	28 (0.1)
Chronic viral hepatitis (%)	405 (1.4)
Liver cirrhosis and hepatic failure (%)	33 (0.1)
Renal diseases	
Chronic kidney disease (%)	613 (2.1)
Glomerulonephritis (%)	184 (0.6)
Endocrine and metabolic diseases	
Diabetes mellitus (%)	4,849 (16.7)
Dyslipidemia (%)	3,101 (10.7)
Hyperuricemia (%)	1,509 (5.2)
Disorders of thyroid gland (%)	47 (0.2)
Respiratory diseases	
Asthma (%)	610 (2.1)
Chronic obstructive pulmonary disease (%)	156 (0.5)
Interstitial lung disease (%)	307 (1.1)
Cerebrovascular and cardiovascular diseases	
Hypertension (HT) and HT related diseases (%)	6,408 (22.1)
Heart failure (%)	1,301 (4.5)
Chronic ischemic heart disease (cIHD) and/or Sequelae of cerebrovascular disease (CVD) (%)	1,205 (4.1)
cIHD (%)	543 (1.9)
Sequelae of CVD (%)	191 (0.7)
Psychiatric diseases	
Depressive disorder (%)	950 (3.3)
Anti-herpes zoster treatment	
Prescription days of antivirals, days, Median (IQR)	8 [7, 8]
Oral drug monotherapy (%)	5,957 (20.5)
Acyclovir (ACV) (%)	3,202 (11.0)
Valaciclovir (VCV) (%)	2,299 (7.9)
Famciclovir (FCV) (%)	328 (1.1)
Amenamevir (ANV) (%)	26 (0.1)
Intravenous monotherapy (%)	21,404 (73.7)
ACV (%)	21,349 (73.5)
Vidarabine (VDB) (%)	55 (0.2)
Combination of oral and intravenous drugs (%)	2,036 (7.0)
Oral and intravenous ACV (%)	209 (0.7)
ACV and VDB (%)	1 (0.0)
VCV and ACV (%)	1,000 (3.4)
VCV and VDB (%)	0 (0.0)
FCV and ACV (%)	292 (1.0)
FCV and VDB (%)	2 (0.0)
ANV and ACV (%)	27 (0.1)
ANV and VDB (%)	1 (0.0)
Medications administered during hospitalization	
Glucocorticoids (%)	9,550 (32.9)
Albumin preparations (%)	245 (0.8)
Globulin preparations (%)	632 (2.2)

ACV, acyclovir; ANV, Amenamevir; BMI, Body mass index; C-CVE, Cerebro-cardiovascular events; cIHD, Chronic ischemic heart disease; CTD, Connective tissue diseases; CVD, Cerebrovascular disease; FCV, Famciclovir; HT, Hypertension; HZ, Herpes zoster; IHD, Ischemic heart disease; VCV, Valaciclovir; VDB, Vidarabine.

regression analysis and logistic regression analysis were used to evaluate independent risk factors for in-hospital mortality and in-hospital C-CVE onset after admission for HZ treatment. The underlying diseases and confounding factors that are risk factors for HZ reported in previous studies were

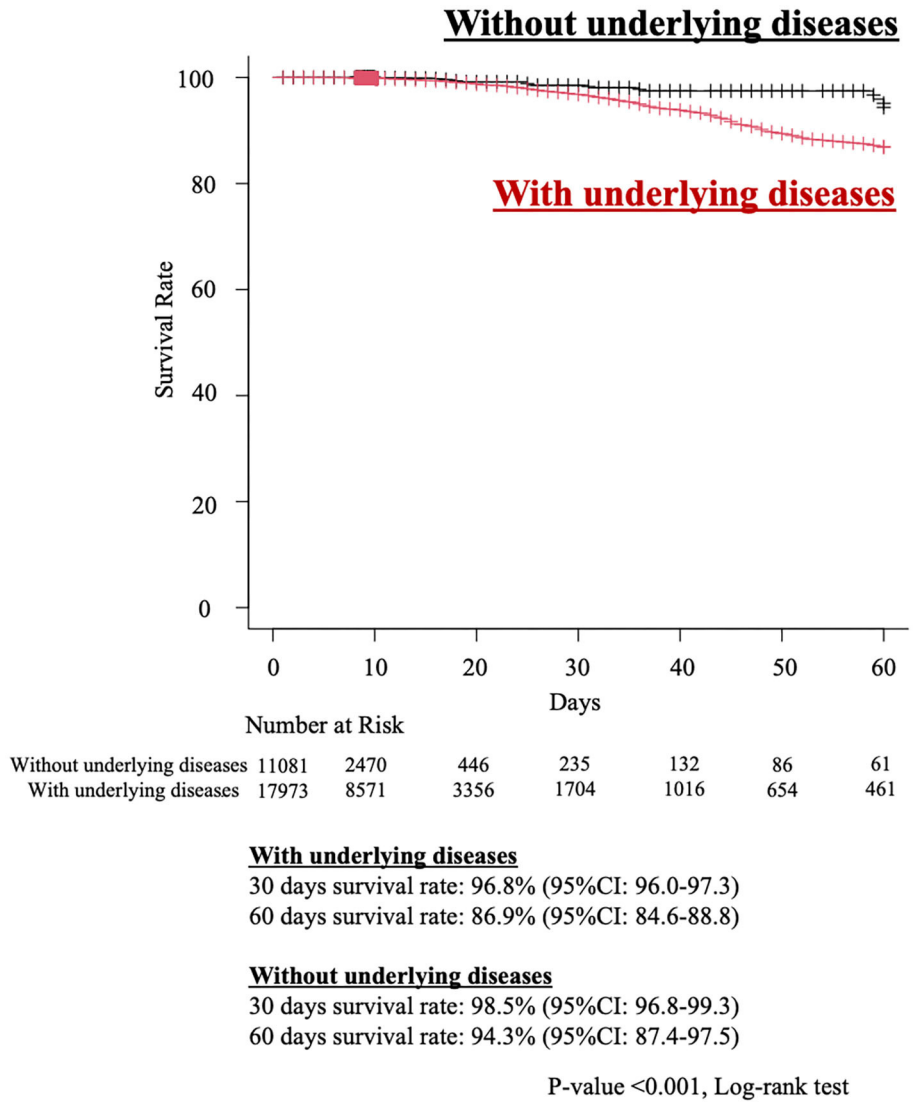

FIGURE 2 | Estimated Kaplan–Meier overall survival curve of herpes zoster patients with or without underlying diseases. 95% CI, 95 percent confidence interval.

preferentially selected as explanatory variables for multivariable analysis using the Cox proportional hazards regression (2, 27). Previously reported risk factors for C-CVE were preferentially selected as explanatory variables for multivariable logistic regression analysis (28, 29). We assumed that continuous variables (body mass index (BMI) and Brinkman index) were missing at random. Variables with missing values were not included in the multivariable analysis because obesity (BMI $\geq$ 25) and smoking history could be considered not to be confounding factors based on the results of univariable analysis. All tests were two-tailed, and the statistical significance was set at $p < 0.05$. All statistical analyses were performed using the R software package (version 4.0.0, R Foundation) (30).

RESULTS

Patient Characteristics

Baseline characteristics of the study cohort are presented in **Table 1**. The median age was 71 years, and 15,350 cases (52.8%) were women. The cohort comprised 9,103 (31.3%), 8,095 (27.9%), and 11,856 (40.8%) cases aged 18–64 years, 65–74 years (pre-old age), and $\geq$75 years (old age) of age, categories based on the Japanese Gerontological Society and the Japan Geriatrics Society (31). A total of 17,973 (51.9%) cases had underlying diseases. Glucocorticoid (GC) was administered during hospitalization in 9,550 (32.9%) cases. The median length of hospital stay after the initiation of HZ treatment was 8 days. Based on the severity of HZ, most cases (21,061 cases [72.5%])

were treated with intravenous antivirals (mostly acyclovir). The median length of antiviral administration was 8 days.

Study Outcomes

Survival Rates and Prognostic Factors

There were 307 in-hospital deaths (1.1%) in the study cohort. The overall survival rates at 30 and 60 days were 97.0% and 87.7%, respectively. The estimated 30- and 60-day survival rates after the start of HZ treatment for the groups with or without underlying disease were 96.8% (95% confidence interval [CI], 96.0–97.3)/86.9% (95% CI, 84.6–88.8), and 98.5% (95% CI, 96.8–99.3) and 94.3% (95% CI, 87.4–97.5), respectively ($p<0.001$) (**Figure 2**). The 30- and 60- day survival rates for each type of HZ are as follows: overall (30-day in-hospital survival rate, 97.0%; [95% CI, 96.3–97.5] and 60-day in-hospital survival rate, 87.7%; [95% CI, 85.7–89.5]), CNS (30-day in-hospital survival rate, 98.0%; [95% CI, 96.7–97.3]) and 60-day in-hospital survival rate, 88.3%; [95% CI, 85.3–89.5]), disseminated (30-day in-hospital survival rate, 96.6%; [95% CI, 93.4–98.3] and 60-day in-hospital survival rate, 85.3%; [95% CI, 75.6–91.3]), ophthalmicus (30-day in-hospital survival rate, 100%; [95% CI, NA–NA] and 60-day in-hospital survival rate, 100%; [95% CI, NA–NA]), and other (30-day in-hospital survival rate, 96.9%; [95% CI, 96.2–97.5 and 60-day in-hospital survival rate, 88.0%; [95% CI, 85.7–89.9]). The baseline characteristics of the survivor and non-survivor groups are summarized in **Table 2**. Compared with survivors, non-survivors were significantly older with higher rates of female sex, obesity, smoking history, malignancies, CKD, DM, chronic viral hepatitis, liver cirrhosis and hepatic failure, COPD, ILD, HF, cIHD and sequalae of CVD (old cerebrovascular events), GC administration, and albumin preparation administration. Comparison of the treatment approaches between the two groups revealed that there were more patients receiving oral antivirals and the combination of oral and intravenous antivirals, immunoglobulin, and albumin preparations, in the non-survivor group than in the survivor group. We analyzed the poor prognostic factors associated with in-hospital mortality due to HZ using the Cox proportional hazards regression model (**Figure 3**). By multivariable analysis, over 75 years of age (hazard ratio [HR], 2.17; [95% CI, 1.53–3.06, $p < 0.001$]), liver cirrhosis and hepatic failure (HR, 6.84; [95% CI, 2.17–21.63, $p = 0.001$]), CKD (HR, 1.88; [95% CI, 1.27–2.78, $p = 0.002$]) and HF (HR, 1.70; 95% CI, 1.24–2.34, $p = 0.001$), and sequalae of CVD (HR, 1.96; [95% CI, 1.08–3.56, $p = 0.028$]) were poor prognostic factors. All results of the Cox hazard regression analysis are shown in **Supplementary Table 1**.

C-CVE In-hospital Onset Rates and Risk Factors

Three hundred and eighty five cases (1.3%) experienced in-hospital C-CVE onset after hospitalization. The baseline characteristics of the non-C-CVE onset and C-CVE onset groups are summarized in **Table 3**. Compared with the non-C-CVE onset group, the C-CVE onset group were significantly older and had significantly higher rates of death, male, smoking history, malignant lymphoma and hematopoietic malignancies, transplanted organ and tissue status, CKD, DM, dyslipidemia, hyperuricemia, asthma, ILD, HT, HF, cIHD, sequalae of CVD,

TABLE 2 | Baseline clinical characteristics between survivors and non-survivors.

	Survivor $n = 28,487$	Non-survivor $n = 307$	*p*-value
Age			
Year, Median (IQR)	71 [61, 80]	77 [67, 85]	<0.001
18–64 (%)	9,041 (31.5)	62 (20.2)	<0.001
65–74 (%)	8,034 (27.9)	61 (19.9)	0.001
75- (%)	11,672 (40.6)	184 (59.9)	<0.001
Gender			
Female (%)	15,202 (52.9)	148 (48.2)	0.108
Body mass index (BMI)			
Median (IQR)	17.8 [16.3, 19.5]	17.8 [16.3, 20.0]	0.024
−18.4 (%)	16,567 (57.6)	157 (51.1)	0.001
18.5–24.9 (%)	10,866 (37.8)	123 (40.1)	0.009
25.0- (%)	137 (0.5)	5 (1.6)	0.016
Missing data	1,177 (4.1)	22 (7.2)	
Smoking			
Brinkman index, Median (IQR)	0.00 [0.00, 0.00]	0.00 [0.00, 357.50]	<0.001
Smoking history (%)	6,397 (22.3)	92 (30.0)	0.007
Missing data	3,151 (11.0)	29 (9.4)	
Length of hospital stay			
Days, Median (IQR)	8 [8, 13]	36 [20, 61]	<0.001
Types of herpes zoster			
Central nervous system (%)	8,995 (31.3)	39 (12.7)	<0.001
Disseminated (%)	3,024 (10.5)	27 (8.8)	0.399
Ophthalmicus (%)	1,068 (3.7)	1 (0.3)	<0.001
Others (%)	19,655 (68.4)	250 (81.4)	<0.001
Underlying diseases			
No underlying disease (%)	11,064 (38.5)	17 (5.5)	<0.001
Malignant diseases			
All malignancies (%)	6,687 (23.3)	195 (63.5)	<0.001
Solid cancer (%)	2,197 (7.6)	86 (28.0)	<0.001
Malignant lymphoma and hematopoietic malignancies (%)	4,686 (16.3)	118 (38.4)	<0.001
Autoimmune diseases			
Connective tissue diseases (CTD) (%)	1,477 (5.1)	15 (4.9)	1.000
Rheumatoid arthritis (%)	750 (2.6)	7 (2.3)	0.858
Systemic lupus erythematosus (%)	278 (1.0)	2 (0.7)	1.000
Systemic vasculitis (%)	130 (0.5)	2 (0.7)	0.407
Other CTD (%)	420 (1.5)	6 (2.0)	0.466
Demyelinating diseases (%)	52 (0.2)	0 (0.0)	1.000
Immune disorder			
Human immunodeficiency virus infection (%)	75 (0.3)	0 (0.0)	1.000
Transplanted organ and tissue status (%)	271 (0.9)	10 (3.3)	0.001
Immunodeficiencies (%)	542 (1.9)	11 (3.6)	0.053
Gastrointestinal and liver diseases			
Inflammatory bowel diseases (%)	97 (0.3)	0 (0.0)	0.630
Autoimmune hepatitis (%)	27 (0.1)	1 (0.3)	0.257

(Continued)

TABLE 2 | Continued

	Survivor $n = 28,487$	Non-survivor $n = 307$	*p*-value
Chronic viral hepatitis (%)	394 (1.4)	11 (3.6)	0.004
Liver cirrhosis and Hepatic failure (%)	29 (0.1)	4 (1.3)	<0.001
Renal diseases			
Chronic kidney disease (%)	580 (2.0)	33 (10.7)	<0.001
Glomerulonephritis (%)	181 (0.6)	3 (1.0)	0.449
Endocrine and metabolic diseases			
Diabetes mellitus (%)	4,784 (16.6)	65 (21.2)	0.038
Dyslipidemia (%)	3,083 (10.7)	18 (5.9)	0.005
Hyperuricemia (%)	1,489 (5.2)	20 (6.5)	0.299
Disorders of thyroid gland (%)	47 (0.2)	0 (0.0)	1.000
Respiratory diseases			
Asthma (%)	604 (2.1)	6 (2.0)	1.000
Chronic obstructive pulmonary disease (%)	151 (0.5)	5 (1.6)	0.025
Interstitial lung disease (%)	291 (1.0)	16 (5.2)	<0.001
Cerebrovascular and cardiovascular diseases			
Hypertension (HT) and HT related diseases (%)	6,334 (22.0)	74 (24.1)	0.406
Heart failure (%)	1,240 (4.3)	61 (19.9)	<0.001
Chronic ischemic heart disease (%)	189 (0.7)	2 0.7)	1.000
Sequelae of cerebrovascular disease (%)	529 (1.8)	14 (4.6)	0.002
Psychiatric diseases			
Depressive disorder (%)	939 (3.3)	11 (3.6)	0.745
Cerebro-cardiovascular events (C-CVE)			
Post-hospitalization onset of C-CVE (%)	369 (1.3)	16 (5.2)	<0.001
Post-hospitalization onset of CVD (%)	164 (0.6)	12 (3.9)	<0.001
Cerebral hemorrhage (%)	31 (0.1)	8 (2.6)	<0.001
Ischemic cerebrovascular diseases (%)	115 (0.4)	3 (1.0)	0.130
Precerebral arteries (%)	11 (0.0)	0 (0.0)	1.000
Cerebral arteries (%)	16 (0.1)	0 (0.0)	1.000
Unexplained (%)	88 (0.3)	3 (1.0)	0.072
Other CVDs (%)	22 (0.1)	1 (0.3)	0.217
Post-hospitalization onset of IHD (%)	209 (0.7)	4 (1.3)	0.293
Anti-herpes zoster treatment			
Prescription days of antivirals, days, Median (IQR)	8 [7, 8]	8 [7, 19]	<0.001
Oral drug monotherapy (%)	5,846 (20.3)	111 (36.2)	<0.001
Acyclovir (ACV) (%)	3,141 (10.9)	61 (19.9)	<0.001
Valaciclovir (VCV) (%)	2,258 (7.9)	41 (13.4)	0.001
Famciclovir (FCV) (%)	321 (1.1)	7 (2.3)	0.091
Amenamevir (ANV) (%)	26 (0.1)	0 (0.0)	1.000
Intravenous monotherapy (%)	21,257 (73.2)	151 (49.2)	<0.001
ACV (%)	21,203 (73.8)	146 (47.6)	<0.001
Combination of oral and intravenous drugs (%)	1,991 (6.9)	45 (14.7)	<0.001
ACV and ACV (%)	194 (0.7)	15 (4.9)	<0.001
VCV and ACV (%)	981 (3.4)	19 (6.2)	0.016
FCV and ACV (%)	288 (1.0)	4 (1.3)	0.556
ANV and ACV (%)	26 (0.1)	1 (0.3)	0.249
Medications administered during hospitalization			
Glucocorticoids (%)	9,361 (32.6)	189 (61.6)	<0.001
Albumin preparations (%)	187 (0.7)	58 (18.9)	<0.001
Globulin preparations (%)	582 (2.0)	50 (16.3)	<0.001
Prescription at discharge for post herpetic neuralgia			
Non-steroidal anti-inflammatory drugs (%)	6,939 (23.9)		
Voltage-gated Ca^{2+} channel α 2 δ ligand (%)	7,882 (27.1)		
Weak opioids (%)	3,016 (10.4)		
Strong opioids (%)	701 (2.4)		
Serotonin-noradrenaline reuptake inhibitor (%)	409 (1.4)		
Tricyclic antidepressant (%)	714 (2.5)		
Antiarrhythmic drugs (%)	59 (0.02)		

ACV, acyclovir; ANV, Amenamevir; BMI, Body mass index; C-CVE, Cerebro-cardiovascular events; cIHD, Chronic ischemic heart disease; CTD, Connective tissue diseases; CVD, Cerebrovascular disease; FCV, Famciclovir; HT, Hypertension; HZ, Herpes zoster; IHD, Ischemic heart disease; VCV, Valaciclovir; VDB, Vidarabine.

The Mann Whitney test, Chi-square test, and Fisher's exact test were used when appropriate to compare the groups.

transplanted organ and tissue status, and GC administration during hospitalization. Comparison of treatment approaches between the two groups revealed that there were more patients receiving oral antiviral monotherapy, immunoglobulin, and albumin preparation in the C-CVE onset group than in the non-C-CVE onset group. We analyzed the risk factors associated with in-hospital C-CVE onset after hospitalization for HZ treatment. By multivariable logistic regression analysis, older age ≥ 75 years (odds ratio [OR], 1.70; [95% CI, 1.30–2.24, $p < 0.001$]), DM (OR, 1.50; [95% CI, 1.19–2.49, $p = 0.001$]), hyperuricemia (OR, 1.65; [95% CI, 1.19–2.30]), HT (OR, 1.76; [95% CI, 1.41–2.30, $p < 0.001$]), HF (OR, 1.85; [95% CI, 1.33–2.57, $p < 0.001$]), and GC administration (OR, 1.63; [95% CI, 1.30–2.05, $p < 0.001$]) were identified as risk factors for in-hospital C-CVE onset (**Figure 4**). The results of the logistic regression analysis are shown in **Supplementary Table 2**.

DISCUSSION

Brief Summary of This Study

We investigated short-term in-hospital mortality and incidence of C-CVE in 29,054 hospitalized cases with HZ and analyzed prognostic factors and risk factors for C-CVE onset after HZ. Over 75 years of age, cirrhosis, liver failure, CKD, HF, and

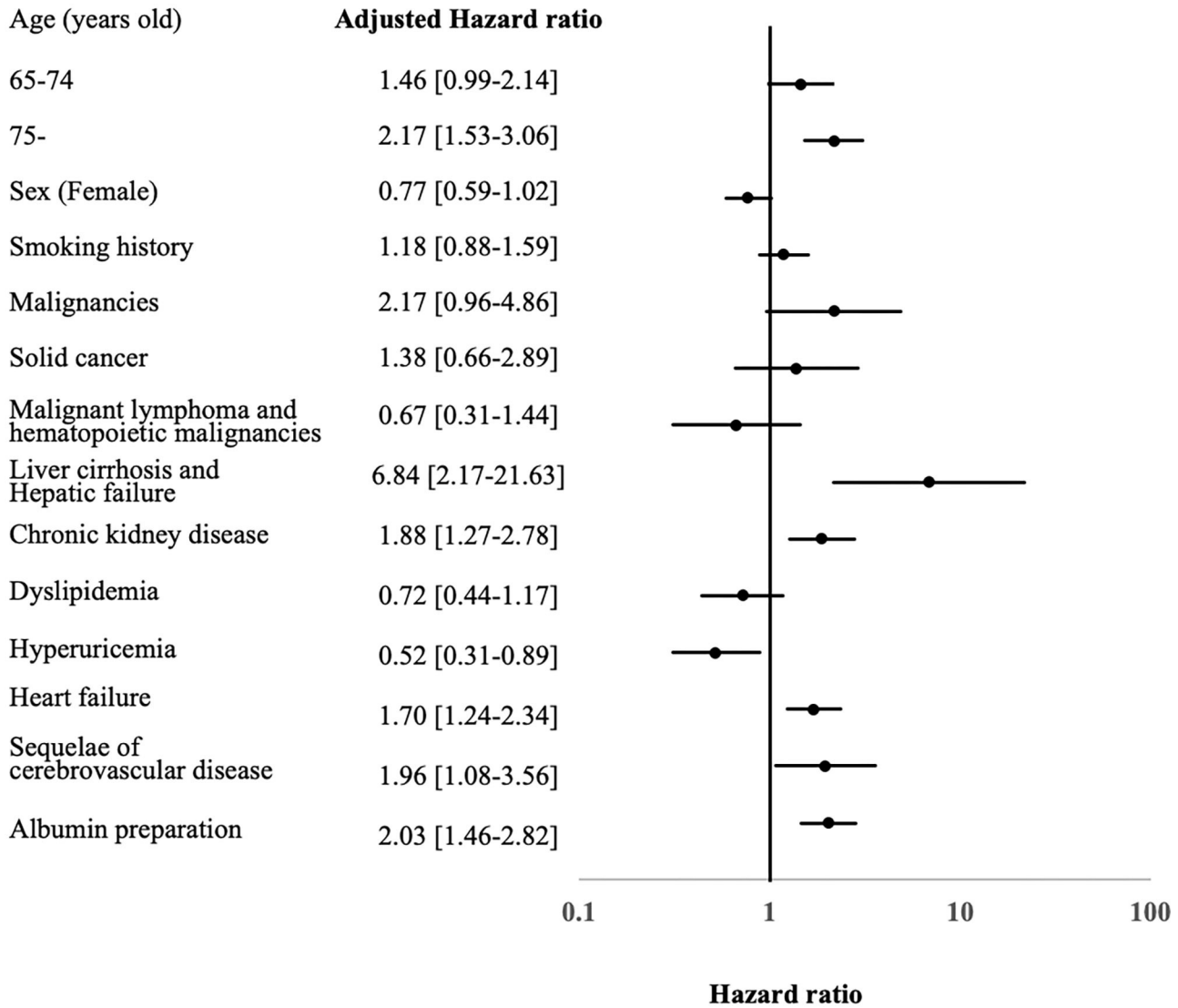

FIGURE 3 | Predictors for poor prognosis of hospitalized herpes zoster cases. aHR, adjusted hazard ratio; C-CVE, cerebro-cardiovascular events; 95% CI, 95 percent confidence interval.

sequelae of CVD were identified as short-term prognostic factors. Traditional C-CVE risk factors such as age ≥75 years, DM, dyslipidemia, hyperuricemia, HT, and HF were identified as risk factors for C-CVE development after hospitalization for HZ treatment, and GC administration was also identified as a new C-CVE risk factor.

Interpretation

The in-hospital mortality for HZ was similar to that reported in the study by Esteban-Vasallo et al. from Spain, conducted between 2003 and 2013. The study included data from the years before the widespread use of recombinant zoster vaccine (RZV), biologics, and JAK-I (32). Since there was no substantial discrepancy in the in-hospital mortality in our study, conducted using data from 2016 to 2018, the period when immunosuppressive therapy was developed, it is conceivable that biologics and JAK-i could have an impact on the development of HZ but might not have a significant impact on the severity of HZ. The incidence of HZ is higher in Japanese RA patients receiving JAK-i, but there may not be as much racial difference in mortality after HZ onset as HZ incidence in the unvaccinated population (5, 10, 33). Cirrhosis and liver failure, CKD, HF, and old cerebrovascular events, identified as risk factors for in-hospital mortality in this study, are also considered to be risk factors for severity of other viral infections such as influenza (34). HZ vaccines have been reported to be effective in preventing the onset and severity of HZ (35). For the prevention of severe conditions, the priority of vaccination might be based on the same criteria as that for vaccinations against other viral infections such as influenza because HZ is a common disease. It is important

TABLE 3 | Baseline clinical characteristics between C-CVE onset cases and no occurrence of C-CVE cases.

	No occurrence of C-CVE *n* = 28,669	C-CVE onset after hospitalization *n* = 385	*p*-value
Age			
Year, Median (IQR)	71 [61, 80]	76 [66, 83]	<0.001
18–64 (%)	9,020 (31.5)	83 (21.6)	<0.001
65–74 (%)	8,002 (27.9)	93 (24.2)	0.109
75- (%)	11,647 (40.6)	209 (54.3)	<0.001
Gender			
Female (%)	18,250 (52.0)	240 (45.1)	0.002
Body mass index (BMI)			
Median (IQR)	17.8 [16.3, 19.5]	18.0 [16.5, 19.7]	0.073
−18.4 (%)	16,512 (57.6)	212 (55.1)	0.258
18.5–24.9 (%)	10,836 (37.8)	153 (39.7)	0.395
25.0- (%)	142 (0.5)	0 (0.0)	0.333
Missing data	1,179 (4.1)	20 (5.2)	
Smoking			
Brinkman index, Median (IQR)	0.00 [0.00, 1.00]	0.00 [0.00, 80.00]	0.221
Smoking history (%)	6,401 (22.3)	88 (22.9)	0.003
Missing data	3,117 (10.9)	63 (16.4)	
Length of hospital stay			
Days, Median (IQR)	8 [8, 13]	12 [8, 22]	<0.001
Types of herpes zoster			
Central nervous system (%)	8,920 (31.1)	114 (29.6)	0.543
Disseminated (%)	3,017 (10.5)	34 (8.8)	0.315
Ophthalmicus (%)	1,057 (3.7)	12 (3.1)	0.682
Others (%)	19,636 (68.5)	269 (69.9)	0.581
Underlying diseases			
No underlying disease (%)	11,081 (38.7)	0 (0.0)	<0.001
Malignant diseases			
All malignancies (%)	6,767 (23.6)	115 (29.9)	0.005
Solid cancer (%)	2,251 (7.9)	32 (8.3)	0.703
Malignant lymphoma and hematopoietic malignancies (%)	4,717 (16.5)	87 (22.6)	0.002
Autoimmune diseases			
Connective tissue diseases (CTD) (%)	1,464 (5.1)	28 (7.3)	0.062
Rheumatoid arthritis (%)	745 (2.6)	12 (3.1)	0.517
Systemic lupus erythematosus (%)	273 (1.0)	7 (1.8)	0.104
Systemic vasculitis (%)	128 (0.4)	4 (1.0)	0.099
Other CTD (%)	419 (1.5)	7 (1.8)	0.518
Demyelinating diseases (%)	51 (0.2)	1 (0.3)	0.501
Immune disorder			
Human immunodeficiency virus infection (%)	75 (0.3)	0 (0.0)	0.629
Transplanted organ and tissue status (%)	273 (1.0)	8 (2.1)	0.035
Immunodeficiencies (%)	549 (1.9)	4 (1.0)	0.261
Gastrointestinal and liver diseases			
Inflammatory bowel diseases (%)	96 (0.3)	1 (0.3)	1.000
Autoimmune hepatitis (%)	28 (0.1)	0 (0.0)	1.000
Chronic viral hepatitis (%)	400 (1.4)	5 (1.3)	1.000
Liver cirrhosis and hepatic failure (%)	32 (0.1)	1 (0.3)	0.356
Renal diseases			
Chronic kidney disease (%)	592 (2.1)	21 (5.5)	<0.001
Glomerulonephritis (%)	182 (0.6)	2 (0.5)	1.000
Endocrine and metabolic diseases			
Diabetes mellitus (%)	4,741 (16.5)	108 (28.1)	<0.001
Dyslipidemia (%)	3,007 (10.5)	94 (24.4)	<0.001
Hyperuricemia (%)	1459 (5.1)	50 (13.0)	<0.001
Disorders of thyroid gland (%)	47 (0.2)	0 (0.0)	1.000
Respiratory diseases			
Asthma (%)	596 (2.1)	14 (3.6)	0.046
Chronic obstructive pulmonary disease (%)	153 (0.5)	3 (0.8)	0.466
Interstitial lung disease (%)	298 (1.0)	9 (2.3)	0.022
Cerebrovascular and cardiovascular diseases			
Hypertension (HT) and HT related diseases (%)	6,246 (21.8)	162 (42.1)	<0.001
Heart failure (%)	1,256 (4.4)	45 (11.7)	<0.001
Chronic ischemic heart disease (%)	183 (0.6)	8 (2.1)	0.004
Sequelae of cerebrovascular disease (%)	530 (1.8)	13 (3.4)	0.036
Psychiatric diseases			
Depressive disorder (%)	933 (3.3)	17 (4.4)	0.194
In-hospital Death (%)	291 (1.0)	16 (4.2)	<0.001
Breakdown of C-CVE			
Post-hospitalization onset of CVD (%)		176 (45.8)	
Cerebral hemorrhage (%)		39 (10.1)	
Ischemic cerebrovascular diseases (%)		118 (30.6)	
Precerebral arteries (%)		11 (2.9)	
Cerebral arteries (%)		16 (4.2)	
Unexplained (%)		91 (23.6)	
Other CVDs (%)		23 (6.0)	
Post-hospitalization onset of IHD (%)		213 (55.3)	
Anti-herpes zoster treatment			
Prescription days of antivirals, days, Median (IQR)	8 [7, 8]	8 [7, 12]	<0.001
Oral drug monotherapy (%)	5,853 (20.4)	104 (27.0)	0.002
Acyclovir (ACV) (%)	3,137 (10.9)	65 (16.9)	0.001
Valaciclovir (VCV) (%)	2,266 (7.9)	33 (8.6)	0.634
Famciclovir (FCV) (%)	324 (1.1)	4 (1.0)	1.000

(Continued)

TABLE 3 | Continued

	No occurrence of C-CVE $n = 28,669$	C-CVE onset after hospitalization $n = 385$	*p*-value
Amenamevir (ANV) (%)	26 (0.1)	0 (0.0)	1.000
Intravenous monotherapy (%)	20,807 (72.6)	254 (66.0)	0.005
ACV (%)	21,095 (73.6)	254 (66.0)	0.001
Combination of oral and intravenous drugs (%)	2,009 (7.0)	27 (7.0)	1.000
ACV and ACV (%)	205 (0.7)	4 (1.0)	0.362
VCV and ACV (%)	988 (3.4)	12 (3.1)	0.888
FCV and ACV (%)	290 (1.0)	2 (0.5)	0.600
ANV and ACV (%)	26 (0.1)	1 (0.3)	0.303
Medications administered during hospitalization			
Glucocorticoids (%)	9,380 (32.7)	170 (44.2)	<0.001
Albumin preparations (%)	238 (0.8)	7 (1.8)	0.046
Globulin preparations (%)	619 (2.2)	13 (3.4)	0.111
Prescription at discharge for post herpetic neuralgia			
Non-steroidal anti-inflammatory drugs (%)	5,525 (19.3)	66 (17.1)	0.329
Voltage-gated Ca^{2+} channel α 2 δ ligand (%)	6,401 (22.3)	69 (17.9)	0.042
Weak opioids (%)	2,316 (8.1)	34 (8.8)	0.572
Strong opioids (%)	271 (0.9)	8 (2.1)	0.033
Serotonin-noradrenaline reuptake inhibitor (%)	244 (0.9)	7 (1.8)	0.051
Tricyclic antidepressant (%)	651 (2.3)	8 (2.1)	1.000
Antiarrhythmic drugs (%)	38 (0.1)	0 (0.0)	1.000

ACV, acyclovir; ANV, Amenamevir; BMI, Body mass index; C-CVE, Cerebro-cardiovascular events; cIHD, Chronic ischemic heart disease; CTD, Connective tissue diseases; CVD, Cerebrovascular disease; FCV, Famciclovir; HT, Hypertension; HZ, Herpes zoster; IHD, Ischemic heart disease; VCV, Valaciclovir; VDB, Vidarabine.
The Mann Whitney test, Chi-square test, and Fisher's exact test were used when appropriate to compare the groups.

to address the prevention of HZ because if the onset and severity of HZ can be prevented, the complications of C-CVE might also be reduced. However, there are still many unclear points, such as the duration of the vaccine effects, therefore, further studies are needed on the timing of vaccination and the selection of priority vaccination targets.

Even in severe HZ, it was suggested that an inflammatory response (vasculitis) to the virus may occur from the acute stage after HZ onset, leading to the development of C-CVE. Inflammatory reactions in the artery and endothelial dysfunction are involved in the development of C-CVE (36, 37). Therefore, patients who have an underlying disease with arteriosclerosis and/or endothelial dysfunction such as diabetes may need to be especially attentive to the development of C-CVE after HZ. In addition to risk factors such as DM and HT, GC administration was newly identified as a risk factor for C-CVE onset after onset of HZ. GC has been previously reported to be a risk factor for C-CVE in CTD (38–40). GC administration may be used as adjunctive therapy for Ramsay-Hunt syndrome or for pain relief and prevention of sequelae of HZ, but administration of GC should be avoided because it may increase the risk of C-CVE (41). Since CTD, which requires a relatively frequent administration of GC, was not identified as a risk factor for C-CVE onset, it is possible that GC administration itself may lead to the C-CVE risk after HZ onset. In patients with a disease which is needed for long-term GC administration such as CTD, it would be desirable to reduce or avoid GC administration as much as possible to prevent HZ development and C-CVE onset after HZ.

Strengths of This Study

The strength of this study lies in the large sample size. We analyzed over 29,000 hospitalized HZ cases, the largest numbers ever studied. In previous studies, it could have been difficult to detect HZ-associated deaths and C-CVE onset associated with HZ during hospitalization due to the relatively low patient numbers. We were able to detect more than 300 cases of both in-hospital death and C-CVE onset, which allowed us to conduct analyses on short-term prognostic factors and risk factors for C-CVE onset.

In addition, the DPC database we used covers many acute care hospitals, including advanced care hospitals such as university hospitals, contributing to the generalization and comprehensiveness of the analysis results (42). Another strength of this study is that it covers a relatively small number of underlying diseases, such as CTD. Because relatively rare underlying diseases were included in the analysis, a more comprehensive analysis was possible.

Limitations

This study has several limitations. First, laboratory test results, imaging findings, and medical records were not available from the DPC database. Therefore, the diagnosis may uncertain. However, the diagnostic accuracy of DPC is moderate or high (43, 44), and previous studies using database have also used the ICD codes (25, 32). We used information on antivirals for HZ to improve diagnostic accuracy. Since antivirals for HZ are not administered for other infections, patients administered with antivirals for more than a certain period are more likely to be true HZ. Second, the DPC database contains no information before hospitalization, such as prescription drugs or HZ vaccination, and post-discharge outcomes. Since there is a possibility that the risk of HZ-related death and C-CVE may increase after discharge from the hospital, a long-term investigation should be conducted. The effect of vaccination on this study could be limited. Few people were vaccinated at the time of this analysis, because ZVL (zoster vaccine live) and RZV were approved in 2016 and 2018, respectively, for those over 50 years in Japan. ZVL is contraindicated during immunosuppressive and anticancer chemotherapy in Japan. Many patients with underlying diseases, such as CTD or malignancies, were not vaccinated. Future studies should examine any change in mortality and C-CVE incidence with

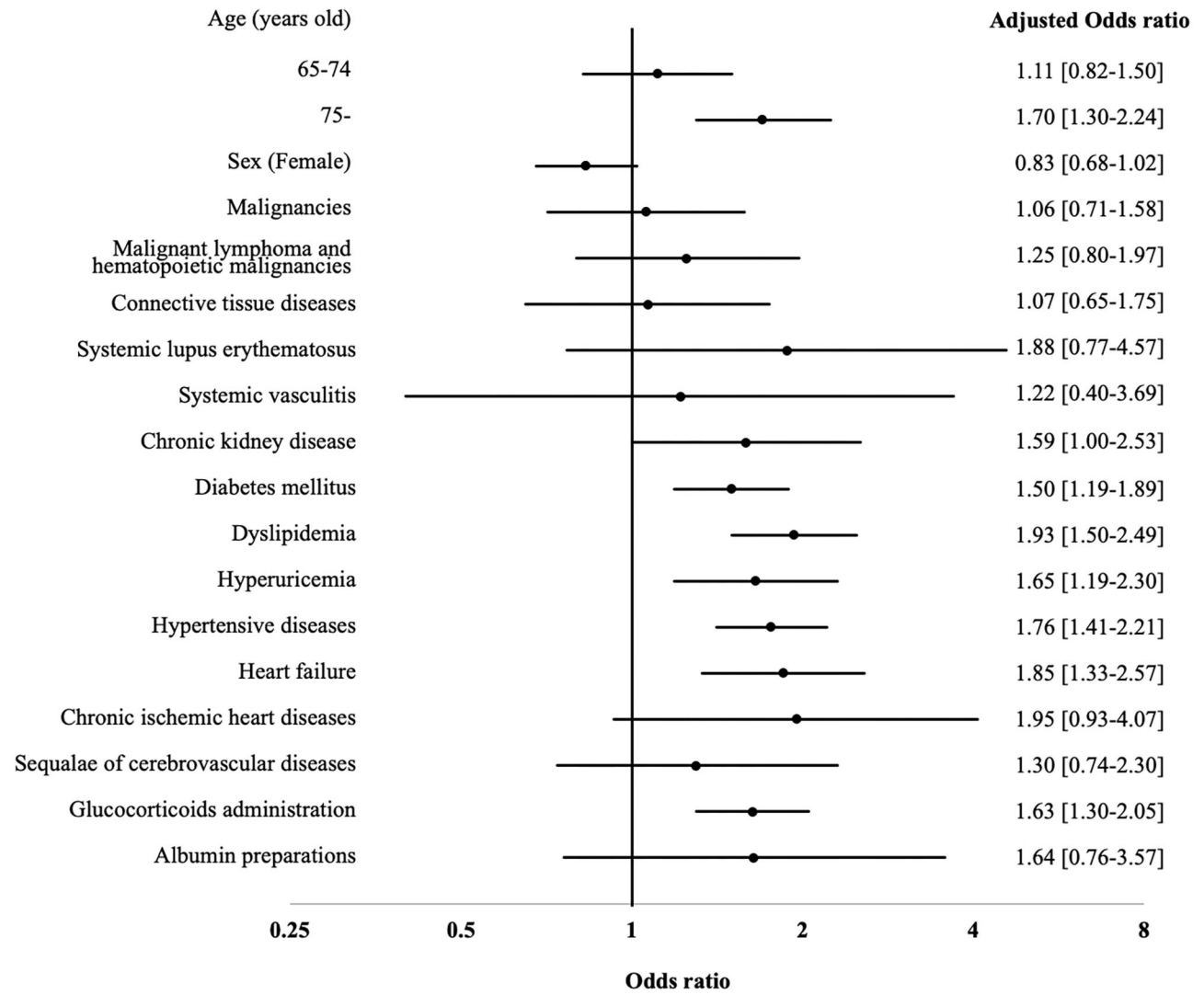

FIGURE 4 | Predictors for risk factors of C-CVE onset after hospitalization. aOR, adjusted odds ratio; C-CVE, cerebro-cardiovascular events; 95% CI, 95 percent confidence interval.

vaccination. These limitations can be overcome by matching DPC data with the National Database of Health Insurance Claims data, which contain information on prescription drugs in outpatient settings. However, there are many institutional and technical problems in linking the two databases. If institutional changes and technological innovations permit us to link the databases before and during hospitalization, we would like to investigate the linking of individuals' data.

CONCLUSION

Aggressive HZ prevention, including vaccination, should be considered for patients older than 75 years and for patients with poor prognostic factors. In addition to the conventional C-CVE risk factors, GC might be a risk factor for the development of C-CVE after severe HZ onset.

DATA AVAILABILITY STATEMENT

YI, KT, and KF had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. In this study, we used the DPC data provided by acute care hospitals in Japan to the DPC Research Institute. We conducted our study using this DPC database at the University of Occupational and Environmental Health, Japan. This database can only be accessed for research purpose.

ETHICS STATEMENT

Informed consent was waived for all patients included in this retrospective cohort study, and all information extracted was anonymized. The Institutional Review Board of the University of Occupational and Environmental Health,

Japan approved this study (approval code: R2-007). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

YI, KT, and KN: conceptualization and design, acquisition, analysis, and interpretation of data. KF: acquisition, analysis and interpretation of data. YI: drafting of the manuscript and statistical analysis. KN, SN, SM, and YT: supervision. All authors: critical revision of the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.843809/full#supplementary-material

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Determinants of COVID-19 Vaccine Uptake in Adolescents 12–17 Years Old: Examining Pediatric Vaccine Hesitancy Among Racially Diverse Parents in the United States

Aaliyah Gray[1*†] *and Celia B. Fisher*[1,2†]

[1] Department of Psychology, Fordham University, Bronx, NY, United States, [2] Center for Ethics Education, Fordham University, Bronx, NY, United States

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***Correspondence:**
Aaliyah Gray
agray11@fordham.edu

[†] *These authors have contributed equally to this work*

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As of December 8, 2021, 9.9 million U.S. adolescents ages 12–17 years old remain unvaccinated against COVID-19 (SARS-CoV-2) despite FDA emergency approval of the Pfizer-BioNTech COVID-19 vaccine for use among this age group in May 2021. A slow-down in adolescent vaccine uptake and increased likelihood of hospitalization among unvaccinated youth highlight the importance of understanding parental hesitancy in vaccinating their adolescent children against COVID-19. Racial/ethnic disparities in pediatric COVID-19 infection and hospitalization further underscore the need to examine parental vaccine acceptance and hesitancy among diverse U.S. parent populations. In October 2021, 242 Hispanic and non-Hispanic Asian, Black, and White parents of adolescents ages 12–17 years participated in a national online survey assessing determinants of COVID-19 pediatric vaccine hesitancy. Compared to Asian, Black, and Hispanic parents, non-Hispanic White parents reported reduced odds of having vaccinated their adolescent. Bivariate analyses and a multivariable binomial logistic regression indicated that identification as non-Hispanic White, parental COVID-19 vaccine status and safety measures, COVID-19 misconceptions, general vaccine mistrust and COVID-19 related collectivist and individualist attitudes accounted for 45.5% of the variance in the vaccine status of their adolescent children. Our findings draw attention to the urgent need to consider the COVID-19 beliefs, attitudes, and behaviors of parents from diverse racial/ethnic groups in developing population tailored public health messaging to increase adolescent COVID-19 vaccine uptake.

Keywords: COVID-19, vaccine hesitancy, pediatric vaccine uptake, racial diversity, adolescents, child, parents, health disparities

INTRODUCTION

On May 10, 2021, the United States (U.S.) Food and Drug Administration (FDA) authorized the Pfizer-BioNTech COVID-19 vaccine for emergency use among 12–17 years old (1). This authorization followed ∼1.5 million COVID-19 cases among adolescents between March 1, 2020 and April 30, 2021 (1). Although severe disease and hospitalization occurs less often among

pediatric populations (2–4), hospitalization rates are approximately 10 times higher among unvaccinated adolescents compared to their fully vaccinated age counterparts (3). As of December 8, 2021, however, just 51% (∼12.8 million) of 12–17 year-olds were fully vaccinated (5). With 9.9 million youth remaining unvaccinated, a slow-down in vaccine uptake has become a growing concern (5–7). Consequently, understanding factors contributing to COVID-19 vaccine uptake among this age group is urgent.

The success of vaccination programs for adolescents is dependent on overcoming parental vaccine hesitancy. Studies evaluating COVID-19 vaccine hesitancy and acceptance among samples of adults and parents have reported lower parental income and educational level (6, 8–13), parental concerns about pediatric vaccine safety (6, 8–11, 13–16), and lack of COVID-19 knowledge and related misconceptions among adults (17–20) are associated with vaccine hesitancy. By contrast, COVID-19 vaccine uptake among parents and associated health behaviors (e.g., masking, social distancing, etc.) have been associated with pediatric COVID-19 vaccine acceptance (6, 17, 21, 22). Although collectivist attitudes (emphasizing the needs of the group over the individual) have been found to increase intentions to vaccinate among international parent populations (16, 23), recent data from the Kaiser Family Foundation suggest that parents in the U.S. may emphasize personal choice over collective responsibility in their COVID-19 vaccine attitudes (6).

In the U.S., racial minority children have born the greatest burden of pediatric COVID-19 infection and hospitalization (4, 24–26). To date, however, few studies have examined potential racial/ethnic group differences in the relationship between adolescent COVID-19 vaccine uptake and related parental behaviors and attitudes. Early data suggest there may be higher levels of vaccine hesitancy among Hispanic and non-Hispanic Black parents (4, 9–13). Since a return to pre-pandemic normality is only achievable with high vaccination rates (1, 27), suboptimal vaccination among 12–17 year-olds underscores the importance of identifying determinants of parental pediatric COVID-19 vaccine acceptance and hesitancy for the development of effective public health initiatives. The aims of the current brief report are to (1) examine the extent to which parental demographic factors and COVID-19 behaviors, beliefs, and attitudes jointly and independently account for pediatric COVID-19 vaccine uptake among their 12–17 years old children, and (2) identify similarities and differences in vaccine uptake and the salience of these factors for parent populations of different racial/ethnic backgrounds.

METHODS

Data were collected as a part of a larger online national non-probability survey examining individual and social determinants of parental vaccine hesitancy for pediatric COVID-19 vaccination of children and adolescents in the U.S. Of the 400 English speaking self-identified female guardians (≥21 years old) included in the larger study, a total of 242 Hispanic (n = 71, 29.3%) and non-Hispanic Asian (n = 48, 19.8%), Black (n = 63, 25%), and White (n = 60, 24.8%) female guardians reported the vaccine status of a child between the ages of 12–17 years old. Among this current sample, 29.8% did not attend college, 40.1% reported <$20,000 in household income, 24.8% were financially insecure endorsing the item "I cannot make ends meet," and 64% lived in the Midwest and South. Recruitment was conducted through Qualtrics XM with data collected in October 2021. The research protocol was approved by the university institutional review board.

The primary outcome measure in the current study was the proportion of parents reporting they have vaccinated or have not vaccinated their 12–17 year-old child. The survey adapted items from prior scales to assess the following factors: [1] parental COVID-19 vaccine status and safety measures (e.g., wearing a mask in public, staying away from large crowds and social distancing when meeting people, frequent hand washing, avoiding close-contact spaces and activities) (28); [2] COVID-19 misconceptions (e.g., children have natural immunity and cannot transmit the virus, COVID-19 health risks have been exaggerated, COVID-19 is not any worse than the flu) (28, 29); [3] general vaccine mistrust (e.g., children receive too many vaccines, immunizing children is harmful and this fact is covered up, vaccine effectiveness research data is often fabricated) (30, 31), [4] COVID-19 collectivist attitudes (e.g., getting my child vaccinated for COVID-19 supports the community by stopping the spread of the disease among other children and adults) (32); and [5] COVID-19 individualist attitudes (e.g., getting my child vaccinated for COVID-19 would violate my family's rights) (32). All items were scored on 6-point Likert-type scales with the exception of the four true/false items assessing COVID-19 misconceptions. Demographic information included parents' age, education, household income, financial security, region of residence, employer requirements for vaccination, vaccination status for other household members, and COVID-19 infection among family members.

Descriptive statistics for all variables are provided in **Tables 1**, **2**. Unadjusted binomial logistic regressions were performed to assess differences in determinants of adolescent vaccination status (**Table 1**) and Pearson Chi-square tests were performed to assess differences among racial/ethnic groups (**Table 2**) for each demographic variable and the above-mentioned COVID-19 beliefs and attitudes scales. A multivariable binomial logistic regression was performed to evaluate the independent influence of demographic characteristics and COVID-19 beliefs, attitudes, and behavior items and scale scores on adolescent vaccination status. According to G*Power *post-hoc* analyses, our sample size achieved sufficient power to assess dichotomous racial difference where non-Hispanic White parents were compared to Hispanic and Non-Hispanic Asian and Black parents ($1–\beta = 0.92$) as well as differences between the four racial groups ($1–\beta = 0.91$).

RESULTS

Only 25.6% (n = 62) of respondents (N = 242) indicated their 12–17 year old adolescent had received the COVID-19 vaccine compared to 74.4% (n = 180) who indicated

TABLE 1 | Frequencies/percentages and means/standard deviations for parental demographic characteristics and COVID-19 related beliefs and attitudes and unadjusted bivariate analyses predicting adolescent vaccine status for the full sample.

	Total sample *N* = 242	Not vaccinated *N* = 180	Vaccinated *N* = 62	*P*-value	OR (95% CI)
	N (%)	*N* (%)	*N* (%)		
Parent age, *M* (*SD*)	35.67 (7.74)	34.66 (7.01)	38.61 (8.99)	0.001*	1.07 (1.03, 1.11)
Race					
Non-Hispanic Asian	48 (19.8%)	34 (18.9%)	14 (22.6%)	0.53	1.25 (0.62, 2.53)
Non-Hispanic Black	63 (26%)	46 (25.6%)	17 (27.4%)	0.77	1.10 (0.57, 2.11)
Hispanic	71 (29.3%)	48 (26.7%)	23 (37.1%)	0.12	1.62 (0.88, 2.99)
Non-Hispanic White	60 (24.8%)	52 (28.9%)	8 (12.9%)	0.02*	0.37 (0.16, 0.82)
Education				0.89	1.05 (0.56, 1.98)
Did not attend college	72 (29.8%)	54 (30%)	18 (29%)		
Some college or higher	170 (70.2%)	126 (70%)	22 (71%)		
Annual household income				0.46	0.86 (0.58, 1.28)
<$20,000	97 (40.1%)	75 (41.7%)	22 (35.5%)		
Between $20,000 and 50,999	111 (45.9%)	79 (43.9%)	32 (51.6%)		
Between $51,000 and 79,999	22 (9.1%)	19 (10.6%)	3 (4.3%)		
Preferred not to answer	12 (5%)	7 (3.9%)	5 (8.1%)		
Financial security				0.83	0.93 (0.48, 1.80)
Cannot make ends meet	60 (24.8%)	44 (24.4%)	15 (25.8%)		
Have just enough or comfortable	182 (75.2%)	136 (75.6%)	46 (74.2%)		
Region of residence					
Northeast	34 (14%)	26 (14.4%)	8 (12.9%)	0.76	0.88 (0.38, 2.06)
Midwest	86 (35.5%)	64 (35.6%)	22 (35.5%)	0.99	1.00 (0.55, 1.82)
South	70 (28.9%)	53 (29.4%)	17 (27.4%)	0.76	0.91 (0.48, 1.72)
West	52 (21.5%)	37 (20.6%)	15 (24.2%)	0.55	1.23 (0.62, 2.45)
Parent vaccine status				<0.001*	14.24 (6.13, 33.11)
No	123 (50.8%)	116 (64.4%)	7 (11.3%)		
Yes	119 (49.2%)	64 (35.6%)	55 (88.7%)		
Parent's employer requires vaccination[a]				0.04*	2.06 (1.02, 4.17)
No	194 (8.2%)	150 (83.3%)	44 (71%)		
Yes	42 (17.4%)	26 (14.4%)	166 (25.8%)		
I don't know	6 (2.5%)	4 (2.2%)	2 (3.2%)		
Other adults in their household are vaccinated[a]				<0.001*	8.81 (4.19, 17.69)
No	136 (52.1%)	115 (63.9%)	11 (17.7%)		
Yes	114 (47.1%)	63 (35%)	51 (82.3%)		
I don't know	2 (0.8%)	2 (1.1%)	0%		
Family members in their household ever had COVID-19				—	—
No	188 (77.7%)	138 (76.7%)	50 (80.6%)		
Yes	0%	0%	0%		
I don't know	54 (22.3%)	42 (23.3%)	12 (19.4%)		
COVID-19 misconceptions, *M* (*SD*)	0.95 (1.16)	1.11 (1.18)	0.53 (.97)	0.001*	0.58 (0.42, 0.81)
Parent COVID-19 safety measures, *M* (*SD*)	4.37 (1.86)	4.21 (1.91)	2.82 (1.61)	0.03*	1.21 (1.02, 1.44)
General vaccine mistrust, *M* (*SD*)	3.32 (1.26)	3.58 (1.20)	2.58 (1.15)	<0.001*	0.50 (0.38, 0.65)
COVID-19 collectivist attitudes, *M* (*SD*)	4.08 (1.52)	3.75 (1.54)	5.05 (.97)	<0.001*	2.12 (1.61, 2.78)
COVID-19 individualist attitudes, *M* (*SD*)	3.24 (1.78)	3.46 (1.71)	2.60 (1.82)	0.001*	0.75 (0.63, 0.89)

Statistical tests: Unadjusted binomial logistic regressions.

[a] *"No" and "I don't know" combined in Chi-square analyses.*

**Indicates significance, $p < 0.05$.*

that their child was unvaccinated. As reported in **Table 1**, the odds of vaccination were higher for parents who were older, already vaccinated, required to be vaccinated by their employer, or living with other vaccinated adults. Across race/ethnicity, parents who had vaccinated their adolescent endorsed significantly fewer COVID-19 misconceptions, less

TABLE 2 | Frequencies/percentages and means/standard deviations for racial/ethnic group differences in adolescent vaccination status and parent characteristics.

	Total sample (*N* = 242)	Hispanic and non-Hispanic Asian and Black parents (*N* = 182)	Non-Hispanic White parents (*N* = 60)	*P*-value
	N (%)	*N* (%)	*N* (%)	
Vaccination status of adolescent (ages 12–17)				0.01*
No	180 (74.4%)	128 (70.3%)	52 (86.7%)	
Yes	62 (25.6%)	54 (29.7%)	8 (13.3%)	
Parent age, *M* (*SD*)	35.67 (7.74)	35.34 (7.12)	36.95 (9.32)	0.14
Education				
Did not attend college	72 (29.8%)	55 (30.2%)	17 (28.3%)	0.78
Some college or higher	170 (70.2%)	127 (69.3%)	43 (71.7%)	
Annual household income				0.29
Less than $20,000	97 (40.1%)	69 (37.9%)	28 (46.7%)	
Between $20,000 and 50,999	111 (45.9%)	87 (47.8%)	24 (40%)	
Between $51,000 and 79,999	22 (9.1%)	15 (8.2%)	7 (11.7%)	
Preferred not to answer	12 (5%)	11 (6%)	1 (1.7%)	
Financial security				0.97
Cannot make ends meet	60 (24.8%)	45 (24.7%)	15 (25%)	
Have just enough or comfortable	182 (75.2%)	137 (74.3%)	45 (75%)	
Region of residence				0.13
Northeast	34 (14%)	20 (11%)	14 (23.3%)	
Midwest	86 (35.5%)	67 (36.8%)	19 (31.7%)	
South	70 (28.9%)	54 (29.7%)	16 (26.7%)	
West	52 (21.5%)	41 (22.5%)	11 (18.3%)	
Parent vaccine status				0.46
No	123 (50.8%)	90 (49.5%)	33 (55%)	
Yes	119 (49.2%)	92 (50.5%)	27 (45%)	
Parent's employer requires vaccination[a]				0.08
No	194 (80.2%)	140 (76.9%)	54 (90%)	
Yes	42 (17.4%)	36 (19.8%)	6 (10%)	
I don't know	6 (2.5%)	6 (3.3%)	0%	
Other adults in their household are vaccinated[a]				0.71
No	136 (52.1%)	93 (51.1%)	33 (55%)	
Yes	114 (47.1%)	87 (47.8%)	27 (45%)	
I don't know	2 (.8%)	2 (1.1%)	0%	
Family members in their household ever had COVID-19				–
No	188 (77.7%)	149 (81.8%)	39 (65%)	
Yes	0%	0%	0%	
I don't know	54 (22.3%)	33 (18.1%)	21 (35%)	
COVID-19 misconceptions, *M* (*SD*)	0.95 (1.16)	0.84 (1.06)	1.32 (1.36)	0.02*
Parent COVID-19 safety measures, *M* (*SD*)	4.37 (1.86)	4.46 (1.78)	4.10 (2.07)	0.24
General vaccine mistrust, *M* (*SD*)	3.32 (1.26)	3.34 (1.26)	3.28 (1.28)	0.77
COVID-19 collectivist attitudes, *M* (*SD*)	4.08 (1.52)	4.20 (1.52)	3.72 (1.50)	0.03*
COVID-19 individualist attitudes, *M* (*SD*)	3.24 (1.78)	3.14 (1.76)	3.53 (1.83)	0.14

Statistical tests: Independent t-tests for parent age, COVID-19 misconceptions, parent COVID-19 safety measures, general vaccine mistrust, COVID-19 collectivist attitudes, and COVID-19 individualist attitudes; Chi-square tests of independence for all other variables.

[a] *"No" and "I don't know" combined in Chi-square analyses.*

**Indicates significance, $p < 0.05$.*

general vaccine mistrust, and less COVID-19 individualist attitudes. These parents engaged in more COVID-19 safety measures and expressed greater COVID-19 collectivist attitudes. **Figure 1** illustrates differences in standardized scale means between parents whose adolescent had or had not been vaccinated.

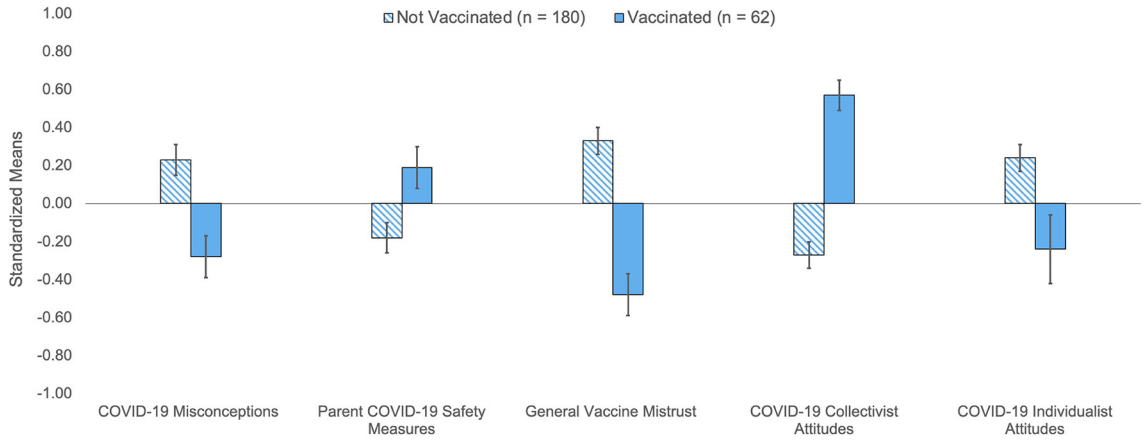

FIGURE 1 | Differences in standardized scale means for COVID-19 attitudes and beliefs by vaccination status among adolescents ages 12–17. Standardized means based on z-scores for COVID-19 attitudes and vaccine beliefs indicate that parents whose older adolescent child ages 12–17 years old was unvaccinated reported above average COVID-19 misconceptions, general vaccine mistrust, and COVID-19 individualist attitudes where parent COVID-19 safety measures and COVID-19 collectivist attitudes were below average. The opposite was true for parents whose child was vaccinated on all scales. Errors bars represent standard error means and 0 in the y-axis denotes the mean score. Independent *t*-tests indicated that both groups were significantly different from each other on all scales, $p \leq 0.001$ to $p = 0.02$.

As reported in **Table 1**, non-Hispanic White parents reported reduced odds of vaccinating their adolescent compared to non-Hispanic Asian, non-Hispanic Black, and Hispanic parents. Further ANOVA and chi-square analyses revealed variable racial/ethnic differences in annual household income and financial security, vaccination status of the respondent and other adults living in the same household, and endorsement of COVID-19 misconceptions. No other differences were found among parent demographics or COVID-19 attitudes and beliefs across all four racial/ethnic groups. Race/ethnic group percentages and ANOVA and chi-square results for all variables are reported in the **Supplementary Table 1** for this report.

To better understand factors underlying differences in adolescent uptake between non-Hispanic White parents and other racial/ethnic groups, we combined the responses of Asian, Black, and Hispanic parents and compared them to the responses of non-Hispanic White parents (see **Table 2**). Our data indicated that just 13.3% of White parents had vaccinated their adolescent compared to a significantly higher proportion (29.7%) of the other race/ethnicity parents. Non-Hispanic White parents also endorsed significantly more COVID-19 misconceptions and significantly lower COVID-19 collectivist attitudes. There were no other significant racial/ethnic differences among parent characteristics when comparing the combined Asian, Black, and Hispanic parent responses to non-Hispanic White parent responses.

A multivariable binomial logistic regression that included parent age, race/ethnicity, parent vaccine status, COVID-19 misconceptions, general vaccine mistrust, COVID-19 safety measures, and collectivist and individualist attitudes explained 46% (Nagelkerke R^2) of the variance in whether adolescents had been vaccinated against COVID-19 infection. **Table 3** reports betas and standard errors, *p*-values, odds ratios, and 95% confidence intervals for factors included in the binomial logistic model. Parental age, vaccine status, and endorsement of COVID-19 collectivist attitudes independently increased the odds of vaccination among 12–17 year old children whereas identifying as non-Hispanic White and endorsing general vaccine mistrust independently decreased the odds of vaccination. Since parental vaccine status was identified as a prominent explanatory determinant of adolescent vaccine uptake, we conducted bivariate correlations examining the relationship between parental vaccine status and other explanatory variables. Results indicate that parental vaccine status was positively correlated with older parent age ($r = 0.19$), greater financial security ($r = 0.20$), having other vaccinated adults in the household ($r = 0.37$), reporting greater engagement in COVID-19 safety measures ($r = 0.21$), and COVID-19 collectivist attitudes ($r = 0.41$) while being negatively correlated with COVID-19 misconceptions ($r = -0.25$), general vaccine mistrust ($r = -0.43$), and COVID-19 individualist attitudes ($r = -0.29$). Correlations between all explanatory variables are provided in the **Supplementary Table 2** for this report.

DISCUSSION

Despite progress in COVID-19 vaccination rates among 12–17 year-olds since FDA emergency authorization in May 2021, to date, 9.9 million or nearly half of U.S. adolescents remain unvaccinated (5–7) in comparison to 61–85% of U.S. adults depending on age group (33). As such, concerns about parental pediatric vaccine refusal are growing. In the current brief report, just 25.6% of parents from diverse racial/ethnic backgrounds in the U.S. reported that their 12–17 year-old had been vaccinated against COVID-19 infection. This percentage is markedly lower than the 51% total U.S. adolescent vaccination rate (5). However, the demographic characteristics of our sample are consistent with factors associated with parental vaccine hesitancy: 29.8% did not attend college, 40.1% reported <$20,000 in household income, 24.8% endorsed the item "I cannot make

TABLE 3 | Adjusted binomial logistic regressions predicting vaccination status of adolescent child ages 12–17.

Variable	*B* (*SE*)	*P*-value	OR (95% CI)
Parent age	0.07 (0.02)	0.01*	1.07 (1.02, 1.12)
Race/ethnicity (Hispanic and Non-Hispanic Asian and Black compared to Non-Hispanic White)	−1.20 (0.50)	0.02*	0.30 (0.11, 0.80)
Parent vaccine status	1.98 (0.50)	<0.001*	7.22 (2.74, 19.05)
Parent COVID-19 safety measures	−0.05 (0.12)	0.68	0.95 (0.76, 1.19)
COVID-19 misconceptions	−0.23 (0.22)	0.32	0.79 (0.50, 1.26)
General vaccine mistrust	−0.48 (0.24)	0.05*	0.62 (0.39, 1.00)
COVID-19 individualist attitudes	0.25 (0.16)	0.11	1.29 (0.95, 1.76)
COVID-19 collectivist attitudes	0.41 (0.17)	0.02*	1.51 (1.08, 2.11)
Parent's employer requires vaccination	−0.17 (0.44)	0.70	0.84 (0.35, 2.00)
Other adults in their household are vaccinated	0.08 (0.19)	0.66	1.09 (0.75, 1.58)

*OR, odds ratio; 95% CI, 95% confidence interval; Nagelkerke $R^2 = 0.46$. The * symbol indicates significance $p < 0.05$.*

ends meet" and 64% lived in the Midwest and South (6, 8–13, 34–36). This study contributes to the growing body of literature on pediatric COVID-19 vaccinations by highlighting characteristics and attitudes that independently and conjointly influence parental vaccine hesitancy and identifying how these determinants and decisions to vaccinate vary across U.S. racial/ethnic groups.

Among our sample, bivariate analyses indicated that race/ethnicity, parental age, vaccine status, employer requirements for vaccination, and vaccination among other adults in the household were significant social determinants of vaccine uptake among 12–17 years old. Among parents who themselves were vaccinated, the unadjusted odds of vaccine uptake for their older child were 14 times higher than unvaccinated parents. Our findings are consistent with previous research reporting that vaccinated parents are more likely than unvaccinated parents to accept the vaccine for their children (6, 8–10, 12, 16, 17, 19, 21, 22). Further, our data point to the influence of one's larger social context on vaccine acceptance. The unadjusted odds of vaccine uptake were twice as high for parents whose employer required vaccination and 7 times higher for parents living with other vaccinated adults. Taken together, our results highlight the importance of considering the ways in which social context normalizes COVID-19 vaccination among parents. Further research is needed to better understand what factors motivate parent COVID-19 vaccine uptake and how these contexts impact parental pediatric COVID-19 vaccine acceptance and hesitancy in general in addition to assessing the extent to which racial/ethnic group identification influences these relationships.

Bivariate analyses also indicated that COVID-19 attitudes and beliefs among parents were significant determinants of adolescent vaccine uptake. Among our sample, parental COVID-19 misconceptions, general vaccine mistrust, and COVID-19 individualist attitudes were found to decrease the odds of vaccine uptake whereas COVID-19 safety measures and collectivist attitudes improved the odds of vaccine uptake. Previous research has found that parents' misconceptions about COVID-19 transmission, symptoms, and severity, and their general attitudes about pediatric vaccine safety are significant barriers to vaccine acceptance (6, 8–11, 13–21). Consequently, future research must identify public health measures that are effective in reducing vaccine misconceptions and mistrust while also being sensitive to differences in the influence of these concerns across different racial/ethnic groups of parents.

Our data are consistent with previous research indicating COVID-19 safety measures such as wearing a mask in public, social distancing, and frequent handwashing are associated with COVID-19 vaccine acceptability among parents (22). While recent data suggests that parents in the U.S. may value personal choice over collective responsibility (6), our data indicate that individualistic and collectivist attitudes play competing roles in parental acceptance of COVID-19 vaccines for children. Understanding the relationships between pediatric vaccine acceptance and the inter-relationships among parental COVID-19 safety behaviors and collectivist and individualist community attitudes is a necessary step for improved public health messaging.

Among our sample, very few racial/ethnic differences were found in parent demographics and COVID-19 vaccine behaviors, attitudes, and beliefs. What did emerge was the finding that in comparison to non-Hispanic Asian, non-Hispanic Black, and Hispanic parents, non-Hispanic White parents were more likely to report that their adolescent had not been vaccinated, and further, were more likely to endorse COVID-19 misconceptions and reject COVID-19 collectivist attitudes. These results are in contrast to reports conducted early in the pandemic which found greater vaccine hesitancy among Hispanic and non-Hispanic Black parents (4, 9–13). However, more recent data suggest a shift in attitudes among adults of color in the U.S. In particular, these findings indicated that Black adults have seemingly "overcome" vaccine hesitancy at a faster pace than White adults over the course of the pandemic (37). Longitudinal data demonstrated that beliefs that COVID-19 vaccines are safe, effective, and necessary to protect oneself and one's community was predictive of personal intentions to receive the COVID-19 vaccinate with Black adults experiencing a faster shift in attitudes than White adults. Findings of the current and past research underscore an urgent need to consider racial/ethnic differences in COVID-19

vaccine concerns and attitudes among parents in order to develop effective public health communication strategies.

Limitations

This brief report is not without limitations. Our findings are based on cross-sectional data which cannot assess causal effects over time of these determinants on parents' pediatric vaccine decisions. Further, participant recruitment and participation were conducted entirely online through a survey panel aggregator, and consequently, participation was limited to individuals who have access to the internet on web-enabled devices and also who have signed up to complete surveys for compensation. Additionally, we observed among this sample that no participant reported COVID-19 infections among family members living in their household: 78% indicated no infections at all and 22% indicated that they don't know if any family member were ever infected. There are a few possible reasons for this. First, about half of the current sample reported being vaccinated and living with family members who are vaccinated. For some individuals, it is likely that their family members have never been infected with COVID-19; and for others, family members could have been infected and not have known due to increased odds of asymptomatic symptomatology among vaccinated individuals. Further, persistent low testing rates and inaccessibility of testing in the U.S. can also mean that participants and their family members were simply not being tested for COVID-19 infection. Although we do not have data on family member testing behaviors, we see glimpses of inadequate testing among our sample. Among parents, although a little more than 50% reported never being infected and receiving negative COVID-19 test results to confirm, 37% reported never having been infected but never being tested for COVID-19 infection and the few parents who did report previous infections (n = 16, 7%) indicated that they had never been tested as well. As a brief report drawn from data available from a larger study, our sample was limited in that we were only able to provide data from parents among our larger sample who reported having both a child between the ages of 5–11 and 12–17, and we did not have demographic data including age or gender of the 12–17 year old child, although these characteristics have not been reported as significant in other studies (10, 12). Finally, although our study was nationally representative, we did not assess rural, suburban, or urban differences which may also be related to vaccine hesitancy or acceptance.

CONCLUSIONS

Stemming the tide of the ongoing and ever-evolving COVID-19 pandemic depends on sufficient vaccination rates among all age groups. For children, vaccine uptake is contingent on hesitancy or acceptance among their parents. This brief report identifies parental sociodemographic differences, behaviors, and attitudes that have unique and inter-related effects on COVID-19 vaccine uptake among 12–17 year-olds. Our findings indicate that among these factors, increasing parental vaccine uptake, promoting COVID-19 vaccine collectivist attitudes, leveraging individualist attitudes, and alleviating general vaccine mistrust within the context of distinct racial/ethnic communities will be instrumental to public health efforts to improve vaccination uptake among adolescents. Our findings also suggest that future research can benefit from purposive sampling that includes sufficient numbers of racial/ethnic groups characteristic of the U.S. demographic mosaic. Continuing to assess racial/ethnic differences is necessary if we are to overcome vaccine refusal currently stunting progress in vaccination among pediatric populations. As such, public health efforts must consider the unique attitudes, beliefs, and concerns among racial groups and target differential sources of misinformation, vaccine disinterest, and vaccine mistrust most likely to be antecedents of vaccine hesitancy among distinct racial/ethnic parental groups. These efforts should utilize culturally relevant messaging campaigns that emphasize both community and personal protection as a larger aspect of ongoing public health efforts to curb COVID-19 infection rates. Future national and local government efforts must also be directed at regaining public trust in public health messaging and improving vaccine science literacy. Overall, these efforts will require an understanding of the unique barriers and facilitators contributing to parental vaccine hesitancy that can inform the effective population tailored public health messaging and interventions needed to improve pediatric COVID-19 vaccine uptake if we are to return to pre-pandemic normalcy.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors and for data files please contact AG, agray11@fordham.edu.

ETHICS STATEMENT

This study involving human participants was reviewed and approved by the Fordham University Institutional Review Board. The participants indicated informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AG and CF: conceptualization, methodology, original draft preparation, writing-review, and editing. AG: data visualization and formal analysis. All authors have read and agreed to the published version of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.844310/full#supplementary-material

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Factors Associated With Psychological Outcomes Among Vaccinated and Unvaccinated Health Care Workers Against COVID-19 Infection in Bangladesh

Md. Dhedharul Alam[1,2], *Sujan Kumer Paul*[3], *Mahmuda Momi*[4], *Li Ni*[5] *and Yi Xu*[1,2]*

[1] Department of Psychiatry, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China, [2] The Key Laboratory of Mental Disorder Management in Zhejiang Province, Hangzhou, China, [3] Department of Periodontology and Oral Pathology, Holy Family Red Crescent Medical College and Hospital, Dhaka, Bangladesh, [4] Department of Restorative Dentistry, Faculty of Dentistry, University of Malaya, Kuala Lumpur, Malaysia, [5] Department of Psychiatry, Fuyang Third Peoples Hospital, Hangzhou, China

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Aida Bianco,
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***Correspondence:**
Yi Xu
xuyizju@zju.edu.cn

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Background: Vaccination of healthcare workers (HCWs) is recommended during the COVID-19 pandemic to reduce the risk of infection for themselves and their patients, as well as to encourage their patients to get immunized. The present study aimed to investigate the psychological outcomes and associated factors among vaccinated and unvaccinated HCWs against COVID-19 infection in Bangladesh.

Methods: From March to August 2021, an online nationwide survey was conducted with a total of 2,038 Bangladeshi HCWs. The frequency of symptoms of general health problems, depression, anxiety, stress, post-traumatic stress disorder, insomnia, and loneliness was assessed using the Bangla versions of the GHQ-12, PHQ-2, GAD-2, PSS-4, PC-PTSD-5, ISI, and UCLA-LS scales, respectively.

Results: Compared with unvaccinated HCWs ($n = 1,058$), vaccinated HCWs ($n = 980$) had a statistically significant lower prevalence of general health problems (16.7 vs. 59.1%), depression (15.6 vs. 31.9%), post-traumatic stress disorder (22.3 vs. 30.8%), insomnia (23.8 vs. 64.9%), and loneliness symptoms (13.9 vs. 21.8%). Among vaccinated HCWs, females were significantly associated with a higher risk of symptoms of general health problems (AOR, 2.71; 95% CI, 0.97–7.60), anxiety (AOR, 2.17; 95% CI, 1.14–4.13), and loneliness (AOR, 2.52; 95% CI, 1.11–5.73). Except for anxiety and post-traumatic stress disorder symptoms, participants living in urban areas had a significantly lower risk of all psychological outcomes (e.g., depression: AOR, 0.43; 95% CI, 0.27–0.67; stress: AOR, 0.64; 95% CI, 0.47–0.88). Respondents who were married were significantly less likely to experience symptoms of general health problems (AOR, 0.10; 95% CI, 0.02–0.39), depression (AOR, 0.31; 95% CI, 0.22–0.82), insomnia (AOR, 0.46; 95% CI, 0.20–1.03), and loneliness (AOR, 0.31; 95% CI, 0.10-0.92). Participants who worked as doctors were significantly less chance of experiencing symptoms of general health problems (AOR, 0.18; 95% CI, 0.08–0.37), depression (AOR, 0.51; 95% CI, 0.30–0.87), and anxiety (AOR, 0.54; 95% CI, 0.37–0.78). On the other hand,

unvaccinated HCWs who were 18–29 years old and had <5 years of work experience were significantly associated with a higher risk of all psychological outcomes except anxiety and insomnia symptoms (e.g., depression among 18–29 years old: AOR, 1.83; 95% CI, 0.27–2.60; stress among those with <5 years of work experience: AOR, 2.37; 95% CI, 0.93–6.07). Participants who worked as nurses were significantly more likely to suffer from depression (AOR, 1.44; 95% CI, 0.84–2.46), anxiety (AOR, 1.42; 95% CI, 0.24–1.73), and stress (AOR, 1.55; 95% CI, 0.31–0.89) symptoms. Except for anxiety and stress symptoms, respondents who worked as frontline workers and provided direct care to infected patients were the significantly higher chance of experiencing all psychological outcomes (e.g., depression among who worked as frontline workers: AOR, 2.41; 95% CI, 0.23–3.73; insomnia among those who provide direct care to infected patients: AOR, 2.60; 95% CI, 0.34–3.06). Participants who were infected with COVID-19 had a significantly less chance of experiencing symptoms of general health problems (AOR, 0.89; 95% CI, 0.65–1.22), depression (AOR, 0.66; 95% CI, 0.48–0.92), and anxiety (AOR, 0.63; 95% CI, 0.46–0.87).

Conclusions: To control the infection and improve psychological outcomes, this study suggests emphasizing the vaccinated to unvaccinated HCWs as soon as possible. They also required special attention, health-related education, and psychological support.

Keywords: Bangladesh, COVID-19, health care workers, immunization, psychological outcomes, refusal, uptake

INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) has now spread throughout the world. Since the commencement of the COVID-19 pandemic in 2019, around 225 countries and 215.7 million people have been afflicted with the virus, which has killed about 4.4 million people (as of August 29, 2021) (1). This unprecedented global epidemic poses a severe challenge to local healthcare systems, with a growing number of daily cases and death counts related to COVID-19. Healthcare workers (HCWs) are more vulnerable to COVID-19 than the general population, particularly those exposed to suspected and confirmed cases, due to the high risk of infection, insufficient protection and disease management experience, heavy workload, substantial lifestyle adjustments, quarantine, and lower social support (2–4). These variables raise the risk of psychological issues among HCWs, including depression, anxiety, insomnia, fear, and suicide, all of which can have a severe impact on work productivity and long-term well-being (5–7).

However, Sanghera et al. (8) conducted a meta-analysis of 44 studies involving 69,499 HCWs, reporting high rates of indications of depression (13.5–44.7%), anxiety (12.3–35.6%), stress (5.2–32.9%), post-traumatic stress disorder (7.4–37.4%), insomnia (33.8–36.1%) and burnout (3.1–43.0%) among HCWs during the COVID-19 outbreak. Another meta-analysis of the effects of SARS, MARS, and COVID-19 on HCWs' physical and mental health found that general health concerns (62.5%), depression (26.3%), anxiety (29.0%), post-traumatic stress disorder (20.7%), insomnia (37.9%), psychological distress (37.8%), fear (43.7%), burnout (34.4%), somatization (16.1%), and stigmatization feelings (14.0%) (9). Bangladesh, where the current study was done, is a South Asian country where COVID-19 has significantly impacted its healthcare system (10). The first COVID-19 case was reported in Bangladesh on March 8, 2020 (11), and as of August 31, 2021, the country had 1.4 million verified COVID-19 cases and 26,195 deaths (12). Bangladesh reported the first death on April 15, 2020, and a nurse on May 30, 2020. Approximately 9,394 healthcare providers had been infected with the virus on August 29, 2021, with 186 of them dying (**Supplementary Figures 1**, **2**) (13, 14). A study examining the impact of the COVID-19 pandemic on Bangladeshi HCWs found that the prevalence of depression, anxiety, insomnia, and loneliness among HCWs were 44, 78, 89, and 87%, respectively (15).

Vaccines are one of the most effective strategies for preventing COVID-19 infection, as well as its consequences and complications (16). Since the first COVID-19 vaccination human clinical trial began on March 3, 2020 (17), 33 vaccines had progressed to stage 3 clinical trials, with 22 vaccines approved in 192 countries by August 31, 2021 (18). More than 5 billion doses of the vaccine were already administered globally as of August 31, 2021 (1). On January 27, 2021, Bangladesh began providing COVID-19 vaccines, with bulk vaccination starting on February 7, 2021, and the second dosage starting on April 8, 2021 (19). As of August 31, 2021, the number of first doses administered in Bangladesh is 18,489,742, and the number of second doses administered is 8,045,469 (**Supplementary Figure 3**) (12). Ideally, a high enough percentage of the population will be immunized, safeguarding those who aren't, a process known as "herd immunity." It has been estimated between 55 to 82% of populations would need to be vaccinated to reach herd immunity for COVID-19, depending

on varying biological, environmental, socio-behavioral factors and infection rates within each country (20).

Given the significant increase in anxiety and depressive symptoms linked to the COVID-19 pandemic's stress (21), it is plausible to believe that vaccination could lead to reduced anxiety and depressive symptoms. However, it is not known whether the psychological status would be affected after COVID-19 vaccination. One study showed that COVID-19 vaccination could positively correlate with COVID-19-related anxiety and fears among 1,779 adults in Germany (22), while another study indicated that psychological stress levels after getting vaccinated significantly decreased among the public in China (23). In addition, a cross-sectional survey of 363 HCWs in Turkey indicated that COVID-19 vaccination was not linked to secondary traumatic stress, anxiety, and depression symptoms among HCWs (24). As a result, it's critical to look into how this COVID-19 immunization affects mental health, particularly among HCWs. However, there have been no studies on the psychological outcomes of COVID-19 vaccination on both vaccinated and unvaccinated HCWs in Bangladesh yet. Therefore, we conducted a cross-sectional survey to assess the factors associated with psychological outcomes among vaccinated and unvaccinated HCWs against SARS-CoV-2 infection in Bangladesh. This study looked into the prevalence of general health problems, depression, anxiety, stress, post-traumatic stress disorder, insomnia, and loneliness among vaccinated and unvaccinated HCWs against SARS-CoV-2 infection in Bangladesh and explored its contributing factors.

Based on these considerations, this study had three objectives. First, we sought to determine the prevalence of general health problems, depression, anxiety, stress, post-traumatic stress disorder, insomnia, and loneliness among vaccinated and unvaccinated HCWs against SARS-CoV-2 infection in Bangladesh. Second, we sought to identify a difference in the prevalence of general health problems, depression, anxiety, stress, post-traumatic stress disorder, insomnia, and loneliness symptoms among vaccinated and unvaccinated HCWs in Bangladesh. Third, we sought to explore which socio-demographic and clinical factors could significantly predict psychological outcomes in the group of vaccinated and unvaccinated HCWs against SARS-CoV-2 infection in Bangladesh. Based on these objectives, we hypothesized that vaccinated HCWs had a lower prevalence of psychological outcomes against SARS-CoV-2 infection in Bangladesh than unvaccinated HCWs. This research will add to our understanding of SARS-CoV-2 vaccination and mental health and assist governments and policymakers in developing an effective vaccine campaign to achieve vaccination coverage and herd immunity among HCWs and the public during the SARS-CoV-2 outbreak.

MATERIALS AND METHODS

Study Design

The study was approved by the Institutional Ethical Review Board (IERB) of the Holy Family Red Crescent Medical College and Hospital, Dhaka, Bangladesh (Approval No: IERB/36) and the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine before it began. Before the participants started the questionnaire, they had to give their informed consent online. Between March and August of 2021, a cross-sectional online study was administered. The data was obtained online using Google Forms and the Bangla language. The two research assistants sent the survey link by e-mail, Facebook, Viber, WhatsApp, Imo, and other social media platforms. They were invited to fill out the form and share the link with their networks to reach more people. They used the convenient and snowball method to circulate the survey link throughout their professional and social networks. Participants were told that taking part in the study was completely voluntary, and they were urged to share the survey link with their friends or acquaintances once it was completed. All participants were assured of their data's privacy and confidentiality, as well as information on the study's goal, protocol, and their right to have their data removed at any time. The current study received a total of 2,067 responses at the onset. After screening, 29 responses were eliminated due to missing information, not being fully vaccinated, and being outside of Bangladesh. Finally, responses from 2,038 HCWs were included in this study. Nine hundred and eighty HCWs had been vaccinated, and 1,058 had not. Vaccinated means they had fully dose vaccinated. The following were the criteria for inclusion: (1) be at least 18 years old, (2) living in Bangladesh at the time of the COVID-19, (3) willingness to engage in this study via online informed consent, (4) completion of the whole questionnaire, and (5) no history of mental health problems.

Participants

The sample size was calculated using OpenEpi software. A previous study on the SARS-CoV-2 outbreak in Bangladesh found that 50% of HCWs had psychological problems (25). This 50% proportion would provide maximum variance and sample size. At 95% confidence level, 80% power, and 1.5 design effect, we arrived at the sample size of 576. The current study inflated our sample by 10% to account for non-response data, so the final sample size required was 634 participants for each group.

Measurements

Demographic Information

The participant's sex (male, female, or not interested), age (18–29, 30–39, 40–49, or 50 years), residence (urban and rural), the status of marriage, whether or not they had children, and educational level were self-reported demographic information. Participants were also asked working position (doctor, nurse, medical technician, hospital workers or other), work types (frontline or second-line), employment titles (senior, intermediate, junior, new or other), work experiences ($\leq$5, 6-10, 11–19, or $\geq$20 years), socioeconomic status (lower, middle or upper class), living with family, and smoking habit. In addition, this study also investigated whether participants had provided direct care to infected patients, whether they had been infected with COVID-19, whether anyone in their family, friends, or colleagues had been infected with COVID-19, and whether anyone in their family, friends, or colleagues had died from COVID-19.

General Health Questionnaire

The 12-item validated Bangla version of the General Health Questionnaire (GHQ-12) (26, 27) evaluates mental health status on a four-point Likert scale, with "1" defining never and "4" defining frequently. For a full score of 0–12, each item can be assigned a value of 0 (if option 1 or 2) or 1 (if options 3 and 4). The overall score of ≥3 indicated that the person's mental health status was terrible. In this study, the internal consistency was $\alpha = 0.81$.

Patient Health Questionnaire

The two-item validated Bangla version of the Patient Health Questionnaire (PHQ-2) (28–30) evaluates depression symptoms rated on a four-point Likert scale, with "1" defining never and '4' defining almost every day. The overall value of ≥3 is suggested to indicate a likely diagnosis of significant depression. In this study, the internal consistency was $\alpha = 0.76$.

Generalized Anxiety Disorder Scale

The two-item validated Bangla version of the Generalized Anxiety Disorder scale (GAD-2) (31, 32) evaluates anxiety symptoms on a four-point Likert scale, with "1" defining never and "4" defining almost every day. The overall score of ≥3 is proposed as revealing a probable anxiety disorder diagnosis. The internal consistency was $\alpha = 0.77$.

Perceived Stress Scale

The four-item validated Bangla version of the Perceived Stress Scale (PSS-4) (33–35) evaluates stress symptoms on a four-point Likert scale, with "1" defining never and "4" defining always. A quartile split was used because no official cut-off for the PSS-4 scale was available. In this study, the internal consistency was $\alpha = 0.72$.

Primary Care PTSD Screen for DSM-5

The Bangla version of the Primary Care PTSD Screen for DSM-5 (PC-PTSD-5) (36) evaluates post-traumatic stress disorder symptoms over the past month by asking five binary questions about re-experiencing, avoidance, physiological reactions, emotional numbness, and trauma-distorted guilt and blame thoughts. This scale was previously used in a Bangladeshi study (37). The total score ranges from 1 to 5, with a 3 as the cut-off value. In this study, the internal consistency was $\alpha = 0.71$.

Insomnia Severity Index

The seven-item validated Bangla version of the Insomnia Severity Index (ISI) (38, 39) evaluates the severity of insomnia on a five-point Likert scale, with "0" defining no problem and "4" defining a major problem. An overall score of ≥8 indicates possible insomnia symptoms in this investigation. The internal consistency was $\alpha = 0.72$.

University of California, Los Angeles, Loneliness Scale

The three-item validated Bangla version of the University of California, Los Angeles, Loneliness Scale (UCLA-LS) (40, 41) evaluates loneliness symptoms on a three-point Likert scale, with "1" defining rarely and "3" defining frequently. Participants who received a score of ≥6 were considered to be lonely to a high degree. In this study, the internal consistency was $\alpha = 0.75$.

Oslo Social Support Scale

The Bangla version of the three-item Oslo Social Support Scale (OSSS-3) (42) was also used to evaluate respondents' social support. The raw scores were added together to create a sum index, ranging from 3 to 14. Social support was labeled as poor, moderate, or strong based on a score of 3-8, 9-11, or 12-14. In this study, the internal consistency was $\alpha = 0.75$.

The PC-PTSD-5 and OSSS-3 scales were first sent to three experts in medicine, public health, and epidemiology, who translated the English version into Bangla and then back into English to ensure internal consistency, validity, and acceptable reliability (43). The scales were then piloted with 30 potential respondents from various categories to ensure that the language in the final version was perfect. The tools used in the pilot study received no corrections or suggestions from respondents regarding the contents developed in Bangla.

Statistical Analysis

The statistical analyses were run by SPSS version 20.0, and figures were prepared in GraphPad Prism version 9. Categorical data was represented using numbers and percentages. To compare categorical variable variations between groups, Chi-square tests were used. The Kolmogorov–Smirnov test, the Shapiro–Wilk test, and normal Q-Q plots were used to determine the data's normality. The median of the interquartile range (IQR) of data from non-normal distributions was shown. When comparing non-normally distributed data between two groups, the Mann–Whitney *U*-test was used, and when comparing data between more than two groups, the Kruskal–Wallis-test was used. Spearman correlations were used to compare the psychological outcomes of vaccinated and unvaccinated HCWs. In addition, binary logistic regression analysis was used to look into potential predictors of psychological outcomes in both groups. The model fitness test was checked using the Hosmer and Lemeshow goodness of fit test. All of the variables were added in the univariate analysis and then the multivariate analysis only included the significant variables in the univariate analysis. For a single predictor, univariate analysis expressed as crude odds ratio (COR) was used, while multivariate analysis expressed as adjusted odds ratio (AOR) was used for multiple predictors, and all psychological outcomes were considered dependent variables. All analyses were conducted at a 95% confidence level, with p-values < 0.05 considered significant.

RESULTS

Sample Characteristics

Finally, 2,038 HCWs were enrolled in our study, with 980 (48.1%) being vaccinated and 1,058 (51.9%) being unvaccinated. The characteristics of the study respondents are shown in **Table 1**. Vaccinated HCWs were significantly more likely to be younger (41.8 vs. 39.3%, $p < 0.01$), doctors (42.9 vs. 22.3%, $p < 0.01$), frontline workers (62.6 vs. 47.1%, $p < 0.01$), junior HCWs (48.4 vs. 38.1%, $p < 0.01$), with <5 years of work experience (52.8

vs. 45.8%, $p < 0.01$), from a middle-class socioeconomic status (59.6 vs. 53.8%, $p < 0.01$), providing direct service to infected patients (68.6 vs. 44.0%, $p < 0.01$), infected with COVID-19 (45.1 vs. 23.8%, $p < 0.01$), and with moderate social support (57.3 vs. 34.8%, $p < 0.01$) than unvaccinated HCWs. On the other hand, unvaccinated HCWs were significantly more male (52.7 vs. 47.2%, $p < 0.01$), married (62.1 vs. 58.2%, $p < 0.01$), had a post-graduate degree (54.9 vs. 45.0%, $p < 0.01$), lived with family (70.0 vs. 51.9%, $p < 0.01$), had family members, friends, or colleagues infected with COVID-19 (57.8 vs. 30.6%, $p < 0.01$) and died from it (33.3 vs. 23.6%, $p < 0.01$) than vaccinated HCWs. Moreover, there were no significant differences between the vaccinated and unvaccinated HCWs in terms of residence ($p = 0.41$), having children ($p = 0.63$), and smoking habits ($p = 0.25$).

Scores of Psychological Outcomes

When compared to unvaccinated HCWs, vaccinated HCWs had significantly lower median of the interquartile range (IQR) of scores for general health problems (2.0 [0–2.0] vs. 4.0 [2.0–6.0]; $p < 0.01$), depression (1.0 [1.0–2.0] vs. 3.0 [2.0-5.0]; $p < 0.01$), post-traumatic stress disorder (1.0 [1.0–2.0] vs. 3.0 [1.0-4.0]; $p < 0.01$), insomnia (3.0 [4.0-7.0] vs. 6.0 [5.0–11.0]; $p < 0.01$), and loneliness (1.0 [3.0–4.0] vs. 2.0 [3.0–5.0]; $p < 0.01$) symptoms, but significantly higher median of the interquartile range (IQR) of scores for anxiety (2.0 [1.0–3.0] vs. 1.0 [2.0–3.0]; $p < 0.01$), and stress (7.0 [8.0–15.0] vs. 5.0 [8.0–13.2]; $p < 0.01$) symptoms (**Table 2**).

Prevalence of Psychological Outcomes

The prevalence of psychological outcomes among vaccinated and unvaccinated health care workers against COVID-19 infection are shown in **Table 3**. The prevalence rates of symptoms of general health problems, depression, anxiety, stress, post-traumatic stress disorder, insomnia, and loneliness symptoms among vaccinated HCWs were 16.7, 15.6, 24.8, 34.7, 22.3, 23.8, and 13.9%, respectively. On the other hand, the prevalence rates of symptoms of general health problems, depression, anxiety, stress, post-traumatic stress disorder, insomnia, and loneliness symptoms among unvaccinated HCWs were 59.1, 31.9, 26.1, 35.0, 30.8, 64.9, and 21.8%, respectively. However, vaccinated HCWs had a significantly lower prevalence rates of general health problems (16.7 vs. 59.1%, $p < 0.01$), depression (15.6 vs. 31.9%, $p < 0.01$), post-traumatic stress disorder (22.3 vs. 30.8%, $p < 0.01$), insomnia (23.8 vs. 64.9%, $p < 0.01$), and loneliness symptoms (13.9 vs. 21.8%, $p < 0.01$) compared to unvaccinated HCWs. Moreover, the vaccinated and unvaccinated HCWs did not differ significantly on anxiety (24.8 vs. 26.1%, $p = 0.50$) and stress (34.7 vs. 35.0%, $p = 0.89$) symptoms.

Correlations of Psychological Outcomes

Spearman's correlations of psychological outcomes among vaccinated and unvaccinated HCWs are shown in **Table 4**. In the vaccinated HCWs, there was a positive correlation between general health problems scores and depression ($r_s = 0.208$, $p < 0.01$), insomnia ($r_s = 0.285$, $p < 0.01$), and loneliness ($r_s = 0.138$, $p < 0.01$) scores, but a negative correlation with post-traumatic stress disorder ($r_s = 0.135$, $p < 0.01$) scores. Moreover, depression scores were positively linked to insomnia ($r_s = 0.153$, $p < 0.01$) and loneliness ($r_s = 0.139$, $p < 0.01$) scores, but negatively related to post-traumatic stress disorder ($r_s = 0.071$, $p < 0.05$) scores. Furthermore, there was a negative relationship between anxiety and post-traumatic stress disorder ($r_s = 0.168$, $p < 0.01$) scores, as well as anxiety and insomnia ($r_s = 0.073$, $p < 0.05$) scores. In addition, we found a positive link between insomnia and loneliness scores ($r_s = 0.147$, $p < 0.01$).

In the unvaccinated HCWs, general health problems scores were positively linked to depression ($r_s = 0.127$, $p < 0.01$), post-traumatic stress disorder ($r_s = 0.147$, $p < 0.01$), insomnia ($r_s = 0.349$, $p < 0.01$), and loneliness ($r_s = 0.079$, $p < 0.05$) scores. Moreover, there was a significant positive correlation between depression and anxiety ($r_s = 0.063$, $p < 0.05$), along with depression and insomnia ($r_s = 0.147$, $p < 0.01$) scores. Only a significant positive relationship existed between anxiety and insomnia ($r_s = 0.090$, $p < 0.01$) scores. Furthermore, there was a positive relationship between post-traumatic stress disorder and insomnia ($r_s = 0.190$, $p < 0.01$), as well as post-traumatic stress disorder and loneliness ($r_s = 0.236$, $p < 0.01$) scores. In addition, the study discovered a positive link between insomnia and loneliness ($r_s = 0.078$, $p < 0.05$) scores.

Risk Factors of Psychological Outcomes

The results of the univariate logistic regression analysis of factors associated with psychological outcomes among vaccinated and unvaccinated health care workers against COVID-19 infection are presented in **Supplementary Table 1**. The variables found to be significant in the univariate logistic regression analysis were included in the multivariate analysis. The multivariate logistic regression analysis (**Supplementary Table 2**) showed that among vaccinated HCWs, females were significantly associated with a higher risk of symptoms of general health problems (AOR, 2.71; 95% CI, 0.97–7.60), anxiety (AOR, 2.17; 95% CI, 1.14–4.13), and loneliness (AOR, 2.52; 95% CI, 1.11–5.73) compared to males. Except for anxiety and post-traumatic stress disorder symptoms, participants living in urban areas had a significantly lower risk of all psychological symptoms than those living in rural areas (general health: AOR, 0.15; 95% CI, 0.09–0.25; depression: AOR, 0.43; 95% CI, 0.27–0.67; stress: AOR, 0.64; 95% CI, 0.47–0.88; insomnia: AOR, 0.41; 95% CI, 0.29-0.59; and loneliness: AOR, 0.29; 95% CI, 0.19-0.44). Respondents who were married were significantly less likely to experience symptoms of general health problems (AOR, 0.10; 95% CI, 0.02-0.39), depression (AOR, 0.31; 95% CI, 0.22–0.82), insomnia (AOR, 0.46; 95% CI, 0.20-1.03), and loneliness (AOR, 0.31; 95% CI, 0.10–0.92) than divorced, separated, or widowed respondents. Participants who worked as doctors were significantly less likely to experience symptoms of general health problems (AOR, 0.18; 95% CI, 0.08–0.37), depression (AOR, 0.51; 95% CI, 0.30–0.87), and anxiety (AOR, 0.54; 95% CI, 0.37–0.78) compared to other working positions.

On the other hand, unvaccinated HCWs who were 18–29 years old and had <5 years of work experience were significantly associated with a higher risk of all psychological outcomes except anxiety and insomnia symptoms (e.g., depression among

TABLE 1 | Sociodemographic characteristics in vaccinated and unvaccinated health care workers against COVID-19 infection.

Characteristics	Total (n = 2038) No. (%)	Vaccinated health care workers (n = 980) No. (%)	Unvaccinated health care workers (n = 1058) No. (%)	*p* value
Sex				
Male	1021 (50.1)	463 (47.2)	558 (52.7)	<0.01
Female	953 (46.8)	461 (47.0)	492 (46.5)	
Not interested	64 (3.1)	56 (5.7)	8 (0.8)	
Age, Y				
18–29	826 (40.5)	410 (41.8)	416 (39.3)	<0.01
30–39	612 (30.0)	257 (26.2)	355 (33.6)	
40–49	407 (20.0)	205 (20.9)	202 (18.1)	
≥50	193 (9.5)	108 (11.0)	85 (8.0)	
Residence				
Urban	1483 (72.8)	705 (71.9)	778 (73.5)	0.41
Rural	555 (27.2)	275 (28.1)	280 (26.5)	
Marital status				
Single	608 (29.8)	342 (34.9)	266 (25.1)	<0.01
Married	1227 (60.2)	570 (58.2)	657 (62.1)	
Divorced/separated/widowed	203 (10.0)	68 (6.9)	135 (12.8)	
Having children				
Yes	1049 (51.5)	499 (50.9)	550 (52.0)	0.63
No	989 (48.5)	481 (49.1)	508 (48.0)	
Education level				
Bachelor (MBBS) or lower degree	625 (30.7)	338 (34.5)	287 (27.1)	
Post-graduate degree	1022 (50.1)	441 (45.0)	581 (54.9)	<0.01
Doctoral degree	383 (18.8)	195 (19.9)	188 (17.8)	
Other	8 (0.4)	6 (0.6)	2 (0.2)	
Working position				
Doctor	656 (32.2)	420 (42.9)	236 (22.3)	<0.01
Nurse	159 (7.8)	69 (7.0)	90 (8.5)	
Medical technician	249 (12.2)	79 (8.1)	170 (16.1)	
Hospital workers	303 (14.9)	99 (10.1)	204 (19.3)	
Other	671 (32.9)	313 (31.9)	358 (33.8)	
Work types				
Frontline	1111 (54.5)	613 (62.6)	498 (47.1)	<0.01
Second-line	927 (45.5)	367 (37.4)	560 (52.9)	
Employment titles				
Senior	311 (15.3)	154 (15.7)	157 (14.8)	<0.01
Intermediate	473 (23.2)	200 (20.4)	273 (25.8)	
Junior	877 (43.0)	474 (48.4)	403 (38.1)	
New	366 (18.0)	143 (14.6)	223 (21.1)	
Other	11 (0.5)	9 (0.9)	2 (0.2)	
Work experiences, Y				
≤5	1002 (49.2)	517 (52.8)	485 (45.8)	<0.01
6–10	387 (19.0)	142 (14.5)	245 (23.2)	
11–19	422 (20.7)	187 (19.1)	235 (22.2)	
≥20	227 (11.1)	134 (13.7)	93 (8.8)	
Socio economic status				
Lower class	591 (29.0)	286 (29.2)	305 (28.8)	<0.01
Middle class	1153 (56.6)	584 (59.6)	569 (53.8)	
Upper class	294 (14.4)	110 (11.2)	184 (17.4)	
Living with family				
Yes	1250 (61.3)	509 (51.9)	741 (70.0)	<0.01
No	788 (38.7)	471 (48.1)	317 (30.0)	

(Continued)

TABLE 1 | Continued

Characteristics	Total (n = 2038) No. (%)	Vaccinated health care workers (n = 980) No. (%)	Unvaccinated health care workers (n = 1058) No. (%)	*p* value
Smoking habit				
Yes	613 (30.1)	283 (28.9)	330 (31.2)	0.25
No	1425 (69.9)	697 (71.1)	728 (68.8)	
Providing direct service to infected patients				
Yes	1138 (55.8)	672 (68.6)	466 (44.0)	<0.01
No	900 (44.2)	308 (31.4)	592 (56.0)	
Have you been infected with COVID-19?				
Yes	694 (34.1)	442 (45.1)	252 (23.8)	<0.01
No	1344 (65.9)	538 (54.9)	806 (76.2)	
Have any of your family members, friends, or colleagues been infected with the COVID-19?				
Yes	912 (44.7)	300 (30.6)	612 (57.8)	<0.01
No	1,126 (55.3)	680 (69.4)	446 (42.2)	
Have any of your family members, friends, or colleagues died of the COVID-19?				
Yes	583 (28.6)	231 (23.6)	352 (33.3)	<0.01
No	1,455 (71.4)	749 (76.4)	706 (66.7)	
Social support				
Poor	807 (39.6)	219 (22.3)	588 (55.6)	<0.01
Moderate	930 (45.6)	562 (57.3)	368 (34.8)	
Strong	301 (14.8)	199 (20.3)	102 (9.6)	

TABLE 2 | The median of the interquartile range (IQR) of psychological outcome scores in vaccinated and unvaccinated health care workers against COVID-19 infection.

Psychological outcomes	Total score Median (IQR)	Vaccinated health care workers Median (IQR)	Unvaccinated health care workers Median (IQR)	*P*-value
General health problems	4.0 (1.0–5.0)	2.0 (0–2.0)	4.0 (2.0–6.0)	<0.01
Depression symptoms	1.0 (1.0–2.0)	1.0 (1.0–2.0)	3.0 (2.0–5.0)	<0.01
Anxiety symptoms	1.0 (2.0–3.0)	2.0 (1.0–3.0)	1.0 (2.0–3.0)	<0.01
Stress symptoms	6.0 (8.0–14.0)	7.0 (8.0–15.0)	5.0 (8.0–13.2)	<0.01
Post-traumatic stress disorder symptoms	2.0 (1.0–3.2)	1.0 (1.0–2.0)	3.0 (1.0–4.0)	<0.01
Insomnia symptoms	6.0 (5.0–11.0)	3.0 (4.0–7.0)	6.0 (5.0–11.0)	<0.01
Loneliness symptoms	2.0 (3.0–5.0)	1.0 (3.0–4.0)	2.0 (3.0–4.0)	<0.01

IQR, Interquartile range.

18–29 years old: AOR, 1.83; 95% CI, 0.27–2.60; stress among those with <5 years of work experience: AOR, 2.37; 95% CI, 0.93–6.07). Participants who worked as nurses were significantly more likely to suffer from depression (AOR, 1.44; 95% CI, 0.84–2.46), anxiety (AOR, 1.42; 95% CI, 0.24–1.73), and stress (AOR, 1.55; 95% CI, 0.31–0.89) than those who worked in other positions. Except for anxiety and stress symptoms, respondents who worked as frontline workers and provided direct care to infected patients were the significantly higher chance of experiencing all psychological outcomes (e.g., depression among who worked as frontline workers: AOR, 2.41; 95% CI, 0.23–3.73; insomnia among those who provide direct care to infected patients: AOR, 2.60; 95% CI, 0.34–3.06). Respondents who were infected with COVID-19 had a significantly less chance of experiencing symptoms of general health problems (AOR, 0.89; 95% CI, 0.65–1.22), depression (AOR, 0.66; 95% CI, 0.48–0.92),

TABLE 3 | The prevalence of psychological outcomes among vaccinated and unvaccinated health care workers against COVID-19 infection.

Measure	Total (n = 2,038) No. (%)	Vaccinated health care workers (n = 980) No. (%)	Unvaccinated health care workers (n = 1,058) No. (%)	*P*-value
General health problems				
Yes	789 (38.7)	164 (16.7)	625 (59.1)	<0.01
No	1,249 (61.3)	816 (83.3)	433 (40.9)	
Depression symptoms				
Yes	491 (24.1)	153 (15.6)	338 (31.9)	<0.01
No	1,547 (75.9)	827 (84.4)	720 (68.1)	
Anxiety symptoms				
Yes	594 (29.1)	243 (24.8)	276 (26.1)	0.50
No	1,444 (70.9)	737 (75.2)	782 (73.9)	
Stress symptoms				
Yes	710 (34.8)	340 (34.7)	370 (35.0)	0.89
No	1,328 (65.2)	640 (65.3)	688 (65.0)	
Post-traumatic stress disorder symptoms				
Yes	545 (26.7)	219 (22.3)	326 (30.8)	<0.01
No	1,493 (73.3)	761 (77.7)	732 (69.2)	
Insomnia symptoms				
Yes	920 (45.1)	233 (23.8)	687 (64.9)	<0.01
No	1,118 (54.9)	747 (76.2)	371 (35.1)	
Loneliness symptoms				
Yes	367 (18.0)	136 (13.9)	231 (21.8)	<0.01
No	1,671 (82.0)	844 (86.1)	827 (78.2)	

TABLE 4 | Spearman's correlations of psychological outcomes among vaccinated and unvaccinated health care workers against COVID-19 infection.

Health care workers	Psychological outcomes	1	2	3	4	5	6	7
Vaccinated health care workers	1	1.00						
	2	0.208**	1.00					
	3	0.055	0.000	1.00				
	4	0.052	0.031	0.000	1.00			
	5	−0.135**	−0.071*	−0.168**	0.032	1.00		
	6	0.285**	0.153**	−0.073*	0.043	0.037	1.00	
	7	0.138**	0.139**	0.054	0.062	0.000	0.147**	1.00
Unvaccinated health care workers	1	1.00						
	2	0.127**	1.00					
	3	0.024	0.063*	1.00				
	4	−0.037	0.019	0.039	1.00			
	5	0.147**	0.047	0.023	−0.051	1.00		
	6	0.349**	0.147**	0.090**	−0.009	0.190**	1.00	
	7	0.079*	−0.013	−0.002	0.023	0.236**	0.078*	1.00

*$p < 0.05$, **$p < 0.01$. 1 General health problems, 2 Depression, 3 Anxiety, 4 Stress, 5 Post-traumatic stress disorder, 6 Insomnia, and 7 Loneliness.

and anxiety (AOR, 0.63; 95% CI, 0.46–0.87) when compared to those who were not.

DISCUSSION

This is the first nationwide study in Bangladesh that has evaluated the factors associated with psychological outcomes among vaccinated and unvaccinated HCWs against COVID-19 infection. A total of 2,038 HCWs were enrolled in this study (980 being vaccinated and 1,058 being unvaccinated). Our study found that the prevalence rates of general health problems, depression, anxiety, stress, post-traumatic stress disorder, insomnia, and loneliness symptoms among vaccinated HCWs were 16.7, 15.6, 24.8, 34.7, 22.3, 23.8, and 13.9%, respectively. On the other hand, the prevalence rates of general health problems, depression, anxiety, stress, post-traumatic stress disorder, insomnia, and loneliness symptoms among unvaccinated HCWs were 59.1, 31.9, 26.1, 35.0, 30.8, 64.9, and

21.8%, respectively. However, our study revealed that vaccinated HCWs showed statistically significant differences in lower prevalence rates of general health problems, depression, post-traumatic stress disorder, insomnia, and loneliness symptoms than unvaccinated HCWs. Moreover, no statistically significant differences in anxiety and stress symptoms between both groups were found. Similarly, as compared to unvaccinated HCWs, vaccinated HCWs had considerably lower median (IQR) scores on general health problems, depression, post-traumatic stress disorder, insomnia, and loneliness symptoms. According to Spearman's correlations, among vaccinated HCWs, there was a positive correlation between general health problems scores and depression, insomnia, and loneliness scores, but a negative correlation with post-traumatic stress disorder scores. In the unvaccinated HCWs, general health problems scores were positively linked to depression, post-traumatic stress disorder, insomnia, and loneliness scores.

This research indicated that vaccinated HCWs had a lower prevalence of psychological outcomes than unvaccinated HCWs against the COVID-19 outbreak in Bangladesh. These findings paralleled a study conducted in the United States among 300 HCWs, which revealed that vaccination against COVID-19 improved HCWs' physical and mental health (44). Another study conducted in China reported that the COVID-19 vaccine could improve the mental health status of vaccinated individuals (45). Moreover, Chen et al. (46) study were done between January 6-June 7, 2021, reported that being vaccinated for SARS-CoV-2 was associated with lower odds of depressive symptoms than those not vaccinated. Furthermore, our findings were also consistent with another study, which showed that human papillomavirus (HPV) vaccination might relieve the depression of vaccinated individuals (47). Based on the information presented above, our hypotheses were partially confirmed. The current study discovered many factors linked to both vaccinated and unvaccinated HCWs.

Our findings showed that females vaccinated HCWs were significantly associated with a higher risk of symptoms of general health problems, anxiety, and loneliness compared to males. This finding was consistent with previous research, which found that female HCWs were poorer psychological outcomes than males before the vaccination program (10, 48–50) and that females were more accepting of COVID-19 vaccination than males (51, 52). This study revealed that except for anxiety and post-traumatic stress disorder symptoms, participants living in urban areas had a significantly lower risk of all psychological symptoms among vaccinated HCWs. These findings were in line with prior Bangladeshi studies (15, 53, 54), which claimed that HCWs working in urban areas had a higher rate of psychological outcomes. In a cross-sectional survey of 3,646 adults in Bangladesh, Avedin et al. (55) discovered that 81% of urban participants wanted to be vaccinated. Similar studies also found that participants who lived in a city were similarly more likely to pay for and take the COVID-19 vaccine (56, 57). In Bangladesh, urban areas may have higher rates of infection and mortality among HCWs and the general population than rural areas (53). Most doctors are located in Dhaka and major cities (58). HCWs working in COVID-19 and non-COVID settings face a high workload, constant exposure, infection risk, ethical decisions about rationing resources among patients, and safety concerns for family members (49, 53). As a result, the concerned authority should pay particular attention and care to vaccinated HCWs from urban areas during this or future pandemics.

Our findings revealed that being married was a common risk factor for general health problems, depression, insomnia, and loneliness symptoms among vaccinated HCWs, which contradicts a recent national cross-sectional study involving 453,167 participants in the United States, which found that widowed, divorced, or separated people have a stronger association between SARS-CoV-2 vaccination and reduced depression and anxiety symptoms (46). However, our findings are in line with previous research, which found that being married is a common risk factor for adverse psychological outcomes (53, 59). However, in a recently published study of HCWs affected by the COVID-19 pandemic, married HCWs reported higher scores in vicarious traumatization symptoms than unmarried HCWs (60). It could be the reason for married HCWs having more occupational exhaustion and family responsibilities than unmarried HCWs.

The current study discovered that being a doctor is an independent risk factor for general health problems, depression, and anxiety symptoms among vaccinated HCWs, which was in agreement with prior studies that found doctors to be more vulnerable to COVID-19 (37, 61, 62). Similarly, in a study of 450 HCWs in Ethiopia, Angelo et al. (63) discovered that physicians were nearly fifteen times more likely than other HCWs to accept the COVID-19 vaccine. Prior studies also found that physicians were more likely than other HCWs to get COVID-19 vaccination (64, 65). It could be due to physicians having a better understanding of the coronavirus and its vaccine than the general public (66). Physicians may also have witnessed the disease's fatality, which may increase the likelihood that they will accept the COVID-19 vaccine.

The present study found that among unvaccinated HCWs, being 18–29 years old and working for <5 years were common risk factors for all psychological outcomes except anxiety and insomnia symptoms. These findings are expected. Because before the vaccination program worldwide there were many studies found that being 18-29 years old and have worked <5 years, HCWs were associated with higher psychological outcomes during the SARS outbreak (59), Avian influenza A (H7N9) virus outbreak (67), and COVID-19 epidemic (68). Moreover, Mohammed et al. (69) showed that in a survey of 614 Ethiopian healthcare practitioners, participants under the age of 30 were nearly five times more likely to be hesitant of being vaccinated than those over the age of 40. Furthermore, a Turkish study of 212 research assistants and 23 specialty physicians at Akdeniz University Hospital found that physicians who had worked for <5 years had lower vaccine uptake (70). These findings could be explained by the lack of a clinical study for any immunization and no evidence for reference about the COVID-19 vaccine's safety in Bangladesh. According to Mahmud et al. (71), 64.86% of people postpone immunization until the vaccine's efficacy and safety are established, or COVID-19 becomes more deadly in Bangladesh. It could be one of the reasons for vaccine apprehension, particularly among the young and those with little work experience. False rumors and misconceptions concerning

the COVID-19 vaccines must be dispelled, and individuals must be educated to the true scientific facts to boost vaccine acceptability among the younger generation and those with minimal job experience.

The present study demonstrated that participants who worked with a nurse were significantly more likely to suffer from symptoms of depression, anxiety, and stress among unvaccinated HCWs. This finding was supported by many other studies (72, 73). A systematic review of 33,062 HCWs, Pappa et al. (74) discovered that nurses have higher rates of psychological symptoms than other medical staff. It may be a fact that nurses are in charge of dealing with patients, performing more invasive procedures, and working for extended periods. This result also corresponds to other studies, which found that nurses were less likely than different working positions to be vaccinated (64, 65). According to Browne et al. (75), the prime causes for vaccine hesitancy among nurses were concerns about adverse effects, the novelty of the vaccine, and a lack of vaccine knowledge. To ensure the success of the national vaccination drive, tailored strategies and vaccine promotion campaigns aimed at nurses are required.

It was not surprising that respondents who worked as frontline workers and provided direct care to infected patients were a significantly higher chance of experiencing all psychological outcomes except anxiety and stress symptoms among unvaccinated HCWs. Many studies evaluated the traumatic effects of COVID-19 and revealed that frontline workers were reported higher symptoms of psychological consequences (68, 76). It could be due to a lack of antiviral materials, unpleasant feelings from patients, quarantine, and loss of communication with their families, all of which led to the poor psychological outcomes of frontline employees. Moreover, this conclusion contradicts recent studies (77) but it was aligned with Nguyen et al. (78), who reported a higher than anticipated rate of vaccine hesitancy among frontline HCWs. Furthermore, direct treatment to infected individuals was also connected to more unfavorable psychological outcomes during the SARS outbreak (5, 79), and the COVID-19 outbreak (76, 80). However, in a survey of 5,287 US healthcare workers, Shaw et al. (81) discovered that direct care providers and COVID-19 patient care providers had lower vaccine acceptability than others. They might want to hold off on analyzing more data until they can see how the vaccination impacts others and learn more about vaccine safety and effectiveness (64, 81). They are trusted and respected community members on public health issues. Their early-stage public acceptance and uptake of COVID-19 immunizations have the potential to affect public perceptions toward the vaccine. As a result, the COVID-19 vaccination should be accepted as soon as possible.

The present study suggests that respondents who were infected with COVID-19 had a significantly less chance of experiencing symptoms of general health problems, depression, and anxiety among unvaccinated HCWs. In contrast to our findings, a recent study done in Bangladesh by Rahman et al. (82) discovered that having positive COVID-19 test results were linked to higher psychological distress. Another study involving 283 HCWs in Saudi Arabia found that being positive for COVID-19 was not associated with an increase in depression and anxiety symptoms (83). However, our findings were consistent with a prior study involving 475 emergency HCWs in the United States, which discovered that those with a history of COVID-19 infection had lower vaccine intent (84). It could be because HCWs believe that natural infection has provided them with sufficient immunological protection against COVID-19, and thus vaccination will be ineffective. It is likely to be true in the short term. However, the risk of infection may increase with time since infection, given evidence concerning waning humoral immunity to COVID-19 and the short-lived immunity after infection with other coronaviruses (85). As a result, our novel findings could be beneficial to HCWs in those regards. However, this does not imply that they were knowingly infected with COVID-19. Whether or not they are infected, the current study suggests that they get vaccinated as soon as possible.

STRENGTHS AND LIMITATIONS

The following are some of the study's advantages: first, the first nationwide study in Bangladesh that has evaluated the factors associated with psychological outcomes among vaccinated and unvaccinated HCWs against COVID-19 infection. Second, this research discovered that fully vaccinated HCWs against COVID-19 infection had a significant positive impact on their mental health. Third, this study had a large sample size and included a variety of HCWs, allowing meaningful findings to be drawn. Finally, this research will add to our understanding of SARS-CoV-2 vaccination and mental health, as well as assist governments and policymakers in developing an effective vaccine campaign to achieve vaccination coverage and herd immunity among HCWs and the general public during the SARS-CoV-2 outbreak.

This study provides novel findings on psychological outcomes and associated factors among vaccinated and unvaccinated Bangladeshi HCWs against COVID-19 infection, but its limitations must not be overlooked. First, psychological outcomes were determined using a self-report tool and an online survey. Future research should include clinical interviews or qualitative studies to get a more complete picture of the problem. Second, this online survey used convenience and snowball sampling, excluding HCWs who do not have internet access. Although the findings of this study may not be representative of all Bangladeshi HCWs, this should not have influenced our conclusions about the risk factors. Third, it is impossible to estimate the response rate because it is unclear how many people received the survey link. Finally, this study did not consider influencing factors such as which developer's vaccine you received and taking any vaccine after the age of 18.

CONCLUSION

A lower prevalence of psychological outcomes was found among vaccinated HCWs against COVID-19 infection as well as risk factors for developing them. To control the infection and improve psychological outcomes, this study suggests emphasizing the vaccinated to unvaccinated HCWs as soon as possible. They also required special attention, health-related education, and psychological support.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Ethical Review Board (IERB) of the Holy Family Red Crescent Medical College and Hospital, Dhaka, Bangladesh (Approval No: IERB/36) and the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MA: conceptualization, methodology, formal analysis, and writing—original draft. MA, SP, and MM: data collection. MA, SP, MM, LN, and YX: writing—review, and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.852922/full#supplementary-material

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Adult Vaccination in the United Arab Emirates—A Physicians' Knowledge and Knowledge Sources Study

Hiba J. Barqawi[1], Kamel A. Samara[2], Mahmoud S. Hassan[3] and Firas B. Amawi[4]*

[1] Department of Clinical Sciences, College of Medicine, Sharjah, United Arab Emirates, [2] College of Medicine, University of Sharjah, Sharjah, United Arab Emirates, [3] University Hospitals Coventry and Warwickshire NHS Trust, Conventry, United Kingdom, [4] Dr. Sulaiman Al Habib Hospital, Dubai, United Arab Emirates

Background: A lack of knowledge on adult vaccination has been documented among physicians. They play a critical role in promoting adult vaccines. This study aimed to review the status of adult vaccination in the United Arab Emirates (UAE) and evaluate physicians' knowledge and knowledge sources regarding adult vaccines.

Methods: Local, regional, and global adult vaccination guidelines were reviewed. A 40-item questionnaire was used to collect data from physicians from June to October 2020, using convenience and snowball sampling. Knowledge score was calculated, and predictors identified using Mann–Whitney *U* and Kruskal–Wallis *H*-tests. Ordinary Least Squares regression was used for Multivariate Analysis.

Results: A total of 500 responses were included. A quarter were internists, and another quarter were family physicians. Fifty-seven percent were medical interns and residents. Both perceived and actual knowledge of adult vaccination were low. Bivariate analysis showed knowledge depending on department, level of training, workplace, and perceived knowledge. All remained significant after multivariable regression except workplace. International and local guidelines were the most common knowledge sources. Forty-two percent were unable to access the local guidelines.

Conclusions: Physicians' knowledge was poor and local guidelines were not clear or easily accessible. Participants were highly receptive to guidance and practice with adult vaccines.

Keywords: adult vaccination, United Arab Emirates (UAE), physician knowledge, adult immunization, vaccine preventable disease

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****Correspondence:***
Hiba J. Barqawi
hbarqawi@sharjah.ac.ae

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BACKGROUND

The World Health Organization's (WHO) third strategic objective aims to ensure that "the benefits of immunization are equitably extended to all people." To ensure this, immunization must be provided to all children, adolescents, and adults. In fact, life-course immunization is among the recommended actions for three of the six strategic objectives for attaining the WHO's Global Vaccine Action Plan 2011–2020 (1). However, there are many recognized barriers to adult vaccination, the most prominent and encapsulating being vaccine hesitancy. It is defined as the delay or refusal of vaccines despite availability and serves as a continuum between proponents and opponents of vaccination. Other barriers include a lack of public support for adult vaccination, complexity of adult vaccination schedules, and prioritization of infant vaccination programs (2).

Globally, the burden of vaccine preventable diseases (VPDs) and vaccine uptake rates have not been explored thoroughly in adults. In the United States of America (USA), VPDs in adults cost the healthcare system $9 billion every year (3). This number will only grow as the United Nations projects that between 2015 and 2030, the number of people in the world aged 60 years or older will grow by 56%, reaching a total of 1.4 billion people (4). Hence, many global organizations have called for increased focus on adult immunizations, particularly in the vulnerable aging population.

Healthcare providers (HCPs) play a critical role in fostering vaccine acceptance among those that are hesitant (5). Out of the six themes that influence the willingness to get immunized, five, including attitudes, beliefs, risk perception and health practices, involved physicians (6). Yet, HCPs have low awareness and leadership when it comes to adult vaccination, possibly due to a lack of training (2). In fact, a lack of knowledge, initiative, belief or pro-vaccination practices has been documented among physicians (5, 7–12).

Hence, there has been a newfound interest in evaluating physicians' knowledge regarding adult vaccines. Yet very few studies have looked at this in the Middle East and North Africa (MENA) region and even less locally. In the United Arab Emirates (UAE), vaccination has been an under-researched topic with only a few studies exploring specific vaccines, such as influenza or Human Papilloma Virus (HPV) (13–15). However, no studies have looked at physicians and their role in promoting general adult vaccination. The aims of this study were to (a) perform a desk review of the status of adult vaccination in the UAE and (b) undertake original research to evaluate physicians' knowledge and knowledge sources regarding adult vaccines.

METHODS

Adult Vaccination Guidelines Review

For the first aim of this study, a desk review of adult vaccination was performed by reviewing the guidelines for three countries, USA, Saudi Arabia (KSA), and UAE. For USA, the Centers for Disease Control and Prevention (CDC) guidelines were used (16). For KSA, the schedule published by the Ministry of Health was used (17). In the UAE, there are three main health authorities: the Dubai Health Authority (DHA), responsible for the Emirate of Dubai (3.4 million; 34.7% of the population), the Abu Dhabi Department of Health (DOH/HAAD/SEHA), responsible for the Emirate of Abu Dhabi (2.9 million; 29.6% of the population), and finally, the Ministry of Health and Prevention (MOHAP) focusing on the remaining Emirates (3.5 million; 35.7% of the population) (18–20). Out of the three health authorities, only the DHA had a full adult vaccination schedule (21). The DOH's and MOHAP's schedules did not touch upon routine adult immunization; they focused on the vaccines for high-risk groups (22). Given the aims of the study, the DHA's schedule was adopted as the prototype for the UAE.

Both the global and local guidelines regarding adult vaccination were reviewed, compiled, compared, and contrasted to highlight areas of deficit. Additionally, the guidelines were simplified and presented as a short schedule to help physicians quickly determine a patient's need for a vaccine.

Study Population

Thereafter, a cross-sectional, descriptive study was designed to collect original data from UAE physicians all over the country. It was conducted between the months of June and October 2020 using convenience and snowball sampling. Participants were approached through email, phone, WhatsApp, and other social media networks making use of contact details listed on the health authority websites. Any physician with at least 1 year of experience who is currently practicing in the UAE was eligible to participate. The minimum sample size needed was 385, assuming an expected prevalence of 50%, a margin of error of 5%, and 95% confidence. The number was increased by 20% to 460 to account for non-response. In total, 534 questionnaires were collected out of which 34 were excluded due to them not fulfilling the inclusion criteria.

Questionnaire Development

A 40-item questionnaire was developed after reviewing the adult vaccination literature and guidelines. Due to the COVID-19 pandemic, data was collected online. Google Forms was used, ensuring the user's privacy by not collecting any personal identifiers. The self-administered questionnaire consisted of two main sections: demographics and adult vaccination knowledge. It included 5-item Likert scales, true and false questions, as well as multiple-choice questions. The questions explored physicians' (a) perceived knowledge, (b) the vaccines they would recommend at different age groups, and (c) their knowledge sources and experience with local guidelines.

The questionnaire was pilot tested several times on different physicians; all provided feedback was evaluated and incorporated, if appropriate. This study was reviewed and approved by the Research Ethics Committee at the University of Sharjah (Reference Number: REC-20-04-09-01-S). It was conducted in accordance with all relevant guidelines and regulations. Informed consent was obtained from all participants.

Data Analysis

The data was exported from Google Forms and imported into Python 3.9 for analysis. Data cleaning and pre-processing was performed. A knowledge score was calculated by categorizing the adult vaccines into four main groups:

- Those that are always recommended, regardless of risk factors, previous exposure, or vaccination status.
- Those that are recommended unless previous exposure or vaccination is documented.
- Those that are recommended based on the patients' risk factors only.
- Those that are not routinely recommended.

Abbreviations: CDC, centers for disease control and prevention; DHA, Dubai health authority; DOH/HAAD/SEHA, department of health; HCP, healthcare provider; KSA, kingdom of Saudi Arabia; MENA, middle east and North Africa; MOHAP, ministry of health and prevention; SCD, shared clinical decision; UAE, United Arab Emirates; USA, United States of America; VPD, vaccine preventable diseases; WHO, World Health Organization.

For every vaccine that a participant recommended, 2 points were awarded if the vaccine is recommended for all healthy adults, or 1 point awarded if it is recommended for all healthy adults lacking immunity, or 1 point deducted if the vaccine is only indicated for specific risk factors or not routinely indicated. All the points were added to calculate the knowledge score. The maximum possible score was 31 while the minimum was −11.

For univariate analysis, the normality of the knowledge score was evaluated using both Q-Q plots and a Shapiro-Wilk test. All reported percentages were calculated by excluding the missing values. All demographic variables and perceived knowledge were evaluated as predictors for the knowledge score. Bivariate analyses were conducted to identify significant predictors using Mann–Whitney U and Kruskal–Wallis H-tests, the former for binary variables and the latter for those with more than two categories. The cut-off for significance was a $P < 0.05$.

All determinants were categorical and hence dummy coded except for perceived knowledge. Ordinary Least Squares regression was used. Heteroskedasticity was tested for using a Studentized Breusch-Pagan test. No outliers were detected. For the linear regression model, the minimum number of cases was met, which was calculated using $50 + 8m$, where m is the number of predictors. No interactions were explored. F score and R-squared values were calculated for the model. All P-values reported are two-sided and all confidence intervals are profile confidence intervals.

TABLE 1 | USA, KSA, and UAE adult vaccination schedules.

Vaccine	CDC	KSA	UAE (DHA)
Influenza I/R	Everyone	Everyone	Everyone
Influenza Live	<50 years	No info	Not available
Tdap	Everyone	Everyone	Everyone
MMR	NEI/PD	NEI/PD	NEI/PD
Varicella	NEI/PD	NEI/PD	NEI/PD
Zoste Recomb.*	≥50 years	≥50 years	Not indicated
Zoster Live*	≥60 years	≥50 years	≥60 years
HPV	19–26: routinely; 27–45: SCD	16–25:catch up	19–59: optional
PPSV	OIRF; ≥65 years routinely	≥65 years	≥65 years
PCV13	OIRF; ≥65 needs SCD	≥65 years	OIRF
Hepatitis B	OIRF	OIRF	OIRF
MCV4**	OIRF	OIRF	OIRF
MenB**	16–23 years based on SCD	No info	OIRF
Hepatitis A	OIRF	OIRF	OIRF
Hib	OIRF	OIRF	OIRF

**For Zoster, the KSA and UAE guidelines do not distinguish between the two types of vaccines.*

***For meningococcal vaccines, UAE adult vaccination guidelines did not distinguish between both types.*

For contraindications and dosing, please refer to original guidelines, links of which can be found in the references section. Influenza I/R, influenza inactivated/recombinant; Zoster recomb, zoster recombinant; NEI/PD, no evidence of immunity or previous disease; OIRF, other indication or risk factor.

RESULTS

Adult Vaccination Guidelines

Adult vaccines can be divided into two main groups: those recommended for the general adult population and those indicated for individuals with specific risk factors such as chronic lung or heart disease, diabetes, compromised immune system, travel, or high-risk occupations (16). **Table 1** shows the guidelines for the UAE, KSA, and USA. UAE guidelines use three age groups: 18–59, 60–64, and 65 or older. The KSA and CDC guidelines take a more granular approach and utilize five age groups: 18–26, 27–49, 50–59, 60–64, and 65 or older.

The three schedules' recommendations are aligned for influenza, Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap), Measles, Mumps, and Rubella (MMR), and varicella vaccines. For the pneumococcal vaccine, the CDC and UAE recommend Pneumococcal polysaccharide vaccine 23 (PPSV23) routinely while KSA recommends both PPSV23 and Pneumococcal conjugate vaccine (PCV13). As for the hepatitis B vaccine, the KSA guidelines routinely recommend it whereas the UAE and the CDC do not. Finally, for hepatitis A and Haemophilus influenzae type B (Hib), they were not discussed in the KSA guidelines and the UAE guidelines only indicated them for those with other risk factors.

Considering the unique healthcare system, demographic distribution and public health policies of the UAE, an outline of the recommended adult vaccines is presented in **Table 2**. It is adopted from the CDC's schedule, considering the regional and local meningococcal and hepatitis B guidelines. With regards to influenza, only the inactivated/recombinant vaccine was included for two reasons (a) the UAE's guidelines state that the live vaccine is not available (21) and (b) the CDC recommends it over the live one (16). Similarly, for the zoster vaccine, the recombinant was included given the CDC's recommendation.

Additional points and comments can be added to the schedule to make it more exhaustive; however, the goal was to present a simple yet accurate representation of the possible vaccinations at different age groups, serving as a quick reference sheet. While indications and risk factors are not highlighted, situations where a physician needs to probe further are indicated. However, still, a few comments are warranted:

- For meningococcal, it is important to vaccinate college students living in residential dorms and military recruits.
- For hepatitis A, while the guidelines recommend administering the vaccine based on indications, the importance of geographical area as an indication cannot be understated. Further studies should evaluate hepatitis A outbreaks in the country to delineate areas that require routine hepatitis A vaccination.

Adult Vaccination Knowledge Among UAE Physicians

Demographics

Table 3 presents the characteristics of the participating physicians. Two hundred and ninety-eight (59.6%) physicians were female with 370 (74%) aged 35 or under. A quarter of the participating physicians were internists and another quarter were family physicians. Medical interns and residents consisted of

TABLE 2 | Recommended adult vaccination schedule.

Vaccine	19–26 years	27–49 years	50–59 years	60–64 years	65 years and above
Influenza I/R	1 dose annually for adults				
Td/Tdap	1 dose of Td every 10 years with the first dose being Tdap for all adults				
MMR	1 or 2 doses if no evidence of immunity or previous disease				Not recommended
Varicella	2 doses if no evidence of immunity				
Zoster Recomb.	Not recommended		2 doses regardless of previous exposure		
HPV	2 or 3 doses	2 or 3 doses; based on SCD	Not recommended (age 45 and above)		
PPSV23*	1 or 2 doses if other indications or risk factors				1 dose for all adults
PCV-13	1 dose if other indications or risk factors				1 dose based on SCD
Hepatitis B	3 doses if no evidence of immunity				
MCV4	1 or 2 doses if other indications or risk factors				
Hepatitis A	2 or 3 doses if other indications or risk factors				
Hib	1 or 3 doses if other indications or risk factors				

**The total number of PPSV23 doses should be two; hence, it is not required to give a dose after the age of 65 if a patient has already received two. Additionally, the second dose should be at least 5 years from the last dose.*

The table is color-coded according to five levels of recommendation:

- *Routinely indicated for all healthy adults.*
- *Recommended if immunity is not shown.*
- *Recommended if there are other risk factors or indications.*
- *Requires shared clinical decision making.*
- *Not recommended.*

Evidence of immunity entails either a written documentation of vaccine administration or laboratory evidence of immunity or disease. SCD (Shared Clinical Decision) recommendations are not for everyone but based on a discussion between the healthcare provider and the patient. Note that some vaccines have contraindications, such as an egg allergy with the influenza vaccine. Refer to CDC guidelines for an exhaustive list of contraindications and dosing instructions. Influenza I/R, influenza inactivated/recombinant; zoster recomb, zoster recombinant.

TABLE 3 | Participant demographics, bivariate analyses, and average knowledge for each group.

Feature	*n* (%)	Result/Score†	Feature	*n* (%)	Result/Score†
Sex (*N* = 500)		MWU; P=0.313	**Level of Training (N=500)**		KW; $P = 0.029$*
Female	298 (59.6%)	9.641	Intern house officer	134 (26.8%)	9.627
Male	202 (40.4%)	9.213	Resident	153 (30.6%)	9.353
Age (*N* = 500)		KW; $P = 0.222$	General practitioner	82 (16.4%)	9.378
≤ 25 years	183 (36.6%)	9.235	Specialist	53 (10.6%)	7.953
≥ 26 years but ≤ 35 years	187 (37.4%)	9.086	Senior specialist	18 (3.6%)	7.639
≥ 36 years but ≤ 45 years	54 (10.8%)	10.843	Consultant	60 (12.0%)	11.417
≥ 46 years	76 (15.2%)	9.993	**Workplace (N=500)**		KW; $P = 0.006$*
Citizenship (*N* = 500)		KW; $P = 0.690$	Government hospital	356 (71.2%)	9.058
Other Arab	304 (60.8%)	9.457	Private clinic/hospital	90 (18.0%)	9.939
Local (Emirati)	115 (23.0%)	9.117	Primary healthcare	54 (10.8%)	11.389
Non-Arab	81 (16.2%)	10.006	**Patients seen in a week (*N* = 500)**		KW; $P = 0.092$
Department (*N* = 364)		KW; $P < 0.0005$*	1–19	110 (22.0%)	8.573
Internal medicine	88 (24.2%)	10.023	20–49	210 (42.0%)	9.407
Family medicine	86 (23.6%)	11.424	50 and above	180 (36.0%)	10.086
Pediatrics	42 (11.5%)	9.345	**Perceived knowledge (*N* = 500)**		KW; $P < 0.0005$*
Others	148 (40.7%)	7.851	Not at all	35 (7.0%)	5.129
Health Authority (*N* = 498)		KW; $P = 0.154$	I know a few	133 (26.6%)	8.075
MOHAP	184 (36.9%)	8.916	I know the important ones	210 (42.0%)	9.817
DHA	161 (32.3%)	9.839	I know most of them	98 (19.6%)	11.724
DOH/ HAAD/ SEHA	153 (30.7%)	9.85	I know all of them	24 (4.8%)	11.25

†For categories (such as Health Authority), this column presents the results of the bivariate test; for possible values, this column presents the average knowledge score. Note that two physicians did not specify a health authority and hence were regarded and treated as missing. All medical interns were not assigned a department. All significant P-values have asterisks after them.

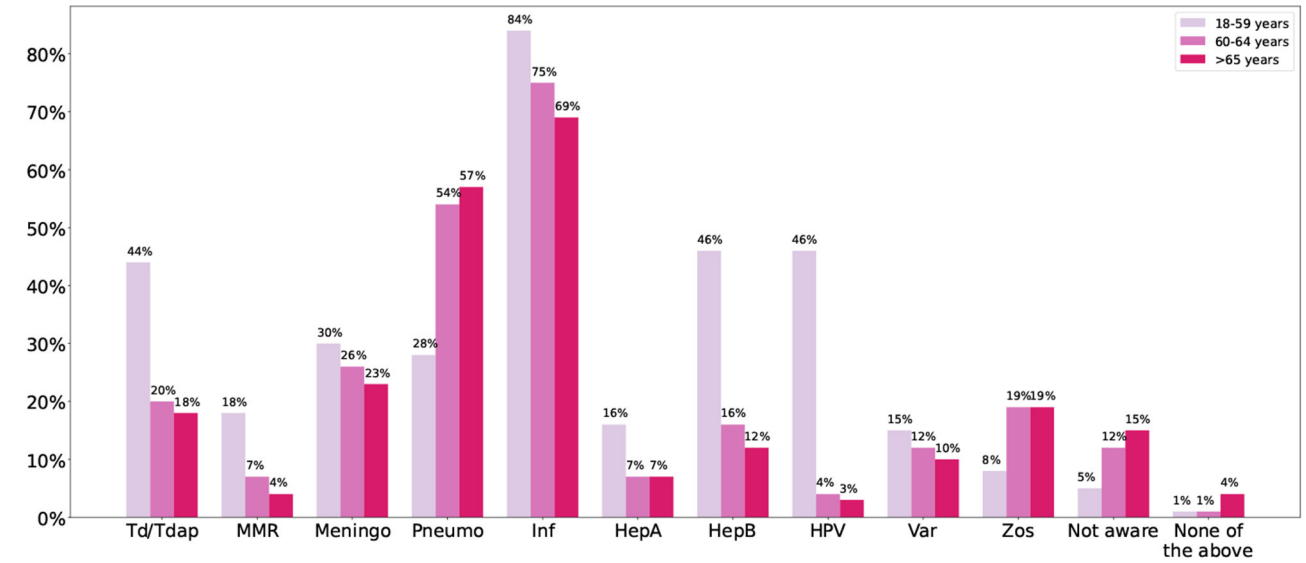

FIGURE 1 | The figure shows the percentage of physicians that would recommend each vaccine for the different age groups. Meningo, meningococcal; Pneumo, pneumococcal; Inf, influenza; HepA, hepatitis A; HepB, hepatitis B; Var, varicella; Zos, zoster.

57% of the participants with the rest being split between general practitioners, specialists, and consultants. Seventy percent of the participants were employed at a governmental hospital. The doctors were equally split among the three health authorities in the country.

Both perceived and actual knowledge were low. Less than 25% of physicians believed they knew most or all the adult vaccines. **Figure 1** shows the vaccines physicians would recommend for different age groups. The most recommended vaccine was influenza. For all the vaccines except pneumococcal and zoster, the recommendation rate decreased as the age increased. When it came to Td/Tdap, only half of the participants would recommend it to any age group. As for adults aged 65 or older, 69% would recommend the influenza vaccine, only 57% would recommend the pneumococcal vaccine, and <20% would recommend the zoster vaccine. Sixty-one percent stated they knew the difference between the Td and Tdap vaccines but only 34% when it came to the zoster and varicella vaccines.

A knowledge score was calculated, and data analysis pursued as discussed in the methodology section. Both Shapiro–Wilk and the Q-Q plots indicated a lack of normality (Shapiro–Wilk *P*-value was <0.0005) and hence non-parametric methods were used to evaluate association between the knowledge determinants and the knowledge score. The maximum attained score was 25. The average score for all physicians was 9.5, with a standard deviation of 5.5. **Table 3** presents the average knowledge score among the different demographic groups.

All demographic features were used as determinants of knowledge along with the number of patients seen each week and the perceived adult vaccination knowledge. Sex, age, citizenship, health authority, and the number of patients seen each week were not found to be associated with the knowledge score. Department, level of training, workplace, and perceived knowledge were fed into a multivariate linear regression model. A Breusch-Pagan test yielded a *P*-value of 0.091, indicating a lack of enough evidence for the presence of heteroskedasticity. The results of the model are shown in **Table 4**. All variables were significant except for workplace.

The model showed that family physicians and internists were more knowledgeable compared to other physicians ($P = 0.001$; $P = 0.022$, respectively), but pediatricians were not. However, there was no significant difference between internists and family physicians. Only residents and consultants showed more knowledge compared to medical interns ($P = 0.001$; $P < 0.0005$, respectively). Workplace showed no significant effect on the level of knowledge. Finally, better perceived knowledge is a significant predictor of better actual knowledge ($P < 0.0005$).

Knowledge Sources

Figure 2 shows the sources of knowledge on adult vaccines chosen by the physicians. Both international and local guidelines were the most common at 72%. Half of the participants also depended on their medical experience with the vaccines. Difficulties physicians faced with the local vaccination schedule are shown in **Figure 3**. Only 37% stated they faced no difficulties with finding or utilizing the guidelines. Several deficits were highlighted with 42% being unable to easily locate the guidelines and another 15% having issues with the clarity and content. Finally, 87% stated they would be interested in additional guidelines and training on adult vaccination.

DISCUSSION

Adult Vaccination: The Global and Local Landscape

Adult vaccination is yet to achieve the same level of success that childhood vaccination has. Many organizations have looked at ways to improve adult vaccine uptake rates through a variety

TABLE 4 | Adult vaccination knowledge—multiple linear regression (ordinary least squares).

Model terms		β-coefficient	RSE	t-Statistic	*P*-value	2.5%	97.5%
Intercept (β_0)		4.347	0.606	7.178	**< 0.0005**	3.156	5.538
Department **(P=0.0005)**	Others	–	–	–	–	–	–
	Family Medicine	**2.991**	**0.921**	**3.247**	**0.001**	**1.179**	**4.802**
	Internal Medicine	**1.593**	**0.691**	**2.305**	**0.022**	**0.234**	**2.951**
	Pediatrics	1.162	0.907	1.282	0.201	-0.621	2.945
Workplace **(P=0.006)**	Government Hospital	–	–	–	–	–	–
	Primary Healthcare	0.489	1.012	0.483	0.629	−1.501	2.479
	Private Clinic/ Hospital	1.089	0.727	1.499	0.135	-0.34	2.518
Training **(P=0.029)**	Intern House Officer	–	–	–	–	–	–
	Resident	**1.601**	**0.471**	**3.398**	**0.001**	**0.674**	**2.527**
	General Practitioner	0.042	0.623	0.068	0.946	-1.183	1.267
	Specialist	−0.007	0.649	−0.01	0.992	−1.283	1.269
	Senior Specialist	−0.41	1.047	−0.391	0.696	−2.469	1.649
	Consultant	**3.121**	**0.633**	**4.931**	**<0.0005**	**1.876**	**4.366**
Perceived Knowledge (*P* < 0.0005)		**1.227**	**0.283**	**4.329**	**< 0.0005**	**0.669**	**1.784**
R-squared: 15.8%	Adjusted R-squared: 13.4%		**$F_{(10,353)}$ = 6.602; (*P* < 0.0005)**				

Table shows the results of the Multivariate regression. Determinants of the knowledge score were fed into an Ordinary Least Squares Regression. Significant P-values are presented in bold.

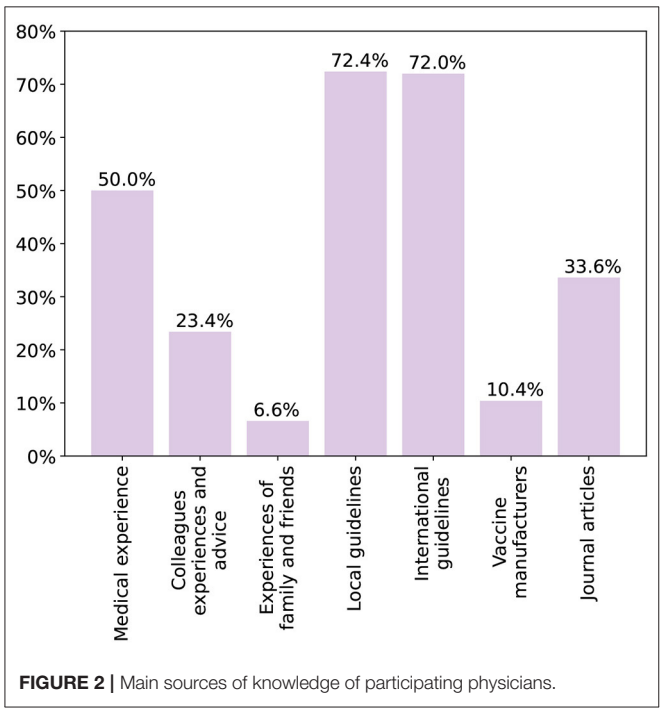

FIGURE 2 | Main sources of knowledge of participating physicians.

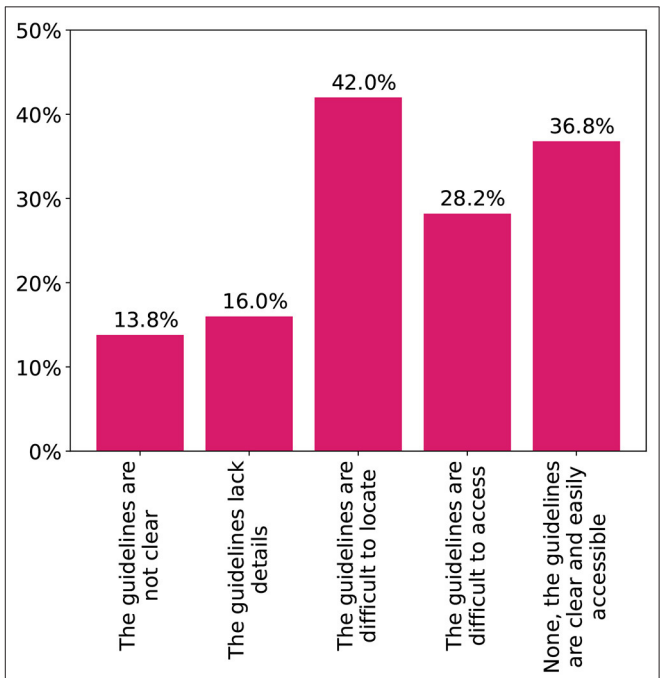

FIGURE 3 | Difficulties participating physicians faced with the local adult vaccination guidelines.

of different frameworks, actions, policies, recommendations, and programs. Yet, its rates remain dismally low locally, regionally, and even globally. In the USA, the rates of adult vaccine coverage in the community are low across the board with the highest uptake rate being for influenza at 44.8% (23). Data from the European Union presents an equally gloomy picture, with eight countries having elderly influenza vaccination rates

of <50% and reaching as low as 4.3% (24). Moreover, out of 31 surveyed advanced economies, only 12 had a comprehensive adult vaccination schedule, with most recommendations geared toward older vaccines such as influenza and hepatitis B (25). As for the MENA region, data and research regarding adult vaccination is severely lacking. Influenza vaccination rates are dismally low in most countries, including the UAE and even among high-risk groups (26). Reasons for the low rates were plentiful, from negative media coverage and fear of side effects to low recommendations by physicians (7).

VPD monitoring and seroprevalence studies in the UAE are very scarce and most do not focus on adults. However, Abu Dhabi releases a quarterly communicable disease bulletin detailing the number of notified cases in the last three months; the latest of which (covering the second quarter of 2019) showed among adults aged 25 and above: 862 cases of chickenpox, 320 cases of hepatitis B, 1,756 cases of influenza, and an average of 25 cases for each of measles, mumps, and rubella (27). The yearly numbers can reach as high as ten times, given that this data represents the number of cases for a third of the population and only for a quarter of the year. Even more worryingly is the expected increased burden due to a rapidly aging population. In 2015, only 2.3% of the UAE's population was aged 60 years or older, compared to the West, where they represented more than a fifth of the population in most countries (4). However, the UAE's elderly population is expected to increase more than five-folds in 2030, reaching 11.3%, with some models predicting it as high as 14.3%. Hence, the effects of poor adult vaccine uptake rates have been masked by a young population, though not for long. As for vaccination studies, those are not extensive and deal with either specific vaccines or specific age groups; however, their results still show a lack of vaccine uptake and a high level of disease susceptibility (13–15).

The UAE's national agenda specifies a wide-ranging work program centered around six national priorities, the fourth of which is a "world-class healthcare" (28). Prevention would be an important pillar in such a healthcare system. Not only is this a fundamental component of a healthy good life, but it is also important as improved health leads to higher workforce participation and productivity. Hence, in any country, the goal is to integrate immunization into the healthcare system as a long-term sustainable service.

Adult Vaccination and Physicians

In this study, the adult vaccination guidelines in the UAE were examined and compared to those in KSA and USA and the knowledge levels of UAE physicians were explored. The UAE guidelines for adult vaccination were found to be dated, unclear and not easily accessible. The guidelines additionally lacked extensive details regarding dosing, indications, and contraindications compared to the CDC's. The results also showed that physicians' knowledge of adult vaccines is lacking with most physicians being aware of this. Many were unable to recognize the vaccines recommended at every age group. Even the elderly vaccination schedule was not well-recognized, with a worryingly low number of physicians recommending the pneumococcal and influenza vaccines, the most fundamental for that age group. Future studies would have to establish whether the lower recommendation rates for the elderly stem from a lack of knowledge or a fear of side-effects in that vulnerable age group.

Very few studies have looked at adult vaccine knowledge in the region. However, AlMansoori et al. explored HPV vaccine knowledge in Al Ain city, UAE. Most knowledge questions were answered incorrectly by more than 40% of the participants and the HPV vaccination schedule was incorrectly recalled by more than 80% (29). In KSA, it was found that around three-quarters of physicians had poor knowledge regarding adult vaccines. The most cited reasons for the low adult vaccination rates were time constraints and a lack of up-to-date records (30).

Knowledge Sources

Healthcare professionals teaching and training programs usually assume that physicians would readily understand, support, and promote vaccination to the general population (31). Yet, it has been found that some HCPs access vaccine-questioning information online that can influence their confidence in vaccines (32). Social media platforms, which have been used to spread such information, can and have exacerbated vaccine confidence crises through negative campaigns, amplifying any existing anxieties (32).

In this study, most physicians reported depending on international and local guidelines with half also utilizing their medical experience. Similarly, a study among German Family Physicians found that 89.5% relied on STIKO, the German Standing Committee on Vaccination, as a primary source of information (33). However, in this study, most participants faced issues with the availability or clarity of the local guidelines. Confusion regarding the immunization schedule may lead to missed vaccination opportunities and reduce the effectiveness of the programs nationally. Moreover, nearly all participants were interested in additional training and guidelines for adult vaccination. Hence, the adult vaccine schedule should be reviewed and made easily accessible.

Promoting Vaccination

The importance of physicians in promoting adult vaccination cannot be understated. Patients have been consistently found to believe they do not qualify for vaccines, either due to not being in a high-risk group or having never been offered any vaccines (32). Physicians play an important role as both a source of information for patients and a promoter of vaccines. In the USA, the National Health Interview Survey found that vaccination coverage was higher among adults who had visited one or more physicians in the last year (23). When adult patients across Europe were questioned about their vaccination information sources, 65% reported physicians (31). Similarly, a physician's recommendation of a vaccine is vitally important, with multiple international studies linking it with better attitudes and practices toward adult vaccines (8, 12, 34, 35).

Barriers

There are deficiencies in the way doctors approach adult vaccination. Hurley et al. (9) found that doctors are prioritizing some vaccines over others and ranking vaccination below other

preventative services. A quarter of American adults visited a physician that did not recommend the influenza vaccine, even though such a recommendation is associated with higher uptake (36). Locally, Rabei et al. (37) found that one out of every five parents in Al Ain community did not receive enough information regarding vaccination from physicians. Even more worryingly, Verger et al. (5) found that some physicians have stated a lack of confidence in the health authorities, expressed doubts regarding the safety of vaccines, or were not convinced of their utility. This highlights the rise of vaccine hesitancy among the front lines of medicine. Other major barriers of adult vaccination include an undervaluation of adult immunization (especially with misinformation perpetuated by anti-vaccination movements), and an inadequate infrastructure and cost system to support and improve access to adult vaccines (38). Finally, the importance of incorporating adult vaccination knowledge into medical school curricula cannot be understated, with future studies needed to evaluate the current status and any pitfalls.

Recommendations

Improving adult vaccination rates will require innovative solutions and a collective effort from both physicians and the community, most importantly, a shift from a passive immunization strategy to an active one. The local adult vaccination schedule needs to be updated and made more accessible to physicians. Physicians need to be informed regarding the availability and effectiveness of adult vaccines. Bach et al. found that provider education is an important step in promoting vaccines, with training being associated with higher vaccine delivery rates and increased vaccine championship (8). Additionally, there would need to be a unified plan across the country with clearly defined and publicly accepted vaccination goals. For this, there must be annual monitoring for adult vaccine uptake rates.

There should be increased patient engagement and education. Tan outlined some of the strategies to improve adult vaccination coverage which include (39):

1. Establishing the value of adult vaccines in the eyes of the public, policy makers, and healthcare professionals.
2. Improving access to recommended adult vaccines through stronger infrastructure and developing public-private partnerships to facilitate effective immunization behaviors.
3. Ensuring fair and appropriate compensation or subsidies for adult vaccines.

These strategies could focus on the patient-side or the provider-side, incorporating both the healthcare workers and regulatory bodies. A lot of work has been done to evaluate the effectiveness and utility of these techniques by global organizations such as the United States Community Preventive Services Task Force, the CDC's Quality Improvement Projects Targeting Immunization, and the National Vaccine Advisory Committee. Each aims to bring about improvements in adult vaccination rates through many new technologies like Reminder & Recall systems. While these associations focus on the American populace, their results may help outline how to improve adult vaccination locally. However, this again requires a local workforce responsible for implementing, measuring, and reporting on the effectiveness of these techniques locally.

Furthermore, the cost-effectiveness of adult vaccination is essential for it to thrive. A systematic review showed the majority of published studies reporting favorable cost-effectiveness profiles across the different age groups and medical conditions (40). However, given the different structure of the healthcare system in the UAE and demographic distribution, further studies would have to ensure these positive gains will hold for the country. Finally, the UAE's overall adult vaccination strategy also needs to be addressed. Any policy shifts can bring changes in the health system and improve health service delivery. Hence, future studies should aim to interview policy makers and outline the feasibility of such changes and any barriers.

Validity

It is important to highlight the possible limitations of any research. This study depended on what physicians reported without any independent verification. Moreover, convenience and snowball sampling were used, yet care was taken to ensure responses were equally distributed among the three major health authorities in the country. No information was collected regarding the dosing that physicians would use. Additionally, as with all surveys, social desirability, and recall and response bias are possible. However, the survey being completely anonymous without any personal identifiers hints at the responses being authentic.

CONCLUSIONS

Adult vaccination is a fledgling practice in the UAE that requires support, growth, and innovation. The burden of VPDs among adults is expected to increase. Physician's knowledge regarding adult vaccines is poor and the local guidelines are not clear or easily accessible. Physicians are highly receptive to more guidance and practice with adult vaccines. The local schedule needs to be updated and unified across the nation and physicians need be empowered and encouraged to promote adult vaccination. A local taskforce needs to be established to measure vaccine uptake rates, establish targets, and evaluate progress.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Sharjah-Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HB: conceptualization, methodology, validation, data curation, writing—original draft preparation, writing—review and

editing, visualization, and supervision. KS: conceptualization, methodology, validation, data curation, software, formal analysis, writing—original draft preparation, writing—review and editing, and visualization. MH: conceptualization, methodology, validation, data curation, writing—original draft preparation, writing—review, and editing. FA: methodology, validation, data curation, writing—review, and editing. All authors have read and agreed to the published version of the manuscript.

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Contrasting Association Between COVID-19 Vaccine Hesitancy and Mental Health Status in India and Saudi Arabia—A Preliminary Evidence Collected During the Second Wave of COVID-19 Pandemic

Saikarthik Jayakumar[1,2], Saraswathi Ilango[3], Senthil Kumar K.[3], Abdullah Alassaf[4], Abdullah Aljabr[2], Anand Paramasivam[1,2], Suresh Mickeymaray[5], Yazeed Mohammed Hawsah[6] and Ahmed Saad Aldawish[6]*

[1] Department of Basic Medical Sciences, College of Dentistry, Majmaah University, Al Majma'ah, Saudi Arabia, [2] Department of Medical Education, College of Dentistry, Majmaah University, Al Majma'ah, Saudi Arabia, [3] Department of Physiology, Madha Medical College and Research Institute, Chennai, India, [4] Department of Preventive Dental Science, College of Dentistry, Majmaah University, Al Majma'ah, Saudi Arabia, [5] Department of Biology, College of Science, Majmaah University, Al Majma'ah, Saudi Arabia, [6] College of Dentistry, Majmaah University, Al Majma'ah, Saudi Arabia

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***Correspondence:**
Saraswathi Ilango
saraswathiddentistt@gmail.com

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Background: Vaccine hesitancy is a global public health threat. Understanding the role of psychological factors in vaccine hesitancy is often neglected and relatively less explored.

Aim and Objectives: To analyze the relationship between mental health and COVID-19 vaccine hesitancy before and after the advent of COVID-19 vaccines (AC19V) in the general population of India and Saudi Arabia (KSA) which vary in severity of the pandemic and vaccine mandates.

Materials and Methods: A total of 677 adult participants from India and KSA participated in this cross-sectional online web-based survey. Sociodemographic details and current COVID-19 status pertaining to infection and vaccination were collected. Depression, anxiety, post-traumatic stress disorder (PTSD) symptoms, and perceptive need for mental health support (MHS) were assessed before and after AC19V. A newly constructed and validated COVID19 vaccine hesitancy scale-12 (COVID19-VHS12) scale was used to evaluate the COVID-19 vaccine hesitancy.

Results: Prevalence and levels of depression and anxiety symptoms decreased significantly in Saudis but not in Indians after AC19V. PTSD symptoms showed a significant reduction in both India and KSA. Anxiety symptoms were higher in KSA than India before AC19V while PTSD was higher in India before and after AC19V. Except for the place of residence and employment status, the subgroups of sociodemographic variables which were at higher risk of negative mental health before AC19V showed improvement in their mental health after AC19V. The prevalence of COVID-19 vaccine

hesitancy in India and KSA was 50.8% (95% CI 45.73–55.89%) and 55.7% (95% CI 50.16–61.31%), respectively. A bidirectional association between vaccine hesitancy and mental health was observed in KSA but not in India. Higher vaccine hesitancy favored higher levels of depression, anxiety, and perceptive need for MHS and vice versa in KSA. None of the mental health parameters predicted vaccine hesitancy in India, while higher vaccine hesitancy increased the risk of anxiety.

Conclusion: Vaccine hesitancy has a negative impact on mental health and vice versa over and above the impact of sociodemographic factors and COVID-19 vaccination and infection status which shows variations between India and KSA.

Keywords: vaccine hesitancy, COVID-19 vaccine hesitancy scale, COVID-19 vaccines, mental health, depression, anxiety, PTSD, mental health support

INTRODUCTION

As of 1st December 2020, globally, there were 61.8 million reported cases of COVID-19 and 1.4 million deaths since the start of the pandemic (1). On 2nd December 2020, the United Kingdom's Medicine and Healthcare products regulatory agency (MHPRA) approved the world's first vaccine against COVID-19, Pfizer-BioN Tech Vaccine, on a temporary emergency basis (2). The center for disease control and prevention (CDC) has stated that the number of new cases and deaths due to COVID-19 was much lower among vaccinated population, especially among the elder population (3). The World health organization (WHO) has also urged people across the globe to get vaccinated, although cautioning that the vaccine is not 100% effective (4).

Despite the benefits of vaccines, WHO has warned against vaccine mandates unless all the options available are exhausted. However, with the spread of the highly contagious delta variant of SARS-CoV-2, some countries executed stringent measures to improve the vaccine rate in their population. Countries like Austria, France, Germany, Italy, Morocco, Canada, United States, and United Kingdom have declared COVID-19 vaccines mandates ranging from permission for allowing access to malls, bars, public, and private establishments to mandating for selected sectors of the population (5). Saudi Arabia has rigid COVID-19 vaccine rules. On 18th May 2021, the Ministry of Interior (MOI) of Saudi Arabia announced vaccine mandates starting from 1st August 2020, for entering all governmental and private educational facilities, establishments, entertainment and sporting events, and public transportation (6). These mandates have resulted in a rise in vaccine rates, a fall in COVID-19 cases, and a rise in workplace visits based on Google mobility data (7). On the other hand, many countries are not keen on vaccine mandates. In India, the ministry of family welfare and health had explicitly stated that getting vaccinated against COVID-19 is voluntary (8). While there have been reports of coercive vaccination by local authorities and employers, the principal reasons behind the delay in achieving desired vaccine rates are vaccine hesitancy and lack of availability and access to vaccines (9). The severity of the pandemic varies between India and Saudi Arabia. Currently, India is the second worst hit country due to COVID-19 only behind the United States. As of 27th February 2022, the total number of SARS-CoV-2 infected cases was 42.9 million, with 514,000 deaths (10). At the same date, Saudi Arabia has reported 744,000 positive cases and 8,994 deaths (10). At the time of manuscript preparation, about 72.3% and 61.1% of the Indian population and 75.7% and 70.9% of the total Saudi population have taken the first dose and second doses of COVID-19 vaccine, respectively (11).

Regardless of the evidence of improved public health to infectious disease, vaccine hesitancy has been a significant area of attention and concern (12). In 2019, the WHO stated that vaccine hesitancy is one of the top 10 global threats to public health (13). It is the tendency of delay in acceptance or refusal to get vaccinated despite the availability of vaccines. As vaccine hesitancy involves many factors, addressing them is not an easy task. Geography, culture, socioeconomic status (14), and behavioral factors such as complacency, confidence, and convenience (15) have been linked to vaccine hesitancy. Globally only a handful of countries have been reported to have no vaccine hesitancy (7/194) (16). Irrespective of economic status, vaccine hesitancy has been noted in mass vaccination campaigns across low-, middle-, and high-income countries (17–19). Recent studies have shown that COVID-19 vaccine hesitancy is highest among the Middle East and North African countries, Europe and Central Asia, Western and Central Africa (20). Among African countries, Cameroon, Senegal, and Liberia had the highest vaccine hesitancy due to lower trust in manufacturing companies (21, 22). Studies in Asia pacific region revealed that Hong Kong, Japan, and Taiwan had higher rates of hesitancy to get vaccinated against COVID-19 (23–25). Mistrust on healthcare providers was the reason behind high vaccine hesitancy amongst Western Europe and Central Asia (26). Urrunaga-Pastor et al. studies have shown that the vaccine acceptance rates were higher in Latin American and Caribbean countries (27). With the exception of Israel and the United Arab Emirates, vaccine hesitancy is very high among the MENA countries (28). Geospatial disparity and low trust were common reasons for higher vaccine hesitancy in the United States and Central Europe (29–31).

Vaccine hesitancy has many reasons, the most common reason is risk-benefit evidence (less than 25%). This was linked with safety concerns and fear of side effects due to the vaccine (32). Understanding the role of psychological factors in vaccine hesitancy is often underplayed and needs to be explored

(33). Globally, very few studies have identified the effect of mental health on vaccine hesitancy. There has been evidence of inconsistent results about the association between mental health status and willingness to get vaccinated. Earlier studies assessing vaccine hesitancy have demonstrated that poor mental health is associated with higher vaccine acceptance toward influenza vaccines (34, 35). In studies conducted assessing the relation of mental health with COVID-19 vaccine hesitancy there were conflicting results across countries (36–38). At the time of the manuscript preparation (18th April, 2022), to our knowledge there were no studies that evaluated the impact of mental health on vaccine hesitancy in India and Saudi Arabia population. Both these countries have been reported to have poor sleep quality and psychological distress during the COVID-19 pandemic (39, 40). Such vulnerable subgroups needed to be prioritized in getting vaccinated (41) just like those with co-morbidities like diabetes mellitus and hypertension.

We hypothesized that with the advent of COVID-19 vaccines, the psychological distress experienced by the public would be eased. However, including the impact of vaccine hesitancy on mental health and vice versa called for ambiguity. Hence, we decided to study the mutual impact of vaccine hesitancy on mental health, if any, in relation to the advent of COVID-19 vaccines. To our knowledge, this is the first study to analyze the relationship between mental health and vaccine hesitancy before and after the advent of COVID-19 vaccines in the general population of India and Saudi Arabia. We also intend to compare the effect of various factors affecting vaccine hesitancy and the influence of mental health. In addition, we also decided to compare the results between India and Saudi Arabia, two countries that are both Asian countries but vary in terms of ethnicity, culture, religion, government type, per capita income, healthcare in addition to the severity of the pandemic and vaccine mandates.

MATERIALS AND METHODS

Study Design

The study was conducted using a cross-sectional design in India and Saudi Arabia. The study was conducted following STROBE guidelines for cross-sectional study (**Figure 1**) (42). Data were collected from 2nd to 16th June 2021, using Computer Assisted Web Interviews by snowball sampling technique. The Google form link was distributed through WhatsApp to all potential participants, and the link was also posted on the Facebook wall, the WhatsApp status, and the twitter handle of all authors in this study. Only those above 18 years and citizens of India and Saudi Arabia residing in their respective countries were asked to participate in the survey. Those who spent lesser than 10 min to fill the survey forms, those with a history of mental health disorders and chronic diseases were excluded from the study.

Sample Size

Employing the method by R Hill (43), as a rule of thumb, the minimal sample size should be at least ten times higher than the number of variables in the study (43). The present study has a total of 18 variables, and so the minimal sample size that would be needed for the study is around 180. We calculated the minimum sample size required for the study using an online sample size calculation tool.[1] With precision at 5%, level of confidence at 95%, and considering the prevalence of COVID-19 vaccine hesitancy in India and Saudi Arabia to be 23% (44) and 24.55% (45), respectively, the minimum sample size was calculated to be 285 and 273, respectively. Considering a non-response rate of 10%, the final sample size needed was 313 and 300 for India and Saudi Arabia, respectively. We collected 412 responses from India and 391 responses from Saudi Arabia. 40 responses from India and 86 responses from Saudi Arabia were not eligible as they did not meet the inclusion criteria. The final working sample size of the study was 372 in India and 305 in Saudi Arabia (**Figure 1**).

Survey Instrument

The survey questionnaire included six sections. The first section described the purpose of the study, ethical approval details, willingness to participate, data anonymity and data confidentiality. Once the participants agreed, the questionnaire moved to section "II." All the questions in the survey were mandatory to be filled. However, the participants were free to exit the survey as and when they pleased. No incentives or rewards in any form were offered for participation. Section "II" collected sociodemographic details such as age, gender, educational qualification, monthly income, place of residence (urban/rural), marital status, occupational status (healthcare/non-healthcare professional). Any known history of chronic health conditions and mental health disorders were also collected.

Section "III" included details pertaining to current COVID-19 status regarding infection and vaccination. The items were whether tested positive for COVID-19 (Yes/No), the present status of COVID-19 vaccination (Yes-1st dose/Yes-2nd dose/No), whether the participants think COVID-19 vaccine is beneficial (Yes/No), whether the participants developed active COVID-19 after vaccination (Yes/No/I don't know).

Section "IV" comprised of questions related to the hesitancy of the participants toward getting vaccinated for COVID-19, which was collected using a self-administered COVID-19 vaccine hesitancy scale made of 12 items (described below). Sections "V" and "VI" assessed the mental health status of the participants using the screening tools, Patient health questionnaire-2 (PHQ-2), Generalized Anxiety Disorder-2 item (GAD-2), Impact of Event Scale-6 (IES-6), and a single item for the perceptive need for mental health support (MHS). In section "V," the participants were asked, "before December 2020, how often were you bothered by the following problems." In section "VI" the participants were asked "When filling this survey, how often in the last 2 weeks, were you bothered by the following problems." Sections "V" and "VI" screened for the symptoms of depression, anxiety, PTSD, and perceptive need for MHS before and after the advent of the COVID-19 vaccine (AC19V), respectively.

[1] http://sampsize.sourceforge.net/iface/

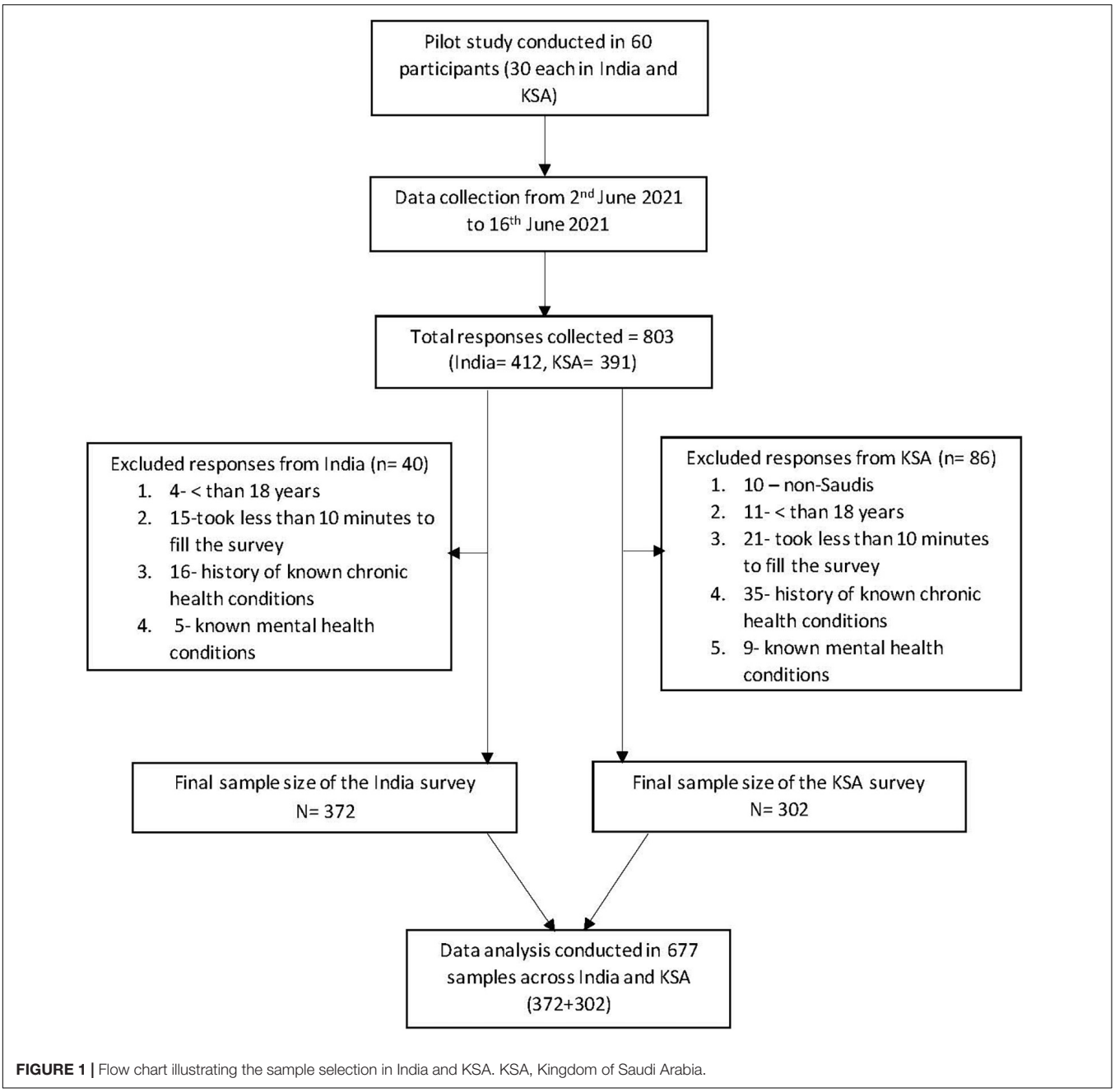

FIGURE 1 | Flow chart illustrating the sample selection in India and KSA. KSA, Kingdom of Saudi Arabia.

The questionnaire used in India were deployed in English. For the study in Saudi Arabia, all the questions were translated into Arabic. The translated version was again retranslated to English to check for clarity of the questions. This translation-retranslation was done by a native Arabic speaker proficient in both English and Arabic (46). A pilot study was conducted prior to the primary survey, in 60 participants with 30 each in India and Saudi Arabia, to check for face validity and average duration to fill the questionnaire. Feedback was collected from the participants, and necessary modifications in the form of simplification of phrasing and vocabulary were made to improve the clarity and simplicity of the questionnaire.

Development of COVID-19 Vaccine Hesitancy Scale-12 Items and Psychometric Analysis

The COVID-19 vaccine hesitancy scale used in the present study was adopted from multiple studies conducted earlier (47–51). The items included were created after extensive literature review, discussion with local experts and peers. Since negative information, personal and family circumstances, and fear can contribute to decision making, negative items were added to the scale (52). Such items were scored on a Likert scale ranging from 1- highly disagree to 5- highly agree. Positive items were constructed and were reverse coded to measure confidence and trust on vaccines. A mix of both positive and negative questions

removes response bias from the participants and improves the reliability of the results obtained (53).

Identification of Latent Variables Using Exploratory Factor Analysis

The 12 items of the COVID-19 vaccine hesitancy scale-12 (COVID19-VHS12) scale were analyzed using exploratory factor analysis (EFA) to identify the latent variables using principal component analysis with varimax rotation. The extracted factors were analyzed for retention using scree plot and Kaiser criterion with Eigen value > 1 and counter validated using parallel analysis. We obtained two factors named Negative and Positive attitude toward the COVID-19 vaccine. Question 5, 9, 10, 11, and 12 were included in the factor-negative attitude toward COVID-19 vaccines, and the remaining questions 1, 2, 3, 4, 6, 7, and 8 were included in the factor—positive attitude toward COVID-19 vaccine. The score of the COVID19-VHS12 was calculated by the summation of individual scores of the 12 items (maximum score 60). The items of the COVID19-VHS12 scale are given in **Figure 2**.

Confirmatory Factor Analysis and Reliability Analysis

The extracted items under the two factors were further analyzed for model fit using confirmatory factor analysis (CFA). Standardized regression weights of < 0.6 were considered as poor loadings. The goodness of fit for the COVID19-VHS12 with two factors had the following indices. For the English version of the scale, root mean square error of approximation (RMSEA) = 0.064; comparative fit index (CFI) = 0.936; Tucker-Lewis index (TLI) = 0.920. For the Arabic version, RMSEA = 0.077; CFI = 0.96; TLI = 0.95. The two-factor solution obtained from EFA demonstrated a good model fit for both the English and Arabic version of the COVID19-VHS12 based on the above-mentioned goodness of fit indices (54).

Further, reliability analysis was performed using Cronbach's alpha coefficient. The Cronbach's value for the positive and negative factors of COVID19-VHS12 for English version was 0.86 and 0.68 and for Arabic version was 0.94 and 0.79, respectively. Based on Cronbach's value, the reliability of the two factors of COVID19-VHS12 ranged from acceptable to excellent for English and Arabic versions (55).

Determination of Cut Off Score for COVID19-Vaccine Hesitancy Scale-12

The Receiver operating characteristic (ROC) curve has been used previously to determine the cut-off scores of various scales (56, 57). The 12 items of COVID19-VHS12 were loaded as the test variable, and a single item binary variable of "Do you think COVID-19 Vaccine is beneficial (Yes/No)" was loaded as the state variable. The AUROC (Area Under Receiver Operating Characteristic Curve) value for the English version was 81.6 and for the Arabic version was 85.5. The cut-off value for English version was 27.5 (sensitivity 81.9% and specificity 36.7%). Arabic version also had the same cut-off score with the sensitivity of 86% and specificity of 30%. This was rounded off to 28, and any value above 28 was considered vaccine hesitant and scores ≤ 28 were considered not vaccine hesitant. The results of EFA, CFA, and ROC analysis are given in **Supplementary Tables 16, 17** and **Supplementary Figures 1–4**.

Reliability Analysis for Mental Health Measures

PHQ-2, GAD-2, and IES-6 are brief screening tools to assess depression, anxiety, and PTSD symptoms, respectively. Earlier studies have used these tools in both countries (58–61). The Cronbach's alpha score for PHQ-2, GAD-2, and IES-6 before AC19V was 0.45, 0.80, and 0.84 for Indian samples and 0.74, 0.82, and 0.80 for Saudi samples. Cronbach's alpha score for PHQ-2, GAD-2, and IES-6 after AC19V was 0.70, 0.85, and 0.90 for Indian samples and 0.83, 0.86, and 0.86 for Saudi samples. All three scales demonstrated good internal consistency and test-retest reliability.

Ethical Considerations

The study was approved by the Majmaah University Research Ethics Committee (MUREC-May.31/COM-2021/35-2) and Institutional Ethical Committee of Madha Medical College and Research Institute (No/009/2021/IEC/APP/MMC&RI). The study was conducted in adherence to Helsinki Declaration for research on human participants.

Statistical Analysis

Descriptive statistics were done for all the variables. Cross-sectional analysis between variables across different subgroups and between the two countries was performed using the Mann-Whitney *U*-test, Kruskal Wallis test (continuous variables), and Chi-square test (categorical variables). Comparison of mental health parameters before and after AC19V was performed using Wilcoxon signed-rank test for continuous variables and McNemar's test for categorical variables. Spearman's correlation test was performed to study the correlation between all the obtained scores.

To study the association between mental health parameters and COVID-19 vaccine hesitancy, binary logistic regression analysis was used for depression, anxiety, and vaccine hesitancy, and generalized linear regression analysis was used for PTSD. To begin with, unadjusted bivariate regression analysis was performed with mental health parameters viz depression, anxiety, PTSD, and perceptive need for MHS before and after AC19V and vaccine hesitancy as the dependent variable and sociodemographic factors as the independent variable. Despite the results, we included all the sociodemographic variables, which are potential confounders in our adjusted regression models.

Three types of regression models were used to explore the contributory factors for each mental health parameter and COVID-19 vaccine hesitancy. Initially, unadjusted regression analysis (regression model 1) was performed, and the results were expressed as crude odds ratio (OR), 95% confidence interval (95% CI), and *P*-value. For COVID-19 vaccine hesitancy (dependent variable), COVID-19 related factors viz tested positive for COVID-19, COVID-19 vaccination status, active infection after COVID-19 vaccination and mental health parameters viz. depression, anxiety, PTSD, and perceptive need for MHS before

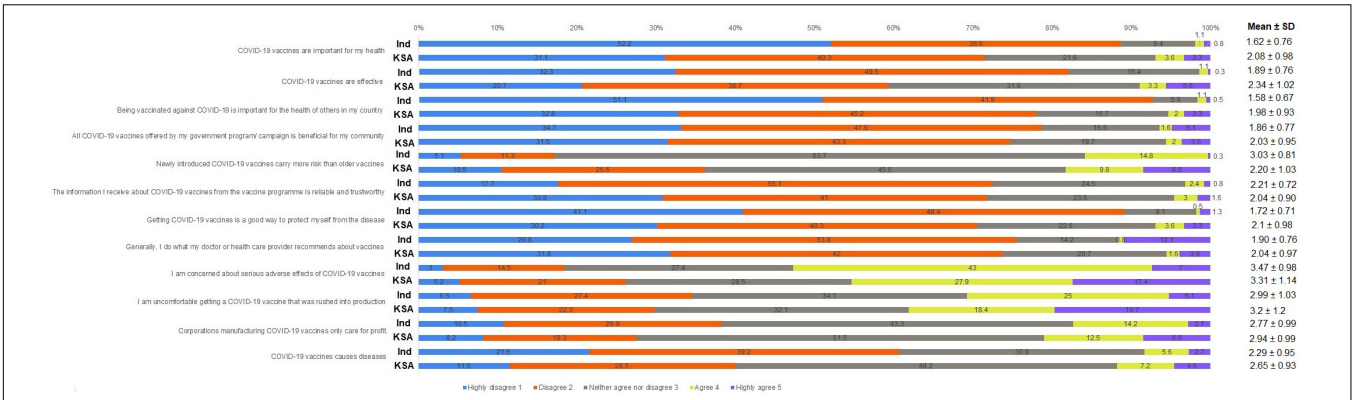

FIGURE 2 | Distribution of responses for each of the 12 items of COVID-19 vaccine hesitancy Scale (in %) with Mean and Standard deviation score of each item in India and Saudi Arabia. Questions 5, 9, 10, 11 and 12 were coded with 1–highly disagree to 5–highly agree. Questions 1, 2, 3, 4, 6, 7 and 8 were reverse coded with 1–highly agree and 5–highly disagree, Ind, India; KSA, Kingdom of Saudi Arabia.

and after AC19V were included as independent variables. For mental health status, depression, anxiety, PTSD, and perceptive need for MHS after AC19V were the dependent variables, and vaccine hesitancy, COVID-19 related factors, and the remaining mental health parameters were included as the independent variables.

In the second regression model, to study the impact of each independent variable over and above the influence of sociodemographic variables, each of the independent variable's effect was adjusted for sociodemographic variables in separate regression models.

In the third regression model, to study the impact of each independent variable over and above the influence of sociodemographic variables and COVID-19 status in relation to infection and vaccination, the effect of each independent variable was adjusted for both sociodemographic variables and COVID-19 related factors in separate regression models. The results of the second and third regression models were expressed as adjusted odds ratio (aOR), 95% confidence interval (95% CI), and *P*-value.

Statistical analysis was performed using SPSS version 26 (IBM, NY, United States). Parallel analysis was performed using scripts from O'Connor (62). CFA was performed using SPSS AMOS version 23 (IBM, NY, United States). Statistical significance was set at two-tailed $P < 0.05$.

RESULTS

This bi-national survey includes 372 and 305 adult participants with an average age of 22.18 ± 6.87 (18–53) and 25.37 ± 9.29 (18–58) years from India and Saudi Arabia, respectively. In both the nations, majority of the participants were females (63.7%—India, 65.6%—KSA), unmarried i.e., single, divorced, or widowed (89.5%—India, 71.5%—KSA), with undergraduate level of education (90.3%—India, 71.4%—KSA), and living in urban areas (68%—India, 82.6%—KSA). The majority of the study participants from India were students in the healthcare field (59.1%) and without income (81.5%), while the majority of the Saudi participants were non-healthcare workers and unemployed individuals (78%) and those with monthly income below 10,000 SAR (54.1%). 16.9 and 22% of the participants had tested positive for COVID-19 in India and Saudi Arabia, respectively. More than twice the number of Indians (26%) were not vaccinated against COVID-19 when compared to that of Saudi Arabia (12.1%) (**Figure 3**).

Comparison of Mental Health Parameters Before and After the Advent of COVID-19 Vaccines

There was a significant reduction in both scores ($P = 0.001$, 0.002) and prevalence (*P*-value = 0.002, 0.035) of depression and anxiety in the Saudi population after AC19V, while no significant changes were observed in India. PTSD scores showed significant reduction after AC19V in both India ($P < 0.001$) and Saudi Arabia ($P = 0.017$). Anxiety scores were significantly higher ($P = 0.012$) in Saudi Arabia than in India before AC19V. PTSD symptoms were significantly higher in India when compared to Saudi Arabia both before and after AC19V ($P < 0.001$) (**Table 1**).

Association Between Sociodemographic Variables and Mental Health Parameters Before and After the Advent of COVID-19 Vaccines

Unadjusted binary logistic regression analysis of mental health parameters with sociodemographic variables as independent variables showed that in the Indian population, educational status ($P = 0.025$) and marital status ($P = 0.035$) was significantly associated with anxiety levels before AC19V, and marital status was significantly associated with perceived need for MHS after AC19V ($P = 0.048$) (**Supplementary Tables 2, 4**).

In the Saudi population, age was a protective factor for depression, anxiety, and perceived need for MHS before and after AC19V. Gender was significantly associated with anxiety and perceived need for MHS before and after AC19V. Marital status was significantly associated with depression before and after AC19V, and anxiety before AC19V. Place of residence

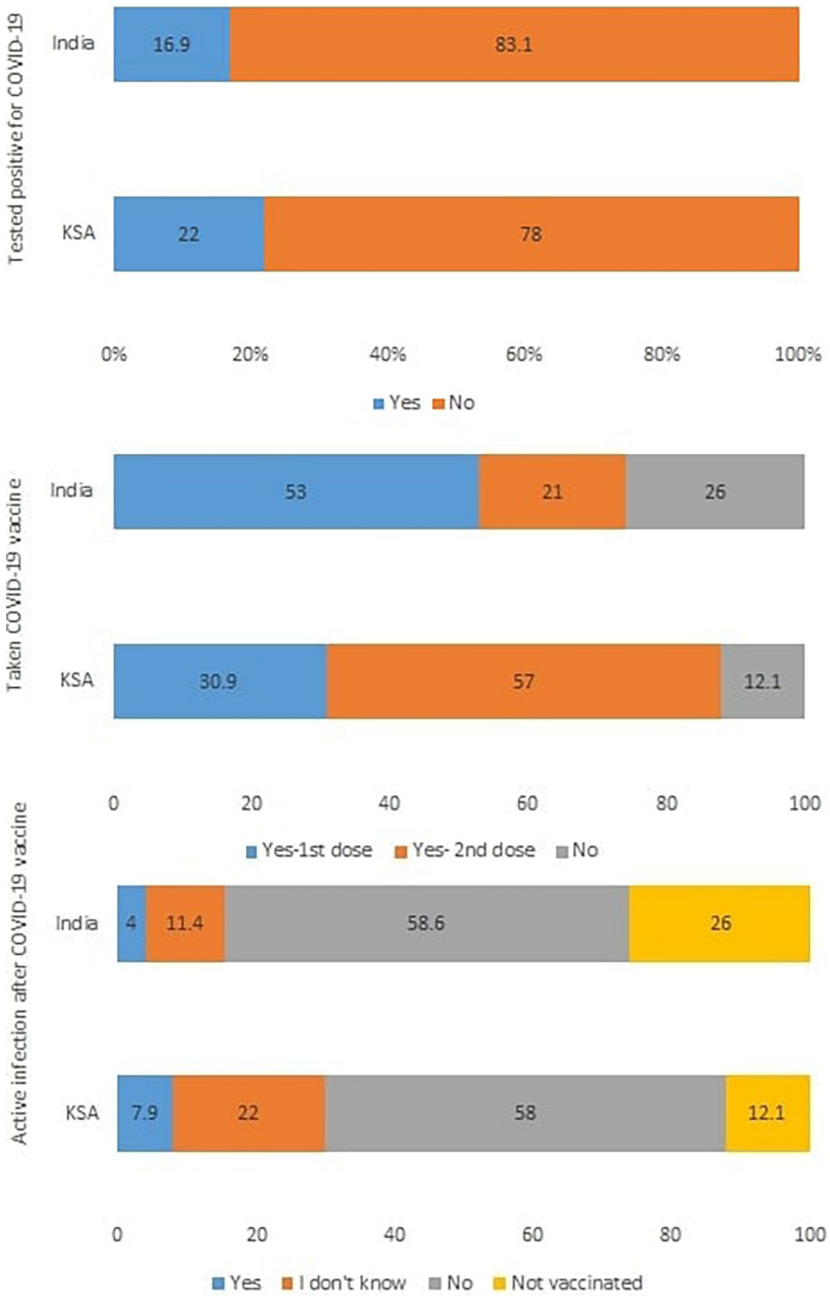

FIGURE 3 | Distribution of responses to COVID-19 status in the self-administered questionnaire (in %). KSA, Kingdom of Saudi Arabia.

was significantly associated with anxiety and the perceived need for MHS before and after AC19V. Employment status was significantly associated with depression before and after AC19V. Monthly income was significantly associated with anxiety before and after AC19V (**Supplementary Tables 6–10**).

Cross sectionally, in the Indian population, females had higher scores of depression than males before AC19V, and those without any monthly income had higher scores of depression compared to others both before and after AC19V and higher anxiety scores before AC19V. In the Saudi population, both before and after AC19V, unmarried participants, those residing in rural areas, and students of healthcare professions had higher scores of depression than married individuals, those from urban areas, and those who were unemployed, non-healthcare workers, and healthcare workers, respectively. Anxiety scores were higher in females compared to males, unmarried individuals compared to married ones, participants residing in rural areas compared to those residing in urban areas before and after AC19V and in those without any income compared to others before AC19V (**Tables 2–4**).

TABLE 1 | Comparison of mental health parameters before and after the advent of COVID-19 vaccines.

Country	Mental health parameter	Before	After	Negative rank (after < before)	Positive rank (after > before)	Ties (after = before)	*P*-value
India (*N* = 372)	Depression Mean ± *SD*	2.02 ± 1.664	2.04 ± 1.851	86	79	207	0.956[a]
	N (%)	134 (36%)	128 (34.4%)	39	33	300	0.556[b]
KSA (*N* = 305)	Depression Mean ± *SD*	2.28 ± 1.917	1.99 ± 1.972	90	51	164	**0.001[a]**
	N (%)	118 (38.7%)	93 (30.5%)	42	17	246	**0.002[b]**
P-value[c]	–	0.183	0.433	–	–	–	–
P-value[d]	–	0.523	0.286	–	–	–	–
India (*N* = 372)	Anxiety Mean ± *SD*	1.58 ± 1.791	1.65 ± 1.858	56	69	247	0.284[a]
	N (%)	92 (24.73%)	97 (26.1%)	24	29	319	0.583[b]
KSA (*N* = 305)	Anxiety Mean ± *SD*	1.90 ± 1.863	1.67 ± 1.801	83	45	117	**0.002[a]**
	N (%)	82 (26.9%)	68 (22.3%)	26	12	267	**0.035[b]**
P-value[c]	–	**0.012**	0.662	–	–	–	–
P-value[d]	–	0.537	0.281	–	–	–	–
India (*N* = 372)	PTSD Mean ± *SD*	11.56 ± 6.013	10.98 ± 6.635	172	98	102	**<0.001[a]**
KSA (N = 305)		8.73 ± 5.723	8.21 ± 6.117	133	94	78	**0.017[b]**
P-value[c]	–	**<0.001**	**<0.001**	–	–	–	–
India (*N* = 372)	Perceptive need for mental health support *N* (%)	161 (43.3%)	161 (43.3%)	19	19	334	1.000[a]
KSA (*N* = 305)		142 (46.6%)	134 (43.9%)	7	15	283	0.134[b]
P-value[d]	–	0.437	0.876	–	–	–	–

[a]Wilcoxon signed rank test; [b]McNemar test; [c]Mann Whitney U-test; [d]Chi-square test; Significant P-values are shown in bold (P < 0.05). KSA, Kingdom of Saudi Arabia.

Comparison of mental health parameters before and after AC19V showed that there was a significant reduction in the scores of depression after AC19V in females ($P = 0.001$), and those with undergraduate level educational status ($P = 0.009$), unmarried individuals ($P = 0.002$), those residing in urban areas ($P = 0.002$), individuals without income (0.009), and unemployed and those employed in non-healthcare professions ($P = 0.005$) in the Saudi population (**Table 2**). The scores of anxiety showed a significant reduction in Saudi females ($P = 0.001$), those with undergraduate level educational status ($P = 0.001$), unmarried individuals ($P = 0.001$), those residing in urban areas ($P = 0.006$), those without income ($P = 0.019$), and those with monthly income less than 10,000 SAR ($P = 0.035$), students in healthcare professions ($P = 0.025$) and those who are unemployed and healthcare workers ($P = 0.013$). There were no significant changes in depression and anxiety scores in any of the subgroups of the Indian population in relation to AC19V (**Tables 2**, **3**). The current study found a reduction in the scores for PTSD after AC19V in the Indian population in both males ($P = 0.006$) and females ($P = 0.018$), those with undergraduate level educational status ($P = 0.001$), unmarried individuals ($P = 0.001$), participants residing in both rural ($P = 0.024$) and urban areas ($P = 0.005$), participants with monthly income above 50,000 INR ($P = 0.047$) and those without any income ($P = 0.001$) and in students in healthcare profession ($P < 0.001$) (**Table 4**). In the case of the Saudi population, the PTSD scores significantly reduced in unmarried individuals ($P = 0.045$), those residing in urban areas ($P = 0.02$), those with monthly income less than 10,000 SAR ($P = 0.006$), and those who were unemployed and non-healthcare workers ($P = 0.009$) after AC19V (**Table 4**).

Comparison of Mental Health Parameters Between India and Saudi Arabia

Comparison of scores of depression between the two countries showed that unmarried individuals ($P = 0.003$), those residing in rural areas ($P = 0.004$) before AC19V, and students in healthcare profession ($P = 0.007$, 0.026) before and after AC19V from India had significantly lower levels of depression when compared to their Saudi counterparts (**Table 2**). In case of anxiety symptoms, females ($P = 0.005$), undergraduates ($P = 0.022$), unmarried individuals ($P = 0.001$), students in the healthcare field ($P = 0.02$), unemployed and non-healthcare workers ($P = 0.018$) before AC19V and rural area residing individuals before ($P = 0.001$) and after ($P = 0.036$) AC19V in India had significantly lower levels of anxiety symptoms when compared to their Saudi counterparts (**Table 3**).

PTSD scores were significantly higher in Indians before and after AC19V in both males ($P = 0.001$, 0.008) and females ($P < 0.001$), married ($P = 0.007$, 0.009) and unmarried individuals ($P < 0.001$), undergraduates ($P < 0.001$), those residing in urban areas ($P < 0.001$), healthcare workers ($P = 0.001$, $P < 0.001$) and non-healthcare workers and

TABLE 2 | Comparison of depression symptoms stratified by sociodemographic variables before and after the advent of COVID-19 vaccines.

Groups	India				KSA				India vs. KSA	
	N	Before (Mean ± SD)	After (Mean ± SD)	*P*-value[a]	*N*	Before (Mean ± *SD*)	After (Mean ± *SD*)	*P*-value[a]	Before *P*-value[c]	After *P*-value[c]
Gender Male	135	1.81 ± 1.686	1.91 ± 1.926	0.459	105	2.04 ± 1.792	1.80 ± 1.789	0.247	0.34	0.757
Female	237	2.14 ± 1.643	2.11 ± 1.808	0.580	200	2.41 ± 1.972	2.08 ± 2.059	**0.001**	0.355	0.416
P-value[c]		**0.04**	0.175			0.162	0.359			
Educational status Postgraduates and higher	33	1.45 ± 1.641	1.39 ± 1.499	0.621	18	1.28 ± 1.074	0.94 ± 0.938	0.196	0.967	0.416
Undergraduates	336	2.07 ± 1.648	2.10 ± 1.871	0.789	218	2.32 ± 1.909	2.02 ± 1.952	**0.009**	0.243	0.472
School level education	3	3.00 ± 3.000	2.67 ± 2.309	0.655	60	2.32 ± 1.961	2.03 ± 2.075	0.141	0.658	0.620
Nil	0	–	–	–	9	3.11 ± 2.619	2.89 ± 2.713	0.157	–	–
P-value[e]		0.069	0.110			0.149[e]	0.158[e]			
Marital status Single/widowed/ divorced	333	2.08 ± 1.671	2.11 ± 1.875	0.779	218	2.61 ± 1.944	2.26 ± 2.018	**0.002**	**0.003**	0.516
Married	39	1.56 ± 1.553	1.46 ± 1.536	0.566	87	1.45 ± 1.576	1.30 ± 1.671	0.292	0.600	0.430
P-value[c]		0.070	0.051			**<0.001**	**<0.001**			
Place of residence Rural	119	1.85 ± 1.650	2.06 ± 1.945	0.115	53	2.83 ± 2.064	2.62 ± 2.281	0.255	**0.004**	0.169
Urban	253	2.10 ± 1.668	2.03 ± 1.809	0.276	252	2.16 ± 1.869	1.85 ± 1.878	**0.002**	0.971	0.159
P-value[c]		0.150	0.934			**0.033**	**0.027**			
Monthly income Above 50,000 INR Above 10,000 SAR	25	1.32 ± 1.725	1.04 ± 1.485	0.356	29	1.83 ± 1.794	1.55 ± 1.804	0.279	NA	NA
Below 50,000 INR Below 10,000 SAR	44	1.48 ± 1.548	1.64 ± 1.780	0.612	165	2.16 ± 1.909	1.92 ± 1.969	0.065	NA	NA
Nil	303	2.16 ± 1.650	2.18 ± 1.860	0.921	111	2.58 ± 1.933	2.20 ± 2.008	**0.009**	NA	NA
P-value[e]		**0.002**	**0.002**			0.077[e]	0.192[e]			
Employment status Healthcare workers	70	1.76 ± 1.756	1.99 ± 2.123	0.161	35	2.11 ± 1.891	1.77 ± 1.734	0.150	0.386	0.967
Students in healthcare profession	220	2.12 ± 1.633	2.07 ± 1.755	0.501	32	3.09 ± 2.006	2.91 ± 2.053	0.273	**0.007**	**0.026**
Non-healthcare workers/unemployed	82	1.98 ± 1.663	1.99 ± 1.876	0.986	238	2.19 ± 1.891	1.89 ± 1.969	**0.005**	0.525	0.531
P-value[e]		0.191	0.598			**0.041**	**0.023**			

[a]Wilcoxon signed rank test; [c]Mann Whitney U-test; [e]Kruskal Wallis test; Significant P-values are shown in bold (P < 0.05). KSA; Kingdom of Saudi Arabia, INR; Indian Rupee, SAR; Saudi Riyal.

unemployed individuals ($P = 0.001$, 0.001) and before AC19V alone in Indian students in the healthcare field ($P = 0.002$) when compared to the corresponding groups in Saudi population (**Table 4**).

Association Between COVID-19 Vaccine Hesitancy and Sociodemographic Variables Between India and Saudi Arabia

Unadjusted binary logistic regression analysis of vaccine hesitancy showed that none of the sociodemographic variables was significantly associated with COVID-19 vaccine hesitancy in India (**Supplementary Table 5**). In Saudi Arabia, females were found to be more likely to have vaccine hesitancy than males ($P = 0.039$) (**Supplementary Table 10**).

Vaccine hesitancy was significantly higher in Saudis than in Indians ($P = 0.001$). Within the subgroups, vaccine hesitancy was higher in Saudi females ($P = 0.002$), undergraduates ($P = 0.004$), unmarried individuals ($P = 0.002$), non-healthcare workers and unemployed individuals ($P = 0.02$) and those residing in both urban ($P = 0.03$) and rural areas ($P = 0.001$) when compared to the corresponding Indians. In Saudi Arabia, Vaccine hesitancy was significantly higher in individuals residing in rural areas than those residing in urban areas ($P = 0.033$) (**Table 5**).

Correlation Between Mental Health Parameters and COVID-19 Vaccine Hesitancy

COVID-19 vaccine hesitancy was positively correlated with depression and anxiety symptoms before and after AC19V in

TABLE 3 | Comparison of anxiety symptoms stratified by sociodemographic variables before and after the advent of COVID-19 vaccines.

Groups	India				KSA				India vs. KSA	
	N	Before (Mean ± *SD*)	After (Mean ± *SD*)	*P*-value[a]	*N*	Before (Mean ± SD)	After (Mean ± *SD*)	*P*-value [a]	Before *P*-value[c]	After *P*-value [c]
Gender Male	135	1.49 ± 1.958	1.56 ± 1.965	0.652	105	1.32 ± 1.418	1.24 ± 1.484	0.525	0.579	0.673
Female	237	1.63 ± 1.691	1.71 ± 1.796	0.303	200	2.20 ± 1.997	1.89 ± 1.912	**0.001**	**0.005**	0.373
P-value[c]		0.091	0.188			**0.001**	**0.005**			
Educational status Postgraduates and higher	33	0.91 ± 1.284	0.97 ± 1.380	0.747	18	0.78 ± 1.060	0.83 ± 0.985	0.792	0.796	0.991
Undergraduates	336	1.63 ± 1.807	1.71 ± 1.890	0.228	218	1.94 ± 1.856	1.64 ± 1.768	**0.001**	**0.022**	0.943
School level education	3	3.33 ± 3.055	2.33 ± 1.528	0.276	60	2.02 ± 1.882	1.90 ± 1.920	0.421	0.399	0.516
Nil	0	NA	NA	NA	9	2.11 ± 2.619	2.44 ± 2.555	0.408	NA	NA
P-value[e]		0.061	0.067			0.053	0.195			
Marital status Single/widowed/ divorced	333	1.64 ± 1.813	1.71 ± 1.895	0.300	218	2.14 ± 1.903	1.86 ± 1.860	**0.001**	**0.001**	0.190
Married	39	1.10 ± 1.535	1.15 ± 1.424	0.772	87	1.29 ± 1.613	1.18 ± 1.552	0.481	0.593	0.948
P-value[c]		0.090	0.124			**<0.001**	**0.002**			
Place of residence Rural	119	1.51 ± 1.822	1.64 ± 1.903	0.401	53	2.66 ± 2.227	2.36 ± 2.193	0.138	**0.001**	**0.036**
Urban	253	1.61 ± 1.780	1.66 ± 1.840	0.514	252	1.73 ± 1.739	1.52 ± 1.676	**0.006**	0.273	0.648
P-value[c]		0.470	0.769			**0.007**	**0.012**			
Monthly income Above 50,000 INR Above 10,000 SAR	25	1.20 ± 1.732	1.04 ± 1.594	0.388	29	1.59 ± 1.842	1.48 ± 1.902	0.709	NA	NA
Below 50,000 INR Below 10,000 SAR	44	0.98 ± 1.422	1.25 ± 1.433	0.179	165	1.66 ± 1.765	1.50 ± 1.724	**0.035**	NA	NA
Nil	303	1.70 ± 1.827	1.76 ± 1.918	0.442	111	2.32 ± 1.945	1.96 ± 1.863	**0.019**	NA	NA
P-value[e]		**0.021**	0.070			**0.009**	0.064			
Employment status Health professionals	70	1.50 ± 1.886	1.59 ± 1.892	0.724	35	1.71 ± 1.808	1.66 ± 1.679	0.642	0.362	0.505
Students in health profession	220	1.67 ± 1.742	1.66 ± 1.835	0.854	32	2.50 ± 1.984	1.97 ± 1.823	**0.025**	**0.020**	0.219
Non-health professionals/ unemployed	82	1.40 ± 1.845	1.70 ± 1.910	0.055	238	1.84 ± 1.846	1.63 ± 1.818	**0.013**	**0.018**	0.911
P-value[e]		0.219	0.871			0.127	0.407			

[a]Wilcoxon signed rank test; [c]Mann Whitney U-test; [e]Kruskal Wallis test; Significant P-values are shown in bold (P < 0.05). KSA; Kingdom of Saudi Arabia, INR; Indian Rupee, SAR; Saudi Riyal.

Saudi Arabia. There was no significant correlation between vaccine hesitancy and any mental health parameters in India (**Tables 6**, **7**).

Adjusted Binary Logistic Regression Analysis of COVID-19 Vaccine Hesitancy

The binary logistic regression analysis results for COVID-19 vaccine hesitancy are given in **Figure 4**. Those who had taken COVID-19 vaccine and those who did not develop active infection after COVID-19 vaccinations were less likely to have vaccine hesitancy when compared to those who were not vaccinated in both India and Saudi Arabia. Higher levels of depression, anxiety, and perceived need for MHS before and after AC19V were associated with higher vaccine hesitancy in Saudi Arabia (**Figure 3**).

Adjusted Binary Logistic Regression Analysis of Mental Health Parameters

The binary logistic regression analysis results for mental health parameters are given in **Figures 5**–**8**. Higher scores of anxiety, PTSD, the perceived need for MHS before and after AC19V, and depression before AC19V were associated with higher scores of depression in both Indian ($P < 0.001$) and Saudi population ($P < 0.001$, $P = 0.003$ for PTSD before). Higher levels of vaccine hesitancy were associated with higher levels of depression ($P = 0.02$) in the Saudi population (**Figure 4**).

Those who were vaccinated against COVID-19 ($P = 0.004$ -1st dose, $P = 0.018$ -2nd dose) and those who developed active infection after COVID-19 vaccination ($P = 0.034$) and those who did not ($P = 0.004$) were found to be significantly less likely to have anxiety symptoms when compared to those who were not vaccinated against COVID-19 in Saudi Arabia. In India, those who were tested positive for COVID-19 were

TABLE 4 | Comparison of PTSD symptoms stratified by sociodemographic variables before and after the advent of COVID-19 vaccines.

Groups	India				KSA				India vs. KSA	
	N	Before (Mean ± SD)	After (Mean ± SD)	*P*-value[a]	*N*	Before (Mean ± SD)	After (Mean ± SD)	*P*-value[a]	Before *P*-value[c]	After *P*-value[c]
Gender Male	135	11.68 ± 5.950	10.82 ± 6.486	**0.006**	105	9.06 ± 5.333	8.51 ± 5.997	0.086	**0.001**	**0.008**
Female	237	11.49 ± 6.060	11.07 ± 6.730	**0.018**	200	8.55 ± 5.923	8.05 ± 6.188	0.092	**< 0.001**	**<0.001**
P-value [c]		0.811	0.487			0.336	0.473			
Educational status Postgraduates and higher	33	11.67 ± 6.096	11.09 ± 6.079	0.380	18	9.94 ± 4.905	9.00 ± 5.626	0.275	0.343	0.286
Undergraduates	336	11.57 ± 6.032	10.99 ± 6.714	**0.001**	218	8.78 ± 5.911	8.35 ± 6.106	0.086	**<0.001**	**<0.001**
School level education	3	10.00 ± 3.606	8.67 ± 3.786	0.593	60	8.22 ± 5.573	7.37 ± 6.273	0.112	0.539	0.571
Nil	0	NA	NA	NA	9	8.33 ± 3.354	8.89	0.888	NA	NA
P-value[e]		0.854	0.793			0.705	0.567			
Marital status Single/widowed/divorced	333	11.46 ± 5.994	10.89 ± 6.669	**0.001**	218	8.56 ± 5.630	8.08 ± 6.101	**0.045**	**<0.001**	**<0.001**
Married	39	12.44 ± 6.181	11.77 ± 6.360	0.258	87	9.14 ± 5.963	8.54 ± 6.179	0.159	**0.007**	**0.009**
P-value [c]		0.364	0.409			0.374	0.466			
Place of residence Rural	119	11.23 ± 6.296	10.69 ± 6.823	**0.024**	53	9.40 ± 6.090	8.92 ± 6.773	0.501	0.079	0.090
Urban	253	11.72 ± 5.881	11.12 ± 6.553	**0.005**	252	8.59 ± 5.645	8.06 ± 5.973	**0.020**	**< 0.001**	**<0.001**
P-value [c]		0.419	0.680			0.378	0.529			
Monthly income Above 50,000 INR Above 10,000 SAR	25	10.28 ± 6.188	8.84 ± 6.681	**0.047**	29	9.97 ± 5.095	9.52 ± 5.026	0.619	NA	NA
Below 50,000 INR Below 10,000 SAR	44	12.30 ± 5.572	12.07 ± 5.683	0.673	165	8.96 ± 6.102	8.10 ± 6.468	**0.006**	NA	NA
Nil	303	11.56 ± 6.061	11.00 ± 6.736	**0.001**	111	8.06 ± 5.240	8.04 ± 5.840	0.715	NA	NA
P-value [e]		0.249	0.097			0.185	0.255			
Employment status Health professionals	70	12.30 ± 6.570	12.54 ± 6.909	0.784	35	7.80 ± 5.218	7.43 ± 5.658	0.600	**0.001**	**<0.001**
Students in health profession	220	11.40 ± 5.919	10.45 ± 6.547	**<0.001**	32	8.25 ± 6.720	9.06 ± 7.255	0.614	**0.002**	0.164
Non-health professionals/unemployed	82	11.37 ± 5.790	11.07 ± 6.494	0.449	238	8.93 ± 5.657	8.21 ± 6.027	**0.009**	**0.001**	**0.001**
P-value [e]		0.717	0.134			0.324	0.760			

[a]Wilcoxon signed rank test; [c]Mann Whitney U-test; [e]Kruskal Wallis test; Significant P-values are shown in bold (P < 0.05). KSA; Kingdom of Saudi Arabia, INR; Indian Rupee, SAR; Saudi Riyal.

found to be less likely to have anxiety symptoms ($P = 0.035$). Higher scores of depression, PTSD, and perceived need for MHS before and after AC19V and anxiety before AC19V were significantly associated with higher scores of anxiety in India and Saudi Arabia ($P < 0.001$). Higher scores of vaccine hesitancy were found to be significantly associated with higher levels of anxiety in India ($P = 0.049$) and Saudi Arabia ($P = 0.009$) (**Figure 6**).

Generalized linear regression analysis of PTSD is given in **Figure 6**. Higher scores of depression, anxiety, and perceived need for MHS before and after AC19V, and PTSD before AC19V were associated with higher scores of PTSD in India ($P < 0.001$) and Saudi Arabia ($P < 0.001$, $P = 0.004$ for depression before, $P = 0.027$, $P = 0.025$ for perceived need for MHS before and after AC19V) (**Figure 7**).

Higher scores of depression, anxiety, PTSD before and after AC19V and perceived need for MHS before AC19V were associated with higher perceived need for MHS in India and Saudi Arabia. Higher vaccine hesitancy was associated with the higher perceptive need for MHS in Saudi Arabia. Indians who were vaccinated against COVID-19 and either developed or did not develop an active infection after the vaccination were more likely to have a higher perceived need for MHS. Saudis who had taken the COVID-19 vaccine second dose and those who developed an active infection after the vaccine were less likely to have a higher perceived need for MHS (**Figure 8**).

DISCUSSION

The present study investigated the mental health status before and after the advent of COVID-19 vaccines and its association with vaccine hesitancy in the adult population of India and Saudi Arabia. We used a new COVID-19 vaccine hesitancy scale and performed psychometric analysis which showed high

TABLE 5 | Comparison of COVID-19 vaccine hesitancy scores stratified by sociodemographic variables between India and Saudi Arabia.

	India		KSA		India vs. KSA
	N	**Mean ± *SD***	***N***	**Mean ± *SD***	***P*-value**
Overall	372	27.22 ± 5.266	305	29.50 ± 8.569	**0.001[c]**
		189 (50.8%)		170 (55.7%)	0.216[d]
Gender	135	26.82 ± 5.707	105	28.75 ± 7.949	0.130[c]
Male					
Female	237	27.45 ± 4.997	200	29.89 ± 8.871	**0.002[c]**
P-value[c]		0.356		0.222	–
Educational status	33	26.36 ± 4.974	18	25.78 ± 6.700	0.508[c]
Postgraduates and higher					
Undergraduates	336	27.32 ± 5.297	218	29.56 ± 8.479	**0.004[c]**
School level education	3	25.00 ± 5.292	60	30.18 ± 9.571	0.286[c]
Nil	0	–	9	31.11 ± 5.600	NA
P-value[e]		0.384		0.188	
Marital status	333	27.31 ± 5.307	218	29.71 ± 8.694	**0.002[c]**
Single/widowed/divorced					
Married	39	26.49 ± 4.909	87	28.99 ± 8.275	0.150[c]
P-value[c]		0.429		0.509	–
Place of residence	119	27.37 ± 5.256	53	31.36 ± 7.913	**0.001**[c]
Rural					
Urban	253	27.15 ± 5.280	252	29.11 ± 8.665	**0.030**[c]
P-value[c]		0.547		**0.033**	–
Monthly income	25	25.92 ± 6.370	29	30.03 ± 9.318	NA
Above 50,000 INR					
Above 10,000 SAR					
Below 50,000 INR	44	28.16 ± 5.225	165	28.99 ± 8.724	NA
Below 10,000 SAR					
Nil	303	27.19 ± 5.166	111	30.12 ± 8.155	NA
P-value[e]		0.340		0.462	
Employment status	70	28.03 ± 5.321	35	29.51 ± 8.853	0.293[c]
Health professionals					
Students in healthcare field	220	27.03 ± 5.261	32	27.31 ± 5.899	0.638[c]
Non-health professionals/unemployed	82	27.04 ± 5.234	238	29.79 ± 8.812	**0.020[c]**
P-value[e]		0.344		0.398	

[c]Mann Whitney U-test; [e]Kruskal Wallis test; Significant P-values are shown in bold (P < 0.05). [d]Chi square test; KSA, Kingdom of Saudi Arabia; INR, Indian Rupee; SAR, Saudi Riyal.

TABLE 6 | Correlation between scores in the Indian sample.

Variables	VHS	Depression before	Anxiety before	PTSD before	Depression after	Anxiety after	PTSD after
VHS	1.000	–	–	–	–	–	–
Depression before	−0.003(0.949)	1.000	–	–	–	–	–
Anxiety before	0.046(0.377)	**0.608(<0.001)**	1.000	–	–	–	–
PTSD before	−0.059(0.255)	**0.230(<0.001)**	**0.352(<0.001)**	1.000	–	–	–
Depression after	−0.032(0.534)	**0.696(<0.001)**	**0.634(<0.001)**	**0.349(<0.001)**	1.000	–	–
Anxiety after	0.067(0.199)	**0.582(<0.001)**	**0.805(<0.001)**	**0.400(<0.001)**	**0.704(<0.001)**	1.000	–
PTSD after	−0.019(0.709)	**0.273(<0.001)**	**0.386(<0.001)**	**0.827(<0.001)**	**0.416(<0.001)**	**0.467(<0.001)**	1.000

The results are expressed as ρ (Rho) value.
Significant P-values are shown in bold (P < 0.05).

validity and reliability in both English and Arabic versions. At the cut off value of 28, the scale demonstrated good sensitivity and moderate specificity (**Supplementary Figures 3, 4**). The prevalence of depression in India and Saudi Arabia was 36% (95% CI 31–41%) and 38.7% (95% CI 33.22–44.15%) before AC19V and 34.4% (95% CI 29.58–39.24%) and 30.5% (95% CI 25.33–35.66%) after AC19V. The prevalence of anxiety in India and Saudi Arabia was 24.73% (95% CI 20.35–29.12%)

TABLE 7 | Correlation between scores in the K Saudi Arabian sample.

Variables	VHS	Depression before	Anxiety before	PTSD before	Depression after	Anxiety after	PTSD after
VHS	1.000	–	–	–	–	–	–
Depression before	**0.295(<0.001)**	1.000	–	–	–	–	–
Anxiety before	**0.258(<0.001)**	**0.655(<0.001)**	1.000	–	–	–	–
PTSD before	0.043(0.459)	**0.115(0.044)**	**0.259(<0.001)**	1.000	–	–	–
Depression after	**0.194(0.001)**	**0.680(<0.001)**	**0.593(<0.001)**	**0.198(<0.001)**	1.000	–	–
Anxiety after	**0.277(<0.001)**	**0.536(<0.001)**	**0.723(<0.001)**	**0.353(<0.001)**	**0.711(<0.001)**	1.000	–
PTSD after	0.044(0.441)	**0.139(0.015)**	**0.296(<0.001)**	**0.743(<0.001)**	**0.264(<0.001)**	**0.383(<0.001)**	1.000

The results are expressed as ρ (Rho) value. Significant P-values are shown in bold (P < 0.05).

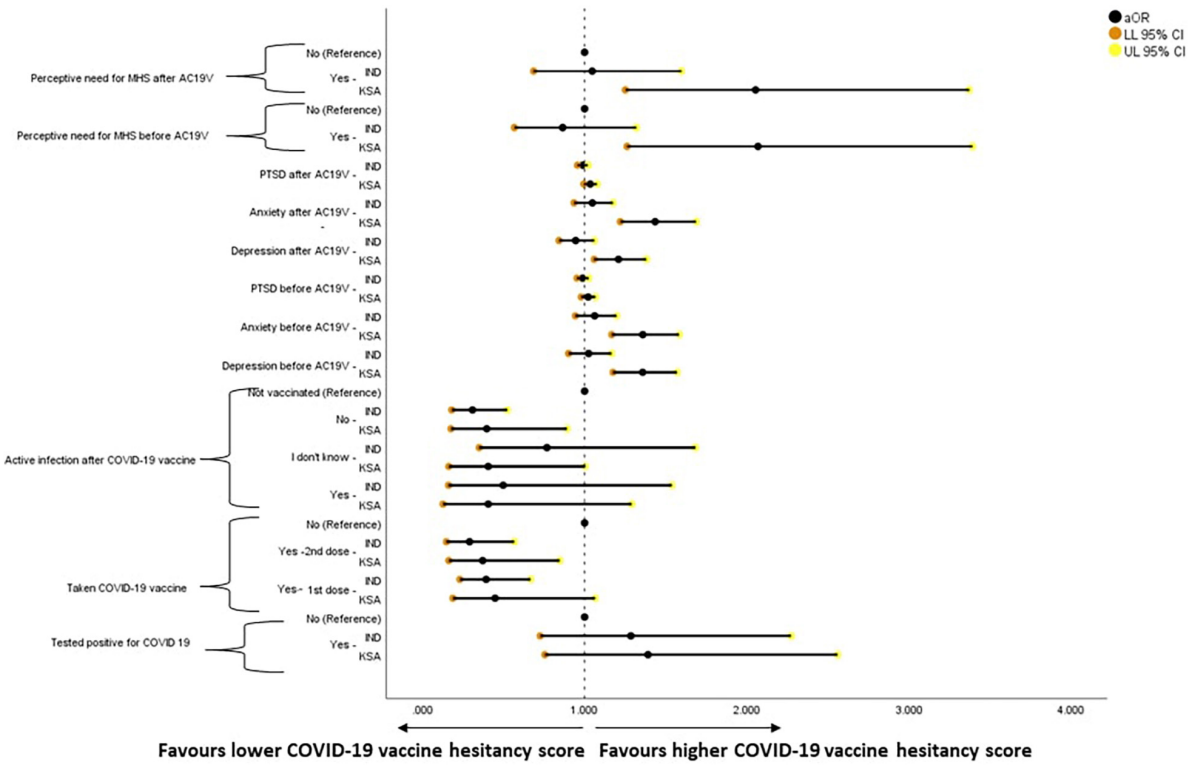

FIGURE 4 | Forest plot showing adjusted binary logistic regression analysis of COVID-19 vaccine hesitancy (regression model 2). aOR, adjusted Odds Ratio; Odds ratio adjusted for Sociodemographic factors. 95% CI—95% Confidence Interval. The results of regression model 1, 2, and 3 in binary logistic regression analysis of COVID-19 Vaccine Hesitancy is tabulated in **Supplementary Table 11**. Ind–India; KSA–Kingdom of Saudi Arabia.

and 26.9% (95% CI 21.91–31.86%) before AC19V and 26.1% (95% CI 21.61–30.54%) and 22.3% (95% CI 17.62–26.97%) after AC19V. 43.3% (95% CI 38.24–48.31%) of the Indians expressed the need for mental health support before and after AC19V while 46.6% (95% CI 40.96–52.16%) and 43.9% (95% CI 38.36–49.5%) of Saudis expressed the need for MHS before and after AC19V.

Mental Health Status

The study found that PTSD symptoms showed a significant reduction in both India and Saudi Arabia after AC19V. However, the prevalence and levels of depression and anxiety symptoms decreased significantly in the Saudi population but not in the Indian population. The anxiety levels were higher in Saudi Arabia than in India before AC19V, but they significantly reduced after AC19V, and levels got almost as same as that of India (**Table 2**). The possible cause for this could be that Saudi Arabia was more severely affected by the earlier Middle East Respiratory Syndrome (MERS) pandemic in 2012 with 80% of global cases while there was no MERS spread in India (63). Given that there were no vaccines against MERS even till date, it is quite plausible that the Saudi's symptoms of anxiety and PTSD reduced following the advent of COVID-19 vaccines (64). On the other hand, PTSD scores were higher in Indians than Saudis both before and after AC19V. Though the PTSD symptoms significantly reduced in India after AC19V, they were still higher than that of Saudi Arabia (**Table 1**). The PTSD symptoms were higher in India than in Saudi Arabia irrespective of gender, marital

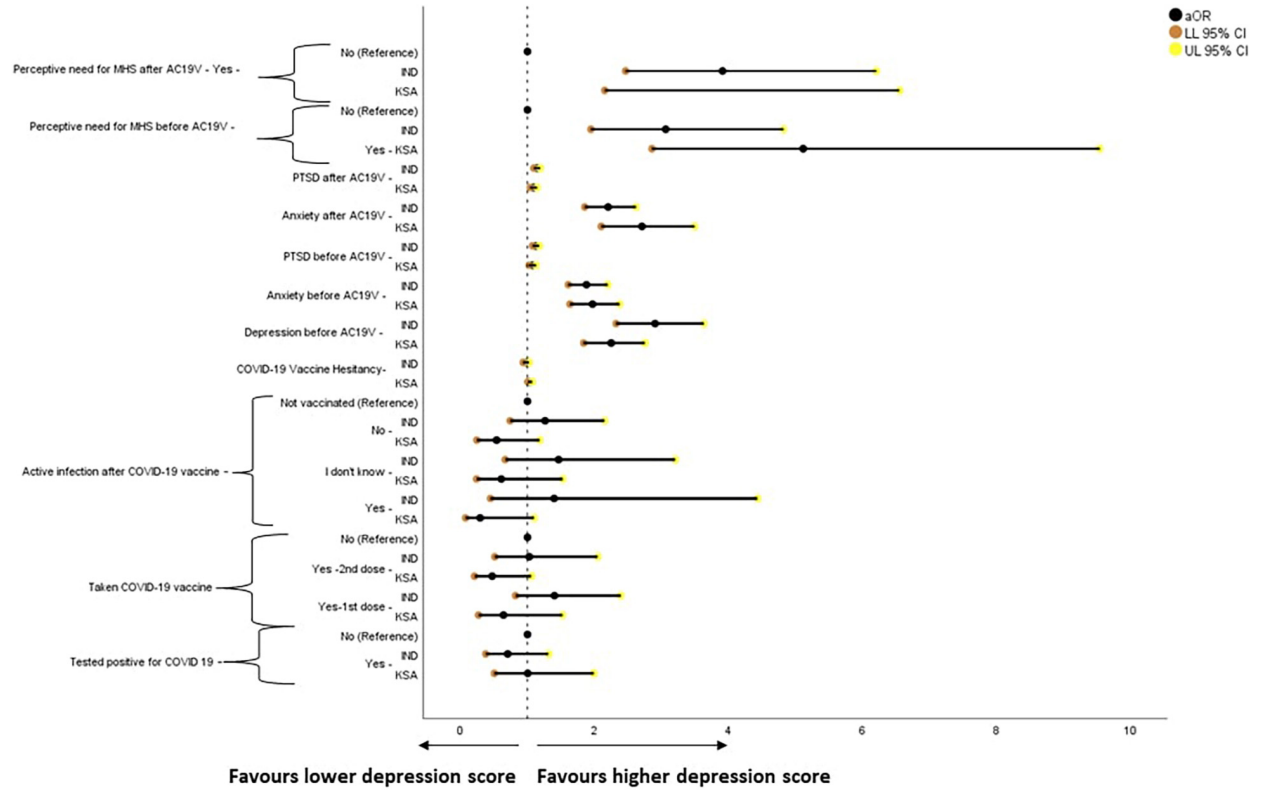

FIGURE 5 | Forest plot showing adjusted binary logistic regression analysis of depression scores (regression model 2). aOR, adjusted Odds Ratio; Odds ratio adjusted for Sociodemographic factors. 95% CI—95% Confidence Interval. The results of regression model 1, 2, and 3 in binary logistic regression analysis of depression scores is tabulated in **Supplementary Table 12**. Ind–India; KSA–Kingdom of Saudi Arabia.

status, employment status, and in undergraduates and urban dwellers before and after AC19V and in Indian students in the healthcare field before AC19V when compared to their Saudi counterparts (**Table 4**). We posit that an earlier experience with a pandemic by Saudis would have been responsible for the reduced PTSD symptoms compared to Indians for whom the unprecedented SARS-CoV-2 outbreak to the extent of a pandemic would have been perceived to be comparatively more traumatic. Another reason could be that the study was conducted when both the nations were experiencing the second wave of COVID-19 outbreak, but the second wave's severity was higher in India than in Saudi Arabia. Thus, despite AC19V the PTSD symptoms were higher in Indians than Saudis due to the second wave's severity. However, further studies are needed to validate this statement. Similar to our results, a recent multinational study found that country of residence is an important predictor for PTSD during the COVID-19 pandemic (65).

Investigation of the influence of sociodemographic variables on mental health status showed high heterogeneity between India and Saudi Arabia. Age was found to be a significant protective factor against depression, anxiety, and perceived need for MHS both before and after AC19V in Saudi Arabia but not in India. Similarly, a study conducted in the United Kingdom found younger age to predict depression and anxiety, while a study conducted in United States found age to be not associated with mental health status (66, 67). We found that gender was significantly associated with anxiety and perceived need for MHS before and after AC19V in Saudi Arabia, while there was no association for gender with any of the mental health parameters in India. Saudi females were twice as likely to present with anxiety symptoms before [OR 2.740, 95% CI (1.491–5.034)] and after AC19V [OR 2.163, 95% CI (1.152–4.063)] than Saudi males. On the other hand, Saudi females who were 1.691(1.045–2.738) times more likely to perceive the need for MHS before AC19V were found to be 1.842 (1.129–3.003) times more likely to do so after AC19V when compared to Saudi males (**Supplementary Tables 7, 9**). Marital status was found to be significantly associated with mental health in both countries. In India, unmarried individuals had thrice the risk of having anxiety symptoms before AC19V [OR 3.143, 95% CI (1.086–9.096)] while after AC19V, they were found to be twice as likely to perceive the need for MHS than married ones [OR 2.086, 95% CI (1.005–4.330)] (**Supplementary Tables 2, 4**). Similar results were observed in Saudis, where unmarried individuals had thrice the risk of having depression symptoms [OR 3.249, 95% CI (1.813–5.820)], twice the risk of showing anxiety symptoms [OR 1.927, 95% CI (1.042–3.562)] before AC19V and twice the risk of showing depression symptoms after AC19V when compared to married individuals [OR 2.204, 95% CI (1.211–4.010)] (**Supplementary**

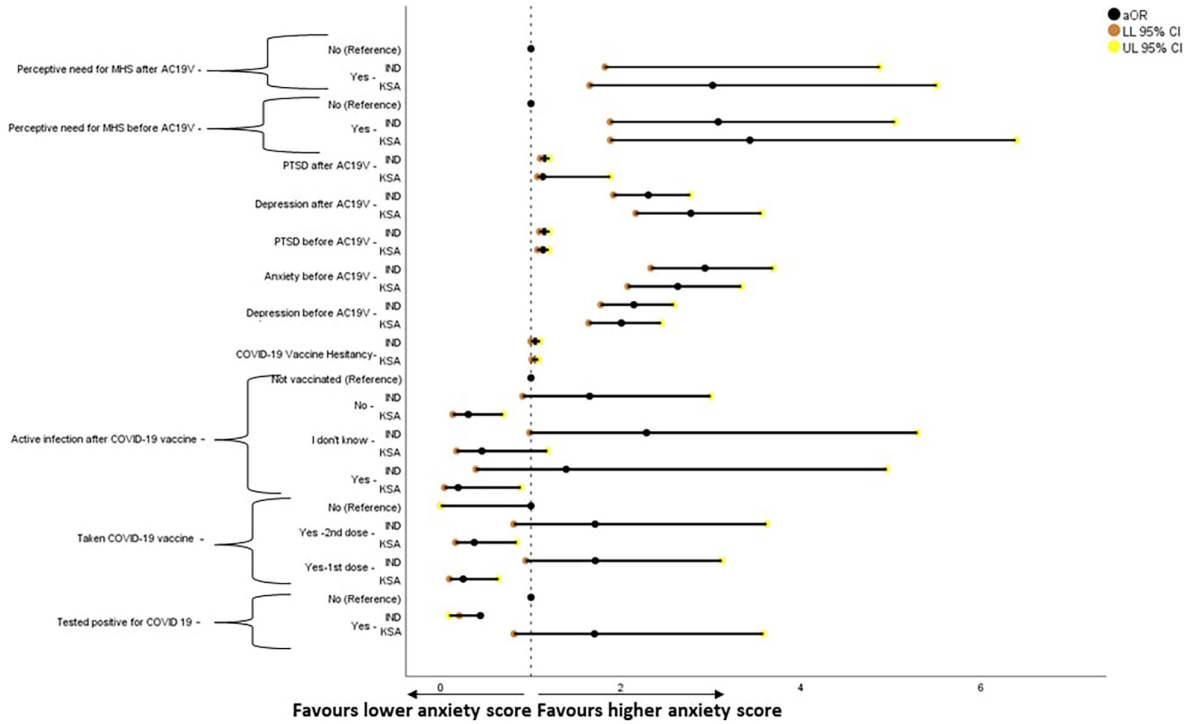

FIGURE 6 | Forest plot showing adjusted binary logistic regression analysis of anxiety scores (REGRESSION model 2). aOR, adjusted Odds Ratio; Odds ratio adjusted for Sociodemographic factors. 95% CI, 95% Confidence Interval. The results of regression model 1, 2, and 3 in binary logistic regression analysis of depression scores is tabulated in **Supplementary Table 13**. Ind–India; KSA–Kingdom of Saudi Arabia.

Tables 6, 7). Educational status was found to be a significant predictor of anxiety symptoms before AC19V in India. Those with a higher level of educational status were found to be less likely to have anxiety symptoms when compared to those with a lower level of educational status [OR 0.032, 95% CI (0.002–0.527)] (**Supplementary Table 2**). On the contrary, there was no association between educational status and mental health in Saudi Arabia. Place of residence was significantly related to mental health in Saudi Arabia but not in India. Saudis residing in urban areas were less likely to have symptoms of anxiety before [OR 0.440, 95% CI (0.237–0.817)] and after AC19V [OR 0.481, 95% CI (0.252–0.919)] while also being less likely to perceive the need for MHS both before [OR 0.419, 95% CI (0.227–0.775)] and after [OR 0.491, 95% CI (0.269–0.895)] AC19V when compared with those residing in rural areas. Economic status was a predictor of negative mental health in Saudi Arabia. Saudis with monthly income less than 10,000 SAR was found to be less likely to have symptoms of anxiety before [OR 0.444, 95% CI (0.258–0.764)] and after AC19V [OR 0.483, 95% CI (0.272–0.859)] when compared to those without any income (**Supplementary Table 7**). Employment status significantly predicted negative mental health in Saudi Arabia but not in India. Saudi students in the healthcare field were three times more likely to have symptoms of depression before [OR 2.841, 95% CI (1.325–6.090)] and after AC19V [OR 3.281, 95% CI (1.545–6.970)] when compared to non-healthcare workers and unemployed individuals (**Supplementary Table 6**). Our results were consistent with similar studies conducted in other countries, which assessed the relationship between sociodemographic variables and mental health during the COVID-19 pandemic (65–75).

Comparison of the influence of sociodemographic variables on mental health before and after AC19V showed an interesting pattern. PTSD symptoms showed significant reduction after AC19V in both Indian males ($P = 0.006$) and females ($P = 0.018$) irrespective of gender. On the other hand, the levels of anxiety in Saudi females, which were higher than that of Indian females before AC19V ($P = 0.005$), showed a significant reduction after AC19V ($P = 0.001$) and became closer to that of the Indian females (**Table 3**). Thus, the females who were at a higher risk of developing anxiety symptoms were the ones who responded well to the advent of COVID-19 vaccines. Despite the reduction in anxiety symptoms, Saudi females were still at a higher risk of having anxiety symptoms, albeit with a minor reduction in the odds after AC19V (**Figure 6**). However, they were also found to have a higher perceived need for MHS than Saudi males, which is an essential step in seeking mental health support (**Figure 8**). In our study, there was a significant reduction in depression ($P = 0.002$), anxiety ($P = 0.001$), and PTSD symptoms ($P = 0.45$) in unmarried Saudis and a reduction in PTSD symptoms in unmarried Indians ($P = 0.001$) after AC19V (**Tables 2–4**). Thus, unmarried individuals who were more at risk of developing depression, anxiety and PTSD during the pandemic were also the ones who fared well with the

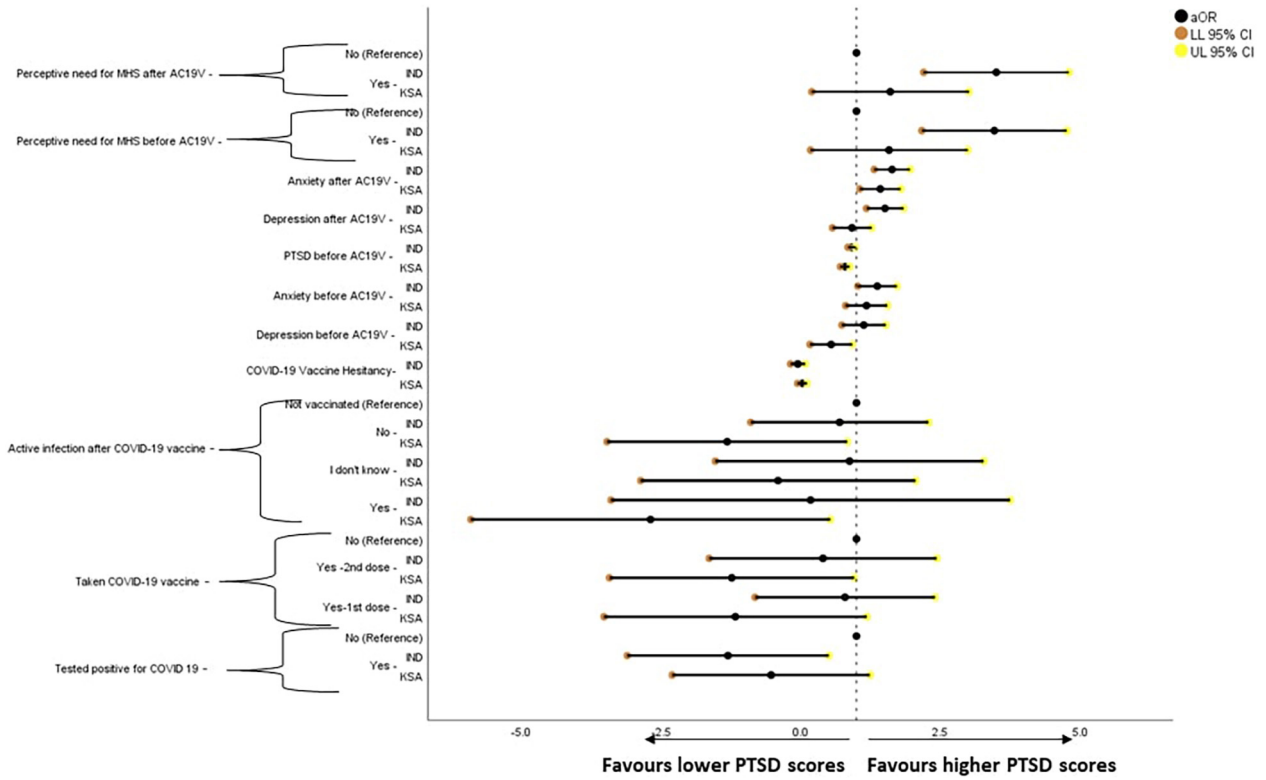

FIGURE 7 | Forest plot showing adjusted generalized linear regression analysis of post-traumatic stress disorder scores (regression model 2). aOR, adjusted Odds Ratio; Odds ratio adjusted for Sociodemographic factors. 95% CI, 95% Confidence Interval. The results of regression model 1, 2, and 3 in binary logistic regression analysis of depression scores is tabulated in **Supplementary Table 14**. Ind–India; KSA–Kingdom of Saudi Arabia.

advent of COVID-19 vaccine (**Supplementary Tables 1–3**). Saudi undergraduates showed a significant reduction in depression ($P = 0.009$) and anxiety ($P = 0.001$) symptoms after AC19V (**Tables 2**, **3**), and Indian undergraduates showed a significant reduction in PTSD symptoms after AC19V (**Table 4**). Those with lower educational status were at higher risk of negative mental health, and it was those with undergraduate level of education who showed improvement in their mental health with AC19V (**Supplementary Tables 1–4, 6–9**). Depression ($P = 0.002$), anxiety ($P = 0.006$), and PTSD ($P = 0.020$) levels of Saudis living in urban areas decreased with AC19V. Saudis in rural areas had higher depression levels ($P = 0.004$) before AC19V and higher anxiety levels before ($P = 0.001$) and after ($P = 0.036$) AC19V than Indian rural dwellers. PTSD levels of Indians residing in both urban ($P = 0.005$) and rural areas ($P = 0.024$) decreased after AC19V. The influence of place of residence on mental health in relation to AC19V was contradictory to other sociodemographic variables. Urban dwellers who were less vulnerable to the negative impact of the pandemic on mental health showed significant improvement with AC19V. Saudis without any income showed a significant reduction in depression ($P = 0.009$) and anxiety ($P = 0.019$) symptoms after AC19V. PTSD symptoms significantly decreased in Indians with monthly income above 50,000 INR ($P = 0.047$) and those without any income ($P = 0.001$) and in Saudis with income less than 10,000 SAR ($P = 0.006$) after AC19V. Even though the changes in PTSD symptoms showed heterogeneity in relation to economic status, depression and anxiety were reduced in the no-income group with the advent of the COVID-19 vaccine which was the high-risk group. Saudi non-healthcare workers and unemployed individuals showed a significant reduction in depression ($P = 0.005$), anxiety ($P = 0.013$) and PTSD symptoms ($P = 0.009$) after AC19V. Saudi students in the healthcare field showed a significant reduction in anxiety symptoms ($P = 0.025$) after AC19V. Saudi students in the healthcare field had higher levels of depression symptoms when compared to those in India both before ($P = 0.007$) and after AC19V ($P = 0.026$). Anxiety levels were higher in Saudi students in the healthcare field ($P = 0.020$) and non-healthcare workers and unemployed individuals ($P = 0.018$) when compared to the corresponding subset in India before AC19V (**Tables 2–4**). The response of the study population to AC19V in both countries showed heterogeneity in relation to their employment status, wherein a reduction in negative mental health symptoms was observed irrespective of the risk of negative mental health before AC19V. Thus, except for the place of residence and employment status, those in the subgroups of sociodemographic variables who were at higher risk of negative mental health before AC19V were the ones who showed improvement in their mental health after AC19V.

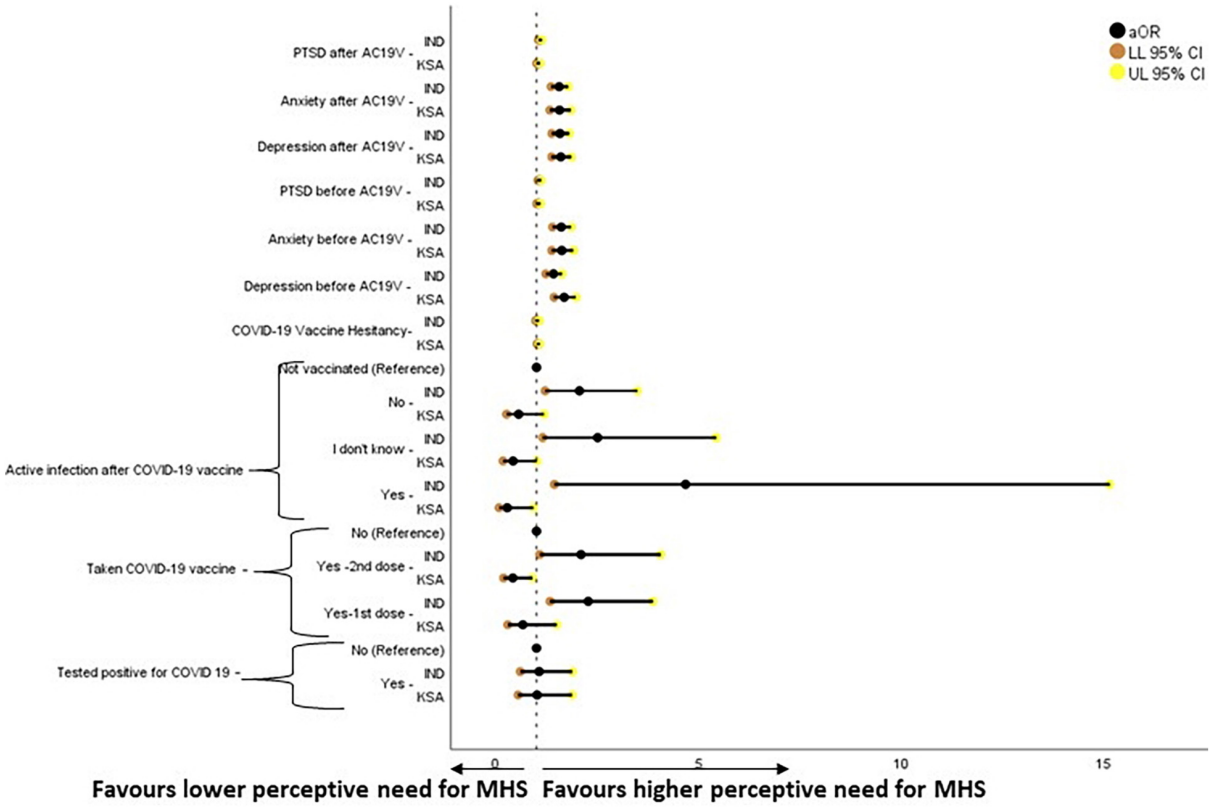

FIGURE 8 | Forest plot showing adjusted binary logistic regression analysis of perception of need for Mental Health Support (regression model 2). aOR, adjusted Odds Ratio; Odds ratio adjusted for Sociodemographic factors. 95% CI, 95% Confidence Interval. The results of regression model 1, 2, and 3 in binary logistic regression analysis of depression scores is tabulated in **Supplementary Table 15**.

COVID-19 Vaccine Hesitancy

The prevalence of COVID-19 vaccine hesitancy in India was 50.8% (95% CI 45.73–55.89%) and in Saudi Arabia was 55.7% (95% CI 50.16–61.31%). Though the percentage of the study participants who were not vaccinated against COVID-19 was less (26% in India and 12.1% in Saudi Arabia), vaccine hesitancy was relatively higher. This shows that even those who got themselves vaccinated against COVID-19 continued to exhibit vaccine hesitancy. Similar results were observed in a study conducted in Israel (76). Lack of data availability regarding the long term effects of the vaccine and the general mistrust regarding its efficacy and safety could be the reasons behind this finding (77). Comparison of vaccine hesitancy between the two countries showed that the levels of vaccine hesitancy were significantly higher in Saudi Arabia than in India though there was no difference in their prevalence (**Table 5**). In Saudi Arabia, among the sociodemographic variables, place of residence and gender was found to be significantly associated with vaccine hesitancy. Females were 1.65 (95% CI: 1.025–2.656) times more likely to have vaccine hesitancy than males (**Supplementary Table 10**) and people living in rural areas had higher vaccine hesitancy than those living in urban areas (**Table 5**). Similar to our results, globally, females have been found to be more vaccine hesitant than males (78). One possible reason could be that females who were pregnant and lactating were excluded from most COVID-19 vaccine clinical trials, and this would not have been reassuring for this subset of women and to those who were trying to get pregnant. Regarding the relation between the place of residence and vaccine hesitancy, the results in other studies vary from no relation (79) to higher vaccine hesitancy in rural area dwellers than urban area dwellers (80, 81). With urban areas being the central hub of activities with higher population size and hence increased disease spread, the rural area dwellers might have felt relatively safer and not compelled to get vaccinated. On the other hand, there was no significant association between any of the studied sociodemographic variables and vaccine hesitancy in India. This finding is in contrast to the study conducted in June 2021 in India, which found age and gender to be significantly related to vaccine hesitancy (82). However, similar to our results, other multinational studies assessing vaccine hesitancy has found the association between sociodemographic variables and vaccine hesitancy to be varying in different countries (83).

Comparison of vaccine hesitancy between India and Saudi Arabia showed that the levels of vaccine hesitancy were higher in Saudi Arabia than in India and in Saudi females, unmarried individuals, those with undergraduate level of educational status, non-healthcare workers and unemployed individuals and those residing in urban and rural areas when

compared to their Indian counterparts. A recent multinational study conducted by Qunaibi et al. (84) in 23 Arab countries and 122 non-Arab countries has found that willingness to vaccinate was higher in countries with higher rates of COVID-19 (84). This explains the higher COVID-19 vaccine hesitancy in Saudi Arabia than India, which had lesser severity of COVID-19 spread than India at the time of the survey.

Analysis of risk and protective factors for vaccine hesitancy showed that above and beyond the effect of sociodemographic factors, COVID-19 status of being vaccinated and not developing an active infection after vaccination was significantly associated with vaccine hesitancy. Being vaccinated against COVID-19 was associated with lower levels of vaccine hesitancy in India and Saudi Arabia. In India, being vaccinated with first [aOR 0.393, 95% CI (0.232–0.666)] and second dose [aOR 0.291, 95% CI (0.149–0.565)] was found to be protective while in Saudi Arabia, being vaccinated with second dose [aOR 0.372, 95% CI (0.164–0.845)] alone was protective against vaccine hesitancy. In contrast, being vaccinated with first dose when adjusted for the effect of confounding sociodemographic variables showed no significant relation (**Supplementary Table 11** and **Figure 4**). Those who did not develop an active infection after COVID-19 vaccinations were found to be less likely to be vaccine-hesitant than those who were not vaccinated both in India [aOR 0.309, 95% CI (0.182–0.522)] and Saudi Arabia [aOR 0.397, 95% CI (0.177–0.890)]. With the COVID-19 vaccine's safety and efficacy being identified as some of the top reasons for vaccine hesitancy the absence of active infection after vaccination would have been reassuring and favored vaccine acceptance (85, 86).

COVID-19 Vaccine Hesitancy and Mental Health

The study found a bidirectional association between COVID-19 vaccine hesitancy and mental health in Saudi Arabia, over and above the effect of sociodemographic factors and COVID-19 status in relation to infection and vaccination. Higher levels of vaccine hesitancy were found to increase the risk of depression [aOR 1.033, 95% CI (1.001–1.067)], anxiety [aOR 1.037, 95% CI (1.002–1.074)] and perceived need for MHS [aOR 1.043, 95% CI (1.012–1.075)] (**Supplementary Tables 12, 13, 15** and **Figures 4**, **5**, **7**). On the other hand, depression [aOR 1.350, 95% CI (1.167–1.563)—before AC19V, aOR 1.200, 95% CI (1.050–1.372)—after AC19V], anxiety [aOR 1.344, 95% CI (1.150–1.570)—before Ac19V, aOR 1.409, 95% CI (1.197–1.659)—after AC19V], and perceived need for MHS [aOR 2.053, 95% CI (1.239–3.403)—before AC19V, aOR 1.958, 95% CI (1.184–3.238)—after AC19V] both before and after AC19V were found to be significant risk factors for vaccine hesitancy with higher levels of these variables favoring higher vaccine hesitancy (**Supplementary Table 11** and **Figure 4**). Contrarily in India, we did not find a bidirectional association between mental health and vaccine hesitancy. None of the mental health parameters was found to predict vaccine hesitancy individually or when adjusted for sociodemographic factors and sociodemographic factors along with COVID-19 status (**Supplementary Table 11**). Notwithstanding, higher levels of vaccine hesitancy was found to increase the risk for anxiety [aOR 1.058, 95% CI (1.007–1.111)] (**Supplementary Table 13** and **Figure 5**). Similarly, a study done in vaccinated individuals showed that vaccine hesitancy increased the risk for depression, anxiety and peritraumatic stress (76). The present study is the first of its kind to highlight the mutual impact of mental health status and vaccine hesitancy in the general population. Most studies assessing the relation between vaccine hesitancy and mental health were conducted in people with existing mental health disorders. A study conducted in the United Kingdom found that diagnosis of anxiety and depression before the pandemic was not associated with vaccine hesitancy (87). Another study conducted on patients with psychiatric disorders found that generalized anxiety disorder, PTSD and major depressive disorder were not related to vaccine hesitancy once adjusted for sociodemographic factors and physical co-morbidities (88). Thus, the present study gives important insights into the mental health status and its association with vaccine hesitancy in the general population which indicates that the issue of vaccine hesitancy should be addressed immediately to mitigate its effect on mental health.

STRENGTHS AND LIMITATIONS OF THE STUDY

The study investigated the relationship between mental health status and COVID-19 vaccine hesitancy before and after the advent of COVID-19 vaccines in the general population of India and Saudi Arabia. We used a newly constructed COVID19-VHS12 scale and performed psychometric analysis and validated the scale in English and Arabic versions which enabled us to use it as a binary response scale. The present study is the first to explore the relation between COVID-19 vaccine hesitancy and mental health during the COVID-19 pandemic in the general population and compare between two countries. The exhaustive analysis of the confounders and predictor variables with respect to the advent of the COVID-19 vaccine had enabled us to assert the pattern and delineate the temporal order of the influence of each predictor variable. The comparative study between the two countries will help better understand the varying relation between vaccine hesitancy and mental health across different sociodemographic groups. This will help the healthcare authorities and policymakers devise strategies and policies to surmount the impact of vaccine hesitancy and the negative impact of the pandemic on mental health.

The study is not without shortcomings. The relatively smaller sample size is the main limitation of our study, though the detailed analysis of the collected data outweighs any frailty that may have arisen with the smaller sample. However, the findings of our study should be generalized with caution as the representativeness of the samples is limited. Due to the online nature of the survey, the study participants were primarily from those who had special keenness to know about COVID-19 pandemic and vaccination. Hence, more samples were drawn from healthcare sector and of younger age groups. Another limitation of this study is the use of mental health screening tools, which included ultrashort screening tools, viz., PHQ-2, GAD-2, and IES-6 which cannot substitute a complete

clinical examination to arrive at a diagnosis. The cross-sectional nature of the study limits the determination of causality. Given the survey nature of the study, social desirability bias and recall bias to answer the questionnaires could be other limitations of our study.

CONCLUSION

COVID-19 vaccine hesitancy is a critical barrier in accomplishing herd immunity against COVID-19. From the results of our study, it is clear that vaccine hesitancy has a negative impact on mental health and vice versa over and above the impact of sociodemographic factors and COVID-19 vaccination and infection status. We demonstrated that the mutual impact of COVID-19 vaccine hesitancy and mental health varied between India and Saudi Arabia which differed in pandemic severity and vaccine mandates. Our study also shows that, vaccine hesitancy is a predictor for depression, anxiety, post-traumatic stress disorder and perceptive need for MHS in Saudi Arabia while, vaccine hesitancy is a predictor for anxiety alone in India. Similarly, all the above-mentioned mental health parameters were predictors of Vaccine hesitancy in Saudi Arabia but not in India. This is a significant finding of this preliminary comparative study which emphasizes variation of mutual impact between vaccine hesitancy and mental health across different borders globally. Future multinational studies are needed to probe further into this phenomenon to devise strategies to address them and better equip vulnerable nations to combat this serious global health threat of vaccine hesitancy.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Majmaah University Research Ethics Committee and Institutional Ethical Committee of Madha Medical College and Research Institute. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SJ and SI: study conception. SJ, SI, and SK: study design. SK, AP, SM, AAla, AAlj, ASA, and YH: data collection. SJ, SI, AP, SM, AAla, and AAlj: data analysis and manuscript drafting. SJ, SI, AAla, AAlj, ASA, and YH: data interpretation. AP, SM, AAla, and AAlj: critical revision of the manuscript. All authors approved the final version, contributed to the article, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.900026/full#supplementary-material

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On Imported and Domestic Human Papillomavirus Vaccines: Cognition, Attitude, and Willingness to Pay in Chinese Medical Students

Liangru Zhou†, Baiyang Gu†, Xiaoxue Xu, Yue Li, Pengxin Cheng, Yue Huo, Guoxiang Liu and Xin Zhang**

School of Health Management, Harbin Medical University, Harbin, China

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***Correspondence:**
Guoxiang Liu
lgx6301@163.com
Xin Zhang
zhangxinzhx0801@126.com

†These authors have contributed equally to this work and share first authorship

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This study aimed to analyze the cognition, attitude, and willingness to pay (WTP) for imported and domestic human papillomavirus (HPV) vaccines in Chinese medical students.

Methods: Medical students in Eastern, Central and Western China were investigated. We used the HPV cognitive list to measure the cognition of participants and implemented contingent valuation method (CVM) to value WTP. Tobit model was used to analyze the factors associated with WTP.

Results: The participants' average score for the 21 cognitive questions was 13.05 (±5.09). Among the participants, 60.82 and 88.01% reported that they would wish to be vaccinated and support the partners to be vaccinated. In addition, 92.54% (670) of the participants were willing to pay for HPV vaccines, at mean values (in RMB) of 1,689.80 (±926.13), 2,216.61 (±1190.62), and 3,252.43 (±2064.71) for imported bivalent, quadrivalent, and 9-valent vaccines, respectively, and at 910.63 (±647.03), 1,861.69 (±1147.80), and 2,866.96 (±1784.41) for their domestic counterparts, respectively. The increase in cognitive score has a positive effect on the WTP for imported vaccines ($P < 0.05$).

Conclusions: Most of the participants were likewise willing to receive the HPV vaccines. Their perceptions of the HPV vaccines valent and origin may affect their willingness to be vaccinated and pay for the vaccines. Increasing awareness of the HPV vaccines and the inclusion of the HPV vaccines in a Medicare reimbursement policy or immunization program could increase the coverage of the HPV vaccine.

Keywords: HPV vaccine, immunization coverage, CVM, Tobit model, willingness to pay

INTRODUCTION

The human papillomavirus (HPV) vaccine was designed to protect humans from the risk of disease caused by HPV. When vaccinated, a vaccinated person can expect their immune system to respond to the virus, if exposed (1). Both males and females of appropriate age can be vaccinated with the quadrivalent or 9-valent vaccines.

The World Health Organization has stated that all three registered HPV vaccines, namely, the bivalent, quadrivalent, and 9-valent vaccines, have good safety, efficacy, and effectiveness (2). Studies have shown that HPV vaccination in 156 out of 179 countries has an incremental cost-effectiveness ratio of less than one time per capita GDP for saving one disability-adjusted life year (DALY), which is very cost-effective (3). The cost of cancer treatment is estimated to be reduced by approximately USD 12,400 for every quality-adjusted life years (QALY) received by adolescents and young adults in the United States receiving the HPV vaccine (4). Mo et al. pointed out that combined with the screening strategy of cervical cancer in mainland China, the vaccination of quadrivalent and 9-valent vaccines has been highly cost-effective (5).

At present, 110 countries and regions worldwide have included the HPV vaccine in their immunization programs and vaccinated the target population for free (6). However, the HPV vaccine has not been included in the medical insurance or immunization program in China. Residents need to purchase the HPV vaccine in full at their own expense. This hinders the coverage of HPV vaccines to a certain extent. The main problems encountered in the promotion of any new vaccine, especially those that require payment, are the public's response and the attitudes of different groups toward the purchase of vaccines (7, 8). Particularly in developing countries, high prices have always been a major obstacle to the introduction of HPV vaccines. Therefore, understanding the WTP for HPV vaccines of residents in developing countries is of great significance to the introduction and pricing of vaccines. Research on willingness to pay (WTP) for HPV vaccines has been carried out in Vietnam (9), Nigeria (10), Thailand (11) and other countries. However, evidence of WTP for HPV vaccines is still lacking in China. Our study aimed to provide more evidence on WTP for HPV vaccines from China and to explore factors associated with WTP for HPV vaccines.

MATERIALS AND METHODS

Study Design and Implementation

We conducted an anonymous survey on medical students in Harbin Medical University, Hebei Medical University, and Chengdu University of Traditional Chinese Medicine, representing central, eastern, and western China, respectively, from November 2020 to March 2021. We used online forms to collect information via https://www.wjx.cn/. We applied the CVM to evaluate the WTP of each participant. Each respondent received 2RMB in cash as remuneration, which was paid through online payment. The Harbin Medical University School of Health Management & nstitutional Research Board approved the study protocol (HMUIRB20210006).

Data Collection and Questionnaire Measures

The online form contained items on the basic information of respondents, the perceptions of the respondents about HPV infections and vaccines and their WTP. A total of 850 medical students were invited. Basic information included demographic information, such as sex, age, educational background, type of family residence, partner status, monthly consumption level, and health behaviors. We used HPV cognitive lists to assess the participants' knowledge of HPV infections and vaccines. The list contains 21 items, to which the participants responded either agree, unclear, or disagree. We compiled the 21 items from existing HPV cognition research, popular discussions on HPV vaccines in popular social media apps (Zhihu, WeChat, Weibo), and supplementary content through derived from pre-surveys and interviews. We mixed all cognitive content into a pool of cognitive items. Duplicate items were eliminated, and the items were further filtered to form the final list (**Table 2**). The score for this measure was the cumulative number of items answered correctly by the participant (1 point per correct response). The score ranged from 0 to 21 points, with higher scores indicating a higher likelihood of the participant having richer knowledge of HPV infections and vaccines. We also calculated the percentage of each item that was answered correctly to analyze the participants' perception of each knowledge item. Those who reported negative responses to the questions "Have you heard of HPV?" and "Have you heard of the HPV vaccine?" were not asked to answer this cognitive list. Notably, before responding to the above two questions related to vaccination attitudes, the respondents read the WHO introduction on HPV(Additional file 1) (12, 13). This approach was implemented to avoid the respondents from making rash decisions attributable to their lack of HPV knowledge when answering questions.

Respondents who expressed acceptance of the HPV vaccine answered the WTP questionnaire. We calculated WTP as the amount of money willing to spend on vaccines. We used the questions "If the HPV vaccine is included in the national immunization program and can be availed for free, would you be willing to be vaccinated?" and "If the HPV vaccine needs to be availed at your own expense, will you get yourself vaccinated?" to analyze respondents' attitude toward the HPV vaccine when it is provided for free and at their own expense. If the respondent was still unwilling to be vaccinated under the assumption of zero price, then the respondent was asked to report the reason. Those willing to pay for vaccination were asked about their views on the different full-dose prices of HPV vaccines.

The contingent valuation method was used to obtain the respondents' WTP. To simulate the real-market environment, we adopted the iterative bidding game (IBG) methods (14) in our investigation of the participants' WTP. IBG is the guiding method of CVM and has been criticized for putting pressure on interviewees owing to repeated inquiries. To address the issues related to repeated price inquiry, we used sliding scale fees to ask the respondents' WTP for imported HPV vaccines. Participants directly slid the price ruler to mark their expected price. They could also directly fill in the expected price in the space to the left of the price ruler. We divided the range of the price ruler according to the responses to the market price. The price scale was divided into two parts based on respondents' response to the initial

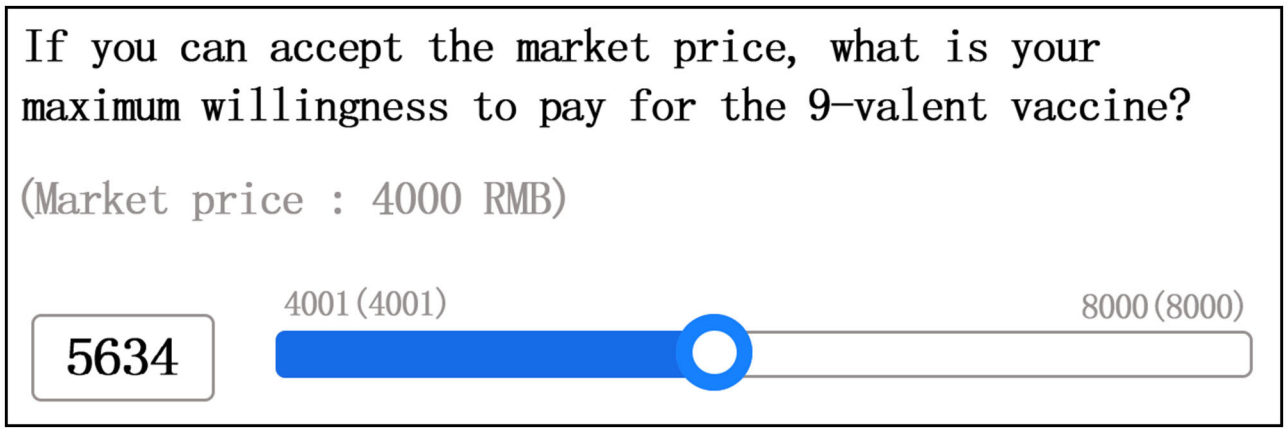

FIGURE 1 | WTP for 9-valent HPV vaccine sliding price (example 1).

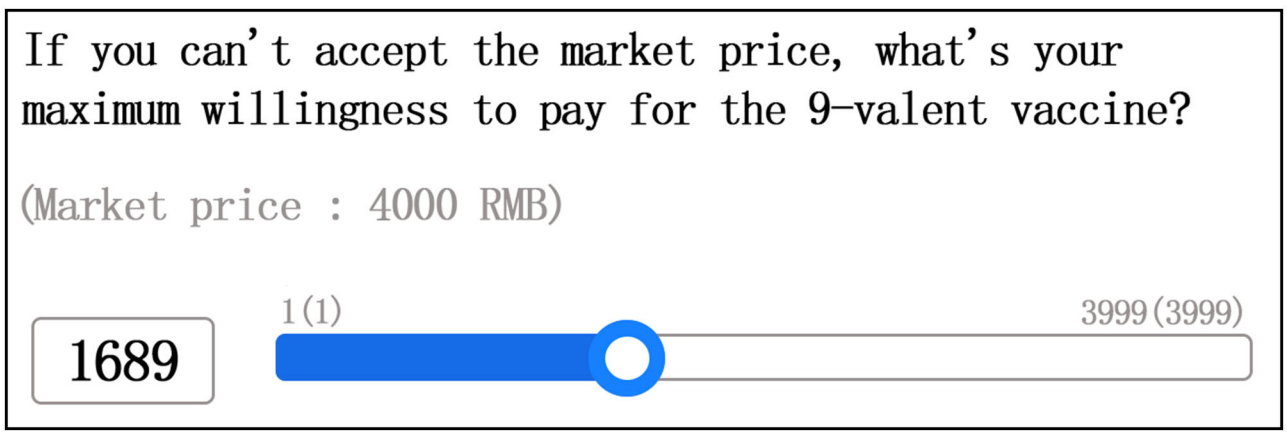

FIGURE 2 | WTP for 9-valent HPV vaccine sliding price (example 2).

price, as shown in **Figures 1**, **2**. The beginning and end price in the ruler fluctuated by 1 RMB according to the market price.

Given that only bivalent vaccines are available as domestic vaccines in China (15), and the other two valence vaccine types are not yet on the market, the WTP for domestic vaccines cannot provide the market price. Thus, we used the IBG method to ask those who were willing to be vaccinated with the domestic vaccine to slide the price ruler directly to mark the price. The price scale range was "1 to Import Vaccine market price * 2 RMB".

We limited the vaccine valence types that the respondents could fill in by setting age limits. Females aged 9–26 years could answer the WTP for full valent vaccines, whereas females aged 27–45 years were only allowed to answer the WTP for bivalent and quadrivalent vaccines (16). In mainland China, the HPV vaccine is not yet recommended for males. But in the United States males were allowed to receive the quadrivalent/9-valent HPV vaccine. Males aged 9–26 years were allowed to answer the WTP for quadrivalent and 9-valent vaccines, whereas males aged 27–45 years could answer the WTP for 9-valent vaccine (17, 18).

Statistical Analyses

Statistical analyses were performed using Stata Version 15 and Microsoft Excel Version 2016. We analyzed the participants' degree of knowledge reserve, vaccination attitudes, and WTP for different valence vaccines. The McNemar's test was used to compare whether there were differences in the acceptance rate of vaccines from different origins. Tobit model was used to analyze the influencing factors of WTP. Respondent who unwilling to pay for the vaccine, his WTP is recorded as 0, and there is a censorship of the lower limit of WTP. At the same time, limited by the scope of the WTP scale, WTP has an upper limit of censorship. Tobit model is suitable for analyzing dependent variable has upper or lower limit. $P < 0.05$ was considered significant.

TABLE 1 | Demographic characteristics of participants.

Characteristics	*N* (%)
Total	809 (100.00)
Sex	
Female	475 (58.71)
Male	334 (41.29)
Age group	
16–26	600 (74.17)
27–45	209 (25.83)
Educational background	
Undergraduate	419 (51.79)
Graduate and above	390 (48.21)
Type of family residence	
Urban	626 (77.38)
Rural	183 (22.62)
Partner status	
No partner	702 (86.77)
Have a partner	107 (13.23)
Consumption level (Monthly)	
≤2,000 RMB	469 (57.97)
>2,000 RMB	340 (42.03)
Hours of exercise (Weekly)	
≤3 h	681 (84.18)
>3 h	128 (15.82)

RESULTS

Participants' Characteristics

Table 1 summarizes the basic characteristics of the respondents. A total of 809 medical students were surveyed, including 475 female (58.71%) and 334 male (41.29%). There are 600 people aged 16–26 (74.17%), and 209 people aged 27–45 (25.83%).

Knowledge of HPV Infection, Related Diseases, and Prevention

Among the respondents, 751 (92.83%) had heard of HPV, and 728 (89.99%) had heard of the HPV vaccine. A total of 728 respondents answered the questions in the cognitive list. The average cognitive score was 13.05 (±5.09) points. The respondents maintained a high level of cognition of HPV infection, transmission, and vaccination population but reported insufficient awareness of post-vaccination. Most of them correctly replied that HPV could be sexually transmitted (86.81%) and that males and females contracted HPV (79.95%) (**Table 2**). Moreover, 60.85% of the respondents were aware that an HPV infection can be transmitted from the pregnant mother to the baby during pregnancy.

Regarding the applicable population of HPV vaccine, 78.16% of the participants knew that males can also get the HPV vaccine, 60.85% knew that vaccination is not be recommended for pregnant females, and 55.49% knew that males need to receive the HPV vaccine. More than half (57.69%) of the respondents knew that those who have contracted HPV could also be vaccinated.

Of the post-vaccination part, 30% did not know that they still need cervical cancer screening after HPV vaccination. About 30% could not clearly recognize that the HPV vaccine reduces the risk of cervical cancer but not eliminate it. Nearly 40% of the respondents hold the erroneous view that 9-valent has the highest protective effect, and that vaccination with other valence types is meaningless if the 9-valent vaccine cannot be vaccinated. Meanwhile, 39.56% reported misinformation that China's vaccines are obsolete abroad, and 30% had the false view that an HPV vaccine is harmful to the health and leads to HPV infection.

Attitudes on HPV Infection and Prevention

We investigated the attitudes of respondents themselves and their partners toward HPV. A total of 60.82% of the people reported that they would like to be vaccinated, 30.90% of the respondents said that they did not have the willingness to be vaccinated at this stage, and a total of 8.28% were unwilling to be vaccinated. **Table 3** summarizes the results.

Willingness to Pay for HPV Vaccines

Excluding 67 people (8.28%) who were unwilling to receive the HPV vaccine, a total of 742 people filled out the WTP questionnaire. Under the condition that the HPV vaccine is contained in the national immunization program, 724 (97.57%) respondents indicated their willingness to be vaccinated. The reluctance of the remaining 18 (2.43%) respondents was due to the unclear complications and low confidence in free vaccines.

In the case of the HPV vaccine charges, 670 (92.54%) of the respondents were willing to be vaccinated. The 54 (7.46%) who were unwilling to pay for the vaccine stated the following reasons other than the price: "I think it is unnecessary," "After vaccination, it is not once and for all," "HPV can be prevented by condoms, and there is no need to spend so much money on vaccination," "Vaccination is painful," and "Lack of authoritative evidence for long-term side effects."

Figure 3 presents the number of people willing to pay for HPV vaccines. The number of people willing to pay for domestic vaccines of various valence was lower than that of imported vaccines ($P < 0.01$). Respondents whose WTP for imported vaccines exceeded the current market price of 1,740 RMB accounted for 76.96% of the target population for the bivalent. Respondents with a WTP higher than 2,469 RMB accounted for 66.38% of the total population of those willing to be vaccinated with a quadrivalent vaccine. Respondents with a WTP higher than 4,000 RMB accounted for 49.14% of the target population of the 9-valent vaccine (**Figure 4**).

Table 4 gives the WTP values in RMB for imported and domestic HPV vaccines. The results revealed that the average WTP of the vaccines was lower than the market price. Moreover, the WTP for domestic vaccines was lower than that for imported vaccines, and the gap in WTP for bivalent vaccines was the largest.

TABLE 2 | Respondents' HPV cognitive list.

Knowledge statement	Response	Correct (N/%)	Not sure (N/%)	Wrong (N/%)
Infection and transmission				
Coitus is one of the main routes of HPV infection	True	632 (86.81)	71 (9.75)	25 (3.43)
There is no need to get the HPV vaccine as long as you have only one regular sexual partner	False	455 (62.50)	107 (14.70)	166 (22.80)
Both male and female can be infected with HPV	True	582 (79.95)	102 (14.01)	44 (6.04)
A woman infected with HPV is bound to develop cervical cancer	False	431 (59.20)	131 (17.99)	166 (22.80)
HPV infection can be passed from mother to child during pregnancy or during childbirth	True	443 (60.85)	217 (29.81)	68 (9.34)
HPV can be transmitted through indirect contact, such as underwear	True	350 (48.08)	175 (24.04)	203 (27.88)
Having HPV increases the chances of contracting HIV	False	100 (13.74)	178 (24.45)	450 (61.81)
A person may be infected with HPV virus without any symptoms	True	589 (80.91)	113 (15.52)	26 (3.57)
Applicable population				
People who have sex can also be vaccinated against HPV	True	569 (78.16)	118 (16.21)	41 (5.63)
Pregnant female are not recommended to receive HPV vaccine	True	443 (60.85)	234 (32.14)	51 (7.01)
If you have been infected with HPV, you don't need to get the HPV vaccine again	False	420 (57.69)	161 (22.12)	147 (20.19)
Male do not need to be vaccinated against HPV	False	404 (55.49)	197 (27.06)	127 (17.45)
Post-vaccination				
The HPV vaccine is harmful to health	False	350 (48.08)	159 (21.84)	219 (30.08)
The HPV vaccine causes an HPV infection	False	357 (49.04)	165 (22.66)	206 (28.30)
Female can not participate in cervical cancer screening after receiving HPV vaccine	False	506 (69.51)	98 (13.46)	124 (17.03)
To prevent HPV, you still need to use condoms if you have sex after getting the HPV vaccine	True	557 (76.51)	115 (15.80)	56 (7.69)
Female who have been vaccinated against HPV will not get cervical cancer	False	497 (68.27)	118 (16.21)	113 (15.52)
HPV vaccines available on the market can treat HPV infections	False	425 (58.38)	131 (17.99)	172 (23.63)
The higher the HPV vaccine order, the more viruses are prevented	True	505 (69.37)	142 (19.51)	81 (11.13)
It is meaningless to vaccinate other valence vaccines except 9 valence	False	445 (61.13)	132 (18.13)	151 (20.74)
The HPV vaccine approved by China was eliminated by other countries	False	440 (60.44)	142 (19.51)	146 (20.05)

TABLE 3 | Respondents ' attitudes toward HPV vaccination.

Vaccination attitudes	*N*	%
Respondents' vaccination attitudes		
Willing to be vaccinated	492	60.82
May be vaccinated in the future	250	30.90
Unwilling to be vaccinated	67	8.28
Vaccination attitudes toward partners/future partners		
Support	712	88.01
It doesn't matter	88	10.88
No support	9	1.11

Multivariate Analysis

The dependent variables of the multiple regression include respondents who are unwilling to pay for the vaccine (**Table 5**). Rural household registration, graduate degree and above had a negative effect on the WTP for various vaccines ($P<0.05$). The increase in cognitive score has a positive effect on the WTP for imported vaccines ($P < 0.05$). Female's WTP for domestic quadrivalent and imported 9-valent HPV vaccines was higher than that of male ($P < 0.05$). After controlling for the fact that WTP has upper and lower limit, female is expected to increase the WTP by 387.23 and 612.72 yuan, ceteris paribus.

DISCUSSION

Our research reported respondents' awareness of HPV transmission, pathogenesis, vaccination, and the applicable population. The results showed that Chinese medical students were no strangers to HPV or its vaccines. Almost all (92.83%) of the respondents had heard of HPV. This result is slightly lower than that of an Italian study of nursing students (96%) (19). It is also slightly lower than that in a study in Fujian, China, in which 96.1% of medical students said they "know HPV"(20). In our study, 89.99% of the respondents reported that they had heard of the HPV vaccine. In contrast to medical students in southern India, only 59.7% of whom reported HPV cognition (21), Chinese medical students may be more aware of HPV vaccines.

Our participants lacked or had poor knowledge of HPV's transmission channels. Most of them knew that HPV is a sexually transmitted virus and that both males

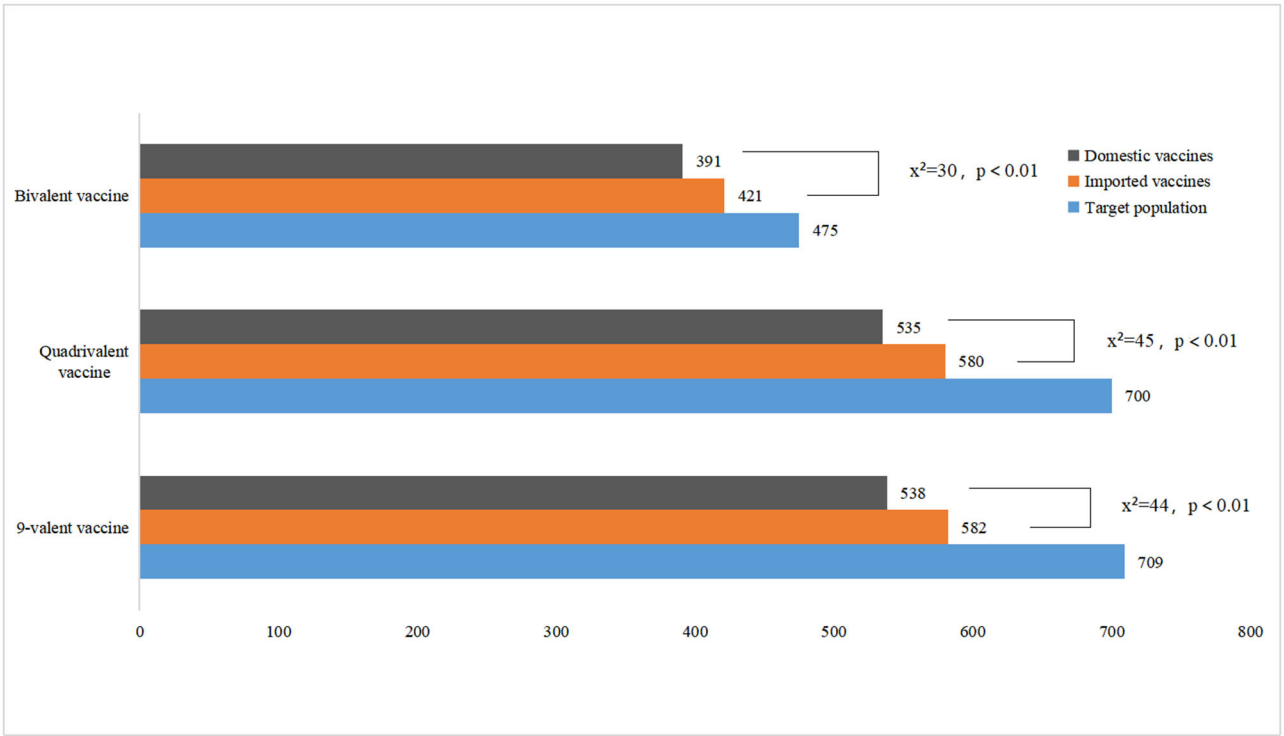

FIGURE 3 | Respondents' willing to pay for HPV vaccination.

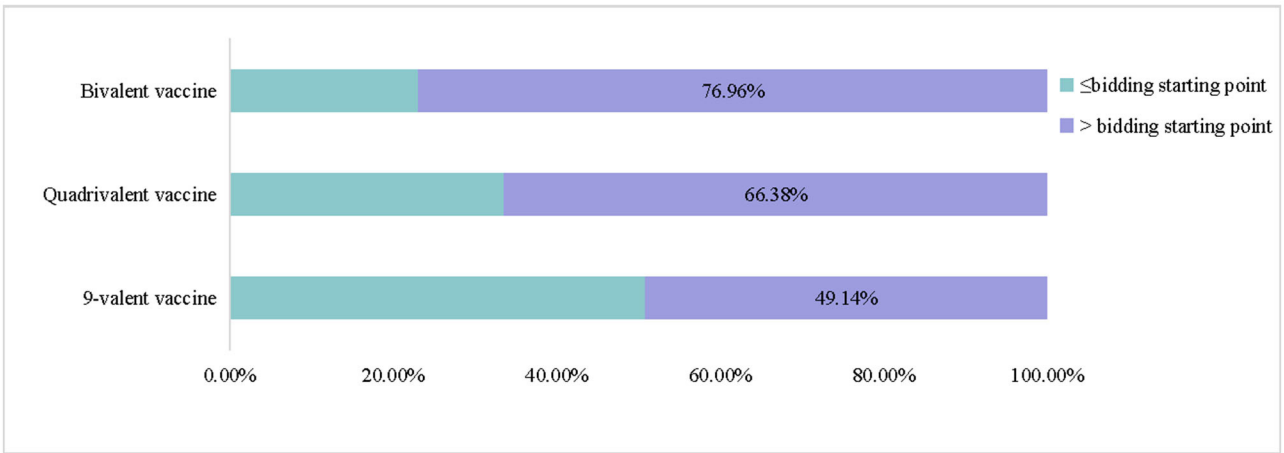

FIGURE 4 | Distribution of respondents' WTP for different valences vaccines.

and females can be infected (>80%). Nonetheless, they did not know that HPV can be transmitted through mother-to-child transmission (60%) and indirect contact (48.08%). Moreover, 20% of them did not understand that males need to be vaccinated against HPV. People often consider HPV vaccines as cervical cancer vaccines. Once a vaccine is labeled as a sex vaccine, more effort is needed to correct misconceptions.

Males can directly benefit from HPV vaccination. A meta-analysis showed that vaccination with a quadrivalent vaccine can reduce the incidence of genital warts in boys (22). In our interview, there were male respondents who believed that they

TABLE 4 | WTP for imported and domestic HPV vaccines, full dose.

Willingness to pay	Bivalent (1740RMB)	Quadrivalent (2469 RMB)	9-valent (4000 RMB)
	Mean±SD (RMB)	Mean ± SD (RMB)	Mean ± SD (RMB)
WTP for imported vaccines	1689.80 ± 926.13	2216.61 ± 1190.62	3252.43 ± 2064.71
≤ Bidding starting point	604.34 ± 400.89	944.08 ± 614.64	1603.23 ± 1033.79
> Bidding starting point	2150.05 ± 578.31	2941.60 ± 603.20	4862.23 ± 1093.44
WTP for domestic vaccines	910.63 ± 647.03	1861.69 ± 1147.80	2866.96 ± 1784.41

TABLE 5 | Tobit model of WTP for HPV vaccines.

Characteristics	Bivalent HPV vaccine		Quadrivalent HPV vaccine		9-valent HPV vaccine	
	Imported	Domestic	Imported	Domestic	Imported	Domestic
	Coef (95%CI)	Coef (95%CI)	Coef (95%CI)	Coef (95%CI)	Coef (95%CI)	Coef (95%CI)
27–45 year	−98.24	70.05	−63.59	90.73	–	–
	(−348.71, 152.23)	(−99.33, 239.42)	(−384.6, 257.42)	(−213.75, 395.22)	-	–
Female	–	–	26.51	387.23*	612.72**	195.55
	–	–	(−373.03, 426.06)	(12.50, 761.96)	(166.96, 1058.47)	(−194.89, 585.98)
Graduateand above	−140.15**	−59.86*	−150.86**	−68.17	−383.81***	−196.89**
	(−228.89, −51.41)	(−118.65, −1.07)	(−252.29, −49.43)	(−162.54, 26.21)	(−553.17, −214.44)	(−344.15, −49.62)
Rural	−341.96**	−191.36*	−297.23*	−438.45***	−734.41**	−596.24**
	(−569.06, −114.86)	(−346.00, −36.71)	(−573.4, −21.05)	(−700.94, −175.96)	(−1,202.5, −266.33)	(−1,000.13, −192.35)
Have partner	194.93	186.38	27.43	168.46	−61.02	−454.24
	(−136.48, 526.35)	(−32.47, 405.22)	(−322.64, 377.5)	(−157.80, 494.71)	(−855.12, 733.08)	(−1110.01, 201.53)
Exercise hours>3 h	343.13*	166.55	315.05*	273.84	−407.44	183.51
	(73.50, 612.77)	(−13.71, 346.81)	(8.76, 621.34)	(−10.57, 558.25)	(−995.41, 180.54)	(−329.62, 696.64)
Cognitive score	35.58**	0.33	45.25***	−7.23	71.56***	−13.45
	(15.14, 56.02)	(−13.96, 14.63)	(21.83, 68.67)	(−29.97, 15.51)	(32.6, 110.51)	(−48.31, 21.41)
>2,000 RMB	118.57	42.56	156.82	125.06	233.86	232.10
	(−92.19, 329.35)	(−86.45, 180.60)	(−91.78, 405.43)	(−113.09, 363.21)	(−203.93, 671.66)	(−148.45, 612.65)
_cons	1587.19***	849.31***	1,984.90**	1154.80	3,693.26***	4,173.61***
	(744.15, 2430.23)	(287.90, 1410.72)	(572.99, 3396.79)	(−163.88, 2473.47)	(1938.73, 5447.78)	(2676.34, 5670.88)

*CI: confidence interval; *P < 0.05; **P < 0.01;***P < 0.001; -:not applicable.*

were not suitable to participate in the survey. This view reflected the prevailing misconceptions in society (23). In 2019, the WHO Strategic Advisory Group pointed out that the current supply of HPV vaccines is limited and called on countries to suspend the implementation of HPV vaccination strategies regardless of gender and age groups until all countries have equitable access to vaccine supplies (24). Only female vaccination is recommended in the clinical application of HPV vaccines (25). However, countries such as the Canada have begun to implement "sex-neutral" immunization programs (26).

The willingness to be vaccinated and to support the partners to be vaccinated tended to paint an optimistic trend. Only 8.28% of the participants clearly indicated their unwillingness to receive the HPV vaccine, and 1.11% did not support the partners to be vaccinated. Our results showed that 60.82% of the respondents were willing to be vaccinated. This result is similar to that in studies in Italian nursing students (65.3%) (19) and medical students in India (67.8%) (27). The results of the Tobit model show the importance of cognitive score to improve HPV vaccination coverage. It is very important to guide the interviewees to hold a positive view of HPV vaccine by popularizing HPV vaccine knowledge.

At present, there are bivalent domestic vaccines in China to replace imported bivalent vaccines. A randomized clinical experimental study in China showed that the domestic bivalent HPV vaccine has a high protection efficacy against uterine cancer (28). However, our participants reported a preference for imported vaccines. The imported HPV vaccine was approved by the US FDA in 2006 and has more than ten years of clinical use experience. In contrast, the first domestically produced HPV vaccine in China was

launched at the end of 2019. From the perspective of vaccine quality, many people have expressed a preference for imported vaccines.

Crowd psychology may be at play in the choice of the 9-valent vaccine, instead of a full understanding of the differences between valence types. From the recommended age group of the 9-valent HPV vaccine, it is ideal for those entering puberty. However, owing to the shortage of imported 9-valent vaccines in the Chinese market, a large number of females are aspiring to be vaccinated with this type, which has further pushed up the market demand. Indeed, the Chinese public has called for high-level evidence to clarify the advantages of domestic and imported vaccines. Clinical trials and health economic evaluation methods can provide more evidence in terms of vaccine safety, effectiveness, and resource allocation efficiency. Meanwhile, more publicity and promotion are needed to expand public understanding of HPV and the different valence vaccines.

Our findings on WTP indicated that most medical students were willing to pay for the HPV vaccine. However, under the premise of free vaccinations, 18 respondents expressed an unwillingness to receive the HPV vaccine for safety and other reasons. When it needs to be paid, the proportion of the respondents who were unwilling to be vaccinated increased from 2.43 to 7.46%. In China, the HPV vaccine is not included in the national immunization program. Many people refuse or postpone vaccination because they cannot pay for the vaccine. A study conducted in Hong Kong showed that 67.60% of doctors and 70.50% of nurses find HPV vaccines expensive (29). China's immunization program and implementation of insurance reimbursement policies for HPV vaccines will help increase the HPV vaccination rate. At present, select regions in China have included HPV vaccines in their insurance reimbursements. In Guizhou, the first HPV vaccine is free and subsequent shots can be paid on balance via personal insurance (30, 31). Assuming that those who are willing to pay less than the bid price will give up vaccination, the vaccination rate of bivalent vaccines at the current price was about 76%, whereas that of quadrivalent vaccines was <70%, and that of the 9-valent vaccine was <50%. Reducing the price of vaccines on the market or promoting the launch and pricing of domestic vaccines can increase willingness to be vaccinated.

The WTP values for imported vaccines were all below the market price. The willingness to import value for 9-valence vaccines was also far lower than the market price. At present, the import price of 9-valent vaccines is deemed to be too high. The respondents reported having limited ability to pay, especially the higher fees for the imported 9-valent vaccines. Meanwhile, bivalent domestic vaccines are consistent with the market price. Domestic quadrivalent and 9-valent vaccines are not yet available; their pricing may refer to our evidence. Nonetheless, the respondents were willing to pay more for imported vaccines and less willing to pay for domestic vaccines. Specifically, the payment willingness for domestic bivalent vaccines was far lower than that for imported bivalent vaccines. This may be because China has already launched a domestic bivalent vaccine, and the respondents already have an anchor price. The bivalent HPV vaccine produced in China costs 329 RMB per vial, about half the price of the imported bivalent vaccine.

Our research provides evidence on Chinese medical student' WTP for HPV vaccines and on HPV awareness and vaccination attitudes. The published studies have involved parents of adolescents (8, 10, 11), and our study provides evidence for the HPV vaccine WTP in medical students. In addition to being the beneficiaries of vaccination, medical students are also important personnel to promote HPV vaccine immunization in the future. Paying attention to medical students' knowledge and attitudes toward HPV vaccine will help accelerate the coverage of HPV vaccine.

The following limitations must be considered when interpreting our findings. First, the respondents' WTP for vaccines may be underestimated owing to the price scale cap. Second, this study may be theoretically underrated given that the nationally produced quadrivalent and 9-valent HPV vaccines are not yet approved and permitted for distribution.

CONCLUSIONS

Most of the respondents were willing to receive the HPV vaccine. The number of medical students who were willing to be vaccinated with domestically produced vaccines was lower compared with the trend for imported vaccines. Medical students' understanding of HPV vaccine valences, place of production, safety, and effectiveness need to be improved. Meanwhile, most of them were willing to pay for the HPV vaccine. Their perceptions of HPV vaccine valences and origin may affect their willingness to be vaccinated and pay for the vaccine. Government departments should fully consider the evidence regarding WTP when pricing vaccines. Medical insurance reimbursement policies or immunization program plans can eliminate the price barrier of vaccination to a certain extent, thus enhancing vaccination rates and protecting a larger population against HPV.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Harbin Medical University School of Health Management institutional Research Board (HMUIRB20210006). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LZ proposed and initiated this study. LZ and BG wrote the first draft of the manuscript. XZ, XX, and GL designed the project and oversaw the analysis and manuscript writing. YL, PC, BG, and YH drawn figures in the manuscript. YL and BG inserted tables in the manuscript. GL supervised the entire project. All co-authors provided feedback during the design and interpretation of the project. They also contributed to revisions of the manuscript. All authors read and approved the final manuscript.

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Research on Knowledge, Attitudes, and Practices of Influenza Vaccination Among Healthcare Workers in Chongqing, China—Based on Structural Equation Model

*Siyu Chen[1], Yueming Jiang[2], Xiaojun Tang[1], Lin Gan[1], Yu Xiong[3], Tao Chen[4] and Bin Peng[1]**

[1] Department of Epidemiology and Health Statistics, School of Public Health and Management, Chongqing Medical University, Chongqing, China, [2] Clinical 5+3 Integration, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China, [3] Chongqing Center for Disease Control and Prevention, Chongqing, China, [4] National Influenza Center, Institute of Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention, World Health Organization Influenza Reference and Research Cooperation Center, Beijing, China

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Alessandra Casuccio,
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***Correspondence:**
Bin Peng
pengbin@cqmu.edu.cn

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Background: Influenza is associated with a large number of disease burdens, and it is generally recommended that all healthcare workers (HCWs) get an influenza vaccination. However, the vaccination rates among HCWs are still low. This study aimed to assess HCWs' knowledge, attitude, and practice (KAP) about the influenza vaccine, and by establishing a structural equation model (SEM) to explore the influencing factors of medical personnel's influenza vaccination in Chongqing, China.

Methods: From September to November 2019, we conducted a cross-sectional survey in four sentinel hospitals and four non-sentinel hospitals in Chongqing, China. We calculated knowledge, attitude, and behavior scores for each study participant and assessed the level of knowledge, attitude, and behavior of the medical staff. An SEM was used to evaluate the relationship between latent variables, and the path graph between knowledge, attitude, and behavior was established.

Results: A total of 1,412 valid questionnaires were collected in this survey, including four sentinel hospitals ($N = 606$, 42.92%) and four non-sentinel hospitals ($N = 806$, 57.08%). Women ($N = 1,102$, 78.05%) were more than men ($N = 310$, 21.95%), with an average age of 32.36 ± 7.78 years old and under 30 years old ($N = 737$, 52.20%), respectively. Nurses (741, 52.48%) were the main subjects, followed by physicians (457, 32.37%). The final SEM model was obtained after the model was modified and adjusted. A bootstrap analysis of path coefficients was carried out on the final model. Knowledge has a direct influence on behavior. The normalized path coefficient is 0.071 (95% CI: 0.002–0.161), and the value of P of the hypothesis test result of the path coefficient is 0.042.

The direct influence of knowledge on attitude standardization was 0.175 (95% CI: 0.095–0.281). The direct influence of attitude on practice standardization was 0.818 (95% CI: 0.770–0.862). The indirect effect of knowledge on the standardization of practice through attitude was 0.144 (95% CI: 0.076–0.235).

Conclusions: According to the SEM, there is a direct positive correlation between KAP and the influenza vaccine. The indirect influence of knowledge on the standard of behavior through attitude is about two times as much as the direct influence on behavior, indicating that attitude plays a strong mediating role between knowledge and practice.

Keywords: knowledge, attitudes, practices, influenza vaccination, health care workers, structural equation model

INTRODUCTION

Influenza is an acute respiratory infectious disease caused by influenza viruses that can lead to serious repercussions on the health of an individual. The influenza virus is highly antigenic and spreads rapidly. It can cause seasonal epidemics every year, and outbreaks can occur in places where people gather, such as hospitals, schools, and nursing homes. Annual seasonal influenza epidemics have a significant impact on the global population in terms of morbidity and mortality; there are an estimated one billion influenza cases each year, of which 3–5 million are severe cases, leading to 290,000–650,000 influenza-related respiratory deaths (1). In particular, in the midst of the coronavirus disease 2019 (COVID-19) global pandemic, there may be a risk of COVID-19 combined with influenza and other respiratory infections this winter and next spring. Vaccination against influenza is the key to reduce the incidence rate of influenza and its related social and economic burden (2). Even if the national influenza virus vaccination guidelines are different, it is generally recommended that we vaccinate not only high-risk patients with pre-existing or high exposure risk, but also the whole population (6 months or more), which decreases the risk of personal infection and improves the immunity of the population (3).

In recent years, there are few studies on the health burden of influenza among healthcare workers (HCWs), especially in domestic data. Previous studies have found that compared with the general population, medical staff have more contact with influenza patients, so the risk of infection with influenza viruses is higher than that of the general population (4). A meta-analysis of 29 global studies showed that the average laboratory-confirmed incidence of influenza per season among unvaccinated medical personnel was about 18.7% (95% CI: 15.8–22.1%), which was 3.4 (95% CI: 1.2–5.7) times higher than among healthy adults (5). A systematic review published in 2016 showed that during the Influenza A (H1N1) pandemic, healthcare professionals were at a higher risk of infection than the general population (odds ratio [OR] = 2.08, 95% CI: 1.73–2.51), while clinicians with direct patient interaction were at a higher risk (OR = 6.03, 95% CI: 2.11–17.8) (6). The World Health Organization (WHO) conducted a rapid assessment of evidence in 2019 also suggested that HCWs were at a higher risk of influenza virus infection than the general population (7), and that influenza virus infection among HCWs may increase the risk of nosocomial infection.

The knowledge, attitude, and practice (KAP) theory model emphasizes the importance of knowledge and attitude in behavioral decision-making, explains the generation of health behavior and predicts the change of behavior by exploring the

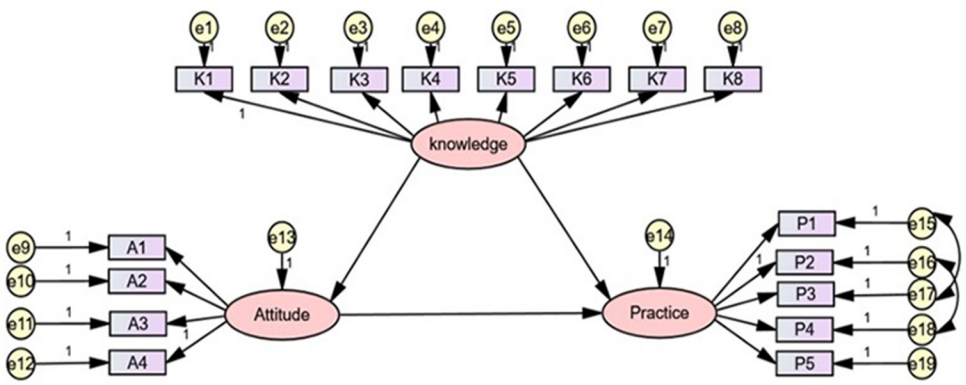

FIGURE 1 | The ideal SEM. Rectangle shows observed variables, ellipses indicate potential variables, and circles represent residual terms.

KAP of high-risk groups (8). KAP theory holds that health knowledge is the basis for establishing a positive attitude and healthy behavior, and attitude is the driving force for behavior change, and the goal is to promote healthy behavior (9).

We know from KAP theory that there is a causal relationship between KAP (10). However, KAP are potential variables that are difficult to measure directly. A structural equation model (SEM) is a new multivariate statistical technology that integrates the traditional statistical analysis methods, such as confirmatory factor analysis, path analysis, and multiple regression analysis. It can deal with potential variables and observe indicators and measurement errors (11). In addition, it can also explore the causal relationship between potential variables and quantitatively evaluate the direct and indirect effects of variables (12).

Variables are divided into explicit variables and potential variables. Potential variables have characteristics that cannot be directly measured, such as knowledge, attitude, and behavior variables in the KAP mode (13). Although knowledge, attitude, and behavior cannot be measured directly, information about the research object can be obtained through a questionnaire. Therefore, we used a questionnaire, which is also a common method in KAP research.

This study aimed to evaluate the associations among KAP regarding the influenza vaccine among HCWs in Chongqing, China based on the KAP theory using an SEM approach.

At present, there is some research on the theory of KAP of HCKs regarding vaccinations in China, but there are few types of research on the relationship among KAP by using the SEM. Because of the rare data, a study needs to target the local Chinese HCWs' KAP for determination of the influenza vaccination status and impact among them. As far as we are concerned, this is the first study that aims to establish the structural equation modeling to explore the relationship among the HCWs' KAP about influenza vaccination in Chongqing, China.

TABLE 1 | Demographic characteristics of 1,412 healthcare workers (HCWs) with influenza vaccination or not.

Variable	Total (%)	Vaccinated	Unvaccinated
Type of hospital			
Non-sentinel hospital	806 (57.08)	117 (14.52)	689 (85.48)
Sentinel hospital	606 (42.92)	120 (19.80)	486 (80.20)
Sex			
Males	310 (21.95)	43 (13.87)	267 (86.13)
Females	1,102 (78.05)	194 (17.60)	908 (82.40)
Age			
≤30	737 (52.20)	108 (14.65)	629 (85.35)
30∼	466 (33.00)	88 (18.88)	378 (81.12)
40∼	161 (11.40)	29 (18.01)	132 (81.99)
50∼	48 (3.40)	12 (25.00)	36 (75.00)
Educational attainment			
College degree and below	310 (21.95)	47 (15.16)	263 (84.84)
Bachelor degree	908 (64.31)	158 (17.40)	750 (82.60)
Postgraduate and above	194 (13.74)	32 (16.49)	162 (83.51)
Marital status			
Married	372 (26.35)	170 (17.03)	828 (82.97)
Unmarried	998 (70.68)	58 (15.59)	314 (84.41)
Others	42 (2.97)	9 (21.43)	33 (78.57)
Department			
Low-risk	784 (55.52)	95 (12.12)	689 (87.88)
High-risk	628 (44.48)	142 (22.61)	486 (77.39)
Profession			
Physician	457 (32.37)	79 (17.29)	378 (82.71)
Nurse	741 (52.48)	136 (18.35)	605 (81.65)
Others	214 (15.16)	22 (10.28)	192 (89.72)
Years in profession			
≤5	536 (37.96)	68 (12.69)	468 (87.31)
6 10	441 (31.23)	80 (18.14)	361 (81.86)
11∼15	202 (14.31)	43 (21.29)	159 (78.71)
≥16	233 (16.50)	46 (19.74)	187 (80.26)
Professional titles			
Primary	891 (63.10)	138 (15.49)	753 (84.51)
Junior	394 (27.90)	75 (19.04)	319 (80.96)
Senior	127 (8.99)	24 (18.90)	103 (81.10)

METHOD

Study Subjects

We used the multistage sampling technique to conduct this cross-sectional survey.

In the first stage, hospitals were divided into sentinel hospitals and non-sentinel hospitals according to whether they participated in the National Influenza Surveillance System. We randomly selected four out of eight sentinel hospitals in Chongqing, and randomly selected four non-sentinel hospitals where the selected sentinel hospitals were located as the research site. In the second stage, departments were divided into high-risk and low-risk departments according to whether they had usual contact with influenza patients. HCWs in high-risk departments, such as respiratory, infection, emergency, pediatrics, and fever clinic department, were randomly selected in each selected hospital as the study subjects. The same in low-risk departments, such as general surgery, obstetrics and gynecology, laboratory, and radiology, were randomly selected in each selected hospital as the study subjects. All participants who had worked in the hospitals for at least 1 year and gave their written and informed consent were eligible for inclusion.

Study Design and Data Collection

A cross-sectional questionnaire survey was conducted by us from September to November 2019. Before the formal investigation, pilot tests were conducted on 50 HCWs to assess accessibility and comprehension, and the questionnaire was revised based on received feedback. Questionnaires are distributed online and offline; respondents can choose to complete paper questionnaires on-site or submit electronic questionnaires through the questionnaire survey website. (Chinese popular online survey platform: http://www.wjx.cn). Before the start

of each face-to-face survey, an investigator went to the office, explained the research to the participating HCWs, and required them for their consent to participate in the research. Participants were also required to sign an informed consent form before filling out the electronic questionnaire.

Influenza vaccine-rated knowledge consists of eight items, for example, "Influenza is transmitted primarily by coughing and sneezing." (K1); "The influenza shot contains live viruses but cannot cause people to get influenza." (K2); "The best time for influenza vaccination is before the influenza season." (K3); "The side effects of the influenza vaccine include headaches" (K4); "The most recommended groups for influenza vaccination include frail people particularly who suffer from chronic diseases"(K5); "The most recommended groups for influenza vaccination include HCWs, pupils, kindergarten children, and pregnant women" (K6–K8). Response options were "Agree" or "Disagree or do not know." The correct answer (agree) was scored 1 and the incorrect answer (disagree or do not know) was scored 0. The final scores of influenza vaccine-rated knowledge ranged from 0 to 8. Higher scores indicated better influenza vaccine knowledge. The total awareness rate of influenza vaccine knowledge was equal to the total number of knowledge questions answered correctly/(the number of knowledge items in each questionnaire × the number of effective response participants) × 100%. The awareness rate of each influenza vaccine knowledge question was equal to the number of participants answered correctly/the number of effective response participants × 100%.

There were four statements set in the attitude section to assess the attitude of HCWs toward the influenza vaccine. They included "I think it's necessary to get the influenza vaccine."(A1); "I don't worry about the side effects of the influenza vaccine."(A2); "I think even if I never get influenza, I still need to vaccinate the influenza vaccine."(A3); "It's important for me to get the influenza vaccine every year." (A4). A five-point Likert scale was used to record the response of the participants, such as "strongly agree," "agree," "neutral," "disagree," and "strongly disagree" in each question. Responses that included "strongly agree" and "agree" were considered to agree with or have a positive attitude toward the statement, while the other responses were considered disagreement or having a negative attitude. To determine the attitude score, we assigned 0–4 points from "strongly disagree" to "strongly agree" respectively to each item, and the total attitude score ranged from 0 to 16. Higher scores represented more positive attitudes toward the influenza vaccine. The overall retention rate of a positive attitude toward the influenza vaccine was equal to the total number of positive attitudes questions/(the number of attitudes items in each questionnaire × the number of effective response participants × 100%). The holding rate of each positive attitudes question was equal to the number of participants who opted "Agree"/the number of effective response participants × 100%.

Influenza vaccine-rated practice was considered using five items, which include "Have you received the influenza vaccine in the past year?"(P1); "Do you take the initiative to learn about flu vaccine-related information?"(P2); "Did you recommend the flu vaccine to the patient in the past year?"(P3); "Are you willing to get the flu vaccination this year?"(P4); "Did you want your family members to get the flu vaccine?"(P5). Participants will obtain 1 score when they answered the question "Yes" and get no score if they say "No", except for question P4. A five-point Likert scale was used to assess the response of the question P4, such as "strongly agree," "agree," "neutral," "disagree," and participants get 0–4 points from "strongly disagree" to "strongly agree." The total practice score ranged from 0 to 8.

Statistical Analysis

For data analysis, IBM® SPSS® Statistics 26.0 and IBM® SPSS® Amos™ 24.0 were used.

Mean ± standard deviation (SD) or frequency and percentage is used to describe demographic information. We used

TABLE 3 | The correlation coefficient among latent variables.

Parameter	Correlation coefficient	*P*-value
Knowledge<->Attitudes	0.177	0.007
Knowledge<->Practice	0.217	0.007
Attitudes<->Practice	0.855	0.016

TABLE 2 | Descriptive statistics for influenza vaccine-related knowledge, attitudes, and practice (KAP).

	M ± SD (range)	*N* (%)		*M* ± SD (range)	*N* (%)		*M* ± SD (range)	*N* (%)
K1	0.99 ± 0.12 (0–1)	1,393 (98.65)	A1	3.12 ± 0.66 (0–4)	1,214 (85.98)	P1	0.17 ± 0.37 (0–1)	237 (16.78)
K2	0.86 ± 0.35 (0–1)	1,211 (85.76)	A2	2.12 ± 0.86 (0–4)	500 (35.41)	P2	0.69 ± 0.46 (0–1)	987 (68.77)
K3	0.73 ± 0.45 (0–1)	1,024 (72.52)	A3	2.94 ± 0.75 (0–4)	1,106 (78.33)	P3	0.18 ± 0.39 (0–1)	259 (18.34)
K4	0.88 ± 0.33 (0–1)	1,237 (87.61)	A4	2.60 ± 0.82 (0–4)	742 (52.55)	P4	2.56 ± 1.03 (0–4)	730 (51.70)
K5	0.90 ± 0.31 (0–1)	1,265 (89.59)				P5	0.81 ± 0.39 (0–1)	1,142 (80.88)
K6	0.93 ± 0.25 (0–1)	1,316 (93.20)						
K7	0.95 ± 0.21 (0–1)	1,347 (95.40)						
K8	0.40 ± 0.49 (0–1)	564 (39.94)						
k	6.63 ± 2.50 (0–8)	82.83%	A	10.78 ± 3.08 (0–16)	63.07%	P	4.41 ± 2.65 (0–8)	47.29%

M, mean; SD, standard deviation; K, overall awareness rate of influenza vaccine-related knowledge; A, overall retention rate of a positive attitude toward influenza vaccine; P, total execution rate of right practice toward influenza vaccine among HCWs.

Spearman's theory to assess the correlation between latent variables. All differences were evaluated using two-tailed tests, and the significance level was set at $P < 0.05$.

An SEM was constructed to determine the relationship between influenza vaccine KAP.

The maximum likelihood estimate (MLE) was used for parameter estimation, and the test level was set to $\alpha = 0.05$. We used the chi-square/degrees of freedom (CMDN/DF), root mean square error of approximation (RMSEA), the goodness of fit index (GFI), adjusted goodness of fit index (AGFI), normed fit index (NFI), incremental fit index (IFI), comparative fit index (CFI), parsimonious goodness of fit index (PGFI), and other indicators to evaluate the fitting effect of the model. A value of CMDN/DF < 3.00, RMSEA < 0.05, GFI > 0.90, AGFI > 0.90, NFI > 0.90, IFI > 0.90, CFI > 0.90, and PGFI > 0.50 can support a good model fit (14).

The bootstrap method was used to test the significance of the mediating effect of related variables in the ideal model. In addition, a bias-corrected bootstrap 95% CI was used to examine the significance of direct and indirect effects (15).

According to our hypothesis, the ideal SEM was established, which was about the association among influenza vaccine-rated KAP in a sample of HCWs in Chongqing, China. We removed some corresponding paths, because the path coefficients of "knowledge" on "attitudes," and "attitudes" on "practice" were not statistically significant in the ideal SEM fitting results (All $P > 0.05$). Ideal SEM is shown in **Figure 1**.

The Cronbach's α value of the final SEM was 0.705 and the Kaiser-Meyer-Olkin (KMO) value was 0.817, showing good reliability and validity (16).

RESULTS

Sample Characteristic

This survey collected 1,412 valid questionnaires, covering four sentinel hospitals ($N = 606$, 42.92%) and four non-sentinel hospitals ($N = 806$, 57.08%).There are more women ($N = 1,102$, 78.05%) than men ($N = 310$, 21.95%), the mean age is 32.36 $\pm$ 7.78 years, and most of the participants were 30 years old or younger ($N = 737$, 52.20%). The respondents were mainly nurses ($N = 741$, 52.48%), followed by physicians ($N = 457$, 32.37%), medical technicians, and others ($N = 214$, 15.16%). The details of demographic characteristics are shown in **Table 1**.

Descriptive Analysis for Influenza Vaccine-Related KAP

The overall awareness rate of influenza vaccine knowledge among HCWs was 82.83%. The overall retention rate of positive attitudes toward the influenza vaccine was 63.07%, which was lower than that of knowledge. The total execution rate of right practice toward influenza vaccine among HCWs was 47.29%. The detailed values are listed in **Table 2**.

Correlation Analysis Among Latent Variables

We used Spearman's correlation to analyze the correlation among KAP one by one. There were positive correlations among influenza vaccine-related KAP ($r = 0.177$, 0.217, and 0.855, all the values of P were significant). The details are shown in **Table 3**.

TABLE 4 | The fit indices of structural equation model (SEM).

Fit index	Goodness of fit index of SEM							
	CMDN/DF	RMSEA	GFI	AGFI	NFI	IFI	CFI	PGFI
Reference index	<3.00	<0.05	>0.90	>0.90	>0.90	>0.90	>0.90	>0.50
Final model index	2.068	0.028	0.981	0.974	0.923	0.959	0.958	0.731

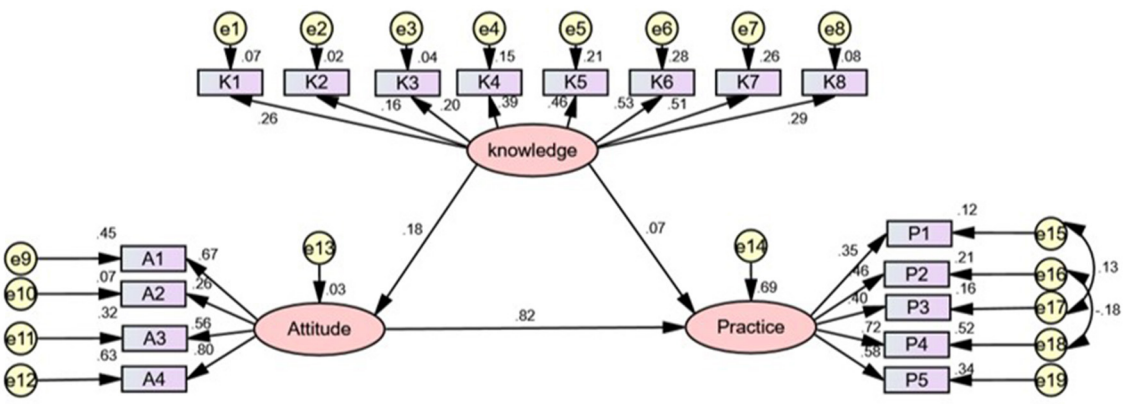

FIGURE 2 | The final SEM. Rectangle shows observed variables, ellipses indicate potential variables, and circles represent residual terms. The values of single-headed arrows represent the standardized coefficients. All paths were significant ($P < 0.05$).

TABLE 5 | Hypothesis testing results for path coefficients of knowledge, attitude and practice.

Statements	Unstandardized estimates	Standardized estimates	SE	*T*-value	*P*-value
Knowledge→ attitude	3.850	0.175	1.014	3.794	0.007
Knowledge→ practice	0.512	0.071	0.260	1.970	0.042
Attitude→ practice	0.268	0.818	0.020	13.177	0.018

TABLE 6 | Bootstrap analysis of mediating effect significance test for the final mode.

Model paths	Standardized direct effects	*P*-value	95% CI		Standardized indirect effects	*P*-value	95% CI	
			LLCI	ULCI			LLCI	ULCI
Knowledge→ attitude	0.175	0.007	0.095	0.281	–	–	–	–
Knowledge→ practice	0.071	0.042	0.002	0.161	–	–	–	–
Attitude→ practice	0.818	0.018	0.770	0.862	–	–	–	–
Knowledge→ practice	–	–	–	–	0.144	0.007	0.076	0.235

Evaluation of the Fitting Effect of the Model

In addition, the covariant relationships between e15 and e17 were established, as well as between e16 and e18. Through repeated modification and fitting of the model, the fit indices of SEM finally reached the adaptation standards: CMDN/DF = 2.068, RMSEA = 0.028, GFI = 0.981, AGFI = 0.974, NFI = 0.923, IFI = 0.959, CFI = 0.958, and PGFI = 0.731. The results are shown in **Table 4**.

Structural Equation Modeling

Figure 2 shows the final SEM. **Table 5** presented the results of hypothesis testing for trajectory coefficients of knowledge, attitudes, and behavior. **Table 6** illustrated the bootstrap analysis of mediating effect significance test for the final model. As is shown in **Figure 2** and **Tables 5**, **6**: knowledge had a standardized direct effect on practice, with a value of 0.071, 95% CI: 0.002–0.161, the value of *P* of the hypothesis testing results for path coefficients was 0.042, which was significant; the standardized direct effect of knowledge on attitude was 0.175 with 95% CI: 0.095–0.281; attitude had a standardized direct effect on practice, which was 0.818, 95% CI: 0.770–0.862; the standardized indirect effect of knowledge on practice through attitudes was 0.144, 95% CI: 0.076–0.235. The standardized total effects of knowledge on behavior were 0.215.

DISCUSSION

Our study aimed to explore the relationship between influenza vaccine-rated knowledge, attitudes, and practice, among HCWs in Chongqing, China.

The vaccine-related knowledge might be an important influential factor for improving influenza vaccination status among HCWs as it may lead to good attitude and practice, which ultimately boost influenza vaccination status. So far, there are few investigations or similar studies about the knowledge, attitudes, and practice on HCWs in our country based on KAP theory.

Previous research showed that the coverage rate of the influenza vaccine was extremely low among medical staff, though the government encourages medical staff to prioritize vaccine. Our study indicated that the overall awareness rate of influenza vaccine-related knowledge was 82.83%, which was satisfactory. This was much higher than the investigation of Austria (66.4%) (17). This research also found that the total retention rate of a positive attitude toward the influenza vaccine was 63.07%, which was significantly higher compared with a similar study (18). However, the final execution rate of right practice toward influenza vaccination among HCWs was 47.29%, which was not optimistic, suggesting that improvement and increased social awareness is needed. In particular, regarding the question P1 "Have you received the influenza vaccine in the past year," the influenza vaccination coverage of HCWs in Chongqing during the 2018/2019 influenza season, was about 16.78%. Notably, we found that the levels of influence vaccine-related knowledge and attitudes were related to the behavior of the influenza vaccine.

Spearman's correlation analysis illustrated that there were positive correlations between the influence vaccine-related KAP among HCWs in Chongqing, China. This result supported the KAP theory about the causal chain of KAP (9). Health education on influenza vaccines may be an effective strategy to improve HCWs' KAP related to influenza vaccines (19).

The structural equation model was constructed based on the KAP theory in our study. The KAP theory was developed as a human health promotion model, and it claimed that the change in human behavior could be divided into three continuous processes: knowledge acquisition, belief generation, and practice/behavior formation (20). KAP should have a positive relationship according to KAP theory (21). In our study, the final model showed that there was a significant positive relationship between influenza vaccine-related knowledge and attitudes,

knowledge and practice, and attitudes and practice. This research showed that influenza vaccine-related knowledge exhibited a direct relationship with practice and exhibited an indirect effect on behavior through attitude, which indicated that attitudes had a mediating effect between knowledge and behavior. This finding was supported by scholars in other fields, and they also confirmed that knowledge can indirectly affect practice through attitudes (21, 22).

It was worth noting that our study demonstrated that the influenza vaccine-related knowledge of medical staff not only has a direct effect on attitude and behavior, but also indirectly affects behavior through attitude. Unexpectedly, the normalization coefficient index of indirect influence of knowledge on behavior through attitude (0.144) is about two times that of the direct influence on behavior (0.071). This indicates that influenza vaccine-related knowledge has a stronger mediating effect than a direct effect on behavior through influencing attitude, which has not been found in previous studies.

The path coefficient for the direct effect of knowledge on practice was estimated to be $\beta = 0.071$, while the indirect effect of knowledge on behavior was 0.144, while the direct effect of knowledge on attitudes was about 0.175. These findings suggested that the influence of knowledge on attitudes and practice was limited. However, the direct effect of attitude on practice was estimated to be $\beta = 0.818$. This coefficient implied attitude that has a strong influence on behavior, and also demonstrated that attitude plays an important role in the causal chain of knowledge, attitudes, and behavior.

Strength and Limitation

As far as we are concerned, this study is the first one to explore the relationship between influenza vaccine-related knowledge, attitudes and behavior among HWCs in Chongqing, China by using SEM. Besides, this research is of great significance for the government to further explore and decide whether to implement the policy of compulsory influenza vaccination targeted at HCWs. However, this study has some limitations. First, there may be a few self-reported HCWs who falsely responded to get a vaccination against influenza due to social pressure, which might cause inevitable bias and lead respondents to provide socially acceptable answers. Second, this research designed to establish the SEM to explore the relationship between knowledge, attitudes, and behavior, but the use of SEM is the inability to explore the inferential causality in this cross-sectional study. Third, we only use the influenza vaccine-related KAP as latent variables according to SEM analysis. However, there are other relevant variables that might not be considered, such as individual characteristics (gender, grade, and major), environmental contexts (family economic annual income and respondents' education level), and social influences (policies and regulations of government) that Wilson and Cleary had put forward (23). Finally, since 2020, the COVID-19 pandemic has spread a lot of influenza-related information, especially HCWs, who will have more opportunities to learn about influenza than before, and they will have a richer knowledge and more positive attitude toward influenza and its vaccines. Our research was conducted before the COVID-19 pandemic, and the results may be quite different from the status quo. Further, more studies on a larger scale are needed in the future.

CONCLUSION

The result of this study illustrated that influenza vaccine-related KAP were satisfactory among HCWs, while their willingness to obtain the influenza vaccine shot was not optimistic. According to the SEM, a direct positive relationship was established between influenza vaccine-related knowledge and attitudes, as well as between knowledge and practice and attitudes and practice. The standardized indirect influence of knowledge on behavior through attitude is about two times that of its direct influence on behavior, which indicated that attitude plays a strong mediating role between knowledge and behavior. Our finding supported the causal chain of KAP in the KAP theory. The relationship between potential variables was also found.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.853041/full#supplementary-material

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Changes of COVID-19 Knowledge, Attitudes, Practices and Vaccination Willingness Among Residents in Jinan, China

Ning Jiang[1], *Cheng Yang*[2], *Wenjing Yu*[2], *Liyan Luo*[1], *Xin Tan*[3] *and Liping Yang*[1]*

[1] *Department of Epidemiology, School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan, China,* [2] *Department of Project Office, Shandong Anke Blockchain Industrial Development Institute, Jinan, China,* [3] *Leshan Community, Jinan, China*

Background: Vaccine hesitancy is responsible for low vaccine coverage and increased risk of epidemics. The purpose of this study was to assess whether public knowledge, attitudes, practices, and willingness to vaccinate against COVID-19 have changed over time and at different stages of vaccination.

Methods: Two consecutive surveys were conducted among residents of the Leshan Community in Jinan from May to June, 2021 ($n = 423$) (basic dose vaccination phase) and from December, 2021 to January, 2022 ($n = 470$) (booster vaccination phase). Randomly sampling was used in residents to complete an anonymous questionnaire. Chi-square test was used to compare the changes in knowledge, attitudes and practices of the subjects in different survey stages. Multivariable logistic regression analysis was used to explore factors related to vaccination hesitancy.

Results: In the booster vaccination phase, protective behaviors (89.9%) of residents increased significantly compared with the basic vaccination phase (74.5%). Residents were more hesitant to receive booster doses than basal doses of COVID-19 vaccine (OR: 18.334, 95% CI: 9.021–37.262). Residents with other marital statuses (OR: 2.719, 95% CI: 1.632–4.528), negative attitudes toward government measures were more hesitant to get vaccinated (OR: 2.576, 95% CI: 1.612–4.118). People who thought their physical condition was very good or good were more likely to be vaccinated than those who thought they were in fair or poor health (OR: 0.516, 95% CI: 0.288–0.925; OR: 0.513, 95% CI: 0.295–0.893). Young people inclined to use new media (such as WeChat and microblog) to obtain information, while the elderly inclined to use traditional methods (such as television). Government propaganda, residents' perception of the importance of vaccines and the risk of disease were the main reasons for accelerating residents to vaccinate. The main reasons affecting residents' lack of vaccination were contraindications to the vaccine or inconvenient time for vaccination.

Conclusions: Vaccine hesitancy increased significantly with change in vaccination stage. Strategies should be adopted to increase vaccination coverage such as improving the convenience of vaccination, promoting through multiple channels.

Keywords: COVID-19, vaccination willingness, vaccination hesitancy, KAP, change, China

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Reviewed by:
Quanman Li, Zhengzhou University, China
Omnia Elseifi, Zagazig University, Egypt
Chenyuan Qin, Peking University, China

***Correspondence:**
Liping Yang
yliping@sdu.edu.cn

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) broke out in December 2019, in Wuhan, Hubei and quickly spread across China, becoming a major global public health problem. The World Health Organization declared COVID-19 a public health emergency of international concern on January 30, 2020 (1). The COVID-19 epidemic has lasted more than 2 years. As of 13 March 2022, over 455 million confirmed cases and over 6 million deaths have been reported globally (2). COVID-19 seriously threatens people's physical and mental health, affects the social order, and hinders countries' economic development (3–5).

Fortunately, the successful development of specific medicine provides help for the treatment of COVID-19, but the role of vaccines in preventing the epidemic of infectious diseases is irreplaceable. vaccines have played critical roles in human struggles against major infectious diseases such as smallpox, polio, rabies, typhoid, plague and many more (6). As of April 2022, there are 68 vaccines in Phase 3 trials globally, 36 of which have been approved for use in at least one country (7). Only when a high rate of vaccination is achieved can an immune barrier be built (8). However, many previous studies have demonstrated vaccine hesitancy in the population (9, 10). And the acceptance of vaccines also varies between countries (11). Vaccine hesitancy refers to delay in acceptance or refusal of vaccination despite availability of vaccination services (12). Vaccine hesitancy is believed to be responsible for decreasing vaccine coverage and an increasing risk of vaccine-preventable disease outbreaks and epidemics (13).

A previous Chinese study investigated guardians' willingness to get COVID-19 vaccine for their children aged 3–17 (14). But parents may have different attitudes about vaccinations for themselves and their children. We surveyed the attitudes of adults toward vaccinating themselves.

The purpose of our study was to assess whether and how the public's knowledge, attitudes, practices, and willingness to vaccinate against COVID-19 changed by time and different stages of vaccination, and to analyse the influencing factors associated with vaccination hesitancy. By focusing on the weaker aspects of residents' knowledge, negative attitudes and unhealthy daily practices, targeted advertising and education can be adopted to increase the comprehensive understanding of the emerging infectious disease, eliminate panic and improve awareness of prevention, which are very important to the stability of social order.

Jinan is located in Eastern China, connecting to the Beijing-Tianjin-Hebei urban agglomeration in the north and the Yangtze River Delta economic circle in the south. It is a national historical and cultural city. The total population of Jinan City is 9.2 million, of which 7.42 million are 18 years old and above. The Leshan Community has complex socio-demographic characteristics and locates in the center of Jinan. It is a representative community that can be regarded as a miniature Jinan.

MATERIALS AND METHODS

Study Design

We conducted two surveys on residents of the Leshan Community in Jinan City at different stages of COVID-19 vaccination. The first survey was conducted from 24 May to 12 June 2021 (first dose vaccination phase). The second survey was conducted from 30 December, 2021 to 9 January, 2022 (booster vaccination phase). Random sampling of residents was used to complete an anonymous questionnaire. $n = \frac{z^2_{(1-\alpha)/2}pq}{d^2} \times deff$ was used to calculate the sample size. The vaccination rate at the time of the first survey was about 70% in Jinan, so $p = 0.7$, $q = 0.3$, $d = 0.1$p, $deff = 2$, $\alpha = 0.05$. Therefore, the sample size was 330. Five hundred people were randomly selected in the research. First, 10 of the 59 residential buildings were randomly selected, and then 50 persons lived in the selected residential buildings were randomly selected. In the first survey, 423 people responded effectively, with an effective response rate of 84.6%. In the second survey, 470 people responded effectively, with an effective response rate of 94.0%.

Inclusion and Exclusion Criteria

Residents aged 18 or older who understood the content of the study, had no barriers to communication or understanding, and agreed to participate in the study.

Questionnaire Content

The content of the anonymous questionnaire was designed with reference to the prevention and control knowledge of the National Health Commission website and the "New Coronavirus Pneumonia Diagnosis and Treatment Protocol (Trial Version 8)"(15, 16). The questionnaire content included five main features. The first referred to the socio-demographic characteristics of the subject (gender, marital status, age group, occupation, and education level). The second involved respondents' knowledge regarding COVID-19, including the pathogen and epidemiology, clinical manifestations of the disease, daily protection and prevention (one point was awarded for correct answers, no points for incorrect answers, the total score of knowledge toward COVID-19 is 10. The total score less than the mean value was interpreted as poor knowledge, and the total score greater than or equal to the mean value was interpreted as good knowledge). The third was the section on attitudes regarding government's prevention and control measures that adopted use of the 5-point Likert scale (a total of 12 points, the total score less than the mean value was interpreted as negative attitudes, and the total score greater than or equal to the mean value was interpreted as positive attitudes.) The fourth was the section investigating the public's daily protective practices which contains eight items, the total score less than the mean value was interpreted as poor practice, and the total score greater than or equal to the mean value was interpreted as good practice. Finally, the section on the COVID-19 vaccine investigated COVID-19 vaccination willingness and reasons. Residents were asked if they would be willing to be vaccinated against COVID-19, and if they answered unwilling or unsure, they were considered vaccine hesitant. Vaccine hesitancy is not considered to exist if the answer

is yes. We then asked vaccine hesitant people why they were reluctant to get vaccinated, and asked people willing to get vaccinated what motivated them.

Quality Control

The survey questionnaire in electronic form was sent to residents by community staff. To ensure integrity of the data, the electronic questionnaire could only be submitted after all questions had been answered. WeChat was used to verify the identity of the respondents and as a way of logging in to answer the questionnaire. Each WeChat account could only be submitted once to avoid repeated answers. Questionnaires that took <180 s were judged to be invalid. Considering the infrequent use of mobile phones by the elderly, we conducted a face-to-face interview with them. Questionnaires were administered and filled out by investigators who had received uniform training to ensure the quality. Before the formal survey, we conducted a preliminary survey of 50 residents to assess the validity and understandability of the questionnaire. Then, some adjustments were made based on the pilot study. Likert5 scale was adopted in the attitude part, so the Cronbach's alpha of the attitude was 0.857. For the parts of knowledge and practice, pre-investigation and expert evaluation were both used to ensure the quality of the questionnaire.

Statistical Analysis

Statistical analysis was performed using SPSS 26.0 software. The composition ratio [n (%)] was used to describe general demographic characteristics and vaccination status. Chi-square test was used to compare the changes of sampling subjects' knowledge, attitude and practice (KAP) and willingness to vaccinate against COVID-19 in different survey stages. Logistic regression analysis was used to explore factors related to vaccination hesitancy. Independent predictors of vaccination hesitancy were assessed using binary logistic regression models. Then, the variables with $p<0.2$ in the univariate logistic regression were included in the multivariable logistic regression model, and the model was constructed by the likelihood ratio test method. The model fitting effect was assessed using the Hosmer-Lemeshow goodness of fit test. The statistical significance level was set at $p < 0.05$.

Ethics

The research protocol was approved by the Public Health Ethics Committee of Shandong University (LL20211201). Our research has been carried out in accordance with the principles stipulated by Helsinki.

RESULTS

Socio-Demographic Characteristics

Table 1 shows the characteristics of the respondents in two surveys. There were no significant differences among participants in terms of gender, age, marital status, occupation, educational level, chronic disease and physical conditions. There were 423 and 470 respondents in the first and second surveys, respectively. According to the level of infection risk and the nature of work, we classified occupations into the following groups: "high risk of infection" (customs officer, medical staff, transportation staff), "occupation in key positions" (teacher, public service industry, government employees), and "other" (students, retirees, enterprise employees). Among survey respondents, more than half were women. The majority of participants were married (84.7–87.2%). Overall, 57.2–58.8% residents had a college and undergraduate degrees or above. Among occupations, "other" accounted for the largest proportion (78.5–82.5%) (**Table 1**).

Ways to Obtain Information About COVID-19

Access to information is age-related. Furthermore, the age composition of the two surveys was similar. Therefore, data from the two surveys were combined to reflect an overall picture of ways to obtain information about COVID-19. Television (75.9%), WeChat (72.8%), community advertising (64.9%), and news websites (55.3%) were identified as the main ways for residents to obtain information. People aged 18–30 most often used WeChat (90.5%) and microblog (82.5%). People aged 31–40 and 41–50 years old used WeChat most frequently, 85.0% and 87.3%, respectively. People aged 51–60 and over the age of 60 used television most often, at 88.0% and 78.0%, respectively. With the increase of age, the number of residents who obtain information through WeChat and microblog gradually decreases. Residents who access information through Television gradually increase with age (**Figure 1**).

Knowledge Regarding COVID-19

In the two surveys, 72.3% and 67.9% residents had good knowledge of COVID-19, respectively. We list the correct rate of residents' knowledge about the COVID-19 in the two surveys (**Table 2**). The correct answer rates of the questions on the COVID-19 knowledge questionnaire were 65.2–97.4%, 60.0–96.8%, respectively. In the stage of booster vaccination, the proportion of respondents who believed that patients with COVID-19 may have nasal congestion, runny nose, sore throat rose to 86.8%, compared with 70.2% in the basic vaccination phase ($p < 0.001$). The proportion of respondents who believed that critical illnesses are more common in the elderly, and in those with underlying diseases rose to 86.4%, compared with 74.2% in the basic vaccination phase ($p < 0.001$). However, the correct perception that wearing multiple masks and antibiotics did not prevent COVID-19 decreased from 78.5% to 60.0% and from 72.1% to 40.8%, respectively ($p < 0.001$).

Attitudes About Government Measures During Lockdown Period

In the two surveys, 76.6% and 80.6% residents displayed a positive attitude about government measures, respectively. Compared with the basic vaccination phase, the booster vaccination phase found that residents were found to be more willing to "very agree" with wearing masks in public places (87.9% vs. 78.7%), taking their temperature when entering supermarkets (85.5% vs. 72.6%), and self-isolating at home during the lockdown period (84.3% vs. 75.2%) (**Table 3**).

TABLE 1 | Comparison of resident characteristics in two surveys.

		Basic vaccination phase ($n = 423$)	Booster vaccination phase ($n = 470$)	
Variables	**Category**	***n* (%)**	***n* (%)**	***P***
Sex				0.554
	Male	172(40.7)	182 (38.7)	
	Female	251(59.3)	288 (61.3)	
Age				0.731
	18–30	30 (7.1)	33 (7.0)	
	31–40	114 (27.0)	113 (24.0)	
	41–50	96 (22.7)	108 (23.0)	
	51–60	58 (13.7)	59 (12.6)	
	>60	125 (29.6)	157 (33.4)	
Marital status				0.274
	Married	369(87.2)	398 (84.7)	
	Others	54(12.8)	72 (15.3)	
Education status				0.537
	Middle school and below	69 (16.3)	94 (20.0)	
	High school and technical secondary school	105 (24.8)	107 (22.8)	
	College and Undergraduate	212 (50.1)	228 (48.5)	
	Master and above	37 (8.7)	41 (8.7)	
Occupation				0.257
	High risk of infection	13 (3.1)	22 (4.7)	
	Key occupations	61 (14.4)	79 (16.8)	
	Others	349 (82.5)	369 (78.5)	
Chronic disease				0.549
	Yes	132 (31.2)	138 (29.4)	
	No	291 (68.8)	332 (70.6)	
Physical conditions				0.654
	Very good	139 (32.9)	168 (35.7)	
	Good	217 (51.3)	229 (48.7)	
	General and low	67 (15.8)	73 (15.5)	
Knowledge				0.146
	Good	306 (72.3)	319 (67.9)	
	Poor	117 (27.7)	151 (32.1)	
Attitude				0.141
	Positive	324 (76.6)	414 (80.6)	
	Negative	99 (23.4)	91 (19.4)	
Practice				<0.001
	Good	315 (74.5)	422 (89.9)	
	Poor	108 (25.5)	48 (10.2)	
Vaccine willingness				<0.001
	Willingness	414 (97.9)	345 (74.5)	
	Hesitancy	9 (2.1)	120 (25.5)	

Chi-square test, $P < 0.05$.

Protective Practices Toward COVID-19

In the two surveys, 74.5% and 89.9% of the residents maintained "good" protective measures, respectively. Compared with the basic vaccination phase, the booster vaccination phase found that residents were more frequently washing their hands in daily life (99.1% vs. 97.2%), maintaining social distancing (94.9% vs. 87.0%), and cleaning their houses (97.7% vs. 91.3%). In the basic vaccination phase, majority of respondents (87.0%) maintained more than one meter of distance when communicating with others, and 91.3% cleaned their home every day. The implementation rates for six other behaviors were all >95.0%. In the booster vaccination phase, the implementation rate of residents' behavior increased and the gap narrowed. The implementation rates for all behaviors were all ≥94.9% (**Table 4**).

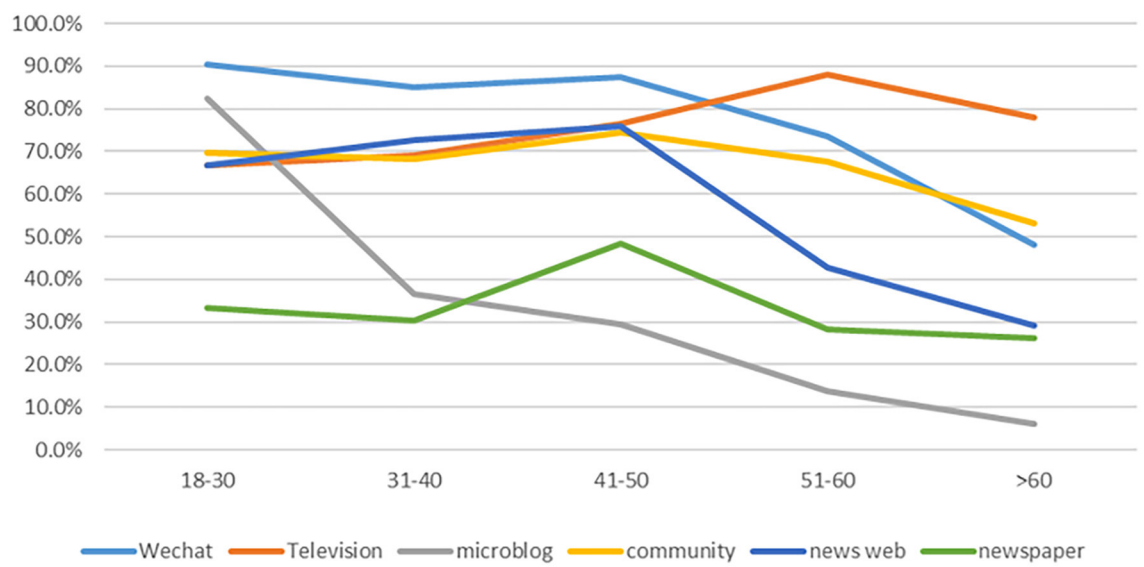

FIGURE 1 | Changes in different access to information by age group.

TABLE 2 | Comparison of correct knowledge about COVID-19 between two surveys.

Questions	Basic vaccination phase *n* (%)	Booster vaccination phase *n* (%)	*P*
COVID-19 is mainly transmitted through the respiratory tract (yes)	412 (97.4)	454 (96.6)	0.484
Asymptomatic infection is contagious (yes)	393 (92.9)	432 (91.9)	0.576
COVID-19 mainly invaded the lungs (yes)	391 (92.4)	415 (88.3)	0.037
Alcohol concentration to eliminate the new coronavirus (75%)	328 (77.5)	341 (72.6)	0.086
Fever, dry cough, and fatigue are the main manifestations of COVID-19 (yes)	402 (95)	455 (96.8)	0.179
Patients with COVID-19 may have nasal congestion, runny nose, sore throat and other symptoms (yes)	297 (70.2)	408 (86.8)	<0.001
Critical illnesses are more common in the elderly, and in those with underlying diseases (yes)	314 (74.2)	406 (86.4)	<0.001
Multiple masks have better protection effect (no)	332 (78.5)	282 (60.0)	<0.001
Antibiotics can prevent COVID-19 (no)	305 (72.1)	234 (49.8)	<0.001
There have specific drugs for the treatment of COVID-19 (no)	276 (65.2)	310 (66.0)	0.824

Chi-square test, $P < 0.05$.

COVID-19 Vaccination Willingness and Situation

In the first survey, 414 (97.9%) residents intended to receive the COVID-19 vaccine, 310 (74.9%) of which had received the first dose of the vaccine, and 110 cases (26.6%) were fully vaccinated. Among those vaccinated, 248 (80.0%) received inactivated vaccines, 93 (37.5%) of which were fully vaccinated, and 155 (62.5%) only received the first dose. In the second survey, 350 (74.5%) residents would like to receive a booster vaccine. 25.5% of residents were skeptical about booster vaccine. Among the 443 residents who received the COVID-19 vaccine, 222(50.1%) residents had received booster dose of COVID-19 vaccine.

Factors Associated With COVID-19 Vaccine Hesitancy

Logistic regression was performed between the vaccine demand group and vaccine delay group to identify the influencing factors of vaccination hesitancy.

TABLE 3 | Comparison of attitudes toward government measures between two surveys.

Attitudes	Basic vaccination phase (*N* = 423)	Booster vaccination phase (*N* = 470)	*P*
Wearing masks in public places			<0.001
Disagree/general	4 (0.9)	6 (1.3)	
Agree	86 (20.3)	51 (10.9)	
Very agree	333 (78.7)	413 (87.9)	
Self-isolating at home during the lockdown period			<0.001
Disagree/general	3 (0.7)	16 (3.4)	
Agree	102 (24.1)	58 (12.3)	
Very agree	318 (75.2)	396 (84.3)	
Taking their temperature when entering supermarkets			<0.001
Disagree/general	9 (2.1)	12 (2.6)	
Agree	107 (25.3)	56 (11.9)	
Very agree	307 (72.6)	402 (85.5)	

Chi-square test, P < 0.05.

In univariate logistic regression analysis, we found that marital status, physical conditions, number of surveys and attitudes were statistically significantly correlated to vaccine hesitancy. In the multivariable logistic regression analysis (**Table 5**), residents' willingness to receive a booster vaccine showed higher hesitancy than their willingness to receive the basic dose (OR: 18.334, 95% CI: 9.021–37.262). Residents with other marital statuses were more hesitant to get vaccinated than married people (OR: 2.719, 95% CI: 1.632–4.528). People with negative attitudes toward government measures were more hesitant to get vaccinated (OR: 2.576, 95% CI: 1.612–4.118). People who thought their physical condition was very good or good were more likely to be vaccinated than those who thought they were in fair or poor health (OR: 0.516, 95% CI: 0.288–0.925; OR: 0.513, 95% CI: 0.295–0.893).

Reasons Affecting COVID-19 Vaccination

In the second survey, we investigated what motivated residents to receive booster vaccine in the vaccinated group and the refusal reasons for vaccine hesitancy in the hesitant group. Among 350 people who would like to be vaccinated, most people believed that the reasons for promoting vaccination were: "the government's propaganda," "to protect family/friends/colleagues from infection," that "job requirements" and "concern about contracting COVID-19" accounted for 66.6%, 60.9%, 56.9%, and 56.6%, respectively. Among 120 vaccine hesitant people, the top two reasons were "inconvenient time for vaccination" and "there are contraindications for vaccination", which accounted for 22.5% and 17.5% respectively.

DISCUSSION

To investigate changes in public knowledge, attitudes, practices, and willingness to vaccinate against COVID-19 in Jinan, two consecutive surveys were conducted during the basic vaccination phase (May–June 2021) and the booster vaccination phase (December–January 2021). Our research showed that, on the whole, knowledge and attitudes of residents about COVID-19 did not change much between the two phases, but behaviors were more positive in the booster vaccination phase than in the basic vaccination phase. Residents were more hesitant to get booster dose than the basic dose. Marital status, physical conditions, investigation stage, and attitudes were the influencing factors of vaccine hesitancy.

One research was conducted online during the first wave and third wave of the local epidemic in 2020 in Hong Kong, China. The results showed that with the time changes, the vaccination willingness declined but the compliance with personal protective behaviors increased (17). It is consistent with our research results.

In the basic vaccination phase, it was found that the research subjects had good knowledge of the epidemiological characteristics and main clinical symptoms of COVID-19, but knowledge about other special clinical symptoms and protective measures of COVID-19 was bad. The similar situations were also appeared in the booster vaccination phase and other studies (18, 19). Obviously, residents have not systematically mastered the relevant knowledge regarding COVID-19, resulting in knowledge weaknesses and blind spots. Therefore, it is necessary to strengthen the depth of residents' health education by formulating a systematic and comprehensive learning plan, thus increasing the awareness rate of COVID-19 knowledge.

After the outbreak of COVID-19, the government adopted many measures which were accepted by the vast majority of residents. This study showed that the attitudes of residents in the booster vaccination phase were similar to those in the basic vaccination phase, and most of them (76.6–80.6%) maintained positive attitudes. During the pandemic of COVID-19, Chinese government has been taking many strategies and measures to prevent, control and therapy the emerging infectious disease. As a result, majority of residents have benefits from the measures, and they believe China can do well against the virus, so they can have positive attitudes against COVID-19.

In the two surveys, more than 95% of respondents wore masks in public places where people gather. Using masks can

TABLE 4 | Comparison of protective behaviors toward government measures between two surveys.

Practice	Basic vaccination phase ($n = 423$)	Booster vaccination phase ($n = 470$)	*P*
Wearing mask in public place			0.315
Yes	403 (95.3)	454 (96.6)	
No	20 (4.7)	16 (3.4)	
Washing hands in daily life			<0.026
Yes	411 (97.2)	466 (99.1)	
No	12 (2.8)	4 (0.9)	
Covering mouth and nose when coughing or sneezing			0.227
Yes	419 (99.1)	461 (98.1)	
No	4 (0.9)	9 (1.9)	
Opening windows every day for ventilation			0.100
Yes	423 (100.0)	467 (99.4)	
No	0 (0.0)	3 (0.6)	
Social distance			<0.001
Yes	368 (87.0)	446 (94.9)	
No	55 (13.0)	24 (5.1)	
Reducing the number of gatherings			1.000
Yes	414 (97.9)	460 (97.9)	
No	9 (2.1)	10 (2.1)	
Cleaning home every day			<0.001
Yes	386 (91.3)	459 (97.7)	
No	37 (8.7)	11 (2.3)	
Eating a balanced diet			0.189
Yes	409 (96.7)	461 (98.1)	
No	14 (3.3)	9 (1.9)	

Chi-square test, $P < 0.05$.

protect healthy people from infection and reduce the spread of the virus (20, 21). However, a survey in Malaysia showed that 51.2% of residents wear masks when went go out. They might believe only people who have symptoms of COVID-19 or similar diseases need to wear medical masks (22). Regarding self-care, more than 96% of respondents in two surveys reflected they performed strengthen exercise, rested regularly. An online survey revealed that the response rate of participating in physical exercise was relatively low (61.7%) during the quarantine period (23). Maybe due to different periods of investigation, we conducted the research during the normalization of the epidemic. While in the quarantine period, staying at room might lead to less physical exercise. According to a survey in Saudi Arabia, 98% of the public adopted social distancing, similar to the results of the booster vaccination phase of this study (24). In addition, our research found residents had better protective behaviors in the booster vaccination phase than the basic vaccination phase (74.5% vs. 89.9%, $p < 0.001$). May be due to the government's emphasis on the importance of protective behavior in preventing COVID-19. With the pandemic of COVID-19, residents' awareness of protective was increasing.

This study showed COVID-19 vaccination willingness among community residents was 97.6% during the basic vaccination phase. It is higher than the willingness (91.7%, 91.9%, 88.6%) of Chinese residents to be vaccinated in the survey from March to June, November– December 2020 (11, 25, 26). In the stage of booster vaccination, it was 74.5% of the COVID-19 vaccination willingness among residents. It was similar to the willingness of Chinese residents to be vaccinated (75.2%) surveyed in April–May 2021 (27). In the basic vaccination phase, 2.1% of residents were hesitant to vaccinate, and the proportion of hesitant to vaccinate increased to 25.5% in the stage of booster vaccination. It was more difficult to vaccinate eligible residents in China with the booster dose than the basic dose ($p < 0.001$). The willingness of residents to receive the booster vaccine was lower than the willingness to receive the basic vaccine.

This study found that people with other marital statuses were more hesitant to get vaccinated than married people which was consistent with other researches (28, 29). Married residents paid more attention to the safety of their mate, children and other family members. They were vaccinated in order to protect the safety of themselves and their families. It indicated that family responsibility drove vaccination.

Additionally, our research showed that respondents with negative attitudes toward government protective measures were more hesitant to get vaccinated than those with general attitudes, which reflected the transformation of attitudes into behaviors. People who thought he or she was healthy have a higher vaccination rate than those with ordinary or poor health, similar

TABLE 5 | Logistic regression analysis of factors affecting COVID-19 vaccine hesitancy of survey subjects.

Variables	Univariate OR (95%CI)	*P*	Multivariable OR (95%CI)	*P*
Age group		0.074		
>60	Reference			
18–30	1.268 (0.639–2.514)			
31–40	0.859 (0.532–1.386)			
41–50	0.472 (0.265–0.838)			
51–60	0.772 (0.419–1.424)			
Gender		0.979		
Male	Reference			
Female	1.005 (0.686–1.472)			
Marital satus		<0.001		<0.001
Married	Reference		Reference	
Other	2.899 (1.861–4.515)		2.719 (1.632–4.528)	
Occupation		0.089		
Others	Reference			
High risk of infection	0.502 (0.151–1.667)			
Key occupations	0.548 (0.299–1.004)			
Education		0.138		
Middle school and below	Reference			
High school and technical secondary school	1.546 (0.735–3.251)			
College and Undergraduate	0.965 (0.457–2.040)			
Master and above	0.888 (0.443–1.783)			
Physical conditions		0.019		0.042
General and low	Reference		Reference	
Good	0.505 (0.310–0.822)		0.513 (0.295–0.893)	0.018
Very good	0.557 (0.333–0.933)		0.516 (0.288–0.925)	0.026
Chronic disease		0.098		
No	Reference			
Yes	1.391 (0.940–2.056)			
Vaccination phase		<0.001		<0.001
Basic vaccination phase	Reference		Reference	
Booster vaccination phase	15.771 (7.893–31.512)		18.334 (9.021–37.262)	
Knowledge		0.086		
Good	Reference			
Poor	1.408 (0.952–2.083)			
Attitude		<0.001		<0.001
Positive	Reference		Reference	
Negative	2.191 (1.460–3.289)		2.576 (1.612–4.118)	
Practice		0.893		
Good	Reference			
Poor	0967(0.589–1.586)			

Logistic regression analysis, $P < 0.05$.

to previous survey results (30). Vaccine hesitancy of COVID-19 is complex, varying across time, place.

This research showed that government calls and perceptions of disease risk promoted vaccination. The perceived importance of vaccines, the risk perception of the disease, and the accessibility and convenience of vaccination services are all important factors affecting vaccination (13). With a higher degree of trust in government information, residents were more likely to receive vaccine against COVID-19.

The study showed that young people were more inclined to use new media (such as WeChat and microblog) to obtain information, while the elderly were more inclined to use traditional methods (such as television). Different age had different levels of access to information, consistent with a study in Malaysia (31). Using traditional methods to obtain information could increase the possibility of vaccination, most likely because they insist on high-quality information sources and share fact-based information (32). People could get information quickly

and easily on news media, but it might also be a source of misinformation (33). Therefore, government departments should continue to use traditional media channels, and try to promote high-quality information to new media platforms to increase the vaccination acquisition rate.

Results indicated 21.7% had registered to receive the vaccination but had not yet been notified to do so. So reasonable and standardized vaccination services would be able to promote vaccination. Previous surveys showed that the main reason for hesitation in vaccines was concern about safety and effectiveness (30, 34, 35). In this study, only a small percentage (5.8%) of those who did not receive vaccination stated because they doubted the effectiveness and safety of the vaccine, it indicated that after a period of advertising and education by the government and related agencies, most of the public were no longer concerned about the safety and effectiveness of the vaccine.

We used longitudinal research to investigate public changes on knowledge, attitudes, practices, and willingness to vaccinate against COVID-19 in Jinan, China. Considering the infrequent use of the Internet by older adults, a combination of online and face-to-face surveys were used to make the sample more representative. But the research was conducted in one region, so the conclusions may not be generalizable to other regions.

In conclusion, different propaganda channels can be adopted for differing groups of residents. Education should be focused particularly on those residents who have inadequate knowledge about COVID-19 to increase the comprehensive understanding of the emerging infectious disease. More measures should be adopted to increase vaccination coverage, such as expanding the number of alternative vaccines, improving vaccine efficiency, researching vaccines to deal with mutant strains. Eliminating the spread of COVID-19 requires not only vaccination, but also maintaining good practices.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Public Health Ethics Committee of Shandong University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

NJ and LY designed research. NJ, CY, WY, LL, and XT curated data collection. NJ analyzed data and wrote the paper. All authors contributed to the article and approved the submitted version.

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Comparative Analysis of the Status and Influencing Factors of Immunization Among Children Between Registered and Floating Population

Yan Xiong[1,2], *Yaqing Xue*[3,4], *Guojin Jiao*[2], *Jun Xie*[5] *and Jingmin Cheng*[2]*

[1] School of Public Health, Shanxi Medical University, Taiyuan, China, [2] School of Management, Shanxi Medical University, Taiyuan, China, [3] School of Public Health, Southern Medical University, Guangzhou, China, [4] School of Health Management, Southern Medical University, Guangzhou, China, [5] School of Basic Medicine, Shanxi Medical University, Taiyuan, China

Background: A vaccine is an effective tool to reduce the gap between the rich and the poor and improve health equity, through which a number of serious childhood diseases can be successfully prevented or eradicated. This study is aimed to compare the current situation of vaccination and related factors among children in China's registered residents and floating population, to provide a reference for achieving the 100% vaccination rate in China.

Methods: The data used for this study are from the 2017 National Migrants Dynamic Monitoring Special Survey data. A self-designed questionnaire was used to collect information, such as socio-demographics, vaccination status of children, and so on, on the registered population and floating population. Descriptive statistics and a chi-square independence test were used to describe the information and to compare the vaccination status of children under different sociodemographic characteristics. Binary logistic regression was employed to analyze influencing factors associated with vaccination of children.

Results: The findings showed that 94.39% of children in registered residence were completely vaccinated, which was significantly higher than that of the floating children (91.68%, $p < 0.001$). The region, parents' education level, and marital status were found to be significant risk factors for complete vaccination of children regardless of the registered or floating population. In addition, ethnicity and length of time to the nearest medical institution were unique risk factors for complete vaccination of children in registered residence. And, health record was an independent influencing factor for vaccination of children of floating population.

Conclusion: Compared with registered population, floating population was at a disadvantage in using basic public health services, especially in children's vaccination. To achieve 100% vaccination for children, particular interventions should be taken for different populations.

Keywords: child health, vaccination, basic public health services, registered population, floating population, comparative analysis

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***Correspondence:**
Jingmin Cheng
jingmincheng@sxmu.edu.cn

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INTRODUCTION

Population mobility is a special and important social phenomenon in the process of China's economic and social modernization. Since the reform and opening up, with the transformation of the economic system and the rapid development of urbanization, a large number of surplus laborers in rural areas have flowed into cities to work (1). In recent years, family migration has become a new trend in the migration process in China. That is, the migration trend has changed from "temporary residence" and "migrant alone" to "long-term residence" and "migration with core family members" (2). This means that floating children are increasingly becoming an important part of the floating population. However, long-term mobility exposes floating children to greater health risks (3). The vulnerability of the floating population is obvious in terms of livelihood insecurity, negligence, and alienation in the new sociocultural environment (4, 5). Studies have shown that the floating population is the high-risk susceptible population to infectious diseases, occupational diseases, chronic diseases, and psychological problems (6, 7). Therefore, how to solve the health inequality caused by population mobility are the problems and challenges faced by the current system promoters.

The health level in childhood not only affects a person's health status throughout the life but also relates to the education, employment, and income in adulthood. Considering the dual characteristics of mobility and children, the health status of floating children deserves more attention.

Immunization has shown to be one of the most cost-effective health interventions worldwide, through which a number of serious childhood diseases can be successfully prevented or eradicated (4). The implementation of immunization programs varies greatly in different countries and regions (8); however, the vaccination situation of floating children in some countries is relatively similar, i.e., the vaccination rate of floating children is generally low. Scholars have conducted empirical research studies on the related factors of children's vaccination and have drawn some conclusions. Studies have found that in addition to immigration or non-immigrant status factors, personal factors, such as parental education, occupation, knowledge, attitude, awareness of autonomous immunity, and family income, were significantly correlated with children's vaccination (9–12). In addition, social integration was found to be positively associated with floating children's vaccination status (13). Meanwhile, accessibility of vaccination services, vaccine supply, and health service policies also affected vaccination information. Are there any differences in the influence of these factors on the vaccination of registered residence children and floating children? At present, the research in this field is still relatively limited.

In addition, as an important part of basic public health services, health education is of great significance to maintain health and reduce the risk of poverty (14). Previous studies have found that there is a current situation of "three low and one high" in the immunization of floating children in China, i.e., low immunization rate, low card building rate, low awareness of parents, and high incidence rate of infectious diseases (15). It can be seen that parents' health education is closely related to children's immunization. Based on the above, the main aim of this study are as follows: first, to compare the vaccination situation of the children in the registered residence population and the floating population and analyze the current situation of the parents of the children who are vaccinated completely. Secondly, the difference in the factors affecting the vaccination of the registered residence children and the floating children is compared, focusing on the factors of parents' health education, to provide a scientific basis for promoting the health equity and improving the children's health.

METHODS

Study Design and Participants

This study used data from the China Migrants Dynamic Survey (CMDS) in 2017, which was provided by the Migrant Population Service Center. CMDS is an annual national sample survey of the internal migrants organized by the National Health Commission (NHC), which aims to understand the changing landscape of internal migration, the utilization of public health services, and the management of family planning services (16). The survey is conducted in 32 provincial units, which cover all 31 provinces and the Xinjiang Production and Construction Corps (XPCCs) of China. In order to understand the epidemic status of key diseases, in addition to the original survey, 8 cities were selected for a special survey in 2017. This study is based on this survey. Sampling sites included Qingdao, Suzhou, Guangzhou, Zhengzhou, Changsha, Jiulongpo District, Urumqi, and Xishuangbanna. From the perspective of location, Qingdao, Suzhou, and Guangzhou are located in the east, which is more economically developed; Zhengzhou and Changsha belong to the central region; Jiulongpo District, Xishuangbanna, and Urumqi belong to the western region. The data were standardized to adjust for bias caused by differences between regions.

The participants were selected by using a stratified multi-stage sampling method with a probability-proportional-to-size (PPS) approach. First, 31 provinces (autonomous regions and municipalities) and XPCCs were taken as the first-level sample units, eight representative provinces were selected. Second, one city in each province was selected, as follows: Qingdao, Suzhou, Guangzhou, Zhengzhou, Changsha, Jiulongpo District, Urumqi, and Xishuangbanna. Then, in each selected city according to the administrative division, township (town, street) attributes were sorted, as the third layer. Next, selected townships (towns and streets) by the PPS method. In the selected township (town, street), the village (neighborhood) committee was selected by the same method. All eligible subjects in the selected village (neighborhood) committees were invited to participate in the study. In each village or neighborhood, floating populations' households were selected by simple random sampling according to a random number table. The floating population that lived in the destination for more than 1 month, aged 15 and over, and were not registered in the district (county or city) were included in the study. Similarly, the registered families were selected according to the same sampling method as the floating populations' households. The registered population aged 15 and above at each sampling point was included in the study.

A household needs to investigate only one mobile population or registered residence population. Finally, a total of 13,998 floating population and 14,000 registered residence population were surveyed. Information collected included participants' basic information, family members, health and public services, social integration, and epidemic influencing factors of key diseases, etc.

Dependent Variable

According to the research needs of this study, the dependent variable was children's vaccination. This variable was measured by the following question: "Has your child been vaccinated on time since birth?." Possible answers were as follows: yes, no, and not applicable. We excluded all "not applicable" responses, resulting in a total of 12,199 participants included.

Independent Variables

Socio-Demographics

Socio-demographic characteristics included the following: region, gender, age, ethnicity, education level, marital status, and chronic disease. The region was classified into the eastern region, central region, and western region. Education level was coded into four categories, namely, primary school or below, junior high school, senior high school, university or college, and above. Chronic diseases were measured through the question, "Do you suffer from chronic diseases diagnosed by doctors, such as hypertension or diabetes?." The possible answer was "yes" or "no."

Health Education

The health education was reflected by the question: "Have you received the following health education in your local community in the past year?." The response options were "yes" and "no." The types of health education mainly consisted of "occupational disease prevention and control," "STD and AIDS prevention and control," "reproductive health and contraception," "tuberculosis prevention and control," "tobacco control," "chronic disease prevention and control," "maternal and child healthcare," "healthy birth and childbearing," "self-help education in public emergencies," and "mental health" education. Respondents should answer the question according to their utilization of health education. In this study, the respondents who have received any one of the above health educations are regarded as having received health education. In view of the delay of the floating population receiving the health education services in the inflow area, the floating population that has lived in the destination areas for <6 months will be excluded.

In addition, length of time to the nearest medical institution, health records, and cognition of basic public health services were included in this study. The length of time to medical institutions is mainly to evaluate the accessibility of individual medical services. The establishment of health records is also one of the contents of basic public health services.

Statistical Analysis

Data were processed and analyzed using STATA version 14.0. Descriptive statistics and a chi-square independence test were used to describe the information and compare the vaccination status of children under different sociodemographic characteristics. To further examine potential factors associated with risk or protection for children vaccination, a binary logistic regression analysis was used, and odds ratios (ORs) and 95% CIs were calculated. All tests were 2-tailed, and statistical significance was set at the 5% level.

RESULTS

Sample Characteristics

The characteristics of the participants are present in **Table 1**. Of the 12,199 participants, 49.82% (6,078) participants were registered population, 50.18% (6,121) participants were floating population. Among the registered population, 51.60% participants were men, and the mean age was 33.74 years (SD, 7.66). The majority of participants (87.46%) were of Han nationality. In total, 52.58% of the individuals had received an education of junior college or above and 95.97% were married. For the floating population, 50.60% were men, the mean age was 34.33 years (SD, 8.29), 88.83% were of Han nationality. Compared with the registered population, the education level of the floating population is relatively low, and only 19.02% had a college degree or above. Chi-square testing showed that there were significant differences in registered and floating populations in the regional classification, age, ethnicity, education level, marital status, length of time to the nearest medical institution, health records, chronic disease, and cognition of basic public health service ($p < 0.05$).

Utilization of Health Education

In this study, the acceptance rates of health education for registered and floating populations were 87.07% (5,292/6,078) and 79.58% (4,871/6,121), respectively, and the difference was statistically significant ($X^2 = 123.034$, $p < 0.001$). Meanwhile, the acceptance rate of health education for all types of the floating populations was significantly lower than that of the registered population ($p < 0.001$; (see **Table 2**).

Current Situation of Vaccination for Children

The data of this study showed that 94.39% (5,737/6,078) of children in registered residence were completely vaccinated, which was significantly higher than that of the floating children (91.68%, $X^2 = 34.430$, $p < 0.001$). Among the registered population, differences in regional classification ($p < 0.001$), ethnicity ($p < 0.001$), an education level ($p < 0.001$), marital status ($p < 0.001$), length of time to the nearest medical institution ($p < 0.001$), and cognition of basic public health service ($p = 0.026$) aspects between completely and incompletely vaccinated children were statistically significant. For the floating population, the analysis showed that there were significant differences in vaccination rates among floating children of different regional classifications, ethnicity, educational levels, marital status, length of time to the nearest medical institution, health records, cognition of basic public health service, and health education ($p < 0.05$; see **Table 3**).

TABLE 1 | Characteristics of participants ($N = 12,199$).

Variables	Registered population *n*%	Floating population *n*%	*P*
Region			<0.001
Eastern region	2,755 (45.33)	2,761 (45.11)	
Central region	1,690 (27.80)	1,358 (22.19)	
Western region	1,633 (26.87)	2,002 (32.70)	
Gender			0.269
Male	3,136 (51.60)	3,097 (50.60)	
Female	2,942 (48.40)	3,024 (49.40)	
Age (years)			0.010
≤30	2,484 (40.87)	2,361 (38.57)	
>30	3,594 (59.13)	3,760 (61.43)	
Ethnicity			0.020
Han ethnic	5,316 (87.46)	5,437 (88.83)	
Minorities	762 (12.54)	684 (11.17)	
Education level			<0.001
Primary school or below	226 (3.72)	747 (12.20)	
Junior high school	1,063 (17.49)	2,585 (42.23)	
Senior high school	1,611 (26.51)	1,625 (26.55)	
University or college and above	3,178 (52.28)	1,164 (19.02)	
Marital status			0.032
Married	5,833 (95.97)	5,919 (96.70)	
Other	245 (4.03)	202 (3.30)	
Length of time to nearest medical institution			<0.001
≤15min	5,211 (85.74)	5,089 (83.14)	
>15min	867 (14.26)	1,032 (16.86)	
Health Records			<0.001
Yes	3,748 (61.67)	2,068 (33.79)	
No	2,330 (38.33)	4,053 (66.21)	
Chronic disease			0.002
Yes	273 (4.49)	207 (3.38)	
No	5,805 (95.51)	5,914 (96.62)	
Cognition of basic public health service			<0.001
Yes	4,651 (76.52)	4,056 (66.26)	
No	1,427 (23.48)	2,065 (33.74)	

Analysis of Influencing Factors of Vaccination in Children

To explore the influencing factors of complete vaccination of children in the registered population and floating population, logistic regression analysis was carried out. Sociodemographic variables and basic public health services (such as, health education and health records) were defined as independent variable X, and vaccination of children was defined as dependent variable Y, as shown in **Table 4**. The findings indicated that region, education level, and marital status were the main influencing factors of children's vaccination, regardless of registered residence, or floating population. Those who live in the East ($OR_1 = 1.546$, $OR_2 = 1.834$) have a high level of education ($OR_1 = 2.341$, $OR_2 = 470$), are married ($OR_1 = 2.682$, $OR_2 = 2.094$), are more likely to have their children fully vaccinated. Besides, ethnicity (OR = 2.219) and length of time to the nearest medical institution (OR = 1.353) were unique risk factors for complete vaccination of children in registered residence. For the floating population, health records (OR = 1.745) were a unique influencing factor for children's vaccination.

DISCUSSION

As an important labor force in urban development, the floating population has made great contributions to promote the rapid development of social economy. However, influenced by the household registration system and other related welfare systems, the floating population cannot enjoy the same public service and social welfare as the registered population (17). Under the condition of low economic income and lack of medical security and basic medical and health service supply, the health of floating children is particularly vulnerable. Vaccination is an effective

TABLE 2 | Comparison of health education utilization between registered residence population and floating population.

Types of health education	Registered population (6,078)	Floating population (6,121)
Occupational disease prevention and control	2,845 (46.81)	2,021 (33.02)
P	<0.001	
STD and AIDS prevention and control	3,428 (56.40)	2,510 (41.01)
P	<0.001	
Reproductive health and contraception	4,354 (71.64)	3,655 (59.71)
P	<0.001	
Tuberculosis prevention and control	2,823 (46.45)	2,072 (33.85)
P	<0.001	
Tobacco control	3,749 (61.68)	3,191 (52.13)
P	<0.001	
Mental health	3,051 (50.20)	2,207 (36.06)
P	<0.001	
Chronic disease prevention and control	3,069 (50.49)	2,251 (36.78)
P	<0.001	
Maternal and child health care	4,579 (75.34)	3,911 (63.89)
P	<0.001	
Self-help education in public emergencies	3,545 (58.33)	2,784 (45.48)
P	<0.001	

There are overlaps in the number of participants who received the different types of health education.

method to prevent infectious diseases and is considered one of the most cost-effective public health services for children (5, 18, 19). This study takes children vaccination as the breakthrough point and analyzes the differences in the utilization of public health services between the registered residence population and the floating population, provide a theoretical basis for promoting health equity.

Analysis of Vaccination Status in Children

In China, planned immunization for children began in 1978. At present, the goal of reaching 85% of children's immunization rate has been achieved. Yet, with the rapid increase of the floating population, the immunization planning and management of floating children have become the focus of current work (20). Our research showed that 94.39% of children in registered residence were completely vaccinated and only 5.61% were incompletely vaccinated, but the proportion of incomplete vaccination among the floating children had reached 8.32%. These results were similar to others from diverse population groups. A study in southern Ethiopia found that compared with children born to non-migrant mothers, children born to rural-rural migrant mothers had significantly less chance of receiving full immunization coverage (21). Kagoné et al. conducted a qualitative study in Burkina Faso and also reported that migration was an important reason for incomplete vaccination (22). It can be seen that although China has made some achievements in immunization, the vaccination status of floating children still needs to be further improved. Addressing this issue will be of high significance to the goal of achieving a 100% vaccination rate among children in China.

Influencing Factors of Immunization Among Children

Univariate analysis showed that regardless of the registered or floating population, regional classification, ethnicity, education level, marital status, length of time to the nearest medical institution, and cognition of basic public health service were related to complete vaccination of children. Parents in the eastern region, Han nationality, college degree or above, married, closer to medical service institutions, and familiar with basic public health services have a higher complete vaccination rate for their children. In addition, the difference in the utilization of basic public health services also has a significant impact on the vaccination of children of the floating population. The complete vaccination rate of children of the floating population who establish health records and understand basic public health services was higher. However, this result seems somewhat less significant in the registered population. According to logistic regression analysis, there were also differences in influencing factors of complete vaccination of children between the two groups.

Region

It is widely known that the economy of Eastern China is relatively developed, followed by the central region. Affected by many factors, such as history, society, and natural conditions, the economic development of the western region is at the lowest level in the country. Empirical evidence suggests that large inequity in resources and services can exacerbate disparities in health outcomes and quality of life (23, 24). As this study found, the possibility of children to be vaccinated completely in the East was 1.546 times that of the Western registered population, and among the floating population, this multiple reached 1.834. This

TABLE 3 | Comparison of complete vaccination among children with different demographic characteristics.

Variables	Completely vaccinated	
	Registered population (6,078)	**Floating population (6,121)**
Region		
Eastern region	2,680 (97.28)	2,606 (94.39)
Central region	1,558 (92.19)	1,244 (91.61)
Western region	1,499 (91.79)	1,762 (88.01)
P	<0.001	<0.001
Gender		
Male	2,964 (94.52)	2,850 (92.02)
Female	2,773 (94.26)	2,762 (91.34)
P	0.660	0.329
Age (years)		
≤30	2,345 (94.40)	2,184 (92.50)
>30	3,392 (94.38)	3,428 (91.17)
P	0.967	0.066
Ethnicity		
Han ethnic	5,068 (95.33)	5,015 (92.24)
Minorities	669 (87.80)	597 (87.28)
P	<0.001	<0.001
Education level		
Primary school or below	190 (84.07)	628 (84.07)
Junior high school	992 (93.32)	2,352 (90.99)
Senior high school	1,519 (94.29)	1,530 (94.15)
University or college and above	3,036 (95.53)	1,102 (94.67)
P	<0.001	<0.001
Marital status		
Married	5,531 (94.82)	5,449 (92.06)
Other	206 (84.08)	163 (80.69)
P	<0.001	<0.001
Length of time to nearest medical institution		
≤15min	4,943 (94.86)	4,690 (92.16)
>15min	794 (91.58)	922 (89.34)
P	<0.001	0.003
Health Records		
Yes	3,554 (94.82)	1,948 (94.20)
No	2,183 (93.69)	3,664 (90.40)
P	0.062	<0.001
Chronic disease		
Yes	256 (93.77)	189 (91.30)
No	5,481 (94.42)	5,423 (91.70)
P	0.650	0.840
Cognition of basic public health service		
Yes	4,407 (94.75)	3,748 (92.41)
No	1,330 (93.20)	1,864 (90.27)
P	0.026	0.004
Health Education		
Yes	4,991 (94.31)	4,489 (92.16)
No	746 (94.91)	1,123 (89.84)
P	0.496	0.008

TABLE 4 | Logistic regression analysis of the influencing factors of complete vaccination.

Variables	Registered population		Floating population	
	OR	*95% CI*	*OR*	*95% CI*
Region				
Western region	1		1	
Eastern region	1.546*	1.066–2.243	1.834***	1.453–2.316
Central region	0.542***	0.386–0.758	1.095	0.845–1.418
Ethnicity				
Minorities	1		1	
Han ethnic	2.219***	1.561–3.154	1.149	0.871–1.514
Education level				
Primary school or below	1		1	
Junior high school	1.818*	1.151–2.872	1.543**	1.199–1.986
Senior high school	1.921**	1.219–3.026	2.347***	1.727–3.189
University or college and above	2.341***	1.506–3.637	2.470***	1.753–3.480
Marital status				
Other	1		1	
Married	2.682***	1.831–3.930	2.094***	1.440–3.045
Length of time to nearest medical institution				
>15min	1		1	
≤15min	1.353*	1.022–1.791	1.227	0.976–1.542
Health Records				
No	1		1	
Yes	1.159	0.899–1.495	1.745***	1.385–2.197
Cognition of basic public health service				
No	1		1	
Yes	1.128	0.845–1.505	0.986	0.801–1.214
Health Education				
No	1		1	
Yes	0.843	0.586–1.214	1.150	0.918–1.440

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

may be related to the regional differences in the distribution of health resources. On the one hand, the eastern developed region has a higher level of resources than the other two regions (25). On the other hand, a higher economic level means that the eastern provinces have a higher financial capacity to fund health services. Besides, the larger size and the higher density of populations in the eastern region mean that its operational costs of health services are relatively cheaper (26). Obviously, the western region lacks such resource advantages, which suggests that policymakers should focus on the current situation of health resource allocation in the western region and give corresponding policy and financial support.

Ethnicity

The current study found that ethnicity was an influencing factor for complete vaccination of children in the registered population. The probability of complete vaccination of the Han population was 2.219 times higher than that of ethnic minorities. Previous studies have shown that under the influence of Confucian traditional culture and the specific culture of ethnic minorities, the health consciousness of ethnic minorities is relatively limited (27). At the same time, some ethnic minorities trust their traditional treatment methods more, which leads to poor awareness of children's vaccination services or eligibility for vaccines free of charge by ethnic minority parents. This suggests that health education and publicity activities should be implemented for this population, especially the knowledge of children's vaccination services. However, this result has not been found in the floating population.

Educational Level

Results from our study also revealed that the educational level of parents is a significant factor that influences the uptake of complete vaccination among children, which is consistent with the previous research results (4, 28). The higher the educational level of parents, the higher the possibility of complete vaccination of their children. This result is applicable to both the registered population and the floating population. In general, highly educated people usually have higher cognitive level and health awareness (29). Parents with higher education levels are more likely to be better educated on immunization and have a good understanding of the value of completely vaccinating

their children as compared to those with primary school and below. On the contrary, the less educated people tend to have poor economic status and weak health awareness and are more likely to make health risk behaviors (30), such as refusing or failing to vaccinate their children on time. This problem is more serious among the floating population, which is similar to the results of some studies. Previous studies indicated that increasing education level of the parents, especially for mothers, can improve the full immunization coverage among floating children (4, 31, 32). Indeed, the higher the education level, the stronger the individual's awareness of self-health management. However, this survey found that the education level of most floating populations was junior middle school or below. Due to mobility, they are not familiar with the process of child vaccination. Therefore, this group is the focus of health education intervention for social workers. In addition, the marital status of parents was associated with the complete vaccination of children. This shows that parents with harmonious family relations are more likely to pay attention to their children's health and complete the vaccination on time. Therefore, attention should be paid to those children whose parents are not around when carrying out health education, especially floating children.

Length of Time to the Nearest Medical Institution

For the registered population, length of time to the nearest medical institution was another unique risk factor for complete vaccination of children. Analysis shows that the closer the medical and health institutions, the higher the possibility to complete vaccination for children, which is related to the availability of medical services. As an important part of public service facilities, the accessibility of medical institutions reflects the opportunity and convenience of public access to medical services (33). Obviously, residents closer to medical institutions are more likely to have access to health services. However, this factor does not apply to the floating population. Limited by their own economic ability and the nature of their work, the floating population has less opportunity to consider the accessibility of medical services when a choosing residence. Therefore, there is little difference in the overall accessibility of medical services among this group (34).

Health Record

Besides, health record was an independent influencing factor for the vaccination of children of the floating population. For the floating population with health records, the complete vaccination of their children is 1.745 times higher than that without records. In China, the Ministry of Health launched the national health record program in 2009. The establishment of the health record is not only an important means to improve residents' health level but also the primary link to realize the equalization of basic public health services. For the floating population, the establishment of health records is one of the most directly beneficial public health services (35). However, due to regional mobility, most of the floating population knows little about relevant health services. Compared with those who have not established health records, the documented floating population has more opportunities to obtain health information. Therefore, they have more opportunities to learn about children's vaccination. This shows that the health publicity for the floating population needs to be further improved.

Health Education

The current study also found that health education had a significant impact on the vaccination of floating children in univariate analysis. According to behavior change theory, individuals with sufficient knowledge and positive attitudes could result in good practice (36). Therefore, accepting and understanding health knowledge and applying it to practice is a complete process of behavior change. Health education is the first step to realize behavior change, i.e., imparting health knowledge. For example, health knowledge lectures can enhance people's understanding of infectious diseases and help people to establish a correct concept of health and improve personal health literacy. Improving personal health literacy will help to further improve health outcomes (37). Thus, for the floating population, receiving health education is not only beneficial to their own health but also conducive to the social stability of the inflow area (38). In this study, although some floating population received health education, they did not receive complete vaccination for their children. This suggests that the publicity and education of planned immunization need to be further improved in order to make the floating population realize the importance of planned immunization to children's health.

CONCLUSION

Compared with other common public health intervention, vaccination makes good economic sense and meets the need to care for the weakest members of societies. This study found that compared with the registered population, the floating population is at a disadvantage in using basic public health services. There are still 8.32% of floating children were incompletely vaccinated. The region, parents' education level, and marital status were found to be significant risk factors for complete vaccination of children regardless of the registered or floating population. In addition, ethnicity and length of time to the nearest medical institution were unique risk factors for complete vaccination of children in registered residence. In addition, health record was an independent influencing factor for the vaccination of children of the floating population. The findings of this study have certain reference value for further improving the planned immunization management system. Based on the above factors, policy makers should take targeted policies and measures, such as establishing various platforms for basic public health services for the floating population, to ensure that they can make more convenient and equitable use of public health services.

LIMITATIONS

There are several limitations to this study. Among the limitations is the questions' subjectivity, such as the dependent variable and the possibility of recall bias. Secondly, a cross-sectional survey cannot be determined the time-effect and

causality accurately compared with the cohort study, so our study only reveals the correlation between factors. In addition, other factors, such as family economic status, vaccine safety, and vaccine hesitance, should be further explored in future studies.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: http://www.ldrk.org.cn/.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

JC designed this study, participated in its implementation, and served as the lead writer. YXi and YXu did the data interpretation and co-wrote the article. GJ helped collect the data and research the literature. JX helped with formatting of this manuscript. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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Willingness to Be Vaccinated Against COVID-19 Among People With HIV in the United States: Results From a National Survey

Jeffrey A. Wickersham[1], Jaimie P. Meyer[1,2], Sheela Shenoi[1], Frederick L. Altice[1,3], Lydia Aoun Barakat[1], Michael Virata[1], Miriam Olivares[4], Francesca Maviglia[1], Antoine Khati[5] and Roman Shrestha[5,6]*

[1] Department of Internal Medicine, Section of Infectious Diseases, AIDS Program, Yale School of Medicine, New Haven, CT, United States, [2] Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, CT, United States, [3] Department of Epidemiology of Microbial Diseases, Yale School of Public Health, New Haven, CT, United States, [4] Marx Science and Social Science Library, Yale University Library, Yale University, New Haven, CT, United States, [5] Department of Allied Health Sciences, University of Connecticut, Storrs, CT, United States, [6] Institute for Collaboration on Health, Intervention, and Policy, University of Connecticut, Storrs, CT, United States

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Francesca Licata,
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New York Institute of Technology, United States
Kamini Doraivelu,
Emory University, United States

***Correspondence:**
Jeffrey A. Wickersham
jeffrey.wickersham@yale.edu

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Background: Approximately 215 million Americans have been fully vaccinated for COVID-19, representing over 65% of the total population. People with HIV (PWH) may be more susceptible to COVID-19 infection or severe disease, elevating the importance of COVID-19 vaccination uptake in the population. We report results from a national survey of PWH to evaluate the likelihood of receiving a COVID-19 vaccine.

Methods: We conducted an online survey of 1,030 PWH living in the United States between December 6, 2020 and January 8, 2021 to evaluate likelihood of receiving a COVID-19 vaccine.

Results: Overall, participants were highly willing to be vaccinated, with 83.8% stating they "strongly agree" (65.7%) or "somewhat agree" (18.1%). Participants' top vaccine-related concerns were side-effects (39.3%), safety (14.7%), and fair/equitable distribution of the vaccine to affected communities (13.6%). Participants were more willing to be vaccinated if they reported receiving an annual influenza vaccination ($p < 0.001$), had previously tested positive for ($p = 0.043$) COVID-19, had been hospitalized for ($p = 0.027$) COVID-19 infection, or had an undetectable HIV viral load ($p = 0.002$). Black ($p < 0.001$), politically conservative ($p < 0.001$), and participants with an annual income of ≤$19,999 ($p = 0.005$) were significantly less willing to be vaccinated for COVID-19.

Conclusions: The vast majority of PWH were willing to be vaccinated, though predominantly those who were already engaged in HIV care or directly affected by COVID-19. Findings from this large survey of PWH suggest intensive outreach efforts are needed to support engagement in vaccination programs, particularly among Black and politically conservative PWH.

Keywords: COVID-19, HIV, people with HIV, vaccine hesitancy, vaccine uptake

INTRODUCTION

High uptake of COVID-19 vaccination is crucial to achieving the level of immunization coverage needed to end the global COVID-19 pandemic (1–3). Prioritizing vaccines for those populations most vulnerable to the disease, including persons who are immunocompromised, has been a key strategy for reducing COVID-19 hospitalizations and in-hospital mortality. Recent evidence suggests that people with HIV (PWH) are at increased risk of hospitalization and death from COVID-19 (4, 5). Data from over 15,000 cases of COVID-19 among PWH showed they were 13% more likely to be hospitalized and had a 30% greater risk of death from COVID-19, regardless of age, sex, disease severity at presentation, and co-morbidities (4). In response, the World Health Organization issued a report, urging that PWH have continued access to antiretroviral treatment during the pandemic and receive priority access to COVID-19 vaccination (6).

However, several challenges persist in ensuring high coverage of COVID-19 vaccination among PWH. A study of COVID-19 vaccine uptake among PWH in Oregon found that as of June 2021 only about two-thirds of PWH had received the vaccine; younger PWH, Hispanic/Latinx PWH, and PWH who inject drugs or reside in rural areas had lower vaccine uptake (7). Attitudes toward vaccination also play a role in vaccine uptake. To date, only two published studies have examined attitudes toward COVID-19 vaccination among PWH in the United States; however, they focus on specific subpopulations (e.g., racial-ethnic minorities), with relatively small sample sizes (8, 9). Understanding attitudes toward COVID-19 vaccination among a broad cross-section of PWH can inform larger-scale interventions to improve vaccine uptake and guide vaccine implementation strategies and programs. In this study, we report findings from a national survey of PWH in the United States regarding their willingness to be vaccinated against COVID-19.

METHODS

We conducted a cross-sectional online survey of PWH living in the United States ($N = 1{,}030$) between December 2020 and January 2021 to evaluate their willingness to be vaccinated against COVID-19 (10). Participants were recruited through targeted social media advertising to participate in an online survey. Participation was limited to adults 18 years or older with self-reported HIV infection. To control for potential duplicate entries, we followed published procedures to ensure data integrity in internet-based research (11). Participation in this study took approximately 10 min. As compensation, participants had the opportunity to take part in a raffle to win 1 of 5 $100 gift cards. Completion of the survey was not required to enter the raffle. The study was approved by the Yale University institutional review board.

Willingness to be vaccinated against COVID-19 was measured with a single-item question: "*When a vaccine for COVID-19 becomes available, I will get it.*" Participants responded using a 5-point Likert scale (from 1 = strongly disagree to 5 = strongly agree), consistent with other measures of COVID-19 vaccine willingness among the general adult population assessed ordinally and dichotomized for analysis (12). Participants were then asked what would make them more likely to get the COVID-19 vaccines and were able to select all options that applied to them. The survey also collected information about participants' socio-demographic characteristics (e.g., age, sex, sexual orientation, race, education level, and income level), political orientation (e.g., conservative, liberal), HIV & health-related attributes (e.g., time living with HIV, CD4 count, HIV viral load, receipt of annual influenza vaccine) and COVID-19 history and experiences (e.g., prior COVID-19 testing history, prior COVID-19 diagnosis).

We used multivariable logistic regression to explore the association of willingness to be vaccinated against COVID-19 with selected covariates. Candidate covariates were selected based on previous literature on vaccine hesitancy (9, 10, 13, 14). The reference group for each variable included all participants not belonging to the indicated category (e.g., the reference group for "Black" included all participants who did not select "Black" as their race). Statistical significance was set at $p < 0.05$, and all analyses were performed using IBM SPSS 25.

RESULTS

Participants were mostly male (89.7%), White/Caucasian (66.0%), and gay or lesbian (84.5%) (13). Participants' mean age was 50.7 years (SD = 12.5), and the mean time living with HIV was 17.0 years (SD = 11.1). Overall, participants were highly willing to be vaccinated, with 83.8% stating they "strongly agree" (65.7%) or "somewhat agree" (18.1%) to receive a COVID-19 vaccine when available.

In the multivariable logistic regression model (**Table 1**), participants who were Black (aOR = 0.47, $p = 0.008$), politically conservative (aOR = 0.39, $p = 0.002$), or had an annual income of ≤$19,999 (aOR = 0.55, $p = 0.005$) were significantly less willing to receive a COVID-19 vaccine, whereas participants who reported being vaccinated annually for influenza (aOR = 6.01, $p < 0.001$) or identified as politically liberal (aOR = 2.63, $p < 0.001$) were more willing to be vaccinated, after adjusting for socio-demographic characteristics, political orientation, HIV & health-related attributes, and COVID-19 history and experiences.

Participants' primary vaccine-related concerns (**Figure 1A**) were side-effects (39.3%), safety (14.7%), and fair/equitable distribution of the vaccine to affected communities (13.6%). Side-effects (48.0%), safety (19.8%), and fair/equitable distribution (17.9%) of the vaccine were also the primary concerns among low-income PWH. Among Black PWH and politically conservative PWH, the most commonly reported concerns were side-effects (respectively, 60.3 and 51.4%), safety (22.4 and 22.2%), and not wanting to be experimented on (20.7 and 23.6%).

Participants reported that they would be more willing to get a COVID-19 vaccine if it were recommended by their doctor (61.5%), the Centers for Disease Control and Prevention (CDC; 56.8%), the World Health Organization (WHO; 47.8%), or if their doctor reported having been vaccinated (33.6%;

TABLE 1 | Bivariate and multivariable logistic regression of COVID-19 vaccine willingness ($N = 1,030$).

Variables	Total Sample	OR	95%CI	*p*	aOR	95%	*p*
Socio-demographic							
Male sex	924 (89.7)	3.28	2.11–5.08	<0.001	1.42	0.71–2.87	0.320*
Race: Black	116 (11.3)	0.25	0.16–0.38	<0.001	0.47	0.27–0.83	0.008*
Race: White	680 (66.0)	2.21	1.57–3.08	<0.001	1.14	0.72–1.80	0.572*
Median age (years)	53	1.02	1.01–1.03	0.002	1.01	0.98–1.02	0.507*
Education: bachelor's or higher	507 (49.2)	2.31	1.62–3.28	<0.001	1.23	0.80–1.88	0.339*
Annual income $\leq$ $19,999	252 (24.5)	0.38	0.27–0.54	<0.001	0.55	0.36–0.84	0.005*
Sexual orientation: gay or lesbian	870 (84.5)	3.16	2.15–4.64	<0.001	1.23	0.68–2.23	0.490*
Political orientation							
Conservative	72 (7.0)	0.23	0.14–0.37	<0.001	0.39	0.21–0.71	0.002*
Liberal	679 (65.9)	4.12	2.91–5.82	<0.001	2.63	1.73–4.02	<0.001*
HIV and Health-related attributes							
Median time living with HIV (years)	17	1.01	0.99–1.02	0.122			
CD4 >200 cells	804 (78.1)	0.63	0.40–0.99	0.045	1.29	0.76–2.20	0.346
HIV Viral Load Undetectable	984 (95.5)	2.65	1.40–5.02	0.003	1.12	0.47–2.66	0.804
Receive annual flu vaccine	867 (84.2)	6.19	4.25–9.02	<0.001	6.01	3.91–9.22	<0.001*
COVID-19 history and experiences							
Ever been tested for COVID-19	675 (65.5)	1.38	0.98–1.94	0.064			
Ever tested positive for COVID-19	81 (7.9)	0.71	0.40–1.23	0.227			

OR, odds ratio; aOR, adjusted odds ratio.
*****statistical significance at $p < 0.05$.*

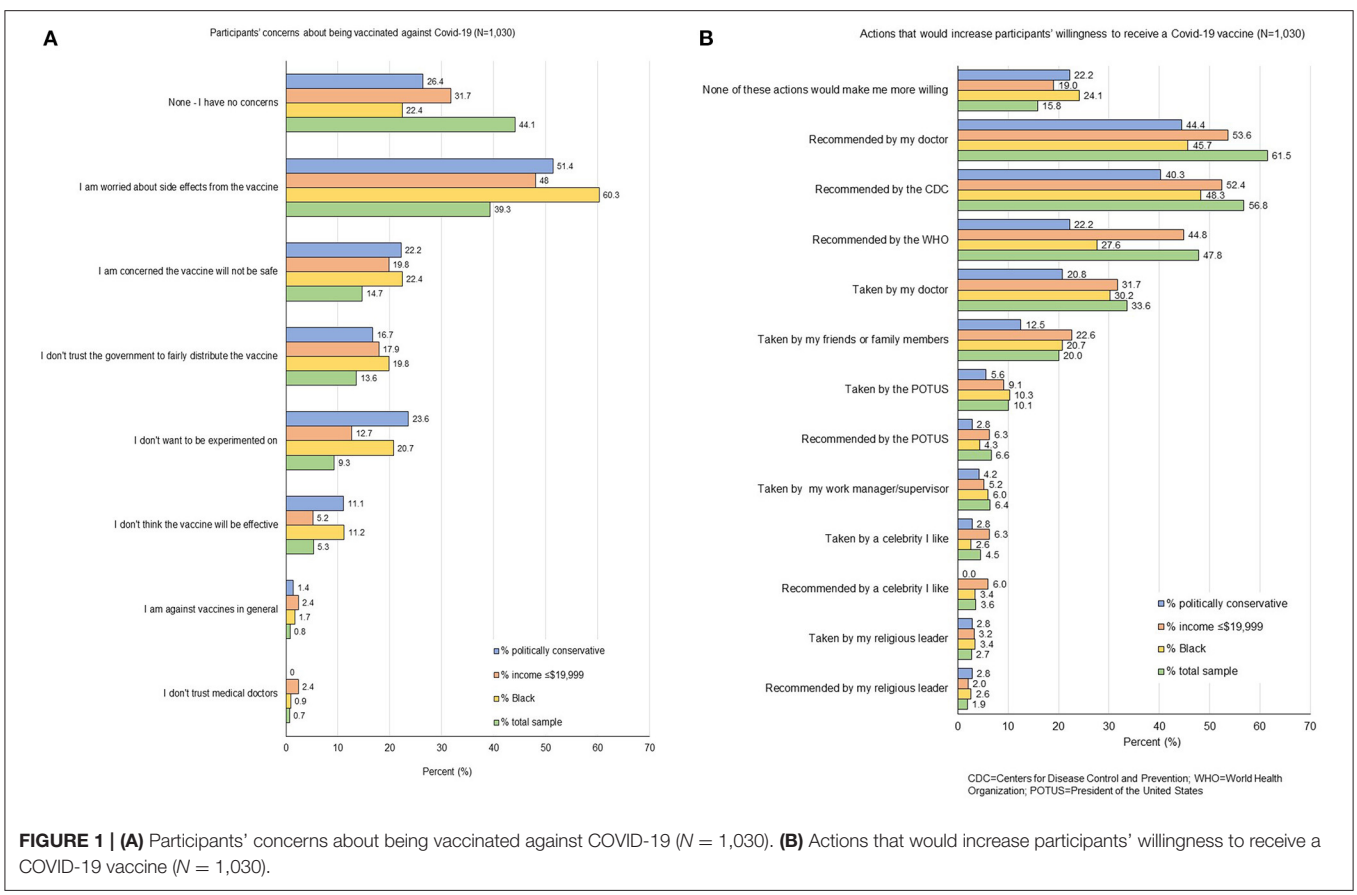

FIGURE 1 | (A) Participants' concerns about being vaccinated against COVID-19 ($N = 1,030$). **(B)** Actions that would increase participants' willingness to receive a COVID-19 vaccine ($N = 1,030$).

Figure 1B). These priorities were similar among politically conservative PWH and low-income PWH. Among Black PWH, however, a recommendation by the CDC was the action most endorsed to increase vaccine willingness (48.3%), followed by a recommendation (45.7%) or a report of having been vaccinated (30.2%) by their doctor, and a recommendation by the WHO (27.6%).

Black PWH and conservative PWH appeared somewhat less likely to increase their willingness to be vaccinated than low-income PWH, with 24.1% of Black PWH and 22.2% of conservative PWH declaring that none of the proposed actions would make them more willing to get vaccinated, compared to 19% of low-income PWH. A recommendation by the WHO would increase the willingness of almost half (44.8%) of low-income PWH, but only 27.6% of Black PWH and 22.2% of conservative PWH. A recommendation by a doctor was also slightly more influential among low-income PWH (53.6%) than among Black or conservative PWH (45.7 and 44.4%, respectively). A CDC recommendation was more influential among Black and low-income PWH (48.3 and 52.4%, respectively) than among conservative PWH (40.3%). Similarly, 30.2% Black PWH and 31.7% low-income PWH reported being more willing to be vaccinated if it were recommended by their doctor, compared to only 20.8% of conservative PWH.

DISCUSSION

Achieving an end to the COVID-19 pandemic hinges on the successful vaccination of a majority of the population. In this national sample of PWH, we found a high degree of willingness to be vaccinated for COVID-19—comparably higher than that of the general U.S. adult population (69%). Side effects and safety were the main vaccine-related concerns among participants. Not wanting to be experimented on was a greater concern among Black and politically conservative PWH, while PWH with an annual income of $\leq$\$19,999 were more concerned about fair and equitable distribution of the vaccine. Importantly, none of the HIV-related variables contributed significantly to COVID-19 vaccine willingness, including participants' CD4 level, HIV viral load status, or time living with HIV.

Our results also reflect current societal race and political divisions. For example, Black PWH who are disproportionately affected by COVID-19 infection and mortality, are also less willing to be vaccinated, further exacerbating race-based disparities. Medical mistrust stemming from histories and experiences of medical abuse and racism within the healthcare system affects Black individuals' access to care in the U.S. (15), and has been found to negatively impact willingness to receive the COVID-19 vaccine among Black PWH (9). Similar to politically conservative US residents at large (16), conservative PWH were also less likely to be willing to receive a COVID-19 vaccine, which may be attributed to the politicization of the COVID-19 pandemic.

Our study presents some limitations. The social media-based recruitment strategy means that this self-selecting sample may have been affected by some selection bias. Indeed, compared to overall PWH in the US, White/Caucasian individuals were overrepresented in this sample (17), affecting the generalizability of results. Additionally, the survey was conducted before the COVID-19 vaccine was widely available. Therefore, willingness to be vaccinated and concerns about the vaccine may have changed now that a significant portion of the US population has received at least one dose.

Despite these limitations, this is the first study to our knowledge to examine attitudes toward the COVID-19 vaccine in a large, national sample capturing a broad cross-section of PWH in the U.S. These results offer a first step toward identifying those PWH most likely to decline vaccination and inform the development of effective, targeted health communication to reduce COVID-19 vaccine refusal among different demographic and social groups.

While our findings identify alarming challenges, they also present an opportunity to combat COVID-19. A recommendation by their doctor or the CDC would increase many PWH's willingness to be vaccinated. Clear and accessible information about the process of development of the COVID-19 vaccine and a frank discussion about safety issues and side effects with a trusted healthcare provider may help alleviate some PWH's concerns about the vaccine. Conducting intensive tailored community outreach efforts, identifying trusted sources of information, closing gaps in health equity, and engaging formal and informal opinion leaders within the HIV community will be critical to supporting engagement in vaccination programs.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board, Yale University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

This manuscript was initially conceptualized and written by JW and RS. All authors meet the criteria for authorship, have made substantial contributions to various facets of the manuscript, reviewed, edited, contributed significantly to writing subsequent versions of the manuscript, read, and approved the final manuscript.

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COVID-19 Vaccine Hesitancy Associated With Vaccine Inequity Among Healthcare Workers in a Low-Income Fragile Nation

Mohammed Noushad[1], Mohammad Zakaria Nassani[1], Mohammed Sadeg Al-Awar[2,3], Inas Shakeeb Al-Saqqaf[4], Sami Osman Abuzied Mohammed[5], Abdulaziz Samran[1], Ali Ango Yaroko[6], Ali Barakat[1], Omar Salad Elmi[7], Anas B. Alsalhani[8], Yousef Fouad Talic[1] and Samer Rastam[9]*

[1] College of Dentistry, Dar Al Uloom University, Riyadh, Saudi Arabia, [2] Faculty of Applied Science, Amran University, Amran, Yemen, [3] Department of Medical Laboratory, College of Medical Science, Al-Razi University, Sana'a, Yemen, [4] School of Social Sciences, University Sains Malaysia, George Town, Malaysia, [5] Emergency Department, King Abdullah Medical City, Mecca, Saudi Arabia, [6] Otolaryngology Department, Usman Danfodiyo University Teaching Hospital, Sokoto, Nigeria, [7] School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia, [8] Vision College of Dentistry and Nursing, Vision Colleges, Riyadh, Saudi Arabia, [9] Vision College of Medicine, Vision Colleges, Riyadh, Saudi Arabia

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Francesca Licata,
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Deema Dababseh,
The University of Jordan, Jordan

***Correspondence:**
Mohammed Noushad
m.noushad@dau.edu.sa;
inya113@yahoo.com

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Objectives: Preventing severe disease and acquiring population immunity to COVID-19 requires global immunization coverage through mass vaccination. While high-income countries are battling vaccine hesitancy, low-income and fragile nations are facing the double dilemma of vaccine hesitancy and lack of access to vaccines. There is inadequate information on any correlation between vaccine hesitancy and access to vaccines. Our study in a low-income nation aimed to fill this gap.

Methods: In the backdrop of a severe shortage of COVID-19 vaccines in Yemen, a low-income fragile nation, we conducted a nation-wide cross-sectional survey among its healthcare workers (HCWs), between 6 July and 10 August 2021. We evaluated factors influencing agreement to accept a COVID-19 vaccine and any potential correlation between vaccine acceptance and lack of access to vaccines.

Results: Overall, 61.7% (n = 975) of the 1,581 HCWs agreed to accept a COVID-19 vaccine. Only 45.4% of the participants agreed to have access to a COVID-19 vaccine, with no sex dependent variations. Although several determinants of vaccine acceptance were identified, including, having a systemic disease, following the updates about COVID-19 vaccines, complying with preventive guidelines, having greater anxiety about contracting COVID-19, previous infection with COVID-19, believing COVID-19 to be a severe disease, and lower concern about the side effects of COVID-19, the strongest was access to vaccines (OR: 3.18; 95% CI: 2.5–4.03; p-value: 0.001).

Conclusion: The immediate and more dangerous threat in Yemen toward achieving population immunity is the severe shortage and lack of access to vaccines, rather than vaccine hesitancy, meaning, improving access to vaccines could lead to greater acceptance.

Keywords: vaccine acceptance, low-income country, Yemen, lack of access, COVID-19

INTRODUCTION

The Coronavirus disease 2019 (COVID-19) pandemic has been a global public health threat for more than 2 years, causing more than 516 million infections and 6.25 million deaths (1). There are also suggestions that globally, at least half of the COVID-19 deaths have been thought to be missed. For example, it has been suggested that the percentage of deaths from COVID-19 reported in the United States is just 78%, and in a highly populated country like India, it is only 10% indicating a public health burden greater than reported (2). This is especially true in resource-poor and conflict countries where intentional or unintentional largescale mortality underreporting, shortages in testing capacity and availability of health care workers (HCWs) are major concerns (3). So far, the World Health Organization (WHO) has identified more than thirteen variants of the SARS-CoV-2 that causes COVID-19, and it is expected to mutate further, unless global population immunity is successfully achieved (4). Currently, the favored pathway to reach that goal is through successful global vaccination programs.

Although several countries are still facing recurrent waves of the virus transmission, the implementation of robust vaccination programs have been instrumental in limiting morbidity and mortality from COVID-19. However, the optimum immunization coverage necessary to reach global population immunity can be achieved only by regulated and inclusive vaccine distribution covering all countries regardless of country income index.

Since healthcare workers (HCWs) work in the frontline in the fight against COVID-19, they are one of the most vulnerable. According to the World Health Organization (WHO), an estimated 80,000 to 180 000 health and care workers could have died from COVID-19 between January 2020 and May 2021 (5). Due to their vulnerability, and to prevent a potential breakdown of the healthcare system, globally they have been prioritized to receive vaccination against COVID-19. Thanks to the implementation of coordinated vaccination programs, as of September 2021, more than 80% of the HCWs in 22 mostly high-income countries (HIC) have been fully vaccinated against COVID-19 (5). Unfortunately, these figures are overshadowed by considerable differences across regions and economic groups. For example, as of November 2021, only 27% of HCWs in the African continent have been fully vaccinated against COVID-19, a result of extreme vaccine inequity (6).

While several HICs are battling vaccine hesitancy in pursuit to achieve maximum vaccine coverage, it is vaccine inequity that has crippled low-income countries (LIC). Even after a year since the approval of several vaccines against COVID-19, LICs are still struggling with extreme shortage in vaccine supply, enough to fully vaccinate only a fraction of their populations, while HICs have fully vaccinated more than 73% of their populations (7). Numerous studies have been conducted worldwide on vaccine hesitancy/acceptance among HCWs and the general population. However, there is inadequate information on the correlation between vaccine hesitancy/acceptance and access to vaccines. In the backdrop of a severe vaccine shortage in Yemen, we conducted an exploratory cross-sectional study among HCWs in Yemen, a low-income conflict nation, to identify predictors of COVID-19 vaccine acceptance and any potential correlation with lack of access to vaccines.

MATERIALS AND METHODS

Study Design

This study is part of a large project on global COVID-19 vaccine acceptance. Therefore, the methodology and the questionnaire followed is similar across all the studies (8). A cross-sectional self-administered survey was conducted among HCWs in Yemen between 6 July and 10 August 2021. The "Report of the SAGE working group on vaccine hesitancy" was used as a guide in preparing the questionnaire (9). As part of the validation of the study, a pilot study was initially carried out on 10 participants, after which expert opinions were taken from specialists in the field. The survey questionnaire, developed on Google Forms, was distributed by dual mode (online and paper based) to prospective participants. The questionnaire required <5 min to complete. Participation was voluntary and the participants provided informed consent on the survey platform before proceeding to the survey items. Participants were not asked to disclose their names or email addresses, and their anonymity was guaranteed during the data collection process. The survey form was designed in such a way that only complete forms would qualify for submission.

This study was approved by the Research Committee of College of Dentistry, Dar Al Uloom University, Riyadh, Saudi Arabia (COD/IRB/2020/2).

Sample

The sample size was calculated using Open Source Epidemiologic Statistics for Public Health–OpenEpi (http://www.openepi.com/Menu/OE_Menu.htm, accessed on 25 June 2021). We used 50% as the 'hypothesized percentage frequency of the outcome factor (vaccine acceptance) in the population, which is recommended for an unknown frequency, and 4% as the absolute precision. The resultant sample size for 99% confidence interval using these parameters was 1,036.

Participants were recruited using convenience sampling. Participants included HCWs from all governorates of Yemen. Participants below the age of 18 years were not included in the study. Participants were not paid compensation for participation in the study.

Measures

Trust in COVID-19 Vaccines, Health Authorities and the International Community, and Access to Vaccines

General attitudes toward vaccines were measured using a 2-item scale and participants' attitudes toward the health authorities were measured using a 4-item scale. Participants were then asked if they had access to COVID-19 vaccines. Responses were rated on a five-point Likert scale from 1 "strongly agree" to 5 "strongly disagree" (8).

TABLE 1 | Sample characteristics: data are presented as *n* (%).

Sample size	*n* (%)
Total	1,581
Sex	
Male	855 (54.1%)
Female	726 (45.9%)
Age	
18–29 years	987 (62.4%)
30–49 years	387 (24.5%)
≥50 years	207 (13.1%)
Nationality	
Yemeni	1,580 (99.9%)
Foreigner	1 (0.1%)
Province	
Aden province	164 (10.4%)
Azal province	832 (52.6%)
Hadhramout province	101 (6.4%)
Jund province	168 (10.6%)
Sheba province	189 (12%)
Tihama province	127 (8%)
Place of work	
Public	487 (30.8%)
Private	911 (57.6%)
Both	183 (11.6%)
Work	
Doctor	142 (9%)
Lab specialist/medical technician	120 (7.6%)
Dentist	158 (10%)
Nurse/dental assistant/midwife	206 (13%)
Pharmacist	409 (25.9%)
Physiotherapist, epidemiology, nutrition	138 (8.7%)
Health care student	137 (8.7%)
Other	271 (17.1%)
Comorbidity	
No	1293 (81.8%)
Yes	288 (18.2%)

TABLE 2 | Awareness about COVID-19 infection.

	n (%)
Have you been updating yourself on the development of vaccine?	
No	288 (18.2%)
Yes	1,293 (81.8%)
In your opinion, how would you rate the severity of COVID-19 disease:	
Mild	132 (8.3%)
Moderate	833 (52.7%)
Severe	616 (39%)
How would you rate your compliance with COVID-19 preventive guidelines?	
Good	846 (53.5%)
Moderate	622 (39.3%)
Poor	113 (7.1%)
To what extent are you anxious about contracting (getting infected with) COVID-19?	
Low	524 (33.1%)
Moderate	856 (54.1%)
High	201 (12.7%)
Have you had COVID-19?	
No	1,144 (72.4%)
Yes	437 (27.6%)
COVID-19 is a threat to public health in Yemen	
Agree	1,175 (74.3%)
Not sure	261 (16.5%)
Disagree	145 (9.2%)
Have you taken the COVID-19 vaccine?	
No	1,408 (89.1%)
Yes	173 (10.9%)

Data are presented as n (%).

Intention to Vaccinate

This was measured using a 7-item scale. Responses were rated on a five-point Likert scale from 1 "strongly agree" to 5 "strongly disagree" (8).

Predictor Variables

Socio-demographic factors included age group, sex, nationality, place of work and region. Participants' reports on chronic medical conditions (e.g., asthma, diabetes, hypertension, heart disease, and/or cancer) were used to indicate the presence or absence of pre-existing co-morbidity. Other variables included participants' self-updating on COVID-19 vaccine development, prior infection with COVID-19, perception of COVID-19 severity, compliance with government COVID-19 guidelines, and anxiety toward contracting COVID-19.

Statistical Analysis

Descriptive statistics were expressed as percentages and numbers for each item/survey question. The main outcome of this study was the agreement to accept a COVID-19 vaccine and potential correlation with access to vaccines. The current study considered any participant to have an intention to vaccinate if he/she agreed or strongly agreed on the item "I will get vaccinated with the COVID-19 vaccine," or if they had already taken the vaccine. Bivariate statistical analysis of the relationship between the main outcome "agreement to accept a COVID-19 vaccine" and demographic and other parameters was performed using the Chi-squared test for trend for ordinal factors, and the Chi-squared test for categorical variables. A multivariate binary logistic regression model was used to determine the predictors for intention to vaccinate. The following factors were examined as potential predictors for "intention to vaccinate:" age group, sex, nationality, presence of any medical condition, following updates on the development of vaccines against COVID-19, opinion about the severity of COVID-19, compliance with COVID-19 preventive guidelines, and anxiety about contracting COVID-19, previous COVID-19 infection, concerns about side effects of COVID-19 vaccines and access to COVID-19 vaccines. We chose possible covariates based on biological plausibility, and all

TABLE 3 | Trust in COVID-19 Vaccines and Health Authorities, and access to vaccines.

	Yemen
Vaccines are necessary to overcome the COVID-19 pandemic and get back to normal life	1,065 (67.4%)
I am concerned about the possible side effects of COVID-19 vaccines	1,092 (69.1%)
I will delay taking the COVID-19 vaccine, as I feel there are others who deserve it more than me	708 (44.8%)
Getting myself vaccinated for COVID-19 is important because I can also protect people with a weaker immune system	1,103 (69.8%)
I will take the COVID-19 vaccine only if it is free	500 (31.6%)
I think that vaccines against COVID-19 have been produced in a hurry without following recommended clinical trials and approval guidelines	698 (44.1%)
I am happy with the way the health authorities have been managing the COVID-19 pandemic so far	726 (45.9%)
I am happy with the health authorities' organization of the COVID-19 vaccination campaigns	677 (42.8%)
I am happy with the way the Non-governmental organizations like the World Health Organization, Medicines Sans Frontiers, etc., have been helping my country in vaccinating its population	768 (48.6%)
I am happy with the way the international community is helping my country in vaccinating its population	761 (48.1%)
I support a mandatory vaccination program for COVID-19	646 (41.5%)
I have access to the COVID-19 vaccine	711 (45.4%)

Data are presented as n (%).

factors that showed significant results in the bivariate analysis. The significance level was set at $p < 0.05$. All statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY, USA: IBM Corp).

RESULTS

Overall, 1,581 HCWs completed the survey questionnaire (response rate 73%). Of the participants, 61.7% ($n = 975$) expressed their agreement to get vaccinated against COVID-19. Males (54.1%) and females (45.9%) were equally distributed. The majority of the participants were from the 19–29 years age group (62.4%) and from the Azal province (52.6%). The majority of the participants had no comorbidities (81.8%). Characteristics and demographics of the participants are shown in **Table 1**. Data regarding participants' awareness about COVID-19 are presented in **Table 2**. It can be noted that more than a quarter of the participants (27.6%) were previously infected with COVID-19, while only 10.9% got vaccinated against COVID-19. At least 74.3% of the participants agreed that COVID-19 is a threat to public health in Yemen, and 81.8% have been updating themselves on the development of COVID-19 vaccines. Less than a half of the participants (39%) rated COVID-19 as a severe disease. Just 7.1% expressed their poor compliance with COVID-19 preventive guidelines, and only 12.7% agreed that they were highly anxious about contracting COVID-19 (**Table 2**).

67.4% of the participants agreed that vaccines against COVID-19 are important to overcome the pandemic, 69.1% were concerned about their side effects and 44.1% thought that the vaccines have been produced in a hurry without following guidelines. 69.8% of the participants agreed that it was important for them to get vaccinated in order to protect those with weaker immune systems, and almost half of them (44.8%) were prepared to delay getting vaccinated for those who deserved it more than them. 68.4% of the participants agreed to pay to get vaccinated. In terms of pandemic management and organization of vaccination campaigns by the health authorities, 45.9 and 42.8% expressed their satisfaction, respectively. Similarly, less than half the participants expressed their satisfaction with the support provided by non-governmental organizations (NGO) (48.6%) and the international community (48.1%). Support for a mandatory vaccination program against COVID-19 was expressed by just 41.5% of the participants. 45.4% of the participants agreed that they have access to a COVID-19 vaccine. The abovementioned results are summarized in **Table 3**.

The bivariate statistical analysis indicated a possible association between participants' intention to vaccinate and eight factors ($p < 0.05$; **Table 4**). The intention to get vaccinated increased significantly with increase in age and in those with systemic disease/s. Updating self on the development of COVID-19 vaccines, increasing severity perception about COVID-19, increasing compliance with preventive guidelines, a higher level of anxiety about contracting COVID-19, and lack of concern about the side effects of COVID-19 vaccines were all associated with a greater agreement to get vaccinated. Importantly, access to COVID-19 vaccine was significantly associated with a higher intention to get vaccinated. Details of the above results are presented in **Table 4**. There was no gender-based association with access to vaccines (**Supplementary Table**).

The logistic regression analysis indicated a possible association between agreement to get vaccinated against COVID-19 and six factors. These include having a systemic disease (OR: 1.49 95% CI: 1.03–2.16; p-value: 0.03), following the updates about COVID-19 vaccines (OR: 1.92; 95% CI: 1.43–2.57; *p*-value: 0.001), those who believed COVID-19 to be a severe disease, those who complied with preventive guidelines, those with greater anxiety about contracting COVID-19 (OR: 3.31; 95% CI: 2.08–5.25; *p*-value: 0.001), previous infection with COVID-19, those less concerned about the side effects of COVID-19 vaccines (OR: 0.49; 95% CI: 0.38–0.64; *p*-value: 0.001) and those who have access to a COVID-19 vaccine (OR: 3.18; 95% CI: 2.5–4.03; *p*-value: 0.001; **Table 5**). Of these, compliance with preventive guidelines, anxiety about contracting

TABLE 4 | Bivariate statistical analysis of the relationship between the main outcome "intention to vaccinate" and potential influential factors.

	Yemen	*p*
All participants	61.7% (975/1,581)	
Age		0.006
18–29 years	59.3% (585/987)	
30–49 years	64.1% (248/387)	
50 years or above	68.6% (142/207)*	
Gender		0.66
Male	61.2% (523/855)	
Female	62.3% (452/726)	
Medical condition		0.001
Healthy	59.8% (773/1,293)	
Has systemic disease/s	70.1% (202/288)**	
Updating self on the development of vaccines against COVID-19		<0.001
No	43.8% (126/288)	
Yes	65.7% (849/1293)**	
Opinion about the severity of COVID-19		<0.001
Mild	42.4% (56/132)	
Moderate	59.8% (498/833)	
Severe	68.3% (421/616)*	
Compliance with COVID-19 preventive guidelines		<0.001
Poor	33.6% (38/113)	
Moderate	57.4% (357/622)	
Good	68.6% (580/846)*	
Anxiety about contracting COVID-19		<0.001
Low	46.9% (246/524)	
Moderate	65.5% (561/856)	
High	83.6% (168/201)*	
Previously infected with COVID-19		0.60
No	62.1% (710/1144)	
Yes	60.6% (265/437)	
Concerned about the possible side effects of COVID-19 vaccines		<0.001
No	72% (352/489)	
Yes	57.1% (623/1092)**	
Access to the COVID-19 vaccine		<0.001
No	48.2% (413/856)	
Yes	78.3% (557/711)**	

**p was calculated using chi-square test for trend. **p was calculated using chi-square test. Significance difference was set at $p < 0.05$.*
The denominators indicate the total number of participants in this subgroup, and the numerators are the number of participants who agreed to accept a vaccine.

COVID-19, and access to a COVID-19 vaccine were showed to have the greatest association.

DISCUSSION

The success in the fight against COVID-19 rests largely on optimum immunization coverage through equitable vaccine distribution. Our study aimed to identify potential determinants of COVID-19 vaccine acceptance and any possible correlation with lack of access to vaccines, in Yemen, a low-income fragile nation. Although we did a similar study on the general population in Yemen, the current study looked for any similarities or differences with the previous study (10). Interestingly, the overall vaccine acceptance rate indicated by participants in our study (61.7%) is comparable to that indicated by HCWs in a similar study we conducted in neighboring Saudi Arabia (64.1%), a high-income country (11). It is however greater than that indicated by the general population, in the similar study we conducted in Yemen (10). Our results are comparable to other studies in HICs in the region, including one on more than 15,000 HCWs in Saudi Arabia (64.9%), one on HCWs in the United Arab Emirates (57.6%) and another one in the general population in Oman (56.8%) (12–14).

Studies in other fragile nations have indicated wide ranging results. For example, in an early multi-country study in Palestine, Syria and Jordan, it was shown that only 32.2% of the participants intended to be vaccinated against COVID-19 (15). Similarly, in two studies in Syria, the agreement to be vaccinated against

COVID-19 was indicated by only about 37% of the participants (16, 17). A study in Iraq among HCWs and the general population revealed a vaccine acceptance rate similar (61.7%) to that of our study, with HCWs indicating higher acceptance rate than the general population (18). However, a study in Somalia indicated a higher acceptance rate of 76.8%, with HCWs indicating greater willingness to accept a COVID-19 vaccine than the general population (19). These results should encourage policymakers to leverage HCWs as a means of vaccine promotion among the general public since they have been shown to be trusted sources of information on vaccines (19, 20).

As in most countries, the burden of COVID-19 in Yemen is still unclear, the main reason being a severe shortage in testing capacity and availability of HCWs (3). Although a geospatial grave counting study in Yemen could not attribute all of the excess deaths to COVID-19, a seroprevalence study conducted in Aden in November 2020 indicates that the virus transmission is far higher than reported (21, 22). Nonetheless, the agreement of at least 74% of the participants on COVID-19 being a public health threat in Yemen, and almost 82% updating themselves on the development of vaccines against COVID-19 indicate their high level of awareness on COVID-19 and the vaccines against it. The challenge now lies in supplying enough doses to fill the gap between supply and demand.

Apart from demographic and other factors (**Table 5**), the strongest determinant of vaccine acceptance in our study was access to vaccines, which is similar to our study on the general population in Yemen (10). Even though access to COVID-19 vaccines was slightly higher among HCWs than the general population (39.9%), only 45.4% of the participants in the current study definitely agreed that they have access to a COVID-19 vaccine, and a mere 10.9% indicated having taken the COVID-19 vaccine (10). This is in sharp contrast to a recent study on vaccine intention among HCWs in neighboring Saudi Arabia, in which all the participants reported having been vaccinated against COVID-19 (23). Fragile nations like Yemen are faced with the double dilemma of vaccine shortage and logistic concerns related to the conflict. For example, in a study in Libya, 71.6% of the participants believed that COVID-19 vaccine distribution would be difficult, given the conflict related challenges there (24). Although access to vaccination facilities can be inconvenient to women and children, especially in low-income and fragile nations, as indicated in our study on the general population in Yemen, this variation may not be apparent among HCWs. With vaccine access rates of 45.7% in males and 45% in females, there was no sex-based differences in access to vaccines among participants in our current study. Unlike the general public, since participants in our study are HCWs who have been prioritized to receive vaccination against COVID-19, this finding is logical.

As of 13 March 2022, just 1.2% of the Yemeni population of more than 30 million have been fully vaccinated against COVID-19, while those in HICs is more than 73%. Moreover, during the same period, while the number of COVID-19 vaccine doses administered per 100 people in HICs is 192.17, that in LICs is a mere 19.52 (7). Although Yemen was promised a supply of 1.9 million vaccine doses throughout 2021, so far it has not received even a third of that number (25). These huge discrepancies and broken promises could lead to further decay of trust in policymakers and the international community. Our results indicate a low level of trust among HCWs in Yemen on NGOs (48.6%) and the international community (48.1%). This should prompt policymakers and stakeholders to take immediate action to gain back the trust, which could indirectly lead to greater vaccine acceptance.

Our results suggest that the immediate and greater threat in Yemen toward achieving population immunity is the lack of access to vaccines, rather than vaccine hesitancy. This is in agreement with a previous similar study on the general population in Yemen, highlighting the importance of provision of access to vaccines in low-income and fragile nations (10). Moreover, apart from vaccine inequity, due to the conflict related

TABLE 5 | Predictors of intention to vaccinate.

	Odds ratio (95% CI)	*p*
Age		
18–29 years	Ref	
30–49 years	1.37 (1.03–1.81)*	0.03
50 years or above	1.02 (0.66–1.56)	0.94
Gender		
Male	Ref	
Female	0.99 (0.79–1.25)	0.94
Medical condition		
Healthy	Ref	
Has systemic disease/s	1.49 (1.03–2.16)*	0.03
Updating self on the development of vaccines against COVID-19		
No	Ref	
Yes	1.92 (1.43–2.57)*	<0.001
Opinion about the severity of COVID-19		
Mild	Ref	
Moderate	1.61 (1.05–2.48)*	0.03
Severe	1.85 (1.18–2.91)*	0.007
Compliance with COVID-19 preventive guidelines		
Poor	Ref	
Moderate	2.1 (1.29–3.42)*	<0.001
Good	3.36 (2.07–5.43)*	0.003
Anxiety about contracting COVID-19		
Low	Ref	
Moderate	1.4 (1.08–1.8)*	0.01
High	3.31 (2.08–5.25)*	<0.001
Previously infected with COVID-19		
No	Ref	
Yes	0.85 (0.65–1.1)	<0.001
Concerned about the possible side effects of COVID-19 vaccines		
No	Ref	
Yes	0.49 (0.38–0.64)*	<0.001
Access to the COVID-19 vaccine		
No	Ref	
Yes	3.18 (2.5–4.03)*	<0.001

Odds ratio and 95% confidence interval was calculated by a binary logistic model.
**Significant difference at $p < 0.05$.*

conditions, residents of these countries, especially women and children, are faced with the additional challenge of difficulty in accessing vaccination facilities. At a time when HICs are racing to provide booster/third dose of the vaccine, consideration should be given to simultaneously accelerate vaccine supplies in low-income and fragile nations, to achieve the minimum threshold necessary to attain population immunity. In light of the emergence of new variants of the wild-type virus, achieving population immunity in LICs is not only critical to protecting their populations, but it is also in the best interest of attaining global population immunity. The WHO, other NGOs operating in Yemen and other low-income and fragile nations, the COVAX and donor nations should work determinedly and inclusively with all parties and stakeholders to ensure that no one is left behind in the pursuit to achieve optimum vaccine coverage.

Notable strengths of our study include the wide coverage of the respondents spanning over all the provinces of Yemen, representing different demographic characteristics, and the large sample size. Moreover, this is the first study on vaccine acceptance among HCWs in Yemen following vaccine rollout, and the first study to assess any potential correlation between vaccine acceptance and lack of access to vaccines among HCWs. A limitation of our study is the inclusion of only complete questionnaires, which could affect the response rate, and the high number of participants from a particular age group (18–29 years old). Another limitation of our study is the web-based administration of the survey questionnaire. Since participants in our study included only those with access to internet facilities, there is a possibility for bias. Moreover, the web-based administration could be a cause for lower motivation of the participants to complete the questionnaire. However, due to the conflict related conditions in Yemen and the COVID-19 related restrictions, this was the best mode currently available. Since the rate of vaccine acceptance of the population could change over time, especially as more vaccines become available and accessibility increases, further studies will provide added value on the evolving vaccine acceptance trend among the public in Yemen. Similar studies in other low-income and fragile nations will provide a wider and global perspective on the correlation between vaccine acceptance and access to vaccines.

CONCLUSIONS

Our results in Yemen, a low-income conflict country suggests vaccine acceptance comparable to those of neighboring countries. The potential correlation between vaccine acceptance and access to vaccines however indicates that a potential increase in supply will lead to an increase in demand. This should prompt policymakers to regulate vaccine supply to ensure that sufficient vaccines are distributed to low-income countries as well. Our results also send a strong message to policymakers on the importance of provision of access to vaccines to LICs and fragile nations in the event of possible future pandemics as well.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This study was approved by the Research Committee of College of Dentistry, Dar Al Uloom University, Riyadh, Saudi Arabia (COD/IRB/2020/2). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MN and MZN: conceptualization, methodology, and writing—original draft. MN, MZN, MA-A, IA-S, SM, AS, AY, AB, OE, AA, YT, and SR: investigation, data collection, and writing—review for important intellectual content and editing. SR, MN, and MZN: data analysis. All authors approved the final draft of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.914943/full#supplementary-material

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Aida Bianco,
University Magna Graecia of Catanzaro, Italy

REVIEWED BY
Ruby Fried,
University of Alaska Anchorage, United States
Gianfranco Di Gennaro,
University of Calabria, Italy

*CORRESPONDENCE
Endeshaw Chekol Abebe
endeshawchekole@gmail.com

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COVID-19 vaccine uptake and associated factors among pregnant women attending antenatal care in Debre Tabor public health institutions: A cross-sectional study

Endeshaw Chekol Abebe[1]*, Gebrehiwot Ayalew Tiruneh[2], Getachew Asmare Adela[3], Teklie Mengie Ayele[4], Zelalem Tilahun Muche[1], Awgichew Behaile T/Mariam[1], Anemut Tilahun Mulu[1], Edgeit Abebe Zewde[1], Nega Dagnaw Baye[1] and Tadesse Asmamaw Dejenie[5]

[1]Department of Biomedical Sciences, College of Health Sciences, Debre Tabor University, Debre Tabor, Ethiopia, [2]Department of Midwifery, College of Health Sciences, Debre Tabor University, Debre Tabor, Ethiopia, [3]Department of Reproductive Health and Nutrition, School of Public Health, Woliata Sodo University, Woliata Sodo, Ethiopia, [4]Department of Pharmacy, College of Health Sciences, Debre Tabor University, Debre Tabor, Ethiopia, [5]Department of Medical Biochemistry, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia

Background: Vaccination is the best means of reducing the increased risk of severe COVID-19 during pregnancy. Data on COVID-19 vaccine uptake among pregnant women in Ethiopia is scarce. Thus, this study aimed to assess COVID-19 vaccine uptake and associated factors among pregnant women.

Method: An institution-based cross-sectional study was conducted among 634 pregnant women attending antenatal care in Debre Tabor public health institutions from March 14 to 30, 2022. Participants were recruited using a multistage sampling technique and data were collected *via* face-to-face interviews using a pre-tested structured questionnaire. Stata version 16.0 software was used for data analysis. Multiple logistic regression analysis was used to assess factors associated with COVID-19 vaccine uptake, with a p-value< 0.05 considered statistically significant.

Result: Only 14.4% (95% CI: 11.7%-17.3%) of participants had received at least one dose of COVID-19 vaccines. The main reasons for declining vaccination were fear that the COVID-19 vaccine may have harmful side effects on the fetus or the mother. Being 45 or older (AOR: 1.75, 95%CI: 1.01–2.95), being married (AOR: 1.26, 95%CI: 1.12, 2.96), having good knowledge (AOR:3.52, 95%CI:1.83–3.87), and a positive attitude (AOR:4.81, 95% CI: 1.42–7.33) were positive predictors of COVID-19 vaccine uptake. But attaining a college or university education (AOR: 0.43, 95%CI: 0.12–0.69) was found to be a barrier to vaccine uptake by pregnant women.

Conclusion: COVID-19 vaccination among pregnant women was substantially low. Old age, being married, low education, good knowledge, and a positive attitude were significant predictors of COVID-19 vaccine uptake. To enhance the COVID-19 vaccine uptake, the government should improve the knowledge and attitude of pregnant women toward the COVID-19 vaccine.

KEYWORDS

pregnant women, COVID-19 vaccine uptake, associated factors, health institutions, Northwest Ethiopia

Introduction

COVID-19 vaccination is one of the most successful and cost-effective public health intervention strategies to mitigate the spread of SARS-CoV-2 and reduce the emergence of new strains (1–4). Reports have shown that vaccination significantly reduces global morbidity and mortality related to COVID-19 (5, 6). COVID-19 vaccination is currently considered an important public health priority to end the pandemic by developing effective immunity against COVID-19 both at the individual and community levels (7). Community protection by vaccination against COVID-19 spread, known as herd immunity, is achieved when at least 75% of the population gets vaccinated, highlighting the need for vaccination on a large scale (8).

Pregnant women are especially vulnerable during the current COVID-19 pandemic because they are at an increased risk of morbidity and mortality from COVID-19 (9, 10). Pregnant women are generally at a greater risk of severe illness, hospitalization, admission to the intensive care unit (ICU), invasive mechanical ventilation, preeclampsia, and death when compared to non-pregnant women with COVID-19 (1, 11–15). Compared to pregnant women without COVID 19, pregnant women with COVID-19 have also a higher risk of adverse birth outcomes such as preterm birth, stillbirth, cesarean delivery, and neonatal ICU admissions, implying a high likelihood of neonatal morbidity and mortality (11, 13, 14, 16–18). Vertical transmission has also been observed in a few cases in SARS-CoV-2 positive pregnant women, albeit it is extremely rare (19). Hence, vaccination against COVID-19 is found to be the best way to protect pregnant women (and the fetus) from serious illness or consequences (14).

Despite the fact that pregnant women were not involved in the initial clinical trials of the COVID-19 vaccine, current solid evidence on vaccine effectiveness and safety suggests that receiving a COVID-19 vaccine far outweighs any possible risk of vaccination during pregnancy (20). Another large body of data from studies done in countries where large numbers of pregnant women were vaccinated also indicates that COVID-19 vaccination during pregnancy is safe for both the mother and fetus, with very rare side effects and pregnancy-specific safety concerns (21–23). Recent clinical data on the safety of the COVID-19 vaccine during pregnancy also observed no difference in side effects between pregnant and non-pregnant women after vaccination (20, 24, 25).

A growing body of evidence shows that COVID-19 vaccination during pregnancy is found to be highly effective, equivalent to nonpregnant people, in preventing severe illness, hospitalization, and death from COVID-19 (26). The vaccine protects against the risk of developing severe COVID-19 in pregnant women by conferring strong protective immunity (14). Vaccination also builds immunity that offers protection for the fetus or neonate against COVID-19 *via* passive transplacental transfer of antibodies from the immunized mother to the fetus during pregnancy or to the newborn during lactation (15, 27). In light of the beneficial role of the vaccine for the mother, fetus, and baby with few or no adverse effects, major guidelines indicate that pregnant women are eligible for and can get any of the WHO approved COVID-19 vaccines and recommend COVID-19 vaccination during pregnancy (14, 15, 20, 28). Consequently, many countries around the world, including Ethiopia, nowadays strongly advise COVID-19 vaccination for people who are pregnant, trying to get pregnant now, or might become pregnant in the future to protect them from COVID-19 (20, 29–31).

COVID-19 vaccination program in Ethiopia commenced on 13 March 2021 by providing priority to health professionals and the elderly. On 16 November 2021, the Ethiopian Federal Ministry of Health (MoH) started a COVID-19 vaccination campaign aimed at vaccinating all people aged 12 years and above, including pregnant women, to end the pandemic (32). AstraZeneca, Janssen, Pfizer-BioNTech, and Sinopharm are currently available vacci nes in Ethiopia for the campaign.

Despite the recommendations of COVID-19 vaccination, low vaccine acceptance is becoming a growing global challenge, hindering vaccine uptake. Low vaccine acceptance among

Abbreviations: ANC, Antenatal care; AOR, Adjusted Odds Ratio; CI, Confidence Interval; COVID 19, Coronavirus Disease 19; DTCSH, Debre Tabor Comprehensive Specialized Hospital; ICU, intensive care unit; MCH, Maternal and Child Health; SARS-CoV-2; Severe Acute Respiratory Syndrome Coronavirus-2; SD, Standard Deviation; WHO, World Health Organization.

pregnant women is evident from studies in different countries, such as Saudi Arabia (50%) (33), Jordan (37%) (34), the US (41%) (35), Turkey (37%) (36), and other large-scale studies involving 16 countries (52.0%) (37). This is due to a global rise in COVID-19 vaccine hesitancy that lowers COVID-19 vaccine acceptance and uptake, especially during pregnancy. In practice, the COVID-19 vaccination rate among pregnant women was found to be low in different countries, such as Saudi Arabia (57.1%) (10), Scotland (32.3%) (31), the US (40%) (29), and England (53.7%) (38). Similarly, a prior study done in Ethiopia conducted among pregnant women to assess their willingness to receive COVID-19 vaccine (if the vaccines were available) indicated that a significant proportion of pregnant women were not willing to receive the vaccine for various reasons if the vaccination started (5). However, data on the actual practice of pregnant women in receiving the COVID-19 vaccine in Ethiopia is not available. Hence, this study aimed to assess COVID-19 vaccine uptake and associated factors among pregnant women. The findings from this study could help women, clinicians, and policymakers to make decisions and increase COVID-19 vaccine uptake during pregnancy.

Methods and materials

Study design, period, and setting

An institution-based cross-sectional study was conducted from March 14 to 30, 2022 at Debre Tabor public health institutions in Debre Tabor, Northwest Ethiopia. Debre Tabor is the administrative town of the South Gondar Zone, which is located 103 km away from Bahir Dar and 667 km Northwest of Addis Ababa. The town has one hospital, known as Debre Tabor Comprehensive Specialized Hospital (DTCSH), and three health centers, namely Debre Tabor Health Center, Leul Alemayehu Health Center, and Atse Seife Areid Health Center, and four health posts. These public health institutions are currently providing various health services, including antenatal care (ANC) services, for the residents of Debre Tabor and the people around the town.

Population

All pregnant women who had attended the MCH clinic of Debre Tabor public health institutions for ANC service were considered as source population. All pregnant women who came for ANC visits in the selected health institutions during the study period were taken as the study population.

Eligibility criteria

All volunteer pregnant women (aged 18 years or above) who came for ANC visits in Debre Tabor public health institutions during the data collection period were eligible to participate in the study. However, pregnant women who had serious medical illnesses (severe hypertension, diabetes mellitus, cardiac illness, kidney diseases, and or liver diseases), severe pregnancy-related conditions (antepartum hemorrhage, pre-eclampsia, hyperemesis gravidarum, premature rupture of membrane), and/or serious psychiatric illnesses (psychotic disorder, major depressive disorder, or anxiety disorder) were excluded from the study. Besides, pregnant women aged <18 years were excluded from the study since their educational level is lower and their knowledge, attitude, and decision-making ability about COVID-19 vaccination are most likely different from that of older women.

Study variables

While COVID-19 vaccine uptake was taken as dependent variables, socio-demographic factors (age, marital status, religion, ethnicity, education, occupation, and residence), obstetric and medical-related variables (gravidity, parity, number of ANC visits, chronic illness, history of contact with COVID-19 cases, history of COVID-19, family history of COVID-19, testing for COVID-19), COVID-19 vaccine knowledge and attitude were considered as independent variables.

Sample size determination and sampling procedures

The sample size was calculated using the formula shown below by considering $Z_{\alpha/2}$ at a 95% confidence level = 1.96 and margin of error (d)=0.05, with the assumption of 50% COVID-19 vaccine uptake (P) due to lack of prior related study done in Ethiopia.

$$n = \frac{(Z_{1-\alpha/2})^2 P(1-P)}{d^2} * Deff$$

Design effect (Deff) was calculated using a formula; Deff =1+(m−1) ICC; where m is the average cluster size and ICC is the intra-cluster correlation coefficient. While m was calculated to be 18, ICC was determined to be 0.03 through a pilot study [ICC= the ratio of the variability between cluster (S^2b) to the sum of variability between cluster (S^2b) and variability within-cluster (S^2w)], making Deff=1.5. Therefore, after multiplying with Deff of 1.5 and adding a 10% non-response rate, the final sample size (n) became 634. A multistage sampling technique was employed to select study participants. Out of all public health institutions in Debre Tabor Town, DTCSH, Debre Tabor Health Center, Leul Alemayehu Health Center, and Atse Seife Areid Health Center were selected using a lottery method. Then the total sample size was proportionally allocated for each health institution. Accordingly, 381, 96, 82,

and 75 participants were taken from DTCSH, Debre Tabor Health Center, Leul Alemayehu Health Center, and Atse Seife Areid Health Center, respectively. Then consecutive sampling technique was employed to select the study participants from each health institution during the data collection period.

Data collection instruments and procedures

Data were collected using a structured questionnaire prepared by adopting different related literature (5, 39). The questionnaire had five parts: Part I: socio-demographic characteristics, Part II: Obstetric and medical-related characteristics; Part III: Knowledge about COVID-19 vaccine; Part IV: attitude toward COVID-19 vaccine, and Part V: COVID-19 vaccination history. Data collection was done (under the supervision of two supervisors) by four BSc nurses who were assigned to their routine work at the MCH clinic of each health institution during the study period.

Operational definition

COVID-19 vaccine uptake

In this study, vaccine uptake was defined as the number of participants who had taken at least one dose of a COVID-19 vaccine at the time of the data collection period. It was measured by the closed-ended question as "Have you ever been vaccinated with any of COVID-19 vaccines at least once recently?" and the response was "Yes" or "No". Those study participants who have taken the vaccine at least once (receipts of ≥1 COVID-19 vaccine dose) responded as "Yes" and the vaccination status was categorized as 'vaccinated', whereas, those who were not vaccinated replied as "No" to the question and their vaccination status was labeled as 'unvaccinated' (40).

Knowledge about the COVID-19 vaccine

An eight-point questions survey module was employed to assess the knowledge of respondents regarding the COVID-19 vaccine. Respondents who answered "yes" for knowledge assessing questions were given a score of 1, while those who responded "no or uncertain" for these questions were given 0. The overall knowledge score was categorized into good knowledge; if participants score the median value or above of the knowledge assessing items, and labeled as having poor knowledge; if participants scored below the midpoint of the scale (5).

Attitude toward COVID-19 vaccine

A total of ten questions were used to assess the attitude of participants toward COVID-19 vaccines. Respondents who answered "agree" for attitude assessing questions were scored 1 and respondents who answered "disagree or neutral" for attitude assessing questions were given a score of 0. Based on the median score of their responses, participants were labeled as having a positive attitude and a negative attitude. Respondents who had scored equal to the median score or above on the attitude assessment questions of the COVID-19 vaccine were considered as having a positive attitude, whereas those who scored less than the median value were classified as having a negative attitude (5).

Data processing and analysis

Data were collected first and then checked for completeness and internal consistency. Then data entry was done using Epi Info (version 7.2.4.0) and all statistical analysis was done using Stata version 16.0 software. Clopper-Pearson's exact method was used to calculate the 95% binomial confidence interval (CI) of the overall proportion of vaccinated pregnant women. Simple and multiple logistic regression models were used to examine the factors associated with COVID-19 vaccine uptake. Predictor variables with $p \leq 0.25$ in simple logistic regression were considered to be candidates in the multiple regression models. Hosmer-Lemeshow test was used to determine the goodness of fit of the logistic regression model. Multiple logistic regression was used to analyze the association between the outcome variable and predictor variables. In multiple logistic regression, the backward variable selection method was used in the analysis. A two-sided $p < 0.05$ and Adjusted Odds Ratio (AOR) at 95% CI were used to consider statistically significant predictors of the outcome variable.

Data quality assurance

The questionnaire was prepared in English and translated to the local Amharic, and then retranslated back to the English version to ensure consistency. Questionnaires were reviewed by a panel of experts for construct and content validity. Then appropriate modifications, such as correction of wording, logical sequence, inconsistencies, and errors in the skip pattern before the commencement of the actual data collection were made. In addition, to ascertain the understanding, validity, and reliability of the questionnaire and to examine practical issues in selecting participants, a pilot study was conducted before the actual data collection period among 25 pregnant women attending Woreta Health Center. The internal consistency of questionnaires in our study setting was assessed using Cronbach's α. The Cronbach's α for COVID-19 vaccine knowledge, attitude, and uptake questions were 0.81, 0.79, and 0.83 respectively, indicating that the questionnaires have scientifically acceptable internal consistency to measure the knowledge, attitude, and uptake of COVID-19 vaccines among study participants. Moreover,

extensive training that lasted for 1 day was given to the data collectors and supervisors on the objectives of the study, the content of the measuring tool, confidentiality, and informed consent. Besides, the data was collected under supervision to ensure the quality of data. The questionnaires were reviewed and checked daily for the completeness of the collected data.

Results

Socio-demographic characteristics

A total of 634 eligible participants were included in this study, making the response rate 100%. The mean (±SD) age of participants was 32.3 ± 4.14 years and ranged between 18 and 50 years. The majority of respondents were Orthodox in religion, 613 (96.7%), married, 618(97.5%), and Amhara in ethnicity, 625(98.6%). About 251(39.6%) of respondents had attained primary education and a sizable portion of them were housewives, 281(44.3%), and urban dwellers, 510 (80.4%) (Table 1).

TABLE 1 Socio-demographic characteristics of pregnant women attending antenatal care in Debre Tabor public health institutions, Northwest Ethiopia, 2022.

Variable	Category	Frequency ($n = 634$)	Percent (%)
Age (years)	<25	70	11.0
	25–34	236	37.2
	35–44	271	42.7
	≥45	58	9.1
Religion	Orthodox	613	96.7
	Muslim	12	1.9
	Protestant	9	1.4
Marital status	Married	618	97.5
	Single	6	0.9
	Divorced	9	1.4
	Widowed	1	0.2
Educational status	No formal education	147	23.2
	Primary education	251	39.6
	Secondary education	203	32.0
	College/University	33	5.2
Occupation	Housewife	281	44.3
	Merchant	222	35.0
	Government employee	104	16.4
	Private employee	18	2.8
	Student	6	1.0
	Daily laborer	3	0.5
Ethnicity	Amhara	625	98.6
	Tigray	4	0.6
	Oromo	3	0.5
	Other	2	0.3
Residence	Urban	510	80.4
	Rural	124	19.6

Obstetric and medical-related characteristics

The majority 557(87.9%) of women were multigravida having two or more pregnancy history including the current one. Only 79(12.4%) of participants never had a live birth (nulliparous), but the rest majority 555(87.6%) had a prior history of at least one live birth (primiparous or multiparous). The current pregnancy of nearly 623 (98.3%) study participants was planned. Almost half 313(49.4%) of them were in the third trimester of the current pregnancy. The greatest proportion

TABLE 2 Obstetric and medical related characteristics of pregnant women attending antenatal care in Debre Tabor public health institutions, Northwest Ethiopia, 2022.

Variables	Category	Frequency ($n = 634$)	Percent (%)
Gravidity	Primigravida	77	12.1
	Multigravida	557	87.9
Parity	Nulliparous	79	12.4
	Primiparous	119	18.8
	Multiparous	436	68.8
Planned (current) pregnancy	Yes	623	98.3
	No	11	1.7
Trimester of the current pregnancy	First trimester	75	11.8
	Second trimester	246	38.8
	Third trimester	313	49.4
Number of ANC visits	<4	368	58.1
	≥4	266	41.9
History of contact with confirmed COVID-19 cases	Yes	49	7.7
	No	585	92.3
Prior history of COVID-19 infection	Yes	42	6.6
	No	592	90.4
Family history of COVID-19 infection	Yes	47	7.4
	No	587	92.6
Tested for COVID-19 infection	Yes	41	6.5
	No	593	93.5
COVID-19 test result ($n = 41$)	Positive	28	68.3
	Negative	13	31.7
Chronic medical illness	Yes	12	1.9
	No	622	98.1
Types of chronic illness ($n = 12$)	Hypertension	5	41.7
	Diabetes mellitus	4	33.3
	Heart disease	2	16.7
	Kidney disease	1	8.3

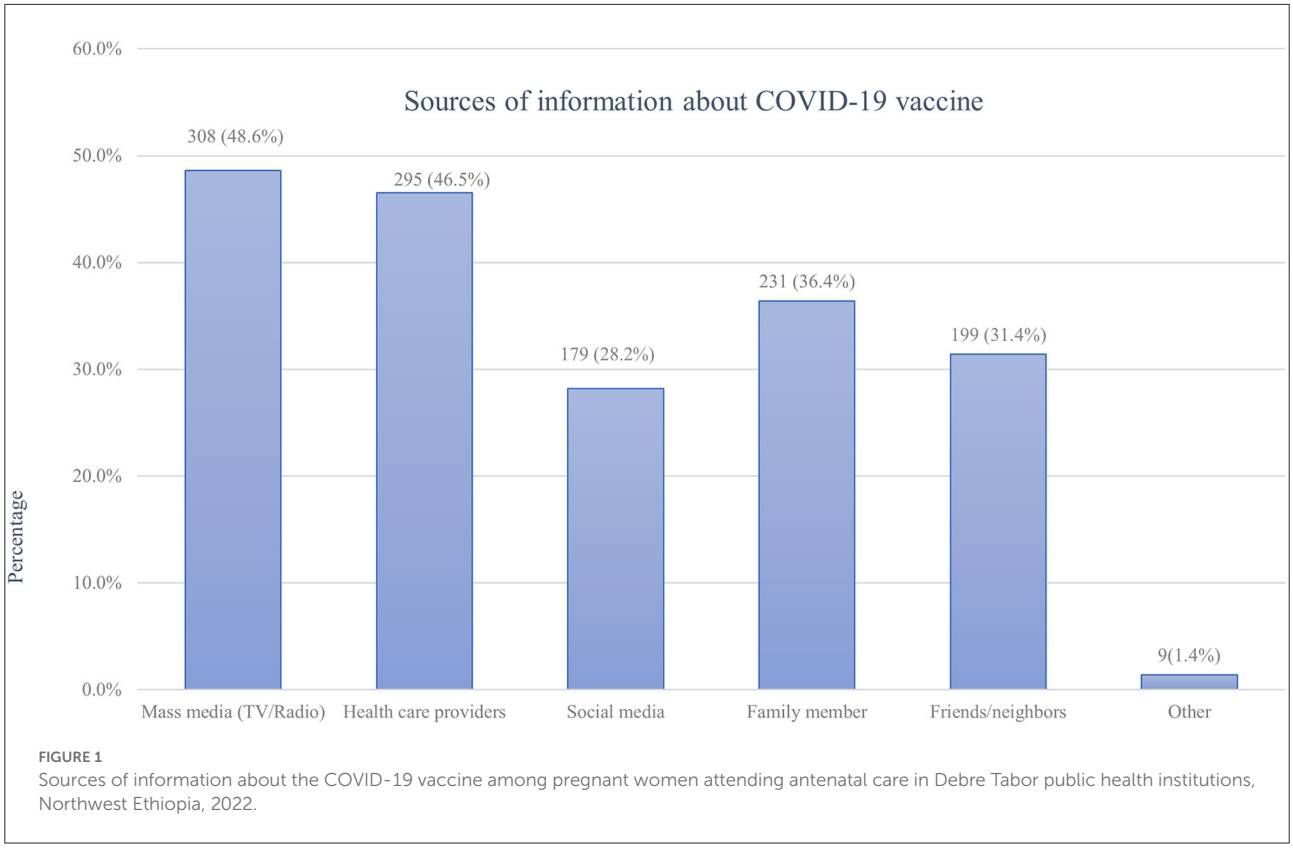

FIGURE 1
Sources of information about the COVID-19 vaccine among pregnant women attending antenatal care in Debre Tabor public health institutions, Northwest Ethiopia, 2022.

24(58.1%) of pregnant women had fewer than four ANC visits at the time of the interview.

A considerable proportion 585 (92.3%) of participants had no known history of contact with confirmed COVID-19 cases. Around 42 (6.6%) respondents had a prior history of COVID-19 infection, while 47 (7.4%) of them had a family history of COVID-19 infection. About 41 (6.5%) of all participants were tested for COVID-19, and 68.3% of those tested were confirmed positive. About 12(1.9%) of participants had a history of chronic medical illness, with hypertension (41.7%) followed by diabetes mellitus (33.3%) reported to be the most prevalent chronic diseases (Table 2).

Knowledge of respondents about COVID-19 vaccine

All study participants (100%) claimed that they heard about COVD 19 vaccine from different information sources. Their main source of information regarding COVID-19 vaccines was mass media such as TV and radio followed by health care providers and family members, accounting for 308(48.6%), 295 (46.5%), and 231 (36.4%) respectively (Figure 1).

The overall knowledge of the respondents about the COVID-19 vaccine was assessed using an eight knowledge assessing questions. Accordingly, more than half 356(56.2%) of respondents were evaluated to score the median value or above and were labeled as having good knowledge. But the remaining 278(43.8%) were below the median score and considered to have poor COVID-19 vaccine knowledge. About 47.6% of respondents replied that pregnant women need to get the COVID-19 vaccination. Besides, more than two-thirds (68.1%) of them correctly responded as a vaccine could protect against COVID 19. Participants also answered that COVID-19 vaccines produce long-term immunity (58.4%), reduce disease severity (51.3%), have no health-related risk (49.0%), and carry no risk of harm to the baby (39.4%) (Supplementary Table 1).

The attitude of respondents toward COVID-19 vaccine

A total of ten questions were used to evaluate the overall attitude of participants toward COVID-19 vaccines. Thus, 264(41.6%) of pregnant women were scored equal to the median or above and categorized as having a positive attitude toward the COVID-19 vaccine, whereas more than half 370(58.4%) of them scored below the median and classified as having a negative attitude. Specifically, the belief of participants COVID-19 vaccine is essential (73.8%) and currently accessible

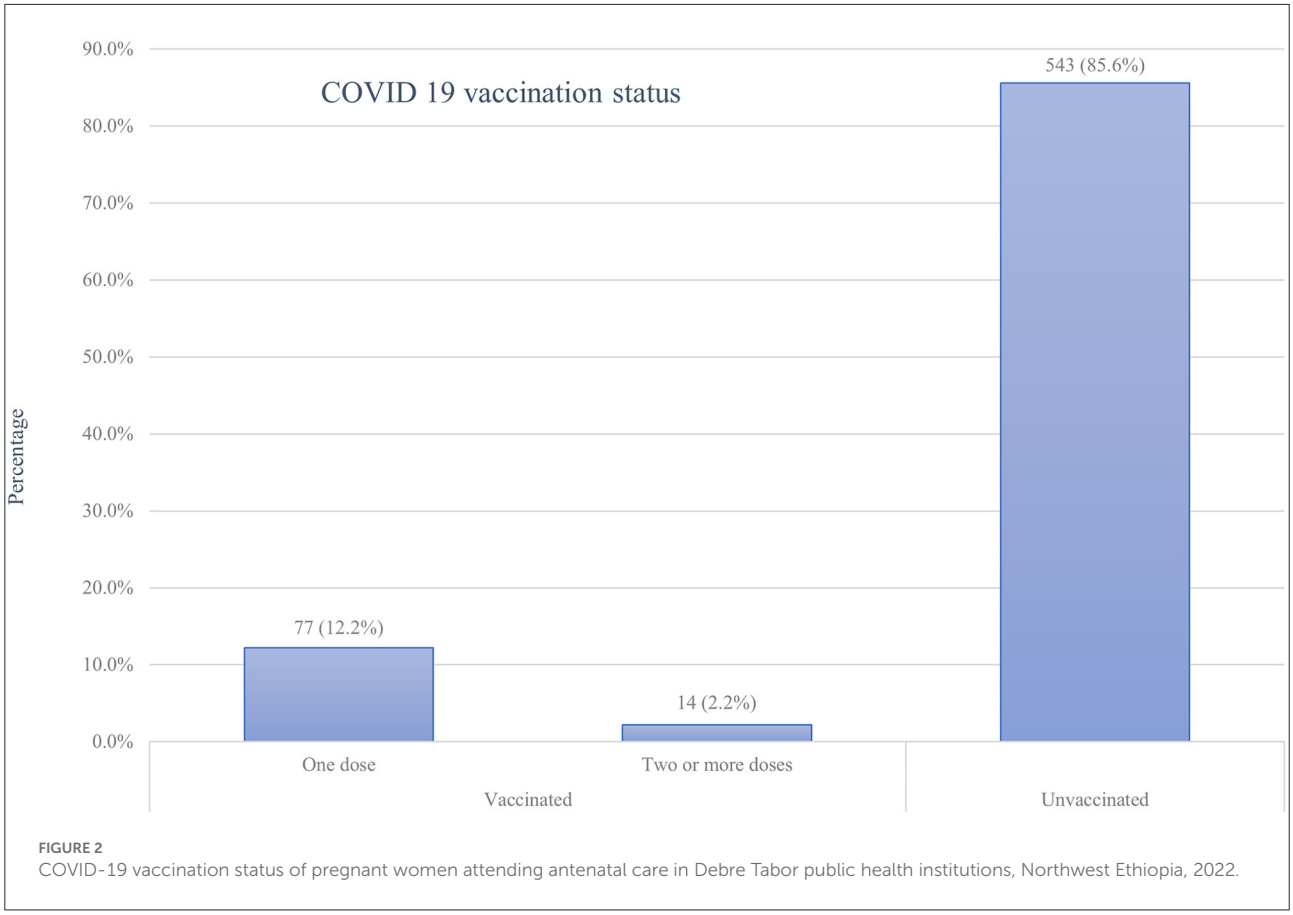

FIGURE 2
COVID-19 vaccination status of pregnant women attending antenatal care in Debre Tabor public health institutions, Northwest Ethiopia, 2022.

for all population (75.4%) were the highest scoring item. Whereas, vaccination reduces the risk of getting COVID-19 (48.6%), reduces the incidence of COVID-19 (42.8%), protects against COVID-19 complications during pregnancy (41.8%), is safe 234(36.9%), and is effective (43.4%) were the lowest scoring items of the attitude assessing questions (Supplementary Table 2).

COVID-19 vaccination history

Of all the respondents, about 91 (14.4%; 95%CI: 11.7%-17.3%) of them had taken at least one dose of the COVID-19 vaccine, with only a minority (2.2%) of all samples being fully vaccinated (Figure 2). Of those vaccinated, the majority 59 (64.8%) did not experience any post-vaccination symptoms, while a few 32(35.2%) faced minor side effects. Fever 13(40.6%), fatigue 12(37.5%), and headache 9 (28.1%) were the main symptoms reported by the participants. Symptoms such as joint pain 6 (18.8%), myalgia 6 (18.8%), chills 5 (15.6%), and others 2 (6.3%) were the rare side effects among the respondents. However, the vast majority of participants, 543 (85.6%), were not vaccinated with any of the COVID-19 vaccines for various reasons. Fear of side effects due to the perception that vaccines may harm their baby (61.3%) or themselves (59.1%) and doubts about vaccine efficacy (58.0%) were the most frequent reasons for denying COVID-19 vaccination (Figure 3).

Factors associated with COVID-19 vaccine uptake

The association between independent variables and COVID-19 vaccine uptake was analyzed using binary logistic regression. A simple logistic regression model was first used and variables with $p \leq 0.25$ were proceeded into multiple logistic regression models to adjust covariates. Based on adjusted logistic regression analysis, age, marital status, educational status, vaccine knowledge, and attitude were significantly associated with COVID-19 vaccine uptake (Table 3). The odds of COVID-19 vaccine uptake in pregnant women aged 45 years or above was 1.75 times (AOR: 1.75, 95%CI: 1.01, 2.95) higher than in those who were under 25 years. Compared to unmarried women, married pregnant women had 1.26-fold (AOR: 1.26, 95%CI: 1.12, 2.96) higher odds of being vaccinated. Pregnant women who had completed college or university education were a 57% (AOR: 0.43, 95%CI: 0.12–0.69) lower likelihood of COVID-19 vaccine uptake than those with no formal education. COVID-19

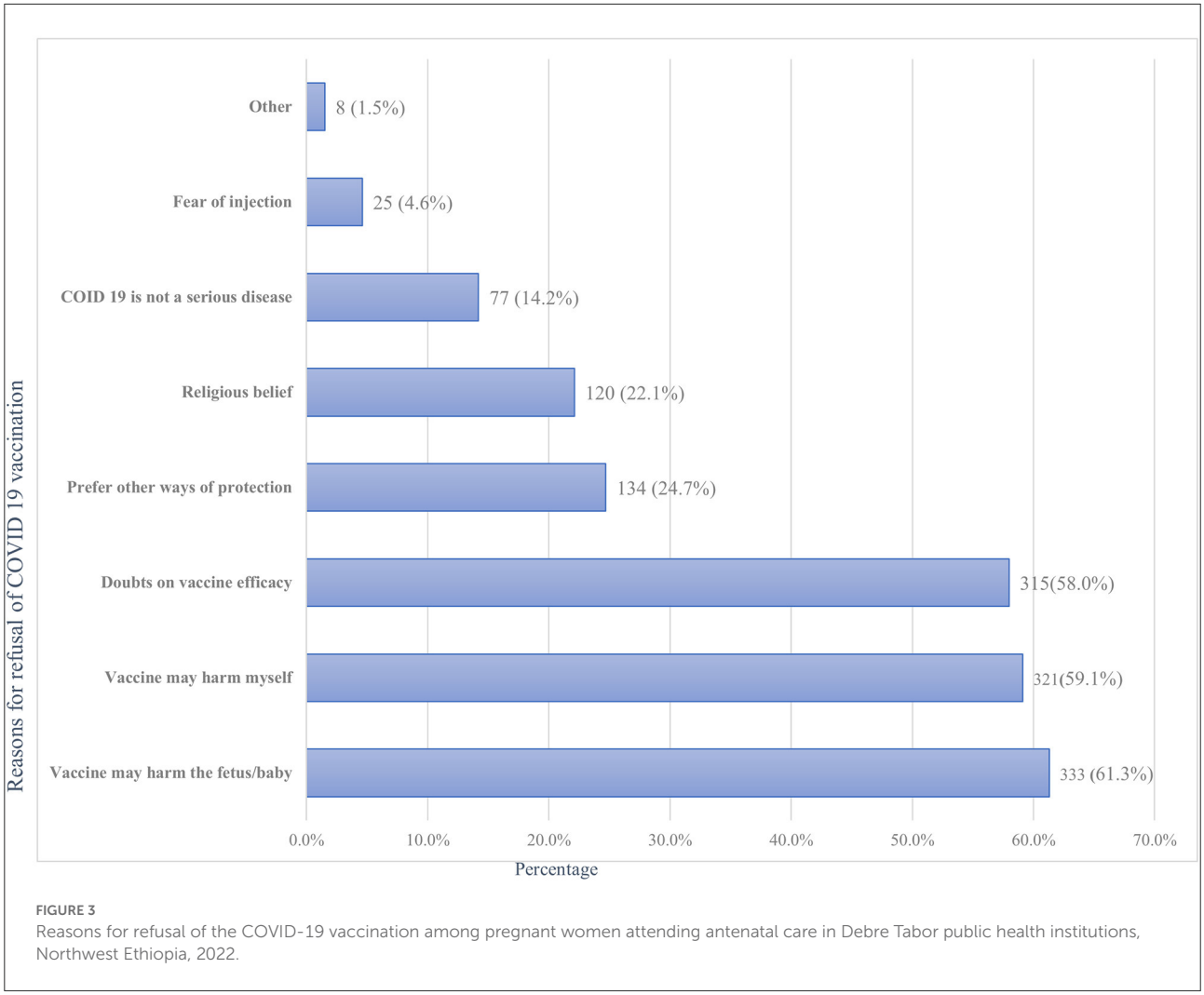

FIGURE 3
Reasons for refusal of the COVID-19 vaccination among pregnant women attending antenatal care in Debre Tabor public health institutions, Northwest Ethiopia, 2022.

vaccination was 3.52 times (AOR:3.52, 95%CI:1.83–3.87) higher likelihood in participants with good knowledge than those with poor knowledge. Whereas, respondents with a positive attitude toward the COVID-19 vaccine had 4.81-fold (AOR:4.81, 95% CI:1.42–7.33) more likely to receive the COVID-19 vaccine than their counterparts.

Discussion

According to the current study, only 14.4% of pregnant women were vaccinated for COVID-19 at least once. This figure is significantly lower than the findings from similar studies conducted in other countries, such as Saudi Arabia (57.1%) (10), Scotland (32.3%) (31), the US (40%) (29), and England (53.7%) (38). This disparity could be attributable to the increased COVID-19 morbidity and mortality rates, as well as improved socioeconomic status, which could promote vaccine uptake among pregnant women in these countries. The late delivery of the vaccine in Ethiopia, as well as a considerably low level of knowledge and attitude toward the COVID-19 vaccination in our study setting, could also be the contributing factors to lowered vaccine uptake.

The vaccine uptake among pregnant women in this study was also lower than other parts of the population in Ethiopia (40, 41). According to a web-based study done among Ethiopian health professionals, 62.1% of them had received the COVID-19 vaccine (40). A previous cross-sectional study was done in Eastern Ethiopia among people aged 50 and above indicates that 39.4% of the participants had taken the vaccine at least once (41). In this context, the lower rate of vaccination among pregnant women than in these population groups could be explained by the late commencement of COVID-19 vaccination in the general population. COVID-19 vaccination for health professionals and the elderly (≥50 years) began on 13 March 2021, which was earlier than the general public (including expecting mothers) launched on 16 November 2021. This was due to the government's prioritization to vaccinate high-risk groups over others as a result of the vaccine shortage. COVID-19 vaccine uptake among pregnant women in this study was

TABLE 3 Factors associated with COVID-19 vaccine uptake among pregnant women attending antenatal care in Debre Tabor public health institutions, Northwest Ethiopia, 2022.

Variable		Vaccine uptake, n(%)		COR (95%CI)	AOR (95%CI)
		Yes (91)	No (543)		
Age (in years)	<25	8 (8.8%)	62 (11.4%)	1	1
	25–34	30 (32.9%)	206 (37.9%)	0.89 (0.73–1.79)	0.75 (0.69–2.67)
	35–44	35(38.5%)	236(43.5%)	1.44 (1.06–3.21)	1.12 (0.94–4.21)
	≥45	18(19.8%)	40 (7.4%)	2.34 (1.21–4.58)*	1.75 (1.01–2.95)*
Marital status	Married	89(97.8%)	529(97.4%)	1.27 (0.89–1.89)	1.26 (1.12–2.96)*
	Unmarried[a]	2 (2.2%)	14 (2.6%)	1	1
Educational status	No formal education	29 (31.8%)	118 (21.7%)	1	1
	Primary education	39 (42.9%)	212(39.0%)	0.92 (0.42–1.97)	0.98 (0.59–2.33)
	Secondary education	20 (22.0%)	183 (33.7%)	0.83 (0.49–0.99)*	0.77 (0.54–1.78)
	College/University	3(3.3%)	30 (5.5%)	0.32 (0.23–0.85)*	0.43 (0.12–0.69)*
Occupation	Housewife	38 (41.8%)	243(44.8%)	1	1
	Other[b]	53 (58.2)	300 (55.2%)	1.44 (0.86–2.13)	1.82 (0.97–2.39)
Residence	Urban	66 (72.5%)	444 (81.8%)	0.93 (0.32–1.26)	0.82 (0.29–1.98)
	Rural	25 (27.5%)	99 (18.2%)	1	1
Gravidity	Primigravida	5(5.5%)	72 (13.3%)	1	1
	Multigravida	86(94.5%)	471(86.7%)	1.54 (0.35–4.32)	0.57 (0.45–2.37)
Parity	Null parous	4(4.4%)	75(13.8%)	1	1
	Primiparous	18(19.8%)	101(18.6%)	0.88 (0.75–2.58)	0.56 (0.26–2.18)
	Multiparous	69 (75.8%)	367(67.6%)	1.33 (0.67–2.71)	1.55 (0.89–2.87)
Number of ANC visit	<4	50 (54.9%)	318(58.6%)	1	1
	≥ 4	41 (45.1%)	225(41.4%)	0.66 (0.54–3.17)	0.85 (0.77–1.73)
Current pregnancy	Planned	88(96.7%)	535(98.5%)	1.44 (0.89–2.38)	1.35 (0.22–2.43)
	Unplanned	3 (3.3%)	8(1.5%)	1	1
History of contact with COVID-19 cases	Yes	8(8.8%)	41 (7.6%)	1.16 (1.00–1.35)	1.2 (0.11–2.15)
	No	83(15.3%)	502(92.4%)	1	1
History of COVID-19	Yes	7(7.7%)	35(6.4%)	1.25 (0.92–2.74)	1.6 (0.71–2.48)
	No	84 (92.3%)	508(93.6%)	1	1
Family history of COVID-19 infection	Yes	5(5.5%)	42 (7.7%)	0.91 (0.67–1.46)	1.44 (0.98–3.21)
	No	86(94.5%)	501 (92.3%)	1	1
Tested for COVID-19	Yes	5(5.5%)	36 (6.6%)	0.71 (0.63–4.84)	0.33 (0.21–1.39
	No	86(94.5%)	507 (93.4%)	1	1
Chronic diseases	Yes	2(2.2%)	10(1.8%)	0.95 (0.89–2.91)	1.03 (0.64–3.91)
	No	89(97.8%)	533(98.2%)	1	1
Knowledge	Good knowledge	62(68.1%)	294(54.1%)	1.57 (1.18–2.91)*	3.52 (1.83–3.87)**
	Poor knowledge	29(31.9%)	249(45.9%)	1	1
Attitude	Positive attitude	57 (62.6%)	207(38.1%)	3.76 (1.51–3.99)**	4.81 (1.42–7.33)**
	Negative attitude	34 (37.4%)	336(62.9%)	1	1

Significant at *$p < 0.05$, **$p < 0.001$; 1 = reference category.
[a]single, divorced, and widowed; [b]government employee, private employee, merchant, daily laborer & student.
COR, Crude odds ratio; AOR, Adjusted odds ratio; CI, Confidence interval.

also significantly lower than receipts of the vaccine among Ethiopia's general population. Preliminary national data from Ethiopia showed that approximately 25.1% of the population has received at least one dose of the COVID-19 vaccine (42). This reveals that pregnant women are more vaccine-resistant than other parts of the population. This is supported by a study done in the UK, showing that pregnant women were more likely to be vaccine-resistant than non-pregnant individuals (43). Consistently, other reports documented that pregnant women were less likely to complete the COVID-19 vaccine series than non-pregnant women, and their vaccination rates remained low (20, 29). This might be due to higher vaccine hesitancy among

pregnant women compared to other parts of the population due to vaccine safety concerns, misconceptions, and fear of harm to the fetus (5, 10).

In the current study, the most common reasons for refusing COVID-19 vaccination were vaccine safety concerns due to the fear of harmful side effects for the fetus or the mother themselves, which is supported by many other studies (37, 44–46). Our study reported that a considerable proportion of respondents were highly concerned about vaccine safety and hence declined COVID vaccination. Similarly, several previous studies have found that a sizable proportion of participants were concerned about the safety of vaccines during pregnancy (36, 37, 47). Taken together, pregnant women are still highly concerned about vaccine safety and refuse to take the vaccine despite the fact that major guidelines reported the seriousness of COVID-19 and the safety of the COVID vaccine during pregnancy (14, 15, 20). Prior studies indicated that the majority of COVID-19 vaccinated pregnant people had no serious post-vaccination symptoms but mild to moderate side effects may sometimes occur in pregnant women similar to nonpregnant women (20, 22). In agreement, our study results demonstrated that the majority of participants did not experience any post-vaccination symptoms. However, a few most commonly reported minor symptoms were fever, headache, fatigue, joint pain, myalgia, and chills, with no serious post-vaccination pregnancy-related adverse effects. This is in line with Kadali et al., which reported that sore arm, fatigue, headache, chills, myalgia, nausea, fever, and sweating are the most frequent side effects reported by both pregnant and non-pregnant women at the same rates (48).

We have also found that age, marital status, educational status, knowledge, and attitude were significantly associated with COVID-19 vaccine uptake. It was shown that COVID-19 vaccine uptake was significantly increased in older pregnant women than in younger women. This agrees with prior studies in the UK (49), Scotland (31), Ethiopia (39, 40), Saudi Arabia (10), Jordan (34), the US (50), and Bangladesh (51). This is possibly due to the fact that there is an increment in the understanding of COVID-19 risk among the elderly. But the contradicting result was reported from another study done in Bangladesh, where young people took the vaccine more than old people (52). More interestingly, married pregnant women were found to have higher odds of being vaccinated than unmarried ones. This is potentially due to marriage may increase women's empowerment and decision-making ability to receive the vaccine. Married women might be more financially stable and are more likely to get vaccinated than unmarried women. Compared to unmarried women, this subset of the population may have a greater level of husbands' support, which increases the likelihood of receiving vaccination. This result, however, disagrees with other studies done in Ethiopia (39, 41).

Furthermore, our study showed that COVID-19 vaccine uptake was lower among participants who had attained college or university education than those with no formal education. This is supported by prior studies, revealing that people who had no education were more likely to be vaccinated than people who had attended above secondary school (41, 53). This might be due to uneducated people being more likely to receive the vaccine without considering the possible adverse effects of the vaccine, while the educated people could have more awareness about the vaccine preparation time, safety, and side effects and may hesitate to take the vaccine. But our finding contradicts other studies that show educated people are more likely to get vaccinated than uneducated people (54–56). But some other studies did not observe any significant association between educational status and COVID-19 vaccination (5, 40).

In addition, this study showed that good knowledge of the COVID-19 vaccine was a significant predictor of the COVID-19 vaccination. This is congruent with several prior studies, which indicate a significant association between vaccine knowledge, intention, and uptake (37, 57–60). This could be explained by the theory of the knowledge-attitude-behavior paradigm, which assumes that knowledge of individuals' health is a key factor to engage in a particular health-related behavior (61). Pregnant women with good COVID-19 vaccine knowledge, in particular, can better understand its potential benefits, resulting in favorable vaccine beliefs and increased vaccine trust and uptake (62, 63). But those with poor knowledge are more likely to associate the vaccines with side effects and believe in misinformation about vaccine safety, potentially increasing the perceived risk of vaccine side effects and refusing of COVID-19 vaccination (64–66). This implies that imparting relevant knowledge about the COVID-19 vaccine matters for vaccination (67). We also found that participants with a positive attitude toward the COVID-19 vaccine had a higher likelihood of taking the COVID-19 vaccine than those with a negative attitude, which is supported by other prior studies (5, 37, 60). This could be explained by the existing theory that individuals' attitude influences their health behavior (61, 68, 69). Thus, attitudes on vaccine adverse effects, safety, and efficacy might influence the willingness and practice of vaccination during pregnancy (5, 70, 71). Expectant women with a positive attitude may trust the vaccines and follow the instructions provided by various guidelines, making them more likely to receive the vaccine.

Despite our best efforts, there are some limitations to our study. Since the study employed a cross-sectional study design, it might not show the temporal relationship between cause and effect. The study may have limited representativeness as it was conducted in institutions.

Conclusion

The COVID-19 vaccine uptake among pregnant women in this study was very low. The main reasons for low COVID-19 vaccination rates were safety concerns due to the fear that the COVID-19 vaccine may have harmful side

effects to the fetus or the mothers themselves. Older age, no formal education, good knowledge, and positive attitude of pregnant women were independent predictors of COVID-19 vaccine uptake. Thus, extensive awareness creation campaigns should be undertaken using different media of communication by providing special consideration for pregnant women to address misunderstandings on adverse effects, vaccine safety, and hesitancy. Besides, health care providers must take the opportunity to routinely assess pregnant women's immunization status and to have a discussion about the benefits of COVID-19 vaccines during each ANC visit. This will enhance the knowledge about and the attitude toward COVID-19 vaccine and draw more attention to promote public trust in the COVID-19 vaccine, thereby increasing the willingness to accept vaccination. In addition, further large-scale clinical studies need to be conducted on the safety and potential side effects associated with vaccination during pregnancy.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Review Committee of Debre Tabor University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas, took part in drafting, revising, or critically reviewing the article, gave final approval of the version to be published, have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.919494/full#supplementary-material

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EDITED BY
Alessandra Casuccio,
University of Palermo, Italy

REVIEWED BY
Yuan Cao,
Hong Kong Polytechnic University,
Hong Kong SAR, China
Qingrui Huang,
Chinese Academy of Sciences
(CAS), China

*CORRESPONDENCE
Maher A. Sughayer
msughayer@khcc.jo
Lina Souan
lsouan@khcc.jo

†These authors have contributed equally to this work

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An update on the impact of SARS-CoV-2 pandemic public awareness on cancer patients' COVID-19 vaccine compliance: Outcomes and recommendations

Lina Souan*†, Maher A. Sughayer*†, Maha Abu Alhowr, Khawlah Ammar and Sara Al Bader

Department of Pathology and Laboratory Medicine, King Hussein Cancer Center, Amman, Jordan

Background: Aside from the pandemic's negative health effects, the world was confronted with public confusion since proper communication and favorable decisions became an ongoing challenge. As a result, the public's perceptions were influenced by what they knew, the many sources of COVID-19 information, and how they interpreted it. With cancer patients continuing to oppose COVID-19 vaccines, we sought to investigate the COVID-19 pandemic and vaccine sources of this information in adult cancer patients, which either helped or prevented them from taking the vaccine. We also assessed the relevance and impact of their oncologists' recommendations in encouraging them to take the vaccine.

Methods: From June to October 2021, an online survey was conducted at King Hussein Cancer Center. A total of 441 adult cancer patients took part in the study. Patients who had granted their consent were requested to complete an online questionnaire, which was collected using the SurveyMonkey questionnaire online platform. Descriptive analysis was done for all variables. The association between categorical and continuous variables was assessed using the Pearson Chi-square and Fisher Exact.

Results: Our results showed that 75% of the patients registered for the COVID-19 vaccine, while 12% refused vaccination. The majority of participants acquired their information from news and television shows, whereas (138/441) got their information through World Health Organization websites. Because the SARS-CoV-2 vaccines were made in such a short period, 54.7 % assumed the vaccines were unsafe. Only 49% of the patients said their oncologists had informed them about the benefits of SARS-CoV-2 vaccines.

Conclusions: We found that SARS-CoV-2 vaccine hesitancy in cancer patients might be related to misinformation obtained from social media despite the availability of supportive scientific information on the vaccine's benefits from the physicians. To combat misleading and unreliable social media news, we recommend that physicians use telehealth technology to reach out to their patients in addition to their face-to-face consultation, which delivers comprehensive, clear, and high-quality digital services that guide and help patients to better understand the advantages of COVID-19 vaccines.

KEYWORDS

survey, COVID-19, cancer patients, vaccine, SARS-CoV-2

Introduction

Coronavirus Disease 2019 (COVID-19) began in Wuhan, China, in 2019 and was caused by a novel strain of coronaviruses called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In March 2020, the World Health Organization (WHO) announced COVID-19 as a worldwide pandemic, with cases ranging from asymptomatic to symptomatic infections with mild, moderate, or severe symptoms (1, 2). By the middle of October 2021, more than 239 million cases of SARS-CoV-2 infections were confirmed worldwide, and nearly 4.87 million deaths had been declared (3).

Since the outbreak of the COVID-19 pandemic began, national and international efforts have been taken to develop effective vaccines against SARS-CoV-2, and the development of vaccines has become the most realistic chance for the world to prevent the transmission of the virus and hence, return to normality (4).

Jordan reported 856,450 cases and 10,986 deaths until October 31st, 2021, accounting for about 5.2% of all confirmed cases and 3.6% of all deaths in the WHO Eastern Mediterranean Region (EMR) (5). Jordan was also one of the first 40 nations to get the vaccines, thus the Jordanian Ministry of Health began a vaccination campaign on January 13th, 2021, targeting healthcare workers, individuals with chronic illnesses, and those over the age of 60 (6). According to a survey conducted in Jordan between December 2nd and December 29th, 2020 (before the start of the vaccine campaign), 72.3 % of Jordanians were willing to receive COVID-19 immunization, and COVID-19 risk of infection was significantly associated with vaccine acceptance (7). Immunocompromised patients, particularly cancer patients, were given special attention because, when infected with the SARS-CoV-2 virus, they have a higher risk of needing mechanical ventilation and admission to the intensive care unit (ICU), and the mortality rates are higher than people without cancer (8–10). COVID-19-related mortality rates among cancer patients are as high as 25.6 % (11). Consequently, national and international efforts emerged to develop practical guidelines to assist healthcare institutions in decreasing cancer patients' exposure to SARS-CoV-2. The most common guideline, derived from Cancer Care Ontario, involved prioritizing clinical management of cancer patients during the pandemic and thus reducing the impact of the pandemic upon healthcare workers and hospitals (12, 13).

Aside from the pandemic's negative health effects, the world faced another issue which was the spread of COVID-19 misinformation, hence increasing the likelihood of worse outcomes for vulnerable groups, such as cancer patients. As a result, public confusion emerged globally since proper communication and favorable decisions became an ongoing challenge (14).

COVID-19 infection had indeed a negative impact on the psychology of cancer patients who had higher levels of stress and anxiety due to their critical health situation (15, 16). For example, coronaphobia, which is described as an extreme fear of COVID-19 (17), was linked to a lot of vaccination skepticism. The lack of evidence on the safety and efficacy of the COVID-19 vaccination in cancer patients who were excluded from the early clinical trials created a knowledge gap, allowing misconceptions and false assumptions to emerge (18). In other words, the world faced a digital pandemic because of the tremendous amount of misinformation in different forms that have been spread worldwide. As a result, the attitudes and behaviors of the population depended on what they know, the various

TABLE 1 The demographic characteristics of the participants.

Demographic characteristics	Response	*N* (%)
Gender	Male	153 (34.7%)
	Female	288 (65.3%)
Age group	20–30	37 (8.4%)
	31–40	66 (15%)
	41–50	109 (24.7%)
	51–60	108 (24.5%)
	61–70	82 (18.6%)
	> 71	39 (8.8%)
Educational level	Below primary education	47 (10.7%)
	Secondary education	124 (27.9%)
	College	80 (18.1%)
	University	150 (33.8%)
	Post graduate	43 (9.5%)
Monthly income	Less than $423	124 (28.3%)
	$ 423.1–$705	127 (29%)
	$ 705.1–$1,410	103 (23.6%)
	$ 1,410.1–$2,116	45 (10.3%)
	More than $2,116	38 (8.7%)
Diagnosis	Breast cancer	202 (40.3%)
	Leukemia	39 (7.8%)
	Lymphoma	55 (11%)
	Lung cancer	46 (9.2%)
	Colon cancer	38 (7.6%)
	Others	80 (16%)
On cancer treatment	Yes	346 (78.5%)
	No treatment (Survivors clinic)	95 (21.5%)
Type of treatment	Chemotherapy	194 (57.6%)
	Radiotherapy	34 (10.1%)
	Others	109 (32.3%)

TABLE 2 Questions that reflect patients' attitudes toward SARS-CoV-2 vaccines.

Questions	Response	*N* (%)
Do you have the flu vaccine in 2020?	Yes	108 (25.2%)
	No	321 (74.8%)
Do you think the flu vaccine will protect you from SARS-CoV-2?	Yes	84 (19.6%)
	No	345 (80.4%)
Have you been infected by SARS-CoV-2?	Yes	132 (30.8%)
	No	297 (69.2%)
Have you registered for the SARS-CoV-2 vaccine?	Yes	321 (75.4%)
	No	105 (24.6%)
Did you take the first COVID-19 vaccine dose?	Yes, I got the first dose	296 (92.2%)
	No, I am still waiting for my schedule	25 (7.8%)
Are you going to take the second dose?	Yes	287 (97.6%)
	No, I suffered from side effects, and I do not want to encounter that again	7 (2.4%)
Are you going to register?	Yes	52 (49.5%)
	No (Anti-vaxxers)	53 (50.5%)

TABLE 3 Association between patients who got the first dose of COVID-19 vaccine and who got the flu vaccine and their opinion on the effectiveness of the COVID-19 vaccine.

		Got the first dose of COVID-19 vaccine		Total	*p-value*
		Yes	Still waiting		<0.05
Vaccinated against flu vaccine in 2020	Yes	97 (97.8%)	2 (2.2%)	99	
	No	199 (89.6%)	23 (10.4%)	222	
Do you think the vaccine will	Yes will decrease symptoms	132 (92.3%)	11 (7.7%)	143	<0.05
	Will decrease infection	125 (94.7%)	7 (5.3%)	132	
	Will not do anything	18 (75.0%)	6 (25.0%)	24	

sources of COVID-19 information, and how they understand this information (19, 20).

Internationally, different studies have been conducted in countries such as England, Portugal, and Serbia to investigate the impact of COVID-19 and acceptance of COVID-19 vaccination in adult patients with cancer (21–23). Tunisia and Lebanon, for example, undertook similar investigations throughout the Arab region (24, 25). Both studies concluded that better communication with patients, whether directly through their oncologists or national campaigns and media, can lead to increased vaccination acceptability. Most patients appear to follow their oncologist's vaccine recommendations, indicating that the oncologist's influence is significant. A cross-sectional survey of 364 adult patients with cancer in Bosnia and Herzegovina found that 85.60% of study participants were willing to follow their oncologist's guidance on COVID-19 vaccination (26).

This issue dramatically increased the need to survey people's attitudes toward the COVID-19 pandemic to enhance the role of healthcare institutions and workers (HCWs) in raising awareness. This study aims to describe the attitudes, and knowledge, related to the COVID-19 pandemic and vaccination in adult patients with cancer, as obtained through survey analysis, to guide the best approaches for relaying COVID-19 information in this vulnerable population. We hypothesize that, despite physicians' advice to their patients to get the COVID-19 vaccine, cancer patients still refuse to get vaccinated because they depend on other sources of information other than their oncologists.

Materials and methods

Survey setting and design

This is an online survey analysis study conducted at King Hussein Cancer Center (KHCC) between June and October 2021 with 441 cancer patients treated at KHCC, regardless of their vaccination status or vaccine type taken. The SurveyMonkey questionnaire tool (San Mateo, California, USA) online platform was used to collect the data. All participants provided their informed consent, which was recorded electronically (https://www.surveymonkey.com/summary/eIPeQx3KkZN1nVl4F6NhevYb2Osxfh_2FjYRjTSwh97mk_3D).

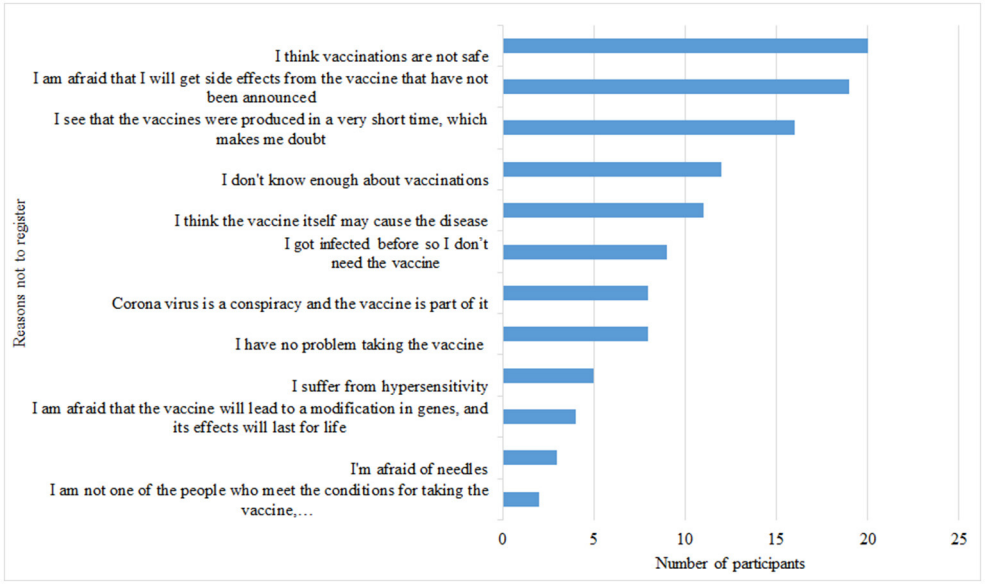

FIGURE 1
Reasons for not registering for the COVID-19 vaccine. Participants had the option of choosing more than one reason not to register for the vaccine.

Survey participation

Cancer patients aged 18 or over were eligible to participate. A hybrid model of data collection was followed including; Electronic SMS messages, social media platforms (WhatsApp and Facebook), and face-to-face interaction with patients. During their routine clinical visit, the research assistant explained the study's purpose to the patient, and once they consented to participate, they were provided the data collection link. To avoid redundancy and ensure data quality, participants were only allowed to submit one response.

Using the SurveyMonkey sample size calculator the recommended sample size should be 306 participants, based on the following assumption: alpha=0.05, Power 95%, using an estimated population size of 1,500 patients visiting the breast, lung, leukemia, lymphoma, and colon outpatient clinics during the survey study. Nevertheless, over the study period, we were able to collect responses from 441 cancer patients (https://www.surveymonkey.com/mp/sample-size-calculator/).

Independent variables

The survey questions were designed to learn about cancer patients' attitudes toward SARS-CoV-2 vaccines, discover the primary source of SARS-CoV-2 vaccine information for cancer patients, and investigate current physician practices for SARS-CoV-2 vaccine counseling as well as compare perception and attitude between the pro-vaccine and anti-vaccine groups of patients.

This survey consisted of 29 closed-format questions divided into five sections. (a) Four questions about the demographic features of the participants, such as age, gender, income, and education level. (b) Three questions regarding the patients' medical conditions, such as the type of cancer, treatment status, and current treatment. (c) Seven questions about vaccination history, with a focus on the flu vaccine and the intention to be vaccinated against COVID-19. (d) Nine questions on vaccine evolution, safety, and importance; and (e) Six questions about COVID-19 information. It was necessary to conduct a pilot study to assess the survey's questionnaire validity and internal consistency. Thirty cancer patients were chosen at random and were not included in the study. A panel of specialists was assembled to review the tool's validity (two physicians, two nurses, a psychosocial support technician, a research assistant, and a survey specialist), and minor language changes were made as a result. Furthermore, we calculated internal consistency and a Cronbach alpha test on the pilot sample, and the result was 0.729, indicating good reliability. The survey and consent form was approved by the Research Ethics Committee (IRB) of King Hussein Cancer Center (IRB # 21 KHCC 053). A translated copy of the survey is provided in the supplementary data (Supplementary Data 1).

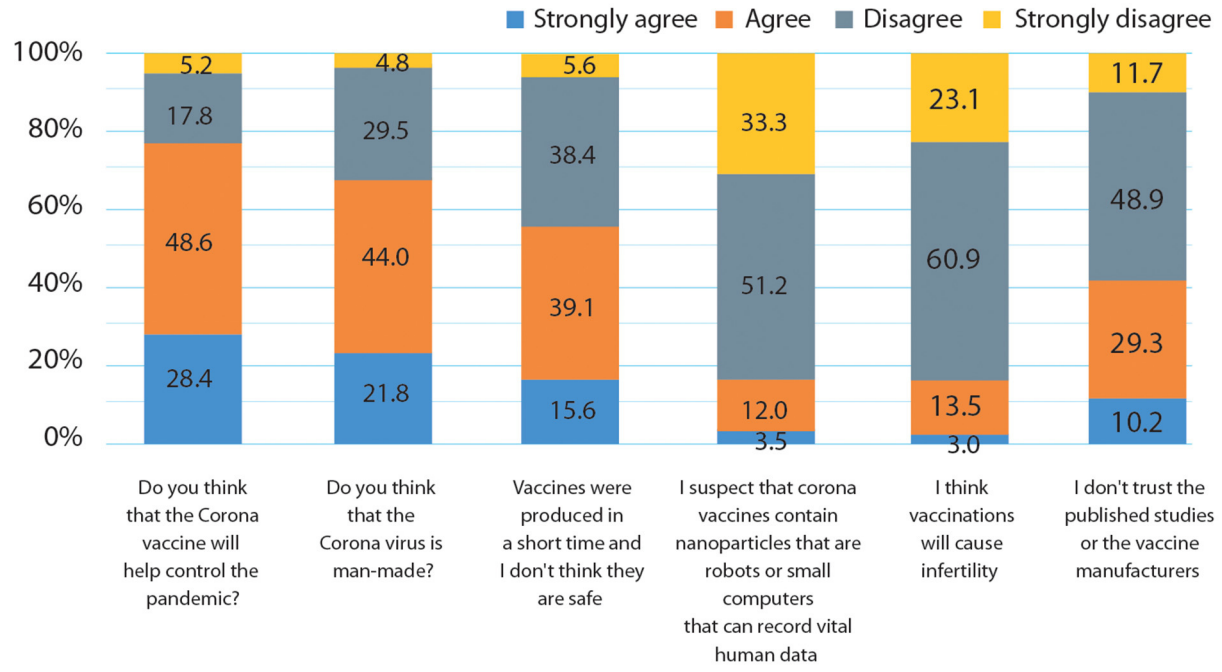

FIGURE 2
Questions and statements reflect patients' attitudes towards SARS-CoV-2 virus and vaccines.

TABLE 4 Patients' opinions toward COVID-19 vaccines.

Questions	Response	*N* (%)
Do you think that the vaccine will protect against infection with the Coronavirus?	Yes, it will protect for a short time	285 (71.8%)
	Yes, it will protect for the lifetime	25 (6.3%)
	No, it will not provide protection	87 (21.9%)
Do you think that the corona vaccine will only help relieve the symptoms of infection?	Yes, the vaccine will only help reduce the symptoms of the disease without protecting me from infection	186 (46.9%)
	Yes, the vaccine will help protect me from infection and will also help to reduce the risk of infection	159 (40.1%)
	No, it will not help relieve the symptoms of the disease and will not protect me from infection	52 (13.1%)
Do you think you have enough information about Corona (SARS-CoV-2) vaccines?	Yes	202 (50.9%)
	No	195 (49.1%)
Would you like to attend an awareness lecture on Corona (SARS-CoV-2) vaccines?	Yes	141 (35.5%)
	No	256 (64.5%)

Data analysis

To collect data, the questionnaire was uploaded to SurveyMonkey, and to ensure quality, it was set to receive only one response from each device to avoid redundancy. The amount of missing data was negligible, and the research team accepted up to 5% of missing data. Categorical data were summarized in tables as proportions and percentages. Statistical analysis was performed using SPSS 26 (IBM, New York, USA). Descriptive analysis was done for all variables, Pearson Chi-square tests of association, and Fisher Exact measured association among categorical and continuous variables respectively. A p-value of <0.05 was defined as the level of statistical significance. Data were anonymously collected, stored, and analyzed in compliance with the General Data Protection Regulations.

Results

Patients' characteristics

A total of 441 patients participated in the study and filled out the questionnaire. Females made up 288 (65.3 %) of the

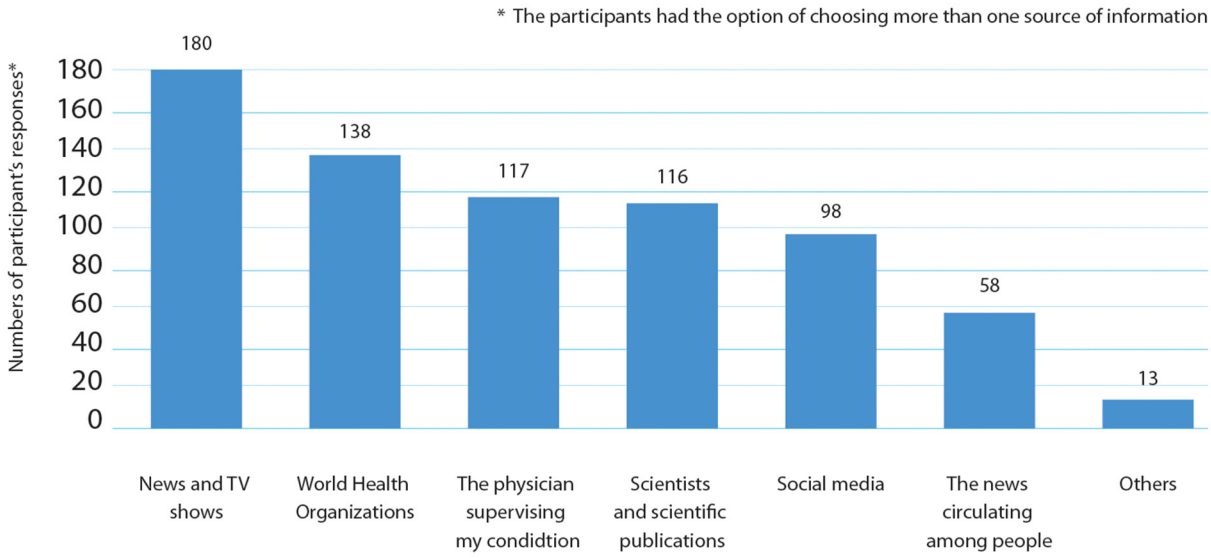

FIGURE 3
Personal stated sources of information about SARS-CoV-2) vaccines declared by cancer patients.

participants, while males made up 153 (34.7 %). Almost half of the participants, 217 (49.2%), were aged between 41 and 60 years, 82 (18.6%) age was between 61 and 70 years, and a minority, 37 (8.4%), were aged between 20 and 30 years. About one-third of participants 150 (33.8 %) have university degrees, followed by 124 (27.4%) who have completed secondary education, while around 47 (10.7 %) of them are below primary education. More than half of the participants had salaries below $705 (251 (57.3%), while 103 (23.6%) had a monthly income between $705.1 and $1,410, and 45 (10.3%) received a salary between $1,410.1 and $2,116. Finally, only 38 (8.7%) have monthly income more than $2,116 [38 (8.7%)] (Table 1).

The majority of recruited subjects were diagnosed with breast cancer, 202 (40.3%), followed by lymphoma, 55 (11%), lung cancer, 46 (9.2%), leukemia, 39 (7.8%), and colon cancer, 38 (7.6%). Three hundred and forty-six (78.5%) were on active cancer treatment, with only 95 (21.5%) survivors (no current treatment) (Table 1).

Patients' attitudes toward SARS-CoV-2 vaccines

Our data showed that almost two-thirds of 297 (69.2%) did not get COVID-19 infection, while 132 (30.8%) had already been infected at the study time. Of the 321 cancer patients who registered for the SARS-CoV-2 vaccine, of them; 296 (92.2%) had already received their first dose of the vaccine at the time of the survey, and 287 (97.6%) of participants were planning to take the second dose (Table 2). Moreover, our data demonstrated a significant association between cancer patients who got the flu vaccine and those who took the first dose of SARS-CoV-2 vaccines ($p < 0.05$) (Table 3).

Participants who did not register *via* the platform to get COVID 19 vaccines 105 (24.6%) reported different reasons for not taking the COVID-19 vaccine. For example, 20 cancer patients did not feel the vaccines were safe, 19 were concerned about unspecified adverse effects, and 16 believed the vaccine was manufactured in a short period, rendering them suspicious (Figure 1).

The COVID-19 vaccination will help control the pandemic, according to 322 (77.6%) of the participants. Two hundred sixty-three (65.8%) participants believed the SARS-CoV-2 virus was created by humans, whereas 137 (34.2%) disagree. Half of the participants, 221 (54.7%), considered that the SARS-CoV-2 vaccinations are unsafe because they were developed in such a short period. The COVID-19 vaccines do not contain nanoparticles that are robots or miniature computers that may record essential human data, according to 338 (84.5%) survey participants. Similarly, 335 (84%) of those surveyed disagree that vaccinations cause infertility. More than half of the participants 244 (60.6%) disagree that published studies and vaccine manufacturers are unreliable (Figure 2).

Most of the participants, 285 (71.8%), believed that the vaccine will protect them for a short time, while 25 (6.3%) only thought that the vaccine will protect them for a lifetime. Furthermore, a vast majority of the participants, 186 (46.9%),

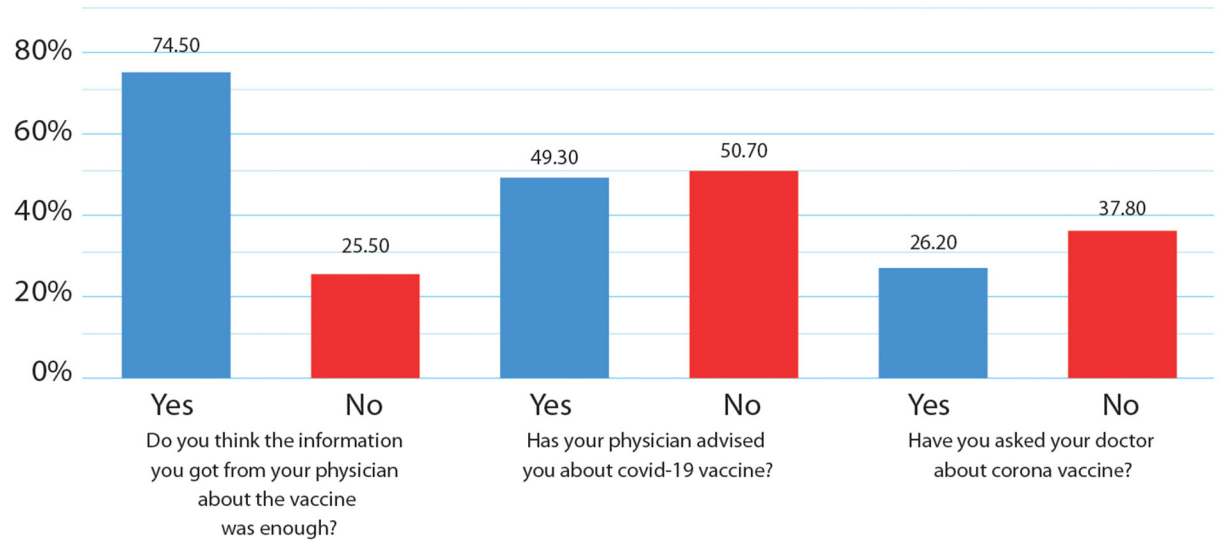

FIGURE 4
Current physician practices concerning counseling on SARS-CoV-2 vaccines.

thought that the vaccine will reduce the disease symptoms, but will not protect them from being infected, and 159 (40.1%) patients believed it would reduce and protect against COVID-19 infection. Almost half of the participants, 202 (50.9%), thought that they had enough information regarding the vaccine. Nevertheless, 141 (35.5 %) of the cancer patients indicated that they preferred attending awareness lectures on COVID-19 vaccines (Table 4). Results from this survey demonstrated a significant positive association between participants who thought that COVID-19 vaccines would protect them from infection and reduce the signs and symptoms of the disease and those who got the SARS-CoV-2 vaccine ($p < 0.05$) (Table 3).

Patients' knowledge sources and attitudes on the COVID-19 pandemic and SARS-CoV-2 vaccines

The sources of information about the SARS-CoV-2 virus vary, as shown in Figure 3; for instance, a substantial number of patients (180/441) got their information from News and TV shows, and (138/441) got their information from the world health organization sites. Moreover, 117 and 116 patients said that their main source of information on COVID-19 was from their oncologists or scientific publications respectively. On the other hand, 98 patients claimed that they relied on social media for their information and 58 admitted they trusted the circulating news to gather the information about the COVID-19 pandemic and vaccines. The participants could choose more than one answer; hence, no percentage was calculated for each subgroup.

There was a positive correlation between patients who got the COVID-19 vaccine and stated that they had enough knowledge about COVID-19 [162/299 (54.2%)] compared to the participants who thought they had good information about the COVID-19 vaccines but did not register for the vaccine [40/98 (40.8%)], $p < 0.05$.

The impact of current physician practices for SARS-CoV-2 vaccine counseling on the vaccination decision-making of cancer patients

Figure 4 shows the physicians' and patients' practices concerning counseling on SARS-CoV-2 vaccines. Almost half of the participants, 201 (49.3%), indicated that their physicians counseled them about the advantages of SARS-CoV-2 vaccines. Although 190 patients (74.5%) thought the vaccine information they received from their oncologists was sufficient, a chi-square test of independence revealed that there was no significant association between claiming to have received sufficient information from their oncologists and their actual registration and willingness to take the COVID-19 vaccine [X^2 (2, $N = 255$) = 2.2, $p > 0.05$]. Moreover, 152 (37.8%) patients did not ask their physicians about the vaccine, and 141 (35.5%) showed interest to attend awareness lectures about COVID-19 vaccines.

TABLE 5 Perception to ward COVID-19 vaccine, comparison between the pro vaccine and anti-vaccine (anti-vaxxers) groups in the sample.

	Pro-vaccine 305		Anti-vaccine (anti-vaxxers) 53		*p*-value
	Agree	Disagree	Agree	Disagree	
Do you think that the Corona vaccine will help control the pandemic?	260	47	16	33	<0.05
	84.7%	15.3%	32.6%	67.4%	
I think vaccinations will cause infertility	33	272	20	24	<0.05
	10.8%	89.2%	45.5%	54.5%	
I don't trust the published studies or the vaccine manufacturers	101	205	36	11	<0.05
	33%	67%	76.6%	23.4%	
Do you think that the Corona virus is manmade?	195	108	41	6	<0.05
	64.4%	33.6%	87.2%	12.7%	
Vaccines were produced in a short time and I don't think they are safe	151	155	42	6	<0.05
	49.3%	50.7%	87.6%	12.4%	
I suspect that corona vaccines contain nanoparticles that are robots or small computers that can record vital human data.	34	271	15	31	<0.05
	11.1%	88.9%	32.6%	67.4%	

Patients opposing taking COVID-19 vaccines (COVID-19 anti-vaxxers)

In our study; 53 patients [53/357 (14.8%)] could be classified as COVID-19 anti-vaxxers (anti-vaccine) because they did not register for vaccines and have no plans to do so (Table 2). We found that there was a significant difference in the perception between the pro-vaccine and anti-vaccine (anti-vaxxers) groups on claims listed in Table 5. For example, 32.6 % (16/53) of the anti-vaxxers participants thought that the COVID-19 vaccine would help contain the pandemic, while 85% (260/305) of pro-vaccine participants thought that the vaccine would control the pandemic ($p < 0.05$). Furthermore, 45.5 % (20/53) of anti-vaccine participants believed that vaccination would result in infertility, whereas 89.2 % (227/305) of pro-vaccine participants did not feel that vaccination would result in infertility ($p < 0.05$). Our data also revealed an association between receiving COVID-19 vaccination and trusting manufacturing companies, with a considerable percentage of anti-vaccine participants (77%) expressing mistrust in these companies ($p < 0.05$) (Table 5).

Discussion

The world currently faces an "infodemic" (19, 27) regarding sources of information on COVID-19 infection and vaccination. Considering that cancer patients infected with SARS-CoV-2 have a higher risk for complications and higher mortality rates, we chose to investigate their attitudes, knowledge, and practices related to the pandemic (28).

Our data showed that 108 patients (25.2%) acknowledged that they took the seasonal influenza vaccine in 2020, similar to the percentage reported in cancer patients from Cyprus (29). A similar number was found in a study of Jordanian university students, with 28.8% having already gotten the flu vaccine (30).

As for SARS-CoV-2 vaccination, most participants in our study, 296 (92.2%), reported that they had already taken the first COVID-19 vaccine shot, which was the only one available at the time of the survey. These results were in line with other published data showing that cancer patients are more willing to take the COVID-19 vaccine than the influenza vaccine (25). On the other hand, a survey performed by Gheorghe et al. on cancer patients in Romania showed that those patients believed that getting the seasonal influenza vaccine would prevent the spread of SARS-CoV-2, and 27.8% declared that they would not get vaccinated against SARS-CoV-2 if a vaccine would become available in Romania (31).

Similar to earlier studies, our findings revealed that the news, TV shows, and the media, in general, were the most common sources of information on the SARS-CoV-2 virus and the COVID-19 pandemic reported by cancer patients (25, 32–34). However, according to a study from Cyprus, social networks were the most prominent source of information for cancer patients (41.2%), while official government websites were the least popular (8.1%) (29). The supervising oncologist was the third most common source of information in our study regarding the SARS-CoV-2 virus similar to data published by Kelkar et al. (35).

The most crucial data in our study found that participants who obtained advice from their doctors and asked their doctors about Coronavirus were 49 and 26%, respectively, which was similar to a study published in Poland (32).

Although, 51% of the participants believed that they had enough information regarding the COVID-19 vaccine, and 75% of those who asked their doctors about the COVID-19 vaccine reported that they got enough information about the vaccine,

35% were still interested in attending awareness lectures, unlike a previous study performed in Jordan on community members where 85% requested more information about COVID-19 vaccines (36).

Our study is the first in Jordan to assess cancer patients' attitudes and knowledge related to the COVID-19 pandemic. It demonstrates the potential influence of sources of information on the tendency to take the vaccines. Although most cancer patients registered for the COVID-19 vaccine, almost 15% of patients still opposed vaccinations. This opposition is most likely due to reliance on misinformation from social media and TV shows based on survey results. We recommend that physicians utilize telehealth technology as an additional resource to their consultation to communicate with their patients, which is akin to online media. Telehealth technology delivers comprehensive, clear, and high-quality digital services that guide and assist patients in better understanding the benefits of COVID-19 vaccines while also saving time during consultations. In addition, involving other hospital services that focus on patients' physical and mental well-being could aid in offering one-on-one guidance to patients during this vital time of uncertainty.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The Institutional Review Board approved this study of King Hussein Cancer Center, Amman, Jordan Center (IRB # 21 KHCC 053) on August 19, 2021. The questionnaire was fully anonymized to protect participants' privacy, and only the collected data were used for analyses and statistical tests. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Concept and study design and review and editing: LS and MS. Literature search and data collection: LS, SB, and MA. Data analysis, figures, tables, and interpretation of the data: LS and KA. Data validation, visualization, and writing—original draft: LS. All authors approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.923815/full#supplementary-material

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EDITED BY
Francesca Licata,
University Magna Graecia of Catanzaro, Italy

REVIEWED BY
Atalay Mulu Fentie,
Addis Ababa University, Ethiopia
Gerardo S. Romo-Cardenas,
Universidad Autónoma de Baja California, Mexico
Madhur Sachan,
Brigham and Women's Hospital and Harvard Medical School, United States
Ritika Kaur,
Independent researcher, Delhi, India,
in collaboration with reviewer MS

*CORRESPONDENCE
Abanoub Riad
abanoub.riad@med.muni.cz

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COVID-19 vaccine booster hesitancy (VBH) of healthcare professionals and students in Poland: Cross-sectional survey-based study

Arkadiusz Dziedzic[1], Julien Issa[2,3], Salman Hussain[4], Marta Tanasiewicz[1], Robert Wojtyczka[5], Robert Kubina[6], Marta Dyszkiewicz Konwinska[2,7] and Abanoub Riad[8]*

[1]Department of Conservative Dentistry with Endodontics, Medical University of Silesia, Katowice, Poland, [2]Department of Diagnostics, Poznań University of Medical Sciences, Poznań, Poland, [3]Doctoral School, Poznań University of Medical Sciences, Poznań, Poland, [4]Czech National Centre for Evidence-Based Healthcare and Knowledge Translation (Cochrane Czech Republic, Czech EBHC: JBI Centre of Excellence, Masaryk University GRADE Centre), Faculty of Medicine, Masaryk University, Brno, Czechia, [5]Department of Microbiology and Virology, Medical University of Silesia, Sosnowiec, Poland, [6]Department of Pathology, Medical University of Silesia, Sosnowiec, Poland, [7]Department of Anatomy, Poznań University of Medical Sciences, Poznań, Poland, [8]Department of Public Health, Faculty of Medicine, Masaryk University, Brno, Czechia

Since healthcare professionals (HCPs) play a critical role in shaping their local communities' attitudes toward vaccines, HCPs' beliefs and attitudes toward vaccination are of vital importance for primary prevention strategies. The present study was designed as a cross-sectional survey-based study utilizing a self-administered questionnaire to collect data about COVID-19 vaccine booster hesitancy (VBH) among Polish HCPs and students of medical universities (MUSs). Out of the 443 included participants, 76.3% were females, 52.6% were HCPs, 31.8% were previously infected by SARS-CoV-2, and 69.3% had already received COVID-19 vaccine booster doses (VBD). Overall, 74.5% of the participants were willing to receive COVID-19 VBD, while 7.9 and 17.6% exhibited their hesitance and rejection, respectively. The most commonly found promoter for acceptance was protection of one's health (95.2%), followed by protection of family's health (81.8%) and protection of community's health (63.3%). Inferential statistics did not show a significant association between COVID-19 VBH and demographic variables, e.g., age and gender; however, the participants who had been previously infected by SARS-CoV-2 were significantly more inclined to reject the VBD. Protection from severe infection, community transmission, good safety profile, and favorable risk-benefit ratio were the significant determinants of the COVID-19 VBD acceptance and uptake. Fear of post-vaccination side effects was one of the key barriers for accepting COVID-19 VBD, which is consistent with the pre-existing literature. Public health campaigns need to highlight the postulated benefits of vaccines and the expected harms of skipping VBD.

KEYWORDS

cross-sectional studies, COVID-19 vaccines, decision making, healthcare professionals, vaccination hesitancy, Poland

Introduction

Over the last 2 years, it became evident that coronavirus disease 2019 (COVID-19) transmission chains can be interrupted by herd immunity achieved either by massive vaccination of the community or natural infection (1, 2). Besides the ethical questions about building herd immunity by infection, cost/benefit analysis of this strategy had never been favorable because the burden of casualties was unpredictable (2). For this reason, achieving herd immunity by vaccination was more convincing and reliable.

Since the start of COVID-19 mass vaccination campaigns in December 2020, about 59.3% of the world population has been fully vaccinated (3). As defined by the U.S. Centers for Disease Control and Prevention (CDC), a fully vaccinated person is an individual who is "2 weeks after receiving all recommended doses in the primary series of their COVID-19 vaccination" (4).

Alongside the increase of fully vaccinated individuals toward achieving herd immunity, a decline in the humoral immunity after 6 months of vaccination with the second dose has been reported leading to a new rise of COVID-19 infections (5, 6). Additionally, several COVID-19 variants have been reported since the beginning of the pandemic where only five are classified as variants of concern (VOC) according to their effect on the pandemic situation; Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529) (7). Consequently, the VOCs affected the incidence of COVID-19 infections through rapid dissemination of the infection leading to hospitalization and mortality. Based on the aforementioned obstacles that restrict the process of attaining herd immunity, the mass vaccination campaign needs to continue side by side with the booster or third dose vaccination as a mediator in increasing the immoral immunity and enhancing the vaccine effectiveness (8).

As of September 2021, booster dose vaccination campaigns have been initiated in Poland (9). Despite the type of primary vaccination, the first to receive the booster does were health care professionals (HCPs) that are at risk of COVID-19 infection, together with the individuals aged 50 years old and above that are fully vaccinated for at least 6 months (9). Subsequently, in December 2021 all people aged from 18 to 49 were able to get vaccinated with the booster dose (10). Reportedly, on April 20, 2022, The Polish Ministry of Health announced the launch of the second booster dose vaccination campaign for people aged 80 years old and above who have received the first booster dose for at least 150 days also the immunocompromised individuals from the age of 12 years old were allowed to take the second booster dose if needed (11). Regardless of the efforts promoting third dose vaccination, only 51.8% of the fully vaccinated Poles have taken the first booster dose (12). A study by Rzymski et al. (13) reported a significant level of hesitancy for receiving the COVID-19 vaccine booster dose among the Polish community; furthermore, another study by Babicki and Mastalerz-Migas (14) reported a low level of booster dose acceptance among Poles. The previously experienced vaccine side effects and the booster dose safety and effectiveness were the primary reasons for the hesitancy toward COVID-19 third dose vaccination (13). Therefore, the present study was carried out to specifically target Polish HCPs and evaluate their views and attitudes toward COVID-19 vaccine booster doses (VBD).

The World Health Organization (WHO) defines vaccine hesitancy as "delay in acceptance or refusal of vaccines despite availability of vaccine services" (15). The risk factors of vaccine hesitancy can be classified according to the 3-C model of the WHO-Strategic Advisory Group of Experts on Immunization (SAGE), including complacency, convenience, and confidence (16). The three core elements of vaccine hesitancy are usually mediated by individuals' vaccine-related knowledge and health literacy levels (17–19). The health-related beliefs and attitudes of HCPs play a significant role in primary prevention and health promotion as they are broadly perceived as role models and credible sources of health information (19, 20). Therefore, COVID-19 booster dose hesitancy among HCPs may negatively impact public confidence in booster doses (21).

The overarching goal of this study was to evaluate COVID-19 vaccine booster hesitancy (VBH) among HCPs and medical universities students (MUSs) in Poland. The primary objective was to estimate the prevalence of COVID-19 VBH among Polish HCPs and MUSc, while the secondary objectives were: (i) to evaluate the demographic, anamnestic, and psychosocial drivers of COVID-19 VBD-related acceptance and (ii) to assess the correlation between COVID-19 VBD-related acceptance and actual VBD uptake among the target population.

Materials and methods

Design

The present work had been designed as an analytical cross-sectional survey-based study that was carried out between December 2021 and January 2022. A self-administered questionnaire (SAQ) was used for the purpose of data collection after being digitally designed using KoBoToolbox (Harvard Humanitarian Initiative, Cambridge, MA, USA, 2021) (22). The study had been designed and reported in full compliance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cross-sectional studies (23).

Participants

The target population of this study were HCPs and MUSc in Poland. The exclusion criteria were: (i) not working as

a HCP or studying at a medical university, (ii) providing insufficient demographic information, and (iii) not providing their informed consent *a priori*. The participation in this study was completely voluntary, the participants received no financial rewards or any other means of incentives to take part in this study. The participants' interest, especially the students, in participating in this study was not coerced by any means of threats. The participants' identity was kept anonymous in order to control the Hawthorne's effect and information bias.

A non-random sampling strategy was used for data collection through convenience recruitment. The participants were invited to this study through multiple channels in two major academic centers, Katowice and Poznan. A uniform resource locator (URL) and quick response (QR) code for the questionnaire were sent to the potential participants as they were able to download it from the project promoting sources, such as Medical Universities websites, scientific societies and professional regulatory bodies.

The pragmatic sample size required for this study was computed using Epi-Info^{TM} version 7.2.5 (CDC. Atlanta, GA, USA, 2021), specifically through the module of "Population Survey" (24, 25). Following the assumptions of 5% as an error margin, 97% as a confidence level, 71% as an expected outcome frequency which was based on a recent study for Polish adults, and 10% as a postulated proportion of faulty responses due to careless/insufficient efforts, the required sample was 427 responses (13).

A total of 456 responses were received from the potential participants, 13 of which were excluded due to insufficiency of demographic information that were crucial to their classification and subsequent analysis.

Instrument

The SAQ that was used in this study had been used in previous studies concerned with evaluating COVID-19 VBH in Czechia and Germany (21, 26). The psychometric validation process comprised of content validity evaluation and test re-test reliability which showed that this SAQ had substantial reliability denoted by a mean Cohen's kappa coefficient of 0.80 ± 0.19 (IQR: 0.60–1.00) (21).

The SAQ was consisted of 17 items that were divided into four basic sections; (i) demographic information: gender, age, profession, and geographic region, (ii) COVID-19-related anamnesis: prior infection, its onset and severity, vaccination history, number of doses, and post-vaccination hospitalization and medical care, (iii) willingness to receive COVID-19 VBD evaluated by a 5-point Likert scale ranging from "Totally Disagree = 1" to "Totally Agree = 5," and (iv) psychosocial drivers of COVID-19 VBH; e.g., protection against severe infection and community transmission.

The attitudes toward COVID-19 VBD were stratified into three levels based on the responses to the 5-point Likert scale: "VBD Rejection" group included those who responded "Totally Disagree" and "Disagree," "VBD Hesitancy" group included those who responded "Not Sure," and "VBD Acceptance" group included those who responded "Agree" and "Totally Agree." To facilitate the subsequent analyses, the participants who received the third dose of the vaccine were denoted as "Triple Vaccinated."

Ethics

The proposed study protocol had been reviewed and approved by the Ethics Committee of the Medical University of Silesia on 20 July 2021 (PCN/CBN/0022/KB/161/21). The Declaration of Helsinki for research involving human subjects and the European Union (EU) General Data Protection Regulation (GDPR) governed the process of data collection, storing, and handling (27, 28). All the participants provided their informed consent digitally prior to their participation, and no information or responses were collected before that point. The study participants were allowed to leave the study at any moment without the need to justify their decision. No identifying personal data, e.g., email or telephone number was collected from the participants; therefore, retrospective identification of the participants was not possible.

Analyses

All descriptive and inferential statistical tests were performed using the Statistical Package for the Social Sciences (SPSS) version 28.0 (SPSS Inc. Chicago, IL, USA, 2021) except for regression analyses that were performed using the R-based open software "Jamovi" (29, 30). Shapiro Wilk test was used to evaluate the distribution of numerical variables with a significance level (*Sig.*) of 5%. Frequencies (*n*) and percentages (%) were used to evaluate present the categorical and ordinal variables such as gender, pregnancy, vaccination status, attitudes toward COVID-19 VBD, and psychosocial drivers, while means, standard deviations and interquartile ranges ($\mu \pm$ SD "IQR") were used for numerical variables, e.g., age. Subsequently, inferential tests such as Chi-squared test (χ^2), Fisher's exact test, and Mann-Whitney (U) test were used to evaluate the association between dependent and independent variables. Bivariate correlation using the non-parametric test of Spearman's rank was performed between COVID-19 VBD attitudes and actual uptake. Finally, the multivariable logistic regression was used to estimate the adjusted odds ratio (*AOR*) of various psychosocial drivers for COVID-19 VBD acceptance and actual uptake. The regression analysis was adjusted for the demographic and anamnestic variables that were found to be

TABLE 1 Demographic characteristics of polish healthcare professionals and students responding to COVID-19 VBH survey, December 2021–January 2022 ($n = 443$).

Variable	Outcome	Professionals ($n = 233$)	Students ($n = 210$)	Total ($n = 443$)	*Sig.*
Gender	Female[†]	175 (75.1%)	163 (77.6%)	338 (76.3%)	*Reference*
	Male	55 (23.6%)	46 (21.9%)	101 (22.8%)	0.636
	Diverse-gender	3 (1.3%)	1 (0.5%)	4 (0.9%)	0.376
Pregnancy[†]	Yes	7 (4%)	0 (0%)	7 (2.1%)	**0.015**
	No	168 (96%)	163 (100%)	331 (97.9%)	
Age	$\mu \pm SD$ (IQR)	38.8 ± 10.9 (31–45)	22.6 ± 2.3 (21–24)	31.1 ± 11.4 (23–36.3)	**<0.001**

Logistic regression, Fisher's exact test, and Mann-Whitney test (U) had been used with a significance level (Sig.) < 0.05.
[†] Refers to female participants.
Bold values - statistically significant with $p < 0.05$.

significant in the univariate analysis. All inferential tests were performed with a confidence level (*CI*) of 95% and a significance level (*Sig.*) of 5%.

Results

Demographic characteristics

A total of 443 participants were included in this study, out of which 233 (52.6%) were HCPs and 210 (47.4%) were MUSc. In general, females were the vast majority (76.3%), followed by males (22.8%) and diverse-gender (0.9%) participants without significant differences between professionals' and students' groups. Out of the 338 participating females, only 7 (2.1%) were pregnant and they all belonged to the professionals' group. The mean age of the sample was 31.1 ± 11.4 with a statistically significant difference (*Sig.* < 0.001) between professionals (38.8 ± 10.9) and students (22.6 ± 2.3) (Table 1).

The most participating region was Silesian Voivodeship (54.4%), followed by the Greater Poland Voivodeship (28.9%), and the Lesser Poland Voivodeship (8.1%).

Anamnestic characteristics

Nearly one-third (31.8%) of the participants reported being infected previously with COVID-19, and the vast majority of them were infected before receiving the first dose (73%), followed by those who were infected after the second dose (22.7%), and those who were infected between the doses (4.3%). According to the Australian guidelines for clinical classification of COVID-19 patients, most of our participants experienced mild infection (66%), followed by moderate (29.1%), asymptomatic (2.8%), and severe infection (2.1%). There was no significant difference between professionals' and students' groups in terms of COVID-19 infection-related anamnesis.

The vast majority of the participants (93.7%) reported receiving at least one dose of COVID-19 vaccines without a significant difference between professionals and students. As expected, the most common vaccine type was Pfizer-BioNTech (78.3%) which was significantly (*Sig.* < 0.001) more common among professionals (89.3%) than students (66.7%). AstraZeneca-Oxford was the second most common vaccine type (13%) and it was significantly (*Sig.* < 0.001) more common among students (22.9%) than professionals (3.7%). To a limited extent, Moderna and Janssen vaccines were received by 4.8 and 3.9% of the participants. Most of the participants were triple vaccinated (74%), with a significant difference (*Sig.* < 0.001) between professionals (79%) and students (68.7%). Only 4.3% of the whole sample received a single vaccine dose, and 3.4 and 4.3% reported post-vaccination hospitalization and seeking medical care (Table 2).

COVID-19 vaccine booster dose (VBD)-related attitudes

Overall, almost three-quarters (74.5%) of the participants indicated their acceptance to receive COVID-19 VBD, while 17.6% indicated their rejection, and 7.9% were hesitant. No significant difference between professionals and students in terms of VBD-related attitudes. The triple vaccinated individuals had a significantly (*Sig.* < 0.001) higher level of VBD acceptance (87.9 vs. 44.1%) and a significantly (*Sig.* < 0.001) lower level of VBD rejection (8.1 vs. 39%) compared with their counterparts who did not receive the third dose, respectively.

When asked about their reasons to accept COVID-19 VBD, the most commonly reported promoted was protection of one's own health (96.3%), followed by protection of family's health (82.5%), and protection of community's health (65%). On the other hand, work or study place endorsement (5%) and avoidance of frequent testing (20%) were the least reported promoters. The students were significantly more inclined to

TABLE 2 Anamnestic characteristics of polish healthcare professionals and students responding to COVID-19 VBH survey, December 2021–January 2022 ($n = 443$).

Variable	Outcome	Professionals ($n = 233$)	Students ($n = 210$)	Total ($n = 443$)	*Sig.*
Prior COVID-19 infection	Yes†	72 (30.9%)	69 (32.9%)	141 (31.8%)	0.659
	No	161 (69.1%)	141 (67.1%)	302 (68.2%)	
Onset†	Before 1st dose	50 (69.4%)	53 (76.8%)	103 (73%)	*Reference*
	Between 1/2 doses	2 (2.8%)	4 (5.8%)	6 (4.3%)	0.475
	After 2nd dose	20 (27.8%)	12 (17.4%)	32 (22.7%)	0.170
Severity†	Asymptomatic	2 (2.8%)	2 (2.9%)	4 (2.8%)	*Reference*
	Mild	49 (68.1%)	44 (63.8%)	93 (66%)	0.916
	Moderate	19 (26.4%)	22 (31.9%)	41 (29.1%)	0.889
	Severe	2 (2.8%)	1 (1.4%)	3 (2.1%)	0.661
COVID-19 vaccination	Yes ‡	214 (91.8%)	201 (95.7%)	415 (93.7%)	0.095
	No	19 (8.2%)	9 (4.3%)	28 (6.3%)	
Vaccine type‡	Pfizer-BioNTech	191 (89.3%)	134 (66.7%)	325 (78.3%)	**<0.001**
	Moderna	9 (4.2%)	11 (5.5%)	20 (4.8%)	0.547
	AstraZeneca-Oxford	8 (3.7%)	46 (22.9%)	54 (13%)	**<0.001**
	Janssen	6 (2.8%)	10 (5%)	16 (3.9%)	0.251
Number of doses‡	One dose	8 (3.7%)	10 (5%)	18 (4.3%)	0.536
	Two doses	37 (17.3%)	53 (26.4%)	90 (21.7%)	**0.025**
	Three doses	169 (79%)	138 (68.7%)	307 (74%)	**0.017**
Booster recipient	Yes	169 (72.5%)	138 (65.7%)	307 (69.3%)	0.120
	No	64 (27.5%)	72 (34.3%)	136 (30.7%)	
Hospital admission‡	Yes	11 (5.1%)	3 (1.5%)	14 (3.4%)	**0.040**
	No	203 (94.9%)	198 (98.5%)	401 (96.6%)	
Medical care‡	Yes	11 (5.1%)	7 (3.5%)	18 (4.3%)	**0.407**
	No	203 (94.9%)	194 (96.5%)	397 (95.7%)	

Logistic regression and Chi-squared test (χ^2) had been used with a significance level (Sig.) < 0.05.
† Refers to the previously infected participants.
‡ Refers to the previously vaccinated participants.
Bold values - statistically significant with $p < 0.05$.

indicate testing avoidance (20 vs. 11.2%) and having easier social life with less restrictions (58.8 vs. 43.5%) than the professionals, respectively (Table 3).

Psychosocial drivers of COVID-19 vaccine booster hesitancy (VBH)

More than three-quarters (76.1%) of the participants agreed with the notion that VBD were capable of preventing severe infection, with a significant difference (*Sig.* < 0.001) between triple vaccinated participants (87.9%) and their counterparts (49.3%) and with no significant difference (*Sig.* $= 0.495$) between professionals (76.4%) and students (75.7%). Similarly, the notion that VBD were able to prevent symptomatic infection was significantly (*Sig.* < 0.001) more accepted by the triple vaccinated participants (73.6%) than their counterparts (38.2%). Moreover, the notion that VBD were able to prevent community transmission was significantly (*Sig.* < 0.001) more accepted by the triple vaccinated participants (65.1%) than their counterparts (27.9%).

Interestingly, 68.4% of the participants did not agree to postpone receiving of their VBD until they found convincing evidence that the VBD would control the emerging variants. While there was no statistically significant (*Sig.* $= 0.407$) difference between professionals (72.1%) and students (64.3%) in the notion of variants control, the triple vaccinated participants (80.8%) were significantly (*Sig.* < 0.001) more inclined to disagree with this notion compared with their counterparts (40.4%).

About three-quarters (75.4%) of the participants agreed with the notion that VBD would be as safe as the primer doses, with a significant difference (*Sig.* < 0.001) between triple vaccinated participants (86.3%) and their counterparts (50.7%) and with no significant difference (*Sig.* $= 0.280$) between professionals (73.8%) and students (77.1%). Almost two-thirds (66.6%) of the participants disagreed with the notion the VBD would cause severe side effects interfering with their daily routine, with a

TABLE 3 Attitudes toward COVID-19 VBD of polish healthcare professionals and students responding to COVID-19 VBH survey, December 2021–January 2022 ($n = 443$).

Variable	Outcome	Employment			Triple vaccinated			Total ($n = 443$)
		Professionals ($n = 233$)	Students ($n = 210$)	*Sig.*	Yes ($n = 307$)	No ($n = 136$)	*Sig.*	
Attitudes	Rejection	45 (19.3%)	33 (15.7%)	0.321	25 (8.1%)	53 (39%)	**<0.001**	78 (17.6%)
	Hesitancy	18 (7.7%)	17 (8.1%)	0.885	12 (3.9%)	23 (16.9%)	**<0.001**	35 (7.9%)
	Acceptance†	170 (73%)	160 (76.2%)	0.436	270 (87.9%)	60 (44.1%)	**<0.001**	330 (74.5%)
Promoter†	Self-protection	160 (94.1%)	154 (96.3%)	0.367	256 (94.8%)	58 (96.7%)	0.746	314 (95.2%)
	Family's health	138 (81.2%)	132 (82.5%)	0.755	220 (81.5%)	50 (83.3%)	0.737	270 (81.8%)
	Patient/colleague	89 (52.4%)	93 (58.1%)	0.292	148 (54.8%)	34 (56.7%)	0.794	182 (55.2%)
	Community's health	105 (61.8%)	104 (65%)	0.542	167 (61.9%)	42 (70%)	0.236	209 (63.3%)
	Testing avoidance	19 (11.2%)	32 (20%)	**0.027**	42 (15.6%)	9 (15%)	0.914	51 (15.5%)
	Easier social life	74 (43.5%)	94 (58.8%)	**0.006**	138 (51.1%)	30 (50%)	0.876	168 (50.9%)
	Work/study place	4 (2.4%)	8 (5%)	0.199	9 (3.3%)	3 (5%)	0.463	12 (3.6%)

Chi-squared test (χ^2) and Fisher's-exact test had been used with a significance level (Sig.) < 0.05.
† Refers to the vaccine-accepting group.
Bold values - statistically significant with $p < 0.05$.

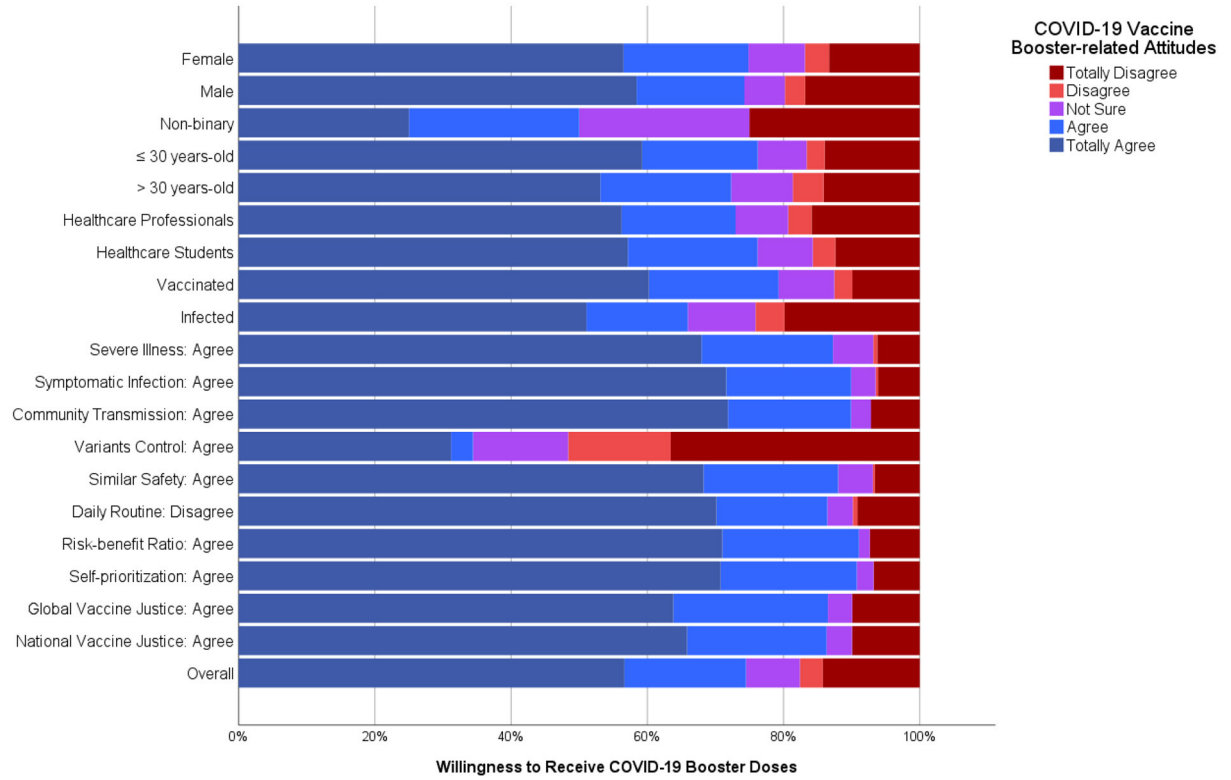

FIGURE 1
Determinants of COVID-19 vaccine booster-related attitudes of polish healthcare professionals and students responding to COVID-19 VBH survey, December 2021–January 2022 ($n = 443$).

significant difference (*Sig.* < 0.001) between triple vaccinated participants (76.9%) and their counterparts (43.4%) and with no significant difference (*Sig.* = 0.777) between professionals (65.7%) and students (67.6%) (Figure 1).

TABLE 4 Determinants of COVID-19 VBH among polish healthcare professionals and students responding to COVID-19 VBH survey, December 2021–January 2022 ($n = 443$).

Variable	Outcome	Employment			Triple vaccinated			Total ($n = 443$)
		Professionals ($n = 233$)	Students ($n = 210$)	*Sig.*	Yes ($n = 307$)	No ($n = 136$)	*Sig.*	
Severe infection	Agreement	178 (76.4%)	159 (75.7%)	0.495	270 (87.9%)	67 (49.3%)	**<0.001**	337 (76.1%)
	Disagreement	39 (16.7%)	29 (13.8%)		19 (6.2%)	49 (36%)		68 (15.3%)
Symptomatic infection	Agreement	144 (61.8%)	134 (63.8%)	0.324	226 (73.6%)	52 (38.2%)	**<0.001**	278 (62.8%)
	Disagreement	52 (22.3%)	38 (18.1%)		30 (9.8%)	60 (44.1%)		90 (20.3%)
Community transmission	Agreement	130 (55.8%)	108 (51.4%)	0.687	200 (65.1%)	38 (27.9%)	**<0.001**	238 (53.7%)
	Disagreement	57 (24.5%)	52 (24.8%)		44 (14.3%)	65 (47.8%)		109 (24.6%)
Variants control	Agreement	47 (20.2%)	46 (21.9%)	0.407	29 (9.4%)	64 (47.1%)	**<0.001**	93 (21%)
	Disagreement	168 (72.1%)	135 (64.3%)		248 (80.8%)	55 (40.4%)		303 (68.4%)
Equal safety	Agreement	172 (73.8%)	162 (77.1%)	0.280	265 (86.3%)	69 (50.7%)	**<0.001**	334 (75.4%)
	Disagreement	36 (15.5%)	25 (11.9%)		19 (6.2%)	42 (30.9%)		61 (13.8%)
Daily routine	Agreement	36 (15.5%)	36 (17.1%)	0.777	37 (12.1%)	35 (25.7%)	**<0.001**	72 (16.3%)
	Disagreement	153 (65.7%)	142 (67.6%)		236 (76.9%)	59 (43.4%)		295 (66.6%)
Risk/benefit ratio	Agreement	164 (70.4%)	150 (71.4%)	0.950	259 (84.4%)	55 (40.4%)	**<0.001**	314 (70.9%)
	Disagreement	40 (17.2%)	36 (17.1%)		25 (8.1%)	51 (37.5%)		76 (17.2%)
Self-prioritization	Agreement	175 (75.4%)	150 (71.4%)	0.456	270 (88.2%)	55 (40.4%)	**<0.001**	325 (73.5%)
	Disagreement	46 (19.8%)	47 (22.4%)		24 (7.8%)	69 (50.7%)		93 (21%)
Global vaccine justice	Agreement	73 (31.3%)	68 (32.4%)	0.591	115 (37.5%)	26 (19.1%)	**<0.001**	141 (31.8%)
	Disagreement	67 (28.8%)	71 (33.8%)		64 (20.8%)	74 (54.4%)		138 (31.2%)
National vaccine justice	Agreement	78 (33.5%)	83 (39.5%)	0.650	128 (41.7%)	33 (24.3%)	**<0.001**	161 (36.3%)
	Disagreement	71 (30.5%)	68 (32.4%)		71 (23.1%)	68 (50%)		139 (31.4%)

Mann-Whitney test (U) had been used with a significance level (Sig.) < 0.05.
Bold values - statistically significant with $p < 0.05$.

A large proportion of the participants agreed that the benefits of VBD would outweigh their risks (70.9%) and that they should be prioritized to receive the VBD based on their occupational risk (73.5%). However, the differences between professionals and students were not statistically significant for both notions, the triple vaccinated participants had significantly higher agreement levels with both of them (84.4 and 88.2%, respectively) compared with their counterparts (40.4 and 40.4%, respectively).

The positions of our participants from the ethical dilemmas of vaccine justice either globally or nationally was almost equally distributed between agreement and disagreement, without significant differences between professionals and students (Table 4).

Determinants of COVID-19 VBD-related attitudes vs. uptake

On evaluating the demographic and anamnestic determinants of COVID-19 VBD-related attitudes, no significant difference was found among genders, age groups, pregnancy statuses, COVID-19 infection onset, COVID-19 infection severity, or vaccine type. The participants who had been previously infected by SARS-CoV-2 were significantly more inclined to reject the VBD (24.1 vs. 14.6%) and less inclined to accept the VBD (66 vs. 78.5%) than their counterparts. Contrarily, the participants who had been previously vaccinated against SARS-CoV-2 were significantly less inclined to reject the VBD (12.5 vs. 92.9%) and more inclined to accept the VBD (79.3 vs. 3.6%) than their counterparts. Hospital admission (35.7 vs. 11.7%) and seeking medical care (33.3 vs. 11.6%) were significantly associated with higher levels of COVID-19 VBD rejection (Table 5).

On evaluating the demographic and anamnestic determinants of COVID-19 VBD actual uptake, no significant difference was found among genders, age groups, pregnancy statuses, COVID-19 infection onset, COVID-19 infection severity, post-vaccination hospitalization, or seeking medical care. The participants who had been previously infected by SARS-CoV-2 had a significantly (*Sig.* < 0.001) lower uptake level (58.2%) than their counterparts (74.5%). The participants

TABLE 5 Demographic and anamnestic determinants of COVID-19 vaccine booster acceptance among polish healthcare professionals and students responding to COVID-19 VBH survey, December 2021–January 2022 ($n = 443$).

Variable	Outcome	Rejection ($n = 78$)	*Sig.*	Hesitancy ($n = 35$)	*Sig.*	Acceptance ($n = 330$)	*Sig.*
Gender	Female*	57 (16.9%)	*Reference*	28 (8.3%)	*Reference*	253 (74.9%)	*Reference*
	Male	20 (19.8%)	0.496	6 (5.9%)	0.442	75 (74.3%)	0.904
	Diverse-gender	1 (25%)	0.670	1 (25%)	0.265	2 (50%)	0.279
Pregnancy*	Yes	1 (14.3%)	1.000	1 (14.3%)	0.457	5 (71.4%)	1.000
	No	56 (16.9%)		27 (8.2%)		248 (74.9%)	
Age group	>30 years-old	33 (18.6%)	0.579	16 (9%)	0.476	128 (72.3%)	0.354
	≤30 years-old	44 (16.6%)		19 (7.2%)		202 (76.2%)	
Prior COVID-19 infection	Yes†	34 (24.1%)	**0.014**	14 (9.9%)	0.280	93 (66%)	**0.005**
	No	44 (14.6%)		21 (7%)		237 (78.5%)	
Onset†	Before 1st dose	29 (28.2%)	*Reference*	8 (7.8%)	*Reference*	66 (64.1%)	*Reference*
	Between 1/2 doses	2 (33.3%)	0.785	0 (0%)	0.993	4 (66.7%)	0.898
	After 2nd dose	3 (9.4%)	**0.039**	6 (18.8%)	0.084	23 (71.9%)	0.418
Severity†	Asymptomatic	2 (50%)	*Reference*	1 (25%)	*Reference*	1 (25%)	*Reference*
	Mild	19 (20.4%)	0.188	8 (8.6%)	0.297	66 (71%)	0.091
	Moderate	13 (31.7%)	0.467	5 (12.2%)	0.483	23 (56.1%)	0.262
	Severe	0 (0%)	0.990	0 (0%)	0.991	3 (100%)	0.990
COVID-19 vaccination	Yes ‡	52 (12.5%)	**<0.001**	34 (8.2%)	0.714	329 (79.3%)	**<0.001**
	No	26 (92.9%)		1 (3.6%)		1 (3.6%)	
Vaccine type‡	Pfizer-BioNTech	38 (11.7%)	0.327	27 (8.3%)	0.871	260 (80%)	0.490
	Moderna	1 (5%)	0.491	2 (10%)	0.674	17 (85%)	0.777
	AstraZeneca-Oxford	5 (9.3%)	0.436	3 (5.6%)	0.599	46 (85.2%)	0.251
	Janssen	8 (50%)	**<0.001**	2 (12.5%)	0.631	6 (37.5%)	**<0.001**
Number of doses‡	One dose	8 (44.4%)	**<0.001**	5 (27.8%)	**0.011**	5 (27.8%)	**<0.001**
	Two doses	19 (21.1%)	**0.005**	17 (18.9%)	**<0.001**	54 (60%)	**<0.001**
	Three doses	25 (8.1%)	**<0.001**	12 (3.9%)	**<0.001**	270 (87.9%)	**<0.001**
Hospital admission‡	Yes	5 (35.7%)	**0.021**	2 (14.3%)	0.321	7 (50%)	**0.013**
	No	47 (11.7%)		32 (8%)		322 (80.3%)	
Medical care‡	Yes	6 (33.3%)	**0.016**	3 (16.7%)	0.175	9 (50%)	**0.005**
	No	46 (11.6%)		31 (7.8%)		320 (80.6%)	

Logistic regression, Chi-squared test (χ^2) and Fisher's exact test had been used with a significance level (Sig.) < 0.05.
* Refers to female participants.
† Refers to the previously infected participants.
‡ Refers to the previously vaccinated participants.
Bold values - statistically significant with $p < 0.05$.

who had been previously vaccinated against SARS-CoV-2 using Pfizer-BioNTech (80%) and Moderna (80%) had higher levels of VBD uptake than those who received AstraZeneca-Oxford (57.4%) and Janssen (0%) (Table 6).

The bivariate correlation between COVID-19 VBD-related attitudes and actual uptake revealed that there had been moderate and positive correlation between VBD-related acceptance and number of doses ($\rho = 0.508$; *Sig.* < 0.001) and being triple vaccinated ($\rho = 0.464$; *Sig.* < 0.001). Contrarily, there correlation was moderate and negative between VBD-related rejection and number of doses ($\rho = -0.437$; *Sig.* < 0.001) and being triple vaccinated ($\rho = -0.373$; *Sig.* < 0.001) (Table 7).

Regression analysis of COVID-19 VBD-related acceptance determinants

The multivariable logistic regression of psychosocial drivers of COVID-19 VBD-related acceptance was adjusted for prior infection, vaccine type, number of doses, hospitalization, and medical care. The participants who agreed with the severe infection notion had an increased adjusted odds ratio (AOR) of 5.142 (CI 95%: 2.346–11.269) times to accept COVID-19 VBD. Similarly, agreement with the symptomatic infection (AOR: 5.502; CI 95%: 2.717–11.139), community transmission (AOR: 5.898; CI 95%: 3.041–11.438), equal safety (AOR: 3.733; CI 95%: 1.622–8.592), favorable risk-benefit ratio (AOR: 9.573; CI 95%:

TABLE 6 Demographic and anamnestic determinants of COVID-19 vaccine booster uptake among polish healthcare professionals and students responding to COVID-19 VBH survey, December 2021–January 2022 ($n = 443$).

Variable	Outcome	Did not receive COVID-19 BD ($n = 136$)	Received COVID-19 BD ($n = 307$)	*Sig.*
Gender	Female*	100 (29.6%)	238 (70.4%)	*Reference*
	Male	36 (35.6%)	65 (64.4%)	0.249
	Diverse-gender	0 (0%)	4 (100%)	0.984
Pregnancy*	Yes	4 (57.1%)	3 (24.9%)	0.202
	No	96 (29%)	235 (71%)	
Age group	>30 years-old	88 (33.2%)	177 (66.8%)	0.174
	≤30 years-old	48 (27.1%)	129 (72.9%)	
Prior COVID-19 infection	Yes†	59 (41.8%)	82 (58.2%)	**<0.001**
	No	77 (25.5%)	225 (74.5%)	
Onset†	Before 1st dose	40 (38.8%)	63 (61.2%)	*Reference*
	Between 1/2 doses	4 (66.7%)	2 (33.3%)	0.197
	After 2nd dose	15 (46.9%)	17 (53.1%)	0.420
Severity†	Asymptomatic	3 (75%)	1 (25%)	*Reference*
	Mild	38 (40.9%)	55 (59.1%)	0.211
	Moderate	17 (41.5%)	24 (58.5%)	0.228
	Severe	1 (33.3%)	2 (66.7%)	0.287
Vaccine type	Pfizer-BioNTech	65 (20%)	260 (80%)	**<0.001**
	Moderna	4 (20%)	16 (80%)	0.529
	AstraZeneca-Oxford	23 (42.6%)	31 (57.4%)	**0.003**
	Janssen	16 (100%)	0 (0%)	**<0.001**
Hospital admission	Yes	7 (50%)	7 (50%)	0.058
	No	101 (25.2%)	300 (74.8%)	
Medical care	Yes	8 (44.4%)	10 (55.6%)	0.095
	No	100 (25.2%)	297 (74.8%)	

Logistic regression, Chi-squared test (χ^2) and Fisher's exact test had been used with a significance level (Sig.) < 0.05.
* Refers to female participants.
† Refers to the previously infected participants.
‡ Refers to the previously vaccinated participants.
Bold values - statistically significant with $p < 0.05$.

TABLE 7 Correlation between vaccine doses & willingness to receive COVID-19 vaccine booster doses.

		Rejection	Hesitancy	Acceptance
Number of dose	Spearman's ρ	−0.437	−0.204	0.508
	Sig.	**<0.001**	**<0.001**	**<0.001**
Triple vaccinated	Spearman's ρ	−0.373	−0.222	0.464
	Sig.	**<0.001**	**<0.001**	**<0.001**

Bivariate correlation had been used with a significance level (Sig.) < 0.05.
Bold values - statistically significant with $p < 0.05$.

4.461–20.544), and self-prioritization (AOR: 17.407; CI 95%: 8.382–36.150) had an increased odd to accept COVID-19 VBD. On the other hand, agreement with the notion of variant control decreased the odds of accepting COVID-19 VBD (AOR: 0.143; CI 95%: 0.072–0.286). Ignoring the ethical dilemmas globally (AOR: 2.584; CI 95%: 1.274–5.242) and nationally (AOR: 2.426; CI 95%: 1.233–4.772) was associated with increased odds of VBD acceptance (Table 8).

Regression analysis of COVID-19 VBD uptake determinants

The multivariable logistic regression of psychosocial drivers of COVID-19 VBD actual uptake was adjusted for prior infection and vaccine type. The participants who agreed with the severe infection notion had an increased adjusted odds ratio (AOR) of 4.283 (CI 95%: 2.051–8.941) times to receive

TABLE 8 Psychosocial determinants of COVID-19 vaccine booster acceptance among polish healthcare professionals and students responding to COVID-19 VBH survey, December 2021–January 2022 ($n = 443$).

Determinant	B (SE)	Wald	AOR	CI 95%	*Sig.*
Severe infection: agree (vs. disagree)	1.637 (0.400)	16.728	5.142	2.346–11.269	**<0.001**
Symptomatic infection: agree (vs. disagree)	1.705 (0.360)	22.442	5.502	2.717–11.139	**<0.001**
Community transmission: agree (vs. disagree)	1.775 (0.338)	27.575	5.898	3.041–11.438	**<0.001**
Variants control: agree (vs. disagree)	−1.942 (0.352)	30.482	0.143	0.072–0.286	**<0.001**
Equal safety: agree (vs. disagree)	1.317 (0.425)	9.591	3.733	1.622–8.592	**0.002**
Daily routine: disagree (vs. agree)	0.461 (0.413)	1.245	1.585	0.706–3.563	0.265
Risk/benefit ratio: agree (vs. disagree)	2.259 (0.390)	33.618	9.573	4.461–20.544	**<0.001**
Self-prioritization: agree (vs. disagree)	2.857 (0.373)	58.706	17.407	8.382–36.150	**<0.001**
Global vaccine justice: agree (vs. disagree)	0.949 (0.361)	6.921	2.584	1.274–5.242	**0.009**
National vaccine justice: agree (vs. disagree)	0.886 (0.345)	6.589	2.426	1.233–4.772	**0.010**

Binary logistic regression had been adjusted for prior infection, vaccine type, number of doses, hospitalization, and medical care with a significance level (Sig.) < 0.05.
Bold values - statistically significant with $p < 0.05$.

TABLE 9 Psychosocial determinants of COVID-19 vaccine booster uptake among polish healthcare professionals and students responding to COVID-19 VBH survey, December 2021–January 2022 ($n = 443$).

Determinant	B (SE)	Wald	AOR	CI 95%	*Sig.*
Severe infection: agree (vs. disagree)	1.455 (0.376)	15.002	4.283	2.051–8.941	**<0.001**
Symptomatic infection: agree (vs. disagree)	1.470 (0.328)	20.016	4.347	2.284–8.275	**<0.001**
Community transmission: agree (vs. disagree)	1.430 (0.312)	21.037	4.179	2.268–7.700	**<0.001**
Variants control: agree (vs. disagree)	−1.780 (0.317)	31.578	0.169	0.091–0.314	**<0.001**
Equal safety: agree (vs. disagree)	0.843 (0.418)	4.063	2.323	1.024–5.273	**0.044**
Daily routine: disagree (vs. agree)	−0.693 (0.404)	2.946	0.500	0.227–1.103	0.086
Risk/benefit ratio: agree (vs. disagree)	1.278 (0.358)	12.732	3.589	1.779–7.241	**<0.001**
Self-prioritization: agree (vs. disagree)	1.944 (0.325)	35.664	6.984	3.690–13.216	**<0.001**
Global vaccine justice: agree (vs. disagree)	0.917 (0.311)	8.699	2.501	1.360–4.600	**0.003**
National vaccine justice: agree (vs. disagree)	0.598 (0.299)	3.998	1.819	1.012–3.269	**0.046**

Binary logistic regression had been adjusted for prior infection and vaccine type with a significance level (Sig.) < 0.05.
Bold values - statistically significant with $p < 0.05$.

COVID-19 VBD. Similarly, agreement with the symptomatic infection (AOR: 4.347; CI 95%: 2.284–8.275), community transmission (AOR: 4.179; CI 95%: 2.268–7.700), equal safety (AOR: 2.323; CI 95%: 1.024–5.273), favorable risk-benefit ratio (AOR: 3.589; CI 95%: 1.779–7.241), and self-prioritization (AOR: 6.984; CI 95%: 3.690–13.216) had an increased odd to receive COVID-19 VBD. On the other hand, agreement with the notion of variants control decreased the odds of receiving COVID-19 VBD (AOR: 0.169; CI 95%: 0.091–0.314). Ignoring the ethical dilemmas globally (AOR: 2.501; CI 95%: 1.360–4.600) and nationally (AOR: 1.819; CI 95%: 1.012–3.269) was associated with increased odds of VBD acceptance (Table 9).

Discussion

Vaccine acceptance is perceived essential to curb the COVID-19 pandemic. The present cross-sectional study involved Polish HCPs and MUSs to understand the drivers of VBH among this particular population subset. Our findings revealed that almost three-quarters (74.5%) of the participants favored receiving the COVID-19 VBD, while 17.6 and 7.9% indicated their rejection and uncertainty, respectively. These results are consistent with the previously published studies by Rzymski et al. (13) and Babicki and Mastalerz-Migas (14), who found that about 71 and 70% of Polish adults were interested in receiving COVID-19 VBD as soon as possible. Likewise, the studies in other high-income countries, such as the Czech Republic (71.3%), Germany (87.8%), Italy (85.7%), Japan (97.9%), Singapore (73.8%), and the United States (92.2%), exhibited high levels of COVID-19 VBD acceptance, especially among HCPs (21, 26, 31–34). On the other hand, the studies in low- and middle-income countries such as Algeria (51.6%), China (60.1%), and Jordan (44.6%) exhibited lower acceptance levels, especially among non-HCPs groups (35–37). A suggested explanation for intra- and inter-country variance in VBH levels

is the respondents' health literacy level which is supposed to be higher among HCPs compared with other population subsets; therefore, the study among adult Americans by Yadete et al. (38) found lower acceptance for COVID-19 VBD (62%) than what Pal et al. (33) reported for American HCPs (92.2%). Similarly, Babicki and Mastalerz-Migas (14) found significant differences in COVID-19 VBD acceptance between Polish HCPs and non-HCPs. It is irrefutable that elements of the health belief model such as perceived susceptibility, perceived benefits, and perceived barriers contribute to this significant difference between HCPs and other groups; therefore, the goal of this study was to explore VBH drivers among HCPs, including the psychosocial benefits and barriers (39–41).

Regarding the representativeness of our sample, the latest figures published by the EU Labor Force Survey in 2021 revealed that 82.5% of Polish HCPs were females, thus justifying the female predominance of our sample (75.1%) (42). Similarly, the Organization for Economic Co-operation and Development (OECD) revealed that about 75% of Polish students enrolled in health and welfare-related programs were females, which is similar to our female students' proportion (77.6%) (43). The median age of the Polish population was 41.7 years in the year 2020, while the mean age of the sample was 31.1 ± 11.4 years, with a statistically significant difference ($Sig. < 0.001$) between professionals (38.8 ± 10.9 years) and students (22.6 ± 2.3 years) (44). According to the Public Opinion Research Center (CBOS; Warsaw, Poland) report of 2021, about 61% of the fully vaccinated Polish citizens, i.e. those who received two primer doses, received Pfizer-BioNTech, while 22% received AstraZeneca-Oxford, 12% received Moderna, and only 3% received Janssen (45). Interestingly, Pfizer-BioNTech was the most administered vaccine among our participants who received primer doses only (60.2%), followed by AstraZeneca-Oxford (21.3%), Janssen (14.8%), and Moderna (3.7%). It is worthy to note that Pfizer-BioNTech was significantly ($Sig. < 0.001$) more common among HCPs (89.3%) than MUSc (66.7%), while AstraZeneca-Oxford were significantly ($Sig. < 0.001$) more common among MUSc (22.9%) than HCPs (3.7%). The decision to prioritize HCPs for receiving COVID-19 vaccines in early 2021 in Poland can explain this significant difference between HCPs and MUSs in terms of vaccines types, as the authorization of Pfizer-BioNTech was earlier and the number of its purchased doses was higher than other COVID-19 vaccine brands (46).

Around one-third (32%) of our participants had a prior COVID-19 infection, with a different severity. As per the WHO data, by April 14, 2022, 5.9 million total COVID-19 cases were reported in Poland, representing 15.5% of the total population, with a total of 54,165,921 vaccine doses have been administered by April 10, 2022 (47). This difference could be attributed to the inclusion of only HCPs and MUSc in our study. In most participants (73%), COVID-19 infections occurred before the vaccination, while around 23% of cases occurred after the second dose of the vaccine. Similarly, Klugar et al. (21) found that around 90.9% of COVID-19 infections occurred before the first dose, while only 7.3% after the second dose among Czech HCPs.

The most common reason influencing VBD acceptance among our participants was the protection of one's health (96.3%), followed by protection of family's health (82.5%), community's health (65%) and patients' or colleagues' health (56.7%). Similarly, Attia et al. (26) found that among German university staff and students, the most commonly reported promoter was the protection of one's health (95.6%), followed by the protection of the community's health (91.6%) and family's health (91.2%). In the Czech Republic, protection of family's health (83%) was the most commonly reported promoter, followed by protection of one's health (82.7%), patients' or colleagues' health (70.4%) and community's health (66.4%) (21). Even for primer doses, the HCPs' most frequently reported reason for accepting them in the United States was the protection of family's health (86.7%), followed by protection of one's health (82.9%), and community's health (68.8%) (48). In Palestine, COVID-19 vaccine acceptance was substantially higher among the nurses who were more concerned about protecting their families and patients (49). Likewise, Szmyd et al. (50) revealed that the most commonly reported COVID-19-related concern among Polish HCPs was health deterioration in family members (70.3%) which was significantly ($Sig. < 0.001$) more common than Polish non-HCPs (55.9%). Moreover, Szmyd et al. (50) found that the physicians' family members (67.5%) were reportedly ($Sig. < 0.001$) more infected by SARS-CoV-2 than non-HCPs' family members (54.7%).

About 13.8% of our participants disagreed with the statement that COVID-19 VBD will be as safe as the primer doses, with a considerable difference between those who were triple-vaccinated (6.2%) and non-tripled vaccinated (30.9%); thus, indicating the role of post-vaccination safety and side effects in determining the attitudes toward COVID-19 VBD. Al-Qerem et al. (37) found that fear of severe side effects following COVID-19 VBD (34.1%) and the incapacity to tolerate primer doses side effects (24.6%) were the most commonly reported reasons for COVID-19 VBD rejection among Jordanian adults. Likewise, post-vaccination side effects were main reasons for COVID-19 VBH in Algeria (35). Heretofore all authorized COVID-19 vaccines have been proven safe since phase II/III trials conducted by manufacturers (51). Therefore, the continuation of phase IV studies conducted by independent institutions and regulators is vital to protect the public confidence in vaccines (51–55).

The participants who had been previously infected by SARS-CoV-2 were significantly more inclined to reject the VBD, whereas the participants who had been previously vaccinated against SARS-CoV-2 were more willing to accept the VBD. A Lebanese web-based cross-sectional study using the health belief model also supported the notion that HCPs who had been previously diagnosed with COVID-19 were significantly associated with a lower level of vaccine acceptance (56). The

misconception of natural immunity triggered by prior infection can explain this finding, and it had been one of the key drivers for vaccine hesitancy proposed by the WHO-SAGE (56, 57).

The applied comprehensive multivariable logistic regression model for the psychosocial drivers of COVID-19 VBD-related acceptance and uptake revealed that the participants who agreed with severe infection, symptomatic infection, and community transmission notions had higher odds of accepting. The effectiveness of vaccines, especially VBD, was a primary promoter for COVID-19 VBD-related acceptance among Algerian adults, American adults, German university students and staff, and Italian university students (26, 34, 35, 38). Using the ministry of health database, a nationwide population-based study from Israel found that COVID-19 VBD reduced the risk of developing COVID-19 infection and severe illness among VBD recipients (58). In our study, effectiveness against the emerging variants was a prominent determinant for VBD-related acceptance and uptake, consistent with what was found earlier among Czech HCPs and German university students and staff (21, 26).

The risk-benefit profile of VBD impacted COVID-19 booster dose acceptance because a positive association between the COVID-19 VBD acceptance and perceived susceptibility, as well as benefit. Public health campaigns are expected to highlight the postulated benefits of vaccines, especially in terms of effectiveness against symptomatic and severe infection, along with the expected harms of unvaccinated population (26, 59).

Strengths

The present study is the first to particularly target HCPs and MUSs in Poland. Participants' identity was kept confidential and anonymous to control Hawthorne's effect. The crucial findings may help promote the booster dose uptake worldwide.

Limitations

The non-random sampling technique used to recruite participants of this study may partially limited the representativeness of obtained results. HCPs and MUSc are much more aware than the general population in terms of the risk-benefit profile of vaccines, and they are more prone to show high vaccine uptake and acceptance; Hence, this study's findings should not be directly applied to the general population. The non-random sampling approach used might be linked with selection bias; whereas, the sample was relatively representative considering metropolitan areas of vast majority of participants. Some professional groups were disproportionally represented in our sample, as a few of their members participated in this study; therefore, future studies on HCPs should aim for representing professional groups proportionately. In addition, online surveys could contribute to measurement bias as fraction of participants tend not to fully respond to the all questionnaire items. Our findings will support a rationale for efficient dissemination of booster doses of COVID-19 vaccines.

Conclusion

A high vaccine acceptance among HCPs and MUSc in Poland indicate the positive attitude of these groups toward mass inoculation. The previous infection by SARS-CoV-2 significantly increased a risk of VBD hesitancy. Protection from severe infection, community transmission, good safety profile, and favorable risk-benefit ratio were the significant determinants of the COVID-19 VBD acceptance and uptake. The enhanced public health campaigns are designed to highlight the postulated benefits of vaccines and the expected harms of skipping VBD.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the Medical University of Silesia. The patients/participants provided their written informed consent to participate in this study.

Author contributions

AR: conceptualization, methodology, and formal analysis. AD: software and funding acquisition. JI and AD: validation. AD, JI, and MK: investigation. AR, JI, and SH: writing—original draft preparation. AD, MT, RW, and RK: writing—review and editing. AR and AD: supervision and project administration. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.938067/full#supplementary-material

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EDITED BY
Francesca Licata,
University Magna Graecia
of Catanzaro, Italy

REVIEWED BY
Elisavet Efstathiou,
European University Cyprus, Cyprus
Luke Shenton,
Drexel University, United States

*CORRESPONDENCE
Hiwot Dejene
hiwotdejene74@gmail.com
Derara Girma
deraragirma24@gmail.com
Leta Adugna Geleta
letaadugna72@gmail.com
Elsabeth Legesse
elsabetlegesse@gmail.com

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Vaccination timeliness and associated factors among children aged 12–23 months in Debre Libanos district of North Shewa Zone, Oromia Regional State, Ethiopia

Hiwot Dejene *, Derara Girma *, Leta Adugna Geleta * and Elsabeth Legesse*

Department of Public Health, Salale University, Fiche, Ethiopia

Background: Globally, vaccination is one of the most cost-effective interventions in promoting child survival, preventing 2–3 million child deaths annually from vaccine-preventable diseases (VPDs). In Ethiopia, timely vaccination is stated as key to the prevention of unnecessary childhood mortality from measles, pneumonia, diarrheal diseases, and other VPDs. However, Ethiopia ranked fifth among the ten countries with the most unprotected children. Furthermore, previous vaccine timeliness studies produced widely disparate results. As a result, it was suggested that more research be conducted to investigate the potential factors behind the high proportion of untimely vaccination. Therefore, this study was intended to explore the association between different factors and the proportion of vaccination timeliness administered under the Expanded Program on Immunization in Debre Libanos district, Ethiopia.

Methods: A community-based cross-sectional study design was employed from 1 May to 30 May 2021 among children aged 12 to 23 months with their mother/caregiver, who had started vaccination and had vaccination cards in the Debre Libanos. Simple random sampling techniques and pretested semi-structured questionnaires were used for data collection. At last, a multivariable logistic regression was used to identify factors associated with the vaccination timeliness.

Result: In this study, 413 children aged 12 to 23 months were interviewed with their mother/caregiver. Overall, 33.7% [95% CI (29.1–38.3)] of children received their vaccines timely. Having a female child [AOR: 2.9, 95% CI: 1.58–5.35], mother/caregiver attending primary [AOR: 6.33, 95% CI: 2.66–15.06] and secondary/above education [AOR: 5.61, 95% CI: 2.41–13.04], sufficient vaccination knowledge [AOR: 3.46, 95% CI: 1.87–6.38], mother/caregiver with least hesitant [AOR: 3.35, 95% CI: 1.51–7.41] and middle hesitant [AOR: 1.89, 95% CI: 1.05–3.58], utilization of ANC [AOR: 2.89, 95% CI: 1.32–6.33], and

giving birth at health facility [AOR: 4.32, 95% CI: 1.95–9.59] were the factors independently associated with vaccination timeliness.

Conclusion: In comparison to Ethiopia's existing vaccination coverage, the proportion of children immunized at the recommended time interval is low in the study district. Policymakers should prioritize vaccine timeliness and integrate it into childhood vaccination strategies.

KEYWORDS

vaccination timeliness, Debre Libanos, North Shewa Zone, Ethiopia, children, 12-23 months

Introduction

The WHO recommends vaccines administration within a specific time frame and schedule during the first year of life (1). The administration of vaccines at the earliest acceptable age and recommended time intervals between vaccine doses are known as vaccination timeliness. Vaccinating children at an appropriate time interval is an important mechanism to develop protective antibodies to protect against diseases adequately. Immunization coverage will only translate to disease protection if an effective vaccine is administered at the appropriate times (2).

Increased adherence to vaccine timeliness protects children before exposure and reduces morbidity by increasing community immunity and limiting the spread of infectious disease, especially during disease outbreaks (3, 4). Consequently, timely vaccination is an important complementary measure to standard metrics of vaccine coverage and provides the indicators in the context of both disease control and population immunity (5). It is critical, particularly for illnesses for which most mortality occurs in the first six months of life, for example, pertussis and Haemophilus influenzae type B (Hib). Furthermore, timely vaccination promotes maximum herd immunity and protects children who are too young to be fully immunized (6).

In contrast to the aforementioned, early vaccination can fail to generate a protective antibody against the diseases (7). Because vaccinations given too soon or without a sufficient time interval between doses may not be completely protective (lead to a false sense of protection) (8). As well, delays in vaccinations also increase the risk of infection with life-threatening VPDs at the individual level (9). These will be resulted in decreasing the intervention success and reducing herd immunity at the community level (10), in completing full vaccination series (11), and increasing the risk to the resurgence of infectious diseases that are under control (12).

Globally, vaccination is one of the most cost-effective interventions in promoting child survival, preventing 2–3 million child deaths annually from vaccine-preventable diseases (VPDs) (13). In 2019, a child died every 20 s from an illness that vaccination may have averted (14). Despite the high-global vaccination coverage of 85% in 2017, some children, especially in the developing countries, face delays in obtaining routine vaccines (15). Regardless of the significance of vaccination timeliness as a public health goal for detecting adherence to vaccination schedules, this information is frequently insufficient because coverage is the most commonly used indicator (8).

Even though vaccine timeliness is an indicator of the immunization program's quality, it has been a relatively neglected aspect of program performance (16). In line with this, globally, in low- and middle-income countries (LMICs), there is a weak supply chain management, poor access to health services, and poor service provider performance contribute to the suboptimal timeliness of vaccine schedule (17). In Sub-Saharan African (SSA) countries also, the need for country-specific further studies to clarify patterns of bottlenecks in schedule completion on the dose-specific delays (18).

In the previous studies so far, factors such as home delivery (19), low-education attainment and below four antenatal care visits (20), unplanned pregnancy and child male sex (21), highest mothers/caregivers age (22), vaccine hesitancy (5), being a multiparous mother (23), and rural children and poorest quintile (17) were independently associated with the vaccine timeliness. However, these factors are different depending on the study context (24).

In Ethiopia, vaccinating children at an appropriate time interval is the key strategy in preventing unnecessary childhood mortality from measles, pneumonia, diarrheal diseases, and other VPDs (25). However, according to the 2019 WHO/UNICEF report, Ethiopia ranked fifth among the ten countries with the most unprotected children vaccination (26).

Although it is critical for Ethiopia's public health goal, there are few studies available to generate evidence about the untimely vaccination among children. Hence, those studies have reported a low rate of child vaccine timeliness such as 55.9% in Addis Ababa (2015) (5) and 78.1% in pastoralist areas with the CORE Group Polio Project (CGPP) intervention woredas (2015) (22). However, the studies were limited to a single residential area

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TABLE 1 National and WHO recommended vaccination timelines.

Vaccine	WHO recommendation		Operational definition	
	Minimum age	Minimum interval	Delayed	Early
BCG and OPV 0	At birth	4 weeks	>4 weeks	_
DTP-HepB1-Hib1, OPV1, PCV1, Rota1	6 weeks	4 weeks	>10 weeks	<42 days
DTP-HepB2-Hib2, OPV2, PCV2, Rota2	10 weeks	4 weeks	>14 weeks	<70 days
DTP-HepB3-Hib3, OPV3, PCV3, IPV	14 weeks	4 weeks	>18 weeks	<98 days
Measles first dose	9 months	4 weeks	>10 month	<270 days
Measles second dose	15-18 months			

(5) and to pastoralist intervention woredas (22) which lacks the generalizability of evidence in a country. The results obtained were vastly discrepant from those investigations. Furthermore, the need for additional studies to identify and investigate the potential explanatory variables behind the high numbers of the untimely proportion of vaccinated in the previous studies (5, 22).

Overall, the timeliness of childhood vaccination has received close consideration in the United States and Europe (27), but in-depth investigations in low-income countries have been limited, particularly in Ethiopia. Therefore, as there had been no previous research in the Debre Libanos district of the North Shewa Zone of Central Ethiopia, the purpose of this study was to investigate the timeliness of childhood vaccination and its associated factors.

Materials and methods

Study design and setting

A community-based cross-sectional study was carried out in the Debre Libanos district, Central Ethiopia from May to June 2021. Debre Libanos district is located at a distance of 81.9 km to the northwest direction from the capital city of Ethiopia, Addis Ababa. The district has two urban and ten rural kebeles. The 2021 estimated number of populations in the district is 66,079. Of which 3,767 were children aged 12–23 months. In the district, there are two health centers and ten health posts that provide primary healthcare services to the community, including vaccination for children.

Participants

All the children aged 12 to 23 months with their mother/caregiver who had started vaccination and had vaccination cards in the Debre Libanos district were the source population. Those children who had a vaccination card but no registration date of vaccination or date of birth on the card were excluded from the study.

Sample size determination and sampling techniques

The sample size was calculated by using Epi Info STAT CALC version 7.2 with the assumptions of 95 % confidence level (CL), 0.05 margin error (d), 55.9% prevalence (P) of timely vaccinated (5), and 10% non-response rate. The final sample size was 417. Then, the sample size was allocated proportionally to the size of each kebele. At last, simple random sampling using a computer-generated random number method was used to select the study participants (i.e., mother/caregiver with their child). Then, the determined sample in each kebele was achieved through exit interviews of the mother/caregiver.

Data collection procedures

The data were collected by using a semi-structured questionnaires. The tool was developed after reviewing different literature (1, 5, 21, 28) to estimate the magnitude of the timeliness of the vaccination among children. Moreover, the questionnaires included the sociodemographic and socioeconomic status of the respondents, knowledge and vaccination hesitancy-related questions, obstetric characteristics of the mothers, and access and health service-related factors. Data were collected using a face-to-face interview with trained 22 health professionals and supervised by 3 public health professionals. Data collectors were assigned for data collection in each kebele and supervisors have been regulated and managed the data collection process. In addition to face-to-face interviews, a chart review was done to know the timelines of vaccination.

Measurements

Timeliness of vaccination: A child is considered to be timely vaccinated if the child received BCG within the first 4 weeks, OP1, Penta 1, PCV1, and Rota 1 from 6 weeks to 10 weeks, OPV 2, Penta 2, PCV 2, and Rota 2 from 14 weeks to

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TABLE 2 Sociodemographic characteristics of the respondents and the child for vaccination timeliness and associated factors among children aged 12–23 months in Debre Libanos district North Shewa Zone, Oromia Regional State, Ethiopia 2021.

Variables	Categories	Frequency	Percentage
Sex of the child	Male	169	40.9
	Female	244	59.1
Residence	Urban	125	30.3
	Rural	288	69.7
Mother/caregiver age	15-24	48	11.6
	25-35	220	53.3
	> 35	145	35.1
Marital status of the mother/caregiver	Married	277	67.1
	Divorced	87	21.1
	Single	49	11.9
Educational status of mother/caregiver	No formal education	111	26.9
	Primary education (1-8)	150	36.3
	Secondary and higher education	152	36.8
Educational status of the father	No formal education	38	13.7
	Primary education (1-8)	120	43.3
	Secondary and higher education	119	43.0
Occupational status of mother/caregiver	Housewife	134	32.4
	Farmer	145	36.1
	Employed {government/non-government}	114	26.7
	Merchant	20	4.8
Occupational status of the father	Farmer	119	43
	Employed {government/non-government}	81	19.6
	Merchant	77	18.6
Birth season of the child	Summer	68	16.5
	Autumn	104	25.2
	Spring	120	29.1
	Winter	121	29.3
Birth order of the child	1	122	29.5
	2-4	228	55.2
	≥ 5	63	15.3
Household wealth index	Lowest wealth index	130	31.5
	Middle wealth index	125	30.3
	Highest wealth index	158	38.2

18 weeks, measles vaccination first dose from 9 to 10 months and for the second dose from 15 to 18 months (1, 28, 29). On the contrary, the child was considered as early vaccinated when the child received at least one dose of the vaccine below the minimum recommended age for each antigen and considered as delayed vaccination when the child received at least one dose of vaccine above the maximum recommended age (**Table 1**).

Knowledge about vaccination: To measure knowledge on vaccination; ten knowledge questions will be used to construct a composite score. The first four questions have multiple responses and add each response from no answer to answering all the options. The rest of the six questions are based on Yes and No by giving 1 to Yes and 0 to No and selecting only one option. Based on the summation score, a score above 50% was considered as having good knowledge about childhood vaccination (5, 21).

Vaccination hesitancy: It was measured by the vaccination hesitancy assessing tool using ten Likert-scaled question items. Each item of the question has 5-point ranging from 1 (very unsatisfied) to 5 (very satisfied). A total score was calculated for each domain and transferred into a 'per cent score' by dividing the score by the possible maximum score and multiplying by 100. Based on the distribution of these sum scores, participants were categorized into three of vaccine hesitancy, dividing the

TABLE 3 Obstetric related factors for vaccination timeliness and associated factors among children aged 12–23 months in Debre Libanos district North Shewa Zone, Oromia Regional State, Ethiopia 2021.

Variables	Categories	Number	Percentage %
Number of pregnancies	Primigravida	54	13.1
	Multigravida	334	80.9
	Grand multigravida	25	6.0
Number of alive children	1 child	127	30.8
	2-4 children	214	51.8
	> = 5 children	72	17.4
Last pregnancy status	Planned	330	79.9
	Unplanned	83	20.1
ANC visit	Yes	331	80.1
	No	82	19.9
Number of ANC visit	1	129	38.9
	2	144	43.5
	≥ 3	58	17.6
TT dose received during the pregnancy	No	72	17.4
	One	194	47.0
	Two or more	147	35.6
PNC service utilization	Yes	326	78.9
	No	87	21.1
Place of delivery	At health facility	316	76.5
	Home	97	23.5

sum scores evenly into the bottom third, the middle third, and the top third of hesitancy scores among mother/caregivers (30).

Wealth index: It was measured by a simplified and updated Ethiopian wealth index equity tool. In total, 15 questions about household assets are included in the tool. As a result, the household's wealth index was divided into five quintiles (quintiles 1–5) and analyzed using principal component analysis. The poorest (40%) were in the first and second quintiles, the middle (20%) were in the third quintile, and the richest (40%) were in the fourth and fifth quintiles (31).

Operational definitions and definition of terms

Vaccination timely: was measured if a child was vaccinated within one month after the minimum age to administer the dose as recommended by WHO (1, 28, 29) (**Table 1**).

Vaccination untimely: was measured if a child was vaccinated earlier and/or delayed than the recommended age (1, 29) (**Table 1**).

Delayed vaccination: was measured as not having received the recommended vaccine doses within one month beyond the minimum age (1, 29) (**Table 1**).

Early vaccination: doses given before the minimum age (1, 29) (**Table 1**).

Data quality control

The questionnaires were translated into the local language (Afan-Oromo) and then back-translated it into English to ensure consistency. The data collectors received two days of training on the study's objective, data gathering methods, and ethical considerations. Supervisors were also trained on how to monitor the data collection techniques. In the Girar Jarso district (adjacent to the study district), a pretest was conducted on 10% of the sample size to ensure that the questions were clear and consistent before data collection. For the actual data collection, a reliability test was performed and Cronbach's alpha of >0.7 was used. During the data collection, supervisors verified each completed questionnaire for completeness, clarity, and consistency at the data collection location to take remedial steps.

Data processing and analysis

Epi Data Manager version 4.41 was used to enter data, which was then exported to STATA-16 for analysis. Data were explored to assess for the completeness and descriptive statistics were employed to describe the data based on their nature. Bivariable binary logistic regression analysis was fitted on each independent variable against an outcome variable to select candidate variables at a *p*-value of ≤0.25. Then, they entered into multivariable analysis to identify factors associated with the outcome variable and to control for confounders. Model fitness was checked by the Hosmer and Lemeshow goodness-of-fit (χ^2 = 5.466, *p*-value = 0.707). Variance inflation factor (VIF) was used to check for multicollinearity and there was no multicollinearity detected. In the multivariable binary logistic regression, a *p*-value of <0.05 with the respective adjusted odds ratio (AOR) and 95% CI was used to declare significantly associated variables.

Ethical consideration

Ethical clearance was obtained from the Ethical Review Committee of Salale University and was given to the North Shewa zone Health Bureau. And, in turn, the permission letter was obtained from the North Shewa zone Health Bureau and the Debre

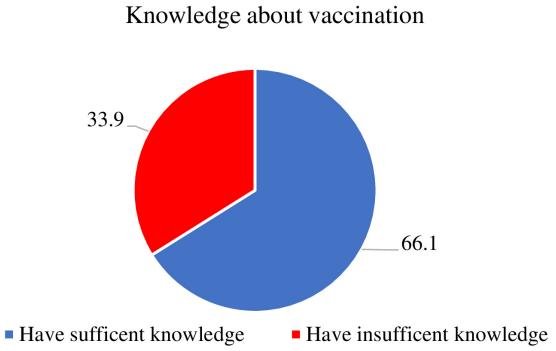

FIGURE 1
Knowledge about vaccination among mothers/caregivers.

Libanos Health office. The permission letter was given to Kebeles. Informed written consent was obtained from each study participant before the interview. The confidentiality was ensured.

Results

Socio-demographic characteristics of the respondents and the child

This study included 413 children aged 12 to 23 months who were indexed by their mother/caregiver. Approximately, 98.7% of the participants were mothers, with the remaining 1.7% caregivers. The mothers/caregivers' mean (SD) age was 29.5 (5.96) years. Half of the respondents belonged to the age group (24–33). The majority of respondents (69.7%) were rural residents. About two-thirds (67.1%) were married, and more than a quarter (26.9%) lack formal education. Regarding the children's characteristics, the mean (SD) age of the children in months was 16.1 (3.1). Approximately 40.9% of the children were males, and one-third were born in the spring and winter seasons (**Table 2**).

Obstetric-related factors

The majority of respondents, 334 (80.9%), had at least one pregnancy or more. The average (SD) number of pregnancies per woman was 3 (1.0). More than three-quarters of the previous pregnancy status was planned, and the majority of respondents had ANC visits for the previous child pregnancy. More than two-thirds of the participants (78.9%) had their current child at the health facility, and the majority (76.5%) used the postnatal care service (**Table 3**).

Mother-related factors

About two-thirds of the participants (66.1%) had sufficient knowledge about vaccination. **Figure 1**: knowledge about vaccination among mothers/caregivers.

About half (43.8%) of the respondents were middle hesitant about vaccination followed by the most hesitant, which accounts for (37.3%) (**Figure 2**: vaccination hesitancy among mothers/caregivers).

Access-related factors

About 59.3% of the respondents took less than 30 min to go to the vaccination site and around 40.9% of the respondents did not use transportation to get to the vaccination site. Nearly, two-thirds of the participants get information about vaccination from health extension workers (**Table 4**).

Vaccination timeliness

Overall, 33.7% [95% CI: 29.1–38.3] of the children received their vaccinations at the recommended time interval. Of the total 66.3% of children who did not receive vaccinations at the recommended interval, 25.5% [95% CI: 20.9–30.1] and 74.5% [95% CI: 69.9–79.1] received their vaccinations earlier and later than the recommended time interval, respectively (**Figure 3**: vaccination timeliness among children aged 12–23 months).

Vaccination timeliness for specific vaccines

About 96.4, 86.0, 81.4, and 77.0% of children received BCG, Penta1, Penta3, and measles vaccines at the recommended time interval, respectively. Moreover, 0.7, 6.3, and 1.9% of children received Penta1, Penta3, and measles vaccines earlier than the acceptable time interval, respectively. On the contrary, 3.6, 13.3, 12.3, and 21.1% of children took BCG, Penta1, Penta3, and measles vaccines later than the acceptable time interval, correspondingly (**Figure 4**: vaccination timeliness for specific antigen among children aged 12–23 months).

Perceived reasons for not vaccinating children timely

The reasons given by mothers/caregivers for not attending vaccination schedules timely were 32.8% forgetfulness, 17.2% being busy with other commitments, and the rest being unaware of the schedule, being distant from the site, and the child being

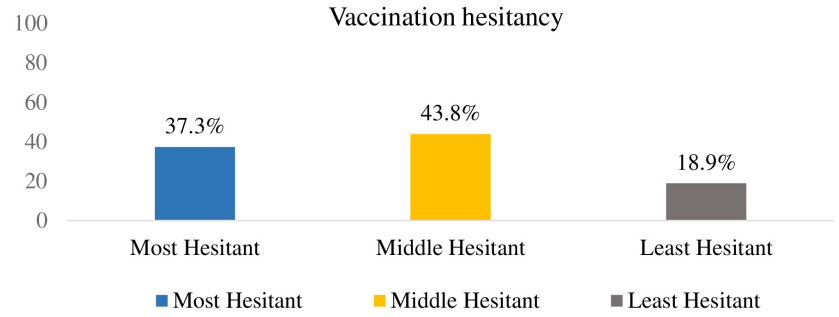

FIGURE 2
Vaccination hesitancy among mothers/caregivers.

TABLE 4 Access-related factors for vaccination timeliness and associated factors among children aged 12–23 months in Debre Libanos district North Shewa Zone, Oromia Regional State, Ethiopia 2021.

Variables	Categories	Number	Percentage %
Time taken to vaccination site	< 30 min	245	59.3
	≥ 30 min	168	40.7
Mode of transportation	On foot	169	40.9
	By vehicle	32	7.7
	By bus	31	7.5
	By cart/ animal	181	43.8
Source of information	Mobile	67	16.2
	Television	35	8.5
	Radio	43	10.4
	Health extension worker	268	64.9
Place of vaccination received	Health center	214	51.8
	Health post	199	48.2

sick at the time of the vaccine schedule (**Figure 5**: perceived reasons for not vaccinating children timely).

Factors associated with vaccination timeliness

In the bivariable logistic regression analysis: a place of residence, sex of the child, educational status of the mother/caregiver, marital status of the mother/caregiver, birth order, knowledge about vaccination, vaccination hesitancy, number of alive children, last pregnancy status, utilization of ANC, utilization of TT dose, place of delivery, and utilization of PNC were candidates for multivariable logistic analysis.

In multivariable logistic regression analysis, variables such as sex of the child, educational status of the mother/caregiver,

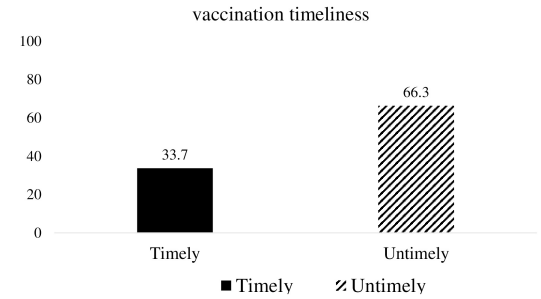

FIGURE 3
Vaccination timeliness among children aged 12-23 months.

knowledge about vaccination, vaccination hesitancy, utilization of ANC, and place of delivery were independently associated with vaccination timeliness.

Accordingly, having a female child was found two times [AOR: 2.9, 95% CI: 1.58–5.35] more likely to get vaccination on time than having a male child. Mother/caregiver who attended primary and secondary and above education was six [AOR: 6.33, 95% CI: 2.66–15.06] and five times [AOR: 5.61, 95% CI: 2.41–13.04] more likely to vaccinate their children timely compared with the mother/caregiver with no formal education, respectively.

A mother/caregiver having sufficient knowledge about vaccination was found to be three times more likely to vaccinate their children timely than a mother/caregiver having insufficient knowledge. [AOR: 3.46, 95% CI: 1.87–6.38] and also a mother/caregiver with the least hesitant and middle hesitant three [AOR: 3.35, 95% CI: 1.51–7.41] and two [AOR: 1.89, 95% CI: 1.05–3.58] times more likely to vaccinate their child timely than the most hesitant, respectively.

The utilization of ANC was another factor that affected the timeliness of vaccination. A mother/ caregiver who utilized ANC was three times more likely to vaccinate their child within the recommended time interval than her counterparts. [AOR: 2.89, 95% CI: 1.32–6.33]. Similarly, place of delivery was an

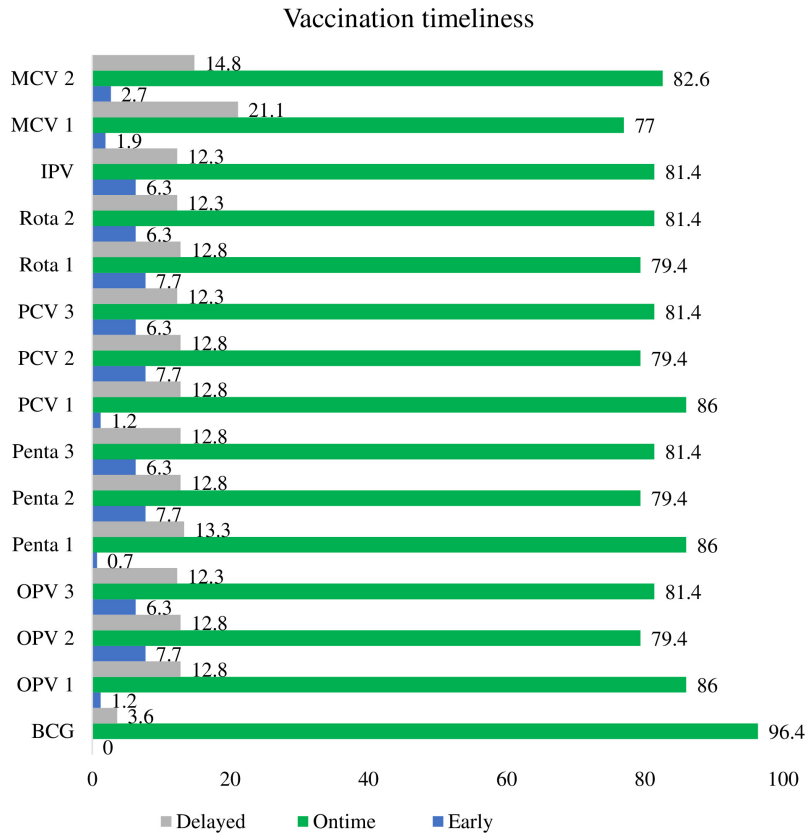

FIGURE 4
Vaccination timeliness for specific antigen among children aged 12-23 months.

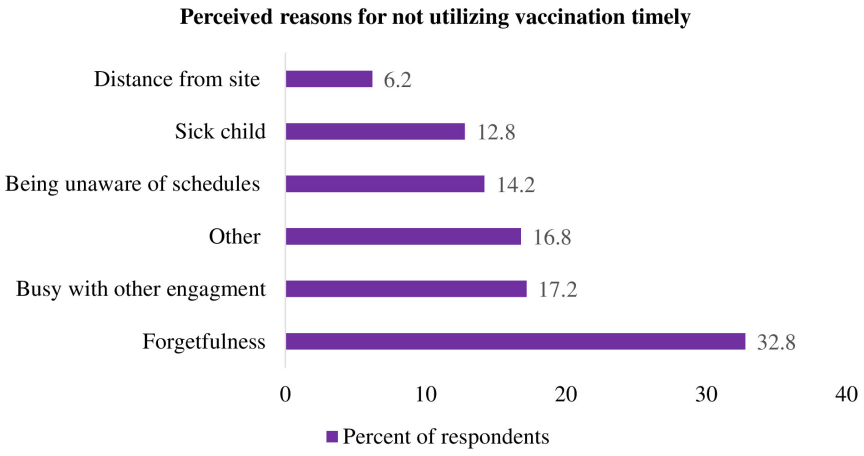

FIGURE 5
Perceived reasons for not vaccinating children timely.

independent factor associated with the timeliness of vaccination. A mother who delivered child in a health facility increases the rate of vaccinating her child within the recommended time interval by four times than a mother who delivered the child at home [AOR: 4.32, 95% CI: 1.95–9.59] (Table 5).

Discussion

This study measures the magnitude and associated factors of vaccination timeliness among children aged 12–23 months. Accordingly, 33.7% of the children received

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TABLE 5 Factors associated with vaccination timeliness among children aged 12–23 months in Debre Libanos district, North Shewa Zone, Oromia Region State, Ethiopia 2021.

Variable	Categories	Vaccination timeliness		COR (95% CI)	AOR (95% CI)
		Timely n (%)	Untimely n (%)		
Residence	Urban	54 (43.2)	71 (56.8)	Ref	Ref
	Rural	85 (29.5)	203 (70.5)	1.82 [1.17-2.81]	1.34 [0.70-2.58]
Sex of the child	Male	29 (17.2)	140 (82.8)	Ref	Ref
	Female	110 (45.1)	134 (54.9)	3.96 [2.47-6.35]	2.91 [1.58-5.35] **
Educational status of the mother/caregiver	No formal education	13 (11.7)	98 (88.3)	Ref	Ref
	Primary	65 (43.3)	85 (56.7)	5.76 [2.97-11.18]	6.33 [2.66-15.06] *
	Secondary and above	61 (40.1)	91 (59.9)	5.05 [2.60-9.81]	5.61 [2.41-13.04] *
Marital status of the mother/caregiver	Married	120 (43.3)	157 (56.7)	3.39 [1.58-7.27]	2.73 [0.99-7.49]
	Divorced	10 (11.5)	77 (88.5)	0.57 [0.22-1.54]	0.36 [0.59-1.38]
	Single	9 (18.4)	40 (81.6)	Ref	Ref
Birth order	1	60 (47.2)	67 (52.8)	3.07 [1.45-6.46]	0.48 [0.10-2.27]
	2-4	57 (26.6)	157 (73.4)	2.55 [1.26-5.17]	2.81 [0.99-17.83]
	≥ 5	22(30.6)	50 (69.4)	Ref	Ref
Knowledge about vaccination	Sufficient knowledge	109 (39.9)	164 (60.1)	2.44 [1.52-3.90]	3.46 [1.87-6.38] **
	Insufficient knowledge	30 (21.4)	110 (78.6)	Ref	Ref
Vaccination hesitancy	Most hesitant	32 (20.8)	122 (79.2)	Ref	Ref
	Middle hesitant	70 (38.7)	111 (61.3)	2.40 [1.47-3.92]	1.89 [1.05-3.58] *
	Least hesitant	37 (47.4)	41 (52.6)	3.44 [1.91-6.21]	3.35 [1.51-7.41] **
Number of alive children	1 child	60 (47.2)	67 (52.8)	2.04 [1.11-3.74]	3.47 [0.26-9.51]
	2-4 children	57 (26.6)	157 (73.4)	0.83 [0.46-1.48]	0.31 [0.13-0.73]
	> = 5 children	22(30.6)	50 (69.4)	Ref	Ref
Last pregnancy status	Planned	128 (38.8)	202 (61.2)	4.15 [2.12-8.12]	3.71 [0.63-5.42]
	Unplanned	11 (13.3)	72 (86.7)	Ref	Ref
Utilization of ANC	Yes	123 (37.2)	208 (62.8)	2.44 [1.35-4.40]	2.89 [1.32-6.33] **
	No	16 (19.5)	66 (80.5)	Ref	Ref
Utilization of TT dose	No	20 (27.8)	52 (72.2)	Ref	Ref
	1 dose only	60 (30.9)	134 (69.1)	1.16 [0.64-2.12]	1.22 [0.54-2.78]
	2 and more dose	59 (40.1)	88 (59.9)	1.74 [0.95-3.22]	1.73 [0.74-4.05]
Place of delivery	Home	22 (22.7)	75 (77.3)	Ref	Ref
	At health facility	117 (37.0)	199 (63.0)	2.00 [1.18-3.39]	4.32 [1.95-9.59] *
Utilization of PNC	Yes	123 (37.7)	203 (62.3)	2.69 [1.49-4.84]	2.23 [0.76-6.51]
	No	16 (18.4)	71 (81.6)	Ref	Ref

*Statistically significant at *P*-value of ≤0.05, **statistically significant at *P*-value of <0.001.

their recommended vaccination timely. The study from Gondar city, north-west Ethiopia reported a consistent finding of 31.9% (32). A similar population age group, sampling technique, and use of an outcome ascertainment tool may result in consistent findings. However, this finding is higher than 6.2% reported in Menz Lalo district of Northeast Ethiopia (21) and 23.9% in Toke Kutaye district, central Ethiopia (28). This disparity could be attributed to variations in study approach, location, healthcare access, and study period.

In contrast, this finding is below the Ethiopian DHS 2019 report of 40% (33). The difference could be attributed to sample size, sampling methods, and geographical area coverage. Moreover, this study is lower than a study from Addis Ababa, Ethiopia that showed vaccination timeliness of 55.9% (5). This could be because the current study was conducted among children living in rural areas and is a community-based study, as opposed to the Addis Ababa study.

Having a female child increased the likelihood of receiving vaccinations timely. Comparable finding was reported from Senegal (34). This could be encouraged in the rural community to maintain equality and a positive attitude toward avoiding child sex preferences. Because, in Ethiopia, there is a sex preference for male child in terms of timely vaccination (21).

A mother/caregiver who attends formal education is more likely to vaccinate her child at the recommended time interval. This finding is comparable with the studies done in Ethiopia (32), India (16), and Iran (35) indicates that mother/caregiver's attending formal education reduce the risk of untimely child vaccinating. This is because a higher education level can facilitate the mother's/caregiver's communication with health workers, influencing their awareness of seeking and utilizing public health services such as child vaccination (32).

Moreover, having sufficient knowledge about vaccination increases the odds of vaccinating the child at the recommended schedule. Similarly, studies done in the northeast Ethiopia (21) and central Ethiopia (28)showed that insufficient knowledge about vaccination increased the delay in vaccinating at the recommended interval. The possible explanation is that knowledge lessens the likelihood of having negative feelings about childhood vaccination, which increases practice and timeliness. Also, knowing the vaccination schedule, VPDs, and reasons for vaccination will increase the likelihood of vaccinating children on time (28). As well, vaccine hesitancy significantly increased the odds of untimely vaccination. This figure is supported by a study done in Addis Ababa (5). This could be because if the mother's/caregiver's were more hesitant about the vaccine, it would increase the delay in vaccine acceptance/refusal.

In the current study, the use of ANC was realized to be another factor that increases vaccination timeliness. A study conducted in northeast (32) and northwest (32) Ethiopia found that ANC utilization have decreased vaccination delays. In this study, giving birth at a health facility was also significantly associated with vaccine timelines. This finding is supported by studies conducted in Ethiopia by analyzing EDHS data (36) and Kutaye district (28), which revealed that if the mother delivers the child at a health facility, it increases the timely initiation of vaccination at the recommended interval. This is because mothers who delivers the child in a health facility had a greater opportunity of being advised about the benefits of EPI services and getting health education (28).

Limitation of the study

The cross-sectional nature of the study design does not allow causality ascertainment. The study participants were selected based on the presence of immunization cards, which might lead to selection bias because infants whose parents did not keep their immunization cards were excluded from the study.

Conclusion

The proportion of children vaccinated at the recommended time interval is low in the study area as compared to the current performance of the vaccination coverage in Ethiopia. Not all children aged 12–23 months in the study area were vaccinated with their recommended vaccine at the schedule. The factors that increase the likelihood of timely vaccination of children were mother/caregiver attended primary and above education level, having female sex child, sufficient knowledge about vaccination, middle and less hesitant for a vaccine, utilization of ANC, and giving birth at the health facility. Therefore, in order to adhere to the recommended schedule, mothers/caregivers should receive prompt attention on the identified factors through a plausible program. Furthermore, to improve children's immunological wellbeing, policymakers should emphasize and incorporate vaccine timeliness monitoring indicators into childhood vaccination strategies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Salale University Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

HD made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data. DG, LG, and EL were involved in the analysis, interpretation of data, and drafting the manuscript or revising it critically for important intellectual content. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Alessandra Casuccio,
University of Palermo, Italy

REVIEWED BY
Iffat Elbarazi,
United Arab Emirates University,
United Arab Emirates
Francesca Licata,
University Magna Graecia of
Catanzaro, Italy

*CORRESPONDENCE
Qing Niu
niuqing@seu.edu.cn
Hui Jin
jinhui_hld@163.com

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Changes of factors associated with vaccine hesitancy in Chinese residents: A qualitative study

Sigui Long[1,2], Jingying Wu[1,2], Shile Wang[1,2], Yaqi Zhao[1,2], Jianli Wang[1,2], Shuangyu Zhao[1,2], Qing Niu[1,2]* and Hui Jin[1,2]*

[1]Department of Epidemiology and Health Statistics, School of Public Health, Southeast University, Nanjing, China, [2]Key Laboratory of Environmental Medicine Engineering, Ministry of Education, School of Public Health, Southeast University, Nanjing, China

Introduction: There is an urgent need to address vaccine hesitancy to achieve booster vaccination. This study aimed to reveal the factors associated with vaccine hesitancy (including COVID-19 vaccine) among Chinese residents, address modifications of the factors since the previous year, and propose vaccination rate improvement measures.

Materials and methods: This qualitative return visit study was performed between January and mid-February 2022, following the last interview conducted between February and March 2021. According to an outline designed in advance, 60 Chinese residents from 12 provinces participated in semi-structured interviews.

Results: Vaccine safety was the biggest concern raised by respondents, followed by self-immunity and vaccine effectiveness, eliciting concern since the interview last year. Notably, online media accounted for a more significant portion of suggestion sources than before, and fear of pain was a novel factor affecting vaccine hesitancy. Moreover, unlike other areas, those from provinces with a per capita gross domestic product of 3–5 (RMB 10,000) reported less concern about vaccine price and effectiveness. They tended to seek advice *via* online media less and were greatly influenced by vaccination policies.

Conclusions: Influential factors of vaccine hesitancy among Chinese residents are changing dynamically. Monitoring these trends is essential for public health measures and higher vaccination levels.

KEYWORDS

vaccine hesitancy, qualitative study, China, influential factor, return visit

Introduction

The global confirmed coronavirus disease (COVID-19) cases were still on the rise, and as of 18 February 2022, they had reached 419.0 million (1). On the same day, 137 new confirmed cases in 31 provinces were reported in China (2), and the fifth wave of COVID-19 in Hong Kong has drawn extensive attention. In the last 2 years, travel bans,

mask-wearing, isolation, and nucleic acid testing have been rigorously implemented to respond to the pandemic. Unfortunately, the rapid spread of Delta and Omicron (3) has become a severe obstacle to ending the pandemic. Chronic prevention and control measures are insufficient to curb this pandemic. Vaccination effectively suppresses pandemics, alleviates their socioeconomic impact, and is an established strategy to prevent infectious diseases (4).

A recent study found that taking two doses of the BNT162b2 vaccine had 93.7% and 88.0% efficacy against alpha and delta variants, respectively (5). The Omicron variant has become the dominant epidemic strain globally. The neutralization efficiency against the Omicron variant was enhanced 100 times after receiving the third dose of the BNT162b2 vaccine (6). Receiving the third mRNA-1273 vaccination enabled us to detect neutralizing titres against the Omicron variant in all participants six months later (7). In addition, receiving a heterologous boost of adenovirus-vectored vaccine (AdV) after receiving two doses of inactivated vaccines (IAV) induced neutralizing antibody levels five times higher than a homologous boost (8). The above results suggest that a vaccine booster is vital for superior protection and reduces the risk of variant infection.

The absence of devastation caused by vaccine-preventable diseases and the spread of anti-vaccine movements through social media (9) undermine the role of vaccines in defending against infectious diseases. Being hesitant about receiving a vaccination or refusing vaccination when one is capable of doing so, namely "vaccine hesitancy," was on the list of the top 10 threats to global health (10).

An online survey (11), carried out from January to March 2021 in seven cities in China, estimated the rate of COVID-19 vaccine hesitancy to be approximately 15.6%. The student group ranked first (23.9%). Those who received negative information about the COVID-19 vaccine or questioned the source of information were more likely to delay vaccination. In the subsequent 4 months, another investigation illustrated that 56.4% of diabetes patients in two hospitals had COVID-19 vaccine hesitancy, resulting from safety concerns and opinion discrepancies with doctors (12). In mid-August 2021, 22.2% of healthcare students in northwestern China showed unwillingness to COVID-19 vaccination due to vaccine safety and effectiveness (13). Another online study in the same month discovered that the rate of COVID-19 vaccine hesitancy among Chinese adults aged 18 years or older was modest (∼ 8.4 %). Vaccination is promoted by lower vaccine conspiracy beliefs, more convenient vaccination services, and more trust in doctors and vaccine developers (14). These findings showed a downward trend in collective COVID-19 vaccine hesitancy among Chinese residents, but the hesitancy of specific groups (e.g., people with other health problems and students) was higher. The overall inoculation rate in China exceeded 85% (15). Therefore, it is imperative to understand and address vaccine hesitancy to bring COVID-19 under control and return to the world without severe acute respiratory syndrome coronavirus (SARS-CoV-2).

Researchers conduct qualitative studies by observing or interacting with people to collect data relevant to the phenomenon of interest. Last spring, we conducted in-depth interviews with Chinese residents to identify the factors influencing vaccine hesitancy. The study demonstrated that vaccine safety, price, effectiveness, and acquisition of professional suggestions were responsible for the reluctance to vaccination (16). Given that vaccine hesitancy is complicated and sets a specific phenomenon, differing in time, place, policies, and vaccines (17, 18), we paid a return visit to capture their perceptions and attitudes toward vaccination the following year, within the context of variant ravaging and vaccine booster popularization. The two interview results were compared to determine the factors influencing vaccine hesitancy in China. Dynamic monitoring of vaccine hesitancy is crucial for identifying unsolved barriers to herd immunity and novel factors affecting vaccination decisions. This study sought to elucidate the factors hindering vaccine uptake, address their modifications since the previous year, and provide policymakers with reference in facilitating booster vaccination to contain the COVID-19 pandemic.

Materials and methods

Study design

This qualitative study was conducted using an individual in-depth interview about vaccine hesitancy. Interviewers primarily used open-ended questions to avoid influencing the participant's opinions and were required to interact with interviewees based on the interview framework. Researchers guided and controlled the interview content appropriately to prevent the interviewee from expressing bias.

The semi-structured interview framework consisted of three components: (1) general information— mainly comprising the participants' age, gender, occupation, annual family income, and education level; (2) 12 open-ended questions about self-funded vaccine hesitancy, based on health beliefs and planned behavior theory, including personal knowledge and attitude toward vaccines, other people's impact, and other factors influencing vaccination; and (3) four types of open-ended questions enquiring about COVID-19 vaccines: (a) how well people understand information about COVID-19 vaccines; (b) how they get access to information about COVID-19 vaccines; (c) how they get to know COVID-19 vaccines; and (d) how their lifestyles have changed since the pandemic outbreak. Section one and two were consistent with the original interview guide used in the first study. Section three was newly added, in which data were not coded but used to determine what people think about

COVID-19 vaccines. The detailed interview guide is displayed in Supplementary Table S1.

Study participants

This study followed Chinese residents who participated in the interviews from February to March 2021 (16). The respondents were interviewed face-to-face, by telephone, or *via* the Internet. Individual face-to-face, in-depth interviews were preferred. Restricted by local epidemic prevention and control measures or cross-region population mobility, face-to-face video calls *via* the Internet were used. Those participants who had poor network communication were interviewed by telephone. This study was conducted from January to mid-February 2022. Based on the last interview quality assessment, cooperation with the interview, availability of revisits, and willingness to be interviewed, 60 participants from the last interview were included in this study. The participants came from 12 provinces across mainland China: Anhui, Gansu, Guangxi, Hebei, Henan, Jiangsu, Jilin, Ningxia, Qinghai, Shandong, Xinjiang, and Zhejiang. The Ethics Committee of Wuxi Center for Disease Control and Prevention (2020No10) approved this study. Informed consent was obtained before completing the interview. Each participant was informed that the responses were used for research only, and personal information was protected. They could quit whenever they had issues with the ethics of this study.

Data collection

Semi-structured interviews were conducted to analyse vaccine hesitancy among Chinese residents and its corresponding influential factors. Before the interview, the interviewees were consulted about when and where to interview. Furthermore, the interviewer requested permission to audio-record the interviews. The interviewer remained neutral throughout the interviews.

Quality control and data analysis

The open-ended questions were designed in advance. The perspectives of instructors and experts on disease control and prevention concerning the research topic and design were collected through pre-interviews. According to feedback, the interview outline was further revised for formal interviews that proceeded smoothly. Researchers possessing medical literacy, communication skills and enthusiasm for disease control and prevention work are the local people in the participants' areas, pivotal to conducting the interviews smoothly and guaranteeing research accuracy (19). When collecting data, we concentrated on the oral expressions of the questions. We remained neutral to guarantee that the results were honest reflections of the participants' thoughts. The audio recordings were transcribed into text within a day after the interview. The text was later analyzed following Colaizzi's 7-step analysis method (20) and coded with the qualitative analysis software NVivo 11.0 (QSR International, Melbourne, Australia). For data entry, the interviewers cleaned and validated the data and provided a clear definition of the categorized framework. Then we coded the data based on the definition (coded twice by two independent coders); internal consistency was also checked. When there were issues, the coders would discuss them until a consensus was reached.

Results

Demographic characteristics of participants and classification framework

Sixty residents from 12 Chinese provinces with varying gross domestic product (GDP) levels (21) completed the interview, and 61.7% ($n = 37$) were female. The participants were categorized into four groups: healthcare workers (n=8), adults aged 18–59 years ($n = 26$), adults aged 60 years and above ($n = 12$), and parents of children aged 0–6 years ($n = 14$). See Table 1 for more detailed sociodemographic information about the respondents. When asked about the willingness to accept the COVID-19 vaccine booster, 93.3% answered "Yes" and believed vaccines would contain the COVID-19 pandemic. These responses verified the decline in vaccine hesitancy among participants, which aroused interest in discovering the factors behind vaccine hesitancy.

Based on the responses to the open-ended questions, the factors in the qualitative data were separated into three categories for subsequent analysis: background, physical, and psychological factors, each of which had a range of sub-categories under which different levels were set up, as shown in Supplementary Table S2. Supplementary Table S2 shows both the original themes and new themes. Supplementary Table S3 presents an overview of vaccine hesitancy factors among Chinese residents.

Compared with the previous study (16), the principal findings of the interviews are as follows. Vaccine safety still occupied the first-factor influencing vaccine hesitancy, followed by self-immunity, which increased by six. Vaccine effectiveness ranked third, climbing by one place. Social network support and policy orientation moved to fourth and tenth place, respectively. Noticeably, online media constituted a more substantial portion of advice sources than before, second only to medical staff. The frequencies of the top 10 factors are shown in Figure 1.

The similarities and discrepancies between the four population groups are shown in Figure 2A. Medical staff

TABLE 1 Demographic characteristics of the study participants ($N = 60$).

Demographic characteristics	Healthcare workers	Adults aged 18–59 years	Older people over 60	Parents of children aged 0–6 years	Total, *n* (%)
Gender					
Male	0 (0.0)	13 (50.0)	6 (50.0)	4 (28.6)	23 (38.3)
Female	8 (100.0)	13 (50.0)	6 (50.0)	10 (71.4)	37 (61.7)
GDP per capita of permanent residence (RMB 10,000)					
3–5	2 (25.0)	5 (19.2)	1 (8.3)	3 (21.4)	11 (18.3)
5–8	3 (37.5)	11 (42.3)	0 (0.0)	3 (21.4)	17 (28.3)
>8	3 (37.5)	10 (38.5)	11 (91.7)	8 (57.1)	32 (53.3)
Education level					
Junior high school	0 (0.0)	3 (11.5)	4 (33.3)	0 (0.0)	7 (11.7)
High school graduate or equivalent	0 (0.0)	3 (11.5)	3 (25.0)	3 (21.4)	9 (15.0)
College or equivalent	8 (100.0)	18 (69.2)	5 (41.7)	10 (71.4)	41 (68.3)
Master's diploma or above	0 (0.0)	2 (7.7)	0 (0.0)	1 (7.1)	3 (5.0)
Annual household income (RMB 10,000)					
<5	1 (12.5)	5 (19.2)	1 (8.3)	1 (7.1)	8 (13.3)
5–10	1 (12.5)	9 (34.6)	5 (41.7)	5 (35.7)	20 (33.3)
11–15	4 (50.0)	6 (23.1)	2 (16.7)	2 (14.3)	14 (23.3)
>16	2 (25.0)	6 (23.1)	4 (33.3)	6 (42.9)	18 (30.0)
Occupation					
Government agencies and institutions		5 (19.2)	0 (0.0)	6 (42.9)	11 (21.2)
Business/enterprise		2 (7.7)	1 (8.3)	3 (21.4)	6 (11.5)
Production staff/worker		0 (0.0)	1 (8.3)	1 (7.1)	2 (3.8)
Full-time student		14 (53.8)	0 (0.0)	0 (0.0)	14 (26.9)
Soldier		1 (3.8)	1 (8.3)	0 (0.0)	2 (3.8)
Retired		0 (0.0)	9 (75.0)	0 (0.0)	9 (17.3)
Else		4 (15.4)	0 (0.0)	4 (28.6)	8 (15.4)
Number of children					
1				9 (64.3)	9 (64.3)
2				5 (35.7)	5 (35.7)
Has the child played in last year's influenza vaccine					
Yes				6 (42.9)	6 (42.9)
No				8 (57.1)	8 (57.1)
Total, *n* (%)	8 (13.3)	26 (43.3)	12 (20.0)	14 (23.3)	60 (100.0)

and adults aged 18–59 emphasized vaccine safety, price, effectiveness, and self-immunity, which differed from the other two groups. The elderly aged 60 years and above focused on policy orientation and support from family, except for vaccine safety and effectiveness. Furthermore, support from family and advice from medical staff were two factors valued by parents of children aged 0–6 years. Moreover, those from provinces with a per capita GDP of 3–5 (RMB 10,000) were less concerned with vaccine price and effectiveness, sought advice *via* online media less, and were considerably affected by vaccination policies (Figure 2B).

Vaccine safety

In this interview, trust in vaccine safety was the most crucial factor affecting vaccine uptake, which was aligned with the previous year's results. When asked about the most significant worries about vaccination, words such as "security," "side effect," and "adverse reaction" were repetitively stated, a total of 129 times. People emphasized the fear of possible adverse reactions occurring after vaccination. An adult aged 18–59 mentioned, "It is unacceptable for me to be injured due to vaccination." Adverse reactions such as fever, chills, and swelling upset those with poor immunity and ill resistance, particularly in children

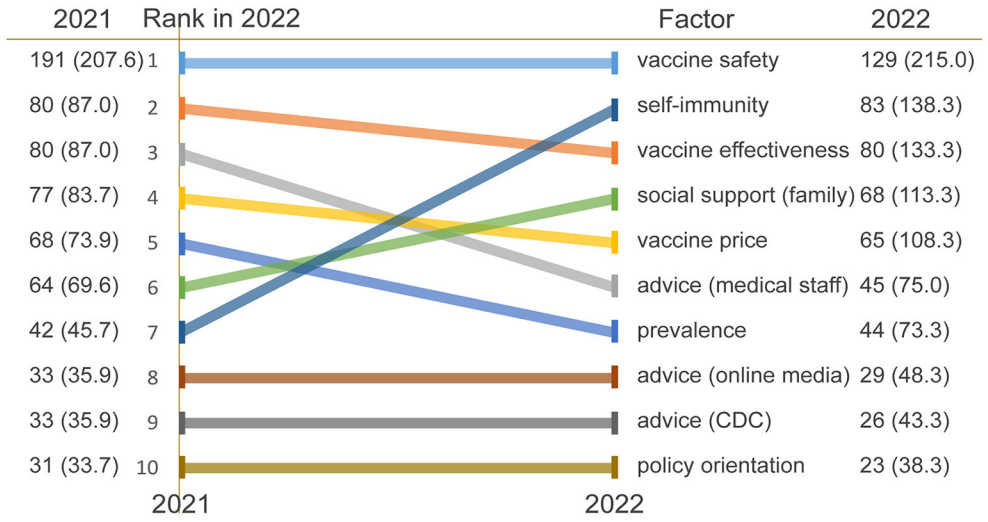

FIGURE 1
Top 10 factors influencing vaccine hesitancy in 2022. Respondents gave more than one response, so totals do not equal 100. CDC, Center for Disease Control and Prevention.

and the elderly. A growing number of people have negative thoughts about the safety of biological agents for which adverse events are to blame. Worse, some feared that adverse events overpassed their effectiveness. One medical staff said, "It is essential to mention the source's reliability and safety first. It is not cost-effective to cause side effects outweighing its protective effect due to vaccination." Except for adverse events, most residents stressed that another concern was transportation, cold-chain preservation, and contamination during shipping. By synthesizing the two interview results, vaccine safety could be a decisive factor in vaccination. People appear to refuse vaccines when they have issues with vaccine safety.

Self-immunity

Self-immunity replacing vaccine safety has become the most influential factor influencing vaccine hesitancy in the elderly. Furthermore, self-immunity caught considerable attention in the remaining three groups. For example, self-immunity rose from seventeenth place to fourth among healthcare workers.

When asked about the need for the vaccine, terms such as "children with poor immunity," "strengthen resistance," and "improve immunity" were mentioned. One parent described that concern about poor immunity contributed to vaccine uptake: "Antibody vanishes entirely in 6 months after birth, leading to fragile health. Vaccination helps children develop antibodies to improve immunity and prevent diseases." This answer was consistent with why most adults choose to be vaccinated. They desired to improve their resistance against communicable diseases, protect their health, and prevent infection *via* vaccination. Like parents, the elderly, who tend to have poorer physical fitness and weaker immunity, also emphasize fitness conditions in determining whether to vaccinate. Specifically, one elderly person expressed, "I would take pneumococcal vaccines if I am prone to pneumonia. Supposed my lungs work well, I will not take vaccination into account." Some respondents primarily increased nutrient, fruit, and vegetable intake to enhance self-immunity during the epidemic. Those with potent immunity thought it unnecessary to receive the vaccination. One participant highlighted this, "Vaccination is not a must for those with strong immunity; for people with ill health, influenza vaccines may decrease infection risk." The balance between self-immunity and the disease's destructive power is decisive when deciding whether to vaccinate. Vaccination may not occur if self-immunity is sufficient to cope with infectious disease hazards.

Vaccine effectiveness

Overall, vaccine effectiveness was the third most mentioned factor influencing vaccine hesitancy. Among adults aged 18–59 years, vaccine effectiveness was second only to vaccine safety as a significant contributing factor to vaccine hesitancy, as mentioned 44 times. It is worth noting that healthcare workers and the elderly focused more on vaccine effectiveness than in the last interview.

Most participants expressed concerns about antibody titer, duration of antibody maintenance, virus mutation coverage, disease prevention effectiveness, and specific vaccine responses. Take an old man, for example, "I am worried

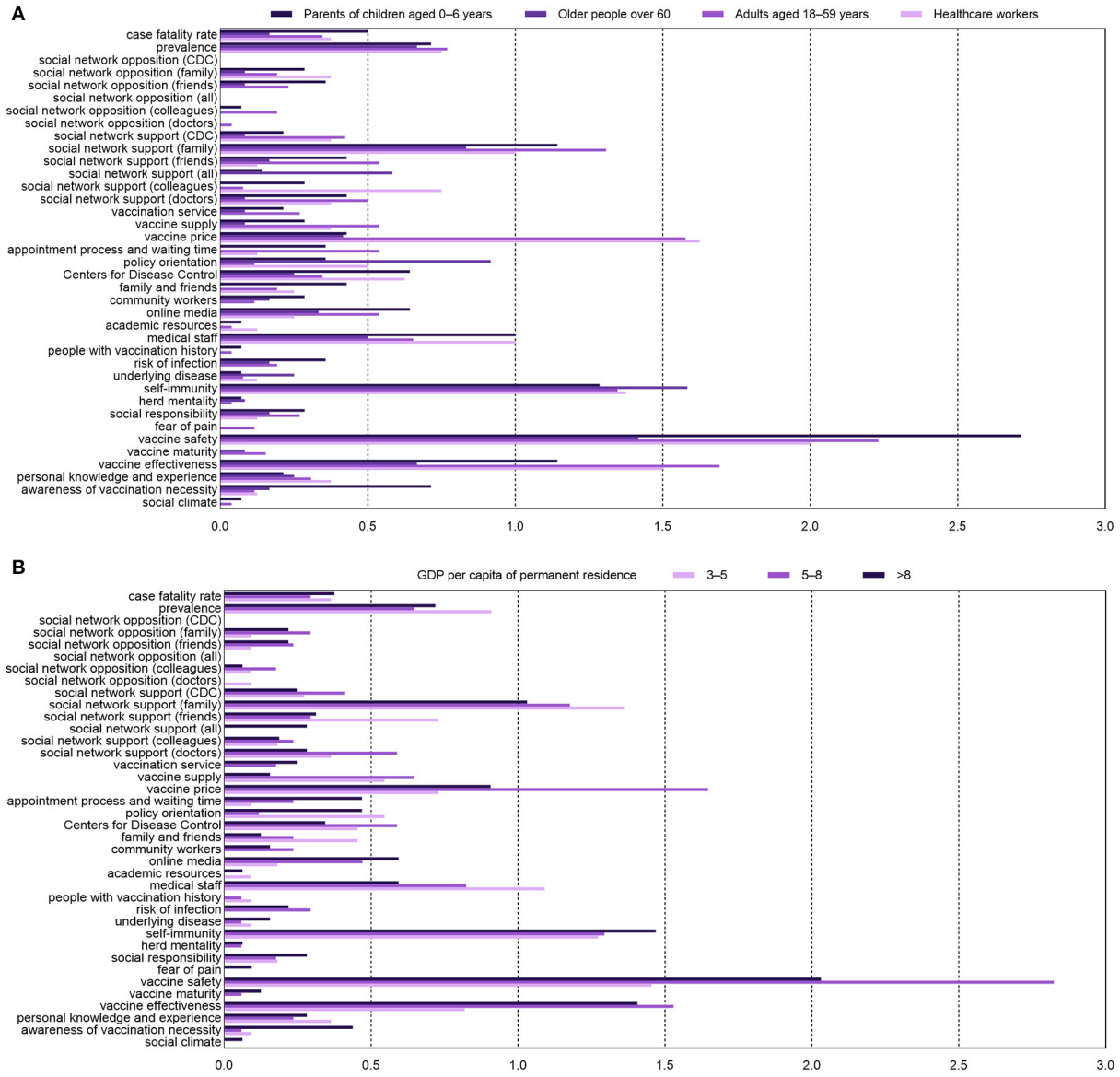

FIGURE 2
Frequency distribution of factors influencing vaccine hesitancy of four population groups **(A)** and areas with various per capita gross domestic product (GDP) of 2021 **(B)**.

about whether the vaccine is effective, like the COVID-19 vaccine booster. I had no idea if it could effectively prevent SARS-CoV-2 infection. Can vaccination protect against all diseases, and how long is the protection?". Breakthrough infections aggravate vaccine hesitancy. Regarding self-funded vaccines, this concern seemed to be more evident, as another respondent depicted, "I was concerned about vaccine effectiveness. Self-funded vaccines prevent diseases that people are less likely to be infected with than free vaccines. However, the duration of antibody protection from infection is unclear. Some were even infected despite advanced vaccination." Additionally, some participants explained their unwillingness to receive influenza vaccines because of their effectiveness. For instance, "The symptoms of influenza are mild, and one can recover quickly from simple disposal, making it unnecessary to be vaccinated. Moreover, influenza viruses mutate faster than the corresponding vaccines." Some respondents desired open access to vaccine effectiveness trial data to enhance their understanding of vaccines and ease their concerns.

Social network support

Social network support has become an increasingly important factor that affects vaccine hesitancy. The family dominated vaccination decisions among social support sources (family, colleagues, friends, healthcare workers, and Center for Disease Control and Prevention staff). One interviewee stated, "My family influences me significantly; I respect their advice. I interact with them daily; I will follow their opinions and get vaccinated against infectious diseases; I will even recommend that they receive vaccines." Nevertheless, healthcare workers were less affected by family than those in the other three groups.

Access to professional advice

Healthcare workers ranked first in both interviews in providing advice on vaccination (42.8 and 35.4 %, respectively). Social media, however, moderately undermined healthcare workers' role in providing professional suggestions, constituting a more significant proportion of advice sources (rising from 17.6 to 22.8%). When asked if they found unknown words when reading or hearing about vaccine information, 15.2% answered "often." When asked about searching for multiple vaccine information sources, 34.8% and 41.3% chose "often" and "sometimes." These results implied improved vaccine literacy among the participants.

Other factors

In addition to these factors, policy orientation and the fear of pain deserve attention. Policy orientation drew more attention among the three groups than in the last interview, except for adults aged 18–59. Several parents voiced their trust in the national government policies, "I will cooperate with the national policies to inject vaccines; it seems to be more effective if the government declares, and I am willing to accept vaccination." "Now that our country produces it, you should believe in government, so there is nothing to be concerned about." Fear of pain was a novel factor mentioned by the participants. When talking about the barriers to vaccination, one respondent replied, "I hate injections, some people said that vaccinations caused swelling, pain, and fever, and because of this, I am hesitant." Another participant stated, "I am afraid of pain, but it is the only way to get vaccinated." The risk of infection gradually faded out of participants' focus, dropping from the eleventh to twenty-second, which might be closely associated with lifestyles benefiting from pandemic control. Since the COVID-19 outbreak, people have changed their lifestyles to reduce infection risk. Wearing a mask when going out, washing hands frequently, avoiding densely populated areas, replacing public transport with private cars or walking, working from home, online learning, and reducing outdoor exercise are lifestyle changes that have lowered the risk of SARS-CoV-2 infection.

Discussion

This study conducted a return visit interview among Chinese residents to explore further the factors that affect vaccine hesitancy. The four main factors influencing Chinese residents' vaccine hesitancy were vaccine safety, self-immunity, vaccine effectiveness, and family support. Considering these above changes fully, proposing advice and possible countermeasures will help improve vaccine literacy and reduce vaccine hesitancy.

Vaccine safety and effectiveness have worried participants greatly since last year. A cross-sectional study showed that more effective and safer vaccines improved vaccination rates (22). Notably, as the controversy over these vaccines' infrequent but severe side effects grows, people cast doubt and hesitation. For instance, the human papillomavirus (HPV) vaccination rate sharply dropped from 70 to 0.6% in Japan due to misinformation on adverse events caused by the HPV vaccine (23). Therefore, increasing transparency in vaccine production, transport, supply procedures and management regarding vaccine safety is vital to dispelling doubts concerning vaccination (24). Strengthening vaccine development and production supervision, and monitoring and compensating for adverse effects following immunization are the leading measures ensuring vaccine safety and effectiveness to alleviate vaccine hesitancy (25, 26).

Despite a slight decline, vaccine price was still an obstruction in vaccination. Reimbursement for the expense of vaccines has laid the foundation for improved vaccination rates in China, similar to many other countries such as Austria, Italy, Germany, and France (27–30). Respondents were more likely to be vaccinated when vaccines were free or subsidized part of the cost. Unaffordable prices contribute to higher vaccine hesitancy (31). Decreasing cost by including it in health insurance or offering free vaccines to high-risk groups is a good way to reduce vaccine hesitancy.

The primary source of professional advice was still the medical staff. Meanwhile, advice from online media exerted a more substantial impact on vaccination than before. More recommendations from doctors boost vaccine confidence dramatically (32). So, we can strengthen the role of medical staff in facilitating vaccination. Consolidating the relevant professional knowledge of doctors through training enables them to discuss vaccines, build trust with patients and colleagues, and ultimately motivate them to accept vaccines (33). Online media is a rapid, cheap method to retrieve information. It could provide up-to-date vaccine information people need and make it possible for advisory groups to develop consultancy services *via* remote means. Even for respondents who fear pain due to vaccination, seeking help from psychological counseling

through online media is conducive to reducing vaccine hesitancy (34, 35). A study demonstrated that regular exposure to vaccination messages *via* mass media contributed to vaccination (36). This inspires governments and public health agencies to disseminate real-time vaccine messages and policies through online media platforms.

Support from family has become a main focus of attention in this interview, producing more positive effects on vaccine uptake than other support. As the most basic and frequently contacted unit in a personal social network, family is closely related to obtaining emotional support, information, opinions, and knowledge. Respondents considered family members' perceptions when determining vaccination, and trusted family members significantly affected individual decisions. Accordingly, it is critical to implement comprehensive interventions for family members, including education, training courses, and post-vaccination incentives (37).

Self-immunity was the most crucial physical deciding factor, soaring to second place. A positive association between intention to be vaccinated and perceptions of becoming infected was found (38). As people learn more about COVID-19 (39), they are increasingly concerned about disease prevalence and whether self-immunity can resist the risk of infection. Vaccine recipients believed vaccines were necessary to enhance self-immunity. So, deepening people's understanding of diseases and the need to be vaccinated for self-immunity can reduce vaccine hesitancy.

This study has several limitations worthy of note. First, the participants did not represent the general population for purposive sampling. More than 88.3% of the participants had a high school diploma or higher, with more favorable opinions than others. Second, our interviews were conducted from January to mid-February 2022, just before the new immunization programmes were declared on 19 February, which might affect attitudes toward vaccination. Third, although we identified altered factors associated with vaccine hesitancy in China, this study did not elucidate the mechanism underlying these changes.

Conclusion

We qualitatively identified changes and novel factors affecting vaccine hesitancy among Chinese residents. Our findings should remind public health authorities of evidence-based interventions to tackle vaccine hesitancy and provide policymakers with reference to successful booster vaccination to contain the COVID-19 pandemic.

Data availability statement

The raw data supporting the findings of this study are available within the article/Supplementary material; further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Wuxi Center for Disease Control and Prevention (2020No10). The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization: SL, QN, and HJ. Methodology and software: HJ. Validation: HJ and QN. Formal analysis and writing—original draft preparation: SL, JWu, SW, YZ, and HJ. Interview: SL, JWu, SW, YZ, JWa, SZ, and QN. Writing—review and editing: SL and HJ. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.929407/full#supplementary-material

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EDITED BY
Francesca Licata,
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REVIEWED BY
Mohammad Ali,
La Trobe University, Australia
Tanvi Kiran,
Post Graduate Institute of Medical Education and Research (PGIMER), India

*CORRESPONDENCE
Gyaneshwer Chaubey
gyaneshwer.chaubey@bhu.ac.in

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Vaccine hesitancy for coronavirus SARS-CoV-2 in Varanasi India

Utkarsh Srivastava[1], Avanish Kumar Tripathi[1], Jagjeet Kaur[1], Sabita Devi[1], Shipra Verma[1], Vanya Singh[2], Debashruti Das[2], Prajjval Pratap Singh[2], Rahul Kumar Mishra[2], Nikhil A. Kumar[3], Vijaya Nath Mishra[3], Pradeep Kumar[4], Vandana Rai[4], Rakesh Tamang[5], Prashanth Suravajhala[6], Rakesh Pandey[7] and Gyaneshwer Chaubey[2]*

[1]Anthropology Division, Department of Sociology, Faculty of Social Sciences, Banaras Hindu University, Varanasi, India, [2]Cytogenetics Laboratory, Department of Zoology, Banaras Hindu University, Varanasi, India, [3]Department of Neurology, Institute of Medical Science, Banaras Hindu University, Varanasi, India, [4]Department of Biotechnology, VBS Purvanchal University, Jaunpur, India, [5]Department of Zoology, University of Calcutta, Kolkata, India, [6]Amrita School of Biotechnology, Amrita Vishwa Vidyapeetham, Amritapuri, Kerala, India, [7]Department of Psychology, Faculty of Social Sciences, Banaras Hindu University, Varanasi, India

With the rollout of the world's largest vaccine drive for SARS-CoV-2 by the Government of India on January 16 2021, India had targeted to vaccinate its entire population by the end of 2021. Struggling with vaccine procurement and production earlier, India overcome these hurdles, but the Indian population still did not seem to be mobilizing swiftly toward vaccination centers. The severe second wave has slowed the vaccination pace and was also one of the major contributing factors to vaccine hesitancy. To understand the nature of vaccine hesitancy and its underlying factors, we conducted extensive online and offline surveys in Varanasi and adjoining regions using structured questions. Most respondents were students (0.633). However, respondents from other occupations, such as government officials (0.10), have also participated in the study. Interestingly, most people (0.75) relied on fake news and did not take COVID-19 seriously. Most importantly, we noticed that a substantial proportion of respondents (relative frequency 0.151; mean age 24.8 years) reported that they were still not interested in vaccination. We observed a significant association between vaccine hesitancy and socioeconomic status ($\chi^2 = 307.6$, $p < 0.001$). However, we failed to detect any association between vaccine hesitancy and gender ($\chi^2 = 0.007$, $p > 0.5$). People who have neither been vaccinated nor have ever been infected may become the medium for spreading the virus and creating new variants, which may lead to the vaccine-resistant variant. We expect this extensive survey to help the Government upgrade their vaccination policies for COVID-19 in North India.

KEYWORDS

vaccine hesitancy, SARS-CoV-2, coronavirus, North India, Varanasi

Introduction

COVID-19 has impacted our lives in multiple ways (1, 2). Studies have observed age and comorbidity as strongly associated factors for the disease severity (3–6). Moreover, the long-COVID and post-COVID complications have added another complexity to this disease (7–11). Since this disease is new, information related to it is not very concrete. With the latest research accumulating daily (3), the WHO and government guidelines have changed substantially. These changes have mystified the general population (3, 12, 13). Thus, several local rumors against the vaccination drive have surfaced in the population (14, 15). Since the flow of information in Indian society heavily depends upon oral transmission, i.e., word-of-mouth, many people are afraid to visit vaccination centers (16).

India began the vaccination drive on January 16 2021. Only ∼200,000 cases were active during this time, and most Indians had overcome the trauma of the first wave (17). With repeated encouragement from the Government, India has achieved 22 million doses per day by the end of March 2021 (18). This number increased exponentially during the first week of April 2021, when the Government decided to vaccinate everyone above 45 years of age (19). However, this was also the time of the beginning of the second wave (20, 21). Due to the severe second wave, the daily vaccine doses administered, which were more than 35 million a day till April 13 2021, have been reduced to $<$ 15 million a day just after a month (18).

Moreover, leaders from several political parties have released public statements against vaccination (22). Those mentioned above appear to significantly contribute to the reduced vaccination rate after the second wave (10). Recent studies on vaccine hesitancy have highlighted the significant reasons and rigorous vaccination campaigns to overcome the problem (14, 23–29). The concern about the side effects was highlighted, and it has been shown that at the global level, females are more hesitant than males (28). Indian society is segregated into various castes and tribal populations. Our recent study has reported that the susceptibility of several smaller tribal populations is significantly higher than the other populations (30). A study on social affiliation and vaccine hesitancy has suggested 3.5 times higher vaccine hesitancy among Scheduled caste populations (31). Thus, it is pertinent that low education and lower socioeconomic status is the primary cause of vaccine hesitancy (23, 26, 28, 29).

So far, the Varanasi and adjoining regions have not been surveyed for vaccine hesitancy. Therefore, to understand vaccine hesitancy in North India, we have systematically uncovered the cause. Some empirical evidence is much needed to understand the nature and cause of the vaccine hesitancy to suggest a potential psychosocial intervention to help the North Indian policymakers and immunization staff to overcome this key hurdle in immunization against COVID-19. To understand the nature and causes of vaccine hesitancy among North Indians, we conducted an extensive survey in Varanasi and adjoining regions. We followed a questionnaire-based survey approach to uncover the factors that inculcate vaccine hesitancy (Table 1). We presented structured questions with a predefined set of responses for each question.

Methodology

Participants

The study was conducted on a relatively sizeable incidental sample of participants (N =603 Males = 337, Females = 266) in the age range of 18 to 40 years (mean age =26.9; SD = 4.4). Only those respondents were included in the study who volunteered themselves and consented to participate in the study. We have also conducted an offline survey together with the online survey (telephonic interview). In the analysis procedures, we have anonymized the participants. The Ethical committees of Banaras Hindu University, Varanasi and VBS Purvanchal University, Jaunpur, India, have approved the study. Though the attempt was made to recruit participants from different occupational backgrounds, most respondents were students (0.633) with relatively few government employees (0.10).

Materials and procedure

We conducted a questionnaire-based survey (Table 1) consisting of 11 questions related to awareness about the COVID-19 pandemic, its spread and vaccination. The survey was primarily conducted through an online platform. The telephonic survey was also done to reach people from rural areas (who could not use the online platform). This was done to understand their attitudes and perspectives regarding the COVID-19 scenario (which is equally crucial for urban people). Such a telephonic survey was done on rural people and frontline health workers to learn about the vaccination drive and related hesitancy among rural masses.

We divided our survey into two sections: Population demographic information- age, gender, and occupation. The 11 questions deal with vaccine hesitancy-related issues (Table 1). Multiple options were supplied in an objective direction. In the second section, participants of telephonic interviews were the frontline health workers, including CHO (Community Health Workers), ANM (Auxiliary Nurse Midwives), ASHA (Accredited Social Health Activists) and ASHA *Sangini*. They have maintained their record and have shared with us their observations. The interview was structured, and the main emphasis was on the two questions that were asked-

Q.1:- What is the primary restraint among people of rural India to participate in COVID-19 vaccination?

TABLE 1 Respondents frequency (with 95% CI) on multiple choice questions investigated during the survey; *n* = number of samples.

		Total Freq. (95%CI)	Male Freq. (95%CI)	Female Freq. (95%CI)
1 What is Coranavirus?		n=727	n=425	n=302
	Natural pandemic	0.317 (0.287-0.349)	0.335 (0.295-0.379)	0.293 (0.249-0.342)
	Lab made virus	0.083 (0.066-0.103)	0.085 (0.064-0.114)	0.079 (0.056-0.111)
	Biological weapon	0.123 (0.102-0.146)	0.081 (0.06-0.109)	0.177 (0.141-0.219)
	Global conspiracy	0.433 (0.4-0.466)	0.465 (0.420-0.509)	0.391 (0.343-0.442)
	Government weapon	0.039 (0.028-0.054)	0.033 (0.021-0.053)	0.060 (0.040-0.089)
2 What does the corona vaccine do?		n=533	n=317	n=216
	Makes you impotent	0.006 (0.002-0.016)	0.003 (0.001-0.017)	0.009 (0.003-0.033)
	Prevents corona	0.899 (0.87-0.921)	0.905 (0.868-0.933)	0.889 (0.84-0.924)
	Population control	0.019 (0.01-0.034)	0.019 (0.009-0.041)	0.019 (0.008-0.047)
	Makes you emotionless	0.019 (0.01-0.034)	0.019 (0.009-0.041)	0.019 (0.008-0.047)
	Leads to death	0.058 (0.041-0.081)	0.054 (0.034-0.084)	0.065 (0.039-0.106)
3 What was the role of the government during the corona pandemic?		n=813	n=482	n=331
	Can be improved	0.389 (0.356-0.423)	0.351 (0.309-0.394)	0.444 (0.392-0.498)
	Irresponsible attitude	0.219 (0.192-0.249)	0.241 (0.205-0.281)	0.187 (0.149-0.233)
	Satisfactory	0.097 (0.0179-0.119)	0.087 (0.065-0.116)	0.112 (0.082-0.15)
	Very good	0.111 (0.091-0.134)	0.116 (0.091-0.148)	0.103 (0.075-0.14)
	Worrying	0.185 (0.159-0.213)	0.205 (0.172-0.244)	0.154 (0.119-0.197)
4 What was the public's role in spreading coronavirus (SARS-CoV-2) related informations?		n=848	n=480	n=368
	Relied on rumors	0.317 (0.287-0.349)	0.335 (0.295-0.379)	0.293 (0.249-0.342)
	Agreed with government	0.083 (0.066-0.103)	0.085 (0.064-0.114)	0.079 (0.056-0.111)
	Followed health instructions	0.123 (0.102-0.146)	0.081 (0.06-0.109)	0.177 (0.141-0.219)
	Didn't take seriously	0.433 (0.4-0.466)	0.465 (0.420-0.509)	0.391 (0.343-0.442)
	Took seriously	0.039 (0.028-0.054)	0.033 (0.021-0.053)	0.060 (0.040-0.089)
5 Which of the following steps would help stop the infection of coronavirus?		n=1218	n=721	n=497
	Total lockdown	0.250 (0.226-0.275)	0.247 (0.217-0.280)	0.256 (0.219-0.296)
	Partial lockdown	0.089 (0.075-0.107)	0.097 (0.078-0.121)	0.078 (0.058-0.106)
	Personal consciousness and awareness	0.380 (0.353-0.407)	0.368 (0.333-0.403)	0.400 (0.358-0.444)
	Total vaccination	0.278 (0.254-0.304)	0.288 (0.257-0.323)	0.266 (0.229-0.306)
6 How do you view the health management of India during COVID-19 second wave?		n=656	n=370	n=286
	Good	0.064 (0.048-0.085)	0.065 (0.044-0.095)	0.063 (0.040-0.097)
	Very Good	0.046 (0.032-0.065)	0.041 (0.025-0.066)	0.052 (0.032-.085)
	Satisfactory	0.168 (0.141-0.198)	0.157 (0.123-0.197)	0.182 (0.141-0.231)
	Unsatisfactory	0.410 (0.373-0.448)	0.422 (0.372-0.473)	0.395 (0.340-0.453)
	Average	0.313 (0.278-0.349)	0.316 (0.271-0.365)	0.308 (0.257-0.364)

(Continued)

TABLE 1 (Continued)

		Total Freq. (95%CI)	Male Freq. (95%CI)	Female Freq. (95%CI)
7 Would you prefer to get vaccinated?		n=603	n=337	n=266
	Yes	0.849 (0.818-0.875)	0.849 (0.806-0.883)	0.850 (0.802-0.887)
	No	0.151 (0.125-0.182)	0.151 (0.117-0.194)	0.150 (0.113-0.198)
8 Did you take the COVID-19 test?		n=603	n=337	n=266
	Yes	0.388 (0.350-0.428)	0.418 (0.367-0.472)	0.350 (0.295-0.409)
	No	0.612 (0.572-0.650)	0.582 (0.528-0.633)	0.650 (0.591-0.705)
9 What was the test result?		n=317	n=175	n=142
	Positive	0.388 (0.350-0.428)	0.418 (0.367-0.472)	0.350 (0.295-0.409)
	Negative	0.612 (0.572-0.650)	0.582 (0.528-0.633)	0.650 (0.591-0.705)
10 Which vaccine are you aware of?		n=1274	n=759	n=515
	All	0.038 (0.029-0.050)	0.025 (0.016-0.039)	0.056 (0.40-0.080)
	Covishield	0.349 (0.323-0.375)	0.358 (0.325-0.393)	0.334 (0.295-0.376)
	Covaxin	0.376 (0.350-0.403)	0.364 (0.330-0.398)	0.394 (0.353-0.437)
	Sputnik-V	0.238 (0.215-0.262)	0.253 (0.223-0.285)	0.216 (0.182-0.253)
11 Will vaccination prevent COVID-19 lifelong?		n=632	n=278	n=351
	Yes	0.082 (0.063-0.106)	0.119 (0.086-0.162)	0.054 (0.035-0.083)
	No	0.441 (0.403-0.480)	0.572 (0.513-0.629)	0.342 (0.294-0.393)
	Not Sure	0.472 (0.433-0.511)	0.572 (0.513-0.629)	0.396 (0.346-0.448)

Q.2:- How do you see the vaccination drive in your area, and if you have to suggest a few reasons, kindly list them to make the vaccination drive more inclusive and widespread. We tend to use it as additional data to have a better and broadened look over the conclusion drawn from our study and whether it complies with it.

Apart from the health workers, we also did a second telephonic interview with people from rural areas. This interview was also structured, and it consisted of two questions-

Q.1:- Do you want to get vaccinated?

Q.2:- If not, then why?

Statistical analyses

The frequency of each response was calculated with a 95% CI (Table 1). The barplot with the 95% CI was drawn separately for the male and female participants. The per month earnings of each participant were recorded in the four categories [<5000 (1); 5001–10000 (2); 10001–50000 (3); 50001–100000 (4])]. The gender of the respondent was recoded to 0 (male) and 1 (female), and vaccine hesitancy answers were recoded to 0 and 1 (No and Yes). The chi-square (χ^2) and logistic regression statistical analyses were conducted using SPSS (ver.26). For statistical significance, a two-tailed *p*-value test was performed.

Results

In order to understand the vaccination drive in a region, it is necessary to focus on the local hurdles behind vaccine hesitancy. Our questionnaire was designed to reflect the mass feeling about the nature of the virus, the second wave, comments on measures taken by the Government during the second wave, and rumors leading to vaccine hesitancy (Table 1). Apart from the highly infective virus variants during the second wave (32), the role of the public was also concerning. A large proportion of participants (0.75) either relied on rumors or did not take the virus seriously. Moreover, according to the respondents, when asked what steps would help prevent the coronavirus, most people think that total vaccination and personal consciousness (0.658) will be a better tool than lockdowns (Table 1).

An exciting result that our study yielded is that in some questions, there was a significant difference (two-tailed *p*-value <0.001) in the responses between male and female respondents (Supplementary Figure 1). For example, a significantly lower number of females think that the coronavirus is a lab-made or biological weapon. In contrast, more females think COVID-19 is a natural pandemic (two-tailed *p*-value < 0.001) (Table 1). Similarly, more females followed the health instructions than the males (two-tailed *p*-value < 0.001).

During the survey, many participants had an impression that the vaccine relates to introducing the second wave. Therefore, we first investigated the vaccine hesitation during the second wave (Table 1 and Supplementary Figure 1). We have looked at the vaccination data during March-June 2021 (18). We found a major vaccination dip during the second wave (two-tailed $p < 0.0001$).

From our research, we found that a large proportion of people (0.849) prefer to get vaccinated. They are aware of vaccines (0.962) and know that the vaccine for SARS-CoV-2 prevents COVID-19 (0.899). However, a substantial proportion of people reported that they would refrain from vaccinating (0.15) (Figure 1). Remarkably, the vaccine hesitancy ratio was similar for both male and female participants. The vaccine acceptance among the studied cohort in India is significantly (two-tailed $p < 0.0001$) higher than the global data (28). It is worthwhile to mention here that the trend of vaccine willingness in the Indian community is similar to the data of Bangladesh (29, 33); nevertheless, the educated community in India is significantly (two-tailed $p < 0.0001$) well aware and is at a greater acceptance.

Our statistical tests have yielded a highly significant association between vaccine hesitancy and the economic status of the participants ($\chi^2 = 307.6$, $p = 0.000$). Nevertheless, the gender-biased association of vaccine hesitancy has not been observed in our survey ($\chi^2 = 0.007$, $p = 0.933$) (Table 2). The logistic regression analysis supported the strong association of vaccine hesitancy with the economic status of the respondents (Table 3).

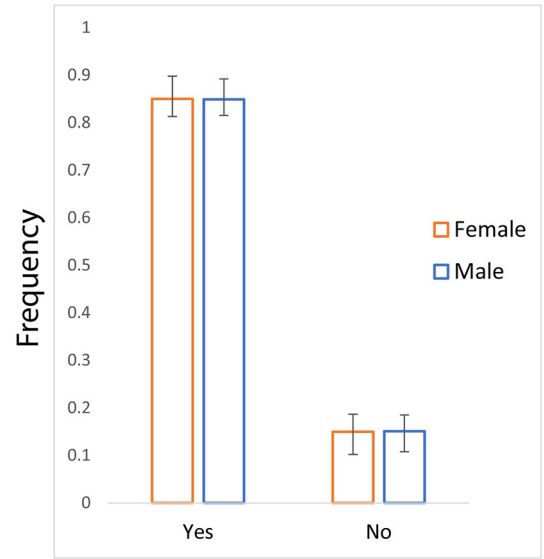

FIGURE 1
The bar plot of frequency (with 95%CI) showing vaccine hesitancy for male and female participants.

TABLE 2 Vaccine hesitancy according to the demographics.

Demographics	Vaccine Hesitancy		
	Pearson Chi Square (χ^2)	Asymptotic Sig (2-sided)	Cramer's V
Income	307.6	0.000	0.714
Gender	0.007	0.933	0.003

TABLE 3 Determinants of vaccine hesitancy.

Determinants	Vaccine Hesitancy		
	Odds Ratio (95%CI)	Wald	*p*-value
Income	61.851 (27.351–139.867)	98.163	0.000
Gender	1.028 (0.544–1.942)	0.007	0.933

Discussion

The present study effectively contributes to the vaccine hesitancy in district Varanasi and adjoining regions of India. We focused primarily on the educated people with a list of a questionnaire. Our findings show a significant (two-tailed $p < 0.0001$) hesitancy among males and females (Figure 1). Strikingly, the Indian cohort studies here had lower vaccine hesitancy than the global data, likely due to our cohort structure. Our cohort in the present study was overwhelmed by people with higher education.

India's vaccine drive fluctuated with a significant drop during the second wave significantly (two-tailed p-value < 0.0001). The most crucial reason for this fall was vaccine hesitancy rumors. Our interview and observation found that people ran for the vaccine as soon as the second wave started to spread. It resulted in enormous rush to the vaccination centers. Many have been infected due to large gatherings at the vaccination centers. This has created confusion in society that the people are being infected after taking vaccines (Table 1 and Supplementary Figure 1). Thus, vaccines are not helping to stop the infection. The spread of this rumor through word-of-mouth has reduced the vaccinations significantly (two-tailed p-value < 0.0001) (18). During the second wave, the daily immunization was low when the positive test rate was at its peak. However, it must be understood that it takes 3–4 weeks to develop the effective antibodies after the vaccination (34).

So far, in the SARS-CoV-2 evolution, we have seen that this virus can create more hazardous variants with time (32). Moreover, we are fortunate that no variant has been found that completely evades vaccine-induced immunity. Still, with a large number of vaccination, a non-vaccinated pool may provide a reservoir for the virus to multiply and mutate. Thus, it may offer the opportunity to emerge new variants. Moreover, the selection pressure on the virus against the background of a primarily

vaccinated population may favor a variant that will be resistant to the vaccine. Therefore, the real danger is from those who have never been vaccinated or infected before. Such people will provide ground for a new variant of the virus. If it develops immunity to the vaccine, it will be a major setback in controlling the epidemic. The progress we have made against this pandemic will be lost.

Consistent with the previous observations, our multiple statistical analyses confirmed the strong correlation of vaccine hesitancy with the economic status of the participants (Tables 2, 3). Whilst, the gender-specific difference has not been observed, which is likely due to the nature of our cohort, where most of the respondents are well educated.

Limitations and future perspectives

We caution that the cohort used in our study is overwhelmed by educated people. Therefore, the hesitancy frequency observed in this study may capture the lower bound data of vaccine hesitancy in North India. Further, we add that a retrospective study following face-to-face or structured telephonic interviews with a qualitative approach such as thematic analysis may bring further insight into the dynamics of vaccine hesitancy among Indians. Similarly, post-second wave vaccine hesitancy status also needs to be explored using the same interview format and contrasted with the retrospective data to understand the extent of vaccine hesitancy and changing factors. Since we have used a structured questionnaire with a predefined response format, the study is fraught with the danger of the researchers' subjective biases as the researchers' proposed factors for vaccine hesitancy were limited. The open-ended questions for listing the reasons for vaccine hesitancy may bring newer insights and additional aspects of vaccine hesitancy that could not be foreseen by us while framing the response to the question of vaccine hesitancy.

Conclusions

In conclusion, our study adds systematic knowledge on various potential factors related to the COVID-19 vaccine hesitancy among North Indians. During the second wave, most people in North India relied on fake news. > 65% population opposed total lockdown. A significant number of females were better at following the official health instructions. Vaccine hesitancy is found among 15% of the studied cohort. Consistent with the previous studies, we have also observed a significant correlation between vaccine hesitancy and socioeconomic status. In contrast, we did not find any correlation between vaccine hesitancy and gender. Thus, a region-specific policy is needed for COVID-19 vaccination in North India.

Data availability statement

The datasets presented in this study is provided in Table 1 and Supplementary File.

Ethics statement

The studies involving human participants were reviewed and approved by VBS Purvanchal University Jaunpur and Banaras Hindu University, Varanasi, India. The patients/participants provided their written informed consent to participate in this study.

Author contributions

GC conceived and designed this study. US, AT, JK, SD, SV, VS, DD, PPS, RM, NK, VM, PK, VR, RT, PS, and RP collected the data and also conducted the online and offline surveys. US, AT, PPS, GC, DD, PK, RT, PS, and VR analyzed the data. GC, US, AT, JK, SD, SV, RT, PS, and RP wrote the manuscript from the inputs of other co-authors. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.892584/full#supplementary-material

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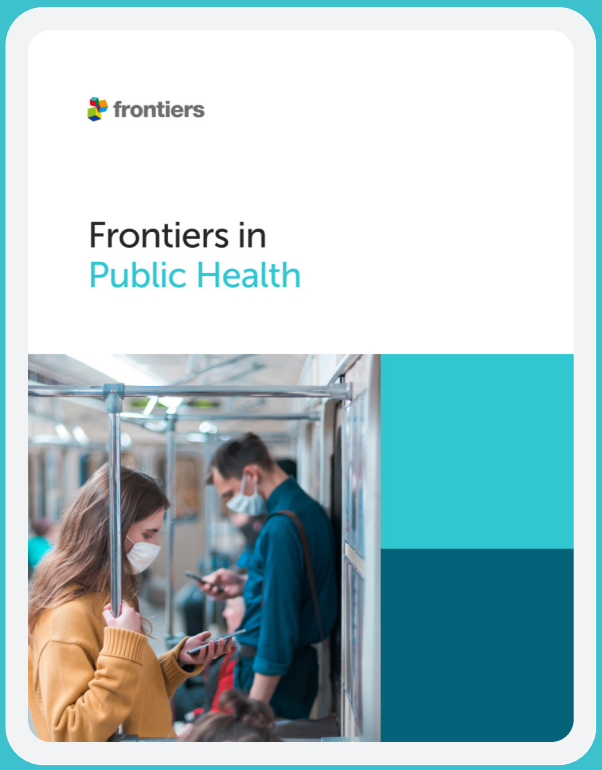

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