



Review article

Multilevel determinants of COVID-19 vaccination hesitancy in the United States: A rapid systematic review

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ABSTRACT

Vaccine hesitancy is a challenge for the success and optimal implementation of COVID-19 immunization programs in the US. The objective of this study was to summarize multilevel determinants of COVID-19 vaccination intention in the US to inform future intervention opportunities. To this end, we conducted a rapid systematic review by searching published articles via PubMed published by October 5, 2021, following the PRISMA guidelines. One hundred and six articles were included. According to nationally representative studies, the overall COVID-19 acceptance rate ranges from 53.6% to 84.4%. Individual (demographics, health history, behaviors and health beliefs), interpersonal (having a close friend/family member impacted by COVID-19), healthcare and societal level factors (healthcare provider recommendations, source/credential of COVID-19 related information, and COVID-19 related conspiracy theories) all contributed to COVID-19 vaccine hesitancy in the US. This study demonstrates that the acceptance to COVID-19 vaccines is influenced by various factors, particularly the role of healthcare providers in enhancing public intent to vaccination. Potential interventions to mitigate people's concerns over the vaccines and address vaccine-related conspiracy/misinformation from social media are also critical to encourage vaccine uptake in the US.

1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by SARS-CoV2, a pathogen that primarily spreads through close contact from person to person and targets the human respiratory system. The most common symptoms reported among people infected with COVID-19 are fever, muscle/body ache, headache, fatigue and various respiratory symptoms (e.g., cough, sore throat and shortness of breath) (Rothan and Byrreddy, 2020). By November 2021, more than 46 million people had been infected and approximately 750,000 died with COVID-19 in the US since the first reported case in January 2020 (Holshue et al., 2020; Mathieu et al., 2021). It is estimated that COVID-19 has resulted in 13.6% of all in-hospital mortality and a median hospital charge of over 40,000 US dollars from April to October 2020 (Di Fusco et al., 2021).

Pfizer/BioNTech and Moderna vaccines have been authorized for emergency use in the US since December 2020. The Food and Drug Administration (FDA) granted full approval to the Pfizer/BioNTech vaccine in August 2021 (Food and Drug Administration, 2021). Both vaccines have been effective in preventing infection with COVID-19 and conferring promising protection against variants of the virus (Polack

et al., 2020; Abu-Raddad et al., 2021; Baden et al., 2021; Wu et al., 2021; Lopez Bernal et al., 2021). Computational models suggest that every 1% increase between 40% and 50% vaccination coverage can prevent 1.5 million new infections, 6 thousand deaths and save more than \$600 million in direct medical costs, assuming 70% vaccine efficacy (Bartsch et al., 2021). Since the scale-up of COVID-19 vaccine programs in the US, a significant reduction in symptomatic infections, hospitalization and mortality caused by the virus has been observed in the past few months, particularly among those who are fully vaccinated (Mathieu et al., 2021; Tenforde et al., 2021; Christie et al., 2021). Evidence also suggests that the preventive value of the vaccines may be further amplified if we can expedite the vaccination coverage as a way to achieve herd immunity among the population in a timely fashion (Bartsch et al., 2021). Therefore, targeted interventions and programs to facilitate timely vaccine uptake represents the key to curtail the spread of COVID-19 and relieve economic/health burden caused by the pandemic.

Despite the proven benefit and increased availability of COVID-19 vaccine in the US, less than optimal proportion of US populations have yet become fully vaccinated. By November 2021, 66.0% of Americans have received at least 1 dose of COVID-19 vaccine and 56.9%

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of Americans have been fully vaccinated (Mathieu et al., 2021). The daily COVID-19 vaccine doses administered have been plummeting since the peak in the middle of April. As of early November, this number has been down almost 70% from the peak (Mathieu et al., 2021). Among all COVID-19 vaccine barriers, vaccine hesitancy, which refers to delay in acceptance or refusal of vaccination despite availability of vaccination services, has been documented by numerous literature as a key modifiable factor that poses critical challenges for the success of the implementation of COVID-19 immunization programs in the US (MacDonald, 2015). A national study conducted in October 2020 reported that 66.9% participants would vaccinate against COVID-19 when available or a few months later after the roll-out of vaccines (Mercadante and Law, 2021). The COVID-19 vaccine acceptance was even lower among healthcare workers (HCWs) in some settings. A study in Los Angeles showed that 65.5% of the HCWs decided to delay their vaccination (Gadoth et al., 2021). More recent surveys after the roll-out of COVID-19 vaccines have also revealed suboptimal vaccine acceptance (51.8%–73.9%) (Agle et al., 2021; Liu et al., 2021; Baack et al., 2021), despite the surge of highly contagious Delta variant and the ongoing successful stories of COVID-19 vaccine in preventing death and severe complications among US populations. Therefore, studies and interventions must be implemented to effectively counter COVID-19 vaccine hesitancy on a continuing basis to strengthen COVID-19 vaccination in the US.

Several nationally representative studies suggest several key factors associated with COVID-19 vaccine hesitancy, including minority race, southern US geographic regions, gender, low socioeconomic status (e.g., education and income), religious considerations, experience of COVID-19 infection among members in their living contexts, community norms, media information, and healthcare resources (Mercadante and Law, 2021; Daly and Robinson, 2021; Szilagyi et al., 2021; Ruiz and Bell, 2021).

Despite an increasing body of literature in investigating COVID-19 vaccine hesitancy and relevant determinants in the US, few aggregated evidence has been presented to render an in-depth, systematic summarization of important barriers/facilitators at multiple socio-ecological levels (e.g., individual, interpersonal, community, healthcare and society) related to vaccine hesitancy specific to the US populations. The objective of this rapid systematic review is to summarize relevant multilevel determinants of COVID-19 vaccination intention and provide insights for designing and implementing targeted and holistic interventions to tackle this public health crisis in the US.

2. Methods

2.1. Literature search strategy

This rapid systematic review was initially conducted by searching published articles via PubMed by February 20, 2021, following the PRISMA guidelines (Moher et al., 2010). The final search terms included: (COVID or coronavirus or COVID-19 or SARS-CoV-2 or 2019nCoV or HCoV-19) and (vaccine or vaccination or immunization) and (hesitancy or anti-vaccine or mistrust or acceptance or willingness or perception or attitude or intention). Reference lists of the included articles were also examined to identify eligible studies for inclusion. An updated search (per the recommendation of peer reviewer) was conducted on October 5, 2021 to include additional relevant articles published between our initial search date (February 20, 2021) and the date we began revising the present review (October 5, 2021) for re-submission to the journal. Based on the initial search terms, we conducted a modified search by: (1) adding the following search terms to limit the study location to the US: United States or US or America or American; and (2) limiting all search terms to the title and abstract field.

2.2. Inclusion/Exclusion criteria

Studies were included in the systematic review if they met the following criteria: (1) published journal articles and pre-prints; (2) included at least one survey question on willingness, confidence, intention and/or hesitancy of getting a COVID-19 vaccine; (3) reported key demographic characteristics of survey participants (e.g., age, gender, race and education level) and facilitators/barriers associated with COVID-19 vaccine hesitancy; (4) conducted in the US; and (5) published in English. Studies conducted in multiple countries were incorporated into this systematic review if characteristics of survey participants and their vaccine acceptance were reported separately for the US participants. Studies that compared willingness to take different types of vaccine (e.g., varying hypothetical effectiveness/price/side effects) were not included. Studies aiming to evaluate participants' willingness to pay for a COVID-19 vaccine or to examine interventions to alter vaccine intention were excluded.

2.3. Study screening and data extraction

Titles and abstracts of all identified records were first screened for relevancy and duplicate removal by two independent reviewers (Y.W. and Y.L.). The full text review and data extraction were then conducted independently by one author (Y.W.), and further cross-checked by the other author (Y.L.) for accuracy. Disagreements were iteratively discussed until agreement was reached. A standardized Excel sheet was used to extract the following information from eligible articles: study location/setting, study period, study design, recruitment/sampling strategy, participant characteristics, analytical sample size, measure of vaccination intention and results, and key factors associated with vaccination intention.

2.4. Ethical compliance

This systematic review utilized data from previously published studies and thus exempt from ethical compliance.

3. Results

3.1. Search results

A total number of 717 articles were initially found through PubMed search. Of 36 full-text papers assessed for eligibility, 33 papers were eligible for final review. We additionally found 73 eligible studies from the updated search. Therefore, a total of 106 papers were included into this systematic review. Study selection process was reported in Fig. 1.

3.2. Study characteristics

Supplemental Table 1 presented the characteristics of 106 papers. Eighty-nine studies (84.0%) were conducted using a cross-sectional design, while only 11 studies (10.4%) were longitudinal. We additionally identified 2 qualitative (1.9%) and 4 mixed methods studies (3.8%). Forty-four (41.5%) studies measured participants' COVID-19 vaccination intent after FDA authorized Pfizer-BioNTech vaccine for emergency use. The 106 studies were conducted across the US, including California (n = 7, 6.6%), New York (n = 5, 4.7%), Texas (n = 4, 3.8%), Florida (n = 3, 2.8%) and Michigan (n = 3, 2.8%). In addition to general population (n = 62, 58.5%), commonly reported participants of these studies were HCWs (n = 14, 13.2%), people with pre-existing medical conditions (n = 8, 7.5%), college students (n = 5, 4.7%), Black population (n = 4, 3.8%), religious population (n = 2, 1.9%), and productive-aged females (n = 2, 1.9%). We additionally identified 2 studies (1.9%) investigating parents' intent to vaccinate their children. All studies measured COVID-19 vaccine acceptance by asking participants their willingness or confidence of getting a COVID-19 vaccine, which were recorded as a

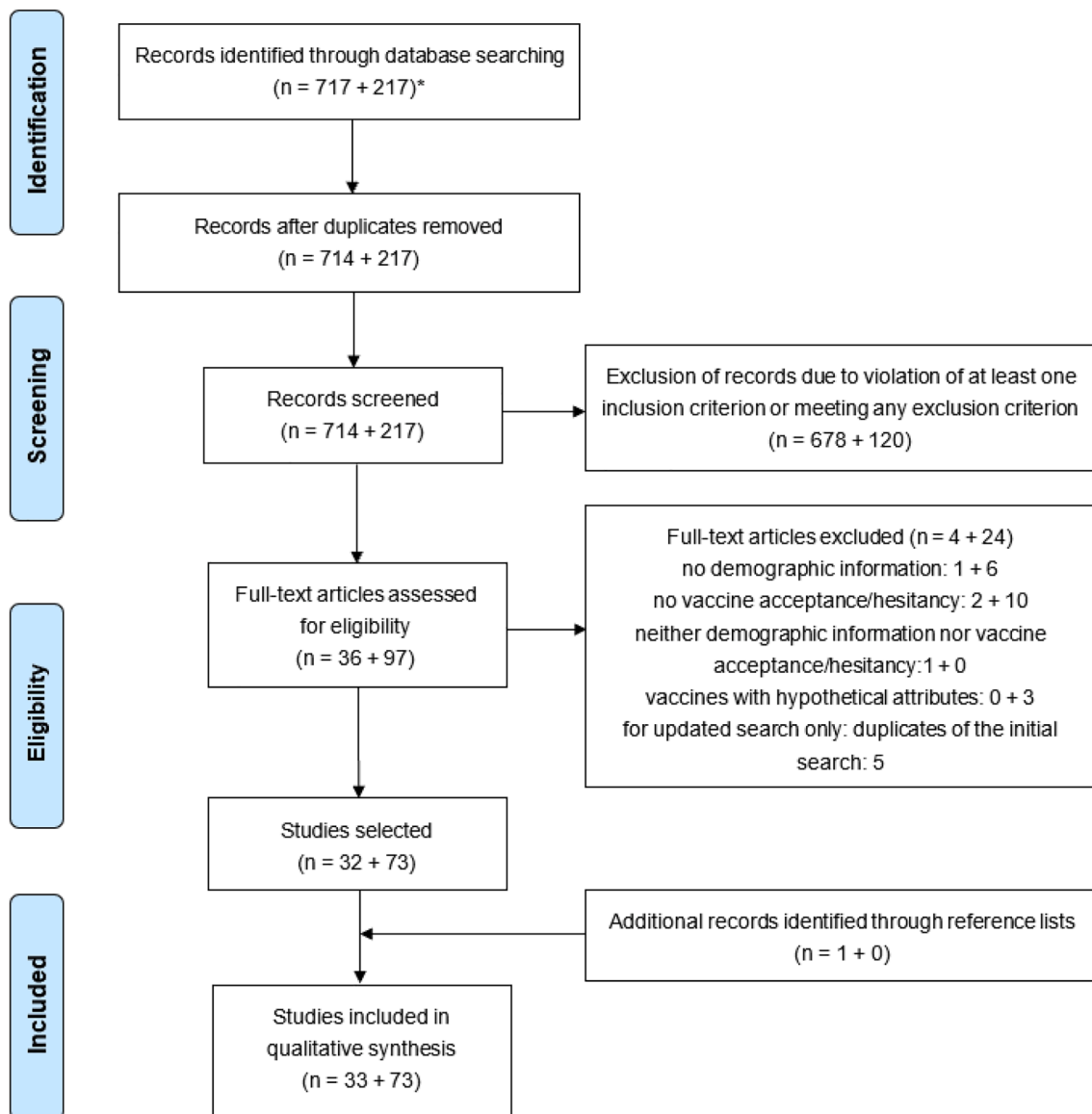


Fig. 1. Flowchart of study inclusion and review process. * indicates numbers from both searches; the former number refers to the initial systematic review conducted in February, the latter one refers to the updated search conducted in October.

categorical ($n = 94$, 88.7%) or continuous variable ($n = 12$, 11.3%).

3.3. Overall COVID-19 vaccine acceptance rate in the US and time trends

Fig. 2 shows the trend of COVID-19 vaccine acceptance rates in the US from 17 nationally representative samples (Mercadante and Law, 2021; Agle et al., 2021; Daly and Robinson, 2021; Szilagyi et al., 2021; Ruiz and Bell, 2021; Romer and Jamieson, 2020; Fisher et al., 2020; Roozenbeek et al., 2020; Malik et al., 2020; Latkin et al., 2021; Callaghan et al., 2021; Allen et al., 2021; Viswanath et al., 2021; Coe et al., 2021; Berg and Lin, 2021; Tram et al., 2021; King et al., 2021). COVID-19 acceptance was defined as already receiving at least one dose of the vaccine, definitely or probably getting it when available. Ten nationally representative studies were excluded from the figure due to the lack of survey period or inconsistent measurement of vaccine acceptance (Baack et al., 2021; Pogue et al., 2020; Bleakley et al., 2021; Meier et al., 2021; Loomba et al., 2021; Salmon et al., 2021; Kreps et al., 2021; Kricorian et al., 2021; Kricorian et al., 2021; Neely et al., 2021). According to the plot, overall COVID-19 acceptance rates ranged from 53.6% (Daly and Robinson, 2021) to 84.4% (Tram et al., 2021). The

percentage of people who were willing to vaccinate against COVID-19 increased from 56.2% (Szilagyi et al., 2021) in December when Pfizer/BioNTech and Moderna vaccines were authorized for emergency use to 82.0% (King et al., 2021) in late May. Longitudinal changes of intent to vaccinate against COVID-19 should be interpreted with caution because methodological limitations arising from these studies may reduce the representativeness of the samples (Mercadante and Law, 2021; Szilagyi et al., 2021; Ruiz and Bell, 2021; Romer and Jamieson, 2020; Roozenbeek et al., 2020; Malik et al., 2020; Latkin et al., 2021; Callaghan et al., 2021).

3.4. Determinants of COVID-19 vaccine intention

Determinants of COVID-19 vaccine intention from individual, interpersonal, healthcare and societal levels before and after Pfizer-BioNTech vaccine was approved under an Emergency Use Authorization were summarized in Table 1. Most determinants presented persistent relationships with vaccine intention regardless of COVID-19 vaccine availability.

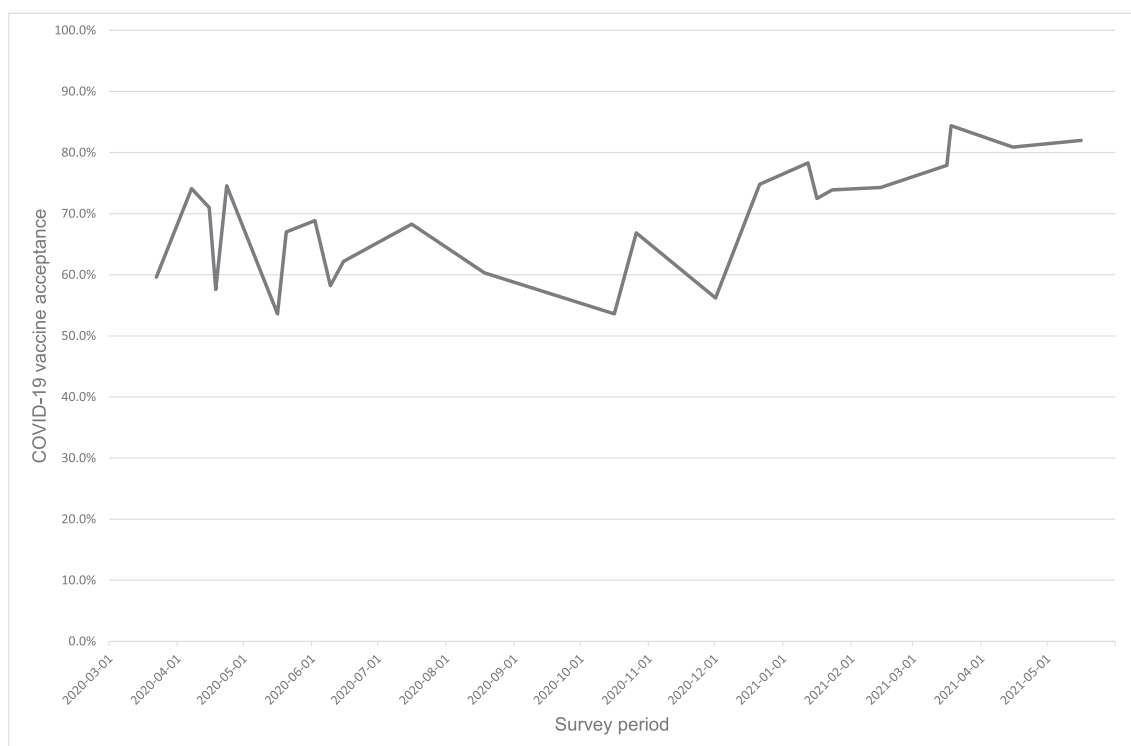


Fig. 2. Trend of COVID 19 vaccine acceptance in the US.

3.4.1. Individual level

3.4.1.1. Demographic characteristics. Gender. More than 70.0% of males would take COVID-19 vaccine when available or recommended for them (Ruiz and Bell, 2021; Malik et al., 2020; Shaw et al., 2021). However, females were associated with 1.3 to 2.5 times the odds of being COVID-19 vaccine hesitant when compared to males after adjusting for multiple covarites (Daly and Robinson, 2021; Latkin et al., 2021; Callaghan et al., 2021; Coe et al., 2021; Tram et al., 2021; Khubchandani et al., 2021; Doherty et al., 2021; Nikolovski et al., 2021; Halbrook et al., 2021; Garcia et al., 2021).

Age. Fifty years of age or older was a significant factor of positive attitude towards vaccination (Gadoth et al., 2021; Daly and Robinson, 2021; Szilagyi et al., 2021; Tram et al., 2021; Salmon et al., 2021; Kreps et al., 2021; Garcia et al., 2021; Dalal et al., 2021; Shekhar et al., 2021; Unroe et al., 2020; Trent et al., 2021; Stern et al., 2021; Saluja et al., 2021). Multivariable results suggested that one year increase in age was significantly associated with 32% reduction in the odds of COVID-19 vaccine hesitancy (odds ratio (OR) = 0.68, 95% Confidence Interval (95% CI): 0.57–0.82) (Latkin et al., 2021). However, being younger than 45 years of age relative to respondents 60 years and older was associated with both low and uncertain vaccine acceptability (Fisher et al., 2020; Caban-Martinez et al., 2021).

Race/ethnicity. Whites (Malik et al., 2020; Dalal et al., 2021; Thompson et al., 2021; Ehde et al., 2021), Asians (Szilagyi et al., 2021; Malik et al., 2020; Shaw et al., 2021; Shekhar et al., 2021; Thompson et al., 2021; Townsel et al., 2021) and American Indians/Alaska Natives (Malik et al., 2020; Stern et al., 2021) were found to be more likely to vaccinate against COVID-19. However, compared to White race, Black race and Hispanic/Latinx origin were associated with 2 to 6-fold (Daly and Robinson, 2021; Fisher et al., 2020; Latkin et al., 2021; Salmon et al., 2021; Nikolovski et al., 2021; Halbrook et al., 2021; Saluja et al., 2021; Caban-Martinez et al., 2021; Townsel et al., 2021; Bass et al., 2021; Jacobi and Vaidyanathan, 2021; Yang et al., 2021; Nguyen et al., 2021) and 2 to 3-fold (Fisher et al., 2020; Latkin et al., 2021; Saluja et al., 2021; Caban-Martinez et al., 2021) higher chance of being COVID-

19 vaccine hesitant, respectively. However, increased vaccine hesitancy among Asian people were observed after the availability of the vaccines (Halbrook et al., 2021; Nguyen et al., 2021).

Education level. A bachelor's degree or higher predicted intent to get a future COVID-19 vaccine (Szilagyi et al., 2021; Tram et al., 2021; Salmon et al., 2021; Khubchandani et al., 2021; Nikolovski et al., 2021; Dalal et al., 2021; Thompson et al., 2021; Niño et al., 2021; Stephenson et al., 2021; Hill et al., 2021). However, people with some college or less education were less likely to receive a COVID-19 vaccine (Daly and Robinson, 2021; Fisher et al., 2020; Halbrook et al., 2021; Caban-Martinez et al., 2021; Earnshaw et al., 2020; Bogart et al., 2021; Willis et al., 2021). For example, a survey of US adults found that people with no high school diploma had a nearly 8-fold higher relative likelihood of vaccine refusal compared with those who had a college degree or higher (risk ratio = 7.8, 95% CI: 3.1–19.6) (Fisher et al., 2020).

Annual household income. An annual household income of \$50,000 or more was associated with 1 to 2 times of vaccine acceptance compared to those with lower household income (Daly and Robinson, 2021; Latkin et al., 2021; Tram et al., 2021; Salmon et al., 2021; Khubchandani et al., 2021; Nikolovski et al., 2021; Trent et al., 2021; Hill et al., 2021; Reiter et al., 2020; Shallal et al., 2021). However, people making less than \$20,000 were more likely to reject a COVID-19 vaccine (Mercadante and Law, 2021; Saluja et al., 2021; Head et al., 2020).

Occupation. HCWs' willingness to get a COVID-19 vaccine differs by their hospital role. More than 80.4% of direct medical providers (e.g., physician and resident) reported their intent to vaccinate against COVID-19 while only 25.2% to 52.5% of direct patient care providers (e.g., nurse, long-term care staff and patient care technician) expressed willingness to be vaccinated (Shaw et al., 2021; Shekhar et al., 2021; Unroe et al., 2020; Amin and Palter, 2021). Compared to clinical roles, non-clinical roles were 2.4 times more likely to reject a COVID-19 vaccine (prevalence ratio = 2.4, 95% CI: 2.1–2.8) (Kociolek et al., 2021).

Political leaning and religiosity. Democrat or liberalism were both positive predictors of future vaccination intention while conservatism significantly predicted refusal intention (Agle et al., 2021; Ruiz and Bell, 2021; Roozenbeek et al., 2020; Callaghan et al., 2021; Tram et al.,

Table 1
Facilitators and barriers of COVID-19 vaccine acceptance.

Factors	Facilitators (+) and barriers (-) of COVID-19 vaccine acceptance	
	Before the availability of Pfizer/BioNTech vaccine	After the availability of Pfizer/BioNTech vaccine
Individual level		
Demographic characteristics		
Gender	+: male (Ruiz and Bell, 2021; Salmon et al., 2021; Jacobi and Vaidyanathan, 2021; Earnshaw et al., 2020; Qiao et al., 2020) -: female (Daly and Robinson, 2021; Szilagyi et al., 2021; Latkin et al., 2021; Callaghan et al., 2021; Coe et al., 2021; Meier et al., 2021; Khubchandani et al., 2021; Doherty et al., 2021; Nikolovski et al., 2021; Thompson et al., 2021; Reiter et al., 2020)	+: male (Berg and Lin, 2021; Niño et al., 2021; Hill et al., 2021; Zhang et al., 2021) -: female (Tram et al., 2021; Halbrook et al., 2021; Garcia et al., 2021; Kociolek et al., 2021; Moore et al., 2021)
Age	+: age greater than 60 (Salmon et al., 2021; Unroe et al., 2020; Trent et al., 2021) +: age ≥ 50 (Gadoth et al., 2021; Daly and Robinson, 2021; Szilagyi et al., 2021) -: age < 60 (Caban-Martinez et al., 2021) -: age < 50 (Mercadante and Law, 2021) -: age < 45 (Fisher et al., 2020; Trent et al., 2021)	+: age ≥ 80 (Garcia et al., 2021) +: age greater than 60 (Kreps et al., 2021) +: age ≥ 55 (Tram et al., 2021) +: age ≥ 50 (Dalal et al., 2021; Stern et al., 2021; Saluja et al., 2021) -: age < 30 (Moore et al., 2021)
Race/ethnicity	+: White, Asian or American Indian/Alaska Native (Szilagyi et al., 2021; Malik et al., 2020; Thompson et al., 2021; Head et al., 2020) -: Black or Hispanic/Latinx (Gadoth et al., 2021; Daly and Robinson, 2021; Szilagyi et al., 2021; Fisher et al., 2020; Latkin et al., 2021; Callaghan et al., 2021; Meier et al., 2021; Salmon et al., 2021; Doherty et al., 2021; Nikolovski et al., 2021; Unroe et al., 2020; Caban-Martinez et al., 2021; Thompson et al., 2021; Bass et al., 2021; Jacobi and Vaidyanathan, 2021; Willis et al., 2021; Reiter et al., 2020; Latkin et al., 2021; Guidry et al., 2021)	+: White, Asian or American Indian/Alaska Native (Tram et al., 2021; Dalal et al., 2021; Stern et al., 2021; Ehde et al., 2021; Townsel et al., 2021) -: Black or Hispanic/Latinx (Agle et al., 2021; Kreps et al., 2021; Halbrook et al., 2021; Garcia et al., 2021; Stern et al., 2021; Saluja et al., 2021; Townsel et al., 2021; Yang et al., 2021; Nguyen et al., 2021; Hill et al., 2021; Kociolek et al., 2021) -: Asian (Halbrook et al., 2021; Nguyen et al., 2021)
Education level	+: Bachelor's degree or higher (Szilagyi et al., 2021; Salmon et al., 2021; Khubchandani et al., 2021; Nikolovski et al., 2021; Trent et al., 2021; Thompson et al., 2021; Qiao et al., 2020) -: no degree (Daly and Robinson, 2021; Fisher et al., 2020; Caban-Martinez et al., 2021; Earnshaw et al., 2020; Bogart et al., 2021; Willis	+: Bachelor's degree or higher (Tram et al., 2021; Dalal et al., 2021; Niño et al., 2021; Stephenson et al., 2021; Hill et al., 2021) -: no degree (Halbrook et al., 2021)

Table 1 (continued)

Factors	Facilitators (+) and barriers (-) of COVID-19 vaccine acceptance	
	Before the availability of Pfizer/BioNTech vaccine	After the availability of Pfizer/BioNTech vaccine
Annual household income	+: ≥\$120,000 (Ruiz and Bell, 2021; Salmon et al., 2021; Nikolovski et al., 2021) +: ≥\$100,000 (Daly and Robinson, 2021) +: ≥\$60,001 (Khubchandani et al., 2021; Trent et al., 2021) +: ≥\$50,000 (Latkin et al., 2021; Reiter et al., 2020) +: ≥\$35,000 (Thompson et al., 2021) -: <\$25,000 (Head et al., 2020) -: <\$20,000 (Mercadante and Law, 2021)	+: ≥\$150,000 (Tram et al., 2021; Shallal et al., 2021) +: ≥\$75,000 (Hill et al., 2021) +: ≥\$35,000 (Niño et al., 2021) -: <\$20,000 (Saluja et al., 2021)
Occupation	+: prescribing clinicians, therapy staff (Gadoth et al., 2021; Unroe et al., 2020) -: nurse, nonclinical roles (Gadoth et al., 2021; Unroe et al., 2020)	-: nurse, nonclinical roles (Kociolek et al., 2021)
Political leaning	+: Democrat, moderate or liberal (Ruiz and Bell, 2021; Meier et al., 2021; Salmon et al., 2021; Reiter et al., 2020; Head et al., 2020) -: Republican or conservative (Roozenbeek et al., 2020; Latkin et al., 2021; Callaghan et al., 2021; Viswanath et al., 2021; Khubchandani et al., 2021; Jacobi and Vaidyanathan, 2021; Latkin et al., 2021)	+: Democrat or independent (Hill et al., 2021) -: Republican or conservative (Agle et al., 2021; Tram et al., 2021; Kreps et al., 2021)
Religiosity	-: a high level of religiosity (Callaghan et al., 2021; Olagoke et al., 2021; Scott et al., 2021)	
Geographic location	+: urban location (Fisher et al., 2020)	+: urban residence (Yang et al., 2021)
Health history		
Underlying medical conditions	+: underlying medical conditions (Daly and Robinson, 2021; Ruiz and Bell, 2021; Trent et al., 2021)	-: underlying medical conditions (Kociolek et al., 2021)
Personal history of COVID-19 diagnosis	+: personal history of COVID-19 diagnosis (Reiter et al., 2020) -: personal history of COVID-19 diagnosis (Caban-Martinez et al., 2021)	+: personal history of COVID-19 diagnosis (Dalal et al., 2021) -: personal history of COVID-19 diagnosis (Kociolek et al., 2021) -: better to develop immunity by getting COVID-19 (Carmody et al., 2021)
Behaviors		
Receipt of influenza vaccination	+: receipt of influenza vaccination in the previous year (Ruiz and Bell, 2021; Fisher et al., 2020; Meier et al., 2021; Trent et al., 2021; Caban-Martinez et al., 2021; Head et al.,	+: receipt of influenza vaccination in the previous year (Ehde et al., 2021; Harhay et al., 2021) +: got or planning to get the flu shot (Garcia et al.,

(continued on next page)

Table 1 (continued)

Factors	Facilitators (+) and barriers (-) of COVID-19 vaccine acceptance	
	Before the availability of Pfizer/BioNTech vaccine	After the availability of Pfizer/BioNTech vaccine
	2020; Latkin et al., 2021; Lennon R.P., Small M.L., Smith R.A., Van Scoy L.J., Myrick J.G., Martin M.A., Group D.A.R., 2021; Berenson et al., 2021)	2021) -: not receipt of influenza vaccination in the last 5 years (Yang et al., 2021; Shallal et al., 2021)
Susceptibility to misinformation	-: susceptibility to misinformation (Roozenbeek et al., 2020; Loomba et al., 2021)	
Beliefs		
Concerned about COVID-19	+: fear, worry (Ruiz and Bell, 2021; Callaghan et al., 2021; Jacobi and Vaidyanathan, 2021; Head et al., 2020; Chu and Liu, 2021)	+: stress (Yang et al., 2021) -: not concerned (Kociolek et al., 2021)
Perceived likelihood of getting COVID-19	+: perceived likelihood of getting COVID-19 (Reiter et al., 2020; Head et al., 2020; Ehde et al., 2021; Guidry et al., 2021) -: not likely to get infected (Khubchandani et al., 2021)	+: perceived likelihood of getting COVID-19 (Ehde et al., 2021)
Perceived harms of a COVID-19 vaccine	+: less concern for serious vaccine side effects (Allen et al., 2021; Lucia et al., 2021) -: perceived harms of a COVID-19 vaccine (Doherty et al., 2021; Reiter et al., 2020; Chu and Liu, 2021; Latkin et al., 2021; Kelekar et al., 2021)	-: expected side effects severity (Kreps et al., 2021)
Perceived effectiveness of a COVID-19 vaccine	+: perceived effectiveness of a COVID-19 vaccine (Callaghan et al., 2021; Allen et al., 2021; Reiter et al., 2020; Latkin et al., 2021)	
Interpersonal level		
Family member/friend affected by COVID-19	-: not having anyone close to me directly affected by COVID-19 (Mercadante and Law, 2021)	+: know someone who died of COVID-19 (Piltch-Loeb et al., 2021)
Healthcare and societal level		
Healthcare provider recommendations for COVID-19 vaccination	+: healthcare provider recommendations (Reiter et al., 2020)	
Source of COVID-19 related information	+: scientists or mainstream TV or print outlets (Romer and Jamieson, 2020; Viswanath et al., 2021; Qiao et al., 2020) -: social media or pharmaceutical companies (Ruiz and Bell, 2021; Qiao et al., 2020)	+: national newspaper, national TV, local TV or public health officials (Harhay et al., 2021; Piltch-Loeb et al., 2021) -: non-medical sources or personal beliefs (Harhay et al., 2021)
Source of COVID-19 related information people trust in	+: experts, scientists, health agencies, pharmaceutical companies or mass media (Roozenbeek et al., 2020; Callaghan et al., 2021; Viswanath et al., 2021; Jacobi and Vaidyanathan, 2021; Latkin et al., 2021; Qiao et al., 2020; Kelekar et al., 2021; Lucia et al., 2021)	+: healthcare providers, pharmaceutical companies or CDC (Ehde et al., 2021; Benis et al., 2021) -: less trust in physicians (Carmody et al., 2021)

Table 1 (continued)

Factors	Facilitators (+) and barriers (-) of COVID-19 vaccine acceptance	
	Before the availability of Pfizer/BioNTech vaccine	After the availability of Pfizer/BioNTech vaccine
COVID-19 related conspiracy theories	-: social media (Qiao et al., 2020) -: conspiracy beliefs (Ruiz and Bell, 2021; Romer and Jamieson, 2020; Earnshaw et al., 2020)	

2021; Meier et al., 2021; Salmon et al., 2021; Kreps et al., 2021; Khubchandani et al., 2021; Hill et al., 2021; Reiter et al., 2020). A high level of religiosity was significantly associated with COVID-19 vaccine hesitancy (Callaghan et al., 2021; Olagoke et al., 2021).

Geographic location. People living or working in the south reported lowest COVID-19 vaccine acceptance (Fisher et al., 2020; Caban-Martinez et al., 2021). Rural location was also a significant barrier to COVID-19 vaccine uptake (Fisher et al., 2020; Shekhar et al., 2021)

3.4.1.2. Health history. Underlying medical conditions. Having underlying conditions was a positive predictor of intent to vaccination (Daly and Robinson, 2021; Ruiz and Bell, 2021; Trent et al., 2021). However, high-risk medical conditions were found to be negatively associated with COVID-19 vaccine uptake among children’s hospital staff after the COVID-19 vaccine was administered to their healthcare systems (Kociolek et al., 2021).

Personal history of COVID-19 diagnosis. Association of personal history of COVID-19 diagnosis with COVID-19 vaccination intention remains inconclusive. People with COVID-19 infection had a 1 to 2-fold higher likelihood of accepting a COVID-19 vaccine (Dalal et al., 2021; Reiter et al., 2020). However, HCWs reported that they would not receive a COVID-19 vaccine because of the history of COVID-19 diagnosis (Amin and Palter, 2021; Kociolek et al., 2021).

3.4.1.3. Behaviors. Receipt of influenza vaccination in the previous year. Receipt of influenza vaccination in the previous year was a facilitator of future COVID-19 vaccination (Ruiz and Bell, 2021; Fisher et al., 2020; Meier et al., 2021; Shekhar et al., 2021; Trent et al., 2021; Caban-Martinez et al., 2021; Ehde et al., 2021; Head et al., 2020; Latkin et al., 2021; Lennon R.P., Small M.L., Smith R.A., Van Scoy L.J., Myrick J.G., Martin M.A., Group D.A.R., 2021; Berenson et al., 2021; Harhay et al., 2021). For example, people who got influenza vaccine in 2019 were associated with 87% reduction in reporting low COVID-19 vaccine acceptability compared to people who refused influenza vaccine (OR = 0.13, 95% CI: 0.11–0.17) (Caban-Martinez et al., 2021).

Susceptibility to misinformation. Nationally representative studies demonstrated that susceptibility to COVID-19 or vaccine related misinformation was significantly associated with vaccine hesitancy (Roozenbeek et al., 2020; Loomba et al., 2021).

3.4.1.4. Health beliefs. Concerned about COVID-19. Negative feelings about COVID-19 such as higher levels of threat appraisal and fear of the pandemic was a significant predictor of future vaccine uptake (Ruiz and Bell, 2021; Callaghan et al., 2021; Jacobi and Vaidyanathan, 2021; Yang et al., 2021; Chu and Liu, 2021). However, people who were not or slightly concerned about COVID-19 were less likely to get a vaccine when available (Kociolek et al., 2021).

Perceived likelihood of getting COVID-19. People were more likely to get vaccinated if they reported risk of being infected with COVID-19 or perceived the severity of COVID-19 infection (Ehde et al., 2021; Reiter et al., 2020; Ehde et al., 2021). A national study found that people who believed that they would definitely not get infected were 6 time more likely to show vaccine hesitancy compared to people who perceived

higher likelihood of COVID-19 infection (OR = 6.47, 95% CI: 3.74–11.21) (Khubchandani et al., 2021).

Perceived harms of a COVID-19 vaccine. Perceived harms associated with a COVID-19 vaccine was a barrier to vaccine uptake. Nationally representative studies found that the first reason people intended not to pursue vaccination against COVID-19 was the skepticism of vaccine safety (Ruiz and Bell, 2021; Callaghan et al., 2021). A study showed that one unit increase in perceived potential harms of a COVID-19 vaccine was associated with 5% reduction in vaccine acceptance (relative risk (RR) = 0.95, 95% CI, 0.92–0.98) (Reiter et al., 2020).

Perceived effectiveness of a COVID-19 vaccine. Individuals who viewed vaccines as effective were less likely to oppose COVID-19 vaccination (Callaghan et al., 2021; Allen et al., 2021; Reiter et al., 2020; Latkin et al., 2021; Burke et al., 2021). However, people who thought the vaccine probably would not work were less likely to accept it (Ruiz and Bell, 2021).

3.4.2. Interpersonal level

Family member/friend affected by COVID-19. A nationally representative study found that respondents not having anyone close to them directly affected by COVID-19 were associated with lower COVID-19 intention compared to those who witnessed COVID-19 infection among members with close contact (Mercadante and Law, 2021).

3.4.3. Healthcare and societal level

Healthcare provider recommendations for COVID-19 vaccination. People were more likely to get vaccinated if their healthcare providers (HCPs) would recommend them to receive a COVID-19 vaccine (RR = 1.73, 95% CI: 1.49–2.02) (Reiter et al., 2020).

Source of COVID-19 related information. Source of COVID-19 related information plays a huge role in vaccine uptake. COVID-19 related information from social media (e.g., publishers without authoritative credentials) or pharmaceutical companies was a negative predictor of COVID-19 vaccination (Ruiz and Bell, 2021; Qiao et al., 2020). However, people who received information from public health officials, scientists, mainstream TV (e.g., ABC and CNN) or mainstream print outlets (e.g., The New York Times) were more likely to vaccinate against COVID-19 (Romer and Jamieson, 2020; Viswanath et al., 2021; Harhay et al., 2021; Qiao et al., 2020; Piltch-Loeb et al., 2021).

Trust in COVID-19 related information. Trust in experts, scientists, health agencies, pharmaceutical companies or mass media was positively associated with COVID-19 vaccinations while trust in social media was negatively associated with future vaccine uptake (Roozenbeek et al., 2020; Callaghan et al., 2021; Viswanath et al., 2021; Ehde et al., 2021; Jacobi and Vaidyanathan, 2021; Latkin et al., 2021; Qiao et al., 2020; Kelekar et al., 2021; Benis et al., 2021).

COVID-19 related conspiracy theories. Belief in COVID-19 related conspiracy theories was a persistent barrier to COVID-19 vaccine uptake (Ruiz and Bell, 2021; Romer and Jamieson, 2020; Earnshaw et al., 2020; Burke et al., 2021). For example, endorsement of conspiracies was found to be associated with a 74% reduced likelihood of accepting a COVID-19 vaccine (OR = 0.26, 95% CI: 0.15–0.44) (Earnshaw et al., 2020).

4. Discussion

4.1. Population with persistent COVID-19 vaccine hesitancy: Women and Black population

At the individual level, we observed significant gender disparities that females were less likely to get a COVID-19 vaccine relative to males (Daly and Robinson, 2021; Latkin et al., 2021; Khubchandani et al., 2021; Reiter et al., 2020), which is consistent with the findings reported in Canada, European and Asian countries (Ogilvie et al., 2021; Patelarou et al., 2021; Murphy et al., 2021; Wang et al., 2020). This result is not surprising as females are more cautious when making health decisions (Ek, 2015). Our review provided additional clues that females did not

believe the vaccine would be safe or effective (Callaghan et al., 2021). Fortunately, despite COVID-19 vaccine hesitancy, females were found to show a tendency of complying with public health recommendations (e.g., wearing a face mask, practicing social distancing and avoiding gatherings) to prevent the spread of the COVID-19 pandemic (Earnshaw et al., 2020; Khubchandani et al., 2020).

According to the US Department of Labor, women are the main medical decision makers, making 80% of healthcare decisions for their children (U.S. Department of Labor). On one hand, mothers with negative attitudes towards the vaccines were more likely to reject it for their children relative to fathers (Goldman et al., 2020; Teasdale et al., 2021). On the other hand, women could have a positive impact on their children's immunization. Young people are susceptible to conspiracy theories surrounding COVID-19 and thus are reluctant to vaccinate (Romer and Jamieson, 2020). Mothers are generally the information intermediaries between HCPs and their children and convey the importance and benefits of COVID-19 vaccination to children. Therefore, tailored programs to address women's concerns over vaccines can not only increase their COVID-19 vaccine uptake but have a significant impact on the health of their family members in terms of vaccination against COVID-19.

Black race was another important individual level factor associated with COVID-19 vaccine hesitancy (Callaghan et al., 2021; Shaw et al., 2021; Shekhar et al., 2021; Amin and Palter, 2021; Kociolek et al., 2021; Olagoke et al., 2021). Of note, despite the mounting evidence of high vaccine acceptance among older adults, the positive association between older age and vaccine acceptance was much weaker among Black participants than among White participants in a nationally representative study (Bleakley et al., 2021). Another study suggested higher vaccine hesitancy was found among Black participants under age 65 with high-risk health conditions (e.g., obesity, smoking or heart disease) relative to other racial/ethnic groups (Saluja et al., 2021). Vaccine hesitancy among Black population is concerning because they may be experiencing double or even triple jeopardy: Black race, older age and high-risk health condition, which are all established risk factors of severe COVID-19 illness (Poulson et al., 2021; Yanez et al., 2020; Chatters et al., 2020). The COVID-19 challenge for Black people are further compounded by the findings that Black race was associated with lower adherence to COVID-19 public health recommendations and even higher COVID-19 treatment hesitancy (Bogart et al., 2021; Block et al., 2020).

Negative attitudes towards vaccines may stem from COVID-19 related conspiracy beliefs or medical mistrust (Romer and Jamieson, 2020; Earnshaw et al., 2020; Bogart et al., 2021). For example, a study conducted among Black participants found that almost all participants (97%) endorsed at least one general COVID-19 mistrust belief (e.g., a lot of information about COVID-19 is held back by the government) (Bogart et al., 2021). Mistrust among Black population may be further exacerbated by the sociopolitical climate in the US (e.g., police brutality in 2020, which was found to increase medical mistrust) (Alang et al., 2020). Other reasons for COVID-19 vaccine hesitancy among Black population included perceived less likelihood of getting COVID-19, perceived potential harms or ineffectiveness of a COVID-19 vaccine and low socioeconomic status (e.g., lack of financial resources or housing insecurity) (Latkin et al., 2021; Callaghan et al., 2021; Shaw et al., 2021; Khubchandani et al., 2021; Moore et al., 2021). Concerted efforts to address Blacks' social determinants of health (e.g., early childhood education, community development and employment) and to build their trust in vaccine (e.g., strategic messaging from credible sources, collaboration between Black communities and healthcare system) are required to foster their COVID-19 vaccine acceptance (Thorn-ton et al., 2016).

4.2. Population vulnerable to COVID-19: People with medical conditions

Individuals with medical conditions were vulnerable to COVID-19.

An epidemiological study found that adults of any age with certain underlying medical conditions were associated with higher odds of mortality with COVID-19 (Harrison et al., 2020). Fortunately, pre-existing medical conditions were reported to be positive predictors of COVID-19 vaccine uptake (Daly and Robinson, 2021; Ruiz and Bell, 2021; Trent et al., 2021).

It should be noted that people with underlying medical conditions who remained hesitant to be vaccinated expressed their concerns that the vaccine would interfere with current medication efficacy (Dalal et al., 2021). They believed that data about vaccine safety/efficacy among patients with the same medical conditions and medications would help them make an informed decision (Dalal et al., 2021). Hence, for future clinical trials of COVID-19 vaccines, it is important to include participants with medical conditions into the trial while maintaining the ethical principles to provide more data about the compatibility of the vaccine with underlying health conditions and current medications. Additionally, HCPs should communicate the protective effect of the vaccine to their patients who are eligible for vaccination to enhance vaccine uptake among those vulnerable people.

4.3. People's negative health beliefs towards COVID-19 vaccines

At the individual level, potential harms associated with COVID-19 vaccines was the most commonly reported concern among people with vaccine hesitancy (Daly and Robinson, 2021; Ruiz and Bell, 2021; Latkin et al., 2021; Callaghan et al., 2021; Pogue et al., 2020; Dalal et al., 2021; Shekhar et al., 2021; Unroe et al., 2020; Bogart et al., 2021; Amin and Palter, 2021; Kociolek et al., 2021; Lucia et al., 2021). For example, a substantial number of people from a national sample worried that the side effects of the vaccine would be even worse than the COVID-19 itself (Pogue et al., 2020). Concerns regarding the effectiveness of COVID-19 vaccines were also prevalent among HCWs (Shekhar et al., 2021; Unroe et al., 2020) and the general populations (Ruiz and Bell, 2021; Callaghan et al., 2021). Other less reported concerns about COVID-19 vaccines included rapidity of the clinical development process, novelty of mRNA method, rapid authorization of the vaccine by FDA, lack of transparency on vaccines and allergic reactions to the vaccines (Gadoth et al., 2021; Ruiz and Bell, 2021; Fisher et al., 2020; Khubchandani et al., 2021; Shekhar et al., 2021; Kociolek et al., 2021). These health beliefs towards COVID-19 vaccines all represent modifiable targets for future communication strategies for reducing vaccine hesitancy (Reiter et al., 2020).

Despite the reported concerns related to the vaccine, most people endorsed the importance of the COVID-19 vaccine. Nearly all respondents (98.8%) from a medical school in Michigan agreed with the importance of developing COVID-19 vaccines, although 22.2% of them remained hesitant to vaccinate against COVID-19 (Lucia et al., 2021). Another national study found that 77.7% of people who were undecided on vaccination agreed that "getting a COVID vaccine would be a good way to protect me from coronavirus disease" or "getting the COVID vaccine will be important for the health of others in my community" (Daly and Robinson, 2021). Therefore, those who supported the importance of receiving a COVID-19 vaccine but remained hesitant may represent a particularly important subgroup for public health scientist to further understand and address their concerns over the COVID-19 vaccine.

Our findings in terms of the associations between negative beliefs about vaccine safety/effectiveness and vaccine hesitancy align with the findings observed in other countries (Aw et al., 2021; Salerno et al., 2021; Sherman et al., 2021; Wang et al., 2021). However, peoples' negative attitudes towards the vaccine differed in terms of the vaccine typology, and high vaccine acceptance was observed for the mRNA vaccine in Poland, Italy and Kuwait (Salerno et al., 2021; Al-Sanafi and Sallam, 2021; Rzymiski et al., 2021). The relative high trust in the mRNA vaccine could be explained by its high efficacy in reducing hospitalization/mortality and sufficient information on mechanism and clinical trials provided by health agencies. We additionally found that people

who were willing to choose the vaccine were less likely to take the vector vaccine in Italy (Salerno et al., 2021). Given the mRNA and vector vaccines are the main types of the vaccine available in the US, the future vaccine campaigns should take into account the differences in vaccine hesitancy in terms of vaccine typology as a way to optimize vaccine allocation to ensure that people get the vaccine of the preferences.

4.4. Social media as the source of COVID-19 related information

Social media has become one of the primary sources for people to obtain vaccine or pandemic related information, despite the fact that conspiracy and misinformation related to COVID-19 vaccine have been widely propagated on social media (Romer and Jamieson, 2020). We observed social media as the source of COVID-19 related information was significantly associated with the susceptibility to misinformation (Roozenbeek et al., 2020), which was found to be associated with less likelihood to vaccinate against COVID-19, less COVID-19 public health policy support and lower compliance with public health guidance (Roozenbeek et al., 2020; Earnshaw et al., 2020). The COVID-19 vaccine challenge is further exacerbated by the finding that anti-vaccination clusters are becoming highly entangled in the main online network, whereas pro-vaccination clusters are more peripheral and less likely to influence people (Johnson et al., 2020).

Vaccine hesitancy caused by conspiracy and misinformation circulating on social media highlights the importance of both limiting the spread of conspiracy/misinformation and educating the public to increase their vaccine uptake. Sharing information that is easy to digest and tailored to specific clusters (e.g., women, Black population and conservatives) on social media could be an effective strategy to leverage the influence of social media for enhancing COVID vaccine uptake among the general public.

4.5. Critical role of healthcare providers

We observed a low likelihood to vaccinate against COVID-19 among some HCPs (Gadoth et al., 2021; Shaw et al., 2021; Shekhar et al., 2021; Unroe et al., 2020; Amin and Palter, 2021). The vaccine hesitancy among this professional subgroup were resulted from less worry about getting COVID-19 and spreading the disease to others, concerns over the safety/effectiveness of the vaccine, novelty of mRNA method, perception of approval of the vaccine under political pressure and prior COVID-19 infection (Shaw et al., 2021; Shekhar et al., 2021; Amin and Palter, 2021; Kociolek et al., 2021). HCPs reported that their vaccination decisions were primarily influenced by self-awareness of COVID risk and/or research evidence. Moreover, most HCPs preferred website for self-learning to receive information on COVID-19 vaccines (Shaw et al., 2021; Kociolek et al., 2021). These findings are not surprising because background in biological science and familiarity with clinical development for vaccines confer autonomy in making health decisions among HCPs. The findings also highlight the importance of clinical trial transparency and data sharing to assist HCPs in making informed vaccination decisions.

According to this systematic review, a vast majority of people including Black population and people holding conspiracy beliefs identified HCPs as a trustworthy source that may influence their vaccine decisions (Malik et al., 2020; Shekhar et al., 2021; Earnshaw et al., 2020; Bogart et al., 2021; Kociolek et al., 2021; Ehde et al., 2021). For example, a national study reported that more than 70% participants viewed HCPs as the most reliable source of information on COVID-19 (Malik et al., 2020). Therefore, at the healthcare and societal level, HCP recommendations is a key determinant of vaccination against COVID-19 and HCP-led intervention targeting population with persistent vaccine hesitancy is promising to address hesitancy-related barriers.

However, HCPs might have missing opportunities in recommending COVID-19 vaccines to their patients due to interruption of healthcare seeking during the COVID-19 pandemic (Qiao et al., 2021; Papautsky

et al., 2021). Even among people with pre-existing health conditions who may need regular medical visits, only a limited number of them obtained COVID-19 related information from their HCPs (Ehde et al., 2021). In light of the time constraint in primary care settings (Konrad et al., 2010), possible solutions may involve training vaccine counselors at pharmacies/healthcare facilities and designing designated apps/platforms for HCPs to deliver COVID-19 vaccine messages. It is also important to note that health communication should be tailored to patients' health literacy and religious belief given the evidence of strong vaccine hesitancy among people with low educational attainment and a high level of religiosity (Daly and Robinson, 2021; Fisher et al., 2020; Callaghan et al., 2021; Halbrook et al., 2021; Caban-Martinez et al., 2021; Earnshaw et al., 2020; Bogart et al., 2021; Willis et al., 2021).

4.6. Study strengths and limitations

Our study is among the few that aggregate important evidence of COVID-19 hesitancy across multiple socioecological levels among populations in the US to shed light on designing targeted intervention programs. There are also limitations in the present review. One of the major limitations is the sole reliance on PubMed for literature search. However, the objective of this review is to conduct a rapid synthesis of factors associated with COVID-19 vaccine hesitancy, and PubMed is a standalone, reliable platform to effectively retrieve most relevant publications. Evidence summarized from PubMed-based articles should provide initial yet informative guidance for informing intervention opportunities and effective communication strategies with people who remain hesitant about COVID-19 vaccine uptake. Second, some studies are subject to selection bias because people needed internet access to participate in the study and complete the survey, so the summarized evidence may not be fully generalizable to the entire population (Mercadante and Law, 2021; Ruiz and Bell, 2021; Malik et al., 2020; Callaghan et al., 2021; Khubchandani et al., 2021). Third, evidence of determinants of vaccination intention on the interpersonal level, which was found to be significantly associated with COVID-19 vaccine hesitancy (Mercadante and Law, 2021; Piltch-Loeb et al., 2021), is limited in the present review. More studies are required to investigate the association of interpersonal level factors with vaccine hesitancy. Last, 58.5% of studies in this review focused on the general population. There remains a need for more research on the determinants of COVID-19 vaccination intention among people with persistent hesitancy (e.g., women, Black population, young adults and religious communities).

5. Conclusion

Vaccine hesitancy is still a challenge for successful implementation of COVID-19 immunization programs in the US. According to nationally representative studies, overall COVID-19 acceptance rate ranges from 53.6% to 84.4%. Our review demonstrates that acceptance to COVID-19 vaccines is influenced by various factors, particularly the role of HCPs in enhancing public intent to vaccination. Potential interventions to mitigate people's concerns over the vaccine and address vaccine related conspiracy/misinformation from social media are also critical to encourage vaccine uptake in the US.

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CRediT authorship contribution statement

Ying Wang: Methodology, Writing – original draft. **Yu Liu:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration.

Declaration of Competing Interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pmedr.2021.101673>.

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