Systematic Review and Meta-analysis on COVID-19 Vaccine Hesitancy

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Abstract

Background:

The presented meta-analysis was developed in response to the publication of several studies addressing COVID-19 vaccines hesitancy. We aimed to identify the proportion of vaccine acceptance and rejection, and factors affecting vaccine hesitancy worldwide especially with the fast emergency approval of vaccines.

Methods:

Online database search was performed, and relevant studies were included with no language restriction. A meta-analysis was conducted using R software to obtain the random effect model of the pooled prevalence of vaccine acceptance and rejection. Egger’s regression test was performed to assess publication bias. Quality assessment was assessed using Newcastle-Ottawa Scale quality assessment tool.

Results:

Thirty-nine out of 12246 articles met the predefined inclusion criteria. All studies were cross-sectional designs. The pooled proportion of COVID-19 vaccine hesitancy was 17% (95% CI: 14-20) while the pooled proportion of COVID-19 vaccine acceptance was 75% (95% CI: 71-79). The vaccine hesitancy and the vaccine acceptance showed high heterogeneity (I²=100%). Case fatality ratio and the number of reported cases had significant effect on the vaccine acceptance as the pooled proportion of vaccine acceptance increased by 39.95% (95% CI: 20.1-59.8) for each 1% increase in case fatality (P<0.0001) and decreased by 0.1% (95% CI: -0.2-0.01) for each 1000 reported case of COVID-19, P= 0.0183).

Conclusion:

Transparency in reporting the number of newly diagnosed COVID-19 cases and deaths is mandatory as these factors are the main determinants of COVID-19 vaccine acceptance.

Keywords: COVID-19, Vaccine hesitancy, vaccine side effects, vaccine immunogenicity, vaccine intake, vaccine acceptance

Abbreviations:

| AESI                  | Adverse Events of Special Interest |
| Abbreviation | Description |
|--------------|-------------|
| CAWI         | Computer Assisted Web Interviews |
| CI           | Confidence Interval |
| COVID-19     | Coronavirus Disease |
| F            | Female |
| FDA          | Food and Drug Administration |
| HCWs         | Health Care Workers |
| M            | Male |
| mRNA         | Messenger Ribonucleic Acid |
| n            | Number |
| NA           | Not Available |
| PRISMA       | Preferred Reporting Items of Systematic Review and Meta-analysis |
| QA           | Quality Assessment |
| RRR          | Relative Risk Ratio |
| SARS-CoV-2   | Severe Acute Respiratory Syndrome Coronavirus 2 |
| SD           | Standard Deviation |
| SMS          | Short Message Service |
| UK           | United Kingdom |
| US           | United States |
| VAERS        | Vaccine Adverse Event Reporting System |
| VPD          | Vaccine Preventable Diseases |
| WHO          | World Health Organization |
Introduction:

The wide use of vaccines has led to decreased mortality and morbidity of different transmissible diseases, this was a crucial factor in elimination of poliomyelitis in the Americas and the worldwide eradication of smallpox (1). Vaccination programs depend on mass vaccination to be able to decrease incidence and prevalence of Vaccine Preventable Diseases (VPD). In addition to the proposed direct protection for vaccinated candidates, wide vaccination scope results in indirect shielding for the overall community by declined conveyance of VPD, thereby dampening the risk of infection for vulnerable individuals in the community (2).

One of the main limiting factors for wide-spread of vaccination programs (especially for newly emerging vaccines) is vaccine hesitancy. The World Health Organization (WHO) named vaccine hesitancy as one of the top ten threats to global health in 2019, calling for research to identify the factors associated with this phenomenon (3). Vaccine hesitancy is defined as a behavior of a delayed vaccine approval or even declined vaccination despite accessible vaccination services (4, 5).

The pandemic COVID-19 caused by the recently discovered coronavirus-2019 (SARS-CoV-2) is strongly influencing the worldwide public health, culture, economy, and human social behavior. Despite all efforts since the beginning of the pandemic there is no approved medicine or treatment to cure COVID-19 till now, whereas vaccine development efforts are taking the highest priority as it can potentially save humanity by inducing immunity against COVID-19 (6).

According to WHO, herd immunity against COVID-19, which is known as population immunity, can be achieved naturally by the exposed people who recovered from the virus by their own protective antibodies or by providing COVID-19 vaccination (7, 8). Herd immunity for COVID-19 can be achieved on 70% of the single vaccinated dose individuals and 90% of the two vaccinated dose individuals (9).

Vaccines typically require years of research and testing before reaching the clinic, but in 2020, scientists were racing against time to produce safe and effective coronavirus vaccines. Currently we have 14 approved vaccines for full use, 6 authorized in early or
limited use, 27 vaccines in phase 3 trials, 36 vaccines in phase 2, 48 vaccines in phase 1 and 4 abandoned vaccines after trials. In addition, at least 77 preclinical vaccines are under active investigation in animals (10). Unfortunately, the newly emerging vaccines for COVID-19 are faced nowadays with hesitancy to use in different countries. People showed concerns about both efficacy and possible side effects of these recently approved vaccines. Such hesitancy can have a heavy influence on vaccine delivery and the aimed wide uptake to control the pandemic (11). After the announcement of several pharmaceutical manufactures the production of COVID-19 vaccines, social media started to discuss vaccine content widely across different platforms. The propagated information provides mostly non-factual data and from non-medical individuals (12).

The presented systematic review & meta-analysis was developed in response to the publication of several studies addressing COVID-19 vaccines hesitancy. Identification of independent factors affecting vaccine hesitancy worldwide especially with the fast emergency approval of these vaccines.

**Methods**

**Data sources**

This meta-analysis was guided by the 2020 Cochrane Handbook of Systematic Review and Meta-Analysis (13), with respect to the preferred reporting items of the systematic review and meta-analysis (PRISMA) checklist (14). Search was conducted for the hesitancy or refusal of COVID-19 vaccination through the published and grey literature using multiple databases; PsycINFO, ScienceDirect, Embase, Scopus, EBSCO, MEDLINE central/PubMed, ProQuest, SciELO, SAGE, Web of science, and Google scholar. Search terms were determined and approved after the consultation of PubMed help desk. The used keywords were added to Annex 1.

**Study selection**

All studies reporting COVID-19 vaccine hesitancy, were included with no language restriction. Abstract-only papers as proposals, conference, editorials, author
responses, reviews, case reports, case series, books and studies with data not accurately
or reliably extracted, duplicate, or overlapping data were excluded.

**Data extraction and selection process**

**Figure(1)** depicts the PRISMA flow chart for the different steps of the systematic
review. All articles were imported into EndNote X7.0.1 to detect and remove the
duplicates with two methods: title, author, year, and then manually using title, author, and
journal. Title and Abstract screening followed by full text screening were done after the
citation’s exportation to an Excel sheet containing the author's name, publication year,
journal, DOI, URL link, and the abstract. Screening was performed independently by 3
reviewers NA Hamdy, EAD fourth reviewer IAA solved any disagreement. The kappa
test of agreement between reviewers was 0.89.

Further manual search for eligible citations was done through careful examination
of the references of included studies as well as studies citing the selected articles using
PubMed and google scholar. All included articles were extracted to an excel sheet with
the following predefined data: year of publication, authors name, country, study design,
study setting, study population, sample size, duration of the study, inclusion and
exclusion criteria, percent refusal, percent acceptance, cause of refusal and cause of
acceptance. Excel sheets are available online for reviewers. At Annex 2
[https://drive.google.com/file/d/12tiK2yW9RGmVnxOTphDKOAuAFyMVub_K/view?usp=sharing](https://drive.google.com/file/d/12tiK2yW9RGmVnxOTphDKOAuAFyMVub_K/view?usp=sharing)

**Investigations of heterogeneity:**

Cochrane Q test and (I^2) test was used to assess and measure heterogeneity
between studies, considering $I^2 \geq 75\%$ represents substantial heterogeneity and strength of
evidence for heterogeneity is the P- value $\leq 0.05$ from the Q test; according to Cochrane
Handbook for Systematic Reviews of Interventions (13). Due to substantial heterogeneity,
DemSimonian and Laird random-effects models were applied to pool the outcomes.

**Publication bias:**
Publication biases were assessed by visual inspection of the funnel plot and statistically by Begg’s modified funnel plot and Egger’s regression test (13).

**Quality assessment**

Quality assessment (QA) was assessed using Newcastle-Ottawa Scale quality assessment tool customized for cross-sectional studies (15). The assessment was performed by two independent reviewers (DMH, EE) and further checked by two additional reviewers (SO EI-ganainy, AA).

**Statistical analysis and data synthesis:**

R software was used to perform the meta-analysis and to pool the effect size (proportion); fixed or random effect model were used according to the studies' consistency. Meta-regression analysis was performed to examine the impact of confounders on the effect of vaccine hesitancy such as age, sex, and country. Results were presented in the Forest plots to visualize the degree of variation between studies. **Leave one-out sensitivity analysis** was conducted to test the effect of each study on the pooled effect to determine the robustness of the obtained outcomes. **Sub-group analysis** was performed to categorize the vaccine hesitancy according to sample size studies.

To investigate the sources of high heterogeneity in the pooled prevalence of vaccine acceptance and hesitancy, meta-regression analysis was performed with different models including the main predictors of vaccine acceptance and hesitancy reported in included studies such as age, sex, educational level and setting. Additionally, number of reported cases, number of reported deaths, case fatality ratio and number of vaccinated people within each country until the end of January 2021 (16, 17), were examined as potential modifiers of vaccine acceptance and hesitancy and included in the meta-regression model.
Results:

Search results:

The flow diagram of the selection process is shown in figure 1. From a total of 12246 potentially relevant articles, 1621 duplicate articles and 2944 citations published before 2019 were excluded. A total of 7681 citations were eligible for title screening. Only 51 articles were eligible for full-text screening after removing irrelevant (7627) and duplicate articles (3). In total 34 articles were excluded after full text screening (2 duplicates and 29 irrelevant), 3 were retracted. Another 22 articles were added manually. For quantitative assessment, there were 39 eligible articles. The inter-rater agreement for inclusion was $\kappa=0.87$ and for the quality assessment was $\kappa=0.91$. 
Figure 1: PRISMA flow chart of studies screened and included.
Figure 2 presents the funnel plot of 38 studies reporting the COVID-19 vaccine hesitancy and Eggers’ test \( t = -1.215, \ P\text{-value} = 0.232 \), show absence of asymmetry and disapprove any publication bias. Figure 3 depicts the studies reporting COVID-19 vaccine acceptance and Eggers’ test \( t = -0.64, \ p\text{-value} = 0.526 \).
Table 1 shows the main findings of included studies; all the studies were cross-sectional surveys. The total sample size was 173213 ranging from 351 in the study of Sharun et al., 2020 (18) reaching 32361 in the study of Paul et al., 2021 (19). The highest presentation of female sex was in the study of Kowk, 2021 (20) followed by Wang 2020 (21) while the lowest proportion of females was in the study of Malik et al. 2020 (22). Age range was 15->85 in the study of Taylor 2020, the mean age of the study participants was the highest in the study of Taylor 2020 (23) (53 years old) and lowest in the study of Al-Mohaithef (24) 31.5 years old. Tools used to assess vaccine hesitancy were online questionnaires either Google forms or Qualtrics forms. Data was collected either through face-to-face interview, online, or both. The quality score of the studies were either very good in 5 studies, good in 20 studies, satisfactory in 12 studies, and unsatisfactory in 5 studies. The main identified predictors of vaccine hesitancy were age, gender, general trust and unknown side effects of the vaccine. The highest vaccine hesitancy were in Wang et al., 2020 study (21) (47.8%) and Unroe et al., 2020 study (25) (45.1%), while Murphy 2021 et al., 2020 study (26) (6%) and Salali and Uysal,, 2020 study (27) (3%) showed the lowest vaccine hesitancy rates.

Table 1: Summary Table of included studies in the meta-analysis

| Author, Year, Country | Population criteria + inclusion and exclusion | Sample size/ Sex/ Age | Tool used in hesitancy% estimation | Predictors | Duration | Qualit y | Qua sc
|-----------------------|-----------------------------------------------|-----------------------|-----------------------------------|------------|---------|---------|-------|
| Taylor, 2020, Canada and USA (23) | Adults who have agreed to be contacted in order to respond to surveys. Excluding careless or incomplete responses | Sample size = 3,674 (USA = 1,772 Canada= 1,902) Sex= 57% male Age = 53±15 | Internet-based self-report survey delivered in English | 1- Mistrust of vaccine benefit. 2-Worry about unforeseen future negative effects. 3- Concerns about commercial profiteering. 4-Preference for natural immunity | May 6–19, 2020 | good |
| Fisher, 2020, Worcester County, Massachusetts, United States (28) | adults residing in the United States excluded participants who did not respond to the question on intent to be vaccinated | Sample size = 991 Sex= 48.5% male Age = 48±18.1 | 1-Receive an initial invitation via email, SMS, or phone. 2-Households without Internet access are included and complete the survey via smartphone or telephone interview | Age group,race,gender,education,setting, guessing as getting the coronavirus within the next 6 months, influenza vaccine | 16 - 20 April 2020 | good |
| La Vecchia, 2020, Italy (29) | A nationally representative survey of the | Sample size = 1055 | Using computer assisted web interviews (CAWI). | ---- | September 16-28, 2020 | satisfactory |
| Study | Country | Sample Characteristics | Methodology | Key Measures | Sample Size | Sample Description | Data Collection Period | Quality of Study |
|-------|---------|------------------------|-------------|--------------|-------------|-------------------|------------------------|-----------------|
| Sherman, 2020 | United Kingdom | Participants were broadly representative of the UK population aged 18 years or over | Online survey | Age, sex, religion, ethnicity, qualification, employment status, key worker, extremely clinical vulnerable, previous influenza vaccination, general vaccination beliefs and attitude, beliefs and attitude towards COVID-19, perceived Risk of COVID-19 to oneself, having or not COVID-19. | 1500 | Sex = 48.24% male; Age = 15-85 | Between 14th and 17th July 2020 | Very good |
| Lucia, 2020 | Southeast Michigan | Medical students aged 18 years or over | Online survey | --- | 168 | Sex = 43.4% male; Age = 18-46 | --- | Satisfactory |
| Salali and Uysal, 2020 | UK and Turkey | All participants aged 18 years or over, residing either in the UK or Turkey. | Online survey | COVID-19 vaccine acceptance, believing in the natural origin of the virus | UK (n = 1088) and Turkey (n = 3936) | Sex = 43.6% male; Age = 46 ± 15.8 | Throughout May 2020 | Very good |
| Al-Mohaithef, 2020 | Saudi Arabia | All participants were above 18. | Online survey | Sociodemographic predictors (age, gender, marital status, nationality, residence, occupation, education), risk and trust to health system | Saudi Arabia (n = 992) | Sex = 34.17% male; Age = 18-45 | ----- | Good |
| Kreps, 2020 | USA | US adults (No = 2000 while only 1971 were respondents) completed the full questionnaire | Online survey | Vaccine efficacy, adverse effects, and protection duration and political factors (e.g., US Food and Drug Administration approval process, national origin of vaccine, and endorsements), Health care attitudes and practices, political partisanship, and demographic characteristics, including age, sex, and race/ethnicity | USA | Sex = 49% male; Median Age = 43 (30-58) | July 9, 2020 | Good |
| Gagneux-Brunon, 2020 | France | General Population and Health Care Workers in France | Combined (Online Survey + written questionnaire) | Age, gender, profession, chronic medical conditions, getting Flu vaccine during the previous season, Fear about COVID-19, Perceived individual risk, Vaccine hesitancy | France (n = 2047) | Sex = 26% male; Age = <30–>65 | From 26th March to 2nd July 2020 | Unsatisfactory |
| Lin, 2020 | China | Participants aged 26 to 35 years old (47.2%). | Online questionnaire | --- | 3,541 | Sex = 48.1%, F = 51.9% | 1–19 May 2020 | Good |
| Barello, Serena, 2020 | Italy | Italian University students | Online survey | --- | 934 | | 1st-19th May 2020 | Unsatisfactory |
| Dror, 2020 | Israel | NA | Qualtrics online survey | --- | 1941 | | 2-weeks | Good |
| Author, Year, Location | Sample Description | Sample Size | Gender Distribution | Methodology | Key Findings | Data Collection Period | Quality Assessment |
|------------------------|--------------------|-------------|---------------------|-------------|--------------|-----------------------|-------------------|
| Akarsu, 2020, Turkey (37) | Social Media and smartphone users | 852 | Female 62.8% Male 37.2% | Online Survey | lower age, female gender, lower education, lower income, black and mixed ethnicities, not being single or widowed, not being a homeowner, not being employed full-time, not retired, a change in working, having a child at school. | good |
| Freeman, 2021, UK (38) | UK adults (38) | 5,114 | Age mean (SD)=46.9 (17.1) Male; female; non-binary; prefer not say=2574; 2515; 20; 5 | Online Survey | | 24th September-17th October 2020 | good |
| Butter, 2020, UK (39) | UK adults who took part in the 1-month follow-up survey of the COVID19 Psychological Wellbeing Study. AND only individuals who reported not having been previously diagnosed with COVID-19 (formally diagnosed, diagnosed by GP or self-diagnosed) | 1605 | Male Key workers 146 (25.0) Non-Key workers 347 (34.3) Female Key workers 437 (75.0) Non-Key workers 664 (65.7) Age Group 18-24 Key workers 60 (10.3) Non-Key workers 211 (20.7) 25-34 Key workers 197 (33.7) Non-Key workers 320 (31.3) 35-44 Key workers 175 (30.0) Non-Key workers 210 (20.6) 45-54 Key workers 100 (17.1) Non-Key workers 136 (13.3) 55+ Key workers 52 (8.9) Non-Key workers 144 (14.1) | Online Survey | | between 22nd April and 18th May 2020 | satisfactory |
| Muqattash, 2020, UAE (40) | (aged 18 and above) living in the UAE | 1109 | M=27.86% F=72.14% Age Group 1-18 to 25[143 12.89% 2-26 to 35] 310 3-36 to 45] 437 4-45 and over] 219 39.40% 19.75% | Google Forms platform survey | | July 4th to August 4th 2020 | satisfactory |
| Ward, 2020, France (41) | Age≥18 | 5018 | | Online survey | Gender male 0.69 [0.59; 0.82] Age <35 y.o 1.36 [1.14; 1.62] >64 y.o 0.29 [0.22; 0.38] COVID-19-related concern | 4 weeks April 2020 | good |
| Unroe, 2020, India (25) | Nursing home and assisted living facility staff | 8,243 | F= 87.2% M=12.8% | Survey via text message or email | Side effects | November 14 and 17, 2020 | satisfact ory |
|-------------------------|------------------------------------------------|-------|------------------|-------------------------------|--------------|------------------------|--------------|
| Wang, K., 2020, China (21) | Nurses, administrative or academic positions excluded | 806 | F=87.5% M=(12.5)% 21.6% nurses aged 18–29, 31.1% aged 30–39, 27.1% aged 40–49 and 20.2% aged 50 or above | Online survey | Gender 2.78 (1.69, 4.58) | Having chronic conditions 1.83 (1.22, 2.77) | Public or private 1.67 (1.11, 2.51) | 26 February and 31 March 2020 | unsatisf actory |
| Goldman, 2020, (USA, Canada, Israel, Japan, Spain, and Switzerland) (42) | Caregiver families | 1541 | F=72% M=25.5% Age mean=59 (SD7.6) | Online survey |  |  |  | 26th March-31st May 2020 | good |
| Reiter, 2020, USA (43) | Adults | 2006 | F=56% M=43% | Online survey |  |  |  | May 2020 | good |
| Wang J, 2020, China (44) | Adults | 2058 | F=54.2% M=45.8 | Online survey | NA |  |  | good |
| Sharun, 2020, India (18) | Adults | 351 | F=58.1% M=41.3% | Online survey | NA |  |  | March 2020 | very good |
| Lazarus, 2020, Global (11) | Adults | 13,426 | F=53.5% M=46.5% | Online survey | NA | NA |  | October 2020 | good |
| Kose, 2020, Turkey (45) | healthcare personnel | 1138 | F=72.5% M=27.5% | Google Forms questionnaire | gender Age group Occupation Flu-vaccination status | 17th -20th September 2020 | satisf actory |
| Biasio , 2020, Italy (46) | Adults | 885 | Males (49.9%) Females (50.1%) | Online survey | NA | 2 weeks | good |
| Grünert, 2020, Germany (47) | - university students who are enrolled in a healthcare degree programme (Healthcare students) - university students who are not (Non-healthcare students) | 2,077 |  | Online survey | NA | 18.5.2020-2.8.2020 | satisf actory |
| Malik, 2020, USA (22) | Adults | 672 | Males (72%) compared to | Qualtrics Online survey |  |  | May 2020 | good |
| Study (year, country) | Sample characteristics | Sample size | Data collection method | Follow-up period | Site contacted | Sample characteristics | Follow-up period | Site contacted | Sample characteristics | Follow-up period | Site contacted |
|----------------------|------------------------|-------------|------------------------|------------------|---------------|------------------------|------------------|---------------|------------------------|------------------|---------------|
| Paul, 2020, UK (19)  | Adults who had started the vaccine module administered from 7 September to 5 October 2020. | 32,361 participants | Data were drawn from the COVID-19 Social Study online survey | Being female RRR = 1.45; 95% CI: 1.27 to 1.65 | Started on March 2020 | Duration NA | satisfactory |
| Kwok, 2020, Hong Kong (20) | 1,205 eligible nurses (mean age = 40.79, SD = 10.47; 90% being female) | online survey | 1-Confidence 2-Complacency 3-Collective responsibility | mid-March and late April 2020 | good |
| Edwards, 2020, Australia (48) | Adults 3,061 adults Age 18-75 | online survey | Age Sex university degree neighbourhood differences household income who downloaded the COVID-Safe App who thought too much fuss who voted for the Coalition who voted for Labor confidence in their state or territory government or in their hospitals and health system religion populist views who were more likely to support migration levels of social distancing | good |
| Detoc, 2020, France (49) | 3259 F=67.4% M=32.6 | online survey | NA | 26th March-20th April 2020 | satisfactory |
| Adebesie, 2020, Nigeria (50) | 517 F=43.1% M=56.9% Age≥15 | online survey | Age employment education level | good |
| Murphy, 2021, UK (26) | NA | 2025 F=51.7 M=48.3% | online survey | Gender Age group | NA | satisfactory |
| Murphy, 2021, Ireland (26) | NA | 1041 F=51.5% M=48.2% | online survey | Gender Age group Mental health history | NA | satisfactory |
| Barry, 2020, Saudi Arabia (51) | Healthcare workers | 1058 F=62.4% M=37.6% | online survey | Efficient data Lack of sufficient safety Potential adverse effects Belief that vaccine would be ineffective Compliance confidence | 4-14 December 2020 | very good |
| Chen, 2021, China (52) | NA | 3195 | online survey | Lack of confidence Complacency Risk of the vacc. Attention frequency | NA | very good |
| Meyer, 2020, USA (53) | Patient-facing HCWs and other roles | 16158 | online survey | Unknown risk Insufficient data Known side effects Don’t trust FDA Privacy concerns about Geisinger and state tracking Depend on which vaccine and concerns about mRNA Not at high risk for serious disease Not at high risk for infection Had COVID or vacc. Unnecessary | December 2020(month) | satisfactory |
| Robertson, 2021, NA | NA | 12,035 | online survey | Future unknown effect | Nov.-Dec.2020 | good |
Predictors of COVID-19 vaccine acceptance and hesitancy

Multiple factors were associated with vaccine hesitancy Table(1). Previously receiving influenza vaccine is the main factor that determines the acceptance of COVID-19 vaccine. Individuals reporting intake of influenza vaccine were more likely to accept COVID-19 vaccine than those who did not receive it previously (21, 28, 33). Some socio-demographic characteristics were considered to influence the acceptance of the vaccine. Being young was associated with no or not sure response towards the intake of COVID-19 vaccine (28, 38, 41), while older individuals were more likely to accept the vaccine intake (24, 33). Regarding the gender, males were more likely to accept the vaccine rather than females (21, 33, 38, 45). Low education levels and income, being not employed in a full time job or retired were associated with refusal of the vaccine(19, 28, 38, 41), while those with professional private work were more likely to accept the vaccine (21). The marital status also affects the response to vaccine acceptance, being single or widowed were associated with hesitancy (38), while married individuals were more likely to accept the vaccine (24). Racial and ethnic groups were noticed to affect the acceptance of vaccine. Black race and mixed ethnicity were associated with hesitancy towards the vaccine (28, 38). Other factors that increase the acceptance towards the vaccine is the presence of trusted health systems (24), the fear from getting infected with the virus (33) and having chronic diseases (21). While factors that increase the refusal of the vaccine involve the suspicion from its efficacy and effectiveness (21), individuals may think
about the side effects and do not believe that the vaccine will work, or they trust their immune system and are not afraid of getting sick (45).

**Pooled proportion of COVID-19 vaccine hesitancy and acceptance**

Using the random effect model, (figure 5) the pooled proportion of COVID-19 vaccine hesitancy among 173213 participants recruited from 39 studies was 17% (95% CI: 14-20). Vaccine hesitancy ranged from 55% (95% CI: 85-87) in the study of Unroe, 2020 (25) to 3% (95% CI: 3-4) in the study of Salali, 2020 (27) and 3% (95% CI: 2-3) in Chen, 2021 (52), with high heterogeneity ($I^2 = 100\%$). To identify the cause of such heterogeneity, researchers conducted Leave one out sensitivity analysis, sub-group analysis, or meta-regression, however, these analyses failed to explain this heterogeneity. On the other hand, the pooled proportion of COVID-19 vaccine acceptance (figure 6) was 75% (95% CI: 71-79). The vaccine acceptance was the highest in Chen, 2021 (97, 95% CI =97-98) and the lowest in Goldman, 2020 (35, 95% CI =32-37). Similar to the vaccine hesitancy, the vaccine acceptance showed high heterogeneity ($I^2=100\%$). However, meta-regression revealed that case fatality, sample size, the number of reported cases per country and the type of study setting explained 38.52% of the model heterogeneity (p-value <0.0001), the estimated amount of residual heterogeneity ($T^2$) was 0.3201 (SE = 0.1350). However, only case fatality and the number of reported cases had a significant effect on vaccine acceptance. The pooled proportion of vaccine acceptance increased by 39.95% (95% CI = 20.1-59.8) for each 1% increase in case fatality ($p<0.0001$) and decreased by 0. 1% (95% CI = -0.2 to -0.01) for each 1000 reported case of COVID-19 ($p = 0.0183$). Figure (4) shows the results of the meta-regression models between the case fatality (%) and the proportion of vaccine hesitancy and vaccine acceptance, respectively by type of setting and study sample size.
Figure (4) the relation between vaccine acceptance (%) and case fatality (%) by sample size and study setting
Figure (5) Forest plot of pooled prevalence of vaccine hesitancy
Figure (6) Forest plot of the pooled vaccine acceptance
Discussion

The vaccine for COVID-19 availability is a critical step to face the COVID-19 pandemic. But vaccine hesitancy represents a great threat to global health during this pandemic and limits the power of health systems to control the COVID-19 pandemic. Hence, estimating the COVID-19 vaccine hesitancy represents a tool to design an action plan to improve the vaccine acceptance.

In this meta-analysis, there was large variability between the studies discussing COVID-19 hesitancy in terms of vaccine acceptance. We aimed to determine the proportion of the population who are rejecting and accepting COVID-19 vaccine worldwide. We included 39 cross-sectional surveys conducted in 21 countries requiring 173213 participants. The quality of studies ranged from unsatisfactory, to very good. Our meta-analysis revealed that the pooled proportion of COVID-19 vaccine hesitancy was 17% (95% CI: 14-20) while the pooled proportion of COVID-19 vaccine acceptance was 75% (95% CI: 71-79). The main reported determinant of vaccine acceptance was case fatality and number of reported cases. Time effect was not associated with vaccine acceptance.

In the same line, a rapid systematic review and meta-analysis on COVID-19 vaccine hesitancy was conducted by Ronbinson et al, (61) to estimate the proportion of individuals refusing COVID-19 vaccine in 13 countries among 58,656 individuals. They reported that about 20% of the participants refused COVID-19 vaccine. They observed that differences across countries were very substantial and resulted in a heterogeneity above 90%. Furthermore, they declared that the trend of rejection increased with time. The main determinants of COVID19 vaccine rejection were being female, of low educational level, or belonging to minor ethnicity.

Another review conducted by Lin et al, (62) compared trends in vaccination receptivity over time across US and international polls. The data sources included academic literature, news and official reports published by 20 October 2020. A total of 126 studies and surveys were included. The authors reported that there was a noticeable decline in vaccine acceptance (from >70% in March to <50% in October) with demographic, socioeconomic, and partisan divides observed. Perceived risk, concerns over vaccine safety and effectiveness, doctors’ recommendations, and inoculation history
were common factors. Impacts of regional infection rates, gender, and personal COVID-19 experience were inconclusive. Unique COVID-19 factors included political party orientation, doubts toward expedited development/approval process, and perceived political interference. Many receptive participants preferred to wait until others have taken the vaccine; mandates could increase resistance.

We speculate that the difference in vaccine acceptance may be affected by vaccine efficacy and side effects. Vaccines' side effects range between local to systemic, and short to long term events. The reported common side effects are generally mild to moderate and last for a few days. These include injection site pain, fatigue, rigors, fever, muscle and joints pains. Less commonly, a vaccine recipient may develop allergic reaction or anaphylaxis, and neurological side effects; however they are rarely reported (63). There is a rising concern particularly related to reported thrombo-embolic events, particularly after administration of AstraZeneca vaccine in Europe, but the European Medicines Agency concluded that the benefits of the vaccine overweighs the potential risk of this rare side effect (64). In this context, Kaplan et al., (65) underlined that vaccine acceptance improved when vaccine efficacy exceeds 70%. Moreover, they addressed that minor side effects, such as a sore arm or fever lasting for a day did not affect vaccine acceptance, while major side effects in 1/100000 greatly affected vaccine acceptance. These side effects may vary according to the type of vaccine used in each country. Emerging evidence suggests that both exposure to misinformation about COVID-19 and public concerns over the safety of vaccines may be contributing to the observed decline in intentions to be vaccinated, and this highlights the need for measures to address public acceptability, trust and concern over the safety and benefit of approved vaccines (66, 67). This finding highlights the power of social media. Some studies emerged in the last months discussing the vaccine confidence in several populations, especially in countries with high burden of diseases like Pakistan (68). The role of recent misinformation was evident in the study of Loomba et al., (Measuring the impact of COVID-19 vaccine misinformation on vaccination intent in the UK and USA), it induced a decline in intent of 6.2 percentage points in the UK and 6.4 percentage points in the USA, among those who stated that they would definitely accept a vaccine. From another perspective, other studies analyzed attitudes toward COVID vaccination like the impact of
education, whether medical or nonmedical students, on their decision (35). With the development of multiple effective vaccines, Immunization programs are only successful when there are high rates of acceptance and coverage (69). To accomplish this, it is critical to understand vaccine-acceptance messaging to effectively control the pandemic and prevent thousands of additional deaths (70). Individuals commonly considered COVID-19 to be a very severe disease, although they expected to experience less severe symptoms themselves. Individuals also worried more about transmitting the disease to others than about falling ill personally (71).

The strongest predictor of intentions to accept a COVID-19 vaccine recommended by authorities was the degree to which respondents trusted the vaccine to be safe. Perceived vaccine safety explained 52% of the variance in intentions to vaccinate (72). The study of Malik et al. shows that COVID-19 vaccine acceptance can be predicted with relatively high accuracy by readily available demographic characteristics. Since the beginning of the COVID-19 pandemic in the United States, it has been clear that low-income and communities of color are at higher risk for infection and death from COVID-19 (22).

**Strengths and limitations**

One of the main strength points in this study is the search strategy, we searched 12 different databases. Each citation was screened by two reviewers and disagreement was solved by a senior author. The same was done for quality assessment to ensure robust evidence. A large proportion of the included studies used quota (as opposed to probability-based sampling) and were pre-prints yet to be peer reviewed (as opposed to published journal articles). However, the type of sampling method used (quota vs. probability) had minimal impact on intentions estimates and that studies reported in pre-prints produced similar effect estimates as peer-reviewed journals. One of the main limitations was different tools used to assess vaccine acceptance in addition, the data collected either through face-to-face interview or through online data collection tools. We think that this may affect the internal validity of the study. However, we segregated analysis based on the method of data collection and the difference was not significant.
Conclusions

COVID-19 vaccine rejection is low; however, continuous health education and social support is necessary to maintain the high acceptance rates. Time and residency have no significant effect on vaccine acceptance. However, the country-level case fatality and the officially reported number of cases were significant predictors of COVID-19 vaccine acceptance. That’s why encouraging the health authorities to accurately follow & announce case fatalities could be a major contributing factor to increasing vaccine acceptance. We believe that this study will demonstrate public hesitancy and help further development of motivational interview sessions and community-based education tailored according to the population education and individual concerns (73).

Although, the main predictor for covid 19 vaccine acceptance or rejection is reporting transparency statement, there are poor transparency of documented information that guide the public decision regarding the vaccine acceptance. Global Health care authorities must report and announce for all transparency international freedom of information act templates (FOIA) to the public for requiring vaccine and providing accurate information regarding all types of vaccines. (74)
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