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Systematic review

Global acceptance and rejection of COVID-19 vaccines: A systematic review and meta-analysis

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Abstract:

The challenging obstacle to the introduction of new vaccine that affects the transmission of certain infections is vaccine hesitancy despite the availability of vaccines.

To assess the theoretical tendencies and public attitudes concerning the COVID-19 vaccinations.

PsycINFO, Science Direct, Embase, Scopus, EBSCO, MEDLINE central/PubMed, ProQuest, SciELO, SAGE, Web of Science, and Google Scholar were searched.

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All papers detailing the rejection and acceptance of the COVID-19 vaccine were included with no language restriction. Abstracts, proposals, conferences, editorials, author responses, reviews, case reports & series, books, and studies with data not accurately extracted, or overlapping data were excluded. A meta-analysis was conducted using the random effect model of the pooled proportion of vaccine acceptance and rejection using the meta-package of R software. Egger's regression test was performed to assess publication bias, and the quality of included studies was assessed using the Newcastle-Ottawa Scale.

Out of 12246 identified records, 36 articles were included in the quantitative analysis. The pooled proportion of COVID-19 vaccine rejection was 16% (95%CI:13-20, I^2=100%), while that of COVID-19 vaccine acceptance was 65% (95% CI:60-70, I^2=100%). Case-fatality ratio and geographical distribution represented, were the main determinants of vaccine acceptance. Vaccine acceptance increased by 27.17% (95% CI:3.46-50.88) for each 1% increase in case fatality ($p \leq 0.02$). The acceptance increased in Africa by 1.86 ($p=0.04$) while the vaccine rejection decreased in Australia by 3.93 ($p \leq 0.0001$).

This meta-analysis demonstrated poor acceptance of COVID-19 vaccines, and the ratio of cases to fatality had a profound effect on public perception of the vaccines. These findings should be used to inform relevant interventions for future pandemic responses.

PROSPERO registration number: CRD42021232805

Keywords: COVID-19 vaccines, vaccine acceptance, vaccine hesitancy, vaccine rejection

1. Introduction

Immunization saves millions of lives every year and is extremely important for public health. The present fight against antibiotic resistance has increased the investment in vaccination efforts and made vaccines essential for the prevention and management of infectious disease outbreaks [(1)]. Mass vaccination is necessary for immunization campaigns to reduce the spread of vaccine-preventable diseases. Extensive vaccination among individuals within a community triggers decreased transmission of vaccine-preventable diseases for the entire community, hence reducing the chance of infection for vulnerable community members[(2)].

Vaccine hesitancy (VH) was listed by the World Health Organization (WHO) as one of the top ten risks to world health in 2019. Vaccine hesitancy could be described as the reluctance or refusal to be vaccinated despite the availability of vaccines which can reduce the transmission of the vaccine-preventable diseases. This is seen as the main barrier and constraint for immunization programs, especially when it is a new program. This is clear in the case of the poliovirus, given the reports of the virus' widespread in Afghanistan and Pakistan. On the other hand, it is possible to completely eradicate cervical cancer by increasing the coverage of the Human Papilloma Virus (HPV) vaccine [(3, 4)].

The global pandemic coronavirus infection (COVID-19) that was sparked by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had a profound effect on public health, culture, and human social behavior. Paxlovid from Pfizer has obtained an emergency utilization approval for the management of mild-to-moderate COVID-19 from the Food and Drug Administration (FDA) of the United States in pediatric (aged 12 years) and adult candidates who are in extreme danger of contracting a critical COVID-19 infection. Paxlovid is offered

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with a prescription and has to be commenced shortly after the diagnosis of COVID-19 is made and within five days of symptoms inception [1]. In contrast, efforts to develop a vaccine were given the highest priority because it could protect humankind by generating immunity to COVID-19 [5].

Herd immunity against COVID-19, which is recognized as population immunity according to WHO, can be attained by the naturally subjected individuals who survived the infection by their defensive antibodies or by offering COVID-19 vaccination [6, 7]. Of note, 70% of people who received a single dose of the vaccine and 90% of people who received two doses of the vaccine were able to develop herd immunity against COVID-19[8].

Before coming onto the market, vaccines generally undergo years of development and testing, but in 2020, researchers were pressed for time to create COVID-19 vaccines. About 100 distinct COVID-19 vaccines had been created by research and development teams in multiple countries by April 2020, some of which had even advanced to the point of human trials. To combat the COVID-19 pandemic, more than 2.88 billion doses were distributed globally by 25 June 2021. [9, 10].

The general public perceived recently manufactured vaccinations that have not been on the market for a long time as being less safe and wanted additional information on the safety profile of the vaccine [10, 11]. Following the revelation that many pharmaceutical companies would be producing COVID-19 vaccinations, the public began to widely discuss vaccine content on various social media platforms. Most of the information being spread was false information from non-health professionals, which may have influenced someone's decision to use a newly designed vaccine [12]. Public trust, which is regarded as the key component of vaccination interventions and policies, is imperative for obtaining high coverage of a newly designed vaccine [13].

It was found that with increasing risk of side effects, more people rejected a hypothetical COVID-19 vaccination, whereas the opposite happened when the theoretical effectiveness increased [14]. Healthcare workers reported rejecting or postponing the disease because they either had, already, earlier pathogen exposure, or they worried about unidentified adverse effects and possibly ineffective treatment [15]. Even with acceptance rates of more than 60% worldwide, the COVID-19 vaccination acceptance varied significantly among nations, with more pronounced VH in Europe, North and Middle East Africa (MENA), and Central Asia [16, 17]. Some meta-analyses only covered the COVID-19 vaccine's genuine acceptance without mentioning any rejection. These meta-analyses contain strong heterogeneity (I^2=100%) and factors like sex, nations among low and middle-income countries, and vaccine effectiveness predicted increased acceptance with heterogeneity (I^2>99%)[18, 19].

The goal of the current meta-analysis was to address the theoretical tendencies and public attitudes concerning the COVID-19 vaccinations, which were provided in a number of published studies. This provided an opportunity to identify the community barriers to the distribution of the novel COVID-19 vaccinations and to meet the government directive to raise public knowledge in order to lower the rejection rates that can obstruct county immunization programs.

2. Materials and methods

2.1.Data sources and search strategy

This meta-analysis was conducted using the 2020 Cochrane Handbook of Systematic Review and Meta-Analysis [20], adhering to the systematic review and meta-analysis

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(PRISMA) checklist's recommended reporting items [21]. The search was done from 30th December 2020 to 5th May 2021 for the rejection, acceptance, and hesitancy of COVID-19 immunization through the published and grey literature. This time period was selected as the start of the meta-analysis before the actual vaccination is available in all countries to reflect the attitude of different nations towards the vaccination during the pandemics. Multiple databases were searched including ProQuest, ScienceDirect, Embase, SciELO, EBSCO, Google Scholar, PsycINFO, Scopus, MEDLINE Central/PubMed, SAGE, and Web of Science. After consulting the PubMed help desk, search terms were chosen and approved. The utilized words were included in **Annex 1**. (Keywords used in search)

2.2. Study selection

Without regard to language, all studies describing the acceptance and rejection of the COVID-19 vaccination were included. Exclusion criteria included abstract-only publications, proposals, conferences, editorials, author comments, reviews, case reports, case series, books, and studies containing duplicate or overlapping data that were not accurately or reliably collected.

The PROSPERO database has a record of the study protocol.

The registration number for PROSPERO is CRD42021232805.

2.3.Data extraction and selection process.

The PRISMA flow chart was used to show the different stages of the systematic review. To find and eliminate duplicate entries, all articles were imported into EndNote X7 using two different methods: title, author, year, and then manually using the title, author, and journal. After the citation was exported to an Excel sheet including the author's name, publication year, journal name, DOI, URL link, and the abstract, the title and abstract were screened, then 3 independent reviewers NAH, EAD, and DMH carried out the full texts Screening. Any disputes were resolved by a fourth reviewer, IAA. The kappa test of reviewer agreement was examined.

Additional manual searches were conducted using PubMed and Google Scholar to carefully review the references of studies that were included in the analysis as well as research that cited the chosen articles. The following predetermined information was retrieved from each included article: publication year, authors' names, nation, study design, study setting, study population, sample size, study duration, inclusion and exclusion criteria, vaccine refusal and acceptance rates, and reasons for each.

(**Annex 2)** Summarized information from retrieved articles.

2.4. Heterogeneity investigation

To evaluate and quantify study heterogeneity, the Cochrane Q test and (I^2) test were used, with I^2 greater than 75% indicating substantial heterogeneity [20]. DerSimonian and Laird random-effects models were used to pool the results due to the significant heterogeneity.

2.5. Bias in publications

Publication biases were evaluated statistically using Egger's regression test and visually using the funnel plot [20].

2.6. Quality assessment

The Newcastle-Ottawa Scale, a quality assessment instrument tailored for cross-sectional research, was employed to measure quality [22]. Either very good (9–10 points), good (7-8 points), satisfactory (5–6 points), or unsatisfactory (0–4 points) studies were of high quality [23]. Two separate reviewers (DMH and EE) carried out the assessment, and two more reviewers double-checked it (SOE, AA).

2.7. Statistical analysis and data synthesis

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R software version 4.1.3 (Package meta) was used, and the random effect model was chosen based on the consistency of the studies. In order to illustrate the degree of difference between research, the results were displayed in Forest plots.

The statistical analysis and data synthesis were carried out using R software version 4.1.3 (Package meta). A meta-regression analysis was conducted using various models that included the key determinants of vaccination acceptance and rejection, including age, sex, educational attainment, and study environment, that were found in the included studies, in order to investigate the causes of the high heterogeneity in the pooled proportion of vaccine acceptance and rejection. Additionally, through January 2021, the number of cases, deaths, case fatality ratio that have been reported, the period following the WHO declaration that COVID-19 is a pandemic, and the number of people vaccinated in each country were all investigated as putative factors of vaccine acceptance and rejection and were included in the meta-regression model [24, 25]. Finally, we performed a leave-one-out sensitivity analysis.

The case fatality, deaths, and number of cases reported according to (worldometer) in May 2021 [26].

The World Health Organization (WHO) defines VH as a "delay in acceptance or refusal of vaccination despite the availability of vaccination services" [27]. Rejection was defined as: " not intending to receive the vaccine even if it was available, similar to the acceptance in which there is an intention to receive the vaccine when it is available [28].

3. Results

Fig. 1 depicts the flow chart for the study selection procedure. A total of 12,246 pertinent articles were removed, along with 1621 duplicates and 2944 citations that were published before 2019. 7,681 items in all were qualified for title screening. After excluding irrelevant and duplicate articles (7,630), a total of 51 articles were eligible for full-text assessment. Then, we added 23 more articles. Finally, 34 articles were excluded after the eligibility assessment of full-text screening (29 were irrelevant, two reports were duplicated, and three were retracted). A total of 40 studies were eligible for the qualitative assessment. For the meta-analysis, there were 36 eligible articles; out of the 40 studies three were excluded due to unsatisfactory quality scores (Gagneux-Brunon *et al.*[29], Barello *et al.*[30], and Wang *et al.*[31] and another study (Dror *et al.*) was excluded as it didn't report a proportion of vaccine acceptance or rejection, rather it only reported their determinants [32]. For eligibility, the inter-reviewer agreement was κ=0.89, and for the quality evaluation, it was κ=0.91.

Fig. 2 represents a funnel plot with non-significant Eggers' test [t = -0.609, p= 0.546] which shows the absence of publication bias for 36 studies reporting COVID-19 vaccine rejection.

Fig. 3 represents a funnel plot with a non-significant Eggers' test [t= 0.232, p = 0.818] which shows the absence of publication bias for 36 studies reporting the COVID-19 vaccine acceptance.

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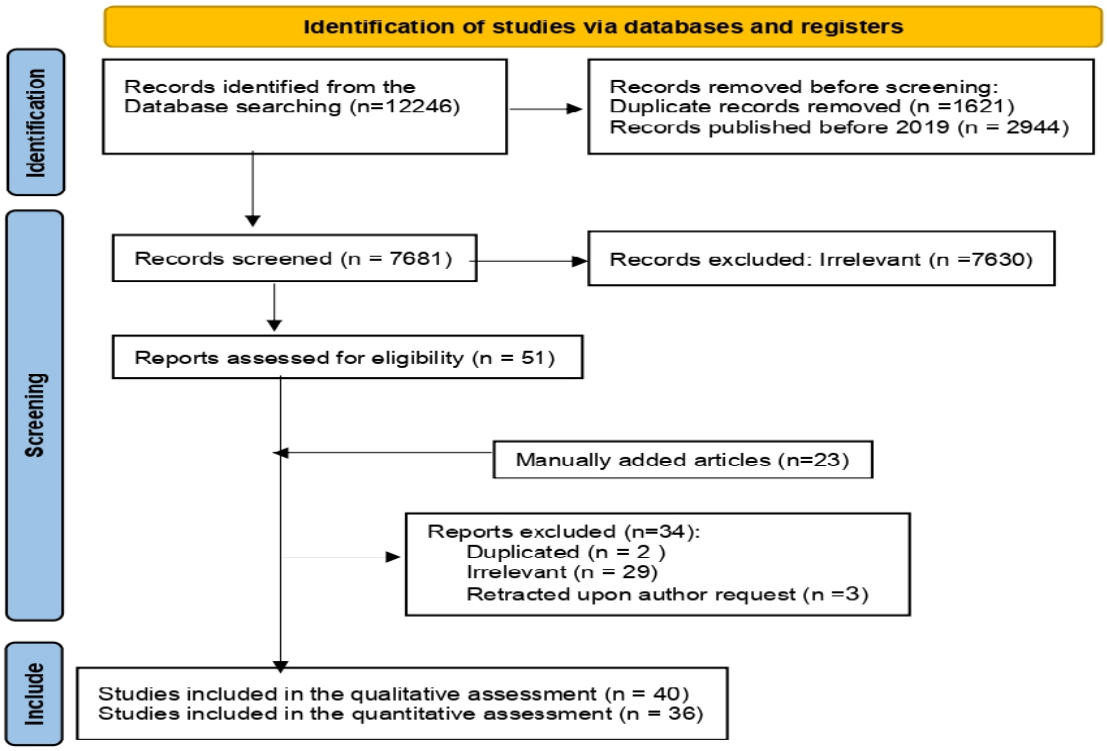

Fig. 1: PRISMA flow diagram showing the included and screened studies

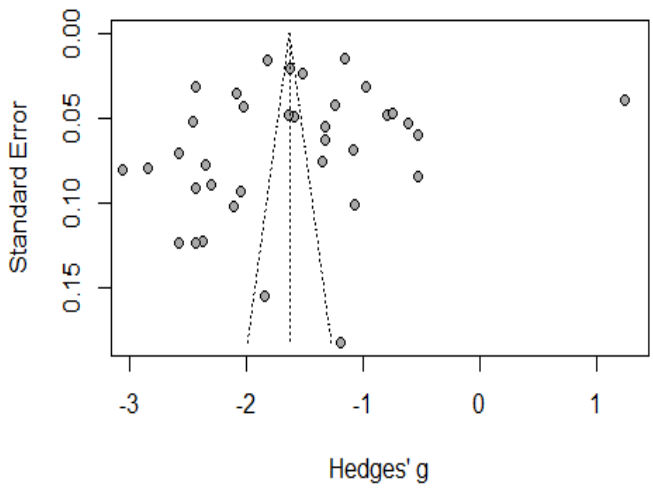

Fig. 2: Funnel plot of studies reporting the COVID-19 vaccine rejection

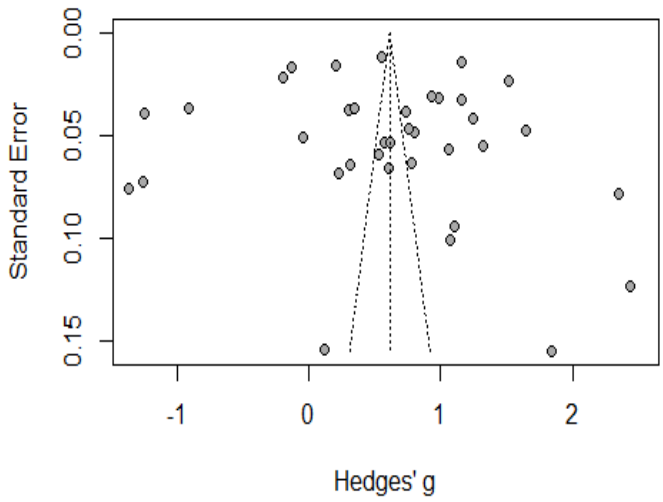

Fig. 3: Funnel plot of studies reporting the COVID-19 vaccine acceptance

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Table 1: Summary table of the included studies

Author, Year	Study design	Quality score	Population criteria + inclusion and exclusion	Sample size/ Sex/ Age	Tool used in rejection% estimation	Significant Predictors	Duration	Outcome measured	Percentage
Taylor, 2020 [38]	cross-sectional study	8 **(good)**	Adults who respond to surveys. Excluding incomplete responses	Sample size = 3,674 (USA = 1,772 Canada= 1,902) Sex= 57% male Age = 53±15	online self-report survey delivered in English	1- lack of trust in vaccine benefit. 2-Worry about future negative adverse effects. 3- Concerns about commercial profiteering. 4-Dependence on natural immunity	May 6–19, 2020	Rejection	25% of Americans' sample and 20% of Canadians' sample
Fisher, 2020 [43]	cross-sectional study	8 (good)	adults United States residents 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-online by 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 infected by COVID-19 within the next 6 months, influenza vaccine	16 - 20 April 2020	Acceptance Hesitancy rejection	57.6% 31.6% 10.8%
La Vecchia, 2020 [44]	cross-sectional study	6 (satisfactory)	The general Italian population	Sample size = 1055 Sex= 48.24% male Age = (15-85)	Computer-assisted web interviews (Computer Assisted Web Interviews).	NA	September 16-28, 2020	Acceptance Hesitancy Rejection	20.4% 58.8% 20.7%
Sherman, 2020 [45]	cross-sectional study	9 (v.good)	UK population aged 18 years or over	Sample size = 1500 Sex= 48.6% male Age =46±15.8	online survey	Age, sex, religion, ethnicity, previous influenza vaccination, qualification, religion, employment status, key worker, extremely clinically vulnerable, general vaccination	between 14th and 17th July 2020	Acceptance Hesitancy Rejection	64% 26.9% 9.1%

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						beliefs and attitude, beliefs and attitude towards COVID-19, perceived Risk of COVID-19, perceived Risk of COVID-19 to oneself, having OR not COVID-19.			
Lucia, 2020 (46)	cross-sectional study	6 (satisfactory)	medical students aged≥ 18 years	Sample size = 168 ((168 of 494 medical students (response rate = 34%)) Sex= 43% male	online survey	NA	A lack of trust and information	Acceptance rejection	53% 23%
Salali and Uysal, 2020 (42)	cross-sectional study	10 (v.good)	Age> 18, residing either in the UK or Turkey.	UK (n = 1088) and Turkey (n = 3936)	online survey	COVID-19 vaccine acceptance, believing in the natural origin of the virus	throughout May 2020	Rejection	3% (31% Turkey 14% UK)
Al-Mohaithef, 2020 (39)	cross-sectional study	8 (good)	All participants were above 18.	Saudi Arabia (n=992) Age = (18-45) Sex= 34.17% male	online survey	Sociodemographic predictors (age, gender, marital status, nationality, residence, occupation, education), lack of trust in health system	NA	Acceptance Hesitancy Rejection	64.7% 28.2% 7%
Kreps,2020 (47)	cross-sectional study	8 (v.good)	US adults	USA 1971 respondents Median Age = 43(30-58) Sex= 49% male	online survey	vaccine adverse effects, efficacy and protection duration and political factors (eg, FDA approval process, national origin of vaccine, and endorsements), Health care attitudes and practices, political partisanship, and demographic characteristics	July 9, 2020.	Acceptance	79%
Gagneux-Brunon, 2020 (29)	cross-sectional study	4 unsatisfactory	General Population and Health Care	France (n=2047) Age = (<30->65)	Hybrid (Online Survey and	chronic medical conditions, Age, gender, professions, Fear about COVID-19, getting Flu	From 26th March to 2nd July 2020.	Acceptance	76.9%

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			Workers in France	Sex= 26% male	written questionnaire)	vaccine during the previous season			
Lin, 2020 (48)	cross-sectional study	8 (good)	NA	3,541 age 26 to 35 years old (47.2%). M=48.1% F=51.9%	Online survey	NA	1–19 May 2020	Acceptance Hesitancy Rejection	28.7% 66.7% 4.5%
Barello, Serena, 2020 (35)	cross-sectional study	2 unsatisfactory	Italian University students	934	Online survey	NA	1st-19th May 2020	Acceptance	86.1%
Dror, 2020 (32)	cross-sectional study	7 (good)	NA	1941	online survey C.S	NA	2-weeks	Acceptance	NA
Akarsu, 2020 (49)	cross-sectional study	8 (good)	Social Media and smartphone users	852 Female 62.8% Male 37.2%	Online Survey	NA	16th June-16th July2020	Acceptance Hesitancy Rejection	55.5 35.9% 8.6%
Freeman, 2021 (50)	cross-sectional study	7 (good)	NA	5,114 UK adults Age mean (SD)=46.9 (17.1) male; female; non-binary; prefer not say=2574; 2515; 20; 5	Online Survey C.S	lower education, lower income, black and mixed ethnicities, lower age, female gender, not being single or widowed, not being a homeowner, not retired, a change in working, not being employed full-time, having a child at school.	24th September-17th October 2020	Acceptance Hesitancy Rejection	71.7% 16.6% 11.7%
Butter, 2020 (51)	cross-sectional study	5 (satisfactory)	UK adults who followed up for 1-month survey of the COVID-19 Psychological Wellbeing Study. AND only individuals who	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 18-24	Online survey	Female1.96 (1.16 – 3.32) Age group 25-342.41 (1.48 – 3.94) Age group 35-441.96 (1.12 – 3.45) Age group 45-542.91 (1.62 – 5.24)	between 22nd April and 18th May 2020.	Acceptance Hesitancy Rejection	74.2% 17.7 % 8.1 %

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			not previously diagnosed with COVID-19	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)					
Muqattash, 2020 [52]	cross-sectional study	6 (satisfactory)	(Aged ≥18) living in the UAE	1109 M=27.86% F=72.14% 1- [18 to 25]143 12.89% 2- [26 to 35] 310 27.95% 3- [36 to 45] 437 39.40% 4- [45 and over [219 19.75%	Google Forms platform survey	NA	July 4th to August 4th 2020	Acceptance Hesitancy Rejection	22.09% 52.75% 25.16%

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Ward, 2020 (53)	cross-sectional study	7 (good)	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 High (>8) 0.68 [0.55; 0.84] Partisan preference Far-Left parties 1.43 [1.07; 1.91] Left/Center/Right 1.47 [1.12; 1.92] No preference and abstained in 2017 1.74 [1.26; 2.41]	4 weeks April 2020	Acceptance Hesitancy Rejection	76 % 16.1 % 7.9 %
Unroe, 2020 (40)	cross-sectional study	6 (satisfactory)	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	Acceptance Hesitancy Rejection	45% 44% 11%
Wang, 2020 (37)	cross-sectional study	4 unsatisfa-ctory	Nurses, Administrative or academic positions excluded	806 F=87.5% M= (12.5%) 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, 5.58) Having chronic conditions 1.83(1.22, 2.77) Public or private 1.67(1.11, 2.51)	26 February and 31 March 2020	Acceptance Hesitancy Rejection	39.95% 42.94% 17.12 %
Goldman, 2020 (54)	cross-sectional study	8 (good)	Caregiver families	1541 F=72% M=25.5% Age mean=39.9(SD7.6)	Online survey	NA	26thMarch-31st May 2020	Acceptance	65%
Reiter, 2020 (55)	cross-sectional study	8 (good)	Adults	2006 F=56% M=43%	Online survey	NA	May 2020	Acceptance	69%
Wang, 2020 (31)	cross-sectional study	8 (good)	Adults	2058 F=54.2% M=45.8	Online survey	NA	March 2020	acceptance	91.3%

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Sharun, 2020 (33)	cross-sectional study	9 (v.good)	Adults	351 F=58.1% M=41.3%	Online survey	NA	October 2020	Acceptance Rejection	86.3% 13.7%
Lazarus, 2020 (56)	cross-sectional study	8 (good)	Adults	13,426 F= 53.5% M=46.5&	Online survey	NA	NA	Acceptance Hesitancy Rejection	46.8% 35% 8.1%
Kose, 2020 (57)	cross-sectional study	5 (satisfactory)	healthcare personnel	1138 F=72.5% , M=27.5%	Google Forms questionnaire	gender Age group Occupation Flu-vaccination status	17th -20th September 2020	Acceptance Hesitancy Rejection	68.6% 19.4% 11.4%
Biasio, 2020 (58)	cross-sectional study	7 (good)	Adults	885 Males (49.9%) Females (50.1%)	Online survey	NA	2 weeks	Acceptance Rejection	92% 8%
Grüner., 2020 (59)	cross-sectional study	6 (satisfactory)	Healthcare students and Non-healthcare students	2,077	Online survey	NA	18.5.2020–2.8.2020	Acceptance	In HC professionals 83.1% In HC students 79.81% In non-HC students 85.67%
Malik, 2020 (35)	cross-sectional study	7 (good)	Adults	672 Males (72%) compared to females, older adults (≥55 years; 78%) compared to younger adults	Qualtrics Online survey	NA	May 2020	Acceptance	67%
Paul, 2020 (34)	cross-sectional study	6 (satisfactory)	Adults who had started the vaccine module administered from 7 September to 5 October 2020.	32,361 participants Male 49.4% Female 50.6%	Data were drawn from the COVID-19 Social Study online survey	Being female key workers People living with children. Socio-economic factors levels of education	Started on March 2020 Duration NA	Acceptance Rejection Hesitancy	63.5% 14% 23%
Kwok, 2020 (36)	cross-sectional study	7 (good)		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	Acceptance	63%

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Edwards, 2020 [60]	cross-sectional study	7 (good)	Adults	3,061 adults Age 18-75	online survey	Age Sex university degree neighborhood differences household income who use the COVID-Safe App who voted for the Coalition or Labor confidence in their government or health system religion populist views who support migration	April to August 2020	Acceptance Hesitancy Rejection	58.5% 35.9% 5.5%
Detoc, 2020 [61]	cross-sectional study	5 (satisfactory)		3259 F=67.4% M=32.6	online survey	NA	26th march-20th April 2020	Acceptance	77.6%
Adebesie, 2020 [62]	cross-sectional study	7 (good)		517 F=43.1% M=56.9% Age≥15	online survey	Age employment education level		Acceptance Rejection	74.5% 25.5%
Murphy, 2021 [41]	cross-sectional study	6 (satisfactory)	NA	2025 F=51.7 M=48.3%	online survey	Gender Age group	NA	Acceptance Hesitancy Rejection	69% 25% 6%
Murphy 2021 [41]	cross-sectional study	10 (v.good)	NA	1041 F=51.5% M=48.2%	online survey	Gender Age group Mental health history	NA	Acceptance Hesitancy Rejection	65% 26% 9%
Barry, 2020 [63]	cross-sectional study	9 (v.good)	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 Complacency confidence	4-14 December 2020	Acceptance (among HCWs)	70%
Chen, 2021 [64]	cross-sectional study	5 (satisfactory)		3195	online survey	Lack of confidence Complacency Risk of the vacc. Attention frequency	NA	Acceptance (vaccination willingness	83.8%
Meyer, 2020 [65]	cross-sectional study	8 (good)	Patient-facing HCWs and other roles	16158	online survey	Unknown risk Insufficient data Known side effects	December 2020(month)	Acceptance Hesitancy rejection	55% 28.5% 16.4 %

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						Don't trust FDA Privacy concerns and state tracking Depend on vaccine type and concerns about mRNA Not at high risk for infection Had COVID			
Robertson, 2021 [66]	cross-sectional study	8 (good)	NA	12,035	online survey	Unknown future effect Lack of trust in vaccine Side effects Gender Age education	Nov.-Dec.2020	rejection	18%
Kerr, 2020 [67]	cross-sectional study	5 (satisfactory)		25,334	Qualtrics online survey	Demographic numeracy Political ideology General social trust Prosociability General trust in medical scientific experts General trust in government Specific trust in national science advisors	March - Oct. 2020	Willingness to receive a vaccine	From 62.6% to 88.1%
Thorneleo 2020 [68]	cross-sectional study	8 (good)	Adults	2152 Males=36.6% Females= 63.2% Age mean= 45.3±16.07 yrs	Survey via e-mail and social media	Age Ethenic group Marital status Employment level Educational level Smoking status COVID status	April- June 2020	Acceptance Rejection	76.9% 23.1%

F=Female, M=Male, NA=Not Available

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Table 1 shows the main findings of the included studies. All the studies were cross-sectional surveys. The total sample size was 173,213 ranging from 351 in the study of Sharun *et al.* [33], reaching 32361 in the study of Paul *et al.* [34]. The lowest proportion of females was in the study of Malik *et al.* [35], while the highest proportion of females was in the study of Kowk *et al.* [36], followed by Wang *et al*.[37], and age range was 15 to > 85 in the study of Taylor *et al.* [38]. In the Taylor *et al.* study, the participants' mean age was the highest [38], 53 years old and lowest in the study of Al-Mohaithef *et al.* [39], 31.5 years old. Data was collected through online surveys using Qualtrics forms or Google Forms. According to Wang *et al*.'s study, vaccination rejection rates were the highest there, [37] (47.8%) and Unroe *et al.* study [40] (45.1%), while Murphy *et al.* study [41] (6%) and Salali and Uysal study [42] showed the lowest vaccine rejection rates (3%). The primary factors found to be predictive of vaccination rejection were sex, age, unknown side effects of the vaccine, and general trust.

The quality score ranges between very good to unsatisfactory quality. Five studies were very good, 20 studies were good, 12 studies were satisfactory, and 3 studies were unsatisfactory.

3.1. Predictors of acceptance and rejection of the COVID-19 vaccination

According to **Table 1**, the most prominent characteristics linked to vaccine acceptance was the previous intake of the influenza vaccination. Those who reported having received an influenza vaccination are more likely to accept the COVID-19 vaccine than those who have not [57]. The acceptance of the vaccine is influenced by certain sociodemographic factors. Young age was linked to an adverse reaction to the COVID-19 immunization, [41] while older individuals responded more positively towards the COVID-19 vaccine [53]. Regarding gender, males showed higher acceptance towards vaccine than females [66]. Low education levels and income and being unemployed were associated with vaccine rejection [50], while those with professional work showed more acceptance towards the vaccine [37]. Apart from the fact that a person's marital status influences the vaccination uptake rate, being unmarried or widower was linked to greater refusal rates [50], while married partners were more likely for vaccine acceptance [39]. The vaccine's acceptance was also influenced by racial and ethnic groups. Mixed-race and black people were linked to higher rejection rates [43, 50]. Case fatality was also a strong predictor of vaccine acceptance as vaccine acceptance increased by 27.17% (95% CI: 3.46-50.88) for each 1% increase in case fatality ($p<0.02$) (**Fig. 4**). The existence of reliable health systems was another element that boosted vaccine uptake [39], the fear from COVID-19 infection [29], and chronic diseases [37]. Suspicion of its effectiveness [37], fear of the side effects, or overtrust in the immune system were the main predictors for COVID-19 vaccine rejection [57].

3.2. Proportions of COVID-19 vaccine rejection and acceptance

Among 173,213 participants recruited from 36 studies, the pooled proportion of COVID-19 rejection by using the random effect model was 16%, (**Fig. 5**) (95% CI: 13-20). Vaccine rejection ranged from 78% (95% CI: 76-79) in the study of Tayor *et al*., 2020 [40] to 4% (95% CI: 4-5) in the study of Lin *et al*., 2020 [42, 64], with high heterogeneity (I^2 = 100%), and the variance between the studies was slightly high (T^2= 0.2979 ±0.1348). To elucidate the origin of this heterogeneity, leave one out sensitivity analysis, Graphic Display of Heterogeneity (GOSH), and sub-group analysis were conducted but failed to explain this high heterogeneity (**Annex 3**). Multiple meta-regression models were built and included many predictors such as case fatality ratio, country, cases reported, continent, development of the country according to the world bank, sample size, and setting. The meta-regression model explained 50.2% of the rejection heterogeneity and included country, case fatality, development of the country, where the continent predictor showed a significant negative contribution in this rejection for America, Asia, Australia, and Europe continent with -2.78, -3.01, -3.93, -3.01 respectively ($p\leq0.01$) and for Africa continent -2.59 ($p\leq0.01$).

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Annex 3. Leave one out sensitivity analysis, Graphic Display of Heterogeneity (GOSH)

As shown in **Figure 6**, the pooled percentage of COVID-19 vaccination uptake was 65% (95% CI: 60-70). The greatest vaccination acceptance was seen in Wang J, 2020,[31] 92 (95% CI =90-92) and the lowest in Taylor, 2020[38] 22 (95% CI =21-24). Also, the vaccine acceptance showed high heterogeneity (I^2=100%). The Leave-one-out sensitivity analysis, Graphic Display of Heterogeneity (GOSH), and sub-group analysis couldn't explain this heterogeneity, but meta-regression of acceptance explained 27.0% of this heterogeneity and estimated acceptance increase by 27.2 (95% CI=3.46-50.88) units for each case fatality (p= 0.02) and the different regions resembled in different continent affect the acceptance in Africa, America, and Europe by 1.86 (p= 0.04), 1.60 (p= 0.01), 1.85 (p< 0.01) respectively. The residual heterogeneity (T^2 =0.33±0.15) can be attributed to the heterogeneity in between-studies. The results of the meta-regression models between the percentage of vaccination acceptance and case fatality, sub-grouped by research sample size and type of environment, are displayed in **Fig. 4**. The VH is reported by only 19 studies of the 39 studies, where Lin, 2020 [48], reported the highest VH with 66.7% and Paul, 2020 [34], reported the lowest VH with 14%.

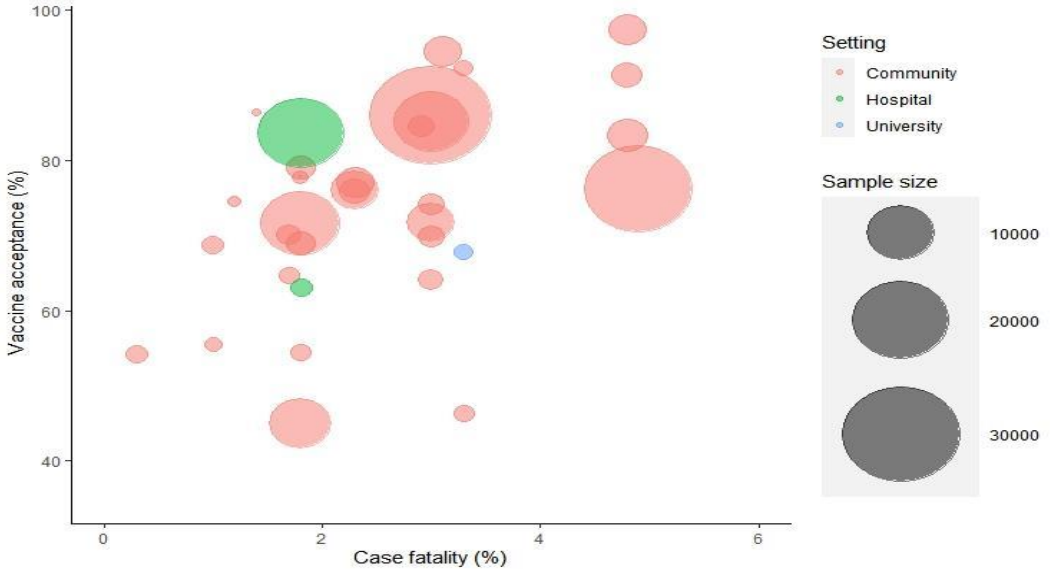

Fig. 4: The relationship, by sample size and research context, between vaccination acceptance (%) and case fatality (%)

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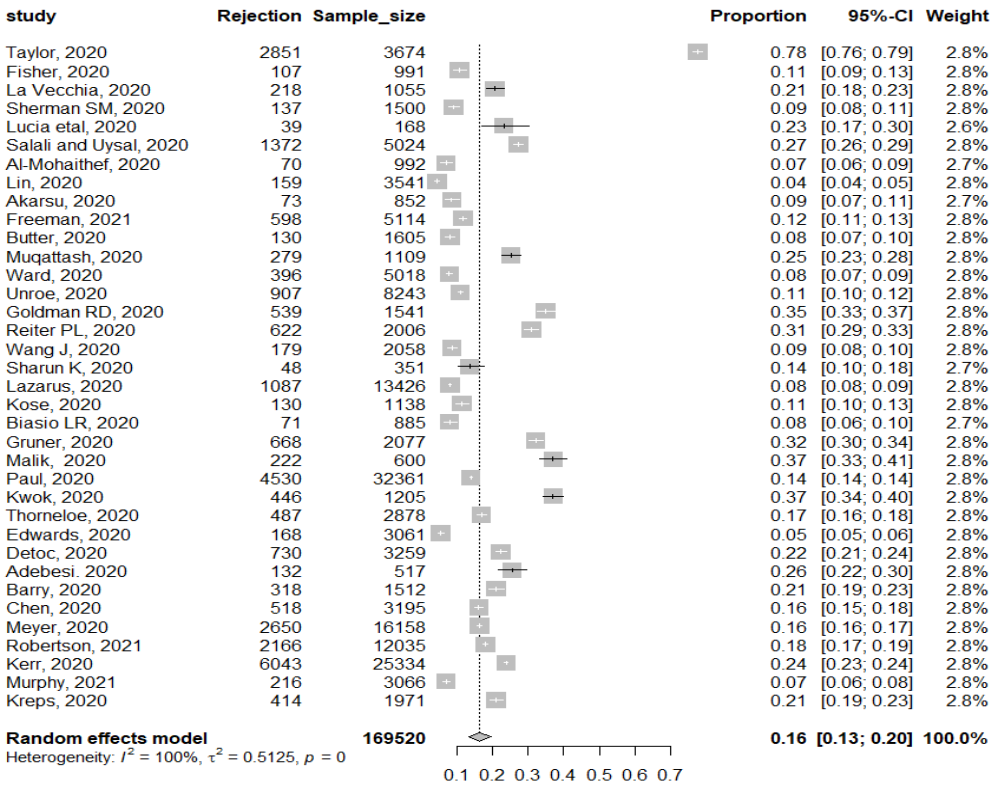

Fig. 5: Forest plot of pooled prevalence of vaccine rejection

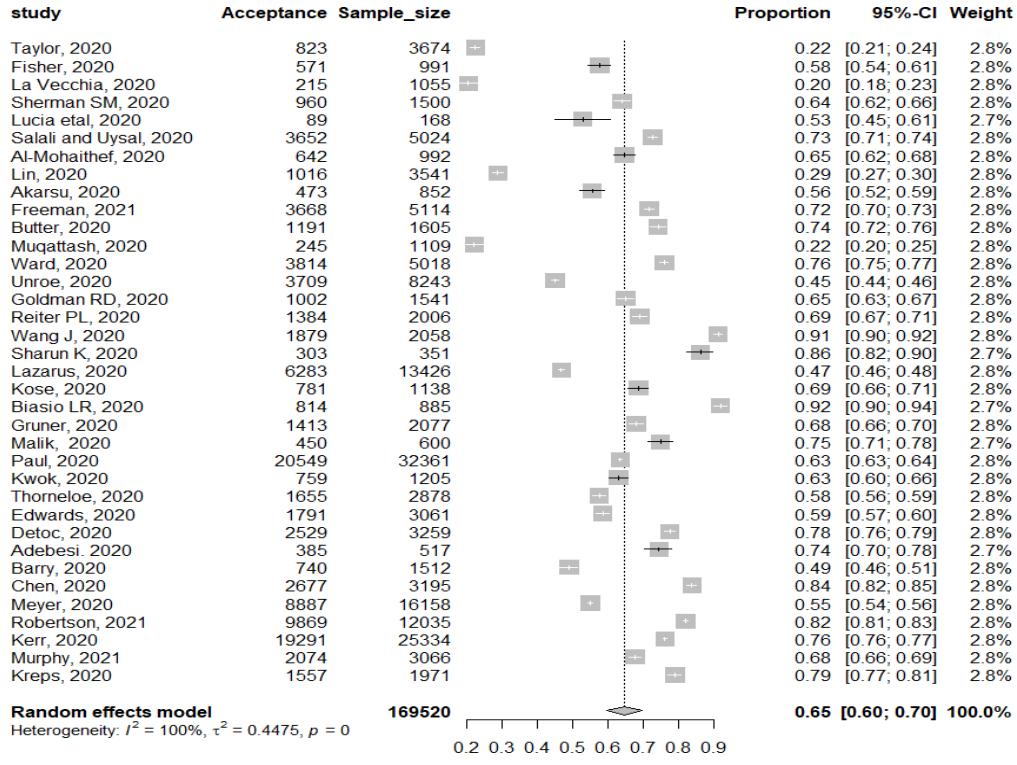

Fig. 6: Forest plot of the pooled vaccine acceptance

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4. Discussion

A crucial first step in combating the COVID-19 pandemic and building population-wide herd immunity is the SARS-CoV-2 vaccine. The COVID-19 pandemic poses a serious threat to world health, and the ability of health systems to contain it, is constrained by vaccine refusal. As a result, estimating the number of people who reject the COVID-19 vaccine serves as a tool for creating an action plan to increase vaccination coverage.

We sought to estimate the percentage of people globally who are accepting and rejecting the COVID-19 vaccines in our meta-analysis. We incorporated 36 cross-sectional studies carried out in 22 nations with 32,134 participants. The quality of the studies ranged from adequate to excellent. In contrast, COVID-19 vaccination rejection of the pooled proportion was 16% (95% CI: 13%-20%), according to our meta-analysis.

Similarly, a systematic review and meta-analysis conducted by Ronbinson *et al.* [(69)] on 58,656 individuals in 13 countries estimated the number of individuals refusing the uptake of the COVID-19 vaccine. A 20% refusal rate for the COVID-19 vaccine was reportedly recorded for the participants. They noted that there were significant variances between nations, with heterogeneity exceeding 90%. Additionally, they stated that the pattern of rejection grew over time. Being a woman, having a poor educational level, or being a member of a minority ethnicity were the primary causes of COVID-19 vaccine rejection. Norhayati *et al.* [(19)] noted that among the 814,691 subjects included in 170 studies conducted across 50 countries, the COVID-19 vaccine acceptance rate was 61% (95% CI: 59-64%). They also discovered that vaccination acceptance was higher in men than in women, highest in Southeast Asia, and lowest in the East Mediterranean. HCWs showed the highest proportion of vaccination acceptance compared to the general population, and their acceptance was strongly influenced by vaccine effectiveness. Another meta-analysis of 24 studies by Nindrea *et al.* [(70)], showed that living in high-income countries, having a fear of COVID-19 and a belief in its benefits, receiving a flu shot the previous season, working as a HCW, being male, married, perceiving risk as low, and trusting the healthcare system were all associated with acceptance of the COVID-19 vaccination. Higher economic standing and more work experience are good indicators of accepting vaccination [(71)]. Rejection of the COVID-19 vaccine was also highly correlated with race and ethnicity, and that's why it is essential to effectively address the causes of rejection to and play a crucial role in recommending vaccines to patients [(72)]. It takes a variety of strategies to improve vaccine adoption globally.

We sought to shed light on the time period when vaccination campaigns had not yet begun in the majority of nations as sentiments against the COVID-19 immunization changed over time. Indeed, this information can serve as a foundation for researchers to compare public opinion on COVID-19 immunization to the rise of variant strains and suggested deterioration in vaccine efficacy over time. A similar pattern was discovered by a global analysis of vaccination acceptability. France, Italy, and China discovered that the percentage of people who approve of vaccinations was lower in their second and third polls. On the other hand, the United States (US) showed an improved trend of vaccination uptake in the second and third polls. In the UK, the percentage started off high in the first survey, increased in the second, fell in the third and fourth, and then increased once again in the fifth. Despite this, the acceptability rate for vaccinations was lower in the fifth poll than it was in the first[(4)]. Lin *et al.*[(48)], conducted another research study that evaluated vaccine receptivity patterns over time across US and international polls. Academic publications, news, and official reports released by October 20th, 2020, were used as data sources. There were 126 research and surveys altogether. According to the authors, the

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vaccine acceptance rate declined in March (from 70% to 50% in October 2020), and party, social, and demographic differences were noted. In reality, a variety of factors, including perceived risk, worries about vaccination safety, doctor recommendations, a loss in vaccine effectiveness over time, and the emergence of mutant strains that the existing immunizations might not be able to prevent, may influence vaccine adoption [(5)]. The effects of gender, geographical infection rates, and individual COVID-19 experiences could not be determined. Political party identification, concern about accelerated development/approval processes, an increase in significant vaccination side effects, and perceptions of political involvement were all distinctive COVID-19 characteristics. While mandates may enhance resistance, many responsive participants wanted to wait until others had received the vaccine.

In this perspective, Kaplan *et al.* [(73)] highlighted that when vaccine efficacy is more than 70%, vaccine acceptability increases. Additionally, they addressed the fact that while small side effects, like a hurting arm or a day-long fever, had no impact on vaccination acceptability, substantial side effects reduced vaccine acceptance in 1/100000 individuals. The type of vaccine administered in each nation may have different adverse effects. The COVID-19 vaccine intention observed a decline, which may be attributed to the misinformation about the vaccine safety which brings up a great need for measures to enhance the public trust in the vaccine to improve acceptability and safety [(74, 75)].

This study emphasized the potency of social media. In recent months, multiple studies have discussed the trust in vaccines among various people, particularly in nations with high illness burdens like Pakistan [(76)]. It was evident from research by Loomba *et al.*, "Measuring the impact of COVID-19 vaccine misinformation on vaccination intent in the UK and USA," how significant current misinformation has been. Among those who claimed they would accept the vaccination, it resulted in a 6.4% percentage point drop in vaccine intention in the US and a 6.2% percentage point fall in the UK. [(77)]. From a different angle, additional research examined beliefs regarding the COVID vaccination, such as the influence of education on students' decisions, whether they are medical or nonmedical [(30)]. Now that numerous vaccines are effective, immunization programs can only be effective when there are high rates of compliance and coverage [(78)]. Understanding vaccine-acceptance messaging is crucial for doing this in order to effectively manage the pandemic and stop thousands more people from dying [(79)]. Despite anticipating less severe symptoms for themselves, people frequently believe COVID-19 to be a serious illness. Additionally, they were more concerned about spreading the illness than they were about being sick themselves [(80)].

The degree to which respondents believed in vaccination safety was the best predictor of their likelihood to adopt a COVID-19 vaccine that had been recommended by authorities. The variation in vaccination intentions was explained by estimated vaccine safety in 52% of cases [(81)]. According to Malik *et al.* study's [(35)], publicly accessible demographic factors can predict COVID-19 vaccination acceptance with a high degree of accuracy. Since the start of the COVID-19 pandemic in the US, it has become abundantly evident that communities of colour and low-income groups are more likely to contract the virus and die from it.

4.1. Strengths and limitations

The fact that we searched 12 different databases is one of this study's key strengths. Two reviewers independently evaluated each citation, and a senior author resolved any disagreements. To ensure strong proof, the same was done for quality assessment. Unlike published journal articles, most of the included papers were pre-prints that had not yet been subjected to peer review and that were sampled using quota instead of

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probability. However, the choice of sampling technique (quota vs. probability) had little bearing on intentions estimates, and studies published as pre-prints provided estimates of the effects that were comparable to those published in peer-reviewed journals. The fact that we have already assessed both acceptance and rejection in the same study is another major point of strength. When it comes to vaccination hesitation, in our study, it was not added to the rejection outcome in research that treated hesitancy as a separate entity rather than a rejection, in contrast to studies that did not make this distinction between rejection and hesitancy. One of the main limitations was the use of several measures to evaluate vaccination acceptance and the fact that the data was gathered either through in-person interviews or online data collection tools. We believe that this might compromise the study's internal validity. Although we divided the analysis based on the way the data was gathered, the difference was not significant. It is crucial to note that research completed at various times as the epidemic developed in each nation was included in the review. Some of the indicated acceptance is, therefore, speculative and may be different with the supply of further information about the present vaccinations available in these countries. At this time, the COVID-19 vaccine was not yet available in all the countries included in the analysis.

5. Conclusions

This meta-analysis demonstrated poor acceptance of COVID-19 vaccines among the general public. The ratio of cases to fatality had a profound effect on public perception and subsequent behavior with regard to vaccination, hence it is critical to ensure a transparent reporting process. These findings should be used to inform relevant interventions to improve the community's acceptance of vaccinations for future pandemic responses.

Declarations

Ethics approval and consent to participate:

Not applicable because it's a review.

Consent for publication:

All authors have read & approved the manuscript.

Availability of data and material

All material is included either in the main manuscript or in Annex 1 & 3 (as supplementary word files) or Annex 2 as a spreadsheet.

Competing interests

The authors have declared that no conflict of interest exists.

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Authors' contributions

SHA: Leading the team, screening title and abstract, data analysis, writing results.

DMH: Data extraction, screening, quality assessment, summary table

IAA: Coordinating activities, database search keeping working, Data extraction, documents and libraries, resolving reviewers' disagreements, revising methods, and data analysis.

NA Hamdy: Writing introduction, database search, title & abstract screening, full text screening, data extraction, revising the final manuscript and corresponding author.

Elhadi YAM: Database search, screening, full text screening, data extraction, quality assessment.

S El-ganainy: Data base search, title and abstract screening, full text screening, data extraction, revision of methodology.

EAD: Title and abstract screening, full text screening, data extraction, results.

A Nour El-Deen: Database search, screening, full text screening, Data extraction

EE: Title and abstract screening, full text screening, data extraction.

AK: Screening, writing manuscript

KMS: Screening, data extraction, distribution, acceptance, and duration.

SGK: Screening title and abstract, full text screening, data extraction, and quality assessment.

RS: Database search, screening, full text screening, and data extraction.

AA: Data extraction.

EAE: Data extraction, writing introduction.

NIE: Data extraction, writing introduction.

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MMT: Title and abstract screening, full text screening, data extraction, final review.
Zel-Khatib: Writing and revising the manuscript.
RMG: Formulation of study idea, databases search, writing the manuscript.

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Abbreviations

COVID-19	:	Coronavirus Disease
FDA	:	Food and Drug Administration
HCWs	:	Health Care Workers
mRNA	:	Messenger Ribonucleic Acid
NA	:	Not Available
PRISMA	:	Preferred Reporting Items of Systematic Review and Meta-analysis
SARS-CoV-2	:	Severe Acute Respiratory Syndrome Coronavirus 2
UK	:	United Kingdom
US	:	United States
WHO	:	World Health Organization

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