

SYSTEMATIC REVIEW: THE RELATIONSHIP BETWEEN VACCINE HESITANCY AGAINST COVID-19 AND ANXIETY DISORDERS

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Abstract

The present systematic review is a qualitative research aimed to synthesize and understand the hesitancy phenomenon of vaccination against COVID 19 for the population experiencing mental health problems, for certain various anxiety disorders. Thematic conclusions from 20 studies that observed the phenomenon of acceptance of vaccination against coronavirus for several types of population were analysed: some studies involve patients from Mental Health Care (n = 6), some are about university students (n = 3), general population with electronic records (n = 6), women from fertility centres (n = 2), refugees (n = 1) and patients with chronic conditions (n = 2). According to the findings of this systematic analysis, avoiding coronavirus vaccination is a complex phenomenon that is strongly linked to anxiety disorders. However, several factors contribute to the observed correlations, both mediating and moderating, allowing us to have a better understanding of the mechanism.

Cuvinte-cheie: COVID-19, Coronavirus, ezitarea vaccinării, tulburări de anxietate, analiza sistematică

Keywords: COVID-19, Coronavirus, Vaccine Hesitancy, Anxiety Disorders, systematic review

1. INTRODUCTION

At the end of 2019 a new variant of coronavirus (COVID-19) appeared in Wuhan province of China. Coronavirus Severe Acute Respiratory Syndrome 2 (SARS COV 2) has spread rapidly worldwide. The World Health Organization (WHO) on 20 January 2020 classified COVID-19 a Public Health Emergency of International Concern (PHEIC). Following that, on 11 March 2020, WHO declared COVID-19 a pandemic (Nishiura, Linton & Akhmetzhanov, 2020). Following these announcements, countries around the world have taken drastic physical measures to try to limit the spread of the virus in the population (Lewnard & Lo,

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2020). Schools were closed, events were cancelled, restaurants, bars, gyms, libraries, community centres and places of worship were closed, travel restrictions were imposed, and people were ordered to “stay home”. The WHO ended its PHEIC declaration on 5 May 2023 (WHO, 2023). Since February 2024, more than 703 million confirmed cases have been reported, more than 6 million deaths and over 674 million people cured worldwide (Wordometer, 2024).

2. STUDY DESIGN AND METHODOLOGY

It is well known that vaccine hesitancy is a multifaceted phenomenon influenced by a wide range of factors. This encompasses factors that vary among various populations and contribute to it, such as cognitive, psychological, socio-demographic, political, and cultural aspects (Sallam, 2021). Regarding the COVID-19 vaccine, a lot of people were hesitant because of the historically quick development of the vaccine.

Based on these premises, the aim of this study was to perform *a systematic review of the existing literature* concerning anxiety disorder and reluctance to receive the COVID-19 vaccination in various geographic contexts. Above all, this review will highlight the questions and obstacles that the public was facing and that add to their reluctance, giving policymakers important information. Simultaneously, it will endeavour to uncover the impact of anxiety disorders on people's positive vaccination intentions.

2.1. OBJECTIVES

The overall objectives of this work were to have a deeper understanding of the vaccination hesitancy phenomenon in the pandemic context and to construct a better perspective on the role that anxiety disorder played in the decision to vaccinate against COVID-19. The research question was developed based on the PICO framework for a qualitative research: “What are the outcomes related to vaccination hesitancy for adults with anxiety disorders in COVID-19 pandemic?” Another objective is to draw some conclusions about the decision to vaccinate among adults with anxiety disorder in the context of uncertainty such as the pandemic that broke out in 2020 and to understand the relationship with coronavirus vaccination hesitancy.

2.2. INCLUSION-EXCLUSION CRITERIA

We applied four inclusion criteria to identify studies according to the objective of this review. The first criterion was the year of publication of the article. We wanted to review articles from the last four years, to capture the topic of COVID-19 vaccine hesitancy in relation with anxiety disorder in adult participants; the final

period considered being 2020-2024. The next criterion was the inclusion of articles published only in scientific journals, not books, with a detailed analysis of the results. The third criterion concerned the language the article was written in, (only English articles were chosen). Clinical trials, review studies and meta-analyses were excluded.

We decided not to include reviews and meta-analyses, since these presuppose the identification of primary research specific to a topic (Pollock & Berge, 2018), or, by selecting them, it would mean using secondary sources of data, and the purpose of our research is not to carry out an umbrella type review (Choi & Kang, 2023). We also excluded studies that addressed the issue of anxiety as a symptom of pandemic context, without a clear distinction between anxiety caused by COVID-19's uncertainty and diagnosis or screening for anxiety disorder, related with mental illnesses. In addition, the articles that fall within the scope of anxiety as a functional or dysfunctional emotion, and the studies that investigated emotions such as fear or anxiety influencing COVID-19 vaccine hesitancy were removed.

There were restrictions related to the age of participants and the type of design. Our study included studies of adults participants. Participants characteristics are: over 18 years old, gender was not a variable, adult participants with anxiety disorder, adult participants with generalised anxiety (GAD) or adult participants with high levels of GAD on screening test were eligible for this review. Studies were excluded if the participants were under 18 years old. We also included observational, case-control studies, cross sectional studies or surveys study designs. These studies were conducted in online surveys or on-site research. Studies with adult participants without anxiety disorder, adult participants without generalised anxiety (GAD) or adult participants with low levels of GAD on screening tests comparator groups were eligible. The outcomes of COVID-19 vaccine hesitancy or vaccine acceptance were also included.

2.3. LITERATURE REVIEW STRATEGY

A systematic literature search (Rother, 2007; Nightingale, 2009; Okoli, 2015) was performed in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Multiple databases were searched, namely PubMed, using a set of developed keywords. Additionally, the peer review process required an update to the systematic search, which was performed several weeks later. Search keywords were developed by the authors in relevance to the research question. When relevant, Boolean operators were utilised to develop the most robust search in the databases chosen. The search keywords used for this literature research fall in two categories: (1) *Generic Topic of Interest* (vaccine [mh] OR vaccination [mh] OR immunization [mh] OR vaccin* [ti] ORimmun* [ti]) AND (hesitancy [mh] OR hesitance [mh]) AND (anxiety disorder [mh] OR anxiety disorders [mh] OR generalized anxiety [mh] OR generalized anxiety disorder [mh] OR

mental disorders [mh] OR mental health disorders [mh] OR mental health [mh]) and (2) *Disease Focus: COVID-19* (COVID-19 [mh] OR 2019 coronavirus disease[tiab] OR COVID19[tiab] OR sarscov 2 infection[tiab] OR 2019 coronavirus infection[ti]). Those keywords were used to run searches on one database, PubMed. Retrieved articles were entered into Zotero reference manager software and duplicates were removed. Upon exclusion of irrelevant articles, full-text articles were accessed and screened for eligibility. Studies were eligible if they: (1) were conducted in English; (2) investigated COVID-19 vaccine hesitancy and anxiety; (3) utilised validated measurement tools to measure hesitancy and anxiety; (4) had a full-text article publicly available; (5) were peer reviewed studies.

Studies were excluded at this stage if they were: (1) not peer-reviewed; (2) written in a language that is not English; (3) did not have full-text available publicly. Additionally, when one study was reported in multiple publications, it was selected the one that reported outcomes and more information that was relevant for our research question, or the one that was published in a more suitable format (for example a research letter vs. an original research article). Restrictions were applied to the publication types. Conference abstracts, theses and articles in press did not appear in our search results. Only the English papers were included. To maximise our chances to identify all relevant studies, as well as search databases, we also manually checked the reference lists of the included studies and used the similar articles feature of a database. Table no. 2 is the supplementary section which summarizes the inclusion and exclusion criteria of the studies screened during *this systematic review*, which is a qualitative research based on literature analysis and the empirical studies that responded to our research questions.

3. RESULTS

3.1. SEARCH RESULTS

Searching for the keywords mentioned above, we obtained a total of 82 studies. After removing duplicates ($N = 21$), 51 studies remained. 42 studies were excluded because they were either unrelated to the topic or did not meet the eligibility criteria. Another study included in the potentially eligible studies from PubMed was identified and entered for analysis, after reviewing the excluded studies for not fitting the objective.

In total, 20 studies were fully and carefully analysed to extract the information necessary for our systematic review. The selection process was recorded in sufficient detail to complete a PRISMA flow diagram (see Figure no. 1).

3.2. STUDY CHARACTERISTICS

In this section we present the *main study characteristics* and findings.

The sample size of studies ranged from 19 to 15.014 participants. The 20 studies were conducted on four different continents, including Africa (n = 1), North America (n = 6), Asia (n = 10) and Europe (n = 3). A total of 11 countries were included in this systematic review.

The participants in this systematic review are from different cohorts: some are patients from Mental Health Care (n = 6), some are university students (n = 3), general population with electronic records (n = 6), women from fertility centers (n = 2), refugees (n = 1) and patients with chronic conditions (n = 2).

Table no 2
Studies identified from data bases

Identified studies	Studies identified from data bases		Studies identified through other methods
	Potentially eligible studies identified in PubMed (N = 32)	Potentially eligible studies identified in Google Academic (N = 50)	
Analyzed studies	Studies excluded for not fitting the objective (N = 13), review (N = 1) or for other reasons (N = 1)	Studies excluded: Duplicates (N = 21) Primary aim irrelevant (N = 27)	Studies identified through other methods
Included studies	Studies included in the review (N = 20)		

3.3. FINDINGS

Thematic analysis generated two major themes which answered the research question “What are the outcomes related to vaccination hesitancy for adults with anxiety disorders in COVID-19 pandemic?”

These themes came from analysis of all selected studies and were triangulated by the authors’ interpretation of the results. Our analysis generated **two main themes** related to factors that affect vaccine hesitancy: Relationship of anxiety disorder and COVID-19 vaccine hesitancy in different contexts, and contribution of other factors to vaccination hesitancy in COVID-19 pandemic.

Theme 1: Relationship of anxiety disorder and COVID-19 vaccine hesitancy in different context

The correlation between anxiety disorders and COVID-19 vaccination avoidance is addressed in six different contexts: *National studies in general population, Inpatients or outpatients in psychiatric-clinical setting, Vaccine hesitancy in adults with chronic illnesses, Vaccination intentions among refugees, Acceptance of the COVID-19 vaccine in university students, Vaccine acceptance in women considering or undergoing fertility treatments.*

C1: National studies from general population

In this part, the trend of selection of individuals with anxiety disorders from some national databases, namely selected from the general population, can be observed. These studies (Sekizawa *et al.*, 2022; Wang *et al.*, 2022; Palgi *et al.*, 2021; Althomali *et al.*, 2023) are based on large samples of participants, thus observing a clear correlation between generalised anxiety disorder (GAD) and vaccination avoidance (VH). The study of Wang *et al.* (2022) brings the component of coronavirus risk perception as a partial mediator of the relationship between GAD and VH, thus, trying to clarify the process by which VH directly or indirectly influences GAD. Also, this study found that vaccination status did not moderate the direct pathway of VH on GAD (Wang *et al.*, 2022). On the other hand, Althomali *et al.* (2023) report that even people without signs of GAD do not want to get vaccinated. It should be noted, however, that these results emerged in the fourth wave of the pandemic.

C2: Inpatients or outpatients in psychiatric-clinical setting

The following studies selected the population experiencing various anxiety disorders from psychiatric centres. These are both inpatients and outpatients who are on clinic lists. In the case of this specific population, the results of the studies are contradictory. A large number of studies (Eyllon *et al.*, 2022; Asadi-Pooya *et al.*, 2021; Yiu *et al.*, 2023; Freeman *et al.*, 2021; Huang *et al.*, 2021; Uvais, 2021) show that anxiety disorder correlates with hesitancy to vaccinate against COVID-19, while others (McNeil & Purdon, 2022; Batty *et al.*, 2022; Hao *et al.*, 2021) did not identify any correlation between psychiatric diagnosis and vaccination hesitancy. In fact, a trend toward higher acceptance was seen for those with anxiety and depression disorders (Hao *et al.*, 2021). It should also be mentioned that those without an anxiety disorder tend to be less reactive to the uncertainty caused by the coronavirus, but nevertheless more concerned about the vaccine and more motivated to get vaccinated by the internalised stigma associated with the infection (McNeil & Purdon, 2022; Hao *et al.*, 2021). McNeil & Purdon (2022) found no difference between the anxiety disorder sample and the control sample for being motivated or for being hesitant to get the COVID-19 vaccine.

C3: Vaccine hesitancy in adults with chronic illnesses

A special feature of the following population is that in addition to the anxiety disorder they are experiencing they also have a diagnosis of chronic illness, which differentiates them from the general population. Three main chronic diseases were studied, such as Marfan syndrome (Udugampolage *et al.*, 2023), epilepsy and diabetes (Asadi-Pooya *et al.*, 2021). The first study does not identify any significant correlation between Marfan syndrome and vaccine hesitancy, however it seems that younger people and those who have not experienced the coronavirus infection are more hesitant. It is worth noting that despite the relatively small sample, the data can be considered relevant because it is a rare disease. In the second study, a relatively low rate (1 in 9) of vaccination hesitancy is observed, patients being taken together.

C4: Vaccination intentions among refugees

In the case of refugees, a single study was initiated with people in Kenya, where their uptake of COVID-19 vaccination and screening for anxiety disorder was measured. The authors (Oyekale *et al.*, 2022) identify various mental health disorders among refugees associated with Sars-CoV-2, but despite all this, vaccination willingness is reported.

C5: Acceptance of the COVID-19 vaccine in university students

In this section anxiety disorders are extracted from highly educated university students and correlated with acceptance or avoidance of vaccination during the Sars-CoV-2 pandemic. Both anxiety disorders (such as generalised anxiety disorder and social anxiety disorder) and other mental health disorders have been studied among university students. A high level of acceptance of vaccination against COVID-19 was observed for both those with generalised anxiety disorder (Li *et al.*, 2022; Artna *et al.*, 2024; Carlton *et al.*, 2022) and those with social anxiety disorder (SAD) engaging in more safety behaviours than those non-SAD (Carlton *et al.*, 2022). However, Artan *et al.* (2024) identified that active psychosis is associated with negative perception of vaccination. An aspect that can explain the high degree of acceptance of vaccination is the advanced level of schooling, research being carried out on university campuses.

C6: Vaccine acceptance in women considering or undergoing fertility treatments

Women undergoing fertility treatments are considered a specific population where follow-up with anxiety disorder diagnosis interacts with vaccine avoidance. The authors (Kassi *et al.*, 2022; Kassi *et al.*, 2024) conducted a two-stage study, following which they identified, for patients in the fertilisation clinic, a slightly low but consistent level of avoiding vaccination against COVID-19. Also, participants with high levels of generalised anxiety disorder symptomatology reported greater distrust of the medical system, but the direction of the relationship is unclear.

THEME 2: Contribution of other factors to vaccination hesitancy in COVID-19 pandemic

A second theme drawn from the selected studies looks at other possible factors that play a significant role in the decision to vaccinate against COVID-19 in addition to the diagnosis of anxiety disorder. It has been sectioned into 5 distinct parts: *Attitudes about COVID-19 itself*, *Socio-demographic characteristics*, *Confidence in healthcare system and government*, *Perceived safety of vaccine and COVID-19 infection*, *COVID-19 vaccine hesitancy related to psychological distress and other clinical disorders*.

C1: Attitudes about COVID-19 itself

Coronavirus infection aroused different attitudes and positioning towards the virus itself and its origin. McNeil & Purdon (2022) identified three big predictors of hesitancy to vaccinate against the coronavirus, namely a higher level of individualism in the perception of the world, multiple beliefs in conspiracy theories

and trust, an aspect that does not link them to the vaccination itself. Thus, people with a high level of individualism tend to avoid vaccination.

C2: Socio-demographic characteristics

The socio-demographic traits of the study participants could be observed and some common characteristics for those hesitant to vaccinate against COVID-19 could be identified. Several authors (Eyllon *et al.*, 2022; Kassi *et al.*, 2024; Uvais, 2021) have identified a correlation between a high educational level and acceptance of vaccinations. On the other hand, low socio-economic status (Eyllon *et al.*, 2022; Artna *et al.*, 2024) and belonging to a minority ethnic group (Eyllon *et al.*, 2022; Batty *et al.*, 2022) are associated with avoiding vaccination, being more prevalent among women (Eyllon *et al.*, 2022; Batty *et al.*, 2022). Other socio-demographic characteristics that relate to the phenomenon of avoiding vaccination against the coronavirus are marginalised identities, such as gender identity or sexual orientation, (Artna *et al.*, 2024) and religious beliefs, namely the Muslim religion because it was believed that vaccines are tested on pigs (Uvais, 2021).

C3: Confidence in healthcare system and government

Another element that plays a key role in the decision to vaccinate is who promoted vaccination, and is closely related to trust in the health and government systems in each country. Two studies on the Chinese population (Hao *et al.*, 2021; Li *et al.*, 2022) have identified a correlation between the acceptance rate of vaccinations against the coronavirus and trust in the medical system, respectively in the government.

C4: Perceived safety of vaccine and COVID-19 infection

Another element that plays a key role in the decision to vaccinate is who promoted vaccination, and is closely related to trust in the health and government systems in each country. Thus, several authors (Sekizawa *et al.*, 2022; Udagampolage *et al.*, 2023; Oyekale, 2022; Althomali *et al.*, 2023) have identified a general low confidence in the effectiveness or adverse reactions of the vaccine leads to hesitancy to vaccination against COVID-19, Artna *et al.* (2024) emphasising the relevance of epistemological trust. While the participants in other studies (Eyllon *et al.*, 2022; Li *et al.*, 2022; Althomali *et al.*, 2023) took into account when making the decision to vaccinate the degree of personal risk or those around him.

C5: COVID-19 vaccine hesitancy related to psychological distress and other clinical disorders

Last but not least, in addition to the already existing anxiety disorders, vaccine hesitancy is associated with significant psychological distress that can make it even more difficult to accept vaccination regardless of specific population characteristics. Depressive disorder has been observed to be often correlated with avoiding vaccination against the corona virus (Palgi *et al.*, 2021; Eyllon *et al.*, 2022; Hao *et al.*, 2021). Researchers have also found correlates with peritraumatic

distress (Pagi *et al.*, 2021) and bipolar disorder (Eyllon *et. al.*, 2022). Likewise, psychological distress could also be observed among people with social anxiety disorder manifested by the fear of contamination (Carlton *et. al.*, 2022).

4. DISCUSSION

Stress, fear, and anxiety are said to be increased by pre-existing depression and anxiety, which are powerful antecedents of COVID-19-related mental health problems (Sakib *et. al.*, 2023). It demonstrates that vaccine hesitancy is dangerous for a person's mental health in addition to its negative effects on their health (Wang *et al.*, 2022).

Concluding the data from this systematic review, the phenomenon of avoiding vaccination against the coronavirus is a complex one that is significantly associated with anxiety disorders. However, there are many factors that contribute to this relationship, both mediating and moderating, which help us to understand the mechanism more deeply. It should not be excluded in the future to understand the phenomenon of vaccination avoidance in correlation with other psychiatric disorders. It is necessary to see the differences between anxiety, as a maladaptive negative emotion, and anxiety as a disorder, either pre-existing or developed during the pandemic.

However, regardless of the precise mechanisms underlying vaccine hesitancy, knowledge about the increased prevalence of vaccine hesitancy among individuals with psychiatric disorders can assist in informing interventions in clinical settings. Furthermore, mental health professionals' outreach could be especially helpful because they can address psychological and structural barriers to vaccination and customise vaccine education to their patients' needs (Warren *et al.*, 2020). Because of the COVID-19 guidelines, which have increased loneliness and stress, as well as a heightened fear of infection, the pandemic has also increased the likelihood of developing mental disorders and made the situation worse for those who already had mental disorders (Clemente-Suarez *et al.*, 2021).

This review is important because it identifies some major gaps in the specialised literature, being a relatively small number of researches on this topic. Also, understanding the clinical population has a particular relevance for sanogenic behaviours, having a higher risk compared to the general population in making decisions related to their own physical and mental health.

In the analysis of the studies, some common limits were identified, which makes it difficult to generalise the data, but they provide an overview. First, due to the pandemic, the vast majority of studies collected data through online questionnaires distributed across various platforms, which may have limited the representativeness of the samples in this study. Second, the information was self-reported, which again may have been affected by reporting bias.

Another limitation is that the data cannot be reported globally, or even nationally, due to the characteristics of the samples. The results can only show a population specific to the place where the data were collected and the socio-demographic characteristics. Also, a higher publication trend can be observed in the period 2021–2023, with the end of the pandemic, the interest of researchers has decreased drastically on this topic.

A significant lack of pre-pandemic and post-pandemic longitudinal studies can be noticed. Future research should focus more on the evolution of the relationship between anxiety disorders and vaccination avoidance over longer periods of time and on more age categories, respectively social classes. It is necessary for public and clinical health professionals to understand these mechanisms as deeply as possible in order to be able to intervene in time with awareness campaigns.

In conclusion, our systematic review highlights the nuanced relationship between vaccine hesitancy against COVID-19 and anxiety disorders. The review also pinpoints effective measures that can address these concerns, such as clear, transparent communication from healthcare providers, the involvement of mental health professionals in vaccination campaigns, and the implementation of supportive environments that reduce anxiety-related barriers to vaccination. By acknowledging and addressing the mental health dimensions of vaccine hesitancy, we can enhance public confidence in vaccination programs, ultimately fostering higher vaccination rates and better public health outcomes. Moving forward, it is imperative for future research to continue exploring this relationship, especially through longitudinal studies that can measure the dynamics of anxiety and vaccine hesitancy over time. Policymakers and healthcare providers must consider the psychological landscape of the populations they serve, ensuring that vaccination efforts are empathetic, inclusive, and responsive to the mental health needs of individuals. Through these concerted efforts, we can better support our communities in overcoming vaccine hesitancy, safeguarding public health, and building a more resilient society in the face of ongoing and future health challenges.

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