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Vaccine hesitancy and psychopathology. A narrative review

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Summary. Vaccine hesitancy is a term used to refer to a series of attitudes ranging from reluctance to undergo vaccination to blatant refusal. In the context of the current pandemic, vaccine hesitancy is viewed as one of the ten major threats to public health. This narrative review, based on analysis of the most important literature reports on this topic, aims to illustrate the dimensions of vaccine hesitancy and the numerous sociodemographic and individual determinants involved, with particular reference to psychopathology, a somewhat neglected, but potentially relevant factor.

Key words. Covid-19, hesitancy, mental disorders, psychopathology, refusal, vaccine.

"Vaccine hesitancy" e psicopatologia. Una revisione narrativa della letteratura.

Riassunto. Il termine "vaccine hesitancy", letteralmente "esitazione vaccinale", è usato per riferirsi a una serie di atteggiamenti che vanno dalla riluttanza a sottoporsi alla vaccinazione al palese rifiuto. Nel contesto dell'attuale pandemia, l'esitazione sui vaccini è stata vista come una delle dieci principali minacce per la salute pubblica. Questa rassegna narrativa, basata sull'analisi dei più importanti studi presenti in letteratura sull'argomento, si propone di illustrare le dimensioni dell'esitazione vaccinale e i numerosi determinanti sociodemografici e individuali coinvolti, con particolare riferimento alla psicopatologia, fattore alquanto trascurato, ma potenzialmente rilevante.

Parole chiave. Covid-19, disturbi mentali, esitazione, psicopatologia, rifiuto.

Introduction

Vaccine hesitancy is generally defined as a «behavioral pattern ranging from a delay in acceptance to a complete refusal of vaccine, in spite of vaccine availability»[1]. Thus, vaccine hesitancy is a concept representing «a shift from the dichotomous anti- versus pro-vaccine perspective to an approach characterizing behavior on a spectrum of potential attitudes and behaviors, ranging from active demand for vaccines to complete refusal of all vaccines», so that «vaccine-hesitant individuals are a heterogeneous group along this continuum»[2]. Vaccine hesitancy is not a new phenomenon, but following onset of the covid-19 pandemic, it has become an important public health issue worldwide[3]. According to a prevalent point of view, a better understanding of vaccine hesitancy is crucial in an attempt to overcome the phenomenon. This narrative review aims to illustrate the actual dimensions of vaccine hesitancy, and the numerous sociodemographic and individual determinants involved, with particular reference to psychopathology, a somewhat neglected, but potentially highly relevant factor.

How widespread is vaccine hesitancy?

A recent survey of 34 different countries reported a discrepancy in the prevalence of vaccine acceptance, with the lowest rates of vaccination against covid-19 found in Kuwait (23.6%), Jordan (28.4%), Italy (53.7), Russia (54.9%), Poland (56.3%), US (56.9%), and France (58.9%)[4]. Vaccine hesitancy appears to vary considerably over the time frame considered, as shown in a recent review reporting an average rate globally of 21% in April 2020, 36% in July 2020 and 16% in October 2020[5]. This wide diffusion of vaccine hesitancy is currently deemed one of the main factors exerting a negative influence on efforts to eliminate covid-19. Indeed, the World Health Organization (WHO) considers vaccine hesitancy one of the 10 greatest threats to public health, highlighting the need to study, understand, and target this construct[6]. It is hard to understand why such a significant proportion of people is so reluctant to accept vaccination, taking into account both the frequently dramatic individual and social consequences produced by the pandemic and the fundamental role of vaccines in protecting against infection, as shown by data attesting to more than 95% effectiveness against infection and more than 90% in protecting against disease or hospitalization, with no relevant safety concerns[7].

What factors might explain vaccine hesitancy?

Several reviews focused on "predictors" of vaccine hesitancy have been published to date. A recent literature review, using a broad search strategy, including all papers published in English considered relevant

to the topic of demographic and individual factors associated with vaccine hesitancy, found that age, income, educational attainment, health literacy, rurality, and parental status were the most frequent demographic factors related to vaccine hesitancy; among individual factors emerging from the literature review the authors reported mistrust in authority, disgust sensitivity, and risk aversion[8]. Another review of 22 studies investigating vaccine acceptance, intention and hesitancy, conducted largely in the general population, found gender, age, education, and occupation to be some of the main socio-demographic variables associated with vaccine acceptance, while individual variables negatively influencing vaccine acceptance were trust in authorities, risk perception of covid-19 infection and vaccine efficacy, current or previous influenza vaccination, and vaccine safety[5].

Several individual factors of specific interest may also be inferred from large community surveys. A web-based survey of a sample of 7678 adults conducted in the USA and Canada[9] at three timepoints (May and July 2020, March 2021) showed how mistrust of vaccine benefit and lower perceived severity of covid-19 infection were the principal determinants underlying vaccine hesitancy; moreover, Right-Wing political affiliation, higher risk propensity and a less negative emotional response to the pandemic emerged as the most relevant sociodemographic and psychological determinants, with other sociodemographic factors including younger age, women, race, and employment status. Overall, the lack of confidence in vaccine and complacency explained 38% and 21% of variance justifying vaccine hesitancy, respectively, whilst sociodemographic and psychological determinants explained 13% and 11% of variance, respectively. Another online survey[10] conducted on 5,114 UK adults in September-October 2020 used the Oxford covid-19 vaccine hesitancy scale to assess intent to receive an approved vaccine; using structural equation modelling to estimate explanatory factor relationships, a model explaining 86% of variance in hesitancy emerged, constituted by beliefs relating to collective importance, efficacy, side-effects, and speed of development of a covid-19 vaccine; moreover, a second model, explaining 32% of variance, was based on two higher-order explanatory factors, namely "excessive mistrust" (including conspiracy beliefs, negative views of doctors, and need for chaos), and "positive healthcare experiences" (including supportive doctor interactions and good NHS care); hesitancy was also associated with younger age, female gender, lower income, and ethnicity, although socio-demographic factors explained little variance (9.8%). A Norwegian online survey[11] conducted in January and February 2021, involving a large sample of the adult population (n=4,571 respondents) investigated a series of putative factors (psychological, contextual, and sociodemographic) associated with vaccine hesitancy, identifying several subgroups displaying this hesitancy including males, rural residents, and parents with children below 18 years of age. The study failed to demonstrate any difference across education or age groups; however, a more frequently reported hesitancy was found among those preferring unmonitored media platforms (e.g., information from peers, social media, online forums, and blogs). In this survey, key variables related to vaccine hesitancy were perceived risk of vaccination, belief in the superiority of natural immunity, fear of significant others being infected by the virus, and trust in health officials' dissemination of vaccine-related information.

Psychopathology and vaccine hesitancy: a literature analysis

It is commonly acknowledged that the wide ambivalence or resistance toward vaccination should not be seen *per se* as irrational or anti-scientific, frequently reflecting legitimate concerns and/or doubts over vaccines. In particular, however, the existence of an extreme wing of vaccine hesitancy comprising subjects displaying an overt refusal to acknowledge covid-19, who are often actively involved in the so-called "anti-vax" movement, has led to speculation as to whether (and to what extent) psychopathological determinants may underlie the assuming of a similar stance. Despite the extensive exploration of individual risk factors, a substantial gap in understanding the associations between psychopathology and vaccine hesitancy still exists. Accordingly, the author will attempt to answer this question on the basis of the limited literature published to date.

Studies of non-clinical samples

A first body of information may be drawn from a series of studies conducted with the aim of evaluating, in samples obtained from the general population, the potential role of psychopathology in terms of psychiatric symptoms, symptomatological dimensions and/or personality traits in vaccine acceptance and/or hesitancy. The main characteristics and findings of these studies are summarized in table 1[12-19].

Studies in clinical populations

A second means of exploring the role of psychopathology in vaccine hesitancy is represented by the evaluation of attitudes towards vaccination amongst clinical populations. In recent years, several published studies have focused on evaluating the rate of vaccine uptake or willingness to receive vaccinations during the influenza pandemic among patients with

Table 1. Studies of non-clinical samples*.

Authors, year (reference)	Study methods	Samples/site	Main results*
Bendau et al.[12]	On line survey	1779 adults of a non-probability convenience sample, Germany	64.5% of subjects accepting the vaccination 10.4% undecided 22.1% absolutely or fairly against vaccine acceptance correlated to covid-19-related anxiety, fears of infection and health-related consequences unspecific anxiety and depressive symptoms showed no significant association with vaccine acceptance
Nguyen et al.[13]	Household survey	nationally representative sample of USA adults ≥18 years (n =77,104)	35% of adults had symptoms of anxiety or depression depressed/anxious people were less likely to receive vaccination (adjusted prevalence ratio (aPR) = 0.94, 95%CI: 0.91–0.98) and more likely to intend to get a vaccine (aPR = 1.13, 95%CI: 1.08–1.19) females with mental health symptoms were less likely to receive vaccination but more likely to intend to get vaccinated anxiety/depression correlate with concerns about vaccine side effects, efficacy, cost, dislike of vaccines and lack of trust in the government
Murphy et al.[14]	On line survey	nationally representative samples of general adult populations of Ireland (N=1041) and United Kingdom (N=2025),	vaccine hesitancy in 35% and 31% of Irish and British samples respectively vaccine hesitants are less likely to have received treatment for a mental health problem (only Irish sample) (AOR=0.63, 95% CI=0.45, 0.88) subjects with vaccine hesitancy or resistance were more likely to hold conspiratorial and paranoid beliefs, impulsive traits, and a more emotionally unstable and less conscientious personality
Freeman et al.[15]	On line survery	Nationally representative sample (n=15,014) of adult UK population	26.2% screened positive for blood-injection-injury phobia screening positive subjects are more likely to report vaccine hesitancy vaccine hesitancy was associated with higher scores on the Specific Phobia Scale, Medical Fear Survey, and injection fears
Zhang et al.[16]	On line survey	non-probability study on 1015 adult Chinese subjects	12% of the sample was made up of vaccine hesitant subjects conspiracy beliefs had significant direct (β=0.294), indirect (β=0.423) and total (β=0.717) effects on vaccine hesitancy
Nazlı et al.[17]	On line survey	Convenience sample of 488 Turkish adults	low fear of covid-19 and conspiracy beliefs positively correlated to vaccine hesitancy
Simione et al.[18]	On line survey	Convenience sample of 374 Italian adults recruited through a social media platform	death anxiety reduced propensity to vaccination through believing in conspiracy theories paranoia reduced vaccination propensity through mistrust in medical science psychological distress reduced vaccination propensity through both conspiracy beliefs and mistrust anxiety increased the propensity to vaccination through reduced belief in conspiracy theories and mistrust in science

(*Continued*) **Table 1.**

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Authors, year (reference)	Study methods	Samples/site	Main results*
Perlis et al.[19]	On line survey	Non probability USA 50 state sample of 15,464 respondents	26.9% of respondents reported moderate or greater depressive symptoms 19.2% of respondents reported vaccine-related misinformation depression increased likelihood of endorsing misinformation (adjusted OR, 2.15; 95% CI, 1.91-2.43) respondents reporting vaccine misinformation reduces the likelihood of being vaccinated (adjusted OR, 0.45; 95% CI, 0.40-0.51) and increase the likelihood of vaccine hesitancy (adjusted OR, 2.68; 95% CI, 2.89-3.13)

*only data regarding mental health issues are reported.

severe mental illness (SMI), highlighting a very low vaccination uptake[20]. On the contrary, other studies reported that the majority of patients affected by SMI believed that vaccinations were safe and effective in general, with 74% reporting moderate willingness to receive vaccination[21,22]. During the current covid-19 pandemic only a limited number of papers have been published with regard to vaccine hesitancy/acceptance among psychiatric patients. Jefsen et al.[23] conducted two surveys in Denmark to compare vaccine willingness in patients with mental illness and in a sample of the general population, demonstrating relatively high vaccine acceptance in both groups, although significantly lower amongst patients with mental illness (84.8%) versus the general population (89.5%). Moreover, these findings persuaded the authors that vaccine hesitancy does not appear to be a major barrier for vaccine uptake in patients with mental illness, at least in Denmark. A cross-sectional study was conducted in Kerala (India)[24] from March to April 2021 to assess covid-19 vaccination hesitancy in ninety patients attending an outpatient psychiatry department in a tertiary care hospital; patients were affected mainly by depressive disorder (51.7%), generalized anxiety disorder (11.2%), adjustment disorder (7.9%), bipolar affective disorder (6.7%), and obsessive-compulsive disorder (5.6%). Only 17.8% reported a definitive intention to receive vaccination, 37.8% reported a definitive intention not to receive vaccination and 36.7% stated that they would probably receive vaccination; 7.8% reported they probably would avoid vaccination. Overall, the findings of this study showed that only 54.5% of respondents reported a definitive or probable intention to receive covid-19 vaccination, whilst 37.8% reported a firm intention not to undergo vaccination. In this study, covid-19 vaccination hesitancy was significantly higher when compared to studies conducted in general populations worldwide. Intention to receive covid-19 vaccine was significantly associated with a higher level of education, while refusal of vaccination was associated with being of Islamic religion, with no statistically significant difference in vaccination intention between patients with neurotic spectrum disorder and psychotic spectrum disorder.

A study was performed in February 2021 at a Mental Health Hospital in Israel[25] on a total of fifty one out of 196 patients suffering from severe mental illness hospitalized at the time of the study in closed, open or day wards and who had received covid-19 vaccines after informed consent; all patients who had not been vaccinated in February 2021 (baseline) were re-approached a month later to assess whether they had been vaccinated since. The majority of participants were severely mentally ill patients. All patients were asked dichotomously (yes/no) if they had been vaccinated and, on receiving a negative reply, were asked whether they intended to do so. The answers provided were checked against the medical files on the ward. The attitude of patient groups to vaccination was very similar to that of the general population, with 70% of patients in the study group having been vaccinated or intending to be vaccinated, similar to survey findings in the general population. The ultimate decision was based largely on attitudes displayed towards vaccination itself, rather than to a fear of covid-19, again similar to observations made in the general population. Patients who were not vaccinated at baseline displayed an oppositional approach to the vaccine, with no significant differences detected in their fear of covid-19 levels or in levels of clinical severity compared to vaccinated subjects. Moreover, in the 29 patients not vaccinated at baseline, approach to the vaccine was a good predictor of getting vaccinated after one month (79% positive predictive value). The authors of this study, focused on

a unique, hard to recruit, vulnerable patient group, commented that despite the small group size, their findings suggested that the majority of patients suffering from severe mental illness show a willingness towards vaccination, highlighting how numerous patients who did not immediately agree to vaccination subsequently displayed a propensity towards vaccination whilst hospitalized or in their respective communities. Furthermore, the authors observed how patients willing to undergo vaccination did not differ from those who chose not to get vaccinated in terms of clinical condition and level of symptoms or fear of covid-19, although the study group was made up of highly distressed patients. In the authors opinion, these data support the hypothesis whereby the decision made by the patient as to whether or not to get vaccinated is based on their personal viewpoint and is not related to the nature and severity of their illness and distress over covid-19.

A multicenter study conducted in China[26] examined the prevalence of vaccine hesitancy and associated factors in 1,853 community-dwelling and hospitalized patients with major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SCZ). This study is unique given that, to date, no other data have been published on vaccine hesitancy in community-dwelling patients with psychiatric disorders or across various diagnostic groups, at least in non-Western settings. The proportion of covid-19 vaccination hesitancy was 45.3% with 45.3% in MDD, 43.6% in BD, and 47.4% in SCZ subgroups. Vaccination hesitancy was 49.2% in community-dwelling and 31.3% in hospitalized patients. Regression analysis revealed that vaccine hesitancy was more prevalent amongst the unemployed and community-dwelling patients with no significant difference in vaccine hesitancy detected across the three major psychiatric disorders. According to the authors, in China vaccine hesitancy rate was considerably high in patients with severe mental illness, independent of diagnosis. The finding relating to unemployment was explained by the strong encouragement from all employers in China for their staff to be vaccinated, while the higher vaccine hesitancy among community-dwelling patients was interpreted according to a lower public awareness of the importance and safety of vaccines compared to hospitalized patients, with the latter being deemed more likely to experience crowded living conditions compared to their community-dwelling counterparts, with a consequent greater awareness of the need to protect themselves. Moreover, the study found that patients with a higher level of perceived stigma were more likely to display reluctance towards vaccination in the light of literature data underlining more limited medical knowledge in this patient group. Another Chinese survey[27] examined the uptake, acceptance, and hesitancy associated with covid-19 vaccines in 906 people affected by mental disorders during the nationwide vaccine rollout consecutively recruited from a large psychiatric hospital in Wuhan. Study subjects were administered a self-report questionnaire, which comprised standardized questions regarding socio-demographics, covid-19 vaccination status, attitudes toward covid-19 vaccines, and psychopathology. Patients displayed a much lower rate of vaccination than Wuhan residents (10.8 vs. 40.0%). Rates of vaccine acceptance and hesitancy were 58.1 and 31.1%, respectively. Factors associated with vaccine uptake included being affected by mental disorders other than psychosis and being an outpatient, while factors associated with vaccine acceptance comprised having good insight into mental illness.

A USA cross-sectional study[28] used data obtained from the second stage of a longitudinal study of mental health and wellbeing during the covid-19 pandemic to assess the prevalence of vaccine hesitancy amongst patients with psychiatric illnesses and associations between psychiatric morbidity and vaccine hesitancy based on information deriving from both electronic health records and a patient survey obtained from 14,365 patients at a group medical practice between February and May 2021. Out of a total of 1,761 participants, 12.3% reported vaccine hesitancy. The latter rate was lower than that detected in the general US population and significantly more prevalent among participants affected by substance use (29.6%), attention deficit and hyperactivity (23.3%), post-traumatic stress (23.1%), bipolar (18.0%), generalized anxiety (16.5%), major depressive (16.1%), and other anxiety (15.5%) disorders, and tobacco use (18.6%). After adjusting for sociodemographic characteristics and physical comorbidities, only substance use disorders and tobacco use remained significantly associated with increased odds for vaccine hesitancy, while bipolar disorder was significantly inversely associated with vaccine hesitancy. These findings suggest that the higher prevalence observed across most conditions may be related to the distribution of socio-demographic characteristics in this population as opposed to intrinsic differences in vaccine hesitancy among those with psychiatric illnesses. Moreover, a similar vaccine hesitancy was observed in subjects affected by anxiety disorders and other conditions, a finding in contrast to previous research showing an association between anxiety and increased preventive behavior. According to the Authors, this finding could be due to the fact that diagnoses were more sensitive in identifying clinically meaningful levels of anxiety and related impairment rather than to a natural variation in anxiety levels amongst otherwise healthy adults. Finally, an Israeli study[29] was conducted to evaluate vaccine hesitancy, depression, anxiety, and peritraumatic distress,

as well as several demographic, health, and covid-19-related factors in 254 psychiatric patients who had received at least their first vaccination. Logistic regressions demonstrated that above and beyond socio-demographic, health, and covid-19-related factors, covid-19 vaccine hesitancy represented the most prominent risk factor for anxiety, depression, and peritraumatic distress. Higher levels of vaccine hesitancy were found to double the risk for depression and peritraumatic stress, and to triple the risk for anxiety. This study, the only one to investigate this topic, demonstrates how vaccine hesitancy in vaccinated populations is associated with negative psychiatric outcomes, supporting the hypothesis that the holding of ambivalent attitudes toward vaccination correlates with mental health morbidity. Moreover, the study highlights how having actually received a covid-19 vaccination does not eliminate the effect of vaccine hesitancy on psychiatric morbidity, as evidenced by the finding that individuals displaying vaccine hesitancy, despite their decision to accept the vaccine, continued to manifest clinical levels of anxiety, depression, and stress, possibly due to their fears relating to the safety and long-lasting effects of the vaccine.

Is psychopathology amongst the factors explaining vaccine hesitancy?

Although somewhat contradictory, findings from the available literature seem to indicate an important contribution of psychopathology to vaccine hesitancy. Data from surveys conducted on samples drawn from the general population should be interpreted in the light of many methodologic limitations which are intrinsically linked to this type of studies, in particular relating to the assessment of psychopathology, mostly based upon self-administered instruments which do not facilitate clinical diagnosis. Indeed, self-assessed evaluation of anxiety/depression in these studies is generally based on a dimensional approach, which may not be capable of discriminating between a clinically significant anxiety/depressive state and an unspecific condition of distress.

Several of these studies highlight how unspecific anxiety and or depressive symptoms seem to be unrelated to vaccine acceptation/hesitancy[12], although other studies report that anxiety/depression symptoms are related to both a higher propensity to vaccination[14] and to higher vaccine hesitancy[13,17], the latter in particular among women[13]. These contradictory findings, to be addressed subsequently, may be interpreted in the light of other psychological factors mediating the behavioral response to emotional arousal. Other studies seem to indicate that vaccine hesitancy or acceptance may be less related to the anxiety dimension in general, but rather to specific types of anxiety, as shown by data regarding the correlation between fears of infection and health-related consequences and vaccine acceptation on the one hand, and between fears of social/economic consequences of the pandemic and vaccine hesitancy on the other[12]. Accordingly, the fact that fearing the health and survival-related consequences of covid-19 may lead to a higher propensity to vaccination is psychologically understandable, while the fact that fearing the social and economic consequences of the pandemic may lead to a lower propensity to vaccination may likely be due to concomitant anger[30] and significant correlation of anger and confrontation, among others, with a greater likelihood of experiencing significant financial difficulties due to the pandemic and greater perceived risk of covid-19[31]. Among the specific typologies of anxiety, the blood-injection-injury fears emerging from a single study[15] are of particular interest, not only in view of the frequency of manifestation, but also as a potentially surmountable barrier to vaccination. A large study[19] shows a link between depression and hesitancy through a mediating role of misinformation, to which depressed subjects may be particularly prone. On the whole, data from community studies seem to indicate that the higher the scores at anxiety/depression, the higher the propensity both for vaccine hesitancy and acceptance, depending on the nature of anxiety, concomitant presence of other related emotions and the mediating role of personality traits, as suggested below. In interpreting this evidence, the above-mentioned limitation relating to self-assessed evaluation of anxiety/depression in line with a dimensional approach should be taken into account, as this type of assessment may not be capable of discriminating between a clinically significant anxiety/depressive state and an unspecific condition of distress.

Studies conducted on non-clinical samples have also detected a series of personality traits indicated as significant factors with regard to vaccine hesitancy/acceptance, including tendency towards conspiratorial and paranoid beliefs, impulsive thinking style, and emotional instability[16-18]. Conspiracist ideation emergence is of particular importance in view of its correlation with psychopathology. Indeed, in the context of the US National Comorbidity Survey-Replication (NCS-R)[32], data relating to conspiracy attitudes were analyzed from a community sample of 5645 people, 1618 of whom (26.7%) endorsed a conspiracy belief; individuals endorsing this belief displayed lower levels of physical and psychological well-being, higher levels of suicidal ideation, weaker social networks, less secure attachment style, difficult childhood family experiences, and were more likely to meet criteria for a psychiatric disorder; specifically, the conspiracy belief was highly associated (odds ratio= 7.81) with

the specific paranoia psychosis item (Did you ever believe that there was an unjust plot going on to harm you or to have people follow you that your family and friends did not believe was true?). The hypothesized causal relationship between vaccine intentions and conspiracy ideas implies that paranoia may be present amongst the causes of this form of ideation. Paranoia may generate a belief in conspiracy theories by inducing fear of external agents and an idea that rather than being a coincidence, intentions are the primary causes of world events[33], thus explaining an association with SARS-CoV-2 conspiracist ideation[34]. Conspiracist ideation may also be induced by a series of reasoning biases influencing the individuals' likelihood of adopting epistemically-suspect alternatives to official versions of the facts, fostering paranoid thinking styles and distrust of official sources of information, including scientists[35]. Moreover, some authors have underlined how bias toward reduced data gathering during reasoning may cause paranoia, increasing the perceived dangerousness of vaccines and thereby reducing willingness to vaccinate[36]. According to several authors[18], seemingly contradictory data on the role of anxiety in vaccine acceptance/hesitancy could be explained taking into account the mediating role of personality traits. Indeed, fears of death and emotional distress related to the current pandemic are differentially related in a very complex way to paranoia, conspiracy theories, mistrust in science, and consequently to the propensity to accept or refuse vaccines. While death anxiety seems to have a direct positive effect on propensity to vaccination, through a decrease in both belief in conspiracy theories and mistrust in science, on the contrary it may be also associated to a reduced propensity to get vaccinated through a mediated path in believing in conspiracy theories, with paranoia linked to a reduction in vaccination adherence through a mediation effect of mistrust in medical science; similarly, psychological distress seems to reduce vaccination propensity by increasing both conspiracy beliefs and mistrust.

As expected, studies conducted on clinical samples provided a response to the question of possible relationships between mental disorders and vaccine hesitancy. Indeed, if the presence of psychopathology was related to a greater propensity to uncertainty towards vaccines and consequently to lower vaccination rates, this was clearly demonstrated by studies conducted on clinical samples, comprising solely subjects with an established clinical diagnosis. Moreover, these studies were expected to demonstrate, at the very least, differences present between patients with a broad range of diagnoses i.e. psychotic vs neurotic, major vs minor disorders. Unfortunately, the limited number of studies published to date and the contradictory findings published, partly justified by methodological reasons and, in particular, sampling methods, currently only provide partial and provisional answers.

The majority of studies conducted on clinical populations from western countries fundamentally indicate that vaccine hesitancy in people affected by mental disorders is as frequent as in the respective general population or even lower[21-23,25], although one study revealed how specific disorders, including substance use disorder, are associated with higher vaccine hesitancy[28], whilst another study found a higher rate of hesitancy compared to influenza vaccination[20]. Moreover, evidence from these studies seems to indicate that vaccine hesitancy is related increasingly to individual factors which are substantially similar to those observed in populations devoid of mental disorders, rather than to the presence of a psychopathology *per se*. Indeed, the largest western study of a psychiatric population conducted in the USA[28] demonstrated how a clear-cut higher prevalence of vaccine hesitancy in patients with mental health conditions, with the exception of alcohol use disorders, was comprehensively attenuated when regression models of data analysis controlling for socio-demographic characteristics, with the sole exception of substance use disorders and tobacco use, were applied. This finding suggested that the higher prevalence observed for the majority of psychiatric disorders may be related to the distribution of socio-demographic characteristics in this population as opposed to intrinsic differences in vaccine hesitancy. However, in line with all other western studies, with the exception of one investigating a sample affected by severe mental illness[25], the patients enrolled in this extensive study did not include individuals affected by non-affective psychotic disorders or Personality Disorder, a diagnostic category that has not been included in any of the studies published to date.

On the contrary, other studies, mainly conducted in eastern countries, report a higher propensity to vaccine hesitancy among psychiatric patients versus the general population, generally together with low rates of vaccination[24,26,27]. The two studies conducted in China were focused on patients with severe mental disorders, including schizophrenia[26,27]. Vaccine hesitancy appears to be substantially independent of diagnosis both in western and eastern studies[24-26]; however it should be taken into account that in one of these studies, conducted in China[26], all diagnoses considered (Major Depression, Bipolar Disorders, Schizophrenia) are included among severe mental illnesses. Another large study conducted in China revealed how vaccine uptake (i.e., the number of patients vaccinated) was significantly lower among inpatients and patients with psychotic disorders, who were less likely to accept the vaccine, likely due to a more frequent impairment of decisional capacity, while vaccine acceptance (i.e., acceptance to be vac-

cinated) was associated with having a lower insight, considered as a factor associated to a lower awareness of health-related needs[27].

In conclusion, data obtained from studies conducted in non-clinical populations indicate that the presence of a masked psychopathological condition may play a contributory role in both vaccine hesitancy and acceptance; indeed, the higher the anxiety/fear due to covid-19, the higher the acceptance or refusal of vaccination, in relation to a mediation role of pathological personality traits such as paranoia. Regrettably, to date, no studies relating to clinical samples of people affected by personality disorders have been published, thus no confirmation is yet forthcoming of the role of these disorders in vaccine hesitancy/acceptance. Studies on other clinical samples seem to highlight how psychopathologies linked to common mental disorders, with the exception of Substance Use Disorder and injection Phobias, do not influence *per se* attitudes displayed toward vaccination; on the contrary, a prevalent association has emerged between severe mental disorders, including psychotic disorders, and vaccine hesitancy. However, further research is warranted in view of the limited number of studies published to date and the lack of large-scale studies in western countries.

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References

1. Kumar D, Chandra R, Mathur M, Samdariya S, Kapoor N. Vaccine hesitancy: understanding better to address better. Isr J Health Policy Res 2016; 5: 2.
2. Dubé E, Ward JK, Verger P, MacDonald NE. Vaccine hesitancy, acceptance, and anti-vaccination: trends and future prospects for public health. Annu Rev Public Health 2021; 42: 175-91.
3. Koslap-Petraco M. Vaccine hesitancy: not a new phenomenon, but a new threat. J Am Assoc Nurse Pract 2019; 31: 624-6.
4. Sallam M. COVID-19 vaccine hesitancy worldwide: a concise systematic review of vaccine acceptance rates. Vaccines 2021; 9: 160.
5. Joshi A, Kaur M, Kaur R, Grover A, Nash D, El-Mohandes A. Predictors of COVID-19 vaccine acceptance, intention, and hesitancy: a scoping review. Front Public Health 2021; 9: 698111.
6. World Health Organization (WHO). Ten Threats to Public Health in 2019. Available online: https://bit.ly/3gQlJLU [last accessed October 28, 2022].
7. Haas EJ, Angulo FJ, Mclaughlin JM, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study national surveillance data. Lancet 2021; 397: 1819-29.
8. Hudson A, Montelpare WJ. Predictors of vaccine hesitancy: implications for COVID-19 public health messaging. Int J Environ Res Public Health 2021; 18: 8054.
9. Gerretsen P, Kim J, Caravaggio F, et al. Individual determinants of COVID-19 vaccine hesitancy, PLoS One 2021; 16: e0258462.
10. Freeman D, Loe BS, Chadwick A, et al. COVID-19 vaccine hesitancy in the UK: the Oxford coronavirus explanations, attitudes, and narratives survey (Oceans) II. Psychol Med 2020; 11: 1-15.
11. Ebrahimi OV, Johnson MS, Ebling S, et al. Risk, trust, and flawed assumptions: vaccine hesitancy during the COVID-19 pandemic. Front Public Health 2021; 9: 700213.
12. Bendau A, Plag J, Petzold MB, Strohle A. COVID-19 vaccine hesitancy and related fears and anxiety. Int Immunopharmacol 2021; 97: 107724.
13. Nguyen KH, Chen S, Morris K, Chui K, Allen JD. Mental health symptoms and association with COVID-19 vaccination receipt and intention to vaccinate among adults, United States. Prev Med 2022; 154: 106905.
14. Murphy J, Vallières F, Bentall RP, et al. Psychological characteristics associated with COVID-19 vaccine hesitancy and resistance in Ireland and the United Kingdom. Nat Commun 2021; 12: 29.
15. Freeman D, Lambe S, Yu LM, et al. Injection fears and COVID-19 vaccine hesitancy, Psychological Medicine 2021; 1-11.
16. Zhang X, Guo Y, Zhou Q, Tan Z, Cao J. The mediating roles of medical mistrust, knowledge, confidence and complacency of vaccines in the pathways from conspiracy beliefs to vaccine hesitancy. Vaccines 2021; 9: 1342.
17. Nazlı SB, Yığman F, Sevindik M, Özturan D. Psychological factors affecting COVID-19 vaccine hesitancy. Ir J Med Sci 2022; 191: 71-80.
18. Simione L, Vagni M, Gnagnarella C, Bersani G, Pajardi D. Mistrust and beliefs in conspiracy theories differently mediate the effects of psychological factors on propensity for COVID-19 vaccine. Front Psychol 2021; 12: 683684.
19. Perlis RH, Ognyanova K, Santillana M, et al. Association of Major Depressive symptoms with endorsement of COVID-19 vaccine misinformation among US adults. JAMA Netw Open 2022; 5: e2145697.
20. Lorenz RA, Norris MM, Norton LC, Westrick SC. Factors associated with influenza vaccination decisions among patients with mental illness. Int J Psychiatry Med 2013; 46: 1-13.
21. Maguire PA, Reay RE, Looi JC. Nothing to sneeze at-uptake of protective measures against an influenza pandemic by people with schizophrenia: willingness and perceived barriers. Australas Psychiatry 2019; 27: 171-8.
22. Miles LW, Williams N, Luthy KE, Eden L. Adult vaccination rates in the mentally ill population: an outpatient improvement project. J Am Psychiatr Nurses Assoc 2020; 26: 172-180.
23. Jefsen OH, Kølbæk P, Gil Y, et al. COVID-19 vaccine willingness amongst patients with mental illness compared with the general population. Acta Neuropsychiatr 2021; 33: 273-6.
24. Uvais NA. COVID-19 vaccine hesitancy among patients with psychiatric disorders. Prim Care Companion CNS Disord 2021; 23: 21br03028.
25. Danenberg R, Shemesh S, Bitan DT, et al. Attitudes of patients with severe mental illness towards COVID-19 vaccinations: a preliminary report from a public psychiatric hospital. J Psychiatr Res 2021; 143: 16-20.
26. Bai W, Cai H, Jin Y, et al. COVID-19 vaccine hesitancy in community-dwelling and hospitalized patients with severe mental illness. Psychol Medi 2021; 1-3.
27. Huang H, Zhu X, Liang P, et al. COVID-19 vaccine uptake, acceptance, and hesitancy among persons with Mental Disorders during the second stage of China's nationwide vaccine rollout. Front Med 2021; 8: 761601.
28. Eyllon M, Dang AP, Barnes JB, et al. Associations between psychiatric morbidity and COVID-19 vaccine hesitancy:

an analysis of electronic health records and patient. Psychiatry Res 2022; 307: 114329.
29. Palgi Y, Bergman YS, David BB, Bodner E. No psychological vaccination: vaccine hesitancy is associated with negative psychiatric outcomes among Israelis who received COVID-19 vaccination. J Affect Disord 2021; 287: 352-3.
30. Yan C, Law M, Nguyen S, Cheung J, Kong J. Comparing public sentiment toward COVID-19 vaccines across Canadian cities: analysis of comments on reddit. J Med Internet Res 2021; 23: e32685.
31. Smith LE, Duffy B, Moxham-Hall V, Strang L, Wessely S, Rubin GJ. Anger and confrontation during the COVID-19 pandemic: a national cross-sectional survey in the UK. J R Soc Med 2021; 114: 77-90.
32. Freeman D, Bentall RP. The concomitants of conspiracy concerns. Soc Psychiatry Psychiatr Epidemiol 2017; 52: 595-604.
33. Darwin H, Neave N, Holmes J. Belief in conspiracy theories. The role of paranormal belief, paranoid ideation and schizotypy. Personality Individ Differ 2011; 50: 1289-93.
34. Freeman D, Waite F, Rosebrock L, et al. P. Coronavirus conspiracy beliefs, mistrust, and compliance with Government Guidelines in England. Psychol Med 2022; 52: 251-63.
35. Pierre JM. Mistrust and misinformation: a two-component, socio-epistemic model of belief in conspiracy theories. J Social Polit Psychol 2020; 8: 617-41.
36. Bronstein MV, Kummerfeld E, MacDonald A, Vinogradov S. Willingness to vaccinate against SARS-CoV-2: The role of reasoning biases and conspiracist ideation. Vaccine 2022; 40: 213-22.

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