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COVID-19 vaccination for people with severe mental illness: why, what, and how?

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Psychiatric disorders, and especially severe mental illness, are associated with an increased risk of severe acute respiratory syndrome coronavirus 2 infection and COVID-19-related morbidity and mortality. People with severe mental illness should therefore be prioritised in vaccine allocation strategies. Here, we discuss the risk for worse COVID-19 outcomes in this vulnerable group, the effect of severe mental illness and psychotropic medications on vaccination response, the attitudes of people with severe mental illness towards vaccination, and, the potential barriers to, and possible solutions for, an efficient vaccination programme in this population.

Introduction

To combat the global COVID-19 pandemic, extraordinary efforts are underway to develop and produce COVID-19 vaccines. Early reports on vaccine safety and efficacy are promising. However, especially in the initial stages of vaccine distribution, doses will be scarce, raising the question of who should be prioritised for vaccination. WHO, the National Academies of Science, Engineering, and Medicine, and others have proposed ethical frameworks to address this issue.^{1–4} A commonality in these frameworks can be found in three guiding principles: (1) maximising benefit and minimising harm in the short term and long term, (2) equal concern for every person in priority setting and vaccine allocation and distribution, and (3) mitigation of health inequities to address the higher burden of COVID-19 in some disadvantaged groups. These principles seem to be consistent with public preferences.^{5,6}

Some populations should be prioritised because of their disproportionately higher risk of infection, having lasting sequelae, or dying of COVID-19 due to medical factors, socioeconomic status, age, or profession. We have argued that people with severe mental illness should be given priority because they are a disadvantaged group based on both medical and socioeconomic risk factors for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, morbidity, and mortality.⁷ Although the term severe mental illness is most commonly used to describe schizophrenia, bipolar disorder, and major depressive disorder, it can be more broadly applied to any mental illness that causes severe functional impairment.^{8,9} According to the World Mental Health Survey, the prevalence of serious mental disorders is estimated to be between 0.4% and 7.7%.¹⁰ However, how the pandemic affects the prevalence of psychiatric disorders is still uncertain.¹¹

Why are people with severe mental illness at higher risk?

Among the first to be prioritised for vaccine allocation are groups of people with medical comorbidities that put them at considerably higher risk of dying or having lasting or more severe consequences from COVID-19. These groups include people with cardiovascular

diseases,^{12,13} chronic obstructive pulmonary disease (COPD),^{12,13} diabetes,¹⁴ chronic kidney disease,¹⁵ immunodeficiency, and cancer.¹⁶ We have previously argued that people with severe mental illness should be added to this list because of their high frequency of comorbidities (although, there are other reasons).⁷

Several studies have found an association between an existing psychiatric disorder and increased risk for SARS-CoV-2 infection and COVID-19-related hospitalisation, morbidity, and mortality.^{17–24} Some of these studies also specifically examined the difference between risks associated with severe mental illness, as described by diagnosis, severity, or previous hospitalisation for a mental disorder, and other psychiatric disorders. These studies point to a higher risk for worse COVID-19-related outcomes for people with severe mental illness than for people with less severe mental illness.^{17,19,23,24}

Individuals with severe mental illness have a two to three times higher mortality rate than do the general population.^{7,25} Compared with the general population, people with severe mental illness are more likely to be obese or have physical diseases, such as cardiovascular diseases, type 2 diabetes, and respiratory tract diseases, all risk factors for worse COVID-19-related outcomes.^{26,27} Furthermore, the prevalence of smoking is up to two to three times higher in people with severe mental illness than in people without psychiatric illness.^{28–31} SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) receptor to gain access into cells and cause infection.^{32,33} Current smokers have higher expression of ACE2 in bronchial epithelial cells than do non-smokers and former smokers.³⁴ Although it was initially thought that higher ACE2 expression in the airways of smokers can predispose them to SARS-CoV-2 infection, epidemiological data do not support the claim that smoking is directly associated with COVID-19.^{35–37} Nonetheless, COPD, usually caused by smoking and prevalent in people with severe mental illness, is associated with worse COVID-19 outcomes.³⁸

Arguably, the increased risk of worse COVID-19-related outcomes in people with psychiatric disorders, and especially in those with severe mental illness, is due to frequent comorbidity with physical diseases related to poor COVID-19 outcomes. However, the aforementioned

studies^{17–23} showed a risk greater than that of physical diseases by correcting for them in the analyses. Therefore, psychiatric disorders confer an additional risk for SARS-CoV-2 infection and COVID-19-related morbidity and mortality. This finding refutes the argument that people with severe mental illness will already be covered by vaccine allocation strategies because of their physical health status.

Severe mental illness is associated with altered immune function, with research showing a pro-inflammatory state and maladaptive T-cell functioning.^{39–44} One factor that is associated with dysregulated immunological function is childhood adversity, which is associated with increased odds for the occurrence of any psychiatric disorder (odds ratios between 1·5 and 3·5 according to the number of childhood adversities).^{45,46} Chronic stress, which has an important role in the onset of severe and impairing psychiatric disorders, is another factor that impairs immune system regulation.⁴⁷

Sleep problems, which are common in many psychiatric disorders and often serious in severe mental illness, are also frequently associated with a dysregulated immune system and increased risk of acute infection.^{48,49} Furthermore, social exclusion and loneliness are associated with increased inflammation and dysregulated anti-viral immunity, which suggests another link between severe mental illness and the immune system.⁵⁰ These dysfunctional immunological alterations can predispose people with severe mental illness to a more severe SARS-CoV-2 infection and clinical trajectory.^{51–54}

Severe mental illness is also associated with several socioeconomic risk factors for SARS-CoV-2 infection.^{55,56} A survey in Switzerland found that people with severe mental illness more often had socioeconomic deprivation or jobs without health-care insurance or with poor working conditions, and lived in poverty compared with people with less severe mental illness and the general population.⁵⁷ These issues might prevent these individuals from accessing health care when feeling ill, out of fear of losing their job or of not being able to pay for the expenses. People with severe mental illness often live in overcrowded settings or are homeless, where safety and physical distancing could be a challenge. Many individuals are either living in institutions or confined in a facility where there is a high risk of SARS-CoV-2 circulation and transmission. Social isolation and social exclusion are also highly prevalent among people with severe mental illness,^{57,58} which can affect their ability to receive necessary care and support when ill.

When people with severe mental illness do reach out to health-care providers, it is often more difficult for them to receive proper care for their physical illnesses. The diagnosis and management of physical diseases in people with severe mental illness is frequently suboptimal because of stigmatisation, discrimination, erroneous beliefs, and negative attitudes associated with severe mental illness.⁵⁶ Individuals with severe mental illness can

experience cognitive dysfunction or delusions,⁵⁹ have symptoms of apathy, avolition, or anhedonia, and, in general, have lower educational attainment^{60,61} and lower health literacy than the general population.^{62,63} As a result, it can be harder for them to find adequate information on COVID-19, to understand the contents and applicability of this information to their personal situation, and to adapt to the continuously changing health safety regulations.⁶⁴ From a public health perspective, knowing how SARS-CoV-2 spreads within certain groups is important to estimate the value of vaccinating the individuals in these groups to stop virus transmission. To our knowledge, no research has yet addressed SARS-CoV-2 transmission in people with severe mental illness.

Clearly, severe mental illness is a serious risk factor for worse COVID-19-related outcomes, resulting from a high risk of infection, a high risk that the infection will have a complex course, and a high risk of dying when infected. In accordance with the second and third guiding ethical principles, people with severe mental illness should therefore be among the first to be vaccinated. Everyone involved in the care of these patients should inform them of the utility and risks of early vaccination.

What is the effect of severe mental illness on vaccination response?

Although the need for vaccination is clear, several problems regarding vaccination for people with severe mental illness exist. Evidence from studies of vaccination against other infectious agents suggests that people with depression might have a reduced immune response to vaccination. Older adults (mostly ≥ 65 years) experiencing a chronic stressor or depressive symptoms were found to have a lower antibody response to influenza virus vaccination,^{65,66} although, depressive symptoms in older adults (mean age 71 years [SD 9]) might be associated with an amplified, prolonged inflammatory response.⁶⁷ One study showed that adults with depression were less likely to test seropositive for measles than were controls who did not have depression and thus had an increased risk for infection.⁶⁸ Depressive symptoms were also found to be associated with lower seroconversion rates for hepatitis B vaccination in people undergoing haemodialysis.⁶⁹ Concerning the varicella zoster virus, a study showed diminished vaccination efficacy and an increased risk and severity of herpes zoster in patients with depression.⁷⁰ To our knowledge, studies examining the effect of other psychiatric diagnoses on vaccination response are scarce. One study on the effects of hepatitis B vaccination in adult patients with either schizophrenia, bipolar disorder, or depression who lived in institutions, reported a weaker immune response in these patients than in the general population.⁷¹ Evidence suggests that depression might impair the maintenance of vaccine-related protection in adults,⁶⁸ whereas by contrast, a study in 11-year-old children found that symptoms of depression and anxiety were associated with persistently

higher antibody responses,⁷² meaning that vaccination responses might partially be age specific. Sleep problems are also associated with a dysregulated immune system and increased risk of acute infection.^{48,49} Studies have shown reduced antibody responses to hepatitis A, hepatitis B, and influenza vaccination when the participants reported reduced sleep duration or quality or were kept awake the night after vaccination.^{73–75} Because disturbed sleep is prevalent in patients with severe mental illness, this comorbidity could partly explain the inhibition of vaccine response in these individuals.

What are the potential interactions between vaccines and psychotropic medications?

Not much is known about the effects of psychotropic medication on vaccination response. Antipsychotics might have a differential effect on several cytokines in people with psychosis, producing an anti-inflammatory effect in some individuals.^{76–78} An anti-inflammatory effect, however, might not always be desirable when considering vaccine efficacy because it might suppress the formation of antibodies. Clozapine use is associated with neutropenia, which can confer susceptibility to infection. A secondary antibody deficiency has been observed in patients with long-term clozapine use, putting these patients at risk of immunodeficiency.⁷⁹ In a retrospective cohort study, clozapine was a possible risk factor for SARS-CoV-2 infection.⁸⁰ Although a small study showed that influenza vaccination had no effect on clozapine serum concentrations,⁸¹ vaccination might affect clozapine concentrations through its action on cytochrome P450 metabolism.⁸² As of Dec 18, 2020, no pharmacodynamic data are available for the COVID-19 vaccines currently in testing to ascertain whether they influence cytochrome P450 metabolism and clozapine metabolism.

Lithium has been proposed as an immunomodulatory adjuvant to increase the efficacy of viral vaccines in humans^{83,84} because it exhibits some pro-inflammatory properties.⁸⁵ However, as lithium has also shown some anti-inflammatory properties in healthy participants and patients,^{86,87} its effects remain unclear and could be dose dependent. Other mood-stabilising agents, such as valproic acid, carbamazepine, and lamotrigine, also show a differential effect on several cytokines in healthy participants.⁸⁶

A meta-analysis showed that antidepressant treatment for people with major depression reduced the concentrations of several pro-inflammatory cytokines, resulting in an anti-inflammatory effect.⁸⁸ Treatment with antidepressants normalised vaccination response to the varicella zoster vaccine in older patients (>60 years) with major depression.⁷⁰ Although most psychopharmacological agents seem to affect several immunological markers and some of these agents interact with the proteins to which SARS-CoV-2 binds,⁸⁹ how psychotropic drugs affect vaccination response and efficacy remains to

be seen. Research is urgently needed to provide people with severe mental illness with adequate information on potential interactions between psychotropic medications and COVID-19 vaccines.

What are the possible neuropsychiatric side-effects of vaccination?

When a vaccine is administered, neuropsychiatric side-effects might develop. In one COVID-19 vaccine trial, a participant was diagnosed with transverse myelitis.⁹⁰ This finding might have been incidental; an analysis of 64 million past vaccine doses showed no association between the occurrence of transverse myelitis and vaccination.⁹¹ In a pilot study, individuals with symptoms of depression or anxiety had, compared with mentally healthy individuals, a more pronounced reduction in positive affect following influenza vaccination.⁹² Several studies in the general population have shown transient changes in cognition, sleep, mood, and psychomotor activity after vaccination with the typhoid vaccine, changes which could be assumed to also occur in people with severe mental illness.^{93–95}

What are the attitudes of people with severe mental illness towards vaccination?

We found no studies of the attitudes of people with mental illness regarding vaccination against SARS-CoV-2. In a study examining the willingness of people with schizophrenia to adopt protective measures during the 2009 H1N1 influenza pandemic in Australia, 74% said they would be moderately willing to be vaccinated.⁹⁶ A study done before the pandemic found that 84% of patients being treated for severe mental illness at a US community mental health clinic believed that, in general, vaccinations are safe, effective, and important.⁹⁷

The race to develop COVID-19 vaccines has been heavily politicised and covered by the media and social media. Concerns have been expressed about vaccine hesitancy in the general population, resulting from the fast advances in vaccine development, fear of premature acceptance of promising results, and paucity of knowledge of possible long-term side-effects.^{98,99} How these factors will affect people with severe mental illness who experience persecutory delusions and thought disorders remains to be seen. Research on this topic is urgently needed.

How can we ensure that vaccines reach people with severe mental illness?

Patients with severe mental illness experience barriers to immunisation, including a lack of knowledge and awareness, accessibility problems, costs, fears about immunisation, and often no recommendations from their primary care providers.⁹⁷ Low uptake (24–28%) of influenza vaccination was found in people attending an outpatient clinic for severe mental illness in Alabama, USA.¹⁰⁰ By contrast, a retrospective analysis of patients aged 65–80 years in a US primary care setting found that

depression and anxiety were associated with greater odds of influenza vaccination, probably because of frequent visits to address their physical comorbidities.¹⁰¹

Patients should be provided with up-to-date information about the benefits of vaccination and invited to the vaccination programme.⁹⁷ Psychiatrists and other health-care professionals treating people with severe mental illness should be aware and knowledgeable of the different types of vaccines that become available, their safety and efficacy for their patients, and the applicable vaccination schemes. It is the responsibility of psychiatrists to reach out to their patients and provide them with the best possible care.¹⁰² At the systems level, barriers to vaccination should be actively mitigated by listening to and engaging the public, including people with severe mental illness, in the design and implementation of immunisation policies and programmes, and addressing their concerns,¹⁰³ to build trust, confidence, and acceptance. The legislature is responsible for developing the legal framework. The logistical organisation of vaccination should be uniform, transparent, and provide ease of access to people at risk. Vaccination rates in people with severe mental illness can be substantially increased with a targeted vaccination programme.⁹⁷ One possibility would be to roll out vaccination programmes in mental health clinics and offices and actively reach out to individuals at risk or assist them in reaching the clinic.¹⁰⁴ This possibility can only be realised if mental health professionals are also trained in administering the vaccine. In the absence of a COVID-19 vaccine in some countries, recommending patients be vaccinated against influenza might also be worthwhile. This kind of vaccination has been associated with reduced admission to hospitals and intensive care units due to COVID-19, possibly caused by natural killer cell activation.¹⁰⁵

What do we do in the case of vaccine refusal?

If a person refuses vaccination, clinicians might find themselves confronted with an ethical dilemma between respect for the autonomy and bodily integrity of their patient and public health concerns. Some have argued that in these circumstances compulsory vaccination in the general population could be ethically acceptable.¹⁰⁶ However, compulsory medical interventions should only be considered as a last resort and should be supported by national and international ethical debate, legislation, and guidelines. Furthermore, compulsory treatment is often traumatic for those who receive it and risks undermining patient trust in the health-care system and public trust in vaccination. In light of these ethical concerns and the consideration that voluntary mass vaccination might result in vaccine coverage levels sufficiently high enough to create effective herd immunity, compulsory vaccination should not be pursued. Clinicians faced with a patient's reluctance or refusal to be vaccinated should make an adequate assessment of that person's mental status, decision making capacity, and knowledge and beliefs about vaccination. Clinicians should provide their patients

Search strategy and selection criteria

We searched PubMed for any articles published in English between database inception and Nov 19, 2020, related to COVID-19, vaccination, and psychiatric disorders to ascertain: (1) the risk for COVID-19-related outcomes in people with severe mental illness, (2) possible mechanisms behind this risk, (3) the effect of severe mental illness on vaccination response, (4) interactions between vaccines and psychotropic medications, (5) the attitudes of people with severe mental illness towards vaccination, and (6) barriers to, and possible solutions for, efficient vaccine distribution in this population. Whenever no peer-reviewed articles were available we expanded our scope to *medRxiv* and *bioRxiv*. We used the following search terms according to topic: "COVID-19", "severe mental illness", "schizophrenia", "bipolar disorder", "depression", "vaccination", "vaccination response", "psychotropic drugs", "attitudes", "ethics", "immunology", and "socioeconomic". All article types were considered. Articles were screened for their applicability to the topic. The reference lists of selected articles were screened for additional articles.

with adequate information and counter misinformation, address negative attitudes in a respectful way, and discuss the advantages and possible risks of vaccination. In the end, it should be left to the individual to weigh the benefits and the risks, and to give informed consent for vaccination.

Conclusion

Because people with severe mental illness are at high risk for SARS-CoV-2 infection and COVID-19-related morbidity and mortality, they must be offered early access to safe and efficacious vaccines. Therefore, we welcome that people with severe mental illness have been specifically recognised by some ethical guidelines as a high-risk group.¹⁰⁷ Future studies should evaluate vaccine efficacy, safety, and interactions with psychotropic medication specifically in people with severe mental illness so they can be properly informed of the benefits and risks of vaccination.

Contributors

VM and MDH did the literature search. VM wrote the manuscript. JD, KVA, and MDH revised the manuscript. All authors approved the final manuscript.

Declaration of interests

We declare no competing interests.

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