vaccines

MDPI

Systematic Review

Effectiveness of COVID-19 Vaccines in People with Severe Mental Illness: A Systematic Review and Meta-Analysis

Wen Dang [1], Iman Long [1], Yiwei Zhao [1], Yu-Tao Xiang [1,2] and Robert David Smith [1,*]

[1] Unit of Psychiatry, Department of Public Health and Medicinal Administration, Institute of Translational Medicine, Faculty of Health Sciences, University of Macau, Macao SAR, China; yc27639@umac.mo (W.D.); yc27652@umac.mo (I.L.); mc24741@connect.um.edu.mo (Y.Z.); ytxiang@um.edu.mo (Y.-T.X.)
[2] Centre for Cognitive and Brain Sciences, University of Macau, Macao SAR, China
* Correspondence: robsmith@um.edu.mo; Tel.: +853-8822-4939

Abstract: Prior to the introduction of COVID-19 vaccines, patients with severe mental illness (SMI) were at greater risk of COVID-19-related outcomes than the general population. It is not yet clear whether COVID-19 vaccines have reduced the risk gap. We systematically searched nine international databases and three Chinese databases to identify relevant studies from December 2020 to December 2023 to compare the risk of COVID-19-related outcomes for SMI patients to those without SMI after vaccination. Random effects meta-analysis was performed to estimate the pooled odds ratio (OR) with 95% confidence intervals (CI). Subgroup analysis, sensitivity analysis, and publication bias analysis were conducted with R software 4.3.0. A total of 11 observational studies were included. Compared with controls, SMI patients were associated with a slightly increased risk of infection (pooled OR = 1.10, 95% CI, 1.03–1.17, I^2 = 43.4%), while showing a 2-fold higher risk of hospitalization (pooled OR = 2.66, 95% CI, 1.13–6.22, I^2 = 99.6%), even after both groups have received COVID-19 vaccines. Limited evidence suggests a higher mortality risk among SMI patients compared to controls post vaccination, but the findings did not reach statistical significance. SMI patients remain at increased risk compared to their peers in COVID-19-related outcomes even after vaccination. Vaccination appears an effective approach to prevent severe COVID-19 illness in SMI patients, and actions should be taken by healthcare providers to improve vaccination coverage in these vulnerable groups.

Keywords: severe mental illness; schizophrenia; bipolar disorder; major depressive disorder; COVID-19 vaccines

check for updates

Citation: Dang, W.; Long, I.; Zhao, Y.; Xiang, Y.-T.; Smith, R.D. Effectiveness of COVID-19 Vaccines in People with Severe Mental Illness: A Systematic Review and Meta-Analysis. *Vaccines* **2024**, *12*, 1064. https://doi.org/10.3390/vaccines12091064

Academic Editor: Seth Pincus

Received: 23 July 2024
Revised: 28 August 2024
Accepted: 5 September 2024
Published: 18 September 2024

Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

Severe mental illness (SMI) refers to individuals with psychological problems that are so debilitating they affect their ability to engage, function within society, and severely impede their ability to take up occupational activities [1]. Although the definition of SMI varies across different studies, the most common conditions of SMI include schizophrenia (SZ) and related psychotic disorders, bipolar disorder (BD), and major depressive disorder (MDD) [2–6]. The prevalence of SMI varies in countries due to heterogeneity in methodological approaches, accounting for 5.5% in the United States (US) [7], 5% in Australia [8], and 1% in the United Kingdom (UK) [9]. Estimations on the global prevalence of SMI diseases show an increasing burden over time [10].

Physical health inequalities exist in the patients with SMI compared with the general population. Evidence has consistently demonstrated approximately 2–3 times the mortality risks in patients with SMI compared with those without SMI [11], with 10–25 years of potential life lost [12,13]. The COVID-19 pandemic has further exacerbated existing health disparities and placed a significant burden on this vulnerable population. Compared to the general population, SMI patients tend to suffer poorer physical conditions, shorter life expectancy, and excessive mortality rates [14,15]. Different studies across different

countries have identified a higher risk of more severe COVID-19 infection, hospitalization, and mortality in people with SMI compared to the general population [2,16–21].

Once widely available, vaccination was recommended as the most effective and cost-effective strategy for reducing COVID-19 infections, severity, and mortality [22–26]. With the advocacy of prioritizing vaccination for vulnerable groups, Denmark, Germany, Netherlands, and the UK implemented policies for SMI patients to be prioritized for vaccination [27–31].

Concerns have arisen regarding the effectiveness and duration of protection provided by first-generation COVID-19 vaccines, due to the emergence of new SARS-CoV-2 variants and a decreasing trend in antibody titers in vaccinated individuals over time [32]. In addition to the increased risk in SMI patients of COVID-19 infection, hospitalization, and mortality, SMI patients are also at lower levels of protection against newer virus variants compared to the general population [33]. Given the increased risk of poor COVID-19 outcomes and possible reduction in vaccine effectiveness for SMI patients, it is important for health providers to have a comprehensive understanding of the effectiveness of COVID-19 vaccines in this group.

It remains unclear if COVID-19 vaccines have contributed to reducing physical health inequalities gap for patients with SMI, with different evidence appearing among studies that are heterogeneous in their methodological approaches. To address this research gap, we conducted a systematic review and meta-analysis to evaluate the evidence related to the effectiveness of the COVID-19 vaccine in SMI patients compared to non-SMI controls.

2. Methods

This systematic review is reported following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist [34] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [35]. The study protocol was registered in the PROSPERO (Registration number: CRD42022360844).

2.1. Search Strategy

To ensure that no relevant studies were missed, our search strategy not only included peer-reviewed published articles, but also actively tracked preprint databases. This allowed us to capture and incorporate any potential studies that might be published in the future. Systematically searches were executed in nine international databases (PubMed, EMBASE, CINAHL Ultimate, PsycINFO, Web of Science, the World Health Organization COVID-19 Database, Cochrane Database of Systematic Reviews, MedRxiv, BioRxiv) and three Chinese databases (CNKI, WanFang, and SinoMed). We restricted articles to those published after 1 December 2020, as December 2020 was the earliest time at which vaccination programs were initiated at the population-level [31,36]. The final search date was on 14 December 2023. The search terms were developed to be highly sensitive to identify all studies relevant to the key concepts of COVID-19 vaccination and SMI (Method S1). Hand-searching was conducted in Google Scholar and in the reference lists of included articles to ensure no omissions.

2.2. Inclusion and Exclusion Criteria

All retrieved articles were screened using the web-based software Rayyan [37]. Using Rayyan facilitated the screening and selection of relevant studies, streamlining the process and enhancing efficiency. Each retrieved study was independently screened by at least two reviewers, first screening titles and abstracts and successively full texts. Study inclusion criteria was based on the PICOS strategy as follows: Participants (P): patients with a broad definition of severe mental illness, including a diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder, or other psychotic disorders; patients aged 18 or above; Intervention (I): COVID-19 vaccines approved by the WHO [38], including inactivated vaccine, protein-based vaccines, viral vector vaccines, RNA or DNA vaccines; Controls (C): individuals without a diagnosis of SMI. Outcome (O):

the cases of COVID-19 infections, COVID-19-related hospitalization, and mortality after vaccination; Study design (S): all observational studies and randomized controlled trials were eligible. Exclusion criteria included cross-sectional design studies, reviews, comments, editorials, conference papers, case-report papers, or animal studies. Publications not in English or Chinese were excluded. Researchers were blinded to each other's decisions. Any disagreement was discussed within the whole review team after unblinding.

2.3. Data Extraction and Quality Assessment

Data extraction was conducted by two reviewers independently, using a standardized form created for the purposes of this review; the information extracted included the first author, publish year, study design, data resources, sample characteristics in the SMI group and non-SMI group, type of the COVID-19 vaccine, outcome of interest, and follow-up period. The missing data or unreported data was filled in by contacting study authors to provide additional details. The Newcastle–Ottawa scale (NOS) was used to assess the methodological quality of the observational study from three perspectives, including selection (4 stars), comparability (2 stars), and exposure/outcome (3 stars), with the highest quality studies achieving 9 stars [39,40]. Any discrepancies between reviewers were solved by consulting with a senior researcher with extensive experience in conducting systematic reviews and meta-analyses in our research team.

2.4. Statistical Analysis

Odds ratio (OR) with 95% confidence intervals (CIs) were calculated as the effect size for the meta-analysis of outcomes. Studies reporting multiple SMI subgroups compared with the same control group were included in the meta-analysis by combining the subgroups to create a single SMI group. The potential sources of heterogeneity between studies were considered prior to analysis as not being limited to sampling; a random effects model based on an inverse–variance approach was used. An I^2 of at least 50% was considered to represent substantial heterogeneity. Subgroup analyses were performed by different variables when there was an adequate number of relevant studies. Leave-one-out analysis was conducted to test the robustness of the result of the meta-analysis. The risk of publication bias was estimated by funnel plot and Egger's test to estimate the likelihood of funnel plot asymmetry. The statistical analysis was conducted by R version 4.3.0 [41] with the *meta*, *metafor* package. Two sides of p values less than 0.05 determined significance.

3. Results

3.1. Search Results and Recruited Studies

Figure 1 shows the flow chart of the study selection. A total of 4009 articles were retrieved, with 3869 articles from international databases and 140 articles from Chinese-based databases. A total of 639 duplicate records were removed before the screening. Of 3370 abstracts and titles screened, 179 (4.5%) were relevant for full-text review. Four articles' authors responded to provide detailed data that could be used in this meta-analysis [42–45]. Finally, 11 articles (0.61%) reporting on 1,592,778 SMI patients and 27,962,772 vaccinated controls were included for meta-analysis [42–52].

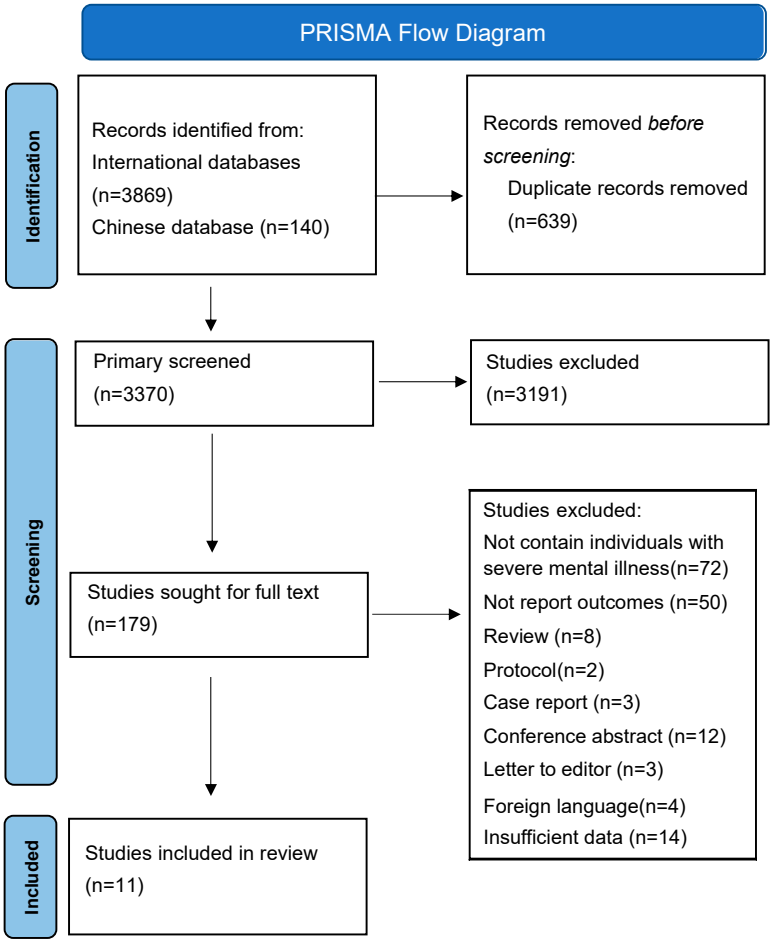


Figure 1. PRISMA flow diagram.

3.2. Characteristics of the Included Studies

All the detailed information for the included studies is listed in Table S1. Five studies were from European countries, two from North American countries, and four from Asian countries. Nine out of eleven studies collected data from large electronic medical records, and two studies in China (mainland and Taiwan) collected data from multiple hospitals and a single medical center. Cohort study designs were conducted by eight studies, and three studies used a case-control study design. The definition and subtype of SMI populations varied among the included studies, which could be divided into three main categories, including SZ group (patients with schizophrenia, psychosis, and other psychotic disorders), BD group (including patients with bipolar disorders) and MDD group (including patients with major depressive disorders). Across all studies, nine studies reported different types of COVID-19 vaccines including mRNA, vector viral, inactivated and protein subunit vaccines, with two studies not reporting detailed information on vaccine type. Three out of eleven studies evaluated the impact of the booster dose of vaccines on severe COVID-19 illness or death, while most did not report outcomes according to the types and dosages of vaccines used.

3.3. Quality Assessment of Included Studies

The total NOS scores for 11 studies ranged from 7 to 9, averaging 8.36, indicating moderate to high methodological quality (Table S2). A total of 8 out of the 11 studies rated high on the domain of selection, as these studies derived from the electronic medical record based on national-level data, suggesting the representativeness of the population. In the domain of comparability, all studies received at least a score of 1, indicating the adequacy of controlling for potential confounders. Additionally, nine studies were evaluated with

the highest score in reporting outcomes, while the Tzur Bitan et al. [46] and Zhu et al. [50] studies were assessed with lower scores due to the insufficient length of follow-up for outcomes to occur.

3.4. Outcomes

The results of the primary analysis for each COVID-19 outcome are listed in Table 1.

Table 1. Result of the meta-analysis for COVID-19 related outcomes.

Outcome	Studies	SMI Group			Non-SMI Group			Estimates	
		Event	Total Sample Size	Proportion (%)	Event	Total Sample Size	Proportion (%)	Pooled OR	I^2 (%)
Infection	6	18,726	115,938	2.60 (0.22–24.05) **	44,820	410,277	3.03 (0.35–21.87) **	1.10 (1.03–1.17) **	43.4
Hospitalization	6	3974	415,274	2.60 (0.24–22.93) **	7677	13,967,886	1.02 (0.05–16.76) **	2.66 (1.13–6.22) *	99.6
Mortality	4	539	1,451,832	0.05 (0.01–0.37) ***	6414	27,484,345	0.02 (0.00–0.61) ***	2.67 (0.27–26.45)	98.3

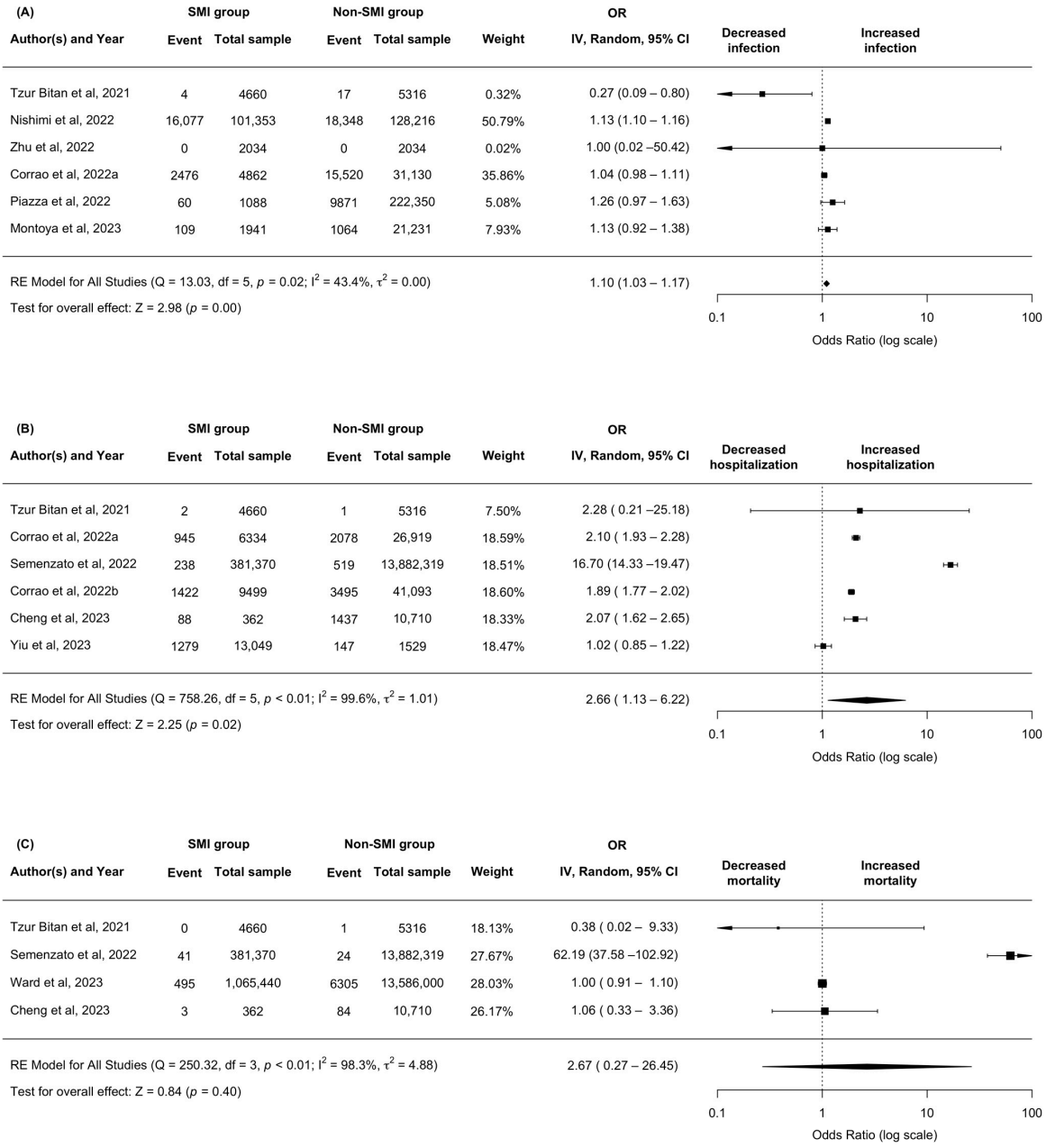
Footnotes: * means $p < 0.05$; ** means $p < 0.01$; *** means $p < 0.001$. SMI = severe mental illness. OR = odds ratio.

The pooled absolute rate of COVID-19 infection, hospitalization, and mortality post vaccination in the SMI group was 2.60% (95% CI: 0.22–24.05), 2.60% (95% CI: 0.24–22.93) and 0.05% (95% CI: 0.01–0.37), respectively (Table 1). SMI patients were at a slightly increased risk of COVID-19 infection (OR = 1.10, 95% CI, 1.03–1.17, $p < 0.01$, $I^2 = 43.4\%$) and hospitalization (OR = 2.66, 95% CI 1.13–6.22, $p = 0.02$, $I^2 = 99.6\%$) compared to the control group. However, the pooled estimates showed an increased but not significant risk of mortality among vaccinated SMI patients than non-SMI control (OR = 2.67, 95% CI 0.27–26.45, $p = 0.40$, $I^2 = 98.3\%$). The I^2 statistic and forest plot indicated substantial and high heterogeneity across studies (Figure 2).

For the outcome of COVID-19 infection, the subgroup analysis by different SMI subtypes showed that a slightly increased risk was observed in the SZ group (OR = 1.06, 95% CI, 1.01–1.12, $p = 0.03$, $I^2 = 0.0\%$) and MDD group (OR = 1.10, 95% CI, 1.02–1.18, $p < 0.05$, $I^2 = 0.0\%$) when compared with control. SMI patients showed a reduced risk of infection in two studies from Asia (OR = 0.29, 95% CI, 0.10–0.84, $p = 0.02$, $I^2 = 0.0\%$). In contrast, two studies from North America reported an increased risk of infection in SMI patients compared to those without SMI (OR = 1.13, 95% CI, 1.10–1.15, $p < 0.001$, $I^2 = 0.0\%$). The subgroup analysis by study design was only conducted in five cohort studies; the consistent results added confidence to our main findings (OR = 1.11, 95% CI 1.09–1.13, $p < 0.001$, $I^2 = 0.0\%$).

For the outcome of COVID-19-related hospitalization, the subgroup analysis by subtype showed patients with SZ (OR = 3.27, 95% CI 1.21–8.84, $p = 0.02$, $I^2 = 99.3\%$) and BD (OR = 1.97, 95% CI 1.53–3.89, $p < 0.001$, $I^2 = 0.0\%$) had significantly increased risks of hospitalization than controls. In subgroup analysis by location, three studies from Europe showed an increased pooled effect size of hospitalization in SMI patients compared to those without SMI (OR = 4.04, 95% CI 1.01–16.21, $p = 0.05$, $I^2 = 99.9\%$). In subgroup analysis by study design, robust results were identified in two different designs.

For the outcome of COVID-19-related hospitalization, the result of the meta-analysis did not show a statistically significant difference between groups (Table 2).



Footnote: (A) COVID-19 infection; (B) COVID-19-related hospitalization; (C) COVID-19-related mortality.

CI=Confidence Interval; OR=Odds Ratio; SMI=severe mental illness.

Event represents the number of cases in the SMI group and non-SMI group.

Total sample represents the number of participants who received COVID-19 vaccines in the SMI group and non-SMI group.

Figure 2. Forest plot illustrating odds ratio of COVID-19-related outcomes post vaccination in patients with severe mental illness [42–52]. Footnote: (**A**) COVID-19 infection; (**B**) COVID-19-related hospitalization;(**C**) COVID-19-related mortality. SMI = severe mental illness; CI = confidence interval; OR =odds ratio. Event represents the number of cases in the SMI group and non-SMI group. Total sample represents the number of participants who received COVID-19 vaccines in the SMI group and non-SMI group.

Table 2. Meta-analysis of COVID-19-related outcomes comparing SMI patients and non-SMI patients in subgroups.

Subgroup	Studies (*n*)	SMI Group (*n*)	Non-SMI Group (*n*)	Pooled OR	I^2 (%)
COVID-19 infection					
SMI subtype					
SZ group	6	16,811	410,277	1.06 (1.01–1.12) *	0.0
MDD group	3	89,037	161,380	1.10 (1.02–1.18) *	62.8
BD group	3	10,090	161,380	0.99 (0.63–1.57)	45.8
Study location					
Asia	2	6694	7350	0.29 (0.10–0.84) *	0.0
Europe	2	5950	253,480	1.09 (0.93–1.28)	45.6
North America	2	103,294	149,447	1.13 (1.10–1.15) ***	0.0
Study design					
Cohort	5	111,076	379,147	1.11 (1.09–1.13) ***	0.0
COVID-19-related hospitalization					
SMI subtype					
SZ group	5	394,155	139,577,176	3.27 (1.21–8.84) *	99.3
MDD group	3	20,201	69,541	1.46 (0.96–2.23)	97.9
BD group	2	556	42,622	1.97 (1.53–3.89) ***	0.0
Study location					
Asia	3	18,071	17,555	1.49 (0.80–2.78)	89.5
Europe	3	397,203	13,950,331	4.04 (1.01–16.21) *	99.9
Study design					
Cohort	3	386,392	13,898,345	4.88 (1.07–22.23) *	98.6
Case-control	3	28,882	69,541	1.61 (1.04–2.48) *	98.4
COVID-19-reltaed mortality					
SMI subtype					
SZ group	2	386,030	13,887,635	6.28 (0.04–904.06)	89.5
Study location					
Asia	2	5022	16,026	0.94 (0.32–2.79)	0.0
Europe	2	1,446,810	27,468,319	7.83 (0.14–447.74)	99.6
Study design					
Cohort	4	1,451,832	27,484,345	2.67 (0.27–26.45)	98.3

Footnotes: * means $p < 0.05$; *** means $p < 0.001$. OR = odds ratio. SMI = severe mental illness; SZ group means patients with schizophrenia, psychosis, and psychotic disorders; BD group means patients with bipolar disorder; MDD group means patients with major depressive disorder.

3.5. Sensitivity Analysis and Publication Bias

The leave-one-out analysis showed the lowest I^2 was achieved when excluding "Tzur Bitan et al., 2021 [46]" and "Semenzato et al., 2022 [47]" in the meta-analysis for the result of infection and mortality, respectively, but without changing the direction of results. The analysis showed no significant change in the results of hospitalization. The forest plot (Figure S1) showed the recalculated pooled effects after each study was omitted. Although there was an observed asymmetry from the funnel plot for each outcome (Figure S2), no significant publication bias was detected based on the result of Egger's test (Table S3). However, the interpretation of the funnel plots should be approached cautiously, as limited articles were included.

4. Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis comparing the effectiveness of COVID-19 vaccinations between SMI groups and non-SMI groups. The results of the meta-analysis indicated that SMI patients remain at higher risk of COVID-19-related outcomes in comparison to individuals without SMI, but the pooled absolute risk for infection or infection-related hospitalization after vaccination was rare for people with SMI post vaccination. No significant increased risk of mortality was identified among vaccinated SMI patients than non-SMI controls. Although there was a low

absolute rate of mortality in SMI patients post vaccination, the findings might be attributed to potential bias, which should be illustrated with caution.

The rates of infection and hospitalization after vaccination appear to be lower compared to other studies that estimated risks in this population before vaccination. The absolute rates of COVID-19-related infection and hospitalization in SMI patients post vaccination across all studies were estimated at 2.6%, which was lower than the reported percentage of patients with SMI without vaccination who tested positive for SARS-CoV-2 antibodies in the cross-sectional study conducted in Denmark [53]. Patients with schizophrenia and BD had over a three-fold increase in the odds of hospitalization pre vaccination compared to those without SMI [2], which seemed higher than the risk of hospitalization from our findings among these patients post vaccination. Additionally, the low absolute mortality rate in the SMI group might indicate the effectiveness of vaccination in minimizing the disparities between SMI patients and the general population. However, the potential selection bias may underestimate the risk of death post vaccination, as SMI patients who died before vaccination could not be taken into consideration.

Despite the protection of vaccines, individuals with SMI still have an increased residual risk to COVID-19 compared with the general population. Poor physical health and behavioral risk factors are potential contributing factors that may explain the higher risk of COVID-19-related outcomes after vaccination in SMI patients [54]. For patients with SMI, the use of antipsychotic medication, higher rates of poor dietary intake, and a high prevalence of smoking may contribute to lower overall physical health conditions. A higher prevalence of co-morbid physical disease compared with the general population may also contribute to the increased risk [15]. The possible pathophysiological mechanism of how physical diseases influence COVID-19 outcomes is the hyperactivation of the immune system. Having SMI with comorbidities is frequently associated with a pro-inflammatory state. When an individual with these conditions contracts SARS-CoV-2, the inflammatory state may exacerbate tissue damage, lead to multi-organ failure, and potentially fatal outcomes [55]. Additionally, a high prevalence of sleep difficulties reported in SMI patients [56], could be another potential mechanism, as poor sleep quality substantially impairs immune function [57]. Combinations of these contributing factors may lead to immune dysregulation, consequently influencing the immune response to vaccines, and SMI patients' overall immune ability to act against a COVID-19 infection.

Although these underlying health conditions of SMI explain the increased risk of more severe courses of COVID-19 and reduce the effectiveness of vaccines received, the continuous evolution of the COVID-19 virus also limited the effectiveness of vaccination. With the continued risk of COVID-19 infections, at the time of conducting this review, five identified variants which were classified as variants of concern, labeled as Alpha, Beta, Gamma, Delta, as well as Omicron, respectively [58]. The consistent results suggested that the virus variants are associated with the effectiveness of vaccines [23,58]. A full vaccination of COVID-19 vaccines showed high effectiveness against the Alpha variant, and moderate effectiveness against the Beta, Gamma, and Delta variants [23,58], while booster vaccination was found more effective against the Delta and Omicron variants [58]. However, lower vaccination uptake rates of initial and booster vaccination were identified in SMI patients in Israel [59] and France [60]. The WHO statement on ending COVID-19 as a public health emergency does not mean this disease is not a global threat [61]. Increasing the promotion of full vaccination regimens, including booster doses, remains a public health priority for people with SMI. In addition, the effectiveness of different types of COVID-19 vaccines varies in preventing COVID-19 infection. Although we collected data from included studies on vaccinated individuals with SMI, the outcomes related to the specific type of vaccination received were not reported sufficiently, which hindered our ability to conduct a subgroup analysis. In a summary of data from the real world, mRNA vaccines displayed higher effectiveness against SARS-CoV-2 infection and variants [58,62].

Notably, we observed that SMI patients had a significantly lower risk of COVID-19 infection compared to non-SMI controls in the Asian population, which was consistent

with the findings from the study conducted in South Korea [63]. This is possibly attributed to the included studies with short time follow-ups and limited sample sizes of the Asian population. Additionally, a wider confidence interval of the results in Asian countries was observed than the study results in Western countries, indicating the need for further improvement in study quality. Furthermore, the specific biological mechanisms underlying the ethnically specific effect of COVID-19 vaccination on COVID-19-related outcomes for individuals with SMI require further investigation.

There were several limitations in our review. First, despite the majority of studies being based on national electronic health records [42,43,46–49,51] providing a typically large sample size with real-world clinical data, these records might cause bias in estimating the outcomes, for example, the potential of underestimation of the population with COVID-19 infection, as these infections were limited to those recorded by healthcare. Other issues for these data could also include the incomplete and inadequate capturing of secondary care information and missing data. In contrast, primary data collection may provide more detailed information but with a limited achievable sample size [44,50]. Additionally, the target sample in one study was focused on veterans with an unbalanced distribution of males and females, which may account for the lack of generalizability [42]. Second, some of the planned subgroup analyses were not conducted due to a lack of sufficient reported data for analysis; an example of this was the underreporting of vaccine types. Future studies may focus on the evaluation of the effectiveness of different vaccine types and dosages among SMI patients. Third, we only evaluated the physical COVID-19-related outcomes in SMI patients and did not take into consideration if there were any psychiatric adverse events following COVID-19 vaccination. Recent evidence from a large population-based cohort study in South Korea has shown that COVID-19 vaccination may increase the risks of certain psychiatric disorders, including depression, anxiety, and sleep disorders, while potentially reducing the risk of conditions like schizophrenia and bipolar disorder [64]. Evaluating the impact of COVID-19 vaccination on psychiatric outcomes in SMI patients can help to provide a comprehensive perspective on the effectiveness of COVID-19 vaccines. Fourth, due to the relatively short observation periods of the included studies, very few were able to report on the outcome of COVID-19-related mortality. In the future, prolonging the observation period will help capture the occurrence of mortality events. Lastly, eight studies were conducted in high-income countries, which may prevent the result from being generalized to lower-income countries.

Medical specialists, especially psychiatrists, play a positive role in addressing vaccine hesitancy or refusal from mental illness patients and ensuring equitable access to the COVID-19 vaccine [65]. They can provide SMI patients with adequate information, respectfully address negative attitudes, and discuss the advantages and possible risks of vaccination [29]. Our findings can give these healthcare providers confidence in improving vaccination coverage within this vulnerable group. Although vaccination has substantially reduced the risk of COVID-19-related outcomes, these risks persist in patients with SMI. Proactively communicating with SMI patients and their caregivers about the increased risk for those patients can encourage further preventive steps for infection or monitoring for severe illness if infected.

5. Conclusions

This systematic review and meta-analysis of 11 observational studies involving 1,592,778 SMI patients and 27,962,772 controls across six countries showed the COVID-19 vaccines are effective against severe illness for patients with SMI. Despite the protection of vaccines, individuals with SMI remain at a higher risk of contracting the infection and developing severe illness post vaccination compared with controls. Health professionals should be aware of the risk disparity between SMI patients and non-SMI individuals and take proactive steps to mitigate health inequality among SMI patients.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/vaccines12091064/s1, Method S1: Search terms; Table S1: Basic characteristics of included studies; Table S2: Quality assessment of included studies (Scores from Newcastle-Ottawa Scale); Figure S1: Leave-One-Out Forest plot illustrating odds ratio of COVID-19-related outcomes in patients with severe mental illness; Figure S2: Funnel plot for publication bias for pooled COVID-19-related outcomes postvaccination in patients with severe mental illness; Table S3: Results of Egger test for COVID-19-related outcomes.

Author Contributions: Conceptualization, W.D. and R.D.S.; methodology, W.D., I.L., Y.Z. and R.D.S.; software, W.D.; validation, R.D.S.; formal analysis, W.D.; investigation, W.D., I.L. and Y.Z.; resources, W.D., I.L. and Y.Z.; data curation, W.D.; writing—original draft preparation, W.D.; writing—review and editing, W.D. and R.D.S.; visualization, W.D.; supervision, R.D.S.; conceptualization, review, editing, supervision, Y.-T.X.; project administration, W.D.; funding acquisition, W.D. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the internal grant of the Faculty of Health Sciences, University of Macau.

Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article and the Supplementary Materials. Raw data and code that support the findings of this study are available from the corresponding author, upon reasonable request.

Acknowledgments: We extend our great thanks to Wan-Ju Cheng, Kristen Nishimi, Maria Francesca Piazza, and Hei Hang Edmund Yiu for their generous contribution to providing detailed information for data synthesis. Their efforts have greatly contributed to the quality of the research. The authors wish to express their gratitude to the editor and reviewers for their constructive insights and kind feedback.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Cucciare, M.A. 6—SUPPORT GROUPS. In *Evidence-Based Adjunctive Treatments*; O'Donohue, W.T., Cummings, N.A., Eds.; Academic Press: San Diego, CA, USA, 2008; pp. 123–140.
2. Hassan, L.; Peek, N.; Lovell, K.; Carvalho, A.A.-O.; Solmi, M.A.-O.; Stubbs, B.; Firth, J.A.-O. Disparities in COVID-19 infection, hospitalisation and death in people with schizophrenia, bipolar disorder, and major depressive disorder: A cohort study of the UK Biobank. *Mol. Psychiatry* **2022**, *27*, 1248–1255. [CrossRef] [PubMed]
3. Ronaldson, A.; Elton, L.; Jayakumar, S.; Jieman, A.; Halvorsrud, K.; Bhui, K. Severe mental illness and health service utilisation for nonpsychiatric medical disorders: A systematic review and meta-analysis. *PLoS Med.* **2020**, *17*, e1003284. [CrossRef]
4. Hassan, L.; Sawyer, C.; Peek, N.; Lovell, K.; Carvalho, A.F.; Solmi, M.; Tilston, G.; Sperrin, M.; Firth, J. COVID-19 vaccination uptake in people with severe mental illness: A UK-based cohort study. *World Psychiatry* **2022**, *21*, 153–154. [CrossRef]
5. Hassan, L.; Sawyer, C.; Peek, N.; Lovell, K.; Carvalho, A.F.; Solmi, M.; Tilston, G.; Sperrin, M.; Firth, J. Heightened COVID-19 Mortality in People with Severe Mental Illness Persists After Vaccination: A Cohort Study of Greater Manchester Residents. *Schizophr. Bull.* **2022**, *49*, 275–284. [CrossRef]
6. Hamada, K.; Fan, X. The impact of COVID-19 on individuals living with serious mental illness. *Schizophr. Res.* **2020**, *222*, 3–5. [CrossRef] [PubMed]
7. National Institute of Mental Health. Mental Illness. 2021. Available online: https://www.nimh.nih.gov/health/statistics/mental-illness (accessed on 18 May 2023).
8. Australian Institute of Health and Welfare. Prevalence and Impact of Mental Illness. 2023. Available online: https://www.aihw.gov.au/getmedia/622ae08e-1c2f-45df-9682-10a3e0c41fe1/prevalence-and-impact-of-mental-illness-2022.pdf.aspx (accessed on 18 March 2024).
9. NHS Digital. Quality and Outcomes Framework, 2022–2023. 2023. Available online: https://digital.nhs.uk/data-and-information/publications/statistical/quality-and-outcomes-framework-achievement-prevalence-and-exceptions-data/2022-23 (accessed on 18 March 2024).
10. GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry* **2022**, *9*, 137–150. [CrossRef] [PubMed]
11. Walker, E.R.; McGee, R.E.; Druss, B.G. Mortality in mental disorders and global disease burden implications: A systematic review and meta-analysis. *JAMA Psychiatry* **2015**, *72*, 334–341. [CrossRef]
12. Hjorthøj, C.; Stürup, A.E.; McGrath, J.J.; Nordentoft, M. Years of potential life lost and life expectancy in schizophrenia: A systematic review and meta-analysis. *Lancet Psychiatry* **2017**, *4*, 295–301. [CrossRef]

13. Chan, J.K.N.; Tong, C.H.Y.; Wong, C.S.M.; Chen, E.Y.H.; Chang, W.C. Life expectancy and years of potential life lost in bipolar disorder: Systematic review and meta-analysis. *Br. J. Psychiatry* **2022**, *221*, 567–576. [CrossRef] [PubMed]
14. Fiorillo, A.; Sartorius, N. Mortality gap and physical comorbidity of people with severe mental disorders: The public health scandal. *Ann. Gen. Psychiatry* **2021**, *20*, 52. [CrossRef]
15. Cunningham, C.; Peters, K.; Mannix, J. Physical Health Inequities in People with Severe Mental Illness: Identifying Initiatives for Practice Change. *Issues Ment. Health Nurs.* **2013**, *34*, 855–862. [CrossRef]
16. Yang, H.; Chen, W.; Hu, Y.; Chen, Y.; Zeng, Y.; Sun, Y.; Ying, Z.; He, J.; Qu, Y.; Lu, D.; et al. Pre-pandemic psychiatric disorders and risk of COVID-19: A UK Biobank cohort analysis. *Lancet Healthy Longev.* **2020**, *1*, e69–e79. [CrossRef] [PubMed]
17. Toubasi, A.A.; AbuAnzeh, R.B.; Tawileh, H.B.A.; Aldebei, R.H.; Alryalat, S.A.S. A meta-analysis: The mortality and severity of COVID-19 among patients with mental disorders. *Psychiatry Res.* **2021**, *299*, 113856. [CrossRef]
18. Wang, Q.; Xu, R.; Volkow, N.D. Increased risk of COVID-19 infection and mortality in people with mental disorders: Analysis from electronic health records in the United States. *World Psychiatry* **2021**, *20*, 124–130. [CrossRef] [PubMed]
19. De Hert, M.; Mazereel, V.; Stroobants, M.; De Picker, L.; Van Assche, K.; Detraux, J. COVID-19-Related Mortality Risk in People with Severe Mental Illness: A Systematic and Critical Review. *Front. Psychiatry* **2021**, *12*, 798554. [CrossRef]
20. Fond, G.; Nemani, K.; Etchecopar-Etchart, D.; Loundou, A.; Goff, D.C.; Lee, S.W.; Lancon, C.; Auquier, P.; Baumstarck, K.; Llorca, P.M.; et al. Association Between Mental Health Disorders and Mortality Among Patients With COVID-19 in 7 Countries: A Systematic Review and Meta-analysis. *JAMA Psychiatry* **2021**, *78*, 1208–1217. [CrossRef] [PubMed]
21. Tokuda, Y.; Barnett, P.B.; Sanji, S.; Takaizumi, Y.; Tomono, M.; Tokuda, H.; Taniguchi, K.; Shibuya, K. Serious mental illness and in-hospital mortality among hospitalized patients with acute COVID-19: A large-database analysis in Japan. *Gen. Hosp. Psychiatry* **2023**, *82*, 1–6. [CrossRef]
22. Zisis, S.N.; Durieux, J.C.; Mouchati, C.; Perez, J.A.; McComsey, G.A. The Protective Effect of Coronavirus Disease 2019 (COVID-19) Vaccination on Postacute Sequelae of COVID-19: A Multicenter Study from a Large National Health Research Network. *Open Forum. Infect. Dis.* **2022**, *9*, ofac228. [CrossRef]
23. Liu, Q.; Qin, C.; Liu, M.; Liu, J. Effectiveness and safety of SARS-CoV-2 vaccine in real-world studies: A systematic review and meta-analysis. *Infect. Dis. Poverty* **2021**, *10*, 132. [CrossRef]
24. Pearson, C.A.B.; Bozzani, F.; Procter, S.R.; Davies, N.G.; Huda, M.; Jensen, H.T.; Keogh-Brown, M.; Khalid, M.; Sweeney, S.; Torres-Rueda, S.; et al. COVID-19 vaccination in Sindh Province, Pakistan: A modelling study of health impact and cost-effectiveness. *PLoS Med.* **2021**, *18*, e1003815. [CrossRef]
25. Utami, A.M.; Rendrayani, F.; Khoiry, Q.A.; Alfiani, F.; Kusuma, A.S.W.; Suwantika, A.A. Cost-Effectiveness Analysis of COVID-19 Vaccination in Low- and Middle-Income Countries. *J. Multidiscip. Heal.* **2022**, *15*, 2067–2076. [CrossRef]
26. Rahmani, K.; Shavaleh, R.; Forouhi, M.; Disfani, H.F.; Kamandi, M.; Oskooi, R.K.; Foogerdi, M.; Soltani, M.; Rahchamani, M.; Mohaddespour, M.; et al. The effectiveness of COVID-19 vaccines in reducing the incidence, hospitalization, and mortality from COVID-19: A systematic review and meta-analysis. *Front. Public Health* **2022**, *10*, 873596. [CrossRef]
27. Marc, D.H.; Victor, M.; Johan, D.; Kristof, V.A. Prioritizing COVID-19 vaccination for people with severe mental illness. *World Psychiatry* **2020**, *20*, 54–55.
28. De Picker, L.J.; Dias, M.C.; Benros, M.E.; Vai, B.; Branchi, I.; Benedetti, F.; Borsini, A.; Leza, J.C.; Kärkkäinen, H.; Männikkö, M.; et al. Severe mental illness and European COVID-19 vaccination strategies. *Lancet Psychiatry* **2021**, *8*, 356–359. [CrossRef] [PubMed]
29. Victor, M.; Kristof, V.A.; Johan, D.; Marc, D.H. COVID-19 vaccination for people with severe mental illness: Why, what, and how? *Lancet Psychiatry* **2021**, *8*, 444–450.
30. Siva, N. Severe mental illness: Reassessing COVID-19 vaccine priorities. *Lancet* **2021**, *397*, 657. [CrossRef] [PubMed]
31. Varshney, P.; Mamtani, H.; Kumar, C.N.; Chandra, P.S. COVID-19 Vaccination for Persons with Severe Mental Illnesses: An Indian Perspective. *Indian J. Psychol. Med.* **2021**, *43*, 436–441. [CrossRef] [PubMed]
32. Stein, C.; Nassereldine, H.; Sorensen, R.J.D.; Amlag, J.O.; Bisignano, C.; Byrne, S.; Castro, E.; Coberly, K.; Collins, J.K.; Dalos, J.; et al. Past SARS-CoV-2 infection protection against re-infection: A systematic review and meta-analysis. *Lancet* **2023**, *401*, 833–842. [CrossRef] [PubMed]
33. Dickerson, F.; Yolken, R. Response to the COVID-19 Vaccine in Persons with Schizophrenia and Other Serious Mental Illnesses. *J. Affect Disord. Rep.* **2023**, *12*, 100534. [CrossRef]
34. Stroup, D.F.; Berlin, J.A.; Morton, S.C.; Olkin, I.; Williamson, G.D.; Rennie, D.; Moher, D.; Becker, B.J.; Sipe, T.A.; Thacker, S.B. Meta-analysis of observational studies in epidemiology: A proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* **2000**, *283*, 2008–2012. [CrossRef]
35. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* **2021**, *372*, n71. [CrossRef] [PubMed]
36. Rosen, B.; Waitzberg, R.; Israeli, A. Israel's rapid rollout of vaccinations for COVID-19. *Isr. J. Health Policy Res.* **2021**, *10*, 6. [CrossRef]
37. Ouzzani, M.; Hammady, H.; Fedorowicz, Z.; Elmagarmid, A. Rayyan-a web and mobile app for systematic reviews. *Syst. Rev.* **2016**, *5*, 210. [CrossRef]

38. World Health Organization. Coronavirus Disease (COVID-19): Vaccines and Vaccine Safety. Available online: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/coronavirus-disease-(covid-19)-vaccines?adgroupsurvey=%7Badgroupsurvey%7D&gclid=EAIaIQobChMIl4bD7c_0_wIVa9QWBR3zuwQHEAAYASAAEgJ5J_D_BwE (accessed on 20 May 2023).
39. Wells, G.A.; Shea, B.; O'Connell, D.; Peterson, J.; Welch, V.; Losos, M.; Tugwell, P. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-Analyses. *Ottawa Hospital Research Institute*. 2000. Available online: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed on 20 September 2022).
40. Gierisch, J.M.; Beadles, C.; Shapiro, A.; McDuffie, J.R.; Cunningham, N.; Bradford, D.; Strauss, J.; Callahan, M.; Chen, M.; Hemminger, A.; et al. *Health Disparities in Quality Indicators of Healthcare Among Adults with Mental Illness*; Department of Veterans Affairs (US): Washington, DC, USA, 2014.
41. R Core Team. *R: A Language and Environment for Statistical Computing*; R Core Team: Vienna, Austria, 2023.
42. Nishimi, K.; Neylan, T.C.; Bertenthal, D.; Seal, K.H.; O'Donovan, A. Association of Psychiatric Disorders with Incidence of SARS-CoV-2 Breakthrough Infection Among Vaccinated Adults. *JAMA Netw. Open* **2022**, *5*, e227287. [CrossRef]
43. Piazza, M.F.; Amicizia, D.; Marchini, F.; Astengo, M.; Grammatico, F.; Battaglini, A.; Sticchi, C.; Paganino, C.; Lavieri, R.; Andreoli, G.B.; et al. Who Is at Higher Risk of SARS-CoV-2 Reinfection? Results from a Northern Region of Italy. *Vaccines* **2022**, *10*, 1885. [CrossRef] [PubMed]
44. Cheng, W.J.; Shih, H.M.; Su, K.P.; Hsueh, P.R. Risk factors for poor COVID-19 outcomes in patients with psychiatric disorders. *Brain Behav. Immun.* **2023**, *114*, 255–261. [CrossRef] [PubMed]
45. Ward, I.; Robertson, C.; Agrawal, U.; Patterson, L.; Bradley, D.T.; Shi, T.; de Lusignan, S.; Hobbs, R.; Sheikh, A.; Nafilyan, V. Risk of COVID-19 death in adults who received booster COVID-19 vaccinations in England. *Nat. Commun.* **2024**, *15*, 398. [CrossRef]
46. Tzur Bitan, D.; Kridin, K.; Cohen, A.D.; Weinstein, O. COVID-19 hospitalisation, mortality, vaccination, and postvaccination trends among people with schizophrenia in Israel: A longitudinal cohort study. *Lancet Psychiatry* **2021**, *8*, 901–908. [CrossRef]
47. Semenzato, L.; Botton, J.; Drouin, J.; Baricault, B.; Bertrand, M.; Jabagi, M.-J.; Cuenot, F.; Vu, S.L.; Dray-Spira, R.; Weill, A.; et al. Characteristics associated with the residual risk of severe COVID-19 after a complete vaccination schedule: A cohort study of 28 million people in France. *Lancet Reg. Health Eur.* **2022**, *19*, 100441. [CrossRef]
48. Corrao, G.; Franchi, M.; Cereda, D.; Bortolan, F.; Leoni, O.; Borriello, C.R.; Della Valle, P.G.; Tirani, M.; Pavesi, G.; Barone, A.; et al. Vulnerability Predictors of Post-Vaccine SARS-CoV-2 Infection and Disease—Empirical Evidence from a Large Population-Based Italian Platform. *Vaccines* **2022**, *10*, 845. [CrossRef]
49. Corrao, G.; Franchi, M.; Cereda, D.; Bortolan, F.; Leoni, O.; Jara, J.; Valenti, G.; Pavesi, G. Factors associated with severe or fatal clinical manifestations of SARS-CoV-2 infection after receiving the third dose of vaccine. *J. Intern. Med.* **2022**, *292*, 829–836. [CrossRef] [PubMed]
50. Zhu, J.; Tian, H.; Wang, H.; Yu, H.; Liu, C.; Wang, L.; Li, Q.; Fang, T.; Jia, F.; Li, Y.; et al. Higher benefit-risk ratio of COVID-19 vaccination in patients with schizophrenia and major depressive disorder versus patients with bipolar disorder when compared to controls. *Am. J. Transl. Res.* **2022**, *14*, 5719–5729. [PubMed]
51. Montoya, A.; Wen, K.; Travers, J.L.; Rivera-Hernandez, M.; White, E.; Mor, V.; Berry, S.D. Resident Factors Associated with Breakthrough SARS-CoV-2 Infections. *J. Am. Med. Dir. Assoc.* **2023**, *24*, 901–905. [CrossRef]
52. Yiu, H.H.E.; Yan, V.K.C.; Wei, Y.; Ye, X.; Huang, C.; Castle, D.J.; Chui, C.S.L.; Lai, F.T.T.; Li, X.; Wong, C.K.H.; et al. Risks of COVID-19-related hospitalisation and mortality among individuals with mental disorders following BNT162b2 and CoronaVac vaccinations: A case-control study. *Psychiatry Res.* **2023**, *329*, 115515. [CrossRef]
53. Sass, M.R.; Juul, T.S.; Skov, R.; Iversen, K.; Harritshøj, L.H.; Sørensen, E.; Ostrowski, S.R.; Andersen, O.; Ekstrøm, C.T.; Ullum, H.; et al. SARS-CoV-2 seroprevalence among patients with severe mental illness: A cross-sectional study. *PLoS ONE* **2022**, *17*, e0264325. [CrossRef]
54. Tregoning, J.S.; Flight, K.E.; Higham, S.L.; Wang, Z.; Pierce, B.F. Progress of the COVID-19 vaccine effort: Viruses, vaccines and variants versus efficacy, effectiveness and escape. *Nat. Rev. Immunol.* **2021**, *21*, 626–636. [CrossRef]
55. Goldfarb, M.; De Hert, M.; Detraux, J.; Di Palo, K.; Munir, H.; Music, S.; Piña, I.; Ringen, P.A. Severe Mental Illness and Cardiovascular Disease: JACC State-of-the-Art Review. *J. Am. Coll. Cardiol.* **2022**, *80*, 918–933. [CrossRef]
56. Seow, L.S.E.; Verma, S.K.; Mok, Y.M.; Kumar, S.; Chang, S.; Satghare, P.; Hombali, A.; Vaingankar, J.; Chong, S.A.; Subramaniam, M. Evaluating DSM-5 Insomnia Disorder and the Treatment of Sleep Problems in a Psychiatric Population. *J. Clin. Sleep Med.* **2018**, *14*, 237–244. [CrossRef] [PubMed]
57. Madison, A.A.; Shrout, M.R.; Renna, M.E.; Kiecolt-Glaser, J.K. Psychological and Behavioral Predictors of Vaccine Efficacy: Considerations for COVID-19. *Perspect. Psychol. Sci.* **2021**, *16*, 191–203. [CrossRef]
58. Zeng, B.; Gao, L.; Zhou, Q.; Yu, K.; Sun, F. Effectiveness of COVID-19 vaccines against SARS-CoV-2 variants of concern: A systematic review and meta-analysis. *BMC Med.* **2022**, *20*, 200. [CrossRef]
59. Tzur Bitan, D.; Kridin, K.; Givon-Lavi, N.; Krieger, I.; Kaliner, E.; Cohen, A.D.; Weinstein, O. COVID-19 Booster Vaccination Among Individuals with Schizophrenia in Israel. *JAMA Psychiatry* **2022**, *79*, 508–512. [CrossRef]
60. Fond, G.; Yon, D.K.; Boyer, L. One-year results from the vaccination campaign against COVID-19 infection in 47 million individuals with severe mental disorders and other chronic diseases. *Eur. Arch. Psychiatry Clin. Neurosci.* **2023**, *273*, 517–521. [CrossRef] [PubMed]

61. World Health Organization. WHO Director-General's Opening Remarks at the Media Briefing—5 May 2023. Available online: https://www.who.int/news-room/speeches/item/who-director-general-s-opening-remarks-at-the-media-briefing---5-may-2023 (accessed on 20 May 2023).
62. Fiolet, T.; Kherabi, Y.; MacDonald, C.J.; Ghosn, J.; Peiffer-Smadja, N. Comparing COVID-19 vaccines for their characteristics, efficacy and effectiveness against SARS-CoV-2 and variants of concern: A narrative review. *Clin. Microbiol. Infect.* **2022**, *28*, 202–221. [CrossRef] [PubMed]
63. Lee, D.W.; Bae, Y.S.; Lee, J.R.; Sohn, J.H.; Lee, H.; Lee, J.Y. COVID-19 vaccination, incidence, and mortality rates among individuals with mental disorders in South Korea: A nationwide retrospective study. *Asian J. Psychiatry* **2023**, *85*, 103600. [CrossRef]
64. Kim, H.J.; Kim, M.-H.; Choi, M.G.; Chun, E.M. Psychiatric adverse events following COVID-19 vaccination: A population-based cohort study in Seoul, South Korea. *Mol. Psychiatry* **2024**, 1–9. [CrossRef] [PubMed]
65. Brown, J.D.; Bell, N. Role of psychiatric hospitals in the equitable distribution of COVID-19 vaccines. *Psychiatr. Serv.* **2021**, *72*, 1080–1083. [CrossRef]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.