Public Health in Practice 7 (2024) 100494

Contents lists available at ScienceDirect

Public Health in Practice

journal homepage: www.sciencedirect.com/journal/public-health-in-practice

Update on Omicron variant and its threat to vulnerable populations

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ARTICLE INFO

Keywords:
COVID-19
Omicron
SARS-CoV-2
Epidemiology
Vaccine

ABSTRACT

Objective: To reduce the incidence of severe illness and fatalities, and promote the awareness of protection and precaution, increased vaccination, strengthen the physical fitness, frequent ventilation, and health education should be enhanced among vulnerable populations as essential measures for the future control of COVID-19.
Study design: Systematic review.
Method: The search was done using PubMed, EMBASE and Web of Science for studies without language restrictions, published up through March 2023, since their authoritative and comprehensive literature search database. Eighty articles were included. Extraction of articles and quality assessment of included reviews was performed independently by two authors using the AMSTAR 2 score.
Results: The articles in the final data set included research on epidemiological characteristics, pathogenicity, available vaccines, treatments and epidemiological features in special populations including the elders, pregnant women, kids, people with chronic diseases concerning Omicron.
Conclusion: Although less pathogenic potential is found in Omicron, highly mutated forms have enhanced the ability of immune evasion and resistance to existing vaccines compared with former variants. Severe complications and outcomes may occur in vulnerable populations. Infected pregnant women are more likely to give birth prematurely, and fatal implications in children infected with Omicron are hyperimmune response and severe neurological disorders. In immunocompromised patients, there is a greater reported mortality and complication compared to patients with normal immune systems. Therefore, maintain social distancing, wear masks, and receive vaccinations are effective long-term measures.

1. Introduction

Since the Coronavirus disease 2019 (COVID-19) emerged in Wuhan in December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has taken place several recombination and mutations, leading to various variants. The Omicron typified by B.1.1.529, was initially found in South Africa on November 9, 2021 which was classified as variants of concern (VOC) by the World Health Organization (WHO) on November 26, 2021 [1]. Subsequently, Omicron has become dominant strain over many regions of the world in 2022 (https://gisaid.org/hcov19-variants/). It has demonstrated that Omicron is more likely to escape immune response stimulated by previous infections or vaccine immunization [2,3]. Hence, although patients infected with Omicron seemed to have a lower risk of severe illness, the higher transmissibility and breakthrough infection rate still indicate that human beings couldn't relax their vigilance [4,5]. Therefore, this review is aimed at summarizing the epidemiological characteristics, pathogenicity, available vaccines, and treatments concerning Omicron, which will better inform public health action and reduce the incidence of severe illness and fatalities, and promote the awareness of protection and precaution to reach more vulnerable populations with tailored, effective prevention and treatment strategies.

2. Virology of Omicron

2.1. Subvariants of Omicron

Unlike other VOCs, Omicron has evolved remarkable diversity, and it is commonly classified into five main sub-lineages, BA.1, BA.2, BA.3, BA.4, BA.5, as well as some subvariants. To date, BQ.1 (a subvariant of BA.5) and XBB (a subvariant of BA.2) have become dominants of COVID-19 pandemic. These sub-lineages have exhibited distinct transmissibility and immune evasion.

BA.2 is popularly known as "Stealth Omicron", and it has become the

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https://doi.org/10.1016/j.puhip.2024.100494
Received 19 May 2023; Received in revised form 20 February 2024; Accepted 15 March 2024
Available online 25 March 2024

dominant strain as of February 2022. Subsequently, BA.2 was rapidly replaced by BA.4 and BA.5 by the first week of July 2022. Notably, the pathogenicity of BA.1 and BA.2 has been lower compared with other VOCs. However, the pathogenicity of BA.4/5 is higher than BA.2 [6]. In addition, BA.4/BA.5 showed increased immune evasion than BA.1, BA.1.1, and BA.2 among cases who had administered inactivated vaccines or infected with SARS-CoV-2 [7]. At present, BQ.1 and BQ1.1 are gradually becoming the major prevalent strains because of stronger immune escape [1]. Taken together, studies related to immune escape of novel subvariants are essential to forecast the disease incidence and promote development of vaccines.

2.2. The mutation characteristics

Since the emergence of Omicron, diverse subvariants have formed along with the continuous mutation in spike (S) protein. Because of the elevated infectivity and immune evasion, Omicron has gradually become the dominant one during COVID-19 pandemic [1] (Fig. 1). More than 60 Omicron mutations have been identified, concerning not only S protein but also other structural or nonstructural proteins compared with SARS-CoV-2 ancestor, including open reading frame 1 ab (ORF1ab), nucleocapsid (N) protein, envelope (E) protein, membrane (M) protein. Previous studies indicated that transmissibility and the ability of immune evasion were enhanced, on account of multiple mutations in Omicron [8]. The enhanced transmissibility can be attributed to the mutations of S477 N, Q498R, S371L, T478K, and N501Y in S protein, which can cause a stronger binding affinity to ACE2 receptor [8]. A cluster of mutations (H655Y, N679K, and P681H) present in the Omicron S protein could contribute to virus transmission and develop resistance to treatment by monoclonal antibodies [9]. Increased rates of reinfection and decreased protective efficiency of immunity against Omicron may also attribute to S protein mutations. Some NTD mutations, including T19I, L24S, del 25-27, G142D, and del 143-14, have caused significant evasion from NTD-targeted neutralizing antibodies (nAbs) [9]. The decreased effectiveness of monoclonal antibody can also be linked to Omicron mutations such as Q493R, which can reduce susceptibility to medicines by disrupting the binding affinity to S protein [9].

Compared with BA.2, the capacity of immune evasion and binding affinity to the receptor are increased due to the mutations in L452R, F486V and R493Q of BA.4/5, leading lower protection from reinfection than BA.1 or BA.2 [10]. Besides, increased neutralization resistance was reported in BQ.1, BQ.1.1 driven by the N460K and K444T mutations, as well as BA.2.75.2 subvariant driven by F486S mutation [10]. Altogether, emerging subvariants should be timely detected by global surveillance.

2.3. Pathogenicity of Omicron

Interestingly, the clinical symptoms of severe cases caused by Omicron infection are less devastating than those of other strains and mainly lead acute inflammation of upper respiratory tract [11]. Omicron spike inefficiently uses the cellular protease TMPRSS2, which promotes cell entry through plasma membrane fusion, with greater dependency on cell entry through the endocytic pathway [12]. During the Omicron pandemic, the number of infected patients who are hospitalized receiving intensive care treatment and mechanical ventilation, or die in-hospital was reduced compared with Delta infection in a prospective cohort study from French [13]. Besides, the rate of mortality showed a decline, from 0.7% (Delta) to 0.4% (Omicron) [5]. Likewise, Butt et al. [4] reported that 0.03% of Omicron infections developed severity compared with 1.5% of those infected with Delta. Although Omicron has a weaker pathogenicity, the higher overall infection rate and much more reinfections has seriously impacted healthcare systems which still can't be ignored [14].

2.4. Omicron can suppress innate immunity

Type I interferons (IFN-α/β) are essential components of innate immunity and protect host from viral infection. RNA of SARS-CoV-2 can trigger innate immune responses [15]. Omicron may also escape innate immune response by targeting related proteins throughout the signaling pathways. SARS-CoV-2 infection will stimulate excessive production of inflammatory mediators by activating both retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated protein 5 (MDA5) [16]. Then mitochondrial antiviral signaling protein (MAVS) is activated to recruit TANK binding kinase 1 (TBK1) and NF-κB kinase-ε (IKKε), which are responsible for the phosphorylation of interferon

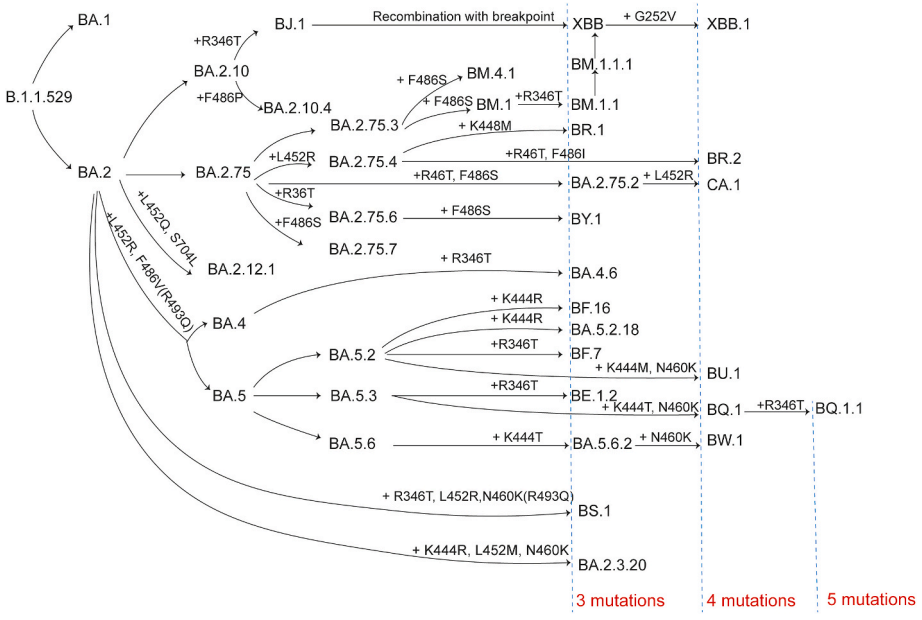

Fig. 1. Evolutionary relationships of Omicron. Omicron contains increasing additional mutations in its S protein compared with the WT variants. An array of different mutations or combinations may help Omicron escape immune responses or therapeutic antibodies (As of January 4, 2023. Available at https://covariants.org/variants).

regulatory factor (IRF3 and IRF7) [17]. The M protein of SARS-CoV-2 can interact with MAVS, diminishing antiviral innate response [18]. Subsequently, the phosphorylated IRF3 and IRF7 dimerize and translocate to the nucleus. Meanwhile, SARS-CoV-2 infection promotes the cGAS-STING signaling axis, resulting in cell death and production of type I IFN [19]. ORF3a of SARS-CoV-2 can effectively suppress innate immune by inhibiting stimulator of IFN genes (STING) [20]. NSP13 of SARS-CoV-2 will decrease the level of TBK1 phosphorylation by binding to TBK1. NSP3 and ORF6 can suppress IFN expression by impairing IRF3 phosphorylation [20]. Meanwhile, SARS-CoV-2 NSP1 can inhibit the phosphorylation of STAT1 and STAT2 to suppress the IFN signaling axis [21](Fig. 2). Therefore, understanding the interaction between innate immune system and SARS-CoV-2 infection is very important for the development of therapeutics and vaccine.

2.5. Re-infection of Omicron

Four weeks after infection, antibodies will appear in the nasal cavity, but return to normal levels after 9 months. However, the level of nasal IgA induced by Omicron infection only retained for a short time, which may be a major factor of reinfection [14]. The reinfection rate has increased from 128.0 cases per 100 000 during Delta pandemic to 355.1 cases per 100 000 during Omicron periods [22]. A current study found the rate of reinfection about BA.4 or BA.5 among patients, who had infected with Omicron previously, was 76.2% during May 7 and July 28, 2023 [23]. Previous infection of Omicron can protect bodies from reinfection of BA.5 for at least 5 months [24]. However, compared with no reinfection, additional risks of death, hospitalization and sequelae were contributed by reinfection [25]. In summary, previous infection has protective ability against reinfection in a short time, but it is still crucial to take precautions against reinfection.

2.6. Transmissibility

Since the emergence of SARS-CoV-2, COVID-19 pandemic has been affecting most countries worldwide over the past 3 years. Enhanced viral loads are shown in many studies about Omicron than other VOCs, suggesting that Omicron has a good affinity to airways [26]. In Danish, the infectivity of Omicron is 3.19 times greater than Delta, which is consistent with the results of a study from South African [27,28]. It had been found that the infectivity of Omicron was almost 10 times than wild type (WT) strain and 3.6 times than Delta variant [29]. As summarized in Table 1, the basic reproduction number (R_0) of Omicron is also higher than other variants [30–38]. The average incubation period for Omicron infection is 3.42 days [39]. Taken together, patients infected with Omicron have higher infectivity and shorter time of incubation period.

3. Pathogenicity

3.1. Clinical manifestations

The data of epidemiological surveillance has revealed that the incidences of hospitalization and mortality doesn't increase with the elevated transmissibility of Omicron [13,40]. The prevalence of olfactory loss is lower in Omicron-infected patients compared with Delta (16.7% vs. 52.7), and no special clinical symptoms are reported in Omicron patients. Compared to Delta, dysphagia, sore throats, and hoarseness are common after Omicron infection instead of Delta [41]. The symptoms, like coughing, expectoration, fatigue, soreness of the

Table 1
The basic reproduction number of SARs-COV-2 variants.

Variants	Location	Date	R_0	Reference
Omicron	Worldwide	November 2021	11.80	[30]
	Worldwide	December 2021	10.00	[31]
	China	December 2022	11.35	[32]
Delta	Worldwide	July 2021	3.20	[33]
	China	21 May - 18 June 2021	3.60	[34]
	China	28 July - August 26, 2021	3.40	[35]
WT	China	December 1, 2019–January 24, 2020	2.56	[36]
	China	January 2020	2.20	[37]
	China	January 19 -January 23, 2020	2.96	[38]

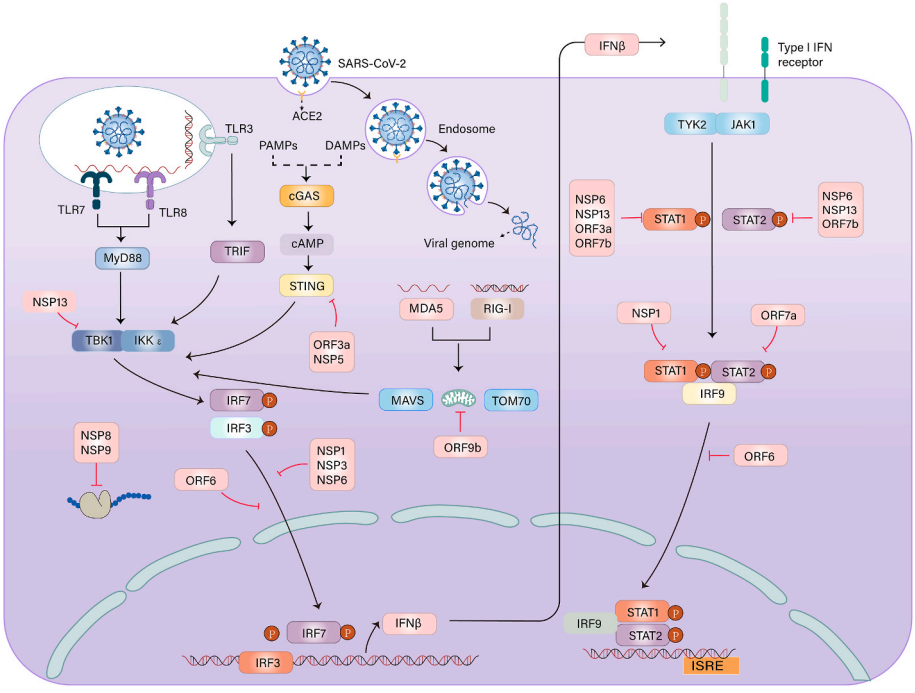

Fig. 2. Immune sensing and antagonism of SARS-CoV-2 to inhibit IFN responses. A diagram illustrates the mechanisms by SARS-CoV-2 to evade the innate immune response. SARS-CoV-2 has employed various strategies to escape immune surveillance and subsequently promote viral replication.

limbs, and thirst are generally reported among unvaccinated populations. Whereas the main five symptoms in vaccine-eligible population were coughing, expectoration, nasal congestion and runny nose, thirst, and sore throat. And multiple symptoms are associated with severe outcomes [11]. Compared with other variants, the incidence of severe disease caused by Omicron has reduced apparently. According to a Chinese study involving 36,168 infections, only 39 cases developed into severe illness (including 1 death), but most of infections were mild [42]. Similar results were found in some studies from Norway and Korea. Cough and nasal congestion are the main symptoms [43,44]. Patients infected with Delta were more likely to develop into severity (0.10% vs 1.13%), in-hospital deaths (0.06% vs 0.76%) [45], intensive care unit (ICU), and admission rates (1.64% vs 4.81%) [46] than Omicron. However, age, fever, cough, fatigue, taste disorders, and comorbidity are potential factors to predict the deterioration of Omicron variant infection. People characterized with above symptoms should get more attention.

3.2. Epidemiological features in special populations

As summarized in Table 2 pregnant women, older people, children, and people with chronic illnesses may be more likely to develop into severity [47–52]. Among infected pregnant women, those who are symptomatic will be more susceptible to occur premature births and severe complications [51]. Although COVID-19-related vaccines are safe for pregnancy, the inoculation rate among pregnant women and women of childbearing age remains too low [53]. Fortunately, pregnant women with Omicron infections, the pooled prevalence (PPs) for required respiratory support, severe or critical illness, intensive care unit (ICU) admission, maternal death, and preterm birth <37 weeks were, respectively, 2.63% (95%CI, 0.98–4.28%), 1.11% (95%CI, 0.29–1.94%), and 1.83% (95%CI, 0.85–2.81%) which were lower than those in Delta period, 27.24% (95%CI, 20.51–33.97%), 24.96% (95%CI, 15.96–33.96%), 11.31% (95%CI, 4.00–18.61%), 4.20% (95%CI, 1.43–6.97%), and 33.85% (95%CI, 21.54–46.17%, respectively [54]. The fatal implications in children infected with Omicron are hyperimmune response and severe neurological disorders. And more children will be affected by SARS-CoV-2 infection because of the enhanced transmission rates [55]. Because the upper airways are narrower in children than in adults, inflammation of the larynx often leads to serious clinical manifestations in younger children [56]. The hospitalization rates in aged 0–4 patients and the number of pediatric patients with croup syndrome increased dramatically when Omicron variant began to predominate in the United States and Boston [56]. Furthermore, older age is an independent risk factor of re-positivity in patients with the Omicron variant. In patients over 60 years old, the odds ratio for re-positivity was 1.82 (95% CI:1.18–2.78) [57]. Besides, Patients over 80 years old, combined with cerebrovascular disease, cardiovascular disease, chronic kidney disease, and respiratory diseases were more likely to develop severe disease [49]. For immunocompromised patients, the higher rates of mortality and complication are reported than patients with normal immune systems [58]. Additionally, in a study conducted in the United States using a large health claims database (the Healthcare Integrated Research Database) from April 2020 to March 2022, 23.5% of the immunocompromised individuals had a COVID-19-related hospitalization [59]. Among patients infected with the Omicron variant, those who were immunocompromised developed more frequent organ failures and day-28 mortality than healthy people (63.6% vs 45.5%, $p = 0.025$; 46.9% vs 26.2%, $p = 0.009$) [58]. Despite vaccines may provide some protection, immunocompromised patients still lag behind the general patient in terms of therapeutic efficacy and outcomes after hospitalization. From the multivariate analysis for the outcome of 1-year mortality, it was found that age were significantly and independently associated with mortality within 1 year [60]. Meanwhile, older age also were identified as severity risk factors [61]. In different groups, fever lasted an average of 5.93 ± 3.37 days for the general population and 10.64 ± 7.12 days for impaired-immunity patients [61].

Therefore, more treatment measures should be taken among pregnant women, older people, children, and people with chronic illnesses. Booster vaccinations and pre-exposure prophylaxis are recommended for the elderly, immunocompromised populations, and those with specific underlying conditions. Therefore, those people should enhance the awareness of vaccination and education.

Table 2
Risk factors of progressing to mortality or severity of Omicron outcomes for vulnerable populations.

Variable	Adjusted Odds Ratio	95% Confidence Interval	Reference
<3 years	11.07	3.68–33.25	[62]
80–89 years	2.90	1.10–7.50	[48]
Heart failure	1.70	1.10–2.70	[48]
Chronic kidney disease	1.70	1.10–2.50	[48]
Diabetes	1.90	1.30–3.00	[48]
Cardiovascular disease	1.48	0.81–2.28	[49]
Cerebrovascular disease	3.28	1.81–5.91	[49]
Hepatic disease	5.77	0.66–50.30	[49]
Immunocompromised patients	2.06	1.48–2.86	[63]
HIV infection	1.39	1.07–1.79	[64]
Unvaccinated pregnancy	2.78	1.39–5.57	[47]
Thoracic tumour	1.84[a]	1.36–2.48	[52]
Gastro-intestinal tumour	1.43[a]	1.07–1.90	[52]
Gynaecological/Genito-Urinary tumour	1.28[a]	0.94–1.73	[52]
hypogammaglobulinaemia	3.22[a]	1.27–8.19	[50]

[a] Adjust hazard ratio.

4. Prevention and treatment

4.1. Vaccines

Since COVID-19 pandemic, various vaccines have been developed. However, studies have shown that the vaccines have reduced effectiveness to prevent COVID infections related to the Omicron variant [2,3,62]. The inactivated whole-virion SARS-CoV-2 vaccines have been used in many countries widespread (CoronaVac, Sinovac Life Sciences, China and Instituto Butantan, Brazil. RNA vaccines, such as BNT162b2 and mRNA-1273, used to be proven the most effective vaccines against WT strains but were completely ineffective against Omicron variant [2]. In serum samples from those who had been vaccinated two doses of BNT162b2 or mRNA-1273, the titers of neutralizing antibodies against the Omicron variant compared were considerable decrease compared with the WT [2,63]. For those who were administered with three doses of mRNA vaccines, the 50% focus reduction neutralization test (FRNT50) against BQ.1.1 and XBB were reduced 21.1 times and 21.6 times, respectively, compared with WT strain [3]. Fortunately, multiple developing vaccines have shown effectiveness against COVID-19. In a recent study, ZF2001 vaccination induced a strong humoral immune response against SARS-CoV-2 in cynomolgus monkeys [64]. In an animal experiment, a ferritin-based COVID-19 nanoparticle vaccine could stimulate potent and durable neutralizing antibodies among non-human primates against known VOCs, including BQ.1 [65].

In terms of Omicron, current available vaccines remain effective efficacy against severe illness, hospitalization, and death. Three immunization doses could decrease the rate of hospitalization after Omicron infection [66]. A cohort study in Chile revealed that CoronaVac's effectiveness was 64.6% against hospitalization and 69.0% against ICU admission in children 3–5 years [67]. Even though significant reduced level of neutralization antibodies against Omicron has been demonstrated, current vaccines are still sufficient for protection against severe diseases. The incidence of severity during Omicron pandemic was 3 and 0.8 cases per 100,000 person-days in 2-dose and 3-dose inactivated vaccines, respectively [68].

Despite the reduced efficacy of vaccines in preventing infection,

booster shots can increase the serum-neutralizing titers against Omicron strains. In fact, the neutralizing activity against the Omicron variant was found to be superior after heterologous boosting with mRNA vaccines or recombinant subunit vaccines as compared to homologous boosting [69]. One month after receiving the third vaccine dose, the Omicron-neutralizing titers increased 23-fold compared to the levels observed after two doses [70]. Moreover, those who received booster doses of mRNA vaccines demonstrated sufficient protection against Omicron variant such as BA.2, BA.4, and BA.5 [71]. Based on a study, a booster dose of mRNA vaccination (either with BNT162b2 or mRNA-1273) produces a strong immune response that effectively guards against COVID-19. At 14–29 days following the mRNA booster, the VE of the BNT162b2 booster was 51.6% in Brazil and 67.1% in Scotland [72]. However, the neutralization of BQ.1, BQ.1.1, XBB, and XBB.1 by sera obtained from vaccinated and infected individuals were significantly impaired, even with sera obtained from those who received a boosted of mRNA vaccine [73]. To conclude, administering booster vaccines remains a prudent course of action, particularly for older adults, individuals with multiple co-morbidities, and those suffering from specific underlying medical conditions [72,74]. Nasal vaccination reduces SARS-CoV-2 viral load, prevents inflammation and pneumonia better, and shows greater neutralization. As a result, its efficiency and convenience make it a promising option for future vaccination strategies [75,76].

4.2. Treatment

Currently, there are several therapeutic options for managing COVID-19 that have been approved under the Emergency Use Authorization (EUA) issued by FDA. These options include antiviral drugs such as molnupiravir, nirmatrelvir and ritonavir, *anti*-SARS-CoV-2 monoclonal antibodies such as Bebtelovimab, Evusheld, anti-inflammatory drugs such as dexamethasone, immunomodulators agents such as baricitinib, tocilizumab, sedatives, and renal replacement therapies. *Anti*-SARS-CoV-2 monoclonal antibodies mainly target the RBD of SARS-CoV-2 S protein, which is highly mutated in Omicron variant. While bertilovemab was previously effective against all SARS-CoV-2 variants [77], it is now completely ineffective against both the BQ and XBB sub-lineages [73]. A study has found that antibiotic resistance is prevalent among ICU patients with COVID-19 at the King Faisal Hospital [78]. However, it has been confirmed through *in vitro* assays that most antiviral drugs, such as remdesivir, molnupiravir, PF-07304814 (nirmatrelvir, a key component of paxlovid), EIDD-1931, ribavirin, favipiravir, nafamostat, camostat, and aprotinin, are effective in treating Omicron [79]. Furthermore, Azivudine, a nucleoside analogue that inhibits HIV-1 RNA-dependent RNA polymerase (RdRp), has been approved by the State Drug Administration of China for COVID-19 treatment. Compared to remdesivir, Azivudine has less frequent and transient side effects [80]. However, the development of targeted drugs for Omicron will face a significant challenge due to consecutive mutations.

5. Conclusion

The COVID-19 pandemic remains a global threat to individual health. The highly transmissible and easily reinfected Omicron variant is a major concern for its potential to cause severe illness and fatalities. The lower efficacy of existing vaccines against the Omicron subvariant highlights the need for prioritizing the development of potential vaccines and targeted drugs to combat this new strain. While living with the coronavirus has become a preventive strategy for many countries worldwide, the elderly, pregnant women, and immunocompromised individuals still require increased attention. Therefore, maintain social distancing, wear masks, and receive vaccinations are effective long-term measures.

Author contributions

Conceptualization, Y.J and H.Y.; writing – original draft preparation, B.D. and Y.J.; writing – review and editing, B.D., Y.J., and H.Y. All authors have read and agreed to the published version of the manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (NO. 82372229, NO. 82002147, NO. 82273695 NO. 82073618); supported by China Postdoctoral Science Foundation (NO. 2019M662543); supported by Open Research Fund of National Health Commission Key Laboratory of Birth Defects Prevention & Henan Key Laboratory of Population Defects Prevention (NO. ZD202301), supported by the Open Grant from the Pingyuan Laboratory (NO. 2023PY-OP-0202), and supported by Open Project of Henan Province Engineering Research Center of Diagnosis and Treatment of Pediatric Infection and Critical Care (NO. ERC202302).

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Conflict of interest form

The authors have declared that no competing interests exist.

Acknowledgements

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhip.2024.100494.

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