REVIEW

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Therapeutic strategies encompassing monoclonal antibodies and vaccines to tackle the SARS-CoV-2 Omicron variant amongst European children

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Omicron is a notable B.1.1.529 variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) comprising 50 gene mutations in total, within which 32 gene mutations were recorded on spike 1 (S1) protein. Omicron beholding higher gene mutations than other prevalent SARS-CoV-2 variants of concern, including the Delta-SARS-CoV-2 variant, exhibited the highest transmission efficacy. About 2152 individuals from 57 countries contracted Omicron in the shortest interval of two weeks proclaiming the variant to be the most contagious SARS-CoV-2 variant amongst all other SARS-CoV-2 variants of concern. The first Omicron contracted patient was diagnosed on 24 November 2021 in South Africa, and the South African population was infected presenting these health ailments: sore throat, headache, body pain, and mild to severe fatigue commonly witnessed among children and adults. In Germany, together with aged people with co-morbidities and young adults, children of 0-4 yrs and 5-14 yrs were profusely affected by Omicron. Omicron contracted Swedish children showed moderate to severe convulsions as adverse symptoms. In the UK, Omicron positive children in higher numbers were examined and treated under hospital care with ventilators and oxygen cylinders. This narrative insight review illustrates the distinct virulence characteristics of Omicron in evading the human-host neutralizing antibodies action in both SARS-CoV-2 convalescent individuals and immunized population in the context of its outbreak in European children. Moreover, the effect of monoclonal antibodies and the appropriate therapeutic dosage of SARS-CoV-2 vaccines, and the common pediatric vaccines that finds promising to tackle Omicron outbreaks in children across Europe have been unveiled in the review.

1. Introduction

Omicron, a unique SARS-CoV-2 variant-B.1.1.529 primarily evolved from the South African population, infected the global population with its incessant transmission efficacy, especially children and adolescents (Bittmann 2022; Lima et al. 2021; Meo et al. 2021; Singhal 2022). Omicron constitutes 32 detrimental mutations at the receptor-binding domain (RBD) of spike 1 (S1) protein (Kannan et al. 2021). Point mutations such as Q493R, N501Y, S371L, S373P, S375F, Q498R, and T478K of RBD-S1-Omicron buttresses its binding affinity with the host-human angiotensin-converting enzyme receptor 2 (ACE-2), attributing to its uncontrolled outbreak among the global population (Kannan et al. 2021; Kumar et al. 2022).

Omicron outbreak among children and young adults are remarkably higher compared with the other SARS-CoV-2 variants, including the Delta-SAR-CoV-2 variant (Kannan et al. 2021; Kumar et al. 2022). Computational studies emphasized these RBD-S1 point mutations of Omicron: T478K; Q493K; Q498R; Q493R; G496S; Y505H; P681H; and Q954H to be crucial in augmenting its binding affinity with the ACE2 plausibly by altering its physicochemical characteristics from polar to positively charged with the incorporation of K, R and H amino acid residues (Cui et al. 2022; Mannar et al. 2022; Shah and Woo 2021). Moreover, the altered physicochemical characteristics of RBD-S1-Omicron have ameliorated its pathogenicity in defending the neutralizing antibodies action induced by the SARS-CoV-2-specific monoclonal antibodies, proven effective against alpha, beta, gamma and Delta-SARS-CoV-2 variants (Agency 2021a; Fang and Shi 2022; Mannar et al. 2022; Shah and Woo 2021).

Omicron contracted children showed moderate to severe symptoms (Bittmann 2022; Lima et al. 2021; Ludvigsson 2022). The mild symptoms encompassed fever, headache, body pain, cough, common myalgia, and intense fatigue (Meo et al. 2021). Nevertheless, its uncontrolled spread rate amongst humans, particularly children, has traumatized the entire health care system of the European nations (Health Professionals 2022; Ren et al. 2022). Belgium reported its first Omicron cases on 24 Nov 2021, followed by France, the UK, Germany, Portugal, and Scotland witnessed the highest Omicron cases exemplifying its interminable human to human transmission chain with its virulence (Banerjee et al. 2021). In this review, the underlining clinical factors favouring Omicron uncontrolled outbreak and its virulence amongst European children, including its pathogenesis in defending the neutralizing antibodies action and undermining host-immune responses, have been discussed briefly. Furthermore, clinical strategies and treatment using monoclonal antibodies and vaccines of both SARS-CoV-2 specific and common pediatric vaccine types that can effectively control Omicron outbreak and any future variants of SARS-CoV-2 among European children are discussed.

2. Omicron, a unique variant of SARS-CoV-2 with deleterious mutations at the receptor binding domain (RBD) of spike 1 (S1) protein

Omicron itself, a mutant variant of the SARS-CoV-2 virus family, is further classified into six groups in compliance with its mutations spotted at the amino acid residue site 214 (Banerjee et al. 2021). Omicron acknowledged as the most contagious variant of the SARS-CoV-2 family, possesses mutations within the open reading frames (ORF)-1a, 1b, and 9b (Kumar et al. 2022). The ORF-1a comprised these point mutations: K856R, L2084I, A2710T, T3255I, P3395H, and I3758V coupled with gene deletions spotted at the residue sites 2083 and 3674-3676 (Kumar et al. 2022). ORF-1b consists of two substitutions, P314L and I1566V. While ORF-9b has one substitution: P10S, with three residues deletions at the residue site 27-29 (Kumar et al. 2022). Of 26-35-point mutations detected at the RBD-S1 of Omicron, these 15-point mutations: N501Y, G339D, S371L, S373P, S375F, N440K, G446S, T478K, G496S, Q498R, K417N, S477N, E484A, Q493R, and Q498R have predominantly associated with its ceaseless human to human transmission chain affecting a larger group of population than any other prevalent SARS-CoV-2 variants of concern (Kumar et al. 2022; Ren et al. 2022). Notably, the substitutions N501Y, S371L, and S373P at the RBD-S1 of Omicron can play a critical role in augmenting its spread rate and virulence *via* buttressing its interaction with the human ACE2 resembling the point mutations of the Delta variant: L452R and T478K governing its virulence and outbreak in the same module (Kumar et al. 2022).

Laboratory studies also affirmed the role of these point mutations at the RBD-S1 of Omicron: K417N, N501Y, Y505H, E484A, Q493R, G477N, and Q498R in presiding its transmission after determining its lowered binding free energy exhibited with the FDA-approved monoclonal antibodies against SARS-CoV-2 virulence (Chen et al. 2022a). The study inference showed that Omicron could defend the neutralizing antibodies action 14 times higher than the dreadful Delta variant exemplifying its virulence efficacy in infecting the immunized population against SARS-CoV-2 variants by overruling the host-antibodies responses (Chen et al. 2022a).

In vitro, antibody-interaction studies using the purified RBD-S1 protein variants unveiled the substitutions E484K/A/Q spotted in Delta and Omicron variants detrimental, undermining the binding affinity of RBD-S1 specific antibodies and its associated neutralizing activity against these mutant variants (Sun et al. 2022). Immunized patients administered with the second dose of SARS-CoV-2 mRNA vaccines, BNT162b2 (Pfizer-BioNTech) and mRNA-1273 were infected with Omicron 178 and 53 days after vaccination, respectively (Zhou et al. 2022). The patients showed elevated neutralizing antibody titers against all SARS-CoV-2 variants of concern, including Omicron (Zhou et al. 2022). Nevertheless, Omicron breakthrough infection occurred *via* resisting the neutralizing antibodies action-induced by the BNT162b2 vaccine (Chen et al. 2022b; Zhou et al. 2022). Convalescent individuals or immunized people infected by Omicron showed diminished neutralizing PRNT50 antibody titers against Omicron comparatively with other SARS-CoV-2 variants of concern (Cheng et al. 2022). Among vaccinated people of n (number) = 31, individuals in lower numbers of n=2 developed sufficient PRNT50 neutralizing antibody titers to tackle the Omicron virulence (Cheng et al. 2022). While against other prevalent SARS-CoV-2 variants, about 30 individuals exhibited adequate neutralizing antibody titers to attenuate its virulence (Cheng et al. 2022). The clinical reports emphasize the likely chances of Omicron infecting immunized adolescents administered BNT162b2 vaccine and SARS-CoV-2 convalescent children aged 2-17 yrs irrespective of the sufficient neutralizing antibody titers witnessed in 38.2% of 34-immunized adolescents and 26.7% of 15-convalescent children (Chen et al. 2022b).

Concertedly, both *in-vitro* and clinical studies inference exemplified Omicron, a distinct SARS-CoV-2 variant: in the context of governing its pathogenesis by defending the neutralizing antibody responses more efficiently than other variants of concern in the vaccinated and convalescent individuals, especially children (Ren et al. 2022; Shah and Woo 2021; Zhou et al. 2022). Moreover, the point mutations at the E484 residue site of RBD-S1-Omicron play a central role in alleviating the neutralizing antibody interactions with the Omicron facilitating its virulence in the immunized population (Sun et al. 2022). Similarly, the other noticeable point mutations shown in **Table 1** at the RBD-S1 of Omicron also contributed to its virulence by tackling the host-immune responses more effectively than other prevalent SARS-CoV-2 variants, affecting younger children and adolescents with or without vaccination (Sun et al. 2022; Wang et al. 2022b).

Table 1: Details of Omicron mutations attributing to its virulence and uncontrolled outbreak in European children

S. No	Types of RBD-S1 point mutations of Omicron	Mechanism by which RBD-S1-Omicron point mutations presides its outbreak and virulence	Effect of RBD-S1-Omicron point mutations in children	References
1	Q493R, N501Y, S371L, S373P, S375F, Q498R, and T478K	It improved the binding affinity of RBD-S1-Omicron with the human ACE2.	The mutations preside Omicron overrule the host immune antibodies responses aggravating its pathogenesis in younger children despite their immunization status.	(Dejnirattisai et al. 2022; Kannan et al. 2021; Kumar et al. 2022; Ledford 2021; Ren et al. 2022)
2	T478K; Q493K; Q498R; Q493R; G496S; Y505H; P681H; and Q954H	Strengthens the binding affirmation of RBD-S1-Omicron with the human ACE2 via altering its physicochemical characteristics from polar to more positively charged with the inclusion of K, R and H amino acid residues.	It profoundly defends the neutralizing antibody action induced by SARS-CoV-2-specific monoclonal antibodies that can establish its virulence in children exposed to SARS-CoV-2-specific monoclonal antibodies.	(Fang and Shi 2022; Mannar et al. 2022; Shah and Woo 2021)
3	N501Y, G339D, S371L, S373P, S375F, N440K, G446S, T478K, G496S, Q498R, K417N, S477N, E484A, Q493R, and Q498R	It augments the binding affinity of RBD-S1 Omicron with the host human ACE2.	It governs Omicron's unprecedented outbreak and virulence among all-age groups of children.	(Kumar et al. 2022; Ren et al. 2022)
4	K417N, N501Y, Y505H, E484A, Q493R, G477N, and Q498R	Responsible for developing the lowered binding free energy with the FDA-approved monoclonal antibodies.	Strengthen its defensive action against host human neutralizing antibodies responses by 14 times higher than the other virulent SARS-CoV-2 variants of concern governing its infiltration and pathogenesis in children.	(Chen et al. 2022a)
5	E484A; Q493K; and Y505H	Inflicts weaker interaction with the light and heavy chain residues, R96 in CDRL3 and R50 in CDRH2, and E012 and R104 in CDRH3 residue sites, respectively of the monoclonal antibody bamlanivimab.	Ameliorates its virulence and severity in pathogenesis in the Omicron-affected children, and therefore its outbreak from the patients subjected to the monoclonal antibody, bamlanivimab treatment.	(Shah and Woo 2021)
6	At the N-terminal domain of S1 protein: A67V; ΔH69-V70; T95I; G142D; Δ143-145; Δ211/L212I; ins214EPE	Regulate its escape from the immune responses of the neutralizing antibodies action induced by the SARS-CoV-2 vaccine and SARS-CoV-2 convalescent plasma.	Notable mutations contribute to Omicron interminable outbreak even among the children exposed to SARS-CoV-2 vaccines and SARS-CoV-2 convalescent plasma treatment.	(Fang and Shi 2022)

RBD, receptor-binding domain; S1-spike 1 protein; ACE2, angiotensin-converting enzyme receptor 2; SARS-CoV-2, severe acute respiratory distress syndrome corona virus 2; FDA, Food and Drug Administration; A, alanine; E, glutamic acid; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; N, asparagine; P, proline; Q, Glutamine; R, arginine; S, serine; T, threonine; V, valine; Y, tyrosine; ins, insertion of genes; P, proline; Δ, deletion of gene-protein nucleotides; CDRL3, complementary determining region light chain 3; CDRH2, complementary determining region heavy chain 2; CDRH3, complementary determining region heavy chain 3.

3. Omicron outbreak and its adverse clinical symptoms witnessed among European children

Omicron outbreak was severe in Austria, Belgium, Czech Republic, Denmark, France, Germany, Sweden, Switzerland, Italy, Netherlands, Norway, and the UK attributed to international travellers (Khandia et al. 2022; Thakur and Ratho 2021). With 100,000, the UK reported the highest number of Omicron cases per day. Following, France, Germany, the Netherlands and other European provinces recorded more Omicron cases (Singhal 2022).

In the UK, the first Omicron-linked mortality was reported on 13 Dec 2021, after which six Omicron case deaths were reported merely in six days span on 19 Dec 2021 (Agency 2021b; 2021c). In Denmark, Scotland, and UK: Omicron patients did not exhibit any adverse symptoms causing mortality with lowered incidence of hospitalization, unlike the Delta SARS-CoV-2 infected patients who developed fatal respiratory ailments with a higher incidence of hospitalization with increased mortality (Singhal 2022). Omicron of UK origin showed a higher proliferation efficiency with a growth timeline of 2 to 2.5 days to establish its virulence than the South Africa-Omicron variant requires about 3.38 days to colonize in the human host (Singhal 2022).

In-vitro laboratory studies affirmed Omicron virulence to be less severe than other prevalent SARS-CoV-2 variants in compliance with its diminished proliferation observed in the cultured human intestinal-epithelial Caco2 cells and lung Calu3 cells (Shuai et al. 2022). The point mutations: T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F spotted at the S2-furin cleavage site of RBD-S1-Omicron drastically attenuated the human protease TMPRSS2-induced cleavage at the S2 loci of RBD-S1, intervened its colonization in the cultured intestinal and lung cells compared with the other prevalent variants of SARS-CoV-2 family (Shuai et al. 2022). Moreover, these specific mutations: T547K, N764K, N856K, and N969K can hinder the infiltration of Omicron in the intestinal and lung cells *via* ameliorating the electrostatic interactions of S1 and S2 furin cleavage sites of the RBD-S1-Omicron absent in other prevalent SARS-CoV-2 variants (Shuai et al. 2022).

In concordance with the *in-vitro* inferences, *in-vivo* studies confirmed Omicron to be less virulent than the other variants of concern, including the Delta variant. Omicron nasal exposure showed a lowered lung infiltration with decreased mortality in the SARS-CoV-2 susceptible K18-hACE2 experimental mice model compared with the other SARS-CoV-2 variants of concern (Shuai et al. 2022). Similarly, *in-vivo* studies employing immunocompetent hamsters and murine models showed Omicron virulence to be negligible without causing severe upper and lower respiratory tract infections compared with other virulent SARS-CoV-2 variants in the respective animal study models (Diamond et al. 2021). Conclusively, laboratory studies performed both *in vitro* and *in vivo* showed Omicron pathogenesis less severe, lacking severe respiratory ailments than the Delta variant causing mortality augmented by critical respiratory conditions (Diamond et al. 2021; Shuai et al. 2022).

The adverse clinical symptoms of Omicron pathogenesis encompassed headache, cough, shortness of breath, fever, fatigue, sore throat, muscle/body ache, olfactory/gustatory dysfunction, and running nose, including the atypical symptoms like vomiting and diarrhoea resembling the disease symptoms of the patients diagnosed with other prevalent SARS-CoV-2 variants (Luxi et al. 2021; Mohiuddin and Kasahara 2022). The proposed incubation timeline to witness Omicron pathogenesis severity on the infected patients ranges between two and three days shorter than the incubation time of five days for patients exposed to other detrimental SARS-CoV-2 variants (Jansen et al. 2021; Singhal 2022).

Clinicians find Omicron virulence risky and alarming despite its diminished pathogenicity: as its symptoms correlate with the common influenza symptoms linked with upper respiratory tract infections with running nose, sore throat, headache, fatigue (moderate to severe), sneezing and night sweat witnessed in diverse age group populations, especially children (Jansen et al. 2021; Singhal 2022).

In the UK, Omicron infected patients in higher counts, particularly adolescents and children, were clinically diagnosed and treated under hospital care akin to the patients infected with the fatal Delta-SARS-CoV-2 variant (Ledford 2021; Thakur and Ratho 2021). Clinicians across Europe and worldwide had been alarmed to tackle the Omicron virulence with sheer diligence and effective therapeutic strategies amongst children commonly witnessed with a smaller nasal airway passage (Kozlov 2022). In the UK, Omicron contracted children below 1 yr were examined and treated under hospital care that provided oxygen supply and ventilator support on demand (Kozlov 2022).

In Sweden, Omicron infected children of n=3 (in counts) showed moderate to severe convulsions. Of three patients, a male patient aged 21 months of African origin showed convulsions for 15-20 minutes resembling epileptic conditions (Ludvigsson 2022). Alternatively, the remaining two patients of African and Swedish ethnicity aged three months and 14 yrs showed convulsions for a shorter timespan lasting 1-3 mins and 30-60 s, respectively (Ludvigsson 2022). Above all, the 14 yr old-Omicron contracted patient showed aggressive behaviour right after convulsion. This clinical observance finds a direct correlation between Omicron virulence and the convulsions in the Swedish pediatric patients (Ludvigsson 2022).

In another case study, Spanish children aged 7 yrs and 11 yrs tested positive for SARS-CoV-2 strain during the Omicron outbreak; were diagnosed with cerebral venous sinus thrombosis. Further, the study inference proposed to unveil the effect of Omicron pathogenicity on thrombosis incidence in the younger child population (Vallejo et al. 2022).

4. SARS-CoV-2 vaccines and monoclonal antibodies are likely to attenuate the Omicron outbreak and its virulence in European children

Omicron that sustains with the neutralizing antibody responses can infect the convalescent individuals more intensely than any other prevalent SARS-CoV-2 variants of concern (Hoffmann et al. 2022). The extraordinary RBD-S1 point mutations of Omicron have strengthened its virulence by 12 to 44-fold (**Table 1**), with which it shall merely bypass the host-immune reactions, including the neutralizing antibodies action triggered in the BioNTech-Pfizer (BNT162b2) immunized population or in SARS-CoV-2 convalescent patients compared with the Delta-SARS-CoV-2 variant (Hoffmann et al. 2022). SARS-CoV-2 vaccines have proven effective in constraining the outbreak of all detrimental SARS-CoV-2 variants, failed to attenuate the Omicron outbreak among the immunized population dominating the neutralizing antibodies responses induced by the heterologous ChAdOx1 (Astra Zeneca-Oxford)/BNT162b2 vaccines or by three doses of BNT162b2 vaccine (Hoffmann et al. 2022).

In the vaccinated cohorts from the UK exposed to the first two doses of homologous Oxford–AstraZeneca's ChAdOx1 nCoV-19 (n=22 subjects) or two doses of BNT162b2 vaccine (n=21 subjects): the serum neutralizing antibodies titer against Omicron markedly reduced by 59-fold-comparatively higher than the antibody titer reductions by 29.8-fold against the very first diagnosed Victoria-SARS-CoV-2 strain (Dejnirattisai et al. 2022). Additionally, the case study inferred the efficacy of Omicron in attenuating the neutralizing antibody titers production in the immunized population (Dejnirattisai et al. 2022). Hoffman et al. (2022) found that immunized individuals administered with the first two doses of BNT162b2 vaccine proven effective against other prevalent SARS-CoV-2 variants, are susceptible to Omicron pathogenesis. However, individuals in a higher percentage count of 80-88% (22-24 study subjects of 25-30 study subjects) exposed to a third booster dose of BNT162b2 vaccine above the first two doses of homologous BNT162b2/CoronaVac vaccines; developed adequate neutralizing antibody titers of ≥ 25.6 against Omicron (Cheng et al. 2022). Alternatively, individuals administered the first two doses of the whole virion vaccine (BBIBP-CorV) are vulnerable to Omicron virulence (Wang et al. 2022a). People

exposed to the third booster dose of BBIBP-CorV/heterologous protein subunit vaccine (ZF2001) generated sufficient neutralizing antibody titers against Omicron virulence (Wang et al. 2022a). Compared with the study subjects who administered the first two doses of each SARS-CoV-2 vaccine such as Moderna COVID-19 (mRNA-1273); BNT162b; and Ad26.CoV2.S, subjects administered with the third booster dose of mRNA-1273 alone showed sufficient neutralizing antibody titers against Omicron virulence (Garcia-Beltran et al. 2022). Furthermore, Garcia-Beltran et al. (2022) unveiled the booster dose administration of the mRNA-1273 vaccine effective in countering the Omicron virulence with sufficient neutralizing antibody titers equivalent to its effect in tackling the wild-SARS-CoV-2 (Wuhan) variant.

During the Omicron outbreak, the booster third dose administration of SARS-CoV-2 vaccines (post-vaccination duration of ≥14 days) have noticeably reduced the hospitalization of patients by 90% than the patients administered with two doses of vaccines (post-vaccination duration of ≥180 days) reduced hospitalization by 57% (Thompson et al. 2022). Comparatively, the booster dose exposure (in ≥14 days) during the Delta-variant outbreak has effectively reduced the hospitalization of patients by 94% compared with those administered with two doses (in ≥180 days), decreased hospitalization by 81% (Thompson et al. 2022). Overall, it is mandatory for all people, especially children across European nations immunized with the third booster dose of SARS-CoV-2 vaccines shown in **Table 2** than with the first two doses to defend or attenuate the Omicron virulence (Thompson et al. 2022).

In-vitro laboratory studies showed the Omicron-S1 protein to be resistant to these neutralizing monoclonal antibody actions: bamlanivimab, etesevimab, imdevimab, and casirivimab (Hoffmann et al. 2022). However, the Omicron-S1 protein infiltration via soluble ACE2 was effectively controlled by sotrovimab but not as effective as sotrovimab attenuated the D614G-B.1-S1-SARS-CoV-2 variant infiltration *via* soluble ACE2 (Hoffmann et al. 2022). A similar *in-vitro* study affirmed that sotrovimab effectively ameliorated the neutralizing antibody titers with a

Table 2: SARS-CoV-2 vaccines, monoclonal antibodies, pediatric vaccines and other therapeutic drugs find promising in tackling Omicron virulence and outbreak among European children

S. No	SARS-CoV-2 vaccines		Monoclonal antibodies		Pediatric vaccines		Therapeutic drugs	
	Types/dosage	Therapeutic effect	Types	Therapeutic Effect	Types	Therapeutic effect	Types	Therapeutic effect
1	BNT162b2-mRNA vaccine-third booster dose exposure	Developed sufficient neutralizing antibodies specific to Omicron (Hoffmann et al. 2022)	Sotrovimab	Effectively ameliorated the neutralizing antibodies production and action against Omicron in in-vitro set-up (Wang et al. 2022a).	Measles, mumps and rubella (MMR) vaccine	MMR sharing 30 homology amino acid residues (R389-K419 of measles virus fusion-F1 glycoprotein & A444-K473 of rubella virus-envelope (E1) glycoprotein) with the N-terminal domain of RBD-S1 protein Omicron can defend its virulence via ameliorating the neutralizing antibodies responses (Sidiq et al. 2020).	Remdesivir/hydroxychloroquine drug combinations (recommended by American Pediatric Society Infectious Disease Society Guidelines; Note: children allergic to remdesivir/hydroxychloroquine combinations would be treated with lopinavir/ritonavir drug combinations)	To tackle severe health ailments, including respiratory ailments inflicted by SARS-CoV-2 pathogenesis in children aged ≤12 yrs (Chiotos et al. 2020).
2	BBIBP-CorV-heterologous protein subunit vaccine (ZF2001)-/ third booster dose treatment	Developed adequate neutralizing antibody titers against Omicron pathogenesis (Wang et al. 2022a)	Monoclonal antibody targeting the N-terminal residue sites (5-7) of the RBD-S1 protein of SARS-CoV-2	It restored prolonged neutralizing antibody action against Omicron virulence (Wang et al. 2022a).	Bacillus Calmette-Guerin (BCG)	BCG can defend Omicron invasion and pathogenesis via enhancing the innate immune responses and non-specific immune responses akin to its therapeutic response exhibited against the virulence of *Candida albicans* and *Staphylococcus aureus* (Covian et al. 2019; Fatima et al. 2020; Gonzalez-Perez et al. 2021).	Remdesivir (recommended by the Italian Society of Pediatric Infectious Diseases)	To tackle SARS-CoV-2 virulence in severely affected child patients diagnosed with or without any renal/liver disorders (Venturini et al. 2020).
3	Moderna-COVID-19-mRNA-1273/third booster dose administration	Generated sufficient neutralizing antibody titers against Omicron virulence (Garcia-Beltran et al. 2022)	Cilgavimab	Established stable interaction with the modelled RBD-S1 protein of Omicron can exhibit prominent neutralizing antibody responses against Omicron virulence (Shah and Woo 2021).	Hepatitis A vaccine	Hepatitis A vaccine could attenuate the pathogenesis of SARS-CoV-2, especially severe respiratory ailments, via elevating the hepatitis A antibody titers in infants and younger children (Beric-Stojsic et al. 2020).	Immunomodulators: anakinra, dexamethasone, and tocilizumab; intravenous immunoglobulins; aspirin; and anticoagulants.	To treat severely ill SARS-CoV-2 affected children diagnosed with severe acute respiratory distress syndrome, and prolonged SARS-CoV-2 pathogenesis with elevated inflammatory cytokines production (Venturini et al. 2020; Younis et al. 2021).
4	SARS-CoV-2 vaccines in common of any modules (mRNA/Vector vaccines)/ third booster dose treatment	Conferred noticeable protection against Omicron virulence reducing the hospitalization percentage count to 90% in the Omicron affected patients (Thompson et al. 2022)	S2K146, S2X324, S2N28, S2X259, and S2H	Can proficiently defend the Omicron infiltration and pathogenesis via targeting these conserved antigenic protein sites-I, II, IV, and V of the SARS-CoV-2 virus family (Cameroni et al. 2022).	Common pediatric vaccines: Pneumococcal, Rotavirus, Diphtheria, Tetanus, Pertussis, Hepatitis B, *Haemophilus influenza*, and Meningococcal, including BCG and MMR.	It could attenuate the SARS-CoV-2 invasion and pathogenesis more effectively by stimulating the innate and adaptive immune responses than by ameliorating the cross-reactive neutralizing antibodies production and action, according to the in-vivo study inference in BALB/C mice (Kandeil et al. 2020).	Remdesivir/ dexamethasone drug combinations (recommended as life-saving drug combinations; Note: children develop allergic reactions to remdesivir/ dexamethasone drug combinations would be treated with tocilizumab/anakinra drug combinations)	To treat and cure critically ill SARS-CoV-2 affected children diagnosed with severe acute respiratory distress syndrome demanding oxygen and invasive ventilator support (Venturini et al. 2020; Younis et al. 2021).
5	SARS-CoV-2 vaccines recommended for younger children and adolescents: CoronaVac, and Comirnaty and Spikevax.	Proposed effective in tackling Omicron virulence via ameliorating the neutralizing antibodies responses/action (Han et al. 2021; Luxi et al. 2021).	-	-	-	-	Molnupiravir (MK-4482) and PaxlovidTM (PF-07321332)	Notable clinical drugs under trial that find promising in tackling SARS-CoV-2 pathogenesis and its uncontrolled outbreak (Fang and Shi 2022).

7-fold reduction against Omicron virulence compared with the wild pseudotyped WT (D614G)-SARS-CoV-2 variant (Wang et al. 2022a). The neutralizing antibodies activity of the monoclonal antibodies raised specifically to the RBD-S1-SARS-CoV-2 protein and SARS-CoV-2-antigenic supersites (5-24, 4-18, and 4-19), shown futile against Omicron (Wang et al. 2022a). Nevertheless, the monoclonal antibody specific to the N-terminal domain site (5-7) residues of the RBD-S1 protein of SARS-CoV-2 alone partially sustained its neutralizing antibody action against the Omicron virulence (Wang et al. 2022a).

Convalescent plasma treatment derived from earlier affected SARS-CoV-2 patients showed a reduced neutralizing antibody titer against Omicron with a 21-fold reduction compared with the neutralizing antibody titers measured against Wuhan-SARS-CoV-2 (WA1/2020) strain isolate (Zahra et al. 2022). Similarly, with the concentrated hyperimmune SARS-CoV-2 intravenous immunoglobulins treatment, the neutralizing antibody titers targeting Omicron were markedly reduced by 12-fold, higher than the fold reduction of 3.3-fold measured against the Delta variant (Zahra et al. 2022). Nonetheless, the intravenous immunoglobulin treatment proved effective against the Wuhan-SARS-CoV-2 (WA1/2020) variant with a 50-fold increase in neutralizing antibody titers (Zahra et al. 2022).

In summary, Omicron can merely evade the neutralizing antibody responses of the human-host that were shown effective against other detrimental SARS-CoV-2 variants. Moreover, neutralizing antibody activity induced in convalescent individuals or immunized populations that can effectively defend the invasion of other prevalent SARS-CoV-2 variants of concern remains inept in tackling Omicron virulence. Omicron pathogenesis can deteriorate the neutralizing antibody titers production stimulated under any substantial clinical therapeutic strategies abided to attenuate the virulence of deleterious SARS-CoV-2 variants.

The RBD-S1-Omicron established a stable interaction with the ACE2 receptor is presided by the steady magnitude shift in the electrostatic potential energies. Indeed, this could be the likely underlining factor of the interminable outbreak of Omicron among the human population, especially children expressing higher ACE2 than the adults and old population (Shah and Woo 2021). Structural protein elucidation of the modelled RBD-S1-Omicron bound SARS-CoV-2 specific monoclonal antibodies complexes revealed a marked reduction in their electrostatic potential energies, affirming its fragile binding affinity (Shah and Woo 2021). Of all FDA-approved SARS-CoV-2 specific monoclonal antibodies that exhibited lowered electrostatic potential energy with the RBD-S1-Omicron, the cilgavimab (AZD1061) monoclonal antibody showed a firm binding affirmation for the modelled RBD-S1-Omicron with a moderately reduced electrostatic potential energy compared with the wild RBD-S1-SARS-CoV-2 variant (Shah and Woo 2021). The RBD-S1 point mutations: E484A; Q493K; and Y505H of Omicron are crucial in refraining its interactions with bamlanivimab at these respective light and heavy chain residues sites-R96 in CDRL3; R50 in CDRH2; E012 and R104 in CDRH3 of bamlanivimab (Shah and Woo 2021). Sotrovimab that can effectively neutralize the virulence of RBD-S1-Omicron showed a steady binding affinity with the S1 protein of Omicron augmented with the appropriate salt bridge formations at its CDRH3 site. Following, this crucial salt bride formation has backed up the weaker interaction established between the RBD-S1-G339D mutant residue site of Omicron and the CDRH3-Y100 residue site of sotrovimab, ameliorating its stable interaction with the S1 protein of Omicron and its neutralization action (Shah and Woo 2021). Alike sotrovimab, studies proponed cilgavimab to defend Omicron virulence efficiently with its profound neutralization antibody action (Shah and Woo 2021). However, clinical studies remain inadequate to assure the neutralizing antibody action of cilgavimab against the Omicron invasion and virulence. Accompanying sotrovimab and cilgavimab, S2K146, S2X324, S2N28, S2X259, and S2H monoclonal antibodies (**Table 2**) can effectively defend the Omicron virulence by targeting these conserved antigenic protein sites-I, II, IV, and V of SARS-CoV-2 virus family (Cameroni et al. 2022).

5. Pediatric vaccines, therapeutic drugs, and other clinical strategies proponed to tackle the Omicron outbreak in European children

Children in all age groups starting from < 1 yr to 18 yrs are highly susceptible to Omicron virulence in concordance to other SARS-CoV-2 variants of concern (Maltezou et al. 2020). They can merely contract the SARS-CoV-2 viruses from their immediate family members, especially from the adults: as confirmed by a case study wherein 125 children of the total 132 child patients contracted the SARS-CoV-2 virus from the adults of their household crew (Maltezou et al. 2020). In common, SARS-CoV-2 infected children appear asymptomatic, but a few child patients developed mild adverse symptoms irrespective of the type of SARS-CoV-2 variants or their virus load (Dhochak et al. 2020; Maltezou et al. 2020).

Adults are more vulnerable to SARS-CoV-2 virulence than children who showed fatal respiratory ailments because of the diminished ACE2 expression, lacking ACE2 regulatory control over the ACE2-dependent capillary leak and inflammation (Dhochak et al. 2020). Children in common can tackle the SARS-CoV-2 virulence more efficiently than the adults due to the following clinical factors: steady innate immune responses induced by the early childhood vaccines and exposure to other viral infections; healthy alveolar epithelial cells that can revitalize swiftly from their deteriorating state; devoid of co-morbidities, including obesity and smoking (Dhochak et al. 2020). Nevertheless, children with genetic disorders and other inborn health ailments could suffer from severe health impairments upon SARS-CoV-2 invasion.

Across UK borders, central London reported the highest number of Omicron cases than other localities, including school-going children aged from 5 to 14 yrs (Agency 2022). Until 29 Dec 2021, about 27 Omicron case deaths were reported in the 28 days interval of diagnosis (Agency 2022). Omicron case deaths were widely reported in the age group of 41-99 yrs, especially in the unvaccinated population in the incubation time of 5 days (after diagnosis) of the proposed 0-14 days of Omicron virulence (Agency 2022). Although Omicron contracted children from the UK developed mild symptoms, child patients in huge counts were examined and hospitalized with supportive oxygen supply and ventilators upon necessary conditions (Ledford 2021; Thakur and Ratho 2021). Indeed, this unprecedented outbreak of Omicron among younger children across Europe terrified the clinicians, presuming this contagious variant to infect a larger group of younger children with recurrent virulence and higher hospitalization rates in the European nations (Health Professionals 2022; Singhal 2022).

Pediatric vaccines such as measles, mumps and rubella (MMR) vaccine could vehemently defend the Omicron virulence with its profound neutralizing antibodies action in the younger children population (Sidiq et al. 2020). About 30 homology amino acid residues of each measles virus-fusion (F1) glycoprotein (R389 to K419) and rubella virus-envelope (E1) glycoprotein (A444 to K473) have mutually shared with the RBD-S1-Omicron at its N-terminal domain. These mutually shared homology peptide residues of the live-attenuated MMR vaccine can markedly elevate the neutralizing antibody titers and their responses against the RBD-S1 of Omicron among the MMR vaccinated child population (Sidiq et al. 2020).

SARS-CoV-2 contracted patients among the MMR vaccinated cohorts from Italy, Germany, and Spain showed severe health ailments: but the elevated rubella IgG antibodies raised specifically to SARS-CoV-2 virulence could undermine its pathogenesis in the vaccinated cohorts (Beric-Stojsic et al. 2020; Young et al. 2020). To have any pronounced effect on Omicron virulence by MMR vaccine, it is necessary to have the mutual 30 homology amino acid residues spotted at the N-terminal domain of the SARS-CoV-2 strain remain unaffected by the Omicron mutations (Fang and Shi 2022). Notably, the gene annotation study affirmed that there are not effective point mutations witnessed at the aforementioned-MMR shared 30 homology residue sites in the N-terminal domain of Omicron, presuming it to be unaffected (Fang and Shi 2022). Instead, it possesses mutation at these N-terminal residues

sites, A67V; ΔH69-V70; T95I; G142D; Δ143-145; Δ211/L212I; ins214EPE that presides its escape from the neutralizing antibodies action induced by SARS-CoV-2 vaccines and SARS-CoV-2 convalescent plasma (Fang and Shi 2022). Henceforth, the neutralizing antibody titers concentering the antigenic 30 homology residues can effectively attenuate Omicron pathogenesis in MMR vaccinated children.

Bacillus Calmette-Guerin (BCG) vaccine induces acquired immunity against mycobacterium tuberculosis in early childhood and lasting until adulthood can defend the SAR-CoV-2/Omicron virulence with its profound innate immune responses in the younger children (Gonzalez-Perez et al. 2021; Vashishtha 2021). SARS-CoV-2 linked mortality was higher in the countries like Italy that abandoned the BCG vaccine administration in the children than in Japan which accredited BCG vaccine administration since 1947 (Beric-Stojsic et al. 2020). Similarly, higher SARS-CoV-2-related mortality was reported across US provinces such as New York, Illinois, Alabama and Florida: that banned BCG vaccine administration, compared with the Pernambuco, Rio de Janeiro, and Sao Paulo provinces in Brazil, and Mexico City that approved BCG vaccine administration in early childhood (Beric-Stojsic et al. 2020). Above all, there are no noticeable benefits witnessed with BCG vaccine administration in countering SARS-CoV-2 virulence among the adult participants aged 35-41 yrs than those without BCG administration (Hamiel et al. 2020).

BCG, a live attenuated tuberculosis vaccine that prevents infiltration of *Mycobacterium tuberculosis via* acquired immunity in early childhood, failed to bestow protective-adaptive immunity against pulmonary tuberculosis in adulthood (Covian et al. 2019; Fatima et al. 2020). This could be the likely reason the adults administered with BCG vaccine during childhood cannot produce any noticeable adaptive immune responses against the SARS-CoV-2 virulence (Pepin et al. 2021). Moreover, BCG vaccine administration that can trigger innate immunity coupled with non-specific immune responses against detrimental pathogens like *Candida albicans* and *Staphylococcus aureus* could defend the SARS-CoV-2 virulence, including Omicron in the same module (Covian et al. 2019; Fatima et al. 2020; Gonzalez-Perez et al. 2021). Clinical research studies are insufficient to exemplify the protective immune action of the BCG vaccine augmented with non-specific innate immune responses engaging immunoregulatory monocytes, macrophages, natural killer cells, and dendritic cells against SARS-CoV-2/Omicron pathogenesis among the BCG vaccinated children (Vashishtha 2021).

In another interesting case study, an infant (< 1 yr) diagnosed with lowered sera maternal hepatitis A antibody titers was prone to suffer from severe respiratory ailments of SARS-CoV-2 virulence (Beric-Stojsic et al. 2020). The study inferred that sustaining adequate hepatitis A antibody titers is crucial in preventing the fatal lung infiltration of SARS-CoV-2 variants causing severe respiratory impairments in infants (Beric-Stojsic et al. 2020).

An *in-vivo* study using BALB/C mice showed the pediatric vaccines BCG, pneumococcal, rotavirus, diphtheria, tetanus, pertussis, hepatitis B, *Haemophilus influenzae*, meningococcal, measles, mumps, and rubella inefficient to spawn adequate neutralizing antibody titers until seven weeks after vaccination against SARS-CoV-2 virulence (Kandeil et al. 2020). In compliance with this study inference, the pediatric vaccines (**Table 2**) can retaliate well against the SARS-CoV-2 invasion/virulence *via* stimulating the innate/adaptive immune reactions than by enhancing the neutralizing antibody titers production and action (Kandeil et al. 2020).

Children aged 5-11 yrs subjected to BNT162b2-SARS-CoV-2 vaccine clinical phase two and three trials showed elevated neutralizing antibody titers akin to the adult subjects (aged 16-25 yrs) with a geometric mean ratio of 1.04 within a month after vaccination with two doses (at each 10 μg dose concentration) completion-administered in two intervals (in 21 days gap) (Walter et al. 2022). During this trial, none of the immunized children showed any adverse reactions of the BNT162b2 vaccine, but three of them contracted the SARS-CoV-2 virus with the onset of diagnosis ≥7 days(Walter et al. 2022).

Collectively, the clinical trial showed that BNT162b2 vaccine administration of two 10-μg doses within 21 days was safer, reliable, and pertinent with higher immunogenicity to defend the SARS-CoV-2 virulence from causing any deleterious clinical symptoms, including respiratory ailments on the 5-11 yrs old children group (Walter et al. 2022).

In a similar clinical phase-BNT162b2 vaccine trial that employed adolescent children aged 12-15 yrs, the study participants spawned adequate neutralizing titers with the measured 50% neutralizing antibody titers-geometric ratio 1.7 in proportionate to the antibody titers measurements ratio of adult participants aged 16-25 yrs (Frenck et al. 2021). In this trial: the adolescent children showed mild adverse reactions such as headache and fatigue to the BNT162b2 vaccine. The immunized adolescents without any prior case history of SARS-CoV-2 infection (symptomatic/asymptomatic) were not susceptible to SARS-CoV-2 virulence, monitored until ≥ 7 days after the second vaccination (Frenck et al. 2021). The above clinical vaccine trials using the mRNA-BNT162b2 vaccine tested on younger and adolescent children showed promising outcomes with sufficient neutralizing antibody titers to tackle the SARS-CoV-2 virulence, including the contagious Omicron outbreak in the younger children and adolescents across Europe (**Table 2**).

Children (aged 3-17 yrs) subjected to CoronaVac vaccine trials developed sufficient neutralizing antibody titers at 3.0 μg dose concentration than at 1.5μg dose concentration with moderate adverse reactions like pain at the injection site upon exposure to two doses administered within a 28 days interval (Han et al. 2021). Furthermore, a clinical trial using the CoronaVac vaccine (3 μg), deploying a larger population of younger children and adolescents, is in progress to study the effect of this vaccine in defending the virulence of SARS-CoV-2 variants with its profound immune responses (Han et al. 2021).

The European Medicines Agency has clinically approved two SARS-CoV-2 vaccines: Comirnaty (on 10 May 2021) and Spikevax (in July 2021), to alleviate the outbreak of SARS-CoV-2 variants, including Omicron, in the children age groups of 12-15 yrs and 12-17 yrs, respectively (Luxi et al. 2021). Unlike the adults and the older population, SARS-CoV-2 virulence is not a major life threat to children commonly diagnosed with mild health ailments over the deleterious adverse symptoms witnessed in a larger population of SARS-CoV-2 infected adults and aged people with co-morbidities (Luxi et al. 2021). Henceforth, immunization of younger children and even adolescents, appeared more trivial than vaccinating adults and the older population. Nevertheless, clinical experts and researchers find vaccination crucial among younger children and adolescents to prevent the long-term SARS-CoV-2 effects such as multiorgan inflammation disorder or Kawasaki disease in their earlier stages of development (Feldstein et al. 2021; Levin 2020; Toubiana et al. 2020). In the US, children aged ≥ 12 yrs must get immunized against the SARS-CoV-2 virus to control the outbreak of diverse SARS-CoV-2 variants, including Omicron or any future SARS-CoV-2 variants (Luxi et al. 2021).

By inferring the emerging case reports on the adverse side effects of mRNA vaccines causing pericarditis and myocarditis in younger adults the UK Joint Committee on Vaccines and Immunization has curtailed the immunization of vulnerable children and adolescents (aged ≥12 yrs) showing severe neurological ailments, Down's syndrome, immunocompromised and cognitive impairments using mRNA vaccines (Luxi et al. 2021).

Remdesivir coupled with anti-viral inhibitors and immunomodulators has been prescribed to treat critically ill SARS-CoV-2 infected children (Younis et al. 2021). To treat SARS-CoV-2 infected children aged ≥12 yrs, remdesivir and hydroxychloroquine have been clinically recommended, as per the American Pediatric Society Infectious Disease Society guidelines (APSIDS) (Chiotos et al. 2020). In the preliminary stages of SARS-CoV-2 medications, hydroxychloroquine finds promising in controlling the SARS-CoV-2 pathogenesis in children aged ≤12 yrs. Clinicians

prescribed hydroxychloroquine over azithromycin and ribavirin, and lopinavir/ritonavir drug combinations to treat SARS-CoV-2 pathogenesis in children at the initial stages in compliant with the APSIDS guidelines (Chiotos et al. 2020).

In late September 2020, the Italian Society of Pediatric Infectious Diseases clinically approved the use of remdesivir in critically ill SARS-CoV-2 children without any renal or liver impairments (Venturini et al. 2020). Child patients allergic to remdesivir have been subjected to hydroxychloroquine and lopinavir/ritonavir drug combinations to tackle the SARS-CoV-2 pathogenesis (Venturini et al. 2020; Younis et al. 2021). Immunomodulators such as anakinra, dexamethasone, and tocilizumab have been clinically recommended to treat severely ill SARS-CoV-2 children suffering from severe acute respiratory distress syndrome, prolonged SARS-CoV-2 pathogenesis, and elevated inflammatory cytokines (Venturini et al. 2020; Younis et al. 2021). Remdesivir and dexamethasone have been solemnly used as life-saving drugs to treat the SARS-CoV-2 children with severe respiratory ailments placed on oxygen and invasive ventilator support (Venturini et al. 2020; Younis et al. 2021).

SARS-CoV-2 pathogenesis showed promising results in attenuating the SARS-CoV-2 virulence effectively, expecting it to be accessible soon in the drug market to manage the unprecedented outbreak of SARS-CoV-2 variants, including Omicron (Fang and Shi 2022).

6. Conclusion

Children across European provinces affected by Omicron virulence are vulnerable to any future SARS-CoV-2 variants of concern. Therefore, SARS-CoV-2 vaccines (with third booster dose administration), pediatric vaccines and other therapeutic agents, including drugs and monoclonal antibodies discussed in this review (Fig.), can be clinically abided to treat Omicron contracted children showing moderate to severe ailment across European nations.

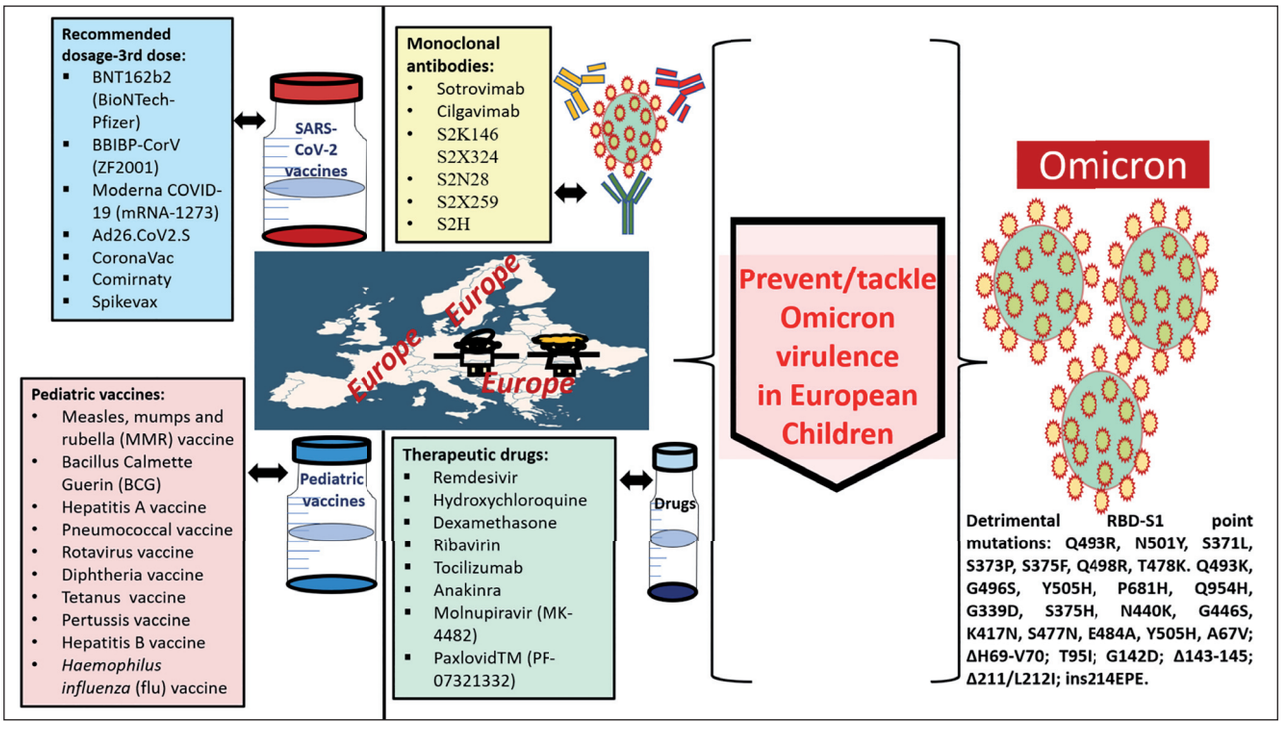

Fig.: Therapeutic modules encompassed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines (with the appropriate dosage), pediatric vaccines, monoclonal antibodies and clinical drugs that find promising in preventing/tackling the uncontrolled outbreak cum virulence of Omicron in European children. A, alanine; E, glutamic acid; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; N, asparagine; P, proline; Q, Glutamine; R, arginine; S, serine; T, threonine; V, valine; Y, tyrosine; ins, insertion of genes; P, proline; Δ, deletion of gene-protein nucleotides.

In the proclaimed guidelines of Children's Hospital of King's daughter, Southeastern Virginia, child patients susceptible to detrimental allergic reactions to remdesivir/dexamethasone drugs that include multiorgan dysfunction; demand vasopressor support; increased alanine transaminase levels; and severe renal impairments are refrained from getting exposed to these drugs (Younis et al. 2021). Tocilizumab and anakinra are the alternative drugs prescribed over remdesivir/dexamethasone to treat SARS-CoV-2 pathogenesis in children allergic to the remdesivir/dexamethasone or during its stock deficit (Venturini et al. 2020; Younis et al. 2021). Clinical treatment with intravenous immunoglobulins, aspirin and anticoagulant exposure was found effective in tackling the multiorgan inflammation disorder in SARS-CoV-2 affected children (Venturini et al. 2020; Younis et al. 2021). The clinical trial that tested the novel antiviral drugs, molnupiravir (MK-4482) and Paxlovid™ (PF-07321332) against

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