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Review

A Systematic Review on the Emergence of Omicron Variant and Recent Advancement in Therapies

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Abstract:
With the ongoing COVID pandemic, the emergence of a novel omicron variant in November 2021 has chaos the world. Despite mass vaccination, this omicron has spread rapidly raising concerns around the globe. The Omicron variant has a vast array of mutations as compared to another variant of concern with overall 50 mutations where 30 mutations are present in its spike protein. This mutation has led to immune escape and more transmissibility compared to other variants, including Delta. A cluster of mutations (H655Y, N679K, and P681H) present at the omicron spike protein could aid in transmission. Currently, no virus-specific data are available to predict the efficacy of anti-viral and mAbs drugs. However, two monoclonal antibody drugs: Sotrovimab and Evusheld are authorized for emergency use in COVID patients. This virus is not fading away soon. The easiest solution and less expensive measure to fight against this pandemic are following COVID appropriate protocols.There is need to strengthen the level of research for development of potential vaccines and anti-viral drugs. It is also important to monitor and expand genomic surveillance to keep track of the emergence of new variants thus avoiding the spread of new diseases worldwide. This article highlights the emergence of omicron and vast number of mutation in its protein. In addition, recent advancement in drugs approved by FDA to treat COVID patients has been listed and focused in this paper.

Keywords: Emergence of Omicron and its mechanism; mutation and sub-lineages; Monoclonal antibodies; Antiviral drugs

Introduction:

The emergence of this ongoing pandemic coronavirus has devastated the world. It's been almost two years since the COVID was detected in Wuhan, China. As of 14 February 2022, more than 5.81 million deaths and 412 million confirmed cases have been detected worldwide, making it one of the deadliest viruses in history [1]. This virus has undergone several recombination and mutation over the past years leading to the emergence of a vast array of new variants of concern (VOC) and variants of interest (VOI) resulting in high global health alerts and panics.

While the world has been tackling with delta variant, the emergence of the novel Omicron variant in December 2021 has taken the world by storm [2]. The emergence of Alpha, Beta, Gamma, Delta SARS-CoV-2 variants, and Omicron (B.1.1.529) variant classified as VOC by WHO on 26 November 2021, has become dominant in many countries since January 2021 (Table 1). The novel omicron variant has a higher mutation as compared to other variants of concern. This has led to a higher rate of infection, higher transmission, and immune escape COVID vaccine resulting in rapid spread worldwide in a shorter period. As per WHO, this novel variant also enhances immune or diagnostic evasion, disease severity, and significant transmissibility. In addition, it poses a detrimental impact on epidemiology and increased variability in clinical presentation. The four most common symptoms of an Omicron infection according to the US Centers for Disease Control and Prevention are cough, fatigue, congestion, and runny nose [3]. Although the omicron variant seems more contagious than

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previous variants as per data available, early findings suggest less hospitalization for Omicron-positive patients as compared to the Delta variant. However, it should not be taken likely. Thus, precautionary measures should be taken such as avoiding crowded spaces, social distances, and wearing masks to prevent the spread of infection [4]. The SARS-CoV-2 Interagency Group (SIG) evaluates and classifies the novel variant as a Variant of Concern (VOC) based on the cases detected in various countries, travel history, rate of transmission, a mutation in the spike protein, and as per data available for other variants. It is also evaluated based on a reduction in the effectiveness of vaccines and monoclonal antibody treatments. This SIG group track and evaluate the emergence of new virus and actively monitor the potential impact of vaccines, therapeutics, and diagnostics against SARS-CoV-2 [5]. This review article highlights the emergence of the Omicron variant, its mechanism, and a vast array of mutations at spike protein which enhances transmissibility and immune escape from the vaccine. The potential impact on diagnosis, the various advancement in anti-viral drugs, and therapeutics treatment to tackle the ongoing COVID-19 pandemic has also been discussed.

The emergence of omicron (B.1.1.529) and its sub-lineage:

South Africa was the first country to detect the novel variant of SARS CoV-2 from a specimen collected on 11 November and 14 November 2021. The first omicron variant was reported to WHO by the South African Department of Health on 24 November 2021 [6]. On November 25, 2021, the United Kingdom Health Security Agency designated the B.1.1.529 omicron variant as a Variant Under Monitoring (VUI-21-NOV-01) and just one day later it was designated as a Variant of Concern by the WHO which was later named OMICRON [7, 8]. The rapid spread of this variant in South Africa and surrounding countries alarmed WHO. This could be due to the high rate of mutation and replication in the Omicron variant as compared to other variants of concern. However, it is less severe than the previous variant as per the report [9, 10]. After the announcement of Omicron by WHO, three days later on 29 November 2021, this novel variant was detected in Australia, Belgium, Canada, Czech Republic, Denmark, France, Germany, Italy, Netherlands, and the United Kingdom [11]. And within a very short time, this new variant has spread to over 108 countries with nearly 1.5 lakh positive individuals and 26 deaths; dated December 25, 2021, creating an alarming situation worldwide [12]. The emergence of the omicron variant in South Africa has also revealed a vaccination gap between the richest and the poorest. Whilst an average of 60% population of Europeans has achieved vaccination, it is appalling to see that only 5-10% of African pollution has been vaccinated [13] and this could be one of the major factors contributing to the emergence of VOC. Japan also reported the first two cases of novel Omicron variant at the end of November 2021 among international travelers returning from the country with undetected omicron [14]. India reported the first two cases of omicron on 3rd December 2021 among international travelers [10]. In Germany, two suspected confirmed cases of the new omicron variant were first reported on 27 November 2021 and as the New Year begins, this novel Omicron became one of the most dominant variants in Germany despite protective measures at the initial stage on January 2022 [15, 16]. This new variant has been spreading worldwide and has been reported in 180 countries as of 4th February 2022. As of 11 February 2022, the UK reported a maximum number of Omicron cases (422,993) followed by the USA (359,236), Denmark (69,789), Germany (48,866), Canada (30,687), and France (27,487), while an increasing number of cases can be seen on daily basis in many other countries [17]. Jansen et al. [18] reported that omicron has a shorter incubation period than the previous variant with similar clinical symptoms. Preliminary data conducted by the National Institute of Infectious Diseases shows a high viral load three to six days after the onset of symptoms [19].

As the omicron variant continues to evolve and mutate, new sequences (sub-lineages) of the omicron variant were reported by WHO in December 2021 namely: BA.1, BA.2, and BA.3 [20]. Over the past two months, BA.1 variant has escalated globally. However, in the last weeks of January 2022, the BA.2 sub-lineage has increased internationally and has already become dominant in Denmark. As of 11 February 2022, BA.2 had been detected in at least 70 countries and 44 U.S. states as per data uploaded in GISAID and a total number of 55,404 sequences in the BA.2 lineage have been detected since the lineage was identified [21,22]. As per a recent preprint uploaded in medRxix [23], it was concluded that Omicron BA.2 is more dominant and transmissible than the parent omicron variant (BA.1). It possesses immune-escaped properties among vaccinated individuals; however, it does not increase its transmissibility to vaccinated individuals with breakthrough infections. India is another country where BA.2 is rapidly replacing the Delta and Omicron BA.1

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variant as per the report [24]. BA.2 Variant is not something to be worried about much but keeps an eye on as there is no specific data available regarding its severity. Data uploaded on GISAID suggest that BA.2 variant is increasing rapidly in proportion to the original BA.1 thus dominating the parent variant based on sequence frequency [25].

Mechanism of Omicron Variant:

Omicron has the highest number of mutations observed so far as compared to the other variant of concern (VOC). This variant contains more than 30 mutations in the spike protein which binds to the ACE2 receptor in the human cells for invasion and out of which, 15 modifications is observed in a Ribosomal Binding Domain (RBD) an area strongly associated with humoral immune evasion [26, 27]. The researchers from china constructed and studied the binding affinity between the complex structure of the human ACE2 protein and the receptor-binding domain (RBD) of Omicron variant Spike protein (S-protein) using atomistic molecular dynamics simulations. They observed that mutation in Ribosomal Binding Domain of SARS-CoV-2 Omicron variant resulted in higher binding affinity to human ACE2 protein. Thus increasing its transmissibility thereby causing possibilities of evading vaccine-induced antibodies [28].

There are two distinct mechanisms for the entry of SARS CoV-2 in a human cell: Cell surface Entry and Endosomal entry, where TMPRSS2-mediated S protein activation takes place at the plasma membrane and cathepsin-mediated activation takes place in the endolysosome at the cytoplasmic region respectively [29]. A researcher from Glasgow University in the UK demonstrated the replication process of different SARS CoV-2 variants and their mechanism in entering the human cell. An HIV pseudotype was evaluated for entry assay. The study reveals that Omicron, like pangolin CoV, uses the endocytosis pathway in entering human cells and is independent of TMPRSS2 present on the cell surface. This study was further supported by using drug inhibitors targeting either TMPRSS2 (Camostat) or cathepsins (E64d). As compared to another variant spike, the Omicron spike shows reduced syncytium formation thereby causing fewer lungs infection [30].

Mutations in omicron:

In November 2021, Omicron (B.1.1.529) emerged as a variant of concern. Wahid et al. [26] earlier reported the triplet mutation (K417N + E484K + N501Y) in Beta (B.1.351) and Gamma (P.1) variants which were highly transmissible leading to greater COVID-19 hospitalization, ICU admissions, and even deaths. Such mutations have increased the immune escape potential leading to a decrease in the neutralization of antibodies (such as Pfizer and Moderna vaccines). The omicron variant contains overall 50 mutations, with 30 mutations on the spike protein which include: A67V, del69/70, T95I, G142D, del143/145, N211I, del212/212, G339D, S371L, S373P, S375F, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F, of which 15 modification is located at the ribosomal Binding Domain (RBD) region [31, 32]. Cecylia et al. [28] conducted atomistic molecular dynamics simulations to study the binding interactions between human ACE2 protein and the receptor-binding domain (RBD) of Omicron Spike protein (S-protein). The analysis shows that the Omicron RBD binds more strongly to the human ACE2 protein than the original Wuhan strain. Most COVID -19 Strains contain at least one change from the original Wuhan sequence, D614G, altering the virus's ability to escape the immune response. N501Y is present in all VOCs, except the Delta variant [33]. Interestingly, Omicron's spike protein mutations such as D614G, N501Y, and K417N are found in some other variants of concern thus making the virus more infectious-a prospect that is very concerning.

Similarly, H655Y, N679K, and P681H mutations in omicron spike protein also found in Alpha and Delta variants could increase the transmission of the virus [34, 35]. It has the deletion at spike protein (Δ69-70) position 69–70, similar to the Alpha and Eta variants that lead to the S gene dropout or S gene target failure. This phenomenon may provide a useful proxy to measure the prevalence of Omicron. Rapid transmission of omicron variant across global could be due to the presence of these larger number of mutations in the spike protein unlike Delta variant and thus evading immune response [36]. However, this phenomenon does not apply to the BA.2 sub-lineage of the omicron variant as it does not contain the deletion at S: 69-70 and is S-gene target positive (SGTP) on PCR diagnostic assays [37]. Comparison and mutual sharing of spike protein mutations of the omicron sub-lineages; BA.1, BA.2, and BA.3 lineages are represented by a Venn diagram as shown in figure 1.

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The combination of N501Y + Q498R may increase binding affinity to ACE2, while other substitutions may lead to decrease in binding affinity to ACE2 in the Omicron spike protein. Kinases such as PI3K/AKT signaling are essential in SARS-CoV-2 entry. Based on molecular docking, Bexultan et al. [38] analyzed the interaction between the potential kinases and N501Y mutation and observed that N501Y mutation did not enhance binding to epidermal growth factor receptor (EGFR) due to the mutations. N501Y mutation containing lineages might become more infectious since several kinases are elevated in cancer patients. And therefore, additional care for cancer management should be taken into consideration. Mannar et al. [39] analyzed a Cryo-electron microscopy structure between spike proteins of omicron variant in complex with human ACE2. The structure depicts two additional new salt bridges and hydrogen bonds formed by mutated residues R493, S496, and R498 in the RBD with ACE2. This enhances other mutations such as K417N which is known to reduce ACE2 binding affinity to Spike protein. These strong interactions at the ACE2 interface may contribute to the rapid spread of the Omicron [40]. Zhuoming et al. [41] reported that E484K could escape neutralization by convalescent sera while S477N was resistant to neutralization by multiple mAbs, thus needing further investigation. The increase in binding affinity to the ACE2 receptor by N501Y could aid increase in transmission. The combination of N501Y and Q498R may also increase binding affinity even more; however, other substitutions in the Omicron spike protein are expected to decrease binding to ACE2. A cluster of mutations (such as H655Y, N679K, P681H) present at the S1-S2 furin cleavage site in the Omicron variant may increase spike cleavage and could aid transmission. N679K present at the furin cleavage site adds to the polybasic nature and is associated with an increase in transmission. P681H mutation (also found in Alpha) enhances spike cleavage, and could also aid transmission. At this position an alternate mutation (P681R) is found in Delta [42]. In India Surendra et al. [43] found a major mutation at the P681 position with an R (P681R) similar to Delta variant (B.167.2) of about 9.71% instead of the H (P681H) mutation. This variant is of considerable public concern, as it is increasing at a high rate in many countries, including the US, due to its increased transmissibility and immune evasion. In Nucleocapsid (N) protein region, the Omicron variant also possesses two additional mutations such as R203K and G204R (found in ancestral mutation) that enhance sub-genomic RNA expression and viral RNA binding with key host proteins thus increasing viral load [44, 45]. Phylogenetic analysis based on the prevalence of high mutation revealed that the Omicron is closely related to the Gamma (P.1) variant [46] and may possess similar characteristics at the molecular level [47].

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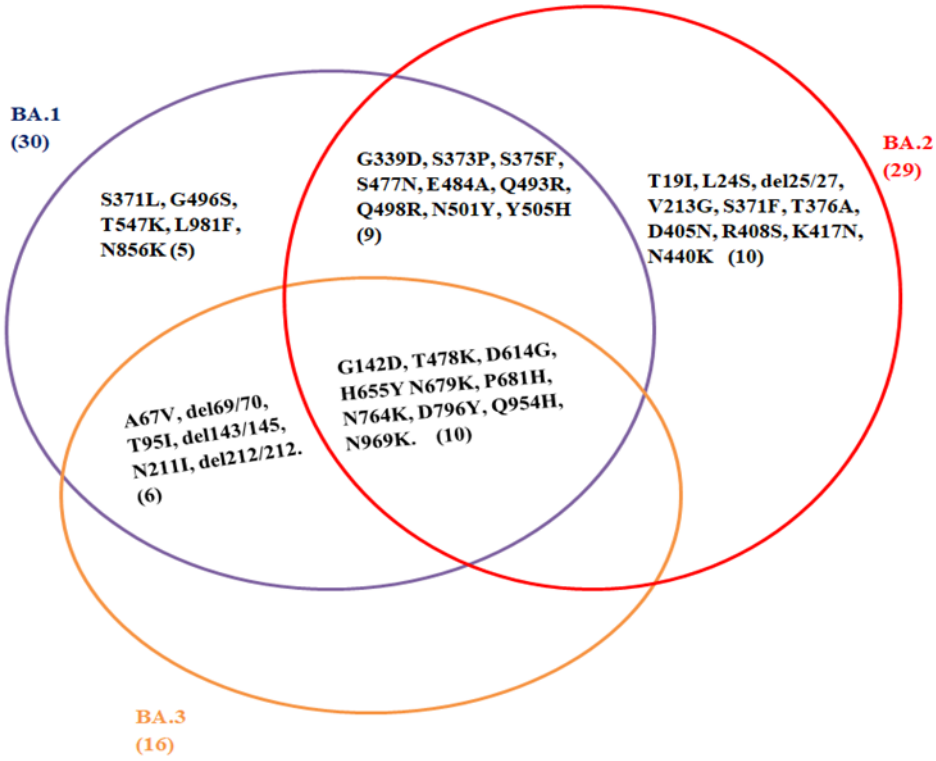

Figure 1: Comparison of spike protein mutation of omicron sub-lineage: BA.1, BA.2, and BA.3. (GISAID: https://www.epicov.org/epi3/frontend#58aca.) (Accessed on 10 February 2022)

Impact of Diagnosis on Omicron Variant:

The emergence of mutation in SARS Cov-2 has resulted in five SARS-CoV-2 variants namely: the Alpha, Beta, Gamma, Delta, and Omicron variants. World Health Organization has designated such variants as variants of concern [48]. This has resulted in investigating the performance of a potential impact on diagnosis. A rapid Diagnostic antigen test is cheap and offers quick results at the point of care when the viral load is high and hence provides utility in clinical and public health settings. The rapid test is approved in many countries including Australia, for self-testing [49]. However, they are less sensitive than the RT-PCR-based method [50].

Deerain et al. [51] evaluated ten commercially available rapid antigen test kits to check their diagnostic performance (sensitivity) among the Delta and Omicron variants. Overall they observed no sensitivity difference among the variants. The detection limit of all the kits for the Delta variant was 6.50 log10 copies per mL (Ct 25.4) and 6.39 log10 copies per mL (Ct 25.8) for the Omicron variant. Similarly, Puhach et al. [52] evaluated seven Ag-RDTs for their sensitivity to Omicron and compared them to other VOCs such as Alpha, Beta, Gamma, and Delta. A trend toward lower sensitivity for Omicron detection compared to the other VOCs was observed. As per the data retrieved on 28 December 2021(the Food and Drug Administration), it suggests that the Antigen test provides a rapid and does detect Omicron variant, but is not a very reliable or sensitive diagnostic testing option [53].

The Paul Ehrlich Institute (PEI) has also investigated and evaluated the sensitivity of 198 rapid antigen tests (Qualitative Lateral Flow Tests) using uniform sample material marketed in Germany until the end of January 2022. The current state of the art was defined as corresponding to a minimum sensitivity of 75% for the pools with Cq ≤25. However, the results do not allow any conclusions regarding the specificity of the tests [54]. Some studies have also demonstrated that up to 50% of the positive cases detected by Rapid test are false positives as compared to PCR diagnostics test. A recent small preprint study that has not been peer-reviewed found that the antigen test fails to detect the virus on day zero of 30 individuals who turn out to be COVID positive in the PCR test. The PCR test also indicated a higher viral load [55]. However, a study performed in

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January 2022 in California on 731 individuals shows that the Abbott BinaxNOW rapid tests could detect omicron as they did with other variants, especially when people have higher viral load and were symptomatic [56]. Abbott BinaxNOW Rapid Antigen Test can be a useful adjunct to RT-PCR testing for the detection of SARS-CoV-2 Infections [57].

The RT-PCR test is considered to be the ‘gold standard’ for detecting Coronavirus. In RT-PCR two or more spike genes are targeted, therefore there are chances to detect one of the genes in case of any mutation. Thus bringing its advantage to mark for omicron variant. Ever since the detection of SARS-CoV-2 in 2019, it has undergone a broad process of replication and mutation in the spike proteins and ribosomal binding domain generating a vast number of Variants of Interest (VoI) and Variants of Concern (VoC). Due to this mutation, a phenomenon called ' S gene dropout' or 'S gene target failure' has been reported. This vast mutation has jeopardized the reliability of currently used Diagnostic kits for detecting SARS-CoV-2 and hence requires a regular re-evaluation of commercially available kits based on emerging VOIs and VOCs [58]. The 'S gene target failure' is being targeted as a marker in identifying the omicron variant. However with the emergence of the new BA.2 Sub-lineage of omicron (which does not contain 69/70del in the spike protein), it cannot be considered as a marker for the presence of omicron and requires confirmation of Omicron by sequencing [59]. This phenomenon has been supported by Metzger et al. [60] where they obtained a piece of information and collected 39 assays most commonly used PCR tests in Switzerland and Liechtenstein targeting genomic loci such as the ORF1ab region, the RdRp gene, the S gene, the E gene, the N gene and, M gene. Only two assays showed S gene dropout for Omicron out of eight assays targeting the S gene. Hence gene sequencing data analysis is required to confirm the presence of Omicron.

Whole-genome sequencing of omicron with next-generation sequencing (NGS) might serve as a golden standard to detect SARS-CoV-2 variants despite being time-consuming and costly. It also requires large data processing. Fu et al. [61] compared and evaluated Allplex SARS-CoV-2 Master Assay and Variants I Assay (a direct PCR-based variant analysis) to detect HV69/70 deletion, Y144 deletion, E484K, N501Y, and P681H spike mutations with NGS for 115 samples and observed sensitivity of 98.7 % with the Master Assay and 100 % with the Variants I Assay. These assays can be utilized as a useful tool to rapidly monitor selected and updated VOCs in resource-limited settings. Currently, CDC is working to understand the new Omicron variant and the effectiveness of commercially available diagnostic tools and authorized medical countermeasures, such as vaccines and therapeutics against this variant, and providing technical support to monitor the epidemiologic and clinical features of novel variants [62].

Advancement in Therapeutics Drugs against Omicron variant.

The emergence of Covid-19 has led to the development of various repurposed and therapeutic drugs including antivirals and antibody drugs. FDA has authorized the use of these drugs for emergency purposes in COVID patients with serious illnesses as per panel recommendation. While many anti-viral drugs and mAbs are still under investigation and clinical trials.

The *In-vitro* studies performed by IGM Biosciences, Inc. indicate Novel Antibody IGM-6268 exhibits potential neutralizing activity against the Omicron variant and all other Variants of Concern and Variants of Interest [63]. Some of the recent advances in therapies that have been authorized for emergency use and are suitable for omicron are being discussed in this section (Table 2).

Immunomodulatory drugs:

Amid Omicron, WHO approves new Covid-19 treatments for hospitalized patients according to their disease severity. Arthritis drugs tocilizumab and sarilumab [64, 65] which have been found to have efficacy in the treatment of COVID patients with moderate-to-severe COVID-19 pneumonia have recently been approved by WHO [66]. Similarly, dexamethasone which is effective at reining in lung-damaging inflammation [67], and Baricitinib a Janus kinase (JAK) inhibitor are also approved by WHO for treatment in COVID patients as per Panel recommendation [68]. Recently studies have shown that dextromethorphan treatment was characterized by regulation of adaptive immunity and other specific local innate, however, it was not associated with the regulation of pro-inflammatory pathways in COVID-19 acute respiratory distress syndrome (CARDS) [69].

Antivirals therapy:

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Recently, the U.S. FDA issued an emergency use authorization (EUA) for Pfizer's Paxlovid (nirmatrelvir tablets and ritonavir tablets) for the treatment of COVID-19 patients with mild-moderate symptoms and those at high risk of progressing into severe illness. This should be prescribed immediately within five days after diagnosis of COVID-19 [70]. During biochemical assay nirmatrelvir drug has shown to inhibit the 3CL protease associated with the Omicron (B.1.1.529) variant [71]. *In-vitro* studies also suggest that Paxlovid has the potential to maintain plasma concentrations thus preventing omicron and other variants from replication.
Molnupiravir, an oral antiviral drug is a small molecule of the synthetic nucleoside derivative N-hydroxycytidine (NHC). It targets viral RNA polymerase and inhibits SARS-CoV-2 replication. It was granted EUA by the FDA's Antimicrobial Drugs Advisory Committee on December 23, 2021, for the treatment of COVID-19 [72].
The IV antiviral drug Veklury (remdesivir) was approved by the U.S. Food and Drug Administration (FDA) in 2020 for the treatment of COVID-19 in adult and pediatric patients and old age [73]. These three drugs; molnupiravir, remdesivir, and paxlovid have shown neutralizing activity against other variants of concern including the novel Omicron variant [74]. Many antiviral drugs such as Ivermectin, Interferons, Nitazoxanide, Hydroxychloroquine or Chloroquine and/or Azithromycin, Lopinavir/Ritonavir, and Other HIV Protease Inhibitors are still under evaluation for the treatment of COVID-19. All these drugs paved as new hopes to fight against the COVID-19 pandemic.

Monoclonal antibodies:

The emergence of Covid-19 has led to the development of various treatments. Monoclonal antibodies (mAbs) are a novel class of antiviral intervention [75]. MAbs target the Ribosomal Binding Domain (RBD) of the SARS-CoV-2 spike protein, which is highly mutated in the Omicron variant [76]. They are one of the most effective therapeutic strategies to neutralized viral replication. This has been shown proven in one of the experiments conducted in animal models where neutralizing mAb therapies reduces viral transmission [77].
Currently, four anti-SARS-CoV-2 mAb products; Bamlanivimab plus etesevimab, casirivimab plus imdevimab (REGEN-COV), sotrovimab and Tixagevimab plus cilgavimab (Evusheld) have been authorized by the Food and Drug Administration (FDA) for emergency used to treat COVID positive non-hospitalized patients who are likely to develop the serious disease at the later stage [78]. Bebtelovimab monoclonal antibody was approved recently [79]. Monoclonal antibodies such as Casirivimab plus imdevimab and Bamlanivimab plus etesevimab, which have shown effectiveness in the previous Variant of concern, have reduced neutralization in the Omicron variant [80].
Recently, Emi et al. [81] assessed the neutralizing activities of monoclonal antibodies using a live-virus focus reduction neutralization assay (FRNT) against the omicron variant and other VoC (Variant of Concern). Etesevimab, Bamlanivimab and Imdevimab did not neutralize omicron. Casirivimab showed reduced neutralization against omicron. COV2-2196 (tixagevimab), COV2-2130 (cilgavimab), and S309 (marketed as sotrovimab) retained neutralizing activity against the omicron variant. Thus there are two authorized monoclonal antibody treatments against omicron- Sotrovimab and Evusheld. Early reports also suggest that Bamlanivimab and C144-LS Antibodies have reduced efficacy against the Omicron variant. Based on early modeling, studies have shown Casirivimab plus Imdevimab (REGN-COV2), as well as the Rockefeller University antibody C135 to be effective against the Omicron variant [82]. Some of the Monoclonal antibodies authorized by the FDA for emergency use are listed below.
Bamlanivimab and Etesevimab: These mAbs bind at the overlapping sites in the spike protein receptor-binding domain (RBD) of SARS-CoV-2; blocking its attachment to the human ACE2 receptor.FDA has banned the use of these mAbs in some areas of the United State due to the progression of variant resistance [83]. However, the FDA has approved an Emergency Use Authorization (EUA) to allow the use of this mAbs injection to certain non-hospitalized adults and children and infants (≥ 2 years of age) who have mild to moderate COVID-19 symptoms with a risk of progressing to serious illness [84].
Casirivimab and Imdevimab mAb: These are recombinant human mAbs that prevents the entry of virus in human cell by targeting the spike protein of SARS-CoV-2. Food and Drug Administration (FDA) has authorized the use of these mAbs to treat mild to moderate SARS-CoV-2 positive adults and pediatric patients. It is also administered to patients above 65 years of age with medical chronic conditions. However, it is not

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authorized for hospitalized COVID patients with oxygen therapy [85]. Recently FDA has authorized not to administer these drugs due to the prevalence of Omicron [86].

Sotrovimab: This mAb targets an epitope region in the spike protein Ribosomal Binding Domain (RBD) that is conserved between SARS-CoV and SARS-CoV-2. This monoclonal antibody has been shown to neutralize Omicron Variant. However, it is not authorized to use for COVID-19 patients hospitalized with mechanical ventilation [87].

Tixagevimab plus cilgavimab: Tixagevimab and cilgavimab monoclonal antibodies bind to non-overlapping sites of the SARS-CoV-2 spike protein, preventing the interaction between virus and ACE2 receptor. FDA has approved an Emergency Use Authorization (EUA) to allow certain adults and children 12 years of age and older to receive this mAbs injection. The combination has shown to somewhat decreased neutralizing activity in *in-vitro* against the Omicron variant [88].

Bebtelovimab (LY-CoV1404): This mAbs has not been approved, but has only been authorized for emergency use by the Food and Drug Administration (FDA) for treatment of mild to moderate COVID-19 patients (≥12 years old) with a high risk of progressing to severe illness. It neutralizes the SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) thereby inhibiting the entry of the virus into a human cell. Bebtelovimab is active and has shown some neutralizing activity against other variants of concern including the Omicron Variant [79].Thus the abilities of all these monoclonal antibodies and anti-viral therapies to fight and neutralize Alpha, Beta, Gamma, and Delta VOCs including the novel omicron variant have paved a way for hope in the future to make a potential therapeutic and diagnostic intervention.

Discussion:

The emergence of the novel Omicron variant has chaos worldwide. Just after the announcement of omicron as a Variant of Concern (VoC) by WHO, this novel variant has already spread globally. This rapid spread of omicron has concerned global health. This is due to a high level of mutation; overall 50 mutations, with 30 mutations on the spike protein. This review gives an overall highlight concerning the emergence of the omicron, its vast array of mutations, the impact of Diagnosis to detect novel omicron variants, and the novel advancement in therapeutic drugs.

The omicron variant possesses a phenomenon called S gene dropout due to deletion of amino acid at spike protein position 69–70. This acts as a marker to measure the prevalence of the omicron during diagnosis. However, this phenomenon does not apply to the BA.2 sub-lineage of the omicron variant. A vast number of mutation and phylogenetic analyses revealed that the Omicron may possess similar characteristics Gamma (P.1) variant at the molecular level predicting that drugs suitable for gamma may equally work for novel omicron.

The recent advancement in Anti-viral drugs may rise as a new hope to stop the spread of this variant. Recent *in-vitro* studies indicated that Novel Antibody IGM-6268 exhibits potential neutralizing activity against the Omicron variant as well as other Variants of Concern and Variants of Interest. Interestingly, three drugs namely: molnupiravir, remdesivir, and paxlovid have been approved and authorized by the FDA for emergency use as it shows neutralizing activity against other variants of concern including the novel Omicron variant. This article has a limitation, as it lacks clinical data on the efficacy of mAbs and anti-viral drugs for the treatment of the patient with Omicron variant. Here we have only articulated mAbs and Anti-viral drugs authorized by FDA for emergencies used for COVID patients with severe illness.

It is almost inescapable for the emergence of a new variant as long as there is a loophole in one part of the world and is unprotected.

Conclusion and prospect:

It has been almost 2 years since the emergence of this COVID pandemic. Despite several measurements and protocols to control this virus, it has dominated the world. High efforts and mass vaccination campaign to restrain the spread of this virus has become baseless with the emergence of novel variant. This COVID-19 has escalated around the globe within a short period and the outcome is devastating with global health concerns and economic dropout. The emergence of a new variant of concern (VoC) every year with the accumulation of a large number of mutations is of concern. This vast array of mutations in SARS CoV-2 has recently given rise to the most mutated Omicron variant of SARS CoV-2. The emergence of mutation could be due to

inequitable access to vaccines and the transmission of virus from person to person. It is the nature of the virus to mutate. This novel omicron has shown to be ineffective for vaccine jab and requires booster dost. The hypothesis of epizootic transfer needs validation and should be thoroughly investigated before making any conclusion. At present, there is no specific data and evidence to get rid of SARS CoV-2. Moreover, the etiology of SARS CoV-2 is poorly understood. As of now, some anti-viral and monoclonal antibody drugs are being authorized by FDA for emergency use as per panel recommendation. This COVID -19 is not getting away this earlier and may remain forever. The only way to tackle this situation is to follow appropriate protocol and measurements as per WHO recommendations such as quarantine, keeping oneself hygiene, social distancing, wearing a mask, and vaccination. In addition, strengthening the level of research field for the development of potential vaccines and anti-viral drugs, and a proper strategy to tackle the situation in case of new variant should be evaluated at the global level. It is also very important to monitor and expand genomic surveillance to keep track of the emergence of new variants thus avoiding the spread of new diseases worldwide.

Author contributions:

CMC conceived the study and supervised all research. All authors agree to be accountable for all aspects of the work.

Declaration of Competing Interest:

None.

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Table 1: WHO designated SARS-CoV-2 Variants of Concern (VOCs): https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/ (Accessed 20 February 2022)

WHO Designation	Country first Origin	Pango Lineages	Variant Prevalence Countries as of 11 February, 2022.	GISAID	Next Strain	Mutation	Additional amino acid changes monitored
Alpha (18-Dec-2020)	United Kingdom, Sep-2020	9 Sub-lineages: B.1.1.7, Q.1, Q.4Q.5, Q.8, Q.7, Q.2, Q.6, Q.3.	United Kingdom (262,616)	GRY, GR/501Y.V1	20I/501Y.V1, 20B/501Y.V1	22 mutations (9 mutation spike protein, with deletion:del69/70, del144/144)	+S:484K +S:452R
Beta (18-Dec-2020)	South Africa, May-2020	B.1.351,B.1.351.3,B.1.351.2, B.1.351.5B.1.351.1	South Africa (6,885)	GH/501Y.V2	20H/501Y.V2	18 mutations (8 mutation at spike protein, with deletion:del241/243)	+S:L18F
Gamma (11-Jan-2021)	Brazil, November 2020.	23 Pango lineages currently associated with the Gamma variant.	Brazil (47,475)	GR/501Y.V3	20J/501Y.V3	23 mutations (12 mutation at spike protein)	+S:681H
Delta (11-May-2021)	India, Oct-2020	216 Pango lineages currently associated with the Delta variant	India (69,457)	G/452R.V3	21A/S:478K	29 mutations (8 mutation at spike protein, with deletion:del157/158)	+S:417N +S:484K
Omicron (26-Nov-2021)	South Africa, November 2021	BA.1,BA.1.1, BA.2BA.3	South Africa (4,930)	GR/484A	21K, 21L, 21M.	~50 mutations (30 mutations at s protein, with deletion: del69/70, del143/145, and del212/212.)	+S:R346K

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Table 2: List of Drugs which has been approved and authorized by FDA for Emergency use in COVID-19 patient. (Source: Medlineplus, medicalletter)

Drugs	Dosage	Method of Administration	Duration	Side Effect	Mode of Action	Efficacy of monoclonal antibodies/drugs against SARS CoV-2 Variants.	Reference
Bamlanivimab Plus etesevimab	700 mg (one vial) of Bamlanivimab and 1400 mg (two vials) of etesevimab	single Intravenous infusion	One-time dose right after COVID-positive test and within 10 days after the onset of infection symptoms	Bleeding, bruising, pain, soreness, or swelling at injection site	Binds to spike protein RBD of SARS-CoV-2.	Active against two SARS CoV-2 variant: Alpha and Delta.	[79, 80 84]
Casirivimab plus imdevimab (REGEN-COV)	600 mg of casirivimab and 600 mg of imdevimabis diluted together in 50, 100, 150, or 250 mL of normal saline at a maximum rate of 310 mL/hr (180 mL/hr if diluted in 50 mL).	Intravenous infusion or Subcutaneous injection	After a positive SARS-CoV-2 test result and within 10 days of COVID-19 symptom onset.	Pain, bleeding, bruising of the skin, soreness, swelling, or infection at injection site	Bind at different sites on the RBD of the spike protein of SARS-CoV-2.	Active against four SARS CoV-2variant: Alpha, Beta, Gamma, Delta, Omicron.	[80,82, 85]
Sotrovimab	500 mg of sotrovimab diluted in 50 or 100 mL of normal saline.	Intravenous infusion	After a positive viral test for SARS-CoV-2 and within 10 days of symptom onset	Rash (2%) and diarrhea (1%). Hypersensitivity reactions, including anaphylaxis,	Binds at the epitope sites on the spike protein and prevent membrane fusion after the virus binds to the human ACE2 receptor.	Active against the entire variant: Alpha, Beta, Gamma, Delta and Omicron.	[78,81,87
Tixagevimab plus cilgavimab	150 mg of each antibody is administered.	Intramuscular injection.	one time as two shots (one after another)	Headache (6%) and fatigue (4%).	Binds to non-overlapping region of the SARS-CoV-2 spike protein.	Active against the entire variant: Alpha, Beta, Gamma, Delta and Omicron.	[78,81,88

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Bebtelovimab	175 mg/2 mL vials.	Intravenous infusion	Treatment should be started within 7 days of symptom onset.	Rash, pruritus, and infusion-related reactions	Binds to the spike protein and prevents its attachment to the human receptor.	Active against the Omicron variant of SARS-CoV-2(Neutralize BA.1 and BA.2omicron variant).	[79]
Remdesivir (Veklury)	200 mg IV on day 1, followed by 100 mg once daily.	Intravenous infusion	Treatment duration is 5-10 days	Nausea, Hypersensitivity reactions.	Inhibits viral RNA-dependent RNA polymerase.	Active against omicron.	73,74]
Molnupiravir	800 mg every 12 hours.	Orally	Treatment should be started within 5 days of symptom onset.	Diarrhea, nausea, and dizziness.	Targets viral RNA polymerase, inducing mutagenesis and inhibiting SARS-CoV-2 replication.	Active against omicron.	[72, 74]
Paxlovid	300/100 mg (2 nirmatrelvir tablets and 1 ritonavir tablet taken together) twice daily.	Orally	Treatment should be started within 5 days of symptom onset	Dysgeusia, diarrhea, hypertension, and myalgia.	Inhibits the SARS-CoV-2 main protease (Mpro), preventing viral replication.	Active against entire SARS CoV-2 variant including, omicron.	[74]