



*Review Article*

## Insights into Viral Zoonotic Diseases: COVID-19 and Monkeypox

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**Abstract:** The onset of the COVID-19 pandemic in 2019 and the sporadic occurrences of monkeypox virus infections have presented substantial hurdles to global healthcare. The appearance of these viruses underscores the persistent menace of infectious diseases. Despite notable strides in medical breakthroughs, encompassing the discovery of novel therapeutics, vaccine advancements, and contemporary surveillance approaches, viral outbreaks persist, leading to millions of infections and fatalities. The consecutive nature of these outbreaks compels us to reassess the depth of our comprehension regarding how viruses transmit, their pathogenicity, and their remarkable adaptability, enabling swift survival. This sequence of events also prompts us to scrutinize the effectiveness of existing therapeutic options, the progress of vaccines, and monitoring procedures within the healthcare sector. This review aims to provide an overview of COVID-19 and monkeypox, delving into their pathogenicity, clinical features, treatment modalities, and challenges.

**Keywords:** COVID-19; monkeypox; infections; vaccines; challenges; SDG 3 Good health and well-being

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### 1. Introduction

Infections that are viral in origin have been occurring without much awareness since the start of recorded history and have previously been described as “plagues of unknown origin” by ancient Greeks and Romans <sup>[1]</sup>. Viruses are deceptively simple yet very intelligent organisms that come in the form of either RNA or DNA nucleic acid <sup>[2]</sup>. This adaptability allows viruses to deftly outmaneuver the human immune system, ensuring their survival and successful adaptation to diverse environments. The elusive nature of these microorganisms

renders containment a difficult challenge, culminating in the threat of widespread global infections.

The historical tapestry of pandemics unfolds with the Russian Flu, a pivotal moment in the late 18th century when the world faced the virulence of a possible virus, the A/H3N8, from 1889 to 1893 <sup>[1]</sup>. During this relatively brief yet impactful span of three years, the Russian Flu exacted a staggering toll, claiming the lives of approximately one million individuals across the globe <sup>[1,3]</sup>. This pandemic, stamped in the pages of history, serves as a distressing reminder of the profound human cost associated with viral infections. The Russian Flu, with its rapid global dissemination, underscored the vulnerability of societies to the whims of infectious agents and laid the groundwork for future endeavours in pandemic preparedness and response.

Spanish Flu, or the Great Influenza pandemic, struck the world after 25 years of Russian Flu, 1918-1920. The Spanish Flu of 1918, caused by the H1N1 influenza A virus, is one of the most devastating pandemics in recorded history. This global outbreak left an indelible mark on societies worldwide, claiming the lives of an estimated 50 million people <sup>[4]</sup>. This influenza A virus became the predecessor and evolved over the years, causing pandemic viruses that appeared in 1957 as H2N2, 1968 as H3N2, and 2009 as H1N1pdm <sup>[5]</sup>. Ebola, Nipah Virus, COVID-19, and Monkeypox are different virus outbreaks, each presenting distinct challenges in our modern world <sup>[6-14]</sup>.

Since 2019, the global community has been in a protracted struggle, contending with the far-reaching consequences of the Coronavirus (COVID-19), a severe respiratory illness attributed to the SARS-CoV-2 virus <sup>[15-17]</sup>. Throughout this period (2019-ongoing), COVID-19 has been a formidable force, surging in waves of infections across nations and significantly impacting public health, economies, and daily life. Moreover, in a narrative of ongoing adaptation and evolution, the virus has given rise to various genetic variants, each presenting distinct challenges regarding transmissibility, severity, and immune escape. The Omicron variant is the most recent addition to this spectrum of variants <sup>[18]</sup>.

While efforts like vaccines and control strategies have helped flatten the peak of the COVID-19 pandemic, a new concern has emerged: monkeypox. Monkeypox was previously endemic to African countries. It has emerged in different parts of the world, forcing the World Health Organization (WHO) to declare it a Public Health Emergency of International Concern in July 2022 <sup>[19,20]</sup>. This demonstrates that even with cutting-edge investigations, surveillance, treatment, and vaccine development, we find ourselves continuously battling against newly emerging viruses, which questions our current understanding of viruses. Hence, this review article aims to shed light on the recent virus outbreaks, specifically COVID-19, emphasizing the Omicron variant and monkeypox, its pathogenicity, clinical features, treatment, and challenges.

## 2. Outbreaks of Omicron variant and monkeypox

### 2.1. Omicron variant

Coronaviruses have caused multiple life-threatening pandemics, with the first one being between 2002-2003, led by Severe Acute Respiratory Syndrome (SARS), followed by Middle Eastern Respiratory Syndrome (MERS) in 2012, and most recently, at the end of 2019, SARS-CoV-2 also known as COVID-19 [21-23]. COVID-19, a zoonotic virus, was first discovered in China in early December 2019 [11, 24, 25]. It was then declared by WHO a Public Health Emergency of International Concern on the 30<sup>th</sup> of January 2020 and a pandemic on the 11<sup>th</sup> of March 2020 [26-28]. This virus has infected over 770 million people, with 6 million deaths, according to data from WHO [29]. While the world entered into the endemic phase, COVID-19 infection is still ongoing due to the virus's ability to evolve into different variants. The Alpha, Beta, Gamma, Delta, and Omicron are among the variants of concerns identified; each present with different key spike protein mutations [30-36].

The WHO first discovered Omicron on 24<sup>th</sup> November 2021 from samples collected from Botswana and Gauteng province in South Africa [37]. The B.1.1.529 Omicron variant can be divided into five lineages, namely: BA.1, BA.2, BA.3, BA.4, and BA.5, and further divided into multiple sub-lineages like BA.1.1, BA.2.23.2, BA.2.11, BA.2.75 and BA.4.6 [38-41]. Evidence has shown that the BA.2 lineage has faster transmission rates and can evade the immune system more efficiently than the original wild-type strain and past variants of concerns, including BA.1 [42]. This novel virus very quickly spread globally after a decrease in Delta cases, with its number doubling every 2-3 days, making it a global concern as it rapidly accounted for 90% of the circulating SARS-CoV-2 virus [37, 42, 43]. Soon, 55 countries reported the presence of this new variant within just two weeks after its initial detection, speculating it was already widespread before its first report by South Africa [37].

Now, the Omicron JN.1 has been classified by WHO as a variant of interest (VOI) with the increasing reported cases in multiple countries caused by JN.1. The Omicron JN.1 evolved from BA.2.86. It was first detected in September 2023 in the United States of America [44], and now it is responsible for the COVID-19 surge in multiple countries worldwide. The JN.1 inherits its predecessor BA.2.86's antigenic diversity and L455S, thus causing a higher host immune invasion [45]. Based on the US Centers for Disease Control and Prevention (CDC), the severity of illness remains low compared to other variants. It is reported that Omicron JN.1 is more transmissible among the community, exhibiting the typical symptoms of COVID-19 [44].

## 2.2. Monkeypox

The monkeypox virus (MPXV) was first discovered in 1958 after macaque monkeys kept in a research facility in Denmark were found to have pox-like disease [46]. This virus belongs to the member of the genus orthopoxvirus [47, 48]. Following this, in 1970, the first ever human case was identified in the Democratic Republic of the Congo (DRC) in a 9-month-old child who was initially suspected of having smallpox but was later found to have monkeypox, after MPXV was isolated from a sample [46, 49-51]. In the next decade (1970-1979), 54 cases of monkeypox were reported by WHO, with the majority of them affecting children (83% of total cases) [49]. This called for an increase in surveillance conducted by WHO, which later revealed a total of 338 cases with 33 deaths from 1981-1986 [49].

Epidemiologically, monkeypox was contained in African countries [52]. The central African (Congo Basin) clade, known as Clade I, and the West African clade, known as Clade II, represent the two phylogenetically distinct clades of the virus [53-55]. Clade II can be further divided into IIa and IIb, IIb being the current primary circulating clade. Of these two, the Congo Basin clade is known to be more virulent, with a higher degree of morbidity, mortality, and viremia compared to the West African clade [46, 56]. In 2003, following the import of infected exotic animals, namely prairie dogs from Ghana, the United States became the first country outside of Africa with a monkeypox outbreak [46]. This outbreak interestingly affected most adults compared to children and was milder in nature owing to the West African clade, with 47 cases and no deaths [49, 52]. Between 2018-2021, over 500 suspected monkeypox cases were discovered in the United Kingdom (UK), Israel, Singapore and the United States of America (USA), all of which were linked with travel to Nigeria [46, 49].

In 2022, a UK resident who recently traveled to Nigeria was confirmed to have the virus following a PCR test [46, 57, 58]. Consecutively, the monkeypox outbreak became widely dispersed, infecting non-endemic areas, including over 50 countries over 5 regions, prompting WHO to declare monkeypox an evolving threat of moderate public health concern on 23 June 2022 [46, 50, 59, 60]. By mid-October 2022, it was reported that there were 72,00 cases in 102 countries worldwide, which is an alarming public health concern [61]. As of 1 May 2023, WHO data revealed a cumulative of 87,301 confirmed monkeypox cases across all 6 WHO regions, with the European region accounting for over 80% of all new monkeypox infections [62]. However, the key distinction between this outbreak and previous outbreaks is there is no clear link to a history of travel to endemic regions or handling of infected animals, which might suggest that this virus has begun community transmission [63].

## 3. Pathogenesis of the viral infections

### 3.1. SARS-CoV-2 infection in human host

SARS-CoV-2 belongs to the *Betacoronavirus* genus and represents a group of enveloped, single-stranded, positive-sense RNA viruses that are highly pathogenic [21, 64]. All coronaviruses share four core structural elements: spike (S), envelope (E), membrane (M),

and nucleocapsid (N) <sup>[64]</sup>. The S protein in SARS-CoV-2 has two subunits: S1 and S2. The S1 subunit encompasses the receptor-binding domain (RBD) responsible for the binding of ACE2. In contrast, the S2 subunit encompasses the transmembrane domain responsible for the attachment of the S protein to the membrane, allowing fusion of the viruses' membrane with the host cellular membrane <sup>[64, 65]</sup>. Additionally, for this virus to attain entry, sequential cleavage of the spike protein at the S1/S2 and S2' cleavage sites are essential <sup>[66]</sup>. This is assisted by furin and type II transmembrane serine protease (TMPRSS2) or cathepsin L which allows two distinct routes of entry either via the cell membrane or endosomally respectively <sup>[21]</sup>. The ACE2 receptor serves as the primary receptor of SARS-CoV-2 and is present on multiple cells such as endothelial cells, pneumocyte-2 cells in the lungs as well as enterocytes found in the gastrointestinal tract <sup>[66]</sup>. This owes to the various presentations of COVID-19. After the virus has gained entry, replication, transcription, and translation of structural proteins takes place. Structural M, N and E are translated and assembled into the virus except the S protein. Subsequently, the virus is released through exocytosis <sup>[64]</sup>.

The spike protein allows spread of the virus by executing cell-cell fusion of infected cells producing large multinucleated cells enabling it to be undetected by antibodies <sup>[65]</sup>. Not only that, the binding of ACE2 and S protein leads to the depletion of the ACE2 receptors thereby inhibiting the protective functions of ACE2 <sup>[65]</sup>. Angiotensin II is converted to angiotensin by ACE2 enabling endothelial cell functions to be protected preventing blood clots <sup>[65]</sup>. Hence, downregulation of ACE2 receptors leads to vascular occlusion in infected patients <sup>[65]</sup>. Additionally, pathogen associated molecular patterns (PAMPs) triggers the immune system causing programmed death also known as pyroptosis of host cells. A cytokine storm is also triggered through the activation of pro-inflammatory damage-associated molecular patterns (DAMPs) released by the virus which consecutively causes the migration of macrophages, monocytes and T-cells <sup>[64, 65]</sup>. This can lead to the classic acute respiratory distress syndrome (ARDS), a common cause of death in COVID-19 infected patients or in severe cases, multi-organ damage <sup>[64]</sup>. The immune system can also get severely injured by the overactivation of T-cells causing CD4 T-cells to release larger volumes of pro-inflammatory cytokines and CD8 T-cells to produce more cytotoxic granules <sup>[64, 66]</sup>.

With a focus on the Omicron variant, a study by Shuai and colleagues discovered that Omicron lacks spike cleavage, rendering inefficient TMPRSS2 utilization <sup>[67]</sup>. Since TMPRSS2 functions primarily to aid entry of the virus into host cells, such as the lung cells through the plasma membrane, Omicron's lack of spike cleavage prevents this process, resulting in a reduction in pathogenicity as well as viral replication <sup>[67]</sup>. Nonetheless, endosomal entry is still possible and is the preferred route of entry for this variant <sup>[67, 68]</sup>. Omicron expresses higher amounts of cathepsin L to support entry through the endosomal pathway <sup>[67, 68]</sup>. Moreover, TMPRSS2 cells are found abundantly in the lung epithelial cells, while the upper airway epithelial cells have low amounts of TMPRSS2 cells <sup>[67, 68]</sup>. Therefore, while other variants replicate faster in the lungs, Omicron has a faster rate of replication in the upper airways <sup>[66]</sup>.

### 3.2. Monkeypox infection in human host

The monkeypox virus has a linear double-stranded DNA (dsDNA) and is described to be enveloped by a lipoprotein-based outer membrane, slightly pleomorphic in shape with a dumbbell-structured core and two lateral bodies [46, 56, 69, 70]. Monkeypox inoculates the body via the oropharynx, nasopharynx, or intradermally [56]. After replication at its site of infection, it spreads to regional lymph nodes, which is also known as primary viremia [71]. Consecutively, secondary viremia occurs with systemic dissemination of the virus to other organs such as the liver, spleen, skin, oral mucosa, thymus, lymph nodes, gastrointestinal tract, and reproductive system [46, 71].

Poxviruses typically do not have host cell receptors or viral receptor-binding proteins and depend on widely abundant glycosaminoglycans like heparin sulphates, chondroitin, and laminin to assist in their attachment to cells [56]. After attachment, the virus gains entry into the host cell either through micropinocytosis endocytosed, which is further enhanced by a low pH of <6, or via direct fusion at a neutral pH [46]. Following entry, the uncoating of the viral core takes place, releasing the viral genome, transcription factors, proteins, and enzymes into the host cytoplasm, which supports the process of transcription of early genes [56]. With the help of virus-encoded multi-subunit DNA-dependent RNA, DNA replication and synthesis and transcription of intermediate and late genes occur [56]. The intermediate genes primarily encode the binding of packaging elements, core proteins, and late transcription factors, while the late genes encode proteins involved in the formation of the membrane of a mature virion and many morphogenesis [72].

After a series of early, intermediate and late transcription, the translation process occurs on the hosts ribosomes [46, 56]. Following these mechanisms, a mature virion is composed after the assembly of viral elements in an immature virion [56]. Most mature virions maintain their site intracellularly and are known as intracellular mature virions (IMV), while some are transported to be enveloped by Golgi-derived membranes enhancing them with a secondary membrane forming intracellular enveloped virion (IEV) [46, 72]. When these IEVs exit the cell, they would be known as extracellular enveloped virions (EEV) [72]. This evacuation process occurs either via cell membrane fusion or by propelling towards the adjacent cell through the process of actin polymerization [46]. It should be noted that both IMVs and EEVs can facilitate an infection with EEVs known for early dissemination and IMVs released during cell lysis [46].

Immunopathologically, poxviruses have been observed to inhibit apoptosis, CD8+ and CD4+ T and natural killer cells through the formation of immunomodulatory proteins [56, 72]. These proteins also prevent expression of IFNs, chemokines, inflammatory cytokines, complements and antibodies [56, 73]. The innate immune response relies heavily on the action of type I IFN reaction, and poxviruses like monkeypox also principally attack type I IFN by producing inhibitory proteins to evade immunity, allowing it to persistently spread, causing threatening clinical manifestations [73].

#### 4. Clinical features of Omicron and monkeypox

Based on a study, the symptoms characterized by Omicron infection are generally milder in vaccinated persons compared to the predecessor's variants, with significantly lower hospital admissions and a shorter period of illness <sup>[74]</sup>. Findings from the same study compared symptoms of the omicron and delta variants and revealed that symptoms such as loss of smell, eye soreness, and sneezing occurred less frequently in those infected with the omicron variant <sup>[74]</sup>. This novel variant is characterized by common symptoms, including a runny nose, headache, fatigue (ranging from mild to severe), sneezing, and sore throat. Interestingly, there is a lower prevalence of fever, cough, and loss of taste or smell in cases associated with the Omicron variant <sup>[75]</sup>. When comparing clinical characteristics in children and adults, a nationwide cross-sectional study observed that symptoms appear rarer and milder in children with 63% of children reporting absent or mild symptoms as opposed to 50% in the adult population <sup>[76]</sup>. In addition to affecting the respiratory system, it's worth noting that SARS-CoV-2 has the potential to impact various organs, including the heart, gastrointestinal system, liver, kidney, and the central nervous system, potentially leading to multi-organ failure <sup>[77]</sup>. This emphasizes the importance of understanding the comprehensive effects of the virus beyond its commonly recognized respiratory impact.

Drawing a parallel to another set of viruses, monkeypox and smallpox, both belonging to the orthopoxvirus family and sharing similar pathobiology, exhibit differing levels of severity in their signs and symptoms. Notably, monkeypox tends to manifest milder symptoms than smallpox, with a distinctive feature being the presence of lymphadenopathy in monkeypox but not in smallpox <sup>[72]</sup>. Additionally, muscle aches, fevers, chills, sore throat, malaise, and fatigue are the classic symptoms of the onset of a MPXV infection <sup>[71]</sup>. Following the manifestation of fever, a characteristic well-circumscribed, non-itchy rash which typically starts on the face and subsequently spreads to the rest of the body develops. This turns into papules and vesicles which eventually crusts and heals <sup>[73]</sup>. However, in the 2022 outbreak, lesions have been found to either be completely absent or minimal in number and are usually localized in the genital or perianal area associated with anal pain and bleeding which are atypical symptoms of this disease <sup>[72]</sup>. Monkeypox has a non-contagious incubation period which typically lasts between 7-14 days. Clinical manifestation and symptoms of this virus becomes evident during the prodromal stage consistent with secondary viremia. The prodromal stage is deemed to be highly infectious <sup>[71, 73]</sup>.

#### 5. Treatment options for Omicron and monkeypox

##### 5.1. Treating Omicron infections

Prior to the development of effective COVID-19 vaccines, treatment of this virus largely depended on the symptoms experienced by the patient and was customized accordingly <sup>[78]</sup>. Treatment options for SARS-CoV-2 consist of mostly repurposed drugs and can be largely grouped into two categories namely antivirals or immune modifiers <sup>[79, 80]</sup>. Remdesivir, an antiviral drug approved by the FDA is a broad-spectrum nucleotide analog

which has been proven to target many viruses including coronaviruses [79, 81]. Its mechanism of action is by inhibiting the activity of RNA polymerase hence preventing replication of the virus [82]. Although there have been mixed results on the efficacy of this drug against the treatment of SARS-CoV-2, studies have shown a reduced recovery time in patients treated with remdesivir [83, 84]. Researchers have also found that these effects are more potent with faster clinical improvement and a decreased recovery period when remdesivir is combined with a Janus kinase-STAT signaling inhibitor called baricitinib [85, 86]. Protease inhibitors such as lopinavir or ritonavir which are known to treat HIV have also been studied to assess their effects on patients with COVID-19 [79]. Poor results were observed with the use of these anti-HIV drugs with no effects on hospitalized patients and were suggested to be possibly more effective when combined with other antivirals [82, 87].

Moreover, hydroxychloroquine, an antimalarial drug has also been suggested as a promising treatment for COVID-19 but has not shown any beneficial effects from clinical trials conducted [88, 89]. Besides antivirals, monoclonal antibodies are also another alternative option in treatment of this disease. In the context of SARS-CoV-2, monoclonal antibodies target the spike protein by neutralizing it preventing viral entry [79, 82]. Currently, sotrovimab also known as VIR-7813, is the single monoclonal antibody approved for use in the United States and has shown to have similar mode of action against all variants including Omicron [90]. Nonetheless, although this therapy has established potential benefits such as reduction in hospitalizations and mortality in mild-moderate severity non-hospitalized patients to prevent escalation into severe illness, most data collected is still preliminary requiring further review [90].

Additionally, COVID-19 vaccines remain the cornerstone of protection against this disease [91, 92]. There is a wide range of COVID-19 vaccine platforms, such as nucleic acid vaccines, which include DNA and mRNA vaccines [93, 94]. These function by introducing genetic material from the virus, which is responsible for mounting an immune response into human cells, allowing the synthesis of antibodies [95]. Pfizer and Moderna vaccines represent two well-known mRNA vaccines [96]. Another vaccine platform would be protein subunit vaccines, with Novavax being the primary example of this vaccine [93]. In this vaccine, the spike protein, whose main action is to facilitate binding of the virus to the ACE2 receptor, is utilized [93, 95]. Johnson & Johnson's Janssen, Sputnik, and AstraZeneca vaccines are examples of viral vector vaccines which contain the virus's genetic material incorporated into a vector and are consecutively introduced into the human cells via intramuscular injection [93, 95]. Finally, inactivated vaccines such as CoronaVac, also known as Sinovac, were developed by a China-based pharmaceutical company Sinovac Biotech against SARS-CoV-2 virus [95]. Studies have reported the current vaccines are effective against the Omicron variant [97-100]. In addition, Chalkias and colleagues have also reported that the bivalent omicron-containing vaccine mRNA-1273.214 was effective against Omicron [101]. To ensure continuous protection against COVID-19, it is advised to receive booster vaccines following the initial two doses [102, 103]. However, concerns about vaccine safety and potential side effects are more obvious among individuals with autoimmune conditions, heart disease, pregnancy, or other



underlying comorbidities <sup>[104-107]</sup>. Additionally, the effectiveness of the vaccines is being scrutinized due to the ongoing mutations and emergence of new variants of SARS-CoV-2. Even those who have received prior vaccinations are experiencing infections with the Omicron variant, raising questions about the ability of current vaccines to effectively combat the evolving virus.

## 5.2. Treating monkeypox infections

Majority of patients with monkeypox infection resolve on their own with no medical intervention. Some may require supportive management of their symptoms such as oral or intravenous hydration, pain relief with analgesics and antibiotic treatment for secondary infections <sup>[108]</sup>. Nonetheless, treatment is indicated for patients who develop severe disease, for patients who possess a high risk of severe disease progression or for those who develop mucocutaneous lesions or eye infections <sup>[109]</sup>. Since smallpox and monkeypox both belong in the same family of orthopoxviruses, antiviral drugs such as brincidofovir, tecovirimat and cidofovir that are used for the management of smallpox have been recognized for the treatment of monkeypox <sup>[110]</sup>. Tecovirimat (also known as TPOXX, ST-246) has been considered the treatment of choice for smallpox and has been shown to be effective against viruses from the same family including monkeypox <sup>[109]</sup>. This drug works by inhibiting the VP37 protein which is a protein essential in viral envelopment of IMV to form IEV. By preventing it from being enveloped, the virus is unable to exit hence transmission of the virus is inhibited from the primary infected cell <sup>[109, 110]</sup>. Brincidofovir and cidofovir have the same mechanism of action as brincidofovir is an oral analogue of intravenous cidofovir. These two drugs function by inhibiting DNA polymerase thereby preventing viral replication <sup>[110]</sup>. With patients who experience severe monkeypox illness, a dual therapy consisting of tecovirimat and brincidofovir may be used <sup>[108]</sup>.

Another option approved by the FDA is Vaccinia Immune Globulin Intravenous (VIGIV) which manufactured from IgG antibodies obtained from the plasma of individuals who had been previously vaccinated against smallpox providing passive immunity <sup>[108, 109]</sup>. This drug is typically used to treat complications arising from smallpox vaccine such as eczema vaccinatum, progressive vaccinia and severe generalized vaccinia <sup>[109, 110]</sup>. Although vaccinia immune globulin (VIG) has obtained license for use, data on its effectiveness and its use on monkeypox virus in humans has yet to be tested <sup>[110]</sup>. VIG is also used as a prophylactic measure in those with severe immunodeficiency in T-cell function as they are contraindicated to receive vaccination with vaccinia virus vaccine also known as smallpox vaccine <sup>[111]</sup>.

Aside from active treatment, preventative measures are also key to combat a monkeypox outbreak. According to CDC, avoiding close contact with people and animals, covering lesions and rashes with gloves or bandages, wearing a well-fitted mask, avoid sharing of personal items including utensils and maintaining good hand hygiene are some precautionary measures that should be practiced by those who have the disease <sup>[112]</sup>. Albeit there is no current vaccine designed for the prevention of monkeypox, data suggests that

vaccinia virus vaccine (smallpox vaccine) such as ACAM2000 and JYNNEOS may have protective features as well as decrease the severity of a monkeypox infection <sup>[113]</sup>.

## 6. Challenges of Omicron and monkeypox infections

The 2022 monkeypox outbreak generated substantial media attraction causing public interest without much awareness. This can cause many negative implications on the society especially those infected with the disease. For example, disturbing media on pox-like deformation as well as misinformation creates stigmatization and heightens fear in the public. Coincidentally, the 2022 outbreak infected primarily gay, bisexual and men who have sex with men (GBMSM) causing stereotyping of this group of people as well as fuels public blame towards them as the source of the disease <sup>[114]</sup>. Misinformation arises as the main mode of transmission is via close physical contact which can happen to anyone regardless of their sexual orientation so although cases predominantly affect the GBMSM population, healthcare professionals as well as the general public should be aware that anyone is susceptible to the infection <sup>[114, 115]</sup>. Failing to do so can result in under detection and over infections.

Moreover, as monkeypox is a zoonotic disease, it has multiple hosts such as rodents and other small mammals allowing for rapid transmissibility which is further exacerbated with international pet trades. Additionally, international travel to endemic countries further facilitates its spread <sup>[20]</sup>. After the declaration of eradication of smallpox by WHO in 1980, smallpox vaccines were ceased. Since smallpox vaccination provides immunity against monkeypox, those who had been vaccinated in the past had significantly lower rates of infection (0.9%) compared to those who had not (7.2%), according to a study conducted in Democratic Republic of the Congo between 1980 to 1984 <sup>[116]</sup>. Hence, considering there is no developed vaccinations for monkeypox available at the moment, a question arises on the need for routine and mass smallpox vaccination as a preventative measure for monkeypox infection. Another challenge faced with the monkeypox infection is there are no definitive treatment available yet <sup>[117]</sup>. Although both brincidofovir and tecovirimat has seen some success in treatment of cases in the United Kingdom, investigations on these drugs are still underway and are mostly reserved for those who are immunocompromised or have severe illness <sup>[117]</sup>.

With respect to SARS-CoV-2, one of the biggest challenges observed with this virus is its continually mutating nature. The large number of mutations in the Omicron variant produced in the S protein makes this variant smarter allowing it to evade the hosts antibodies and immune responses produced by T cells <sup>[118]</sup>. With newly emerging mutations, more research and investigations are to be carried out to identify how it affects the human body <sup>[119]</sup>. Not only that, new upcoming variants also calls for the need to assess vaccination efficacy against this mutant virus and whether modifications are required to offset these mutations. Data from the United Kingdom demonstrated that all COVID-19 vaccines showed poorer efficacy against the Omicron variant compared to the Delta variant <sup>[91]</sup>. This is most likely due to the mutations present on the Spike protein of the Omicron variant <sup>[91]</sup>. A study

done in Egypt demonstrated poor inhibition towards Omicron based on serum collected from individuals five months after receiving Pfizer or AstraZeneca vaccination.

Additionally, patients who were previously infected with COVID-19 6-12 months prior proved to have low to no neutralizing effect against the Omicron variant <sup>[120]</sup>. Even a third booster dose following the initial 2-dose vaccinations revealed minimal protection against Omicron <sup>[121]</sup>. All of this shows that Omicron along with future variants of SARS-CoV-2 poses a dangerous threat towards existing therapies and vaccines demanding production of newer interventions that anticipate the trajectory of this ever-changing virus <sup>[89]</sup>. As herd immunity is crucial to cope with this pandemic, continual immunity is also of utmost importance <sup>[119]</sup>. Previous studies of coronaviruses have discussed and confirmed that immunity begins to deplete after 1-3 years which poses the question of the need for annual doses as well as possibility of it being part of the childhood immunization schedule <sup>[122-125]</sup>. Moreover, with the development of vaccines, most people have become complacent, neglecting precautionary measures <sup>[119]</sup>. However, this could very easily get out of hand as new variants such as Omicron have shown increased transmissibility, ability to bypass the immune system and a decrease in protection from vaccinations <sup>[126]</sup>. Other challenges circulating the topic of vaccination include issues with affordability, accessibility, distribution as well as dealing with anti-vaxxers <sup>[127]</sup>. Continual emergence of new variants could also be attributed to issues like vaccine hesitancy and unequal distribution of vaccines <sup>[127]</sup>.

Some challenges that these two viruses, the Omicron and monkeypox have in common include rapid genetic mutations. Although monkeypox is a DNA virus making it more stable compared to SARS-CoV-2, in the 2022 outbreak, 15 single nucleotide polymorphism mutations were detected <sup>[128]</sup>. SARS-CoV-2 on the other hand is known for its rapid spread mutating within 4 years from the Alpha form to Beta, Gamma, Delta, and now the Omicron with differing clades <sup>[128]</sup>. These can pose as a challenge as treatment options including vaccinations can have major implications demanding further investigation and revision.

Moreover, both infections have overlapping initial presentations such as fever which might make it difficult to distinguish between the two resulting in failure to diagnose accurately and inaccurate management <sup>[115]</sup>. Lesions found in monkeypox might be helpful in differentiating the two infections, however, as recent studies have shown, some patients might present with undetectable lesions making it harder to formulate a diagnosis <sup>[115]</sup>. Besides this, with emerging monkeypox in the era of COVID-19, a co-infection of the two viruses is also a possibility <sup>[128]</sup>. As an infection with SARS-CoV-2 is known to cause low immunity with a decrease in total leucocyte count, an opportunistic co-infection with monkeypox is highly feasible <sup>[128]</sup>. This in turn may change the course of the disease subsequently affecting response to treatment and vaccinations. The healthcare system has also taken a hit with its facilities and resources being exhausted due to the COVID-19 pandemic since 2020 <sup>[129]</sup>. Healthcare workers working relentlessly, increased hospitalizations with insufficient hospital beds as well as increasing death rates have caused

a massive impact on the medical sector<sup>[129]</sup>. With the emergence and rise of monkeypox and the need for resources to facilitate its diagnosis and management, the healthcare system could once again be overwhelmed, posing yet another challenge<sup>[129]</sup>.

## 7. Preventive measures against viral infections

As we reflect on the period spanning from 2019 to 2023, it becomes evident that despite the passage of time, viral infections continue to loom over our global community. While considerable strides have been made, and societies have acclimated to the new normal life, complete liberation from the threat of viruses remains elusive. However, humanity's resilience has manifested in the widespread adoption of preventive measures aimed at curbing the transmission of infections<sup>[130]</sup>. Individuals worldwide have embraced a proactive lifestyle marked by the consistent use of face masks, meticulous hand hygiene practices, and a collective commitment to avoiding densely populated spaces. These preventive measures, highly advocated by health ministries across nations, have proven instrumental in reducing the incidence of viral infections. Yet, as we navigate the ongoing challenges posed by infectious agents, a burgeoning focus on fortifying the body's natural defence mechanisms has gained prominence.

One pivotal aspect of this newfound emphasis revolves around boosting the immune system to mount a formidable defence against viral invaders. Recognizing that a robust immune response is integral to maintaining overall health, individuals are increasingly exploring strategies to enhance their immune function. In this context, the supplementation of vitamin C and other multivitamin supplements has emerged as a key consideration in promoting immune health<sup>[131]</sup>. Vitamin C, a powerful antioxidant, is renowned for its ability to support the immune system by aiding in the production and function of white blood cells, which are essential components of the body's defense against infections. In addition, studies have reported the potential role of probiotics in contributing to the optimization of immune function and promoting general well-being<sup>[132-136]</sup>. These beneficial microorganisms are believed to stimulate the production of antibodies, enhance the activity of immune cells, and contribute to the maintenance of a balanced immune response<sup>[137-139]</sup>. The combination of stringent preventive measures and a growing emphasis on immune system fortification, with the potential integration of probiotics, marks a holistic approach to safeguarding our communities against the ongoing and future threats that may arise.

## 8. Conclusions

The novel SARS-CoV-2 pandemic was an outbreak that the world did not see it coming. Although it is no longer declared as a public health emergency of international concern by the WHO, the virus is ever so frequently mutating producing new variants challenging us to relentlessly maintain surveillance in order to prevent another global outbreak<sup>[140]</sup>. Moreover, with the lifting of travel bans, international travel has been roaring, granting individuals to travel to countries endemic to certain diseases such as monkeypox, facilitating its spread. Mutations within the monkeypox genome have also been detected

allowing this virus to spread to non-endemic countries and may be responsible for the unusual clinical manifestations in the 2022 outbreak as discussed above. Regardless of whether a virus is composed of a DNA nucleotide such as monkeypox or an RNA nucleotide such as SARS-CoV-2, mutations constantly take place allowing these viruses to grow smarter in pursuance to adapt, evade the hosts immune system, decrease vaccine efficacy and potentially an increase in morbidity and mortality. This teaches us that in the interest of containing viral outbreaks, there must be vigilance in maintaining surveillance and monitoring of the sequencing and emergence of other clades or variants of circulating viruses. Not only that, advancement in research and development of up-to-date therapeutics to keep up with these viruses are also of utmost importance. In keeping with this, equal access and distribution of therapeutics globally especially to third world countries is also necessary to ensure that these outbreaks are contained and hopefully eradicated.

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