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NAVIGATING THE ENDEMIC COVID-19 LANDSCAPE: EVOLVING CHALLENGES AND MANAGEMENT STRATEGIES FOR PRIMARY CARE

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ABSTRACT

As COVID-19 transitions to an endemic state, primary care physicians play a crucial role in managing this evolving health challenge. This article provides an updated overview of COVID-19 management in primary care settings. We discuss the current epidemiology, including the emergence of new variants such as JN.1 and its sublineages, and their implications for clinical practice. Prevention strategies are outlined, emphasising the importance of vaccination with updated formulations and appropriate non-pharmaceutical interventions. Additionally, we review the latest recommendations for antiviral therapies in non-hospitalised adult patients, focusing on Paxlovid, Remdesivir, and Molnupiravir, including their efficacy, administration, and considerations for special populations. The challenges of COVID-19 re-infections and post-COVID sequelae, including long COVID, are addressed, highlighting the need for vigilant monitoring and management. We also discuss the implications of co-circulation with influenza and the importance of differential diagnosis. Finally, the article explores emerging therapies and future directions in COVID-19 treatment, including new antivirals, monoclonal antibodies, and vaccine updates. This comprehensive review aims to equip primary care physicians with the latest knowledge and strategies to effectively manage COVID-19 in an ever-changing landscape.

Keywords: Omicron subvariants, antiviral therapy, COVID-19 vaccination, vaccine efficacy, post-acute SARS-CoV-2 sequelae

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INTRODUCTION

The Role of Primary Care in Managing Adults with COVID-19

Primary care physicians remain at the forefront of managing COVID-19 as the dynamic landscape continues to evolve. They play an indispensable role in patient management and public education and must continuously navigate the complexities of variant-induced changes in clinical presentation and symptoms profiles, diagnostic test accuracy, and treatment efficacy. Primary care providers can quickly assess, diagnose, and initiate appropriate care to significantly impact patient trajectories and outcomes, and help mitigate community spread. Additionally, they need to understand, communicate, and address concerns on vaccine effectiveness of current formulations against emerging strains and reinfection risks, as well as manage misinformation on vaccine adverse effects.

Beyond acute care, primary care physicians are uniquely positioned to address the longer-term health consequences of COVID-19, including its impact on mental health and chronic disease management. By leveraging telemedicine and other innovative care models, primary care physicians can provide comprehensive, patient-centred care that adapts to the ongoing challenges posed by COVID-19. Finally, primary care physicians play an important role in surveillance and monitoring of disease presentations and trends, contributing to broader public health efforts in managing the evolving pandemic landscape.

CURRENT EPIDEMIOLOGY AND EMERGING COVID-19 VARIANTS

New COVID-19 variants and subvariants continue to emerge globally, causing periodic fluctuations in case numbers. The World Health Organization (WHO) and other global health bodies monitor these variants closely, categorising them as Variants of Concern (VOC), Variants of Interest (VOI), or Variants Under Monitoring (VUM) based on their transmissibility, severity, and ability to evade immune responses or diagnostics.[1] The latest subvariant of interest, JN.1, is an Omicron descendent initially tracked under the BA.2.86 strain (otherwise known as BA.2.86.1.1). Except for a single variation in the spike protein, these two strains are otherwise almost identical. JN.1 and its sublineages KP.1, KP.2, and KP.3 have now become predominant in many regions around the world since September 2023. These subvariants are part of the "FLiRT" group, named for specific mutations (F456L and R346T). While they do show increased transmissibility, there has been no evidence of increased disease symptomatology or severity.[2-5] In Singapore, as of May 2024, KP.1 and KP.2 account for more than 66 percent of COVID-19 infections. However, despite seeing a peak of cases in mid-May 2024, the proportion of COVID-19 hospitalisations remained very low at 0.01 percent; likewise, the average daily critical cases requiring ICU care.[6]

It is worthwhile to note that due to significantly reduced testing, surveillance, and reporting requirements for COVID-19, global reported numbers now likely represent an underestimate of the true case burden.

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Healthcare providers cannot afford to let our guard down, however, as there remain vulnerable at-risk groups in the population, including the elderly, unvaccinated individuals, immunocompromised persons, and those with multiple medical comorbidities.

COVID-19 PREVENTION STRATEGIES

COVID-19 Vaccination Updates

For COVID-19 prevention, vaccination remains the main strategy. As of June 2024, the Singapore Ministry of Health recommends two initial primary series vaccination doses at eight weeks apart for all individuals above six months of age, with any of the four locally approved COVID-19 vaccines. An additional dose is further recommended one year after the last dose of vaccine. This is strongly advised for individuals with risk factors (age 60 years and above, medically vulnerable, residents of long-term care facilities) and highly encouraged for other population groups. To note, only the Pfizer-BioNTech/Comirnaty, Moderna/Spikevax, and Novavax/Nuvaxovid vaccines have been updated with a monovalent XBB.1.5-derived formulation and these are available in Singapore.[7]

JN.1 contains more than 30 substitutions in the spike protein when compared to XBB.1.5, thus raising concerns about its robust capability for immunoevasion.[5] However, multiple large population studies from the US Centers for Disease Control and Prevention (CDC) and European countries show consistent evidence placing overall vaccine effectiveness of the updated monovalent XBB vaccines at around 50-70 percent for severe disease (specifically 49 percent for JN.1 CDC report). These studies were done when there was a mix of circulating Omicron subvariants and included at-risk groups.[8-10] Laboratory studies also show these vaccines elicit broadly cross-protective neutralising antibodies against XBB lineages and JN.1, supporting their continued use in the face of viral evolution.[11,12] Another study found that even for healthy working adults, the vaccine still offers some protection against infection (19 percent), but the more noteworthy finding was that previous XBB (and other recent lineages) infection and multiple vaccine doses lower the risk of COVID-19.[13]

This real-world evidence for vaccine efficacy and evidence supporting additional updated dosing underscores the importance of promoting vaccination in primary care settings as a key strategy in preventing COVID-19 and its complications, especially to counter waning vaccine-induced immunity with time.

Non-Pharmaceutical Interventions

Non-pharmaceutical interventions continue to play an essential role in reducing transmission, especially in healthcare settings and during periods of high community spread. While it is no longer feasible or favourable to recommend universal masking in all community settings, there are specific scenarios where masking remains advisable, e.g., to prevent spread of symptomatic infections. For at-risk populations, it is prudent to encourage masking when attending higher-risk activities and social interactions, e.g., when visiting crowded and/or poorly ventilated areas for prolonged periods of time, especially during periods of high community disease prevalence. Other general practices such as maintaining good personal hygiene including regular handwashing should still be encouraged for all persons.

ANTIVIRAL THERAPIES FOR NON-HOSPITALISED ADULT PATIENTS[14,15]

Risk assessment and stratification are crucial in tailoring treatments for COVID-19 seen in the outpatient setting, enabling resources to be directed effectively, and optimising clinical outcomes. High-risk individuals, including those over 65 years old (and further increasing with age), or those with comorbidities like diabetes, cardiovascular disease, or chronic kidney or lung disease, require prompt diagnosis, evaluation, and intervention. Other conditions include immunosuppression, and lifestyle factors such as obesity and smoking independently increase the risk of severe outcomes. Initiating COVID-19 treatment is most often a joint decision, hence patients and their families must receive unbiased and factual information to make an optimal, informed decision. The provider must ensure treatment thresholds are appropriately calibrated to the individual's risk level.

The primary goal of managing non-hospitalised patients with mild to moderate COVID-19 infections is to prevent progression to severe disease, hospitalisation, or death. Oral antiviral medications have become an established treatment modality in outpatient management. Paxlovid and Remdesivir have demonstrated high efficacy in preventing hospitalisation and death in high-risk patients, while Molnupiravir provides an additional option when the preferred treatments are not available or suitable.

Paxlovid

Among the available treatments, ritonavir-boosted nirmatrelvir, commonly known as Paxlovid, has emerged as the preferred first line of oral antiviral treatment for non-hospitalised adults with mild to moderate COVID-19 who are at high risk of disease progression. Paxlovid works by inhibiting the SARS-CoV-2 main protease, effectively halting viral replication. It is approved for patients aged 12 years and older weighing at least 40 kg. To maximise its benefits, Paxlovid should be initiated as soon as possible after diagnosis and within five days of symptom onset. The standard regimen consists of 300 mg nirmatrelvir with 100 mg ritonavir, taken twice daily for five days, with dosage adjustments necessary for those with renal impairments (eGFR ≥30 to <60 mL/min).

Although a recent study[16] has shown that vaccinated patients with low risk for disease progression and mild symptoms might not receive significant benefits; on the other end of the spectrum, Paxlovid remains an important treatment modality for reducing adverse outcomes in

patients at higher risk. In several international real-world studies[17-19] following the initial EPIC-HR trial, covering more than half a million participants, Paxlovid consistently showed a high range of approximately over 50-70 percent risk reduction of hospitalisation and death. Importantly, these post-marketing studies included large proportions of patients who were vaccinated (and with multiple doses) and were performed across different COVID-19 variant surges including Omicron XBB.1.5. To date, there is also no evidence that Paxlovid has lost its efficacy due to continuous SARS-CoV-2 viral mutations.[20,21]

The main challenge with Paxlovid is managing drug-drug interactions caused by its ritonavir component, which inhibits the CYP3A4 enzyme. Prescribers must carefully review patients' existing medications, especially statins, calcium channel blockers, and anticoagulants. Adjustments may include substituting medications or modifying dosages where possible. Resources like the University of Liverpool COVID-19 Drug Interactions website[22] and the NIH Guide to Paxlovid Drug-Drug Interactions[23] provide easy access to online tools to help healthcare professionals identify and manage these interactions safely.

A phenomenon known as "rebound COVID" gained interest with the increased use of Paxlovid; however, no definitive association has been proven. It is characterised by initial symptomatic improvement followed by a recurrence of symptoms or positive test results within 2-8 days post-treatment. Symptoms are generally mild and self-limiting, with no evidence of increased mortality or severe outcomes, and retreatment is not recommended. Of note, symptom fluctuation is not unique to antiviral therapy and has been reported in up to one-third of untreated COVID-19 cases even prior to using Paxlovid.[24,25] Despite this, the benefit of Paxlovid in effectively preventing severe disease outcomes undoubtedly outweighs this risk.

Remdesivir

Remdesivir has been a pivotal antiviral in managing COVID-19 due to its broad antiviral activity against all known coronaviruses. It inhibits viral RNA polymerase, disrupting viral replication. Its recent approval for use in patients with renal impairments (including those on dialysis) significantly expands its utility across all stages of renal disease without needing dose adjustments.[26] For patients who cannot take Paxlovid due to severe drug-drug interactions or other absolute contraindications, Remdesivir offers a suitable alternative option. Following the PINETREE trial demonstrating the efficacy of Paxlovid, subsequent real-world studies also consistently report the efficacy of Remdesivir at lowering risk of hospitalisation or death when administered for non-hospitalised adult patients with risk factors for disease progression.[27,28] There is similarly reassuring evidence to show that Remdesivir has retained its effectiveness against the Omicron subvariants.[21] Although it requires intravenous (IV) administration, which can present logistical challenges in outpatient settings, Remdesivir has shown significant efficacy in preventing disease progression and patients may be referred to several "Hospital at Home" programmes in Singapore.

Molnupiravir

A third antiviral option is Molnupiravir, which functions by introducing errors into the viral genome, causing lethal mutagenesis. Although it offers the convenience of oral administration, it is a less desirable alternative in cases where Paxlovid and Remdesivir are contraindication, unobtainable, and/or logistically unable to be administered. This is due to its much lower efficacy profile, both from the initial phase III (MOVE-OUT) trial and subsequent real world data.[29] There are also concerns about promoting SARS-CoV-2 viral mutation[30] with regular usage. Due to potential foetal harm, use should be avoided in pregnancy or for women of childbearing age not using contraception, and breastfeeding is advised against during treatment and for four days post-treatment. It is also not authorised for use in patients under 18 years of age given its potential effects on bone and cartilage growth.

In addition to antiviral therapies, comprehensive outpatient management of COVID-19 includes supportive care and symptom management. It is helpful to provide patient education about the expected course of illness, and to appropriately advise patients to seek escalated medical attention if they experience persistent or worsening symptoms, particularly dyspnoea, low oxygen saturation, or chest pain.

Special Patient Populations in Primary Care

Special patient populations require careful consideration in primary care. Immunocompromised patients require more cautious and aggressive management due to their increased risk of severe outcomes and diminished vaccine response. Early initiation of treatments like monoclonal antibodies (if and when available in future) and antivirals is essential, with careful monitoring for potential drug interactions. Pregnant individuals are also at higher risk for severe COVID-19, and while vaccination is recommended during pregnancy, treatment approaches similar to the general population are used, with increased focus on foetal and maternal safety. Paediatric patients typically experience milder disease but can develop severe complications, especially with underlying conditions. Treatment is overall guided by symptom severity and health status, and vaccination should be strongly encouraged for age-appropriate persons.

COVID-19 RE-INFECTIONS AND POST-COVID SEQUALAE[31-35]

The issue of COVID-19 re-infections has gained importance as individuals with a history of COVID-19 may experience reduced levels of neutralising antibodies over time, increasing their vulnerability. Re-infections can exacerbate existing symptoms, precipitate new complications, delay recovery times, or confound clinical management. Additionally,

the risk of long COVID increases, especially in older adults or those with prior post-acute sequelae of SARS-CoV-2 infection (PASC). Primary care providers must remain vigilant, as testing and early intervention during re-infections are important to prevent severe outcomes and further complications.

Long COVID has emerged as a significant public health challenge affecting millions worldwide. It encompasses a tremendously diverse range of symptoms, and physical and mental health complications that persist for weeks to months after the acute phase of the infection has passed. The currently widely accepted definition of long COVID is a condition occurring in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually within three months from the onset of COVID-19, with symptoms lasting for at least two months that cannot be explained by an alternative diagnosis. Research into pathological factors is still ongoing, but potential mechanisms proposed include direct viral damage, persistent viral components, dysregulated immune responses, hormonal changes, clotting abnormalities, and reactivation of latent herpesviruses.

Risk factors for developing long COVID vary in reports but often include severe initial illness, older age, female sex, and certain underlying medical conditions. Recent reports suggest an increased incidence of long COVID after Omicron infections, though this may be influenced by the growing number of reinfections seen with the natural progression, and due to the higher transmissibility of the Omicron variants.[36,37]

In primary care, long COVID patients may present with a diverse range of symptoms ranging from fatigue and brain fog to cardiovascular, neurological, and psychological issues. The variability in symptoms and severity necessitates a high index of suspicion for early recognition, and a comprehensive, integrated approach to management. This includes a tailored approach to symptomatic treatment, referral to specialist and rehabilitative services when necessary.

Clinical trials studying potential treatments for long COVID have yielded inconclusive results. Research on Paxlovid's effects on long COVID symptoms has produced mixed findings. A January 2024 study found no significant association between Paxlovid treatment during acute infection and reduction in subsequent long COVID symptoms,[38] in contradiction to an earlier 2023 study.[39] However, a recent randomised controlled trial in June 2024 failed to show significant benefits from a prolonged course of Paxlovid for treating long COVID.[40]

While treatment data is divided, research consistently indicates that COVID-19 vaccination significantly reduces the risk of developing long COVID and is associated with decreased prevalence and severity of long-term symptoms.[41,42] A meta-analysis from October 2023 showed vaccine effectiveness against long COVID symptoms ranged from 30 to 69 percent with two to three doses received.[43]

COVID-19 AND INFLUENZA[44]

The co-circulation of SARS-CoV-2 and influenza viruses, particularly during influenza seasons, presents additional challenges to primary care physicians. Differentiating COVID-19 from other respiratory illnesses is challenging due to overlapping symptoms. Key considerations include a combination of the symptom profile, clinical context, epidemiological factors and exposure history, vaccination status, and local disease trends. While coinfection is uncommon, it has been reported and may lead to more severe outcomes.

Diagnostic testing remains fundamental in facilitating appropriate management. As dual-assay or multiplex testing kits are not widely available, clinicians should decide whether performing additional viral testing is beneficial and can potentially change clinical management. For example, for patients who are eligible for both COVID-19 and influenza antiviral treatments, especially for those with risk factors, achieving a confirmed diagnosis will enable prompt and targeted treatment. It is useful to note there are no clinically significant drug-drug interactions between influenza antivirals and COVID-19 treatments, allowing for concurrent treatment when necessary.

On the note of diagnosis, COVID-19 antigen rapid tests (ARTs) remain the mainstay of point-of-care testing, being inexpensive and yielding fast results. However, it is important to bear in mind that COVID-19 ARTs have become less sensitive with the evolving variants, particularly in asymptomatic individuals. False negatives can occur, especially early in infection, necessitating repeat testing if clinical suspicion remains high. In the end, reliance on clinical vigilance remains key for early detection and diagnosis.

Vaccination again remains a key strategy for preventing both COVID-19 and influenza. COVID-19 and influenza vaccines can be safely co-administered at different injection sites during the same sitting, with evidence suggesting this could potentially even enhance the immune response against SARS-CoV-2, without compromising the defence against the flu.[45]

EMERGING THERAPIES AND FUTURE DIRECTIONS IN COVID-19 TREATMENT

Looking towards the future, several emerging therapies and directions are noteworthy. In the realm of oral antivirals, VV116 (deuremidevir hydrobromide),[46] which is an oral nucleoside analogue, and Simnotrelvir,[47] which is an oral 3-chymotrypsin-like (3CL) protease inhibitor, have been developed by Chinese researchers and approved for use by the Chinese National Medical Products Administration (NMPA) in 2023. Ensitrelvir[48] (Xocova) is another 3CL protease inhibitor developed by Japanese researchers and approved by the Japan Ministry of Health, Labour, and Welfare (MHLW). These drugs have mainly shown effectiveness in reducing symptom duration and viral load

in mild-to-moderate COVID-19 cases. Although they have not received approval for use outside their home countries, it is encouraging that there are several newer, convenient oral antivirals emerging from ongoing drug research and development.

Monoclonal antibody research continues to evolve, with innovative developments in intranasal antibodies like SA58 showing promise in preventing symptomatic COVID-19, and engineered proteins such as the trimeric sherpabody TriSb92.[47,48] Intranasal treatments providing direct delivery to the upper respiratory tract and achieving viral neutralisation can be a valuable addition to enhancing preventive measures by simplifying administration and potentially reducing systemic side effects.

In March 2024, a new monoclonal antibody, Pemivibart (Pemgarda), was granted Emergency Use Authorization (EUA) by the US Food and Drug Administration (FDA) for pre-exposure prophylaxis in immunocompromised individuals. However, it comes with a notable risk of allergic reactions, necessitating careful monitoring during administration.[49] Pursuing real-world data on its effectiveness and safety will be vital.

Interestingly, studies are also ongoing for "outdated" antibodies like sotrovimab, and several in-vitro animal studies found that it might retain efficacy against Omicron subvariants through non-neutralising mechanisms.[50,51] This showcases the extremely complex interplay between laboratory-measured antibody levels and the human immune system, and requires robust in vivo correlation studies.

Vaccine updates continue to be a crucial area of focus. In June 2024, the FDA recommended updating COVID-19 vaccines for the 2024-2025 fall/winter season to include an Omicron JN.1-specific antigen, replacing the current XBB.1.5 spike antigen. Manufacturers were advised to use the KP.2 strain of the JN.1-lineage if feasible, aiming to match the vaccines more closely with circulating SARS-CoV-2 strains to provide more robust protection.[52] This change is not expected to delay vaccine availability for the later quarters of 2024, and the monovalent XBB COVID-19 vaccines remain approved for use in the meantime.

CONCLUSION

The ongoing evolution of SARS-CoV-2 necessitates continual updates and adaptations in treatment strategies. As new variants emerge, the ability of current and pipeline treatments to offer protection will need constant evaluation. Primary care providers play a critical role in managing and preventing COVID-19 in the community, as well as public education. It is imperative for PCPs to stay informed about the latest developments and integrate new findings into their practice, to continue to provide comprehensive and patient-centred care, leveraging both pharmaceutical and non-pharmaceutical interventions, promote vaccination, educate patients and the public, and address misinformation.

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LEARNING POINTS

- **Evolving COVID-19 Variants: The emergence of new variants like JN.1 and its sublineages highlights the need for ongoing surveillance and vigilance in primary care. While these variants show increased transmissibility, they have not demonstrated increased disease severity. It remains important to stay informed about variant characteristics and their potential impact on clinical practice.**
- **Comprehensive Prevention and Treatment Strategies: Vaccination remains a cornerstone of COVID-19 management, with updated vaccines showing continued effectiveness against new variants. For high-risk patients, prompt initiation of antiviral therapies like Paxlovid or Remdesivir is crucial. Primary care physicians should consider factors such as age, comorbidities, and vaccination status when tailoring prevention and treatment approaches.**
- **Challenges of Diagnosis and Co-infections: Primary care physicians face the ongoing challenge of differentiating COVID-19 from other respiratory illnesses, particularly during influenza seasons. Differential diagnosis is crucial in guiding appropriate treatment. COVID-19 and influenza vaccines can be safely co-administered, potentially enhancing immune response against SARS-CoV-2.**