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UJEMI PERSPECTIVES

Are the newly authorized antiviral drug treatment for non-severe COVID-19 may change the course of the pandemic?

Iris Zhou

Department of Microbiology and Immunology, University of British Columbia, Vancouver, British Columbia, Canada

SUMMARY Since the emergence of the coronavirus disease-2019 (COVID-19) pandemic has killed over 6.83 million and infected 670 million people worldwide. The disease is evolving, and numerous COVID-19 prevention and treatment have been approved or suggested. The only antiviral currently approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 is remdesivir (brand name Veklury). Molnupiravir (brand name Lagevrio) and ritonavir-booster nirmatrelvir (brand name Paxlovid) have been granted Emergency Use Authorizations (EUAs) for the treatment of COVID-19. Despite these antivirals having demonstrated efficacy for the treatment of mild-to-moderate COVID-19 in authorized patients; however, there is a restriction to who can take these antivirals due to the inaccessibility and drug-to-drug interactions that can be lethal to many immunocompromised and severe liver disease patients. With thousands of new COVID-19 cases reported daily, there needs to be more effective strategies to increase the accessibility of antivirals to stir the course of the pandemic and move out of it. This paper will review the current knowledge on antivirals for the treatment of SARS-CoV-2 and its mechanisms and highlight key research areas in the field that remain to be understood regarding antivirals, focusing on 1) why antivirals are inaccessible to many patients, 2) explore possible new treatments that could mitigate COVID-19 related inequalities and drug accessibility. By understanding the accessibility and mechanisms of the antivirals for COVID-19, researchers and health authorities will be able to promote effective and novel treatments and bring hope for more antivirals to change the course of the pandemic.

INTRODUCTION

On March 11th, 2020, the World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory system coronavirus 2 (SARS-CoV-2), a pandemic (1). Since then, there have been more than 672 million confirmed cases and 6.84 million deaths worldwide, making it one of the deadliest pandemics in recorded history (2). It is suggested that these figures may be significantly underestimated, with more than official counts by millions (2,3).

Despite the large-scale implementation of vaccination and isolation, there is still an increase of over 60,000 cases daily (4). The efficacy of current COVID-19 vaccines and antibody therapies may be compromised due to the extensive mutations found in its spike protein (5). Highly transmissible variants like Delta (B.1.617.2) and Omicron (B.1.1.529) continue to circulate, and the risk of contracting SARS-CoV-2 may persist, as shown by the serum antibody levels developed from the vaccine decrease a few months after the last dose (6). In addition, omicron lineage can immune escape from the vaccine-acquired humoral immunity, further increasing the risk of transmission (6,7). According to Aschwanden (2021), if 60–70% of the population can gain immunity, either through vaccination or previous exposure to the virus may achieve herd immunity (8). Nevertheless, the path to herd immunity and normality appear to be out of reach due to several factors, including vaccine hesitancy, the emergence of new variants, and the delayed introduction of vaccinations for children (8).

The approval of several therapeutics following the implementation of vaccination has sparked optimism for better control of the spread of SARS-CoV-2. Many pharmaceutical drugs, including hydroxychloroquine, ritonavir, interferons, favipiravir, chloroquine,

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Address correspondence to: https://jemi.microbiology.ubc.ca/

tocilizumab, and dexamethasone, have been repurposed for the treatment of COVID-19 (9). Although the monoclonal antibodies were successful in targeting the SARS-CoV-2 spike protein, therapeutic effectiveness has dramatically decreased as a result of the spike protein's ongoing mutation (10).

Currently, the Food and Drug Administration (FDA) approved remdesivir for the treatment of COVID-19 and issued an emergency use authorization for molnupiravir and nirmatrelvir (11, 13). However, the Health of Canada has only approved remdesivir and nirmatrelvir (12).

Remdesivir is administered intravenously and is the first antiviral to be FDA-approved for the treatment of COVID-19 in October 2020 (13). Remdesivir (brand name Veklury) is a nucleoside analog and inhibits the RNA-dependent RNA polymerase (RdRp), therefore inhibiting viral replication in the host (13, 14). It is approved for the treatment of COVID-19 in hospitalized adults and children 12 years older (13).

Ritonavir boosted nirmatrelvir (brand name Paxlovid), an oral antiviral protease inhibitor for COVID-19, received the first emergency use authorisation from the FDA in December 2021 (13). Molnupiravir received its EUA shortly after (13). This cocktail drug contains two components; nirmatrelvir, a 3CL protease inhibitor, inhibits the polyproteins of SARS-CoV-2, preventing transcription and replication of the viral genome (15); ritonavir, a pharmacokinetic boosting agent, stabilizes the 3CL protease inhibitor, slowing the body's breakdown of active antiviral, enables nirmatrelvir to remain at a therapeutic level for a prolonged period of time (15). Molnupiravir (brand name Lagevrio) is a prodrug derivatized from ribonucleoside analog β-d-N-hydroxycytidine (NHC) that functions as a mutagen by increasing the frequency of transition mutations (G to A and C to U) in the SARS-CoV-2 genes (16, 17). This mutagenic effect has raised many concerns as it could create new variants that drive and prolong the pandemic- this is one of the reasons why it is not approved in the Canada (16).

Although the three antivirals are effective for the treatment of mild-to-moderate COVID-19 patients, there are restrictions to who can be prescribed them due to many factors. This is a serious issue since antiviral therapies require implementation as soon as possible after contracting the virus to stop viral replication. If antivirals are administered later, they may result in a lack of effectiveness, development of long COVID and long-term complications (22, 23). The reasons behind why antivirals are inaccessible and possible strategies that could mitigate warrant further investigation.

PROPOSED RESEARCH QUESTIONS

Given the threat of COVID-19 poses to global public health and the rise in of long COVID cases, it is critical to evaluate our healthcare approaches and have readily accessible antiviral treatments. Thus, considering strategies to combat COVID-19 in the long term by making antivirals more accessible, is critical. By allowing more patients to access the care they require, the availability of antivirals can lessen the severity and minimize the development of long-term COVID, hospitalizations, and COVID-19-related deaths (24). Additionally, increasing antiviral treatment can help reduce the spread of COVID-19 by allowing people to recover from the virus quickly and return to their normal lives. This will lessen the financial burden on individuals, families, the health care system and society and as a result, can improve our economy (25). Lastly, improving access to antivirals can aid in addressing health disparities since antiviral treatments are disproportionately distributed and affect marginalized communities such as people living in poverty or developing countries (26). Therefore, a better understanding of antiviral accessibility and strategies to mitigate inaccessibility is needed to move out of the pandemic. To advance the knowledge in this field, I propose two key areas of research: first, why are antivirals inaccessible to patients; second, what are possible strategies that could mitigate COVID-19-related inequalities and drug accessibility.

PROPOSED PROJECT NARRATIVE

Why are antivirals inaccessible to patients? Although various types of antiviral treatments are available for COVID-19 and have shown to be effective for the treatment of mild-to-moderate COVID-19 in authorized patients; however there are many restrictions and barriers for patients to obtain the drugs (22). By understanding the potential factors why antivirals are inaccessible and discussing potential strategies to mitigate COVID-19-related inequalities and drug accessibility is critical for moving out of the pandemic As it will highlight the need for global organizations to work together for policy changes to increase affordability and accessibility and improve public health outcomes worldwide.

There are six main factors as to why antiviral treatments for COVID-19 may not be accessible to everyone. First, these antivirals are inaccessible because of the clinical drug-drug interactions (DDIs), which can be lethal to numerous patients who are immunocompromised and have severe liver, kidney, heart, and pregnancy (27). For instance, the antiviral Paxlovid contains the pharmacokinetic drug ritonavir, which suppresses a key liver enzyme called CYP3A (28). CYP3A is one of the most important cytochrome P450 isoforms and is responsible for drug metabolism by humans (29). As a result, patients taking a medication that requires the liver for metabolization may be at risk for adverse side effects (Table.1). Posing a barrier for patients to receive the medications that are required to stop the viral replication in the body and have the potential progression of long COVID.

TABLE. 1 Overview of three antivirals. Describes the effectivity, patients who are unsuitable and common side effects of each antivirals.

	Remdesivir	**Paxlovid (nirmatrelvir/ritonavir)**	**Molnupivir**
Effectivity	Reduces the risk of hospitalization by 87% (11)	Reduced 88% and 75% in death and hospital admission rate, respectively (15)	Doesn't cut Omicron hospitalization, death but can speed recovery (18)
Indicators of unsuitability	Renal insufficiency, pregnancy, chronic kidney disease, sinus bradycardia (11)	Had an organ transplant, severe liver disease, HIV/AIDs, immunocompromised , down's syndrome, pregnant (11, 20)	Severe liver problems, Heart problems, including an irregular heartbeat, Blood disorders, pregnant (11)
Common side effects	Increased levels of liver enzymes, liver injury, blood pressure and heart rate, low blood oxygen level, fever, shortness of breath, wheezing, swelling, rash, nausea, sweating or shivering (19)	Hives, trouble swallowing or breathing, swelling of the mouth, lips, or face, throat tightness, hoarseness, skin rash (20)	Nausea, Diarrhea, Headache, Fatigue, Muscle or joint pain, Allergic reactions, Liver problems, Changes in heart rhythm, Blood disorders (21)

Second, antivirals have age restrictions and are not recommended for children under the age of 12 (30). However, children are usually asymptomatic and SARs-CoV-2 carriers, so to halt the transmission of virus there needs to be antiviral specifically targeting primary and elementary schools (31). Finding antivirals for children is rather difficult due to the following reasons: 1) different dosages are needed as children's physiology are different from adults, which can affect how drugs are absorbed, distributed metabolized in their bodies (32), 2) conducting clinical trials in children is difficult as it requires very special ethical considerations and protections, as children may not give informed consent (32).

Thirdly, the demand for antivirals has grown significantly, but the supply has struggled to keep up. According to Pfizer the active ingredients in Paxlovid takes around 6-8 months for production (33). Further aggregating the problems for those living in rural areas or countries without the supply of these antivirals (25, 26). Preventing everyone from being

granted the same opportunity to receive the care they need, prohibits the possibility of moving out of the pandemic.Furthermore, many countries do not have health insurance that covers the cost of antiviral treatments, which adds another barrier to accessing these antivirals. For example, in China, health insurance does not cover the cost of Paxlovid, and the price point of Paxlovid increased to CNY 1,890 (US $282) (34). Even then, many Chinese citizens cannot obtain one package of Paxlovid (34). The scarcity of antivirals has caused inequalities for patients that need to acquire these medications.

Lastly, accessibility is also impacted by a lack of knowledge regarding these antivirals. Some individuals may believe that antivirals should only be prescribed to severely ill patients, but in fact, antivirals work best when they are administered early in the course of the infection (35). Moreover, practitioners also prioritize those who are more susceptible to COVID-19-related severe illness and mortality, such as the elderly or those with underlying medical conditions (23). Meaning patients who would also benefit from these treatments are now not able to acquire these medications. Therefore, may increase the number of patients developing long COVID or complications.

Overall, the lack of accessibility to antiviral treatments for COVID-19 is a complex issue that is influenced by many factors including DDI, age restrictions, high demand and scarcity and soaring prices, disparities in distribution and lack of knowledge of these antivirals leading to prioritization. Therefore, without overcoming these barriers moving out of the pandemic will be an unceasing problem.

What are possible strategies that could mitigate COVID-19 related inequalities and drug accessibility? To ensure that everyone who needs antiviral treatments for COVID-19 may obtain them, regardless of their health condition, location, or socioeconomic status, our present healthcare system needs ways to overcome these barriers to antiviral accessibility. To counteract the DDI in Paxlovid, efforts must be undertaken to repurpose drugs (23). Ritonavir can be substituted with the drug nelfinavir, which is in the same class as ritonavir and is effective in treating HIV patients who are unable to take ritonavir due to its severe side effects (36, Table.1). Thus, allowing Paxlovid to be used by many potential patients.

Secondly, to reduce inaccessibility for all patients, including children, a global organization for children's antivirals outside of WHO can be established. This organization would be more transparent for the general public to monitor. Consequently, if everyone has access to these antivirals that are safe for usage, the transmission of SARs-CoV-2 may significantly decrease.

Next, to promote equity, drug availability and accessibility, governments can work together with pharmaceutical companies to increase the production of antiviral treatments ensuring that there is a sufficient supply to meet the demand (23). Furthermore, the government needs to regulate the prices of antiviral treatments to make them more affordable for everyone. Many antiviral drugs are protected by patents therefore, governments need to negotiate with the pharmaceutical companies to add price caps, and subsidies to solve the problem (23). Fourthly, to improve the distribution of these antivirals across the globe in areas that are currently underserved, there needs to be more investment in infrastructures and resources to ensure that these treatments are available to everyone when needed.

These potential strategies will be difficult to implement, but if approached from a One Health (Fig 1) perspective, there may be a way to lessen the issue because the One Health approach acknowledges the connection between human health, animal health and our common environment (37, 38). Veterinary epidemiologist and parasitologist Calvin W. Schwabe (1927–2006), developed and promoted the term "One Medicine or One Health" (39). One Health Institute at the University of California, Davis, suggests the definition: 'One Health is an approach to ensure the well-being of people, animals and the environment through collaborative problem solving—locally, nationally, and globally' (40). This multidisciplinary approach at local, national, and international levels focuses on a holistic, integrated approach, which enables researchers to find influencing factors that have not been seen previously, which can facilitate more informed intervention design, improve antiviral discovery and improve response to future variants of concerns (20).

The approach depends on shared and efficient governance, communication, collaboration and coordination and can be used at community, sub-national, national, regional and global levels (38, 40). The implementation of the One Health approach makes it easier to

comprehend the benefits and benefits to increases the chances to develop equitable and comprehensive solutions for COVID-19(20, 37, 38). For this approach to be successful, it needs to be supported by global organizations, and countries around the world. Following a one health approach may allow us to significantly improve antiviral accessibility, rapid COVID-19 responses and exit the pandemic.

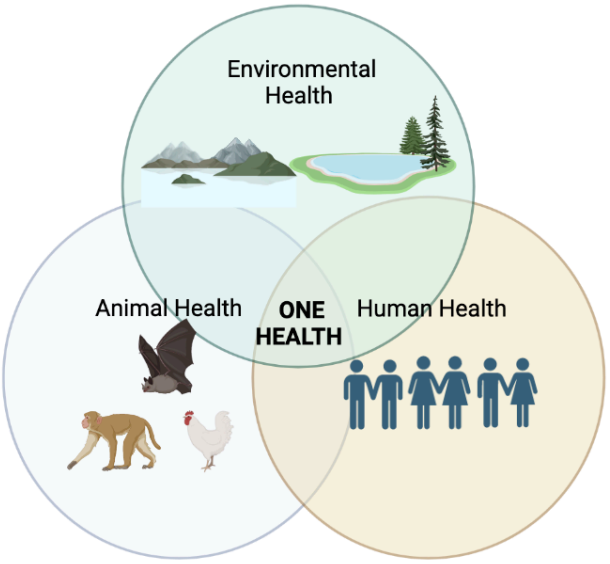

FIG. 1 One Health approach. One Health approach acknowledges the connection between human health, animal health and our common environment. Figure created with BioRender.com

POTENTIAL IMPACT/CONCLUSIONS

As the pandemic continues to proceed it creates a burden on individuals, families and society as a whole (23). The need to continue with the development and accessibility of antiviral treatments for SARS-CoV-2 is a critical area of research that has the potential to save numerous lives and families. While there are many emerging challenges associated with ensuring equitable distribution and access to these antivirals, ongoing efforts between the government and pharmaceutical companies need to be made to make affordable, accessible and equitable treatments. The one health basis will be hard to implement as many individuals may prioritize themselves and their needs before others; however, the pandemic is a global health issue and to fully move out of the course of the pandemic, global efforts need to be made (38, 40). Global efforts may be extremely hard as different countries have different guidelines making it difficult to implement actions that may benefit the world. Funding a global health organization may also be difficult as politics may come into play.

This article gives an overview of current problems regarding antiviral inaccessibility and ways to mitigate antiviral accessibility. Factors influencing antiviral inaccessibility includes DDI, age restrictions, high demand and scarcity and soaring prices, disparities in distribution and lack of knowledge of these antivirals leading to prioritization. Strategies to mitigate antiviral accessibility and promote equality includes repurposing drugs, creating a global health organization, collaborations between governments and pharmaceutical companies and implementation of One Health approach. This may help with the pandemic and may raise hope for people wanting things to return to normal. If these strategies can be implemented and learn to change our healthcare system, we may potentially change the course of the pandemic after 4 years. However, there is still a need to take rigour scientific, public health and societal actions, including significantly increasing funding for basic and applied research addressing disease emergencies to prevent this tragic history from repeating itself when another pandemic comes.

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