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Considerations for prevention and standby emergency treatment for travellers at high risk of COVID-19 hospitalization

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Introduction

At present, rapid initiation of oral antiviral agents is the standard of care in the USA for ambulatory patients with mild-to-moderate COVID-19 who are at high risk of progression to severe disease.¹ To prevent further transmission, for SARS CoV-2 self-test positive non-travellers, telehealth visits are preferred rather than physical clinic visits for persons with mild to moderate symptoms. Antivirals are prescribed, if no contraindications are identified, with education on when and how to seek any urgent in-person follow-up.

COVID-19 is a potentially life-threatening disease in high-risk travellers because they do not have established medical care in the countries they are visiting. If no contraindications are identified, antivirals may be prescribed along with education on when and how to seek urgent in-person follow-up. A basic tenet of travel medicine in the USA is to strive to ensure the provision of a standard of care at the destination that would lead to similar outcomes as at home. This tenet guides diplomatic services, government agencies, non-government organizations and multinational corporations as to whether an expensive medical evacuation should be undertaken. This equally applies to decisions made by travel insurance providers covering individual travellers abroad. For international travellers, in 2025, the physician who is already familiar with the patient's baseline medications and medical history and is readily available for telehealth might consider providing travellers with an off-label use prescription

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of a COVID-19 antiviral prior to travel and providing medical care remotely. As with malaria standby emergency therapy, which has been recommended for the past 30 years, telemedicine and self-treatment utilizing a reliable supply of carried medication should not replace seeking in-person medical care among high-risk travellers. Here we will discuss how to ensure that high-risk adult travellers can initiate timely treatment at the many destinations where COVID-19 antivirals are not readily accessible currently, including well-resourced destinations. Limiting factors may include high cost, but also strict government controls, restricted access points and different indications in destination countries. Clinicians who prescribe COVID-19 antivirals for travellers should consider many factors before doing so to ensure appropriate treatment and care by a medical professional. We outline several important considerations below.

Definition of high-risk traveller for antiviral use

Age is a major factor in determining risk for severe outcomes, and given current COVID-19 epidemiology, all persons 65 years or older and persons of any age with immunocompromising conditions or who use immunosuppressive medications, such as chemotherapy, should be considered for treatment regardless of history of prior infection or vaccination status. Additionally, people with specific medical conditions such as heart disease, obesity, diabetes or chronic lung disease are likely to benefit from treatment with risk for severe disease increasing with the presence of multiple medical conditions. Assessing a patient's risk for severe COVID-19 before infection occurs and predetermining the appropriate regimen can facilitate timely treatment. Clinical judgement by a provider who is familiar with the patient and their medical history is needed to accurately assess a person's risk on a case-by-case basis and determine whether treatment is indicated. This is especially important for physicians considering prescriptions for travellers.

COVID-19 antivirals

Three therapies are recommended among eligible adult outpatients: nirmatrelvir/ritonavir, and remdesivir are approved by the Food and Drug Administration and preferred options and molnupiravir is still under an emergency use authorization and only recommended if the preferred therapies are inaccessible or contraindicated (see Table 1).¹ Nirmatrelvir/ritonavir and remdesivir have been shown to reduce the risk of hospitalizations and death among high-risk, unvaccinated outpatients with mild to moderate COVID-19 illness by 89% and 87%, respectively.^{2–4} Molnupiravir reduced hospitalization and death by 31% among similar high-risk outpatients in clinical trials.⁵ Because remdesivir requires parenteral administration, the oral antivirals nirmatrelvir/ritonavir and molnupiravir are more feasible for widespread use. Nirmatrelvir–ritonavir is the most used COVID-19 antiviral in the USA and remains highly effective.⁶ However, ritonavir can interfere with the metabolism of many medications. Clinicians need to check for drug–drug interactions before using nirmatrelvir/ritonavir. Molnupiravir induces RNA mutagenesis, which interrupts viral replication, therefore, pregnant women should not take molnupiravir, and persons of reproductive age require birth control during treatment. Given the limitations of each of the recommended COVID-19 antivirals, new therapeutics that are highly efficacious but easier to use are needed.

Drug–drug interactions with nirmatrelvir–ritonavir. As with man-aging anticipated patient-specific drug interactions with other standby medications, such as doxycycline, fluoroquinolones, azithromycin, mefloquine, primaquine, acetazolamide and anxiolytics, travel medicine clinicians need to assess whether nirmatrelvir/ritonavir can be safely prescribed and whether adjustments to the patients' current medication regimen are needed. Using an easy to access database such as the University of Liverpool COVID-19 drug interactions tool can facilitate a timely assessment; we have summarized results for some commonly prescribed medications (Table 2). Because many older adults also have multiple medical conditions, they are likely to be taking medications that might result in interactions leading to potentially severe, life-threatening or fatal events. There have been over 320 severe events reported, of which 14 were fatal, due to drug–drug interactions.⁷ It is imperative to conduct a thorough review of the traveller's medications because some common medications, such as certain HMG-CoA reductase inhibitors (simvastatin, atorvastatin) and calcium channel blockers (amlodipine), require dose adjustments or should be stopped.⁸ For patients with complicated medical histories and medication regimens, the primary provider or specialist who manages these conditions regularly might be best suited to assess whether nirmatrelvir–ritonavir can be safely prescribed, make adjustments to a patient's medications and advise the patient if they do get sick overseas.

Prescribing standby treatment as off-label use

If a travel medicine clinician ascertains that no contraindications to nirmatrelvir–ritonavir exists in a traveller and provides a standby prescription for nirmatrelvir–ritonavir, they should be aware that this would be considered off-label use. The prescription should be accompanied by easy-to-understand written instructions on precise medication adjustments necessary to complement nirmatrelvir–ritonavir use with the understanding that consultation with a clinician via telehealth or in-person is still necessary prior to initiation. Furthermore, travellers ought to develop a plan to seek medical care if they become sick overseas, including identifying accessible clinical care centres and insurance coverage or anticipated costs, prior to leaving the country. Physicians providing care remotely from the USA via telehealth need to consider any potential for the patient to deteriorate or suffer from an adverse event and need urgent care at the destination country.

SARS CoV-2 activity and variant surveillance. Clinicians should make every effort to understand respiratory virus activity in the destination country, particularly SARS CoV-2 and influenza, for which there are available antivirals to guide appropriate treatment. Knowing which virus is predominant in the destination country would be helpful to the clinician, especially if a strain resistant to nirmatrelvir–ritonavir emerges. Therefore, it is important for clinicians to assess the SARS CoV-2 variants that are circulating at the destination country. Circulating variants change over time and vary in different regions of the world. Clinicians should be aware of which variants are prone to immune escape and more virulent as in these cases breakthrough infections will be more common and need for acute care more likely. These data are often not widely available and require the clinician to stay abreast of the literature. Ideally a tool or dashboard that readily provides this information would be developed for clinicians to make informed decisions about patient care.

Testing for respiratory pathogens

To discern between respiratory pathogens, testing symptomatic individuals is important, especially to ensure early initiation of treatment. For COVID-19, treatment should be initiated within 5 days and for influenza within 2 days. Molecular testing (e.g. polymerase chain reaction and nucleic acid amplification) is the gold standard in the USA because they are most reliable to differentiate between pathogens. A positive test is not required to initiate treatment. The antigen-based rapid tests for SARS CoV-2 that came into widespread use during the pandemic in the USA are convenient and acceptable but can produce false negative results and require repeat testing 48 h after initial negative test because they are less sensitive than molecular tests. Travellers who wish to carry rapid antigen tests should be aware of these limitations and consider other options. Although rapid molecular multiplex tests, namely combination influenza and SARS CoV-2 tests, are available, they are more expensive (~\$80/test) than rapid antigen tests for only SARS CoV-2 (~\$15–20/test) so their use will likely be limited to people who can afford and are willing to buy them. However, for high-risk travellers, rapid molecular multiplex tests are a great option, especially if travelling to remote destinations. Travellers may wish to consider where they can receive molecular testing in the destination country if they become ill with a respiratory infection.

Global access of COVID-19 antivirals

It is important that COVID-19 antivirals, which are life-saving medications, are available to all worldwide. Although the medications are readily available in the USA, they remained out of reach for most people in low- and middle-income countries for some time after their approval. As a result, Pfizer has agreed to permit generic manufacture of nirmatrelvir–ritonavir and signed an agreement with the Medicines Patent Pool, an UN-backed public health agency, for voluntary licensing, which will reach 95 countries. This agreement is a comprehensive strategy in collaboration with worldwide governments, international global health leaders, including WHO's Access to COVID-19 Tools Accelerator, and global manufacturers to optimize supply globally, including 17 European Union member states. This ensures that nirmatrelvir–ritonavir will be available at most destinations for a lower cost than in the USA. Currently, a course of nirmatrelvir/ritonavir costs \$1300–1500, which will not likely be reimbursed for off-label use such as standby treatment. Given the complexities of insurance coverage for prescriptions for off-label use, it is vital that travel medicine clinicians have a comprehensive understanding of the availability of antivirals at destination countries where they will also likely be available at lower costs, potentially as low as \$50. A map that identifies where the high-quality medications are available would be a useful tool for manufacturers to provide. It is anticipated that availability of affordable, high-quality COVID-19 antivirals worldwide will continue to improve in the future.

An ounce of prevention is worth a pound of cure

Travel medicine clinicians should consider counselling patients on measures to prevent respiratory infection while they travel. Non-pharmaceutical measures, such as masking, practicing good hygiene and physical distancing, can prevent infection from a number of respiratory pathogens, including the current SARS CoV-2 variants.⁹ Staying up to date on vaccinations is paramount, especially for travellers at high risk of severe disease. It

is common for travel medicine clinicians to recommend vaccines prior to travel, and they should counsel patients on COVID-19 vaccination.¹⁰ For the 2024–25 COVID-19 vaccine, Advisory Committee on Immunization Practices (ACIP) recommends that everyone 6 months of age and older receive one dose of the COVID-19 vaccine. People 65 years and older are recommended to receive two doses separated by 2–6 months regardless of vaccination history. People >6 months with moderate or severe immunocompromise should get two doses separated by 2–6 months and may also get additional doses under shared clinical decision-making. If previously unvaccinated or receiving initial vaccination series, more doses may be needed. Additionally, persons with moderate or severe immunocompromise are eligible for pre-exposure prophylaxis with pemivibart (PemgardaTM). Pemivibart is a monoclonal antibody for COVID-19 pre-exposure prophylaxis in people who are moderately or severely immunocompromised and unlikely to mount an adequate immune response to COVID-19 vaccination and who meet the FDA-authorized conditions for use. Pemivibart is not a substitute for COVID-19 vaccination. Per the pemivibart emergency use authorization (EUA), administration of pemivibart should be deferred for at least 2 weeks after a dose of COVID-19 vaccine. Travel medicine clinicians should ensure that prevention interventions are maximized before travel.

Conclusions

A perception may exist that there is currently so little severe COVID-19, even in the vulnerable, that the framework discussed here is unnecessary. However, new surges, evolving variants/sublineages, new antivirals and vaccine fatigue will continue to create a dynamic landscape in COVID-19 epidemiology. Vaccines and therapeutics are available to prevent severe disease, and we should make every effort to use them. This is an opportune time to ensure they are up to date on their COVID-19 vaccinations and to counsel patients on non-pharmaceutical interventions. Self-treatment with nirmatrelvir–ritonavir requires careful consideration. Travel medicine providers need to be empowered with tools that provide information about antiviral availability and resistance in countries as well as global variants circulation and their susceptibility to vaccines and treatment, to inform their decision-making about standby treatment. Travel medicine providers are in a unique position to increase COVID-19 vaccine uptake and educate clients on prevention measures, including testing and treatment, especially among high-risk travellers. They can be vital stewards of public health and use their encounters with high-risk patients to improve uptake and education about available interventions to prevent morbidity and mortality from COVID-19.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

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COVID-19 antiviral treatment options for outpatients who are at higher risk of progression to severe disease

Table 1

COVID-19 antiviral treatment	Who	Route	Duration	Time from illness onset	Specific Issues
Nirmatrelvir–ritonavir (paxlovid)	Adults; children aged 12 years and older and at least 40 kg	Oral	5 days	≤5 days	Adjust dosing in some cases; drug–drug interactions; severe kidney and liver contraindications
Remdesivir (Veklury)	Adults; children aged 28 days and older and at least 3 kg	Intravenous	3 days	≤7 days	Infusion over 30–120 min; infusion over 3 consecutive days; Need to check liver function and prothrombin time before initiation
Recommended to use if above medications cannot be used or are unavailable.					
Molnupiravir (Lagrevio)	Adults	Oral	5 days	≤5 days	Women who are able to become pregnant and their partners should use birth control; avoid in pregnant women

Table 2

Drug interactions for select medicines with molnupiravir and nirmatrelvir/ritonavir

Medication	Molnupiravir	Nirmatrelvir/ritonavir (5 days)
Acetazolamide	◆	◆
Alprazolam	◆	▲
Amlodipine	◆	▲
Apixaban	◆	▲
Atorvastatin	◆	▲
Atovaquone	◆	◆
Azithromycin	◆	◆
Buspirone	◆	▲
Diazepam	◆	■
Diltiazem	◆	▲
Doxycycline	◆	◆
Gemfibrozil	◆	◆
Levofloxacin	◆	◆
Lorazepam	◆	◆
Losartan	◆	●
Lovastatin	◆	■
Mefloquine	◆	▲
Midazolam (oral)	◆	■
Nifedipine	◆	▲
Primaquine	◆	◆
Proguanil	◆	◆
Rivaroxaban	◆	■
Simvastatin	◆	■
Temazepam	◆	◆
Triazolam	◆	■
Verapamil	◆	▲
Warfarin	◆	▲
Zolpidem	◆	▲

REF: University of Liverpool, COVID-19 drug interactions. Available at: www.covid19-druginteractions.org/checker#

Legend: ◆ , No interaction expected; ● , Potential weak interaction; ▲ , Potential interaction; ■ , Do not coadminister.