with COVID-19 antiviral pills, an independent organization must critically examine the role of such pharmaceutical companies.

In addition, these drugs could develop early resistance, making this drug a failure. Whatever the outcome, if these drugs are approved for a wider population, then the LMICs should get their proper and proportionate share. Unequal distribution will not only have a disastrous impact on global health but also socioeconomic recovery in low-income countries. The impact of this pandemic on these countries may last until 2024, whereas in affluent countries a recovery in terms of GDP may occur by the end of 2021.[9] All higher authorities should intervene now, including the World Health Organization and United Nations, to ensure this proportionate distribution before it is too late.

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Coronavirus disease 2019 (COVID-19) oral antivirals stewardship: Establishing game rules

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To the Editor—Vaccines against coronavirus disease 2019 (COVID-19) are the cornerstone of preventive strategies during this pandemic.[1] However, COVID-19 vaccine immunity wanes over time,[2] while specific population groups, such as the immunocompromised, may not be able to mount an adequate immune response to COVID-19 vaccination.[3] In addition, new variants with spike-protein mutations continue to emerge, raising concerns about immune escape and breakthrough infections in vaccinated individuals.[4]

Recently, based on the results of relevant clinical trials, an emergency use authorization was granted by the FDA for 2 new oral antivirals against COVID-19: molnupiravir by Merck and Ridgeback Biotherapeutics and Pfizer's nirmatrelvir-ritonavir. These antivirals, when administered within 5 days of symptom onset in adult patients with mild to moderate COVID-19, reduced the risk of hospitalization and death.[5,6] Both target specific enzymes and functions other than the spike protein and can complement vaccines. Nevertheless, the urgent need for effective outpatient treatment amid ongoing transmission entails the risk of irrational use of these antivirals. Thus far, data regarding the potential to induce resistance in case of inappropriate use are lacking. Cost should also be taken into consideration because each treatment course costs hundreds of dollars.[7,8]

For these reasons and to optimize their use, antiviral stewardship initiatives are necessary. These initiatives should target various sectors and levels of the medication prescription chain, including the healthcare system, prescriber and patient education, prescription practices, patient monitoring and feedback, communication, and diagnostics (Fig. 1).

From a healthcare system perspective, administration monitoring via electronic prescription is an efficient way to control

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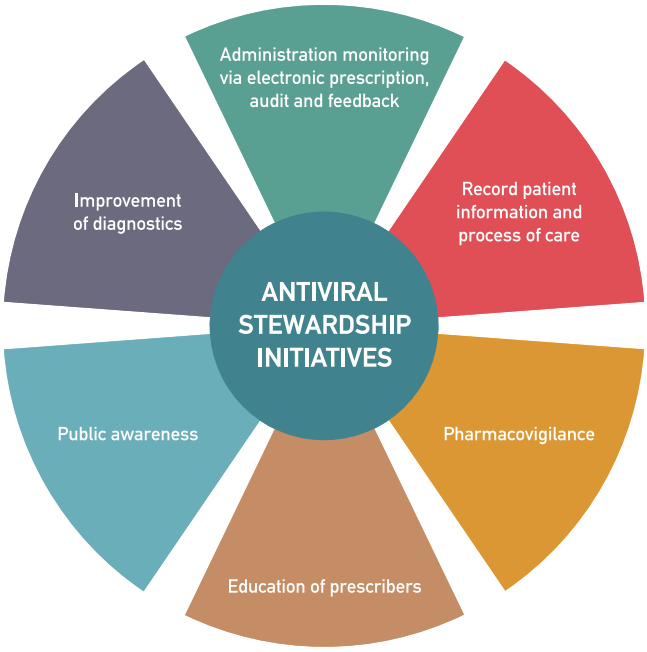

Fig. 1. Antiviral stewardship initiatives for the judicious use of the new oral treatments against COVID-19.

antiviral usage. For instance, electronic health system templates could automatically preauthorize administration only within the first 5 days after symptom onset. National healthcare authorities should adjust electronic prescribing systems so that essential clinical information is required in the form of a checklist before allowing submission of the prescription. Such information could include patient age, symptoms and date of onset, date of laboratory confirmed diagnosis, prior COVID-19 history, vaccination status, chronic medical conditions predisposing to severe disease, and exclusion of contraindications (eg, pregnancy). Currently, limited drug availability and high treatment cost dictate these antivirals should only be given to high-risk outpatients. Postprescription review and feedback according to predetermined criteria can help improve outcomes; several studies have shown that audit and feedback is a more effective stewardship tool than prior authorization and restriction.[9]

It is the physician's responsibility to inform patients about the indications as well as the dose and duration of therapy, and to urge them to start their treatment on time and to complete their course of medication. In addition, feedback from patients is beneficial regarding information about symptom attenuation, possible adverse effects or disease progression, in parallel with organized pharmacovigilance activities. For example, an electronic platform connected to the online prescription system could be completed by patients who receive antiviral medicaiton, while healthcare systems obtain, analyze, and communicate this information to prescribers, patients, and the public. Such information could contain type of treatment, time of initiation, adverse events, drug interactions, time to symptom improvement, need for hospital admission, and other patient outcomes. Continuous surveillance will allow for early identification of opportunities for improvement through targeted interventions.

The aforementioned tools are directed toward optimization of organizational, surveillance, and prescribing preparedness. However, to ensure a minimum competency skill set for all prescribers, prompt, accessible, and effective educational resources are necessary.[10] This is particularly critical during the early phase of disposal of these antiviral medications to promote appropriate prescribing practices. Training should include prescription criteria, basic pharmacology, drug interactions, and guidance regarding patient monitoring. Ease of access to specific tools should be ensured, including clinical guides, checklists, and data resources. Evidence-based and effective communication for prescribers and patients should be provided. It is also important to continue to emphasize the significant differences between prevention of disease through vaccination and treatment of disease with medications.[1] Communication extends to public awareness campaigns that inform, present data, and enhance trust in the scientific and medical community.

The evolution of diagnostics is a relevant and important field, necessary for effective stewardship.[11] Early diagnosis guides appropriate management, including administration of antiviral treatment in those in need. This factor is pivotal in the case of the antivirals discussed here, which are more effective during the early stages of COVID-19. Countries that are investing in these medications are expected to enhance their diagnostic yield by supporting their testing capacity (either molecular or antigen testing or both) to meet the expected needs of prompt diagnosis.

In conclusion, health services around the world are overwhelmed by the ongoing pandemic, and new oral antiviral medications represent an important addition in our limited armamentarium against COVID-19. Early implementation of antiviral stewardship interventions is required to ensure their appropriate use and to monitor their real-world effectiveness until we can determine their true role in the fight against the COVID-19 pandemic.

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Antibiotics against viruses: Brazilian doctors adrift

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To the Editor—As of the beginning of April 2021, Brazil is experiencing a unique moment in the coronavirus disease 2019 (COVID-19) pandemic. The number of cases of and deaths from the disease has never been so high. At the same time, drugs that have not been scientifically demonstrated to be effective against COVID-19 are increasingly being prescribed, both for early treatment and even for prevention.

This growing phenomenon is dangerous. An increasing number of doctors, and even doctors' associations, support the so-called COVID kit, a set of innocuous drugs, which supposedly would stop the progress of the disease. These doctors implicitly endorse a health policy[1] that wastes resources and efforts that could otherwise be directed to purchase of material to combat the disease, planning of pandemic control actions, and support of vaccination efforts.

Misinformation (ie, "fake news") and conspiracy theories about the disease and supposedly effective treatments against the severe acute respiratory coronavirus virus 2 (SARS-CoV-2) virus abound.[2] In the academic world, there is no doubt that the improper and indiscriminate use of any medication can adversely affect the health of the population, and it is no different with COVID-19, even though many Brazilian doctors claim exactly the opposite on social networks. A responsible doctor would refrain from recommending (or prescribing) a medication without any discussion of its risks and possible side effects.[3]

One of the great achievements in the history of medicine, revolutionizing the treatment of bacterial infections, was the systematic discovery and use of antibiotics, starting with the work of Alexander Fleming[4] in the first half of the last century and continuing to the present day. Antibiotics should be used to prevent and treat infections caused by bacteria, not those caused by viruses, since they are not effective against viruses.

Nevertheless, in the fight against COVID-19 in Brazil, azithromycin is prescribed on a large scale. In 2020, sales of the antibiotic increased 43.6%. This use of the drug is based on in vitro studies[5] that demonstrated some antiviral effect. But it would be necessary to test it on patients to prove any practical results, which unfortunately did not occur before it started to be prescribed. Since the first months of the pandemic, azithromycin has been prescribed either preventively or in early treatment. When compared to the standard treatment, there were no significantly better results for azithromycin.[6]

Exacerbating the problem is that azithromycin is being widely prescribed in conjunction with other medications, such as the anthelmintic ivermectin, which had a large increase in sales in Brazil in 2020, and the antimalarial hydroxychloroquine, which is widely touted for use against COVID-19, although clinical trials have found it ineffective and dangerous. Useless against COVID-19 and potentially dangerous separately, these drugs pose even more of a potential danger in combination.[7]

Azithromycin is a formidable drug, capable of fighting a broad spectrum of bacterial infections by inhibiting protein synthesis, very safe with relatively mild side effects at the doses indicated for its intended use and has proven to be very effective against infections of the respiratory tract, skin, and genital tract in particular. Azithromycin is an important tool for the control of diseases worldwide.[8] It may play a limited role even in the treatment of COVID-19, if there is a bacterial coinfection of the lungs.[9]

But when used in a way inconsistent with its established protocol, dosage, and usage, it is unclear what its effect on patients who are ill with COVID-19 would be. Therefore, the first recommendation should be caution, abundant caution, until well-designed clinical trials can be developed and completed.[10] But the Brazilian logic, even among many physicians, is that since we do not have any drug effective against SARS-CoV-2, we should try anything, at any dose, without considering the risks.

If the effect of the misuse of azithromycin on COVID-19 patients is unclear, the effect of its misuse on the general population is not. Intense use of azithromycin selects for bacterial resistance. A populous and diverse country suffering from social inequalities and chronic deficiencies in basic sanitation and prevention of sexual diseases, Brazil may serve as a perfect evolutionary laboratory for azithromycin-resistant strains of bacteria. Consequently, there is a very real risk that Brazil will have difficulties treating severe cases of many infectious diseases, such as childhood diarrhea, typhoid fever, syphilis, and gonorrhea, in the coming years. Thanks to the wide misuse of azithromycin to treat COVID-19 patients in Brazil, a well-tested and relatively

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