Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Availability of oral antivirals against SARS-CoV-2 infection and the requirement for an ethical prescribing approach

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The first two oral antivirals, molnupiravir and nirmatrelvir–ritonavir, are now becoming available in many countries. These medicines will be indicated to treat mild-to-moderate COVID-19 in non-hospitalised patients who are at high risk of progressing to severe COVID-19. These antivirals should be prescribed within 5 days of symptom onset, and after SARS-CoV-2 infection has been confirmed. However, the availability of these antivirals will be scarce for some time due to manufacturing constraints. Each country should establish a policy on the conditions under which these antivirals can be prescribed. Such a policy should be based on the fulfilment of five ethical elements: transparency, relevance, appeals, enforcement, and fairness. Following the principles of distributive justice, molnupiravir and nirmatrelvir–ritonavir should be prescribed according to a hierarchy of predicted efficacy, ideally on the basis of an evidence-based scoring system. The placebo-controlled randomised trials that supported the temporary authorisation of these two antivirals were conducted in unvaccinated patients with COVID-19, so an evidence-based prescription practice would only use these drugs for unvaccinated patients until further data become available. However, in the countries that authorised these antivirals in 2021 (the UK and the USA), both vaccinated and unvaccinated patients meeting particular requirements have access to these antivirals. Due to the complexity of prioritisation, national health authorities should start issuing their draft policies as soon as possible and these policies should be regularly updated. The effectiveness of these antivirals against the omicron variant of SARS-CoV-2 must be urgently assessed. Once implemented, molnupiravir and nirmatrelvir–ritonavir must show their effectiveness and safety in the real world, and health systems must be adequately adapted for the correct use of these antivirals.

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Introduction

There is a substantial unmet medical need for safe and efficacious oral medications for non-hospitalised patients with COVID-19. Currently there are five medicinal products authorised for treating patients with COVID-19 who do not require supplemental oxygen—four monoclonal antibodies (bamlanivimab–etesevimab, casirivimab–imdevimab, regdanvimab, and sotrovimab) and one antiviral (remdesivir). However, these products require parenteral administration and should be given in health-care facilities with trained staff to manage potential severe hypersensitivity reactions.[1–7] It is expected that in a few months, two oral antivirals, molnupiravir and nirmatrelvir–ritonavir, will become available in many countries. These oral antivirals have shown their clinical efficacy against COVID-19 in placebo-controlled, double-blind, randomised controlled trials (RCTs). However, using these antivirals in the real world will be challenging since their availability will be low across almost all countries for some time.

Molnupiravir

On Nov 4, 2021, molnupiravir was temporarily authorised in the UK for the treatment of mild-to-moderate COVID-19 in adults, provided they meet particular requirements.[8] 2 weeks later, the European Medicines Agency (EMA) issued advice on the use of molnupiravir and started evaluating the application for marketing authorisation of molnupiravir in the EU (table 1).[9,30] On Dec 23, 2021, the US Food and Drug Administration (FDA) granted emergency use authorisation for molnupiravir. At the planned interim analysis (n=775, for efficacy) of the pivotal RCT (MOVe-OUT), the external data monitoring committee recommended stopping enrolment due to efficacy with regard to the primary endpoint. Following the assessment of the full study population (n=1433) of this trial, molnupiravir treatment resulted in a 3 percentage point absolute risk reduction in hospitalisation or death when compared with the placebo.[12,13] This finding means that 35 patients must be treated to prevent one patient from being hospitalised or dying.

There are concerns over whether molnupiravir could speed up emergence of SARS-CoV-2 mutants[19] because this prodrug causes multiple viral mutations, which leads to impaired viral fitness and ultimately viral extinction.[31] Zhou and colleagues have shown that N-hydroxycytidine (NHC), the initial metabolite of molnupiravir, displays host mutational activity in an animal cell culture assay.[32] Theoretically, NHC might cause birth defects or long-term damage to patients' DNA, but according to the UK regulatory agency, it is of low risk for genotoxicity and mutagenicity in clinical use.[33]

Although all participants in the pivotal RCT were unvaccinated, the indication comprises all patients with mild-to-moderate COVID-19, regardless of patients' vaccine status. It is noteworthy that the USA emergency use authorisation requires that to prescribe molnupiravir, no other alternative treatment options (nirmatrelvir–ritonavir or even remdesivir or monoclonal antibodies) should be accessible or clinically appropriate,[12] which will restrict use of molnupiravir.

Nirmatrelvir–ritonavir

The second oral antiviral, nirmatrelvir (PF-07321332), is a 3C-like protease inhibitor developed by Pfizer that inhibits SARS-CoV-2 replication (table 1). Nirmatrelvir is administered with a low dose of ritonavir. The FDA

	Molnupiravir	Nirmatrelvir–ritonavir
Mechanism of action[8–11]	Molnupiravir is a prodrug that is metabolised to the ribonucleoside analogue NHC; NHC distributes into cells where it is phosphorylated to form the pharmacologically active ribonucleoside triphosphate (NHC-TP); NHC-TP incorporation into viral RNA by the viral RNA polymerase results in an accumulation of errors (error catastrophe) in the viral genome leading to inhibition of replication	Nirmatrelvir (PF-07321332) is a 3C-like protease inhibitor, preventing viral replication; ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir, resulting in increased plasma concentrations of nirmatrelvir
Indication		
EU[9] and UK[8]	Adult patients (aged ≥18 years) with mild-to-moderate COVID-19 diagnosis (not requiring supplemental oxygen) with a duration of symptoms of ≤5 days and positive SARS-CoV-2 diagnostic test; patients at increased risk of progressing to severe COVID-19; patients having at least one risk factor for developing severe COVID-19; not recommended during pregnancy or breastfeeding with a 4-day post-treatment window for use of effective contraception and interruption of breastfeeding	..
UK[11]	..	Adults who do not require supplemental oxygen and who are at increased risk of progression to severe COVID-19
USA[10,12]	Adult patients (aged ≥18 years), with mild-to-moderate COVID-19 diagnosis with a duration of symptoms of ≤5 days, positive SARS-CoV-2 diagnostic test, and for whom alternative COVID-19 treatment options are not accessible or clinically appropriate; patients should be at high risk for progressing to severe COVID-19, including hospitalisation or death; according to animal studies, molnupiravir might cause fetal harm during pregnancy; is not recommended for use in pregnancy	Adult and adolescent patients (aged ≥12 years, weighing ≥40 kgs), with mild-to-moderate COVID-19 diagnosis with a duration of symptoms of ≤5 days, with positive SARS-CoV-2 diagnostic test; patients should be at high risk for progressing to severe COVID-19, including hospitalisation or death
Contraindications[10–12]	None identified so far	Co-administration with medicines highly dependent on CYP3A for clearance or with potent CYP3A inducers; patients with severe hepatic or severe renal impairment; patients with a history of clinically significant hypersensitivity to the active substances
Adverse events[8–12]	Common: dizziness, headache, diarrhoea, nausea; uncommon: vomiting, rash, urticaria	With incidence of ≥1% and a difference in number of participants affected of five or more versus the comparator group were dysgeusia, diarrhoea, hypertension, myalgia; common adverse reactions: dysgeusia, diarrhoea, vomiting
Phase 2 and 3 clinical trial data—primary outcome measure	MOVe-OUT (NCT04575597):[12,13] at enrolment, patients should be unvaccinated and should present at least one of the following risk factors for disease progression: aged ≥60 years, diabetes, obesity (body-mass index>30 kg/m^2), chronic kidney disease, serious heart condition, chronic obstructive pulmonary disease, or active cancer; all-cause hospitalisation or death until day 29 (primary endpoint): molnupiravir, 6·8% (48/709); placebo, 9·7% (68/699); absolute risk reduction: 3·0 (95% CI 0·1–5·9) percentage points; relative risk reduction: 30%; number of deaths by day 29: molnupiravir, 0·14% (1/709); placebo, 1·3% (9/699); patients with baseline positive antibodies (recent infection): molnupiravir, 19·1% (137/678); placebo, 20·5% (147/666); total, 19·8% (284/1346); recruiting sites in Africa, Asia, Europe, North America, and South America	EPIC-HR (NCT04960202):[10] all-cause hospitalisation or death through day 28 (primary endpoint): nirmatrelvir–ritonavir, 0·8% (8/1039); placebo, 6·3% (66/1046); absolute risk reduction: 5·6 (95% CI 4·0–7·2) percentage points; relative risk reduction: 88%; number of deaths by day 28: nirmatrelvir–ritonavir, 0% (0/1039); placebo, 1·1% (12/1046); having received or expecting to receive any dose of a SARS-CoV-2 vaccine before the day 34 visit was an exclusion criterion; recruiting sites in Africa, Asia, Europe, Latin America, and the USA
Number of patients needed to treat to prevent one hospitalisation or death	35 (95% CI 17–1000)	19 (95% CI 14–25)
Posology[8–12]	800 mg every 12 h for 5 days; oral route	300 mg (nirmatrelvir) + 100 mg (ritonavir) every 12 h for 5 days; oral route
Price and manufacturing	US$700 in the USA,[14] $750 in Japan,[15] per treatment course; estimated cost-based generic price: $17·74;[16] Merck signed a license agreement with The Medicines Patent Pool to facilitate affordable access of the product in 105 low-income and middle-income countries;[17] although in this agreement 100% of south Asian and sub-Saharan African populations are covered, only 5% of European and central Asian populations and 18% of Latin American and Caribbean populations are covered;[18] Merck manufacturing capacity: 10 million courses by the end of 2021;[19] the manufacturing capacity of licensee companies must also be taken into account; 13 Indian companies will roll out molnupiravir at a price of Rs2000–3000 ($26·9–40·4) per treatment course[20]	$530 (USA)[21] per treatment course; Pfizer signed a license agreement with The Medicines Patent Pool to facilitate affordable access of the product in 105 low-income and middle-income countries,[22] although some countries (eg, Brazil, Iraq, Kazakhstan, Lebanon, Peru) are excluded;[23] Pfizer manufacturing capacity: 180 000 treatment courses by the end of 2021, and 120 million by the end of 2022;[24] the manufacturing capacity of licensee companies must also be taken into account
Countries where it is authorised	Temporary authorisation granted in India,[25] Israel,[26] Japan,[27] the UK,[8] and the USA[12]	Temporary authorisation granted in Israel,[28] South Korea,[29] the UK,[11] and the USA[10]

NHC=N-hydroxycytidine. NHC-TP=N-hydroxycytidine triphosphate.

Table 1: **Main characteristics of molnupiravir and nirmatrelvir–ritonavir as of Dec 31, 2021**

granted emergency use authorisation for this medicine on Dec 22, 2021, whereas the UK Medicines and Healthcare products Regulatory Agency (MHRA) granted conditional authorisation for nirmatrelvir 9 days later. Nirmatrelvir is under evaluation by the EMA, who have issued advice on its use based on interim results of the pivotal phase 3 RCT

(EPIC-HR).[34] At the planned interim analysis (n=1219, for efficacy) of this RCT, the external data monitoring committee recommended stopping enrolment due to efficacy with regard to the primary endpoint. Nirmatrelvir–ritonavir provided a 5·6 percentage point absolute risk reduction in hospitalisation or death when compared with the placebo.[10] Therefore, 19 patients must be treated to prevent one patient from being hospitalised or dying.

As a protease inhibitor, nirmatrelvir–ritonavir has no risk of displaying host mutational activity. Although this medicinal product will be given for a short period of time (5 days), prescribing physicians should bear in mind that ritonavir (given at 100 mg every 12 h) can interact with various medicines.[35] Both the FDA and the MHRA provided lists of medicinal products that are contra-indicated for concomitant use with nirmatrelvir–ritonavir and lists of established and potential clinically significant drug interactions.[10]

It is noteworthy that, although only unvaccinated adults were included in the pivotal RCT, the use of nirmatrelvir–ritonavir in the USA is temporarily authorised in both adolescent and adult patients, regardless of their vaccination status.[10] In the UK, only vaccinated and unvaccinated adults can receive this antiviral.[11]

Interim results of an additional phase 3 trial (NCT05011513), which included both fully vaccinated adults who are at risk of progression to severe COVID-19 and unvaccinated adults at low risk of hospitalisation or death, showed that 0·6% (two of 333) of the antiviral group were hospitalised versus 2·4% (eight of 329) of the placebo group, an absolute difference of 1·8 percentage points. No deaths have been reported and the trial is ongoing.[36]

Practical and ethical issues on the prescription of oral antivirals with limited availability

Molnupiravir and nirmatrelvir–ritonavir will initially be available in many countries under temporary authorisation schemes (as has already happened in the UK and the USA), so many months will elapse before a full marketing authorisation might be granted. In this Personal View, we assume that both medicines will be available—although in small quantities for some time—in many countries. The actual availability depends on the agreements reached by each country and the manufacturing companies (table 2).

The first decision to be made by the health authorities of each country is whether molnupiravir and nirmatrelvir–ritonavir should be provided under research protocols, or whether these oral antivirals should be available without prospectively registering any type of scientific data from patients. This decision is relevant because clinical trial protocols will need approval from research ethics committees and regulatory agencies, and investigators must seek informed consent from all participants. Trial protocols of these ideally large and

	Number of treatment courses		Percentage of the total population who are fully vaccinated*
	Molnupiravir	Nirmatrelvir–ritonavir	
Australia	300 000	500 000	77%
Belgium	10 000	..	76%
Canada	500 000	1 000 000	77%
Germany	..	1 000 000†	71%
Indonesia	600 000–1 000 000	..	41%
Israel	..	100 000	64%
Italy	50 000	50 000	74%
Japan	1 600 000	..	78%
Malaysia	150 000	..	78%
Philippines	300 000	..	34%
South Korea	200 000	70 000	83%
Switzerland	8640	50 000‡	67%
Thailand	200 000	..	65%
UK	2 230 000	2 750 000	70%
USA	3 100 000	10 000 000	62%

Data are from Reuters,[37] except where noted. *Data are from Our World in Data.[38] †Data are from Deutsche Welle.[39] ‡Data are from Südwestrundfunk.[40]

Table 2: **Number of molnupiravir and nirmatrelvir–ritonavir orders by country, and percentage of fully vaccinated individuals as of Dec 31, 2021**

Panel: Treatment guidance pertaining to molnupiravir for patients with COVID-19, as issued by the UK NHS*[42]

Indication

Patients who have tested positive for the virus and are at highest risk of getting seriously ill. This includes patients who have:

- Down syndrome
- A rare condition affecting the brain or nerves (including multiple sclerosis, motor neuron disease, Huntington's disease, or myasthenia gravis)
- Sickle cell disease
- Some types of cancer
- HIV or AIDS
- A severe liver condition (such as cirrhosis)
- Chronic kidney disease, stage 5
- Had an organ, bone marrow, or stem cell transplant recently
- Had chemotherapy grades B and C in the previous 12 months
- Had chemotherapy in the previous 6 months

How to get molnupiravir

Patients with one of the main symptoms of COVID-19 (high temperature, a new continuous cough, or loss of or change to the sense of smell or taste) will be sent a free PCR test kit at home.

The NHS will contact the patient (by text, email, or phone call) within 24 h of a positive PCR test result to check if the antiviral is right for the patient. The treatment is free of charge. Molnupiravir will be delivered to the patient through a hospital pharmacy, or can be collected by a friend, relative, or NHS volunteer responder.

NHS=National Health Service. *These requirements are also applicable to sotrovimab. On Dec 16, 2021, casirivimab–imdevimab was the monoclonal antibody chosen by the NHS. The change to sotrovimab a few days later was probably due to the lack of in-vitro activity of casirivimab–imdevimab against the SARS-CoV-2 omicron variant.

simple trials will describe in detail the selection criteria of participants and how to assess clinical outcomes. In December, 2021, this approach is being used in a UK-wide adaptive platform trial, PANORAMIC (ISRCTN30448031).[41] This trial aims to assess novel treatments for COVID-19 in the community. In addition, the UK National Health Service has established the prescription requirements for molnupiravir (panel). Only people at the highest risk of getting seriously ill have been included in the list of eligible patients with COVID-19, regardless of the patient's vaccination status.[42] The approach taken by other countries remains to be seen. Large differences in initial availability of both antivirals are expected between countries on the basis of antiviral orders made so far (table 2).

The practical issues

The main advantage of molnupiravir and nirmatrelvir–ritonavir is the option to dispense them at community pharmacies. However, this mode of distribution is unlikely to happen in many countries because, as mentioned previously, molnupiravir and nirmatrelvir–ritonavir will only be temporarily authorised, meaning that access to them will be controlled by the local health authorities rather than the normal channels of marketed pharmaceutical products. In some countries, available supplies might also be so low that dispensing the stock to community pharmacies could be inefficient. We presume that in almost all countries, molnupiravir and nirmatrelvir–ritonavir will primarily be prescribed outside of any research study, and could be dispensed at primary care centres, hospital pharmacies (or similar health-care facilities), or even in nursing homes with appropriate health-care professional resources, after the prescription has been filled out by a physician. In many settings and for most patients with COVID-19, mandatory rapid testing of SARS-CoV-2 infection by certified laboratories or health-care providers will not be followed by an in-person visit with their physician—telemedicine will be the norm.[43,44] Some health systems could try to implement a circuit that includes at-home diagnostic tests, telemedicine, and rapid turnaround of definitive laboratory testing.[45] In any case, withdrawal of the medication after the prescription will require a visit to the point of care.

Ethical issues

Assuming that both oral antivirals are authorised (as a result of having enough scientific evidence to support their positive benefit–risk assessment), the principles of distributive justice should be followed such that these medicines are prescribed according to a hierarchy of predicted efficacy, since all clinically similar patients deserve the same consideration. In other words, patients with COVID-19 who are most likely to benefit from these antivirals should be prioritised. This prioritisation should ideally be based on an evidence-based scoring system—as has been used with monoclonal antibody treatment for patients with mild-to-moderate COVID-19 who are at high risk of progressing to severe COVID-19.[46] This scoring system is based on the FDA eligibility criteria for monoclonal antibody therapy, and a direct correlation between the number of comorbidities and the rate of hospitalisations in this type of patient was shown; therefore, patients with higher scores should have higher priority.[46]

With limited availability of these antivirals, rationing is mandatory—as was the case with N-95 masks, ventilators, and other interventions in previous phases of this pandemic.[47] Consequently, it is necessary that each country establish a policy on the conditions under which these oral antivirals can be prescribed. Policies that set limits on health care in hospitals must meet five ethical elements[48] to be considered fair. These ethical elements are derived from the Accountability and Reasonableness framework,[49,50] and are applicable to the case we are addressing. The five elements are: transparency (the policy should be open to all stakeholders for review), relevance (the policy must be clinically relevant to the patient population), appeals (patients must have the opportunity to appeal a decision), enforcement (health authorities must guarantee the implementation of the policy), and fairness (clinically similar patients should be treated similarly across the country).[48]

Appeals and fairness, the third and fifth of these elements, deserve special reflections. Patients must be informed of the availability of SARS-CoV-2 antivirals and (if applicable) be told why they were not prescribed the antiviral by their physician. Since these antivirals must be prescribed and taken within 5 days of the onset of COVID-19 symptoms, appeals must be implemented and the final decision must be made in a very short period of time (ideally <12 h), following the decision not to prescribe an antiviral to a patient. This need for an effective and quick appeals process creates specific logistical challenges in health systems where seeking second (and definitive) opinions is not common.

Regarding fairness, health authorities will have to distribute the limited number of available packages of these antivirals to point-of-care sites according to pre-established criteria (eg, adult population at risk of severe COVID-19 served by each primary care centre, or percentage of fully vaccinated adults). Physicians should have clear guidance on how to prioritise the prescription of these products, since a first come, first served approach is inefficient and inequitable. While access to these oral antivirals is limited, health authorities must help prescribers with their decision-making process by issuing a guidance document with a list of characteristics—and absence of contraindications—that priority patients must present. For example, should patients with two risk factors (eg, obesity and diabetes) be prioritised over those with one risk factor (eg, aged ≥60 years)? Should patients at highest risk of progression to severe COVID-19 always be prioritised, and who are those patients? Should

immunocompromised patients always have priority over any other non-immunocompromised patients eligible for any of these antivirals? As mentioned previously, an evidence-based scoring system will be of crucial value. Furthermore, with substantial differences in efficacy and varying safety profiles, should a distinction be made between the patients who are prescribed one or the other antiviral according to the risk criteria of progression to severe COVID-19 presented by each patient? Prioritising nirmatrelvir–ritonavir over molnupiravir, as the FDA has done, does not appear to completely solve the problem of to whom these antivirals should be prescribed first when availability is limited.

SARS-CoV-2 oral antivirals and vaccinated patients with breakthrough infections

A debate has emerged in the USA over which patients should be treated with molnupiravir and nirmatrelvir–ritonavir. If, as we believe, predicted efficacy is the most crucial factor to consider, unvaccinated patients should be prioritised over vaccinated patients, even if the temporary authorisations include both vaccinated and unvaccinated patients with COVID-19 (as was the case with both antivirals in the UK and the USA). If there is a shortage of treatment courses available for these two antivirals, it seems reasonable to prioritise unvaccinated patients over vaccinated patients, since vaccinated individuals have a substantially lower risk of developing severe COVID-19 than unvaccinated individuals.[51] This approach has been rejected by some US bioethicists, who argue that "refusing a medicine to a vaccinated person with a breakthrough infection while giving it to a vaccine refuser ... was impossible to justify", and that this approach will reward people "who ignored public health advice and penalise those who heeded it".[52] There are two problems with this line of argument. First, when scarcity is the norm, predicted efficacy should be a key factor to consider, and since these two antivirals have been tested solely in unvaccinated patients, there is reason to prioritise unvaccinated over vaccinated patients. The efficacy (and the effect size) of these antivirals in vaccinated patients with COVID-19 should not be taken for granted and should be demonstrated in double-blind, placebo-controlled RCTs. In a few months' time, Pfizer will show the final results of a trial (NCT05011513) that, as mentioned previously, recruited fully vaccinated participants. Second, research has shown that vaccine hesitancy is much more prevalent in some ethnic groups than others, in groups with low levels of education, and in socioeconomically deprived groups and areas.[53–55] Some of the unvaccinated groups might have dismissed public health advice, but many others will either not have been reached by the advice, or not have fully processed the information.

Since these oral antivirals are expected to be less effective in vaccinated individuals with breakthrough SARS-CoV-2 infections than in unvaccinated individuals, the therapeutic use of these medicines in all patients regardless of vaccination status might reduce the positive benefit–risk assessment of these antivirals. From a cost-effectiveness perspective, this reduction in the positive benefit–risk assessment will result in the need to treat more patients to prevent a hospitalisation or death.

Omicron variant of SARS-CoV-2: an emerging and crucial factor

The appearance of the SARS-CoV-2 omicron variant (and other variants that could arise in the near future) might change the clinical effectiveness of nirmatrelvir–ritonavir and molnupiravir. Actual clinical effectiveness must be urgently assessed to ensure that the prescription of these medicines is indicated regardless of the SARS-CoV-2 variant causing the infection. This assessment is especially relevant after observing that—with the likely exception of sotrovimab—the monoclonal antibodies mentioned previously have little or no in-vitro activity against omicron;[56] although, this lack of in-vitro activity does not necessarily mean an absence of clinical effectiveness. In the USA, four treatment options are recommended in the following order of preference: nirmatrelvir–ritonavir, sotrovimab (single intravenous infusion), remdesivir (intravenous infusion for 3 consecutive days as off-label use, but backed by a placebo-controlled RCT[57]), and molnupiravir (only when none of the others can be used). These options are recommended to treat non-hospitalised patients with mild-to-moderate COVID-19 who are at high risk of clinical progression.[58] All of these medications have shown in-vitro activity against the omicron variant of SARS-CoV-2.[56]

Conclusion

Most patients with COVID-19 who begin treatment with a SARS-CoV-2 oral antiviral in the upcoming months will not be included in any research protocol. Although it would be expected that international organisations (eg, WHO[59] and the European Centre for Disease Prevention and Control[60]) and professional infectious diseases associations (eg, the European Society of Clinical Microbiology and Infectious Diseases[61] and Infectious Diseases Society of America[62]) would be diligent in including these antivirals in their guidelines on the treatment of patients with COVID-19, this guidance is unlikely to address the issue discussed. All countries aiming to make nirmatrelvir–ritonavir and molnupiravir available for their patients should prepare a policy that ensures the fair prescription of these medicines to all eligible patients. Some countries might decide not to use one of these antivirals (as France did with molnupiravir)[63] or to restrict the use of one antiviral to a very specific list of eligible patients (as the UK did with molnupiravir).[42] Due to the complexity of prioritisation, national health authorities should start issuing their draft policies as soon as possible, so that all stakeholders can provide their input. Ideally, the final consensus policy should be ready before these products

arrive in each country. This timeline should enable health systems to prepare, thereby maximising the benefits these antivirals can provide. The policy should be regularly updated, taking into account the availability of the two antivirals over time, the inclusion of novel treatments for non-hospitalised patients with mild-to-moderate COVID-19 who are at high risk of clinical progression, and the emergence of new SARS-CoV-2 variants. Health systems' point-of-care managers and prescribing physicians should have clear guidance on how to manage the number of treatment courses received and how to proceed with any eligible patient with COVID-19. The population should be appropriately informed about what to expect from their health system with regards to these two oral antivirals, which should be fundamental tools to fight the pandemic.

Research studies should assess the effect of different SARS-CoV-2 variants in conjunction with the number of patients with COVID-19 (clinically diagnosed and who have tested positive) who, as per each country's policy, fulfil the requirements for a prescription of nirmatrelvir–ritonavir or molnupiravir in the 5-day period from symptom onset. Any factor preventing proper process compliance in eligible patients must be identified and addressed.[64] The effectiveness of nirmatrelvir–ritonavir and molnupiravir needs to be shown in the real world, and health systems must show that they are properly adapted to prescribe and use these antivirals correctly. Health systems in high-income countries might find it challenging to show they are properly adapted, whereas this task could be insurmountable for health systems in low-income and middle-income countries, which could increase inequity in access to these medications.

To appropriately address the need for an ethical prescribing approach for these oral antivirals, each health system will need to decide upon a scoring system that prioritises eligible patients (this scoring system might differ between health systems), and, closely related, the most appropriate location from which to provide available oral antivirals and other treatments for non-hospitalised patients with mild-to-moderate COVID-19 who are at high risk of clinical progression to severe COVID-19.

Contributors

RD-R conceived the idea and wrote the first draft of the manuscript. All authors provided comments and edits throughout the drafting process for important intellectual content. All authors approved the final version of the manuscript and are accountable for all aspects included in it.

Declaration of interests

SLB declared speaker fees from Pfizer and Shionogi as well as advisory board fees from Pfizer (for ceftazidime with avibactam) and Shionogi (for cefiderocol), outside the submitted work. All other authors declare no competing interests.

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