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.

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Commentary

Hospitalization as an outcome in ambulatory COVID-19 trials—not applicable in every setting

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The COVID-19 pandemic has stressed hospitals worldwide [1]. Thus, most randomized trials have focused on hospitalized patients, and their primary outcomes have frequently included mechanical ventilation and death. It is only until recently that treatments for ambulatory patients (remdesivir, molnupiravir, and nirmatrelvir) have been included by the Infectious Diseases Society of America in their COVID-19 guidelines [2]. The randomized trials behind these drugs have a composite of hospitalization and death as their main outcome [3–5]. However, hospitalization and death are challenging outcomes in resource limited settings. The choice of outcome in ambulatory trials was discussed early during the pandemic by the WHO Working Group on the Clinical Characterization and Management of COVID-19 infection, who recommended (in addition to hospitalization and death) including a form of clinical assessment and frequent follow-up to better determine the extent of a treatment's effect on COVID-19 [6]. For these outcomes to be meaningful, hospitalization requires hospital space and resources and death requires a high mortality [7]. Let us analyse these trials to illustrate the problem.

Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients (PINETREE), Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients (MOVe-OUT), and Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-HR) trials

The PINETREE trial evaluated the use of remdesivir in ambulatory patients with a high risk of developing severe COVID-19 [5]. While studies evaluating remdesivir in hospitalized patients have not demonstrated to consistently improve clinical outcomes, PINETREE showed a decreased hazard of hospitalization or death (its composite primary outcome) among those who received remdesivir (0.7% vs. 5.3%, favouring remdesivir) [5,8]. The MOVe-OUT study evaluated molnupiravir, an oral antiviral, among people with early COVID-19 with one or more risk factors for severe COVID-19 [4]. It also found a lower risk of the composite COVID-19 related hospitalization or death in the molnupiravir group (6.3% vs. 9.2%, favouring molnupiravir). Finally, the EPIC-HR trial evaluated oral nirmatrelvir among non-hospitalized unvaccinated adults with COVID-19 at high risk for disease progression [3]. It too found a lower risk of developing the composite outcome of hospitalization and death in the nirmatrelvir group (0.77% vs. 7.01%, favouring nirmatrelvir). These results generated the current recommendations included in the Infectious Disease Society of America guidelines [2].

As stated previously, hospitalization capacity is a variable resource during a pandemic [9]. If hospital strain occurs, patients lose healthcare access, and with it, the possibility of being hospitalized. Even when a composite outcome of hospitalization and death can account for this, the mentioned trials had extremely low mortality (of note, the PINETREE study had no deaths), which prevented death from adding meaningful information. Therefore, the outcome is only driven by an event dependent on the availability of hospital space. In the ambulatory trials, it is unknown if

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hospitalization was available for everybody or if people received out-of-hospital care. Additionally, large variability within each trial is possible given different sites could have different hospital capacity, hospital occupancy, and COVID-19 caseload could be different according to the geographical area. While randomization may help to reduce this bias, different recruitment rates at distinct sites may still introduce variability.

Steps towards improvement

The rationale behind using hospitalization as an outcome is that it represents a degree of disease progression that requires treatment in a hospital. To better estimate the impact of the treatment on disease progression, standard hospitalization criteria would need to be defined for each trial, as a saturated hospital is more likely to defer admission to someone that has slight hypoxemia, but an empty hospital could opt to admit the same patient. For example, the PINETREE trial had a considerable number of patients living in assisted homes (15%), which could facilitate access to supplementary oxygen or medical personnel, something that could save the need for hospitalization. Thus, a patient could develop mild hypoxemia but receive supplementary oxygen out of a hospital, which would represent undocumented disease progression. A treatment's effect on COVID-19 progression could be better estimated by establishing criteria for need of medical assessment, emergency department visits (similar to PINETREE), and documenting if a patient received treatment out of a hospital. Hypoxemia (the most important reason for hospitalizing a person with COVID-19) could be detected by participants at home with a pulse oximeter, which could be established as a trigger to visit the emergency department. This would require a short training in the correct use of pulse oximeters and providing participants with a device tested in that population [10]. In the rare case of illiteracy, a color-coded device could be used. Additional alarming symptoms (such as dyspnea and chest pain) should be set to prompt emergency department visits.

Lack of applicability is a problem in trials other than the ones in COVID-19. For example, equivalence between oral and intravenous antimicrobial therapy for low-risk febrile neutropenia was shown in an early landmark trial [11]. However, outpatient management of febrile neutropenia may not be feasible due to socio-demographic factors, such as the lack of a care-taker or long distance from a hospital, compromising applicability in other contexts. Accordingly, current guidelines include very strict criteria in which viability must be assured [12]. Lack of applicability is particularly pressing in the current pandemic. For example, in Mexico, there has been a higher proportion of deaths out of hospitals when COVID-19 cases increase [13]. During the same period, an increase in the demand for oxygen tanks occurred, a demand that was unfortunately not well met [13]. This highlights that hospitalization is not an outcome that translates well in every context, and these factors should be considered when pondering the wide use of ambulatory treatments in contexts where healthcare saturation is present or likely to occur. Target trials, which are observational studies that emulate clinical trials, could be particularly valuable given the trials were conducted among unvaccinated individuals (a threat to applicability even in high-income countries) [3–5]. Also, the emergence of new SARS-CoV-2 variants could mean different treatment effectiveness, which would pass unnoticed if it is not routinely evaluated [14]. As an enormous number of antivirals would have to be obtained to secure wide distribution and early treatment, these types of studies can help lower- and middle-income countries obtain evidence on meaningful outcomes to better inform policy [7,15].

Transparency declaration

The authors declare that they have no conflict of interest.

Author contributions

IN conceived the manuscript, performed the literature review, and wrote the manuscript. SIVF and ASM aided in the literature review and in writing the manuscript.

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