Commentary

Antiviral treatment for COVID-19: ensuring evidence is applicable to current circumstances

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In related research, Pitre and colleagues[1] present the findings of a network meta-analysis that sought to establish the relative efficacy of oral antiviral therapies in reducing the risk of hospital admission or death in patients with mild-to-moderate COVID-19. This is an important patient population to enroll in randomized trials, as most patients with COVID-19 have mild disease and are treated as outpatients. The authors conclude that there is compelling evidence supporting the efficacy of nirmatrelvir–ritonavir and molnupiravir in reducing the risk death or hospital admission.

The challenge lies in applying the findings to current patients with COVID-19. The largest trial on nirmatrelvir–ritonavir, EPIC-HR, which was included in the network meta-analysis, enrolled unvaccinated participants who were infected with the Delta variant and had no evidence of previous SARS-CoV-2 infection.[2] Yet, currently, 83% of eligible people in Canada have received 2 doses of SARS-CoV-2 vaccine, which confers a high degree of protection against the same outcomes as these therapies have been shown to prevent.[3–5] Many people who acquire SARS-CoV-2 now have had a previous infection, and most recent cases have been infected with Omicron subvariants, which are less virulent than Delta.[6]

Nirmatrelvir–ritonavir is likely less effective in the real-world setting than suggested by the findings of the related network meta-analysis. Indeed, the manufacturer of nirmtrelvir–ritonavir recently terminated a trial that included vaccinated patients who were enrolled during the Omicron wave after an interim analysis found no statistically significant reduction in hospital admissions or deaths.[7] A recent observational study examining the effectiveness of nirmatrelvir–ritonavir among vaccinated patients infected with Omicron and without evidence of previous infection concluded that it was effective in reducing severe COVID-19; however, estimates of its effectiveness in preventing severe COVID-19 or death was lower than was observed in the EPIC-HR trial.[8] Indeed, the study suggested that vaccination alone was as or more effective than nirmatrelvir–ritonavir, and that the effectiveness of nirmatrelvir–ritonavir did not vary by vaccination status.[8]

Applying available evidence to clinical and policy decisions as the virus and population characteristics evolve is challenging. This is reflected in current Canadian guidelines for the use of novel antiviral drugs, which vary by province in terms of the age groups and comorbidities that define "high risk" to determine eligibility for publicly funded oral antiviral therapy. These therapeutic decisions would benefit from additional evidence from randomized controlled trials (RCTs), but this evidence is unlikely to emerge soon.

Key points

- Evidence from randomized controlled trials has shown that nirmatrelvir–ritonavir and monulpiravir likely reduce the risk of severe COVID-19, hospital admission and death in unvaccinated patients infected with early variants of SARS-CoV-2.
- Whether these novel antiviral drugs will have similar effectiveness for preventing serious outcomes in vaccinated patients or in those infected with more recent SARS-CoV-2 variants of concern, however, remains unclear.
- Adaptive platform trials, which iteratively integrate novel therapies, and large-scale observational studies using linked administrative health care data, which can estimate outcome risks in important clinical subgroups, represent the best options for rapidly evaluating the effectiveness of novel antiviral drugs and other COVID-19 therapeutics as both the virus and population characteristics evolve.
- These trials can be conducted succesfully in Canada, but they require dedicated funding support, policy changes to facilitate data sharing by administrative data custodians, and integration of trial enrolment at the point of care.

In a search of clinicaltrials.gov, the World Health Organization International Clinical Trials Registry Platform and the Cochrane CENTRAL register, we identified only 4 RCTs of monulpiravir or nirmatrelvir–ritonavir with clinical outcomes that were recently completed or actively recruiting, with 1 additional trial in children underway. None of these trials specifically addressed high-risk subgroups (e.g., older adults, immunocompromised people, pregnant patients), which were underrepresented in preapproval trials. The PANORAMIC adaptive platform trial, based in the United Kingdom, is evaluating COVID-19 therapeutics in patients with mild-to-moderate COVID-19 and only recently added nirmatrelvir–ritonavir to its list of study medications.[9]

Coordinated national and international approaches to rapidly generate the evidence required to guide clinical and policy decisions for COVID-19 therapeutics are sorely needed. National and international adaptive platform trials, which allow researchers to

compare multiple interventions simultaneously, and integrate new therapies into comparison arms as they are developed, offer the best opportunity to rapidly develop clinically relevant evidence. These trials allow for the addition and removal of study medications as evidence of effectiveness or futility accrues. They are large enough to adequately power evaluations of COVID-19 therapeutics in specific subgroups of patients, including the immunocompromised, pregnant patients and those with important comorbidities. Changing disease or population characteristics can reduce certainty regarding drug effectiveness, and adaptive platform trials can reopen treatment arms to address emerging evidence gaps. Evidence from adaptive trials have been used successfully to evaluate COVID-19 therapeutics in patients with severe COVID-19 and to support or refute the utility of therapeutic agents, including dexamethasone, remdesivir and immune modulators.[10–13] These types of trials should be employed to rapidly evaluate the therapeutic effectiveness of novel antiviral drugs in outpatients with nonsevere COVID-19. Trialists should harmonize inclusion criteria, therapeutic protocols and outcomes to facilitate updated meta-analyses.

Adaptive platform trials have been used for the evaluation of COVID-19 therapeutics in Canada,[11] but structural changes to health care and research funding systems are needed to make these trials easier to conduct. The Canadian Institutes of Health Research recently received a large federal investment for a Clinical Trials Fund. A portion of these funds should be allocated for infrastructure to maintain research networks that are capable of conducting large, well-coordinated platform trials. Successfully undertaking these trials also requires buy-in from health care institutions, provincial departments of health, COVID-19 therapeutics committees and clinicians to ensure that trial access can be integrated at the point of care.[14]

Real-world, postmarketing observational studies can also provide evidence to guide clinical and policy decisions. Large, pan-Canadian observational studies that use linked administrative health care data to quantify outcomes are most likely to generate this evidence quickly, and with adequately powered estimates of effectiveness in clinically important subgroups of patients. As previously noted in *CMAJ*,[14,15] policies that enable rapid, interprovincial linkage of data sets from observational studies and clinical trials to administrative health care data — including data on SARS-CoV-2 vaccination, testing and sequencing — are urgently needed to facilitate this work.

As the virus and population dynamics evolve, ongoing research is required to inform clinical and policy decisions. Adaptive platform trials and large observational studies offer the best opportunities to generate timely evidence on the effectiveness of COVID-19 therapeutics. These studies can be completed in Canada, but need to be supported by Canadian research funders, health care institutions, data custodians, health care providers and patients.

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