HEALTHCARE DELIVERY

Essential medicine selection during the COVID-19 pandemic: Enabling access in uncharted territory

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The COVID-19 pandemic requires urgent decisions regarding treatment policy in the face of rapidly evolving evidence. In response, the South African Essential Medicines List Committee established a subcommittee to systematically review and appraise emerging evidence, within very short timelines, in order to inform the National Department of Health COVID-19 treatment guidelines. To date, the subcommittee has reviewed 14 potential treatments, and made recommendations based on local context, feasibility, resource requirements and equity. Here we describe the rapid review and evidence-to-decision process, using remdesivir and dexamethasone as examples. Our experience is that conducting rapid reviews is a practical and efficient way to address medicine policy questions under pandemic conditions.

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The COVID-19 pandemic has posed unprecedented challenges for healthcare globally. Clinicians and policymakers have had to make urgent decisions regarding therapeutic interventions in the face of rapidly evolving evidence of variable quality. Some publications have become available as preprints prior to peer review,[1] while others have been retracted following concerns raised regarding data reliability.[2,3] To date, much of the preliminary evidence for new or repurposed interventions is from observational studies that are subject to bias and confounding, or from randomised controlled trials (RCTs) with limitations. RCTs of potential COVID-19 treatments are often unblinded and under-powered, and may report endpoints of limited clinical or local relevance.[4] Preliminary RCT results, even from apparently high-quality trials, may be reversed by the accrual of subsequent information.[5]

The South African (SA) National Essential Medicines List Committee (NEMLC) is a ministerially appointed, non-statutory advisory committee responsible for development and management of the national Essential Medicines List (EML) and Standard Treatment Guidelines (STGs).[6] Medicine selection for the STGs is based on principles of equity, evidence-based medicine, public health relevance, safety, effectiveness, cost-effectiveness, affordability and implications for practice. The STGs and EML are reviewed on an iterative basis, using an extensive peer review process. NEMLC decisions inform provision of medication in the public sector. Public sector standard of care frequently informs Prescribed Minimum Benefits entitlements in the private sector.[7,8]

In March 2020, an NEMLC COVID-19 subcommittee was formed to address the need for rapid appraisal and synthesis of evidence

in order to inform COVID-19 treatment guidelines. The subcommittee conducts accelerated evidence reviews and provides recommendations to the national COVID-19 Clinical Guideline Writing Committee, which in turn produces national guidelines on the clinical management of suspected or confirmed COVID-19 disease, issued by the National Department of Health (NDoH)/National Institute of Communicable Diseases.[9]

We describe the rapid review process developed by the COVID-19 subcommittee using corticosteroids and remdesivir reviews to illustrate the evidence-to-decision (EtD) framework used to arrive at a recommendation.

Rapid reviews

Systematic reviews of high-quality RCTs are considered the pinnacle of evidence and are increasingly used to inform clinical guidelines, and health and social care policies.[10,11] Systematic reviews use transparent and explicit methods to identify, select, critically appraise and synthesise data from relevant primary research based on *a priori* protocols. Full systematic reviews can take months, or even years, to complete.

In the context of a pandemic, there is an urgent need for rapidly synthesised and appraised evidence to inform policy decisions.[12] Rapid systematic reviews are a simplified but rigorous process to synthesise relevant evidence within a short period of time.

The rapid review process is outlined in Fig. 1. We developed a standard guidance document based on evolving methods from the Cochrane Rapid Reviews Methods Group.[13,14] When a topic is identified, the subcommittee defines the question and scope of the review by specifying the population (e.g. hospitalised or ambulatory), intervention and comparison characteristics, types of studies that are eligible for inclusion, and importantly, the outcomes that are relevant to inform a policy decision (the PICO – population, intervention, comparison and outcomes – framework is used). A lead reviewer from the subcommittee oversees the process, and independent reviewers with experience in conducting evidence syntheses may be co-opted to assist (e.g. members of technical expert review committees of NEMLC[6] and the South African GRADE Network[15]). All reviewers complete standardised conflict of interest and confidentiality forms. The aim is to complete an initial draft version of a rapid review report within a week (Fig. 1). If additional clinically relevant data on a previously reviewed product become available, rapid re-evaluation is undertaken.

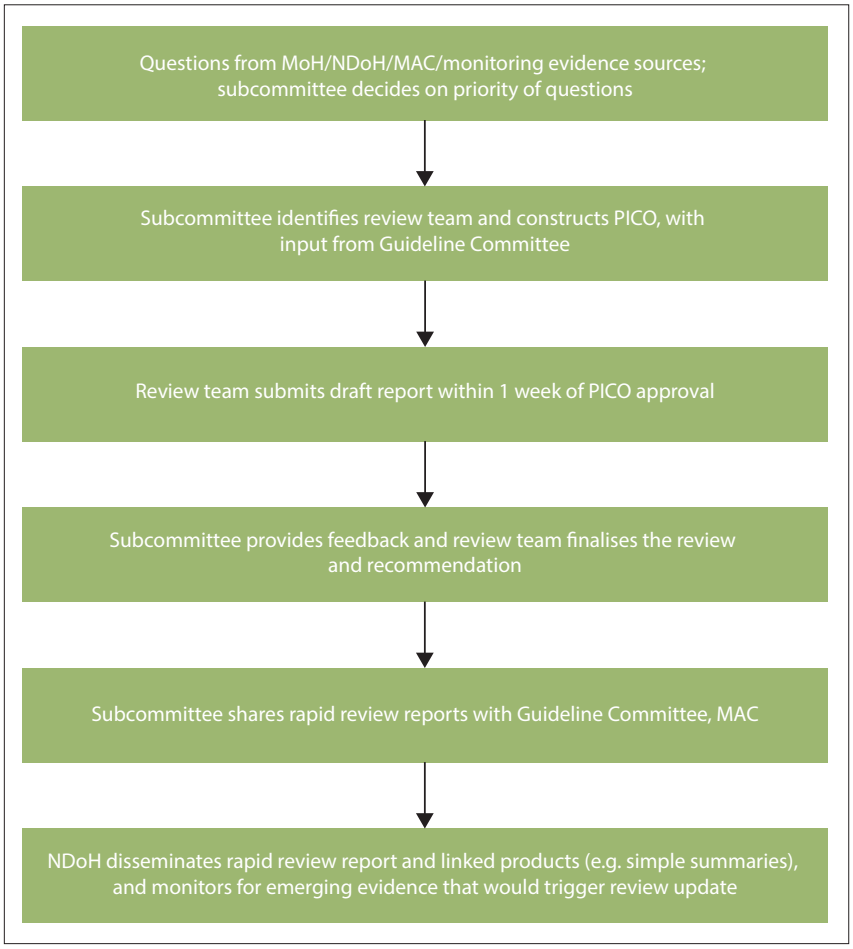

Fig. 1. Steps in conducting a rapid review for the COVID-19 guideline processes. (MoH = Minister of Health; NDoH = National Department of Health; MAC = ministerially appointed committee; PICO = the population, intervention, control and outcomes to be considered in the evidence review.)

The subcommittee reviews the evidence and uses an explicit EtD framework to make recommendations.[16,17] EtD frameworks were developed as part of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to support systematic and transparent consideration of all factors relevant for a clinical or public health recommendation.[18] The EtD framework has three main components: a clearly formulated question; assessment of the evidence and additional considerations for each decision criterion; and a final recommendation.[19]

The criteria applied in the EtD framework are quality of evidence, balance between benefit and harm, feasibility, infrastructure/resource use, variability in stakeholders' values and preferences, and healthcare equity. These factors influence the strength of the recommendation, as shown in Table 1.[19]

Importantly, all rapid reviews and recommendations from the NEMLC COVID-19 subcommittee are placed in the public domain and can be accessed on the NDoH website.[20] Acceptance and implementation of the guidelines depends on the level of trust and confidence clinicians have in the reliability and transparency of the process followed. To date, the subcommittee has reviewed 14 potential COVID-19 treatments (of which 3 were subsequently updated), and 4 are currently underway.

Remdesivir for the treatment of severe COVID-19

Remdesivir is an antiviral that inhibits viral RNA polymerases and has broad-spectrum activity against several virus families, including filoviruses (e.g. Ebola) and coronaviruses (e.g. severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV)).[21-23] It is being investigated as a potential treatment for COVID-19.

Table 1. Criteria that inform recommendations[19]

Criteria	Description and link with strength of a recommendation
Problem	The problem is determined by the importance and frequency of the healthcare issue that is addressed (burden of disease, prevalence, or baseline risk). If the problem is of great importance, a strong recommendation is more likely to be made.
Values and preferences	This describes how important health outcomes are to those affected, their variability and any related uncertainty.
Certainty of the evidence	The higher the certainty in the evidence, the more likely it is that a strong recommendation will be made.
Health benefits and harms and burden and their balance	The greater the net benefit or net harm, the more likely it is that a strong recommendation for or against the option will be made.
Resource implications	This describes how resource-intense an option is, if it is cost-effective and if there is incremental benefit. The more advantageous or clearly disadvantageous these resource implications are, the more likely it is that a strong recommendation will be made.
Equity	The greater the likelihood of an option reducing inequities or increasing equity and the more accessible it is, the more likely it is that a strong recommendation will be made.
Acceptability	The greater the acceptability of an option to all or most stakeholders, the more likely it is that a strong recommendation will be made.
Feasibility	The greater the feasibility of implementation of an option (specifically in the local context) to all or most stakeholders, the more likely it is that a strong recommendation will be made. Where there are key barriers to implementation of an option, these should be addressed.

The review team searched two electronic databases (PubMed and Epistemonikos) and the Cochrane living systematic reviews website, and checked the clinicaltrials.gov database for ongoing studies.

The review identified two RCTs that compared remdesivir with usual care. Both were terminated early: one for challenges with recruitment and the other as further randomisation was considered unnecessary.[24,25] Both trials found that remdesivir had no impact on mortality, with no increase in adverse events. One trial showed that remdesivir was associated with a reduction in median time to recovery, from 15 to 11 days.[25]

In the absence of a mortality benefit, the subcommittee considered reduction in intensive care unit (ICU) stay to be the most relevant clinical outcome, given SA's limited ICU bed capacity. However, there are as yet no data showing that remdesivir reduces ICU admission duration, or prevents progression to invasive ventilation. Preliminary results of the ACTT-1 (Adaptive Covid-19 Treatment Trial) study showed modest benefit among patients hospitalised for hypoxia, with a difference in median time to recovery of 2 days (7 v. 9 days; rate ratio 1.47; 95% confidence interval 1.17 - 1.84), but not among patients with severe disease (managed with high-flow nasal oxygen, other non-invasive ventilation, or invasive mechanical ventilation/ extracorporeal membrane oxygenation).[25]

The subcommittee contextualised the results to the SA setting, given that our admission and treatment practices, and median hospital length of stay, differ from those in the study setting. Retrospective data from the DATCOV Sentinel Hospital Surveillance dataset (which includes all private hospitals and an increasing number of public sector hospitals) show a median hospital stay of 6 - 7 days for COVID-19 patients in SA.[26] However, currently patients requiring oxygen therapy may be kept in hospital longer while completing a 10-day course of corticosteroids. SA's hospital utilisation patterns may therefore differ from those outlined in the ACTT-1 study.

The subcommittee concluded that the benefits of remdesivir in SA would be modest at best, and that these potential benefits need to be balanced against considerations of applicability, feasibility, costs and equity. Remdesivir is not yet registered by the South African Health Products Regulatory Authority, but is accessible on a named-patient basis (in terms of section 21 of the Medicines and Related Substances Act 101 of 1965). Both the originator and generic products are expensive, and global supply is unreliable. For these reasons, the subcommittee did not recommend the use of remdesivir in the state sector, except in the context of clinical trials, which would generate much-needed local data and address the question of mortality impact.

At the time of publication, the review was in the process of being updated owing to recent publication of a further RCT.[27]

Corticosteroids for the treatment of severe COVID-19

Corticosteroids were investigated as a treatment for COVID-19 based on their anti-inflammatory effects. Using a similar process to that described for remdesivir, the subcommittee conducted a rapid review of the evidence for corticosteroids in severe COVID-19.

The review identified a well-conducted, adequately powered RCT that compared dexamethasone with usual care in hospitalised patients. Dexamethasone reduced mortality in patients who required oxygen or invasive ventilation.[28] Adverse effects were not reported. The subcommittee considered the evidence of benefit to be clinically relevant, and of moderate quality. On this basis, it was agreed that the potential clinical benefit in SA would be substantial. In contrast to remdesivir, corticosteroids (including injectable dexamethasone) are inexpensive, are widely available, and have been shown to reduce mortality. Given these considerations, the subcommittee recommended that corticosteroids be used in all COVID-19 patients who require oxygen or mechanical ventilation.

The paucity of evidence for the safety and efficacy of corticosteroids in people living with HIV and in children was acknowledged.

Conclusions

The current health crisis has driven changes to the process of making prompt essential medicine policy decisions for COVID-19 clinical care questions. Rapid reviews are feasible and have been conducted successfully in the SA healthcare environment. They are a useful way of evaluating the best available information to urgently address specific clinical questions under pandemic conditions. In addition, using an EtD framework enables structured consideration of potential

resource implications, practical issues and healthcare equity, ensuring that justifiable policy decisions are reached. It is also envisioned that trust in the associated recommendations will be enhanced through readily accessible results of a robust and transparent decision-making process.

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Conflicts of interest. JN and HR are co-principal investigators for the World Health Organization-sponsored SOLIDARITY trial conducted in SA. TK is co-lead of the South African GRADE Network. RW is employed by Liberty Health (Pty) Ltd, a private health insurer operating in SA and across the broader African continent.

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