

Managing therapeutic uncertainty in the COVID-19 pandemic: rapid evidence syntheses and transparent decision-making

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Managing therapeutic uncertainty in the COVID-19 pandemic:

rapid evidence syntheses and transparent decision-making

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An explicit evidence-to-decision framework has allowed for global evidence to be adapted to local needs and context.

The outbreak of the COVID-19 pandemic posed challenges to the practice of evidence-informed decision-making. Soon after the index case was identified in South Africa, the first local clinical guidelines were developed, reliant on preliminary evidence. Quick decisions were essential to inform practice and procurement at a time of exceptional global demand for medicine supply. This chapter describes how a rapid review mechanism was implemented to enable the development of evidence-informed and context-specific clinical treatment and prevention recommendations for COVID-19 in South Africa. The chapter reflects on the extent to which there is evidence for the implementation of these recommendations in clinical practice, using medicines-utilisation data from the public sector. In order to manage the 'infodemic' of research evidence of variable quality, a robust mechanism of rapid evidence review, transparent decision-making, and dissemination of trustworthy,

accurate and context-specific recommendations was developed. Rapid evidence syntheses were produced by a sub-committee of the National Essential Medicines List Committee, supported by the South African GRADE Network and SAMRC Cochrane Centre. A generic rapid review protocol was developed, relying on GRADE principles and an evidence-to-decision framework. Consensus recommendations informed the National Department of Health/National Institute for Communicable Diseases clinical guidelines. Reviews were published on the National Department of Health website to advance transparency and were updated as new evidence emerged. Medicines-utilisation data showed increased use of corticosteroids, but there was also evidence of increased use of medicines not recommended. Further investment in technical capacity and support is needed to strengthen implementation, monitoring, and evaluation of clinical guidelines.

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Introduction

Since the World Health Organization (WHO) declared the novel Coronavirus disease (COVID-19) – caused by the SARS-CoV-2 virus – a Public Health Emergency of International Concern (PHEIC) on 30 January 2020, more than 195 million cases and 4 million fatalities have been recorded globally.^{1,2} Initially, little was known about the pathophysiology of COVID-19, which patients were at higher risk of poor clinical outcomes, and how cases were to be treated or prevented.

The global response was swift. Within two weeks, the WHO hosted a Global Forum on research and innovation for COVID-19 in collaboration with the Global Research Collaboration for Infectious Disease Preparedness and Response (GLOPID-R), and issued a co-ordinated global research roadmap.³ The WHO had previously developed guidance on what was termed “monitored emergency use of unregistered and investigational interventions” (MEURI) during infectious disease outbreaks.⁴ The immediate research focus was on repurposing existing medicines predicted to have some antiviral or immune-modulating activity, and investigating agents previously tested against other coronaviruses and viruses such as Ebola. Early targets included hydroxychloroquine/chloroquine, azithromycin, remdesivir, interferons, lopinavir/ritonavir, and corticosteroids.⁵

Despite the WHO guidance, many poor-quality clinical studies were rapidly and widely reported. These studies ranged from individual case reports and case series to underpowered and unblinded randomised controlled trials (RCTs), relying on questionable clinical endpoints. Such studies were therefore at high risk of bias. The conundrum was clearly articulated by Kalil: “A common interpretation of off-label use and compassionate use of drugs is that if the patient died, they died from the disease, but if the patient survived, they survived because of the given drug. This is not true.”⁶ Any pandemic would be expected to disrupt the usual conduct of clinical trials, and also to challenge the usual processes for assessing evidence for safety and efficacy of medicines for prevention and treatment.^{7,8,9} A pandemic lends weight to libertarian calls for the ‘right-to-try’ experimental options, even without the requisite evidence. In the face of therapeutic uncertainty, and under extreme pressure from healthcare professionals and the public, various health authorities have rapidly developed clinical guidance, while also working to improve the quality of guideline development methods. Rome and Avorn have warned that the pandemic would “inevitably leave considerable morbidity, mortality, and loss in its wake”, but that “damage to the country’s medication-assessment process – and the public’s respect for it – should not be part of its legacy.”¹⁰

The persuasive power of poor-quality evidence was clearly demonstrated in the initial advocacy for the use of hydroxychloroquine and azithromycin in COVID-19.¹¹ Based

on an uncontrolled case series of 20 French patients, off-label use of both medicines was adopted in many settings. In South Africa, the 19 March 2020 version of the National Department of Health/National Institute for Communicable Diseases (NDoH/NICD) clinical guidelines stated “Although there is currently no good evidence for any specific therapy for COVID-19, consider chloroquine for cases requiring hospitalisation, as well as for mild cases who have risk factors for severe disease.”¹² This questionable recommendation spurred the National Department of Health (NDoH) and National Essential Medicines List Committee (NEMLC) to develop a more robust local response.

In South Africa, the NDoH Essential Drugs Programme relies on the ministerially appointed NEMLC to select medicines to be used in the public sector and to develop Standard Treatment Guidelines (STGs) for their use. The NEMLC uses standardised evidence-informed processes in developing STGs. This chapter, written by members of the NEMLC and the NDoH secretariat, describes how a rapid review mechanism was implemented to enable the development of evidence-informed and context-specific clinical treatment and prevention recommendations for COVID-19 in South Africa. We reflect on the extent to which there is evidence of the implementation of these recommendations in clinical practice.

The global response to therapeutic uncertainty

The first element of the global response was to ensure that decision-makers had timely access to research evidence.¹³ Evidence repositories were rapidly developed by the WHO,¹⁴ national structures (such as in Australia¹⁵), by various Cochrane bodies (including the Cochrane COVID-19 Study Registry¹⁶ and the COVID-NMA initiative¹⁷), and non-governmental organisations (such as the Epistemonikos L.OVE platform¹⁸). Living-evidence syntheses were updated as evidence emerged. By 13 April 2021, the COVID-NMA living map included 2 846 RCTs from the International Clinical Trials Registry Platform (ICTRP), of which 2 322 were for COVID-19 treatment, 306 for prevention and 218 were vaccine trials. Of these, 252 RCTs had been included in evidence syntheses, following data extraction from published papers or preprints (214 on treatments, 10 on prevention and 26 on vaccines). The COVID-NMA living map^a depicts not only how widespread this research effort has been, with RCTs conducted on every continent, but how partnerships connected efforts across continents. The largest number of RCTs in Africa (n=39) were conducted in South Africa. Cochrane South Africa engaged with the COVID-NMA initiative, allowing South African decision-makers to use global materials, with adaptation to the local context. In this way, duplication of effort and *de novo* evidence retrieval and analysis was avoided.

a <https://covid-nma.com/dataviz/>

A second element of the global response was the design and rapid deployment of pragmatic trials of potential treatments. So-called 'platform' trials allowed for a common infrastructure to consider a range of possible treatments, adding or deleting options as the evidence accumulated. Key to this effort was the selection of common, clinically relevant study endpoints. The WHO SOLIDARITY trial, for example, assessed the impact of treatments on mortality, the need for assisted ventilation, and duration of hospital stay. In six months, and based on data from 30 countries, SOLIDARITY was able to show that remdesivir, hydroxychloroquine, lopinavir/ritonavir, and interferon regimens had little or no effect on clinically relevant outcomes in hospitalised patients. In the United Kingdom, the RECOVERY trial enrolled 39 658 participants from 181 trial sites; and within three months, RECOVERY reported the benefit of dexamethasone in hospitalised patients.²⁰

A feature of the fevered global research effort was the rush to release results, either as press releases or preprints, prior to peer review.²¹ However, two peer-reviewed papers were retracted after questions were raised about data integrity.^{22,23} Careful consideration was therefore required to ensure that guideline decisions were reasonable and unbiased, with clear assessment of study rigour and methodological strengths and weaknesses.²⁴

The South African response

The South African government invoked the Disaster Management Act (57 of 2002) on 15 March 2020, establishing a National Coronavirus Command Council, which was advised by a series of ministerial advisory committees.^{25–27}

To strengthen the process for developing clinical guidelines, a sub-committee of the pre-existing NEMLC was created, consisting of clinicians, infectious disease specialists, epidemiologists, pharmacologists, methodologists, public health specialists, and a board representative from the South African Health Products Regulatory Authority (SAHPRA). The sub-committee conducted rapid evidence reviews and made recommendations, ratified by the NEMLC, that informed the NDoH/NICD clinical guidelines. The SA-GRADE Network, Cochrane South Africa (South African Medical Research Council) and Centre for Evidence Based Healthcare (Stellenbosch University) and the Health Economics and Epidemiology Research Office (HE²RO) (University of the Witwatersrand) provided additional support. At the time of writing, recommendations had been published for convalescent plasma, azithromycin, interferons, tocilizumab, chloroquine (prophylaxis), chloroquine/hydroxychloroquine (treatment), colchicine, ivermectin (prophylaxis), ivermectin (treatment), lopinavir-ritonavir, remdesivir, mucolytics,

corticosteroids (systemic and inhaled), heparin, favipiravir, BCG vaccine, vitamin C, and intravenous immunoglobulin.

The scope of each review was pre-specified and searches (conducted in a minimum of two databases) were screened using the Covidence online systematic review management software.^b Where possible, credible living reviews such as those produced by COVID-NMA were used, including risk of bias assessments and meta-analyses, where appropriate. Findings were tabulated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.²⁸ An explicit evidence-to-decision (EtD) framework was used to document the basis for each recommendation.²⁹ The elements of the EtD framework were: size of the beneficial and harmful outcomes; balance of desirable and undesirable consequences; certainty of the evidence; feasibility of implementation; resource requirements; acceptability among stakeholders; and the potential impact on health inequity. Explicit criteria were developed to assess the need for review updates, as new evidence emerged.

To enhance the trustworthiness of the selection process, the necessary governance documents – such as routine management of interests and the rapid review protocol template – were placed in the public domain.^c Enhancing access to high-quality evidence syntheses (especially when evidence is uncertain) can prompt compliance with public health measures, and trigger discussion among the wider scientific community.³⁰ The NEMLC rapid reviews with recommendations were thus disseminated and shared on a number of platforms such as the NDoH website, NICD website^d and the EM Guidance mobile application.

Reflections on the process and outcomes

Providing firm and clear recommendations is challenging when the evidence is uncertain and rapidly changing. Implementing such policy choices is also complex. In a pandemic, relying on clinical evidence alone cannot resolve the complex trade-offs between health, economic, social, and other goals.³¹ Operational research may be needed to assess the impact of decisions that have been made.³²

The turn-around time for rapid reviews conducted by the NEMLC sub-committee ranged from seven to 21 days, as quick decisions were essential to inform practice and procurement at a time of exceptional global medicine supply demands.³³ On particular issues, such as access to unregistered medicines, there has been close engagement with SAHPRA. The sub-committee was able to draw on considerable global resources as well as additional local expertise in identifying evidence

b <https://www.covidence.org>

c <http://www.health.gov.za/covid-19-rapid-reviews/>

d <https://www.nicd.ac.za/diseases-a-z-index/covid-19/covid-19-guidelines/guidelines-for-case-finding-diagnosis-management-and-public-health-response/>

and preparing summaries that could inform consensus decisions. In particular, COVID-NMA and Epistemonikos were relied upon. However, local decisions needed to take into account additional factors, as included in the EtD framework.

Although no formal assessment of the medicines selection and guideline development process for COVID-19 has been conducted, the authors have reflected on their experiences during the pandemic. This is, of necessity, an 'insider' view of those experiences. The following examples illustrate the challenges faced in developing consensus guidelines, applying the EtD framework, and assessing the extent to which the guidelines were implemented.

Corticosteroids: accessible and affordable

Consensus was quickly reached regarding the use of dexamethasone in hospitalised patients requiring oxygen support, but there were concerns regarding a signal of harm when corticosteroids were used in ambulatory care.²⁰ The initial rapid review was updated in October 2020, following publication of a meta-analysis of eight RCTs, showing an almost 7% absolute reduction in mortality.³⁴ The rapid review also recommended alternative corticosteroids, based on dose equivalence. The question of whether inhaled corticosteroids should be recommended in ambulant patients not requiring oxygen support was more challenging. Although a large platform trial in the United Kingdom showed a benefit in time to resolution of symptoms³⁵, the NEMLC sub-committee did not recommend their use.³⁶ Noting that inhaled corticosteroids might be a "very attractive option for primary care providers, who are aware of the paucity of treatment options for ambulant patients not requiring oxygen therapy", the EtD summary pointed out that "this option could, if adopted, impact negatively on the availability of inhaled corticosteroids for patients with asthma or chronic obstructive pulmonary disease". Communicating the reasons for not recommending a treatment which is supported in other countries is critical, and should explicitly reference locally relevant issues such as availability.

Chloroquine: evolving evidence

Despite very limited, low-quality evidence for clinical efficacy at the time¹¹, chloroquine/hydroxychloroquine received emergency authorisation for use in severe COVID-19 in France and the United States in March 2020.³⁷ Hydroxychloroquine is not registered in South Africa. When local guidelines supported the use of chloroquine, there were concerns about the impact this would have on the limited stock available for patients with rheumatoid arthritis and systemic lupus. An initial rapid review of available evidence was conducted in April 2020, noting paucity of evidence for clinically important outcomes, and concerns about serious adverse effects. Chloroquine was therefore recommended only to be used in clinical trials. An updated review in March 2021 included findings from a Cochrane systematic review^{38,39}, and reported no evidence of benefit with increased risk of harm, strengthening the recommendation that chloroquine should not be used to treat COVID-19. Subsequently, evidence of the possible impact of off-label use on access to chloroquine for other indications has been reported in the Western Cape.⁴⁰

Ivermectin: uncertain evidence and misinformation

Being transparent about uncertain evidence for ivermectin (an anti-parasitic medicine not previously registered in South Africa) has posed considerable challenges. In the face of anecdotal reports of benefit⁴¹, a rapid review was conducted in January 2021.⁴² The review concluded that there was insufficient evidence to recommend ivermectin. The existing evidence was considered to be of low methodological quality, based mostly on pre-prints that had not been peer-reviewed. Medicines regulatory authorities, including SAHPRA⁴³, the US Food and Drug Administration⁴⁴ and the European Medicines Agency⁴⁵, advised against the use of ivermectin outside of clinical trials. The original manufacturer of ivermectin also noted the paucity of meaningful clinical evidence for ivermectin in COVID-19.⁴⁶ In March 2021, WHO's living review reached the same conclusions.⁴⁷ Internationally, the uncertain evidence for ivermectin has blurred the boundaries between science, policy and politics.⁴⁸ Locally, there has also been much public debate and misinformation from scientific groups – amplified by some press media and social media – regarding the efficacy and safety of ivermectin.⁴⁹ An updated review, and an addendum addressing published reviews, were posted online on 18 June and 2 July 2021 respectively.^{50,51} In July 2021, a Cochrane Review came to the same conclusion, that "the reliable evidence available does not support the use of ivermectin for treatment or prevention of COVID-19 outside of well-designed randomized trials".⁵² It is worth noting the use of the term "reliable evidence". The Cochrane Review characterised the available evidence as "very low- to low-certainty". In order to clearly communicate with the medical profession, the sub-committee published a commentary in the *South African Medical Journal* in August 2021.⁵³

Remdesivir: benefits, costs, and equity considerations

The first rapid review of remdesivir, an antiviral agent with *in vitro* activity against SARS-CoV-2, was conducted in April 2020, and included just one observational cohort (n=61) and a case report. By December 2020, the review⁵⁴ had been updated four times, and included a meta-analysis⁵⁵ of five RCTs (n=7747), illustrating the rapid evolution of evidence. Although none of the studies showed a mortality benefit, one RCT reported a shortened time to recovery, potentially reducing the need for hospital beds. However, remdesivir was not registered in South Africa and limited stock was expected to be available under section 21 approval, at a high acquisition cost. The key question, though, was whether the demonstrated benefit was generalisable to the South African setting, where decisions on how long to keep patients in hospital might vary. Thus, the NEMLC sub-committee recommended against the routine use of remdesivir, citing the lack of local clinically relevant benefits, and equity concerns.

Tocilizumab: effective but unaffordable

Given that severe COVID-19 has been linked to an excessive immune response, medicines that could be combined with corticosteroids were of interest. In early

March 2021, an updated rapid review of tocilizumab identified a systematic review and meta-analysis of 9 RCTs.⁵⁶ In hypoxic patients with evidence of severe inflammation, use of tocilizumab (with corticosteroids) was associated with an additional 3.2% absolute reduction in mortality. The evidence was considered robust, although specific patient sub-groups most likely to benefit could not be identified. A rapid estimation of the number of individuals in the public sector who might benefit from tocilizumab, based on the expected magnitude of a potential third wave, was conducted to assess potential budget impact. The review acknowledged that the medicine was probably cost-effective, but was unaffordable. The potential opportunity costs of foregoing other interventions, in the context of constrained funding, were considered, as well as equitable access and supply stability in the face of high demand in high-income countries.

Monitoring implementation of clinical practice guidelines

Guidelines should be applied in practice to achieve improvements in patient outcomes. Monitoring the implementation of clinical guidelines by means of retrospective audits of health records in the South African public sector is difficult, as most patient records are paper-based. Some evidence can, however, be obtained from medicines utilisation data, even though patient-specific details (e.g. patient characteristics, indications for use,

and clinical outcomes) are lacking.⁵⁷ Globally, medicines-utilisation data during the pandemic showed considerable disruptions, especially in high-income countries.⁵⁸ While medicines used in intensive care increased markedly during the first wave in such countries, utilisation of other medicines for acute care decreased.

The NDoH National Surveillance Centre (NSC) aggregates medicines procurement data from provincial health departments and suppliers for medicines that are on national contracts. NSC data on the utilisation of medicines recommended (corticosteroids) and not recommended (colchicine, vitamin C, azithromycin) for COVID-19 in the public sector for the periods January to October 2019 (pre-pandemic) and 2020 (pandemic), were compared. Data were not available for chloroquine, which is procured through a provincial buy-out process. In each case, the number of dosage forms (tablets, ampoules or vials) procured was reported, normalised by the estimated uninsured population, per province and nationally. Utilisation was expressed as the ratio of 2020 to 2019 utilisation (Table 1). A ratio greater than 1 would represent increased utilisation, and a ratio less than 1 would represent decreased utilisation. Accounting for differences in COVID-19 caseload per province, in both ambulatory and hospital settings, was not attempted. Ethics approval was not required as no individually identifiable data were retrieved.

Table 1: Utilisation of selected medicines, at provincial and national level, 2020 compared to 2019

Province	RATIO OF UTILISATION PER 1 000 UNINSURED POPULATION – 2020:2019									
	EC	FS	GP	KZN	LP	MP	NC	NW	WC	ZA
Corticosteroids										
Prednisone 5mg tablet	1.2	1.5	0.6	1.5	1.2	1.2	0.9	1.6	1.0	1.1
Betamethasone 0.5mg tablets	1.1	NR ^b	NR ^b	0.0 ^a	NR ^b	NR ^b	0.0 ^a	NR ^b	0.0 ^a	1.3
Betamethasone 4mg/1ml injection	1.7	1.9	1.4	1.5	0.7	38.5	1.1	2.0	0.9	1.3
Dexamethasone 4mg/1ml injection	2.8	1.7	1.1	2.5	0.4	8.3	2.0	0.9	2.0	1.6
Methylprednisolone 500mg/8ml injection	1.0	3.1	0.8	1.5	0.4	1.4	1.9	2.2	0.9	1.0
Methylprednisolone 125mg/2ml injection	1.4	0.3	1.9	0.9	NR ^b	6.1	2.0	1.6	0.9	1.2
Hydrocortisone 100mg/2ml injection	0.3	1.0	0.8	1.1	0.1	0.9	0.9	1.2	1.0	0.8
Azithromycin 500mg tablet	1.2	1.2	1.0	1.2	1.4	1.0	NR ^b	1.0	1.0	1.0
Colchicine 0.5mg tablet	1.1	1.7	0.7	1.2	0.8	1.8	1.0	1.1	0.9	1.0
Vitamin C 500mg/5ml injection	1.2	4.3	1.7	8.5	0.4	1.0	NR ^b	1.0	3.4	2.2

EC=Eastern Cape, FS=Free State, GP=Gauteng, KZN=KwaZulu-Natal, LP=Limpopo, MP=Mpumalanga, NC=Northern Cape, NR=not reported, NW=North West, WC=Western Cape; ZA=South Africa
mg=milligram, ml(s)=millilitre(s)

a: Utilisation for 2020 was reported as nil.

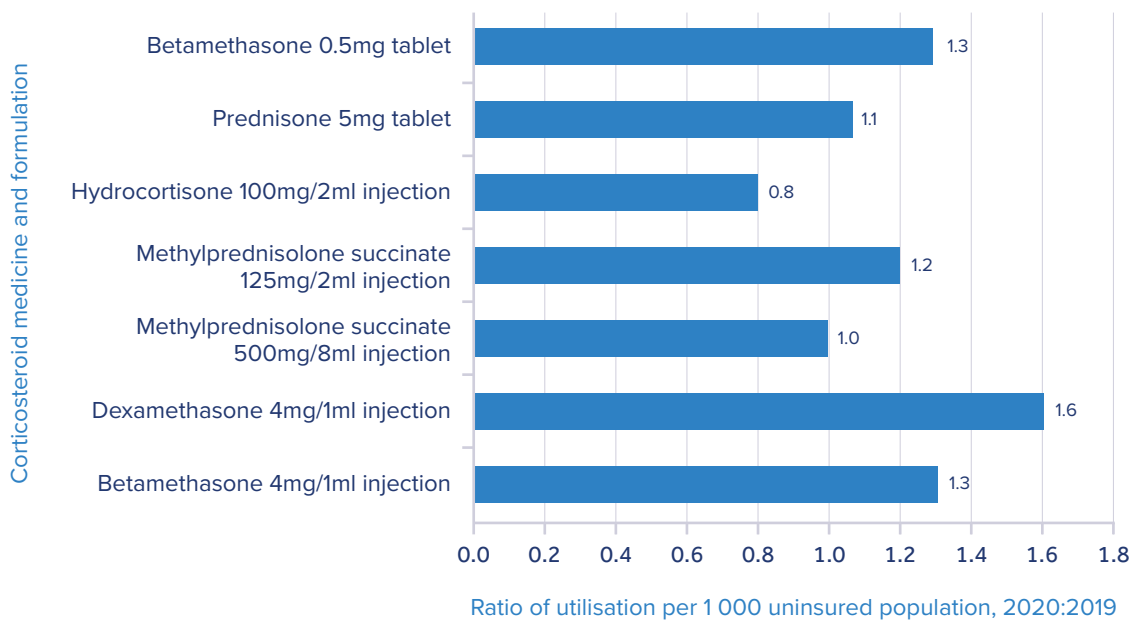
b. Provinces did not report any utilisation data for 2019 or 2020.

Given the recommendation that corticosteroids be used in hospitalised COVID-19 patients requiring oxygen support, an increase in the use of intravenous dexamethasone between 2019 and 2020 was expected. At a national level, utilisation increased 1.6 fold, but there were marked differences between the provinces. Utilisation increased in the Eastern Cape, Free State, Gauteng, KwaZulu-Natal, Mpumalanga, Northern Cape and Western Cape, but decreased in Limpopo and North West. The scale of the increase in Mpumalanga (8.3 fold) is difficult to explain. The increase in utilisation of betamethasone and methylprednisolone injections in Mpumalanga was also

markedly higher than in other provinces, perhaps reflecting stockpiling. At the national level, smaller increases in the utilisation of other corticosteroids occurred, with a small decline in the use of injectable hydrocortisone, as shown in Figure 1.

There are limitations to this analysis, as the data periods compared do not include the peak of the second wave (December 2020 to February 2021). Continued analysis of NCS data is therefore required, complemented with more in-depth medicines use evaluations (MUEs) conducted in selected health facilities in the provinces.

Figure 1: Utilisation of corticosteroids at the national level, 2020:2019



In April 2021, the recommendation against using azithromycin (unless indicated for other indications) was updated.⁵⁹ Although no data were available for the Northern Cape, utilisation increased 1.2 to 1.4 fold in the Eastern Cape, Free State, KwaZulu-Natal and Limpopo, but remained largely unchanged in Gauteng, Mpumalanga, North West and the Western Cape. This was contrary to anecdotal data of increased utilisation. Consideration should be given to the disruption of access to other essential services during lockdown, as azithromycin is also used for other conditions. The NSC data do not include any private-sector procurement, so the potential impact on antimicrobial stewardship efforts of possible increased use of this antibiotic in the private sector cannot be discounted.

The use of colchicine, except in the context of clinical trials, was not recommended.⁶⁰ Although the volumes of colchicine procured in the public sector are modest, increases in utilisation were seen in the Free State (1.7 fold) and Mpumalanga (1.8), and to a lesser extent in KwaZulu-Natal (1.2). Decreased utilisation was seen in Limpopo and the Western Cape, perhaps indicating that off-label use for COVID-19 treatment was not common in those provinces.

Although a rapid review of the use of vitamin C had not been conducted at the time of analysis, the NDoH/NICD guidelines recommended against its use, citing the paucity of evidence. The marked increase in utilisation of injectable vitamin C in KwaZulu-Natal (8.5 fold), Free State (4.3), and Western Cape (3.4) during the pandemic is therefore of concern.

Overall, therefore, while clear guidance was provided on which medicines to use in the management of COVID-19 and which not to use, the available evidence in terms of medicines utilisation in the public sector is mixed.

Conclusions

Drawing extensively on international collaborations and resources, a rapid yet robust evidence-informed approach for therapeutic recommendations under pandemic conditions was developed. An explicit EtD framework has allowed for global evidence to be adapted to local needs and context. The consensus decision-making

process allowed for consideration of the available clinical evidence of benefit and safety, resource use, feasibility of implementation, and equity considerations. However, as data were not available, assumptions had to be made about acceptability to stakeholders. Compared to the standard STG development process, both efficiency and transparency were improved. Reviews of the evidence were rapidly produced in order to guide the NDoH/NICD guidelines, which were updated electronically. The rapid review reports were disseminated on various platforms, and were updated as new evidence emerged that was assessed as being sufficient to change the type and strength of the recommendation.

However, the extent to which the resulting guidelines actually altered clinical practice, even in the public sector, is uncertain. While increased use of corticosteroids was evident in most provinces, this was not universally the case. There was also concerning evidence of increased use of medicines that were not recommended in some provinces, such as azithromycin, colchicine, and vitamin C. Despite the advice and guidelines being disseminated on various platforms, healthcare providers and patients may still not access them, or be aware of them. Conflicting messages are also communicated in the media, including on social media.

Recommendations

The processes for medicines selection and clinical practice guideline development will undergo considerable changes as National Health Insurance is implemented. Far greater attention will need to be paid to health economic evidence than has been the case in the past.⁶¹ However, important lessons learnt during COVID-19 can also be addressed. Firstly, improved transparency of the process is required, with evidence reviews, and explanations of how evidence has led to decisions, being placed in the public domain. The voice of stakeholders, including patients, must be strengthened. Although the compressed timeframes applied during the pandemic are not sustainable over the longer term, adequate resourcing of the clinical guideline process is needed to ensure more timely decisions.

Secondly, far greater efforts are needed to address clinical audit and feedback mechanisms. The data on the implementation of clinical practice guidelines that are available to facility-based and provincial Pharmacy and Therapeutics Committees are inadequate. Even in the absence of electronic health records, retrospective MUEs, linking medicine use to diagnoses of interest, in hospital and ambulatory care, are essential if a more nuanced picture of prescribing behaviour is to be developed. Such data would strengthen knowledge translation efforts and aid effective communication with all stakeholders.

Thirdly, the longer-term challenge of improving healthcare providers' understanding and use of evidence should be confronted. Addressing this challenge requires attention to undergraduate curricula, continuing professional development processes and offerings, and specialist training.

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