ORIGINAL ARTICLE

Prospective study of policies and use of therapies for COVID-19 among Australian health services during 2020

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Abstract

Background: The COVID-19 pandemic has generated significant debate about how emerging infections can be treated in the absence of evidence-based therapies to combat disease. In particular, the use of off-label therapies outside of a clinical trial setting has been controversial.

Aim: To longitudinally study policies and prescribing practices pertaining to therapies for COVID-19 in Australian health services during 2020.

Methods: Prospective data were collected from participating Australian health services who may care for patients with COVID-19 via an electronic portal. A single informant from each health service was emailed a survey link at regular intervals. Information was sought regarding changes to COVID-19 policy at their service and use of therapies for COVID-19.

Results: Overall, 78 hospitals were represented from 39 respondents with longitudinal data collection from May to December 2020. All Australian states/territories were represented with the majority (34/39; 87%) of respondents located in a major city. Just over half (20/39) of respondents had a written policy for COVID-19 therapy use at their health service at survey enrolment and policies changed frequently throughout the pandemic. Therapy use outside of a clinical trial was reported in 54% of health services, most frequently in Victoria, correlating with higher numbers of COVID-19 cases. At study commencement, hydroxychloroquine was most frequently used, with corticosteroids and remdesivir use increasingly throughout the study period.

Conclusion: Our results reflect the reactive nature of prescribing of therapies for COVID-19 and highlight the importance of evidence-based guidelines to assist prescribers.

Introduction

The Coronavirus disease 2019 (COVID-19) pandemic has generated significant debate about how health professionals treat emerging infections in the absence of

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evidence-based therapies to combat disease. In particular, the use of therapy outside of a clinical trial setting with the use of off-label antiviral and immunomodulatory therapies has been controversial.[1] Therapies might be lacking in safety and efficacy data, with little information to guide appropriate dosing, and there might be significant cost to health services.[2,3] In addition, there have been a unique set of external pressures in this pandemic given the extensive discussion in the media and the political sphere.[4] Therapies outside of a trial setting have

likely been utilised more in Australia because low case numbers have meant randomised controlled trials (RCT) have been challenging to facilitate.

At the start of the pandemic, an array of observational studies were published evaluating therapies such as remdesivir and tocilizumab,[5–8] largely without comparator groups, for the treatment of COVID-19. These studies likely influenced health service policy and prescribing practices outside the bounds of RCT. Several national and international bodies have published treatment recommendations for COVID-19,[9,10] initially with little supporting evidence to inform recommendations. Early versions of these guidelines therefore advised against the use of therapies outside of a clinical trial setting.[10–12]

Throughout the pandemic there have been several RCT in countries most affected by COVID-19,[13–16] which have shown variable benefit however have guided clinical practice, leading to changes in guidelines and policy. In Australia, the National COVID-19 Living guidelines have been developed to support healthcare professionals with continually updated clinical guidelines.[11]

We aimed to longitudinally study Australian Health Service's policies and prescribing practices pertaining to antiviral and immunomodulatory therapies for the treatment of COVID-19 during 2020, to examine how policies and drug usage changed over this time period and what information informed these changes.

Methods

Definitions

Off-label therapy: A drug is prescribed for an indication, a route of administration or a patient group that is not included in the approved product information document for that drug.

Study period

May to December 2020.

Participating sites

We aimed to enrol a representative sample of Australian health services. These were engaged through multiple channels including: (i) contact with lead investigators of sites participating in the Australasian COVID-19 trial;[17] (ii) 'Ozbug', an email list of infectious disease physicians who are members of the Australasian Society of Infectious Diseases (ASID);[18] (iii) expressions of interest through the ASID Clinical Research Network; and (iv) direct email contact with hospital infectious disease physicians or pharmacists at sites not already enrolled. A

single informant was used to report regular information from each health service. A health service could comprise an individual hospital or a hospital network. We asked that the nominated representative have contemporaneous knowledge of the policy and practice of treatment of COVID-19 at their health service.

Survey design and distribution

An online survey was designed by the authors using a web-based survey platform. It was piloted by four sites with feedback received on survey content. Participants were emailed a link to the survey; on enrolment, an 8–10-min survey collected baseline data from each site, after which a brief survey was sent at regular intervals to the nominated representative seeking information regarding changes in COVID-19 policy, approximate volume of admitted cases of COVID-19 and use of therapies at that health service. During the months of June to September 2020, sites were surveyed at 2 weekly intervals. From October onwards, the frequency of surveys decreased to monthly to account for decreasing COVID-19 cases in Australia. A reminder was sent to respondents, up to three times, if the survey was not completed.

Therapies surveyed included those that were Therapeutic Goods Administration (TGA) approved and available for other indications in Australia or those that became available in Australia for COVID-19 therapy. Included therapies were: hydroxychloroquine, azithromycin, lopinavir/ritonavir (lopinavir/r), remdesivir, tocilizumab, corticosteroids, anakinra, interferon–beta-1a and convalescent plasma.

Statistical analysis

Completed surveys were analysed using STATA Version 16 (StataCorp., College Station, TX, USA).

Ethics

Approval to conduct the study was provided by Monash Health Human Research Ethics Committee: RES-20-0000-289A.

Results

Survey enrolment was conducted from May to August 2020. Thirty-nine participants (representing a total of 78 hospitals) were enrolled with the majority (90%; 35/39) responding in May or June. Of the 39, 33 (85%) participants representing 71 hospitals completed surveys until the end of the study period. The number of

Table 1 Baseline demographics of survey respondents and representative health services at enrolment

Demographic	Number of sites (%)	
Location of health service (n = 39)		
Victoria	11 (28.2)	
New South Wales	11 (28.2)	
Queensland	9 (23.1)	
Western Australia	3 (7.7)	
South Australia	2 (5.1)	
Tasmania	1 (2.6)	
Northern Territory	1 (2.6)	
Australian Capital Territory	1 (2.6)	
Site type (n = 39)		
Individual hospital	25 (64.1)	
Hospital network	14 (35.9)	
Patient service type (n = 39)		
Adult	31 (79.5)	
Paediatric	8 (20.5)	
Role of survey informant (n = 39)		
Infectious diseases physician	25 (64.1)	
AMS pharmacist	10 (25.6)	
Other	4 (10.3)	
Health service demographics	Individual hospital (n = 25)	Hospital network (n = 14)
Median number of inpatient beds (range)	400 (102–958)	716 (50–2000)
Median number of intensive care beds (range)	26 (8–98)	25 (0–90)
Health service facilities (n = 39)		
Solid organ transplants	15 (38.5)	
Stem cell transplants	16 (41.0)	
Acute leukaemia therapy	23 (59.0)	
ECMO	16 (41.0)	
Participation in COVID-19 clinical trials (n = 39)	Anti-viral	Immunomodulatory
Multi-centre	31 (79.5)	11 (28.2)
Local investigator	3 (7.7)	1 (2.6)
Industry sponsored	3 (7.7)	1 (2.6)
AIHW classification of hospital group (n = 78)		
Principal referral centre	21 (26.9)	
Medium or large acute public	25 (33.0)	
Small or very small acute public	8 (10.3)	
Children's/women's hospitals	7 (9.0)	
Public forensic and psychiatry	2 (2.6)	
Other public hospital	4 (5.1)	
Medium or large acute private	4 (5.1)	
Small acute private	1 (1.3)	
Rehabilitation	6 (7.7)	
AIHW classification of remoteness area (n = 78)		
Major city	67 (85.9)	
Inner regional	10 (12.8)	
Outer regional	1 (1.3)	

AIHW, Australian Institute of Health and Welfare; AMS, Antimicrobial Stewardship; ECMO, extracorporeal membrane oxygenation.

hospitals represented from each participating health service ranged from one to seven.

Sample characteristics

The demographics of health services and respondents are summarised in Table 1. The majority (25/39; 64%) of

survey respondents were infectious diseases physicians. There was at least one health service from each Australian state or territory. The majority of respondents represented adult patient populations, with only 20% of respondents from paediatric sites.

Approximately 30% (21/78) of hospitals were principal referral centres and 87% were located in a major city
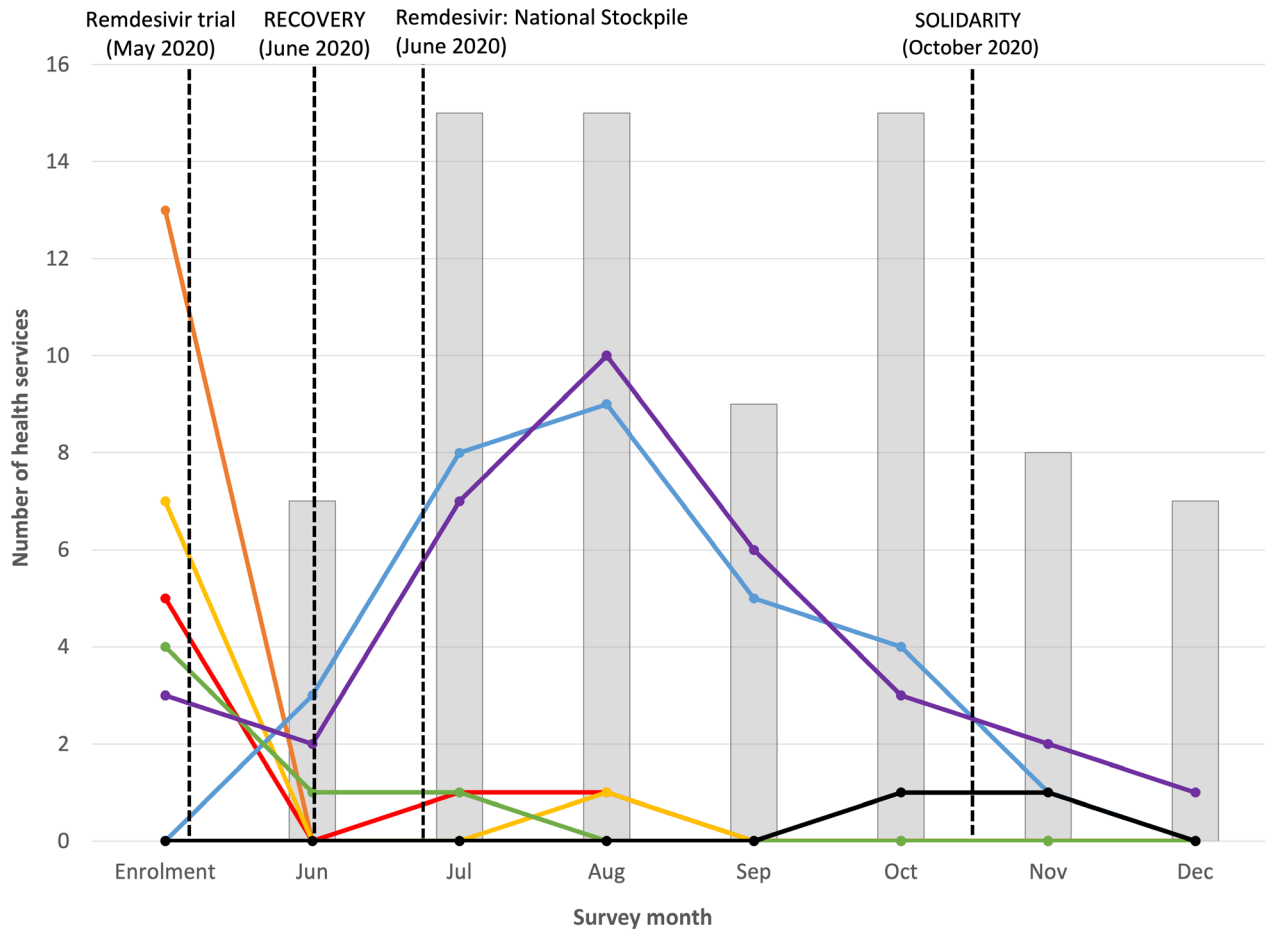
Figure 1 Summary of therapy use in COVID-19 per month in respondents from Australian health services. The grey bars represent the number of health services reporting patients with COVID-19 being admitted to their health service during the same time period. Displayed results represent use from the previous 2 weeks from enrolment to August, and from the last month for September to December. The dotted lines represent key time points that likely resulted in a change in clinical practice: remdesivir trial preliminary data published in NEJM (22 May 2020);[16] press releases of RECOVERY trial hydroxychloroquine data (5 June 2020)[14] and dexamethasone (16 June 2020);[13] remdesivir added to national stockpile (25 June 2020);[21] press release of SOLIDARITY trial data (15 October 2020).[22] (▭), Sites with incident COVID-19; (●─●), HCQ; (●─●), azithromycin; (●─●), lopinavir; (●─●), remdesivir; (●─●), tocilizumab; (●─●), corticosteroids; (●─●), convalescent plasma.

(Australian Institute of Health and Welfare classification).[19] Survey respondents represented 67% (4/6) and 64% (7/11) of principal referral hospitals in Victoria and New South Wales (NSW) respectively.[20] With regards to health service facilities, a large proportion of respondents reported sub-specialty referral services at their health service. Almost 80% of health services were involved in antiviral COVID-19 RCT at the time of study enrolment, with only 30% involved in immunomodulatory therapy trials, none of which was at paediatric sites.

COVID-19 cases

Eight health services reported COVID-19 cases in June, which increased in July and August to 15 health services

reporting cases. The majority of respondents reported low volume of hospitalised COVID-19 patients. Throughout August, health services reported increasing cases in the 2-week period preceding each survey response. The highest number of cases from one health service was 143. Overall, the number of health services reporting COVID-19 cases decreased towards the end of 2020 (Fig. 1).

Health service policies

At survey enrolment, just over 50% (20/39) of respondents had a written policy for the use of therapies for COVID-19 at their health service (Table 2). A combined policy for the use of antiviral and immunomodulatory

Table 2 Health service policies for therapy for COVID-19

Policy	Number of sites (%)	
Written hospital policy (enrolment) (*n* = 39)		
Combined antiviral and immunomodulatory	14 (35.9)	
Separate policies	6 (15.4)	
No policy	19 (48.7)	
Type of policy (*n* = 26)		
Units have their own policy	4 (15.4)	
Agreed health service	12 (46.2)	
State/territory policy	8 (30.8)	
External policy	2 (7.7)	
Sources for writing policy (*n* = 14)		
Local expertise	13 (92.9)	
Other health service procedures	11 (84.6)	
External policies	14 (100.0)	
Pre-print non-peer reviewed literature	8 (57.1)	
Peer reviewed literature	12 (85.7)	
Therapies permitted by health service (*n* = 39)	Survey start (May–June)	Survey end (December)
Antivirals	21 (53.8)	28 (71.8)
Immunomodulatory therapy	14 (35.9)	21 (54.0)
Convalescent plasma	2 (5.1)	1 (2.6)
Policy changes throughout study period (*n* = 39)		
Any policy change	17 (43.6)	
>1 change	10 (25.6)	
Factors informing change:		
International guidelines	5 (12.8)	
National guidelines	10 (25.6)	
RCT evidence	13 (33.3)	
Non-RCT evidence	1 (2.6)	
TGA provisional licensing of remdesivir in Australia	6 (15.4)	

RCT, randomised controlled trial; TGA, Therapeutic Goods Administration.

therapies was reported by 14 respondents, whereas separate policies for the two types of therapy were reported at six health services, giving a total of 26 policies to analyse. The most common type of policy in use was an agreed health service wide policy (12/26; 46%). Respondents who reported a unit specific or agreed health service policy were asked to identify sources they used for writing the policy. All respondents reported the use of external policies. Local expertise, use of other health service procedures and peer-reviewed literature were reported as sources for policy development in 92%, 85% and 86% of respondents respectively.

Antiviral therapy for COVID-19 outside of a clinical trial was permitted in almost 54% of represented health services at the start of the study period, increasing to almost 72% by December 2020. Immunomodulatory therapies were only permitted in 36% of health services and only two health services permitted the use of convalescent plasma. The most frequent factor reported in considering eligibility to receive therapy for COVID-19 outside of a trial was severe COVID-19 (71%), with the ineligibility to be in a clinical trial (67%) and the patient declining participation in a clinical trial (29%) being other reported factors.

The criteria required for the use of both antiviral and immunomodulatory therapies was most commonly approval for single patient use (Fig. 2). The number of health services permitting the use of hydroxychloroquine and lopinavir/r decreased over the study period, whereas those permitting the use of corticosteroids and remdesivir increased with 54% and 62% of health services allowing their use by December 2020 respectively.

Policy changes occurred frequently, with 17 respondents reporting a change in their policy between June and December 2020. The majority of changes were reported in surveys from July 2020 in Victoria and NSW. A total of 12 health services reported no policy for the entire study period.

RCT evidence was reported as the main factor prompting the policy change (*n* = 13), with the RECOVERY trial[13–15] referenced most frequently along with the clinical trial for remdesivir use.[16] Changes to National COVID-19 Living Guideline and the TGA licensing of remdesivir in Australia were also referenced in 26% and 15% of respondents reporting policy changes respectively.[11,21]

Use of therapies

At study commencement, 15 health services (retrospectively) reported the use of therapy outside of a clinical trial for COVID-19 since the start of the pandemic. Overall, the use of therapy was low, with hydroxychloroquine being the most commonly used agent in 13 health services, followed by lopinavir/r in eight health services. Anakinra and interferon were not used at any health service during the survey period. The use of remdesivir and corticosteroids increased during the follow-up period, with peak use reported in July and August 2020 (Fig. 1).

Therapies were never used outside of a clinical trial in 46% (18/39) of health services. Respondents from South Australia, Northern Territory, Tasmania, Western Australia and the Australian Capital Territory all reported no use of therapy. The major reason cited at enrolment for not using therapy for COVID-19 was the lack of safety data for the therapy (59%). During the follow-up period, a lack of patients with a specific indication for therapy was reported most frequently (54%). Other common reasons cited were no inpatients with

(A)

(B)
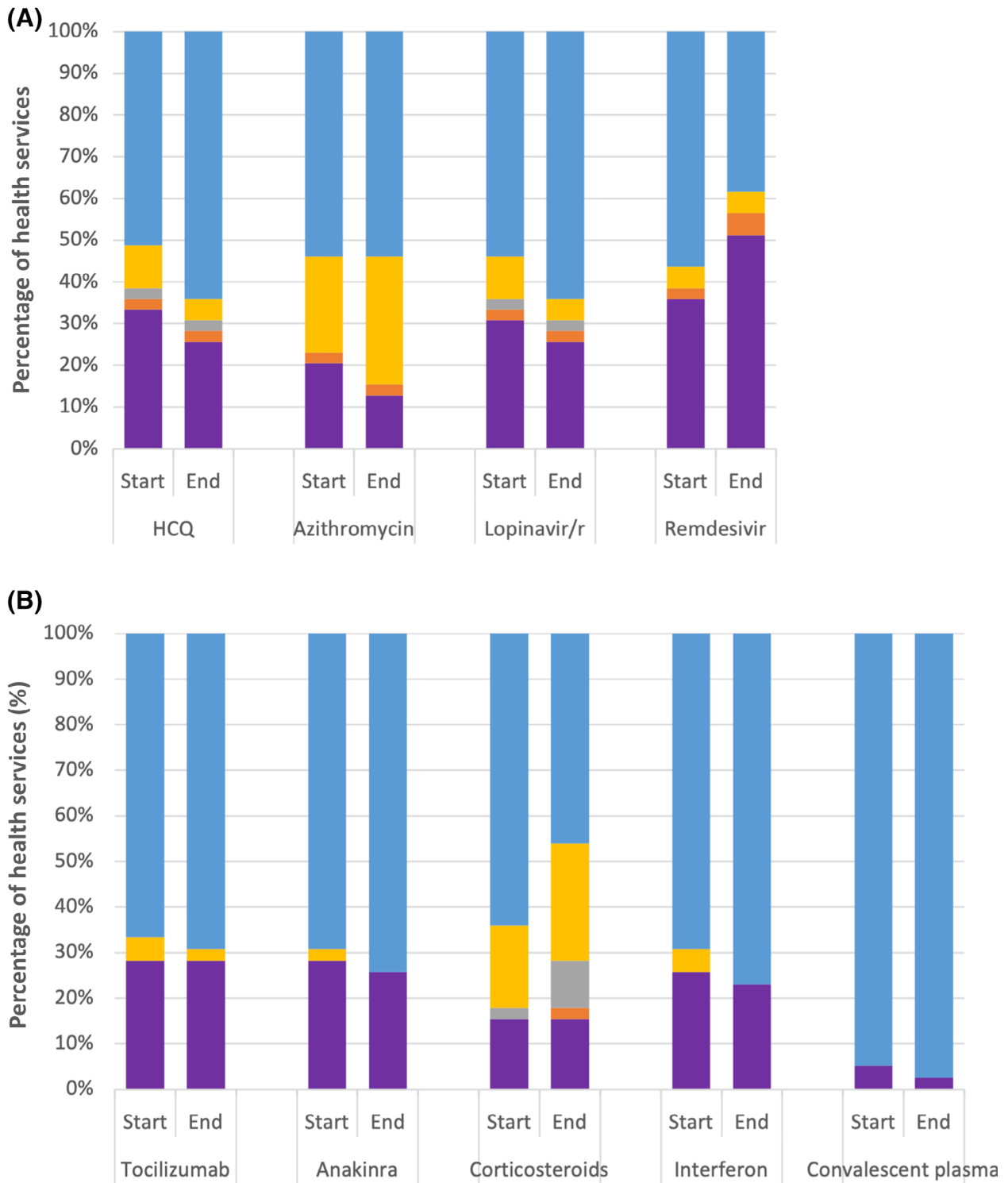
Figure 2 Summary of criteria required to permit therapy outside of a clinical trial for COVID-19 at Australian Health Services. (A) Criteria for antiviral therapy at the start of the study period compared with the end in December 2020. (B) Criteria for immunomodulatory therapy and convalescent plasma at the start of the study period compared with the end in December 2020. (■), Not permissible; (■), individual decision; (■), non-compulsory criteria met; (■), compulsory criteria met; (■), approval for single patient use. HCQ, hydroxychloroquine; Lopinavir/r, lopinavir/ritonavir.

COVID-19 and the health service not permitting the use of therapy outside of a trial setting. Lack of availability of a given therapy occurred at five health services, in both metropolitan and regional health services. Remdesivir was the most common therapy reported to have availability issues ($n = 5$), with hydroxychloroquine, anakinra and lopinavir/r also being reported as unavailable at the start of the study.

Use in paediatric health services

None of the paediatric health services retrospectively reported therapy use at survey enrolment. Throughout the follow-up period, four health services reported hospitalised COVID-19 cases, with only one reported the use of therapy, with tocilizumab, corticosteroids and remdesivir.

Discussion

We report the first study in Australia on health service policy development for therapy use outside of a clinical trial for COVID-19 and the use of these therapies over the first year of the COVID-19 pandemic. The survey respondents represented all states or territories of Australia, with both adult and paediatric sites included, with a high overall response rate of 85% until survey completion.

Survey enrolment occurred 2–3 months following COVID-19 being declared a pandemic. At this time, 50% of represented health services reported having a written policy for the use of therapies for COVID-19 outside of a clinical trial, and this increased to almost 75% by December 2020. It is likely there was uncertainty within health services about how to develop a policy for off-label therapy use in this context given the rarity of a new infection occurring on such a large scale. The majority of respondents reported the use of multiple resources for policy development. Despite an abundance of pre-print non-peer reviewed literature on COVID-19 at the start of the pandemic, this was the least reported source, although was still used by almost 60% of health services.

The permitted use of therapy varied widely between states and territories with health services in Victoria and NSW permitting use more frequently as well as those representing an adult health service compared with paediatrics. This likely reflects a greater need to consider therapy for COVID-19 given the significantly higher rate of COVID-19 cases in these states over the survey time period. Policy changes were reported frequently as a response to health services reviewing emerging data and adapting their policies based on this. RCT evidence was the major factor driving this change and was reflected in the permitted use of specific therapies, particularly the decreased use of hydroxychloroquine and lopinavir/r over the study period. In May 2020, an analysis of a multinational registry was published in the *Lancet*, analysing the use of hydroxychloroquine or chloroquine for COVID-19; however, the data were later retracted.[23] The 'SOLIDARITY' clinical trial for COVID-19 treatments showed that hydroxychloroquine and lopinavir/r produce little or no reduction in the mortality of hospitalised COVID-19 patients.[22,24] These studies along with updates to the National Living guidelines were likely the major reason for a change in clinical practice away from the use of these therapies.

The RECOVERY trial, which showed a mortality benefit in the use of dexamethasone for patients hospitalised with COVID-19,[13,15] was referenced frequently as a factor influencing policy change and coincides with an increase in the permitted use of corticosteroids. It is surprising that despite evidence of this benefit, corticosteroids were only permitted at approximately 55% of represented health services. This might reflect the low numbers of COVID-19 cases and in particular lack of severe COVID-19 and therefore a perceived lack of necessity to update health service policy. Corticosteroids are also relatively more easily available in hospital wards and clinicians may have been able to prescribe this therapy without policy approval.

Similar observations were made in the reported use of therapies by health services, with corticosteroid use dramatically increasing in July and August 2020 coinciding with the increase in COVID-19 cases particularly in Victoria. TGA provisional approval for the use of remdesivir for hospitalised COVID-19 patients was reported as a significant factor in change of policy permitting the use of remdesivir and is likely a factor relating to the increased use of remdesivir later in the study period. Despite no evidence of mortality benefit with remdesivir,[22,24] the number of health services permitting its use was higher than that of corticosteroids (62% vs 55%), which again might reflect the easy availability of the medication from the national stockpile.[21]

Overall, the use of therapy was less in the paediatric health services, although the number of represented health services was small. Severe COVID-19 cases in the paediatric population tend to be paediatric multisystem inflammatory syndrome[25] and therefore we would expect to see more use of biologics in this population. The low use of remdesivir may be explained by a lack of TGA approval of the therapy for children aged <12 years.

There are several limitations of the present study. Our overall survey captured a small fraction of Australian hospitals with the majority of survey respondents working at health services in a major city, at principal referral centres and medium-large acute public hospitals. It is likely that both policy development and the use of therapies would be different in more rural, smaller health services and our results may therefore not be generalisable to all Australian health services. However, we believe our results reflect the policies and practices of those health services most affected by COVID-19 in 2020. By the end of December 2020 when our survey ended, there had been 28 408 reported cases of COVID-19 in Australia, with 25 291 (89%) cases occurring in Victoria and NSW.[26] The majority of our survey respondents worked in these states and represented a total of 22 health services in these states. Furthermore, 75% of COVID-19 diagnoses in Australia in 2020 were made in patients residing in major cities, and this was higher in both NSW and Victoria with 77% and 80% of COVID-19 cases occurring in major cities.[27] Survey respondents also represented 64% (7/11) and 67% (4/6) of all principal referral hospitals in NSW and Victoria respectively.[20] It would be useful for future surveys to target the enrolment of additional rural sites to allow for comparison, although in this context there were very low numbers of COVID-19 cases at rural sites. There was use of only one key respondent from each health service; however, we requested that this respondent had the appropriate knowledge of the health service policy and also the use of therapies for COVID-19. In future studies, it would be useful to ascertain how well health service policies aligned with clinical practice, which was not specifically assessed in this survey.

In an emerging pandemic, being able to rapidly develop policies to support clinicians and standardise therapy is important. Established mechanisms in health services such as medication governance committees and therapeutics reference groups can be used to support this. This ensures evidence-based practice by regular review of the scientific literature and also ensures monitoring of the safety of any therapies. Emerging evidence and policy changes are the major influencers of prescribing practices in a pandemic. The results of this study reflect the reactive nature of prescribing of therapies and importance of evidence-based, living guidelines to guide our response to the current COVID-19 pandemic and also in the event of other emerging infections in the future.

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