Rapid Research Information Forum

Update: The most promising therapeutics for COVID-19

6 July 2020

IMPORTANT NOTICE: *COVID-19 research is developing rapidly. Rapid Research Information Forum (RRIF) briefings summarise the best available evidence at the time of writing and each is clearly marked with the relevant submission date. This update expands on the content of the briefing dated 17 May 2020 and should be read in conjunction with that document. Further updates may be published and consultation with the Australian Academy of Science is possible if the reader has questions.*

The original brief, provided at the end of this update, responded to the question: What are the most promising COVID-19 therapeutics in development globally and nationally, and what are their mechanisms of action, their stage of development and their strengths and limitations.

Key findings (updated)

- There are over 300 potential COVID-19 therapeutics being explored in pre-clinical testing and of these, 200 are in clinical trials.
- Preliminary Phase III clinical trial data are now available for remdesivir and indicate that it may quicken recovery for COVID-19 patients. However, there is no statistically significant evidence of a reduction in mortality rates. The National COVID-19 Clinical Evidence Taskforce in Australia has given remdesivir a conditional recommendation, meaning its use as a therapeutic outside the context of clinical trials may be considered.
- Emerging results on the use of hydroxychloroquine as a therapeutic suggest it may not be effective, but these data are still being peer reviewed. Use for post-exposure prophylaxis is still under investigation but early results have not shown a benefit. Use for pre-exposure prophylaxis is still under investigation.
- Dexamethasone, a corticosteroid, is the first drug shown to improve the survival of hospitalised COVID-19 patients requiring respiratory support, including supplemental oxygen and invasive ventilation.
- Emerging evidence suggests that anticoagulation therapy could be used to prevent thrombotic complications in patients with severe COVID-19.
- The first randomised clinical trial of convalescent plasma therapy suggests it may not improve time to recovery for hospitalised patients, but the available data are currently limited.

There are now over 300 COVID-19 therapeutic candidates in pre-clinical stages of testing and almost 200 are progressing through clinical trials.[1] As noted in the original RRIF briefing, combination therapies have been successful in other viral infections and this remains an important avenue of investigation for SARS-CoV-2.

COVID-19 therapeutic candidates: progress into and through clinical trials

Remdesivir

Emerging data for the use of remdesivir as a therapeutic suggest that it may result in a faster recovery for COVID-19 patients.

The US National Institute of Allergy and Infectious Diseases (NIAID) published results from a Phase III clinical trial on 22 May 2020.[2,3] Patients who received remdesivir for 10 days had a shorter time to recovery (11 days) than patients in the placebo group (15 days). This difference was statistically significant, although there was no statistically significant difference in mortality rates.

Results of another Phase III trial of remdesivir, carried out in China, were published on 29 May 2020.[4,5] The study was terminated early because the trial could not attain the predetermined sample size due to the significant decline in the number of active COVID-19 cases in China. Nevertheless, some results were still obtained but researchers reported that in hospitalised COVID-19 patients, there was no significant difference in clinical outcome between therapeutic and placebo groups. Researchers observed that patients in the study who had displayed symptoms for less than 10 days and received remdesivir recovered more quickly than those in the placebo group, but the difference was not statistically significant.

Trials have also explored whether duration of therapy with remdesivir affects outcomes. Results of a Phase III trial conducted by Gilead Sciences, USA, which manufactures remdesivir, showed no difference in efficacy of 5-day versus 10-day therapeutic courses in patients with severe disease.[6] This may mean that a limited supply of remdesivir could be conserved by using shorter therapy durations. Gilead Sciences also announced results from another Phase III clinical trial in a media release on 1 June 2020. The trial tested remdesivir on COVID-19 patients with moderate disease and results indicate that those treated with remdesivir recovered more quickly, but the full results are not yet published.[7]

Australia's National COVID-19 Clinical Evidence Taskforce has released a conditional recommendation for the use of remdesivir in Australia.[8] The Taskforce stated that "*Whenever possible remdesivir should be administered in the context of a randomised trial with appropriate ethical approval. Use of remdesivir for adults with moderate, severe or critical COVID-19 outside of a trial setting may be considered*." It is not recommended in pregnant patients, children or adolescents outside of a trial. In the US, remdesivir is available for patients with severe COVID-19 only, through an Emergency Use Authorisation from the Food and Drug Administration.

Hydroxychloroquine

Emerging evidence of the benefits and harms of using hydroxychloroquine as a therapeutic for COVID-19 suggests that hydroxychloroquine is not effective, at least as a single agent. These results are still being peer reviewed. The potential role of hydroxychloroquine in combination therapy remains unclear.

On 22 May 2020, a paper published in The Lancet reported that the use of hydroxychloroquine in hospitalised COVID-19 patients was associated with increased mortality rates and cardiovascular problems.[9] On 3 June 2020, following an independent review of the published paper, editors from The Lancet raised concerns regarding the reliability and validity of data used in the published paper.[10,11] On 4 June, the paper was retracted at the request of three of the paper's four authors.[12]

A meta-analysis of 23 studies using hydroxychloroquine published on 27 May 2020 concluded that results to date are insufficient to draw any definitive conclusions.[13]

On 5 June 2020, chief investigators of the RECOVERY (Randomised Evaluation of COVID-19 Therapy) Trial – a large, randomised controlled trial of COVID-19 therapeutics in the UK – reported no beneficial effect of hydroxychloroquine in hospitalised COVID-19 patients.[14] The full results are yet to be published. The hydroxychloroquine arm of the trial had enrolled 1,543 patients but has now stopped enrolling patients.

On 17 June 2020, the World Health Organization (WHO) announced that the hydroxychloroquine arm of the Solidarity trial was being stopped.[15]

Use of hydroxychloroquine for post-exposure prophylaxis continues to be investigated. On 3 June 2020, Boulware *et al,* US, published results from a trial of 821 participants reporting that there was no significant difference in disease onset between the use of hydroxychloroquine for post-exposure prophylaxis and placebo groups.[16] Another post-exposure prophylaxis study in Spain has reported similar results, which have been submitted for publication.[17,18] Use of hydroxychloroquine for pre-exposure prophylaxis (such as among healthcare workers) is under investigation, including in Australia.[19]

Dexamethasone (corticosteroid)

On 22 June 2020, a preprint reported findings from the dexamethasone arm of the RECOVERY trial.[20] These results indicated that when given to patients with severe COVID-19 who are receiving supplemental oxygen or invasive mechanical intervention, dexamethasone reduced patient mortality rates by 20% and 35% respectively. No significant difference in mortality rates was observed in COVID-19 patients who were not receiving respiratory support. The trial compared 4,321 patients who received standard care with 2,104 COVID-19 patients who received dexamethasone in addition to standard care. This is the first randomised trial to demonstrate reduced mortality from an intervention in treating COVID-19. Australia's National

COVID-19 Clinical Evidence Taskforce has indicated its intention to incorporate dexamethasone into its rapid guideline development process, once peer reviewed results are available, to make an appropriate recommendation.[21]

Anticoagulation therapy to prevent thrombotic complications in COVID-19 patients

The original RRIF brief noted that thrombosis is a major complication in severe cases of COVID-19. Several studies (including the full publication of the preprint reference in our original briefing) have reported that COVID-19 patients admitted into intensive care have a higher incidence of thrombotic complications than hospitalised patients not in intensive care.[22–28] However, the true prevalence of thrombotic complications in COVID-19 patients remains unknown as these published studies observed relatively small patient cohorts.

A small population of COVID-19 patients who were already receiving long-term anticoagulants appear to be protected from developing thrombosis.[25] Evidence is emerging showing that anticoagulation therapy may be used to reduce mortality risk in severe COVID-19 patients.[29–31]

Convalescent plasma for therapeutic use

Results from the first randomised clinical trial using convalescent plasma to treat COVID-19 were published on 3 June 2020. Patients given both standard care and plasma collected from individuals who had recovered from COVID-19 (convalescent plasma, which contains neutralising antibodies), compared with patients given standard care alone, did not recover more quickly.[32] The study recruited 103 patients but was terminated early because the COVID-19 outbreak in China was contained, limiting patient enrolment. Interpretation of this data is therefore limited. The effectiveness of convalescent plasma varies depending on factors such as the time of administration and the results of completed trials are not available.

Monoclonal antibodies for therapeutic use

Work to develop monoclonal antibodies is ongoing and in the preclinical phase. As noted in the original RRIF briefing, antibodies can be isolated from recovered patients and cloned in the laboratory to enable large scale production of monoclonal antibodies, which can be administered as a therapeutic. Regeneron Pharmaceuticals, USA, has recently published the discovery of several antibodies that are highly potent in suppressing replication of SARS-CoV-2 in mouse models, which could potentially be developed for use in human COVID-19 patients.[33,34] Clinical trials investigating combination antibody therapy for COVID-19 will begin shortly in the USA.[35]

The original report, this update and future updates are developed to the best of our knowledge. We acknowledge that they may be incomplete and invite research organisations, companies, individuals and

consortia to send scientific publications and clinical trial references for COVID-19 therapeutic candidates to science.policy@science.org.au or reports@aahms.org. Future updates provided will focus on COVID-19 therapeutic candidates that have reached, or are moving through, clinical trials.

APPENDIX

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Australian Government

Chief Scientist

17 May 2020

The Hon Karen Andrews MP
Minister for Industry, Science and Technology

The Hon Greg Hunt MP
Minister for Health

Parliament House
CANBERRA ACT 2600

CC:
Dr Brendan Murphy, Chief Medical Officer

Dear Ministers

Please find attached a response to your request for an analysis of the available evidence to respond to your question:

> *What are the most promising COVID-19 therapeutics in development globally and nationally, and what are their mechanisms of action, their stage of development and their strengths and limitations?*

This rapid response has been prepared by the Rapid Research Information Forum that I Chair. The report synthesises the evidence base on this matter and has been informed by relevant experts and has been peer reviewed. Details of the authors and peer reviewers can be found in the Appendix.

I hope this document proves useful to you and your colleagues.

Yours sincerely,

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17 May 2020

This rapid research brief responds to the question: What are the most promising COVID-19 therapeutics in development globally and nationally, and what are their mechanisms of action, their stage of development and their strengths and limitations?

- There are over 200 potential COVID-19 therapeutics being tested in more than 1,100 clinical trials.
- As of 17 May 2020, no therapeutic has been shown to be fully effective.
- Trials investigating therapeutics are still in the early stages and findings should be approached with caution while further data are collected and analysed.
- Remdesivir has captured headlines because of a press release announcing that the drug reduces time to recovery in a large study with over 1,000 participants, but the full report of this trial is as yet unpublished. Hydroxychloroquine and chloroquine are the most tested therapeutics, but there are no completed studies of large randomised trials and there are toxicity concerns when used at higher doses.
- Different therapeutics will be needed for mild disease, severe disease and for complications of the disease. Timing of administration of antivirals also appears to be important. Antivirals are being explored for both therapeutic purposes and prevention.
- Researchers globally, including in Australia, are testing repurposed drugs as well as developing new therapeutics. There are many large-scale and likely definitive international clinical trials underway, with one of these including Australian investigators (REMAP-CAP).
- Given our knowledge derived from developing therapeutics for other RNA viruses such as HIV and hepatitis C, and the intense global effort for COVID-19, it is reasonable to expect a range of effective therapeutics in the next 12-24 months.

As of 17 May 2020, there are more than 200 different COVID-19 therapeutics being tested globally in more than 1,100 registered clinical trials.[1,2]

This brief describes the major approaches and evaluates findings, based on current evidence, but new findings are emerging at a rapid pace.

COVID-19 therapeutics are applicable at three stages of the disease: to prevent early infection from progressing to severe disease, to treat severe symptomatic disease and to address complications of the disease, primarily blood clots.

COVID-19 therapeutics are also being used for prevention of infection as either pre-exposure prophylaxis or post-exposure prophylaxis, based on these approaches working well in HIV infection.

Therapeutics are being repurposed from existing products or are being newly developed. If effective, repurposed drugs are likely to be the first approved. But the real gains are likely to come from the next generation of therapeutics, designed to specifically target SARS-CoV-2.

When interpreting the results of COVID-19 clinical trials, it is important to note that not all trials are equal. Randomised controlled trials (RCTs) provide the most robust evidence. Here patients are randomly allocated to an intervention or a control group that receives a placebo or standard care. However, in the early stages of a pandemic, data from RCTs are not yet available and we must often rely on other trial methods such as observational studies. Here health professionals monitor patients and the therapeutics they receive but do not allocate them to a particular intervention. Since such studies do not include a control group they are subject to bias. However, even with RCTs, it is important to scrutinise several factors, including the baseline characteristics of the patients studied (such as the severity of disease), the primary endpoint of the study (such as time to recovery or death) and the timing of the intervention.

As of 17 May 2020, research is still in its early stages and we await well-designed RCTs with sufficient statistical power to deliver conclusive results. Approaches to accelerate high-quality RCTs are being used. These include adaptive trial designs, where the trial is adjusted along the way to optimise the intervention, and collaborative multi-centre international studies.

Early on in the development of therapeutics, it is important to identify any potential barriers to widespread access. These include intellectual property barriers and the prohibitive costs of manufacturing complex molecules.

Therapeutic approaches

Therapeutics can target the host response or the virus itself and are required at different stages of disease.

1. At the early stage, **target the virus** with agents that reduce its ability to infect and grow in host cells, to prevent progression to severe disease.
2. In severe symptomatic disease, **suppress the problematic immune response** that is associated with acute respiratory distress syndrome (ARDS), using immunomodulatory and anti-inflammatory drugs.
3. **Address the life-threatening complications of COVID-19**, such as blood clots.

Experience with other viral infections suggests that:

- antiviral drugs are more effective if given earlier in the course of the disease. This has been a key feature of treating influenza
- for HIV and hepatitis, a combination of therapies has been successful. It will also be important to test combination therapies for COVID-19
- HIV has also demonstrated the value of using antiviral therapeutics to prevent infection – so called pre-exposure and post-exposure prophylaxis. Anti-viral therapeutics might likewise be used prophylactically to reduce transmission of COVID-19 and this is being explored.[3]

1. Targeting the virus

Both small molecules (the most common form of pharmaceutical drugs) and antibodies are being tested for their ability to target SARS-CoV-2.

Small molecules – therapeutics in clinical trials

Two of the drugs currently in trials – remdesivir and hydroxychloroquine – have been given 'Emergency Use Authorization' (EUA) status by the US Food and Drug Administration (FDA), allowing use in the pandemic outside of a clinical trial.

- **Remdesivir** was originally developed for Ebola, but is not yet approved for any purpose. There are now seven large studies of remdesivir underway, each with different inclusion criteria and primary endpoints.[2] A Chinese study published in *The Lancet* on 29 April 2020 reported reduced time to clinical improvement with remdesivir compared to placebo in a study involving 237 patients. However, this difference was not statistically significant partly because of declining numbers of severely ill patients to enrol, leading to the study being halted prematurely.[4] On the same day, the US National Institute of Allergy and Infectious Diseases (NIAID) reported a 31% reduction in time to recovery in hospitalised patients on remdesivir compared to placebo.[5] Time to recovery was 11 days with remdesivir and 15 days with placebo, which was statistically significant. The NIAID study also reported a non-significant reduction in death (8% for remdesivir, 11% with placebo). While these preliminary findings are promising, the results should be interpreted with caution until the full results of the study are published, including details of the participants enrolled and the statistical analyses used. Another trial led by Gilead (the manufacturer of remdesivir) compared a 5-day to a 10-day course of remdesivir.[6] Based on a preliminary report on the company's website, it found no difference in clinical improvement delivered by the two regimens, but noted a greater likelihood of recovery if remdesivir was given early on (within 10 days of symptom onset) compared to late. In this trial, recovery was defined as no longer requiring oxygen support and medical care or discharge

form hospital. Four other large randomised studies are underway.[2] The drug is not currently approved in Australia, but Gilead is making it available to at least four sites in Australia, with full details still to be confirmed.[7,8]

- **Chloroquine and hydroxychloroquine** were originally licensed as anti-malarial and anti-arthritis agents. Since then, they have also been tested in laboratory and animal experiments to treat MERS and SARS-CoV-1, and they have been effective at killing the SARS-CoV-2 virus in human cells in culture dishes.[9–13] These drugs are currently being tested in 24 trials with over 25,000 participants – the largest number for any COVID-19 therapeutic. So far there is no conclusive evidence of their effectiveness.[2,14] The most recent and largest, but non-randomised, study of hydroxychloroquine found no evidence of benefit.[15] Furthermore they are known to raise the risk of potentially fatal heart arrhythmia.[14]
- Studies have also explored the antibiotic, **azithromycin**, in combination with hydroxychloroquine, but these studies are limited by their small size.[16] Again, there is concern about increased risk of cardiac toxicity with this combination.[17]
- **Repurposed HIV drugs – lopinavir and ritonavir** used in combination (under the brand name **Kaletra**) has been the HIV therapeutic most studied so far, with seven trials in total.[2] So far studies in COVID-19 patients have not yet shown clear clinical benefits.[14,18] **Nelfinavir (Viracept)**, another HIV drug, has shown activity against COVID-19 in cell culture models. The combination of **tenofovir and emtricitabine (Truvada)**, licensed to prevent HIV infection as pre-exposure prophylaxis, is also being tested for COVID-19 in Spain.[19]
- **Repurposed drugs for influenza and other respiratory infections – favipiravir (Avigan)** and **umifenovir (Arbidol)** are two examples under investigation, but again have not yet yielded conclusive results.[20,21]
- **Combination antiviral therapy –** Based on experience with HIV, hepatitis C and influenza, it is highly likely that combinations of therapeutics will be required. In a recent randomised clinical trial, the combination of Kaletra, interferon B and the antiviral drug ribavirin (previously used for hepatitis C but has widespread antiviral activity) was compared to Kaletra alone. Combination treatment resulted in a significantly greater reduction in virus in nasopharyngeal swabs and a quicker time to clinical recovery.[22] These results are promising – importantly, trial participants were enrolled only if they had symptoms for less than seven days. The triple combination treatment demonstrated clear antiviral activity and an association with improved clinical outcomes.

Small molecules – therapeutics in lab development or pre-clinical trials

Other small molecules are being explored and developed, including:

- **Ribonucleoside analogue β-D-N^4-hydroxycytidine (NHC, EIDD-1931)** has shown promise as a broad-spectrum antiviral *in vitro*, including for SARS-CoV-2, SARS-CoV-1 and MERS-CoV.[23]
- **Ivermectin –** Ivermectin is a drug used for parasitic infection and also has some antiviral activities against dengue, HIV and SARS-CoV-2 in cell culture.[24] The drug levels required to inhibit SARS-CoV-2 in these studies would be toxic if administered to people. Further work is being done to determine if lower doses of ivermectin (or related compounds) could be developed as therapeutics for COVID-19.[25]
- **siRNA** – small interfering RNAs (siRNA) can inhibit viral replication and are being designed and screened for potential efficacy for SARS-CoV-2. Studies in cells and trials in patients with other respiratory conditions indicate that siRNAs could be effective.[26–29]

Antibodies – therapeutics in clinical trials

Antibodies are a key part of the immune system response to infection. The therapeutic use of antibodies is now well established in both HIV and Ebola and is being tested for SARS-CoV-2. It is anticipated that some antibody-based therapeutics will be available for emergency use by the end of 2020.

- **Convalescent plasma** containing high concentrations of antibodies from recovered COVID-19 patients has been approved for use in critically ill COVID-19 patients through a special access scheme by the US FDA.[30] Research has suggested improvements in the clinical status of seriously ill patients who received plasma.[31–33] However, these studies were very small with no control group. Randomised controlled trials are now recruiting patients.[34,35] Even if successful this approach will be limited in the short term because it relies on harvesting plasma from patients who have recovered – still a small population in Australia at this time.

Antibodies – therapeutics in lab development or pre-clinical trials

- **Hyperimmune globulin** – individual doses of convalescent plasma vary from unit to unit, but it can be processed to produce hyperimmune globulin, a safer, more standardised, concentrated and consistent product.
- **Monoclonal antibodies (mAbs).** A person who has successfully recovered from infection may produce highly effective antibodies. The cell that makes those antibodies can be isolated and cloned in the laboratory to enable large scale production of the pure 'monoclonal' antibody. Monoclonal antibodies that target SARS-CoV-1 and MERS-CoV have been identified, and have been used as therapeutics for both Ebola and HIV.[36]

- **Broadly neutralising antibodies (bNAbs)** are similar to monoclonal antibodies but can act against multiple different strains of a virus. If a potent bNAb can be identified, this could be a promising strategy.[37]

Enhancing the immune response

Non-specific immune enhancement can also induce clearance of viruses. These therapies are not virus specific but can also effectively reduce virus replication.

- **Interferons** activate many arms of the immune system and have activity against viruses. Interferons have been used for years for the management of hepatitis B and C. In COVID-19, the administration of interferons is being explored through both the subcutaneous and inhaled routes, alone and in combination with other therapeutics. When used in combination in a clinical trial, interferon β, ribavirin and Kaletra led to clear clinical benefit, when administered within 7 days of symptom onset.[22] A strategy that involves administering interferons needs to be explored carefully, given the risk of exacerbating the immune response potentially leading to worsening disease.

2. Suppressing the problematic immune response

About 5% of people infected with SARS-CoV-2 will progress to severe disease, often requiring an increase in oxygen therapy and mechanical ventilation. This happens more commonly in the elderly and in people with co-morbidities such as hypertension and cardiovascular disease, and usually in the second or third week of infection. Although the cause of this deterioration is still a subject of research, the decline is characterised by an exaggerated immune response – a 'cytokine storm' – that leads to acute respiratory distress syndrome (ARDS). Several options are under investigation to modify this response.

Therapeutics currently in clinical trials

- **Anti-cytokine therapies** – **tocilizumab** (**Actemra**, approved for conditions including rheumatoid arthritis) blocks a cytokine called interleukin-6 (IL-6). Some studies show it improves clinical outcomes in severe or critical COVID-19 patients, but to date these have been non-randomised observational studies and although announcements about randomised studies have been made, these have not yet been published.[38,39] Further research is investigating this drug and **sarilumab (Kevzara)**, another IL-6 inhibitor. Agents that inhibit other cytokines are also being investigated, for example interleukin-1 (IL-1) blockers.
- **Anti-inflammatory therapies** – dampening down the immune response can also be achieved through inhibiting pathways leading to inflammation that are targeted for the treatment of conditions such as rheumatoid arthritis. An anti-arthritis drug called **baricitnib (Olumiant)** is

currently being tested in a large randomised study, in combination with the antiviral drug remdesivir.[40]

- **Corticosteroids** are commonly used to non-specifically suppress the immune system. They are not currently recommended for use in COVID-19, other than in exceptional circumstance. Research in some other viral pneumonias has reported no overall improvement in outcomes and some studies have suggested complications.[14] Direct evidence for use in COVID-19 patients is currently limited.

3. Addressing the complications of COVID-19

A major complication of COVID-19 is blood clots that cause pulmonary embolism (a blocked artery in the lung), strokes or heart attacks. Trials of different anti-clotting agents such as heparin and clot-busters commonly used for heart attacks and strokes are underway. An observational study based on 2,733 ICU patients at Mt Sinai Hospital in New York suggests the use of heparin reduced deaths from 63% to 29% for patients on ventilators.[41]

Research is still at an early stage in COVID-19, with the optimal timing and dose of delivering anti-clotting agents requiring considerably more investigation.[42,43]

The Australian research landscape

Australian researchers, often working with global partners, are testing repurposed drugs as well as developing new therapies. Below is a snapshot of some Australian research that relates to the strategies described above.

- REMAP-CAP* is an international trial for COVID-19 patients in intensive care with severe pneumonia. Australia currently has more than 50 intensive care units participating in this trial.[44] The trial is testing several different therapies, including lopinavir-ritonavir and hydroxychloroquine, alone or in combination; as well as an immunomodulator called Interferon-beta-1a and an anti-cytokine agent, Kineret (Anakinra, an IL-1 inhibitor). Tocilizumab and sarilumab have been submitted for approval as additions to the study trial options. Proposals to add anticoagulation, vitamin C, and convalescent plasma to the trial have been submitted or approved in other countries and will be submitted in Australia. The trial uses an adaptive design to evaluate a number of therapeutic options simultaneously and efficiently, meaning that the trial can adapt to increase the likelihood that patients will receive the therapeutic that is most likely to be effective for them. Where specified, the trial can also identify the therapeutic effect of combination therapy. It is important to note that

* Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP)

REMAP-CAP only enrols patients in the advanced stage of disease, where antivirals may have limited benefit.

- The ASCOT[†] study, led by the Doherty Institute, is investigating hydroxychloroquine and lopinavir-ritonavir for COVID-19.[45] The ASCOT trial will enrol people with mild to moderate disease who are in hospital, but will not include patients in intensive care.
- The CoPEP[‡] study, led by Monash University, is exploring the use of hydroxychloroquine and other antivirals (e.g., interferon, which stimulates the immune system) for post-exposure prophylaxis in high-risk contacts using an adaptive randomised trial design, performed at sites in Australia and New Zealand.
- The *COVID-Shield* study, led by the Walter and Eliza Hall Institute, is investigating hydroxychloroquine for pre-exposure prophylaxis for healthcare workers in Australia.
- Cell culture studies on ivermectin were undertaken by investigators from Monash University and the Doherty Institute. Further work is being carried out in Australia to determine the efficacy and safety of ivermectin in humans.[24]
- The design, screening and development of siRNAs that target SARS-CoV-2 is being undertaken at the Kirby Institute, the University of Melbourne, RMIT and the Walter and Eliza Hall Institute.
- Planning and pre-clinical work is underway in Australia on the development of hyperimmune globulin – driven by CSL and the Australian Red Cross Blood Service, in association with Monash University, the Doherty Institute, the Kirby Institute and Westmead Hospital. Trials will begin later in 2020.
- Australian researchers are also actively working to identify and develop monoclonal antibodies and broadly neutralising antibodies for COVID-19, including at the Kirby Institute, Garvan Institute, Doherty Institute and Burnet Institute.
- CSL has three anti-cytokine antibody products in early clinical trials, which could potentially be repurposed. Rigorous testing would be needed, but if successful the manufacturing process is well understood and is available at CSL facilities in Australia.

[†] Australasian COVID-19 Trial (ASCOT) study
[‡] Preventing COVID-19 with post-exposure prophylaxis for high risk contacts (CoPEP)

An important note on available COVID-19 research

Although current COVID-19 research is available through pre-print servers, many of these articles have not yet been peer reviewed (an imperative pillar of the scientific method) and the relatively short time length of the current outbreak has resulted in variable testing and reporting practices in different countries. As such, conclusions drawn need to be interpreted with caution. Pre-prints are marked with a § in the reference list.

The development of vaccines and therapeutics for COVID-19 is a rapidly developing area of research with almost daily updates. This brief is accurate at the time of writing and may become out of date at a later time of reading. Consultation with the Australian Academy of Health and Medical Sciences is possible if the reader has questions.

APPENDIX

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Acknowledgements

The production of this rapid research report was supported by staff of the Australian Academy of Health and Medical Sciences: Ms Catherine Luckin and Ms Katrin Forslund, and staff of the Australian Academy of Science: Dr Jana Phan and Mr Chris Anderson. Edited by Dr Elizabeth Finkel AM and Ms Robyn Diamond.

Conflicts of interest

This briefing incorporates input from Australian experts directly involved in the development of therapeutics for COVID-19. Many of these contributors are working with international partners and collaborators and have a strong understanding of the current global research and innovation landscape. The contributing authors and peer reviewers are drawn from a range of institutions, initiatives and fields, and collectively provide an independent, authoritative perspective on this topic.

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RAPID RESEARCH INFORMATION FORUM

The most promising treatments for COVID-19

The Rapid Research Information Forum (RRIF) is a forum for rapid information sharing and collaboration within the Australian research and innovation sector. It is convened by Australia's Chief Scientist, Dr Alan Finkel AO FTSE FAA FAHMS, and its operations are led by the Australian Academy of Science.

RRIF provides a mechanism to rapidly bring together relevant multidisciplinary research expertise to address pressing questions about Australia's response to COVID-19, as they emerge.

RRIF enables timely responses to be provided to governments based on the best available evidence. RRIF also informs the Chief Scientist's interactions and collaboration with other national chief scientific advisers. It demonstrates the critical value of research and innovation in driving societal as well as economic progress now and into the future.

RRIF participants

- Australia's Chief Scientist (Chair)
- Australian Academy of Science (AAS)
- Australian Academy of Health and Medical Sciences (AAHMS)
- Australian Academy of Technology and Engineering (ATSE)
- Academy of the Social Sciences in Australia (ASSA)
- Australian Academy of the Humanities (AAH)
- Royal Society Te Apārangi (New Zealand)
- Australian Council of Learned Academies (ACOLA)
- State and Territory Chief Scientists and representatives
- Chief Science Advisor to the Government of New Zealand
- Scientific expert members of the National Science and Technology Council (NSTC)
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This report has been enabled through the contribution of RRIF participants and support from Australian philanthropists.