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Biography

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Therapeutics for COVID-19: established and in development

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The authors advise that on page 219 of their published article (*Microbiology Australia*, Volume 41, Issue 4, pages 217–223, doi:10.1071/MA20058), in the first sentence under the heading 'Repurposed drugs with cellular targets used for viral entry: ACE2 and TMRPSS2 inhibitors', 'acetylcholinesterase (ACE)-2 receptor' should read 'angiotensin-converting enzyme (ACE)-2 receptor'. The correct text is shown here:

SARS-CoV-2 uses the angiotensin-converting enzyme (ACE)-2 receptor for cell entry, and serine protease TMPRSS2 for S-protein priming, both potential targets for antiviral intervention[31].

Also, the label for RdNP inhibitors is misplaced in Figure 2: it belongs at the region of RNA replication.

Therapeutics for COVID-19: established and in development

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Abstract. **COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first recognised in late 2019, with over 30 000 000 cases and over 1 000 000 deaths reported by the end of September 2020. SARS-CoV-2 infection is usually associated with fever, cough, coryza, dyspnoea, anosmia, headache and fatigue and may cause pneumonia and hypoxemia. An excessive/dysregulated inflammatory response may lead to lung damage including acute respiratory distress syndrome (ARDS), coagulopathy and other complications. Mortality amongst hospitalised patients is higher in those needing intensive care. In Australia over 27 000 cases with 882 deaths had been reported by 30 September, most in Victoria. Two therapies have proven beneficial in treatment of hospitalised patients in expedited randomised placebo-controlled trials and are now in widespread use. Dexamethasone improved survival of those requiring respiratory support and the antiviral agent remdesivir decreased time to recovery in mild-moderate disease. Remdesivir was authorised by the Australian Therapeutic Goods Administration in July 2020. Over 200 other therapeutics are being tested for COVID-19 in more than 2000 clinical trials, and many more agents are in preclinical development. We review the evidence for some of the candidates for therapy in COVID-19.**

The aim of treatment for COVID-19 is to reduce disease severity and prevent mortality. Therapeutics may also be used to prevent or abort infection (pre- or post-exposure prophylaxis) and reduce post-infectious complications (Figure 1). In Australia, the National COVID-19 Clinical Evidence Taskforce has been established to review rapidly emerging evidence in real-time and maintain a 'living document' for COVID-19 management guidelines[2], available at https://covid19evidence.net.au/#living-guidelines. Interventions may be grouped into those targeting the virus and those targeting the immune response (Figure 2, Table 1). Adjunctive therapies including anticoagulation and optimising oxygenation are also critical elements of management but are beyond the scope of this review.

Therapeutic approaches

Antiviral small molecules

Repurposed drugs for Ebola: remdesivir

In a Phase III randomised placebo-controlled trial (ACTT-1, NCT04280705) including 1063 adults with COVID-19 with lower respiratory tract infection, participants receiving up to 10 days of **remdesivir** had shorter time to recovery than those in the placebo group (median 11 and 15 days, rate ratio for recovery 1.32; 95% CI 1.12–1.55, $P < 0.001$)[5]. Stratification by severity showed improved time to recovery for patients receiving oxygen at baseline, but not for those receiving no oxygen nor for those receiving high-flow oxygen or mechanical ventilation. There was no significant difference in mortality rates, although further follow-up data is awaited.
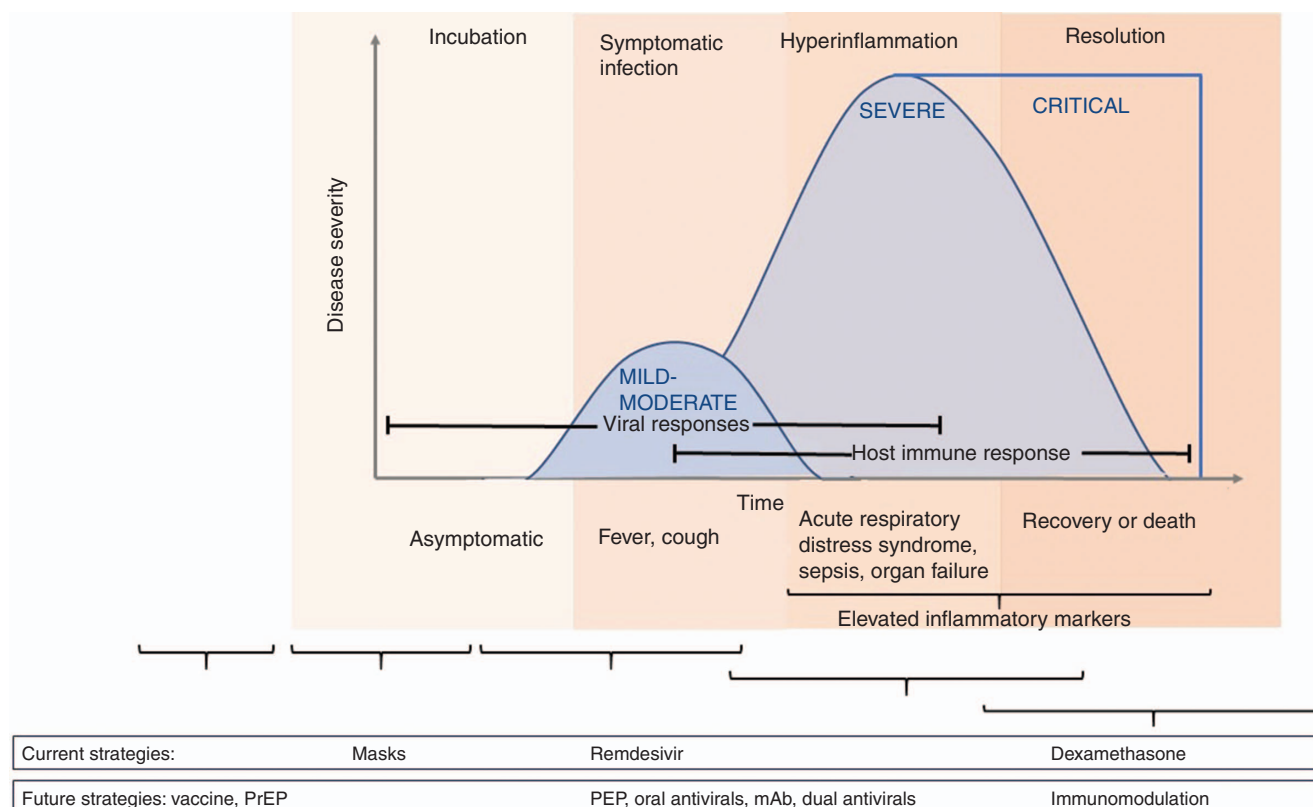
Figure 1. Course and severity of COVID-19 disease. COVID-19 illness ranges from asymptomatic, mild-moderate illness, severe/critical then either recovery or death. There are limited current strategies to reduce both the spread and progression of COVID-19 disease. Future strategies include vaccines, pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP). mAb, monoclonal antibody. Adapted from [1].

Questions remain about the optimal time and duration of administration of remdesivir. In one study ($n = 397$), 10 days treatment was associated with better outcomes than 5 in those going on to need mechanical ventilation; however, no control arm was included (mortality 17% with 10 days ($n = 41$), 40% with 5 days ($n = 25$))[6]. Whether there is incremental benefit above treatment with dexamethasone is not yet clear. Studies are ongoing including use of inhaled remdesivir (NCT04480333) and use in combination with other agents.

Repurposed drugs for influenza: favipiravir and umfenovir

Favipiravir is an oral RNA-dependent RNA polymerase inhibitor with *in vitro* antiviral activity at high concentrations[7]. An open-label study in mild-moderate COVID-19 ($n = 80$) in combination with inhaled interferon-α reported positive results, and favipiravir was approved for marketing in China for COVID-19 in March 2020[8]. Multiple phase 2 trials are active including in Australia[9]. Concerns exist about the pharmacokinetics of favipiravir, with low trough levels in critically ill patients and potential for the emergence of resistance[10].

Umfenovir (Arbidol) is a non-nucleoside antiviral targeting the viral spike (S-)protein-ACE2 host receptor interactions, inhibiting membrane fusion of the viral envelope[10]. Umfenovir may also promote interferon synthesis. Published results so far are inconclusive[12,13], with randomised studies in progress.

Non-specific immune enhancement with antiviral activity: interferons

Type I interferons have broad antiviral activities and recombinant IFN-I proteins (parenteral and inhaled) are being trialled in COVID-19[14,15]. Use of interferons in acute infection needs to be explored carefully, as type I interferons have been associated with exacerbation of inflammation in progression to severe COVID-19, with potential to worsen disease[16,46]. Timing may be critical. In a retrospective study in COVID-19 ($n = 446$), late use of IFN-α led to increased mortality and delayed recovery, whilst earlier use was associated with reduced mortality[17].

Repurposed anti-parasitic agents: ivermectin and nitazoxanide

Ivermectin (used to treat infections such as strongyloidiasis, scabies and onchocerciasis), and **nitazoxanide** (used in giardia and cryptosporidium) have *in vitro* activity against SARS-CoV-2 and are in preclinical early clinical trials against COVID-19[18]. Nitazoxanide also has reported immunomodulatory activity, suppressing murine IL-6 levels[18,19].
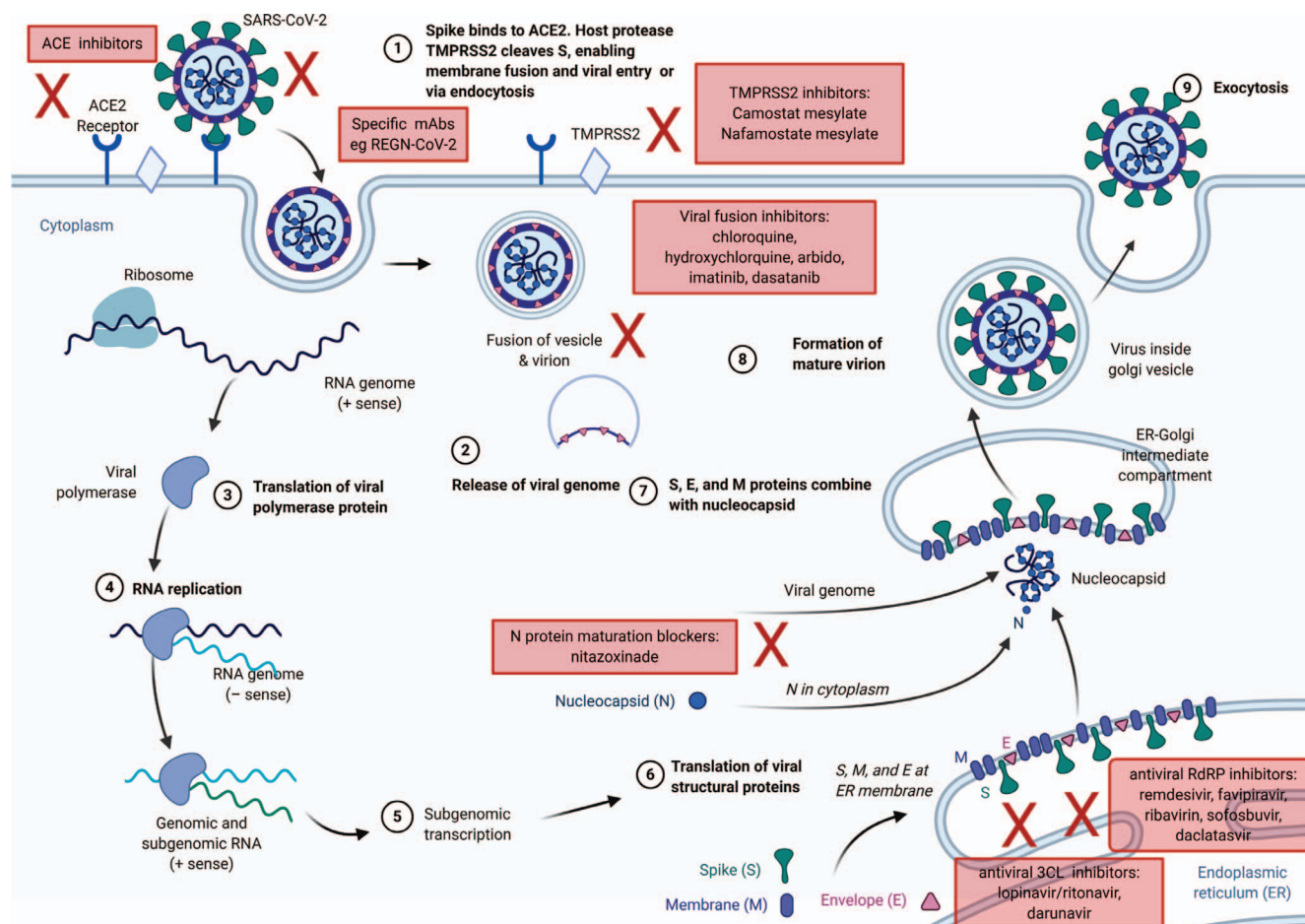
Figure 2. SARS-CoV-2 replication cycle and stages where various antiviral drug activity occurs. ACE2, angiotensin converting enzyme 2; ER, endoplasmic reticulum: E, envelope; mAb, monoclonal antibody; M, membrane; N, nucleocapsid; RdRP, RNA-dependent RNA polymerases; S, spike; TMPRSS2, transmembrane serine protease 2; 3CL, 3C-like protease. Figure was created with BioRender.com.

Repurposed anti-HIV drugs: lopinavir/ritonavir and other anti-HIV proteases

The HIV protease inhibitor **lopinavir** has *in vitro* activity against SARS-CoV-1 and MERS, and possible activity *in vivo*[20]. *In vitro* activity was demonstrated against SARS-CoV-2[21], but no benefit in treatment of COVID-19 was reported in randomised published studies or in press release of results from the large UK 'RECOVERY' (Randomised Evaluation of COVID-19 Therapy) and WHO 'Solidarity' Trials[13,22–24]. Other studies are ongoing with lopinavir/ritonavir and other antiretrovirals including nelfinavir, tenofovir, lamivudine and others, either alone or in combination.

Repurposed drugs for malaria: hydroxychloroquine and chloroquine.

Hydroxychloroquine (licensed as an antimalarial and anti-arthritis agent) and **chloroquine** were widely used in the early days of the COVID-19 pandemic, due to their potential to block viral entry, immunomodulatory impact and *in vitro* activity against SARS-CoV-2[25]. Potential toxicities include prolonged QT interval, lowered convulsive threshold, retinopathy and cardiac myopathy. Randomised trials in mild, moderate and severe disease show no benefit in

COVID-19[26–29] and the WHO have discontinued the hydroxychloroquine arm in the 'Solidarity' trial. A US federal drug administration (FDA) emergency use authorisation (EUA) for hydroxychloroquine in COVID-19 issued in March was revoked in June. Hydroxychloroquine has also been shown not effective for SARS-CoV-2 post-exposure prophylaxis[28]. Studies investigating its utility for prevention of COVID-19 in healthcare workers are continuing, including in Australia[30].

Repurposed drugs with cellular targets used for viral entry: ACE2 and TMRPSS2 inhibitors

SARS-CoV-2 uses the acetylcholinesterase (ACE)-2 receptor for cell entry, and serine protease TMPRSS2 for S-protein priming, both potential targets for antiviral intervention[31]. Agents that block these interactions are in clinical trials, including the serine protease inhibitor **nafamostat mesylate** which also has anticoagulant activity and is approved in Japan for treatment of pancreatitis[32,33]. The upregulation of ACE-2 receptors with use of the common antihypertensive agents **ACE-inhibitors** and **angiotensin receptor blockers** (ARB) was theorised to potentially lead to poorer outcomes in COVID-19 by enhancing viral entry; however, this has not

Table 1. Therapeutics for COVID-19 (selected).

Compound/name	Indication other than COVID-19 (approved unless stated)	Target(s) or postulated mechanism of action	Studies in COVID-19	
			Phase of testing/ approval	Number of recruiting trials[A]
Antiviral small molecules				
Remdesivir[5,6]	Ebola (Phase 2/3)	Viral RNA polymerase	Approved (India, Australia), EUA (USA)	27
Favipiravir[7–10]	Influenza (Japan)	Viral RNA polymerase	Phase 3, approved (India)	56
Umifenovir[11–13]	Influenza (China, Russia)	S protein-ACE interaction (target not disclosed)	Phase 4	19
Type I interferons (interferon-α, -β)[14–17]	Multiple sclerosis, hepatitis B, C, D	Induce expression of interferon-stimulated genes that confer antiviral activities to host cells	Preclinical to phase 4	65
Ivermectin Nitazoxanide[18,19]	Parasitic infections	Glutamate decarboxylase 2	Preclinical	48
Lopinavir[14,15,20–23]	HIV	3CL Protease inhibitor	Phase 4	108
Hydroxychloroquine, chloroquine[24–30]	Malaria, arthritis	Inhibits viral entry and endocytosis (multiple mechanisms) Immunomodulatory effects	Phase 3 EUA revoked	344
Nafamostat mesylate[31–33]	Pancreatitis, anticoagulant (Japan)	Transmembrane protease serine 2 (TMPRSS2), anticoagulant	Preclinical to phase 4	–
Antibodies				
Neutralising monoclonal antibodies[34–37]	(monoclonal antibody)	e.g. REGN-CoV-2 (REGN10933 + REGN10987) targets SARS-CoV-2 spike protein	Phase 2/3	79 (all mAb)
Plasma-based therapy. Convalescent plasma, hyperimmune immunoglobulin[38,39]	Argentine haemorrhagic fever, influenza, Ebola (limited evidence)	Anti-viral activity, suppress viremia, enhance host humoral response	Phase 2/3, in clinic	164
Immunomodulation				
Steroids[40,41]	Inflammatory conditions	Corticoid receptors	Phase 3/4, in clinic	62 (corticosteroids)
Tocilizumab[42,43]	Rheumatoid arthritis	Interleukin-6 (IL-6) receptor (CD126)	Phase 3	69
Baricitinib[44,45]	Rheumatoid arthritis, graft versus host disease	Janus Kinase (JAK)-1,2 or 3	Phase 2/3	45 (all JAKi)

[A]Number of trials recruiting as of 22 October 2020 (selected registered trials[3,4]). –, data not available; EUA, emergency use authorisation; mAb, monoclonal antibodies; JAKi, Janus Kinase inhibitors.

been borne out by clinical data[47]. Conversely, ARBs could provide benefit via receptor blockade, impairing viral cell entry[48].

Antibodies

SARS-CoV-2 specific neutralising antibodies

In Ebola and HIV, pathogen-targeting antibodies have been identified and cloned for therapeutic use[34]. Regeneron Pharmaceuticals (USA) published their discovery of several antibodies highly potent in suppressing SARS-CoV-2 replication in mouse models[35]. **REGN-CoV-2** (includes both REGN10933 and REGN10987) is designed to bind to two points on the SARS-CoV-2 S-protein to prevent it entering healthy cells. It is being assessed for safety and efficacy in preventing secondary infection or symptom onset amongst 2000 household contacts of people with SARS-CoV-2[36].

Another investigational monoclonal antibody **LY-CoV555,** developed after identification from blood from a patient who had recovered from COVID-19, is being studied in COVID-19 under an adaptive trial master protocol ('ACTIV-2' (outpatients) and 'ACTIV-3' (inpatients)) designed to enable phase 2 testing of investigational agents with the capacity to expand smoothly to phase 3[37].

Convalescent plasma

In SARS, improved outcomes with convalescent plasma were reported in small retrospective case series[38]. A randomised trial in severe COVID-19 suggests no benefit, although the study was stopped early due to insufficient numbers, and plasma was given late (median 30 days from symptoms onset)[39]. Many other randomised studies are in progress. Meanwhile, over 50 000

patients have received convalescent plasma for treatment of COVID-19, mainly outside of clinical trial settings and an FDA EUA was issued on 23 August for its use in COVID-19.

Immunomodulation: blocking the pathogenic host immune response

Steroids

The 'RECOVERY' trial showed a reduction in 28-day mortality in patients hospitalised with COVID-19 receiving oxygen or invasive mechanical ventilation treated with **dexamethasone**[40]. 2104 patients receiving IV/oral dexamethasone (6 mg/day up to 10 days, median 6 days) had lower mortality compared to 4321 receiving usual care (22.9% vs 25.7%, age adjusted rate ratio 0.83 (0.75–0.93, $P < 0.0001$). Mortality was reduced by 35% among those receiving invasive mechanical ventilation, 20% in those on supplemental oxygen only and no impact was seen amongst those not receiving any respiratory support at randomisation. These results are consistent with respiratory compromise being driven by an overactive inflammatory response. Patients with symptoms for over 7 days had greater mortality benefit in response to dexamethasone treatment, compared to those with more recent onset. A recent meta-analysis combines results from 'RECOVERY' with six other studies to demonstrate a mortality benefit of steroids (including dexamethasone and **hydrocortisone**) in severe COVID-19[41].

Anti-cytokine therapies

IL6 plays a key role in driving the dysregulated inflammatory response in COVID-19 with higher levels associated with greater disease severity[49]. **IL-6 receptor antagonist tocilizumab** is used to treat rheumatoid arthritis and is FDA-approved to treat cytokine release syndrome associated with CAR T-cell immunotherapy. It has beneficial effects *in vitro* and in animal models of sepsis and influenza[42]. Thousands of patients are reported to have been treated with tocilizumab; however, assessment of efficacy is impaired by lack of control groups and follow up.

A non-randomised study of tocilizumab in patients requiring mechanical ventilation reported a 45% reduction in hazard of death (hazard ratio 0.55 (95% CI 0.33–0.90)) in patients receiving tocilizumab ($n = 78$) compared to those who did not ($n = 76$) with follow up 47 days (median), although superinfections were more common (54% vs 26%, $P < 0.001$)[43]. Another IL6 receptor blocking agent, sarilumab and IL6 antagonist siltuximab are also in phase 3 trials.

The **Janus kinase (JAK) 1/2 inhibitor**, **baricitinib**, licensed for rheumatoid arthritis, has been identified as a candidate for therapy against SARS-CoV-2 due to potent anti-inflammatory effects and possible off-target antiviral effects[44]. A case series describing use in patients with moderate-severe COVID-19 reported safety and

suggests improved outcomes[45]. Randomised studies are in progress and will be imperative in ascertaining the benefit of these agents, particularly in combination with direct acting antivirals, and the balance with immunocompromise and adverse events.

Other considerations

Personalisation

Different factors drive disease manifestations at different stages of SARS-CoV2 infection, and optimal management may depend on stage of illness at time of presentation. Furthermore, the course of COVID-19 differs significantly amongst individuals, with higher risk of progression to severe disease seen in the elderly. Individualised therapy using informatics strategies based on stage and prediction of disease progression have been associated with improved patient outcomes[50]. Therapy based on immunophenotyping has also been suggested, based on readily identifiable immunological signatures associated with different disease trajectories[51,52].

Combination therapy

The benefit of therapeutic antiviral combinations is also being explored. In a randomised trial in early COVID-19 (<7 days onset), the combination of **lopinavir/ritonavir**, **interferonβ-1B** and **ribavirin** resulted in greater reduction of virus in nasopharyngeal swabs and quicker time to recovery compared to lopinavir/ritonavir alone[14]. Combining antiviral and immunomodulatory agents may be important in management of COVID-19 given the role of the inflammatory response in disease evolution severity. Timing of different therapeutics should be considered carefully in trial design.

Conclusions

Repurposing existing therapies will be the quickest way to find effective intervention and improve outcomes in COVID-19; however, bigger gains are likely through the development of new agents specific to SARS-CoV2. These are being rapidly engineered using high-throughput screening platforms. Websites tracking COVID-19 clinical trials and the development of new agents show over 300 novel agents are in pre-clinical testing. Their diverse actions reflect the range of pathology seen in COVID-19 that is a consequence of both viral action as well as immune response. Their introduction into clinical trials will be the next exciting phase of therapeutics.

Conflicts of interest

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Biographies

Dr Kasha Singh is an infectious diseases physician with a wide range of interests including public and refugee health and translational research. Dr Singh worked in the UK for 10 years, completing a HIV fellowship at Chelsea and Westminster Foundation Trust in London. While based in London, Dr Singh was also involved in running international clinical trials of tuberculosis treatment with the MRCP/UCL, including capacity development and education. Dr Singh is interested in persistent viral infections and the public health impact and management of infectious diseases, particularly HIV, hepatitis B, tuberculosis and now also COVID-19.

Associate Professor Joe Sasadeusz is an infectious diseases physician who subspecializes in medical virology. He has particular interests in viral hepatitis in both HIV uninfected as well as coinfected individuals. He also works in infections in immunocompromised hosts, especially patients who have undergone a haematopoietic stem cell transplant. He is heavily involved in the education of general practitioners via the VHITTAL program. He also conducts clinical trials and has multiple research projects in the above areas.

Professor Sharon Lewin, is the inaugural Director of the Doherty Institute. She is also a Melbourne Laureate Professor, The University of Melbourne and a National Health and Medical Research Council (NHMRC) Practitioner Fellow. As an infectious diseases physician and basic scientist, her laboratory focuses on basic, translational and clinical research aimed at finding a cure for HIV and understanding the interaction between HIV and hepatitis B virus. Her laboratory is funded by the NHMRC, the National Institutes of Health, The Wellcome Trust, the American Foundation for AIDS Research and multiple commercial partnerships. She is also the Chief Investigator of a NHMRC Centre of Research Excellence (CRE), The Australian Partnership for Preparedness Research on Infectious Diseases Emergencies (APPRISE) that aims to bring together Australia's leading experts in clinical, laboratory and public health research to address the key components required for a rapid and effective emergency response to infectious diseases.

Dr Jennifer Audsley is a Clinical Research Fellow based at the Doherty Institute. She has specific research interests in HIV-hepatitis co-infection and PrEP (Pre-exposure prophylaxis) for HIV prevention. Her research in HIV focuses on long-term treatment in people living with HIV and hepatitis B virus (HBV), liver disease pathogenesis in people living with HIV and HBV, and HBV cure in the setting of HIV-HBV co-infection. She leads the HIV-Hepatitis group within Professor Lewin's research program.

Epidemic poliomyelitis, post-poliomyelitis sequelae and the eradication program

Margaret M Peel

The author advises that on page 198 of their published article (*Microbiology Australia*, Volume 41, Issue 4, pages 196–200, doi:10.1071/MA20053), under the heading 'Late-onset sequelae of poliomyelitis (LOSP)', 'osteomyelitis' should read 'osteoporosis' in the fourth line from the end of the first paragraph. The correct text is shown here:

A broader category of sequelae, the Late Effects of Polio (LEoP), includes the consequences of musculoskeletal deformities and weakness such as scoliosis, osteoporosis, joint instability and pain, osteoarthritis and nerve entrapments[8].