

Monitoring International Trends

March 2020

The NBA monitors international developments that may influence the management of blood and blood products in Australia. Our focus is on:

- Potential new product developments and applications;
- Global regulatory and blood practice trends;
- Events that may have an impact on global supply, demand and pricing, such as changes in company structure, capacity, organisation and ownership; and
- Other emerging risks that could put financial or other pressures on the Australian sector.

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1. Safety and patient blood management

The NBA follows current issues in patient safety and achieving favourable patient outcomes.

Appropriate transfusion and bleeding risk

- The **US National Blood Collection and Utilization Survey (NBCUS)** for 2017 is summarised in a report that was released in March 2020. The main finding was a **stable adverse transfusion reaction rate**¹.
- Researchers² say that haemorrhaging from the lower gastrointestinal (GI) tract is more than just a manageable adverse effect of oral anticoagulation for [atrial fibrillation](#). It may be a clue to colorectal cancer. Peter Vibe Rasmussen³ said⁴ “we think our data support that all **eligible patients presenting with a sign or symptom of lower GI bleeding should be offered examinations to rule out cancer**”.

Other

- The virtual [American College of Cardiology \(ACC\)](#) meeting was told that the direct oral anticoagulant (DOAC) **apixaban (Eliquis) was as good as the low molecular weight heparin dalteparin (Fragmin) for the treatment of patients with cancer-associated thrombosis** - with no increase in risk of major bleeding. The findings were published simultaneously online in the [New England Journal of Medicine](#)⁵.
- Data presented at the American College of Cardiology scientific sessions showed that a **combination of Bayer’s blood thinner Xarelto and aspirin decreased the risk of major limb and cardiovascular events by 15 per cent over aspirin alone in symptomatic peripheral artery disease patients** who had recently undergone surgery to unblock arteries in their lower limbs⁶.
- A multinational study⁷ in 3,604 patients has shown that the oral anticoagulant **rivaroxaban is preferable to subcutaneous enoxaparin for preventing venous thromboembolism in immobilised patients** after non-major orthopaedic surgery.

¹ NBCUS employed a web-based survey of around 3,000 US collection centres and transfusing hospitals. The national estimate for adverse transfusion reactions which needed intervention was 281.8 reactions per 100,000 components transfused in 2017, similar to the 2015 rate of 274.6 reactions per 100,000 transfused components. Life-threatening reactions requiring major medical intervention were lower in 2017 (4.7 per 100,000 components transfused compared with 2015 (9.4 reactions per 100,000). More than 99 per cent of platelets and 96 per cent of whole blood red cells were leukoreduced in 2017. Fewer than 25 per cent of collection facilities and hospitals implemented other blood safety measures. Only 11.3 per cent of blood collection centres surveyed screened for *Babesia*, and 19.4 per cent used pathogen reduction technology. The percentage of hospitals conducting secondary testing of platelets for bacterial contamination increased from 3.8 per cent in 2015 to 5.7 per cent in 2017.

² Peter Vibe Rasmussen et al., “Gastrointestinal bleeding and the risk of colorectal cancer in anticoagulated patients with atrial fibrillation”, published 7 February, *European Heart Journal*, ehz964, <https://doi.org/10.1093/eurheartj/ehz964> also at <https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehz964/5728596>

³ University of Copenhagen, Hellerup, Denmark

⁴ theheart.org | *Medscape Cardiology*.

⁵ Giancarlo Agnelli et al., “Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer”, *New England Journal of Medicine*. 29 March 2020. DOI: 10.1056/NEJMoa1915103 https://www.nejm.org/doi/full/10.1056/NEJMoa1915103?query=featured_home

⁶ At 28 weeks of treatment, 17.3 per cent of patients treated with the Xarelto-aspirin combination suffered acute limb ischemia, major amputation for vascular cause, heart attack, ischemic stroke or cardiovascular death compared with 19.9 per cent who were treated with aspirin alone.

⁷ C.Marc Samama et al., “Rivaroxaban or Enoxaparin in Non-major Orthopedic Surgery”, *New England Journal of Medicine*. 29 March 2020 DOI: 10.1056/NEJMoa1913808 <https://www.nejm.org/doi/full/10.1056/NEJMoa1913808>

2. Products and treatments

The NBA follows the progress in research and clinical trials that may, within a reasonable timeframe, either make new products and treatments available or may lead to new uses or changes in use for existing products.

Treating haemophilia

- Researchers have found⁸ that **cells taken from haemophilia A patients — genetically reprogrammed to produce a functional clotting factor VIII — were successfully grafted into haemophiliac mice, restoring blood levels of factor VIII and substantially improving clotting.**
- On 26 March [uniQure N.V.](#) announced⁹ it had achieved the **targeted dosing¹⁰ of patients in the HOPE-B pivotal trial** of [etranacogene dezaparvovec \(AMT-061\)](#), its investigational [AAV5](#)-based gene therapy incorporating the patent-protected FIX-Padua variant for the treatment of patients with severe and moderately severe haemophilia B.

Treating beta thalassemia and sickle cell disease

- A study based on hospital records¹¹ suggest that **acute chest syndrome**, a serious complication of sickle cell disease that can accompany a [vaso-occlusive crisis](#), is **more likely in patients who during these episodes have high fevers, low blood oxygen levels and poor spleen function.**

Treating other conditions

- A study¹² in Hungary found that [Pharming's Ruconest \(rhC1INH\)](#) is **safe and effective as an on-demand therapy for hereditary angioedema (HAE)** to treat acute swelling attacks, and as a short-term prophylaxis to prevent attacks. Researchers found that early administration of Ruconest speeds the full resolution of an attack, and repeated use does not lessen its efficacy.

⁸ Joseph Neumeyer et al., "Bioengineering hemophilia A-specific microvascular grafts for delivery of full-length factor VIII into the bloodstream", *Blood Advances*. (2019) 3 (24): 4166–4176.

<https://doi.org/10.1182/bloodadvances.2019000848> also at <https://ashpublications.org/bloodadvances/article/3/24/4166/429666/Bioengineering-hemophilia-A-specific-microvascular>

⁹ <https://pipelinereview.com/index.php/2020032774138/DNA-RNA-and-Cells/uniQure-Announces-Achievement-of-Target-Patient-Dosing-in-HOPE-B-Pivotal-Trial-of-AMT-061-Etranacogene-Dezaparvovec-in-Hemophilia-B.html>

¹⁰ The targeted number of patients to be dosed per the clinical trial protocol was 50. In total, 54 patients have received the one-time dose of etranacogene dezaparvovec.

¹¹ Salam Alkindi et al., "[Predictors of impending acute chest syndrome in patients with sickle cell anaemia](#)," in *Nature Scientific Reports*. 12 February 2020. 10, Article number: 2470 (2020) <https://www.nature.com/articles/s41598-020-59258-y>

¹² Noemi Andrasi et al., "[Evaluation of the efficacy and safety of home treatment with the recombinant human C1-inhibitor in hereditary angioedema resulting from C1-inhibitor deficiency](#)," in *International Immunopharmacology*. Volume 80, March 2020, 106216 <https://doi.org/10.1016/j.intimp.2020.106216>

3. Regulatory

The NBA monitors overseas regulatory decisions on products, processes or procedures which are or may be of relevance to its responsibilities.

- **ARUP Laboratories** announced that the US Food and Drug Administration (FDA) had filed its pre-market approval application for its **AAV5 total antibody assay, which is a companion diagnostic test for valoctocogene roxaparovec**, BioMarin's gene therapy for severe haemophilia A.
- The FDA issued guidance for expanded use of certain **remote monitoring devices**¹³ **to facilitate patient management** while limiting physician-patient contact during the COVID-19 pandemic. The guidance, issued March 20, is in effect only during the national COVID-19 public health emergency.
- At the end of February, the **FDA gave fast track**¹⁴ **and rare paediatric disease**¹⁵ **designations to FT-4202, a potential disease-modifying oral treatment for sickle cell disease** (SCD) being developed by [Forma Therapeutics](#). FT-4202 is a small molecule activator of [pyruvate kinase-R](#) (PKR)¹⁶ designed to reduce anaemia and [vaso-occlusive crises](#) in people with SCD. FT-4202 also increases the levels of [adenosine triphosphate](#) (ATP) — the “fuel” that supplies energy to cells — inside red blood cells, improving their overall health and survival. Forma is investigating the safety, pharmacokinetics¹⁷ and pharmacodynamics¹⁸ of FT-4202 in a first-in-human [Phase 1 trial \(NCT03815695\)](#). Currently recruiting SCD patients in the US, the trial is expected to conclude in September 2020.

4. Market structure and company news

The NBA's business intelligence follows company profitability, business forecasts, capital raisings or returns, mergers and takeovers, arrangements for joint research and/or development, contracts for supply of manufacturing inputs, and marketing agreements. Companies considered include suppliers, potential suppliers and developers of products which may be of interest.

- **Codexis has signed a collaboration and licence agreement with Takeda** Pharmaceutical for the research and development **novel gene therapies** for certain disease indications, **including blood factor deficiencies**. Codexis will create novel enzyme sequences for advancement as gene therapies into pre-clinical development. Takeda is responsible for pre-clinical and clinical development and commercialization.

¹³ including those used to monitor BP, heart rate, respiratory rate and body temperature.

¹⁴ Fast track status accelerates the development and review of the treatment, facilitates discussions with the FDA and, if specific criteria are met, it enables the drug to qualify for priority review and accelerated approval.

¹⁵ With the rare paediatric disease program, if FT-4202 is approved for sickle cell disease, Forma may qualify for a priority review in marketing applications.

¹⁶ PKR is a key metabolic enzyme that plays an important role in maintaining the health of red blood cells, and reducing the levels of [2,3-diphosphoglycerate](#) (2,3-DPG). The red blood cells of SCD patients have higher levels of 2,3-DPG — a by-product of cellular metabolism that decreases the ability of haemoglobin to bind oxygen. By increasing PKR activity, FT-4202 is thought to lower the levels of 2,3-DPG, potentially helping hemoglobin hold on to oxygen longer and reducing the sickling of red blood cells — a hallmark of SCD.

¹⁷ bioavailability and distribution in the body

¹⁸ the drug's action in the body

5. Specific Country Events

- *The NBA keeps informed of events and policies in other countries for comparison purposes. In Australia, twelve haematology and oncology bodies endorsed interim consensus guidelines regarding the management of patients during the COVID-19 pandemic*¹⁹. Amongst the topics covered are blood transfusion, stem cell transplantation, palliative care and clinical trials²⁰.
- Researchers in China reported that **cancer patients** being cared for at a single centre in Wuhan were **twice as likely to be diagnosed with COVID-19** as the general population²¹.
- In the UK, **haematologists** at Oxford University Hospitals NHS Trust **offered suggestions**²² **on how to reduce patient exposure to COVID-19 infection** and its complications, and on how to minimise demands on healthcare services which are critically stretched²³.

¹⁹ Robert Weinkove et al., "Managing haematology and oncology patients during the COVID-19 pandemic: interim consensus guidance", *The Medical Journal of Australia*, published online 20 March 2020. <https://www.mja.com.au/journal/2020/212/10/managing-haematology-and-oncology-patients-during-covid-19-pandemic-interim>

²⁰ The authors noted that

- i) alternative and secondary infections – bacterial, viral and fungal – were also a possibility in immunocompromised patients with symptoms of COVID-19;
- ii) treatment-related pneumonitis could mimic the clinical and radiological features of COVID-19;
- iii) temporary discontinuation of cancer therapies may be warranted for patients with symptoms of COVID-19 to minimise treatment-related immunosuppression and the risk of drug interactions; community spread of COVID-19 may reduce the blood donor pool, and threaten blood supplies, due to deferral of donors, blood service staff shortages, or shortages of consumables and reagents;
- iv) while there is no precedent for transfusion transmission of respiratory viruses, donor deferral is the only current mechanism in place to prevent transmission via blood components;
- v) iron, folic acid, vitamin B12 or erythropoietin should be considered as alternatives to red cell transfusion for some patients to help limit transfusion requirement;
- vi) platelets are likely to be impacted by blood supply shortages early due to their short shelf-life;
- vii) most unrelated donor stem cell products in Australasia come from international donors and are therefore vulnerable to disruption;
- viii) the impact of COVID-19 on international transport may also affect the supply chain for autologous chimeric antigen receptor T-cells;
- ix) it is unclear whether SARS-CoV-2 is transmissible by cellular therapy products; and
- x) it may be necessary to reduce routine follow-up appointments, institute remote or telehealth reviews or modify treatment plans and strategies for treatment delivery in the interest of clinical trial participants as the pandemic progresses.

²¹ Jing Yu et al., "SARS-CoV-2 Transmission in Patients With Cancer at a Tertiary Care Hospital in Wuhan, China", *JAMA Oncology*, 25 March 2020. doi:10.1001/jamaoncol.2020.0980 <https://jamanetwork.com/journals/jamaoncology/fullarticle/2763673>

²² John Willan et al., "Care of haematology patients in a COVID-19 epidemic", *British Journal of Haematology*, 15 March 2020 <https://doi.org/10.1111/bjh.16620>

²³ Their suggestions included.

- i) establishing phlebotomy facilities where patients can queue in their cars;
- ii) extending the interval between monitoring blood tests;
- iii) deferring maintenance chemotherapy and offering oral chemotherapy where possible;
- iv) prioritising curative chemotherapy;
- v) pausing supportive treatments, such as venesection to reduce iron burden;
- vi) replacing outpatient clinics with video consultations; and

- In the **UK**, **healthcare workers** in the West Midlands were **instructed not to begin chest compressions or ventilation in patients in cardiac arrest if they have suspected or diagnosed covid-19, unless they are in the emergency department and each staff member involved is wearing an FFP3 mask, full gown with long sleeves, gloves, and eye protection**²⁴. Guidance from the University Hospitals Birmingham NHS Foundation Trust says that patients in cardiac arrest outside the emergency department can be given defibrillator treatment if they have a “shockable” rhythm; but if this does not restart the heart “further resuscitation is futile.”
- The British Society for Haematology’s Haemostasis and Thrombosis task force said in a [statement](#) that **regular INR monitoring of patients on warfarin was an essential part of safe anticoagulation and cannot be omitted during the social distancing** that is required in response to the pandemic. **Clinicians were advised to assess their patients for suitability for direct oral anticoagulants**, noting that not all patients would be able to switch.
- In the **US**, the **Critical Care Society Collaborative**²⁵ issued a joint statement at the end of March urging the Trump administration and Congress to **strengthen social distancing requirements** to slow the spread of COVID-19²⁶.

6. Research not included elsewhere

A wide range of scientific research has some potential to affect the use of blood and blood products. However, research projects have time horizons which vary from “useful tomorrow” to “at least ten years away”. Likelihood of success of particular projects varies, and even research which achieves its desired scientific outcomes may not lead to scaled-up production, clinical trials, regulatory approval and market development.

- **Artificial intelligence (AI) has been used to measure blood flow accurately and instantly and so predict chances of death, heart attack and stroke.** A study²⁷, funded by the British Heart Foundation, was led by University College London and Barts Health NHS Trust. Researchers took routine cardiovascular magnetic resonance (CMR) scans from 1,000 patients and used AI to analyse the images. They quantified the blood flow to the heart muscle and provided the results to treating doctors. Comparing flow results with the health outcomes of individual patients established that those with reduced blood flow were more likely to have adverse health outcomes. James Moon, University College professor of cardiology, said: “Artificial intelligence is ... carrying out some tasks better than doctors could do alone. We have tried to measure blood flow manually before, but it is tedious and time-consuming²⁸.” With the knowledge gained through AI, clinicians can prescribe treatments to improve a patient’s blood flow.

vii) deferring bone marrow transplants.

²⁴ <https://www.bmj.com/content/368/bmj.m1282>

²⁵ which includes the American Thoracic Society, the American College of Chest Physicians, the American Association of Critical-Care Nurses and the Society of Critical Care Medicine

²⁶ <https://www.healio.com/pulmonology/practice-management/news/online/%7B3d80b87d-bb00-477a-bf11-1958d7c3e3a0%7D/pulmonary-critical-care-societies-strengthen-social-distancing-requirements>

²⁷ Kristopher D Knott, James C Moon et al., “The Prognostic Significance of Quantitative Myocardial Perfusion: An Artificial Intelligence Based Approach Using Perfusion Mapping”, published 14 Feb 2020 <https://doi.org/10.1161/CIRCULATIONAHA.119.044666> and abstract at <https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.119.044666>

²⁸ Tests to measure blood flow can be high-risk and invasive, and non-invasive assessments like CMR imaging can be difficult to analyse with precision.

- The **conservative use of oxygen**, as compared with usual care, had **no significant effect on the number of ventilator-free days in patients undergoing mechanical ventilation** in the ICU, according to data published in *The New England Journal of Medicine*²⁹.
- Researchers have found³⁰ that “**Hypertension was not associated with increased mortality at ages above 85** or at ages 75–84 with moderate/severe frailty, perhaps due to complexities of coexisting morbidities.”
- Researchers used **data from Italy’s nationwide registry to characterize the clinical profiles of patients with Diamond-Blackfan anaemia**³¹. As at June 2019, the registry contained data regarding 283 patients across 215 families; the incidence ratio in the preceding 15 years had been 14 patients per million births. A similar number of male and female patients were diagnosed, 80 per cent within the first year of life (median of 3 months and range, 0-58 years).

7. Infectious diseases

The NBA takes an interest in infectious diseases because: the presence of disease in individual donors (e.g. influenza), or potential disease resulting from travel (e.g. malaria) means a donor must be deferred; temporary disease burden within a community (e.g. dengue in North Queensland) may limit blood collection in the community for a time; and some people may not be permitted to donate at all (e.g. people who lived in the UK for a period critical in the history of vCJD). Blood donations are tested for a number of diseases (e.g. HIV and Hepatitis B), but there are also emerging infectious diseases for which it may become necessary to test in the future (e.g. Chagas disease, Zika virus and the tick-borne babesiosis and Lyme disease).

Covid-19

- The emergence of a new, highly infectious³² and potentially lethal virus³³ has offered researchers a range of scientific challenges in the context of a need for speed. The **scale of the outbreak and the market** it offers has also driven companies large and small into a **search for both an effective vaccine (see Appendix A) and an effective treatment (see Appendix B)**. Some of the vaccine work has been able to build on previous work with other coronaviruses, while on the treatment side the **possibility of repurposing already approved drugs has seemed an attractive,**

²⁹ The ICU-ROX Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group, “Conservative Oxygen Therapy during Mechanical Ventilation in the ICU”, [March 12, 2020](https://doi.org/10.1056/NEJMoa1903297) N Engl J Med 2020; 382:989-998 DOI: 10.1056/NEJMoa1903297 with abstract at <https://www.nejm.org/doi/full/10.1056/NEJMoa1903297>

³⁰ Jane Masoli et al., “Blood pressure in frail older adults: associations with cardiovascular outcomes and all-cause mortality”, *Age and Ageing*, 5 March 2020. afaa028, <https://doi.org/10.1093/ageing/afaa028>

³¹ Quarello P, Garelli E, Carando A, et al. [A 20-year long term experience of the Italian Diamond-Blackfan Anaemia Registry: RPS and RPL genes, different faces of the same disease?](https://doi.org/10.1111/bjh.16508) *British Journal of Haematology*, published online February 21, 2020. *Br J Haematol.* doi: 10.1111/bjh.16508

³² A study found that COVID-19 is more contagious than SARS or MERS <https://redandblackonline.com/chinese-study-finds-that-new-corona-virus-is-more-contagious-than-sars-or-mers/>

³³ causing the World Health Organisation to declare a pandemic on 11 March <https://www.abc.net.au/news/2020-03-12/coronavirus-updates-who-declares-pandemic/12047598>

but not necessarily successful option. There has also been a rush round the world to develop (and approve) **rapid and accurate diagnostic tests**³⁴.

- Of particular interest to the blood sector have been **suggestions that “convalescent plasma” may be a useful treatment.** A report of limited early use in Wuhan sparked interest. In March [Takeda Pharmaceutical Company Limited](#) announced that it was initiating the development of an anti-SARS-CoV-2 polyclonal hyperimmune globulin (H-IG) to treat high-risk individuals with COVID-19³⁵. Then on 25 March Grifols announced that it had agreed to work with the US FDA and other agencies to collect plasma from patients who had recovered from COVID-19 and produce hyperimmune immunoglobulin which would be subjected to pre-clinical and clinical tests of their suitability as a treatment for the pandemic. On 6 April, CSL Behring announced it had formed an alliance with Biotest, BPL, LFB, Octapharma and Takeda in an “investigational development of one, unbranded anti-SARS-CoV-2 polyclonal hyperimmune immunoglobulin medicine with the potential to treat individuals with serious complications from COVID-19”. On 8 April the US FDA issued *Recommendations for Investigational COVID-19 Convalescent Plasma*³⁶. These covered [pathways for use of investigational COVID-19 convalescent plasma, patient eligibility, collection of COVID-19 convalescent plasma, including donor eligibility and donor qualifications, labelling, and record keeping.](#)
- Researchers in four countries are **testing whether a century-old vaccine against the bacterial disease tuberculosis can activate the human immune system to fight the virus that causes COVID-19**, and even prevent infection altogether. The trials will be carried out in physicians and nurses, and in the elderly. The bacillus

³⁴ The University of Sydney-affiliated start-up, DetectED-X, had access to technology originally developed to improve the accuracy of breast cancer detection; it modified this to identify COVID-19 using lung CT scans from Italy and China. The company’s CEO (Professor Patrick Brennan) said the technology permitted people interpreting lung scans to have each diagnosis reviewed in real time. The technology is being supplied without cost, to any medical facility worldwide that requests it, ensuring it is available to health workers who have no expertise in interpreting lung CT scans. Scientists from The Hong Kong Polytechnic University claim to have developed a diagnostic system that can identify 30 to 40 pathogens in one single test within an hour. The fully automated machine and a multiplex full-screening panel for point-of-care genetic testing can, they say, identify respiratory infectious diseases, including COVID-19. Amongst other pathogens that can be identified are seasonal influenza viruses, avian influenza viruses H5, H7 and H9, human respiratory syncytial virus, SARS-CoV and MERS-CoV. The research team is led by Terence Lau Lok-ting, director of Innovation and Technology Development and adjunct professor at the Department of Applied Biology and Chemical Technology. Patent applications have been filed for the technologies involved.

<https://www.bioworld.com/articles/433094-researchers-develop-diagnostic-system-that-detects-up-to-40-infectious-respiratory-pathogens-in-one-test>

Tired of Delays, U.S. Labs Ask FDA to Develop Their Own Coronavirus Tests

<https://www.medscape.com/viewarticle/925652>

FDA opens the gates to commercial coronavirus testing without agency review

<https://www.fiercebiotech.com/medtech/fda-opens-gates-to-commercial-coronavirus-testing-without-agency-review>

LGC, Biosearch Technologies works with partners to accelerate coronavirus diagnostic solutions

<https://www.selectscience.net/industry-news/lgc.-biosearch-technologies-works-with-partners-to-accelerate-coronavirus-diagnostic-solutions/?artID=50760>

Co-Diagnostics nets European approval for its coronavirus PCR test

<https://www.fiercebiotech.com/medtech/co-diagnostics-nets-european-approval-for-its-coronavirus-pcr-test>

³⁵ <https://www.europeanpharmaceuticalreview.com/news/114818/development-initiated-plasma-derived-therapy-covid-19/> and <https://www.jewishpress.com/news/business-economy/japanese-company-developing-covid-19-treatment-using-recovered-patients-plasma/2020/03/10/>

³⁶ <https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma>

Calmette-Guérin (BCG) vaccine contains a live, weakened strain of *Mycobacterium bovis*, a cousin of *M. tuberculosis*, the microbe that causes TB. The vaccine is given to children in their first year of life in most countries round the world. It is safe and cheap. It prevents about 60 per cent of TB cases in children on average, with large differences between countries. A research group at the University of Melbourne is setting up one of the BCG studies among health care workers.

- Amongst the **many clinical issues with COVID-19** that have been debated are:
 - i) whether nonsteroidal anti-inflammatory drugs (NSAIDs), such as [ibuprofen](#), could worsen coronavirus disease³⁷;
 - ii) whether induced sputum is better than throat swabs for detecting COVID -19 virus³⁸;
 - iii) whether people can catch COVID-19 twice³⁹;
 - iv) whether early gastro-intestinal symptoms in COVID-19 indicate faecal transmission⁴⁰;
 - v) whether COVID-19 persists in stool samples after samples from the respiratory tract test negative⁴¹
 - vi) whether chest CT findings for COVID-19 may overlap with adenovirus⁴²
 - vii) whether COVID-19, like SARS, may induce liver damage⁴³
 - viii) what the risk factors are for dying from COVID-19⁴⁴
 - ix) whether COVID-19 is a seasonal disease⁴⁵;
 - x) what factors are associated with acute respiratory distress syndrome in COVID-19?⁴⁶;
 - xi) why do children seem to have more chance of escaping COVID-19?⁴⁷;
 - xii) why do people aged 65 and over have a higher death rate from COVID-19?⁴⁸

³⁷ Are Warnings Against NSAIDs in COVID-19 Warranted?

<https://www.medscape.com/viewarticle/926940>

³⁸<https://www.medscape.com/viewarticle/926889>

³⁹ Can you get coronavirus twice? This Nobel prize winner is sceptical

<https://www.abc.net.au/news/2020-03-22/doubt-over-contracting-coronavirus-covid-19-twice/12075878>

⁴⁰<https://www.medscape.com/viewarticle/926682> and

<https://www.healio.com/gastroenterology/motility/news/online/%7Bbe83bd7b-e901-4f87-85d4-c1ae26ace2ac%7D/diarrhea-may-be-common-symptom-in-patients-with-covid-19>

⁴¹ Yongjian Wu, "Prolonged presence of SARS-CoV-2 viral RNA in faecal samples", *The Lancet Gastroenterology and Hepatology*, online March 19, 2020. [https://www.thelancet.com/journals/langas/article/PIIS2468-1253\(20\)30083-2/fulltext](https://www.thelancet.com/journals/langas/article/PIIS2468-1253(20)30083-2/fulltext)

⁴² Yan Li and Liming Xia, "Coronavirus Disease 2019 (COVID-19): Role of Chest CT in Diagnosis and Management", *American Journal of Roentgenology*.

<https://www.ajronline.org/doi/full/10.2214/AJR.20.22954>

⁴³<https://www.medpagetoday.com/infectiousdisease/covid19/85315>

⁴⁴ <https://www.labonline.com.au/content/life-scientist/article/risk-factors-identified-for-death-from-covid-19-1550523310>

and

<https://www.medpagetoday.com/infectiousdisease/covid19/85519>

and

COVID-19 and Tobacco Harm Reduction: What's the Relationship?

<https://filtermag.org/coronavirus-tobacco-harm-reduction/amp/>

⁴⁵ <https://www.healio.com/primary-care/infectious-diseases/news/online/%7B0a14f604-44fb-4d50-9df8-b10af77fe519%7D/seasonality-of-covid-19-remains-uncertain>

⁴⁶ <https://www.healio.com/pulmonology/critical-care/news/online/%7B396c0e9d-c9a4-473a-a264-900eb414dd0a%7D/study-identifies-factors-associated-with-ards-in-covid-19>

⁴⁷ <https://www.the-scientist.com/news-opinion/possible-biological-explanations-for-kids-escape-from-covid-19-67273>

⁴⁸ <https://www.businessinsider.com.au/most-us-coronavirus-deaths-ages-65-older-cdc-report-2020-3?r=US&IR=T>

- xiii) what did doctors in China learn while treating the disease?⁴⁹;
- xiv) are household pets at risk from COVID-19? Can they carry it asymptotically? Can they transmit to humans?⁵⁰ and
- xv) Are there “super-spreaders”?⁵¹

- **Chinese officials detailed⁵² national COVID-19 mortality and age distribution** in the early stages of the outbreak. Most of the cases occurred in patients aged 30-79 years, while 10 per cent were in patients 29 years and younger, and 3 per cent in patients at 80 years and older. Australia’s population has a greater proportion of elderly people, so the distribution of mortality is expected to be different.
- At a [webinar co-sponsored by the Chinese Cardiovascular Association and American College of Cardiology](#), **Chinese clinicians said that endothelial damage and subsequent clotting is common in severe and critical COVID-19 patients.** Bin Cao, of the National Clinical Research Center for Respiratory Diseases in Beijing⁵³, described “clots in the small vessels of all organs, not only the lungs but also including the heart, the liver, and the kidney”⁵⁴. He said: “Anticoagulation therapy should be initiated for severe COVID-19 patients [unless] otherwise contraindicated.” Harlan Krumholz, of Yale University, advocated first testing whether anticoagulation helps.
- The **American Heart Association (AHA) issued interim guidance for CPR and emergency cardiovascular care** for patients with known or suspected COVID-19 infection to help reduce the risk for transmission of SARS-CoV-2, the virus responsible for COVID-19⁵⁵.

⁴⁹<https://www.medpagetoday.com/infectiousdisease/covid19/85520>

⁵⁰ On 21 Mar 2020 from Dr. Thomas Sit, chief veterinary officer/assistant director (Inspection & Quarantine), Agriculture, Fisheries and Conservation Department, Hong Kong Special Administrative Region Government, reported to Promed: *two dogs were placed under quarantine on [18 Mar 2020] after their owner was hospitalised due to COVID-19 infection. Following veterinary examination nasal, oral, and rectal swab samples were taken after the dogs' admission to the quarantine facility. Samples from one of the dogs taken on [18 and 19 Mar 2020] tested positive for SARS-CoV-2. Both animals did not exhibit any specific clinical signs. Investigations are continuing. Risk management measures are in place for this case, including cleansing and disinfection of the premises, and proper personal hygiene and protection. Mammalian pets from households with confirmed human cases of COVID-19 will be placed under quarantine and veterinary surveillance for 14 days. Samples will be collected for testing of SARS-CoV-2 as appropriate.*

⁵¹ Beldomenico PM. “Do super-spreaders generate new super-spreaders? A hypothesis to explain the propagation pattern of COVID-19.” <https://www.researchgate.net/publication/340227854>>

⁵² Wu Z, McGoogan JM. “Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention” *JAMA*. Online 24 February 2020 [doi: 10.1001/jama.2020.2648](https://doi.org/10.1001/jama.2020.2648).

⁵³ And also president-elect of the Chinese Society of Respiratory Medicine.

⁵⁴ His group [reported March 11 in The Lancet](#). Fei Zhou, Bin Cao et al., “Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study”, 11 March 2020.

⁵⁵ Aerosol-generating procedures such as CPR and endotracheal intubation should be performed in airborne infection isolation rooms; personnel should use respiratory protection. Only providers essential for patient care and procedural support should be present during the procedure and the room should be cleaned and disinfected following the procedure. Patients with known or suspected COVID-19 should be cared for in a single-person room with the door closed and airborne infection isolation rooms should be reserved for patients undergoing aerosol generating procedures.

N95 respirators or respirators that offer a higher level of protection should be used instead of a face mask during aerosol-generating procedures.

Providers should put on a respirator or facemask (if a respirator is not available) before entering a patient's room or care area. Facilities should return to use of respirators for patients with known or suspected COVID-19 once the supply chain is restored.

Wear eye protection, gloves, and gowns.

- The European Commission pledged financial support to a German firm⁵⁶ after it was told that the US President was trying to persuade the company to move its research to the US and produce vaccine for Americans. **EU leaders then reportedly discussed how to prevent hostile US takeovers of EU-based research firms at the forefront in developing drugs and vaccines against the coronavirus.** Previously the Commission committed up to 45 million euros for research.
- To facilitate research relevant to the pandemic a number of **scientific publishers are making relevant content freely available**⁵⁷.
- Some scientists are interested in determining **what animal species first transmitted COVID-19 to humans**, perhaps as an intermediate host rather than as an initial carrier⁵⁸.
- Other researchers are interested in finding out **whether the virus is mutating**, with multiple strains in circulation⁵⁹.

Influenza

- **The FDA received Genentech's New Drug Application for Xofluza for the treatment of influenza in children, one year and older.** The additional formulation is as granules for oral suspension. The FDA also received a supplemental New Drug Application for the use of Xofluza for post-exposure prophylaxis, potentially offering Xofluza as a preventive treatment for influenza after exposure to an infected individual.

When gowns are in short supply, they should be prioritized for aerosol-generating procedures, care activities where splashes and sprays are anticipated, and high-contact patient care activities that provide opportunities for transfer of pathogens to the hands and clothing of providers. If intubation is needed, consider using rapid sequence intubation with appropriate personal protective equipment (PPE).

If possible, avoid procedures which generate aerosols, such as bag-valve mask, nebulizers and non-invasive positive pressure ventilation.

Consider proceeding directly to endotracheal intubation in patients with acute respiratory failure. Avoid the use of high-flow nasal oxygenation and mask CPAP or bilevel CPAP due to greater risk of aerosol generation.

Emergency medical dispatchers should ask callers about the possibility of COVID-19 in the patient. The query process should not supersede the provision of prearrival instructions to the caller when immediate lifesaving interventions are needed.

Prehospital care providers and healthcare facilities should be notified when COVID-19 is suspected in a patient requiring emergency transport.

Emergency clinician practices should be based on the most up-to-date COVID-19 clinical recommendations and information from appropriate public health authorities and EMS medical direction.

The AHA's interim guidance for CPR and emergency cardiovascular care during the COVID-19 outbreak are at cpr.heart.org

⁵⁶ The Commission promised 80 million euros to CureVac, which said it had developed new technology that could reduce costs for vaccines and provide a rapid response to COVID-19.

⁵⁷ E.g. <https://www.elsevier.com/connect/coronavirus-information-center>

[The Lancet Coronavirus Hub](https://www.cell.com/2019-nCoV)

<https://www.cell.com/2019-nCoV>

COVID-19: Cell Press. Link to COVID-19 research

⁵⁸ Y. Wan et al., "Receptor recognition by novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS," *J Virology*, doi:10.1128/JVI.00127-20, 2020.

⁵⁹ Coronavirus's Genetics Reveal Its Global Travels: Random mutations in the SARS-CoV-2 pathogen's genome help researchers track the spread and transmission of COVID-19, the disease it causes.

<https://www.the-scientist.com/news-opinion/coronaviruss-genetics-reveal-its-global-travels-67183>

Appendix A – Companies seek an effective Covid-19 vaccine

The scale of the outbreak and the market it offers has driven companies into a search for an effective vaccine (page 7 refers).

- China gives go-ahead for human trials of potential COVID-19 vaccine: state media <https://www.reuters.com/article/us-health-coronavirus-china-vaccine/china-approves-coronavirus-vaccine-for-clinical-trials-state-media-idUSKBN2141T1>
- NIH clinical trial of investigational vaccine for COVID-19 begins <https://www.nih.gov/news-events/news-releases/nih-clinical-trial-investigational-vaccine-covid-19-begins>
- CureVac Receives €80M from EU to Fund Coronavirus Vaccine Amid US Dispute <https://www.labiotech.eu/medical/curevac-coronavirus-rna-covid/>
- Biopharma's no-holds-barred fight to find a COVID-19 vaccine: The full list <https://www.fiercebiotech.com/biotech/biopharma-s-no-holds-barred-fight-to-find-a-covid-19-vaccine-full-list>
- J&J sets sights on November for COVID-19 vaccine trial <https://www.fiercebiotech.com/biotech/j-j-sets-sights-november-for-covid-19-vaccine-trial>
- Covid-19 vaccine in development by J&J and BIDMC. <https://www.pharmaceutical-technology.com/news/jj-janssen-bidmc-covid-19-vaccine/>
- Pfizer, BioNTech strike COVID-19 deal, commit multiple R&D sites to vaccine development <https://www.fiercebiotech.com/biotech/pfizer-biontech-strike-covid-19-deal-commit-multiple-r-d-sites-to-vaccine-development>
- Medicago Announces Production of a Viable Vaccine Candidate for COVID-19 <https://pipelinereview.com/index.php/2020031374022/Vaccines/Medicargo-Announces-Production-of-a-Viable-Vaccine-Candidate-for-COVID-19.html>
- Novavax Awarded Funding from CEPI for COVID-19 Vaccine Development <https://pipelinereview.com/index.php/2020031073984/Vaccines/Novavax-Awarded-Funding-from-CEPI-for-COVID-19-Vaccine-Development.html> and Novavax Begins Animal Testing for Coronavirus Vaccine Candidate <https://www.thestreet.com/>
- CEL-SCI Initiates Development of Immunotherapy to Treat COVID-19 Coronavirus Infection <https://pipelinereview.com/index.php/2020030973977/Vaccines/CEL-SCI-Initiates-Development-of-Immunotherapy-to-Treat-COVID-19-Coronavirus-Infection.html>
- Mount Sinai and Harbour BioMed Collaborate to Advance Novel Biotherapies for the Treatment of Cancer and Coronavirus COVID-19 <https://pipelinereview.com/index.php/2020030873967/Vaccines/Mount-Sinai-and-Harbour-BioMed-Collaborate-to-Advance-Novel-Biotherapies-for-the-Treatment-of-Cancer-and-Coronavirus-COVID-19.html>
- Vir Biotechnology Announces Research Collaboration with the National Institutes of Health Vaccine Research Center on Antibodies Against Coronaviruses <https://finance.yahoo.com/news/vir-biotechnology-announces-research-collaboration-120010619.html>
- A Better Approach to Coronavirus Vaccine Plausible? Synthetic Biologists Think So <https://www.sciencetimes.com/articles/24997/20200310/a-better-approach-to-coronavirus-vaccine-plausible-synthetic-biologists-think-so.htm>
- Texas-based company claims to have developed coronavirus vaccine <https://m.jpost.com/International/Texas-based-company-claims-to-have-developed-coronavirus-vaccine-620364> and <https://www.dailymail.co.uk/health/article-8021285/Texas-scientists-say-discovery-lead-coronavirus-vaccine.html>
- Sanofi teams up with U.S. agency against coronavirus <https://www.reuters.com/article/us-china-health-sanofi/sanofi-teams-up-with-u-s-agency-against-coronavirus-idUSKBN20C1YJ>
- Zydus Cadila launches a fast -tracked programme to develop vaccine for the novel coronavirus, 2019-nCoV (COVID-19) <https://pipelinereview.com/index.php/2020021773810/Vaccines/Zydus-Cadila-launches-a-fast-tracked-programme-to-develop-vaccine-for-the-novel-coronavirus-2019-nCoV-COVID-19.html>

Appendix B – Companies seek an effective Covid-19 treatment

The scale of the outbreak and the market it offers has driven companies into a search for an effective treatment (page 7 refers).

- 'Favilavir': First Approved Drug to Treat Coronavirus
<https://www.sciencetimes.com/articles/25053/20200317/favilavir-first-approve-drug-treat-coronavirus.htm>
- Sobi to initiate a clinical study to evaluate whether anakinra and emapalumab may relieve complications associated with severe COVID-19 disease
<https://www.sobi.com/en/press-releases/sobi-initiate-clinical-study-evaluate-whether-anakinra-and-emapalumab-may-relieve>
- Japanese flu drug 'clearly effective' in treating coronavirus, says China
<https://www.theguardian.com/world/2020/mar/18/japanese-flu-drug-clearly-effective-in-treating-coronavirus-says-china>
- Despite 'heroic' effort, coronavirus study finds little benefit to repurposed HIV drug
<https://www.biopharmadive.com/news/coronavirus-kalettra-clinical-trial-nejm/574435/>
- Biopharma's leading treatment hopes against COVID-19
<https://www.fiercebiotech.com/biotech/biopharma-s-leading-treatment-hopes-against-covid-19>
- Inside Regeneron's R&D war room, sleepless nights and 'esprit de corps' in hunt for COVID-19 therapy
<https://www.fiercepharma.com/pharma/regeneron-s-r-d-war-room-sleepless-nights-and-esprit-de-corps-hunt-for-covid-19-therapy>
- FDA opens up Bellerophon's gas therapy for COVID-19, stock rockets
<https://www.fiercebiotech.com/medtech/fda-expands-access-to-bellerophon-s-nitric-oxide-gas-for-covid-19-lung-symptoms>
- Moleculin advances plan to strip and starve COVID-19
<https://www.fiercebiotech.com/biotech/moleculin-advances-plan-to-strip-and-starve-covid-19>
- COVID-19: Could Hydroxychloroquine Really Be the Answer?
https://www.medscape.com/viewarticle/927033?nlid=134577_1842&src=WNL_mdplsfeat_200320_mscpedit_wir&uac=206033FY&spon=17&impID=2318495&faf=1
- Trump Says FDA Approved Anti-Malaria Drug Chloroquine To Test As Coronavirus Treatment
<https://www.forbes.com/sites/lisettevoytko/2020/03/19/trump-says-fda-approved-anti-malaria-drug-chloroquine-to-test-as-coronavirus-treatment/>
- Bayer donates millions of tablets of chloroquine to help in COVID-19 fight
<https://www.fiercepharma.com/pharma/bayer-preps-u-s-donation-malaria-med-chloroquine-to-help-covid-19-fight-report>
- Novartis, Mylan and Teva to supply tens of millions of chloroquine tablets to fight COVID-19
<https://www.fiercepharma.com/pharma/new-commitments-mylan-and-teva-move-to-supply-tens-millions-hydroxychloroquine-tablets-to>
- WHO to launch multinational trial to jumpstart search for coronavirus drugs
<https://www.statnews.com/2020/03/18/who-to-launch-multinational-trial-to-jumpstart-search-for-coronavirus-drugs/>
- Roche launches late-stage study of Actemra for COVID-19
<https://seekingalpha.com/news/3553236-roche-launches-late-stage-study-of-actemra-for-covidminus-19>
- Monkeys Develop Protective Antibodies to SARS-CoV-2
<https://www.the-scientist.com/news-opinion/monkeys-develop-protective-antibodies-to-sars-cov-2-67281>
- AbCellera and Lilly to Co-develop Antibody Therapies for the Treatment of COVID-19
<https://pipelinereview.com/index.php/2020031374018/Antibodies/AbCellera-and-Lilly-to-Co-develop-Antibody-Therapies-for-the-Treatment-of-COVID-19.html>
- Emergent BioSolutions Initiates Development of Plasma-Derived Product Candidates for the Treatment and Prevention of Coronavirus Disease
<https://pipelinereview.com/index.php/2020031274009/Antibodies/Reply-Forward-Delete-View-Source-Save-Emergent-BioSolutions-Initiates-Development-of-Plasma-Derived-Product-Candidates-for-the-Treatment-and-Prevention-of-Coronavirus-Disease.html>

- Kamada Provides Update on Progress Related to its Proprietary Hyper-Immunoglobulin (IgGs) Platform Technology including its Commercial Anti-Rabies IgG and its Pipeline Products Anti-Corona (COVID-19) and Anti-Zika IgGs
<https://pipelinereview.com/index.php/2020031174006/Antibodies/Kamada-Provides-Update-on-Progress-Related-to-its-Proprietary-Hyper-Immunoglobulin-IgGs-Platform-Technology-including-its-Commercial-Anti-Rabies-IgG-and-its-Pipeline-Products.html>
- Takeda Initiates Development of a Plasma-Derived Therapy for COVID-19
<https://pipelinereview.com/index.php/2020030473942/Antibodies/Takeda-Initiates-Development-of-a-Plasma-Derived-Therapy-for-COVID-19.html> see more of this on the following page
- ImmunoPrecise Announces Artificial Intelligence Collaboration with EVQLV to Accelerate Vaccine and Antibody Discovery for SARS-CoV-2 Coronavirus
<https://pipelinereview.com/index.php/2020030273926/Antibodies/ImmunoPrecise-Announces-Artificial-Intelligence-Collaboration-with-EVQLV-to-Accelerate-Vaccine-and-Antibody-Discovery-for-SARS-CoV-2-Coronavirus.html>
- Airway Therapeutics Announces Filing with NIH to Evaluate AT-100 as a Therapy for Novel Coronavirus
<https://pipelinereview.com/index.php/2020031174003/Proteins-and-Peptides/Airway-Therapeutics-Announces-Filing-with-NIH-to-Evaluate-AT-100-as-a-Therapy-for-Novel-Coronavirus.html>
- Pluristem and Charité University of Medicine Berlin Join Forces Targeting Potential Treatment for Respiratory and Inflammatory Intratissue Complications Caused by COVID-19
<https://pipelinereview.com/index.php/2020031374023/DNA-RNA-and-Cells/Pluristem-and-Charite-University-of-Medicine-Berlin-Join-Forces-Targeting-Potential-Treatment-for-Respiratory-and-Inflammatory-Intratissue-Complications-Caused-by-COVID.html>
- Mesoblast to evaluate anti-inflammatory cell therapy remestemcel-L for treatment of COVID-19 lung disease |
<https://pipelinereview.com/index.php/2020031073981/DNA-RNA-and-Cells/Mesoblast-to-evaluate-anti-inflammatory-cell-therapy-remestemcel-L-for-treatment-of-COVID-19-lung-disease.html>
- AlloVir and Baylor College of Medicine are collaborating to develop T-cell therapies against COVID-19. The alliance uses existing work to create off-the-shelf cell therapies that identify and eliminate specific viruses.
- CEL-SCI Initiates Development of Immunotherapy to Treat COVID-19 Coronavirus Infection
<https://www.pharmiweb.com/press-release/2020-03-10/cel-sci-initiates-development-of-immunotherapy-to-treat-covid-19-coronavirus-infection>
- Gilead gains 4.8% as WHO sees potential in its antiviral drug
<https://seekingalpha.com/news/3544811-gilead-gains-4-8-who-sees-potential-in-antiviral-drug>
see also NIH clinical trial of remdesivir to treat COVID-19 begins
<https://www.nih.gov/news-events/news-releases/nih-clinical-trial-remdesivir-treat-covid-19-begins>
- Johnson & Johnson to Expand Partnership with U.S. Department of Health & Human Services to Accelerate the Discovery of Potential COVID-19 Treatments
<https://pipelinereview.com/index.php/2020021973816/Vaccines/Johnson-Johnson-to-Expand-Partnership-with-U.S.-Department-of-Health-Human-Services-to-Accelerate-the-Discovery-of-Potential-COVID-19-Treatments.html> see also www.jnj.com/coronavirus.
- Harvard, Guangzhou Institute Launch \$115M Coronavirus Research Collaboration
<https://www.genengnews.com/news/harvard-guangzhou-institute-launch-115m-coronavirus-research-collaboration/>