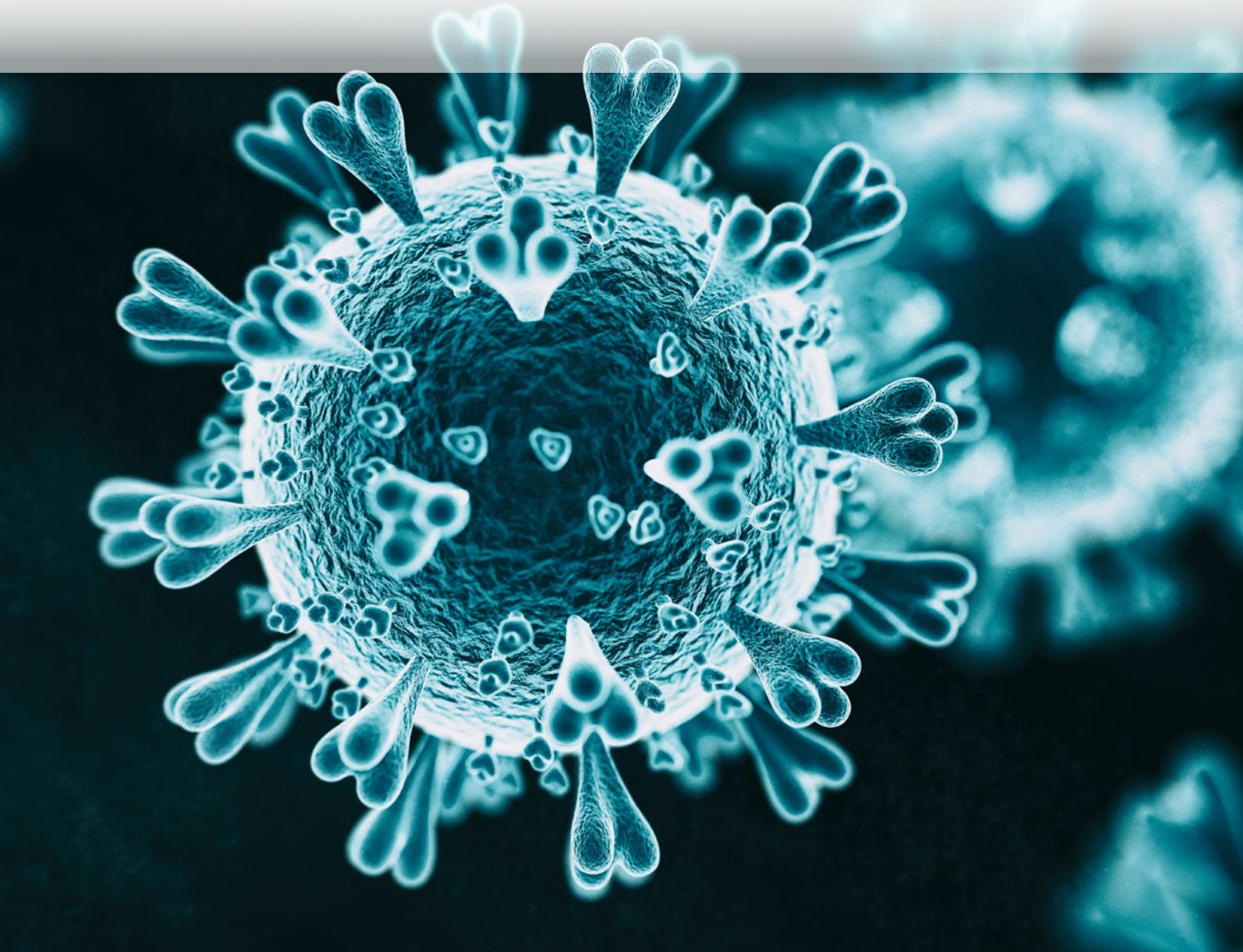
Australia's National
Science Agency

Strengthening Australia's Pandemic Preparedness

Science and technology-enabled solutions

2022



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This report was authored by Anthea Moisi, Laura Thomas, and Greg Williams with input from over 140 government, industry and research leaders.

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Acknowledgement

CSIRO acknowledges the Traditional Owners of the land, sea and waters, of the area that we live and work on across Australia. We acknowledge their continuing connection to their culture, and we pay our respects to their Elders past and present.

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- Australian Government Department of Defence
- Australian Government Department of Foreign Affairs and Trade
- Australian Government Department of Health and Aged Care
- Australian Government Department of Home Affairs
- Australian Government Department of Industry, Science and Resources
- Australian Infectious Disease Network
- Certara
- CEPI
- DMTC
- James Cook University
- MTPConnect
- The University of Queensland

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Foreword

On the back of the 1918 influenza pandemic, advocacy for national leadership in public health management of infectious disease was the primary influence in the establishment of the Commonwealth Department of Health in 1921.

Most recently, much of the world is emerging from the COVID-19 pandemic, the most significant pandemic the world has seen since 1918. This pandemic has had wide ranging social, health and economic impacts, some of which are still to be understood.

This year has also required a coordinated national response to the incursion and spread of Japanese Encephalitis Virus (JEV) into mainland Australia, the first ever JEV outbreak detected on the mainland despite the virus being widespread in South-East Asia.

Australia's planning and preparedness for a public health emergency has served us well in the response to the COVID-19 pandemic. From 2004 to 2017, various reviews on Australia's capacity to respond to a communicable disease outbreak were undertaken and progress was demonstrated as evidenced by evaluations of status evolving from 'critical, but stable' to 'a comprehensive system of capabilities and functions to prepare, detect and respond to health security threats'.

The framework for this success was the effective utilisation of existing government health committees, engagement with external experts and committees, and whole of government leadership and responsiveness at all levels including industry and the community.

The foundations of Australia's COVID-19 public health response were agile early risk assessments leading to international border closures, high case and contact ascertainment and management, public health strategies to control transmission, and high vaccination coverage.

However, in a rapidly evolving and changing situation, rapid and agile decisions are often required to manage the public health impact in the face of a dearth of evidence and uncertainty. There are still many lessons to be learned from Australia's response to the COVID-19 pandemic to inform and improve our response to any future pandemics.

Planning and preparedness for future infectious disease outbreaks, building on lessons learned, will continue to require cross sectoral engagement and coordination across a range of areas. This is particularly true for zoonoses which are the primary driver of pandemics and where a One Health approach will be critical.

CSIRO Futures' Strengthening Australia's Pandemic Preparedness: Science and technology-enabled solutions represents the first of such cross sectoral reports. The science and technology priorities for improvement presented here have been, and will continue to be, important to pandemic preparedness in Australia. I welcome the report.

Dr Sonya Bennett
Deputy Chief Medical Officer,
Australian Government Department
of Health and Aged Care

Executive summary

This report assesses a range of science and technology (S&T) areas that were identified as being critical to a more technology-enabled approach to pandemic preparedness against viral diseases. These S&T areas, and the recommendations listed to further enhance their impact on Australia's pandemic preparedness, were developed through deep system wide engagement, including contributions from over 140 experts across industry, research and government (see Appendix A).

Large-scale viral disease outbreaks result in significant economic, health and social costs.

Globally, the COVID-19, H1N1, HIV, Influenza, MERS and SARS pandemics have caused more than 45 million deaths since 1981.[1] At the national level, there was a cumulative difference of $144 billion between the pre-COVID-19 GDP trendline and actual GDP, from December 2019 through to March 2022. Less quantifiable indirect costs including impacts on mental health, social cohesion, employment, childhood development, and equity can be longer lasting and may far outweigh the direct costs.

Viral disease outbreaks are increasing in frequency and severity.

The increasing occurrence of virus spill-over from animal populations over the last 100 years has largely been driven by environmental destruction, climate change, urbanisation, human encroachment on natural habitats, and increased global trade and travel**.** In addition to known viruses, on average, two novel viruses are appearing in humans each year, and the proportion that give rise to larger outbreaks is growing.[2]

Travel restrictions and quarantine measures are useful tools for the immediate public health response.

Australia's success in keeping COVID-19 infections lower than most countries has largely been the result of early border closures and the public's broad acceptance of social distancing, lockdown measures, mask wearing and vaccinations. However, many of these interventions involve travel restrictions and quarantine measures that result in significant economic, social and indirect health costs when implemented and are increasingly difficult to implement as the duration of a pandemic grows.[3]

However, enhanced and nationally coordinated investments in science and technology can provide a wider range of complementary preparedness and response approaches.

This can significantly reduce the economic, social and indirect health costs associated with travel restrictions and quarantine measures by facilitating the important transition away from crisis response and towards an integrated cycle of prevention, detection, response and recovery.[4] An integrated cycle can both defend against the emergence of a pandemic and ensure the functions needed to respond are optimised to reduce direct and indirect impacts.[5]

1 CSIRO Futures analysis.

2 Bernstein AS, Ando AW, Loch-Temzelides T, Vale MM, Li BV, Li H, Busch J, Chapman CA, Kinnaird M, Nowak K, Castro MC, Zambrana-Torrelio C, Ahumada JA, Xiao L, Roehrdanz P, Kaufman L, Hannah L, Daszak P, Pimm SL, Dobson AP (2022) The costs and benefits of primary prevention of zoonotic pandemics. Science Advances 8(5).

3 World Health Organization (WHO) (2016) Anticipating Emerging Infectious Disease Epidemics. WHO, Geneva. <https://apps.who.int/iris/bitstream/handle/10665/252646/WHO-OHE-PED-2016.2-eng.pdf> (accessed 28 March 2022).

4 Bedford J, Farrar J, Ihekweazu C, Kang G, Koopmans M, Nkengasong J (2019) A new twenty-first century science for effective epidemic response. Nature 575 (7781), 130-136.

5 Carlin EP, Machalaba C, Berthe FCJ, Long KC, Karesh WB (2019) Building resilience to biothreats. EcoHealth Alliance, USA.

Key areas of science and technology for strengthened pandemic preparedness.

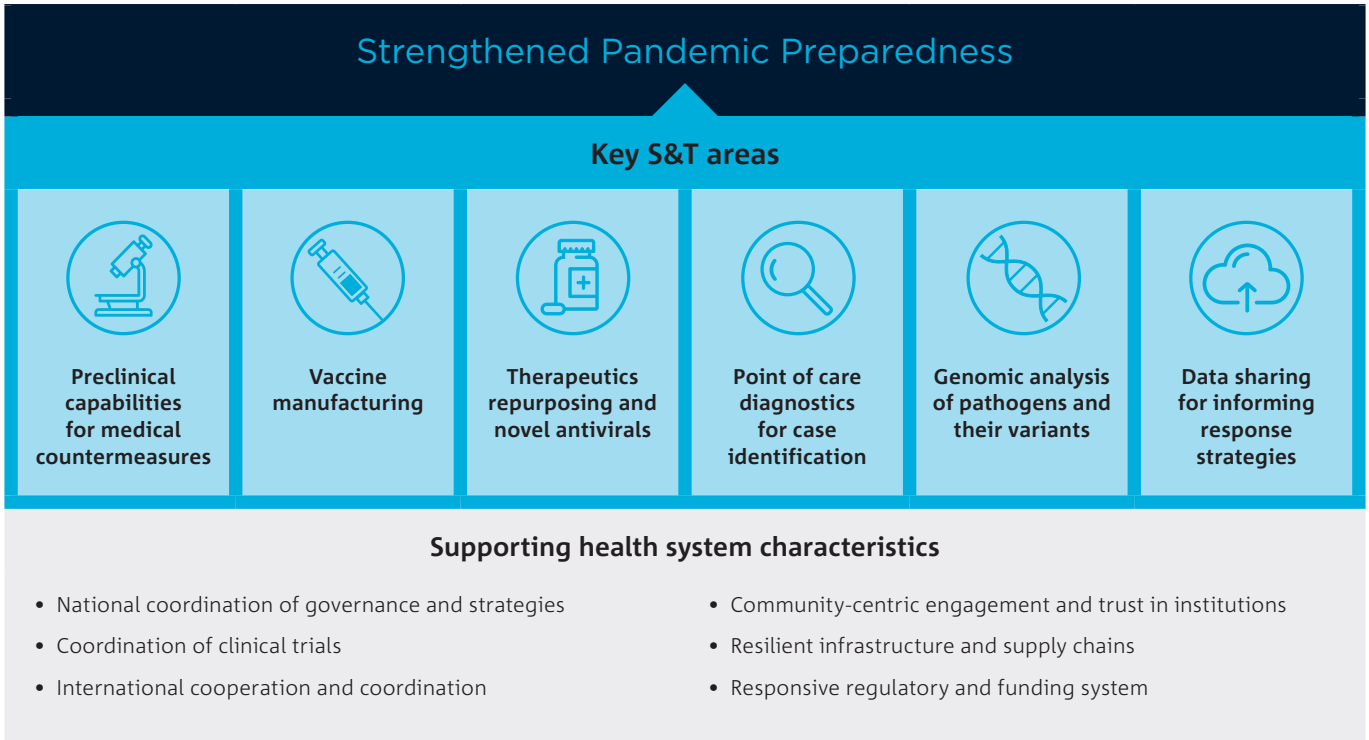
Through a survey and guidance from the project's external steering committee, six S&T areas were prioritised for discussion in this report (see figure below). These areas were selected based on where consulted stakeholders identified further investment would have the most impact on Australia's pandemic preparedness.

These S&T areas do not operate in isolation and investments in one S&T area can pay dividends for others. As such, it is important to consider these linkages, and associated data flows, standards and stakeholders, when developing solutions in these areas and implementing the proposed recommendations (see table on next page).

Consideration and implementation of the proposed recommendations would benefit from national coordination, and so it is likely that the Australian Government would lead initial decision making in these areas, however many of the recommendations will require strong support and implementation from other levels of government as well as industry and research.

While not the focus of this report, it is important to acknowledge that S&T development and implementation is supported by a range of broader health system characteristics. These include strong national coordination, community-centric engagement and collaboration with global initiatives like CEPI and the World Health Organization to ensure Australia is well positioned to identify areas where the nation is uniquely positioned to lead or support.

Key S&T areas and supporting health system characteristics



Challenge, vision and recommendations for key science and technology areas that can enable pandemic preparedness

S&T AREA	CHALLENGE	2030 VISION	RECOMMENDATIONS
Preclinical capabilities for medical countermeasures	Globally, viral families with pandemic potential are poorly understood, which prevents health systems from being adequately prepared for most threats. Australian efforts to contribute to this global understanding are not nationally coordinated and require prioritisation, given investment is finite.	Australia contributes to global efforts to improving virus and host knowledge across *Coronaviridae*, *Flaviviridae*, *Orthomyxoviridae*, *Paramyxoviridae* and *Togaviridae* families. Preclinical studies and associated infrastructure for priority viral families are adaptable to responding to Disease X. Preclinical studies are coordinated with product development pathways including translational science, manufacturing and health system requirements.	1. Improve virus and host knowledge across priority viral families (*Coronaviridae*, *Flaviviridae*, *Orthomyxoviridae*, *Paramyxoviridae* and *Togaviridae*) 2. Engage with global networks to optimise research efforts across priority viral families and for the development of medical countermeasures 3. Expand research capabilities in animal models for priority viral families 4. Enhance R&D into alternatives to animal models 5. Strengthen translational science to help bridge the gap between research, industry and the health system
Vaccine manufacturing	The absence of manufacturing capabilities across diverse vaccine technologies reduces Australia's capability to produce vaccines onshore for an emergent viral threat. Australian companies face barriers, such as high input costs and small population for clinical trial enrolments, to scale-up manufacture onshore.	Australia has onshore vaccine manufacturing capabilities and infrastructure supporting Phase I to III clinical trials across a diverse range of vaccine technologies. This infrastructure is available to pivot to relevant vaccines in a pandemic, increasing security of vaccine supply.	6. Diversify manufacturing capabilities across vaccine types, including recombinant protein and viral vector technologies 7. Expand the number of contract development and manufacturing facilities to support Phase I to III trials for vaccines
Therapeutic repurposing and novel antivirals	Commercial and candidate therapeutic repurposing is not mapped to viral families with pandemic potential. Early commercial development of direct-acting antivirals that target priority viral families has not been undertaken.	Several direct-acting antivirals that target priority viral families are in development. Australia has a national database of potential therapeutics for repurposing with estimated effectiveness mapped against priority viral families.	8. Expand high throughput screening of commercially available therapeutics to include mapping to priority viral families 9. Develop a central database of therapeutics with repurposing potential for future pandemics 10. Undertake early-development into direct-acting antivirals that act against priority viral families
Point of care diagnostics for case identification	Inconsistencies in jurisdictional diagnostics requirements, and the increasing demands on laboratories during outbreak peaks means Australia needs a diverse range of diagnostic options.	Australia has a national pandemic response strategy that enables rapid and scaled deployment of POCT diagnostics in healthcare settings and in the community to complement IVD capabilities. The country continues to contribute R&D capabilities to the global sector, with strengths in multiplex POCT platform technologies. Biotechnology companies are supported to grow their businesses onshore and Australia has expanded the biobanking capabilities needed to validate commercialised discoveries.	11. Develop a diagnostics deployment strategy for scaling POCT applications 12. Enhance R&D capabilities for multiplex POCT platform technologies 13. Implement a diagnostics development program aimed at small and medium sized enterprises 14. Develop a biobanking repository for diagnostics validation samples
Genomic analysis of pathogens and their variants	The absence of clear national coordination leads to disconnects in the targeted application and integration of genomic analysis at scale during pandemics.	Australia has a national genomic analysis program for routine surveillance which is effectively scaled and targeted during pandemics, utilising cross-sectoral data. The nation's strengthened genomics workforce and pathogen-agnostic capabilities position Australia as a leader for genomic analysis in the region and globally.	15. Establish a national genomic analysis authority to coordinate cross-sectoral collaboration and data sharing 16. Design and coordinate the implementation of a national pathogen agnostic genomic analysis platform 17. Strengthen workforce skills across bioinformatics, metagenomics, statistical genomics modelling, and genomic epidemiology
Data sharing for informing response strategies	Australia faces data sharing limitations due to the varying governance of health systems within and across jurisdictions, and the limited adoption of interoperability systems. This restricts policy decisions being made in a timely and well-informed manner, especially during pandemics.	Australia has national health data standards that are implemented in all jurisdictions and have adaptable guidelines for pandemic responses. These underpin health data collection systems that are interoperable, allowing for the safe, efficient and timely transfer of data insights. These developments enable the use of non-health and sensitive data as deidentified insights to inform government decision making during pandemics.	18. Develop national pandemic data standards to streamline data collection and sharing 19. Improve capabilities to link health data with non-health data 20. Design and integrate smart analytics that can share and analyse sensitive data at a national level

Contents

Glossary

Antimicrobial Resistance (AMR)	Occurs when bacteria, viruses, fungi or parasites that cause infections resist the effects of the medicines used to treat them. This may lead to 'treatment failure', or the inability to treat the cause of the infection.
Biobank	A biobank is a type of biorepository that stores biological samples (usually human) for use in research, validation and assessment.
Contract development and manufacturing organisation (CDMO)	A company that serves other companies in the pharmaceutical industry on a contract basis to provide services from development through to manufacturing.
Data standards	Agreed attributes and processes designed to ensure that a data product, service or method will perform consistently.
Direct-acting antivirals (DAA)	A type of therapeutic that acts by directly targeting viral factors that enable virus replication; reducing the ability of the virus to cause disease.
Disease X	A placeholder name adopted by the World Health Organization (WHO) to represent a hypothetical, unknown pathogen that could cause a future epidemic or pandemic.
Health data	Patient and healthcare data crucial for informing pandemic response strategies. Includes case numbers, case characteristics (co-morbidities), patient outcomes (recuperation and adverse events), incubation/ infection durations, genomic information, phenotypic information, treatment and response, healthcare capacity and workforce data.
In vitro diagnostic (IVD)	A diagnostic medical device with a reagent, calibrator, control material, kit, specimen receptacle, software, instrument, apparatus, equipment or system, whether used alone or in combination with other diagnostic goods for in vitro use.
Inactivated viruses	Vaccines that contain viruses whose genetic material has been destroyed by heat, chemicals or radiation.
Interoperability	The ability of a system or product to transfer meaningful information within and between systems or products without special effort on the part of the user. Interoperability is made possible by the implementation of data standards.
Live attenuated viruses	Vaccines that are a weakened form of a virus, which can grow and replicate, but does not cause disease.
Medical countermeasures	Regulated products used in the event of a potential public health emergency. While broader definitions exist, this report refers only to vaccines, diagnostics and therapeutics.
mRNA	mRNA (messenger RNA) is a single-stranded molecule that can produce an immune response when used in a mRNA vaccine.
Multiplex diagnostics	Diagnostic technologies that can test for the presence or absence of multiple pathogens in a single test, using a single sample.
One Health	A multi-sector approach to better health outcomes that leverages the relationships between human health, animal health, plant health and the environment.
Pathogen	An organism that causes disease in its host.
Polymerase chain reaction (PCR)	An IVD technology that allows identification of pathogenic organisms that are difficult to culture by detecting their DNA or RNA.
Point of Care Test (POCT)	A diagnostic test where the analysis is performed close to the patient by a healthcare professional, or by an individual in the community.
Priority viral families	*Coronaviridae*, *Flaviviridae*, *Orthomyxoviridae*, *Paramyxoviridae* and *Togaviridae (alphaviruses).*
Recombinant protein	Protein antigen produced using recombinant technology from mammalian, insect, plant, bacterial or yeast host systems.
Small and medium sized enterprise (SME)	Businesses that maintain revenues, assets, annual turnover or a number of employees below a certain threshold (0–199 employees; small business annual turnover <$10 million; medium business annual turnover $10–250 million).
Vector-borne disease	Human illnesses caused by viruses, parasites and bacteria that are transmitted by vectors (living organisms that can transmit infectious pathogens e.g., mosquitoes).
Viral vector	Genes of interest are inserted into a viral vector (e.g., adenovirus or vaccina). The gene of interest codes for a particular antigen.
Zoonoses/Zoonotic disease	An infectious disease caused by a pathogen (e.g., bacteria, virus, or parasite) that has crossed species from an animal to a human.

1 Introduction

Report scope: While several pathogens have the potential to cause infectious disease in humans, viruses are the most likely to result in pandemics due to their high rates of mutation and spill-over from animal populations.[6] As such, this report focuses on pandemic preparedness for viral threats. However, many of the report's recommendations would also assist in improving Australia's preparedness against other pathogens and the increasing risks of antimicrobial resistance (AMR).

1.1 Impacts of large-scale viral outbreaks

Epidemics and pandemics caused by viruses result in widespread economic, health and social harm. Examples include COVID-19, H1N1, HIV, Influenza, Middle Eastern Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) which combined have caused more than 45 million deaths globally since 1981 (excluding seasonal influenza).[7] Further, respiratory viruses are the leading cause of disease in humans.[8]

1.1.1 Economy-wide impacts

Common responses to large-scale viral outbreaks include travel and trade restrictions and social distancing requirements. Combined with lower levels of physical and mental health among the workforce, these changes generally result in reduced productivity, industry revenue and tax revenue. There was a cumulative difference of $144 billion between the pre-COVID-19 GDP trendline and actual GDP in Australia, from December 2019 through to March 2022 (Figure 1).

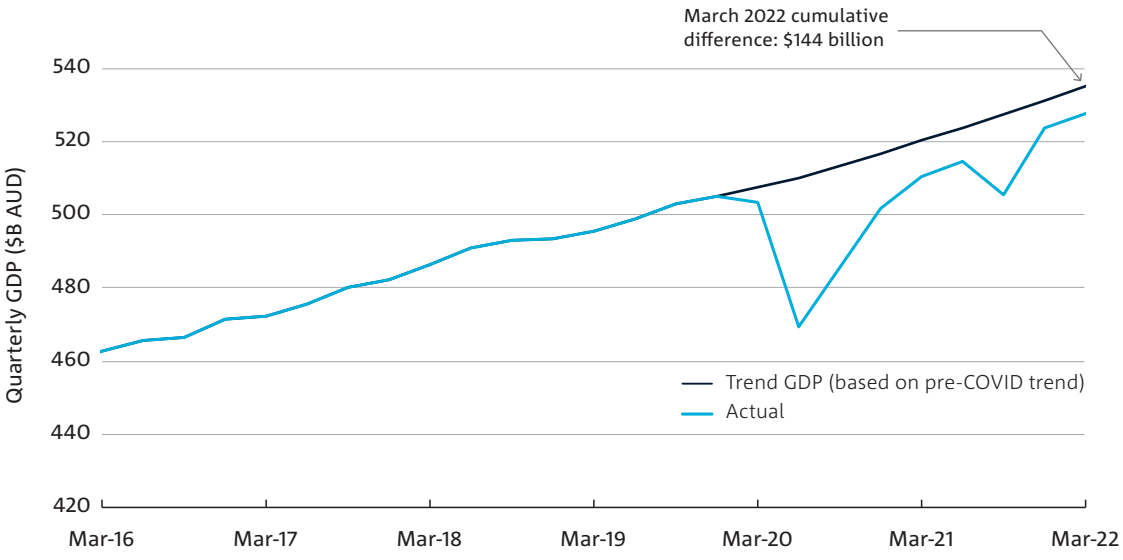


Figure 1: Actual national GDP compared to pre-COVID-19 trendline[9]

6 King A (2020) Characteristics that Give Viruses Pandemic Potential. The Scientist, August 17.; Rahman MT, Sobur MA, Islam MS, Ievy S, Hossain MJ, El Zowalaty ME, Rahman AT, Ashour HM (2020) Zoonotic Diseases: Etiology, Impact, and Control. Microorganisms 8(9).

7 CSIRO (2021) Infectious disease resilience: Co-developing a national mission. CSIRO, Australia.; World Health Organization (WHO) (2022) WHO Coronavirus (COVID-19) Dashboard. WHO, Geneva. <https://covid19.who.int/> (accessed 11 February 2022).

8 Weston S, Frieman MB (2019) Respiratory Viruses. Encyclopedia of Microbiology. 85-101.

9 Australian Bureau of Statistics (ABS), Deloitte Access Economics analysis

These losses are not evenly distributed across the economy. Accommodation, food services, and arts and recreation industries may be disproportionately affected by lockdowns and border control measures as these are sectors that are both dependent on tourists and discretionary spending by households and are difficult to pivot to a digital or contactless environment. For example, Australia's tourism industry was valued at $81 billion in 2020–21; 41% less than in 2019 before the COVID-19 pandemic.[10] Further, revenue for the June 2020 quarter relative to the December 2019 quarter was down 43% for hospitality, 26% for arts and recreation and 25% for transport, postal and warehousing.[11] Agricultural industries may also be directly impacted if the source of the outbreak is zoonotic in nature (e.g., required culling of animals or negative public perceptions).

The ongoing waves of the COVID-19 pandemic have also contributed to supply chain disruptions and shifts in consumer behaviour,[12] causing market uncertainty and elevated inflation levels.[13]

1.1.2 Health and social impacts

The management of large-scale viral outbreaks has significant direct and indirect impacts on the health system. Direct health impacts include lost lives, increased demand on the health system, and the financial costs of treating outbreak-related illnesses, contact tracing, quarantine, vaccinations and other preventive measures.

While difficult to quantify, the indirect health and social costs of outbreaks can be longer lasting and may far outweigh the direct costs. Health system workforce shortages cause many lasting impacts; this may be due to quarantine requirements or burnout caused by increased health system demand. A constrained health system restricts access to preventive health services, which can lead to delayed or missed diagnoses and treatments.[14] Further, large scale outbreaks can disrupt clinical trials. During the early stages of COVID-19, CSL put approximately 90% of their clinical trials on hold globally.[15]

Indirect costs also arise from the impact of case and contact management, lockdown measures and border closures used to limit the spread of the virus. Examples include negative impacts on social cohesion, mental wellbeing, long term employment opportunities, childhood development (through social and education impacts), domestic and family violence, and equity gaps in social determinants of health. During the first wave of the COVID-19 pandemic and the nationwide lockdown in 2020, the number of mental health related prescriptions (Pharmaceutical Benefits Scheme (PBS) subsidised and co-payment prescriptions) dispensed in Australia increased by 18.6% in the four weeks to 29 March 2020 when compared to the same period ending 31 March 2019.[16]

10 Australian Trade and Investment Commission (ATIC) (2021) Insight – A report card on the Australian tourism industry in 2020-21. ATIC, Australia. <https://www.austrade.gov.au/news/insights/insight-a-report-card-on-the-australian-tourism-industry-in-2020-21> (accessed 11 November 2021).

11 Deloitte Access Economics (unpublished) A strong infectious disease resilience system in Australia. Report prepared for CSIRO.

12 Camilleri AR (2022) How COVID-19 changed the way we shop – and what to expect in 2022 and beyond. The Conversation, January 4. <https://theconversation.com/how-covid-19-changed-the-way-we-shop-and-what-to-expect-in-2022-and-beyond-172973> (accessed 28 March 2022).

13 Australian Bureau of Statistics (ABS) (2022) Consumer Price Index, Australia. <https://www.abs.gov.au/statistics/economy/price-indexes-and-inflation/consumer-price-index-australia/latest-release> (accessed 20 November 2021).

14 Australian Institute of Health and Welfare (AIHW) (2021) MyHospitals Database - Elective surgery. <https://www.aihw.gov.au/reports-data/myhospitals> (accessed 28 March 2022).

15 MTPConnect (2020a) MTPConnect COVID-19 Impact Report – The Impact of COVD-19 on the Australian Medical Technology, Biotechnology & Pharmaceutical Sector. MTPConnect, Australia.

16 AIHW (2022) Mental health services in Australia. <https://www.aihw.gov.au/reports/mental-health-services/mental-health-services-in-australia/report-contents/mental-health-impact-of-covid-19> (accessed 21 February 2022).

1.2 The frequency of viral disease outbreaks is increasing

Most severe viral human diseases are zoonotic; meaning they cross the species barrier from animals.[17] The increasing occurrence of large-scale zoonotic disease outbreaks over the last 100 years (Figure 2) has largely been driven by environmental destruction, climate change, urbanisation, human encroachment on natural habitats, and increased global trade and travel.[18]

As the world continues to better understand these connections between human, animal, plant and environmental health (i.e., One Health), it is becoming clearer that viruses are shifting between species at alarming rates. In addition to known viruses, on average, two novel viruses are appearing in humans each year, and the proportion that give rise to larger outbreaks is growing.[19] Many of these viruses have pandemic potential; the potential to spread across multiple continents.

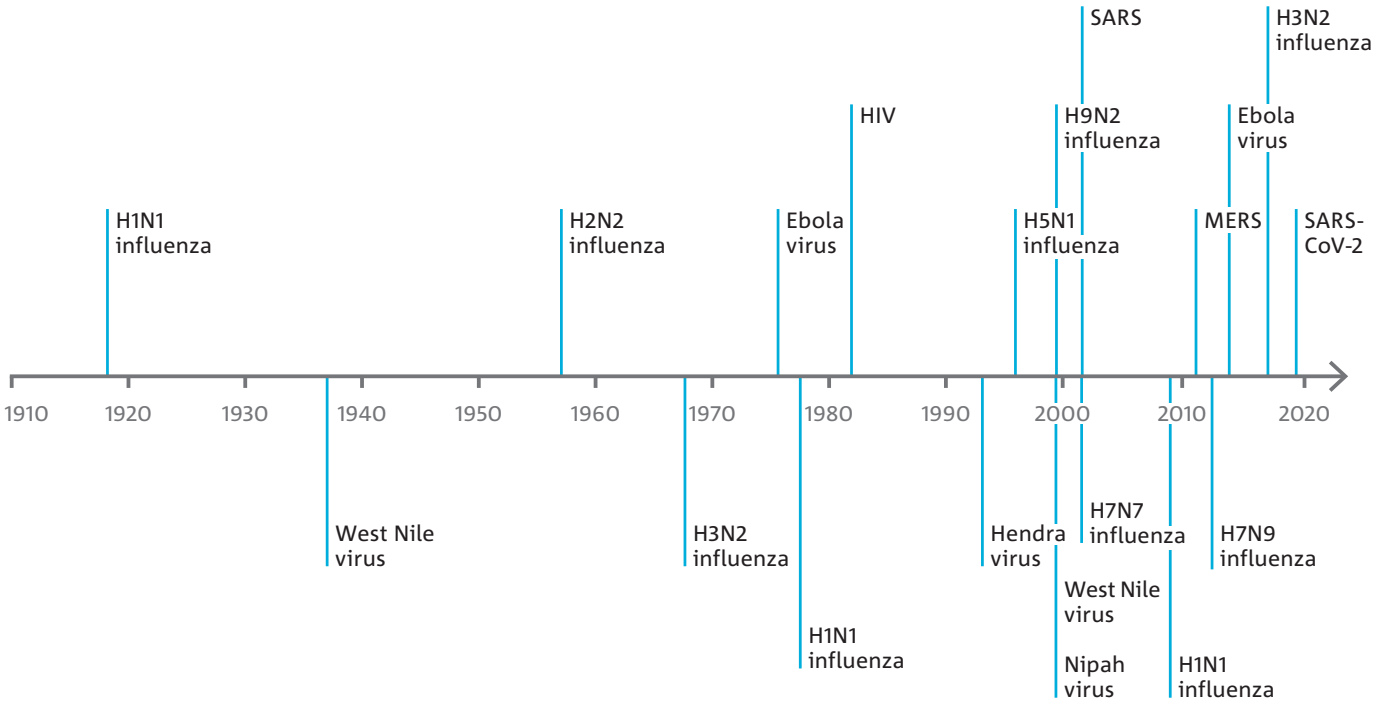


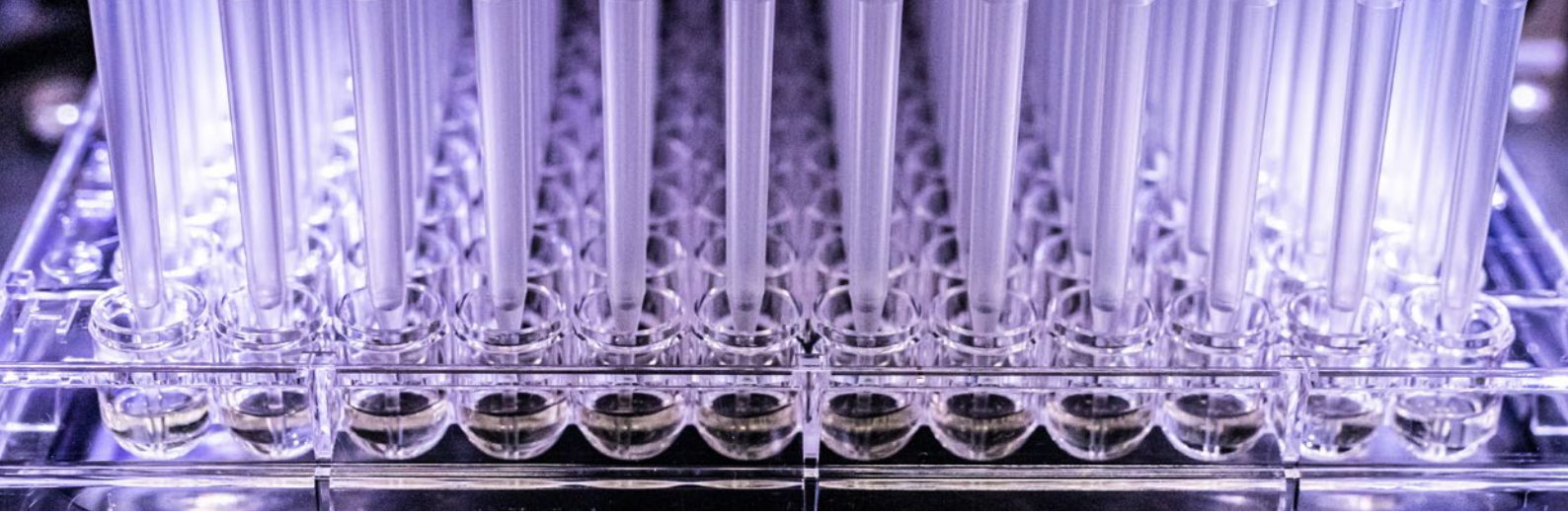
Figure 2: Major infectious disease outbreaks occurring from zoonoses (1910–2020)[20]

17 Wang LF, Crameri G (2014) Emerging zoonotic viral diseases. Revue Scientifique et Technique 33(2). 569-81.; Rahman MT et al. (2020) Zoonotic Diseases: Etiology, Impact, and Control. Microorganisms 8(9).

18 United Nations Environment Programme and International Livestock Research Institute (2020) Preventing the next pandemic: Zoonotic diseases and how to break the chain of transmission. Kenya. <https://www.unenvironment.org/resources/report/preventing-future-zoonotic-disease-outbreaks-protecting-environment-animals-and> (accessed 28 March 2022).

19 Bernstein AS et al. (2022) The costs and benefits of primary prevention of zoonotic pandemics. Science Advances 8(5).

20 CSIRO Futures analysis.



1.3 Technology-enabled approaches can be a major tool in improving Australia's pandemic preparedness

The emergence of new zoonotic diseases is inevitable but their evolution rate and spread into epidemics and a pandemic is dependent on society's response.[21] Australia's success in keeping COVID-19 infections lower than most countries has largely been the result of early international border closures and the public's broad acceptance of social distancing, lockdown measures, mask wearing and vaccinations. Many of these tactics involve travel restrictions and quarantine measures that result in significant economic, social and indirect health costs when implemented and are increasingly difficult to maintain as the duration of a pandemic grows.[22]

Future pandemics with higher transmissibility, or with similar transmissibility but higher mortality rates (e.g., H5N1 – 60%[23] or SARS – 15%[24]), combined with the continuing rise of AMR, will be even more challenging to manage using current resources and approaches.

Travel restrictions and quarantine measures will always be useful response tactics for easing the immediate pressure on a health system. However, Australia can better leverage science and technology (S&T) to provide a wider range of complementary preparedness and response approaches. This can significantly reduce the economic, social and indirect health costs associated with these tactics by facilitating the important transition away from crisis response and towards an integrated cycle of prevention, detection, response and recovery.[25] An integrated cycle can both defend against the emergence of a pandemic and ensure the functions needed to respond are optimised to reduce direct and indirect impacts.[26]

This report assesses a range of key S&T areas that were identified as being critical to enhancing Australia's technology-enabled approach to pandemic preparedness against viral diseases. These S&T areas, and the recommendations listed to further enhance their impact on Australia's pandemic preparedness, were developed through deep system-wide engagement with over 140 individuals across industry, research and government.

21 WHO (2016a) Anticipating Emerging Infectious Disease Epidemics. WHO, Geneva. <https://apps.who.int/iris/bitstream/handle/10665/252646/WHO-OHE-PED-2016.2-eng.pdf> (accessed 28 March 2022).

22 WHO (2016a).

23 McCullers JA (2008) Preparing for the next influenza pandemic. The Pediatric Infectious Disease Journal 27(10), S57-S59.

24 WHO (2003) Consensus document on the epidemiology of severe acute respiratory syndrome (SARS). WHO, Geneva.

25 Bedford J, Farrar J, Ihekweauzu C, Kang G, Koopmans M, Nkengasong J (2019) A new twenty-first century science for effective epidemic response. Nature 575 (7781), 130-136.

26 Carlin EP, Machalaba C, Berthe FCJ, Long KC, Karesh WB (2019) Building resilience to biothreats. EcoHealth Alliance, USA.

2 Key science and technology areas for strengthened pandemic preparedness

This section identifies developments across six S&T areas that will be important for strengthening Australia's pandemic preparedness and contributing to regional and global preparedness efforts (Table 1). The six areas were prioritised from a longer list through a survey (see Appendix B) and guidance from the project steering committee. Consulted stakeholders selected these areas based on where they identified further investment would have the most impact on Australia's pandemic preparedness.

Each S&T section includes a 2030 vision outlining areas of strategically important growth and provides a series of recommendations that can be implemented today to help put Australia on this trajectory. Recommendations span research and development (R&D) activities, infrastructure, governance and workforce, and were developed through consultation across industry, research and government.

Consideration and implementation of the proposed recommendations would benefit from national coordination, and so it is likely that the Australian Government would lead initial decision making in these areas. However, many of the recommendations will require strong support and implementation from other levels of government as well as industry and research.

These S&T areas do not operate in isolation and investments in one S&T area can pay dividends for others. As such, it is important to consider these linkages, and associated data flows, standards and stakeholders, when developing solutions in these areas and implementing the proposed recommendations.

'Preclinical capabilities for medical countermeasures' (Section 2.1) and 'Data sharing for informing response strategies' (Section 2.6) were observed to have the strongest linkages with other S&T areas as well as Australia's broader health system. For example, strong preclinical capabilities help enable the rapid development of novel medical countermeasures, and improved interoperability can facilitate the efficient transfer of information between all S&T areas.

Table 1: Prioritised S&T areas and their role in strengthening pandemic preparedness

S&T AREA	ROLE IN PANDEMIC PREPAREDNESS
Preclinical capabilities for medical countermeasures	These capabilities can expedite the development of medical countermeasures (vaccines, therapeutics, and diagnostics) prior to and during a pandemic.
Vaccine manufacturing	Onshore manufacturing across a diverse range of vaccine technologies can assist with securing vaccine supply, particularly during pandemics when supply chains risk disruption.
Therapeutic repurposing and novel antivirals	Repurposed therapeutics can offer a short-term response for treating infected and at-risk individuals, while targeted novel antivirals can offer a more effective solution once developed.
Point of care diagnostics for case identification	Coordinated prioritisation of diagnostic resources in a pandemic can reduce delays in accurately identifying cases and help limit the spread of disease.
Genomic analysis of pathogens and their variants	Genomic analysis facilitates the early detection and tracking of emerging pathogens during an outbreak to inform subsequent public health decisions around response activities.
Data sharing for informing response strategies	Sharing consistent and timely data from the health system with governments enhances decision making for pandemic response strategies.

2.1 Preclinical capabilities for medical countermeasures

2.1.1 Role in strengthening pandemic preparedness

Preclinical studies use biological and chemical research to analyse the safety and efficacy of a medical countermeasure, prior to clinical (human-based) studies (as shown in Figure 3). Examples include drug discovery chemistry, host and pathogen characterisation and animal models.

Preclinical studies play an important role in expediting the development of medical countermeasures during a pandemic.[27] Medical countermeasures include vaccines, diagnostics and therapeutics that support the response to a pandemic. Preclinical studies can identify which medical countermeasure technologies are likely to be most effective to respond to a pandemic, reducing time spent in initial technology exploration. In the COVID-19 pandemic, prior studies into the human immune response pathways to other *coronaviruses* and rapid ethics and regulatory pathways fast-tracked vaccine development. Several vaccines were approved by regulators for use in humans within 12 months, where previous vaccine development timelines were closer to 10 years.[28]

Improving preclinical capabilities across a range of viral families will also assist in preparing the research sector to respond to 'Disease X', a pathogen that is not currently known to pose a threat to human health and wellbeing.[29]

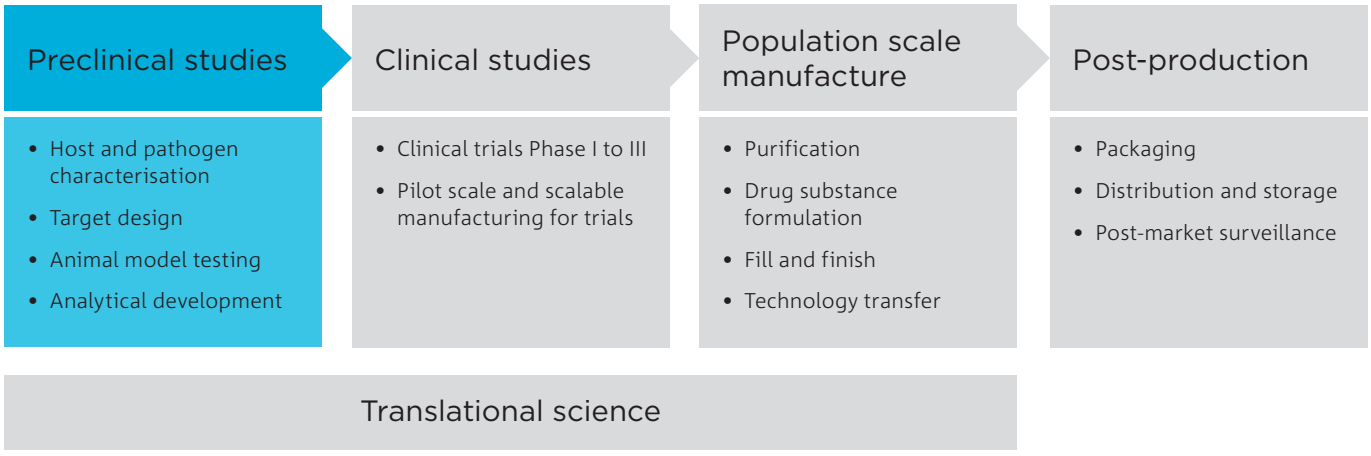


Figure 3: Role of preclinical studies in the initial stages of the medical countermeasure value chain[30]

27 WHO (2016b) An R&D Blueprint for Action to Prevent Epidemics: Plan of Action. WHO, Geneva.

28 Ball P (2020) The lightning-fast quest for COVID vaccines -and what it means for other diseases. Nature, December 18.

29 Kessler R (2021) Disease X: The Next Pandemic. EcoHealth Alliance, USA. <https://www.ecohealthalliance.org/2018/03/disease-x> (accessed 28 March 2022).

30 This figure does not intend to provide an exhaustive list of activities within each step of the value chain but rather highlight key examples.

2.1.2 Current context

The pharmaceutical industry and philanthropic organisations are seeking to reduce timeframes for medical countermeasure development, in part by supporting preclinical advancements. For example, CEPI aspires for the world to be able to respond to Disease X via a vaccine in 100 days. This would see vaccine candidates go from pathogen characterisation to having clinical data for regulatory approval processes within this time. Efforts to reduce development timeframes can be streamlined by research into viral families with pandemic potential, of which there is currently poor knowledge globally.

Australia's preclinical research capabilities are typical for similarly sized high income countries, but the nation possesses niche areas of global strengths. Stakeholders noted that Australia has globally recognised strengths in the detection and identification of viruses, target discovery, rapid evaluation of viruses in cell models, cell and animal proof-of-concept models, and *in vitro* studies of medical countermeasures.

Preclinical research is supported by high containment facilities for animal studies, such as Physical Containment 3 or 4 laboratories. Australia has several high containment facilities that are equipped for studies of animals of varying size (e.g., CSIRO's Australian Centre for Disease Preparedness, James Cook University and The Peter Doherty Institute for Infection and Immunity); however, surge capacity of these facilities is limited. This can be a challenge as availability and access to these laboratories is critical in the early stages of a pandemic, particularly for novel viruses. Enhancing baseline preclinical activities in Australia can assist with growing surge capacity, including maintaining an adequately trained workforce. Without supplying ongoing demand for these skills, upskilling critical capabilities at the commencement of a pandemic can take up to 18 months.

Australia is well positioned to provide preclinical services internationally, given the nation's competitive advantage in early-stage clinical trials. This includes the Clinical Trial Notification scheme that puts the onus on the relevant Human Research Ethics Committee to determine whether a product is safe for Phase I trials. This reduces regulatory requirements to submit applications to Therapeutic Goods Administration (TGA) prior to 'first in human' trials.[31]

31 Therapeutic Goods Administration (TGA) (2021) Clinical trials. TGA, Australia. <https://www.tga.gov.au/clinical-trials> (accessed 7 January 2022).

2.1.3 Vision and recommendations

2030 Vision: Australia contributes to global efforts to improving virus and host knowledge across *Coronaviridae*, *Flaviviridae*, *Orthomyxoviridae*, *Paramyxoviridae* and *Togaviridae* families. Preclinical studies and associated infrastructure for priority viral families are adaptable to responding to Disease X. Preclinical studies are coordinated with product development pathways including translational science, manufacturing and health system requirements.

Recommendation 1: Improve virus and host knowledge across priority viral families (*Coronaviridae*, *Flaviviridae*, *Orthomyxoviridae*, *Paramyxoviridae* and *Togaviridae*)

Global understanding across most viruses of pandemic potential is insufficient to mount a medical countermeasure response in a relatively short timeframe. With finite resources, Australia could benefit from focusing preclinical efforts on viral families posing a high pandemic risk to humans.

To identify which viral and bacterial threats pose the greatest global risk, the World Health Organization (WHO) and CEPI have developed lists. Priority viral families for this report were identified by focusing on viral pathogens and evaluating the current geographical spread, zoonotic or human transmission, and transmission risk against WHO and CEPI lists (see Appendix C). This results in *Coronaviridae*, *Flaviviridae*, *Orthomyxoviridae*, *Paramyxoviridae* and *Togaviridae* (*alphaviruses*) as the viral families with the highest pandemic potential (as shown in Table 2).

This prioritisation could change over time as risk profiles change. For example, the geographical spread of vector-borne families (such as *Nairoviridae*) may differ significantly in the future as climate change impacts the distribution of intermediatory hosts.

While pandemic viruses are likely to enter Australia from overseas, risk factors that are specific to Australia have also been noted in the table to demonstrate where local research efforts could focus.

Research activities to support maturing knowledge across these priority viral families could include:

- Developing *in vitro* cell culture models that can be used for characterising multiple viruses and host responses.
- Developing a range of biomarker tools, specific to a viral family, that can enable rapid analysis for disease research. For example, assays that support research into cytotoxicity, enzyme function, reporter gene, potency tests and cell proliferation.
- Collaborating with One Health initiatives to identify where pandemic prone families exist in animals likely to interact with humans, to guide preclinical studies based on zoonotic risk.

Stakeholders noted that there would be value in the federal government publicly committing to priority viral families – be they those proposed in this report or otherwise – to guide research and investment in Australia. This prioritisation could feed through to decision making by existing funding mechanisms such as the Medical Research Future Fund (MRFF) and the National Health and Medical Research Council (NHMRC).

To identify more granular gaps in the Australian preclinical landscape, individual roadmaps for each priority viral family can be used to map the nation's capabilities against the likely infrastructure (e.g., Physical Containment 3 or 4 laboratories), cell and animal models, and technology requirements. This mapping work would also assist with coordinating Australia's relevant infrastructure, including access to reagents and biobanks.

Table 2: Proposed priority viral families for Australia

VIRAL FAMILY	DISEASE EXAMPLES	GEOGRAPHICAL SPREAD	ZOONOTIC OR HUMAN TRANSMISSION	TRANSMISSION RISK FACTORS	AUSTRALIAN SPECIFIC RISKS
Coronaviridae	COVID-19, MERS, SARS	Global	Zoonotic and human	• Largely respiratory viruses that can be transmitted by droplets and aerosols.[32] • Hundreds of *coronaviruses* circulating among animals.[33] • Most animal-to-human coronaviruses are transmitted via the faecal-oral route.	• Potential for cross-species transmission from Australia's endemic bat population.[34] • Camels are suspected to be the primary source of MERS infection and Australia has one of the largest populations of wild camels in the world.[35]
Flaviviridae	Dengue fever, Japanese encephalitis, Zika, West Nile fever	Global[36]	Zoonotic (arthropods) and human (relatively uncommon and via bodily fluids)[37]	• High rate of asymptomatic cases; however, some cases can result in severe life-threatening disease.[38] • Domesticated vertebrate animals play a role supporting transmission to humans and the introduction of new viral species.[39] • Risk extension of vector range with increasing impact of climate change.	• Dengue fever occurs in tropical areas, including northern Australia.[40] • In 2022, Japanese encephalitis was detected in southern areas of Australia.[41]
Orthomyxoviridae	Influenza	Global	Zoonotic and human	• Highly infectious as transmission can occur in humans by aerosols and droplets.[42] • Pre-disposed to quickly and efficiently mutating to generate new strains.[43] • Historically caused epidemics and pandemics in humans.[44]	• None identified.
Paramyxoviridae	Nipah virus infection, Hendra virus disease[45]	Asia, Australia[46]	Zoonotic and human	• Largely respiratory viruses transmitted by aerosols and contaminated surfaces.[47] • Historically high morbidity and mortality in humans.[48]	• Hendra virus disease currently poses a risk of infection from horses in north-eastern parts of Australia.[49] • New variants of Hendra virus have been identified in host animals with greater geographic distribution.[50]
Togaviridae (alphaviruses)	Chikungunya fever, Ross River fever, Eastern equine encephalitis, Western equine encephalitis, Venezuelan equine encephalitis	Global[51]	Zoonotic (arthropods, particularly blood sucking species)	• Infections are seasonal and are acquired in endemic areas.[52]	• Ross River fever is the most common insect-borne viral disease in Australia.[53]

32 Dutch RE (2008) Paramyxoviruses. Encyclopedia of Virology (third edition), 52-57.

33 National Institute of Allergy and Infectious Diseases (2021) Coronaviruses. <https://www.niaid.nih.gov/diseases-conditions/coronaviruses> (accessed 23 February 2022); Payne S (2017a) Family Coronaviridae. Viruses, 149-158.

34 Peel AJ, Field HE, Aravena MR, Edson D, McCallum H, Plowright RK, Prada D (2019) Coronaviruses and Australian bats: a review in the midst of a pandemic. Australian Journal of Zoology 67. 346-360.

35 Centre for Invasion Species Solutions (2021) Feral camels. <https://pestsmart.org.au/toolkits/feral-camels/> (accessed 20 November 2021).

36 Pierson TC, Diamond MS (2020) The continued threat of emerging flaviviruses. Nature Microbiology 5, 796-812.

37 North Dakota Department of Health (2016) Flaviviridae. <http://www.ndhealth.gov/disease/documents/faqs/flaviviridae.pdf> (accessed 23 February 2022).

38 Pierson et al. (2020).

39 Pandit P, Doyle MM, Smart KM, Young CW, Drape GW, Johnson CK (2018) Predicting wildlife reservoirs and global vulnerability to zoonotic Flaviviruses. Nature Communications 5425.

40 Health Direct (2021) Dengue fever. <https://www.healthdirect.gov.au/dengue-fever> (accessed 23 February 2022).

41 Australian Government Department of Health (2022) Japanese encephalitis virus (JEV). <https://www.health.gov.au/health-alerts/japanese-encephalitis-virus-jev/about> (accessed 24 February 2022).

42 MacLachlan J, Dubovi E (2016) Fenner's Veterinary Virology: Chapter 21 Orthomyxoviridae, 389-410.

43 Payne S (2017b) Viruses: From Understanding to Investigation. Chapter 23 - Family Orthomyxoviridae, 197-208.

44 Payne (2017b).

45 Measles and Mumps have been excluded from analysis due to existing effective vaccines.

46 Virus Pathogen Resource (2021) About the Paramyxoviridae family. <https://www.viprbrc.org/brc/aboutPathogen.spg?decorator=paramyxo> (accessed 28 March 2022).

47 Dutch (2008).

48 Thibault P, Watkinson RE, Moreira-Soto, Drexler JF, Lee B (2017) Chapter One - Zoonotic Potential of Emerging Paramyxoviruses: Knowns and Unknowns. Advances in Virus Research 98, 1-55.

49 WHO (2022) Hendra virus infection. <https://www.who.int/health-topics/hendra-virus-disease#tab=tab_1> (accessed 20 December 2022).

50 CSIRO (2022) New genetic type of Hendra virus. <https://www.csiro.au/en/research/health-medical/diseases/Infectious-diseases/HendraVirus_NewGeneticType> (accessed 20 March 2022).

51 European Centre for Disease Prevention and Control (2022) Chikungunya worldwide overview. <https://www.ecdc.europa.eu/en/chikungunya-monthly#:~:text=India%20%3A%20In%202021%20and%20as,cases%2C%20since%2030%20September%202021> (accessed 28 March 2022).

52 Schmalijohn AL, McClain D (1996) Chapter 52 – Alphaviruses (Togaviridae) and Flaviviruses (Flaviviridae). Medical Microbiology, USA.

53 Department of Health Victoria (2022) Ross River virus disease. Department of Health, Victoria. <https://www.health.vic.gov.au/infectious-diseases/ross-river-virus-disease> (accessed 4 March 2022).

Recommendation 2: Engage with global networks to optimise research efforts across priority viral families and for the development of medical countermeasures

Australia's population size and scale of R&D investment limits the number of viral families on which the nation can conduct preclinical studies. Coordinating research priorities across priority viral families with established international networks can allow the nation to strengthen collaboration opportunities in areas that Australia is seeking to lead in, while also fostering relationships in areas Australia does not have strategic interest in. This could include expanding engagement with the Global Research Collaboration for Infectious Disease Preparedness and the NHMRC, as well as collaborating with the Centers for Research in Emerging Infectious Disease Network, and the International Society for Influenza and other Respiratory Virus Diseases.[54]

As the scale of national investment is finite, collaborating with organisations that have integrated product development expertise can ensure product development is efficient. Evaluating where candidate medical countermeasures may be effective against priority viral families will benefit from collaborations with international organisations, such as Wellcome Trust, WHO, National Institute of Allergy and Infectious Disease, and the US Biomedical Advanced Research and Development Authority. Such networks can support the screening of medical countermeasure candidates for Australia without requiring research to be localised.

Recommendation 3: Expand research capabilities in animal models for priority viral families

Animal model testing, as required by regulators globally, is a pre-requisite for commercialising most medical countermeasures. However, Australia has a limited number of high containment facilities for animal studies.

Expanding capabilities in animal models could be supported by:

- Mapping priority viral families to animals that are likely to be effective models and can support gathering decision-enabling data for a range of medical countermeasures. This may include infrastructure for animal models Australia currently has limited access to, such as hamsters, and emerging models, such as transgenic and humanised mice. Mapping should include consideration for Good Laboratory Practice (GLP) standards in existing and new facilities, to ensure Australia's capabilities meet regulatory and industry standards.
- Assessing where public-private partnerships can facilitate the development of animal model facilities or ensure existing facilities have appropriate surge capacity. These capabilities should be distributed across jurisdictions and align to GLP standards.

Given Australia has a higher proportion of rodent (e.g., mouse, rat and guinea pig) models compared to other animal models,[55] this expansion could also look to develop capacity in other animal models.

Broader animal model testing is supported by non-human primate testing as these models remain key to regulatory approval. However, assessment of Australia's non-human primate infrastructure requires further analysis, including whether the nation should build more capacity onshore or leverage international partnerships to expand this capability. Consultations suggested that there is political hesitation to expand non-human primate capacity as other countries reduce their use to only targeted applications due to ethical concerns and public pressure.

54 Global Research Collaboration for Infectious Disease Preparedness (GloPID-R) (2020) Members. GloPID-R, Vienna. <https://www.glopid-r.org/about-us/members/> (accessed 10 December 2021).

55 Analysis from DMTC led National Health Security Resilience Assessment (2022).

Recommendation 4: Enhance R&D into alternatives to animal models

Alternatives to animal models can reduce the number of animals required for testing and optimise experiments prior to beginning animal studies (which are a regulatory requirement for medical countermeasures to progress to clinical studies). This can also help reduce costs, development timeframes and ethical challenges in Australia. The types of studies where alternatives can complement or replace animal models, and the granularity of the study, are summarised in Table 3. Additional information on alternatives to animal models can be found in Appendix E.

Alternatives to animal models are likely to require upfront investment for specialised facilities and equipment. Where specialised infrastructure is not required, existing Physical Containment 3 and 4 facilities and their associated workforce could be used, however this would place additional pressure on these facilities that are traditionally used for animal models. Therefore, additional infrastructure may be required to support expanding facility use in the short term.

Table 3: Alternatives to animal models

		TYPES OF STUDIES WHERE MODEL CAN COMPLEMENT OR REPLACE ANIMAL MODELS			GRANULARITY OF STUDY		
MODEL	DESCRIPTION	TOXICITY	EFFICACY	DOSAGE	CELLULAR	CULTURE	WHOLE ORGANISM
In vitro	Model replicates phenotypic expression of genetic differences.[56]	✓	✓		✓		
Ex vivo	Isolates human cells that are targeted by the virus for greater testing.	✓	✓		✓		
Organoids	Builds on ex-vivo cultures to produce a three-dimensional culture system of cell interactions that exist within a natural organ.	✓	✓	✓		✓	
Tissue explants	Uses extracted cells, preserved in their native three-dimensional structure for testing of biological or mechanical factors.	✓	✓			✓	
Human challenge	Models the natural infection process of humans in a small sample group.		✓	✓			✓
Multi-omics	Uses systems immunology to triangulate multiple high throughput-omics studies, based on data from multiple patients.[57]		✓	✓		✓	
In silico	Mathematical and computer models that identify and predict transmission patterns, candidates and host-pathogen interactions.[58]		✓				✓

56 National Academies of Sciences, Engineering and Medicine (2018) Advancing Disease Modelling in Animal-Based Research in Support of Precision Medicine. In Proceedings of Roundtable on Science and Welfare in Laboratory Animal Use. 30 May, Washington DC. Institute for Laboratory Animal Research, Washington DC, USA.

57 Ward R, Aghaeepour N, Bhattacharyya RP, Clish CB, Gaudilliere B, Hacohen N, Mansour MK, Mudd PA, Pasupneti S, PResti RM, Rhee EP, Sen P, Spec A, Tam JM, Villani AC, Woolley AE, HSU JL, Vyas JM (2021) Harnessing the Potential of Multiomics Studies for Precision Medicine in Infectious Disease. Open Forum Infectious Disease 8(11).

58 Chesnut M, Munoz LS, Harris G, Freeman D, Gama L, Pardo CA, Pamies D (2019) In vitro and in silico Models to Study Mosquito-Borne Flavivirus Neuropathogenesis, Prevention, and Treatment 9.

Recommendation 5: Strengthen translational science to help bridge the gap between research, industry and the health system

Several stakeholders noted that the research sector was often poor at articulating the commercial risks, benefits, costs and unmet need that their research into medical countermeasures supports. One example of this is a lack of knowledge of how to develop a comprehensive Target Product Profile (TPP) for vaccines, therapeutics and diagnostic candidates.

Translational science bridges the gap between preclinical and clinical studies, as it further advances product commercialisation prior to significant scale up. Improving translational science skills in early-stage research can ensure that preclinical characterisation of virus and host responses provides useful information for medical countermeasure product development and is appropriately transferred to commercial organisations.

Bridging the gap between translational science and research may be enabled by:

- Training researchers in TPP development and building industry expertise into the assessment and evaluation of grant applications to further support translation from funding.
- Funding processes that require researchers to articulate a clear pathway to commercialisation (where commercial success is an objective) as a metric for the value of the research.
- Conducting an environmental scan of existing training initiatives and their success, as a model for national expansion.
- Integrating translational science with preclinical expertise to prioritise assets, experimental design, process sequence, data collection and target characteristics that are most efficient for the market they serve (i.e., medical countermeasure development).
- Training researchers in process pathway development for scaling up product from bench to population scale, including chemistry, manufacturing and controls development. This should include consideration of where community acceptance and health system capacity may limit the ability to deliver medical countermeasures at scale.
- Upskilling preclinical researchers to consider business case development, health system requirements and health economics.

2.2 Vaccine manufacturing

2.2.1 Role in strengthening pandemic preparedness

Vaccines are a key medical countermeasure for responding to a pandemic as they reduce disease transmission, which saves lives, keeps people out of hospital, and protects populations that are disproportionately vulnerable to the impacts of disease. This reduces pressure on the healthcare system. Effective vaccines can also reduce pressure on development and scale-up of other medical countermeasures, including therapeutics.

Managing vaccine supply during a pandemic is likely to require a combination of industry partnerships and onshore manufacturing. However, consultations suggested that the emergence of a novel virus could favour onshore manufacturing strategies as an immediate response, as importing products from international manufacturers can face competition from other countries.

2.2.2 Current context

Nearly all of Australia's vaccines are imported, creating potential for supply chain disruption, particularly during a pandemic.[59] However, the nation does have established population scale manufacturing capabilities in inactivated viruses and live attenuated viruses at CSL (as shown in Figure 4). Population scale manufacturing refers to production of market-ready vaccines that can service at least the population of Australia. The products from this onshore manufacturing capability are currently exported at large volumes and the development of CSL's cell-based facility will see further scale-up of production volume and speed.[60]

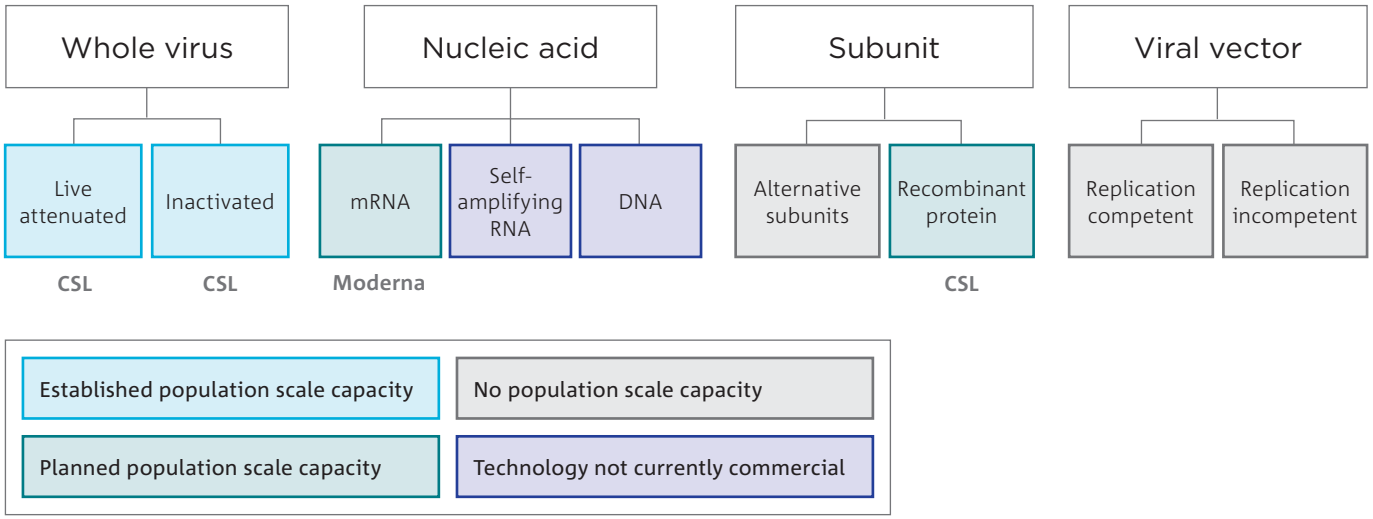


Figure 4: Established and planned population scale manufacturing capability in Australia

59 Butler S, Sorrell T (2020) Strengthening Australia's life sciences sector and medical supply chain beyond COVID-19. PwC Australia, Australia. <https://www.pwc.com.au/health/health-matters/strengthening-australias-life-sciences-sector-and-medical-supply-chain-beyond-covid-19.html> (accessed 10 February 2022).

60 Butler et al. (2020).

There are also planned population scale manufacturing capabilities in mRNA and recombinant proteins through Moderna[61] and CSL, respectively. While CSL's recombinant protein capacity was pivoted to produce the University of Queensland COVID-19 molecular clamp vaccine candidate that is no longer in development, this capacity has not been demonstrated at population scale for market-ready vaccines.

Development of infrastructure, skills and processes for onshore manufacturing has intrinsically long lead times, requiring ongoing investment to maintain supply chains, keep facilities 'warm' and a workforce appropriately trained. Onshore manufacturing is complemented by partnerships with international vaccine manufacturers to secure supply of vaccines, including Pfizer and Moderna.

As shown in Table 4, Australia also has a range of research institutes and contract development and manufacturing organisations (CDMOs) that further develop candidates for manufacture at a scale to support clinical trials.

Table 4: Clinical trial scale vaccine manufacturers and infrastructure

ORGANISATION	ORGANISATION TYPE	CLINICAL TRIAL PHASE SUPPORTED
UNSW RNA Institute	Research	Early phase trials[62]
Translational Research Institute and Translational Manufacturing Institute	Research/scale-up facility	Phase I, II and III trials[63]
UTS Biologics Innovation Facility	Research/CDMO	Early phase trials[64]
Westmead's Viral Vector Manufacturing Facility	Research/CDMO	Early phase trials[65]
CSIRO's Biologics Manufacturing Facility and Quality Control Laboratory	Research/CDMO	Early phase trials[66]
National Biologics Facilities	Research/CDMO	Phase I and II trials[67]
Luina Bio	CDMO	Early phase trials[68]
Sypharma	CDMO	Phase I, II and III trials[69]
Patheon	CDMO	Phase I, II and III trials to small scale commercialisation[70]
Biocina	CDMO	Phase I, II and III trials to small scale commercialisation[71]

61 There is an agreement to produce 100 million doses of mRNA vaccine in Victoria, supported by the Australian and Victorian government.

62 UNSW (2021) UNSW RNA Institute. UNSW, Australia. <https://www.science.unsw.edu.au/unsw-rna-institute> (accessed 17 February 2022).

63 Translational Research Institute (2021) What is translational research? Translational Research Institute, Australia. <https://www.tri.edu.au/our-research> (accessed 10 February 2022).

64 University of Technology Sydney (UTS) (2019) Biologics Innovation Facility. UTS, Australia. <https://www.uts.edu.au/climate-change-cluster/partner-us/biologics-innovation-facility/about-biologics-innovation-facility> (accessed 8 February 2022).

65 AusBiotech (2021) Australia's Regenerative Medicine Manufacturing Capability & Capacity. AusBiotech, Australia. <https://www.ausbiotech.org/documents/item/666> (accessed 10 February 2022)

66 CSIRO (2022) Recombinant Protein Production and Purification Facility. CSIRO, Australia. <https://www.csiro.au/en/work-with-us/use-our-labs-facilities/Recombinant-protein-facility> (accessed 23 March 2022).
CSIRO's facility will come online in 2022 with TGA approval required for GMP accreditation.

67 National Biologics Facility (2022) National Biologics Facility. Therapeutic Innovation Australia, Australia. <https://www.nationalbiologicsfacility.com/> (accessed 20 March 2022).

68 Luina Bio (2022) Biopharmaceutical Manufacturing from Luina Bio. Luina Bio, Australia. <https://luinabio.com/> (accessed 10 March 2022).

69 Sypharma (2022) Our Capabilities. Sypharma, Australia. <https://www.sypharma.com.au/our-capabilities/> (accessed 23 March 2022).

70 Patheon (2021) Brisbane, Australia. <https://www.patheon.com/sites/brisbane-au/> (accessed 15 December 2021).

71 BioCina (2021) PR Release – BioCina officially opens full-service CDMO in Adelaide, Australia, including mRNA and pDNA cGMP manufacturing. BioCina, Australia. <https://www.biocina.com/news-resources/biocina-expands-into-full-service-cdmo-with-full-control-of-pfizer-manufacturing-facility-in-adelaide-australia-anlyn> (accessed 10 March 2022).

2.2.3 Vision and recommendations

2030 Vision: Australia has onshore vaccine manufacturing capabilities and infrastructure supporting Phase I to III clinical trials across a diverse range of vaccine technologies. This infrastructure is available to pivot to relevant vaccines in a pandemic, increasing security of vaccine supply.

Recommendation 6: Diversify manufacturing capabilities across vaccine types, including recombinant protein and viral vector technologies

Australia's population scale manufacturing capabilities are limited to live attenuated and inactivated virus vaccines technologies. These technologies are likely to continue to play a role in global vaccine products and be supported by planned mRNA manufacturing capacity. However, other vaccine technologies may be the most effective at responding to Disease X.

Diversifying onshore manufacturing to include additional vaccine technologies can help prepare for the next pandemic. Based on Australia's established population scale manufacturing capabilities, planned mRNA manufacturing capabilities, and technologies that are not currently commercial (i.e., DNA and self-amplifying RNA), recombinant proteins and viral vector technologies should be prioritised for future investments (as outlined in Appendix D).

Manufacture of recombinant proteins and viral vector technologies have varied inputs, scale of production and required infrastructure. Recombinant proteins are often complex products as they require mass purification of intermediatory products and often require an adjuvant (a substance that enhances the immune response) to be developed. Conversely, there are more than 10 different vectors that can be used in viral vector technologies and therefore infrastructure requirements vary.

While it is unlikely Australia will be able to produce multiple additional vaccine technologies at population scale without significant government investment, Australia could export vaccine components across a variety of vaccine technologies if the nation diversifies its small-scale manufacturing capabilities. For example, there is potential between pandemics for Australia to value-add by exporting drug substances for fill and finish to be conducted offshore for international markets. Leveraging offshore markets can support scale-up between pandemics; however, this will carry a risk for securing supply in a pandemic.

Recommendation 7: Expand the number of contract development and manufacturing facilities to support Phase I to III trials for vaccines

As vaccine candidates progress through to Phase II and III clinical trials, fewer are conducted in Australia, and intellectual property (IP) value is lost offshore due to high input costs and a comparatively small population to support trial patient enrolments. Australia also faces barriers to onshore manufacturing at population scale due to high input costs and limited export opportunities as the surrounding region is well serviced by existing manufacturers.

CDMO facilities operate at clinical scale, which is increasingly important in the vaccine value chain during a pandemic, as the value chain is no longer linear (as shown in Figure 5). Fast tracking products in a pandemic is also enabled by overlapping clinical trials phases, undertaking analytical services earlier in the value chain, and streamlining regulatory approvals.

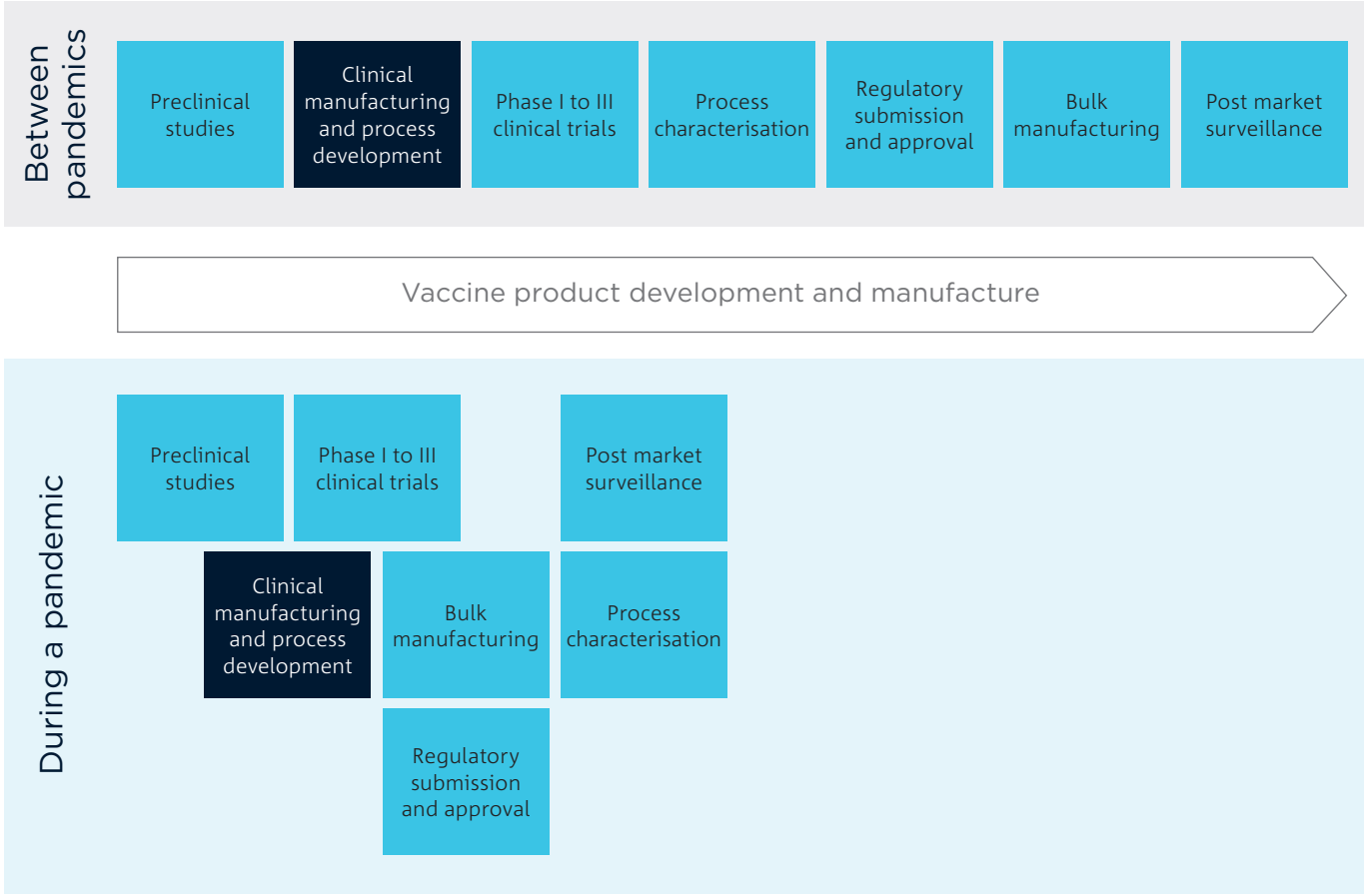


Figure 5: Comparison of vaccine value chain between pandemics and during a pandemic

Increasing the number and breadth of CDMO facilities, including in technologies where Australia does not have established population scale manufacturing, can attract and offer flexibility to companies looking to bring emerging vaccine technologies to market. Access to versatile CDMO infrastructure can reduce the timelines and cost to vaccine developers, as it reduces financial risk until the vaccine is shown to be effective in late-stage clinical trials.[72]

Existing Australian CDMOs have competing commercial pressures in a pandemic and are unlikely to be suitably reliable for national needs. Further, it is not feasible for government to provide ongoing financial support for new CDMO facilities across all available vaccine technologies, particularly between pandemics. Public-private partnerships provide an alternative to the status quo in Australia (see Case study 1). A public-private model would assist with securing the supply of vaccines in a pandemic as multiple facilities would have existing partnerships with government.

Such CDMO facilities could service Phase I to III clinical trials and small end commercial manufacture (e.g., cancer vaccines or vaccines for small scale infectious disease outbreaks) with batch sizes in the low millions. These facilities should target commercial opportunities, particularly in between pandemics, to keep infrastructure 'warm' and pivot capacity to respond to a pandemic.

The scale of production (i.e., the size of the bioreactor) for clinical trials varies across vaccine technologies. For example, a 50-litre bioreactor can produce millions of doses of a mRNA vaccine, but a recombinant protein would need a much larger production scale. Greater analysis is required to determine the ideal scale of these CDMO facilities and which vaccines technologies initial facilities should focus on.

As the number and scale of manufacture of CDMO facilities increases, opportunities to attract international companies will also increase. This will be enabled by proven process validation at a facility and gaining international regulators' approval for safety by meeting stringent current good manufacturing practice (cGMP) requirements. Engagement with international companies can improve knowledge and expertise in delivering commercially ready manufacturing services.

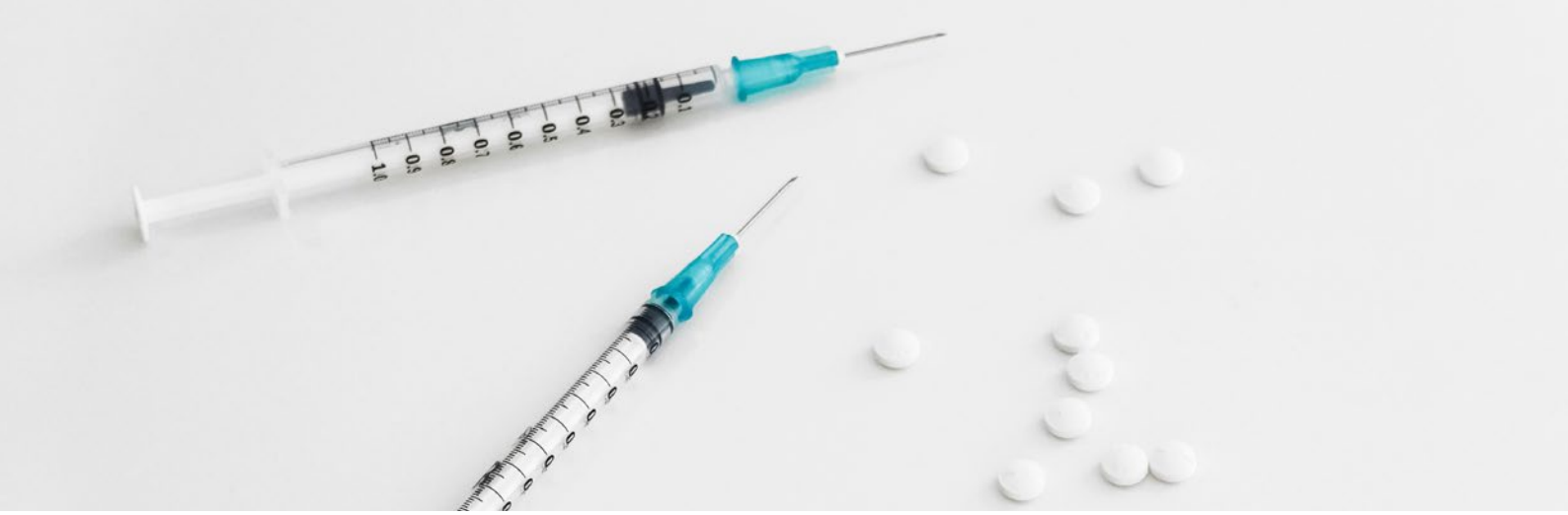
Case study 1: Patheon's CDMO facility in Brisbane[73]

In 2013, the Federal and Queensland Governments provided the capital investment to set up a new mammalian cell culture facility.[74] This investment attracted international manufacturer Patheon, a subsidiary of Thermo Fisher Scientific, to develop a CDMO business at this facility in Brisbane. The site specialises in good manufacturing practice (GMP) for clinical (Phase I to III) and small-scale commercial manufacturing and is co-located with the Translational Research Institute. The facility collaborates with domestic universities on development of mammalian cell lines and has grown local advanced manufacturing jobs.

72 Centre for Health Security (2019a) Vaccine Platforms: State of the Field and Looming Challenges. John Hopkins Bloomberg School of Public Health, USA. <https://www.centerforhealthsecurity.org/our-work/pubs_archive/pubs-pdfs/2019/190423-OPP-platform-report.pdf> (accessed 10 March 2022).

73 Queensland Government (2019) Queensland life sciences: globally competitive. Queensland Government, Brisbane.

74 DSM Biologics (2010) DSM Biologics Announces Entering an Agreement with the Australian Governments to Build and Operate a Biopharmaceutical Manufacturing Facility in Brisbane. Cision PR Newswire, May 3. < https://www.prnewswire.com/news-releases/dsm-biologics-announces-entering-an-agreement-with-the-australian-governments-to-build-and-operate-a-biopharmaceutical-manufacturing-facility-in-brisbane-92647719.html> (accessed 10 March 2022).



2.3 Therapeutic repurposing and novel antivirals

2.3.1 Role in strengthening pandemic preparedness

Therapeutics play an essential role in treating patients that have been exposed or infected by a virus and are particularly important before a vaccine is available and widely accepted.[75] For some viruses, a therapeutic approach will offer a better or more achievable medical countermeasure compared to a vaccine (e.g., HIV). Therapeutics can also act as a prophylactic, where they prevent disease in a patient.

Repurposing existing therapeutics can reduce the time and cost associated with getting a product to market, compared to developing a novel therapeutic. While repurposed products must still undergo proof of concept, dose determination and regulatory approvals, the need for preclinical studies and some regulatory steps can be reduced. This includes regulatory approval for safety considerations, assuming that the required dose is not higher.[76] For example Remdesivir, a broad-spectrum antiviral, was repurposed in the COVID-19 pandemic and was approved for provisional use in Australia in July 2020, approximately six months after the virus entered Australia.[77]

In contrast, the testing and approval of novel therapeutics that are likely to be more effective, such as Molnupiravir, took almost a year from when the outbreak first emerged.[78]

However, repurposing therapeutics has yielded limited success stories to date, and as a pandemic continues in duration and targeted therapeutic development advances, the efficacy of novel direct-acting antivirals (DAA) is likely to be favoured.[79] DAAs are a type of therapeutic that act by directly targeting viral factors that enable virus replication; reducing the ability of the virus to cause disease.[80] While DAAs usually take longer to develop compared to vaccines, they are often cheaper to manufacture in bulk.

This section discusses a two-prong approach to pandemic preparedness for therapeutics where globally available (or in development) products are considered for their repurposing potential, and DAAs are considered for their improved efficacy.

75 Keusch GT, Lurie N (2020) The R&D Preparedness Ecosystem: Preparedness for Health Emergencies. Global Preparedness Monitoring Board, USA.

76 MTPConnect (2021) Drug Repurposing: Building the path to Australian success. Australian Government Department of Industry, Science, Energy and Resources, Australia.

77 TGA (2021) COVID-19 treatment: Gilead Sciences Pty Ltd, remdesivir (VEKLURY). TGA, Australia. <https://www.tga.gov.au/covid-19-treatment-gilead-sciences-pty-ltd-remdesivir-veklury> (accessed 15 February 2022).

78 Painter GR, Batchus MG, Cohen O, Holman W, Painter W (2021) Developing a direct acting, orally available antiviral agent in a pandemic: the evolution of molnupiravir as a potential treatment for COVID-19. Current Opinion in Virology 50, 17-22.

79 Teoh SL, Lim YH, Lai NM, Lee SWH (2020) Directly Acting Antivirals for COVID-19: Where Do We Stand? Frontiers in Microbiology 11.

80 Milwaukee Institute for Drug Discovery (2022) Direct Acting Antivirals for Pandemic Prevention. University of Wisconsin, USA. <https://uwm.edu/drug-discovery/projects/direct-acting-antivirals-for-pandemic-prevention/> (accessed 10 March 2022).

2.3.2 Current context

Therapeutics may be used beyond their initial purpose in clinical practice, and in some cases this may be done without regulatory approval; this is known as 'off-label' use.[81] Despite this use, regulatory approval remains integral to repurposing as it can assist with addressing medico-legal concerns, increase patient and prescribers' confidence in the quality, safety and efficacy of the therapeutic, and provide opportunities for reimbursement through the PBS.[82] Examples of products that have been repurposed include bisphosphonates for breast cancer, metformin for cancer and morphine for breathlessness.[83]

Industry often has fewer incentives to explore new uses for their products after launch and can be unwilling to invest in further R&D as there are very few ways to recoup that investment, particularly where some or all of the patent timeframe has expired.[84] There are also additional costs associated with filing for new regulatory approvals and ongoing post-market surveillance for multiple products. Further, there is little incentive for pharmaceutical companies to develop therapeutics for viruses that do not currently cause disease or represent an insignificant threat to high income country markets.

Development of antivirals, including DAAs, has historically been slow, and focused on major chronic infections as opposed to acute infections, with over two-thirds of all U.S. Food & Drug Administration (FDA) approved antiviral drugs targeting HIV and Hepatitis C.[85] This has been further highlighted in the COVID-19 pandemic, where the first oral antiviral was approved by the FDA in December 2021, approximately 22 months after the virus entered the USA.[86] Australia has capabilities in therapeutics R&D which can be directed towards development of DAAs. This includes CSIRO's efforts on Hendra virus, Griffith Institute for Drug Discovery,[87] Monash University's Drug Discovery Centre,[88] Queensland Emory Drug Discovery Initiative,[89] University of Sydney's Drug Discovery Initiative,[90] and Walter and Eliza Hall Institute's National Drug Discovery Centre[91].

Australia's R&D capabilities in therapeutic repurposing includes the Australian National University Centre for Therapeutic Discovery,[92] Australian Translational Medicinal Chemistry Facility,[93] Cell Screen SA,[94] Centre for Drug Repurposing and Medicines Research,[95] National Drug Discovery Centre,[96] and Queensland Drug Repurposing Initiative.[97]

There are several therapeutics manufacturers in Australia; however, most production is at small scale or is not directly relevant to infectious disease. This includes small molecule production by Mayne Pharma and Pfizer, and AstraZeneca's production of corticosteroids for nebulisation. There is, however, potential for these organisations to direct their manufacturing capabilities towards repurposed products or DAAs in the event of a pandemic, if supported by appropriate government incentives.

81 MTPConnect (2021).

82 TGA (2022a) Repurposing of Prescription Medicines. TGA, Australia. <https://consultations.tga.gov.au/tga/repurposing-of-prescription-medicines/> (accessed 11 March 2022).

83 MTPConnect (2021).

84 MTPConnect (2021).

85 Chaudhuri S, Symons JA, Deval J (2018) Innovation and trends in the development and approval of antiviral medicines: 1987–2017 and beyond. Antivrial Research 155.

86 U.S. Food & Drug Administration (FDA) (2021) Coronavirus (COVID-19) Update: FDA Authorizes First Oral Antiviral for Treatment of COVID-19. FDA, USA. <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19> (accessed 10 March 2022).

87 Griffith University (n.d.) Griffith Institute for Drug Discovery (GRIDD). <https://www.griffith.edu.au/institute-drug-discovery> (accessed 31 March 2022).

88 Monash University (2022) Our Drug Discovery Activities. <https://www.monash.edu/pharm/research/drug-discovery> (accessed 8 March 2022).

89 Queensland Emory Drug Discovery Initiative (2021) Capabilities. UniQuest Pty Ltd, Australia. <https://www.qeddi.com.au/capabilities> (accessed 8 February 2022).

90 The University of Sydney (2021) Drug Discovery Initiative. <https://www.sydney.edu.au/research/centres/drug-discovery-initiative.html> (accessed 15 March 2022).

91 The Walter and Eliza Hall Institute of Medical Research (WEHI) (2022) Drug Discovery. <https://www.wehi.edu.au/research/research-technologies/drug-discovery> (accessed 10 February 2022).

92 The John Curtin School of Medical Research (2021) About. Australian National University, Australia. <https://jcsmr.anu.edu.au/research/centres/actd/about> (accessed 8 March 2022).

93 Australian Translational Medicinal Chemistry Facility (2022) About us. Monash University, Australia. <https://www.monash.edu/atmcf#:~:text=The%20Australian%20Translational%20Medicinal%20Chemistry,targeted%20therapeutics%20for%20clinical%20development.> (accessed 10 March 2022).

94 Flinders Health and Medical Research Institute (2022) Cell Screen SA. Flinders University, Australia. <https://www.flinders.edu.au/health-medical-research-institute/facilities/cell-screen-sa> (accessed 10 March 2022).

95 Centre for Drug Repurposing & Medicines Research (2022) Drug Repurposing & Medicines Research. The University of Newcastle Australia, Australia. <https://www.newcastle.edu.au/research/centre/cdrmr> (accessed 5 March 2022).

96 WEHI (2022) Our facilities. <https://nddc.wehi.edu.au/our-facilities> (accessed 15 March 2022).

97 Analysis from DMTC led National Health Security Resilience Assessment (2022); Centre for Clinical Research (2022) Queensland Drug Repurposing Initiative. The University of Queensland, Australia. <https://clinical-research.centre.uq.edu.au/qdri> (accessed 10 February 2022).

2.3.3 Vision and recommendations

2030 Vision: Several direct-acting antivirals that target priority viral families are in development. Australia has a national database of potential therapeutics for repurposing with estimated effectiveness mapped against priority viral families.

Recommendation 8: Expand high throughput screening of commercially available therapeutics to include mapping to priority viral families

Globally, there is limited understanding of where commercially available therapeutics can be potentially effective for alternative uses. Expanding Australia's screening of globally available therapeutics for repurposing can expedite scale up in response to a pandemic by pinpointing potential candidates before a virus has emerged. This could position Australia as a global leader in the underserviced area of therapeutic repurposing (see Case study 2).

High throughput screening for priority viral families can be supported by:

- Leveraging existing libraries, such as Compounds Australia, to curate a comprehensive set of compounds for testing.[98]
- Artificial intelligence (AI) modelling that can be used to assess where preserved viral characteristics may be susceptible targets for existing therapeutics or where the patient immune response can be reduced.
- AI technologies that can screen compound libraries of existing medications to identify non-virological therapeutics that show *in vivo* efficacy, even in the absence of a rational reason for efficacy.
- Biologically engineered reporter viruses, to identify pre-pandemic strains that may be capable of replication in human cells.[99]
- Consideration of analogues (i.e., different chemical variations of the active ingredient) that may have improved activity and have not previously been studied for therapeutic applications.[100]

After high throughput screening has identified potential candidates, considerations should be made for the manufacturing implications of successful selection, including security of supply, to ensure the timely scale-up and distribution. This includes flexibility in existing manufacturing processes to manage dose regimen changes between traditional and emerging uses of a therapeutic.

Adjacent studies should also consider how the healthcare system could deliver a repurposed therapeutic. For example, determining whether regulators are likely to support distribution over the counter at pharmacies, via prescription or administered in hospital.

Case study 2: National Drug Discovery Centre[101]

The Walter and Eliza Hall Institute (WEHI) of Medical Research plans to launch the National Drug Discovery Centre in 2022, which will offer high throughput screening of drug-like chemicals against a pathogen characteristic. The facility will offer virological and phenotypic screening of therapeutics. Importantly, the robotic based infrastructure will support the drug discovery pipeline and can be used to assess approved therapeutics. The National Drug Discovery Centre will service WEHI projects, research collaborations, industry projects through a fee for service model, and government subsidised projects.

98 Compounds Australia (2021) Drug discovery and compound management logistics. Griffith University, Australia. <https://www.griffith.edu.au/griffith-sciences/compounds-australia> (accessed 10 March 2022).

99 Meganck RM, Baric RS (2021) Developing therapeutic approaches for twenty-first-century emerging infectious viral diseases. Nature Medicine 27 (3), 401-410.

100 Meganck et al (2021).

101 WEHI (2022) Drug Discovery. <https://www.wehi.edu.au/research/research-technologies/drug-discovery> (accessed 10 February 2022).

Recommendation 9: Develop a central database of therapeutics with repurposing potential for future pandemics

Therapeutic repurposing studies are conducted by research institutes and to a lesser extent, pharmaceutical companies. However, outputs from these studies are not centralised into a national database or mapped to priority viral families. A national database can bring together learnings on the preservation of therapeutic targets across viral families, protein responses, docking models and host targets.[102]

Management of the repurposing database will need to be overseen by a central body, who manages the input data from a range of sources (as shown in Figure 6). The database should leverage existing capabilities in Australia, such as collaborating with the National Medical Stockpile to explore strategic reserves of therapeutics for a pandemic.[103]

Domestic and international organisations who house libraries of approved and in-pipeline therapeutics are likely to be key partners for any repurposing database, as they can provide the input candidates for high-throughput screening. The database should also leverage learnings from the MRFF's Clinical Evidence Taskforce during COVID-19, which undertook global scans for treatments being used and their effectiveness.

A centralised and freely available database provides a pathway for clinicians to contribute information on 'off-label' use of therapeutics and associated observational data on patient outcomes. Clinical networks, which engage clinicians and consumers to improve care and service delivery, should be engaged to identify the appropriate incentives to encourage clinicians to input into this database.

Industry incentives can encourage the limited number of onshore manufacturers to contribute to the central database. Incentives could include free screening of candidates across panels of viruses to indicate if it may be effective against a viral family.[104] This may be extended to therapeutics that failed efficacy studies but have repurposing potential, creating a stronger business case to recoup sunk costs. Efforts should be aligned to ongoing work by the TGA, who is consulting with stakeholders on repurposing of medicines, including appropriate incentivises for industry.[105]

When therapeutics reach the end of their patent life, it is difficult for industry to protect any investments in repurposing studies. As such, research into repurposing 'off-patent' products are often undertaken by research groups and small biotechnology companies.[106] Screening off-patent therapeutics will be a key input into an Australian database, given the small scale of local manufacture.

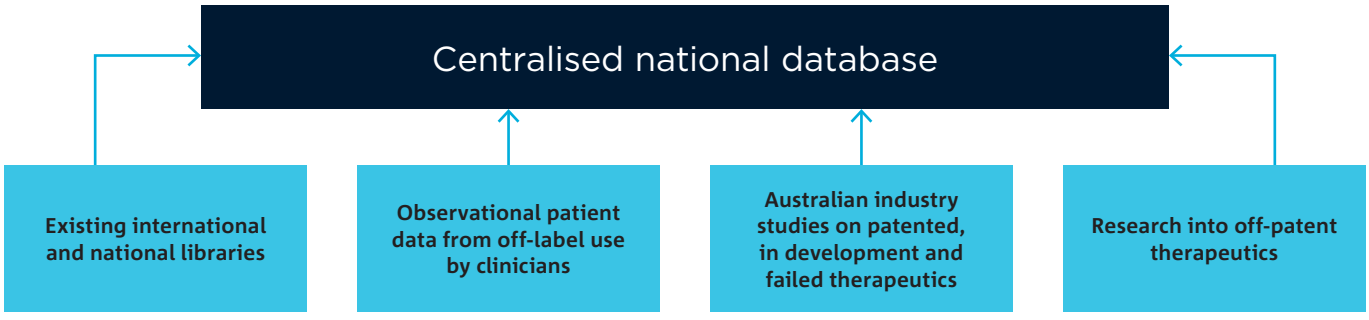


Figure 6: Input data for a centralised national database of therapeutics with repurposing potential

102 Meganck et al (2021).

103 Australian Government Department of Health (2020) National Medical Stockpile. <https://www.health.gov.au/initiatives-and-programs/national-medical-stockpile> (accessed 29 March 2022).

104 Meganck et al (2021).

105 TGA (2022b) Consultation: Repurposing of medicines. <https://www.tga.gov.au/consultation/consultation-repurposing-medicines> (accessed 10 March 2022).

106 MTPConnect (2021).

Recommendation 10: Undertake early-development studies into direct-acting antivirals that act against priority viral families

Globally, discovery and development of antivirals including DAAs, has been limited and focused on major chronic infections as opposed to acute infections. As such, there is a lack of available or in development antivirals targeting priority viral families.

While an ideal therapeutic would be an agent that can act against a broad range of viruses, the target of an antiviral will likely vary for different viruses. Therefore, targeting characteristics that are preserved across viral families can enable pre-emptive drug development, allowing for rapid therapeutic deployment in a pandemic. Efforts to develop DAAs for pandemics can also be leveraged for known diseases, such as influenza (*Orthomyxoviridae* family).

Pre-emptive early development of DAAs for priority viral families can also provide co-benefits for other systems, such as development of a smallpox inhibitor (*Orthomyxoviridae* family) to respond to potential biosecurity threats.[107] Early development of DAAs can be driven by:

- Breakthroughs in basic biological and chemical understanding of viral families (aligned to Recommendation 1).
- Traditional high-throughput screening for new chemical molecules that target viral enzymes.[108]
- Fragment-based drug design that uses simple compounds and gradually increases in complexity until an inhibitor is identified.[109]
- Investigating where nucleoside analogues can be deployed to build efficacy across viral families.[110]

107 Chaudhuri S, Symons JA, Deval J (2018) Innovation and trends in the development and approval of antiviral medicines: 1987–2017 and beyond. Antiviral Research 155, 76-88.

108 Clyde A, Galanie S, Kneller DW< Ma H, Babuji Y, Blaiszik B, Brace A, Brettin T, Chard K, Chard R, Coates L, Foster I, Hauner D, Kertesz V, Kumar N, Lee H, Li Z, Merzky A, Schmidt JG, Tan L, Titov M, Trigan A, Turilli M, Van Dam H, Chennubhotla SC< Jha S, Kovalevsky A, Ramanathan A, Head MS, Stevens R (2022) High-Throughput Virtual Screening and Validation of a SARS-CoV-2 Main Protease Noncovalent Inhibitor. Journal of Chemical Information and Modelling 62(1), 116-128.

109 Li Q (2020) Application of Fragment-Based Drug Discovery to Versatile Targets. Frontiers in Molecular Biosciences 7.

110 Dolgin E (2021) The race for antiviral drugs to beat COVID - and the next pandemic. Nature, April 14.

2.4 Point of care diagnostics for case identification

2.4.1 Role in strengthening pandemic preparedness

Strong diagnostic testing capacity is a key feature of effective pandemic response.[111] Diagnostics contribute to pandemic preparedness through screening and surveillance, early identification and classification of emerging pathogens and viruses, enabling clinical research and trials, and case ascertainment supporting timely clinical and public health intervention.[112]

Most diagnostics for viral diseases are performed in controlled laboratory environments using *in vitro* diagnostics (IVD) technology by trained laboratory personnel.[113] However, over the past decade some testing has shifted from IVDs to point of care test (POCT) technology. POCTs can broadly be distinguished by the setting they are used: in healthcare settings and in community/home-use. The technologies utilised for POCTs in healthcare settings are predominantly small-scale quality-assured analytical devices utilising technologies used in traditional IVDs (e.g., rapid polymerase chain reaction (PCR) POCTs), while POCTs used by people in the community are often lateral flow immunoassays.

POCTs provide benefits IVDs do not, including the ability to deliver quicker test results, and providing access to testing when IVDs are not readily available (i.e., in remote areas). POCTs can be platform technologies where one device can be varied to test different things, or multiplex where a single device can test for multiple diseases from a single sample. Table 5 highlights different features of POCTs and IVDs. While both diagnostic approaches should be utilised as part of broader pandemic preparedness and response strategies, this section focuses on the role of POCT diagnostics in healthcare settings and in the community.

Table 5: Typical features of POCT and IVD laboratory-based diagnostics

	POINT OF CARE DIAGNOSTICS (POCT TECHNOLOGY)	CENTRAL LABORATORY DIAGNOSTICS (IVD TECHNOLOGY)
Time to result	<30min	>2h–24hrs
Skill / training to operate	Low	High
Cost of test	Varies – mostly lower	Higher
Cost of equipment	Lower	Higher
Portable	Yes	No
Sample collection	Simple	Varies
Remote application	Yes	No
Sensitivity/Specificity	Varies – mostly lower	High
Quality Assurance Programs	Minimal	Established
Simultaneous tests (multiple patients)	Limited	Yes
Multiple diseases (single sample)	Limited	Yes
Integrated data capture	Limited	Yes
Output of data	Simple	Complex

111 WHO Regional Office for the Eastern Mediterranean (2018) Early warning alert and response network in emergencies: evaluation protocol. WHO, Cairo. <https://apps.who.int/iris/handle/10665/327304> (accessed 29 March 2022).

112 Barac A, Poljak M, Ong DS (2020) Innovative approaches in diagnosis of emerging/re-emerging infectious diseases. Frontiers in Microbiology 11:619498, 3079; Keusch GT, Lurie N (2020) Report to the Global Preparedness Monitoring Board: The R&D Preparedness Ecosystem: Preparedness for Health Emergencies. US National Academy of Medicine. <https://www.glopid-r.org/wp-content/uploads/2020/10/a-world-In-disorder-a-report-by-the-global-preparedness-monitoring-board.pdf> (accessed 29 March 2022).

113 Li, C (2019) Special Topic: Point-of-Care Testing and In Vitro Diagnostics. Journal of Analysis and Testing 3, 1–2.

2.4.2 Current context

Over the past decade, the prevalence and application of POCT devices has expanded greatly.[114] Market forecasting from 2021 suggests the global POCT diagnostics market is expected to reach USD 83.0 billion by 2028 from USD 3.6 billion in 2021; growing at a compound annual rate of 12.7% over this period.[115]

While the application of POCTs globally has increased in recent years, Australia's diagnostics capabilities for infectious diseases are predominantly structured around IVD technologies. Outside of infectious diseases, Australia has integrated POCTs for chronic and non-communicable disease management (e.g., glucose meters for diabetes management), reproductive health (e.g., pregnancy and ovulation tests), and for drug detection. The implementation of POCTs for COVID-19 began when they were included into legislation and public health reporting processes in late 2021.[116]

In healthcare settings, POCTs are used for processing samples near the patient for infectious disease and AMR, primarily utilising rapid PCR POCT platforms such as GeneXpert.[117] A range of rapid PCR POCT technologies have emerged over the past decade and were increasingly adopted during the COVID-19 pandemic. However, the technology (the devices themselves, and necessary quality assurance and data reporting protocols) are relatively immature, and the associated equipment is expensive. POCTs also have different sensitivity and specificity depending on whether they are for community use, or at the bedside in healthcare.

An over-reliance on IVDs for high burden diseases can overwhelm central laboratories and cause flow-on issues for POCT supplies during outbreak peaks. While Australia has the R&D capacity to develop novel POCTs and other diagnostics, it does not have the manufacturing capacity to produce all diagnostics and necessary components that the health system (and the region) depends on. Australia's diagnostics materials capacity relies predominantly on imports.

Laboratory systems vary in each jurisdiction, with a combination of public and private pathology providers accredited for diagnostic testing. This is similar for biobanking facilities in each jurisdiction, with bespoke banks for different samples, diseases or research purposes that do not integrate with each other. Centralised laboratories are predominantly located in urban areas, which impacts access and timeliness of results for remote communities. Some recent initiatives are seeking to expand the clinical application of POCT diagnostics in remote areas to alleviate access issues (see Case study 3).

Case study 3: POCT program for infectious diseases in remote Indigenous communities[118]

Timely testing, which is critical for clinical management of infectious disease, is not readily available for many remote Aboriginal and Torres Strait Islander communities. A consortium, led by the Kirby Institute, has been funded to develop a national framework to scale up healthcare POCTs (and the necessary skilled workforce) for infectious diseases in remote communities. This program utilises GeneXpert platforms to provide real-time laboratory services and clinical support to communities. The Kirby Institute has worked in partnership with Aboriginal communities for over a decade and established a network of over 100 molecular POCT platforms in remote communities.

This network enabled the rapid scaling of POCT PCR testing during COVID-19 for Aboriginal communities. The program is the first of its kind globally to take a fully integrated, multi-disease health systems approach to decentralised infectious disease testing, with in-built capacity for scale-up and ongoing linkage to care providers for better health outcomes for remote Aboriginal communities.

114 Larsson A, Greig-Pylypczuk R, Huisman A (2015) The state of point-of-care testing: a European perspective. Upsala Journal of Medical Sciences 120(1), 1-10.

115 The Insight Partners (2012) Point of Care Diagnostics Market Forecast to 2028 - COVID-19 Impact and Global Analysis by Product, Prescription Mode, and End User, and Geography. <https://www.researchandmarkets.com/reports/4841372/point-of-care-diagnostics-market-forecast-to-2028#rela4-4859240> (accessed 29 March 2022).

116 TGA (2022b) COVID-19 test kits included in the ARTG for legal supply in Australia. <https://www.tga.gov.au/covid-19-test-kits-included-artg-legal-supply-australia> (accessed 29 March 2022); Public Health Laboratory Network (2021) Public Health Laboratory Network – Communicable Diseases Network Australia: Joint Statement on SARS-CoV-2 Rapid Antigen Tests. <https://www.health.gov.au/sites/default/files/documents/2021/12/phln-and-cdna-joint-statement-on-sars-cov-2-rapid-antigen-tests.pdf> (accessed 29 March 2022).

117 Cepheid (2022) GeneXpert® Systems. <https://www.cepheid.com/en_US/systems/GeneXpert-Family-of-Systems/GeneXpert-System> (accessed 17 February 2022).

118 The Kirby Institute (2021) Kirby Institute-led consortium receives $9.97m to scale up infectious disease testing in remote Indigenous communities. <https://kirby.unsw.edu.au/news/kirby-institute-led-consortium-receives-997m-scale-infectious-disease-testing-remote-indigenous> (accessed 29 March 2022).

2.4.3 Vision and recommendations

2030 Vision: Australia has a national pandemic response strategy that enables rapid and scaled deployment of POCT diagnostics in healthcare settings and in the community to complement IVD capabilities. The country continues to contribute R&D capabilities to the global sector, with strengths in multiplex POCT platform technologies. Biotechnology companies are supported to grow their businesses onshore and Australia has expanded the biobanking capabilities needed to validate commercialised discoveries.

Recommendation 11: Develop a diagnostics deployment strategy for scaling POCT applications

Poor diagnostic preparedness and capacity, and the absence of a coordinated national plan for the scaled implementation of diagnostic resources, has been identified as a significant contributor to delays in responding to pandemics.[119] Developing a strategy that coordinates the scaling of POCT diagnostic resources to complement Australia's strong IVD implementation capabilities would reduce delays in identifying cases and help limit the spread of disease. It could also inform pathways to support neighbouring countries to access and implement diagnostics as needed.

Elements of a strategy that could inform the deployment of POCTs include:

- Guidelines for when and how to appropriately scale and adapt diagnostics across both IVDs in central laboratories and POCTs in healthcare settings and community.
- A framework to anticipate and manage shortages of diagnostic materials (raw materials and devices) and supply chain interruptions during outbreaks, and to ensure POCT acquisition, supply and deployment in a timely manner to suit a pandemic context.
- A national approach to POCT and IVD result reporting, linked with other health data sources.
- Guidelines for the safe but expedited approval process for the inclusion of novel diagnostics on the Australian Register of Therapeutic Goods during pandemics for emergency use, coupled with provisions for accelerated or designated customs procedures (i.e., emergency use authorisation equivalents to facilitate market entry).[120]

A POCT deployment strategy should be pathogen agnostic and have different scenarios for different epidemiological situations and pathogens.[121] It should align with strategies already developed in other areas of health, including the *Australian Health and Emergency Management Plans for COVID-19* and *Influenzas*,[122] *National AMR Strategy*,[123] and the *National Biosecurity Strategy 2030*.[124] The strategy could be added as a module to any future national pandemic preparedness and response strategy.

119 Kelly-Cirino CD, Nkengasong J, Kettler H, Tongio I, Gay-Andrieu F, Escadafal C, Piot P, Peeling RW, Gadde R, Boehme C (2019) Importance of diagnostics in epidemic and pandemic preparedness. BMJ Global Health 4(Suppl 2), 001179.

120 TGA (2022b).

121 WHO (2021a) Recommendations for national SARS-CoV-2 testing strategies and diagnostic capacities. <https://www.who.int/publications/i/item/WHO-2019-nCoV-lab-testing-2021.1-eng> (accessed 29 March 2022); WHO (2021b) WHO COVID-19 Strategic preparedness and response plan: Operational planning guideline. WHO, Geneva.

122 Australian Government Department of Health (2020a) Australian Health Sector Emergency Response Plan for Novel Coronavirus (COVID-19). Department of Health, Canberra. https://www.health.gov.au/sites/default/files/documents/2020/02/australian-health-sector-emergency-response-plan-for-novel-coronavirus-covid-19_2.pdf (accessed 29 March 2022); Australian Government Department of Health (2019a) Australian Health management Plan for Influenza. Department of Health, Canberra. <https://www1.health.gov.au/internet/main/publishing.nsf/Content/519F9392797E2DDCCA257D47001B9948/$File/w-AHMPPI-2019.PDF> (accessed 29 March 2022).

123 Australian Government Antimicrobial Resistance (2020) National AMR Strategy. Australian Government, Canberra. <https://www.amr.gov.au/australias-response/national-amr-strategy> (accessed 29 March 2022).

124 Australian Government Biosecurity (2022) National Biosecurity Strategy. Australian Government, Canberra <https://www.biosecurity.gov.au/about/national-biosecurity-committee/nbs> (accessed 29 March 2022).

Recommendation 12: Enhance R&D capabilities for multiplex POCT platform technologies

There are limited available POCTs with capacity to distinguish between pathogen types (e.g., bacterial, viral or fungal), viral families, or multiple specific pathogens. Those that are available on the market are generally limited to testing capacity for two or three pathogens.

Multiplex technologies test for the presence or absence of multiple pathogens in a single test with a single sample. While in its infancy, the pipelines for multiplex POCT technologies for both healthcare and community settings are robust (e.g., GeneXpert, Cobas Liat System, Ellume-Lab).[125] These technologies could also have broad applications between pandemics to act as a triage tool for the identification of diseases and can be applied during pandemics to distinguish between variants of novel viruses as well as between novel viruses and endemic viruses in healthcare settings.

Australia has established diagnostic research strengths across research organisations and small biotechnology companies that could prioritise this work. Investments to improve virus and host knowledge across priority viral families (see Recommendation 1) could have flow-on benefits to inform multiplex POCT platform research.

Recommendation 13: Implement a diagnostics development program aimed at small and medium sized enterprises

Australia has invested well in research diagnostics discovery; however, this does not always translate into onshore commercialisation. This results in lost value for the Australian market. Stakeholders raised that small and medium sized enterprises (SMEs) frequently shift from Australian to overseas markets during their scale-up phases due to greater access to funding and guaranteed procurement contracts on successful commercialisation. This has happened to several Australian-founded diagnostics companies including Ellume, Healius, and I-MED.

Prioritising investment and incentives for established SMEs that are looking to scale could retain both discovery and commercialisation value in Australia. Programs could prioritise the use of products that are already produced at scale but can be pivoted for pandemics. This can be leveraged to build redundancy into the supply chain during pandemics and satisfy domestic and potentially international demand between pandemics. This could also include advanced market commitments to drive both innovation and distribution. Additional incentives could include risk sharing agreements with global biotechnology companies, procurement contracts, and specialist infrastructure investments. Harmonised approval processes for POCTs, Emergency Use Authorisations, and quality assurance and validation processes could also incentivise and lower risk for developers prioritising POCTs for emerging infectious diseases.[126]

There are several successful models in the USA for fostering and growing commercial diagnostics that could be adapted for Australia, such as SBIR/STTR program, BARDA program and RADx Program (see Case study 4).[127]

125 Cepheid (2022); Ellume Limited (2022) Ellume lab. <https://www.ellumehealth.com/products/professional-products/ellumelab/> (accessed 29 March 2022); Hansen G, Marino J, Wang ZX, Beavis KG, Rodrigo J, Labog K, Westblade LF, Jin R, Love N, Ding K, Garg S (2021) Clinical performance of the point-of-care cobas Liat for detection of SARS-CoV-2 in 20 minutes: a multicenter study. Journal of clinical microbiology 59(2), 2811-20.

126 Centre for Health Security (2019b); Defence Science and Technology (2018) Medical Countermeasures Initiative: National Capability Audit 2017 Summary. <https://www.dst.defence.gov.au/publication/medical-countermeasures-initiative-national-capability-audit-2017-summary> (accessed 29 March 2022).

127 SBIR STTR (2020) About the SBIR and STTR Programs. <https://www.sbir.gov/about> (accessed 29 March 2022); US Department of Health & Human Services National Institutes of Health (2021a) RADx Programs. < https://www.nih.gov/research-training/medical-research-initiatives/radx/radx-programs> (accessed 29 March 2022); US Department of Health & Human Services Public Health Emergency (2021) BARDA's Programs to Combat Emerging Infectious Diseases. <https://www.phe.gov/about/barda/Pages/EID.aspx> (accessed 29 March 2022).

Case study 4: Rapid Acceleration of Diagnostics (RADx) Programs

In 2020, the National Institutes of Health in the USA launched the RADx initiative for rapid development, commercialisation and implementation of technologies needed for COVID-19 testing.[128] The technology development program highlights the importance of public-private partnerships and leveraging industry-wide knowledge to speed up the delivery of testing technologies.[129] Offering competitions for funding and support from technology, clinical testing, regulatory affairs and business experts has resulted in 32 USA FDA emergency use authorisations.[130] Companies that received these authorisations have supplied more than 840 million tests to the USA market between September 2020–October 2021.[131]

Recommendation 14: Develop a biobanking repository for diagnostics validation samples

The validation of new IVD and POCT diagnostics requires access to a range of qualified biological virus samples to be used in the assessment process. However, laboratories undertaking these assessments do not have consistent access to these samples. A nationally available biobank repository (either central or a network of biobanks) that can be accessed on application would ensure consistent sample collection, storage, handling and testing processes. It could also enable the standardised application of future quality assurance frameworks.

Applications to use samples could be open to any party that has valid human ethics approvals in place and be reviewed by a biobanking governance committee. This could include paid access for commercial companies to validate products seeking TGA approval. This would allow for streamlined and equitable access to samples with clear criteria for use and extraction.

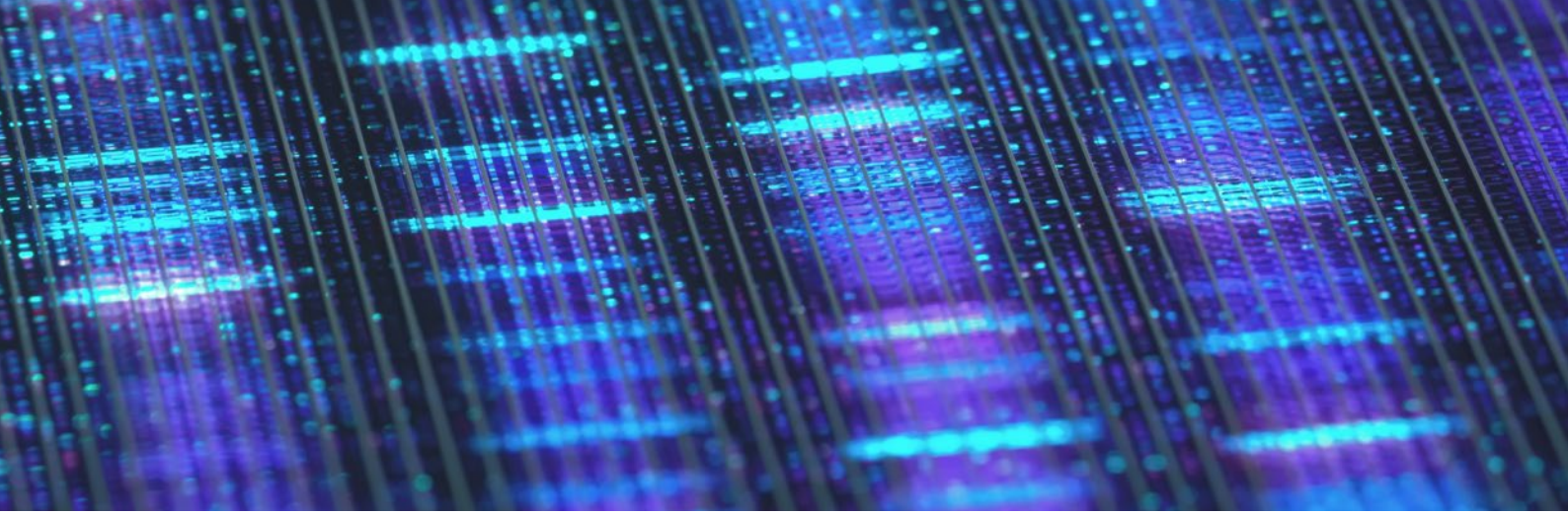
A range of samples should be collected for this biobank (e.g., serum, plasma, nasopharyngeal swabs, saliva, urine, and faeces). These biological samples would need to be updated as new viral variants arise in the community, and large volumes of samples need to be available to meet demand. Australia has existing expertise in this area and has bespoke biobanks for research and quality assurance that could be expanded or networked. Areas of expansion could include storage and sharing of pseudo-viruses and developed targets for standardising and validation; storage of samples for assessing susceptibility to new pathogens and variants; clinical sample biobanking with qualified longitudinal samples from confirmed cases; and access to standards for validation (and TGA approval) of commercial testing.

128 US Department of Health & Human Services National Institutes of Health (2021a).

129 Walsh B, Hosoi A, Kingsley M, Moreira S, Ramakrishnan S, Tessier P, Gagliano N (2021) The RADx Tech Deployment Core: A Model for Academic/Government Based Support of Large-Scale Manufacturing and Implementation of Medical Technologies. IEEE Open Journal of Engineering in Medicine and Biology 2,158-162.

130 US Department of Health & Human Services National Institutes of Health (2021b) NIH RADx initiative expands COVID-19 testing innovation for additional types of rapid tests. <https://www.nih.gov/news-events/news-releases/nih-radx-initiative-expands-covid-19-testing-innovation-additional-types-rapid-tests> (accessed 29 March 2022).

131 US Department of Health & Human Services National Institutes of Health (2021b).



2.5 Genomic analysis of pathogens and their variants

2.5.1 Role in strengthening pandemic preparedness

The analysis of pathogen genomes – combining local and global whole genome sequencing (WGS) datasets with bioinformatic methodologies – can shed light on pathogen spread, epidemiology of transmission, and possible sources, times, and geographic origins of pathogen emergence.[132] Genomic analysis can assist with pandemic preparedness in a range of ways, including facilitating early detection and providing data to inform diagnostic design.[133] However, this section focuses on the use of genomic analysis to track emerging pathogens and their variants during an outbreak and inform public health decisions and response activities.

2.5.2 Current context

WGS is a generally mature technology, and a variety of sequencing platforms are on the market, each with specific spatial and temporal capacities.[134] The UK, USA and EU are leaders in integrated genomic analysis. Both the USA and UK have implemented national WGS services, and in 2016, 26 European countries reported the use of WGS in routine public health practice.[135] These programs have been expanded to respond to pandemics, for example:

- **The COVID-19 Genomics UK (COG-UK) Consortium** – A recent evaluation found that COG-UK's data, research analytics, and dissemination efforts influenced how decision makers valued and viewed the field of pathogen genomics and strengthened capacity for pathogen genomics.[136]
- **The Centers for Disease Control and Prevention (CDC)** – The CDC's genomic sequencing program generated substantial sequencing data that was integrated into pandemic surveillance programs. This data was made publicly available to inform public health decision making in the USA and globally, via the Global Initiative on Sharing Avian Influenza Data (GISAID).[137]
- **GISAID (Global)** – This initiative was expanded in response to the COVID-19 pandemic as a mechanism for rapid sharing of both published and unpublished genomic data to help understand how the SARS-CoV-2 virus evolves and spreads.[138]

132 Berry IM, Melendrez MC, Bishop-Lilly KA, Rutvisuttinunt W, Pollett S, Talundzic E, Morton L, Jarman RG (2020) Next Generation Sequencing and Bioinformatics Methodologies for Infectious Disease Research and Public Health: Approaches, Applications, and Considerations for Development of Laboratory Capacity. The Journal of Infectious Diseases 221 (Suppl 3), 292–307; Gardy JL, Loman NJ (2017) Towards a genomics-informed, real-time, global pathogen surveillance system. Nature Reviews Genetics 19(1), 9–20.

133 WHO (2020) GLASS whole-genome sequencing for surveillance of antimicrobial resistance. WHO, Geneva. <https://www.who.int/publications/i/item/9789240011007> (accessed 29 March 2022).

134 Meera Krishna B, Khan M.A, Khan ST (2019). Next-Generation Sequencing (NGS) Platforms: An Exciting Era of Genome Sequence Analysis. In: Microbial Genomics in Sustainable Agroecosystems (Eds. V Tripathi, P Kumar, P Tripathi, A Kishore, M Kamle) 89-109. Springer, Singapore.

135 Ferdinand AS, Kelaher M, Lane CR, da Silva AG, Sherry NL, Ballard SA, Andersson P, Hoang T, Denholm JT, Easton M, Howden, B (2021) An implementation science approach to evaluating pathogen whole genome sequencing in public health. Genome Medicine 13(1), 1–11; outbreak investigation and infection prevention and control. However, to date, there are limited data regarding (iGardy JL and Loman NJ (2017).

136 Marjanovic A, Romanelli RJ, Ali G, Leach B, Bonsu M, Rodriguez-Rincon D, Ling T (2022) COVID-19 Genomics UK (COG-UK) Consortium: Final Report. RAND Corporation, Santa Monica. <https://www.rand.org/pubs/research_reports/RRA1277-1.html> (accessed 29 March 2022).

137 Centre for Disease Control and Prevention (CDC) (2021a) CDC's Role in Tracking Variants. <https://www.cdc.gov/coronavirus/2019-ncov/variants/cdc-role-surveillance.html> (accessed 29 March 2022).

138 GISAID Initiative (2022) GISAID Initiative Mission. <https://www.gisaid.org/about-us/mission/> (accessed 29 March 2022).

Australia has globally competitive capabilities for genomic analysis across several infectious diseases. WGS has been integrated into some public health laboratories for small-scale outbreak investigations and routine public health surveillance of several other diseases with epidemic potential, most recently with COVID-19.[139] For example, wastewater genomic techniques trialled by CSIRO and adopted in some jurisdictions identified areas where COVID-19 outbreaks were and were not occurring, which informed targeted and early public health interventions, and gathered information regarding the circulation of virus in the community.[140]

While Australia has strong sequencing and analysis capabilities, the nation's capacity for WGS investigations during a pandemic does not perform at scale (i.e., in outbreak peaks). Early in the COVID-19 pandemic, Australia's genomic response was one of the best globally, largely enabled by the initial low numbers of cases in Australia. As case numbers increased, Australia was unable to maintain this volume of testing as the genomic systems were not able to keep up with the increase in cases (Figure 7). While WGS investigations are not required for every case in an outbreak, successful pandemic genomic analysis requires capacity to implement a scaled sampling protocol to accurately inform decision making.

The Communicable Diseases Genomics Network (CDGN) is an Expert Reference Panel under the Public Health Laboratory Network that is comprised of representatives from public health laboratories with genomics capabilities from every state and territory in Australia. It leads the implementation of pathogen genomics in Australia's public health system. Australia's current *National Microbial Genomics Framework and Implementation Plan* provides the first nationally consistent strategic view for integrating microbial genomics in the public health system. It also identifies microbial genomics policy issues and challenges. It was developed in collaboration with the CDGN and prioritises genomic analysis for monitoring respiratory and vaccine preventable diseases, foodborne diseases, sexually transmitted infections and AMR.[142]

Figure 7: Proportion of COVID-19 cases sequenced in Australia and shared with GISAID[141]

139 Lane CR, Sherry NL, Porter AF, Duchene S, Horan K, Andersson P, Wilmot M, Turner A, Dougall S, Johnson SA, Sait M (2021) Genomics-informed responses in the elimination of COVID-19 in Victoria, Australia: an observational, genomic epidemiological study. The Lancet Public Health 6(8), 547-556; Octavia S, Wang Q, Tanaka M, Kaur S, Sintchenko V, Lan R (2015) Delineating community outbreaks of Salmonella enterica serovar Typhimurium using whole genome sequencing: insights into genomic variability within an outbreak. Journal of Clinical Microbiology 53(4), 1063-71; Outhred AC, Holmes N, Sadsad R, Martinez E, Jelfs P, Hill-Cawthorne GA, Gilbert GL, Marais BJ, Sintchenko V (2016) Identifying likely transmission pathways within a 10-year community outbreak of tuberculosis by high-depth whole genome sequencing. PLoS ONE 11(3), e150550; Rockett RJ, Arnott A, Lam C, Sadsad R, Timms V, Gray KA, Eden JS, Chang S, Gall M, Draper J, Sim EM (2020) Revealing COVID-19 transmission in Australia by SARS-CoV-2 genome sequencing and agent-based modeling. Nature medicine 26(9), 1398-404; Rockett RJ, Oftadeh S, Bachmann NL, Timms VJ, Kong F, Gilbert GL, Sintchenko V (2018) Genome-wide analysis of Streptococcus pneumoniae serogroup 19 in the decade after the introduction of pneumococcal conjugate vaccines in Australia. Scientific Reports 8(1), e16969; Williamson DA, Kirk MD, Sintchenko V, Howden BP (2019) The importance of public health genomics for ensuring health security for Australia. Medical Journal of Australia 210(7), 295-297.

140 CSIRO (2021) COVID-19 Research: Monitoring wastewater for COVID-19. https://www.csiro.au/en/research/health-medical/diseases/covid-19-research/monitoring-wastewater (accessed 29 March 2022).

141 Hoang T, da Silva AG, Jennison AV, Williamson DA, Howden BP, Seemann T (2022) AusTrakka: Fast-tracking nationalized genomics surveillance in response to the COVID-19 pandemic. Nature Communications 13(1), 1-4; Chen AT, Altschuler K, Zhan SH, Chan YA, Deverman BE (2021) COVID-19 CG enables SARS-CoV-2 mutation and lineage tracking by locations and dates of interest. Elife 10 <https://covidcg.org/?tab=global_sequencing> (accessed 14 February 2022).

142 Australian Government Department of Health (2021) Implementation plan for the National Microbial Genomics Framework 2021-2022. Department of Health, Canberra; Australian Government Department of Health (2019a) National Microbial Genomics Framework 2019-2020. Department of Health, Canberra.

2.5.3 Vision and recommendations

2030 Vision: Australia has a national genomic analysis program for routine surveillance which is effectively scaled and targeted during pandemics, utilising cross-sectoral data. The nation's strengthened genomics workforce and pathogen-agnostic capabilities position Australia as a leader for genomic analysis in the region and globally.

Recommendation 15: Establish a national genomic analysis authority to coordinate cross-sectoral collaboration and data sharing

A range of data is needed for a national genomics initiative that can rapidly understand the emergence of new pathogens and undertake emergency response surveillance. There is no single authority or universal governance arrangement for the coordination of effective cross-sectoral data sharing for genomic analysis (i.e., human, animal, and environmental health).

For cross-sectoral collaboration and data coordination to be effective, a responsible authority would require a legal or statutory mandate to prioritise this and to overcome the cultural and systemic barriers that have prevented data sharing in the past. Such an authority could also lead the implementation of a pathogen agnostic genomic analysis platform (Recommendation 16) including coordinating jurisdictions to enable cross-sector data mobilisation, and leading governance arrangements and pre-approvals.

The CDGN could be expanded to have this authority. It currently endorses cross-jurisdictional data sharing for sequence data, however, does not have statutory authority to mandate or implement this. The CDGN is nationally representative, and duties include advocating for health genomic data collection, analysis and research. The CDGN has also established networks and data sharing agreements between jurisdictional public health units and is responsible for a substantial portion of actions under the *National Microbial Genomics Framework and Implementation Plan*.[143]

Recommendation 16: Design and coordinate the implementation of a national pathogen agnostic genomic analysis platform

Australia's genomic analysis platforms are largely pathogen-specific and are often jurisdiction-specific. The development and application of high-throughput pathogen agnostic technology could enable real-time surveillance systems that inform local and global responses to emerging infectious diseases.[144] A national platform that could encompass multiple pathogens would enable rapid and responsive understanding of pandemics while strengthening routine surveillance between pandemics.

The design, coordination and implementation of a pathogen agnostic platform should include:

- Developing data sharing and mobilisation guidelines to overcome barriers to collaboration, including cross-jurisdictional data collection, defining minimum data sets, reporting requirements and governance.
- Building functionality that supports interoperability and information sharing.
- Designing a real-time analytic system that can handle raw or summarised federated data provided by organisations and jurisdictional systems that collect and process the raw data.
- Incentivising jurisdictional laboratories to adopt the platform and standards in a timely and consistent fashion.
- Aligning with the Global Alliance for Genomics and Health (GA4GH) standards and common methods for collecting, storing, transferring, accessing and analysing data.[145]

Multi-pathogen platforms are currently being investigated at a national level by the CDGN (see Case study 5).

143 Australian Government Department of Health (2021); Australian Government Department of Health (2019a).

144 Lane et al. (2021).a rapid recrudescence of COVID-19 was observed in the state of Victoria in June, 2020. We aim to describe the genomic findings that located the source of this second wave and show the role of genomic epidemiology in the successful elimination of COVID-19 for a second time in Australia. Methods: In this observational, genomic epidemiological study, we did genomic sequencing of all laboratory-confirmed cases of COVID-19 diagnosed in Victoria, Australia between Jan 25, 2020, and Jan 31, 2021. We did phylogenetic analyses, genomic cluster discovery, and integrated results with epidemiological data (detailed information on demographics, risk factors, and exposure

145 Global Alliance for Genomics & Health (2020) GA4GH 2020-2021 Roadmap. <https://www.ga4gh.org/how-we-work/2020-2021-roadmap/> (accessed 29 March 2022).

This could inform the design of a pathogen agnostic platform, which has platform capacity and does not need to be adapted regardless of the pathogen. This would provide a secure and private online location to share, store, analyse and view aggregated national and jurisdictional genomic data. Some jurisdictions may require additional resourcing and facility upgrades to meet the required digital infrastructure standards.

The implementation of a pathogen agnostic platform should be overseen by a single responsible body with the authority to mandate its adoption, as per Recommendation 15.

Case study 5: AusTrakka[146] and the Australian Pathogen Genomics (AusPathoGen) Program[147]

AusTrakka is a pathogen-agnostic genomics surveillance platform developed by the Microbiological Diagnostic Unit Public Health Laboratory and operationalised by the CDGN in collaboration with all jurisdictional public health laboratories. It is a nationally recognised platform for real-time analysis of integrated pathogen genomic data for public health. The platform development was fast-tracked during the COVID-19 pandemic and was endorsed as Australia's SARS-CoV-2 genomics surveillance platform. The platform demonstrated utility in real-time with genomic analysis and reporting. Since its implementation, AusTrakka has extended its capabilities to include other public health pathogens, such as Salmonella.

The AusPathoGen Program is a large-scale infectious disease genomics research program funded by the MRFF. The program aims to integrate national genomics analysis to inform responses to infectious diseases into public health. This program plans to deploy AusTrakka for consistent analysis and reporting and will collaborate with state and territory health departments and public health laboratories to implement national genomics-based responses. It aims to evolve to be a multi-disease platform for specific respiratory and vaccine preventable diseases, foodborne diseases, sexually transmitted infections and antimicrobial resistance.

Recommendation 17: Strengthen workforce skills across bioinformatics, metagenomics, statistical genomics modelling, and genomic epidemiology

These skills are required to implement integrated genomic analysis but are concentrated in the research sector and not commonly found in government and public health units where they are also needed. This has resulted in substantial limitations in workforce skill and capacity in these areas. A range of activities could be considered to address these workforce skills gaps, including:

- Developing collaborative partnerships between the research sector, laboratories and public health to support strengthening the integration of these skills into public health.
- Incentives to retain graduates with these skills in public health, as often graduates apply these relevant skills in other sectors or move abroad for employment opportunities.
- Industry placements for early career researchers and industry PhDs to enhance employability of genomic researchers and allowing industry to develop their genomic analysis capacity.
- Expanding the CDGN Teaching and Training Working Group development and implementation of end-to-end pathogen genomic training programs.[148]

146 Communicable Diseases Genomics Network (CDGN) (2020a) AusTrakka Real-time pathogenic genomics surveillance. <https://www.cdgn.org.au/austrakka> (accessed 29 March 2022).

147 CDGN (2020b) Australian Pathogen Genomics Program overview: integrating pathogen genomics into public health. <https://www.cdgn.org.au/auspathogen> (accessed 29 March 2022).

148 CDGN (2021) CDGN teaching, training and curriculum working group terms of reference. <https://static1.squarespace.com/static/5e4f5b7ee8b790561bbb65e4/t/60ee6bdebb85ab7f02bfc874/1626237919215/CDGN+TTC+WG+ToR_v1.0_April+2021.pdf> (accessed 29 March 2022).

2.6 Data sharing for informing response strategies

2.6.1 Role in strengthening pandemic preparedness

Data sharing across the healthcare system in a pandemic is critical for the efficient and effective operation of health services and for the benefit of patient outcomes and treatment.[149] Extending human health data sharing to include environmental and animal health systems is also a core component of pandemic surveillance given most viral human diseases are zoonotic.

Data sharing governance, incentives, legislation and policy instruments are instrumental to successful data sharing across the healthcare system both during and between pandemics. However, given the scope of this report, this section focuses on the core S&T systems and standards that enable data sharing. Specifically, the process of sharing data from the health system with governments to help understand the spread of disease and inform pandemic response strategies. Patient and healthcare data ('health data') that is crucial for informing pandemic response strategies includes case numbers, case characteristics including co-morbidities, patient outcomes (recuperation and adverse events), incubation and infection durations, genomic information, phenotypic information, treatment, and response data, as well as healthcare capacity and workforce data.

A core component of ensuring a health system has the capability to share data between institutions and jurisdictions is the standards that underpin data collection, terminology, storage and sharing processes. These standards underpin interoperability in a health system and enable access and sharing of health data in a useful and timely manner to inform decision making.[150]

The benefits of improved data sharing can be substantial. The ongoing annual benefits realised from various levels of interoperability in Australia were modelled in 2007 to be between $348 million and $2.1 billion (expressed in 2002–2003 Australian Dollars).[151] Benefits to both healthcare providers and society are expected to accrue from improved interoperability.

149 OECD (2015) Health Data Governance: Privacy, Monitoring and Research. OECD, Paris. <https://www.oecd.org/health/health-systems/Health-Data-Governance-Policy-Brief.pdf> (accessed 29 March 2022); Wan KK, Davis D, Lee TN, Ford-Scheimer SL, Andreu AL, Bietrix F, Bryans J, Castro MT, Chiba N, Faupel-Badger JM, Haynes B (2022) A call to action for translational sciences in COVID-19 and future pandemics. Nature Reviews Drug Discovery 21(3), 165-166.

150 Australian Digital Health Agency (2021) Draft National Healthcare Interoperability Plan. Australian Digital Health Agency, Canberra; Healthcare Information and Management Systems Society (2021) HIMSS Dictionary of Healthcare Information Technology Terms, Acronyms and Organizations. <https://www.himss.org/resources/interoperability-healthcare> (accessed 29 March 2022).

151 Sprivulis P, Walker J, Johnston D, Pan E, Adler-Milstein J, Middleton BB, David W (2007) The economic benefits of health information exchange interoperability for Australia. Australian Health Review 31, 531-539.

2.6.2 Current context

Australia faces data sharing limitations due to the varying governance of health systems within and across jurisdictions, and the inconsistent adoption of technologies and standards. This limits timely and well-informed policy decision making, especially during pandemics. *The Global Health Security Index (GHSI) 2021 Report* scored Australia 66.7 (out of 100) on the coverage and usage of electronic health records. Comparatively, several high-income countries scored above 80 for this metric.[152]

Australia has existing strengths in the development of novel technologies that integrate diverse data inputs for policy decision-making across the health system, but this is not as mature for pandemic responses. Novel technologies for data sharing include the use of natural language processing and machine learning to rapidly synthesise published global research (e.g., the 'living evidence' model, which is a world first end-to-end, closed-loop evidence system for near real-time updating of systematic reviews and clinical practice guideline recommendations within the Australian health system).[153]

However, stakeholders noted that there are multiple limitations with access and sharing of health data in Australia for decision making, including: varying jurisdictional legal and privacy frameworks, an inability to share identifiable information, the completeness of routinely collected datasets, and difficulty utilising non-traditional forms of data outside health that can have high value in pandemic responses (e.g., behavioural and mobility data, and data on animal and environmental health).

As part of the *National Digital Health Strategy*,[154] the Australian Digital Health Agency has developed a *Draft National Healthcare Interoperability Plan* (the Plan) which was released at the end of 2021 for consultation.[155] The Plan outlines the current state of interoperability in Australia and identifies priority actions to foster a more connected healthcare system. While the Plan sets the direction for a nationally coordinated future state for the entire health system, there are opportunities for technology-enabled interventions that can be implemented in parallel with the Plan to satisfy data sharing needs for pandemic preparedness.

152 Bell JA, Nuzzo JB (2021) Global Health Security Index: Advancing collective action and accountability amid global crisis. <https://www.ghsindex.org/wp-content/uploads/2021/12/2021_GHSindexFullReport_Final.pdf> (accessed 29 March 2022).

153 Australian Living Evidence Consortium (2020) About Living Evidence – Australian Living Evidence Consortium. <www.livingevidence.org.au> (accessed 29 March 2022).

154 Australian Digital Health Agency (2017a) National Digital Health Strategy. Australian Digital Health Agency, Canberra.

155 Australian Digital Health Agency (2017b) Framework for Action: How Australia will deliver the benefits of digitally enabled health and care. Australian Digital Health Agency, Canberra. <https://www.digitalhealth.gov.au/sites/default/files/2020-11/Framework_for_Action.pdf> (accessed 29 March 2022); Australian Digital Health Agency (2021).

2.6.3 Vision and recommendations

2030 Vision: Australia has national health data standards that are implemented in all jurisdictions and have adaptable guidelines for pandemic responses. These underpin health data collection systems that are interoperable, allowing for the safe, efficient and timely transfer of data insights. These developments enable the use of non-health and sensitive data as de-identified insights to inform government decision making during pandemics.

Recommendation 18: Develop national pandemic data standards to streamline data collection and sharing

Australia's health system does not have uniform data standards, and each jurisdiction collects and presents health data in different formats making it difficult to exchange data across systems.[156] This is exacerbated during response to a pandemic, especially for novel pathogens, as these standards are often developed in real-time, and independently in each jurisdiction (and sometimes independently in institutions).

Data recording and messaging standards (i.e., technology for standardising communication at the point of data collection) are needed to improve data quality at the point of entry, which is important for enabling interoperability. This allows data that is already routinely collected to be reused across the system without significant manual intervention.

Specific pandemic response data collection standards and implementation guides could be developed for major diseases caused by each of the priority viral families (see Table 2). Implementation guides, with specific pandemic use cases and adaptable fields for data collection (requiring minor updates in terminology), would prevent the need to develop new processes during a pandemic. For these standards to be effective, they require supporting legislation in all jurisdictions.

The burden of adopting the standards should not be greater than benefits generated. Engaging with existing data authorities and key stakeholders in standards development, and providing implementation incentives to health providers, would assist universal adoption.

Development can be streamlined by building on existing initiatives, for example:

- Expanding the remit of the Australian Digital Health Agency to build on the digital standards catalogue it is developing to include data standards to support a pandemic response.
- Using existing standards in various stages of implementation across Australia as a foundation (e.g., SNOMED CT for clinical data and HL7 FHIR for exchanging information (see Case study 6)).
- Aligning national standards with international standards to aid global collaboration.

156 Australian Government Department of Health (2020b) National Contact Tracing Review. Department of Health, Canberra. <https://www.health.gov.au/resources/publications/national-contact-tracing-review> (accessed 29 March 2022).

Case study 6: HL7 v2 and HL7 Fast Healthcare Interoperability Resources

Exchange of pathology reports between different health systems is an example of successful data sharing in Australia. All hospitals and most primary health clinics in Australia can receive electronic pathology reports using the HL7 v2 standard. However, HL7 v2 is a data standard developed in the 1980s for use by the computer systems of the time and is limited in how information can be exchanged and reused – particularly beyond pathology results.

The Fast Healthcare Interoperability Resources (FHIR) standard was accredited in 2019 and is now mandated in the USA under the *21st Century Cures Act* to ensure patient data is available across institutions.[157] The impact of this application has seen users aggregate and access personal health data on their mobile devices, and helped payers and providers improve clinical quality, cost and care management outcomes.[158] FHIR has associated standards for incorporating clinical data and is adaptable to incorporate specific modules to ensure interoperability for a particular set of applications (e.g., a pandemic response data collection standard and implementation guide).

Since 2017, CSIRO's Australian e-Health Research Centre has been working to develop a *FHIR Implementation Guide* for the primary health sector. As this develops and is implemented by software vendors, this will greatly increase the ability to exchange patient data between healthcare providers.

Recommendation 19: Improve capabilities to link health data with non-health data

Australia has limited capacity to utilise non-health data to inform pandemic preparedness and responses. Non-health data valuable for decision making during pandemics includes geo-referenced socio-economic, intervention compliance, movement, and environmental data. Successfully linking health and non-health data can help to anticipate patterns of spread during pandemics, provide projections on the success of interventions, and inform response decision making by utilising predictive modelling and epidemiology methodologies. This can provide additional (often near real-time) insights on behaviours and activities, contributing to the ability to assess the effectiveness of public health interventions.

Linking health data with non-health data at a national level to inform decision making is only possible where there is consistency in ethics requirements, government approvals, and legal instruments across jurisdictions.[159] As this is often difficult to achieve, health and non-health data linkage projects are often limited to research groups. The development of partnerships between research, private organisations that own the non-health data, and governments are needed to enhance the utilisation of such resources (see Case study 7).

Governments in Europe and Asia have data use agreements and transparency guidelines to enable the sharing of de-identified aggregate data from private organisations for pandemics and natural disaster responses.[160] These collaborations require coordinated information exchanges between government and private organisations, and strict measures to protect and ensure cybersecurity.

157 National Archives Federal Register (2020) 21st Century Cures Act: Interoperability, Information Blocking, and the ONC Health IT Certification Program. <https://www.federalregister.gov/documents/2020/08/04/C2-2020-07419/21st-century-cures-act-interoperability-information-blocking-and-the-onc-health-it-certification> (accessed 29 March 2022).

158 Health IT Analytics (2022) FHIR Interoperability Basics: 4 Things to Know. <https://healthitanalytics.com/news/4-basics-to-know-about-the-role-of-fhir-in-interoperability> (accessed 29 March 2022).

159 Australian Law Reform Commission (2011) Australian Privacy Law & Practice – Key Recommendations for Health Information Privacy Reform. Australian Law Reform Commission, Canberra. <https://www.alrc.gov.au/news/australian-privacy-law-practice-key-recommendations-for-health-information-privacy-reform/> (accessed 29 March 2022).

160 Lai S, Bogoch II, Ruktanonchai NW, Watts A, Lu X, Yang W, Yu H, Khan K, Tatem AJ (2020) Assessing spread risk of Wuhan novel coronavirus within and beyond China, January-April 2020: a travel network-based modelling study. MedRxiv; Maas P, Iyer S, Gros A, Park W, McGorman L, Nayak C, Dow PA (2019) Facebook Disaster Maps: Aggregate Insights for Crisis Response & Recovery. KDD 19, 3173.

Case study 7: Mobile phone data used to inform and evaluate public health interventions for COVID-19

During the COVID-19 pandemic, governments around the world collaborated with private companies, most notably mobile network operators, social media and location intelligence companies, to estimate the potential effectiveness of interventions and forecast the spread of disease.

Countries that used this data include Australia, Austria, Belgium, Chile, China, Germany, France, Israel, Italy, South Korea, Spain, United Kingdom, and the United States.[161]

Mobile phone data was used in South Korea to monitor both adherence to public health interventions and the spread of disease as public health interventions were eased.[162] This has been reported as being highly effective with supporting high compliance with pandemic rules and South Korea's response cited as 'world leading.'[163]

Recommendation 20: Design and integrate smart analytics that can share and analyse sensitive data at a national level

Australia has limited capacity to utilise sensitive data at a national level to inform pandemic preparedness and response due to complex legal, privacy and ethics arrangements. Sensitive data can include patient outcomes, vaccination status, and pre-existing conditions. Analysing these data types alongside other health data could provide continuous real-time insights to inform pandemic responses in a secure manner (e.g., variant tracking, clinical impacts of novel diseases and variants, geographical modelling of spread of disease, and real-time evaluation of the impact of public health interventions).

While analysing complete datasets that include this sensitive information would offer the greatest value, this would require more substantial legislative and governance changes that support broader data sharing arrangements; a worthy longer-term goal. In the nearer-term, developments in smart analytics systems and software technology can analyse sensitive data within the system it is collected (either at a healthcare provider or jurisdiction level) and then provide valuable deidentified summary data for government decision making at a national level. Such platforms can offer value at the broader healthcare level and be rapidly launched and adapted in response to a pandemic.

The core elements to integrating smart analytics into Australia's health data sharing processes are:

- Infrastructure to allow analytics on distributed data sources (i.e., cloud systems analyse data within each organisation's account rather than copying all data to a single location for analysis).
- Smart analytics software that is responsive to different input data granularity from different sources (e.g., aggregate data and de-identified individual-level data).
- Interoperable systems to provide continuous real-time insights to the health system (e.g., FHIR).
- Dynamic access permissions that allow real-time access and control of the data by the contributing organisations.

161 Oliver N, Lepri B, Sterly H, Lambiotte R, Deletaille S, De Nadai M (2020) Mobile Phone Data for Informing Public Health Actions across the COVID-19 Pandemic Life Cycle. Science Advances 6.

162 Embassy of the Republic of Korea (2020) Bilateral Relations: Flattening the curve on COVID-19: How Korea responded to a pandemic using ICT. <https://overseas.mofa.go.kr/gr-en/brd/m_6940/view.do?seq=761548> (accessed 29 March 2022); Chekar SK, Moon JR, Hopkins M (2021) The secret to South Korea's COVID success? Combining high technology with the human touch. The Conversation. <https://theconversation.com/the-secret-to-south-koreas-covid-success-combining-high-technology-with-the-human-touch-170045> (accessed 29 March 2022).

163 Dighe A, Cattarino L, Cuomo-Dannenburg G, Skarp J, Imai N, Bhatia S, Gaythorpe KA, Ainslie KE, Baguelin M, Bhatt S, Boonyasiri A (2020) Response to COVID-19 in South Korea and implications for lifting stringent interventions. BMC Medicine 18, 321; Ryu S, Hwang Y, Yoon H, Chun BC (2020) Self-Quarantine Noncompliance During the COVID-19 Pandemic in South Korea. Disaster Medicine Public Health Preparation 12, 1-4.

3 Health system characteristics for pandemic preparedness

While this report focuses on the role that S&T can play in strengthening Australia's pandemic preparedness, S&T is only one element of the health system and is co-dependent on a range of multidisciplinary activities to be successfully developed and implemented.

This chapter summarises other key characteristics of a health system that supports strong pandemic preparedness. These summaries are intended to describe best-practice, rather than assess Australia's current state. A range of existing systems-focused reports focus on the latter, including *The New Frontier – Delivering better health for all Australians,*[164] *Biotechnology in Australia – Strategic plan for health and medicine,*[165] *Joint External Evaluation of IHR Core Capacities of Australia,*[166] and a range of reports from MTPConnect.[167]

Stakeholders noted that no country is excelling across all characteristics and Australia performs comparatively well by international standards. Most national challenges raised by stakeholders related to national coordination and community-centric engagement.

3.1 National coordination of governance and strategies

Strong health systems involve states, territories and regions aligning to national strategies with minimal inter-jurisdictional competition for funds and limited system complexity. Relevant strategies include public health response strategies, recovery strategies, surge workforce planning, data sharing strategies and R&D strategies. These plans are most effective when informed by a diverse range of skills including epidemiology, public health, primary healthcare, One Health, social sciences, ethics, science and technology translation, communication and engagement.[168]

Nationally consistent health systems, processes, data formats and decision-making bodies also make it easier for international organisations to collaborate with a country, and to assess the relevance and feasibility of applying trial results and implementation practices from one country to another.

164 Parliament of the Commonwealth of Australia (2021) The New Frontier – Delivering better health for all Australians. House of Representatives Standing Committee on Health, Aged Care and Sport, Canberra. <https://parlinfo.aph.gov.au/parlInfo/download/committees/reportrep/024755/toc_pdf/TheNewFrontier-DeliveringbetterhealthforallAustralians.pdf;fileType=application%2Fpdf> (accessed 30 March 2022).

165 Australian Government Department of Health (2022) Biotechnology in Australia – Strategic plan for health and medicine. Department of Health, Canberra. <https://www.health.gov.au/sites/default/files/documents/2022/03/biotechnology-in-australia-strategic-plan-for-health-and-medicine.pdf> (accessed 7 April 2022).

166 WHO (2018) Joint External Evaluation of IHR Core Capacities of Australia. WHO, Geneva.

167 MTPConnect (2022) MTPConnect Reports. <https://www.mtpconnect.org.au/reports> (accessed 30 March 2022).

168 Bedford J, Farrar J, Ihekweazu C, Kang G, Koopmans M, Nkengasong J (2019) A new twenty-first century science for effective epidemic response. Nature 575(7781), 130-136.

3.2 Coordination of clinical trials

A coordinated clinical trial network and associated ethics processes can streamline research and avoid duplication of effort during the response to a pandemic. Best practice involves a networked approach to clinical trials that is available at a jurisdictional, national, and global level. The UK's Clinical Research Network Coordinating Centre is one example of a clinical network that operates across geographies and therapy areas and is led by a centralised coordinating body.[169]

While distributed clinical trials can promote competition and in turn high quality results, multiple competing studies can increase the burden on trial patients, particularly where the national population and total number of affected individuals is limited. Therefore, public funding available for clinical trials could be prioritised through funding arrangements to support national and jurisdictional R&D goals.[170]

A network of coordinated clinical trials that are responsive in a pandemic should be enabled by:

- Digitisation of trial information through purpose-built systems to store and analyse patient data across international and jurisdictional borders.[171]
- Development of fast-track procedures for research organisations, government agencies and clinical trial administrators prior to a pandemic.[172]
- A comprehensive database of trials that brings together multiple different registers and allows users to access up-to-date information on research developments and emerging products.[173]
- Coordinated and streamlined cross-jurisdictional ethics processes that can be adapted for rapid evaluation in response to pandemic needs.

3.3 International cooperation and coordination

Pandemics are a global risk and require strong international relationships to navigate successfully. International purchasing partnerships can secure resources in a climate when supply chains may be disrupted.[174] Other international partnerships (e.g., global surveillance programs or R&D collaborations) can expose local researchers and companies to world-leading capabilities as well as up-to-date information about health systems and regulatory requirements in markets outside of Australia.

Best practice international collaboration includes strong linkages with global initiatives such as CEPI, The Global Fund and the WHO-led process towards a convention or agreement for strengthening pandemic prevention, preparedness, and response.[175] Further, aligning to international standards (e.g., data forms, data sharing protocols or personal protective equipment standards) assists in efficient collaborations and helps to ensure local innovations adhere to the needs of export markets.

Proactively working to build regional and global resilience to infectious disease threats can also reduce the indirect economic losses associated with outbreaks that do not become established within the national border. During the 2003 SARS outbreak, while Australia only reported six confirmed cases of SARS and no deaths, the economy was disrupted as many major trading partners were in the regions most affected.[176] During the June quarter of 2003, Australia's export volumes declined by around 4.4% and short-term visitor arrivals declined by 9% between March and August compared to the previous year.[177]

International collaboration is also important to support equitable distribution of essential pandemic response tools and equipment, including vaccines, therapeutics, diagnostics and personal protective equipment. An emerging lesson of the COVID-19 pandemic is that a failure to collaborate effectively can prolong the pandemic and increase the risk of new variants emerging.

169 National Institute for Health Research (2022) Clinical Research Network. <https://www.nihr.ac.uk/explore-nihr/support/clinical-research-network.htm> (accessed 30 March 2022).

170 Bowen AC, Tong SY, Davis JS (2021) Australia needs a prioritised national research strategy for clinical trials in a pandemic: lessons learned from COVID-19. The Medical Journal of Australia 215(2), 56.

171 MTPConnect (2020a) MTPConnect COVID-19 Impact Report 2nd edition. MTPConnect, Melbourne. <https://www.mtpconnect.org.au/images/V5_MTPC_COVID-19%20Phase%202%20Report_Web%20Version.pdf> (accessed 30 March 2022).

172 Seidler AL, Aberoumand M, Williams JG, Tan A, Hunter KE, Webster A (2021) The landscape of COVID-19 trials in Australia. Medical Journal of Australia.

173 National Institute for Health Research (2021) NIHR launches innovative searchable database of global clinical trials. <https://www.nihr.ac.uk/news/nihr-launches-innovative-searchable-database-of-global-clinical-trials/27660> (accessed 30 March 2022).

174 Haldane V, Jung AS, Neill R, Singh S, Wu S, Jamieson M, Verma M, Tan M, De Foo C, Abdalla SM, Shrestha P (2021) From response to transformation: how countries can strengthen national pandemic preparedness and response systems. BMJ, 375.

175 WHO (2021c) World Health Assembly agrees to launch process to develop historic global accord on pandemic prevention, preparedness and response. <https://www.who.int/news/item/01-12-2021-world-health-assembly-agrees-to-launch-process-to-develop-historic-global-accord-on-pandemic-prevention-preparedness-and-response> (accessed 30 March 2022).

176 Australian Treasury (2003). The economic impact of Severe Acute Respiratory Syndrome. Australian Treasury, Canberra.

177 Australian Treasury (2020). Ministerial Submission - Economic Impacts – Severe Acute Respiratory Syndrome. Australian Treasury, Canberra.

3.4 Community-centric engagement and trust in institutions

Pandemics start and end in communities, with community voices providing the local realities that are essential to making sustained change during and between pandemics.[178]

Strong health systems are capable of drawing on social and behavioural science to segment populations in a timely fashion to tailor age, location, occupation, language, and culture-appropriate interactions and messaging. Governments, health systems, companies, research institutions, and non-governmental organisations that maintain strong relationships with these communities in a systemic way can effectively co-develop, implement and monitor public health interventions and technologies. Guidelines for these approaches can form part of a national emergency response plan and be customised at local levels as needed.

These forms of tailored engagement assist in acquiring and maintaining institutional trust which helps communities cooperate with public health measures, develop ownership over reducing the drivers of infectious diseases, and reduce the spread of misinformation.

Consistent, comprehendible and transparent communication of rapidly evolving statistics, recommendations and requirements, including the rational, is key.[179] While this responsibility typically falls on larger institutions, in many instances smaller communities and individuals have demonstrated the ability to act faster in developing data visualisation platforms. Governments that can rapidly endorse or work with these community-led initiatives can further facilitate trust building and timely response activities.

3.5 Resilient infrastructure and supply chains

Australia imports over 90% of its medicines[180] and no country – even those with substantial manufacturing sectors – produces every input to their medical and health supply chains. Given this, international partnerships, effective procurement policies and comprehensive medical stockpiling strategies are critical to ensuring the continuity of essential health services and systems. Consideration could also be given to how stockpiles are managed and whether there are opportunities to leverage capabilities and resources to assist neighbouring countries (e.g., through emergency donation or pooled procurement arrangements).

Building adaptable industry manufacturing capabilities can also reduce exposure to international trade and supply chain disruptions. While focused on commercial products, these facilities can respond in a timely manner when called upon during a pandemic response.

In addition to ensuring Australians have access to goods and services, resilient supply chains also protect key revenue sources. For example, medicinal and pharmaceutical exports fell by 51% from June 2020 to June 2021 as a result of COVID-19 related industry restrictions both in Australia and in priority export markets.[181]

Resilient infrastructure and supply chains are equally important for the research sector. Resilience can be built by ensuring platform capabilities (e.g., biobanks, physical containment facilities, clinical trials and the data standards that help connect them) are networked and link with other research institutions and downstream manufacturers.

178 WHO (2021d) Community-centred approaches to health emergencies: progress, gaps and research priorities. <https://cdn.who.int/media/docs/default-source/blue-print/who-covid-19-social-science-in-outbreak-report_15.08.21.pdf?sfvrsn=ddbb00b3_9&download=true> (accessed 30 March 2022).

179 Abdalla SM, Koya SF, Jamieson M, Verma M, Haldane V, Jung AS, Singh S, Nordström A, Obaid T, Legido-Quigley H, McNab C (2021) Investing in trust and community resilience: lessons from the early months of the first digital pandemic. BMJ, 375.

180 Institute for Integrated Economic Research (2020). Australia's Medicine Supply <https://sldinfo.com/2020/02/australias-medicine-supply-a-case-study-in-security-and-resilience/> (accessed 30 March 2022).

181 ABS (2021) International Merchandise Trade, Preliminary, Australia <https://www.abs.gov.au/statistics/economy/international-trade/international-merchandise-trade-preliminary-australia/latest-release> (accessed 30 March 2022).

3.6 Responsive regulatory and funding systems

Inconsistent regulations across countries can limit participation in international supply chains. While internationally consistent requirements are a worthy goal, it is not a short-term reality. Regulators who can adapt regulations in times of supply chain disruption, while maintaining strong safety standards, can help to ensure the efficient development of medical countermeasures locally. High performing regulators also work strongly with regulators and technology developers from other countries to share information, including new product assessments.

When it comes to financing medical countermeasures, the revenue generated from sales may not be sufficient to pay for the cost associated with R&D, manufacturing and approval. Further, vaccines and antimicrobial therapeutics are generally undervalued by reimbursement systems relative to the benefits they bring to society.[182] Stakeholders noted novel regulatory and value-based reimbursement models can help address this market failure by providing more predictable revenue for manufacturers.

International examples of novel funding approaches either actioned or being considered include:

- **Priority review vouchers (USA)** – These allow the FDA to grant companies that obtain approval for a drug for a tropical disease a one-time transferable priority review voucher for an unrelated future drug.[183]
- **Orphan drug designations (USA and Europe)** – These offer benefits such as extended market exclusivity, clinical trial subsidies and regulatory assistance.[184]
- **The National Institute for Health and Care Excellence (NICE) pilot program (UK)** – This pilot uses a model where companies are paid an annual subscription fee to supply as much or as little of an agreed antimicrobial as needed. The payment is based on the expected value of the antimicrobial to the health system and population as a whole, rather than volume of sales.[185]

Where government investments are made directly into R&D, stakeholders noted best practice involves considering the full potential pipeline of work, rather than short-term investments in single phases of projects. This could include performance-based contracting with clear stage-gates for review to provide research and industry with greater certainty while funding agencies maintain appropriate exit rights. The use of offtake agreements and advanced local purchasing commitments in the event that a technology matures into production were also noted as key tools for successful funding arrangements.

182 MTPConnect (2020b) MTPConnect Fighting Superbugs: a report on the inaugural meeting of Australia's antimicrobial resistance stakeholders. MTPConnect, Melbourne. <https://www.mtpconnect.org.au/images/mtpc_fighting_superbugs_web_230920.pdf> (accessed 30 March 2022); Shawview Consulting (2021) Valuing Vaccines: Ensuring Australia's access to vaccines today and tomorrow. Shawview, Sydney. <https://www.shawview.com/_files/ugd/8a9719_c61751a436ac49638ceed8b75cbf62af.pdf> (accessed 30 March 2022).

183 MTPConnect (2020b).

184 MTPConnect (2020b).

185 Policy Research Unit in Economic Evaluation of Health and Care Interventions (EEPRU) (2022) Assessing the value of novel antimicrobials under new payment models. EEPRU, Sheffield. <https://eepru.sites.sheffield.ac.uk/projects/assessing-the-value-of-novel-antimicrobials-under-new-payment-models#h.gh7kpdll1kzu> (accessed 13 April 2022).

4 Implementation considerations

This report identifies key S&T areas for strengthening Australia's pandemic preparedness. However, transitioning towards an integrated cycle of prevention, detection, response and recovery will require collaborative planning with other adjacent sectors and systems. There are several questions that will require ongoing consideration in parallel with the recommendations described in this report, including:

- How can pandemic preparedness efforts feed into adjacent national systems with similar needs (e.g., emergency planning for climate events, biosecurity and AMR)?
- How can these S&T solutions assist non-health related industries improve their pandemic preparedness (e.g. hands-free equipment, airflow in building design and use of digital tools)?
- What wider health system characteristics (see Section 3) can be strengthened to support the response to a pandemic?
- What additional nuances to the recommendations arise when you apply this structured system-level thinking to individual viral families or viruses?
- How are viral risk profiles likely to change over time and how would these impact Australia's S&T priorities?

The emergence of large-scale viral outbreaks is inevitable and future pandemics will continue to have significant direct and indirect impacts for Australia. The current global focus and investments in pandemic preparedness is an opportunity to strengthen Australia's capabilities to minimise the impacts of future pandemics.

In developing this report, CSIRO brought together diverse stakeholders including Australian and international experts from industry, research and government to discuss what S&T investments would have the most impact on Australia's pandemic preparedness. This approach reflects the importance of the collaborative effort that will be needed to refine and implement the report's recommendations.

National mission-oriented initiatives – those bringing together diverse organisations and skillsets to tackle a single significant challenge or objective – can be a useful mechanism for generating the sufficient scale and system efficiencies required across these interconnected S&T areas. CSIRO stands ready to support Australia's governments and health system to pursue these opportunities and capitalise on the benefits that these S&T areas provide.

Appendix A – Consulted organisations

CSIRO would like to thank the following organisations for their contributions to the project through interviews, survey responses and reviews. The insights expressed throughout this report were developed by considering the collective views obtained alongside independent qualitative research and may not always align with the specific views of one of the consulted individuals or organisations.

APPRISE Centre of Research Excellence

AstraZeneca Australia

Australasian Virology Society

Australian Digital Health Agency

Australian Government Department of Defence

Australian Government Department of Foreign Affairs and Trade

Australian Government Department of Health and Aged Care

Australian Government Department of Home Affairs

Australian Government Department of Industry, Science and Resources

Australian Government Department of Prime Minister & Cabinet

Australian Infectious Disease Network

Barwon Health

BioCina

BioCurate

Burnet Institute

Centre of Excellence for Biosecurity Risk Analysis

CEPI

Certara

CSL

Department for Health and Wellbeing (SA)

Department of Health (TAS)

Department of Health (VIC)

DMTC

Ellume

Foundation for Innovative New Diagnostics (FIND)

Government of South Australia

Griffith University

GSK

Herston Infectious Diseases Institute

James Cook University

Lumos Diagnostics

Medicines Australia

Medicines Development for Global Health

Menzies School of Health Research

Monash University

MSB Consulting

MTPConnect

National Centre for Immunisation Research and Surveillance

NSW Health

Office of the Chief Scientist

Office of the National Data Commissioner

Opal BioSciences

Patheon

Pfizer Australia

Planet Innovation

PPB Technology

Productivity Commission

Public Health Laboratory Network

Resolve to Save Lives

Roche Diagnostics Australia

Seqirus

South Australian Health and Medical Research Institute

Swinburne University of Technology

Sypharma

The Kirby Institute

The Peter Doherty Institute for Infection and Immunity

The University of Melbourne

The University of Queensland

The University of Sydney

The University of Western Australia

The Westmead Institute for Medical Research

Therapeutic Goods Administration

Therapeutic Innovation Australia

Translational Research Institute

Walter and Eliza Hall Institute

Appendix B – Survey results

In October 2021, a short survey was sent to 102 individuals across the Australian and international infectious disease ecosystem. Survey recipients were identified by the project Steering Committee and were invited to identify and assess priority S&T areas that could help improve national and global resilience to infectious diseases by 2030. Participants were asked to consider where further economic investment and research efforts would provide the greatest improvement for Australia's pandemic preparedness and how progress can be enabled in these areas.

Participants were asked to identify the top five priority S&T areas (from a list of 22). A short description accompanied each area in Table 6 to help further describe the scope of the topic.

There were 30 respondents to the survey and the Steering Committee assisted CSIRO in refining the top responses into the S&T areas explored in this report.

Table 6: Summary of survey results

S&T AREA	OCCURRENCES IN TOP 5
Early-stage diagnostics	14
Platform vaccine and therapeutic manufacturing capabilities	14
Data sharing between health bodies and research	10
Social science informed community engagement (public health measures)	9
Next generation sequencing and genome analytics	9
Preclinical vaccine and therapeutics studies into targeted viral families	8
Social science informed community engagement (risk reduction)	7
Animal models	7
Data acquisition systems for clinical trials	6
Big data analytics for risk identification	5
Pathogen characterisation	4
Spill-over risk analysis mapping	4
Serosurveillance	4
Quantitative systems pharmacology modelling and simulation	4
Modelling of pathogen movement to inform design of built environments	4
Virtual biobanks	3
Syndromic surveillance	3
Digital contact tracing	3
Individual based models and simulation	3
Environmental surveillance	2
Virtual healthcare delivery mechanisms	2
Modelling of low bio-risk locations for agriculture and aquiculture	0

Appendix C – Prioritisation of viral families

WHO's R&D Blueprint for Action to Prevent Epidemics and *CEPI's Priority diseases* provide a global perspective on viral families that pose a high risk of epidemics.[186] In order to assess pandemic potential for the Australian context, this report used the list of priority diseases identified by WHO and CEPI and evaluated the current geographical spread, zoonotic or human transmission modes, and transmission risk.[187] This was supported by expert stakeholder opinion.

VIRAL FAMILY	DISEASE EXAMPLES	WHO/CEPI PRIORITY	GEOGRAPHICAL SPREAD	ZOONOTIC OR HUMAN TRANSMISSION	TRANSMISSION RISK FACTORS	AUSTRALIAN SPECIFIC RISKS
Arenaviridae	Lymphocytic choriomeningitis, Lassa fever, and Junin, Machupo, Guanarito, Sabia[188]	WHO	Africa, Asia, Europe, and North America, South America[189]	Zoonotic and human (direct contact with bodily fluids)[190]	• A long infectious period.[191] • Human transmission can occur through exposure to infected rodent excretions.[192] Rodent control is effective in disease prevention.[193] • All arenaviruses can form infectious aerosols.[194]	• Lymphocytic choriomeningitis has been found in Australia[195]
Coronaviridae	COVID-19, MERS[196], SARS[197]	WHO CEPI	Global	Zoonotic and human	• Largely respiratory viruses that can be transmitted by droplets and aerosols.[198] • Hundreds of coronaviruses circulating among animals.[199] • Most animal-to-human coronaviruses are transmitted via the faecal-oral route.	• Potential for cross-species transmission from Australia's endemic bat population.[200] • Camels are suspected to be the primary source of MERS infection and Australia has one of the largest populations of wild camels in the world.[201]
Filoviridae	Ebola virus disease, Marburg virus disease	WHO CEPI	Africa, Asia[202]	Zoonotic and human (direct contact with bodily fluids)[203]	• Secondary outbreaks can occur from nosocomial infection.[204] • Disease spill-over occurs in humans exposed to wildlife reservoirs.[205] • High mortality rate and therefore likely self-limiting.[206]	• None identified.
Flaviviridae	Dengue fever, Japanese encephalitis, Zika, West Nile fever	WHO	Global[207]	Zoonotic (arthropods) and human (relatively uncommon and via bodily fluids)[208]	• High rate of asymptomatic cases; however, some cases can result in severe life-threatening disease.[209] • Domesticated vertebrate animals play a role supporting transmission to humans and the introduction of new viral species.[210] • Risk extension of vector range with increasing impact of climate change.	• Dengue fever occurs in tropical areas, including northern Australia.[211] • In 2022, Japanese encephalitis was detected in southern areas of Australia.[212]
Nairoviridae	Crimean-Congo haemorrhagic fever, Dugbe	WHO	Africa, Asia[213]	Zoonotic (arthropods and able infect livestock animals) and human (relatively uncommon and via bodily fluids) [214]	• Tick-borne viruses that are globally distributed.[215] • Historically high morbidity and mortality.[216]	• None identified.

Appendix C continued on next page

186 CEPI (2020) Priority diseases. <https://cepi.net/research_dev/priority-diseases/> (accessed 10 November 2021); WHO (2016b).

187 Brookes VJ, Hernandez-J M, Black PF, Ward MP (2014) Preparedness for emerging infectious diseases: pathways from anticipations to action. Epidemiology and Infection 143(10), 2043-2058; Grange ZL, Goldstein T, Johnson CK, Anthony S, Gilardi K, Daszak P, Olival KJ, O'Rourke T, Murray S, Olson SH, Togami E, Vidal G, Mazet JAK (2021) Ranking the risk of animal-to-human spill-over for newly discovered viruses. PNAS 118(25).

188 McCormick JB (2008) Lassa, Junin, Machupo and Guanarito Viruses. Encyclopedia of Virology, 203-212.

189 McCormick (2008).

190 CDC (2021b) Arenaviruses (Arenaviridae). <https://www.cdc.gov/vhf/virus-families/arenaviridae.html> (accessed 23 February 2022).

191 CDC (2021b).

192 CDC (2021b).

193 Virus Pathogen Resource (n.d. -a) About the Arenaviridae family. <https://www.viprbrc.org/brc/aboutPathogen.spg?decorator=arena> (accessed 23 February 2022).

194 Virus Pathogen Resource (n.d. -a).

195 Holdsworth RL, Downie E, Georgiades MJ, Bradbury R, Druce J, Collkett J (2022) Lymphocytic choriomeningitis virus in western New South Wales. The Medical Journal of Australia 216(2), 71-72.

196 Middle East Respiratory Syndrome.

197 Severe Acute Respiratory Syndrome.

198 Dutch (2008).

199 National Institute of Allergy and Infectious Diseases (2021); Payne S (2017a).

200 Peel et al. (2019).

201 Centre for Invasion Species Solutions (2021).

202 WHO (2021) Ebola virus disease. WHO, Geneva. <https://www.who.int/news-room/fact-sheets/detail/ebola-virus-disease> (accessed 28 February 2022).

203 CDC (2021c) Filoviruses (Filoviridae). <https://www.cdc.gov/vhf/virus-families/filoviridae.html> (accessed 23 February 2022).

204 Languon S, Quaye O (2019) Filovirus Disease Outbreaks: A Chronological Overview. <https://journals.sagepub.com/doi/10.1177/1178122X19849927> (accessed 23 February 2022).

205 Languon et al. (2019).

206 Languon et al. (2019).

207 Pierson (2020).

208 North Dakota Department of Health (2016).

209 Pierson (2020).

210 Pandit et al. (2018).

211 Health Direct (2021) Dengue fever. <https://www.healthdirect.gov.au/dengue-fever> (accessed 23 February 2022).

212 Australian Government Department of Health (2022).

213 WHO (2013) Crimean-Congo haemorrhagic fever. <https://www.who.int/news-room/fact-sheets/detail/crimean-congo-haemorrhagic-fever> (accessed 20 February 2022).

214 Virus Pathogen Resource (n.d. -b) Nairoviridae. <https://www.viprbrc.org/brc/aboutPathogen.spg?decorator=nairo> (accessed 23 February 2022).

215 Virus Pathogen Resource (n.d. -b).

216 Virus Pathogen Resource (n.d. -b).

Appendix C continued – Prioritisation of viral families

VIRAL FAMILY	DISEASE EXAMPLES	WHO/CEPI PRIORITY	GEOGRAPHICAL SPREAD	ZOONOTIC OR HUMAN TRANSMISSION	TRANSMISSION RISK FACTORS	AUSTRALIAN SPECIFIC RISKS
Orthomyxoviridae	Influenza	–	Global	Zoonotic and human	• Highly infectious as transmission can occur in humans by aerosols and droplets.[217] • Viruses in this family in particular are pre-disposed to quickly and efficiently mutate to generate new strains.[218] • Viruses in this family have historically caused epidemics and pandemics in humans.[219]	• None identified.
Paramyxoviridae	Nipah virus infection, Hendra virus disease[220]	WHO CEPI	Asia, Australia[221]	Zoonotic and human	• Largely respiratory viruses transmitted by aerosols and contaminated surfaces.[222] • Historically high morbidity and mortality in humans.[223]	• Hendra virus disease currently poses a risk of infection from horses in north-eastern parts of Australia.[224] New variants of Hendra virus have been identified in host animals with greater geographic distribution.[225]
Phenuiviridae	Rift Valley fever	WHO CEPI	Africa	Zoonotic (arthropods) and human (contact with blood/ organs)[226]	• Highly pathogenic in humans, animals and plants. • Can be challenging to control transmission given the range of arthropod vectors.	• None identified.
Togaviridae (alphaviruses)	Chikungunya fever, Ross River fever, Eastern equine encephalitis, Western equine encephalitis, Venezuelan equine encephalitis	WHO CEPI	Global[227]	Zoonotic (arthropods, particularly blood sucking species)	• Infections are seasonal and are acquired in endemic areas.[228]	• Ross River fever is the most common insect-borne viral disease in Australia.[229]

217 MacLachlan (2016).
218 Payne (2017b).
219 Payne (2017b).
220 Measles and Mumps have been excluded from analysis due to existing effective vaccines.
221 Virus Pathogen Resource (2021).
222 Dutch (2008).
223 Thibault et al. (2017).
224 WHO (2022).
225 CSIRO (2022).
226 Kroeker AL Babiuk S, Pickering BS, Richt JA, Wilson WC (2020) Livestock Challenge Models of Rift Valley Fever for Agricultural Vaccine Testing. Frontiers in Veterinary Science 7.
227 European Centre for Disease Prevention and Control (2022).
228 Schmalijohn (1996).
229 Department of Health (2022).

Appendix D – Advantages and disadvantages of vaccine technologies

TECHNOLOGY	DESCRIPTION	ADVANTAGES	DISADVANTAGES	TECHNOLOGY MATURITY
RNA (mRNA or self-amplifying RNA)	Lipid encased RNA for translation *in vivo*. This technology does not require the nucleic membrane to be crossed.	• Self-amplifying RNA requires a lower dosage • No need to use viral products that may cause safety risks or compete with the antigen for immunodominance • Unlikely to cause disease • Common technologies (e.g., nucleic acid synthesis machinery) requires little alteration across vaccine target • Small footprint manufacturing	• More testing is required to determine the immune response timeframe for mRNA • Limited use in immunocompromised people • Poor product stability requiring cold chain infrastructure	• Growing maturity. • Commercial for COVID-19 with ongoing trials for other pathogens (e.g., Moderna is in Phase II clinical trials for HIV/AIDS). Self-amplifying RNA is in early-stage development.
DNA	Plasmid DNA containing genetic code is translated by cells to produce antigens *in vivo*.	• Unlikely to cause disease • Common technologies (e.g., nucleic acid synthesis machinery) requires little alteration across vaccine targets • Useful for inducing cyto-toxic T cell immune response	• Scale-up of manufacturing is expensive • Underlying risk of anti-DNA autoimmune responses • Potential for integration of viral DNA into host chromosomes • Must cross nuclear and cellular membrane (comparative to RNA), indicating a more difficult delivery pathway • Poor immunogenicity often recorded	• Early stage.
Subunit (Alternative subunits or recombinant protein)	A protein antigen is produced using recombinant technology from mammalian, insect, plant, bacterial or yeast host systems.	• Low dosage requirements • Longer term immune response • Recombinant proteins are likely to be the safest technology as no risk of causing disease	• Recombinant proteins have longer production timelines than mRNA • Recombinant proteins typically require adjuvants for optimal efficacy	• High. • Commercially available (e.g., Novavax for COVID-19 and Hepatitis B vaccine).
Viral vector (Replication incompetent or replication competent)	Genes of interest are inserted into a viral vector (e.g., adenovirus or vaccina). The gene of interest codes for a particular antigen.	• Scaled-up production can be low-cost • Higher immunogenicity than whole virus vaccines	• Can be less effective for those already infected with virus but efforts underway to overcome this • Replication competent are dependent on full replication • Risk of virus reverting to virulent form • Risk of evolution removing the gene of interest over time	• High. • Commercially available (e.g., Zabdeno for Ebola).

Appendix E – Alternatives to animal models

MODEL	DESCRIPTION	WHERE DOES THIS MODEL HAVE POTENTIAL REPLACE OR COMPLEMENT ANIMAL STUDIES?	WHAT ARE THE LIMITATIONS TO ANIMAL MODEL REPLACEMENT?
In vitro	Models replicate phenotypic expression of genetic differences, to test toxicity and efficacy at a cellular level.[230]	• Can be used to replace some animal model investigations at a cellular level for example, infection kinetics, host and cell tropism, and local cellular pathogenesis.[231] • Can determine appropriate concentrations of therapeutics (effective and non-toxic).	• Therapeutic dosage estimations are often verified in animals.[232] • Limited ability to model more complex biological systems.[233]
Ex vivo	Isolates human cells that are targeted by the virus for testing.	• Can be used to replace some animal model investigations at a cellular level for example, infection kinetics, host and cell tropism, and local cellular pathogenesis.[234] • Can allow for faster testing of antiviral treatments.[235] • Can determine appropriate concentrations of therapeutics (effective and non-toxic).	• Therapeutic dosage estimations are often verified in animals.[236]
Organoids	Builds on *ex vivo* cultures to produce a three-dimensional culture of cell interactions that exist within a natural organ.	• Can evaluate whether an antiviral treatment is likely to be effective in a specific group of patients (for example, high-risk infants).[237] • Human organ-on-a-chip devices could support rapid repurposing of existing antiviral drugs during a pandemic.[238] • Offers an advantage when studying infectious disease pathogenesis, given viruses often infect specific species or cell types.[239]	• Some techniques for collecting organoid samples are invasive and limited by the availability of patients and physicians. Non-invasive techniques are still under development.[240] • Limited ability to study multi-organ effects of disease and treatment.[241] • Dosage estimates and toxicity are still likely to require animal model studies.
Tissue explants	Uses extracted cells, preserved in their native three-dimensional structure, for testing of biological or mechanical factors.[242]	• Can study cell to cell or cell to pathogen interactions.[243] • Tissue blocks maintain their structure allowing for viral replication that mimics *in vivo* models.[244]	• Multiple tissue samples are required to overcome tissue heterogeneity.[245] • Experiment life is only 2 to 3 weeks due to sample degradation.[246] • Variation in samples amongst donors.[247]
Human challenge	Models the natural infection process of humans in a small sample group.	• Can be used to predict efficacy more accurately during the development of a vaccine or therapeutic.[248] • Can shorten the time to assess the efficacy of a new vaccine or treatment.[249]	• More restricted access and use due to safety, cost and ethical challenges.[250] • Not used for highly pathogenic diseases.[251] • Requires preliminary experiments to prove vaccine is safe and immunogenic before use in humans.[252]
Multi-omics	Systems immunology to triangulate multiple high throughput -omics approaches to study immune response and phenotype based on data from multiple patients.[253]	• Can offer accuracy advantages when studying human biology of complex diseases.[254]	• Animal model studies are still likely to be required.[255]
In silico	Mathematical and computer models used to identify and predict transmission patterns, candidates and host-pathogen interactions.[256]	• Can be used with other biotechnological tools, genome sequencing and clinical tests to significantly reduce vaccine development times.[257] • Large amounts of data can be analysed quickly and cost-effectively to speed early-stage candidate drug discovery.[258]	• Animal model studies are still likely to be required for product development.[259]

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