Dear inquiry,

My submission underscores the significance of Australia directing its attention towards preventing rather than just the preparation or 'cure' for future pandemics. Specifically, a focus on early detection for "Disease X" and how that will have co-benefits for medical care, non-pandemic public health and antimicrobial stewardship.

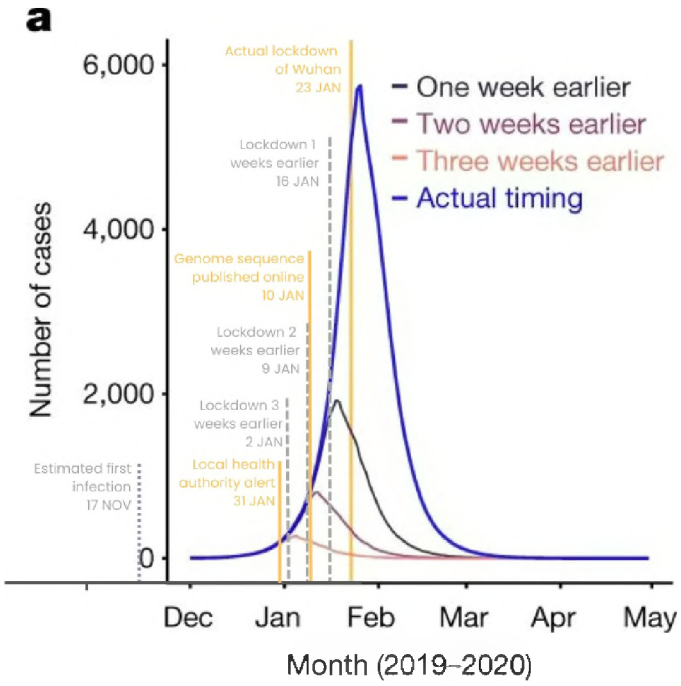
As a young Australian, COVID-19 was incredibly disruptive and I know my life would have looked wildly different if the initial SARS-CoV-2 outbreak wasn't allowed to become a pandemic. While obviously this inquiry should explore all the ways the government can better help individuals and communities in a future pandemic – even the best-managed pandemic will have terrible consequences. That's why I think the main goal should be pandemic prevention.

During the pandemic, I was in the process of finishing my degree majoring in Bioinformatics. It completely befuddled me why this amazing technology existed and me - an undergraduate - was using it but it couldn't be adopted in the biggest health emergency of the century.

If we don't have novel pathogen early detection, there will be a "Disease X" pandemic

Due to the exponential nature of case numbers in pandemics, time is a precious commodity. For example, Measles is highly contagious, with an R0 ranging from 12 to 18. This means that, on average, one person with measles can infect 12 to 18 others in a fully susceptible population. If, on average, each person with measles infects 15 others, after one generation, there would be 15 cases. After two generations, there would be 15 x 15 = 225 cases, three generations = 15 x 15 x 15 = 3,375 cases, four generations 50,625 cases, five generations 759,375 and so on.

Detecting a novel pathogen after three generations of transmission rather than four generations, might be the difference between a localised outbreak and millions of excess deaths, billions of dollars in economic losses, and years of ill-wellbeing due to being a global pandemic. Modelling has suggested that if Wuhan had locked down one (16 Jan), two (9 Jan) or three weeks (2 Jan or 2 days after epidemiological alert) earlier, cases of COVID-19 could have been reduced by 66%, 86% or 95% respectively.[1]



Annotated plot from Shengjie Lai and others, 'Effect of Non-Pharmaceutical Interventions to Contain COVID-19 in China' (2020) 585 Nature 410. Grey and yellow annotations from the authors of this submission.

We expect Wuhan to have done better but could Australia really have done better if we were in their place? I would argue no simply because we have public health sequencing capacity materially similar to theirs. If a pathogen emerges in Australia, we would undergo the same process. Doctors would see

case upon case with similar but undiagnosed symptoms until someone figured (in an adhoc way) that it's time to figure out what bug is causing all the illness. By that time there could be thousands of cases in Australia and it is impossible to achieve zero community transmission.

Recommendations

1. **Fund the Australian CDC to support a portfolio of diagnostics that for early detection and are rapidly scalable in a "Disease X" outbreak**

Investing in the right mix of technologies for "Disease X" will be important. When the cost, time and resource requirements for pathogen agnostic diagnostics come down, they may supplant pathogen specific diagnostics entirely despite the transition costs. This is not only because of their ability to identify a "Disease X' but also the depth of clinical information that they can provide. Until then we will need cheap, fast, simple preliminary diagnostics that rule out common illnesses to complement pathogen agnostic diagnostics.

Pathogen agnostic diagnostics: Metagenomic sequencing
Currently, metagenomic sequencing (mNGS) is the only technology capability that can identify a novel pathogen and its whole genome sequence. It works by sequencing all the DNA or RNA fragments in a sample, and then assembling those fragments into larger ones. Large enough fragments can be compared with existing databases of pathogens to identify if it is novel and what its closest relative is. Knowing the exact DNA/RNA sequence of the genome is key to developing vaccines, innovating medical countermeasures, and tracking new viral variants.

Pathogen specific diagnostics: Rapid multiplexed diagnostics
PCR was the main diagnostic technology throughout the COVID-19 pandemic and. It is the current gold standard. However, other promising technologies have simpler sample preparation, use less reagents, don't require heat cycling and can test many more samples for many more pathogens at a time. The Bipartisan Commission on Biodefense's Apollo Program for Biodefense[2] advocates for massively multiplexed detection capabilities such as assays that use CRISPR-based microfluidics,[3] semiconductor biochips,[4] multiplexed PCR arrays[5] and cross-hybridisation of highly conserved sequence motifs.[6]

Crucially, some diagnostics like the CRISPR-based SHERLOCK assay[7]are programmable and could be conceivably designed and tested in a week after the sequence of "Disease X" is known. It also uses ubiquitous well plates that can be stockpiled. Most importantly it is also very high-throughput, providing results for 5000 patient samples per day (24 h) based on a single liquid handling robot. As with PCR,[8] 5 samples may be pooled together while infection prevalence is still low to further increase testing throughput. This could mean 25,000 tests per day per robot.

2. **Deploy a "Threat Net"-like clinical mNGS architecture and routinely screen/diagnose a sample of ILI in the next 10 years**

A pandemic pathogen is likely to be highly transmissible, capable of causing great death and disruption to society, and unknown to the immune systems of current people. ILIs are often caused by respiratory viruses which score highly on each of these criteria.[9] Respiratory pathogens are readily spread by close contact, aerosols in the air and droplets, making quarantine of sick people difficult. Viruses also mutate faster than other pathogens, making it possible for them to evade the immune system multiple times (e.g. contracting the delta strain of SARS-CoV-2 did not completely

protect against the omicron strain). This increases the costs to society in terms of both deaths and disruption.

For these reasons, the next global pandemic is likely to also be a respiratory virus. Monitoring this subset of diseases is therefore likely to cover a majority of future pandemic risk. Furthermore ILIs may not be a self limiting cold virus but a more serious illness such as Meningitis, HIV or Strep throat.[10] Furthermore, an Australian study has shown that testing for flu does result in a decrease of inappropriate antibiotic use, limiting the development of antimicrobial resistance and an increase in appropriate antiviral use.[11] Antimicrobial resistance is driven by overuse of antibiotics and it is estimated that more than 10,000 Australians will die as a result of antimicrobial resistance between 2015 and 2050.[12]

Sharma et al (2023) Threat Net: A Metagenomic Surveillance, Health Security estimates that for $400-800 million it would have a 95% change of detecting a novel SARS-CoV-2 like respiratory pathogen after 10 emergency department presentations and 79 infections across the US.[13]

3. **Assign the CDC the responsibility and funding to design and implement a "Disease X" early detection system. Use this system in peace time for routine functions like data to improve the National Notifiable Diseases Surveillance System (NNDSS)**

Clinical metagenomics would only be part of a robust sequencing based public health system. Depending on what sort of pathogen "Disease X" is, clinical metagenomics might not always be the best to detect disease. The pre-print by Liu et al (2023) Quantitatively assessing early detection strategies for mitigating COVID-19 and future pandemics[14] estimates that hospital monitoring could have detected COVID-19 ~1000 cases earlier. However, wastewater surveillance could provide an early warning for pandemics with long incubation periods like HIV and air travel monitoring does best for diseases with low fecal shedding and when hospitalisation time and R0 is very high. Accordingly there should be a national strategy to iterate towards an early detection system that gets this mix of technologies and sampling methods right.

The other challenge with an early detection system is ensuring it is funded into perpetuity. Liang et al (2023) Managing the Transition to Widespread Metagenomic Monitoring: Policy Considerations for Future Biosurveillance, Health Security outlines a number of policy obstacles that need to be overcome for a public health monitoring system with sequencing as it's backbone to be successful over the next decades. Therefore, I would expect that such a system needs to be useful not just in a crisis but also in 'peace-time', therefore I would urge the CDC to make this system be useful for providing data to the National Notifiable Diseases Surveillance System (NNDSS).

In conclusion, I think Australia can and needs to be ambitious with integrating genome sequencing into the public health and diagnostic systems of health and medicine. We also need to figure out how to fund this system into perpetuity as a detection system can't bounce between being funded and not funded at the whims of the political cycle. Simply, the costs of pandemics are too high, why not spend a fraction of those costs on prevention. Just in the way that fires are inevitable but out of control wildfires aren't, novel pathogen outbreaks may be inevitable but outbreaks escalating into pandemics aren't. It's time we take pandemic prevention as seriously as bushfire prevention.

Yours faithfully,
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Citations

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