LEADERSHIP INSIGHTS

ON HEALTH AND MEDICAL RESEARCH AND INNOVATION



ISSUE 02

Contributors

Professor Tony Cunningham AO
Westmead Institute for Medical Research

Mr Jeppe Theisen
Novo Nordisk Oceania

Professor Shitij Kapur
The University of Melbourne

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LEADERSHIP INSIGHTS

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As Australia's peak body for health and medical research, we represent organisations whose leaders are some of the key influencers in our sector. Drawing on this collective wisdom, we seek perspectives and insights on a broad range of topics from across our membership. The areas include disease specific topics, driving change and innovation in our sector, and pausing for thought and sharing ideas.

The INSIGHTS series features these opinion pieces from our diverse membership across the entire pipeline; from our Universities and MRIs through to the charities supporting HMR and commercial participants, all of whom play a vital role in Australia's health and medical research.

We are delighted to publish another of our Leadership INSIGHTS, featuring Professor Tony Cunningham AO from the Westmead Institute and Jeppe Thiesen from Novo Nordisk Oceania.

We thank them for their contributions and look forward to sharing further INSIGHTS from the organisations we so proudly represent.



Prof Anthony L Cunningham AO FAHMS MD FRACP FRCPA FASM, Co-Director of Centre for Virus Research, Westmead Institute for Medical Research and Faculty of Medicine and Health, University of Sydney

A pragmatic approach to managing the covid-19 epidemic

In this era important new knowledge is being posted urgently without peer review on databases such as MedRxiv and BioRxiv, or even rapidly published in prestigious journals where sometimes impact has been considered ahead of careful review. We have seen two key examples of this recently e.g. despite several high-profile publications on hydroxychloroquine for treatment and prophylaxis of COVID-19 we still have no clear evidence of whether it has any efficacy or indeed if it is harmful.

I am of the view that inspection of the worldwide and Australian response to the COVID-19 pandemic caused by the Coronavirus, SARS CoV-2, reveals several clear lessons.

The first is that a national response must be based on strong relationships between the best available scientific advice and government. Nevertheless, even this can be misleading as seen with the misguided UK and Swedish approaches to allow natural infection to develop herd immunity while urging the vulnerable (those over 70 or with chronic diseases) to stay home. In contrast, in Australia this relationship between Chief Health Officers and Commonwealth and State governments has been excellent and the evidence-based advice mostly transparent and accepted.

We need to avoid complacency as occurred after the last (influenza) pandemic which fizzled out with relatively low mortality; continuing vigilance at national and international levels is required for future zoonoses which will be of varying communicability and virulence. We must not dilute our national plans or the agencies able to implement them on either cost-cutting or ideologic grounds.

Assumptions about previous viral epidemics or pandemics may not be directly relevant to this one and may be misleading. In this case the relevant ones are SARS1 and influenza.

We must closely monitor and critically analyse the rapidly changing knowledge base and its implications and implement key lessons rapidly.

Much is still being learnt about transmission of SARS-CoV-2, especially in individual variability, which is difficult to convert into simple clear advice for the public. This research requires a combination of complementary aspects of basic virology, epidemiology and mathematical modelling. For example there is variability in the distance distribution of expelled large droplets after various events such as sneezing, coughing, singing, the proportion of droplets containing SARS-CoV-2, the effects of the environment (whether indoor or outdoor),

of wind, temperature and humidity, and the modulating effects of masks and artificial ventilation, especially in aeroplanes.

Confirming and defining the frequency of 'superspreaders' who expel much more virus than others at the peak of illness, and the level of infectivity during symptomatic and preceding asymptomatic infection is urgently needed. Although this type of research is very useful as a base it needs careful evaluation in the real world through controlled epidemiologic studies. Recent studies of masks in confined environments like ships is one example. This knowledge will help mathematical modellers and public health officials produce new and more sophisticated recommendations about the relative risks of various venues, from air travel to bars, clubs, restaurants, concert and sports venues. More pragmatic recommendations will help control the spread of the virus as nations emerge from 'lockdown', while awaiting a vaccine or other highly effective methods of reducing the morbidity and mortality of COIV-19. WHO and the London School of Hygiene are currently examining over 170 different parameters of individual national response to COVID-19 to guide the best future responses.

The difficulty of obtaining sufficient herd immunity through natural infection has been well enunciated. For measles where one person infects on average 18 others (Ro =18) herd immunity needs to be 95% of the community. For SARS-CoV-2 where one person is currently thought to infect between 3.3 and 5 this has been estimated at 60-80% but could be higher. As not even New York has achieved levels of >20% infection this level clearly cannot be achieved in the first round of the pandemic.

Furthermore the frequency of immunity to reinfection is still unclear, as is how long it lasts, whether this varies according to severity of infection or age, and whether it depends on both neutralizing antibody and T cell immunity; and, if so, what are the levels of protective immunity? The influence of prior infection with seasonal coronaviruses that cause the common cold on severity of COVID-19 is also not known, although there is cross reactivity between T cell responses to them and SARS-CoV-2.

In the absence of a vaccine, expert modelling studies have suggested recurrent epidemics of COVID-19 will occur, possibly each winter, with the severity varying mainly according to the success of maintaining social distancing, augmented by widespread testing and efficient contact tracing. Without a vaccine, it is important to focus on limiting morbidity and mortality, especially in the vulnerable and to avoid overloading the health system. Development of prognostic tests to determine who of those infected will deteriorate and also of effective antivirals for early treatment and prevention of progressive disease are urgently needed and may be easier than a vaccine.

Safe and effective vaccines are the ultimate aim. To achieve >80% immunity in a population an efficacy of >90% and uptake (coverage) of >90% will be required as soon as possible. Most vaccines will be trialled in the 20-60 year age group. However, the most vulnerable age group is that over 65 years of age and all but one vaccine has failed to consistently exceed efficacies of 60% in this group. Unless population (herd) immunity exceeds a key threshold of say >80% the virus will leak through to these people. Special vaccines such as the adjuvanted Recombinant Zoster Vaccine with an efficacy of >90% will probably be needed in this age group. By analogy different (adjuvanted) influenza vaccines to the general population have recently been administered to those >65 YOA in Australia.

Furthermore, scale up for the global population of >6 billion people is required. During the H1N1 pandemic 90 million doses of adjuvanted vaccine were produced by GSK, well short of this target. Some vaccines are more easily

produced than others. It is likely that multiple types of vaccines produced by multiple companies will be needed and, hopefully, global rules adopted to ensure equitable distribution.

How quickly can such vaccines be developed urgently in this time of need? The shortest development time was 4 years for a relatively simple mumps vaccine, but times are changing. For example, new types of RNA and hybrid viral vector vaccines are being rapidly produced, although these have not previously achieved licensure in humans. However, the pneumonitis of severe COVID-19 is caused by aberrant immune responses and previously vaccines for the closely related SARS-CoV-1 and MERS coronaviruses have caused similar lung inflammation in experimental animal models. Non-neutralizing antibodies to these viruses can actually enhance infection.

Therefore it is critical to test adequate numbers of subjects for safety during vaccine trials ie probably >30,000. Novel and pragmatic approaches to vaccine implementation are also in progress, guided by experience in previous influenza pandemics and from other sectors, such as in HIV vaccine trials. These include simultaneous scaleup of vaccine production concurrently with phase III trials (after promising phase II results), standardised laboratory testing, attention to auxiliary materials such as vials and wipes, and accelerated licensing evaluation.

All of these facets of managing COVID-19 must be subject to the most innovative and rigorous multidisciplinary research. The new phenomenon of publishing well formatted papers, but prior to peer review, is helpful but potentially dangerous as public policy may be prematurely and erroneously influenced.

Our leading journals have a major responsibility to ensure rigorous and knowledgeable review of submitted papers, despite the rush to publish, if we are to maintain public confidence in them and in science. We must insist on key results being reproduced in more than one centre or group. Pragmatism cannot be achieved by lowering of research standards but by faster and more efficient communication of key reproducible results and their implementation.

The Westmead Institute
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Diabetes presents a significant problem in Australia – COVID-19 reinforces the urgent need for commitment and multi-stakeholder engagement



Mr Jeppe Theisen,
Vice President and
Managing Director,
Novo Nordisk Oceania

The burden of diabetes is rising in every part of the world despite long-running, collective efforts to fight the disease and its devastating impact on people and societies. By 2045, over 730 million people could be living with diabetes.

In Australia, the prevalence of diabetes has more than tripled over the past 25 years and there is no sign that this is slowing down. It is estimated that there are more than 1.2 million Australians with known diabetes and over 2 million people at high risk of developing diabetes. I find this development and projection particularly alarming.

The University of Sydney and Western Sydney University, with the support of an unrestricted grant from Novo Nordisk, explored the applicability of the 'Rule of Halves' framework to illustrate the burden of diabetes in Australia. This work draws our attention to the large number of people, approximately 50%, who are living with diabetes and not receiving standard care, including not being monitored at regular intervals for glycaemic control. In addition, over half are not achieving treatment targets and are therefore living with significant increased risk of developing complications.[1] This highlights the significant problem that diabetes presents for Australia and where our actions must be focused to achieve optimal diabetes care.

Despite strong evidence that shows us the development and progression of complications can be prevented with appropriate care and management, it is sad to see so many people living with poorly controlled diabetes and micro and macrovascular complications, around the world – and in Australia. Consequently, we see significant personal, economic and societal burden - all avoidable with earlier diagnosis, improved screening and surveillance for complications and better access to diabetes care.

COVID-19 only highlights the scale of the problem of chronic diseases – not least diabetes. During lockdown the rates of visits to general practice, allied health professionals and emergency departments dropped, and the number of pathology tests being performed reduced significantly. COVID-19 exacerbates

1 Sainsbury E et al. *Burden of Diabetes in Australia: It's Time for More Action. July 2018.* Available at: https://www.novonordisk.com.au/content/dam/australia/affiliate/www-novonordisk-au/Home/Documents/Copy%20180712_Burden%20of%20Diabetes_Its%20Time%20for%20More%20Action%20Report_Digital_%20FINAL....pdf. Accessed July 2020.

the existing diabetes burden and makes existing challenges such as early detection and monitoring even more challenging. Concerted efforts are needed to improve the rule of halves and achieve better outcomes for those living with diabetes, their families and society overall. If we do not take the necessary actions now, we will see major health problems in the years to come.

We need to drive change to defeat diabetes. Scientific breakthroughs are fundamental to progress and Novo Nordisk will continue to drive innovation until we defeat diabetes. I am proud to be part of an organisation that, together with patients and partners transforms bold ideas into life-changing medicines and makes long-term investments into novel treatments and technologies, including potential curative stem cell-based therapies.

But it takes more than innovative medicine to defeat diabetes, so our efforts must go further than this. I strongly believe that collaboration between governments, health stakeholders, business and society, focused on the prevention of type 2 diabetes, is urgently required to bend the curve on the huge rise in diabetes prevalence in Australia and globally. I have closely observed what the power of collaboration and aligned goals can achieve since the Steno Diabetes Center Copenhagen, University College London, and Novo Nordisk launched Cities Changing Diabetes in 2014. The programme has enabled more than 20 cities around the world to set goals and create action to halt the rise of type 2 diabetes in their city, and to work across sectors and disciplines to unite stakeholders behind a common cause.

To address the significant burden of diabetes in Australia, the report by the University of Sydney and Western Sydney University proposed clear strategies for earlier diagnosis, better access to diabetes care, and improving outcomes for people living with diabetes. Each of these strategies are reinforced by and closely aligned with the Australian National Diabetes Strategy 2016-2020. As I write, there has been the announcement of funding by Hon Greg Hunt MP and Hon Karen Andrews MP to deliver the Accelerator program to improve the management and treatment of diabetes and cardiovascular disease. I welcome and look forward to the cross-sector collaboration this initiative will stimulate to help reduce the burden of diabetes in Australia.

We must keep our eyes closely focused on the many Australians that are at risk of developing diabetes, whilst providing optimal care for those living with diabetes. Actions are already being taken but we must step up our efforts, working in partnerships, to change the outlook of diabetes at a time of acute need.



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How unlocked Victoria can learn to live with the virus

As published in the Australia Financial Review 19 August, 2020



Professor Shitij Kapur,
Dean of the Faculty of Medicine Dentistry & Health Sciences & Assistant Vice-Chancellor (Health), University of Melbourne

A post-lockdown plan for the state and the rest of Australia will need change in political stance, operational strategy and public acceptance.

Plan A for COVID-19 was the national effort led from the front by Scott Morrison and former chief medical officer Brendan Murphy. The entire nation was in a uniform lockdown. The plan ended in May and delivered four states and two territories with no local transmission. Quite a success. And then came the problem in Victoria.

Plan B for COVID-19 was the massive Victorian effort fronted by Dan Andrews and state Chief Health Officer Brett Sutton. Victoria was forced into the harshest lockdown to date. The plan is working, slowly. One can be reasonably confident it will bring the Victorian numbers down into the tens. It is also becoming clear that it will take a miracle to eliminate local transmission by September 13 when the lockdown is due to end.

There are only three countries of size in our region that have come close to elimination. And they all started from much better positions than Victoria. All three of them had a modest first wave, but none had a second wave of transmission. More importantly, the density of their local transmission was an order of magnitude lower than Victoria's – 322 per million in New Zealand, less than 50 per million in Taiwan and Thailand versus 2500 per million and rising in Victoria.

Crucially, data from other major Western cities that have had dense outbreaks like London, New York and Geneva tells us when infections become this prevalent, for every confirmed case there may be 10 others with asymptomatic exposure. And these lurking infections and "mystery cases" becomes harder and harder to eliminate once there is widespread community transmission.

The right place for complex deliberations is in our parliaments and cabinet rooms, not in news conferences.

Barring a miracle by September 13, it is thus likely that Victoria and Australia will have a Hobson's choice: either impose an extension of strict lockdown in the search for elimination or, call for a loosening of restrictions in the presence of some continuing community infections and "mystery cases".

And that is when we will need Plan C – the pragmatic acceptance that we cannot eliminate local transmission from Australia and will need to learn to live with the virus. Plan C will have to differ from the earlier plans in four different ways.

First, the daily "crisis-management by news-conference" approach will have to cease. The political and health care leaders not only need

relief from this daily game show of morbid numbers and the ritual condemnation but also need the time and space to formulate complex responses. The right place for complex deliberations is in our parliaments and cabinet rooms, not in news conferences. This is not to relieve our political leaders of their accountability or the health leaders of the need to make their recommendations transparent. This shift would tacitly acknowledge that we are now in the long stretch, and the endgame is not near.

Risk tradeoff

Second, our political leaders need to engage Australians in determining our appetite for acceptable risk. Health at all costs is neither achievable nor affordable. Since the start of the year among Australians under 40, two have died from COVID-19. In the same time, 200 have died from road traffic accidents. Yet we drive merrily. Finding the right balance of risk is a societal dialogue, not a technical calculation. The daily one-sided doorstops should be replaced with a mature conversation about risks and tradeoffs that engages all Australians and respects their collective wisdom.

Third, Australia's response has been commendable for its egalitarianism. All of us, across all states, are in it together. It was a strong display of solidarity. That ideal has to now face the facts: the risk of death from COVID-19 if you are under 40 is less than one in 5000; above 70, it is closer to one in 10. On the other hand, more than 1 in 10 of the young have lost their jobs and livelihood to COVID-19 with many more to follow when JobKeeper expires. There are more than one vulnerable groups to COVID-19. We need to protect them all. Differently.

Finally, we are a vast nation with varying degrees of success. The states that have successfully implemented Plan A will be wary about losing what they have gained by allowing unrestricted movement between states. Plan C must work out how we run a single country with different rules for different states. We do it all the time – a bushfire in Victoria does not spark a CFA Code Red in Queensland.

In sports as in war, you change your strategy as you get to know your adversary better. Over the last six months and through Plans A and B we have learnt a lot about SARS CoV-2: how tenacious its infectiousness, how global its spread, how numerous the asymptomatic cases, how disproportionate its impact on people who are older or with existing health conditions.

We have also learnt how sensible measures – hand washing, use of masks, social distancing, testing-tracing-isolation – can manage, but don't easily eliminate, this virus.

Plan C will require a shift in political stance, operational strategy and public acceptance. We must start the conversation now. September 13 is less than a month away.

These are Professor Shitij Kapur's personal views and not those of his institution.

THE UNIVERSITY OF MELBOURNE

unimelb.edu.au

RESEARCH AUSTRALIA

CONNECTING ▪ ENGAGING ▪ INFLUENCING



384 Victoria Street
Darlinghurst, NSW 2010

T + 61 2 9295 8546
E admin@researchaustralia.org

www.researchaustralia.org

ABN 28 095 324 379