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LAURA TINGLE

RAINA MacINTYRE

VACCINE NATION

Science, reason and the threat to 200 years of progress

VACCINE NATION

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‘Vaccines helped us emerge from the worst of the COVID pandemic, yet rather than being a triumph, we now see anti-vaccine claims eclipsing public health policies. Raina MacIntyre outlines the history of vaccines and despairs at how the medical profession is among those pushing anti-vaccine myths. This important book documents where opposition to vaccination is leading the world and how science can reclaim centre stage.’

Laura Tingle, author and journalist

‘For the first time in human history, we have the scientific know- how to vaccinate against most of the infectious diseases that killed our ancestors. *Vaccine Nation* takes us through exciting developments in using vaccines to protect against non-infectious threats such as cancer and heart disease. MacIntyre shows how these advances are being counterbalanced by a spreading mistrust of science in general and vaccines in particular. This book, by one of the world’s leading biosecurity experts, tells the story of how vaccines transformed the public health landscape and suggests what we might do to restore public trust in their efficacy and safety.’

Professor Trish Greenhalgh OBE, University of Oxford

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UNSW Press acknowledges the Bedegal people, the Traditional Owners of the unceded territory on which the Randwick and Kensington campuses of UNSW are situated, and recognises the continuing connection to Country and culture. We pay our respects to Bedegal Elders past and present.

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Dedicated to my parents,
Ernest and Nalini MacIntyre,
a literary couple who provided me
with a love of books and writing.
It was late in life that I realised
unconditional love and support,
regardless of life choices, is a rare thing.

And in memory of my grandmother,
Nirmala Mather (nee Chanmugam),
who was denied the education she wanted
because she was a woman.

1

THE MIRACLE OF VACCINES

When Martha Lillard turned five, she had a birthday party at an amusement park. It was a crowded public place designed for having fun, but it was also where contagious infections may be rife. A week later she developed a fever and a sore throat, and soon after she began to get weak. Her parents suspected the worst because a deadly infectious disease was all around them. Their fears were confirmed when Martha was diagnosed with polio. She needed an iron lung to breathe and her entire body was placed inside the machine, with only her head free of the encasement. The virus had paralysed her diaphragm, the muscle essential for breathing, and the iron lung would need to breathe for her. The iron lung is a large metal contraption designed to create intermittent negative pressure to simulate breathing and take the place of the stricken diaphragm, helping the lungs expand and deflate. It was 1953, the peak of a polio epidemic in the United States, when hospital wards were full of people encased in iron lungs.

As of 2021, Martha Lillard remained one of the very few people still kept alive by an iron lung. The machine looks like a small submarine, big enough to encase the whole body, with the head sticking out at the top. Imagine being imprisoned in a metal casing, being unable to walk or see the world. People have lived like that for up to 70 years. To make matters worse, spare parts for iron lungs are hard to come by these days, and power blackouts can be life-threatening. If there was a power blackout, family and neighbours had to help by manually pumping air into the iron lung using bellows. While the rest of us have forgotten the horrors of polio epidemics

and images of hospital wards filled with iron lungs, parents at the time lived in fear of their child becoming paralysed, or worse, killed by polio. Up to this time, about 35 000 people a year in the United States were paralysed or disabled by polio. The introduction of polio vaccines in 1955 quickly turned this around, making polio extremely rare in the country and eliminated by 1994. There are now only two countries – Afghanistan and Pakistan – that still experience polio epidemics, and both are linked to low vaccination rates and opposition to vaccination.

The first vaccine to be developed was against smallpox, a deadly disease documented in Egyptian mummies, which had plagued the world for over 3000 years. Until it was eradicated, one in three people with smallpox died, and in the 20th century alone there were somewhere between 300 and 500 million deaths from smallpox in the world. Smallpox was finally eradicated in 1980 thanks to effective smallpox vaccines and a determined, decade-long campaign for eradication from the World Health Organization (WHO). It appears that in ancient times and in multiple countries simultaneously, people realised that the technique of variolation, or introducing small quantities of the actual smallpox virus to a non-immune person, could be protective. Usually, this involved lancing a pustule on the skin of an infected person and transferring the material from that pustule using a sharp instrument to someone else. This was called inoculation or variolation and could be quite dangerous because the person might develop full-blown smallpox. It could also result in the spread of other infections such as syphilis because of this unsterile method. An English aristocrat, Lady Mary Wortley Montagu, brought this technique to England after her travels in Turkey and catching smallpox herself in 1715. It turns out there are a range of similar viruses in the orthopoxvirus group of DNA viruses, and immunity against one can confer immunity against the others. Monkeypox, now called mpox, is also in the orthopoxvirus group. In 2022, when an unprecedented mpox epidemic swept the world, the vaccines used to control the epidemic were smallpox vaccines based on the cowpox virus.

Edward Jenner, considered the father of modern vaccines, discovered that exposure to cowpox, a disease that affects cattle, provided immunity against smallpox. He observed as a teenager that dairy maids, who were exposed to cowpox in the course of their work, did not get smallpox. In 1796, he took some pus from a cowpox lesion on a dairy maid and inoculated an eight-year-old boy with the pus. Two months later he inoculated the boy with smallpox, something that would never get approval from a modern human research ethics committee. The boy did not develop smallpox, and this was the basis for using the cowpox virus, also called ‘vaccinia’, as a smallpox vaccine. Jenner called this procedure ‘vaccination’. At the time, his research was rejected for publication and not accepted in the scientific community. Nonetheless, by 1800 the practice of vaccination had spread across Europe. Another Englishman, Benjamin Jesty also discovered that material from infected cows could prevent smallpox more than 20 years before Jenner’s discovery, and local doctors in dairy farming communities also had knowledge of this method.

The first mass vaccination programs were for smallpox, and it took another 180 years to eradicate the infection. Smallpox is still the only human infection to have been eradicated. Eradication means that the virus does not exist in nature. Only some infections can be feasibly eradicated, typically those that only infect humans (not animals). An infection that exists in wild animals or insects would be very difficult to eradicate, and human infections would continue to occur. WHO tried to eradicate malaria prior to the smallpox campaign, but this was beset with obstacles, including the lack of a vaccine and the fact that malaria is carried by mosquitoes. In this respect, smallpox was the ideal infection to eradicate, because it only affected human beings, and we had an effective vaccine.

The smallpox vaccine was followed by an early rabies vaccine and cholera vaccine by microbiologist Louis Pasteur in the 1880s, and the discovery of diphtheria in 1894 was pivotal in creating anti-toxin for the disease. Following the deadly Spanish influenza pandemic of 1918, research began into developing influenza vaccines, and the first of these was approved in 1945. This began a period of rapid expansion in

vaccination, first with successful polio vaccines in the 1950s, the measles vaccine in 1963, the combined measles, mumps and rubella vaccine in 1971, and the hepatitis B vaccine in 1981. In 1974, WHO established the Expanded Programme on Immunization, targeting global vaccination against diphtheria, whooping cough (pertussis), measles, polio, tetanus and tuberculosis. During the 20th century, a range of new vaccines were introduced, and one by one they successfully controlled deadly infections that used to routinely kill many children.

Today, we expect our babies to survive, live healthy lives and grow old. We take for granted the miracles of sanitation, vaccination and modern medicine – and forget that infant death was once normal. In the late 19th century, things were very different. In 1899, Australian poet Henry Lawson wrote a poem called ‘Past Carin’’ that described the hardship of life in the bush and the regular death of young children:

> Our first child took, in days like these,
> A cruel week in dyin’,
> All day upon her father’s knees,
> Or on my poor breast lyin’;
> The tears we shed – the prayers we said
> Were awful, wild – despairin’!
> I’ve pulled three through, and buried two
> Since then – and I’m past carin’.

It was common in the 1800s and early 1900s for people to have a dozen children, mostly because of a lack of contraception, but also because most would not survive. Until 1800, only half of all children would reach their first birthday. The substantial decline in infant mortality rates over the last 150 years reflects a combination of successes in public health through improved sanitation, safe water, better nutrition, antibiotics and vaccines. In the pre-vaccine era, infectious diseases were the leading cause of death in children. In most countries today, over 99 per cent of children survive to adulthood, and even in the most disadvantaged parts of the world, the survival rate is 90 per cent or more. When we live with the vast gains achieved by public health and vaccination, we can take these gains for

granted. A 2024 study in *The Lancet* estimated that the WHO Expanded Programme on Immunization had prevented 154 million deaths since 1974, which comprised 146 million children under five years and 101 million infants under one year whose lives were saved by vaccines.

The miracle of vaccines eradicated smallpox from the planet, then it fought off other deadly infections like polio, tetanus, diphtheria, measles and meningitis. Yet vaccine-preventable diseases, including COVID, are still with us. Some, like measles, are re-emerging, and new viruses will emerge and continue to be a threat to our health. New vaccines will be developed to fight not only infectious diseases but cancer and other chronic diseases as well. In the future, we may view cancer as a distant, forgotten disease of the past, and start questioning the worth of cancer vaccines. If existing vaccination programs are discontinued, epidemics will occur and cause many deaths. This has been proven over and over again in history. There are examples where successful vaccination programs have been disrupted and epidemics have occurred. In the 1990s, following the fall of the former Soviet Union, a previously strong public health infrastructure crumbled and vaccination rates plummeted. Epidemics of previously rare infectious diseases, such as diphtheria followed, causing thousands of deaths. In the UK in the 1970s, following an unfounded scare about the safety of the whooping cough vaccine, vaccination rates dropped and massive epidemics of whooping cough followed, resulting in infant deaths.

While working at the health department in Victoria in the early 1990s, I witnessed the first Australian vaccination program against meningitis, which successfully eliminated the most common cause of bacterial meningitis in kids at the time, haemophilus influenzae type B (Hib). Don’t be fooled by the word ‘influenza’ in the name. Hib has nothing to do with influenza. It’s a bacteria, not a virus, and was the most common cause of bacterial meningitis until 1993, when a new vaccine against Hib was introduced. The infection may also cause epiglottitis, which can obstruct breathing and be life-threatening, and a range of other complications like pneumonia and septic arthritis. Before Hib vaccination in Australia, there were at least 500 cases of Hib disease and 10 to 15 deaths in kids under six

years of age every year. If you survived, you had a 20 to 40 per cent chance of permanent neurological damage.

Meningitis is a feared and potentially fatal infection of the lining of the brain, and the most severe kinds of meningitis are caused by three bacteria, all of which have a capsule (like a shell) around them – Hib, pneumococcus and meningococcus. Children and teens are commonly affected, but adults may also get bacterial meningitis, especially young adults. It begins usually with a non-specific flu-like illness, which may be followed by a rash, and then severe headache, neck stiffness and sensitivity to light. After this, progression to death or permanent brain damage can be very rapid. In many cases, doctors mistake it for the flu and send the child home from the emergency department, and the child dies overnight at home. A diagnosis involves a ‘spinal tap’ or lumbar puncture, where doctors insert a needle into the spinal canal to extract some spinal fluid for testing. The capsulated bacteria Hib, pneumococcus and meningococcus all present this way. Only a sample of spinal fluid or a blood culture can differentiate between them and a viral meningitis.

Many infections are worse in infants because babies cannot fight infection as effectively as adults. Think of our immune system as having two arms: an infantry (T cells) and artillery (B cells) that fight invading infections. The thymus is the immune organ of the body that produces T cells, the white blood cells that are essential to fighting infections. The thymus is immature in babies, which is why they are more susceptible to severe infections, and why we have a robust infant immunisation program against an array of serious infections. From birth to six months, babies depend on antibodies circulating in their blood from their mother (maternal antibodies). While these are critical in the first months of life to protect the baby, they wane by six months of age. Some infections are very sneaky and can get around our defences. Because Hib, pneumococcus and meningococcus have a capsule around them, it makes the design of vaccines more complex. Children less than two years of age are unable to mount an antibody response to the capsule, even when infected with the bacteria, which is why Hib meningitis is worst in this age group.

The capsule contains sugars called polysaccharides, which can be used to make vaccines and elicit protection against the bacteria. The body gets tricked into thinking it has encountered the bacteria, even though it has only encountered a harmless part of the capsule. Purified polysaccharide (PRP) from the Hib capsule was used in early Hib vaccines, but these were not effective in children under the age of two. The same is true of polysaccharide vaccines against pneumococcus and meningococcus. The breakthrough in Hib vaccines came by using a process called ‘conjugation’. When PRPs are chemically linked (‘conjugated’) to harmless proteins, they become a highly effective vaccine, in this case, over 90 per cent protective in babies. The breakthrough of conjugation began with Hib vaccines in 1993 and later led to effective vaccines against streptococcus pneumoniae and meningococcus.

In 1992, I started my field epidemiology training in Australia, a program designed by the US Centers for Disease Control and Prevention (CDC) and taught in over 100 countries in the world. The training involved being placed in an operational site, such as a health department, and learning about outbreak investigation and control, surveillance and vaccination on the job. I was placed at the health department in Victoria, and when the new Hib vaccine was rolled out in 1993, they needed all hands on deck. In addition to being at the Immunisation Advisory Committee meetings, which oversaw the planning for this vaccination program, I sat on the floor of the infectious diseases unit and collated piles of colourful posters and flyers to be sent out to GPs and immunisation clinics. There was a palpable sense of excitement in the team about this new vaccine and the prospect of conquering Hib infection. The Hib vaccine saw Hib plummet from the most common cause of bacterial meningitis to a rare disease, from 502 cases in 1992 to 35 cases in 1998 and 16 cases in 2017. Over 95 per cent of Australian children are now vaccinated against Hib, but we still see occasional cases in unvaccinated kids.

The other vaccine I was involved with was the influenza vaccine. Victoria was the first state in Australia to introduce a free influenza and pneumococcal vaccine for people aged 65 years and older, and I was given

the task of establishing a surveillance system so we could monitor the impact of vaccination. Today, many countries offer a free influenza vaccine to adults 65 years and over, but that wasn't the case in 1993. One of my projects as a trainee field epidemiologist was to integrate data from formal laboratory diagnosis with data on influenza-like illness from selected general practices, workplace absenteeism data, and a community survey to measure self-reported influenza and pneumococcal vaccine uptake. In subsequent years, this evolved to become a nationwide survey to estimate the proportion of older adults vaccinated against these two diseases. This experience was the start of my lifelong interest in adult vaccination and led to my research on the vaccination of older adults and immunosuppressed people, spanning vaccines for influenza, pneumococcus, herpes zoster (shingles) and COVID-19. It also triggered my interest in vaccine equity, as I quickly realised that there was a gap in vaccination rates in fully funded vaccines for children compared to adults. Our childhood vaccination rates are extremely high by global standards, over 95 per cent for several vaccines and over 90 per cent for most. In contrast, vaccination rates for influenza in adults have hovered around 70 per cent for a long time, plummeting to 60 per cent after the COVID-19 pandemic, and pneumococcal vaccines are even lower. There has been an enormous amount of research done around the world on why rates of adult vaccination are consistently lower than paediatric vaccines. They all showed there is lower awareness of vaccination for adults in the community, and less belief in vaccination for older people among doctors.

You see, vaccines have enjoyed a privileged position in public health compared to other public health interventions. Childhood vaccines are often over 90 per cent effective in preventing disease. This contrasts with accepted public health interventions for other chronic conditions, which usually have a much lower effectiveness. For instance, the use of lipid-lowering drugs (statins) to prevent heart attacks has an effectiveness of 20 to 25 per cent. Smoking cessation and treatment of high blood pressure have a similar range of about 25 per cent effectiveness against heart disease. Yet these are universally accepted as important pillars of prevention for

cardiovascular disease. While chronic disease experts understand that even modest effectiveness can have a massive impact on population health, vaccinologists have been somewhat spoiled, being used to sky-high rates of effectiveness for childhood vaccines. So, when they hear that the influenza vaccine is 60 to 70 per cent effective in preventing influenza, they think it's a complete flop. But in truth, 60 per cent is awesome. If the disease is extremely common and causes a large burden on the health care system, then even modest effectiveness will have a significant population health impact on the burden of disease. Today, we see the same misconceptions affecting rates of COVID-19 vaccination, and worse, widespread dissemination of anti-vaccination sentiment about COVID-19.

Sometimes, anti-vaccination sentiment has political origins. In Pakistan and Afghanistan, the use of a vaccination program to find Osama Bin Laden's hiding place in Pakistan led to over 70 health workers being murdered. A vaccination program was used as a cover to get DNA samples from children to identify Bin Laden's relatives and find his location – and this caused a backlash against vaccines in parts of Pakistan. In Nigeria, which has finally managed to control wild polio, the ISIS-inspired militant group Boko Haram, which controls parts of northern Nigeria, fuelled anti-vaccination sentiment and vaccine disinformation by claiming that vaccines caused infertility and other alleged harms. This hindered polio elimination in Nigeria for many years. In Western countries, we have always seen examples of localised opposition to vaccination, usually in specific geographic areas where people with a similar mindset around wellness culture and alternative lifestyles gather together.

Even the inventor of smallpox vaccines, Edward Jenner, was subject to anti-vaccine propaganda, including scaremongering cartoons showing that getting the smallpox vaccine might turn you into a cow. In 1802, a cartoon by James Gillray showed Jenner vaccinating a terrified woman, who is turning into a cow. Yet 180 years later, this deadly disease was eradicated thanks to vaccines. When I first started working at the Victorian health department in the early 1990s, I was initiated in the methods of the anti-vaccination lobby. Until the COVID-19 pandemic, rates of anti-vaccination

were consistently around 2 per cent due to a small but vocal lobby group that believed natural infection was good for children and vaccines were dangerous. It was well understood that countering anti-vaccinationists with facts and statistics was not effective. They relied on emotive anecdotes, such as stories and photos of children with serious illness or disability, which they blamed on vaccines. Parents of children with conditions that are not well understood, or multifactorial, such as autism, are vulnerable to anti-vaccination propaganda. Given that almost all children receive vaccines, some diseases will coincidentally occur at some time after vaccination. This makes vaccines an easy target to explain otherwise unexplained diseases.

As soon as the genome for SARS-CoV-2 was released in January 2020, dozens of groups around the world began developing COVID vaccines, including pharmaceutical companies, start-ups and researchers in universities. Two types of vaccines, which had never been used at scale before – mRNA and vectored vaccines – were the first on the scene. Vectored vaccines piggyback a piece of SARS-CoV-2 on another harmless live virus – in this case, several groups used an adenovirus as the vector. The mRNA vaccines were made by Pfizer and Moderna, and the adenovirus vaccines by Oxford University and AstraZeneca, Janssen and the Russian government–backed ‘Sputnik’ vaccine. Later, the protein vaccine by Novavax was available. The vaccines were designed against the original virus that arose in Wuhan, but by the time vaccines were available in September 2020, the virus had already mutated into the Alpha variant. Still, the first clinical trials of these vaccines showed high protection against infection with Alpha, especially the mRNA vaccines. More importantly, even if you got infected after vaccination, the vaccines protected against severe infection, hospitalisation and death. However, after initial enthusiasm for COVID vaccines in 2020, not just in the community but also among medical and health professionals, we have seen a drop in booster rates and loss of confidence in these vaccines. We have also seen a fall in vaccination rates for other diseases like measles, mumps, rubella and polio, not just in low-income countries but even in high-income countries like the

United States. Globally, including in Australia, public health suffered a blow during the COVID-19 pandemic, with any mention of public health measures to reduce disease and disability being met with resistance by politicians and many in the community. The lockdowns of 2020, which comprised a few months or less of the whole year in most countries, have become conflated with any kind of public health measure. So instead of being strong and confident, public health messaging has become timid and apologetic, with health departments issuing messages like ‘be kind to people who choose to wear a mask’. The implication in that message is that the community has a right to be aggressively opposed to visible public health measures and that authorities should plead for the safety of mask-wearers. We now risk losing the gains of the last two centuries in a post-truth era embraced by the community and medical experts alike.

The COVID-19 pandemic has caused growth in anti-vaccination sentiment. It has also seen a coming together of groups that were mostly separate, such as the alternative lifestyle communities and right-wing extremists, who have become united in their common belief that COVID-19 vaccines are harmful. In countries like the United States, in particular, there has been a conflation of all public health measures, particularly lockdowns, face masks and vaccines, as being evil, state-sponsored tools for control and suppression of populations. A study done in 2021 showed that hardcore anti-vaccination rates have risen to 7 per cent in the United States, and 3 per cent in the UK. Being strongly or generally supportive of vaccination was only 60 per cent in the US and 76 per cent in the UK. In other words, there has been substantial growth in the grey area between being outright anti-vaccination and supporting vaccination – what we term ‘vaccine hesitancy’. Extensive research done on anti-vaccination shows there is not much point in trying to change the mind of a hardcore vaccine refuser. However, the group that is undecided or vaccine-hesitant can be swayed by effective health promotion and addressing their concerns with sensitivity and acknowledgment of their fears. Many countries also have specialist clinics for children who have had genuine adverse reactions (such as anaphylaxis) to vaccines, which provide thorough medical assessment and, where

feasible, safe completion of a vaccination course. Yet there are few such clinics for adults, even after four years of COVID-19 vaccination, which has been the largest whole-of-life vaccination program since smallpox eradication, reflecting the gap in priority between childhood and adult vaccines.

To me, what has been most frightening is the mainstreaming of anti-vaccination sentiment among the medical profession, where misinformation and misconceptions about COVID vaccines are common. A friend of mine, a medical doctor, was extremely ill with COVID-19 recently. When I spoke to him on the phone, I asked when he last had a booster. He replied, ‘Oh no, I haven’t had any booster. I only had the first two doses in 2021. I don’t want mRNA in my body.’ Given he was so ill, I didn’t want to upset him with the news that he already had plenty of mRNA in his body, and that it was a natural part of cells. I was shocked that a doctor was so misinformed and suffering so badly with COVID-19 as a result. Medical mainstreaming of anti-vaccination appears to be more common in countries that deny young children vaccination, such as the UK and Australia. In the UK, Australia and some Scandinavian countries, healthy children under five years are not included in national vaccine guidelines and therefore cannot get a vaccine. In contrast, the US recommends COVID vaccines for children who are six months to four years old because research shows they are safe and effective.

As late as 2023, a prominent vaccine expert and paediatrician was commenting widely on social media that COVID was not a concern for children, and that influenza was much more serious. By this stage, there was plenty of data in the medical literature and from official sources such as the US CDC showing that COVID-19 was the leading infectious cause of death in children, surpassing influenza, which held this dubious honour previously. Yet this expert had not progressed from early misconceptions held in 2020, when it was apparent that the most severe complications of COVID-19 were in the elderly. In early 2020, you could be forgiven for thinking COVID-19 was trivial in children because we were focused on the pointy end of things, with hospitals overflowing with older patients with

pneumonia. After the onset of the Omicron waves in late 2021, the amount of infection globally increased astronomically because these variants were much more contagious, and with this, the impact on children became more apparent. While it is true that COVID-19 is much more severe in older people, there is still a significant burden in younger people and children, including long COVID, which can be prevented by vaccines. There are now numerous studies showing that vaccination protects children against acute and chronic complications of COVID-19. Another popular argument among vaccine experts who do not think we should be vaccinating young kids against COVID-19 is that low-income countries cannot afford it. That argument would lead to the conclusion we should do away with sanitation, clean water, curative surgery for complex congenital heart disease, expensive chemotherapy for childhood cancers and so on, so that all countries have the lowest possible level of health care.

In most children, infections that we routinely vaccinate against are mild, but in a small proportion, they can be severe or fatal. COVID is no different. Take polio, for instance. WHO statistics show only 0.5 per cent of infections lead to paralysis, but in the 1950s, polio infection was so widespread that this equated to a lot of people on an iron lung or left with permanent paralysis. In public health, a complication that occurs in a small percentage of people can result in a massive population burden of disease. Again, people who work with vaccines do not fully understand this, because we are used to vaccines having an efficacy of 80 to 90 per cent plus. For a disease that causes a massive public health burden, even modest efficacy can make a huge difference to the health of the population. So, in that context, COVID vaccines don’t look bad at all – as long as you understand that the relatively high efficacy they provide wanes within three to six months, and that the virus keeps mutating to become less and less related to the vaccines we have. These two factors, as well as lack of access to vaccines, either in low- and middle-income countries or in high-income countries due to very restrictive vaccine policy, and reluctance to use other COVID mitigations, such as air purification or masks, mean that we haven’t

been able to fully get on top of the virus. Understanding the public health benefit of vaccines and how they work is the first step.

2

HOW DO VACCINES WORK?

My son was born in 2001 and a new pneumococcal conjugate vaccine was available on the private market in 2002 but not yet on the national immunisation program. My kids had all their scheduled vaccines, but this was an optional extra for those ‘in the know’. I was working at the National Centre for Immunisation Research and Surveillance at the time, so I knew the vaccine was available and that my son, being an infant, was at high risk. I intended to get him vaccinated privately but hadn’t got around to it yet. When he was seven months old, he developed a fever and became unwell, prompting me to take him to the emergency department of a children’s hospital. They did a few tests, including a blood culture (to identify bacteria in the blood, or septicaemia), and sent him home thinking it might have been influenza. He didn’t improve and I knew something was wrong because he was a smiley little chap, and previously, whenever he’d had a cold or flu-like infection, he still smiled at me. This time he wasn’t smiling or feeding well, both signs that it may have been serious.

I took him back to emergency the next day, still worried and with a mother’s instinct that something was wrong. The tests they had done the previous day had come back positive for the bacteria pneumococcus, a potentially fatal infection. No one had bothered to check or call me, and he could have died if I had not taken him back. He was admitted immediately and started on antibiotics, and the next day he was smiling again. I kicked myself for not having vaccinated him before this time. My son had a narrow escape, all of which may have been prevented with a vaccine.

Vaccines work by creating immunity to a virus or bacteria – without causing the actual disease. They provide immunity against an infection that someone may or may not acquire, and if they do acquire it, it may be many years into the future. This is called primary prevention and is one of the reasons why we saw infant mortality plummet in the last century and why potentially fatal diseases like polio and Hib meningitis are rare today. Prevention is a large part of public health and is applied to people who are well. Success in public health vaccine programs is when people remain well and nothing happens. This is quite different from treating someone who is acutely unwell with cancer or pneumonia, or who has been hit by a car. Over 90 per cent of resources in health care are devoted to acute care of people who are unwell, and only a small fraction to prevention. The human papillomavirus (HPV) vaccine can prevent cervical cancer and all the consequences of cervical cancer, such as surgery, chemotherapy and even death. The survival from stage 4 cervical cancer is only 15 per cent, so getting an HPV vaccine makes sense. Pneumonia is caused by several different viruses and bacteria, and a number of vaccines can prevent it, including influenza and pneumococcal vaccines and a COVID-19 booster, all of which would drastically reduce your risk of being hospitalised or dying from pneumonia. A seatbelt can prevent serious injury or death during a car accident. It may seem obvious, but for most people, a bird in the hand is worth two in the bush. In other words, something available to you right now, with a tangible, immediate benefit, is more valued than something that may or may not bring you benefits in the future, such as a seatbelt or a vaccine. In medicine, we call this the rule of rescue, where we place a higher value on treating someone who is acutely ill compared to preventing illness in someone who is well.

Vaccines are a classic example of primary prevention. Not only have vaccines eliminated or eradicated serious infections and reduced infant mortality, but some vaccines like hepatitis B and HPV not only prevent infection but also prevent cancers caused by these infections. HPV is the cause of cervical cancer in women and hepatitis B can cause liver cancer, in both cases many years or decades after the initial infection. In countries like

Taiwan, where cancer of the liver was exceedingly common 20 years ago, mass universal vaccination with the hepatitis B vaccine has reduced the incidence of liver cancer. We are now seeing similar gains in the reduction of cervical cancer and genital warts with the HPV vaccine. In the UK, the HPV vaccine was provided to girls aged 11 to 12 years from 2008, and the rate of cervical cancer was slashed by 87 per cent when they reached adulthood by 2021. A Scottish study found that women born between 1988 and 1996 and vaccinated against HPV as 12–13-year-olds had no invasive cervical cancer detected by 2020. They also found that the risk of cervical cancer was higher in women from more deprived backgrounds, but even people from these areas had a huge reduction in cervical cancer risk. Mass vaccination is a great equaliser because it provides advantage regardless of socioeconomic status. Despite these phenomenal gains to human health, we continue to see disinformation about vaccines. We continue to see the promotion of unproven diets and treatments with vitamins and supplements as alternatives to vaccines. Understanding the immune system is the first step to understanding what works and what doesn't work.

White blood cells (lymphocytes and neutrophils) are key weapons in our immune system. Neutrophils are important in fighting bacterial infections, and they're also a major component of pus in a wound or abscess. The immune system is broadly divided into two arms: cellular immunity and humoral immunity. Cellular immunity, created by lymphocytes called T cells, involves the generation of a range of cytokines, which are special signalling proteins that help the body fight off infections. Cellular immunity is particularly important in some kinds of infections such as tuberculosis or HIV. Cellular immunity is more complex to measure, and there are few routine tests in clinical practice to measure cellular immunity. We are more familiar with antibodies, also known as humoral immunity and commonly measured in blood tests to see if we have been infected with influenza, whooping cough or other bugs. Humoral immunity is created through lymphocytes called B cells, a different kind of white blood cell, which recognise foreign substances (antigens) such as viruses and bacteria, and produce antibodies against them. The concept of antigen (a part of the

virus that the body reacts to) and antibody (the protective defence our B cells produce) is key to vaccinology. Think of B cells as sentinel guards patrolling the body for invaders. When they recognise the invader (for example, the measles virus), they hunt it down, and produce antibodies which bind to it and kill it. Antibodies we produce tend to exist at high levels soon after exposure to the vaccine or infection but wane over time and may exist at very low levels or be barely detectable many years or decades later. A special kind of lymphocyte called a memory cell helps the body remember antigens it encountered a long time ago and rapidly proliferates to create an army of B cells that can generate enough antibodies to kill the invader.

Cellular and humoral immunity work together, like infantry and artillery, in the battle against an infection. Whereas the antibodies directly bind the invading virus or bacteria, the cellular response involves the generation of protein substances that are toxic to the invader, like interferons, chemokines and interleukins, which each provide signals to the cells to help fight infection. Autoimmune diseases like lupus and rheumatoid arthritis involve abnormal activation of the immune system, which goes into overdrive and starts acting against the body. Some infections also trigger an abnormal activation of the immune system. The 1918 Spanish influenza pandemic was highly lethal to young healthy adults, and it is thought that this involved something called a ‘cytokine storm’, which is an abnormal activation of cellular immunity. Instead of helping to fight the infection, there is an over-production of cytokines, which has the opposite effect on the body. Young adults were affected the worst during the Spanish flu pandemic because they had strong immune systems that were more likely to go into overdrive with a cytokine storm. For most infections and most people, however, the immune system works exactly as it is meant to and fights off infection with a multi-pronged attack.

Vaccines work by using a range of techniques to simulate the body’s natural response to infection, but without making people sick. We have come a long way since the earliest method of variolation against smallpox using the actual smallpox virus. Today, some in the anti-vaccination

community expose people deliberately to viruses. They hold infection parties where their children can be exposed to other infected children, whether it be to measles, chickenpox or COVID-19, in the mistaken belief that infection is good for children. Vaccines we use today to protect people against infection use different technologies to achieve the same aim – tricking the body into believing it's been exposed to an infection and producing an immune response, including memory cells, that can remember the infection years later and help mount an effective response against it.

For many vaccines, more than one dose is required to achieve good immunity. The first dose causes a rise in antibodies, a peak and then a decline in the antibodies over time. Typically, when you give a second dose, the second peak is much higher than the first and the antibodies stay at a higher level for much longer and do not wane as rapidly as they do after the first dose. This is why many childhood vaccinations like those against tetanus, diphtheria, whooping cough, hepatitis B and Hib require two or more doses for the primary course. The primary course is the number of doses required to achieve the required immunity, and boosters are additional doses that are required to boost immunity after the primary course. For example, kids get five doses of a whooping cough (pertussis) vaccine at 2, 4, 6 and 18 months, and then at five years, followed by a booster when they are adolescents. A further booster is recommended in older adulthood if more than ten years have elapsed since the last pertussis vaccine. Pertussis is an example where immunity wanes quite a bit after vaccination, hence the requirement for many doses and boosters. In contrast, the measles vaccine provides high, durable, often lifelong protection, and requires only a two-dose primary schedule, and no booster. In fact, 90 per cent of people achieve protection after a single dose of the measles vaccine, but the second dose is given to capture those who failed to respond to the first dose.

For all vaccines, there is a small percentage of what we call 'vaccine failures'. These are people who do not mount an immune response, either because the vaccine was not stored properly and lost potency, or because their immune system was impaired. Sometimes, this is due to long-term impairment of the immune system. More often, it is due to transient

immunosuppression, either due to medications or recent viral illness. Vaccines also require cold chain integrity to maintain their potency. This means they must be kept at the correct temperature from the time they are manufactured to the time they are injected into the arm of the patient, and at every point in between. Occasionally, cold storage of vaccines in the correct temperatures fails at some point in the cold chain. This may be due to inadequate transport conditions, power failures or poor fridge maintenance in a doctor's practice, or failures anywhere else in the cold chain, resulting in the inactivation of the vaccine. In the case of the measles vaccine, a second dose improves the protection offered by the first dose by catching those people who were transiently unable to respond to the first dose, or who received a dose that was inactivated by cold chain failure. In well-functioning health systems, cold chain failures are relatively rare. They are more common in weak or poorly resourced health systems, in rural and remote areas where health systems may be less resourced or transport distances much longer, or during war and conflict. Doctors, clinics and pharmacists who provide vaccinations have proper vaccine fridges that monitor and log temperatures continuously and provide a warning if the temperatures fall outside the required range for storing vaccines. Most vaccines need refrigeration, but a few, such as COVID-19 mRNA vaccines, must be stored frozen.

There are many different ways vaccines can be made. This includes protein subunit vaccines, live attenuated vaccines, vectored vaccines, whole killed virus vaccines, and more recently, mRNA vaccines. A protein vaccine is simply a small part of the outer surface of a virus or bacteria that provides immunity to the whole organism. Examples include current whooping cough or influenza vaccines. The mRNA vaccines achieve the same effect but by getting the body to create the protein instead of injecting the protein itself – mRNA sends a message to our own protein factory inside our cells to make the desired protective protein. A live attenuated vaccine is where the disease-causing organism is engineered in a laboratory to make it harmless while still eliciting an immune response and providing protection. Examples include measles, mumps and rubella vaccines, which are

modified versions of these viruses. They do not cause illness but elicit a strong immune response against the natural virus. Sometimes a related virus or bacteria can be used, such as the vaccinia virus to protect against smallpox, or bacille Calmette–Guérin (BCG) to protect against TB. Some live virus vaccines can replicate in the body, while others do not. An example of the latter is modified vaccinia Ankara, which is used in the newer vaccines against smallpox and mpox. These are particularly suitable for people who are immunosuppressed, as giving a live virus vaccine is not recommended for people with an impaired immune system. Live viral or bacterial vaccines may spread in patients with impaired immunity and cause serious infection or even death, which is why live vaccines are usually not permitted in such patients. Occasionally, a live virus vaccine may be accidentally given to a patient with immune suppression – with tragic consequences if the vaccine virus spreads through the body and causes illness. An example is the old shingles vaccine, Zostavax, which contains a super-high dose of the varicella zoster virus (the same vaccine strain is used for the chickenpox vaccine in much lower doses). There have been three deaths in Australia from inadvertent administration of Zostavax to people with immunosuppression. This is why it is essential, and spelled out in all vaccine guidelines, that live virus vaccines are not permitted for people with immunosuppression. When giving a live virus vaccine, doctors must always check and ask the patient about impaired immunity. The most common reason for impaired immunity is immunosuppressive medications, but some medical conditions, such as HIV or diseases of the blood or bone marrow, can also result in impaired immunity. Among the most vulnerable immunosuppressed patients are those who have had or are having a bone marrow or organ transplant. A bone marrow transplant involves wiping out all the bone marrow before transplanting the new bone marrow, and because the bone marrow is the source of blood cells, these patients are extremely vulnerable to infection. Cancer patients are also vulnerable as chemotherapy treatment can temporarily impair immunity. My friend and colleague Professor Eva Segelov, an oncologist, conducted a large study to examine immune responses to COVID-19 vaccines in adult and child

cancer patients, some after chemotherapy and others between courses of treatment. These specialised studies are needed so we know how to tailor vaccine guidelines for people with immunosuppression.

Whole killed vaccines use the entire virus or bacteria after it has been destroyed, which means they are incapable of causing disease in the body, but like a live attenuated vaccine, they can elicit an immune response. Examples include the earliest vaccines against whooping cough and the Salk polio vaccine.

Vectored vaccines are where you use a harmless, unrelated virus to piggyback an antigen from the disease-causing bug. Several of the first COVID-19 vaccines were vectored on an adenovirus. Modified vaccinia virus is also used as a vector in some vaccines. There is a concern with these vaccines that after repeated doses, the body may develop antibodies against the vector (in the case of COVID-19 vaccines, adenovirus), which may make subsequent doses less effective. Finally, there is what we call passive immunisation, which generally involves giving people antibodies to an infection. Normal human immunoglobulin contains high levels of antibodies to some infections, such as hepatitis A, and can be used during outbreaks to protect people who have already been exposed to infection (termed post-exposure prophylaxis). Specialised immunoglobulin against specific infections, such as smallpox or varicella zoster infections, are also available. Any human immunoglobulin product has a limited supply because it requires human donors, similar to blood donation. COVID-19 monoclonal antibodies are also an example of passive immunisation, and although they rely on an initial human antibody, these can be cloned in a laboratory. New respiratory syncytial virus (RSV) monoclonal antibodies are also available and can protect infants against this deadly infection for about 12 months. The protection provided by passive immunisation is only temporary, however.

In addition to these vaccine technologies, there are special tweaks that can improve the immune response to vaccines. This is necessary at the extremes of age because young children have an immature immune system and do not respond well to some vaccines, especially those with capsulated

bacteria, while older adults experience immunosenescence. This is the natural and entirely predictable phenomenon of decline in our immune systems, which begins around the age of 50. It doesn't matter how fit you think you are, how many supplements you take or what diet you consume – immunosenescence occurs in everyone, and the decay in our immunity is not linear but exponential. This means that as we get older, we are more at risk of having severe infections, but we're also less able to mount a robust response to vaccines. One of the first elegant demonstrations of this was by a British doctor, Robert Edgar Hope-Simpson, who showed that the risk of shingles increases exponentially after the age of 50 years. Shingles is a painful rash that occurs years after chickenpox. It is caused by the varicella zoster virus, which causes both chickenpox and shingles. After recovering from chickenpox, the virus hides in the nerves of the body, lying in wait until the immune system is weak, and it can then reactivate as shingles. The shingles rash occurs along the peripheral nerves coming off the spinal cord and the head and neck. The most serious kind affects the eye and can cause blindness, and shingles can also cause meningitis. In 10 to 20 per cent of people, shingles can be followed by a very painful chronic condition called postherpetic neuralgia. What Hope-Simpson showed was that shingles is a good model for immunosenescence. The exponential increase in the risk of shingles with age corresponds to the exponential decline in the human immune system, especially the cellular immune system, after the age of 50. We know that cellular immunity is important in immunosenescence. In the case of shingles, people may have high antibody levels to the varicella zoster virus but still develop the infection. This phenomenon of immunosenescence makes it important to find better vaccines and methods to improve the performance of vaccines in older adults.

Adjuvants are the oldest method for improving vaccine immunity. Think of an adjuvant like spices added to a meal. They are an enhancement that improves the final product but not the core product itself. An adjuvant is a substance that does not generate immunity to a particular infection, but when paired with a vaccine, it can enhance the immune response. In 2018, following a severe influenza season that was particularly bad for older

adults, two enhanced influenza vaccines were approved in many countries, including Australia, which had some extra kick to boost the immune response in older adults. One of these contained an adjuvant, which improved the immune response by about 25 per cent compared to the standard influenza vaccine. One of the oldest adjuvants is aluminium. Other adjuvants are based on natural fats such as squalene or cholesterol. Many doctors do not believe vaccines are as effective in older people because of their faltering immune systems. The newest vaccine against shingles, Shingrix, blew this theory out of the water by using a novel adjuvant based on cholesterol and other lipids. It achieved protection rates against shingles that no one ever imagined possible in older people – 91 to 97 per cent – which is better than many childhood vaccines. Another method for boosting the immune response is providing a higher dose of the vaccine. One of the enhanced influenza vaccines introduced in 2018 for older adults was a high-dose vaccine, and the other was an adjuvanted vaccine, both of which provided an improvement of about 25 per cent compared to a standard dose. Together, these enhanced flu vaccines have provided better protection for older people.

Another method for improving the response to vaccines includes conjugation, which is used in Hib, pneumococcal and meningococcal vaccines. After Hib vaccines, the conjugation revolution was upon us, followed by conjugate pneumococcal vaccines, and then conjugated meningococcal vaccines. Conjugated pneumococcal vaccines burst onto the market in 2001 and were incorporated into national immunisation programs by 2005, initially for children under the age of two years. They were a huge success and solved the problem of a poor response to the older pneumococcal vaccines. Rates of serious pneumococcal infection plummeted in children following the implementation of vaccination programs in many countries. Pneumococcal infection, which my infant son had in 2002, can cause pneumonia, septicaemia, ear infections or meningitis, with meningitis being more severe than that caused by meningococcal infection.

I knew these miraculous pneumococcal vaccines were probably going to work well in older adults too. I applied for a research grant to compare the new conjugate vaccine with the old polysaccharide vaccine in frail, hospitalised older people. Pneumococcus is a complicated bacteria that has many different serotypes (like variants, but which all exist simultaneously), and a vaccine is required against each serotype. The first conjugate vaccine worked against seven serotypes, while the old vaccine worked against 23 serotypes. We began that trial in 2005, the same year that the conjugate vaccine was put onto the national immunisation program for infants in Australia. Simultaneously, and years after Victoria started their pneumococcal program, the old polysaccharide vaccine was approved for adults 65 years and over in Australia. One of the interesting things we found in our study was that both vaccines worked equally well in older people. We also found that older, frail adults, even those who had very weak immune responses, were still capable of mounting a good response to vaccines. This makes it clear we should not give up on vaccines for older people. Our trial also measured antibodies in the blood using tests for one type of long-lasting antibody called IgG, which rises after infection and stays elevated longer than other antibodies, which only rise in the short term. Most commercial tests use a method called ELISA to measure IgG. However, there are special antibody tests that are not routinely done commercially. These can measure more than just the amount of antibodies and can give you an idea of how well those antibodies are functioning. We did these tests in our trial (a specialised test called opsonophagocytic assays or OPA) to look at the functioning of the pneumococcal antibodies and confirm the ability of people with very low OPA levels to mount a robust response to both vaccines. I also did trials of the pneumococcal conjugate vaccine in immunosuppressed adults who had had bone marrow transplants, working with a range of haematologists who took vaccination of their patients very seriously. These trials showed that the new vaccine could be given earlier than the old one and provided protection sooner.

Since that time, and following a large clinical trial of conjugate vaccines to prevent pneumonia in adults by Pfizer, conjugated pneumococcal

vaccines have become the gold standard for older adults as well as infants, and now cover many more of the different pneumococcal serotypes. We followed up on patients who had been in our clinical trial of hospitalised older adults and found that six years after we vaccinated them, while most had reasonable levels of ordinary antibodies, the OPA levels were quite low for several serotypes. In other words, six years after being vaccinated, older people could benefit from a booster. Inexplicably, in 2019, the Australian Technical Advisory Group on Immunisation (ATAGI) downgraded the recommendation for a pneumococcal vaccine dose every five years, changing this to a single dose only. It would not be at the age of 65, as it had always been, but at the age of 70, thereby hitting older people with a double whammy of having to wait longer to be protected against pneumonia, and not being able to have a subsequent dose. The new guidelines became incredibly complex and difficult to understand. Several experts in adult immunisation wrote to various stakeholders to question this decision, but the COVID-19 pandemic arrived soon after, and this blow to older Australians was forgotten. Ironically, numerous studies show that coinfection with COVID-19 and other infections such as pneumococcus is relatively common. We already knew this from past influenza pandemics, including from pathology samples from the 1918 Spanish flu pandemic, which showed that bacterial pneumonia could complicate the initial viral infection and prove fatal. Sadly, pandemic planning often forgets to consider bacterial pneumonia. The most common of these is pneumococcal pneumonia, which can be prevented with vaccines. Yet we faced the COVID pandemic in Australia with newly downgraded pneumonia protections for the elderly. I honestly thought the COVID-19 pandemic would make them rethink this decision, but it was not to be. In the US and the UK, the age for this vaccine remains 65 years, and older adults may receive the conjugated vaccine followed by the polysaccharide vaccine.

In addition to substances or methods that enhance the immune response to vaccines, many vaccines also contain preservatives or antimicrobials. One of the great advances in medication security has been the use of methods to preserve and protect food, beverages and medications from

bacterial or fungal contamination. For example, drinking raw milk increases your risk of contracting serious and potentially fatal diseases that affect cows, such as H5N1 avian flu, bovine tuberculosis and brucellosis. Louis Pasteur introduced pasteurisation, which uses heat to kill bacterial contaminants in milk or other consumables. Prior to pasteurisation in the early 20th century, thousands of people regularly died of tuberculosis and other diseases contracted from raw milk. It's ironic that today, after more than a century of health gains and lives saved because of pasteurisation, there is a fad for drinking raw milk in certain communities, and a rise in outbreaks linked to this practice. Vaccines, like food and medications, may also contain preservatives to prevent bacterial or fungal contamination and to keep the vaccine sterile. An example is thimerosal, which contains very small amounts of mercury. Thimerosal has been shown to be safe in adult vaccines but controversial in childhood vaccines, which is why it has not been used in vaccines for children for over 20 years. Other substances in vaccines include stabilisers, such as sugars and gelatine. Gelatine is often derived from pigs, which has been a cause of vaccine hesitancy in some Muslim countries. The process of making vaccines may also involve the use of porcine enzymes. However, in most Muslim countries, religious leaders deem vaccines to be acceptable, even if they contain porcine products.

The process of developing vaccines is long and arduous and begins with preclinical or animal studies, which may involve identifying suitable targets to use as vaccines. Some take decades to develop. Today, the use of artificial intelligence has made this faster and more efficient, enabling the processing of vast amounts of available scientific data at record speeds as well as characterising and identifying the best vaccine targets. Once suitable vaccine candidates are identified, they are tested in laboratory studies and on animals. If the results are promising, the research moves to human clinical trials, which are conducted over at least three phases. These must be approved by a human research ethics committee and be reviewed for safety implications, and people must provide written, informed consent to participate. Phase 1 trials usually look at the side effects and best dosage and involve small numbers, such as 10 to 15 people. Phase 2 trials are larger

studies looking at the frequency of side effects and may involve 20 to 100 people. If a vaccine is deemed safe based on phase 1 and 2 trials, it will move to larger phase 3 trials, which measure the safety and efficacy in preventing the infection of interest. Typically, these require much larger numbers of people, often in the thousands, who are randomly allocated to two or more groups termed ‘arms’. The size of the trial is calculated statistically to ensure it can detect differences between arms. These are usually controlled and sometimes double-blinded. That means neither the doctor nor the patient knows which treatment is being administered. This reduces bias that may arise if either party believes they are getting the active vaccine. A controlled trial measures a vaccine against a placebo or other vaccine for comparison. Sometimes, it is unethical to give nothing to people in one arm of the trial. For example, if there is already an approved vaccine for this infection and the trial is testing a newer vaccine, the test intervention is the new vaccine, and the control is the old vaccine, and these are compared for their ability to prevent infection and for the rate of side effects.

The standard approach to measuring vaccine side effects in a clinical trial is to measure anything untoward that happens to a person within a set period of time following the vaccination, typically 28 days, but longer-term follow-up also occurs. Vaccine side effects can be divided into local and systemic effects. The local effects include redness, swelling and pain at the injection site, while systemic effects are those that affect areas or parts of the body beyond the injection site. The most common systemic side effect is fever, which can occur after almost all vaccines. Other systemic side effects include aches and pains, tiredness and headaches, also common after many vaccines. Most of these side effects are transient and do not result in long-term complications. However, we are interested in identifying potentially serious adverse effects, so anything that occurs within 28 days of vaccination is recorded. If someone has a ruptured appendix or falls off a ladder and breaks their leg, these will all be recorded as ‘adverse events following immunisation’. Some of these may be unrelated to vaccination and some may be related to vaccination. If an adverse event is unrelated to

vaccination, it will be seen at the same frequency in the control arm. Trials usually have a data safety monitoring board that reviews the safety data as the trial progresses and can terminate it if there is a serious safety signal. After the trial is over, safety data are analysed carefully between the intervention (vaccine) arm and the control arm to see if any observed events are statistically more likely after the vaccine.

During clinical trials, doctors may observe the placebo effect. This describes the reporting of symptoms by people following the administration of a placebo, which is a dummy drug or vaccine that does not contain any pharmacologically active material. In the case of a vaccine, the placebo may simply be saline, which should not cause any side effects. The placebo effect refers to the tendency of people to report non-specific side effects following something they believe to be the drug or a vaccine. The placebo effect may also result in patients reporting subjective improvements or positive effects. The randomised placebo-controlled clinical trial design eliminates the placebo effect, allowing measurement of the side effects that are specific to the vaccine. Randomisation also distributes any unmeasured characteristics that can affect the outcome across the study arms, accounting for other factors that may affect the risk of infection or side effects. For example, smoking may increase your risk of respiratory infections. In a randomised control clinical trial of a pneumonia vaccine, smokers should be equally distributed between all the arms of the trial, nullifying the effect of smoking on respiratory symptoms or pneumonia. Trials for medications used to treat diseases, whether it be a new drug for cancer or diabetes, follow this same process of randomised controlled clinical trials.

COVID-19 vaccines were produced in record time in late 2020 compared to the very long time it usually takes to develop vaccines. All the vaccines against COVID-19 that we use today were subject to clinical trials, including phase 3 trials, which showed that the first-generation COVID-19 vaccines were highly effective in preventing infection and serious complications against the earlier variants of COVID such as Alpha and even Delta. People repeat the mantra ‘COVID vaccines do not prevent infection or transmission’, but all we have to do is look at the first clinical trials of

these vaccines to see this is not true. The problem is that the immunity provided by COVID-19 vaccines wanes over a period of three to six months, necessitating boosters to maintain protective immunity. In addition to that, the virus itself has continued to mutate, and each mutation is less and less related to the virus that the vaccine was designed to protect against. The process of updating the vaccines has been far slower than the speed of mutation of the virus, largely due to regulatory frameworks rather than technical difficulty. One of the benefits of mRNA technology is that these vaccines can be updated in as little as six weeks. During the COVID-19 pandemic, there was no problem with the clinical trials done to approve these vaccines. They followed the usual process for vaccine trials, albeit with fast-tracking under the emergency provisions of organisations like the US Food and Drug Administration (FDA). Most regulatory agencies have the option to fast-track drugs or vaccines during an emergency, such as a pandemic, and there is no doubt we would have seen a substantially higher loss of life without this. The greatest benefit of COVID-19 vaccines is their protection against hospitalisation and death, which, unlike protection against infection, does not wane as rapidly and tends to persist even in people who are not up to date with their boosters. Without the emergency provisions of regulatory agencies like the FDA, we may still be waiting for approval of COVID-19 vaccines.

The other reason clinical trials were conducted rapidly for COVID-19 vaccines was the enormous amount of infection all over the world, making it highly feasible to do clinical trials that measured the prevention of infection, hospitalisation and death. The other difference was the enormous and concerted effort, funding and resources poured into developing vaccines against the worst pandemic of our lifetime. We saw unprecedented collaborations, even between vaccine makers like GSK and Sanofi, which are usually competitors. Platform technologies that had been developed for Ebola and Marburg virus vaccines were quickly pivoted towards developing COVID-19 vaccines, with adenovirus vectored vaccines being one example. The mRNA vaccines, built on over a decade of past research – companies like Moderna and BioNTech were working on different mRNA

vaccines – rapidly switched focus to COVID-19 vaccines in 2020. We saw unprecedented funding from multiple directions, including governments, non-government organisations and philanthropists. Singer Dolly Parton provided funding towards the development of the Moderna vaccine and sang a song called ‘Vaccine’ to the tune of her hit song ‘Jolene’ while she was filmed receiving her first dose. We saw various vaccines developed around the world, including mRNA, adenovirus vectored, whole virus inactivated and protein subunit vaccines. The star performers as objectively measured by the clinical trial data were the mRNA vaccines made by Pfizer and Moderna, and the protein vaccine made by Novavax.

The numerous clinical trials of COVID-19 vaccines and boosters published from 2020 onward measured prevention of infection, hospitalisation, ICU admission and death. So, we have tangible clinical data that show that COVID-19 vaccines protect against infection, hospitalisation and death. Some vaccines, however, are approved based on the immune response they elicit as measured in a randomised clinical trial rather than actually measuring the prevention of disease. For example, meningococcal meningitis is quite rare, so it would be unfeasible to do phase 3 clinical trials due to the enormous number of people required. Therefore, these vaccines have been approved based on the measured immune response and protective levels of antibodies generated by the vaccine. Influenza vaccines, too, are approved based on levels of antibodies generated by the vaccine. Generally, the immune response to the vaccine is a good proxy for clinical protection.

You may have heard the term phase 4 trial, which refers to studies of safety and efficacy, including long-term effects after the vaccine is approved and rolled out in a population. There is no medication or vaccine anywhere in the world that is 100 per cent effective and 100 per cent safe. All drugs and vaccines have side effects, but when they are licensed for use in the community, it means they are generally safe, and the benefits vastly outweigh any potential side effects. This also depends on the incidence of the disease in question. For example, when smallpox was rife in the world, the risks of the disease far outweighed the risks of the vaccine. Shortly after

the 9/11 terror attacks and the anthrax attack in the United States, there was heightened fear of a smallpox attack, despite the virus being eradicated. Stockpiles of the virus are held in the US and Russia, and it is also possible to create the virus synthetically in a lab. There were also concerns about illicit stockpiles of viruses and biological weapons in other countries. As a result, the US began vaccinating military and civilian personnel against smallpox. However, the smallpox vaccine does have some serious side effects in a small proportion of people, including myocarditis (inflammation of the heart) and a skin condition called eczema vaccinatum. This occurs in people who have existing skin diseases and can be fatal. The vaccinia virus that forms the smallpox vaccine is a live virus, and in people with impaired immunity it can cause widespread vaccinia infection in the body. In 2001, there was no smallpox in the US, so when vaccinated people started experiencing severe side effects such as myocarditis at a rate of about one per 10 000 vaccinees, the vaccination program was halted because it was clear the risk of the vaccine exceeded the risk of the disease (the latter being non-existent). If, however, smallpox re-emerged, it has a death rate of 30 per cent, so the risk of smallpox would outweigh the risk of vaccination.

Sometimes, very rare side effects will not be detected in a typical phase 3 clinical trial. This is why robust safety monitoring systems are present in many countries, with the gold standard being the Vaccine Adverse Event Reporting System (VAERS) in the United States. Such systems have data on millions and millions of people who have received vaccines and allow a very comprehensive study of vaccine side effects. They also work well in detecting rare side effects that clinical trials cannot detect. There are also similar large datasets that allow us to measure the population impact of vaccines, including herd immunity.

3

VACCINE SAFETY

When I’m vaccinating someone with the influenza vaccine, one of my routine questions is: ‘Are you allergic to eggs?’ That’s because the vaccine is made in eggs and someone with an egg allergy can have an anaphylactic reaction. On one occasion, the patient replied, ‘Oh yes, I am allergic to eggs!’ Phew, I thought, thankful I had asked. Then she added, ‘I can eat them scrambled, but I can’t eat them boiled. Boiled eggs make me feel sick.’ I explained to her that this wasn’t an allergy and that she could have the flu vaccine safely.

Just as patients can have different perspectives on vaccine side effects, so too can doctors and researchers. However, there are accepted scientific methods and regulatory systems for assessing vaccine safety, which I will outline in this chapter. This doesn’t stop a range of inadequate studies from being conducted. For example, some studies seek out people who believe they have been injured by vaccines and report on their symptoms without any comparator group. Some symptoms may be unrelated to vaccines, so without a comparison of vaccinated and unvaccinated people, you cannot draw any conclusion about vaccines as a cause of symptoms. Yet this kind of study is common. It is called a case series, which is a description of a collection of people experiencing a particular illness or condition. A good example is the case series of 12 children published in *The Lancet* in 1998 suggesting that the measles vaccine in the combined measles-mumps-rubella (MMR) vaccine caused autism. Without any scientific method that could prove causation (that the vaccine caused autism), they suggested that

both the measles virus and the measles vaccine could cause inflammatory bowel disease, which then went on to cause autism. The lead author, Dr Andrew Wakefield, developed a following, including many parents of children with autism who were looking for answers. Parents of kids with complex diseases are vulnerable to influence from anyone alleging they have a solution, and so Dr Wakefield became the hero for many parents of children with autism. The study had no control group and multiple methodological problems, and there was no way the study could prove that MMR caused autism. Yet this study elevated Dr Wakefield to become a hero to the anti-vaccine movement, wreaked havoc on MMR vaccine programs worldwide, resulted in a sustained drop in MMR vaccination rates in the UK, and caused a measles resurgence. Eventually, *The Lancet* retracted the paper after most of the original authors distanced themselves from the study and serious ethical breaches and financial conflicts of interest were exposed. I will describe more about that later in chapter 4.

While it is important to always listen to patients and acknowledge the symptoms they are experiencing, assessing causality is a specific science. This was first outlined by Sir Austin Bradford Hill, who began studying whether cigarettes caused lung cancer. To prove causation, you must assess a series of criteria (called the Bradford Hill standards) using a range of scientific methods. Yet even today, many researchers and scientists do not understand the science of assessing if an exposure (such as a vaccine) caused a particular outcome (e.g. death). We see similar case series of patients who believe COVID vaccines have injured them, without any comparator group or proper scientific method. All vaccines, including COVID vaccines, can have side effects, and there is a scientifically accepted method for assessing their safety.

No drug or vaccine is 100 per cent safe or 100 per cent effective. They all have side effects, and they don’t always work. For example, antibiotics may cure 90 per cent of infections but may not work in some people, either due to drug resistance or the wrong antibiotic being given. If your child has ADHD, the doctors may try a few different medications because one medication may not work as well as another in your child. All drugs have

side effects, which are mostly minor and rarely serious. In the case of ADHD medicines, they can cause irritability, loss of appetite and even high blood pressure. A small proportion of people are allergic to antibiotics, and rarely, some may get fatal side effects such as Stevens-Johnson syndrome. They may only find out when they have a serious infection and are treated with the offending antibiotic, which then causes an allergic or other reaction. Vaccines are no different. They may protect 60 to 90 per cent of people, depending on the vaccine, and they may have side effects. Sometimes, bad things happen to people – coincidentally – after a vaccine. Therefore, we refer to adverse events *following* immunisation. This makes it clear there is a temporal relationship between the vaccine and the adverse event (which may range from fever to breaking a leg in a car accident) but makes no judgment about causation. Causation is then established through a range of mechanisms, including clinical trials and post-marketing surveillance to look at the expected baseline rate of any events (such as a sore arm, headache or more serious events such as death) and analyse whether the same events occur at a higher rate after vaccination.

A very common adverse event occurs at a frequency of more than 10 per cent, a common one from 1 to 10 per cent, an uncommon one from 0.1 to 1 per cent, a rare one from 0.01 to 0.1 per cent and a very rare one occurs in less than 0.01 per cent of vaccinated people. Fortunately, vaccine adverse event monitoring systems in countries with large populations, such as the VAERS, Vaccine Safety Datalink also in the US and the yellow card system in the United Kingdom, provide us with data on millions of reports of adverse events after vaccination, which allows us to evaluate safety at a larger scale than a clinical trial. Anyone, including doctors or members of the community, can report suspected vaccine adverse events to these systems. It is important to note that a patient may have a different understanding of a side effect than a doctor. For example, my patient who believed she was allergic to eggs was not allergic according to the medical definition.

There is a rigorous step-by-step process for the development of new vaccines and drugs, which involves the phased clinical trials process. If a

drug or vaccine is safe in a phase 3 clinical trial, we can be confident there are no common serious side effects. However, very rare side effects may still be possible. Regulatory authorities consider the risks of the disease and the risks of the drug or vaccine in making their final recommendation. However, further scrutiny is carried out after the drug or vaccine is used, a process called post-licensure safety surveillance. The best example of this is the first vaccine against rotavirus. Rotavirus is a common diarrhoeal disease that can be fatal to infants. In 1998, the first rotavirus vaccine, RotaShield, was approved in the United States. The vaccine was rolled out in October 1998, and within seven months, a safety signal was picked up by the VAERS system, comprising nine cases of intussusception in infants who had been vaccinated. Intussusception is a kind of telescoping and twisting of the bowel, which can result in blockage and be fatal. There were nine cases in seven months in the US compared to only four cases over the seven years before the vaccination program started. At this point, the vaccination program was temporarily suspended and further detailed safety studies were conducted. This confirmed there was indeed a risk of intussusception in about one in 10 000 vaccinated infants. The vaccine program was permanently ceased in October 1999. Second-generation rotavirus vaccines had to be tested in clinical trials large enough to pick up this rare side effect. It necessitated over 60 000 people to participate in the trials, which was a large enough sample size to detect the side effects. The initial trials were much smaller, with 27 trials comprising about 10 000 children. The safer, second-generation rotavirus vaccines are still used today and have a lower risk of intussusception – about one in 20 000 to 100 000 – compared to the first vaccine. In this case, the risk–benefit equation favours vaccination compared to the risks associated with rotavirus infection. The key lesson is that robust surveillance for vaccine adverse reactions will pick up rare side effects that are not detected in clinical trials.

Another well-known example of failure in vaccine safety was the Cutter polio vaccine incident in 1955. Cutter Laboratories was a manufacturer of the Salk inactivated polio vaccine (a killed rather than a live virus polio vaccine), which promised to end the epidemics of paralytic polio that were

plaguing the United States. Jonas Salk, a doctor from Mount Sinai Hospital in New York, began working on a polio vaccine in 1947 at the University of Pittsburgh. He developed an inactivated polio vaccine by using formaldehyde to kill the polio virus, then used the killed virus, which could no longer cause illness, to provide immunity against polio. Salk's vaccine was proven to be 80 to 90 per cent effective and safe in a large 1954 trial, and his blueprint was licensed to manufacturers to mass-produce the vaccine. The Cutter labs, however, had failed to properly inactivate the vaccine, resulting in 120 000 children being injected with live polio virus. Over 40 000 children contracted polio, with 51 becoming paralysed and five dying. A series of missteps and a lack of adequate safety procedures at the laboratory were responsible for this tragedy. Prior to the vaccination program commencing, a scientist at the National Institutes of Health identified the problem after she tested the Cutter vaccine on monkeys and found half the samples caused polio in the animals. She reported it to her supervisor, who failed to take action or tell anyone else. As a result, the mass vaccination program began with the Cutter vaccine and vaccines from four other manufacturers. Reports of vaccinated children and their family members developing polio soon followed, only after receipt of the Cutter vaccine, and the offending vaccine was withdrawn within the month it started – April 1955. The whole polio vaccination program, even the safe vaccines, was paused as a result. This was a huge blow to vaccination programs and public confidence in vaccines. The Cutter incident sounded the death knell for the inactivated polio vaccine. Another American physician, Albert Sabin, was working on a different kind of vaccine for polio. Sabin engineered the live polio virus to make it harmless and used it as a vaccine. The vaccine could be given orally as drops and was used in most of the world for over 40 years. After polio was well controlled in the world, it became apparent that the Sabin vaccine, which is excreted in the faeces and can end up in waterways, could sometimes mutate back to a virulent form. This is called 'vaccine-derived paralytic polio'. In 1999, the risk of vaccine-associated paralytic polio caused a switch back to the Salk-type inactivated vaccine in the US. The vaccine is extremely safe and there

has not been a Cutter-like incident since 1955. This incident was the catalyst for the stringent safety systems we now have, including the testing of vaccines by the US FDA. The substandard practices in the Cutter Laboratories could not occur today. Now, most high-income countries use the inactivated vaccine, which is much more expensive than the oral polio vaccine. The live, oral polio vaccine continues to be used in low- and middle-income countries. This highlights global inequity in vaccines. We have all heard conspiracy theories about COVID-19 vaccines causing all kinds of side effects, from having microchips in them to control people to causing the spate of sudden deaths we have witnessed recently in young healthy people. The latter is likely related to COVID-19 infection, with many studies showing that infection increases your risk of heart attacks, strokes and cardiac arrest. There are also numerous studies showing the pathological mechanism by which SARS-CoV-2 affects blood vessels and multiple organs in the body. The most serious side effects of COVID-19 vaccines occur with the adenovirus vectored vaccines, such as those made by AstraZeneca and Johnson & Johnson. A condition of abnormal clotting, affecting the brain, digestive system, lungs or other organs, occurs in a very small proportion of people who receive these vaccines, most commonly after the first dose. It is thought to be due to the adenovirus vector binding to certain proteins in the blood and then affecting clotting. The risk of this complication, termed ‘thrombosis and thrombocytopenia syndrome’ (TTS) or vaccine-induced thrombosis and thrombocytopenia (VITT), is about one in 26 000 to one in 260 000 doses and is more common in younger people. The death rate once VITT is diagnosed has varied in different countries, generally ranging from 18 per cent to 40 per cent. Due to poor procurement strategy, Australia invested heavily in this vaccine and had very few other options when the vaccination program began in 2021. There were almost 14 million doses of the AstraZeneca vaccine given in Australia, and from these, 170 cases of VITT and two deaths were attributed to VITT (with a much lower fatality rate of around 5 per cent in Australia compared to other countries) at a time when Australia had its international borders closed and very little COVID-19. The oddly low fatality rate in Australia was attributed

to vastly superior detection and treatment. But Australia does not stand out as vastly superior in other areas of diagnosis and treatment compared to Germany, the US, the UK or other countries with well-functioning health systems, so it begs the question of whether there is another explanation for the low fatality rate in Australia. Another plausible explanation is a difference in how deaths are attributed to vaccination or not. If some deaths that were vaccine-related were not attributed to the vaccine, for example, then this would give a falsely low fatality rate. In fact, there was inconsistency in the classification of VITT between different countries for several years and it wasn't until 2024 that an attempt was made by the Brighton Collaboration to make guidelines consistent across countries. The Brighton Collaboration is a group that works to standardise the measurement of vaccine side effects so it is objective and consistent across countries. It also evaluates the risks and benefits of vaccines and has been an important part of the vaccine safety landscape for over 20 years.

In 2021, when reports hit the media of younger people dying suddenly from TTS after being vaccinated with the AstraZeneca vaccine, and international data started accruing about this vaccine, I was extremely concerned about the risk–benefit equation not being favourable to vaccinating younger people at this stage, given we had very little COVID-19 in Australia. I went ahead and did a research study with other colleagues to measure the risk–benefit of using the AstraZeneca vaccine in Australians under the age of 60 years. In this study, I also compared the rate of VITT following the AstraZeneca vaccine with the rate of other notable vaccine adverse events that resulted in the cessation of three past vaccine programs. This included smallpox post-9/11, intussusception following the first rotavirus vaccine, and switching from live to inactivated polio vaccines in high-income countries.

Vaccine-associated paralytic polio has been increasing around the world, especially in countries with low polio vaccination rates. This was the rationale for high-income countries switching from the oral polio vaccine to the more expensive inactivated polio vaccine. In low-income countries, the oral polio vaccine continues to be used. In the US after 9/11, hot on the

heels of the anthrax attack in 2001, there were fears of further bioterrorism attacks, including smallpox, and vaccination against the virus was commenced on over 450 000 military personnel in 2002. Serious side effects included one case of encephalitis and 37 cases of myocarditis or pericarditis after vaccination. There were no deaths. More than 37 000 additional civilians were vaccinated in 2003, and there were 21 cases of myocarditis or pericarditis. That translates to about 5.5 per 10 000 vaccinations, ten times higher than myocarditis or pericarditis after COVID-19 vaccines, which is about 2–8 per 100 000 vaccinations. This, together with other rare, serious side effects, prompted the cessation of the civilian smallpox vaccination program, as the risk of smallpox disease was zero at the time, so such risks of the vaccine were unacceptable. If smallpox were to re-emerge, however, it could kill 30 per cent of infected people, so the risk of disease is far greater than the risk of side effects from vaccination, so the risk–benefit decision would change in favour of vaccination.

In evaluating the risks and benefits of the AstraZeneca vaccine, we looked at the side effects data for smallpox, polio and rotavirus vaccines, and the threshold for ceasing these vaccination programs. Then, we compared these to the available data for AstraZeneca and VITT. We showed that the data for VITT showed greater risk than for rotavirus or polio policy changes and similar risk to the smallpox policy change in the US. In Australia, the problem was an over-investment in a single vaccine, AstraZeneca, so policymakers had dug in to defend their position. Not only were differences in the side effect profile becoming apparent, but the clinical trials clearly showed that the mRNA vaccines had superior efficacy. The government silenced doctors from speaking out about their safety concerns by using a two-pronged approach of threatening us with litigation under the Therapeutic Goods Administration laws (designed to prevent doctors from advertising products) and punitive action by the Australian Health Practitioner Regulation Agency. Doctors were explicitly forbidden from saying that one vaccine was better or safer than another and could only repeat official government messaging to avoid repercussions. I shared

this analysis, and the conclusion that it was best to avoid this vaccine in people under the age of 60 at that point in Australia, with health authorities in April 2021. Later the same day, the policy was changed to recommend the vaccine only be used in people over the age of 50 years. Our paper was later published in the journal *Vaccine*. By June of that year, the policy was changed again to increase the age cut-off to 60 years, as we had recommended. By the end of the year, more data had accrued on the risk of VITT, and most countries that could afford mRNA vaccines (high-income countries) had abandoned the use of adenovirus vectored vaccines like AstraZeneca and the similar Janssen vaccine. Even the UK, where the AstraZeneca vaccine was developed, does not use it any longer. However, it continued to be used in low- and middle-income countries, including India, which manufactured it under the name Covishield and also made the Russian Sputnik adenovirus vectored vaccine. By mid-2024, however, the vaccine stopped being manufactured.

The mRNA vaccines, too, have rare and serious side effects, with a safety signal for myocarditis and pericarditis becoming apparent early on and also seen in clinical trials. This affects mainly males in their teenage or young adult years and tends to resolve within a short period of time. However, COVID-19 infection also causes myocarditis and pericarditis at a rate much higher than seen following vaccination (50–180 per 100 000 following infection compared to 2–8 per 100 000 after vaccination). In both cases, this is thought to be a response of the immune system to the spike protein, which is in both the vaccine and the virus. In fact, myocarditis and pericarditis also occur at a similar rate following the Novavax protein vaccine, which is not an mRNA vaccine. The SARS-CoV-2 virus turns out to be dangerous to the heart and blood vessels in many ways, causing widespread clotting, risk of heart attacks, abnormal rhythm of the heart and sudden cardiac death. It can also directly invade the heart muscle and kill the cells within the heart muscle. Numerous studies show that the COVID-19 vaccines have an overall protective effect on the heart and reduce the serious cardiac effects of the virus.

I have been researching the effect of infections on the heart since 2007, including influenza and COVID-19, and have published many studies on this topic, including the use of vaccines to prevent heart attacks following influenza. As a trainee physician, I had originally wanted to be a cardiologist and did quite a bit of clinical cardiology with some of the great cardiologists, including Dr David Richmond and Professor David Kelly at Royal Prince Alfred Hospital, and this has remained a lifelong interest for me. In fact, I was in the middle of my specialist physician training when I decided to do the Australian field epidemiology program, which caused a major detour in my professional journey. I had intended to do cardiology as my specialty, but wanted to learn epidemiology, so did the Master of Applied Epidemiology at the Australian National University, which threw me headfirst into infectious disease outbreaks. I also completed my physician training and became immersed in infectious disease outbreaks and the prevention of the same from 1992 onward. Influenza was one of the infections I started studying 30 years ago, and it remains a key focus of my research. In 2006, when I began doing a study of influenza, influenza vaccines and their relationship to heart attacks, I began working with a cardiology trainee who later went on to be a cardiologist at a teaching hospital in Sydney. We continue to collaborate today on a range of studies of infection and the heart. So, I have been very interested in studying the effects of COVID-19 and its vaccines on the heart.

In 2021, having looked at all the available evidence around mRNA vaccines, I was confident in recommending to my then 19-year-old son and 21-year-old daughter that they should get vaccinated and continue to get boosters. In 2021, the NSW health department did a phenomenal job in establishing mass vaccination clinics in Sydney to enable rapid scale-up of the COVID-19 vaccination program in the largest city in Australia. My daughter, who had grown up hearing me talk about vaccines, got a job in 2021 at the biggest vaccination hub at the former Olympic site in Homebush. Her job was to provide directions and guide the long queues of people waiting for their vaccines. When she was a toddler, she was in day care at the same hospital where I worked, the Children’s Hospital at

Westmead, where the National Centre for Immunisation Research and Surveillance is based. She would be in the car with me as I drove to work, strapped into her booster seat on a 40-minute drive. To make it a fun learning experience for her, I used to teach her the alphabet as we drove. I would give her a letter and she had to say a word beginning with that letter. The first time I did this, I had to laugh when she said, 'V is for Vaccine.' Anyway, despite the myocarditis risk of mRNA vaccines, the risk–benefit analysis clearly favours the vaccine over the disease, especially now that data are accruing on the serious and debilitating impacts of long COVID in a significant proportion of people. Multiple studies show that not only does vaccination prevent serious complications of COVID-19 but it can also reduce your risk of long COVID.

Another recent case of vaccine adverse events was the Sanofi vaccine Dengvaxia. The dengue virus causes thousands of deaths a year globally. It can cause a haemorrhagic fever (somewhat like Ebola) in the most severe cases. Haemorrhagic fevers are caused by four families of viruses – filoviruses (Ebola, Marburg), flaviviruses (dengue, yellow fever), arenaviruses (Lassa fever) and bunyaviruses (hantavirus, Crimean–Congo haemorrhagic fever, Rift Valley fever) – with dengue being the most common globally. Many countries suffer repeated and severe epidemics of dengue, including the Philippines. As I write this in 2024, Brazil is suffering a major epidemic, with over 9 million cases up to September 2024. Many had tried and failed to develop dengue vaccines in the past as the immunology of dengue is quite complicated because the virus has four different serotypes (each like a separate virus) and is characterised by a specific complication of the infection called antibody-dependent enhancement (ADE). ADE means that if you already have antibodies to dengue, being re-exposed to the infection can cause more severe disease. After 20 years of research, Sanofi developed the first dengue vaccine, Dengvaxia, which was launched with health authorities in the Philippines in 2016. The country was suffering a severe dengue epidemic, with hundreds of children dying of dengue every year, so there was great interest in a vaccine. Over 800 000 children received the vaccine in the Philippines over

six months when a safety signal became apparent. It was causing ADE in children who had never had dengue before. In other words, children were at risk of developing ADE triggered by antibodies from the vaccine if they later got infected with the virus. The vaccine was only safe in children who had been infected in the past. About 14 children died as a result of the vaccine between 2016 and 2017. The case resulted in the prosecution of several government officials in the Philippines and set back all vaccination programs in the country. There was a huge backlash against all vaccines and rates of vaccination against measles, other childhood vaccines and COVID-19 vaccines were impacted by this case. As a result, measles and rubella cases had increased by 335 per cent by December 2023 according to the Department of Health. Dengvaxia remains approved in many countries, including Australia, the US and many European countries, but with the proviso that it can only be used in people who have been infected before with dengue virus. This means that people need to be tested and screened for antibodies to the virus before they can be safely vaccinated. Since then, two new dengue vaccines have been developed, including one made by Japanese company Takeda and a new vaccine by The Butantan Institute and Merck, so there is still hope for wider prevention of this deadly disease.

Another example of a rare vaccine adverse event occurred in Syria and Samoa. Both incidents, apparently unrelated, were with the measles vaccine. The measles vaccine, like many other vaccines, is lyophilised, which means it comes as a dried powder that must be reconstituted with liquid. We call the liquid a diluent, which is a sterile, inert fluid. The first incident occurred in Syria in 2014 and involved around 30 or more deaths of infants vaccinated with the measles vaccine, which was accidentally reconstituted using the anaesthetic agent atracurium instead of a harmless diluent. In that case, the vaccines had been packed and shipped together with the atracurium (instead of the real diluent) as part of a WHO vaccination program. The vial is a similar colour to that of atracurium, but it still seems an improbable mistake. In Syria, depending on which report you read, 15 to 35 babies died as a result, unable to breathe when the atracurium paralysed their respiratory muscles. A full investigation by WHO concluded

it was just a tragic accident. Inexplicably, the same mistake occurred in Samoa in 2018, resulting in two babies dying. The two nurses who administered the vaccines were charged with manslaughter and jailed, and the incident resulted in a drop in measles vaccination rates to 31 per cent compared to well over 90 per cent in neighbouring Pacific Island countries. Predictably, a massive measles epidemic occurred in 2019, with 53 deaths and over 4000 cases, prompting the government to declare a state of emergency in November 2019. Measles hits the immune system hard and causes immune paresis, a temporary state of dysfunction of the immune system, leaving it less able to respond to infections for up to three years. This results in an increased risk of all kinds of other infections for two to three years after measles. Worryingly, the COVID-19 pandemic began hot on the heels of the Samoan measles epidemic, with the population extremely vulnerable so soon after a measles epidemic. I had been following the measles epidemic in Samoa closely and was extremely worried when COVID-19 hit. We published a paper showing the possible heightened impact of COVID-19 should it have reached the shores of Samoa in 2020. Fortunately, Samoa closed its borders and kept COVID-19 out, buying valuable time until the vaccines were available.

There are some important case studies of genuine safety issues with some vaccines, how they were handled and what changes occurred as a result. Serious side effects are rare and large safety databases show that approved vaccines are safe. The flip side of genuine safety concerns is fake news and immunisation myths. Risk perception is key to understanding how a community perceives and responds to vaccines. If the risk of disease is high and the disease is perceived to be serious, there is greater acceptance of vaccines and willingness to be vaccinated. Interestingly, when vaccination campaigns are successful, and diseases are controlled, fear of disease is forgotten, and fear of potential adverse events is highlighted. A good example is the scare about the MMR vaccine – which protects against measles, mumps and rubella – and autism. This was featured widely in the global media and impacted rates of MMR vaccination for two decades. On the other hand, when the disease is common and visible, fear of the disease

far overrides fear of adverse events. In Australia, *60 Minutes* ran a program on meningococcal meningitis in 2003. In this program, they highlighted the horrors of this deadly, vaccine-preventable disease and called for the protection of the Australian people with the available vaccine. The program raised so much public concern and demand for the vaccine that the government responded within two days of the *60 Minutes* feature with an announcement that it would fund a national meningococcal C vaccination program. This resulted in a dramatic decline in meningococcal meningitis in Australia. Even with COVID-19, we saw people rush out to get vaccinated in 2021 when vaccines first became available. But gradually, as disinformation spread around the world and governments trivialised the infection, the anti-vaccination sentiment grew, not just among outright vaccine refusers but also among people who may have willingly received their first two doses in 2021.

A popular social media commentator wrote in upper case ‘HALF of OMICRON DEATHES [sic] WERE IN VACCINATED PPL’. This is the ‘paradox of vaccination’, which is when total deaths reduce after vaccination, but the proportion of deaths in vaccinated people rises. Before a new vaccine is introduced, all deaths after infection are in unvaccinated people, and after a vaccine is introduced and a high proportion of the population is vaccinated, the proportion of deaths that are in vaccinated people rises. The social media commentator didn’t get the point that COVID vaccines have dramatically cut the number of deaths from infection, and her observation was the paradox of vaccination. Vaccinated people still die of COVID, especially if their last booster was a few years ago, but severe cases are far less common thanks to vaccination.

Vaccines have been one of the greatest public health advances in human history. At the same time, there have been lessons learned about infrequent but serious safety events around some vaccines, which have improved vaccine safety processes. The ability of public health agencies and public health leaders to communicate about vaccines and vaccine safety is key. Individual doctors who give vaccines should also be able to discuss the potential side effects of vaccines and listen to the concerns of their patients.

Vaccination is a medical procedure and requires valid informed consent from the patient or their parent. Coercive measures such as financial penalties to improve vaccination rates can backfire if things go wrong. There are plenty of ways we can ensure high vaccination rates and still provide people with choice, which I discuss further in chapter 11. But first, it is important to consider the anti-vaccine lobby and conspiracy theories around vaccines. It is important to understand and acknowledge that people are exposed to unscientific information in a wide variety of ways today, that it is difficult to sort through factual versus fabricated information, and that patients may have genuine concerns about vaccines. It is important for medical professionals to communicate with their patients, acknowledge and discuss their concerns and address them. On a societal level, when there is anti-vaccination propaganda being disseminated in the media or on social media, leaders and governments should address it. If we fail as individuals or as a collective to communicate adequately and empathetically, then we risk handing the stage to the anti-vaccine lobby. Even worse, we risk the anti-vaccination movement growing from a fringe movement to a mainstream phenomenon.

4

ANTI-VACCINATION – FROM FRINGE TO THE MEDICAL MAINSTREAM

A friend of mine was diagnosed with early stage breast cancer in 2024. She was booked to have the cancer surgically removed but cancelled the appointment after doing ‘research’ on alternative cures. I tried to encourage her to get the cancer removed, but she began refusing my calls and ignoring my messages. When I called her partner, he was distraught about the number of ‘friends’ giving her advice about alternative cures and was unable to convince her to get medical treatment. Even her sister, who’d had breast cancer decades earlier and survived due to medical therapy, happily supported her alternative therapy approach. In desperation, I reached out to oncologist friends to find out if there was a website or other resources I could refer my friend to, so she could make more informed choices about her treatment. They all told me that the rise in health disinformation since the COVID pandemic had also affected cancer treatment. They were seeing an increase in people shunning medical treatment of cancer and seeking ‘cures’ with herbs, supplements, prayers and other methods, including rubbing honey on the cancer. These same people would then turn to modern medicine when their herbal cures failed and the cancer had spread widely in their body, by which time it is too late for a medical cure.

The impact of the anti-science movement and medical disinformation since the COVID-19 pandemic has been far-reaching, seeping into other areas of medicine beyond vaccines. I had been following the impact of disinformation on vaccination rates, so it made sense that the impact was

wider. It also means business is booming for con artists willing to sell hope and wellness to vulnerable people. My friend has put her life in the hands of such a wellness ‘therapist’.

A catalyst for the backlash against medicine and science was COVID lockdowns, which remain emotionally triggering for many people. In 2023, eminent scientist Dr Francis Collins, the former director of the US National Institutes of Health, albeit not a public health expert, talked about the impact of lockdowns in rural Minnesota in 2020:

> If you’re a public health person, and you’re trying to make a decision, you have this very narrow view of what the right decision is, and that is something that will save a life. Doesn’t matter what else happens, so you attach infinite value to stopping the disease and saving a life. You attach zero value to whether this actually totally disrupts people’s lives, ruins the economy, and has many kids kept out of school in a way that they never might quite recover from. Collateral damage. This is a public health mindset. And I think a lot of us involved in trying to make those recommendations had that mindset – and that was really unfortunate; it’s another mistake we made.

Part of Collins’s comment is about school closures, which are written into every pandemic plan as a last-resort strategy to stop transmission of a pandemic. Periodic lockdowns were used in the pre-vaccine period of the pandemic in many countries in 2020 when there were no drugs or vaccines available, health systems were crashing, mass graves were being dug, bodies were piling up in refrigerator trucks and the virus was spreading uncontrollably. At the early stage of a pandemic, the only available methods to control it are non-pharmaceutical – testing, contact tracing, masks, social distancing, banning mass gatherings and, when all that fails, lockdowns. Lockdowns were rarely used for more than 4–8 weeks at a time around the world, and in the US, most of Australia and many other countries, most of 2020 was not spent in lockdown. The glaring exception was the state of Victoria in Australia, which had the longest continuous period of lockdown in the world – 111 days in 2020, and a total of 200 days of lockdown over three lockdown periods. Victorians were understandably angry about this. The lockdown in Minnesota, in contrast, was for two weeks. Public health measures to stop pandemic transmission are draconian because to stop a

virus from spreading, you must stop people mingling together. In 2020, Minnesota and other states were watching the unfolding horror in New York and taking precautionary action, which is entirely reasonable during a new pandemic about which little is known. In fact, in rural areas, health systems are less resilient and resources less available, so the impact of a pandemic may be greater. Dr Collins was concerned about impacts on business interests and on the freedoms of people to carry on as they wish. Yet this argument could be applied to the banning of vapes, control of tobacco, drink driving legislation and a range of other successful public health measures that curtail certain freedoms and impact the economy. The banning of vapes, tobacco control and alcohol control are detrimental to revenue generation for the tobacco and alcohol industries. In other words, these public health measures cause collateral damage to the economy. They are also detrimental to people's freedom to drink while driving, smoke and vape. However, we often place public health above profits for corporations. Sadly, Collins's comment led to a 'gotcha' moment for the proponents of the Great Barrington Declaration, who Collins had earlier rebuked for their proposed mass infection strategy early in the pandemic. They gleefully said they were right all along, and (essentially) public health had no role in pandemic control.

Worse than general anti–public health sentiment has been the adoption of anti-vaccine posturing by experts who sit on vaccine advisory committees. In fact, early in the pandemic, there was a deliberate strategy in several countries like the UK and Sweden to infect children to achieve mythical 'herd immunity' by mass infection, which was expected to protect older people. Herd immunity never arrived, and instead, we have had recurrent and ongoing waves of COVID-19. While the United States recommended routine vaccination for children based on the clear data that it was needed, the UK, Sweden and Australia have dug their heels in and continued to restrict vaccination of children. The US vaccinates children aged six months to five years, allows boosters for older kids, and recommends these in their national immunisation program. In contrast, the UK, Sweden and Australia do not allow routine vaccination of children

under the age of five and restrict boosters for older kids, even though all the clinical trials show that boosters are needed. It is a popular medical belief that although vaccine protection against getting infection wanes, protection against severe consequences like hospital admission or death is preserved in the long term. However, research shows that the protection vaccines offer against dying from COVID-19 also wanes eventually. A study from Denmark, which also denies vaccination to children under five, showed that long COVID occurs in children and is highest in kids under five, likely because they lack the protection offered by vaccines. It's tragic for Australia, which has very high vaccination rates and a vaccine-accepting population but a very minimalistic approach to COVID-19 mitigation. This, combined with public messaging that COVID-19 is trivial, means we are now experiencing low rates of COVID-19 booster vaccines, even in the highest risk groups, such as people living in nursing homes. When health leaders publicly minimise COVID and tell people it's over and 'just a cold', it is expected that booster rates will be low.

The UK and the US have always had a larger influence of the anti-vaccine lobby and have less trust in the government compared to Australia, which is more like its Asian neighbours, who are more trusting of their government and comply with public health orders. Research we did early in the COVID-19 pandemic showed this to be the case, highlighting differences in government trust in Australia, the US and the UK. Our study showed that in the US, under the Trump government, people who trusted that government were less likely to get vaccinated, whereas in the UK and Australia, people who trusted the government were more likely to get vaccinated. It is a matter of public record that President Trump advocated for unproven treatments such as hydroxychloroquine and ivermectin. Belief in unscientific treatments tends to go hand in hand with anti-vaccination, so it's no surprise that people who trusted the US government in 2020 were less likely to want vaccination.

In the US, the popularity of anti-vaccination is related to their unique and highly individualistic culture, while in the UK, there have been several historical events, such as the fallacious association of whooping cough

vaccines with encephalitis in the 1970s, the MMR autism scare and the mad cow outbreak in British cattle, which have impacted trust in vaccines and in government. Whooping cough itself causes encephalitis, but in the 1970s, an unfounded scare and misinformation about the vaccine causing encephalitis resulted in a dramatic fall in vaccination rates in the UK, and subsequent epidemics resulted in infant deaths from whooping cough. ‘Mad cow’ is the colloquial term for bovine spongiform encephalopathy, a universally fatal disease caused by a distorted protein called a prion, which causes progressive and ultimately fatal brain disease. Mad cow disease arises from the unnatural practice of feeding cattle, which are herbivorous creatures, bone meal, offal and other meat products, often from sheep, in their feed. Sheep are also subject to a prion disease called scrapie, and somehow the diseased brain of sheep with scrapie must have got into the cattle feed. Humans who consume infected beef can then develop the human form, called variant Creutzfeldt-Jakob disease (vCJD). The first case of mad cow disease in cattle was detected in 1986 in the UK. The government spent years denying the problem. In 1990, then agriculture minister John Gummer tried to feed his daughter a beef burger on national television to prove that British beef was safe. Even the chief medical officer at the time, Sir Donald Acheson, reassured the public that British beef was perfectly safe to eat. By 1993, over 70 000 British cattle had died of mad cow disease, and then in 1995, the first human death occurred in a 19-year-old man. This should have been a huge red flag because vCJD typically takes decades after consumption to occur and is usually seen in older adults. Ultimately, 226 people died of the disease and millions of cattle had to be slaughtered to stem the epidemic. Yet the government continued to dig in and defend British beef. This was an example of the government trying to protect the economic interests of the cattle industry over the health of the population. Minimising and denying the problem for years was the first response of the government, and it wasn’t until other countries started banning British beef that any definitive action was taken to control the epidemic. It took 14 years for the British government to finally admit that British beef had caused human vCJD. The image of John Gummer feeding

his daughter beef stuck with the people and eroded trust in the government. In 2001, I recall visiting a distant relative in London who cooked me a steak, insisting that British beef was now safer ‘than anywhere in the world’.

The controversy about the MMR vaccine also had origins in the UK when *The Lancet* published a paper in 1998 suggesting that MMR caused autism. The lead author was British doctor Andrew Wakefield from the Royal Free Hospital, who suggested that both the measles virus and the measles vaccine could cause a type of inflammatory bowel disease, which then went on to cause autism. The study itself comprised only 12 children, did not undergo ethical review, had no control group and had multiple methodological problems. It is astounding that this paper passed peer review and was published in a journal as prestigious as *The Lancet*. The media picked up on this research and it sparked a worldwide backlash against the MMR vaccine, which in turn generated a large, decades-long body of research to debunk the study. *The Lancet* initially refused to retract the paper, even after concerns about fabricated data began to arise and some of the co-authors retracted the main interpretation. Serious concerns about the validity of the science continued to be raised, causing most of the co-authors on the paper to withdraw their support for it, and in 2001, Wakefield left the Royal Free Hospital and moved to Texas in the US, where he set up a new institute and became a leading figure in the US anti-vaccination movement.

Following investigative journalism by British journalist Brian Deer, and a slow and protracted investigation by the General Medical Council, the paper was found to contain falsified data, and Wakefield to have undisclosed conflicts of interest. In 2010, the General Medical Council found that Wakefield had acted ‘dishonestly and irresponsibly’ in his research, and he was struck off the medical register in the UK, forcing *The Lancet* to finally retract the paper after 12 years of immeasurable damage to public health globally. During this time, vaccination rates for MMR had dropped, especially in the UK, but worldwide as well. Predictably, the UK began having measles outbreaks and deaths as a result. He later went on to

make an anti-vaccination film, continues to defend his 1998 study, and is embraced by the US anti-vaccination community. In 2024, London MMR vaccination rates for two doses by five years of age stand abysmally low at about 74 per cent, compared to over 95 per cent in Australia. In comparison, rates across the US are about 90 per cent, despite being a country with a large anti-vaccination movement. As I write, large outbreaks of measles are occurring in the UK as a result.

The anti-vaccination lobby has always existed, but it comprised a small but vocal lobby group, estimated to be less than 2 per cent of the population, a rate that had remained quite steady over the past few decades. The COVID-19 pandemic changed this and caused vaccine hesitancy and anti-vaccination sentiment to increase to unprecedented levels. One of the reasons may be that COVID-19 vaccination was the first time in 40 years (since smallpox eradication) that a vaccination was recommended for just about everyone in the population. Prior to that, vaccine programs were generally restricted to certain age groups, such as infants or the elderly, or certain risk groups (such as people with chronic illness). Suddenly, we needed vaccination for everyone, including young, healthy adults. In the first year that vaccination was introduced, vaccination certificates were required in many settings, such as when flying overseas or attending health care facilities, nursing homes and certain public venues. Although these requirements no longer exist, along with masks and lockdowns, the unprecedented scale of population vaccination against COVID-19 has resulted in vaccines becoming conflated with the bogeyman known as public health. Many people experienced loss and suffering during the pandemic, whether it was loss of work, business opportunities, freedom or loved ones. I believe the massive pushback against public health, such as the rise in anti-vaccination and anti-mask sentiment resulting from the COVID-19 pandemic, is possibly a case of shooting the messenger. People deal with loss and grief in different ways, but anger is part of this, and so public health and people advocating for the prevention of COVID-19 are easy targets for that anger. Much of that anger has been directed at lockdowns, but also at masks and vaccines. I have personally been blamed

for lockdowns by angry people on social media. They conflated my advocacy for public health with the personal suffering they experienced during a lockdown. In reality, I had no part in enacting lockdowns, and was not even in the inner circle of trusted government advisors. It was entirely a government decision. This anger has been noted by governments, who are afraid to poke the bear of public anger. As a result, they avoid talking about COVID-19 and pretend that everything's back to normal.

Before the medical mainstreaming of anti-vaccination during COVID-19, the anti-vaccine lobby had long been alleging that vaccinations cause complex conditions (most of which have no clear single cause) such as sudden infant death syndrome (SIDS), autism, Alzheimer's disease, brain damage, multiple sclerosis, diabetes, cancer, mad cow disease, AIDS and even shaken baby syndrome. Unbelievably, one prominent anti-vaccine campaigner with no credentials in health claimed that fractured skulls and retinal haemorrhages in babies who have been shaken are actually caused by vaccines rather than violent carers.

Most arguments against immunisation appeal to the concerns of parents for the health and wellbeing of their children, or in the case of adult vaccination, concerns about their own health. When we inject healthy babies with a vaccine, it causes physical pain, which can be an emotional and difficult experience for parents. Parents or patients may find it difficult to express their fears about vaccination to their doctor, and these failures in communication may make people more sympathetic to anti-vaccine arguments, which are widely available on every corner of the internet today – even in medical journals. There has been an explosion in medical publishing in the last decade, with an enormous number of journals that take on very similar names to established, reputable journals and charge high fees. Almost anyone who wants to publish something can get it published in one of these vanity publications that masquerade as serious science. I have seen medical colleagues confused by papers published in these journals, including one journal established by the anti-vaccination community. In medicine, you can find a publication to support whatever position you want to take, and the explosion in vanity publications in the

medical field has made this so much easier. Even journals that are not outright predatory are under pressure to generate revenue, which comes from authors paying fees to the journal, usually thousands of dollars per published paper. Recently, I attended a conference, where one of the speakers, a supposed top expert, presented data on the safety of COVID-19 mRNA vaccines, and instead of using reputable studies of vaccine safety, they flashed up a slide of a systematic review (which is a review of other people's research) from a little-known journal, which contains some misleading pie charts suggesting that the vaccines cause all kinds of side effects that are not known to be associated with these vaccines. I looked up the paper and immediately saw serious methodological problems with the study, and that it wasn't even registered. Just as clinical trials should be registered, it is now accepted practice that a systematic review should be registered in a database such as PROSPERO. This is yet another example of medical mainstreaming of anti-vaccination in the era of COVID-19.

When I worked in the health department in Victoria in the early 1990s, I learned from Dr Rosemary Lester, who later went on to become the chief health officer of Victoria, that presenting facts and figures to the anti-vaccine lobby didn't work. At that stage in 1992, public health figures were often invited to debate with anti-vaccine activists about the safety of vaccines, and Rosemary quickly learned that you could present science, data, graphs, charts and statistics until you were blue in the face, but it made no difference. Research on the anti-vaccination movement and lived experience of dealing with anti-vaccine disinformation shows that science, statistics and facts have very little impact when trying to debate or discuss vaccines with anti-vaccine activists. Anti-vaxxers often use emotive anecdotes of children with complex illnesses or who have died, often with graphic photographs, attributing these tragic cases to vaccination, without any evidence. They typically appeal to people's natural fears and desire to understand complex diseases and conditions for which simple explanations are not available. Some of the most successful approaches to countering anti-vaccination messaging have been to use similar, powerfully moving anecdotes. For example, newborn baby Riley Hughes developed whooping

cough in 2015 and tragically passed away in hospital when he was just one month old. His death was widely reported in the news, and the moving account of his story and his brief life had a powerful impact in Australia and is maintained on the website of the Immunisation Foundation of Australia. In addition, the Light for Riley project launched by his parents, Catherine and Greg Hughes, helped introduce maternal vaccination in the third trimester, which was already used in several other countries at the time Riley passed away, and introduced to Australia soon after. The Immunisation Foundation of Australia provides a range of powerful stories that show the importance of vaccination for children. This approach tends to be more successful in engaging with parents and tackling vaccine hesitancy than statistics and facts. When I say ‘anti-vaxxer’, I refer to committed vaccine refusers. There is a larger group of people who haven’t had a recommended vaccine simply because they were too busy or had other priorities and just hadn’t got around to it. Yet another group of people are ‘vaccine-hesitant’. They may not have made up their minds either way and could still be persuaded to vaccinate. It is these undecided people that both the anti-vaccine lobby and health authorities can successfully influence.

The reason that vaccines are so often implicated in causing so many diseases is that vaccination is universal – all (or most) children and now most adults (since COVID-19), receive vaccinations. When vaccination programs reduce disease burden and diseases become rare, there is an increased focus on potential or perceived adverse events. The timing and universal nature of childhood vaccination mean it will be coincidentally associated with many diseases and conditions that occur around that age. Consider that all (or most) children aged six months of age eat rice cereal. Some six-month-old children in the population will, tragically, be subject to various diseases or accidents, and some may even die. If we look at what all children who died had in common, superficially, it seems that eating rice cereal is associated with death. Eating rice cereal may be shown to be associated with death, but it is not necessarily a cause. The same applies to vaccines. For example, SIDS deaths occur during the age range 0–6 months, when many vaccinations are given, and thus you would expect

vaccinations to precede SIDS in some cases simply by chance. Several studies have shown that immunisation does not increase the risk of SIDS and may even lower the risk.

In France, a scare about hepatitis B vaccination causing multiple sclerosis arose several years after mass immunisation against hepatitis B commenced in 1994. France was one of the first countries in the world to introduce mass immunisation against hepatitis B. Over a third of the French population had been vaccinated against the disease when neurologists reported a small number of people presenting with multiple sclerosis following hepatitis B vaccination. There had also been mass vaccination in Taiwan and New Zealand around the same time, and no association with multiple sclerosis was noted. The French government ceased the hepatitis B vaccination program and a range of studies were conducted to investigate a possible association with multiple sclerosis. None of these confirmed such a relationship. This is an example of a mass vaccination program where a substantial proportion of the population is exposed to the vaccine and some may coincidentally get diseases that are unrelated to the vaccine. It is now accepted that the hepatitis B vaccine is quite safe, and it is included in infant vaccination schedules in many countries around the world, including France and Australia.

Interestingly, there is a lesson to be learned from hepatitis B vaccination and the arguments around protecting only the vulnerable during the COVID-19 pandemic. Hepatitis B infection has chronic complications, including cirrhosis of the liver and a deadly cancer, hepatocellular carcinoma. Most people clear the infection and develop antibodies. A small proportion become chronic carriers, which can be measured by testing for something called the E antigen, which is a part of the virus. It is chronic carriers who are most at risk of cirrhosis of the liver and hepatocellular carcinoma. The highest risk is infection of newborns and infants because the younger you are, the less likely you are to clear the infection, and the greater the risk of becoming a chronic carrier and developing complications. Therefore, vaccination has the greatest impact on infants. In many countries, up to the early 2000s, targeted vaccination was used for

infants born to high-risk mothers, usually identified by country of birth, as some countries have much higher rates of hepatitis B than others and newborns can become infected from a carrier mother. Vaccination research over many decades has shown that targeted programs (that only target a specified at-risk sub-population) rarely achieve adequate vaccination rates in that targeted group. This was shown in Australian studies as well, identifying that infants of high-risk mothers were not adequately vaccinated. This is the rationale for universal infant hepatitis B vaccination in Australia and other countries. When all babies receive it as part of the routine vaccination program, the most at-risk are protected. It seems many of the long-understood lessons of vaccinology were lost during the COVID-19 pandemic.

Individuals have every right to hold whatever beliefs they choose, however erroneous or dangerous those beliefs may be. It's a different matter when those individuals force their beliefs on innocent, dependent children, or, if unvaccinated, they get infected and infect another person who then suffers serious consequences. In the early 2000s, when I was working at the National Centre for Immunisation Research and Surveillance, I vividly remember the case of an Australian couple who shunned traditional nutrition and health beliefs and fed their infant daughter a diet consisting solely of rice milk, causing her to suffer for months and die of malnutrition. Many other cases like this continue to be reported, including the death of a baby fed quinoa milk in Belgium. Such parents believe in their cause and believe they know better than traditional medicine. They wilfully defy medical advice or shun it altogether, resulting in the suffering and death of babies. In a similar way, many anti-immunisation lobbyists are passionate, cannot be reasoned with, and will deliberately withhold immunisation from their children and refuse it for themselves. In 2020, there were many news stories from the US of COVID-19 deniers who believed the pandemic was fiction, even when they were in intensive care dying of COVID. I heard such stories from medical colleagues in the US, shocked to witness patients dying of COVID and still screaming that COVID was a hoax. One 30-year-old man from Texas attended a COVID-19 party in mid-2020 before

vaccines were available. The purpose of the party was to test if COVID was real and see if attendees got ill. Tragically, he ended up dying of COVID-19.

Why, then, do conspiracy theories appeal to people or strike a chord of fear in us? In the case of COVID-19, various geopolitical influences came into play early in the pandemic, and political polarisation resulted in community polarisation of opinions and beliefs. These were additional factors that caused the spread of disinformation about COVID-19 globally, but there are long-standing factors that also come into play. The COVID-19 pandemic, combined with unprecedented dissemination of dis-information on social media and a rise in populist politics and authoritarianism, has drastically increased vaccine hesitancy and anti-vaccination sentiment. Professor Richard Carpiano and colleagues explain in *The Lancet* the historical roots of anti-vaccine activism, and how COVID-19 was a catalyst that accelerated and expanded the influence of this agenda. They write:

> Before the pandemic, anti-vaccine activism increasingly aligned with conservative political identity. Two developments were crucial to this conservative shift. One was California's 2015 legislative effort to eliminate personal-belief exemptions for school vaccinations (bill SB-277), during which anti-vaccine activists mobilised to broaden their following beyond its traditional natural-living, left-leaning base through deliberate activation of, and outreach to, potential Tea Party and libertarian allies. The other was the formation of influential political action committees (e.g., Texans for Vaccine Choice) that lobbied state legislatures and promoted conservative political candidates with anti-vaccine positions … Reflecting broader, growing trends in anti-intellectual or anti-science populist discourse (especially in right-wing media outlets), clinicians and other health professionals who were publicly involved in pro-vaccine policy or commentary in advance of the pandemic were subject to harassment, physical threats, and violence by anti-vaccine activists. Media coverage documented numerous harassment campaigns, including those targeting vaccine scientist Peter Hotez, California State Senator and paediatrician Richard Pan … and paediatrician Nicole Brown for her popular, vaccine-promoting TikTok content.

In fact, we have seen mainstream media articles with an anti-vaccine flavour, and many more social media posts opposing vaccination. However, it was unprecedented for a medical leader to adopt an anti-vaccination stance. This is exactly what happened in Florida in 2023 when the Surgeon General, Dr Joseph Ladapo, called for cessation of COVID-19 vaccines on

the basis that he believed contaminants in the vaccine could alter human DNA. The mRNA vaccines are made using a DNA template initially (as are several other vaccines), and the resulting vaccine is then treated with an enzyme that digests any residual DNA. Regulatory bodies specify an upper limit for an acceptable amount of residual DNA in any drug or vaccine, which is a minuscule amount. There are no biologically plausible mechanisms for this to alter human DNA. Ladapo specifically alleged that DNA from a chimpanzee virus called SV40 is present in mRNA vaccines, and can cause cancer. A SV40 promoter sequence is used in several biological products and has been found in Pfizer COVID vaccines, but there is no data to support this theory, and federal health authorities in the United States countered his arguments. The FDA responded with a formal letter, which stated that the COVID-19 mRNA vaccines meet rigorous safety standards and that SV40 virus or proteins are not part of the vaccine. The letter also reiterated the vaccine safety systems, which have collected data on over a billion doses of mRNA vaccines and affirm safety. In January 2024, Ladapo issued a statement in response to the FDA's refutation of his claims:

> DNA integration poses a unique and elevated risk to human health and to the integrity of the human genome, including the risk that DNA integrated into sperm or egg gametes could be passed onto offspring of mRNA COVID-19 vaccine recipients. If the risks of DNA integration have not been assessed for mRNA COVID-19 vaccines, these vaccines are not appropriate for use in human beings.

With no supporting evidence and despite a thorough refutation by the FDA, he escalated from his initial position to now create the fear of sperm and eggs being altered and the prospect of genetically altered babies. He would be better served looking into purposeful human genome editing, which is widespread now, with very low public awareness. Chinese scientist He Jiankui caused an international uproar in 2018 when he revealed that he had engineered two human embryos that resulted in live births. After the initial outcry by the global scientific and ethical community, which resulted in He Jiankui being jailed for three years in China, many countries eagerly

jumped on board to join the new arms race to engineer superhumans. By 2018, WHO had convened an expert group and issued guidelines, while the UK and the US have begun research into creating super soldiers, with features for combat superiority. Genetic engineering of humans is now established globally.

Meanwhile, malaria, which was eliminated in the United States in the 1950s, has re-emerged in Florida and Texas, with endemic local transmission from mosquitoes to humans. The last time there was locally acquired malaria was 20 years ago. Measles, which was declared eliminated in 2000 in the United States, has been causing large epidemics since 2018, and the US just scraped by in 2019 to retain its elimination status, despite New York City declaring a state of emergency due to measles epidemics in 2019. It quietened down during the COVID-19 pandemic as measles, like COVID-19, is spread by the airborne route, so measures such as social distancing and masks worked just as well against measles. But it has been back with a vengeance, both in the US and globally, since 2023.

In another backward slide, life expectancy has dropped by more than two years in the United States since 2020, largely due to the impact of COVID-19. However, mass disinformation has filled the vacuum in public messaging by claiming sudden deaths of healthy younger people are due to the vaccine rather than COVID-19 itself. Many studies show that the vaccine reduces your risk of sudden death, including cardiac death and death from all causes, and that COVID-19 increases your risk of cardiovascular events such as heart attacks and strokes as well as cardiac arrest and sudden cardiac death. Yet again, governments have failed to counter this misinformation.

The demonisation of public health during the pandemic, fear of electoral unpopularity and fear of being forthcoming with strong public health messaging have allowed anti-vaccination proponents and conspiracy theorists to flood social media and even mainstream media with disinformation. Strong public health messaging needs to emphasise how serious COVID-19 is, including long-term complications such as long COVID, cardiovascular disease, cognitive impairment and impaired

immunity, and encourage boosters as an important part of protection against these complications. There are ample data that vaccination protects against death, cardiac complications, hospitalisation and long COVID, yet the rates of booster vaccination remain low in countries that offer it. When public health agencies and governments contribute to misinformation that COVID-19 is trivial, how can we expect people to take it seriously and get a booster? We have done research projecting the burden of long COVID in Australia, which shows that this will be substantial and ongoing. We found the greatest burden is in working-age adults. The economic impacts of this will be crippling unless we reverse course and try to prevent COVID-19 and offer every available means of prevention to as many people as possible.

Meanwhile, the threat of a H5N1 influenza pandemic (which we'll explore in more detail in chapter 7) is looming. The use of mRNA technology would speed up the availability of pandemic vaccines, which would otherwise be delayed by a minimum of four months using current influenza vaccine technology. In the 2009 influenza pandemic, vaccines rolled out after the pandemic peak. If a deadly H5N1 influenza pandemic arises, every day of delay will cost lives, and mRNA is one of the quickest vaccine technologies to minimise this delay. Yet, anti-vaccination disinformation has overwhelmingly focused on mRNA vaccines, which may derail attempts to save lives in a new pandemic.

5

‘I DON’T WANT MRNA IN MY BODY!’

On 3 October 2023, I heard that Professor Katalin Karikó had won the Nobel Prize for Physiology or Medicine, along with her colleague Professor Drew Weissman. My heart soared, for I knew some of her story and the hardships she had endured in her career. In 2022, I had emailed her to invite her to speak at the 16th Vaccine Congress, a conference organised by the journal *Vaccine*, of which I was an associate editor. She replied and said she was unavailable, but I was thrilled just to get a reply from her. I had also suggested her for the Jenner Prize, an award presented at that conference and named after Edward Jenner, who first discovered the smallpox vaccine.

Karikó migrated from Hungary to the United States in 1985 and began her research of mRNA for therapeutics and vaccines in the 1990s, believing mRNA held the key to breakthrough medical technologies. During her first job at Temple University, her supervisor tried to have her deported after a disagreement. She then found a position at the Ivy League University of Pennsylvania. Her work was so prescient that no one recognised how important it was until decades later. At the time, she was told to stop working on mRNA. In interviews after she won the Nobel Prize, she explained that when she wanted to continue working on mRNA during the early stages of her career, she was demoted from her tenure track role, informed that she was ‘not of faculty quality’ and had her pay cut. She was also battling a cancer diagnosis at that time. The mRNA she used in her early research was unsuitable for medical treatments because it caused an unwanted reaction in the test mice injected with it. While being paid less

than a lab technician at Penn, she met immunologist Dr Drew Weissman in 1997, and together they figured out which part of the mRNA triggered the unwanted immune reaction. They created a modified version of mRNA, which fixed the problem. The landmark paper that won them the Nobel Prize was published in 2005, with little recognition at the time from the medical research community. The US company Moderna and German company BioNTech were, however, interested in this technology and licensed it soon after. In an interview after her Nobel Prize win, Karikó reported that when she left Penn in 2013 to join BioNTech as a senior vice president, they laughed at her, saying that BioNTech did not even have a website. Karikó and BioNTech had already begun trials of vaccines using mRNA before the COVID-19 pandemic hit, as had Moderna, who also believed this to be a breakthrough technology. The pandemic provided the impetus to scale up global efforts enormously, resulting in COVID-19 vaccines less than a year after the pandemic was first declared. It was also heartening that in a climate of disinformation and anti-vaccine propaganda, Karikó and Weissman's Nobel win was a recognition of vaccines and the momentous discovery of mRNA technology. The full potential of this technology is yet to be realised. The use of mRNA technology for vaccines is probably the biggest breakthrough in vaccine technology (and possibly in all of medicine) for 50 to 100 years.

We all have mRNA in our body, so my doctor friend who refused boosters by saying 'I don't want mRNA in my body' was misinformed. To understand mRNA, we must also understand the basics of deoxyribonucleic acid (DNA), the genetic blueprint for all living organisms. This genetic blueprint, or genotype, determines the physical features of a living creature. In humans, we have DNA that codes for hair colour, eye colour, height, predisposition to certain diseases and all physical aspects of our body. To use this genetic code to make proteins (required to create hair or muscles, for example), DNA is copied to RNA (ribonucleic acid), which then forms messenger ribonucleic acid (mRNA), which can be read by the protein factory in human cells, the ribosomes. It is then transcribed in the ribosome to produce a corresponding protein. The mRNA tells the ribosome what

protein to make, and these proteins are the building blocks of the body. mRNA is a bit like computer code, and the ribosome is like a 3D printer that takes the code and prints a protein using the factory in our own cells. One of the most common types of vaccines, protein vaccines, involves injecting proteins corresponding to parts of a virus or bacteria to elicit an immune response. The Novavax COVID-19 vaccine, for example, is a protein vaccine. This way, you can develop immunity to a virus without being infected by the virus as the protein subunit is not a living virus but simply a small, inert component of it. If, instead, we use synthetic mRNA with the code for that same protein, we can achieve the same result by using the protein factory within human cells to make the desired protein and elicit an immune response. The result is the desired protein in the body, which triggers and trains the immune system to recognise and fight a specific infection.

One of the challenges with this technology is that mRNA is inherently unstable. Over 30 years of research on mRNA technology was needed to learn that it can be stabilised by coating it with tiny particles of fat made from natural products – lipid nanoparticles or LNPs – found in normal cell membranes. This breakthrough coating technology has occurred in the last ten years of mRNA research and now provides a platform for other mRNA vaccines. By simply changing the genetic coding sequence, we can produce a new vaccine or medicine using this same technology. We already have a microscopic 3D printer inside our body (the ribosomes in our cells), and mRNA is the code that tells the printer what to print. Vaccine makers are now working on mRNA vaccines and treatments against infectious diseases, cancer and rare genetic diseases. This includes vaccines against HIV, cytomegalovirus and Zika virus (the latter two causing congenital birth defects in babies), which have proven elusive so far. Cancer vaccines are also being developed. Of course, we have had two cancer vaccines for a long time – against hepatitis B (which causes liver cancer) and human papillomavirus (the cause of cervical cancer). But current vaccines being developed include therapeutic vaccines that can be used to treat someone already diagnosed with cancer, and personalised vaccines directed to the

specific cancer of an individual. For example, Moderna is developing a vaccine for melanoma, which is personalised for the actual tumour. Other cancer vaccines are being developed for lung, colon, ovarian and pancreatic cancers. Some of these are in early phase trials, but some are in phase 3 trials, so it will be a few years before we see the result. However, it is likely that mRNA will advance the treatment of cancer substantially.

Although synthetic mRNA was in development for decades before the COVID-19 pandemic, the first mRNA vaccines rolled out in humans were the COVID-19 vaccines. Along with the success of these vaccines came the rise in disinformation about mRNA. One of the first myths was that being genetic material, mRNA vaccines were going to alter one's DNA. However, the mRNA is very specific for the COVID-19 spike protein, and that is the only signal that it provides the cell. This then results in the ribosomes inside the cell producing the desired protein, which would otherwise be contained in the other types of COVID-19 vaccines, including the whole killed virus vaccines, adenovirus vectored vaccines and protein vaccines. In addition, mRNA is much shorter than DNA and contains only a fraction of what is in the full DNA of the virus. Our bodies are made of cells situated in extracellular material. The cell is the engine room of all life. An example of the extracellular material, in the case of blood cells, is the plasma in which the blood cells travel. Antibodies created by vaccines are generated by white blood cells, but once generated, antibodies are found in the plasma, not inside the cells. Human DNA is stored inside the nucleus of the cell, which is a walled-off command centre in the cell, a bit like the yolk of an egg. Around it is the cytoplasm, which is like the egg white. The mRNA does not enter the nucleus of the cell and so cannot mix with our DNA or change it. It simply acts like computer code telling our own intracellular 3D printer, the ribosomes, what protein to generate. There are many kinds of cells in the body, such as muscle cells, nerve cells, skin cells, blood cells and a range of other cells specific to different organs of the body. Some cells, such as skin cells, can divide and multiply, while others, such as brain cells, cannot. So, if you cut your hand, the skin will regenerate and grow back. On the other hand, if you have a brain or spinal cord injury, the injury

cannot repair itself. Many scientists are working on regenerative medicine, which aims to regenerate tissue that cannot repair itself. This work could help treatment of paraplegia, quadriplegia, stroke, heart failure and other conditions that result from damage to cells that cannot regenerate or repair themselves. It is likely that mRNA technology will enable breakthroughs in regenerative medicine too.

As the myths about mRNA were debunked, the anti-vaccine narrative around mRNA gradually changed from the alteration of DNA to contaminants in the vaccine. Early on, an alternative therapist claimed they saw tentacled creatures swimming in the vaccine. Other propaganda videos show graphene (a carbon compound that is not used in making vaccines) squirming around under a microscope. Researchers published a preprint (an unedited research paper that has not undergone peer review) suggesting the vaccine was contaminated with DNA and that this contaminant (rather than the spike protein itself) can alter human DNA. This is not supported by any scientific data, and the vial of vaccine allegedly tested in this study may have been open and contaminated accidentally (or deliberately). Another suggestion was that the vaccines were contaminated with a monkey virus called SV40. Again, this was not found in any other study, and it is not plausible because SV40 is not used in the manufacture of the vaccines. A non-peer-reviewed preprint published in June 2023 suggested that vials of the Pfizer vaccine contained DNA from SV40 and that this virus causes cancer. However, the virus is not used in manufacturing mRNA vaccines, although a small piece of SV40 DNA called a starter sequence is incorporated into plasmids during manufacturing, not to produce the vaccine's mRNA itself. Further, SV40 is not established as a cause of human cancer. The vaccine vials used in the study were mailed anonymously to the authors and their integrity and authenticity cannot be verified. No other study has confirmed these findings. Other conspiracies postulate that mRNA vaccines contain microchips to track movement and generate a magnetic field. Yet mRNA vaccines do not contain metal, chips, cells or viruses.

However, cells (which contain DNA) are used in the manufacturing process for many widely available vaccines, including influenza and hepatitis B, but DNA is removed using an enzyme in that process. To make mRNA vaccines, a DNA template is required as the first step. These vaccines use plasmid DNA in the first step. Plasmids are found naturally in bacterial cells. The manufacturing process then uses purification methods to remove the plasmid DNA. However, fragments of residual DNA can be found in vaccines, but regulatory agencies specify (and test for) acceptable levels of DNA per milligram of RNA in vaccines. Our own bodies naturally detect and remove these DNA fragments, and there is no plausible mechanism for them to enter the nucleus of cells and alter our DNA. One batch of Pfizer's vaccine submitted to the European Medicines Agency did contain DNA levels above the upper limit, but routine testing conducted by such regulatory agencies ensures the quality and safety of vaccines.

Whether we like it or not, mRNA technology will revolutionise medicine and many other areas of modern life. Just as we had the Stone Age, Bronze Age and Iron Age, we are now well and truly in the Genome Age, as technology and health care futurist Jamie Metzl pointed out in an excellent article in *Newsweek* about mRNA vaccines and the promise of mRNA technology. This opens the door to not just preventive vaccines against infections and cancers, but personalised medicine. If we can provide genetic code to the human body so that the ribosome can generate the desired protein, we can design customised treatments specifically for individuals and their particular illnesses. In fact, Moderna has partnered with pharmaceutical giant Merck to develop a personalised vaccine for melanoma and lung cancer, combined with Merck's blockbuster anti-cancer drug Keytruda. Keytruda is an immunotherapy that has shown excellent results with a range of cancers, causing regression of difficult-to-treat cancer in up to half of patients. BioNTech is also developing personalised vaccines for cancer. When I was a medical student and young doctor, colleagues and friends who went on to become oncologists dreamed of curing cancer. Of course, there have been many breakthroughs in cancer treatment and diagnosis in the decades since then, but we are now closer

than ever with mRNA technology. I would guess that if detractors of mRNA vaccines were faced with a life-threatening cancer that could be cured with an mRNA therapy, they would be lining up for that treatment.

There is a flip side to this technology, as there is with any technology, in that it can be used for good or for harm. In my previous book, *Dark Winter*, I explored some of the dangers of biological technology, human weakness, error, terror and the motivations of bad actors. I also explored the quantum advances in technology that now allow engineering of viruses alongside engineering of human beings, which opens the door to new kinds of warfare that could include the double whammy of weakening of human populations followed by a biological weapons attack. Suffice it to say, the promise of this technology must also be accompanied by adequate checks and balances as well as mechanisms for global governance.

The threat of a pandemic caused by H5N1 influenza is a reason we should be thankful for mRNA vaccines. The platform technology can be used to create a new genetic code within about six weeks, which is a phenomenal speed compared to traditional egg-based influenza vaccine manufacturing methods. In the swine flu pandemic of 2009, Australia saw the first case in May, the pandemic peaked in August and vaccines were available in September. This means the largest surge in pandemic flu was not prevented as vaccines only became available after the peak. Unlike COVID-19, which disproportionately affected older adults severely, influenza pandemics can cause two patterns, both of which affect children. The first is a U-shaped pandemic, with peaks of deaths in children and the elderly; the second, seen in the 1918 pandemic, is a W-shaped pandemic, which causes peak deaths in children and the elderly, but a third peak in young, working-age adults. During a serious influenza pandemic with high mortality, as would be expected with a H5N1 pandemic, the sooner we can get vaccines into arms, the more lives we can save.

6

INFLUENZA

At an international influenza conference in 2024, I listened to speaker after speaker puzzle over falling vaccination rates since the COVID-19 pandemic. Rates of vaccination for most diseases, including the flu vaccine for adults and the measles vaccine for children, had fallen in wealthy and poor countries alike since 2020. The conference had over 1000 delegates from around the world, all experts in respiratory infectious diseases, and I estimated that about 20 per cent of them were sick. When I asked, some even confessed they never tested as it was ‘just a cold’. Every session had one or more people coughing and sneezing into the shared air around them, and none was masked. I wore a mask and spotted three other people wearing them during the event. Yet these delegates were advocates for public health and vaccines, and some were experts on the transmission of respiratory viruses. I took the mask off to present, eat in the exhibition hall where food was served, over long conversations with others – and caught COVID as a parting gift. I have no doubt many others went home sick after mingling in this global cauldron of international virus strains. I saw research at the conference that suggested my infection was more likely from someone who was asymptomatic and infectious than from one of my coughing colleagues. Many respiratory viruses can spread silently from people who look and feel well, but COVID is the undisputed king of silent spread, which is why it is so rampant. Influenza, too, can spread silently.

Right now, the diseases that keep me awake at night are avian influenza, mpox and its scarier cousin, smallpox. Influenza is front of mind for anyone

who studies epidemic respiratory infections as it has long been the most consequential pathogen. Pandemics have occurred throughout history and arise when a new strain of an influenza virus that has not circulated in humans before, adapts to spread easily between humans. There are seasonal influenza A and influenza B viruses that spread easily between humans, causing the usual seasonal flu epidemics. Influenza B viruses only infect humans, whereas influenza A viruses can infect birds, animals and humans. Some influenza A viruses are mainly bird viruses, and we refer to these as avian influenza or bird flu. The latter are further classified into highly pathogenic and low pathogenic avian influenza viruses. Most avian influenza viruses are low pathogenic and cause asymptomatic infection in birds. The highly pathogenic ones cause severe illness and death in birds. There are also influenza C viruses, which is less important. Unlike COVID, which is perennial, flu is typically a winter illness, causing a single winter peak in temperate regions, and two annual peaks in tropical regions. Influenza infection is transmitted through the air in aerosols and is most commonly acquired by inhalation. Numerous studies have documented airborne transmission. In one US study, a viable influenza virus was detected in the air of the emergency department three hours after the infected patient had left. The highest concentration of virus is in the finest aerosols that come from deep in the lung, with less virus in large droplets originating from the nose and throat. It’s likely there are super-spreaders who infect many more people than average, as studies where people have been deliberately exposed to influenza (called human challenge studies) show that transmission rates are low. Yet one study showed that one person with influenza on a plane infected 70 per cent of the passengers on board. The plane was delayed from taking off for three hours after boarding, so passengers waited in their seats during that time. The ventilation systems of aircraft (which are very good at cleaning the air) only start operating after the plane is airborne, so waiting on the tarmac is the riskiest time for catching infections. In this case, one infected person was exhaling enough virus to infect almost everyone, no matter where they were seated.

Influenza A is our biggest fear of causing a new pandemic. The influenza A viruses that cause seasonal flu today were once pandemic viruses that have circulated for so long that our immune systems 'remember' them and fight them, so the infection is not as severe as a new pandemic virus would be. Influenza A is the most severe seasonal influenza virus, although influenza B can be severe in children. The proteins on the surface of an influenza virus are called antigens, and when the human body encounters these proteins, it reacts and creates antibodies. The main antigens we are concerned about are hemagglutinin (H) and neuraminidase (N), which are used to make influenza vaccines. Each influenza A virus is characterised by its H and N composition. For example, the most severe seasonal flu is H3N2. The other seasonal influenza A virus is H1N1. The seasonal vaccine contains variants of each. Influenza A viruses mutate at a high rate, with most mutations being relatively minor (we call this drift). Occasionally, mutations can be major (we call this shift). A major antigenic shift would involve the emergence of a new pandemic influenza virus that spreads easily between humans and contains an H antigen that humans have not previously been exposed to. This could be H5, H9, H7 or a range of other H antigens.

Up to a quarter of people can get infected in a severe influenza epidemic. Common clinical symptoms for seasonal influenza include sudden onset of fever, cough, sore throat, muscle aches, fatigue and sometimes vomiting and diarrhoea. In adults, influenza B infections more frequently present with vomiting, diarrhoea, abdominal pain, headache, general weakness and runny nose compared to influenza A. Fever is more common in children than adults. In fact, our research showed that over 60 per cent of adults with confirmed infection with a range of respiratory viruses, including influenza, do not have an accompanying fever. Kids, on the other hand, have high rates of fever with the same infections. Without a test, however, you cannot prove influenza infection as there are over 90 other cold and cough viruses, as well as SARS-CoV-2, that can cause similar symptoms. One indicator is the season. Influenza and most other respiratory viruses circulate mainly in winter, so if you have flu-like

symptoms in summer, it is more likely to be COVID-19. When people tell me they ‘have the flu’ in summer, I just roll my eyes because I know the statistical probability is that they have COVID-19. The lower sensitivity of COVID-19 rapid antigen tests to newer variants can give a repeated false negative test, but if it’s summer, the odds are it is COVID. However, in winter, when a known epidemic of flu is occurring, a flu-like illness is more likely to be flu. Triple antigen tests for COVID-19, influenza and RSV are available and useful for rapidly characterising outbreaks in aged care. Knowing the cause matters as there are different antivirals for influenza and COVID-19.

Influenza can cause death or serious complications, including primary viral pneumonia, which occurs early in the course of illness, or secondary bacterial pneumonia, with onset later (1–2 weeks after initial symptoms). Bacterial pneumonia is the most common influenza-associated complication, especially in children and the elderly. Bacterial infection can be complicated by antibiotic resistance and there are vaccines available for the most common bacterial pneumonia, pneumococcal infection. Unfortunately, despite being provided free to people over 70 years and other risk groups, rates of vaccination against pneumococcal disease in adults are low. Other complications can be worsening of asthma and respiratory diseases and exacerbation of underlying comorbidities in persons who are at risk of the infection. Heart failure, heart attacks and sinusitis may also occur. I will go into more detail on how influenza affects the heart and blood vessels in chapter 14. Occasionally, encephalitis and complications of other organ systems may occur. As an asthmatic, any respiratory infection affects my lungs badly, and pre-COVID, it was routine for me to get severe asthma following respiratory infections every winter. Since using masks in public settings and taking precautions to reduce my risk of inhaled respiratory threats, I have had very few such infections, which has improved my quality of life substantially. Of course, primary prevention is vaccination with influenza vaccine annually, and I have been getting vaccinated annually for over 30 years. People aged 65 years and over, and those with medical or other risk factors, are recommended and

funded for free influenza vaccines in Australia. Ideally, vaccination should occur 2–3 months before the start of winter. Waning immunity occurs over 12 months, and some have suggested vaccinating later, but our research shows that the best timing is in the couple of months before winter. However, the vaccine can be given at any time of the year.

The frequent mutation of the virus from year to year means influenza vaccines need to be exactly matched for the circulating strains, which can be a combination of A and B strains. The WHO meets each year and determines the optimal composition of seasonal flu vaccines. The vaccine is safe and effective, even in older, frail people. However, effectiveness can vary year to year, depending on how well the vaccine is matched to circulating strains. Mostly, the vaccine adequately covers circulating flu viruses, but occasionally, the vaccine may be mismatched for one or more influenza strains that are circulating. A mismatch means the circulating influenza virus is different from the one anticipated by the WHO. In our research, we found that the B strain was mismatched about 30 per cent of the time. This was the rationale for switching from a trivalent to quadrivalent vaccine in 2016. Both contain two A strains, with only one B strain in the trivalent vaccine and two in the quadrivalent one. Because influenza B is much more stable than influenza A, the quadrivalent vaccine provides excellent protection against influenza B. Influenza A, on the other hand, mutates far more, and vaccine mismatch can occur more frequently. Influenza vaccine effectiveness is 60 to 70 per cent in healthy people but can be lower in older people or if there is a vaccine mismatch. It is important to understand the difference between vaccine match and other factors that can affect vaccine effectiveness, such as immunosenescence in the elderly. We have shown in our research that even an incompletely matched vaccine can protect the vulnerable during a nursing home outbreak, so vaccination is always worthwhile. Explosive outbreaks of influenza in highly vaccinated aged care facility populations have been well documented in the past and may reflect the intensity of transmission within the closed setting of a nursing home, as well as lower immunity in the frail elderly. This could explain the observation that some elderly people who are

vaccinated still contract influenza. However, even if you get the flu after vaccination, the vaccine will protect against severe illness and death. Even a vaccine of modest effectiveness can have a public health impact when the disease burden is high, as I explain in chapter 13.

On average, about 80 per cent of circulating influenza is A and 20 per cent is B. The two B strains that circulate in humans are B Victoria and B Yamagata. Until 2016, flu vaccines contained two A strains and one B strain. Over a decade of repeated flu seasons, the wrong B strain was in the vaccine about a third of the time. The quadrivalent vaccine, introduced in 2016, allows protection against four strains (two A and two B strains) and essentially removes the risk of B strain mismatch. However, B Yamagata disappeared after the COVID-19 pandemic, prompting many experts to assume it was ‘extinct’. In 2024, the US CDC switched from the quadrivalent seasonal flu vaccine to a trivalent vaccine covering two A strains and B Victoria. I personally think this is premature, as B Yamagata disappeared after the 2009 influenza pandemic too, but then returned after about three years. Even in Australia, which has good surveillance, only 2 per cent or so of B strains are characterised further into Victoria or Yamagata, so we can’t really be confident that Yamagata is not circulating somewhere in the world. The beauty of influenza vaccines, however, is that if we need a quadrivalent vaccine in the future, we can easily switch. Research is underway for a universal flu vaccine that will remove the need for an annual jab. There are also combined COVID and flu vaccines in the pipeline.

Of seasonal influenza, type A results in the most complications and fatalities, and H3N2 is the most severe. The H1N1pdm09 (the virus that caused the 2009 pandemic and is now a seasonal flu virus) can also cause severe disease and a high case fatality rate. Past severe H3N2 epidemics, which featured deaths in healthy children, include the 2003, 2007, 2012, 2017 and 2019 seasons. One of the most severe seasonal flu epidemics in recent history occurred in 2017 when the predominant circulating strain was influenza A H3N2. My father, an asthmatic in his early 80s and living independently at the time, ended up hospitalised with this strain of flu. He

and my mother received the flu vaccine every year, but he still got severe influenza. In that case, there was a vaccine mismatch and the effectiveness against that circulating strain was low. As a result, there were severe consequences such as deaths and hospitalisations across the country. The most severely affected populations are the very young and the very old. Healthy young toddlers, infants or older adults may die of H3N2 influenza. That year, five children under 14 years died of influenza in Australia, including two aged 0–4 years. Severe infection may also occur in pregnant women, Indigenous people and people with chronic diseases. Many high-income countries fund and provide vaccination for adults 65 years and over, and some countries, like the US, also provide it for children aged six months and over. Aged care facilities are often severely affected, with outbreaks that can result in facilities having to close their doors to new admissions, illness and death in residents, and illness and absenteeism in staff. Older people are at greater risk for most infectious diseases but also respond less well to vaccines. Globally, the severe epidemic in 2017 prompted the introduction of enhanced influenza vaccines for older adults. The two main enhanced vaccines were the high-dose vaccine, which elicits better immune responses by providing a greater dose of the influenza antigens, and an adjuvanted vaccine, which uses a novel adjuvant to elicit a stronger immune response. Both these vaccines improve the performance of the flu vaccine by about 20 to 25 per cent in older adults, and one or both are now routine in national immunisation programs in high-income countries.

Debilitating outbreaks can occur in hospitals and aged care facilities, which usually experience more intense transmission due to the congregation of patients or residents in shared rooms and inadequately ventilated buildings. In 2017, influenza H3N2 outbreaks in institutions in New South Wales were more than four times higher than the past five-year average. Workers in health care, aged care and childcare can be a source of transmission of infectious diseases to vulnerable people in their care and to other staff. Immunisation is recommended for these occupational groups to prevent transmission of vaccine-preventable diseases. The annual influenza

immunisation rate in Australian health workers varies widely, ranging from 22 to 70 per cent, but it is mostly low. The NSW Ministry of Health introduced mandated health worker vaccination in 2007, with a revision of the policy in 2011, but influenza vaccination was not included in this legislation and remained recommended but not compulsory. Most other states followed the lead of New South Wales and mandated that health workers be vaccinated against a range of infections if they worked in clinical areas. There was not much known about vaccination rates in aged care workers, but rates were even lower until the H3N2 season of 2017. This season was so severe that it prompted calls for mandatory influenza vaccination for workers in aged care. Revised policy after this placed the onus on aged care providers to ensure workers received influenza vaccine. Further updates to policy occurred in 2020 after the COVID-19 pandemic, which raised vaccination rates in aged care workers. Good ventilation in indoor settings and infection control measures are also vital to prevent further spread of infection, and personal protective equipment such as masks and respirators are recommended during outbreaks. Our research showed that nursing homes where staff used masks suffered fewer and smaller outbreaks of COVID-19 than those that did not.

Specific antivirals are available for the treatment of influenza. Neuraminidase inhibitors (NAIs) like Tamiflu can be used as prevention or treatment, and when used as prevention can curtail outbreaks. NAIs are most effective if they are taken within 48 hours after the onset of illness. Antivirals can reduce severe complications of influenza infection and can also shorten the duration of illness and transmission risk to others. They are also proven to mitigate severe, hospitalised cases of influenza, and should be given even after the 48-hour window (up to 72 hours) for patients in intensive care. However, despite the availability of NAIs for decades, doctors do not use them widely. Testing for influenza is a prerequisite for prescribing NAIs, and many patients do not get tested, either because they do not go to their doctor for diagnosis or the doctor fails to test and prescribe. We are doing badly in terms of availing ourselves of available

vaccines and treatments for influenza, while influenza A keeps mutating and presenting new challenges.

In my own research, we showed that the rate of new influenza A viruses emerging and infecting humans is higher than ever. This increases the risk of a pandemic. For example, from 1918 to 1957, only one new influenza virus emerged, and from then it took a decade for the next virus to emerge. In the five years from 2012 to 2017, there were seven new influenza viruses infecting humans from China, Egypt, the US and Europe. This has since escalated with the global spread of a new mutation of H5N1. The reasons behind this escalation are unknown but could be due to changes in climate, urbanisation and agricultural practices as well as better diagnostics. However, the rate of change of these factors is not as high as the rate of emergence of new influenza viruses, so questions remain about why we are seeing so many new viruses and epidemics. It is also clear that the risk of a pandemic is higher now than in the past due to the sheer number of new emerging infections.

The greatest concern now is an H5 pandemic arising as a result of the mutation of the avian virus H5N1. H5 viruses typically circulate in birds, so for a pandemic to arise, bird viruses need to mix with animal or human viruses and mutate to become transmissible between humans. Wild waterfowl (ducks, geese and swans) are the super-spreaders of avian influenza viruses because they migrate great distances across the world, carrying these viruses and then infecting poultry farms along the way. Waterfowl travel along very specific flyways (a bit like an airline route for birds) and the Heathrow airport for birds is in Qinghai Lake in China, which is a major hub for birds and the second-largest saltwater lake in the world. I visited Qinghai around 2010. It is the largest province of China, with a relatively low population density and the most stunningly beautiful landscape on the Tibetan plateau. There is also a Tibetan monastery high up in the mountains where the Buddhist priests carve sculptures out of yak butter. In this beautiful region of China is a great lake, which has been a source of fascination for ornithologists worldwide as it sits at the intersection of two major flyways: the East Asian and Central Asian

flyways. Birds fly thousands of kilometres from this hub and can spread avian influenza viruses in their migratory path. The wild birds typically carry low pathogenic avian flu viruses that do not cause symptoms, but when they infect poultry, the virus mutates in the poultry to become highly pathogenic, setting off a chain of two-way infections between poultry and wild birds. When this happens, mass die-offs of wild birds are observed. Highly pathogenic H5N1 epidemics in poultry farms began in 1997 in Hong Kong. Massive culling of infected poultry appeared to control the situation, and we thought it was gone, but the virus resurfaced in China in 2003, causing more poultry and wild bird outbreaks. In the last 20 years, H5N1 epidemics in birds have been sporadic and die down after the culling of infected poultry. But a new variant of H5N1 in 2020 has changed all that.

7

FUR, FEATHERS AND FARMS – THE SPECTRE OF H5N1

In February 2024, dairy farmers in Texas began noticing their cows were producing less milk, and that the milk was discoloured, yellow and thicker than it should be. News outlets reported on a mystery illness in cows. Then, in March, H5N1 avian flu was diagnosed as the cause of the illness. It was unheard of for cows to get bird flu, so the diagnosis was not suspected at first. The epidemic spread rapidly across the US, affecting 14 states across the country by October, including the biggest dairy producer in the country, the state of California. In August, as I was about to depart for the US for a pandemic war game I had designed for military stakeholders at the United States Indo-Pacific Command, I received an invitation from the Los Alamos National Laboratory (of Oppenheimer fame) to speak at a special symposium they were holding in Washington DC. The meeting had been convened around the spread of bird flu in the US and the risk this posed for a human pandemic. There was a sense of urgency and concern in the email. We had already started researching how the H5N1 bird flu virus was spreading, so I extended my trip and flew from Honolulu to Washington DC to attend the meeting. Bird flu used to be contained and sporadic, but there is a pandemic occurring in birds and animals at a scale we have never seen before.

In late 2020, a specific new variant of H5N1 called clade 2.3.4.4b emerged and has continued to spread over the last four years, moving into more and more bird and mammalian species. It has infected over 100 types

of wild birds that are not waterfowl and that migrate on different routes from the traditional routes that avian influenza spreads. These include the eagle, pheasant, penguin, bar-tailed godwit, Pacific golden plover, bristle-thighed curlew, great sand plover, eastern curlew, Asian dowitcher, black-tailed godwit, broad-billed sandpiper, grey-tailed tattler, terek sandpiper, grey knot, red knot, ruddy turnstone and others. This variant has shown some worrying features, including severe neurological signs in infected birds and animals. Other unusual presentations have included conjunctivitis, so it's not the classic severe respiratory illness we would expect. A strain found in eagles in the United States has been shown to be severely invasive to the brain and neurological system. If this strain mutated to become a pandemic strain, we may see severe effects on the brain in addition to the lungs. H5N1 2.3.4.4b has caused 70 human cases as of March 2025 in the US alone, but does not transmit easily between humans. It remains a virus adapted to birds. Most cases were farm workers who had close contact with infected cattle or poultry. However, one person in Missouri developed H5N1 without any known risky exposures. Several people around this person also had symptoms, including health workers who treated them and family contacts, but only one family contact tested positive. The risk to humans from mutation of H5N1 is higher than ever, simply because of the unprecedented spread, which increases the statistical probability of a mutation that will cause a pandemic. If the probability of the dreaded mutation is related to the rate of infection in wild birds, farmed and domestic animals, and the mixing of humans and such animals, then there are far more chances for this to occur today than at any time in the past.

Influenza viruses must bind to a suitable receptor in the cells of humans, birds or animals to invade the body and cause infection. The key event that could cause a human pandemic is a mutation that switches the affinity of the virus from bird to human. Such a switch means the virus can bind to receptors in the human respiratory tract and invade the body. Humans have different receptors in the upper respiratory tract from birds, and this is why the avian strains do not easily spread between humans. Bird flu preferentially binds to the throats of birds, and does not attach easily to the

human nose and throat. Some mammals, however, such as ferrets and pigs, have similar respiratory tract receptors to humans. That is why ferrets are used in influenza research in the lab. Pigs are a genetic mixing vessel because they have both bird and human receptors, so flu viruses can mutate in a pig to cause a human pandemic. Many new mammalian species have been infected since 2021, and some of these animals may be more like humans and therefore suitable genetic mixing vessels to create a human pandemic strain. Also, the infection of terrestrial wild animals that live close to human communities, like red foxes and squirrels, increases the risk of infection of domestic animals like cats and dogs, which can bring the virus into households. This is a possible new route for a human pandemic. In the past, H5N1 epidemics in birds were sporadic and would die down after culling of infected poultry. Since 2021, the pattern has changed and it has not gone away or subsided but steadily increased and infected a wider range of birds and animals. This is a completely new pattern for avian influenza. I have been following H5N1 since 1997, and the current situation is unprecedented and extremely worrying.

Historically, the epicentre of bird flu epidemics was Asia, particularly China, Indonesia and Vietnam, with Egypt also affected a decade ago. Since 2021, the global hotspots have shifted from Asia to Europe, the Americas and Africa, where H5N1 clade 2.3.4.4b has spread in an unprecedented manner to an increasing array of wild birds, wild mammals and farmed animals. In the past, wild birds would largely infect farmed poultry, but we are now seeing unprecedented epidemics in farmed cattle and even goats. Wild animals that have been infected for the first time include seals, sea lions, red foxes, coyotes, raccoons, mountain lions, skunks, squirrels and others. Infections have also been documented in domestic cats. New pathways for human pandemic emergence that fly in the face of traditional thinking (which is that wild birds infect pigs or poultry with bird flu, which then mutates to infect humans and cause a pandemic) are now open. Another new route is newly infected species of wild birds that have never been the carriers of avian influenza in the past. Birds use specific flyways that are like airline routes, and in the past, the spread of bird flu has been

restricted to the flyways of ducks, swans and geese (waterfowl). So, we need to think beyond the traditional flyways of waterfowl as the routes of avian influenza spread. Think of it as multiple new airlines open for business and flying down new routes, which pose a new way for infections to spread. This matters for Australia, which has been spared H5N1. In 2024, it was the only continent free of the virus. The waterfowl flyways that spread this virus around the world bypass Australia because it has a boundary called the Wallace Line, which separates the fauna of Asia and Australia. H5N1 has not crossed that line. However, H5N1 reached Antarctica in 2024, so there are now new flyways through which the virus can reach Australia. The impact on our farming and our unique native wildlife, some of which are endangered, could be devastating. In the US, the outbreaks in farms also pose a threat by increasing the likelihood of H5N1 mixing with human or animal influenza strains to cause a pandemic. The more mixing there is between humans and infected animals or poultry, the greater the risk of a pandemic.

H5N1 spread was predictable by waterfowl flyways and poultry trade routes from 1997 for the first 15 years but began showing unusual patterns in the last decade. The events of the last four years have changed the risk landscape. In 2013, when avian influenza H7N9 started causing avian epidemics and human infections, we researched the way it was spreading and found that it was very different from the historical way that H5N1 spread. The H5N1 spread occurred along the wild bird waterfowl routes of migration as well as poultry trade routes, but H7N9 did not fit that pattern at all, with more geographic clustering in localised areas suggesting terrestrial animals may have played some part. Another difference we found in our research was that H5N1 human cases are more clearly explained by close contact with sick poultry or birds than H7N9. Then, in 2015, an explosive outbreak of H5N1 and H5N2 occurred in turkey farms across the United States, causing massive economic losses. Again, we studied the timing and relationship of these outbreaks to the wild bird flyways and their direction of migration and found that the spread of turkey farm epidemics could not be explained by wild bird migration.

The current epidemics in dairy farms in the US are not easily explained, either. It may be due to a combination of spread by wild birds, terrestrial animals, trade of livestock and agricultural practices. Our research suggests the virus was first introduced into US farms by wild birds, but that subsequent spread from farm to farm and state to state has been due to domestic agricultural practices, as well as two-way spread between cattle and poultry. Some interstate spread has been linked directly to the importation of cattle from affected states. Cattle feed may include poultry litter, which includes feathers, faeces and other refuse from chickens. This practice is banned in Australia and many other countries, but not in the US. The spread of the epidemic across farms may in part be due to the use of poultry litter for cattle feed. There have been poultry outbreaks of this virus in the US preceding the cattle outbreak, which supports this hypothesis. Other farming practices that may have spread the virus include the milking machines, as a very high concentration of virus has been found in the milk. The process of using and cleaning those machines results in widespread aerosolisation of the milk. There is now genetic evidence of spread from cattle back to poultry, thus completing a never-ending cycle of farm infections.

The US dairy farm outbreaks began sometime in February 2024, with the first-ever case of transmission from a cow to a human documented in Texas in late March that year. The strain of H5N1 isolated in the farm worker in Texas was an avian virus that had some genetic mutations but did not show adaptation for human transmission. However, the reason for concern is the increased opportunities for mutation of the virus from farm animals or poultry in close proximity to humans. This may include people working on farms, but also contamination of the food supply with H5N1. In fact, traces of H5N1 have been confirmed through polymerase chain reaction (PCR) testing in the commercial milk supply in a high proportion of cartons sampled. PCR testing is the most common way of testing for viruses and identifies fragments of RNA of the virus, but it cannot tell you if the virus is live and infectious. To date, a live virus has only been found in raw milk; however, the first publicly available data were from

independent scientists who tested milk and milk products off the supermarket shelves. They found that 38 per cent of samples tested had H5N1 viral fragments detected, which indicates that the epidemic in dairy farms is more widespread than reporting would suggest. The US Department of Agriculture has been guarded, and concerned about the economic impact on dairy farms. They were slow in sharing H5N1 genetic data through the public platform Global Initiative on Sharing All Influenza Data (GISAID), which provides free public access to influenza virus genomic data. The FDA, meanwhile, has assured the public that pasteurisation guarantees the milk is safe to drink. Theoretically, pasteurisation should kill viruses and bacteria; however, there is a growing alternative lifestyle movement that prefers unpasteurised, raw milk, which provides fertile ground for a pandemic to emerge. There are also anecdotal reports of many humans suffering influenza-like illness at the same time as cattle are being infected but refusing to be tested. The dairy farm outbreaks were detected because the infected cows were producing less milk, and the quality of the milk was visibly different – yellow, thick and viscous compared to normal milk. No such obvious signal would be present among beef cattle, and beef farmers are reluctant to test their herds. Eating beef, especially a rare steak, may well be a risk in the US, but the highest risk is dairy, as the concentration of virus is greatest in milk. There have also been outbreaks in farmed goats in the US, so the infection may be widespread in farmed animals. If farmers are not compensated financially, they will not test and report H5N1. Unless the government substantially compensates farmers and expands surveillance to other farmed animals, this situation is unlikely to subside and will increase the risk of a H5N1 pandemic in humans. The case fatality rate in humans to date since H5N1 first emerged in 1997 is around 50 per cent, but only one of the human cases in the US have been fatal.

The good news is that we are better prepared for an influenza pandemic than we were for the COVID-19 pandemic because influenza is a highly researched virus. There has been much more research done on it than on coronaviruses when SARS-CoV-2 first emerged. We also have seasonal flu

vaccines, and the same technology can be used to create a pandemic vaccine that is an exact match to a new pandemic strain. The Holy Grail of influenza vaccines is a universal vaccine that will protect against any influenza strain. Although many groups are researching such a vaccine, it remains elusive. Current vaccines target the surface proteins of the virus, the H and N antigens, which are also the parts of the virus that mutate the most. This is why we need an annual seasonal flu vaccine, because each year the virus mutates to be distinct from the previous year's virus.

We have come a long way in influenza vaccine technology in the last 20 years. The last human pandemic of influenza was in 2009 (in that case, arising from pigs, but with the virus originating in birds). It is estimated that 40–90 million people became infected in the first 12 months. The novel virus emerged in Mexico in March 2009, the first cases in Australia occurred in May and WHO declared a pandemic on 11 June because the virus was a novel one arising from swine. Vaccines were available four months after the first cases, but the pandemic peak in Australia was a month before that. At that time, we relied on old egg-based methods for making flu vaccines, which is a slow process. For over 50 years, flu vaccines have been made by growing the virus inside hens' eggs and extracting the protective proteins from there. Most seasonal vaccines are still made this way. The process cannot be easily scaled up to massively increase the quantity of vaccines that would be needed in a pandemic. The added complication with H5N1 is that the virus itself (needed to make the vaccines) kills the eggs required to make the vaccines, which slows down the production even more. We now have many new vaccine technologies, such as recombinant, cell-based and mRNA vaccines, that can be made faster than egg-based vaccines, but how fast we can get these into arms during a pandemic will depend on the agility of regulatory bodies. Live attenuated influenza vaccines, which use a modified live but harmless influenza virus, are also available in some countries but have a chequered history. In the 2016/17 and 2017/18 winter seasons, the US CDC recommended against live intranasal vaccines because of poor effectiveness against the H1N1 strain. This has subsequently been fixed and these vaccines have similar

effectiveness to the inactivated one. In a pandemic, they may have the advantage of being needle-free, which may make it easier to vaccinate children. However, there is the possibility of a lab mishap causing illness from live influenza viruses. The 1977 Russian flu pandemic is now accepted as originating from an incompletely attenuated live flu vaccine being developed in China or Russia. This was denied for 30 years, probably because scientists on both sides of the Cold War did not want to inflame political tensions, but there were clear signs it was not a natural virus right from the start. The virus had been extinct for decades and had the characteristic signature of a vaccine strain – sensitivity to temperature.

A pandemic is a serious epidemic that spreads globally, like COVID-19. The WHO declares a pandemic if its Emergency Committee deems it to be one. It assesses how contagious it is, whether it has spread globally and how many people are hospitalised or die from the infection. Usually, they first declare a Public Health Emergency of International Concern, and if things get worse, a pandemic declaration follows. If a pandemic were to arise today, we have many vaccine technologies to choose from. The likely manufacturers of pandemic flu vaccines will also be the ones who make seasonal or pre-pandemic vaccines. As mentioned, seasonal vaccine composition changes annually and this is approved based on serological (immunity) data. A pandemic vaccine will be like seasonal vaccines but matched for the pandemic strain, so this should allow a quicker roll-out. The mRNA vaccines can be made in as short a time frame as six weeks, but getting shots to arms will take longer because of the regulatory process. During COVID-19, we saw emergency authorisation allow vaccines to be made available faster, so a similar process will likely occur during an influenza pandemic. We also have pre-pandemic H5 vaccines that will give partial protection. Getting your seasonal flu shot can also confer a small amount of cross-protection but will not provide proper protection. We also have antivirals against the flu, such as the neuraminidase inhibitors (Tamiflu, Relenza and intravenous alternatives), which work against all flu strains. At this stage, drug resistance is low, but with widespread use for

treatment, this may become more problematic. Prevention by vaccines is always better than cure.

We can do even better, though, than waiting for a pandemic to start and then developing vaccines. We can prevent pandemics altogether, because they grow exponentially. If we can identify very early signs of a pandemic, it can be stopped in its tracks. For example, if the pandemic had been detected in Wuhan early, further spread could have been prevented by identifying cases, isolating them, tracing their contacts and quarantining their contacts. Governments conduct surveillance for many infections to enable quick action if there is an uptick. This is done through laboratories and doctors reporting cases of diseases that are mandated as 'notifiable'. In Australia, over 70 infectious diseases are notifiable, including measles, whooping cough, HIV and other serious or vaccine-preventable infections.

Surveillance for H5N1 or pandemic influenza requires testing of animals, birds and humans and rapid reporting of infections. It also requires enablers and incentives for farmers to test and report, as well as sharing genetic sequence data as soon as possible. In early March 2024, a human case of H5N1 occurred in a two-year-old child in Victoria. They had acquired the infection in India and apparently had no close contact with birds, animals or sick people. Public disclosure of the case did not occur until 22 May 2024, more than two months later. This kind of delay is not ideal, and shows that delays in reporting can occur anywhere. Open-source intelligence such as our EPIWATCH system, which uses artificial intelligence to identify serious epidemics, can also help provide early warnings and overcome delays. News agencies report on, and people talk about, unusual or concerning epidemics long before the health department knows about them, so tapping into open-source intelligence can help identify early warnings. This can assist with vaccine development by speeding up the process of identifying an epidemic and then actively going in to test and characterise the pathogen at an earlier stage. For example, the genome sequence for SARS-CoV-2 was released in January 2020 and was required by vaccine manufacturers to enable them to develop a vaccine. However, there is now ample evidence that patient zero may have been in

November 2019 or even earlier, and that epidemic activity was present before the WHO was notified. By late December, when the WHO was notified, the infection had already spread to Europe and the US. We know this from blood tests done on people in those countries, which showed evidence of exposure to the virus between November and December 2019. If countries in those regions knew there was a concerning epidemic in China in late 2019, although they could not go into China and investigate, they could have started testing and characterising the virus in their own locations long before it was disclosed by China. Despite censorship of reporting from China, EPIWATCH was able to detect severe unknown pneumonia in Wuhan prior to the official disclosure date.

Reasons for censorship, delay or lack of reporting need to be understood to increase the chance of early detection of pandemics. In October 2024, journalist Katherine Eban published a detailed analysis in *Vanity Fair* outlining how the dairy farm outbreak was mishandled by US government authorities, allowing it to spread around the country. She argued that commercial interests of the dairy industry were put ahead of public health, which ironically made things much worse for the industry. She interviewed veterinarians who were silenced and sometimes sacked for trying to do the right thing. They agreed that rapid action in March 2024 could have stopped the outbreak and prevented further spread. So, in addition to early warning, testing and surveillance, managing the economic impacts for farmers is critical. If there is no financial compensation for farmers, it will result in cover-ups of outbreaks, drive a black-market trade in infected animals and accelerate the risk of a human pandemic. With increasing farm epidemics, there are major economic disincentives to testing or reporting infection, so financial compensation for farmers is essential or we may end up with infected products in the food chain. We saw that happen with mad cow disease in the UK many years ago, with the government in denial and trying to protect British beef. They did not act until the rest of the world started banning British beef. The widespread H5N1 epidemic in US cattle farms increases the risk of a human pandemic. In Australia, two poultry farms were simultaneously infected with different highly pathogenic avian

influenza viruses, H7N3 and H7N9 in May 2024. We had only experienced eight outbreaks prior to that, and never H7N9, which is the virus that emerged in China in 2013 and caused as much concern as H5N1. There are genome sequences in GISAID of H7N9 from Australian wild birds in 2013. At the same time, Western Australia had a poultry outbreak of H9N2, a low pathogenic virus that has been causing severe human infections in China. Three outbreaks in rapid succession in a country normally spared from avian influenza is a warning. However, with Europe and the Americas the new epicentre of H5N1, these are the likely sites for the emergence of a human pandemic. A pandemic is a global concern and requires pandemic planning domestically as well as preparedness for an influenza virus spread from overseas.

Global governance during a pandemic remains a weakness. The International Health Regulations (IHR) is a key instrument for pandemic planning. It considers disease, trade and economic impacts, and is equally concerned with protecting commerce as it is with health – and so argues against border closure during a pandemic. Many countries closed their border during COVID-19 anyway, demonstrating the unenforceable nature of the IHR. Further, many countries cannot comply with the IHR, and it did not serve the world well during the COVID-19 pandemic. The Global Health Security Index (GHSI) was launched the year before COVID-19 began but failed to predict which countries would respond effectively. It weighted gross domestic product and economic factors heavily and did not consider leadership, culture and universal access to health care. It ranked the US the highest in pandemic preparedness, yet we saw severe impacts in New York and other parts of the US early in the pandemic, with massive failures in testing and other aspects of pandemic control. Our epidemic risk analysis tool called EpiRisk had a similar ranking to the GHSI. However, after COVID-19 and seeing that some low- and middle-income countries had fared better than high-income countries, we went back to the drawing board and worked out what parameters were missing from the model to provide a better prediction of preparedness. The model was then tested against COVID-19 responses in a range of different countries and adjusted

to incorporate other influential factors like leadership, culture and universal health care until it was better able to predict pandemic response. This is the kind of risk analysis that should be routine in pandemic preparedness.

With the dark cloud of H5N1 above us, adequate stockpiling is another action that can mitigate a pandemic. In addition to pre-pandemic vaccines, this would include influenza antivirals, antibiotics to treat bacterial secondary infections, pneumococcal vaccines as a preventive measure against pneumonia, and, of course, personal protective equipment. We likely will have forgotten the lessons about masks, just like we did after the 2009 influenza pandemic. We will see shortages of masks and health workers being mowed down at the front line because, sadly, the COVID pandemic has resulted in a backlash against many public health measures. We have gone backwards in public health pandemic control since COVID, and that will be a setback during a new influenza pandemic. Ultimately, however, risk perception drives human behaviour and tolerance for public health measures, and a H5 pandemic may be much more severe than COVID. When people see friends, family and neighbours dying or becoming seriously ill with pandemic influenza, most will avail themselves of any available protection measures.

8

A POX ON YOUR HOUSES

My interest in smallpox started in 2006 when I was on a committee that had to plan for potential biological warfare or terrorism. Bacteria and viruses that can be used as bioweapons are classified into three groups, with the highest risk group referred to as ‘Category A’. This includes smallpox, anthrax, plague and Ebola. When I studied bioweapons, I felt that smallpox, caused by the variola virus, was the most serious threat as it was highly contagious and killed one-third of the people who caught it. It was a scourge on Earth for thousands of years, causing recurring epidemics and at least 500 million deaths. One in three infected people died until it was eradicated in 1980 using vaccines. I did a study to quantify the risk of Category A bioweapons and found that smallpox and anthrax ranked at the top of the list. Yet policymakers thought smallpox was unlikely because it was eradicated. Intelligence agencies worry that some countries may have secret stockpiles of the virus, but also that it could be made in a lab. A decade later, virologists in Canada created a very closely related virus from scratch, proving that smallpox, too, could be made in a lab. This is called synthetic biology.

Mpox and smallpox belong to the orthopoxvirus family of DNA viruses, which have a very large genome compared to the small genomes of influenza and SARS-CoV-2, both RNA viruses. The orthopoxviruses are closely related, differing only by a few base pairs from each other. The smallpox vaccine uses the vaccinia virus, which causes cowpox. Edward Jenner’s discovery of the vaccine led to eradication, but the story of

eradication is an interesting one. Initially, the WHO aimed to use mass vaccination, which is when the entire population is vaccinated. Since smallpox, COVID-19 is the first time we have seen mass vaccination. Usually, vaccination programs are targeted in some way, either by age group or risk group. For example, infant vaccines are given to young babies, while other vaccines are given to older adults. Some vaccines are recommended in policy documents for people with specific disease risk factors, such as respiratory or cardiovascular disease or immunosuppression. Other vaccines may target a population subgroup, such as Indigenous people or pregnant women. The initial eradication campaign against smallpox began with mass vaccination, but countries like India, with large sections of the population living in villages and rural areas, were unable to achieve this at the levels required for herd immunity. This led to a change in strategy and the use of ring vaccination instead, which is largely responsible for the eradication of smallpox.

Dr William (Bill) Foege, former director of the US CDC from 1977 to 1983, came up with the brilliant idea of ring vaccination while working on smallpox eradication in Africa. The WHO first tried to vaccinate everyone in the world, but this was difficult if not impossible in some countries because of vast distances and widely dispersed remote and rural populations. Dr Foege figured out that if you can trace the contacts of a case of smallpox and vaccinate them, you can bring an epidemic under control without having to vaccinate the entire population. We now refer to this as ‘ring vaccination’. Because of the relatively long incubation period of smallpox, the vaccines work well even if given after exposure to smallpox, albeit with reduced effectiveness compared to primary prevention. In the era of smallpox, about 60 per cent of contacts of a case of smallpox became infected, so Dr Foege’s solution of vaccinating contacts was an efficient strategy. The time it takes to become ill after being exposed to the smallpox virus is 12 days on average, which allows time for public health teams to trace contacts and vaccinate them. This requires far fewer doses of vaccine than mass vaccination, so it is also highly cost-effective. This is how eradication of smallpox was achieved, and how epidemics were controlled

in the last hotspots of the world, such as India. It was far more feasible to find outbreaks and vaccinate affected villages than to try to vaccinate the entire population. Should smallpox re-emerge today, ring vaccination would ensure it could be brought under control swiftly, unless it was engineered to be vaccine-resistant. Finding cases is key to the ring vaccination strategy, so good surveillance is required. In India, community volunteers were paid to report cases or outbreaks. The strategy of ring vaccination also avoids exposing people who are at low risk of catching smallpox to the side effects of the vaccine.

Ring vaccination won't work for a disease with a very short incubation period, like influenza or even SARS-CoV-2, which had a long incubation period in 2020 but mutated over time and now has a very short incubation. What this means is that by the time you have traced a contact, they are already ill. With a long incubation period, you can still find contacts before they become ill. There are many different interpretations of ring vaccination. During the smallpox eradication campaign, it usually meant vaccinating an entire village where smallpox was identified. The concept of ring vaccination has been adapted for the control of Ebola and other infections more recently, and in this context, it tends to be contacts, as well as contacts of contacts. I learned mathematical modelling of epidemics in 2001, when my boss at the time, Professor Margaret Burgess, sent me to the University of Warwick in England to do a course on this science. Since then, I have published many studies on epidemic modelling. Smallpox is a good example of a virus where mathematical modelling is helpful. As it has been eradicated, modelling can help us predict how it would spread if it re-emerged and compare different disease control strategies. In our research modelling the use of ring vaccination instead of mass vaccination, we only looked at direct contacts of each case and it was still highly effective in controlling an epidemic. The greats of smallpox eradication like Dr Bill Foege, Dr Donald Henderson, Dr Frank Fenner and my mentor Dr Mike Lane were not awarded the Nobel Prize in medicine. Sadly, the Nobel Prize is not awarded posthumously, and only Dr Foege remains alive. He has won

many other awards, of course, but it’s not too late to recognise him for devising the strategy of ring vaccination.

Smallpox vaccines confer protection against other orthopox-viruses, including mpox. Several countries in West and Central Africa have endemic mpox, which means animals carry the virus and can occasionally infect humans. In parts of these countries, the infection is endemic in rodents, mice and monkeys. Mpox can be zoonotic (spread from animals to humans) or can spread from human to human, usually in close contacts. The first human case was documented in 1970, with small, sporadic outbreaks since then and until 2017. The clinical picture can be similar to smallpox, but less severe. Like smallpox, the rash is more common on the face, hands, feet and extremities than the trunk. This is one way to differentiate chickenpox and orthopoxvirus infections as chickenpox tends to be more severe on the trunk. The chickenpox virus, varicella zoster, is a herpes virus and unrelated to orthopoxviruses. The other difference is that chickenpox lesions are at different stages of development. In smallpox or mpox, all lesions are typically at the same stage of development. One complication is the surprising frequency of coinfection with mpox and chickenpox. Studies in Brazil and Nigeria showed coinfection rates of 20 to 30 per cent. This means diagnosis and surveillance for mpox could be masked by chickenpox. Tests for chickenpox are more readily available than for mpox, so if the test is positive, the patient may be assumed to have only chickenpox and further testing may not be done. One way to improve surveillance in countries with low diagnostic capacity is the use of open-source epidemic intelligence for outbreaks of rash and fever, such as EPIWATCH. Local news reports or social media may report outbreaks before health departments know about them, and early warnings can trigger investigation and diagnosis.

The pattern of spread of mpox changed in 2017 when much larger epidemics in humans began occurring in Nigeria and the Democratic Republic of Congo (DRC). Our research showed that this was related to reduced population immunity to orthopox viruses. Although vaccines against smallpox protect against mpox, few people in the world are

vaccinated. More than four decades have passed since the eradication of smallpox, and older people who were vaccinated in the 1960s or ’70s have little residual immunity and comprise a smaller fraction of the population. When smallpox was widespread in the world, there was exposure to both infection and vaccination, which resulted in a high level of immunity in the population. However, by the 1970s, most vaccination programs against smallpox had ceased, and we have not had mass vaccination for 40–50 years. Our research found that around 2017, the existing immunity in the population of Nigeria dropped below 2 per cent, and that seemed to be the threshold for escalating epidemics. Large epidemics of mpox began in Nigeria in 2017, corresponding to this drop in population immunity. It is possible we may see other novel orthopoxviruses, like borealpox (previously known as Alaskapox), also cause epidemics due to loss of immunity. Many other zoonotic orthopoxviruses may also cause human epidemics, but mpox is the most concerning.

There are two clades (types or variants) of mpox, clade I and II, with clade I being more severe. Clade I infection can kill up to 10 per cent of infected people. Clade II is less severe, killing less than 1 per cent. The epidemic of mpox in North America and Europe in 2022 was related to clade II, with a pattern that differed from past epidemics in Africa as it appeared to be sexually transmitted. This variant has been classified as clade IIb. Prior to the 2022 epidemic, typical outbreaks occurred in villages where the first case was in a human exposed to an animal such as a rodent or a monkey, with subsequent limited human-to-human transmission among their close contacts. These were small outbreaks and easily contained by infection control measures. In fact, mpox was uncommon in Nigeria, with the first case being in 1971 and no further cases after 1978 until 2017, when a large outbreak affected at least 115 people. In the DRC, there was a similar outbreak with over 4000 suspected cases and 171 deaths in 2017. With this spike in Africa, travel-related cases of mpox occurred in the UK, Singapore and Israel in 2018 and 2019 in travellers from Nigeria. Despite this disturbing re-emergence, mpox remained a low priority globally until the 2022 epidemic, which spread through high-income countries in Europe

and the US. The epidemic spread among men who have sex with men, a different pattern from African epidemics, but genetically it had originated from the 2017 clade II epidemic in Nigeria. Strangely, genetic analysis of the clade IIb epidemic showed rapid, continuous viral evolution during 2022. This was unexpected because orthopoxviruses are stable DNA viruses. We expect RNA viruses like HIV, influenza and SARS-CoV-2 to mutate rapidly, but not orthopoxviruses. We now have a situation where clade IIb epidemics are ongoing in countries that have historically never had mpox, with a resurgence of infections in Australia in 2024. With ongoing transmission, this means the virus can infect animal hosts in Europe, the Americas and other non-endemic areas. Once established in animals, it may become endemic, causing a permanent risk of zoonotic outbreaks well outside the African continent. Meanwhile, the epidemics escalated in the African continent, with thousands of cases in the DRC.

The WHO estimated nearly 15 000 suspected clade I mpox cases in DRC in 2023 alone, with a case fatality rate of 4.6 per cent. Unlike the US and European epidemics, which affected mostly adult males, in the DRC, 70 per cent of the cases and 88 per cent of deaths are in children. Less than 10 per cent of these were tested by PCR due to low diagnostic capacity in that country. The predominance of children in the DRC epidemic suggests transmission may be respiratory, and there are reports of outbreaks in schools. In fact, smallpox and mpox are respiratory viruses, and mpox has been identified in ambient air in clinics. Smallpox was highly airborne, with the potential to transmit over long distances. In the last 100 years before eradication, when community outbreaks were uncommon, the British observed that smallpox would occur in a radius of about 1 kilometre from smallpox hospitals in the community. They noticed the same thing in communities around smallpox ships on the River Thames. These ships were used to treat smallpox cases and separate them from the community, with very strict rules forbidding patients from coming on shore. The British termed this phenomenon ‘aerial convection’. They also introduced policy changes to restrict the location of such facilities close to highly populated areas. Much of this knowledge has been lost since eradication, and I have

no doubt that if a smallpox epidemic occurred, the infection control experts would tell us to wash our hands, as they did with COVID-19. I led research documenting and collecting all the long-range transmission events that showed how far smallpox could be transmitted through the air. In many cases, it was 1 kilometre or more. There were also several examples of transmission inside buildings, from floor to floor. The 1978 infection and subsequent death of Janet Parker, a photographer, working on the floor above a smallpox laboratory, is one example. The scientist working in the lab below was careless with safety around his experiments, resulting in the virus somehow floating up to the floor above (assumed to be through ventilation ducts) to infect poor Janet Parker. His lab was shut down after this incident, which delayed the eradication of smallpox, and as a result, only two high-security labs in the world, in Russia and the US, were allowed to stock smallpox after that.

The most extreme example of accidental transmission of smallpox was in 1971. A Soviet ship, the *Lev Berg*, was travelling 15 kilometres away from a military bioweapons facility called Aralsk-7 on Vozrozhdeniya Island in the Aral Sea. At the time, the Soviets were testing the weaponisation of smallpox on that island and exploded a smallpox bomb. The Soviets forbade ships from sailing within 40 kilometres of the island, but for some reason, the *Lev Berg* was within the banned area. A crew member was collecting plankton samples on the deck and became infected, sparking an epidemic in the town of Aralsk, with a very high rate of haemorrhagic smallpox. The Americans suspected this was a genetically modified strain and called it the Aralsk strain. The Soviets denied everything and did not make any specimens available for testing. It is known, however, from Soviet defector Ken Alibek (who had been deputy director of the Soviet bioweapons program) that they were genetically modifying the most severe natural strain, the India strain (also known as the I strain). Thankfully, that was in the 1970s, when today's genetic engineering technology was not available. It may have been *game over* if the Soviets had CRISPR-Cas9 or the synthetic biology methods of today as they would have succeeded in creating a more deadly strain.

So, it is against this backdrop of smallpox, which was highly airborne, that the mutations in mpox are a worry. If clade I mpox becomes highly transmissible between humans, it may pose a greater pandemic threat than clade IIb. A recent study of an outbreak in Kamituga, DRC, near the Rwanda border, identified a new mutation of clade I mpox, termed clade Ib, which may pose a pandemic threat as it is more readily transmissible between humans. The lack of diagnostic capacity and the need for heightened surveillance in the DRC is a dilemma. However, the specific nature of the rash makes it possible to count cases when a laboratory diagnosis cannot be made. If clade I mpox becomes more contagious, it may grow exponentially and spread worldwide. Our research on smallpox showed that even one week of delay impacts the size and spread of an epidemic, so early diagnosis and containment are key. In the DRC, however, there is very limited access to mpox vaccines. Unless this inequity is addressed, a highly contagious strain could seed a pandemic. The Africa CDC, the WHO, vaccine manufacturers and other organisations are working together to provide diagnostic tests and vaccines to the DRC and other affected countries in Africa. Individual countries like Japan and the United States have also donated vaccines.

Smallpox, too, may come back through the use of synthetic biology. In 2018, virologist David Evans and his team published the methods for synthesising horsepox, a closely related orthopoxvirus, and these methods are freely available online. The orthopoxviruses are closely related genetically, so if you can synthesise one, you can synthesise any of them, including smallpox. Chillingly, Evans published a paper showing the exponential decline in the cost of synthetic biology, and greater access to it, stating that ‘The advance of technology means that no disease-causing organism can forever be eradicated’. In the 40 years since smallpox eradication, the WHO has attempted to eradicate two other infections – polio and measles – but to eradicate an infection, it is essential to achieve ‘herd immunity’.

9

HERD IMMUNITY

Early in the COVID-19 pandemic, we heard many TV and social media ‘experts’ talk about herd immunity, usually calling for mass infection to achieve it. It was a mythical hope that allowing mass infection would stop the pandemic. Even expert committees in countries such as Sweden and the UK, who should have known better, were pushing ‘herd immunity by natural infection’, which became a household narrative during the pandemic. Herd immunity is a concept that arose from vaccine programs, and anyone with knowledge of the epidemiology of infections which are now prevented by vaccines, understands that no infection ever controlled itself without the use of vaccines. Smallpox caused recurrent, large-scale epidemics in the pre-vaccine era, as did measles, and this behaviour can be predicted mathematically. Only vaccines have succeeded in controlling infections, and they do so by providing immunity without causing the target illness.

When it became clear that reinfection with SARS-CoV-2 was common and vaccine immunity waned, the hot phrase changed from herd immunity to ‘hybrid immunity’, and experts began advocating for infection as the best hope to prevent infection, without realising how ridiculous it sounded. And of course, now we have come full circle, with these experts calling again for mass infection to prevent infection. One paediatrician on social media suggested that getting infections was like exercising a muscle and that it made you stronger, specifically mentioning measles and smallpox, another myth related closely to that of ‘immunity debt’. This term was never

mentioned in medical literature until the COVID pandemic. It was used to explain massive waves of infection with group A streptococcus, RSV and other infections that seemed to be surging in an unprecedented manner after the COVID-19 mitigations ended. The implication of the conjured-up term ‘immunity debt’ is that preventing COVID-19 (by measures such as masks, distancing and lockdowns, which also prevented other respiratory pathogens) was bad and leaves you with a debt to other infections that needs to be repaid. Logically, then, it’s better to be infected now than to prevent infection. In truth, immunity debt was a cunning construct in the war against public health, waged by media, medical professionals and health leaders simultaneously. The logical conclusion would be that we remove all the great gains of public health of the last century to avoid immunity debt. We would stop chlorinating the water supply, stop vaccinating children against childhood infections and return to the 19th century with high infant mortality rates, low life expectancy and ongoing cholera epidemics.

While advocating herd immunity through mass infection, these experts bemoaned that COVID vaccines did not provide ‘sterilising immunity’ – another new catch phrase that had never appeared in scientific literature – which meant that the vaccines did not prevent infection. Perhaps they forgot to read the phase 3 clinical trials of COVID-19 vaccines, which showed high efficacy against infection. The COVID-19 vaccines did prevent infection against variants of the virus that were genetically closer to the original virus used as the template for these vaccines. It turned out we had a twofold problem. Firstly, that vaccine immunity waned and that you needed a booster to retain efficacy against infection, and secondly, that the virus had other ideas and kept mutating to become more and more genetically distant from the virus the vaccine was designed to protect against. In other words, the vaccines were targeted to a different virus from the one circulating. Unfortunately, our regulatory processes are too slow to keep up with the virus, and we have played a constant game of catch-up with updated boosters, learning more and more as we go. The first release of updated bivalent boosters against either BA.1/2 or BA.4/5 helped

somewhat, but it turned out that adding two vaccines into one shot slightly reduced the efficacy. This prompted the WHO to change their recommendation by May 2023 to a monovalent vaccine against the prevailing variant, XBB, and a year later to JN.1. By September 2024, the US released updated boosters matched to the KP.2 variant, which came after JN.1 and was a better match to variants that were circulating later in 2024.

Yet how quickly people lose hope about vaccines when the development of highly efficacious vaccines in less than a year after SARS-CoV-2 emerged is a miracle. This has been compounded by restrictive vaccine guidelines in many countries, including restriction of boosters to older people only, and denial of vaccination to children under five years by many countries. So, any hope of 'hybrid immunity' for working-age adults and children relies solely on repeated infections, a Machiavellian prospect. What about herd immunity, then? The real one, not the manufactured one.

Vaccines are different from drugs used to treat acute illnesses because they prevent an infection that may or may not happen sometime in the future. This is called primary prevention and requires mass vaccination to have an impact on population health. When herd immunity is achieved through vaccination, infections can be controlled, eliminated or eradicated. Mass vaccination was used to eradicate smallpox and control serious childhood infections like diphtheria, polio and Hib meningitis. Herd immunity is critical to population protection. It is when a high enough proportion of the population is immune to protect everyone, including unvaccinated people, from infection. It is a direct function of the infectiousness of the pathogen, vaccine efficacy and how many people get vaccinated (also termed 'vaccine coverage'). The infectiousness of the pathogen is determined by the reproductive number (R0), which is the average number of people who will get infected by one infectious person in an unvaccinated population that has never been exposed to that pathogen. For example, if I have measles and I enter a room full of 100 people who have never been vaccinated nor had measles before (we call this an 'immunologically naive' population) and I infect 15 of them, and if we repeat this experiment and find that on average 15 people get infected from

one infectious person, then the R0 is 15. Highly contagious infections include measles, SARS-CoV-2 and whooping cough (pertussis). A single case of measles or whooping cough, on average, infects about 15–18 people, while one case of smallpox, on average, infected three people. The original SARS-CoV-2 that emerged in Wuhan only infected about two people (R0 of 2), but as it mutated it became more and more contagious. Estimates of the R0 now range from 6 to 15. In the case of SARS-CoV-2, an added complication is the immune evasion of ongoing mutations, which means antibodies against older variants do not protect as well against new mutations.

The R0 is a determinant of the pattern of disease a particular infection follows, and there are three main patterns under which almost all infections will fall. These are endemic, epidemic and sporadic. An endemic disease may occur at very high levels or lower levels but does not change rapidly over time. Typically, an endemic disease exists permanently in a particular region or population. A classic endemic infection is malaria, and other endemic diseases include diabetes and heart disease. The term endemic is not defined by the number of cases – endemic diseases can exist in very high numbers. Changes in the incidence of endemic diseases occur over years or long periods of time, if at all. In contrast, a true epidemic disease displays a rapid increase over time and affects many people at the same time. Typically, epidemic diseases spread through a population rapidly. The term epidemic is widely misused, often appropriated to convey a sense of urgency and importance for a particular disease. You may have heard people refer to an epidemic of drug overdoses or diabetes or obesity, but these are not epidemic diseases. In fact, the term epidemic has a mathematical definition. It is defined by the rate of growth, typically days or weeks, and by the reproductive number. If it is more than one, the number of cases increases, and an epidemic may occur. Conversely, if it is less than one, the number of cases decreases, transmission cannot be sustained and the infection dies out. When R=1, this is called the epidemic threshold. The speed of growth of an epidemic, which is typically exponential, is what causes sudden disruption to the normal functioning of

society and health systems. True epidemic and pandemic diseases require immediate surge capacity in health systems, whether it is for the winter surge in influenza (which requires planning for extra hospital beds) or a pandemic, like COVID-19 in 2020, where we saw health systems collapse in multiple countries, and the inability to deal with accumulating dead bodies. We saw hospitals overrun, shortages of oxygen, masks, staff and medical supplies, refrigerator trucks and ice rinks piled up with dead bodies, and mass graves being dug in cities like New York. No endemic disease does this, only a truly epidemic disease. An epidemic that becomes global is called a pandemic and follows the same pattern. SARS-CoV-2 is a typical epidemic infection, and will always retain this pattern, much like measles. The last pattern of disease is sporadic, and this is where the number of cases is low, does not meet the endemic or epidemic definition, and the pattern is unpredictable. Typically, these are infections that spread from insects, birds or animals to humans, such as avian influenza or tick-borne typhus. Occasionally, we may see a cluster of cases or single cases. Zoonotic infections like mpox, which historically caused sporadic infections following human contact with animals, can transmit from human to human and cause epidemics. Mpox is a particularly puzzling infection, with changing epidemiology since about 2017 in countries like Nigeria. Our research described in the previous chapter showed this was due to waning vaccine-induced immunity as well as an increasing proportion of the population who had never been vaccinated against smallpox. We then saw an unprecedented global epidemic in countries that had never experienced mpox infections, and a pattern that was much more like sexual transmission than close contact or respiratory transmission as it had been historically. So, sometimes, patterns of disease can change and become quite complex.

Herd immunity is achieved when vaccination rates are high enough to stop transmission within a population and mass vaccination protects the entire population, whether individuals have been vaccinated or not, because the number of people susceptible to infection is too small to sustain ongoing transmission. Even people who refuse to get vaccinated are protected if most other people have been vaccinated. It is also a great equaliser,

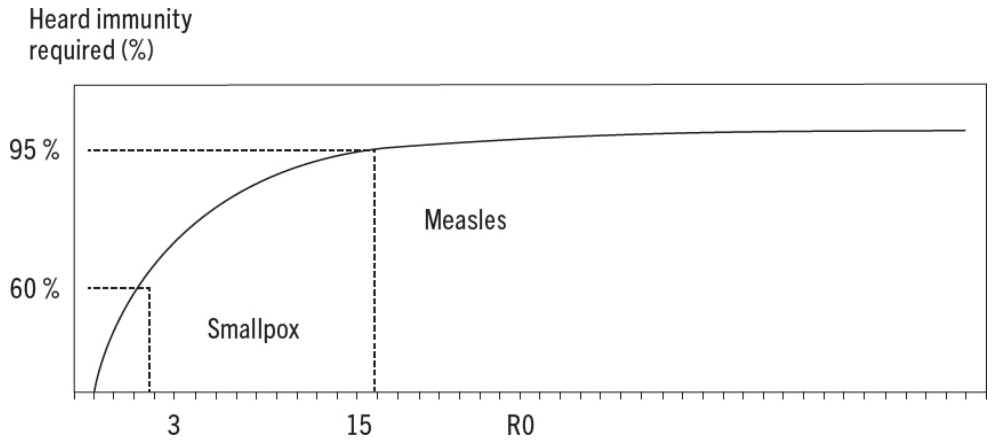
protecting the most disadvantaged populations who may otherwise be at greatest risk. We can calculate the required immunity in the population for herd immunity (H) using the basic reproductive number (R0). The formula to calculate herd immunity is $H=1 (1/R0)$.

The higher the reproductive number, the higher the herd immunity required to control disease, which is a key concept for control of infections through vaccination. Key concepts for infectious disease prevention, in increasing order of impact, are control, elimination, eradication and extinction. Extinction is when the pathogen does not exist on Earth in animals, humans or laboratories. During the COVID-19 pandemic, influenza B Yamagata declined substantially and apparently ceased being detected. Many experts began speculating that it was extinct, but the virus certainly exists in labs around the world, so technically, it cannot be termed extinct. After extinction is eradication. Smallpox is eradicated as it does not occur in nature, but it is not extinct as the virus is kept in two laboratories in the world.

Elimination is a local version of eradication within a region or country, whereas eradication is a global phenomenon. The only human infection to be eradicated is smallpox. The first SARS virus, which caused an epidemic in 2003, has not occurred in humans since but exists under the radar in animal species, so it has not been eradicated. Whether a virus can be eradicated depends on several factors, including the reproductive number, whether there is an effective vaccine and whether the infection has an animal host. Some infections, like smallpox and measles, only affect humans, and these are suitable for eradication. Infections such as SARS, influenza A, mpox and Ebola, in contrast, affect various animals as well as humans, which makes eradication difficult, if not impossible. Even if you get rid of it in humans, like SARS, it can be reintroduced if an animal infects a human. The reproductive number determines the required herd immunity (the proportion of the population with immunity to prevent transmission in the population). Measles, technically, could be eradicated as it only infects humans and we have a very effective vaccine. However, it has a very high reproductive number, estimated to be around 15, making it

one of the most infectious viruses known. The graph opposite is one I created to teach this concept to my students. It is called an elimination graph and shows the relationship of R0 (on the X-axis) to the required population immunity for herd immunity (on the Y-axis), comparing measles (R0 15) and smallpox (R0 3).

Elimination graph



Smallpox, which had a much lower R0 than measles, could be eradicated by achieving immunity (by vaccination) of about 60 per cent of the population, whereas measles, having a much higher R0, requires more than 93 per cent of the population to be immune to prevent transmission. While measles elimination in some countries, including Australia, has been achieved, eradicating measles globally (a goal of the WHO), will be a much harder task than eradicating smallpox. The WHO tried to eradicate malaria in the 1950s and ’60s and failed, which is unsurprising given there was no vaccine, and the malaria parasite exists in mosquitoes.

A vaccine that cannot achieve herd immunity, either because it does not have high enough efficacy or because the virus mutates rapidly (like SARS-CoV-2) or not enough people are vaccinated, will result in ongoing, long-term and continuing risk of outbreaks. The proportion of people vaccinated in a population is referred to as ‘vaccine coverage or uptake’. High vaccine coverage is a key target of public health programs. The reason that many countries in the world have eliminated serious infections like polio and

measles, or controlled infections such as diphtheria so they are now very rare, is herd immunity. Herd immunity is like a wall that needs to be built up but can be broken down. The fall of the Soviet Union is an example of what happens when a strong public health infrastructure is broken down and vaccination programs weakened. Previously rare diseases that had been controlled by vaccination, such as diphtheria, suddenly became rampant. Sometimes, the wall of immunity may have a few bricks that have fallen out, leaving holes in the wall. In this case, there may be small under-vaccinated pockets of people in a population that is otherwise well vaccinated. They may be pockets of vaccine refusers, congregated in alternative lifestyle communities, or they may be people in one age band who missed out on a new vaccination given to younger people. They may also be migrants who have come from a country that provides fewer childhood immunisations, leaving them vulnerable to outbreaks. We use the term ‘catch-up vaccination’ to target specific under-vaccinated groups with a one-off vaccination campaign to help get their vaccination rates up or add bricks to close up the holes in the wall.

Many migrant and refugee communities may be under-immunised because of less access to health care, difficulty navigating the health system in a new country or being unable to meet out-of-pocket costs. About 20 years ago, I worked in a clinic in Sydney that saw refugee patients, and when following up on a family that never attended appointments, learned that the problem was transport. The family had seven members who were unable to travel in a single vehicle and were too far from public transport routes. One of my PhD students, Mohammed Sheikh, a Kenyan who went back home after graduating and became a politician, researched barriers to access to care for refugees and migrants in South Western Sydney. He found they did not know how to access primary care, so they would only seek health care when desperately ill, and then at an emergency department, which does not offer routine immunisation. Except for dedicated refugee health services, which are few and far between, there is no way to identify people who may be under-vaccinated and in need of catch-up vaccination. An immunisation register is a good start.

Australia was one of the first countries to introduce a childhood immunisation register in 1997 and later a whole-of-life immunisation register in 2016. I led the Centre for Research Excellence in Immunisation from 2012 to 2016 where gaps in vaccination and special risk groups were a focus. We had long advocated for the importance of a whole-of-life register and held a national workshop with key stakeholders on this topic in 2016 to inform the development of the register. Having a register is the first step, but being able to identify people at risk of under-vaccination during primary care encounters is one important way registers can help improve vaccination rates. Some groups may not be captured on immunisation registers because they are not Australian citizens. These may be people on temporary visas, international students or migrants. A large outbreak of measles in Western Sydney in 2012 is a good case study. The immunisation registers showed very high rates of measles vaccination in that part of Sydney, so they did not detect any risk. Yet there were communities of Pacific Islander migrants from New Zealand who were under-vaccinated and were the main group affected by this large outbreak. The outbreak also affected infants who were too young to have been fully vaccinated. Nonetheless, the immunisation register is a valuable tool for most of the population. It enables reminders to be sent when people are late for a scheduled vaccination, generates vaccine certificates and prompts GPs to vaccinate their patients when indicated. The current whole-of-life register in Australia doesn’t prompt GPs to check refugee status or other indicators of under-vaccination. Certain refugee health services provide vaccination, but these are ad hoc and vary by jurisdiction. In 2013, the Centre for Research Excellence in Immunisation brought together, for the first time, all stakeholders in traveller, migrant and refugee immunisation. The report arising from this identified that people of migrant or refugee backgrounds are at greater risk of being under-immunised and that a gap in immunisation policy for refugees and migrants was lack of funding for catch-up immunisation. We also advocated for a whole-of-life immunisation register so that GPs could easily identify people of refugee or migrant background and check their immunisation status. Finding the gaps in the ‘immunity

wall’ that provides herd immunity, and acting on them, is a key part of any vaccination program.

Another issue that affects herd immunity is the waning of vaccine-induced immunity. In the past, when large proportions of the population had immunity to measles conferred from natural infection, it was assumed that immunity conferred by the measles vaccine was lifelong. Today, in countries like Australia, the proportion of people with immunity as a result of having been infected with measles (mainly older people) is much lower than 20 years ago. There is now evidence that, despite the efficacy of the measles vaccine, the waning of vaccine immunity can occur, even after two doses. This is an unfolding story, and more evidence is needed, but waning may threaten elimination status in countries like Australia if a sufficiently large proportion of the vaccinated population becomes susceptible to measles over time. Different dosing schedules with varying spacing between doses, and consideration of an additional dose (three versus two) are questions that need to be asked in the future. To add to this problem, there have been declining vaccination rates for measles after COVID-19. In some countries, it is because COVID-19 vaccination programs took up available resources at the expense of other vaccine programs, but in others, it was a general rise in vaccine hesitancy following propaganda about the safety of COVID-19 vaccines. This has affected measles vaccination rates globally, with a surge in epidemics worldwide.

10

MEASLES, MEASLES EVERYWHERE

I began researching measles outbreaks in 2001 when an inspiring British mathematical modeller, Dr Nigel Gay, spent some time at the National Centre for Immunisation Research and Surveillance where I was working at the time. I collaborated with him on the modelling of measles in Australia, and that began a long-term research interest in measles. Measles is a serious viral respiratory infection that remains a major cause of illness and death in low-income countries. It can cause pneumonia, ear infections and gastroenteritis, but the most serious complications are measles encephalitis and a rare condition called subacute sclerosing panencephalitis (SSPE). SSPE occurs years later, typically in children and younger people, and is a progressively deteriorating and mostly fatal neurological condition causing cognitive impairment, behavioural disturbance, jerking movements of the arms and legs, and seizures. Autopsy results have found the mutated measles virus in the brains of affected people.

There is a safe and effective live, attenuated measles vaccine, most often given in combination with mumps and rubella vaccines. The WHO's goal is to eradicate measles, but the virus continues to cause epidemics worldwide, not just in developing countries. The efficacy of the measles vaccine is extremely high – over 95 per cent – and protection tends to be long-lasting. However, because measles is so contagious and has such a high reproductive number, extremely high global rates of vaccination are needed to eradicate it. Meanwhile, some countries have achieved WHO-certified elimination status for measles, but many low- and middle-income

countries have not. Before the COVID-19 pandemic, massive measles epidemics were occurring in Ukraine, Romania, Italy and many other countries. Those that have achieved elimination still experience outbreaks of measles, but they do not become uncontrollable. Many people have forgotten that even in Australia, measles was rampant not so long ago. When I was 17 years old in the early 1980s, I caught measles six weeks before my final HSC exams. I remember how ill I was, bedridden for at least two weeks. A teacher at my school (not one who taught me but one from the same ethnic community as me) telephoned my mother to tell her I had not been attending school. Offended, my mother informed her she was well aware I was not at school as I was ill with measles. We migrated from Sri Lanka to Australia in 1973 when I was nine years old and I missed out on adolescent vaccination, which began 20 years later in 1993. That's the classic migrant story of under-vaccination.

Epidemics of measles have been in the news for over a decade globally, even in high-income countries with good immunisation programs. In 2014–15, a large outbreak occurred in Disneyland in the US, despite high vaccination rates in the country. Unsuspecting families and holiday-makers from all over the US and the world were widely exposed to someone with measles. After visiting the theme park, people returned to their home states with more than 100 cases of measles in more than 14 states of the US. This outbreak probably originated from an infected overseas visitor spreading to mostly unvaccinated Americans, including infants too young for vaccination.

At the time, I had done research about face masks, showing that an N95 respirator protects health workers from infections but a surgical mask does not. This prompted outrage in the US as the finding challenged prevailing hospital infection control dogma that a surgical mask was adequate. A doctor from the California Department of Public Health, who I had known since 2009, reached out to me and explained some of the politics and ideology behind the outrage. It turned out we had more in common than an interest in masks – she was an immunisation expert. We began discussing the Disneyland measles outbreak, and a previous one in Sydney in 2012, the

largest measles outbreak since 1997, with 168 cases in Western and South Western Sydney. The complexity of measles transmission is the fact that measles epidemics can occur despite high rates of vaccination and despite the vaccine itself having high efficacy (more than 95 per cent) because of pockets of under-vaccination. Furthermore, measles is declared eliminated in both the US and Australia, so how is it possible for outbreaks to occur? Elimination means that ongoing, sustained transmission cannot occur because herd immunity has been achieved. It does not mean that outbreaks will not occur; those outbreaks will be self-limiting and will not continue in an uncontrollable fashion. Overall vaccination rates were 92 per cent in the US at the time of the Disneyland outbreak, and over 95 per cent in Australia. In the affected areas in Sydney in 2012, measles vaccination rates, according to the Australian Childhood Vaccination Register, were very high. However, the register only captured children under the age of seven registered in Australia and who have a Medicare card. It did not capture people on temporary visas or who are not Australian citizens. In the 2012 outbreak, highly mobile groups of New Zealanders of Pacific Islander ethnicity moving between New Zealand and Australia were under the radar for routine vaccination coverage measurements and appear to have introduced the epidemic. Some were children, but some were young adults. In response, a high school vaccination campaign and other targeted efforts were conducted in the affected area.

Nigel Gay taught me the basics of modelling, and then I did a course at the University of Warwick in the UK in 2001, a leading mathematical modelling centre led by Professor Graham Medley. I learned hands-on skills on how to build and run a model and how to use a ‘who acquires infection from whom’ (WAIFW) matrix. The matrix has age on each axis and describes the level of interaction or mixing between and within age groups, which allows you to estimate transmission risk for a respiratory pathogen in a population. Using a WAIFW matrix that Nigel Gay provided me, I built a model for measles and showed that overall vaccination coverage rates are only part of the picture, and that large variations can exist in vaccine uptake between small geographic areas. Those who are vulnerable to outbreaks can

be predicted using mathematical modelling so health authorities know where future location outbreaks are most likely to occur. In 2005, while I was working at the University of Sydney, I recruited a postdoctoral researcher, Dr James Wood, a physicist with no background in health or medicine, to join my team. He cut his teeth on the measles modelling I had started. Later, when I moved to UNSW in 2008, I negotiated to bring my team, including Dr Wood (now a professor), with me. He built on my earlier measles work to predict New South Wales and Queensland as hotspots for future measles outbreaks in Australia. We were also able to show that the modelling predictions correctly identified small geographic areas where outbreaks later occurred. The presence of under-vaccinated pockets of the population gives rise to ideal conditions for an epidemic, should measles be imported into the country.

While outbreaks of measles do occur in communities of vaccine refusers, measles is mostly an imported infection in countries such as the US and Australia, brought in by travellers who are unvaccinated or under-vaccinated. This is confirmed by genotyping studies, which show that such outbreaks are caused by imported strains of measles. However, once introduced into the community, other people can also be affected, especially infants too young to have had their full vaccination course. In addition, many travel-related cases of measles occur in adolescents or young adults. In a study of measles in Australia, we found that almost 60 per cent of people with measles had travelled overseas (mainly for holidays). A large proportion were adults and adolescents, and less than 20 per cent were young children of vaccine refusers. This is quite a mixed bag and shows that strategies like No Jab, No Pay in Australia (which I discuss further in chapter 11) would impact less than 20 per cent of preventable measles cases as most of them occur in older children and adults.

In Australia, measles vaccination is given as a two-dose schedule at 12 months and 4 years; in the US at 12–15 months and then 4–6 years. The Australian measles control campaign in 1997–98 included moving the second dose of vaccine from 12 years down to 4 years of age and simultaneously rolling out a catch-up vaccination program for adolescents.

This resulted in a dramatic decline in measles in Australia in the next decade. However, measles won't be going away in a hurry. Currently, we have a large measles epidemic in the Philippines, ongoing since 2017, precipitated by very low vaccination rates in the conflict areas of the south. Measles control has been worsened by a loss of public trust in vaccine programs following the withdrawal of the dengue vaccine after serious side effects occurred. Samoa also had a large measles epidemic in 2019, precipitated by a loss of trust in vaccination following the contaminated measles vaccines and resulting fatalities. Global hotspots for measles include Asia, Africa and Europe (where cases tripled even before the COVID pandemic). Romania has experienced large epidemics since 2016, and in the US and the UK, outbreaks continue to occur while vaccination rates have fallen. The UK situation is particularly concerning, with nearly 1500 suspected cases between October 2023 and May 2024. There is also the issue of waning vaccine immunity, which has not been recognised until recently. In the past, when large proportions of the population had immunity to measles conferred from natural infection, it was assumed that immunity conferred by the measles vaccine was lifelong. Today, in countries like Australia, the proportion of people with naturally induced immunity (mainly older people) is much lower than 20 years ago. There is now evidence that despite good efficacy, the waning of vaccine immunity can occur even after two doses. This is an unfolding story, and more evidence is needed, but waning may threaten elimination status in countries like Australia if a sufficiently large proportion of the vaccinated population becomes susceptible to measles over time. Different dosing schedules with varying spacing between doses, and consideration of an additional dose (three versus two doses), are questions that may need to be asked in the future.

Measles is technically eradicable as humans are the only host. However, it has a very high reproductive number, estimated to be around 15, making it one of the most infectious viruses known. As we have already seen, smallpox had a much lower reproductive number than measles and could be eradicated by achieving immunity (by vaccination) of about 60 per cent of

the population, whereas measles, having a much higher reproductive number, requires more than 93 per cent of the population to be immune. While measles elimination in some countries has been achieved, eradicating measles globally will be a much harder task than eradicating smallpox. We are going backwards in 2024 as measles epidemics soar globally. In many low-income countries, measles vaccination rates have fallen because these countries were unable to meet the demands of both COVID-19 vaccination and routine childhood immunisation. In other countries like the UK and the US, anti-vaccination sentiment has increased, resulting in the resurgence of measles. In the UK, which has embraced mass infection of children with COVID-19 – on the back of decades of damage caused by the MMR autism scare – measles vaccination rates have plummeted to 85 per cent nationally and 74 per cent in London. We are seeing the country regress to the bad old days right before our eyes.

Another problem is recurrent failure to diagnose measles in the health system, resulting in further spread of the disease in hospital waiting rooms. We often see failure to diagnose serious infections in hospitals, whether it is Ebola in Dallas, Texas, in 2014, or Middle East respiratory syndrome (MERS) in South Korea in 2015, leading to preventable epidemics. In Dallas, at the peak of the West African Ebola epidemic in 2014, which was in news headlines daily, a sick patient from West Africa presented to a local hospital. Despite having a fever, no one thought he may have Ebola and the diagnosis was delayed. In South Korea in 2015, a traveller from the Middle East, where MERS is endemic, presented to a major hospital in Seoul where the diagnosis was missed and a large outbreak resulted. Multiple examples of delayed diagnosis of measles cases have been seen in Australia, often resulting in exposure of other patients in waiting rooms and causing outbreaks. Usually, an infectious patient with measles would be isolated in a single room after the laboratory test comes back positive for measles. However, that patient may have sat in the emergency waiting room for hours, and then in the emergency ward for more hours, all the while spreading measles to others. The first port of call in the emergency department is triage. This is when a nurse calls up patients from the waiting

room and evaluates them for the relevant level of care. Part of this triage involves taking blood pressure, pulse and temperature measurements. Fever should alert triage staff to potential contagious infections that can pose a risk to staff and patients. Having guidelines for patients with fever, with prompts for health workers to ask febrile patients about their travel history, can help, particularly if linked to data on outbreaks in different parts of the world. An automated decision support tool could generate a red flag if a patient has a fever and mandate that the triage nurse ask if the patient has travelled. If they have, an automated system could generate a list of outbreak diseases in the country of origin. Our EPIWATCH system has global outbreak data and could feed into an ER triage system in this way. That way, triage staff can be alerted to possible emerging infections that pose a risk to others. Decision support tools to assist in triage, and recommendations for isolation based on clinical syndromes alone (rather than waiting for a lab diagnosis), may prevent the spread of dangerous infections inside hospitals.

Finally, we can expect more information warfare about measles transmission as the epidemics escalate. Exhausted by the propaganda during COVID-19 telling us that handwashing was the best defence against a respiratory virus, on 22 February 2024, I tweeted: ‘Waiting for the experts to tell us #measles is not airborne. No FFP needed. Just keep your distance and wash your hands?’ This was, of course, sarcastic, as I have been researching measles for 23 years and am fully aware it is airborne. In fact, many infection control experts in 2020 cited measles as a ‘true airborne infection’ when talking down the airborne transmission potential of SARS-CoV-2. Dr John Conly and colleagues wrote an article in which they said SARS-CoV-2 was

> very different than an airborne virus like measles with a R0 widely cited to be between 12 and 18 … Airborne transmission refers to the presence of microbes within droplet nuclei (generally considered to be particles < 5–10 μm in diameter), which result from the evaporation of larger droplets and/or exist within dust particles and may remain in the air for long periods of time and may be transmitted to others over longer distances such as the measles virus.

We wrote a response to this paper arguing that SARS-CoV-2 was indeed airborne and that the R0 of a virus is not (and never has been) an indicator of transmission mode. We pointed out that tuberculosis, with a lower R0 than the earliest SARS-CoV-2 variants, is airborne, and a range of other arguments refuting their thesis.

Given the measles epidemics in 2024, I was fully expecting that these same experts would start a new narrative to deny that measles is airborne. The flood of replies to the tweet caused me to sigh in unhappiness as many people pointed out that the UK had indeed begun measles revisionism. The February 2024 guidelines from the UK Health Security Agency state that ‘The transmission route of measles is mostly airborne by droplet spread or direct contact with nasal or throat secretions of infected persons; much less commonly, measles may be transmitted by articles freshly soiled with nose and throat secretions, or through airborne transmission with no known face-to-face contact.’ This word salad appears to be the beginning of a new narrative.

Meanwhile, in Florida, which experienced a measles outbreak in the first quarter of 2024, the surgeon general revoked standard practice from the pre-pandemic era, allowing unvaccinated children to attend school during an epidemic. For decades, most countries have enacted legislation that prevents unvaccinated children from attending school during an outbreak of diseases they are not vaccinated against. At all other times, they are free to attend school, and this is a pragmatic solution that allows parents greater choice in whether they vaccinate their children, but it also protects other schoolchildren in the event of an outbreak. It was reported an estimated 100 unvaccinated students were allowed to attend school in the outbreak epicentre, Broward County. COVID-19 was the excuse to trigger the dismantling of public health in many countries. The COVID-19 pandemic resulted in loss and anger for many, and that anger was misdirected towards public health. Florida, with its anti-science political environment, is the bellwether state in the US, providing early signals of the decline of public health in that country. From malaria and dengue to measles and the banning

of books, we are getting a glimpse of a dystopian future that may take us back to a bygone era.

11

COERCION OR PERSUASION TO INCREASE VACCINATION RATES?

Vaccination rates are falling globally, not just in low- and middle-income countries, whose public health infrastructure was stretched beyond capacity during COVID-19, but also in high-income countries where anti-vaccination propaganda has swamped communities while governments have failed to respond. As a result, we're seeing a resurgence of vaccine-preventable infections like measles, whooping cough and diphtheria. There are many strategies used by public health authorities to improve vaccination rates. If there is a gap in the 'immunity wall' due to under-vaccination in specific subpopulations, catch-up vaccination programs can be used to successfully plug that gap. A great example is catch-up campaigns for measles vaccination. In 1997, when the age of the second dose of measles vaccine was shifted from 12 years to 4 years in Australia, an additional catch-up campaign was used to mop up people who would have missed out – in this case, older children, adolescents and young adults. This certainly contributed to the elimination of measles in Australia.

Other methods to increase vaccination rates include government funding of vaccines to make them free to the community, health promotion campaigns, incentives (including financial incentives) to encourage vaccination, administrative obstacles to make it more difficult to be unvaccinated and coercive measures such as punishment for being unvaccinated. In low-income countries or remote areas, ensuring easy access to vaccination is important, especially if there are no or few health

services in a community. Empathetic and persuasive measures are the best way to improve vaccination rates, because if something goes wrong, such as an unanticipated rare side effect, like the first rotavirus vaccine, coercion can backfire, damage public trust and affect vaccination rates against all other vaccines.

Australia is one of the few countries to provide financial incentives for vaccination. A key year for immunisation in Australia was 1997 when the Seven Point Plan to Immunise Australia was introduced by then health minister Dr Michael Wooldridge. This included the establishment of a childhood immunisation register, one of the first in the world; a measles vaccination campaign; establishment of the National Centre for Immunisation Research and Surveillance; and financial incentives for vaccination of infants and children, including a maternity immunisation benefit and a childcare benefit payable upon timely vaccination of children. In my opinion, no health minister since Dr Wooldridge has done as much for health in Australia or made such impactful changes. Before Dr Wooldridge, of course, a great success story is the response to HIV by then Labor minister Dr Neal Blewett, with bipartisan support from shadow minister Dr Peter Baume. I knew Dr Baume, who had been the head of the School of Public Health and Community Medicine at UNSW, prior to my taking on the role in 2008. He reached out to me when I started the job and we have stayed in touch since. He is someone I admire and respect, and he mentored me during my Head of School tenure. About a decade after Dr Wooldridge's immunisation reforms, we saw the politicisation of health and the gradual loss of independent health advice from experts. This probably began after the 2009 influenza pandemic, after which there were less transparent and functional key committees. This also corresponded with the downsizing of the public service workforce in the Commonwealth, and increased outsourcing of functions to corporate consulting firms. By 2015, health was well and truly politicised, and the idea of punitive financial measures for parents who did not vaccinate was first floated by the government. This was the No Jab, No Pay policy, which would punish parents who failed to vaccinate their children with loss of maternity and

childcare benefits. Several vaccine experts initially expressed concern but quickly became silent for fear of losing favour with the government. I published a blog in 2015 cautioning against coercive measures. Curiously, a columnist in a major newspaper read my blog and wrote an outraged article about me.

The No Jab, No Pay policy went ahead anyway in 2016, with the rousing support of many journalists, doctors and vaccine experts. This legislation removed religious or philosophical objections to vaccination, which had been in place since Dr Wooldridge's Seven Point Plan in 1997, allowing families to still receive the childcare and maternity payments if they registered a conscientious objection. Once this was removed, anyone who was unvaccinated and did not have a valid medical exemption would be denied the payments. A few years later, the cheering continued when an increase in vaccination rates was observed. It's not rocket science that punishment will raise vaccination rates, just as any kind of penalty or threat of penalty will improve vaccination rates. Buoyed by the success of No Jab, No Pay, the government then introduced No Jab, No Play, which banned children from attending day care or childcare if unvaccinated. Until that time, such children would have been excluded from childcare if there was an outbreak of a disease for which they were unvaccinated, which is a reasonable public health policy. Banning children from childcare outright if they are unvaccinated further increases coercion, yet this was enacted with cheering or acquiescence from medical leaders.

I, along with other experts, expressed concern that coercive measures could disproportionately disadvantage working parents (especially working women) and their children. There is also the risk that such a policy would create a vindictive and bullying culture in the health care system and wider society. This may result in ostracising some people, including children, which is quite contrary to the principles of public health. At the time of these legislations being introduced, there were reports of unvaccinated children being denied medical care.

There were already measures in place before 2016, including state-based laws that allowed unvaccinated children to be excluded from

childcare in the event of an outbreak. There was really no evidence that banning unvaccinated children from childcare altogether was going to be any more effective than excluding them temporarily during an epidemic. The important question is whether coercion is ethical and equitable. Just like the earlier No Jab, No Pay, it was a no-brainer that No Jab, No Play would cause hardship, inconvenience and financial disadvantage for ordinary working parents and therefore improve vaccination rates. If vaccine-hesitant parents cannot go to work because they do not have childcare, or if they depend on childcare payments or family tax benefits, then they may have no option but to vaccinate their child. Affluent families, on the other hand, are not affected by such measures as they have enough money to hire a nanny or organise their own private childcare. So clearly, these policies affect low- and middle-income earners much more than high-income earners, making them inequitable. Families often depend on both parents working, and childcare enables parents to work and contribute to the economy and to society. The policy will disproportionately affect women, who on average have lower-paying jobs than men, and may be forced to leave the workforce to take care of children who are banned from childcare. On the other hand, highly affluent parents can afford to continue to object to vaccination, if they wish, with no change to their lifestyle. Australia is the only country in the world that imposes financial penalties on tax-paying parents for refusing vaccination. There is also an equity issue for parents as taxpayers who have a right to expect childcare benefits.

Children, who are not to blame for their parents' decisions, are also impacted. They would miss all the benefits of socialisation and learning that they would receive in childcare. Furthermore, banning or putting financial penalties on anything generally results in a black market. It happened with alcohol during prohibition, and it occurs now with tobacco. Anyone who knows a smoker knows that they buy most of their cigarettes off the back of a truck and not from the supermarket. This is the elephant in the room that's never spoken about by public health experts, who laud the high taxes on cigarettes while failing to consider the roaring black market in tobacco. The Australian Taxation Office estimates this loses the country billions in

revenue. Almost a decade ago, it was estimated that 15 per cent of tobacco consumption in Australia was from the black market. Similarly, it is conceivable that vaccine objectors may band together and form their own illegal childcare centres, but allowing unvaccinated children to congregate in such settings would increase the risk of epidemics to all of society. In my view, it is a regressive step in disease control and would ultimately work against the objective sought by the policy.

At the time, it struck me that there was a medical ethics issue as coercion breaches the principle of valid consent to a medical procedure. Unlike other public health measures like wearing a seatbelt, vaccination is a medical procedure and, according to our national immunisation guidelines, requires legally valid consent to vaccination. The wording in the *Australian Immunisation Handbook* states 'consent must be given voluntarily in the absence of undue pressure, coercion or manipulation'. For parents who depend on maternity benefits or childcare payments, the No Jab policies may result in undue coercion. When I asked this question publicly, the Australian Medical Association issued advice to doctors that they must make sure they obtain appropriate valid consent before vaccinating.

Improving vaccination rates should and can be done without causing hardship or financial stress. Other countries have achieved high vaccination rates without punitive and coercive measures. This includes the provision of vaccines free of charge, having a register of immunisations so that parents can be sent reminders when vaccines are due, and providing vaccines in schools. School vaccination is used for vaccines for HPV and meningitis, and is convenient for parents and children. Then there are regulations such as requiring proof of vaccination for school entry or childcare. While not a reward for parents, it prompts busy parents who may have otherwise forgotten to get their kids vaccinated. I began researching this issue in the early 2000s and started collaborating with Professor Dan Salmon, a US expert in this area. We published a paper in 2006 in *The Lancet* on the history of compulsory vaccination and its ethical implications. The points made in this paper were that most people are willing to be vaccinated anyway, so authorities must be sure that their vaccines are safe and effective

and should avoid coercion. We argued that allowing conscientious objection is smart as it prevents backlash in the case of something going wrong. We also compared different cultures and showed that the degree of acceptability for coercive measures may vary by country, with Australians being more accepting of public health mandates than Americans, for example.

Another consideration is how low vaccination rates are. Is it worth risking coercive measures for small incremental gains? At the time that the No Jab legislation came in, Australia had one of the highest immunisation rates in the world, with over 93 per cent of children under 15 months fully vaccinated. The incremental gain, therefore, was very small. The policy was introduced without any problem statement or data on areas of need. There was no systematic evaluation of gaps in the immunisation program prior to implementing these laws. I argued at the time that it made much more sense, given our high vaccination rates, to identify specific vaccine-preventable disease risks by age group, and devise strategies to target them. Before banning unvaccinated children from childcare, we should have done our research and identified where outbreaks of vaccine-preventable diseases were occurring and what age groups were affected. For example, hepatitis A causes outbreaks in childcare and there is an effective and safe vaccine against it. Yet this vaccine is only on the immunisation program for Aboriginal and Torres Strait Islander children. In the United States, the hepatitis A vaccine is on the immunisation schedule for all children 12–23 months. For other infections that cause outbreaks, such as measles or whooping cough, affected children are usually too young to have been fully vaccinated, so the No Jab policies would not have had any impact on these cases.

Other preventable epidemics are in age groups that do not attend childcare, such as adolescents and adults. Measles is a good example. Cases are usually adults, adolescents or infants too young to have been fully vaccinated, none of whom would have been protected by the No Jab policies. By identifying and targeting risk by age group, we can protect the vulnerable and reduce the chance of epidemics occurring. For infants too young to be fully vaccinated, maternal vaccination is a useful strategy for

protection against some infections, such as whooping cough and COVID-19. This cocooning strategy is also used to protect infants from whooping cough by vaccinating their parents and other immediate close contacts.

Research shows that true vaccine objection forms a small proportion of the population, usually about 2 per cent. Efforts to change the minds of people who truly object to vaccination are generally unsuccessful. However, there is a larger group of people, maybe comprising about 10 per cent of the population, who are uncertain or hesitant about vaccination. Health promotion efforts can be targeted to hesitant people to improve vaccination rates, and communication with their GP or health provider is also important. Coercive measures can backfire with hesitant people, who may respond better to inclusive and empathetic methods that acknowledge their fears or concerns. There is a risk of driving hesitant parents, who may otherwise have been open to persuasion, to become outright objectors. In this context, coercion gives fuel to the anti-vaccination lobby. Infant vaccination rates would benefit from focusing on hesitant parents who have delayed vaccination simply because they're too busy rather than trying to force vaccination on outright objectors. The other effective way to raise vaccination rates is to make it cumbersome and time-consuming to obtain a conscientious objection. Logistic and administrative barriers, for example, having parents fill out multiple forms to register as an objector, make vaccination the path of least resistance. This would easily separate parents who are hesitant or simply have not got around to vaccination from true vaccine objectors.

From a public health perspective, it's important to take the long view on vaccination programs and to ensure these remain trusted, accepted and resilient, and last beyond the short political electoral cycle. An inclusive approach, which builds the trust of people, is far better in the long run. As discussed earlier, no vaccine is 100 per cent safe or 100 per cent effective, and sometimes, serious vaccine side effects do occur. A coercive policy may destroy public trust or trust in the government if serious adverse events do occur. Sometimes we get it wrong, as in the case of the first rotavirus vaccine or the Cutter polio vaccine incident, both of which resulted in

deaths. If that happens, coercion can undermine a public vaccination program, especially in a country that does not have no-fault vaccine compensation. A dogmatic and bullying approach to public health can erode public trust in government and is antithetical to the principles of public health.

At the time that Australia introduced the No Jab legislation, we did not have a no-fault vaccine compensation system in the country, although a limited version was introduced during the COVID-19 pandemic. There are about 25 countries in the world that have one for vaccinations. Generally, they do not require the claimant to prove negligence by the vaccine provider or the state, or that the adverse event was caused by the vaccine. Instead, they provide no-fault compensation for adverse events that occur following immunisation. For Australia to introduce financial control over human health without such a system at the time was very risky.

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THE DARK UNDERBELLY OF MEDICINE AND GLOBAL HEALTH

Vaccination helps achieve equity in a way that few other interventions can. For example, achieving high coverage of vaccination against measles in a country will protect everyone in the population, including the most disadvantaged, which is the objective of herd immunity. Nonetheless, there remain inequities in vaccination, and two areas I have been interested in are global health inequities and inequities in our approach to prevention. A recent paper in *The Lancet* by Professor Mishal Khan and colleagues explored the role of colonialism in medicine and medical publishing, stating that the journal *The Lancet* 'legitimised and continues to promote specific types of knowers, knowledge, perspectives, and interpretations in health and medicine'. The paper provides numerous examples to demonstrate how the journal promoted people from wealthy, privileged and usually white or Western backgrounds as the ultimate knowers of truth. It platformed the same people and legitimised their perspectives in medicine as the gold standard to which the subjects of colonialism had to aspire. In other words, it was part of colonial empire building, and other journals without a colonial history also contributed to sustaining colonialism globally. The themes it explores are universal in medicine and are especially prominent in the field of global health, where vast imbalances of power exist between privileged researchers and organisations from high-income countries and the subjects they study in low-income countries. This creates ideal conditions for exploitation.

Many vaccine and drug trials are conducted in low- or middle-income countries, but the benefits and availability are seen first in high-income countries. Vaccine trials may be conducted in low- or middle-income countries because the disease burden is higher and this makes efficacy endpoints easier to evaluate, and sometimes because the disease itself (for example, the Ebola or Marburg virus) is specific to particular countries. The infrastructure required to conduct clinical trials is also cheaper in low- and middle-income countries. Large trials of pneumococcal conjugate (pneumonia) vaccines were done in The Gambia, but the introduction of these vaccines for children occurred several years after they were introduced in high-income countries. I have already mentioned that my son became ill with pneumococcal septicaemia when he was seven months old and that it could have been prevented by this vaccine. The pneumococcal conjugate vaccines, however, are expensive and unaffordable for many low-income countries. The work of Gavi, the Vaccine Alliance, has done much to reduce inequities in vaccine access across countries and has made pneumococcal conjugate vaccine available in many low-income countries. Established in 2000 by the Bill and Melinda Gates Foundation and partners, it has helped vaccinate over a billion children in 78 countries against 17 diseases, including pneumococcal disease.

Pneumococcal disease affects people everywhere, but in other cases, infections like Ebola and Marburg affect geographically specific populations in African nations but not elsewhere – so research on these infections needs to occur in the affected countries. A large epidemic of the Marburg virus, which causes a haemorrhagic fever like Ebola, began in late 2024 in Rwanda. It was also simultaneously affected by mpox, which had spread from neighbouring DRC. The Marburg virus is named after the town in Germany where the first human outbreak occurred, imported to Europe through African green monkeys used in laboratory medical research. Lab workers were the victims of that outbreak. It has caused intermittent outbreaks in the African continent since then, with the 2024 Rwandan outbreak among the largest documented. Most cases have been in health workers, highlighting the risk that nurses and doctors face during

epidemics. Vaccine and treatment trials for Marburg have commenced in Rwanda.

The majority of published medical research is about the health concerns of wealthy countries, and there is very little research on infections affecting only low-income countries. Until 2014, there was very little research done on Ebola. After decades as a neglected, poorly researched disease, the unprecedented 2014 West African Ebola epidemic resulted in the acceleration of research into drugs and vaccines for Ebola. Prior to this, the virus had never occurred in West Africa, nor in more than one country simultaneously, nor in large cities. Until 2014, there were less than 3000 peer-reviewed scientific publications on Ebola compared to over 80 000 on influenza. Ebola virus belongs to the filovirus family, which includes the Marburg virus. Filoviruses are one of several families of viruses that cause viral haemorrhagic fever. That's the kind of illness fictionalised in zombie apocalypse movies, where people are bleeding from every orifice. Haemorrhagic fever begins as a non-specific febrile illness but progresses to a rash that begins bleeding and may include internal bleeding. Dengue, yellow fever, Lassa fever and a range of other viruses may cause haemorrhagic fever, but the most severe and fatal are Ebola and Marburg. Bats are the natural reservoir, and the Ebola virus also infects non-human primates. It was typically a zoonotic infection, acquired after contact with bats or monkeys, usually in small villages, and sometimes leading to small outbreaks affecting household contacts, health workers and mortuary workers. Before 2014, outbreaks were usually contained by hospital infection control measures and were usually of short duration. The largest past outbreak in Uganda in the year 2000 had a total of 425 cases, compared to over 28 000 cases in 2014. There are five strains, and the most severe is the Zaire strain, which has a case fatality rate of 50 to 90 per cent.

Ebola is predominantly spread by contact with blood and body fluid, but every other mode of transmission has been documented in outbreaks and animal studies, including airborne transmission, transmission after needlestick injury, sexual transmission and transmission from mother to baby in utero. It is important to acknowledge and understand that no

infection is spread strictly by one mode – spread can usually occur by multiple modes, even if there is one dominant mode of transmission. A well-studied outbreak in Kikwit in the DRC showed that 5 out of 19 people who did not have any direct contact with an Ebola patient got infections, suggesting respiratory transmission is also possible. Several animal studies also show transmission without contact, which suggests aerosol transmission is possible. In fact, the virus has been found in the lungs of infected people, which supports the possibility of Ebola being transmitted through the respiratory route.

The West African outbreak began in Guinea in December 2013 but was not identified by the WHO until March 2014. It then spread to Liberia and Sierra Leone in 2014, followed by Nigeria and Senegal. The largest burden of this epidemic was in the three Mano River countries: Liberia, Sierra Leone and Guinea. These are among the poorest nations in the world, with weak health systems and lower numbers of health care workers than most other countries. Over 28 000 cases and 11 000 deaths occurred, and for most of 2014, control efforts were unable to stem the spread of the infection. Research into Ebola vaccines intensified during this epidemic. Vaccine trials started in late 2014, but these were designed to measure clinical efficacy (in other words, prevention of infection), which required high case numbers.

Early predictions were that the epidemic would not be controlled until June or July of 2015 at the earliest, so vaccine trials were planned under this assumption. Late in 2014, however, the epidemic was under control, with a decline in cases in the three main affected countries by early 2015. The dilemma facing researchers and pharmaceutical companies at that point was that the largest planned vaccine efficacy trials (planned in Liberia) could not continue without enough cases of Ebola occurring. Perversely, the disease must occur in high numbers to prove it can be prevented by vaccines. As a contingency, the trials were moved to Guinea, where cases were still occurring, yet there, too, the epidemic was under control by 2015. Other vaccine and drug trials continued in Sierra Leone, which had the most cases, but there were less than 100 cases a week by then.

Another problem facing the vaccine trials was a lack of trust among the West African people. For instance, in Liberia, there was mistrust and suspicion about the vaccine trials and fears of citizens being deliberately infected with Ebola to gain funding from international donors. Others believed the vaccines were being slipped into the childhood immunisation program without consent. In this environment of fear and mistrust, recruitment into the trials became difficult, and volunteers had to be paid to participate, usually hundreds of times more than they earned in a week. Payments to participants as compensation are accepted in many clinical trials and must be approved by ethics committees, but in this situation, with case numbers dwindling and fear among the community, it may also be seen as an inducement, which raises ethical questions. In Liberia, a trial participant reported to the *New York Times* that his family members refused to be in the trial: 'They said they want more Ebola patients because government is using them to make money,' he said. 'The more dead and infections, the more money.'

Is it ethical in the context of a waning epidemic to persevere with clinical efficacy trials that depend on there being many cases of Ebola? Persevering in this situation creates a conflict of interest. With large financial and research investment in trials, there is pressure on researchers to meet clinical efficacy endpoints, which in turn depends on large numbers of cases of disease being present. This is the crux of the conflict between the public health goal of disease control versus the 'need' of researchers for the epidemic to be ongoing to test the vaccines. The affected countries in West Africa are vulnerable to exploitation, with a background of civil wars and being among the poorest countries in the world prior to the epidemic. The power relationship between the people of Liberia, Sierra Leone and Guinea and the foreign companies and powerful research organisations running the trials is hugely imbalanced, posing a risk of ethical breaches. At the time, I wrote that an ethical solution to the vaccine trial dilemma is to amend the protocols to use immunological instead of clinical endpoints. That way, the trials do not depend on there being Ebola disease in the populations and can be completed by testing for antibodies and immune

reactions to the vaccine, which correlate well with protection. Other vaccines such as meningococcal conjugate vaccines and influenza vaccines are often tested in the same way, without clinical efficacy endpoints. This overcomes the catch-22 situation that requires evidence of the clinical efficacy of vaccines before they can be rolled out into populations. For many vaccines, the disease that is being prevented is relatively rare, and so unfeasibly large randomised controlled clinical trials are needed to measure the prevention of disease.

In vaccinology, using antibody levels as correlates of protection are widely accepted, including for licensure of vaccines. For instance, the meningococcal C conjugate vaccine was rolled out to the UK population as a childhood immunisation program in 1999 (and subsequently in Australia a few years later) based on trials that measured immunological responses to the vaccine rather than actual prevention of meningitis, which is a fairly rare disease. Meningococcus is a bacterial cause of severe meningitis and there are multiple variants, including A, B, C, Y, W and others. Meningococcal C was the first available conjugate vaccine against the C variant of this bacteria. After vaccination programs were commenced, an impressive reduction in meningococcal C disease was observed as a result, showing that antibody correlates of protection can be robust and valid. For the influenza vaccine, too, we rely on immunological cut-off points as surrogates for efficacy. So, the same is possible for Ebola or other vaccines when disease incidence is low. In this case, a pragmatic approach was taken to conduct large serological studies of Ebola immunity as well as studies of vaccination used as post-exposure prophylaxis. That is, vaccinating contacts of cases of Ebola who have been exposed to the infection. This removes perverse incentives and ethical risk, and still maintains benefits for all stakeholders. A similar pragmatic approach was taken to estimate vaccine effectiveness for mpox vaccination in 2022.

There were several other ethical concerns during the West African Ebola epidemic of 2014. For several months, as the epidemic raged, Western researchers flocked to the area and published papers in leading journals simply describing the epidemic. There were no concerted efforts to

understand non-pharmaceutical measures that could have been used to reduce transmission at that stage – until researchers at the CDC in the US published a paper showing that increasing available hospital beds to isolate patients with Ebola could control the epidemic. Simultaneously there was a morbid fascination with the disease and death associated with Ebola, and bloggers wrote graphic descriptions of the patients, including identifying details such as names and passport numbers. Any concept of privacy and dignity normally afforded to patients was abandoned. I attended a talk given by an Australian public health professional who had been in one of the affected countries. They sombrely described how a West African colleague had died of Ebola and proceeded to put up a slide of this man in his hospital bed while he was ill, days before he died. I am still shocked and dismayed when I think about the complete lack of respect shown by this Australian for the privacy and dignity of his deceased colleague. Sadly, such vicarious voyeurism and inappropriate dissemination of images are common in public health and medicine.

The power imbalance in global health is in part related to race. Medical research itself is beset with racism, which is a touchy subject to raise. When you are non-white, you are subject to a lower threshold of tolerance for any kind of deviation from expected standards. You are expected to be quiet, to blend in, to not draw attention to your race and to not cause waves. You may find yourself publicly attacked by a politician or media commentator in a way that white men are rarely attacked and with utter disrespect for your expertise. If you are brown, you are better tolerated as the subject of medical research rather than a researcher. Global health is a good example, where research leaders from wealthy countries flock to epidemics and other disasters in low-income countries, often with the promise of funding and research papers in high-impact journals. I published a paper about this problem during the 2014 West African Ebola epidemic. In it, the late Professor Joanne Travaglia and I wrote:

> The long-term weakening of organizational and society infrastructures due to postcolonialism, civil wars, and dependence on foreign assistance has also been highlighted. West African voices were not heard in the throng of media and attention about

> the epidemic, and relatively few of the scientific papers which [had] arisen from the epidemic to date have been led or informed by West Africans, despite most requiring the collaboration of African experts. Of a paper led by U.S. authors, five coauthors, all Sierra Leonians, died of Ebola before the paper was published.
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> The unspoken fact is that scientists, while making important contributions, also profit from high-profile health disasters. They gain research funding, publications, and recognition, and thus many flock to build reputations on disasters such as Ebola. A PubMed search in January 2015 finds a near doubling of publications on Ebola after the current West African epidemic, with many being opinion pieces. Still, the 3000 publications on Ebola at this time compares to more than 80,000 publications for influenza, highlighting how poorly studied Ebola has been, particularly prior to the current epidemic.

A past prime minister of Australia said, ‘We want to see women rise. But we don’t want to see women rise only on the basis of others [men] doing worse.’ The same sentiment applies to race in medical research. The first time I spoke up about racism in medicine was on International Women’s Day 2017. I have always been enthusiastic about International Women’s Day, especially for women in science and medical research and after chairing the relevant committee for women’s advancement in our faculty of medicine for several years. But in 2017, as I scrolled through the various tweets and promos for International Women’s Day in the different faculties, I noticed that the smiling faces of contemporary female medical researchers promoted by the medical faculty were all white. There was not even an Indigenous woman, despite there being a growing number of Aboriginal and Torres Strait Islander academics in Australian universities. Interestingly, the faculties of engineering and science featured a diverse range of women in their promotions that year, which was more truly representative of their actual faculty. It was only medicine that stood out as lily white.

The promotion of women in medical research, despite their great work and important role, overwhelmingly uses white imagery and white role models. Through their celebration of whiteness, organisations for women in STEMM subtly convey that their business is to advocate for white women’s advancement. The rest of us are invisible, and I have never felt included in such groups. If we do join the club, we are tolerated if we blend in and don’t raise the issue of race. This is not the case in other disciplines such as

science and engineering, where there is less privilege and entitlement and more open celebration of diverse researchers. The diversity agenda does not delve deeply enough into structural racism. The more apparent kind involves verbal abuse, spitting or violence, which I experienced in the school playground in the Eastern suburbs of Sydney in the early 1970s, where there were few non-white children. However, the more dangerous and damaging kind of racism is structural and embedded in medicine. In February 2023, the *Journal of the American Medical Association* (now known as *JAMA*), which boasts predominantly white male editors, ran a podcast on structural racism in medicine without any black physicians. In the podcast, a white physician spoke, complaining that the term 'structural racism' alienates white people. *JAMA* promoted the podcast with a tweet that read: 'No physician is racist, so how can there be structural racism in healthcare?' It caused a huge backlash and outrage, which led to the resignation of the editor-in-chief. The less obvious implication of this tweet is that 'No physician' actually means 'No white physician', with the underlying implication that only the viewpoint of the white physician, always the protagonist in medicine, matters.

In January 2021, former prime minister Malcolm Turnbull tweeted a YouTube explainer video I made on the principles of public health vaccination programs and how these principles applied to COVID vaccines. The content put pressure on the government to speed up the vaccine roll-out and diversify vaccine options based on arguments I made, which have since been vindicated. Yet this resulted in a personal attack by a politician in a public forum for stating simple scientific truths about the best approach to the national vaccine program. They did not name me but referred to some past comments of mine, which I believe made me identifiable. In fact, I received several shocked phone calls and messages from colleagues who realised it was me and felt that this public attack was laden with disdain reserved for women of colour who do not know their place. I have been attacked publicly in the same way by people from both major political parties at different times. Speaking truth to power is more personally costly when you are a black woman.

With personal experience of racism in medicine and academia, I see global health through a different lens. I see the opportunism, the exploitation and the personal profit gained on the backs of disempowered people. Global health and pandemics are especially ripe for exploitation of the vulnerable because these fields offer more opportunities for privileged people to swan around as saviours among vulnerable people, driven mainly by the opportunity to advance their own careers. A pandemic is a disaster where health systems are collapsing, corpses are piling up and the capacity of society to respond is exceeded. A pandemic is a situation where the capacity of a community or country to respond and recover is overwhelmed, and accountability is reduced. There is an entire class of researchers who thrive in this environment of reduced accountability and heightened vulnerability, which is a magnet for generating publications in major journals without making an iota of difference to the plight of affected people. That's exactly what we saw in the first few months of the Ebola epidemic in 2014 – a barrage of papers in top journals that simply described the carnage but offered no solutions and had no impact on the spiralling epidemic.

A colleague of mine, the late Dr Vijay Nath Kyaw Win from the WHO, who worked in disasters his whole career, told me of his experience during the first Bali bombing. A Burmese national, he was working for the WHO in Indonesia at the time. Vijay's father was an Indian national who fought for India's independence, and his mother was a Burmese national. Vijay became a doctor and devoted his career to disaster response. We had many conversations about exploitation and power imbalances during disasters, and he began documenting his career experiences of disasters such as both Bali bombings and the Aceh tsunami in a doctoral thesis. Unfortunately, he did not get to complete it. He was part of the responding team from the WHO after the Bali bombing. In the chaos of the aftermath, while he was treating the injured in one of the emergency tents, he heard screaming coming from a nearby tent. When he went to investigate, he found an Australian doctor sawing off the perfectly good leg of a victim. He was able to intervene and save the patient and later found out that the doctor had

been deregistered for malpractice in Australia. Yet this doctor was free to turn up in Bali and start mutilating patients. This is an example of reduced accountability and heightened vulnerability during a disaster and how it can lead to exploitation, harm and human rights abuses. I lost contact with Dr Kyaw Win, a beautiful soul, in 2021, but kept emailing him from time to time until I got a response from his son, who informed me that he had passed away in Myanmar in 2022. I am glad that some of his compassion, wisdom and insight into Global Health can be documented in this book.

13

PNEUMONIA IS NOT THE OLD MAN'S FRIEND

Have you heard the saying, 'Pneumonia is the old man's friend'? This implies that an older person who develops pneumonia should be left to die, meaning they do not have the right to prevention or treatment, meaning their suffering, such as gasping for breath or having pain in the chest, should be ignored. Pneumonia is a terrible illness, associated with suffering, pain and distress. Why would pneumonia be anyone's friend when it can be prevented by vaccination? Forty years ago, having a heart attack led to reduced life expectancy. Today, with innovations such as rapid time from chest pain to catheter lab, early re-opening of blocked arteries, and statins for lipid-lowering, people with coronary heart disease can have a normal life expectancy. Coronary artery disease is never referred to as 'the old man's friend'.

This saying exemplifies ageism in health care. A popular book among young medical residents is *The House of God* by Samuel Shem. Published in 1978, it is a humorous tale of a group of young interns in a fictional hospital inspired by Beth Israel Hospital in Boston. The book follows the trials and tribulations of the protagonist, Dr Roy Basch, and his intern colleagues, with a special focus on withholding treatment from GOMERs. The term 'GOMER', short for 'Get Out of My Emergency Room', is usually reserved for elderly people. The protagonist is taught by his house senior that doing nothing is the best course of medical action for GOMERs. Ageism in health care is real, and anyone who works in the hospital system

has seen it. When I worked in the emergency department, the use of degrading acronyms for vulnerable older people was common, and even written up as the cause of admission on the whiteboard that listed all the patients. This included ‘PFO’ (‘pissed and fell over’), which was reserved for older people who had fallen after being intoxicated. There were also terms used for older people who had faecal impaction and needed an enema to clear their bowels. In medicine, you need to remain objective and emotionally detached to treat a patient effectively, and, understandably, making up humorous acronyms is part of a coping strategy. However, there were more degrading acronyms for older people than for others. More serious, however, is the inadequate care that many older people receive.

In 2018, my 84-year-old father, who was independent and active at the time, with a rich social and intellectual life, was hospitalised with what was probably a mini-stroke. He was on a serious blood thinner, and overnight he kept telling staff he needed antacids for his gastritis. He told them repeatedly that without these he would vomit. They ignored him, and when I came in the next morning, I found him holding a vomit bag filled to the brim with bright red blood. They had left him vomiting all night, to the point where he began vomiting blood, and even then did not give him the antacid he requested nor take any action about the bleeding. I called the staff and told them he needed something to stop the vomiting. He needed a blood transfusion because of the degree of blood loss. And then, to top things off, a doctor, who turned up for his ward round soon after, asked me if he was ‘not for resuscitation’ if he had a cardiac arrest. I advised yes, he was for resuscitation as he had a full and active life, a wife waiting for him, and that if he had a cardiac arrest it would be from the massive blood loss. What should have been a short admission of a week or less became a three-month stay in hospital for multiple cascading complications that had nothing to do with his reason for admission. Thankfully he made it out, but he had me, a medical doctor, to advocate for him. How many similar patients have no one to advocate for them, or if they do, do not have the medical knowledge to navigate the problems? We need to acknowledge and reflect on ageism and value judgments in health care.

Equity in disease prevention means that older people have equal rights to available vaccines for disease prevention. They also have a right to autonomy, self-determination and informed choice about vaccines. Too often, when older people are unvaccinated, and asked why, they reply that their doctor never told them. Informed choice can only be made if seniors are given access to information that affects their health. One of the dilemmas of vaccination for older people is that the immune system fails progressively and predictably with age after 50 years. We see a wide range of defects in immunity occur with ageing, and this causes an increase in the risk of infections. Older people are therefore doubly disadvantaged because they have a higher risk of infection, and immunosenescence makes vaccines less effective. This may explain the negative view that many doctors have about vaccinating older people.

Babies have an immature immune system and are more vulnerable to infection, relying on maternal antibodies and vaccines for protection in the first six months of life. These are antibodies generated in the mother's blood that circulate in the baby's blood for the first six months of life. The infant immune system matures with age and each dose of vaccine is given on the background of progressive strengthening of the immune system, which is a winning game with big rewards. The opposite is true of older people. Each vaccine is given on the background of progressive decline of the immune system, which is a losing game, and not as rewarding. Yet in my research, we have shown that even frail elderly people with no baseline immunity to pneumococcal vaccines can still mount a robust immune response to vaccines, so this is no reason to deny vaccination. Yet doctors commonly believe that vaccinating older people is not as important as vaccinating infants. This is not a reason to deny vaccination to the elderly. It is simply a challenge that requires innovative solutions and a change in perspective. It is true that vaccines wane faster in the elderly, but does it matter if a vaccine wanes to unacceptably low levels after ten years if you only have ten years of life expectancy left? Vaccinologists worry a lot about waning and tend to view waning through the paediatric lens. Waning

matters a lot if you are a baby and have 80 years of life ahead of you, but less so if you are 80 and only have a decade or so left.

Pneumonia may be acquired in the community or may occur in hospital as a complication of other illnesses. The latter is often due to a range of dangerous bacteria, but most pneumonia is community-acquired. Pneumonia may be caused by bacteria (like pneumococcus) or viruses (like influenza and COVID-19) and bacterial pneumonia may complicate viral infections such as influenza or SARS-CoV-2. Pneumococcal infection is the commonest cause of pneumonia, and there are effective vaccines to protect against it. It can also cause deadly septicaemia (as it did in my son when he was an infant) and meningitis. Pneumococcal meningitis is as lethal as meningococcal meningitis, and there are up to seven times as many deaths from pneumococcal disease as there are from meningococcal disease. The incidence of invasive pneumococcal disease is highest at the extremes of age – in infants and older adults. The highest number of hospitalisations and deaths for pneumococcal infections in Australia occurs in people aged over 65 years. The causative bacteria, streptococcus pneumoniae (also known as pneumococcus), has over 90 different serotypes. These are like variants, and vaccines must cover all the serotypes that cause illness in humans. There are two types of pneumococcal vaccine: the older polysaccharide, and newer, more effective conjugate types, with varying coverage of serotypes depending on the vaccine. The conjugate vaccines are provided to infants and older adults in our national immunisation program.

The conjugation revolution in vaccines began because researchers were seeking better vaccines for infants, but there has been less research into better vaccines for older people. The COVID-19 pandemic has shifted this as adults comprise the largest proportion of the population, and as such are the largest consumers of COVID-19 vaccines. Influenza vaccine research has also created solutions for better vaccines for adults. Research on better vaccines includes new technologies, such as mRNA; conjugation; high doses; novel routes of administration, such as intra-dermal, adjuvants, novel combination schedules (for example, a conjugate followed by polysaccharide pneumococcal vaccines); or simply identifying the right

antigen that will elicit a strong immune response. Influenza vaccine research had already had breakthroughs, with two different enhanced vaccines that significantly improved the protection provided by flu vaccines for older people. These vaccines are now routinely administered to older adults in many countries, including Australia. Another breakthrough occurred in 2015, with a magic bullet achieving amazingly high vaccine efficacy in older people. The breakthrough was in shingles (herpes zoster) vaccines. Herpes zoster is different from herpes. It is caused by the chickenpox virus, varicella zoster. The first time we get infected with the virus, we develop chickenpox. The virus can stay in the body, hidden in the nerves for years or decades, until the immune system weakens and causes a localised, painful infection called shingles. The older shingles vaccine had 50 to 65 per cent efficacy against shingles, but efficacy waned over a decade after vaccination. Defying everything we know about vaccines in the elderly, the newer, inactivated shingles vaccine has demonstrated efficacy of more than 97 per cent in adults in a trial published in 2015, a finding that stays constant across age groups from 50 to 70 years and above. An efficacy of 97 per cent is greater than most childhood vaccines, let alone vaccines for the elderly. This vaccine uses the gE antigen and an adjuvant called AS01. The protection was improved by the adjuvant, and this astounding efficacy is the result of a combination of the right choice of vaccine antigen and a high-performing adjuvant. This is a very exciting breakthrough that shows older people can respond well to vaccines. What is needed is better technology, and a better understanding of antigenic properties, adjuvants and other immune-stimulating technologies. The COVID-19 pandemic resulted in more such research progressing.

We have far fewer vaccines on national immunisation programs available for adults compared to children. For indicated vaccines for adults, the rates of vaccination are much lower than vaccination rates in children – a glaring immunisation gap. For example, influenza vaccine is funded and recommended for adults 65 and over in Australia and in many other countries. However, vaccination rates hovered around 70 per cent prior to COVID compared to more than 94 per cent for childhood vaccinations. In

2024, flu vaccination rates in people over 65 years plummeted to around 60 per cent, while childhood vaccination rates have only fallen slightly to 93 per cent. Over 82 per cent of the Australian population is aged over 15 years and 15 per cent of the population is over 65 years. It is predicted that a quarter of the population will be over 65 years of age by 2064. The number of older adults in aged care facilities is also rising, with over 20 per cent of people 85 years and older in a nursing home. These numbers are predicted to rise in the coming years. Acute hospital care consumes over 90 per cent of the health budget in all countries, and ageing of the population will increase the burden on acute health services. This provides a strong argument for primary prevention of disease in older people and positive ageing. Ageing populations are also faced with an ageing workforce, delayed retirement and increased reliance on older people to maintain the economy. In the last 20 years, the average age of people in the Australian workforce has risen. There are many arguments for healthy ageing – economic, ethical, social and human rights. Immunisation is an important part of positive ageing, especially in residential aged care but also in the community. Aged care outbreaks of influenza and COVID-19 are a substantial burden, causing illness in residents, staff and family members.

Over time, more and more adult vaccines have become available, with influenza, pneumococcal, COVID-19, tetanus and shingles being recommended in Australia for older people. Yet immunosenescence poses a challenge, with most adult vaccines performing better in healthy younger adults than in the frail elderly. At the same time, the disease burden is far higher in the frail elderly group for most vaccine-preventable diseases, leaving us with a situation of high need for vaccines but lower vaccine effectiveness in this group. Vaccine effectiveness is an estimate of the degree of protection provided by a vaccine in a population. Vaccine ‘efficacy’ refers to data generated from randomised controlled clinical trials, whereas ‘effectiveness’ is data generated from observational (real-world) epidemiologic studies. While the influenza vaccine may be more than 70 per cent effective in healthy younger adults, this drops to 50 to 60 per cent or lower in the elderly. Pneumococcal vaccines are effective against

bloodstream pneumococcal infection in the elderly, but the efficacy against pneumonia is less than 50 per cent for the 13-valent conjugate vaccine. This is still good enough and will have public health benefits, given the high burden of pneumonia. Efficacy is not the full story, however. It is only part of the equation, and this is something many policymakers and experts alike do not understand. The public health benefit of a vaccine is a function of both preventive efficacy and the burden of disease (total number of infections). In the table on page 170, I illustrate the point of burden of disease with the example of pneumococcal disease. I extracted actual numbers for a specific year of cases of pneumococcal disease in children under five and adults. The number of infections is always greater in the older age group. I then put in the high vaccine effectiveness in young kids (95 per cent) compared to the hypothetical vaccine effectiveness in older people (ranging from 30 to 70 per cent), and showed the number of cases prevented in each case. What it shows is that in all scenarios, whether the vaccine effectiveness is 30 per cent or 70 per cent in older people, more cases are prevented in the older age group than in children under five years (in whom the vaccine is much more effective) because the number of cases is so much higher in older people. When the burden of infection is high, even a vaccine of modest effectiveness is still worthwhile in terms of population health benefits. This is why statins, with an efficacy of 25 per cent, have a major public health impact on the reduction of cardiovascular disease.

Despite the high burden of disease, preventing pneumococcal pneumonia in adults has been an uphill battle, with Australia setting a global precedent in 2020 by removing a recommendation for the vaccine for a whole five-year age group, raising the age cut-off for the vaccine from 65 years to 70 years. There was no clear justification provided for this, nor for selectively axing pneumococcal vaccination in older adults, with cost-cutting being the only consideration. Other high-income countries recommend pneumococcal vaccination for people aged 65 years and above, as well as at-risk groups, because the evidence supports it, including the overwhelming preventable burden of disease in older adults. The removal

of a five-year age group in 2020, as the COVID-19 pandemic emerged, was especially disappointing. The accompanying guidelines that were issued were a complicated maze of options and caveats that many doctors were confused by. Vaccines are a population health intervention, and guidelines should be simple and easy to follow to ensure doctors vaccinate the target population. If doctors cannot understand guidelines, we risk seeing a drop in vaccination rates.

Public health benefit by vaccine effectiveness and burden of disease

Age group	Cases (n)	Vaccine effectiveness	Cases prevented
0–4 years	50	95%	47
65 years and over	160	70%	112
65 years and over	160	60%	96
65 years and over	160	50%	80
65 years and over	160	40%	64
65 years and over	160	30%	48

Viral infections like influenza or COVID-19 may be complicated by bacterial pneumonia. In our previous pandemic research, most pandemic plans failed to mention the prevention or treatment of bacterial pneumonia as a secondary complication in an influenza pandemic. In the 1918 Spanish influenza pandemic, studies of tissue samples revealed bacterial pneumonia was a common and significant cause of death. In other research, we found that the 2009 influenza pandemic also involved significant secondary infection with bacteria, most commonly pneumococcus. The COVID-19 pandemic also resulted in a substantial amount of bacterial pneumonia as a complication, with studies showing pneumococcus to be the most common. In 2024, during an immunisation conference in Australia, I questioned a speaker who was presenting on adult pneumococcal vaccine policy. I questioned the changes in 2020, mentioning the importance of preventing bacterial pneumonia during a viral pandemic, and he publicly admitted the decision was made to save money. There are more costly vaccines given to prevent less common infections in infants (which is rightly a high priority), but from an equity perspective, cost-cutting should not be applied

selectively to vaccines for older people. If anyone had taken the time to calculate the costs associated with people being hospitalised for pneumococcal pneumonia, they would have realised that vaccinating everyone 65 years and over would have saved lives and money.

Furthermore, no cost-effectiveness analysis has yet considered the benefits of vaccination in reducing antibiotic resistance by preventing bacterial infections. The WHO and Australia recognise antimicrobial resistance (AMR) as a serious problem. With rising AMR, including in cases of pneumonia, primary prevention by vaccination is far better than trying to treat drug-resistant infections. For many AMR infections, we have no vaccines. Up to 25 per cent of pneumococcal infections are drug-resistant, but we do have effective vaccines that will prevent infection whether or not it is drug-resistant. Consideration of the direct cost of vaccine-preventable AMR infections is essential if we are serious about AMR prevention strategies. In addition, there is a complex relationship between influenza and pneumococcal disease, with each infection predisposing to the other. Pneumococcal pneumonia is the leading cause of secondary bacterial pneumonia complicating influenza infection. Therefore, pneumococcal vaccination may also prevent complications of influenza, a cause of high morbidity and mortality every year. As I will discuss in more detail later, there is a growing body of evidence that infections can precipitate acute cardiovascular events and that vaccines (including the pneumococcal vaccine) can prevent these events. Cardiovascular disease is the leading cause of death and illness worldwide, so any reduction by vaccination will have a public health impact.

In 2005, Australia simultaneously introduced an infant vaccination program with the 7-valent conjugate pneumococcal vaccine, designed specifically to improve immune response in infants, and a program for adults aged 65 years and over with the older polysaccharide vaccine. There has been a decline in pneumococcal infections since, even in people not in the infant or older adult groups, reflecting herd immunity effects. However, the exact contribution of the elderly and infant vaccination schedules in Australia to the burden of disease in adults has not been estimated well. It is

clear the introduction of infant conjugate vaccination has resulted in herd immunity in other age groups; however, there is accepted evidence of efficacy against invasive pneumococcal disease in adults over 65 years, and also evidence of reduction in pneumonia. An Australian study showed a 65 per cent effectiveness of the polysaccharide vaccine in adults over 65 years. Given Australia started the funded infant and adult vaccination programs simultaneously, a more nuanced analysis of the epidemiologic data is required to determine the separate impact of each vaccine program rather than dismissing adult vaccination and attributing all reduction of disease to herd immunity from the infant program. Research on vaccination of frail older people shows good immune responses to both pneumococcal vaccines, even when they have low immunity. There is possibly also a benefit in giving a sequential schedule of the conjugate followed by the polysaccharide vaccines. Our own study shows a waning of functional immunity in older adults after five years, which raises the question of whether booster doses should be reinstated after they were removed in 2011.

Pneumococcal vaccination is a glaring example of ageism in health care, with lower value placed on treatment and disease prevention in older people, despite an ageing population. Acute care consumes most of the health budget, and the majority of acute care in Australia is provided to older people. Facing an ageing population, vaccination is low-hanging fruit for the prevention of disease and the burden it places on the health care system. Surely, then, prevention of disease in older people makes sense not only from a burden of disease perspective but also from an economic perspective.

14

IF THERE WAS A VACCINE AGAINST HEART ATTACKS, WOULD YOU TAKE IT?

We are increasingly understanding the relationship between different infectious diseases and chronic diseases. In 2023, it was finally uncovered that the Epstein–Barr virus is a leading cause of multiple sclerosis (MS). Imagine a vaccine against MS, and a substantial reduction in the burden of MS after that vaccine is rolled out to populations. If you are affected by this debilitating disease or know someone who is, it will resonate that it may be preventable in the future. Human papillomavirus is the main cause of cervical cancer, and we are already seeing substantial declines in the rate of cervical cancer in countries that implemented vaccination of pre-teens. Hepatocellular carcinoma, a deadly form of liver cancer, is caused by the hepatitis B virus. Forty years after the introduction of hepatitis B vaccines, we are seeing a dramatic decline in liver cancer in countries that implemented universal infant vaccination. We will soon have mRNA vaccines that act directly against cancers. The leading cause of death and disease in the world, however, is cardiovascular disease. Heart attacks and strokes comprise the biggest burden of cardiovascular disease. If there were a vaccine against acute myocardial infarction, would you use it? After ten years of working on the topic, this was the title of a paper I published in 2017.

There’s a well-documented relationship between respiratory viruses and cardiovascular disease. The largest body of evidence is around influenza, but studies also show that other viruses such as RSV and shingles, and the

pneumococcus bacteria, can trigger heart attacks. For over 100 years, it's been recognised that rates of death due to all causes peak in parallel to flu epidemics. About 20 years ago, a swag of studies showed a massive increase in the risk of heart attack in the weeks following a respiratory infection, especially influenza. The work of epidemiologists Professor Liam Smeeth and Professor Charlotte Warren-Gash from the London School of Hygiene and Tropical Medicine in the UK was particularly ground-breaking. They published a large body of work that showed the association of heart attacks and strokes with influenza, and several other infections, that set the scene for many others to follow. In a study led by Professor Smeeth, a heart attack or stroke was more likely to occur within one to three days after a respiratory tract infection, and influenza vaccination reduces this risk. Our own study, conducted in Sydney, found that almost 10 per cent of patients admitted with a heart attack had undiagnosed influenza, which may have triggered their heart attack, and that it may have remained undiagnosed had we not tested everyone on admission. One study using the US National Inpatient Sample with 22 million hospitalisations found that the influenza vaccine was protective against heart attack, stroke, cardiac arrest and death.

Coronary artery disease begins with a process called atherosclerosis. This involves the formation of a plaque (an abnormal, raised, rough patch) inside the lining of the coronary artery, made up of cholesterol, calcium and other substances. These plaques grow over time and may eventually block the artery completely. Autopsy studies of people who died of other causes show that even 20-year-olds often have the beginnings of atherosclerosis. A common symptom of a heart attack is chest pain. Chest pain means your coronary artery is almost completely blocked. People can have normal function and no symptoms at all with blockages of 50 to 80 per cent. Some people may die of other causes, having never had a heart attack, but with substantial atherosclerosis that does not completely block the coronary arteries (and therefore allows blood flow and causes no symptoms). Think of it like plumbing in your kitchen – you may have a substantial build-up of fat and debris in the pipes, but you do not notice it until the drainage of

water down your sink is obstructed. Influenza can cause sudden disruption of atherosclerotic plaques and clotting around them, causing complete blockage of an artery. In other words, influenza can trigger a heart attack in someone who has some underlying coronary artery disease but who would not otherwise have had a heart attack at that stage in their life. So, flu infection can cause a clot to completely block an artery in your heart, your brain or elsewhere. The way that influenza triggers heart attacks and strokes is likely through direct viral effects on the arteries and indirect inflammatory mechanisms, including the release of pro-inflammatory and pro-clotting cytokines, and damage to the lining of blood vessels, causing sudden, complete obstruction of coronary and other arteries. There are other mechanisms that contribute to acute cardiovascular events, including lowering of blood oxygen, increase of heart rate, fever and changes in blood pressure, that can all act simultaneously with clotting in the arteries to cause a heart attack. By preventing infection, the propensity of influenza to trigger heart attacks and strokes is also prevented.

Many studies show that influenza vaccination is protective against heart attack. We conducted a meta-analysis of all the available observational studies that contained data to calculate influenza vaccine effectiveness against heart attack and found that flu vaccines provided 29 per cent protection against heart attack. This is in the same range as protection provided by statins, stopping smoking and blood pressure–lowering drugs, all of which are accepted as key to preventing cardiovascular events. Another large study from the US showed a 28 per cent reduction in the occurrence of a first heart attack. By the early 2000s, small randomised clinical trials of the flu vaccine against heart attack began being published, suggesting the vaccine was protective. Still, there was no shift in policy in accepting influenza vaccines as a routine part of the prevention of acute cardiovascular events. Then, a large, randomised, double-blind, placebo-controlled trial of influenza vaccination across multiple countries was published in 2021, led by Dr Ole Frøbert, a Swedish cardiologist. I was fortunate to be a co-investigator in that trial, along with my long-standing collaborator and cardiologist, Dr Tim Tan, in Australia. Tim was a trainee

cardiologist in 2007 when we began the Sydney study, and we have collaborated on research on infections and the heart ever since. That trial showed the flu vaccine is significantly protective against all-cause death, heart attack or stent thrombosis at 12 months after vaccination. In 2023, the European Society of Cardiology was the first to consider this trial and update their guidelines on acute coronary syndromes, recommending influenza vaccination annually for all patients who have had an acute coronary syndrome, including hospitalised patients who are unvaccinated.

When I was a medical student in the 1980s, if you had a heart attack, your chance of survival to old age was greatly reduced. That is no longer the case because of amazing advances in rapidly restoring blood flow to blocked arteries. First, there was the use of drugs to dissolve clots in coronary arteries, and then the technology to insert a stent into a blocked artery and thereby open it up. Advances in the medical treatment of coronary artery risk factors have also been substantial. The one aspect of heart attacks that has not changed much in terms of survival is a cardiac arrest. A cardiac arrest occurs when the heart goes into an abnormal rhythm, usually ventricular fibrillation, that does not allow the heart to pump blood as it normally does to the rest of the body. Survival from sudden cardiac arrest remains low. If you happen to have a cardiac arrest in hospital, where there is a resuscitation team and a defibrillator, your chance of survival is good. However, most people have their cardiac arrest in the community. When the heart is unable to pump blood to the brain and the body, it takes six minutes for brain death to occur. It’s estimated that about 20 per cent of the first presentation of a heart attack will be cardiac arrest. This is therefore the least preventable aspect of heart attacks, and it’s a very compelling reason to expand influenza vaccination to people in the age group where diagnosis of heart disease has not yet been made but who are at high risk. In our research, we showed that extending free influenza vaccines (currently available for people 65 years and over) to adults 50–64 years would achieve significant cost-benefit for Australia by preventing the fraction of cardiac arrests associated with influenza.

Other vaccines can also reduce the risk of cardiovascular events, such as heart attack or stroke. Having shingles (herpes zoster) increases your risk of stroke and coronary artery disease, and vaccination is protective. I started researching shingles in the early 2000s while working at our National Centre for Immunisation Research and Surveillance. The first study I published, showing severe outcomes, including a 1 per cent rate of death after shingles. This was scoffed at by a disbelieving paediatrician colleague who said, ‘No one dies of shingles.’ Studies now show that having shingles can trigger a stroke or a heart attack, so it makes perfect sense that having shingles can kill you. Other serious complications of shingles include blindness if the virus reactivates around the eye, a condition called ophthalmic zoster. It can also cause meningitis, and I have personal experience of this. My ex-husband, then in his late 20s, developed a very minor rash around the eye that may have been mistaken for a pimple. Eventually, I realised he had symptoms of meningitis, including neck stiffness and sensitivity to light, so I took him to hospital. The doctors at a major teaching hospital disagreed when I said it could be shingles (based on the slight rash around his eye), but a spinal tap (lumbar puncture) and a sample of cerebrospinal fluid confirmed he had herpes zoster meningitis. Fortunately, there are effective antivirals for shingles and he recovered with treatment. The most common serious complication of shingles is postherpetic neuralgia, a very painful condition that affects about 10 per cent of people with shingles and causes chronic pain after the rash has resolved. It’s a nasty, debilitating disease. Studies also show that the shingles vaccine protects against shingles, post-herpetic neuralgia and cardiovascular events, especially stroke. Despite being recommended and funded for older adults, the rate of vaccination is extremely low for this vaccine.

About 30 per cent of people in hospital with pneumococcal disease also suffer a major cardiovascular event, such as a heart attack or stroke. Pneumococcal disease is caused by the bacteria streptococcus pneumoniae (also known as pneumococcus) and is the leading cause of pneumonia worldwide. Pneumococcal vaccines reduce that risk, especially of heart

attacks, and especially in people 65 years and over, across multiple different studies. Yet in Australia, we stripped away the recommendation for people 65 to 69 years. The kindest explanation I can think of is that they forgot to factor in the prevention of heart attacks into their cost-effectiveness analysis, although pneumonia prevention alone would have made it worth it. And in 2020, the year this recommendation came in, it would have been even more cost-effective given pneumococcal disease was the most common bacterial complication of COVID-19. An alternative explanation is simply ageism – selectively slashing spending on older adults, despite having worked hard and paid their taxes all their lives.

RSV is another virus that has been found to increase the risk of heart attacks and strokes in older adults. It commonly causes outbreaks in aged care. In a nursing home study that I was involved in, RSV outbreaks were not as common as influenza, but they do occur and can have high mortality. In 2024, new RSV vaccines for adults 60 years and over became available – two have been approved in Australia – but are not provided free to eligible adults as yet. Like influenza, RSV causes severe disease in infants and the elderly. There is also a new RSV monoclonal antibody for infants, as well as a vaccine that can be given to pregnant women to protect the infant. Monoclonal antibodies are a type of vaccine called ‘passive immunisation’ because the required antibody to fight the infection is directly injected into the patient. Most vaccines stimulate the body to create those antibodies. The infant RSV vaccine was approved for Australian infants in 2024, which is great news. The adult vaccines are too new for us to know if they reduce the risk of heart attacks and strokes, but on principle, they should.

COVID-19 also causes major effects on the heart. Numerous studies have shown an increase in the risk of heart attacks, strokes, blood clots and a range of other cardiovascular events for at least 12 months after infection. The mechanism by which COVID-19 affects the heart is somewhat similar to influenza, but different in many respects. The virus can also cause a heart attack in the same way that influenza does, but can also directly infect and kill heart muscle cells. We measure damaged heart muscles through an enzyme called troponin, and studies show that even infants with COVID-19

have raised levels. So, the virus has the capacity to damage the heart muscle and cause heart failure, the risk of which may increase after repeated infections. One study showed that even after mild infection, people with persistent symptoms, such as shortness of breath, had swelling of the heart. The ACE2 receptor, which is one of the main receptors for binding of SARS-CoV-2, is found throughout the body, including in blood vessels, the heart and a range of other organs. The virus has been shown to cause myocarditis, pericarditis, abnormal rhythms of the heart, heart attacks, strokes and sudden cardiac death. Large studies show that vaccination protects the heart against all these events.

Dr Ziyad Al-Aly, a clinician and scientist at the US Department of Veterans Affairs (DVA), was named in the TIME100 Most Influential People of 2023 for his seminal work on the long-term effects of COVID-19. Using data from the DVA, he published many high-impact studies showing that a single episode of COVID-19 can increase your risk of heart attacks, strokes, pulmonary emboli, other blood clots, new-onset diabetes and a range of other serious diseases, with the risk persisting for at least 12 months after the infection. Studies confirm that the virus can persist in the body long after the initial infection. This can lead to ongoing immunological and inflammatory effects. The COVID-19 vaccines show substantial protection against all these effects, including myocarditis and pericarditis. Although myocarditis and pericarditis can occur after vaccination in about 0.005 per cent of people, especially adolescent and young adult males, the risk after infection is much higher.

We have been told that repeated exposure to COVID-19 will make it mild, but research shows the opposite – reinfection can be more severe and result in worse outcomes. Dr Al-Aly and his team showed that COVID-19 reinfections result in worse outcomes and more complications (including effects on the heart), and he has been a leading advocate for the prevention of long COVID. We were fortunate to host him at UNSW during a visit in 2023, where he gave a hard-hitting talk about his research on long COVID. Long COVID is a term coined by patients, and the medical profession has been slow to recognise and research it. Dr Al-Aly’s research has found that

long COVID is caused by the virus affecting many different organs, but the common denominator is symptoms persisting more than three months after the initial infection. The symptoms can be caused by disease of the heart, lungs, brain, immune system or other organs, but doctors have yet to work out a proper approach to diagnosis. For example, fatigue may be caused by heart failure, damaged lungs, immunological dysfunction or other pathology. Shortness of breath may be caused by heart failure or lung damage, and sometimes by anaemia. Therefore, it's essential that when a patient presents with a non-specific symptom, such as fatigue or shortness of breath, the correct tests are done to diagnose the underlying cause. Unfortunately, many patients are still in diagnostic limbo, with many doctors lacking the knowledge or awareness to do appropriate tests, or to organise appropriate specialist follow-up. Some patients are told it's all in their heads. Others are told to do graded exercise therapy, which can be quite dangerous if the underlying cause of the symptoms is a damaged heart.

In our work on COVID-19 and the heart, we argued that clear diagnostic decision support tools are needed for doctors, providing a pathway to appropriate testing and referral. The research shows that common tests used in general practice are often inadequate to pick up some of the subtle organ damage caused by COVID-19. For example, a chest X-ray may look normal in someone who has very abnormal function of the lung. We are still a long way from providing the medical profession with clear guidelines on testing, diagnosis and management of long COVID, and from supporting patients suffering from it. It is true that many people recover from symptoms of long COVID, but a small proportion do not, and this small proportion is enough to cause a massive impact on our population and health systems. Reinfection with SARS-CoV-2 may also disable people who were previously healthy and add to the burden of long COVID. The true rate of infection and reinfection is likely vastly underestimated as few people do a test when they have infection symptoms, and there is very little reporting of test results. There is no doubt, however, that COVID-19 will contribute a major burden of chronic disease to the world. Cardiovascular

disease is the leading cause of death and disability in the world and affects about 5 per cent of people. Long COVID will make this burden greater and will cause other kinds of chronic diseases that will substantially impact the health system. Sadly, policymaking bodies have not caught up with the science, and we find ourselves with restrictive policies for booster vaccines and antivirals, both of which may reduce this chronic burden of disease.

Another interesting development has been the association of dementia with infections. A number of viruses and bacteria have been associated with Alzheimer's disease, including herpes simplex virus, human herpes virus 6, varicella zoster virus, HIV, Epstein–Barr virus, cytomegalovirus, Helicobacter pylori, E coli, chlamydia and hepatitis C virus. It is believed these infections can directly infect or cause chronic inflammation of the brain and may result in the deposition of an abnormal protein called amyloid in the brain. COVID-19 has been associated with an increased risk of dementia, both exacerbation of existing dementia and new-onset diagnosis of dementia. One study showed a 17-fold increase in new-onset dementia after severe COVID-19, and a doubling of the risk of cognitive impairment after any COVID-19 infection. Blood tests for markers of neurodegeneration are also elevated in people after COVID-19 compared to people without COVID-19. Multiple studies show cognitive impairment in people of all ages, including young people, following COVID-19. Studies also show that COVID-19 vaccination substantially reduces the risk of dementia. I have already discussed how COVID-19 causes widespread vascular disease. One of the common causes of dementia is vascular disease, so this could be the putative mechanism through which COVID-19 increases your risk of dementia, and vaccination protects against it. However, other studies show an increase in amyloid deposition in the brain following COVID-19, which is a feature of Alzheimer's disease, the other common cause of dementia. Just as we should be worried about epidemics of heart failure in the future due to COVID-19, so too should we be worried about the rising incidence of dementia.

Another infection that has been associated with dementia in multiple studies is shingles, with one study finding a tripling of the risk of

Alzheimer's in the five years after a shingles infection. Shingles is a reactivation of the varicella zoster virus, which lays dormant in the spinal nerves. The initial infection manifests as chickenpox, and then the classic shingles rash can emerge decades later. The virus certainly does have a predilection for the nervous system, but studies have been mixed, with some showing an association with dementia, and others not. However, a large meta-analysis concludes that vaccination for herpes zoster protects against dementia. A large population study in Wales also found that vaccination protected against dementia, especially the vascular kind. We do know that the shingles vaccine also protects against cardiovascular events such as heart attacks, so the Welsh study is quite consistent with the vaccine having a vascular protective effect. I've already discussed the high-efficacy recombinant shingles vaccine, and for those eligible for the vaccine, if the thought of getting shingles isn't enough to get vaccinated, then preventing dementia is.

Syphilis used to be called 'the great imitator' because infection could affect every organ of the body and present with different illnesses affecting different organ systems. COVID-19 is the great imitator of our times. It can cause heart attacks, strokes, diabetes, kidney disease, dementia, pulmonary emboli, gastritis, pancreatitis and a range of other complications. Given the general minimising of COVID-19 by governments and the media, many doctors are unaware of these associations and may simply diagnose these diseases at face value. If we don't act to reduce the burden of COVID-19 by widening access to testing, treatment and vaccination, as well as addressing non-pharmaceutical interventions such as safe indoor air, ventilation and masks, COVID-19 will be the gift that keeps on giving for decades to come. Reversing the damage that COVID-19 will cause to population health will be an uphill battle, and any action to mitigate it will likely be too little and too late, especially for today's children. Vaccines, however, are low-hanging fruit, especially if they can also prevent cardiovascular disease.

15

COVID KILLED PUBLIC HEALTH

The COVID-19 pandemic has resulted in a drop in life expectancy in many countries. In the United States, it dropped by two years between 2020 and 2021 from 79 to 77 years. Despite the public messaging telling us that ‘only old people’ are dying of COVID-19, life expectancy only drops when younger people die. So, although most deaths are in older people, there have been enough deaths in younger people, including children, to cause life expectancy to drop. In the US, COVID-19 was the leading infectious cause of death in children 0–19 years by mid-2022, despite COVID vaccines being available for children under five years, unlike the UK, Australia and Sweden, where kids in this age group cannot routinely get vaccinated.

A common approach by policymakers is calculations of the ‘number needed to vaccinate’, a concept that arose from a tool used in clinical medicine for the treatment of acute illness – the ‘number needed to treat’. It is calculated by estimating how many people need to be treated to prevent one death, hospitalisation or other serious outcome. If you have to treat a million people to prevent one death, it may not be a cost-effective treatment, but if treating 1000 people prevents one death, this makes the treatment more favourable to policymakers. The application of ‘number needed to treat’ to vaccination has some useful applications but should not necessarily drive vaccine policy as it does not account for contagion and herd immunity achieved by vaccination, and the population benefits that come with it. The ‘number needed to vaccinate’ for the influenza vaccine

for children is 1852. In other words, you have to vaccinate 1852 children to prevent one hospitalisation. Many countries recommend influenza vaccination for children. Yet the WHO has not recommended COVID-19 vaccines for children based on an estimated high ‘number needed to vaccinate’ to prevent hospitalisation. A US study estimated 8000 vaccinations were needed to prevent one hospitalisation, while a UK study estimated vastly higher numbers. Neither makes sense to me based on the available data when COVID-19 causes more deaths and hospitalisations in children than influenza.

Many countries rightly recommend influenza vaccines for kids six months and over, but while the flu and COVID are both serious infections, COVID causes more deaths in kids and is the leading infectious cause of death in children. In fact, it is the eighth leading cause of death in children, while influenza is in ninth place, which is why the calculations of ‘number needed to vaccinate’ appear to be incorrect. In the US, 50 per cent of children 0–17 years who died from COVID-19 had no underlying medical condition and were healthy. Even though the fatality rate of a single infection in children is higher for influenza, it causes fewer infections than SARS-CoV-2. Firstly, this is because influenza typically causes a winter peak and is less common at other times of the year, whereas COVID-19 is perennial. In Australia, the largest epidemics have been in summer, with multiple epidemic peaks throughout the year. Secondly, aside from the lack of seasonality, the scale of COVID-19 and total number of cases is much greater as it is far more contagious than influenza. Vaccine policy that denies vaccination or boosters to kids fails to grasp that public health impact is a function of severity per case plus the total number of cases (burden of disease). To date, vaccine policy also fails to acknowledge the burden of long COVID and the clear evidence that vaccines can reduce that burden. There is now a large body of evidence that SARS-CoV-2 is much more than just a common cold. It is a virus that can persist in the body for a long period of time after the initial illness and cause a range of vascular, cardiac, neurological, immunological and other organ system damage. There are many studies, including those by Dr Al-Aly, and one we

published in the *Medical Journal of Australia*, to show that the burden of long COVID in Australia is in the same range of major causes of global burden of disease, as diseases such as ischaemic heart disease and stroke. Many experts dismiss long COVID, scoffing that ‘most people recover’. Yes, many do recover, but a small proportion do not. Even if 5 per cent of the population has long COVID, that is substantial on a population health level. For example, it is estimated that 5 per cent of Australians live with coronary heart disease, which is the leading cause of death and disability in Australia and the world. Therefore, 5 per cent with long COVID will cause a significant global burden of disease. It is likely that it will also make the existing cardiovascular burden worse as we are already seeing increases in heart disease, stroke, dementia, diabetes and other chronic illnesses that have been triggered by COVID-19. This means there will be a long and vicious sting in the tail of COVID-19 that results in a chronic burden of disease in the population, not just in older people but also in children and young people. In fact, our research showed that the greatest burden of long COVID-19 is in the age group 30 to 49 years, who are working-age adults. This is already impacting workforces and economies around the world and is not going to magically disappear. Most disturbing of all is the impact of repeated infection on our children, the youngest of whom cannot even get a vaccine in countries like Australia and the UK. It is possible that a proportion of today’s children will develop early-onset heart disease, cognitive impairment and other organ system damage after repeated COVID-19 infections. One study of infants with acute COVID-19 showed an increase in cardiac troponin, which is a specific marker of damage to the heart muscle. Another study showed developmental impairment of foetuses in mothers who became infected during pregnancy. It is time for vaccine policymaking bodies to pay attention to the large body of research on the long-term complications of COVID-19. If they want to use ‘number needed to vaccinate’ to drive policy, they should be counting the burden of long COVID. Unfortunately, Australian and UK policy is stuck in 2020 and has not yet moved with the evidence.

In contrast, the US Advisory Committee on Immunization Practices is an excellent model in transparent vaccine policy-making. They hold public meetings where anyone can watch the decision-making process in action. They also provide all the data and slides from presentations made at the committee meetings on their website. No such transparency in policy exists in the UK, Sweden or Australia to justify the denial of vaccines to young children and boosters to older children. Rhetoric from supposed vaccine experts in these countries often cites the risk of myocarditis and pericarditis, a rare complication in teenage and young adult males, as a reason for restricting vaccine access to children. Myocarditis and pericarditis occur at a rate of 2–8 per 100 000 doses of vaccines in young males. Yet the risk of myocarditis and pericarditis is far higher after COVID-19 (50–180 cases per 100 000 infections) than after the vaccines, and vaccines offer net protection against myocarditis. I attended a conference in 2024 where a member of a peak policy making committee gave a presentation on the side effects of vaccines. They showed a slide of a poorly conducted review of other studies, with some pie charts as evidence of ‘substantial’ cardiac and vascular events after the administration of mRNA vaccines. This was a misleading, unregistered study that aggregated a bunch of other studies that reported on side effects following vaccination. There was no data on the denominator, that is, how many vaccinations in total occurred, nor any assessment of causality or background rates of the same effects in unvaccinated people. For example, a number of people may have a car accident or a fall or even die each day, and some of them would have been coincidentally vaccinated in the last week. If we create a pie chart of deaths after mRNA vaccines, we would see that car accidents and falls appear in the pie. Without any data on background rates of these events, you would conclude that mRNA vaccines cause car accidents. This is exactly what this paper did, and the presenter went on to suggest deaths, stroke and heart attack were common after mRNA vaccines, without any data on how often these occur normally. Most of the purported complications in the pie charts are not recognised as adverse events of mRNA vaccines, nor were they seen in a large, multi-country study of over 99 million vaccinations, which may

be the most definitive study yet of COVID-19 vaccine safety. That study showed that myocarditis and pericarditis do occur after mRNA vaccines (that was already well established) but at a far lower rate than after COVID-19 infection. The only complication associated with blood clotting was following the adenovirus vectored vaccines, which resulted in a tripling of the risk of a specific kind of brain clot. Those vaccines are no longer manufactured. It was also disturbing to see the platforming of misinformation at a medical conference, and how far we have fallen in public health.

It is worrying that vaccine experts are adopting the same arguments against COVID vaccines that anti-vaxxers have used since the first vaccine against smallpox. There has been extensive dissemination of anti-vaccine disinformation since the COVID-19 pandemic began, which has spread unchecked in mainstream and social media. When our social media streams tell us that young athletes suddenly dropping dead were killed by vaccines, and governments fail to counter that disinformation, the effect of such propaganda seeps through all of society. Yet the National Collegiate Athletic Association in the US released data on all deaths of athletes over a 20-year period, showing none were due to vaccines. In 2021, Danish football star Christian Eriksen collapsed during a televised game, and social media was abuzz with claims it was caused by COVID vaccines. Later, it was revealed that he had not even received the vaccine. The cumulative effect of these rumours and misinformation, however, is substantial. Other athletes like bodybuilder John Eyers refused the vaccine and died of COVID-19.

Privately, many doctors and health leaders bemoan falling vaccination rates and stay silent while anti-vaxxers claim the stage, free to make whatever outlandish anti-vaccine claims they wish. I was in the emergency department with an injury in 2024 and the man in the cubicle next to me had been scratched and bitten by his cat. The doctor recommended a tetanus booster and he refused. He demanded IV antibiotics instead, which the doctor assured him was not required. She asked him why he did not want

the tetanus shot, and he replied, ‘I know thirty people who dropped dead. I don’t want it. I’m *not* having it.’

‘Dropped dead from what?’ asked the doctor.

‘You know, COVID vaccines. Thirty people I know died after getting COVID vaccines.’

Instead of countering the misinformation, the doctor gave him the antibiotics he demanded. I needed a tetanus shot for my own injury and dutifully received it without arguing. I asked the doctor why they didn’t advise the other patient that his assessment of deaths from COVID vaccines is highly unlikely, given the Therapeutic Goods Administration has assessed there have been 14 deaths from COVID vaccines in all of Australia, all before 2022, with none in children and 13 of these after the now-ceased AstraZeneca vaccine. The doctor was weary and did not have the energy to argue with him, finding it easier to give in. Medical leaders see vaccination rates falling and don’t know what to do about it. At the same time, many fail to provide the role modelling needed for change, stricken by the same fear as politicians. They are more comfortable speaking out about vaping than about COVID because the latter is so triggering for large sections of the community.

I have worked in vaccines since the early ’90s, and written myth-busting fact sheets to counter anti-vaccine arguments in Australia. They typically follow this line of reasoning: ‘Infection is mild in most children, natural immunity (infection) is good for children, and vaccines are dangerous.’ Committed anti-vaxxers even have measles parties and chickenpox parties to deliberately infect their children. The most terrifying thing I have witnessed post-COVID is the mainstreaming of anti-vaccination rhetoric in the medical community. When my doctor friend got sick with COVID in 2023 and said they never had a booster because they didn’t ‘want mRNA in [their] body’, I was shocked. If doctors can be influenced by anti-vaccine rhetoric, what hope is there for the community in general?

In the United States, it is estimated that about a third of over 1 million deaths from COVID-19 by January 2023 were preventable. One study looked at the spread of misinformation by physicians between 2021 and 2022. They found that 52 physicians, many with very large social media followings, were propagating misinformation and conspiracy theories that included anti-vaccine and anti-mask sentiment. Other reports from the US suggest there are few consequences for such doctors. The UK General Medical Council, normally tasked with upholding the professional standards of medical practitioners, decided not to investigate doctors who spread vaccine misinformation. The Good Law Project and doctor X challenged the General Medical Council about doctor Y, who had a very large social media following and was calling for mRNA vaccines to be withdrawn and falsely alleging they cause coronary disease and death. Later, the General Medical Council accepted that its decision not to investigate doctor Y was flawed, yet it remained sympathetic to him and agreed to pay some of his legal costs. The story is still unfolding, but it's highly disturbing that a body such as the General Medical Council would take no action against a medical practitioner wilfully spreading disinformation. Meanwhile, in 2023, the Joint Committee on Vaccination and Immunisation in the UK took a backward step in both influenza and COVID-19 vaccinations, denying it for approximately 12 million people aged 50 to 64 who had been eligible to get vaccinated the previous year.

The COVID-19 pandemic can explain much of the mainstreaming of anti-vaccination information. The pandemic occurred in an era of mass social media and real-time interconnectedness of the world. It was a time when young adults did not follow mainstream media as much as their older counterparts but instead relied on social media streams. The first frightening months of the pandemic were accompanied by images of overwhelmed health systems in China, Spain and the United States. We saw mass graves being dug in New York and ice rinks used to temporarily store bodies in Spain. These graphic images were beamed all over the world, and people rightly perceived the risk to be high. Before we had vaccines and antivirals, we had to use non-pharmaceutical measures to control the carnage and

prevent health systems from collapsing. We all learned about ‘flattening of the curve’ and how social distancing and masks could help to achieve this. Lockdowns have always been a last-resort measure, when nothing else is working, when there is no treatment or vaccine, and when health systems are collapsing. That is the context in which they were used. How quickly we have forgotten the domino effects on society of the pandemic, with workplace absenteeism contributing to supply chain collapses, shortages of essential items in supermarkets, weakened critical infrastructure and a range of other effects. The lockdowns caused hardship for many people, especially those whose livelihoods were affected, such as those in the hospitality and entertainment industries, when restaurants and entertainment venues were unable to stay open. Entire central business districts became ghost towns, affecting all the industry in the areas. There were also perceived inequities, where some states or local areas were locked down and others were not in different countries. People also lost loved ones or lost their own health or their jobs as a result of COVID-19.

As a community, we tolerated the intolerable, even in countries that did not provide much financial support to citizens. In 2021, when vaccines were available, people rushed to get them because there was hope this would end the pandemic, that we could go back to the lives we lived in 2019, and that the immunity from these vaccines would be permanent. When vaccines did not live up to the early promise, with waning immunity and rapid mutations of the virus itself, it did not provide the desired end of COVID-19. Instead, we had ongoing mass transmission in populations that were exhausted and ready to get back to normal. To some extent, vaccines have enabled this because they reduce the risk of death and severe disease. But many governments shifted to a set-and-forget mentality. They felt they had done their bit, provided vaccines and now could shift their focus to other things. We then saw the dismantling of public health measures, such as masks in crowded spaces during periods of high transmission, and even mandatory isolation for people infected with COVID-19. In mid-2024, my colleagues in the US were upset when the mandatory isolation of five days was reduced to one day. Australia abandoned all mandated COVID isolation in

late 2021, a full two years ahead of the US, who still retain a one-day isolation period. In late 2021, the narrative by governments was that people were sick of masks, didn't want to isolate and wanted to move on. However, research that we conducted showed that even as late as early 2023, most people did not agree with abolishing mandatory isolation for COVID, and over 60 per cent of people preferred mask mandates in crowded public spaces and mandatory isolation. People also reported peer pressure made them unlikely to wear a mask unless everyone else was wearing one.

A combination of the 'move on' mentality and anger in the community resulted in public health – and anyone advocating for it – becoming the scapegoat. I published a piece in *The Saturday Paper* in 2022 where I wrote: 'Sadly, the weaponisation of lockdown as a point-scoring issue and emotional trigger has led to a conflation of lockdown with all other public health measures, most of which do not impinge on freedoms.' During the pandemic, and ongoing, I received many enraged emails and was the subject of angry social media posts after any media appearances or interviews. I was also the target of anger against public health, including vaccines. One email said, 'Australians suffered economic loss as well as mental and emotional harm because you and the Burnet Institute [a medical research institute (not my own)] worked in concert with extreme politically motivated public officials to commit acts contrary to the public interest.'

Another email was a long tirade accusing me of promoting masks and vaccines and causing mass deaths as a result. The writer was also angry with the public broadcaster, the ABC: 'You Raina and the ABS [*sic*] media are COMPLICIT in all Deaths, maiming and harm that has occurred from these "experimental toxic jabs". Looking the other way will not be an excuse. Doing your job will not be an excuse. You are COMPLICIT!' Another email said: 'You are just so f*cking useless, like 95 per cent of females with "careers". Do something constructive and cook a decent meal, and clean the house!' Other social media posts and emails personally blamed me, not the governments who enacted them, for lockdowns. I have a

whole collection of emails, many worse than these examples, as do most genuine public health advocates who have done media interviews.

The removal of public health measures like mask and vaccine mandates was synonymous with a return to normal, so it was easy to blame public health rather than the pandemic as the cause of so much unhappiness and loss. The effects of this have been quite far-reaching. First, we saw the scapegoating of public health and experts who advocated for it as the enemy rather than accepting that we suffered a terrible, once-in-a-lifetime pandemic. Then, along with a backlash against lockdowns, we have seen a rise in anti-vaccination sentiment and distrust of governments. I have heard from public health officials in Australia and other countries that the community is tired of COVID and that they have to be careful about public messaging around it. Health departments collect data on community sentiment and pay close attention to the mood of the public. I suspect governments around the world may have a fear of advocating for public health because it has become conflated with lockdowns and the anger they caused, and that advocating for public health measures against COVID-19 may be ‘triggering’ for many people and electorally unpopular. The Labor government was outspoken while in opposition about better measures to mitigate COVID, including wider access to testing, speeding up vaccine programs and holding a Royal Commission into the handling of the COVID-19 pandemic, but it did not follow through when in government. In September 2023, when a limited COVID-19 review was announced, the Australian Medical Association, the human rights commissioner and other health and legal experts publicly criticised the narrow terms of reference of this review and the low likelihood of any meaningful outcomes.

Governments are in a difficult position. They are trying to be sensitive to the public mood while countering disinformation and advocating for public health around COVID-19. More often than not, governments everywhere stayed silent while anti-vaccine players (including trusted expert doctors) flooded social media and even mainstream media with disinformation about COVID-19 vaccines. Even five years ago, just before the COVID-19 pandemic, I am certain governments would have responded

to vaccine disinformation with public health communications campaigns. Yet we've seen very little of this. Instead, we have seen vaccination policy become more and more stringent in many countries, including Australia, even making it difficult for people who want a booster to receive one. ATAGI brought in their most restrictive guidelines ever in November 2023, saying adults under 65 years and children under 18 should not receive a booster unless severely immunocompromised. Vaccine rates were so low that the Department of Health quietly updated them in December of that year and again in February 2024 to make them slightly less restrictive. These now allow adults of any age to get a booster but still remain firm that children under 18 are not eligible. But pharmacies only seem to remember the highly restrictive guidelines. When I made an appointment for my COVID booster in 2024, being 59 years of age at the time, the pharmacy called me to cancel the appointment. They told me I wasn't over 65 years of age and was therefore ineligible for a booster. I know multiple other people who had the same experience. As an informed public health figure, I simply printed out the updated guidelines from the Department of Health website, went to the pharmacy, showed them I was eligible, and finally received my booster. However, many people in my position – but without my expert knowledge – simply gave up after being turned away at pharmacies. The decision to restrict COVID boosters to certain people required a complex decision tree to be published so GPs and pharmacists could understand the guidelines. Numerous people on social media also attempted to create decision trees to help people navigate the confusion caused by these restrictive and conditional guidelines.

No wonder our booster rates are low, and no wonder rates of vaccination, even in aged care facilities, are low. I know of people who are privileged enough to travel overseas to receive boosters for themselves and their children because they are unable to receive them in Australia. This includes the updated 2024 vaccines, which became available in September 2024 in the US but were not available in Australia at that time. In May 2024, the WHO recommended JN.1 boosters to match a variant that circulated in 2023. The US realised the virus had mutated further and

released KP.2 boosters, which are more current. Australia announced they would purchase the older JN.1 vaccines. The restrictive and slow approach to public health resulted in a waste of antivirals and vaccines. Towards the end of 2023, the government had been so restrictive in allowing access to antivirals that they had a large number of expiring doses that had been unused. Antivirals reduce death, hospitalisation and long COVID in patients with COVID. In Australia, antiviral pills are recommended and provided at a subsidised cost of around $30 for adults 70 years of age or older. People 50 years of age or older with two chronic conditions, First Nations people 30 years of age or older and with one chronic condition, and people 18 years of age or older with rare conditions can receive antivirals at a subsidised cost. The majority of the Australian population are ineligible and would have to pay over $1200 for a private prescription – if they can convince their GP. I have heard of people who requested a private prescription and were refused.

I also suspect there may be the same wastage with boosters. To make matters worse, the rise in anti-vaccination post-COVID has caused a decline in the rates of other vaccines. In Australia, where flu vaccination for people over 65 usually hovers around 70 per cent, the rate dropped to around 60 per cent in 2024. Rates of COVID boosters are low even in nursing homes. A 2024 study from the US found that parental vaccine hesitancy has risen to a staggering 30 per cent for vaccines such as influenza and HPV. In Texas, promoting COVID vaccines is banned, and in Idaho, one health district has stopped providing COVID vaccines altogether. Meanwhile, we have seen a resurgence of measles in many countries, endemic malaria in the US and a range of other infectious diseases surging in an unprecedented manner, likely due to the immune dysregulation caused by SARS-CoV-2 and falling vaccination rates. We now have H5N1 influenza knocking on the door, and a new pandemic will have the added challenge of dealing with widespread anti-vaccination sentiment.

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WHO WILL RECLAIM THE STAGE?

In a recent study, we estimated there were 5.4 per cent of people living with long COVID-19 in Australia in 2022–23 alone. Working with leading economists, we estimated this would result in over $9 billion in losses to the economy due to people being unable to work or unable to work at full capacity for a period of time. The disease burden is in the same ballpark as coronary heart disease, so it will undoubtedly have an enormous impact on health and the health system. Unlike ischaemic heart disease and the other major cause of the global burden of disease, cancer, which disproportionately affects older adults, we found the major burden of long COVID was in working-age adults 30 to 49 years of age. Pause to think about that. During the pandemic, we heard dismissive comments about old people dying. Long COVID is projected to have a massive impact on healthy younger adults and children, and thereby a much greater burden on the economy and workforce than diseases that peak at the end of life. The pandemic also saw the ‘othering’ of people with chronic illness as expendable and less valuable, but our own research and official data show that about half of all Australians have a chronic disease. Individuals who don’t care only start caring when they or their own loved ones become affected. Peer pressure and gaslighting may also force people into silence when the rest of the world is telling them COVID-19 is just a cold.

The 2024 Paris Olympic Games and the Tour de France saw mask mandates introduced for athletes because they were fully aware that COVID-19 can remove an athlete from competition. But many teams did

not take precautions, and we saw several athletes pull out or compete while ill with COVID, ruining their chances of a medal. US track star Noah Lyles, also an asthmatic, won the 100m sprint and was hoping to achieve the double of 100m and 200m wins, which few runners have achieved. However, he developed COVID and competed while sick, finishing third in a race where he was the favourite to win. He collapsed after the event with chest pains and shortness of breath and had to be taken off the field in a wheelchair. At Davos in 2023, the World Economic Forum employed maximum COVID mitigations, including PCR testing, HEPA-filtered air, ultraviolet light to kill viruses, and masks at some events. While elite sections of society like the World Economic Forum mitigate COVID, the rest of us seem to be trapped in a dystopian, global-scale conspiracy of silence. Bosses may start caring when work productivity drops because of workers who are affected, but mass denial and silence are still in effect. Within this silence, the stage is free for anti-vaxxers, snake oil salesmen and people with other agendas to get out their megaphones and flood the world with disinformation because governments are unwilling to challenge them. Even tobacco companies are emboldened and back with a vengeance with vapes, aggressively targeting children and teens with pretty packaging and enticing flavours, with less resistance facing them than at any other time in recent history. An initial proposal by the government to require a prescription for sales of vapes at pharmacies was watered down to allow over-the-counter sales.

Revisionist science is now a major force in the disinformation landscape. There have always been pseudoscientific groups, usually well funded and running interference for powerful commercial interests, but these have exploded since COVID. Science revisionism is why it took 100 years for medicine to accept that smoking is harmful to health. I devoted a whole chapter to this in my previous book and provided examples such as tobacco, climate change and gastric ulcers where the push-pull of narrative and counter-narrative research greatly slowed progress as vested interests tried to deny the science. Now, there is a concerted effort by such groups and their acolytes to attack research that contradicts their narrative, which is

that COVID is a nothingburger. This comprises relentless letters to the editor, publishing critiques on their own websites and often harassing medical journals to the point of capitulation. I had one experience of this when a well-respected group of scientists at the Burnet Institute asked me to collaborate on a study they were doing on face masks. They did an epidemiologic study to assess the impact of mask mandates in 2020, which were introduced on 20 July, weeks after other restrictions such as lockdown. This provided an opportunity to study the effect of the mask mandates alone, and the paper was an excellent piece of work, showing the impact of the mask mandates on COVID-19. It was relentlessly attacked by a PhD student (not qualified in infectious diseases or epidemiology), and the authors responded to his complaints reasonably and factually, showing why they were unfounded, but the student was unrelenting and the journal capitulated to the escalating attacks and published an ‘expression of concern’ on this paper, essentially casting shade on the research.

Another group that attacks any scientific research that negates the narrative that COVID-19 is mild was formed in 2020 by a group of people ‘who perceived the global reaction to Covid – from lockdowns to mandates – as overwrought and damaging to the point of causing a great tear in the fabric of society’. This is an anti-vaccination, anti-mask group who do not even believe older people in aged care facilities should be vaccinated against COVID. In 2022, they published a demand for the retraction of another excellent paper, *Global impact of the first year of COVID-19 vaccination: a mathematical modelling study* by a highly regarded research group from Imperial College London. The paper showed that COVID-19 vaccines prevented over 14 million deaths. The article, written by an author with an undergraduate degree in aerospace engineering, was titled ‘False Covid-19 Vaccine Claims by Lancet: A Call for Retraction’. At least the *Lancet* editors, unlike *PLoS* with the Burnet paper, didn’t capitulate. This group has no expertise in epidemiology, infectious diseases or modelling, the discipline areas of the authors from Imperial College London. The article cherrypicked data and applied a US CDC estimate of deaths in older people to the whole world, but this is in a high-income country with good

health care access. One cannot apply US estimates to a low-income country. The US had one of the highest ratios of ICU beds per head of population in 2020, and the ratio of hospital beds and ICU beds per head of population was strongly correlated with survival. We saw examples where survivable infections resulted in death in younger people simply because hospitals were full, or oxygen supplies had run out (for example, in India during the Delta wave). There are also many deaths not officially counted as COVID because they may be presentations like cardiac arrest or other cardiovascular events, which are associated with the vascular pathology of COVID. The excess all-cause mortality data globally are showing this clearly now. UNICEF estimates that in the absence of a vaccine, the world would have seen 5 million deaths due to smallpox every year in the mid-1990s. I am sure anti-vaccine groups would be raging against the statistic that smallpox vaccines, by achieving eradication, has saved over 190 million deaths since 1980.

OzSAGE, the Australian independent expert group formed to provide multidisciplinary scientific advice during the COVID-19 pandemic, has been attacked repeatedly by certain journalists and some ‘useful idiots’ in the academic community. OzSAGE issued advice about COVID-19 in October 2021, using data from my team. However, a young epidemiologist with zero track record in pandemics published an opinion piece in a newspaper, attacking OzSAGE estimates about COVID in children. This young man then began emailing me and people on my team with a barrage of arrogant, entitled emails demanding answers to a series of uninformed questions. He appeared to be utterly obsessed with me and our research. I doubt he would have done this to a white male professor. At the very least, this young man would have contacted a white male professor *before* publishing his diatribe in the online article. He offered us no such courtesy, instead making inappropriate demands after publishing his hit piece. Finally, tired of his harassment, I lodged a complaint with his employer, requesting that he never contact me or anyone on my team again. That stopped the harassment. But such bullying attacks in science are widespread now, with a strong agenda by some to revise the history and science around

the COVID-19 pandemic. An article by Dr Lukas Engelmann and Dr Dora Vargha outlined the concerted and widespread pandemic revisionism of mainstream media. They concluded: ‘It is the voices of those lost to the pandemic, of those most vulnerable to the virus, past and present, of those most affected by the debilitating effects of long COVID and of those advocating for a pandemic response based on principles of equity, that are written out of this increasingly popular, populist and revisionist picture.’

Then there are the junk studies published in reputable journals, such as the study that correctly identified excess deaths since the COVID pandemic but incorrectly attributed them to vaccines and other public health measures. Somehow, it got published in *BMJ Public Health*. In addition to misleading use of data and incorrect science, the authors appear to have plagiarised text and data from another, unrelated publication. A leading epidemiologist, Dr Lone Simonsen, published a scathing commentary on this paper and called for it to be retracted. *BMJ Public Health* added an ‘expression of concern’ on 14 June 2024 but is yet to retract the paper. Journal editors are often very busy and rely on reviewers to examine research in detail. It’s possible that the editors did not scrutinise the work carefully enough and allowed it to slip through the goalposts. This should also be seen in the larger context of information warfare, with some influential players seeking to minimise the impact of COVID-19 and promoting misinformation about vaccines and public health.

In addition to pseudoscience appearing in reputable journals and orchestrated attacks on research and researchers, there has also been a proliferation of junk journals, including one run by anti-vaccination leaders, which publish pseudoscientific disinformation. The rise of predatory publishing and junk journals pre-date the pandemic, but new journals that provide a platform for anti-vaccination activists have sprung up. For the layperson, or even for doctors or researchers, it can be difficult to navigate the crowded space of medical journals, some legitimate and others not. For those of us in universities, the email inbox is flooded with offers to publish papers in journals that sound legitimate and often have a name very similar to well-known journals. They charge thousands of dollars to publish a paper

and often publish without proper peer review. They appeal to vanity, and junior researchers often get fooled, thinking they have been ‘spotted’ as new talent by a journal. Junk conferences, too, have proliferated, and invitations to speak at these also flood our inboxes. These are money-making rackets for the most part, but specific anti-vaccine journals with scientific-sounding names have also arisen. In 2023, a prominent doctor in Australia was circulating an article from a newly minted anti-vaccine journal that was crafted to look credible. This doctor was clearly fooled by the paper, which suggested vaccines were harmful, and disseminated it to their medical networks as if it were genuine science. Unless there is strong leadership and public health messaging to the community, we will drown in disinformation, a terrible position to be in when the next pandemic hits, which could be influenza, orthopoxvirus or something completely left of field.

The performance of governments in 2020 was mixed but shocking in many high-income countries. Imagine facing a new pandemic against the backdrop of the post-COVID backlash against public health. It would be worse than 2020. Many Western democracies failed catastrophically in 2020 as evidenced by mass graves in New York and bodies piled up on ice rinks in Spain. Prior to the COVID-19 pandemic, global health experts in Western countries controlled the narrative, which was that only low-income countries would fare badly in a pandemic – and of course, these same privileged experts were ready to step in and save people of colour in low-income countries. The GHSI launched just before the COVID pandemic rated the US number one in preparedness. Vietnam and Samoa were ranked 50 and 162 respectively, but they outperformed the US in pandemic control in 2020. Samoa, hot on the heels of a devastating measles epidemic, simply closed its international borders, even though the WHO maintained no country should close borders. Border closure is also how New Zealand and Australia were kept relatively COVID-free until vaccines were available. An island nation like Australia can use border closure very effectively. In fact, we have a long history of protecting our biosecurity, including during the 1918 influenza pandemic. Public health measures during a pandemic

aim to reduce the spread of infection using a combination of non-pharmaceutical and pharmaceutical measures. Early in a pandemic, if no vaccine or drug is available, all we have are measures like masks and distancing. For infections with a long incubation period, contact tracing and monitoring of contacts is highly effective in flattening the curve. Case finding and isolation of infectious people is also highly effective, which is how the 2014 West African Ebola epidemic was finally contained.

In 2020, we saw that money, expertise and scientific technology do not guarantee good pandemic control. Leadership, culture, appropriate experts informing policy decisions, as well as the willingness of the public to follow expert advice, matters too. Some countries succeeded in pandemic control using tried and tested public health measures such as border closure, case finding, contact tracing, quarantine and social distancing. Pandemic revisionism has erased the fact that lockdowns are never a first-line measure – they are a last resort when everything else is failing, health systems are collapsing and you have no drugs or vaccines. Trust in government and a culture of public good have also proven to be important in pandemic control. We showed in our research that Australians trust the government and are more willing to follow public health orders compared to Americans and British. There is, therefore, more opportunity in Australia to use good leadership to achieve better public health outcomes during a pandemic. There was resistance to public health orders in both the US and the UK, with different factors in each country. A highly individualistic culture in the US makes public health more difficult to implement as individual freedom is valued much more than the collective public good. In the UK, a history of mistrust around infectious diseases, from ‘mad cow’ disease to whooping cough and MMR vaccine myths, has created a problem. We saw poor leadership in both countries, with unscientific theories about herd immunity from natural infection promoted in the UK, and anti-public health messaging from health and political leaders in the US. Instead of building trust or confidence, we saw standard public health measures such as masks and vaccines being politicised and demonised. The then-director of the US CDC, Dr Rochelle Walensky, publicly referred to masks as a ‘scarlet letter’

when mask mandates were lifted just as the Omicron wave surged in early 2022. She said, ‘We want to give people a break. The scarlet letter of this pandemic is the mask … It reminds us that we’re in the middle of a pandemic.’ The Florida Surgeon General advised against mRNA COVID-19 vaccines. The dark anti-public health undercurrent that has permeated the political narrative and mainstream media will derail our response to a future pandemic.

Another problem for the future of vaccines is that vaccination is a population health intervention. Yet political leaders rarely understand public health or confuse public health with primary care (treatment of individuals in the community) or provision of acute health care in public hospitals. So, naturally, politicians seek their public health advice from clinicians or scientists who have little understanding of public health. I wrote an editorial in the *MJA* in 2012, outlining the massive omission of public health in a major health reform initiative by the Labor government of the time, which had been launched with great fanfare. Public health is defined as the organised response by society to protect and promote health, and to prevent illness, injury and disability. The three pillars of public health are health protection, health promotion and disease prevention. Health protection is the use of legislation, such as the plain packaging of cigarettes or banning smoking in public spaces, mandatory use of seatbelts, and laws about food additives or food safety. For pandemic control, most countries have laws that confer emergency powers, which allow measures such as lockdowns or mask mandates. States have laws that can even imprison someone who is flouting a requirement for quarantine for a deadly disease. These laws have been used to incarcerate people who have refused to take medication for tuberculosis or who have knowingly spread HIV. Health promotion is ‘enabling people to increase control over, and to improve their health’. This is done by providing educational materials to engage consumers, for example, encouraging a COVID-19 booster or annual influenza vaccine. Finally, disease prevention is the largest of the three pillars of public health. It includes surveillance to monitor trends in disease and detect early signals of concern, screening to identify risk factors or early signs of disease (such

as a Pap smear), and prevention programs. Vaccination programs are a major contributor to disease prevention and one of the most successful disease prevention interventions in history.

Public health requires specialised training, skills and a dedicated workforce. In Australia, the government understood it had to plan for hospital surge capacity and managed this well, but it did not understand public health surge capacity. A severe epidemic of COVID in 2020 in the state of Victoria was exacerbated by a lack of surge capacity in contact tracing and outbreak investigation in a decimated health system, eroded over decades since the 1990s. This oversight left hospitals and primary care physicians doing contact tracing, and hiring airline staff to do phone follow-up. The specialised expertise for epidemic and pandemic control lies with field epidemiology and trained staff in state health departments, with outbreak investigation being their bread and butter. Field epidemiologists are trained in the science of detecting, preventing and controlling epidemics, and understand that epidemic control needs contact tracing and case finding. Operational state health department staff do this routinely for measles, hepatitis A, meningococcal disease and a range of other infections. There is also TEPHINET, a global network of Field Epidemiology Training Programs, which is a field-based workforce program arising from the United States Epidemic Intelligence Service (EIS) training program of the CDC. The EIS was developed by epidemiologist Dr Alexander Langmuir in 1951 in response to the threat of biowarfare during the Korean War. Outbreak investigation, field response, contact tracing, case finding, surveillance, prevention and use of vaccines and other measures to control outbreaks are core competencies in field epidemiology. Despite the availability of such qualified people, few drove the pandemic response in 2020, or even during the West African Ebola epidemic of 2014. Instead, researchers in search of their *Nature* or *New England Journal* publications flooded the stage and drove policy.

What we saw in 2020 around pandemic control in many countries was the equivalent of me walking into a major hospital, flashing my specialist medical qualifications and performing coronary angiography on a patient

suffering a heart attack. The patient may not know the difference based on my qualifications on paper, and in this hypothetical scenario, the hospital management may be suitably bedazzled by me. Another example would be getting the air traffic controller to fly the plane. It would never happen, right? Yet we have seen exactly that happen during the pandemic when it comes to public health expertise. Clinicians and basic scientists were driving policy on expert committees, and public health experts were absent, resulting in a bumbling, learn-as-you-go public health response. In the US, a radiologist was put in charge of the US pandemic response. Then there were the infection control experts, whose bread and butter are treatment and prevention of wound infections and antimicrobial resistance, for which handwashing is key. They posed as all-knowing curators of all science and denied airborne transmission of SARS-CoV-2 within a month of the pandemic when knowledge about the virus was limited. They made policies and decisions on health worker safety without consulting aerosol scientists, engineers or ventilation experts. It's the 'Never heard of it, therefore it's not true' school of policy. Control of SARS-CoV-2 requires very multidisciplinary expertise, yet it was led by infection control experts, which meant that much of 2020 was spent on promoting handwashing, actively discouraging mask use and installing ineffective devices like perspex screens. As a result, there was low awareness among the general public of the importance of ventilation and masks in reducing their personal risk. Similarly for boosters, the public has been aggressively force-fed messages that COVID-19 is trivial or over, and so booster rates are appallingly low. You cannot expect people to rush out to get boosted while hammering them with the message that COVID-19 is over.

The active, orchestrated and coordinated denial that SARS-CoV-2 is airborne is an example of how powerful disinformation can be in the hands of health leaders. Guidelines in many countries still do not reflect airborne transmission. No aerosol scientists or engineers who understand the transmission of respiratory viruses and the movement of aerosols were on the WHO committee in the first few years of the pandemic, and their expertise was not sought until years later. Many scientists called for the

WHO to acknowledge airborne transmission, all while the pandemic continued to spiral out of control to the sound of frantic handwashing. In 2024, WHO did release a consultation, which included engineers and aerosol scientists, that proposed changing the terminology for ‘airborne’ or ‘droplet’ transmission. They proposed changing ‘pathogens that transmit through the air’ with a range of other confusing terminology, such as ‘puff cloud’, and no recommendations on how this would change policy or guidelines. I am very glad to have met a handful of amazing researchers during the pandemic who came together over shared concern about the active promotion of disinformation by governments and health agencies. One of these is Professor Trish Greenhalgh, who led a blistering and fearless letter about the WHO’s attempt to change terminology about airborne pathogens. She titled the letter ‘Airborne pathogens: controlling words won’t control transmission’. Acknowledging airborne transmission has direct implications for mask use in public health. Masks, like vaccines, are also under attack after the COVID-19 pandemic. My first anti-mask hate experience was in Brisbane in 2024. I was wearing a mask and trying to find the right building for a meeting. I asked a man on the street, ‘Excuse me. Is this Mary Street?’ He replied, ‘I’m not talking to anyone wearing a mask. You look like a criminal.’ On the same trip, a senior medical colleague said to me, ‘You look like the mafia in your all-black outfit and black mask.’

In North Carolina, the State Senate voted to ban any mask-wearing in public in May 2024, with no allowance for medical exemption for immunocompromised or other vulnerable people. This occurred after various protests around the situation in Gaza, where protesters were allegedly wearing masks. In fact, many States in the US had historical laws against masking crafted to prevent the Ku Klux Klan, who wear hoods. The final legislation that was enacted in North Carolina in June reinstated medical exemptions and the wearing of masks to prevent illness, but it allows law enforcement and property owners to ask people to remove their masks to verify identity. The *Washington Post* reported a woman

> … said a man confronted her for wearing a surgical mask when she walked into an auto service center in the Raleigh area to get an oil change. After she tried to explain that she has Stage 4 breast cancer and a weakened immune system … the man called her a ‘f---ing liberal’ and insisted masks were now illegal. He later coughed on her and said he hoped the cancer would kill her.

Parts of New York followed with mask bans, citing similar security concerns. Yet a research study published in *Nature Scientific Reports* showed that facial recognition software fails more commonly with sunglasses than it does with masks. If facial recognition for security reasons is the reason for banning masks, a ban on sunglasses should also occur. So much for freedom and the 2022 catchcry of ‘you do you’. It seems freedom is restricted to a select group of people conforming to a particular political agenda. Everyone else will be crushed into obedience under this brand of ‘freedom’. In one state, where thousands of people were catching COVID in hospitals, often with dire outcomes, the state government removed historical comparator data for hospitals and set a ‘new normal’ benchmark. Federal actuarial data reporting followed. This means if the COVID numbers worsen, there will be less ability to prove it is worse by comparing it against historical data. In the UK, the government noted poor school attendance and realised a major contributing factor was increased rates of illness in children. Instead of changing their vaccination policy to offer vaccines to kids under five or expanding booster eligibility for older kids, they ran a campaign encouraging parents to send sick kids to school. The posters featured smiling children and captions like ‘This morning he had a runny nose, but look at him now!’. So much for the rights of sick children, their peers, families and teachers to be in a safe environment. In the US, a booster is available to children under five, and a large study showed it significantly reduced the need for emergency and urgent care. The UK, however, is leaving their youngest unvaccinated and forcing sick kids to attend school.

The UK General Medical Council appears to be struggling to uphold good medical practice and sanction doctors who spread disinformation about vaccines. Predictably, vaccination rates are falling and epidemics of

vaccine-preventable diseases like measles are on the rise. Together with a de-medicalisation of health care in the UK, by shifting care from doctors to physician associates, the overall trends do not bode well for that country. In the US, too, it seems there are few repercussions for doctors who wilfully spread disinformation about COVID-19 or vaccines. In Australia, the government was quick to silence and punish doctors in 2021 who rightly raised concerns about the national vaccination strategy or the safety of the AstraZeneca vaccine in younger people, but notorious doctors who spread false information appeared to be rewarded and platformed. Globally, authorities have failed to tackle anti-vaccination disinformation. For example, many mainstream media outlets have run stories suggesting a spate of deaths of young, healthy athletes and celebrities is caused by COVID-19 vaccines. In fact, a 2023 survey of Americans showed that one-third of adults (like the hapless man in the emergency room who refused his tetanus booster) believed that COVID vaccines killed thousands of healthy people. I am certain that in pre-COVID times, governments would have jumped in with counter-campaigns to correct the disinformation. Instead, today we see silence, and conspiracy theories proliferating unchecked. So where is the leadership that will prevent further losses to public health and help us get back on track? Governments have not been forthcoming, probably fearing a COVID-19 backlash that may impact their electability. To date, it has been voluntary groups around the world, consumer advocacy groups and other independent groups like OzSAGE and the John Snow Project that have advocated and promoted public health. Sometimes, individuals in the community have spoken out about vaccine disinformation. In Ireland, a far-right newspaper falsely claimed an 18-year-old boy and others were killed by COVID vaccines. It turned out the boy had not been vaccinated at all, and his mother took action against the newspaper for lying about her son. Other young people featured in the article as being supposedly killed by vaccines had died of causes such as meningitis, a swimming accident and a head injury. Instead of apologising to the mother, the newspaper launched a campaign of online harassment against her.

This anti-vaccination sentiment has filtered to the community. In the winter of 2024, influenza vaccination rates in people 65 and over in Australia dropped to 60 per cent, when 70 per cent was the norm a few years ago. Rates of COVID-19 vaccination in nursing homes are also low. In other countries like the US and the UK, rates of childhood vaccination have also fallen. A well-known doctor in Australia boasted in the media that they did not get any further COVID-19 boosters after their first, citing ‘no need’. Meanwhile, in many countries, vaccine policymaking committees are comprised of ‘experts’ who appear to restrict vaccination wherever they can, especially for children. In the UK in 2023, ahead of their winter, the Joint Committee on Vaccination and Immunisation clawed back influenza and COVID-19 vaccines for people under 65 years. The philosophy is ‘give as little as possible to as few people as possible’, despite clear evidence that even protection against hospitalisation and death wanes over time without a booster, and despite the burden of long COVID being highest in working-age adults. Saving a few pennies now will cost the economy billions in the long run. In the US, which remains one of the few high-income countries to make evidence-based, transparent vaccine recommendations, community anti-vaccination sentiment is rising nonetheless, and vaccination rates are falling. Even among health workers in the US, rates of influenza vaccine have dropped post-pandemic from over 90 per cent to about 80 per cent. This supports my contention that mass, unopposed brainwashing against vaccines post-COVID has affected everyone, health professionals included. The same US survey that found a third of Americans believed COVID vaccines killed thousands of healthy people also found that a quarter thought MMR vaccines caused autism. Alberta, in Canada, appears to have a government not just paralysed by inaction but also sympathetic to the anti-vaccination movement. They moved in 2023 to dismantle the Alberta public health system in a massive restructure, which was seen as retribution for COVID-19 public health interventions.

Returning to pseudo-caveman lifestyles – while cherrypicking the benefits of modern technology, such as electricity, the internet and high-quality medical care – is also a trend in many high-income countries. Part

of this includes a fad for raw food and milk, which will only accelerate the risk of emerging infections. Before the pasteurisation of milk, diseases like TB and brucellosis were spread to humans through contaminated milk. Now, with over 30 per cent of milk samples on supermarket shelves in the US contaminated with H5N1, coupled with the popularity of raw milk consumption, the probability of the genetic reassortment of that virus to transmit efficiently between humans and cause an influenza pandemic is higher than ever before. I have looked at it from many different angles, but I am not optimistic about us being well prepared for the next pandemic.

Leaving aside pandemics, globally, we are also seeing a rise in epidemics of group A streptococcus, TB, mycoplasma, RSV and other infections. Five years later, the anti-vaccine medicos are still blaming lockdowns and the fictitious ‘immunity debt’ for this. Anything they cannot understand or explain must be due to lockdowns, but it is likely a result of the immune dysfunction caused by COVID-19, now the most widespread infection in the world. In most countries, studies of antibodies in the blood show it is likely over 80 to 90 per cent of people have been infected at least once, so even if a small proportion have their immune systems messed up as a result, the population health impact is enormous. Children in countries that deny them vaccination or boosters have the most to lose as they have the greatest life span ahead of them. We are now stuck in a dystopian hell where governments, doctors and mass media have conveyed COVID-19 is trivial, which prevents us from taking collective action to reduce the harms caused by COVID. In some cases, as outlined by Dr Jonathan Howard, the intention seems to deliberately inflict as much infection as possible on children.

Anti-vaccination was a fringe movement prior to the COVID-19 pandemic, but with the enthusiastic support of a section of the medical community and media, it is now very much mainstream. This will leave us in a worse position than we were in 2020, with a large mountain to climb in terms of undoing the brainwashing of the community and the medical profession against vaccines. Much of this, together with the minimisation of COVID-19, is driven by misguided economic theories that disease control

will hamper the economy. Yet vaccines are infinitely cheaper than even one day spent in hospital, and prevention of pneumonia has been proven in multiple studies to be highly cost-effective. Similarly, for COVID-19, inaction will only end up causing a much larger economic cost to society and the government from the resulting burden of chronic disease and disability, as we showed in our research.

The only silver lining is that COVID-19 proved the world could galvanise all of its expertise and pharmaceutical technology to develop vaccines in less than a year. We saw unprecedented events, such as two pharmaceutical giants who had historically been competitors, collaborating and working together to develop a vaccine. We saw agreements between companies and low- to middle-income countries enable vaccine manufacturing domestically in the latter. We are seeing this again during the mpox epidemic in the DRC, with moves to enable the manufacture of mpox vaccines in Africa. The number and variety of COVID-19 vaccine candidates that were available by 2021 was inspiring. The scale and brilliance of the scientific developments, building on decades of past work, was mind-blowing. It also launched mRNA technology on a mass scale, which now opens the door to using this technology more widely in medicine, including for the treatment of cancer. Meanwhile, new developments in vaccines keep rolling in, including RSV vaccines for infants and older adults. Vaccines against EBV, the putative cause of multiple sclerosis, and cytomegalovirus, one of the major causes of congenital birth defects, are also in the pipeline, as are personalised cancer vaccines. I have no doubt that in the next decade, we will see scientific breakthroughs that we cannot even imagine right now. Seizing these advances in science will be harder because of the lack of leadership that allows disinformation and obstacles to be placed in the way of this progress. These scientific breakthroughs will still occur but against a backdrop of self-inflicted loss of disease control and increases in infections, which will set us back decades in life expectancy and health.

What can we do? Action can occur on individual, societal and governmental levels, and by non-government organisations. The major

obstacle is that we now live in a post-truth world of social media, where it is difficult to differentiate fact from fiction. German historian and philosopher Hannah Arendt said:

> The result of a consistent and total substitution of lies for factual truth is not that the lie will now be accepted as truth, and truth be defamed as lie, but that the sense by which we take our bearings in the real world – and the category of truth versus falsehood is among the mental means to this end – is being destroyed.

While Arendt was referring to the effect of propaganda in Nazi Germany, her statement still applies today. The effect, however, is magnified because we are exposed to far more information, and from a far wider range of sources and media (such as deepfakes) than in the 1940s. There are attempts to counter misinformation using AI tools, such as a chatbot called 'DebunkBot', which addresses users' specific concerns, and in a research study reduced belief in conspiracy theories by 20 per cent. However, even these require people to use the tool on a mass scale and engage with the information provided.

Governments can make a difference by using early warning tools for disinformation, which can trigger active health promotion to counter the disinformation. We are developing this as a capability in EPIWATCH. Governments can also collaborate with non-government organisations, such as the collaborations between countries, the Africa CDC and pharmaceutical companies to provide mpox vaccines in heavily affected African countries in 2024. Governments also need to upgrade regulatory processes to ensure there are efficient and faster pathways to treatments and vaccines during a pandemic or health emergency. They also need to manage the procurement of medical supplies carefully. Some countries did this better than others during the COVID-19 pandemic, but Australia has room for improvement. In their new book *Australia's Pandemic Exceptionalism: How we crushed the curve but lost the race*, economists Richard Holden and Steve Hamilton state:

> We put all our vaccine eggs in just two baskets [AstraZeneca and the failed University of Queensland vaccine] … Even if we'd got lucky and both were effective and safe, it was a

> terrible risk to take. Pandemics are times for insurance, not gambling … And while our tax and statistical authorities marshalled their forces to operate much faster and more nimbly to serve the desperate needs of a government facing a once-in-a-century crisis, our medical–regulatory complex repeatedly ignored international evidence and experience, and our political leaders capitulated to their advice.

Holden and Hamilton recommend distributing risk in procurement, ensuring testing at scale is enabled and funded, investing in domestic mRNA manufacturing capability and a major overhaul of the medical–regulatory complex, including the Therapeutic Goods Administration and slow-moving expert committees like ATAGI. They argue that the slow processes and response resulted in more deaths, longer lockdowns and delayed re-opening of society.

Since 2020, we now have mRNA manufacturing capability in Australia, which is a positive step, but our inflexible ‘business as usual’ systems and committees for vaccine approval and recommendations have not changed. Perhaps some guidelines for transparent and low-risk vaccine procurement, crafted in a way that makes it difficult for governments to override them, would be beneficial for future pandemics and avoid costly mistakes. Performance targets for key committees would hold expert advisors to account and reduce poor policy. The restrictive approach to vaccines and antivirals is also a mistake, and cost-effectiveness analyses could inform the best use of these.

We also need better early warning systems for pandemics so we can be prepared sooner and identify concerning epidemics in other countries. Governments tend to think of domestic threats and may not be agile enough to respond to threats outside their borders. We wait and rely on the WHO and other countries to tell us about serious epidemics, but open-source intelligence can get us ahead of this. For example, our EPIWATCH system could have detected a signal of unknown pneumonia in China by mid-November 2019, before it spread to other countries in December that year. Yet no one acted because we did not know until official reporting in January, which was delayed. Initially, the WHO thought the outbreak was not spreading, and they stated there was no evidence it was contagious.

These delays were critical in enabling global spread. For example, if the US or Europe, where spread occurred in late 2019, had obtained an independent early warning, they could have tested people with unusual pneumonia and obtained the genome sequence from patients in their own countries long before January 2020. This would have enabled earlier vaccine development, better preparedness and possibly mitigated health system collapse seen in places like New York, Bergamo and Barcelona.

Most of all, we need political will, global cooperation and an integrated approach to improve community perception of public health and vaccines. These need to be tailored to the context, including cultural and social norms. We need to aspire to the best protection for everyone, rather than the lowest common denominator under the guise of ‘equity’. I have heard numerous vaccine experts, including ones on influential committees, argue we should not give COVID vaccines to children or boosters to adults in high-income countries because low-income countries cannot afford them. True equity means every person in the world has equal access to the best available vaccines. The lessons of the COVID-19 pandemic also need to be seriously considered and changes made in areas that can make a difference – such as procurement, manufacturing and roll-out of vaccines. The speed of getting vaccines into arms has a major impact on flattening the curve and mitigating the impacts of a serious epidemic or pandemic. I am not overly optimistic, however, as there is a significant opposing force of mainstreamed disinformation, including among some political leaders and medical experts. Navigating the modern landscape of vast and contradictory information in search of truth is harder than ever before. Information and communication are key, as well as the recognition that truth itself can be manipulated with the sophisticated digital technology and platforms available today. We must also call out the players, including medical leaders, who use these platforms to undermine public health and vaccines, and find ways to earn back the trust we have lost, including through leadership and role modelling.

Some vaccine-preventable diseases like whooping cough or influenza affect all of us in all countries, while others, like Marburg virus, are

country-specific and may seem remote and irrelevant to others. Yet serious epidemics anywhere in the world matter for us all, and they may only be a plane ride away from our backyard, as we saw with COVID-19. We must ensure we do not slide backwards and lose the gains of the last century that vaccines have gifted us. Ultimately, however, risk perception drives human demand and action, and if a high-fatality pandemic occurred, most people would see the impacts in their own lives, and this would shift the perception of vaccines. A crisis also galvanises key stakeholders, governments and other groups into action, but we don't want to hobble from crisis to crisis without strengthening our preparedness and systems during the quiet times. This includes investing in domestic manufacturing for drugs, vaccines, masks and other essential medical equipment. It also includes transparent vaccine policy backed by publicly disclosed evidence. Strong health promotion is also critical, and ensuring we hear the concerns of the community with empathy and provide a strong counterpoint to the sea of disinformation. We need a return to solid public health principles that ensure vaccines are widely accessible and not restricted for widespread, serious diseases like COVID-19. A new pandemic will occur – the question is when, not if. Lifesaving cancer vaccines will also shift the pendulum towards vaccines, and there is a real prospect of new vaccines for elusive infections like HIV, malaria and EBV, the virus that causes multiple sclerosis. The world may have forgotten iron lungs and half of all children dying of infectious diseases, but medical breakthroughs in vaccinology will continue. Despite the backward slide post-COVID, progress cannot be stopped.

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