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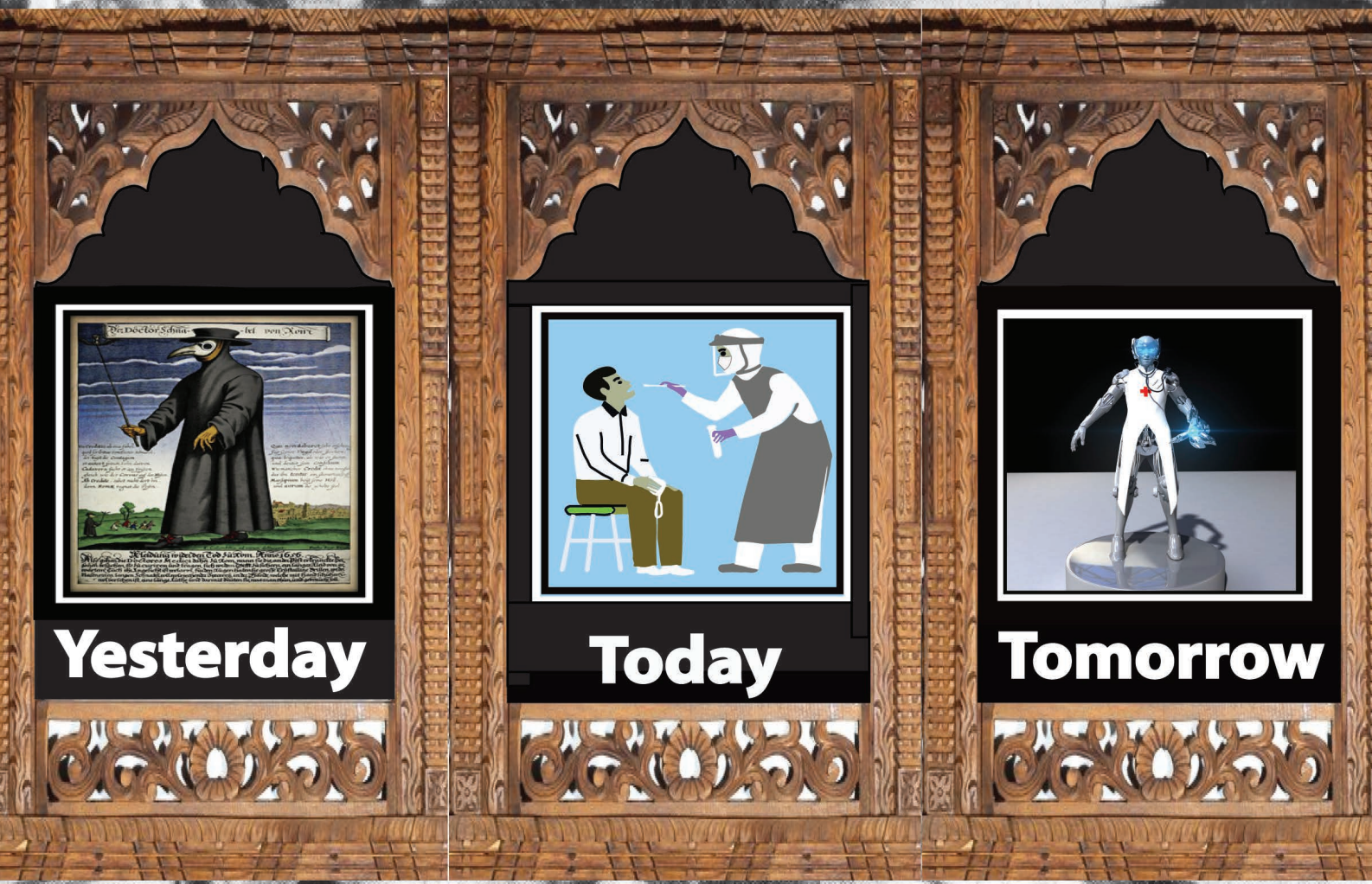
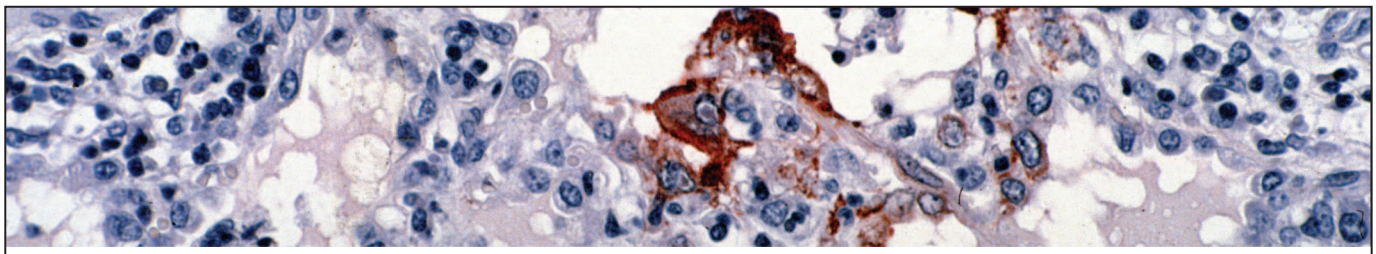


Plagues, Pestilence and Pandemics

plus Hot Topic: COVID-19 therapeutics



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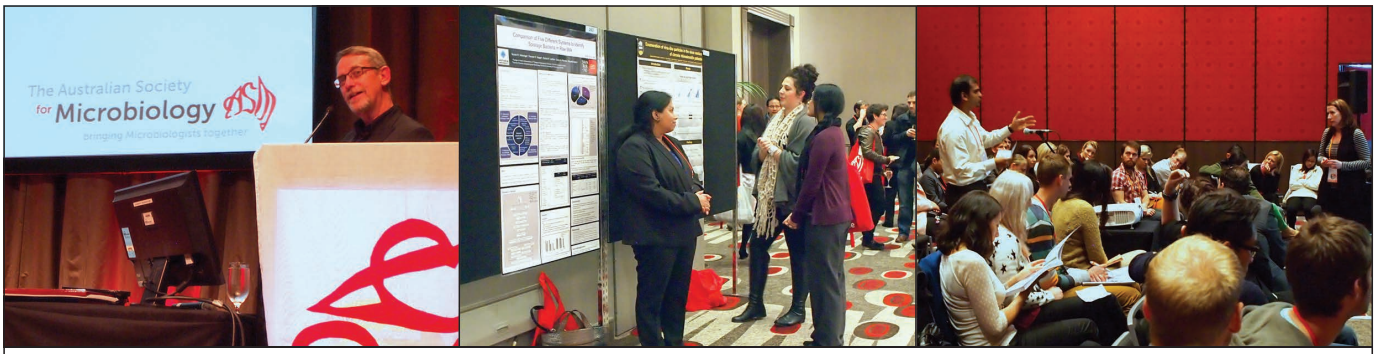

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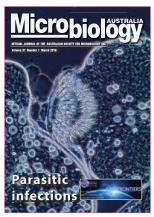

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Contents

Cover image: Cover image designed by Sudip Dhakal. Background: influenza beds at the Exhibition Building in 1919 (Museums Victoria); inserts in Nepalese window: Plague Doctor, 17th century (Paul Fürst), and medical robot, produced by Ashish Basukala (Nav3d Animation Academy).

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Dena Lyras
President of ASM

I hope that this Vertical Transmission finds you and your families, friends and colleagues safe and well. Across Australia, we continue to deal with the COVID-19 pandemic, mostly through the restrictions that have been imposed to prevent transmission of the virus. Thankfully these measures have been highly effective and we have not seen the high case numbers and deaths that we see reported daily in other countries.

One impact of the pandemic for the ASM this year has been the postponement of the Annual Scientific Meeting. We are not alone here – many national and international meetings have been cancelled and efforts are being made to find alternative ways to share our work and ideas and to interact with colleagues. We have made similar efforts – ASM held a very successful 'virtual' EduCon for our Microbiology Educators this year, and has been holding monthly ASM Hour multi-presenter seminars online, as well as other state-based virtual meetings.

Before the pandemic, the ASM had already begun considering ways to make virtual participation available for those who were unable or unwilling to travel to meetings; this crisis has expedited this process. We had discussed making meetings more accessible to a wider set of our members, for instance those from regional areas and those with disabilities, as well as those with caring responsibilities, who find it difficult to travel. Many of our members were also travel fatigued from attending too many meetings and were concerned about the carbon footprints they created by taking international flights.

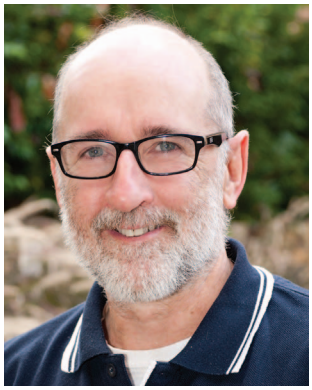
The situation we find ourselves in this year has pushed us to rethink the concept of meetings entirely. One benefit of the changes catalysed by the pandemic is the improvement to online platforms as a way of sharing work and creating virtual meetings. The tools for online conferencing have been rapidly developed and refined this year, and offer us an excellent opportunity to bring new and accessible meeting formats to our broad membership. It is hoped that they will also allow greater participation and be more inclusive of those who find it difficult to travel to meetings. Virtual meetings offer other advantages; for example, submitting questions online through moderated chats can help students or early career staff feel less intimidated and become more engaged, and recordings can be distributed for even greater outreach through 'asynchronous delivery' – a term familiar to our teaching colleagues.

Although online meetings mimic some aspects of conventional meetings, they cannot substitute for the face-to-face interactions that are necessary for forging working relationships and the serendipitous encounters that foster discussions and collaborations. Poster presentations can also fall flat in an online setting.

Many of our members have suggested that they would like the best of both of these options after the threat of this pandemic has passed. Now that the idea of virtual meetings has become acceptable, and the technology has been developed to make them work well, it is possible that the ASM may be able to open up conferences, meetings, workshops and seminars to remote participation. We will take the best of all of these options to serve as many of our members as possible. It is certain that meetings will be very different in the coming years, but we can take advantage of the experiences of 2020.

As always, and to be informed of the changes to our meetings at state and national levels, please visit our website www.theasm.org.au to access information regarding upcoming meetings and awards. Our website showcases content created by our wonderful ASM Communication Ambassadors and I encourage you to read the interesting and entertaining content created by our younger members. You may also like to follow and contribute to ASM on Twitter, @AUSSOCMIC or on Facebook to make sure you keep up with the latest news, trends and developments in Microbiology in Australia and around the world.

Lessons from history

Cheryl Power and Ross Barnard

Approximately 6 months ago, as COVID-19 became the focus of our day-to-day life, it was constantly referred to as unprecedented. In fact, this word has been used to describe almost everything that has subsequently occurred. Unprecedented of course means 'without previous instance, never before known or experienced'. At the same time the general thrust of many headlines in the media was to cast SARS-CoV-2 as a killer virus wreaking havoc on an undeserving and unsuspecting population.

Both these descriptions annoyed us intensely because they completely denied the history of infectious disease as we know it. Our hope is that, after reading this issue of *Microbiology Australia*, you will understand our frustration – if you didn't already share it. The theme of this issue is, as the triptych on the cover declares, *Yesterday, Today and Tomorrow: Plagues, Pestilence and Pandemics*.

To illustrate the power and persistence of infectious disease there are articles on some of the all-time greats: influenza, leprosy, poliomyelitis, tuberculosis and gonorrhoea. There are articles about great scientists, CJ Martin, Pasteur, Burnet and many others who are less well known. They not only contributed to countering these scourges but also helped to build the great institutions, CSL or Commonwealth Serum Laboratories and AAHL as it is affectionately remembered, now renamed ACDP or the Australian Centre for Disease Preparedness. The history of vaccination takes a special place for two reasons – that it is the only way infectious disease has ever been eliminated and that it is so much the current focus for our path back to normality.

There is no doubt that COVID-19 is a huge problem, but humans should not be seen purely as passive players in this or any other microbial drama. Humans have always played an instrumental role, whether knowingly or inadvertently, in the emergence of plagues and pestilence, whether by a failure to control vector populations, or by providing favourable conditions for vector proliferation (for example, rats and mosquitoes), or by providing favourable conditions for the survival and transmission of the microbes themselves. These phenomena accompanied the transition from hunter gatherer mode to sedentary farming, entailing higher human and animal population density and living closely with domesticated wild animals and their microbial boarders. In retrospect it is clear humans have unwittingly taken severe risks. Whether by massing ourselves in mega cities or onboard gigantic cruise ships, we have set the scene for amplification events. And while we have changed, socially and culturally, so have the microbes, more randomly but very effectively.

Theodosius Dobzhansky wrote in 1973 that 'Nothing in biology makes sense except in the light of evolution'. Looking at the current pandemic as an evolutionary event thus gives us the final perspective on our current predicament, a situation that was faced yesterday and that will be faced again tomorrow, albeit with different microbes, but possibly using remarkably similar strategies to those used in times past.

Histories, according to Hannah Arendt (1959), are more than just a record of a chronological sequence of events but rather they are stories that are 'significant objects of reflection and understanding'. By engaging with the past we can learn the lessons of those who came before us and use them to guide our actions today.

History has shown the value of quarantine, and of keeping a distance from disease, whether by physical barriers or behavioural changes. Basic hygiene, good nutrition provided by safe food chains, and clean water supplies, are all vital. Dirty cities needed to be drained and cleaned before infectious disease could be conquered or controlled. These measures are the pillars on which modern medicine, including antivirals, antibiotics and vaccines, developed by armies of committed scientists, can deliver miracles, but only if they are strongly supported and funded by both society and government.

We should never forget the lessons from the past. As Edmund Burke (1765) said, 'In history a great volume is unrolled for our instruction drawing the materials of future wisdom from the past errors and infirmities of mankind'.

Finally, we are greatly indebted to members of Sharon Lewin's team, in the midst of it all, for responding to the challenge to produce an article on COVID-19 Therapeutics for our ongoing Hot Spot.

What history teaches us about vaccines and pandemics

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Abstract. The history of immunisation is full of heroes but also full of villains, and our successes are tempered by tragedies. Despite the urgent need for a vaccine against SARS-CoV-2, we should not neglect the lessons of history. These include ethical issues relating to vaccine safety, such as the possible risks of vaccine-induced enhancement witnessed with dengue vaccine in the Philippines, and how our decisions may be represented by the anti-vaxx movement.

Nature is the world's greatest terrorist[1]. Any doubt about the veracity of this pithy aphorism, shamelessly purloined from an inspirational lecture by Nobel laureate Sir Peter Doherty, has been put to rest by COVID-19[2,3], a pandemic better understood through an historical lens of vaccines and pandemics.

The Greek historian Thucydides, who survived catching 'the plague of Athens' during the Peloponnesian War 2400 years ago, described the devastating epidemic of what may have been typhus or bubonic plague which killed 100 000 Athenians and led to the defeat of Athens by Sparta.[1] Thucydides also recognised that survivors like himself were protected against catching the disease again, the first recorded description of the concept of immunity.[1]

Smallpox has been recognised as a human scourge since Egyptian times[4]. Smallpox devastated Indigenous populations in Central and South America and in Australia (where a horrific 1789 outbreak among the Aboriginal people living around Sydney Harbour may have been deliberately introduced by the First Fleet[5]). Smallpox survivors were often blinded or suffered terrible facial scarring. In 1950, smallpox infected 50 million people and killed 10 million[1,4]. By 1978, immunisation had eradicated smallpox, undoubtedly one of humanity's greatest ever achievements.

Variolation, inoculation of smallpox scabs nasally using a blowpipe in 15th century China, or dermally elsewhere in India, Asia, Africa and Europe, is the oldest known human form of immunisation[6]. Variolation was introduced into the UK from Turkey by Lady Mary Wortley Montague, feminist wife of the British Ambassador to Turkey. However, variolation could cause smallpox, not infrequently killing the recipient[6].

The history of vaccines is full of fascinating figures, often with moral flaws, because we are all only human. Edward Jenner was a Gloucestershire country general practitioner. He had prestige as a Fellow of the Royal Society awarded, not for his work on smallpox, but for describing the groove in cuckoo chicks' back used to evict other birds' eggs from their nest. Jenner himself was variolated aged 8. Jenner variolated a large number of people in his parish. Some developed mild smallpox, some severe, but a small number developed no rash. From his records, Jenner noted all those who developed no rash had previously had cowpox. Some were milkmaids or had caught cowpox from milkmaids (Figure 1). Jenner knew the folklore that milkmaids were characteristically unmarked by smallpox scars. In a traditional poem, a soldier courts a milkmaid:

> 'Where are you going to, my pretty maid?'
>
> 'I'm going to market, sir' she said.
>
> 'What is your fortune, my pretty maid?'
>
> 'My face is my fortune, sir', she said.
>
> 'Then I cannot marry you, my pretty maid'.
>
> 'Nobody asked you, sir' she said.

Good for her.

We should hesitate to judge erstwhile experiments by modern standards, but Jenner's seminal experiment is ethically challenging. In 1796, Jenner famously lanced cowpox vesicles on the hand of milkmaid Sarah Nelmes, then injected cowpox into two small cuts he made in the arm of 8-year-old James Phipps (the son of Jenner's labourer-gardener). Six weeks later, Jenner inoculated

Figure 1. A milk maid shows her cowpoxed hand to a physician, while a farmer or surgeon offers to a dandy inoculation with cowpox that he has taken from a cow. Coloured etching, c.1800 (Wellcome Library, London).

James with material taken from a smallpox victim. Thankfully James survived this challenge. . .and the more than 20 subsequent times Jenner injected poor James with smallpox material. Jenner was a cautious man, although perhaps more concerned about scientific proof than poor James' welfare.

Jenner presented a paper on James Phipps to the Royal Society in 1798[1]. Within two years Jenner's vaccine was being used around the world. Catherine the Great named the first vaccinated Russian child *Vaccinov*; the state paid for his education. There was vigorous opposition from anti-immunisation movements, particularly after 1853 when the British Government questionably made infant smallpox immunisation compulsory. In 1885, 80 000 people marched through Leicester carrying banners, an effigy of Jenner and a child's coffin. Opposition in North America was also fierce but more litigious. However, as records and public health improved, it became clear that smallpox vaccine worked. In 1967, the World Health Organization (WHO) introduced an ambitious new Intensified Smallpox Eradication Programme trying to eliminate smallpox. Major contributors included Donald Ainslie (DA) Henderson (1928–2016) and the late great Australian virologist Sir Frank Fenner (1914–2010)[1,7]. That year, 1967, an estimated 10–15 million people globally contracted smallpox and two million died. Eleven years later, none did.

Louis Pasteur, another giant of vaccines, was also a country boy, one who preferred fishing and drawing to study[1,8]. Louis witnessed wolf attacks in rural France, and his playmates' agonised screams as the blacksmith cauterised their wounds. Pasteur swore he would prevent rabies. He would succeed, but took a strange path, becoming Professor of Chemistry and then

Figure 2. Pasteur inoculating a sheep against anthrax (Wellcome Library, London).

Professor of Physics at the University of Strasbourg, but never a doctor or microbiologist.

Pasteur was the first scientist to describe the phenomenon of attenuation, initially through serendipity. Chicken cholera could wipe out a flock in 3 days. Pasteur identified and cultured the cholera bacillus. Inoculated bacillus killed chickens rapidly. Pasteur left Paris one summer to escape the heat, leaving his cultures on the laboratory shelf. On his return he found that if he inoculated chickens with the stored cultures they stayed healthy. If he then challenged them with fresh bacillus they survived, whereas the fresh bacillus was fatal to naive chickens. Attenuated bacillus protected them. Not famed for false modesty, Pasteur said: 'In the fields of observation, chance favours only the prepared mind'. Recognising that attenuation had parallels with Jenner's earlier use of cowpox (*vacca* is Latin for cow), Pasteur coined the name 'vaccination' in honour of Jenner.

Pasteur developed a vaccine against anthrax. In 1882, he accepted a challenge to prove its efficacy, conducting a remarkable, controlled field trial. Pasteur gave 25 sheep his anthrax vaccine; 25 controls had no vaccine. Weeks later he challenged them by injecting live anthrax on a Parisian hillside watched by a huge crowd (Figure 2). The Press including the London Times reported daily. After two days, all 25 controls died and all 25 vaccinated sheep survived. In the next ten years, 3 500 000 sheep and 500 000 cattle were vaccinated against anthrax, with over 99% survival. Mass immunisation was born.

In 1888, Pasteur sent his nephew Dr Adrien Loir by steamer to Australia to make and sell anthrax vaccine [the word nepotism

derives from the Italian *nipotini* for nephews, referring to the Popes who called their illegitimate sons their 'nephews']. Loir successfully repeated Pasteur's field trial on 39 sheep and four cows in Junee Junction in country NSW. Incidentally, Loir also found time to have a fling with French actor Sarah Bernhardt who was touring Australia[1].

Pasteur and Dr Émile Roux attenuated rabies virus by repeated passage through preparations of rabbit spinal cord. Their live attenuated rabies vaccine was safe and effective in dogs (although a posthumous analysis of Pasteur's notebooks showed he 'exaggerated' the number of dogs tested)[1,9]. In 1885, Roux immunised 9-year-old Joseph Meister, bitten 14 times by a rabid dog. Joseph survived and became caretaker at the Pasteur Institute. Pasteur was sometimes economical with scientific truth, and secretly used the work of other colleagues like Émile Roux without acknowledgement. But Louis Pasteur was a genius; we owe him as great a debt as we do to Edward Jenner for the development of the vaccines we use today.

The 20th century was the golden age of immunisation[1]. Microbiologists led the way. In 1884, Klebs and Löffler described *Corynebacterium diphtheriae*; in 1888, Émile Roux and Alexandre Yersin showed that a filtrate of *C. diphtheriae* caused diphtheria-like disease when injected into laboratory animals. Inactivating this diphtheria toxin led to diphtheria toxoid vaccine. The first human diphtheria toxoid vaccine was developed in 1923, the first tetanus toxoid vaccine just a year later. Routine childhood immunisation started in the early 1940s in Australia using diphtheria and tetanus toxoid vaccines (DT). In 1949, they were combined with a whole-cell pertussis vaccine made using killed *Bordetella* pertussis, to make DTP, the 'triple vaccine'[1].

The history of polio vaccine development is a book of its own. Polioviruses caused fatal or crippling infections in children and young adults (Figure 3). In the USA, two Jewish refugees Albert Sabin and Jonas Salk competed to develop live oral (OPV) and killed injected vaccines (IPV), respectively. US President Franklin Delano Roosevelt, permanently wheelchair-bound after contracting polio as a young father, started the March of Dimes to fund vaccine development. The March of Dimes funded a successful trial of IPV involving two million 'Polio Pioneer' children. In 1955, four US companies gained the tender to manufacture Salk's killed vaccine. One of them, a small family-based Californian firm, Cutter Laboratories, did not inactivate poliovirus effectively. Over 200 000 children received the Cutter vaccine, 40 000 developed polio, 200 were paralysed permanently and

Figure 3. 'Sad inheritance' by Joaquin Sorolla of Valencia, 1899 shows children crippled by poliomyelitis (Wikimedia Commons).

10 died[1,10]. Despite the 'Cutter Incident', polio was so feared that the IPV programme soon resumed. Meanwhile the USSR adopted Sabin's OPV. OPV became the main vaccine used in developing countries, with such success that paralytic polio cases fell from 350 000 globally in 1988 to 33 in 2018[1].

Anti-vaxxers say vaccines can cause cancer. On the contrary, hepatitis B vaccine prevents liver cancer, while human papillomavirus vaccine (HPV), a novel virus-like particle developed by Ian Frazer and Jian Zhou at the University of Queensland, prevents cervical cancer[11].

We are fortunate to live in a golden age of immunisation. Australian children are routinely immunised against 13 major infections. Mortality and morbidity in the elderly has been reduced with vaccines against influenza, pneumococcus and zoster. Vaccines are available to protect travellers. We are privileged to be so well protected against diseases that ravaged our ancestors.

The urgent need for a vaccine against SARS-CoV-2 should not lead us to neglect the lessons of history about vaccine safety, such as the possible risks of vaccine-induced enhancement witnessed with dengue vaccine in the Philippines[12]. Nor should we neglect our ethical obligation to distribute any SARS-CoV-2 vaccine as equitably as possible, recognising that the poorest people of the world are those at greatest risk from COVID-19 with the fewest resources to treat infection.

Conflicts of interest

The author declares no conflicts of interest.

Acknowledgements

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Biography

Professor David Isaacs is a paediatric infectious disease specialist at the Children's Hospital at Westmead and the University of Sydney. David has an identical twin brother, Stephen, who is a child psychiatrist. They went to different schools and once swapped schools for a day. David trained in London, Sydney and Oxford, moving permanently to Sydney in 1989 to head a Department of Immunology and Infectious Diseases at the Children's Hospital. He was the only member of the Department. He loves writing and has written letters to his twin every week for 30 years and editorials for the *Journal of Paediatrics and Child Health* every month for 10 years. He is the author of *Defeating the Ministers of Death. The Compelling History of Vaccination*, reviewed in this issue.

The puzzle of plague transmission

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Abstract. Bubonic plague is among the most feared diseases in human history, not only because of its death toll but also for its consequential impact on the way of life and economic endeavour of human society. Every few hundred years the advance of a pandemic has raised impotent fear, until the early 20th century when microbiological research solved the mystery of how it is transmitted to its victims, opening the way to protective measures.

History of bubonic plague

Recent archaeological evidence has pushed the existence of bubonic plague back to about 3000 BC, at a Neolithic burial site in Sweden[1]. More recent and well recorded evidence of the devastating impact of plague includes the sixth century pandemic that came from the East to hasten the end of the Roman Empire; the 14th century pandemic that travelled the Silk Road from China to devastate the people and economy of Europe in wave after wave of infection; Plague advanced again across Europe in the 17th century when infection was believed to come from foul air.

Of special interest today is the pandemic that came from China's Yunnan province in the late 19th century, a time when modern scientific research was homing in on the bacterial source of many diseases. This pandemic reached Hong Kong in 1894 and spread to the world along shipping routes. However, the popular medieval belief that the disease was contagious and was carried in bad air had not changed much. A decade of scientific work had identified rats as carriers of plague, but bacteriologists held a variety of conflicting beliefs about how it might be carried to humans.

Alexandre Yersin of the Pasteur Institute discovered the plague bacillus in rats in 1894[a]. It was initially named *Pasteurella pestis*, and not renamed *Yersinia pestis* until 1944. Yersin demonstrated that plague bacilli were present in both rats and humans that had died from the disease, but the means of its transmission across the last link in the rat-flea-man chain remained a mystery. The idea of such a link was passionately rejected by advanced societies who could not accept that the insignificant flea, carried by animals, could be a carrier of plague to humans. Epidemiological studies had, however, noted that the infection of humans seemed to be related to the accessibility of dwellings to rats.

Sydney's bubonic plague

John Ashburton Thompson, an epidemiologist and President of the NSW Board of Health, kept abreast of the southward movement from Hong Kong of plague outbreaks and prepared for its arrival in Sydney. On 19 January 1900 the first reported case, a wharf carter, caused panic because it was believed, even by many in the medical profession that bubonic plague, like the rare pneumonic variety, could pass from person to person and would therefore lead to widespread contagion. The terrified Sydney community readily accepted the strict public health measures arranged by Thompson: quarantine of exposed individuals; catching of rats and demolition of rat-infested areas; the disinfection of victims' houses; doctors' visits with kits to prepare cultures from the pus of the buboes on victims and to dispense an unproved vaccine of doubtful benefit. Public health measures

[a]Kitasato Shibasaburo's discovery of the bacillus at about the same time led to a long dispute over who was first.

seemed to have ended Sydney's epidemic by September 1900, after it had infected 303 people, of whom 103 died[2].

Thompson's epidemiological examination of the circumstances of each case demonstrated the abundance of plague-affected fleas on rats, and confirmed that the disease was not transmitted by its human victims to others. He also confirmed, on epidemiological grounds, that the flea was the agent of transmission[3]. In the laboratory his assistant, Frank Tidswell, Australia's first native-born microbiologist, identified the bacillus in plague rat fleas *(Xenopsylla cheopis)* and confirmed earlier work that showed that crushed fleas from a diseased rat transmitted plague when injected into mice[4]. In Sydney's second but smaller outbreak of bubonic plague in 1902 he attempted to convey plague from rat to rat via fleas but the outbreak ended in June, cutting off the supply of specimens, before he could complete the task[5].

Thompson and Tidswell had arrived at a plausible theory on the etiology of plague, but there was still no evidence as to how the flea transmitted the plague bacillus to its victims.

Lister Institute and plague in India

Since its arrival in 1896 plague in India had spread at an alarming rate, killing 80% of the people it infected. In September 1904 the British Government's India Office asked the Lister Institute for help and Director Charles Martin accepted the challenge. A Commission for the Investigation of Plague in India was appointed, led by Martin, who had previously taught medical sciences at the Universities of Sydney and Melbourne.

Martin chose districts of Bombay (now Mumbai) for investigation, and arranged the organisation of the project with Indian officials. From October 1905 to September 1906 over 100 000 rats were caught and examined, 15% found to be infected with plague. The circumstances of over 10 000 humans who had died from plague in that period were written up. The Indian Government, having recognised the calibre of the Lister's work, appointed its key scientists to take charge of the project in 1906. Laboratory experiments explored the transmission of plague from rats to domestic animals, and the infectivity of human housing conditions. Studies also extended to two isolated villages in the Punjab to find out how plague spread over distances. The Plague Commission's reports provided a mass of data on the incidence and transmission of plague, with recommendations for its management. However, it was unable to reach a conclusion on the question of how plague was transmitted by fleas to its victims.

Back in London Martin's first priority was to deal with the refusal of British doctors and plague experts to accept that fleas bite humans. Hundreds of experiments using Lister Institute volunteers, who exposed their arms to different species of healthy fleas, starved for up to 14 days, showed that they do. He concluded the doubters were ignorant of 'the variety and distribution of fleas' in the world so were relying on 'conclusions drawn from too meagre experimentation'[6].

Solving the puzzle of transmission

With Arthur Bacot, a self-educated entomologist, Martin set out to discover how infected fleas transmitted plague bacilli to humans. Of approximately six possible candidates (Chrystos Lynteris more recently investigated another theory[7]) there were two credible ways: by the rat rubbing flea-faeces into recent flea bites on the victim; or infection by the flea in the act of sucking blood from the victim. They rejected the first of these on the grounds that flea faeces 'do not as a rule contain many bacilli, and soon dry up', and bacilli that have passed through the flea gut do not have 'a high degree of virulence'. They then turned to the remaining possibility[8].

A series of experiments showed that plague can be conveyed to another animal during the act of an infected flea's feeding, but only sometimes, even when many opportunities were made available for the flea to feed on its victim. However, careful observation through a hand lens showed that some feeding fleas had no pink streak of rat blood: despite sucking strongly and persistently, no blood was entering their stomachs.

This chance observation spurred them on, redoubling their efforts at delicate flea dissection. They needed to get a sequential understanding of the growth of plague bacilli in the flea, and how it impacted on the workings of the flea's alimentary canal, in particular the pumping mechanism that sucked flea-blood along its oesophagus, pushing it through a one-way valve (proventriculus) into the stomach.

After many flea dissections Martin and Bacot acquired a succession of infected specimens. This showed, two days after feeding on an infected rat, blood in the flea's stomach contained minute brown specks of plague bacilli, the first of four stages illustrated in Figure 1. At Stage 3 in Figure 1 the gelatinous mass of bacilli led to failure of the one-way valve, allowing a plug of bacilli culture to extend up the oesophagus, stopping fresh rat blood from entering the flea's stomach despite continued efforts at sucking (Stage 4 in Figure 1). At any momentary pause in sucking the elastic recoil of the oesophageal wall regurgitates blood back into

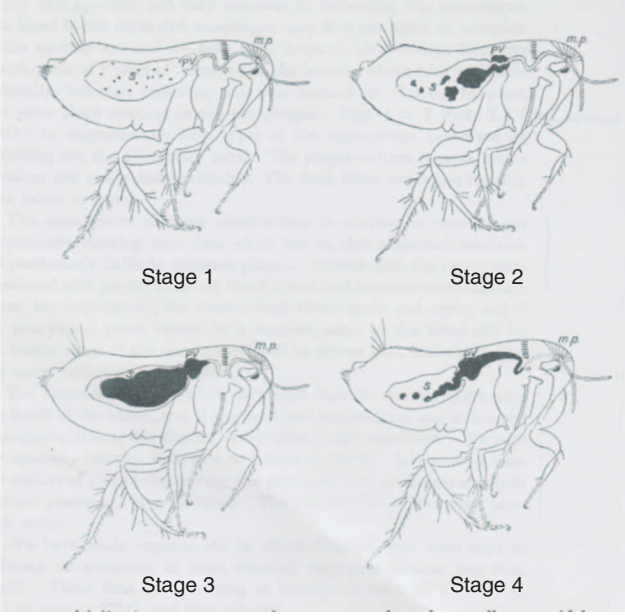

Figure 1. Stages in growth of plague bacilli in the flea.

the wound, carrying with it plague bacilli[8]. They found that two species of rat flea, *Xenopsylla cheopis* and *Ceratophyllus fasciitis* could transmit plague during the act of sucking, and were probably responsible for all of the infections obtained by experiment.

Conclusions

Martin and Bacot's step by step persistence was typical of Martin's research methodology, making him an 'Unstoppable Plugger' in the eyes of his students at Melbourne University. This, combined with his inspirational enjoyment of the 'game' of research, gave him an aura known in medical circles as 'The Martin Spirit' (reviewed in [9]).

Martin and Bacot's demonstration of how bubonic plague was transmitted to its victim encouraged public health authorities to promote the rat-proofing of houses. However, this was rarely possible for people in the developing world, where bubonic plague remains regionally endemic. Despite a century of work on vaccines, no long-lasting one seems yet to be available. However, medical protection, in support of intravenous fluids and respiratory aid, did come in mid-century in the form of antibiotics[10].

Conflicts of interest

The authors declare no conflicts of interest.

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Biographies

Patricia Morison took a history major at the University of Western Australia. She acquired an interest in medical affairs when working in public health in Canberra and London. While tutoring at the Australian National University she contributed a number of entries to the *Australian Dictionary of Biography* in the field of medical science. As an independent scholar in this field her books are *J T Wilson and the Fraternity of Duckmaloi* (1997) and *The Martin Spirit: Charles James Martin and the Foundation of Biological Science in Australia* (2019).

Ian Morison, civil engineer and town planner, was transport planner for Canberra with the National Capital Development Commission, before entering the Commonwealth Public Service. In retirement he has acted as a research assistant to Patricia.

A history of human quarantine in Australia: settlement to 1980

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Abstract. Quarantine has been widely used for infection control in Australia since the time of settlement by Europeans. The history of human quarantine stations in Australia is discussed briefly here.

During the plague (black death) of the 14th century various Italian states set out rules to protect their subjects. The Duke of Lombardy ordered that no person should be allowed to enter his kingdom from any infected place under the penalty of the yoke[1], thus beginning the practice of quarantine.

Before the development of modern medicine, infectious diseases posed a major public health threat. The only means of protecting communities from outbreaks of infectious diseases such as typhus fever, cholera and smallpox was by isolating sufferers and those with whom they had been in contact[1].

The first definite step towards the differentiation of aetiological factors was the differentiation between typhus and enteric fevers (particularly typhoid fever). The bacteria involved are *Salmonella* Typhi causing typhoid and *Rickettsiae* causing typhus. This differentiation of typhus from typhoid was not adopted in official nosology in Australia until 1869[2]. Prior to 1869, typhus was used to describe both fevers.

In 1825 Britain passed comprehensive laws to protect the people against such diseases as plague, cholera, and yellow fever. The British Quarantine Act shaped early Australian quarantine principles. The first Quarantine Act passed in 1832 in New South Wales was to protect the health of the new colony.

The gold discoveries of the early 1850s and the consequent mass migration forced authorities to take more strenuous action to protect public health. With the opening of the Suez Canal in 1869, passage from Europe to Australia became a shorter journey, thus putting at risk the country's isolation from disease. Typhus/typhoid and smallpox were common on immigrant ships and each Colony brought in legislation over a number of years in an attempt to control the spread of disease. In 1908 the Commonwealth Department of Health took over the responsibility for all quarantine in Australia[1] (Commonwealth Quarantine Act 1908).

In 1918–19 a serious attempt was made to protect Australia from pandemic influenza by quarantine, and the disease was excluded for a few months. When it did arrive, early 1919, the cases were less severe and the outbreak less extensive than in countries in which the disease had arrived during the 'first wave in 1918'[3].

A new Department of Health was created in 1921. The Director of Quarantine, John Howard Lidgett Cumpston became Director-General of Health[3].

Methods of quarantine have evolved to meet the needs of the current society. Factors such as infection control, antibiotics, clean water, sewage control, and vaccination have led to much greater control of infectious diseases in the community. Many hospitals have their own quarantine facilities and recently hotels have been used for quarantine. However, the same principles of quarantine, relevant in the past, are still relevant in 2020 COVID-19 pandemic.

New South Wales

In February 1833, North Head on Port Jackson near the Sydney settlement was reserved for quarantine purposes. In fact, it was first used in 1828 for the landing of convicts and guards from the ship *Bussorah Merchant* on which there had been a smallpox outbreak during the voyage. Work on the construction of a quarantine station commenced in October 1837[4]. Thus, the first permanent Australian quarantine station was established at North Head. It closed in 1984[4]. Non-compliance with the system of self-reporting led to the passage of the Quarantine Act in 1832, which made it mandatory for all ships to fully disclose diseases and authorised the establishment of places for the purpose of

quarantine[4]. The growing number of commercial vessels entering Port Jackson from the 1830s, together with large-scale assisted immigration, made quarantine by proclamation increasingly difficult to enforce. Between 1837 and 1840 some 30 000 free immigrants arrived in NSW.

Victoria

When the boat *Glen Huntley* entered Hobson's Bay on 17 April 1840 flying the yellow flag, indicating contagion on board, port authorities ordered it to anchor off Red Bluff (now Point Ormond). This was the site of the first quarantine station in Victoria.

The Point Nepean Quarantine Station, established in 1852, was the major place for quarantine services until 1979. It was closed in 1980. This site was used by the army as Officer Cadet School from 1952–85 and as the School of Health from 1985–98[1].

In 1889 Dan Astley Gresswell was appointed medical inspector of new Victorian Board of Public Health and in 1896 he initiated and chaired the first of the intercolonial quarantine conferences.

Influenza first appeared in Australian troops in France in 1918. Although widespread, it was initially mild, but when it recurred in October it was in a much more severe form. The second wave was due to reach Australia, and did in fact reach her nearest neighbours during the first stages of the repatriation of the Australian Imperial Forces. Cumpston, the Australian Director of Quarantine, decided to exclude the disease from Australia by quarantine. From 1918 to April 1919 the quarantine service dealt with 149 uninfected and 174 infected vessels. Pandemic influenza occurred in some of the ships detained in quarantine, but for some months there was no escape from them to the shore population. When influenza did occur in Melbourne in January 1919, and subsequently in all other states it was milder than the disease experienced elsewhere in the world[3].

Tasmania

As a result of the first all-colony conference on public health in Sydney in 1884, Tasmanian action resulted in the establishment of a quarantine station at Barnes Bay, Bruny Island[5]. The most intensive and significant usage of the Barnes Bay Station was during and after World War 1, first, as an internment camp for 'enemy aliens' in 1914, and second, as a quarantine station for returning service personnel and travellers during the world influenza pandemic of 1917–19[5]. By October 1939 the quarantine station was not required and eventually the Barnes Bay quarantine site was abandoned as a human quarantine station.

South Australia

The establishment of a quarantine station on Torrens Island was first proposed in 1850 and its location at the mouth of Adelaide's Port River isolated from the main settlement made it an ideal location. Torrens Island officially became a quarantine station in 1879 and was used to quarantine passengers from the 1880s to the 1960s[6]. Since European settlement in Adelaide in 1836 it has been used for a number of purposes: a quarantine station, an internment camp, a power station, a protected areas and for military use.

Western Australia

Woodman Point, on a headland located in Munster (South Fremantle) was being used for the quarantining of people and of cargo as far back as the 1830s. However, it was not until 1885 that a tender for a quarantine station at Woodman Point was agreed on and the first building was completed in 1886. The facility continued to be used as a quarantine station until about 1979 when it closed[7].

Queensland

There were no human quarantine facilities at Moreton Bay during the penal era of 1824–42 as all immigration came via Sydney. Following the opening of the district to free settlement in February 1842, a quarantine station was established at Dunwich on North Stradbroke Island, a site of the former goods transfer depot established by convicts in the late 1820s. From 1864, Dunwich served as both quarantine station and benevolent asylum. The quarantine station was relocated briefly to St Helena Island in Moreton Bay in 1866–67 but was soon returned to Dunwich. From 1874–1915 Peel Island in Moreton Bay served as Brisbane's human quarantine station. Between 1873 and 1896 many ships were quarantined at Peel Island[8].

In the 1880s a quarantine station was established at West Point on Magnetic Island. Because of the severe cyclones, *Sigma* in 1896 and *Leonta* in 1903, and owing to a lack of water and the difficulty of the distance from the mainland, the government decided to build an alternative station on the mainland. This station was used particularly during the influenza epidemic in 1919 and during sporadic outbreaks of bubonic plague that occurred until the early 1920s.

A new quarantine station was established at Pallarenda in 1915 and closed in the 1970s[9]. The Lytton Quarantine Station[8] was established in 1913–14, to accommodate newly arrived immigrants and persons considered to be at risk of causing infection to the general public. Situated at an isolated location at the mouth of the Brisbane River. It is important as part of a continuum of sites in and adjacent to Moreton Bay and was used for

quarantine purposes from 1844. By the late 1980s the Lytton facility had closed completely.

Northern Territory

Channel Island in Darwin Harbor is connected to the mainland by a bridge. A quarantine station was erected on Channel Island in 1914. This site was used during the influenza pandemic of 1918–19. In 1930 a new quarantine station was opened at East Arm (on the mainland) and the Channel Island site was converted into a Leprosarium.

Conclusion

Increased human population, human travel, humans taking over animal habitats and climate change have all contributed to the speed at which micro-organisms spread around the world via humans, animals and foodstuffs. The issue of quarantine is just as relevant today as it was in the past. The past informs the future.

Conflicts of interest

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Biography

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The 1918 Spanish influenza pandemic: *plus ça change, plus c'est la même chose*

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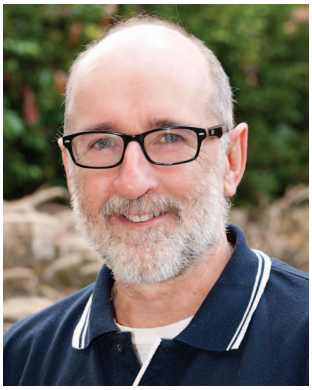

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Abstract. Towards the end of world war one, the world faced a pandemic, caused not by smallpox or bubonic plague, but by an influenza A virus. The 1918–19 influenza pandemic was possibly the worst single natural disaster of all time, infecting an estimated 500 million people, or one third of the world population and killing between 20 and 100 million people in just over one year. The impact of the virus may have influenced the outcome of the first world war

and killed more people than the war itself. The pandemic resulted in global economic disruption. It was a stimulus to establishment of local vaccine production in Australia. Those cities that removed public health restrictions too early experienced a second wave of infections. Unfortunately, it seems that the lessons of infection control and epidemic preparedness must be relearnt in every generation and for each new epidemic.

Introduction

In 1917 an influenza virus causing mild symptoms appeared in the USA. Due to the movement of soldiers from the USA to the European front in 1917 and 1918 the virus spread rapidly, causing numerous mild epidemics amongst the troops in March of 1918. The 1918–19 pandemic was subsequently called 'Spanish influenza', not because it originated in Spain, but because Spain was neutral during the war and allowed the press to report cases of infection, whereas such information was censored elsewhere. In September to October of 1918 a second wave of infection spread rapidly across the world causing a more severe clinical disease with symptoms including cyanosis, pulmonary oedema, pulmonary haemorrhage, aches, fever, coughing and an overwhelming weariness[1]. A third wave of infection occurred in the winter and spring of 1919, also with severe clinical signs. The disease in the second and third waves had an unusually high morbidity and mortality, with case fatality rates of more than 2.5 percent, compared with less than 0.1 percent in the first wave and normal seasonal influenza epidemics. The viruses of the second and third waves caused a higher case-fatality rate among 20–40-year-old people than in other age groups[2–4]. This is in stark contrast to normal seasonal influenza in which case-fatality rates are highest in the very young and very old. It is well documented that, in those pre-antibiotic times, many who died of 'influenza' died with, or because of secondary bacterial pneumonia[2,4,5]. So great was the impact of the virus that one German general blamed his country's defeat in world war one, not on the 1917 influx of troops from the USA, but on the effects of the pandemic on his soldiers[6]. As a single cause of death, the pandemic may have been responsible for more deaths than the first world war (17 million military and civilian deaths), the second world war (60 million military and civilian deaths), and possibly the combined total of both[4].

Origins of the virus

It was reported that influenza pneumonia mortality cases increased sharply in some US cities and states in December 1915 and January 1916, which may or may not have been related to the 1918–19 pandemic. One theory is that the 1918–19 pandemic influenza virus originated as early as December 1917 in the Midwest of the USA[2]. Although it is likely that the exact geographical source will never be established conclusively, Camp Funston, a US army training camp in Kansas, was the location of the first reported outbreak of influenza in the USA[2]. Outbreaks of influenza were also reported in several European countries before the first wave in the April and May of 1918 and later in June and July in Asia, before spreading to the Pacific and South America and then the rest of the world[2]. In less than one year a more virulent virus had emerged and was transported around the world by soldiers demobilised after the war[4].

The 1957 H2N2 and 1968 H3N2 pandemic influenza viruses arose from reassortment between human and avian viruses[2,3]. The 2009 H1N1 pandemic virus was a reassortant between human, swine and avian influenza viruses[2]. Taubenberger *et al*.[7] initially hypothesised that the 1918–19 H1N1 pandemic virus was introduced directly into the human population from an avian host (without reassortment) as the eight gene segments appeared to have evolved in the same, as yet unidentified, host. However, subsequent analyses by two independent groups[8,9] contested this, arguing that the phylogenies were more characteristic of those that would result from the presence of an intermediate host. It is also possible that the 1918–19 pandemic virus was a reassortant between avian, swine and human viruses prior to 1918, although other evidence weighs against this. The gene sequences are distinct from other avian and mammalian influenza viruses, but without sequence data from before 1918 we may never identify the host. What is clear is that the viruses from the second and third waves were more virulent.

Seasonal influenza epidemics usually occur once per year, in late winter in temperate climates, or twice a year in the tropics, so the occurrence of three waves of the 1918–19 virus within one year is highly unusual. The first wave began in the northern hemisphere spring of 1918 and persisted into summer (March–August). The majority of morbidity and mortality associated with the first wave occurred in young adults between 15 and 34 years of age. The disease was typically mild and the fatality rate was 0.65 people per thousand. Fatalities in young soldiers may have been a consequence of overcrowding and poor general health on the European battle fields (dysentery was rife)[10] and the lack of treatments for secondary bacterial infections associated with influenza cases. Many soldiers were affected by gas attacks, which may have exacerbated the effects of influenza infection.

Infections were recorded throughout most of the world, although South America and Australia initially remained free[1,2].

In summer of 1918 the number of reported cases of influenza began to decrease and it was hoped that the pandemic would be over by August. However, it is considered likely that a new strain of virus appeared, containing either mutations or a reassortment of genes, which could kill healthy young adults within days of infection. This virus was extremely virulent, with infected people showing a high fever, cyanosis and pulmonary oedema. In 5% of the cases death occurred within 3 days of clinical signs appearing although in most cases the time between symptoms and death was 7–10 days[1,2]. Between August and November large numbers of troops were being moved around the world, initially to the battlefields and later, home from the battlefields. During this period the second wave rapidly spread to the rest of the world and caused the majority of the recorded morbidities and mortalities. The third wave began in early 1919, but was generally less virulent and did not affect every country. It is thought that by this time much of the population was immune, hence reducing the transmission of the virus. In some countries the pandemic persisted, and was still claiming lives until 1920, before finally disappearing[3,4,7].

Although most of those who died during the 1918–19 pandemic died from secondary bacterial infections, for which antibiotics were not available[3,4], many others died in less than 5 days, showing clinical signs of cyanosis, pulmonary haemorrhage or pulmonary oedema. Necropsy findings showed that pathology was restricted to the respiratory tract with no evidence of systemic infection. These findings suggest that the virus was well adapted to replication in the human respiratory tract. An unusual feature of the 1918–19 pandemic virus was that the mortality rate in 15–34 year olds was more than 20 times higher than the usual mortality rate of seasonal influenza viruses in this age group[4]. Another unusual feature was that the mortality rate in people older than 65 was less than the mortality rate in people younger than 65. More than 99 percent of all influenza related deaths in 1918–19 were in people younger than 65 years old and almost 50% of all influenza related deaths were in the 20-40 age group[1,2]. Together these factors are responsible for the 'W-shaped' mortality curve characteristic of the 1918–19 pandemic[1]. The lower mortality in those older than 65 may have been due to immunity from previous exposure to influenza viruses of the same subtype but even allowing for this skewing, the high mortality in younger adults may have been be due to viral or host factors.

The influenza A virus from the 1918–19 outbreak was not reconstructed until July 1996, by Amy Krafft, working with Ann Reid and Jeffery Taubenberger[11]. The first recovered virus fragments came from formaldehyde fixed lung tissue, obtained at autopsy from an army private named Roscoe Vaughn, who was in an army camp in South Carolina. The virus was named Influenza A/South Carolina/1/18 (H1N1). He had died five days after admission to hospital, at the age of 21[12]. Subsequent RNA fragments were recovered from material collected by Johan Hultin from 1918 influenza victims buried in permafrost in the village of Brevig, Alaska. The haemagglutinin gene did not have the cleavage site mutation that is now known to make the H5 and H7 strains so deadly, so other factors were clearly at play in the exceptional virulence of this H1N1 virus.

It is of interest to note that influenza was first observed in swine in the autumn of 1918, corresponding with the second pandemic wave in humans. The clinical signs and pathological features of the disease in swine were remarkably similar to those in humans[2]. The absence of reports of any disease resembling swine influenza prior to 1918 suggests the possibility that influenza viruses had not infected swine prior to this time and that the virus spread from humans to pigs during the second wave of the 1918–19 pandemic. Outbreaks of influenza-like disease were also reported in swine in Europe and China in the autumn and winter of 1918 and 1919. Since 1918, influenza viruses of swine origin (for example A/California/04/2009 (H1N1)) have continued to circulate in North America, Europe and Asia[2,3].

Spanish influenza in Australia

Reports of an epidemic of influenza circulating in Europe reached Australia in July of 1918, followed by reports of a highly virulent second wave in September. As the pandemic spread through Europe, Africa and Asia the newly created Australian Quarantine Service introduced strict quarantine measures at all Australian ports on 17 October 1918. Australia's remoteness from Europe and North America, and the fact that the only way to reach Australia was by sea meant that the length of time taken to reach Australia by sea was longer than several incubation periods. This meant that most (but not all) troops on ships had either recovered or died before reaching Australia, delaying the introduction of the virus into Australia. However, some troop ships returning from Europe after the November armistice had large numbers of influenza infections. The first infected ship arrived in Australia on 18 October 1918 and over the next 6 months 174 of 323 vessels checked and 1102 of 81 510 people checked were diagnosed with influenza. Many deaths occurred at sea and in Australian quarantine stations before the virus first appeared in Melbourne on 9 or 10 January 1919[1,13,14].

In the six months following the introduction of the virus to Australia it is estimated that at least 15 000 people died of influenza and as many as two million people (40% of the population at the time) were infected. Almost one-third of deaths were in young adults 24–34 years of age, consistent with case-fatality patterns reported elsewhere[1,13,14]. Mortalities occurred in two waves, the first wave between mid-March and late May, affected twice as many males as females and caused approximately 31 per cent of total deaths over that time period[8]. The second wave peaked in June and July and was more virulent than the first; produced a higher mortality rate, affected a greater proportion of females and far more people over the age of 50 years. Mortality rates varied greatly between countries. In Australia the overall mortality rate was three deaths per thousand whereas in New Zealand it was almost double this. Indigenous people were particularly susceptible. In Western Samoa there were 8500 deaths from a population of only 38 000. In New Zealand, Maoris had a death rate of 42.3 per thousand, seven times that of European New Zealanders. Indigenous Australians were severely affected with some communities suffering mortality rates approaching 50%[13,14].

Australia was not prepared for a natural disaster of the scale of the 1918–19 pandemic. The whole of society and the economy had been disrupted by the war and the infection of key staff with the virus affected Australia's ability to control the pandemic and to treat the sick. Quarantine was a key part of the Australian control program, with state borders closed and quarantine camps set up at border crossings. Places where people gathered in large numbers (schools, theatres, churches) were closed, roads were disinfected and the wearing of masks was made mandatory (Figure 1). People were asked to practice enhanced personal hygiene measures including hand washing, disinfection and cough protection. Hospital beds filled quickly and temporary hospitals were set up to cope with the overflow of patients. Medical staff were increasingly infected, putting further strain on health care services. Any hope of providing normal services and activities disappeared as more and more people became ill[1,13,14].

The Commonwealth Serum Laboratories was established during world war one to produce vaccines locally. In 1918 it produced its first vaccine against pneumonic influenza. At the time, the cause of influenza was not known, and a vaccine was produced against the cause of the secondary bacterial infection[1]. At that time the aetiology of this disease was unclear; influenza was believed to be caused by a bacterium such as *Bacillus influenza* (*Haemophilus influenzae)* also known as Pfeiffer's bacillus (Richard Pfeiffer described it during the 1889–1892 influenza epidemic). In the same period, the French microbiologists Charles Nicolle (1866–1936), Charles L. Bally and Ren. Dujarric de la Rivière (1885–1969) of the Pasteur Institute had shown that the influenza pathogen could pass through a fine filter[15]. However, despite their brilliant experiments, the virus hypothesis continued to be neglected until the virus was isolated from nasal secretions in 1932–33 by English scientists Wilson Smith (1897–1965), Christopher Andrewes (1896–1988) and Patrick Laidlaw (1881–1940), working at the Medical Research Council at Mill Hill, demonstrating the intranasal human transmission of the virus[15].

Figure 1. Emergency volunteers, May 1919. Source: State Library of Queensland, John Oxley Library.

In 1935, Frank Macfarlane Burnet published the first of his 114 papers on influenza virus, showing that it could be grown on the chorioallantoic membrane of embryonated hens' eggs[16]. This was also discovered independently by Wilson Smith. It was subsequently demonstrated that the formalin inactivated virus was immunogenic in humans, that the influenza virus grew easily in fertilized hen eggs, and that the virus could be purified by means of high-speed centrifugation, a procedure that is still used today to manufacture most influenza vaccines[17].

Many lessons from Australia's experience during with the 1918–19 influenza pandemic are applicable to the current COVID-19 pandemic; lessons on people's reactions to a pandemic, the importance of inter-governmental co-operation, the importance of maintaining a well-resourced health system and epidemic response capacity during non-pandemic times. As we have seen with the present COVID-19 pandemic, in the 1918–19 influenza pandemic many people attempted to 'run' the state border quarantine, refused to obey movement restrictions or wear masks[1,2,14]. It is also of interest to note that the second wave occurred in Australia after social restrictions were relaxed following a decrease in cases in the Australian autumn. This paralleled the experience in several US cities when relaxation of social restrictions was quickly followed by a resurgence of infections[18–21].

Australia's experience in the 1918–19 pandemic demonstrated that cooperation between various governments and government authorities during such crises cannot be taken for granted. In late November 1918, state ministers of health, medical authorities and the Commonwealth Government met for a national influenza planning conference. The meeting adopted a 13-point plan for dealing with the spread of the virus, with the federal government taking responsibility for proclaiming which states were infected and organising maritime and land quarantine. The states would arrange emergency hospitals, vaccination depots, ambulance services, medical staff and public awareness campaigns. Under the agreement, state authorities were required to promptly report any cases to the Commonwealth, which would then close that state's borders to protect its neighbours. Victoria did not report positive influenza cases until 28 January 1919, the day after New South Wales confirmed an outbreak. Other states viewed Victoria's delay in reporting as a breach of the November agreement and the agreement collapsed, with each state imposing its own conditions and organising its own containment policies[14].

The Experience in the USA

Strochlic and Champine[18] elegantly summarised the findings of three studies on the effects of public health measures on the spread of 1918 influenza in the United States. A study published in 2007 in the *Journal of the American Medical Association* analysed data from the US census taken during the 1918 pandemic[19]. Death rates in 43 US cities were charted. Two other studies published in the same year examined how public health responses influenced the spread of the disease in cities across the United States[20,21]. By comparing fatality rates and timing of public health interventions, they discovered that death rates were approximately 50 percent lower in cities that implemented preventative measures early, versus those that did so late, or not at all. The most effective actions were those that simultaneously closed schools, churches, and cinemas, and banned public gatherings; measures intended to lessen the strain on health care systems.

Those authors reached the important conclusion that relaxing intervention measures too early could cause an otherwise stabilised city to experience another spike in case numbers. The city of St. Louis, for example, encouraged by its initially low death rate, lifted restrictions on public gatherings less than two months after the outbreak began. A wave of new cases followed[19], with the surge particularly evident after restrictions on public gatherings were lifted. Of the cities that kept interventions in place, none experienced a second wave of high death rates. In 1918, the key to 'flattening the curve' was social distancing. This remains true a century later, in the current battle against coronavirus. Unfortunately, it seems that the lessons of infection control and epidemic preparedness must be relearned in every generation and for each new epidemic. We still face major delays and bottlenecks in vaccine production 100 years on from the 'Spanish' flu[22].

In 1957, although the US government was aware that H2N2 was on the way, the government would not commit to a huge public health vaccination program. On the other hand, pharmaceutical companies would not risk producing large quantities of vaccine without financial guarantees, until they were certain that it was needed. The trouble with influenza A is that by the time the need for a vaccine becomes clear it is too late to start production. Hence the introduction of the advance warning systems and advance vaccine production systems now in place for influenza. The WHO Collaborating Centre for Reference and Research on Influenza at the Victorian Infectious Diseases Reference Laboratory in Melbourne is part of the World Health Organization Global Influenza Surveillance and Response System. The network was established in 1952 to monitor the seasonal changes in influenza viruses, and to anticipate emerging subtypes, with the aim of reducing the impact of influenza through enabling the early preparation of vaccines containing currently circulating subtypes[23].

Most of the evidence indicates that the economic effects of the 1918 influenza pandemic were short-term[24]; however, many businesses, especially those in the service and entertainment industries, suffered double-digit losses in revenue. Other businesses that specialized in health care products experienced an increase in revenues[24]. The Great Influenza Pandemic is estimated to have caused an average reduction in real *per capita* GDP of 6.2 percent. Given the cross-country range of experience with flu intensity, this result accords with the observation that the pandemic could have caused a substantial number of macroeconomic disasters in the sense of declines in real *per capita* GDP by 10 percent or more[25].

Australian medical authorities dealing with the present COVID-19 pandemic would do well to carefully study the 1918–19 influenza pandemic for, in the words of George Santayana, 'Those who do not remember the past are condemned to repeat it'.

Conflicts of interest

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Biographies

Paul Selleck has been at the Australian Animal Health Laboratory, now the Australian Centre for Disease Preparedness, since 1983. In this time, he was head of the Avian Disease Diagnostic Laboratory, incorporating the National, OIE and FAO Reference Laboratory for Avian Influenza and Newcastle Disease and an OIE Reference Expert for Avian Influenza and Newcastle Disease. He was also involved in the Australian equine and swine influenza outbreaks in 2007 and 2009 respectively and has worked with Hendra, Nipah and SARS at physical containment level 4. Paul now works extensively in Asia, running training courses on biosafety and biosecurity and laboratory diagnosis. He also audits laboratories and runs training courses on quality systems and ISO laboratory accreditation.

Emeritus Professor Ross Barnard, FASM, was director of the biotechnology program at the University of Queensland from 2000 to 2019. Prior to that he was at Panbio Ltd (as program leader for nucleic acid diagnostics development) and the Cooperative Research Centre for Diagnostic Technologies. He has worked on diagnostics development for a variety of infectious agents. In 2005 he undertook a sabbatical at the Australian Animal Health Laboratory (Geelong), now the Australian Centre for Disease Preparedness, during which time he collaborated on the development of a broad spectrum, RT-PCR based Influenza A diagnostic. He was an NHMRC C.J. Martin Fellow at the University of Queensland and the University of California, Santa Cruz.

CSL, from blood stock to blue chip

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Abstract. From its modest beginning in 1916 with a staff of 20, CSL has grown into a major company, which now employs more than 25,000 people, operates in more than 70 countries and has a market capitalization of over A$130 billion.

Few Australian companies survive for 100 years let alone survive and thrive. CSL, by constantly adapting to changing circumstances, is one of the few to have done so. Its history has three phases: a lengthy period as a Government business enterprise producing a range of biological products for the local market; a period of diminishing importance when the organization became uncompetitive with the private sector; and a renaissance following its transformation into an independent company supplying innovative products to the world.

At the beginning of the 20th century, infectious diseases were responsible for approximately half of all deaths in industrialised countries. In Australia, one in 10 children died before the age of 5 and the average life expectancy was about 50 years. Due to the pioneering work of Louis Pasteur, Emil von Behring and Robert Koch, the germ theory of disease had been established and the possibility of active and passive immunisation demonstrated. Once passive immunisation was found to dramatically improve the survival of patients with diphtheria and tetanus, Government funded organisations in Paris, Marburg and London began to produce antisera in horses and to provide these products to local physicians and in some instances, to countries without local production facilities.

The advent of WWI, with its dramatically increased requirements for tetanus antiserum to treat battlefield wounds and the disruption of traditional supply lines, caused a problem for remote countries like Australia, creating a demand for national self-sufficiency. In 1915 the Australian Government established the Federal Serum Institute (now CSL Ltd) funding the purchase of a farm on the outskirts of Melbourne, construction of laboratories, stables for the horses and a house for the Director – the Edinburgh trained bacteriologist, William Penfold. By the time that Penfold took up his position a year later, similar organisations had been, or were being, established in Russia, Scandinavia, Japan, Canada and the US.

With a staff of 20, the Institute soon began producing horse antisera to diphtheria and tetanus toxins as well as tuberculin and smallpox vaccine. One of CSL's first challenges was to respond to the devastating pandemic of Spanish influenza. As the viral aetiology of the disease had not yet been demonstrated, a mixed bacterial vaccine was developed in the hope that it would reduce the incidence of severe pneumonia, which, to some extent, it did.

In the early 20th century, as Australia was extremely dependent on exports of beef and wool, the company established a veterinary division, subsequently producing a wide range of vaccines against economically important diseases of livestock and later of companion animals. For the first phase of its existence the organisation was led by microbiologists or public health experts (Penfold, Frank Morgan, Val Bazeley, Bill Lane, Ron Greville) whose aim was to harness scientific advances being made overseas, to improve the health of the Australian community. During this period CSL and its sister organisations in other countries thrived and fulfilled a vital role in public health.

Advances in microbiology provided the basis for development of vaccines against important childhood diseases such as diphtheria, whooping cough and tetanus as well as diseases encountered by travellers, such as cholera, typhoid and paratyphoid. None of these products required access to intellectual property rights.

As oversight of the production process was minimal and the clinical data required to support use of new products, modest, the investment required to develop and introduce a new product for Australia was within the means of a Government funded entity. Because of its mission to safeguard Australian's health, CSL was able to respond rapidly to new developments overseas. In 1923 it was one of a handful of organisations to license the process for extracting insulin from animal tissue from the University of Toronto and continued to provide this product to the Australian community until 1990.

It was similarly opportunistic in benefiting from the discovery of penicillin by Alexander Fleming. Once the significance of this work was recognised and Florey and Chain had demonstrated that was possible to produce penicillin at scale, the eminent public health worker, Bill Keogh convinced the War Cabinet that Australia needed to be self-sufficient and that Val Bazeley, a CSL veterinarian, then serving in the army in New Guinea (with a reputation for being able to get things done), should lead the effort. Bazeley flew to the US in September 1943 and after visiting major manufacturers, returned in December, setting CSL the ambitious target of producing penicillin within six weeks which he achieved.

By February 1944, 10 weeks after his return from the United States, sufficient penicillin had been produced to save the life of a soldier with septicaemia and, by April that year, Australia became the first country in the world with the capacity to provide penicillin to both soldiers and civilians. World War II triggered a dramatic growth in the use of blood transfusion and certain products such as albumin, which could be extracted from plasma by the newly developed process of Cohn fractionation.

In 1949 the Australian Government authorised the Australian Red Cross to provide unused plasma from volunteer blood donors to CSL and funded the organisation to extract a range of plasma proteins and clotting factors which could then be provided to the public, free of charge. It was a far-sighted initiative which was later copied by many countries. CSL was soon able to supply albumin, a range of immunoglobulins and a number of clotting factors to the community.

In the 1950s cell culture technology enabled scientists in the US to develop an inactivated vaccine against poliomyelitis and later, live attenuated vaccines against measles, mumps and rubella. In 1952 Bazeley, who would later become Director, was sent to the US to work with Jonas Salk, who had developed a candidate polio vaccine. Bazeley established large scale production techniques which, on his return in 1955, he replicated at CSL so that the organisation was soon able to supply Australia's needs for the vaccine. The late 1950s, when it was manufacturing polio vaccine, a wide range of human and veterinary vaccines, antisera to some of Australia's most venomous snakes and spiders, insulin, penicillin and a suite of blood products, was probably the peak of CSL's period as a Government owned entity. The organisation and its staff were widely admired and Bazeley became a national hero.

From the early 1970s CSL encountered strong headwinds because the circumstances that had allowed publicly funded producers of therapeutic products to thrive were changing.

If I had to choose a date that the winds of change began to blow, it would be almost 20 years earlier, on 25 April 1955, when a child in Chicago, who had been injected with polio vaccine 9 days previously, developed paralysis. The so called 'Cutter incident' (because the vaccine was produced by a small US manufacturer, Cutter laboratories), in which 94 children who had been immunised and 166 close family and community members, developed paralysis as a result of an inadequately inactivated batch of polio vaccine, threw a spotlight on the lack of rigour around vaccine manufacture and regulation and the need for careful monitoring and oversight of all aspects of production. It also drew attention to the inherent conflict of interest when the government was simultaneously the producer, regulator and major purchaser of therapeutic products. Independent Regulatory authorities were established and provided with significant resources and powers and manufacturers were required to demonstrate that their production processes were reliable and their products safe and effective.

For public sector manufacturers, complying with these new requirements to produce a suite of generic products, required major investments in plant and equipment, which Governments were loath to provide. Additionally, development of novel vaccines required major investments in research and development, large and expensive clinical trials and construction of dedicated production facilities. Oversight of the development process required sophisticated management skills, a tolerance of risk and a willingness to wait a decade or more for the outcome. None of imperatives sat comfortably with Governments faced with tight budgets and short electoral cycles.

From the 1960s, while the Australian Government, continued to support CSL, it failed to do so at a level that would have enabled the organisation to develop new products and remain internationally competitive. As a consequence, the organisation became a relic of a bygone era, a biologics museum producing a limited number of generic products.

The factors which were affecting CSL had a similar impact elsewhere; from the 1970s many comparable organisations in the developed world were closed, while others limped along with Government support until they could be sold to industry or transformed into institutions with a different role. By virtue of Australia's geographical isolation and a respect for the organisation's historical role in national security, CSL escaped scrutiny longer than most. Management changes in the 1970s including the appointment of a Director (Neville McCarthy) with pharmaceutical industry experience who introduced a more commercial approach, extended the organisations life, but failed to deliver the new products essential for long term survival.

In 1990, when Brian McNamee became CEO, although the organisation was still producing human and veterinary biologicals and had a biosciences and blood products division, its future was in doubt. When the Government announced its intention to sell the enterprise to a multinational pharmaceutical company, McNamee was able to persuade the Minister of Health, Brian Howe, that privatising CSL would not only provide the Government with a greater financial return but give the organisation a chance to flourish.

The initial public offering in 1994 returned A$300 million to the government and gave the company control over all of its plant, including an uncompleted plasma fractionation facility at Broadmeadows, which was based on a novel and at that time unproven technology, large scale chromatography.

The opportunity to complete the construction of the facility and validate the new technology was a turning point for CSL, while its release from Government control gave the CEO and Board the opportunity to respond rapidly to new opportunities. As the local market is too small to sustain a pharmaceutical company, McNamee's genius was to find a way for the organisation to expand internationally and to develop a suite of new products to meet unmet medical needs. While he considered human health, specifically plasma products and human pharmaceuticals as the company's core business, McNamee gave each division a chance to succeed, initially focussing on expanding the animal health and biosciences capabilities through modest acquisitions in New Zealand, the UK and the US. In each case the head of the relevant division and their family relocated, to run the newly acquired business and in each case CSL's knowledge, insight and commitment was able to add value. Some years later, these businesses were sold for almost 20 times CSL's original investment.

With this success, the organisation recognised that it had the knowledge and skills to operate internationally, which provided the confidence to attempt transformative transactions. In addition to expanding overseas, McNamee recognised that new product development was the key to long term success and began investing a significant proportion of the company's profits into Research and Development. This emphasis has seen the organisations direct spending on R&D rising from around A$10 million in 1990 to over A$30 million in 2000 to over A$1 billion in 2020.

The area of business in which CSL had the deepest skills and the only area in which it had world leading technology, was plasma fractionation. In 2000, armed with the knowledge provided by Jack Wood, a Canadian executive with a long history in the industry, the analysis of a team from the London School of Economics and his engaging personality, McNamee was able to persuade the owners of the Swiss fractionator ZLB, that CSL was a suitable acquirer. The transaction, which was sealed after McNamee, who had been severely ill, travelled to Bern to present his case to the ZLB board, has become part of company folklore.

When coupled with the acquisition of NABI's plasma collection facilities in the US, a year later, it was truly transformative. On each occasion it proved relatively easy to raise the funds to support the acquisitions because the market was able to see their logic and how they would create value. The subsequent acquisition of Aventis - Behring's plasma business in 2004 and its successful integration, enabled the company to operate internationally and at scale. The integration of these businesses has enabled CSL to extract the maximum number of therapeutic proteins from each unit of plasma at the lowest cost and to invest in developing a range of products generated by recombinant DNA technology.

This approach has been very successful; whereas in the period 1974–1990, only a single new human product had been developed by CSL, (exclusively for use in Australia), since 1990 more than 20 new products have been licenced for International markets. The acquisitions provided CSL with production facilities in Europe, the US and Australia, staff with world class technical skills, a suite of interesting research projects and sophisticated marketing capabilities.

With access to major markets in the Northern Hemisphere and recognition of the potential provided by the emerging market in Asia, Paul Perrault, a senior executive with extensive marketing experience was chosen, on the retirement of McNamee, to lead the company into its second century.

CSL has designated its Melbourne laboratories, which are located in the Bio21 Institute on the campus of the University of Melbourne as its primary source of innovation, whilst conducting most of its clinical development in the US. Plans are underway to move its administrative headquarters and laboratories to a new site adjacent to the University and Parkville precinct.

The acquisition of a research-based company, Zenyth therapeutics, has provide additional technical depth and a pipeline of recombinant products and monoclonal antibodies, while the acquisition of Calimmune has provided an opportunity to enter the exciting field of gene therapy.

By ceasing production of generic childhood and travellers' vaccines to focus on influenza vaccines, through its new business

unit Seqirus, CSL has adopted a similar strategy to that it employed in plasma fractionation. The recent acquisition of Novartis's worldwide influenza vaccine business has provided the company with considerable scale, production facilities in three continents capable of producing both cell culture and egg derived vaccines and a suite of products designed to meet a range of public health needs.

From its modest beginning in 1916 with a staff of 20, CSL has grown into a major company, which now employs more than 25 000 people, operates in more than 70 countries and has a market capitalisation of over A$130 billion.

Given the importance of acquisitions to its strategy and the success that CSL has had with its acquisitions, when so many others in the pharmaceutical industry have been value destroying, it is interesting to ask why? There were probably a number of factors involved. First, CSL has developed a deep understanding of what have been relatively unfashionable areas (plasma fractionation and influenza vaccines) and recognised the benefits that consolidation of production activities and R&D pipelines could provide. Second, it has generally acquired businesses that were small parts of much larger organisations and not receiving the management attention or resources that would enable them to flourish. Third, it had a clear understanding of how it could add value to any business it acquired and quickly put in place plans to unlock this value. Fourth, being based in Australia and relatively unknown, the company was able to fly under the radar and thus able to make acquisitions at reasonable prices. Fifth, it had great respect for the skills of the personnel that it acquired and the culture that they brought with them and sought to create a situation where 1 + 1 = 3. Last, and perhaps most importantly, as the company grew it retained the ability to act swiftly while maintaining an appetite for risk. Clearly, while all these ingredients were necessary, they would have been insufficient for success without outstanding leadership and a laser like focus on outcomes.

Despite its transformation over the past 30 years, CSL has retained fidelity to its original mission and culture. It is fascinating to see an organisation whose first major challenge was responding to a pandemic of influenza now turning its formidable skills and resources to combat the challenge of COVID-19.

Conflicts of interest

Ian was the R&D Director of CSL from 1990–2000 and continues to hold shares in the company.

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Biography

Professor Ian Gust AO is a medical virologist with a distinguished career in public health including the development of vaccines against hepatitis A and human papillomavirus infection and membership of the International Task Force for Hepatitis B Immunisation which accelerated the introduction of HB vaccine into routine immunisation programs. During his 20 years at Fairfield Hospital he built an internationally renowned research team, founded and directed the Burnet Institute, established the National HIV reference laboratory and directed the NHMRC special unit for AIDS virology. During his subsequent period as R&D Director at CSL Ltd, he reorganised the research division and laid the basis for the company's new product portfolio. Ian is the author of three books, more than 300 papers and has received several major awards for his work. Since 'Retirement' in 2000, he has been appointed a Professorial Fellow in the Department of Microbiology and Immunology at The University of Melbourne and has been a board member of several biotech companies and a number of non profits including the International AIDS Vaccine Initiative, International Vaccine Institute, ICDDR,b and the Human Vaccines project.

Stigma, separation, sorrow: leprosy in Australia

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Abstract. Leprosy (Hansen's disease) was introduced to Australia in the mid-1800s and its story reflects the attitudes of the 19th and 20th centuries, with treatment including segregation, paternalism, and racism. The approaches taken within the Australian states were similar and based on isolating people affected by leprosy, as both a measure to assist the patient but, more importantly, to protect the European society. The most devastating effects of this introduced disease and these approaches were on Indigenous Australians. With the advent of effective antimicrobials, isolation practices were slowly replaced with community-based treatment. However, the term 'leper' still evokes negative images in Australian society today.

Introduction

Leprosy (Hansen's disease), a treatable disease affecting peripheral nerves, skin and mucous surfaces, is caused by *Mycobacterium leprae* and *Mycobacterium lepromatosis*[1]. As a clinical illness, it only manifests in a small percentage of people who come in contact with infectious patients; however, immunological tests show that most such contacts process the organism without developing clinical symptoms or signs[2]. The disfigurement caused by the disease has traditionally incited fear of those diseased and has led to exclusion and stigma.

The term 'leper' is offensive to persons affected by leprosy and is only used in this article where historically appropriate. The terms 'leper colony/station', 'lazaret' and 'leprosarium' all broadly refer to areas set aside for the segregation of persons affected by leprosy, with the term 'leprosarium' indicating a more medical approach to isolation. Derby Leprosarium is now known as Bungarun, but its previous name is used in this article.

Early records

Following European colonisation, the earliest records of leprosy in Australia date from the 1850s, with no evidence of its presence among Indigenous Australians before this time[3–5]. The disease pattern varied between the colonies. In Victoria, Chinese immigrants on the goldfields were the earliest reported cases, but the disease did not become established in the European settlers. However, in New South Wales and Queensland, early epidemiological studies suggested that the disease spread to Europeans from both Chinese immigrants and South Sea Islanders brought to Australia as indentured labour[3–5]. Leprosy was introduced in the northern areas of Western Australia during the 1880s, with the probable sources being Chinese labourers or lugger crews (originating from endemic countries) in the pearling industry[6]. By 1890, leprosy had been reported in the Northern Territory, presumed to have been introduced by Chinese immigrants working on railway construction and in mines[4,7]. The earliest cases of leprosy in South Australia and Tasmania were reported in the mid-20th century and notifications remained low in these states[8]. In the early years, leprosy was difficult to diagnose, and records were incomplete and not accurate[4].

Quarantine and isolation

In the late 19th century, all Australian states enacted Public Health Acts and all states except Tasmania included leprosy in these Acts or in succeeding legislation specific for leprosy[4]. Quarantine stations were established at this time, to protect the population from infectious exotic diseases, including leprosy. The fear associated with the disease meant that facilities for people affected by leprosy were sited away from existing quarantine station buildings or were constructed on islands, removed from centres of population.

In New South Wales, The Coast Hospital, Little Bay, Sydney, replaced the North Head Quarantine Station in 1881. Chinese leprosy-affected patients were initially housed in huts, with a lazaret replacing an isolation ward in 1890. A contemporary report describes the lazaret's surroundings in glowing terms and the inmates as contented[9].

In Victoria, the 1897 description of the 'leper camp' some distance from the Point Nepean Quarantine Station was less flattering, with the leprosy-affected inmates 'calmly awaiting the end of their misery . . . with philosophical resignation'[10]. In the

1930s, those remaining were moved to Coode Island, Melbourne[11,12]. In the 1940s, when definitive treatment became available, leprosy-affected persons were sent to the Exotic Diseases Hospital, a stand-alone institution originally built to house sufferers of such diseases as typhus and smallpox, situated next to the Queen's Memorial Infectious Diseases Hospital, Fairfield (M. Sandland, pers. comm.).

In Queensland, Peel Island Quarantine Station (Figure 1) in Moreton Bay was the successor in 1907 to lazarets at Dayman Island and Friday island in the Torres Strait (for non- Europeans) and Stradbroke Island in Moreton Bay (for Europeans). Peel Island housed both Indigenous Australians and Europeans, but in 1940 the Indigenous Australians were transferred to a separate facility at Fantome Island, North Queensland[13].

In Western Australia, early isolation facilities were at Woodman Point and Wooroloo Sanatorium in the south, and Bezout Island, Derby, Cossack and Beagle Bay in the north. In the 1930s, Indigenous Australians affected by leprosy were transported to Channel Island, Darwin, Northern Territory. After years of delay and argument between local communities and Government officials, Derby Leprosarium (Figure 2) was opened in 1936[6].

In the Northern Territory (part of South Australia until 1911) the 'leprosy station' on Mud Island, Darwin (functioning from 1884) (Figure 3) was described as a 'living hell lazaret'[14]. The choice of Channel Island as a replacement in 1931 was only marginally better, with scarce water and fuel supplies and inadequate medical care. It was only in 1955 that a leprosarium was built on the mainland at East Arm[7].

In South Australia, the Torrens Island Quarantine Station, established in 1877, records three persons with leprosy admitted to the hospital between 1944 and 1968[15].

In Tasmania, the Quarantine Station on Bruny Island (1884–1955) does not appear to have hosted any people affected by leprosy[16].

Indefinite detention challenged

In the interwar years of the 20th century, lifetime segregation of leprosy-affected people was challenged by EH Molesworth and Leonard Rogers[17]. Molesworth, an Australian leprologist, sharply criticised the inhumanity of this practice[18]. Rogers, drawing on international experience, argued that indefinite isolation was ineffective because those in the early stages of the disease would not come forward for treatment if threatened with incarceration and because medical practitioners would be reluctant to expose their patients to such a fate. Patients segregated with advanced disease would not benefit from the treatment offered to them (injected chaulmoogra and hydnocarpus oils, reported to arrest symptoms if administered in the early stages), and those with early symptoms would remain in the community, able to spread leprosy to their (untraced) contacts[19]. However, CE Cook (Chief Medical Officer of the Northern Territory) and Raphael Cilento (Director-General of Health, Queensland) both opposed these arguments and argued persuasively for isolation. Their views prevailed and indefinite detention practices continued[13,17].

Indigenous Australians

The earliest cases in Indigenous Australians were reported in the 1890s; by the 1920s, these notifications outnumbered all others[4].

Figure 1. Lazaret Huts on Peel Island, Queensland, built in 1907, photographed 2010 (Thom Blake, used with permission).

Figure 2. Hospital and Administration Block, Derby Leprosarium, 1948 (State Library of Western Australia, 022248PD, used with permission).

Figure 3. Mud Island Leper Station, ca 1890, Northern Territory (State Library of South Australia, B 9761, used with permission).

Unlike Europeans, Indigenous Australians did not traditionally fear leprosy and did not reject those who were affected[17]. However, in the first half of the 20th century, the leprosy control strategies of State and Commonwealth Governments dictated that all cases should be identified and placed in isolation. Rounded up in police-assisted 'leprosy raids' in Queensland[13], or by 'leprosy patrols' in northern Western Australia[6], becoming a 'leper suspect' transported in chains in the Northern Territory[17], facing lifelong separation from their communities and removal of babies at birth[13] – it was entirely reasonable that Indigenous Australians would make every effort to flee and hide from authorities, or escape from custody. If unsuccessful, they were kept in prison-like conditions, with the prospect of painful injections of chaulmoogra oil and poorly funded, inadequate facilities[17]. A telling statistic in 1940 is the allowance per patient on Fantome Island (£100 per annum), compared with the European patient on the Peel Island Lazaret (£1000 per annum)[13].

The first really effective treatment for leprosy, sulphone therapy, was available in Australia in1947[20]. In 1953, the first report of the

World Health Organization (WHO) Expert Committee on Leprosy called for a reconsideration of compulsory isolation practices[21]. Australia did not change its policies through the 1950s, although treated patients could then be released from isolation under certain conditions, which included access to medical care, separate accommodation, and no domiciliary contact with children. These conditions automatically excluded most Indigenous Australians, with prevailing attitudes being expressed in this 1952 description by Dr AH Humphry, Commonwealth Department of Health, Darwin: 'his standard of hygiene is poor, he will not sleep apart, nor can he restrain his intense fondness for children.'[20,22].

In the late 1950s, European patients in Queensland and Western Australia were beginning to move from Peel Island and Wooroloo to hospital and then home isolation[20]. Yet the facilities for Indigenous Australians did not close until the 1970s (Fantome Island) or the 1980s (Derby, East Arm), with many Fantome Island patients simply transferred to Palm Island. This treatment reflected both official attitudes (that Indigenous Australians were irresponsible with their health) and structural shortfalls in Government health and welfare services for Indigenous Australians[20].

Leprosy in Australia today

Triple antibiotic therapy (dapsone, rifampicin and clofazimine) was introduced in the 1980s, and the treatment of leprosy changed to outpatient consultation and monitoring of antimicrobial therapy and any adverse reactions. Responsibilities for leprosy diagnosis and treatment shifted to specific infectious diseases hospitals (e.g. Fairfield Infectious Diseases Hospital, Melbourne) or to major hospitals. Leprosy-affected persons today are treated in outpatient clinics, unless there is a clinical indication for hospitalisation, such as planned corrective surgery or treatment of immune reactions (M. Sandland, pers. comm.). Since 1925, leprosy notifications have had peaks in 1940, 1944 and 1957 (dominated by Western Australia and the Northern Territory numbers), with occasional reports today, predominantly in those from endemic countries[8,23,24].

From the harrowing descriptions in 1867 of Victorian Chinese immigrants with a 'loathsome disease'[11] to the appropriate outpatient treatment in the Northern Territory today[25,26], it is clear that Australian approaches to leprosy have undergone radical improvement. Nevertheless, within Australian society in 2020, the term 'leper colony' is still used as a description of shame and isolation[27], an attitude that reflects the ignorance, paternalism and racism in our all too recent past.

Conflicts of interest

The author declares no conflicts of interest.

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Biography

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COVID-19 microbiology experience with a difference

Dr Samantha Byrne
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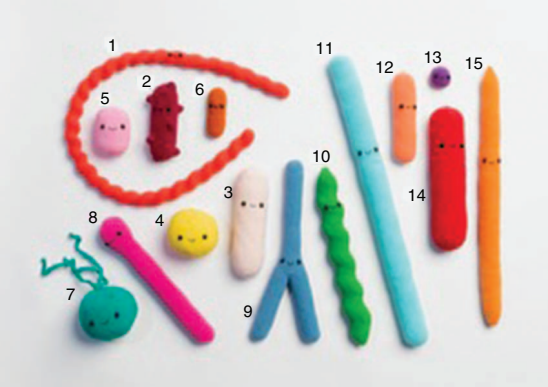
While many microbiologists (and microbiologists-at-heart like myself) turned to nurturing sourdough starters to keep their hands busy and buoy their spirits during the periods of COVID-19-related lockdown in 2020, I turned to the crochet hook. The rhythmic nature of crochet was not only therapeutic, but the feeling of productivity was the perfect accompaniment to morning shifts supervising primary school for my three children.What started as teaching myself to crochet ended up as a collection of the most abundant genus of bacteria found in the oral cavity, plus a couple of disease-associated species. The beady eyes and smiling mouths may be artistic license, but each microbe is crocheted to scale (1 μM = 10 cm). I teach oral microbiology at the University of Melbourne Melbourne Dental School, and these creations will be making an appearance in class next year as my students explore the incredible diversity of microorganisms that call the mouth home.



(1) *Treponema denticola*
(2) *Porphyromonas gingivalis*
(3) *Lactobacillus*
(4) *Streptococcus*
(5) *Neisseria*
(6) *Haemophilus*
(7) *Lautropia*
(8) *Corynebacterium*
(9) *Actinomyces*
(10) *Campylobacter*
(11) *Leptotrichia*
(12) *Prevotella*
(13) *Veillonella*
(14) *Tannerella forsythia*
(15) *Fusobacterium*

Quiz

Who am I?

(1) We are considered part of the core microbiome' of the mouth, and are some of the earliest colonisers of the teeth. However, some of our genus can cause nasty infections such as meningitis and gonorrhoeae.

(2) We are some of the earliest bacteria to colonise the mouth after birth, and make up a large proportion of bacteria found at different oral sites. We are a heterogenous genus – some of us are associated with tooth decay by turning the sugars you eat into acid, whereas others can produce alkaline substances that balance this acid out. Under a microscope we are often found in pairs or short chains.

(3) One of my relations is responsible for syphilis, while I am associated with gum disease (periodontitis). I use my periplasmic flagella to get around.

(4) Members of my genus are found in many places in the human body including the gastrointestinal tract and the vagina. Some of us can also be used in the production of fermented dairy products such as cheese and yoghurt.

(5) My extracellular vesicles might look cute, but I am considered one of the major aetiologic agents of gum disease. I may also be related to systemic conditions such as Alzheimer's disease and cardiovascular disease when I escape the mouth.

Answers available on page 216.

Tuberculosis: yesterday, today and tomorrow

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Abstract. Tuberculosis (TB) remains an important public health challenge globally and in Australia. For the more than 10 million people who become sick with TB each year, the disease can cause immense personal and economic hardship, including loss of income and education through ill health, prolonged and arduous treatment, and stigmatisation – perpetuating a cycle of disadvantage. Past efforts to control TB have taught us much about modern disease control and public health. As the world grapples with the coronavirus (COVID-19) pandemic, the response to TB provides valuable lessons which can inform our response to COVID-19.

Yesterday

Tuberculosis (TB), the disease caused by the closely related group of mycobacteria within the *Mycobacterium tuberculosis* complex, is spread person-to-person through infectious aerosols generated within the lungs of persons with pulmonary TB disease. *M. tuberculosis* emerged as a human pathogen in pre-historic times. It has been hypothesised that changes in early human behaviour around the use of controlled fire may have facilitated the evolution of *M. tuberculosis* from an environmental organism to human pathogen[1,2]. Through history, TB has caused more deaths than any single other infectious disease[3].

TB is facilitated by economic disadvantage – overcrowded living conditions and substandard housing aid its spread. Modern changes in human behaviour brought on by the industrial revolution during the 18th and 19th centuries were exploited by the organism. At a time before the advent of effective treatments, the concentration of human populations within urban centres and large factories, characterised by cramped and overcrowded quarters, and poor sanitation and ventilation facilitated the amplification of TB spread[4]. These factors led to a peak in deaths from TB during the 1800s, when the disease is believed to have been responsible for around a quarter of all deaths in Europe[5].

In 1882, Koch discovered the bacillus responsible for TB disease[5]. The early 20th century saw progress in reducing disease rates through improvements in sanitation and living standards, pasteurisation of milk – effective in controlling disease caused by *M. bovis*[6] – and development of the Bacille Calmette Guérin (BCG) vaccine in the 1920s[7]. In the late 1940s, streptomycin and para-aminosalicylic acid were first used as anti-tuberculous treatments, followed by isoniazid, pyrazinamide, ethambutol and rifampicin – the four drugs which still constitute the standard first-line regimen for TB treatment[8].

As in the Northern hemisphere, TB was a leading cause of death in Australia at the turn of the 20th century[9]. Between 1948 and 1976, the Australian Tuberculosis Campaign provided free diagnostic and treatment services, and social support to those with TB. Anti-tuberculous drugs, once available, were also provided free[10]. The period of the Australian Tuberculosis Campaign saw a marked decrease in TB incidence in Australia; the program ended in 1976. The success of the Campaign highlights the role of active case finding in disease control. Australia has since maintained a low TB incidence, with <10 cases per 100 000 population reported annually[11]. This has led many to consider TB a disease of the past.

Today

Despite the advent of effective modern treatments, TB has exploited modern circumstances and remains a major global

public health threat. The emergence of HIV, which increases the risk of activation of TB disease approximately 20-fold, became a driver of the TB epidemic, particularly in sub-Saharan Africa[12,13]. Meanwhile, drug-resistance has become a dangerous threat to TB control, with resistance emerging faster than the drug development pipeline. Increasing frequency of global travel and migration has aided disease spread across borders and meant that Australia and other low-burden countries must maintain robust systems for early detection of TB disease in high-risk groups[14].

In 2015, the World Health Organization (WHO) published its Global End TB Strategy – marking a redirection from past TB control efforts to a more pro-active elimination strategy. The Strategy included ambitious targets to reduce TB-related deaths by 95% and the global incidence of TB by 90%, and to ensure that no TB-affected family faces catastrophic costs associated with TB treatment by 2035[15]. In 2018, the President of the United Nations General Assembly took the exceptional measure of convening a United Nations High Level Meeting on TB to garner political commitment to achieve the Strategy[16]. Despite significant efforts, the world is not on track to meet the End TB Strategy Targets. The WHO reported an estimated 10 million incident cases of TB and 1.5 million TB deaths in 2018[17].

Following the reduction in Australia's TB incidence during the Australian Tuberculosis Campaign, progress has plateaued – with essentially no reduction in TB incidence seen in the past three decades[18]. To achieve further progress, Australia must: scale up prevention of TB among those most likely to be infected who may go on to develop future TB disease; close the gap in TB burden faced by vulnerable and higher risk groups within the population; and contribute to addressing the TB epidemic at its source – beyond Australia's borders.

A hallmark of *M. tuberculosis* is its ability to achieve a dormant state and cause asymptomatic infection in exposed hosts. This greatly complicates diagnosis and control. Previously termed 'latent TB', the preference is now to describe this as 'TB infection' to emphasise its importance and justify treatment. Nearly one-quarter of the world's population is estimated to be infected with TB[19], and approximately 10% will go on to develop TB disease[20]. Treatment of TB infection is effective at preventing activation of TB disease, but testing and treatment of TB infection is limited by poor diagnostic and treatment options, and incomplete reach to at-risk populations. Scaling up management of TB infection among high risk groups such as recently arrived migrants from high-burden countries would reduce the pool of people at risk of becoming new TB cases in the future.

The incidence of TB among Aboriginal and Torres Strait Islander Australians remains around six times higher than that of the Australian born non-Indigenous population. The failure to close this gap highlights ongoing socioeconomic inequities and shortcomings in the health system's ability to provide patient-centred, culturally sensitive care. Social factors such as overcrowded housing and medical factors such as delayed diagnosis of TB and worse treatment outcomes among Aboriginal and Torres Strait Islander patients, contribute to continued transmission of disease in some communities[21].

Cross-border spread of TB, including drug-resistant TB, from Papua New Guinea to Australia's Torres Strait Islands has been documented[22]. This demonstrates that whilst having strong systems for detection and treatment of TB within Australia is important, it is insufficient to eliminate TB. As a high-resource setting with access to vast expertise in TB control, Australia has a responsibility to support its neighbours in the Asia-Pacific, where there is a large burden of disease and limited resources for TB control. Investment in regional TB control is likely to have direct benefits for Australia too. In the United States, it has been estimated that strategic investment in TB control in other countries could lead to a reduction in TB morbidity and mortality and overall cost savings in the United States[23]. Australian researchers and TB experts are making significant contributions to regional TB control through collaborative efforts with countries in the region[24–26].

Tomorrow

Tomorrow undoubtedly holds new challenges and opportunities on the path towards TB elimination. Globally there remains a large pool of people with latent TB infection. Given aging populations and the increasing burden of diabetes and other non-communicable disease which may increase the risk of progression to active TB disease, we may expect to see a shift in the burden of TB towards older people with more complex health needs. Drug-resistant TB continues to emerge as an epidemic within an epidemic – facilitated by major gaps in case detection and treatment[17].

Effective diagnostics and treatments are available for TB, yet these have not enabled us to overcome the global TB epidemic. Future efforts to eliminate TB will require both new tools and better use of existing ones. Molecular diagnostics such as GeneXpert® nucleic acid amplification test have improved detection of *M. tuberculosis* and rifampicin resistance and are now recommended first-line in place of microscopy[27]. However, access remains limited in many settings. Safer and more effective

drugs would be welcomed for drug-resistant TB, but meanwhile, there are opportunities to improve the use of existing drugs. Several significant changes in drug-resistant TB treatment have been recently recommended by WHO, including a shorter (9-12 month) all-oral regimen for treatment of multi-drug resistant TB and a new 6–9 month regimen for multi-drug resistant TB with resistance to fluoroquinolones[28]. Shorter rifamycin-based regimens for treatment of latent TB infection are being increasingly utilised, with potential to improve uptake and completion of preventive therapy. Significant efforts are being made to develop new, more effective TB vaccines, with around 16 candidate vaccines currently in the pipeline[29]. One of these candidates – *M72/AS01E,* shows promise for the prevention of TB disease among adults who already have evidence of TB infection[30].

Reflecting on progress made in reducing the global burden of TB provides relevant lessons for the response to COVID-19 and other communicable disease threats. It is clear that TB burden is intrinsically linked to the social determinants of health; addressing these underlying social and economic factors is critical. Public health responses should be guided by the principles of equity and social justice and services for diagnosis, treatment and care should be universally accessible and patient centred. Specifically, free testing for communicable diseases is essential; charging individuals for diagnostic tests diminishes case-finding and fosters disease transmission. Also, economic support is needed to keep people away from work – mandatory time off work while contagious with TB or COVID-19 is impossible for those on low incomes[31]. Early diagnosis through active case finding and appropriate procedures for isolation of infectious cases and infection control in health facilities is needed to prevent transmission both in communities and healthcare facilities. Finally, and perhaps most importantly, what we know from TB is the need for affected communities to be engaged and active in the response – to support one another, protect the most vulnerable and eliminate stigma and discrimination.

Conflicts of interest

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Biographies

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Epidemic poliomyelitis, post-poliomyelitis sequelae and the eradication program

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Abstract. **Epidemics of paralytic poliomyelitis (polio) first emerged in the late 19th and early 20th centuries in the United States and the Scandinavian countries. They continued through the first half of the 20th century becoming global. A major epidemic occurred in Australia in 1951 but significant outbreaks were reported from the late 1930s to 1954. The poliovirus is an enterovirus that is usually transmitted by the faecal–oral route but only one in about 150 infections results in paralysis when the central nervous system is invaded. The Salk inactivated polio vaccine (IPV) became available in Australia in 1956 and the Sabin live attenuated oral polio vaccine (OPV) was introduced in 1966. After decades of stability, many survivors of the earlier epidemics experience late-onset sequelae including post-polio syndrome. The World Health Organization launched the global polio eradication initiative (GPEI) in 1988 based on the easily administered OPV. The GPEI has resulted in a dramatic decrease in cases of wild polio so that only Pakistan and Afghanistan report such cases in 2020. However, a major challenge to eradication is the reversion of OPV to neurovirulent mutants resulting in circulating vaccine-derived poliovirus (cVDPV). A novel, genetically stabilised OPV has been developed recently to stop the emergence and spread of cVDPV and OPV is being replaced by IPV in immunisation programs worldwide. Eradication of poliomyelitis is near to achievement and the expectation is that poliomyelitis will join smallpox as dreaded epidemic diseases of the past that will be consigned to history.**

Epidemics of poliomyelitis

It was Easter 1951 and I was climbing the mango tree in the grounds of our family's Mareeba home in Far North Queensland when malaise and a headache forced me to bed. After a couple of hours, my leg was paralysed and I was taken to the Mareeba hospital, diagnosed with poliomyelitis (polio), placed in isolation and subsequently transported by ambulance to the Cairns Base Hospital where I remained until Christmas 1951.

I was one of the 1108 Queensland cases of paralytic polio among the peak number of 4940 Australian cases reported to the Commonwealth Director General of Health in the 1951 epidemic. New South Wales with 1608 cases and South Australia with 1488 cases also reported their peak numbers in 1951. Other Australian states reported maximum numbers of paralytic polio in different years, e.g. 1469 in Victoria in 1937, 704 in Tasmania in 1938 and 436 in Western Australia in 1954. For the period from 1951 to 1953, the incidence of polio per 100 000 of the Australian population was 32.30, exceeded only by Denmark with 59.90 incidence and Canada with 35.90[1].

Polio had been endemic in the human population for millennia. The first epidemics were reported from the Western world, e.g. Stockholm in 1887 with 44 paralytic cases and Vermont in the United States in 1894 with 132 cases. In 1905, a much larger epidemic occurred in the Scandinavian countries with more than 1000 cases[2]. A major epidemic was reported from the United States in 1916 with some 27 000 paralytic cases and 6000 deaths of which more than 9000 cases and more than 2000 deaths were reported from New York City alone[3]. These early epidemics mainly affected babies and young children but adolescents and adults were increasingly involved as the waves of epidemics became global and continued into the 1950s. The severity of the paralysis and the case-fatality rate also increased with age[4]. Ironically, improved public sanitation and personal hygiene meant that passive immunity, which was previously acquired by infants from their mothers when polio was endemic, no longer occurred to provide protection from paralytic polio[4]. Prior to the introduction of the US vaccination program in the mid-1950s, about 21 000 cases of paralytic polio were reported annually in the first half of that decade[3]. The year 1947 marked the largest and most widespread epidemic of polio in England and Wales, after which epidemics continued until vaccines became available[5].

Widespread fear gripped communities as parents faced the possibility of their children being crippled for life or even dying in these epidemics. In Australia, cinemas, swimming pools and playgrounds were closed and advice issued against attendance at large gatherings. Siblings of polio cases were placed in quarantine for 14 days and some schools were closed. For the protection of Queen Elizabeth and Prince Phillip during their 1954 Australian tour, handwashing was encouraged and indoor activities minimised. Most Australians viewed their Queen in open areas while she wore long white gloves.

Poliovirus and the disease

In 1908, Karl Landsteiner and Erwin Popper showed that a transmissible agent caused polio. The researchers' attempts to grow bacteria from the cerebro-spinal fluid and homogenate of brain tissue from a fatal case of polio proved negative. When the homogenate was injected intraperitoneally into monkeys, they developed polio and subsequently died[6]. Monkeys remain the only animals that are naturally susceptible to the disease.

Poliovirus is an enterovirus of the *Picornaviridae* family of small RNA viruses that are transmitted generally by the faecal–oral route. Australians, Sir Macfarlane Burnet of the Walter and Eliza Hall Institute and Dame Jean Macnamara, first showed that the poliovirus had at least two serotypes in comparative studies of immunity in monkeys to a Victorian isolate of poliovirus and one provided by the Rockefeller Institute in the United States[7]. Three serotypes of poliovirus (1, 2 and 3) have been identified and all can cause paralysis but type 1 is the most virulent and is the main serotype responsible for epidemics[4]. Seroprevalence of antibodies to the poliovirus indicate that only one in about 150 viral infections results in paralysis[4].

The virus multiplies in the oropharyngeal and intestinal mucosa and is shed from the oropharynx and in faeces. It spreads to the bloodstream via lymph nodes. Most infections end at this stage having caused a minor disease with non-specific symptoms and an antibody response. If the spinal cord is invaded, destruction of the motor neurons leads to weakness and temporary or permanent flaccid paralysis in muscles, especially of the limbs. Less often, the brain stem is invaded resulting in bulbar polio affecting swallowing, speaking and breathing. Life-threatening cardiac complications may also accompany bulbar polio[8].

Treatment of paralytic cases

Orthopaedic specialist Jean Macnamara championed the orthodox method of initial immobilisation to prevent deformity by bandaging and strapping the polio-affected body with legs spreadeagled to a cross-shaped Thomas splint. Some weeks later, physiotherapy was introduced. I was the recipient of this treatment. The alternative method of Sister Elizabeth Kenny involved the use of moist, heated wool packs to relieve muscle spasms and pain along with massage and gentle stretching and exercising of the muscles. She did not believe in immobilisation. Kenny had some followers amongst the medical profession in Australia but more detractors. In 1940, she introduced her method to the United States where it was better received and adopted but remained controversial[9].

Negative-pressure cylindrical or rectangular shaped 'iron lungs' enabled those with paralysed respiratory muscles to breathe again[8]. Most patients could be weaned off the iron lungs after a couple of weeks but a few spent their entire lives so confined. Death was the frequent outcome of paralysed respiratory muscles in the early epidemics.

Development of vaccines

Nobel Prize-winning research by John Enders, Thomas Weller and Frederick Robbins, which was published in 1952, showed that the poliovirus could grow in non-neural cell cultures from human tissues and in cultures of monkey kidney cells[10]. This paved the way for the production of adequate quantities of poliovirus for vaccine development.

American Jonas Salk developed the formaldehyde-inactivated polio vaccine (IPV) from cultures of poliovirus grown in monkey kidney cells. The culture fluids were first filtered to remove larger particles and then passed through a bacteria-retentive filter. Timing of the inactivation procedure required knowledge of the infectious titres of the culture fluids and control of the formaldehyde concentration, temperature and pH of inactivation. Final tests for safety were carried out by inoculation of monkey kidney tissue cultures and injection into monkeys. The latter were also subsequently tested for antibody responses[11]. Percival (Val) Bazeley of the Commonwealth Serum Laboratories (now CSL) left Australia in 1952 to join in the development of IPV and is a co-author of the relevant publication[11]. In 1955, he returned to Australia to direct production of IPV where it was used for routine vaccination starting in 1956.

Albert Sabin subsequently developed a live, attenuated oral polio vaccine (OPV) that was easily administered and cheaper to produce[12]. Oral administration of OPV meant that mass immunisation campaigns could be undertaken by untrained personnel. After multiplication in the intestinal tract of vaccinees, the attenuated poliovirus spreads through communities thus contributing to herd

immunity[4,12]. Although the live, attenuated vaccine was recognised as having the potential to revert to neurovirulence, this was considered to be an occasional and very rare event[3]. OPV was introduced into Australia in 1966.

As trivalent vaccines, IPV and OPV require multiple doses and usually a booster dose later to ensure immunity. OPV is also produced as a monovalent (mOVP) or bivalent (bOVP) vaccine. IPV is administered by injection and stimulates the production of serum neutralising antibodies. In addition to serum antibodies, OPV also produces local secretory IgA, which provides mucosal immunity in the intestinal tract.

Late-onset sequelae of poliomyelitis (LOSP)

After several decades of stability, many polio survivors – as well as some with no residual paralysis – develop LOSP including post-polio syndrome (PPS)[13]. These sequelae were not reported in the medical literature until the mid-1980s. The main symptoms of PPS are new muscle weakness and fatigability, joint and muscle pain and overwhelming fatigue. Other symptoms that may occur include cold intolerance, muscle atrophy and cramps, pulmonary dysfunction, sleep disorders and speech and swallowing difficulties[14]. A broader category of sequelae, the Late Effects of Polio (LEoP), includes the consequences of musculoskeletal deformities and weakness such as scoliosis, osteomyelitis, joint instability and pain, osteoarthritis and nerve entrapments[8]. No medication or dietary supplement has been shown to relieve the fatigue of LOSP[15]. I have now developed LOSP.

Post-polio support networks have been formed in most Australian states. The national organisation, Polio Australia Inc., provides health information and publishes resource material on LOSP for polio survivors. Polio Australia also conducts Clinical Practice Workshops to assist health-care providers in the diagnosis and management of polio survivors with LOSP.

Global polio eradication initiative

During his tenure as World President of Rotary International (RI) in 1978–79, Australian Sir Clement Renouf, inspired by the successful eradication of smallpox, asked American Rotarian and Paediatrician, Paul Severs, to suggest a vaccination program in which RI could participate. Dr Severs recommended vaccination against polio by the easily administered OPV. In 1985, RI started its PolioPlus program by immunising 6 million children in the Philippines[6].

In 1988, the World Health Organization (WHO) launched the global polio eradication initiative (GPEI) based on OPV[16]. Since then, the number of wild poliovirus cases has declined by 99.99%. The eradication of wild poliovirus type 2 was certified in 2015 and of type 3 in 2019[17]. By mid-2020, only Pakistan and Afghanistan are reporting cases of wild poliovirus type 1 (WPV1), as shown in Table 1[18–20].

Paralytic cases of polio due to circulating vaccine-derived poliovirus (cVDPV) as a result of reversion to neurovirulence of the serotypes of OPV are shown in Figure 1.

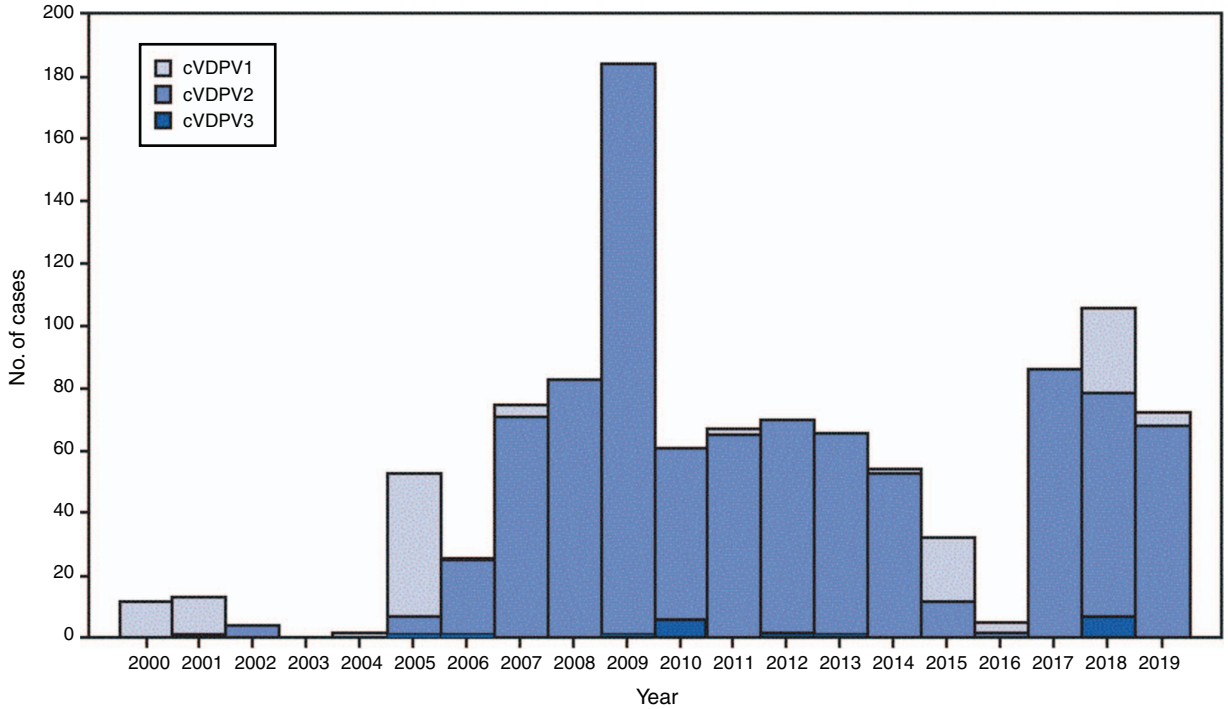

Figure 1. Cases of circulating vaccine-derived poliovirus (cVDPV) according to OPV serotypes[17].

Table 1. Cases of wild polio virus type 1 (WPV1) showing a significant upsurge in 2019 and 2020[18–20].

Country	Full year total					1 January to 30 June (half year)		Date of most recent case
	2015	2016	2017	2018	2019	2019	2020	
Pakistan	54	20	8	12	147	41	56	8 June 2020
Afghanistan	20	13	14	21	29	10	29	13 June 2020
Total	74	33	22	33	176	51	85	

Cases of circulating vaccine-derived poliovirus (cVDPV) occur in populations with low immunity[4,17]. Circulating VDPV2 has spread into multiple countries of four of the six WHO world regions: African, South-East Asia, Eastern Mediterranean and the Western Pacific[17]. One reason for low levels of immunity is the inhibitory effect of concurrent enteric infections on the OPV response in communities with poor sanitary conditions[21]. Other ongoing challenges to the eradication program are issues of inaccessibility in Afghanistan[19] and vaccine hesitancy and refusals, polio campaign fatigue and difficulties in reaching mobile populations in Pakistan and Afghanistan[20]. In addition, house-to-house vaccinations ceased for many months in 2018 and 2019 in both countries[20]. An outbreak of 26 cases of paralytic polio due to cVDPV1 occurred in Papua New Guinea in 2018[22]. Since January 2018, the frequency and geographic extent of cVDPV outbreaks have increased with transmission currently in 26 countries including Pakistan and Afghanistan[20].

In April 2016 after the eradication of poliovirus wild type 2 had been certified, a coordinated switch was made from trivalent OPV to bivalent OPV types 1 and 3 to prevent further emergence of VDPV2. Along with the switch, IPV was included in immunisation schedules to mitigate the loss of type 2 immunity[23]. As IPV does not confer intestinal immunity, the transmission of cVDPV is prevented by monovalent or bivalent OPV. A novel, genetically stabilised, monovalent nmOPV2 vaccine that is highly unlikely to mutate to neurovirulence has been developed recently to stop the emergence and circulation of VDPV2[24]. After the eradication of cVDPV, IPV will replace OPV in immunisation programs to eliminate the emergence and spread of all neurovirulent revertants. Australia and other countries in the WHO Western Pacific region were declared polio free in 2000[25] and OPV was replaced by IPV in Australia in 2005. By 2010, more than 50 countries were using IPV for their immunisation programs[6].

The WHO Polio Regional Reference Laboratory in the Doherty Institute in Melbourne is responsible for ongoing surveillance of the polio-free status of Australia and other countries in the WHO Western Pacific region. Faecal samples from cases of acute flaccid paralysis are investigated to exclude or confirm polio and sewage samples are investigated for the presence of poliovirus. The Reference Laboratory will also play a role in the final certification of polio-free countries in the region and the containment of laboratory stocks of poliovirus and destruction of any materials that might harbour poliovirus.

Apart from WHO and RI, the partners in the Global Polio Eradication Initiative (GPEI) are the US Centers for Disease Control and Prevention (CDC), UNICEF and the Bill and Melinda Gates Foundation. The Gavi Vaccine Alliance joined these partners in 2019 to promote the Polio Endgame Strategy 2019–2023. John Mackenzie is the Australian representative on the WHO Emergency Committee under the International Health Regulations (IHR) regarding the international spread of poliovirus. The risk has been assessed as a public health emergency of international concern (PHEIC) since 2014. At its meeting on 23 June 2020, the Committee agreed that, in view of the recent rise in numbers of WPV1 in 2019 and 2020 in Pakistan and Afghanistan and of the increasing frequency and geographic spread of cVDPV, the risk remains a PHEIC[26].

Because of the coronavirus pandemic, WHO suspended the Polio Endgame Strategy in March 2020 and the polio surveillance networks were diverted to help with COVID-19 tracking and tracing. In July 2020, Pakistan resumed house-to-house polio vaccination with vaccinators in personal protective equipment (PPE) administering the vaccine without touching the children.

To reach its goal of eradication, GPEI plans the safe resumption and scale-up of polio field activities, with the introduction of the genetically stabilised novel OPV2 to combat cVDPV2, when and where the COVID-19 pandemic allows[20]. Clem Renouf had hoped to live long enough to witness the fulfilment of his vision with the declaration of a polio-free world but he died on 11 June 2020 at 99 years of age.

Conflicts of interest

The author declares no conflicts of interest.

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Biography

Dr Margaret M Peel was the Principal Scientist at the Microbiological Diagnostic Unit Public Health Laboratory in the Department of Microbiology and Immunology at the University of Melbourne where she also gave lectures in microbiology to students as an Academic Associate. Margaret's first qualification was a Diploma in Medical Science, after which she obtained a BSc (Hons) from the University of Queensland (UQ). She then taught microbiology at the Queensland Institute (now University) of Technology. Margaret subsequently travelled to London to undertake the Academic Postgraduate Diploma in Bacteriology (Dip Bact) at the LSHTM, which she obtained with a mark of Distinction. She stayed on to receive a PhD from London University for studies on the immune response to vaccines. Her published contributions are in the areas of immunisation, public health microbiology and epidemiology, identification of bacterial isolates and sterilisation, disinfection and infection control. Margaret was awarded Doctor of Science (DSc) from UQ in 2009 for an annotated thesis of her published works. She is a Fellow of ASM (FASM).

Pasteur, rabbits and Cumberland disease

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Abstract. This article outlines the generally well known story of the attempt by Louis Pasteur to win the significant reward offered by the colonial governments of what would become Australia for biological control of the rabbit plague then infesting the continent. While the Pasteur bid, led by his nephew Adrien Loir, was not awarded the prize, there were significant flow-on benefits for agriculture in the colonies. The major benefit was the production of an effective vaccine for what the colonials called Cumberland disease (now known as anthrax). Loir also developed and/or provided vaccines for bovine pleuropneumonia and blackleg of cattle. Benefits also flowed back to France as the funds from the Cumberland disease vaccine sales to the colonial farmers helped support the newly established Pasteur Institute. The on-going controversy in the colonies and in the early days of the new nation of Australia over the use of a biological control agent (the organism we now know as *Pasteurella multocida*) is covered. This includes how a proposed biological control program using *P. multocida* became part of a class war. Finally, the irony that history continues to repeat itself – Hollywood's recently most famous dogs (Pistol and Boo) were simply repeating the story line of Star and Chouette - is covered.

The central story

Rabbits were first introduced into Australia with the First Fleet as a food source[1]. Rabbits released into the wild from those original stocks had become a problem in Tasmania by late 1820s[1]. New introductions into Victoria and South Australia in the 1850s, for recreational hunting and food, added to the developing problem[1]. By 1878, the rabbits had crossed the Murray River and 'steadily and surely overran the western division of New South Wales continued their march northwards till they are now in possession of a considerable area of Queensland, and are still advancing in a north and north-westerly direction towards the Northern Territory and the Gulf of Carpentaria'[2]. In less than three years from 1883 to 1886, the colonial New South Wales Government spent the enormous sum of £435 000 in efforts to exterminate the pest with around 8 million being killed[2].

The colonial governments of the time recognised the severity of the problem and the failure of the conventional control programs. Following a Rabbit Conference held in 1885, the colonial New South Wales government offered, in 1887, a prize of £25 000 (approximately today's equivalent of A$10 000 000) for an effective biological control agent with the judging panel being the Rabbit Commission[2]. The prize drew the attention of Louis Pasteur who had just demonstrated the bacterium (now known as *Pasteurella multocida*) causing chicken cholera (now known as fowl cholera) was able to control a rabbit plague in the Pommeroy estate in which the rabbit burrows were threatening to undermine the famous champagne cellars[3].

The Pasteur team, headed by Adrien Loir – the nephew of Pasteur – arrived in Australia in 1888. Henry Parkes, then premier of the colony of New South Wales but soon to be hailed as the 'Father of the Federation', supported the Pasteur team and organised for the construction of a Pasteur Institute on Rodd Island in Iron Cove at the western end of Sydney Harbour (Figure 1). The planning of the Institute was a sophisticated approach with the laboratory being supported by a 'wash room', a 'gasometer' and a 'crematorium', the latter three facilities all located at the far end of the laboratory building. Secure animal facilities that included concrete rabbit burrows, stalls to hold cattle and other livestock and an aviary for bird experiments were all constructed. The animal facilities were also covered with insect-proof gauze[4].

Matters soon deteriorated between the Rabbit Commission appointed supervisor of the work (Dr Katz) and the Pasteur team. Essentially, the Commission wanted evidence that the chicken cholera agent would pose no danger to native animals or domestic livestock and that the agent could spread amongst rabbits under Australian conditions. The Pasteur team insisted that they could only perform the experiments outlined by Pasteur and would only undertake the trials originally planned

Figure 1. Views of Rodd Island (images from NSW National Parks).

by Pasteur. The Pasteur team performed the pre-planned experiments and left the island. Dr Katz obtained the Pasteur culture from the heart blood of an infected rabbit (with the approval of the Pasteur team). He continued to work and reported that the chicken cholera could infect native birds. His work was also cited as evidence of limited rabbit to rabbit transmission, although that claim is doubted[5]. By early 1889, the Rabbit Commission rejected the Pasteur proposal (on the grounds of limited transmission) and by late 1889 had rejected all submitted proposals. Loir and team departed Australia following this rejection.

Cumberland disease (and other diseases)

While working on the rabbit problem, Loir also investigated a disease of cattle and sheep then sweeping the Cumberland district around Leppington. Loir was able to isolate a bacterium (*Bacillus anthracis*), which on the basis of microscopic appearance and the disease caused in experimentally infected rabbits, he confirmed as the same agent as that causing charbon (the French name) or anthrax (the English name)[6]. Loir then produced a vaccine according to the Pasteur method and demonstrated a high level of protection in vaccinated sheep and cattle exposed to an artificial challenge involving the injection of blood from a sheep that had died of Cumberland disease. All 20 sheep and four cattle given the Pasteur vaccine survived the challenge: all 19 control sheep and one of the two control cattle died within 60 hours (Figure 2)[6]. The farmers were convinced of the efficacy of the Pasteur approach and the colonial NSW government asked Loir to produce the vaccine on an on-going basis.

With approval from Pasteur, Loir did return to Australia and the Rodd Island laboratory complex in 1890. Over the following eight years, Loir and his team vaccinated some 3 million sheep and 50 000 cattle against anthrax (https://www.asap.unimelb.edu.au/bsparcs/exhib/pasteur/pasteur.htm). As well, Loir worked

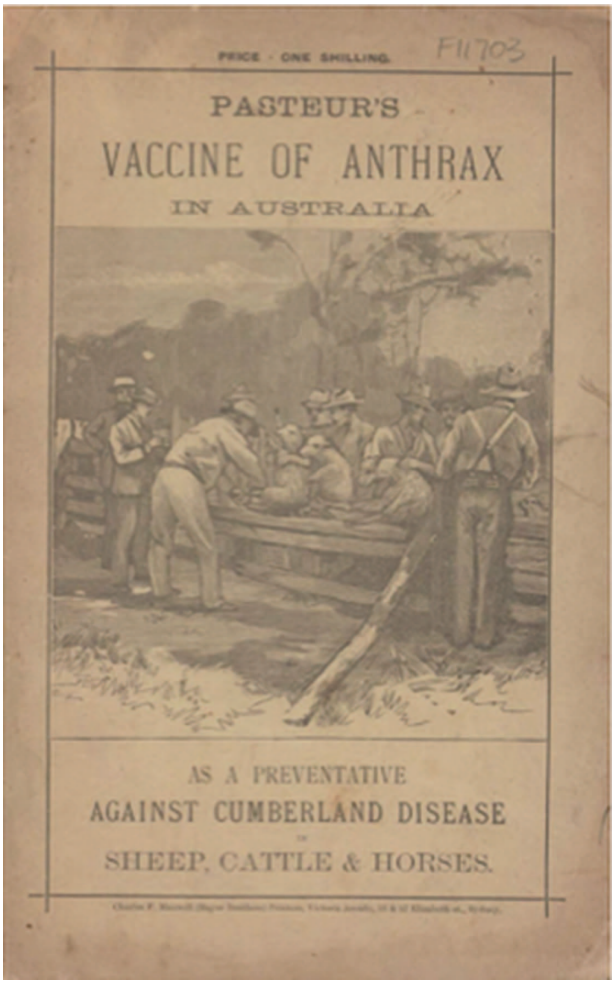

Figure 2. Cover page of the 1891 report by Loir on Pasteur's Anthrax Vaccine.

closely with the colonial government in Queensland and developed a bovine pleuropneumonia vaccine (causative agent – *Mycoplasma pleuropneumoniae)* and introduced the use of the Pasteur blackleg vaccine (causative agent – *Clostridium chauvoei*)[5]. Considerable funds flowed back to France from these activities – some 450 000 francs from the sales of the anthrax vaccine and 250 000 francs from the grateful Queensland government for the work on bovine pleuropneumonia. These returns at least matched the original rabbit control prize,

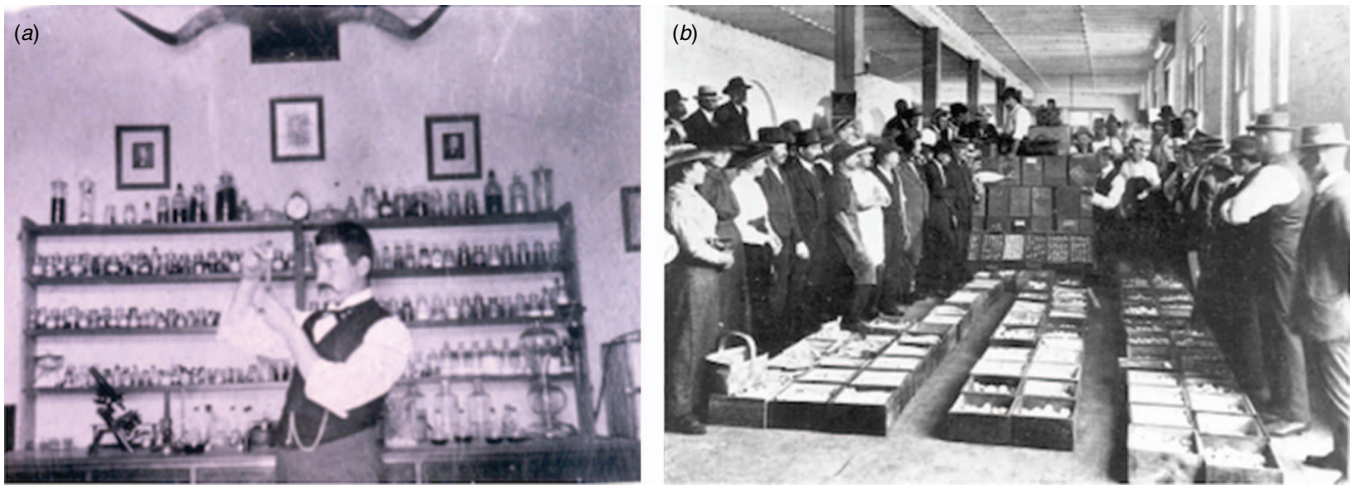

Figure 3. (*a*) CJ Pound at work in his laboratory at the Stock Institute in Brisbane. (*b*) CJ Pound talking to farmers about chicken cholera and the possibility of using that disease as a control for the rabbit plague.

although Pasteur himself remained bitter and upset with the colonial New South Wales government[5]. Rodd Island ceased to be a vaccine facility in 1894 and the laboratory and animal facilities were removed. The living quarters of the original Pasteur Institute remain on Rodd Island, which is now a popular NSW National Park.

On-going biological control attempts

While Loir left Australia permanently in 1893 for family reasons (his young French bride never adapted to life on Rodd Island), interest continued in biological control of the rabbit problem. The colonial Queensland government had been so impressed with the work of Loir that they had offered him the Directorship of the first Australian veterinary diagnostic/research institute, the newly established Stock Institute. The offer was declined and CJ Pound was appointed[7]. CJ Pound was an active supporter of the Pasteur proposal for rabbit control (Figure 3). Pound[8] definitively proved that fowl cholera was present in poultry in Australia, dismissing the belief that fowl cholera was not present in Australia. As well, in trials performed at the Stock Institute and 'large scale natural conditions in open country' (around Thargomindah), Pound showed that 'pollard soaked with half-a-pint of *P. multocida*' can 'infect with certainty at least 1,000 rabbits'[9]. Remarkably, Pound also reported that the bacterium can be 'injected into and taken internally by human beings, horses, cattle, sheep, pigs, or in fact almost any domesticated or wild animals (excluding birds and rabbits), without producing the slightest harm or inconvenience'[9]. While current molecular studies support the possibility of host specificity for *P. multocida*[10], no modern research team would have a chance to confirm the cited findings about avian or leporine isolates of Pound[9] due to animal and human ethical concerns. Indeed, the claim by Pound stands in contrast to the fact that until recent times mouse inoculation (via the intra-peritoneal route) was a preferred means of recovering *P. multocida* from a range of contaminated environments[11].

Class wars and science

Throughout the work investigating the biological control of rabbits by Loir and others, there was always considerable heated public debate. One of the most unusual of these debates occurred when work was undertaken in 1906 by a Dr Danysz (from the Pasteur Institute) who claimed to have a 'new' rabbit specific strain of *P. multocida* that could not infect other animals[12]. Danysz was given facilities on Broughton Island, near Newcastle. While Danysz felt his experiments proved his theory of host specificity, a Government Commission concluded that the work was simply inconclusive[13].

The public debate on this matter was encouraged when several staff had to be evacuated from Broughton Island because of ill health. While the public debate focussed on the possibility of a laboratory acquired infection, the formal conclusion was that the research team had, embarrassingly for a bacteriology research unit, suffered from 'ptomaine poisoning'[13]. The public debate also focussed on a class war argument[1]. In this argument, the work on Broughton Island was characterised as 'the abominable, filthy disease cultivated by Dr Danysz'[1]. The argument was that the control of rabbits by disease was 'capitalist-class' action with the working man being denied a means of obtaining cheap food and income, the latter via the sale of rabbit pelts[1]. The suggestion was that an export trade of rabbit meat based on 'freezing-houses' in regional areas would ensure a viable income for the working man and control the plague[1].

History repeats itself

Many will remember the saga of Pistol and Boo, two dogs smuggled into Australia by a high-profile Hollywood couple during filming on the Gold Coast[14]. However, this was simply an example of history repeating itself. Rodd Island starred as a centre of a quarantine row when Sarah Bernhardt, a French actress who was described as the world's most famous woman, arrived in Sydney in 1891 with two dogs (Star and Chouette) as part of a tour of Australia. Ever the gentleman, Loir offered Rodd Island as a quarantine facility to prevent the forced return of the dogs to France. Bernhardt and Loir developed a relationship that resulted in a cancellation of the Brisbane leg of the tour to allow Bernhardt to spend a week on Rodd Island[14]. While the details are now hazy with time, the stories circulating at the time include long nights of celebration on Rodd Island following performances by Bernhardt in Sydney, including champagne parties on the roof of the laboratory!

Conclusion

Biological control of the rabbit plague in Australia remained a dream for many years till myxoma virus was introduced after World War II and supported by the pioneering work of Frank Fenner and colleagues[15].

Conflicts of interest

The author declares no conflicts of interest.

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Biography

Pat Blackall is a bacteriologist working at the Queensland Alliance for Food and Agriculture Innovation at the University of Queensland. Pat has spent most of his career at the Animal Research Institute, the institute that replaced the Stock Institute founded by CJ Pound. Pat has had a long and continuing research interest in *Pasteurella multocida* and the diseases associated with the organism in both domestic livestock as well as Australian native animals.

Presidential viral exchanges

Donald Trump is not the first US President to be involved in a potentially deadly viral exchange with his personal staff. President Abraham Lincoln was struck down with smallpox hours after delivering his Gettysburg address on 19 November 1893. His famous, albeit very short speech, was given during the American Civil war at the dedication of the Soldiers National Cemetery in Gettysburg Pennsylvania, 4.5 months after the defeat of the Confederate armies by those of the Union.

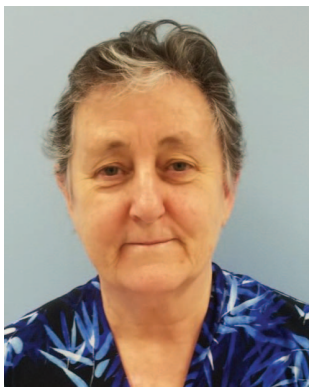
Smallpox was spreading rapidly through Washington at the time.

Bedridden with head and neck pain, Lincoln was cared for by his body man or valet, William H Johnson, a black man from Illinois, whose main task was to hold a cold towel to Lincoln's head. Lincoln recovered in a few weeks but Johnson did not - he died the following January. The president did not think he had infected Johnson, but subsequent historians believe he did. Whatever the case, the president ensured his loyal carer's debts were paid, his family provided for, and that he was buried in Arlington National Cemetery in Section 32, alongside the 1500 US Coloured Troops who fought for the Union.

In 1980 the WHO declared smallpox eradicated, solely through vaccination.

Gonorrhoea: past, present and future

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Abstract. The sexually transmitted infection (STI) gonorrhoea is an ancient human disease caused by the Gram-negative bacterial pathogen *Neisseria gonorrhoeae*. Despite decades of research focused on preventing, diagnosing, and treating gonorrhoea, it remains a major global health concern due to its high prevalence, high rates of asymptomatic cases, the severe sequelae that can result from untreated infections, and the increasing difficulty in treating infections caused by multi-drug resistant strains of *N. gonorrhoeae*. It is estimated that there are more than 87 million cases of gonorrhoea worldwide each year, and the WHO, CDC and Australian National Antimicrobial Resistance (AMR) Strategy have prioritised *N. gonorrhoeae* as an urgent public health threat for which new therapeutics and a vaccine are needed.

Where did it all begin? The long history of gonorrhoea

Gonorrhoea is an ancient disease of humans, with symptoms resembling gonorrhoea reportedly described in ancient Chinese and Middle Eastern records dating as far back as 3500 BC[1]. There is also reference to urethral discharge, believed to be gonorrhoea, in the book of Leviticus in the Old Testament of the Bible (Leviticus 15:1-3). The name gonorrhoea is credited to Greek physician Galen (AD 130-200), which means the flow of semen, derived from the Greek words 'gonos' (semen) and 'rhoia' (to flow)[1]. In the 16th century, as STIs were recognised as being more common in prostitutes, gonorrhoea became known as 'the clap,' likely in reference to the old Le Clapiers district of Paris where prostitutes were housed. It was not until 1879, however, that the bacteria responsible for gonorrhoea was identified and named *Neisseria gonorrhoeae* after Albert Neisser the German microbiologist who first isolated the bacteria (Figure 1). Over time, gonorrhoea has been described extensively in scientific literature, as well as in essays such as 'Boswell's Clap' that describe James Boswell's nineteen episodes of gonococcal urethritis between 1760–1790 based on his detailed diary accounts[2], and news articles describing its antibiotic resistance status, including 'Man has 'world's worst' super-gonorrhoea' (BBC News, UK, 28 March 2018).

Where are we now? Current clinical aspects of gonorrhoea

The WHO estimates that more than 1 million STIs occur every day[3]. There are an estimated 87 million gonorrhoea

infections occurring each year[3] and *N. gonorrhoeae* has been prioritised as an urgent public health threat by the WHO[4], CDC[5] and Australian National AMR Strategy[6]. STI surveillance systems vary widely within and across WHO regions, which means that current figures likely underestimate the burden of gonorrhoea due to limitations in diagnosis and reporting. Several systems currently exist in Australia for the surveillance of *N. gonorrhoeae* infections, including state-level reporting via the Notification of Communicable Diseases, as well as the Australian Gonococcal Surveillance Programme (AGSP) conducted by the National Neisseria Network (NNN). These systems provide incidence, demographic, and antimicrobial resistance data to inform clinical and public health responses to continue towards gonorrhoea control. Rates of gonorrhoea have continued to increase in Australia over the last 10 years, with an 80% increase between 2013 to 2017[7]. Rates of gonorrhoea are particularly high in gay and bisexual men (GBM), Australia's First Peoples and younger populations (19–29 years) and there has been a recent resurgence of gonorrhoea in urban heterosexuals[7]. In 2019 there were 34 265 gonococcal infections notified in Australia[8].

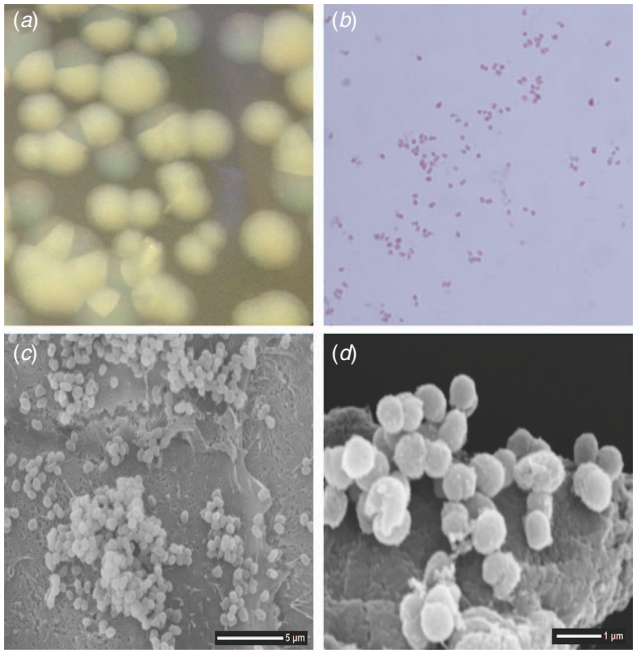

Figure 1. *Neisseria gonorrhoeae* (Ng) under the microscope. (A) Light microscope image of Ng colonies on an agar plate (×4 magnification). Opaque and translucent colonies are seen due to phase variation of opacity (Opa) proteins. (B) Light microscope image of Gram-stained Ng (×100 magnification). Scanning electron micrograph of Ng microcolonies on the surface of urethral epithelial cells, acquired at (C) ×5000 magnification (scale bar represents 5 µm) and (D) ×17 000 magnification (scale bar represents 1 µm).

The gold standard for *N. gonorrhoeae* diagnosis remains culture due to its high specificity and the ability to perform antibiotic sensitivity tests to guide treatment. However, culture yields are highly dependent on bacterial loads, storage and transport of specimens. This impacts extragenital site sampling where culture rates could be as low as 64% in pharyngeal infections[9]. In addition, the intimate and invasive nature of obtaining urethral and cervical samples limit its utility for widespread screening and testing programmes. Since 2002 nucleic acid amplification tests (NAATs) have been preferred as the screening tool for *N. gonorrhoeae* infection. NAATs have demonstrated superior detection rates with 97–99% sensitivity, and outperform culture by up to 2-fold for rectal and 5-fold for pharyngeal gonorrhoea infections[10]. NAATs have also been pivotal in improving access and uptake of gonorrhoea screening programmes, with a high level of acceptability and effectiveness for detecting gonorrhoea infection[11]. Multiplex NAATs testing are also being developed, so that samples can be tested for up to nine different pathogens including *Chlamydia trachomatis*, *Trichomonas vaginalis* and *Mycoplasma genitalium*[12]. Concomitant infection of *N. gonorrhoeae* with these infections occur in up to 30% of cases. Finally, NAAT tests have the ability to deliver a result in a matter of hours. A study in the UK demonstrated that the rapid

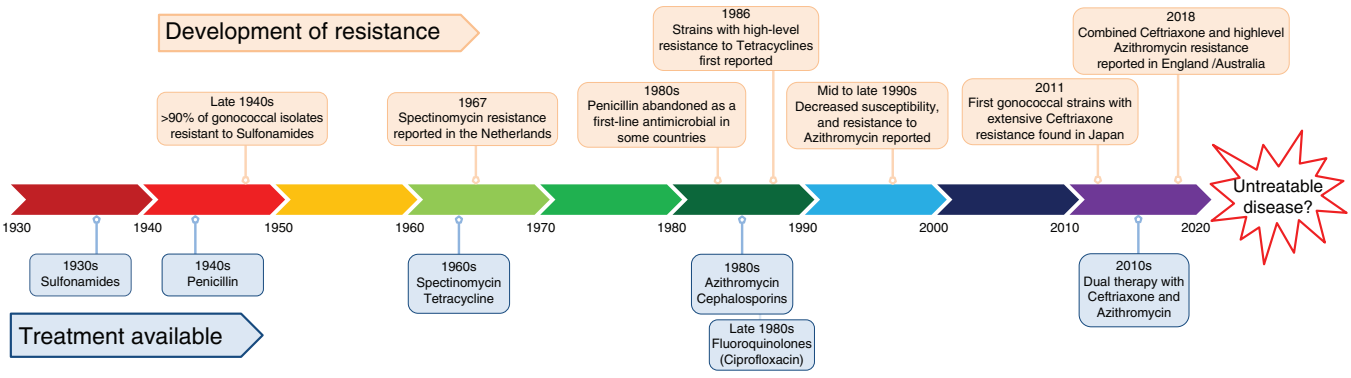

Figure 2. Timeline of *Neisseria gonorrhoeae* antibiotic treatments and antibiotic resistance. The recommended antimicrobials for treatment of *N. gonorrhoeae* since the 1930s are shown below the timeline. The evolution of resistance in *N. gonorrhoeae* is shown above the timeline. Adapted from Unemo and Shafer[15].

turnaround of results would reduce time to diagnosis by more than 8 days leading to potential reduction in transmission[13].

The outcome of *N. gonorrhoeae* infection varies by site of infection and by sex[14]. Symptomatic infections predominantly affect the genito-urinary tract with 90% of penile infections presenting with purulent discharge or dysuria, whilst approximately 50% of cervical infections present with changes in vaginal discharge, intermenstrual or post coital bleeding. Complications of *N. gonorrhoeae* can occur leading to epididymo-orchitis and pelvic inflammatory disease subsequently leading to an increased risk of infertility and ectopic pregnancy. Rarely, haematogenous spread can occur causing skin lesions, arthritis and tenosynovitis (disseminated gonococcal infection). Extragenital *N. gonorrhoeae* infections also occur leading to pharyngitis, proctitis and uveitis, though asymptomatic pharyngeal and rectal infections are common. Though gonorrhoea remains a curable infection, treatments have changed rapidly over time to

Table 1. Antimicrobials and vaccines under development for *Neisseria gonorrhoeae* (Ng).

Name	Description	Mode of action/function	Stage	Reference
Antimicrobials				
Lefamulin	Antibiotic	Protein synthesis inhibitor	Clinical trial	18
Gepotidacin	Novel antibiotic	DNA replication/topoisomerase inhibitor	Clinical trial	
Zoliflodacin	Novel antibiotic	DNA replication/topoisomerase inhibitor	Clinical trial	
SMT-571	Novel antibiotic	Disrupts cell division	Preclinical	24
DIS-73285	Novel antibiotic	Electron chain protein disruption	Preclinical	25
Fenamic acids	Repurposed drug	Anthranilic acid derivatives/NSAIDs, mode of action against Ng unknown	Preclinical	26
Methyldopa	Repurposed drug	Hypertension medication, adherence blocking	Preclinical	27
Carbamazepine	Repurposed drug	Anticonvulsant medication, adherence blocking	Preclinical	27
LL37	Host-derived cationic peptide	Disrupts bacterial membrane	Preclinical	28
Self-inhibitory peptides	Engineered synthetic peptides	Destabilizes target protein function/activity	Preclinical	29
Mannosides	Class of small drugs that contain sugar – mannose	Adherence blocking	Preclinical	30
Vaccines/candidate vaccine antigens				
4CMenB	Licensed meningococcal serogroup B vaccine: MeNZB OMV, NadA, NHBA-GNA1030, fHBP-GNA2091	Induces antibodies to Ng, OMV component calculated to have 31% effectiveness against gonorrhoeae in a retrospective study of MeNZB	Clinical trial	21,23
2C7	Peptide mimic of Ng LOS epitope 2C7	Bactericidal antibodies	Preclinical	14
AniA	Nitrite reductase	Function blocking and bactericidal antibodies	Preclinical	
BamA	Outer membrane protein assembly factor	Bactericidal antibodies	Preclinical	
MetQ	Methionine-binding protein of ABC transporter	Adherence blocking and bactericidal antibodies	Preclinical	
MsrA/B	Methionine sulfoxide reductase	Function blocking and bactericidal antibodies	Preclinical	
MtrE	Outer membrane channel protein of MtrCDE efflux pump	Bactericidal antibodies	Preclinical	
NHBA	Neisseria Heparin Binding Antigen	Function inhibiting, adherence blocking and bactericidal antibodies	Preclinical	
OMV	Naturally secreted outer membrane vesicles	Contain repertoire of Ng outer membrane proteins	Preclinical	
PilQ	Type IV pilus biogenesis and competence protein	Bactericidal antibodies	Preclinical	
TbpA/B	Transferrin binding proteins A and B	Bactericidal and growth inhibitory antibodies	Preclinical	
TdfH	TonB-dependent transporter H	Function blocking antibodies	Preclinical	

overcome emerging drug-resistant *N. gonorrhoeae* (Figure 2). The future effectiveness of antibiotic treatment has been significantly compromised by the fact that *N. gonorrhoeae* has developed resistance to all classes of antibiotics used to treat it[15]. Worldwide, penicillin, ciprofloxacin and cefixime are no longer recommended first-line treatments. Instead dual antibiotic combination of ceftriaxone and azithromycin are preferred, though there is increasing concern of azithromycin resistance. In 2018, 'Super gonorrhoea' resistant to all routine antibiotics, including the recommended dual therapy of intramuscular ceftriaxone/oral azithromycin, was reported in the UK[16] and Australia[17].

Where to next? Future therapeutic and vaccine development for gonorrhoea

This century, scientists have made significant advances in understanding gonococcal biology, as well as its mechanisms for causing disease and evading the immune system. Most importantly, they have also discovered new approaches to prevent and treat the infection, many of which are in final stages of development. Currently there are three new antibiotics in clinical trials and there are also several other novel drugs or treatment methods in development or preclinical settings (Table 1)[18]. Novel diagnostics and genotyping technologies are also being developed for rapid detection of mutations to guide antibiotic therapy[19].

It is widely considered that vaccination will be the best long-term solution to gonorrhoea. However, gonococcal vaccine development is challenging. *N. gonorrhoeae* infection does not protect against subsequent infection, therefore there are no correlates of protection from natural immunity to guide vaccine development[14]. Four gonococcal vaccine candidates have been tested in human clinical trials (all pre-2000) but none provided any protection against *N. gonorrhoeae* infection[14]. However, several new vaccine antigens are currently in preclinical development (Table 1)[14,20]. Considerable funding from the US National Institute of Health (NIH) was recently allocated for creation of large collaborative research groups, aiming to deliver a gonococcal vaccine into clinical trials within 5 years.

The feasibility of a gonococcal vaccine was supported by recent findings from a retrospective study that showed decreased *N. gonorrhoeae* rates following vaccination with an outer membrane vesicle (OMV)-based vaccine (MeNZB) licenced to protect against the closely related bacteria *Neisseria meningitidis*[21]. MeNZB was estimated to have a vaccine effectiveness of 31% against *N. gonorrhoeae*[21]. Mathematical modelling has indicated that a gonococcal vaccine with 30% efficacy would be expected to halve gonorrhoea prevalence within 20 years[22]. The MeNZB vaccine was succeeded by a multicomponent meningococcal serogroup B vaccine – 4CMenB (tradename Bexsero), that in addition to the MeNZB OMVs, contains additional recombinant antigens. 4CMenB has been shown to induce cross-reactive antibodies to *N. gonorrhoeae* in humans[23], and is now in clinical trials to investigate its efficacy against gonorrhoea. One of these studies is underway in a population at high risk of contracting *N. gonorrhoeae* in Australia (MenGO; ANZCTR Identifier: 12619001478101). Two additional efficacy studies will commence shortly in Australia (GoGoVax; ClinicalTrials.gov Identifier: NCT04415424) and United States (NCT04350138), with estimated completions dates in 2023.

Conclusions

The discovery of antibiotics ushered a new age in medicine, allowing treatment of many bacterial infections that plagued mankind, including millennia old gonorrhoea. However, the gonococcus was able to acquire resistance to new antibiotics as quickly as they were developed and we have reached the point where strains resistant to 'last line of defence' antibiotics have emerged, prompting urgent action. Currently there are several new antibiotics and vaccine antigens being investigated at all stages of the clinical development pipeline, which will hopefully deliver new treatments and a cure for the clap.

Conflicts of interest

The authors declare no conflicts of interest.

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Biographies

Evgeny Semchenko is a Postdoctoral Researcher at the Institute for Glycomics at Griffith University. He is a microbiologist and an expert in the field of pathogenic Neisseria, working on investigating interactions between bacteria and host glycans, identifying and characterising bacterial glycan-binding proteins and applying this knowledge to the development of new vaccines and treatment options.

Xiaofan Chen is a student at the Institute for Glycomics at Griffith University. She just finished her honours degree and continues to focus on pathogenic Neisseria during her PhD, investigating new ways to treat gonorrhoea.

Caroline Thng is a Sexual Health and HIV physician at Gold Coast Sexual Health. She has worked as a specialist in both the UK and Australia, and is an expert in complex STI and HIV management. She has delivered clinical trials, observational cohort studies, social research, and epidemiological research both locally and in collaborative projects. She is the co-PI in the first Australian trial using Meningococcal B vaccine as a potential prevention strategy against gonorrhoea infection.

Maree O'Sullivan is the Clinical Director at the Gold Coast Sexual Health Service. She has clinical trials experience over 20 years, including multinational drug trials predominately in the HIV and vaccine sectors. She has also undertaken self -initiated, and collaborative, qualitative and quantitative clinical research in HIV and Chlamydia.

Kate Seib is a Research Leader and the Associate Director (Research) at the Institute for Glycomics at Griffith University. Her expertise is in the field of molecular microbiology, with a focus on understanding virulence mechanisms and characterising vaccine antigens of human mucosal pathogens (e.g. *Neisseria gonorrhoeae, Neisseria meningitidis, Moraxella catarrhalis, Haemophilus influenzae*).

A brief history of AAHL

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Abstract. The CSIRO Australian Animal Health Laboratory (AAHL) was officially opened on 1 April 1985. After that day the laboratory switched to secure mode and has operated as such ever since. AAHL was constructed to be the primary national diagnostic facility for exotic animal diseases but has expanded its role to become a national and international reference laboratory for many diseases. AAHL has supported disease control within the region by providing training, reagents and proficiency testing, both within Australia and internationally. AAHL's role has evolved even further to include a focus on one-health which resulted in AAHL being renamed the Australian Centre for Disease Preparedness (ACDP) in March 2020.

Establishment of AAHL

In 1958 CSIRO established the Animal Health Research Laboratory in Parkville, Melbourne. Australia had little expertise in viral diseases of farm animals and depended on international advice and disease diagnosis. In 1962 an Exotic Diseases Committee of the Australian Veterinary Association recommended that a central Commonwealth Exotic Disease Laboratory be established. Over the 1960s various reports decided that the laboratory should be built as a matter of urgency, its functions determined and that it should be managed and operated by CSIRO[1]. A panel was convened and agreed that its functions should be to:

- Establish techniques for the rapid diagnosis of exotic or foreign animal diseases
- Conduct research on endemic virus infections of animals and assist in their control
- Train field staff in the recognition and presumptive diagnosis of virus diseases, and laboratory staff in techniques for the isolation and identification of viruses
- Provide highly trained virologists, and maximum-security laboratory and animal accommodation

A Proposal Evaluation Team (PET) was established to visit international high security facilities, discuss operation of high security facilities and evaluate the systems used to maintain security. From 14 October to 20 December 1970 the PET visited 15 high-security laboratories in Australia, the USA, UK and Europe that handled animal and human pathogens, agents that may be used for germ warfare and vaccine production facilities. The PET concluded that it would be feasible to construct a high security laboratory and estimated the construction costs to be $25 million ± 25%.

Selection of a site

In 1972 the government gave in-principle support for the establishment of AAHL and 35 potential sites were evaluated. Following a change of government in 1972 plans for the development of the Geelong region were released, a further search made and the Geelong Rifle Range site selected. Government commitment for the construction of AAHL wavered over the next 5 years. In October of 1977 Bluetongue virus was confirmed as being present in Australia. In January 1978 the Prime Minister agreed that the construction of AAHL be included in the civil works program for 1977–78 and in February 1978 CSIRO signed the requisition for the Commonwealth Department of Works to construct AAHL at a cost of $83 million. On 20 March 1978 the Prime Minister, Malcolm Fraser turned the first sod to start construction[1].

Construction

Many of the systems identified as essential for microbiological security by the PET during planning did not exist so the Commonwealth Department of Works set about their design and development. Seals for maintaining wall airtightness, airtight doors with inflatable seals, sewerage collection and treatment systems, high efficiency particulate air filter cannisters, floor finishes, ventilation system and air pressure controllers were all developed and tested in an AAHL protype building, constructed at the CSIRO Maribyrnong Field Station. AAHL was constructed so that every system critical for biosecurity has at least 100% backup; including electricity, water, gas, generators, compressors, fuel, incinerators and air handling[1].

The construction and biosecurity were reviewed by a group of experts from the USA. Their report stated, 'The facility contains

almost every conceivable containment feature desired in a high hazard animal disease research and diagnostic laboratory. This is the world's most advanced facility of its kind. Many of its features are expected to be used over the next 25–30 years as models for high hazard biomedical and animal laboratories throughout the world'[1]. As at October 1977 the estimated cost of constructing AAHL was estimated at $83 million. On completion of construction and commissioning in 1984 the cost was $158 million. If AAHL was constructed today the cost of construction would be $1.2 billion.

The science

In February 1984 a group of about 20 scientists from the Animal Health Research Laboratory in Parkville relocated to AAHL and began the set to work phase. A priority was the development of a foot and mouth disease (FMD) diagnostic capability and two AAHL staff were sent to the Animal Virus Research Institute, Pirbright to develop diagnostic ELISA's, confirm that the reagents contained no live FMD and send the reagents to AAHL[2]. Validation of the reagents in the field was done by AAHL staff at the Thai Northern Veterinary Research and Diagnostic Laboratory in Lampang.

AAHL's first challenge was an outbreak of respiratory disease in commercial chickens in late 1984 in NSW, caused by a Newcastle disease virus (NDV). As the laboratory was not yet operating in secure mode the south suite of laboratories was put into Physical Containment Level 3 mode to handle samples from the outbreak, the only time at AAHL that one suite has been isolated from the rest of the facility. Although this NDV was not virulent the virus persisted in poultry for years afterwards. A virulent NDV that evolved from the 1984 respiratory virus reappeared in September 1998 to cause an outbreak of severe neurological disease in commercial chickens in NSW[3] and continued to cause outbreaks until 2002, when vaccination was introduced.

Newcastle disease also caused a major political problem for AAHL when, in 1987, a laboratory technician became infected with virulent Newcastle disease virus following laboratory exposure, developing conjunctivitis and other clinical signs. A review of the incident was critical of the laboratory procedures that lead to the spill but was more critical of the management of the incident; the clean-up, on-going health monitoring, lack of movement restrictions on the infected staff member and reporting of the incident to stakeholders[1]. One change in response to the review was the construction of an on-site quarantine unit to isolate staff exposed to an infectious agent. To date this has been used three times, for potential exposure to vesicular stomatitis, Newcastle disease and Hendra viruses respectively[1]. In all cases the staff did not become infected.

On 1 April 1985 AAHL was officially opened. A month later, in late May 1985, AAHL responded to an outbreak of highly pathogenic avian influenza on a Bendigo poultry farm caused by an H7N7 Influenza A virus[4]. Outbreaks caused by H7 avian influenza viruses occurred in 1992, 1994, 1997, 2012 and, at the time of writing, with another three outbreaks in Victoria in 2020. AAHL has also been central to Australia's response to the H5N1 epizootic in Asia. It has an externally funded overseas program to assist with the diagnosis and control of H5N1 in the region, which is on-going to the present.

AAHL took over the rabies diagnostic role from the Commonwealth Serum Laboratory in 1986. In 1987 AAHL confirmed a fatal case of human rabies in a young boy who had recently travelled overseas, the first recorded case of human rabies in Australia in over 100 years. In 1990 AAHL confirmed another rabies case in a young girl who arrived in Australia 5 years before and had not travelled overseas since. In both cases the viruses were sequenced and confirmed as Asian dog rabies[5].

The transmissible spongiform encephalopathy (TSE) laboratory was established at AAHL in 1988 and did scrapie associated fibril extractions and mouse inoculations of brains from animals showing clinical disease suggestive of TSE. In 1992 samples were submitted from a cheetah in Broome Zoo, which tested positive for TSE. Its litter mate was tested and was also positive[6]. Both animals were imported from the United Kingdom so were most likely infected there. More zoo cats were tested and in 2002 a golden cat from Melbourne Zoo was found to be TSE positive[7]. These cases did not pose a risk of introduction into Australia as both animals were in indefinite quarantine.

In 1989 the Australian Fish Disease Reference Laboratory (FDRL) relocated to AAHL from the Benalla Regional Veterinary Laboratory. The FDRL have been involved in many fish disease investigations and research, including the pilchard die off, orthomyxoviruses in farmed salmon, abalone herpes virus and white spot disease in prawns amongst many others. It played a key role in the diagnosis and control of the recent white spot disease outbreak in farmed prawns in Queensland.

AAHL has proved its value to Australia on many occasions in the diagnosis of many known and unknown virus diseases. The best example of this was in 1994, when on 22 September AAHL was notified by the Queensland CVO that there was an outbreak of severe respiratory disease in horses at a stable in the Brisbane suburb of Hendra. The samples arrived on 23 September and all

tests for known agents gave negative results. On 26 September a virus was observed growing in cell cultures, which was identified as a previously unknown paramyxovirus by electron microscopy and gene sequencing. Koch's postulates were demonstrated by reproducing the disease in experimentally infected horses. By the end of that week I had developed a virus neutralisation test for antibodies and were testing in-contact animals and humans. Eventually AAHL was able to demonstrate that the infection was confined to 21 horses and two humans on a small number of properties[8].

In 1995 AAHL confirmed another case of Hendra in a sugar cane farmer from Mackay who had died 12 months after infection with Hendra virus in August of 1994[9]. AAHL then played an important role in the 1996 identification of Pteropid bats as the reservoir species[10]. The subsequent increased testing of bats resulted in the identification of Australian bat lyssavirus in Australian bats[11]. Eighteen years after the emergence of Hendra virus AAHL was central to the research and development of a Hendra virus vaccine to reduce the risk of Hendra virus infections in horses and the associated risk to attending veterinarians[12].

AAHL deals with many disease agents and is a reference laboratory for some of these agents. It is an Australian national reference laboratory for avian influenza, Newcastle disease, rabies and Brucellosis, a Food and Agriculture Organisation (FAO) and World Animal Health Organisation (OIE) reference laboratory for avian influenza and Newcastle disease and a foundation member of OFFlu, the OIE/FAO Animal Influenza network. AAHL is an OIE reference Laboratory for Hendra/Nipah, bluetongue, African swine fever, classical swine fever, abalone herpes virus, ranavirus, epizootic haemopoietic necrosis virus and yellowhead viruses. It is also an OIE Collaborating Centre for New and Emerging diseases, a Collaborating Centre for Veterinary Laboratory Capacity building, and a Collaborating Centre for Diagnostic Test Validation. AAHL's role has changed with time and it has achieved accreditation as a provider of proficiency tests to Australian and international laboratories.

Prior to AAHL opening there was more than 20 years of consultation, lobbying, laboratory visits, planning and debate with government, politicians, farmers and industry. The reasons for the longevity of AAHL (ACDP) are the attention to detail in planning, prototype testing and quality of the construction. Without the vision and leadership of Bill Snowdon the design and construction of a national animal health laboratory may have remained only a dream. Even after 35 years of operation ACDP is still one of the foremost high security infectious disease laboratories in the world and a multi-million-dollar refit and upgrade currently underway will ensure that ACDP continues to be a centre of excellence for infectious diseases for many years to come.

Conflicts of interest

The author declares no conflicts of interest.

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Biography

Paul Selleck has been at the Australian Animal Health Laboratory, now the Australian Centre for Disease Preparedness since 1983. In this time he was head of the Avian Disease Diagnostic Laboratory and an OIE Reference Expert for Avian Influenza and Newcastle Disease. He was also involved in the Australian equine and swine influenza outbreaks in 2007 and 2009 respectively and now works extensively in Asia on the diagnosis and control of H5N1, biosafety and biosecurity.

Understanding the SARS-CoV-2 pandemic as evolution in action

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Abstract. In the midst of our pandemic, when we are up to our necks in a torrent of news, opinion and speculation, it is important to step back from our personal interests in SARS-CoV-2 to consider the broader biological and social evolutionary context of what we are experiencing.

First, we are not unique – many other organisms are also currently experiencing pandemics for which humans are at least partly responsible – rabbits, pigs, frogs, chestnut and other trees, and even bats[1–7]. Disease outbreaks in human populations are manifest simultaneously as biological, geopolitical, sociocultural and ecological evolutionary events. They have been shaped in part by the evolution of opportunities for disease transmission offered by our transformation from nomadic hunter-gatherers to urbanised world travellers.

It is important to remember that evolution is a journey without a destination or a goal – it is a consequence, not a response. In a world of unfathomably complex and interdependent ecosystems, the random chance of mutations and the vast complexity of interindividual interactions across and between species shape the probability that individuals and their social groupings will fail or succeed.

For social organisms, the viability of the complex emergent phenomenon of community is driven by the genetically driven behaviours of its members[8,9]. Human evolution, biological and cultural, is further complicated by our talents for overriding the effects of genes and learning novel behaviours. Most commonly, and in the absence of calamity, the social evolution of humans plays out over long time frames. For those interested in exploring these issues more broadly, I suggest the following references[10–13].

So, how is this pandemic an evolutionary event? Coronaviruses evolve. The replication of viruses is an imperfect process and a random array of new variants emerge. Most new forms will be mutant duds and incapable of using any animal as a host. Occasionally, either in their original host and/or perhaps facilitated by recombination with viruses of or in another host, infected cells produce genetic variants that are more virulent.

Once in a while, a successful new variant coronavirus will latch on to a human cell, subvert its molecular machinery to replicate itself repeatedly, make us cough and sneeze through a runny, snotty, virus-laden nose to spread their countless viral offspring to other humans, disrupt our organ function and physiology in novel ways, and perhaps kill some of us.

Early research suggested that SARS-CoV-2 was transferred from bats to pangolins (a low likelihood event in a human-free world but plausible in an environment of exotic culinary tastes), and perhaps evolved further in their new host before infecting humans[14]. If so, this was a journey to human parasitism via an intermediate animal host similar to several other bat-derived viral infections: Hendra (horses), severe acute respiratory syndrome – SARS (palm civet cats) and Middle East respiratory syndrome – MERS (camels). Further molecular analyses indicate that SARS-CoV-2 emerged unnoticed in horseshoe bats about 40–70 years ago, and either passed via the pangolin, or jumped directly to humans[15,16].

However, we are not passive in this relationship. While for pathogenic viruses we are simply a prospective substrate for reproduction, the challenges posed by parasites over countless millions of years has induced the consequence of the evolution of the attributes that comprise immune systems. Those that were more successful in sustaining their respective roles of host and parasites are our ancestors and those of our parasites.

Leaving aside our individual acquired personal susceptibilities, it is simply chance whether or not our genes render us non-susceptible or provide us with an immune system that might protect us when we meet a particular novel parasite. Sickle cell and similar diseases are examples of defences that emerged as

random mutations that, although causing some morbidity and mortality, offer resistance to a parasite (malaria). These genes persisted in places where malaria is a risk because they have found a place of delicate balance in the probabilities of survival that characterises the evolution of a group of individuals[17]. There is of course no predicting the characteristics of the future novel parasites that jump from other species. We may all have attributes waiting to be exploited by an organism with the means to turn our trait into an opportunity[18,19].

Contemporaneous records show that outbreaks of novel parasites have on occasions killed a huge proportion of human populations – over 50% mortality in some naïve communities[20]. Indeed, an epidemic in 1616–19 killed perhaps 90% of the native Americans of coastal Massachusetts who might have resisted the Pilgrims when they landed at Plymouth Rock in 1620[21,22].

Evolution can be rapid when selective mortality is very high: the genetics of a population of New Guinea highlanders who engaged in the mortuary ritual of endocannibalism was changed very significantly by the deaths of those who were genetically susceptible to Kuru, a transmissible prion disease related to Creutzfeldt Jacob disease (CJD)[23].

We do learn behaviours (cultural evolution) that reduce risk: not eating raw pigs (or polar bears or walruses!) because they may carry Trichinosis; cultural sanctions against eating sick marmots (in which plague bacteria – *Yersinia pestis* – are endemic) that are ignored at individual peril; and the public health measures of quarantine, masks and isolation[24].

An outbreak of a species-jumping illness in a small and isolated community may burn out without spreading beyond the confines of that population. If numerous enough, the less susceptible or more robust survivors can endow their successors with genes that offer a diminished vulnerability to that disease.

The evolution of human culture – the increasing complexity of technology and farming, of travel and trading practices, and of our networks of larger settlements – created opportunities for a range of new microparasites.

Descriptions of smallpox and measles did not appear in literature prior to a few thousand years ago[25]. Measles outbreaks stopped depending on the parasite jumping repeatedly from another species and became endemic in humans only after our community size reached a minimum of perhaps 100 000. As confirmation, a recent study of the genetic clock of measles found that its antecedent rinderpest, a disease of cattle, became a separate endemic disease of humans about 2600 years ago[26]. Our short and meaningful relationship with smallpox seems to have been a far more complicated tale of mummies, Vikings and mutations[27].

In 1492 Columbus, and the Spaniards who followed him, introduced smallpox and measles to the Americas. Having been isolated from the rest of the world for tens of thousands of years, before pandemics became possible, the indigenous populations were genetically naïve and died in droves from what were for them novel illnesses. Weakened, or even deconstructed, their civilisations were easily overwhelmed by small numbers of Spanish and Portuguese soldiers, and subsequently by northern Europeans. Other pandemic or epidemic diseases still require intermediate hosts that may be facilitated by human behaviour.

It was not until the development of extensive trade – along the Silk Road, across the Black Sea and throughout the Mediterranean – that humans were able to accelerate the spread of plague in our cohabiting and hitch-hiking fellow-traveller black rats and their fleas. Multiple outbreaks over many centuries killed over one-third of the population of Europe and shaped human social, cultural and political evolution[13,20].

Plague arrived in North America and Australia[28] around the end of the 19th century only because the invention of fast steam ships allowed its importation from China. In North America it caused short-lived epidemics and became endemic in native burrowing rodents with some help from ranchers seeking to control gophers. When my family and I arrived in Townsville in 1978, a new concrete slab on ground still required a 600 mm deep ratwall around the edge to exclude burrowing rodents. A friend and I shared ownership of a ratwall shovel!

African slaves imported to the Caribbean to grow sugar brought with them Yellow Fever and its vector mosquito *Aedes aegypti*. Together, Yellow Fever, to which Europeans were genetically naive, and rebellious slaves, who were resistant because they had evolved with the virus, eventually erased Napoleon's hopes for empire in the Americas. Subsequently, Napoleon's invasion of Russia was thwarted in large part by epidemics of Shigellosis and Typhus[13].

Massive human mortality from recurring epidemics of microparasites only subsided with scientific understanding of diseases, their life cycles and their transmission, followed by effective public health measures and vaccination. A simple graph (Figure 1) shows how mortality in New York City from a wide range of microparasites has declined over the past ~217 years[29]. Notably, the peak of mortality in the 1918–19 global influenza pandemic was lower than in any year of the 19th century.

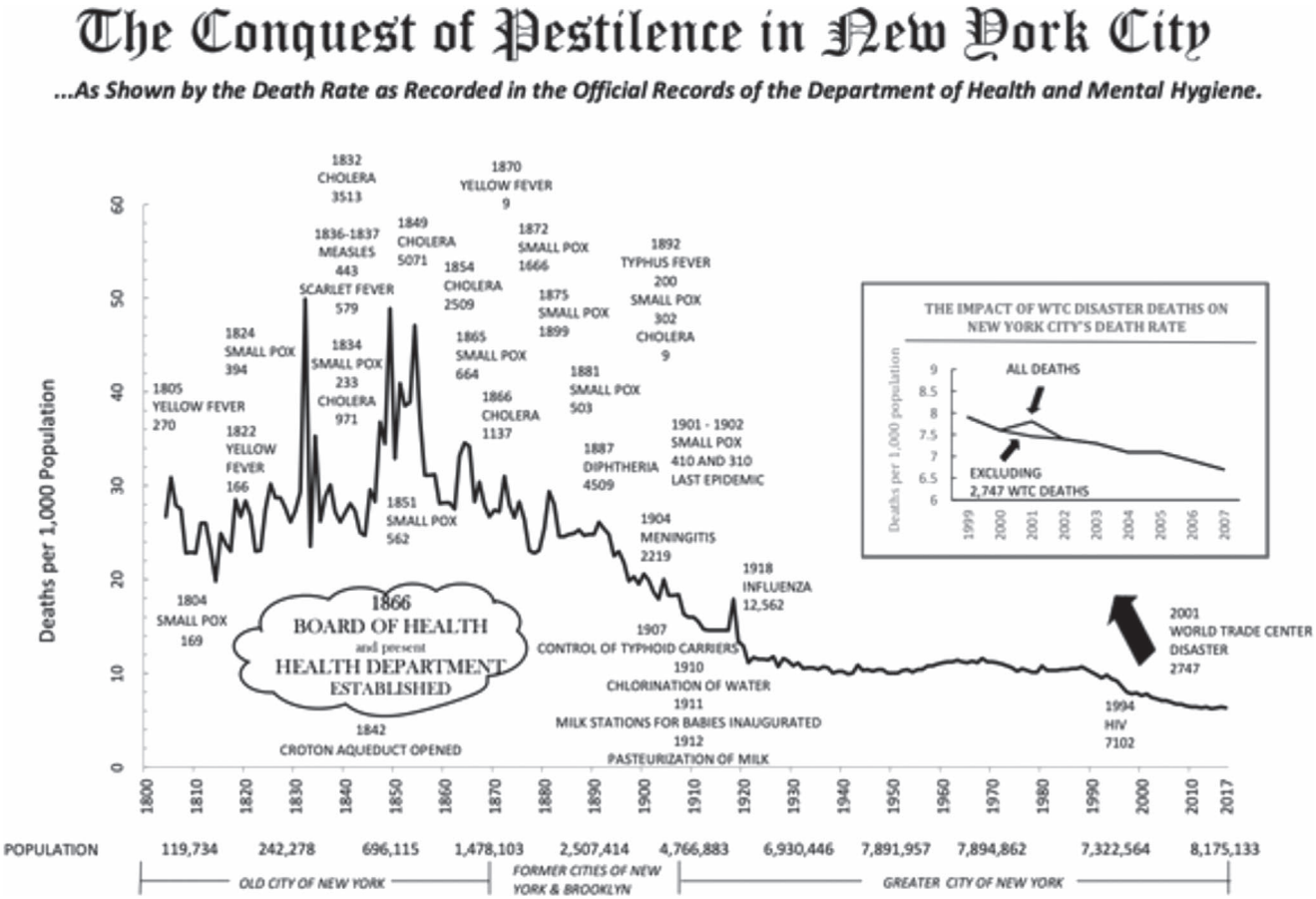

Figure 1. The conquest of pestilence in New York City (New York City Department of Health and Mental Hygiene[28]).

Where does all that leave us? SARS-CoV-2 is simply the latest of a stream of organisms that have chanced upon the means to take advantage of the molecular structure and function of our cells, our behaviour and/or our social organisation, and spread through our population.

Our biological and cultural evolution in a minimally changing environment generally unfolds so slowly as to be imperceptible in one lifespan. However, a major event that eliminates a subset of the population, disrupts the complex systems on which we all depend, unsettles our entrenched social order and exposes our failings may induce dramatic changes that are apparent in real time.

Two hundred and fifty years ago, SARS-CoV-2 would have been yet another evolutionary upheaval; those most vulnerable would die, and the genetic mix of the population as a whole would have moved on after it had swept around the world, perhaps eventually becoming another endemic disease. Over those 250 years, our world has changed a great deal. While for now we rely on traditional behavioural measures, it seems highly likely that science and the power and ingenuity of modern technology will eventually provide means for preventing and treating SARS-CoV-2.

Our communities have become far more complex[30]. This pandemic is exposing the extent of inequalities in social and health outcomes around the world. It will take some time for the consequences of the disruption of our social, political, economic and healthcare systems to play out; so far, there has been little discussion about remedial measures.

Pandemics also remind us of the reality that, while all lives are enmeshed in the biology of the natural world, too few of us consider the complexity of the consequences for the global environment in our pursuit of short-term personal gain[31]. In a destabilised world we all face an increasing risk of new microparasitic threats[32,33]. Sooner or later, another pandemic, perhaps promoted by global climate change, will emerge from the vast panoply of parasites circulating on our planet and, like SARS-CoV-2, it will be different from anything we have met before.

A basic requirement for life, and perhaps even intrinsic to its definition, is the unbroken sequence of its success[34]. On our unpredictably everchanging planet, this is only sustainable as an evolutionary process by which instability produces a collection of novel opportunities to be tested by probability and chance. The success of SARS-CoV-2, and its disruption of our lives, our

cultures, our communities and our genomes, are simply manifestations of the benefits of mutability for the necessity of evolution of life on earth[35].

Conflicts of interest

The author declares no conflicts of interest.

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Biography

Dr Will Cairns OAM FRACGP FAChPM was educated in Australia, the US, and the UK before settling in Townsville in 1978. After working as a GP for a decade he moved into specialist palliative care and was deeply involved in the creation of the specialty of Palliative Medicine. He has a long-standing interest in the provision of palliative care in disasters and has written extensively on the matter. He is an active member of the Australian COVID-19 Palliative Care Working Group.

Answers to Quiz on page 191:

(1) *Neisseria*
(2) *Streptococcus*
(3) *Treponema denticola*
(4) *Lactobacillus*
(5) *Porphyromonas gingivalis*

Therapeutics for COVID-19: established and in development

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Abstract. COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first recognised in late 2019, with over 30 000 000 cases and over 1 000 000 deaths reported by the end of September 2020. SARS-CoV-2 infection is usually associated with fever, cough, coryza, dyspnoea, anosmia, headache and fatigue and may cause pneumonia and hypoxemia. An excessive/dysregulated inflammatory response may lead to lung damage including acute respiratory distress syndrome (ARDS), coagulopathy and other complications. Mortality amongst hospitalised patients is higher in those needing intensive care. In Australia over 27 000 cases with 882 deaths had been reported by 30 September, most in Victoria. Two therapies have proven beneficial in treatment of hospitalised patients in expedited randomised placebo-controlled trials and are now in widespread use. Dexamethasone improved survival of those requiring respiratory support and the antiviral agent remdesivir decreased time to recovery in mild-moderate disease. Remdesivir was authorised by the Australian Therapeutic Goods Administration in July 2020. Over 200 other therapeutics are being tested for COVID-19 in more than 2000 clinical trials, and many more agents are in preclinical development. We review the evidence for some of the candidates for therapy in COVID-19.

The aim of treatment for COVID-19 is to reduce disease severity and prevent mortality. Therapeutics may also be used to prevent or abort infection (pre- or post-exposure prophylaxis) and reduce post-infectious complications (Figure 1). In Australia, the National COVID-19 Clinical Evidence Taskforce has been established to review rapidly emerging evidence in real-time and maintain a 'living document' for COVID-19 management guidelines[2], available at https://covid19evidence.net.au/#living-guidelines. Interventions may be grouped into those targeting the virus and those targeting the immune response (Figure 2, Table 1). Adjunctive therapies including anticoagulation and optimising oxygenation are also critical elements of management but are beyond the scope of this review.

Therapeutic approaches

Antiviral small molecules

Repurposed drugs for Ebola: remdesivir

In a Phase III randomised placebo-controlled trial (ACTT-1, NCT04280705) including 1063 adults with COVID-19 with lower respiratory tract infection, participants receiving up to 10 days of **remdesivir** had shorter time to recovery than those in the placebo group (median 11 and 15 days, rate ratio for recovery 1.32; 95% CI 1.12–1.55, $P < 0.001$)[5]. Stratification by severity showed improved time to recovery for patients receiving oxygen at baseline, but not for those receiving no oxygen nor for those receiving high-flow oxygen or mechanical ventilation. There was no significant difference in mortality rates, although further follow-up data is awaited.

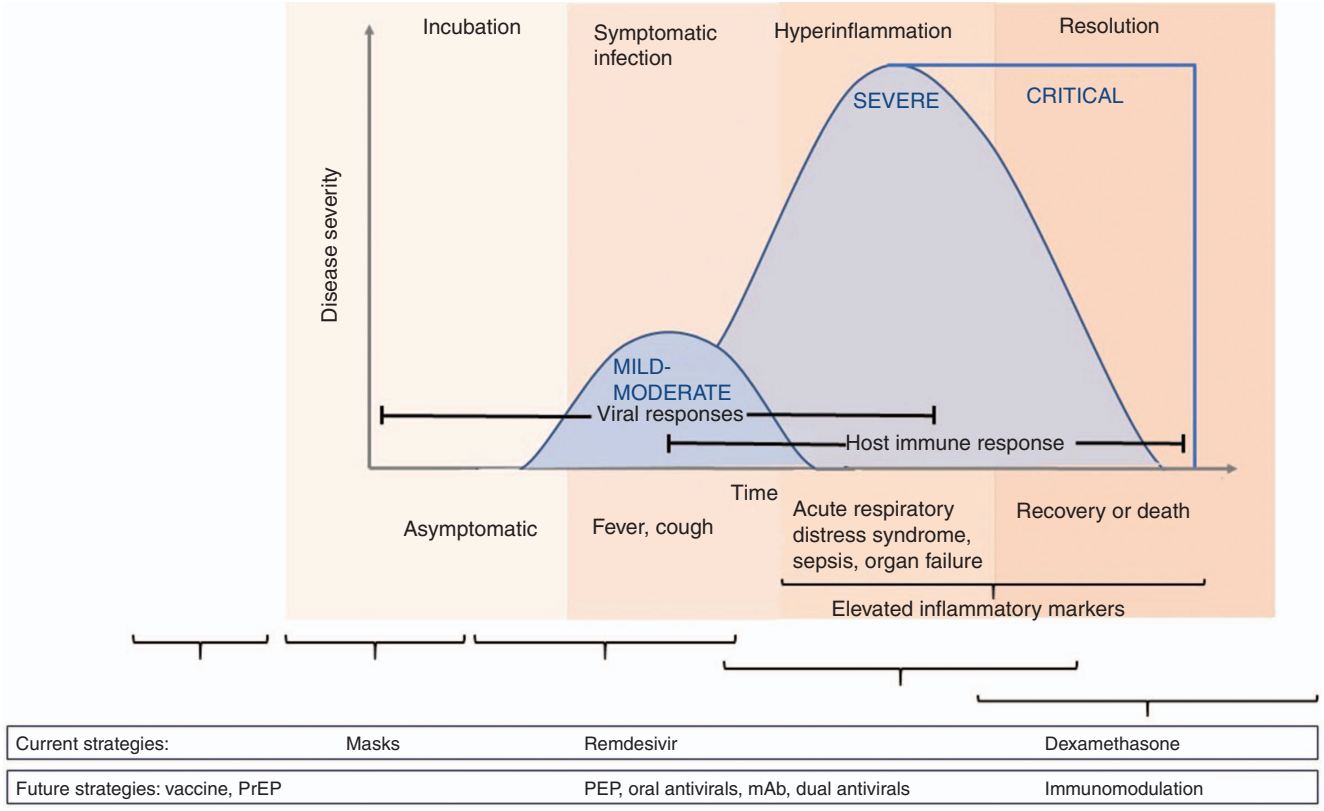

Figure 1. Course and severity of COVID-19 disease. COVID-19 illness ranges from asymptomatic, mild-moderate illness, severe/critical then either recovery or death. There are limited current strategies to reduce both the spread and progression of COVID-19 disease. Future strategies include vaccines, pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP). mAb, monoclonal antibody. Adapted from [1].

Questions remain about the optimal time and duration of administration of remdesivir. In one study (n = 397), 10 days treatment was associated with better outcomes than 5 in those going on to need mechanical ventilation; however, no control arm was included (mortality 17% with 10 days (n = 41), 40% with 5 days (n = 25))[6]. Whether there is incremental benefit above treatment with dexamethasone is not yet clear. Studies are ongoing including use of inhaled remdesivir (NCT04480333) and use in combination with other agents.

Repurposed drugs for influenza: favipiravir and umfenovir

Favipiravir is an oral RNA-dependent RNA polymerase inhibitor with *in vitro* antiviral activity at high concentrations[7]. An open-label study in mild-moderate COVID-19 (n = 80) in combination with inhaled interferon-α reported positive results, and favipiravir was approved for marketing in China for COVID-19 in March 2020[8]. Multiple phase 2 trials are active including in Australia[9]. Concerns exist about the pharmacokinetics of favipiravir, with low trough levels in critically ill patients and potential for the emergence of resistance[10].

Umfenovir (Arbidol) is a non-nucleoside antiviral targeting the viral spike (S-)protein-ACE2 host receptor interactions, inhibiting membrane fusion of the viral envelope[10]. Umfenovir may also promote interferon synthesis. Published results so far are inconclusive[12,13], with randomised studies in progress.

Non-specific immune enhancement with antiviral activity: interferons

Type I interferons have broad antiviral activities and recombinant IFN-I proteins (parenteral and inhaled) are being trialled in COVID-19[14,15]. Use of interferons in acute infection needs to be explored carefully, as type I interferons have been associated with exacerbation of inflammation in progression to severe COVID-19, with potential to worsen disease[16,46]. Timing may be critical. In a retrospective study in COVID-19 (n = 446), late use of IFN-α led to increased mortality and delayed recovery, whilst earlier use was associated with reduced mortality[17].

Repurposed anti-parasitic agents: ivermectin and nitazoxanide

Ivermectin (used to treat infections such as strongyloidiasis, scabies and onchocerciasis), and **nitazoxanide** (used in giardia and cryptosporidium) have *in vitro* activity against SARS-CoV-2 and are in preclinical early clinical trials against COVID-19[18]. Nitazoxanide also has reported immunomodulatory activity, suppressing murine IL-6 levels[18,19].

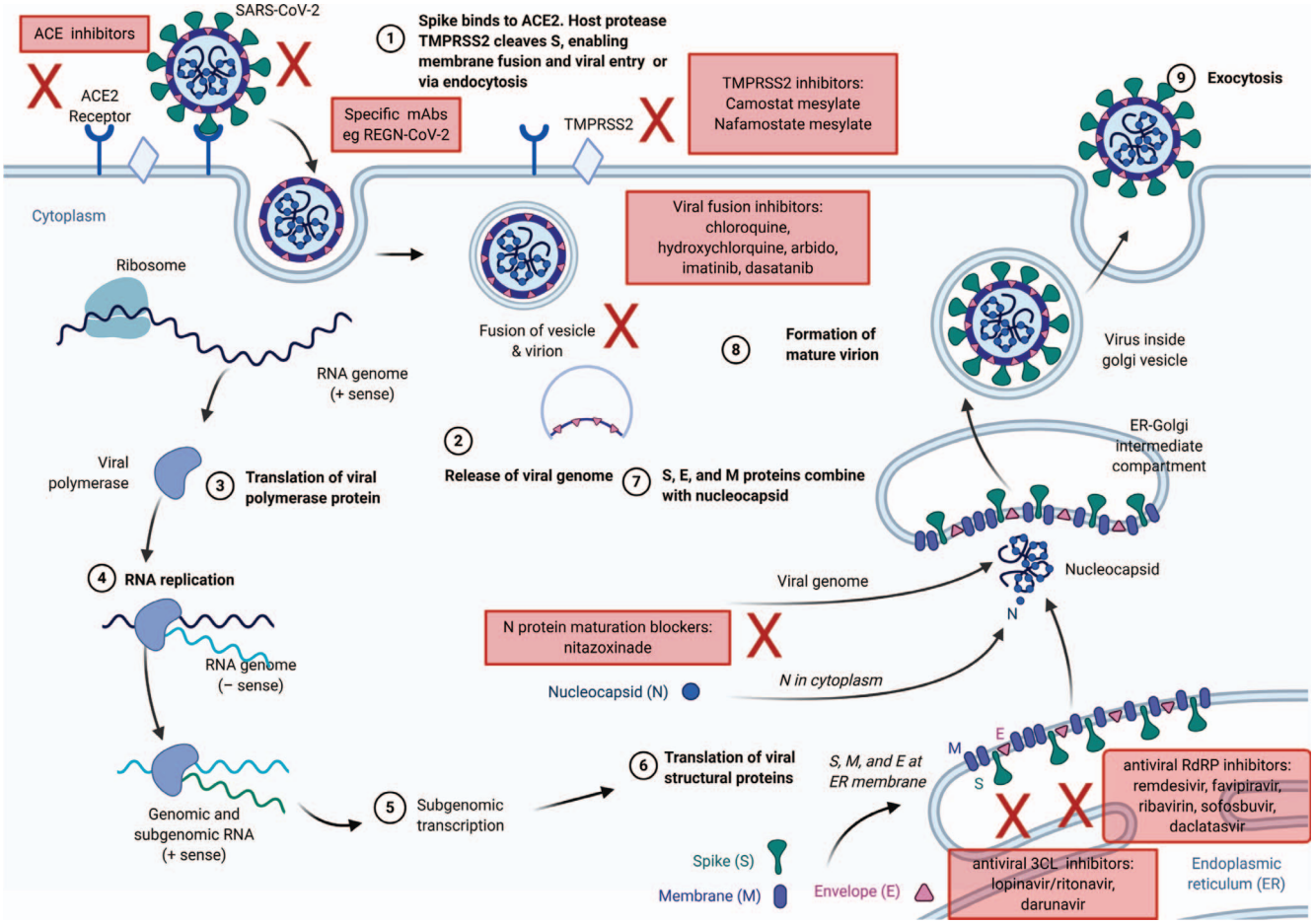

Figure 2. SARS-CoV-2 replication cycle and stages where various antiviral drug activity occurs. ACE2, angiotensin converting enzyme 2; ER, endoplasmic reticulum: E, envelope; mAb, monoclonal antibody; M, membrane; N, nucleocapsid; RdRP, RNA-dependent RNA polymerases; S, spike; TMPRSS2, transmembrane serine protease 2; 3CL, 3C-like protease. Figure was created with BioRender.com.

Repurposed anti-HIV drugs: lopinavir/ritonavir and other anti-HIV proteases

The HIV protease inhibitor **lopinavir** has *in vitro* activity against SARS-CoV-1 and MERS, and possible activity *in vivo*[20]. *In vitro* activity was demonstrated against SARS-CoV-2[21], but no benefit in treatment of COVID-19 was reported in randomised published studies or in press release of results from the large UK 'RECOVERY' (Randomised Evaluation of COVID-19 Therapy) and WHO 'Solidarity' Trials[13,22–24]. Other studies are ongoing with lopinavir/ritonavir and other antiretrovirals including nelfinavir, tenofovir, lamivudine and others, either alone or in combination.

Repurposed drugs for malaria: hydroxychloroquine and chloroquine.

Hydroxychloroquine (licensed as an antimalarial and anti-arthritis agent) and **chloroquine** were widely used in the early days of the COVID-19 pandemic, due to their potential to block viral entry, immunomodulatory impact and *in vitro* activity against SARS-CoV-2[25]. Potential toxicities include prolonged QT interval, lowered convulsive threshold, retinopathy and cardiac myopathy. Randomised trials in mild, moderate and severe disease show no benefit in COVID-19[26–29] and the WHO have discontinued the hydroxychloroquine arm in the 'Solidarity' trial. A US federal drug administration (FDA) emergency use authorisation (EUA) for hydroxychloroquine in COVID-19 issued in March was revoked in June. Hydroxychloroquine has also been shown not effective for SARS-CoV-2 post-exposure prophylaxis[28]. Studies investigating its utility for prevention of COVID-19 in healthcare workers are continuing, including in Australia[30].

Repurposed drugs with cellular targets used for viral entry: ACE2 and TMRPSS2 inhibitors

SARS-CoV-2 uses the acetylcholinesterase (ACE)-2 receptor for cell entry, and serine protease TMPRSS2 for S-protein priming, both potential targets for antiviral intervention[31]. Agents that block these interactions are in clinical trials, including the serine protease inhibitor **nafamostat mesylate** which also has anticoagulant activity and is approved in Japan for treatment of pancreatitis[32,33]. The upregulation of ACE-2 receptors with use of the common antihypertensive agents **ACE-inhibitors** and **angiotensin receptor blockers** (ARB) was theorised to potentially lead to poorer outcomes in COVID-19 by enhancing viral entry; however, this has not

Table 1. Therapeutics for COVID-19 (selected).

Compound/name	Indication other than COVID-19 (approved unless stated)	Target(s) or postulated mechanism of action	Studies in COVID-19	
			Phase of testing/ approval	Number of recruiting trials[A]
Antiviral small molecules				
Remdesivir[5,6]	Ebola (Phase 2/3)	Viral RNA polymerase	Approved (India, Australia), EUA (USA)	27
Favipiravir[7–10]	Influenza (Japan)	Viral RNA polymerase	Phase 3, approved (India)	56
Umifenovir[11–13]	Influenza (China, Russia)	S protein-ACE interaction (target not disclosed)	Phase 4	19
Type I interferons (interferon-α, -β)[14–17]	Multiple sclerosis, hepatitis B, C, D	Induce expression of interferon-stimulated genes that confer antiviral activities to host cells	Preclinical to phase 4	65
Ivermectin Nitazoxanide[18,19]	Parasitic infections	Glutamate decarboxylase 2	Preclinical	48
Lopinavir[14,15,20–23]	HIV	3CL Protease inhibitor	Phase 4	108
Hydroxychloroquine, chloroquine[24–30]	Malaria, arthritis	Inhibits viral entry and endocytosis (multiple mechanisms) Immunomodulatory effects	Phase 3 EUA revoked	344
Nafamostat mesylate[31–33]	Pancreatitis, anticoagulant (Japan)	Transmembrane protease serine 2 (TMPRSS2), anticoagulant	Preclinical to phase 4	–
Antibodies				
Neutralising monoclonal antibodies[34–37]	(monoclonal antibody)	e.g. REGN-CoV-2 (REGN10933 + REGN10987) targets SARS-CoV-2 spike protein	Phase 2/3	79 (all mAb)
Plasma-based therapy. Convalescent plasma, hyperimmune immunoglobulin[38,39]	Argentine haemorrhagic fever, influenza, Ebola (limited evidence)	Anti-viral activity, suppress viremia, enhance host humoral response	Phase 2/3, in clinic	164
Immunomodulation				
Steroids[40,41]	Inflammatory conditions	Corticoid receptors	Phase 3/4, in clinic	62 (corticosteroids)
Tocilizumab[42,43]	Rheumatoid arthritis	Interleukin-6 (IL-6) receptor (CD126)	Phase 3	69
Baricitinib[44,45]	Rheumatoid arthritis, graft versus host disease	Janus Kinase (JAK)-1,2 or 3	Phase 2/3	45 (all JAKi)

[A]Number of trials recruiting as of 22 October 2020 (selected registered trials[3,4]). –, data not available; EUA, emergency use authorisation; mAb, monoclonal antibodies; JAKi, Janus Kinase inhibitors.

been borne out by clinical data[47]. Conversely, ARBs could provide benefit via receptor blockade, impairing viral cell entry[48].

Antibodies

SARS-CoV-2 specific neutralising antibodies

In Ebola and HIV, pathogen-targeting antibodies have been identified and cloned for therapeutic use[34]. Regeneron Pharmaceuticals (USA) published their discovery of several antibodies highly potent in suppressing SARS-CoV-2 replication in mouse models[35]. **REGN-CoV-2** (includes both REGN10933 and REGN10987) is designed to bind to two points on the SARS-CoV-2 S-protein to prevent it entering healthy cells. It is being assessed for safety and efficacy in preventing secondary infection or symptom onset amongst 2000 household contacts of people with SARS-CoV-2[36].

Another investigational monoclonal antibody **LY-CoV555,** developed after identification from blood from a patient who had recovered from COVID-19, is being studied in COVID-19 under an adaptive trial master protocol ('ACTIV-2' (outpatients) and 'ACTIV-3' (inpatients)) designed to enable phase 2 testing of investigational agents with the capacity to expand smoothly to phase 3[37].

Convalescent plasma

In SARS, improved outcomes with convalescent plasma were reported in small retrospective case series[38]. A randomised trial in severe COVID-19 suggests no benefit, although the study was stopped early due to insufficient numbers, and plasma was given late (median 30 days from symptoms onset)[39]. Many other randomised studies are in progress. Meanwhile, over 50 000

patients have received convalescent plasma for treatment of COVID-19, mainly outside of clinical trial settings and an FDA EUA was issued on 23 August for its use in COVID-19.

Immunomodulation: blocking the pathogenic host immune response

Steroids

The 'RECOVERY' trial showed a reduction in 28-day mortality in patients hospitalised with COVID-19 receiving oxygen or invasive mechanical ventilation treated with **dexamethasone**[40]. 2104 patients receiving IV/oral dexamethasone (6 mg/day up to 10 days, median 6 days) had lower mortality compared to 4321 receiving usual care (22.9% vs 25.7%, age adjusted rate ratio 0.83 (0.75–0.93, $P < 0.0001$). Mortality was reduced by 35% among those receiving invasive mechanical ventilation, 20% in those on supplemental oxygen only and no impact was seen amongst those not receiving any respiratory support at randomisation. These results are consistent with respiratory compromise being driven by an overactive inflammatory response. Patients with symptoms for over 7 days had greater mortality benefit in response to dexamethasone treatment, compared to those with more recent onset. A recent meta-analysis combines results from 'RECOVERY' with six other studies to demonstrate a mortality benefit of steroids (including dexamethasone and **hydrocortisone**) in severe COVID-19[41].

Anti-cytokine therapies

IL6 plays a key role in driving the dysregulated inflammatory response in COVID-19 with higher levels associated with greater disease severity[49]. **IL-6 receptor antagonist tocilizumab** is used to treat rheumatoid arthritis and is FDA-approved to treat cytokine release syndrome associated with CAR T-cell immunotherapy. It has beneficial effects *in vitro* and in animal models of sepsis and influenza[42]. Thousands of patients are reported to have been treated with tocilizumab; however, assessment of efficacy is impaired by lack of control groups and follow up.

A non-randomised study of tocilizumab in patients requiring mechanical ventilation reported a 45% reduction in hazard of death (hazard ratio 0.55 (95% CI 0.33–0.90)) in patients receiving tocilizumab ($n = 78$) compared to those who did not ($n = 76$) with follow up 47 days (median), although superinfections were more common (54% vs 26%, $P < 0.001$)[43]. Another IL6 receptor blocking agent, sarilumab and IL6 antagonist siltuximab are also in phase 3 trials.

The **Janus kinase (JAK) 1/2 inhibitor**, **baricitinib**, licensed for rheumatoid arthritis, has been identified as a candidate for therapy against SARS-CoV-2 due to potent anti-inflammatory effects and possible off-target antiviral effects[44]. A case series describing use in patients with moderate-severe COVID-19 reported safety and suggests improved outcomes[45]. Randomised studies are in progress and will be imperative in ascertaining the benefit of these agents, particularly in combination with direct acting antivirals, and the balance with immunocompromise and adverse events.

Other considerations

Personalisation

Different factors drive disease manifestations at different stages of SARS-CoV2 infection, and optimal management may depend on stage of illness at time of presentation. Furthermore, the course of COVID-19 differs significantly amongst individuals, with higher risk of progression to severe disease seen in the elderly. Individualised therapy using informatics strategies based on stage and prediction of disease progression have been associated with improved patient outcomes[50]. Therapy based on immunophenotyping has also been suggested, based on readily identifiable immunological signatures associated with different disease trajectories[51,52].

Combination therapy

The benefit of therapeutic antiviral combinations is also being explored. In a randomised trial in early COVID-19 (<7 days onset), the combination of **lopinavir/ritonavir**, **interferonβ-1B** and **ribavirin** resulted in greater reduction of virus in nasopharyngeal swabs and quicker time to recovery compared to lopinavir/ritonavir alone[14]. Combining antiviral and immunomodulatory agents may be important in management of COVID-19 given the role of the inflammatory response in disease evolution severity. Timing of different therapeutics should be considered carefully in trial design.

Conclusions

Repurposing existing therapies will be the quickest way to find effective intervention and improve outcomes in COVID-19; however, bigger gains are likely through the development of new agents specific to SARS-CoV2. These are being rapidly engineered using high-throughput screening platforms. Websites tracking COVID-19 clinical trials and the development of new agents show over 300 novel agents are in pre-clinical testing. Their diverse actions reflect the range of pathology seen in COVID-19 that is a consequence of both viral action as well as immune response. Their introduction into clinical trials will be the next exciting phase of therapeutics.

Conflicts of interest

JA, JS and SRL have received investigator-initiated funding for research from Gilead Sciences for work unrelated to COVID-19. SRL has received honoraria for education activities supported by Gilead Sciences and Viiv Healthcare. SRL has received research support from Gilead Sciences, Viiv Healthcare and Merck. SRL is a

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Biographies

Dr Kasha Singh is an infectious diseases physician with a wide range of interests including public and refugee health and translational research. Dr Singh worked in the UK for 10 years, completing a HIV fellowship at Chelsea and Westminster Foundation Trust in London. While based in London, Dr Singh was also involved in running international clinical trials of tuberculosis treatment with the MRCP/UCL, including capacity development and education. Dr Singh is interested in persistent viral infections and the public health impact and management of infectious diseases, particularly HIV, hepatitis B, tuberculosis and now also COVID-19.

Associate Professor Joe Sasadeusz is an infectious diseases physician who subspecializes in medical virology. He has particular interests in viral hepatitis in both HIV uninfected as well as coinfected individuals. He also works in infections in immunocompromised hosts, especially patients who have undergone a haematopoietic stem cell transplant. He is heavily involved in the education of general practitioners via the VHITTAL program. He also conducts clinical trials and has multiple research projects in the above areas.

Professor Sharon Lewin, is the inaugural Director of the Doherty Institute. She is also a Melbourne Laureate Professor, The University of Melbourne and a National Health and Medical Research Council (NHMRC) Practitioner Fellow. As an infectious diseases physician and basic scientist, her laboratory focuses on basic, translational and clinical research aimed at finding a cure for HIV and understanding the interaction between HIV and hepatitis B virus. Her laboratory is funded by the NHMRC, the National Institutes of Health, The Wellcome Trust, the American Foundation for AIDS Research and multiple commercial partnerships. She is also the Chief Investigator of a NHMRC Centre of Research Excellence (CRE), The Australian Partnership for Preparedness Research on Infectious Diseases Emergencies (APPRISE) that aims to bring together Australia's leading experts in clinical, laboratory and public health research to address the key components required for a rapid and effective emergency response to infectious diseases.

Dr Jennifer Audsley is a Clinical Research Fellow based at the Doherty Institute. She has specific research interests in HIV-hepatitis co-infection and PrEP (Pre-exposure prophylaxis) for HIV prevention. Her research in HIV focuses on long-term treatment in people living with HIV and hepatitis B virus (HBV), liver disease pathogenesis in people living with HIV and HBV, and HBV cure in the setting of HIV-HBV co-infection. She leads the HIV-Hepatitis group within Professor Lewin's research program.

Epidemic poliomyelitis, post-poliomyelitis sequelae and the eradication program

Margaret M Peel

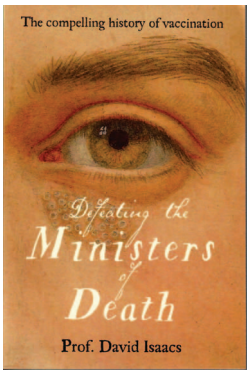
The author advises that on page 198 of their published article (*Microbiology Australia*, Volume 41, Issue 4, pages 196–200, doi:10.1071/MA20053), under the heading 'Late-onset sequelae of poliomyelitis (LOSP)', 'osteomyelitis' should read 'osteoporosis' in the fourth line from the end of the first paragraph. The correct text is shown here:

A broader category of sequelae, the Late Effects of Polio (LEoP), includes the consequences of musculoskeletal deformities and weakness such as scoliosis, osteoporosis, joint instability and pain, osteoarthritis and nerve entrapments[8].

Book reviews

Defeating the Ministers of Death. The Compelling History of Vaccination

Author: David Isaacs
Publisher: HarperCollins, Sydney, 2019
Paperback ISBN 978 14607 5684 3. 357 pages, including comprehensive footnotes and an index. Also available as an e-book.



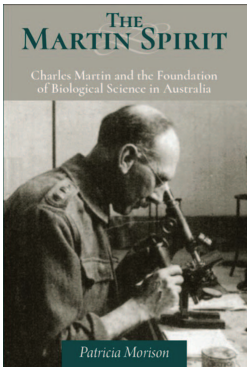
David Isaacs, an Australian paediatrician and infectious diseases specialist, has written an enchanting, enthralling and comprehensive account of the history, impact and shortcomings of vaccines for diseases of humans.

This personal account is filled with wonderful anecdotes, matched by a finely tuned sense of humour. Particularly notable is Isaacs' even-handed, thoughtful approach to the ethics of immunisation, the anti-vaccination movement and the burden that poverty imposes on access to vaccines. Although factual and teeming with useful information, this work is easily accessible and highly recommended for lay people and students of all ages, as well as for professional microbiologists.

Vaccines represent the greatest achievement of modern medicine, having saved many millions of lives. Even more impressive is the ability of vaccines to eradicate devastating diseases, exemplified by smallpox, with more on the cards. The current COVID-19 pandemic has reminded us of the importance of infection control and our reliance on immunisation to combat infections in the long term. I am looking forward to the second edition of Isaacs' book with a new chapter on how medical science defeated SARS-CoV-2.

Reviewed by Roy Robins-Browne, Department of Microbiology and Immunology, Peter Doherty Institute for Infection and Immunity, The University of Melbourne

The Martin Spirit: Charles Martin and the Foundation of Biological Science in Australia



Author: Patricia Morison
Publisher: Halstead Press
Paperback ISBN 978 1925043 471. 292 pages including comprehensive footnotes, Bibliography and an index.

Martin Gibbs, Charles Martin's grandson, gave the author access to 40 years of correspondence with his daughter Maisie, and to his letter books as an officer in the Australian Army Medical Corps. The outcome, following extensive additional research, is a very intimate and insightful study of an entirely remarkable and yet almost forgotten figure in the history of biomedical science in Australia.

Most Australian biomedical researchers will no doubt be familiar with the CJ Martin scholarships, but probably have no idea of the man after whom they are named. Patricia Morison's meticulously researched book on CJ Martin aims to redress that issue.

Martin left school at 15 and began work as a junior clerk in his father's business but hankered to study medicine. Eventually he achieved this goal, and after graduation another, to marry, by taking up a position as a Demonstrator in Physiology at Sydney University. During his 12 years in 'the colony', where he played a pivotal role in the development of medical courses in both Sydney and Melbourne, his mantra was that to learn Science the student needed to experience it.

Martin returned to London to head up the Lister Institute for 27 years but never forgot his Australian mates, joining the AIF to combat infectious diseases at Gallipoli and in later years serving CSIR(O). His work with troops during the First World War exemplifies why Science must always be the basis for informed decisions about life and its dilemmas.

Martin loved Australia and made a lasting contribution to Australian science. *The Martin Spirit* is not only a fascinating account of the man and his work but also of the many Australian scientists who he inspired and mentored. I commend Patricia Morison for her mammoth effort for breathing life into *The Martin Spirit* and bringing it to our notice in such vibrant and intricate detail.

Reviewed by Ross Barnard, School of Chemistry and Molecular Biosciences, Australian Infectious Diseases Research Centre and ARC Training Centre for Biopharmaceutical Innovation, The University of Queensland and Cheryl Power, Department of Microbiology and Immunology, Peter Doherty Institute for Infection and Immunity, The University of Melbourne

The Forest in the Tree: How Fungi Shape the Earth

Authors: Ailsa Wild, Aviva Reed, Briony Barr, Gregory Crocetti
Publisher: CSIRO Publishing

Hardback ISBN 978 1486313310. 48 pages

This book is the fourth book in the Small Friends Books series (https://www.publish.csiro.au/books/series/81) and its focus earns respect for amazing soil fungi and the role they play in ecosystems. It engages readers by telling a story of growth and drought survival from a fungal spore's perspective. Its symbiosis with a cacao tree is clearly and attractively illustrated. It is targeted for readers aged 8–12 years, teachers, librarians and parents. Learning is enhanced by a set of freely downloadable teacher notes and questions, making this a valuable learning resource.

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Animal Production Science
Food, fibre and pharmaceuticals from animals

The APPEA Journal
The journal of the Australian Petroleum Production & Exploration Association

Australian Health Review
The journal of the Australian Healthcare & Hospitals Association

Australian Journal of Botany
Southern hemisphere botanical ecosystems

Australian Journal of Chemistry
An international journal for chemical science

Australian Journal of Primary Health
Issues influencing community health services and primary health care

Australian Journal of Zoology
Evolutionary, molecular and comparative zoology

Australian Mammalogy
The journal of the Australian Mammal Society

Australian Systematic Botany
Taxonomy, biogeography and evolution of plants

Crop & Pasture Science
Plant sciences, sustainable farming systems and food quality

Environmental Chemistry
Chemical approaches to environmental problems

Functional Plant Biology
Plant function and evolutionary biology

Historical Records of Australian Science
The history of science, pure and applied, in Australia and the southwest Pacific

International Journal of Wildland Fire
The journal of the International Association of Wildland Fire

Invertebrate Systematics
Systematics, phylogeny and biogeography

Journal of Primary Health Care
The journal of The Royal New Zealand College of General Practitioners

Marine and Freshwater Research
Advances in the aquatic sciences

Microbiology Australia
The journal of the Australian Society for Microbiology

Pacific Conservation Biology
Conservation and wildlife management in the Pacific region

Proceedings of the Royal Society of Victoria
Promotion and advancement of science

Reproduction, Fertility and Development
Vertebrate reproductive science and technology

Sexual Health
Publishing on sexual health from the widest perspective

Soil Research
Soil, land care and environmental research

The Rangeland Journal
Rangeland ecology and management

The South Pacific Journal of Natural and Applied Sciences
Research and review papers in the area of science, engineering and mathematics

Wildlife Research
Ecology, management and conservation in natural and modified habitats

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MEMBERSHIP MATTERS

Re-evaluating how we bring microbiologists together

Queensland

Our vision for 2021 is to combine the best of two worlds – we are very excited to organize face-to face meetings again, but will continue to offer online attendance to facilitate participation for members located in regional areas, as well as overseas in the pacific region. Please get in touch and let us know which 2020 event you liked best, and what other events you would like to see in the future.

Ulrike Kappler
u.kappler1@uq.edu.au

South Australia/Northern Territory

The SA/NT ASM Branch AGM was held the second week of October. It was nice to connect in person with members! We have been hosting monthly online "Zoom-In" seminars. Our plan is to continue to host them through the end of the year and will potentially consider the format for our scientific events at the beginning of 2021.

Andrea McWhorter
andrea.mcwhorter@adelaide.edu.au

New South Wales/Australian Capital Territory

We have set up a number of Zoom seminars and online conferences over the next few months. These include:

⁎A lunchtime double header on antibiotic resistance by Profs Peter Lewis (UON) and Antoine van Oijen (UOW) October 29th 12.30-1.30pm
⁎A joint ASM/JAMS talk by journalist Nick Evershed on data visualization & COVID-19 November 2nd (5.30 pm).
⁎November 20th "Bugs by the Beach" is online, with speakers Danielle Ingle (ANU) & Claire O'Brien (ANU).
⁎Annual Molecular Micro One-day meeting will be held online! January 31st 2021.

Jim Manos
jim.manos@sydney.edu.au

Western Australia

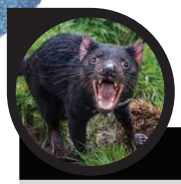
Our road ahead is busy in the WA bubble. Tune in Tuesdays have allowed our conference-starved researchers to present data to us since July. Our AGM was online AND face-to-face and Zoom continues to allow our young parent committee members to participate – how great is that? Our first live conference is next week with others planned.

Megan Lloyd
megan.lloyd@uwa.edu.au

Victoria

I'm very proud of is that the ASM Vic branch (and I'm sure all the others too) have kept serving our members and running events and initiatives even in these tough times. We have actually had far more attendees than usual, so there are things we can build on for the future too.

Catherine Satzke
catherine.satzke@mcri.edu.au



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Tasmania

With such a small membership number in Tasmania the online meetings have been wonderful for our members. We will continue to advertise these to all members as they become available.
With our borders opening up to the rest of the nation over the coming weeks we will make a decision on our Christmas functions in the coming weeks but we are hoping for a function in both the north and south of the state.
Keep safe

Belinda McEwan
belinda.mcewan@ths.tas.gov.au

Office Manager, Shona Kennedy is happy to help you to renew your membership or assist in how to defer payment but retain your membership if you are experiencing financial hardship.

admin@theasm.com.au | 1300 656 423