Influenza pandemics and their control: Case Study

Influenza pandemics have caused death and social tragedy for hundreds of years, and the control of influenza was a priority for health and medical researchers in Australia during the twentieth century. From the 1930s to the 1960s, Frank Macfarlane Burnet and his team of NHMRC-funded researchers at The Walter and Eliza Hall Institute (WEHI) made major contributions to our understanding of the influenza virus and how to prevent and treat infection. This work led the development of vaccines and pharmaceuticals that are extensively used today. It also involved the Commonwealth Serum Laboratories (now CSL Limited), CSIRO, the John Curtin School of Medical Research (JCSMR) at The Australian National University (ANU), and Monash University.

Origin

Influenza is a highly contagious respiratory illness that impacts all countries in the world. The World Health Organisation estimates that, every year and worldwide, there are 1 billion cases of influenza, 3-5 million severe cases, and 290,000-650,000 deaths from influenza-related respiratory illness.

The influenza pandemic of 1918-19 caused millions of deaths worldwide. In Australia, two million Australians were infected and more than 15,000 died, a significant proportion of whom were young adults. Indigenous Australians were severely affected, with a mortality rate approaching 50 per cent in some communities.

Hospitals were overwhelmed, medical and healthcare workers were incapacitated and many temporary hospitals had to be staffed by lay volunteers. Schools, theatres, dance halls, churches, pubs and other places of public congregation were closed. Streets were sprayed with disinfectant and people were compelled to wear masks in public. Movement by public transport was restricted and state borders were closed.

As a consequence of the 1918-19 pandemic, research into influenza became a long-term focus for medical researchers in Australia.

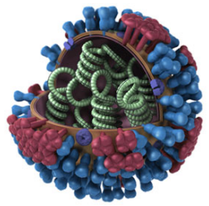
Volunteers responding to the influenza epidemic in Brisbane, Queensland, 1919. Source: State Library of Queensland

Grants and Investment

WEHI and CSL
In 1915, an institute for research in pathology and medicine was established, supported by the Walter and Eliza Hall Trust.

The following year, the Australian Government established the Commonwealth Serum Laboratories (CSL), in response to the loss of access experienced by Australia during the war to international supplies of vaccines and other bacteriological products. During the first 18 months of its existence, CSL was housed in WEHI's laboratories, establishing a close relationship between the two organisations that continues today.

NHMRC
NHMRC grants for health and medical research commenced in 1937, and for most of the next three decades a team of virologists led by Dr Frank Macfarlane Burnet were prominent recipients. This team included Dora Lush (1934-1939), Gordon Ada and Patricia Lind (1948-1965) and Alfred Gottschalk (1950-1958). NHMRC also funded Peter Colman's research on the crystalline structure of the influenza virus, and development of an antiviral drug.



The genome of influenza viruses consists of 7 or 8 pieces of RNA which are contained within an envelope from which 'spikes' protrude. In this image the red spikes are neuraminidase, which plays an essential role in influenza virus replication.

Source: Centers for Disease Control and Prevention.

Research and Collaborations

Informed by the 1933 discovery that influenza was caused by a virus, Burnet made extensive use of the chorioallantoic membrane (CAM) of chicken eggs to grow the virus, a technique that he pioneered. In his 1941 report to NHMRC, Burnet records that the development of this technique "has made it technically possible to produce unlimited amounts of . . . any strain of influenza virus".

Lush worked on the herpes simplex, pseudorabies, Louping Ill, Shope's Fibroma, influenza and myxomatosis viruses. The use of the CAM for virus growth was a feature of much of this work.

Lind worked on the mumps, Newcastle Disease and influenza viruses, including on the genetic interaction of influenza virus strains, such as the Asian influenza A virus. She also worked with Gottschalk on virus surface and cell interactions and was responsible for WEHI's Virus Reference Laboratory.

Ada commenced his NHMRC-funded work by investigating methods for removing fat from human serum (the fluid component of blood) in order to prevent the serum's deterioration, and viral interactions with blood remained a focus of his work. In addition, he worked on the 'receptor destroying enzyme' (RDE) of viruses.

Gottschalk studied virus surface and cell interactions and found that the RDE was an enzyme (neuraminidase) that was an intrinsic part of the influenza virus.

The work of these researchers, and the experience they gained while investigating a broad range of viruses, gave WEHI a position of global leadership during the 1950s and 1960s in what became known as the 'golden age of virology'.

Trials and Results

Vaccine: At the outbreak of World War II, Burnet focused WEHI's research program on producing an influenza vaccine. In 1941, Burnet's team developed and trialled live nasal spray influenza vaccines. The trials were successful and in early winter 1942 approximately 35,000 troops were immunised. In 1943, another large-scale field test was undertaken and about 9,000 troops were immunised with influenza Type A vaccine and an equal number with Type B. By 1945, large scale production of influenza vaccine had been transferred completely to CSL.

Recombination and RNA: Burnet's report to NHMRC in 1949 indicated that he and Lind had discovered that "the qualities of two different influenza virus strains can be combined in a new pure 'recombinant' strain". This finding was a world first, as was Ada's 1953 finding that "Influenza virus contains no significant DNA and a much smaller amount of RNA (0.5-1 per cent) than is stated in previous work". More recent research has demonstrated that single-stranded (RNA) and/or smaller viruses mutate faster than do double-stranded (DNA) and/or larger viruses. Together, these findings have been vital to our understanding of why influenza viruses change, why vaccines fail and how pandemic influenza viruses emerge.

Neuraminidase: Informed by Gottschalk's work on neuraminidase, in 1983, Dr Peter Colman (CSIRO), Dr Jose Varghese (CSIRO) and Dr Graeme Laver (JCSMR, ANU) solved the three-dimensional structure of neuraminidase. This enabled Prof Mark von Itzstein and his group (Monash), supported by Biota Holdings Ltd, to develop a new class of antiviral agent and the first ever clinically-used 'neuraminidase inhibitor' – zanamivir. Zanamivir (Relenza®), approved in 1999 by the US FDA for the treatment of influenza, was one of the first drugs produced by 'rational design' and the first specific anti-influenza drug.

Outcomes and Impact

In a typical Australian winter, around 3,000 deaths are caused either directly by influenza or by severe complications such as pneumonia. Influenza vaccination is the primary method for preventing influenza and reduces the risk of influenza illness by 40-60%.

In 2015, the global seasonal influenza vaccine production was about 1.467 billion doses. Burnet's CAM technique, improved but fundamentally the same, was used to produce about 90% of this supply, enabling easier, cheaper and higher volume production of influenza vaccine globally.

Seqirus (a part of the Australian owned CSL Limited and the second largest influenza vaccine company in the world) manufactures seasonal influenza vaccine in Melbourne and in the process uses more than one million fertilised eggs every week. In 2020, 16.5 million influenza vaccinations were available for Australians, with 9 million manufactured by Seqirus.

Zanamavir (and the closely related pharmaceutical oseltamivir (Tamiflu®)) can reduce the incidence of major, life-threatening secondary complications of influenza illness, including bacterial pneumonia.

In 1996, Colman, Laver and von Itzstein shared the Australia Prize for their contributions to developing zanamavir.

Peter Colman (right) showing a 3D model of neuraminidase to Sir Macfarlane Burnet, during the 1980s.

Source: CSIRO

Sir Frank Macfarlane Burnet

Sir Frank Macfarlane Burnet (1899-1985) commenced work at WEHI in 1923 and was its director from 1944 to 1965. Under his leadership, scientists at the Institute made significant contributions to virology and immunology. He was elected a fellow of the Royal Society in 1942 and was a co-recipient of the 1960 Nobel Prize in Physiology or Medicine, for the discovery of acquired immunological tolerance.

Professor Gordon Ada AO

Professor Gordon Ada (1922-2012) was an Australian virologist and immunologist who first worked at CSL on problems related to blood serum (1944-46). After a period at the UK National Institute for Medical Research (NIMR) (1946-48) he joined Burnet's team at WEHI (1948-68) then moved to JCSMR, ANU.

Professor Alfred Gottschalk

Professor Alfred Gottschalk (1894-1973) was a German biochemist who became Director of the Biochemical Department at the General Hospital in Szczecin, Poland. He emigrated to Australia in 1939 and joined WEHI. In 1959 he moved to JCSMR, ANU and then in 1963 to the Max Planck Institute for Virus Research in Tubingen, Germany.

Dr Patricia Lind

Dr Patricia Lind (d 1983) moved from CSL to WEHI in 1943, where she co-authored 16 papers with Burnet in virology and later worked with Sir Gustav Nossal in cellular immunology. Lind also undertook research at: the Imperial Cancer Research Fund Laboratories, London; the Karolinska Institute, Stockholm; and the Pasteur Institute, Paris.

Dora Lush MSc

Dora Mary Lush (1910-1943) was an Australian virologist who worked with Burnet at WEHI from 1934-39 and with Sir Patrick Laidlaw – a co-discoverer of the influenza virus and Deputy Director of the NIMR – from 1939-1942.

In 1942 she returned to WEHI, bringing with her work she began in support of the war effort, developing a vaccine for scrub typhus. This frequently deadly bacterial disease, which was affecting troops in East Asia and Northern Australia, also took her life after she was accidentally infected.

In 1993, 50 years after her death, NHMRC named its Basic Science Postgraduate Scholarships in her honour.

Professor Peter Colman AC

Professor Peter Colman, after postdoctoral studies in the US and Europe, became a QEII Fellow at The University of Sydney before joining CSIRO's Division of Protein Chemistry. Following two decades of research there, largely on the influenza virus protein neuraminidase, Colman moved to WEHI to work on mechanisms of protein-regulated cell death (apoptosis).

Dr Jose Varghese

Dr Joseph (Jose) Varghese is an expert on X-ray crystallography who was awarded postdoctoral fellowships at The University of Western Australia and the University of Sussex (UK) before joining CSIRO in 1980. Since that time his research has included a focus on structural biology, virology, immunology, neurodegeneration and enzyme mechanisms.

Professor Graeme Laver

Professor Graeme Laver (1929-2008) received a PhD in biochemistry from the University of London, supported by a CSIRO scholarship, then returned to Australia to establish a laboratory focused on influenza at JCSMR, ANU. Laver's work developing neuraminidase crystals was essential for the development of zanamivir and oseltamivir.

Professor Mark von Itzstein AO

Professor von Itzstein was an Alexander von Humboldt Fellow in the Department of Chemistry at the Universität Marburg, Germany. He commenced working on influenza drug discovery in 1986 at the Victorian College of Pharmacy (now part of Monash University). Professor von Itzstein is currently the Director of Griffith University's Institute for Glycomics.