

Rubella and pregnancy: Case Study

In 1940, Australia experienced an epidemic of rubella: a contagious, viral illness also known as German measles. The following year, an ophthalmologist working in Sydney observed that babies he was treating for an unusual type of congenital cataract had been born to mothers who had contracted rubella early on in their pregnancies. NHMRC, noting the importance of this world-first discovery, acted quickly to investigate rubella's potential to cause abnormal fetal development, and played an important role in bringing this to the attention of clinicians in Australia before a vaccine became available. Today, vaccination against rubella is part of the National Immunisation Program Schedule.



Origin

Rubella is a viral disease that may manifest as a rash and a low grade fever. In 50% of cases the symptoms may be so mild as to be inapparent. During the 1700s, rubella was first described by German scientists who thought it was related to measles or scarlet fever. It was identified as a separate disease in 1814.

Immediately following a widespread epidemic of rubella in 1940, Dr Norman Gregg, senior ophthalmic surgeon at the Royal Alexandra Hospital for Children (RAHC) in Sydney, began seeing an increased number of cases of infants who had congenital cataracts of an unusual variety. These infants were frequently undersized and also had congenital heart and other impairments. In the majority of these cases the mother had been infected by rubella. Surveying his colleagues in other Australian states, he found a total of 78 such cases. He published these results in 1941 in an article titled 'Congenital Cataract following German Measles in the Mother' in *Transactions of the Ophthalmological Society of Australia*.

In the 1940s, the prevailing scientific understanding was that congenital malformations were inherited, and that viruses could not harm a developing fetus, so Gregg's finding was questioned by some in the research community. NHMRC, however, took a proactive approach and appointed a committee chaired by Gregg to further investigate.

In 1943, NHMRC-funded virologist and Director of Australia's Walter and Eliza Hall Institute (WEHI), Dr Frank Macfarlane Burnet, toured the United States and promoted Gregg's discovery. From 1946-1950, Burnet chaired an NHMRC expert committee on rubella in pregnancy.

Investment and Research

During several decades following Gregg's discovery, NHMRC funded a number of researchers who pioneered investigations into the rubella virus and made significant contributions to knowledge.

Dr Charles Swan

Working at The Institute of Medical and Veterinary Science in Adelaide, Swan was already an NHMRC funded virologist when he started investigations into rubella during pregnancy and its associated congenital defects – now called congenital rubella syndrome (CRS). He was the first to document that rubella could cause deafness in children.

Dr S Gray Anderson

During the period 1947-56, NHMRC supported rubella research undertaken at WEHI, led by Burnet and primarily undertaken by Anderson, to induce immunity experimentally in human volunteers, and to grow the rubella virus in the laboratory.

Professor Henry Lancaster

Lancaster was a physician and medical statistician based at The University of Sydney who served on several NHMRC committees. NHMRC encouraged grantees to use his statistical services before publishing their research.

Professor Margaret Burgess

Burgess and her colleagues at RAHC, Drs Jill Forrest, David C. Dorman and John D. Harley, worked on virological and immunological aspects of CRS. Burgess trialled the rubella vaccine and later advised NHMRC on rubella vaccination schedules.

Dr Kathleen Hayes

A virology laboratory was established at Fairfield Infectious Diseases Hospital, Melbourne, in 1950 to undertake clinical, diagnostic and research services. Hayes – a laboratory-based virologist working on congenital rubella – and her colleagues at Fairfield (including Noreen Lehmann), were leaders in virology during the 1970s and 1980s.

Results

- Swan analysed all of the existing studies on the effects of maternal rubella. These data confirmed the harmful effects of rubella on the developing fetus (including on the child's sight, hearing, heart and general growth), and identified the period of pregnancy when the disease caused the most damage. In 1949, the British Medical Association formally acknowledged the value of Swan's work by awarding him the Katherine Bishop Harman Prize.
- Anderson's research on the transmission of rubella showed the experimental disease was infective for susceptible contacts and that subjects with a history of rubella failed to develop the disease.
- Lancaster's careful examination of Australian institutional records and census data led him to discover a causal connection between rubella epidemics prior to 1940 and congenital deafness.
- Burgess and her team confirmed that most infants affected by intrauterine rubella were still infected at birth and were infectious. They also found a causative relationship between congenital rubella and diabetes. In the 1970s, Burgess conducted the first clinical trials of rubella vaccines in Australia. Follow-up of 191 schoolgirls 5 years after vaccination and 56 girls 8 years after vaccination showed that all had detectable rubella antibody, whereas 24% of 239 unvaccinated young men of similar age (18-23 years) were sero-negative. By 1983, 96% of 8,226 pregnant women were seropositive for rubella antibody, as compared with only 82% of a similar group of women in 1971.
- Noreen Lehmann was a laboratory scientist at Fairfield Hospital who investigated viral infections in the community. Lehmann was the first person in Australia to isolate rubella virus in cell culture and to establish a sensitive assay to detect rubella antibodies.

Translation

In 1943, Swan suggested to NHMRC that the public be informed of the danger of contracting rubella during pregnancy. NHMRC communicated this information to state health departments and the Ophthalmological Society of Australia.

In 1962, during a worldwide outbreak, the rubella virus was isolated by researchers in the United States and an antibody test and vaccine developed. In the late 1960s, NHMRC recommended mass immunisation campaigns for girls between 12-14 and that a guide to the administration of rubella virus vaccines be circulated to all medical practitioners. NHMRC further recommended that a trial take place following introduction of the vaccine to assess the campaign's effectiveness. The national schoolgirl rubella vaccination program commenced in 1971.

In 1980, NHMRC recommended that an additional campaign using the combined measles, mumps, rubella (MMR) vaccine during childhood would achieve early rubella immunity and ultimately reduce the incidence of the disease and CRS. In 1982, an NHMRC Working Party was set up to examine the MMR vaccination program.



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Impact

NHMRC acted quickly to investigate rubella's potential to cause birth defects and played an important role in bringing CRS to the attention of clinicians in Australia.

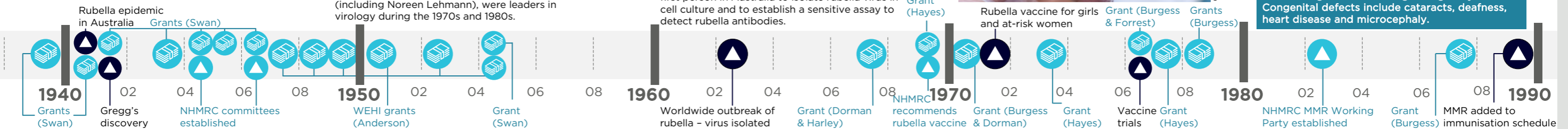
After the commencement of rubella immunisation, hospital and population studies in the 1980s and 1990s demonstrated high antenatal sero-positive rates of 95%-96%. The National Acoustic Laboratories estimated a fall in the incidence of congenital deafness attributed to rubella from well over 0.51 to 0.05 per 1000 live births between 1964-70 and 1977-82. Rubella and CRS became notifiable diseases in all Australian jurisdictions in 1991.

Mass infant MMR vaccination produced a 99% reduction in both rubella and CRS incidence by 2010 compared to the pre-vaccination era (1960-70). Statistics from a 2019 report show that there is now (on average) less than one incident case of CRS in Australia each year.¹

In 2018, the World Health Organisation officially declared that Australia had eliminated rubella, but cases of rubella can still occur. Unvaccinated pregnant women may be exposed to rubella, especially when travelling overseas as some countries still have not implemented rubella vaccination programs.

The processes through which rubella leads to CRS are complex and incompletely understood. Recent discoveries of similar viruses in animals may facilitate comparative studies and animal models of rubella and CRS.

Women infected with rubella may develop temporary arthritis. However, if a pregnant woman is infected with rubella during her first trimester it can cause miscarriage and also have devastating effects on her growing baby. Congenital defects include cataracts, deafness, heart disease and microcephaly.



Sir Norman Gregg

Sir Norman McAlister Gregg (1892-1966) graduated from medicine in 1915 then served with the Royal Army Medical Corps in France. He received postgraduate training in London and Birmingham, UK, before working at RAHC. In 1953, he was made a Knight Bachelor for services to medical science.

Dr Charles Swan

Dr Charles Spencer Swan (1912-1963) worked at the Institute of Medical and Veterinary Science in Adelaide. His research in the 1940s confirmed Gregg's findings about the effect of maternal rubella on the unborn child.

Prof Henry Lancaster AO

Professor Henry Oliver Lancaster (1913-2001) was an expert medical statistician who served on several NHMRC committees. Among his many contributions to medical science was his finding (reported in 1956) that melanoma was associated with latitude (i.e. intensity of sunlight). Oliver was made an Officer of the Order of Australia (AO) in 1992 for services to science.

Dr Jill Forrest AM

Dr Jill Forrest conducted research into the effects of rubella infection on fetal development. She was Research Fellow at the Children's Medical Research Foundation, RAHC (1973-1977).

Dr S Gray Anderson

Dr Stewart Gray Anderson (1918-2014) became a medical practitioner, then worked at WEHI from 1945 to 1960. He moved to England in 1961 to work for the National Institute for Medical Research.

Noreen Lehmann

Noreen Lehmann (1932-2020) was responsible for isolating a wide range of respiratory and enteric viruses as well as the viruses responsible for many of the infectious rashes of childhood. Her assays became widely used for screening pregnant women and created a new market for industry.

Prof Margaret Burgess AO

Professor Margaret Burgess (nee Mensor) worked at the Children's Medical Research Foundation at the RAHC from 1965-1984 as a Research Fellow (1965-1970) and as a Norman Gregg Senior Research Fellow (1970-1984). In the 1990s she conducted large community-based studies on hepatitis B vaccination.

Professor Burgess was the Director of the National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases from 1997-2004. She was awarded the Queen Elizabeth II Silver Jubilee Medal for services to the community in 1997, the Order of Australia in 2003, and the RACP Howard Williams Medal in 2006.

Dr Kathleen Hayes

Dr Kathleen Hayes commenced studying congenital rubella at the Great Ormond Street Hospital for Children, London (1964-67).

Hayes conducted prospective and other studies to clarify the complex nature of maternal, prenatal and early postnatal cytomegalovirus (CMV) infection while based at Royal Children's Hospital, Melbourne and Monash University Dept. of Paediatrics, Queen Victoria Hospital, (1968-78). Thereafter she headed the Rubella-CMV Section of Virology at Fairfield Hospital to 1996.

MMR vaccine

In 1983, a measles-mumps (MM) vaccination program was funded in Australia for infants from 12 months onward (9 months for Indigenous babies in the Northern Territory). Protection against rubella was added through the combined MMR in 1989. A second dose of MMR vaccine was recommended and funded for both males and females in 1992. In 1994, an MMR program was commenced for both teenage boys and girls. In 1998, the second dose of MMR vaccine was changed from teenage to 4 years of age. MMR catch-up vaccination programs for adults have been instigated by various State governments since 2000.