GARDASIL® — the HPV vaccine: Case Study

Human papillomavirus (HPV) infections result in a substantial burden of disease globally, particularly because they can cause cervical cancer.[1] In Australia, cancers of the cervix and uterus were once leading causes of cancer-related deaths for women.[2] NHMRC-funded researchers at The University of Queensland (UQ) made an important contribution to preventing cervical cancer through their development of the technology that underpins the world's first HPV vaccines, which are used worldwide today.

Origin

Human papillomaviruses (HPV) are a family of viruses that infect skin. Some HPVs produce skin warts which generally resolve. Others – usually transmitted through sexual intercourse – can cause genital warts (HPV 6 and 11) which are generally cleared naturally by the immune system, and other genital infections (HPV 16 and 18) which sometimes persist and progress to cancer. 80-90%[3] of people are infected with one of these cancer promoting HPVs at some point in their lifetime.

Cancer of the cervix was first discussed by NHMRC as early as 1928. In 1965, the Council considered an order of priority for cervical cytological screening for women and, in 1968, it developed a statement on the *Frequency of Cervical Cytology* which was revised and updated regularly with new evidence and information throughout the 1980s.

In 1983, papillomavirus DNA was isolated from human cervical cancer tissue and further research showed that almost all cases of cervical cancer are caused by persistent HPV infections, particularly with two HPV types (16 and 18).[4] In 1984, after visiting the laboratory in Germany where these initial discoveries were made, University of Queensland (UQ) clinician-scientist Ian Frazer—whose work focused on immunology—turned his attention to understanding why HPV infections sometimes persist and progress to cancer.

Cervical screening

Cervical cancer is one of few cancers with an effective screening test that can detect pre cancerous abnormalities before their potential progression to cancer.[5] In 1991, Australia introduced the National Cervical Screening Program (NCSP) to provide screening and early detection to women between the ages of 18 and 70.[6] NCSP offered effective secondary prevention (i.e., early diagnosis and treatment to prevent the progression of an HPV infection to pre cancer or cervical cancer) but not a primary prevention method to stop initial HPV infection in uninfected women (*refer Figure 1*).

In 1994, NHMRC's Health Advisory Committee approved the *Screening to prevent cervical cancer: guidelines for the management of asymptomatic women with screen detected abnormalities.* These guidelines, which assist health professionals to treat women with HPV, were reviewed in 2005 and again with the renewed NCSP in 2014.

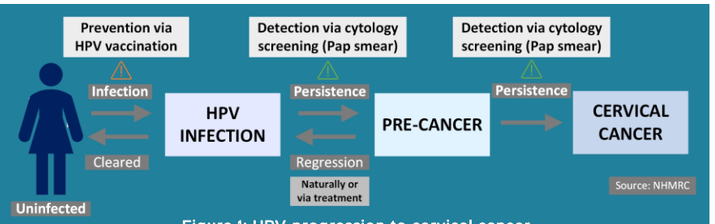


Figure 1: HPV progression to cervical cancer

Grants and Research

Between 1986 and 2022, NHMRC funded Frazer's research on the role of the immune system in cancer and other chronic illness, including the immune response to HPV infection.

In 1989, while on sabbatical in Cambridge, Frazer met Chinese clinician researchers Jian Zhou and Xiao-Yi Sun. He invited them to join him at UQ, and together they undertook research to develop a vaccine to prevent the HPV infections that could initiate cancers.

Frazer, Zhou and Sun isolated and undertook research on the genes from the cancer promoting HPV strains. To study these genes and the proteins they produced, the team used animal cells, rather than bacteria, as was common at the time. Using another virus to carry HPV viral genes into animal cells, they were able to make HPV surface proteins which could self-assemble in animal cells to produce a virus-like particle (VLP).

With the help of electron microscopist Dr Deborah Stenzel, Frazer and team showed that the VLPs resembled the natural virus in appearance. These VLPs sufficiently resembled the infectious virus that they could trigger the immune system to make defensive antibodies, which could protect against HPV infection.

Commercialisation Journey

In 1991, through UQ's commercialisation company UniQuest, Frazer's team filed the initial patent for the immunogenic VLP technology that could be used to develop an HPV vaccine.

Research on this technology continued at UQ until 1994, when UniQuest licensed the intellectual property to Australian biotechnology company CSL Limited, which funded further research and development of an HPV vaccine. In 1996, CSL sub-licensed the technology to American multinational pharmaceutical company Merck & Co., Inc., known as MSD in Australia, while retaining the rights to market HPV technology within Australia and New Zealand.

Merck & Co., Inc. conducted several clinical trials in over 13 countries including Phase 3 studies involving more than 12,000 women between the ages of 15 and 26 who received either a quadrivalent HPV-6/11/16/18 vaccine or placebo, where they were followed over a three-year period to investigate the incidence of infection with the high-risk HPV strains.[7] Results published in 2007 indicated that young women not previous infected with HPV strains 16 and 18 in the vaccine group had a significantly lower occurrence of high-risk cervical abnormalities than those in the placebo group in the three years following vaccination.[7]

Translation

The MSD/Merck & Co., Inc. vaccine GARDASIL® was approved by the Australian Therapeutic Goods Administration in 2006. It provided protection against the four HPV strains known to cause almost all cases of genital warts and a high number of cases of cervical cancer (types 6, 11, 16 and 18).

By 2007, Australia became the first country in the world to include the HPV vaccine in its National Immunisation Program (NIP) for Year 7 girls aged 12 to 13 years. Catch-up programs for girls aged 14 to 18 and for young women between 18 and 26 years were introduced from 2009. In 2013, boys aged 12 to 13 were also included. A catch-up program for Year 9 boys aged 14 to 15 was carried out between 2010 and 2015.

GARDASIL® was used in Australia until 2017, when it was replaced with GARDASIL®9 (9vHPV), an improved version of the vaccine that protects against 9 HPV strains (6, 11, 16, 18, 31, 33, 45, 52 and 58) known to cause genital warts and cervical and other HPV-related cancers.[8]

The 9vHPV vaccination is recommended for females and males aged 12-13 years in a 2-dose schedule, with the second dose administered 6 to 12 months following the first.

Since the introduction of GARDASIL® in 2007, both immunisation (via the NIP) and screening (via the NCSP) are recommended for the prevention and early detection of cervical cancer. Almost all Australian schools participate in the NIP.

Source: MSD Australia

Health Outcomes and Impact

In 2022, the best way in Australia to prevent cervical cancer and other HPV-associated cancers is immunisation against HPV for 12-year-old boys and girls, together with participation of women aged 18 and over in the national screening program.[9]

Since the implementation of the National HPV Vaccination Program, there have been significant decreases in the age-standardised incidence rate of cervical cancer, and death rate from cervical cancer, per 100,000 females. The incidence rate decreased from 14.2 (in 1982) to 7.4 (in 2014), while the death rate decreased from 5.2 (in 1982) to 1.7 (in 2014).[10]

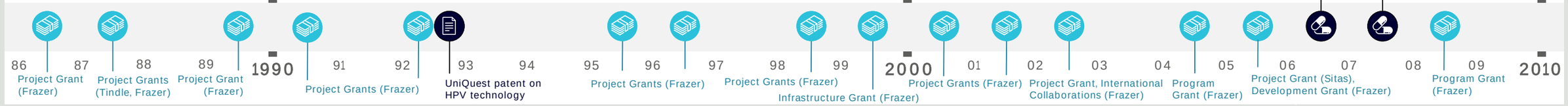
The steady decline in the detection of pre-cancerous cervical abnormalities in younger women between 2007 and 2014 has been attributed to the HPV vaccine during the school-based and catch-up programs.[10]

NHMRC-funded research into cervical cancer elimination has indicated that, if high-coverage vaccination and screening is maintained across Australia, cervical cancer mortality is likely to decrease to an annual rate of less than one death per 100,000 women by 2034.[11]

As of 2019, one hundred countries have included the HPV vaccine (GARDASIL® and/or Cervarix) as part of their national vaccination schedules.[12]

NHMRC's Centre of Research Excellence in Cervical Cancer Control (C4), established in 2017, brings together researchers from the Cancer Council NSW, Australian Centre for the Prevention of Cervical Cancer, Kirby Institute at UNSW Sydney, and The University of Melbourne.

These researchers have developed innovations in public health, including improvements in implementation of HPV vaccination and cervical screening. C4 runs projects across Australia and globally, including clinical trials to support the NCSP and projects to eliminate cervical cancer in the Western Pacific.



Papillomavirus strains

There are more than 100 strains of HPV that cause a range of conditions. Of these strains, 2 'low risk' strains (types 6 and 11) of HPV are known to cause almost all cases of genital warts. 13 strains (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) are identified as 'high risk' due to their causal association with cancer, including cervical, vaginal, anal, penile, head and neck cancers. Types 16 and 18 alone are responsible for over 70% of cervical cancer cases. The largest burden of HPV associated cancers in Australia is attributable to cervical cancer.

While an infection with HPV is necessary for the development of these cancers, not all HPV infections progress to cancer.

Virus like particle

Virus like particles (VLPs) are molecules that have diverse uses in immunisation and therapeutics. A VLP is a particle that closely resembles the structure of virus but contain no viral genetic material and hence is non infectious. VLPs can occur naturally or can be synthesised through the expression of the structural proteins found on the virus.

VLPs can elicit strong immune responses, and as such, offer an ideal vaccine platform. Apart from GARDASIL®, VLP based vaccines currently used worldwide included Engerix (hepatitis B) and Cervarix (HPV types 16 and 18). Clinical trials are underway for VLP based vaccines for other infectious diseases including malaria, influenza, rotavirus and tuberculosis.

Professor Ian Frazer AC

Ian Frazer studied medicine at the University of Edinburgh in Scotland, training as a renal physician and clinical immunologist. In 1981, Frazer relocated to Melbourne where he continued his clinical training at the Walter and Eliza Hall Institute. In 1985, he moved to UQ where he taught, established the Centre for Immunology and Cancer Research and concurrently worked at the Princess Alexandra Hospital. Along with many other awards, Frazer was recognised as Australian of the Year in 2006. He received the Prime Ministers Prize for Science in 2008 and was made a Companion of the Order of Australia in 2013.

Dr Jian Zhou

Jian Zhou (1957 1999) received a MBBS, Master's Degree and PhD from Wenzhou Medical University, Zhejiang Medical University and Henan Medical University in China before undertaking postdoctoral research at Beijing Medical University. From 1988, he worked as a research fellow at ICRF in Cambridge, UK. In 1990, Zhou moved to the Centre for Immunology and Cancer Research at UQ. He gained his Doctor of Medicine at UQ in 1994.

Zhou subsequently worked as an Assistant Professor at Loyola Medical University, Chicago, before returning to UQ in 1996.

Dr Xiao Yi Sun

Xiao Yi Sun obtained an MBBS at Wenzhou Medical University, where she was classmates with Dr Jian Zhou. After graduating, she worked as an ophthalmologist. In 1989, she joined Zhou as his research assistant at ICRF (Imperial Cancer Research Fund) in Cambridge and followed Zhou's subsequent moves throughout Australia and the United States as his research assistant for the next eight years.

Sun returned to the eye clinic at Queensland's Princess Alexandra Hospital and Laser Sight Centre in 1997.

C4

NHMRC's Centre of Research Excellence in Cervical Cancer Control (C4) comprises Australia's leaders in HPV vaccination and cervical screening who are working to ensure Australia can achieve cervical cancer elimination.

The work of C4 is divided into four streams: cervical screening, HPV methods, HPV vaccination strategies and global health. C4 currently runs Australia's largest clinical trial, Compass, which is providing world first evidence on the interaction between the HPV vaccination and cervical screening.

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References

This case study was developed with input from Professor Ian Frazer and Dr Xiao-Yi Sun in partnership with The University of Queensland.

The information and images from which impact case studies are produced may be obtained from a number of sources including our case study partner, NHMRC's internal records and publicly available materials.

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