

Institution: Queen Mary University of London		
Unit of Assessment: 1		
Title of case study: Validating the Improved Vaccine Gardasil9 for Protection Against HPV Associated Cancers		
Period when the underpinning research was undertaken: 2014-2017		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
1) Jack Cuzick	1) Director, Wolfson Institute of Preventive Medicine	1) 12/2002-present
Period when the claimed impact occurred: 2015-2020		
Is this case study continued from a case study submitted in 2014? N		
<p>1. Summary of the impact (indicative maximum 100 words)</p> <p>The Gardasil9 vaccine, validated by Queen Mary's research, addresses seven oncogenic human papillomavirus (HPV) types (16, 18, 31, 33, 45, 52, 58). HPV is responsible for at least 95% of cervical cancers, around 85% of anal cancers, 70% of vaginal, vulval, and oropharyngeal (now the most common HPV associated cancer in the US) cancers, and 60% of penile cancers. Gardasil9 offers an important advance over Gardasil, which only addressed two oncogenic HPV types. Among women vaccinated with Gardasil9 before infection, virtual elimination of cervical cancer is likely. While HPV vaccination was originally aimed at cervical cancer protection, Gardasil9 offers additional protection against multiple cancers, and immunisation programmes are changing accordingly, with vaccination being offered to both males and females, with increased age ranges, around the world. From 2017, Gardasil9 has been the only HPV vaccine available in the US. It is routinely offered to school children in publicly funded programs in Canada, Denmark, New Zealand, and Australia. By 2020, Gardasil9 had been approved for use in 83 countries.</p>		
<p>2. Underpinning research (indicative maximum 500 words)</p> <p>Human papillomavirus (HPV) causes premalignant and malignant lesions in the cervix, vagina, vulva, anus, penis and oropharynx, as well as genital warts. The World Health Organisation recommends HPV vaccines in its Essential Medicines List, and since the first vaccine became available in 2006, 90 countries have included it in their routine vaccinations. However, HPV vaccinations, prior to this research conducted at Queen Mary, addressed 70% of cervical cancers through protection from HPV-16 and HPV-18.</p> <p>Between 2015 and 2017, a series of publications presented the results of a randomised international double-blind study of the use of the 9valent virus-like particle vaccine, Gardasil9 (NCT00543543 - the Broad Spectrum HPV Vaccine Study). Prof. Cuzick, as the only statistician appointed to the Study Scientific Advisory Committee, and as a co-author on the resulting publications, played a "major role in the design, regular review, and analysis of...and especially in the interpretation of the data" [5.1]. Gardasil9 not only addressed the two oncogenic HPV types (16 and 18) included in the existing quadrivalent (Gardasil) vaccine, but also five additional oncogenic types (31, 33, 45, 52, and 58). These seven HPV types account for about 90% of cervical cancers. Between 2007 and 2013, 14,215 women aged 16-26 from 105 study centres in 18 countries received three doses of either the existing Gardasil vaccine or Gardasil9. Median follow up was in excess of 42 months. Serum was collected for antibody response analysis, swabs of labial, vulvar, perianal, endocervical and ectocervical tissue were obtained and used for HPV-DNA testing, and Pap testing was conducted regularly. Tissue obtained by biopsy or as part of definitive therapy was tested for HPV. In the per protocol analysis, high grade cervical, vulvar, and vaginal lesions associated with HPV 31, 33, 45, 52 and 58 were reduced by 96.6% in the Gardasil9 arm. Antibody responses to the other four HPV types were non-inferior to those generated by the standard Gardasil vaccine. Immunogenicity was very strong, with virtually 100% seroconversion of all per protocol patients within one month of the third vaccine dose [3.1, 3.2]. A 2017 publication [3.3] reported that the vaccine prevented infection, cytological abnormalities, high grade lesions, and cervical procedures related to HPV 31, 33, 45, 52, and 58, and had a similar immunogenic profile to the Gardasil vaccine with respect to HPV 6, 11, 16, and 18. It concluded that the Gardasil9 vaccine could potentially prevent 90% of cervical cancer cases worldwide.</p> <p>An additional study, co-authored by Cuzick in 2016 [3.4], assessed the safety profile of the</p>		

Gardasil9 vaccine in a combined analysis of seven phase III clinical trials, and the vaccine was found to be well tolerated. Further publications evaluated the effect of baseline characteristics of subjects on vaccine-induced HPV antibody responses to the Gardasil9 vaccine [3.5], and the proportion of cervical cancer cases attributed to the HPV types addressed by Gardasil and Gardasil9 according to geographical region [3.6].

Thus, Queen Mary's research validated the effectiveness and safety of the Gardasil9 vaccine and its superiority to the existing Gardasil vaccine. This has led to worldwide changes to immunisation programmes.

3. References to the research (indicative maximum of six references)

[3.1] Joura, E. A., Giuliano, A. R., Iversen, O. E., Bouchard, C., Mao, C., Mehlsen, J., Moreira, E. D. Jr, Ngan, Y., Petersen, L. K., Lazcano-Ponce, E., Pitisuttithum, P., Restrepo, J. A., Stuart, G., Woelber, L., Yang, Y. C., Cuzick, J., Garland, S. M., Huh, W., Kjaer, S. K., Bautista, O. M., Chan, I. S., Chen, J., Gesser, R., Moeller, E., Ritter, M., Vuocolo, S. & Luxembourg, A. (2015). Broad Spectrum HPV Vaccine Study. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *The New England Journal of Medicine*, 372 (8), 711-723.

<https://doi.org/10.1056/NEJMoa1405044>

[3.2] Cuzick, J. (2015). Gardasil 9 joins the fight against cervix cancer. *Expert Review of Vaccines*, 14 (8), 1047-1049. <https://doi.org/10.1586/14760584.2015.1051470>

[3.3] Huh, W. K., Joura, E. A., Giuliano, A. R., Iversen, O. E., de Andrade, R. P., Ault, K. A., Bartholomew, D., Cestero, R. M., Fedrizzi, E. N., Hirschberg, A. L., Mayrand, M. H., Ruiz-Sternberg, A. M., Stapleton, J. T., Wiley, D. J., Ferenczy, A., Kurman, R., Ronnett, B. M., Stoler, M. H., Cuzick, J., Garland, S. M., Kjaer, S. K., Bautista, O. M., Haupt, R., Moeller, E., Ritter, M., Roberts, C. C., Shields, C. & Luxembourg, A. (2017). Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16-26 years: a randomised, double-blind trial. *The Lancet*, 390 (10108), 2143-2159.

[https://doi.org/10.1016/S0140-6736\(17\)31821-4](https://doi.org/10.1016/S0140-6736(17)31821-4)

[3.4] Moreira, E. D. Jr, Block, S. L., Ferris, D., Giuliano, A. R., Iversen, O. E., Joura, E. A., Kosalaraksa, P., Schilling, A., Van Damme, P., Bornstein, J., Bosch, F. X., Pils, S., Cuzick, J., Garland, S. M., Huh, W., Kjaer, S. K., Qi, H., Hyatt, D., Martin, J., Moeller, E., Ritter, M., Baudin, M. & Luxembourg, A. (2016). Safety Profile of the 9-Valent HPV Vaccine: A Combined Analysis of 7 Phase III Clinical Trials. *Pediatrics*, 138 (2), e20154387. <https://doi.org/10.1542/peds.2015-4387>

[3.5] Petersen, L. K., Restrepo, J., Moreira, E. D. Jr, Iversen, O. E., Pitisuttithum, P., Van Damme, P., Joura, E. A., Olsson, S. E., Ferris, D., Block, S., Giuliano, A. R., Bosch, X., Pils, S., Cuzick, J., Garland, S. M., Huh, W., Kjaer, S. K., Bautista, O. M., Hyatt, D., Maansson, R., Moeller, E., Qi, H., Roberts, C. & Luxembourg, A. (2017). Impact of baseline covariates on the immunogenicity of the 9-valent HPV vaccine - A combined analysis of five phase III clinical trials. *Papillomavirus Research*, 3, 105-115. <https://doi.org/10.1016/j.pvr.2017.03.002>

[3.6] Castellsagué, X., Ault, K. A., Bosch, F. X., Brown, D., Cuzick, J., Ferris, D. G., Joura, E. A., Garland, S. M., Giuliano, A. R., Hernandez-Avila, M., Huh, W., Iversen, O. E., Kjaer, S. K., Luna, J., Monsonego, J., Muñoz, N., Myers, E., Paavonen, J., Pitisuttithum, P., Steben, M., Wheeler, C. M., Perez, G., Saah, A., Luxembourg, A., Sings, H. L. & Velicer, C. (2016). Human papillomavirus detection in cervical neoplasia attributed to 12 high-risk human papillomavirus genotypes by region. *Papillomavirus Research*, 2, 61-69. <https://doi.org/10.1016/j.pvr.2016.03.002>

4. Details of the impact (indicative maximum 750 words)

Preventing cancers caused by HPV [5.2]

Worldwide, HPV causes more than 630,000 new cancers annually according to the [US National Cancer Institute](#), around 5% of the global cancer burden.

Cervical cancer

In 2020 there were an estimated 604,000 new cases of cervical cancer worldwide according to the [World Health Organization](#). The Gardasil9 vaccine could prevent 90% of these cases, representing an additional 15% protective advantage over Gardasil. Gardasil9 could also prevent up to 70-85% of high grade cervical dysplasia (pre-cancers).

Anal cancer

There were approximately 50,000 new cases of anal cancer worldwide in 2020, around 90% of which were caused by HPV. Gardasil9 could prevent 85-90% of HPV-related anal cancers, offering an additional 8% protection compared with Gardasil.

Vaginal and vulval cancers

In 2020 there were around 63,000 new cases of vaginal and vulval cancers worldwide, about 70% of which were HPV related. Gardasil9 could prevent 85-95% of vaginal and vulval cancers. Gardasil9 offers additional protection of 18% for vaginal and 14% for vulval cancers over Gardasil.

Oropharyngeal cancers

Of the expected 98,000 new cases of oropharyngeal cancer worldwide each year, an estimated 70% are caused by HPV. Oropharyngeal cancer is now the most common HPV associated cancer in the United States, killing around one person per hour each day. Of those diagnosed with this cancer, only 57% will survive five years. Whilst Gardasil could potentially prevent an estimated 60.2% of these cancers, Gardasil9 could offer protection against an extra 6% of HPV related oropharyngeal cancers.

Penile cancer

Around 36,000 new cases of penile cancer were diagnosed worldwide in 2020, with 60% caused by HPV. Gardasil9 offers additional protection of 9% over Gardasil in the prevention of penile cancer.

Influencing worldwide immunisation programmes

Since the vaccine's rollout in 2015, millions of doses of Gardasil9 have been distributed worldwide. Prof. Cuzick's work [3.1, 3.4] is provided to patients as the clinical evidence supporting the efficacy of the vaccine in the product package insert [5.3].

In Northern America

In February 2015, the Advisory Committee on Immunisation Practices (ACIP) within the Centers for Disease Control and Prevention (CDC) recommended the introduction of Gardasil9 as a routine HPV vaccine [5.4]. By December 2017, about 28,000,000 doses of Gardasil9 had been distributed in the US [5.5]. By 2017, almost half of all adolescents (aged 13-17) in the US were up to date with their HPV vaccinations [5.6], and from 2017 Gardasil9 has been the only HPV vaccine available in the US [5.5]. In October 2018, the US Food and Drug Administration approved the expanded use of Gardasil9 to include women and men aged 27-45 (in addition to those aged 9-26) [5.7]. This will make Gardasil9 available to another (approximately) 60,000,000 Americans.

Gardasil9 was approved by Health Canada on 5 February 2015, and as of July 2020, was available free to students in 6th or 7th grade in 10 of the 13 Canadian provinces [5.8].

In Europe

In March 2015, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended that Gardasil9 is approved for use in the EU, on the basis that "Gardasil9 offers a broader protection against cancer than its precursor, Gardasil, since it protects against an additional 5 new types of HPV" [5.9]. The European Commission granted marketing authorisation on 10 June 2015 [5.9]. From Autumn 2017, all girls aged 12 in Denmark have been offered the Gardasil9 vaccination [5.10].

In Australia and New Zealand

In New Zealand, Gardasil9 was introduced into school immunisation programmes from January 2017, and into general practices throughout 2017 as stocks of Gardasil ran out [5.11]. From 2018, all 12 and 13 year old school children in Australia (both boys and girls) have received free Gardasil9 vaccinations [5.12].

In summary, Gardasil9 has now been licenced in 83 countries [5.13], including the populous countries of India and China in 2018, and Iran in 2019.

Commercial success of Gardasil9

In the second quarter of 2018, Merck reported USD886,000,000 in global sales for Gardasil9, exceeding their previous year's second quarter earnings by 46%, and positioning the vaccine to surpass total sales of USD3,150,000,000 for 2018 [5.14]. Merck is now turning its focus towards increasing production volume for Gardasil9. After approval of Gardasil9 for use in China in 2018, a temporary deficiency of Gardasil9 stock in the country resulted in thousands of women seeking vaccination in neighbouring countries, and Merck was forced to "borrow" supplies from the US Centers for Disease Control stock [5.14]. To avoid similar situations in other markets, Merck has announced a USD1,600,000,000 investment in the construction of new production plants for Gardasil9, which are expected to generate over 500 jobs [5.14].

5. Sources to corroborate the impact (indicative maximum of 10 references)

[5.1] E. Joura. Associate Professor of Gynaecology. *Medical University of Vienna (Medizinische Universität Wien)* (testimonial letter, 3 June, 2015). [Corroborator 1]

[5.2] Saraiya, M., Unger, E., Thompson, T. D., Lynch, C. F., Hernandez, B. Y., Lyu, C. W., Steinau, M., Watson, M., Wilkinson, E. J., Hopenhayn, C., Copeland, G., Cozen, W., Peters, E. S., Huang, Y., Saber, M. S., Altekruse, S. & Goodman, M. T. (2015). HPV Typing of Cancers Workgroup. US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. *Journal of the National Cancer Institute*, 107 (6). <https://doi.org/10.1093/jnci/djv086>

[5.3] Merck. (2020). *Patient Information about GARDASIL®9*. <https://www.medicines.org.uk/emc/product/7330/pil#gref>

[5.4] Centers for Disease Control and Prevention. (2015, 27 March). Morbidity and Mortality Weekly Report. *Use of 9-valent human papillomavirus (HPV) vaccine: Updated HPV vaccination Recommendations of the Advisory Committee on Immunization Practices*. <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6411a3.htm>

[5.5] Centers for Disease Control and Prevention. (2018, 27 September). *Questions about HPV vaccine safety*. <https://www.cdc.gov/vaccinesafety/vaccines/hpv/hpv-safety-faqs.html>

[5.6] Centers for Disease Control and Prevention. (2017). *Human Papillomavirus (HPV): Understanding HPV Vaccine Coverage*. <https://www.cdc.gov/hpv/partners/outreach-hcp/hpv-coverage.html>

[5.7] US Food and Drug Administration. (2014). *GARDASIL®9 (Human Papillomavirus 9-valent Vaccine, Recombinant)*. <https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm426457.pdf>

[5.8] Gardasil9. (2020). *Provincially-funded vaccination programs*. <https://www.gardasil9.ca/provincial-programs/>. Accessed 4 February 2020.

[5.9] European Medicines Agency. (2016). *EPAR Summary for the public: Gardasil9*. https://www.ema.europa.eu/en/documents/overview/gardasil-9-epar-summary-public_en.pdf

[5.10] Valentiner-Branth, P. (2017). *Novel HPV vaccine in the childhood vaccination programme*. Statens Serum Institut, Denmark. <https://en.ssi.dk/news/epi-news/2017/no-39---2017>

[5.11] New Zealand Ministry of Health. (2017). *Questions and Answers about HPV immunisation*. <https://www.health.govt.nz/your-health/healthy-living/immunisation/immunisation-older-children/human-papillomavirus-hpv/questions-and-answers-about-hpv-immunisation>

[5.12] Australian Broadcasting Corporation News. (2017, 8 October). *Gardasil9: What will the improved vaccine protect against?* <http://www.abc.net.au/news/2017-10-08/gardasil-9-what-will-the-improved-vaccine-protect-against/9027960>. Accessed 20 November 2020.

[5.13] Merck. (2020). *V503 GARDASIL 9 – Worldwide Marketing Approval Status*.

[5.14] Media stories on Merck's Gardasil9 sales. GlobalData Healthcare (2019, 12 August).

Unprecedented global demand for Gardasil 9. Pharmaceutical Technology.

<https://www.pharmaceutical-technology.com/comment/unprecedented-global-demand-for-gardasil/>.

Accessed 11 December 2020. Hargreaves, B. (2019, 30 October). *Merck forced to borrow half of*

CDC stockpiles of Gardasil to meet demand. BioPharma-Reporter.com. [https://www.biopharma-](https://www.biopharma-reporter.com/Article/2019/10/30/Merck-borrows-doses-of-Gardasil-to-meet-demand)

[reporter.com/Article/2019/10/30/Merck-borrows-doses-of-Gardasil-to-meet-demand](https://www.biopharma-reporter.com/Article/2019/10/30/Merck-borrows-doses-of-Gardasil-to-meet-demand). Accessed 11

December 2020.