

Institution: University of Strathclyde		
Unit of Assessment: A3 Allied Health Professions, Dentistry, Nursing and Pharmacy		
Title of case study: Changes to cervical screening policies following the roll out of human papillomavirus (HPV) vaccination		
Period when the underpinning research was undertaken: 2010 - 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Kimberley Kavanagh	Role(s) (e.g. job title): Senior Lecturer	Period(s) employed by submitting HEI: 01/10/2006 - present
Period when the claimed impact occurred: 2016 – July 2020		
Is this case study continued from a case study submitted in 2014? No		
<p>1. Summary of the impact</p> <p>Extensive national studies, including advanced analysis and modelling from Kavanagh, were the first population-based demonstrations of a reduction of cervical and precancerous disease due to the human papillomavirus (HPV) vaccine, freely available in Scotland since 2008. The studies led the Scottish Government to change the age range of the Scottish Cervical Screening Programme and replace cytology with HPV testing as the initial stage of screening. Wider impact of the research caused UK policy makers to extend HPV vaccination to males, and the World Health Organisation (WHO) to advocate continued worldwide vaccination of girls aged 9-14. Global media coverage of the research also raised public awareness of successful vaccination initiatives at a time of growing misinformation related to vaccination.</p>		
<p>2. Underpinning research</p> <p>Cervical cancer is commonly diagnosed in females, with 80-90% of cases attributable to HPV infection. Organised cervical screening programmes, introduced in the 1980s, dramatically reduced cervical cancer in Scotland by enabling treatment of pre-cancerous disease. Since 2008, HPV vaccination has been available through the NHS to girls, typically 12-13 years old, protecting them against two of the common genotypes of HPV (HPV16 and HPV18) implicated in over 70% of cervical cancer cases, with hypothesised cross-protection against three other similar genotypes (HPV 31/33/45) which also exhibit a high risk of causing cervical disease. To assess the impact of the vaccine in the population, researchers from academia and the Scottish Government established the Scottish Cervical Cancer Prevention Programme in 2008, which modelled the impact of the vaccine on cervical screening and other strategies to prevent the cancer. As part of this programme, two researchers from the University of Strathclyde, Chris Robertson and Kim Kavanagh, collaborated with Health Protection Scotland and the Scottish HPV Reference Laboratory to determine the impact of immunisation on cervical screening and colposcopy, to consider possible future triage of cervical disease, and determine the impact of HPV vaccination on public health. Robertson designed the initial epidemiological studies (REF2014 impact case submitted to B10) and was joined in this activity for studies in the national surveillance programme by Kavanagh who, as detailed below, led on the statistical analysis and modelling of the data, and on leading and co-authoring manuscripts.</p> <p>Assessing the impact of HPV vaccination on public health (HPV prevalence and pre-cancerous disease)</p> <p>By annually linking individual vaccination, screening and HPV testing records, a 2009-2012 study with Kavanagh as principal analyst and lead author demonstrated a clear reduction in the prevalence of HPV 16/18, as well as cross-protective effects with other high risk types of HPV, among girls vaccinated at age 13-17 [R1]. A separate seven-year cross-sectional study, led by Kavanagh, was the first internationally to present population-based evidence of the effectiveness of the bivalent HPV vaccine in girls vaccinated routinely at age 12-13 and attending cervical screening at age 20 [R2]. The study showed that the vaccine-specific HPV genotypes (16/18) and</p>		

the cross-protective genotypes (31/33/45) had almost disappeared in this population seven years after the introduction of the vaccine, with evidence of herd protection for all these types.

To better assess the population-level consequences and herd effects following female HPV vaccination programmes, two further studies co-authored by Kavanagh combined the results of the Scottish cross-sectional assessment with those of other international studies, verifying the high efficacy reported in randomised controlled clinical trials of the HPV vaccine [R3, R4]. Kavanagh was the only academic researcher from Scotland invited to join other leaders in HPV epidemiology in the international HPV Vaccination Impact Study Group. The Group's purpose was to capture the impact of HPV vaccination on HPV infection levels and precancerous disease in high income countries. Both of the studies conducted by the Group demonstrated the population-level impact and herd effects arising from HPV programmes. The first study focussed on individuals vaccinated at an older age who may not have had maximum benefit from vaccination as they could have been exposed to HPV prior to immunisation [R3]. The second study analysed evidence collated over a broader timeline. It was able to produce more definitive conclusions because it included individuals much younger than in the first evaluation [R4]. In both highly cited seminal studies, Kavanagh advised on the combination of the data across studies, validated the rigour of the statistical analysis in publications and the appropriateness of associated public health messages.

Assessing the impact of HPV vaccination on the Scottish Cervical Screening Programme (SCSP) (cytology and colposcopy)

The SCSP in the pre-HPV vaccination era was based fully on cytological screening, the examination of a smear sample of cervical cells under a microscope, as an initial triage to identify individuals with potential cervical disease. As cytology is subjective, it is more difficult to accurately classify abnormalities seen following the introduction of HPV vaccination due to markedly lower rates of precancerous disease. Retrospective analysis of routinely collected data from the SCSP, found that lower rates of HPV in vaccinated women led to significant reductions in positive predictive and abnormal predictive values for detecting precancerous disease, such that cytologists were referring a greater proportion of patients without abnormal cytology for colposcopy [R5].

To understand possible impacts of HPV vaccination on colposcopy – the diagnostic procedure used to classify cervical disease - routinely collected data were extracted from the Scottish National Colposcopy Clinical Information Audit System for a cohort of women who entered the SCSP and were aged 20–21 in 2008–2012. Analysis revealed a downward trend in the proportion of those referred to colposcopy with abnormal cytology, suggesting that demand for colposcopy as part of the SCSP will continue to fall. It also showed that the positive predictive value of colposcopy for the detection of high grade cervical intraepithelial neoplasia in vaccinated women to be at 65%, the lowest acceptable level of the UK national cervical screening programme guidelines [R6].

A significant reduction in diagnoses of all stages of the precancerous disease attributable to HPV was observed. These were the first population-based demonstrations of the impact of the vaccine on cervical disease [R5, R6] and indicated that revision of the SCSP was merited.

3. References to the research (Strathclyde-affiliated authors in **bold**; FWCI at 25/02/21)

- R1 K. Kavanagh**, K.G.J. Pollock, A. Potts, J. Love, K. Cuschieri, H. Cubie, **C. Robertson**, M. Donaghy (2014) Introduction and sustained high coverage of the HPV bivalent vaccine leads to a reduction in prevalence of HPV 16/18 and closely related HPV types, *British Journal of Cancer*, 110: 2804–2811. <https://dx.doi.org/10.1038/bjc.2014.198> [FWCI: 6.87; REF2]
- R2 K. Kavanagh**, K.G. Pollock, K. Cuschieri, T. Palmer, R. Cameron, C. Watt, R. Bhatia, C. Moore, H. Cubie, M. Cruickshank, **C. Robertson** (2017) Changes in the prevalence of human papillomavirus following a national bivalent human papillomavirus vaccination programme in Scotland: a 7-year cross-sectional study, *Lancet Infectious Diseases*, 17(12): 1293-1302 [https://dx.doi.org/10.1016/S1473-3099\(17\)30468-1](https://dx.doi.org/10.1016/S1473-3099(17)30468-1) [FWCI: 11.58; REF2]
- R3 M. Drolet**, E. Bénard, M. Boily ... **K. Kavanagh**... (2015) Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and

meta-analysis, *Lancet Infectious Diseases* 15(5): 565-580 [http://doi.org/10.1016/S1473-3099\(14\)71073-4](http://doi.org/10.1016/S1473-3099(14)71073-4) [FWCI: 31.20; REF2]

R4 M. Drolet, E. Bénard, N. Pérez ... **K. Kavanagh** ... (2019) Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. *Lancet* 394: 497-509. [http://dx.doi.org/10.1016/S0140-6736\(19\)30298-3](http://dx.doi.org/10.1016/S0140-6736(19)30298-3) [FWCI: 60.92; REF2]

R5 K. Pollock, **K. Kavanagh** ... H. Cubie, **C. Robertson**, M. Cruickshank, T. Palmer, S. Nicoll, M. Donaghy (2014) Reduction of low- and high-grade cervical abnormalities associated with high uptake of the HPV bivalent vaccine in Scotland, *British Journal of Cancer* 111: 1824–1830. <https://doi.org/10.1038/bjc.2014.479> [FWCI: 5.82; REF2]

R6 T.J. Palmer, M. McFadden, K.G.J. Pollock, **K. Kavanagh**, K. Cuschieri, M. Cruickshank, S. Cotton, S. Nicoll, **C. Robertson** (2016) HPV immunisation and cervical screening — confirmation of changed performance of cytology as a screening test in immunised women: a retrospective population-based cohort study, *British Journal of Cancer*, 114: 582-589 <https://doi.org/10.1038/bjc.2015.474> [FWCI: 2.38]

Notes on the quality of research: All articles are published in peer-reviewed journals. Kim Kavanagh was awarded the 2018 Royal Society of Edinburgh Sir Thomas MakDougall Brisbane Medal for ‘*outstanding, internationally renowned research in public health epidemiology and health informatics*’, based mainly on her assessment of the HPV vaccination programme. The programmes received funding from the Chief Scientist Office, the Scottish Government:

- Cruickshank, **Robertson** (Strathclyde PI). The Scottish Cervical Cancer Prevention Programme: Assessing and modelling the impact of HPV 16/18 immunisation on the performance of current cervical screening performance and the effectiveness of alternative cervical screening strategies to optimise cancer prevention in the HPV immunisation era. Chief Scientist Office (CSO). 01/04/2010-31/03/2016. GBP523,278 (Strathclyde GBP171,695).
- Howie, **Kavanagh** (Strathclyde PI). Development of CINck (CIN Chemokine panel) as an objective laboratory triage test for HPV infected women with clinically significant cervical disease. Chief Scientist Office. 01/03/2014-29/02/2016. GBP224,788 (Strathclyde GBP11,876).
- Cubie, **Robertson** (Strathclyde PI). Scottish Cervical Cancer Prevention Programme: Establishing an HPV Clinical Research Centre for long-term follow-up of HPV infection and associated disease in a vaccination era, through the creation of a population based sample archive. Chief Scientist Office. 02/06/2009-31/07/2014. GBP671,310 (Strathclyde GBP15,849).

4. Details of the impact

Kavanagh’s analysis and modelling of large observational health datasets in the above body of research demonstrated the success of the HPV vaccine in reducing the prevalence of HPV infection and subsequent precancerous cervical disease in Scotland. The studies have had a substantial public health impact as they have:

- Caused the Scottish Government to change the Scottish Cervical Screening Programme;
- Stimulated improvements to the UK cervical screening process;
- Influenced UK and international policy;
- Raised global awareness of the effectiveness of vaccination programmes.

Influenced a change to the Scottish Cervical Screening Programme (SCSP)

In June 2016, a review panel for the SCSP changed the age range for cervical screening from 20-60 to 25-64 on account of the low predictive value of cytology screening for women aged 20-25. The panel directly referred to work involving Strathclyde researchers [**R1**, **R5**] when justifying and communicating the reason for the change [**S1a**]. By supporting this delay to the age of screening, research by Kavanagh and colleagues has contributed to reducing the number of unnecessary and potential stressful screenings for low risk young women. The impact of the evidence of reduced disease prevalence has also been mentioned by The Director of the Scottish

HPV Reference Laboratory: *'The change in infection and disease prevalence has been so profound – that Immunisation status is now being factored into standard national reports on disease prevalence and screening performance for the Scottish Cervical Screening Programme. Additionally, [the] impact of immunisation has informed national modelling work undertaken by the Scottish Cervical Screening Programme to support the configuration of screening services planned for 2020'* [S2]. The interim Clinical Director at Health Protection Scotland (HPS) writes that *'the data analysis research carried out by Dr Kim Kavanagh has had a great impact at HPS'* and that *'the outputs of this programme of work provided evidence to support changes in vaccine and cervical screening policy'* [S1b].

Informed improvements to UK cervical screening process

A 2015 report from the Advisory Committee on Cervical Screening (ACCS) to the UK National Screening Committee (UK NSC) [S3] cited one of the above studies [R5], which had reported a significant reduction in precancerous disease attributable to HPV following the introduction of HPV vaccination. In particular, the UK National Screening Committee report noted, *'A recent report from Scotland, where screening still begins aged 20 years, has shown a significant reduction in CIN3 [Cervical Intra-epithelial Neoplasia – abnormal cells found on the surface of the cervix]... amongst the vaccinated cohort. In a screening programme where HPV status determines the number of women requiring any further action, the expected impact of vaccination would therefore be considerable in terms of the proportion requiring reflex cytology, referral to colposcopy and treatment for high grade CIN'* [S3 p.5]. In other words, if there is not likely to be much precancerous disease in the screened group, then the current programme is unlikely to be efficient or fit for purpose in the younger age groups.

The research in R5 had predicted a significant drop in the cytological predictive value for precancerous disease (a suggestion later confirmed in R6) and envisaged a consequent drop in the overall efficiency of the cervical screening programme. These findings informed a 2018 policy decision by NHS National Services Scotland (implemented in 2020) to replace cytology as the initial stage of screening with HPV testing, and to reserve cytology for women found to be HPV positive, to provide a more sensitive initial test for underlying disease in a population with decreasing HPV prevalence [S4].

Supported UK and international vaccination policy recommendations

From 2014 to 2016, results from the underpinning research were fed into and discussed by the UK Joint Committee on Vaccination and Immunisation (JCVI), an advisory body to the Secretary of State on the provision of vaccination and immunisation in the UK. The research findings were used by the JCVI to monitor the success of the vaccination campaign and then advise the UK government on vaccination policy [S5, S6]. At the 2014 JCVI meeting [S5], the Scottish data were presented as part of surveillance update on the impact of HPV vaccination in the UK. The Scottish data [R1, R5] summarised the initial impact of the HPV vaccination on HPV infection and precancerous disease in women who were vaccinated as part of the catch-up campaign (when they were older school children). In 2016, the JCVI were informed about the effect of the vaccination in girls vaccinated at a younger age [S6]. The committee also learned about the first evidence of cross-protection against the non-vaccine types HPV 31/33/45 and evidence of herd protection in unvaccinated females of the same age [R2]. The Scottish team also demonstrated equitable coverage of HPV vaccine uptake between deprived and less deprived groups – giving hope for wiping out inequalities in cervical disease between these groups.

Subsequently, the 2014 study demonstrating the effectiveness of the vaccination in women [R1] was cited by the British Medical Association in an April 2018 parliamentary briefing supporting the extension of the immunisation programme to males. Later that year the JCVI, after reviewing research including R3, considered gender neutral HPV vaccination to be cost effective compared to no vaccination programme, although they stressed that the vaccination of girls should remain the priority where resources were limited [S7]. In light of this, by April 2019 the devolved health

boards of England, Wales, Scotland and Northern Ireland all made the decision to offer HPV vaccination to boys aged 11-13 from the beginning of the 2019/20 academic year.

The underpinning research studies [R1, R2, R3, R5] have also informed the recommendations made by the World Health Organization's (WHO) Strategic Advisory Group of Experts on Immunization (Working Group on HPV Immunization). Specifically, this relates to recommendations that the WHO continues to support worldwide HPV vaccination of girls aged 9-14, as well as the use of multiple age cohort vaccination and gender neutral vaccination as ways of speeding up population level impacts of HPV immunisation. This influence is noted in various documents including the evidence to recommendations framework which confirms that R3 informed 'SAGE deliberations on the potential of gender-neutral immunization programmes' in 2016 [S8, S9].

Raising global awareness of a successful vaccination initiative

By demonstrating the success of the HPV vaccine, Strathclyde's body of research has attracted media attention from BBC News, the Guardian and the Scotsman, among others. The 2019 Lancet paper [R4], in particular, generated substantial global media coverage in North and South America, Europe, Australia, Africa and Asia. By raising awareness of successful vaccination initiatives, this research has provided important pro-vaccination information to the public at a time of unprecedented and growing public scepticism of vaccination. The Chief Executive of Jo's Cervical Cancer Trust, commented in the Kenyan Star: *'This study furthers the growing evidence to counteract those who don't believe that this vaccine works...'* [S10a]. When reporting the Lancet study [R4], NBC News mentioned that, *'Despite the widespread benefits of the vaccine...HPV vaccination rates in the USA are still lagging behind those of other adolescent immunizations'* [S10b]. This point was also mentioned in the Washington Post's coverage, which included a statement from a gynaecologist at MD Anderson Cancer Center, *'I just think it is really important to educate the public that it [i.e. the vaccine] is most effective [for children] both because of the kids' immune response but also because they haven't been exposed yet'* [S10c]. Public communication like this is essential if decreasing HPV vaccine uptake rates in some countries are to be reversed.

5. Sources to corroborate the impact

- S1 a.** Public Health Scotland, Cervical Screening Programme Change in Age Range and Frequency 2016, [Questions and Answers paper](#), pp.4,7.
- b.** Factual statement from Interim Clinical Director of Public Health Scotland (earlier Health Protection Scotland), dated 04/03/2021.
- S2** Factual statement from Director of the Scottish HPV Reference Laboratory, dated 20/01/2018.
- S3** Advisory Committee on Cervical Screening, Report to the UK National Screening Committee, June 2015, p.5.
- S4** NHS National Services Scotland, ['New HPV test more effective for identifying the risk of cervical cancer'](#), 8 October 2020.
- S5** HPV Sub-committee of the Joint Committee on Vaccination and Immunisation, [Minute of the meeting held on Monday 20 January 2014](#), p.4.
- S6** HPV Sub-committee of the Joint Committee on Vaccination and Immunisation, [Minute of the meeting held Friday 26 February 2016](#), p.4.
- S7** Joint Committee on Vaccination and Immunisation, [Interim Statement on Extending Vaccination to Adolescent Boys](#), 2017, pp.8,18.
- S8** World Health Organization, Strategic Advisory Group of Experts (SAGE) on Immunization [HPV immunization schedules and strategies: background paper for October 2016 meeting](#) pp.16-18.
- S9** World Health Organization, Strategic Advisory Group of Experts (SAGE) on Immunization, [Evidence to recommendations framework](#) noting deliberations at [October 2016 meeting](#), p.1.
- S10** Media coverage:
 - a.** The Star, Kenya, [Hopes raised of cervical cancer eradication](#), 28/06/2019;
 - b.** NBC News, USA, [HPV vaccine benefits 'exceed expectations'. may lead to elimination of cervical cancer](#), 27/6/2019;
 - c.** The Washington Post, USA, [HPV vaccine now recommended through age 45 in some cases](#), 26/06/2019.