

<b>Institution: University of Warwick</b>		
<b>Unit of Assessment: B10 – Mathematical Sciences</b>		
<b>Title of case study: Introduction of UK gender-neutral HPV vaccination programme following mathematical and economic modelling</b>		
<b>Period when the underpinning research was undertaken: 2016 – 2019</b>		
<b>Details of staff conducting the underpinning research from the submitting unit:</b>		
<b>Name(s):</b>	<b>Role(s) (e.g. job title):</b>	<b>Period(s) employed by submitting HEI:</b>
Matt Keeling Stavros Petrou	Professor Professor in Health Economics	Jan 2002 – Present Sept 2010 – Jun 2019
<b>Period when the claimed impact occurred: 2016 – 2020</b>		
<b>Is this case study continued from a case study submitted in 2014? N</b>		
<b>1. Summary of the impact</b> (indicative maximum 100 words)		
<p>The Joint Committee on Vaccination and Immunisation (JCVI) provides expert advice to the British government on vaccination policy. Based on state-of-the-art mathematical modelling and cost-benefit analyses led by Keeling, the JCVI recommended in 2018 that the existing human papillomavirus (HPV) vaccination programme should be extended from girls-only to also cover adolescent boys as well. Accordingly, Public Health England began gender-neutral HPV vaccination from September 2019, in a move described as a 'victory for the public's health'.</p> <p>Between September 2019 and March 2020 a significant 54.4% of boys aged 12-13 received their first dose of HPV vaccine, compared to 59.2% of girls. While school closures caused by the Covid-19 pandemic reduced the total number of vaccinations provided in 2020, ongoing administration of the gender-neutral vaccination programme at full strength is predicted to result in 12,800 and 230,000 fewer cases of cancer and genital warts respectively over the next 50 years.</p>		
<b>2. Underpinning research</b> (indicative maximum 500 words)		
<p>The Zeeman Institute for Systems Biology &amp; Infectious Disease Epidemiology Research specialises in interdisciplinary research focussed on understanding and predicting the spread and control of many infectious diseases. Working closely with clinicians and public-health officials including the Joint Committee on Vaccination and Immunisation, Prof Matt Keeling led a work programme in collaboration with Prof Stavros Petrou (Warwick Medical School) and funded by the National Institute for Health Research (NIHR) [G1] which generated novel quantitative insights into vaccination against a number of infections [3.1, 3.2]. In particular, the team evaluated the cost-effectiveness of the current Human Papilloma Virus (HPV) vaccination strategy targeting 12-13 year old girls, and alternative strategies including gender-neutral vaccination.</p> <p>The work involved a combination of epidemiological simulations for the transmission of HPV and the impact of different vaccination programmes in the UK, and health economic modelling for calculating costs and health benefits in the future. Both transmission and economic models are matched to the latest data and represent a considerable advance in model complexity over previous predictions.</p> <p>The transmission simulation model captured the full dynamics of the sexually active population in the UK, with sexual mixing patterns inferred to agree with age- and gender-specific data from the Natsal surveys [3.3]. By simulating the pattern of sexual encounters in a synthetic population, the spread of the 9 strains of HPV could be replicated with transmission parameters inferred using a Bayesian approach to generate consensus from 13 different data sources.</p>		

Simulation of historic vaccine uptake and a range of future strategies allowed calculation of the likely health impacts of any new programme together with the associated health and economic costs. In particular, the model focused on the introduction of gender-neutral vaccination (targeting 12-13 year old boys in addition to the current program that vaccinates 12-13 year old girls) and considered different vaccines that protect against 2, 4 or 9 strains [3.4, 3.5].

Results were regularly presented to JCVI and associated sub-panels. Following advice from the main JCVI panel, which led to using a lower economic discounting and a higher level of oropharyngeal cancer attributable to HPV, the Warwick model indicated that gender-neutral vaccination was cost effective [3.5]. The models also highlight that the UK is in a unique situation given its history of high vaccination coverage in girls, such that gender-neutral vaccination should be even more cost effective in other countries.

### 3. References to the research (indicative maximum of six references) **Warwick = Bold**

#### All research papers were published in peer-reviewed journals

[3.1] **Keeling, Matt J., Broadfoot, Katherine A. and Datta, Samik** (2017) *The impact of current infection levels on the cost-benefit of vaccination*. *Epidemics*, 21. 56-62. doi:[10.1016/j.epidem.2017.06.004](https://doi.org/10.1016/j.epidem.2017.06.004)

[3.2] **Shiri, Tinevimbo, Datta, Samik, Madan, Jason, Tsertsvadze, Alexander, Royle, Pamela, Keeling, Matt J., McCarthy, Noel D. and Petrou, Stavros** (2017) *Indirect effects of childhood pneumococcal conjugate vaccination on invasive pneumococcal disease: a systematic review and meta-analysis*. *The Lancet Global Health*, 5 (1). pp. e51-e59. doi:[10.1016/S2214-109X\(16\)30306-0](https://doi.org/10.1016/S2214-109X(16)30306-0)

[3.3] **Datta, Samik, Mercer, Catherine H. and Keeling, Matt J.** (2018) *Capturing sexual contact patterns in modelling the spread of sexually transmitted infections: Evidence using Natsal-3*. *PLOS ONE*, 13 (11). pp. e0206501. doi:[10.1371/journal.pone.0206501](https://doi.org/10.1371/journal.pone.0206501)

[3.4] **Pink, Joshua, Parker, Ben and Petrou, Stavros** (2016) *Cost Effectiveness of HPV Vaccination: A Systematic Review of Modelling Approaches*. *PharmacoEconomics*, 34 (9). pp. 847-861. doi:[10.1007/s40273-016-0407-y](https://doi.org/10.1007/s40273-016-0407-y)

[3.5] **Datta, Samik, Pink, Joshua, Medley, Graham F., Petrou, Stavros, Staniszweska, Sophie, Underwood, Martin, Sonnenberg, Pam and Keeling, Matt J.** (2019) *Assessing the cost-effectiveness of HPV vaccination strategies for adolescent girls and boys in the UK*. *BMC Infectious Diseases*, 19 (1). pp. 552. doi:[10.1186/s12879-019-4108-y](https://doi.org/10.1186/s12879-019-4108-y)

#### Key Grant

[G1] **Keeling, M. J. (PI), Staniszweska, S. (Co-I), Petrou, S. (Co-I), Medley, G. F. (Co-I) and Underwood, M. (Co-I)**, *Infectious Disease Dynamic Modelling in Health Protection*. **Sponsor:** NIHR [[027/0089](https://doi.org/10.1016/0270089)] **Duration:** Nov 2013 - Oct 2019 **Award:** GBP1,420,729

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

Over GBP200,000,000 per year is spent in the UK on vaccines and vaccine delivery, and infectious disease and health economic models are used to assess whether any change in the immunisation programme is cost-effective. The UK Department of Health and Social Care Joint Committee on Vaccination and Immunisation (JCVI) advises UK health departments on immunisation. The JCVI recommends a vaccination policy only if it is considered both safe and cost-effective. HPV is the world's most common sexually transmitted infection and is strongly associated with the development of cervical cancer in women and other health conditions in both sexes including anal, oropharyngeal, mouth, and throat cancers, and genital warts. In 2008 the UK introduced bi-valent

HPV vaccination of girls to safeguard against cervical cancer, changing to a quadra-valent vaccine in 2011 to provide additional protection for genital warts. On the basis of both gender equality and the risk of disease in males, there was considerable social and political pressure to introduce HPV vaccination of boys. Gender-neutral vaccination against HPV was discussed with the committee at a number of JCVI meetings from 2014 onwards.

As a member of the JCVI from 2010, with substantial experience modelling the spread and control of many infectious diseases, and with input from a Patient and Public Involvement (PPI) panel established at Warwick to advise on model assumptions and other details of research, Keeling was uniquely placed to provide expertise and evidence to the dialogue surrounding HPV vaccination. Keeling presented Warwick's modelling on HPV to the JCVI HPV subcommittee in February 2016, January 2017 and May 2018. Commissioned work from the JCVI on HPV was originally intended to form a second opinion to parallel work undertaken by researchers at Public Health England (PHE) [5.1].

The predictions from the University of Warwick were the main quantitative results used to assess the cost-effectiveness; Keeling and co-workers determined that at 1.5% discounting adding boys to the programme would be cost effective if the vaccine could be procured for less than £36-47. From the meeting minutes: "*The subcommittee agreed that it did not need to go further with the PHE model and that it could reach a decision based on the Warwick modelling work, which was robust, and the findings made so far by PHE alongside the meta-analysis of published models by Brisson et al.*" The Warwick model therefore became the primary model used in the HPV vaccination policy decision making process [5.1].

The JCVI Statement on HPV vaccination in July 2018 recommended extending the HPV vaccination programme to include adolescent boys in the UK for the first time. Their recommendation was based on the findings from the Warwick model: "*Using a 1.5% discount rate it is likely that a gender neutral programme would be cost-effective, and on the basis of these findings JCVI would advise extending immunisation to adolescent boys*" [5.2]. The statement contributed to the Republic of Ireland's Health Information and Quality Authority health technology assessment (HTA) on extending their own HPV vaccination to boys in December 2018 [5.3]. In spite of the relatively recent release of the JCVI statement, this is a clear indicator that the analysis is already informing cost-effectiveness modelling and the wider international debate on gender-neutral HPV vaccination.

Concerning this move by the JCVI Shirley Cramer CBE, Chief Executive of Royal Society for Public Health, stated, "*The JCVI's decision to advocate for a gender neutral vaccination programme against HPV is a victory for the public's health. Boys have been left insufficiently protected against HPV for too long and it is good news that the UK is following in the footsteps of the other 20 countries already vaccinating boys against HPV*" [5.4].

Following the JCVI recommendation, from September 2019 Public Health England (PHE) extended the HPV vaccination programme to adolescent boys [5.5], with similar announcements made for Scotland, Wales and Northern Ireland. The extension protects men who have sex with men because they do not benefit from the herd effects of female vaccination. News of the HPV vaccination programme was referenced over 100 times in the media across 6 countries. For UK media outlets covered, a readership of approximately 26,000,000 was estimated from statistics by PAMCo.

Between September 2019 and March 2020, gender-neutral HPV vaccination started in 83% of the 150 local authorities in England, with 5% of these fully completing the programme before school closures due to the COVID-19 pandemic in March 2020 which led to a temporary pause in the campaign [5.6]. The JCVI subsequently re-affirmed the ongoing importance of the campaign when it restarted in June 2020, issuing a statement in July 2020 prioritising "*the first HPV vaccine dose for all eligible children and the catch up of those who missed the first dose*" [5.7]. As a result, the entirety of NHS England and NHS Improvement (NHSEI) commissioned school aged providers

were asked to implement HPV vaccination restoration and recovery plans, with some catch-up having been carried out from all providers [5.6].

Despite these difficult circumstances, the gender-neutral HPV vaccination programme succeeded in covering an impressive 54.4% of year 8 boys in England with the recommended priming dose [5.6]. This represents approximately 170,000 12- to 13-year-old boys based on Department of Education statistics [5.8]. This is in addition to 59.2% of year 8 girls who were also vaccinated (approximately 177,500), and 64.7% of year 9 girls completing a 2-dose HPV schedule (approximately 188,000) [5.6, 5.8]. These values all represent minimum coverage, as data from at least 19 local authorities out of the 66 total NHSEI-provider respondents only captured values up to March 2020 without subsequent data from programme restoration beginning July 2020. A drop in coverage for girls based on 80% coverage in previous years was reasonably concluded to be "mainly due to the impact of the COVID-19 pandemic" [5.6].

The public health benefits of HPV vaccination have been quantified in a recent independent meta-analysis that reviewed 65 studies covering 60,000,000 people after 8 years following initial vaccination for both bi-valent and quadra-valent girls-only vaccination campaigns [5.9]. It was found that cervical intraepithelial neoplasia decreased by 51% and 31% for girls 15-19 and women 20-24 respectively, and for the quadra-valent vaccine genital warts cases decreased 67%, 54% and 48% in girls 15-19, women 20-24 and boys 15-19 respectively. Extending vaccination to include boys will further improve these benefits. The switch to a gender-neutral national policy on vaccination against HPV in the UK is predicted over the next 50 years to lead to the prevention of approximately:

- 5800 cases of oropharyngeal cancer,
- 4000 cases of cervical cancer,
- 2000 cases of anal cancer,
- 1000 cases of penile cancer,
- 25,000 cases of cervical intraepithelial neoplasia, and
- 230,000 cases of genital warts.

This is in addition to the 60,000 cases of cervical and 40,000 other cancers prevented by the previous policy of vaccination of girls only.

Several statements from leading public health figures and politicians help quantify the magnitude of the gender-neutral vaccination programme [5.5]. Head of Immunisation at PHE Dr Mary Ramsay stated, "This universal programme offers us the opportunity to make HPV-related diseases a thing of the past and build on the success of the girls' programme." Public Health Minister Seema Kennedy added, "The success of the HPV vaccine programme for girls is clear and by extending it to boys we will go a step further to help us prevent more cases of HPV-related cancer every year. Through our world-leading vaccination programme, we have already saved millions of lives and prevented countless cases of terrible diseases. Experts predict that we could be on our way toward eliminating cervical cancer for good."

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

[5.1] JCVI HPV Sub-Committee May 2018 meeting minutes agreeing that the Warwick modelling could inform the JCVI decision <https://tinyurl.com/y33n3zb8>

[5.2] Statement on HPV Vaccination which extended the programme to boys (JCVI, July 2018) <https://tinyurl.com/ycvqdqwh>

[5.3] Health technology assessment (HTA) of extending the national immunisation schedule to include HPV vaccination of boys (Health Information and Quality Authority (Republic of Ireland), December 2018) <https://tinyurl.com/y4qlctz7>

## Impact case study (REF3)

- [5.4] *RSPH hails HPV vaccination for boys as a victory for the public's health* (Royal Society for Public Health press release, July 2018) <https://tinyurl.com/y2v4u6n5>
- [5.5] *HPV vaccine could prevent over 100,000 cancers* (PHE press release, July 2019) <https://tinyurl.com/y536tcyd>
- [5.6] *Human papillomavirus (HPV) vaccination coverage in adolescent females and males in England: academic year 2019 to 2020* (Public Health England, October 2020) <https://tinyurl.com/yyouxwa3>
- [5.7] Statement on delivering HPV vaccination during COVID-19 (JCVI, July 2020) <https://tinyurl.com/yylafloe>
- [5.8] England school census data for the 2019-2020 school year (Department of Education) <https://tinyurl.com/yyczdmr7>
- [5.9] Drolet, Mélanie, et al. (2019) *Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis*. *The Lancet*, 394 (10197). pp. 497-509. doi:[10.1016/S0140-6736\(19\)30298-3](https://doi.org/10.1016/S0140-6736(19)30298-3)