Milestones in HPV prevention

Achievements and future potential of the cervical screening and HPV immunisation programmes
As we look back over the past 100 years in public health, it is impossible to ignore the enormous impact of population-wide immunisation programmes. In the space of just a few decades, vaccines have reduced – and in some cases effectively eliminated – the threats posed by diseases such as smallpox, diphtheria, polio and measles.

It was against this impressive record of public health achievement that in 2008 the first NHS National Immunisation Programme against human papillomavirus (HPV) was rolled out to school-age girls, with older girls also targeted as part of a “catch-up” campaign. Alongside the national cervical screening programme, it held the promise of reducing suffering and deaths from cervical cancer among women. Ten years down the line, most women under the age of 25 years have received the vaccine and there is every indication that the programme has been a success. Recent data from both England and Scotland has shown a reduction in infection with HPV16/18 and there has been a consequent drop in referral rates for abnormal smear tests.

This report captures the successes of the first decade of this important programme, but it also identifies the further questions that we must answer if we are to remove HPV infection as a public health threat.

Most importantly, we need to maintain vaccination coverage if the public health benefits of HPV vaccination are to be properly realised in any given population. We know that cervical cancer is not the only public health threat posed by HPV, and we know that teenage girls are not the only group that could benefit from protection against it. Whilst coverage in the UK is among one of the highest in the world, we are not complacent, and we know that high vaccine coverage is essential so that more males as well as females realise the benefits of the programme. The UK has also led the way in piloting a programme for vaccinating men who have sex with men, as this high-risk group may not benefit as much from the girls programme.

While there is no doubt we have come a long way since 2008, there is still more we can do to ensure that all sectors of society benefit from this successful programme. In the next few years, we expect to demonstrate a real decline in cases of cervical cancer, and this will be powerful evidence to further advocate for vaccination.

The elimination of preventable HPV-related disease is an ambitious public health goal. A decade on from the start of the nationwide programme, we need to celebrate and demonstrate our success to the world.

Mary Ramsay
Head of Immunisation at Public Health England
We have come a long way since human papillomavirus (HPV) was identified as a causative agent of cervical cancer in the 1980s. National programmes for cervical screening and HPV vaccination in the UK have achieved high uptake rates. They have resulted in major improvements in public health, and taken us a long way towards the goal of protecting the population against certain HPV infections and the diseases they cause.

Compiled to mark the tenth anniversary year of the HPV vaccination programme and the thirtieth anniversary year of the screening programme, this report focuses on the important milestones in our journey in preventing HPV, celebrates the successes of the national programmes, and recognises the enormous contribution that has been made by health professionals, scientists, administration staff and charities towards the goal of eliminating HPV-related diseases. But there is more that we can do to reach this goal. This report hopes to inspire dialogue on how the current screening and immunisation programmes can be further improved.

HPV is a common and highly-infectious virus, infecting up to 80% of people at some point in their life. About 130 types of HPV have been identified, with more than a dozen types identified as ‘high risk’ because they are associated with the development of some cancers in women and men. Persistent infection of a high-risk HPV type is the single most important risk factor for the development of certain cancers such as cervical cancer.

In 1988, the UK government established a national cervical screening programme, systematically inviting women for screening every few years, and calling them back if they need further investigation. With developments in the way cervical samples are tested, and the incorporation of HPV testing, the current programme saves around 4,500 lives each year in England.
However, to try and achieve the goal of preventing HPV-related cancer, an important step is to prevent HPV infection. In 2008, the UK rolled out an HPV vaccination programme as part of the NHS childhood vaccination programme to girls aged 12-13 years at secondary school. Uptake rates for HPV vaccination have been high, with 83.7% of girls eligible for the programme receiving both recommended doses with the vaccination schedule.

Clear evidence of reductions in high-risk HPV types 16 and 18 have been seen in young women since the introduction of the national HPV vaccination programme in 2008. A study of almost 10,000 sexually active women aged 16-24 years showed that the prevalence of HPV 16/18 infection decreased by two-thirds after the introduction of the HPV vaccination. A more recent study revealed a decline of nearly 40% in the number of women showing early signs of cervical cancer in Scotland following the introduction of the HPV vaccination programme.

But there are still improvements we must make to move closer to the elimination of HPV-related diseases in the UK. In 2016-17, 16.3% of girls in the main UK cohort for the HPV vaccination did not receive it, and in 2016-17 uptake rates of the cervical screening programme fell to 72% from 80.6% in 2004.

This report identifies a number of steps to further protect the population from HPV infections and related disease, including:

- Encouraging women to take part in the cervical screening programme
- Changing the cervical screening programme to primary screening for HPV
- Maximising the benefits of the HPV vaccination programme
- Extending the HPV vaccination programme
- Vaccinating teenage boys
- Vaccinating men who have sex with men

For more information on HPV and HPV prevention please click here.
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Chapter one: Historical milestones

The history of our understanding of human papilloma virus (HPV) has all the elements of a high drama: villains (high-risk HPV strains causing cancer); a quest for a seemingly impossible goal (to prevent cervical cancer and other cancers and diseases caused by HPV); heroes (the researchers and people who took part in studies to further our understanding and the policymakers who put innovations into practice); and, last but not least, sex.

The story starts, somewhat surprisingly, with nuns. In the mid-19th century Dr Domenico Rigoni-Stern found that cervical cancer was relatively common in women living in the Italian city of Verona, with a higher risk in ‘ladies of the night’ and moderate risk in married women, but was quite rare in the nuns living in convents in the surrounding countryside. This epidemiological profile pointed to a sexually transmitted agent as the potential cause.2

Even more surprisingly, rabbits with horns gave the next clue. In the early 20th century, trappers in the US Midwest reported bizarre sightings of rabbits with horn-like growths. When some of these rabbits were caught, scientific tests at the Rockefeller Institute in New York City showed that inoculating healthy rabbits via scarification with some of the ground up horn, resulted in their sprouting horns. Under a microscope these horns turned out to be warts containing virus particles. This was the first discovery of papillomavirus.3

We jump next to the early 1980s, when papillomaviruses were first implicated in cervical cancer. Researchers noticed that tissue changes occurring before the cancer develops (precursor lesions) looked like skin warts under the microscope.4 Skin warts are caused by HPV infection, so could these two very different conditions share a common cause?
Harald zur Hausen, a virologist working in Heidelberg, Germany, started to search for HPV in tumour samples. He drew a blank with the HPV types causing common warts on the hands and verrucae on the feet. So, he went on to biopsy 63 typical warts of ano-genital origin, and discovered HPV 6 or HPV 11 in 86 of the biopsies. The team also found HPV 11 in four out of 24 malignant tumours which led to suggesting a link between HPV 11 or other related HPV types and malignant genital tumours. The team then discovered HPV 16, which they found in more than half of cervical cancers they tested, and HPV-18, which was present in a significant proportion of cervical cancer samples. The link between HPV 16 and HPV 18 and cervical cancer was clear and the importance of this finding led in part to his winning one half of the Nobel Prize in medicine/physiology in 2008. We now know that there around 12 different HPV strains which are cancer-causing (also known as high-risk type).

Within the first two years after isolating HPVs 16 and 18 it became clear that these viruses must play an important role in cervical cancer development. Fortunately, this was soon supported by other researchers who received our clones. I am delighted to see that effective vaccines are available right now, preventing high-risk HPV infections. If both genders, females and males will be vaccinated, I trust that this will have a major impact on the reduction of HPV-linked cancers in the future.

~ Professor Dr Harald zur Hausen, Virologist and Professor Emeritus, Nobel Laureate in Medicine
During the 1990s, Jan Wallboomers and his colleagues, including Julian Peto in the UK, tested a large number of cervical cancer samples from around the world and found that virtually all (99.7%) contained the HPV virus. So, the case was compelling – certain types of HPV infection is therefore the trigger for cervical cancer.

The good news was that work on early detection of high-grade cervical disease was already underway. In the 1940s, Georgios Papanicolaou found that early changes in cervical cells that occur in the development of cervical cancer (later identified as being caused by HPV infection) could be seen under a microscope in a sample of cells collected from the cervix smeared onto a glass slide.

Doctors in the UK began offering a simple test, known as the ‘cervical smear test’ (‘Pap test’ in the US), to women in the 1960s. Smear tests were initially offered on an opportunistic basis, but the government soon realised the need to screen all women at risk, to screen them regularly enough to pick up early cell changes before they progressed to cancer, and to have a system for calling women back for further tests and treatment if their smear was abnormal.

In 1988, the UK government established a national cervical screening programme, systematically inviting women for screening every few years (three-yearly for women aged 25-49 and five-yearly for those aged 50-64 in the latest scheme) and calling them back if they needed further investigation. The test shows abnormal changes in cervical cells in around one in every 20 women tested, most reverting to normal but those that do not are removed to prevent progression to cancer.
More recently, scientists have shown that testing cervical cells for the HPV virus can more accurately identify women at risk for developing cervical cancer than simply examining cells under a microscope.\textsuperscript{14}

The NHS cervical screening programme has already incorporated testing for high grade HPV into its testing programme. Cervical samples are examined and those with abnormal cells are tested for HPV. In July 2016, the screening programme in England started to roll out changes to the way it looked for precancerous lesions. Rather than looking for cervical cell changes in samples first and then for HPV, it began testing for HPV first, after finding this worked well in pilot studies.\textsuperscript{15} Cervical screening currently saves around 4,500 lives each year in England, with cost savings estimated to be £36,000 per life saved and £18,000 per cancer prevented.\textsuperscript{15,12}

HPV testing will ensure women at risk for cervical cancer are spotted and treated earlier, potentially preventing a further 600 cancers a year.\textsuperscript{15} In this new approach, only cervical screening samples which test positive for HPV in a viral DNA test are then examined to check for cell changes. These women can then be followed up further or receive treatment as necessary.

To try to achieve the ultimate goal of preventing HPV-related cancer, an important step is to prevent HPV infection. After Harald zur Hausen first identified the links between HPV and cervical cancer in the 1980s, he helped identify a need for a vaccine, and his pioneering work provided other researchers with the tools to do this.\textsuperscript{8}

In the 1990s, researchers Ian Frazer and Jian Zhou, working at the University of Cambridge, UK, and then at the University of Queensland, Australia, as well as other scientists, discovered an infectious virus-like particle that could trigger an immune response against HPV.\textsuperscript{17} This immune response was based on the ability of a papillomavirus protein (L1 protein) to self-assemble into virus-like particles that can elicit neutralising antibodies against HPV in mice.\textsuperscript{18}

Cost per patient for treating HPV-related cancers\textsuperscript{16}

- Cervical cancer: £15,000
- Vulvar and vaginal cancers: £13,650
- Anal cancer: £13,050
Companies then developed HPV vaccines commercially and ran clinical trials that showed they were effective in helping to prevent HPV infection and cervical disease related to the HPV types contained within the vaccines.\textsuperscript{19,20}

In 2008, the UK rolled out an HPV vaccination programme as part of the NHS childhood vaccination programme to girls aged 12-13 years at secondary school.\textsuperscript{21} Because the HPV types contained in the vaccines are sexually transmitted, the aim is to vaccinate girls before they become sexually active and so help to prevent HPV infection, thereby helping to protect them from developing diseases, such as cervical cancer, that are triggered by persistent infection with high-risk HPV types. The HPV vaccination programme is part of a prevention strategy which encompasses educational campaigns in schools, and the advocating of safer sex.

\textbf{The NHS cervical screening programme has made a dramatic impact on the incidence and mortality from cervical cancer over the past 30 years. Indeed the UK has been a world leader in the implementation and governance of an efficient, population based primary care screening programme with integrated colposcopy services.}

\textit{However, prevention of the disease process is clearly better than identification and treatment of premalignant disease, and the excellent uptake of the HPV vaccination programme in the UK promises to have a dramatic reduction in the number of women who require treatment for high grade cervical intra-epithelial neoplasia (CIN).}

\textit{~ Dr Andy Nordin, Gynaecologist / Gynaecological Oncologist President, British Gynaecological Cancer Society (BGCS) Clinical Advisor, National Cancer Registration & Analysis Service (NCRAS)}
National programmes for cervical screening and HPV vaccination in the UK have achieved major improvements in public health since their introduction, representing an enormous contribution from health professionals, scientists and administration staff running the programmes and the women and teenagers taking part.

Chapter two: How cervical screening and the HPV vaccination programme have contributed to UK public health

Screening programmes

Cervical screening
The UK government first established a national cervical screening programme in 1988. The programme systematically invites women for screening every few years - three-yearly for women aged 25-49 and five-yearly for those aged 50-64 years - and calls them back if they need further investigation or treatment.\textsuperscript{12,13} The cervical screening programme aims to detect and refer for treatment, women with any abnormalities and pre-invasive cervical disease that may otherwise progress to cervical cancer.

Over the 30 years since the cervical screening programme was first introduced, the incidence of cervical cancer in England has nearly halved.
In 1988, the year the screening programme was introduced, 4,132 women were diagnosed with cervical cancer (incidence of 16.2 per 100,000 women). Twenty years later, in 2008, 2,369 women were diagnosed with cervical cancer (incidence of 8.3 per 100,000 women, after adjusting for the age of the population). Since then, the incidence has stabilised, with around 2,500 newly diagnosed cases of cervical cancer in England in 2015 (incidence of 9 cases per 100,000 women). The death rate due to cervical cancer across the UK has decreased from around 10.5 deaths per 100,000 women in 1971, to 2.8 deaths per 100,000 women in 2014.

The cervical screening programme has achieved good population coverage. In England in 2004, 80.6% of eligible women (aged 25-64) had been screened at least once in the previous five years. But coverage rates over each of the last ten years have not improved beyond this, and fell to 72% in 2016-17. The one exception was in 2009, where there was a slight increase in uptake that was associated with media attention around the diagnosis and subsequent death of a media personality. These changes in coverage rates have been similar for Scotland, Wales and Northern Ireland over the last ten years. Figures for screening warn that coverage is lower for women aged 25 to 29 years than for other age groups (62.0% in women aged 25-29 years in 2013, compared to 77.8% overall for women aged 25-65 years).

To see cervical screening coverage falling so consistently across the UK is a real concern. The barriers to non-attendance are wide ranging and a concerted effort to understand and tackle the barriers that exist for each group of women is the only way we will see attendance increase. This includes physical, psychological and gaps in awareness and understanding. Our cervical screening programme is an excellent programme providing women with the best protection against cervical cancer therefore to see fewer women taking up their invitation must serve as a call to action to increasing attendance.

~ Robert Music, Chief Executive of Jo’s Cervical Cancer Trust
Groups less likely to attend for cervical screening in the UK include young women (25-29), women from ethnic minorities and those in low socioeconomic groups. In addition, the rate of screening also falls in women after the age of 50 years. The reasons behind this include inconvenience, a fear of cancer diagnosis, apathy and anxiety over the screening procedure. Despite the evidence of the benefits of cervical screening, a survey by Jo’s Cervical Cancer Trust found that 25% of women were put off screening because of embarrassment, while 35% said they would attend if GP appointments could be more flexible.

Cervical screening and testing for HPV
Because almost all cervical cancer is caused by persistent HPV infection, HPV testing has been incorporated into the NHS cervical screening programme in England. Cervical cytology samples which show abnormal cells are tested for HPV. Those women whose samples show abnormal cells and which are HPV positive are invited back for further screening and or treatment. From June 2016, the programme was changed to test samples for HPV first, and then to look for cell abnormalities only in those samples which are HPV positive. This follows on from a successful pilot study. Full roll out of the programme across the UK is expected by the end of 2019. Public Health England has noted that early detection of HPV and treatment can prevent 75% of cervical cancers.

The earlier treatment of cervical cancer resulting from the screening programme currently saves around 4,500 lives each year in England. HPV testing will help ensure women at risk for cervical cancer are spotted and treated earlier, potentially preventing a further 600 cancers a year.
Screening for other HPV-related cancers

There are currently no systematic screening programmes for other cancers that can be associated with HPV, including vaginal and vulval cancers in women, and anal cancers in both women and men, underlining the need for other approaches for reducing these diseases.

HPV vaccination programme

In 2008, the UK rolled out an HPV vaccination programme as part of the NHS childhood vaccination programme to girls aged 12-13 years at secondary school.\textsuperscript{32} A catch-up campaign for girls up to 18 years ran over the subsequent three years to extend the age range vaccinated against HPV.\textsuperscript{28} The current vaccination programme recommends routine vaccination of girls aged 11-13 years.\textsuperscript{33}

Uptake rates for HPV vaccination within the programme in the UK have been high, with 83.7\% of girls in the main cohort\textsuperscript{1} in 2016-17 receiving both recommended doses within the vaccination schedule.\textsuperscript{34} There are a number of factors which may explain the remaining 16.3\% of girls who were eligible for vaccination but did not receive it, including religion and culture, geography, level of school attendance and socioeconomic status.\textsuperscript{35} School-led vaccination programmes are associated with higher uptake rates than those offered in other settings. Uptake in Cornwall, which had historically offered its vaccination programme through GP surgeries, has been lower than in other regions and the vaccination programme has now been moved into a school setting to tackle this.\textsuperscript{36}

HPV vaccination programmes have proved highly successful in reducing HPV infections. A systematic review and meta-analysis of findings from nine countries with HPV vaccination programmes including more than 140 million person-years of follow-up showed that programmes with vaccine uptake of at least 50\% of adolescent girls led to significant falls in the prevalence of HPV type 16 and 18 infections in girls aged 13-19 years.\textsuperscript{36} A recent study in Scotland has shown a 90 per cent fall in levels of HPV in Scottish women since the vaccine was made available in 2008.\textsuperscript{37}

“School nurses have been - and will continue to be - pivotal to the delivery of a world-leading HPV immunisation programme. Our nurses are proud to play a key role in preventing HPV-related cancers in girls and women, and hopefully boys to follow soon, and protecting their health and fertility. As trusted, expert public health professionals, school nurses help young people and families make informed and positive decisions regarding the HPV vaccination.”

~ Sharon White OBE, RGN, SCM, SCPHN, CEO School and Public Health Nurses Association
Clear evidence of reductions in high-risk HPV types 16 and 18 have been seen in young women in England since the introduction of the national HPV vaccination programme in 2008.\textsuperscript{38} A recent study of almost 10,000 young sexually active women aged 16-24 years attending for chlamydia screening in England showed that the prevalence of HPV 16/18 infection decreased by two-thirds after the introduction of HPV vaccination, from 17.6% in 2008, when the vaccination programme was introduced, to 6.1% in 2012-13.\textsuperscript{38} Furthermore, a study carried out by the University of Aberdeen revealed a decline in the number of women showing early signs of cervical cancer in Scotland following the introduction of the HPV vaccination programme. Before the vaccine was offered, 1,294 women were referred for an abnormal smear in 2008/09, compared to 758 in 2013-14, a reduction of 41%.\textsuperscript{39} In school year 2016/17, HPV vaccination uptake rates in Scotland surpassed 80%, but although uptake was high, rates were lower in the most deprived areas.\textsuperscript{40}

The UK’s national cervical screening and HPV vaccination programmes are both long-term strategies to improve public health. Any impact on cervical cancer will not be seen for some time because of the time lag between infection and development of cancer, and will depend on a number of factors, including continued high uptake of and compliance with the vaccination programme to ensure herd immunity. A recent 2017 study, however, has modelled that if screening coverage fell to 50%, European age-standardised rates (EASR) of cervical cancer in England could increase by 27%.\textsuperscript{41}
What is HPV?

HPV is a common and highly-infectious virus infecting up to 80% of people at some point in their life. About 130 types of HPV have currently been identified, of which about 40 can infect the anogenital tract. There are about 12 types of HPV that have been identified as ‘high risk’ because they are associated with the development of some cancers in women and men. In most cases HPV infections are transient and resolve without treatment. However in some individuals the infection persists and may result in clinical disease such as precancerous cervical, vaginal, vulval and anal lesions, and cervical and anal cancers.

It is this persistent infection of a high-risk HPV type that is the single most important risk factor for the development of HPV-related cancer.

HPV is the most common viral sexually transmitted infection

HPV infection has a huge impact on human health and wellbeing. It is the most common viral sexually transmitted infection worldwide. The global prevalence of HPV infection is around 11-12%, based on testing women with no signs of cervical cancer. In Europe and North America, HPV prevalence is highest (over 20%) in women younger than 25, but continually decreases in women from the age of 25.
Cervical cancer

Cervical cancer is the fourth most common cancer in women worldwide and the second most common cancer in young women aged 15-44 years of age, and includes 84% of all HPV-related cancers. In 2012, just over half a million women were diagnosed with cervical cancer and more than 250,000 women die from the disease each year worldwide, accounting for 8% of all cancer deaths in women, according to latest estimates.

In the UK, cervical cancer is the 20th most common cancer, with around 3,200 new cases diagnosed in 2014. This equates to around nine cases every day.

All cervical precancerous lesions are HPV-related, with between 267,350 and 510,609 estimated new cases of high-grade precancerous lesions occurring annually in women in Europe.

**Estimated mean annual number of new HPV-related cancer cases in women and men in Europe**

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Number of new cancers attributable to HPV (95% bound)</th>
</tr>
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<tbody>
<tr>
<td>Cervix</td>
<td>34,708 (32,640 – 36,793)</td>
</tr>
<tr>
<td>Vulva</td>
<td>1,842 (1,377 – 2,381)</td>
</tr>
<tr>
<td>Anus</td>
<td>3,996 (3,151 – 4,855)</td>
</tr>
<tr>
<td>Vagina</td>
<td>1,544 (1,046 – 2,107)</td>
</tr>
<tr>
<td>Total</td>
<td>42,090</td>
</tr>
</tbody>
</table>
Cancer of the vulva
Cancer of the vulva (the external part of the vagina) is a rare cancer, but there are an estimated annual number of 9,544 new cases in Europe. Approximately 60% of cases of vulval cancer occur in more developed countries of the world.53

Vaginal cancer
Cancer of the vagina is rarer than vulval cancer, with an estimated 2,171 new cases each year in Europe. Most vaginal cancers are squamous cell carcinomas, of which 90% of cases are attributable to HPV.53

Anal cancer
Anal cancer occurs at a rate of one in every 100,000 people but is increasing in developed countries. An estimated 4,562 people are diagnosed with anal cancer each year throughout Europe. Women have a higher incidence of anal cancer than men, but this type of cancer is more common in men who have sex with men, women who have had cervical or vulval cancer and people who are immunosuppressed, including those with HIV.53

Reducing the impact of HPV infection: cervical screening and HPV vaccination programmes across the world
Because genital HPV is almost exclusively transmitted sexually it is not greatly affected by improvements in medical treatments or living standards, unlike other important cancer-causing infections such as Helicobacter pylori (which causes stomach cancer) and hepatitis B and C viruses (causing liver cancer). This means that the key solutions to reducing HPV-associated diseases are safer sex, cervical screening and HPV vaccination programmes.46

Map of age-standardised incidence rates of cervical cancer in the world (estimates for 2012)54
Milestones in HPV prevention

Cervical screening programmes

Cervical screening programmes have been very effective in preventing cervical cancer and have been credited for achieving the large reductions in cervical cancer deaths seen in many developed countries since the 1960s.\textsuperscript{51,54} Cervical screening strategies differ between different countries. Some countries, such as the UK, have population-based programmes, where women in the target population are invited to attend for screening at regular intervals.

The most frequently used cervical screening method is cytology, taking a sample of cervical cells and looking for abnormal, precancerous cell changes under the microscope.\textsuperscript{53} Recently, several countries including the UK, have introduced screening programmes based on testing cervical cells for HPV and then examining samples testing positive for abnormal cell changes.

Some low- and middle-income countries use a simple screening strategy based on visually inspecting the cervix after applying a staining solution of acetic acid or Lugol’s iodine, which highlight precancerous lesions that can then be treated with cryotherapy. However, effective coverage rates for cervical cancer screening are very low in many developing countries. A study in 2008 found that coverage of cervical screening in developing countries was 19%, on average, compared with 63% in developed countries, and it ranged from 1% in Bangladesh to 73% in Brazil.\textsuperscript{55} Several parts of the world, including countries in Africa and Eastern Europe, still have no public national cervical screening programmes.\textsuperscript{53}

HPV vaccination programmes

HPV vaccines offer a highly effective method for primary prevention of cervical cancer and other vaccine-type HPV-associated diseases. The World Health Organization recommended in 2007 that HPV vaccination of 9-13 year-old girls should be considered as part of comprehensive cervical cancer control through effective, affordable and equitable delivery strategies.\textsuperscript{56} A recent study in 2017 has projected that the modelled impact of HPV vaccination could see cervical cancer rates in women aged 25-29 decrease by 55% in England by 2036-40.\textsuperscript{41}

Coverage of HPV vaccination 2015 –16

Compared to England average rate:
- Better
- Same
- Worse

The herd (community) immunity threshold for HPV coverage is 85%
Many countries globally have since implemented publicly funded HPV vaccination programmes, to help provide protection against certain high-risk types of HPV.

By March 2017, HPV vaccination had been introduced into national immunisation programmes for girls in 71 countries around the world (37% of countries globally), and also for boys in 11 countries.51 Australia, the UK, the USA and Canada were among the first countries to introduce HPV vaccination programmes.

All country programmes target young adolescent girls but differ in specific target age groups and catch-up recommendations.59 Some countries, such as the UK, deliver HPV vaccination in schools, whereas others deliver through health centres or primary care providers.60 In general, countries with school-based delivery and publicly financed vaccination programmes have achieved higher coverage of the target population than those with opportunistic, clinic-based or primary care-based programmes.47

Some countries have also begun to target certain other high-risk groups, for instance in the UK in November 2015, it was recommended that certain men who have sex with men (MSM), who may otherwise have been outside of the protection offered from the HPV immunisation programme, should receive the HPV vaccination.61 A pilot vaccination programme for this began in June 2016 at certain GUM and HIV clinics in England and all clinics in the rest of the UK.

According to Public Health England statistics, in 2014-15, in England, HPV immunisation coverage was generally above 86%, and more than 40% of primary care trusts (PCTs) achieved at least 90% coverage.62 For comparison, in France, by the end of 2013, vaccination coverage of three doses reached 20% of 16-year-old women.63

It should be noted, however, that Public Health England’s regional-level data demonstrate a significant regional variation of coverage in England. The HPV coverage data by local authority for England from September 2016 to August 2017 for cohort 13 (born 2002-3) show a 1st dose vaccine coverage rate ranging from 68.4-99.3%, and a 2nd dose vaccine coverage rate range from 48.3-95.3%, indicating that in some local authorities, up to 31.6% of girls remain unvaccinated and up to 51.7% have not received a full course and cannot be assumed to be fully protected.34

...in some local authorities in the UK, up to 29% of girls remain unvaccinated and up to 55% have not received a full course and cannot be assumed to be fully protected.
Very few low- or middle-income countries introduced HPV vaccination programmes in the first few years of its availability. However, Bhutan and Rwanda started national immunisation after receiving vaccine supply through donation programmes in 2010 and 2011, respectively. The Global Alliance for Vaccines and Immunization (GAVI) decided in 2011 to support HPV vaccination, so this should increase implementation in low-income countries.61

**Real world safety profile of HPV vaccines**

In 2016, 47 million women across the world received the full course of HPV vaccine, and 59 million women received at least one dose.64

The World Health Organization (WHO) Global Advisory Committee for Vaccine Safety regularly reviews the evidence on the efficacy and safety of HPV vaccination programmes.65 Further, results from routine nation-specific surveillance of HPV vaccination programmes have continued to support the safety and value of HPV vaccination in preventing HPV-related diseases.

Recent vaccine safety issues reported in the media such as the occurrence of Complex Regional Pain Syndrome (CRPS), Postural Orthostatic Tachycardia Syndrome (POTS) and chronic fatigue occurring in individuals following HPV vaccination have proved unfounded. In November 2015, the European Medicines Agency (EMA) reviewed the HPV vaccine and found no evidence that it was linked to these conditions.66 In January 2016, the European Commission endorsed the conclusion of the EMA.67 Similarly, the World Health Organization (WHO) also brought out a position paper in May 2017 on the Human Papillomavirus that echoes these conclusions.68

The national cervical screening programme is credited with saving around 4,500 lives each year in England. 47% of the women who develop cervical cancer in the UK have not been screened in the previous five years or never attended screening.
Chapter four: Steps to further protect the population from HPV infections and related disease

We’ve come a long way since the first observation of the link between cervical cancer and sexual activity in the 1850s and the identification of HPV as the causative agent in the 1980s. Understanding that precancerous changes can be seen in cervical cells years before the cancer develops led to the highly effective national cervical screening programme in the UK, which first started in 1988. And teasing out how to make vaccines that help protect against certain HPV infections and rolling out HPV vaccination to teenage girls as part of the NHS childhood vaccination programme from 2008, has taken us a long way towards the goal of protecting the population against certain HPV infections and some of the diseases they cause.

But there is more we can do to reach that goal.

Encouraging women to take part in the cervical screening programme and changing to primary screening for HPV

The national cervical screening programme has been very effective in reducing the number of women developing cervical cancer and is credited with saving around 4,500 lives each year in England.69

But the number of women taking part in the screening programme has fallen over the last few years. After peaking at around 82% in the late 1990s, rates in England have decreased to around 78%, with similar rates in Scotland, Wales and Northern Ireland.70 Young women aged 25-29 have the lowest screening rates; in 2014 only 63.3% of this age group had been screened in the previous three and a half years.71

This drop-off in cervical screening matters. Nearly half (47%) of the women who develop cervical cancer in the UK have not been screened in the previous five years or never attended screening.71 So we need renewed efforts to reach out to these women and encourage them to benefit from cervical screening.
The good news is that we already know the groups of women least likely to attend the cervical screening programme: young women (25-29), women from ethnic minorities and those from low socioeconomic groups.\textsuperscript{71,72} And we also know some of the reasons that lead women to not take part in screening: fear about the screening procedure, lack of understanding about the purpose of screening, underestimating the risk of developing cervical cancer and problems attending screening appointments.\textsuperscript{71,73}

An innovative research study conducted in England and Scotland, the STRATEGIC trial, explored ways to boost cervical screening in young women.\textsuperscript{73} Findings suggested that timed appointments, and sending out self-sampling kits to non-attenders at six months are likely to be a cost-effective means of increasing uptake and should be considered further. Additionally, HPV vaccination was associated with an increased uptake of cervical screening;\textsuperscript{73} this is important as the HPV vaccine does not protect against all cancer-causing HPV types. It also provides an opportunity for healthcare professionals to encourage women to get their daughters vaccinated.

The importance of boosting screening coverage among women aged over 29 remains. Women born before 1991 are less likely to have received the HPV vaccination and are, therefore, at greater risk for cervical cancer. A recent study suggests for this reason that with current screening coverage, EASR of cervical cancer at ages 25–79 years will decrease by only 10% in England by 2036-40, and that the peak age of cancer diagnosis will shift from the ages of 25–29 years in 2011–15 to 55–59 years in 2036-40.\textsuperscript{41}

The recent change in NHS cervical screening programme in England, from cervical cytology to testing cervical cells for HPV as primary screening, will also help to further reduce cervical cancer. Studies have shown that HPV testing as an initial screen is significantly more effective as an early warning system against developing cervical cancer than cervical cytology.\textsuperscript{74} Government figures suggest that primary HPV screening will potentially prevent a further 600 cases of cervical cancer each year in addition to the 4,500 lives already saved by the cervical screening programme.\textsuperscript{69}
Maximising the benefits of the HPV vaccination programme

Although uptake rates for HPV vaccination are indicated to be over 83% of girls in the main cohort, according to Public Health England’s data, their regional data (which is broken down to local authority level) suggest a significant regional variation in England. These variations are especially concerning since at present only girls are vaccinated as part of the National Immunisation Programme and the resultant herd immunity is relied on by males as well.

Perceived safety concerns have led to reductions in HPV vaccination rates in some countries, such as Ireland and Denmark, despite health authorities providing reassurance that clinical experience with these vaccines does not identify any safety concerns. Independent health organisations, including the World Health Organization, the Centres for Disease Control and Public Health England closely monitor the safety of HPV vaccines, as they do other vaccines, and continue to recommend the vaccination programmes based on real-world use in millions of people.

Research shows that an eventual reduction of 63% in invasive cancer among women aged 25-29 can be expected by 2025 in the UK, but only if we maintain an uptake rate of 80% in girls aged 12-13 years of age.
**Extending the HPV vaccination programme**

The benefits of the HPV vaccination programme could be increased by extending the programme from teenage girls to include boys. The reductions in cervical cancer achieved by the screening programme means that the burden of HPV-associated disease in men is now comparable to that in women in developed countries such as the UK. High-risk HPV types, particularly types 16 and 18 included in current HPV vaccines, are associated with anal cancer. There is no routine anal cancer screening programme in the UK, so offering HPV vaccination to teenage boys would potentially help to further reduce the incidence of HPV-related disease.

With the substantial burden of HPV-disease in men, several countries, including the USA, Canada and Australia are now recommending that HPV vaccination programmes are gender neutral. This places the UK behind other countries, but with a real opportunity to press for elimination of the types of HPV contained within the vaccine.

**Vaccinating teenage boys**

The Joint Committee on Vaccination and Immunisation has been considering whether to offer HPV vaccination to all teenage boys. After analysing the results of impact and cost effectiveness modelling developed by Public Health England in 2014, and updated in June 2017 (based on an original impact and cost effectiveness model developed in 2008) on protecting adolescent boys against HPV infection by vaccination, the committee advised in their statement that it was not yet in a position to finalise its recommendation on boys’ vaccination, and would await confirmation on the accuracy of the latest findings.

**Recommendations for gender-neutral HPV vaccination programmes across Europe**

<table>
<thead>
<tr>
<th>Country</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Austria</td>
<td>Universal HPV vaccination was introduced in 2014</td>
</tr>
<tr>
<td>Croatia</td>
<td>National recommendation and funding for boys to be vaccinated</td>
</tr>
<tr>
<td>France</td>
<td>HPV vaccination for men who have sex with men (MSM) since 2016</td>
</tr>
<tr>
<td>Greece</td>
<td>HPV vaccination for MSM is recommended</td>
</tr>
<tr>
<td>Ireland</td>
<td>Universal vaccination can be provided privately and outside of national programmes, and an MSM* programme was introduced in 2016</td>
</tr>
<tr>
<td>Italy</td>
<td>Universal HPV vaccination is recommended at a national level since 2016</td>
</tr>
<tr>
<td>Norway</td>
<td>Universal HPV vaccination is recommended since 2016</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Universal HPV vaccination was introduced in 2016</td>
</tr>
<tr>
<td>UK</td>
<td>No country-wide universal HPV vaccination programme. Pilot HPV vaccination programme for MSM up to age 45 and at-risk transgender men and women, sex workers and HIV-positive men and women</td>
</tr>
<tr>
<td></td>
<td>MSM and high-risk groups HPV programme rolled out in Scotland, Wales and Northern Ireland in 2017</td>
</tr>
<tr>
<td>Germany</td>
<td>Permissive recommendation was issued locally in Saxony in 2013 and vaccination is offered to males through voluntary funding by some sickness funds</td>
</tr>
</tbody>
</table>
Several countries, including Australia, have already extended national HPV vaccination programmes to include teenage boys. Modelling studies, based on the Australian programme, predict that including teenage boys in HPV vaccination will reduce the rates of HPV type 16 infection by an additional 24% by 2050 compared with vaccinating only girls, if vaccination rates for teenage boys reach and maintain the high levels achieved for teenage girls in Australia (73% coverage rate).\(^8^4\) This would help to further reduce the burden of HPV-related disease.

Vaccinating men who have sex with men

Men who have sex with men (MSM) have a higher risk of anal cancer (one of the cancers that can be associated with HPV infection) than men who do not. So, in 2015 the Joint Committee on Vaccination and Immunisation, which advises the UK Department of Health on vaccination programmes, recommended that HPV vaccination should be offered to men who have sex with men who attend sexual health and HIV clinics subject to delivery of the programme at a cost-effective price.\(^8^6\)

A pilot study is now underway in England to see how this programme could be delivered most effectively, while Scotland, Wales and Northern Ireland have committed to offering HPV vaccination to MSM in all sexual health and HIV clinics.\(^8^7\) The HPV-MSM immunisation pilot study in England will offer HPV vaccination opportunistically to eligible MSM attending certain clinics.\(^8^8\)

For more information on HPV and HPV prevention please click here.

Over the past 30 years, the national cervical screening programme has had a major impact on the public’s health, with thousands of lives saved every year across the UK. The HPV national immunisation programme is the next chapter in this public health success story, with the majority of girls receiving all the recommended doses of the vaccine and clear evidence already of reductions in high-risk HPV strains.

Looking to the future, maintaining and improving the high level of coverage of the HPV vaccine in all regions of the UK is vital in achieving the expected reduction in cancer rates. It is also imperative that the immunisation programme is extended to boys as well as girls, to ensure complete and equitable protection, with no weak links, for the entire population.

~ Shirley Cramer CBE, Chief Executive, Royal Society for Public Health
Cervical cancer in women is a cancer with two special characteristics

- It is caused by a virus – the human papillomavirus (HPV) – for which there are highly effective vaccines that prevent infection with 90% of the cancer-causing HPV types

- The changes in the cervix cells that precede the appearance of the life-threatening cancer can be detected in cervical smears – scrapes taken from the surface of the cervix. These changed areas or precancers can then be cut out with simple day surgery and the development of the cancer prevented

The combination of a vaccination programme preventing infection and an established cervical cancer screening programme detecting precancers make cervical cancer a largely preventable disease in the UK in the medium to long term. The UK HPV vaccine programme which started in 2008 is a stunning success with ≥85% of girls in school year 9 immunised annually.\(^{100}\)

In Scotland in 2017 big declines (up to 90%) in the precancers were reported in young women immunised in their early teens and arriving for their first smear at age 20.\(^{101}\) Since around 850 cervix cancers occur in women aged 25-34 years each year in the UK, this is hugely encouraging raising the real possibility that cervix cancer in this age group will plummet in the coming decade as vaccinated girls grow up and enter the screening programme.\(^{102}\) To date the vaccines used have only targeted HPV 16 and HPV 18; the two major cancer causing types which cause 70-80% of cervix cancers. But future vaccines target additional HPV cancer types and are likely to raise that to >90%.

Cervical cancer screening is also a success story in the UK with the overall uptake consistently at 75%.\(^{103}\) The programme, which has been in place since 1988 has, it is estimated, prevented many thousands of cancers and cancer deaths. Even in the era of vaccination, screening has to continue since not all cancer-causing HPV types are targeted by the vaccines, and not all women are vaccinated or were vaccinated before being infected. But things will change in the era of vaccination. Screening methods will change – detecting HPV infection first before further testing, women may take the sample for screening themselves as self-sampling kits

HPV-caused cancers – preventable diseases in the 21st Century?

Margaret Stanley OBE, Emeritus Professor of Epithelial Biology
So, can we make cervical cancer and other HPV associated cancers largely diseases of the past? Yes is the answer, we have the tools and we have the will.

bcome available and the number of times a woman will need to be screened will be much less – perhaps 3 times only in her lifetime.

HPV associated cancers do not only occur in women – cancer of the anus and the throat, most of which are HPV associated, occur in both men and women and the HPV cancer burden in men in the UK is comparable to that in women.\textsuperscript{104} It is either not practical or possible to screen for precancers in these other sites and vaccination is the only prevention strategy. Men who have sex with men are particularly vulnerable to anal cancer, but in contrast to men who have sex with women, they receive no protection from female only vaccination. Countries such as Australia and the USA immunise boys as well as girls to prevent cancer in men irrespective of their sexual preferences and to give additional protection to women – after all it takes two to tango. In the long term if HPV vaccines are to achieve their full potential of reducing circulating virus in the population to virtually zero, both males and females will have to be vaccinated.

The HPV vaccine programme and the screening programmes are successful but it is important not to be complacent. Anti-vaccine groups may spread false news frightening women and their daughters, and vaccine uptake can fall dramatically leaving young women unprotected. False news needs to be shown to be exactly that and vigorously repudiated.

Vaccinated women may think they don’t need screening, young women dislike the process of smear taking, and visiting clinics or GP practices may seem to be too much of a hassle. The good news about the success of vaccination and screening needs to be constantly broadcasted.

So, can we make cervical cancer and other HPV associated cancers largely diseases of the past? Yes is the answer, we have the tools and we have the will.
References


17. K.S. Kim et al., ‘Current status of human papillo- 


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