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Human Papillomavirus (HPV) Vaccination

Should we be vaccinating boys too? Impact for Northern Ireland.

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INTRODUCTION

Prevention of human papillomavirus (HPV)-related cancers is an increasingly prominent public health issue. HPV is widely known for causing cervical cancer, but what is less well known is that it also causes cancer in males. The current UK strategy of vaccinating girls alone does not provide males with adequate protection against HPV infection and HPV-related diseases, particularly men-who-have-sex-with-men (MSM). In response to this, in November 2015, the Joint Committee on Vaccination and Immunisation (JCVI) published a statement on HPV vaccination of MSM. This statement recommended that the vaccination programme be extended to MSM aged up to 45 years via a genitourinary (GUM) or Human Immunodeficiency Virus (HIV) clinic, or opportunistic vaccination via a GP. There are doubts that HPV vaccinations can be effectively targeted to MSM pre-exposure, and it has been argued that the only feasible way to protect MSM is by vaccinating all adolescent boys. The JCVI are currently considering the merit of extending the vaccine to all adolescent males. There are a number of countries that currently recommend and provide universal, gender-neutral HPV vaccination.

In order to inform the current HPV vaccine policy discussion around universal vaccination and providing adequate protection against HPV-related cancers for males, we will present our work on knowledge and attitudes to HPV and HPV vaccination in MSM and parents of adolescent boys. We will also present data on the cost-effectiveness of including males in HPV vaccination programmes.

BACKGROUND

HUMAN PAPILOMAVIRUS

HPV is one of the most common sexually transmitted infections worldwide, so predominant and so easily acquired that nearly all sexually active men and women will be exposed to the virus at some point in their lives. The rate of genital HPV infection is similar in males and females; however males have a lower immune response

to natural HPV infection than their female counterparts (Guiliano et al., 2011), meaning that there is not the same association between age and HPV prevalence in men as there is in women. In women, HPV prevalence peaks between 18–24 years and subsequently declines (Burchell et al., 2006). In contrast, in men, there is a consistently higher prevalence of HPV (Anic and Guiliano, 2011).

There are many different types of HPV, and varying degrees of risk associated with persistent infection with each type. Many HPV infections are short-lived and clinically insignificant, but continual infection with certain types of HPV causes a considerable burden of disease in both sexes. In women, cervical cancer has been linked to HPV, with only a small fraction of cervical cancers being HPV-negative (The Cancer Genome Atlas Research Network, 2017). HPV has also been linked to other cancers and non-cancerous conditions in both men and women, for example genital warts, oropharyngeal cancer (OPC), anal cancer or penile cancer. Estimated incidence of HPV-related cancers for 2008 has been calculated globally; of the estimated 12.7 million cancers, 610,000 could be attributed to HPV infection (Forman et al., 2012). According to Stanley (2012), in Europe around 23,250 cases of cervical cancer each year plus vaginal and vulval cancer (3,850 cases), several head and neck (15,230 cases) as well as anal cancers (4,630 cases) in both sexes and penile cancer (1,090 cases) can be attributed to HPV (Stanley, 2012). Successful HPV vaccination in females in combination with adequate screening programmes has resulted in remarkable progress in the reduction and prevention of cervical cancer; less progress has been made with other HPV-related cancers affecting both sexes.

Oropharyngeal cancer

The incidence of OPC is rising in the UK (Prue et al., 2016). In fact, the fastest growing cancer among all cancers in Scotland has been reported to be OPC, especially among men (Junor et al., 2010). Local estimates suggest that the incidence of OPC in Northern Ireland rose from 15 in 2000 to 40 in 2011 (M Moran, personal communication). Researchers have reported that men are twice as likely to develop HPV-OPC as women (D'Souza et al., 2016); in Canada in 2012 the incidence rate of HPV-OPC was more than 4.5 times higher in males than females (Canadian Cancer Statistics, 2016). In the USA, it is predicted that the number of HPV-related OPCs diagnosed per year will soon surpass the annual number of cervical cancer cases (Chaturvedi et al., 2011).

Anal cancer

Anal cancer incidence has increased rapidly in recent years in both males and females (Wilkinson et al., 2014), and is on the increase in the UK. Since the early 1990s, anal cancer incidence rates have increased by almost three-fifths (56%) in the UK, and rates are projected to rise by 43% in the UK between 2014 and 2035 (Cancer Research UK, 2017). Figures from the Northern Ireland Cancer Registry (NICR) show the incidence of anal cancer in NI increasing from 3 in 1993 to 17 in 2009. MSM, who are estimated to be 5% of men, are disproportionately more likely to develop anal cancer (15:1 compared with heterosexual men) (Palefsky, 2010). These rates of HPV in males are similar to cervical cancer rates before the introduction of screening (Qualters et al., 1992). HPV infection in men may also increase the risk of acquiring HIV infection (Chin-Hong, 2009) as it potentially increases the permeability of the genital lining to HIV (Houlihan et al., 2012). Accordingly, anal cancer incidence rates are significantly higher in HIV-positive men than HIV-negative men (70-100 versus 35 per 100,000 person years) (D'Souza et al., 2008).

Other HPV-related diseases

In addition to cancer, infection with low-risk HPV strains (i.e. 6/11) is implicated in the development of anogenital warts (AGW) (Lacey et al., 2006). AGW are a significant burden in both men and women, with prevalence estimates suggest 160-289 per 100,000 with a peak in males between the ages of 25-29 years (Patel et al., 2013). HPV infection can also be transmitted to a foetus by a pregnant mother, which could lead to recurrent respiratory papillomatosis (RRP) (Palefsky, 2010). There is a low prevalence of RRP (1-4 per 100,000), but it

carries a high economic burden given the many medical procedures required by each patient (Larson and Derkay, 2010).

HPV VACCINATION

Three HPV vaccines are licensed for use: a bivalent vaccine which protects against the two high risk HPV types (HPV16/18), a quadrivalent vaccine protecting against HPV 16/18, genital warts and RRP (by eliminating the maternal reservoir for HPV) (twHPV6/11); and a nonavalent vaccine that protects against nine of the most common virus types (HPV6/11/16/18/31/33/45/52/58). As the vaccine was initially approved for cervical cancer prevention in females, there are fewer studies of the vaccines' preventative effect in males (Daley et al., 2016). However, the HPV vaccine has shown a good safety profile and efficacy in younger (aged 9 to 15) (Lehtinen et al. 2016; Van Damme et al. 2015, 2016; Yang and Bracken, 2016) and older males (aged 16-26) (Castellsague et al. 2015). Furthermore, immunogenicity of the nonavalent vaccine in males was shown to be similar to that in same age females (Petrosky et al., 2015). Pinto et al., (2016) demonstrated that HPV antibodies in the oral cavity in males can be generated through vaccination, but it will take many years before the research will be able to ascertain the effectiveness of HPV vaccination on male cancer outcomes.

THE CASE FOR UNIVERSAL VACCINATION

To date, to our knowledge, the following countries have HPV vaccination programs for boys: Australia, Austria, Barbados, Canada, Israel, New Zealand, Italy, Liechtenstein, Switzerland, and the United States.

Countries offering female-only vaccination (of which the UK is currently one), do so as males will be protected from HPV-related illness as a result of herd protection i.e. a reduction in the risk of infection in males due to reduced exposure as a result of female vaccination (Brisson et al., 2011). A high coverage in females (>80% female uptake) may promote herd protection, however, even if herd protection is achieved, men are not protected as soon as they move outside of the 'herd'. Men will live and work in other countries where females are not vaccinated and as a result likely become infected with HPV. It is important to highlight that even with a 90% female uptake, 10% of females are unprotected from HPV. This remaining 10% are important. There is increasing evidence to suggest that unvaccinated women demonstrate more risky sexual behaviour; for example multiple sexual partners, anal intercourse and a smoking history (Sadler et al., 2015). These unvaccinated females have the highest attributable risk for HPV-related cancers, and are at a higher risk of sexually transmitted infections and thus cervical and pre-cervical cancer. However, even though girls in UK/Ireland may receive the vaccine at no cost, they may not be currently doing so at levels that adequately confer herd immunity. The most recent figures indicate that uptake in the Republic of Ireland has dropped to below 50%, and it would appear that Northern Ireland vaccine rates may also be decreasing significantly. This dramatic drop in uptake has been linked to a vocal anti-vaccine campaign on the island of Ireland.

With this in mind, we undertook a study of parental HPV knowledge in Northern Ireland.

Study 1:

Assessing Parental knowledge and attitudes towards Human Papillomavirus vaccination.

A cross-sectional survey was administered between May and November 2016 to parents of adolescents (aged 11 – 14 years) in three schools in Northern Ireland. Items assessed socio-demographic characteristics and knowledge of HPV and HPV vaccination.

A total of 598 parents (M=43 years, 96% white, 89% females) participated. Most respondents were parents of both sexes (60%), with 20% parents of girls only or boys only. Overall, parents had low knowledge of HPV and HPV vaccination; 16% of respondents scored 0/34 and 50% of respondents scored 17/34 or less. A sizeable minority of parents (22%) were not aware of their child's HPV vaccination status. Knowledge of HPV was not

associated with child's gender, but was associated with HPV vaccination status. Those unaware of their child's vaccination status scored significantly lower than those who reported their child was/was not vaccinated ($p < 0.001$). Despite low knowledge, 40% of parents stated that if offered they would vaccinate their son against HPV.

Female vaccination rates on the island of Ireland have dropped significantly since an active anti-vaccination campaign led by parents who are concerned about HPV vaccination side effects. Low knowledge levels may make parents more susceptible to vaccine conspiracy theories. In this current climate, it is vital to educate parents on the safety and benefits of HPV vaccination to ensure adequate coverage. It may be necessary to implement universal HPV vaccination to improve protection.

TARGETTED VACCINATION OF HIGH RISK GROUPS

MSM do not benefit from a female-only vaccination programme and are at higher risk of HPV infection (Zou et al. 2014; Latini et al. 2014; Glick et al. 2014). In 2015 the JCVI recommended the vaccine for MSM up to age 45 in GUM and HIV clinics (Department of Health and Public Health England 2015). In August, then Health Minister, Michelle O'Neill announced a commitment of over £100,000.00 for MSM in Northern Ireland. <https://www.health-ni.gov.uk/news/michelle-oneill-announces-investment-hpv-vaccination-programme>

While this was a welcome announcement, there can be no certainty that enough of the MSM population will be reached – or reached at the optimal time – to produce herd immunity in this group. A targeted MSM HPV vaccination programme may be difficult to implement, and may have limited efficacy in preventing HPV-related disease, as the HPV vaccine is thought to be most effective when given at a younger age (9-15 years), before exposure to HPV through sexual contact and when immunogenicity is at its highest (CDC, 2011). In addition, most MSM are likely to have delayed in their presentation to a healthcare provider (HCP) and to have had multiple sexual partners with increased risk of HPV acquisition before they attend a sexual health clinic (Rank et al., 2012; Zou et al., 2014). There are also MSM who do not identify as gay or homosexual and will not disclose their sexual activity to a HCP, meaning that they will never be offered the vaccination.

In response to this we undertook a Cancer Research UK funded study to attempt to understand young MSM's knowledge and attitude towards HPV vaccination and to explore whether an intervention would be needed to support adherence to the MSM vaccine recommendation.

Study 2

Young HIMMS (Human Papillomavirus in men-who-have-sex-with-men study).

A mixed method study included questionnaires and focus groups with young (16-24 years) MSM was conducted to investigate MSM HPV knowledge and attitudes to targeted vaccination.

18 MSM (Median age=20) participated, most were aware of HPV (55.6%), but only 16.7% discussed HPV vaccination with their HCPs. Of the young men who participated in the focus groups in Northern Ireland and Yorkshire, most indicated that they were sexually active. Given that the HPV vaccine is most effective if administered before sexual contact, experiences of specific conversations with HCPs about their sexuality were discussed. Participants agreed that these experiences were very 'unfamiliar and clinical'. One participant specifically highlighted the difference between having to ask for the vaccine instead of his preferred approach of being offered the vaccine on his HCP's initiative. Knowing that HPV is becoming more common, and wanting to be responsible for their own sexual health were both offered as reasons for asking for the HPV vaccine. The relative advantages of speaking to the GP were weighed up against the specialist knowledge available at a GUM clinic. One participant raised the issue that it should be made available to everyone through the school

vaccination programme, in order to ensure universal coverage for all young people... ‘Why wouldn’t it be offered to young males in the school...why would they not just approach everyone?’

COST-EFFECTIVENESS

The major argument against implementation of universal vaccination has been the cost of this programme, and a number of studies initially did not find universal vaccination cost-effective (Seto et al., 2012). However, there is mounting evidence that universal vaccination is cost-effective in western populations (Bogaards et al., 2015), particularly when the costs associated with OPC (Graham et al., 2015) and genital warts treatment (Bresse et al., 2014) are considered, and the dose schedules are changed from 3 to 2 doses (Laprise et al., 2016). It has been proposed that considerations on the cost of universal HPV vaccination should be expanded to encompass the broader economic consequences and benefits to society. When universal vaccination is approached from the perspective of a lifetime cost-benefit analysis, wider economic benefits are demonstrated such as increased productivity, increased earnings and enhanced tax revenue (Kotsopoulos et al., 2015).

Using current prevalence data for HPV-related diseases in Northern Ireland, the incurred financial burden is estimated at greater than £2.5 million annually. Investigation of more precise local cost data is underway. The estimated additional cost of a universal vaccination programme in Northern Ireland is approximately £700,000. Due to the escalation in cases of HPV-related oropharyngeal cancers, and the significant financial and physical cost of this disease, data from a Canadian study was used to aid insight into potential cost savings associated with vaccination for the prevention of this disease.

Study 3:

A cost-effectiveness analysis of human papillomavirus vaccination of boys for the prevention of oropharyngeal cancer.

After an extensive literature review regarding HPV-related OPC in Canadian males, health care costs and clinical effectiveness estimates were obtained. A Markov (static cost effectiveness) model was used to compare the potential costs and effectiveness of the quadrivalent HPV vaccine (HPV4) versus no vaccination among boys aged 12 years. A theoretical cohort based on a Canadian population of 192,940 boys aged 12 years in 2012 was assumed to apply the model. A 3-month cycle length was used with a “lifetime” time horizon. The outcome of the analysis was the incremental cost per quality-adjusted life-year (QALY). Sensitivity analyses were conducted on variables, including the vaccine uptake rate and vaccine efficacy.

Assuming 99% vaccine efficacy and 70% uptake, HPV4 produced 0.05 more QALYs and saved \$145 Canadian dollars (CAD) per individual compared with no vaccine (QALYs and costs were discounted at 5% per year). Assuming 50% vaccine efficacy and 50% uptake, HPV4 produced 0.023 more QALYs and saved \$42 CAD. The results indicated that HPV4 in males may potentially save between \$8 and \$28 million CAD for the theoretical cohort of 192,940 over its lifetime.

On the basis of this model, HPV vaccination for boys aged 12 years may be a cost-effective strategy for the prevention of OPC in Canada.

HUMAN COST

The human cost of HPV related diseases should be the primary consideration for including boys in HPV vaccination programmes. HPV-related lower genital tract lesions and genital warts significantly impair psychosocial wellbeing and health-related quality of life (Dominiak-Felden et al., 2013). Patients with head and neck cancer experience profound visible, functional and psychological consequences from their disease and treatment. A decision on whether or not to vaccinate boys should not solely be made on the basis of cost - the

psychosocial impacts of HPV-related disease must be considered when calculating the benefit of male HPV vaccination.

Withholding a vaccine from any group of individuals at risk of developing that vaccine-preventable disease is unethical. It is also unfair for females to be expected to carry the responsibility for HPV prevention through vaccination, particularly when HPV is a virus that is sexually transmitted, and affects both sexes so prolifically. The burden of HPV-related diseases is now almost the same in men as in women. Unlike cervical cancer, there are no reliable and cost-effective screening methods to prevent cancers caused by HPV among men. A gender-neutral vaccination programme would achieve real herd immunity; without male vaccination men who move outside of the herd, and especially MSM, remain at risk of HPV infection and life-threatening and life-altering HPV related diseases.

SUMMARY AND RECOMMENDATIONS (see figure 1)

- There is an equivalent burden of HPV-related disease in men and women.
- A significant proportion of the young women not being fully vaccinated are ‘hard to reach’, at risk of making other ‘poor life decisions’, and at higher risk of sexually transmitted infections.
- Recent drop in female vaccination rates in Ireland may lead to a reduction in herd protection.
- Parents’ knowledge of HPV in Northern Ireland is low; they may therefore be more susceptible to anti-HPV vaccine messages.
- The HPV vaccine is most effective before sexual activity and offering it to 12/13 year olds provides the best opportunity for maximum efficacy. Vaccinating all boys would obviate the need for MSM having to self-present to a sexual health clinic.
- To optimise the vaccine effectiveness in MSM it should be offered to young MSM prior to sexual debut. Young MSM have low awareness of the vaccine.
- Vaccinating boys as well as girls is the only way to achieve herd immunity.
- The human cost of HPV related diseases should be the primary consideration for including boys in HPV vaccination programmes.
- From an ethical perspective, to “not fund” a vaccine for any group of individuals at risk of developing a vaccine-preventable disease is questionable; thus, including boys in vaccination campaigns is important to ensure equity in protection from HPV-related diseases.

According to HPV Action, in the UK each year, some 2,000 cases of cancer in men are caused by HPV. Some 48,000 men also develop genital warts as a result of HPV infection and about 600 men and boys live with RRP. The time has come for the introduction of a comprehensive vaccination programme targeted at all adolescent males and females. In every year that passes, over 400,000 boys in the UK miss out on the opportunity to be protected against a virus that causes 5% of all cancers. Northern Ireland has an opportunity to lead the way and comprehensively protect its adolescents by vaccinating both its boys and girls. Anything else is discriminatory, inequitable and less effective.

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Figure 1



