HPV Vaccination of Boys and Men

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1 Introduction

The human papillomavirus (HPV) is a DNA virus that infects the squamous epithelial cells. There are over 100 different types of HPV, over 40 of which infect the anogenital and oropharygeal tracts. HPV types are further differentiated into low-risk and high-risk types based on their association with carcinoma development. The two types which are most highly associated with cancer are HPV types 16 and 18. They account for approximately 70% of HPV related cancer cases. Typically, HPV is associated with the development of cervical cancer in women. However, HPV has also been linked to anal cancer (90% of which), penile cancer, vaginal cancer, and throat and neck cancers. In particular, cancers infecting the oropharyngeal tracts are increasing in many countries.

Because HPV has traditionally been associated with cervical cancer, many vaccination programs only consider vaccinating girls and not boys. However, because HPV is associated with many other cancers, the inclusive of boys in vaccination programs have been explored. Many cost-effectiveness analysis models have been constructed. In summary, the inclusion of boys and men in the vaccination program is more cost-effective when considering HPV-related diseases in men, and when the vaccine provides protection against these diseases. Furthermore, many of these models show that if vaccination in women is high, then vaccinating men may not be as beneficial due to protection from herd immunity. However, there remain some issues with these models.

The main goals of our cost-effectiveness model are:

1. Showcasing that men also provide some herd immunity effects for women

2. Including the effects of the MSM (and potentially the WSW) community into the model

3. Reconciling the impacts of HPV on men

Male-induced Herd Immunity

I don't really know why. We would have to explore this. It's pretty obvious, if there are some women that are not immunized, they are at risk to acquire HPV from an infected man/woman and then continue to spread it. Because men act as a vector in this situation, vaccinating women to produce herd immunity may be difficult. In other vector-bourne illnesses, vector-control is a method by which to help prevent the spread of disease. While we cannot do population control on men, we can vaccinate them preventing them from acting as a vector between infected and susceptible women.

Queer Perspective

One particular area that researchers are aware of but currently has been neglected is the effects of including MSM in the cost-effectiveness models for HPV vaccination. It is known that men who have sex with men (MSM) are at risk for acquiring HPV infections at various sites: penis, anus, oropharyngeal tracts. These infections also may lead to persistent infections and progress to pre-malignancies and cancers. It has been show that MSM, like women, are more likely to acquire anal HPV infections than heterosexual men [1]. Furthermore, anal HPV infections present a higher risk of being persistent than oral HPV infections, a requirement for the progression to cancer [1]. Because of these effects, not including MSM in the cost-effectiveness models may be under-estimating the protective effects of the HPV vaccine on men.

Furthermore, MSM do not receive any benefits, or minimal benefits, from the herd immunity presented in female only HPV vaccination strategies. These concerns have been discussed in a number of opinion editorials to various scientific journals.

We aim to include MSM into the transmission and cost-effectiveness models to understand the protective effects of vaccinating all boys and men or just the target vaccination of MSM boys along side girls and women.

Impacts of HPV on Men

We have already discussed that HPV infections can present themselves in men at a number of sites, and these infections can develop into persistent infections and subsequently into cancers. Specifically, we highlighted the MSM can be affected by anal HPV infections and how these effects may have been missing from previous cost-effectiveness models.

Here we highlight some of the more general effects of HPV on men and discuss in some more detail some of the concerns with HPV infections in heterosexual men. It is known that there is a rise in oropharyngeal cancer cases in both men and women. However, men are disproportionately affected by these HPV infections. A study by Beachler et al. actually showed that heterosexual men had a higher risk of oropharyngeal HPV infections than homosexual men [1]. They discuss that this may be due to the method of transmission from vagina to mouth. However, these results were not confirmed by comparing it to WSW or MSM exclusively.

If the rates of HPV-related oropharyngeal cancers in men are on the rise, then the current models may not be capturing the protective effects of vaccine for boys and men.

2 Canada's HPV Vaccination Programme

Currently, Canada provides free vaccination against HPV for girls aged 12-13 and is administered in schools. The inclusion of boys in this vaccination programme varies by province. Currently only two provinces (P.E.I. and Alberta) provide free vaccination against HPV for boys aged 12-13, and Nova Scotia will be rolling out their vaccination programme for boys in the future. Other provinces such as Ontario are currently reviewing whether vaccinating boys against HPV will be beneficial economically.

A similar discussion is currently happening British Columbia as well. As it stands, boys who are at risk (MSM or those who live on the street) are included in the free vaccination programme. However, this inclusion has some clear. Street involved youth may be difficult to initially find and vaccinate. As well, follow-up will be difficult to implement for these at risk individuals. Furthermore, gay or bisexual boys in high school may not feel comfortable or safe disclosing this information. That's also assuming that these boys identify as queer at this age, which for some men does not occur until later

in life. Moreover, by only targeting these specific groups of boys, there is limited vaccination to boys and men in general, which could put them at risk of HPV infection and subsequently developing HPV related cancers, particularly in the neck and throat region.

3 HPV Epidemiology

Disease Burden

HPV is known to be the cause of all cases of cervical cancer. Furthermore, HPV types 16 and 18 together case 70% of all cervical cancer cases. In addition to cervical cancer, HPV is also associated with cancers of various sites including the vagina, vulva, anus, penis, oral cavity, and oropharynx. As well, HPV types 16 and 18 are some of the most oncogenic types at these other sites as well.

The following is a table outlining the Canadian average annual incidence (per 100,000) and number of cases, but also contains the estimated proportion of cases attributable to HPV and more specifically HPV-16 and -18.

Sex	Site	Average annual incidence (per 100 000)	Average annual number of cases	Estimated Attributable (%)	
				Any HPV	HPV-16,-18
Males	Penis	1.0	127.4	50	63
	Anus	1.6	208.2	90	92
	Oral Cavity	6.5	853.1	25	89
	Oropharynx	0.64	84.3	35	89
Females	Cervix	10.1	1356.8	100	70
	Vagina/Vulva	4.2	651.8	40	80
	Anus	1.7	267.0	90	92
	Oral Cavity	3.3	501.2	25	89
	Oropharynx	0.18	27.2	35	89

Table 1: Average annual number of cases and age-standardized incidence of HPV-associated cancers among persons aged 15 years and older in Canada (1997-2006) and estimated attributable proportion due to HPV taken from the PHAC website.

Here we can see that a significant portion of HPV-related cancers are

caused by the HPV-16 and -18, which supports vaccination against these particular types.

The cases for HPV vaccination for girls and women to protect against cervical cancer and other cancers is robust and well supported. Here we will discuss some of issues surrounding men and HPV infections.

Men in general have lower rates of anal cancer than women do. However, incidence of anal cancer has increased for both men and women over the past several decades, and increasing more rapidly in men. Factors related to anal cancer in men include lifetime number of sexual partners, receptive anal intercourse, human immunodeficiency virus (HIV), and cigarette smoking. There is some evidence as well that men have a lower five-year survival percentage than women (58% versus 64% using the SEER data).

Penile cancer is quite rare. Rates increase with age and aside from HPV infection, risk factors include smoking, lack of circumcision, phimosis, chronic penile inflammation, and immunosuppression.

Suprisingly, oropharyngeal and oral cavity cancers are more common in men than in women. The factors most highly associated with these cancers is alcohol and tobacco usage. However, recently it has been shown that HPV is becoming a strong factor for the development of these cancers. It is believed that about 35% of all oropharyngeal cancers are caused by HPV, predominately HPV-16. However, a study by Chaturvedi et al. in 2011 shows that HPV related cancers of the oral cavity and oropharynx are on the rise, especially in men [2]. This, coupled with the decrease of tobacco use, means that HPV could be the leading cause of oral cancers in the near future. As well, we could be underestimating the future burden of HPV-related oral cancers if we do not consider how rapidly these rates are increasing.

4 HPV Transmission Dynamics

There are some interesting dynamics regarding HPV transmission and vaccination that should be considered when developing these cost-effectiveness models.

1. Transmission occurs when an infected individual comes into successful contact with a susceptible person.

2. Infections may progress to disease.

3. A disease my regress back to a regular infection.

4. Infections and diseases may also be fully cleared and the individual may or may not seroconvert following clearance.

5. Those who seroconvert have some protection against subsequent infection, while those who do not seroconvert have no added protection.

6. Seroconverted individuals may lose their protection as they serorevert. (I think it is important to consider these populations differently than susceptible for vaccination catch-up).

7. Vaccination programs should occur before entering the susceptible class (before sexual debut), but catch-up rates may occur in later years.

8. Catch-up vaccination for susceptible individuals moves them into the vaccinated class.

9. Catch-up vaccination for previously infected individuals moves them into

10. If someone who is vaccinated and clear the infection should probably go back to "vaccinated" class because they most likely have better protection than those recover from natural infection.

This is a diagram explaining the infection cycle:

Because these oncogenic HPV types are sexually transmitted and because we are concerned with the effects of vaccination on both men and women, we separate the population by gender. Many HPV models consider solely heterosexual transmission. Because MSM have limited benefits from the female herd immunity, we also consider MSM and exclusively heterosexual men (xM), and WSW and exclusively heterosexual women (xW).

MSM and WSW may have sexual intercourse with both men and women, but homosexual interactions are averaged over the spectrum. For example, p_m is the probability that a man has sexual intercourse with a man and p_w is the probability that a woman has sex with a woman.

The following system of differential equations outlines the movement out

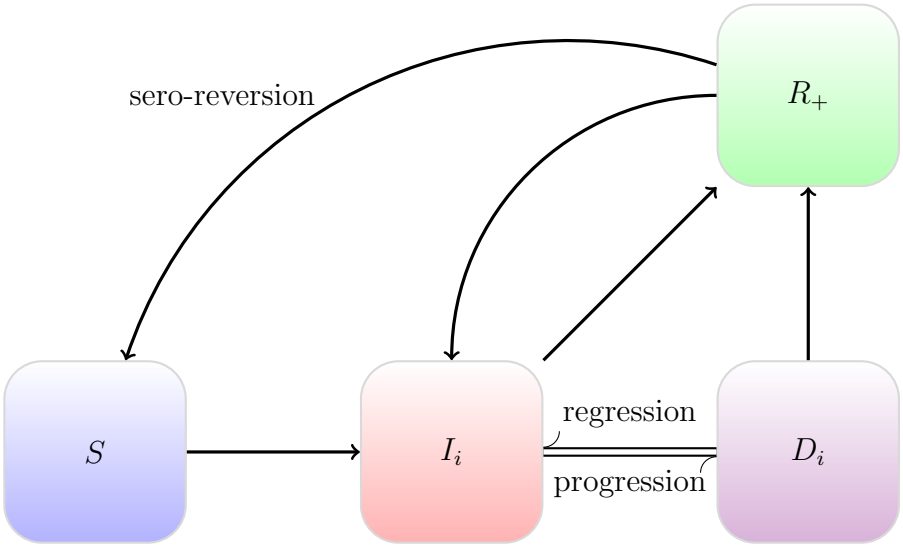

Figure 1: Compartmental diagram for the disease progression of site specific HPV infections. We have individuals in the susceptible S class when they are infection free. Individuals move into the infection class after they come into contact with another infected individual. They move into a site specific infection class I_i based on gender (vagina vs. penis) and based on probability of infection in a particular site (oropharynx, anus, and genitals). These infected individuals may progress to disease D_i or they may clear the infection. If the individual seroconverts, they move into the $R+$ category, which provides them some protection from subsequent infection, otherwise, they move back to the S class. Seroconverted individuals may also sero-revert and move into the S class, losing protective effects against subsequent infection.

of the susceptible class due to HPV transmission.

$$\frac{\mathrm{d}S_{xM}}{\mathrm{d}t} = -\beta_{fm} S_{xM} I_{xW} - (1-p_w)\beta_{fm} S_{xM} I_{WSW} \tag{1}$$

$$\frac{\mathrm{d}S_{xW}}{\mathrm{d}t} = -\beta_{mf} S_{xW} I_{xM} - (1-p_m)\beta_{mf} S_{xW} I_{MSM} \tag{2}$$

$$\frac{\mathrm{d}S_{MSM}}{\mathrm{d}t} = -p_m \beta_{mm} S_{MSM} I_{MSM} - (1-p_m) S_{MSM}[\beta_{fm} I_{xW} + (1-p_w)\beta_{fm} I_{WSW}] \tag{3}$$

$$\frac{\mathrm{d}S_{WSW}}{\mathrm{d}t} = -p_f \beta_{ff} S_{WSW} I_{WSW} - (1-p_w) S_{WSW}[\beta_{mf} I_{xM} + (1-p_m)\beta_{mf} I_{MSM}] \tag{4}$$

4.1 Vaccination Programme Strategies

Currently, there is a vaccination program for pre-pubescent adolescent girls, around the age of 12 years. Vaccination prior to first sexual experience provides ideal efficacy of the vaccine. There is current a debate about whether to include pre-pubescent adolescent boys in the vaccination programme.

In 2015, British Columbia has approved vaccination programme for at-risk boys which include the following groups. BC has defined at-risk boys as identifying as gay or questioning (MSM) and those who are "street involved". itemize

References

[1] Daniel Beachler, Gypsyamber D'Souza, Elizabeth Sugar, Wiehong Xiao, and Maura Gillison. Natural history of anal vs. oral HPV infection in HIV-infected men and women. *JID*, 208, 2013.

[2] Anil Chaturvedi and Eric Engels et al. Human papillomavirus and rising oropharyngeal cancer incidence in the united states. *Journal of Clinical Oncology*, 29(32), 2011.