“Assessment of Current Human Papillomavirus Dynamic Vaccination Modelling Strategies”

Brian McKay
Ariella Perry

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Dr. Andreas Handel
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Background

Human papillomavirus (HPV) has risen in importance in the last ten years due to the development of a vaccine; there were over 1660 articles published related to HPV in 2016 to date in PubMed [PubMed]. HPV is associated with significant morbidities and mortalities. Nearly all cervical and anal cancers, more than half of other male and female reproductive cancers, and cancer of the back of the throat can be attributed to an HPV infection [1]. There are currently over 100 identified viral serotypes of HPV; serotypes 16 and 18 are the primary etiologic agents of the cancers previously mentioned. The vaccine, which has been available since 2006, protects against four serotypes: 6,11,16, and 18. Since its introduction into the market, the HPV vaccine target population has been a subject of scrutiny. As with many sexually transmitted infections (STIs), the difference between genders and sexual behavior can have an impact on transmission of HPV and any subsequent outcomes. Therefore, a comprehensive HPV vaccination model for cancer outcomes that appropriately incorporates related behaviors will contribute significantly to current research.

Approach

We will conduct a systematic review of the literature following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [2]. Our PRISMA flowchart is presented below as Figure 1. The object of our research is a systematic consideration of all previously published deterministic dynamic models assessing the impact HPV vaccination has on transmission or cancer diagnosis. We will identify articles by a systematic search of PubMed, and works cited of screened articles. Included articles will meet the following inclusion criteria: reports using deterministic dynamic models to address questions related to the effects of HPV vaccination. If multiple papers are published using the same underlying model in different populations, the paper which first described the model will be included. Articles included in the search will be published before 9-15-16. After duplicate studies, have been removed, two independent investigators will screen the article titles removing unrelated articles. We will review the full text of the remaining articles and identify those that meet the inclusion criteria. We will critically examine the models and create a table highlighting important aspects of each model. A visual representation of the model will be created if not provided by the authors and tables of important parameters values. After considering all the models, we will propose a single expanded model to answer a relevant question, and we will address deficiencies of parameter values that may prevent the efficient use of the models.

Expected Outcomes

1. Literature search and review of current peer reviewed models to determine whether HPV vaccination reduces transmission of HPV among sexually active persons.
2. Literature search and review of current peer reviewed models to determine whether HPV vaccination reduces cancer diagnosis (because of HPV infection) among sexually active persons.
3. Identify strengths and weaknesses of current models to propose an expanded model well fitted for an infectious disease that leads to cancer outcomes.

Results

We used the following search strategy in PubMed "((((Dynamic) OR Dynamical) AND HPV) AND infection) AND cancer" which yielded 46 results. We then conducted a second review of PubMed using the search strategy of "(((dynamic model) OR dynamical model) AND human papillomavirus)" which yielded 81 results. We identified and removed 27 duplicates. Each reviewer assessed the 100 remaining abstracts independently for inclusion into our synthesis. Figure 1 illustrates our article selection process. Once we had our nine eligible articles, we abstracted descriptive and model parameters. A brief description of each study can be found in Table 1.

Table 2 presents the transmission model parameters in each of the nine models. The age at sexual debut varied amongst the patients, ranging from 8 to 19.1. The assumed vaccine protection also ranged across the nine studies, with a range of 0-100%. Waning immunity was considered in 6 of the nine studies. Natural immunity was also included in 7 of the nine studies but varied between a waning natural immunity and a lifelong natural immunity parameter. Indirect protection was included in 7 of the nine studies. Despite the inclusion of many of these previous parameters in the transmission models, only 4 of the nine models considered the difference between a male to female and female to male transmission of HPV.

Table 3 presents some of the natural history model parameters of each of the nine models. Each parameter is simply listed as present or absence for ease of comparison since this is an initial query into the current HPV dynamic models. Of the nine models, 7 incorporated a parameter for the spontaneous clearance of a cervical intraepithelial neoplasm (CIN) or infection. Mean duration by HPV type was also included in 8 of the nine models. Only one model by Chesson et al. considered other kinds of cancers and the risk of cancer in men [10]. The other eight models simply looked at HPV infection prevalence or cervical cancer in women, if cancer was considered at all. Chesson et al. assessed for cervical, anal, vaginal, vulvar, and oropharyngeal cancers [10].

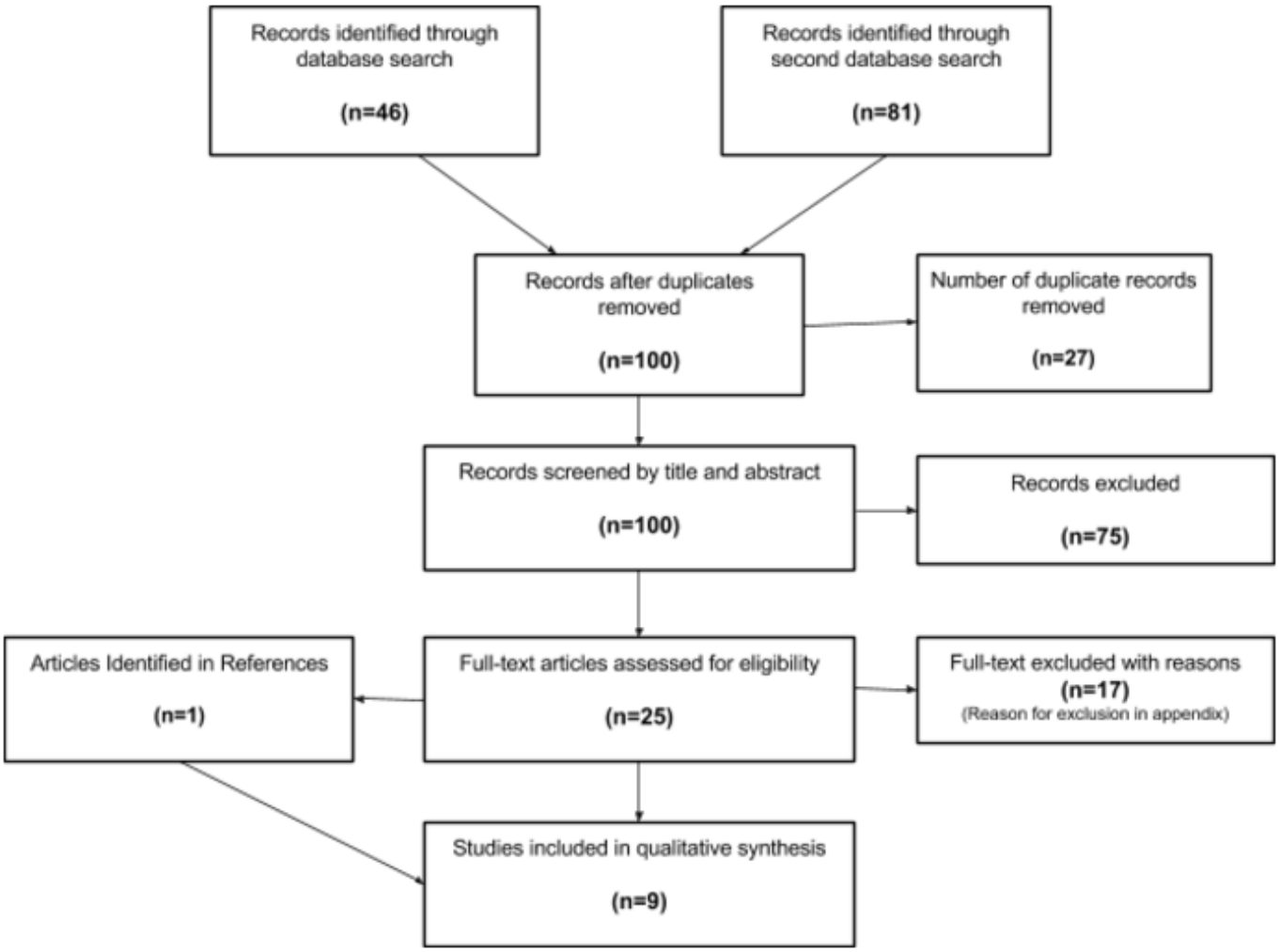

Figure 1. PRISMA schematic of systematic review for HPV vaccination models.

Author [Reference no.]	Type	Purpose/ Goal	Outcomes	Strategies evaluated	Key Assumptions	Main Findings
Elbasha 2007 [3]	SIR	Vaccine Strategies	-Incidence of Cervical Cancer -Incidence of cervical intraepithelial neoplasia -Male and Female Genital Warts	5	-Efficacy assumed to be 90% -Those infected and vaccinated do not progress to disease -Immunity is lifelong from vaccine -70% vaccine coverage -Only considers heterosexual partnerships	-All strategies reduced the incidence of all outcomes.
Kim 2007 [4]	SIS	Vaccine Strategies	-Lifetime risk of cancer -Prevalence of cervical cancer	8	-The previous infection provides some level of immunity -Movement between CIN1,2,3 can occur anytime and does not have to be sequential. -There is no spontaneous regression for the invasive cancer compartment -Does not consider the impact of genital warts or cancers for males	-Reduction in cervical cancer mortality will not be observed for many years. -High coverage in both boys and girls increases the effectiveness of the vaccine in preventing cancer, but higher coverage in girls alone is more cost effective.
Baussano 2010 [5]	SIS SIR	Vaccination Strategies	-Prevalence of HPV infection -Cervical Cancer mortality -Lifetime cervical cancer risk -Cervical cancer cases prevented	2	-Assumptions about natural acquired immunity and infection clearance	-Vaccination of boys more than doubled the cases of cervical cancer prevented -Vaccination before sexual behavior began increased the effects of herd immunity
Korostil 2013 [6]	SIS SIs SIR	Vaccination Strategies	-Reduction of HPV serotype prevalence	12	-There is no co-infection -Everyone is assumed to be sexually active by 24 -Clearance rates of infection is the same regardless of age	-Impacts of vaccine strategies on herd immunity, and natural immunity via infection -Indicated that SIR models may greatly underestimate the impact on HPV prevalence

Ribassin-Majed 2013 [7]	SIS	Vaccine strategies	-HPV 6/11 prevalence stratified by gender	2	-Exit and entrance of sexually active population, so N remains constant. -Vaccination coverage remains constant over time. -A Certain percentage of the population received all three doses in each scenario (30% and 10% respectively).	-Prevalence of HPV 6/11 infection decreases as quadrivalent HPV vaccination increases. -The model can be used to control HPV epidemic by using targeted vaccine coverage.
Horn 2013 [8]	SIR	Vaccine Strategies	-Treated Warts -Treated CIN -Treated CIS -Treated CIN+CIS -FIGO I -FIGO II -FIGO III -FIGO VI -Total Cancer Cases -CIN2+ -Cancer Deaths -Life Years Lost	4	-10% per year of waning immunity -Sexually active population of 12 years and older -7% of female population never participated in screening -Age-dependent sensitivity of Pap-test -Treatment always removes CIN, CIS -HPV-infection persists in 34%of women after the treatment of CIN or CIS and in 47%of women after the treatment of invasive cancer. -98% of those vaccinated are fully protected against any new HPV-infections -Assumed quadrivalent vaccine was 100% effective against HPV 16/18 -Vaccination coverage is 50% for the base case scenario in the model -Swapped between lifelong immunity and immunity for 20 years.	-37-44% reduction in cervical cases over the next 100 years after the introduction of HPV vaccination (assuming 50% vaccination coverage).
Vanska 2013 [9]	SIRS+V	vaccination	-hrHPV prevalence -hrHPV infections		-Sexual activity is dependent on age, gender, and lifetime partner number -Lifetime partner number in does not depend on vaccination status or calendar time. -Infections by hrHPV types are independent of each other. -In females, hrHPV types clear with an infection-age dependent rate g(t). -HPV vaccination does not change natural history (like clearance rates)	-The high rate of waning immunity against hrHPV infection is unlikely.

Chesson 2011 [10]	SIR	Vaccine strategies	-Death -Prevalence of HPV 16 related health outcomes -Prevalence of HPV-18 and HPV 6/11 related health outcomes	2	-Naturally acquired immunity provides lifelong protection against HPV 16. -Reduction in health outcomes over a year was assumed to be proportional to the reduction lifetime probability of acquiring HPV-16. -Current cervical cancer screening practices in the US did not change over time. -Proposed HPV vaccination program would be available over 100 years. -No protection if subjects did not complete all three doses. -Vaccine protection is lifelong. -No catch-up vaccinations were done post 12 years old.	-CIN 1-3 -Genital Warts -Cervical, anal, vaginal, vulvar, oropharyngeal, penile, cancer -RRP
Hughes 2002 [11]	SIR	Vaccine strategies	-Predicted prevalence of HPV (model 1) -Incidence of carcinoma in situ -Incidence of invasive cervical cancer	2	-Individuals become sexually active at 16. -Women who have had a hysterectomy are not at risk for getting HPV. -The vaccine is 100% effective in providing life-long immunity to both genders once received. -Male to female transmission rate is assumed to higher than female to male transmission. -HPV vaccine can prevent 60% of high-risk HPV infections. -Different types of HPV have different natural histories. -Screening prevents 30% of CIS and 75% ICC.	-The burden of disease shifts to older individuals. -A 60% removal of high-risk HPV infections results in a 46% reduction in CIS and 47% reduction in ICC.

Table 1. Description of 9 included studies.

Model Parameter	Elbasha	Kim	Baussano	Korostil	Ribassin-Majed	Horn	Vanska	Chesson	Hughes
Age at sexual debut	12	12	15	13	N/A	12	19.1	8	16
Assumed vaccine protection against infection	90%	0-90%	90%	80-100%	90%	98%	NA	75-100%	100%
Waning Immunity Considered	Yes: Time 10 Years Linear to 0%	Yes: Time Not reported	Yes: Time 7y 100% 7-14ys Linear to 50%	No: Lifelong	No: Lifelong	Yes: Time 10y 100% 10-20 Linear to 0%	Yes: 5y	No: Lifelong	Yes: Mean 10y
Considers Natural Immunity: Level of protection assumed	Yes: Not clear Does wane	Yes: Lifelong 50 and 53% specific to type	Yes: Not reported	Yes: Varying 0-100%	No	Yes: Waning from 30% to 0% over three years	Yes: Waning	Yes: Lifelong 100%	No
Considers Indirect Protection	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Difference in transmission F to M vs. M to F	Yes	Yes	No	No	No	No	Yes	No	Yes

Table 2. Comparison of Transmission Model Parameters for 9 Included Studies.

Model Parameter	Elbasha	Kim	Baussano	Korostil	Ribassin - Majed	Horn	Vanska	Chesson	Hughes
Spontaneous Clearance of any CIN or infection level	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Mean Duration of Infection by type	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Risk of other cancer by site	No	No	No	No	No	No	No	Yes	No
Includes Other related cancers: List	None	None	None	None	None	None	None	Cervical Vaginal Anal Vulvar Oropharyngeal Penile	None
Includes risk of cancer in Men	No	No	No	No	No	No	No	Yes	No

Table 3. Natural History Model Parameters for 9 Included Studies.

Discussion

Important Considerations for STI Dynamics

One of the most important aspects to capture in a dynamic model of STIs is heterogeneity in sexual behavior. Accurately identifying the distribution of sexual behavior can have a significant effect on estimating R0 and the equilibrium of the STI prevalence. This heterogeneity also has a significant impact on who is targeted in an intervention and how it is implemented. The model should also be frequency dependent since population density does not necessarily increase the number of sufficient contacts required to transmit an STI. Using a frequency dependent model supports that only individuals engaged in sexual behavior can transmit the disease or are at risk of becoming infected. Data on sexual behavior among different age or social groups is difficult to obtain due in part to social norms, taboos, or fear. How people mix is also an important consideration. A study by Monson indicated that an individual's interactions with others are strongly related to age. In many STI models mixing by age and level of sexual activity is included in the model [12]. Mixing by sexual activity level is the idea that people who have more sexual contact have this contact with other people who also have more than "average" sexual contact. Both forms of heterogeneous mixing are incorporated in some the included STI models. The actual structure of the model can also have an impact on how well the model fits the real world. As demonstrated by Korostil et al. the assumption of SIR or SIS disease structure can have a significant impact on the results generated by the model [6]. It is crucial that the model architecture accurately reflects the disease's transmission, natural history, and host related complexities.

Host type can also have an impact on transmission probabilities. If transmission rates from one group to another is different, it should be captured in the model. In the case of most STI's, there is a difference between male to female and female to male transmission probabilities. For most STI's male to female transmission is much greater than female to male transmission, but this is not the case for HPV. Most data indicate female to male transmission is more likely for HPV transmission in heterosexual couples [13,14,15,16,17]. Only a single study in China showed an increased risk of male to female transmission [18].

Proposed Model Expansion

Of the included models none consider the impact HPV may have in male populations. While the total impact of HPV on the male population is small modeling, the high-risk population may be worth the effort to help inform those at risk the benefit that may be provided. All the models assumed only heterosexual partnerships. A model considering homosexual relationships may help identify additional groups that would benefit from HPV vaccination. There is also no consideration of the impact coinfection with multiple HPV strains have on disease progression or transmission. There are models that investigate the impact of multiple STI infections, and the estimated impact coinfection has on transmissibility. For example, HIV and syphilis coinfection can lead to enhanced transmission of HIV (9). Since HPV types 16 and

18 are associated with warts, there may be an increased risk of transmission for any subtype of HPV due to the presence of open sores. Coinfection by other STIs and HPV may also need to be considered. Only one of the models accounts for differences in transmission risk. Transmission from female to male is more likely than male to female in the case of HPV. The addition of this difference in future models may help provide better insight into the actual effects of vaccination on transmission.

Beyond deterministic models, an agent-based or network model may better capture the impact of HPV vaccination. Men who have sex with men is a small enough subset of the population that a network model could be utilized. In the case of STI's this type of model is ideal since the required contact for transmission is a sexual act and not just causal interaction reducing the impact of recall bias when collecting the data. There are limits and in the case of sexual behavior reported data could be greatly altered by fear or lack of trust. So, the data used to develop the model could be influenced by these biases. While it would be nice to model the whole population using network models the required computing power and time to build the models make it prohibitive. The network approach would clearly highlight the impact vaccination of high-risk populations or individuals would in the total population. The only problem with this type of targeted approach is that vaccination needs to occur before sexual debut. This means that individual sexual behaviors have not been developed or are otherwise unknown at the time of vaccination.

Conclusions

The models included were very intricate and accounted for a nearly all the critical aspects of modeling STI transmission and natural history. We propose an expansion of the current deterministic models to consider the impact of HPV on non-heterosexual populations, differences in gender-specific transmission probabilities, as well as incorporating coinfections.

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