

Unresolved questions concerning human papillomavirus infection and transmission: a modelling perspective

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Abstract. Mathematical transmission models are widely used to forecast the potential impact of interventions such as vaccination and to inform the development of health policy. Effective vaccines are now available for the prevention of cervical cancer and other diseases attributable to human papillomavirus (HPV). Considerable uncertainties remain regarding the characterisation of HPV infection and its sequelae, infectivity, and both vaccine-conferred and naturally-acquired immunity. In this review, we discuss the key knowledge gaps that impact on our ability to develop accurate models of HPV transmission and vaccination.

Additional keywords: dynamic model, infectiousness, knowledge gaps, mathematical transmission model, vaccination.

Introduction

Two prophylactic vaccines are currently available to provide protection against the most important human papillomavirus (HPV) types. Clinical trials have demonstrated that these vaccines are safe and highly effective at preventing infection and precancerous lesions caused by the vaccine HPV types, and that they provide a degree of cross-protection against certain related non-vaccine types.^{1–4} Several therapeutic vaccines are also under development.⁵ With the advent of effective vaccines for the prevention of disease caused by HPV, mathematical models have been widely used to estimate the potential health and economic benefits of HPV vaccination, with the aim of developing evidence-based health policy.^{6–9}

Because HPV is a transmissible infection, transmission models are necessary to capture the full impact that vaccination will have in reducing the burden of disease in the population. In particular, transmission models are required to capture the herd immunity benefits of vaccination. In this context, herd immunity refers to the indirect protection afforded to unvaccinated susceptible individuals (those who have not acquired immunity through prior exposure to infection) as a consequence of reduced exposure to infection, because a proportion of the population have acquired immunity through vaccination or prior exposure to infection.¹⁰ In general, the prevalence of infection in the population will change with time as vaccination is introduced and thus an individual's risk of exposure to infection will also change with time. Therefore, in order to predict the impact of vaccination at a population level, we must use dynamic models of transmission that are able to capture these dynamic processes.^{8,11–14}

The key element of all transmission models is the transmission event that can occur when there is contact between an infected and a susceptible individual. The probability that transmission will occur depends on the degree of infectiousness and susceptibility of these individuals, and the effect that vaccination has on both of these properties. In this review, we discuss the knowledge gaps concerning HPV infection and transmission, in the context of vaccination, from the point of view of developing accurate transmission models.

Overview of transmission modelling

An understanding of the basic reproduction number (R_0)^{12–14} is often useful for a structured discussion of key uncertainties. The basic reproduction number is the number of secondary infections resulting, on average, from the introduction of a typical primary infective (index case) to a totally infection-naïve population. A simple model for R_0 is:

$$R_0 = \beta cd \quad (1)$$

where β is the per-contact transmission probability, c is the frequency of contact and d is the duration of infection.^{11,15} Because HPV is an endemic pathogen for which vaccines are available, R_0 tells only part of the story; it is also necessary to consider who is wholly or partially immune. Even so, this simple model for R_0 has the important implication that relative uncertainties in each of these three quantities (β , c , d) contribute similarly to the overall uncertainty in the model conclusions. Formally, if ΔR_0 , $\Delta\beta$, Δc and Δd represent the uncertainty in

these quantities, applying simple calculus to Eqn 1 gives the relation:

$$\Delta R_0/R_0 = \Delta\beta/\beta + \Delta c/c + \Delta d/d. \quad (2)$$

In this section and Table 1, we show that quantities affecting c have been measured most precisely, that there is more uncertainty in d and that β is very poorly known.

A model of sexual contact (represented in Eqn 1 by a single parameter c) is central to every HPV transmission model. Contact may be expressed in terms of partnerships or sexual acts. Because the burden of disease is predominantly among females who are at risk from infection obtained through heterosexual intercourse, the emphasis in HPV transmission models is usually given to heterosexual vaginal intercourse. However, the burden of disease is significant amongst men who have sex with men (MSM)¹⁶ and, to our knowledge, the transmission of HPV from MSM to females has not been explicitly studied.

We have listed some estimates of important values, with their associated uncertainties, in Table 1. While these parameters are not themselves a complete model of sexual mixing and require interpretation, they very closely reflect a frequency of contact (i.e. c). Parameters such as these have been measured from large, population-based surveys for the Australian population and others,^{17–20} and have relatively high precision. If full use were made of these datasets, uncertainties in sexual contact models would make a relatively small contribution to the overall uncertainty in most model conclusions.

Durations of HPV infection, as determined by polymerase chain reaction (PCR)-detected DNA positivity, have been carefully measured, in both men and women, for types 6 and 16 in particular, and, to a lesser extent, for types 11 and 18 (e.g.^{21–23}). The coefficient of variation for the duration of infection of HPV-16 reported by Trottier *et al.*²³ is 8.1%, so these values are no longer key uncertainties. What is not clear, as will be discussed below, is that these durations of infection correspond to durations of infectiousness.

The per-act probability of transmission, β , is important for transmission models but is difficult to measure by direct experiment because it requires the identification of pairs of individuals where one partner is susceptible and the other infectious, and observing the outcome of sexual activity. A few studies have made interesting preliminary observations,^{24–26} but with insufficient detail, power and temporal resolution to measure β precisely. The coefficient of variation in β is unknown.

The uncertainty in c contributes least to the overall uncertainty of the model, and the uncertainty in d is also modest. Any remaining difficulties are in interpreting values that have been carefully measured. The lack of knowledge concerning β dominates any uncertainty in c or d .

Measuring infectiousness

For the foreseeable future, comparing modelling results with epidemiological data will be an important task of mathematical modellers. Such comparison will allow improved inference of all parameters, and will continue to have the greatest impact on the parameters with the greatest uncertainty. To support this comparison and inference process, it is necessary to know who may transmit HPV, and as much as possible about their infectiousness.

How do we interpret DNA positivity?

Several technologies have been developed for detection, genotyping and viral-load quantification of HPV infection.^{27–32} These methodologies, which generally involve detection of HPV nucleic acid (DNA, mRNA) in samples taken from the genital tract or tissue biopsies, have been applied primarily in determining the clinical and prognostic outcomes of HPV infection, and in epidemiological studies of HPV incidence and prevalence, distribution and natural history. However, to our knowledge, none of these technologies has been studied or validated for determining the infectiousness or transmissibility of infections. Infectiousness may depend on HPV viral load and this, in turn, may depend on the stage of infection. It has been suggested that the detection of mRNA may be a better indicator of a productive viral infection, and several studies have been conducted to investigate the prognostic value of this test^{33–39} but as yet, no large-scale study has been conducted to establish a correlation between the presence of mRNA transcripts or viral load with transmissibility.

PCR DNA tests have been the most widely used in epidemiological studies for the detection of HPV infection. However, it is implausible to denote all people who yield a positive result to this test as being equally infectious. The problem arises when attempting to reconcile population-based epidemiological studies of HPV prevalence with a mathematical model: on one hand, it is easiest to use simple classifications in a model (such as 'susceptible', 'infectious' or 'recovered'), but on the other hand, there is no empirical test for dividing the population into these classes. Most mathematical models do not

Table 1. Estimates for six values reflecting the frequency of contact (c) and the duration of infection (d) from large, representative studies

The right-hand column, variability, is a coarse measure of the precision of the empirical estimate and was obtained by dividing one-quarter of the 95% confidence interval (CI) by the estimate itself

Parameter	Source	Estimate	95% CI	Variability (%)
Number of partners past year (males)	De Visser <i>et al.</i> ¹⁷	1.5	1.3–1.7	6.7
Number of partners past 5 years (males)	De Visser <i>et al.</i> ¹⁷	3.9	3.5–4.2	4.5
Number of partners past year (females)	De Visser <i>et al.</i> ¹⁷	1.0	1.0–1.1	2.5
Number of partners past 5 years (females)	De Visser <i>et al.</i> ¹⁷	1.9	1.8–2.1	3.9
HPV-16 clearance (per 1000 months)	Trottier <i>et al.</i> ²³	82.4	70.2–96.8	8.1
HPV-18 clearance (per 1000 months)	Trottier <i>et al.</i> ²³	91.9	68.8–122.7	14.7

adequately address this issue. A simple calculation illustrates how difficult it is to interpret DNA-based population surveys for HPV. For example, Peto *et al.*⁴⁰ reported a mean HPV-16 prevalence of 3.3% for women aged 15–69 and Trottier *et al.*²³ reported a mean HPV-16 prevalence of 2.7% for women aged 18–60. Consider the following calculation, which illustrates how simple interpretations of DNA positivity and immunity cannot be reconciled with epidemiological data. Assume that infection occurs at most once and clears with a mean duration of 11 months.²³ Assuming further that the DNA surveys were conducted under equilibrium conditions (i.e. HPV prevalence is not changing temporally), the proportion of women infected (p_{inf}) during the survey's age-range (w) is given by:

$$p_{\text{inf}} = pw/d, \quad (3)$$

where p is the mean prevalence measured over the age-range w and d is the duration of infection. For the Peto and Trottier studies,^{23,40} this calculation suggests that the proportion of women infected during their lifetime is 1.98 and 1.27, respectively; in either case, this corresponds to a lifetime risk of infection that exceeds the maximum possible value of 1.

A few different solutions to this problem are possible. The assumption of equilibrium is questionable, and in summary, it is possible that HPV-16 incidence and prevalence are higher now than they ever have been or will be in the future, and that this makes it difficult to decide how to use age-dependent epidemiological data. The model of infection implied by Eqn 3 is also simplistic. If the observed overall prevalence includes either re-infections or persistent infections, prevalence cannot be transformed into a lifetime risk of infection by the simple calculation given above. The Trottier study²³ reported a difference in the duration of prevalent and incident infections of 8.2 months and 7.1 months, respectively, when averaged across all HPV types, but this 15% difference is not great enough to explain the discrepancy illustrated in the calculation above.

This argument illustrates that the assumptions underlying Eqn 3 are inconsistent. However, as it seems improbable that even most women are infected with HPV-16, a few simple changes to the model or the estimates will not resolve this problem. We believe that a much more complex model of infection, incorporating ideas such as persistence, viral load, reactivation and re-infection, together with a sophisticated model of immunity, will be required to explain survey data. Only some DNA-positive individuals will be typically infectious, while others may have low or effectively zero infectivity.

Measuring immunity

How do we interpret HPV seropositivity?

For the modeller, it would be simplest to assume that HPV infection leads to seroconversion in every individual and that seropositivity is maintained for the individual's lifetime. Under this assumption, and also assuming that sexual behaviour is not changing over time, we would expect seropositivity, as obtained from serosurveys, to increase monotonically with age; however, this is not the case.^{41,42}

First, only ~50–75% of individuals who have been infected mount a serologically detectable response^{28,42} with the sensitivity of current tests. The implication of this observation

for modelling is that it may not be reasonable to assume that all those who have recovered from infection are equally protected against further challenge. This is discussed in more detail below. Second, women older than 50 years are less often seropositive than women aged 30–50 (e.g.^{41,43}). As most models are built with the intention of modelling the transmission of HPV in the most sexually active groups, a modeller may choose to ignore this observation on the basis that the older cohorts were less sexually active in their youth (e.g.⁴⁴) and therefore their seroprevalence cannot be used to assess the correctness of a current model of transmission.

Does naturally acquired infection confer immunity to re-infection?

HPV is adept at evading the immune system, but most anogenital and cutaneous lesions resolve spontaneously as a result of a successful cell-mediated immune response.⁴² When immunity is impaired, e.g. in organ transplant recipients and those infected with HIV, clearance of HPV is hindered and rates of HPV-related cancers are higher.^{45–48} Although seroconversion does occur in some individuals following natural infection, antibody concentrations are low. However, it has been shown that previously infected animals remain resistant to infection when challenged with high doses of virus of the same type, even in the absence of detectable antibodies.⁴⁹ In humans, it appears to be uncommon for re-infection to occur with the same type as has previously been resolved.⁴⁸ There is, therefore, considerable evidence to support the notion of naturally acquired immunity to re-infection. Because we currently have no immune correlate of protection (i.e. no measurable indicator that a person is immune), it is difficult to determine the duration of naturally acquired immunity. From a modelling perspective, the assumed duration of naturally acquired immunity is an important parameter (e.g.⁵⁰). In particular, the impact on transmission will be most significant if naturally acquired immunity is assumed to wane while individuals remain sexually active.

Some modelling studies have assumed that infection with HPV confers no protection against subsequent infection (e.g.^{51–53}). Others (e.g.^{54,55}) have assumed lifelong (type-specific) immunity following infection on the basis of observations detailed above and because age-specific population prevalence tends to peak fairly quickly following the commencement of sexual activity and fall sharply after the age of ~25 (e.g.⁴⁰). It should be noted that most prevalence studies have been conducted in female populations and it is not clear the extent to which the age-specific prevalence profile for men mirrors that for women.⁵⁶ Yet other studies have compared scenarios in which naturally acquired immunity is either lifelong or of finite duration (e.g.⁵⁷), or have allowed the rate at which immunity wanes to vary over a given range (e.g.⁵⁰). To illustrate the importance of this assumption, the model of Regan *et al.*⁵⁷ predicts that the relative reduction in incidence of HPV infection due to mass vaccination is considerably higher when it is assumed that naturally acquired immunity is of 10 years duration than when it is assumed to be lifelong; the model of Jit *et al.*⁵⁰ finds that the assumed duration of naturally acquired immunity is second in importance only to the duration of

vaccine-conferred immunity in the estimation of the cost-effectiveness of vaccination.

How effective are the current vaccines at preventing infection?

Clinical trials for the two currently licensed HPV vaccines have demonstrated very high efficacy for preventing persistent infection and precancerous anogenital lesions caused by infection with HPV types 16 and 18; in the case of the quadrivalent vaccine, high efficacy has also been demonstrated for the prevention of genital warts due to HPV types 6 and 11.⁵ Evidence of a degree of cross-protective efficacy against related HPV types has also been demonstrated for both vaccines.^{2,58} However, from a transmission modelling point of view, we are primarily concerned with the effect vaccination will have on the acquisition and transmission of infection. Evidence from the clinical trials strongly suggests that vaccinated individuals may be transiently infected and thus may also be infectious (e.g.^{59,60}). For example, Gardasil® (quadrivalent HPV vaccine; Merck, NJ, USA) demonstrated 90.4% efficacy against external genital lesions and 85.6% efficacy against persistent infection, but only 44.7% efficacy against DNA detection in the per-protocol population of the trial in males.⁵⁹ The problem for the modeller is how to interpret these findings, and make appropriate assumptions regarding the infectiousness of both the apparent transient infections and the small number of persistent infections that have been observed in the vaccine arm of the trials. It may be fair to assume that the persistent infections in vaccinated individuals should be treated as being equivalent to those in unvaccinated individuals, but it is also possible that both their duration and their infectiousness are different. The infections in vaccinees recorded on the basis of PCR-detected DNA positivity may be associated with low viral load and not infectious at all. If this is the case, they can be ignored from a transmission point of view. Unfortunately, as discussed above, no test is currently available for determining the infectiousness of an apparent infection.

A fairly clear picture has now emerged regarding the mechanism of protection conferred by the current vaccines.⁵ The vaccines induce very high concentrations of neutralising antibodies, much higher than for natural infection, and the seroconversion rates in the trials approach 100%.⁵ Because the evidence for this mechanism of protection is very convincing, it would simplify model development and parameterisation to assume that successfully vaccinated individuals are completely protected from infection and thus cannot transmit infection. However, as discussed above, data from the clinical trials suggest that transient infections and a small number of persistent infections can occur in vaccinated individuals,^{59,60} and these may or may not be transmissible. Regan *et al.*⁵⁷ considered transient infection in estimating the impact of an HPV-16 vaccine in Australia, and showed that this has significant implications for herd immunity and overall effectiveness of vaccination. In particular, this modelling demonstrates that the impact of vaccination on reducing incidence and prevalence is reduced significantly if transient breakthrough infection can occur and is transmissible.

We are also interested in the duration of vaccine-conferred protection. To date, the bivalent and quadrivalent vaccines have

proven efficacy for 6.4 and 5 years, respectively,⁵ and a monovalent HPV-16 vaccine has proven efficacy through 8.5 years.⁶¹ Evidence that vaccination induces immune memory has also been demonstrated for the quadrivalent vaccine.^{60,62} The observed anamnestic response is a hallmark of vaccines that induce long-term immune protection (like the hepatitis B vaccine, which is also a virus-like particle vaccine comprised of viral coat protein). It is thus considered likely that vaccine-conferred immune protection will be long-lasting and booster vaccination will not be required. Despite these encouraging results, it is still necessary to consider the implications of waning vaccine-conferred immunity until we can be certain that protection lasts at least beyond the age at which sexual activity places individuals at risk of developing cancer later in life. There is as yet no experimental evidence to suggest that the observed cross-protection will be as enduring as for the vaccine types and there are strong theoretical arguments to suggest that it may not be.⁴⁹

A three-dose regimen has been used in the major vaccine efficacy trials and is recommended for both currently licensed HPV vaccines. However, the impact of incomplete vaccination (i.e. less than three doses) has not yet been established and, to our knowledge, has not been considered in mathematical models. While it is generally considered that one dose will not be effective, preliminary data from a trial of a two-dose regimen of the quadrivalent vaccine in adolescent girls, which show that antibody responses were not inferior to those for a three-dose regimen, suggest that a two-dose regimen could be sufficient,^{63,64} and the distinction between the recipients of two doses and three doses can be ignored in mathematical models. A large randomised trial of two v. three doses of the quadrivalent vaccine in India is planned and will help to resolve this question.⁶⁵

Other issues for consideration

The importance of modes of HPV transmission other than vaginal intercourse, and the prophylactic efficacy of condoms and male circumcision have been largely overlooked in HPV transmission models to date.

Are non-vaginal–penile modes of transmission important?

HPV can clearly be transmitted through sexual acts other than vaginal intercourse. These could be incorporated into transmission models to better estimate overall transmission and burden of disease at all anatomical sites. Clearly, their impact depends on the extent to which other anatomical sites are reservoirs of infection for onward transmission, and sites in themselves for the development of disease attributable to HPV infection. We would need to consider the frequency at which the different types of sexual act occur, the probability that transmission will occur for each type of act, and whether this is different for the insertive and receptive partners. As discussed above, accurately measuring the probability of HPV transmission in sexual partnerships is difficult and it is even more difficult for specific types of sexual act.^{26,66,67}

It is still not clear whether anal intercourse is the primary mechanism for anal infection because anal HPV infection is common in both men and women who have not reported this

behaviour.^{25,68,69} Furthermore, transmission of HPV from the anus of the female to the male genitals, and vice versa, has been observed in couples not practising anal intercourse.²⁵ The recent study by Goodman *et al.*⁷⁰ further asserts that auto-inoculation of HPV to and from the anus also occurs. In women and men, partner change is a more important indicator of the probability of anal HPV acquisition than a history of receptive anal intercourse.^{68,69} HIV-positive men appear to be at high risk of anal HPV infection in the absence of anal intercourse, again suggesting that this is not an essential route for anal HPV acquisition.⁷¹ However, anal intercourse with numerous partners does appear to be a risk factor for anal HPV infections in HIV-positive MSM.⁷¹ An important issue for modelling is to estimate the probability of HPV transmission for anal sex (in both heterosexuals and MSM), and to establish whether it is different for the insertive and receptive roles. This would help to determine whether partner change rates or sexual practices are the main risk factor for HPV infection, particularly in MSM.

It has been suggested that the practice of oral sex has been increasing in recent decades.⁷² However, there appears to be considerable cultural and contextual (e.g. sex work) variation in trends in this behaviour,^{73–75} making an overall trend difficult to determine. Similarly, estimating the role of oral sex in HPV transmission and the development of oropharyngeal cancers is complicated because, as with anal intercourse, partner change seems to be associated with an increased risk of HPV-related disease as much or more than reported oral sex.^{76,77} While there is evidence for oral transmission of HPV,^{67,72} a study of HPV transmission in 38 sexually active monogamous heterosexual couples found no evidence of sero-concordant oral HPV infection emerging in couples with discordant HPV sero-status at commencement *v.* seven cases of genital transmission.²⁵

Are circumcision and condoms protective against infection?

A variety of studies have been conducted to investigate the effectiveness of circumcision in the prevention of HPV infection^{78–88} and the interpretation of the findings from these is currently under debate. Recent randomised control trials have reported beneficial effects of circumcision on HPV acquisition and clearance in males in Africa.^{82,84,86} However, Van Howe has suggested that these results can be completely explained by sampling bias⁸⁷ and has highlighted inadequacies in the methods used for sampling the penis in another study.^{80,81}

The evidence for whether condoms are a highly effective barrier against transmission of HPV between partners is conflicting.⁸⁹ Overall, condoms appear to offer minimal protection against incident infection with HPV but greater protection against progression to disease (warts or intra-epithelial lesions).^{89–91} Two studies have shown more rapid resolution of clinically defined HPV lesions in both males and females with consistent condom use,^{92,93} and Shew *et al.*⁹⁴ found reduced duration of infection with condom use in women. Thus, if condoms reduce the time taken for resolution of HPV-associated lesions, they may also indirectly reduce onward transmission. Winer *et al.*⁹⁵ showed a prophylactic effect of consistent condom use in a cohort of young female university students, although again this was stronger for prevention of

cervical lesions than for incident infections. It should be noted that the benefits of condom use in general may be mitigated by higher risk behaviours amongst condom users.^{18,66}

Thus, despite numerous studies, there remain considerable uncertainties regarding the efficacy of condoms and circumcision in preventing the transmission of HPV, and the published literature provides conflicting findings. However, because the practice of circumcision and use of condoms are widespread in many settings, it is important to consider their potential prophylactic efficacy in transmission models.

Summary

In this review, we have identified the key gaps in knowledge related to infection with and transmission of HPV from a modelling perspective. We believe that the greatest uncertainties impacting on the development and parameterisation of HPV transmission models lie in the biological descriptions of infectiousness and immunity. While sensitive methods are available for the detection of viral genetic material (DNA and RNA), we do not have a definitive method for determining when an individual is infectious from the point of view of transmitting infection. Furthermore, as we currently have no reliable correlate of immune protection against infection, we are unable to say precisely whether an individual has acquired immunity to infection, either through exposure to infection or vaccination; what level of protection has been conferred or how long it will last; or whether this protection prevents onward transmission. Clinical trials have shown that the current vaccines are highly effective at preventing precancerous lesions and, in the case of the quadrivalent vaccine, anogenital warts, but they have not ruled out the possibility of transient infection that may lead to transmission.

We have discussed several areas of uncertainty of lesser importance. The extent to which condoms and circumcision are protective against infection has not been firmly established. To date, modellers have assumed transmission occurs via heterosexual penile–vaginal intercourse because the greatest burden of disease is cervical cancer, and this mode of transmission is the most studied and the best understood. However, other modes of transmission will need to be considered more closely if their role in other diseases such as anal and oropharyngeal cancers is to be studied.

Unfortunately for modellers, most studies of HPV natural history have not been designed to inform models but to answer broader questions. Studies of transmission in couples have not been carried out on a large enough scale or with sufficient sampling frequency to clearly observe and measure the transmission event. It is our hope that as the demand for accurate quantitative modelling studies to evaluate the impact of vaccination programs increases, studies will increasingly be designed with model parameterisation in mind.

Conflicts of interest

None declared.

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