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Chapter 6: Epidemiology and transmission dynamics of genital HPV infection

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Abstract

This chapter provides an overview of the epidemiology of human papillomavirus (HPV) infection, with a focus on the dynamics of sexual transmission. We explore concepts related to the spread of sexually transmitted infections, including population prevalence, duration of infectivity, patterns of sexual contacts, and transmissibility, including modifiers of susceptibility and infectivity. HPV prevalence and incidence are high in most studies, particularly amongst young women. There is strong evidence that transmission occurs primarily via sexual activity, most commonly vaginal and anal intercourse. Although the duration of infectivity may be short, current evidence suggests that HPV is highly transmissible. The implications of transmission dynamics for the success of future HPV vaccines are discussed.

Keywords: Human papillomavirus; Prevalence; Transmission

1. Introduction

This chapter provides an overview of the epidemiology of HPV infection, with a focus on the dynamics of sexual transmission. We explore concepts related to the spread of sexually transmitted infections (STI), including population prevalence (an indicator of the burden of disease and of the probability of encountering an infected partner), duration of infectivity, patterns of sexual contacts, and transmissibility, including determinants of susceptibility and infectivity [1,2]. The implications for a future HPV vaccine are also discussed.

2. Prevalence

Genital HPV infection is the most common STI among women [1]. HPV infects the mucosal areas of the cervix, vagina, vulva, and anus. Detection of HPV types by polymerase chain reaction (PCR) assays varies greatly by age and by geography, as shown in a pooled analysis conducted by the International Agency for Research on Cancer (IARC) [3] and in a meta-analysis of published studies [46].

2.1. Age-specific prevalence and geographic variation of HPV infection in women

Among asymptomatic women in the general population, the prevalence of HPV infection ranges from 2 to 44% [4]. A recent meta-analysis estimated HPV prevalence among women with normal cytology using data from 78 published studies [46]. As shown in Table 1, the adjusted global prevalence was 10.41% (95% confidence interval, CI: 10.2–10.7%), with considerable variation by region. No data were available for Oceania. The number of women harboring HPV-DNA worldwide is estimated to be 291 million, and around 105 million women worldwide will have an HPV-16 or -18 infection, the most common oncogenic types in cervical carcinomas, at least once in their lifetime. The IARC

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Table 1
HPV prevalence[a] estimated from a meta-analysis of 78 studies of women with normal cytology, by world regions

	No. of studies	No. of women tested	No. of women HPV+	Adjusted HPV prevalence, % [95% CI]
Global estimate	78	157,879	15,764	10.41 [10.16–10.67]
Africa	8	6226	1429	22.12 [20.87–23.43]
America	24	40,399	6291	12.95 [12.41–13.51]
Europe	27	70,129	4649	8.08 [7.77–8.41]
Asia	19	41,125	3395	7.95 [7.53–8.40]

[a] Adjusted for region, study type, study design, publication year, sampling collection device, cell storage medium, HPV assay, primer used and youngest and oldest age of each included study (adapted from [46]).

pooled analysis used the same PCR method to evaluate specimens collected systematically throughout the world, and largely corroborates these observations [3].

The meta-analysis also indicated that prevalence is highest for young women and decreases in the middle age groups (see Fig. 1). At age 65 and older, an increase of the HPV prevalence is observed in the crude analysis. However, the adjustment for potential confounding factors (such as study design, sampling collection device, and HPV assay) results in a flattening of the age-specific prevalence in these age groups. The crude and adjusted estimates are not statistically significantly different in the ≥60 age group. This pattern is observed in many studies all over the world, with the exception of Asia, where the age-specific curves decrease smoothly with increasing age and no second peak is observed [4,47]. The reasons for the second peak and its geographic variation are unclear, but may be influenced by one or more non-mutually exclusive mechanisms [4]; for example, reactivation of previously undetectable infections acquired earlier in life could occur due to a gradual loss of type-specific immunity or to a sudden loss due to hormonal influences during the postmenopausal years. The second peak could also originate from acquisition of new infections due to sexual contacts with new partners later in life. Also plausible is a cohort effect, for example, the varying prevalence at different ages may reflect the changing experience of successive birth cohorts in being exposed to HPV in different eras. Because the changes in sexual morals over the last several decades have affected some cultural groups more than others, this explanation cannot be ruled out. Further, birth cohort differences in cofactors that may affect HPV progression or clearance (e.g., smoking, parity, oral contraceptives) and competing risks (e.g., mortality due to other causes) could also be involved. Finally, in populations without routine screening, a dip in prevalence in middle-aged women may not occur because underlying lesions remain undiagnosed and untreated.

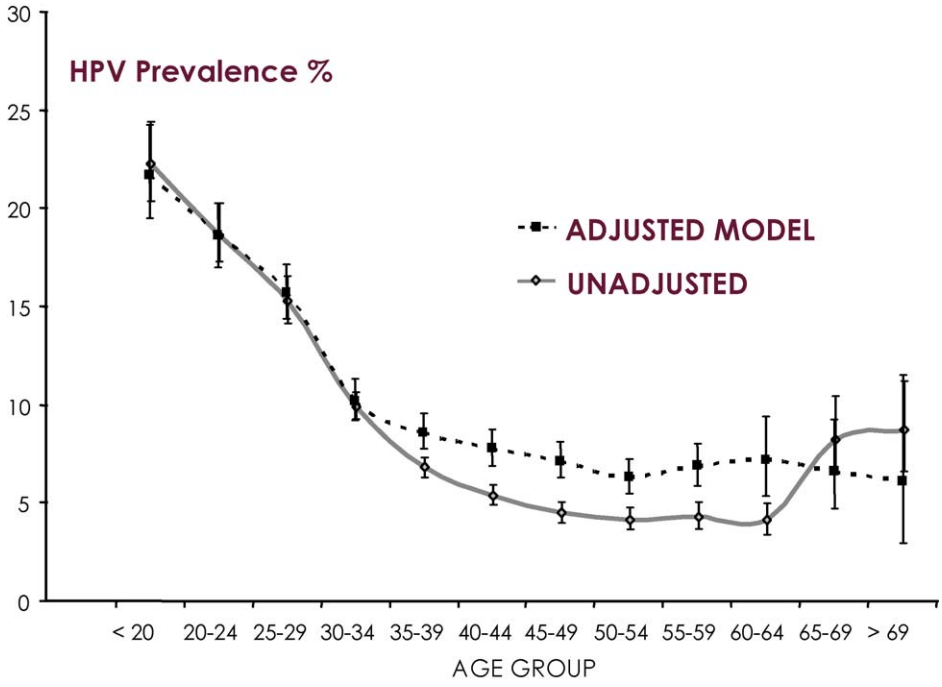

Fig. 1. Age-specific HPV prevalence among women with normal cytology. Crude and adjusted estimates are presented based on the meta-analysis of 78 studies. Age-specific prevalence estimates were calculated by means of logistic models based on a discriminatory analysis that included geographical area, study type, study design, youngest and oldest age values of each study, publication year, sampling collection device, cell storage medium, HPV assay, primer used and HPV type-specific assay. Adapted from [46].

Geographic and cultural variations in sexual behaviour of women and their male partners may result in differential rates of new HPV acquisition, and older men's behaviour may be more critical than women's. Data from 29 countries indicate, with considerable regional homogeneity, that 80% of men and 65% of women aged 40–80 years were sexually active in the past year, with the exception of Asia, where both men and women reported lower sexual activity [5]. In this same study, 5–11% of men compared to 1–6% of women reported more than one current partner (E.O. Laumann, personal communication, 2006). It will be difficult to elucidate the causes of age-related changes without frequent and long-term follow up of cohorts in multiple settings [4].

2.2. HPV prevalence in men

HPV-DNA has been clearly identified in the male genitalia, anal mucosa and oral cavity. Sampling methods for HPV-DNA in men are more variable and have not been thoroughly validated, and there are also difficulties associated with collecting cell specimens by exfoliation of cornified epithelium, which further contributes to the heterogeneity in methods. Partridge and Koustky [6] have reviewed 13 studies, and observed an HPV prevalence ranging from 3.5 to 45% for all types, and 2.3 to 34.8% for high-risk (HR) HPV. In all but one study, the most common type was HPV-16. The prevalence of low-risk (LR) HPV ranged from 2.3 to 23.9%. Penile HPV prevalence increased with the increasing number of sexual partners and with the number of sex worker partners [6,7]. Homosexual and bisexual men have been observed to have a particularly high prevalence of HPV (see Chapter 16). Few HPV serological studies have been conducted among males. The largest one reported lower seropositivity than among women and a peak prevalence among men aged between 30 and 39 [8]. Overall, the HPV data in men suggest that HPV prevalence in men (7.9%) is lower than in women (17.9%) and penile tissues may be less receptive to HR-HPV types [6].

3. Duration

The duration of infectivity is an important component of the rate of spread of an STI in a population, with infections of longer duration having a potentially greater impact [1]. Longitudinal research has consistently shown that most HPV infections detected by molecular hybridisation techniques are transient and are no longer detectable within 1–2 years [4] (see Chapter 5). HR infections seem to persist longer than LR ones [4]. Among HR types, there is some evidence that HPV-16 may persist longer than other types. This suggests that the rate of spread of HR-HPV in populations, including HPV-16, would be greater than for LR-HPV, assuming equivalent sexual contact patterns and transmissibility.

HPV infection among men seems also to be of short duration, with most infections no longer detectable after 1 year [9,10], although there is some evidence that more HR than LR male infections persist [10,11].

It is not known whether HPV is sufficiently infectious to result in transmission for the entire duration of detectable infection. Infectiousness may vary with viral load, since HPV positivity has been shown to correlate with viral load in the partner [12], but few data are available.

4. Incidence

The key measure to determine the spread of an STI is incidence, that is, the number of new HPV infections in a susceptible population over time. Other demographic influences notwithstanding, young women have high rates of HPV acquisition, although the influence of age is not so clear for men. Several studies have reported cumulative incidences of 40% or greater after 3 years of follow-up [4]. Rates of HPV infection in young women are high following first sexual intercourse ("sexual debut"), and remain high with acquisition of each new sexual partner [13,14]. As with prevalence, incidence in women tends to decline with age, although second peaks are sometimes observed in older women [15,16]. Incidence rates are generally higher for HR-HPV types than for LR types, with varying estimates according to the population studied and the number of HPV types tested [4]. Incidence rates for HPV-16 tend to be higher than those observed for other HPV types [4]. Co-infection with multiple HPV types and sequential infection with new types are common, and the risk of acquiring new HPV types appears to be independent of prior infection with other types [4].

Few studies have evaluated HPV acquisition in men. Nevertheless, the evidence suggests that incidence is similarly high among men than among women, with cumulative incidences ranging from 14 to 21% within 3–8 months of follow up [6].

5. Routes of infection

Data supporting sexual intercourse as the primary route of genital HPV infection include documented transmission of genital warts between sexual partners [17], concordance in sexual partners for type-specific and HPV-16 variant-specific HPV-DNA (see Table 2), the rarity of genital HPV infection in women who have not had vaginal intercourse [18], the strong and consistent associations between lifetime numbers of sexual partners and HPV prevalence in women [18] and men (albeit less consistently) [6], and increased risk of HPV acquisition from new and recent sexual partners [19]. Sexual intercourse includes both vaginal and anal intercourse. Receptive anal sex is strongly associated with HPV detection in the anal canal in homosexual and bisexual men [6], and to a lesser degree for women [20]. One explanation for the latter is that some anal HPV infections in women may occur due to viral shedding of cervical or vaginal HPV infections in vaginal discharge [20].

Table 2
Review of studies of HPV-type-concordance among couples

Reference	Population	Sample	Age	Relationship duration	Finding
Hippeläinen et al. [36]	Women with abnormal Pap smear and their male partners (Finland)	270 couples	♀: mean 27 (range 15–62); ♂: mean 32 (range 17–74)	Median: 18 months; mean: 41 months; range: 1–300	6% (15/270) of couples were HPV-positive concordant for the same type
Kyo et al. [37]	Women evaluated for infertility or who had cervical intraepithelial neoplasia (CIN) or cervical cancer, and their male partners (Japan)	53 couples	Not reported	All married for 2+ years	17% (9/53) of couples were HPV-16 positive concordant. In couples where at least one partner had HPV ($n = 26$), 35% were concordant. Discordancy was more likely to be female positive and male negative than female negative and male positive
Baken et al. [29]	Heterosexual partners attending STD clinic (Seattle, USA)	50 couples, 45 with HPV result	♀: mean 26; ♂: mean 29	Unspecified	29% (13/45) of couples were concordant for the same HPV type. In couples where at least one partner had HPV ($n = 41$), 32% were concordant. Concordance decreased with time since last intercourse
Castellsagué et al. [7]	Women enrolled in case-control studies for cervical neoplasia, and their husbands (Spain and Columbia)	816 couples, 431 with HPV result	♂: mean 45	Excluded relationships <6 months duration	(66%) 286/431 of couples were HPV-positive. Of these, 2% (7/286) were HPV-positive-type-concordant
Franceschi et al. [38]	Women enrolled in case-control studies for invasive cervical carcinoma (ICC) and *in situ* cervical cancer (CIS), and their husbands (Spain, Columbia, Brazil, Thailand, and the Philippines)	964 couples	♂: median 45, 50, and 38 for husbands of control women, women with ICC, and women with CIS, respectively	Excluded relationships <6 months duration	HPV-16 positive concordance observed in 0.02% (1/465), 4% (17/383) and 3% (4/116) of couples where the wife was a control, an ICC case, or a CIS case, respectively.
Bleeker et al. [12]	Women with CIN lesion and their male partners (The Netherlands)	238 couples, 181 with HPV result	♀: mean 34.7 (range 19–55); ♂: mean 37.6 (range 22–58)	Mean: 10.6 years; range: 0.6–35 years	37% (67/181) of coupes have type-specific HPV-positive concordance. In couples where HPV was present in at least one partner, 38% (67/176) were type-positive concordant. Increasing association between viral load in one partner and HPV positivity in the other

Although plausible, mechanisms other than sexual intercourse are less common routes of genital HPV infection (see Table 3). While oral and digital infection with genital HPV types clearly occurs, the risk of transmission by digital–genital or oral–genital contact appears to be minimal. Similarly, HPV infection by perinatal transmission or in children also occurs, as both HPV-DNA and serum antibodies have been detected in infants and children. The data suggest that this is rare and unlikely to result in persistent infection.

6. Sexual behaviour leading to exposure to HPV

A knowledge of patterns of sexual behaviour and sexual networking in populations is fundamental for the understanding of HPV transmission dynamics [21]. Generally, the trend in many Western countries is that sexual behaviours and attitudes have become more permissive over time [1]. Many aspects of sexual behaviour affect the likelihood of encountering an HPV-infected partner (Table 4).

6.1. Sexual debut

Several cross-sectional studies have reported that earlier sexual debut or shorter intervals between menarche and sexual debut are risk factors for prevalent HPV infection [22]. However, the reasons for this relationship are unclear. Earlier intercourse may be a marker for other risky sexual behaviour, such as greater lifetime numbers of partners and concurrent partnerships [1]. Indeed, one study has reported that the association of HPV-DNA acquisition with age at first intercourse is mediated by other sexual behaviour variables [23]. In a

Table 3
Review of selected studies evaluating HPV transmission via non-sexual intercourse contact

Reference	Population	Findings
Genital HPV infection associated with sexual contact other than intercourse		
Marrazzo et al. [39]	Cross-sectional study of women who have sex with women, including 21 women reporting only female sexual partners (USA)	HPV-DNA detected in genital tract specimens from 19% of women reporting only female sexual partners
Sonnex et al. [40]	Cross-sectional study of 14 men and 8 women with genital warts (UK)	27% of subjects tested positive for the same HPV-DNA type in both finger brush and genital samples
Winer et al. [19]	Longitudinal study of female university students, including 148 women reporting no history of vaginal intercourse at enrolment (USA)	The 24-month cumulative incidence of HPV-DNA infection in virgin women was 7.9% (95% CI: 3.5–17.1); any type of non-intercourse sexual contact (finger–vulvar, penile–vulvar or oral–penile) reported by virgin women was associated with an increased risk of HPV infection.
Oral HPV infection associated with oral sex		
Coutlée et al. [41]	Cross-sectional study of 178 (158 ♂, 20 ♀) HIV+ and 109 HIV− (73 ♂, 36 ♀) individuals (Canada)	32 of 287 (11.2%) oral samples tested positive for HPV-DNA; a univariate association between unprotected oral sex and oral HPV (odds ratio, OR = 5.5; 95% CI: 1.6–18.4) was no longer apparent after adjustment for other sexual behaviour variables and genital infections
Winer et al. [19]	Longitudinal study of 603 female university students (USA)	Only 5 of 2619 (0.02%) oral samples tested positive for HPV-DNA; there was no association between oral HPV and report of oral–penile contact in the past 12 months (hazard ratio, HR = 0.5; 95% CI: 0.07–3.5).
Kreimer et al. [42]	Cross-sectional study of 190 (108 ♂, 82 ♀) HIV+ and 396 HIV− (231 ♂, 165 ♀) individuals (USA)	18 of 583 (3.1%) oral samples tested positive for HPV-DNA; associations between oral sex and oral HPV were inconsistent and varied according to HIV serostatus and reports of oral sex with same-sex vs. opposite-sex partners; ORs for ≥2 vs. 0–1 recent oral sexual partners: HIV-negative 0.2 (95% CI: 0.0–1.2); HIV-positive 12.8 (95% CI: 3.1–52.7)
Rintala et al. [43]	Longitudinal study of 131 heterosexual married couples (Finland)	The 24-month cumulative incidence of oral HPV-DNA in both men and women was around 10%; oral HPV was not associated with oral sex habits
HPV infection in children and infants		
Smith et al. [44]	Longitudinal study with type-specific HPV-DNA testing in 574 mother–infant pairs (USA)	1.6% of oral and genital samples taken from infants a median of 65 h post delivery were positive for HPV-DNA. Type-specific concordance between mother and infant pairs was less than 1%. At 3-month follow-up, no HPV-DNA was detected in any of the infants tested
Dunne et al. [45]	Cross-sectional HPV-16 seroprevalence survey of 1316 children aged 6–11 (United States)	2.4% of children were seropositive, with higher prevalence in boys than girls (3.5% vs. 1.2%) and in children >7 years than in children ≤7 years (3.3% vs. 0.4%)

recent longitudinal study of 15–19-year-old women sampled within 1 year since sexual debut, the risk of HPV infection increased with the interval between menarche and first intercourse, probably due to the tendency of older women to form partnerships with older, more sexually experienced partners [14]. Biological mechanisms, including cervical immaturity, inadequate production of protective cervical mucus and increased cervical ectopy, may make younger women and adolescents more susceptible to HPV infection [22].

In developed countries, the age at sexual debut appears to be decreasing over time [1], although some recent data suggest a reversal of this trend in the United States [24]. In developing countries, there is considerable variability in the prevalence of virginity, age of sexual debut and premarital sex among women aged 15–24 [25]. In 10 countries from sub-Saharan Africa, Latin America and the Caribbean, the prevalence of premarital sex was greater in countries in sub-Saharan Africa (see Fig. 2a) [25]. However, in Latin America, there is evidence that the prevalence of virginity among young women is declining over time and premarital sex is increasing (see Fig. 2b) [25]. The trend of increased exposure to HPV at younger ages has important implications for vaccination programs.

6.2. Number of partners and acquisition of new partners

The associations between numbers of new and recent sexual partners and likelihood of detecting HPV-DNA in female genital tract specimens are strong and consistent [18,19]. The rate of acquisition of partners (contact rate) plays a key role in STI transmission dynamics [2]. Population surveys show heterogeneity in the number of lifetime and recent sexual partners, with a majority having none or one partner, and a

Table 4
Proposed risk factors* for HPV acquisition and transmission, according to hypothesized mechanism of action: Summary of results from published epidemiologic studies

	Hypothesized to affect likelihood of exposure to HPV-infected partner	Hypothesized to affect likelihood of transmission upon exposure through effects on. . .	
		Infectivity/duration	Susceptibility
Early age at sexual debut	↑		↑
Greater number of partners	↑		
Similarity or dissimilarity between individuals and their sexual partner(s)	↑/↓		
Acquisition of new partner	↑		
Concurrent/extra-dyadic partners	↑		
Short intervals between partners	↑		
Concomitant infection with other STI	↑	↑	↑
Male circumcision	↓	↓	↓
Condoms	↑/↓	↓	
Immune suppression (e.g., HIV infection, transplantation)			↑
Certain human leukocyte antigen (HLA) complex alleles and haplotypes		↑	↑
Hormonal contraceptives		↑	↑
Diet deficient in certain micronutrients		↓	
Smoking		↑	↑

Refer to text for details and strength of evidence.
* Arrows indicate the direction of the association, i.e., whether they increase or decrease risk via the proposed mechanism.

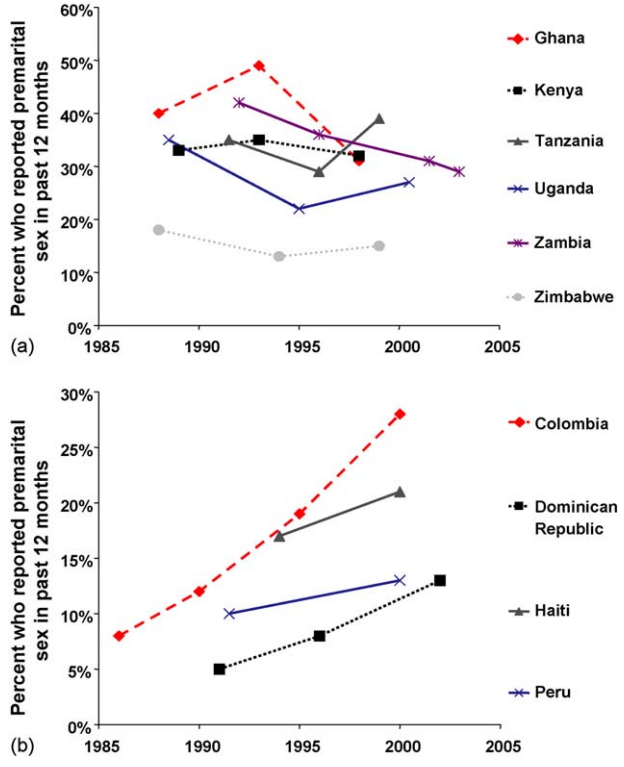

Fig. 2. (a) Percentage of never-married women aged 15–24 years who reported sex in the past 12 months in selected countries in Africa. Adapted from [25]. (b) Percentage of never-married women aged 15–24 years who reported sex in the past 12 months in selected countries in Latin America and the Caribbean. Adapted from [25].

minority having multiple partners [1]. More sexual partners and non-spousal/non-cohabitating partners are more often reported among men than women, and among the young than the old [1,25]. Gender differences could be explained by a small proportion of women having sex with many partners (e.g., sex workers), or by under-reporting of sexual activity by women or men's over-reporting [25].

6.3. *Characteristics of partners and sexual networks*

The characteristics of male partners are critical for female HPV acquisition. In case-control studies of cervical cancer, male partners of cases report higher numbers of partners than those of controls [19]. Female HPV prevalence and acquisition have been positively associated with women's estimates of their male partners' lifetime number of partners [13] or not knowing a male partner's prior sexual history [13,14].

Patterns of sexual networking are also critical for transmission dynamics [21]. Sexual networks are made up of individuals who are sexually connected, either directly or indirectly. Important network features that increase the chances of transmission are larger network size, higher contact rates and the patterns of sexual mixing or partner choice [21]. Random mixing occurs when an individual is equally as likely to have sex with any other individual [2]. Assortative mixing occurs when similar individuals tend to form contacts, whereas dissortative mixing occurs when individuals tend to form contacts with individuals who are different from them, and it is the latter that tends to increase the risk for STI transmission [21]. Most surveys show that mixing tends to be moderately assortative with respect to age, race/ethnicity or number of sexual partners [2], but not always [1,21]. For

example, in many cultures women tend to form partnerships with older men [2,21]; this could explain, in part, the high HPV prevalence among younger women, and its geographical variation.

"Core groups", or groups of highly sexually active individuals with many partners, are believed to contribute disproportionately to the spread of most STIs [2,21]. HPV infection is not restricted to core groups, however, as it is also relatively common among moderately sexually active individuals [1,18]. This may be due to inherent biological properties of HPV as a virus that is well adapted to be transmitted by skin-to-skin contact and to infect only the epithelial lining of susceptible body areas without the need to invade connective tissue or to be disseminated regionally or systemically, in addition to the generally silent nature of the infection. Bridging occurs when sexual linkages are formed between members of high and low prevalence subpopulations, which provide a conduit for infection between them [1]. For example, STI transmission between the homosexual and heterosexual populations is possible through bisexual activity [26], and could have implications for female-only vaccination strategies.

Should HPV vaccines reduce HPV transmission in the general population, HPV could then become concentrated in core groups, and the behaviours of these highly sexually active individuals will be of greater importance for research and prevention [26]. Direct targeting of vaccines to core groups would not be expected to reduce HPV population prevalence, given the lessons learned from the hepatitis B vaccine (see Chapter 14).

6.4. Concurrency and serial monogamy

The timing of sexual partnerships plays a role in determining STI spread. An example is sexual partner concurrency, in which sexual partnerships overlap each other in time [21]. Concurrent partnerships are not uncommon—they are reported by 32–54% of adolescents and 12–40% of adults in the US [27]. Since awareness of whether one's partner has other partners has been shown to be poor [27], this implies that long-term monogamy on the part of one partner may not necessarily reduce the risk of infection.

The timing of non-overlapping partnerships, or serial monogamy, may also be important. A survey of sexual behaviour in the US found that, among serially monogamous women, the mean gap between partners was 8 months for women aged 15–19, 11 months for women in their twenties, and 18 months for women aged 30–44 [28]. Given the average duration of HPV infection among women, serial monogamy must contribute to HPV transmission. Knowing a partner for more than 8 months has been associated with a lower risk of HPV acquisition among women [13], which could be explained by clearance or waning infectivity in the male. Likewise, intercourse with a partner who has had no other recent partners would be expected to reduce infection risk [13].

7. Transmissibility and factors affecting transmission

7.1. Probability of transmission upon exposure

To our knowledge, there have been no published reports of the transmissibility of HPV based on empirical data [18]. A study of the transmissibility of genital warts, conducted before HPV was identified as the causal agent, observed that 60% of sexual partners of patients with warts subsequently acquired them [17]. This suggests high transmissibility, at least for HPV types that cause genital warts.

To date, research on HPV in couples has consisted of cross-sectional assessment of prevalent HPV infection in both partners, rather than transmission per se (Table 2). Most, but not all, of these studies found relatively poor concordance for type-specific HPV positivity. In two studies, however, the HPV-type-specific positive concordance was greater than expected by chance [12,29]. Concordance was associated with more recent sexual intercourse [29] and higher viral load [12]. Methods for HPV testing among men are in the process of being refined, and it is possible that some of these previous studies have limited ability to detect HPV infections. Nevertheless, HPV status in couples where the woman has cervical lesions is likely not reflective of those in couples where the female is lesion-free. Furthermore, couples in these studies tended to be older, with relationships of long duration. The transmission event likely occurred years prior to enrolment, and many infections would have resolved. To study HPV transmission, one would ideally recruit relatively young couples that have newly formed relationships.

A stochastic computer simulation study has investigated values of HPV transmissibility that were consistent with observed incidence among female university students [30]. The probability of HPV transmission per coital act ranged from 5 to 100%, with a median of 40%. Similarly, Barnabas et al. [31] have recently estimated the per-partner male-to-female transmission probability as 60% for HPV-16 using Finnish data on seroprevalence. This is identical to the observed per-partner transmission probability for genital warts [17].

These results suggest that HPV is more transmissible than other viral STIs, but is comparable to bacterial STIs. Studies of HIV or herpes simplex virus-2 (HSV-2)-discordant couples indicate that the probability of transmission is 1 per 1000 acts of intercourse [2,32]. Per-partnership transmission probabilities for bacterial STIs range from 20% for chlamydia, 50% for gonorrhoea and 60% for syphilis to 80% for *Haemophilus ducreyi*, the causal agent of genital ulcers [2]. With high transmissibility, vaccines would need to reduce infectivity several-fold in breakthrough infections to stop the chain of transmission. This could happen by a reduction in viral load.

7.2. Factors affecting the probability of transmission

A number of factors may influence the probability of transmission of an STI, such as viral load, other STIs, cir-

cumcision, use of condoms, immune mediators of susceptibility or infectivity and nutrition (Table 4). Cervical infection with other STIs, such as *C. trachomatis*, may increase susceptibility to HPV infection by cervical inflammation or microabrasions, or facilitate persistence of HPV infection through immunological mechanisms [33]. The similar sexual behaviour risk-factor profiles for HPV and other STIs, however, make it difficult to discern whether other STIs are simply markers for exposure to HPV or act as true cofactors by increasing susceptibility or infectivity [4].

Evidence for male circumcision as a risk factor for genital HPV infection in both men and women is conflicting [6]. One study has reported a protective association against prevalent HPV infections and repeat detection of prevalent infections at a 1-year follow-up visit, but not against detection of new infections [10]. Male circumcision has not been linked to female HPV acquisition, although some, but not all, case-control studies have reported that male partners of women with cervical cancer are less likely to be circumcised than male partners of control women [19]. If male circumcision does contribute to the spread of HPV infection, it is unclear whether it affects men's susceptibility to infection and/or infectivity and persistence upon infection.

Use of condoms is an effective barrier against genital HIV transmission; however, data for other STIs, including HPV, are equivocal [34]. Condom use appears to offer some protection against developing high-grade cervical neoplasia and invasive cervical cancer [34], and have been shown to promote regression of cervical neoplasia and penile lesions and clearance of infection in men and women (see Chapter 5). Nonetheless, most studies evaluating the relationship between condom use and HPV infection have failed to demonstrate a protective effect of condoms [34]. This may, in part, be due to a tendency for condoms to be used more often in casual relationships, where the probability of encountering an infected partner is higher [4]. Data from a recent prospective cohort study of female university students enrolled prior to or within 2 weeks of their first intercourse, however, did show a more than three-fold protective effect of condoms on HPV acquisition [48]. Even with consistent condom use, however, HPV infections can still be transmitted through contact with areas of unprotected genital skin. Furthermore, a protective effect of condom use, even if one exists, may diminish over multiple sex acts in ongoing relationships due to high infectivity [30].

Increased genital HPV prevalence has been observed in men and women with immunodeficiencies, regardless of the cause. High HPV prevalence has been consistently observed among HIV-seropositive populations of women and men (see Chapter 16). Some HLA class II polymorphisms have also been shown to influence risk of acquisition and clearance of HPV infections [4].

While there is evidence to suggest that hormonal factors may influence susceptibility to HPV infection [18], associations between hormonal contraceptive use and HPV infection have been inconsistent [35]. Hormonal contraception may increase susceptibility to infection (e.g., by increased ectopy [35]) or it may also be confounded by unmeasured sexual behaviours. Most studies have not reported associations between hormonal contraceptive use and HPV infection, independent of sexual behaviour [35]. Risk of persistent HPV infection seems to be negatively associated with consumption of fruits and vegetables, dietary intake or circulating levels of vitamins C and E, and several carotenoids [4].

Finally, the effect of smoking on HPV acquisition is unclear. Most studies in both men and women have failed to associate smoking with HPV detection, or positive associations were attenuated after controlling for sexual behaviour [18,19]. One study has reported a significant positive association between current smoking and incident HPV infection, even after controlling for measured sexual behaviour variables [13]. While one explanation for this finding is that smoking increases susceptibility to infection, smoking may also be a proxy measure of unmeasured sexual behaviours.

8. Implications for vaccines and future research

There is strong evidence that transmission occurs primarily via sexual activity, most commonly vaginal and anal intercourse, although perinatal and non-sexual transmission does sometimes occur. The common tools for STI prevention, namely the promotion of abstinence or delay in sexual activity, monogamy, condoms and treatment of existing infections, are not all equally applicable to HPV. Delay in coitarche and monogamy should reduce risk, but will not eliminate it, since HPV is highly prevalent and any sexual activity poses a risk. Condoms may provide some protection, but transmission may still occur via unprotected areas of genital skin. Currently, no treatment of existing infections is available to reduce the duration of infectiousness.

The features of transmission dynamics have important implications for future HPV vaccines. With longer duration of infectivity, more frequent formation of sexual partnerships that facilitate exposure between infected and susceptible individuals, and/or higher transmissibility, the extent of vaccine coverage necessary to reduce population HPV prevalence increases. Many of these issues vary across populations, thereby suggesting that the potential vaccine impact will be population-specific, even with equivalent coverage. Furthermore, the nature of transmission dynamics will reduce the impact of vaccines in the face of vaccine failure. This would include scenarios where the vaccine has no effect in some individuals, if the vaccine does not fully eliminate susceptibility, or if there is loss of protective immunity over time.

To further our understanding of HPV transmission dynamics, data on acquisition and persistence among heterosexual men as well as homosexual and bisexual men are urgently needed. The natural history of HPV infection and patterns of viral load, and how this impacts on infectiousness, remains to be understood in both men and women. Frequent and long-term follow-up of women is necessary to determine the causes

of age-related changes in HPV positivity. In particular, longitudinal studies of older women are needed to evaluate whether new partner acquisition is associated with HPV detection at all ages, and patterns of viral load by age. Ideally, studies of HPV acquisition would also determine the HPV status of sexual partners.

Disclosed potential conflicts of interest

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