Chapter 4: Burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease

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Abstract

Human Papillomavirus (HPV)-6 and -11 are the causative agents of ano-genital warts (GWs) and recurrent respiratory papillomatosis (RRP). They are low-risk HPV types that are uncommonly found in malignant lesions. GWs are an extremely prevalent sexually transmitted disease, whereas RRP is a rare disease that can be life threatening and requires multiple surgical procedures. GWs and RRP cause substantial healthcare costs. A quadrivalent HPV-6/11/16/18 vaccine (Merck/SPMSD) has shown essentially 100% protection against GWs in women in early studies. Cost-effectiveness analyses are needed to assess the benefits of the HPV-6/11 virus-like particle (VLP) components of the quadrivalent vaccine in population-based vaccination programmes.

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1. Low-oncogenic-risk HPV types

HPV-6 and -11 were first cloned from genital warts (GWs; also known as ano-genital warts or condylomata acuminata) and laryngeal papillomas in 1981 and 1982, respectively [1]. The use of the terms “low and high oncogenic risk” or “low-risk and high-risk” (LR and HR) HPV became commonplace in the late 1980s. Around that time the Bethesda system for reporting cytology and histology was put forward. This proposes the concepts of low-grade (low-grade squamous intraepithelial lesions, LSIL) and high-grade (high-grade squamous intraepithelial lesions, HSIL) pre-cancer lesions, and such a dual classification system encompassing both HPV virology and disease was subsequently reinforced by phylogenetic analyses. New mucosal HPV types continue to be described and their phylogenetic classification has continued to evolve [1]. Within the genus alpha-papillomavirus, five species are entirely composed of LR viruses (and genotypes as yet categorised as undetermined; see Chapter 1). These are Species 1 (HPV-32 and -42), Species 3 (HPV-61, -62, -72, -81, -83, -84, -86, -87 and -89), Species 4 (HPV-2a, -27 and -57), Species 8 (HPV-7, -40, -43 and -91) and Species 10 (HPV-6, -11, -13, -44, -55 and -74). Nevertheless, an HPV type that is clearly LR by its pathologic associations is found within a species of predominantly HR viruses, namely HPV-70 (Species 7). Thus, phylogenetic characteristics cannot solely predict LR/HR status, and the essential criterion for such classification is the predominant disease association of the HPV type in question. In terms of clinical disease caused by LR viruses, HPV-6/11 overwhelmingly predominate by virtue of the frequency of GWs in the population; recognised clinical lesions caused by other LR types are infrequent. Whereas HPV-6/11 are normally associated with purely benign disease, they can much more rarely be associated with various malignancies, including Buschke–Lowenstein tumours, and occasionally anal, vulval and penile carcinoma (causing around 2.5–5% of these lesions). Recurrent respiratory papillomas (RRP) can also rarely undergo malignant conversion.
2. Genital warts

Condylomata bearing HPV-6 or -11 have identical clinical manifestations and histology [2]. Recent studies have shown that about 100% of GWs are caused by either HPV-6 or -11 but that 20–50% of lesions also contain co-infections with HR HPV types [3,4]. GWs do not usually result in major morbidity or mortality, but cause significant psychological morbidity and very substantial healthcare costs. Occasionally GWs persist for long periods of time and, rarely, such long-standing lesions may progress to malignancy. GWs are highly infectious, with a transmission rate of about 65% within sexual partnerships from an infected to a susceptible sexual partner, and an incubation period of between 3 weeks and 8 months, with the majority developing warts at around 2–3 months [3]. Once GWs have developed, they may show minimal change over time, become more numerous or larger, or regress spontaneously. The majority of placebo-controlled GW therapy trials show low rates of regression (around 5% complete clearance) in the short term, although in one study over 16 weeks 20% of women and 5% of men using placebo completely cleared their warts, and 38% of women and 22% of men using placebo cleared over 50% of their baseline warts [3]. Regressing warts contain significantly more CD4 positive T cells, both within the stroma underlying the lesions and the condylomata themselves, and greater expression of activation markers [3]. There is no report of the rate of spontaneous regression that may occur in the longer term. Following GW clearance with therapy, recurrence is common and is often seen within 3 months in 25% of cases, although rates of up to 67% have been observed [3]. In clinical practice recurrences are often seen at sites of previous lesions, and in these cases HPV infection in stem cells or slow-turnover cells at the site of previous clearance has persisted and then reactivated. The proportion of HPV-6/11 infections that are either completely cleared or persist in a latent form after clinical resolution is unknown, and, indeed, animal models suggest that both outcomes can occur [3].

2.1. Epidemiology of GWs

There are a number of studies that have examined the association of GWs with behavioural variables [5,6]. These show that the occurrence of GWs is strongly linked with sexual behaviour, more weakly associated with cigarette smoking, and also shows non-reproducible/inconsistent associations with oral contraceptive use. Consistent use of condoms decreases the risk of GWs by 60–70% [7]. It is possible that cigarette smoking is associated with more risky sexual behaviour. However, there is a putative biological basis for the link with GWs in that smoking has been shown to be associated with decreased S-100- and CD1a-positive Langerhans’ cells in both normal cervical epithelium and cervical epithelium showing HPV/cervical intraepithelial neoplasia (CIN) [8]. It has been shown that GWs occur in a geographically widespread fashion throughout urban communities, and that peak attack rates occur in girls aged 15–24 years and boys aged 20–29 [9]. Thus, these age groups act as the “core group” in terms of ongoing transmission of HPV-6/11, therefore the overall prevalence of GWs in the community will be sensitive to behavioural changes in these age groups that involve either increased numbers of sexual partners or increased transmissibility of HPV-6/11. HIV infection is associated with an increased prevalence of ano-GWs in both homosexual men (relative risk, RR = 2.7) [10] and women (RR = 3.2 and 2.7 in two separate cohorts) [11]. An increased prevalence of HPV-6/11 in HIV infection was also shown (RR = 5.6 and 3.6) in these women, along with an increased risk of GWs in HIV-infected women with CD4 counts of below 200.

2.2. Genital warts: UK data

Genital warts are a very significant public health problem in the UK. Data compiled by the Health Protection Agency recorded 79,618 new cases of GWs reported from STI clinics in the UK in 2004 [12]. The UK National Survey of Sexual Attitudes and Lifestyles conducted in the year 2000 was a stratified probability population-based survey of 11,161 men and women aged 16–44 years. This found that 3.6% of men and 4.1% of women reported having been diagnosed with GWs, which was the most common reported sexually transmitted infection [13]. The number of reported GWs cases in 2004 is a 32% increase over the 1995 total. Even more remarkably, since 1971, when GWs diagnoses were first recorded, the total number of cases per year in England and Wales has increased 8-fold in men and 11-fold in women [12] (Fig. 1). In the UK there is well-documented evidence of a sustained increase in teenage sexual activity over the past four decades, and a significant ongoing increase in a variety of measures of sexual behaviour over the period between 1990 and 2000 [14]. However, there is no evidence of an increase in the population prevalence of cigarette smoking or oral contraceptive usage in young men and women during the period 1971–2004. Thus, it is reasonable to conclude that changes in sexual behaviour are the primary, and perhaps sole factor
associated with the increasing frequency of GWs over that time.

2.3. Genital warts: data for the USA and the rest of the world

In general, less robust data for the population incidence of GWs are available for the rest of the world compared to the UK. Data are available for the USA from the National Disease and Therapeutic Index, which records initial visits for GWs to private physicians’ offices; 316,000 diagnoses were recorded in 2004. Data are available from 1966 to 2004, and show a substantial increase in numbers of reported cases, although the pattern of increase over time differs from the UK data [15] (Fig. 2). Similar to the UK, there was a steady rise from 1966 to 1987, but then there was a fall in incidence in the mid-1990s, which, in turn, was followed by a further increase, although only now are the numbers of reported cases beginning to match those seen in 1987. There is evidence that the decline in age at first intercourse stabilised in the late 1980s in the USA, unlike in the UK [14], and it is tempting to postulate that this might explain the differences in epidemiology. Although there are few other countries that have formalised national reporting systems for GWs, the data that exist suggest that GWs occur worldwide at similar rates to those observed in the UK and USA. Some examples include national data from New Zealand, population-based data from Copenhagen, Denmark, and antenatal clinic data from Zambia and Tanzania [5,16–18].

2.4. Genital warts: current management options

Genital warts are usually perceived as unsightly and disfiguring by the infected person, and have been shown to be associated with psychological morbidity and feelings of shame [3]. Therefore, many or most people with GWs will seek treatment for their lesions. However, treatment is by no means straightforward: as there are a large variety of therapies in use, they are not always used in a logical and efficient way, and inadequate response and recurrence after apparent clearance are seen very frequently. This is not only a problem for the infected subjects but also a problem for service providers, as large amounts of time and money are diverted to management of GWs, which, in turn, detracts from other healthcare interventions. Current therapies for GW can be classified under broad headings relating to their mechanism of action.

2.4.1. Antiproliferative agents

Papillomavirus replication is intimately linked to the keratinocyte differentiation programme, and requires both cellular factors (human DNA polymerase α and δ, replication protein A, topoisomerase I and II) and viral factors (the HPV origin, and E1 and E2 proteins) [3]. A number of therapies in this category have been described (podophyllin, podophyllotoxin, 5-FU,cidofovir), and current in vitro data suggest that all of them act on cellular factors involved in HPV replication. Recently, true antiviral inhibitors of HPV have been described that inhibit the ATPase and helicase activities of E1 or E2 via the E1–E2 interaction in vitro, but these are not yet in clinical development. Podophyllotoxin is now a widely used first-line self-treatment for GWs, and is available in solution, cream and gel formulations. Cure rates of 70–80% over 4 weeks are seen for first episode GWs, therefore the therapy is cost-effective compared to clinic-based therapy, although subsequent recurrence after clearance remains a problem [19].

2.4.2. Destructive/excision therapies

Clinic-delivered cryotherapy, often over multiple sessions, is another widely used therapy. Animal model data show that the mechanism of action is via epidermal and dermal necrosis, and also through dermal vascular thrombosis of HPV-driven neovascularisation. Trichloroacetic acid is a caustic agent that is useful for small, discrete lesions. A variety of excision methods have been described (scalpel, curette or scissors excision, electrosurgery, laser, photodynamic therapy), but whether these have additional action through vascular or other mechanisms has not been determined. Excision under local anaesthesia is a very useful one-stop therapy, particularly for persistent lesions.

2.4.3. Immunomodulators/therapeutic vaccines

Although a variety of immunomodulators have been described as therapy for GWs (e.g. interferons, contact hypersensitivity), only Imiquimod is nowadays used routinely in clinical practice. Imiquimod acts by stimulation of immune cells to produce a Th1-like response [3]. Imiquimod is a self-treatment used three times a week and produces cure rates of around 77% in women, 40% in circumcised men, and 62% in uncircumcised men over 4–12 weeks [3,20]. It is more expensive than other modalities, but is useful in extensive and recalcitrant GWs. An HPV-6 L2E7 therapeutic vaccine for GWs was recently evaluated, but did not show efficacy [4]. Possible future therapeutic agents include E1/E2 DNA vaccines, which have shown promise in animal models [21].
Full details of all these therapies have recently been reviewed [3]. There are also US [22], UK [23] and European [24] treatment guidelines, and the latter contain a useful algorithm for determining management in individual cases that closely corresponds to current practice (Fig. 3).

3. HPV-6/11 as a cause of cervical neoplasia

HPV-6 and -11 are frequently associated with LSIL. A recent meta-analysis of 55 studies reported HPV-6 to be present in 8.1% of HPV-positive LSIL cases and HPV-11 in 3.2% of cases [25]. However, it remains unclear in what proportion of these HPV-6/11-positive LSIL cases there is concomitant co-infection with a HR type, and whether such HR co-infections would be “minority passenger” infections as described in GWs, or represent true multiple-morphology cervical lesions.

4. Recurrent respiratory papillomatosis

Recurrent respiratory papillomatosis, also known as laryngeal papillomatosis, is a rare condition characterised by the recurrent growth of benign papillomas in the respiratory tract. The papillomas occur anywhere in the respiratory tract but most commonly in the larynx. The disease may have onset in childhood (juvenile onset RRP, JORRP), with most of the cases occurring in the first 4 years of life [26], or in adult life (adult onset RRP, AORRP) with a small peak at 21–30 years. Hoarseness of voice and respiratory obstruction are the most common presenting symptoms. Although the papillomas are benign, their recurrent nature and location in the airways require frequent surgical removal to keep the respiratory tract free of obstruction. The frequency of surgery is highest in children with an early age of onset and declines over time after diagnosis. The number of lifetime surgeries may exceed 100 in children with severe disease [27]. Complications include extra-laryngeal spread into the trachea and bronchi and malignant conversion. The risk of extension of disease into the lower respiratory tract seems to increase in patients who have had tracheotomy. The disease is rarely fatal but it imposes a tremendous burden on the patients and their families. Although the estimates are imprecise, the annual number of new cases of JORRP in the USA may be around 1000 [28]. Incidence rates of JORRP of $3.5 \times 10^6$ per annum were recorded in Denmark (population 5.4 million) during the period of 1974–1999 [29].

HPV types 6 and 11 are the causative agents of almost 100% of JORRP and AORRP. In comparison with HPV-6, HPV-11 is associated with more severe disease [30] and with a greater risk of malignant conversion [31]. In a child with JORRP, the virus is readily recovered from normal mucosal tissue of the respiratory tract [32]. The reservoir for HPV-6 and HPV-11 is the genital tract. In the case of JORRP, the virus is transmitted from the infected genital tract of the mother to the child during birth as the baby passes through the infected birth canal. For AORRP, the infection is very likely not acquired at birth but probably results from sexual or non-sexual contact with an infected lesion. Maternal condyloma during pregnancy is the overwhelming risk factor for JORRP. In a retrospective cohort study in Denmark, maternal condyloma during pregnancy conferred a greater than 200-fold increased risk of JORRP in the child [33]. Even in this high-risk group of mothers with condyloma, the risk of JORRP in the child was low and estimated to be less than 1%. Furthermore, the majority of children who developed JORRP were born to mothers who did not have a history of condyloma during pregnancy; these mothers were presumably infected with the virus sub-clinically. Caesarean delivery may be protective against JORRP but, because of the rarity of the disease, it has not been possible to evaluate this question.
directly. Indirect evidence in mothers of JORRP cases suggests that Caesarean delivery affords some, but not complete, protection against JORRP [28].

The course of RRP varies greatly between affected individuals. In many instances, there are no recurrences after a few surgical procedures [34]. In those with continued recurrent disease, however, surgical removal is still the mainstay of the treatment. For the many adjuvant therapies under evaluation, success is measured by an increase in the time interval between surgeries. Adjuvant treatments in use or under evaluation include oral indole-3-carbinol, intra-lesional mumps vaccine, cidofovir injections, alpha interferon therapy, celecoxib therapy and a potentially therapeutic HSP-E7 vaccine [34].

5. HPV-6/11/16/18 VLP vaccines

The first report of the efficacy of the HPV-6/11 component of a prophylactic HPV-6/11/16/18 virus-like particle (VLP) vaccine was in a phase-2 trial of the Merck quadrivalent HPV-VLP vaccine [35]. A 90% efficacy against persistent infection and disease with HPV-6/11/16/18 was reported, and there were no cases of HPV-6/11 persistent infection or disease in the active vaccine arm, compared to 16 cases in the placebo arm. The first results from the Merck phase-3 trials, referred to as FUTURE I and FUTURE II, were presented at three scientific meetings in late 2005. Both trials used the Merck HPV-6/11/16/18 vaccine, but there was a more intensive follow-up schedule in FUTURE I, and this trial recorded all external genital lesions as well as cervical disease as endpoints. Some of the outcome data concerning CIN, GWs and other external genital lesions from the FUTURE I study at a mean of 20 months follow-up are reproduced in Table 1 [36]. As can be seen, a 100% efficacy against a combined endpoint of GWs, vulval intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VAIN) was reported in the per-protocol (PP) analysis, with 95% efficacy in the modified intention-to-treat (MITT) analysis.

Therefore, the Merck quadrivalent vaccine is fully protective against the GWs typically seen in clinical practice. However, FUTURE I represents a unique (to date) prospective study of some of the aspects of the natural history of GWs. Data will emerge subsequently to answer the question of how frequently incident GWs are caused by genotypes other than HPV-6/11/16/18. Existing data arising from studies of prevalent lesions suggests that this is extremely infrequent, but prospective data will be valuable. An important question not answered by the FUTURE I study, however, is whether such HPV-6/11/16/18 VLP vaccines will prevent GWs in men. To date, we know that the Merck quadrivalent vaccine produces equally high anti-VLP antibody titres in young boys as in young girls aged 11–15 years [37]. Prospective studies of the efficacy of the Merck HPV-6/11/16/18 vaccine against GWs in men are underway, and the results are awaited with anticipation. Another potential use of an HPV-6/11 vaccine is the prevention of JORRP in individual cases where there is a high risk of incident disease. Studies are needed to assess whether vaccination of pregnant women with GWs is effective in prevention, whereas the rationale for vaccination of infants born to women with GWs is stronger. Formal clinical studies in these areas post-licensure are indicated.

6. Costs of HPV-6/11 disease

The principal healthcare costs caused by HPV-6/11 are through GWs and RRP. Recent UK- and USA-specific data on the costs of treatment of GWs in routine clinical practice [38,39] estimated the cost of a single successful episode of treatment of a case of GWs to be £216 ($ 377) in the UK and $ 436 in the USA. Using the UK STI clinic 2004 GWs prevalence data, this equates to around £31 million ($ 54 million) per annum for the UK. One study from the USA estimated the annual direct healthcare costs of GWs as $ 200 million [40]. In a report from the Task Force on RRP, the annual cost for surgical procedures in the USA was estimated to be $ 109 million for JORRP and $ 42 million for AORRP [27]. In countries with cervical screening programmes there will also be significant costs associated with HPV-6/11-associated abnormal cytology and consequent procedures, although estimates of these costs are not available.

| Vaccine          | Placebo          | Efficacy (%) | Confidence Intervals
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<td>GWs, VIN, VAIN</td>
<td>2620</td>
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a Future I; A randomised trial of a quadrivalent HPV vaccine vs. placebo. Vaccine contains HPV-6, -11, -16, -18 VLPs.

b 97.5% CI for per protocol analysis, 95% for modified-intention-to-treat analysis.

c Cases/subject years at risk × 100.

d P<0.001.
7. Aspects of implementation of HPV vaccination programmes: should HPV-6/11 be components of the HPV VLP vaccine?

Different countries across the world will make decisions regarding introduction of particular HPV vaccine programmes in very different ways. Cost-effectiveness modelling studies of various HPV vaccination strategies are underway and the results of these studies as well as public acceptability of potential strategies will inform these decisions. Many unknowns remain, however, including the costs of the vaccines and their efficacy in men. A significant factor both in cost-effective analyses and of programmatic relevance is that the benefits of HPV-6/11 vaccination should be observed within 10 years. If, for example, 11–12-year-olds were vaccinated with sufficient population coverage one would expect the peak age-specific GW burden to be averted within 5–10 years. This would be in contrast to HPV-16/18 vaccination, where declining rates of cervical cancer may take some decades to achieve. Similarly, with respect to JORRP, declines in the incidence of the disease should be expected within 10 years with widespread population coverage of vaccination. Because of the readily observable benefits of HPV-6/11 vaccination, post-vaccination surveillance programmes for GWs and incident JORRP should be implemented as they will be efficient ways of evaluating vaccine effectiveness.

Disclosed potential conflicts of Interest

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