Vaccines for the Prevention of Human Papillomavirus Infections
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**ABSTRACT**

Human papillomavirus (HPV) infection is the known cause of almost all cases of cervical cancer. An understanding of the HPV genome has allowed the development of two prophylactic vaccines capable of protecting against both persistent HPV infection and cervical intraepithelial neoplasia (CIN) with 100% efficacy in fully vaccinated women. The vaccines, manufactured by Merck (Gardasil\(^6\), which was approved by the US FDA in June, 2006) and GlaxoSmithKline (Cervarix\(^4\), which will be submitted for US FDA approval by the end of 2006), both target HPV types 16 and 18, which together account for 70% of cervical cancer. Merck’s vaccine also targets HPV 6 and 11, covering ≥90% of genital warts. These vaccines are highly immunogenic and have an excellent safety profile. HPV vaccines promise to offer an exciting contribution to healthcare and cancer prevention. However, many questions remain concerning who to vaccinate, the duration of protection, cost, public acceptance, and the potential for worldwide distribution.

**Key Words:** human papillomavirus, HPV infection, cervical intraepithelial neoplasia, HPV vaccine

**HPV and Cervical Cancer**

Cervical cancer is the second most common cause of death from cancer, after breast cancer, among women worldwide. The American Cancer Society estimates that over 9,700 women will be diagnosed with cervical cancer in 2006 and approximately 3,700 will die from it. Worldwide >500,000 develop cervical cancer resulting in 290,000 deaths annually. Persistent infection with high-risk HPV genotypes is the main cause of most, if not all, cervical carcinogenesis. HPV infects the stratified squamous epithelia of skin and mucous membranes, potentially causing a range of epithelial proliferative lesions ranging from warts to cancer. About 30–40 of the 100 known genotypes of HPV are sexually transmitted and cause genital infection. While there is no routine screening for HPV infection, it is thought to be the most common sexually transmitted disease in the United States. Approximately 6.2 million new cases of genital HPV occur each year, with an estimated prevalence of about 20%–40% among sexually active young women. The lifetime risk for women is thought to be at least 75% for one or more genital HPV infections.\(^1\)\(^4\)

HPVs are small, nonenveloped viruses whose 8-kb circular genome is comprised of three regions: the long control region (LCR), the early region (E), and the late region (L). The early region consists of genes E1–E8 which encode
nonstructural proteins responsible for transcription, plasmid replication, and transformation. The late region codes for the major (L1) and minor (L2) proteins that form the viral capsid. The development of a prophylactic HPV vaccine stemmed from findings that L1, the major capsid protein, self-assembles into empty capsids, called virus-like particles (VLPs), when it is expressed from eukaryotic vectors such as recombinant vaccinia, baculovirus, and yeast.\(^5,6\) VLPs are free of viral DNA and are noninfectious. Their morphologic similarity to virions provides a source of neutralizing epitope that elicits an antibody response.

### Prophylactic Vaccine Development

Two pharmaceutical companies, Merck and GlaxoSmithKline (GSK) have each developed an L1 VLP vaccine. Merck’s vaccine, Gardasil\(^®,\) is quadrivalent and targets HPV types 16/18/6/11. HPV 16 and 18 account for about 70% of cervical cancer (50% and 20%, respectively)\(^7,8\), while types 6 and 11 account for ≥90% of genital warts. Gardasil\(^®\) received a unanimous 13–0 vote on May 19, 2006 from a US FDA Advisory Committee endorsing the vaccine, and on June 8th it received full US FDA approval for use in women 9–26 years of age. It will be marketed as a prevention of cervical cancer, precancerous genital lesions, and genital warts due to HPV types 6, 11, 16, and 18. The Centers for Disease Control’s (CDC) Advisory Committee on Immunization Practices (ACIP) will draft recommendations and schedules for the administration of the vaccine in the US. Merck Executive Director of Medical Affairs, Rick Haupt, said the company is prepared to make Gardasil\(^®\) available “within weeks” of the FDA’s decision.\(^7\)

The catalog price for Gardasil\(^®\) is $120 for each of the three doses, a possible impediment to worldwide vaccination campaigns.

GlaxoSmithKline’s vaccine, Cervarix\(^®,\) is a bivalent HPV 16/18 vaccine that is currently in Phase III clinical trials. GSK submitted a marketing application for Cervarix\(^®\) in March of this year to the European Agency for the Evaluation of Medicinal Products (EMEA). Filings will follow in Australia, parts of Asia, and Latin America, with submission to the US FDA anticipated by the end of 2006.

### Safety, Efficacy, and Duration of Protection

Clinical trials by both companies have been randomized, double-blinded, placebo-controlled, multicenter trials conducted in HPV-negative young women ranging from 15–25 years of age. The safety profile is excellent, with the most common side-effect being brief soreness at the injection site.

To evaluate vaccine efficacy, the end points used were a reduction in the incidence of moderate (CIN2) and high-grade (CIN3) dysplasia. In Merck’s FUTURE II trial, more than 12,167 women ages 16–23 were randomly assigned to receive three doses of Gardasil\(^®\) or placebo over 6 months. Women were followed for an average of 2 years after enrollment, and no one in the Gardasil\(^®\) group developed persistent infection with HPV strains 16 or 18. Gardasil\(^®\) prevented 100% (n=5,301) of cases of CIN 2/3 associated with HPV types 16 and 18 compared with 21 cases in the placebo group (n=5,258). Efficacy was found to be 97% when analyzing a broader group, which included the women who did not receive all of the Gardasil\(^®\) doses or did not follow the study protocol. All participants experienced 100% antibody responses to the HPV strains 6, 11, and 16, and 99.1% developed strain 18 antibodies. Merck has studied the vaccine in males, who also displayed ≥99% antibody response. However, vaccine efficacy in males is difficult to evaluate considering that HPV-related anogenital cancer is very rare in the US, with the exception of HIV-positive homosexuals. In an effort to find out how long the vaccine will be protective, Merck will be following participants of the FUTURE II study for several years.\(^5,9\)

GSK’s Cervarix\(^®\) vaccine has also been shown to be 100% effective in preventing infection with HPV strains 16 and 18. A follow-up study looked at 776 of the 1,113 women aged 15–25 years in the US, Canada, and Brazil enrolled in the 2004 study in which women were given three doses of Cervarix\(^®\) or a placebo. This study reported high levels of antibodies for up to 4.5 years after receiving the vaccine, providing useful information regarding duration of protection.\(^6\)

### Type Specificity and Therapeutic Potential

Cross-protection and therapeutic potential are important issues under continued investigation by both companies. GSK’s Cervarix\(^®\) has been associated with some cross-protection against HPV45 and HPV31, although this protection was less complete than that offered against types 16 and 18.\(^8\) Merck has noted a potential therapeutic benefit of the vaccine for women who already have an HPV infection. In one study a subcohort of women who were HPV16 DNA-positive at enrollment but anti-HPV16-seronegative were found to be less likely to develop subsequent HPV16-related CIN2–3 than those who received placebo injections. A therapeutic vaccine could be used to halt the progression or prevent the recurrence of established disease.
**Implementation Issues**

There are many questions surrounding the implementation of the HPV vaccine. Debate concerning who should be vaccinated will soon be revealed by the CDC, but the public’s recognition, understanding, and acceptability of the vaccine is yet to be determined. Critics are also concerned that women will consider the vaccine a replacement for routine Pap smears; however, vaccinated women will still be vulnerable to other types of HPV, accounting for 30% of all cases of cervical cancer, and will need to continue to be screened. The challenge remains for feasible distribution in developing countries, where 80% of cervical cancers occur. Despite these concerns, the potential for a vaccine that protects against HPV-related cervical cancer is a tremendous advancement in public health. It will have a powerful impact on healthcare costs, the future of cancer prevention, and the overall well-being of women worldwide.

**References**


Novel Flaps for Lip Reconstruction

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ABSTRACT
Reconstruction of the lips requires careful attention to aesthetic and functional goals. We describe our approach to lip repair and present novel methods to maintain symmetry and function, and optimize cosmetic results.

Key Words: Lip repair, vermillion

Reconstruction of the lips is a challenging task for the dermatologic surgeon. From a functional standpoint, the lips serve a critical role in speech, eating, and demonstrative emotions. Aesthetically, there are numerous subtle, but very important, variations in contour, color, and texture. With no underlying bony or cartilaginous framework, they are extremely sensitive to distortion. The lips are a focus of facial beauty, and their central location does not permit concealment of unsightly scars or asymmetrical results.

As with most repairs on the face, repair along relaxed skin tension lines and within cosmetic subunits optimizes cosmetic outcome. Cosmetic subunits of the upper lip include two lateral segments and one central or philtral unit. While the lower lip is a single unit, it is helpful to consider whether the defect is more central or lateral. Another cosmetic subunit to consider is the vermillion, and defects involving only the vermillion should be reconstructed within that cosmetic subunit whenever possible.

Categorization into partial or full-thickness defects also identifies ideal reconstructive methods. Defects that involve a full-thickness portion of the lip (i.e., skin, muscle, and mucosa) require full-thickness repair. The size of the surgical defect also impacts alternatives for repair. The dermatologic surgeon should strive to keep incision lines within or parallel to relaxed skin tension lines and place incisions at the boundaries between cosmetic units or subunits whenever possible.

We will describe our approach to reconstruction of the lips and some novel methods of repair. As mentioned, the first step is to consider the location of the defect and what tissue has been lost.

Partial Thickness Surgical Defects

Vermillion
Small superficial defects limited to the vermillion may be allowed to heal by secondary intention with good results; however, larger or deeper defects or wounds near the vermillion border risk distortion if allowed to heal in this manner. Full-thickness grafts from the labial or buccal mucosa may be used, but often develop trapdoor deformity or mismatch color, texture, and thickness with the surrounding vermillion.

For defects approaching 50% of the vermillion width or greater, a complete vermillionectomy and mucosal advancement flap repair may be performed (Figures 1A–C). By removing the entire vermillion the risk of subsequent malignancy from adjacent actinic cheilitis is lessened, and the uniform repair and scarring help maintain symmetry of the lip. Like other repairs of the perioral area, mucosal advancement flaps should be marked out prior to the injection of local anesthesia. Mucosal advancement flaps are undermined below the level of the minor salivary glands, but above the orbicularis muscle. They are dissected back to a point where there is minimal closure tension at the vermillion border, and then closed by the rule of halves with absorbable and nonabsorbable sutures. While useful for large defects, mucosal advancement flaps have potential disadvantages. Advancement of mucosa to reconstruct vermillion often decreases the anterior-posterior dimension of the lip and can give a more rounded and reddish color to the reconstructed vermillion. Patients also frequently complain of persistent hypoesthesia, and men may note redirection of beard hair upward, causing irritation to the upper lip.

Another approach to vermillion repair for defects that are <40% of the vermillion width is a bilaterally vermillion rotation flap (Figures 2A–C). This
Figure 1A: Vermillion defect prior to reconstruction.

Figure 1B: Residual dry vermilion is removed (vermillionectomy), and defect repaired with mucosal advancement flap.

Figure 1C: Healed result.

Figure 2A: Medium-size vermilion defect prior to repair.

Figure 2B: Bilateral vermilion rotation flap completed by incision along vermilion border bilaterally to oral commissures with backcuts to permit rotation. Undermine widely deep to salivary glands on the labial mucosa and rotate and secure flaps centrally. Central tricone excised at end.

Figure 2C: Short-term healed result.
Advancement flaps are generally undermined in the tissue distortion if this is not accounted for. Burrow’s triangles or crescents should be taken to minimize this difference and the risk of vermilion distortion. Advancement flaps are generally undermined in the

Cutaneous Lip, Lateral

In many instances, surgical defects in the lateral cutaneous lip may be closed in a simple, linear fashion along the relaxed skin tension lines radiating from the lip. Although M-plasties can be performed to shorten the length and keep the repair from crossing the vermilion border, violating the vermilion border with a linear closure is generally not an aesthetic problem at all, as long as the vermilion border is properly aligned during closure. It is certainly better to violate the border than leave an elliptical closure too short and create a protrusion of tissue or tricone on the lip. Also, remember that elliptical excisions may push tissue at the poles outward. This force on the lip can create a displeasing downward displacement of the lip and should be watched for and avoided during closure. To reduce motion and tension on the wound during healing, a novel trick is to use a small amount of botulinum toxin injected around the perioral area (i.e., place 0.5–1 unit in four sites circumferentially around the vermilion border) during the immediate postoperative period. For defects too large for side-to-side repair, advancement flaps are the most useful repair for partial-thickness defects of the lateral cutaneous lip. The procedure works well for the upper and lower lip due to the abundant reservoir of cheek and jowl tissue. Advancement flaps are generally drawn along the vermilion border with redundant tissue or tricone excised (superiorly on the upper lip and inferiorly on the lower lip) along relaxed skin tension lines radiating from the lip. Since a pure advancement flap has unequal lengths being drawn together (X vs. X + the length of the defect), there is significant potential for tissue distortion if this is not accounted for. Burrow’s triangles or crescents should be taken to minimize this difference and the risk of vermilion distortion. Advancement flaps are generally undermined in the deep subcutaneous fat above the orbicularis muscle. When defects are located in the superior aspect of the upper cutaneous lip, the flap may be drawn, extending along the nasal sill with a crescent taken lateral to the ala and the redundancy taken inferiorly along a relaxed skin tension line radiating from the lip. When designing and executing advancement flaps in the upper lip, care should be taken not to flatten or pull the philtrum crests asymmetrically. Pulling the philtrum too far to one side creates an aesthetically displeasing effect.

Another option for lateral defects of the upper or lower lip is the inferior-based rotation flap (Figure 3A–C). One of the benefits of this repair in this location is that the arc of the incision is kept at the junction between cosmetic units, the melolabial fold on the upper lip and the labiomental crease on the lower lip. One of the basic tenets of reconstructive surgery, keeping an incision line at the junction between cosmetic units or subunits, helps to hide some of the incision lines in this repair.

In a similar fashion the island pedicle flap is useful for defects of the lower lip and the upper lip. This is another example where at least half of the incision from the flap is hidden along the melolabial fold and more along the nasal sill. Great care must be taken to adequately undermine and dissect this flap to assure minimal tension on the mobile vermilion border.

Transposition flaps may be useful for partial thickness defects of the lateral upper or lower lip, especially in instances where an advancement flap does not provide adequate tissue or mobility. One of the advantages of this flap is that part of the incision can be hidden along the melolabial or labiomental folds. However, a distinct disadvantage is the tendency to trapdoor, especially on the more mobile upper lip.

Cutaneous Lip, Medial

Defects in the central area of the lower lip and defects of the upper lip too large for repair with a unilateral procedure can be reconstructed using a bilateral advancement flap (Figures 4A–C). Large amounts of tissue can be recruited from the cheeks for repair, especially in elderly individuals. However, in men the reconstructed upper lip may lack beard hair. The key to successful aesthetic repair is to keep incision lines at cosmetic unit/subunit boundaries and avoid deviation of the lip (eclabium). Undermining in these large random flaps should be carried out in a plane that is superficial to the underlying facial musculature. Avoid trauma to neurovascular structures.

For defects of the philtrum, several options are available. For defects <50% of the philtral width, a
Figure 3A: Partial-thickness defect of lateral upper cutaneous lip.

Figure 3B: Rotation flap completed keeping incision line in melolabial fold and tricone excised in same direction as perioral rhytides.

Figure 3C: Healed result.

Figure 4A: Partial-thickness defect of central upper cutaneous lip.

Figure 4B: Bilateral rotation flap to reconstruct defect. Incision lines are kept at junctions of cosmetic subunits (vermillion inferiorly, alar sill superiorly) and tissue superior to defect is sacrificed to better hide surgical scars.

Figure 4C: Healed result.
complex repair works well. Defects 50%–100% of
the philtral width can be reconstructed using an island pedicle flap, keeping the incisions along the philtral ridges, intersecting to a point at the base, or extending far up the nasal columella if necessary (Figures 5A–C). In this regard, the incision lines are kept at the junction of cosmetic subunits (philtral ridges) and similar vascularized tissue is utilized in the repair. If the defect extends to involve the vermilion, the defects should be repaired separately, using a mucosal advancement flap for the vermilion portion. Another option for defects involving most of the philtrum is to enlarge the defect to the full size of the philtrum and use a full-thickness skin graft. The obvious disadvantage to this option is the difference in skin characteristics, most obvious in men due to the lack of beard hair. In some rare instances, bilateral rhombic transposition flaps may be used to close philtral defects. The secondary defects of the rhombic flaps are taken along the philtral crests on each side of the philtrum and transposed into the defect.

An excellent flap for closure of small defects on or just above the vermilion border involving both the cutaneous lip and vermilion lip is the Cupid’s bow repair as described by Mellette. The flap is drawn similar to a mucosal advancement flap, but incorporates a bow shape, mimicking the patient’s Cupid’s bow in the upper cutaneous lip. A disadvantage of this flap is the upward pull of the vermilion lip. If it is a relatively small defect, the slight pull can give a pleasant increase in upper lip fullness. Unfortunately, there is a limit to the amount of pull that is aesthetically acceptable and the flap is thereby limited to small defects in patients that would like a more full upper lip.

**Full-Thickness Surgical Defects**

Full-thickness surgical defects involve loss of various degrees of cutaneous, muscular, and mucosal lip. Defects up to 25% of the upper lip and one-third of the lower lip can be closed in a wedge-excision fashion. The key to success with this and other full-thickness repairs is careful and complete repair of the mucosa, orbicularis, and skin, and accurate approximation of the vermilion border.

Larger defects necessitate repair with a “lip switch” staged procedure or a repair that moves tissue around the oral commissures. Fortunately, with the growth of Mohs micrographic surgery and its resultant tissue preservation and higher cure rates, the need for these larger repairs is less for the dermatologic surgeon. The original “lip switch” flap was described by Sabatinni, and later by Abbe, as a staged procedure where donor tissue is transposed from the unaffected lip across the oral aperture to the surgical defect, maintaining an
intact vascular pedicle. The transposed flap should approximate one-half the size of the defect and should not exceed one-third of the donor lip width. After vascular ingrowth has developed within the flap from the recipient site, the pedicle is severed and inset. This flap may be used for defects up to 50% of the lip width, but disadvantages include prolonged denervation with incomplete recovery, risk of the trapdoor phenomenon, inconvenience of a transoral pedicle, and the need for two or more procedures. Other alternatives are available that avoid some of the disadvantages of a “lip switch” procedure. The Estlander flap moves tissue around the commissure in a single-stage procedure, though blunting of the oral commissure, necessitating revision surgery, is not uncommon. A circumferential incision permits the Karapandzic flap or Gillie’s flap to move donor tissue around the oral commissures, and is able to repair defects up to two-thirds of the lip. By maintaining an innervated and vascularized pedicle, there is good potential to maintain motor and sensory function. On the downside, there is frequent distortion of the oral commissures, requiring commissuroplasty, and the circumferential incision gives some patients a “clown-like” appearance.

Conclusion
The perioral area is a focal point of both spoken and nonspoken communication and an area of great aesthetic importance. Its mobile nature and varied contours make it a reconstructive challenge. However, as in reconstruction in any area of the face, by understanding the anatomy (superficial and deep), keeping tension off the free margin (the vermillion lip), and placing incision lines in cosmetic unit junctions and/or along relaxed skin tension lines, aesthetically pleasing reconstruction can be consistently achieved. Given its place as a central focus of facial beauty, successful reconstruction of the perioral area is immensely rewarding.

References
### Antiviral Agent

**Zoster Vaccine Live**  
Zostavax®  
*Merck*

The US FDA approved this new vaccine in May 2006 for the prevention of herpes zoster (shingles) in individuals 60 years of age and older. It is given as a single dose by injection.

### Rosacea

**Doxycycline, 40mg**  
Oracea®  
*CollaGenex Pharmaceuticals*

The US FDA approved this product in May 2006 for the treatment of inflammatory lesions (papules and pustules) of rosacea in adult patients.

### Antiaging Agent

**Hyaluronic Acid Dermal Filler**  
Juvéderm® Gel  
*Allergan*

The US FDA approved this dermal filler in June 2005 for the treatment of facial wrinkles and folds. Juvéderm® should only be administered by a trained and qualified health care provider.

### Immunomodulatory Agent

**Mycophenolate Mofetil**  
CellCept®  
*Aspreva Pharmaceuticals/Roche*

The US FDA granted orphan drug designation for this immunosuppressive agent in June 2006 for the treatment of pemphigus vulgaris.

### Oncologic Agent

**Suberoylanilide Hydroxamic Acid (SAHA)**  
Zolinza®  
*Merck*

The US FDA accepted a New Drug Application for this investigational histone deacetylase inhibitor in June 2006 for the treatment of advanced cutaneous T-cell lymphoma. This NDA has been granted priority review.

### Vaccine

**Quadrivalent Human Papillomavirus Recombinant Vaccine**  
Gardasil®  
*Merck*

The US FDA approved this vaccine in June 2006 for the prevention of cervical cancer and vulvar and vaginal precancers caused by HPV types 16 and 18 and to prevent low-grade and precancerous lesions and genital warts caused by HPV types 6, 11, 16 and 18.

### TNF-blocking Agent

**Adalimumab**  
Humira®  
*Abbott*

The European Medicines Agency approved this tumor necrosis factor (TNF)-blocking agent in June 2006 for the treatment of severe ankylosing spondylitis.

### Drug News

**Antipsoriatic Agent**

Twelve-week data were recently published* from a multinational, randomized, double-blind, placebo-controlled, parallel-group clinical study designed to evaluate the safety and efficacy of efalizumab (Raptiva®) 1.0mg/kg once weekly when compared with placebo. Investigators found that efalizumab produced significant clinical improvements and was generally well tolerated among patients with moderate-to-severe plaque psoriasis.


**Treatment Resistance**

According to a recent study of Welsh school children published in the *Archives of Disease in Childhood*, four out of five head lice are resistant to common treatments containing pyrethroids (permethrin and phenothrin). Whether this pattern is reflected elsewhere will depend on how head lice treatments are used. However, they suggest that where resistance develops, a newer silicone-based lotion might be a suitable alternative.