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Paradigm shifting vaccines: prophylactic vaccines against latent varicella-zoster virus infection and against HPV-associated cancer

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Abstract

We compare the design, mechanism of action, and clinical efficacy of two recently licensed paradigm shifting vaccines. Zostavax is the first vaccine licensed to prevent disease in patients already infected with a pathogen, and is contrasted with Gardasil and Cervarix, the first vaccines designed and licensed specifically to prevent cancers.

Human papillomavirus (HPV) vaccines (see Table 1)

Pathophysiology and epidemiology of HPV infection

Papillomaviruses are a family of largely species-specific dsDNA viruses that productively infect keratinocytes. Infection is non-lytic. Most HPV genotypes replicate without producing evident host pathology or inducing a measurable immune response. The majority of humans are chronically infected with multiple genotypes of these “non-pathogenic” HPVs [1]. Some HPV genotypes, including HPV 1 and 2, induce hyper-proliferative lesions of keratinizing skin, commonly known as warts. These infections are almost universal in childhood. Other HPV genotypes, including HPV 6 and 11, induce warty lesions on mucosal surfaces, which are extremely common in young adults and are transmitted through sexual contact.

A limited subset of about 10 so-called “high risk” HPVs, transmitted through sexual contact, can initiate warty or non-warty epithelial dysplastic changes at mucosal surfaces, particularly in the genital tract [2]. Evidence of current or past infection with these HPV genotypes is found in the majority of sexually active individuals, though only 1–2% of infections become chronic and can then induce, over many years, invasive squamous or adenosquamous cancer of genital epithelia, particularly the cervix [3]. Nearly 100% of cervical cancers, and a substantial proportion of other anogenital squamous cancers, are associated with high risk HPV infections. HPV 16 and HPV 18 are the genotypes most commonly associated with anogenital cancer, accounting for about 70% of cervical squamous cancers [4]. HPV 18 is associated more commonly with adeno- and adenosquamous cervical cancer. Cancers associated with infection with high risk HPV are

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found at other sites, especially tonsillar crypt epithelium. Some HPVs of skin, notably HPV 5, 8, and 38 are associated with development of squamous cell skin cancer in patients with chronically impaired immune responses [5], and proliferative lesions induced by mucosal “low risk” HPV genotypes 6 and 11 are much larger and last longer in immunosuppressed patients [6]. These observations demonstrate that host immunity is necessary to control HPV infection.

Papillomaviruses encode two structural proteins, L1 and L2, and up to 8 non-structural proteins (Figure 1). Oncogenesis associated with high risk HPV infection occurs in association with high level expression of two non-structural proteins, E6 and E7, which together delay differentiation and promote proliferation of epithelial cells. E7 binds to and inhibits the function of pocket proteins including Rb, permitting cells to cycle and proliferate when no longer in contact with the epithelial basement membrane, while E6 enables replication of cells with damaged DNA by promoting ubiquitination and destruction of p53 [7]. Both proteins have other actions which destabilize host cell DNA. These proteins have similar actions in high and low risk HPV infections. Together, the E6 and E7 proteins of HPV 16, expressed as transgenes in keratinocytes are sufficient to induce epithelial tumours in mouse skin [8]. The reason why only some HPV infections persist, and why persisting high risk HPV infections can transform cells, remains uncertain. While immune suppression increases the risk of HPV persistence and malignant transformation of high risk HPV infections, the majority of patients with persistent HPV infection and cervical cancer have apparently normal innate, humoral, and cellular adaptive immune systems, though there is a suggestion that the adaptive cellular immune responses to HPV E2, E6 and/or E7 non-structural proteins may be impaired in patients with persisting HPV infection [9]. Malignant transformation is generally associated with integration of the HPV genome into cellular DNA and high level expression of E6 and E7 proteins. Little immune response to HPV nonstructural proteins is detected, except in invasive cancer [10]. Immune response to the major L1 capsid protein, which is the basis of current vaccines to protect against HPV infection, is weak and not always observed during or after natural infection [11, 12].

Steps leading to development of HPV vaccines

HPVs are encapsidated in an icosahedral coat comprised of 360 copies of the L1 capsid protein, arranged as 72 pentamers, and a smaller but uncertain number of copies of the minor L2 protein [13]. Immune responses to the HPV capsid following natural infection are directed to conformational epitopes on the external surface of the virus [14, 15]. These responses are weak and are apparently not fully protective against further infection with the same virus genotype [16]. There are sequence differences in the L1 protein between HPV genotypes, which result in type-specific epitope presentation on the external face of the virus, such that genotype cross-reactive antibodies are seen only between closely related HPV genotypes.

The association of high risk HPVs with cervical cancer was first proposed by Prof Harald zur Hausen in the early 1980s [17] who found that HPV genetic material was integrated within 70% of cervical cancers. Infections with the high risk HPV genotypes was initially thought to be rare, though it has subsequently been established that high risk HPV infection is common after the onset of sexual activity, although persistence and progression of such infection to cancer is rare [18]. This, together with the association of a limited number of HPV genotypes with cervical cancer, led to interest in development of prophylactic vaccination. A major obstacle was the inability to replicate HPVs efficiently in vitro to produce a vaccine from live virus by heat or chemical inactivation. A non-live vaccine was considered preferable, since the association of HPV infection with malignancy raised concerns about the safety of any vaccine produced from a live attenuated virus. Fortunately, the then nascent technologies for expression of viral protein from recombinant DNA could

be used to produce recombinant proteins from the HPV 16 genome. HPV L1 protein, when expressed in eukaryotic cells efficiently assembled into viral capsomers and empty capsids. To achieve this, the protein had to be expressed from the second potential translational start site in the L1 open reading frame [19, 20], and a L1 gene without a mutation present in the genome originally cloned from a cervical cancer was required [21]. Viral capsomer material produced in this manner, the basis of the currently available HPV vaccines, was demonstrated in early phase clinical trials to generate high titres of HPV-specific antibody in blood [22] and vaginal secretions [23], and to neutralize HPV virions in a number of in vitro assays. Antibody alone is sufficient for viral neutralization in vivo, as passive transfer of capsid-specific antibody is sufficient to protect dogs against challenge with canine oral PV [24]. Antibody-mediated viral neutralization in vivo may involve blockade of binding of PV capsids to receptors on cells or the epithelial basement membrane, and may also prevent furin-mediated proteolytic cleavage of the L2 capsid protein, necessary for infectivity [25]. A wide range of expression systems have been used, though yeast-based [26] and insect cell-based [21] systems are the most efficient and provide the basis of the current commercial vaccines. Addition of the L2 protein was initially thought desirable to enhance particle production [19] and to improve immunogenicity, but particle production with L1 alone is quite efficient in most systems, and L2 within capsids does not contribute measurably to the virus neutralizing antibody response to capsid-based vaccines [27].

Pivotal trials

Several phase II trials [28–30] of HPV virus like particle vaccines were conducted in the early 2000s, and demonstrated protection against high risk HPV infection. These were based on HPV 16 and HPV 18 empty capsids (virus like particles), adjuvanted with alum, with or without addition of toll-like receptor (TLR 4) agonist monophosphoryl lipid A. Subsequent pivotal phase III trials [31–34], which involved over 20,000 women, documented the ability of the vaccines to protect women naïve to high risk HPV 16 and HPV 18 from development of premalignant genital lesions induced by persisting virus in the cervix, vulva and anus, termed intraepithelial neoplasia (CIN, VIN, AIN) [35]. Efficacy data has been extended to show protection of older women naïve to HPV [36], and to show some cross protection against high risk genotypes not incorporated in the vaccines [37]. Remarkably, studies showed near 100% protection over as long as 8 years against infection and development of CIN [38]. Protection against new infection has also been demonstrated in women without current infection, but with serological evidence of past infection [16]. However, there has been no evidence of protection against development of CIN for the many women recruited to the pivotal trials with DNA evidence of anogenital HPV infection at the time of vaccination, even if no clinical disease was present at the time of immunization [39].

Immunogenicity as a surrogate for vaccine efficacy

High titres of neutralizing antibody to viral capsid were observed after three doses of vaccine in all women immunized in the pivotal trials. Antibody titres declined more than 90% over the first two years after vaccination, and then plateaued, but could be rapidly boosted by repeat immunization, demonstrating effective B cell memory responses [40]. After immunization against HPV 18, up to 50% of subjects had lost measurable antibody after 3 years, although vaccine efficacy was maintained during a 5 years follow-up period [41]. Thus, currently, no level or specificity of HPV antibody conveyed through natural infection or vaccination is validated as a surrogate measure of protection against subsequent virus challenge.

Indications and safety profile

Given the need to immunize prior to exposure to high-risk HPVs, and the worldwide global incidence of cervical cancer, with over 250, 000 annual deaths (Fig 2), the two licensed

HPV vaccines are recommended for use in 12–14 year old girls globally. The vaccines are licensed in most countries, including developing countries, for females between the ages of 9 and 45 years. In many countries the recommendations include young males. Population-based programs for immunization have been introduced in the United States, Australia, Canada, the United Kingdom, many European countries, Bhutan, and Malaysia. Vaccine safety is excellent, with only local reactogenicity as a common side effect, and very rare allergic reactions reported (about 1 per 10⁶ immunized subjects) [42, 43].

Other issues and future considerations

One of the two commercially available vaccines also incorporates virus like particles of HPV 6 and 11, which together are responsible for 95% of genital warts. This vaccine was protective against genital wart disease in clinical trials [35]. Field efficacy in Australia, where between 2006 and 2008 approximately 80% of women between the ages of 12 and 26 received HPV vaccine, was demonstrated by a decline of more than 70% in the incidence of genital warts in young women, but not in men or in older women [44].

Some unanswered questions for the HPV vaccines are

- The duration of protection, which currently is under investigation [45], particularly in Finland and Australia, through linkage of cervical cytology and cancer registry data with a vaccination registry.
- The utility of immunizing both males and females to protect against other HPV-associated cancers, including genital, anal, and tonsillar cancers, for which protective efficacy could reasonably be predicted from the association of a high proportion of these cancers with HPV 16. Establishing efficacy through randomized clinical trials is unlikely because of the cost and size.
- The impact of mass vaccination on design of screening programs for early detection of premalignant cervical disease; this will become an important feature of cost-benefit analyses in some countries.
- Development of second generation vaccines incorporating up to seven more high risk HPV genotypes, which could give >95% protection against cervical cancer, and are currently in early phase clinical trial. It will be necessary to establish that the inclusion of multiple extra HPV genotypes will not impair induction of protection against the genotypes already incorporated in available vaccines [46]. Additional cost may also be an issue.
- The cost of implementing global immunization.
- The efficacy for prevention of reinfection and disease recurrence after surgical treatment of HPV-associated CIN, as the risk of malignancy arising from persistent HPV infection is partly genetically determined.
- The efficacy of HPV vaccines targeted at skin genotypes for prevention of skin cancer in sun exposed individuals.
- The possibility that two doses of vaccine might be sufficient to induce adequate duration of full protection; this is currently under trial.
- The efficacy of the HPV vaccine if given along with other pediatric vaccines, perhaps as a 2 dose regimen with a single adolescent booster [47]. Feasibility will be determined largely by proven duration of protection.
- Establishment of a surrogate (immunological) marker of current or future protection following vaccination.

- Establishment in humans of the efficacy of single protein vaccines against HPV-associated anogenital disease based on epitopes of the L2 capsid protein that are conserved among all high risk HPV genotypes and are protective in animals. These might provide a broad protection against cervical cancer at lower cost.
- Development of a therapeutic vaccine to prevent progression of persistent high risk HPV infection to cervical cancer.

Herpes zoster (HZ) vaccine (see Table 1)

Pathophysiology and epidemiology of herpes zoster (HZ) infection

HZ is a dermatomal (defines the area of skin innervated by a single sensory nerve) vesicular eruption (Figure 3) that is typically painful prior to, during, and often for long periods after, the skin has healed. Approximately one million cases of HZ occur annually in the United States; 30% of people will get HZ in their lifetime [48, 49]. The lifetime risk may reach 50% for those living to be at least 80 years of age. HZ increases in frequency with increasing age (Figure 4), and causes the greatest morbidity in elderly patients [50]. This morbidity is largely due to the associated pain, which can have a significant effect on productivity of working individuals (P. Singhal et al., unpublished, [51]) and the quality of life of patients with persisting pain [52]. Involvement of the eye, neurologic dysfunction, and secondary bacterial infection are some important complications of HZ [49].

HZ occurs only in patients that previously developed varicella (chickenpox), usually during their childhood many decades earlier. The viremia that naturally occurs during varicella seeds the skin, causing the typical vesicular lesions on an erythematous base [53]. The virus that causes varicella and (ultimately) HZ, varicella-zoster virus [VZV]), is believed, based on clinical observations, to ascend in sensory axons that end at the base of varicella lesions [54]. By this route it reaches sensory neurons in cranial nerve and dorsal root ganglia. VZV may also reach these neurons as a consequence of the viremia. VZV remains latent in sensory neurons for the life of anyone that develops varicella. Approximately 5% of trigeminal ganglion neurons (and only neurons) contain latent VZV [55]. The VZV DNA copy number is usually 5–50 copies per neuron, indicating that VZV replication is blocked shortly after the neuron is infected.

Clinical evidence suggests that latent VZV can reactivate randomly in ganglia at unpredictable intervals [56]. Reactivation most often remains silent, but when the reactivating VZV is able to propagate in a ganglion it can cause a ganglionitis that involves many neurons and non-neuronal cells. This is the cause of the pain in the sensory distribution of the ganglion that precedes the skin eruption of HZ (termed “prodromal” pain). The replicating VZV can then descend in the sensory nerve to cause the characteristic dermatomal skin eruption of HZ. This in turn, is painful because of the progressive skin involvement - in addition to the ongoing ganglionitis. Even after the skin heals, the inflammation and disordered architecture of the involved ganglion can result in persistent pain (called postherpetic neuralgia) that can last for months. Although there is effective antiviral therapy for HZ, this natural history explains why antiviral therapy is almost invariably administered after considerable damage has been done in the sensory ganglion, especially considering the delay imposed by the prodromal stage and the unavoidable delay before the correct diagnosis is made and appropriate therapy administered.

The mechanism that normally maintains latency is not fully understood. However, it is clear that a robust immune response is required to maintain latency and/or to prevent propagation of reactivated VZV in ganglia. This is demonstrated by the high frequency of HZ in patients who are immune suppressed [57]. Clinical observations document that patients with an immune defect limited to antibody synthesis do not have an increase in incidence or severity

of HZ, whereas those that lack T-cell-mediated immunity (eg, HIV, chemotherapy, or organ transplantation) have frequent and morbid HZ. This essential requirement for VZV-specific T-cell-mediated immunity also explains the relationship of age to the incidence of HZ, since VZV-specific T-cell-mediated immunity declines progressively with increasing age, starting about age 35 years, whereas VZV-specific antibody is well maintained into the 8th and 9th decade of life [58, 59].

Steps leading to developing HZ vaccine

It was hypothesized that the immune responses most likely to protect against HZ would be best induced by a live, attenuated VZV vaccine. From 1985 to 1994 a series of experiments demonstrated that such a live vaccine (Oka VZV strain) prepared to prevent varicella could be safely administered to elderly subjects and that this vaccine stimulated the desired type of immune response [60]. Dose-response experiments led to a formulation, ultimately chosen for development as the HZ vaccine, that was 14-times more potent (in terms of viral titre) than the varicella vaccine (MJ Levin et al., 99th Annual Scientific Assembly of the Southern Medical Association, San Antonio, TX, 2005). The HZ vaccine contains no adjuvant. Safety and immunogenicity studies were performed, including administration to elderly subjects with commonly encountered chronic diseases, such as diabetes or chronic obstructive pulmonary disease (K Schmader et al., American Geriatrics Society Annual Scientific Meeting, Chicago, IL, 2006). These early trials suggested that persistence of induced immune responses would be at least 5 years [48]. From 1994–1999 planning for the pivotal trial was undertaken, including validation of assessment tools for a pain endpoint [61]; for the VZV PCR used to establish the HZ diagnosis [62]; and protocol development.

Pivotal trial

The pivotal trial (1999–2004) was a double-blind, placebo-controlled trial involving 38,500 subjects at least 60 years of age (>40% were ≥70 years) [48]. Efficacy against HZ was 51%; efficacy against a composite measure of pain over time was 61%; and efficacy against postherpetic neuralgia (significant pain ≥90 days after onset of skin lesions) was 66.5% (Table 2). The vaccine was safe and persistence of efficacy was determined to be at least 7 years during a long-term follow-up study of a subset of the original cohort (K Schmader et al., In: Programs and Abstracts of the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy and the 46th Annual Infectious Disease Society of America Meeting, Alexandria, VA, 2008). Cases of “breakthrough” HZ that occurred in vaccinees were caused only by latent wild-type VZV and not by vaccine-strain virus, indicating that vaccine strain VZV does not become latent in people that have pre-existing immunity (MN Oxman et al., Shingles Prevention Study Group, unpublished).

As with all vaccines for the elderly, the efficacy of the vaccine was less effective at preventing HZ in the older age strata (Table 2). However, the protection against HZ and postherpetic neuralgia remained considerable into the 9th decade. Moreover, the morbidity of HZ increases with age and people of advanced age are disproportionately more affected by HZ than younger patients. The vaccine attenuates the severity of HZ when it occurs in very old vaccinees, as demonstrated by measuring the effect of HZ on their activities of daily living (ADL; as a measure of quality of life). The HZ vaccine substantially preserved ADL in subjects over 80 years old who developed HZ [52].

The efficacy in subjects at least 60 years old was sufficient for many countries to license the HZ vaccine for individuals 50–59 years of age, arguing that the booster response would be even greater in younger vaccinees. In the United States licensure required an efficacy trial of 22, 400 subjects, which demonstrated an efficacy against HZ of 69.8% (K Schmader et al, submitted for publication).

Immunogenicity as a surrogate for vaccine efficacy

Unlike the HPV prophylactic vaccines, where the capsid-specific antibody response is believed to be the essential component for preventing infection by an exogenous pathogen, perhaps by transudation of antibody to potential sites of infection (sterilizing immunity), the T-cell-mediated immune response to the HZ vaccine is both *necessary* and sufficient for protection, and does so by maintaining the clinical latency of an endogenous pathogen. An immunology substudy of the pivotal trial documented the appearance and persistence of both effector and memory CD4 cells, as well as antibody, after vaccination [63]. As described for the HPV vaccine, immune responses peaked during the first year and then declined by about 50% before reaching a plateau at years 2 and 3 post-vaccination (Figure 5). The persistence of these responses correlated with the persistence of the clinical effect. The magnitude of the T-cell-mediated VZV response was a function of the age of the vaccinee, explaining the effect of age on the efficacy profile of the vaccine (Figure 6). A subsequent study of the immune response to HZ in placebo recipients who developed HZ confirmed the importance of the rapid appearance of VZV-specific T-cell-mediated immunity for preventing severe HZ and postherpetic neuralgia [64]. Although a correlation between protection against HZ and the level of the immune boost was demonstrated, no precise level was determined as a strong surrogate of protection.

Indications and safety profile

HZ is indicated in many developed countries for people ≥ 50 years of age. The addition of the 50–59 year target group is important because many people in this age group are employed and HZ is associated with significant absenteeism, and decreased function while at work (P Singhal et al., unpublished, [51]). Because this is a live, attenuated virus, potential vaccinees must be immune competent. This concern is not applicable to the HPV vaccine. Prior HZ is not a contraindication to vaccine administration, since it is argued that this may prevent second cases of HZ (which are uncommon, but not rare). Potential vaccinees should not have recently received blood products and must not be taking antiviral drugs active against VZV, since these would inhibit replication of the administered live vaccine virus.

Other issues and future considerations

The HZ vaccine is an important addition to the medical care of aging individuals. However, because of immune senescence, this vaccine, as is the case for other vaccines that protect elderly people (influenza; pneumococcal polysaccharide), is not fully protective. The limitations of the HZ vaccine increase with advancing age. This remains an obstacle to the complete prevention of HZ.

The major future questions are:

- The persistence of HZ vaccine efficacy remains uncertain (may well exceed 7 years, but this may be age-specific).
- Studies are underway in previously vaccinated elderly people to see if a booster dose of HZ vaccine might be valuable a decade after receiving a first dose.
- Additional formulations and delivery of HZ vaccine need to be studied to increase its immunogenicity, especially in people of advanced age; potential approaches are the addition of an adjuvant, use of a non-live recombinant vaccine, or intradermal administration of vaccine. The latter would also be of potential value for immunocompromised patients.
- HZ vaccine in most countries requires a freezer, even though a refrigerator-stable formulation exists. This formulation is lacking because making sufficient quantities

of this live vaccine has been problematic, thus limiting supply in general, and preventing wide-spread availability of refrigerator-stable vaccine (which requires more VZV).

- HZ vaccine is expensive and public health systems in many countries have not been adapted to support widespread use of the vaccine. However, cost-benefit analyses for this vaccine in many developed countries support its use, especially in people between 60 and 80 years of age. Such analyses are underway for 50–59 year-old vaccinees.
- HZ vaccine could be important for mildly immune suppressed patients, and for those that will become immune suppressed. This needs to be determined by a series of targeted clinical trials.

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Highlights for the HPV work

- HPV vaccines are effective at preventing HPV related anogenital disease in men and women previously uninfected with HPV
- Evidence of field efficacy of HPV vaccines is now available
- As with most vaccines, induced antibody is of limited efficacy as a surrogate marker for protection

Highlights for the herpes zoster work

- the herpes zoster vaccine is the first to prevent the consequences of reactivation of a latent infection
- this vaccine prevents herpes zoster and often attenuates the disease when prevention fails
- these beneficial effects of vaccination decline significantly at age 80 and greater

Figure 1.

The natural history of papillomavirus infection in the cervix. Infection results in expression of viral non-structural proteins inducing minor alterations to epithelial architecture (CIN 1). Infectious virions in the nucleus of superficial epithelial keratinocytes are associated with nuclear abnormalities (koilocytosis). CIN 1 regresses over months to years in >95% of patients. However, for high risk HPV infections, integration of viral genetic material into cellular DNA can result in overexpression of the E6 and E7 nonstructural proteins, promoting genetic abnormalities. These increase over years to histologically evident nuclear atypia and failure of epithelial cell differentiation (CIN 3). Further genetic changes in keratinocyte DNA in CIN 3 lesions enables clones of cells to acquire invasive properties leading to cancer, in about 30% of patients. Cancer cells generally express only the E6 and E7 non-structural proteins of HPV (Figure adapted from [65]).

Figure 2. Global distribution of cervical cancer, and of HPV vaccine licensure. Upper Panel: Distribution of cervical cancer deaths world wide as reported through Globocan. Lower Panel: Licensure of the bivalent and quadrivalent vaccines by country in 2009.

Figure 3.
Herpes zoster of right 5th cervical ganglion demonstrating dermatomal vesicular eruption

Figure 4. Relationship of herpes zoster incidence to age in different parts of the world From [49,66–72]

Figure 5.
increase in VZV-specific immunity as a function of time after zoster vaccination

1. RCF value = responding cells per 100,000 peripheral blood mononuclear cells (PBMC); ELISPOT counts = spot-forming cells per million PBMC; gpELISA titer = gpELISA units/ml. RCF and ELISPOT are measures of T-cell-mediated immunity; gpELISA measures VZV antibody
2. Error bars indicate 95% confidence intervals of the geometric mean.
3. N is the number of subjects with blood drawn in the age group. (from reference 62); V= vaccines; P=placebo recipients

Figure 6.

Age effect on immune response to zoster vaccination (from reference 62)

1. RCF value = responding cells per 100,000 peripheral blood mononuclear cells (PBMC); ELISPOT counts = spot-forming cells per million PBMC; gpELISA titer = gpELISA units/ml. RCF and ELISPOT are measures of T-cell-mediated immunity; gpELISA measures VZV antibody
2. Error bars indicate 95% confidence intervals of the geometric mean.
3. N is the number of subjects with blood drawn in the age group.

Table 1

Comparison of the HPV and VZV vaccines

	Papillomavirus vaccines	Herpes Zoster vaccine
Vaccine construction	Recombinant capsid proteins ^a of HPV 16, 18 ^b (+ HPV 6, 11 ^c)	Live attenuated varicella-zoster virus
Adjuvant	Proprietary alum +monophosphoryl lipid A ^c	Nil
Delivery schedule	3 doses over 6 months intramuscular	Single dose subcutaneous
Target population	Children aged 10–12 years ^d	Adults age > 50 years
Data supporting licensure	>95% Prevention of anogenital precancer caused by HPV 16, 18 in HPV naïve subjects ^{b,c} >90% protection against anogenital warts ^b	> 50% Reduction in age-specific incidence of herpes zoster; some reduction in severity if herpes zoster occurs
Therapeutic efficacy	No prevention of HPV-related disease in recipients already infected with HPV	Reduction in disease incidence and severity in those with latent infection
Mechanism of action	Capsid-specific neutralizing antibody is sufficient; possibly not necessary	Virus-specific T-cell-mediated immunity is necessary and sufficient
Surrogate measure for current state of protection	None established	None established
Duration of action	>8 years	>7 years
Contraindications	Prior allergic reaction to HPV vaccine; pregnancy (though believed safe)	Immune compromise; prior allergic reaction to components of the VZV vaccine
Cautions	Unable to prevent progression of existing HPV infection to malignancy	Nil

^a as virus-like particles (VLP)^b Gardasil^c Cervarix^d prior to sexual debut; catch-up vaccination for women up to age 26 years

Table 2

Therapeutic efficacy of the VZV therapeutic vaccine in the elderly

Clinical Endpoint	Efficacy (%) ¹			
	All Ages (years)	60–69	70–79	≥80
Herpes Zoster	51	64	41	18
Postherpetic neuralgia	67	66	74	42
Preserving Activity ²	66	70	61	59

¹ Efficacy is the ratio of the observed frequency of each clinical endpoint in vaccine recipients and placebo recipients in a randomized placebo controlled trial (data from reference 48)

² Preserving activity refers to preserving the activity of daily living in spite of herpes zoster as described in reference 51.