Can cervical cancer be eradicated by prophylactic HPV vaccination? 
Challenges to vaccine implementation

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Cervical cancer is the first cancer to be shown to be 100 per cent attributable to a virus; oncogenic human papillomaviruses (HPV), particularly types 16 and 18, collectively worldwide contribute to 70 per cent squamous cell carcinomas, 85 per cent of adenocarcinomas. Cervical cancer is the second commonest cancer of women, yet largely preventable with high-quality, well-organized screening of the appropriate population. Screening programmes are either nonexistent, or function opportunistically in many poorer countries, resulting in high incidence and mortality. Recently developed, prophylactic HPV vaccines against HPV 16, 18, as cervical cancer preventative vaccines, in phase 3 clinical trials have been shown, to be highly efficacious, safe and immunogenic. With the potential for cross protection against related HPV types, estimates for prevention are in the order of 75 to 80 per cent. Thus a further option exists in the battle to reduce these cancers in women. Challenges however include implementing a vaccination programme with wide coverage to the target populations to be a successful public health tool, integration and maintenance of current screening programmes where they are in existence, the need for reduced costs of the current vaccines, long-term immunogenicity (will there be a need for further doses?), appropriate education messages to the general community, governments, as well as the medical profession.

Key words Human papillomavirus - implementation - vaccination

Cervical cancer: burden of disease

Cervical cancer is a common cancer of women in developing countries, being either number one or two in many. Worldwide, the region of Asia Oceania covers a vast and diverse area geographically and ethnically, supporting around 60 per cent of the world’s population and contributing to just over half of the world burden of cervical cancer. (See Fig. 1). India, in particular, has one of the highest reported incidences and mortality for the region. Overall these higher rates reflect lack of widespread screening and treatment facilities, as well as a greater proportion of persistent HPV infections, as indicated by the very high rates of positivity in older women, a likely consequence of the former.

Screening prevention strategies

In contrast, in developed countries, cervical cytology (Pap smear) screening programmes have resulted in significant reductions in incidence of cervical cancer, as well as mortality. However, to be successful, such programmes need to be well organized and this comes at great costs. They also need to be implemented to cover a high proportion of the appropriate target population,
must have adequate cervical cytology quality control, incorporate quality assurance programmes, as well as be able to offer appropriate treatment for those found to have precancerous lesions or invasive cancer.

In the Asia Pacific region where cervical cytology programmes have been proposed and implemented, successful programmes are rather limited. For example, in Australia and New Zealand, where long-standing and highly effective cytology programmes have been implemented for several decades, incidence and mortality rates have declined significantly\(^2\). In Australia, in 2003, the age standardized incidence of cervical cancer was 7.0/100,000 and mortality 2.2/100,000 women\(^3\). It is noteworthy however, that notwithstanding the success of the National Cervical Screening Programme in the general population, indigenous women were over four times more likely to die of cervical cancer than non-indigenous women in 2001-2004; cervical cancer incidence was 4-5 fold higher in indigenous women\(^4\). Whilst overall for the Australian population, the estimated lifetime screening participation rate is 88 per cent (62% for over two years, 73% for over three years), the increased rates in indigenous women reflects poorer access to cervical cytology screening programmes\(^5\).

In contrast, within the Asia-Pacific region, Thailand and the Philippines despite having cervical cytology programmes for decades, significant reductions in incidence and mortality have not emanated\(^5\). This perhaps reflects the lack of organised programmes reaching a high proportion of the appropriate population. As programmes become more sophisticated, as seen in the more affluent and urbanised states of Singapore, Hong Kong, Taiwan, where higher compliance with opportunistic screening occurs, cervical cancer incidence and mortality rates are declining in all three areas, although they still remain relatively high in Taiwan\(^6\). Assisting further with this decline in these States too is the fact that programmes have more recently become nationally based\(^6\).

**Human papillomavirus (HPV): aetiological agent of cervical cancer**

Molecular epidemiological studies have conclusively established the causal association between high-risk HPV genotypes and cervical cancer, with relative risks in the hundreds fold and being far greater than the association between cigarette smoking and lung cancer\(^7\). In fact cervical cancer is the first cancer to be 100 per cent attributable to an infection. Papillomaviruses are a very heterogeneous group of viruses, and now recognized as a separate family of their own\(^8\). They are widely distributed in nature, infecting not only humans but other higher vertebrates such as dogs, horses, and cattle. In general, they are highly species-specific, with each animal species having its own papillomavirus [for example, bovine papillomaviruses (BPV) of cattle, and human papillomaviruses (HPV) of man], with no crossing of the species barriers.

**HPV virology**

HPVs are small (~55 nm), non-enveloped viruses with a double-stranded circular DNA genome wrapped into a protein shell of icosahedral symmetry (Fig. 2).
Sequence analysis of cloned HPVs show they are highly conserved, with the genome not prone to mutation, in contrast to some other viruses, such as human immunodeficiency virus (HIV). The 8 kilobase circular genome of HPV is made up of early (E) (necessary for replication of the viral DNA, transcription of the non-structural early proteins E1, E2, E4, E5, E6 and E7 and assembly of newly produced viral particles) and 2 late (L) genes (L1 and L2), which encode for the proteins making up the major viral capsid. It is to conformational epitopes on the L1 protein displayed on the outer surface of the intact virion, that much of the natural host immune response is directed. Moreover, the L1 protein, when expressed via recombinant yeast or viral vectors, folds and self-assembles into empty capsids [or viral-like particles (VLPs)], which antigenically and morphologically resemble wild virus, forming the basis of current prophylactic vaccine candidates.

Over 200 papillomaviruses are now recognized, with over a hundred cloned to date. Of the large number of HPVs, there is tropism of infection for different tissues by various genotypes; i.e., skin types (e.g., HPV 1-4, 10, 26-29, 37, 38, 46, 47, 49, 50, 57), and genital types (e.g., HPV 6, 11, 16, 18, various 30s, 40s, 50s, 60s, 70s). Around 40 genotypes are able to infect the genital tract. Of these, some have oncogenic potential (established high risk include 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82; with probable high risk 26, 53, 66) whilst others are low risk (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, CP6108). Of the high risk group, HPV genotypes 16 and 18 contribute the greatest, with these now known formally as human carcinogenic agents. HPV 16 and 18 contribute to around 70 per cent of cervical squamous cell carcinomas, and in the order of 80 to 85 per cent of adenocarcinomas, those more difficult to detect on cytological screening.

Phylogenetically, HPVs are within the alpha genus. The two common oncogenic types 16 and 18 are quite distinct, being in separate species of 9 and 7 respectively, whereas types 6 and 11 are closely related and in the same species.

**HPV infection**

HPV specifically infect epithelial cells of the skin or mucosa. Either through minor abrasions of the squamous epithelium or through the single cell junction of the squamocolumnar junction of the transformation zone at the cervix, viral particles of genital HPVs infect the basal cellular layers. It is here that a low copy number of the viral genome is maintained allowing for latency in a proportion of cases. In contrast the complete and complex life cycle of HPV only occurs in the suprabasal compartment where the keratinocytes lose their ability to replicate, but initiate terminal differentiation. As the epithelium is shed, so the full virions are ready to infect the next host (Fig. 3).

It is because of this complex interaction with the differentiating keratinocyte, that HPV cannot be propagated in vitro in cell lines, in contrast to other viruses that are readily cultured for diagnostic purposes. However by various molecular hybridization assays, HPV nucleic acid can be detected as DNA or RNA in tissues or clinical samples.

**HPV immunology**

With HPV infection of squamous epithelium, it is noteworthy that there is no associated viraemia, nor inflammatory response with keratinocyte death: it is as if the virus hides from the immune system. Innate immunity (nonspecific, not antigen specific, consisting of responses from phagocytes, macrophages, monocytes, cytokines, complement and epithelial barriers, none of which results in immune memory) is responsible for clearing some of the transient infections. In addition, systemic adaptive immune responses also occur, end to these are antigen-specific and show immune memory. There is an humoral response with the...
production of type-specific antibodies, but these are slow to develop, weak in response, and seen in only around 60 per cent of those found to be HPV DNA positive in the genital tract. These antibodies are neutralizing to extracellular virus (to L1 epitopes), preventing an individual from further re-infection due to the particular genotype. This has been shown by following infected individuals longitudinally and performing variant analysis on new HPV DNA: invariably the same type does not cause reinfection. Although there is this natural protection, antibody titres may wane beyond the level of detection of current assays. Whether such an individual is still protected or susceptible to reinfection is not clear. It should be realized too that the virus can remain within basal epithelial cells at non-detectable levels, in a latent state for many years and then become reactivated, particularly with immune senescence or immune-suppression. The extent to which this occurs is unknown, but may well explain exacerbation of disease particularly with defective cell mediated immunity or immune senescence, yet with no reinfection or new exposure.

**HPV: natural infection and epidemiology**

Of viral sexually transmitted infections (STIs), genital genotypes of HPV are the commonest. They are readily transmissible, with estimates of HPV prevalence among women ranging from 2 to 44 per cent, depending on age and numbers of partners, with a lifetime risk of infection being 50-80 per cent. As the predominant route of transmission for genital HPVs is sexual, it is not surprising that just as other STIs, the prevalence of HPV infection is very common in those less than 25 yr of age, declining after the 30s generally. Of note, the majority of young women clear infection within one to two years, without ever having overt clinical disease. In those communities with no screening this pattern varies however, with some showing a flat prevalence curve with increasing age.

In a small proportion of women (~5%), persistent (or chronic) infection occurs. Although the determinants of this are not well understood, they are likely to be genetic factors and/or environmental. Recognized cofactors are as those for cervical cancer: cigarette smoking, high parity, long-term use oral contraceptive pill, other sexually transmitted infections such as *Chlamydia trachomatis*, genital herpes infection. Persistence is defined as detection of the same HPV genotype on a least two separate occasions. The actual timing of the interval has not been defined, but for the purpose of disease risk it will likely be in the order of 6-12 months, or more.

A small proportion of infection is also transmitted by other routes such as mother to child during delivery.

**HPV: clinical manifestations**

The clinical spectrum of disease ranges from asymptomatic infection, to benign warts otherwise known as condylomata acuminate, (primarily caused by low risk HPV genotypes 6 and 11) to anogenital malignancy (with over 70% of cervical cancers caused by the high risk genotypes 16 and 18). For cervical cancer, oncogenic HPVs are the necessary causative agent. These viruses, particularly HPV 16 are also responsible for squamous HPV related vulvar cancers in young women, as well as for the respective precursor lesion, vulvar intraepithelial neoplasia (VIN grade 2/3). Similarly, a proportion of vaginal (around 50%), anal cancer (around 90%), penile (45 to 50%) and oropharyngeal cancers (20%) are due to these oncogenic viruses. In addition there is recurrent respiratory laryngeal papillomatosis due to HPV 6 and 11. This is a rare disease occurring at an incidence of 0.3-1.0/100 000, with both paediatric as well as adult onset types, and with significant morbidity and mortality.

**HPV vaccines: Phase 3 clinical trials: summary of efficacy, immunogenicity, safety data**

Results of two large, phase three, randomized, double blinded, controlled trials of prophylactic HPV vaccines conducted over many countries worldwide have been published and form the basis for the recently licensed HPV vaccines. These represent a quadrivalent L1 VLP (HPV types 6, 11, 16, and 18) vaccine under the names of Gardasil (Merck and Co., Inc.) and a bivalent L1 VLP (HPV types 16 and 18) vaccine under the name of Cervarix (GlaxoSmithKline).

1) **quadrivalent vaccine efficacy**

This vaccine contains L1 VLPs of HPV types 6, 11, 16, and 18 expressed in *Saccharomyces cerevisiae*. Each 0.5-mL dose contains 20 µg HPV 6 L1 protein, 40 µg HPV 11 L1 protein, 40 µg HPV 16 L1 protein, and 20 µg HPV 18 L1 protein, and 225 µg aluminum hydroxyphosphate sulfate a proprietary adjuvant. The quadrivalent HPV vaccine is administered intramuscularly at months 0, 2, and 6.

For the quadrivalent vaccine, FUTURE I and FUTURE II studies examined the efficacy,
immunogenicity, and safety of the quadrivalent HPV vaccine in women 15 to 26 yr of age, for an average of 3 yr\textsuperscript{24,25}. In the per-protocol analysis of FUTURE I, the quadrivalent HPV vaccine was 100 per cent effective (95\% confidence interval [CI], 94-100; 0 versus 65 cases for vaccine versus placebo, respectively) in preventing CIN 1 to 3 or adenocarcinoma in situ (AIS) associated with vaccine-related HPV types, in those naïve to the relevant HPV type. The vaccine was also 100 per cent effective (95\% CI, 94-100; 0 cases in the vaccine group versus 60 cases in the placebo group) in preventing vaccine-type-related genital warts, VIN/VaIN, and perianal intraepithelial lesions\textsuperscript{24}.

An analysis of the intention-to-treat population, which included women with prevalent infection or disease caused by vaccine-type and nonvaccine-type HPVs, showed a reduction in the incidence of cervical lesions and vulvar or vaginal perianal lesions regardless of the causal HPV type by 20 per cent (95\% CI, 8-31) and 34 per cent (95\% CI, 15-49), respectively\textsuperscript{24}. Vaccine efficacy was also estimated in an unrestricted susceptible population which included all women who were negative on PCR analysis and serological testing for the relevant vaccine-type HPV at enrolment, thus representing an analysis of prophylactic efficacy under variable vaccine dose intervals. Efficacy was found to be 95 per cent for combined all grades of anogenital or vaginal lesions (four cases in the vaccine group versus 81 in the placebo group), six to 98 per cent for the combined all grades of cervical lesions (two cases versus 89 respectively)\textsuperscript{24}. For high-grade vulvar or vaginal lesions (one versus 11 cases respectively) the efficacy was 91 per cent, and for AIS (zero versus six cases respectively) was 100 per cent\textsuperscript{24}.

In FUTURE II, efficacy was 98 per cent (95.89\% CI, 86-100) against high-grade cervical lesions in the per-protocol susceptible population\textsuperscript{25}. In the placebo group, 42 women had a diagnosis of CIN 2/3, cervical cancer, or AIS associated with HPV 16, 18, or both, compared with only 1 woman in the vaccine group. In this case, the woman tested positive for HPV 52 at baseline and in 5 histology specimens collected thereafter, and thus the likely cause of disease. However, as HPV 16 DNA was detected in one of the histology specimens, but at no other time points, and it was counted as a case as per the endpoint definitions\textsuperscript{25}.

In a combined efficacy analysis including data from four clinical studies (the Phase I trial of the HPV 16 monovalent vaccine, the Phase II trial of the quadrivalent vaccine, Future I, and Future II), showed a vaccine efficacy in protecting against any CIN attributed to HPV 6, 11, 16, or 18 was 95.2 per cent (CI = 87.2 - 98.7), and for protection against HPV 16 or HPV 18-related CIN 2/3 or AIS of 100 per cent (CI = 92.9 – 100)\textsuperscript{27}.

Efficacy in mid-adult women aged 24 to 45 yr was assessed in the FUTURE III study. The vaccine was 91 per cent (95\% CI, 74-98) effective in reducing the combined incidence of HPV 6/11/16/18-associated persistent infection (defined as the detection of the same HPV genotype 2 or more times over a median follow-up time of approximately 6 to 12 months), CIN, or genital warts\textsuperscript{28}. Therefore, even in a sexually experienced more mature population, there is a significantly reduced reduction of HPV vaccine type related abnormal Paps and CIN.

Emerging research indicates that the quadrivalent HPV vaccine may confer cross-protection against several nonvaccine oncogenic, but phylogenetically related HPV types. A recent analysis of FUTURE I and FUTURE II patients demonstrated efficacy against persistent infection, as well as combined efficacy for CIN 2/3 or AIS associated with HPV 31 or 45 (the 2 most common high-risk HPV types after HPV 16 and 18) to be 45 per cent (95\% CI: 18, 63) and 62 per cent (95\% CI: 10, 85), respectively and for combined efficacy for CIN 2/3 or AIS associated caused by 10 non-vaccine types (31/33/35/39/45/51/52/56/58/59) of 38 per cent (95\% CI: 6, 60)\textsuperscript{29}. The effect for combined HPV 31 or 45 was statistically significant for HPV 31 only.

2) bivalent vaccine efficacy

The bivalent vaccine includes VLPs assembled from recombinant HPV 16 and HPV 18 L1, 20 micrograms of each type. The L1 VLPs are produced using a Baculovirus expression system which uses Hi-5 Rix4446 insect cells\textsuperscript{30}. The vaccine utilizes an adjuvant known as “ASO4” that contains aluminum hydroxide, hydrated (Al(OH)\textsubscript{3}) and 50 µg of 3-\textit{O}-desacyl-4’-monophosphoryl lipid A (MPL), a potent inducer of the immune system. In addition, there is aluminum at 500 µg in each dose. The bivalent vaccine is given as an intramuscular injection at months 0, 1 and 6.

Phase II clinical trials of the bivalent HPV vaccine have shown 100 per cent efficacy against persistent infection (47.0-100) due to HPV 16 or 18 in women previously unexposed to these vaccine types in an
according-to-protocol analysis of data up to 18 – 27 months\textsuperscript{30,31}. In the intention to treat analyses, efficacy was 95.1 per cent (63.5-9 9 .3) against persistent infection and 92.9 per cent (70.0-98.3) against cytological abnormalities associated with HPV 16 or 18.\textsuperscript{30} In a follow-up study to 4.5 yr, vaccine efficacy against CIN grades 1 to 3 associated vaccine types was 100 per cent (42.4-100), with continued efficacy against persistent infection or 16 or 18 of 100 per cent (33.6-100).

Of note, was the statistically significant protection against six month persistent infection with HPV 31 (vaccine efficacy: 36.1%; 97.9% CI: 0.5–59.5), HPV 45 (vaccine efficacy: 59.9%; 97.9% CI: 2.6–85.2), and HPV 52 (vaccine efficacy: 31.6%; 97.9% CI: 3.5–51.9), that was not observed for 12 month persistent infection against any of these three non-vaccine HPV types or other non-vaccine types. No data on clinical disease cross-protection was provided for any non-vaccine HPV type.

Further follow-up up to 6.4 yr has showed sustained efficacy against incident infection, persistent infection, CIN 1+ or AIS for 16/18, cross protection for incident infections as well as persistent infections for types 31 and 45 independently\textsuperscript{32}. Preliminary evidence has also demonstrated that the bivalent vaccine confers cross-protection against persistent infection, with some non-vaccine oncogenic HPV types, but cross protection of lesions is not yet reported\textsuperscript{31,33}.

A pre-specified interim report of an extensive phase 3 randomized controlled trial assessed the efficacy of the bivalent HPV 16/18 vaccine in preventing CIN 2+ lesions associated with HPV 16 or 18 in women aged 15 to 25 yr\textsuperscript{26}. Median follow-up time was 15 months, with efficacy determined in a modified intention to treat analysis, which included women with HPV and low-grade dysplastic lesions at recruitment. The bivalent HPV vaccine demonstrated 90.4 per cent ($P<.0001$) efficacy in preventing HPV 16 or 18 CIN 2+ lesions and was 89.2 per cent ($P<.0001$) effective against CIN 1+ lesions in women uninfected with HPV 16 or 18 at baseline, but possibly infected with other oncogenic HPV types. Efficacy was statistically significant for HPV 16 CIN 2+, but likely due to small numbers and short follow-up time, not yet for HPV 18 CIN 2+. When mixed infections were taken into account, it was noted that 2 cases in the vaccinated group contained several oncogenic HPV types. Additional analyses concluded that the 2 cases in the vaccine arm were likely HPV 58-related and excluding these cases would show an estimated vaccine efficacy of 100 per cent (97.9% CI, 74.2-100)\textsuperscript{26}.

### Immunogenicity

Efficacy against HPV vaccine-related disease correlates with the presence of serum neutralizing antibodies. All recipients of both vaccines have very high seroconversion rates near 100 per cent; they show rapid, development high titre (way higher than that seen with natural infection) IgG neutralizing antibodies which are thought to transudate across into cervical secretions, into tissues and neutralizing any wild virus type infection\textsuperscript{31,34}. Follow-up trials have shown that protection against HPV lasts for at least 5 yr post vaccination for the quadrivalent vaccine\textsuperscript{34} and 6.4 yr for the bivalent vaccine\textsuperscript{32}. The quadrivalent vaccine study groups similarly report high titres peaking a month following the third dose of vaccine, with a gradual decrease to reach a plateau of titres at around 24 months\textsuperscript{35}. At 36 months, seropositivity rates were 94, 96, 100 and 76 per cent to HPV 6, 11, 16, and 18, respectively. Despite a lower proportion having measurable antibodies for HPV 18 at four years, it is still 100 per cent efficacious in protecting against 18 related CIN\textsuperscript{35}.

No correlate of protection has been defined as yet (for either vaccine) as there have been no breakthrough cases of vaccine HPV related CIN in the trial recipients and who were naïve to the respective types at baseline and hence no level at which one can say below which a woman will not be protected. Moreover, these vaccines could behave like that of hepatitis B virus, where titres \textit{per se} may not be measurable, yet immune memory exists. Supportive of this principle is that a challenge dose of quadrivalent HPV vaccine at month 60 resulted in a rapid sharp rise, and anamnestic response likely due to the induction of immune memory mediated by memory B cells\textsuperscript{36}. Furthermore, vaccinating women who have had prior infection in general induce higher antibody titres as compared to those naïve to the relevant HPV type at baseline, suggesting boosting of natural infection induced immunity by vaccination\textsuperscript{37}. Just like those with HBV vaccines of yesteryear, we need to follow-through in phase four studies \textit{i.e., “time will tell”}.

As a general principle of vaccinology, the immune response is inversely correlated with age, with the maximal response in the prepubertal age group. For both HPV vaccines, this principle rings true; in fact
specific antibodies have been used as a surrogate to bridge efficacy from young women to pre-adolescence, as well as to mature age women up to 45 yr of age. Specifically in the 25 to 45 yr of age approximately 70 per cent of geometric mean titres found in 16-23 yr olds) as shown by the FUTURE III study.

As vaccines induce a polyclonal response to many different antigens, and serological assays utilize different antigens to measure vaccine induced immune responses, it is important to note that one cannot compare titres from one assay to another even of the same assay type, and particularly not from different assays to one another.

Safety

The number of adverse events (AEs) was similar between the quadrivalent vaccine and placebo (the proprietary aluminum adjuvant) groups in all 3 trials. However, vaccine recipients were significantly more likely than placebo recipients (87% vs 77%, respectively; 95% CI, 7.8-12.1) to have injection site reactions, with pain at the site of injection as the most common AE. Injection site reactions were the most common AEs in both vaccines and were reported more frequently in the vaccine recipients.

Current licensure/registration of the two prophylactic HPV vaccines

The quadrivalent HPV vaccine was approved in June 2006 by the US Food and Drug Administration (FDA) as well as the Therapeutic Goods Administration (TGA) in Australia for the prevention of HPV 6/11/16/18-associated cervical cancer, adenocarcinoma in situ (AIS), and cervical intraepithelial neoplasia (CIN) grades 1 to 3, vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VaIN) grades 2/3, and genital warts in women. Whilst the quadrivalent vaccine was registered for use in females aged 9-25 yr as in the USA, it was also registered for males 10 to 15 yr in Australia. To date, licensure or registration of the quadrivalent vaccine has occurred in just over an hundred countries worldwide (Fig. 4).

For the bivalent vaccine, licensure first occurred in Australia in May 2007 and in Europe in September 2007. In Australia the bivalent vaccine was registered for use in females aged 10-45 yr of age, and was recently recommended for government funding up to 26 yr of age. Australia was the first country to approve an HPV vaccine for the older age group of women, on the basis of safety and immuno-bridging data. However, women over the age of 26 yr who wish to be

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Fig. 4. Approvals for quadrivalent vaccine as of July 2009 [Published with permission form Carlos Sattler (Merck)].
vaccinated do have to pay the full price of the vaccine course ($A450), plus the cost of a general practitioner (GP) consultation. It is currently problematic for GPs to advise women over the age of 26 yr as to the potential benefit of the vaccination in the absence of published type specific HPV incidence data by age group and risk-group in Australia, and until vaccination efficacy data for mature aged women is published. To date the bivalent vaccine is licensed in 64 countries (Fig. 5) and is currently under review by the FDA, USA. (Personal communication Huges Bogaerts. GSK).

Challenges to implementation of vaccination programmes

Target age and gender

The HPV vaccines will be most beneficial when administered before exposure to HPV; hence this will be largely determined by mean age of sexual debut within a community. In many countries, this age is decreasing over time. For example in Australia, the mean age in females is 16, whereas in various parts of Asia it is higher. Consequently, to date young girls nine to 15 are being targeted for vaccination programmes. As HPV is sexually acquired, in the long term if the vaccines are shown to be protective against male disease (we await data from ongoing efficacy studies of the quadrivalent HPV vaccine in men), then from a stigmatization point of view, overall effectiveness and impact on herd immunity, this may well be preferential.

Delivery systems

In Australia, in November 2006, the Federal Government announced funding of HPV vaccination for all 12 yr old female cohorts in Australia, starting in 2007, with a 2 yr catch up programme for females 13-26. The school programme (12-18 yr) commenced in April 2007, and the GP programme (for females aged 18-26 yr) in July 2007. To date, the vast majority of schools are cooperating with the HPV vaccination programme, although there have been isolated reports of schools refusing to participate. State health department records indicate uptake of 3 doses of HPV vaccine in the first year’s cohort of the school based programme at just below 80 per cent.

Australia adopted a school-based programme, and largely because data has indicated low immunisation uptake in adolescents outside of school-based immunization programmes. For example, the effectiveness of school-based delivery of hepatitis B vaccine compared with general practitioner delivery in a population of 10 yr old adolescents in 106 schools in South-Western Sydney, New South Wales found the

*Fig. 5. Approvals for bivalent vaccine as of May 28, 2009 [Reprinted with permission from Scott Preiss, GSK].*
school-based delivery to be 10 times more effective than GP delivery. The United Kingdom has commenced a government funded school-based vaccine starting late 2008, utilizing the bivalent vaccine. Initial compliance rates with vaccine uptake are not dissimilar from Australian first-year figures.

In some poorer countries, delivery to school age girls will be a challenge, as girls may well not be at school in adolescent years. Ultimately, and given that the extended infant immunisation programme is well adhered to globally, with well-established delivery infrastructure systems, being able to distribute HPV vaccines to infants would be a feasible alternative. However, we await data on long-term immunogenicity and safety in infants, before this could be realized.

**Finances**

In many other countries worldwide, particularly within Asia, whilst vaccines have been registered or licensed (Figs 4 and 5), individuals need to pay for the cost of vaccine and delivery. Consequently uptake of the vaccines has been too low to have an impact as public health tool. For poorer countries, the endorsement and involvement of GAVI will be critical.

**Communication**

However, without effective communication these preventative vaccination tools may have little impact on disease burden. The relatively new society of the Asia Oceania Research Organisation in Genital Infection and Neoplasia (AOGIN) bring together clinicians and scientists whose work is related to genital infections, particularly HPV, cervical dysplasia and neoplasia, as well as other anogenital cancers, with the aim of improving communication on prevention through human papillomavirus (HPV) vaccination and screening in Asian countries. AOGIN is committed to improving communication with patients, health authorities, professional organisations and opinion leaders towards strengthening cervical cancer prevention in Asia, to achieve a timely steep reduction in this cancer.

**Vaccine effectiveness measures**

In Australia, an important component of the National HPV Vaccination Programme is the establishment of a National HPV vaccine register, which will measure coverage, maintain a record of recipients should a booster dose of vaccine be required in the future and provide documented vaccination status for assessments of vaccine effectiveness at a population level, such as through linkage to cytology registers. Any changes in Pap screening attendance amongst vaccinated women will be detectable through this linkage mechanism. GPs will be paid a financial incentive for each dose of administered vaccine that they report to the register.

Linkage of HPV type specific surveillance data to the HPV vaccine register, cervical cytology registers, and cancer registers will be important for ultimate assessment of vaccination programme success. Prior to vaccine rollout, a large study, currently near completion, is collecting cervical specimens, for HPV DNA testing from women across Australia, at the time of a routine Pap smear. The study WHINURS (Women, Human papillomavirus, Indigenous, Non indigenous, Urban, Rural Study) focuses on establishing age specific trends in prevalence and establishing whether there are any appreciable differences in circulating HPV types amongst Indigenous women and women residing in rural and remote locations. To date, analysis of 2,461 samples from women aged 14-72 yr demonstrated a prevalence of high-risk HPV of 23.6 per cent, with highest rates in the youngest women (44% age 15-19, 42% age 20-24, 34% age 25-29), and falling below 10 per cent after age 40. The overall rates of HPV16 and 18 positivity were 5.9 and 2.4 per cent respectively (peaking at 13% and 6% in the youngest age group). Among women with normal Paps, a similar pattern was observed; with overall HPV positivity of 19 per cent (40% in those 15-19 yr and 32% in women 20-24 yr).

In addition serosurveillance will be important in monitoring, somewhat crudely the past exposure to vaccine related HPV genotypes. In a recent survey of over 2,500 men, women and children aged 0-59 yr for neutralizing antibodies to HPV types 16, 18, 6 and 11, by the age of 30-39 yr, 30 per cent of Australian women and 19 per cent of men have antibodies to at least one of HPV-16 or 18.

**Ongoing vaccine surveillance**

In the near future, monitoring the serological levels of vaccine-induced antibodies may be a useful method for monitoring the coverage of vaccination programmes in target populations in a post-vaccination period. To date, no immune parameter or correlate has been directly linked to long-term protection and there is no long-term data beyond six years for either immunogenicity or disease prevention. Reliable, sensitive, and highly reproducible assays for HPV DNA and serological responses will be useful tools in evaluating the impact of vaccination programmes. This has been addressed by the recent establishment by the WHO of a global HPV laboratory network...
(known as the HPV LabNet), the goal of HPV LabNet is to ensure the availability of competent laboratory services worldwide for evaluating HPV DNA and antibody detection in biological specimens through capacity-building and strengthening for those in need, by providing up-to-date technical information, training on laboratory practice, technical advice and guidance.

Adequate surveillance will require monitoring the local prevalence of HPV genotypes in women within the general population with no cytological abnormality, those with cervical lesions and cervical cancer, before and after the introduction of a vaccine programme. In addition, detection of changes in HPV type-specific prevalence following the implementation of HPV vaccination to monitor for genotype “replacement”, an hypothesis that postulates that other oncogenic HPV types may potentially fill the niche left after the removal of HPV-16 and 18 with high vaccine coverage and represents the emergence of unanticipated disease risks. Monitoring of HPV vaccination programmes will not be achievable in all countries and will preferably be carried out in those where effective cytological screening and vaccine registries exist, and where linkages between these data can readily occur. Several such sentinel populations have already been identified in the Nordic countries in Europe.

References


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