HPV, CIN & Ca Cervix: The Least You Need to Know

Pneumococcal Infection In Young Children: Management & Prevention

FAQ on HPV Vaccines

The Role of HPV Antibody Levels in Prevention of Cervical Intra-Epithelial Neoplasia and Invasive Cancer
A human papillomavirus (HPV) is a member of the papillomavirus family of viruses that is capable of infecting humans. Over 120 HPV types have been identified and are referred to by number. Types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 are “high-risk” HPV.

Epidemiological studies have shown a strong association between human papillomavirus (HPV) and cervical cancer and its precursors. An overall HPV prevalence of 99.7% among cervical cancers worldwide has been reported and HPV-negative cervical carcinoma appears to be extremely uncommon, if it exists at all.

Globally, types 16 and 18 together account for more than 70 per cent of all cervical cancer cases. HPV 18 is also involved in the development of a slightly different cancer type called adenocarcinoma, which also can affect the cervical tissues and it is more difficult to detect through routine cervical cancer screening.

Most infections clear within a few months to 3 years. Persistent infection with oncogenic HPV is necessary biologically to drive the process of carcinogenesis. When infection persists in 5% to 10% of infected women - there is high risk of developing cervical precancer, which can progress to invasive cervical cancer. This process usually takes 15–20 years, providing many opportunities for detection and treatment of the pre-cancerous condition, often with high cure rates.

Women with untreated CIN3 are at high risk of cervical cancer, whereas the risk is very low in women treated conventionally throughout. Treatment can be excision or ablation, eg. LEEP (loop electrosurgical excision procedure), laser ablation or cone biopsy. In LEEP, an electric current is passed through a hand-held wire loop which is then used to excise the area on the cervix which contains the precancerous change. LEEP is usually performed as an outpatient or day surgery procedure. The cumulative incidence of invasive cancer of the cervix or vaginal vault was 31.3% (95% CI 22.7-42.3) at 30 years, and 50.3% (37.3-64.9) in the subset with persistent disease within 24 months. However, cancer risk at 30 years was only 0.7% (0.3-1.9) when initial treatment was adequate.
Treatment options for cervical cancer include surgery, radiotherapy and chemotherapy or in combination. Prognosis depends on the stage of the cancer. With treatment, the 5-year relative survival rate for the earliest stage of invasive cervical cancer is 92%. Only 25 to 35% of women with stage III cancer and 15% or fewer of those with stage IV cancer are alive after 5 years.

Regular screening allows pre-cancerous changes and early stage cervical cancers to be detected and treated early. Pap smear forms the basis of cervical cancer screening programmes round the world. With vaccination alongside screening, the risk of cervical cancer will be further reduced than screening alone, and will also significantly reduce the number of abnormal screening results requiring follow-up.
Pneumococcal Infections In Young Children: Management & Prevention

Diseases caused by the encapsulated Streptococcus pneumoniae (or pneumococcus) are a major public health problem worldwide. Pneumococcal infections are a common cause of acute otitis media, sinusitis, pneumonia, bacteremia and meningitis in young children (see figure). Pneumonia, bacteremia and meningitis constitute invasive pneumococcal diseases (IPD) that tend to occur at the extremes of age – children less than 5 years and the elderly. Infants under 1 year are at risk for pneumococcal bacteremia and meningitis, whereas children from 2 to 5 years old often develop pneumonia, empyema, acute otitis media or sinusitis. Immuno-deficient children such as those with HIV infections, receiving chronic steroid or immunosuppressant therapy are at higher risk of contracting IPD. In 2005, the World Health Organization estimated that up to 1 million children died of pneumococcal infections every year, most of whom were young children below 2 years old.

Disease Transmission

Pneumococci are transmitted by direct contact with respiratory secretions from patients and healthy carriers. Following incubation of up to 3 days, the infected child develops fever, cough and dyspnoea. Diagnosis of pneumococcal disease is based on bacterial identification in normally sterile sites, such as blood, cerebro-spinal fluid or tracheal aspirate. Mortality in pneumococcal meningitis is high. After recovery from IPD, the child may develop long-term sequelae such as hearing loss, neuro-developmental delay, seizures or intellectual disability.

Management

Treatment of IPD consists of a 7- to 14-day course of intravenous antibiotics, such as IV penicillins (augmentin) and macrolides. However, antibiotic resistance to the bacterium is growing over time and increasing with patient age. Hence the mortality and morbidity of pneumococcal disease is best managed by prevention through vaccination programs.

Pneumococcal conjugate vaccines (PCV) are approved for infants and toddlers. Introduction of the PCV in USA led to declining admission rates for all-cause pneumonia in children under 2 years old and lowering rates of antibiotic-resistant IPD. The “Expert Committee on Immunization” (ECI) of the Ministry of Health Singapore has recommended that PCV be included into the National Childhood Immunization Programme, since it has been shown to be safe and effective. Pneumococcal polysaccharide vaccines are not suitable for children under 2 years old because of inability to mount a response to them.
7-Valent Pneumococcal Conjugate Vaccine (PCV7)
The currently licensed 7-valent pneumococcal conjugate vaccine (PCV7, marketed as Prevenar®) covers S. Pneumonia serotypes 4, 6B, 9V, 14, 18C, 19F and 23F. It is targeted for children from 6 weeks to 9 years. In the era before vaccination, the serotypes included in PCV7 represented about 86% of paediatric invasive strains of S. Pneumoniae in the USA.

The ECI recommends a schedule of 2 primary doses given at 3 and 5 months respectively, followed by a booster dose at age 12 to 24 months (~2 + 1’ schedule). PCV7 can be concurrently administered with the other childhood vaccines (such as DTPw-polio-Hib-HBV) but in a separate syringe and at a separate intra-muscular injection site. Studies showed that co-administration of PCV with the routine DPT-polio vaccines did not affect vaccine efficacy. The efficacy, immunogenicity and safety of PCV7 administered to preterm (gestational age 32-36 weeks, birth weights 980-3320 grams) infants in an Italian study employing a “2+1” schedule (3, 5, 11 months) was similar to that for full-term infants.

In previously unvaccinated children who are under 5 years old, catch-up immunization is recommended but the number of doses depends on age. The ECI recommends that healthy children who are under 12 months old receive 2 primary doses of PCV7 eight weeks apart (minimum interval 4 weeks), followed by a booster dose given at least 8 weeks after the second dose of the primary series. In children who are 1 to 5 years old with asplenia, splenic dysfunction, compromised immunity or sub-optimal vaccine response, the ECI recommends that they receive 2 doses of PCV7, with an interval of 8 weeks between doses. In addition to PCV7, children aged 2 to 5 years in high risk groups should receive a single dose of the 23-valent pneumococcal polysaccharide vaccine (PPSV23, marketed as Pneumovax23®). The high risk groups include children with chronic heart/ lung/ kidney diseases, cochlear implants or splenic dysfunction.

While the protective efficacy of PCV7 against pneumococcal pneumonia and invasive disease has been documented in developing and developed countries, its efficacy against pneumococcal otitis media has been somewhat modest. In a study in Finland, PCV7 was shown to have efficacy against culture-confirmed pneumococcal otitis media of 34% and efficacy against any-cause otitis media of only 6 to 7%.

Children should not proceed with PCV7 vaccination if they had a serious (anaphylactic) allergic reaction to a previous dose of this vaccine or its components. The commonest adverse reactions to primary vaccination with PCV7 were redness at the injection site and irritability. The duration of protection against IPD caused by vaccine serotypes is at least 2 – 3 years following primary PCV7 vaccination in infancy, although it could be longer.

10-Valent Pneumococcal Conjugate Vaccine
A 10-valent pneumococcal conjugate vaccine (PHID-CV, marketed as Synflorix®) was developed containing 3 more serotypes (1, 5, 7F) than the PCV7 vaccine. It is a mixed carrier vaccine containing 8 capsular polysaccharides (1, 4, 5, 6B, 7F, 9V, 14 and 23F) conjugated individually to non-typeable Hemophilus influenza protein D and the remaining 2 conjugated to tetanus (serotype 18C) or diphtheria (serotype 19F) toxoids. The 10-valent PCV was found to be immunogenic against each of the 10 pneumococcal vaccine serotypes when co-administered with other childhood vaccines (such as the DTPw-polio-Hib-HBV, MMR and Rotavirus vaccines). It is given intra-muscularly.

A European study investigated the immunogenicity of a 10-valent pneumococcal conjugate vaccine that was administered as either a “2 + 1” schedule (consisting of primary doses at 3 and 5 months) or as a “3 + 1” schedule (consisting of primary doses at 3, 4, 5 months), followed by the booster dose at 11-12 months. The 10-valent vaccine was found to be immunogenic in both schedules, indicating that both regimens had elicited adequate priming. For most vaccine serotypes, a trend towards lower post-primary and post-booster immune response was observed in children primed with 2 instead of 3 vaccine doses. This trend appeared to be more pronounced for functional opsono-phagocytic activity response, but its clinical relevance was unknown.

The commonest adverse reactions to primary vaccination with the 10-valent PCV were redness at injection site and irritability, of mild to moderate severity. Children should not proceed with the 10-valent PCV if they had a serious (anaphylactic) allergic reaction to a previous dose of this vaccine or its components. The commonest adverse reactions to primary vaccination with 7-valent PCV were redness at the injection site and irritability. The duration of protection against IPD caused by vaccine serotypes is at least 2 – 3 years following primary PCV7 vaccination in infancy, although it could be longer.

Implications of PCV immunization
Apart from the intended benefit of PCV in protecting unimmunised children against invasive pneumococcal disease, PCV is beneficial in raising herd immunity against vaccine serotypes. The result of increased herd immunity is better protection of elderly persons living in the same household as the child. This is particularly relevant in Singapore where elderly grand-parents (who are often the care-givers of an asymptomatic child with pneumococcal nasal carriage) may unknowingly be at risk for IPD themselves because of age and presence of chronic conditions. PCV thus has wide-ranging effects in protecting the entire household against vaccine serotypes, not just the infant or toddler alone.

Although PCV immunization prevents colonization of the naso-pharyngeal area with particular vaccine serotypes, it does not reduce the overall rate of pneumococcal nasal carriage because of replacement of non-vaccine serotypes through naso-pharyngeal carriage. Factors affecting the emergence of replacement disease are multiple and are associated with persons having compromised immunity. However, replacement disease is not expected to result in vast increases in the prevalence of pneumococcal disease although it may attenuate the anticipated benefit of introducing the pneumococcal conjugate vaccine in the community.

Conclusion
Pneumococcal infections are a common cause of acute otitis media, sinusitis, pneumonia, bacteremia and meningitis in young children. Treatment poses an increasing challenge to doctors caring for the infected child because of antibiotic resistance. Prevention through vaccination is the best way to reduce its mortality and morbidity.

Reference: MOH circular Mh 34:55/2, 13 Oct 09.
1) **Are HPV vaccines safe and effective?**

All vaccines have to undergo thorough clinical trials and monitoring before being approved for prescription. FDA has licensed the vaccines as safe and effective. Both vaccines were tested in thousands of people around the world. These studies showed no serious side effects. Common mild side effects include pain where the shot was given, fever, headache, and nausea. There have been recent reports about girls who have died after being vaccinated. Subsequent analysis has shown that the deaths were coincidental and are not linked to the vaccine. Brief fainting spells and related symptoms (such as jerking movements) can happen after any medical procedure, including vaccination. Sitting or lying down for about 15 minutes after a vaccination can help prevent fainting and injuries caused by falls. As with all vaccines, CDC and FDA continue to monitor the safety of these vaccines very carefully.

2) **How are HPV vaccines administered?**

The vaccines Cervarix and Gardasil are given as intramuscular injections, 3 doses over a 6 month period. For Cervarix, the 2nd dose is given a month after the first dose and for Gardasil, the 2nd dose is given 2 months after the first dose. The 3rd dose for both vaccines are given 6 months after the first dose. Women are advised to take precautions to avoid pregnancy until the 3 doses are completed.

3) **Should pregnant women be vaccinated against HPV?**

The vaccines are not recommended for pregnant women although studies show no difference in pregnancy outcome and in babies born to women who got the HPV vaccine while they were pregnant. Getting the HPV vaccine when pregnant is not a reason to consider ending a pregnancy. Women who are found to be pregnant before completion of the three dose regime are advised to defer completion of the regimen until pregnancy is over. It is not known whether the antigens or antibodies are excreted in human milk. Hence caution should be exercised when the vaccine is administered to nursing women.

4) **Who should receive the HPV vaccine?**

Anyone who is allergic to any of the ingredients in the vaccine or develops an allergic reaction after receiving the first dose of the vaccine should not receive the vaccine. Any women who is pregnant should not be given the vaccine.

5) **If a woman is sexually active, would the HPV vaccine still be effective?**

Yes, the vaccine is still effective. Thousands of women in the clinical trials for vaccination were already sexually active and the vaccine prevented all the precancerous lesions caused by new infections with HPV 16/18. However, vaccination does not protect against any HPV infection you may already have. The vaccines are prophylactic and not therapeutic vaccines.

6) **Can a woman with a previously abnormal Pap smear receive HPV vaccination?**

Yes, she can still be vaccinated. There are a number of reasons for an abnormal smear test result - which may or may not be a result of an HPV infection. Even if a patient has had an abnormal smear in the past caused by an HPV infection, this does not mean that she won’t benefit from the protection a vaccine may offer. However, the previous abnormal pap smear needs to be followed up appropriately.

7) **If a woman is sexually active, does she need HPV DNA testing before vaccination?**

No, it is not necessary to test for the high risk HPV subtypes before getting the vaccine. Current HPV testing methods are not type-specific, so a woman will not know which HPV type she is infected with. It is also rare for a woman to be infected with both HPV 16 and HPV 18. Therefore, if she has an HPV 16 infection, she will still benefit from protection against HPV 18. Once her HPV 16 infection clears, the vaccine will protect against future HPV 16 infections. Vaccination will not treat the existing infection, but will prevent future infections.

8) **For how long will HPV vaccines be effective in protecting? Is a booster vaccine required?**

Current studies have shown that the vaccines are still effective after 10 years of evaluation and mathematical modelling data has predicted the vaccine to last for at least 20 years. Current recommendations do not show a need for booster doses but results from future studies will provide more data.

9) **Do women still need regular Pap smear screen after they receive the HPV vaccine?**

Yes, it is very important to continue with pap screening after vaccination. The current vaccines do not include all oncogenic types although they would reduce 80% of the disease burden. Screening and vaccination are complementary strategies. Neglecting screening because vaccination programmes are in place could paradoxically lead to an increase in cervical cancer.

10) **Can the use of condoms reduce the risk of HPV transmission?**

Condoms can reduce the risk of transmission of HPV between partners but are not fully effective. Condoms also cannot reduce transmission in areas of exposed skin not covered by the condom, for example in the vulva, perineum and scrotum, hence these areas can still be a source of infection.

11) **Is the HPV vaccine recommended in men and boys?**

One of the available vaccines is licensed to be safe and effective for males ages 9 through 26 years. Boys and young men may choose to get this vaccine to prevent genital warts. Men and boys are generally not included in immunisation programmes because it has been shown not to be cost effective to immunize men. Vaccinating women alone could reduce the prevalence of infection by 30% and that the additional vaccination of men would only further reduce the prevalence by 44% and the cost of immunising men would need to be justified. However, parents of boys and young men interested should speak to their doctor if they are keen to have the vaccine.
The Role of HPV Antibody Levels in Prevention of Cervical Intra-Epithelial Neoplasia and Invasive Cancer

Introduction

Oncogenic human papillomavirus (HPV) plays a central role in cervical cancer development. Among these, HPV-16 and HPV-18 are causatively responsible for more than 70% of invasive cervical cancer cases and approximately 50% of cervical intraepithelial neoplasia grade 2 and grade 3 (CIN2+). They also distinctively differ from the other dozen oncogenic HPV subtypes by being more likely to cause persistent infection and more rapidly transform normal to neoplastic epithelium. It is, therefore, logical and most clinically relevant to focus efforts in preventing HPV-16 and HPV-18 infection in any cervical cancer control and prevention programmes.

In this short presentation, the mechanism of cervical neoplasia prevention by HPV vaccination is reviewed from the perspective of preventing HPV infection. Other potential mechanisms involving cell mediated immunity in eradication of HPV infected and transformed cells are beyond the scope of this article.

The Nature of the Current Anti-HPV Vaccines

The capsid proteins of HPV is made up of L1 and L2 viral proteins. L1 protein is 30 times more prevalent than L2. The L1 and L2 conformational epitopes play an essential role in the entry of the virus into the host cells. The currently available anti-HPV vaccines for clinical use are virion-like particles (VLP) composed of recombinant L1 proteins. The resultant neutralizing antibodies bind to L1 proteins of specific HPV subtypes and induce conformational changes which inhibit viral entry into the host cells. These are therefore prophylactic vaccines for prevention of HPV infection of the host cells.

Intramuscular injection of the virion-like particles combined with an adjuvant substance elicits an intense host humoral immune response with serum anti-HPV antibodies reaching a concentration several orders higher than what is seen with natural HPV infection. With the vaccines administered in 3 doses over a period of 6 months, high sustained anti-HPV-16 antibody levels for more than 8 years have been demonstrated for both the quadrivalent (Gardasil) and bivalent (Cervarix) vaccines. Similar characteristic of serum anti-HPV-18 antibody levels is seen with Cervarix vaccine. Following Gardasil vaccination, the initial high serum levels of anti-HPV-18 antibody decline with time and, by the end of 3 years, reaching a level as low as that observed with natural HPV infection in 40% of the vaccinated women in clinical trials. Mathematical modeling studies predict that vaccination with Cervarix will result in sustained high concentrations of serum anti-HPV-16 and anti-HPV-18 antibodies for 20 or more years.

The difference in antibody concentrations between Cervarix and Gardasil has been studied in a randomized controlled study. For comparability, antibody levels for both vaccines were measured with the same laboratory assay methodology, the pseudovirion netralisation assay. Compared to Gardasil, Cervarix vaccination yielded, on average, a higher anti-HPV-16 antibody levels of 2.3 to 4.8 folds at 7 months and 2.7 – 4.4 folds at 12 months. The difference between Gardasil and Cervarix is even greater for anti-HPV-18 antibody levels which were 6.8 – 9.1 and 7.0 – 8.1 folds higher in Cervarix at 7 and 12 months respectively. The difference in antibody response between Gardasil and Cervarix is most probably the effect of adjuvant in the vaccine formulation. Gardasil employs aluminum salt while Cervarix uses ASO4, a combination of aluminum hydroxide and monophosphoryl lipid A (MPL).

The antibodies elicited by Gardasil and Cervarix are IgG antibodies. The serum antibodies transudate into cervical secretion to reach the site targeted for prevention of HPV infection. There is a linear correlation of antibodies levels between the serum and cervical secretion.

Serum Anti-HPV Antibody Level After Natural HPV Infection

HPV is epitheliotropic. Once the virus enters the basal cells of the epithelium, it loses the viral capsid and releases viral DNA into the cytoplasm. The DNA enters the nucleus and is replicated as the epithelial cells multiply. During cell differentiation and maturation towards the luminal layers of the epithelium, viral genes for different proteins express and full virions are assembled before discharging into the vaginal lumen. The entire viral life cycle occurs within the epithelium. Without access to the blood circulation, the virus readily evades the host immune system. Not surprisingly, only a small number of women infected by HPV exhibits significant circulating anti-HPV antibody and most women with past HPV infection are susceptible to re-infection by the same HPV subtypes. The risk of re-infection is inversely co-related to the serum level of anti-HPV antibody as demonstrated by Ault et al (2005). This study demonstrated that there is a threshold antibody level below which protection against HPV-16 infection is ineffective.
Clinical Efficacy of HPV Vaccines

Short-Term Efficacy

Results from phase 3 randomised placebo controlled trials of Gardasil showed that, in subjects naive to a given HPV type(s) at baseline and throughout the three dose vaccination, vaccine efficacy against CIN 2+ or adenocarcinoma in situ was 99% (95% confidence interval 93% to 100%). In the similar trial with Cervarix, the HPV type assigned efficacy was 100% (96.1% CI 91.0-100.0%) and 92.3 % (45.7 -99.9) for protection against HPV-16 related and HPV-18 CIN2+ respectively. These results were observed over 3-4 years of the trials. They represent the efficacy of the short-term protection of the vaccines. Data on the efficacy of the vaccines for long-term protection will take many years before they are available.

Long-Term Efficacy

Although both Gardasil and Cervarix stimulate cellular immune responses, the humoral immune response is the key mechanism for preventing HPV-16 and HPV-18 infection in the cervix. A high circulating antibody level should provide a better confidence for a longer duration of protection against HPV infection. It is a rule rather than an exception that serum antibody levels decline after eradication of the offending virus. Long-term or permanent immunity against an infection is provided by memory B cells which, upon re-challenge of the virus, mount an exaggerated specific antibody response to neutralize the virus immediately and rapidly. Experience with hepatitis B vaccination programme showed that despite waning circulating antibody levels with time, vaccinated subjects remained immune to hepatitis B infection. However, extrapolating the role of memory B cells in hepatitis B vaccination to HPV vaccination is met with great uncertainty as hepatitis B virus invades the blood circulation and is exposed to systemic immune system, whereas HPV infection is confined to epithelium with little exposure to the systemic immune response. Doubts exist if natural HPV infection in the cervix poses a challenge to the memory B cells. Until further data is available, long term clinical efficacy is, at least theoretically, more likely to be associated with vaccines resulting in long-term higher circulating antibody levels.

Conclusion

HPV vaccines consist of recombinant viral-like particles. Gardasil is a quadrivalent vaccine against HPV-6, 11,16 and 18 while Cervarix is a bivalent vaccine against HPV-16 and HPV-18. With intramuscular administration, the vaccines induce a strong humoral immune response to targeted HPV subtypes. Serum antibody levels are several folds higher than that observed after natural HPV infections. Serum levels for both anti-HPV-16 and anti-HPV-18 antibodies are well maintained for 8 or more years of follow up with Cervarix. Data from trials with Gardasil also confirmed a well-maintained high level of HPV-16 antibody. Serum anti-HPV-18 antibody levels, however, declined and, by the end of three years, reached a level similar to that observed in women with natural HPV infection. Anti-HPV antibodies are important for prevention of HPV infection in the cervix and there appears to be a threshold antibody level for effective protection. Short-term results from clinical trials confirmed the very high efficacy in prevention of HPV-16 and HPV-18 related high grade CIN. Long-term protection from vaccination is predicted with vaccines producing high antibody levels maintained over a long period of time.