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Review

Reduced dose human papillomavirus vaccination: An update of the current state-of-the-art

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ABSTRACT

Human papillomavirus (HPV) infection is the primary cause of genital warts, some oropharyngeal cancers and anogenital cancers, including cervical, vagina, vulvar, anal and penile cancers. Primary prevention of cervical cancer requires the prevention of high-risk HPV infections, particularly HPV genotypes 16 and 18. Both Gardasil® and Cervarix® vaccines when administered by a three-dose schedule have been demonstrated to be effective against cervical, vulva, and vagina cancer precursors from vaccine genotypes in phase III clinical trials, and post-marketing studies; Gardasil® vaccine also offer additional protection against anal cancer precursors. However, high costs of HPV vaccines and the logistics of delivering a three-dose schedule over 6 months are challenging in countries with limited resources. Several studies have demonstrated non-inferiority in antibody response between adolescents (9–15 years old) who received two doses (6 months apart) and women (>15 years old) who received the standard three-dose schedule. These studies provided evidence for the World Health Organization and European Medical Association to revise its recommendation to give two instead of three doses of HPV vaccine to adolescents below 15 years of age, provided the 2nd dose is given 6 months apart. Although reduced dose schedules can alleviate costs and logistics associated with HPV vaccination, especially in resource-poor countries, there are still gaps in this area of research, particularly regarding long-term protection. This review discusses the findings on antibody response and clinical outcomes in studies evaluating reduced dose HPV schedules, and highlights the important considerations of its implementation. In addition, other important immunological biomarkers that may be associated with long-term protection are highlighted and discussed.

1. Introduction

Q3 Human papillomavirus (HPV) is the main causal agent of cervical cancers. This association was first reported by zur Hausen and his team in the early 1980s [1]. HPV was then verified as the cause of cervical cancer, following a number of molecular epidemiological studies [2,3]. Since then, research has focused on the prevention of cervical cancer, including the prevention of HPV infection through vaccination. The major breakthrough in vaccine development was the discovery of the self-assembly L1 capsid viral proteins into virus-like particles (VLPs), and which induced the production of high-level neutralizing antibodies, forming the basis for the current HPV vaccines [4].

There are currently more than 170 HPV types identified, with at least 13 types classified as carcinogenic. With the exception of the newly licensed nonavalent HPV vaccine (Gardasil® 9), which requires more long term studies to evaluate its efficacy and impact

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on cervical cancers globally (particularly to the 5 new cancer causing types included in the vaccine), the two HPV vaccines (Cervarix® and Gardasil®) currently used in most developed countries only protects against two oncogenic HPV types (HPV 16 and 18; accounting for 70% of cervical cancers) [5]. Also, as HPV vaccines are only available to a minority of the world's women, and many of these countries do not have a comprehensive effective cervical screening program with treatment of precursor lesions, cervical cancer is the fourth most common cancer in women worldwide, according to recent data from the World Health Organization (WHO) [6]. Approximately 530,000 new cases of cervical cancer occur every year, with 85% of these cases occurring in developing countries [6]. Highly successful cervical cancer secondary prevention activities are often not available or accessible to the world's poorest women. Furthermore, the high cost of HPV vaccines is a major obstacle in low- and middle-income countries. The GAVI Alliance (formerly known as Global Alliance of Vaccines and Immunizations) has subsidized and supported the introduction of HPV vaccine in low-income countries, but to date, Bhutan and Lao PDR are the only GAVI-eligible Asian countries to take up this offer. Although low-income countries are eligible for GAVI support, middle-income countries are ineligible and struggle to afford the vaccines. There are also logistical issues in administering the vaccine in a three-dose schedule over 6 months. These issues have led to the exploration of alternative schedules, which could potentially alleviate the issues of vaccine cost and delivery. Based on the increasing evidence of non-inferior antibody responses between girls receiving two doses of HPV vaccine and women receiving three doses, the WHO and European Medical Association (EMA) have revised their recommendation from giving three doses to two doses to girls below the age of 15, provided the second dose is administered 6 months apart. Several countries (i.e. Canada and United Kingdom) have already implemented a two-dose HPV schedule. However, long-term protection is yet to be determined and the immunology of reduced dose HPV schedules is still unclear. This review will focus on the immunology of evaluating reduced dose HPV vaccine schedules as compared with the standard three-dose schedule.

2. Immune response to HPV during natural infection

The immune response to natural infection with HPV is weak and very slow (up to 18 months), as important signals for the induction of immune responses are absent, due to the ability of the virus to evade the immune response. HPV's replication is exclusively intra-epithelial, and there is minimal or no exposure of viral proteins in infected cells, preventing the activation of the immune system [7]. Furthermore, HPV infection is not blood-borne, and does not induce cell death, resulting in very weak inflammatory responses [7].

The majority of people who become infected with HPV do not exhibit any clinical symptoms, and most HPV infections are cleared by the host response within a few months, with 90% of infected cases cleared within 2 years [8]. Those women who develop benign cervical lesions usually mount a late, but successful cell mediated immune response, which causes the lesion to regress [9]. The role of cell-mediated immunity in the clearance of HPV infection is evident in immunosuppressed individuals (i.e. HIV-infected individuals), who have multiple recurrences of HPV infection, higher incidence of genital warts, and an increased risk of progression from sub-clinical to clinical disease [10–12]. Serum neutralizing antibodies against the L1 capsid protein are generated in approximately 50–70% of infected individuals [13]. However, the level of antibodies generated even at peak titers is low, reflecting the ability of the virus to cause an exclusive intra-epithelial infection [13,14]. The long term significance of immunity induced by natural infection is still uncertain, with some clinical studies suggesting that antibodies elicited by natural infection from the virus may not provide complete protection in the long term [15]. Hence, it is recognized that antibody levels detected following natural infection may be less reliable in predicting protection from infection by the HPV types.

3. Immune responses induced by HPV vaccination

There are currently three licensed HPV vaccines (Table 1); Gardasil® (Merck & Co., Inc.; 4vHPV) a quadrivalent vaccine with Alum adjuvant that protects against four genotypes (HPV 6, 11, 16 and 18) and Cervarix® (GlaxoSmithKline; 2vHPV), a bivalent vaccine with the novel adjuvant AS04 (made up of an aluminum salt and monophosphoryl lipid A) that activates innate immunity [16], and protects against infection with HPV 16 and 18. A new next-generation nonavalent HPV vaccine, Gardasil® 9 (Merck & Co., Inc.; 9vHPV), which contains an additional five cancer-causing HPV types (HPV 31, 33, 45, 52, and 58) in addition to the four types in Gardasil®, was recently approved by the U.S. Food and Drug Administration (FDA) (December 2014) and Canada Health (February 2015). This vaccine may potentially prevent 90% of cervical cancer. In a randomized, international, double-blind study, greater than 96% vaccine efficacy against cervical, vulva and vaginal pre-cancer and cancer caused by HPV 31, 33, 45, 52, and 58 was reported for 9vHPV, when compared with 4vHPV in a per-protocol efficacy population of 16–26 years old women [17,18]. In addition, similar antibody responses against the common vaccine types were also reported in women vaccinated with 9vHPV or 4vHPV, 1 month post-dose 3 [18]. Due to the recent licensure and limited reduced dosage studies on 9vHPV, this review will focus on data from 2vHPV and 4vHPV.

Immunization against HPV is achieved by a course of three doses of vaccine, delivered intramuscularly at 0, 2, and 6 months (4vHPV) or 0, 1, and 6 months (2vHPV). The administration of the vaccine intramuscularly helps to circumnavigate the virus's strategies of intra-epithelial evasion of the immune system. The prophylactic vaccines are virus-like particle (VLP) based vaccines, which does not contain the viral genome, so the particles contain no DNA and are not infectious. Studies have shown that administration of 4vHPV to 15–26 years old women had 96–100% effectiveness in the prevention of HPV 16- and HPV 18-related grade 1–3 cervical intraepithelial neoplasia, adenocarcinoma in situ, invasive cervical carcinoma, vulvar intraepithelial neoplasia, vulvar cancer, and vaginal cancer [19–21]. It demonstrated a higher prevention rate (98–100%) against HPV 6- and HPV 11-related genital warts and cervical, vulva, vaginal, and anal intra-epithelial neoplasia as surrogates to respective cancers [19,20]. Similar vaccine effectiveness against cervical intra-epithelial neoplasia grade 3 or greater (CIN3+) was also shown with the administration of 2vHPV to 15–26 years old women [22–24].

Antibody responses peak at month 7 (1 month after dose three) at titers between 10 and 100 fold higher than following natural infection, depending on the HPV type and vaccine [24–26]. Following an initial decline, they appear to plateau at 18–24 months, remaining stable for at least 5 years at levels above or at least equivalent to those seen with natural infection [25–28]. The longest duration of antibody response induced by HPV vaccination for 2vHPV and 4vHPV are 9.4 and 8 years, respectively [29,30]. Overall, seroconversion occurs in 99–100% of those vaccinated [27,31].

4. HPV vaccination immunobridging studies

Due to ethical issues of evaluating clinical outcomes in adolescents below the age of 15 years, safety and immunogenicity bridging studies of HPV vaccination are conducted instead, so that

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