

Long-term efficacy of human papillomavirus vaccination

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Abstract

Achieving long-term protection following vaccination is crucial to ensuring that high levels of immunity are maintained within a population while eliminating the need to introduce booster vaccinations. Based on an analysis of the hepatitis B virus vaccine, several factors have been shown to contribute to long-term protection, namely: specific lymphoproliferation, the *in vivo* humoral response, and immune memory. To ensure protection against persistent human papillomavirus (HPV) infection and the subsequent development of cervical lesions, an effective HPV vaccine must be able to induce strong humoral immune responses. Mathematical modeling analyses based on a three-dose regimen of HPV type 16 prophylactic vaccine indicated that 99% of 16- to 23-year-old women would have almost life-long detectable anti-HPV-16 levels. Available data on the quadrivalent HPV vaccine demonstrated that long-term immune memory was induced, with anti-HPV geometric mean titers after 5 years remaining at or above those observed with natural infection. Vaccination also resulted in a substantial reduction in the combined incidence of HPV-6/11/16/18 related persistent infection or disease, and there were no cases of precancerous cervical dysplasia compared with six cases in women receiving placebo. Similarly the bivalent HPV vaccine has been shown to induce long-term immunity with >98% seropositivity maintained after 4.5 years of follow-up and geometric mean titres at this time point remaining substantially higher than those noted with naturally acquired infection. Countrywide registration regarding population and health events in a stable population of approximately 25 million makes the Nordic countries an ideal setting for the evaluation of long-term cervical cancer control. Population-based long-term efficacy trials conducted in these countries aim to investigate the long-term efficacy of HPV vaccination with regard to invasive cervical cancer, and the results of these trials are awaited with interest.

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Mechanisms of long-term protection: An analysis of the hepatitis B virus vaccine

Achieving long-term protection following vaccination is crucial to ensuring that high levels of immunity are maintained within a population while eliminating the need to introduce booster vaccinations [1]. The mechanisms by which vaccination confers long-term protection have been elucidated for the hepatitis B virus (HBV) vaccine. Several factors have been shown to contribute to long-term protection, such as: specific lymphoproliferation, the *in vivo* humoral response, and immune memory. Generation of memory B and T cells occurs after the

primary immune response to vaccination [2]. Immune memory is mainly driven by the B-cell response; however, T cells enhance B-cell persistence and memory most likely results from the interaction between memory B cells, memory T-helper cells, memory cytotoxic T cells and antigen/antibody complexes [3,4]. The contribution of immune memory to long-term protection is evidenced by the rapid increase in antibodies after booster vaccination and by the persistent immunity in individuals with decreasing antibody levels [5].

The primary antibody response to vaccination and subsequent development of immune memory may potentially be influenced by the vaccine antigen dose and structure [6]. When the HBV antibody levels fall below detectable levels, prolonged protection results from immune memory which may be related to antigen persistence on immunologically active cells. This persistence is determined by the antigen content of the HBV

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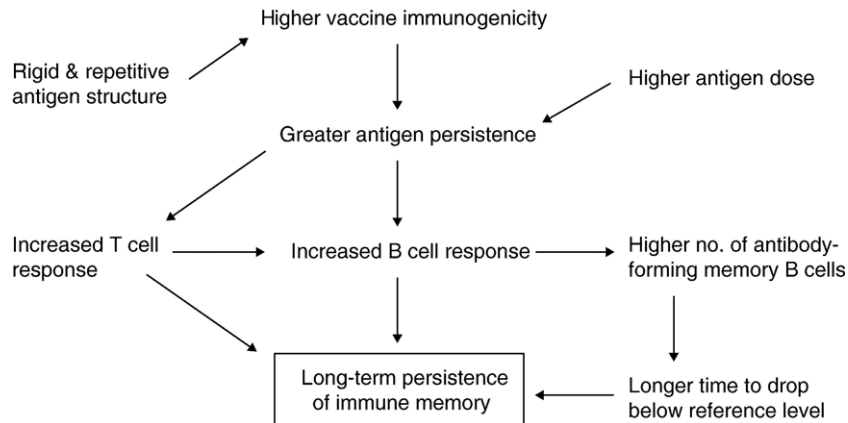


Fig. 1. The contribution of vaccine immunogenicity, and humoral and cellular immune responses to long-term immune memory (Reprinted with permission from Elsevier [1]).

vaccine which is thought to contribute to the duration of immunity (Fig. 1) [1,5].

Enhancement of protective immunity through vaccination

Prophylactic human papillomavirus (HPV) vaccines are highly immunogenic and, in clinical trials, have demonstrated up to 100% efficacy against persistent HPV infection and cervical lesion development [7–9]. In order to provide protection against persistent HPV infection and the subsequent development of cervical lesions, an effective HPV vaccine must be able to induce strong humoral immune responses [12]. Vaccine formulations that significantly increase the level and persistence of serum antibodies will also effectively enhance cellular immune memory, including the induction of memory B cells [10].

The bivalent HPV-16/18 vaccine, formulated with the ASO4 (3-*O*-desacyl-4'-monophosphoryl lipid A (MPL) and aluminium hydroxide) adjuvant system, produces an enhanced immune response that persists for ≥ 3.5 years after vaccination [10]. The ASO4 adjuvant also induces a higher frequency of HPV L1 virus-like particle (VLP)-specific memory B cells and a higher antibody response, compared with aluminium hydroxide.

The results of a double-blind placebo-controlled study ($n=522$), in women aged 16 to 23 years followed for up to 5 years indicated that following a three-dose quadrivalent HPV (6/11/16/18) (containing a proprietary amorphous aluminium hydroxyphosphate sulfate) vaccination regimen, serum antibodies against HPV declined, reaching a plateau at 2 years and remaining stable through to 5 years [11]. A challenge HPV vaccine dose delivered at 5 years confirmed the long-term protection provided by the quadrivalent vaccine; levels of antibodies against HPV levels at 1 week and 1 month post-challenge were higher than those observed 1 week and 1 month after the three-dose vaccination program. These findings demonstrate the induction of robust immune memory following routine vaccination with a quadrivalent vaccine against HPV in young women. This aluminum adjuvant was shown, in a mouse model, to be more immunogenic in the context of HPV L1 VLP

vaccines than aluminium hydroxide or aluminium phosphate, and most likely enhanced memory immune responses to L1 peptides [12].

Mathematical modeling analyses have been utilized in an attempt to determine the long-term antibody response of a three-dose regimen of HPV VLP type 16 prophylactic vaccine administered to 16- to 23-year-old women [13]. An antibody decay model, fitted to serum anti-HPV-16 levels measured over a 48-month period, estimated that in 50% of women anti-HPV-16 levels would remain above those induced naturally by HPV infection for 12 years, and above detectable levels (>5.9 mMU/mL) for 32 years. A modified model (with a better data fit) predicted that 99% of women would have almost life-long detectable anti-HPV-16 levels [13].

The findings of HPV vaccination trials with bivalent and quadrivalent vaccines suggest that the mechanisms of protection induced by HPV vaccination appear similar to immunity induced by HBV vaccination. This includes high rates of seroconversion and the establishment of immune memory including memory B cell population. Earlier studies of specific lymphocyte responses have also found similarities in host response with these two vaccines. Emeny et al. studied an experimental monovalent HPV-11 vaccine and found lymphoproliferative responses in women receiving the vaccine when compared to the placebo group [14]. Likewise, Pinto et al. found similar cytokine responses to HPV VLP vaccination [15].

Long-term protection: Human papillomavirus vaccine

Clinical trials of the bivalent and quadrivalent HPV vaccines have evaluated long-term efficacy against HPV infection to a maximum of 5 years [7–9,16,17]. The long lag-time between exposure to HPV infection and the development of invasive cervical cancer raises certain considerations with regard to the extension of these trials and the evaluation of long-term outcomes [18]. Furthermore, participants in phase III HPV vaccination trials are routinely screened and cervical lesions are detected and treated at an early stage. Population-based long-

term efficacy trials conducted in Nordic countries, in parallel with phase III clinical trials, aim to investigate the long-term efficacy of HPV vaccination with regard to invasive cervical cancer [19].

Countrywide registration regarding population and health events in a stable population of approximately 25 million makes the Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) an ideal setting for the evaluation of long-term cervical cancer control. Mass-screening programs for cervical cancer have been underway in the Nordic countries for the past four decades; over the past thirty years these programs have reduced cervical cancer-related mortality by 59% (Denmark) to 76% (Sweden) [16]. Currently, there are two ongoing double-blind, population-based phase III–IV Nordic trials which aim to determine the long-term protection of HPV vaccination against invasive cervical cancer and cervical intraepithelial neoplasia (CIN) grade 3 utilizing cancer-registry follow-up [16]. These trials will have high power to detect the impact of HPV vaccination on high-grade squamous intraepithelial lesions by the years 2015 to 2020 [19].

Long-term efficacy with the quadrivalent HPV vaccine

In clinical trials of up to 5 years' duration, the quadrivalent vaccine administered in a three-dose regimen, demonstrated vaccine efficacy in the order of 98% to 100% and effectively prevented persistent HPV infection in women aged 16 to 23 years [9,16]. Data from a phase II randomized, multicentre study ($n=552$), indicated that vaccine efficacy was maintained at 5 years. In the vaccinated women, there was a 96% reduction in the combined incidence of HPV 6/11/16/18-related persistent infection or disease, and there were no cases of precancerous cervical dysplasia compared with six cases in the placebo arm [9]. Vaccination with the quadrivalent vaccine also induced long-term immune memory with anti-HPV geometric mean titers after 5 years remaining at or above those observed with natural infection [9].

The Females United To Unilaterally Reduce Endo/Ectocervical Disease (FUTURE I and II) phase III clinical trials followed women aged between 15 and 26 years for up to three years and indicated that the quadrivalent vaccine has the potential to substantially reduce the incidence of HPV-16 and -18-related cervical precancers and cancers [8,16,17]. After 3 years, there was a significant reduction in the incidence of high-grade CIN related to either HPV-16 or -18 in women vaccinated with the quadrivalent HPV vaccine: CIN grade 2 or 3 or adenocarcinoma *in situ* developed in 1 woman receiving the HPV vaccine and 42 placebo recipients [8,16]. In a combined analysis of several randomized clinical trials, the per-protocol analysis demonstrated that after a mean of three years, vaccine efficacy for the primary endpoint of the combined incidence of HPV-16 and -18-related CIN 2/3, or adenocarcinoma *in situ* was 99% (Table 1) [17].

A long-term, placebo-controlled, phase III trial evaluating vaccine efficacy in 16- to 17-year-old women (22,412 invited participants) and 18-year-old unvaccinated controls (30,947 invited participants) is currently ongoing in Finland [20]. The

Table 1

Quadrivalent vaccine efficacy in women with cervical disease aged 16 to 26 years after a mean of 3 years (per protocol susceptible population)

	Vaccine ^a			Placebo ^a			Efficacy (%; 95% CI)
	N	Cases	Rate	N	Cases	Rate	
HPV-6/18-related CIN 2/3 or AIS	8579	1	<0.1	8550	85	0.4	99 (93–100)
CIN2	8579	0	0	8550	56	0.3	100 (93–100)
CIN3	8579	1	<0.1	8550	51	0.2	98 (89–100)
AIS	8579	0	0	8550	7	<0.1	100 (31–100)
HPV-16-related	7455	1	<0.1	7265	73	0.4	99 (92–100)
HPV-18-related	7450	0	0	7381	18	0.1	100 (78–100)

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AIS=adenocarcinoma *in situ*; CI=confidence interval; CIN=cervical intraepithelial neoplasia; HPV=human papillomavirus.

^a Numbers with ≥ 1 follow-up post-dose: 8492 vaccine vs. 8462 placebo for HPV-16/18-related endpoints; 7401 vs. 7203 for HPV-16 endpoints; 7381 vs. 7314 for HPV-18 endpoints.

study cohort will be linked to the Finish Cancer Registry using cervical carcinoma *in situ* and invasive cervical carcinoma as endpoints.

Long-term efficacy with the bivalent HPV vaccine

The bivalent HPV vaccine (16/18), administered according to a three dose regimen, has been shown to provide sustained efficacy for up to 4.5 years duration [7]. In a randomized, controlled, extended follow-up study in 776 women (mean age of 23 years) >98% seropositivity was maintained at 4.5 years [7]. Geometric mean antibody titres slowly declined from the peak response recorded 1 month after the third vaccine dose, reaching a plateau at 18 months. At 51 to 53 months, vaccine-induced geometric mean titres were in the order of 17- and 14-fold higher for HPV-16 and -18, respectively, relative to titres observed with naturally acquired infection [7].

In 2007, phase III results from the bivalent vaccine were published. Over 18,000 women were randomized in the clinical trial and the mean follow up was approximately 15 months. In this trial, the bivalent vaccine was 90.4% effective [21].

The bivalent vaccine is also currently being evaluated with the goal of providing long-term efficacy data on the HPV-16/18 vaccine against cervical carcinoma *in situ* by the year 2020 [22]. A total of 24,046 women aged 16 to 17 years were invited to participate in the vaccination arm and 58,996 8- to 19-year-old women were invited to participate as unvaccinated controls. These women will be passively followed for the cumulative incidence of cervical carcinoma *in situ* using a population-based cancer registry.

Summary

Long-term vaccine efficacy is dependent on the persistence of a robust immune memory. Studies evaluating the relationship between the immune response and the HBV vaccine have determined that the B cell response is the main factor driving immune memory although other mechanisms also contribute to a persistent immune response. To be effective in the prevention

of cervical cancer, HPV vaccines must induce long-term protection through a strong immune memory response. The immunogenicity of HPV vaccines also appears to be determined by the form of adjuvant that is used. Both an enhanced immune response and immune memory were generated in response to an HPV VLP vaccine containing either amorphous aluminum hydroxyphosphate sulfate or the AS04 adjuvant system. Evidence from clinical trials indicates that both bivalent and quadrivalent HPV vaccines induce strong immune memory responses over periods of up to 5 years. Available data demonstrate that this long-term protection confers a reduced risk of HPV-16 and -18-related CIN 2/3, adenocarcinoma *in situ*, or cervical cancer. The results of the Nordic trials will provide more definitive data on the long-term protective efficacy of the HPV vaccine against cervical cancer.

Question and answer

What is the relationship between HPV infections and cervical cancer?

Infection with human papillomavirus is a necessary cause of cervical cancer. Nearly all cervical cancers contain HPV DNA. For the past two to three decades, a large number of epidemiological and laboratory studies have confirmed this relationship. Epidemiological studies show that a large number of women acquire HPV infections. These infections are sexually transmitted and usually happen within the first few years of becoming sexually active. Most of these infections clear without causing neoplastic changes. However, in a small minority of women persistent HPV infection develops. This persistent infection leads to ongoing production of the two HPV oncogenes, E6 and E7. Preinvasive and invasive malignancies can develop as a result of these persistent HPV infections. HPV 16 and HPV 18 are the two strains of HPV most closely associated with cervical cancer.

Conflict of interest statement

KA has received grant/research support and is a consultant for Genzyme, GlaxoSmithKline, Merck, Gen Probe and Advaxis

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