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SHORT REPORT

Antibody persistence after a single dose of quadrivalent HPV vaccine and the effect of a dose of nonavalent vaccine given 3-8 years later – an exploratory study

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ABSTRACT

The objective of this study was to assess the persistence of antibodies after a single dose of quadrivalent HPV vaccine (4vHPV) and the effect of a dose of nonavalent HPV vaccine (9vHPV) given 3–8 years later. Such data might be of interest in the decision-making process regarding the 2-dose course completion in non-compliant vaccinees in jurisdictions which switched from 4vHPV to 9vHPV. Girls who previously received a single dose of 4vHPV were eligible to participate. Blood specimens were collected just before and one month post-9vHPV administration. The specimens were tested by ELISA for the presence of antibodies to 9 HPV types included in the 9vHPV. Thirty-one girls aged 13–18 years (mean 15.5 years) participated in the study. Pre-9vHPV administration, all participants were seropositive to 4 HPV types included in 4vHPV and 58%-87% were seropositive to the five other HPV types included in the 9vHPV. GMTs were 6.1 AU/ml, 7.7 AU/ml, 20.1 IU/ml and 6.3 IU/ml to HPV6, HPV11, HPV16 and HPV18, respectively. The GMTs for the other five HPV types varied from 1.0 to 2.9 AU/ml. One month post-9vHPV administration all 31 participants were seropositive to all 9 HPV types with a 36.1 to 89.1-fold increase of GMTs. High seropositivity rates observed several years after a single dose of 4vHPV and 100% seropositivity after a dose of 9vHPV suggest that this schedule might be used in non-compliant vaccinees or when switching immunization programs from 4vHPV to 9vHPV.

Introduction

More than a decade of worldwide experience with HPV vaccines has shown that they are safe, highly immunogenic and ensure excellent protection against related disease.[1–3] Initially HPV vaccines were tested and approved for clinical use in a 3-dose schedule. Subsequently, 2-dose schedules were approved and are presently used in most jurisdictions which implemented an HPV vaccination program.[4,5]

Reports from different countries systematically show higher vaccine uptake for the first dose when compared to the second or the third vaccine dose.[6–8] Although the differences per dose uptake vary in time and among jurisdictions, on average 4–7% of those who received the first dose do not return for the second dose on schedule.[9] This is also observed in the province of Quebec, Canada[10] where 9–10-year-old girls and boys are eligible for school-based 2-dose HPV vaccination. With an annual provincial birth cohort of about 89 000 children and a 5% drop out in the uptake of the second dose we estimate that every year around 4000 children are vaccinated with a single dose of vaccine.

As a general rule, individuals who began but did not finish the full course of vaccination may complete it at any time later. In the case of grade 4 school-based HPV vaccination programs, such as that in Quebec, an update of the vaccination status is usually done during high school years (grade 9). However, the available data regarding the persistence of immunity after a single dose of HPV vaccine is relatively limited,[11,12] and to our knowledge no data are available regarding the effect of a dose of nonavalent vaccine (Gardasil®9; 9vHPV) given to individuals who received a single dose of quadrivalent vaccine (Gardasil®; 4vHPV) several years earlier. Generally, vaccination series are recommended to be completed with the same vaccine if possible; this applies also to HPV vaccines. One of the reasons for this recommendation is that it is not known how mixed dose schedules would work. Data on mixed HPV vaccination schedules might be valuable when deciding about the completion of the 2-dose vaccination course in jurisdictions that switched from 4vHPV to 9vHPV vaccine, for the completion of vaccination in non-compliant vaccinees in jurisdictions were 4vHPV vaccine is no longer available, and in case of vaccine supply problems. The objective of this study was to assess the persistence of antibodies after a single dose of 4vHPV and the effect of a dose of 9vHPV vaccine given 3–8 years later.

Results

We recruited and administered a dose of 9vHPV to 31 girls aged between 13 and 18 years (mean age 15.5 years) whose vaccination records showed that they previously received only one dose of 4vHPV vaccine. The interval between 4vHPV dose administration and first blood collection varied from 3 to 8 years (mean 5.4 years) and between 9vHPV administration and second blood collection from 28 to 35 days (mean 32 days).

Antibody persistence and GMTs after a single dose of 4vHPV vaccine

All participants were seropositive to the HPV types included in the 4vHPV administered 3 to 8 years earlier and 58% to 87% had antibodies to the five other HPV types included in the 9vHPV vaccine. GMTs were 6.1 AU/ml, 7.7 AU/ml, 20.1 IU/ml and 6.3 IU/ml for HPV6, HPV11, HPV16 and HPV18, respectively (Table 1). GMTs for the other five HPV types not included in the 4vHPV vaccine varied from 2.0 to 5.2 AU/ml in subjects seropositive for these HPV types and from 0.3 to 1.3 in those classified as seronegative (Table 2).

Immunogenicity of a dose of 9vHPV vaccine

One month post-9vHPV vaccine administration, the 31 participants (100%) were seropositive to all nine HPV types with a 36.1 to 89.1-fold increase of GMTs. (Table 1). The post-9vHPV vaccine GMTs to HPV31, HPV33, HPV45, HPV52 and HPV58 were slightly higher (all $p > 0.05$) in subjects seropositive pre-9vHPV dose administration, increasing 24.3–82.1-fold in those seropositive and 62.1–236.0-fold in those seronegative (Table 2).

Safety of 9vHPV

The 9vHPV was well tolerated. No serious adverse events were reported during one month of follow-up.

Discussion

To our knowledge, this is the first study which assessed the seropositivity to HPV types included in the 9vHPV vaccine several years after a single dose of 4vHPV, and the effect of a dose of 9vHPV vaccine when administered 3–8 years later. The observed 100% seropositivity after a single dose of vaccine to four HPV types included in the 4vHPV vaccine is in line with previous studies results.[13–15] Interestingly, 3–8 years after a single dose of vaccine 58–87% of participants (were seropositive to 5 HPV types not included in the 4vHPV vaccine. Although we did not recorded sexual history of participating subjects, in our opinion, it is unlikely that such a high proportion of 13–18 year-old girls were exposed to so many HPV types and have post-infection antibodies. It is plausible these antibodies were induced by previous vaccination with one dose of 4vHPV vaccine.

One month post-9vHPV vaccine administration, a vigorous immune response (36 to 89-fold GMTs increase) was observed for all 9 HPV types included in the 9vHPV vaccine. Such a response suggests that priming was induced by the dose of 4vHPV given several years before the 9vHPV dose and that the response observed after 9vHPV administration might be interpreted as a booster effect. Although the clinical importance of antibody titers is not well understood, the observed increase of GMTs after a dose of 9vHPV in this study suggests that a single dose of this vaccine might be sufficient to ensure protection in girls previously vaccinated with a dose of 4vHPV vaccine.

This study has several limitations. First, the number of participants enrolled is small (n = 31). However, we observed 100% seropositivity rates with the lower limit of 95% confidence interval at 88.7%. Such a precision seems reasonable in this context. Second, no control group of previously unvaccinated girls was available for comparison. However, in another parallel study conducted by our team (unpublished data) antibody GMTs one month after a single dose of 9vHPV given to previously unvaccinated girls and boys were significantly lower when compared to this study GMTs to all 9 HPV types included in the vaccine (serological tests done at the same laboratory by using the same methodology). This observation suggests that the 4vHPV induced priming for the five other HPV types present in the 9vHPV. Third, the range in interval between 4vHPV dose administration and blood sample collection (3 to 8 years) and the small number of participants preclude the analysis of the impact of time on antibody dynamics. Finally, this study addresses only the peak antibody response following the second dose and long-term persistence is not determined. However, the 100% seropositivity regardless of the time delay since the first dose and previously published data indicating antibody titers plateau 18–84 months post-vaccination,[11,13,16–18] as well as the previously reported high efficacy of one and two doses of HPV vaccines[19–21] are reassuring.

In contrast to several previous studies which measured HPV antibody titers by using competitive Luminex immunoassay (cLIA) we used multiplex direct IgG ELISA immunoassay (M9ELISA). Comparisons of cLIA and ELISA assays for HPV[22,23] show these assays are generally in good to moderate agreement. The largest discrepancies are observed in low titer situations observed in unvaccinated individuals, particularly for HPV18. The agreement is the best in high-titer post-vaccination situations. These peculiarities are most probably dues to the fact that the HPV18 monoclonal component used in the cLIA was selected mainly for specificity at the price of some loss in sensitivity. Given the high titers observed in our study, it is unlikely results would have been significantly impacted by the assay.

In summary, this study findings lead us to believe that priming to HPV6, 11, 16, 18, 31, 33, 45, 52 and 58 is induced by a single dose of 4vHPV. The results suggest that one dose of 9vHPV might be used to complete the series in girls who received only one dose of 4vHPV and failed to receive a second dose on schedule. In addition, the data is reassuring for immunizations programs that shift formulation from 4vHPV to 9vHPV vaccine.

Methods

Population and study design

This is an exploratory single group study. Girls living in the Quebec City area who received a single dose of 4vHPV between 2008 and 2013 through regular publicly funded school-based immunization programs were identified from the regional vaccination registry. Immunosuppressed girls

Table 1. Anti-HPV seropositivity and GMTs 3–8 years after a dose of quadrivalent and one month after a dose of nonavalent HPV vaccine.

	Post-4vHPV vaccine* n = 31		Post-9vHPV vaccine** N = 31		
HPV type	% seropositive (95% CI)	GMT† (95% CI)	% seropositive (95% CI)	GMT (95%CI)	GMTs-fold increase post/pre 9vHPV administration (95%CI)
HPV6	100.0 (88.8–100.0)	6.1 (3.5–10.6)	100.0 (88.8–100.0)	405.5 (271.6–605.3)	66.8 (34.1–130.9)
HPV11	100.0 (88.8–100.0)	7.7 (4.5–13.1)	100.0 (88.8–100.0)	552.9 (348.5–877.2)	71.7 (36.0–143.1)
HPV16	100.0 (88.8–100.0)	20.1 (12.0–33.7)	100.0 (88.8–100.0)	1640.5 (1094.7–2458.3)	81.5 (42.9–154.8)
HPV18	100.0 (88.8–100.0)	6.3 (3.8–10.2)	100.0 (88.8–100.0)	374.7 (246.7–569.1)	59.8 (31.8–112.5)
HPV31	87.1 (70.2–96.4)	2.2 (1.4–3.2)	100.0 (88.8–100.0)	192.0 (121.7–302.8)	89.1 (48.9–162.2)
HPV33	64.5 (45.4–80.8)	1.6 (1.0–2.3)	100.0 (88.8–100.0)	107.0 (66.6–172.03)	69.3 (37.9–126.6)
HPV45	58.1 (39.1–75.5)	2.9 (2.0–4.0)	100.0 (88.8–100.0)	103.5 (66.7–160.5)	36.1 (20.9–62.1)
HPV52	67.7 (48.6–83.3)	1.0 (0.7–1.6)	100.0 (88.8–100.0)	71.1 (50.9–99.2)	68.6 (39.5–119.1)
HPV58	64.5 (45.4–80.8)	1.8 (1.1–2.8)	100.0 (88.8–100.0)	118.5 (81.3–172.5)	66.0 (37.1–117.6)

*4vHPV – quadrivalent HPV vaccine; 9vHPV – nonavalent HPV vaccine; †GMT – anti-HPV geometrical mean titers.

Table 2. Anti-HPV geometrical mean titers to HPV31, HPV33, HPV45, HPV52 and HPV58 in subjects seropositive and seronegative before nonavalent vaccine dose administration.

HPV type	Anti-HPV GMTs† in subjects seropositive pre-9vHPV			Anti-HPV GMTs in subjects seronegative pre-9vHPV		
	Pre-9vHPV** dose administration (95%CI)	Post-9vHPV dose administration (95%CI)	GMTs-fold increase post/pre 9vHPV administration (95%CI)	Pre-9vHPV dose administration (95%CI)	Post-9vHPV dose administration (95%CI)	GMTs-fold increase post/pre 9vHPV administration (95%CI)
HPV31	2.8 (2.0–4.1)	232.7 (145.1–373.2)	82.1 (46.1–146.4)	0.3 (0.2–0.5)	52.4 (17.1–160.8)	154.5 (61.0–391.1)
HPV33	2.9 (2.1–4.0)	133.6 (82.3–216.8)	45.8 (26.1–80.6)	0.5 (0.4–0.7)	71.5 (23.7–216.2)	146.6 (49.7–433.0)
HPV45	5.2 (3.7–7.3)	125.8 (67.9–233.1)	24.3 (12.3–48.0)	1.3 (0.9–1.7)	78.9 (40.0–155.7)	62.2 (30.9–125.2)
HPV52	2.0 (1.4–2.9)	77.4 (53.7–111.5)	38.1 (23.1–62.6)	0.3 (0.2–0.4)	59.4 (26.5–133.1)	236.0 (99.4–560.6)
HPV58	3.6 (2.4–5.5)	140.0 (94.7–206.8)	38.7 (22.18–7.6)	0.5 (0.4–0.7)	87.5 (36.7–208.5)	173.9 (72.3–418.7)

**9vHPV – nonavalent HPV vaccine; †GMT – anti-HPV geometrical mean titers.

and those who had blood coagulation disorders were excluded.

Prior to any study intervention a written informed consent was obtained from all participants. During the first study visit the medical history was collected and at each study visit eligibility criteria were verified. A research nurse collected a blood sample (10 mL) and then administered a single 0.5 mL dose of 9vHPV intramuscularly in the deltoid muscle. A second blood sample (10 ml) was collected one month later.

The study was approved by the local research ethics board (CHU de Québec – Université Laval; project number approval: CÉ: 2017–3036-21) and is registered with ClinicalTrials.gov: NCT03431246.

Laboratory procedures

Laboratory assays were performed at the Centers for Disease Control and Prevention (CDC, Atlanta, USA) using multiplex direct IgG ELISA to HPV L1 + L2 virus-like particles (VLPs) on Meso Scale Discovery platform as previously described with minor modifications.[23]

The M9ELISA used VLPs for HPV6, 11, 16, 18, 31, 33, 45, 52 and 58 pre-coated on 10-spot standard plates (Meso Scale Discovery, MSD, Gaithesburg, MD). Test sera were 3.16 fold serially-diluted for at least 3 dilutions starting at 1:100 or higher. Dilutions of reference sera were used in each plate to allow titer determination using the parallel line method (PLL). PLL analysis was performed as described in the WHO HPV Labnet Manual,[24] using raw signal for each HPV type. Cut-off values (COV) were determined using serum samples from children (n = 50, Gift from Dr. J Dillner, Lund University). Test samples were considered positive if they passed PLL conditions as well as were above median+2 standard deviations of the PLL/titer generated from the children sera. Cut off value for HPV6, 11, 16, 18, 31, 33, 45, 52 and 58 were 0.1 AU/ml, 0.1 AU/ml, 0.5 IU/ml, 0.4 IU/ml, 0.5 AU/ml, 1.3 AU/ml, 2.5 AU/ml, 0.7 AU/ml and 1.2 AU/ml, respectively.

Data analysis

We estimated the proportion of subjects with detectable anti-HPV and geometrical mean antibody titers (GMTs) with their 95% confidence intervals. As all subjects had detectable antibodies, the GMT calculation included values below COV for seropositivity. All statistics were 2-tailed. SAS Institute software version 9.2 (Cary, NC, USA) was used for statistical analysis.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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Disclaimer

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