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Use of the nonavalent HPV vaccine in individuals previously fully or partially vaccinated with bivalent or quadrivalent HPV vaccines

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ABSTRACT

With the availability of the nonavalent human papillomavirus (HPV) vaccine, vaccinees, parents and healthcare providers need guidance on how to complete an immunization course started with the bi- or quadrivalent vaccine and whether to revaccinate individuals who have completed a full immunization course with the bi- or quadrivalent vaccine. To answer these questions three parameters should be considered: age at the start of vaccination (9 to 14 years of age versus 15 years and older, the cut-off for 2 or 3 doses schedule), the number of doses already received and the time interval between doses. Based on a number of scenarios, we propose that the 9-valent vaccine can be used to complete an incomplete vaccination regimen or might be added to a previous completed schedule to extend protection.

The new nonavalent HPV vaccine (9vHPV, trade name Gardasil9) has been approved for use in USA [1], Canada [2], Australia [3], and the European Union [4]. This vaccine includes high-risk HPV types 16, 18, 31, 33, 45, 52, and 58 in addition to the low-risk HPV types 6 and 11.

This new vaccine comes in addition to two HPV vaccines already commercially available in a large number of countries. Cervarix® is a bivalent vaccine (2vHPV) that targets HPV16 and 18, two HPV types that cause cervical cancer. Gardasil® (4vHPV) targets the same oncogenic types, as well as HPV6 and 11, which cause external genital warts. Thus far, millions of women and a smaller number of men have been immunized with these two HPV vaccines, with a well-documented safety profile [5–9]. Both vaccines protect against HPV type 16/18 related genital diseases, essentially against 50% of cervical intraepithelial neoplasia (CIN) 2/3 and 70% of cervical cancer [10]. The 5 additional types in 9vHPV increase the protection against cervical cancer to approximately 90%. For CIN1, CIN2 and CIN3 lesions, the increases are 20%, 30% and 30%, respectively [11], see Fig. 1.

With the availability of the 9vHPV, vaccinees (and their parents) and healthcare providers may wonder how to complete an immunization course started with the bi- or quadrivalent vaccine and whether to revaccinate individuals who have completed a full immunization course with the bi- or quadrivalent vaccine. The European summary of product characteristics of the three HPV vaccines states that individuals who received a first dose with a given HPV vaccine should complete the vaccination course with that same vaccine [12–14]. The US Advisory Committee on Immunization Practices (ACIP) [15,16] on the other hand, states that "any available HPV vaccine product may be used to continue or complete the series for females for protection against HPV 16 and 18". Taking the above into consideration, we propose a pragmatic approach

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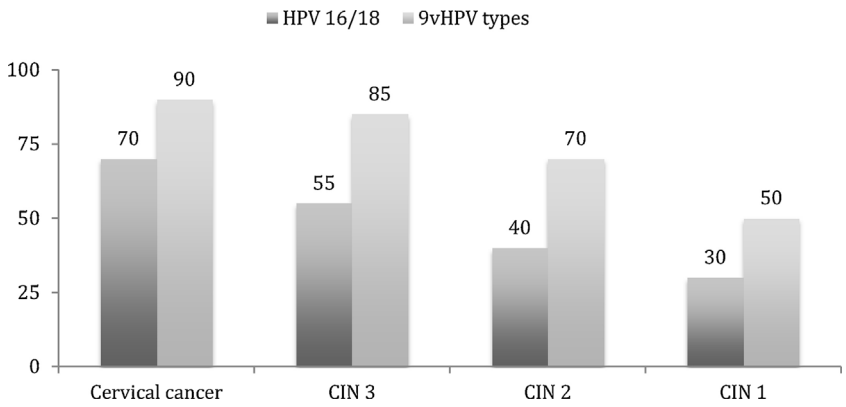

Fig. 1. Contribution of high risk HPV types covered by the bi- and quadrivalent vaccines and the nonavalent vaccine to cervical cancer and precancerous cervical lesions. 9vHPV types are: 6, 11, 16, 18, 31, 33, 45, 52, and 58. The overall contribution of HPV to CIN 1 = 73%, CIN 2 = 86%, CIN 3 = 93%, cervical cancer = 100%. Figure adapted from Hartwig et al. [11].

based on limited existing data, and where data are not yet available, on expert opinion. The proposed guidelines are drafted for a transitional period, and address the questions raised on an individual rather than on a programmatic level. While drafting the different scenarios we did not take economic considerations into account, as the proposed schedules have not been sufficiently evaluated economically [15,16].

A pivotal randomized, controlled clinical trial (RCT) [17] comparing 9vHPV with the 4vHPV vaccine demonstrated a high vaccine efficacy of 9vHPV against high-grade cervical, vulvar, or vaginal disease related to the new HPV types 31, 33, 45, 52, and 58 of 96.7% (95% confidence interval, 80.9% to 99.8%). Simultaneously, antibody responses to HPV-6, 11, 16, and 18 were non-inferior to those generated by the 4vHPV vaccine. Consequently, efficacy for 9vHPV against persistent infection and disease related to HPV types 6, 11, 16, or 18 can be inferred to be comparable to that of 4vHPV [17]. Finally, immunization with 9vHPV was shown to be well tolerated and safe in the pivotal RCT, and although it resulted in more adverse local reactions than vaccination with the 4vHPV vaccine, as expected due to the higher dose of antigen and/or adjuvant, more than 90% of these reactions were mild to moderate in intensity [17].

Subsequent injection (using 9vHPV to complete a HPV vaccination course initiated with a bi- or quadrivalent vaccine) has not been assessed in the clinical development program so far. Similarly, no data are available on revaccination with 9vHPV of subjects who completed an immunization course with 2vHPV. Revaccination was investigated in a clinical trial (study V503-006, ClinicalTrials.gov Identifier: NCT01047345), which assessed the safety and immunogenicity of complete 3 doses 9vHPV administration in 4vHPV recipients (3-dose schedule) with a minimum 12-month interval (with the third dose of 4vHPV administered at least one year prior to the first dose of 9vHPV) [18]. 9vHPV was found to be highly immunogenic without safety concerns. In the group that received 3 doses of 4vHPV and then 3 doses of 9vHPV, the geometric mean titers (GMTs) to HPV types 6, 11, 16, 18 were higher than in the 4vHPV vaccine naïve population from other studies, whereas the GMTs to HPV Types 31, 33, 45, 52 and 58 were lower than in 9vHPV-vaccinated, 4vHPV vaccine naïve subjects, see Fig. 2 [18]. The expectation is that these girls will be protected against the 5 new HPV types. Whether protection is comparable to that against HPV types 6, 11, 16, 18 is yet unknown.

To answer the two questions on how to complete an immunization course started with the bi- or quadrivalent vaccine and the usefulness of revaccinating individuals who have completed a full immunization course with the bi- or quadrivalent vaccine, three parameters should be considered: age (9 to 14 years of age versus 15 years and older, the cut-off for 2 or 3 doses schedule), the number of doses already received and the time interval between doses. For those countries considering male vaccination, our recommendations for girls are also valid for boys, as immunogenicity in boys is similar, if not higher, compared to girls [19].

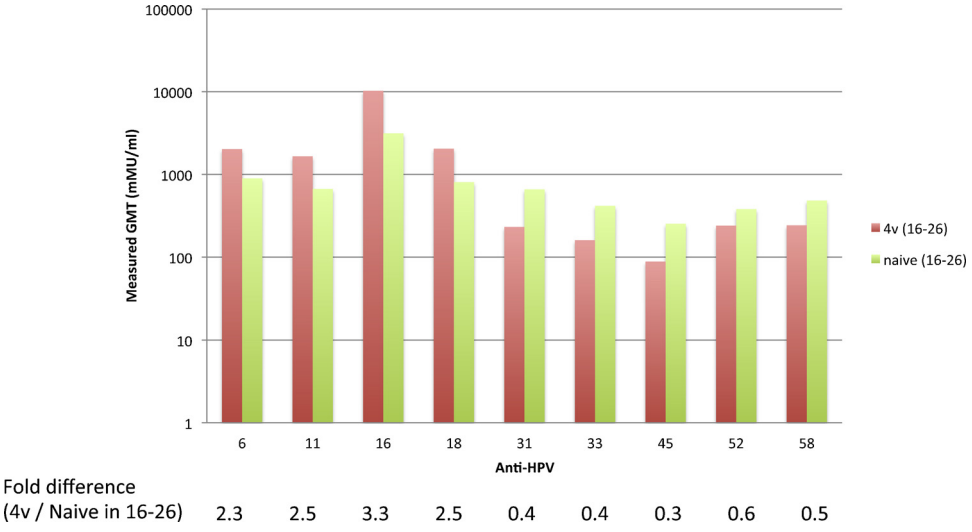

Fig. 2. Geometric mean titers in 4vHPV naïve and 4vHPV-vaccinated women (16–26 years old). Figure adapted from Garland et al. [18].

Table 1
Scenarios and proposed approaches, for girls 9–14 years of age.

Scenario	Month 0	Month 2	Month 6	Month 12	Month 18	Expected protection*
Sequential doses administration						
A	2vHPV		2vHPV			2 types
	2vHPV		2vHPV	9vHPV	9vHPV	2 types and likely protection for the 7 extra types
	4vHPV		4vHPV			4 types
	4vHPV		4vHPV	9vHPV	9vHPV	4 types and likely protection for the 5 extra types
B	2vHPV	2vHPV				No evidence
	2vHPV	2vHPV	9vHPV			2 types
	2vHPV	2vHPV	9vHPV	9vHPV		2 types and likely protection for the 7 extra types
	4vHPV	4vHPV				Incomplete
	4vHPV	4vHPV	9vHPV			4 types
	4vHPV	4vHPV	9vHPV	9vHPV		4 types and likely protection for the 5 extra types
C	2vHPV					No evidence
	2vHPV		9vHPV			2 types
	2vHPV		9vHPV	9vHPV		2 types and likely protection for the 7 extra types
	4vHPV					No evidence
	4vHPV		9vHPV			4 types
	4vHPV		9vHPV	9vHPV		4 types and likely protection for the 5 extra types
Revaccination						
D	2vHPV	2vHPV	2vHPV			2 types
	2vHPV	2vHPV	2vHPV	9vHPV	9vHPV	2 types and likely protection for the 7 extra types
	4vHPV	4vHPV	4vHPV			4 types
	4vHPV	4vHPV	4vHPV	9vHPV	9vHPV	4 types and likely protection for the 5 extra types

: already received : additional

* Expected according to currently available data and expert judgment, the role of cross-protection provided by the bi- and quadrivalent vaccines was ignored.

We first consider the situation in girls less than 15 years of age, where we can distinguish 4 scenarios:

In *scenario A*, revaccination, i.e., a girl has received two doses of the bi- or quadrivalent HPV vaccine six months apart. Based on immunogenicity results, two doses of HPV vaccine, minimum six months apart should offer protection against the two, respectively, four types in the vaccine, in girls between 9 and 14 years of age [20,21]. Consequently, in view of the immunogenicity data, WHO changed its previous recommendation of a 3-dose schedule to a 2-dose schedule with a 6-month interval between doses for both the bi- and quadrivalent HPV vaccines, in females younger than 15 years [22]. In most EU countries the vaccination schedule has been reduced from three to two doses in the adolescent population. A clinical trial is ongoing comparing safety and immunogenicity of a 2-dose 9vHPV regimen in boys and girls 9 to 14 years of age to a 3-dose schedule of 9vHPV in females 16 to 26 years of age (V503-010, ClinicalTrials.gov Identifier: NCT01984697): available immunogenicity and safety data support the administration of a 2-dose regimen of 9vHPV, where the second dose is administered 6 to 12 months (±1 month) following the first dose, as an alternative to the 3-dose regimen for girls and boys 9 to 14 years of age (data on file). Based on these results, and using the same approach as that previously accepted for licensure of a 2-dose regimen of 4vHPV, efficacy findings in young women who received the 3 dose regimen of 9vHPV can be extended to girls and boys 9 to 14 years of age who received the 2-dose (0, 6) or (0, 12) regimen including full protection against the 5 additional types. For scenario A, to achieve protection against the new types, the girl would therefore have to be vaccinated with the 9vHPV vaccine, with 2 injections—6 to 12 months apart.

In *scenario B*, a girl has received only two doses of the bi- or quadrivalent HPV vaccine two months apart which is not the timing recommended by WHO for a 2-dose vaccination schedule [22]. She may therefore not be fully protected against the 2 or 4 HPV

types [22]. This is likely to be remedied with an extra dose of 9vHPV between month 6 and month 12 – after the second dose of the original vaccine – to be fully protected against the original types she was vaccinated against (two or four HPV types, respectively). However, to achieve some extra protection against the 7 or 5 additional types (depending whether her initial doses were the bi- or the quadrivalent, respectively), she would need at least a second dose of 9vHPV vaccine 6 to 12 months later, as there is no data supporting that only 1 dose of 9vHPV will offer full protection.

In *scenario C*, a girl has received only one dose of the bi- or quadrivalent HPV vaccine. Currently there is no HPV vaccine licensed for single dose administration and there is no robust clinical disease data supporting protection against the 2–4 HPV types after one dose of bi- or quadrivalent vaccine, although some evidence has been presented that a single dose of the bivalent vaccine protects against HPV 16/18 infections for at least four years [23]. An extra dose of 9vHPV given 6 to 12 months after the first one should reasonably provide protection against the 2–4 original types. However, to achieve extra protection against the additional types, she would need at least a second dose of 9vHPV vaccine 6 to 12 months after, as described in scenario B.

Scenario D represents a girl who has finished her bi- or quadrivalent HPV vaccination schedule with 3 doses. She is therefore fully protected against HPV types 16 and 18 (and HPV types 6 and 11 for the quadrivalent vaccine). To achieve extra protection against the new types, the girl in this scenario should be vaccinated with the 9vHPV vaccine at least with 2 doses given 6 to 12 months apart (if under the age of 15). As discussed above, this may result in a lower immune response (expressed as lower GMTs) to the additional HPV types, with an as yet unknown clinical significance [24].

Table 1 summarizes, for each scenario, the vaccines, the interval and number of doses that should be considered, and the expected protection resulting from the extra doses.

In girls older than 15 years of age whose initial series was given before 15 years of age and in women), as in scenario D revaccination should be considered; 3 doses 9vHPV vaccine, according to a 0, 2 and 6 months schedule should be administered to provide full protection against the extra types in 9vHPV.

As previously mentioned, the scenarios described are not necessarily limited to girls, but may also apply to boys. Proposed guidance is based on available immunogenicity data supporting the administration of a 2-dose regimen of 9vHPV, where the second dose is administered 6 to 13 months (±1 month) following the first dose, as an alternative to the 3-dose regimen for girls and boys 9 to 14 years of age. (Data on file; ongoing clinical trial V503-010, ClinicalTrials.gov Identifier: NCT01984697).

We are fully aware that there are limitations to the presented scenarios, but so far no concrete data exist as vaccine trials with the proposed schedules have not been performed. The results of the 9vHPV vaccine study in females 12–26 years of age, previously completely vaccinated with 4vHPV, showed that the time interval between both series had no impact on the 9vHPV immunogenicity at month 7 [24]; the authors therefore do not expect a time interval to have any impact, but age at the moment of vaccine administration does. We are also aware that what is proposed in this paper should be regarded as valid for a transitional period in time. In addition, it is not proposed that vaccines and visits to existing programs (which would be major programmatic challenges) should be made. With the proposed scenarios the authors aim to address questions raised on an individual level (by a healthcare provider or vaccinee), rather than recommending that countries amend their HPV immunization program. Finally, we need to take into consideration that the durability of the response and the long-term efficacy of any 2-dose HPV vaccine regimen remains to be demonstrated, the impact on HPV, in particular on CIN2+, needs to be measured, and safety to be further documented.

In conclusion, the introduction of the new 9vHPV vaccine offering a significantly broader protection raises the question of what is the most appropriate and practical way for completing a vaccination course already started. We propose that the 9-valent vaccine can be used to complete an incomplete vaccination regimen (scenario B and C) or be added to a previous completed schedule (scenario A and D) to extend protection. The number of doses and timing depends on the doses already given, and the age of the vaccinee. Finally, for those countries considering male vaccination, this position can also be applied to the vaccination of boys.

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