What are the optimal schedules Human papilloma virus vaccines for adolescent girls?

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Today's Questions

May the HPV immunization schedule for adolescent girls be reduced from 3 to 2 doses ?

Are antibody responses after 2 adolescent doses non inferior to 3 doses in women *(efficacy demonstrated)*

- **peak titers**
- **plateau** **"immunological bridging"**

If yes, with which schedule ?

- **prime – prime (0 – 2 months)**
- **prime – bost (0 - ≥ 6 months)**

If yes: does this apply to both qHPV and bHPV vaccines ?

Protection after 3 or 2 adolescent doses of HPV

Assumptions:

The magnitude and kinetics of antibody persistence is expected to confer several decades (≥ 20 years) of protection *(cf HAV)*

- waning of individual efficacy is expected to occur at some point (progressively)
- this waning is expected to occur with similar rates / kinetics after 3 doses (prime-prime-boost) in adults as after 2 doses (prime-boost, ≥ 6 months interval) given in adolescents
- regardless of the vaccine used (bi- quadri – nonavalent)

because Ab titers are elicited / persist >>> protective thresholds

Protection after 3 or 2 adolescent doses of HPV

Assumptions:

Protection is expected to outlast antibody disappearance

Sexually transmitted disease with demonstrated strong vaccine-induced herd protection ↔ ↓↓ exposure

Countries/regions that have adopted or are planning to adopt a 2-dose schedule

Country	Schedule	Date implemented	Remarks
Quebec	2+0 (0, 6 m)	2013	Girls attending 4th Grade
Switzerland	2+0 (0, 6 m)	2012	
South Africa	2+0	March 2014	
UK	2+0 (0, 6 m)	2014	Minimum interval between doses 6 m, maximum 24 m
France	2+0 (0, 6 m)	2014	For 9-14 years
The Netherlands	2+0	unknown	
Chile	2+0 (0, 12 m)	2014	
Spain	2+0 (0, 6 m)	2014	Bivalent vaccine for girls 9-14 years

Countries/regions with an extended schedule

Country	Schedule	Date implemented	Remarks
Mexico	2+1 (0, 6, 60)	2008	Extended schedule. Follow-up of 60 months to assess the need of 3rd dose
Brazil	2+1 (0, 6, 60)	2014	
Colombia	2+1 (0, 6, 60)		
British Columbia	2+1 (0, 6, 60)	2013	Girls and young women born after 1994

Number of doses

Summary statement

- **Two doses of HPV vaccine in girls 9-14 years of age are non-inferior to 3 doses in terms of immunogenicity** when compared to 3 doses in girls 9-14 years or 3 doses in older women 15-24 years of age.
- The magnitude of the vaccine response is determined by the age at the first dose.
- **The inference is that a 2-dose vaccine schedule will be as efficacious as 3 doses, even though clinical efficacy data in girls are not available**.
- Limited data on efficacy and effectiveness with limited follow – up (e.g. up to 4 years) support these findings.
- *The bivalent vaccine has obtained EMA approval for a 2-dose schedule and the quadrivalent vaccine has already obtained a positive opinion of the CHMP.*

Number of doses

Recommendation	**Two dose (prime-boost) schedules (including at least 6 months between the first and the 2nd dose) are expected to provide similar protective efficacy compared to 3 dose schedules.** • A 2-dose schedule may be recommended to adolescent girls 9-14 years of age. • For girls primed before the age of 15 years, even if older at time of boosting (second dose), a 2-dose schedule may be considered.
Caution	There are fewer data comparing the efficacy of 2 versus 3 dose schedules. Longer term studies are underway.

Intervals between doses

Summary statement	• A second dose of vaccine given ≥ 6 months after the first dose (prime-boost) elicits an immune response non-inferior to that of a 3-dose schedule that uses a prime-prime-boost approach. • Data from one RCT reported that the 6-month interval resulted in superior GMCs compared with the 2-month interval one month after the last vaccine dose in all age groups enrolled (9-14, 15-19, 20-25 years). • Results from a multi-centric study will be available in the mid-term.
Recommendation	**For 2-dose schedules, the minimal interval between doses should be 6 months.** The interval between the first and second dose may be extended up to 12 months, should this facilitate administration – for example in school settings.
Caution	Data available is from one RCT

Special populations

Summary statement	Although the immunogenicity and efficacy of HPV vaccines may be reduced in HIV-infected females, the potential benefit of vaccination in this group is particularly great owing to their increased risk of HPV-related disease, including cervical cancer.
Recommendation	**A 3-dose schedule should be offered to individuals known to be immunocompromised** at time of immunization. The recommendation to target very young (9-10 year old girls) prior to sexual debut and risk of HIV acquisition is especially important in areas where HIV is prevalent.
Caution	There are limited data from HIV-infected individuals receiving a 3-dose schedule and, no data from HIV-infected individuals receiving a 2-dose schedule.

Proposed recommendations for SAGE

Number of HPV vaccine doses	• A 2-dose schedule may be recommended to adolescent girls 9-14 years of age. • For girls primed before the age of 15 years, even if older at time of boosting (second dose), a 2-dose schedule may be considered.
Intervals between doses	**For 2-dose schedules, the minimal interval between doses should be 6 months.** The interval between the first and second dose may be extended up to 12 months, should this facilitate administration – for example in school settings.
Special populations	• A 3-dose schedule should be offered to individuals known to be immunocompromised at time of immunization • Target very young (9-10 year old girls) prior to sexual debut and risk of HIV acquisition is especially important in areas where HIV is prevalent