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Human Papillomavirus (Types 6, 11, 16, and 18) Vaccine, Recombinant: Alternate Dosing Intervals

SUMMARY

CLINICAL TRIALS

There are no data in MSD clinical trials evaluating the efficacy of the vaccine administered at alternate intervals. The efficacy and immunogenicity analyses in the clinical trial program were conducted in subjects who had received all doses of the 4-valent HPV vaccine on the recommended schedule.

Several published studies have evaluated the immunogenicity of the 4-valent HPV vaccine administered according to alternative 3-dose schedules:

- **Widdice et al**.[1] A prospective study evaluating various dosing intervals found that prolonged intervals between doses did not appear to diminish antibody responses and may even enhance responses to the vaccine.

- **LaMontagne et al**.[2] A long-term extension of a previous publication by **Neuzil et al**[3] confirmed immunogenicity at up to 32 months of follow-up post-Dose 3.

- **Russell et al**.[4] A small prospective study evaluated antibody titers to the 4-valent HPV vaccine with delayed administration of Dose 2 and/or Dose 3 in 331 females 9-18 years of age. The results demonstrated that delays of Dose 2 or 3 do not interfere with immune responses after completion of the 3-dose series.

- **Zimmerman et al**.[5] A randomized trial compared the standard vaccination schedule for the 4-valent HPV vaccine to a prolonged alternate dosing regimen with the 3rd dose administered at 12 months. The analysis determined that Geometric Mean Titers (GMTs) with the alternate schedule were non-inferior to the standard schedule for all vaccine HPV types ($p<0.0001$);
    - In addition, responses were significantly higher with the alternate schedule for HPV 6, 11, and 16.

- **Gilca et al**.[6] A randomized, blinded study evaluated the immunogenicity and safety of a booster dose of 4vHPV or 2vHPV vaccine when administered to 12–13 year-old girls who were vaccinated at 9–10 years old with 2 doses of 4vHPV vaccine (0–6 months),
    - Three years after vaccination with 2 doses of 4vHPV, 99-100% of subjects had detectable antibodies to HPV 6, 11, 16, and 18.
    - After a booster dose of 4vHPV, a ≥4-fold increase of antibody titers to genotypes included in the vaccine was observed in 88–98% of subjects.
    - 4vHPV has an acceptable safety profile when given as a booster dose.

- **Donken et al**.[7] Immunogenicity of 2-dose (2D) vs. 3-dose (3D) schedules of the 4vHPV vaccine in girls and women up to 10 years after the first dose.
    - At 10 years, GMT ratios (cLIA) for both 2D and 3D girls were noninferior to 3D in adult women for HPV6/11/16/18.
    - Study demonstrated the continued antibody responses of 2D compared with 3D of HPV vaccine with follow-up to 10 years.
    - The 2D schedule of the 4vHPV vaccine is highly immunogenic, and antibody responses persisted up to 10 years postvaccination.

GUIDELINES

The **World Health Organization (WHO)** published an updated **WHO Position Paper** in December 2022[8]. Recommendations on the use of HPV vaccines were issued by the WHO Strategic Advisory Group of Experts (SAGE) on Immunization at its meeting in April 2022[9], and subsequently endorsed by WHO.

- *Two-dose schedule.* The current evidence supports the recommendation that a 2-dose schedule be used in the primary target group from 9 years of age and for all older age groups for which HPV vaccines are licensed. The minimum interval between first and second dose is 6 months. A 12-month schedule results in higher GMTs and is suggested for programmatic and efficiency reasons. There is no maximum recommended interval between doses and longer intervals – up to 3 or 5 years – can be considered if useful from a programme perspective.
- *Alternative single-dose schedule.* As an off-label option, a single-dose schedule can be used in girls and boys aged 9–20 years. Current evidence suggests that a single dose has comparable efficacy and duration of protection as a 2-dose schedule and may offer programme advantages, be more efficient and affordable, and contribute to improved coverage. From a public health perspective, the use of a single dose schedule can offer substantial benefits that outweigh the potential risk of a lower level of protection if efficacy wanes over time, although there is no current evidence of this.
- *Schedule for Immunocompromised persons.* Individuals known to be immunocompromised or HIV-infected (regardless of age or antiretroviral therapy status) should receive at least two HPV vaccine doses (minimum 6 months interval) and, where possible, three doses.

In the United States, the **Advisory Committee on Immunization Practices (ACIP)**[10-12] provides recommendations relevant to altered dosing schedules such as minimum dosing intervals, interruption of the vaccine schedule, and completion of the series following pregnancy. Summaries of these guidelines are provided below.

The **Joint Committee on Vaccination and Immunisation (JCVI)** is an expert scientific advisory committee which advises the UK government on matters relating to vaccination and immunisation. The JCVI has been considering the issue of a potential move to one dose of the HPV vaccine for several years.

- The JCVI published an interim statement[13] in February 2022 followed by a final statement[14] in August 2022, and is now ready to conclude its advice on the issue of one dose and sets out the key aspects and final conclusions of the committee.
    - JCVI advises the following schedules for the HPV programme:
        - one-dose schedule for the routine adolescent programme and MSM programme before the 25th birthday.
        - 2-dose schedule from the age of 25 in the MSM programme.
        - 3-dose schedule for individuals who are immunosuppressed and those known to be HIV-positive.
    - If policy decision is in agreement with JCVI advice the earliest date indicated is the academic year 2023 to 2024.
    - The 4-valent HPV vaccine data that was assessed on the topic of alternate dosing is provided.[15-18]

RESPONSE DETAILS

In response to your inquiry, a search of the published literature and/or other resources including internal databases pertaining to your inquiry was conducted. The following represents an overview of relevant information and may not be inclusive of all available data.

PRODUCT LABELING

Please refer to the full product labeling for complete information that may be pertinent to your inquiry.

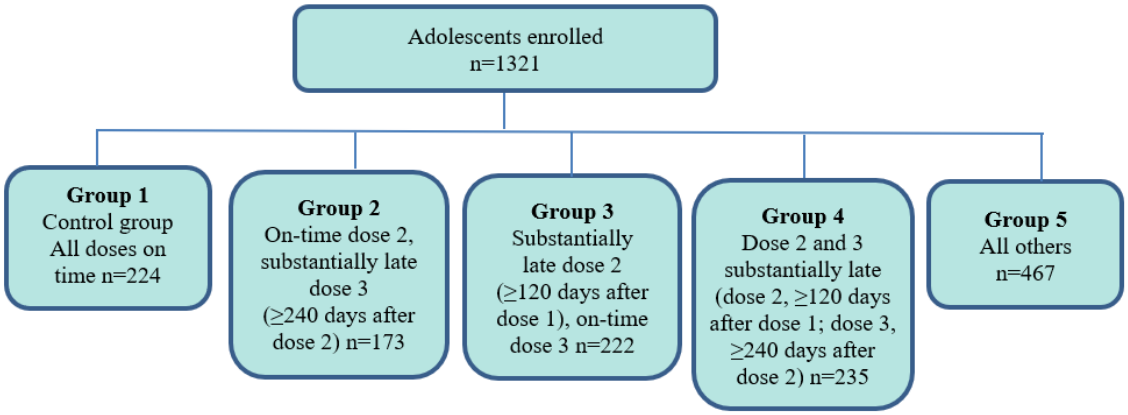
CLINICAL TRIALS

Immunological Response to Alternative Two and Three-Dose Regimens: Females 9 to 17 Years of Age

Widdice et al.[1] A prospective study evaluated the immunogenicity of alternate dosing intervals compared to the 0, 2, 6-month recommended schedule for the 4-valent HPV vaccine. The study included 1,321 girls 9-17 years of age who were categorized into these groups:

Objectives

- Compared age-adjusted geometric mean titers (GMTs) at 1 month and 6 months post-dose 3.
- Evaluated the effect of delaying the second dose.
- Compared 2 versus 3 doses.
- Determined post-dose 2 GMTs.



Results

- Compared to on-time dosing of the 4-valent HPV vaccine, prolonged intervals between doses did not appear to diminish antibody responses and may even enhance responses to the vaccine.

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LaMontagne et al.[2] Provided follow-up data up to 32 months after Dose 3 from a previous study[3]. Of the 809 girls who completed the original base study, 518 participated in this follow-up analysis.

Results at 32 Months Post-Dose 3

• The immunogenicity of the 4-valent HPV vaccine demonstrated that any of the 3 alternative schedules were non-inferior for all 4 vaccine HPV types (6, 11, 16, 18) compared to the standard schedule.
• These results are in contrast to the base study findings where the 0, 12, 24-month schedule was inferior to the standard schedule for 2 of the HPV types at 1-month post-dose 3.

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Immunological Response to Alternative Three-Dose Regimens: Females 9-18 Years of Age

Russell et al.[4] A prospective study evaluated antibody titers to the 4-valent HPV vaccine with delayed administration of Dose 2 and/or Dose 3. Overall, there were 331 females 9-18 years of age allocated to 1 of 4 groups depending upon timing of vaccine receipt:

- Dose 2 and 3 on time

- Dose 2 delayed more than 90 days
- Dose 3 delayed more than 180 days
- Both Dose 2 and 3 delayed

Pre- and post-Dose 3 samples were assayed for HPV antibody titers for Types 6, 11, 16, and 18.

Immunogenicity Results:

- Post-Dose 3 GMTs for all HPV types were not significantly lower for any of the delayed dosing groups when compared to those administered on time.
- When compared to the on-time group, the post-Dose 3 GMTs in the delayed Dose 3 group were significantly higher ($p<0.05$) for HPV types 6, 11, and 16.
- The results demonstrated that delays of Dose 2 or 3 do not interfere with immune responses after completion of the 3-dose series.

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Immunological Response to Alternative Three-Dose Regimens: Females 18 to 23 Years of Age

Zimmerman et al.[5] A randomized trial compared the standard vaccination schedule for the 4-valent HPV vaccine to an alternate dosing regimen in women 18 to 23 years of age. Two-hundred college-aged women were randomized to receive the 4-valent HPV vaccine by either the standard regimen of 0, 2, and 6 months or the alternate schedule of 0, 2, and 12 months. HPV antibody titers at 2 to 6 weeks after Dose 3 were determined by a competitive Luminex immunoassay for each HPV type.

Results

- GMTs with the alternate schedule were non-inferior to the standard schedule for all vaccine HPV types ($p<0.0001$);
- In addition, responses were significantly higher with the alternate schedule for HPV 6, 11, and 16.

GMTs Post-Dose 3 by HPV Type and Schedule
Per-Protocol Population

HPV Type	Standard Schedule (0, 2, 6 Months)		Alternate Schedule (0, 2, 12 Months)	
	N	GMT (95% CI) *mM units/mL*	N	GMT (95% CI) *mM units/mL*
6	94	2,011 (1671-2318)	81	4,440 (3080-5696)†
11	95	1,842 (1309-2338)	86	5,688 (3960-7291)†
16	95	5,774 (4043-7393)	79	12,443 (8611-15977)†
18	94	1,290 (1096-1466)	86	2,129 (1183-3063) †

** CI=confidence interval; mM=milliMerck units; GMT=Geometric Mean Titer*
† The GMT ratios (alternate/standard schedule) for all HPV vaccine types were all non-inferior (p<0.0001)

- Safety
- Most self-reported side effects (81.5%) were soreness at the injection-site that typically disappeared in 1-2 days. No serious events were reported.

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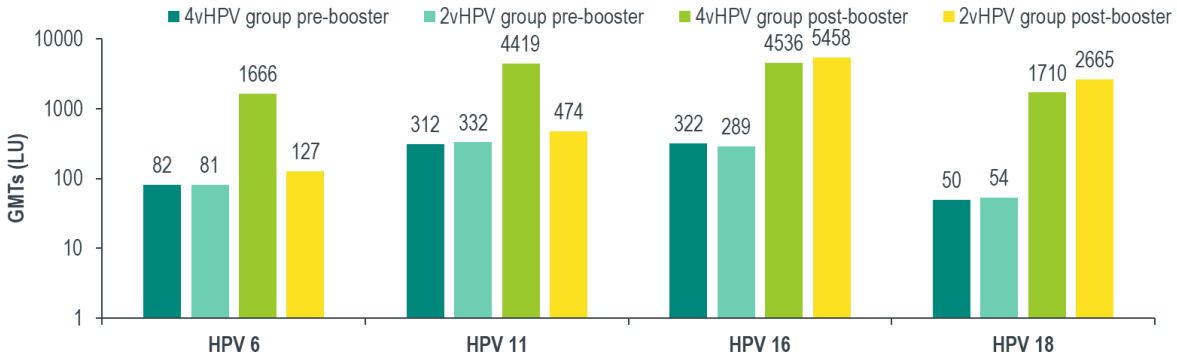
Immunological Response to Alternative Three-Dose Regimens: Females 12-13 Years of Age

Gilca et al.[6] A randomized, blinded study evaluated the immunogenicity and safety of a booster dose of 4vHPV or 2vHPV vaccine when administered to 12–13 year-old girls who were vaccinated at 9–10 years old with 2 doses of 4vHPV vaccine (0–6 months),

Results

- Three years after vaccination with 2 doses of 4vHPV, 99-100% of subjects had detectable antibodies to HPV 6, 11, 16, and 18.
- After a booster dose of 4vHPV, a ≥4-fold increase of antibody titers to genotypes included in the vaccine was observed in 88–98% of subjects.
- 4vHPV and 2vHPV have an acceptable safety profile when given as a booster dose.

Proportion of Subjects with Detectable Anti-HPV GMTs
After a Deferred Dose 3 with Either 4vHPV or 2vHPV Vaccine



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Immunological Response in 2D vs. 3D Regimens: Females 9-13 Years of Age

Donken et al.[7] Post hoc analysis of a Phase 3, post licensure, age-stratified, noninferiority, immunogenicity trial of 4-valent HPV vaccine, N=103. Evaluated the antibody responses of 2D or 3D of 4-valent HPV, 10 years (120 months) post vaccination.

Results

- Seropositivity rates by cLIA were above 95% for all HPV vaccine types and all schedules, except HPV 18, which had the lowest seropositivity observed among women who received 3 doses (60%; 95% CI: 40.6%, 77.3%).
- At 10 years, GMT ratios (cLIA) for both 2D and 3D girls were noninferior to 3D in adult women for HPV6/11/16/18.
- Study demonstrated the continued antibody responses of 2D compared with 3D of HPV vaccine with follow-up to 10 years.
- The 2D schedule of the 4vHPV vaccine is highly immunogenic, and antibody responses persisted up to 10 years postvaccination.

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GUIDELINES

World Health Organization (WHO)

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GMTs and is suggested for programmatic and efficiency reasons. There is no maximum recommended interval between doses and longer intervals – up to 3 or 5 years – can be considered if useful from a programme perspective.

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- *Schedule for Immunocompromised persons.* Individuals known to be immunocompromised or HIV-infected (regardless of age or antiretroviral therapy status) should receive at least two HPV vaccine doses (minimum 6 months interval) and, where possible, three doses.

Advisory Committee on Immunization Practices (ACIP) Recommendations for HPV Vaccination

In the United States, the **ACIP** recommendations relevant to altered dosing schedules such as minimum dosing intervals, interruption of the vaccine schedule, and completion of the series following pregnancy are provided below.

Minimum Dosing Intervals and Interrupted Schedules[10,11]

- The minimum interval between the first and second doses of HPV vaccine (either 4-valent HPV vaccine or 2-valent HPV vaccine) is 4 weeks.
- The minimum recommended interval between the second and third dose of vaccine is 12 weeks.
- The minimum interval between the first and third dose is 24 weeks.
- Inadequate doses or vaccine doses received after a shorter-than-recommended dosing interval should be re-administered. If the vaccine schedule is interrupted for either 4-valent HPV vaccine or 2-valent HPV vaccine, the vaccine series does not need to be restarted. If the series is interrupted after the first dose, the second dose should be administered, and the second and third doses should be separated by an interval of at least 12 weeks.

Vaccination During Pregnancy[10,11]

- HPV vaccines are not recommended for use in pregnant women. The vaccines have not been associated causally with adverse outcomes of pregnancy or adverse events in the developing fetus. However, if a woman is found to be pregnant after initiating the vaccination series, the remainder of the 3-dose series should be delayed until completion of pregnancy.
- Pregnancy testing is not needed before vaccination. If a vaccine dose has been administered during pregnancy, no intervention is needed.

2-dose schedule: Interrupted schedules[12]

- If the vaccination schedule is interrupted, the series does not need to be restarted. The number of recommended doses is based on age at administration of the first dose.

2-dose schedule: Persons vaccinated previously[12]

- Persons who initiated vaccination with the 9-valent, 4-valent, or 2-valent HPV vaccine before their 15th birthday and received 2 doses of any HPV vaccine at the recommended dosing schedule (0, 6–12 months), or 3 doses of any HPV vaccine at the recommended dosing schedule (0, 1–2, 6 months), are considered adequately vaccinated.

- Persons who initiated vaccination with the 9-valent, 4-valent, or 2-valent HPV vaccine on or after their 15th birthday and received 3 doses of any HPV vaccine at the recommended dosing schedule, are considered adequately vaccinated.

- The 9-valent HPV vaccine may be used to continue or complete a vaccination series started with the 4-valent or 2-valent.

- For persons who have been adequately vaccinated with the 2-valent or 4-valent HPV vaccines, there is no ACIP recommendation regarding additional vaccination with the 9-valent.

Joint Committee on Vaccination and Immunisation (JCVI)

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REFERENCES

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