Does single-dose HPV vaccination offer enough protection for a schedule change?

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Human papillomavirus (HPV) vaccination has fundamentally altered the market of cervical cancer prevention. For years, multi-dose schedules have been the standard, but the logistical challenges, particularly in low-resource settings, have spurred interest in a single-dose approach. The question for clinicians is whether this simplified regimen provides equivalent, durable protection against the oncogenic strains of HPV.

KEY TAKEAWAYS

- The Pivot: Global health initiatives are exploring single-dose HPV vaccination to improve coverage and simplify administration.
- The Data: Immunogenicity studies show a single dose can elicit antibody responses comparable to multi-dose regimens, particularly in younger adolescents.
- The Action: Clinicians should be aware of evolving guidelines and the potential for single-dose options, especially for public health programs.

Cervical cancer remains a significant global health burden, with HPV infection being the primary cause. Prophylactic HPV vaccines target the most common oncogenic types, primarily HPV16 and HPV18, which are responsible for the majority of cervical cancers. The established multi-dose schedules, typically two or three doses, have demonstrated high efficacy in preventing persistent infection and precancerous lesions.

The challenge with multi-dose regimens lies in completion rates. Many individuals, particularly in regions with limited healthcare access, do not complete the full series, diminishing the population-level impact of vaccination. This unmet need has driven the exploration of simplified schedules, including a single-dose option, to maximize vaccine uptake and coverage. The impact of vaccination on cervical cancer elimination is clear, but only if the vaccine reaches enough people.

Immunogenicity as a proxy for protection

The primary evidence supporting a single-dose HPV vaccine schedule comes from immunogenicity studies. These trials measure antibody responses following vaccination, comparing the levels achieved with a single dose to those from established multi-dose regimens. The assumption is that a strong and sustained antibody response correlates with long-term protection against HPV infection and associated disease.

Studies have consistently shown that a single dose of bivalent or quadrivalent HPV vaccines can induce antibody titers that are non-inferior to, or even comparable with, those achieved after two or three doses, especially in younger adolescents (typically 9-14 years of age). This observation is important, as younger individuals tend to mount stronger

immune responses to vaccines. The antibody levels generated by a single dose are often sustained for several years, though long-term data extending beyond a decade are still accumulating.

Comparing single-dose responses

When comparing antibody responses, researchers often focus on geometric mean titers (GMTs) and seroconversion rates. A single dose of HPV vaccine typically achieves seroconversion rates approaching 95-100% for HPV16 and HPV18 in adolescent girls. These rates are similar to those observed after two or three doses. The GMTs, while sometimes lower than those after multiple doses, are generally considered to be above the threshold believed to be protective, based on correlates of protection established from efficacy trials of multi-dose schedules.

The persistence of these antibody responses is a key concern. While initial data show sustained levels for 5-10 years, the durability beyond this period is still under investigation. The immune memory generated by a single dose is also a factor. The presence of memory B cells and T cells, even if circulating antibody levels wane slightly, could provide rapid protection upon subsequent exposure to HPV. This aspect of the immune response is harder to quantify but is essential for long-term efficacy.

The age factor and vaccine type

Age plays a significant role in the immunogenicity of a single HPV vaccine dose. Younger adolescents, particularly those aged 9-14 years, exhibit a more vigorous immune response compared to older adolescents or young adults. This enhanced immunogenicity in younger age groups is attributed to a more naive and responsive immune system. For this reason, many discussions around single-dose schedules are specifically focused on this younger cohort.

The type of HPV vaccine also influences immunogenicity. Both bivalent (targeting HPV16/18) and quadrivalent (targeting HPV6/11/16/18) vaccines have shown immunogenicity that achieves seroconversion rates approaching 95-100% for HPV16 and HPV18 after a single dose. The nonavalent vaccine, which covers nine HPV types, is also being evaluated in single-dose regimens. Early data suggest that the nonavalent vaccine also elicits strong antibody responses after a single dose, though more extensive studies are needed to confirm long-term protection across all nine types. The broader policy implications of child vaccine schedule changes are complex and extend beyond immunogenicity alone.

Efficacy versus immunogenicity

It is important to distinguish between immunogenicity and clinical efficacy. Immunogenicity data, while compelling, are surrogate markers. Direct evidence of clinical efficacy, meaning the prevention of persistent HPV infection, precancerous lesions, and ultimately cervical cancer, from large-scale, long-term single-dose randomized controlled trials is still emerging. The ethical challenges of conducting such trials, given the established efficacy of multi-dose regimens, are considerable.

But observational studies and programmatic data from countries that have implemented single-dose or reduced-dose schedules are providing real-world insights. These studies track HPV prevalence and incidence of precancerous lesions in vaccinated populations. Initial findings from these real-world settings generally support the protective effect of fewer doses, aligning with the immunogenicity data. This is a critical point for public health decision-makers, who must balance optimal individual protection with the practicalities of widespread vaccine delivery.

Where the evidence falls short

The main caveat with single-dose HPV vaccination is the lack of definitive, long-term clinical efficacy data from head-to-head trials against multi-dose regimens. While immunogenicity is a strong indicator, it is not a direct measure of disease prevention. The duration of protection, especially against less common oncogenic types, remains an area requiring further investigation. The potential for waning immunity over decades is a theoretical concern that requires continued surveillance.

The evidence base is strongest for younger adolescents. Whether a single dose provides equivalent protection for older adolescents or young adults, who may have already been exposed to HPV or have a less robust immune response, is less clear. Most of the compelling immunogenicity data are from populations without prior HPV exposure, which is a critical consideration for broader implementation. For a deeper dive into vaccine schedules, the single-dose option for influenza treatment offers a parallel discussion on adherence.

Public health implications and future directions

The potential for a single-dose HPV vaccine schedule to dramatically increase vaccine coverage, particularly in low- and middle-income countries, is immense. Simplified logistics, reduced costs, and improved adherence could accelerate progress towards cervical cancer elimination goals. The World Health Organization (WHO) has already acknowledged the potential of a single-dose schedule, recommending it as an alternative to the two-dose schedule for girls aged 9-14 years, citing the strong immunogenicity data and the urgent need to improve global coverage.

Continued monitoring of vaccinated cohorts will be essential to track long-term efficacy and the duration of protection. This includes surveillance for HPV infection rates, incidence of precancerous lesions, and cervical cancer rates in populations vaccinated with a single dose. The integration of HPV vaccination with other public health interventions, such as cervical cancer screening, will also be vital to maximize impact. Clinicians can find comprehensive guidance on various medical topics, including preventive health, in the Oxford Handbook of General Practice, 5th Edition.

> **CLINICAL IMPLICATIONS**
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> The shift towards a single-dose HPV vaccine schedule, driven by immunogenicity data, presents a pragmatic solution to a significant public health challenge. For general practitioners, this means a potential simplification of vaccination protocols, which could dramatically improve uptake, especially in hard-to-reach populations. The evidence, while not yet a decade of direct efficacy data, is compelling enough for global health bodies to act.
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> But clinicians must understand the nuances. The strongest evidence for single-dose efficacy is in younger adolescents, typically those aged 9-14 years. Extending this recommendation to older age groups or those with potential prior HPV exposure requires more extensive data. It is not a one-size-fits-all solution, and patient counseling must reflect this.
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> The primary benefit of a single-dose approach is population-level impact, not necessarily superior individual protection compared to a completed multi-dose course. If a patient can reliably complete a two-dose schedule, that remains the established standard. The single-dose option is about maximizing coverage where multi-dose completion is a known barrier, a trade-off that prioritizes accessibility and broad protection.
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> The move to a single-dose schedule reflects a calculated risk based on strong immunogenicity and early real-world data. It is a necessary step to accelerate cervical cancer elimination, but ongoing surveillance will be critical to confirm long-term effectiveness and to identify any unexpected gaps in protection.

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