FREQUENTLY ASKED QUESTIONS

Human papilloma virus (HPV) causes almost all cases of cervical cancer. Most of these deaths occur in low- and middle-income countries, but worldwide vaccine coverage in girls under 15 years of age was only 21 perecent in 2022.

In response to a strong and growing evidence base, in December 2022, the World Health Organization (WHO) endorsed an alternative single-dose HPV vaccination schedule in women and girls ages 920.

High-quality evidence assessing single-dose HPV vaccination suggests that implementing a single-dose schedule is scientifically sound and provides the greatest public health benefit. ***A single-dose HPV vaccination schedule has the potential to reach more girls and avert a greater number of cervical cancer cases than reaching fewer girls with a two-dose regimen****.*

Below are frequently asked questions and answers about the evidence around single-dose HPV vaccination and the current policy landscape.

EVIDENCE

WHAT INFORMED THE SWITCH FROM THREE DOSES TO TWO DOSES OF HPV VACCINE?

- Immunization schedule updates are driven by scientific evidence.
- Clinical data on licensed HPV vaccines showed a higher immunogenicity in younger ages, which prompted an evaluation of a two-dose schedule in 9-14-year-old girls. Two doses in this group demonstrated non-inferiority compared to three-dose efficacy results in an adult population. This allowed researchers to infer two-dose efficacy in young girls.

WHAT INFORMED WHO'S ENDORSEMENT OF A SINGLEDOSE HPV VACCINE? CAN A SINGLE-DOSE HPV VACCINATION SCHEDULE PREVENT CERVICAL CANCER?

- As with the switch from a three-dose to a two-dose schedule, the endorsement was driven by scientific evidence.
- Data accumulated to date from clinical trials and high-quality observational clinical studies provide strong evidence of comparable efficacy and effectiveness between single and multidose schedules in preventing HPV infections, causing almost all cases of cervical cancer.
- For a detailed review of the evidence, view the Trials Summary (in the Appendix below) or download the Consortium slide deck.

WHAT DO WE KNOW ABOUT THE DURATION OF PROTECTION OF A SINGLE-DOSE HPV VACCINE?

- Data available for more than a decade (12 years post-vaccination in India; 11 years post-vaccination in Costa Rica) show comparable rates of HPV infection prevention between single and multidose schedules.
- Data available from 10 years post-vaccination in India and 16 years post-vaccination in Costa Rica show persistent antibody response, with no evidence of waning.
- Based on large body of evidence on the durability of HPV antibodies generated by virus-like particle vaccines, protection is likely to persist throughout life.

- For a detailed review of the evidence, view the Trials Summary (in the Appendix below) or download the Consortium slide deck.

IS THERE MORE EVIDENCE COMING?

- Results from a randomized control trial (RCT) in Costa Rica that directly compares a single-dose cohort with a two-dose cohort within the same study to confirm non-inferiority are expected in 2025. Longer-term immune response data from ongoing RCTs in Costa Rica, Kenya, Tanzania, and The Gambia are also forthcoming.
- Additional studies are underway to assess a single-dose regimen in varying age groups and HIV-positive populations.

WHY SHOULD COUNTRIES CONSIDER SWITCHING TO A SINGLE-DOSE SCHEDULE?

- Scientific data show that one dose provides sufficient protection against HPV.
- Modeling based on a high-quality evidence base suggests that reaching a greater number of girls with one dose of HPV vaccine will prevent a much higher number of cervical cancer cases than vaccinating fewer girls with two doses.
- See more at "Global impact and cost-effectiveness of one-dose versus two-dose human papillomavirus vaccination schedules: a comparative modelling analysis" in *BMC Medicine*.

IS THERE ONE PRODUCT MORE EFFECTIVE AS A SINGLE DOSE THAN ANOTHER?

- In RCTs assessing the performance of single-dose HPV vaccination, Gardasil, Gardasil9, and Cervarix each generated antibody response approximately ten times higher than natural infection and provided comparably high levels of protection against persistent HPV infection.

POLICY LANDSCAPE

DOES WHO RECOMMEND SINGLE-DOSE HPV?

- In December 2022, the WHO Position Paper on HPV was updated to recommend a one or two-dose schedule for the primary target of girls aged 9-14 years and for young women aged 15-20 years. Women over 21 years old should have two doses with at least six-month interval.
- Immunocompromised individuals, including those with HIV, should receive at least two doses and, ideally, three doses.
- See the WHO updated position paper on HPV vaccination schedules.

WHY DOES WHO RECOMMEND EITHER A SINGLE DOSE OR A TWO-DOSE SCHEDULE?

- Based on the strength of the evidence available to date, WHO recommended one or two doses to expand HPV vaccine schedule options available to countries and enable stronger vaccine coverage.
- WHO is also anticipating confirmatory evidence from a RCT that directly compares vaccine efficacy in a single-dose cohort to a two-dose cohort within the same study in 2025.

WHY IS IT RECOMMENDED BOYS MAY USE THE SAME SCHEDULES AS GIRLS IF THERE IS LIMITED DATA ON BOYS?

- While data in boys are limited, a single-dose HPV vaccine elicits a comparable immune response in girls and boys aged 9-14 years.
- Males can transmit HPV infection to females, and HPV is the main cause of cervical cancer in women. Protecting boys is another way to protect girls.

WHAT ARE THE RECOMMENDATIONS FOR THOSE LIVING WITH HIV?

- Evidence is still being collected on the performance of single-dose HPV in immunocompromised individuals, including those living with HIV. For now, WHO recommends women and girls living with HIV receive at least two doses and, where possible, three doses.

WHAT ARE THE POTENTIAL PROGRAMMATIC BENEFITS OF A SINGLE-DOSE HPV VACCINATION SCHEDULE?

- Single-dose HPV vaccination schedule can accelerate broader access to HPV vaccines by:
    - Lowering vaccine costs for programs.
    - Reducing potential risks for global supply shortages.
    - Leading to new distribution options, such as co-delivery with other vaccine campaigns, which could reduce overall costs, or a shift gender-neutral programming without major cost implications.
- The programmatic benefits are especially pronounced given the poor uptake and coverage of HPV vaccination.

CAN NATIONAL PROGRAMS ADOPT A SINGLE-DOSE SCHEDULE EVEN THOUGH THIS CONSTITUTES AN OFF-LABEL USE?

- Science moves faster than label updates. Due to the high-quality evidence base supporting the use of single-dose HPV vaccine, WHO includes in their recommendations the off-label use of a single-dose regimen as an alternative to a multi-dose schedule.
- WHO has previously made off-label recommendations when the evidence supports it. Previous vaccine examples of WHO off-label recommendations include pneumonia conjugate vaccine and hepatitis A vaccine.
- It is ultimately up to national regulatory authorities to decide to implement an off-label recommendation.

WHAT NATIONAL POLICY-LEVEL CHANGES ARE NEEDED TO PROCEED WITH THE SHIFT TO SINGLE-DOSE?

- Each country has its own national immunization advisory authorities, who ultimately will review evidence and decide on implementing a single-dose schedule according to their country-specific processes.

WILL GAVI SUPPORT COSTS ASSOCIATED WITH SWITCHING FROM TWO- TO ONE-DOSE SCHEDULES?

- Yes, Gavi provides financial support (switch grants) for vaccine schedule switches.

WILL MORE RECENTLY LICENSED HPV VACCINES BE CONSIDERED FOR THE SINGLE-DOSE REGIMEN?

- For new vaccine products to be considered effective in a single-dose schedule, they must demonstrate single-dose efficacy or immunological non-inferiority compared to vaccines for which one-dose efficacy data exists. WHO has indicated that two years post-vaccination immunobridging data for recently licensed products is required.

To access the full review of current evidence, visit the Single-Dose HPV Vaccine Evaluation Consortium landing page. For information about implementing single-dose HPV vaccination programs, including decision-making, Gavi applications, planning, communication, implementation and monitoring, visit the TechNet-21 toolkit.

APPENDIX: TRIALS SUMMARY

- The most impactful RCT evidence to date on single-dose HPV vaccination is from the KENya Single-dose HPV vaccine Efficacy (KEN SHE) trial in African adolescent girls and young women launched in 2018. It showed that a single dose of HPV vaccination was ~98% effective in preventing new onset persistent HPV 16/18 (the strains that cause the majority of cervical cancer cases) in a sexually active population (15-20 year-olds).
    - The KEN SHE RCT builds on follow-up studies using previous RCTs that sought to measure performance of two- or three-dose HPV vaccine schedules, but which inadvertently generated single-dose cohorts when participants didn't receive subsequent doses for various reasons unrelated to the study objectives.
        - One such example of a high-quality observational study is the International Agency for Research on Cancer's (IARC) HPV vaccine trial in India launched in 2009. The incidence of HPV infections were comparable among the one-, two-, and three-dose groups 12 years after vaccination.
        - The other example is the Costa Rica HPV Vaccine trial (CVT) launched in 2004 that provides evidence that following one dose of HPV vaccine the level of protection against HPV infections is similar to two or three doses in healthy young females up to 11 years post-vaccination.
- The RCT Dose Reduction Immunobridging and Safety study (DoRIS) of two HPV vaccines in Tanzanian girls provides immunogenicity evidence after receipt of a single dose of HPV vaccine.
    - An immunobridging analysis found that the immune response 24 months post-vaccination of a single dose of HPV in girls aged 9–14 years was non-inferior to a single dose in historical cohorts for which single-dose efficacy was shown (for ages 18–25 in Costa Rica and ages 10–18 in India).
- While immune responses following a single dose have shown to be lower than after two or three doses, single-dose vaccination elicits significantly higher levels of antibodies than those induced after natural infection that remains stable through 10 and 16 years of post-vaccination data collection (in the India IARC trial and the Costa Rica HPV Vaccine trial, respectively).