

Protection from a Single Dose of HPV Vaccine

A major public health impact from IARC studies of vaccine efficacy

International Agency for Research on Cancer



Summary

Every year cervical cancer kills nearly 350 000 women globally, 90% of whom live in low- and middle-income countries (LMICs). More than 95% of cervical cancers are caused by oncogenic types of human papillomavirus (HPV).

The vaccine against HPV is very safe and highly effective in preventing cervical cancer. Thus, a fundamental pillar of the strategy to eliminate cervical cancer is reaching the goal of vaccinating 90% of girls with the HPV vaccine by the age of 15 years.

However, sufficient and regular access to HPV vaccines remains a significant challenge in LMICs. Moreover, the multiple-dose schedule of HPV vaccination can

make vaccination programmes logistically more complex, more expensive, and less resilient to vaccine supply disruptions. The optimization of the HPV vaccination schedule is expected to improve access to the vaccine, offering countries the opportunity to expand the number of girls who can be vaccinated and alleviating the burden of the often complicated and expensive follow-up required to complete the vaccination series. It is vital that countries strengthen their HPV vaccination programmes, expedite implementation, and reverse the declines in coverage.

IARC has implemented studies to accelerate cervical cancer elimination by making HPV vaccination more efficient

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and effective. These include (i) evaluating the efficacy of single-dose HPV vaccination, (ii) evaluating a new HPV vaccine, and (iii) making evidence-based projections of the public health impact of single-dose HPV vaccination.

Introduction

In 2020, WHO launched a Global Strategy to Eliminate Cervical Cancer as a Public Health Problem.

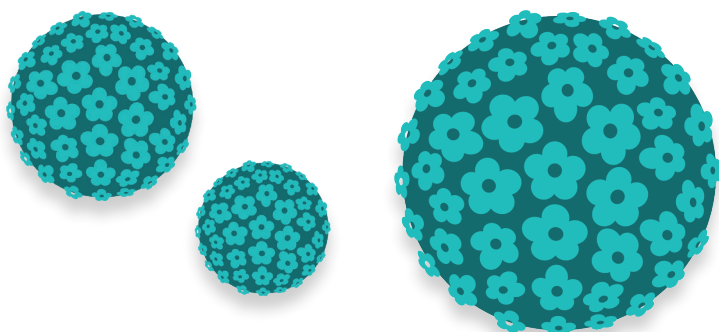
That goal is supported by three key strategic pillars, with the following targets: primary prevention (90% of girls aged 9–14 years vaccinated with the HPV vaccine), secondary prevention (70% of women screened using a high-performance test twice in their lifetime, by ages 35 years and 45 years, and 90% of women with precancer treated), and tertiary prevention (90% of women with invasive cancer managed).

Introduction of the HPV vaccine has been slow, particularly in LMICs but also in high-income countries. In 2021, global coverage with two doses was only 15%. Reasons for the low coverage of HPV vaccination include:

- the HPV vaccine is one of the most expensive vaccines to be introduced in routine immunization programmes;
- a shortage of vaccine supply forced many LMICs to defer the planned introduction of vaccination;
- contacting adolescent girls for the second dose is challenging; and
- vaccine hesitancy has been exceptionally high for this gender-specific vaccine (girls are the priority target population).

Major strengths of IARC's evidence of single-dose vaccine efficacy

- Previous studies have suggested that one dose of HPV vaccine could be as efficacious as two or three doses in healthy women. However, the small numbers of participants highlighted the need for additional evidence to confirm the preliminary results.
- IARC conducted a large study in which 15 000 girls who received one, two, or three doses of HPV vaccine were followed up for more than 10 years with immunological testing; after women were married, vaccine efficacy against persistent HPV infection was evaluated by paired age groups.
- The strong evidence provided by this study contributed significantly to the World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization (SAGE) changing the recommendation on HPV vaccination to one dose (the off-label single-dose option).



Key evidence messages

- With one third or one half of the cost per person, policy-makers and governments can save financial resources.
- One dose of HPV vaccine provides similar protection to that provided by two or three doses against persistent infection with HPV16 and HPV18, the genotypes responsible for nearly 70% of cervical cancers.
- A single-dose schedule should reduce programme costs and facilitate the scaling up of HPV vaccination to improve the vaccination coverage.
- A single-dose schedule is likely to simplify logistics and make programmes more resilient by enabling multi-age catch-up and vaccination of boys.
- A single-dose schedule will probably be more acceptable to the population.
- Adequate supplies of new vaccines will be a huge step to accelerate cervical cancer elimination in LMICs and globally.
- With the three or two doses previously used per girl, a boy and a girl could now be vaccinated, increasing the herd effect and improving programme resilience.



“The outcomes of this trial are expected to improve accessibility of HPV vaccine and improve vaccine supply, especially for LMICs.”

*– Dr Partha Basu,
Early Detection, Prevention, and Infections Branch, IARC*

Evaluating the efficacy of single-dose HPV vaccination

In September 2009, IARC initiated a multicentre randomized trial, funded by the Bill & Melinda Gates Foundation, to compare the efficacy of two versus three doses of the quadrivalent HPV vaccine (Gardasil) in unmarried girls aged 10–18 years in India.

The trial was converted into a longitudinal cohort study by default after the abrupt suspension of HPV vaccination

in any trial by the Government of India in April 2010. By then, 4348 participants had received three doses, 4980 had received two doses (at 0 and 6 months), and 4949 had received one dose. After they were married, vaccinated women and a control cohort of 1484 unvaccinated women provided samples annually for surveillance of HPV infection. At age 25 years, vaccinated women and a control cohort of 3500 unvaccinated women were invited for cervical screening. Women

who were HPV-positive at screening underwent colposcopy and biopsy.

In addition, blood samples for immunological assays were obtained at different time points (at 7, 12, 18, 24, 36, 48, and 60 months) up to 10 years after vaccination from a convenience sample of vaccinated participants and a control group of age-matched unvaccinated women. All laboratory assays were performed independently and in a blinded manner.

Call to action



Policy-makers globally should introduce HPV vaccination with one or two doses for girls, as recommended by WHO.



Vaccine manufacturers should ensure equity in access to HPV vaccines, particularly in LMICs.



Immunization programme managers should assess strategies to improve HPV vaccination coverage that could include the use of a single-dose schedule.

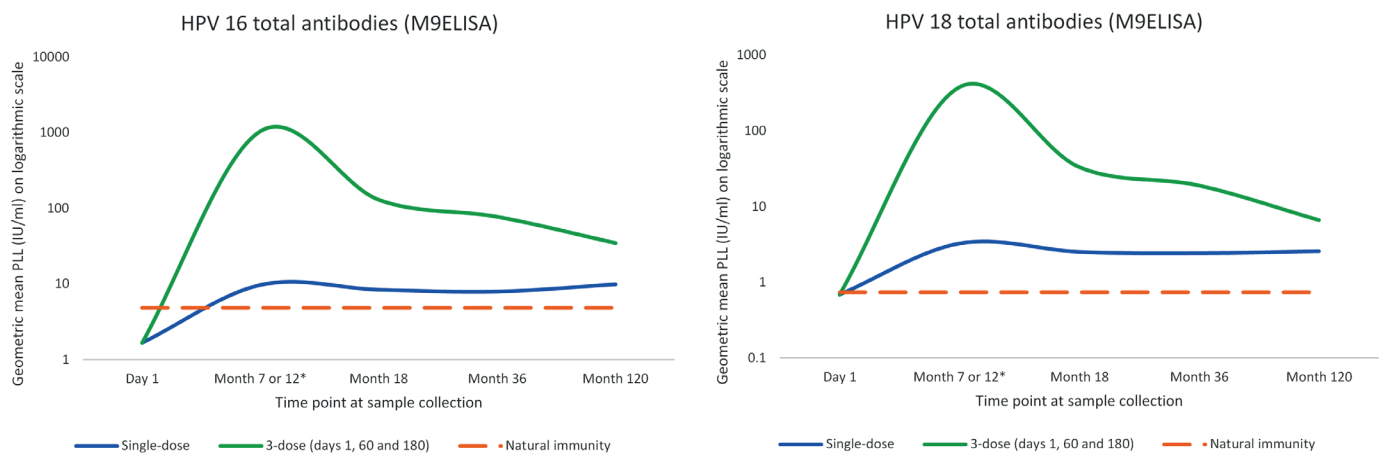


Fig. 1 Evolution of immune responses against HPV16 and HPV18 over time in the recipients of a single dose or three doses of HPV vaccine. *Blood was collected from three-dose recipients at 7 months and from single-dose recipients at 12 months after dose 1.

Key findings of IARC's single-dose vaccine efficacy trial

The IARC study found that even after only one dose of vaccine, there is a high and long-lasting immune response 10 years later. The antibody response indicates that the protection is unlikely to fade anytime soon. The immunological findings are consistent with the single-dose vaccine's high efficacy against persistent HPV16/18 infections. The results show that a single dose of the vaccine is as effective as two or three doses in preventing persistent HPV16 and HPV18 infections (see Figure 1).

No cases of high-grade cervical precancers were associated with HPV16 or HPV18 in any of the vaccinated women who underwent screening.

Evaluating a new HPV vaccine

Currently there are six licensed HPV vaccines: three bivalent vaccines (Cecolin, Cervarix, and Walrinvax), two quadrivalent vaccines (Cervavac and Gardasil), and one nonavalent vaccine (Gardasil 9). For these vaccines, most LMICs pay about US\$ 10 per dose for their immunization programmes, and there is a global shortage of supply.

“Eliminating cervical cancer is a commitment we have made and can do. We can accelerate the timeline towards elimination by investing in research and innovation. These important trials from IARC have helped inform policy recommendations by WHO and facilitate our support to governments and other stakeholders to eliminate cervical cancer together.”



– Dr Bente Mikkelsen,
Director of Noncommunicable Diseases, WHO

The Serum Institute of India has developed a quadrivalent HPV vaccine (Cervavac), which is likely to cost less than previous HPV vaccines as a result of a novel production system and local production in India.

IARC was part of a collaboration between the Serum Institute of India, the Department of Biotechnology of the Government of India, and the Bill & Melinda Gates Foundation to design phase II/III randomized trials to evaluate

this new vaccine and to implement the trial at several sites in India.

The Drugs Controller General of India, the country's licensing authority, agreed to license the new vaccine if its immunogenicity could be proved to be non-inferior to that of Gardasil with a good safety profile.

The study, which involved girls and boys aged 9–14 years (two-dose cohort) and women and men aged 15–26 years (three-dose cohort), was completed

Definitions

- **Quadrivalent vaccine** protects against HPV types 6, 11, 16, and 18, which cause most HPV-associated cancers and genital warts.
- **Vaccine efficacy** was calculated as 1 minus the HPV infection rate in the vaccinated group, divided by the HPV infection rate in the unvaccinated group.
- **Incident infection** was defined as the detection of an HPV type in any one sample.
- **Persistent infection** was defined as the detection of the same HPV type in two consecutive samples taken at least 10 months apart.
- Each enrolled participant contributed **once to persistent infections, once to incident infections**, or both.
- **Immunogenicity** is the antibody response.



successfully. The new vaccine was found to be highly immunogenic, and immunogenic non-inferiority compared to women aged 15–26 years who received Gardasil was demonstrated in both girls and boys against the targeted HPV types. The safety profile was also comparable to that of Gardasil. After reviewing the study outcomes, the Indian regulators approved marketing authorization for the new vaccine for females and males aged 9–26 years.

An approval by the Drugs Controller General will enable the Government of India to procure enough doses of HPV vaccine produced by the Serum Institute of India because nearly 50 million girls aged 9–14 years in India are waiting to receive the vaccine. The introduction of the new HPV vaccines that have recently been developed (Cervavac, Cecolin, and Walrinvax) will be a huge step to accelerate cervical cancer elimination in India and globally, and an option to improve access and affordability.

Evidence-based projections of the public health impact of single-dose HPV vaccination

IARC projected the health benefits and potential economic impact of a national single-dose HPV vaccination programme for girls in India. The study found that such a vaccination programme could substantially reduce the incidence of cervical cancer, to below the incidence rate established by WHO as the threshold for the elimination of cervical cancer as a public health problem (see Figure 2).

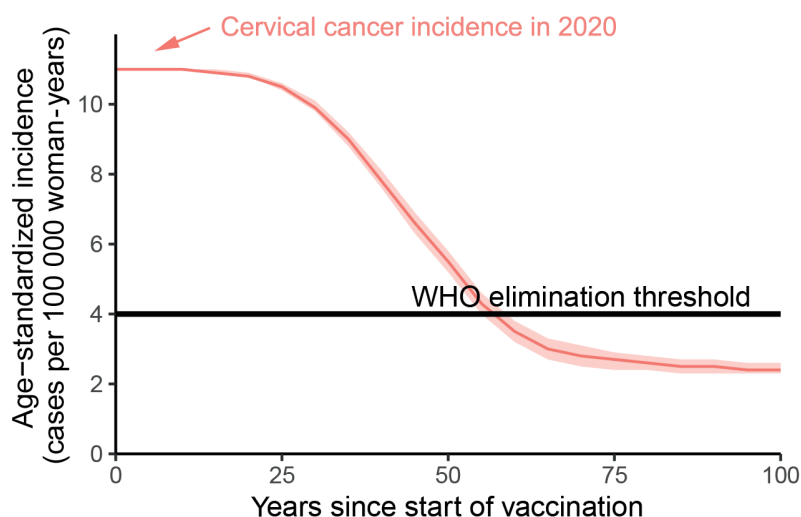


Fig. 2 Projected impact of single-dose HPV vaccination of girls on cervical cancer incidence in India.

“With the new safe, highly effective, and affordable vaccine, LMICs are on the way to universalizing national-level HPV vaccination programmes.”

– Professor Neerja Bhatla,
Past Chair of Women’s Cancer Committee, FIGO

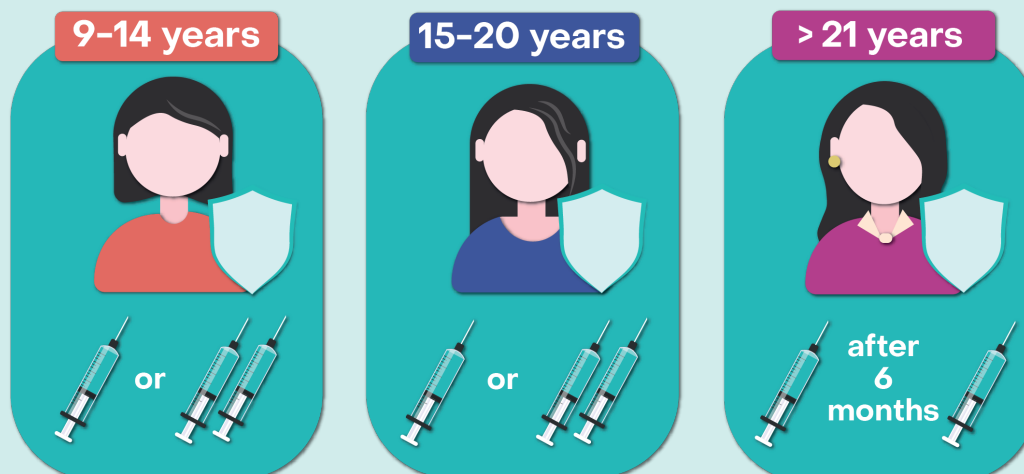


If HPV vaccination is introduced now, it could prevent almost 1 million cases of cervical cancer over the lifetime of the birth cohort currently aged 10 years or younger. This study complements existing evidence that single-dose HPV vaccination could be an effective, efficient, and cost-effective strategy for

cervical cancer prevention in India and other LMICs.

This mathematical economic modelling study showed that the introduction of single-dose HPV vaccination in India is likely to be cost-effective. Two-dose vaccination would have a less favourable cost-effectiveness profile. These results

Current WHO HPV vaccine recommendations (2022):



could be used by health officials in the Indian government in their decision-making on the introduction of HPV vaccination and could convey several lessons for implementation in other LMICs.



“These recommendations will pave the way for more girls and women to be vaccinated and thus prevent cervical cancer.”

– Professor Rakesh Aggarwal,
WHO SAGE member

New WHO recommendations

In April 2022, WHO SAGE evaluated the evidence that has recently emerged that single-dose schedules provide comparable efficacy to two-dose or three-dose schedules.

The WHO SAGE review concluded that a single-dose HPV schedule delivers solid protection against HPV, comparable to that of a two-dose schedule. WHO advised that countries may now choose between a one-dose or two-dose schedule for girls aged 9–14 years.

Implications: early policy changes after the new WHO recommendations

IARC studies contributed significantly to the new single-dose recommendation from WHO, and countries in all parts of the world are planning to switch or have already switched to a one-dose schedule, including Albania, Australia,

Cabo Verde, Ireland, Mexico, Solomon Islands, Tonga, and the United Kingdom.

Several National Immunization Technical Advisory Groups in GAVI-eligible countries have already recommended a single-dose schedule and may soon introduce HPV vaccination, including in Bangladesh, India, and Nigeria.

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For more information about HPV vaccine trials, please email basup@iarc.who.int

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