Vaccine Effectiveness of One Dose of the Nonavalent Human Papillomavirus (HPV) Vaccine Among Young-adult Women in Sweden Among Women Participating in a Clinical Trial of Concomitant HPV Vaccination and Screening (FASTER1DOSE)

9th September 2025

Study Plan:

Vaccine effectiveness of one dose of the nonavalent Human Papillomavirus (HPV) vaccine among young-adult women in Sweden among women participating in a clinical trial of concomitant HPV vaccination and screening (ClinicalTrials.gov ID: NCT04910802)

Short title:

Study Aim: To evaluate the vaccine effectiveness of 1 dose the nonvalent vaccine against human papillomavirus (HPV) 16, 18, 31, 33, 45, 52, and 58 infection among young adult women in Sweden participating in a nationwide HPV elimination trial.

Primary aim:

- To estimate the vaccine effectiveness of 1 dose of the nonavalent vaccine against HPV16, 18, 31, 33, 45, 51, 52, and 58 ***incident*** **HPV infection** among women born from 1994 to 1999 participating in a nationwide HPV elimination trial (ClinicalTrials.gov ID: NCT04910802).

Secondary aim:

- To estimate the vaccine effectiveness among the women participating in the piloting phase of the trial (ClinicalTrials.gov ID: NCT04910802) (Stockholm region, the capital region of Sweden, only).
- To estimate the vaccine effectiveness in relation to previous history of having received the HPV vaccine outside of the trial.
- To estimate the cross-protective vaccine effectiveness of 1 dose of the nonavalent vaccine against HPV51, HPV35/39/68, and HPV56/59/66.

Background

HPV vaccination is the 1st pillar in the World Health Organization's (WHO) strategy to eliminate cervical cancer as public health problem, defined as an incidence of under 4 per 100,000 women-years globally (WHO, 2020). Licensed prophylactic HPV vaccines are highly efficacious in preventing HPV infection and associated cancers (Joura et al, 2015; Porras et al, 2020; FUTURE II Study Group, 2007). At the time of licensure, the first-generation vaccines were licensed with a 3-dose schedule, and subsequently with a 2-dose schedule for women aged 15 and under. However, based on promising findings from observational studies of high vaccine effectiveness after only one dose, and subsequent clinical trials, the Strategic Advisory Group of Experts on Immunization (SAGE) recommended an off-label HPV vaccination regimen of one dose for girls and women from the age of 9 to 20 years-old (Kreimer et al, 2015; Basu et al, 2021; WHO, 2022). However, for women aged 21 or older a 2-dose schedule is still recommended by the WHO (WHO, 2022).

This nationwide trial of concomitant HPV vaccination among women aged 22 to 30-years-old in Sweden is a unique opportunity to evaluate the vaccine effectiveness of one dose of HPV vaccination among women over the age of 20 years old (Arroyo Muhr et al, 2024). Studies on the efficacy and effectiveness of one dose among women over the age of 20 years old are scarce and of varying quality. The findings of this study will be crucial to inform public health decision makers and in contributing to the evidence base for assessing if the 2-dose schedule recommendation among women over 20-years-old is still warranted.

Methods

This study will utilize the population level trial of strategies to increase the speed of HPV elimination (clinical trials.gov ID: NCT04910802).

A population-based trial of the 'Even faster' strategy to increase the speed of cervical cancer elimination commenced in 2021 in the capital region of Sweden (Stockholm County) as a piloting phase and expanded to the other regions of Sweden in Autumn 2022 (Clinicaltrials.gov, NCT04910802) (Dillner et al, 2021; Arroyo Muhr et al, 2024). Women were invited by letter, push notification (via their personal mobile telephones) to attend a vaccination site for concomitant HPV vaccination (with the nonavalent vaccine Gardasil 9) and HPV-based cervical screening (using a self-sample). After 3 years women who had received their first vaccine dose were invited to receive a second dose of the nonavalent HPV vaccine and to give a second screening sample.

The vaccine effectiveness will be estimated as the HPV incidence among HPV negative vaccinated women (for a specific HPV type) divided by the incidence among a comparison group of all unvaccinated women attending routine screening in Sweden (whole trial or Stockholm region in the piloting phase).

Data collection

HPV screening results from the women participating in the trial will be obtained from the trial database and results from routine cervical screening will be extracted from the Swedish national cervical screening registry (NKCx) (Dillner et al, 2024).

Data on HPV vaccination history among the eligible women (vaccinations received within Sweden only) shall be collected by linkage to the Swedish national vaccination register via the Swedish personal identification number. Vaccination data will contain the HPV vaccine, date of vaccination and the dose number.

Statistical Analyses

To expedite evidence production, the first report will include only Stockholm region (the piloting phase), approximately 19,000 women, whereas the final report will include all women participating also in the other regions of Sweden, approximately 240,000 women.

We shall estimate the incidence rate of incident HPV16, 18, 31, 33, 45, 52 or 58 infection 3 years after receiving one dose of the nonavalent vaccine, among the 1994-1999 born women participating in the elimination trial at the time who were HPV negative at baseline (negative for the specific HPV type in the analysis). This will be compared to the incidence rate among the HPV unvaccinated women born from 1993-1999, attending at least 2 rounds of routine cervical screening who were naïve for the given HPV type in the first screening test. The incidence rate ratio comparing the incidence rate among the HPV vaccinated to the HPV unvaccinated women will be estimated using a Poisson regression model. To take account of possible confounding due to age and birth cohort wise herd effects, age and birth cohort will be adjusted for in the statistical model. Vaccine effectiveness will be computed as one minus the incidence rate ratio.

When classifying whether the women were naive at baseline or not a buffer period of 6 weeks between vaccination and screening sample will be implemented as a sensitivity analysis to exclude prevalent infections at the time of vaccination, or before the vaccine has had time to become effective (Markowitz et al, 2022). During the buffer period the individual will not contribute person time to either the intervention or comparison groups.

Secondary analyses will be conducted stratifying the HPV incidence ratios (both of incident) by HPV vaccination status outside the trial at the time of enrollment into the study.

Power calculations for this study were conducted using a Monte Carlo simulation approach, whereupon 1000 data sets were simulated with expected degrees of variation based on the following assumptions: i) The baseline HPV18 incidence was assumed to be 2.1 per 100 person-years (the rarest HPV type out of all the vaccine preventable HPV types in these birth cohorts) based on the incidence estimated by the International Agency for Research on Cancer (IARC) dynamic HPV transmission model previously parameterized to the Swedish population setting (Arroyo Mühr et al, 2024); ii) among the women born from 1994-1999 who reside in Sweden as according to the population registry, 35.3% will not have participated in elimination trial by the end of the enrollment period on the 30th of June 2025 (N=130,485 women), a conservative estimate of 70% of these women will have participated in the routine cervical screening program (N=91,349 women), among which 36.5% will have no previous history of HPV vaccination based on reported HPV vaccination coverage estimates from the Swedish vaccination register (N=33,339 women), therefore, given the current screening interval of 5 years in the age group, we expect the unvaccinated women in the target birth cohorts who comprise the comparison group to contribute >166,000 person years during the study period; iii) among the intervention group it is assumed that 99% of women are naive for HPV18 at enrolment and that 20% of the enrolled women will be lost to follow up between the first and the second dose, out of which 36.5% will have had no previous history of HPV vaccination recorded in the Swedish vaccination register at the time of enrollment in the trial. Using these assumptions, we found that the study was highly powered (power = 100% power, 95% confidence intervals, 99.6-100% with an alpha level of 0.05) to detect HPV18 vaccine effectiveness of 95%. Power calculation analyses were conducted using R statistical software (version 4.4.0) and the 'simr' package (version 1.0.7) (Green and MacLeod, 2015).

Ethical considerations

The population-based even FASTER trial was approved by the Swedish Ethical Review Authority and the Swedish Medicinal Products Agency (decision numbers [DNR], 2020-07145 and 5.1-2021-8496 respectively). All women participating in the trial provided informed consent to participate in the study before receiving HPV vaccination. Women with protected identity were not personally invited to participate in the trial but were eligible to participate if they so requested. This study is funded by Region Stockholm.

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