

**Test file:** Effectiveness of HPV Vaccination Programs on Cervical Cancer Incidence: A Population-Based Study

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**Abstract**

This population-based study evaluates the impact of human papillomavirus (HPV) vaccination programs on cervical cancer incidence across eight countries with established vaccination programs. Using cancer registry data from 2000-2022, we analyzed cervical cancer trends before and after vaccine introduction. Early-adopting countries demonstrated significant reductions in cervical cancer incidence, with the most pronounced decreases observed in cohorts vaccinated before sexual debut. These findings provide compelling real-world evidence supporting the effectiveness of HPV vaccination in cervical cancer prevention and highlight the importance of high vaccination coverage for achieving population-level impact.

**Keywords:** HPV Vaccination; Cervical Cancer; Cancer Epidemiology; Vaccine Effectiveness; Population Health; Cancer Prevention; Public Health Programs

**1. Introduction**

Cervical cancer remains a significant global health burden, with an estimated 604,000 new cases and 342,000 deaths annually worldwide [1]. The causal relationship between persistent infection with high-risk human papillomavirus (HPV) types and cervical cancer development is well-established, with HPV types 16 and 18 responsible for approximately 70% of all cervical cancer cases [2]. This understanding led to the development of prophylactic HPV vaccines, which have demonstrated high efficacy in clinical trials against HPV infection and related precancerous lesions [3].

Following vaccine licensure in 2006-2007, many countries implemented national HPV vaccination programs, primarily targeting adolescent girls before sexual debut. While clinical trials established vaccine efficacy under controlled conditions, population-level effectiveness depends on multiple factors including vaccine coverage, target population, catch-up vaccination strategies, and program implementation quality [4]. Monitoring the real-world impact of vaccination programs on cervical cancer incidence is essential for evaluating program success and informing future prevention strategies [5].

This multinational population-based study aims to assess the early impact of HPV vaccination programs on cervical cancer incidence trends, examine differential effects by age cohort and vaccination strategy, and discuss implications for global cervical cancer elimination efforts.

**2. Methods**

**2.1 Study Design and Data Sources**

We conducted an ecological trend study analyzing cervical cancer incidence data from population-based cancer registries in eight countries with established HPV vaccination programs: Australia, Canada, Denmark, England, Scotland, Sweden, Norway, and the United States. The study period spanned 2000-2022, encompassing pre-vaccination (2000-2007) and post-vaccination (2008-2022) eras.

Data were obtained from the following sources: national cancer registries, HPV vaccination program databases, population demographic statistics, and published literature on vaccination coverage. All registries included in the analysis met quality standards for completeness, validity, and comparability as defined by the International Association of Cancer Registries [6].

## **2.2 Vaccination Program Characteristics**

The eight countries implemented varied vaccination strategies including: school-based programs (Australia, England, Scotland), primary care-based programs (Canada, US, Scandinavian countries), different target ages (primarily 12-13 years, with catch-up to varying upper age limits), and varying vaccine types (quadrivalent and nonavalent vaccines). Vaccination coverage rates ranged from 60% to 86% for the primary target population across countries and years.

## **2.3 Statistical Analysis**

We employed joinpoint regression analysis to identify significant changes in cervical cancer incidence trends, calculating annual percentage changes (APCs) with 95% confidence intervals. Age-period-cohort models were used to disentangle age, period, and cohort effects on incidence trends. We calculated incidence rate ratios (IRRs) comparing post-vaccination to pre-vaccination periods, stratified by age group and birth cohort.

To estimate vaccine impact, we used negative binomial regression models adjusted for age, period, screening intensity, and socioeconomic factors. The prevented fraction was calculated as  $(1 - \text{IRR}) \times 100\%$ . Sensitivity analyses included: (1) exclusion of countries with changing screening recommendations during the study period, (2) adjustment for hysterectomy rates, and (3) evaluation of potential diagnostic changes over time.

## **3. Results**

### **3.1 Overall Cervical Cancer Trends**

Pooled analysis of all eight countries demonstrated a significant acceleration in the decline of cervical cancer incidence following vaccine introduction. The pre-vaccination period (2000-2007) showed an average annual decrease of 1.2% (95% CI: 0.8-1.6%), while the post-vaccination period (2008-2022) demonstrated an average annual decrease of 4.8% (95% CI: 4.2-5.4%). The joinpoint analysis identified 2009-2011 as significant inflection points across most countries, corresponding to the period when early-vaccinated cohorts began entering age groups at risk for cervical cancer.

### **3.2 Age-Stratified Analysis**

The most substantial reductions in cervical cancer incidence occurred in younger age groups. Among women aged 20-24 years, incidence decreased by 62% (95% CI: 58-66%) comparing the late post-vaccination period (2017-2022) to the pre-vaccination era. Smaller but significant reductions were observed in women aged 25-29 years (38% decrease, 95% CI: 34-42%) and 30-34 years (17% decrease, 95% CI: 13-21%). No significant changes were observed in women aged 45+ years, consistent with limited vaccination in these cohorts.

### **3.3 Birth Cohort Effects**

Analysis by birth cohort revealed striking patterns aligned with vaccination eligibility. The 1993-1996 birth cohorts (largely included in catch-up vaccination programs) showed 25-40% lower incidence rates compared to earlier cohorts at similar ages. The most pronounced reductions (65-80% lower incidence) were observed in the 1997-2000 birth cohorts, representing the first groups with high coverage through routine adolescent vaccination before sexual debut.

### **3.4 Country-Specific Variations**

The magnitude of vaccine impact varied across countries, with the strongest associations observed in countries achieving high vaccination coverage through school-based programs. Australia, with particularly high coverage (>80%) since program inception, demonstrated the most substantial reductions, including early evidence of impact on advanced cancers and adenocarcinoma incidence. Countries with lower or delayed coverage showed more modest but still significant reductions.

### **3.5 Herd Protection Effects**

In countries with high female vaccination coverage (>70%), significant incidence reductions were also observed in young unvaccinated women, suggesting herd protection. Additionally, two countries with gender-neutral vaccination programs demonstrated more rapid declines in cervical cancer incidence compared to female-only programs, though longer follow-up is needed to confirm this pattern.

## **4. Discussion**

### **4.1 Principal Findings and Interpretation**

This multinational population-based study provides compelling evidence that HPV vaccination programs have significantly accelerated declines in cervical cancer incidence in early-adopting countries. The strong birth cohort effects, with the most substantial reductions in cohorts vaccinated before sexual debut, support the biological plausibility of vaccine impact and highlight the importance of targeting adolescents before HPV exposure.

The differential effects by age group reflect both the natural history of cervical carcinogenesis (typically requiring 15-20 years from HPV infection to cancer development) and the cohort-specific vaccination opportunities. The early appearance of impact in young women suggests that vaccination may prevent not only persistent infection but also rapid progression pathways in some cases.

### **4.2 Public Health Implications**

These findings have important implications for cervical cancer prevention strategies globally. First, they provide strong support for maintaining and enhancing high-coverage HPV vaccination programs. Second, they suggest that countries with well-established vaccination programs may achieve cervical cancer elimination targets earlier than previously projected. Third, they highlight the importance of catch-up vaccination for older cohorts and consideration of gender-neutral vaccination to enhance herd protection.

The World Health Organization's global strategy for cervical cancer elimination, targeting incidence below 4 per 100,000 women, appears achievable in countries sustaining high vaccination coverage [7]. However, ongoing surveillance, maintaining vaccination coverage, and ensuring equitable access remain critical challenges.

### **4.3 Limitations and Research Needs**

Several limitations should be considered. Ecological study design precludes individual-level causal inference, though the strong cohort-specific effects strengthen causal interpretation. Variations in cancer registration practices, screening programs, and hysterectomy rates across countries and over time may confound trends, though sensitivity analyses suggested robust findings. Longer follow-up is needed to assess impact on older age groups and overall population burden.

Future research should focus on: (1) impact on cervical cancer mortality and advanced stage disease, (2) effectiveness in low-resource settings, (3) duration of protection and potential need for booster vaccination, and (4) interactions between vaccination and screening programs as prevention strategies evolve.

## 5. Conclusion

This comprehensive population-based study demonstrates substantial early impact of HPV vaccination programs on cervical cancer incidence in high-income countries. The significant reductions, particularly in cohorts vaccinated before sexual debut, provide real-world evidence supporting the effectiveness of HPV vaccination as a primary prevention strategy for cervical cancer. These findings reinforce the importance of achieving and maintaining high vaccination coverage and support global efforts toward cervical cancer elimination through scaled-up vaccination programs. Continued surveillance and research will be essential to monitor long-term impact, inform program improvements, and guide the integration of vaccination with screening in comprehensive cervical cancer prevention strategies.

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