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Population Impact of HPV Vaccines: Summary of Early Evidence

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Abstract

Human papillomavirus (HPV) vaccines are available in the United States and around the world to prevent HPV-associated diseases including cervical cancer and genital warts. HPV vaccination is currently recommended for adolescents: target ages for routine and catch-up vaccinations vary by country. Because the time from vaccination to cancer development can be several decades, many studies are evaluating more immediate outcomes. In the 4 years since the vaccine was introduced, reductions in HPV vaccine type prevalence and genital warts have been reported in young females in the United States and other countries. Many questions remain about the long-term impact, but the initial studies show promising results for the relatively new HPV vaccine.

Keywords

HPV vaccine; Cervical cancer; Prevention

Two prophylactic human papillomavirus (HPV) vaccines are available and have been introduced in many countries [1]. Both the bivalent and quadrivalent vaccines protect against HPV16 and 18 that cause 70% of cervical cancers; the quadrivalent vaccine is also directed against HPV6 and 11 that cause 90% of genital warts. Most vaccination programs recommend routine use in adolescent girls, and some offer vaccination in older females who were not previously vaccinated. More recently, some countries have added routine adolescent male vaccinationwith the quadrivalent vaccine to their immunization programs. Although both vaccines had high efficacy in the clinical trials [2,3], monitoring real-world effectiveness is important for program and policy [4]. Because of the long interval between infection and cancer development, efforts are under way to evaluate impact on more proximate outcomes.

Early and mid-endpoints include HPV type prevalence, genital warts (for quadrivalent vaccine), and HPV-associated cervical lesions, all of which pose unique monitoring

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challenges [5]. Monitoring HPV infection requires sampling from the site of infection, DNA extraction, and genotyping to evaluate trends in prevalence of HPV types. Genital warts are not notifiable in most countries. High-grade cervical lesions were used as the primary endpoint in vaccine clinical trials, but can only be detected through routine cervical cancer screening. Therefore, changes in screening could affect detection of these lesions and complicate interpretation of vaccine impact. For example, new guidelines that recommend initiation of screening at older ages and less frequent screening will be partially responsible for declines in diagnosed cervical lesions in the United States [6]. Despite these limitations, data demonstrating vaccine impact on early outcomes have become available just a few years after vaccine introduction. Results from published studies are summarized in Table 1 and described in the following sections. During the period of these evaluations, no country had recommended routine vaccination for males.

HPV Infection

Reductions in vaccine type infections among young women have been reported from several post licensure studies using consensus polymerase chain reaction assays with type-specific HPV detection. In the United States, a recent analysis of data from the National Health and Nutrition Examination Survey, a nationally representative survey of the non-institutionalized population, found a 56% decrease in population prevalence of vaccine type HPV in self-collected cervical-vaginal samples from females aged 14–19 years in the 4 years after vaccine introduction, whereas no significant changes were observed in older females [7]. Estimated vaccine effectiveness was 82% in sexually active 14- to 19-year-old female participants who reported receiving at least one vaccine dose.

Clinic-based studies from the United States also show impact of vaccination on type-specific HPV infection. One study reported a 79% decrease in vaccine type prevalence among 14- to 17-year-old females attending three urban clinics based on clinician-collected cervical or self-collected vaginal samples [8]. Another reported significant reductions in 13- to 26-year-old females who received at least one dose of HPV vaccine (69%) as well as among unvaccinated women in the same age group (>50%) [9]. In Australia, where vaccine coverage is more than 80% in the target age group and high coverage was also achieved in the catch-up age group, a decrease in vaccine type HPV prevalence, from 28.7% to 6.7%, was reported in females aged 18–24 years seen at family planning clinics [10].

Genital Warts

The earliest indication of quadrivalent vaccine impact on genital warts was from postlicensure monitoring studies from Australia. An ecologic evaluation conducted in a sexual health clinic in Melbourne showed a sharp decrease in new genital warts diagnoses in young women within 2 years after vaccine introduction [11]. There was also a smaller decrease in new genital warts in young heterosexual males even though they were not included in the vaccination program, suggesting indirect protection through herd immunity. Subsequent Australian studies conducted in sexual health centers have reported even larger declines among vaccine-eligible females and young heterosexual males through 2011 [12–15]. Emerging data from other countries further strengthen evidence of direct and indirect

impact of the quadrivalent HPV vaccine. These include countries with high vaccination coverage (Denmark [16] and Sweden [17]), but also countries with lower coverage such as the United States [18,19], Germany [20], and New Zealand [21]. In the United States, an ecologic analysis of private health insurance claims data found a 38% decrease in genital warts claims in 15- to 19-year-old females, from 2.9 to 1.8 per 1,000 person-years, and a smaller decrease in females aged 21–30 years, but no change in those older than 30 years [18]. Although most evidence to date has been from ecologic evaluations, one cohort study based on national registry data from Denmark found significantly lower risks of genital warts incidence in those who were vaccinated with one or more doses compared with unvaccinated females, with the largest decrease in the youngest birth cohort [22].

High-Grade Cervical Lesions

Compared with HPV infection and genital warts, vaccine impact on HPV-associated high-grade cervical lesions is expected to take longer to demonstrate. However, in Australia, where screening recommendations still include those aged younger than 18 years, reductions in high-grade lesions were observed in girls <18 years old who were reported to the Victoria Cervical Cancer Register within 3 years after vaccine introduction; no declines were seen in older women in the same screened population [23]. Early data from sentinel surveillance systems established in the United States to monitor vaccine impact on histologically confirmed cervical cancer precursor lesions are also encouraging. A study of women diagnosed with high-grade cervical lesions between 2008 and 2010 found that those who were vaccinated at least 24 months before their diagnosis were less likely to have HPV16/18-associated lesions compared with their unvaccinated counterparts [24].

In conclusion, a variety of activities are ongoing worldwide to demonstrate the impact of HPV vaccines on biologic outcomes. Reports of substantial declines in some vaccine-associated outcomes provide compelling evidence of impact shortly after vaccine introduction. In addition to strengthening existing data, a critical role of future efforts will be to address several remaining questions, including those related to efficacy of less than three doses, cross-protection, potential type replacement, and duration of protection. Sustainability of these evaluations will be important to consider. Evidence of HPV vaccine impact has been reassuring thus far, and additional data will undoubtedly bring HPV vaccine benefits into sharper focus in ensuing years.

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Table 1

Summary of published studies of HPV vaccine impact on biologic endpoints

Country (year vaccine introduced)	Data source and/or location	First author, publication year, [reference no.]	Population	Study design	Results[b]
HPV infection[a]					
Australia (2007)	Family planning clinics in Victoria	Tabrizi, 2012 [10]	Females 18–24 years	Ecologic, compared pre- to postvaccine periods	VT prevalence decreased from 28.7% (2005–2007) to 5.0% (vaccinated, 2010–2011) and 15.8% (unvaccinated, 2010–2011)
USA (2006)	Adolescent/community health clinics in Ohio	Kahn, 2012 [9]	Females 13–26 years	Compared pre- to postvaccine periods by vaccination status	VT prevalence decreased from 31.8% (2006–2007) to 9.9% (vaccinated, 2009–2010) and 15.4% (unvaccinated, 2009–2010)
	Urban STD/community health clinics in Indiana	Cummings, 2012 [8]	Females 14–17 years	Ecologic, compared pre- to postvaccine periods	VT prevalence decreased from 24% (1999–2005) to 5.3% (2010)
	Nationally representative survey	Markowitz, 2013 [7]	Females 14–59 years	Ecologic, compared pre- to postvaccine periods	VT prevalence decreased in 14–19 year olds from 11.5% (2003–2006) to 5.1% (2007–2010). No decrease in older age groups
Genital warts					
Australia (2007)	Sexual health clinic in Melbourne	Fairley, 2009 [11]	Females and males, all ages	Ecologic, trend analysis	New GW diagnoses decreased from 12.7% (2004–2007) to 6.6% (2008) in females <28 years and from 14.3% (2004/7) to 11.8% (2008) in heterosexual males. No decrease in females ≥28 years or homosexual males
		Read, 2011 [15]	Females and males, all ages	Ecologic, trend analysis	New GW diagnoses decreased from 18.6% (2007–2008) to 1.9% (2010–2011) in females <21 years and from 22.9% (2007–2008) to 2.9% (2010–2011)in heterosexual males <21 years. No decrease in females, heterosexual males ≥30 years or homosexual males
	Sexual health clinics throughout country	Donovan, 2011 [12]	Females and males, all ages	Ecologic, trend analysis	New GW diagnoses decreased from 11–12% (2004–2007) to 4.8% (2010–2011) in female residents aged 12–26 years and from 13–14% (2004–2007) to 8.9% (2010–2011)in heterosexual males. No decrease in females >26 years or homosexual males
		Ali, 2013 [13]	Females and males, 3 age groups (<21, 21–30, >30 years)	Ecologic, compared pre- to postvaccine periods	New GW diagnoses decreased from 11.5% (2007) to .85% (2011, unvaccinated) and 0 (2011, vaccinated) in females <21 years, from 11.3% (2007) to 3.1% (2011) in females 21–30 years, and from 18.2% (2007) to 8.9% (2011) in heterosexual males
	Medicare registry	Ali, 2013 [14]	Females and males, 15–44 years, 10-year age groups	Ecologic, trend analysis	In-patientvulvar/vaginal and penile GW treatments decreased 85% (from 285 [2007] to 42 [2011]), in females 15–24 years, 24%(from 202 [2007] to 153 [2011]), infemales25–34, 71%(from51 [2007] to 15 [2011]) in males 15–24 years, and 59% (from 39 [2007] to 16 [2011]) in males 25–34 years. No decrease in males or females 35–44 years
New Zealand (2008)	Sexual health clinic in Auckland	Oliphant, 2011 [20]	Females and males, two age groups (<20, ≥20 years)	Ecologic, trend analysis	GW diagnoses decreased from 13.7% (2007) to 5.9% (2010) in females <20 years and from 11.5% (2007) to 6.9% (2010) in males <20 years. No decrease in older males or females

Country (year vaccine introduced)	Data source and/or location	First author, publication year, [reference no.]	Population	Study design	Results[b]
Denmark (2009)	National patient registry	Baandrup, 2013 [21]	Females and males, all ages	Ecologic, trend analysis	GW incidence per 100,000 person-years decreased from 381.5 (2008) to 39.8 (2011) in females 16–17 years. Smaller decrease in females 18–19, 20–21, 22–25, and 26–29. Nonsignificant decrease in males 22–25 and 26–29 years
		Blomberg, 2013 [16]	Females, birth cohorts eligible for vaccination (1989–99)	Retrospective cohort	Decrease in risk of GW among vaccinated (≥1 dose) girls compared with unvaccinated girls. Significant trend in relative risk from oldest to youngest cohort: .62, .25, .22, .12. No GW in vaccinated girls in youngest age cohort
Germany (2007)	Research database	Milolajczyk, 2013 [19]	Females and males, 10–79 years	Ecologic, trend analysis	New GW diagnoses per 100,000 person-years decreased from 316 (2005) to 242 (2008) in females 15–19 years
Sweden (2007)	National patient registry	Leval, 2012 [17]	Females, 10–44 years	Ecologic, trend analysis	GW incidence per 100,000 person-years decreased from 617 (2006) to 523 (2010) in females 15–19 years, from 1,038 (2006) to 885 (2010) in females 20–24 years, from 584 (2006) to 500 (2010) in females 25–29 years, and from 1,070 (2006) to 1,028 (2010) in males 20–24 years. Nonsignificant increase in older males and females
USA (2006)	Administrative data from family planning clinics in California	Bauer, 2012 [19]	Females and males, 4 age groups (<21, 21–25, 26–30, >30 years)	Ecologic, trend analysis	New GW diagnoses decreased from 1% (2007) to .6% (2010) in females <21 years, from 2.7% (2007) to 2.2% (2010) in males <21 years, from 1% (2007) to .9% (2010) in females 21–25 years, and from 5.1% (2006) to 4.5% (2010) in males 21–25 years. Increase in older males and females
	Private health insurance claims data throughout country	Flagg, 2013 [18]	Females and males, 10–39 years	Ecologic, trend analysis	GW prevalence decreased per 1,000 person-years from 2.9 (2006) to 1.8 (2010) in females 15–19 years and from 2009–2010 in females 20–24 years (5.5–4.8/per 1,000 person-years). No decrease in other groups
Cervical lesions					
Australia (2007)	Cervical cytology registry in Victoria	Brotherton, 2009 [24]	Females, 5 age groups (<18,18–20, 21–25, 26–30, >30 years)	Ecologic, compared pre- to postvaccine periods	Decrease in high grade cervical lesions from 2007 to 2009 in females <18 years. No decrease in older age groups
USA (2006)	Population-based catchments throughout country	Powell, 2012 [23]	Females 18–31 years diagnosed with high-grade cervical lesions	Indirect cohort	Lower proportion of HPV16/18-related[a] lesions in women diagnosed from 2008 to 2011 who received ≥1 vaccine dose at least 24 months before their diagnosis compared with those who were not vaccinated

GW = genital warts; VT = vaccine-type.

[a] Used consensus polymerase chain reaction and HPV typing.

[b] Results are statistically significant except where noted.