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REVIEW

Impact of 2-, 4- and 9-valent HPV vaccines on morbidity and mortality from cervical cancer

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ABSTRACT

Cervical cancer causes significant morbidity and mortality worldwide. Most cervical cancers are associated with oncogenic human papillomavirus (HPV), and vaccination with any of 3 available HPV vaccines is anticipated to greatly reduce the burden of cervical cancer. This review provides an overview of the burden of HPV, the efficacy and clinical effectiveness of the bivalent (HPV 16, 18), quadrivalent (HPV 6, 11, 16, 18) and 9vHPV (HPV 6, 11, 16, 1831, 33, 45, 52, 58) vaccines in order to assess the anticipated impact on cervical cancer. All three vaccines show high efficacy in prevention of vaccine-specific HPV-type infection and associated high-grade cervical dysplasia in HPV-naïve women. Early clinical effectiveness data for the bivalent and quadrivalent vaccine demonstrate reduced rates of HPV 16 and 18 prevalence in vaccinated cohorts; data evaluating cervical dysplasia and cervical procedures as outcomes will shed further light on the clinical effectiveness of both vaccines. The bivalent vaccine has demonstrated cross-protection to non-vaccine HPV types, including the types in the 9vHPV vaccine. No clinical effectiveness data is yet available for the 9vHPV vaccine. While HPV vaccination has great promise to reduce cervical cancer morbidity and mortality, estimated benefits are largely theoretical at present. Large population-based clinical effectiveness studies will provide long-term immunogenicity and effectiveness, as well as assessment of cervical cancer as an endpoint, particularly as young vaccinated women enter the appropriate age range to initiate screening for cervical cancer. Strengthening screening and treatment programs will likely have the greatest impact in the short-term on cervical cancer morbidity and mortality

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Introduction

Cervical cancer is the fourth leading cause of cancer deaths in women worldwide. In 2012, there were 527,600 cases of newly diagnosed cervical cancer and 265,700 deaths from cervical cancer.[1] Underlying these statistics are wide disparities in cervical cancer incidence and mortality by geographic region. For instance, in sub-Saharan Africa, there were 34.8 new cases and 22.5 deaths per 100,000 women, whereas in Western Asia there were only 4.4 new cases and 1.9 deaths per 100,000 women in 2012.[2] While North America is the region with the third lowest cervical cancer rate, in 2015 nearly 13,000 women in the United States will still be newly diagnosed with cervical cancer and approximately 4,100 will die from the disease.[3] Cervical cancer has a bimodal age distribution with the majority of cases occurring among women in their 30s and 40s[4] the age at which women are often raising families and ensuring the financial viability of their families and communities. In addition to the risk of death, cervical cancer is associated with significant morbidity, including bleeding, pain and kidney failure, which are difficult to treat, especially in communities with poor access to health care.

The presence of human papillomavirus (HPV) in cervical cancer specimens was established in the 1980s.[5] HPV is a small, non-enveloped, double stranded DNA virus belonging to the family Papovaviridae. More than 120 HPV types have been identified, and they infect mucosal, genital and cutaneous sites. Approximately 40 types have been found in the genital tract, and 15 of those are classified as high-risk or intermediate-risk types which are potentially oncogenic.[6] While 90% of HPV infections are cleared or become dormant within 1–2 y of infection, the persistence of detectable high-risk HPV infection increase the risk of progression to cervical cancer,[7,8,9] and over time it has become clear that the majority of cervical cancers are associated with high-risk HPV infection.[10]

Cervical cancer screening has consistently been associated with a reduction in cervical cancer incidence and mortality, regardless of the precise screening modality.[11,12] Developed countries have achieved such reduced incidence and mortality from cervical cancer over the past 40 y largely as a result of the implementation of cytologic screening with the Papanicolaou (Pap) smear.[13-15] Over the past several years, national and international recommendations for screening have developed to include HPV testing, where available.[16] Despite marked advances in knowledge about cervical cancer and effective screening, cervical cancer screening programs have variable efficacy depending on available resources, implementation strategies, quality of laboratory and pathology testing and community awareness.[17-19] Effective Pap smear and HPV screening programs require materials, logistics and specialists that are prohibitively complex and expensive for many low- and middle-income countries.[20] Even in developed countries with

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advanced infrastructure and long-standing cervical cancer screening programs, screening is not perfect and cervical cancer screening falls short of national targets which limits the impact on the incidence and mortality from the disease.[21]

Given the role of HPV infection to the development of cervical cancer, a unique opportunity exists to shift from secondary to primary prevention of cervical cancer. Two vaccines, a quadrivalent and a bivalent vaccine, both targeting the two HPV types associated with the highest proportion of cervical cancers have been on the market for several years. The quadrivalent vaccine also provides protection against the 2 HPV types most associated with anogenital warts. A new 9vHPV vaccine has recently been approved which protects against an additional 5 oncogenic HPV types. In this review we will provide an overview of the burden of HPV, the efficacy and clinical effectiveness of the bivalent and quadrivalent vaccines, as well as the data available to date about the efficacy of the 9vHPV vaccine in order to assess the anticipated impact on morbidity and mortality from cervical cancer.

Link between HPV infection and cervical cancer

While there are many types of HPV, those linked to cancer include HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82.[22] The oncogenicity of HPV is mediated by E6 and E7 open-reading frames, which encode proteins that induce accelerated and disordered cellular proliferation. Such proliferation leads to cervical dysplasia or precancerous lesions, ranging from cervical intraepithelial neoplasia (CIN) 1 through 3, to cancer. CIN1 is a low-grade cervical dysplasia, and 70–90% of CIN1 lesions spontaneously regress. CIN2 and CIN3 are considered high-grade dysplasia, though they differ in that CIN2 is a heterogeneous entity with less common progression onto cancer. Approximately 40% of CIN2 lesions regress in the first year of infection and up to 68% of untreated CIN2 lesions spontaneously regress within 3 y in women under the age of 25.[23,24] Approximately 2% of CIN2 lesions progress to CIN3 within a year, while 15–22% of untreated CIN2 lesions progress to CIN3 or worse over 3 y[6] 0.2–4% of CIN3 lesions progress to cervical cancer within a year and 14–50% of all CIN3 lesions progress to squamous cell carcinoma in-situ, the immediate precursor to squamous cell carcinoma, or squamous cell carcinoma itself.[25] Adenocarcinoma of the cervix is distinct from squamous cell carcinoma as it arises from the glandular epithelium of the endocervical canal and its immediate precursor is adenocarcinoma in situ (AIS). Though rapidly progressive cervical cancers do rarely develop in young women, time from HPV infection to cervical cancer development is typically 20 y[26]

HPV prevalence in the general population and in invasive cervical cancer

HPV infection is common, though its prevalence and type distribution in women with normal cytology worldwide is heterogeneous.[27] A large, international meta-analysis found that 10.4% of women with normal cytology have co-existing detectable HPV DNA. Women younger than 25 y of age and women in less developed countries have higher point prevalence, ranging from 15–45%.[28,29] Yet single site studies have found particular populations have higher risk for infection. In a study of teenagers in Kampala, Uganda, the prevalence of HPV infection was found to be significantly higher at 74.6%, with 51.4% being high-risk types. Eight.6% of the study population was HIV positive, and among the HIV positive population, the prevalence of HPV infection was 87.8%, and 64.6% were infected with multiple HPV types.[30]

Point prevalence data does not fully reflect the lifetime risk of HPV infection because up to 85% of HPV infections are detectable for only 16 months after the time of infection,[31] and lifetime incidence rates of HPV are estimated to be high. Among one college-aged female cohort followed over 3 years, initial prevalence of HPV was 26% yet an additional 43% of the women developed HPV over the course of the study period.[32] Early age of sexual debut and multiple sexual partners place women at higher risk of HPV infection. The most common HPV types in women with normal cytology were HPV 16, 18, 31, 52, and 58, all high-risk types.[28]

With the development of highly sensitive HPV DNA testing, studies have confirmed that most cervical cancer specimens have detectable HPV DNA, and greater than 90% contain DNA for HPV 16, 18, 31, 33, 39, 45, 52, or 58.[33] Importantly, women who develop cervical cancer, have often had the same type of high-risk HPV detected in cervical specimens 3 to 5 y prior to their cancer incidence.

Regional differences in the HPV-specific prevalence in squamous cell carcinoma have been noted. In a meta-analysis of 85 studies, which included 10,058 women with cervical cancer, HPV 16 prevalence predominated in squamous cell carcinoma, ranging from 46% in Asia to 63% in North America. HPV 18 was the second most prevalent type, found in 10–14% of squamous cell carcinoma specimens. While squamous cell carcinoma histology predominates, the proportion of adenocarcinoma among all invasive cervical cancers is significant, ranging from 4% in Africa to 32% in North America. HPV 18 is the predominant HPV type found in adenocarcinoma, ranging from 37–41%, followed by HPV 16, found in 26–36%, and HPV 45 found in 5–7% of specimens.[35] In a follow-up meta-analysis that included 133 studies and 14,595 women, HPV 16 and 18 combined were found to contribute to 74–77% of squamous cell carcinoma in Europe and North America, and 65–70% of squamous cell carcinoma in Africa, Asia and South/Central America.[36] Both studies demonstrated that after HPV 16 and 18, subtypes 31, 33, 35, 45, 52 and 58 were the next most frequently found HPV types found in invasive cervical cancer on all continents, though their individual relative contribution varies from 2–8%, with a relatively higher prevalence of subtypes 52 and 58 in Asia and subtype 45 in Africa. Other HPV types, including 39, 51, 56, 59, 66, 68, 70, 73 and 82 were found to be present in <2 % of invasive cervical cancer cases.

While data from meta-analyses are limited by their reliance on the HPV DNA testing methods of each individual study, multiple studies collecting samples from large cohorts have confirmed the presence of the same HPV types in invasive cervical cancer specimens. An international case-controlled study which included 1918 women with cervical cancer, tested cervical cancer cells directly for HPV types and found the most

Table 1. Comparison of efficacy and effectiveness of HPV vaccines.

HPV Vaccine type		Bivalent	Quadrivalent	Nonavalent
HPV types included		16, 18	6, 11, 16, 18	6, 11, 16, 18 31, 33, 45, 52, 58
Efficacy in HPV-naïve women*	Prevention of vaccine-specific HPV type infection	94.3%+ (HPV16/18) at 3.6y 87.9% (HPV16/18) at 4y	97% 2+ (HPV16) at 3.7y 100% (HPV18) at 3.7y	96%2++ (HPV16/18) at 4.5y
	Prevention of CIN2+ associated with vaccine-specific HPV types	92.9% at 3.6y	100% (CIN2) at 3.7y 97% (CIN3) at 3.7y	96.3% at 4.5y
	Prevention of CIN2+ associated with any HPV type	61.9% at 3.6y	No data	NS
Efficacy in all women (including HPV-exposed)	Prevention of vaccine-specific HPV type infection	76.4% at 4y	42% (HPV16) at 3.7y 79% (HPV18) at 3.7y	80.2% at 4.5y
	Prevention of CIN2+ associated with vaccine-specific HPV types	52.8% (CIN2+) at 3.6y 33.6% (CIN3+) at 3.6y	57% (CIN2) at 3.7y 45% (CIN3) at 3.7y	NSD from quadrivalent
	Prevention of CIN2+ associated with any HPV type	30.4% (CIN2+) at 3.6y 33.4% (CIN3+) at 3.6y	17% (CIN2+) at 3.7y	NSD from quadrivalent
Cross-protection	Efficacy in preventing CIN2 lesions associated with HPV types 31, 33, 45, 52, 58	31.5% at 3.6y (all women) 51.3% at 4y (HPV-naïve, and only 31,33,45)	NS$	N/A
Immunogenicity	Vaccine-specific HPV types	100% at 3.6y 99% at 4.5y	100% (HPV16) at 3y 76% (HPV18) at 3y	NSD from quadrivalent at 7m
HPV 16/18 change in prevalence pre- and post-vaccination		19.1% → 6.5% in 16–18 y/o	11.5% → 5.1% in 14–19 y/o	N/A
Commonly reported adverse events		Injection site reaction Fatigue Headache Myalgia	Injection site reaction Syncope Dizziness Nausea Headache Fever	Injection site reaction Headache Fever DizzinessNausea Fatigue

*HPV-naïve in the bivalent vaccine efficacy trial included women who were naïve to 14 high-risk HPV types, including 16 and 18, at start of study in this analysis. HPV-naïve in the quadrivalent vaccine efficacy trial included women who were naïve to HPV 16/18 at start of study in this analysis. HPV-naïve in the nonavalent vaccine efficacy trial included women who were naïve to HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59.
+Follow-up data at median 3.6 y is from industry-funded efficacy study designed for FDA approval.
2+Follow-up data at median 3.7 y is from industry-funded efficacy study designed for FDA approval.
2++Follow-up data up to maximum of 54 months is from industry-funded study designed to show non-inferiority to quadrivalent vaccine for FDA approval.
$When lesions co-infected with HPV 16 and 18 are excluded.

prevalent types in descending order of frequency to be HPV 16, 18, 45, 31, 33, 52, 58, and 35.[22] Similarly, an international study conducted in 38 countries which tested for HPV in invasive cervical cancer paraffin block specimens from 10,575 women found HPV DNA in 8977 (85%) of the samples. HPV 16 or 18 was detected in 71% and types 31, 33, 35, 45, 52, or 58 were detected in an additional 20% of the HPV positive samples. Four.4% of the invasive cervical cancer specimens were adenocarcinoma, and 94% of these were positive for HPV 16, 18 or 45.[37]

Bivalent and quadrivalent vaccines

Two vaccines targeting HPV have been publically available for several years. Both vaccines against HPV are composed of capsid antigen L1 virus-like particles that resemble native virions and induce immunogenicity, but are non-infectious.[38] A quadrivalent vaccine (Gardasil; Merck & Co, Inc., Whitehouse Station, New Jersey) that targets HPV 6, 11, 16, and 18 was approved by the Food and Drug Administration (FDA) in June 2006 for prevention of cervical cancer and genital warts (caused primarily by HPV types 6 and 11) in females aged 9 to 26 y of age.[39] A bivalent vaccine (Cervarix; GlaxoSmithKline, Rixensart, Belgium) that targets HPV 16 and 18 was approved by the FDA in October 2009 for the prevention of cervical cancer in females aged 9 to 26 y of age.[40] The protocol for both vaccines is a 2 or 3-shot series administered over a period of 6 months.[41]

Since availability of the vaccine in 2006, HPV vaccination has been introduced in an increasing number of national vaccination programs. The United States, Canada, Australia and the United Kingdom were the first to introduce HPV vaccination, and were quickly followed by other European, and high-income countries. Middle-income and some low-income countries have introduced the vaccine in the past 5 y In 2012, GAVI negotiated rates of $5 per dose for eligible countries, which has opened the door to more low-income countries to pilot vaccination campaigns. By 2014, 57 countries had included HPV vaccination in their national health programs.[42] Mechanisms for vaccination have included school-based and primary care programs with variable success and uptake rates.[43,44,45]

Bivalent vaccine efficacy, immunogenicity and cross-protection

The clinical efficacy of the bivalent vaccine on prevention of cervical cancer precursors was evaluated in the PATRICIA trial (Papilloma trial against cancer in young adults), which was funded by GlaxoSmithKline, the maker of the vaccine. In this phase III, multi-national prospective, double-blind, placebo controlled trial of more than 18,000 women aged 15 to 25 years, the vaccine was found to have 92.9% efficacy in preventing HPV16 and 18 associated CIN2 or worse (CIN2+) lesions in women who were HPV-naïve at the start of the study. Among those with a history of HPV infection, the vaccine had 52.8%

efficacy in preventing HPV16 and 18-associated CIN2 lesions and 33.6% efficacy in preventing HPV 16 and 18-associated CIN3 lesions.[46] An independent research group in Costa Rica found slightly lower efficacy against HPV 16 and 18 incident infection at 4-year follow-up of 87.9% in HPV-naïve women and 76.4% in all women regardless of initial HPV infection status.[47]

At 6.4-year follow-up of a subgroup of 776 HPV-naïve women, the bivalent vaccine demonstrated 95.3% efficacy for prevention of incident infection with HPV 16 and 18, 100% efficacy for prevention of incident HPV 16 and 18 associated CIN2+ lesion, and 71.9% efficacy for prevention of any CIN2+ lesion.[48] At 9.4-year follow-up of a subgroup of the same cohort, the vaccine had 100% efficacy for prevention of incident HPV 16 and 18 but showed no statistically significant prevention of HPV 16- and 18-associated high-grade cervical dysplasia nor high-grade cervical dysplasia associated with any oncogenic HPV infection. The lack of significance in dysplasia may be due to a small number of events (0 in the vaccine group and 3 in the placebo group related to HPV 16 and 18, and 5 in the vaccine group versus 10 in the placebo group related to any oncogenic HPV type).[49]

The immunogenicity of vaccinated women against HPV 16 and 18 in the PATRICIA trial was 100% at 36 months.[46] At 4.5 year follow-up, antibody titers in 99% of immunized individuals were 17-fold and 14-fold higher for HPV 16 and 18, respectively, than in individuals with natural immunity.[50] A subset of this population was followed, and at 6.4 and 9.4 years, antibody titers remained 12-fold and 10-fold higher, respectively, for both HPV types relative to natural immunity.[48,49]

The next leading oncogenic types associated with invasive cervical cancer following HPV 16 and 18 are HPV types 31, 33, 45, 52, and 58. The bivalent vaccine has demonstrated cross-protection against these non-vaccine HPV oncogenic types, with 31.5% efficacy in preventing associated CIN2 lesions.[46] In the Costa Rica study, cross protection at 4-year follow-up was demonstrated against HPV 31, 33 and 45 infection, with efficacy of 51.3% in HPV-naïve women and 45.2% in all women regardless of initial HPV infection status.[47] At 9.4-year follow-up, the bivalent vaccine continued to demonstrate efficacy against incident HPV 45 but not against other non-vaccine HPV types.[49]

Quadrivalent vaccine efficacy, immunogenicity and cross-protection

The clinical efficacy of the quadrivalent vaccine on cervical cancer precursors was evaluated in the Future II trial (Females United to Unilaterally Reduce Endo/Ectocervical Disease), which was funded by Merck, the maker of the vaccine. In this phase III, multinational, prospective, double-blind, placebo-controlled trial of more than 12,000 women aged 15 to 26 y of age, the vaccine had 98% efficacy in preventing the primary composite outcome (CIN2, CIN3, AIS, and HPV 16 and 18 infection) in women who were HPV 16 and 18 naïve. Among all women, including those with a history of HPV infection, the vaccine had an efficacy of 42% and 79% against incident infection with HPV 16 and 18, respectively. In this same population, the vaccine had efficacy of 57% and 45% in preventing HPV16 and 18 associated CIN2 and CIN3, respectively. The efficacy in CIN2+ associated with any HPV type was low at 17%.[51]

In the FUTURE I trial, which was a similarly designed, smaller study also funded by Merck, the vaccine had 100% efficacy in protecting against development of CIN2 and CIN3 lesions in women who were HPV-naïve. Among all women, including those with history of HPV infection, there was no statistically significant effect on the incidence of CIN2 or CIN3 lesions.[52]

The measured immunogenic response in vaccinated individuals to the 4 HPV types in the vaccine were generally high at greater than 96%.[52,53] At 36-month follow-up, 100% of vaccinated individuals reached 17-fold higher immunogenicity for HPV 16 relative to individuals with natural infection, while only 76% of those vaccinated reached immunogenicity for HPV 18 equivalent to individuals with natural infection. Higher antibody titers were achieved in vaccinated individuals with prevalent HPV infection, which may suggest that the vaccine serves as a "booster" in this population.[54]

The quadrivalent vaccine has demonstrated relatively limited cross-protection to the leading non-vaccine oncogenic HPV types. In the FUTUREs trials, the vaccine had efficacy of 32.5% in preventing CIN2, CIN3 and AIS related to HPV types 31, 33, 45, 52, and 58, however, this cross protection was not statistically significant in sexually active women.[55,56] An independent meta-analysis clarified that cross-protection of the quadrivalent vaccine was limited to HPV 31, however, this protection is not significant when lesions co-infected with HPV 16 or 18 are excluded.[57] While studies of the bivalent vaccine have shown that cross-protective efficacy tends to wane with time, longer-term data is not available for the quadrivalent vaccine.

Limitations of efficacy studies

While both the bivalent and quadrivalent vaccines show greater than 90% efficacy against new vaccine-type specific HPV infections in HPV-naïve individuals over the course of 3–4 y efficacy trials, it is too soon to know how this data correlates to the impact vaccination will have on cervical cancer morbidity and mortality. There is generally a long timeframe of progression from HPV infection to cervical cancer, and thus numerous intermediary indicators have been used to evaluate both vaccines, including anogenital warts (for the quadrivalent vaccine), any cervical dysplasia, high-grade cervical dysplasia (CIN2+) and HPV DNA detection. Because low-grade cervical dysplasia often spontaneously regresses, high-grade cervical dysplasia and persistent HPV DNA positivity are better indicators of likelihood of progression to cervical cancer, but how accurate these proxies are is unknown.[58] Now that the HPV vaccine is recommended, there is unlikely to be any longer term prospective follow-up data comparing vaccinated to unvaccinated women.

There is little data regarding the impact of the bivalent and quadrivalent vaccines on colposcopy referrals, and diagnostic and treatment procedures for cervical abnormalities. Data from the industry-funded bivalent vaccine study demonstrated marked reductions in colposcopy referral and need for excisional procedures, however, this was not replicated in an independent trial with 4-year follow-up.[46,59] Data projected from

the industry-funded quadrivalent vaccine study predicts a significant reduction in definitive cervical therapy, however, concrete evidence is lacking.[60]

The correlation of the serologically measured immune response to protection against HPV is unclear, particularly because natural infection does not always induce a serologically detectable immune response.[61] Both the bivalent and quadrivalent vaccines have demonstrated relatively favorable immunogenic responses, with 9.4 y and 3 y of follow-up data for the bivalent and quadrivalent vaccine, respectively, though it is difficult to compare the immunogenicity studies of the bivalent and quadrivalent vaccine because they use different assays and measurements of efficacy endpoints.[62] Furthermore, there is uncertainty as to whether the addition of subtypes to the vaccine creates immune interference with lower long-term type-specific immunity. If vaccine immunogenicity wanes with time, the impact on cervical cancer may be less than projected by the data currently available.

Similarly, data on the cross-protection of non-vaccine HPV types are encouraging, particularly for the bivalent vaccine. However, there is evidence that the immunogenic response against non-vaccine types wanes with time, and thus the impact on development of lesions associated with non-vaccine types later in life is unknown.[57]

Perhaps the most important factor highlighted by efficacy studies is the need to time vaccination prior to sexual debut to achieve maximal impact; a large discrepancy has been demonstrated in vaccine efficacy among HPV-naïve vs. exposed individuals.

Bivalent and quadrivalent vaccine clinical effectiveness

While vaccine clinical effectiveness studies do not resolve the limitations of proxy indicators of cervical cancer and uncertainty regarding the validity of extrapolation of short-term immunogenicity and cross protection data, they do account for external factors that impact the implementation of HPV vaccination in real clinical settings. National vaccination guidelines, compliance with vaccine schedules, and vaccine uptake rates have major impacts on clinical effectiveness of HPV vaccination and the resultant anticipated impact of HPV vaccination on cervical cancer morbidity and mortality.

Australia rolled out a national vaccination campaign with the quadrivalent vaccine from 2007–2009 for women aged 12–26 y of age. Vaccine coverage rates in school-based programs were between 71–79%. A population level evaluation of trends in cervical screening abnormalities before and after implementation was performed from a national database that included over 2 million screened women. The vaccination campaign correlated to a significantly reduced incidence of CIN2+ in women younger than 18 y of age (-0.38% $p = 0.003$).[63] Interestingly, the same study showed that the campaign also correlated to significantly higher rates of high-grade abnormalities in all women older than 20 years, specifically including the 21–25 age group, which was eligible for vaccination. Of note, self-reported vaccination coverage in the 18–28 y old age group was lower than school-based programs, with only 56% of women reporting receipt of all 3 doses. These results perhaps again emphasize the relevance of timing the vaccine during school age years to reach girls before the onset of sexual debut.

Another Australian study of women aged 18 to 24 y of age attending family planning clinics in 3 major urban centers showed a significant decline in HPV prevalence (any type) on specimens collected by clinicians from 59.9% to 48.0%. The prevalence of HPV 16 and 18 specifically declined dramatically from 28.7% to 6.7%, correlating to a vaccine effectiveness of 73% for HPV 16 and 18. There was no significant decline in HPV types 31, 33, 35, or 45.[64] A follow-up study with a larger group from the same cohort validated vaccination history and found a statistically significant vaccine effectiveness of 86% for HPV types 16 and 18 and 58% for 31, 33, 45 when comparing fully vaccinated to unvaccinated women.[65] Additionally, of vaccinated women, 48% reported sexual debut prior to vaccination and 18% reported sexual debut during the year of vaccination, which may lend support to the utility of catch-up vaccination programs.

The United States recommended vaccination of women aged 9 to 26 y of age with the quadrivalent vaccine in June 2006 and added the option of the bivalent vaccine in October 2009. An evaluation of HPV prevalence in patient self-swab specimens from the pre-vaccine era (2003–2006) to the post-vaccine era (2007–2010) showed that overall HPV prevalence in 14 to 19 y old females declined from 32.9% to 26.1% and HPV 16 and 18 prevalence specifically declined from 11.5% to 5.1%.[66] This effect was statistically significant despite a reported uptake rate of 62.4% for all 3 doses in this age group (though provider confirmed uptake rates for all 3 doses are much lower at $<$ 40%[67,68]). Vaccination uptake rates in women aged 20 to 24 were self-reported as 53% and rates of HPV 16 and 18 infection did not significantly change in this group from the pre- to post-vaccine eras.

Denmark initiated vaccination with the quadrivalent vaccine from 2006 to 2012. Danish national vaccination and cervical abnormality databases were linked to evaluate individual outcomes in 399,244 women, including 247,313 vaccinated women during the rollout period. A significant reduction in CIN3 lesions of 75% was seen in women in the 1993–1994 birth cohorts.[69] A smaller and non-statistically significant reduction in CIN3 was seen in older birth cohorts, likely related to prevalent HPV infection. Women in the younger birth cohorts have not reached the age for initiation of screening at the time of this study. These findings correlate to the findings of the Australian study showing the most significant impact of the vaccine on women less than 18 y of age.

The trend in reduction in HPV infection and high-grade cervical dysplasia seen in younger cohorts was corroborated by a meta-analysis of ecological studies evaluating clinical effectiveness defined by a reduction in HPV infection and CIN2/CIN3 lesions. In women younger than 20 y of age, HPV 16 and 18 prevalence decreased by 64%, with a significant inverse correlation between vaccination coverage and disease detection. HPV 31, 33, and 45 decreased significantly by 28%, but when HPV 31, 33, and 45 were grouped with HPV 52 and 58, no significant decrease in prevalence was seen. Though not significant, there was a trend of reduced HPV 16 and 18 prevalence among 20 to 24 y olds (31%).[70] The meta-analysis only identified 2 studies with CIN2 and CIN3 as endpoints, one being the

Australian ecological study cited above showing reduction in high-grade lesions in women under 18 y of age, while the other was conducted in the United States where screening has not been initiated in the cohort under 21 y of age. Still the latter did not find statistically significant reductions in the incidence of high-grade cervical dysplasia in women 20 y of age or older, which is consistent with the findings of the Australian study.[71]

Effectiveness studies of the bivalent vaccine alone have been limited, as it entered the market after the quadrivalent vaccine, and was largely incorporated into vaccination programs already utilizing the quadrivalent vaccine. However, the United Kingdom introduced HPV vaccination exclusively with the bivalent vaccine in 2008. Vaccination was targeted to 12 y old girls through school-based programs and catch-up vaccination was administered to 13–17 y olds, with coverage of 80% and 56%, respectively. HPV 16 and 18 prevalence declined among 16–18 y olds from 19.1% to 6.5% from 2008 to 2011. There was no significant reduction in other high-risk HPV type prevalence, specifically types 31, 33, and 45, to which the bivalent vaccine had suggested cross-protection in efficacy studies.[72]

There are limitations to these evaluations. The primary limitation is that the age groups in which the vaccine is expected to be most effective have not yet reached the ages with highest HPV infection rates and prevalence of high-grade cervical lesions. Additionally, cervical cancer screening protocols have shifted to initiate screening at later ages and to occur less frequently, which may affect detection of HPV prevalence and high-grade lesions. Finally, longer-term data are needed to see if these early encouraging results hold true as young vaccinated women approach the age of peak cervical dysplasia and cancer incidence.

9vHPV vaccine outcomes to date

The 9vHPV HPV vaccine (Gardasil9; Merck Sharp & Dohme Corp., Whitehouse Station, New Jersey), which targets HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 was approved by the FDA in December 2014 for use in females aged 9 to 26 y old and males aged 9 to 15 y old.[73]

The 9vHPV vaccine was evaluated in an international, randomized, double-blind, phase 2b-3 study funded by Merck. Fourteen,215 women aged 16 to 26 y were randomized to receive either the 9vHPV or the quadrivalent vaccine 3-dose series. The trial was designed to assess non-inferiority to the quadrivalent vaccine; no placebo was utilized given pre-existing data on the efficacy of the quadrivalent vaccine. In the HPV-naïve population, the 9vHPV vaccine had 96% efficacy in preventing high-grade cervical disease (CIN2, CIN3, adenocarcinoma-In Situ, and cervical cancer) associated with HPV-types 31, 33, 45, 52, 58 (0.1 versus 1.5 cases per 1000 person years in the 9vHPV vs. quadrivalent vaccine cohorts), as well as 96% efficacy in preventing persistent infections related to the same HPV-types (2.1 versus 52.4 cases per 1000 person years in the 9vHPV vs. quadrivalent vaccine cohorts). However, in analysis of all women regardless of prior HPV infection, there was no difference in cervical, vaginal or vulvar disease between the 9vHPV and quadrivalent vaccine recipients (14.0 cases per 1000 person years in both cohorts).[74]

Because the 9vHPV vaccine is newly available on the market, there is no clinical effectiveness data yet to assess its impact in general practice. Theoretically, based on the prevalence data of HPV types in invasive cervical cancer, the quadrivalent and bivalent vaccine could potentially prevent approximately 70% of invasive cervical cancer while the 9vHPV could prevent an additional 20% of invasive cervical cancer.[75,76] This projection depends on perfect administration of the vaccine in all females prior to sexual debut, perfect long-term immunogenicity and no evolution of HPV-type prevalence in cervical cancer.

Modeling has been used to estimate the impact of the bivalent, quadrivalent and 9vHPV vaccines. The bivalent and quadrivalent vaccines are estimated to reduce CIN2 and CIN3 by 62.1% and 58.6%, respectively, and to reduce squamous cell carcinoma by 70.5% and 64.8% (due to cross-protection of bivalent vaccine). The 9vHPV vaccine is estimated to further reduce the cumulative number of cases of high-grade cervical dysplasia (CIN2 and CIN3) by 9.3 and 12.5% and squamous cell carcinoma by 4.8 and 6.6%, over the quadrivalent and bivalent vaccines, respectively. For this model to hold true, the vaccine type efficacy of the 9vHPV vaccine must be greater than 80–85%, assumes vaccination prior to acquisition of HPV and life-long protection against the HPV types in the respective vaccines.[77] Time is needed to prove whether these assumptions are true and to assess the true clinical effectiveness over time of all of the available vaccines.

Safety

The bivalent, quadrivalent and 9vHPV vaccines are generally well tolerated with mild and self-limited injection site reaction being the most common adverse event. Other frequently reported events do not appear to be more common in vaccine versus control recipients, nor in HPV vaccine recipients vs. recipients of other types of vaccines. Additionally, no increased risk of new-onset autoimmune disease, venous thromboembolism, and syncope has been seen. No death related to HPV vaccination has occurred.[78–88] Though no HPV vaccine is recommended in pregnancy, no increased risk of adverse pregnancy outcomes, including spontaneous abortion, late fetal death and congenital anomalies, have been seen in pregnant women who inadvertently receive the bivalent or quadrivalent vaccine.[89] There is on-going monitoring of reports of neurologic symptoms developing after vaccination, including postural orthostatic tachycardia syndrome and complex regional pain syndrome.[90–95]

Projected impact of hpv vaccines on cervical cancer morbidity and mortality

Based on the data we have to date, a few things about HPV vaccination are clear. Regardless of the type of vaccine utilized, vaccination should be targeted to individuals prior to exposure to HPV infection. Catch-up vaccination in older age groups may also have a long-term benefit,[65,96] though there is no definitive clinical effectiveness data to support this, nor the preferential use of the 9vHPV vaccine in this cohort. No studies to date have information on cancer incidence, and thus the impact on cervical cancer morbidity and mortality is theoretical and based

on best estimates. Time and future clinical effectiveness studies are needed, particularly as young vaccinated women enter the appropriate age range to initiate screening. Large population-based studies are needed to assess cervical cancer incidence as an endpoint, with ongoing prevention and screening programs in place.

The greatest impact of HPV vaccines on cervical cancer morbidity and mortality will likely be seen with increased implementation in low- and middle-income countries, which carry 85% of the cervical cancer burden. While there is no effectiveness data regarding HPV vaccination yet available from low- and middle-income countries, because of the disproportionately high rates of cervical cancer in these countries, modeling has suggested that HPV vaccination would be cost-effective.[97] On-going research is needed in coordination with implementation of vaccination programs given the greater burden of cervical cancers related to HPV types other than HPV 16 and 18 as well as higher prevalence of immune compromising factors.[98]

The HPV vaccine will likely have a relatively lesser impact on cervical cancer morbidity and mortality in high-income countries because of the lower overall burden of cervical cancer and the existence of effective screening and treatment programs. Still, disparities do exist in access to and compliance with screening protocols in high-income countries, and the vaccine will ideally mitigate this effect over the long-term by reducing the number and regularity of visits needed to prevent cervical cancer. The greatest effect of the vaccine that we are likely to see in high-income countries is a reduction in invasive cervical procedures, though long-term clinical effectiveness data is needed to evaluate this hypothesis.

Many uncertainties remain. More time is needed to assess clinical effectiveness of all 3 vaccines, even in HPV-naïve vaccinated individuals, where imperfect adherence to dosing schedules and lack of data on long-term immunogenicity poses an unclear risk for future HPV infection and progression to cervical cancer. The real impact of the 9vHPV vaccine is theoretical at this point and long-term immunogenicity and effectiveness, particularly given the greater number of HPV types covered in the vaccine, needs to be proven.

Given the higher prevalence of non-HPV 16 and 18 related invasive cervical cancer in low- and middle-income countries, the 9vHPV vaccine is arguably needed the most in these settings, however, the cost of the vaccine has the potential to be disproportionately prohibitive in low- and middle-income countries. While GAVI has negotiated rates for the bivalent and quadrivalent vaccines, it is not clear that the same rate will be available for the 9vHPV vaccine.[99]

In October 2009, the FDA approved vaccination of males aged 9–26 for prevention of genital warts.[100] Increasing uptake of vaccination in males will ultimately reduce HPV transmission and contribute to herd immunity, particularly when there is only low to moderate uptake of vaccination in females.[101] Improved herd immunity will likely contribute to reduced morbidity and mortality from cervical cancer in the long-term.[102] The impact and cost-effectiveness of male vaccination needs ongoing assessment so that national vaccination strategies can be adapted according to the data.

National strategies, public acceptance and uptake of the HPV vaccines still pose a challenge. Denmark provided the vaccine free of charge to girls aged 12–15 as part of the national vaccination campaign and achieved greater than 85% vaccination coverage, whereas, vaccine coverage rates were only 20% among women aged 16–19 who had to pay for the vaccine.[69] Australia reported 3-dose coverage rates in school based programs of 79% for first year high school students and 71% for final year high school students, while a phone survey of Australian women aged 18–28 showed only 56% 3-dose coverage rates.[63] Similarly, Scotland achieved greater than 85% coverage of girls aged 12–17 in school-based programs, however, vaccine coverage was only 30% for 15–17 y olds not in school.[103] The United States has had less success, with only 39% of 13–17 y olds completing the 3-dose vaccine series.[66] Low- and middle-income countries with roll-out through pre-existing school and health center based vaccination programs have achieved high rates of vaccine coverage.[104,105] Rwanda has achieved the highest coverage rates of any country for a targeted age group with 93% coverage of girls in the sixth grade through school- and community-based programs, and a nationwide public sensitization campaign.[46]

Importantly, cervical cancer screening and treatment programs continue to be important, even among vaccinated individuals and cannot suffer at the cost of implementation of primary prevention programs.[18] Cervical cancers caused by HPV types not covered by available vaccines will continue to develop and prevalent HPV infection in vaccinated individuals may still lead to cervical cancer.

Conclusion

Although primary prevention of cervical cancer with HPV vaccination is exciting in theory, actual effects on cervical cancer incidence, morbidity and mortality remain to be seen. Secondary prevention with known effective screening approaches, and treatment of precancerous changes or early cancers will likely have the greatest short-term impact on cervical cancer outcomes worldwide. Simultaneous targeted patient education and creative vaccination implementation strategies should be prioritized to maximize vaccination rates.

Through combined efforts to improve screening and management of adult women, and vaccination of their children, the morbidity and mortality from cervical cancer should improve worldwide.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

References

[1] Torre L, Bray F, Siegel R, Ferlay J, Lortet-Tieulent J, Ahmedin J. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65:87-108; http://dx.doi.org/10.3322/caac.21262

[2] Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. Eleven [Internet]. Lyon, France: International Agency for Research on Cancer 2013 Available from http://globocan.iarc.fr

[3] Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) Cancer Statistics Review (1973–2012), National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2015. Accessed 6/25/2015

[4] Olusola A, Kulasignam S, Virnig B. Cervical cancer trends in the United States: A 35-year population-based analysis. J Womens Health 2012; 21(10):1031-7; http://dx.doi.org/10.1089/jwh.2011.3385

[5] Reid R, Stanhope CR, Herschman BR, Booth E, Phibbs GD, Smith JP. Genital warts and cervical cancer. I Evidence of an association between subclinical papillomavirus infection and cervical malignancy. Cancer 1982; 50(2):377-87; PMID:6282442; http://dx.doi.org/10.1002/1097-0142(19820715)50:2<377::AID-CNCR2820500236>3.0.CO;2-A

[6] Asiaf A, Ahmad S, Mohammad S, Zargar M. Review of the current knowledge on the epidemiology, pathogenesis, and prevention of huma papillomavirus infection. Eur J Can Prev 2014; 23:206-24; http://dx.doi.org/10.1097/CEJ.0b013e328364f273

[7] Nobbenhuis M, Walboomers J, Helmerhorst T, Rozendaal L, Remmink A, Risse EK, van der Linden HC, Voorhorst FJ, Kenemans P, Meijer CJ, et al. Relation of human papillomavirus status to cervical lesions and consequences for cervical-cancer screening: a prospective study. Lancet 1999; 354:20-5; PMID:10406360; http://dx.doi.org/10.1016/S0140-6736(98)12490-X

[8] Rositch A, Burke A, Viscidi R, Silver M, Chang K, Gravitt P. Contributions of recent and past sexual partnerships on incident human papillomavirus detection: Acquisition and reactivation in older women. Cancer Res 2012; 72(23):6183-90; PMID:23019223; http://dx.doi.org/10.1158/0008-5472.CAN-12-2635

[9] Gravitt P, Rositch A, Silver M, Marks M, Change K, Burke A, Viscidi RP. A cohort effect of the sexual revolution may be masking an increase in human papillomavirus detection at menopause in the United States. J Infect Dis 2013; 207:272-80; PMID:23242540; http://dx.doi.org/10.1093/infdis/jis660

[10] de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, Plummer M. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol 2012; 13:607-15; PMID:22575588; http://dx.doi.org/10.1016/S1470-2045(12)70137-7

[11] Peirson L, Fitzpatrick-Lewis D, Ciliska D, Warren R. Screening for cervical cancer: a systematic review and meta-analysis. Syst Rev 2013; 2:35; PMID:23706117; http://dx.doi.org/10.1186/2046-4053-2-35

[12] European Centre for Disease Prevention and Control. Guidance for the introduction of HPV vaccines in EU countries. 2008 Accessed 20 July 2015: http://ecdc.europa.eu/en/Documents/4940_0801_HPV_guidance.pdf

[13] Engholm G, Ferlay J, Christensen N, et al; Association of the Nordic Cancer Registries; Danish Cancer Society. NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries. Version 6.1 (25.04.2014). ancr.nu. Accessed June 25, 2015

[14] Cancer in Norway 2009. Special issue: Cancer screening in Norway (Haldorsen T, ed) Cancer Registry of Norway, Oslo, 2011

[15] Gibb R, Martens MG. The impact of liquid-based cytology in decreasing the incidence of cervical cancer. Rev Obstet Gynecol 2011; 4(Suppl 1):S2-S11; PMID:21617785

[16] World Health Organization. WHO guidance note: comprehensive cervical cancer prevention and control: a healthier future for girls and women. Geneva 2013

[17] Coleman DV, Poznansky JJ. Review of cervical smears from 76 women with invasive cervical cancer: cytological findings and medicolegal implications. Cytopath 2006; 17:127-36; http://dx.doi.org/10.1111/j.1365-2303.2006.00310.x

[18] Glick S, Clarke A, Blanchard A, Whitaker AK. Cervical cancer screening, diagnosis and treatment interventions for racial and ethnic minorities: A Systematic Review. J Gen Intern Med 2012; 27(8):1016-32; PMID:22798213; http://dx.doi.org/10.1007/s11606-012-2052-2

[19] Chase DM, Osann K, Sepina N, Wenzel L, Tewari KS. The challenge of follow-up in a low-income colposcopy clinic: characteristics associated with noncompliance in high-risk populations. J Low Genit Tract Dis 2012; 16(4):345-51; PMID:22622340; http://dx.doi.org/10.1097/LGT.0b013e318249640f

[20] Sankaranarayanan R, Anorlu R, Sangwa-Lugoma G, Denny L. Infrastructure requirements for human papillomavirus vaccination and cervical cancer screening in Sub-Saharan Africa. Vaccine 2013; 31S:F47-52; http://dx.doi.org/10.1016/j.vaccine.2012.06.066

[21] Sabatino SA, White MC, Thompson TD, Klabunde CN. Cancer screening test use – United States, 2013. MMWR Morb Mortal Wkly Repo 2015; 64(17):464-8

[22] Munoz N, Bosch F, De Sanjose S, Herrero R, Castellsague X, Shah KV, Snijders PJ, Meijer CJ. Epidemiologic classification of human papillomavirus types associated with cervical cancer. NEJM 2003; 348(6):518-27; PMID:12571259; http://dx.doi.org/10.1056/NEJMoa021641

[23] Moscicki AB, Ma Y, Wibbelsman C, Darragh TM, Powers A, Farhat S, Shiboski S. Rate of and risks for regression of CIN-2 in adolescents and young women. Obstet Gynecol 2010; 116:1373-80; PMID:21099605; http://dx.doi.org/10.1097/AOG.0b013e3181fe777f

[24] Castle PE, Schiffman M, Wheeler CM, Solomon D. Evidence for frequent regression of cervical intraepithelial neoplasia-grade 2. Obstet Gynecol 2009; 113:18; PMID:19104355; http://dx.doi.org/10.1097/AOG.0b013e31818f5008

[25] McCredie MR, Sharples KJ, Paul C, Baranyai J, Medley G, Jones RW, Skegg DC. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. Lancet Oncol 2008; 9:425-34; PMID:18407790; http://dx.doi.org/10.1016/S1470-2045(08)70103-7

[26] Wheeler C. Natural history of human papillomavirus infections, cytologic and histologic abnormalities, and cancer. Obstet Gynecol Clin N Am 2008; 35:519-36; http://dx.doi.org/10.1016/j.ogc.2008.09.006

[27] Clifford GM, Gallus S, Herrero R, Munoz N, Snijders JF, Vaccarella S, Anh PT, Ferreccio C, Hieu NT, Matos E, et al. Worldwide distribution of human papillomavirus types in cytologically normal women in the International Agency for Research on Cancer HPV prevalence surveys: a pooled analysis. Lancet 2005; 366:991-8; PMID:16168781; http://dx.doi.org/10.1016/S0140-6736(05)67069-9

[28] de Sanjose S, Diaz M, Castellsague X, Clifford G, Bruni L, Munoz N, Bosch FX. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. Lancet Infect Dis 2007; 7:453-9; PMID:17597569; http://dx.doi.org/10.1016/S1473-3099(07)70158-5

[29] Dunne EF, Unger ER, Sternberg M, McQuilan G, Swan DC, Patel SS, Markowitz LE. Prevalence of HPV infection among females in the United States. JAMA 2007; 297(8):813-9; PMID:17327523; http://dx.doi.org/10.1001/jama.297.8.813

[30] Banura C, Franceschi S, van Doorn L, Arslan A, Wabwire-Mangen F, Mbidde EK, Quint W, Weiderpass E. Infection with human papillomavirus and HIV among young women in Kampala, Uganda. J Infect Dis 2008; 197:555-62; http://dx.doi.org/10.1086/526792

[31] Oakeshott P, Aghaizu A, Reid F, Howell-Jones R, Hay PE, Sadiq ST, Lacey CJ, Beddows S, Soldan K. Frequency and risk factors for prevalent, incident and persistent genital carcinomgenic human papillomavirus infection in sexually active women: community based cohort study. BMJ 2012; 344:e4168; PMID:22730542; http://dx.doi.org/10.1136/bmj.e4168

[32] Ho G, Bierman R, Beardsley L, Chang C, Burk R. Natural history of cervicovaginal papillomavirus infection in young women. NEJM 1998; 338(7):423-8; PMID:9459645; http://dx.doi.org/10.1056/NEJM199802123380703

[33] Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, Snijders PJ, Peto J, Meijer CJ, Muñoz N. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 1999; 189:12-19; PMID:10451482; http://dx.doi.org/10.1002/(SICI)1096-9896(199909)189:1<12::AID-PATH431>3.0.CO;2-F

[34] Wallin K, Wiklund F, Angstrom T, Bergman F, Stendahl U, Wadell G, Hallmans G, Dillner J. Type-specific persistence of human papillomavirus DNA before the development of invasive cervical cancer. NEJM 1999; 341(22):1633-8; PMID:10572150; http://dx.doi.org/10.1056/NEJM199911253412201

[35] Clifford GM, Smith JS, Plummer M, Munoz N, Franceschi S. Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. Brit J Cancer 2003; 88:63-73; PMID:12556961; http://dx.doi.org/10.1038/sj.bjc.6600688

[36] Smith J, Lindsay L, Hoots B, Keys J, Franceschi S, Winer R, Clifford GM. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: A meta-analysis update. Int J Cancer 2007; 121:621-32; PMID:17405118; http://dx.doi.org/10.1002/ijc.22527

[37] de Sanjose S, Quint WG, Alemany L, Geraets DT, Klaustermeier JE, Lloveras B, Tous S, Felix A, Bravo LE, Shin HR, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol 2010; 11:1048-56; PMID:20952254; http://dx.doi.org/10.1016/S1470-2045(10)70230-8

[38] Harro CD, Pang YY, Roden RB, Hildesheim A, Wang Z, Reynolds MJ, Mast TC, Robinson R, Murphy BR, Karron RA, et al. Safety and immunogenicity trial in adult volunteers of a human papillomavirus 16 L1 virus-like particle vaccine. J Natl Cancer Inst 2001; 93(4):284; PMID:11181775; http://dx.doi.org/10.1093/jnci/93.4.284

[39] US. Food and Drug Administration. Approval letter – human papillomavirus quadrivalent (types 6, 11, 16, 18) vaccine, recombinant. Eight June 2006. Accessed on 20 July 2015 at: http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm111283.htm

[40] US. Food and Drug Administration News Release. FDA approves new vaccine for prevention of cervical cancer. Sixteen October 2009. Accessed on 20 July 2015 at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm187048.htm

[41] European Centre for Disease Prevention and Control. HPV vaccination in EU countries: review of new evidence. Twenty-three Apr 2014. Accessed 14 August 2015 at: http://ecdc.europa.eu/en/activities/sciadvice/_layouts/forms/Review_DispForm.aspx?List=a3216f4c-f040-4f51-9f77-a96046dbfd72&ID=758

[42] Herrero R, Gonzalez P, Markowitz LET. Present status of human papillomavirus vaccine development and implementation. Lancet Oncol 2015; 16(5):e206-16; PMID:25943065; http://dx.doi.org/10.1016/S1470-2045(14)70481-4

[43] Markowitz L, Tsu V, Deeks S, Cubie H, Wang S, Vicari A, Brotherton JM. Human papillomavirus vaccine introduction – the first five years. Vaccine 2012; 30S:F139-148; http://dx.doi.org/10.1016/j.vaccine.2012.05.039

[44] LaMontagne DS, Barge S, Le NT, Mugisha E, Penny ME, Gandhi S, Janmohamed A, Kumakech E, Mosqueira NR, Nguyen NQ, et al. Human papillomavirus vaccine delivery strategies that achieved high coverage in low- and middle-income countries. Bull World Health Organ 2011; 89:821B-30B; http://dx.doi.org/10.2471/BLT.11.089862

[45] Binagwaho A, Wagner CM, Gatera M, Karema C, Nutt CT, Ngabo F. Achieving high coverage in Rwanda's national human papillomavirus vaccination programme. Bull World Health Organ 2012; 90(8):623-8; PMID:22893746; http://dx.doi.org/10.2471/BLT.11.097253

[46] Paavonen J, Naud P, Salmeron J, Wheeler CM, Chow SN, Apter D, Kitchener H, Castellsague X, Teixeira JC, Skinner SR, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomized study in young women. Lancet 2009; 374:301-14; PMID:19586656; http://dx.doi.org/10.1016/S0140-6736(09)61248-4

[47] Kreimer A, Gonzalez P, Katki H, Porras C, Schiffman M, Rodriguez A, Solomon D, Jiménez S, Schiller JT, Lowy DR, et al. Efficacy of a bivalent HPV 16/18 vaccine against anal HPV 16/18 infection among young women: a nested analysis within the Costa Rica Vaccine Trial. Lancet Oncol 2011; 12:862-70; http://dx.doi.org/10.1016/S1470-2045(11)70213-3

[48] The GlaxoSmithKline Vaccine HPV-007 Study Group. Sustained efficacy and immunogenicity of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine: analysis of a randomized placebo-controlled trial up to 6.4 years. Lancet 2009; 374:1975-85; PMID:19962185; http://dx.doi.org/10.1016/S0140-6736(09)61567-1

[49] Naud P, Roteli-Martins CM, DeCarvalho NS, Teixeira JC, de Borba PC, Sanchez N, Zahaf T, Catteau G, Geeraerts B, Descamps D. Sustained efficacy, immunogenicity, and safety of the HPV-16/18 AS04-adjuvanted vaccine. Hum Vac Immunother 2014; 10:2147-62; http://dx.doi.org/10.4161/hv.29532

[50] Harper DM, Franco EL, Wheeler CM, Moscicki AB, Romanowski B, Roteli-Martins CM, Jenkins D, Schuind A, Costa Clemens SA, Dubin G. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomized control trial. Lancet 2006; 367:1247-55; PMID:16631880; http://dx.doi.org/10.1016/S0140-6736(06)68439-0

[51] Villa L, Perez G, Kjaer S, Paavonen J, Lehtinen M, Munoz N, et al. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. NEJM 2007; 356(19):1915-27; PMID:17494925; http://dx.doi.org/10.1056/NEJMoa061741

[52] Garland S, Hernandez-Avila M, Wheeler C, Perez G, Harper D, Leodolter S, Tang GW, Ferris DG, Steben M, Bryan J, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. NEJM 2007; 356(19):1928-43; PMID:17494926; http://dx.doi.org/10.1056/NEJMoa061760

[53] Block S, Nolan T, Sattler C, Barr E, Giacoletti KE, Marchant CD. Comparison of the immunogenicity and reactogeniity of a prophylactic quadrivalent human papillomavirus (types 6,11,16, and 18) L1 virus-like particle vaccine in male and female adolescents and young adult women. Pediatrics 2006; 118:2135-45; PMID:17079588; http://dx.doi.org/10.1542/peds.2006-0461

[54] Villa L, Ault K, Giuliano A, Cost R, Petta C, Andrade R, Brown DR, Ferenczy A, Harper DM, Koutsky LA, et al. Immunologic responses following administration of a vaccine targeting human papillomavirus Types 6, 11, 16, 18. Vaccine 2006; 24:5571-83; PMID:16753240; http://dx.doi.org/10.1016/j.vaccine.2006.04.068

[55] Brown D, Kjaer SKSigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, Perez G, Koutsky LA, Tay EH, Garcia P, et al. The impact of quadrivalent human papillomavirus (HPV; Types 6,11,16, and 18) :L1 virus-like particle vaccine on infection and disease due to oncogenc nonvaccine HPV types in generally HPV-naïve women aged 16-26 years. J Infect Dis 2009; 199:926-35; PMID:19236279; http://dx.doi.org/10.1086/597307

[56] Wheeler CM, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Perez G, Brown DR, Koutsky LA, Tay EH, García P, et al. The impact of quadrivalent human papillomavirus (HPV; Types 6,11,16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in sexually active women aged 16-26 years. J Infect Dis 2009; 199:936-44; PMID:19236277; http://dx.doi.org/10.1086/597309

[57] Malagon T, Drolet M, Boily MC, Franco EL, Jit M, Brisson J, Brisson M. Cross-protective efficacy of two human papillomavirus vaccines: as systematic review and meta-analysis. Lancet Infect Dis 2012; 12:781-9; PMID:22920953; http://dx.doi.org/10.1016/S1473-3099(12)70187-1

[58] Lowry D, Herrero R, Hildesheim A. Primary endpoints for future prophylactic human papillomavirus vaccine trials: towards infection and immunobridging. Lancet Oncol 2015; 16:e226-33; PMID:25943067; http://dx.doi.org/10.1016/S1470-2045(15)70075-6

[59] Rodríguez AC, Solomon D, Herrero R, Hildesheim A, González P, Wacholder S, Porras C, Jiménez S, Schiffman M; CVT Group. Impact of human papillomavirus vaccination on cervical cytology screening, colposcopy, and treatment. Am J Epidemiol 2013; 178(5):752-60; http://dx.doi.org/10.1093/aje/kwt047

[60] Munoz N, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, Perez G, Brown DR, Koutsky LA, Tay EH, et al. Impact of human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV-associated genital diseases in young women. J Natl Cancer Inst 2010; 102(5):325-39; PMID:20139221; http://dx.doi.org/10.1093/jnci/djp534

[61] Markowitz LE, Dunne E, Saraiya M, Chesson HW, Curtis CR, Gee J, Bocchini JA Jr, Unger ER. Human papillomavirus vaccination:

Recommendations of the advisory committee on immunization practices (ACIP). MMWR Morb Mortal Wkly Repo 2014; 63 (RR05):1-30

[62] Einstein M, Baron M, Levin MJ, Chatterjee A, Edwards RP, Zepp F, Carletti I, Dessy FJ, Trofa AF, Schuind A, et al. Comparison of the immunogenicity and safety of Cervarix and Gardasil human papillomavirus (HPV) cervical cancer vaccines in healthy women aged 18-45 years. Human Vaccines 2009; 5(10):705-19; PMID:19684472; http://dx.doi.org/10.4161/hv.5.10.9518

[63] Brotherton J, Fridman M, May C, Chappell G, Saville AM, Gertig D. Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. Lancet 2011; 377:2085-92; PMID:21684381; http://dx.doi.org/10.1016/S0140-6736(11)60551-5

[64] Tabrizi SN, Brotherton JM, Kaldor JM, Skinner SR, Cummins E, Liu B, Bateson D, McNamee K, Garefalakis M, Garland SM. Fall in human papillomavirus prevalence following a national vaccination program. J Infect Dis 2012; 206:1645-51; PMID:23087430; http://dx.doi.org/10.1093/infdis/jis590

[65] Tabrizi S, Brotherton J, Kaldor J, Skinner SR, Liu B, Bateson D, McNamee K, Garefalakis M, Phillips S, Cummins E, et al. Assessment of herd immunity and cross-protection after a human papillomavirus vaccination programme in Australia: a repeat cross-sectional study. Lancet Infect Dis 2014; 14(10):958-66; PMID:25107680; http://dx.doi.org/10.1016/S1473-3099(14)70841-2

[66] Markowitz LE, Hariri S, Lin C, Dunne EF, Steinau M, McQuillan G, Unger ER. Reduction in human papillomavirus (HPV) prevalence among young women following HPV vaccine introduction in the United States, National Health and Nutrition Examination Surveys, 2003-2010. J Infect Dis 2013; 208:385-93; PMID:23785124; http://dx.doi.org/10.1093/infdis/jit192

[67] Stokley S, Jeyarajah J, Yankey D, Cano M, Gee J, Roark J, Curtis RC, Markowitz L. Human papillomavirus vaccination coverage among adolescents, 2007-2013, and postlicensure vaccine safety monitoring, 2006-2014 – United States. MMWR Morb Mortal Wkly Repo 2014; 63(29):620-4

[68] Reagan-Steiner S, Yankey D, Jeyarajah J, Elam-Evans L, Singleton J, Curtis CR, MacNeil J, Markowitz LE, Stokley S. National, regional, state and selected local area vaccination coverage among adolescents aged 13-17 years – United States 2014. MMWR Morb Mortal Wkly Repo 2015; 64(29):784-92; http://dx.doi.org/10.15585/mmwr.mm6429a3

[69] Baldur-Felskov B, Dehlendorff C, Munk C, Kjaer S. Early impact of human papillomavirus vaccination on cervical neoplasia – nationwide follow-up of young Danish women. J Natl Cancer Inst 2014; 106(3):djt460; PMID:24552678; http://dx.doi.org/10.1093/jnci/djt460

[70] Drolet M, Benard E, Boily MC, Ali H, Baandrup L, Bauer H, Beddows S, Brisson J, Brotherton JM, Cummings T, et al. Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis. Lancet Infect Dis 2015; 15:565-80; PMID:25744474; http://dx.doi.org/10.1016/S1473-3099(14)71073-4

[71] Niccolai LM, Julian PJ, Meek JI, McBride V, Hadler JL, Sosa LE. Declining rates of high-grade cervical lesions in young women in Connecticut, 2008-2011. Cancer Epidemiol Biomarkers Prev 2013; 22:1446-50; PMID:23704476; http://dx.doi.org/10.1158/1055-9965.EPI-13-0272

[72] Mesher D, Soldan K, Howell-Jones R, Panwar K, Manyenga P, Jit M, Beddows S, Gill ON. Reduction in HPV 16/18 prevalence in sexually active young women following the introduction of HPV immunization in England. Vaccine 2014; 32:26-32; http://dx.doi.org/10.1016/j.vaccine.2013.10.085

[73] US. Food and Drug Administration News Release. FDA approves Gardasil 9 for prevention of certain cancers caused by five additional types of HPV. Ten December 2014. Accessed on 1 July 2015 at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm426485.htm

[74] Joura EA, Giuliano AR, Iversen OE, Bouchard C, Mao C, Mehlsen J, Moreira ED Jr, Ngan Y, Petersen LK, Lazcano-Ponce E, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med 2015; 372(8):711-23; PMID:25693011; http://dx.doi.org/10.1056/NEJMoa1405044

[75] Riethmuller D, Jacquard AC, St Guily J, Aubin F, Carcopino X, Pradat P, Dahlab A, Prétet JL. Potential impact of a nonavalent HPV vaccine on the occurrence of HPV-related diseases in France. BMC Public Health 2015; 15:453-59; PMID:25934423; http://dx.doi.org/10.1186/s12889-015-1779-1

[76] Hariri S, Unger ER, Schafer S, Niccolai LM, Park IU, Block KC, Bennett NM, Steinau M, Johnson ML, Markowitz LE. HPV type attribution in high-grade cervical lesions: assessing the potential benefits of vaccines in a population-based evaluation in the United States. Cancer Epidemiol Biomarkers Prev 2015; 24(2):393-9; PMID:25416715; http://dx.doi.org/10.1158/1055-9965.EPI-14-0649

[77] Van de Velde N, Coily MC, Drolet M, Franco E, Mayrand MH, Kliewer EV, Coutlée F, Laprise JF, Malagón T, Brisson M. Population-level impact of the bivalent, quadrivalent, and nonavalent human papillomavirus vaccines: a model-based analysis. J Natl Cancer Inst 2012; 104(22):1712-23; PMID:23104323; http://dx.doi.org/10.1093/jnci/djs395

[78] Food and Drug Administration. Product approval-prescribing information [Package insert]. Gardasil [human papillomavirus quadrivalent (types 6, 11, 16, and 18) vaccine, recombinant], Merck & Co, Inc. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2014. Available at http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM111263.pdf

[79] Food and Drug Administration. Product approval-prescribing information [Package insert]. Cervarix [human papillomavirus bivalent (types 16, 18) vaccine, recombinant], Glaxo Smith Kline. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2014. Available at http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM186981.pdf

[80] Food and Drug Administration. Product approval-prescribing information [Package insert]. Gardasil9 [human papillomavirus 9-valent vaccine, recombinant], Merck & Co, Inc. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2014. Available at http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf

[81] Descamps D, Hardt K, Spiessens B, Izurieta P, Verstraeten T, Breuer T, Dubin G. Safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine for cervical cancer prevention: a pooled analysis of 11 clinical trials. Hum Vaccin 2009; 5:332-40; PMID:19221517; http://dx.doi.org/10.4161/hv.5.5.7211

[82] Verstraeten T, Descamps D, David MP, Zahaf T, Hardt K, Izurieta P, Dubin G, Breuer T. Analysis of adverse events of potential autoimmune aetiology in a large integrated safety database of AS04 adjuvanted vaccines. Vaccine 2008; 26:6630-8; PMID:18845199; http://dx.doi.org/10.1016/j.vaccine.2008.09.049

[83] Slade B, Leidel L, Vellozzi C, Woo EJ, Hua W, Sutherland A, Izurieta HS, Ball R, Miller N, Braun MM, et al. Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. JAMA 2009; 302(7):750-57; PMID:19690307; http://dx.doi.org/10.1001/jama.2009.1201

[84] Gee J, Naleway A, Shui I, Baggs J, Yin R, Li R, Kulldorff M, Lewis E, Fireman B, Daley MF, et al. Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink. Vaccine 2011; 29:8279-84; PMID:21907257; http://dx.doi.org/10.1016/j.vaccine.2011.08.106

[85] Chao C, Klein NP, Velicer CM, Sy LS, Slezak JM, Takhar H, Ackerson B, Cheetham TC, Hansen J, Deosaransingh K, et al. Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine. J Intern Med 2012; 271:193-203; PMID:21973261; http://dx.doi.org/10.1111/j.1365-2796.2011.02467.x

[86] Arnheim-Dahlstrom L, Pasternak B, Svanstrom H, Sparen P, Hviid A. Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent

human papillomavirus vaccine in Denmark and Sweden: cohort study. BMJ 2013; 347:f5906; PMID:24108159; http://dx.doi.org/10.1136/bmj.f5906

[87] Grimaldi-Bensouda L, Guillemot D, Godeau B, Bénichou J, Lebrun-Frenay C, Papeix C, Labauge P, Berquin P, Penfornis A, Benhamou PY, et al. Autoimmune disorders and quadrivalent human papillomavirus vaccination of young female subjects. J Intern Med 2014; 275:398-408; PMID:24206418; http://dx.doi.org/10.1111/joim.12155

[88] Macartney KK, Chiu C, Georgousakis M, Brotherton JM. Safety of human papillomavirus vaccines: a review. Drug Saf 2013; 36:393-412; PMID:23637071; http://dx.doi.org/10.1007/s40264-013-0039-5

[89] Goss MA, Lievano F, Seminack MM, Dana A. No adverse signals observed after exposure to human papillomavirus type 6/11/16/18 vaccine during pregnancy: 6-year pregnancy registry data. Obstet Gynecol 2014; 123(Suppl 1):93S; http://dx.doi.org/10.1097/01.AOG.0000447430.00051.ba

[90] Buttery JP, Madin S, Crawford NW, Elia S, La Vincente S, Hanieh S, Smith L, Bolam B. Mass psychogenic response to human 23 papillomavirus vaccination. Med J Aust 2008; 189:261-2; PMID:18759721

[91] Martinez-Lavin M. Hypothesis: Human papillomavirus vaccination syndrome – small fiber neuropathy and dysautonomia could be its underlying pathogenesis. Clin Rheumatol 2015; 34:1165-9; PMID:25990003; http://dx.doi.org/10.1007/s10067-015-2969-z

[92] Blitshteyn S. Postural tachycardia syndrome following human papillomavirus vaccination. Eur J Neurol 2014; 21:135-9; PMID:24102827; http://dx.doi.org/10.1111/ene.12272

[93] Kinoshita T, Abe RT, Hineno A, Tsunekawa K, Nakane S, Ikeda S. Peripheral sympathetic nerve dysfunction in adolescent Japanese girls following immunization with the human papilloma- virus vaccine. Intern Med 2014; 53:2185-200; PMID:25274229; http://dx.doi.org/10.2169/internalmedicine.53.3133

[94] Brinth L, Theibel AC, Pors K, Mehlsen J. Suspected side effects to the quadrivalent human papilloma vaccine. Dan Med J, 2015; 62:A5064

[95] World Health Organization. Weekly Epidemiological Record. 2013; 88:301-12. Available at http://www.who.int/wer/2013/wer8829.pdf?ua=1; PMID:23909011

[96] Apter D, Wheeler C, Paavonen J, Castellsague X, Garland S, Skinner R, Naud P, Salmerón J, Chow SN, Kitchener HC, et al. Efficacy of human papillomavirus 16 and 18 (HPV-16/18) AS04-adjuvanted vaccine against cervical infection and precancer in young women: Final event-driven analysis of the randomized, double-blind PATRICIA trial. Clin Vaccine IMmunol 2015; 22(4):361-73; PMID:25651922; http://dx.doi.org/10.1128/CVI.00591-14

[97] Jit M, Brisson M, Portnoy A, Hutubessy R. Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study. Lancet Glob Health 2014; 2:e406-14; PMID:25103394; http://dx.doi.org/10.1016/S2214-109X(14)70237-2

[98] Nakalembe M, Mirembe F, Banura C. Vaccines against human papillomavirus in low and middle income countries: a review of safety, immunogenicity and efficacy. Infect Agents Can 2015; 10:17; http://dx.doi.org/10.1186/s13027-015-0012-2

[99] Gavi The Vaccine Alliance. Factsheet on human papillomavirus. February 2014. Accessed on 21 July 2015 at: http://www.gavi.org/support/nvs/human-papillomavirus-vaccine-support/

[100] US. Food and Drug Administration. Approval letter – Gardasil. Sixteen October 2009. Accessed on 20 July 2015 at: http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm186991.htm

[101] Lehtinen M, Dillner J. Clinical trials of human papillomavirus vaccines and beyond. Nat Rev Clin Oncol 2013; 10:400-10; PMID:23736648; http://dx.doi.org/10.1038/nrclinonc.2013.84

[102] Crosignani P, De Stefani A, Fara G, Isidori A, Lenzi A, Liverani CA, Lombardi A, Mennini FS, Palu' G, Pecorelli S, et al. Towards the eradication of HPV infection through universal specific vaccination. BMC Public Health 2013; 13:642-52; PMID:23845195; http://dx.doi.org/10.1186/1471-2458-13-642

[103] Sinka K, Kavanagh K, Gordon R, Love J, Potts A, Donaghy M, Robertson C. Achieving high and equitable coverage of adolescent HPV vaccine in Scotland. J Epidemiol Community Health 2014; 68(1):57-63; PMID:23986492; http://dx.doi.org/10.1136/jech-2013-202620

[104] Erickson B, Landers E, Huh W. Update on vaccination clinical trials for HPV-related disease. Clin Therap 2014; 36(1):8-16; http://dx.doi.org/10.1016/j.clinthera.2013.11.003

[105] Jemal A, Simard EP, Dorell C, Noone AM, Markowitz LE, Kohler B, Eheman C, Saraiya M, Bandi P, Saslow D, et al. Annual Report to the Nation on the Status of Cancer, 1975-2009, featuring the burden and trends in human papillomavirus (HPV)-associated cancers and HPV vaccination coverage levels. J Natl Cancer Inst 2013; 105(3):175; PMID:23297039; http://dx.doi.org/10.1093/jnci/djs491