HHS Public Access

Author manuscript

Prev Med. Author manuscript; available in PMC 2022 March 04.

Published in final edited form as:

Prev Med. 2021 March ; 144: 106363. doi:10.1016/j.ypmed.2020.106363.

Monitoring HPV vaccine impact on cervical disease: Status and future directions for the era of cervical cancer elimination

Carlos R. Oliveira[a], **Linda M. Niccolai**[b,*]

[a]Yale School of Medicine, Department of Pediatrics, USA

[b]Yale School of Public Health, Department of Epidemiology of Microbial Diseases, USA

Abstract

Post-licensure monitoring of the impact of HPV vaccines is critical to track the progress being made toward cervical cancer elimination and to identify areas where further progress can accelerate the achievement of this important public health goal. Over the past decade, a large body of evidence has revealed convincing benefits of HPV vaccination in preventing cervical infections and precancers at the individual-level (i.e., direct effectiveness) as well as in reducing the population-level burden of disease (i.e., overall effectiveness). At this time, effectiveness of the vaccines on preventing cervical cancer is just beginning to emerge given that there is a prolonged latency period for invasive disease. As we enter the era of cervical cancer elimination, these early and promising results may be expected in other countries in the near future. Thus, monitoring the direct and overall effectiveness for cervical cancer is an urgent research priority. In this article, we summarize what is known about the effectiveness of HPV vaccines on precancerous outcomes, and we highlight considerations for continuing these important public health activities going forward to monitor progress toward cervical cancer elimination.

Keywords

Human papillomavirus; Vaccine; Vaccination; Effectiveness; Monitoring

1. Introduction

Vaccines against human papillomavirus (HPV) were first introduced in 2006, and three vaccines have been available for the prevention of HPV infections and HPV-associated diseases. All vaccines prevent infections with HPV types 16 and 18 that are associated with 70% of cervical cancers. The bivalent vaccine (2vHPV) provides substantial cross-protection against non-vaccine types HPV 31, 33, and 45 (Kavanaugh et al., 2017). The quadrivalent vaccine (4vHPV) includes additional protection against HPV types 6 and 11 that cause

*Corresponding author at: Yale School of Public Health, 60 College Street, New Haven, CT 06520, USA. Linda.niccolai@yale.edu (L.M. Niccolai).

Credit author statement

Carlos Oliveira: Conceptualization, Writing – Original draft. Linda Niccolai: Conceptualization, Writing – review and editing, Literature reviews.

Declaration of Competing Interest

Linda Niccolai has served as a Scientific Advisor for Merck.

>90% of anogenital warts. The newest vaccine, 9vHPV, was introduced in 2015 and prevents infection with five additional high-risk types (HPV 31, 33, 45, 52, 58) associated with an additional 15% of cervical cancers. By the end of 2019, the World Health Organization (WHO) reported that over 100 countries had introduced HPV vaccination in their national programs (World Health Organization, n.d.-a).

Evaluating the clinical and public health benefits of vaccination programs requires rigorous pre-licensure studies to measure vaccine efficacy and post-licensure studies to measure vaccine effectiveness. A longstanding framework for measuring these benefits (Halloran et al., 1997) and related writings by others (Weinberg and Szilagyi, 2010; Clemens et al., 1996) provides a useful approach for HPV vaccines and is summarized in Table 1. Briefly, vaccine efficacy measures the direct protection to individuals conferred by a full course of vaccination in the idealized conditions of randomized controlled trials that are typically conducted in highly restricted populations. This efficacy is considered to reflect an intrinsic property of the vaccine (i.e., biologic efficacy). Prelicensure placebo-controlled clinical trials demonstrated a very high efficacy (>95%) of all HPV vaccines against vaccine-type cervical HPV infections and precancers (Arbyn and Xu, 2018). This near-perfect efficacy indicates the maximum potential benefit of HPV vaccines and signals the tremendous potential that could be achieved in real-world settings.

In contrast to efficacy, vaccine effectiveness is measured in post-licensure monitoring studies that often utilize real-world data and observational (not randomized) study designs. These studies can estimate both direct and overall effectiveness. Direct effectiveness reflects the protective benefits at the individual-level, and it measures the proportion of infection or disease that is prevented among vaccinated individuals in real-world clinic settings. This is estimated by comparing the frequency of vaccine-associated outcomes in vaccinated and unvaccinated individuals. Overall effectiveness, on the other hand, measures the population-level benefit of vaccines by accounting for both direct effects as well as indirect (i.e., herd) effects. Indirect effects refer to the benefit that unvaccinated individuals experience because of lower transmission in populations due to some proportion of the population being vaccinated. This is influenced not only by efficacy and direct effectiveness, but also by vaccination coverage in the population and mixing patterns between vaccinated and unvaccinated individuals.

Unfortunately, the benefit of vaccines as used in real-world settings (i.e., effectiveness) does not always equate to that achieved in controlled prelicensure studies (i.e., efficacy). Thus, post-licensure monitoring is critical to identify reasons for the differences between the potential and achieved benefits. The lower observed benefits of vaccines when used in clinical practice and population-based settings may be due to several factors (Halloran et al., 1997; Weinberg and Szilagyi, 2010; Clemens et al., 1996). First, clinical trial participants must meet stringent eligibility criteria and need to be willing to participate in these randomized studies. Thus, their characteristics do not always reflect the general population that is targeted for vaccination post-licensure. For example, pre-licensure HPV vaccine trials have largely restricted enrollment to healthy individuals which is a relatively narrow and limited subgroup of the population. The immunization programs for most countries, however, target a far more heterogeneous group of people, many of whom may

have underlying health conditions or other differences that can significantly influence the protective effect of the vaccine. Second, vaccine administration and storage in real-world settings is often far from ideal. For example, age at administration and the number of doses received frequently deviates from recommendations. Third, the duration of protection in pre-licensure trials can only be assessed for the duration of the trials and cannot measure the possibility of waning immunity over longer periods of time. These factors, among others, may all contribute to the lower post-licensure benefits of vaccines. Because these influences cannot be predicted before a vaccine has been introduced in an immunization program, post-licensure monitoring is critical to identify these gaps.

As cervical cancer elimination has been identified as a global public health priority (World Health Organization, n.d.-b), monitoring HPV vaccine impact will continue to be critical to determine if further improvements in national immunization strategies are needed to achieve this important public health goal around the world. In this manuscript, we highlight key findings about what is currently known regarding the effectiveness of HPV vaccines against cervical infections and precancerous disease. Based on this body of literature, we discuss considerations for monitoring effectiveness on cervical cancer going forward. The current literature is nearly exclusively from high-income countries (HIC), and implications for low- and middle- income countries (LMIC) are discussed. It is not the goal of this manuscript to review all of the evidence in a systematic way as that has recently been done by others (Drolet et al., 2019). Rather, we discuss how this work can inform monitoring the effectiveness of HPV vaccines for prevention of cervical cancer and provide specific recommendations. Furthermore, there are also important bodies of work on other outcomes (e.g., anogenital warts and outcomes in males) and vaccine safety considerations that are both beyond the scope of this manuscript.

2. Direct effectiveness

The current evidence about the direct effect of HPV vaccines on preventing cervical infections and precancerous cervical disease is robust. A systematic review that surveyed the literature ten years after the 4vHPV vaccine had been introduced (through February 2016) identified16 peer-reviewed studies from high-income countries on this topic (Garland et al., 2016). A descriptive review of this research revealed effectiveness estimates for preventing vaccine-type cervical infections ranging from 36%–89% based on the number of doses received and age at the time of immunization. Effectiveness against high-grade cervical lesions was demonstrated to be 12%–84%. Similar findings about effectiveness have also been observed for 2vHPV. For example, in Spain, the effectiveness of 2vHPV against HPV 16/18 infections was estimated to be 94% among women ages 18–26 (Purrinos-Hermida et al., 2018) and in England, an effectiveness of 82% was observed among women vaccinated before age 15 (Mesher et al., 2018). As expected, effectiveness has consistently been demonstrated to be higher for younger birth cohorts, given the greater likelihood of vaccination at younger ages and before natural exposure.

While these findings on the direct effectiveness of HPV vaccines against cervical outcomes are very encouraging, the reported studies did have some limitations. For example, studies that rely on disease registries may be disadvantaged by a lack a depth of information,

for example, data about important confounders. To address this limitation, we have been conducting a population-based case-control study to estimate HPV vaccine effectiveness in a diverse US population that collects data to control for numerous potential confounding such as utilization of health care, sexual behaviors, and underlying health conditions. Preliminary results from this ongoing study indicate that the adjusted vaccine effectiveness of at least one dose is 43%; when the first dose was given at ≤18 years of age, the vaccine effectiveness is 77% (Oliveira et al., 2020). Studies such as this can provide greater clarity on vaccine effectiveness that is unconfounded by other factors, but it is important to note that this may not be the only goal of post-licensure monitoring studies. In some settings, it may also be important to understand the reasons for varying effectiveness levels by directly examining potential reasons, for example, through effect modification analyses. Ecological analyses that examine patterns in other STI, including non-vaccine HPV infections, can further elucidate this important consideration.

The consistency of the estimates of direct effectiveness across a large body of research is encouraging. At this same time, however, these estimates do fall below the efficacy demonstrated in pre-licensure clinical trials, suggesting that an efficacy-effectiveness gap does exist and that much work still needs to be done to realize the cancer elimination goals. Two important considerations for the gap are age at vaccination and number of doses received. Because current HPV vaccines are prophylactic and not therapeutic, administration before natural exposure is critical for effectiveness; thus age at administration is likely a key driver of effectiveness and this has been empirically demonstrated (Oliveira et al., 2020; Tabrizi et al., 2014; Silverberg et al., 2018; Herweijer et al., 2016). Regarding the number of doses, the greatest effectiveness has been shown for 3 doses but there is also evidence for substantial effectiveness of 1 and/or 2 doses that is often not significantly different from 3 doses (Markowitz et al., 2018; Johnson Jones et al., 2020).

3. Overall effectiveness

Numerous studies have also highlighted the success of HPV vaccines in reducing the burden of cervical infections and precancerous disease at the population-level (i.e., overall effectiveness). A recent systematic review and meta-analysis summarized these data using 36 published reports from 14 high-income countries (published though 2018) that included up to 9 years of post-vaccination follow-up (Drolet et al., 2019). Meta-analyses reported the following declines in HPV 16/18 infections: 83% among females aged 13–19 years, 66% among females 20–24 years, and 37% among females 25–29 years. Declines were comparable in studies that examined 4vHPV (11 studies) and 2vHPV (3 studies). Declines in precancerous lesions among screened women were as follows: 51% among females 15–19 years and 31% among 20–24 years. For both HPV infections and cervical disease, declines were greater in countries that had higher HPV vaccination coverage. The authors concluded that this body of evidence provides compelling evidence of the substantial population-level effectiveness of HPV vaccines.

An advantage of studies that measure overall effectiveness is their ability to capture herd effects, or the benefit that unvaccinated individuals receive from the lowered incidence in the entire population as a consequence of vaccinated individuals. As previously noted, this

is a function of both direct effectiveness as well as population-level vaccine coverage. This is most evident in countries that had female-only vaccination programs yet still observed significant declines in the trends of anogenital warts among males. For example, within five years of implementing a national vaccination program for females only, young heterosexual men in Australia experienced significant declines in the rates of anogenital warts of up to 80% (Ali et al., 2013). There is also some evidence for herd effects among females. In a clinic-based study in the US, declines in vaccine-type HPV infections were observed within four years of a national vaccination program among unvaccinated females of up to 30% (Kahn et al., 2012). Additional evidence from population-based surveillance data also supports herd effects in younger women. Approximately 50% of all incident high-grade cervical lesions are attributable to one of the HPV types included in the quadrivalent HPV vaccine (Smith et al., 2007). Thus, the 70% declines in precancerous cervical lesions observed among women <21 years of age in the US likely reflects, in part, the effects of herd immunity as it exceeds the expected reduction based on the proportion of lesions that are attributed to vaccine types (50%) (Niccolai et al., 2017). It is also likely due to the cross-protective effectiveness of HPV vaccines.

4. Cervical cancer outcomes

To date, there has been limited though emerging evidence of HPV effectiveness (direct or overall) on cervical cancer. One study from the US reported declines in cervical cancer incidence among young women using a population-based cancer registry data between the 4-year periods of 2003–2006 and 2011–2014 (Guo et al., 2018). Though the authors note that this may indicate the early effects of HPV vaccination, it is difficult to make this attribution because of the secular trends of declining incidence during the previous decades due to screening. Furthermore, the progression of HPV infection to invasive cancer is thought to take approximately 5–20 years or longer (Cogliano et al., 2005). Thus, it is unlikely that any observed reduction in rates within 8 years of vaccine introduction will reflect the true impact of the vaccine. Indeed, modeling studies from Australia, where much higher and much earlier HPV vaccination coverage was achieved, predict declines in cervical cancer will be detectable beginning around the year 2020 (Hall et al., 2019).

Notably, a very recent report from Sweden reported vaccine effectiveness of 88% in preventing cervical cancer in women age 30 years and younger if they had been vaccinated by age 17 years (Lei et al., 2020). Effectiveness was estimated to be 53% for women vaccinated at ages 17–30 years. Methods of this study are robust, including a large population-based approach (>1.6 million girls and women followed 2006–2017) and adjustment for several factors including age, calendar year, and several sociodemographic factors. These findings are very promising and hopefully will be replicated in other countries in the near future.

5. Knowledge gained, gaps identified, and implications for future monitoring for cervical cancer

Overall, the robust evidence for HPV vaccine effectiveness is encouraging. However, gaps between efficacy and effectiveness have been identified and need to be addressed to

accelerate progress toward cervical cancer elimination. The barriers to realizing the full potential benefits of HPV vaccines are likely multifactorial and not driven by a single factor. Based on the literature reviewed and summarized above, the two most important factors are likely to be vaccination coverage at the population level and age at vaccination at the individual level. These two areas should be priorities for public health, immunization, and other programs. At the same time, other factors at both the individual and population levels may also be important and likely vary by setting. These factors include, but are not limited to, the current prevalence of HPV in the population, health status of the population (e.g., immune function and co-morbidities such as human immunodeficiency virus), immunization programs, and access to quality health care. Thus, when aiming to optimize the potential benefits of HPV vaccines, these factors should be explored and addressed as needed at the local, regional, and national levels.

An important consideration for future studies measuring the impact of the vaccine against long-term outcomes like cervical cancer is the need to disentangle the effects of the vaccine from that of other preventative or therapeutic interventions. The growing body of literature on the impact of the vaccine on cervical precancers underscores the importance of accounting for screening for precancers (Drolet et al., 2019; Hariri et al., 2015). Because screening is a prerequisite to being diagnosed with precancer and often precedes a diagnosis of cervical cancer, understanding how frequently screening occurs and how screening practices change over time will be important to interpret the trends of both cancer and precancers. Of further importance is the need to consider the effect of access, quality, and timeliness of various treatment options for precancers, as these will further influence the trends of cancer diagnosis.

Sociodemographic health disparities are another likely contributor to the unrealized potential of the vaccine, yet limited attention has focused on this to date. It is known that the burden of HPV-associated conditions including cervical cancer is disproportionally high among individuals with low income and of racial and ethnic minority groups (McDougall et al., 2007). Yet, in a recent systematic review, we reported how few studies of effectiveness or impact have included measures of race, ethnicity, or income (Avni-Singer et al., 2020). However, the few places that have done this provide examples that can be implemented in other settings. For example, studies in Scotland use a measure of deprivation that takes into account employment, income, health, crime, housing, education, and access to services (Cameron et al., 2017). Research conducted in Australia has included measures of indigenous status and remoteness as markers of social vulnerabilities (Smith et al., 2015). Studies from the US have used area-based measures of the proportion of the resident population that is black, Hispanic, or living in poverty (Brackney et al., 2020). The recent study from Sweden about effectiveness against cervical cancer included measures of parent characteristics including education, income, country of birth, and health status (Lei et al., 2020). HPV vaccines have the potential to reduce or exacerbate these differences based on different levels of coverage, but this remains poorly understood and should be a priority for future research in this area. Importantly, underpinning many of these factors are the fundamental social determinants of health. While it is relatively more straightforward to measure characteristics such as race, ethnicity, and poverty, it is critical to remember

that these measurable characteristics reflect the social context and lived experiences of individuals.

Specific strategies to fill this important gap in knowledge are as follows. First, where data on sociodemographic characteristics are available, we suggest including them in analyses and reporting of data. This may be done either by including these factors in multivariate analyses to control for confounding, or by stratifying analyses by these factors to examine effect modification, depending on the goals of the analysis. Second, in places where such data are not available, the feasibility of adding measures of sociodemographic characteristics to existing disease registries or other data sources should be explored. Finally, where individual-level sociodemographic measures are not or cannot be gathered, the use of area-based measures may be implemented. This approach involves using external data sources that capture aggregate information about characteristics of communities (e.g., postcodes, census tracts) and then mapping individuals to these communities as a way of capturing the social environment in which people live. This approach has been used widely in public health assessments including monitoring of HPV vaccine impact (Cameron et al., 2017; Brackney et al., 2020).

There is also a lack of data on impact and effectiveness from low and middle-income countries (LMIC) with limited known published reports to date. A recent report from Argentina, currently classified as upper middle income, that has used both 2vHPV and 4vHPV vaccine reported substantial declines in both vaccine type HPV infections and HPV31/45 (Gonzalez et al., 2020). Similarly, a recent report from Bhutan, classified as a lower-middle income country, vaccine effectiveness has been estimated to range from 78 to 93% (Baussano et al., 2020). These reports are encouraging for both the impact of HPV vaccine in non-high income countries and the ability of vaccine impact studies to be conducted in these settings.

Though there are reasons why effectiveness and impact results from high-income countries may not apply to LMIC, the results are encouraging nonetheless, and LMIC may derive the greatest benefit from spending their limited resources on vaccination programs. However, the extent to which nation-specific monitoring efforts are needed to inform their immunization programs is an important consideration. As previously noted, vaccination coverage is an important determinant of overall effectiveness, and this will be a critical consideration for LMIC. Such data can be used to identify unique challenges that need to be addressed, and they can also be used to promote national immunization programs. LMIC should consider implementing cancer registries when possible, and/or conducting in-depth studies when resources are available. Programs in HIC can be used as models for adaptation to LMIC settings. Of particular importance to LMIC will be current and future work about dosing regimens. Post-hoc analysis of data from the prelicensure trials suggests that a single dose of the vaccine provides a degree of protection against cervical infections that is similar to that of a three-dose schedule (Markowitz et al., 2018), clinical trials assessing the efficacy of this reduced-dose regimen are underway (ClinicalTrials.gov identifier: NCT03180034, n.d.). If these results suggest it is a viable regimen, this would be of great value for resource-constrained LMIC that bear a disproportionate burden of cervical cancer incidence and mortality. If rolled out, this experience would be quite different from

high-income countries that have used two- and three-dose regimens, making post-licensure monitoring of a single-dose regimen critical.

6. Conclusions

Strong program implementation and monitoring for both HPV vaccination and cervical cancer screening are needed to make and monitor progress toward the goal of cervical cancer elimination. Numerous countries have added HPV vaccines to their routine immunization schedules and have already seen evidence that they are, in fact, effectively reducing the burden of cervical infections and precancers. Unfortunately, similar progress in establishing HPV vaccination programs in some LMIC is farther behind and developing strong programs that can achieve high coverage among the targeted ages (ages 13 and younger) is an area of critical importance. Post-licensure monitoring programs of HPV vaccine impact on cervical cancer will certainly be variable around the world. Establishing ideal programs will be challenged by resources, and particularly so in the LMIC that currently have the greatest burden of disease. In all settings, programs will be shaped by the availability of data, the ability to link various data sources, and the opportunities to collect additional meaningful individual-level data.

Despite compelling evidence that HPV vaccines are also likely to have a significant impact on the rates of cervical cancer, this works remains to be done. The lack of current evidence in this area (due to the timing of vaccination programs and latent period for invasive carcinoma) has been cited as a significant reason for why providers are not strongly recommending the vaccine for their adolescent patients (Cheruvu et al., 2017; Casillas et al., 2011). Empirical estimates of benefit directly against a cancerous outcome, rather than a cancer proxy like high-grade cervical lesions, may boost the acceptance of the vaccine and could serve to increase the strength and consistency of the health-care providers' recommendations to immunize.

Data from post-licensure studies that assess direct and overall effectiveness of vaccines may not only provide evidence for sustaining the uptake of HPV vaccine but may also fuel the development of strategies that optimize the implementation of the vaccine. Consequently, post-licensure studies of the vaccine's impact will be a key public health priority in the coming years as we work toward the elimination of cervical cancer. Robust monitoring programs will need to account for the timing of vaccination in individuals and programs at the country level in relation to outcomes, given the incubation period of cervical cancer. Programs should also consider the highly variable and rapidly evolving landscape of cervical cancer screening, as that may be another determinant of cancer incidence and affect trends over time. Finally, ideal programs will include measures of socioeconomic status such that trends in health disparities can also be monitored and addressed as needed for a more equitable vaccine impact.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

Ali H, Donovan B, Wand H, et al. , 2013. Genital warts in young Australians five years into national human papillomavirus vaccination programme: national surveillance data. BMJ 346, f2032. [PubMed: 23599298]

Arbyn M, Xu L, 2018. Efficacy and safety of prophylactic HPV vaccines. A Cochrane review of randomized trials. Expert Rev Vaccines 17, 1085–1091. [PubMed: 30495978]

Avni-Singer LR, Yakely A, Sheth SS, Shapiro ED, Niccolai LM, Oliveira CR, 2020. Assessing sociodemographic differences in human papillomavirus vaccine impact studies in the United States: a systematic review using narrative synthesis. Public Health 178, 137–150. [PubMed: 31698136]

Baussano I, Tshomo U, Tenet V, Heideman DAM, Wangden T, Franceschi S, Clifford GM, 2020. Prevalence of human papillomavirus and estimation of human papillomavirus vaccine effectiveness in Thimphu Bhutan in 2011–2012 and 2018. Ann. Intern. Med 173, 888–894. [PubMed: 32956600]

Brackney MM, Gargano JW, Hannagan SE, Meek J, Querec TD, Niccolai LM, 2020. Human papillomavirus 16/18-associated cervical lesions: differences by area-based measures of race and poverty. Am. J. Prev. Med 58, e149–e157. [PubMed: 32001053]

Cameron RL, Kavanagh K, Watt DC, Robertson C, Cuschieri K, Ahmed S, Pollock KG, 2017. The impact of bivalent HPV vaccine on cervical intraepithelial neoplasia by deprivation in Scotland: reducing the gap. J. Epidemiol. Community Health 71, 954–960. [PubMed: 28756395]

Casillas A, Singhal R, Tsui J, et al. , 2011. The impact of social communication on perceived HPV vaccine effectiveness in a low-income, minority population. Ethn Dis 21, 495–501. [PubMed: 22428357]

Cheruvu VK, Bhatta MP, Drinkard LN, 2017. Factors associated with parental reasons for “no-intent” to vaccinate female adolescents with human papillomavirus vaccine: National Immunization Survey - teen 2008–2012. BMC Pediatr. 17, 52. [PubMed: 28193249]

Clemens J, Brenner R, Rao M, Tafari N, Lowe C, 1996. Evaluating new vaccines for developing countries: efficacy or effectiveness? JAMA 275, 390–397. [PubMed: 8569019]

ClinicalTrials.gov identifier: NCT03180034.

Cogliano V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, 2005. Carcinogenicity of human papillomaviruses. Lancet Oncol 6, 204. [PubMed: 15830458]

Drolet M, Benard E, Perez N, et al. , 2019. Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. Lancet 394, 497–509. [PubMed: 31255301]

Garland SM, Kjaer SK, Munoz N, et al. , 2016. Impact and effectiveness of the quadrivalent human papillomavirus vaccine: a systematic review of 10 years of real-world experience. Clin. Infect. Dis 63, 519–527. [PubMed: 27230391]

Gonzalez JV, Deluca GD, Correa RM, et al. , 2020. Strong reduction in prevalence of HPV 16/18 and closely related HPV types in sexually active adolescent women following the introduction of HPV vaccination in Argentina. Papillomavirus Research 10, 100208. [PubMed: 33161174]

Guo F, Cofie LE, Berenson AB, 2018. Cervical cancer incidence in young US females after human papillomavirus vaccine introduction. Am. J. Prev. Med 55, 197–204. [PubMed: 29859731]

Hall MT, Simms KT, Lew J-B, et al. , 2019. The projected timeframe until cervical cancer elimination in Australia: a modeling study. Lancet Public Health 4, e19–e27. [PubMed: 30291040]

Halloran ME, Struchiner CJ, Longini IM, 1997. Study designs for evaluating different efficacy and effectiveness aspects of vaccines. Am. J. Epidemiol 146, 789–803. [PubMed: 9384199]

Hariri S, Johnson ML, Bennett NM, et al. , 2015. Population-based trends in high-grade cervical lesions in the early human papillomavirus vaccine era in the United States. Cancer 121, 2775–2781. [PubMed: 26098295]

Herweijer E, Sundstrom K, Ploner A, et al. , 2016. Quadrivalent HPV vaccine effectiveness against high-grade cervical lesions by age at vaccination: a population-based study. Int. J. Cancer 138, 2867–2874. [PubMed: 26856527]

Johnson Jones ML, Gargano JW, Powell M, et al. , 2020. Effectiveness of 1, 2, and 3 doses of human papillomavirus vaccine against high-grade cervical lesions positive for human papillomavirus 16 or 18. Am. J. Epidemiol 189, 265–276. [PubMed: 31680146]

Kahn JA, Brown DR, Ding L, et al. , 2012. Vaccine-type human papillomavirus and evidence of herd protection after vaccine introduction. Pediatrics 130, e249–e256. [PubMed: 22778297]

Kavanaugh K, Pollock KG, Cuschieri K, Palmer T, Cameron RL, Watt C, et al. , 2017. Changes in the prevalence of human papillomavirus following a national bivalent vaccination program in Scotland: a 7-year cross-sectional study. Lancet Infect. Dis 17, 1293–1302. [PubMed: 28965955]

Lei J, Ploner A, Elfstrom KM, Wang J, Roth A, Fang F, Sundstrom K, Dillner J, Sparen P, 2020. HPV vaccination and the risk of invasive cervical cancer. N. Engl. J. Med 383, 1340–1348. [PubMed: 32997908]

Markowitz LE, Drolet M, Perez N, Jit M, Brisson M, 2018. Human papillomavirus vaccine effectiveness by number of doses: systematic review of data from national immunization programs. Vaccine 36, 4806–4815. [PubMed: 29802000]

McDougall JA, Madeleine MM, Daling JR, Li CI, 2007. Racial and ethnic disparities in cervical cancer incidence rates in the United States, 1992–2003. Cancer Causes Control 18, 1175–1186. [PubMed: 17805982]

Mesher D, Panwar K, Thomas SL, Edmudson C, Choi YH, Beddows S, Soldan K, 2018. The impact of the national HPV vaccination program in England using the bivalent HPV vaccine: surveillance of type-specifi HPV in young females, 2010–2016. J. Infect. Dis 218, 911–921. [PubMed: 29917082]

Niccolai LM, Meek JI, Brackney M, et al. , 2017. Declines in human papillomavirus (HPV)-associated high-grade cervical lesions after introduction of HPV vaccines in Connecticut, United States, 2008–2015. Clin. Infect. Dis 65, 884–889. [PubMed: 28520854]

Oliveira CR, Weinberger DM, Shapiro ED, Niccolai LM, 2020. Effectiveness of human papillomavirus vaccine: a case-control study with Bayesian model averaging. IPVC.

Purrinos-Hermida MJ, Santiago-Perez MI, Trevino M, Dopazo R, Canizares A, Bonacho I, et al. , 2018. Direct, indirect, and total effectiveness of bivalent HPV vaccine in women in Galicia, Spain. PLoS One 13, e0201653. [PubMed: 30075010]

Silverberg MJ, Leyden WA, Lam JO, et al. , 2018. Effectiveness of catch-up human papillomavirus vaccination on incident cervical neoplasia in a US health-care setting: a population-based case-control study. Lancet Child Adolesc Health 10, 707–714.

Smith JS, Lindsay L, Hoots B, Keys J, Franceschi S, Winer R, Clifford GM, 2007. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. Int. J. Cancer 121, 621–632. [PubMed: 17405118]

Smith MA, Liu B, McIntrye P, Menzies R, Dey A, Canfell K, 2015. Fall in genital warts diagnoses in the general and indigenous Australian population following implementation of a national human papillomavirus vaccination program: analysis of routinely collected national hospital data. J. Infect. Dis 211, 91–99. [PubMed: 25117753]

Tabrizi SN, Brotherton JM, Kaldor JM, et al. , 2014. Assessment of herd immunity and cross-protection after a human papillomavirus vaccination programme in Australia: a repeat cross-sectional study. Lancet Infect. Dis 14, 958–966. [PubMed: 25107680]

Weinberg GA, Szilagyi PG, 2010. Vaccine epidemiology: efficacy, effectiveness, and the translational research roadmap. J. Infect. Dis 201, 1607–1610. [PubMed: 20402594]

World Health Organization. Major milestone reached as 100 countries have introduced HPV vaccine into national schedule. https://www.who.int/news-room/detail/31-10-2019-major-milestone-reached-as-100-countries-have-introduced-hpv-vaccine-into-national-schedule.

World Health Organization. World Health Assembly adopts global strategy to accelerate cervical cancer elimination, 19 8 2020. https://www.who.int/news-room/detail/19-08-2020-world-health-assembly-adopts-global-strategy-to-accelerate-cervical-cancer-elimination.

Table 1

Overview of vaccine efficacy and effectiveness studies.

Efficacy
Description
• Measures the direct protection to individuals conferred by full course of vaccination in idealized conditions
• Reflects the intrinsic property of vaccine (i.e., biologic efficacy)
• Also known as phase III
Approaches
• Conducted pre-licensure
• Randomized controlled clinical trial
• Typically conducted in highly restricted populations
Direct effectiveness
Description
• Measures the direct protection to individuals conferred by vaccination as administered in real-world ordinary conditions
• Typically conducted in heterogeneous populations
• Reflects the net benefit of vaccination as given in clinical practice
• Also known as phase IV
Approaches
• Conducted post-licensure
• Cohort studies and case-control studies are common study designs
• Typically conducted in heterogeneous populations
• May involve primary data collection from clinic or study populations, or linkage of surveillance databases at the individual level
Overall effectiveness
Description
• Measures the population-level benefit of vaccination programs that captures effects on both vaccinated and unvaccinated individuals (i.e. herd immunity) as administered in real-world ordinary conditions
• Typically conducted in heterogeneous populations
• Reflects the impact for total populations including unvaccinated by accounting for their mixing patterns and the proportion of population that is vaccinated (i.e., coverage)
• Also known as phase IV or impact studies
Approaches
• Conducted post-licensure
• Cohort studies and case-control studies are common study designs
• Ecological trend studies also commonly used
• Typically conducted in heterogeneous populations
• May involve primary data collection from clinic or study populations, or use of surveillance databases that are or are not linked at the individual level