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# *The Role of Human Papillomavirus Vaccines in Cancer Prevention*

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***Abstract:*** The human papillomavirus (HPV) affects millions of people globally and is a leading cause of anogenital cancers, such as cervical cancer. Since its creation, the HPV vaccination has dramatically decreased infection rates, proving its efficacy in preventing cancers linked to HPV. Disparities in access and uptake, particularly in nations with low and moderate incomes, continue to exist despite compelling clinical evidence in favor of vaccination. This research investigates at the effectiveness of HPV vaccine, which also highlights how it reduces the risk of HPV infections and cervical cancer. It examines how single-dose regimens can improve accessibility, especially in environments with low resources. In addition, issues like vaccine hesitancy, policy constraints, and differences in worldwide dissemination are examined. The results highlight the importance of vaccination in preventing cancer as well as the need for more studies on long-term immunity, fair access, and coordination with public health initiatives. The burden of diseases linked to HPV might be significantly decreased by bolstering international immunization campaigns.

***Keywords:*** HPV Vaccination, Cervical Cancer Prevention, Vaccine Efficacy, Global Health Disparities, Single-Dose Immunization

## 1. Introduction

Penile, anal, and a subset of oropharyngeal cancers are among the disorders that can be diagnosed with the human papillomavirus (HPV), a sexually transmitted infection caused by DNA viruses that attack basal epithelial cells. The virus will cause growth of warts on the skin and internal squamous mucosae.

While 80% of women have contracted the virus by the age of 50, and all people on the planet despite their genders have an equal 50% chance of contracting it once in their lives, and this infection is particularly prevalent in the United States. There are numerous unique HPV genotypes, which are identified as “high-risk”, “intermediate-risk”, or “low-risk” genotypes. A sequence homology lower than 90% in E6, E7, and L1ORFs in an HPV compare with other types of HPV is classified as a new type of HPV. Genotypes 16, 18, 45, and 56, associated with a few mucosal anogenital and head and neck cancers as well as cervical cancer, are considered as “high-risk”. Genotypes 6, 11, 42, 43, and 44 are examples of "low-risk" genotypes that do not cause cancer but do induce benign or low-grade genital warts and alterations in cervical tissue. The remaining genotypes (31, 33, 35, 51, 52, and 58) are sorted as “intermediate-risk” genotypes. HPV 16 and 18, the prevalent common types of HPV, can both be prevented by vaccination [1].

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Genital skin-to-skin contact is the main way that genital HPV infection is spread. HPV infection has been documented in young, healthy children and can happen at any age. In a cross-sectional assessment involving more than 20,000 women without cervical lesions aged from 15 to 74, age-standardized HPV prevalence differed over ten times between groups. The prevalence of HPV and age are inversely correlated in several nations. However, in a number of the study's poorest communities, the incidence of HPV was significant across all age groups. Cohort and cross-sectional studies in a number of nations present a U-shaped curve, with a second peak among female aged 55 to 64 and a first peak among those under 30. Compared to women without HIV, women experiencing HIV are more inclined to have multiple HPV genotypes at the same time. HIV-positive patients are more likely to develop anal cancer linked to HPV. The number of past and present sexual partners is associated with a woman's or her the partner's chance of contracting HPV. Although multiple cross-sectional studies did not show that condom usage reduced HPV frequency, a long-term investigation found that habitual condom use protected American undergraduates against new HPV infections and tended to offer protection against the onset of CIN lesions. Additionally, women who use condoms with their regular partners have been found to have a decreased prevalence of HPV. It has also been demonstrated that women who have circumcised partners are shielded against the risk of cervical cancer and HPV infection.

Virus-like particles (VLP), which are empty protein shells created by recombinant technology, are used to make HPV vaccinations. Since they don't contain any DNA or living biological materials, they are not communicable. The quadrivalent vaccine offers immunity to low-risk genotypes 6 and 11, whereas present HPV vaccines development aimed for withholding from HPV 16 and 18. The majority of vaccination research has been carried out in North America, Europe, and Latin America. However, research on vaccinations has not yet been carried out in Africa. A month following the third dosage, almost all women in the vaccine trials, who were between the ages of 15 and 26, developed antibodies averse to each HPV genotypes that were discernible, with levels 10 to 104 times above those in unconstrained infections. Age has an inverse relationship with the antibody levels acquired following vaccination. Whether given at identical visit or at different visits, the antibody responses toward quadrivalent HPV vaccine and the recombinant hepatitis B vaccine were comparable. Research has been conducted on the concurrent administration of both bivalent and quadrivalent vaccines along with other vaccines that are frequently given to teenagers, like the conjugate vaccine for meningococcal disease and the combination vaccine for diphtheria, tetanus, and pertussis (Tdap). The vaccines have not yet been evaluated for co-occurring helminth or malarial diseases, acute malnutrition, or HIV. The final outcome of CIN 2/3 OR AIS has been largely recognized as a viable and ethical study point for female cervical cancer in order to receive vaccination authorization. Bridging studies are carried out in children or young teens by contrasting the immune system reaction of younger individuals to women for whom clinical endpoint data for CIN 2/3 OR AIS will also be available [2]. This research will discuss the role of HPV vaccines in cancer prevention.

## 2. HPV vaccination and the risk of invasive cervical cancer

Superior cervical lesions have been demonstrated to be prevented by the HPV vaccine efficiently and effectively. Alternatively, data required for proving HPV vaccination's ability to intervene risk of invasive cervical cancer has always been considering insufficient. However, within our study, a reduced likelihood of malignant cervical cancer is linked to HPV vaccination.

Utilizing national Swedish demographic and healthcare statistics, the relationship between HPV vaccination and the likelihood of progressive cervical cancer is examined in an open sample of 1,672,983 girls between the ages of 10 and 30 [3]. Of the 527,871 female members of the vaccinated population, 438,939 (83.2%) were female and received their vaccinations before to the age of 17. The research participant is assessed for cervical cancer after turning thirty-one. According to the study,

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538 women who were not scheduled to receive the quadrivalent HPV vaccine were diagnosed with such cancer, compared to 19 women who did. At the age of 23, whereas Swedish women are first encouraged to take part in the cervical cancer examination program, the overall prevalence of cervical cancer rose dramatically for both inoculated and untreated women. By the age of 30, the total incidence for women who had received vaccinations was 47 instances per 100,000. However, among women who had not received vaccinations, the total prevalence skyrocketed to 94 cases per 100,000. Among women who started vaccinations between the ages of 17 and 30, the overall prevalence was 54 cases per 100,000 by the age of 30. At the age of 28, the average number of cases was 4 instances per 100,000 among women who had started vaccinations before becoming adults.

The incidence rate ratio between vaccinated and unvaccinated women was 0.51 after controlling for follow-up age. The incidence rate ratio was 0.37 after controlling for parental factors, residence, and calendar year. The fully adjusted frequency ratios for cervical cancer for women who were vaccinated before the age of 17 and those who were vaccinated between the ages of 17 and 30 were 0.12 and 0.47, respectively, after adjusting for age at vaccine commencement.

Based on three standardized base-case scenarios (girls who receive only vaccinations and screenings once in their lives, twice in their lifetime, and only a vaccination once in their lifetime), the WHO Cervical Cancer Elimination Modelling Consortium (CCEMC) predicted that occurrence of cervical cancer would decrease gradually in 78 low- and middle- income countries (LMIC) [4]. The CEMC used three distinct transmission-dynamic models that the WHO identified based on predetermined criteria. Starting at age 9, girls received vaccinations against a wide range of HPV genotypes, assuming 90% coverage and 100% lifelong protection (with an additional coverage required until age 14). From 45% in 2023 to 90% beginning in 2045, the prevalence of cervical screening—which includes HPV testing once or twice during a person's lifetime at the ages of 35 and 45—rose. The elimination benchmarks that were examined were an incidence drop of 85% or more, ten or less incidences per 100,000 women-years, and a cervical cancer age-standardized frequency of four or fewer cases per 100,000 women-years on average. Sensitivity experiments were carried out with various presumptions and screening and immunization techniques. The results were summarized through the median of the model projections.

According to estimates, HPV vaccination for girls alone would prevent 61 million cases of cervical cancer throughout the next century and reduce the median age-standardized incidence of cervical cancer in LMICs from 19.8 to 2.1 incidences per 100,000 women-years. By employing twice-lifetime screening, the incidence was decreased to 0.7 cases per 100,000 women-years, and an extra 12.1 million cases were prevented. In 60% of LMICs, 99% of LMICs, and 87% of LMICs, vaccination of girls alone was expected to eradicate the disease based on a threshold of 85% or greater decrease, based on a cutoff point of four cases per 100,000 women-years or less. Adding twice-lifetime screening resulted in eradication for all three thresholds in 100% of LMICs. Depending on the threshold and region, cervical cancer might be eliminated between 2059 and 2102 if all nations implemented vaccinations for females. The eradication process was sped up by 11–31 years with the use of twice-lifetime screening. Elimination required long-term protection against vaccinations.

Due to the high rates of HPV vaccination among girls, cervical cancer may be eradicated in most LMICs before the end of this modern century. In nations with the highest prevalence, high-uptake screening will hasten decreases and be required to eradicate cervical cancer [4].

## 3. Efficacy of HPV vaccines

The most current goal of the studies is to analyze the effectiveness of single dose, two dose, and three dose vaccines in avoiding infections with HPV 16 and 18 ten years after the immunization [5]. The randomized trial included unmarried females from nine different locations in India who were between the ages of 10 and 18. Following that, they were chosen at random to get two or three doses of the

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HPV vaccine's quadrivalent form. Using the protocol, participants were split into four groups according to how many doses of the vaccine they received: the two-dose group (vaccinated on day 1 and no sooner than day 180), the three-dose group (vaccinated on days 1, 60, and 180 or afterwards), the two-dose default group (vaccinated on days 1 and 60 or afterwards), and the single-dose default group. When enrollment and vaccination were halted, this immediately changed the study's design to a prospective, longitudinal cohort study.

To assess HPV infection incidence and persistence, cervical specimens were taken from respondents either six months after the arrival of the firstborn or eighteen months after marriage, whichever came first. After controlling for a difference in the distribution of possible uncertainties between the vaccinated and unvaccinated groups, the efficacy of the vaccine against persistent HPV 16 and 18 transmission (the main outcome) was evaluated for single-dose patients versus those who received two or three doses. The vaccinated participants were recruited within September 2009 and April 2010 (date of immunization dismissal) and were monitored for a median of nine and a half years (IQR 8.2–9.6). 4348 individuals received three treatments, 4980 individuals received two doses, and 4949 individuals received a single dosage. Among participants evaluated for the outcome, 95.4% of the single-dose default cohort, 93.1% of the two-dose cohort, and 93.3% of the three-dose cohorts demonstrated vaccination effectiveness against HPV 16 and 18 infection. A single dosage of the HPV vaccine provides comparable defense towards recurrent HPV 16 as well as 18 infections, which are responsible for over 70% of cervical cancers, as opposed to multiple doses.

The HPV vaccine is widely acknowledged to be 100% effective. However, in many countries, the implementation of HPV vaccination has been delayed due to problems such dosage compliance and financial limitations. A single dosage of the HPV vaccination may be a workable solution to these issues, according to the encouraging findings of several trials (Figure 1).

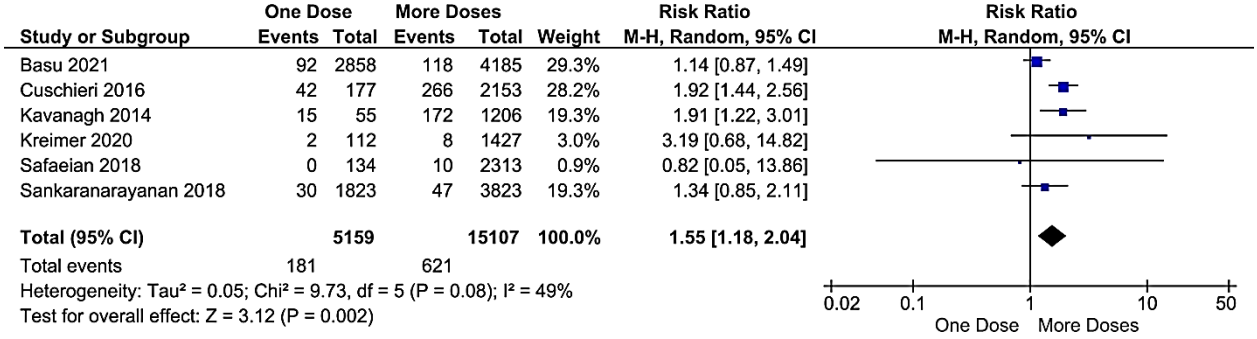


Figure 1: The ability of single and multiple doses of the HPV vaccine to prevent infection with HPV16 and HPV18 [6]

In contrast to two- and three-dose regimens, the relative durability of a single HPV vaccine is investigated in this thorough review and meta-analysis (Figure 2). In order to avoid pre-cancer/caner development, such as the incidence of HSIL or ASC-H and CIN2/3, as well as HPV 16, HPV 18, or all hrHPV infections, the investigation's primary goal is clinical efficacy. The incidence of HPV infection and pre-cervical malignancies is taken from each group that receives an intervention (one dosage or a combination of multiple doses) in order to do a meta-analysis. This meta-analysis also investigated the effects of a single dose of HPV vaccine against two or three doses on (1) HSIL or ASC-H and (2) CIN2/3, using a variety of medical consequences. By comparing the number of occurrences in groups that received a single dose of the HPV vaccination to those that received several doses, the Risk Ratio (RR), which was used to assess the efficacy and/or efficiency of the vaccine, was computed [6]. The heterogeneity value for this method ranges from 0% to 100%. The Cochrane prescription defines considerable heterogeneity as I2 of 50% or above.

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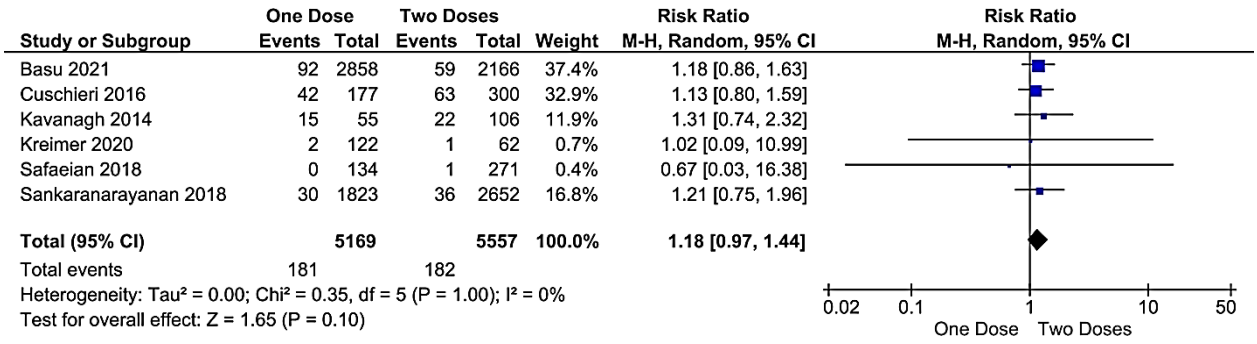


Figure 2: The ability of one- and two-dose HPV vaccines to prevent infection with HPV16 and HPV18 [6]

HPV16 and HPV18 infections are the most common among the many HPV serotypes in individuals with cervical cancer. Thus, a strong correlation among the incidence of HPV16 and HPV18 infections and cervical cancer cases is portrayed. According to six comprised studies, the one-dose group's probability of contracting HPV16 and HPV18 is somewhat higher than that of the more-dose group. The primary source of this conclusion is a research conducted in India and Scotland (weight 29.3% and 28.2%), whose findings may have understated the potential efficacy in younger females. Additionally, the HPV16 and HPV18 infection rates in the two groups differed when comparing the one- and two-dose HPV vaccines.

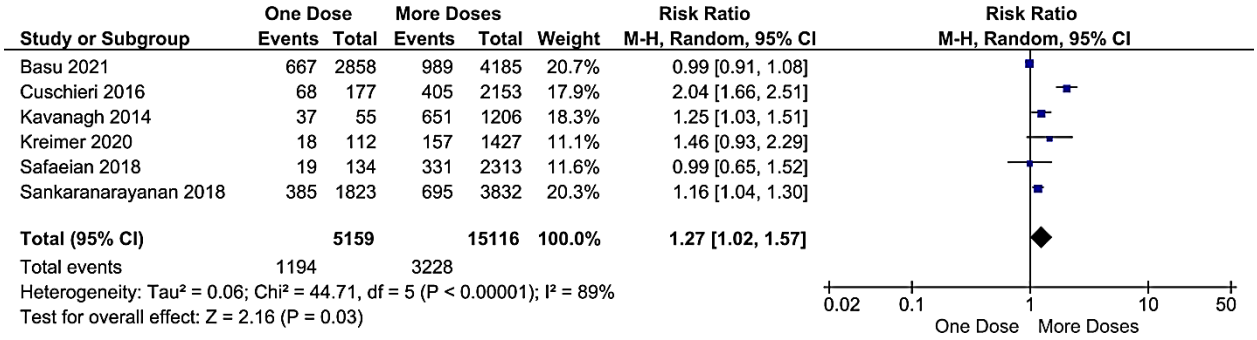


Figure 3: The ability of HPV vaccinations administered in one or more doses in prevention of hrHPV infection [6]

The frequency of cervical cancer is significantly influenced by a wider range of high-risk HPV types. Notably, about 90% of HPV strains are responsible for cases of cervical cancer, including HPV 16, 18, 31, 33, 45, 52, and 58. This thorough discussion of high-risk HPV variants emphasizes the value of vaccinations like the 9-valent HPV vaccine, which particularly targets these strains to reduce the chance of cervical cancer. The potency of the hrHPV vaccination in preventing vaccinated girls is also investigated in this study (Figure 3). According to this meta-analysis, one dosage of an HPV vaccine is somewhat less efficient than several doses and two doses alone for hrHPV infection prevention (Figure 4).

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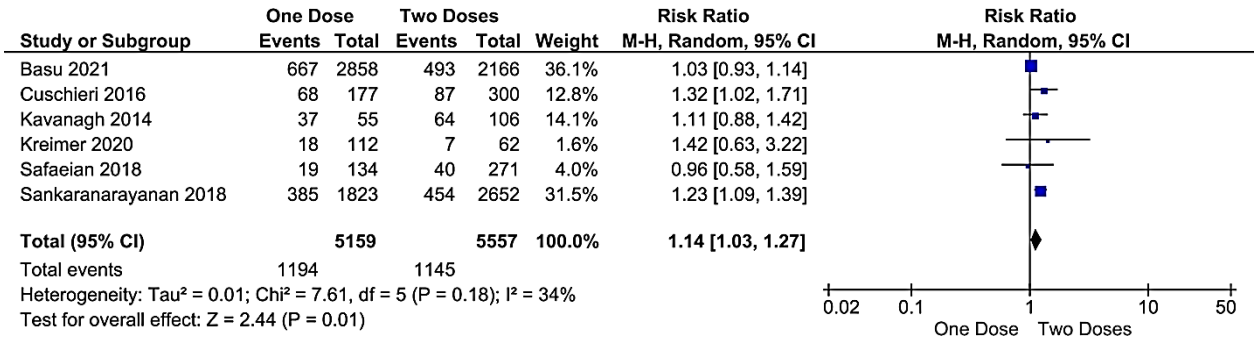


Figure 4: The ability of HPV vaccinations administered in one or two doses in prevention of hrHPV infection [6]

Atypical Squamous Cell-H (ASC-H) may be a component of High-Grade Squamous Intraepithelial Lesion (HSIL), a pre-cancer category in the pap smear test, despite not being classified as a cancer cell. Because HSIL can develop into cervical cancer if treatment is delayed, a second confirmation test is necessary. The effect of a single HPV vaccine dosage in preventing the incidence of HSIL or ASC-H appears to be comparable to that of multiple doses or two doses only (Figure 5). Despite the small number of studies that yielded this result, the results and patterns from each study were almost same, especially when comparing a single dose to several doses (Figure 6). These analyses, however, revealed variability between the supported research (I2 of 51% and 88%).

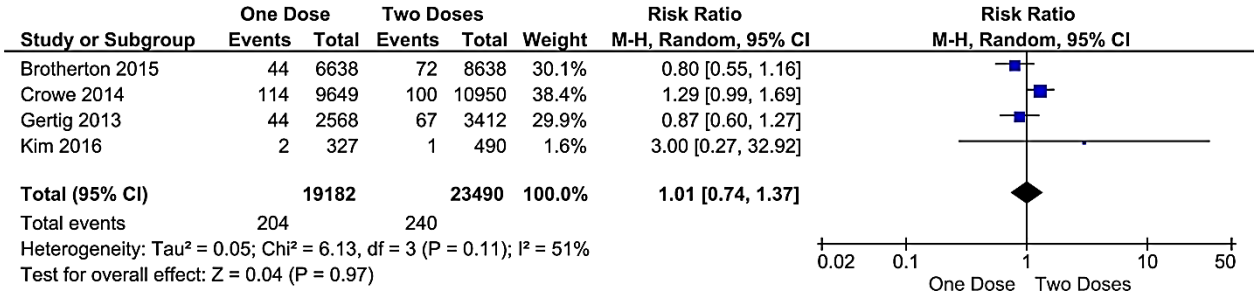


Figure 5: The ability of HPV vaccinations administered in one or two doses in prevention of the incidence of ASC-H or HSIL [6]

Cervical Intraepithelial Neoplasia (CIN) is a precancerous stage in which abnormal cells form on the cervix's surface. Cervical screening techniques that can identify CIN include pap smear testing and Visual Inspection with Acetic Acid (VIA). CIN is classified according to the percentage of tissue in the cervix, particularly the surface of the epithelium. According to CIN 2, one-third to two-thirds of the epithelium is frequently affected by dysplasia. Nevertheless, CIN 3, considered the most severe type of CIN, demonstrates the alteration of about two-thirds of the cervix's epithelial layer. Women receiving only one HPV vaccine dose were equally effective at preventing CIN2/3 as those who received several doses, per this meta-analysis (Figure 7). Nonetheless, the analysis's findings exhibit a significant degree of variability.

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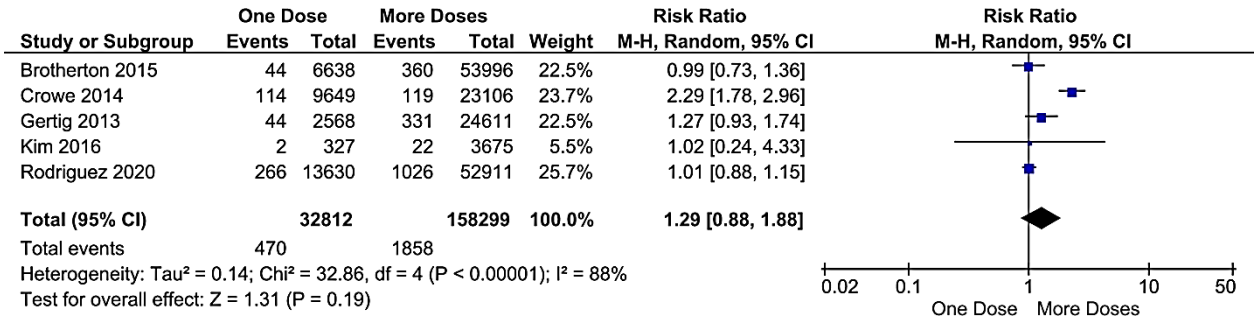


Figure 6: The ability of HPV vaccinations administered in one or more doses in prevention of the incidence of ASC-H or HSIL [6]

One dosage of the HPV vaccine could be just as effective as two or three doses, according to analysis. Its capacity to lower infections and precancerous occurrences and to offer immunogenic protection for a minimum of eight years of follow-up is the basis for this outcome. Although the study's results highlight the potential of an HPV vaccine administered as a single dose, more investigation and longer study periods are required to provide solid proof in favor of this suggestion. Therefore, more research will be necessary to guide vaccination plans [6].

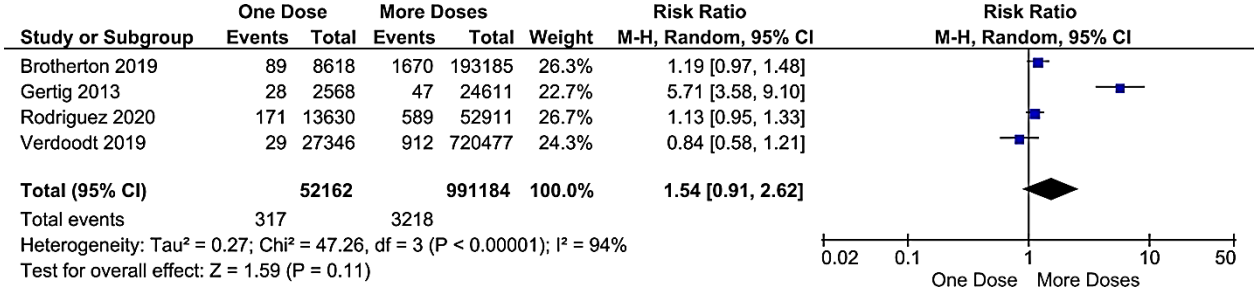


Figure 7: The ability of HPV vaccinations administered in one or more doses in prevention of the incidence of CIN2/3 [6]

## 4. HPV vaccination promotion

France's HPV vaccination rate is still lower than that of the majority of high-income countries. A study using a combination of techniques was carried out as part of the diagnostic phase of the national PrevHPV program to evaluate school staff members' knowledge, beliefs, and attitudes regarding HPV, the HPV vaccine and vaccination in as a whole, and the part affiliated schools play in advocating HPV vaccination [7]. The numerical information gathered from 301 independently administered online surveys is analyzed using descriptive statistics, while the qualitative information from three focus groups (n=14) is examined using theme analysis. Just 18% of respondents were aware that there is no antiviral cure for HPV, and less than half were aware that the virus can cause mouth cancer or genital warts. Nearly 90% of respondents were aware that the HPV vaccine existed, but some did not understand why it was advised for males and before their first sexual encounters. 56% had concerns about its safety, primarily because they believed there was insufficient information available. Although school nurses indicated that teaching students about HPV was an integral part of their job duties and had more expertise than other professionals, they rarely discuss this subject because they lack the necessary resources. Due to the negative reactions of parents, a lack of resources, and the belief that vaccinations are pointless, the professionals who took part in the focus groups were against vaccines in schools. These results highlight how important it is to increase school personnel's knowledge of HPV. Parents should participate in programs that encourage HPV vaccination to

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prevent any adverse reactions that school personnel might be concerned about. Additionally, a number of barriers need be eliminated before vaccination campaigns are introduced in French schools [7].

## 5. HPV vaccination programs in LMICs

LMICs account for over 90% of cervical cancer mortality, which lack the resources necessary to establish extensive to avoid the majority of these deaths with national monitoring and precancer therapy initiatives. The advent of HPV vaccinations has brought about a substantial change in the perspective of cervical cancer prevention. 41% of all LMICs, had started nationwide HPV vaccination campaigns as of the middle of 2020 [8]. This contribution examines the experiences of such nations that have incorporated the HPV vaccination in their nationwide initiatives, emphasizing important takeaways, obstacles to the long-term viability and expansion of HPV vaccination, and potential mitigating strategies.

As international standards evolved and nations gained experience, national introduction strategies varied in terms of their intended audiences, delivery location and time, strategy and preparation, communications and social mobilization, and, lastly, surveillance, monitoring, and analysis. Although a sizable portion of eligible girls have been reached by LMICs, countries continue to face major challenges in eradicating rumors, contacting females who do not attend school, completing the vaccine series, determining target demographics, retaining focus on program effectiveness, and guaranteeing the sustainability of vaccinations. With the help of new prospects, such are new vaccine manufacturers entering the market and continuous studies to assess one-dose dosing, the remaining barriers to increased coverage and long-term financial viability may be overcome. By making good use of the knowledge gained thus far and the developments that lie ahead, all LMICs may be able to progress toward the coverage levels required to eventually achieve elimination.

## 6. Conclusion

The HPV vaccine has proven to be very effective in lowering the risk of invasive cervical cancer and preventing HPV infections. Numerous studies, including meta-analyses and large-scale cohort studies, have repeatedly demonstrated that vaccination significantly lowers the incidence of high-risk HPV infections and cervical cancer cases. Widespread vaccination programs can effectively reduce HPV-related cancer rates and, in some situations, even lead to the potential elimination of cervical cancer in specific locations, according to the results of research done in Sweden and LMICs. Additionally, the effectiveness of single-dose vaccinations points to a viable substitute for enhancing accessibility and adherence in environments with limited resources. Despite the indisputable advantages, there are still obstacles in the way of guaranteeing universal access to HPV vaccination. The effectiveness of HPV prevention initiatives is hampered by disparities in vaccination rates, especially in lower-income nations. Concerns regarding vaccine uptake, long-term immunity, and integration with other public health measures also underscore the necessity of ongoing research and policy development. All things considered, the HPV vaccination is a significant development in public health that provides a proactive strategy for lowering the prevalence of illnesses linked to HPV. By avoiding cervical and other HPV-associated malignancies, worldwide HPV vaccination programs could save millions of lives with sustained efforts in policy implementation, education, and outreach. In order to improve coverage and efficacy, future studies should concentrate on maximizing vaccine distribution, assessing long-term immunity, and investigating innovative immunization techniques.

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