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# Efficacy of a Single Dose HPV vaccine and its Potential Outcomes in Low-Income Countries

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Efficacy of a Single Dose HPV vaccine and its Potential Outcomes in Low-Income Countries

By

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**Abstract**

Cervical cancer is a leading worldwide cause of cancer mortality in women and disproportionately burdens low-income countries. Human papillomavirus (HPV) has been proven as the primary cause of genital warts, some oropharyngeal cancers, and anogenital cancers such as cervical, vulvar, anal, and penile malignancies. HPV vaccination coupled with regular HPV screenings are major strategies for preventing HPV infections, but with high costs and infrastructure complexities associated with current vaccination and screening programs, many world regions are unable to provide protection against HPV infection and its sequelae. If unabated, cervical cancer incidence is expected to increase worldwide over the coming decades with the largest impact on developing regions. Currently there exists a good amount of evidence suggesting single-dose HPV vaccination may provide long-term protection against infection and subsequent malignancies and if sufficiently effective would promote broader vaccination in the neediest populations. Extensive literature analysis was conducted with the primary objective to summarize and assess the evidence to date supporting a change to a single-dose HPV vaccination schedule. Additionally, significant gaps are identified within the available research and discussion surrounding forthcoming evidence aims to provide insight into future developments surrounding a one-dose HPV vaccination option.

## Introduction

Cervical cancer is the third most common cancer worldwide and is also the leading cause of cancer mortality in women of low-income countries (LICs).<sup>1</sup> It has been estimated cervical cancer affects more than half a million women annually, with 88% of deaths occurring in LICs, a statistic, if unabated, is expected to increase as the population grows and lifetime risk is further exacerbated by longer life spans.<sup>2</sup> Cervical cancer is considered a sexually transmitted disease resulting from human papillomavirus (HPV), most commonly HPV 16 (50%) and HPV 18 (20%) with the remaining 30% of cases attributed to ten other carcinogenic types.<sup>3</sup> According to the World Health Assembly's evidenced based interventions for preventing and controlling cervical cancer, it was determined vaccinating females ages 9-13 against HPV as well as screening women ages 30-49 is both cost effective and feasible.<sup>2</sup>

Vaccines have been shown as highly efficacious against high grade precursors of vulvar, vaginal, and anal cancers suggestive of comprehensive protection against ano-genital tract cancers. Currently three HPV vaccines are commercially available which include a bivalent vaccine, 2vHPV (Cervarix), protecting against HPV 16 and HPV 18, a quadrivalent vaccine, 4vHPV (Gardasil), targeting HPV strains 6, 11, 16 and 18, and a 9-valent HPV vaccine, 9vHPV (Gardasil 9), covering types 6, 11, 16, 18, 31, 33, 45, 52, and lastly strain 58.<sup>4</sup> These vaccines were originally approved in three-dose regimens and later, after serological testing, data provided evidence that two doses administered at least 6 months apart evoked an immune response noninferior to the original recommended three doses.<sup>5</sup>

Despite this progress vaccine uptake has been poor in many developing countries because of high costs and the intensive infrastructure needed for administering consequent doses.<sup>5</sup> Because of these barriers, it is important to consider the possibilities if a single dose were

deemed effective. This would reduce vaccine costs substantially and simplify vaccination logistics enabling the implementation of HPV vaccination programs in low-income countries. This literature review explores evidence surrounding whether or not a single dose of human papillomavirus vaccine can prevent cervical cancer.

## **Background: Literature Review**

### *HPV Vaccine History and its Current Status in Developing Countries*

In the early 1980s an association between HPV and cervical cancers was reported by Harold zur Hausen and his team and was later verified as the cause of cervical cancer after subsequent molecular epidemiological studies.<sup>6</sup> Research since that time has largely focused on the prevention of cervical cancer by focusing on the prevention of HPV infection. Protection against HPV 16 and HPV 18 strains in reduced dose schedules is of particular importance considering these two HPV types account for around 70% of all HPV-associated cancers worldwide.<sup>5</sup> A major breakthrough in HPV vaccine research involved the discovery of the L1 viral capsid using recombinant technology; this capsid was found to self-assemble and has since been used to form empty shells referred to as virus-like particles (VLPs). These VLPs are used today when preparing the current HPV vaccines.<sup>6,7</sup> It has been shown that all vaccines (bivalent, quadrivalent and 9-valent) are highly immunogenic, provide both indirect and direct protection against HPV, and are ultimately safe. Implementation of these vaccines at a national level with at least 50% coverage of either the 2 or 3 dose schedules has aided in lowering population level HPV prevalence, genital warts, and cervical intraepithelial neoplasias.<sup>8</sup>

The first licensure of the HPV vaccine was of the 4vHPV vaccine in 2006 followed by the licensure of the 2vHPV-16/18 vaccine in 2007. By the end of 2008, twenty-five percent of high-income and upper-middle-income countries (HIC/UMIC) had implemented national HPV

vaccination programs.<sup>8</sup> Unfortunately, this was not the case for low and lower-middle-income countries (LIC/LMIC) where no national introductions occurred; in fact, it was found that by 2014 only 1.1% of girls between the ages of 10-20 had been vaccinated with one or more doses in all 84 LIC/LMICs. This is particularly alarming considering the same study stated that 70% of cervical cancers occur in countries with no HPV vaccination program. Since then, a significant amount of progress has been made with over 80 countries worldwide now having an HPV vaccination program. This has in large part been a result of funding available through GAVI, the Vaccine Alliance and with continuing aid from such an alliance, it is projected 40 million girls will have the potential to become vaccinated by 2020.<sup>8</sup>

The World Health Organization has recognized that routine HPV vaccination should be included in national immunization programs and should be introduced as part of a coordinated and comprehensive strategy which considers unique product characteristics such as price, supply and programmatic considerations.<sup>9</sup> This being said, it is necessary to investigate the current evidence supporting that a one dose regimen of HPV vaccine may be enough to provide a protective immune response. If such a single dose regimen is deemed valid, it could reduce vaccination and administration costs, extend existing vaccine supply for a longer period and improve uptake ultimately overcoming barriers that prohibit vaccine administration in poorer world regions.<sup>3,8</sup>

#### *Data from nonrandomized observational clinical trials*

To determine the efficacy of a single dose HPV vaccination regimen, it is helpful to evaluate past studies including the Costa Rica Vaccine Trial (CVT), the PATRICIA trial as well as a multicenter prospective cohort study in India. These provide the strongest evidence to date involving the efficacy and immunogenicity of single-dose HPV vaccination. It is critical to

mention that each of these trial's randomization was impaired from women missing scheduled vaccinations for reasons unrelated to each study resulting in observational studies of different vaccinated cohorts.

CVT, a phase III randomized control trial, was the initial study conducted that produced evidence supporting one dose of the 2vHPV-16/18 vaccine (Cervarix), provided durable protection against HPV infection.<sup>2</sup> This publicly funded four-year study began in June of 2004 with 7466 consenting women who were originally randomized to receive either the Cervarix or a control hepatitis A vaccine (Havrix, GlaxoSmithKline Biologicals). The main eligibility requirements included being between ages 18-25, being in good health, and not being pregnant nor breastfeeding.<sup>3</sup> This was to be done in a 1:1 ratio at 0,1 and 6 months with the women followed for four years annually.<sup>2</sup> In this trial around 20% of women received less than the three dose regimen even though the study design intended them to receive all 3 doses. Missed vaccinations were independent of trial arm and mostly involuntary due, in large part (~35%), to pregnancy and colposcopy referral.<sup>2,5</sup> Infection rates were evaluated and used to determine vaccine efficacy in this CVT study. Vaccine efficacy was found to be 80.9% (95% CI, 71.1%-87.7%) for three doses, 84.1% (95% CI, 50.2%-96.3%) for two doses and 100% for one dose (95% CI, 65.5%-100%). This suggested that two doses of the HPV-16/18 vaccine and potentially one dose are as protective as three doses.<sup>10</sup>

Later, this trial's durability was assessed involving extending the post hoc evaluation out an additional three years to evaluate HPV vaccination seven years post vaccination in those who received three, two and one dose.<sup>5</sup> At year 7 they found low prevalence of HPV16 and HPV18 infection that did not have a statistically significant differences between doses. It was determined only 1.0%, 1.3%, and 0.0% had prevalent HPV16 or HPV18 infection after receiving three-dose,

two-dose and 1-dose, respectively. Additionally, women remained seropositive at year 7 no matter the number of doses received and there was little difference from antibody levels when comparing to year 4. For comparison, women who were not vaccinated had a 6.6% prevalence of HPV 16/18 infection. Furthermore, carcinogenic types of HPV that were not protected by Cervarix were detected with similar frequency in the vaccinated group (15%) when compared to the unvaccinated women (13%) confirming both populations had similar exposure.<sup>11</sup> These findings suggest that long-lived protection may be afforded even by a single dose.<sup>5</sup>

In 2004, the PATRICIA trial, a second large-scale, double-blinded randomized control clinical trial, confirmed the CVT trial's results by showing HPV-16/18 vaccine efficacy against a one-time detection for three doses was 76.8% (95% CI 74.2-79.2), two doses was 73.3% (95% CI, 40.4-89.2) and one dose was 72.2% (95% CI, 13.6-92.4).<sup>3</sup> These results strengthened CVT's findings with the main difference between trials being women provided cervical samples twice annually for HPV DNA in the PATRICIA trial, instead of annually as in the CVT trial.<sup>3,7</sup> Cumulative incidence of protection against HPV 16/18 infection hovers around 80% four years post vaccination in both the CVT and PATRICIA trials therefore demonstrating one dose is noninferior to three doses of HPV viral exposure.<sup>11</sup>

In addition to the CVT and the PATRICIA study, a multicenter prospective study conducted in India warrants attention because of its findings pertaining to immune response after one dose of the 4vHPV vaccine Gardasil.<sup>12</sup> In September of 2009, the International Agency for Research on Cancer (IARC), Lyon, France, set out to evaluate efficacy of two versus three doses of Gardasil in preventing HPV infection as well as cervical neoplasia.<sup>4</sup> The plan included 20,000 unmarried girls ages 10-18 years with half of the girls randomly assigned to receive either two doses on days 1 and 180 and the other half the girls to receive three doses on days 1, 60 and 180.

Vaccinations were administered until April of 2010, when Indian authorities suspended further vaccinations because of unrelated events to the study. This left 17,729 girls (89% of target population) having received at least one dose Gardasil™. By this default 4,950 (28%) received only a single dose. When examining cumulative HPV 16 and 18 infection in all study groups seven years later, frequencies were uniformly low. Of the 1,481 unvaccinated women, 6.2% had infection while women vaccinated with either three, two or one dose of Gardasil™ all showed less than 1.7% of infection within each group. One dose recipients showed only a 1.6% infection rate.<sup>4</sup>

*Data provided by Immunogenicity Studies*

Two non-related observational studies were conducted in Fiji and Uganda beginning in 2008. Fiji looked at 4vHPV antibody response after one, two and three doses while Uganda did the same but for the 2vHPV vaccine. Both studies evaluated this by determining seropositivity and antibody titers to each vaccine type.<sup>11</sup>

The Fiji ministry of Health and Medical Services received a donation of 4vHPV which provided 200 girls ages 15-19 with vaccination of either one, two, or three doses. These girls were evaluated in 2015 examining antibody responses to assess for differences between doses. Results showed that 90-100% of the girls who were vaccinated in 2008 were seropositive in 2015. It was determined that girls who received one dose of the quadrivalent vaccine had significantly lower geometric mean antibody titers (GMTs) for each of the 4 targeted types of HPV when compared to girls who received the two or three doses, however their titers for the 4 HPV types were 5-30 folds higher than the unvaccinated group.<sup>11,13</sup>

In Uganda blood draws were taken from 195 three-dose, 145 two-dose and 36 one-dose recipients; after 33,39, and 33 months respectively. It was found that 99% of the women were HPV16 and HPV18 seropositive. Immune responses were inferior in the single dose group, but it

is important to note that they were still 4-fold higher than natural infection. Furthermore, in the CVT trial, effective GMT thresholds were defined at HPV16 = 124 EU/mL and HPV 18=69 EU/mL and it was found that in Ugandan girls who received one-dose 2vHPV were not lower than this threshold. <sup>10,14</sup>

#### *Cost effectiveness of a one-dose HPV vaccination regimen*

Informants from LMICs have reported that the key factor in their governments' hesitancy to include a national HPV vaccine regimen is the sustained financial commitment for the cost of vaccine procurement and delivery. Because of this hesitancy, it is important to display the cost effectiveness of a one-dose HPV vaccine schedule in the hopes that its implementation is given a serious and realistic chance in the future. With the long natural history of HPV and cervical malignancies, empirical studies have focused on evaluating efficacy and effectiveness of HPV vaccination by relying on intermediate endpoints which include the incidence of persistent HPV infection as well as cervical intraepithelial neoplasia (CIN). Simulating HPV disease burden in different populations is done using mathematical models by accumulating data and projecting long-term outcomes of decision-making interests such as cancer causes and deaths averted, or life expectancy gained. This aids in generating evidence where data does not exist which is used to determine health and epidemiological impacts, budget impacts and finally cost effectiveness strategies to prevent HPV-related ailments around the world.<sup>11</sup>

According to a review on single-dose HPV vaccine by the Evaluation Consortium, one analysis conducted in the United Kingdom and one in the United States have evaluated single-dose HPV16 and HPV18 vaccination models in HICs and have now aimed to apply models to Uganda, a LIC, to evaluate impact and cost-effectiveness here. It is understood in both studies that the

duration of protection by fewer dose HPV vaccines is critical information when determining impact and cost-effectiveness.<sup>11</sup>

The UK analysis determined a single-dose vaccination results in substantial reduction in cervical cancer (18-74%) and this single dose is cost-effective even when protection was only for 10 years. In the US study, the epidemiological impact of a single-dose vaccination was explored looking at its effectiveness for 10 years, 15 years and a lifetime. The analysis projected that one-dose and two-dose vaccinations protect against HPV infection and sequelae by providing substantial reductions in population HPV 16 prevalence over time, even without lifetime protection. Similar themes emerged from both analyses and concluded that a single-dose HPV vaccination yields “substantial health benefits and is good value for money, even at lower vaccine efficacy (80%) and when duration of reduced-dose protection is only 10 years.”<sup>11</sup> Furthermore, the cost effectiveness and impact of adding a second dose is dependent on single-dose vaccination protection and its ability to provide higher coverage than multiple-dose regimens.<sup>11</sup>

## **Methods**

The research topic exploring the efficacy of fewer doses of HPV vaccine surfaced as a result of personal upcoming international travel to Costa Rica and an interest in current research being done there. A general internet search involving studies being done within the country provided a leading study on HPV vaccine by the Costa Rica Vaccine Trial based in the Guanacaste province. A broad literature search was then performed to uncover information related to the history and progress of HPV vaccination as well as cervical cancer prevalence worldwide. Additionally, current research evaluating the efficacy of fewer than a three-dose regimen of HPV vaccination was sought after using PubMed, PubMed Central, and ScienceDirect. The following terms were used in the search: human papillomavirus, HPV vaccines, Costa Rica vaccines, vaccine

efficacy, reduced dose schedules, long term protections, cervix cancer protection, low income countries and single-dose protection. While reading through articles, additional sources were obtained, if relevant, from in text citations as well as from references lists.

Research coalesced into key topics: HPV vaccine history, current status in developing countries, nonrandomized observational studies, observational immunogenicity studies and cost effectiveness with lower dose regimens. All resources used were assessed for quality and validity and were included if recently published and peer reviewed. Initially, 22 articles were analyzed and evaluated based upon date of publication, and relevance to the topic. Ultimately, 16 articles were used in this literature review based upon the above criteria.

## **Discussion**

There is no doubt that data provided in the CVT, PATRICIA, and Indian studies each provide encouraging evidence that a single dose HPV VLP vaccine could potentially provide long standing protection against HPV infection worldwide. All were well-organized with rigorous enrollment and good retention to follow up and have provided the strongest evidence to justify ongoing and additional research in this field of study.

This is not to say these trials are without weaknesses, however. The large limitation in each of these studies was the fact they were not randomized to a reduced-dose schedule.<sup>5</sup> Women received one dose by default which does not offer the same protection against selection bias as a randomized trial comparing a single dose to more doses would have. Additionally, in the CVT and PATRICIA trials there was a small sample size in the one-dose group and infection occurrence was used as a primary endpoint, an endpoint not accepted by cervical cancer regulators. Because of this, policy surrounding vaccine regimens is unlikely to change as a result of these studies

alone.<sup>2</sup> Furthermore, these studies are heterogenous both in design and outcome assessment; comparing immune response is challenging with the use of different assays and laboratories.

When examining the immunogenicity studies in Fiji and Uganda a prominent weakness is the sample sizes were small which introduces potential bias in relation to individuals age and education levels. The Ugandan study did show consistency for laboratory outcomes measure by using enzyme-linked immunosorbent assay (ELISA) and calibrated standards equivalent to the ones used in the CVT trial. In doing so, these results can be compared using the EU/mL standards from ELISA, although differences between particular labs should still be considered.<sup>11</sup>

When looking to the future of HPV vaccination policy around the world, it crucial to identify the gaps in research, research priorities, and forthcoming evidence that will be necessary to motivate policy change. There is no question that additional evidence is needed to determine if a single dose of HPV vaccine provides adequate and durable protection. This evidence needs to come from studies providing data on the immunogenicity, efficacy and effectiveness of one-dose HPV vaccine regimens compared to two and three dose schedules that are truly randomized to compare vaccination groups free of bias.

It is encouraging that there is a great deal of forthcoming evidence pertaining to fewer dose HPV vaccination regimens. The CVT specifically has stated they aim to provide further long-term data and have three complimentary component parts to do so. The first includes the extension follow-up of the one-dose women in the CVT trial which is referred to as the “CVT Extend.” With this extension long-term stability of antibody response will be evaluated in groups having received one, two or three doses out to 15 years post vaccination.<sup>2</sup>

The India study will also contribute to the data pool as they intend to extend follow-up of participants until at least the end 2026 by working with population cancer registries that will

generate data on HPV16/18 infections and cervical neoplasia.<sup>3</sup> Already, around 300 women in the single-dose group have initiated cervical cancer screening with an additional 500 women per year being screened up to 2021.<sup>11</sup>

As stated previously there is a gap in available data involving immunogenicity, efficacy and effectiveness of a one-dose HPV vaccine regimen compared to two and three dose schedules that is randomized. This gap is currently being addressed by ESCUDDO, a large-scale randomized control trial in Costa Rica, whose goal is to identify if one dose of either 2vHPV or 9vHPV vaccine is as effective as two doses of this vaccine. One-dose will be tested for noninferiority compared to two-doses, separately for each vaccine type.<sup>2</sup> This will be done by evaluating 20,000 adolescent girls ages 12-20 who are to be randomized into two stages to receive either one or two doses of the vaccines in 2019 and followed for four years, with results available in 2023.<sup>2,11</sup> The ESCUDDO trial will consider both infection rates as well as immune response. Assessing virologic endpoints is necessary when evaluating a single dose schedule because antibody titers are inferior to two-doses and the minimum level required for protection is unknown for one-dose regimens.<sup>2</sup>

Additional trials are underway in Gambia (HANDS), and Tanzania (DoRIS) as well as an upcoming study in Kenya (KEN-SHE). These trials are dependent on the concept of ‘immunobridging’ which is defined as, “antibody titers generated in young adolescents that are the same or higher than generated in HPV-naive 16- to 26-year-old women, the population in which efficacy is proven.”<sup>15</sup> These studies will immunobridge to efficacy trials and will be important to draw conclusions about potential protection of a single dose across different world populations and age ranges. For example, In Tanzania, the DoRIS trial (Dose Reduction Immunobridging and Safety Study of Two HPV Vaccines in Tanzanian Girls) intends to display whether or not a single-dose of HPV vaccine can produce an immune response protective against cervical cancer. Results

will be available in 2021 and used to immunobridge to the CVT, Indian studies and ESCUDDO studies.<sup>11</sup>

## **Conclusion**

From a global perspective, the majority of HPV infection and cervical cancer mortality occurs in the developing world where HPV vaccination and screening are significantly lacking resulting in high morbidity and mortality rates. Substantial progress has been made with just over 80 countries, the large majority HICs, adopting HPV vaccine programs leaving an enormous need for new strategies to help implement programs in LICs/LMICs. This comprehensive literature review has identified a substantial amount of evidence supporting one dose HPV vaccine could possibly be sufficient in protecting women from HPV infection and sequelae, most importantly cervical malignancies.

There are limitations of previous studies on one-dose HPV vaccination, but current and upcoming research with stronger data analyses may provide evidence shared around the globe which can spark the potential for real change. The CVT Extend trial, ESCUDDO as well as several immunobridging studies are promising efforts to demonstrate protection provided by a single dose vaccination regimen and need critical and thorough examination when considering their validity to promote policy change. A viable one-dose HPV vaccination schedule would substantially reduce costs, facilitate policy and programmatic advantages over multiple dose regimens, and ultimately widen vaccination coverage in counties with the highest burden of cervical cancers. In conclusion, important research questions to evaluate long-term protection of a single-dose HPV vaccine schedule and the benefits it could provide globally are of the utmost importance. Future studies aimed at addressing these concepts will be of greatest benefit.

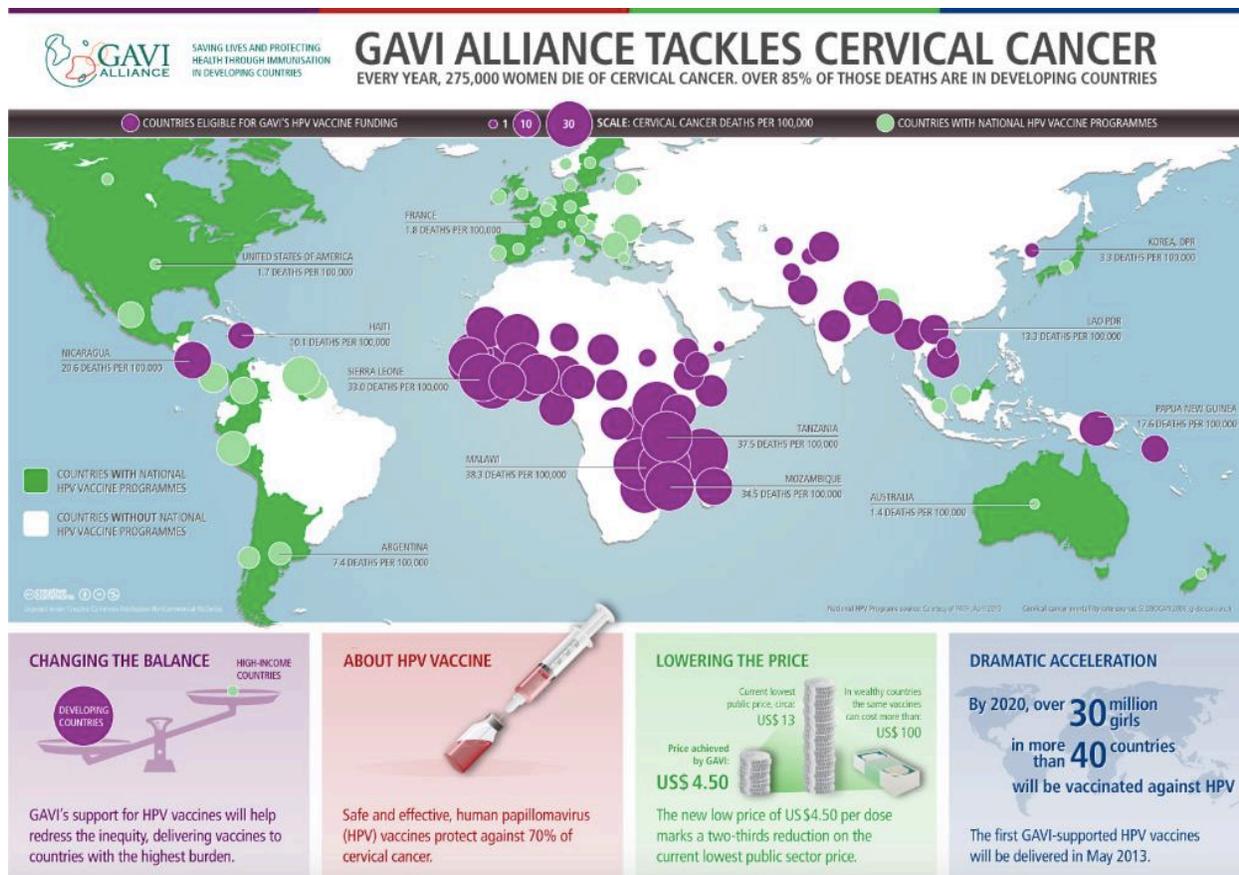
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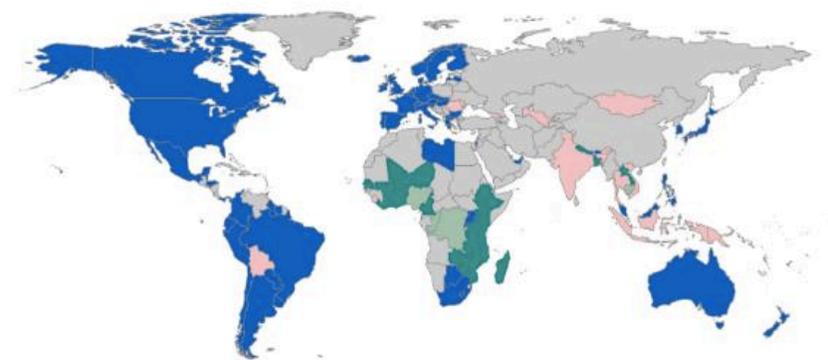
## Appendices

Appendix A: Death estimates in 2013 per 100,000 women from cervical cancer worldwide from [www.gavi.org](http://www.gavi.org)

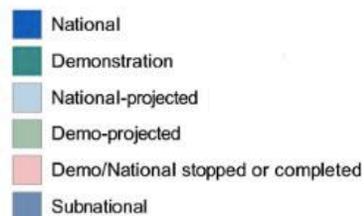


Appendix B: Global HPV vaccine experience, October 2016.<sup>8</sup>

K.E. Gallagher et al. / Vaccine 36 (2018) 4761–4767



\* Reproduced with permission from the author [7]. Demonstration projects in 'stopped' status mainly had fixed 1 or 2 year time periods of implementation which were not continued due to project funding ending.



Appendix C: Future one-dose HPV vaccination data with anticipated impact markers from the Evaluation Consortium.<sup>11</sup>

Timing of available additional data

Study		Study details	1-dose n	Current	2018	2019	2020	2021	2022	2023
Effectiveness	Costa Rica NCI	ESCUDDO n=20,000 girls, 12-16 yo HPV2/9 arms, 1,2 dose arms	n=10,000			Complete enrollment				Final data (4-yr + follow-up)
		CVT* n=3,727 girls, 18-25 yo HPV2, 1,2,3 dose arms	n=196	7-yr immuno Effectiveness (196 women)	11-yr immuno Effectiveness (11 yr)	13-yr immuno		15-yr immuno		
		India IARC* n=17,729 girls, 10-18 yo HPV4, 1,2,3 dose arms	n=4,950	5-yr immuno Effectiveness (959 women) 5-yr immuno	Effectiveness (~2000 women)	Effectiveness (~2800 women)			10-yr data (CIN2+ data)	
Immunogenicity	Africa	DoRIS Tanzania n=900 girls, 9-14 yo HPV2/9 arms, 1,2,3 dose arms	n=300				Interim immuno at 2 yrs	Final data at 3 yrs		
		Uganda / Fiji* Uganda: n=376 girls, 11-12 yo HPV2, 1,2,3 dose arms Fiji: n=200 girls, 15-19 yo HPV2, 1 dose	Uganda: n=36 Fiji: n=200	2 and 6-yr immuno (Uganda / Fiji, resp.)						
		U.S. Immuno n=132 girls, 57 boys, 9-11 yo Delayed 2 <sup>nd</sup> /3 <sup>rd</sup> doses to 24/30 months	n=143 girls 57 boys				Final data at 30 mos			
		Quebec			HPV2 vs. HPV9 1-dose persistence					
	HPV Immunoassay Comparison			CVT/India inter-assay 1-dose results	Global assay standardization	Correlate from India? (HPV4)				

Legend: Moderately impactful data (light blue), Lower impact data (medium blue), Most meaningful data (dark blue). Note: \*post-hoc studies

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