Can we use one dose of HPV vaccine to ensure long term protection?

INTERVIEW WITH
Aimée R. Kreimer, PhD
Senior Investigator, Infections & Immunoepidemiology Branch
Bethesda, MD, United States

Two doses of the HPV vaccines administered 6- to 12-months apart is the current recommendation for adolescents. What makes you think a single dose might be enough?

In the pre-licensure HPV vaccine trials, women were randomized to receive three doses of either the HPV vaccine or the control vaccine. Yet, not all women in the studies received all the doses. This enabled us to look at the efficacy of the HPV vaccines by number of doses received. We did this first in the Costa Rica HPV Vaccine Trial (CVT), which tested the bivalent HPV vaccine. We showed similar vaccine efficacy over four years among women who received one, two and three doses of the bivalent HPV vaccine. We also observed durable antibody responses in single-dose women, which suggested... (page 4)

The Biological Rationale For A One Dose HPV Vaccine

John T. Schiller, PhD | Bethesda, MD, United States

Although the antigens in the HPV vaccines are designated “virus-like particles” (VLPs) because they mimic the outer shell of authentic HPV virions, they are generally considered to be a type of subunit vaccine in that they are composed of a single highly purified protein, in this case the L1 major capsid protein, and are entirely noninfectious.

It was therefore surprising when post-hoc dose-stratified analyses from the bivalent and quadrivalent HPV vaccines efficacy trials suggested non-inferior protection... (page 15)
Can one dose of HPV vaccine ensure long term protection?

Clinical trials and vaccination programs continue to provide new insights into the potential of HPV vaccines. Since 2006 when the first indications for vaccine recommendations were drafted a number of issues have become apparent to the scientific and medical communities and are influencing the use of HPV vaccines:

1) The burden of HPV induced diseases and cancer also effects males. The relevance of genital warts amongst young males was well known, but the rising trends in anal cancer incidence in both genders and of oropharyngeal cancer mostly amongst males in several developed countries has been noticeable.

2) Some of the HPV-caused male cancer cases can be prevented because of the strong herd protection effect observed when a substantial fraction of the female population is vaccinated (i.e. by vaccinating greater than 50% of the female population in an extended program that included women to age 26 in Australia). However, herd protection is lost when non-vaccinated individuals leave the herd.

Consequently indications of routine male vaccination are gaining momentum and several populations are gradually adopting gender-neutral vaccination in the public programs.

3) The first generation vaccines, typically indicated for young girls, have proven to be almost equally effective amongst adult women (i.e. up to 45-50 years of age) in the per-protocol phase III trials (about 85% vaccine efficacy) and in the intention-to-treat analyses (about 50% vaccine efficacy).

4) The vaccination program in the Quebec province of Canada and in Mexico, both designed an interesting exploratory program of 3 doses that included postponing the third dose to 5 years (0, 6, 60 months) under strict surveillance for safety and efficacy. Over time, these programs became part of the rationale for a simplified two-dose vaccination scheme that was subsequently recommended by World Health Organization (WHO) for girls under 15 years of age.

5) The cost of the vaccines for public programs has been dramatically reduced from the initial prices in 2006 and tender negotiations are commonplace in developed countries and to some extent to middle income developing populations.

Consequently regulatory agencies in Europe recommend female vaccination ages 9+ without an upper age limit (the US maintained the upper limits of age according to the results of Phase III trials) and two-dose regimes for young girls are generalized.

6) The most visible early impact of generalized vaccination has been, as expected, the reduction of HPV infections and soon after, the reduction of cellular abnormalities (Low-grade Squamous Intraepithelial Lesions (LSIL) and High-grade Squamous Intraepithelial Lesions (HSIL)) related to HPV16 and 18. The Australian example clearly illustrates that by extending the vaccination program to age 26 the impact on HSIL can be perceived within the first decade.

7) The dramatic reduction in HPV type specific infections and lesions, prompted the redesigning of the screening programs.

8) Models also anticipate that by extending to at least a few cohorts the number of vaccinated women, the time to effect is shortened.

Consequently many countries are considering extending the routine programs to include several catch upcohorts and reshaping their screening programs to rely on HPV tests as the first screening tool and to simplify the screening requirements (i.e. less frequent lifetime screens) without compromising safety.

Two areas of great Public Health interest in cervical cancer prevention research currently include:

a) The value of self-sampling for HPV screening in developing and developed populations and

b) The opportunities of offering long term protection with one dose vaccination across age groups.

The former was addressed in the first issue of HPVWORLD (see www.hpvworld.com) and the latter is the object of this issue. It seems plausible that one-dose vaccination programs result in a increased vaccination uptake and compliance while reducing costs, thus facilitating deployment in developing countries. However, the proposal needs to be stringently tested under trial conditions before embarking on “one-dose HPV vaccination programs”. The prospects of finding too late that one dose is insufficient to maintain long term protection and that a booster is required (i.e. after several generations are informed of and vaccinated with a scheduled one dose) would be logistically challenging and may probably end up mean eroding the public trust in the global campaign.

Consequently several carefully designed trials are under way and results are awaited in the coming years.

In the main time, extending the vaccination programs to developing countries, increasing coverage in gender neutral programs and continued monitoring of vaccine efficacy and safety remain a significant task to which this newsletter will be proactively contributing.
Also in this issue
SEPTEMBER 2017 - Year 1

4 (Year 1 No. 17)
Interview with
Aimée R. Kreimer, PhD
Bethesda, MD, USA

6 (Year 1 No. 18)
Global vaccine uptake and projected cervical cancer disease reductions
Laia Bruní, MD, PhD
Hospitalet de Llobregat, Spain

10 (Year 1 No. 19)
Why has global HPV vaccine uptake lagged? A contextual reframing of vaccine introduction
D. Scott LaMontagne, PhD, MPH, FRSPH, CS
Seattle, WA, USA
Katherine E. Gallagher, PhD
London, United Kingdom
Deborah Watson-Jones, PhD, MD
London, United Kingdom / Mwanza, Tanzania

13 (Year 1 No. 20)
The Biological Rationale For A One Dose HPV Vaccine
John T. Schiller, PhD
Bethesda, MD, USA

17 (Year 1 No. 21)
Single-dose efficacy using the bivalent HPV vaccine: Post-hoc results from two phase 3 randomized clinical trials
Paula Gonzalez, MD
San José, Costa Rica
Joshua Sampson, PhD
Bethesda, MD, USA
Lígia A Pinto, PhD
Frederick, MD, USA
Aimée R. Kreimer, PhD
Bethesda, MD, USA

20 (Year 1 No. 22)
Single-dose efficacy using the quadrivalent HPV vaccine: Early results from an Indian study
Rengaswamy Sankaranarayanan, MD
Lyon, France
Neerja Bhatia, MBBS, MD
New Delhi, India
Bhagwan M Nene, MD, FRCP
Maharashtra, India
Partha Basu, MD
Lyon, France

23 (Year 1 No. 23)
Vaccine Effectiveness Data from National Immunization Programs
Mélanie Drolet, PhD
Québec, Canada
Lauri E. Markowitz, MD
Atlanta, Georgia, USA
Marc Brisson, PhD
Québec, Canada / London, UK

26 (Year 1 No. 24)
Could 1 dose be less efficacious than 2 doses but still be a great public health intervention?
Jane J. Kim, PhD
Boston, MA, USA

29 (Year 1 No. 25)
Could the HPV FASTER concept utilize 1 dose? What additional data are needed?
Mark Schiffman, MD, MPH
Nicolas Wentzensen, MD, PhD, MS
Rockville, MD USA

32 (Year 1 No. 26)
Perspectives on accelerating HPV vaccines toward impact
Peter Dull, MD
Seattle, WA, USA
Why is HPV vaccination important?
Cervical cancer affects more than half a million women annually, with 88% of mortality occurring in low-income nations, where cervical cancer is a leading cause of cancer death among women. Sadly, if current trends go unabated, the number of cases is expected to increase due to population growth alone. Yet, we have the tools to interrupt this devastating trajectory.

In May 2017, the 70th World Health Assembly endorsed an updated list of evidence-based interventions for some of the deadliest diseases, including cancer. Of 88 proposed interventions, 16 were considered the most cost-effective and feasible for implementation—vaccinating girls aged 9-13 years against HPV and screening women aged 30-49 years for cervical cancer made this important list.

It is our greatest hope that governments can facilitate the implementation of these life-saving measures. But, HPV vaccine uptake and cervical cancer screening implementation has been poor in many world regions. The first issue of HPV WORLD focused on bringing cervical cancer screening via HPV detection methods to emerging economies. This present issue focuses on HPV vaccines. Of 88 proposed interventions, 16 were considered the most cost-effective and feasible for implementation—vaccinating girls aged 9-13 years against HPV and screening women aged 30-49 years for cervical cancer made this important list.

In the pre-licensure HPV vaccine trials, women were randomized to receive three doses of either the HPV vaccine or the control vaccine. Yet, not all women in the studies received all the doses. This enabled us to look at the efficacy of the HPV vaccines by number of doses received. We did this first in the Costa Rica HPV Vaccine Trial (CVT), which tested the bivalent HPV vaccine. We showed similar vaccine efficacy over four years among women who received one, two and three doses of the bivalent HPV vaccine. We also observed durable antibody responses in single-dose women, which suggested the observed efficacy may be real. Our confidence in this finding grew when similar results were observed in the industry-sponsored PATRICIA trial.

Of 88 proposed interventions, 16 were considered the most cost-effective and feasible for implementation—vaccinating girls aged 9-13 years against HPV and screening women aged 30-49 years for cervical cancer made this important list.

We are also excited about the new 48-month data from an interrupted post-licensure trial in India that utilized the quadrivalent HPV vaccine. Again, similar protection against HPV16/18 cervical infection was observed regardless of number of vaccine doses. The compilation of the data is compelling and led us to hypothesize that one dose may be enough.

Moreover, in the CVT long-term follow-up, we now have data out to seven years following initial vaccination showing that women who received only one dose of the HPV vaccine are still similarly protected against HPV16/18 infections as those who received two or three doses.

So, what is some of the newest research that will test the hypothesis that one-dose of the HPV vaccines may provide durable protection?
Several new trials have been initiated to directly evaluate the hypothesis of the protection afforded by one-dose schedules of the HPV vaccines. The US NCI, again in collaboration with the Costa Rica Agencia Costarricense de Investigaciones Biomédicas, will conduct a large, 20,000 subject, randomized, controlled, trial (ClinicalTrials.gov identifier: NCT03180034; PIs: Aimée R Kreimer and Paula Gonzalez) in Costa Rica, with two of the licensed HPV vaccines: the first-generation bivalent vaccine Cervarix® (GlaxoSmithKline [GSK]) and the second-generation nonavalent vaccine Gardasil® (Merck). The main goals of the trial are to evaluate whether, in adolescent girls, one dose or two doses of the bivalent or nonavalent vaccines can confer strong, durable protection against persistent HPV infections. Virologic endpoints are necessary in the evaluation of a one-dose schedule, as the antibody levels are inferior to that of two doses, and, as yet, we do not know the minimum level required for protection. Separately for each vaccine, one-dose will be compared to the two-dose regimen in a formal randomized trial. Analyses will also be conducted to estimate vaccine efficacy versus no vaccination using a concurrent population survey of comparable, unvaccinated age-matched females in the same region, who will be tested for HPV.

Two doses of the HPV vaccines administered 6- to 12-months apart is the current recommendation for adolescents. What makes you think a single dose might be enough?

In the post-licensure HPV vaccine trials, women were randomized to receive three doses of either the HPV vaccine or the control vaccine. Yet, not all women in the studies received all the doses. This enabled us to look at the efficacy of the HPV vaccines by number of doses received. We did this first in the Costa Rica HPV Vaccine Trial (CVT), which tested the bivalent HPV vaccine. We showed similar vaccine efficacy over four years among women who received one, two and three doses of the bivalent HPV vaccine. We also observed durable antibody responses in single-dose women, which suggested the observed efficacy may be real. Our confidence in this finding grew when similar results were observed in the industry-sponsored PATRICIA trial.

Why do some women not receive the HPV vaccine?
HPV infection is a very common infection, and it is typically asymptomatic. However, it is important to note that some women may not receive the HPV vaccine for various reasons, such as cost, lack of awareness, or concerns about the vaccine. It is crucial to educate the public about the benefits of HPV vaccination and address any concerns they may have.
DNA and then immediately vaccinated. The trial is intended to provide the level of proof required to modify public health policies.

Complementary to this large effort are three immunogenicity trials. The first is the DORIS trial in Tanzania (PI: Deborah Watson-Jones). This study will randomize 900 girls to six arms (one, two and three doses of the bivalent or nonavalent HPV vaccines). Girls in this trial will be followed for three years and will have blood collected and tested for HPV antibody levels. The main goal is to document non-inferiority of HPV seropositivity comparing girls who received one to three doses. In the Gambia a similar study is being implemented using the nonavalent HPV vaccine only, which will also look at reduced dose schedules in younger females (PI: Ed Clarke). Finally, there is a US-based HPV vaccine trial that aims to evaluate a two-year deferred dosing schedule, but in doing so, will also be able to assess short-term HPV antibody levels among girls and boys who received one dose of the nonavalent HPV vaccine (Protocol Co-Pi: Anna-Barbara Moscicki and Yi Zeng). Several immunogenicity studies are planned with these immunogenicity-only studies, in that serology samples from the trials will be tested with samples from the existing and new Costa Rica HPV vaccine trials. If one-dose protection is documented using virologic endpoints in the Costa Rica trial for either or both HPV vaccines, and non-inferiority in antibody levels is observed in immunogenicity studies, we can immunobridge the efficacy findings in the Costa Rica study to other populations around the world.

We will also continue to follow the initial one-dose women from Costa Rica, as the India study will as well, so that the field can continue to investigate and document the duration of protection from a one-dose regimen.

What will the audience of HPV WORLD read about in this issue?

First, Dr. Bruni will share her newest data on the uptake of HPV vaccination by world region. Despite these vaccines being initially approved more than a decade ago, less than 10% of adolescent girls have been vaccinated, even with a single dose. She also points out that the world regions with the greatest cervical cancer disease burden have introduced HPV vaccination to a lesser degree. Next, Drs. LaMontagne, Gallagher and Watson-Jones provide context for the perceived lag in HPV vaccine uptake, and challenge us to consider key issues related to broad vaccine implementation. Importantly, the authors contrast HPV vaccine uptake with that of other recent vaccines, and present ongoing barriers. As price remains an important consideration, adoption of a one-dose HPV vaccination schedule may be part of the solution.

We then move on to multiple articles focused on the biological rationale and existing evidence around the protection afforded by one-dose HPV vaccination. Dr. Schiller presents, from both the immunologic and virologic perspectives, the rationale why one-dose of a subunit vaccination may actually work, challenging the current science that a prime-boost regimen is required for durable immunity. Then, Drs. Sankaranarayanan, Gonzalez and colleagues present non-randomized data from phase 3 trials on the efficacy/effectiveness of one-dose regimens—these are the main data that continue to drive the field towards the continued evaluation of single dose HPV regimens. Drs. Brisson, Drolet and Markowitz present post-licensure vaccine effectiveness data, by number of doses received, from national immunization programs. Critical insights on vaccine protection for the recommended dosing regimen have been garnered using post-licensure data. Yet, the authors present important caveats to using these data sources for understanding dose-stratified, individual-level efficacy, given the biases present in the reduced-dose recipients and the complexities in the analysis to control for prevalent HPV infections at time of initial vaccination.

Dr. Kim then addresses the important question: what if a single dose isn’t as good as two doses? She uses modeling to inform population-level reductions in HPV prevalence under varying scenarios of an inferior one-dose HPV vaccine. Based on her work, there are multiple aspects of a vaccine program that can compensate for reduced efficacy—this is especially true when the comparison is reframed to illustrate the potential gains from one-dose HPV vaccine introduction can be compared to no HPV vaccination.

Moreover, in the CVT long-term follow-up, we now have data out to seven years following initial vaccination showing that women who received only one dose of the HPV vaccine are still similarly protected against HPV16/18 infections as those who received two or three doses.

This issue closes with Drs. Shiffman and Wentzensen discussing opportunities to merge single-dose HPV vaccination with HPV screen and treat approaches (see the previous issue of HPVWORLD for a reminder), and with Dr. Dull presenting the perspective from the Bill & Melinda Gates Foundation for accelerating the potential HPV vaccine impact.

One overarching goal for the HPV vaccine research community is to generate evidence that will translate to expanded access to this vaccine. The compilation of articles in this issue of HPV WORLD highlights the collaborative efforts of our scientists moving toward this shared goal of faster cervical cancer eradication. I hope you enjoy reading this issue of HPV WORLD as much as we enjoyed writing it!
Global vaccine uptake and projected cervical cancer disease reductions

Since HPV vaccines first licensure in 2006, at least 82 (42%) countries have included HPV vaccines in their national immunization programmes (Table 1). The introduction has been progressive, predominantly in high-income western countries first, followed by Latin American countries alongside scattered countries from the remainder of the regions. The introduction of this vaccine has been especially challenging due to issues including initial high prices, a non-infant population target, sensitivities around the sexual transmission of the infection, and the involvement of numerous unique stakeholders, many from cancer control and women’s health fields not previously familiar with immunizations [1]. Its addition to the national schedules of so many countries can be thus considered a significant achievement.

Yet, there is still a marked imbalance between where most of the cervical cancer burden lies versus where most of these national prevention efforts are led. At present, 70% of current cervical cancer cases occur in countries that have not yet introduced HPV vaccination (Table 1). Lower-middle and low income countries (LMLIC) share more than half (40% and 16%, respectively) of the current cervical cancer burden. Remarkably, almost all (95 and 93%, respectively) of these cancer cases happen in LMLIC countries that do not currently have national HPV immunization programs (Figure 1). This burden is expected to soar in the coming years based on population growth forecasts alone. While there have been several HPV vaccine demonstration projects conducted in LMLIC (both GAVI and non-GAVI initiatives), few countries have scaled up to national programs [2,3]. Thus, most LMLIC women remain fully unprotected against cervical cancer, due not only to the lack of national HPV immunization programs, but also the lack of effective screening programs.

Using data accumulated by the end of 2014, we estimated that 59 million females had received at least one dose of HPV vaccine (8.2% of girls aged 10-14 years; and 7.1% of girls aged 15 to 19 worldwide) [4]

There continue to be profound differences in the number of vaccinated girls by income level (Figure 2A). Among 10 to 14 years old, 32.0%, 15.2%, 0.2% and 1.0% had received at least one dose of HPV vaccine in high, upper-middle, lower-middle and low income countries, respectively. At older ages, high income countries account for most of the vaccinated females, with an estimated coverage of 48.9% among 15-19 years old, whereas in upper-middle income countries the statistic was 3.5%. High income countries tend to vaccinate girls across a broader age range and target the largest proportion of girls; consequently, they accumulate the highest absolute number of vaccinated girls (42.6 millions) even though they have a dramatically smaller population of females.

While in 2014 low and middle income countries (LMIC) tended to target one single cohort of younger aged girls, new recommendations that endorse targeting of multiple age cohorts at HPV vaccine introduction will likely change the initial approach moving forward [5]. LMIC
Table I:
Countries including HPV Vaccine in their National Immunization programs by year of introduction.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panama</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argentina</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guyana</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peru</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colombia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mexico</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paraguay</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suriname</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trinidad &amp; Tobago</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uruguay</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barbados</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bahamas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ecuador</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antigua &amp; Barbuda</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belize</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Honduras</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liechtenstein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luxembourg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greece</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liechtenstein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denmark</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norway</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Russia(P)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slovenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iceland</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monaco</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulgaria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Czech Rep.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malta</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andorra</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hungary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slovakia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Croatia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyprus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lithuania</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rwanda</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesotho</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uganda</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Libya</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seychelles</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Africa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Botswana</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sao Tome &amp; Principe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Senegal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United Arab Emirates (P)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buthan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaysia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singapore</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brunei</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Israel</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kazakhstan(P)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Philippines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R.Korea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turkmenistan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marshall Is.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micronesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palau</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kiribati</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fiji</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vanuatu</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(P) = Partially introduced

Bold = High income countries

Figure I:
Number and proportion (%) of cervical cancer cases by income level

- **530,000 cases per year**

<table>
<thead>
<tr>
<th>Income Level</th>
<th>Number of Cases</th>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High income countries</td>
<td>74,000 (14%)</td>
<td>6%</td>
</tr>
<tr>
<td>Upper-middle income countries</td>
<td>160,000 (30%)</td>
<td>56%</td>
</tr>
<tr>
<td>Lower-middle income countries</td>
<td>212,000 (40%)</td>
<td>95%</td>
</tr>
<tr>
<td>Low income countries</td>
<td>84,000 (16%)</td>
<td>93%</td>
</tr>
</tbody>
</table>

Globally, 70%
Based on [4]. Methods comprised the compilation of the most comprehensive database to date on publicly-funded National HPV Immunization Programmes, the conversion of all retrieved coverages from multiple sources into birth cohort specific coverage, design of an imputation algorithm to treat missing data, and the use of global population estimates. To approximate the expected reduction on cervical cancer in vaccinated cohorts we further applied current cancer statistics to population projections.

Figure 2
Vaccinated female population and cervical cancer cases averted before age 75 years by income and age group in women targeted by HPV vaccination programmes by the end of 2014.
Panel A shows by 5 years age groups and by income the 10 to 29 years old female population, the number of female targeted by a National HPV vaccination program, and the number of female who finally received at least one dose of the HPV vaccine by the end of 2014. For example, from the 42 million girls aged 10-14 years in high-income countries (grey bar), 25 million had been targeted for HPV vaccination at least once until 2014 (pink bar) but only 15 million received at least one dose (bordeaux bar). As bars are superimposed, the visible portion of the red bar represents therefore missed vaccination opportunities (the difference between targeted and vaccinated women).

Panel B shows for these same populations of panel A the number of expected cervical cancers by the age of 75 based on current estimates and population forecasts (dark blue bar). The light blue bar represents the fraction of cases that would be averted taking into account only estimated vaccinated females until the end of 2014, and assuming 70% effectiveness and long-term protection of one dose vaccination.

About 365,000 [cervical cancer] cases and 150,000 deaths would already be averted in the same women aged 10-29 who received at least a single dose of HPV vaccines by 2014, assuming life-long protections and 70% vaccine effectiveness

For the next 65 years, in a non-vaccine scenario we would roughly expect 19 million cases and 10 million deaths from cervical cancer in women currently aged 10-29. The estimate is generated by directly applying current cervical cancer rates to population projections.

Taking into account the 2014 vaccination coverage rates, we calculated that from this expected burden, about 365,000 cases and 150,000 deaths would already be averted in these same women aged 10-29 who received at least a single dose of the HPV vaccines by 2014, assuming life-long protection and 70% vaccine effectiveness. (i.e.: a 100% efficaceous vaccine that covers 70% of the HPV types that cause cervical cancers).

Remarkably, as a result of a higher cervical cancer incidence and mortality rates, vaccinating less than half of the vaccine-age-eligible girls in upper-middle income countries would prevent more cases and deaths than in high-income countries. Still, expected cases largely outnumber the prevented ones in all income levels, and LMLIC women will disproportionately harbor most of the future cases.

Conclusion

In the first 10 years of HPV vaccination, many countries have made substantial efforts to introduce and expand HPV vaccination programs. However, the expected global impact presents marked disparities by geographical region and income level, determined by large differences in vaccine introduction, coverage and disease burden across countries. A significant number of cervical cancer cases will continue to be diagnosed for the next 50 years, mostly from unvaccinated and under-screened populations. Efforts need to continue to expand vaccination globally, but it is also indispensable to increase uptake in those countries already vaccinating. If efficacious and durable, a one-dose regimen may help reach these goals.

References

countries vaccinated 16.6 million females, although most of them were from upper-middle income countries of Latin America. Despite these impressive figures on the global absolute number of vaccinees, most of the world’s female population remains unprotected. For the time being, more than 90% of the ~600 million females aged 10-19 fall outside HPV vaccination programs (visible part of grey bars in Figure 2A) and few will have the opportunity to receive HPV vaccination in the near future unless multiple age-cohort vaccination is introduced or extensive catch-up campaigns are conducted, which is not expected.

These low global coverage figures and disparities on cervical cancer burden directly affect the expected impact in future cervical cancer cases (Figure 2B).

For the next 65 years, in a non-vaccine scenario we would roughly expect 19 million cases and 10 million deaths from cervical cancer in women currently aged 10-29. The estimate is generated by directly applying current cervical cancer rates to population projections.

For the next 65 years, in a non-vaccine scenario we would roughly expect 19 million cases and 10 million deaths from cervical cancer in women currently aged 10-29. The estimate is generated by directly applying current cervical cancer rates to population projections.
Why has global HPV vaccine uptake lagged? A contextual reframing of vaccine introduction

Vaccines against cervical cancer and other diseases caused by human papillomaviruses have been licensed for use since 2006. There have been concerns that introduction of HPV vaccines in low and middle-income countries (LMICs) – which account for more than 85% of all cases of cervical cancer – has lagged behind the adoption of other new life-saving vaccines, such as rotavirus (ROTA) and pneumococcal (PCV) vaccines. This paper will challenge the notion that HPV vaccine is lagging behind other vaccines by contextualizing the mechanisms of introduction in place for ROTA and PCV, which were absent for HPV. Five key factors are discussed: price, financial markets, access models, timing, and hesitancy by global partners.

1. Price
When first commercialized in 2006, HPV vaccines were the most expensive vaccines in the global marketplace: prices per dose averaged US$130 (three-dose schedule). By comparison, when released for commercial use in 2009, ROTA vaccines were US$83 per dose (two-dose schedule) and US$57 per dose (three-dose schedule). PCV7 was US$71 per dose (three-dose schedule).

For LMICs, there are global vaccine financing and procurement mechanisms in place through Gavi, the Vaccine Alliance and the PAHO Revolving Fund for countries in the Americas. Gavi negotiated bulk procurement of ROTA vaccine (2010) around the same time of the global recommendation for introduction by WHO (2009). The 2012 procurement price of US$5.00 for the two-dose version (Rotarix®, GSK), with co-financing as low as US$0.20 per dose, was a significant achievement for affordability. Introductions of ROTA vaccines in LMICs through Gavi began in 2010.

The procurement of PCV vaccines through Gavi involved an innovative financing mechanism called Advance Market Commitment (AMC) [1]. Donor funding guarantees for PCV vaccine purchases incentivize manufacturers to produce the supply needed; Gavi then ensures country access and uptake of these vaccines. This agreement was finalized in 2009, two years after the original WHO position paper on pneumococcal vaccines (2007). LMIC introductions of PCV began in 2010.

Even though the vaccine was available in 2006 and WHO made a global recommendation for use in 2009, price negotiations between Gavi and the manufacturers concluded in 2012.
2. Healthy financial markets
In advance of Gavi’s price negotiations for ROTA vaccine and the AMC mechanism for PCV vaccines, the global financial markets were strong and predicted to continue to grow. However, an extraordinary economic recession occurred towards the end of the first decade of the 21st century. For HPV, even though the vaccine was available in 2006 and WHO made a global recommendation for use in 2009, price negotiations between Gavi and the manufacturers concluded in 2012, resulting in the procurement price for Gavi at US$4.50 per dose (Merck, quadrivalent HPV vaccine) and US$4.60 per dose (GSK, bivalent HPV vaccine). Introductions of HPV vaccines in LMICs through Gavi began in 2013.

3. Access Models
The Accelerated Development and Introduction Plans (ADIPs) were created in 2002, with significant funding from the Bill & Melinda Gates Foundation and Gavi, to accelerate the development and rapid introduction of both ROTA and PCV in LMICs [2] (Figure 1). HPV vaccine did not have an ADIP for rapid introduction or an innovative financing model like the AMC for PCV. HPV vaccine was also seen as “different” from childhood vaccines since the target population recommended for vaccination by WHO were girls aged 9 to 13 years. National and international partners were concerned about the acceptability of the vaccine among parents and girls, the feasibility of vaccine delivery in a non-infant population, and program affordability. To encourage successful national introduction of HPV vaccines, countries securing HPV vaccine from Gavi had to first demonstrate their readiness to deliver the vaccine through a two-year ‘demonstration project’ in at least one district of the country. Direct national introduction was only available for countries with experience of delivering a
multi-dose vaccine to adolescents. In reality, few countries were eligible to apply to Gavi for national introduction of HPV in 2013, and most had to first conduct a two-year demonstration program (Figure 1).

It should be noted that LMICs also gained critical experience in delivering HPV vaccines through more than 60 different non-Gavi HPV vaccine ‘demonstration projects’ across 40 countries supported by the Gardasil Access Program (Merck), manufacturer donations to non-governmental organizations (NGOs) and governments, and support from PATH, the Australian Cervical Cancer Foundation, amongst others [3].

4. Timing
When analyzing the rate of national vaccine introductions for ROTA, PCV, and HPV vaccines the timing of the WHO’s global policy recommendations, the availability of affordable pricing from manufacturers and the availability of sustainable introduction models facilitated and funded by Gavi and donors, should be considered.

For the 11-year period of ROTA vaccine availability, 85 introductions have occurred: 37 in high- and upper-middle income countries and 48 in LMICs [4] (Figure 1). Among LMICs, initial scale up occurred from 2006 (the first year of Gavi support to countries), with accelerated introductions occurring from 2010 to 2016. For the 17-year period of PCV availability, 140 introductions have occurred: 76 in high- and upper-middle income countries and 64 in LMICs [4]. Similar to ROTA vaccines, rapid scale up in LMICs was greatly enhanced after the AMC mechanism became available in 2010.

During the 10 years of HPV vaccine availability, 74 high- and upper-middle income countries and 12 LMICs have introduced nationally. However, in reality the availability of the vaccine in LMICs did not materialize until 2013 and then was restricted largely to only demonstration programs. The context of the Gavi-funded mechanism would suggest the starting point for expected national scale up could be no earlier than 2015. Recent changes to Gavi’s program model and new projections of country uptake suggest that by 2019, 40 LMICs will have introduced HPV vaccine (Figure 1). The pace of introductions for HPV is starting to increase.

5. Global hesitancy
In contrast to ROTA and PCV, HPV vaccines did not get immediate and enthusiastic prioritization by global partners who influence country decisions. Instead, global conversations were cautious: HPV is expensive; HPV is different; acceptability and adherence may be low; delivery to adolescents will be difficult; cervical cancer is not a priority; HPV vaccination introduction should be undertaken slowly [5].

An alternative framing of HPV vaccine uptake
Now might be the time to reconsider how we view HPV vaccine uptake in LMICs. Has it really lagged? On the surface, one could just look at the numbers; however, broader analysis of the context and mechanisms that allow for successful new vaccine introductions in LMICs may lead us to a different conclusion.

HPV vaccine uptake may prove to be similar to ROTA vaccine, if we compare the same time period of vaccine accessibility starting in 2010 for ROTA and 2015 for HPV. Over the past seven years, 58% of LMICs have introduced ROTA vaccine; seven years from 2015, 50% of LMICs are expected to introduce HPV vaccine (Figure 1).

Despite barriers to access and an unexpected financial crisis, NGOs, donors and others provided unique avenues for 45 different LMICs to gain experience with HPV vaccines. Lessons were learned about how to increase the acceptability and feasibility of delivery to young adolescent girls [3]. The grassroots demand for HPV vaccine is strong. Local organizations, country advocates, national governments, and political leaders of LMICs have voiced their support and expressed the desire to prevent cervical cancer through HPV vaccination [3]. They see the consequences of this disease in their everyday lives – their mothers, sisters, aunts, grandmothers, and neighbors suffering unnecessarily. It is now up to the global community to continue to make this life-saving vaccine available.
Although the antigens in the HPV vaccines are designated "virus-like particles" (VLPs) because they mimic the outer shell of authentic HPV virions, they are generally considered to be a type of subunit vaccine in that they are composed of a single highly purified protein, in this case the L1 major capsid protein, and are entirely noninfectious.

All licensed subunit vaccines are administered in multi-dose prime/boost regimens. It was therefore surprising when post-hoc dose-stratified analyses from the bivalent and quadrivalent HPV vaccines efficacy trials suggested non-inferior protection from incident infection by vaccine-targeted HPV types in young women who received only a single priming dose compared to the per protocol three-dose series [1,2].

Although there was no indication that risk of HPV acquisition differed by number of vaccine doses received, the fact that the women were not randomized to receive less than three doses raises the possibility that differences in HPV exposure or other factors in the dose groups could bias the results. Before embarking on a large trial to rigorously evaluate the efficacy of less than three doses of the HPV vaccines, it therefore seems prudent to consider if it is biologically plausible that the HPV vaccines could be effective after a single dose, whereas other subunit vaccines are not. It is reassuring that consideration of both immunologic and virologic factors support the exceptional efficacy of HPV vaccines, even after a single dose.

**Immunologic Factors.**

The most compelling support for the conjecture that HPV vaccines will induce long term protection after a single dose are the findings that the vaccines induce strong and durable neutralizing antibody responses against the targeted types in essentially all one dose recipients. For the bivalent HPV vaccine, the geometric mean of antibody titers (GMT) after four years were only four-fold lower in one dose compared to three-dose recipients [3] (Figure 1), and this ratio has been maintained out to seven years [4]. For the quadrivalent HPV vaccine, similar differences between the antibody levels in the one- and three-dose recipients were reported in a three-year interim analysis. Direct comparison between the levels induced by these vaccines among one-dose recipients is currently not possible because different assays were used to quantify the antibody responses. The exceptional immunogenicity of HPV vaccines can largely be attributed to the structure of the HPV vaccine antigen. Typical subunit vaccines are composed of monomeric or low valence multimeric proteins or carbohydrate/protein conjugates. In contrast, HPV VLPs are composed of 360 ordered protein subunits that form a particulate 55nm structure displaying a repetitive array of epitopes on their surface. The engagement of these repetitive elements by the B-cell receptors (BCRs) on naive B-cells is believed to transmit exceptionally strong activation and survival signals to the cells leading to consistent induction of memory B-cells, and, most importantly, long lived plasma cells (LLPCs) that continuously produce antibodies for many years [5] (Figure 2).
Epitope spacing of 50-100Å appears to be critical. This spacing is commonly found on microbial surfaces but not on body surfaces normally exposed to the systemic immune system. The particulate and repetitive structure of VLPs likely contributes to B-cell immunity in several additional ways. Particles of this size efficiently traffic to lymph nodes and are also efficiently phagocytized by antigen presenting cells for the initiation of immune responses and the generation of cognate T helper cells. The poly-valence of VLPs also leads to stable binding of nature low avidity IgM and complement, promoting their acquisition by follicular dendritic cells, which are key components in inducing humoral immune responses in the lymph node. Note that the hepatitis B vaccine is also considered a VLP but appears to be much less immunogenic after a single dose, perhaps because it has a fewer subunits and/or because they float in a lipid bilayer.

To summarize, by mimicking the key structural features of authentic viruses, the HPV VLPs consistently induce potent and long lasting humoral responses that more closely resemble the anti-virion responses to an acute virus infection or a single dose of a live-attenuated virus vaccine than the response to simple subunit vaccines.

By mimicking the key structural features of authentic viruses, the HPV VLPs consistently induce potent and long lasting humoral responses

Virologic Factors.
Several virologic factors also likely contribute to the exceptional efficacy of the HPV vaccines. First, Papillomaviruses (PVs) have an unusual life cycle that is entirely confined to a stratified squamous epithelium. By producing their virions in the superficial layers and shedding them from the epithelial surface, the viruses minimize exposure of these highly immunogenic structures to the systemic immune system, and thereby can persistently produce infectious virions that are not subject to inactivation by neutralizing antibodies. Overall, PVs have evolved to maintain immune ignorance rather than evolving mechanisms to actively counteract systemic immunity. This mechanism of immune escape can be easily overcome by parenteral injection of the VLPs.

Second, studies in animal models have found that the mechanism that the viruses use to infect their target tissues make them exceptionally susceptible to vaccine-induced virion neutralizing antibodies [6]. To initiate infection, the virions must bind to specifically modified forms of heparan sulfate restricted to the basement membrane in normal tissue (Figure 1). Exposure of the basement membrane requires epithelial disruption. Direct exudation of systemic antibodies occurs at these sites, such that the virions are subject to an increasing gradient of antibody concentration as they approach their binding site. Basement membrane binding initiates a series of conformational changes that are required for exposure of the keratinocyte receptor-bind-
The slow kinetics of infection, much slower than for other well-characterized viruses, provides an exceptional length of time for vaccine-induced antibodies to disrupt the process. Inactivation can occur even after basement membrane binding, perhaps due to Fc receptor-mediated phagocytosis of the virion/antibody complex. Note that neutrophils and macrophages are specifically attracted to sites of epithelial disruption.

Experiments in mice involving passive transfer of sera from VLP vaccine individuals into naïve recipients indicate that levels of circulating antibodies that are 100-fold lower than the minimum detected in in vitro assays are sufficient to protect from high-dose cervicovaginal challenge in vivo, implying that there are potent mechanisms of antibody-mediated infection inhibition that are not measured in vitro [7]. In light of these observations, it is not surprising that the four-fold lower long-term antibody titers in one-dose recipients did not diminish the apparent protective efficacy of the HPV vaccines.

Figure 2
B-Cell Recognition of Dense Repetitive Protein Arrays Promotes the Induction of Exceptionally Potent Antibody Responses

References


A disrupted epithelium is depicted. The L2 minor capsid protein is cleaved by furin after a heparan sulfate proteoglycan (HSPG) binding-induced conformational change in the capsid, as shown in pink. This results in the exposure of the keratinocyte receptor-binding site on the surface of the virion.
Single-dose efficacy using the bivalent HPV vaccine: Post-hoc results from two phase 3 randomized clinical trials

The Costa Rica Vaccine Trial and PATRICIA trial

Paula Gonzalez, MD
Director/ Principal Investigator
Agencia Costarricence de Investigaciones Biomédicas (ACIB), formerly Proyecto Epidemiológico de Guanacaste
Fundación INCENSA
San José, Costa Rica
pgonzalez@acibcr.com

Joshua Sampson, PhD
Senior Investigator, Biostatistics Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute (NCI)
Bethesda, MD, United States
joshua.sampson@nih.gov

Aimée R. Kreimer, PhD
Senior Investigator, Infections & Immunoepidemiology Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute (NCI)
Bethesda, MD, United States
kreimera@mail.nih.gov

Ligia A Pinto, PhD
Senior Principal Scientist
HPV Immunology Laboratory, Head
Leidos Biomedical Research, Inc.,
Frederick National Laboratory for Cancer Research,
Frederick, Maryland, United States
pintol@mail.nih.gov

The Costa Rica HPV Vaccine Trial (CVT), a phase 3 randomized clinical trial that was initiated prior to licensure of the HPV vaccines, provided the first indication that one dose of the HPV vaccine might provide protection against HPV16/18 infections. Although the intention was to give all women in our trial three doses of the HPV vaccine (or control vaccine), 20% of women did not receive the full three-dose regimen, mostly due to either pregnancy or colposcopy referral. In 2011, we showed that, in terms of the primary endpoint of persistent HPV infection, a single dose of the bivalent HPV vaccine was just as efficacious as three doses of the vaccine during the first four years of the trial [1]. These findings were confirmed by the PATRICIA trial [2] (Figure 1). We also showed that the antibody levels after a single vaccine dose, although lower than levels elicited by three doses, were nine-times higher than levels elicited by natural infection [3]; importantly, the antibody levels were essentially constant over time, suggesting that the observed protection provided by a single dose might continue to last. To document long-term protection by number of doses received, we extended the follow-up of CVT participants for a total of 10 years [4].

We now have data from women in the CVT out to seven years after their initial vaccination [...] and show that the apparently strong protection afforded by a single dose of the bivalent HPV vaccine offers no sign of dissipating.

We now have data from women in the CVT out to seven years after their initial vaccination. The most recent results, from that 7th year, show that the apparently strong protection afforded by a single dose of the bivalent HPV vaccine offers no sign of dissipating. Infection rates by types inhibited by the vaccine, although lower than those reported in the initial studies, remain consistently low and antibody levels remain relatively stable. Among the 134 trial participants who received a single dose, there were 0 (0%; 95%CI: 0.0 to 2.2%) HPV 16/18 and 2 (1.5%; 0.3 to 4.8%) HPV31/33/45 cervical infections detectable at year 7 [5] (Figure 2). This is similar to the incidence rates amongst the 2043 women who received the historical gold standard three-dose regimen, where there were 20 (1.0%; 0.6 to 1.5%) HPV 16/18 and 48 (2.3%; 1.8 to 3.1%) HPV31/33/45 infections. For comparison, the HPV prevalence among the unvaccinated women was considerably higher for both vaccine HPV16/18 types (6.6%; 5.7 to 7.7%) and the related types HPV31/33/45 (5.5%; 4.7 to 6.5%), suggesting that even a single dose is providing robust protection. Of note, carcinogenic HPV types not protected against by the HPV vaccine were detected with similar frequency among vaccinated and unvaccinated women, indicating similar exposure to HPV infections. HPV antibody levels remain, effectively, unchanged over the course of the 7 years and all subjects continued to be seropositive for both vaccine-targeted HPV types at year 7. Among those trial partici-
pants receiving a single dose the bivalent HPV vaccine, the geometric mean titer (GMT) levels of the HPV16 antibody were stable at years 2, 4, and 7, as follows: 124 EU/ml (95% CI= 93 to 167), 137 (107 to 177), and 130 (89 to 190). The same conclusion was made for HPV18, where the respective GMT levels for the HPV18 antibody were 69 EU/ml (52 to 89), 70 (55 to 90), and 79 (55 to 112) at the same time points (Figure 3).

Thus, the next phase of our research is to conduct a formal randomized, controlled, trial evaluating the efficacy of a single dose of the HPV vaccine

While the evidence does seem to suggest that a single vaccine dose provides strong and lasting protection against HPV16 and 18, we acknowledge that the group of women receiving one dose of the bivalent HPV vaccine in the CVT and PATRICIA trials was relatively small, and that they were not a randomly selected subset of all trial participants nor blinded to the number of doses received.

Thus, the next phase of our research is to conduct a formal randomized, controlled, trial evaluating the efficacy of a single dose of the HPV vaccine (ClinicalTrials.gov identifier: NCT03180034). We will compare the HPV16/18 infection rates and VLP antibody responses after one and two doses of two of the licensed HPV vaccines: the first-generation bivalent vaccine, Cervarix® (GlaxoSmithKline [GSK]) and the second-generation nonavalent vaccine, Gardasil®9 (Merck). Analyses will also be conducted to estimate vaccine efficacy of a single dose, using rates estimated in an unvaccinated survey, to complement the trial. The trial is intended, if sufficient single-dose protection is demonstrated, to provide the level of proof required to modify public health policies.

References


Figure 1

Four-year vaccine efficacy against cumulative incident HPV16/18 infections, by dose group, in the Costa Rica HPV vaccine trial (CVT) and PATRICIA trial

This analysis was conducted in a modified total vaccinated cohort (M-TVC), which excludes women who had prevalent HPV16/18 infections at the time of first vaccination. VE: Vaccine efficacy, with corresponding 95% CIs.
In this figure, we see little evidence for HPV vaccine type prevalence and related types among women who received 3, 2, or 1 dose of the HPV vaccine, compared to higher prevalence rates among unvaccinated women. The prevalence of non-vaccine HPV types is similarly high across vaccinated and unvaccinated groups, indicating similar exposure to HPV infection.

**Figure 2**
HPV prevalence measured seven years after initial vaccination among women who received 3, 2, 1, and 0-doses in the Costa Rica HPV Vaccine Trial

**Figure 3**
HPV16 and 18 immunogenicity seven years after initial HPV vaccination, among women who received three and one doses in the Costa Rica HPV Vaccine Trial
Ten national institutions in India, in collaboration with the International Agency for Research on Cancer (IARC), Lyon, France, initiated a multi-centre cluster randomised study in India in September 2009 to evaluate the comparative efficacy of two versus three doses of quadrivalent HPV vaccination in preventing persistent HPV infection and cervical neoplasia. The study planned to recruit 20,000 unmarried girls aged 10-18 years and randomly allocate them to receive either two doses on days 1 and 180 (n=10,000) or three doses (n=10,000) on days 1, 60 and 180 of the quadrivalent HPV vaccine [1]. However, vaccination in the study was suspended in 2010 due to events unrelated to the study which led to 17,729 girls recruited who had received varying doses of the HPV vaccine: 4,950 had one dose only by default; 3,452 had two doses on days 1 and 60 by default; 4,979 received two doses on days 1 and 180 or later; and 4,348 had three doses on days 1, 60 and 180 or later. Thus, what was planned as a randomised trial of two vs three doses of HPV vaccination became an observational cohort study of multiple HPV dose groups, with a particularly large number of single-dose HPV vaccine recipients.

Our preliminary findings suggest high vaccine effectiveness in preventing incident HPV16/18 infections, as well as persistent infections, regardless of the number of doses received

Study participants are followed up at regular intervals to monitor and evaluate outcomes such as safety, immunogenicity, HPV infection and persistence of both the vaccine-HPV types (HPV16 and 18) and other HPV types. In due course, cervical precancer, particularly high-grade cervical intraepithelial neoplasia (CIN2 and 3), will be evaluated by screening of married participants at 5-year intervals when they reach 25 years of age. Participants will be linked with existing population-based cancer registries so that the extent of long-term protection against cervical cancer can be documented by dose group. An age-matched cohort of unvaccinated married women was recruited from the different study sites in 2011 to serve as unvaccinated controls. Cervical samples were collected from them at recruitment and yearly after that for HPV genotyping.

We now have four years of follow-up data for immunogenicity assessments. At this time point, women who received one dose of the HPV vaccine demonstrated a sustained immune response by generating antibodies against vaccine-targeted HPV types, albeit inferior to that of three or two doses (Figure 1). Our preliminary findings based on virologic endpoints assessed over a 7-year follow-up period from first dose of vaccination suggest high vaccine effectiveness in preventing incident HPV16/18 infections, as well as persistent infections, regardless of the number of doses received (Table 1). A similarly low incidence of HPV16/18 infections was observed among all dose groups,
while nearly 6% of unvaccinated women had HPV16/18 infections. Of note, HPV types not targeted by the HPV vaccine were detected with similar frequency among vaccinated and unvaccinated women, indicating similar exposure to HPV infections.

Our findings documenting the continued protection afforded by a single-dose of the quadrivalent HPV vaccine are promising. In our early assessment of virologic outcomes, a single dose of the HPV vaccine prevented incident HPV16 and 18 infections. Antibody levels among participants who received one dose were lower than those who received two or three doses; yet, the levels were stable over a four-year period.

Together, these data suggest a single dose of the HPV vaccine may generate long-lasting immune response and provide protection against HPV infections and ultimately cervical neoplasia.

We will continue to actively accrue data for 20 full years. With further follow-up, this study will generate a substantial amount of data on the frequency of persistent HPV16 and 18 infections and cervical neoplasia among study participants. Participants will additionally be linked with existing population-based cancer registries so that the extent of long-term protection against cervical cancer can be documented by dose group.

The India HPV Vaccine Trial is positioned to provide data on the long-term protection afforded by one dose of the quadrivalent HPV vaccine, and will complement ongoing efforts that aim to evaluate a single dose of the HPV vaccines, data that are needed before policy guidelines regarding a single dose can be formulated and implemented.

### Table I

Incident HPV infections accumulated over a 7 year follow-up period from first vaccination among women vaccinated with the quadrivalent HPV vaccine, and among unvaccinated women.

<table>
<thead>
<tr>
<th>Group</th>
<th>HPV16/18 incident infections</th>
<th>HPV31/33/45 incident infections</th>
<th>Non-vaccine HPV infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N positive /Total</td>
<td>% (95%CI)</td>
<td>N positive /Total</td>
</tr>
<tr>
<td>Three Doses (Days 1, 60, 180+)</td>
<td>9/1008</td>
<td>0.9% (0.4 to 1.7%)</td>
<td>52/1008</td>
</tr>
<tr>
<td>Two Doses (Days 1, 180+)</td>
<td>8/1028</td>
<td>0.8% (0.3 to 1.5%)</td>
<td>48/1028</td>
</tr>
<tr>
<td>Two Doses (Days 1, 60)</td>
<td>19/1256</td>
<td>1.5% (0.9 to 2.4%)</td>
<td>47/1256</td>
</tr>
<tr>
<td>One Dose (Day 1)</td>
<td>22/1558</td>
<td>1.4% (0.9 to 2.1%)</td>
<td>93/1558</td>
</tr>
<tr>
<td>Unvaccinated women</td>
<td>88/1481</td>
<td>5.9% (4.8 to 7.3%)</td>
<td>108/1481</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

95%CI: confidence interval

### References
Figure 1
Mean median florescent intensities (MFI) for HPV16 and 18 L1 antibodies at different time points among girls receiving different doses of the quadrivalent HPV vaccine.

- For the three-dose (Day 1, 60, 180 or later), and two-dose (Day 1, 180 or later) groups, one month after last dose MFI values are used, while for single dose group, month 12 MFI values are used.

Adapted from [3].
The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention

While all HPV vaccines were originally licensed and recommended as a three-dose schedule, in 2014, the World Health Organisation (WHO) recommended a two-dose HPV vaccination schedule for girls starting the vaccination series at age 9 through 14 years [1]. This decision was based on immunogenicity data showing non-inferior immune response of two doses in this age group compared to three doses in women in the age group for whom data are available from efficacy trials [2]. Studies using post-licensure data from national immunisation programs have been undertaken to compare the effectiveness of one, two or three vaccine doses. The aim of this article is to summarise the results of post-licensure studies assessing HPV vaccine effectiveness by the number of doses and discuss some limitations of these studies.

We performed a literature search and identified 11 published studies examining the post-licensure effectiveness of HPV vaccination by number of doses [3-13]. These studies, conducted in 7 countries within the context of a three-dose schedule of either the bivalent or quadrivalent HPV vaccine, examined the effectiveness by number of doses for three HPV-related endpoints: HPV infections, anogenital warts (AGW), and cervical lesions or abnormal cytology (Table I). The great majority of studies showed that two or three doses significantly decreased the incidence/prevalence of HPV-related endpoints. Several studies also suggest limited effectiveness with one dose. Furthermore, most studies showed a dose-response relationship, although not always statistically significant, between HPV vaccination effectiveness and number of doses.

Greater decreases in HPV-related endpoints were generally observed with three doses, followed by two doses, and one dose. However, there are important caveats when using post-licensure effectiveness studies to understand dose-specific efficacy that could bias results; these should be taken into account when interpreting the findings.

There are important caveats when using post-licensure effectiveness studies to understand dose-specific efficacy that could bias results; these should be taken into account when interpreting the findings.

Girls vaccinated with one, two or three doses are different

Firstly, these post-licensure studies were all conducted in settings of a national three-dose recommendation and girls who
received one or two doses differed from those completing the recommended schedule. Most of the studies published to date included girls who were vaccinated beyond the routine target age group, in the early years of the vaccination programs. In several studies, the partially vaccinated girls were older at the time of vaccination, had lower socio-economic status, and/or had indicators of earlier sexual exposure (e.g., younger cervical screening, vaccination at a family planning clinic, screening for a sexually transmitted infection). Therefore, these partially vaccinated girls were at higher risk of HPV infection and related diseases, which biases the studies’ results towards a greater effectiveness of three doses compared to one or two doses. Although several studies attempted to control for this bias by adjusting their analyses for some risk factors which differed between partially and fully-vaccinated girls, there is likelihood that residual confounding remains (it is often impossible to control for all factors associated with non-completion of a vaccination schedule).

**Post-licensure studies examining HPV vaccine effectiveness by number of doses have several challenges that bias the results towards greater effectiveness of three doses compared to two or one dose(s)**

Girls infected prior to vaccination are more likely to have incident AGW between the first and third dose than after. Secondly, in population-level databases, it is impossible to identify individuals who were already infected with HPV at the time of vaccination. Since HPV vaccination is prophylactic, it has no curative effect on these prevalent infections; this is the reason that HPV vaccination is recommended to pre-adolescents prior to sexual debut and potential HPV infection. However, in reality, a non-negligible proportion of individuals are already infected at the time of vaccination, and this proportion increases with older age at vaccination. AGW is more likely to occur between the 1st and 3rd doses of the vaccine, considering that the median delay between HPV6/11 infection and anogenital warts appearance is 2.9 months [14]. Prevalent infections at the time of vaccination consequently biases towards lower vaccine effectiveness of one and two doses. Furthermore, as previously mentioned, girls vaccinated with one or two doses in the studies were often older when vaccinated and had indicators of earlier sexual exposure. They were thus more likely to have prevalent HPV infections at the time of vaccination, further reducing the effectiveness of vaccination with one or two doses (vs three doses). To overcome this problem, researchers have introduced “buffer” periods in their analyses, which delay the case counting to exclude conditions caused by a prevalent infection. For example, in Herweijer et al., the effectiveness of 1 dose compared to no vaccination was 16% (p-value=0.06) without any buffer period [3]. However, with a buffer period of only one month (i.e., cases started to be counted 1 month after vaccination), the effectiveness of one dose compared to no vaccination increased to 28% (p-value <0.0001) and effectiveness increased to more than 50% with buffer periods greater than 4 months. While ideally buffer periods should be used for effectiveness studies, they reduce the number of person-years with one or two doses, which is generally small in post-licensure studies; this results in low statistical power (i.e., insufficient power to detect statistically significant differences in effectiveness between one, two and three doses).

In conclusion, post-licensure studies examining HPV vaccine effectiveness by number of doses have several challenges. The caveats discussed in this article consistently bias the results towards greater effectiveness of three doses compared to two or one dose(s).

Since many countries have recently switched to a two-dose schedule, it will be important to continue to examine the real-world impact of reduced-dose schedules.

**References**

### Table I
Studies examining the post-licensure effectiveness of HPV vaccination by number of doses

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>STUDY DESIGN</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quadrivalent HPV vaccine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anogenital warts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belgium</td>
<td>Retrospective cohort study using sick-fund/ insurance data</td>
<td>Dominik Felden, 2015, [4]</td>
</tr>
<tr>
<td>Denmark</td>
<td>Retrospective cohort study using national registries</td>
<td>Blomberg, 2015, [5]</td>
</tr>
<tr>
<td><strong>Cervical lesions</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>Retrospective cohort using linked data from registries</td>
<td>Gertig, 2013, [6]</td>
</tr>
<tr>
<td>Australia</td>
<td>Case control study using linked data from registries</td>
<td>Crowe, 2014, [7]</td>
</tr>
<tr>
<td>Australia</td>
<td>Retrospective cohort using linked regional data registries</td>
<td>Blomberg, 2015, [8]</td>
</tr>
<tr>
<td>United States</td>
<td>Retrospective cohort study using medical center records</td>
<td>Hofstetter, 2016, [9]</td>
</tr>
<tr>
<td>Canada</td>
<td>Nested case-control study using linked data from registries</td>
<td>Kim, 2016, [10]</td>
</tr>
<tr>
<td><strong>Bivalent HPV Vaccine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV prevalence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scotland</td>
<td>Cross-sectional study using screening registry data with additional sampling of those with &lt;3 doses</td>
<td>Cuschieri, 2016, [12]</td>
</tr>
<tr>
<td><strong>Cervical lesions</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scotland</td>
<td>Retrospective cohort study using linked national registry data</td>
<td>Pollock, 2014, [13]</td>
</tr>
</tbody>
</table>

*cervical lesion include cytology and/or histology outcomes
Could 1 dose be less efficacious than 2 doses but still be a great public health intervention?

Single-dose HPV vaccination has the potential to enhance the feasibility and affordability of primary prevention against HPV-related cancers worldwide. Evidence to date suggests that the efficacy of one-dose HPV vaccination is high [1,2], but even if demonstrated to be statistically inferior to that of two doses, the population-level effectiveness may still be great and worth the investment. The magnitude of effect – both absolute and relative to two doses – hinges on several key factors, including vaccine efficacy, duration of vaccine-induced protection, and achievable coverage. While clinical trials and studies are underway to resolve these uncertainties, decisions regarding the adoption of HPV vaccination – either with one or two doses – are being considered globally.

As we await more robust empirical data, mathematical models can be used to capture the burden of disease in a population and assess the impact and cost-effectiveness of HPV prevention strategies to inform decision-making. “Dynamic” models simulate the transmission of infectious diseases and the corresponding herd immunity benefits from interventions, such as vaccination. Using a previous dynamic model of HPV16 and 18 infections [3]– recently expanded to reflect sexual partnerships at the individual level and include additional HPV types – we conducted preliminary explorations of one-dose HPV vaccination, varying key parameters expected to have the greatest impact on health outcomes.

Mathematical models can be used to capture the burden of disease in a population and assess the impact and cost-effectiveness of HPV prevention strategies to inform decision-making

Scenarios were restricted to routine vaccination of 12-year-old girls, assuming efficacy for one-dose vaccination of 80% against incident HPV16 and 18 infections, based on the lower-bound target efficacy for single-dose regimens of HPV vaccines in a new, formal randomized control trial [4] (ClinicalTrials.gov Identifier: NCT 03180034). Given the unknown longevity of one-dose protection, we explored simplified waning assumptions, including no waning (i.e., lifetime protection), and 15 or 10 years of full protection followed by linear waning of vaccine protection over an additional 20 years. The effect of vaccination coverage was also explored. Vaccination with two doses was included as a baseline comparator, assuming 100% lifetime protection against HPV16/18 infections with achievable coverage of 70%. Model-projected outcomes included prevalence of HPV16 and 18 infections in a population of women over time.

Figure 1 shows the projected HPV16 prevalence in females over a 35-year period since initiation of routine HPV vaccination with either one dose or two doses, assuming protection is lifelong (i.e., no waning) with either dosage. At 70% coverage, both one-dose and two-dose vaccination scenarios are shown to greatly reduce HPV16 prevalence over time compared to no vaccination. For example, 30 years after routine vaccine implementation, two doses at 100% efficacy achieve 85% reduction in HPV16 prevalence compared to no vaccination, whereas one dose at 80% efficacy achieves 70% reduction. While it is not surprising that, assuming all else is equal, prevalence reduction is lower with one dose given its assumed lower efficacy (80%). We found that increasing one-dose vaccination coverage (from 70% to 90%) can almost completely offset this lower prevalence reduction. This relationship held true even when baseline vaccination coverage was assumed to be lower at 50%.

Figure 2 displays these projections under assumptions of waning vaccine protection with one dose, assuming 80% protection against HPV16/18 for 15 years, followed
by a linear reduction to 0% protection over an additional 20 years. Here, HPV16 prevalence again drops considerably over time with one-dose vaccination even if protection is not lifelong. In this scenario, increasing one-dose vaccination coverage from 70% to 90% is able to achieve similar reductions in HPV16 prevalence compared to two-dose vaccination until roughly 20 years post vaccine initiation, after which the effects of one-dose waning begin to diminish the population effect. The gap between one-dose and two-dose vaccination is even more pronounced and occurs sooner when one-dose vaccination begins to wane earlier (e.g., at 10 years; data not shown). At a lower baseline coverage of 50%, an increase in one-dose coverage up to 90% is required to offset lower prevalence reduction associated with lower and waning one-dose efficacy (data not shown). Under all scenarios, a similar trend can be observed for HPV18, although absolute prevalence is lower.

These projections must be interpreted with caution given the uncertainty and limitations in the model itself. This particular model was calibrated to the US population in order to leverage available data on sexual behaviors; to the extent that sexual behaviors vary across populations, especially in low and middle income countries where questions regarding one-dose vaccination are most pressing, results may not be generalizable. The analyses projected only the short-term outcomes of HPV infection over a relatively short time horizon; however, the model can be used to project longer-term outcomes of cancers averted, life expectancy gains, and cost-effectiveness, which will be included in ongoing work. Finally, only a limited number of coverage and efficacy values were explored and simplified vaccine waning scenarios were included. For example, vaccination coverage under both dosage regimens was assumed to be immediate without a more realistic period of scale-up, and no other (non-linear) specifications of waning were tested. We chose 15 years for waning to begin given new seven-year protection data for the bivalent HPV vaccine [5] but acknowledge that a shorter duration of protection would result in more modest HPV reductions.

First, the absolute population-level benefit associated with one-dose HPV vaccination stands to be great, even at lower efficacy and durability than two-dose vaccination.

Despite these limitations, this preliminary analysis offers several important insights. First, the absolute population-level benefit associated with one-dose HPV vaccination stands to be great, even at lower efficacy and durability than two-dose vaccination. Second, a one-dose vaccination program may be able to compensate for lower vaccine efficacy and durability if it can achieve higher coverage, depending on if and how vaccine efficacy wanes. Given the high number of countries that have yet to adopt an HPV vaccination program—and paired with its inherently lower cost and greater feasibility—one-dose HPV vaccination has the potential to boost HPV vaccine impact globally.■

References


Vaccine efficacy against HPV16/18 infections was assumed to be 100% for two doses, and 80% for one dose over the lifetime. HPV16 prevalence was among females aged 12 to 60 years.

**Figure 1**
Model-projected HPV16 prevalence in females over time, no waning

![Graph showing model-projected HPV16 prevalence in females over time, no waning](image)

**Figure 2**
Model-projected HPV16 prevalence in females over time, waning after 15 years

![Graph showing model-projected HPV16 prevalence in females over time, waning after 15 years](image)
Could the HPV FASTER concept utilize 1 dose? What additional data are needed?

Mark Schiffman, MD, MPH
Senior Investigator
Division of Cancer Epidemiology and Genetics
National Cancer Institute (NCI)
Rockville, MD, United States
schiffmm@mail.nih.gov

Nicolas Wentzensen, MD, PhD, MS
Senior Investigator
Division of Cancer Epidemiology and Genetics
National Cancer Institute (NCI)
Rockville, MD, United States
wentznenn@mail.nih.gov

HPV-FASTER AND SIMPLER: Cervical cancer prevention based on one dose of vaccine and simplified screening strategies

In this personal perspective, we support consideration of the HPV-FASTER strategy to control cervical cancer [1], simplified by using a one-visit vaccination and screening approach. We present underlying assumptions for discussion, and highlight remaining research gaps.

We know the fundamentals of how HPV causes cervical cancer [2]. Prophylactic vaccines and sensitive screening methods enable both primary and secondary prevention, offering the best opportunity to control a major malignancy. However, it is equally certain that 10 years following the introduction of vaccination, global cervical cancer control has barely begun. Without a radical change in direction, world rates are projected to rise substantially in the decades ahead.

Radical change might be possible, based on accumulating evidence that a single dose of HPV vaccine protects individuals and populations against infection much more completely than previously hoped. Preliminary evidence suggests one-dose protection might last at least a decade; optimistically, the finding will be confirmed within five years by large studies already underway. Due to herd protection, the effectiveness of vaccine programs has been greater than what was predicted solely based on completion of full vaccine series. Since a single dose is highly protective, initiation of vaccination schedules rather than completion might be the better metric of population coverage.

A simplified HPV-FASTER approach is exciting, because it might work even in low-resource, disorganized settings where cervical cancer is a leading cause of cancer death. If successful, the proposed strategy of one-visit HPV-FASTER could shorten the time to cervical cancer control by decades compared with waiting for the long-term effect from vaccination of preteens and continued, separate efforts to screen older women. Importantly, both efforts are not mutually exclusive, but may even be combined in some settings.

Younger participants would be vaccinated with one dose to reduce the peak of HPV acquisition and mid-adult women would be screened by HPV testing of self-samples to address the secondary peak of precancers

Given the great effort it takes to launch large prevention campaigns, we would argue that now is the time (as some “early adopter” groups are already doing [3]) to begin serious planning for cervical cancer control campaigns. Such campaigns would be designed around a single-visit strategy from the perspective of population effectiveness, rather than individual-level efficacy. Younger participants would be vaccinated with one dose to reduce the peak of HPV acquisition and, with some age overlap; mid-adult women would be screened by HPV testing of self-samples to address the secondary peak of precancers.

To succeed in controlling cervical cancer, it is not necessary to demonstrate “non-inferiority” of one-dose vaccination compared with three or even two doses, or have proof of decades of vaccine efficacy, or achieve extremely sensitive cervical screening.

While we can start planning now for prevention campaigns, we need in parallel to verify several essential supporting facts. These points are listed below, grouped by topic. Importantly, we do not seek perfection, but we are choosing substantial progress made possible by a focus on practicality.
First peak in the natural history model: Acquisition and early natural history of HPV infections (Figure 1)

1. Most cases of cervical cancer arise from high-risk HPV infections acquired in adolescence and young adulthood. In most countries, the majority of causal infections are acquired before age 35.

2. More than 90% of high-risk HPV infections of the male and female anogenital tract are controlled immunologically or clear within five years of acquisition; most clear within two years.

3. Transmission is unlikely after an infection becomes undetectable.

4. Persistent detectability of a high-risk HPV infection is linked to high risk of cervical precancer.

Second peak in the natural history model: Cervical precancer

5. The population risk of cervical precancer peaks about a decade after the peak of HPV acquisition.

6. Precancers tend to grow slowly and remain intraepithelial for many years before acquiring somatic changes leading to invasiveness.

Third “peak” in the natural history model: Cervical cancer


One-dose vaccination and protection against HPV infection

8. Preliminary evidence suggests a high likelihood of a decade or more of protection from one-dose vaccination with the bivalent vaccine. While there is less follow-up time, evidence is also promising for the quadrivalent vaccine, and we presume that the nine-valent vaccine is likely to act similarly.

9. Natural HPV infection leads to seroconversion in only a fraction of those exposed and most seropositive/DNA negative women have low titers conferring only weak protection. High titers indicate immunity but are uncommonly found. Therefore, although HPV vaccination is most efficacious in vaccinees naive to the targeted HPV types, it offers some protection to the majority of previously exposed women as well[4].

10. Antibody titers post-vaccination are higher in pre-adolescents than adult women, but achieved levels are still high at least through age 30 and probably older.

Program assumptions and deductions

11. A one-visit campaign that includes a broad age range refocuses HPV vaccination on cervical cancer prevention, not issues of sexuality, which could increase participation.

12. We are concentrating on campaigns among women, emphasizing women’s health, and aiming for high coverage that lessens the need for male vaccination.

13. Importantly, long-term immunity is not necessary to control HPV endemicity if broad coverage can be achieved within a short period of time; if most male and female infections clear faster than herd protection wanes, HPV prevalence will plummet as transmission networks are interrupted.

14. We need to settle the ages of vaccination for each region around the age distribution of first sexual intercourse and peak transmission of causal infections. Vaccination through age 35 might be sufficient but the age limit needs study.

15. Health economics modeling should address how often campaigns would need to be repeated to keep endemicity low.

16. One visit screening and triage can be achieved using self sampling; beginning at age 25-30 is rational but the starting age needs refinement.

17. Virtually all participants will have a single visit, either for vaccination, self-sampled screening that shows HPV negativity, or both vaccination and negative screening in the decade or so of overlap (25-35).

18. Only currently HPV-positive women at highest risk of developing cancer will need follow-up and treatment.

19. Inexpensive HPV tests, both high-throughput and point-of-care, are feasible and affordable but not yet finalized; producing several usable tests is important.

20. To prevent massive overtreatment and overwhelming clinical resources, restriction of HPV screening to the most carcinogenic types (possibly HPV16, 18, 45, 31, 33, 52, 58, and 35) might be advantageous.

21. Developing triage methods focused on finding precancer among HPV-positive women is a priority; possibilities include improved visual triage with image-recognition software operating on smartphones, and automated cytologic or molecular methods that work off the screening self-sample.

22. Research on low-morbidity simple treatment of screen/ triage-positive women is lagging and might be the biggest remaining hurdle in cervical cancer control.

23. Surveillance of the success of the suggested program can make use of spot surveys of sentinel STI clinics and does not require full population surveillance.

Adoption of a population-based approach is not accepting second-rate methods, but rather permits reaching a level of cancer control that would take much longer with conventional approaches
Adoption of a population-based approach is not accepting second-rate methods, but rather permits reaching a level of cancer control that would take much longer with conventional approaches. Reducing HPV endemicity on the population level is helpful to the young woman on the individual level, perhaps as much as getting a second dose.

While designing cervical cancer prevention with almost zero tolerance of any cases might be societally mandated in the U.S., it is not a “gold standard” due to very high cost, overtreatment and associated iatrogenic morbidity.

In conclusion, we hope that the chance to save hundreds of thousands of lives, by crushing the pyramid of HPV infection, precancer, and cancer, will invigorate donors and all stakeholders. Currently, we have to maintain global vaccination of pre-adolescents and screening of older women for a generation or two before we control cervical cancer. How much more inspiring would it be to talk about control starting now?

References

Figure 1
Prevalence of HPV infections, precancer, and cancer by age

The figure shows the natural history model and the corresponding prevalence of HPV infection, precancer, and cancer in the population. Exemplary cervical cancer prevention strategies based on one-dose HPV vaccination and HPV screening and triage are shown. Adapted from [2]
Cervical cancer is the 2nd most common cancer in women. Globally more than 500,000 cases of cervical cancer and ~270,000 deaths occur every year—disproportionately among disadvantaged populations of women in developing countries that have weak health systems. Preventing cervical cancer deaths in world’s most resource-poor settings is an important part of the global health strategy at the Bill & Melinda Gates Foundation.

To drive toward deeper impact on disease incidence, the Foundation developed an HPV strategy that increasingly focuses effort and resources on maximizing the reach, effectiveness and sustainability of HPV vaccination programs while continuing to generate evidence on efficiency models of delivering screening and preventive treatment by leveraging existing investments. The focus on vaccines is in part to build on the depth of experience the Foundation has in vaccine-based interventions and also the excellent safety and efficacy profiles of existing vaccine interventions, which provide ready and new opportunities for catalytic support.

What guided the development of the vaccine and vaccination portfolio strategy was the hypothesis that three critical areas will drive and enable transformative changes in disease impact by HPV immunization: (1) lower-costs and improved deliverability for existing and follow-on HPV vaccines; (2) success in introducing and scaling existing HPV vaccines through the Gavi Alliance; and (3) the robust and careful evaluation of a single-dose HPV vaccination schedule.

Support existing and new HPV vaccine suppliers.
The Foundation has devoted considerable resources and effort in broadly supporting vaccine development targeting pathogens most relevant to poor resources settings. This has been done both by facilitating product development activities so existing vaccines can reach lower costs in more deliverable formats as well as supporting new suppliers to develop more affordable vaccines with a target to achieve World Health Organization (WHO) Pre-qualification status to ensure global access.

HPV vaccines are no exception to this strategy and the Foundation and its partners have supported multiple suppliers, including those in China (Walvax, Innovax) and India (Serum Institute of India), to advance their bivalent, quadrivalent and nonavalent HPV vaccines through development. This includes developing vaccines with appropriate characteristics such as small cold chain footprint, out of cold chain stability profiles and multi-dose vials where technically feasible. It is our belief that a market with multiple high-quality, reliable suppliers is healthier and more sustainable to ensure long-term disease impact.

The Foundation’s HPV vaccine delivery goal is closely aligned with that of Gavi, which is aimed at immunizing 40M girls in world’s poorest populations by 2020

Supporting Gavi in introducing and scaling of existing vaccines – The Foundation’s HPV vaccine delivery goal is closely aligned with that of Gavi, the Vaccine Alliance, which is aimed at immunizing 40M girls in world’s poorest populations by 2020. After Gavi added HPV vaccine to its portfolio of supported vaccines in 2012, the pace of HPV national introductions in Gavi countries has been slower than hoped for even after more than 20 countries implemented the Gavi-supported HPV vaccine demonstration programs. It is likely that a mix of factors had led to this lackluster progress, e.g., limited know-how and experience by countries in achieving effective coverage of the HPV vaccine in an entirely new cohort while managing operational costs efficiently, a prolonged process to receive Gavi sup-
Accelerating national-scale introductions is essential to achieve high disease impact. Girls being missed now for vaccination will be difficult to reach later via other preventative measures. It is also important that only with large-scale vaccine uptake can the value of lower-cost follow-on vaccines be enabled to achieve lower costs.

Evaluating and supporting single-dose HPV vaccination schedules.

The data that has been generated on single-dose HPV vaccination by the studies from Costa Rica [1-4] and India [5] (reviewed earlier in this issue) have provided a surprising and unique opportunity to think differently about these remarkable vaccines. A limitation of these studies was that neither was designed to prospectively assess single-dose schedules. Nonetheless, the authors have used ancillary data to demonstrate similar HPV risk profiles across the study groups which supports their effectiveness conclusions. These surprising results will require further analysis and deeper discussion but provide confidence for sustained efficacy of up to 7 years post-vaccination [4].

The Foundation has made several investments to support further evaluations of single-dose schedules

Among the anticipated new data, the most compelling will likely be from the continued follow-up in the India HPV Vaccine Trial where almost 5000 girls aged 10-18 years of age received a single-dose in 2009 along with two-dose, three-dose, and unvaccinated control groups [5]. As assessments for HPV infection and precancerous lesions only begin after the marriage of enrolled subjects, subsequent analyses will report on increasingly larger numbers of subjects with important clinical endpoints.

A single-dose HPV vaccine schedule could have a significant impact for country decision-making, in particular in settings where there is high sensitivity to cost or delivery challenges. Although much work has been done to understand optimal delivery strategies of this multi-dose vaccine in developing world settings, opening up alternative delivery pathways may be one of the most critical considerations for country implementation. As one example, many countries have deep and highly relevant experience in reaching large and difficult-to-reach populations quickly through campaign style approaches to vaccination (e.g., Meningitis A vaccine, Yellow fever vaccine). These and other options could now be opened with a single-dose vaccine schedule.

The Foundation has made several investments to support further evaluations of single-dose schedules, including immunoassay standardization and support for immunobridging studies in Africa.

As discussed earlier in this issue, a large effectiveness study conducted by the US NCI and the Agencia Costarricense de Investigaciones Biomédicas (ACIB; formerly Proyecto Epidemiológico Guanacaste) of Costa Rica, partially supported by the foundation, is anticipated to begin enrollment in the 2nd half of 2017. [6] (ClinicalTrials.gov identifier: NCT 03180034). This study will prospectively assess comparative effectiveness of a single dose of both the bivalent and nonavalent HPV vaccine with a planned timeline for available data around 2023. While these data remains critical to the body of knowledge on single-dose efficacy, other studies or demonstration projects are under discus-
sion to evaluate single-dose schedule in “real-world” settings and potentially accelerate the impact of single-dose HPV. One strategy previously deployed in Canada and Mexico during the transition from three to two-dose schedule was a bridging period where the third dose would be administered at 60 months after the start of the series. As additional confidence around the immunogenicity of the two-dose schedule accumulated, countries were able to decide whether to give the third dose. Such an approach may be appropriate to evaluate with a single-dose schedule where the second dose would be administered 60 months after the first dose, if needed.

Summary

The Bill & Melinda Gates Foundation is deeply committed to accelerating impact of highly effective interventions to decrease cervical cancer in populations where the need is highest. Opportunities abound to do more through HPV vaccination and the foundation will continue to support work toward delivering the existing and new vaccines with improved coverage and decreased cost. A single-dose HPV vaccine schedule offers a further opportunity to accelerate impact through multi-cohort vaccination programs which otherwise may not be feasible. Advancing decision-making around the next steps for acting on a single-dose HPV schedule will require a broad coalition of stakeholders, including the scientific and public health community, manufacturers, global, regional and national policy makers and the communities that they serve.

References


A tribute to Stefania Jabłońska

Prof. Stefania Jabłońska died on May 8, 2017 in Warsaw, at the age of 96. She chaired the Department of Dermatology of the Warsaw School of Medicine between 1954 and 1990, and trained many students motivated by clinical science. As professor emeritus, she remained remarkably active until she had to face serious health problems. Despite the cold war, S. Jabłońska established many international contacts and collaborations and gained a worldwide recognition for her work on immunological aspects of cutaneous autoimmune diseases, and on HPVs. After her seminal paper “Epidermodysplasia verruciformis as a model in studies on the role of Papovaviruses in oncogenesis”, S. Jabłońska started collaborating with Gérard Orth at the Pasteur Institute in 1976. EV was soon shown to be associated with a specific group of related HPVs and HPV-5 to be the major risk factor for EV skin cancers. Further work dealt with EV HPVs and novel cutaneous or mucosal HPV types, cutaneous warts, nonmelanoma skin cancer, cell-mediated immunity defects in EV, and the possible role of EV HPVs in psoriasis and epidermal repair processes. Stefania Jabłońska will be remembered for her extraordinary intellectual curiosity and power of conviction, and for her impressive propensity to translate new knowledge into the benefit of her patients.

Gérard Orth
NEXT EVENTS

15 hour virtual course on cervical cancer prevention.

Available in English, Spanish, French, Russian, Portuguese, Chinese and Japanese.

With the scientific endorsement of: FIGO, UICC, IARC, WHO/ICO HPV Information Centre, and Elsevier.

With the participation of WHO. Available worldwide free of charge.

More than 12,000 participants enrolled, 70% certified and 85% of students rated the course as good/excellent.

For more information go to www.e-oncologia.org/courses/cervical-cancer-prevention or courseccp@iconcologia.net.

A new scientific Journal devoted to HPV and other small DNA tumor viruses and the official journal of the International Papillomavirus Society.

In 2016, PVR received and evaluated 118 manuscripts and published 36. Published material are currently indexed in PubMed.

Thanks very much to all contributors and supporters.

This issue has been supported by unrestricted educational grants from
### PUBLISHED ARTICLES

| Year 1 No. 01 | Dr. Jose Jeronimo, MD | Interview: The concept of HPV tests adapted to emerging Economies |
| Year 1 No. 02 | Rolando Herrera, MD, PhD | Cervical cancer screening in low and middle-income countries |
| Year 1 No. 03 | Dr. Silvina Arrossi, MPH, PhD | HPV testing in self-collected samples |
| Year 1 No. 04 | Claudia Camel, MD | The careHPV test |
| Year 1 No. 05 | Mauricio Maza, MD, MPH | Use of the GeneXpert test in Malawi |
| Year 1 No. 06 | Prof. Heather Cubie, MBE, BSc, MSc, PhD, FRCPA, FRSE | Experience with care HPV implementation in China |
| Year 1 No. 07 | Dr. Christine Campbell, BSc (Hons), PhD, MPH | Programmatic implementation of HPV testing in Central America |
| Year 1 No. 08 | Dr. Youlin Qiao, MD, PhD | HPV Testing in self collected samples in Uganda |
| Year 1 No. 09 | Dr. Francesca Holme, MPH | Screen & Treat with HPV testing in Low and Medium-Income Countries: pros & cons |
| Year 1 No. 10 | Dr. Francis Contreras, MD | Treatment of precancer lesions: overcoming the bottleneck |
| Year 1 No. 11 | Dr. Gina Ogilvie, MD, MSc, FCFP, DrPH | HPV vaccination impact on a cervical Cancer Screening program: the HPV Fastertialpan study in Mexic |
| Year 1 No. 12 | Dr. Carol Nakisige, MD | HPV vaccination status is not associated with increased risky sexual behavior |
| Year 1 No. 13 | Dr. Usha Rani Poli, DNB, DGO | Interview: From disease elimination to elimination of the oncogenic HPVs |
| Year 1 No. 14 | Prof. Patrick Petignat, MD | Elimination of cervical cancer from developing countries |
| Year 1 No. 15 | Dr. David Morton, PhD | Elimination of cervical cancer from Europe |
| Year 1 No. 16 | Dr. Francis Contreras, MD | Cost-effectiveness of elimination of HPV-cancers |

### OPEN ACCES SUBSCRIPTION  www.hpvworld.com

HPV WORLD will be distributed in e-formats amenable to most standard receptors.

Printed versions will be occasionally prepared for relevant events.

You can contribute by:

1. Subscribing as an interested reader at the web site
2. Inviting subscriptions and dissemination to your agenda
3. Suggesting topics / contributions of interest

Contact us: hpv@hpvworld.com