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Celebrating
HPV Awareness Day
March 4th
CELEBRATING THE HPV DAY 2019

Dear HPV World reader:
2019 and 2020 will witness the definition of the strategy and hopefully the commitment of the World Health Assembly to the WHO’s campaign “Cervical Cancer Elimination as a Public Health Problem”.

The effort will require the direct engagement of hundreds of thousands of health professionals worldwide interacting with populations around screening and vaccination activities and programs, improved access to cancer diagnostics and treatment as well as in issues of palliative care. It will also require a gigantic effort in communication and education to which the HPV community is fully committed.

HPV WORLD is an international project to disseminate to the health community at large the critical consolidated facts on HPV and specially, on its clinical implications (see also www.hpvworld.com)

This issue contains the editor’s choice of contributions published in 2018 including several interviews with prominent scientists in the HPV field.

Xavier Bosch
Director of HPV World
On behalf of the editorial team
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HPV Awareness day: towards cervical cancer elimination

Why an HPV Awareness Day?
Through the work of many scientists in the International Papillomavirus Society (IPVS) and around the world, excellent tools have become available to prevent HPV infection through vaccination, and to better diagnose HPV infection to facilitate screening and secondary prevention of cervical cancer. The advent of these tools has led to a call for elimination of cervical cancer by the World Health Organization, a development that IPVS strongly supports. At the same time, there are key gaps in knowledge among the general population that if addressed, would greatly facilitate the campaign to eliminate cervical cancer, along with other HPV-related cancers that affect both men and women. One of those gaps is awareness of the causative agent of these cancers, HPV.

We believe that awareness of HPV is an important step toward accelerating the implementation of the new tools at our disposal to eliminate cervical and other HPV-related cancers. The International HPV Awareness Day campaign therefore has a global focus on both women and men with a broad age range.

Who is the driving force of the HPV Awareness Day?
International HPV Awareness Day is an initiative of IPVS. This initiative is being implemented in partnership with more than 40 organizations around the world. IPVS believes that increasing the knowledge among the general public of HPV specifically is an important part of the campaign to eliminate HPV-related cancers. By raising awareness of HPV itself, we help people to understand that both men and women are affected by HPV-related disease; that HPV infection is very common, hopefully reducing stigma associated with HPV infection, and that HPV infection is an issue that binds people of all ages, races, sex, gender and geographic location.

Which is the theme for the 2019 campaign?
The theme of the 2019 International HPV Awareness Day Campaign is “Uncover the most viral secret: Ask About HPV”. The campaign makes the point that we spend a lot of time and ener-
The theme of the 2019 International HPV Awareness Day Campaign is “Uncover the most viral secret: Ask About HPV”

gy spreading information that has limited social value; what if instead of “going viral” about sneezing pandas and dress colors, we communicated with each other about viruses that have the potential to kill people, but which can at the same time be prevented from doing so? Having the knowledge is the first step toward taking action, be it getting the vaccine, being screened for cervical cancer and its precursors, encouraging others to be vaccinated or screened, and working with local authorities to improve access for all people to these life-saving measures. We hope that encouraging people to ask about HPV and learn more about this “viral secret” will stimulate people to get more information about HPV and to take preventive measures where possible.

Which activities will take place in the 2019 edition?

Most of the activities will be on International HPV Awareness Day itself, March 4 of every year, but we anticipate that going forward there will be campaign-related activities year-round. Campaign activities will include press releases, rallies, print ads and conversations on a wide variety of social media. People who see our campaign video (www.askaboutHPV.com) will hopefully share it with others and will be stimulated to obtain more information about HPV. This will be in the form of reading the FAQs on the campaign website targeted toward specific demographic groups, and to obtain information from our campaign partners around the world.

How is the 2019 campaign structured?

The campaign is a two-part effort. The first involves publicizing the campaign materials, is designed to attract people’s attention, pique their interest about HPV and start the conversation going. The same materials for this part of the campaign are going to be used worldwide but will be translated into the local language. As in the first year of the campaign, that will be English, French, Spanish, Hindi and Malay.

The second part will give people the tools to educate themselves further about HPV and the measures that they can take for themselves or their loved ones to prevent HPV-related cancers. This part of the campaign is very local and our partner organizations in the different locations will provide web links to educational resources and other prevention tools that are suitable for that location.

What are the future perspectives for the HPV Awareness Day?

In the first year, we targeted 10 countries and we will target the same countries in the second year. In the future we expect to expand the number of countries in subsequent years of the campaign. And even though we are targeting 10 countries in 2019, IPVS has assembled a group of more than 40 organizations around the world who will promote the campaign in many other locations. In future years of the campaign we will expand the number of target countries, languages in which the materials are translated, and number and scope of campaign activities. And each year will have a slightly different theme. In 2019 we will also begin to collect data on the current knowledge of people in different locations about HPV and start the process of measuring the impact of our campaign on that knowledge.

When do you expect to see the impact of the HPV Awareness Day campaign?

We do not expect to see dramatic changes in the...
IPVS has assembled a group of more than 40 organizations around the world who will promote the campaign in many other locations.

level of awareness of HPV right away. However, we do expect that in the long run we will see measurable impact of the campaign as we implement it over several years, and as we adapt our messaging in response to the lessons learned.
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 issue of HPV WORLD (HPW Sept 2017, No 23-32) focuses on HPV vaccination, and presents the state-of-the-science around its use, barriers and promising data suggesting that a single dose, which would ease finance and infrastructure requirements, may be sufficient.

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 the observed efficacy may be real. Our confidence in this finding grew when similar results were observed in the industry-sponsored PATRICIA trial.

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.

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.
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’s 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 Gardasil9® (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 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 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-PIs: Anna-Barbara Moscicki and Yi Zeng). Several immunobridging 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

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.
and document the duration of protection from a one-dose regimen.

What will the audience of HPV WORLD read about in this issue (HPW Sept 2017 No 23-32)?

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.

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!

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*Quote this article as:*

The way forward: the role of the IPV Society now and in the future

The membership of the International Papillomavirus Society (IPVS) covers the spectrum of professionals engaged in all areas of research and practice related to infection and disease caused by Human Papillomaviruses (HPVs). It is a global authority on Papillomaviruses. The Society provides the organisational structure to support this professional community, promoting and facilitating the worldwide exchange of ideas and knowledge, and the translation of these into best practice for clinical and public health interventions in disease prevention and control. These viruses are not a niche group of interest only to the cognoscenti. HPV infection and disease is a global public health problem with infection by one of a small subset of HPVs responsible for 5% of all human cancers, the majority of which are cervical cancers in women.

Scientists and health professionals first met to share their knowledge and ideas about Papillomavirus biology in health and disease in 1975. The small meeting grew to become the International Papillomavirus Conference (IPVC), managed by the Society, and the biggest international papillomavirus conference, with more than a thousand attendees. The last edition of IPVC took place on October 2-6th 2018 in Sydney, Australia, where the latest developments in papillomavirus research from hard core molecular virology to new developments in vaccines, diagnostics and therapies were presented, achievements in the field celebrated and challenges for the future acknowledged.

The mission of IPVS is to contribute to the elimination of papillomavirus-related diseases. A fundamental part of this is raising public awareness about HPV – what is it, how do you get infected, what diseases does HPV cause, can we prevent the infections, can we treat the infections and the diseases, how can we prevent these diseases? International HPV Awareness Day, an initiative sponsored by IPVS, is central to this aim of raising the level of consciousness about HPV in civil society, putting HPV prevention and control on the agenda of policy makers and governments. We, in the Society, recognise the need to engage and inform all stakeholders, from individuals to international bodies, if our mission to “contribute to the elimination of papillomavirus-related disease” is to be achieved. The individual members of IPVS are the authorities on HPV infection and disease control, so the society provides the resources for the global community to access authoritative, independent,

The IPVS is the global authority on papillomaviruses whose mission is to contribute to the elimination of papillomavirus-related diseases

Quote this article as:
A key policy statement for 2018 is a call to action to health authorities to adhere to the WHO international standards to develop prevention plans. Objective evidence-based information and advice on all aspects of HPV. IPVS is therefore ideally placed to coordinate the efforts to meet the objective of International HPV Awareness Day. HPV Awareness Day on 4 March is only the first of a series of steps, each of which builds on the previous one, creating momentum and a sense of urgency to the wider community to meet the challenge of the HPV epidemic.

Advocacy, education and communication about HPV by IPVS are not restricted to one day out of the year but are continuous. Education is fundamental to raising awareness, particularly amongst front-line health professionals who give the vaccines, take the smears and nurse the cancer patients. Developing educational tools for health professionals that dispel the myth about HPV is one of the objectives of the Education Committee for the coming year. The policy committee of the Society is active, generating evidence-based statements of best practice (published in the society journal, Papillomavirus Research) of central issues in the field, such as HPV vaccine safety and immunisation of immunocompromised subjects (Figure 1). A key policy statement for 2018 is a call to action to health authorities to adhere to international standards developed by WHO to develop national, regional and local plans that should ultimately lead to the elimination of cervical cancer. This statement is only the first of what will be a series of policy statements on the interventions we have for the prevention of HPV infection and disease and best practice for implementation of these. These statements will be communicated both via our journal and social and conventional media outlets; we need to engage the wider audience. These are ambitious plans but IPVS brings unique authority, expertise and experience in HPV to the table, to partner with charities, professional societies, international and national institutions and organisations to achieve our mission.

References:
IPVS policy statements. The IPVS Policy Commi-
tee participates in the development of position
statements on central issues in the field related
to papillomaviruses and the development of
prevention of their associated diseases.

IPVS policy vaccine safety statement September
2015
• IPVS strongly endorses HPV vaccination of
all girls and women per the indications spe-
cified by the relevant national regulatory
authorities and vaccination of boys and
men wherever already approved.

• IPVS urges national regulatory authorities
in countries where HPV vaccination is not
currently available to implement HPV vac-
cination in girls and women as soon as pos-
able and to strongly consider vaccination
of boys and men.

The Cape Town Declaration on the Prevention of
Human Papillomavirus Disease
• IPVS believes all countries should consider
and promote national guidelines and pro-
grams to prevent HPV-related diseases, su-
ported by international guidelines, access-
to international expertise and support for
implementation through increased access
to more affordable vaccines and screening
technology.

IPVS statement on HPV vaccination and immu-
nocompromised hosts
• HPV vaccination is safe in immunocompro-
mised people
• HPV vaccines will likely benefit immuno-
compromised men and women, when vac-
cinated in the recommended age range.

IPVS Statement: Moving towards Elimination of
Cervical Cancer as a Public Health Problem
• Combining HPV vaccination at high covera-
ge for adolescents and high coverage of
cervical screening, with appropriate treat-
ment, can eliminate cervical cancer as a pu-
blic health problem.
• Broad dissemination of HPV vaccines has
been achieved in some low and high re-
source countries, but needs to be scaled
up globally.

The IPVS Policy Committee is chaired by S.Garland and includes A.Kaufmann, J. Brotherton, R.
Sankaranarayanan, M. Stanley, N. Bhatla and AB. Moscicki.
All policy statements available at https://ipvsoc.org/.
HPV vaccine hesitancy

What makes the HPV vaccine special?
While vaccines to prevent Human Papillomavirus (HPV) infection have proven to be extremely effective in both protecting against HPV, as well as reducing the risk of cervical cancer caused by HPV strains, acceptance of cancer-preventing vaccine has struggled to reach high levels of acceptance in many countries. Most importantly, it has the least coverage in the poorest countries that have some of the highest burdens of cervical cancer.

What are the main reasons for this low acceptance rates?
The reasons for less-than-optimal coverage are varied, but there are a few themes. The most frequent reasons for hesitation and refusal of vaccination are safety concerns. Some also feel as if the vaccine is too new and without enough safety evidence. Another barrier, especially in low and middle-income countries, is the cost of the multi-dose vaccine. Other reasons for reluctance and refusal include the sensitivities around the vaccine protecting against a sexually transmitted infection. In some settings, cultural mores inhibit doctors from discussing the vaccine with parents. Some parents think the vaccine is given at too young an age to be relevant to their daughter who is not old enough to be engaged in sexual relationships. Other parents have expressed concerns, and refuse the vaccine for their daughters, as they are worried that the vaccine may promote promiscuity - a perception that has been disproved by multiple studies. In some settings, populations have distrusted the vaccine because of suspicions as to why it is only given to girls and not boys, sparking rumours that the vaccine is a ploy to sterilize girls and can cause infertility. Gender-neutral vaccination programmes are more likely to be acceptable and raise fewer questions, rather than those who single out girls only, and targeting reproductive ages.

These are largely reasons expressed by individuals – parents or caregivers, doctors or other vaccinators, or the adolescent girls themselves. In other cases, the introduction of the vaccine is debated at a policy level, with constituencies pushing for and against the vaccine for reasons of cost, debates as to whether the vaccine is needed given options of cervical screening, and notions that big business is influencing government decisions. This mix of reasons for vaccine questioning and refusal, has led in some cases to the suspension of HPV vaccination programmes such as in India in 2010, and the suspension of the HPV vaccine recommendation in Japan in 2014.
A vaccine scare can provoke a dramatic drop in vaccine acceptance across the population as in Japan, where acceptance dropped from over 75% to under 1% or in Colombia, where acceptance dropped from over 85% to 5%, after groups of girls reported neurological and mobility problems suspected to be related to their HPV vaccination. In other instances, there are small pockets of those hesitating or refusing a vaccine, with the general population largely accepting. In cases where there is an individual – or individuals – who lead a constituency against the vaccine, the impacts on the confidence of the population can be significant.

Which is the best approach to deal with a crisis of confidence? When vaccine scares do occur, the most important thing to remember is that facts do not calm emotions. Prompt empathy and listening is very important to those who feel that they – or their children – have been negatively affected by the vaccine. The longer there is no response or no effort to consult with and listen to those affected, the more time there is to spread anxiety, seed suspicions and fuel panic.

Although some encourage focusing on the cancer prevention value of the HPV vaccine as a way to distract from the more sensitive issues around sexuality, it is important to also be transparent about the mode of HPV transmission. HPV is a sexually transmitted infection. Pretending it is only about cancer prevention does not build trust. Celebrate the power of the vaccine in both reducing the risk of HPV infection and preventing cervical and other cancers.

Figure 1: Vaccine scare can provoke a substantial decline in HPV vaccine coverage. In Japan, due to the HPV vaccination crisis, uptake rates dropped from over 75% to under 1%. In Colombia, the vaccine uptakes dropped from over 85% to 5%, after groups of girls reported neurological and mobility problems suspected to be related to their HPV vaccination.
What has been your area of expertise in relation to HPV screening?

Currently our main expertise comprises synthesizing the evidence related to prevention and treatment of HPV-related cancer by performing systematic reviews, meta-analyses and Cochrane reviews. Within our Unit of Cancer Epidemiology which is part of the Belgian Cancer (Scientific Direction of Public Health & Surveillance) of the Sciensano (previously Institute of Public Health) in Brussels, we have built up a core group of young scientists who have learnt the methodology of performing high-quality meta-analyses who are sharing their skill with other international teams. This work is done as contribution to the development of evidence-based practice guidelines. We also have developed new statistical methods and software synthesizing data, such as the \textit{metaprop} for procedure to pool proportions, diagnostic network meta-analysis and pretest-posttest probability plots. Pooling of survival data by digitizing Kaplan-Meier curves is an ongoing statistical project that was initiated at our unit. We also conducted age-cohort-period analyses of the incidence of and mortality from cervical cancer at European and world level.

What is the Cochrane collaboration and which contributions have they made to the HPV field?

The Cochrane Collaboration is an international, independent not-for-profit organization involving a network of researchers, health professionals, patients, carers and people interested in health. Its main objective is to evaluate interventions for prevention, treatment & rehabilitation by producing systematic reviews of primary research using established methods for summarising and reporting evidence. These reviews are published in the Cochrane Database of Systematic Reviews (http://www.cochranelibrary.com/cochrane-database-of-systematic-reviews/).

A few years ago, we received a grant from the Gynaecological Cancer Cochrane Review Collaboration to conduct a number of Cochrane reviews. Several new Cochrane reviews have been accomplished such as those on triage of women with minor cervical cytological abnormalities, the comparison of the accuracy of cytology and HPV tests in primary cervical cancer screening, safety and efficacy of HPV vaccines, and on obstetrical harm associated with treatment of cervical precancer.\textsuperscript{1-4}

We observe today that systematic reviews of important clinical questions are too often repeated by national or regional health technology assessment agencies. This yields a multiplicity of reports of
EU Guidelines on Quality Assurance of Cervical Cancer Screening recommend primary HPV screening in all member states at an interval of at least 5 years and starting from the age of 30-35 years.

heterogeneous quality, sometimes with conflicting conclusions. We advocate international collaboration and coordination to avoid a waste and dilution of resources and maximising quality. The Cochrane collaboration has a world-wide focus and is accessible for all motivated and skilled experts. It can contribute in making future high-quality reviews. We invite young scientists to contact the Cochrane website and to follow their courses. We are happy to observe that our unit in Brussels receives funding from the European Union and also from national organisations (France, the Netherlands, Germany, USA, Australia…) to perform reviews on HPV testing on self-samples, triage of HPV+ women and obstetrical complications following excision of cervical precancer.

Which are currently the guidelines of the EU in relation to HPV screening?
The 2nd edition of the EU Guidelines on Quality Assurance of Cervical Cancer Screening published in 2008 recommended HPV testing in triage of women with atypical cervical cytology and in surveillance after treatment of cervical precancer. The supplements to these guidelines, published in 2015, recommend primary HPV screening in all member states at an interval of at least 5 years and starting from the age of 30-35 years.

Which countries in Europe have clearly switched to HPV screening as an alternative to cytology-based screening?
An overview of countries that have switched or that are planning to switch to HPV-based screening is included in the 2016 Eurogin Roadmap. The Netherlands and Sweden were the two first countries that introduced nationwide HPV-based screening in 2017. In Italy, HPV-based screening is running already in several regional programmes. Several other European countries have made decisions to introduce screening with validated HPV assays. We are proud to announce that also in my country, ministers of health decided (July 2018) to introduce screening with HPV testing only instead of cytology, after long discussions on screening with both cytology and HPV (co-testing).

What is your view on self-sampling for HPV testing in Europe?
From our reviews we concluded that HPV testing on vaginal self-samples using a valid PCR-based assay is as accurate as on a clinician-taken self-samples. Offering devices for self-sampling generally is more effective to reach non- or under-screened women than sending mailed invitations to have a cervical sample taken by a clinician. More details from an updated meta-analysis can be found in Arbyn et al. (HPW 2018 nº 57).

How many HPV tests are considered validated for screening programs?
Two high-risk (hr) HPV tests were validated for cervical cancer screening in randomised trials showing improved protection against cervical cancer: Hybrid Capture II test and the GP5/6+ PCR-EIA. Five more hrHPV DNA tests, fulfilling all the international minimal accuracy and reproducibility criteria, were included in a review of 2015 listing all the validated tests. Three other tests fulfilled partially the criteria. An updated list, actualised in July 2018, adding three more test, is included in Arbyn and Hillemanns (HPW 2018 nº 55).
Integrating the implementation of these new screening tools with vaccination of young girls and young women should make cervical cancer a rare disease in many parts of the world.
REFERENCES:


Self-sampling to reach under-screened women

Even the best organised, free of charge, national cervical cancer screening programs only attracts approx. 3 out of 4 invited women for screening. In Denmark, the 25% non-attending women accounts for almost half the cervical cancers diagnosed annually¹. Reasons for non-attendance varies across the globe, yet universal motives include not liking/embarrassment in connection with the gynaecology examination, issues with access to doctor’s appointments, or quite simply that women don’t think they need screening for one reason or the other². Self-sampling in the comfort of the woman’s own home, in her own good time, and without risk of social, cultural or religious stigmatization offers an opportunity to target one of the largest single challenges of organised cervical cancer screening, the participation rate¹,³,⁴. Here, we will summarize some of our experiences and considerations with self-sampling from the Copenhagen Self-sampling Initiative (CSI), inviting almost 24.000 screening non-attenders for self-sampling.⁵,⁶

Two main strategies have been evaluated: the opt-out (also called “mail-to-all”) strategy where identified non-responders are mailed a self-sampling kit directly, or opt-in where identified non-responders are invited to request a self-sampling kit. Opt-in or Opt-out: That’s the question…

How to best recruit non-attenders to screening is the question, and several clinical trials have investigated self-sampling as alternative to clinical taken samples. Two main strategies have been evaluated, the opt-out (also called “mail-to-all”) strategy where identified non-responders are mailed a self-sampling kit directly, or opt-in where identified non-responders are invited to request a self-sampling kit. The former strategy has the advantage of presenting the self-sampling kit to all non-responders in the hope that more will accept and return a sample for analysis, but the disadvantage is a high loss of unused kits never returned for analysis. In other words, you may recruit more non-responders but it comes at a (costly) premium. The opt-in strategy has the advantage of lower costs by only shipping the kits to women who after invitation actively request the kit. The disadvantage is that non-responders will have to go through the additional step of actively ordering the self-sampling kit which may lead to a lower participation.² Table 1 shows key features from a selection of HPV self-sampling studies.

In terms of participation, the studies vary widely. From 6.4% (Szarewski et al, UK, Opt-out) to 39% (Sanner et al, Sweden, Opt-in), reflecting the design of the self-sampling approach, the population targeted, when and where². At
### Table 1
Summary of studies assessing different invitation strategies for self-sampling

<table>
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<tr>
<th>Invitation strategy</th>
<th>Country &amp; Study design</th>
<th>Study size</th>
<th>Target age (years)</th>
<th>Participation Rate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opt-in</strong></td>
<td>Denmark Cross sectional</td>
<td>N=4874</td>
<td>27-64</td>
<td>20% by self-sampling+10% by clinician taken samples after invitation</td>
<td>Lam J.U.H. et al., Int J Cancer 2017</td>
</tr>
<tr>
<td></td>
<td>Sweden Cross sectional</td>
<td>N=369</td>
<td>35-50</td>
<td>32.0%</td>
<td>Stenvall H. et al., Acta Derm Venereol 2007</td>
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<td></td>
<td>Sweden Cross sectional</td>
<td>N=3000</td>
<td>30-58</td>
<td>39.0%</td>
<td>Sanner K. et al., Br J Cancer 2009</td>
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<td></td>
<td>Sweden RCT</td>
<td>N=800</td>
<td>30-62</td>
<td>16.0%</td>
<td>Broberg G. et al., Int J Cancer 2014</td>
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<td><strong>Opt-out</strong></td>
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<td>N= 2546</td>
<td>30-50</td>
<td>28.9%</td>
<td>Bais A.G. et al., Int J Cancer 2007</td>
</tr>
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<td></td>
<td>UK RCT</td>
<td>N=27,792</td>
<td>30-60</td>
<td>26.6%</td>
<td>Gök M. et al., BMJ 2010</td>
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<tr>
<td></td>
<td>Finland RCT</td>
<td>N=8000</td>
<td>30-65</td>
<td>39.0%</td>
<td>Gyllensten U. et al., Br J Cancer 2011</td>
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<td></td>
<td>Sweden RCT</td>
<td>N=1500</td>
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<td>6.4%</td>
<td>Szarewski A. et al., Br J Cancer 2011</td>
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<td></td>
<td>UK RCT</td>
<td>N=2,397</td>
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<td>Virtanen A. et al., Cancer Epidemiol Biomarkers Prev 2011</td>
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<td></td>
<td>Finland RCT</td>
<td>N=2000</td>
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<td>Wikström I. et al., Br J Cancer 2011</td>
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<td>Netherlands RCT</td>
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<td></td>
<td>Sweden RCT</td>
<td>N=1000</td>
<td>32-65</td>
<td>14.7%</td>
<td>Darlin L. et al., J Clin Virol 2013</td>
</tr>
<tr>
<td></td>
<td>France RCT</td>
<td>N=8,829</td>
<td>35-69</td>
<td>18.4%</td>
<td>Sancho-Garnier H. et al., Int J Cancer 2013</td>
</tr>
<tr>
<td></td>
<td>UK RCT</td>
<td>N=3,000</td>
<td>25-65</td>
<td>13.0%</td>
<td>Cadman L. et al., J Med Screen 2014</td>
</tr>
</tbody>
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current it is not possible to point to Opt-in or Opt-out as the universally superior option, and HPV self-sampling as a supplement to organised cervical screening should be designed and operationalized with respect to the screening program it is proposed to supplement. In our setting, of 23,632 women invited, 20% returned the self-sample for analysis with 39% of those being long-term unscreened (≥10 years unscreened).5

Figure 1
Response and participation rate by letter, webpage, phone and email

The effect of HPV self-sampling on screening participation
Most often, in studies on HPV self-sampling, a group of women are offered clinician-based sampling. We however, also focused on the screening participation by clinician-taken samples after the non-attenders received the invitation for self-sampling, acknowledging that the total participation rate of a self-sampling initiative will consist of both. In our setting, an additional 10% of the non-attenders invited for self-sampling chose to have a clinician-taken sample. Overall, this resulted in 30% participation rate.

HPV self-sampling to screening non-attenders should not only be evaluated on the number of returned samples, but also include derived screening activity

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Figure 2
Proposed follow-up strategy for HPV-positive women by self-sampling.
The point is, that introducing HPV self-sampling as an alternative to screening non-attenders should be evaluated not only on the directly measurable effect in terms of returned brushes for analysis. The derived “motivational effect” for screening participation may be substantial amongst non-attenders. Passive register follow-up in 2017 of the women invited for CSi showed that two years after the invitations for self-sampling, 18.2% of the invited women had a regular, clinician-taken sample registered. This is an increase from the 10% in the implementation period. Without arguing this as a direct effect of the self-sampling invitations, at least it indicates that a large proportion of screening non-attenders are susceptible to accept screening. In retrospect, it may not be surprising that women presented with options for screening actively choose between those options.

The power of communication
“The single biggest problem in communication is the illusion that it has taken place” wrote George Berhard Shaw. Communication strategies are pivotal to informing women about screening and why it is important to participate. One of the key design items we focused on in CSi was to provide relevant information and facilitate easy access to “Opt-in” by offering a web-based response platform. The special designed web-page system with app-like features included a re-directing QR code on the invitation letter for smart phone, tablets or computer use knowing that 95-98% of all Danish women have access to a smart phone or similar devices. Moreover we focused on offering language options other than Danish on the web-platform, thereby attempting to bridge any linguistic divides. Looking at all responders, almost 40% used the electronic platform for opting in (Figure 1), underlining that offering easy ways to accept the invitation is beneficiary for accruing participation. The effect of multi-language information is yet to be reported, but almost 30% of those accepting self-sampling were of non-Danish origin, which is double-up compared to the proportion of non-Danes in the general population.

HPV self-sampling is a viable supplement to recruit screening non-responders
From an operationalization point of view these are interesting points. Firstly, communication through web and app-based platforms holds a huge potential to improve the user experience compared to letter-based correspondence, but it also confers large cost savings on postage for the program. Secondly, language versions of invitation and web-based contents require a small effort for a potentially great gain in participation. We are currently exploring these items in more detail in the coming three years, 2017-2019, as self-sampling is rolled out as a supplementary offer to screening non-attenders in our program.

Bringing HPV self-sampling into the organised screening program
HPV self-sampling to increase screening participation is becoming an essential supplement to organised screening. Yet, a number of key features still need to be addressed to ensure optimal performance of self-sampling in organised screening programs. Firstly, how to follow up HPV-positive women by self-sampling? Here we propose a conservative strategy (Figure 2) referring HPV-positive women for a clinician-taken sample for cytology and HPV co-testing. Based upon this follow-up sample, the woman can be referred in concordance with standard-of-care practice, national recommendations or guidelines, in effect shuttling her into the organised screening program. Loss to follow-up after self-sampling has been voiced as a concern, but in CSi, 87% (N=639) of the self-sampling positive women went for follow-up. This resulted in an initial detection of 101 ≥CIN2 cases with more to come as follow-up becomes more complete over...
time. But does the follow-up necessarily have to be by regular, clinician-taken sample? Or could a subset of women benefit from being referred directly for colposcopy saving them at least one gynaecological examination? This is still an open question that should be addressed weighting the balance between the absolute minimum required versus too many examinations, knowing that the examinations are often the barrier to screening.

Risk-based triage strategies using genotype information or methylation markers could potentially come in play, given that both types of analysis can be conducted directly on the original self-sample. Finally, routine self-sampling emphasises the need for HPV assay validation criteria on self-samples. However, no joint international recommendations or requirements have been established to this end.

In conclusion, HPV self-sampling is a viable supplement to recruit screening non-attenders. How and in which way HPV self-sampling will be part of organised screening programs must be defined locally, in order to get the best synergy effects with the regular screening program. At the end of the day, what matters is getting non-responders screened.

Disclosure of interests:
JB used to serve as a paid advisor to Roche and Genomica, and has received honoraria from Hologic/Gen-Probe, Roche, Qiagen, Genomica, and BD diagnostics for lectures. He is principal investigator on studies funded by BD diagnostics, and Qiagen Ltd. DE has no interests to declare.

References:


Italian consensus conference on cervical cancer screening in HPV-vaccinated women: recommendations

In Italy, HPV vaccination is actively offered free of charge to 12-year-old girls since 2007–2008 (depending on the region). In addition, some Italian regions have extended active offer to older female age-groups, including also girls in their 15th year of age.

In the near future, these cohorts of women will be reaching the age for screening (25 years). This happens while screening is moving from being cytology-based to HPV-based. This situation represents a challenge but also an opportunity for unprecedented reorganisation of cervical cancer prevention.1

In November 2015, the National Screening Monitoring Centre Directive and the Italian Group for Cervical Screening (GISCi) Coordination Committee in collaboration with different scientific professional societies for gynaecology, colposcopy, histo- and cytopathology, virology and virology organised a Consensus Conference aimed at the collection of available evidence required to define the best screening policy for girls vaccinated against HPV. The Consensus Conference identified and defined the central and local actions to be implemented in order to optimize the integration of primary prevention programs with secondary prevention programs, as well as research activities connected with the knowledge needed for change. Further, for each question, a Jury made recommendations and expressed an answer, which could be: (I) consensus for the recommendation; (II) consensus for the recommendation but need for reformulation, providing relevant indications; (III) no consensus for the recommendation.

The Italian integral report is published on the internet,2,3 and has been officially presented to decision makers: the Ministry of Health and the State-Regions Conference. An English summary has been also published.4 Here we present the recommendations as answers to four main policy questions handled by the group.

Question 1: Do the protocols for screening programs need to be changed upon the arrival of the cohorts of vaccinated women? If so, which policy appears to be the most effective and operatively manageable, a tailored or a one-size-fits-all strategy? Recommendation: First, the Jury stresses the fact that screening activity must continue and be performed within organized screening programs also for vaccinated women.
Second, the Jury considers changing the screening program protocols upon the arrival of the vaccinated cohorts as appropriate. The Jury recommends that tailored protocols, according to vaccination status, are gradually extended to all Italian Regions, in parallel with the implementation and validation (for quality and completeness) of IT systems.

Tailored screening could at some point be replaced by one-size-fits-all screening protocols, when the vaccination coverage has reached such levels that infections from HPV16/18 (included in the vaccines currently used) can be considered practically negligible. This, according to the Jury, could be well below 95%.

**Question 2: At what age should screening start? Which test should be used? How often should it be done?**

**Recommendation:** For girls vaccinated in their 12th year, the Jury accepts the proposal to move the starting age for screening from 25 to 30 years, using HPV test as primary screening test. For non-vaccinated women, the current protocol must be continued, with cytological screening in the frame of 25-29 years and HPV test with cytology triage from age 30 to 64.

The Jury recognizes the lack of evidence on the optimal interval between screening rounds in vaccinated women, while acknowledging the strong rationale for an interval longer than 5 years, the interval currently recommended in the female population in general. Furthermore, the Jury adheres with full consent to the proposal to promptly start studies on this issue.

**Question 3: Should the strategy be different for the cohorts vaccinated in their 15th year (or later) with respect to those in their 12th year?**

**Recommendation:** The Jury is favorable to the recommendation not to change current screening protocols with primary Pap test for women vaccinated in their 15th year or later. Indeed, the estimated median age of sexual debut in Italy is 17 years old. Hence, it can be assumed that less than half of the girls vaccinated in their 16th year and more than half of those vaccinated subsequently have already had sexual intercourse and therefore may not be HPV-naive at vaccination (Table 1).

**Question 4: Which actions need to be scheduled from now and up to 2021 in order to acquire missing evidence and to make the integration of primary and secondary prevention practically possible?**

**Recommendation:** The Jury underlines the need to implement a link between vaccination records (indicating the number of doses, vaccination date of each dose and type of vaccine administered) and screening registers, and recommends the construction of archives at a regional and national level reciprocally connected.

The Jury also considers that a substantial effort should be dedicated to training healthcare operators, so that they can provide to the general population useful and scientifically correct information on the changes to screening practices, their efficacy, the type of test used and the starting age.

The Consensus Conference identified and defined the central and local actions to be implemented in order to optimize the integration of primary prevention programs with secondary prevention programs.
Vaccination at 12th year of age
( primary target of the organized vaccination program)

**Background:** Presumably HPV-naïve at the time of vaccination and thus with an expected high vaccine efficacy.

**Strategy:** A tailored strategy (according to vaccination status), followed by one-size-fits-all strategy when the high vaccination coverage minimize the burden of HPV16/18 infections.

Primary screening using HPV-test (with cytological triage in HPV-positive), with a screening starting age delayed to 30 years.

**Screening interval:** Strong rationale for an extension of interval over 5 years. Needs to be evaluated in clinical studies.

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Vaccination at ≥15th year of age

**Background:** A relevant number of these girls may have already been infected at the time of vaccination, and thus the level of protection of HPV vaccines is not well identified at this time.

**Strategy:** Current protocol must be continued (cytological screening in the frame of 25-29 age and HPV test, with cytology as triage, from age 30 to 64).

**Screening interval:** To be decided after the CIN3+ detection rate at the 2nd round in HPV-negative women.

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Moreover, the Jury also underlines the need to promote conducting studies:

1. to monitor the activities of both programs and to provide appropriate epidemiologic surveillance. As vaccination implementation increases and more cohorts will be involved, the evidence of protection will also increase and therefore we will have more robust post-vaccination data.

2. to identify conservative protocols using HPV test also in women between 25 and 29 years.

3. to conduct surveys aimed at identifying tools/methods and appropriate ways to communicate the change of screening to women and clinicians.

4. to assess whether the nonavalent HPV vaccine may change the fundamental elements of the decision-making tree presented in this document. Indeed, in the future predicted scenario of higher prevention with the new vaccine of cervical pre-cancer lesions (which are the target of the screening program) harms of screening may outweigh its benefits. □

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**Table 1**

Recommendations for cervical cancer screening in vaccinated women
References:


HPV vaccines: the herd protection impact

Since 2007, 87 countries around the world have implemented publicly-funded HPV vaccination programmes.\(^1\) The decision to introduce HPV vaccination programmes was mainly based on results from large international randomized clinical trials showing the safety and high efficacy of HPV vaccines against HPV infections, anogenital warts, and precancerous cervical lesions, and on mathematical models predicting substantial decreases of HPV-related diseases in the population through vaccination. Now that a decade has elapsed since the introduction of HPV vaccination, it is crucial to examine how the results from randomized trials and mathematical models are translating in the real world. When examining this real world impact, we have to keep in mind that the unique characteristic of vaccination is that it not only decreases the occurrence of infection and diseases among vaccinated individuals, but it also indirectly protects unvaccinated and susceptible individuals.\(^2\) Indeed, when a large proportion of a population becomes immune against an infection, it provides indirect protection for those not immune; the greater the proportion of immune individuals in a population, the smaller the probability of contacting an infectious individual and getting infected. This concept of indirect protection of unvaccinated individuals is known as “herd immunity or herd effects”.

To estimate the population-level effects of girls-only HPV vaccination programs, we performed a systematic review and meta-analysis of time-trends studies examining changes in HPV-related endpoints (HPV infections, anogenital warts, precancerous cervical lesions), between the pre- and post-vaccination periods, in girls and young women targeted for vaccination (direct effect) as well as in boys, men and older women (herd effect).\(^3\) For anogenital warts, we identified 10 studies from 7 high-income countries (HIC) using the quadrivalent vaccine (U.S.A., Canada, Sweden, Denmark, Germany, New Zealand, and Australia)\(^4\)\(^-\)\(^13\) that examined the changes in anogenital warts between the pre- and post-vaccination periods. Figure 1, previously published in Lancet Infectious Diseases (Drolet et al.\(^3\)), illustrates the pooled changes in anogenital warts during the first 4 years of girls-only quadrivalent HPV vaccination (compared to the pre-vaccination period). In countries with high vaccination coverage of girls (≥ 50%), there was a steep and significant decrease of anogenital warts among girls and women aged less than 30 years old (A). On the other hand, in countries with vaccination coverage below 50%, the decrease was observed exclusively among girls aged less than 20 years old, and it became statistically significant in the third year of the start of vaccination (B). Interestingly, the steep and significant decrease of anogenital warts also occurred among boys and men aged less than 30 years old, in countries with high vaccination coverage of girls (C). Noteworthy, at the time of performing this meta-analysis, boys were not yet included in HPV vaccination programs. Therefore,

Our meta-analysis was the first to show a substantial difference in the population-level effects of HPV vaccination between countries with high vaccination coverage compared to low vaccination coverage

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**Figure 1**

Pooled changes in anogenital warts during the first 4 years of girls-only HPV vaccination programs with the quadrivalent vaccine*.

A) Females – High female coverage (≥50%)³

B) Females – Low female coverage (<50%)†

* Reprinted from Lancet Infectious Disease, 2015 May; 15(5): 565-80, Copyright (2017), with permission from Elsevier
C) Males - High female coverage (≥50%)

D) Males – Low female coverage (< 50%)

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¥ High coverage: the results from the following studies were combined depending on the years of follow-up available: Year 1 and 2: Oliphant 2011, Baandrup 2013, Ali 2013; Year 3 and 4: Ali 2013.

† Low coverage: the results from the following studies were combined depending on the years of follow-up available: Year 1: Leval 2013, Kliewer 2012, Flagg 2013, Nsouli-Maktabi 2013, Mikolajczyk 2013; Year 2, 3, 4: Leval 2013, Flagg 2013, Nsouli-Maktabi 2013; Bauer 2013.

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re, the decreases in anogenital warts observed in boys and young men are most likely attributable to herd effects from girls-only HPV vaccination. It is also important to note that these herd effects are observed exclusively in countries with high vaccination coverage of girls. Indeed, most of these countries had vaccination coverage higher than 70% and/or vaccinated multiple cohorts of girls. The main results presented here for anogenital warts were also observed for the prevalence of HPV infections in our meta-analysis.3

To our knowledge, our meta-analysis was the first to show a substantial difference in the population-level effects of HPV vaccination between countries with high vaccination coverage compared to low vaccination coverage. Meta-analyses are, by definition, a statistical approach that combines the results of multiple studies and they represent a powerful tool to examine questions that are difficult or impossible to examine within single studies.14, 15 In the current context, our meta-analysis made it possible to examine the direct and herd effects of different HPV vaccination programs by comparing data from countries with different programmes and vaccination coverage. However, this meta-analysis pooled data from time-trend ecological studies and, therefore, we cannot conclude about a causal relation between HPV vaccination and the observed decreases in anogenital warts. Nonetheless, several observations strongly suggest that the observed decreases in anogenital warts are associated to HPV vaccination. Firstly, the decreases were larger in groups targeted for vaccination (girls and young women) compared to the other groups. Secondly, these decreases were also larger in countries with high vaccination coverage compared to countries with low vaccination coverage. Thirdly, these decreases are getting larger over time as the number of vaccinated cohorts increases. The results of our meta-analysis are likely generalizable to most HIC, but should be generalized with caution to LMIC.

In conclusion, this meta-analysis cumulated data from 125 million person-years of follow-up from 7 HIC and clearly illustrated that HPV vaccination programs are effective at the population-level and quickly provide herd effects when vaccination coverage is high. These results reinforce the need for vaccinating a high proportion of the targeted population to maximize and accelerate the direct and herd effects of HPV vaccination in the real world.
References:


Responding to false or misleading media communications about HPV vaccines

Scientists have traditionally responded to vaccination opposition by providing reassuring safety and efficacy evidence from clinical trials and post-licensure surveillance systems. However, it is equally critical for scientists to communicate effectively the scientific evidence and the public health benefits of implemented vaccine programs. This is most challenging when the media focus on adverse events, whether real or perceived, and when non-scientific information about vaccination is presented as fact. Such attention has often been handled effectively (e.g. Australia, Canada, and UK). In some countries however, media coverage has negatively influenced public perception and HPV vaccine uptake because of the lack of a rapid, organized scientific response. Such a case arose in 2013 in Japan regarding the HPV vaccine. The situation there was compounded by the national government’s decision to suspend its recommendation of the vaccine. Not surprisingly, HPV vaccine coverage plummeted despite substantial safety evidence (figure 1).

Given the potential for adverse public health impacts, advocacy by scientists and health care providers is vitally important to maintain public confidence in vaccination and to support program resilience. We believe that scientists have a moral duty to participate in public life by sharing their knowledge when false or misleading media coverage threatens public health. This moral duty exists because: 1) misinformation can directly cause harm (e.g. by preventing the potentially life-saving benefits of vaccination from being achieved); and 2) scientists are able to explain the scientific evidence that can counter false and misleading claims. To increase our effectiveness in communicating such knowledge, it is essential to understand the fundamental differences between scientific and journalistic modes of communication.

Science aims to build knowledge by reason, experimentation, creation, aggregation, and analysis of data. Scientific communications tend to be concise, conservative in reaching conclusions, and written in technical language relatively inaccessible to those outside the field. Journalism aims to inform and to entertain non-expert audiences. Stories told from individual perspectives, and with high emotional content, are much more easily understood and remembered by the public than a data heavy, peer-reviewed medical journal article that provides facts couched in scientific dense language. Consequently, the story of a single adverse event can carry more weight in the public imagination than safety data generated by a study of millions of vaccinated people.

A particular concern in media reporting of vaccination issues is the issue of ‘false balance’, which is the equal presentation of scientifically unequal claims.
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The Global Advisory Committee On Vaccine Safety (GACVS) considers HPV vaccines to be extremely safe.  
There is overwhelming international support for HPV vaccination.

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www.HPVWorld.com, 73
A particular concern in media reporting of vaccination issues is the issue of ‘false balance’, which is the equal presentation of scientifically unequal claims. Journalists tend to seek opposing perspectives on an issue in order to provide, or appear to provide, objectivity and neutrality in reporting. Such reporting can create a false sense of balance, giving readers the impression that two opposing positions have equal credibility or weight, even if the overwhelming consensus of opinion and data supports one side. By giving an equal voice (and thus equal legitimacy) to a non-expert such as an anti-vaccination campaigner or to an adverse case report, even well-intentioned journalists may cause significant erosion of trust in vaccination. They may inadvertently create the impression that there is controversy when in fact there is none. It is challenging to convey the weight of scientific evidence in such a context.

Scientists believe people should be persuaded by data and reason; however people tend to filter messages and arguments through their pre-existing beliefs and experiences, and are more preoccupied by risks than benefits. Anti-vaccine activists’ fallacious claims about vaccination harm are refractory to scientific reasoning. Audiences who hold beliefs that are incongruent with the message will often reject the message, reject the scientific evidence, or reconstruct the message to accord with their own beliefs. Messages most affect those who are undecided or whose beliefs are already consonant with the message. People also have a tendency not to interpret mass media messages as being about them personally, but about society at large. When people do not think a particular issue is relevant to them personally, then they may process the message superficially, and be more vulnerable to new and contradictory information.

With these points in mind, the following suggestions may help scientists to craft effective messages to respond to false or misleading HPV vaccine media stories (Box 1). Speaking with the media is a particular skill and not all scientists or practitioners will wish to, or need to, assume this role (see Box 2 for other important advocacy roles). Helpful resources are available online (e.g. http://sciencemediasavvy.org/dealing-with-the-media/) and formal media training is invaluable for anyone who will regularly speak to journalists. For more in-depth guidance, we recommend the WHO’s guidelines on responding to vaccine deniers and its HPV vaccine program resources (at http://www.who.int/immunization/diseases/hpv/resources/en/). Importantly, though we focus here on traditional media, online and social media have changed the landscape from top-down (expert to public) communications to horizontal dialogues. It is increasingly necessary to develop effective tools to respond to false and misleading discussions that take place online.

It is increasingly necessary to develop effective tools to respond to false and misleading discussions that take place online.
Box 1
Suggestions for publically responding to negative communications in the media

1) Check that you are the right spokesperson
Is it appropriate for you to provide comment (do you have the relevant expertise?)

2) Be prepared
Understand the background facts and issues under discussion. Check with your jurisdiction’s immunisation program before commenting on a breaking story concerning adverse events following immunisation to ensure that you have the relevant scientific and policy information and that key messages are aligned.

3) Identify your audience
Anti-vaccination campaigners are unlikely to be swayed by scientific evidence. Your audience is the general public, some of whom will be undecided and receptive to scientific evidence, and will use the media to gather information on HPV vaccination. The goal generally will be to mitigate the negative impact of the media story on this audience. The message should be tailored for the general public and take into account their likely pre-existing beliefs.

4) Identify the story’s angle, and how your scientific expertise supports the story
Ask in what context the information will be published or aired. If the piece is written, then ask whether you can review the text including any quotes attributed to you before publication. (If you are writing a response, then build a compelling story to help your audience better recall your message.)

5) Choose one or two key messages to repeat
The audience will generally recall only a few take-home messages from a media story. Identify the message that is most important to convey. Repeat it during the interview so that the message will more likely be used as a ‘sound bite’ by the journalist and be remembered by the audience.

6) Correct the content and unmask any fallacious arguments. Do not reiterate your opponent’s arguments
Avoid repeating inflammatory questions from journalists or the fallacious arguments because repetition can reinforce the misinformation in the audience’s mind, and your words may subsequently be taken out of context. Do not take on anti-vaccination campaigners point for point. You will likely lose your audience and your patience. Instead, focus on what you wish to convey and on providing accurate information about the important role of vaccines.

7) Underline scientific consensus
It is important to convey the weight of the scientific evidence to counter false journalistic balance and the fallacious perception that all media respondents have an equal claim to the truth. You represent not only your own research or clinical practice, but also the scientific consensus on HPV vaccine efficacy and safety.

8) Make the issue relevant to the individual
Emphasize the personal benefits of HPV vaccination and the personal responsibility and value of vaccinating one’s children to help audience members become more invested in the message, and more likely to believe that vaccination recommendations apply to them. Concrete examples consistent with scientific evidence can have powerful effects. Inviting parents to consider how they might feel if their child becomes ill with a vaccine-preventable illness can make the issue relevant to the individual.

9) If your work or scientific evidence has been inaccurately reported in the media, write a concise letter to the editor suitable for publication
While the inaccuracy may not be immediately rectified, the editors may pay further attention in the future. If the editor does not take your letter seriously, you may also file a complaint with your country’s regulatory media agency (e.g. National NewsMedia Council, Press Complaints Commission).

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Box 2

Advocacy for vaccine science: some suggestions

1) **Share positive vaccine stories on social media and with individual patients**
   Health care providers and public health professionals are often parents themselves, and may even have seen first-hand cases of HPV-related diseases. Parents can be reassured by knowing why a health professional chose to vaccinate his or her own children. Telling non-identifying stories about what people suffer when they have HPV-related cancer can present a compelling counterpoint to alleged vaccine injury stories. Vaccination also prevents precancerous cervical lesions, which are much more common than cervical cancer and whose diagnosis and treatment cause substantial emotional and physical suffering, including early delivery and resulting prematurity. Adding personal comments or anecdotes will help the message resonate and encourage further sharing.

2) **Respond when someone posts dubious or anti-vaccine material**
   It can be hard to speak up when you don’t want to be seen as argumentative or difficult; yet by merely posting that you disagree and linking to relevant articles, blogs or sites which contain further information can assist those with no or little knowledge of the field to see that the posted information is inaccurate. Your small intervention can provide reassurance about what most other people actually think and do in relation to vaccination.

3) **Monitor anti-vaccine and junk science publications in your own field of expertise**
   Such articles are often published in predatory journals but they can sometimes appear in mainstream journals that like to attract controversy. Call out the scientific issues. Write a concise letter to the editor (suitable for publication) arguing for the retraction of unsound science.

4) **Communicate with like-minded scientists**
   There are many vaccine supportive communities for both professionals and the public online. Examples include The Vaccine Page on Facebook for parents and vaccineinfo.org which provides links to helpful resources for vaccine advocacy and information. Useful resources for countering vaccine misinformation include summaries of current issues in skeptic community blogs (e.g. skepticalraptor.com).

**References:**

Latency or new infection? Evidence-based counseling in the era of HPV-based screening

High-risk (HR)-HPV testing is rapidly replacing Pap smear cytology as the primary cervical cancer screening modality in both high and low-middle income countries. The use of HR-HPV testing in routine screening is strongly supported by a well-accepted natural history model of cervical cancer (Figure 1) and evidence from numerous observational studies and randomized trials. However, we operate in a context of relative uncertainty when it comes to our ability to provide evidence-based answers to patients’ concerns about their HR-HPV test results. All cancer screening programs are associated with the anxiety of screening positive for cancer or precancer. However, testing for HPV, which is a sexually transmitted infection (STI), introduces an entirely new psychosocial burden in women participating in cervical cancer screening. In our zeal to validate and implement HR-HPV-based screening advances, we have perhaps neglected to generate a complete individual-level understanding of the natural history of HPV infection over a woman’s lifespan.

Testing for HPV, a sexually transmitted infection (STI), introduces an entirely new psychosocial burden in women participating in cervical cancer screening

To illustrate these gaps, consider a woman who was 35 years old when HPV testing was introduced as part of her routine screening program, and has completed three cycles of HPV testing. Her first ever HPV test was positive, the second negative, and the third again positive. As illustrated in Figure 2, each step of the diagnostic chain precipitates new anxieties and concerns about what the testing results mean, her risk of cancer, her ability to proactively intervene, and the implications on her intimate relationships. These questions are complex and the answers elusive because of the remaining uncertainties in our understanding of the natural history of HPV infection in individuals across their lifespan. The green natural history transitions in Figure 1 illustrate the two most critical areas of uncertainty in an otherwise well-established model: First, do the antibodies developed after natural infection confer protection against reinfection with the same HPV type? and second, once we test HPV negative, has the virus completely cleared or has it become latent? While extant data cannot provide unequivocal answers, a comprehensive review of HPV natural history studies does, in fact, provide strong ‘circumstantial evidence’ that the HPV natural history in an individual can follow a number of non-mutually exclusive pathways over the course of a lifetime. While we are still trying to understand which of these pathways predominate in any population or at various ages, the evidence is strong enough to provide more specific answers to address individual patient concerns.
Natural history model of HPV infection and cervical cancer. Transition states in red represent a well-established natural history model of cervical cancer caused by HPV infection. Transition states in green represent transition states in the natural history of the HPV infection over the course of a lifetime. These transitions are supported in the literature but consensus agreement regarding the frequency of the transition and proportion of all infections following these paths has not been reached. The dashed lines reflect the uncertainty in the natural history of HPV. Namely, it is unclear whether anti-HPV antibody developed following natural HPV infection protects against reinfection (1), and whether loss of HPV detection reflects virologic clearance or establishment of viral latency (2).

In Figure 3, we illustrate in the center an initial HPV-positive screening test result. The collective literature suggests that the answer to the question “How did I get HPV?” may reasonably be one of several options as shown in the upper part of Figure 3. This may be a recently acquired infection from a new sex partner or possibly a re-infection from a long-term partner. It could also represent a false-positive result due to deposition of HPV DNA from a recent sexual encounter that is present in the genital tract but not causing an infection. These explanations are more likely if the woman is young and sexually active. While younger women acquire new partners at a much higher rate than older women, we note that new partners increase the risk for new HPV detection at any age. However, since new partner acquisition rates decline as women age, the fraction of detectable HPV that is attributable to a new partner is estimated to be substantially lower in older, compared with younger women2,3. It is also possible that this first HPV test result re-
fects long-term persistent infection. This path is more highly correlated with lifetime sexual history than with current sexual behaviors. Finally, the positive result could reflect autoinoculation to the genital tract from the anus or another epithelial site. In general, the lack of an HPV testing history in a woman dealing with her very first HPV test result allows us to make generalized explanations for “where did this come from and how long have I had it?” The best we can do is to say “probably from sexual activity, either recently or sometime in your distant past”.

The answers to the questions that follow next in this accumulated HPV testing history are less straightforward. In our example, this woman is re-tested 1 year later and her test is negative. This is a reassuring result in the context of worry about a disease diagnosis since it is widely accepted that persistent detection of HR-HPV is the primary risk factor for progression to precancer/cancer. However, it raises different concerns about what going from HPV test positive to test negative means about her future risk. Can we assure her that the virus is really gone or is just ‘hiding out somewhere’? (Figure 2 uncertainty #5). Can she get re-infected now that she has ‘cleared’ the virus and if yes, should she get the vaccine to protect against re-infection? (Figure 2 uncertainty #3)? When she is tested again in 3 years, she is again positive for HR-HPV, raising questions about partner infidelity and/or whether she is destined to have this virus and the associated cancer risk for the rest of her life.

Figure 2
Patient concerns through repeated HPV screening results
To answer these questions, the literature provides credible evidence that a ‘cleared’ HPV result may represent at least two different natural history paths. It may truly indicate viral eradication; in this case the woman is no longer infected, and either develops protective immunity from re-infection or does not, in which case she is at continued risk of either re-infection with the offending type from her same partner or from a new partner. If recurrent HPV detection occurs on this natural history path, it will be due to her current sexual activity. It is believed that a susceptible woman in this scenario would benefit from prophylactic HPV vaccination.

In a second scenario, the ‘cleared’ HPV does not represent viral eradication at all, but simply control of the infection below the limits of detection. Convincing evidence from multiple studies of immune compromised, sexually abstinent, older, less sexually active populations, and adolescents with long-term intensive follow-up support the existence of this path. This scenario is sometimes referred to as ‘HPV latency’, though it is still unclear whether HPV establishes a strictly defined latent viral state or just persists at extremely low viral loads that are not detectable by most assays. These semantic differences are irrelevant distinctions in the clinical context. The important fact is that in this path, an infected woman tests HPV negative. The evidence is clear that there is a definable and not uncommon risk that these ‘controlled, undetectable’ infections recur. Studies suggest that recurrent detection of the same type occurs in at least 10-20% of type-specific infections observed to clear. We note in Figure 3 that a return to positivity through this path is related to the ability to retain immune control rather than recent sexual exposures, and therefore there is no need to suspect infidelity in a relationship as a requisite explanation for an HPV test result transition from negative to positive. Rather, the latency path is dependent on the cumulative sexual history (i.e., past exposures), as the likelihood of harboring a latent infection with reactivation potential increases with higher number of past sexual partners. And, since women accumulate more partners with age, the fraction of HPV-positive tests that are attributable to this path of latent virus reactivation (or intermittent detection of low viral loads) is higher in older than younger women.

With respect to the value of HPV immunization in this natural history scenario, it has long been assumed that prophylactic vaccines will only protect against newly acquired infection. However, data from the mid-adult female vaccine trials show very clear efficacy in the subgroups of women who have baseline antibodies against vaccine type HPV (suggesting past infection). Because current sexual activity was not included in this analysis, it is unclear whether vaccine-induced antibodies protected against re-infection (if natural antibodies from seropositive individuals were not protective), or whether vaccines reduced the risk of HPV reactivation, perhaps through reduced lateral spread and autoinoculation. The validity of proposals such as HPV-FASTER, which seek to implement an integrated screening and vaccination program in women up to age 45 years, would benefit greatly from studies designed to differentiate these two possible explanations for vaccine effectiveness in women with prior infection.

Finally, a history of non-consecutive positive HPV screening results will become more and more common as women accumulate an HPV test history. While we know that persistent detection in consecutive tests poses a significantly greater risk of progression, we will need to continue to moni-

**We will need to continue to monitor whether risk of precancer/cancer is increased in women with non-consecutive positive tests relative to those who consistently test negative.**
HPV infection: natural history paths over a woman’s lifetime and impact on HPV-based screening test results. Shaded rectangles represent clinical HPV screening test results; red shading indicates HPV test positive, green shading HPV test negative. Green font represents scenarios in an HPV uninfected individual, red font represents an HPV infected individual.

Figure 3
Individual HPV natural history paths over a lifespan

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tor whether risk of precancer/cancer is increased in women with non-consecutive positive tests relative to those who consistently test negative.

The integration of HR-HPV testing into screening has enabled the development of more sensitive, feasible, and cost-effective programs to accelerate the reduction in global cervical cancer burden. As we continue to scale-up these programs and hone optimal screening and management algorithms, development and delivery of educational messages to address women’s questions and concerns about their HR-HPV testing results remains critical. In addition, continued research is needed to fill in the gaps in our understanding of individual-level HPV natural history to guide patient-provider counseling about test results.

References:


International e-learning program on cervical cancer prevention

- 15 hour virtual course on cervical cancer prevention.
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