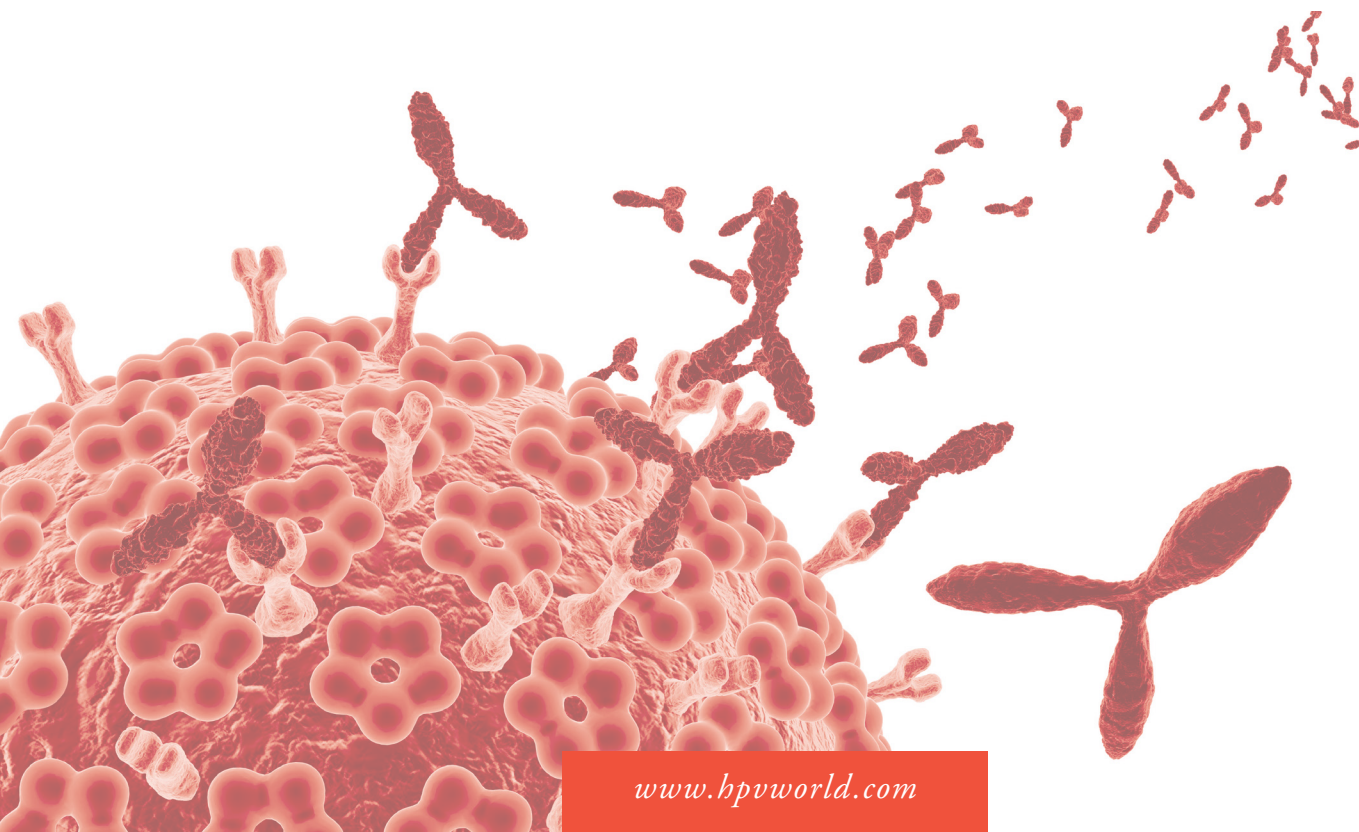


# HPVWorld

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Mireia Montserrat, Olga Guillen, Jo Waller, Laura A.V. Marlow, Gregory D. Zimet, Mark A. Kane  
& Xavier Bosch*



*Celebrating*  
**HPV Awareness Day**  
*March 4th*



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C/Octavi Bruix, 7  
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The Association for Strategic Innovation Vegga (Vegga) is a non-profit association regulated and compliant with all regulatory rules and public audits that are applicable under the Spanish laws (National Registry of Associations and Foundations numb: 7.172.15-july-2003).

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# HPVWorld

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*We know HPV is a family of viruses that can cause cancer*

*We have excellent HPV vaccines and screening tests*

*We can envisage cervical cancer elimination*

# Edit



# orial

## HPV Awareness day

In 2018, the International Papillomavirus Society (IPVS) is launching the project “**INTERNATIONAL HPV AWARENESS DAY**”, with the concept “**GIVE LOVE. NOT HPV**”. The day is to be celebrated every 4 March and over 70 international and national societies have already joined in a consortium of partners to promote the activity. The slogan selected for the 2018 HPV awareness day is “**HPV AFFECTS EVERYONE**”.

Estimating the burden of disease outcomes caused by HPV deals firstly with the number of HPV infections and HPV-related diseases, including cancer. To this end, HPW has teamed up with the HPV information Centre and other research teams. Created in 2003, the IARC/ICO Information Centre compiles and updates scientific data on HPV infection and HPV-related cancers for each one of the 192 countries in the world, in an open-access and reader-friendly format. The Centre also provides standard summaries of the existing preventive options and opportunities. The “national fact sheet” query offers a global overview of the impact of the viral infections and its reported preventive options for each country. The “data query” option allows for more targeted searches to be displayed on demand. Any interested party in the world can access the system and generate the data of interest to increase awareness on this relatively new virus, and its consequences and the status of the national preventive options (<http://www.hpvcentre.net/> and [info@hpvcentre.net](mailto:info@hpvcentre.net)).

Three contributions based on the Information Centre program summarise the burden of HPV infections (**Bruni L.**), the spectrum of diseases linked to HPV (**De Sanjosé S. and Tsu V.**) and the HPV type distribution in anogenital and head

and neck cancer in an international context (**Alemany L. and Serrano B.**).

The finer details of the concept “HPV affects everyone” are addressed by the gender-neutral nature of HPV infections as shown by the HPV studies in male cohorts (**Giuliano A. and Albero G.**). The lifetime risk of HPV-related cancers in survivors of an HPV-related cancer or even transient episodes of genital warts points at the existence of highly susceptible groups and is clearly suggested by a population-based study in Denmark (**Kjaer S.**). The study encourages further research on the mechanisms that determine HPV persistence or clearance and, thus, the lifetime risk of HPV-induced cancers.

Over and above statistics, the HPV story also includes the largely hidden social and emotional impact of a still relatively unknown sexually transmitted infection and its relation to cancer. Issues around sexuality seem to be a relevant determinant of the HPV vaccine acceptance rates and remain strongly affected by the sexual taboos predominant in most communities around the world. The personal impact of HPV detection on self-esteem and the circle of individuals affected around an “HPV case”, as well as the critical role of access to information, are explored (**Waller J. et al.**). The potency of the e-learning technology in disseminating information is presented as well as an invitation to a free access educational course. (**Diaz M. et al.**) ([www.e-oncologia.org](http://www.e-oncologia.org)).

Lastly, some of the critical next steps forward in education and prevention are provided by the forthcoming president of the IPVS (**Stanley M.**), the chair of the 2018 HPV awareness day (**Palefsky J.**) and the launch of the scientific discussion towards disease elimination (**Kane M. and Giuliano A.**).

The definition of the achievable impact afforded by current vaccines and diagnostic tools for HPV screening is the clearest indication on the way the scientific community perceives the way forward and signals the challenge of setting the international goal to the relevant decision makers.

**F.X. Bosch**  
*Editor HPW*

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## **Eliminating HPV related diseases as a public health problem: Let's start with cervical cancer**



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# Joel Pal

## Why an HPV Awareness Day?

International HPV Awareness Day is an initiative of the International Papillomavirus Society (IPVS). This initiative is being implemented in partnership with more than 70 organisations around the world. It has emerged out of the acknowledgment that few people are aware of HPV as an infectious agent and its role in several important cancers including cervical cancer, anal cancer and oropharyngeal cancer.

Unlike other campaigns, this campaign is not focused on a specific disease but rather on the virus that causes it, i.e., HPV. Another major difference between International HPV Awareness Day and other campaigns is a global focus on both women and men with a broad age range. Our focus on HPV allows us to educate the public about the high proportion of people who acquire a genital HPV infection at some point in their lives; that HPV affects both men and women; and that even if a given person does not have HPV infection themselves, there is a high likelihood that they care about so-

**The tagline for the campaign is "Give Love. Not HPV", emphasizing that prevention of HPV-related cancers is an act of love**

meone in their life who is at risk of HPV-related cancer.

An understanding among the general public of the role of HPV supports the continuum of measures designed to prevent HPV-associated cancers, from vaccination to screening. Ultimately, we believe that elimination of HPV-related cancers is possible but it will require a sustained prevention effort among both women and men worldwide. We believe that International HPV Awareness Day is an important step in that direction.

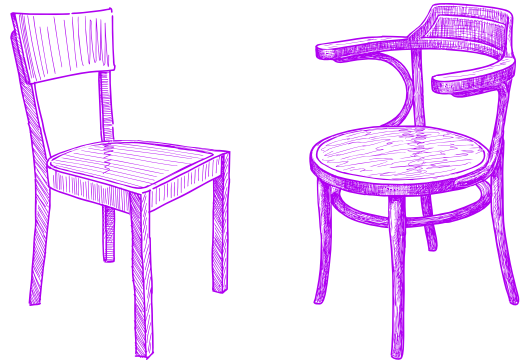
The tagline for the campaign is "Give Love. Not HPV", emphasising that taking care of yourself and/or your loved ones to prevent HPV-related cancers is an act of love. The logo shows a red heart representing love merging below into a black X, representing stopping HPV (Figure 1). We think that this is a powerful and positive message that we hope will stimulate people to get more information and to take preventive measures where possible. In parts of the world where preventive measures are not yet fully in place, we hope the campaign will increase public awareness with the goal of accelerating the implementation and availability of these measures.

## What is the proposal for the 2018 edition?

This will be an ongoing campaign but the theme of the first year is "HPV affects everyone".



# efsky

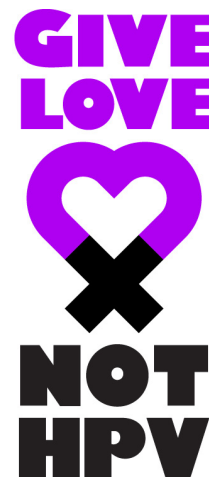


Most of the activities will be on International HPV Awareness Day itself, March 4 of every year, but we anticipate that going forward there will be campaign-related activities year-round.

Campaign activities will include press releases, rallies, print ads and conversations on a wide variety of social media. The campaign is really a 2-part effort. The first part of the campaign, which 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. For the first year of the campaign that will be English, French, Spanish, Hindi and Malay. The second part is designed to 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?

For our first year, we are targeting 10 countries but we expect to expand the number of countries in the following years of the campaign. And even though we are targeting 10 countries in 2018, IPVS has assembled a group of more than 70 organisations 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 although the campaign logo will remain the same, each year will have a slightly different theme. ■



*Figure 1:* Logo of the International HPV Awareness Day. The tagline for the campaign is "Give Love. Not HPV". The logo shows a purple heart representing love merging below into a black X, representing stopping HPV.

**The first edition of the HPV Awareness day will take place on March 4th 2018, and annually thereafter**



**LOVE IS EVERYWHERE.  
UNFORTUNATELY,  
SO IS HPV.**



Over 80% of people will get HPV at some point in life.  
Protecting ourselves and loved ones requires both  
detection and prevention.

[GiveLoveNotHPV.com](http://GiveLoveNotHPV.com)



n° 28

# 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. This year, from 2-6 October, IPVC will take place in Sydney, Australia, where the latest developments in papillomavirus research from hard core molecular virology to new developments in vaccines, diagnostics and therapies will be 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 PVs whose mission is to contribute to the elimination of PV-related diseases**



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## **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. ■

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Figure 1  
IPVS policy statements



**IPVS policy statements.** The IPVS Policy Committee 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 specified 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 vaccination in girls and women as soon as possible 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 programs to prevent HPV-related diseases, supported 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 immunocompromised hosts**

- HPV vaccination is safe in immunocompromised people
- HPV vaccines will likely benefit immunocompromised men and women, when vaccinated in the recommended age range.

**IPVS Statement: Moving towards Elimination of Cervical Cancer as a Public Health Problem**

- Combining HPV vaccination at high coverage for adolescents and high coverage of cervical screening, with appropriate treatment, can eliminate cervical cancer as a public health problem.
- Broad dissemination of HPV vaccines has been achieved in some low and high resource 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



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# The frequency of HPV infection worldwide

Epidemiological research over the last decade has demonstrated that Human Papillomaviruses (HPV) are the most widespread and common sexually transmitted infections worldwide (1). It has been estimated that more than 80% of sexually active women and men will acquire at least one HPV infection by the age of 45 years (2). However, most of them will be transient infections without any clinical impact. In women, 90% of incident HPV genital infections clear within two years (3).

To quantify and compare the burden of HPV infection across populations, in 2010 we combined 194 studies from 59 countries (4) through meta-analysis. This analysis pooled results from close to one million women with normal cytological findings who were tested for HPV with PCR techniques or Hybrid capture 2. Findings showed that on average, 12% of women worldwide had a detectable cervical HPV infection (5). The estimate varied by geography and age (Figure 1 and Figure 2). These cross-sectional measures include both incident and persistent HPV infections, and average the differences that are observed with age in a single estimate.

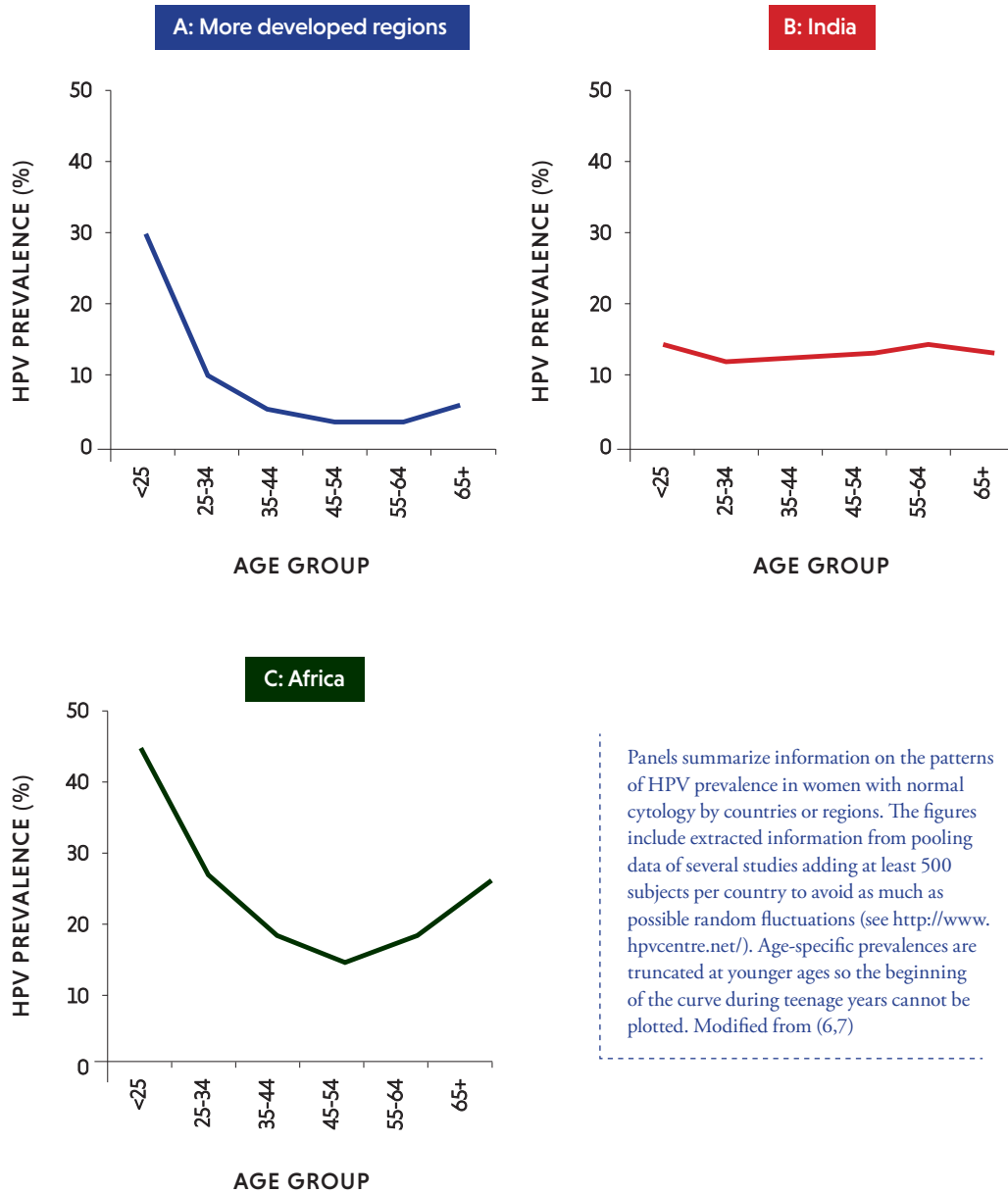
**On average, 12% of women worldwide had a detectable cervical HPV infection varying by geography and age**

HPV prevalence is strongly associated with age. We observed three main patterns of HPV distribution by age (Figure 1). Most of the populations showed a large peak of HPV incidence in the first years after the onset of sexual activity (mostly during adolescence and in their twenties), which decreased and stabilised thereafter (Figure 1A). The two additional patterns included a flatter pattern across age groups observed mainly in Asian countries, represented here by the data in India (Figure 1B), and a bimodal pattern (Figure 1C), especially in Latin America but also observed in Africa, with a first prevalence peak at younger ages (just after sexual debut), a lower prevalence plateau at middle ages, and a variable rebound at older ages ( $\geq 45$  years).

Age-specific and overall HPV prevalence is significantly determined by long-term patterns of sexual behaviour of the population both in women but also in their male counterparts, and the impact of cervical cancer preventive practices (7). These age and sexual patterns translate into the observed geographical differences in the overall prevalence (Figure 2). African and Latin American regions showed higher average HPV prevalence estimates than European, Northern American and Asian regions. Country-specific adjusted HPV prevalence ranged from 1.6% to 41.9%. It is important to note that in our meta-analysis, we found that heterogeneity in the HPV detection methods and the selection and representativeness of the populations were the most influential variables to explain geographical differences.

Figure 1

HPV prevalence estimates in women with normal cytology by age group



When including more recent surveys, the ICO/IARC HPV Information Centre ([www.hpvcentre.net](http://www.hpvcentre.net)) shows increasing prevalence from the low-risk regions depicted in [Figure 1](#) and a tendency towards similar levels of baseline HPV prevalence globally (6). In recent years, with the widespread use of HPV DNA detection techniques and their inclusion in screening programmes, the number of studies reporting the prevalence of HPV infection in samples approximating the general population has rapidly expanded, as has the use of more standardised and therefore comparable methodologies. One of the main challenges in the interpretation of meta-analyses is to accommodate the methodological heterogeneity across studies.

## **In women with normal cytology, high-risk HPVs account for 70% of HPV infections**

Another important aspect of this study's findings referred to type-specific HPV prevalence in women with normal cytology. The vast majority of detected HPV infections included high-risk HPV types. HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59—classified as group 1, “carcinogenic to humans” by IARC—were found to be the most common types everywhere, accounting for 70% of HPV infections. Vaccine-targeted types 16 and 18 were the most frequent types worldwide, with HPV16 being the most common type everywhere. HPV18 and other oncogenic types, such as types 52, 31, 58, 39, 56, and 51, shared similar prevalence and were the most common HPV types after HPV16. HPV31 was very common in Europe and Latin America but was much less common in North America or Asia, where it was surpassed by HPV52. HPV18 ranked in the top positions in most regions. ■

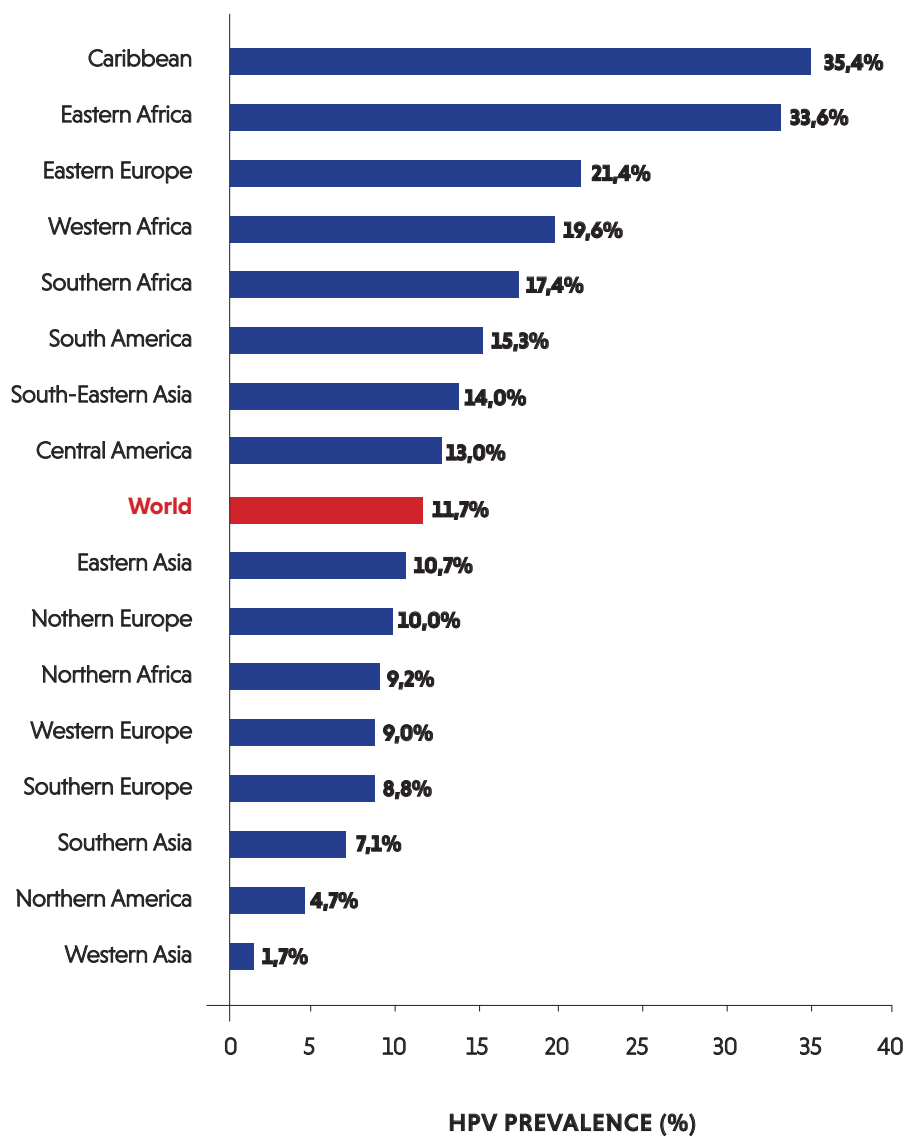
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Figure 2

HPV Prevalence in women with normal cytology by geographical regions



Meta-analysis of 1,016,719 women with negative cytological results. Adjusted HPV prevalence standardized by the regional geographical structure. Ref. (6)



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# Spectrum of HPV related diseases

## Anogenital cancers

Human Papillomavirus (HPV) affects many of us. Some HPV infections are powerful biological agents that use human cells to survive and spread to other hosts, largely through sexual contact, causing disease in humans. Although a generally good immunological status usually prevents these infections from persisting in the host, some will remain and induce disease of various types. The spectrum goes from relatively benign lesions, like genital warts, to cancer. HPV accounts for one of the most common cancers in women, which is cervical cancer (Figure 1). Approximately 4.5% (640,000 cases) of new cancer cases diagnosed in the world are associated with a persistent HPV infection. In women this represents around 570,000 cases per year (or 1,561 each day!), of which 80% will be cervical cancer (1-2).

In addition to cervical cancer, persistent HPV infection is responsible for a variable fraction of cancers of the anogenital region including vulva, vagina, penis and anus, adding up to approximately 68,500 cancer cases annually. Of these, 30,000 cases will be in men (17,000 in the anus and 13,000 in the penis) and 38,500 cases in women (18,000 in the anus, 8,500 in the vulva and 12,000 in the vagina) (1).

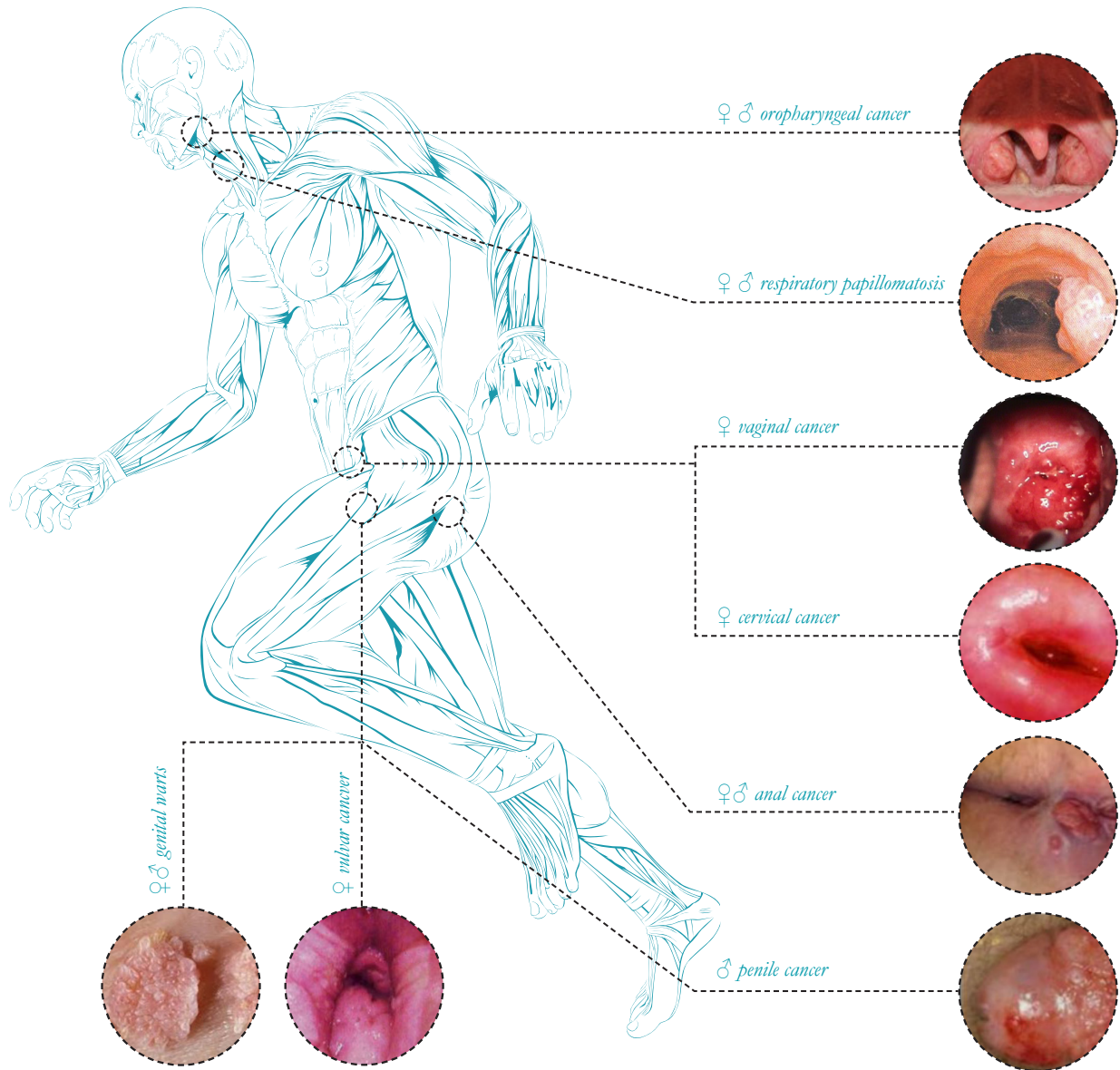
**HPV infection causes up to  
4.5% (640,000 cases) of all  
new cancer cases worldwide**

Cervical cancer is the fourth most frequent cancer among women and the fourth leading cause of cancer deaths worldwide, with an estimated 528,000 new cases and 266,000 new deaths in 2012 [2]. Cervical cancer is particularly observed in women with no use of (or no access to) cervical cancer screening. Out of 100 cases of invasive cervical cancer, 84 will be reported in women living in poor resource settings where access to cervical cancer screening and treatment remain scarce (Figure 2).

Sustained decreases in the incidence of cervical cancer have been recorded in most developed countries during the last part of the 20th century followed by stability of the rates during the 21st century. Recently, some Latin American and Asian countries are reporting declines in the incidence rates [3]. Although introduction of regular screening followed by adequate treatment are the most obvious triggers of such trends, changes in co-factors such as reproductive and sexual behaviour can also contribute to time variations in risk. For example, delaying age of sexual initiation, reducing the number of sexual partners or having fewer children may indirectly contribute to lower acquisition of HPV infections and ultimately affect incidence of HPV related cancers.

Of all the HPV types with oncogenic potential, HPV16 remains in the pre-vaccination era the most predominant type in all locations, and particularly in sites other than the cervix. The contribution of HPV16 exceeds 80% of all HPV-positive cancer cases [4].

*Figure 1*  
Spectrum of HPV-related diseases in women and men



Annually, in women HPV infections cause 530,000 cancer cases in the cervix, 18,000 in the anus, 8,500 in the vulva, 12,000 in the vagina and 5,500 in the oropharynx. In men, HPV infections cause 17,000 cancer cases in the anus, 13,000 in the penis and 24,000 in the oropharynx. Ref. (1)

### Precancerous anogenital lesions

HPV infection is involved in the majority of precancerous anogenital lesions, including cervical intraepithelial neoplasia (CIN). Their early detection is strongly dependent on screening practices, as they are generally asymptomatic. Data are, however, limited as these precancerous lesions are rarely reported in cancer registries. Nevertheless, between 263,227 and 503,010 cases of CIN2+ were diagnosed in Europe in 2015. To these, an additional 51,763 cases of high-grade anogenital lesions in men and women add to the overall burden [5]. A variable proportion of these lesions could regress spontaneously, but once they are detected, they require treatment and close follow up. The majority will probably benefit from surgical elimination. Multiple infections and a wider spectrum of different HPV types are more commonly detected in precancerous lesions compared to cancer cases, but HPV16 is still the commonest type detected in all sites [4].

## Genital warts have decreased significantly since the HPV vaccine was introduced

### Genital warts

Genital warts are a common, relatively benign manifestation of HPV infection, largely attributable to HPV6 and 11. Genital warts occur around 12 months after initial exposure [6]. Genital warts are not a notifiable disease in most countries, and as a result, available data on the burden of these lesions in the general population are limited and derive from few studies. It is estimated that 85 to 205 cases of genital warts per 100,000 people occur annually. The incidence is higher in younger adults and in women [6-7].

Between 379,330 and 510,492 new cases of genital warts in women and between 376,608 and 427,720 in men are estimated in Europe every year [5]. Surgical or topical treatment of the lesions is not always satisfactory and relapses are common. However, in recent years after the introduction of national immunisation programmes using HPV vaccines that cover HPV6 and 11 types, a substantial reduction in the incidence of genital warts in vaccinated populations has been observed. Genital warts have also decreased in non-vaccinated men in countries with high vaccine uptake, indicating a herd protection effect [8].

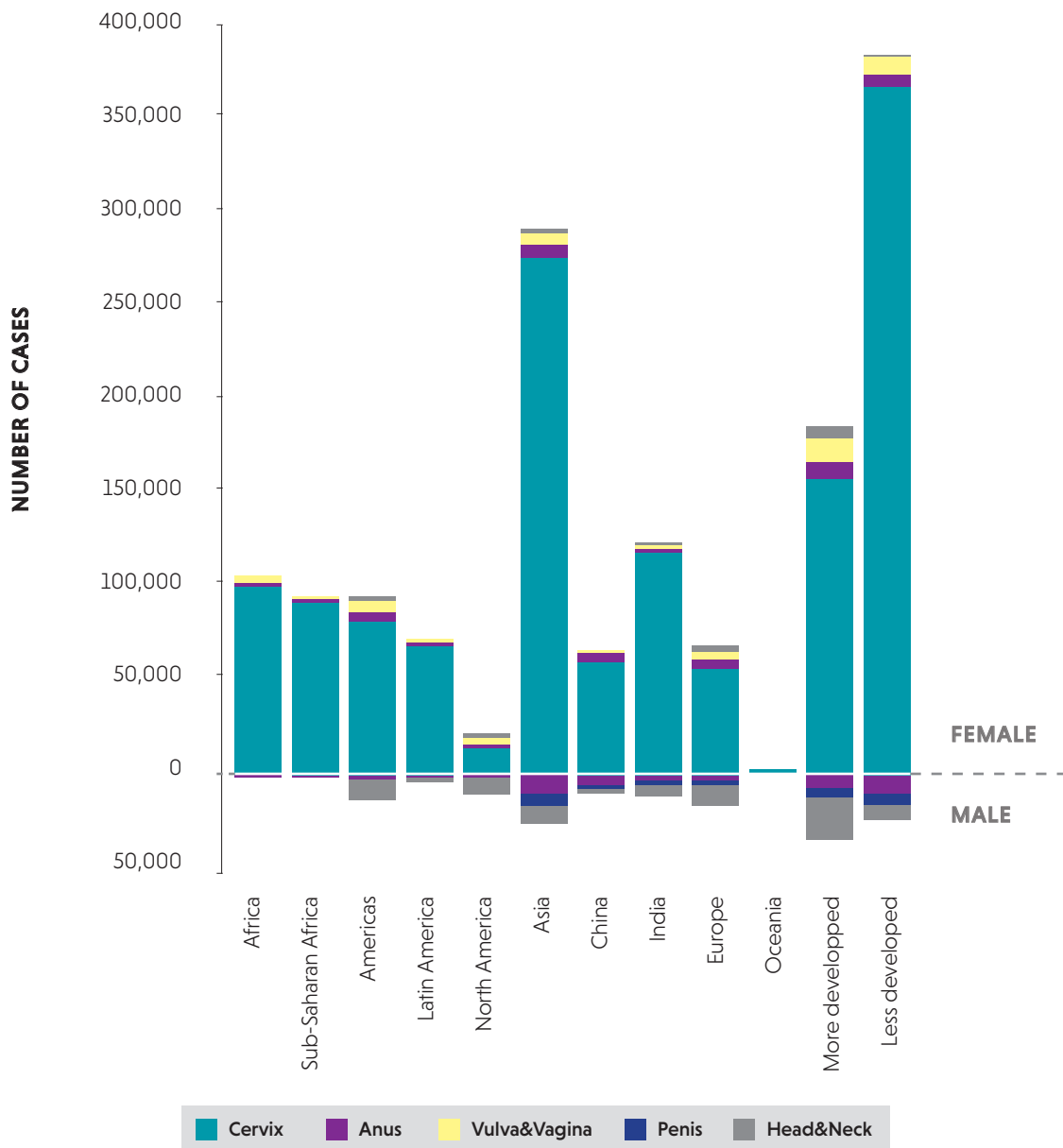
### Head and neck cancers

In recent years, an unexpected development in HPV cancer epidemiology has been observed with the increasing contribution of HPV to head and neck cancers. While traditionally these cancers were almost uniquely attributed to tobacco and alcohol exposure, it is now recognised that HPV is also in the aetiological pathway, particularly in the oropharynx. HPV-related oropharyngeal cancers constitute an epidemiological, molecular, and clinically distinct form as compared to non-HPV-related cancer. Globally, 456,000 head and neck cancer cases are diagnosed every year worldwide, and 37,200 cases are attributable to HPV-- specifically 29,000 in the oropharynx, 4,400 in the oral cavity and 3,800 in the larynx [1]. HPV-associated cancers of the head and neck are more commonly seen in high-income countries, while they are rarely diagnosed in low-resource settings. The natural history of HPV-related cancers remains poorly understood, but evidence is being accumulated

## HPV-associated cancers of the head and neck are more commonly seen in high-income countries

Figure 2

Burden of cancer cases attributable to HPV infection by region, cancer site and sex



Adapted from (1)

that HPV infection through oral sex is one of the most consistent independent risk factors with an additional synergistic effect of smoking or alcohol consumption [9]. The impact of amygdalectomy remains unclear, although this surgical procedure was extensively applied in those countries where increasing incidence trends of head and neck cancers are seen.

## Conclusions

HPV-related diseases represent an important health burden worldwide. Full quantification of their burden is limited by the absence of routine data in many countries. The best available estimations indicate that, in addition to cancers, precancerous lesions and genital warts create a substantial burden of disease worldwide. Vaccination and screening are important interventions that could lead to a major reduction of HPV-related diseases. ■

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# HPV Type specific contribution to cancer

Human papillomavirus- (HPV) related cancers remain a major cause of cancer in both men and women. Worldwide, HPV infection causes up to 4.5% (640,000 cases) of all new cancer cases (8.6% in females; 0.9% in males), representing 29.5% of all infection-related cancers (1,2). HPV infection is unequivocally linked to almost all cervical cancer cases and a large proportion of anal cancer (approximately 88% of cases are attributable to HPV infection) (2). HPV is also causally associated with a varying percentage of cancers of the vulva (25%), vagina (78%), penis (50%) and a subset of head and neck cancers, particularly oropharyngeal cancer (31%) (2).

Prophylactic HPV vaccines have been introduced worldwide since 2006 with a high efficacy and safety record in the prevention of vaccine-type HPV infection and disease. Furthermore, the vaccines show a high effectiveness profile on preventing infections, precancerous lesions and genital warts, as well as a robust herd-protection effect in non-vaccinated population when a high vaccine coverage rate is achieved (3). Currently, three HPV vaccines are commercially available (bivalent, tetravalent and nonavalent). All three contain virus-like particles (VLPs) of HPV types 16/18. The tetravalent vaccine also contains VLPs from HPV types 6/11. The nonavalent vaccine additionally protects against HPV types 31/33/45/52/58. The World Health Organisation (WHO) recognises the importance of HPV-related diseases as global public health threats and has reiterated the recommendation to include HPV vaccines in national immunisation programmes (4). By October 2014, 80 countries (mainly

high- and upper-middle income) had implemented HPV vaccination programmes and 47 million women had received the full course of vaccine.

In this context, precise knowledge on the HPV type distribution in HPV-related cancers is essential in order to estimate the potential impact of HPV vaccines and HPV testing in screening programmes.

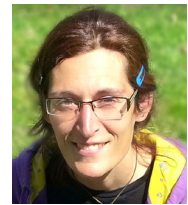
Original data from the ICO international studies on HPV in HPV-related cancers included 10,575 cervical cancer cases, 496 anal, 1,709 vulvar, 408 vagina, 1,010 penile, and 3,685 head and neck cancers (5-10). These surveys aimed to give robust estimates on HPV prevalence and type-specific relative contribution (type distribution among HPV positive cases) in HPV-related cancers. HPV positivity based on at least two biomarkers related to HPV (HPV DNA and p16 or mRNA E6\*I) ranged from 83% in anal cancer to around 4% in laryngeal and oral cavity cancers. In other sites, the percentages of HPV positivity found were: 71% vagina, 28% penis, 25% vulvar and 22% oropharyngeal cancers. Regarding HPV detection in oropharyngeal cancer, it is worth noting that a high geographical variation in the HPV attributable fraction was described. For type-specific contributions we consistently estimated that HPV16

**High risk HPVs included in the nonavalent HPV vaccine accounted for almost 90% of the cervical cancer burden worldwide**



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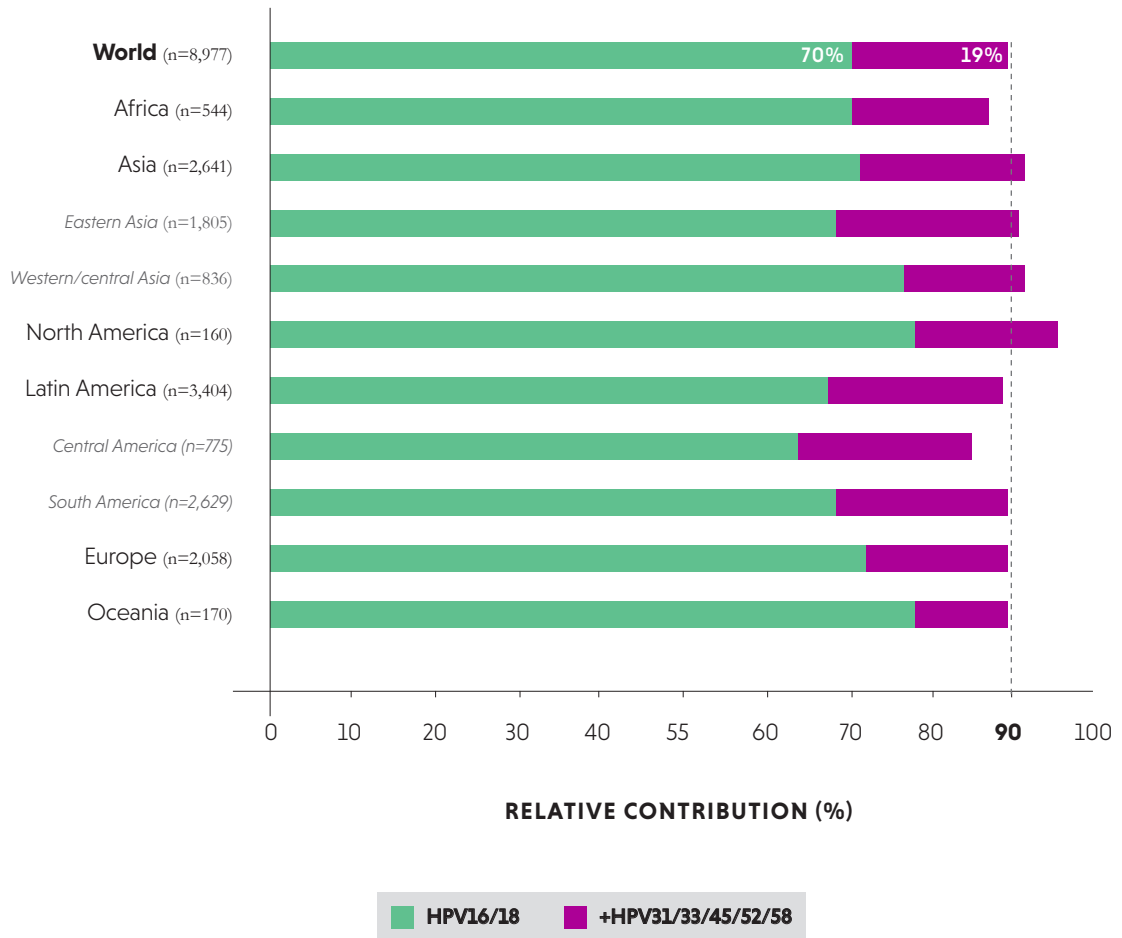


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Figure 1

Relative contribution (%) of 7 HPV vaccine types among HPV/DNA positive cervical cancer cases by region



Modified from (11)

and 18 account for 70% of cervical cancers worldwide. The additional 5 high-risk types included in the nonavalent vaccine accounted (together with HPV16/18) for almost 90% of the entire cervi-

cal cancer burden in the world. These estimates slightly varied and were consistent across all geographical regions (Figure 1). For other anogenital and head and neck cancers, HPV16 was by far the most



Figure 2

Ranking of the 7 most common HPV types in HPV-related cancers

	Cervix	Vulva	Vagina	Penis	Anus	Head and Neck
1 <sup>st</sup>	HPV16	HPV16	HPV16	HPV16	HPV16	HPV16
2 <sup>nd</sup>	HPV18	HPV33	HPV31	HPV6	HPV18	HPV33
3 <sup>rd</sup>	HPV45	HPV18	HPV18	HPV33	HPV33	HPV35
4 <sup>th</sup>	HPV33	HPV45	HPV33	HPV45, 35	HPV31	HPV18
5 <sup>th</sup>	HPV31	HPV52	HPV45,58	HPV59	HPV58,6	HPV26
6 <sup>th</sup>	HPV52	HPV31, 56	HPV52	HPV18,52,11	HPV35	HPV45
7 <sup>th</sup>	HPV58	HPV58, 6	HPV51	HPV58	HPV11	HPV52
<b>AF among HPV positive cancers (%)*</b>	<b>90</b>	<b>88</b>	<b>86</b>	<b>88</b>	<b>95</b>	<b>96+</b>
<b>TOTAL AF (%)**</b>	<b>80</b>	<b>25</b>	<b>64</b>	<b>30</b>	<b>84</b>	<b>12</b>

The attributable fraction (AF) in red\* refers to the proportion among HPV positive cancers that is attributable to any of the 7 HPV types. The AF in black\*\* refers to the fraction of total organ-specific cancer attributable to any of the 7 HPV types. Ref. (5-10)

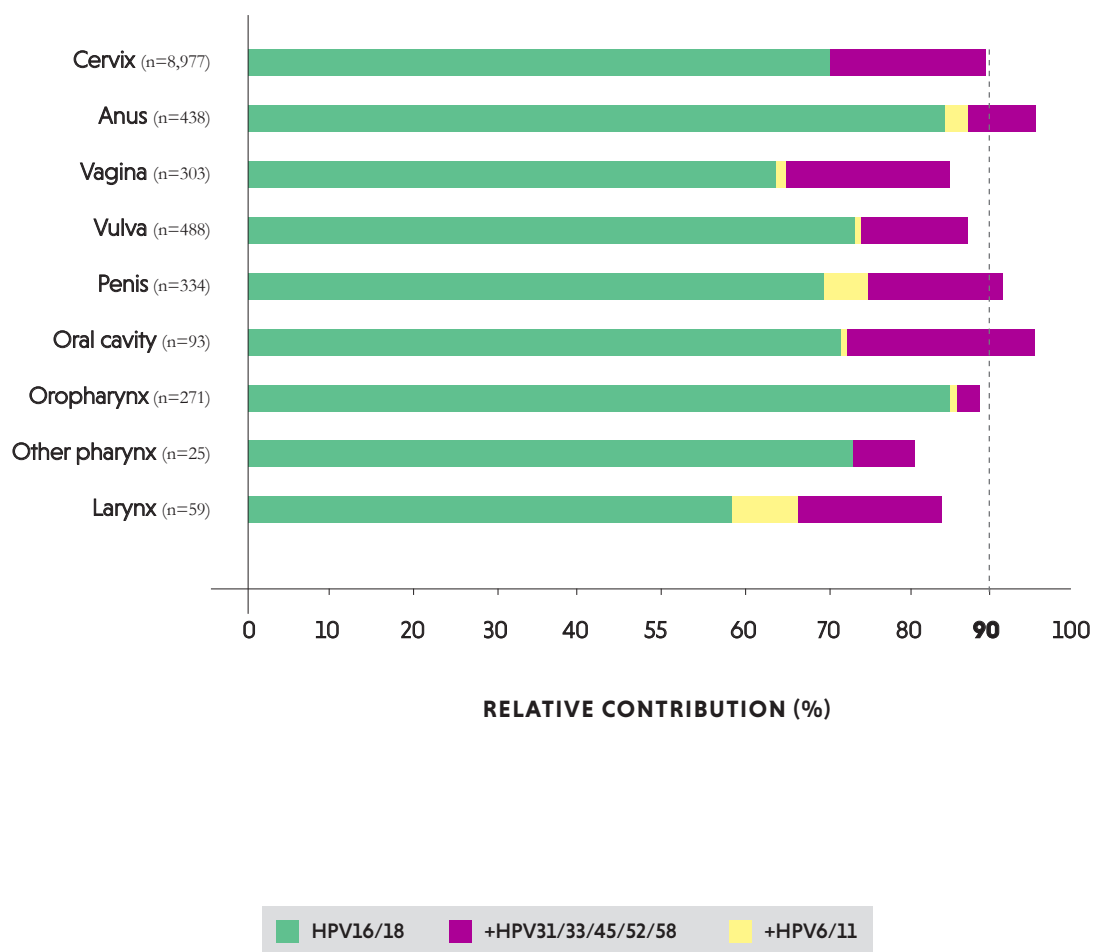
frequently detected type across all anatomical sites (Figure 2). HPV16/18/31/33/45/52/58/6/11 accounted for more than 80% of the HPV-positive cases, surpassing 90% of HPV-related anal and oropharyngeal cancers, in which HPV16 was extremely common (Figure 3).

In summary, overall the HPV type specific distribution does not differ for the most common types

across world regions and account for the vaccine types (HPV16,18,31,33,45,52,58,6,11) for 90% or more in cervical, anal, penile, oral cavity and oropharyngeal cancers, and more than 80% for other anogenital and head and neck HPV positive cancers. It is expected that HPV vaccines will have a significant impact in reducing not only cervical cancer burden but also the burden of other HPV-related cancers. ■

Figure 3

Relative contribution (%) of 9 HPV vaccine types among HPV/DNA positive anogenital and head and neck cancers



Refs. (5-10)

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# HPV Infection and Diseases Among Men: Results from the HPV Infection in Men (HIM) Study

Infection with human papillomavirus (HPV) is the cause of several different diseases in men. Until recently, the natural history of HPV among males was relatively unknown. The *HPV infection in men (HIM)* Study was designed and implemented to fill this information gap.

## The HIM Study: population and procedures

The *HIM Study* was a prospective study of the natural history of HPV infections in men in three countries. Participants were healthy men, aged 18-70 years, residents of southern Florida (USA), Sao Paulo (Brazil) or Cuernavaca (Mexico); and willing to comply with scheduled visits every 6 months for up to 7 years of follow-up. Study recruitment occurred between July 2005 and September 2009. A total of 4,299 men provided consent to participate.

At each study visit, questionnaire data and specimens from the genital area and anal canal, and oral rinse-and-gargle samples were obtained. Samples were analysed for the detection of individual HPV genotypes. Also, visually distinct external genital lesions such as genital warts (condyloma) and penile intraepithelial neoplasia (PeIN) were biopsied. Blood samples were also collected at each study visit to test for herpes simplex virus type 2 (HSV-2) serostatus and to measure serum antibodies against four HPV genotypes (HPV6, 11, 16, and 18). Finally, men provided a first-void urine specimen for Chlamydia trachomatis (CT) infection testing.

One of the most important findings to arise from the *HIM Study* was the observation that HPV natural history differs across anatomic sites. As shown in [Table 1](#), HPV prevalence is highest in the genitals, followed by the anal canal, and lowest in the oral cavity.

## Genital HPV infection

At the external genitalia (coronal sulcus, glans penis, shaft and scrotum), HPV prevalence was high (50.4%) and did not vary with age ([Figure 1](#)). The incidence of a new genital HPV infection was correspondingly high (38.4 per 1,000 person-months) with a median duration of 7.5 months for any HPV ([Table 1](#)) (1).

Factors independently associated with genital HPV detection were race (lower risk among Asian men), condom use (lower risk among men who always use condoms), smoking (higher risk among current smokers), CT infection and HSV-2 serostatus (higher risk among antibody-positive men), and circumcision (lower risk for non-oncogenic HPV types only).

The rate of progression from infection to disease differed by HPV type. Whereas high rates of genital HPV infection progression to genital warts were observed (16-22% of men with a genital HPV6/11 infection developed an HPV6/11 condyloma), very low rates of disease progression to PeIN following genital HPV16 infection were noted (2).



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Table 1

HPV natural history by anatomic site of infection in men. Ref. (1)

ANY HPV TYPE			
	Prevalence	Incidence rate per 1,000 person-months	Median time to clearance (months)
Genital HPV	50.4%	38.4	7.5
Anal HPV*	12.0%	8.1	--
Oral HPV	4.0%	5.6	6.9

\* Heterosexual men.

### Anal HPV infection

Anal HPV prevalence differs by sexual behaviour. Anal canal HPV prevalence was 12.2% among men who have sex with women (MSW) and 47.2% among men who have sex with men (MSM) (Figure 2). Hence, although anal HPV infection is commonly acquired by both MSW and MSM, incident events and persistence occurred more often among MSM (3).

### Oral HPV infection

Although genital and anal HPV prevalence was relatively common in the *HIM Study* cohort, oral HPV prevalence was rare (~4%). Oral HPV prevalence was lowest in the youngest age category (18-24 year old) and increased with increasing age, with men aged 55-74 years having the highest oral HPV prevalence (Figure 3). Newly acquired oral oncogenic HPV infections in healthy men were rare. However, once acquired, oral HPV16 had a high rate of persistence (4).

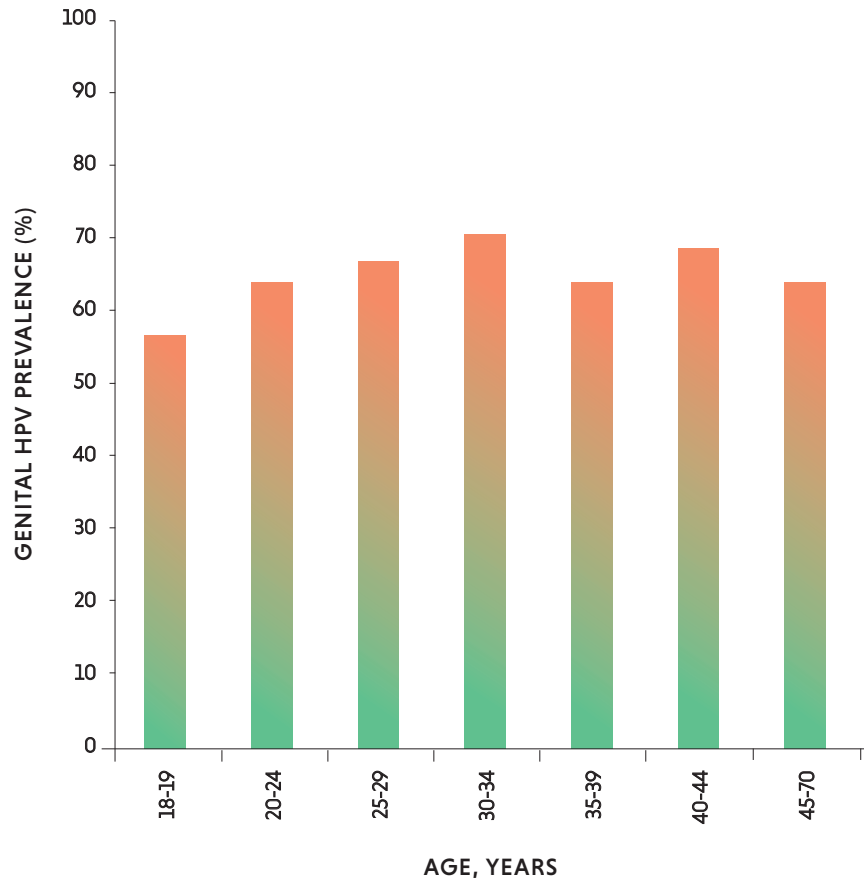
**Anal canal HPV prevalence differs by sexual behavior, being higher in MSM (47,2%) than in MSW (12,2%)**

### HPV serology

While HPV is common among men, the antibody response to HPV appears to be much lower than observed among women. Indeed, HPV6, 11, 16, and 18 seroprevalence was relatively low at 8.1%, 13.9%, 12.7%, and 10.8%, respectively. Moreover, this response appears not to confer protection against subsequent infection. HPV seropositivity following natural infection with HPV6, 11, and 16 was not associated with protection against subsequent type specific genital infection, with only a possible protective effect against persistent HPV18 infection (5).

Figure 1

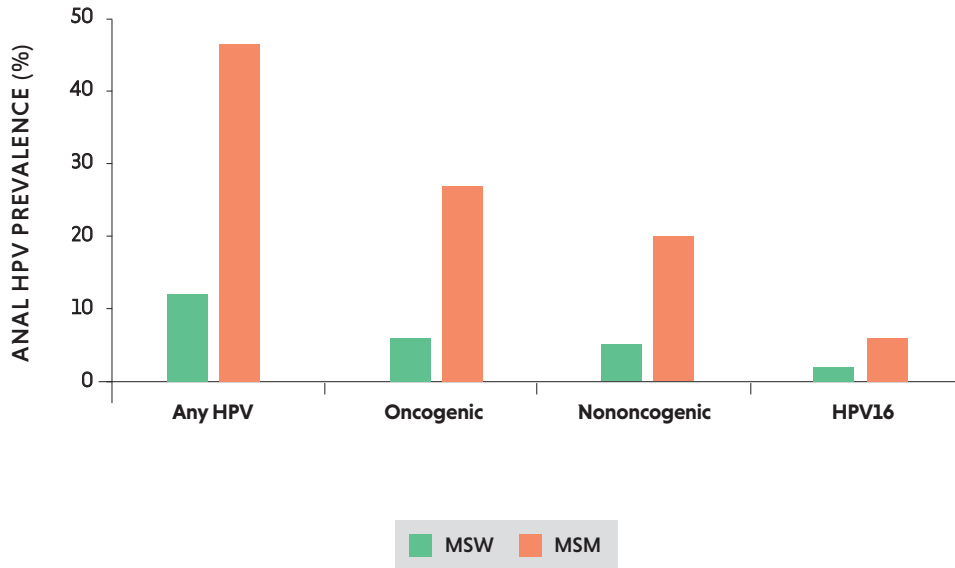
Age-specific prevalence of any genital HPV infection among men



Genital HPV prevalence remained high among all age groups. Ref. (1)

Figure 2

Anal canal HPV prevalence by sexual behavior



The HPV prevalence is higher in men who have sex with men (MSM) compared to men who have sex with women (MSW) for all HPV groups. Ref. (3)

## Among men, the natural antibody response to HPV appears not to confer protection against subsequent infection

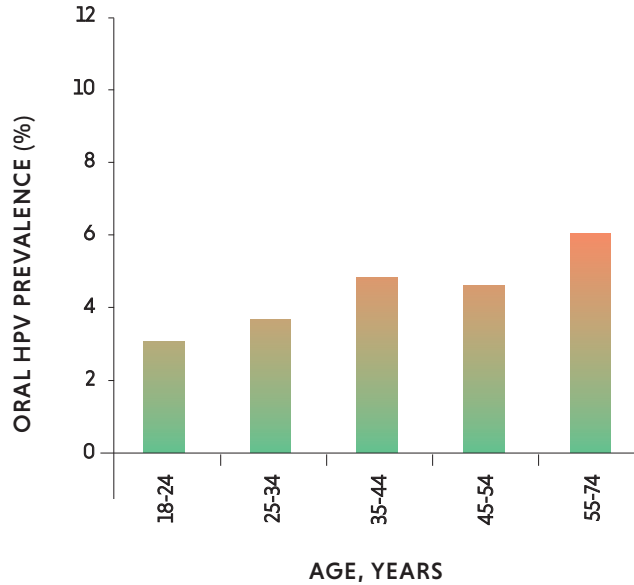
### Heterosexual HPV transmission

Among 65 discordant *HIM Study* heterosexual couples (the partners were discordant for  $\geq 1$  HPV type), HPV transmission was higher from females to males (12.3 per 1,000 person-months) than from males to females (7.3 per 1,000 person-months) (6).

Collectively, these findings demonstrate the susceptibility of men to HPV infection at multiple anatomic sites where HPV causes cancer and highlight the importance of HPV prevention programmes, such as gender-neutral HPV vaccination. ■

Figure 3

Age-specific prevalence of any oral HPV infection



Oral HPV prevalence was lowest in the youngest age category (18-24 year olds) and increased with increasing age, with men aged 55-74 years having the highest oral HPV prevalence. Ref. (4)

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# HPV infections in High-Risk groups

Infection with human papillomavirus (HPV) is most often asymptomatic. In the majority of cases, the infection is transient. However, some individuals develop clinical manifestations such as genital warts, and in some the infection becomes persistent and can cause severe intraepithelial lesions e.g. on the cervix (CIN3), vulva (VIN3), vagina (VaIN3), anus (AIN3) or the penis (PeIN3) or cancer at the same sites. It is still not known why some individuals seem less able to clear an HPV infection.

More than 90% of genital warts are associated with HPV6 and 11. These HPVs are non-oncogenic but often coexist with other HPVs, both non-oncogenic and oncogenic types. As most HPV infections are transient, subjects who develop genital warts may represent a vulnerable group of individuals in whom HPV infections tend to become persistent. Hence, this group would have – in theory – an increased risk of developing HPV-related high-grade lesions or cancers, such as anogenital cancers and some specific types of head and neck cancer. Similarly, it remains unclear whether individuals with a persistent infection at one site are at increased risk of developing high-grade lesions or cancer at another anatomical site in the long run.

Using data from high-quality nationwide Danish registries, we identified a cohort of individuals diagnosed with genital warts from 1978 - 2008 (1). After excluding individuals with previous cancer, the cohort comprised nearly 50,000 individuals with a diagnosis of genital warts (16,155

men and 32,933 women). In Denmark, all citizens are assigned a unique personal identification number, which is used universally in society, and this allows accurate linkage between population-based registries. Information on cancer occurrence in the study cohort was obtained by linkage to the Danish Cancer Registry. We followed the patients from 1 month after the genital warts diagnosis until death, emigration, or end of 2009, whichever came first. The number of cancer cases observed in the cohort with genital warts was compared with that expected in the general Danish population.

During follow-up, we observed 2,363 cancers, 815 in men and 1,548 in women, yielding a significantly increased risk of cancer when compared to the general population, with a higher standardised incidence ratio (SIR) in men (SIR=1.5; 95% CI: 1.4–1.6) than in women (SIR=1.2, 95% CI: 1.2–1.3). Most of these increased risks were related to increased risk of HPV-related cancers (men: SIR=7.2; 95% CI: 5.5–9.2) (women: SIR=2.8; 95% CI: 2.4–3.1) (Table 1).

The risk for all the specific types of HPV-related cancer was significantly increased in both men and women compared to the general population, with the highest risk estimate for vulvar cancer in

**Individuals with a record of genital warts have a lifetime increased risk of HPV-related cancers, especially for vulvar cancer in women and anal cancer in men**



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## The risks of cancer remained elevated for >10 years following genital warts diagnosis

women (SIR=14.8; 95% CI: 11.7–18.6) and anal cancer in men (SIR=21.5; 95% CI: 14.4–30.9) (Table 2). Examining head and neck cancers according to their association with HPV showed that the risk was highest for HPV-associated cancers - especially tonsillar cancer (men: SIR=4.6; 95% CI: 2.7–7.2) (women: SIR=4.7; 95% CI: 2.3–8.4), followed by potentially HPV-associated cancer (Table 3). It is noteworthy that for all HPV-related cancers, the relative risk remained high for up to 10 years or more, exemplified by anal cancer and tonsillar cancer in Table 4.

These results may point to individuals with genital warts as being a vulnerable population. One explanation is that this could be caused by an immunological dysregulation, which in theory could predispose some to a higher tendency toward persistence of the HPV infection and therefore to an increased risk of cancer (1,2). Similar results have been found among women with CIN3 (a proxy for persistent HPV infection), who have been shown to have a long-lasting (>25 years) increased risk of both anogenital cancers and some head and neck cancers compared to the general female population (3, 4). These results may raise the question as to whether it would be beneficial to vaccinate women with high-grade CIN and individuals with genital warts. ■

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*Table 1*

Risk of cancer among men and women who received a diagnosis of genital warts in Denmark from 1978–2009

CANCER GROUP	MEN		WOMEN	
	Observed number	SIR (95 % CI)	Observed number	SIR (95 % CI)
All cancers	855	1.5 (1.4-1.6)	1548	1.2 (1.2-1.3)
All smoking-related cancers	255	1.8 (1.6-2.1)	407	1.9 (1.7-2.1)
All HPV-related cancers	60	7.2 (5.5-9.2)	245	2.8 (2.4-3.1)

Individuals with a record of genital warts have an increased risk of HPV-related cancers. SIR: Standardised incidence ratio. CI: Confidence Interval. Modified from (1)

*Table 2*

Risk of anogenital cancer among men and women who received a diagnosis of genital warts in Denmark from 1978–2009

TYPE OF ANO-GENITAL CANCER	MEN		WOMEN	
	Observed number	SIR (95 % CI)	Observed number	SIR (95 % CI)
Cervix	-	-	117	1.5 (1.3-1.8)
Vagina	-	-	6	5.9 (2.2-12.9)
Vulva	-	-	74	14.8 (11.7-18.6)
Anus	29	21.5 (14.4-30.9)	33	7.8(5.4-11.0)
Penis	11	8.2 (4.1-14.6)	-	-

Individuals with genital warts have an increased risk of developing anogenital cancer, especially in the vulva in women and in the anus in men. SIR: Standardised incidence ratio. CI: Confidence Interval. Modified from (1)

*Table 3*

Risk of head and neck cancer among men and women who received a diagnosis of genital warts in Denmark from 1978–2009 according to likelihood of HPV relationship

HEAD AND NECK CANCER	MEN		WOMEN	
	Observed number	SIR (95 % CI)	Observed number	SIR (95 % CI)
HPV-associated	20	3.5 (2.2-5.5)	15	4.8 (2.7-8.0)
Potentially HPV-associated	33	2.2 (1.5-3.1)	24	3.3 (2.1-4.8)
No or weakly HPV-associated	6	2.0 (0.7-4.3)	1	0.5 (0.0-3.0)

The risk of individuals with genital warts to develop head and neck cancer was highest for HPV-associated cancers. SIR: Standardised incidence ratio. CI: Confidence Interval. Modified from (1)

*Table 4*

Risk of anogenital cancer among men and women who received a diagnosis of genital warts in Denmark from 1978–2009

FOLLOW-UP TIME BY CANCER TYPE	MEN		WOMEN	
	Observed number	SIR (95 % CI)	Observed number	SIR (95 % CI)
<b>Anal cancer</b>				
< 1 y	9	190.2 (86.8-361.2)	10	66.5 (31.9-122.4)
1-4 y	3	14.7 (3.0-42.9)	10	14.5 (7.0-26.7)
5-9 y	7	25.6 (10.2-52.6)	14	14.1 (7.7-23.7)
> 10 y	10	12.2 (5.8-22.4)	28	7.5 (5.0-10.8)
<b>Tonsillar cancer</b>				
< 1 y	0	0 (0-31.0)	0	0 (0-68.5)
1-4 y	1	1.9 (0-10.6)	0	0 (0-14.5)
5-9 y	4	5.7 (1.5-14.7)	2	5.4 (0.6-19.5)
> 10 y	13	5.0 (2.7-8.6)	9	5.4 (2.5-10.2)

The subsequent risk of cancer amongst individuals that suffered from genital warts remains high after 10 years of follow up. SIR: Standardised incidence ratio. CI: Confidence Interval. Modified from (1)

# The e-learning options



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Health education is a major step in the fight against preventable diseases such as cervical cancer. Information on new HPV vaccines and new screening options must be scientifically accurate and technically impartial. The introduction of a new prevention technology worldwide means that thousands of health professionals and managers need to understand its significance and use, and they in turn must be able to transmit this information appropriately to millions of families living in environments with completely different languages, cultures and beliefs. Hence, the information must be accurate, informative, and disseminated honestly.

In recent years, distance learning has made great strides and has become an increasingly important part of the global mandate of the Education for All movement led by UNESCO (1). Distance learning has been all the rage in western countries and is becoming increasingly essential in less developed countries (2). Wider spread of internet-ba-

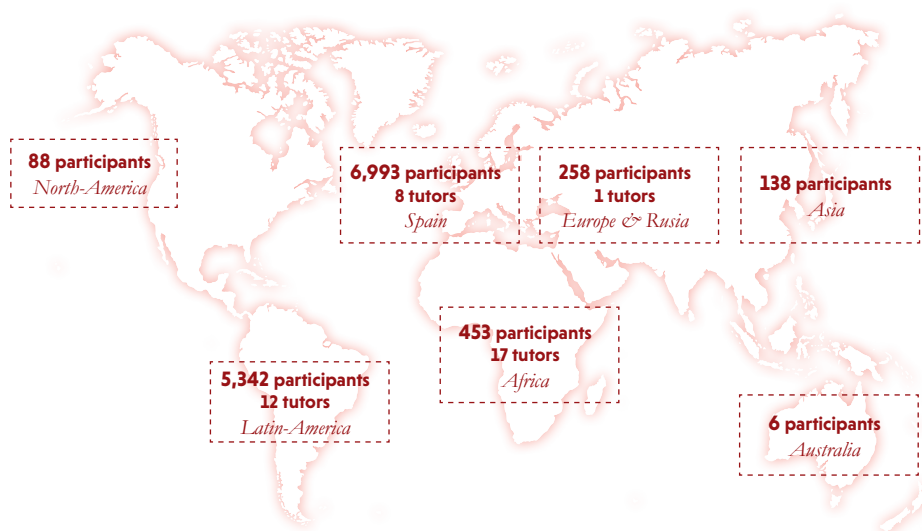
## Distance learning has greatly influenced the level of education of less developed countries

sed technologies has provided unique possibilities for training without barriers of distance, time and space. They also facilitate widespread access to and consultation with the best specialists from around the world. It has been shown that distance learning has greatly influenced the level of education of less developed countries (3).

The Cancer Epidemiology Research Programme at the Catalan Institute of Oncology (ICO) has been developing an extensive training and information Programme on HPV and associated diseases (4) for over 10 years. This programme aims to provide basic knowledge or to expand the understanding of concepts in clinical practice, epidemiology, prevention and public health of human

*Figure 1*

Distribution of students of the e-learning course on prevention of cervical cancer by continent



Over 15,000 students from 50 countries have participated in the e-learning program

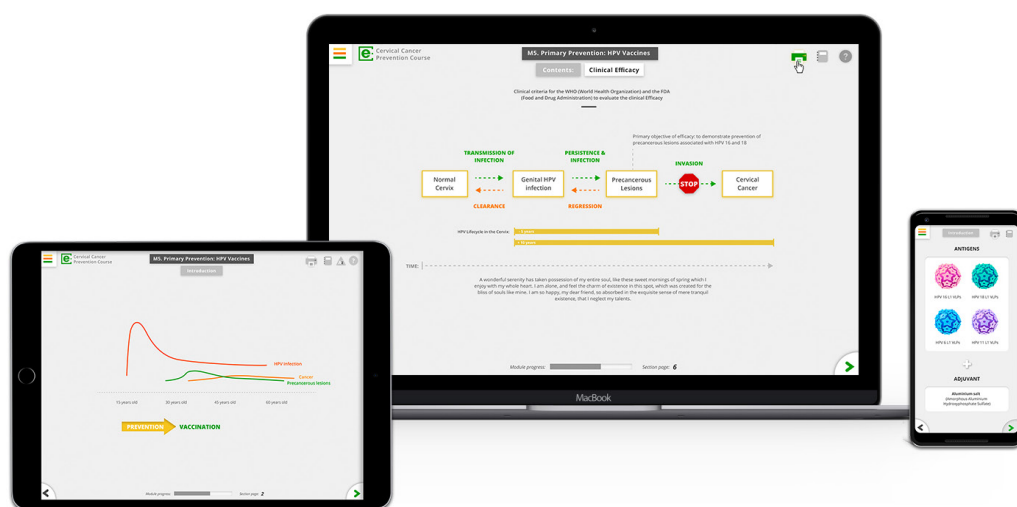
papillomavirus (HPV) and related diseases for a broad spectrum of health professionals. The main components of ICO's learning Programme are:

**The ICO/IARC Information Centre collects information on HPV, associated diseases and preventive options**

**1. The ICO/IARC Information Centre on HPV and cancer** (<http://www.hpvcentre.net/>). This initiative was launched in 2004 by ICO in cooperation with World Health Organization (WHO). At present, ICO and the International Agency for Research on Cancer (IARC) have joined forces to maintain an interactive web-based platform with the aim of accelerating the development and introduction of HPV prevention strategies worldwide. For this purpose, the Centre collects, edits and spreads scientific

Figure 2

Screenshots of the e-learning course on cervical cancer prevention



The course is available in 10 languages: English, German, Spanish, Japanese, Portuguese, Greek, Chinese, Italian, Russian and French

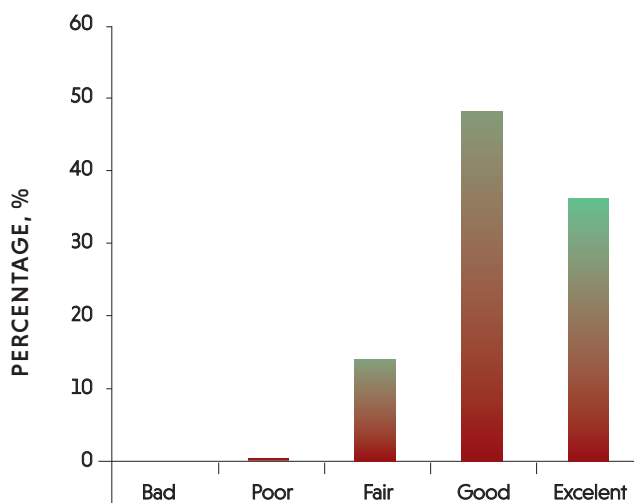
information on the HPV virus and associated diseases worldwide through the website, which can be accessed completely free of charge.

**2. ICO's International Monographs Programme on HPV and the prevention of associated diseases** (<http://www.hpvcentre.net/scientificreviews.php>). Several international scientific reviews and regional reports have been published in scientific papers on HPV disease and prevention authored by leading experts in the field. The first monograph in the

series was published in 2006, followed by 10 regional reports and the last update in the general report in 2012. Individual peer-reviewed articles cover issues related to natural history and biology, HPV therapies, current screening strategies for cervical cancer including new technologies and prospects, prophylactic HPV vaccines and their introduction, economic analyses and gaps in knowledge. The scientific content of the monographs has provided the basis for developing the e-learning course on cervical cancer prevention.

Figure 3

Overall results of the satisfaction survey for the e-learning course on prevention of cervical cancer



**3. E-learning on the prevention of cervical cancer** (<http://www.e-oncologia.org/en>). This online training course, translated into 10 languages, has been designed for health professionals involved in cervical cancer prevention, public health professionals, health planners, health programme managers, researchers and educators and is also suitable for specialised nurses and midwives (Figure 1 and Figure 2). The course has been developed jointly with the International Federation of Gynaecology and Obstetrics (FIGO), the Union for International Cancer Control (UICC), the International Atomic Energy Agency (IAEA), and the International Agency for Research on Cancer (IARC).

There are two modes of access to the course: (i) classrooms that are permanently open with free access to any participant, and (ii) closed or

premium classes for specific groups of students with similar interests selected by the tutor.

Students spend approximately 18 hours for four weeks participating in the course and completing all assignments. To date, over 15,000 students from 50 countries have participated and 85% have completed the course. At the end of the course, students are evaluated and answer a questionnaire to assess their degree of satisfaction. Eighty-five percent (85%) of participants rated the course as good or excellent (Figure 3). Successful students receive an ICO/FIGO diploma granted with 15 CME european credits and 1 AMA PRA credit.

In conclusion, as shown in the “e-oncología” programme on the prevention of cervical cancer, e-learning has demonstrated its utility in continuing education for health professionals regardless of their place of work or residence. ■



Figure 4

The ICO/FIGO e-learning course on HPV and Cancer prevention. Table of contents



The subjects covered in 6 pre-recorded modules include:

- **Module 1.** Introduction
- **Module 2.** Natural history of HPV infections and cervical cancer
- **Module 3.** Burden of HPV infections and cervical cancer
- **Module 4.** Other HPV-associated diseases
- **Module 5.** Control and prevention of cervical cancer:
  - 5.1. HPV vaccine
  - 5.2. Male condom and male circumcision
  - 5.3. Current options for cervical cancer screening
  - 5.4. Strategies for the prevention of cervical cancer
  - 5.5. Education and health guidance
- **Module 6.** HPV in specific populations

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# The psychosocial impact of HPV

In parallel to the basic scientific discoveries about HPV over the past two decades, behavioural science has explored the psychological, social and communication challenges posed by the virus and its link with cancer. This work is essential to develop ways of minimising the negative psychosocial consequences of an HPV diagnosis.

## HPV awareness

HPV remains unfamiliar to many people in the general population, even with the advent of widespread testing and vaccination. Population-representative data from a UK-based survey in 2014 found just 0.1% of adults could name HPV as a possible cause of cancer in response to an open question, and only 29% recognised it as a cancer cause when prompted (1). Awareness varies by socio-demographic group (Figure 1).

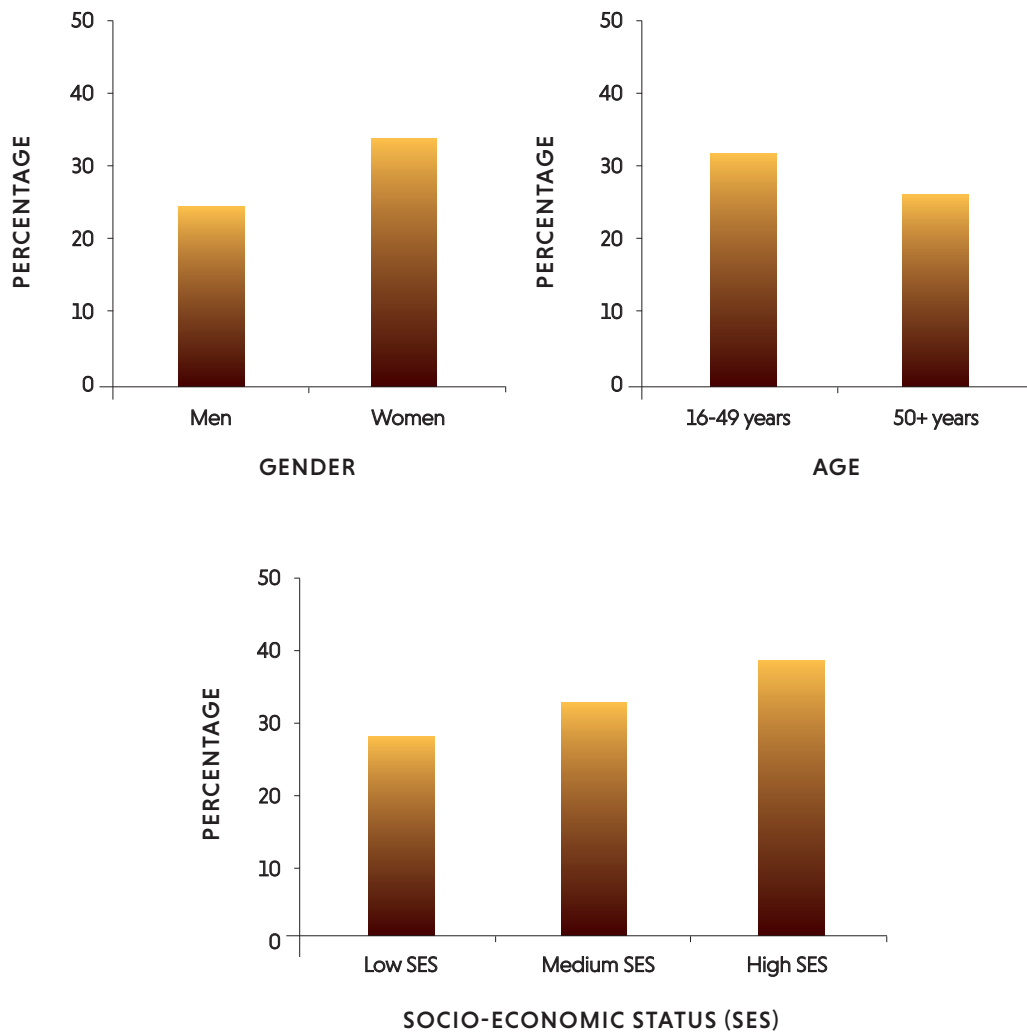
## Testing positive for HPV

Lack of awareness can contribute to adverse psychological responses to an HPV-positive result, with early work in the cervical screening context showing many women were shocked by the link between a sexually transmitted infection (STI) and cancer (2). Additional negative psychological responses have been described (3) (Figure 2). Many of these stem from the fact that HPV is sexually transmitted and are consistent with documented responses to other STIs. In the absence of cytological abnormalities, women frequently focus on the sexually transmitted nature of HPV, which can have implications for their sexual partners and relationships. Some of these issues are now also starting to be described in head and neck cancer patients with HPV-related disease (4).

The psychological impact of HPV increases with disease progression. If HPV is asymptomatic, people may be unaware of the infection and, unless tested, are likely to clear the infection, or have it become undetectable, with no adverse consequences. If HPV is diagnosed in the absence of cytological abnormalities, in the context of cervical screening, confusion and anxiety may ensue, although the magnitude and duration of the impact is not always great (5,6). The psychological impact of an HPV infection on a woman in this context will depend on her level of understanding of the virus and the extent to which infection with an STI is consistent with her sexual history and identity. If HPV is diagnosed when it has already caused pre-cancerous abnormalities, the psychological impact can be greater, because fears regarding cancer come into play. In these cases, HPV itself may become a minor consideration for the patient, with the focus being on cancer risk and needing further tests or treatment. However, even in cancer patients, the negative connotations of an STI can add additional psychological challenges to the already considerable psychological burden of a cancer diagnosis.

## Lack of awareness can contribute to adverse psychological responses to an HPV positive result

*Figure 1*  
Recognition of HPV as a cause of cancer

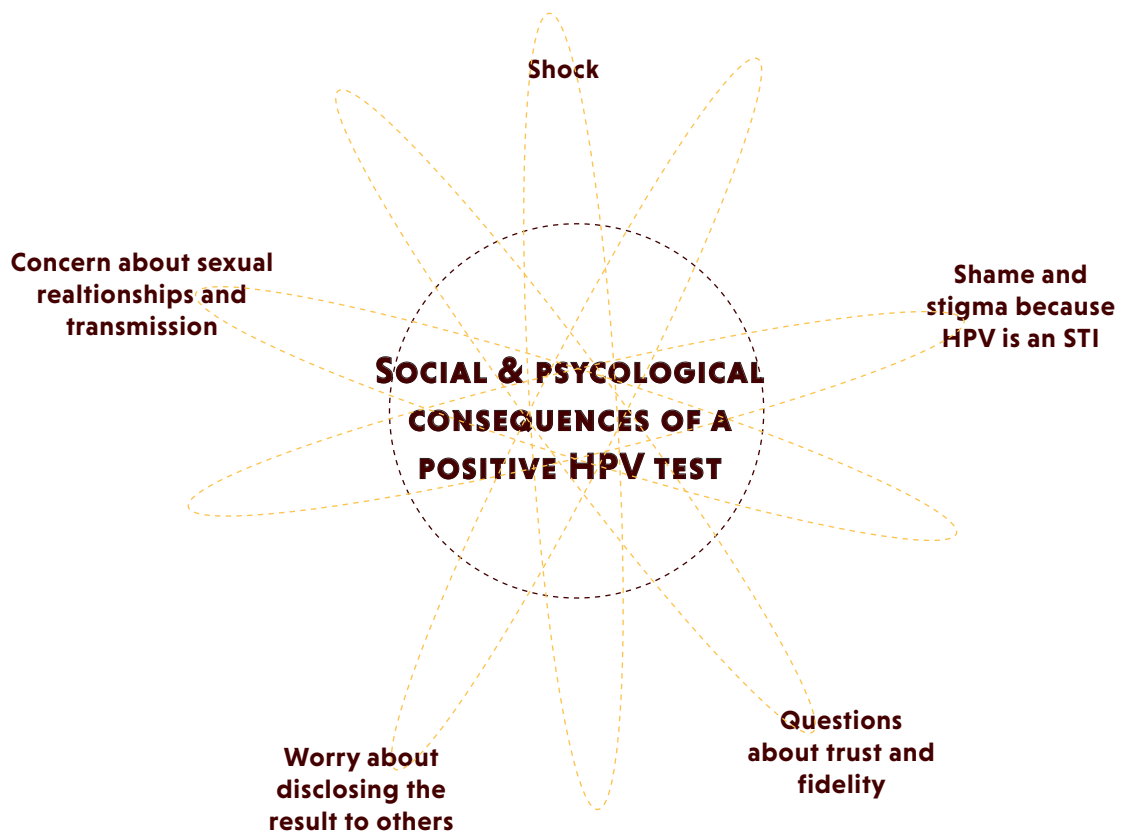


Population-representative data from a UK-based survey in 2014 (n=1,896 adults). The figure shows the percentage responding “yes” to the question: Do you think that HPV could increase a persons’s chance of getting cancer? Results are stratified by gender, age and socio-economic status (SES). Ref.(1)

*Figure 2*

Psychosocial impact of a positive HPV test result. Ref. (3)

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## Interventions

Information is likely to be key to minimising the negative psychological consequences of HPV positive results, but so far little empirical evidence is available to guide provision of information. Information on high prevalence seems to offset the potentially stigmatising impact of sexual transmission in hypothetical studies (7) (Figure 3), and there is emerging evidence that additional information may alleviate anxiety in the screening context. A recent study in Hong Kong found that information provided either by a leaflet or face-to-face successfully increased HPV knowledge and psychological well-being in HPV-positive women (8). However, more work is needed to understand how best to prevent psychological distress in the increasing numbers of people undergoing HPV testing.

## HPV testing should be accompanied by extensive health education to inform women and to de-stigmatise infection

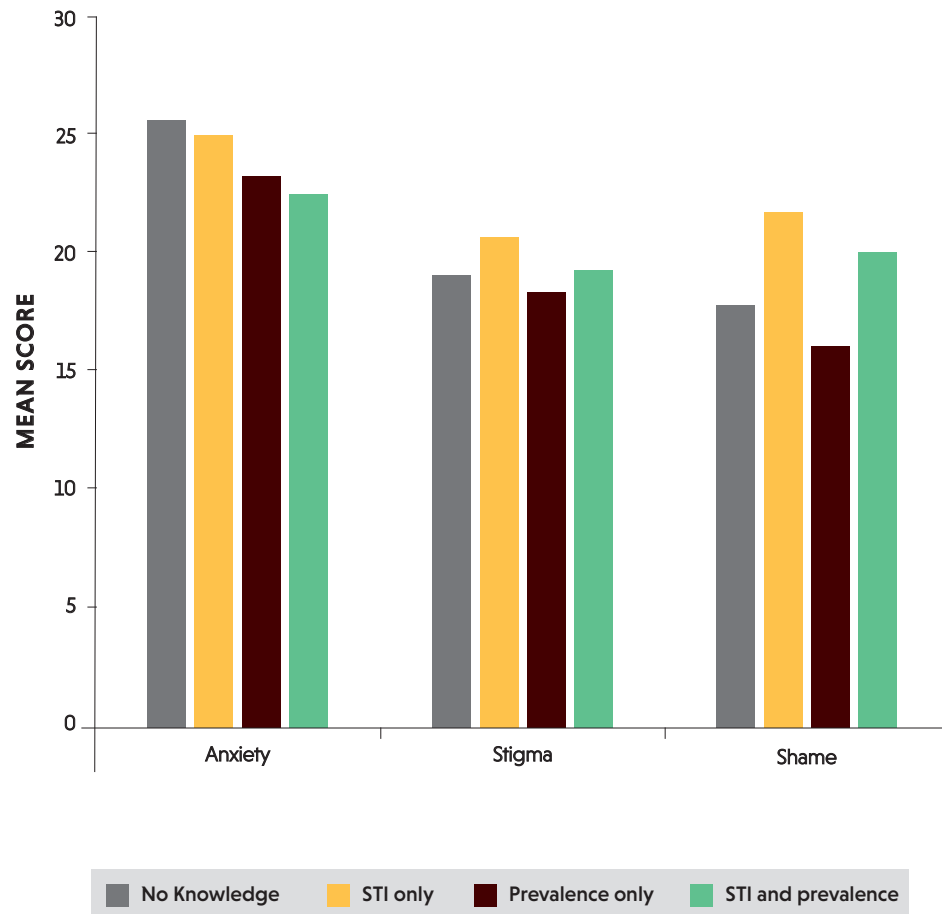
Additional research is also needed to better understand the psychosocial consequences of anal cancer and pre-cancer diagnoses as well as head and neck cancers. Furthermore, as cervical cancer screening policies and practices change, moving away from cytology to HPV DNA testing, the impact on communication needs and psychosocial adjustment should be considered and investigated. Lastly, the broader issue of working to de-stigmatise STIs is of central importance. The stigmatisation of HPV and other STIs impedes our ability to provide the most effective care, both in terms of prevention and treatment. ■

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Figure 3

Mean score for stigma, shame and anxiety of women by their HPV knowledge



Participants were classified into four groups according their knowledge: No knowledge (unaware of the prevalence or that human papilloma virus (HPV) is sexually transmitted); STI only (aware that HPV is sexually transmitted but unaware of its high prevalence); Prevalence only (aware of the high prevalence of HPV but unaware that it is sexually transmitted); STI and prevalence (aware of both the high prevalence and the mode of transmission). Participants responded to items assessing anticipated stigma (8-items, e.g. 'people would avoid me'), shame (5-items, e.g. 'How ashamed do you feel') and anxiety (4-items, e.g. 'How anxious would you feel'). Total scores were calculated for the three outcome scales and these were standardised to take account of the different number of items in each scale. Modified from (7).

# Eliminating HPV-related diseases as a public health problem: Let's start with cervical cancer

The effectiveness of cervical cancer (CC) screening in reducing the morbidity and mortality of CC has been known for decades and is standard medical practice in high-resource countries. In the last decade, HPV vaccines, highly effective, safe, and cost effective tools to prevent the HPV infections that cause CC and other HPV-related diseases, have become available. The greater than expected vaccine immunogenicity, efficacy, and impact on HPV have given rise to global recommendations for its use. Discussions are beginning on whether it is time to move from a goal of controlling HPV-related diseases to a goal to eliminate HPV-related diseases as a public health problem. We and others believe that elimination of CC as a public health problem is feasible in countries with effective screening, treatment and immunisation (<http://www.who.int/ncds/un-task-force/un-joint-action-cervical-cancer-leaflet.pdf>). Demonstrating this is the logical first step towards the broader goal of elimination of HPV-related diseases in men and women worldwide.

The terms “control”, “elimination”, and “eradication” have specific meaning in the public health community (1). Control refers to the reduction of disease incidence, prevalence and mortality to acceptable levels, such as has been accomplished in several high-resource countries where CC incidence is now <10 cases/100,000 women. Elimination is the reduction of infection and disease to zero or near zero in a defined geographical area (e.g.,

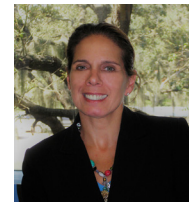
state within a country, country), whereas eradication refers to the permanent extinction of the infectious agent worldwide. Only one human disease (smallpox) has ever been eradicated, allowing immunisation to end. HPV chronically infects billions worldwide with multiple virus types and does not produce lifetime immunity following natural infection; therefore, HPV is not a good candidate for eradication.

Nevertheless, CC does fulfil the conditions required for elimination. HPV vaccination probably confers long-lasting immunity against infection and disease. Today, there are multiple approaches available to both low- and high-resource countries to detect (e.g., cytology, HPV DNA testing, visual inspection with acetic acid) and treat (e.g., surgical, ablative methods) cervical pre-cancerous lesions (2). HPV transmission can be disrupted by vaccination, as demonstrated by the herd protection observed against genital wart prevalence in males when only females were vaccinated in Australia (3).

**The great burden of cervical cancer occurs in low resource countries, where neither screening nor vaccination has achieved sufficient coverage to impact rates of disease**



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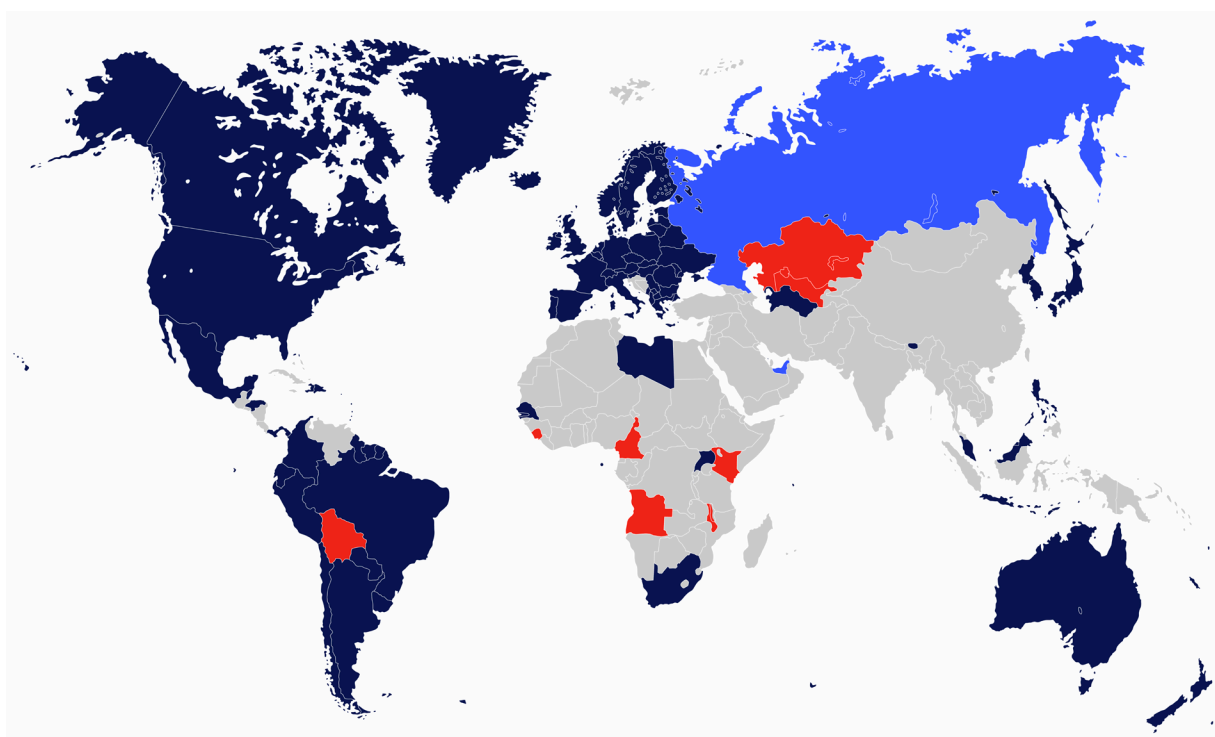


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*Figure 1*

Countries that include HPV vaccine in their National Immunisation programmes (NIPs) for females and males in 2016

At least 82 countries (42%) have introduced the HPV vaccine in their NIPs for females. Updated from ref. (7).



FEMALES:

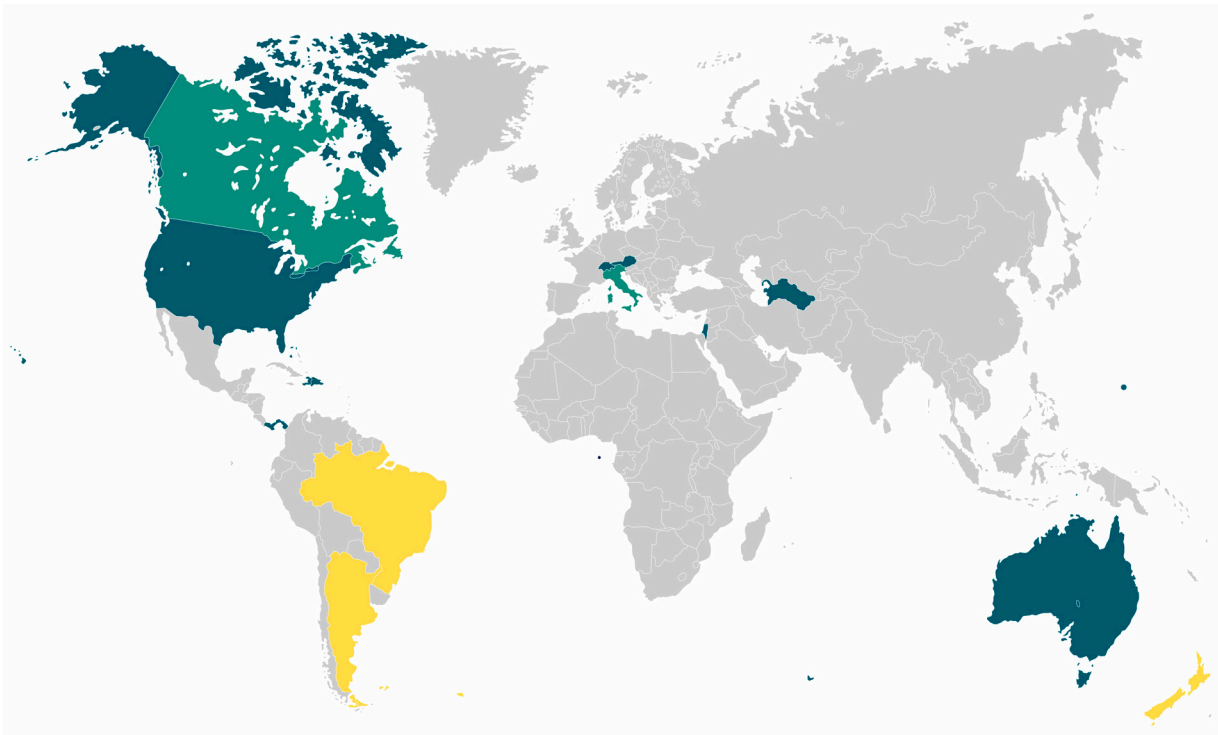
■ National

■ In some regions

■ Announced



At least 13 countries (7%) have introduced the HPV vaccine in their NIPs for males. Updated from ref. (7).



**MALES:**

- National
- In some regions
- Announced

The elimination strategy is, to varying degrees, being implemented in many high-resource countries. However, the great burden of CC occurs in low-resource countries, where to date neither screening nor prevention through vaccination has achieved sufficient coverage to impact rates of disease. Nevertheless, there is reason for optimism on several fronts.

First, HPV vaccine is more immunogenic and effective than originally predicted. The vaccine induces seroconversion and long lasting antibodies (> 15 years so far) in essentially 100% of vaccine recipients of all ages studied (4). Initially studied in a three-dose schedule, it is now recommended in a two-dose schedule for 9-14 year olds, and active research is underway to study the hypotheses that a single dose may suffice for long-term protection. Moreover, the protection against HPV infection and lesions caused by HPV types found in the vaccines (including cervical pre-cancerous lesions, and lesions of the anus, vulva, vagina and genital warts) is in the range of 90-100%. Studies of vaccine effectiveness have demonstrated dramatic reductions in genital wart cases (early indicator of vaccine effectiveness), strong evidence of herd protection and significant reductions in cervical pre-cancerous lesions caused by vaccine-related HPVs and in overall cervical lesions. Importantly, the vaccines have an excellent record of safety, with more than 200 million doses given and many studies showing the safety of these products. Unfortunately, anti-vaccine groups have damaged vaccine uptake in a number of countries despite the evidence of vaccine safety.

CC elimination requires development and implementation of strategies with clearly defined targets and resources, including infrastructure, budgets and milestones. Progress should be assessed by monitoring public health measures,

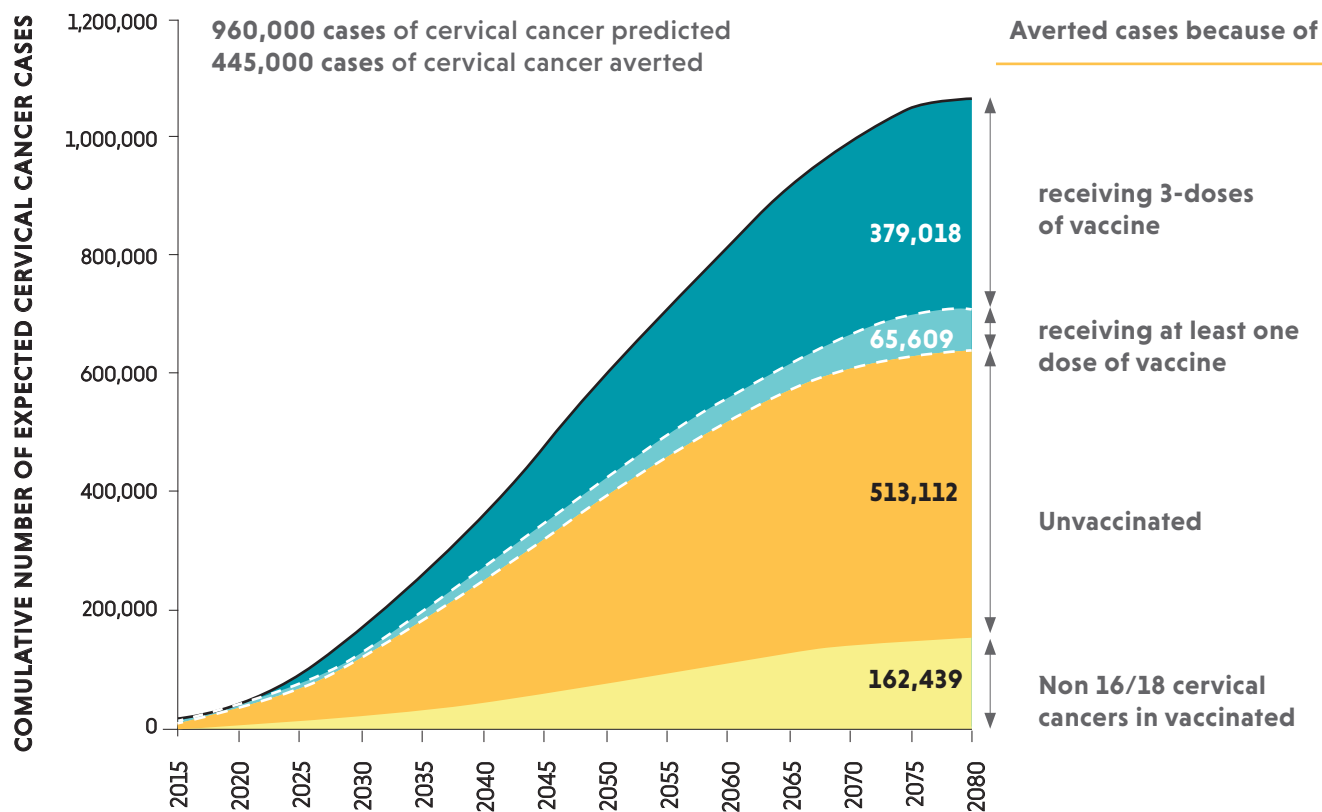
such as percent of age-eligible cohorts vaccinated and screened, and epidemiological outcomes such as incidence of pre-cancerous lesions and cancer. This approach is being used for other vaccine-preventable diseases, for example, hepatitis B virus (HBV). WHO has called for the elimination of HBV as a public health problem, defining a prevalence of HBV carriers in children to be achieved by the year 2030. Similar to HPV, chronic HBV is a vaccine-preventable infection, primarily asymptomatic in childhood, which decades later causes death from cirrhosis and liver cancer. While the impact of HBV vaccination on cancer will be largely seen decades in the future, WHO has issued a call for the elimination effort now.

## **Elimination of HPV-related cancers will require a gender-neutral approach to vaccination**

Elimination of HPV-related cancers, most of which are caused by HPV 16, will require a gender-neutral approach to vaccination (5). Even in high income countries the problems of elimination are compounded by a strategy of only giving the vaccine to girls and young women in most countries. This is still the official WHO SAGE recommendation, but gender-neutral vaccination is becoming recommended in an increasing number of countries (Figure 1). The weakness of female only vaccination is apparent when one considers that in most low-resource countries, where there is no CC screening programme, reduction of HPV-related disease will be entirely dependent on achieving high rates of uninterrupted vaccine coverage (Figure 2). In high-resource countries, with relatively good CC screening, the morbidity and mortality of non-cervical HPV-related diseases exceeds or equals that of cervical cancer. Many of

Figure 2

Estimated incidence of cervical cancer cases predicted and averted before age 75 in 118 million women targeted by HPV vaccination programmes by the end of 2014



The solid line shows the cumulative number of expected cervical cancer cases up to age 74 if targeted cohorts had not been vaccinated. The dashed line shows the cumulative number of expected cervical cancer cases up to age 74 in targeted cohorts considering 2014 HPV vaccination coverage. Modified from (7)

these diseases occur in men, as oropharyngeal and other cancers, and rates of HPV-related disease in men who have sex with men (MSM) exceed rates of CC in women before screening was available. Immunising women to protect men is not ethical, decreases resiliency of vaccine programmes and may lead to poor community protection when vaccine programmes are interrupted. Female-only programmes will not work for MSM. Finally, a female-only programme is not workable as an overall strategy if our goal is elimination of HPV infection and all HPV-related cancers, not just lowering rates of disease for the least possible cost. As usual, elimination is much more difficult in low-resource countries. While GAVI funding in the poorest countries makes HPV vaccination possible, the prior requirement for demonstration projects means that national-level programmes are just beginning (6). The PAHO Revolving Fund also negotiated low prices (~8.5 USD/dose) for its Latin American partners. A primary problem is that of middle-income countries not eligible for GAVI support. These countries have been unable to obtain affordable prices and are also interested in introducing Rotavirus, Pneumococcal and other vaccines. The Global Immunisation Community and the manufacturers must cooperate to help them acquire affordable vaccines.

many of these countries primarily reliant on HPV immunisation for preventing HPV-related cancers, delaying the goal of CC elimination for many years. Fortunately, even the poorest countries can deliver vaccines effectively if they can afford them.

Ultimately, elimination of cervical cancer and other HPV-related diseases as a public health problem is both a political and public health issue. Advocating for elimination will increase the awareness of this disease and galvanise political will. We should endorse and embark on this strategy with enthusiasm and without delay. ■

## **Advocating for elimination will increase the awareness of this disease and galvanize political will**

Screening and treatment of cervical lesions in low-resource countries has generally been unsuccessful, with less than 10% of women are screened. New strategies such as HPV-FASTER (8), and new technologies mentioned above will help, but lack of trained personnel, infrastructure and budgets to afford effective treatment will make

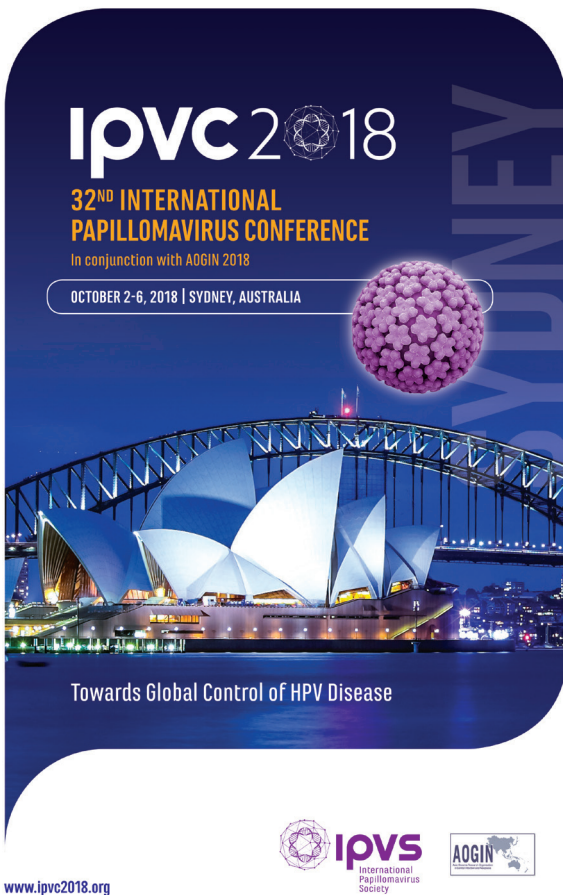
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