Papillomavirus Research 1 (2015) 90–100

Contents lists available at ScienceDirect

Papillomavirus Research

journal homepage: www.elsevier.com/locate/pvr

Estimation of the epidemiological burden of HPV-related anogenital cancers, precancerous lesions, and genital warts in women and men in Europe: Potential additional benefit of a nine-valent second generation HPV vaccine compared to first generation HPV vaccines

Susanne Hartwig [a,*], Jean-Jacques Baldauf [b], Géraldine Dominiak-Felden [a], François Simondon [c], Laia Alemany [d], Silvia de Sanjosé [d], Xavier Castellsagué [d]

[a] Department of Epidemiology, Sanofi Pasteur MSD, Lyon, France
[b] Département de gynécologie et obstétrique, Hôpital de Hautepierre, Strasbourg, France
[c] IRD UMR216, Mère et enfant face aux infections tropicales, Paris, 75006, France; COMUE Sorbonne Paris Cité, Université Paris Descartes, Faculté des Sciences Pharmaceutiques et Biologiques, Paris, 75270, France
[d] Cancer Epidemiology Research Program, Institut Català d'Oncologia (ICO)-IDIBELL, CIBERESP, L'Hospitalet de Llobregat, Catalonia, Barcelona, Spain

ARTICLE INFO

Article history:
Received 10 April 2015
Received in revised form
5 June 2015
Accepted 5 June 2015
Available online 16 June 2015

Keywords:
HPV
Burden of disease
Cancer
Precancerous lesions
Genital warts
HPV vaccine

ABSTRACT

Introduction: A second generation HPV vaccine has been developed for the prevention of anogenital cancers and precancerous lesions of the cervix, vulva, vagina, anus and of genital warts due to nine HPV types.

We estimated the annual burden of these diseases attributable to the nine HPV types compared to HPV types from first generation vaccines in women and men in Europe.

Material and methods: Incidence rates from the IARC database, cancer registries, the literature and Eurostat population data were used.

The burden attributable to the HPV types targeted by both vaccines was estimated by applying the relative contribution of the respective HPV types from epidemiological studies.

Results: In 2013, the number of new anogenital HPV-attributable cancers was 44,480 with 39,494 of these cases related to second vs. 33,285 to first generation vaccine types.

Among the 284,373 to 541,621 new HPV-attributable anogenital precancerous lesions 235,364–448,423 and 135,025–256,830 were estimated to be related to second and first generation vaccine types, respectively.

The annual number of new genital warts was 753,608–935,318, with 90% related to HPV6/11.

Conclusions: These data demonstrate how the large public health impact that was achieved by the first generation HPV vaccines could be further increased by second generation vaccines.

1. Introduction

The discovery of human papillomavirus (HPV) as the necessary cause of cervical cancer has led to the development of different prophylactic HPV vaccines. The International Agency for Research on Cancer (IARC) has identified twelve HPV types as carcinogenic to humans: HPV16/18/31/33/35/39/45/51/52/56/58/59 [1]. In addition to cervical cancer, HPV is responsible for a significant proportion of cancers and precancerous lesions of the vulva, vagina, and anus in women; cancers and precancerous lesions of the anus and penis in men; and a subset of head and neck cancers and genital warts in both sexes.

Two HPV vaccines have been licensed so far in Europe: the quadrivalent HPV vaccine, Gardasil® 9 (Sanofi Pasteur MSD)/ Silgard® (Merck Sharp & Dohme), and the bivalent HPV vaccine, Cervarix® (GlaxoSmithKline Biologicals). Both vaccines have reassuring safety profiles, as demonstrated in clinical trials, and are indicated for the prevention of cervical, vulvar and vaginal premalignant lesions and cervical cancer related to HPV16/18. The quadrivalent HPV vaccine is also indicated against premalignant anal lesions and anal cancer and protects against low-risk HPV6/11, which are responsible for about 90% of genital warts [2] and a fraction of precancerous lesions.

Abbreviations: AIN, anal intraepithelial neoplasia; CI, confidence interval; CI5, Cancer Incidence in Five Continents; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; IARC, International Agency for Research on Cancer; VIN, vulvar intraepithelial neoplasia; VaIN, vaginal intraepithelial neoplasia

* Corresponding author.
E-mail address: SHartwig@spmsd.com (S. Hartwig).

http://dx.doi.org/10.1016/j.pvr.2015.06.003

As it takes several decades for HPV infection to progress to cancer, it will be some time before the real effects of current HPV vaccination programs will be seen in terms of a reduced incidence of HPV-related cancers. In the meantime, in countries like Australia, where vaccination coverage is high, a reduction of 77% in the prevalence of infections with the HPV types targeted by the vaccines has been observed in young women [3], along with a 92.6% reduction in the incidence of genital warts ($p_{trend} < 0.0001$) [4]. Moreover, just 3 years after the implementation of the HPV vaccination program in Australia, the incidence of high-grade cervical precancerous lesions in women under 18 years of age decreased, from 0.85% in 2006 (1 year before vaccine introduction) to 0.22% in 2009 ($p=0.003$) [5]. This ecological observation was confirmed in two recent studies. One was a data-linkage study [6] that reported an adjusted vaccine effectiveness of 47.5% (95% confidence interval [CI]: 22.7–64.4%) to prevent cervical intraepithelial neoplasia (CIN) grade 3/adenocarcinoma in situ or worse among women who received all required doses of the quadrivalent vaccine (i.e., were fully vaccinated). The other study [7] reported a vaccine effectiveness of 46% (95% CI: 33–57%) for histologically confirmed high-grade cervical precancerous lesions among young women who were fully vaccinated before they initiated cervical cancer screening. Additionally, as a reflection of herd immunity, there has been a significant reduction in the frequency of genital warts in young men. In Australia, where there is an estimated 83% coverage of the first dose of HPV vaccine in girls aged 12–13 years, the reduction in the proportion of new genital warts cases among young men was in the order of 60% [8,9]. In 2013, Australia became the first country to implement a school-based vaccination program for boys aged 12–13 years. Currently the United States, Ireland, New Zealand, and Canada are also recommending HPV vaccination for boys.

After HPV16/18, high-risk HPV31/33/35/45/52/58 are the six most frequently detected HPV types in invasive cervical cancer worldwide [10]. Merck has developed a second generation nine-valent HPV L1 virus-like particle vaccine (Gardasil® 9), which aims to protect against the seven high-risk HPV types (HPV16/18/31/33/45/52/58) most frequently responsible for cervical cancer development worldwide, and the low-risk HPV types (HPV6/11) responsible for about 90% of genital warts. Thus, the nine-valent vaccine is designed to protect against five 'new' high-risk HPV types (HPV31/33/45/52/58) that are not targeted by the quadrivalent or the bivalent vaccine. The vaccine is indicated to protect against premalignant lesions and cancers affecting the cervix, vulva, vagina and anus caused by vaccine HPV types as well as genital warts caused by specific HPV types.

In a Phase III study, the nine-valent vaccine prevented 97% of high-grade precancerous lesions of the cervix, vulva, and vagina caused by the five new high-risk HPV types (HPV31/33/45/52/58) [11]. The nine-valent vaccine also generated immune responses to HPV6/11/16/18 that were as good as or better than those generated by the quadrivalent vaccine.

The aim of this study was to estimate the annual burden of selected cancers, precancerous lesions, and genital warts attributable to the HPV types targeted by the second generation nine-valent HPV vaccine Gardasil 9® (high-risk HPV16/18/31/33/45/52/58, low-risk HPV6/11) in women and men in Europe in 2013, and to compare this to the estimated annual burden of the same lesions related to the HPV types targeted by the first generation HPV vaccines.

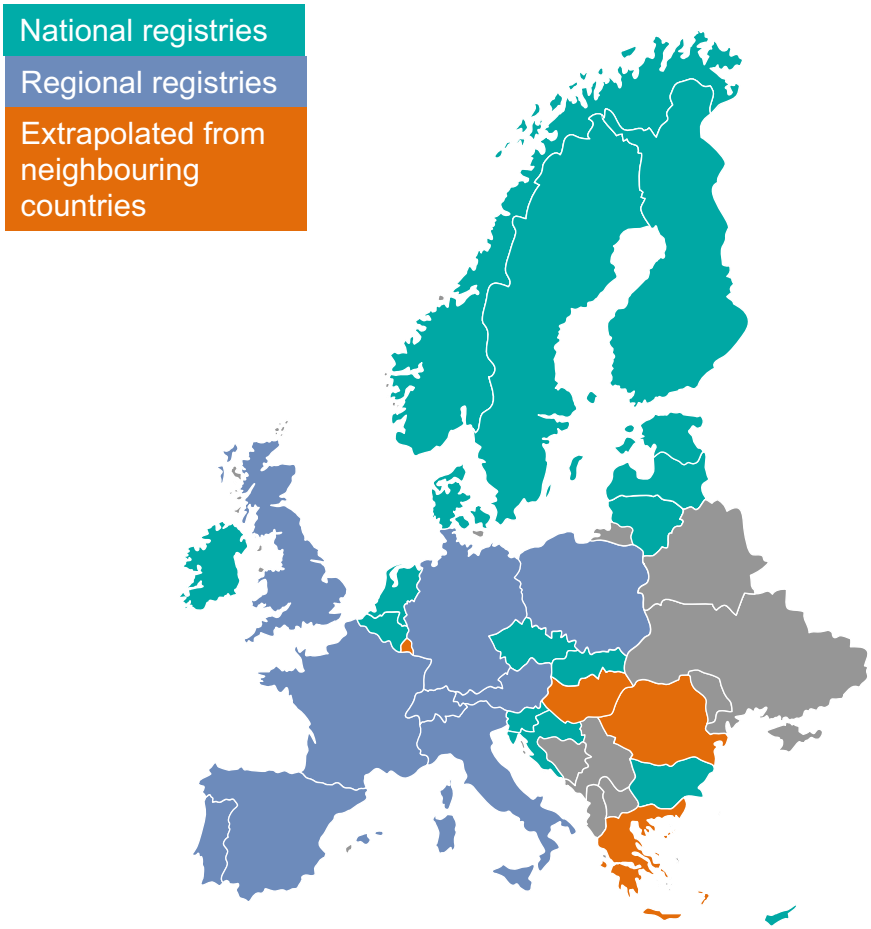

Fig. 1. Selected countries: European Medicines Agency region and Switzerland (32 countries).

2. Material and methods

2.1. Estimation of the annual burden of cancer in Europe

The Cancer Incidence in Five Continents (CI5) database, available on the IARC website [12], contains worldwide data on cancer incidence rates classified by International Classification of Diseases 10th Revision (ICD-10) codes. These data are obtained from regional or national registries, depending on the country, but to be included in CI5 these registries must meet the IARC's quality criteria, i.e., they must have reliable cancer registry data. The present report includes cancer incidence data from CI5 Volume X, which were collected from 2003 throughout 2007. We selected a total of 32 countries: all 31 countries covered by the European Medicines Agency (Austria, Belgium, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxemburg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Slovakia, Spain, Sweden, and the United Kingdom) plus Switzerland.

The information in CI5 Volume X was obtained from national cancer registries for Belgium, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, Iceland, Ireland, Latvia, Lithuania, Malta, the Netherlands, Norway, Slovenia, Slovakia, and Sweden. The information in CI5 Volume X was obtained from regional cancer registries for Austria, France, Germany, Italy, Poland, Portugal, Spain, Switzerland, and the United Kingdom (Fig. 1).

To ensure that national populations were adequately represented in countries where only regional cancer registries exist, we assessed the geographical coverage and distribution of these registries.

Five of the 32 countries selected did not have data available in CI5 Volume X, as they did not have reliable cancer registry data: Greece, Hungary, Liechtenstein, Luxemburg, and Romania. We excluded Lichtenstein from our analysis, but for the remaining four countries we extrapolated the age-specific average cancer incidence rates of neighboring countries, or from cancer registries in the same area as the countries selected. The choice of countries used for extrapolation was the same as that in the Globocan database [13]. Thus for Greece data from Bulgaria, Cyprus, and Central Serbia were used; for Hungary data from Austria, Croatia, Central Serbia, Slovakia, and Slovenia were used; for Luxemburg data from French and German cancer registries were used; and for Romania data from Bulgaria, Slovakia, and one regional registry in Romania were used.

In conclusion, our results are referring to a geographical region of 31 European countries.

2.2. Estimation of the annual number of new selected HPV-related cancers in Europe

The following HPV-related cancer sites were selected: cervix (ICD-10 code C53), vulva (C51), vagina (C52), and anus (C21, both sexes). We estimated the mean annual number of new cancers at these sites in the selected countries based on the sex- and age-specific cancer incidence data available in CI5 Volume X [14], and extrapolated to the population of each country using 2013 Eurostat population data (for Italy we used 2012 population data, as 2013 data were not yet available) [15] as follows:

where AIR is the age- and sex-specific annual incidence rate, and population is the age- and sex-specific population. The estimated numbers of new HPV-related cancer cases for all the selected countries were then summed to obtain the overall European burden. Sex-specific data were available for anal cancer. However, as preference was given to European data, sex-specific data were not used, as they were not considered robust enough due to the small sample size. When adjusted and crude data were available, preference was given to adjusted data.

The number of new cancers attributable to HPV overall, to HPV16/18, and to HPV16/18/31/33/45/52/58 was then estimated by applying the corresponding cancer site-specific HPV prevalence. Data on HPV prevalence were extracted from the most relevant published cancer site-specific data. To avoid overestimating the prevalence of individual HPV types due to multiple infections, different adjustment methods, which are described in the cited paper for each cancer site, were used.

There are other cancers known to be associated with HPV, including penile cancer in men and a subset of head and neck cancers in both sexes. We did not estimate the burden of these cancers in this work, as the currently licensed HPV vaccines don't have an indication for cancers at these anatomical sites.

Moreover, the data currently available did not allow us to calculate the burden associated with the seven high-risk HPV types targeted by the nine-valent vaccine. Robust studies to estimate the prevalence of HPV in these cancer sites, and more specifically the attributable fraction of the seven high-risk HPV types targeted by the nine-valent vaccine, are still ongoing.

$$\text{Total } nb \text{ of new cases} = \frac{\sum_{\text{Countries}} \left\{ \sum_{age=0}^{85+} (\text{AIR in male} * \text{population} + \sum_{\text{type of cancer}} (\text{AIR in female} * \text{population})) \right\}}{100,000}$$

2.3. Estimation of the annual number of new selected HPV-related precancerous lesions in Europe

We performed a literature review to retrieve robust age-specific incidence data for cervical pre-invasive neoplasia CIN2+ (including CIN2, CIN3 and adenocarcinoma in situ (AIS), vulvar intraepithelial neoplasia grades 2 and 3 (VIN2/3), and vaginal intraepithelial neoplasia grades 2 and 3 (VaIN2/3) in Europe.

Nygard et al. estimated the incidence rates of CIN2+ (including CIN2/3 and AIS) per 100,000 woman years in 2004–2006, the period prior to the availability of the quadrivalent vaccine. The estimates were presented by age group and were age-standardized using the European standard population. Data were available for four Nordic countries: Denmark, Iceland, Norway, and Sweden. Moreover, we had access to incidence data on CIN2+ for the period 2009–2011 from the French cancer registry of the Alsace Region, where an organized screening program has been in place since 1994 in Bas–Rhin and since 2001 in Haut–Rhin (unpublished data). Based on the data from these five countries we estimated incidence rate ranges for CIN2+ by age group, which we then extrapolated to the combined female population of the 31 included countries. The study by Nygard et al. [16] also contained incidence data for VIN2/3 and VaIN2/3 by age group from Denmark, Iceland, Norway, and Sweden for the period 2004–2006. However, as only VIN3 and VaIN3 were recorded in Sweden, we excluded the Swedish data and based our estimates on the data from the remaining three countries.

We then estimated the number of CIN2+ (including CIN2/3 and AIS), VIN2/3, and VaIN2/3 cases attributable to the HPV types targeted by the nine-valent vaccine and the quadrivalent vaccine, respectively. For CIN2+ we applied the site-specific overall HPV prevalence, the relative contribution of HPV6/11/16/18, and that of HPV6/11/16/18/31/33/45/52/58, respectively. As no specific European data for CIN2+ have yet been published, the authors of the

recently published paper [17] kindly provided us with information specific to Europe. We applied HPV prevalence and type attributable fractions from published literature for VIN2/3 [18] and VaIN2/3 [19], as well as additional data we requested from the authors of these studies. The adjustment methods that were used to account for multiple infections are described in the cited papers for each lesion type.

As no age-specific incidence data are available for anal intraepithelial neoplasia grades 2 and 3 (AIN2/3), we used sex-specific, age-standardized incidence rates from the Danish Registry of Pathology [20] and extrapolated them to the female and the male population, respectively, of all 31 European countries. The estimated annual number of AIN2/3 attributable to HPV overall, HPV6/11/16/18, and HPV6/11/16/18/31/33/45/52/58, respectively, was based on HPV prevalence data extracted from Alemany et al. [19], as well as additional data we requested from the authors of that study.

2.4. Estimation of the annual number of new genital warts cases in Europe

To estimate the annual number of new genital warts cases we used the methodology previously described [21]. Briefly, two European publications were identified that, based on their design, provided the most robust incidence data for Europe [22,23]. Both are retrospective cohort studies carried out using databases, including very large samples of routinely collected data. We extrapolated the value from each publication to the 2013 population of the 31 European countries to provide an estimated range of the annual number of new genital warts cases in women and men in Europe. The estimated prevalence of HPV6/11 of 90% in genital warts was then applied to estimate the number of cases attributable to the HPV types targeted by the nine-valent and quadrivalent vaccines.

3. Results

3.1. Women

3.1.1. HPV-related cancers in women

3.1.1.1. Cervical cancer. The estimated annual number of new cervical cancers in 2013 was 34,708 (95% bound: 32,640–36,793) in the 31 selected European countries combined. It is generally accepted that HPV infection is necessary for the development of cervical cancer [24], thus 100% of these cases are believed to be HPV-positive. HPV16/18 are the predominant types in cervical cancer, accounting for 72.8% (95% CI: 70.8–74.7) of cases [10]; high-risk HPV16/18/31/33/45/52/58 were estimated to be responsible for 89.0% (95% CI: 87.5–90.3) of cases in Europe (Table 1). Accordingly, a total of 25,267 (95% bound: 23,062–27,528) cases were estimated to be attributable to HPV16/18 versus 30,890 (95% bound: 28,539–33,242) cases attributable to HPV16/18/31/33/45/52/58. The estimated annual number of new cervical cancer cases attributable to the five new HPV types targeted by the nine-valent vaccine (HPV31/33/45/52/58) was thus 5623 (95% bound: 4681–6640) (Table 2).

3.1.1.2. Vulvar cancer. The estimated annual number of new vulvar cancers was 9544 (95% bound: 8509–10,596). Given the overall HPV prevalence in vulvar cancer in Europe of 19.3% (95% CI: 16.7–22.0) [18], 1842 (95% bound: 1377–2381) cases were estimated to be attributable to HPV. The relative contribution of HPV16/18 and HPV16/18/31/33/45/52/58 were estimated at 73.6% (95% CI: 66.4–79.9) and 84.0% (95% CI: 77.6–89.0), respectively [18] (Table 1). After applying these relative contribution estimates, 1356 (95% bound: 903–1911) cases were estimated to be attributable to HPV16/18 versus 1547 (95% bound: 1061–2124) cases attributable to HPV16/18/31/33/45/52/58. The estimated annual number of new vulvar cancer cases associated with the five new HPV types targeted by the nine-valent vaccine (HPV31/33/45/52/58) was thus 193 (95% bound: 71–401) (Table 2).

3.1.1.3. Vaginal cancer. The estimated annual number of new vaginal cancer cases was 2171 (95% bound: 1676–2684). Of these cases, 1544 (95% bound: 1046–2107) are estimated to be attributable to HPV, assuming an overall HPV prevalence in vaginal cancer of 71.1% (95% CI: 63.2–78.1) in Europe [25]. The relative contribution of HPV16/18 and HPV16/18/31/33/45/52/58 was estimated to be 71.2% (95% CI: 61.8–79.6) and 85.6% (95% CI: 77.1–91.3), respectively (Table 1). Applying these values, 1099 (95% bound: 635–1685) cases were estimated to be attributable to HPV16/18 versus 1322 (95% bound: 799–1927) cases attributable to HPV16/18/31/33/45/52/58. Thus the estimated annual number of new vaginal cancers in Europe associated with the five new HPV types targeted by the nine-valent vaccine was 222 (95% bound: 69–483) (Table 2).

3.1.1.4. Anal cancer. The estimated annual number of new anal cancer cases was 4562 (95% bound: 3875–5265) among women in Europe, irrespective of HPV status. Given the overall HPV prevalence in anal cancer of 87.6% (95% CI: 81.6–92.1) [19], 3996 cases (95% bound: 3151–4855) were estimated to be attributable to HPV. The relative contribution of HPV16/18 in HPV-positive anal cancers was estimated at 87.1% (95% CI: 80.7–92.1) and the relative contribution of HPV16/18/31/33/45/52/58 at 89.8% (95% CI: 83.8–94.2). After applying these values, 3481 (95% bound: 2533–4477) cases were estimated to be attributable to HPV16/18 versus 3589 (95% bound: 2632–4577) attributable to HPV16/18/31/33/45/52/58 (Table 1). Thus an additional 108 (95% bound: 13–356) cases were estimated to be attributable to the five new HPV types targeted by the nine-valent vaccine (Table 2).

3.1.2. HPV-related precancerous lesions in women

3.1.2.1. Cervical intraepithelial neoplasia grade 2 or worse. Age-standardized incidence rates of CIN2+ (including CIN2/3 and AIS) in the five countries for which data were available ranged between 138.8 (Norway) and 183.2 (Iceland) per 100,000 woman-years (Appendix A). Incidence was very low in the youngest age group (<20 years) in the four Nordic countries considered (there were no data available for this age group in France, where cervical cancer screening starts at age 25 years) [16]. However, in Iceland, where organized cervical cancer screening begins at 20 years of age, incidence rates in this age group were slightly higher, and the highest rates were observed from age 20 to 30 years. After the age of 50 years age-specific incidence rates in Iceland were the lowest of the four Nordic countries considered.

All CIN is HPV-related, with HPV6/11/16/18 accounting for 23–25% of CIN1, 38.4–39% of CIN2, and 58% of CIN3. The HPV types targeted by the nine-valent vaccine account for 46–51% of CIN1, 71–74.3% of CIN2 and 85–90% of CIN3 (worldwide data) [17] (Table 3). Based on the age-specific incidence rates, the estimated annual number of new CIN2+ cases in women in Europe ranged between 267,350 and 510,609. 45.5% and 82.3% of these cases were estimated to be attributable to the HPV types targeted by the quadrivalent vaccine (HPV6/11/16/18) and nine-valent vaccine (HPV6/11/16/18/31/33/45/52/58), respectively [17 with additional information on European data kindly provided by the authors] (Table 3, (Fig. 2). After applying these values, 121,644 to 232,327 of the 267,350 to 510,609 new annual CIN2+ cases were estimated to be attributable to HPV6/11/16/18 versus 220,029 to 420,231 cases for HPV6/11/16/18/31/33/45/52/58. Therefore an additional 98,385 to 187,904 CIN2+ cases annually are estimated to be related to the

Table 1
Overall HPV prevalence and the relative contribution[a] of HPV16/18 and HPV16/18/31/33/45/52/58 by cancer site.

Cancer site	ICD-10 code	HPV prevalence %, (95% CI)	HPV16/18 attributable fraction among HPV+ cases %, (95% CI)	HPV 16/18/31/33/45/52/58 attributable fraction among HPV+ cases%, (95% CI)	HPV 31/33/45/52/58 attributable fraction among HPV+ cases%	Reference
Cervix	C53	100	72.8 (70.8–74.7)	89.0 (87.5–90.3)	+ 16.2 (14.6–17.8)	de Sanjosé et al. [10]
Vulva	C51	19.3 (16.7–22.0)	73.6 (66.4–79.9)	84.0 (77.6–89.0)	+ 10.5 (6.2–15.9)	de Sanjosé et al. [18]
Vagina	C52	71.1 (63.2–78.1)	71.2 (61.8–79.6)	85.6 (77.1–91.3)	+ 14.4 (7.9–21.9)	Alemany et al. [25]
Anus	C21	87.6 (81.6–92.1)	87.1 (80.7–92.1)	89.8 (83.8–94.2)	+ 2.7 (0.7–6.8)	Alemany et al. [19]

HPV: human papillomavirus; ICD-10: International Classification of Diseases, 10th Revision; CI: confidence interval.
[a] Adjusted for multiple infections.

Table 2
Estimated mean annual number of new HPV-related cancer cases in women and men in Europe.

Cancer site	*N* of new cancers irrespective of HPV status (95% bound)	*N* of new cancers attributable to HPV (95% bound)	*N* of new cancers attributable to HPV16/18 (95% bound)	*N* of HPV16/18/31/33/45/52/58+ cancers (95% bound)	*N* of cases attributable to additional types (9v vaccine vs 2v/4v vaccine)
Cervical cancer	34,708 (32,640–36,793)	34,708 (32,640–36,793)	25,267 (23,062–27,528)	30,890 (28,539–33,242)	5623 (4681–6640)
Vulvar cancer	9,544 (8,509–10,596)	1,842 (1,377–2,381)	1,356 (903–1,911)	1,547 (1,061–2,124)	193 (71–401)
Vaginal cancer	2,171 (1,676–2,684)	1,544 (1,046–2,107)	1,099 (635–1,685)	1,322 (799–1,927)	222 (69–483)
Anal cancer (F)	4,562 (3,875–5,265)	3,996 (3,151–4,855)	3,481 (2,533–4,477)	3,589 (2,632–4,577)	108 (13–356)
Total (women)	50,985 (47,018–54,983)	42,090 (38,436–45,863)	31,203 (27,319–35,353)	37,347 (33,230–41,609)	6146 (4880–7780)
Anal cancer (M): Total (men)	2,729 (2,195–3,279)	2,390 (1,783–3,025)	2,082 (1,431–2,790)	2,147 (1,487–2,852)	65 (6–226)
Total (both sexes)	53,714 (49,296–58,165)	44,480 (40,294–48,795)	33,285 (28,818–38,055)	39,494 (34,787–44,372)	6210 (4892–7981)
%	100	83	62	74	12

HPV: human papillomavirus; CIN: cervical intraepithelial neoplasia; VIN: vulvar intraepithelial neoplasia; VaIN: vaginal intraepithelial neoplasia; AIN: anal intraepithelial neoplasia; CI: confidence interval.

Table 3
Overall HPV prevalence and the relative contribution[a] of HPV6/11/16/18 and HPV6/11/16/18/31/33/45/52/58 by precancerous lesion.

Precancerous lesion	HPV prevalence %, (95% CI)	HPV6/11/16/18 attributable fraction HPV+ cases %, (95% CI)	HPV 6/11/16/18/31/33/45/52/58 attributable fraction among HPV+ cases %, (95% CI)	HPV 31/33/45/52/58 attributable fraction among HPV+ cases %	Reference
CIN 1[b]	100	23–25	51–46	+23–26	Joura et al. [17]
CIN 2[b]	100	38.4–39	71–74.3	+32–35.9	Joura et al. [17]
CIN 3[b]	100	58	85–90	+27–32.	Joura et al. [17]
CIN 2+[c]	100	45.5	82.3	+36.8	Joura et al. [17] with additional information kindly provided by the authors
VIN 2/3[c]	86.9 (82.6–90.4)	82.2 (77.2–86.6)	94.4 (91.0–96.9)	+12.2	de Sanjosé et al. [18]
VaIN 2/3[c]	95.8 (91.8–98.2)	64.1 (56.6–71.2)	77.6 (70.6–83.3)	+13.5	Alemany et al. [25]
AIN 2/3[c]	95.3 (84.2–99.4)	75.4 (59.4–87.4)	81.5 (66.4–91.9)	+6.1	Alemany et al. [19]

HPV: human papillomavirus; CIN: cervical intraepithelial neoplasia; VIN: vulvar intraepithelial neoplasia; VaIN: vaginal intraepithelial neoplasia; AIN: anal intraepithelial neoplasia; CI: confidence interval.
[a] Adjusted for multiple infections.
[b] Worldwide data.
[c] European data.

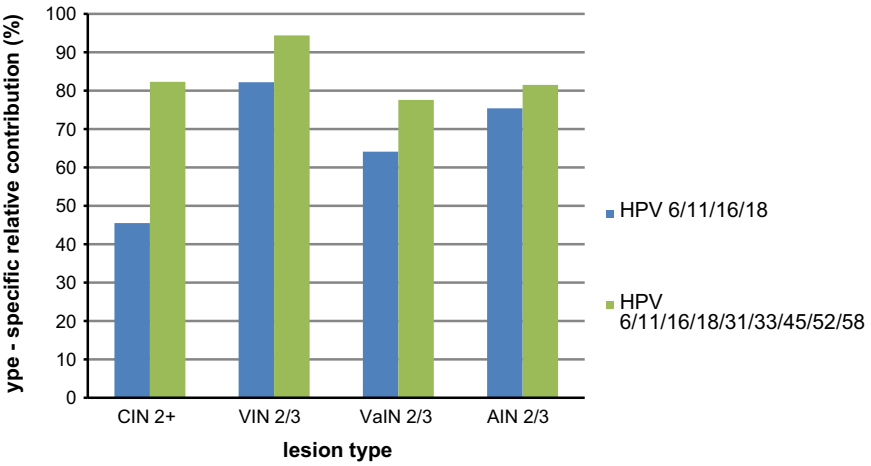

Fig. 2. Relative contribution of HPV types 6/11/16/18 versus 6/11/16/18/31/33/45/52/58 in precancerous lesions. HPV: human papillomavirus; CIN: cervical intraepithelial neoplasia; CIN2+ includes CIN2/3 and AIS; VIN: vulvar intraepithelial neoplasia; VaIN: vaginal intraepithelial neoplasia; AIN: anal intraepithelial neoplasia.

Table 4
Estimated annual number of new CIN2+, VIN 2/3, VaIN 2/3 and AIN 2/3 cases in women and men in Europe.

Precancerous lesion	*N* of new precancerous lesions irrespective of HPV status	*N* of cases attributable to HPV	*N* of cases related to quadrivalent vaccine types (range)	*N* of cases related to nine-valent vaccine types (range)	Additional *N* of cases related to five new HPV types
CIN 2+	267,350–510,609	267,350–510,609	121,644–232,327	220,029–420,231	98,385–187,904
VIN 2/3	13,886–27,592	12,067–23,977	9,919–19,709	11,391–22,635	1,472–2,925
VaIN 2/3	2,549–4,719	2,442–4,521	1,566–2,898	1,895–3,508	329–610
AIN 2/3 (F)	1,545	1,472	1,110	1,200	90
AIN 2/3 (M)	1,093	1,042	786	849	63
Total (both sexes)	**286,423–545,558**	**284,373–541,621**	**135,025–256,830**	**235,364–448,423**	**100,339–191,592**
%	**100**	**99**	**47**	**82**	**35**

HPV: human papillomavirus; CIN: cervical intraepithelial neoplasia; CIN 2+ includes CIN2/3 and AIS; VIN: vulvar intraepithelial neoplasia; VaIN: vaginal intraepithelial neoplasia; AIN: anal intraepithelial neoplasia; *N*: number.

five new HPV types included in the nine-valent vaccine (31/33/45/52/58) (Table 4).

3.1.2.2. Vulvar intraepithelial neoplasia grades 2 and 3. The age-standardized incidence rates of VIN2/3 in the three Nordic countries for which data were available ranged between 4.8 (Norway) and 8.8 (Iceland) per 100,000 woman-years (Appendix B). Based on the age-specific incidence data from these countries, the estimated annual number of new VIN2/3 cases in Europe was estimated at between 13,886 and 27,592. Of these cases 86.9% (95% CI: 82.6–90.4) are believed to be HPV-related, with HPV16/18 accounting for 82.2% (95% CI: 77.2–86.6) and HPV16/18/31/33/45/52/58 accounting for 94.4% (95% CI: 91.0–96.9) of HPV-positive cases [18] (Table 3, Fig. 2). Based on these estimates, 12,067 to 23,977 of the VIN2/3 cases were estimated to be HPV-positive, with 9919 to 19,709 cases attributable to HPV16/18 versus 11,391 to 22, 635 attributable to HPV16/18/31/33/45/52/58. Thus the estimated annual number of new VIN2/3 cases associated with the five new HPV types included in the nine-valent vaccine ranged between 1472 and 2925 in women in Europe (Table 4).

3.1.2.3. Vaginal intraepithelial neoplasia grades 2 and 3. Age-standardized incidence rates of VaIN2/3 in the three Nordic countries for which data were available ranged between 0.9 (Norway) and 1.3 (Iceland) per 100,000 woman-years (Appendix C). Based on age-specific incidence data from these countries, the estimated annual number of new VaIN2/3 cases in women in Europe ranged between 2549 and 4719. Of these cases, 95.8% (95% CI: 91.8–98.2) are expected to be HPV-related, with HPV16/18 accounting for 64.1% (95% CI: 56.6–71.2) and HPV16/18/31/33/45/52/58 accounting for 77.6% (95% CI: 70.6–83.3) of HPV-positive cases [25] (Table 3, Fig. 2). Based on these estimations, 2442 to 4521 of the 2549 to 4719 new annual VIN2/3 cases were expected to be HPV-positive, with 1566 to 2898 cases attributable to HPV16/18 versus 1895 to 3508 cases attributable to HPV16/18/31/33/45/52/58. The estimated annual number of new VaIN2/3 cases associated with the new HPV types included in the nine-valent vaccine (HPV31/33/45/52/58) thus ranged between 330 and 610 (Table 4).

3.1.2.4. Anal intraepithelial neoplasia grades 2 and 3. Based on the age-standardized rate of 0.58 (per 100,000 person-years) for AIN2/3 in women [20], 1545 new AIN2/3 cases were estimated to occur each year in women in the 31 European countries. Of these cases, 95.3% (95% CI: 84.2–99.4%) are believed to be HPV-related [19]. Applying these values resulted in 1472 cases attributable to HPV, with 75.4% (95% CI: 59.4–87.4) and 81.5% (95% CI: 66.4–91.9) attributable to the HPV types targeted by the quadrivalent and the nine-valent vaccine, respectively (Table 3, Fig. 2), corresponding to 1110 and 1200 cases, respectively (Table 4).

3.1.3. Genital warts

The most robust data on the incidence of genital warts come from Germany and the United Kingdom. Based on these studies, a lower incidence estimate of 142.0 per 100,000 woman-years [23] and an upper estimate of 191.1 per 100,000 woman-years [22] were extracted, and so the estimated annual number of new genital wart cases in women in Europe ranged between 378,141 and 508,893. Assuming an HPV6/11 prevalence in genital warts of

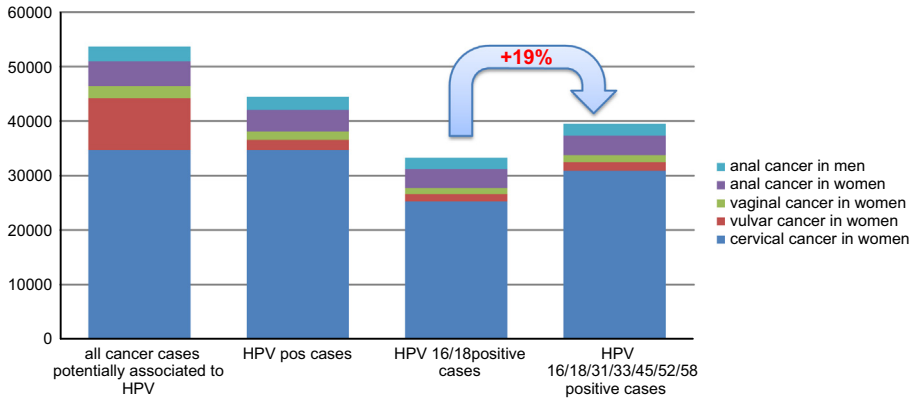

Fig. 3. Estimated annual number of new HPV-related cancer cases in women in Europe associated with the HPV types targeted by the quadrivalent and the nine-valent vaccine. HPV: human papillomavirus.

Table 5
Estimated annual number of new genital wart cases in women and men in Europe.

	N of new annual cases (range)	*N* of new annual cases related to HPV6/11 (range)
Women	378,141–508,893	340,327–458,003
Men	375,467–426,425	337,921–383,782
Total (both sexes)	**753,608–935,318**	**678,248–841,785**

HPV: human papillomavirus; *N*: number.

90% [2], between 340,327 and 458,003 of these cases were estimated to be attributable to HPV6/11 (Table 5).

3.2. Men

3.2.1. HPV-related cancers

3.2.1.1. Anal cancer. The estimated annual number of new anal cancers in men in Europe was estimated at 2729 (95% bound: 2195–3279), irrespective of HPV status. Given the overall HPV prevalence of 87.6% (95% CI: 81.6–92.1) in anal cancer [19], 2390 (95% bound: 1783–3025) of these cases were estimated to be attributable to HPV. The relative contribution of HPV16/18 in HPV-positive anal cancer has been estimated at 87.1% (95% CI: 80.7–92.1), with the relative contribution of HPV16/18/31/33/45/52/58 at 89.8% (95% CI: 83.8–94.2). After applying these values, 2082 (95% bound: 1431–2790) cases were estimated to be attributable to HPV16/18 versus 2147 (95% bound: 1487–2852) attributable to HPV16/18/31/33/45/52/58 (Table 1), thus an additional 65 (95% bound: 6–226) cases were estimated to be attributable to five new HPV types included in the nine-valent vaccine (Table 2).

3.2.2. HPV-related precancerous lesions

3.2.2.1. Anal intraepithelial neoplasia grades 2 and 3. Based on the age-standardized rate of AIN2/3 in men of 0.43 [20], 1093 new AIN2/3 cases were expected to occur each year in men in the 31 European countries and an 95.3% (95% CI: 84.2–99.4%) of AIN2/3 are HPV-related [19]. This rendered 1042 cases, with 75.4% (95% CI: 59.4–87.4) and 81.5% (95% CI: 66.4–91.9) attributable to the HPV types targeted by the quadrivalent and the nine-valent vaccine, and corresponded to an estimated annual number of 786 and 849 cases, respectively (Tables 3 and 4).

3.2.3. Genital warts

The most robust data on the incidence of genital warts come from Germany [22] and the United Kingdom [23]: Based on these studies, a lower incidence estimate of 147.66 per 100,000 man-years and an upper estimate of 167.7 per 100,000 man-years were extracted, and so the estimated annual number of new genital wart cases in men in Europe ranged between 375,467 and 426,425. Assuming an HPV6/11 prevalence in genital warts of 90% [2], between 337,921 and 383,782 of these cases were estimated to be attributable to HPV6/11 (Table 5).

4. Discussion

Our estimates demonstrate the high burden of cancer and precancerous lesions associated with the HPV types targeted by the new nine-valent HPV vaccine (HPV6/11/16/18/31/33/45/52/58) that are expected to occur every year in women and men in Europe. Overall, 39,494 (95% bound: 34,787 to 44,372) of the 53,714 (95% bound: 49,296 to 58,165) new HPV-related cancers of the cervix, vulva, vagina, and anus in women and men in Europe are expected to be associated with the high-risk HPV types included in the nine-valent vaccine, versus 33,285 (95% bound: 28,818 to 38,055) associated with high-risk HPV16/18. This represents an additional 6210 cancer cases (95% bound: 4892–7981), corresponding to a relative increase of 19% (Fig. 3).

The proportion of cervical cancer attributable to the seven high-risk HPV types targeted by the nine-valent vaccine is similar worldwide. The combined relative contribution of these seven high-risk types in Europe was 89.0% (95% CI: 87.5–90.3) compared to worldwide values of 89.4% (95% CI: 88.8–90.1), which range from 84.6% (95% CI: 81.9–87.1) in Central America to 95.5% (95% CI: 91.2–98.2) in North America [26].

Furthermore, the estimated annual number of new cases of precancerous lesions occurring in women and men in Europe (CIN2/3+AIS, VIN2/3, VaIN2/3 and AIN2/3) was 286,423 to 545,558, with 284,373 to 541,621 HPV-positive cases. Of these, 235,364 to 448,423 cases are associated with HPV6/11/16/18/31/33/45/52/58 versus 135,025 to 256,830 associated with HPV6/11/16/18. The five new HPV types 31/33/45/52/58 were thus associated with an additional 100,339 to 191,592 cases per year, corresponding to a relative increase of 75% (Table 4, (Fig. 4). We did not estimate the expected annual number of new low-grade precancerous lesions of the cervix (CIN1). Indeed, no robust incidence data are available on CIN1 as these cases are not usually reported to cancer registries, and a high amount of this cases regress spontaneously. Thus records of CIN1 incidence very much depend on the national screening system and cannot be extrapolated. Even if CIN1 is not currently considered a precancerous lesion, the potential psychological and economic impact (due to medical follow-up) on affected women is very important. The additional number of CIN1 cases related to the five new HPV types 31/33/45/52/58 is expected to be very high, as

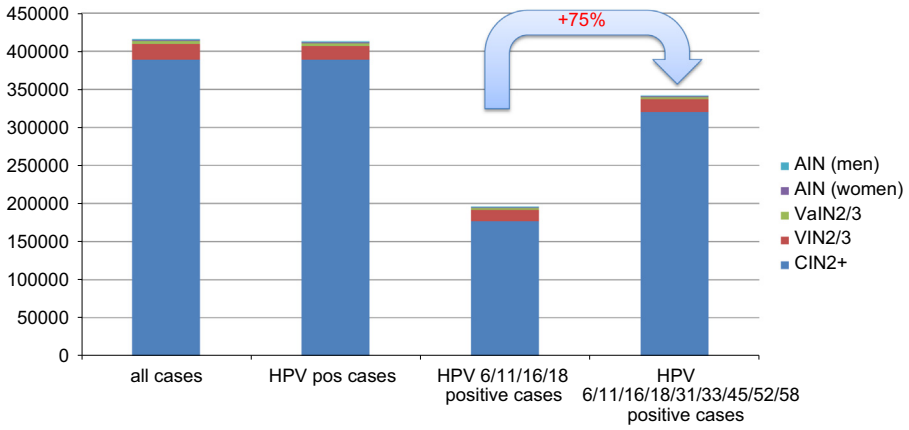

Fig. 4. Estimated annual number of new HPV-related precancerous lesions of the cervix, vulva, vagina and anus associated with the HPV types targeted by the quadrivalent and the nine-valent vaccine in women in Europe. HPV: human papillomavirus; CIN: cervical intraepithelial neoplasia; CIN2+ includes CIN2/3 and AIS; VIN: vulvar intraepithelial neoplasia; VaIN: vaginal intraepithelial neoplasia; AIN: anal intraepithelial neoplasia.

worldwide 46–51% of CIN1 are related to the HPV types targeted by the nine-valent vaccine compared to 23–25% for the quadrivalent vaccine types [17].

As previously mentioned, there are other cancers known to be associated with HPV, including penile cancer in men and a subset of head and neck cancers in both sexes. The currently licensed HPV vaccines don't have an indication for cancers at these anatomical sites and up to now efficacy of the vaccines against these cancers has not been demonstrated. However, it can be expected that future studies based on routine use of the vaccines may demonstrate their efficacy against head and neck cancers and penile cancers.

Based on the above described methodology we estimated the overall burden of head and neck cancers in women and men and penile cancer in men in Europe. 17,676 new head and neck cancer cases were estimated to occur every year in women, with 2089 and 1915 related to second and first generation vaccine types, respectively. For men the number of head and neck cancers was 80,062, of which 7911 were related to second and 7144 cases to first generation vaccine types. The burden of penile cancer was 4096 this region with 1070 and 932 cases related to second and first generation vaccines, respectively (work in progress). These data are preliminary, as the key studies estimating the prevalence of HPV at these sites, and more specifically the attributable fraction of the seven high-risk HPV types targeted by the nine-valent vaccine, are still ongoing. The data currently available in the literature are very heterogeneous, as only a subset of head and neck cancers is HPV-related, and many other risk factors exist, like alcohol and tobacco consumption, which differ from region to region. Moreover, differences in the results of HPV prevalence between studies might be due to contamination and the variability of HPV detection methods. Studies considering more accurate biomarkers of oncogenic HPV activity, such as E6/E7 mRNA or p16INK4a in addition to HPV DNA prevalence, are still ongoing.

Recurrent respiratory papillomatosis is also highly associated with HPV. It is a very rare disease, which is difficult to treat and has high recurrence rates. However, incidence data in Europe are scarce [27], and thus it was not possible to estimate the number of new annual cases in Europe. Low-risk HPV6/11 are prevalent in virtually all cases [27,28]. and no additional burden is expected to be associated with the five new HPV types.

4.1. Strengths and limitations

A short-term prediction method was used to estimate the number of new cancer cases in 2013 from the most recent data collected from 2003 to 2007. Therefore these estimates were accurate only if the incidence rates of the cancers under study remained stable over time. In the case of increasing incidence, they would slightly underestimate the expected number of cases, and the opposite would be true in the case of decreasing incidence.

As mentioned above, the CI5 database contains national cancer incidence rates for 19 European countries. Eight of the countries included in this report had only regional incidence rates available, which were extrapolated to the entire country. Although we assessed the geographical coverage and distribution of these regional registries, other factors could vary and influence regional incidence rates. For the remaining four countries no robust regional or national data were available. We thus extrapolated the mean incidence data from surrounding cancer registries to these countries, but we had no means to check the robustness of this method. Therefore the results should thus be interpreted with particular caution.

For some cancer sites additional tests such as p16 or mRNA had been performed to confirm causality in the presence of HPV DNA (lack of data availability). Indeed, the mere presence of HPV is insufficient to prove causation, as the infection may be transient and not related to the carcinogenic process. Therefore our application of previously published HPV prevalence to an estimated number of new cancer cases may have yielded an overestimation of cases attributable to HPV.

Our calculations were based on the relative contribution estimates extracted from one study per cancer site. However, for each cancer site we selected the study with the most robust design and a large sample size, and that provided individual data allowing weighting for multiple infections. We used only European data and, when available, adjusted data rather than crude data. Sex-specific data for HPV prevalence in anal cancers were available, but we decided not to use it, as sample size by sex was not sufficient to obtain meaningful, precise estimates. In any case, there were no sizeable differences between the data for both sexes. It was not possible to compare the extracted data to results from meta-analyses, as to our knowledge no meta-analysis contains information about multiple infections in precancerous lesions, and thus the relative contribution of individual HPV types, taking multiple infection into account (i.e., to avoid double counting) could not be estimated. A literature search that we performed in parallel showed large differences in the prevalence of the different HPV types between studies and regions. However, it is not clear if these differences are due to real differences in the distribution of HPV types among European women, or to differences in HPV detection methods. Furthermore, most of the published studies contained no information about individual multiple infections or had low sample sizes. The calculation of a robust relative contribution of specific types was thus not possible based on these data, as it would have provided less meaningful results.

The method used to calculate the estimated annual number of new CIN cases also has some limitations. For CIN2+ we based our estimations on data extracted from one published epidemiological study covering four Nordic countries and one French study (unpublished). To calculate the estimated annual number of new CIN2+ cases in women in Europe we extrapolated the lower and the upper mean value of each age group to the population of each included European country. However, the incidence of CIN may vary throughout Europe, not only due to regional differences in the prevalence of HPV, but also due to different screening and prevention methods.

In Iceland for example, screening starts at age 20, with a 2-year interval until age 69. This might explain the high incidence rates observed in the youngest age groups and lower incidence rates in the age group over 50 in Iceland compared to the other four countries (personal communication from Kristján Oddsson).

We used data from countries with well-organized screening, thus reflecting the real high burden of precancerous lesions. By extrapolating these data to countries without or with less organized screening, we overestimated the detected burden in those countries. However these lesions do exist, even if not detected, and have a high potential to develop to cancer if not recognized and treated: 5% of CIN2 and more than 12% of CIN3 progress to invasive cancer [29]. Mc Credie et al. found that the cumulative 30 year incidence of invasive cancer in women with CIN3 was 30% and increased to 50% in women with persistent CIN3 [30]. Therefore we consider that the estimation of the detectable burden (referring to a real but not recognized burden in countries without or with limited screening) is of high value.

Another limitation is that our estimations of CIN2+ were based on estimates of the relative contribution of HPV observed in a population of young women (aged 16 to 26 years), who may have more multiple infections than older women. The burden of precancerous lesions is most important in the younger age group, and in the absence of age-specific relative contribution estimates, it seemed appropriate to use the data for all age groups combined.

Finally, it has to be considered that all results on the incidence of cancers and cervical precancerous lesions in this study have been estimated in a post-screening context.

The reporting of VIN2/3 and VaIN2/3 might not be exhaustive as there is no dedicated screening program, thus the reported burden is probably underestimated. Differences in the incidence of these lesions were observed between the different countries and it remains unclear to what extent the observed discrepancies can be explained by the completeness of registries, differences in clinical practice and management, or different background risk. Compared to a study from the Netherlands [31], much higher rates of VIN2/3 were reported in the study from Nygard et al. [16]. To our knowledge the data that we used for our estimation are the best data available in Europe as there is no organized screening and mandatory notification for these precancerous lesions. However, the results have to be considered with caution. Additional studies in the future are necessary to give a better insight on the real burden of these lesions.

5. Conclusions

A total number of 53,714 new cases (95% bound: 49,296–58,165) of cancers of the cervix, vulva, vagina in women, and anus in women and men, were estimated to occur in Europe every year, of which 44,480 (95% bound: 40,294–48,795) were estimated to be HPV-positive. Of the latter, 89%, i.e., 39,494 cases (95% bound: 34,787–44,372) were estimated to be related to HPV types 16/18/31/33/45/52/58 versus 75% to HPV16/18, corresponding to 33,285 cases (95% bound: 28,818–38,055).

Additionally, the estimated annual burden of CIN2+, VIN2/3, VaIN2/3 in women, and AIN2/3 in women and men ranged between 286,423 and 545,558 new cases per year, of which 82% were related to HPV6/11/16/18/31/33/45/52/58 (i.e., 235,364 to 448,423 cases versus 47% related to HPV6/11/16/18), corresponding to 135,025 to 256,830 cases.

In addition to cancers and precancerous lesions, between 753,608 and 935,318 new annual genital warts cases were estimated to occur in women and men in Europe, of which 90% (between 678,248 and 841,785 cases) were estimated to be related to HPV6/11.

The relative increase in the number of new cancers attributable to HPV16/18/31/33/45/52/58 compared to HPV16/18 was 19%. For precancerous lesions this increase was 75% when comparing HPV6/11/16/18/31/33/45/52/58 and HPV6/11/16/18

These data demonstrate how the large public health impact in the prevention of cancer that was achieved by the first generation HPV vaccines could be further increased by the second generation nine-valent HPV vaccine, due to additional cancer prevention and notably the prevention of precancerous lesion in women.

Competing interests

SH and GDF are employees of Sanofi Pasteur MSD; JJB has been a member of the scientific advisory board of MSD Sanofi-Pasteur and GSK, has received speaker's fees and travel grants from MSD Sanofi-Pasteur and GSK, and research supports from MSD Sanofi-Pasteur; FS was employee of Sanofi Pasteur MSD at the time of study initiation; LA received occasional travel grants to attend scientific meetings from MSD and Sanofi Pasteur MSD; SDS received travel grants from MSD, GSK and Qiagen and unrestricted research grants through ICO from Merck & Co. Inc. and Glaxo Smith Kline.; XC has received speaker honoraria, travel grants to attend scientific meetings from SPMSD, and research funding through ICO to undertake HPV studies from Merck & Co. Inc., Glaxo Smith Kline, and Sanofi Pasteur MSD.

Authors' contributions

SH contributed to the study design, literature research, data analysis, interpretation of findings and drafting of the manuscript. JJB contributed to the data collection and interpretation of findings. GDF contributed to the study design, and interpretation of findings. FS contributed to the study design, data-analysis, interpretation of findings, and critical editing of the manuscript. LA contributed to the interpretation of findings. SDS contributed to data collection, interpretation of findings, and critical editing of the manuscript. XC contributed to the study design, data collection, interpretation of

Table A1
Incidence of CIN2+ per 100,000 woman-years in five European countries.

Age group	Denmark	Iceland	Norway	Sweden	France	Range
<20	4.0	10.8	4.9	2.1	N.D.	2.1–10.8
20–24	540.1	723.3	327.0	417.0	N.D.	327.0–723.3
25–29	540.1	723.3	327.0	417.0	316.5	316.5–723.3
30–34	442.1	399.2	359.9	363.1	255.9	255.9–442.1
35–39	442.1	399.2	359.9	363.1	255.9	255.9–442.1
40–44	165.3	158.4	185.9	164.2	138.6	138.6–185.9
45–49	165.3	158.4	185.9	164.2	138.6	138.6–185.9
50–54	56.1	39.5	74.0	64.6	49.3	39.5–74.0
55–59	56.1	39.5	74.0	64.6	49.3	39.5–74.0
60–64	14.6	8.8	53.0	30.3	21.9	8.8–53.0
65–69	14.6	8.8	53.0	30.3	N.D.	8.8–53.0
>70	6.7	6.8	13.8	14.1	N.D.	6.7–14.1
ASR	169.7	183.2	138.8	145.0	160.8	138.8–183.2

CIN: cervical intraepithelial neoplasia; ASR: age-standardized rate.

Table B1
Incidence of VIN2/3 per 100,000 woman-years in three European countries.

Age group	Denmark	Iceland	Norway	Range
< 20	0.7	0.1	0.5	0.1–0.7
20–24	5.3	10.7	2.5	2.5–10.7
25–29	5.3	10.7	2.5	2.5–10.7
30–34	9.7	8.0	4.9	4.9–9.7
35–39	9.7	8.0	4.9	4.9–9.7
40–44	15.3	16.9	9.4	9.4–16.9
45–49	15.3	16.9	9.4	9.4–16.9
50–54	14.2	13.2	8.7	8.7–14.2
55–59	14.2	13.2	8.7	8.7–14.2
60–64	7.9	20.6	8.0	7.9–20.6
65–69	7.9	20.6	8.0	7.9–20.6
> 70	5.4	6.8	6.2	5.4–6.8
ASR	7.7	8.8	4.8	4.8–8.8

VIN: vulvar intraepithelial neoplasia; ASR: age-standardized rate.

Table C1
Incidence of VaIN2/3 lesions per 100,000 woman-years in three European countries.

Age group	Denmark	Iceland	Norway	Range
< 20	0.1	0.1	0.1	0.1
20–24	1.4	0.1	0.6	0.1–1.4
25–29	1.4	0.1	0.6	0.1–1.4
30–34	1.6	0.1	0.6	0.1–1.6
35–39	1.6	0.1	0.6	0.1–1.6
40–44	1.5	3.1	1.2	1.2–3.1
45–49	1.5	3.1	1.2	1.2–3.1
50–54	1.7	1.9	1.5	1.5–1.9
55–59	1.7	1.9	1.5	1.5–1.9
60–64	2.3	2.9	2.8	2.3–2.9
65–69	2.3	2.9	2.8	2.3–2.9
> 70	2.0	2.3	1.9	1.9–2.3
ASR	1.2	1.3	0.9	0.9–1.3

VaIN: vaginal intraepithelial neoplasia; ASR: age-standardized rate.

findings, and critical editing of the manuscript. All authors critically reviewed the manuscript and approved the final version.

Acknowledgements

We thank Perrine Bertet for data extraction, Xavier Cornen for data extraction and analysis, Stephane Thomas for statistical assistance and Trudy Perdrix-Thoma for editorial assistance.

Appendix

See Table A1–C1.

References

[1] IARC: Monographs on the Evaluation on Carcinogenic Risks to Humans. Volume 100: A Review of Human Carcinogens. Part B: Biological Agents, Lyon: International Agency for Research on Cancer, 2012.
[2] European Centers for Disease Prevention and Control: Introduction of HPV Vaccines in EU Countries—An Update. Stockholm: European Centers for Disease Prevention and Control, 2012.
[3] S.N. Tabrizi, J.M. Brotherton, J.M. Kaldor, S.R. Skinner, E. Cummins, B. Liu, D. Bateson, K. McNamee, M. Garefalakis, S.M. Garland, Fall in human papillomavirus prevalence following a national vaccination program, J. Infect. Dis. 206 (2012) 1645–1651.
[4] Luciano Mariani, Patrizia Vici, Barbara Suligoi, Giovanni Checcucci-Lisi, Rosybel Drury, Early direct and indirect impact of quadrivalent HPV (4HPV) vaccine on genital warts: a systematic review, Adv Ther 32 (2015) 10–30.
[5] J.M. Brotherton, M. Fridman, C.L. May, G. Chappell, A.M. Saville, D.M. Gertig, Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study, Lancet 377 (2011) 2085–2092.
[6] D.M. Gertig, J.M. Brotherton, A.C. Budd, K. Drennan, G. Chappell, A.M. Saville, Impact of a population-based HPV vaccination program on cervical abnormalities: a data linkage study, BMC Med. 11 (227) (2013).
[7] E. Crowe, N. Pandeya, J.M. Brotherton, A.J. Dobson, S. Kisely, S.B. Lambert, D.C. Whiteman, Effectiveness of quadrivalent human papillomavirus vaccine for the prevention of cervical abnormalities: case-control study nested within a population based screening programme in Australia, BMJ 348 (2014) g1458.
[8] H. Ali, B. Donovan, H. Wand, T.R. Read, D.G. Regan, A.E. Grulich, C.K. Fairley, R.J. Guy, Genital warts in young Australians five years into national human papillomavirus vaccination programme: national surveillance data, BMJ 346 (2013) f2032.
[9] H. Ali, R.J. Guy, H. Wand, T.R. Read, D.G. Regan, A.E. Grulich, C.K. Fairley, B. Donovan, Decline in in-patient treatments of genital warts among young Australians following the national HPV vaccination program, BMC Infect. Dis. 13 (2013) 140.
[10] S. de Sanjosé, W.G. Quint, L. Alemany, D.T. Geraets, J.E. Klaustermeier, B. Lloveras, S. Tous, A. Felix, L.E. Bravo, H.R. Shin, C.S. Vallejos, P.A. de Ruiz, M.A. Lima, N. Guimera, O. Clavero, M. Alejo, A. Llombart-Bosch, C. Cheng-Yang, S.A. Tatti, E. Kasamatsu, E. Iljazovic, M. Odida, R. Prado, M. Seoud, M. Grce, A. Usubutun, A. Jain, G.A. Suarez, L.E. Lombardi, A. Banjo, C. Menéndez, et al., Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study, Lancet Oncol. 11 (2010) 1048–1056.
[11] No Authors Listed: **HPV Vaccine Works Against Nine Viral Types.** Cancer Discov 4 (2014) OF2.
[12] IARC. **Website of the International Agency for Research on Cancer** [www.iarc.fr].
[13] IARC: **Globocan** 2012**: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. Data Sources and Methods** [http://globocan.iarc.fr/Pages/DataSource_and_methods.aspx].
[14] Forman D., Bray F., Brewster D.H., Gombe Mbalawa C., Kohler B., Piñeros M., Steliarova-Foucher E., Swaminathan R., Ferlay J.: Cancer Incidence in Five Continents**, vol. X**. [http://ci5.iarc.fr].
[15] European Commission: Eurostat homepage. [http://epp.eurostat.ec.europa.eu/portal/page/portal/eurostat/home].
[16] M. Nygard, B.T. Hansen, J. Dillner, C. Munk, K. Oddsson, L. Tryggvadottir, M. Hortlund, K.L. Liaw, E.J. Dasbach, S.K. Kjær, Targeting human papillomavirus to reduce the burden of cervical, vulvar and vaginal cancer and pre-invasive neoplasia: establishing the baseline for surveillance, PLoS One 9 (2014) e88323.
[17] E.A. Joura, K.A. Ault, F.X. Bosch, D. Brown, J. Cuzick, D. Ferris, S.M. Garland, A.R. Giuliano, M. Hernandez-Avila, W. Huh, O.E. Iversen, S.K. Kjaer, J. Luna, D. Miller, J. Monsonego, N. Munoz, E. Myers, J. Paavonen, P. Pitisuttithum, M. Steben, C.M. Wheeler, G. Perez, A. Saah, A. Luxembourg, H.L. Sings, C. Velicer, Attribution of 12 high-risk human papillomavirus genotypes to infection and cervical disease, Cancer Epidemiol. Biomarkers Prevent. 23 (2014) 1997–2008.
[18] S. de Sanjosé, L. Alemany, J. Ordi, S. Tous, M. Alejo, S.M. Bigby, E.A. Joura, P. Maldonado, J. Laco, I.G. Bravo, A. Vidal, N. Guimerà, P. Cross, G.V. Wain, K.U. Petry, L. Mariani, C. Bergeron, V. Mandys, A.R. Sica, A. Félix, A. Usubutun, M. Seoud, G. Hernández-Suárez, A.M. Nowakowski, G. Wilson, V. Dalstein, M. Hampl, E.S. Kasamatsu, L.E. Lombardi, L. Tinoco, et al., Worldwide human papillomavirus genotype attribution in over 2000 cases of intraepithelial and invasive lesions of the vulva, Eur. J. Cancer 49 (2013) 3450–3461.
[19] L. Alemany, M. Saunier, I. Alvarado-Cabrero, B. Quiros, J. Salmeron, H.R. Shin, E.C. Pirog, N. Guimerà, G. Hernandez-Suarez, A. Felix, O. Clavero, B. Lloveras, E. Kasamatsu, M.T. Goodman, B.Y. Hernandez, J. Laco, L. Tinoco, D.T. Geraets, C.F. Lynch, V. Mandys, M. Poljak, R. Jach, J. Verge, C. Clavel, C. Ndiaye, J. Klaustermeier, A. Cubilla, X. Castellsagué, I.G. Bravo, M. Pawlita, et al., Human papillomavirus DNA prevalence and type distribution in anal carcinomas worldwide [Epub ahead of print], Int. J. Cancer (2014), May 10.
[20] A. Nielsen, C. Munk, S.K. Kjaer, Trends in incidence of anal cancer and high-grade anal intraepithelial neoplasia in Denmark, Int. J. Cancer 130 (2012) 1168–1173.
[21] S. Hartwig, S. Syrjanen, G. Dominiak-Felden, M. Brotons, X. Castellsagué, Estimation of the epidemiological burden of human papillomavirus-related cancers and non-malignant diseases in men in Europe: a review, BMC Cancer 12 (2012) 30.
[22] A.A. Kraut, T. Schink, R. Schulze-Rath, R.T. Mikolajczyk, E. Garbe, Incidence of anogenital warts in Germany: a population-based cohort study, BMC Infect. Dis. 10 (2010) 360.
[23] S. Desai, S. Wetten, S.C. Woodhall, L. Peters, G. Hughes, K. Soldan, Genital warts and cost of care in England, Sex. Transm. Infect. 87 (2011) 464–468.
[24] J.M. Walboomers, M.V. Jacobs, M.M. Manos, F.X. Bosch, J.A. Kummer, K.V. Shah, P.J. Snijders, J. Peto, C.J. Meijer, N. Muñoz, Human papillomavirus is a necessary cause of invasive cervical cancer worldwide, J. Pathol. 189 (1999) 12–19.
[25] L. Alemany, M. Saunier, L. Tinoco, B. Quiros, I. Alvarado-Cabrero, M. Alejo, E.A. Joura, P. Maldonado, J. Klaustermeier, J. Salmerón, C. Bergeron, K.U. Petry, N. Guimerà, O. Clavero, R. Murillo, C. Clavel, V. Wain, D.T. Geraets, R. Jach, P. Cross, C. Carrilho, C. Molina, H.R. Shin, V. Mandys, A.M. Nowakowski, A. Vidal, L. Lombardi, H. Kitchener, A.R. Sica, C. Magaña-León, et al., Large contribution of human papillomavirus in vaginal neoplastic lesions: a worldwide study in 597 samples, Eur. J. Cancer 50 (2014) 2846–2854.
[26] B. Serrano, L. Alemany, S. Tous, L. Bruni, G.M. Clifford, T. Weiss, F.X. Bosch, S. de Sanjosé, Potential impact of a nine-valent vaccine in human papillomavirus related cervical disease, Infect. Agents Cancer 7 (2012) 38.

[27] C.J. Lacey, C.M. Lowndes, K.V. Shah, Chapter 4: burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease, Vaccine 24 (Suppl. 3) (2006), S3-35-S3/41.
[28] A.J. Donne, L. Hampson, J.J. Homer, I.N. Hampson, The role of HPV type in recurrent respiratory papillomatosis, Int. J. Pediatr. Otorhinolaryngol. 74 (2010) 7–14.
[29] K.J. Syrjanen, Spontaneous evolution of intraepithelial lesions according to the grade and type of the implicated human papillomavirus (HPV), Eur. J. Obstet. Gynecol. Reprod. Biol. 65 (1996) 45–53.
[30] M.R. McCredie, K.J. Sharples, C. Paul, J. Baranyai, G. Medley, R.W. Jones, et al., Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study, Lancet Oncol. 9 (2008) 425–434.
[31] H.P. van deNieuwenhof, L.F. Massuger, I.A. van der Avoort, R.L. Bekkers, M. Casparie, W. Abma, L.C. van Kempen, J.A. de Hullu, et al., Vulvar squamous cell carcinoma development after diagnosis of VIN increases with age, Eur. J. Cancer 45 (2009) 851–856.

Annex 1 - Estimated mean annual number of new HPV-related cancer cases in women and men per European country

A Cervical cancer

Country	N of new cancers irrespective of HPV status (95% CI)	N of new cancers attributable to HPV (95% CI)[1]	N of new cancers attributable to HPV16/18 (95% CI)[2]	N of HPV16/18/31/33/45/52/58+ cancers (95% CI)[3]	N of cases attribu-table to additional types Gardasil9 vs Gardasil
Austria	626 (577 - 675)	626 (577 - 675)	456 (414 - 498)	557 (511 - 603)	101 (81 - 121)
Belgium	693 (641 - 745)	693 (641 - 745)	504 (460 - 548)	617 (568 - 666)	112 (91 - 133)
Bulgaria	1094 (1029 - 1159)	1094 (1029 - 1159)	796 (741 - 851)	974 (913 - 1035)	177 (151 - 203)
Croatia	345 (309 - 381)	345 (309 - 381)	251 (220 - 282)	307 (273 - 341)	56 (41 - 71)
Cyprus	28 (18 - 38)	28 (18 - 38)	21 (12 - 30)	25 (15 - 35)	5 (2 - 12)
Czech Republic	1095 (1030 - 1160)	1095 (1030 - 1160)	797 (742 - 852)	975 (914 - 1036)	177 (151 - 203)
Denmark	397 (358 - 436)	397 (358 - 436)	289 (256 - 322)	353 (316 - 390)	64 (48 - 80)
Estonia	164 (139 - 189)	164 (139 - 189)	119 (98 - 140)	146 (122 - 170)	27 (17 - 37)
Finland	164 (139 - 189)	164 (139 - 189)	119 (98 - 140)	146 (122 - 170)	26 (16 - 36)
France	3400 (3286 - 3514)	3400 (3286 - 3514)	2475 (2377 - 2573)	3026 (2918 - 3134)	551 (505 - 597)
Germany	5299 (5156 - 5442)	5299 (5156 - 5442)	3858 (3736 - 3980)	4716 (4581 - 4851)	858 (801 - 915)
Greece	1488 (1412 - 1564)	1488 (1412 - 1564)	1084 (1019 - 1149)	1325 (1254 - 1396)	241 (211 - 271)
Hungary	985 (923 - 1047)	985 (923 - 1047)	717 (665 - 769)	877 (819 - 935)	160 (135 - 185)
Iceland	15 (8 - 25)	15 (8 - 25)	11 (5 - 20)	13 (7 - 22)	2 (0 - 7)
Ireland	278 (245 - 311)	278 (245 - 311)	202 (174 - 230)	247 (216 - 278)	45 (32 - 58)
Italy	2645 (2544 - 2746)	2645 (2544 - 2746)	1926 (1840 - 2012)	2354 (2259 - 2449)	429 (388 - 470)
Latvia	214 (185 - 243)	214 (185 - 243)	156 (132 - 180)	191 (164 - 218)	35 (23 - 47)
Lithuania	489 (446 - 532)	489 (446 - 532)	356 (319 - 393)	436 (395 - 477)	79 (62 - 96)
Luxem-bourg	30 (19 - 41)	30 (19 - 41)	22 (13 - 31)	27 (17 - 37)	5 (2 - 12)
Malta	12 (6 - 21)	12 (6 - 21)	8 (3 - 16)	10 (5 - 18)	2 (0 - 7)
Norway	313 (278 - 348)	313 (278 - 348)	228 (198 - 258)	279 (246 - 312)	51 (37 - 65)
Poland	3691 (3572 - 3810)	3691 (3572 - 3810)	2687 (2585 - 2789)	3285 (3173 - 3397)	598 (550 - 646)
Portugal	1009 (947 - 1071)	1009 (947 - 1071)	734 (681 - 787)	898 (839 - 957)	163 (138 - 188)

Romania	2691 (2589 - 2793)	2691 (2589 - 2793)	1959 (1872 - 2046)	2395 (2299 - 2491)	436 (395 - 477)
Slovakia	622 (573 - 671)	622 (573 - 671)	453 (411 - 495)	553 (507 - 599)	101 (81 - 121)
Slovenia	180 (154 - 206)	180 (154 - 206)	131 (109 - 153)	160 (135 - 185)	29 (18 - 40)
Spain	2308 (2214 - 2402)	2308 (2214 - 2402)	1680 (1600 - 1760)	2054 (1965 - 2143)	374 (336 - 412)
Sweden	466 (424 - 508)	466 (424 - 508)	339 (303 - 375)	415 (375 - 455)	76 (59 - 93)
Switzer-land	261 (229 - 293)	261 (229 - 293)	190 (163 - 217)	232 (202 - 262)	42 (29 - 55)
The Nether-lands	702 (650 - 754)	702 (650 - 754)	511 (467 - 555)	625 (576 - 674)	114 (93 - 135)
United Kingdom	3004 (2897 - 3111)	3004 (2897 - 3111)	2187 (2095 - 2279)	2674 (2573 - 2775)	487 (444 - 530)

[1] HPV prevalence: 100%, [2] HPV 16/18 attributable fraction among HPV+ cases: 72.8% (70.8–74.7) , [3] HPV 31/33/45/52/558 attributable fraction among HPV+ cases: 89.0% (87.5–90.3) (ref: de Sanjosé et al [10])

B Vulvar cancer

Country	N of new cancers irrespective of HPV status (95% CI)	N of new cancers attributable to HPV (95% CI)[4]	N of new cancers attributable to HPV16/18 (95% CI)[5]	N of HPV16/18/31/33/45/ 52/58+ cancers (95% CI)[6]	N of cases attributable to additional types Gardasil9 vs Gardasil
Austria	134 (111 - 157)	26 (16 - 36)	19 (11 - 30)	22 (13 - 31)	3 (1 - 9)
Belgium	196 (169 - 223)	38 (26 - 50)	28 (18 - 38)	32 (21 - 43)	4 (1 - 10)
Bulgaria	128 (106 - 150)	25 (15 - 35)	18 (11 - 28)	21 (12 - 30)	3 (1 - 9)
Croatia	75 (58 - 92)	15 (8 - 25)	11 (5 - 20)	12 (6 - 21)	2 (0 - 7)
Cyprus	9 (4 - 17)	2 (0 - 7)	1 (0 - 6)	1 (0 - 6)	0 (0 - 4)
Czech Republic	224 (195 - 253)	43 (30 - 56)	32 (21 - 43)	36 (24 - 48)	4 (1 - 10)
Denmark	101 (81 - 121)	20 (11 - 29)	14 (8 - 23)	16 (9 - 26)	2 (0 - 7)
Estonia	29 (18 - 40)	6 (2 - 13)	4 (1 - 10)	5 (2 - 12)	1 (0 - 6)
Finland	84 (66 - 102)	16 (9 - 26)	12 (6 - 21)	14 (8 - 23)	2 (0 - 7)
France	753 (699 - 807)	145 (121 - 169)	107 (87 - 127)	122 (100 - 144)	15 (8 - 25)
Germany	2485 (2387 - 2583)	480 (437 - 523)	353 (316 - 390)	403 (364 - 442)	50 (36 - 64)
Greece	189 (162 - 216)	37 (25 - 49)	27 (17 - 37)	31 (20 - 42)	4 (1 - 10)
Hungary	194 (167 - 221)	38 (26 - 50)	28 (18 - 38)	32 (21 - 43)	4 (1 - 10)
Iceland	3 (1 - 9)	0 (0 - 4)	0 (0 - 4)	0 (0 - 4)	0 (0 - 4)
Ireland	52 (38 - 66)	10 (5 - 18)	7 (3 - 14)	8 (3 - 16)	1 (0 - 6)
Italy	1133 (1067 - 1199)	219 (190 - 248)	161 (136 - 186)	184 (157 - 211)	23 (14 - 32)
Latvia	42 (29 - 55)	8 (3 - 16)	6 (2 - 13)	7 (3 - 14)	1 (0 - 6)
Lithuania	59 (44 - 74)	11 (5 - 20)	8 (3 - 16)	10 (5 - 18)	1 (0 - 6)
Luxem-bourg	10 (5 - 18)	2 (0 - 7)	1 (0 - 6)	2 (0 - 7)	0 (0 - 4)
Malta	9 (4 - 17)	2 (0 - 7)	1 (0 - 6)	1 (0 - 6)	0 (0 - 4)
Norway	97 (78 - 116)	19 (11 - 30)	14 (8 - 23)	16 (9 - 26)	2 (0 - 7)
Poland	500 (456 - 544)	96 (77 - 115)	71 (54 - 88)	81 (63 - 99)	10 (5 - 18)
Portugal	109 (89 - 129)	21 (12 - 30)	15 (8 - 25)	18 (11 - 28)	2 (0 - 7)

Romania	325 (290 - 360)	63 (47 - 79)	46 (33 - 59)	53 (39 - 67)	7 (3 - 14)
Slovakia	79 (62 - 96)	15 (8 - 25)	11 (5 - 20)	13 (7 - 22)	2 (0 - 7)
Slovenia	42 (29 - 55)	8 (3 - 16)	6 (2 - 13)	7 (3 - 14)	1 (0 - 6)
Spain	706 (654 - 758)	136 (113 - 159)	100 (80 - 120)	114 (93 - 135)	14 (8 - 23)
Sweden	169 (144 - 194)	33 (22 - 44)	24 (14 - 34)	27 (17 - 37)	3 (1 - 9)
Switzer-land	127 (105 - 149)	24 (14 - 34)	18 (11 - 28)	21 (12 - 30)	3 (1 - 9)
The Nether-lands	318 (283 - 353)	61 (46 - 76)	45 (32 - 58)	52 (38 - 66)	6 (2 - 13)
United Kingdom	1162 (1095 - 1229)	224 (195 - 253)	165 (140 - 190)	188 (161 - 215)	23 (14 - 32)

[4] HPV prevalence: 19.3% (16.7–22.0), [5] HPV 16/18 attributable fraction among HPV+ cases: 73.6% (66.4–79.9), [6] HPV 31/33/45/52/558 attributable fraction among HPV+ cases: 84.0% (77.6–89.0) (ref: de Sanjosé et al [18])

C Vaginal cancer

Country	N of new cancers irrespective of HPV status (95% CI)	N of new cancers attributable to HPV (95% CI)[7]	N of new cancers attributable to HPV16/18 (95% CI)[8]	N of HPV16/18/31/33/45/52/58+ cancers (95% CI)[9]	N of cases attributable to additional types Gardasil9 vs Gardasil
Austria	61 (46 - 76)	43 (30 - 56)	31 (20 - 42)	37 (25 - 49)	6 (2 - 13)
Belgium	54 (40 - 68)	38 (26 - 50)	27 (17 - 37)	33 (22 - 44)	6 (2 - 13)
Bulgaria	29 (18 - 40)	20 (11 - 29)	15 (8 - 25)	18 (11 - 28)	3 (1 - 9)
Croatia	16 (9 - 26)	12 (6 - 21)	8 (3 - 16)	10 (5 - 18)	2 (0 - 7)
Cyprus	1 (0 - 6)	1 (0 - 6)	0 (0 - 4)	0 (0 - 4)	0 (0 - 4)
Czech Republic	53 (39 - 67)	38 (26 - 50)	27 (17 - 37)	32 (21 - 43)	5 (2 - 12)
Denmark	26 (16 - 36)	19 (11 - 30)	13 (7 - 22)	16 (9 - 26)	3 (1 - 9)
Estonia	6 (2 - 13)	4 (1 - 10)	3 (1 - 9)	4 (1 - 10)	1 (0 - 6)
Finland	22 (13 - 31)	15 (8 - 25)	11 (5 - 20)	13 (7 - 22)	2 (0 - 7)
France	232 (202 - 262)	165 (140 - 190)	117 (96 - 138)	141 (118 - 164)	24 (14 - 34)
Germany	477 (434 - 520)	339 (303 - 375)	242 (212 - 272)	290 (257 - 323)	49 (35 - 63)
Greece	44 (31 - 57)	31 (20 - 42)	22 (13 - 31)	27 (17 - 37)	4 (1 - 10)
Hungary	49 (35 - 63)	35 (23 - 47)	25 (15 - 35)	30 (19 - 41)	5 (2 - 12)
Iceland	0 (0 - 4)	0 (0 - 4)	0 (0 - 4)	0 (0 - 4)	0 (0 - 4)
Ireland	14 (8 - 23)	10 (5 - 18)	7 (3 - 14)	8 (3 - 16)	1 (0 - 6)
Italy	240 (210 - 270)	171 (145 - 197)	121 (99 - 143)	146 (122 - 170)	25 (15 - 35)
Latvia	9 (4 - 17)	6 (2 - 13)	4 (1 - 10)	5 (2 - 12)	1 (0 - 6)
Lithuania	11 (5 - 20)	8 (3 - 16)	6 (2 - 13)	7 (3 - 14)	1 (0 - 6)
Luxem-bourg	2 (0 - 7)	1 (0 - 6)	1 (0 - 6)	1 (0 - 6)	0 (0 - 4)
Malta	1 (0 - 6)	1 (0 - 6)	1 (0 - 6)	1 (0 - 6)	0 (0 - 4)
Norway	17 (10 - 27)	12 (6 - 21)	9 (4 - 17)	10 (5 - 18)	2 (0 - 7)
Poland	114 (93 - 135)	81 (63 - 99)	58 (43 - 73)	70 (54 - 86)	12 (6 - 21)
Portugal	73 (56 - 90)	52 (38 - 66)	37 (25 - 49)	44 (31 - 57)	7 (3 - 14)
Romania	78 (61 - 95)	55 (40 - 70)	39 (27 - 51)	47 (34 - 60)	8 (3 - 16)

Slovakia	21 (12 - 30)	15 (8 - 25)	11 (5 - 20)	13 (7 - 22)	2 (0 - 7)
Slovenia	8 (3 - 16)	6 (2 - 13)	4 (1 - 10)	5 (2 - 12)	1 (0 - 6)
Spain	121 (99 - 143)	86 (68 - 104)	61 (46 - 76)	73 (56 - 90)	12 (6 - 21)
Sweden	43 (30 - 56)	31 (20 - 42)	22 (13 - 31)	26 (16 - 36)	4 (1 - 10)
Switzer-land	31 (20 - 42)	22 (13 - 31)	16 (9 - 26)	19 (11 - 30)	3 (1 - 9)
The Nether-lands	56 (41 - 71)	40 (28 - 52)	28 (18 - 38)	34 (23 - 45)	6 (2 - 13)
United Kingdom	261 (229 - 293)	186 (159 - 213)	132 (109 - 155)	159 (134 - 184)	27 (17 - 37)

[7] HPV prevalence: 71.1% (63.2–78.1), [8] HPV 16/18 attributable fraction among HPV+ cases: 71.2% (61.8–79.6), [9] HPV 31/33/45/52/558 attributable fraction among HPV+ cases: 85.6% (77.1–91.3) (ref: Alemany et al [25])

D Anal cancer

Country	Sex	N of new cancers irrespective of HPV status (95% CI)	N of new cancers attributable to HPV (95% CI)[10]	N of new cancers attributable to HPV16/18 (95% CI)[11]	N of HPV16/18/31/33/45/52/58+ cancers (95% CI)[12]	N of cases attributable to additional types Gardasil9 vs Gardasil
Austria	Women	97 (78 - 116)	85 (67 - 103)	74 (57 - 91)	76 (59 - 93)	2 (0 - 7)
	Men	38 (26 - 50)	33 (22 - 44)	29 (18 - 40)	30 (19 - 41)	1 (0 - 6)
	Both sexes	135 (112 - 158)	118 (97 - 139)	103 (83 - 123)	106 (86 - 126)	3 (1 - 9)
Belgium	Women	86 (68 - 104)	75 (58 - 92)	66 (50 - 82)	68 (52 - 84)	2 (0 - 7)
	Men	58 (43 - 73)	51 (37 - 65)	44 (31 - 57)	46 (33 - 59)	1 (0 - 6)
	Both sexes	144 (120 - 168)	126 (104 - 148)	110 (89 - 131)	113 (92 - 134)	3 (1 - 9)
Bulgaria	Women	26 (16 - 36)	22 (13 - 31)	20 (11 - 29)	20 (11 - 29)	1 (0 - 6)
	Men	34 (23 - 45)	30 (19 - 41)	26 (16 - 36)	27 (17 - 37)	1 (0 - 6)
	Both sexes	59 (44 - 74)	52 (38 - 66)	45 (32 - 58)	47 (34 - 60)	1 (0 - 6)
Croatia	Women	16 (9 - 26)	14 (8 - 23)	12 (6 - 21)	12 (6 - 21)	0 (0 - 4)
	Men	9 (4 - 17)	8 (3 - 16)	7 (3 - 14)	7 (3 - 14)	0 (0 - 4)
	Both sexes	24 (14 - 34)	21 (12 - 30)	19 (11 - 30)	19 (11 - 30)	1 (0 - 6)
Cyprus	Women	3 (1 - 9)	3 (1 - 9)	2 (0 - 7)	2 (0 - 7)	0 (0 - 4)
	Men	2 (0 - 7)	2 (0 - 7)	2 (0 - 7)	2 (0 - 7)	0 (0 - 4)
	Both sexes	5 (2 - 12)	4 (1 - 10)	4 (1 - 10)	4 (1 - 10)	0 (0 - 4)
Czech Republic	Women	76 (59 - 93)	67 (51 - 83)	58 (43 - 73)	60 (45 - 75)	2 (0 - 7)
	Men	45 (32 - 58)	39 (27 - 51)	34 (23 - 45)	35 (23 - 47)	1 (0 - 6)
	Both sexes	121 (99 - 143)	106 (86 - 126)	92 (73 - 111)	95 (76 - 114)	3 (1 - 9)
Denmark	Women	72 (55 - 89)	63 (47 - 79)	55 (40 - 70)	56 (41 - 71)	2 (0 - 7)
	Men	35 (23 - 47)	30 (19 - 41)	26 (16 - 36)	27 (17 - 37)	1 (0 - 6)
	Both sexes	106 (86 - 126)	93 (74 - 112)	81 (63 - 99)	84 (66 - 102)	3 (1 - 9)

Estonia	Women	10 (5 - 18)	9 (4 - 17)	8 (3 - 16)	8 (3 - 16)	0 (0 - 4)
	Men	4 (1 - 10)	3 (1 - 9)	3 (1 - 9)	3 (1 - 9)	0 (0 - 4)
	Both sexes	14 (8 - 23)	12 (6 - 21)	11 (5 - 20)	11 (5 - 20)	0 (0 - 4)
Finland	Women	25 (15 - 35)	22 (13 - 31)	19 (11 - 30)	20 (11 - 29)	1 (0 - 6)
	Men	15 (8 - 25)	13 (7 - 22)	12 (6 - 21)	12 (6 - 21)	0 (0 - 4)
	Both sexes	40 (28 - 52)	35 (23 - 47)	30 (19 - 41)	31 (20 - 42)	1 (0 - 6)
France	Women	804 (748 - 860)	705 (653 - 757)	614 (565 - 663)	633 (584 - 682)	19 (11 - 30)
	Men	313 (278 - 348)	274 (242 - 306)	238 (208 - 268)	246 (215 - 277)	7 (3 - 14)
	Both sexes	1117 (1051 - 1183)	979 (918 - 1040)	852 (795 - 909)	879 (821 - 937)	26 (16 - 36)
Germany	Women	1025 (962 - 1088)	898 (839 - 957)	782 (727 - 837)	806 (750 - 862)	24 (14 - 34)
	Men	586 (539 - 633)	514 (470 - 558)	447 (406 - 488)	461 (419 - 503)	14 (8 - 23)
	Both sexes	1611 (1532 - 1690)	1411 (1337 - 1485)	1229 (1160 - 1298)	1267 (1197 - 1337)	38 (26 - 50)
Greece	Women	45 (32 - 58)	39 (27 - 51)	34 (23 - 45)	35 (23 - 47)	1 (0 - 6)
	Men	51 (37 - 65)	45 (32 - 58)	39 (27 - 51)	40 (28 - 52)	1 (0 - 6)
	Both sexes	96 (77 - 115)	84 (66 - 102)	73 (56 - 90)	76 (59 - 93)	2 (0 - 7)
Hungary	Women	58 (43 - 73)	51 (37 - 65)	44 (31 - 57)	46 (33 - 59)	1 (0 - 6)
	Men	30 (19 - 41)	26 (16 - 36)	23 (14 - 32)	24 (14 - 34)	1 (0 - 6)
	Both sexes	88 (70 - 106)	77 (60 - 94)	67 (51 - 83)	69 (53 - 85)	2 (0 - 7)
Iceland	Women	2 (0 - 7)	2 (0 - 7)	2 (0 - 7)	2 (0 - 7)	0 (0 - 4)
	Men	1 (0 - 6)	1 (0 - 6)	1 (0 - 6)	1 (0 - 6)	0 (0 - 4)
	Both sexes	4 (1 - 10)	3 (1 - 9)	3 (1 - 9)	3 (1 - 9)	0 (0 - 4)
Ireland	Women	22 (13 - 31)	19 (11 - 30)	17 (10 - 27)	17 (10 - 27)	1 (0 - 6)
	Men	16 (9 - 26)	14 (8 - 23)	12 (6 - 21)	12 (6 - 21)	0 (0 - 4)
	Both sexes	38 (26 - 50)	33 (22 - 44)	29 (18 - 40)	30 (19 - 41)	1 (0 - 6)
Italy	Women	601 (553 - 649)	526 (481 - 571)	458 (416 - 500)	473 (430 - 516)	14 (8 - 23)
	Men	418 (378 - 458)	366 (329 - 403)	319 (284 - 354)	329 (293 - 365)	10 (5 - 18)
	Both sexes	1019 (956 - 1082)	892 (833 - 951)	777 (722 - 832)	801 (746 - 856)	24 (14 - 34)
Latvia	Women	10 (5 - 18)	9 (4 - 17)	8 (3 - 16)	8 (3 - 16)	0 (0 - 4)
	Men	6 (2 - 13)	5 (2 - 12)	5 (2 - 12)	5 (2 - 12)	0 (0 - 4)

	Both sexes	16 (9 - 26)	14 (8 - 23)	12 (6 - 21)	13 (7 - 22)	0 (0 - 4)
Lithuania	Women	11 (5 - 20)	9 (4 - 17)	8 (3 - 16)	8 (3 - 16)	0 (0 - 4)
	Men	8 (3 - 16)	7 (3 - 14)	6 (2 - 13)	6 (2 - 13)	0 (0 - 4)
	Both sexes	18 (11 - 28)	16 (9 - 26)	14 (8 - 23)	14 (8 - 23)	0 (0 - 4)
Luxem-bourg	Women	5 (2 - 12)	5 (2 - 12)	4 (1 - 10)	4 (1 - 10)	0 (0 - 4)
	Men	3 (1 - 9)	3 (1 - 9)	2 (0 - 7)	2 (0 - 7)	0 (0 - 4)
	Both sexes	8 (3 - 16)	7 (3 - 14)	6 (2 - 13)	6 (2 - 13)	0 (0 - 4)
Malta	Women	2 (0 - 7)	2 (0 - 7)	1 (0 - 6)	2 (0 - 7)	0 (0 - 4)
	Men	1 (0 - 6)	1 (0 - 6)	1 (0 - 6)	1 (0 - 6)	0 (0 - 4)
	Both sexes	3 (1 - 9)	2 (0 - 7)	2 (0 - 7)	2 (0 - 7)	0 (0 - 4)
Norway	Women	49 (35 - 63)	43 (30 - 56)	38 (26 - 50)	39 (27 - 51)	1 (0 - 6)
	Men	22 (13 - 31)	19 (11 - 30)	17 (10 - 27)	17 (10 - 27)	1 (0 - 6)
	Both sexes	72 (55 - 89)	63 (47 - 79)	55 (40 - 70)	56 (41 - 71)	2 (0 - 7)
Poland	Women	232 (202 - 262)	203 (175 - 231)	177 (151 - 203)	183 (156 - 210)	5 (2 - 12)
	Men	113 (92 - 134)	99 (79 - 119)	86 (68 - 104)	89 (71 - 107)	3 (1 - 9)
	Both sexes	345 (309 - 381)	302 (268 - 336)	263 (231 - 295)	271 (239 - 303)	8 (3 - 16)
Portugal	Women	84 (66 - 102)	74 (57 - 91)	64 (48 - 80)	66 (50 - 82)	2 (0 - 7)
	Men	38 (26 - 50)	33 (22 - 44)	29 (18 - 40)	30 (19 - 41)	1 (0 - 6)
	Both sexes	122 (100 - 144)	107 (87 - 127)	93 (74 - 112)	96 (77 - 115)	3 (1 - 9)
Romania	Women	75 (58 - 92)	66 (50 - 82)	57 (42 - 72)	59 (44 - 74)	2 (0 - 7)
	Men	76 (59 - 93)	66 (50 - 82)	58 (43 - 73)	59 (44 - 74)	2 (0 - 7)
	Both sexes	150 (126 - 174)	132 (109 - 155)	115 (94 - 136)	118 (97 - 139)	4 (1 - 10)
Slovakia	Women	23 (14 - 32)	20 (11 - 29)	18 (11 - 28)	18 (11 - 28)	1 (0 - 6)
	Men	15 (8 - 25)	13 (7 - 22)	11 (5 - 20)	11 (5 - 20)	0 (0 - 4)
	Both sexes	38 (26 - 50)	33 (22 - 44)	29 (18 - 40)	30 (19 - 41)	1 (0 - 6)
Slovenia	Women	10 (5 - 18)	9 (4 - 17)	8 (3 - 16)	8 (3 - 16)	0 (0 - 4)
	Men	10 (5 - 18)	9 (4 - 17)	8 (3 - 16)	8 (3 - 16)	0 (0 - 4)
	Both sexes	20 (11 - 29)	18 (11 - 28)	16 (9 - 26)	16 (9 - 26)	0 (0 - 4)
Spain	Women	173 (147 - 199)	151 (127 - 175)	132 (109 - 155)	136 (113 - 159)	4 (1 - 10)

	Men	217 (188 - 246)	190 (163 - 217)	166 (141 - 191)	171 (145 - 197)	5 (2 - 12)
	Both sexes	390 (351 - 429)	342 (306 - 378)	297 (263 - 331)	307 (273 - 341)	9 (4 - 17)
Sweden	Women	98 (79 - 117)	86 (68 - 104)	75 (58 - 92)	77 (60 - 94)	2 (0 - 7)
	Men	44 (31 - 57)	39 (27 - 51)	34 (23 - 45)	35 (23 - 47)	1 (0 - 6)
	Both sexes	142 (119 - 165)	124 (102 - 146)	108 (88 - 128)	111 (90 - 132)	3 (1 - 9)
Switzer-land	Women	142 (119 - 165)	125 (103 - 147)	108 (88 - 128)	112 (91 - 133)	3 (1 - 9)
	Men	55 (40 - 70)	49 (35 - 63)	42 (29 - 55)	44 (31 - 57)	1 (0 - 6)
	Both sexes	198 (170 - 226)	173 (147 - 199)	151 (127 - 175)	155 (131 - 179)	5 (2 - 12)
The Nether-lands	Women	83 (65 - 101)	73 (56 - 90)	63 (47 - 79)	65 (49 - 81)	2 (0 - 7)
	Men	68 (52 - 84)	60 (45 - 75)	52 (38 - 66)	53 (39 - 67)	2 (0 - 7)
	Both sexes	151 (127 - 175)	132 (109 - 155)	115 (94 - 136)	119 (98 - 140)	4 (1 - 10)
United Kingdom	Women	597 (549 - 645)	523 (478 - 568)	455 (413 - 497)	469 (427 - 511)	14 (8 - 23)
	Men	400 (361 - 439)	350 (313 - 387)	305 (271 - 339)	314 (279 - 349)	9 (4 - 17)
	Both sexes	996 (934 - 1058)	873 (815 - 931)	760 (706 - 814)	784 (729 - 839)	24 (14 - 34)

[10] HPV prevalence: 87.6% (81.6–92.1), [11] HPV 16/18 attributable fraction among HPV+ cases: 87.1% (80.7–92.1), [12] HPV 31/33/45/52/558 attributable fraction among HPV+ cases: 89.8% (83.8–94.2) (ref: Alemany et al [19])

HPV: human papillomavirus; CI: confidence interval.

Table 4 - Estimated annual number of new precancerous lesions in women and men in the European countries

A. CIN2+

Country	N of new cases irrespective of HPV status (range)	N of new cases attributable to HPV (range)[1]	N of cases related to quadrivalent vaccine types (range)[2]	N of cases related to nine-valent vaccine types (range)[3]	Additional N of cases related to five new HPV types (range)
Austria	4422 - 8422	4422 - 8422	2012 - 3832	3639 - 6932	1627 - 3099
Belgium	5632 - 10802	5632 - 10802	2562 - 4915	4635 - 8890	2072 - 3975
Bulgaria	3762 - 7262	3762 - 7262	1712 - 3304	3096 - 5977	1384 - 2673
Croatia	2151 - 4135	2151 - 4135	979 - 1882	1771 - 3403	792 - 1522
Cyprus	532 - 1032	532 - 1032	242 - 469	438 - 849	196 - 380
Czech Republic	5695 - 10931	5695 - 10931	2591 - 4973	4687 - 8996	2096 - 4023
Denmark	2738 - 5251	2738 - 5251	1246 - 2389	2254 - 4322	1008 - 1932
Estonia	700 - 1357	700 - 1357	318 - 617	576 - 1116	257 - 499
Finland	2598 - 5043	2598 - 5043	1182 - 2295	2138 - 4151	956 - 1856
France	32263 - 61861	32263 - 61861	14679 - 28147	26552 - 50912	11873 - 22765
Germany	40242 - 76655	40242 - 76655	18310 - 34878	33119 - 63087	14809 - 28209
Greece	5680 - 10764	5680 - 10764	2584 - 4897	4674 - 8858	2090 - 3961
Hungary	5260 - 10072	5260 - 10072	2393 - 4583	4329 - 8289	1936 - 3707
Iceland	169 - 327	169 - 327	77 - 149	139 - 269	62 - 120
Ireland	2539 - 4826	2539 - 4826	1155 - 2196	2089 - 3972	934 - 1776
Italy	29603 - 55625	29603 - 55625	13469 - 25309	24363 - 45779	10894 - 20470
Latvia	1089 - 2110	1089 - 2110	495 - 960	896 - 1737	401 - 776
Lithuania	1553 - 2993	1553 - 2993	707 - 1362	1278 - 2463	572 - 1102
Luxembourg	293 - 555	293 - 555	133 - 253	241 - 457	108 - 204
Malta	220 - 430	220 - 430	100 - 196	181 - 354	81 - 158
Norway	2567 - 4933	2567 - 4933	1168 - 2244	2113 - 4060	945 - 1815
Poland	21847 - 42462	21847 - 42462	9940 - 19320	17980 - 34946	8040 - 15626
Portugal	5457 - 10315	5457 - 10315	2483 - 4693	4491 - 8490	2008 - 3796
Romania	10578 - 20246	10578 - 20246	4813 - 9212	8706 - 16662	3893 - 7450
Slovakia	3123 - 6031	3123 - 6031	1421 - 2744	2570 - 4964	1149 - 2219
Slovenia	1061 - 2022	1061 - 2022	483 - 920	873 - 1664	390 - 744
Spain	25035 - 46996	25035 - 46996	11391 - 21383	20604 - 38678	9213 - 17295
Sweden	4753 - 9199	4753 - 9199	2163 - 4186	3912 - 7571	1749 - 3385
Switzerland	4231 - 8052	4231 - 8052	1925 - 3664	3482 - 6627	1557 - 2963
The Netherlands	8326 - 15934	8326 - 15934	3788 - 7250	6852 - 13113	3064 - 5864
United Kingdom	33230 - 63965	33230 - 63965	15120 - 29104	27349 - 52643	12229 - 23539

[1] HPV prevalence: 100%, [2] HPV6/11/16/18 attributable fraction among HPV+ cases: 45.5%, [3] HPV 6/11/16/18/31/33/45/52/58 attributable fraction among HPV+ cases: 82.3% ref: Joura et al. [17] with additional information from authors

B. VIN2/3

Country	N of new cases irrespective of HPV status (range)	N of new cases attributable to HPV (range)[4]	N of cases related to quadrivalent vaccine types (range)[5]	N of cases related to nine-valent vaccine types (range)[6]	Additional N of cases related to five new HPV types (range)
Austria	229 - 454	199 - 394	164 - 324	188 - 372	24 - 48
Belgium	288 - 574	250 - 499	206 - 410	236 - 471	31 - 61
Bulgaria	202 - 406	175 - 353	144 - 290	165 - 333	21 - 43
Croatia	116 - 229	101 - 199	83 - 164	95 - 188	12 - 24
Cyprus	22 - 45	19 - 39	15 - 32	18 - 37	2 - 5
Czech Republic	280 - 571	244 - 496	200 - 408	230 - 468	30 - 61
Denmark	143 - 288	124 - 251	102 - 206	117 - 237	15 - 31
Estonia	37 - 73	32 - 63	26 - 52	30 - 60	4 - 8
Finland	141 - 285	123 - 248	101 - 203	116 - 234	15 - 30
France	1691 - 3370	1470 - 2928	1208 - 2407	1387 - 2764	179 - 357
Germany	2274 - 4431	1976 - 3850	1624 - 3165	1865 - 3635	241 - 470
Greece	299 - 590	260 - 512	214 - 421	246 - 484	32 - 63
Hungary	275 - 550	239 - 478	196 - 393	225 - 451	29 - 58
Iceland	7 - 15	6 - 13	5 - 11	6 - 12	1 - 2
Ireland	108 - 220	94 - 191	77 - 157	89 - 181	11 - 23
Italy	1681 - 3270	1461 - 2841	1201 - 2336	1379 - 2682	178 - 347
Latvia	58 - 116	51 - 101	42 - 83	48 - 95	6 - 12
Lithuania	85 - 167	74 - 145	60 - 119	69 - 137	9 - 18
Luxembourg	14 - 27	12 - 23	10 - 19	11 - 22	1 - 3
Malta	11 - 22	9 - 19	8 - 16	9 - 18	1 - 2
Norway	123 - 250	107 - 217	88 - 178	101 - 205	13 - 26
Poland	1014 - 2066	882 - 1795	725 - 1476	832 - 1695	108 - 219
Portugal	293 - 577	255 - 502	209 - 412	241 - 474	31 - 61
Romania	532 - 1066	462 - 926	380 - 762	436 - 875	56 - 113
Slovakia	141 - 289	123 - 251	101 - 207	116 - 237	15 - 31
Slovenia	55 - 109	48 - 95	40 - 78	45 - 90	6 - 12
Spain	1255 - 2471	1090 - 2147	896 - 1765	1029 - 2027	133 - 262
Sweden	241 - 487	209 - 423	172 - 348	197 - 400	26 - 52
Switzerland	214 - 427	186 - 371	153 - 305	176 - 350	23 - 45
The Netherlands	436 - 874	378 - 760	311 - 624	357 - 717	46 - 93
United Kingdom	1620 - 3273	1408 - 2844	1157 - 2338	1329 - 2685	172 - 347

[4] HPV prevalence: 86.9% 82.6– 90.4, [5] HPV6/11/16/18 attributable fraction among HPV+ cases: 82.2% 77.2–86.6, [6] HPV 6/11/16/18/31/33/45/52/58 attributable fraction among HPV+ cases: 94.4% 91.0–96.9 ref: de Sanjosé et al. [18]

C. VaIN 2/3

Country	N of new cases irrespective of HPV status (range)	N of new cases attributable to HPV (range)[7]	N of cases related to quadrivalent vaccine types (range)[8]	N of cases related to nine-valent vaccine types (range)[9]	Additional N of cases related to five new HPV types (range)
Austria	42 - 78	40 - 75	26 - 48	31 - 58	5 - 10
Belgium	53 - 98	51 - 94	32 - 60	39 - 73	7 - 13
Bulgaria	38 - 69	37 - 66	23 - 42	28 - 51	5 - 9
Croatia	22 - 39	21 - 38	13 - 24	16 - 29	3 - 5
Cyprus	4 - 7	3 - 7	2 - 5	3 - 6	0 - 1
Czech Republic	51 - 95	49 - 91	31 - 59	38 - 71	7 - 12
Denmark	26 - 49	25 - 47	16 - 30	20 - 36	3 - 6
Estonia	7 - 13	7 - 12	4 - 8	5 - 9	1 - 2
Finland	27 - 48	26 - 46	17 - 30	20 - 36	3 - 6
France	314 - 576	301 - 552	193 - 354	233 - 428	41 - 74
Germany	432 - 772	414 - 740	265 - 474	321 - 574	56 - 100
Greece	55 - 102	53 - 98	34 - 63	41 - 76	7 - 13
Hungary	51 - 93	49 - 89	31 - 57	38 - 69	7 - 12
Iceland	1 - 3	1 - 2	1 - 2	1 - 2	0 - 0
Ireland	17 - 36	17 - 35	11 - 22	13 - 27	2 - 5
Italy	317 - 572	304 - 548	195 - 351	236 - 425	41 - 74
Latvia	11 - 20	11 - 19	7 - 12	8 - 15	1 - 3
Lithuania	16 - 29	15 - 28	10 - 18	12 - 21	2 - 4
Luxembourg	2 - 5	2 - 4	1 - 3	2 - 3	0 - 1
Malta	2 - 4	2 - 4	1 - 2	1 - 3	0 - 0
Norway	22 - 42	21 - 40	13 - 26	16 - 31	3 - 5
Poland	179 - 343	172 - 328	110 - 211	133 - 255	23 - 44
Portugal	54 - 99	52 - 95	33 - 61	40 - 74	7 - 13
Romania	96 - 180	92 - 173	59 - 111	72 - 134	12 - 23
Slovakia	24 - 48	23 - 46	15 - 29	18 - 35	3 - 6
Slovenia	10 - 19	10 - 18	6 - 11	8 - 14	1 - 2
Spain	222 - 425	213 - 407	136 - 261	165 - 316	29 - 55
Sweden	45 - 83	43 - 79	28 - 51	33 - 62	6 - 11
Switzerland	38 - 73	37 - 70	24 - 45	29 - 54	5 - 9
The Netherlands	79 - 147	76 - 141	49 - 90	59 - 109	10 - 19
United Kingdom	291 - 553	279 - 530	179 - 340	217 - 411	38 - 72

[7] HPV prevalence: 95.8% 91.8– 98.2, [8] HPV6/11/16/18 attributable fraction among HPV+ cases: 64.1% 56.6–71.2, [3] HPV 6/11/16/18/31/33/45/52/58 attributable fraction among HPV+ cases: 77.6% 70.6–83.3 ref: Alemany et al. [25]

AIN 2/3

Country	Sexes	N of new cases irrespective of HPV status	N of new cases attributable to HPV	N of cases related to quadrivalent vaccine types	N of cases related to nine-valent vaccine types	Additional N of cases related to five new HPV types
Austria	Women	25	24	18	20	1
	Men	18	17	13	14	1
	Both sexes	43	41	31	33	2
Belgium	Women	33	31	24	26	2
	Men	24	22	17	18	1
	Both sexes	57	54	41	44	3
Bulgaria	Women	22	21	16	17	1
	Men	15	15	11	12	1
	Both sexes	37	35	27	29	2
Croatia	Women	13	12	9	10	1
	Men	9	8	6	7	1
	Both sexes	22	21	16	17	1
Cyprus	Women	3	2	2	2	0
	Men	2	2	1	1	0
	Both sexes	4	4	3	3	0
Czech Republic	Women	31	30	22	24	2
	Men	22	21	16	17	1
	Both sexes	53	51	38	41	3
Denmark	Women	16	16	12	13	1
	Men	12	11	9	9	1
	Both sexes	28	27	20	22	2
Estonia	Women	4	4	3	3	0
	Men	3	3	2	2	0
	Both sexes	7	6	5	5	0
Finland	Women	16	15	12	12	1
	Men	11	11	8	9	1
	Both sexes	27	26	20	21	2
France	Women	196	187	141	152	11
	Men	137	130	98	106	8
	Both sexes	333	317	239	258	19
Germany	Women	242	230	174	188	14
	Men	173	165	125	135	10
	Both sexes	415	396	298	322	24
Greece	Women	33	31	24	25	2
	Men	23	22	17	18	1
	Both sexes	56	53	40	44	3
Hungary	Women	30	29	22	23	2
	Men	20	19	15	16	1

	Both sexes	50	48	36	39	3
Iceland	Women	1	1	1	1	0
	Men	1	1	1	1	0
	Both sexes	2	2	1	1	0
Ireland	Women	13	13	10	10	1
	Men	10	9	7	8	1
	Both sexes	23	22	17	18	1
Italy	Women	179	170	128	139	10
	Men	124	118	89	96	7
	Both sexes	303	289	218	235	18
Latvia	Women	6	6	5	5	0
	Men	4	4	3	3	0
	Both sexes	10	10	7	8	1
Lithuania	Women	9	9	7	7	1
	Men	6	6	4	5	0
	Both sexes	15	14	11	12	1
Luxembourg	Women	2	1	1	1	0
	Men	1	1	1	1	0
	Both sexes	3	3	2	2	0
Malta	Women	1	1	1	1	0
	Men	1	1	1	1	0
	Both sexes	2	2	2	2	0
Norway	Women	15	14	10	11	1
	Men	11	10	8	8	1
	Both sexes	25	24	18	20	1
Poland	Women	115	110	83	90	7
	Men	80	76	58	62	5
	Both sexes	196	186	140	152	11
Portugal	Women	32	30	23	25	2
	Men	21	20	15	17	1
	Both sexes	53	51	38	41	3
Romania	Women	60	57	43	46	3
	Men	42	40	30	33	2
	Both sexes	101	97	73	79	6
Slovakia	Women	16	15	12	13	1
	Men	11	11	8	9	1
	Both sexes	27	26	20	21	2
Slovenia	Women	6	6	4	5	0
	Men	4	4	3	3	0
	Both sexes	10	10	7	8	1
Spain	Women	138	131	99	107	8
	Men	99	94	71	77	6
	Both sexes	237	225	170	184	14
Sweden	Women	28	26	20	22	2
	Men	20	20	15	16	1

	Both sexes	48	46	35	38	3
Switzerland	Women	24	23	17	18	1
	Men	17	16	12	13	1
	Both sexes	41	39	29	32	2
The Netherlands	Women	49	47	35	38	3
	Men	36	34	26	28	2
	Both sexes	85	81	61	66	5
United Kingdom	Women	188	179	135	146	11
	Men	135	129	97	105	8
	Both sexes	323	308	232	251	19

[10] HPV prevalence: 87.6% 81.6–92.1, [11] HPV6/11/16/18 attributable fraction among HPV+ cases: 87.1% 80.7–92.1, [12] HPV 6/11/16/18/31/33/45/52/58 attributable fraction among HPV+ cases: 89.8% 83.8–94.2 ref: Alemany et al. [19]

HPV: human papillomavirus; CIN: cervical intraepithelial neoplasia; CIN2+ includes CIN2,

CIN3 and AIS, VIN: vulvar intraepithelial neoplasia; VaIN: vaginal intraepithelial neoplasia;

AIN: anal intraepithelial neoplasia; N: number

Table 5 - Estimated annual number of new genital wart cases in women and men in the European countries

Country	Sex	N of new annual cases (range)	N of new annual cases related to HPV6/11 (range)
Austria	Women	6146 - 8271	5531 - 7444
	Men	6089 - 6915	5480 - 6224
	Both sexes	12235 - 15187	11012 - 13668
Belgium	Women	8057 - 10843	7252 - 9759
	Men	8103 - 9202	7292 - 8282
	Both sexes	16160 - 20046	14544 - 18041
Bulgaria	Women	5310 - 7146	4779 - 6432
	Men	5235 - 5945	4711 - 5351
	Both sexes	10545 - 13091	9490 - 11782
Croatia	Women	3132 - 4215	2819 - 3794
	Men	3037 - 3449	2733 - 3104
	Both sexes	6169 - 7664	5552 - 6897
Cyprus	Women	632 - 850	569 - 765
	Men	622 - 706	560 - 635
	Both sexes	1253 - 1556	1128 - 1401
Czech Republic	Women	7600 - 10227	6840 - 9205
	Men	7626 - 8661	6863 - 7795
	Both sexes	15225 - 18888	13703 - 16999
Denmark	Women	4010 - 5396	3609 - 4857
	Men	4103 - 4660	3693 - 4194
	Both sexes	8113 - 10056	7302 - 9051
Estonia	Women	1000 - 1345	900 - 1211
	Men	910 - 1033	819 - 930
	Both sexes	1910 - 2379	1719 - 2141
Finland	Women	3919 - 5274	3527 - 4747
	Men	3938 - 4472	3544 - 4025
	Both sexes	7857 - 9746	7071 - 8772
France	Women	48016 - 64619	43215 - 58157
	Men	46904 - 53269	42213 - 47942
	Both sexes	94920 - 117888	85428 - 106099
Germany	Women	59177 - 79638	53259 - 71675
	Men	59576 - 67662	53619 - 60896
	Both sexes	118753 - 147300	106878 - 132570
Greece	Women	8022 - 10796	7220 - 9716
	Men	7993 - 9078	7194 - 8170
	Both sexes	16015 - 19874	14414 - 17886
Hungary	Women	7374 - 9924	6636 - 8931
	Men	6964 - 7909	6267 - 7118
	Both sexes	14337 - 17832	12904 - 16049

Iceland	Women	228 - 307	205 - 276
	Men	238 - 271	215 - 244
	Both sexes	466 - 577	420 - 520
Ireland	Women	3292 - 4430	2963 - 3987
	Men	3356 - 3811	3020 - 3430
	Both sexes	6648 - 8242	5983 - 7418
Italy	Women	43730 - 58850	39357 - 52965
	Men	42658 - 48448	38393 - 43603
	Both sexes	86388 - 107298	77749 - 96568
Latvia	Women	1558 - 2097	1402 - 1887
	Men	1368 - 1554	1231 - 1398
	Both sexes	2926 - 3651	2634 - 3286
Lithuania	Women	2276 - 3063	2049 - 2757
	Men	2021 - 2296	1819 - 2066
	Both sexes	4298 - 5359	3868 - 4823
Luxembourg	Women	381 - 513	343 - 462
	Men	396 - 450	357 - 405
	Both sexes	778 - 963	700 - 867
Malta	Women	300 - 404	270 - 364
	Men	310 - 352	279 - 317
	Both sexes	610 - 756	549 - 681
Norway	Women	3572 - 4807	3215 - 4326
	Men	3745 - 4253	3370 - 3827
	Both sexes	7316 - 9060	6585 - 8154
Poland	Women	28235 - 37998	25412 - 34198
	Men	27538 - 31275	24784 - 28147
	Both sexes	55773 - 69273	50196 - 62346
Portugal	Women	7798 - 10494	7018 - 9445
	Men	7377 - 8378	6639 - 7540
	Both sexes	15175 - 18872	13657 - 16985
Romania	Women	14567 - 19604	13110 - 17644
	Men	14414 - 16370	12972 - 14733
	Both sexes	28981 - 35974	26083 - 32377
Slovakia	Women	3940 - 5303	3546 - 4772
	Men	3892 - 4421	3503 - 3978
	Both sexes	7833 - 9723	7049 - 8751
Slovenia	Women	1476 - 1987	1329 - 1788
	Men	1505 - 1709	1354 - 1538
	Both sexes	2981 - 3696	2683 - 3326
Spain	Women	33668 - 45310	30302 - 40779
	Men	33988 - 38601	30589 - 34741
	Both sexes	67656 - 83911	60891 - 75520
Sweden	Women	6802 - 9154	6122 - 8238
	Men	7037 - 7992	6334 - 7193
	Both sexes	13839 - 17146	12455 - 15431

Switzerland	Women	5780 - 7779	5202 - 7001
	Men	5860 - 6655	5274 - 5990
	Both sexes	11640 - 14434	10476 - 12991
The Netherlands	Women	12031 - 16190	10828 - 14571
	Men	12267 - 13931	11040 - 12538
	Both sexes	24297 - 30122	21867 - 27110
United Kingdom	Women	46111 - 62055	41500 - 55850
	Men	46400 - 52697	41760 - 47427
	Both sexes	92511 - 114752	83260 - 103277

HPV: human papillomavirus; N: number.