Forpath 20121117 Yves Couvreur 26/11/2012


From cytology screening to HPV screening.
And much more……
Forpath 20121117 Yves Couvreur 26/11/2012

700 cancers du col de l'uterus

Par Vincent Liévin dans Chiffre du jour , le 10 octobre 2011 08h01 |

En Belgique, environ **700** cancers du col utérin sont recensés chaque année. Une étude européenne a montré que ce cancer demeure la principale cause de décès par cancer chez les femmes **entre 15 et 44 ans**. Dans notre pays, deux vaccins contre les principaux papillomavirus humains (HPV) cancérigènes sont disponibles. Ils protègent contre les virus **HPV 16 et HPV 18, qui sont responsables d'environ 70%** des cas de cancers du col de l'utérus. Les HPV (Human Papilloma Virus) sont une grande famille de virus qui se transmettent lors de rapports sexuels ou de contacts intimes. Il en existe une centaine de types différents. La plupart sont inoffensifs, mais certains d'entre eux peuvent causer une infection chronique. Celle-ci peut alors déclencher, à terme, un cancer du col de l'utérus. (source : cancer.be)
La ministre de la santé de la Fédération Wallonie-Bruxelles, Fadila Laanan a décidé de prendre une mesure pour changer cela. Sur le terrain, le vaccin contre le cancer du col de l'utérus sera gratuit dans les écoles de la Fédération Wallonie-Bruxelles dès la prochaine rentrée scolaire. Le vaccin contre le virus HPV (papillomavirus) sera proposé aux adolescentes de 2ème secondaire, dans le cadre de la vaccination scolaire. Les élèves auront le choix de recourir à ce vaccin ou non. Il n'est évidemment pas obligatoire. 26.000 élèves sont concernées et sans nécessairement de limite d'âge trop stricte dès cette rentrée scolaire. Même si a priori, ce sont des jeunes filles de 12 ans.
Evidemment, c'est dans le cadre de la médecine scolaire que la vaccination va avoir lieu. Un formulaire d'accord devra d'ailleurs être signé par les parents. Un contact sera pris avec les médecins généralistes et les pédiatres. Une campagne d'information et de sensibilisation a eu lieu en septembre.
Pour rappel, depuis 2008, il existe deux vaccins contre le papillomavirus, remboursés par l'Inami pour les filles entre 12 et 18 ans. L'un des grands défis sera la qualité de la couverture vaccinale. Du côté des autorités publiques, on table dès 2011-2012 sur une couverture de 60%. A trois ans, l'objectif est d'atteindre les 80%. Il faut en outre rappeler que les vaccins disponibles ne protègent que contre 70 % des souches de virus qui peuvent provoquer les lésions qui entraînent parfois le cancer. Le dépistage reste donc nécessaire.

http://blogs.rtl.be/santevousbien/2011/10/10/700-cancers-du-col-de-luterus/

General results, 2008

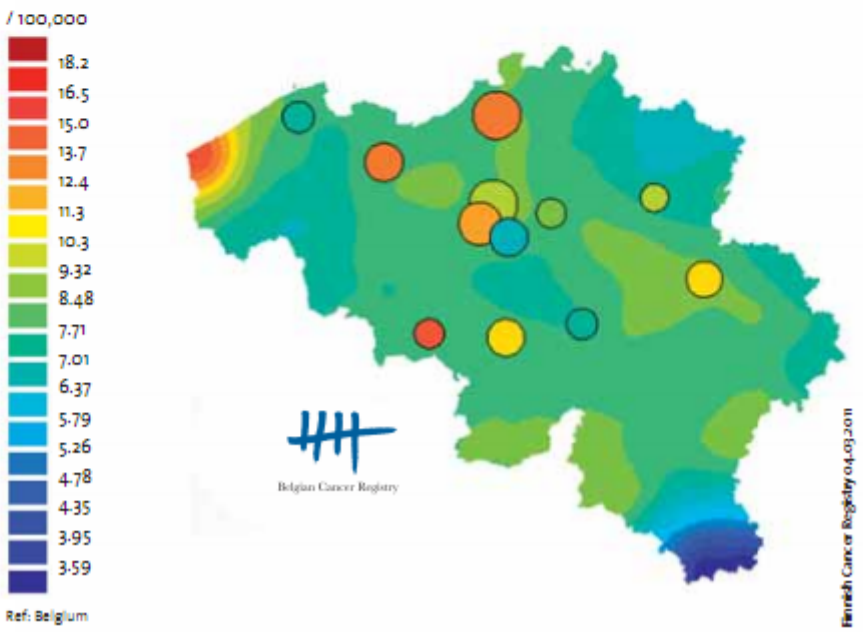
Table 32 Cervical cancer incidence and mortality by region, 2008

	Incidence				Mortality		
Females	**N**	**CR**	**WSR**	**CRI**	**N**	**CR**	**WSR**
Belgium	643	11.8	8.2	0.8	186	3.4	1.8
Flemish Region	360	11.5	7.8	0.8	129	4.1	2.1
Brussels Capital Region	72	13.3	9.5	1.0	16	2.9	1.8
Walloon Region	211	11.9	8.6	0.8	41	2.3	1.2

CR: crude (all ages) rate (n/100,000 person years)
WSR: age-standardised rate, using the World Standard Population (n/100,000 person years)
CRI: cumulative risk 0-74 years (%)

- Cervical cancer is the 8th most frequent tumour in females (2.3%). Cancer of the cervix is the 3rd most frequently occurring gynaecological tumour.
- Cervical cancer is a rare cause of cancer death (1.6%).
- The highest incidence rates are observed in the Brussels Capital Region.
- Mean age at diagnosis is 54 years.

Figure 61 Cervical cancer incidence in Belgium, 2004-2008



Epidemiology and costs of cervical cancer screening and cervical dysplasia in Italy

BMC Public Health 2009, **9:**71doi:10.1186/1471-2458-9-71

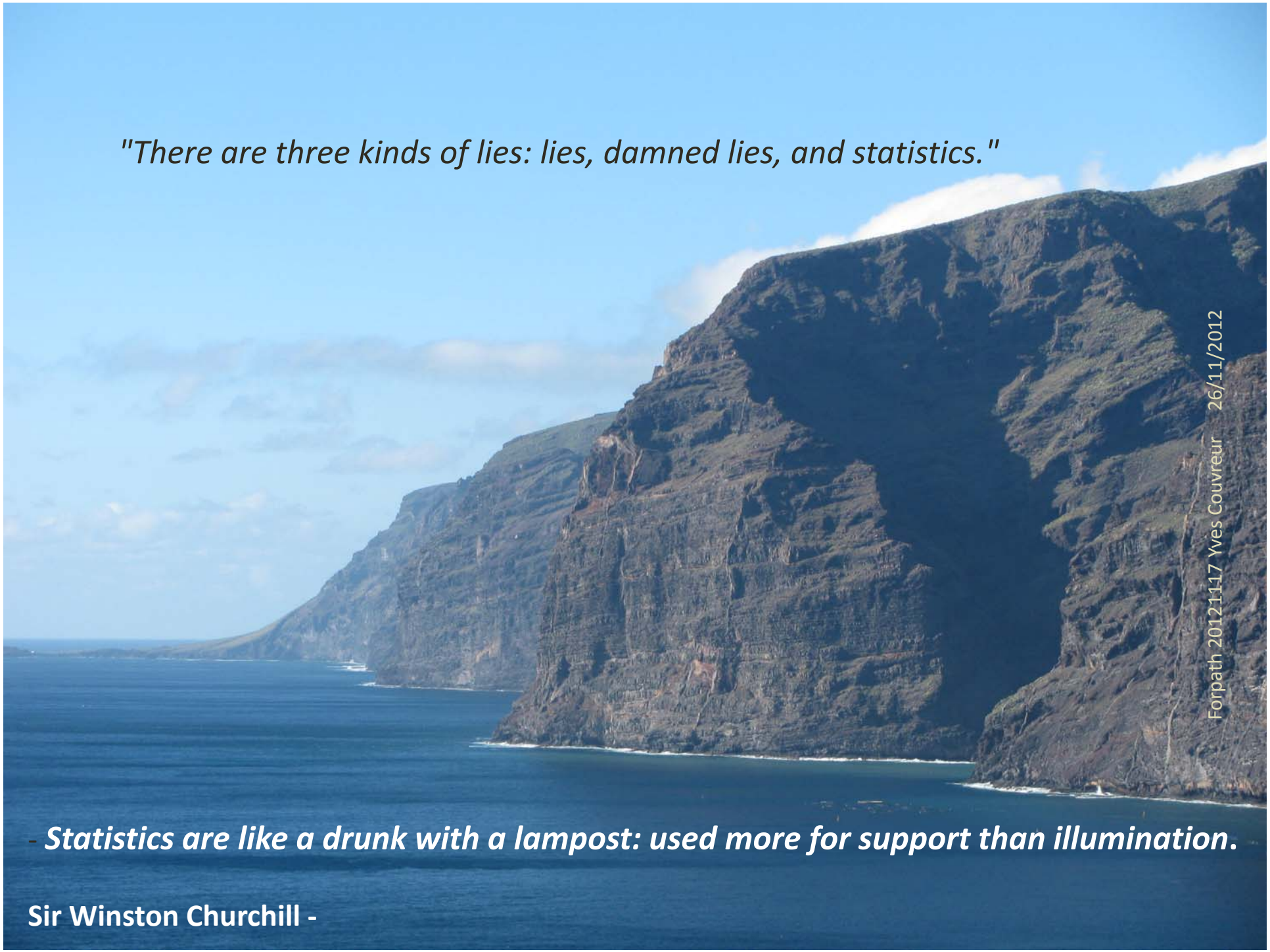
Abstract

Background
We estimated the number of women undergoing cervical cancer screening annually in Italy, the rates of cervical abnormalities detected, and the costs of screening and management of abnormalities.

Methods
The annual number of screened women was estimated from National Health Interview data. Data from the Italian Group for Cervical Cancer Screening were used to estimate the number of positive, negative and unsatisfactory Pap smears. The incidence of CIN (cervical intra-epithelial neoplasia) was estimated from the Emilia Romagna Cancer Registry. Patterns of follow-up and treatment costs were estimated using a typical disease management approach based on national guidelines and data from the Italian Group for Cervical Cancer Screening. Treatment unit costs were obtained from Italian National Health Service and Hospital Information System of the Lazio Region.

Results
An estimated 6.4 million women aged 25–69 years undergo screening annually in Italy (1.2 million and 5.2 million through organized and opportunistic screening programs, respectively). **Approximately 2.4% of tests have positive** findings. There are approximately 21,000 cases of CIN1 and 7,000–17,000 cases of CIN2/3. Estimated costs to the healthcare service amount to €158.5 million for screening and €22.9 million for the management of cervical abnormalities.

Conclusion
Although some cervical abnormalities might have been underestimated, the total annual cost of cervical cancer prevention in Italy is approximately €181.5 million, of which 87% is attributable to screening


"There are three kinds of lies: lies, damned lies, and statistics."
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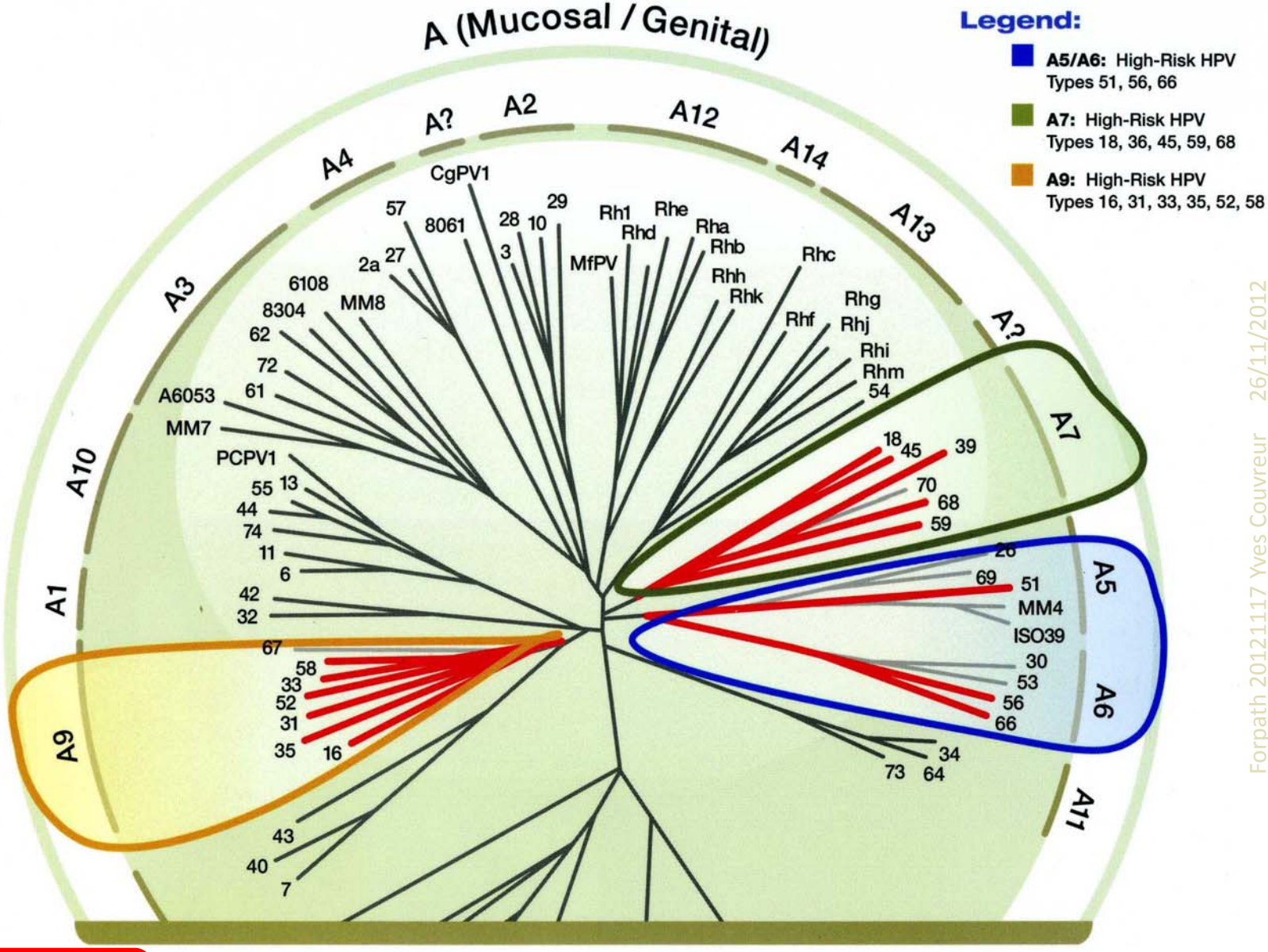
- Statistics are like a drunk with a lampost: used more for support than illumination.
Sir Winston Churchill -

HPV L1 Consensus Primer Region (CPR) Phylogenetic Tree



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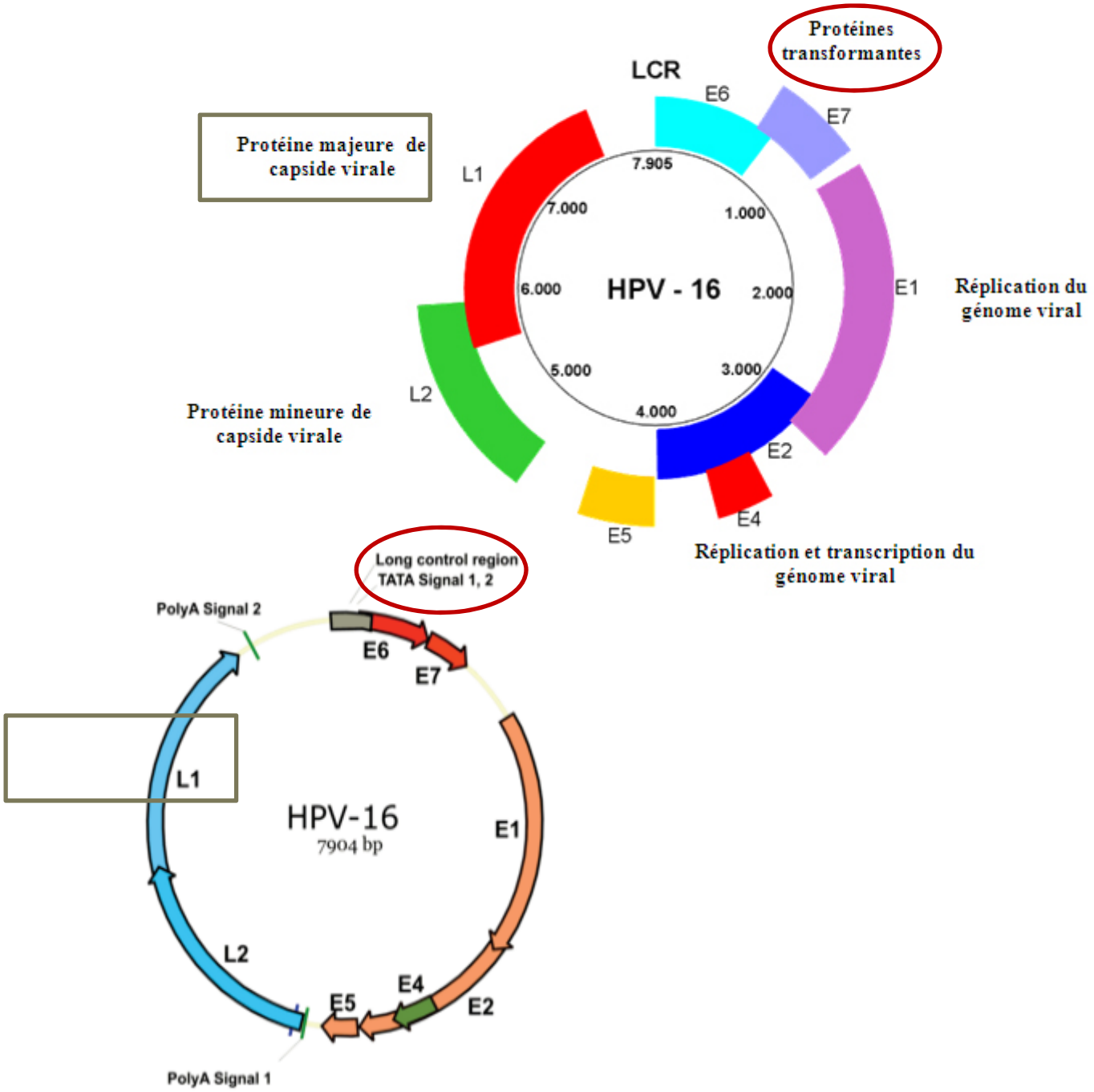
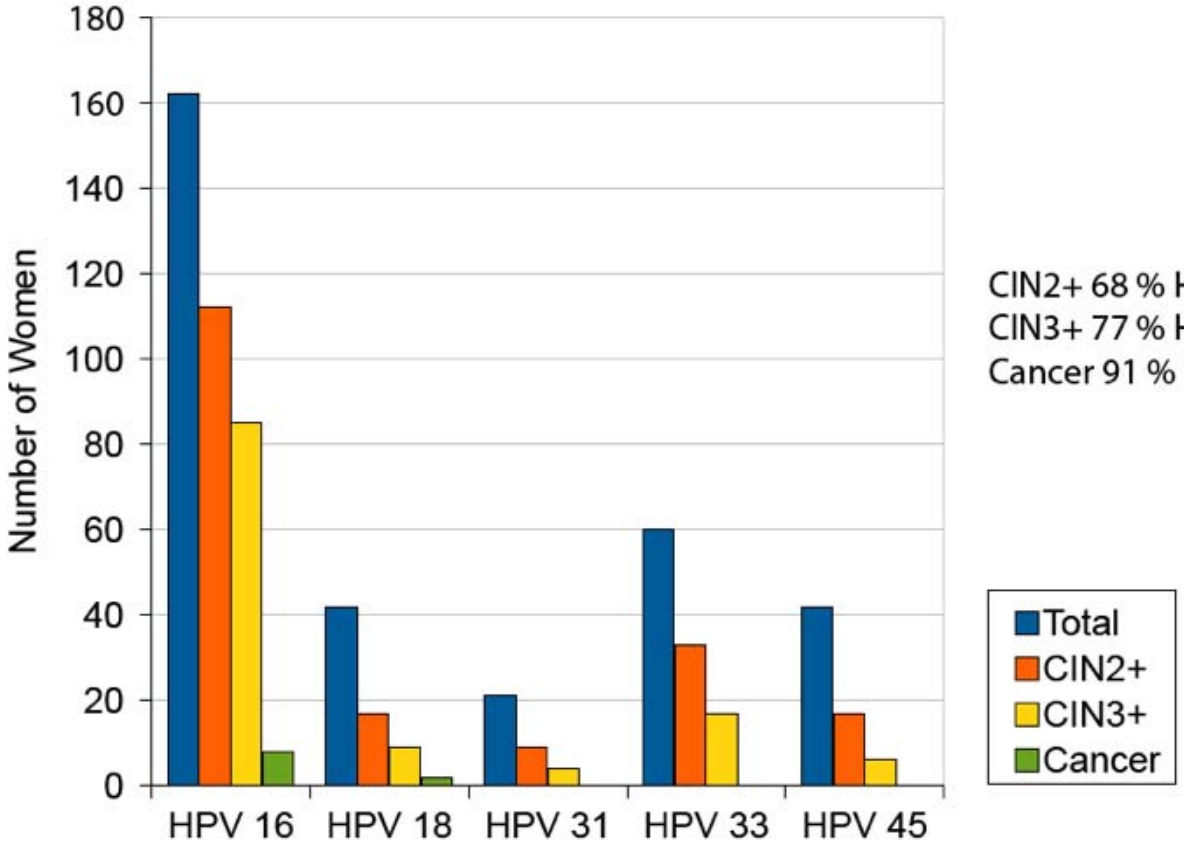
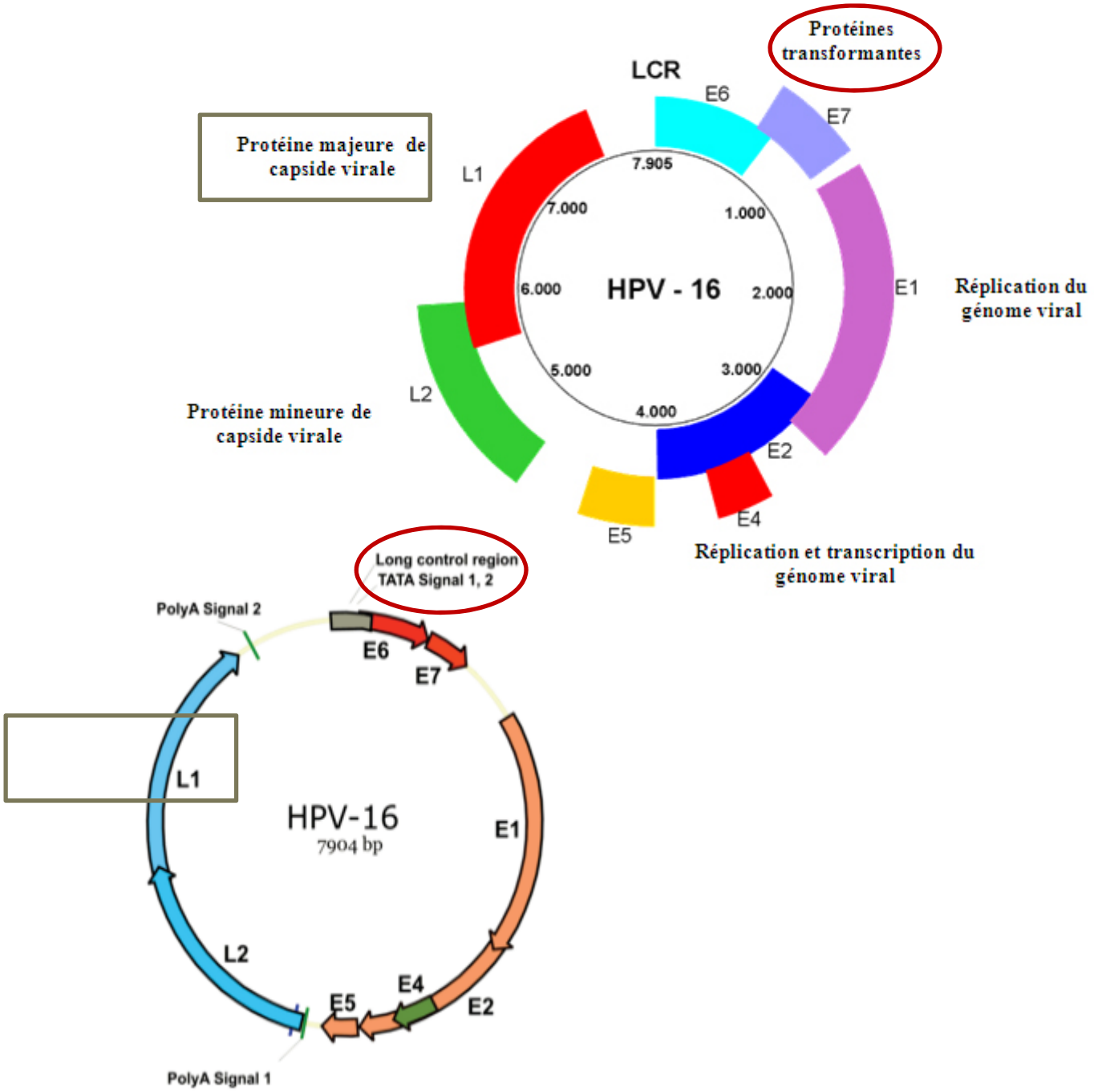
Human Papillomaviruses: A complilation and Analysis of Nucleic Acid and Amino Acid sequences, Los Alamos National Laboratory. Published online, hpv-web.lanl.gov.


Protéines transformantes
LCR
E6
E7
Protéine majeure de capside virale
L1
7.905
1.000
7.000
6.000
HPV - 16
2.000
E1
Réplication du génome viral
5.000
3.000
L2
4.000
Protéine mineure de capside virale
E2
E4
E5
Réplication et transcription du génome viral
Long control region
TATA Signal 1, 2
PolyA Signal 2
E6
E7
L1
HPV-16
7904 bp
E1
L2
E4
E5
E2
PolyA Signal 1

HPV type, dysplasia and cancer



CIN2+ 68 % HPV 16/18
CIN3+ 77 % HPV 16/18
Cancer 91 % HPV 16/18


Protéines transformantes
LCR
E6
E7
Protéine majeure de capside virale
L1
7.905
1.000
7.000
6.000
HPV - 16
2.000
E1
Réplication du génome viral
5.000
3.000
L2
4.000
Protéine mineure de capside virale
E2
E4
E5
Réplication et transcription du génome viral
Long control region
TATA Signal 1, 2
PolyA Signal 2
E6
E7
L1
HPV-16
7904 bp
E1
L2
E4
E5
E2
PolyA Signal 1

Cervarix (GSK)

[papillomavirus humain de types **16, 18** (protéines L1) [biosynthétique]]
amp. ser. i.m.

1 x 0,5ml € 124,22

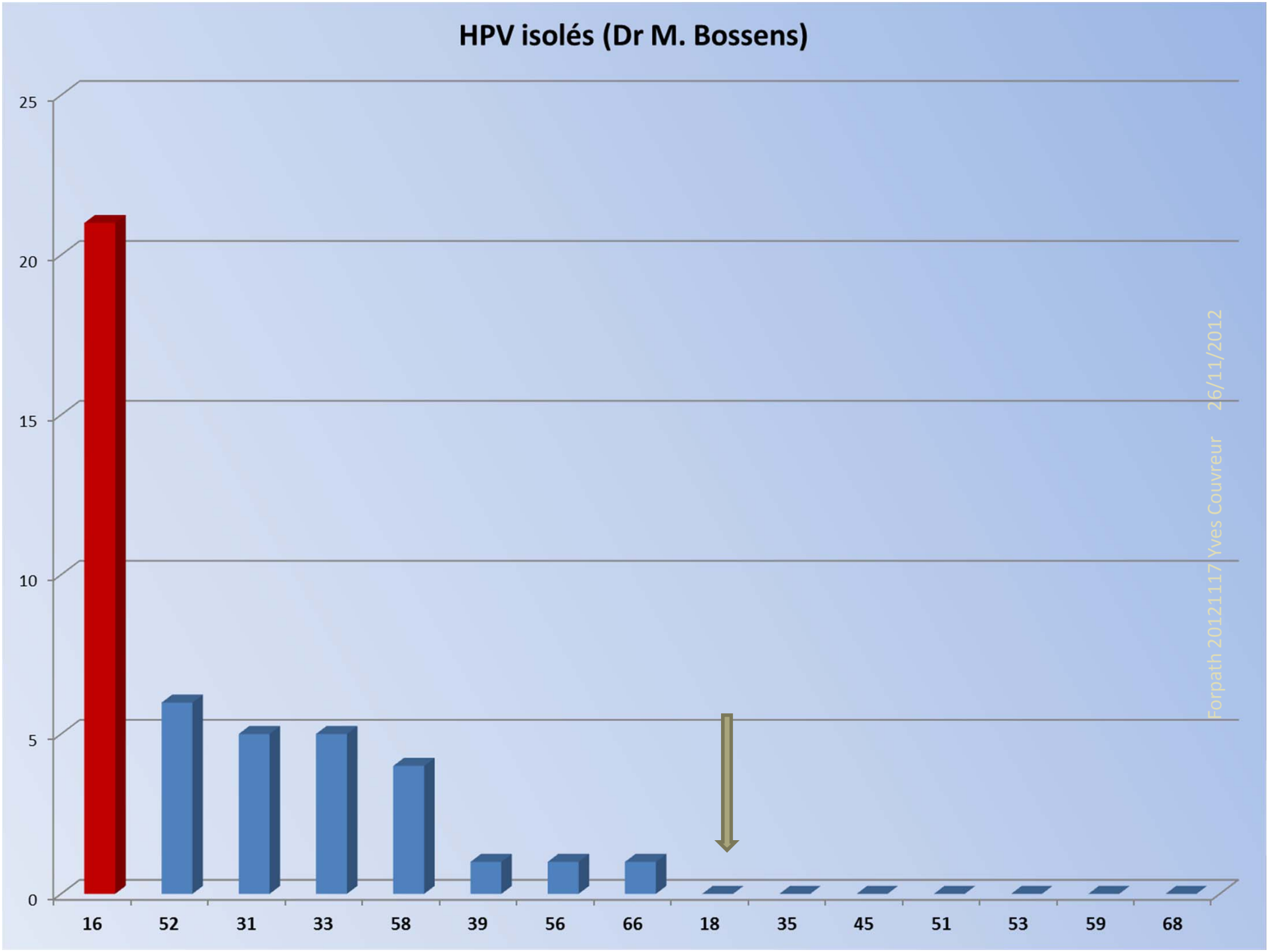
(vaccin non vivant; contient de l'aluminium et un adjuvant)

Gardasil (Sanofi Pasteur MSD)

[papillomavirus humain de types **6, 11, 16, 18** (protéines L1) [biosynthétique]]
amp. ser. i.m.

1 x 0,5ml € 124,22

(vaccin non vivant; contient de l'aluminium)


HPV isolés (Dr M. Bossens)
25
20
15
10
5
0
16
52
31
33
58
39
56
66
18
35
45
51
53
59
68
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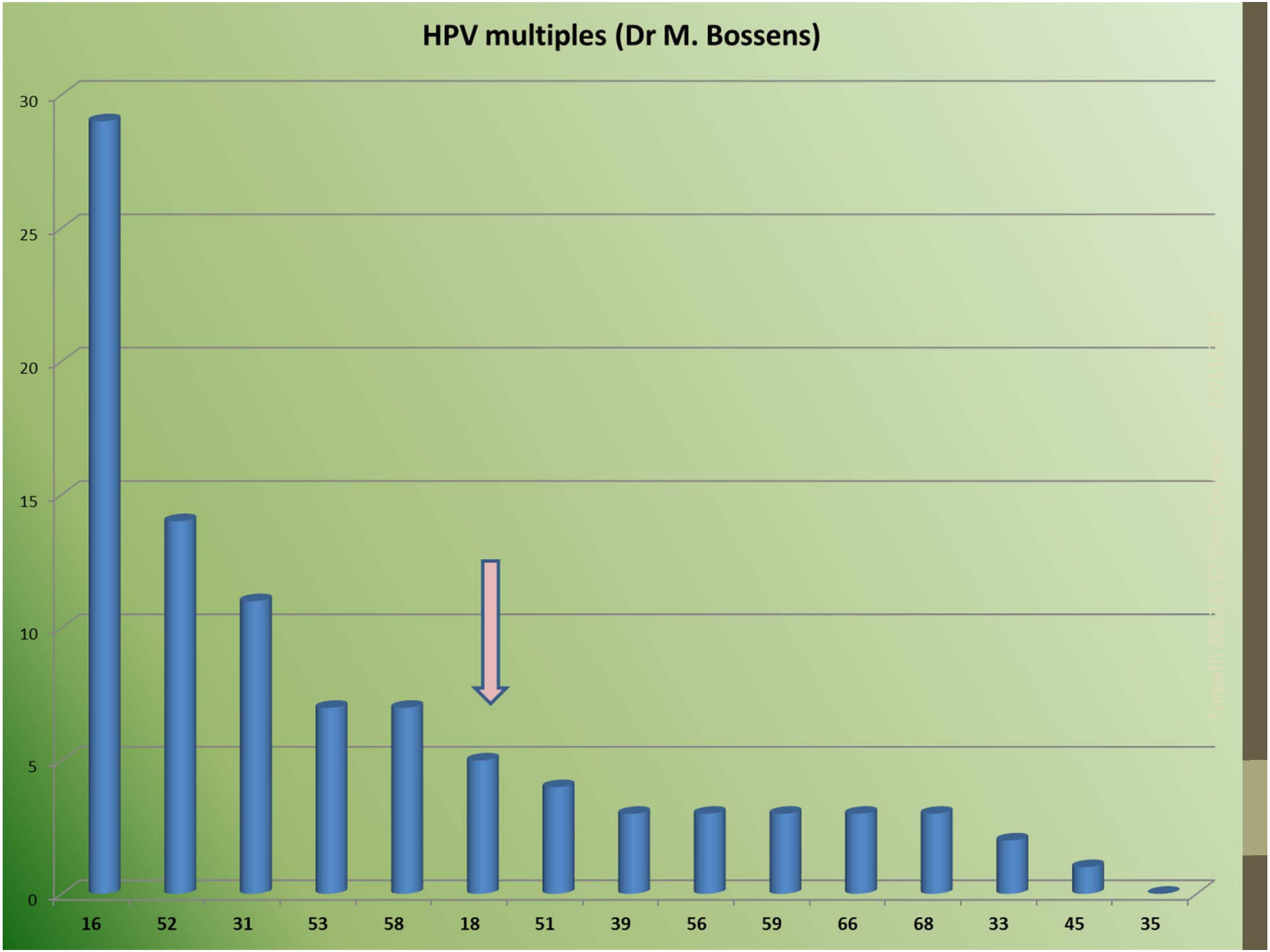
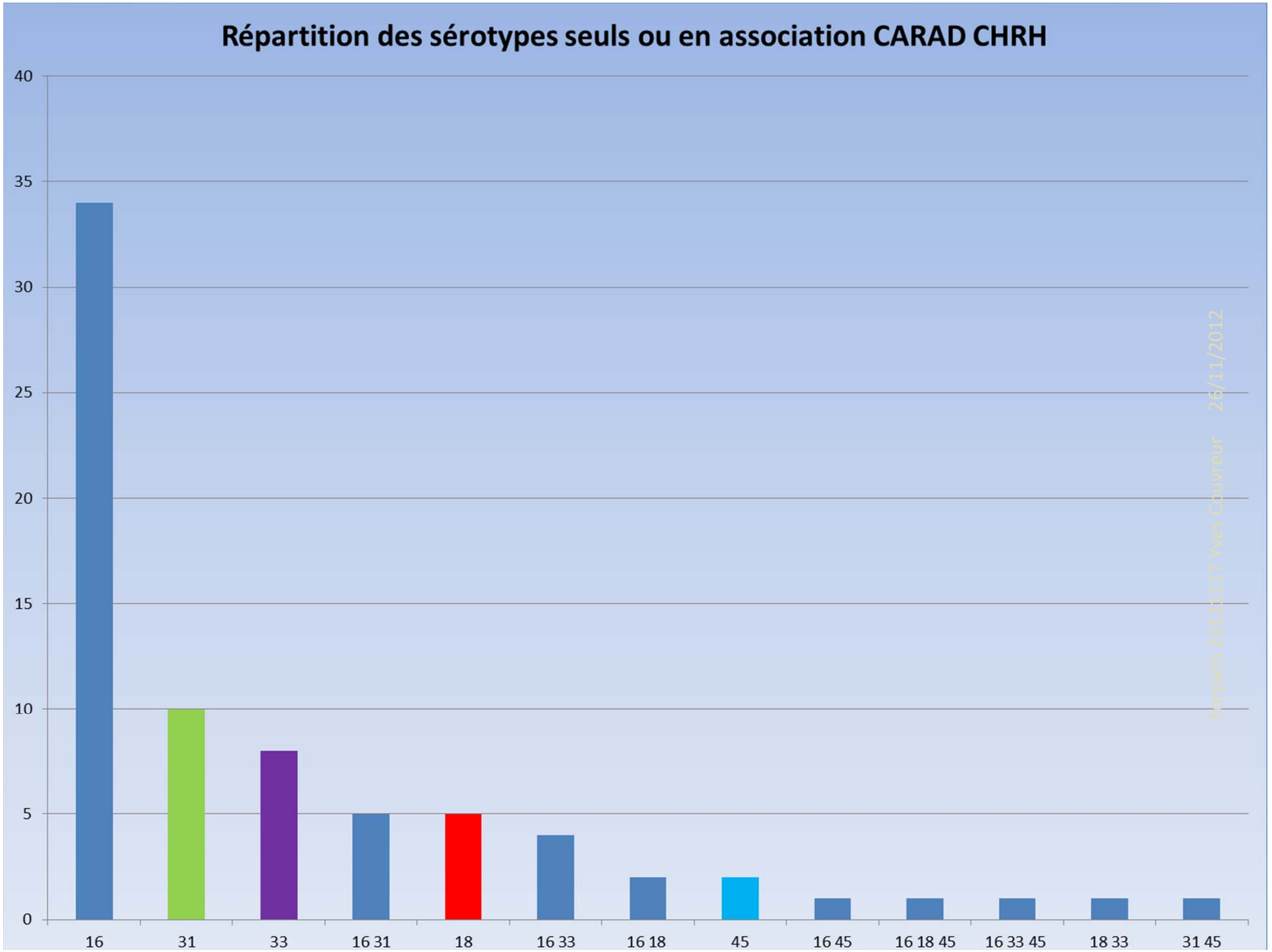
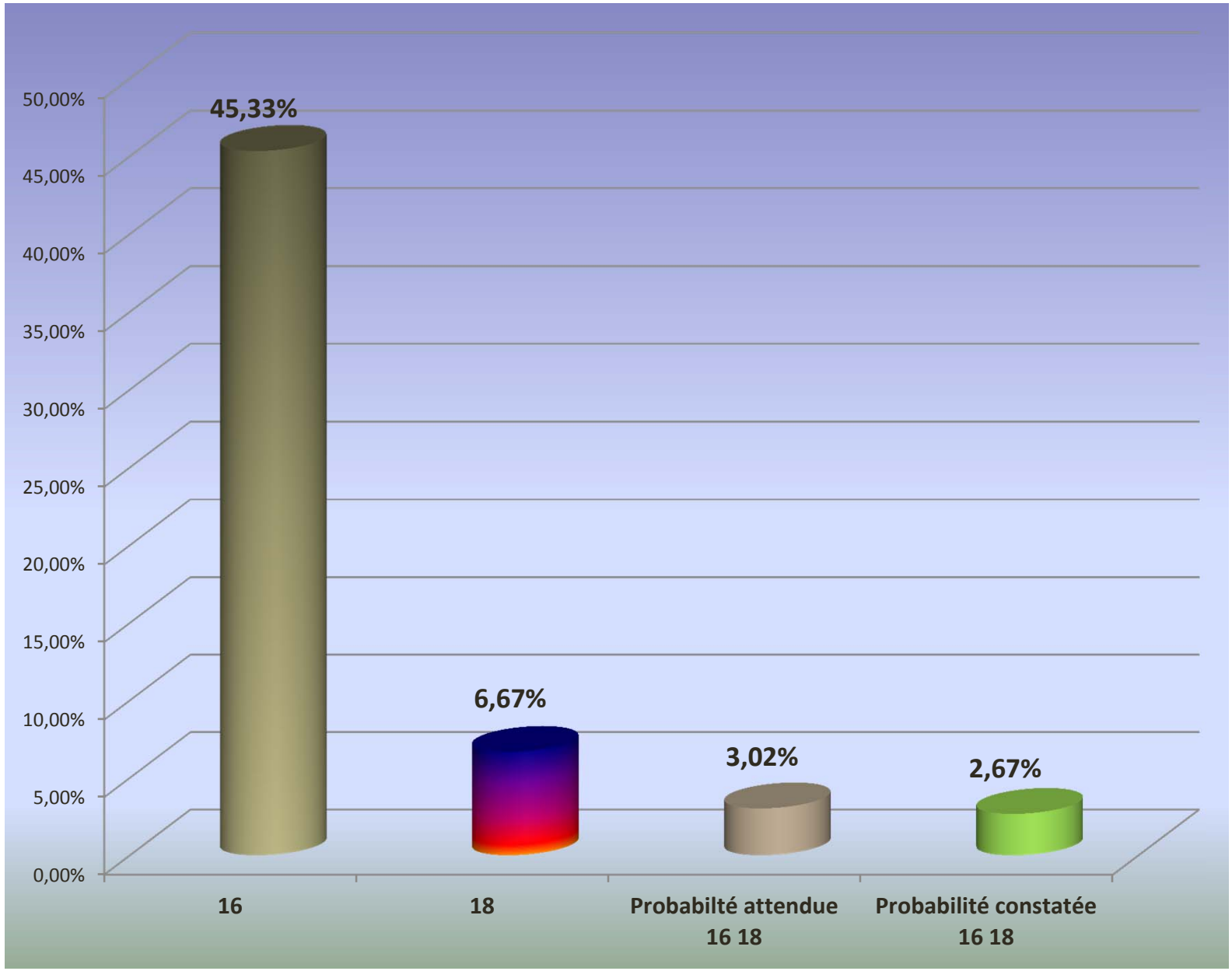
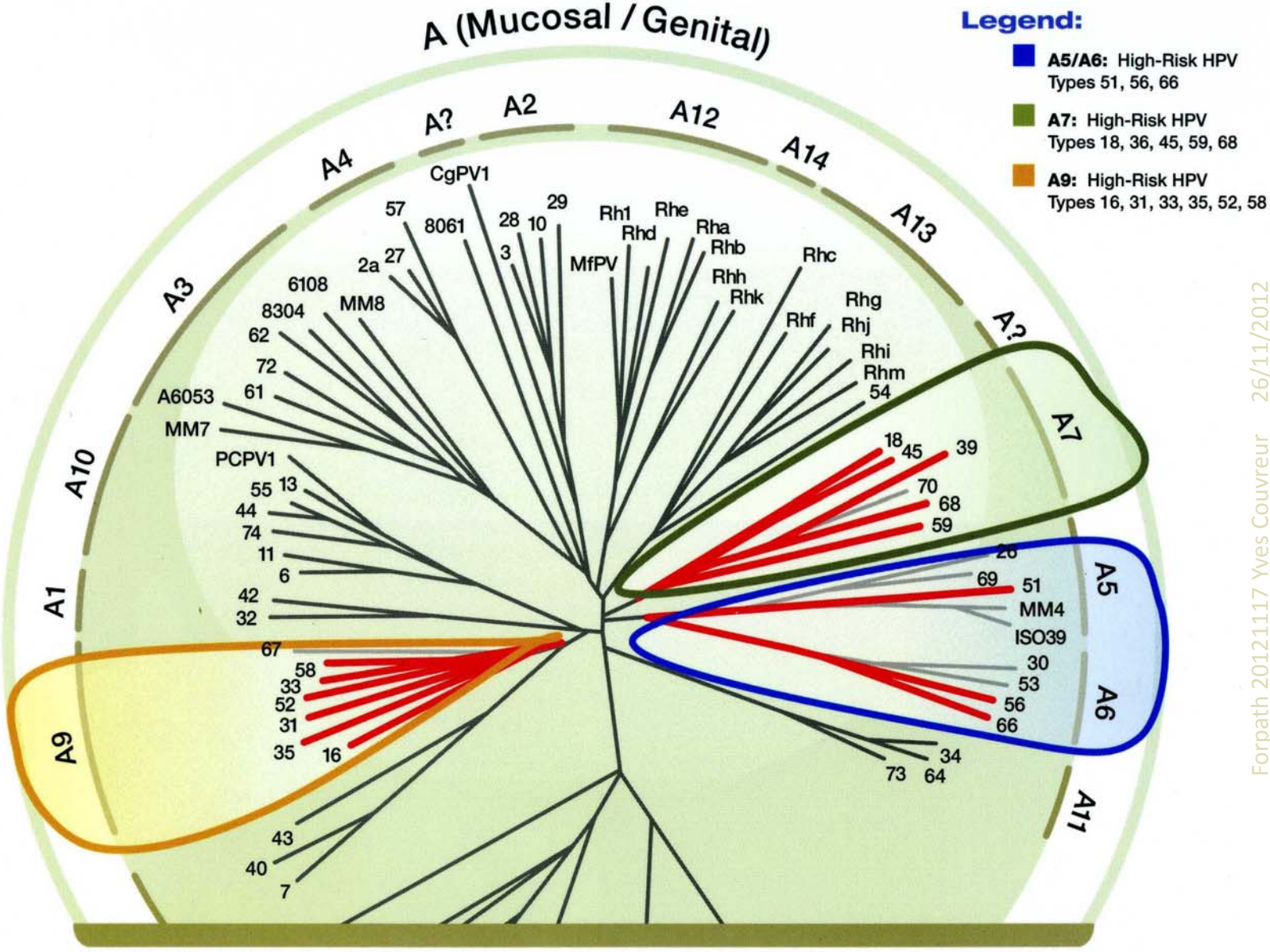

HPV multiples (Dr M. Bossens)
30
25
20
15
10
5
0
16
52
31
53
58
18
51
39
56
59
66
68
33
45
35


Répartition des sérotypes seuls ou en association CARAD CHRH
40
35
30
25
20
15
10
5
0
16
31
33
16 31
18
16 33
16 18
45
16 45
16 18 45
16 33 45
18 33
31 45
Forpath 2012 1117 Yves Couvreur 26/11/2012

Co infections = phénomènes aléatoires



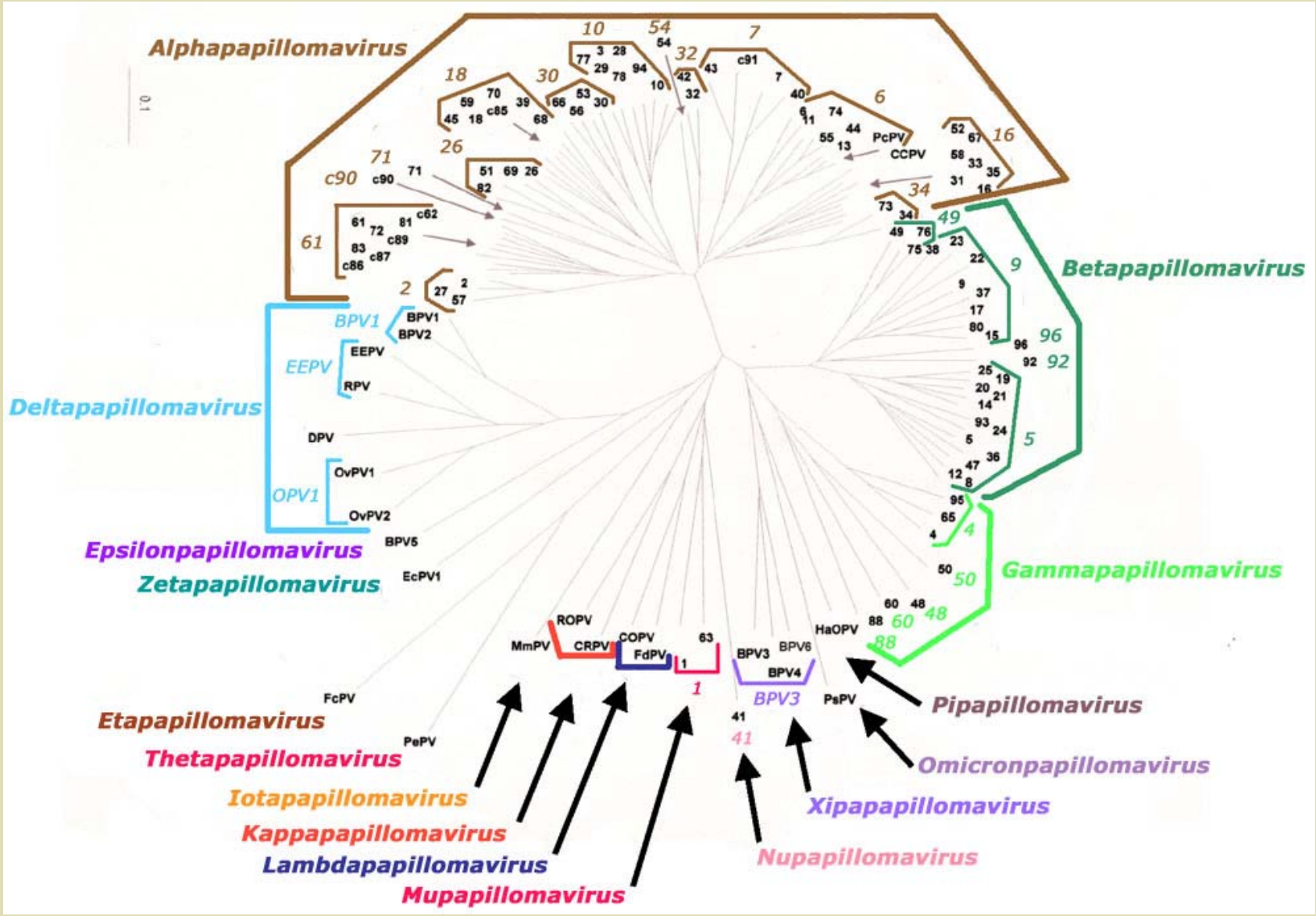
HPV L1 Consensus Primer Region (CPR) Phylogenetic Tree



Legend:

- **A5/A6:** High-Risk HPV Types 51, 56, 66
- **A7:** High-Risk HPV Types 18, 36, 45, 59, 68
- **A9:** High-Risk HPV Types 16, 31, 33, 35, 52, 58

Human Papillomaviruses: A complilation and Analysis of Nucleic Acid and Amino Acid sequences, Los Alamos National Laboratory. Published online, hpv-web.lanl.gov.


Alphapapillomavirus
Betapapillomavirus
Gammapapillomavirus
Deltapapillomavirus
Epsilonpapillomavirus
Zetapapillomavirus
Etapapillomavirus
Thetapapillomavirus
Iotapapillomavirus
Kappapapillomavirus
Lambdapapillomavirus
Mupapillomavirus
Pipapillomavirus
Omicronpapillomavirus
Xipapillomavirus
Nupapillomavirus
BPV1
EEPV
OPV1
ROPV
CRPV
COPV
FdPV
BPV3
BPV4
BPV6
HaOPV
PcPV
CCPV
PsPV
FcPV
PePV
MmPV
DPV
RPV
OvPV1
OvPV2
BPV5
EcPV1
0.1

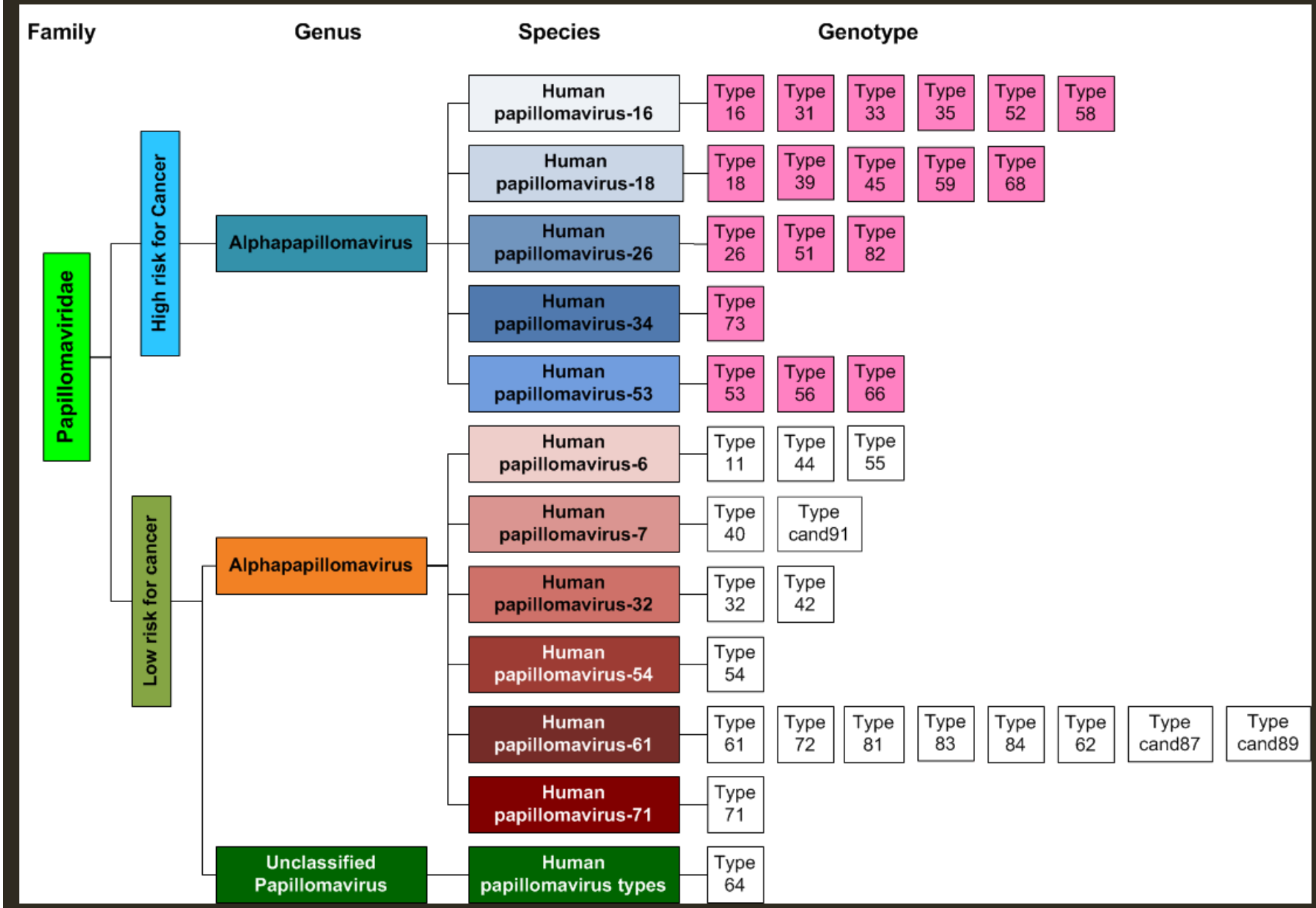

Family
Genus
Species
Genotype
Papillomaviridae
High risk for Cancer
Low risk for cancer
Alphapapillomavirus
Alphapapillomavirus
Unclassified Papillomavirus
Human papillomavirus-16
Human papillomavirus-18
Human papillomavirus-26
Human papillomavirus-34
Human papillomavirus-53
Human papillomavirus-6
Human papillomavirus-7
Human papillomavirus-32
Human papillomavirus-54
Human papillomavirus-61
Human papillomavirus-71
Human papillomavirus types
Type 16
Type 31
Type 33
Type 35
Type 52
Type 58
Type 18
Type 39
Type 45
Type 59
Type 68
Type 26
Type 51
Type 82
Type 73
Type 53
Type 56
Type 66
Type 11
Type 44
Type 55
Type 40
Type cand91
Type 32
Type 42
Type 54
Type 61
Type 72
Type 81
Type 83
Type 84
Type 62
Type cand87
Type cand89
Type 71
Type 64

Table 1.1 HPV Types and Disease Associations

Disease	Frequent association	Less frequent association
Cutaneous warts	1, 2, 4	3, 7, 10, 26, 27, 28, 29, 38, **41**[a], 49, 57, 63, 65, 75, 76, 77,80, 83, 84, 86, 87
Epidermodysplasia verruciformis	**5**, **8**, 9, 12, **14**, 15, **17**	19, **20**, 21–25, 36–38, **47**, 49, 50, 93
Condylomata acuminata	6, 11	**30**, 42, 43, 44, **45**, **51**, 54, 55, 70
Intraepithelial neoplasias	6, 11, **16**, **18**	**30**, **31**, **33**, 34, **35**, **39**, 40, 42, 43, 44, **45**, **51–53**, **56**, 57, **58**, **59**, 61, 62, 64, **66**, 67, **68**, 69, 71, 72, 74, **82**
Carcinomas	**16**, **18**	**31**, **33**, **35**, **39**, **45**, **51**, **52**, **56**, **58**, **59**, **66**, **67**, **68**, **70**, **73**, **82**

[a]The genotypes in bold have an established or possible oncogenic potential.

« Il y a plus faux que le faux,
c'est le mélange du vrai et du faux. »

Paul Valéry

Different population-level vaccination effectiveness for HPV types 16, 18, 6 and 11

Sex Transm Infect2011;87:41-43 doi:10.1136/sti.2010.044412

Background Given that the human papillomavirus (HPV) vaccine types have different durations of infectiousness and infectivity, the population-level vaccine effectiveness of these types may differ even if vaccine efficacy is identical.

Objective To compare the type-specific effectiveness of vaccination against HPV types 16, 18, 6 and 11.
Methods An individual-based stochastic model of HPV transmission (18 HPV-types) in a population stratified by age, gender and sexual activity was developed. Multiple parameter sets were identified by fitting the model to sexual behaviour data and age- and type-specific HPV prevalence.

Results Under base case assumptions (70% coverage, 99% vaccine efficacy per act and **20** years' duration of protection), vaccinating 12-year-old girls is predicted to reduce HPV-16, HPV-18 and HPV-6/11 prevalence by 61% (80% uncertainty interval (UI) 53–77), 92% (80% UI 65–100) and 100% (80% UI 97–100), respectively, **50** years after the start of the vaccination programme. Differences in type-specific vaccine effectiveness increased over time, and decreased with improved vaccine efficacy characteristics.

Conclusions : For the same vaccine efficacy, the population-level impact of HPV vaccination will most likely be different, with HPV-16, the most oncogenic type, having the lowest effectiveness. These results should be taken into account when designing and interpreting post-vaccination surveillance studies.

JNCI J Natl Cancer Inst (2010) 102 (5): 325-339. doi: 10.1093/jnci/djp534

Background The impact of the prophylactic vaccine against human papillomavirus (HPV) types 6, 11, 16, and 18 (HPV6/11/16/18) on all HPV-associated genital disease was investigated in a population that approximates sexually naive women in that they were "negative to 14 HPV types" and in a mixed population of HPV-exposed and -unexposed women (intention-to-treat group).

Methods This analysis studied 17 622 women aged 15–26 years who were enrolled in one of two randomized, placebo-controlled, efficacy trials for the HPV6/11/16/18 vaccine (first patient on December 28, 2001, and studies completed July 31, 2007).
Vaccine or placebo was given at day 1, month 2, and month 6.
All women underwent cervicovaginal sampling and Papanicolaou (Pap) testing at day 1 and every 6–12 months thereafter.
Outcomes were any cervical intraepithelial neoplasia; any external anogenital and vaginal lesions;
Pap test abnormalities; and procedures such as colposcopy and definitive therapy. Absolute rates are expressed as women with endpoint per 100 person-years at risk.

Results The average follow-up was 3.6 years (maximum of 4.9 years). In the population that was negative to 14 HPV types, vaccination was up to 100% effective in reducing the risk of HPV16/18-related high-grade cervical, vulvar, and vaginal lesions and of HPV6/11-related genital warts. In the intention-to-treat group, vaccination also statistically significantly reduced the risk of any **high-grade cervical lesions (19.0% reduction**; rate vaccine = 1.43, rate placebo = 1.76, difference = 0.33, 95% confidence interval [CI] = 0.13 to 0.54) , **vulvar and vaginal lesions (50.7% reduction**; rate vaccine = 0.10, rate placebo = 0.20, difference = 0.10, 95% CI = 0.04 to 0.16), genital warts (62.0% reduction; rate vaccine = 0.44, rate placebo = 1.17, difference = 0.72, 95% CI = 0.58 to 0.87), **Pap abnormalities (11.3% reduction**; rate vaccine = 10.36, rate placebo = 11.68, difference = 1.32, 95% CI = 0.74 to 1.90), and cervical definitive therapy (23.0% reduction; rate vaccine = 1.97, rate placebo = 2.56, difference = 0.59, 95% CI = 0.35 to 0.83), irrespective of causal HPV type.

Conclusions High-coverage HPV vaccination programs among adolescents and young women **may** result in a rapid reduction of genital warts, cervical cytological abnormalities, and diagnostic and therapeutic procedures. In the longer term, substantial reductions in the rates of cervical, vulvar, and vaginal cancers **may** follow.

O3-S2.02 Long-term efficacy of human papillomavirus vaccination against CIN3 and invasive carcinoma: registry based follow-up of a phase iii trial (FUTURE II)

Background Human papilloma viruses (HPV) 16/18 are known to cause approximately 70% of cervical cancers. Phase III clinical trials of HPV vaccination have demonstrated >95% efficacy against persistent HPV type 16/18 infections and associated cervical intraepithelial neoplasia (CIN) grade 2+ lesions, and up to 90% efficacy against all CIN3+ lesions.
A long-term follow-up is, however, needed to confirm the protective efficacy against cervical carcinoma.

Results & Conclusions **Currently the incidence of CIN3+ at the age of 20–24 years is 95 per 100 000** person years in Finland. The incidence doubles in 5 to 10 years as the cohorts age.
Thus, in less than 10 years the cumulative incidence yields 80% power to demonstrate 90% vaccine efficacy against cervical CIN3+. **During the first 2 years this passive registry-based follow-up identified no CIN3+ cases in the HPV vaccine cohort, two cases in the placebo vaccine cohort, and 21 cases in the unvaccinated reference cohort suggesting that the vaccine efficacy translates into efficacy against cervical cancer.** The passive follow-up continues and new cases emerging in future will be monitored by redoing linkage with the population-based cancer register at specific time intervals in the future, which will effectively add up person years to our follow-up study.
In conclusion, valid comparisons between the vaccine and placebo recipients (excluding cross-vaccinated placebo vaccine recipients) and the reference cohort not exposed to intervention are feasible, and will be critical to define more definitively the long-term protection provided by HPV vaccination against the hard endpoints

Genetic variability in the major capsid L1 protein of human papillomavirus type 16 (HPV-16) and 18 (HPV-18)

Abstract **Infection, Genetics and Evolution**
Available online 26 June 2011.

HPV-16 and HPV-18 infections result in nearly 73% of cervical cancers worldwide. The L1 protein comprising HPV vaccine formulations elicit high-titre neutralizing antibodies. The aim of this study was to detect L1 HPV-16 and HPV-18 gene polymorphisms and analyze intratypic variations. HPV-16 (n = 29) and HPV-18 (n = 5) L1 gene sequences were obtained from cervical samples harvested from Italian women.
Phylogenetic trees were constructed using the Neighbor-Joining and the Kimura 2-parameters methods (MEGA software).
To estimate selection pressures acting on the L1 gene,
codon-specific non-synonymous (dN) and synonymous (dS) substitutions were inferred using the Nei–Gojobori method and Jukes–Cantor model (MEGA software) and integrated analyses carried out using SLAC, FEL and REL methodologies.
All the **HPV-16** L1 sequences analyzed fell into the European branch (99.4–99.7% similarity).
Thirty-four single nucleotide changes were observed and 18 (52.9%) were non-synonymous mutations (7/18 were identified in sequences encoding an immunodominant loop and one occurred in the sequence encoding the α-4 domain associated with VLP conformation).
There was no evidence of positive selection in the sequence alignment of L1 HPV-16 genes (P-value < 0.1).
One mutation was identified in a negatively selected codon.

HPV-18 L1 analyzed sequences fell into two phylogenetic branches: the HPV-18 European branch (99.5–100% similarity) and the HPV-18 African branch (99.8% similarity).
Nine single nucleotide changes were observed and 4/9 (44.5%) of these nucleotide mutations were non-synonymous and one was present in a sequence encoding the immunodominant FG loop. There was no evidence of positive selection in the sequence alignment of L1 HPV-18 genes (P-value < 0.1). This study identified polymorphisms of undefined biological activity I n HPV-16 and HPV-18 L1 sequences.

Information regarding the genetic diversity of HPV-16 and HPV-18 L1 gene sequences may help define the oncogenic potential of respective strains and to better understand immune escape mechanisms.

HPV16/18 L1 VLP vaccine induces cross-neutralizing antibodies that may mediate cross-protection

Abstract

Human papillomavirus (HPV) L1 VLP-based vaccines are protective against HPV vaccine-related types; however, the correlates of protection have not been defined.
We observed that vaccination with Cervarix™ induced cross-neutralizing antibodies for HPV types for which evidence of vaccine efficacy has been demonstrated (HPV31/45) but not for other types (HPV52/58). In addition, HPV31/45 cross-neutralizing titers showed
a significant increase with number of doses (HPV31, $p < 0.001$; HPV45, $p < 0.001$) and correlated with HPV16/18 neutralizing titers, respectively.

These findings raise the possibility that cross-neutralizing antibodies are effectors of cross-protection observed for the HPV16/18 vaccine.

Dans un couple, l'un au moins doit être fidèle, de préférence l'autre.

[Marcel Achard]

Forpath 20121117 Yves Couvreur 16/11/2012

Summary of Recommendations for Cervical-Cancer Screening.*

Variable	ACS–ASCCP–ASCP Draft 2011	ACOG 2009	USPSTF Draft 2011
Age to start	21 yr	21 yr	21 yr
Testing frequency			
Age 21 to 29 yr (Pap alone)	Every 3 yr	Every 2 yr	Every 3 yr
Age 30 yr and older			
Pap alone	Every 3 yr	Every 3 yr	Every 3 yr
Pap and HPV cotesting	Recommended but no more frequently than every 3 yr	Allowed but no more frequently than every 3 yr	Insufficient data to recommend
Age to stop	65 yr after three negative Pap tests or two negative HPV tests in past 3 years	65–70 yr after three negative tests in preceding 10 years	65 yr after adequate screening
After hysterectomy	Discontinue if no dysplasia or cancer	Discontinue if no dysplasia or cancer	Discontinue if no dysplasia or cancer
Screening after HPV vaccination	Same as when unvaccinated	Same as when unvaccinated	Not addressed

* ACOG denotes American College of Obstetricians and Gynecologists, ACS American Cancer Society, ASCCP American Society for Colposcopy and Cervical Pathology, ASCP American Society for Clinical Pathology, HPV human papillomavirus, Pap Papanicolaou, and USPSTF U.S. Preventive Services Task Force.

"*If you understood what I said, then I must have misspoken.*"

A. Greespan Chairman of the Federal Reserve (2001)

Squamous cell carcinoma of the oropharynx in Australian males induced by human papillomavirus vaccine targets

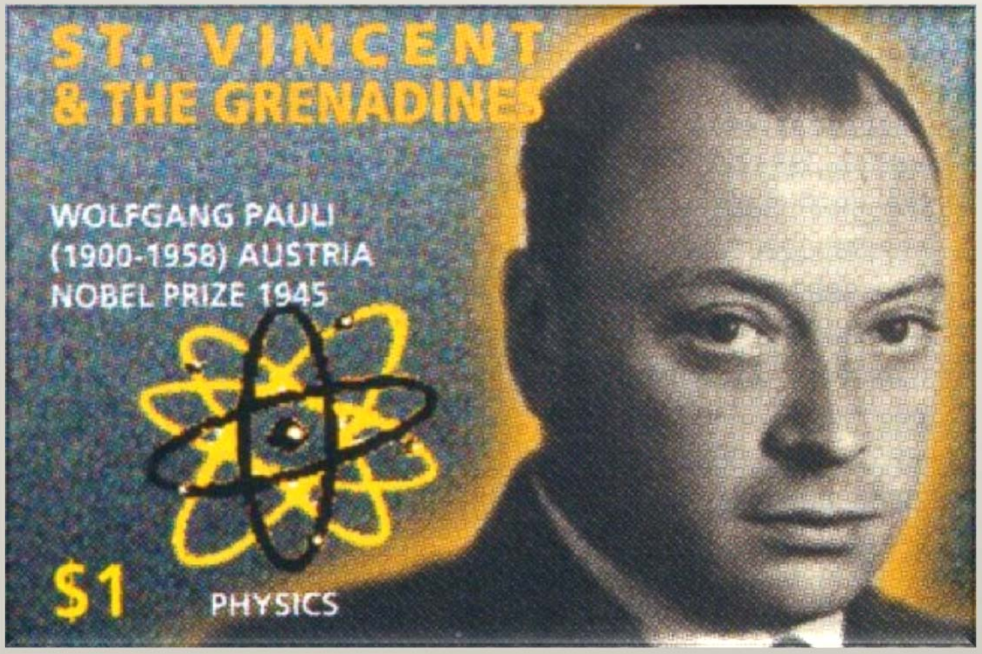
Vaccine
Volume 28, Issue 19, 26 April 2010, Pages 3269–3272

This study provides Australian data on the incidence of human papillomavirus (HPV)-related oropharyngeal cancer to aid the debate on extending the HPV vaccination programme to males.
1.56 cases of oropharyngeal cancer per 100,000 males per year were associated with HPV types targeted by the vaccine.
Vaccinating males may substantially reduce the burden of oropharyngeal cancer in Australia.

"I don't mind your thinking slowly;

I mind your publishing faster than you think."

W E Pauli



Forpath 20121117 Yves Couvreur 26/11/2012

Making Sense of the New Cervical-Cancer Screening Guidelines Sarah Feldman, M.D., M.P.H.

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Over the past 60 years, U.S. mortality from cervical cancer has dropped by 70%, thanks to a successful screening program. In 1995, the American College of Obstetricians and Gynecologists (ACOG) recommended screening with the Papanicolaou (Pap) smear and pelvic examination at the initiation of sexual activity or by 18 years of age and annually thereafter. Although not evidence-based, this guideline was easy to remember, timed to coincide with the onset of legal adulthood, and well received by patients and clinicians. Linking the Pap smear to an annual visit, and often to the provision of other health care services such as contraception, breast care, and blood-pressure checks, made the patient likely to comply and the physician likely to remember to offer the test as part of routine care. **Furthermore, although the Pap smear's sensitivity is poor — roughly 50 to 60%** — the frequency of repetition made it likely that in screened patients, an abnormality missed one year would be found the next. Hence, the system worked.

Cervical cancer is rare before 20 years of age, and the incidence doesn't start to rise significantly until women reach the age of 25 or 30. Most cancers detected in screened women tend to be early-stage, so those found through screening are largely curable. For many women with early-stage disease, less-radical, fertility-sparing procedures can be curative, so even if early-stage cancers are detected, morbidity and mortality may be minimal.

Therefore, in 2009, the ACOG recommended that screening for "**average-risk" women begin at the age of 21**. Although the expert groups all agree that cervical cancer is rare before that age, they define high-risk younger groups somewhat differently; the ACOG defines average-risk women as **immunocompetent** women.

Studies consistently show that for previously well-screened healthy women 30 years of age or older, the interval between Pap screenings can be lengthened **to 3 years** without significantly increasing their risk of cancer. It's also known that when screening takes place only every 5 years, or when women with abnormal Pap tests are not correctly triaged and treated to prevent cervical dysplasia from progressing to cancer, cancer rates increase. **For women between 20 and 30 years of age, the optimal frequency is less well studied, but given the poor sensitivity of any single Pap test, the goal is to obtain at least two consecutive normal Pap results during this period to ensure that there are no missed opportunities for detecting and treating a precancerous lesion before lengthening the interval.**

The USPSTF, ACOG, and ASCCP–ACS–ASCP vary dramatically on whether evidence supports HPV cotesting for women 30 years of age or older. The USPSTF argues that Pap testing every 3 years for women over 30 is both safe and more cost-effective than cotesting and that no data support cotesting at the current screening intervals. It seems reasonable to use Pap testing alone every 3 years in this age group, unless the clinician seeks reassurance about lengthening the interval for a particular woman — for instance, if she has an uncertain Pap history or impaired immune status or may have difficulty complying with returning in 3 years. In such cases, HPV testing could be added or the Pap-testing interval shortened.

In patients who have been treated for high-grade dysplasia, the risk of cervical cancer is increased by a factor of two to three for at least 20 years, but the risk of dying from cervical cancer is low, since most cancers are diagnosed at an early stage. Because it has long been the standard of care to screen these patients annually, we don't have good prospective data on whether this more frequent testing has contributed to early cancer diagnoses. Given that mortality rates have remained low with current practices, however, all groups recommend screening this population for at least 20 years after treatment.

Increasing screening in previously unscreened populations will further reduce the incidence of cervical cancer and related mortality. **Reaching out to patients who face cultural, language, or educational barriers to care is important.** Creating systems to remind clinicians that patients who come for episodic care must have appropriate cancer-screening tests is essential. Finally, making the guidelines for managing abnormalities easier for patients and clinicians to follow is important for both optimizing outcomes and containing costs for unnecessary referrals and treatment.