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Human Papillomaviruses (HPV)



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Bibl Haematol. 1975 Oct;(43):569-71.

Human papilloma viruses and cancer.

zur Hausen H, Gissmann L, Steiner W, Dippold W, Dreger I.

PMID: 183728 [PubMed - indexed for MEDLINE]

[MeSH Terms, Substances](#)

[LinkOut - more resources](#)



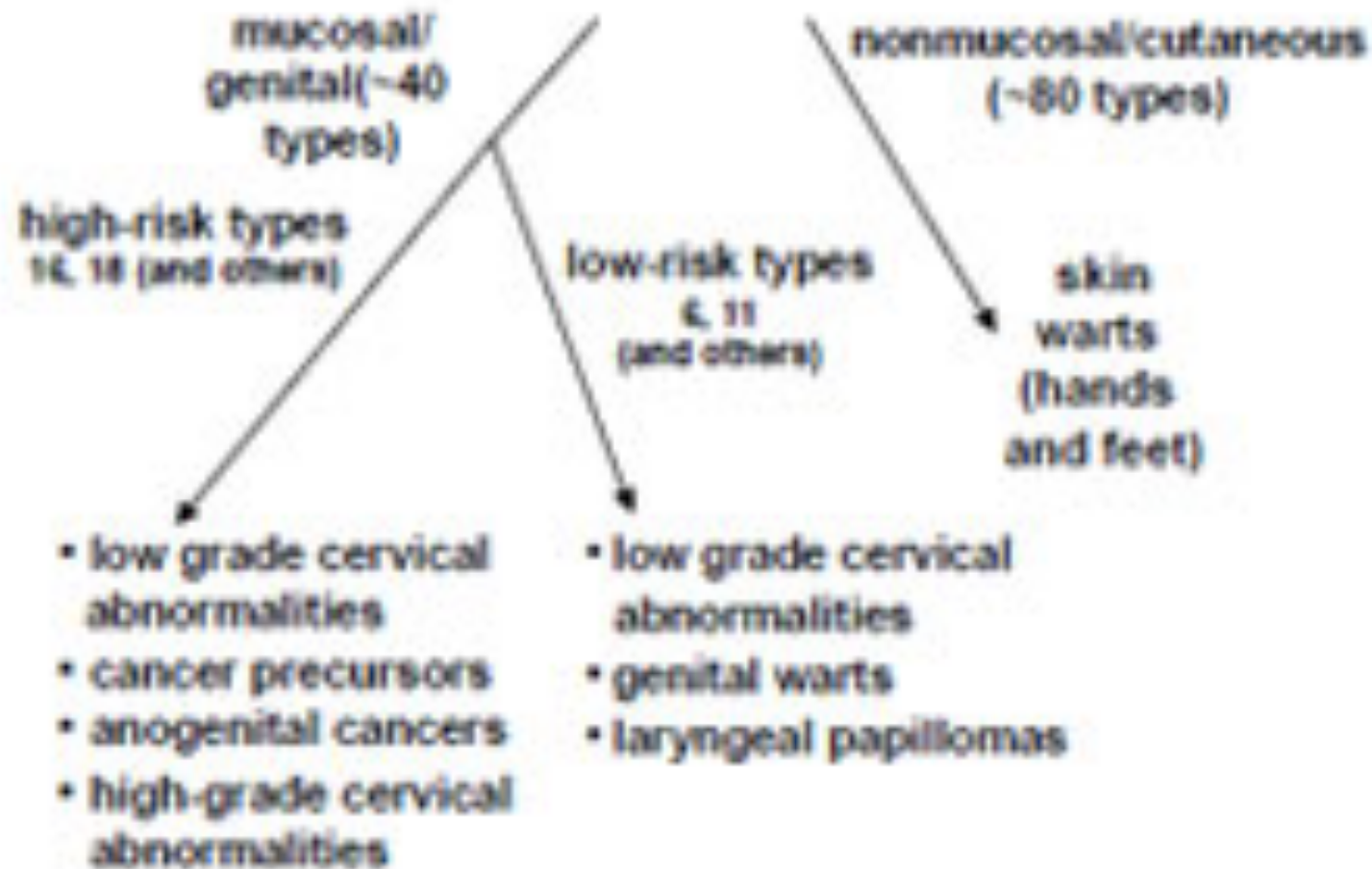
Human Papilloma Virus

- Small DNA virus
- More than 120 types identified based on the genetic sequence of the outer capsid protein L1
- About **40 types** infect the mucosal epithelium



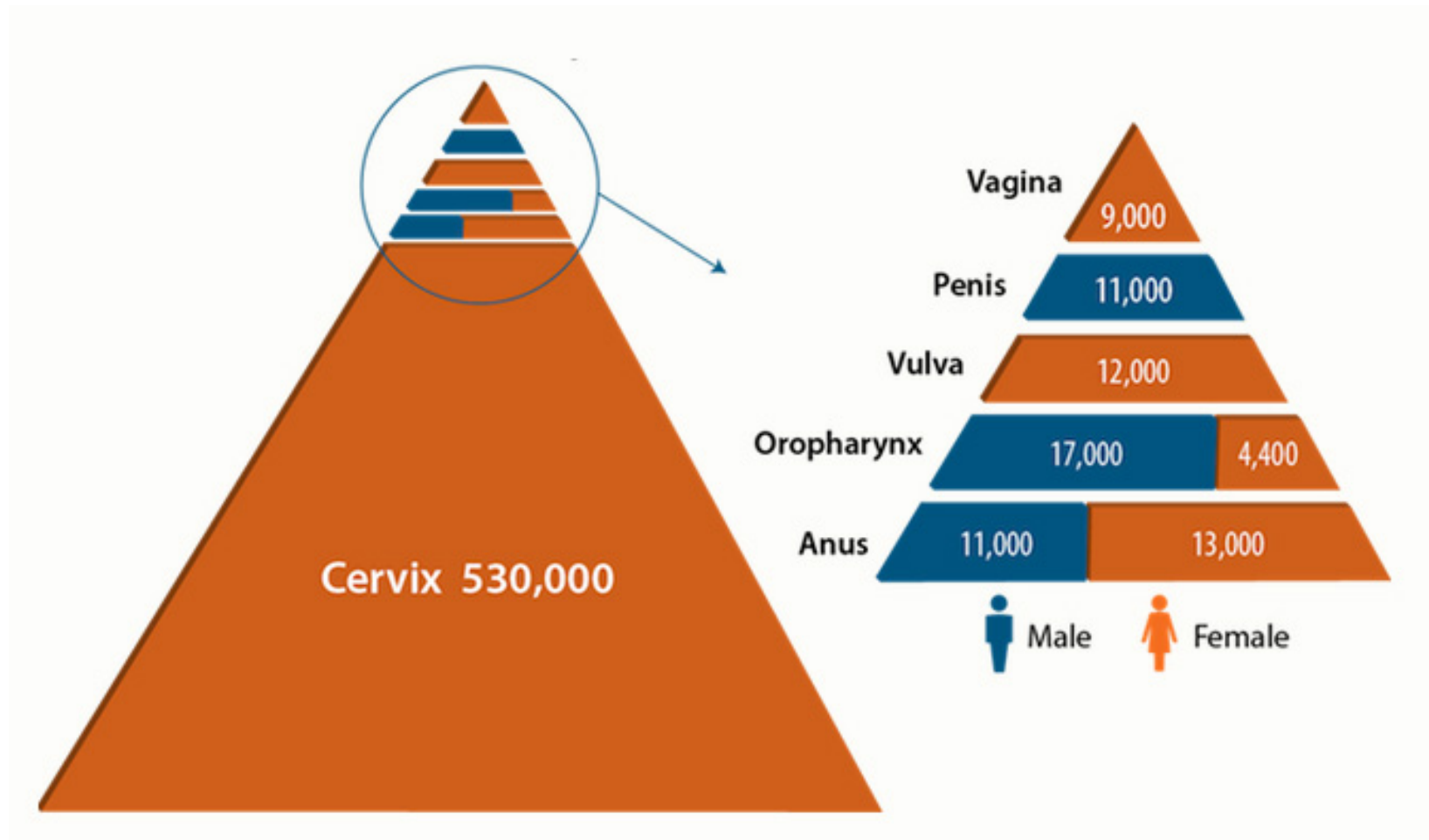


Human Papillomavirus Types and Disease Association



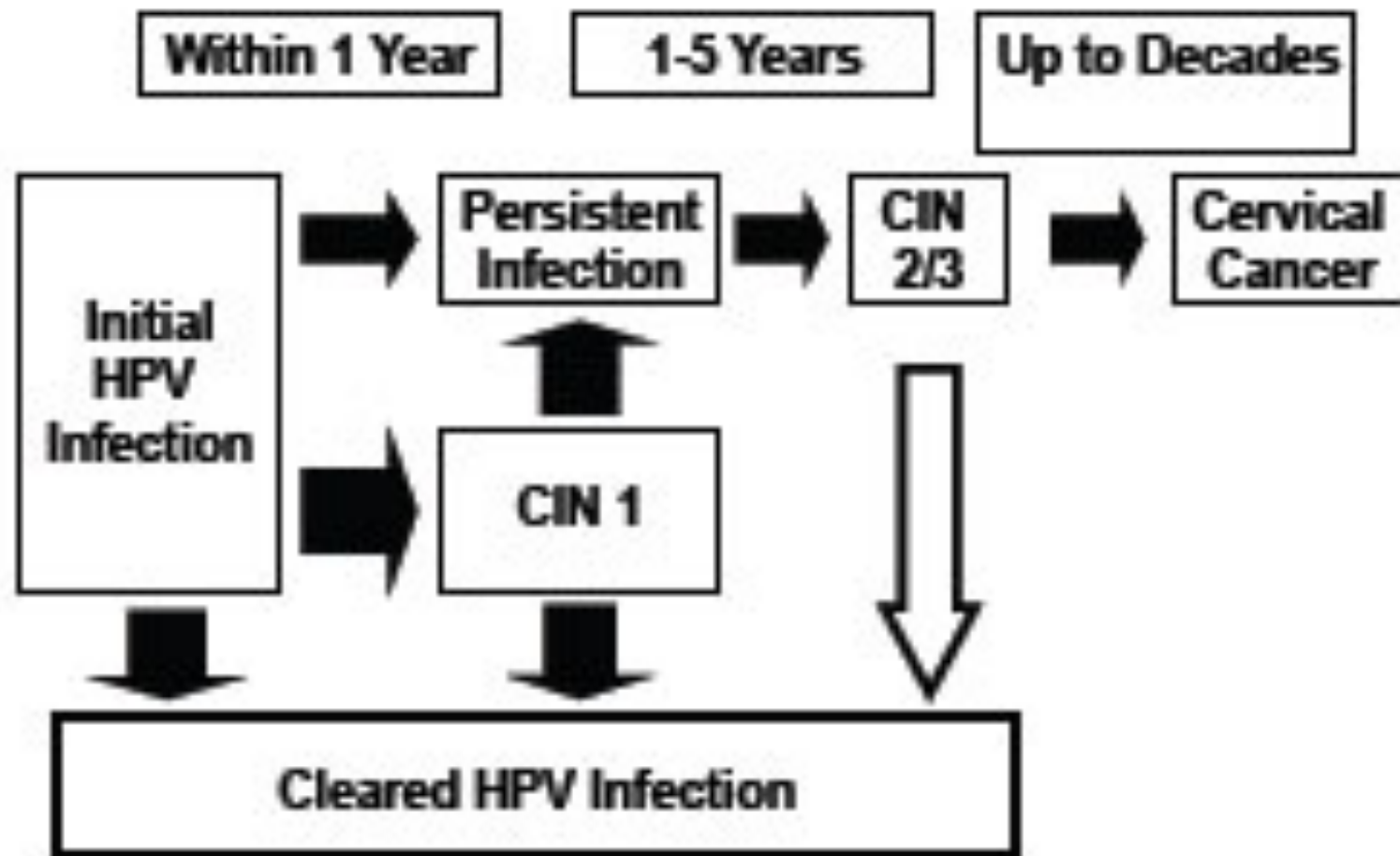


HPV-related cancers





Natural History of HPV Infection





Format: Abstract ▾

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J Infect Dis. 2016 May 1;213(9):1444-54. doi: 10.1093/infdis/jiv753. Epub 2015 Dec 21.

Natural Acquired Immunity Against Subsequent Genital Human Papillomavirus Infection: A Systematic Review and Meta-analysis.

Beachler DC¹, Jenkins G¹, Safaeian M¹, Kreimer AR¹, Wentzensen N¹.

⊕ Author information

Abstract

BACKGROUND: Studies have been mixed on whether naturally acquired human papillomavirus (HPV) antibodies may protect against subsequent HPV infection. We performed a systematic review and meta-analysis to assess whether naturally acquired HPV antibodies protect against subsequent genital HPV infection (ie, natural immunity).

METHODS: We searched the MEDLINE and EMBASE databases for studies examining natural HPV immunity against subsequent genital type-specific HPV infection in female and male subjects. We used random-effects models to derive pooled relative risk (RR) estimates for each HPV type.

RESULTS: We identified 14 eligible studies that included >24,000 individuals from 18 countries that examined HPV natural immunity. We observed significant protection against subsequent infection in female subjects with HPV-16 (pooled RR, 0.65; 95% confidence interval, .50-.80) and HPV-18 (0.70; .43-.98) but not in male subjects (HPV-16: 1.22; .67-1.77 [P= .05 (test for heterogeneity)]; HPV-18: 1.50; .46-2.55; [P= .15]). We also observed type-specific protection against subsequent infection for a combined measure of HPV-6/11/31/33/35/45/52/58 in female subjects (pooled RR, 0.75; 95% confidence interval, .57-.92). Natural immunity was also evident in female subjects when analyses were restricted to studies that used neutralizing assays, used HPV persistence as an outcome, or reported adjusted analyses (each P< .05).

CONCLUSIONS: HPV antibodies acquired through natural infection provide modest protection against subsequent cervical HPV infection in female subjects.

Published by Oxford University Press for the Infectious Diseases Society of America 2015. This work is written by (a) US Government employee(s) and is in the public domain in the US.



HPV Clinical Features

- Most HPV infections are asymptomatic and result in no clinical disease
- Clinical manifestations of HPV infection include:
 - anogenital warts
 - recurrent respiratory papillomatosis
 - cervical cancer precursors (cervical intraepithelial neoplasia)
 - cancer (cervical, anal, vaginal, vulvar, penile, and oropharyngeal cancer)



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HPV- anogenital warts





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HPV- respiratory papillomatosis





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HPV- respiratory papillomatosis



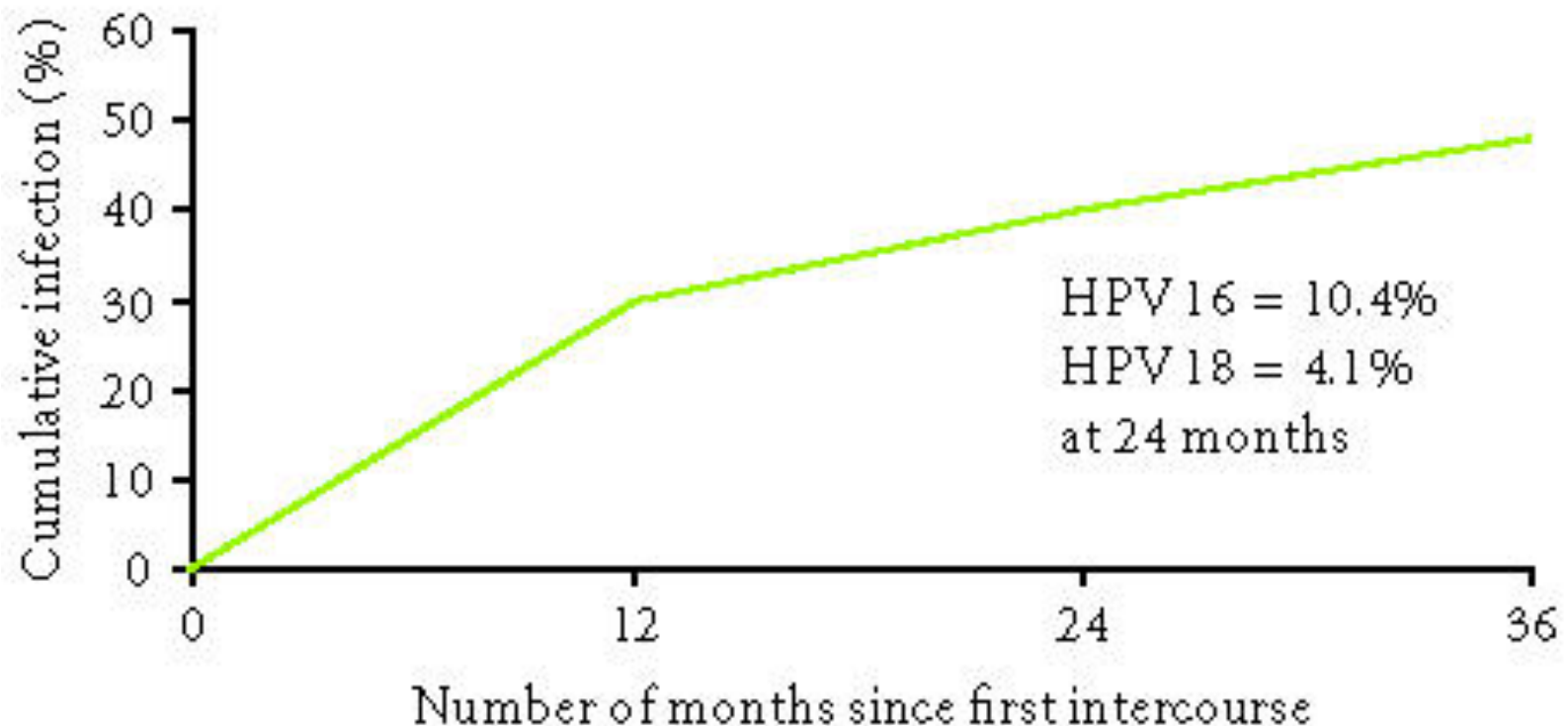


HPV Epidemiology

- Reservoir
 - Human
- Transmission
 - Direct contact, usually sexual
- Temporal pattern
 - None
- Communicability
 - Presumed to be high

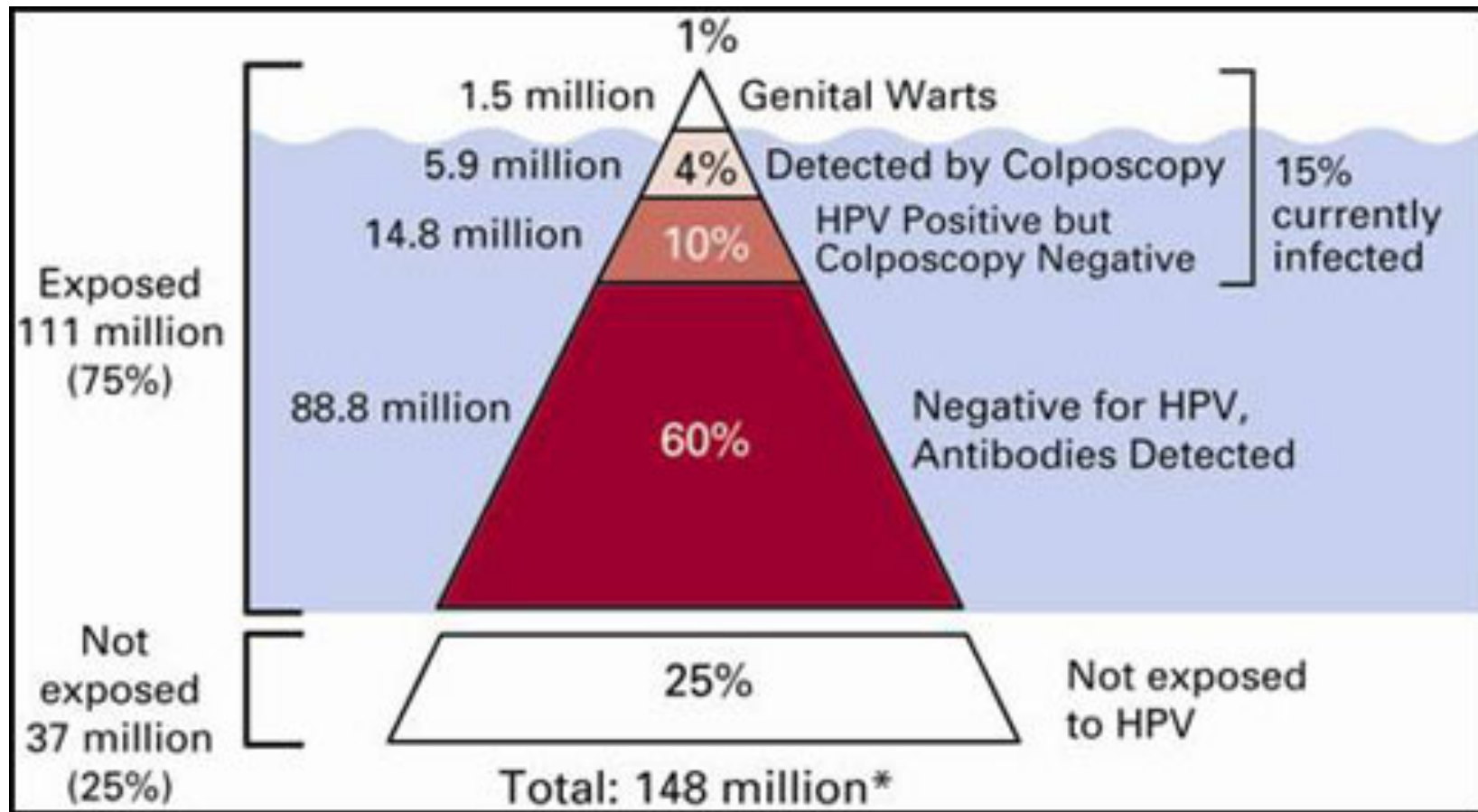


Cumulative rate of HPV infection among college-aged women who were virgins at baseline.





Hierarchy of Clinically-apparent & Sub clinical Human Papillomavirus Infections



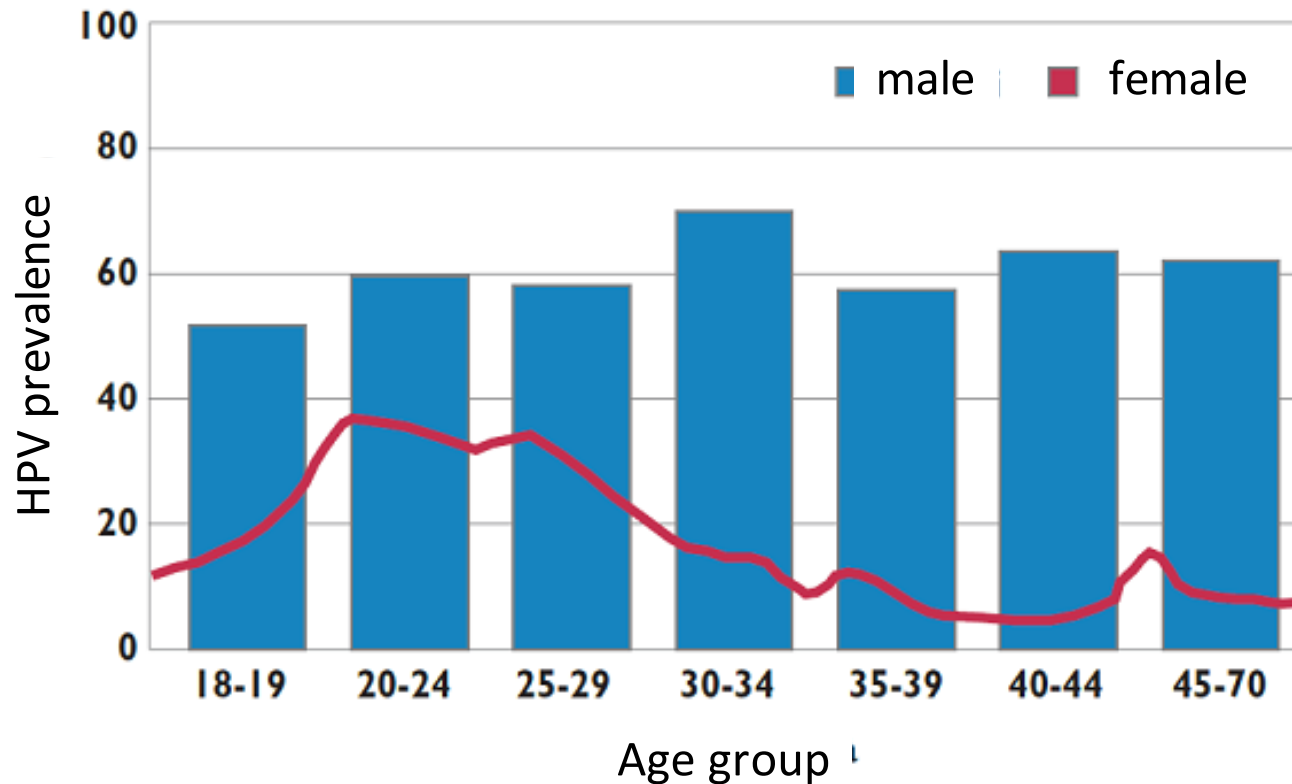


Determinants of HPV infection

- Risk factors
 - mixing sex with alcohol
 - black partner
 - >3 lifetime sex partners
 - being single
 - illegal drug use
- Protective factors
 - Having a current sex partner
 - receptive oral sex



Prevalence of HPV infection, per age classe and gender



Audisio RA, et al. La vaccinazione anti-HPV universale. Valore sanitario, sociale ed economico a supporto delle decisioni di Sanità Pubblica. Il SOLE 24 ore Sanità. Dic 2014.



HPV among male

- **HPV DNA** has been detected

- **External genitals**
- **Urethra**
- **Deferent duct**
- **Epididymis**
- **Seminal fluid**

- Among males it is higher the proportion of healthy carriers

TABLE 1. HPV DNA results by genital site for 50 men

| No. of men | Genital site examined by: | | |
|------------|---------------------------|----|-----------------|
| | PB | UB | SE |
| 6 | + | + | + |
| 5 | + | + | - |
| 3 | + | - | + |
| 3 | + | + | ND ^a |
| 3 | ND | + | + |
| 11 | + | - | - |
| 1 | - | + | - |
| 2 | + | ND | - |
| 2 | + | - | ND |
| 14 | - | - | - |

^a ND, not determined due to a negative β -globin result.



HPV burden of diseases

HPV are responsible of:

- 100% of cervical cancer
- 88% of anal cancer
- 70% of vaginal cancer
- 50% penis cancer
- 43% vulvar cancer
- 72% oral and head cancer
- Around all genital warts

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Case–Control Study of Human Papillomavirus and Oropharyngeal Cancer

Gypsyamber D'Souza, Ph.D., Aimee R. Kreimer, Ph.D., Raphael Viscidi, M.D., Michael Pawlita, M.D., Carole Fakhry, M.D., M.P.H., Wayne M. Koch, M.D., William H. Westra, M.D., and Maura L. Gillison, M.D., Ph.D.

ABSTRACT

BACKGROUND

Substantial molecular evidence suggests a role for human papillomavirus (HPV) in the pathogenesis of oropharyngeal squamous-cell carcinoma, but epidemiologic data have been inconsistent.



HPV genotypes involved in 7 HPV related cancers

16/18 (2/4-HPV)

6/11 (4-HPV)

31/33/45/52/58 (9-HPV)

| Position | cervical cancer | vulvar cancer | vaginal cancer | penis cancer | anus cancer | oral cancer |
|----------|-----------------|---------------|----------------|--------------|-------------|-------------|
| 1 | 16 | 16 | 16 | 16 | 16 | 16 |
| 2 | 18 | 18 | 40 | 18 | 18 | 33 |
| 3 | 33 | 33 | 6-11 | 6-11 | 33 | 35 |
| 4 | 45 | 6-11 | 31 | 22 | 31 | 18 |
| 5 | 31 | 45 | 33 | 74 | 6-11 | 26 |
| 6 | 58 | 52 | 18 | 31 | 45 | 45 |
| 7 | 52 | 51 | 58 | 45 | | 52 |

de Sanjosè et al. 2012, Gardasil 9 – RCP 27/01/2017. Azzari et al. Rivista di Immunologia e Allergologia Pediatrica vol. 3 2016. Gardasil – RCP 04/2017. Cervarix – RCP 18/08/2016.



HPV Disease Burden in the United States

- Anogenital HPV is the most common sexually transmitted infection in the US
 - estimated 79 million infected
 - 14 million new infections/year
- Common among adolescents and young adults



Cervical Cancer Screening USA

- Revised in 2012
- Screening should begin at age 21 years
- Screen women 21 to 65 years of age with Pap test every 3 years
- Co-testing (Pap and HPV testing) every 5 years in women 30 to 65 years of age



Key statistics on Europe and its regions

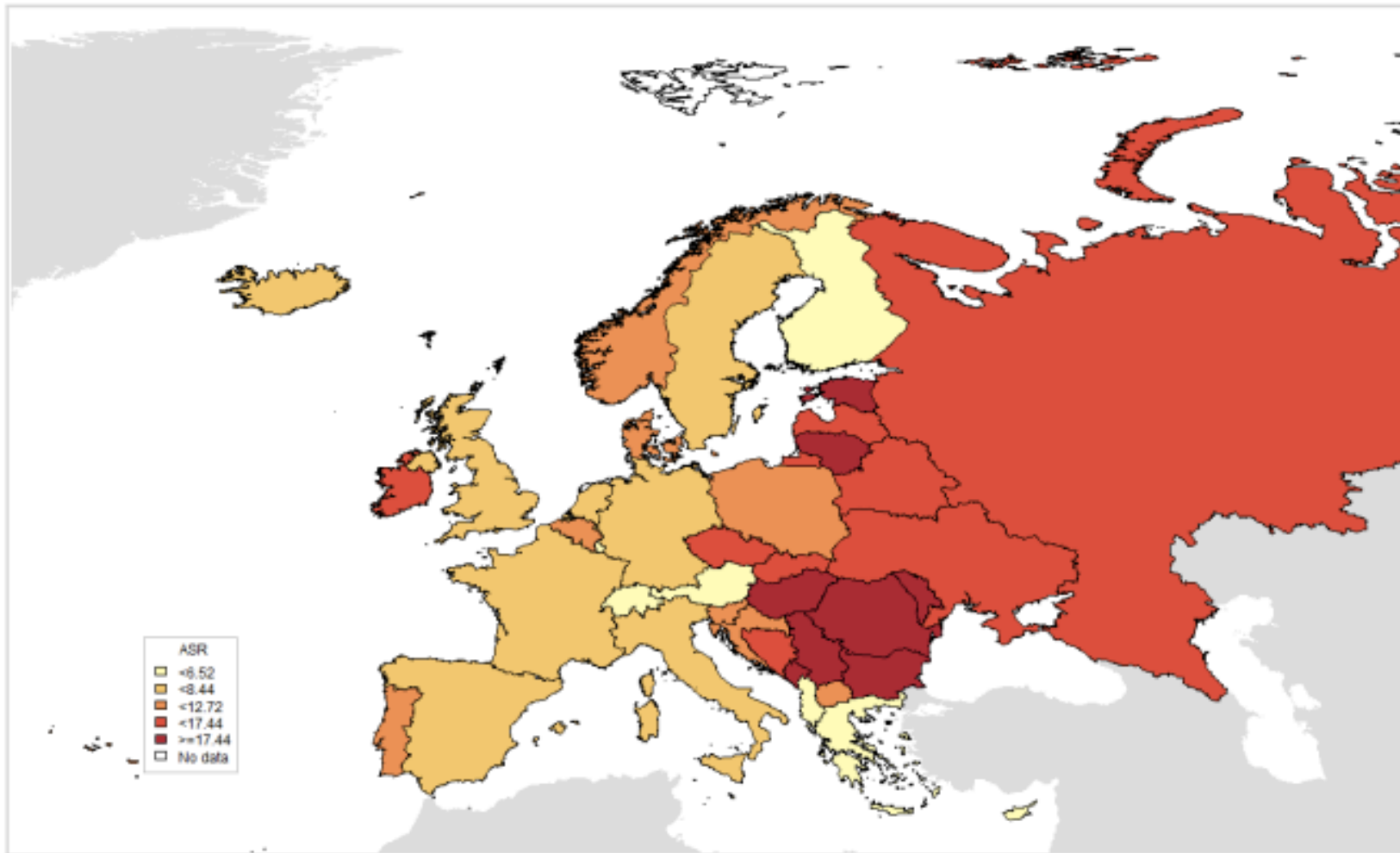
| | Europe | Eastern Europe | Northern Europe | Southern Europe | Western Europe |
|--|--------|----------------|-----------------|-----------------|----------------|
| Population | | | | | |
| Women at risk for cervical cancer (Female population aged ≥ 15 yrs) in millions | 325.7 | 132.4 | 43.1 | 67.3 | 82.8 |
| Burden of cervical cancer | | | | | |
| Annual number of new cervical cancer cases | 58,373 | 33,882 | 5,382 | 9,285 | 9,824 |
| Standardised incidence rates per 100,000 population | 11.4 | 16.3 | 8.7 | 8.5 | 7.3 |
| Annual number of cervical cancer deaths | 24,404 | 15,436 | 1,963 | 3,526 | 3,479 |
| Standardised mortality rates per 100,000 population | 3.8 | 6.2 | 2.2 | 2.4 | 1.8 |
| Burden of cervical HPV infection | | | | | |
| Prevalence (%) of HPV 16 and/or HPV 18 among women with: | | | | | |
| Normal cytology | 3.8 | 9.7 | 4.2 | 3.8 | 2.6 |
| Low-grade cervical lesions (LSIL/CIN-1) | 26.9 | 31.6 | 30.6 | 25.5 | 25.1 |
| High-grade cervical lesions (HSIL/ CIN-2 / CIN-3 / CIS) | 54.1 | 59.3 | 55.4 | 51.1 | 58.3 |
| Cervical cancer | 73.4 | 84.8 | 76.6 | 67.8 | 78.3 |



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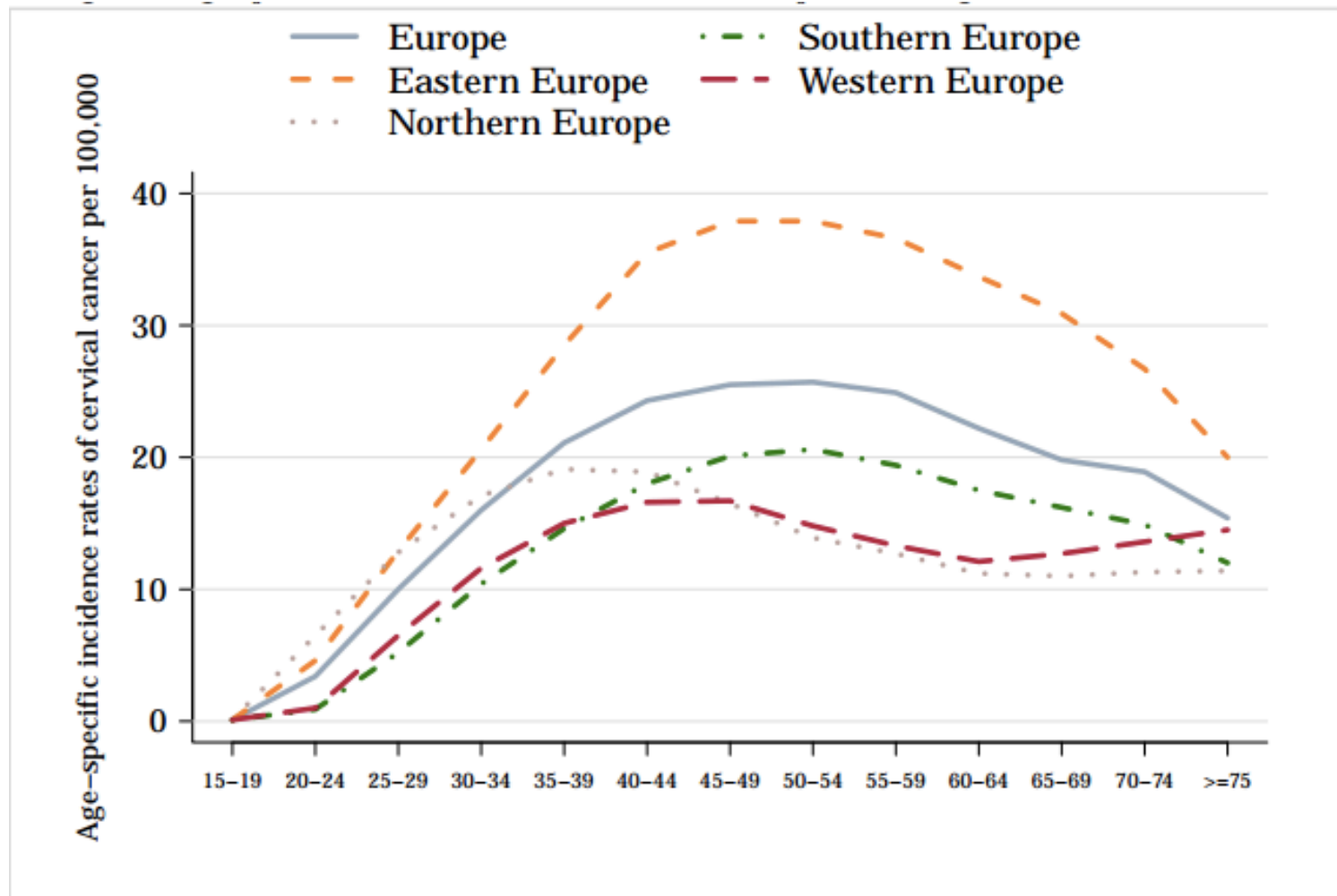
Age-standardised incidence rates of cervical cancer in Europe (estimates for 2012)



<http://www.hpvcentre.net/statistics/reports/XEX.pdf>



Age-specific incidence of cervical cancer in Europe and its regions (estimates for 2012)





Human Papillomavirus Vaccine

- HPV L1 major capsid protein of the virus is antigen used for immunization
- L1 protein produced using recombinant technology
- L1 proteins self-assemble into virus-like particles (VLP)
- VLP are noninfectious and nononcogenic



HPV Vaccines

HPV4 (Gardasil, Merck)

- approved for females and males from 9 through 45 years of age
- contains types 16 and 18 (high risk) and types 6 and 11 (low risk)
- **a 9-valent vaccine licensed in December 2014**

HPV2 (Cervarix, GlaxoSmithKline)

- approved for females 10 through 25 years of age
- contains types 16 and 18 (high risk)



HPV Vaccine Efficacy

- High efficacy among females without evidence of infection with vaccine HPV types
- No evidence of efficacy against disease caused by vaccine types with which participants were infected at the time of vaccination
- **Prior infection with one HPV type did not diminish efficacy of the vaccine against other vaccine HPV types**



HPV Vaccination Recommendations

- ACIP recommends routine vaccination at age **11 or 12 years** with HPV4 or HPV2 for females and HPV 4 for males
- The vaccination series can be started as young as 9 years of age
- Vaccination also recommended for females 13 through 26 years of age



HPV Vaccination Recommendations

Males

- Vaccination also recommended for **males 13 through 21 years of age**
- All immunocompromised males (including HIV infection) and MSM through 26 years of age should be vaccinated
- Males aged 22 through 26 years may be vaccinated



HPV2 schedule

| Age | schedule | interval |
|------------|----------|-------------------|
| 9-14 years | 2 doses | 5-13 months |
| >14 years | 3 doses | 0, 1, 6 months |



HPV4 schedule

| Age | schedule | interval |
|------------|----------|----------------|
| 9-13 years | 2 doses | 6 months |
| >13 years | 3 doses | 0, 2, 6 months |



HPV schedule

- an accelerated schedule using minimum intervals is not recommended
- **Series does not need to be restarted if the schedule is interrupted**
- Prevacination assessments not recommended
- No therapeutic effect on HPV infection, genital warts, cervical lesions



HPV Vaccine Contraindication and Precautions

- **Contraindication**
 - severe allergic reaction to a vaccine component or following a prior dose
- **Precaution**
 - moderate or severe acute illnesses (defer until symptoms improve)



HPV Vaccination During Pregnancy

- Initiation of the vaccine series should be delayed until after completion of pregnancy
- If a woman is found to be pregnant after initiating the vaccination series, remaining doses should be delayed until after the pregnancy
- If a vaccine dose has been administered during pregnancy, there is no indication for intervention
- Women vaccinated during pregnancy should be reported to the respective manufacturer

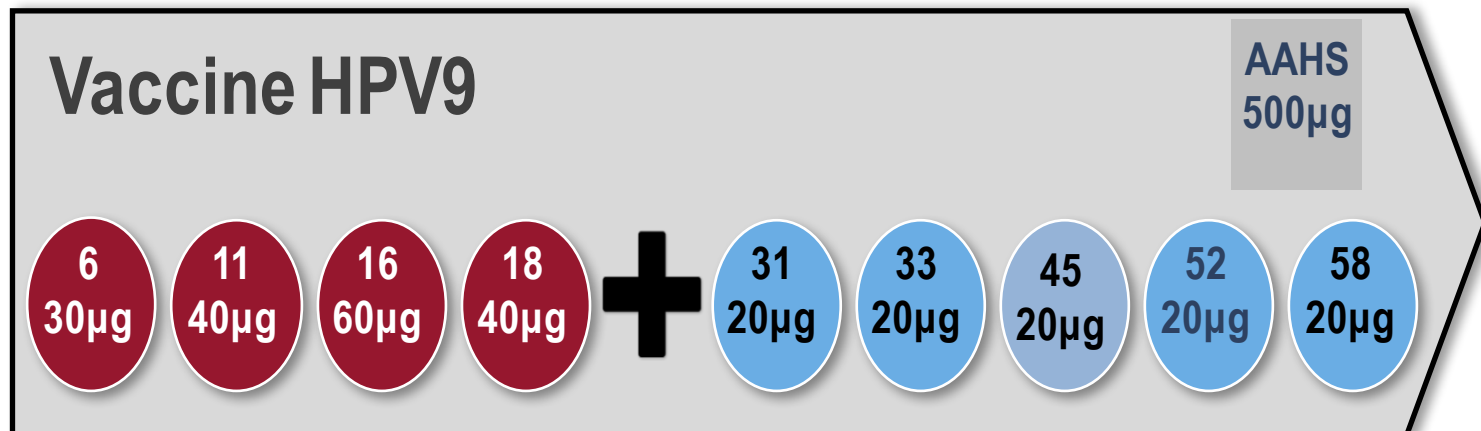
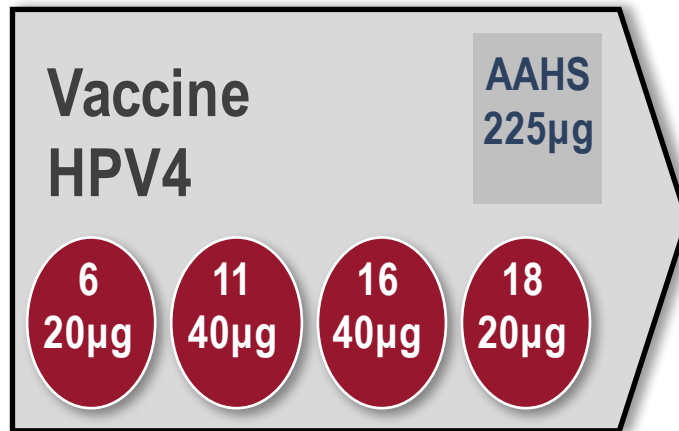


HPV Vaccine Adverse Reactions

- Local reactions (pain, redness, swelling)
 - 20%-90%
- Fever (37.8°C)
 - 10%-13%*
- No serious adverse reactions associated with either vaccine



The new HPV9 vaccine



AAHS =Amorphous aluminum hydroxyphosphate sulfate,
adiuvante



HPV9 schedule

| Age classe | I dose | II dose | III dose |
|------------|--------|-------------|----------|
| 9-14 years | 0 | 6-12 months | NA |
| >14 years | 0 | 2-months | 6 months |



HPV9 efficacy data: female

| Disease Endpoints | GARDASIL | | AAHS Control | | % Efficacy (95% CI) |
|---|----------|-----------------|--------------|-----------------|---------------------|
| | N | Number of cases | N | Number of cases | |
| 16- through 26-Year-Old Girls and Women† | | | | | |
| HPV 16- or 18-related CIN 2/3 or AIS | 8493 | 2 | 8464 | 112 | 98.2 (93.5, 99.8) |
| HPV 16- or 18-related VIN 2/3 | 7772 | 0 | 7744 | 10 | 100.0 (55.5, 100.0) |
| HPV 16- or 18-related VaIN 2/3 | 7772 | 0 | 7744 | 9 | 100.0 (49.5, 100.0) |
| HPV 6-, 11-, 16-, or 18-related CIN (CIN 1, CIN 2/3) or AIS | 7864 | 9 | 7865 | 225 | 96.0 (92.3, 98.2) |
| HPV 6-, 11-, 16-, or 18-related Genital Warts | 7900 | 2 | 7902 | 193 | 99.0 (96.2, 99.9) |
| HPV 6- and 11-related Genital Warts | 6932 | 2 | 6856 | 189 | 99.0 (96.2, 99.9) |

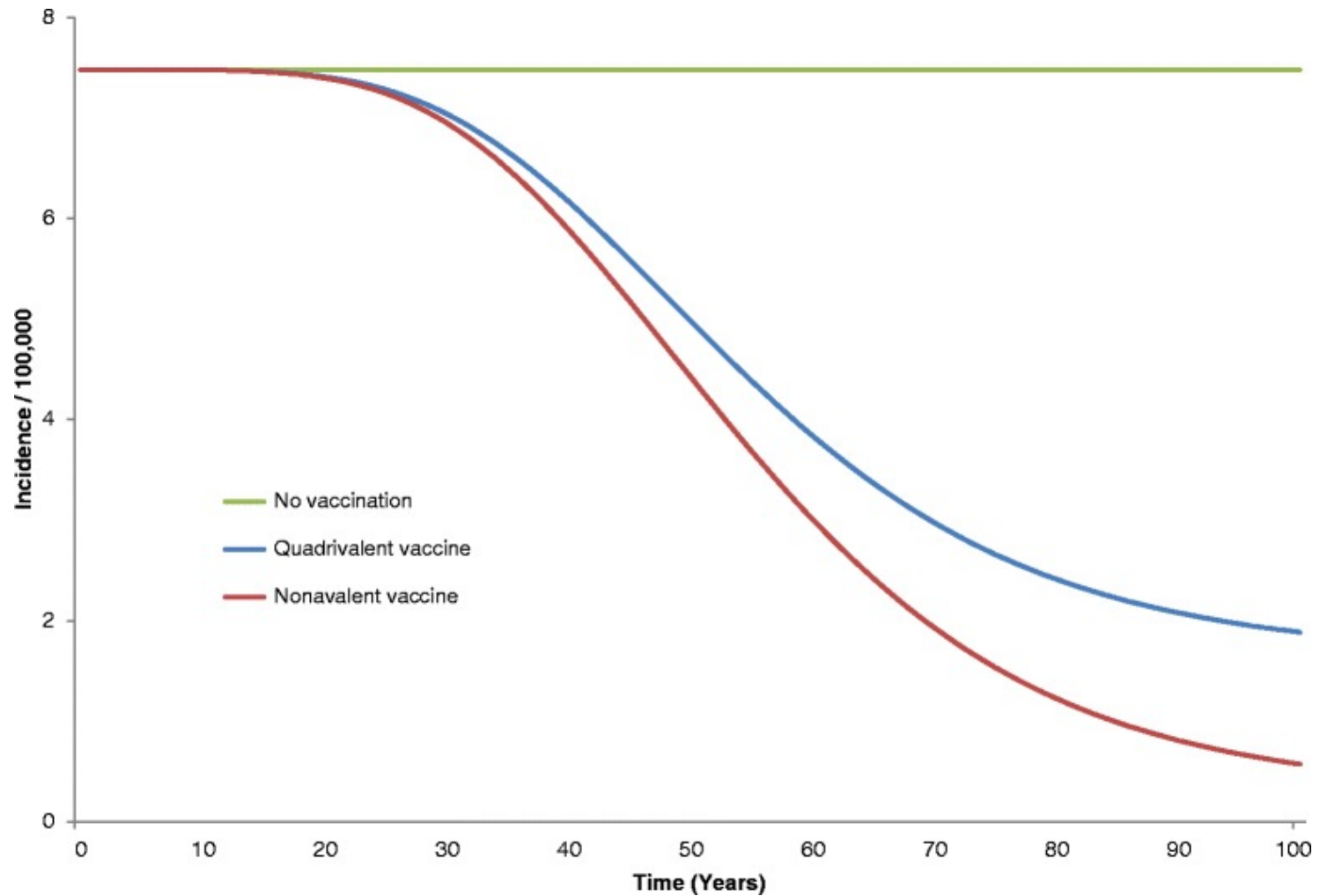


HPV9 efficacy data: male

| 16- through 26-Year-Old Boys and Men | | | | | |
|---|------|---|------|----|----------------------|
| External Genital Lesions HPV 6-, 11-, 16-, or 18-related | | | | | |
| External Genital Lesions | 1394 | 3 | 1404 | 32 | 90.6 (70.1, 98.2) |
| Condyloma | 1394 | 3 | 1404 | 28 | 89.3 (65.3, 97.9) |
| PIN 1/2/3 | 1394 | 0 | 1404 | 4 | 100.0 (-52.1, 100.0) |
| HPV 6-, 11-, 16-, or 18-related Endpoint | | | | | |
| AIN 1/2/3 | 194 | 5 | 208 | 24 | 77.5 (39.6, 93.3) |
| AIN 2/3 | 194 | 3 | 208 | 13 | 74.9 (8.8, 95.4) |
| AIN 1 | 194 | 4 | 208 | 16 | 73.0 (16.3, 93.4) |
| Condyloma Acuminatum | 194 | 0 | 208 | 6 | 100.0 (8.2, 100.0) |
| Non-acuminate | 194 | 4 | 208 | 11 | 60.4 (-33.5, 90.8) |



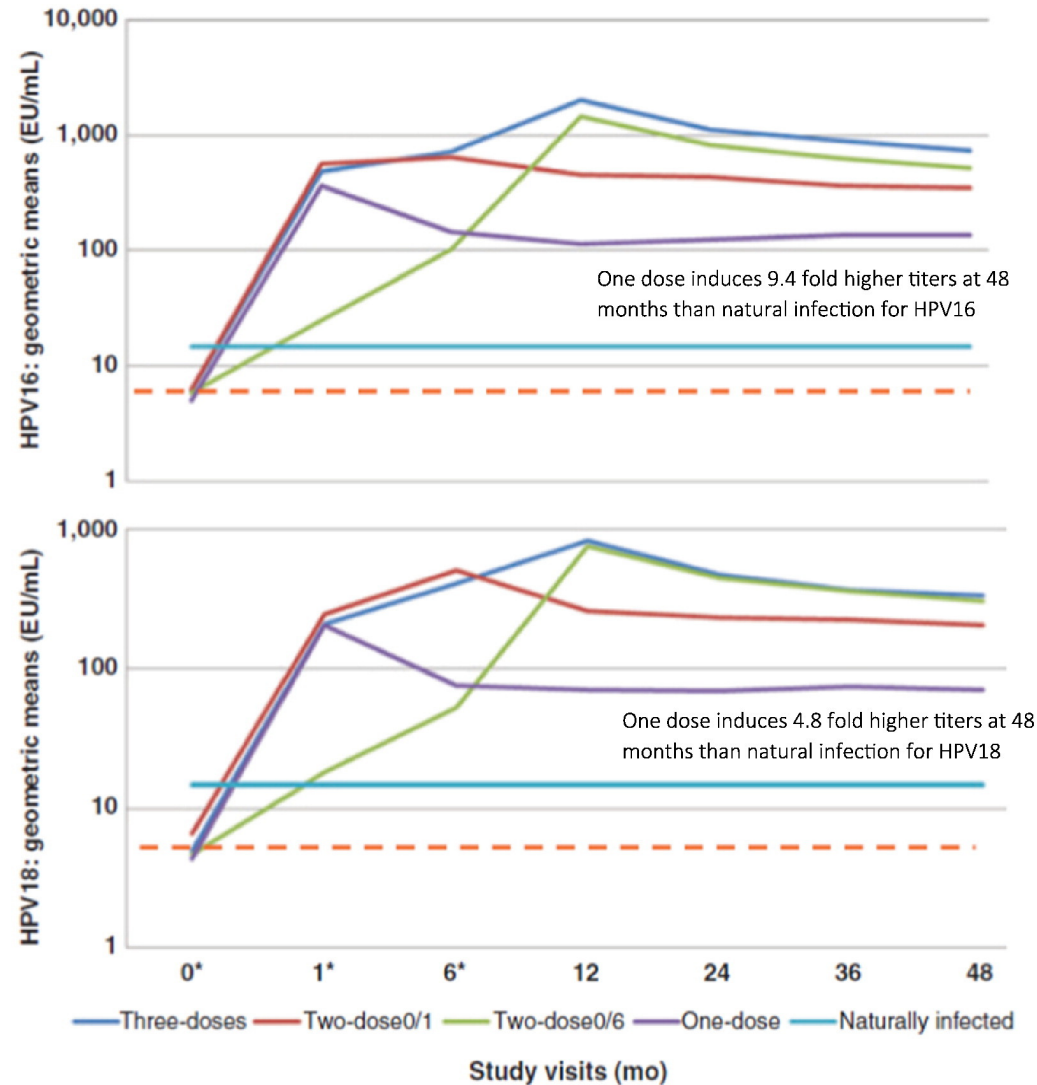
Mathematical model of HPV9 vaccine impact



Boiron L, Joura E, Largeron N, Prager B, Uhart M. Estimating the cost-effectiveness profile of a universal vaccination programme with a nine-valent HPV vaccine in Austria. *BMC Infectious Diseases* (2016) 16:153



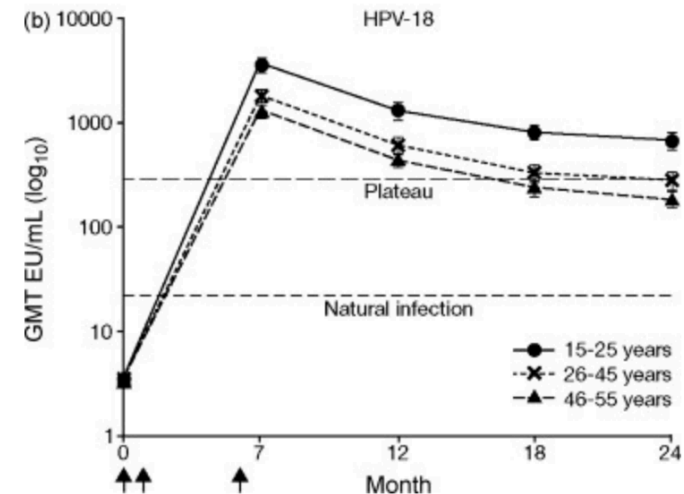
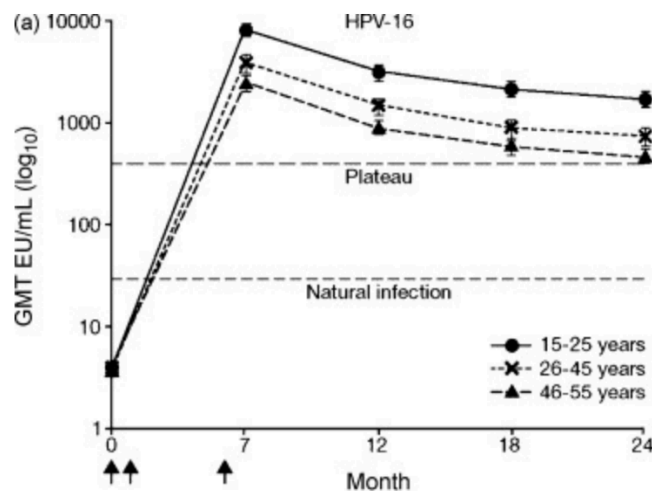
Immunogenicity of vaccination vs natural infection



Harper D, De Mars L. Durable Antibody Responses Following One Dose of the Bivalent Human Papillomavirus L1 Virus-Like Particle Vaccine in the Costa Rica Vaccine Trial. *Gynecologic Oncology*, 2017



Immunogenicity and safety of an HPV-16/18 vaccine in women aged 26–55 years and compared with women aged 15–25 years





Immunogenicity among male: HPV4 vs HPV0

Table 3

Summary of month 7 GMTs in the 9vHPV vaccine and qHPV vaccine groups; HPV-specific per-protocol immunogenicity set.

| Assay | 9vHPV vaccine N = 249 | | | qHPV vaccine N = 251 | | | Estimated GMT ratio 9vHPV/qHPV (95% CI) |
|--------------------|-----------------------|--------------|----------------|----------------------|---------------------------|---------------------|---|
| | n | GMT (mMU/mL) | 95% CI | n | GMT (mMU/mL) ^a | 95% CI ^a | |
| <i>Anti-HPV 6</i> | | | | | | | |
| All | 228 | 758.3 | 665.9; 863.4 | 226 | 618.4 | 554.0; 690.3 | 1.23 (1.04; 1.45) ^b |
| 16-17 y | 36 | 1284.5 | 1009.0; 1635.2 | 36 | 1012.7 | 794.0; 1291.5 | |
| 18-26 y | 192 | 686.9 | 594.8; 793.2 | 190 | 563.2 | 500.2; 634.2 | |
| <i>Anti-HPV 11</i> | | | | | | | |
| All | 228 | 681.7 | 608.9; 763.4 | 226 | 769.1 | 683.5; 865.3 | 0.89 (0.76; 1.04) ^b |
| 16-17 y | 36 | 1138.6 | 889.4; 1457.5 | 36 | 1119.3 | 859.7; 1457.2 | |
| 18-26 y | 192 | 619.2 | 548.1; 699.7 | 190 | 716.3 | 629.3; 815.3 | |
| <i>Anti-HPV 16</i> | | | | | | | |
| All | 234 | 3924.1 | 3513.8; 4382.3 | 237 | 3787.9 | 3378.4; 4241.0 | 1.04 (0.89; 1.21) ^b |
| 16-17 y | 36 | 5868.0 | 4486.1; 7675.6 | 37 | 6045.7 | 4445.0; 8221.9 | |
| 18-26 y | 198 | 3647.2 | 3237.5; 4108.7 | 200 | 3474.0 | 3079.9; 3911.6 | |
| <i>Anti-HPV 18</i> | | | | | | | |
| All | 234 | 884.3 | 766.4; 1020.4 | 236 | 790.9 | 683.0; 915.7 | 1.12 (0.91; 1.37) ^b |
| 16-17 y | 36 | 1390.4 | 989.6; 1953.6 | 36 | 1346.2 | 951.1; 1905.4 | |
| 18-26 y | 198 | 814.5 | 696.9; 951.8 | 200 | 718.7 | 613.1; 842.3 | |

CI, confidence interval; GMT, geometric mean titres; mMU, milli-Merck units; N, number of randomised participants in the respective vaccination group; n, number of participants contributing to the analysis; y, years.

^a The estimated GMT ratio and associated CI are based on an analysis of variance (ANOVA) model including group and age strata as independent variables.

^b Non-inferiority was achieved if the lower bound of the 2-sided 95% CI for the GMT ratio was greater than 0.50.



HPV9 safety profile

| Outcome | Description | Rate per 100 doses | | |
|----------|---|--------------------|--------|----------|
| | | 9v-HPV | 4v-HPV | 2v-HPV |
| Local | Injection site reaction | | 83 | --- |
| | Pain | | ---- | 78 |
| | Swelling | 26.9 - 40.3 | 25 | 26 |
| | Erythema | 24.9 - 34.0 | ---- | 30 |
| | Severe - injection site erythema and/or swelling > 2 inches in size and pain severe | | 5.7 | ---- |
| Systemic | Fatigue | | ---- | 33 |
| | Pyrexia | | 13 | 3 |
| | Urticaria | | 3 | 28 |
| | Headache | | 26 | 30 |
| | Myalgia | | 2 | 28 |
| | Arthralgia | | 1 | 10 |
| | Gastrointestinal disorders | | 17 | 13 |
| | Rash | | ---- | 1 |
| | Urticaria | | ----- | 0.46 100 |

COLLECTION REVIEW

Human Papillomavirus Infection and Fertility Alteration: A Systematic Review

Tiatou Souho^{1,2}, Mohamed Benlemlih², Bahia Bennani^{1,3*}

Conclusions

It appears from this study that HPV detection and genotyping could be of great value in infertility diagnosis at least in idiopathic infertility cases. Like for the risk of carcinogenesis, another classification of HPV regarding the risk of fertility alteration may be considered after deep investigations.

The Effect of Vaccination Against Human Papillomavirus on Fecundability.

McInerney KA¹, Hatch EE¹, Wesselink AK¹, Mikkelsen EM², Rothman KJ^{1,3}, Perkins RB⁴, Wise LA¹.

+ Author information

Abstract

BACKGROUND: The human papillomavirus (HPV) vaccine was developed to prevent infection with strains of HPV that cause cervical cancer. While HPV infection has been associated with reduced semen quality and lower pregnancy rates in some studies, no studies have examined the relationship between HPV vaccination and fecundability. We hypothesize that HPV prevention via vaccination will protect fecundity.

METHODS: We analysed data from Pregnancy Study Online (PRESTO), a preconception cohort of North American pregnancy planners. Between 2013 and 2017, we followed 3483 female pregnancy planners and 1022 of their male partners for 12 months or until reported pregnancy, whichever came first. At baseline, participants reported whether they had been vaccinated against HPV and their age at vaccination. We estimated fecundability ratios (FR) and 95% confidence intervals (CI) using proportional probabilities models adjusted for sociodemographics, smoking, and abnormal Pap test before HPV vaccination (females only).

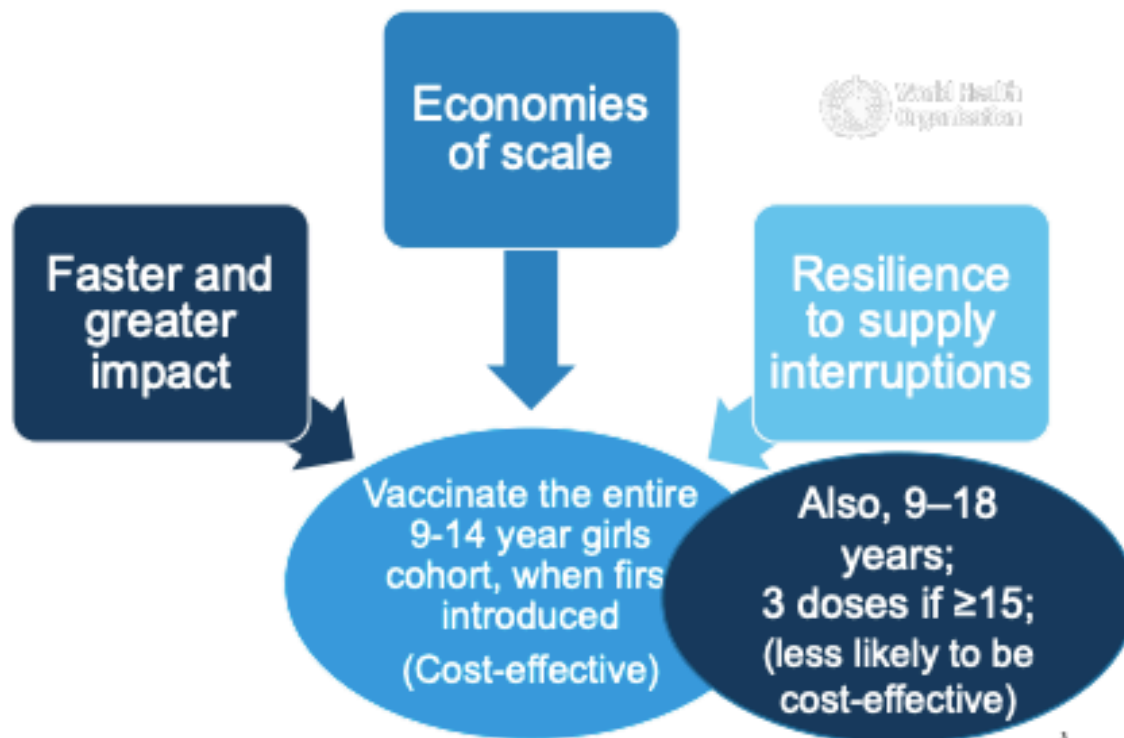
RESULTS: HPV vaccination was more prevalent among females (33.9%) than males (5.2%). There was little overall association between female vaccination (FR 0.98, 95% CI 0.88, 1.09) and fecundability. Among females with a history of sexually transmitted infections (STIs) (n = 1022), those vaccinated had higher fecundability than those not vaccinated (FR 1.35, 95% CI 0.99, 1.86).

CONCLUSION: Although HPV vaccination had little effect on fecundability overall, HPV vaccination was positively associated with fecundability among women with a history of sexually transmitted infections.

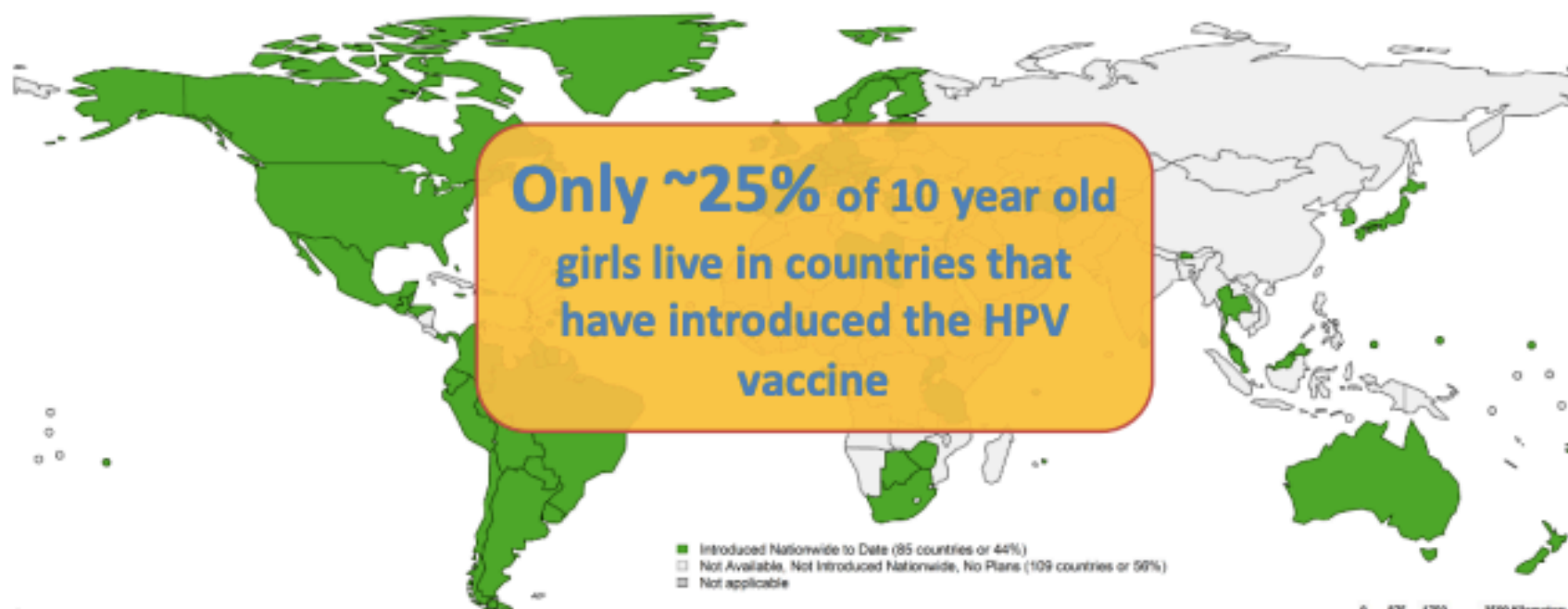
WHO recommendations for HPV vaccination (2017)

- Primary target pop: girls 9-14 years
- 2 doses (6 months apart)
- No max interval (suggested not more than 12-15 months)
- If interval < 5 months, give another dose 6 months after 1st dose
- 3 doses if ≥15 years or immunocompromised

Multi-Age Cohort Vaccination (MAC)



85 countries have introduced the HPV vaccine (as of Oct. 2018)



Date of data: 2018-10-23

Map production: Immunisation, Vaccines and Biologicals (IVB), World Health Organization(WHO)

Data source: IVB database as at 18th October 2018

Disclaimer:

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.
World Health Organization, WHO, 2018. All rights reserved.

0 475 950 1900 Kilometers



Call to Action: Towards Elimination of Cervical Cancer (WHA May 2018)

Vision: A world without cervical cancer

Goal: Eliminate cervical cancer as a public health problem by reducing the incidence of cervical cancer to below **4 cases per 100,000 woman-years**

**2030
TARGETS**

90%

of girls fully vaccinated with HPV vaccine by 15 years of age

70%

of women screened with an HPV test at 35 and 45 years of age and all managed appropriately

30%

reduction in mortality from cervical cancer

The 2030 targets and elimination threshold are subject to revision depending on the outcomes of the modeling exercise (SAGE Oct 2018)