HPV Vaccination: Update on Efficacy & Safety

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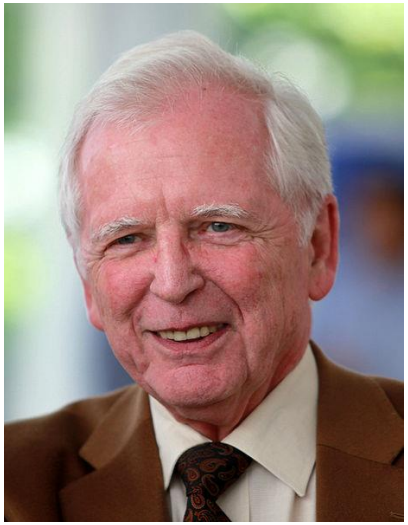
HPV Vaccine introduction

Principles for screening programs

Principle - Natural history understood

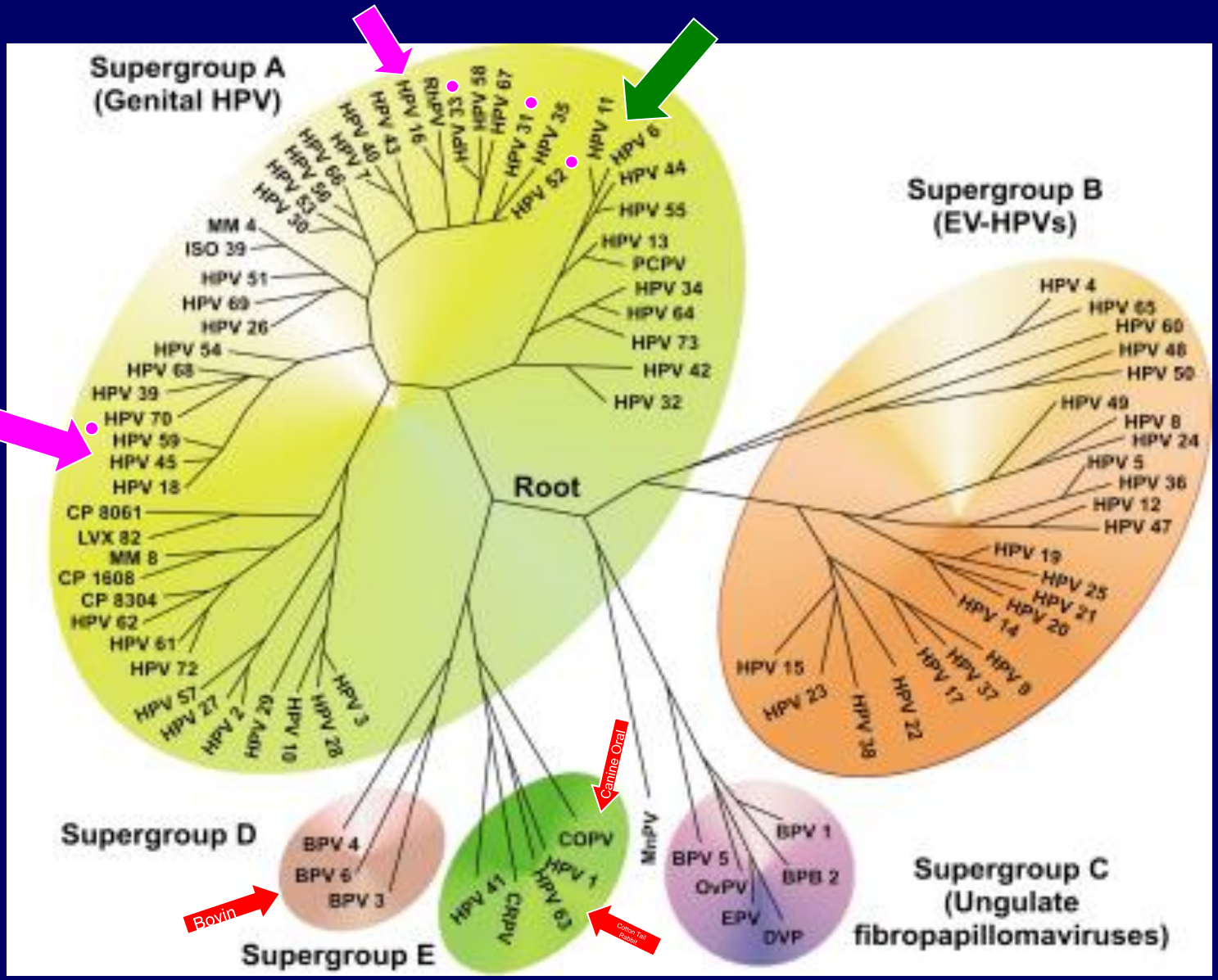


In 1983, HPV16 and HPV18 were identified in cervical cancers

1940s 1950s 1960s 1970s 1980s 1990s 2000s 2010s 2020s

In 1976, Harald zur Hausen published the hypothesis that human papillomavirus plays an important role in the cause of cervical cancer

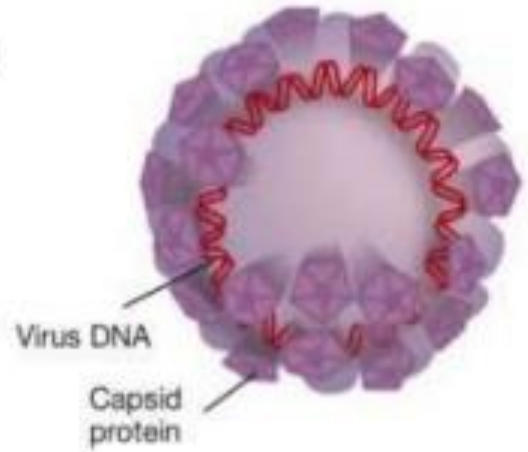
HPV Clades: Genetic Conservation and Biological significance



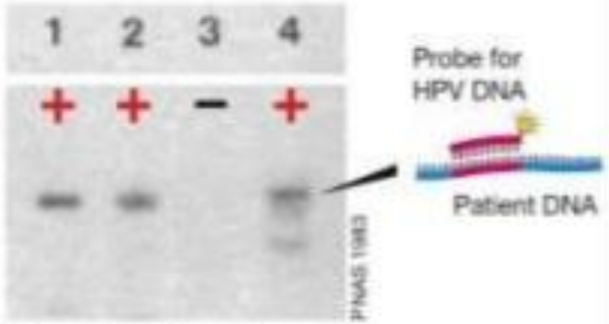
HPV– human papilloma virus

HPV has a circular, double stranded DNA, protected by capsid proteins.

More than 100 HPV-types are known. HPV16 and 18 cause 70% of all cervix cancers.



Discovery of HPV DNA in cancer cells



Harald zur Hausen found HPV DNA in patient DNA (+).

Infection by HPV

HPV infects epithelial cells in the cervical mucosa. HPV DNA integrates into the cellular genome when causing cancer.

 Illustration: Annika Röhl

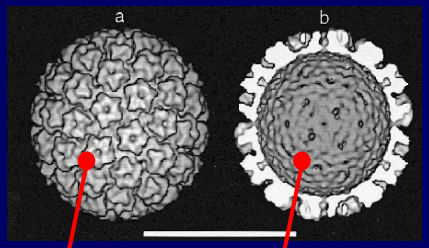
The Nobel Assembly at
Karolinska Institute
has decided on 6 October 2008
to award

The Nobel Prize in
Physiology or Medicine for 2008
with one half to

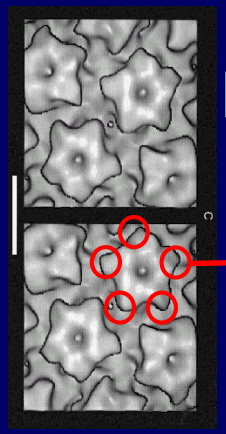
Harald zur Hausen

for his discovery of **"human papilloma viruses causing cervical cancer"**

The vaccine mimics the virus shell



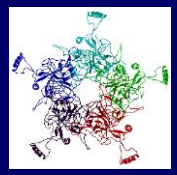
L1 L2



5 x L1

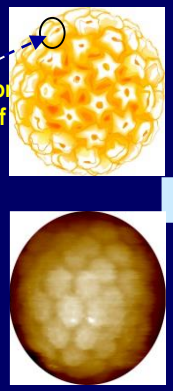
L1 protein

L1 capsomere



Virus-Like Particle (VLP)

(Atomic for image of



Type 18

Type 16

Type 11

Type 6

HPV virus :
L1 = external protein
L2 = internal protein

HPV 4: Production in yeast (Quadrivalent) or HPV 2: baculovirus (Bi-valent)

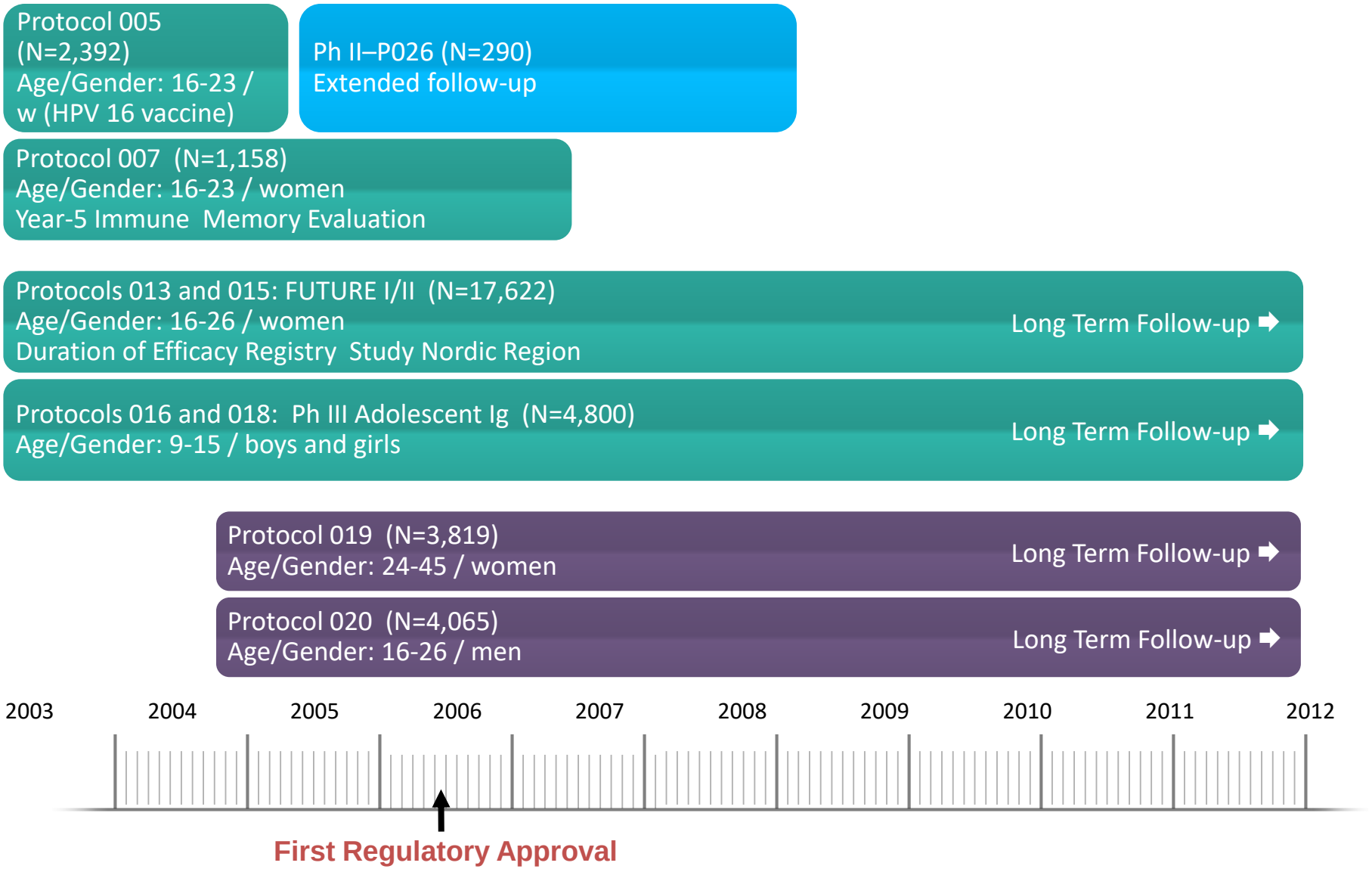
HPV VLP vaccine

The Quadrivalent HPV Vaccine

- HPV Types 6, 11, 16, 18
- Manufactured in *Saccharomyces cerevisiae*
- Amorphous aluminum hydroxyphosphate sulfate (AAHS) adjuvant – 225 µg per dose
- 0-, 2-, 6-month dosing regimen and a simplified regimen for below 15 years (0 and 6 month, 0 and 12 months)
- Does not contain viral DNA and therefore not infectious

GARDASIL is a registered trademark of Merck & Co., Inc., Whitehouse Station, NJ, USA.

Clinical Program for HPV 4



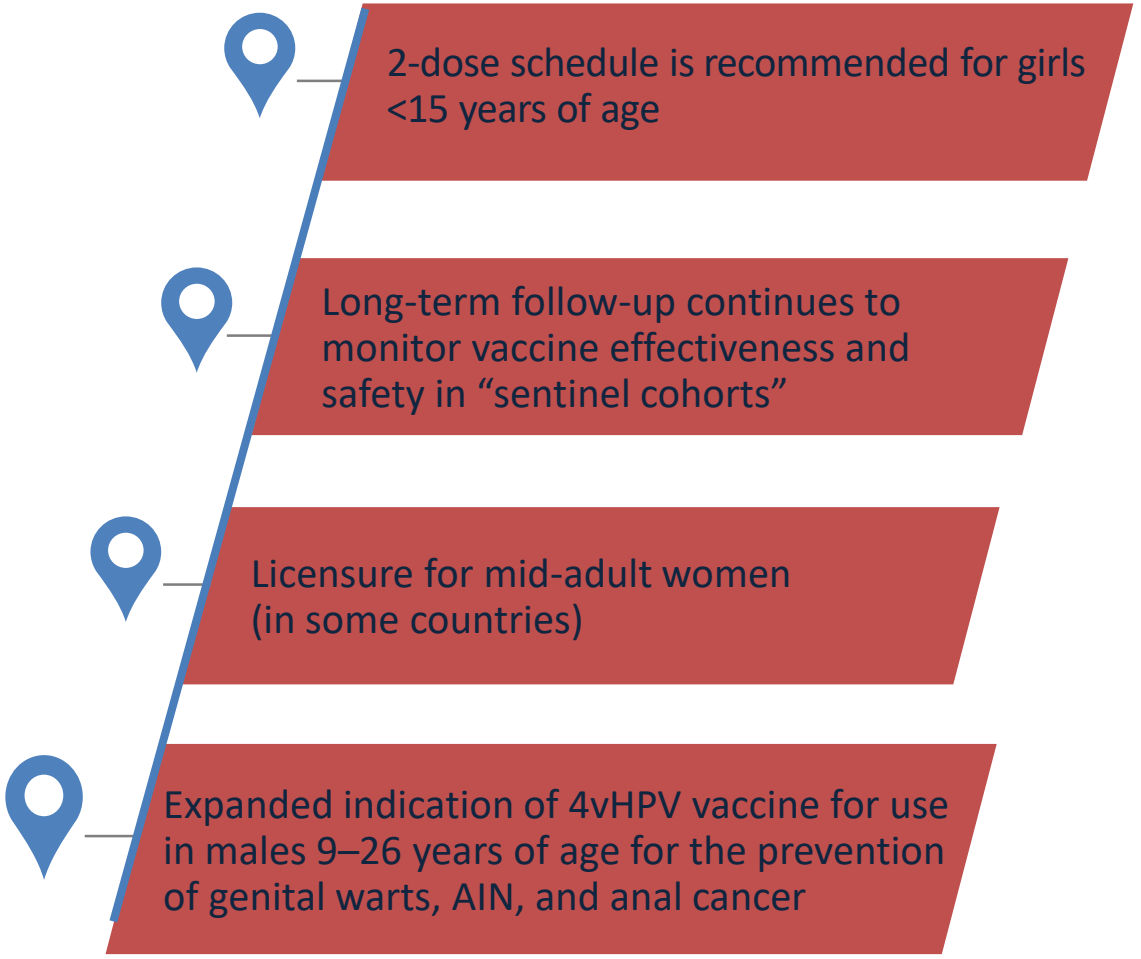
Established Efficacy for HPV Types 6, 11, 16, and 18 — Results From Clinical Trials for HPV4

The efficacy of HPV 4 was established in 6 double-blind, randomized clinical studies evaluating 24,596 individuals (20,541 girls and women 16 to 26 years of age and 4,055 boys and men 16 to 26 years of age at enrollment).

HPV 16- and 18-related CIN 2/3 or AIS, Cervical cancer	**98% efficacy**
HPV 16- and 18-related VIN 2/3 or VaIN 2/3, vulvar/vaginal cancer	**100% efficacy**
HPV 6-, 11-, 16-, and 18-related AIN 2/3, anal cancer	**75% efficacy**
HPV 6- and 11-related genital warts	**89% efficacy in males** **99% efficacy in females**

Study results for data above
Cervical: 2 CIN 2/3 or AIS cases in the group receiving GARDASIL (n=8,493) vs 112 cases in the group receiving placebo (n=8,464) [95% CI, 93.5–99.8].
Vulvar/Vaginal: No VIN 2/3 or VaIN 2/3 cases in either group receiving GARDASIL (n=7,772) vs 10 cases in the VIN 2/3 group receiving placebo (n=7,744) [95% CI, 55.5–100.0], and 9 cases in the VaIN 2/3 group receiving placebo (n=7,744) [95% CI, 49.5–100.0].
Anal: 3 AIN 2/3 cases in the male group receiving GARDASIL (n=194) vs 13 cases in the male group receiving placebo (n=208) [95% CI, 8.8–95.4].
Genital Warts: 3 genital warts cases in the male group receiving GARDASIL (n=1,394) vs 28 cases in the male group receiving placebo (n=1,404) [95% CI, 65.3–97.9] and 2 genital warts cases in the female group receiving GARDASIL (n=6,932) vs 189 cases in the female group receiving placebo (n=6,856) [95% CI, 96.2–99.9].

Notable Clinical Developments Post-Licensure for HPV 4[1-4]



AIN=anal intraepithelial neoplasia.
Please see corresponding slide note for references.

Long-term Follow-up Studies

Clinical Infectious Diseases
REVIEWARTICLE

Impact and Effectiveness of the Quadrivalent Human Papillomavirus Vaccine: A Systematic Review of 10 Years of Real-world Experience

Suzanne M. Garland,[1] Susanne K. Kjaer,[2] Nubia Muñoz,[3] Stan L. Block,[4] Darron R. Brown,[5] Mark J. DiNubile,[6] Brianna R. Lindsay,[6] Barbara J. Kuter,[6] Gonzalo Perez,[6,7] Geraldine Dominiak-Felden,[8] Alfred J. Saah,[6] Rosybel Drury,[8] Rituparna Das,[6] and Christine Velicer[6]

1Royal Women's Hospital, University of Melbourne, Murdoch Childrens Research Institute, Victoria, Australia; 2Danish Cancer Society Research Center and Department of Gynecology, Rigshospitalet, University of Copenhagen, Denmark; 3Colombian National Institute of Cancer, Bogota; 4Kentucky Pediatric and Adult Research, Bardstown; 5Indiana University School of Medicine, Indianapolis; 6Merck & Co, Inc, Kenilworth, New Jersey; 7Universidad del Rosario, Bogota, Colombia; and 8Sanofi Pasteur MSD, Lyon, France

Long-Term Follow-Up Results With HPV4 Vaccine

Endpoint	Population	Time[a]	Cases (Time Since Day 1)	Rate[b] %	Ref
HPV 16/18-related CIN 2+	F, 16–23 y	10 y	**0**	**0.0**	1
HPV 6/11/16/18-related CIN (any grade)	F, 16–23 y	10 y	**1 (>6–8 y)**	**0.0**	1
HPV 6/11/16/18-related vulvar or vaginal cancer	F, 16–23 y	10 y	**0**	**0.0**	1
HPV 6/11/16/18-related disease	F & M, 9–15 y	10 y	**0**	**0.0**	2
HPV 6/11/16/18-related persistent infection ≥12 months	F & M, 9–15 y	10 y	**0**	**0.0**	2
HPV 6/11/16/18-related CIN or condyloma	F, 24–45 y	8 y	**1 (>0–2 y)**	**0.4**	3
HPV 6/11-related genital warts	M, 16–26 y	6 y	**0**	**0.0**	4
HPV 6/11/16/18-related external genital lesions	M, 16–26 y	6 y	**0**	**0.0**	4
HPV 6/11/16/18-related AIN or anal cancer	M, 16–26 y	6 y	**0**	**0.0**	4

[a]Total time since vaccination.
[b]Per 100 person-years at risk.
AIN=anal intraepithelial neoplasia; CIN=cervical intraepithelial neoplasia; F=female; M=male; y=years.

1. Kjaer SK et al. Abstract OC 6–1. Presented at: EUROGIN Congress; 4–7 February 2015; Sevilla, Spain. **2.** Ferris D et al. *Pediatrics.* 2014;134:e657–e665. **3.** Das R et al. Abstract OC 4–9. Presented at: EUROGIN Congress; 4–7 February 2015; Sevilla, Spain. **4.** Goldstone S et al. Presented at: 29th International Papillomavirus Conference; 20–25 August 2014; Seattle, WA.

10-Year Follow-up for Immunogenicity, Effectiveness, and Safety of HPV4 Vaccine in Adolescents

- Through 10 years postvaccination with qHPV, pre-adolescents and adolescents have:
  - Persistent anti-HPV immunity
  - Durable protection from persistent infection with vaccine-type HPV
  - Long-term protection from HPV-related genital warts and genital precancers/cancers (girls: cervix, vagina, and vulva; boys: penile, perineal, and perianal)
- Gardasil is safe and well tolerated in this population

10-Year Follow-up for Immunogenicity, Effectiveness, and Safety of Quadrivalent Human Papillomavirus (qHPV) Vaccine in Adolescents. Poster presented at AOGIN congress, Singapore, 2016

HPV4 Vaccination Programs Among Countries With Reported Effectiveness Data

	 Australia[1,2]	 New Zealand[3,4]	 Denmark[5-7]	 Sweden[8]	 United States[7,9]	 Germany[10–12]	 Canada[7,13,14]
Type of Program	**School and clinic based**	**School and clinic based**	**Clinic based**	**School and clinic based**	**Clinic based**	**Clinic based**	**School based**
Routine Cohort (Age, Years)	**F & M: 12–13**	**F: 12**	**F: 12**	**F: 10–12**	**F & M: 11–12**	**F: 9–14**	**F & M: 9–17**[b]
HPV Vaccination Coverage Rates[a,b]	**F: 73.1%** **M: 60.0%** (aged 15, 2014)[b]	**F: 54%**	**F: 69%–83%**	**F: 80%**[c] (ages 13–14, 2012–2013)	**F: 38%** **M: 14%** (ages 13–17, 2013)	**F: 40%**	**F: 51%–85%**[b]

[a]Full 3-dose completion.[2,4,5,9,12,14]
[b]Varies by region/province.[2,7,14]
[c]Coverage for those receiving at least 1 dose.[8]

F=female; M=male.
Please see corresponding slide note for references.

Early Population Impact Data With HPV4 Vaccine

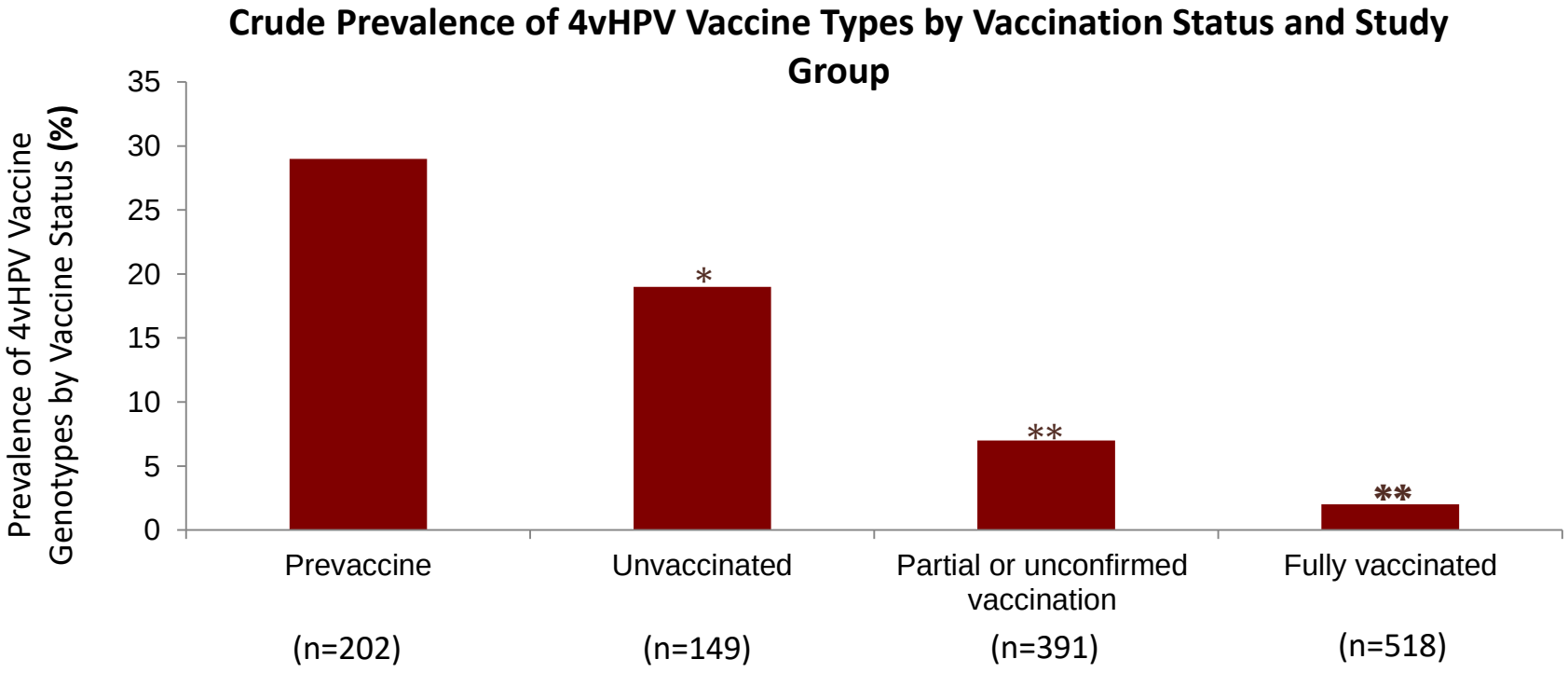
	Australia	New Zealand	Denmark	Sweden	United States	Germany	Canada
Decline in genital warts in young females	✓ Refs 1,2	✓ Ref 5	✓ Ref 6	✓ Ref 8	✓ Ref 9	✓ Ref 12	**NR**
Decline in high-grade cervical abnormalities	✓ Ref 3	**NR**	✓ Ref 7	**NR**	✓ Ref 10	**NR**	✓ Ref 14
Decline in vaccine HPV type prevalence	✓ Ref 4	**NR**	**NR**	**NR**	✓ Ref 11	✓ Ref 13	**NR**

F=female M=male; NR=not reported.

Please see corresponding slide notes for references.

Decline in Prevalence of HPV4 Vaccine Types in Australian Females in the Postvaccine Period[1]

- Postvaccine implementation,[a] the prevalence of 4vHPV vaccine types (6/11/16/18) significantly declined in all women, irrespective of vaccination status.
  - Decreases in prevalence of 4vHPV vaccine types in unvaccinated women suggests a benefit from herd immunity after vaccine implementation.

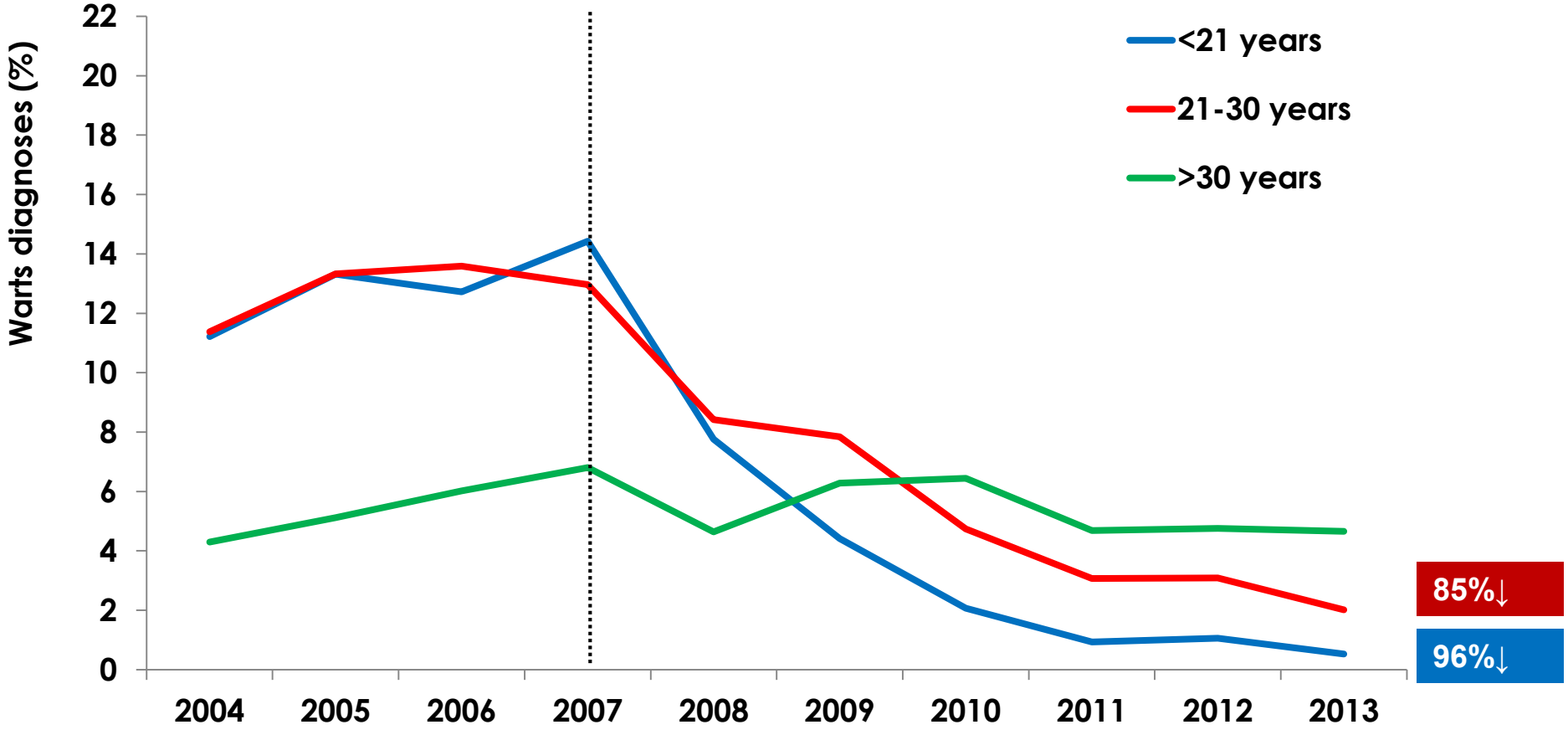


*P<0.05 or **P<0.0001 denotes significant differences in prevalence compared to the prevaccine study group.

[a]Postvaccine implemention encompasses 3 categories denoting vaccination status: unvaccinated, partial/unconfirmed vaccination, or fully vaccinated, and compared to the prevaccine implementation study.

1. Tabrizi SN et al. *Lancet Infect Dis*. 2014;14:958-966.

Proportion of Australian born women diagnosed with genital warts at first visit, by age group, 2004-2013



Ali H et al. *BMJ* 2013 (extended data)

FDA News Release

FDA approves Gardasil 9 for prevention of certain cancers caused by five additional types of HPV

For Immediate Release December 10, 2014

Release

Español

The U.S. Food and Drug Administration today approved Gardasil 9 (Human Papillomavirus 9-valent Vaccine, Recombinant) for the prevention of certain diseases caused by nine types of Human Papillomavirus (HPV). Covering nine HPV types, five more HPV types than Gardasil (previously approved by the FDA), Gardasil 9 has the potential to prevent approximately 90 percent of cervical, vulvar, vaginal and anal cancers.

Worldwide Burden of HPV Disease

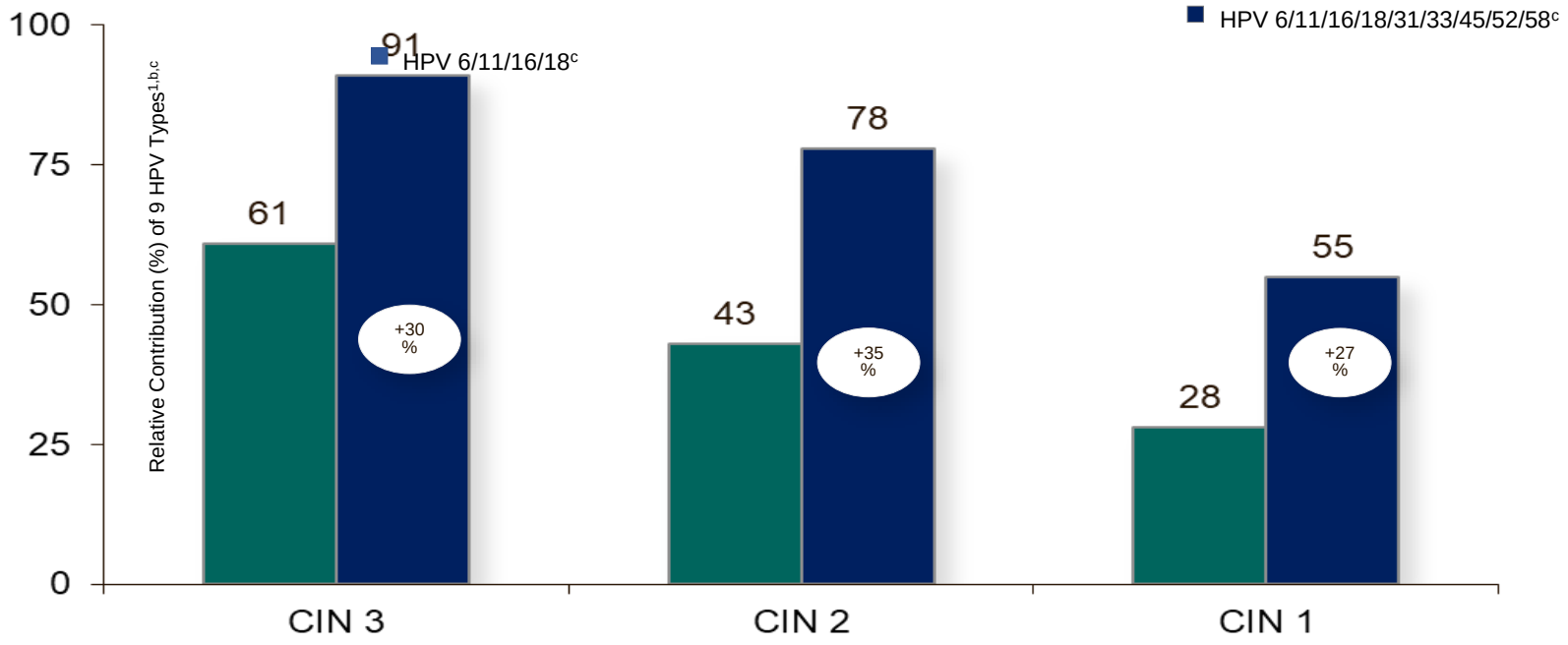
- HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 are 9 of the most common types in HPV-related cancers and diseases in males and females[1–6]

Estimated Type Contribution for Certain HPV-Related Cancer and Disease Cases		
	4 HPV types cause: (6, 11, 16, and 18)	**9 HPV types cause a total of:** (6, 11, 16, 18, 31, 33, 45, 52, and 58)
Cervical cancer cases	70%[1]	90%[1]
Vulvar cancer cases[a]	75%[2]	90%[2]
Vaginal cancer cases[a]	65%[3]	85%[3]
Anal cancer cases[a]	85%[4]	90%–95%[4]
High-grade cervical precancers[a,b]	50%[5]	80%[5]
Low-grade cervical lesions[a]	25%[5]	50%[5]
Genital warts cases	90%[6]	90%[6]

[a]Not all cervical precancers and lesions, and vulvar, vaginal, and anal cancer cases are caused by HPV. Approximately 90% of high-grade cervical precancers,[7] 75% of low-grade cervical lesions,[7] 30% of vulvar cancer cases,[2] 70% to 75% of vaginal cancer cases,[3] and 85% to 90% of anal cancer cases[4] are HPV related. [b]High-grade cervical precancers defined as cervical intraepithelial neoplasia (CIN) 2/3.

1. de Sanjosé S et al. *Lancet Oncol.* 2010;11:1048–1056. 2. de Sanjosé S et al. *Eur J Cancer*. 2013;49:3450–3461. 3. Alemany L et al. *Eur J Cancer*. 2014;50:2846-2854. 4. Alemany L et al. *Int J Cancer*. 2015;136:98–107. 5. Joura EA et al. *Cancer Epidemiol Biomarkers Prev*. 2014;23:1997−2008. 6. Garland SM et al. *J Infect Dis*. 2009;199:805–814. 7. Guan P et al. *Int J Cancer*. 2012;131:2349–2359.

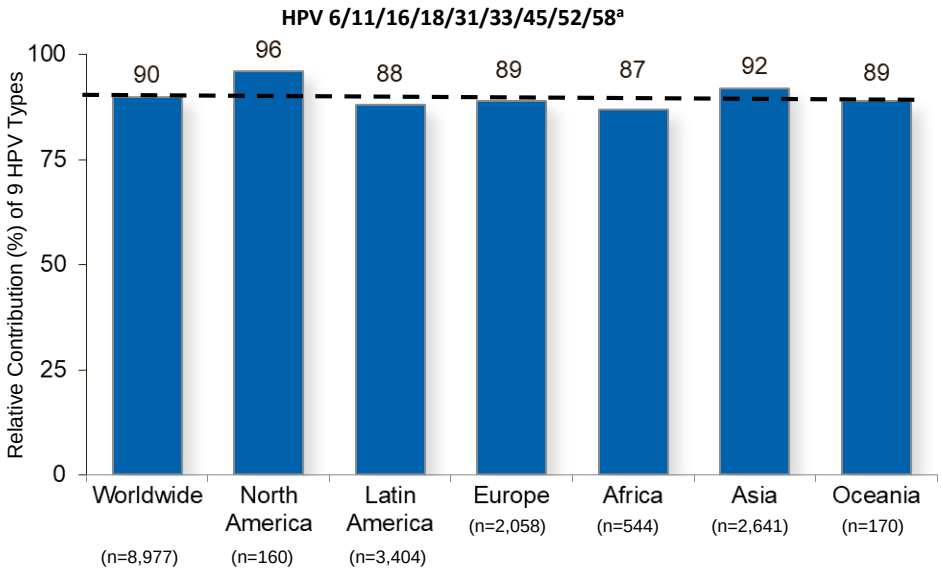
Attribution for 9 HPV Types in Cervical Dysplasia[a] Worldwide



[a]In women 15 to 26 years of age.
[b]Overall contribution of HPV in cases of CIN 1=73%, CIN 2=86%, and CIN 3=93%.[2]
[c]HPV 6 and HPV 11 have negligible contributions to CIN 2/3 and ~8% contribution to CIN 1. Data in figure do not reflect any contribution of HPV 6/11.

CIN=cervical intraepithelial neoplasia.
1. Joura E et al. *Cancer Epidemiol Biomarkers Prev*. 2014;23:1997–2008. 2. Guan P et al. *Int J Cancer*. 2012;131:2349–2359.

Nine HPV Types in Cervical Cancer: Consistency Across World Regions[1]

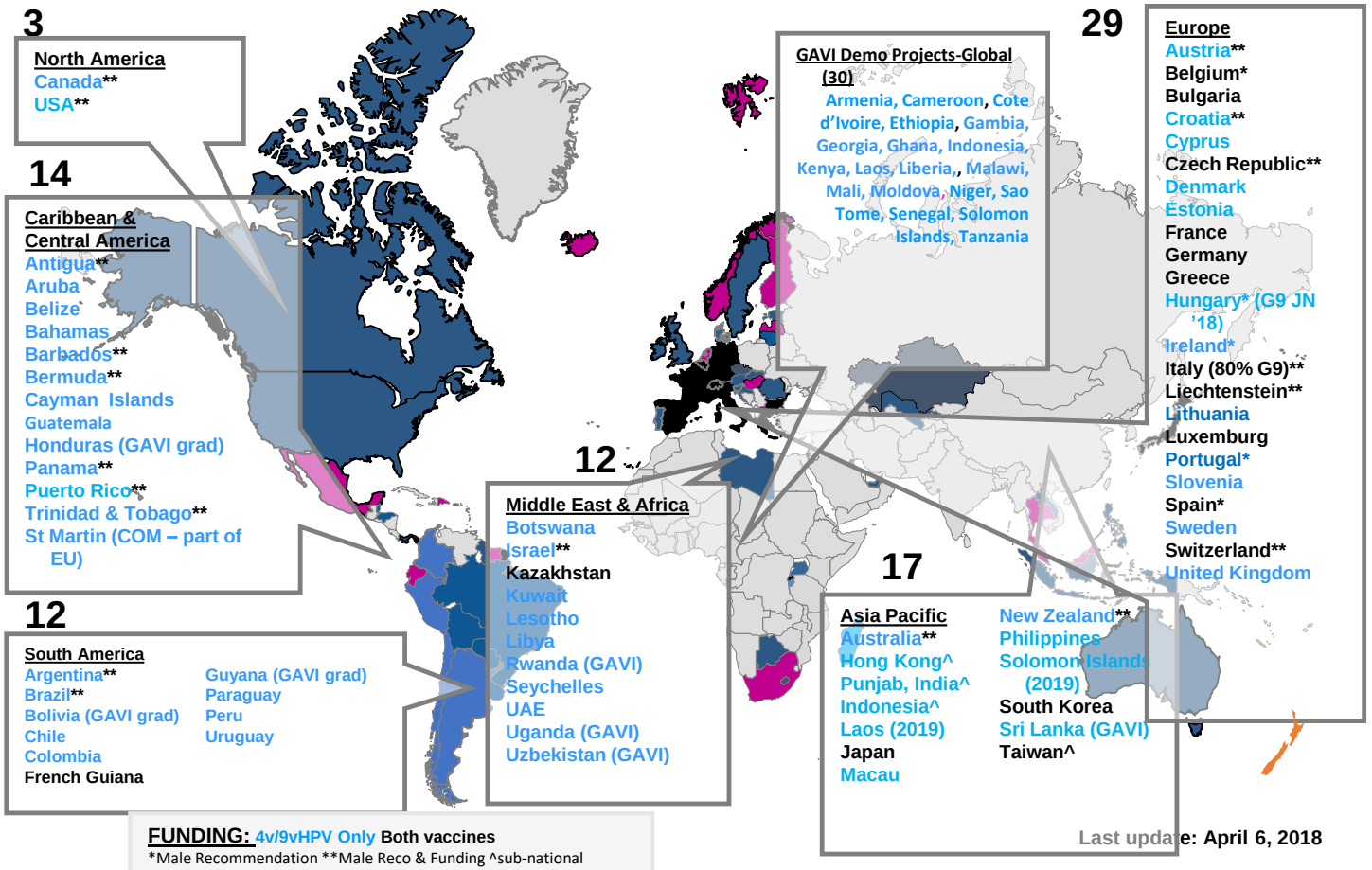


[a]Chart represents the relative contribution of the 9 HPV types in HPV-positive cervical cancer cases in an international study of 8,977 HPV-positive cases; the dashed-line highlights the worldwide relative contribution of ~90%.

1. Serrano B et al. *Infect Agent Cancer*. 2012;7:38.

Publically Funded / Reimbursed HPV4 Immunization Programs: 89 (does not include GAVI Demos)

Female only program: 69 Countries; Gender-neutral: 20 countries



FUNDING: 4v/9vHPV Only **Both vaccines**

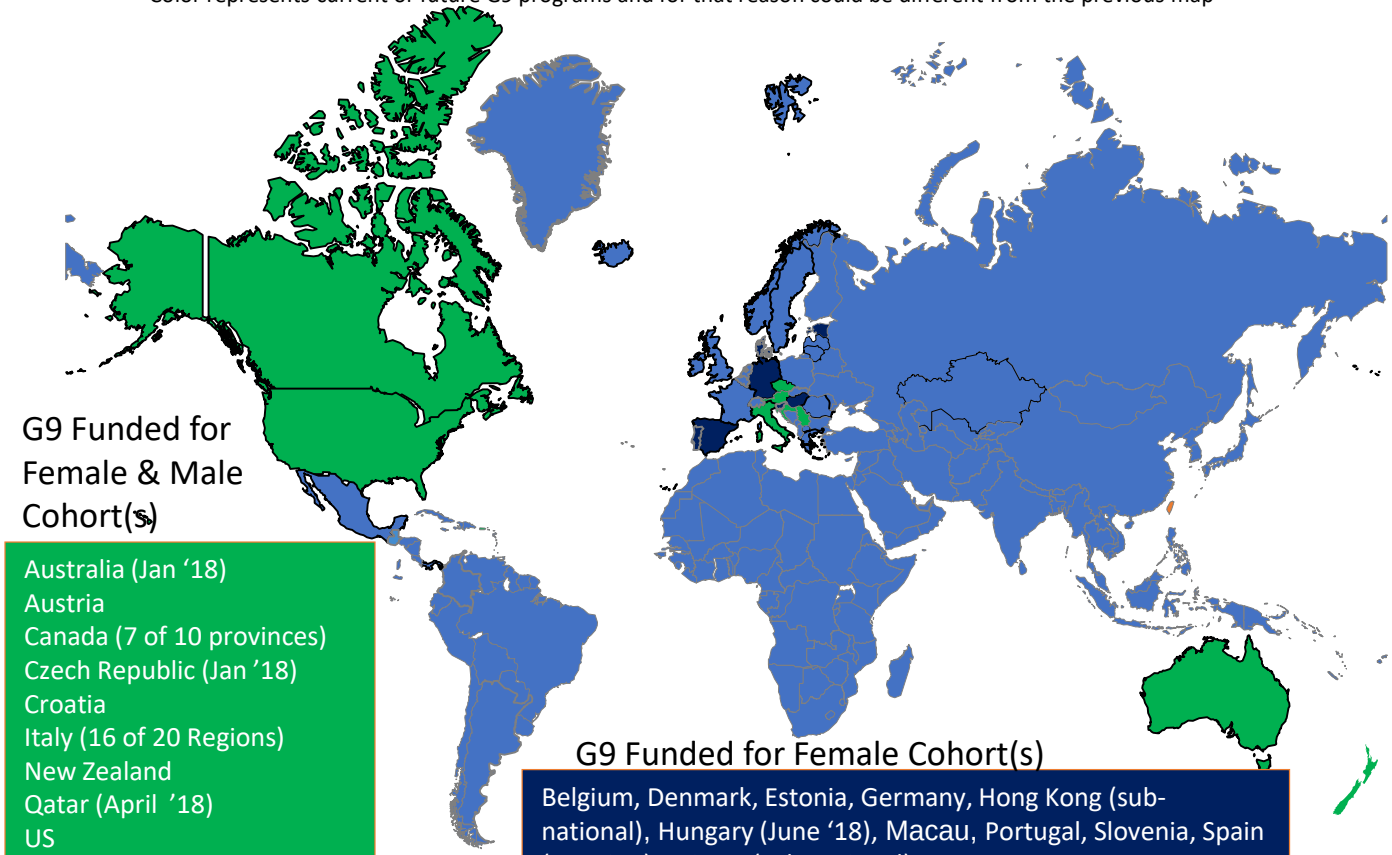
*Male Recommendation **Male Reco & Funding ^sub-national (<50%)

Last update: April 6, 2018

Publically Funded / Reimbursed Gardasil 9 Immunization Programs: 20

Gender-neutral: 9 countries; Female only program: 11 Countries

- Color represents current or future G9 programs and for that reason could be different from the previous map



G9 Funded for Female & Male Cohort(s)

Australia (Jan '18)
Austria
Canada (7 of 10 provinces)
Czech Republic (Jan '18)
Croatia
Italy (16 of 20 Regions)
New Zealand
Qatar (April '18)
US

G9 Funded for Female Cohort(s)

Belgium, Denmark, Estonia, Germany, Hong Kong (sub-national), Hungary (June '18), Macau, Portugal, Slovenia, Spain (1 region), Taiwan (sub-national)

Last update: April 6, 2018

HPV Vaccine safety:

- HPV 4/9 is **contraindicated** in individuals with hypersensitivity, including severe allergic reactions to yeast, or after a previous dose of HPV vaccine.
- **The most common adverse reaction** was headache. Common adverse reactions that were observed among recipients of HPV 4/9 at a frequency of at least 1.0% and greater than placebo were fever, nausea, dizziness; and injection-site pain, swelling, erythema, pruritus, and bruising.
- In addition, syncope has been reported following vaccination with HPV 4/9, sometimes resulting in falling with injury. Observation for 15 minutes after administration is recommended.

Increasing supply and global access to our HPV vaccines: a top priority for MSD!

Unprecedented increase in global demand for HPV vaccines from new or expanded vaccination programs

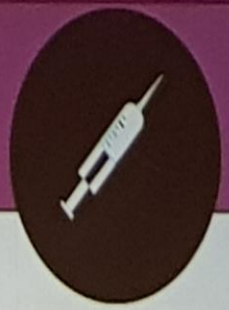
2x demand

In 2018, there was a significant inflection point—with demand for HPV vaccines more than doubling compared to 2017—after a 5-year period of stable demand.

To meet this growing demand around the world, we are making **significant capital investments** to further expand our manufacturing capacity.

3x increase in global distribution

This investment is leading to a **more than 40% increase in doses** distributed in 2018 compared to 2017, and we are planning to **more than triple global distribution over the next five years.**



In 2019, the majority of our **HPV vaccines will be distributed to low and mid-income countries.**

3x supply to Gavi in 2018

In 2018, we more than tripled the distribution of our HPV vaccine to Gavi compared to 2017.

https://www.m[illegible]ewsroom.com/news/company-statements/mercks-continued-commitment-towards-meeting-hpv-vaccine-dema[illegible]nd-equitable (November 30, 2018)

CONCLUSIONS

Summary

- HPV Vaccination is very effective against HPV related diseases, esp. cervical, vaginal and vulval cancers and precancers

- HPV Vaccine is safe with adverse reactions comparable to other vaccines.

Thank you !