HPV vaccination: an update

FIGO Committee on Women's Cancer

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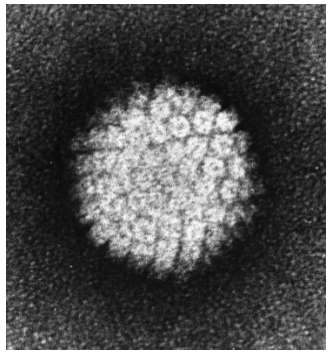
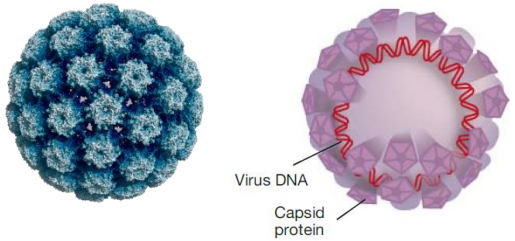
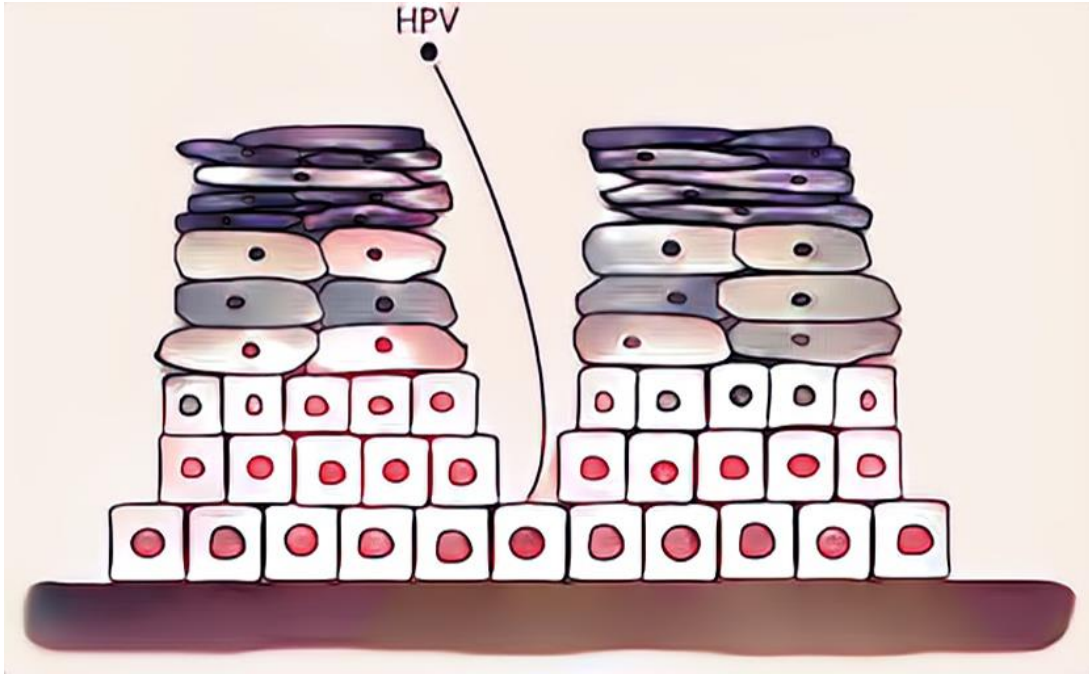
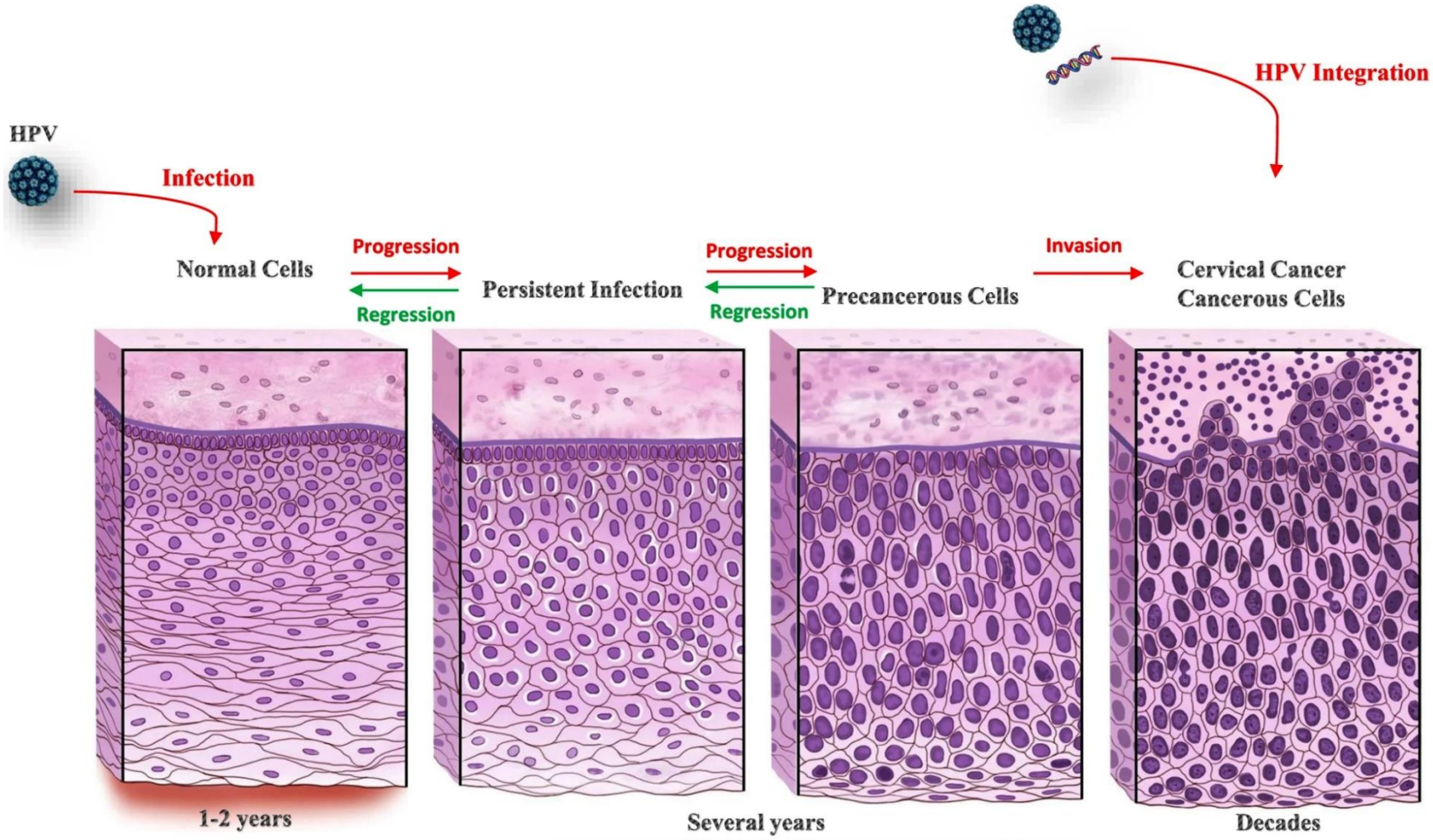
Human papillomavirus (HPV)





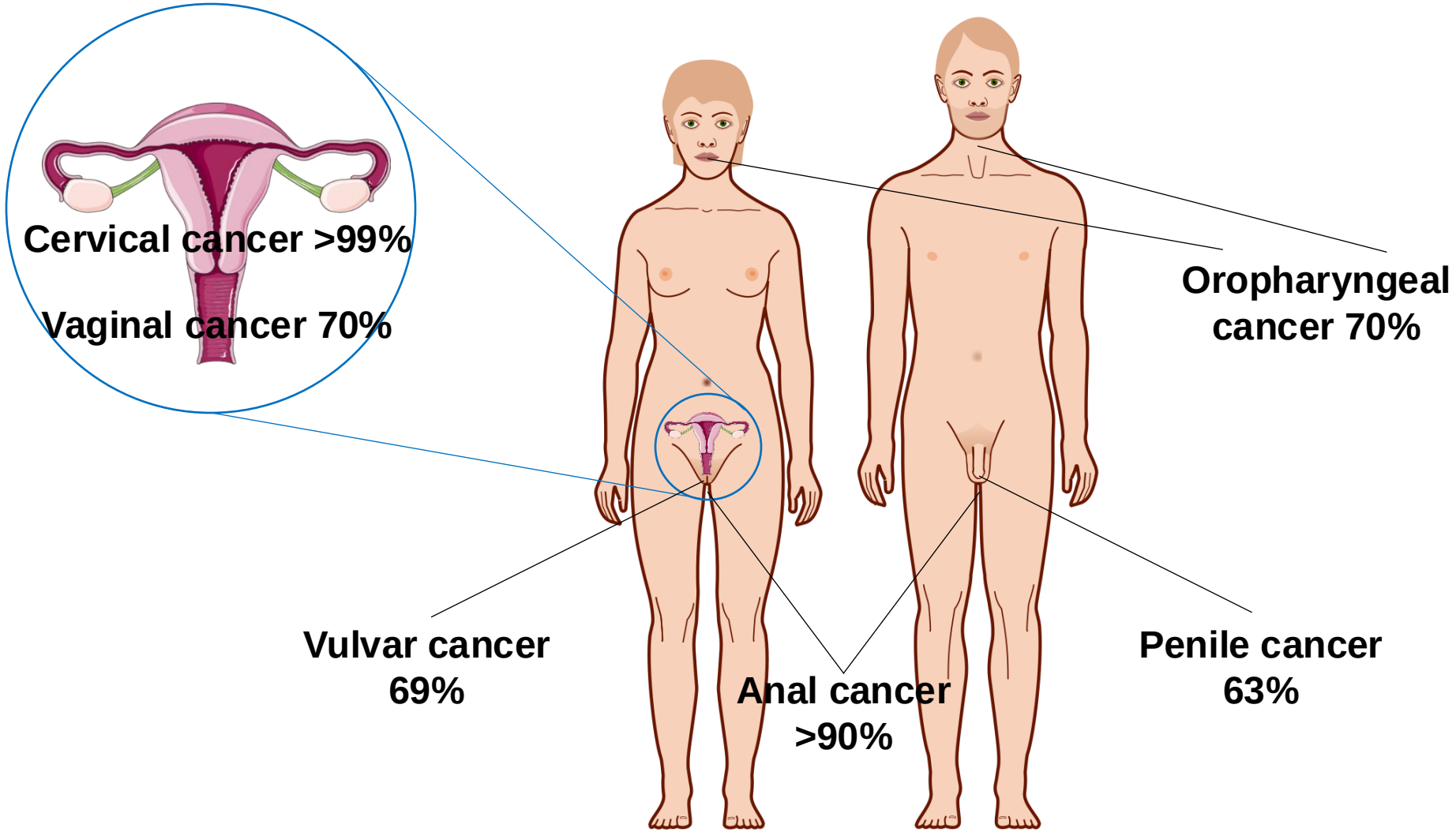
HPV is a DNA virus, about 50-55 nm in diameter, that can easily infect the basal layer of epithelium via microtrauma.





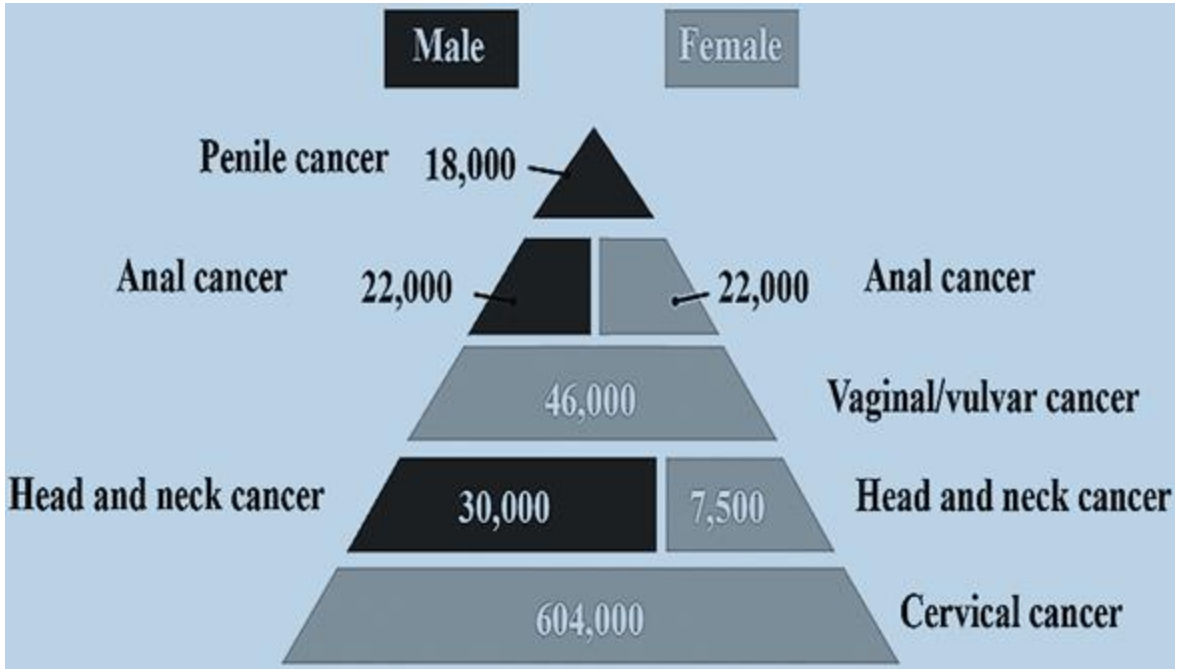
Only 10% of women will have a persistent cervical HPV infection, which may progress to cervical cancer decades later.

HPV is associated not only with cervical cancer but also with other anogenital cancers and oropharyngeal cancer.



https://commons.wikimedia.org/, https://www.cancer.gov/

HPV-associated cancers



The burden of cancers attributable to HPV infection by site and gender worldwide each year

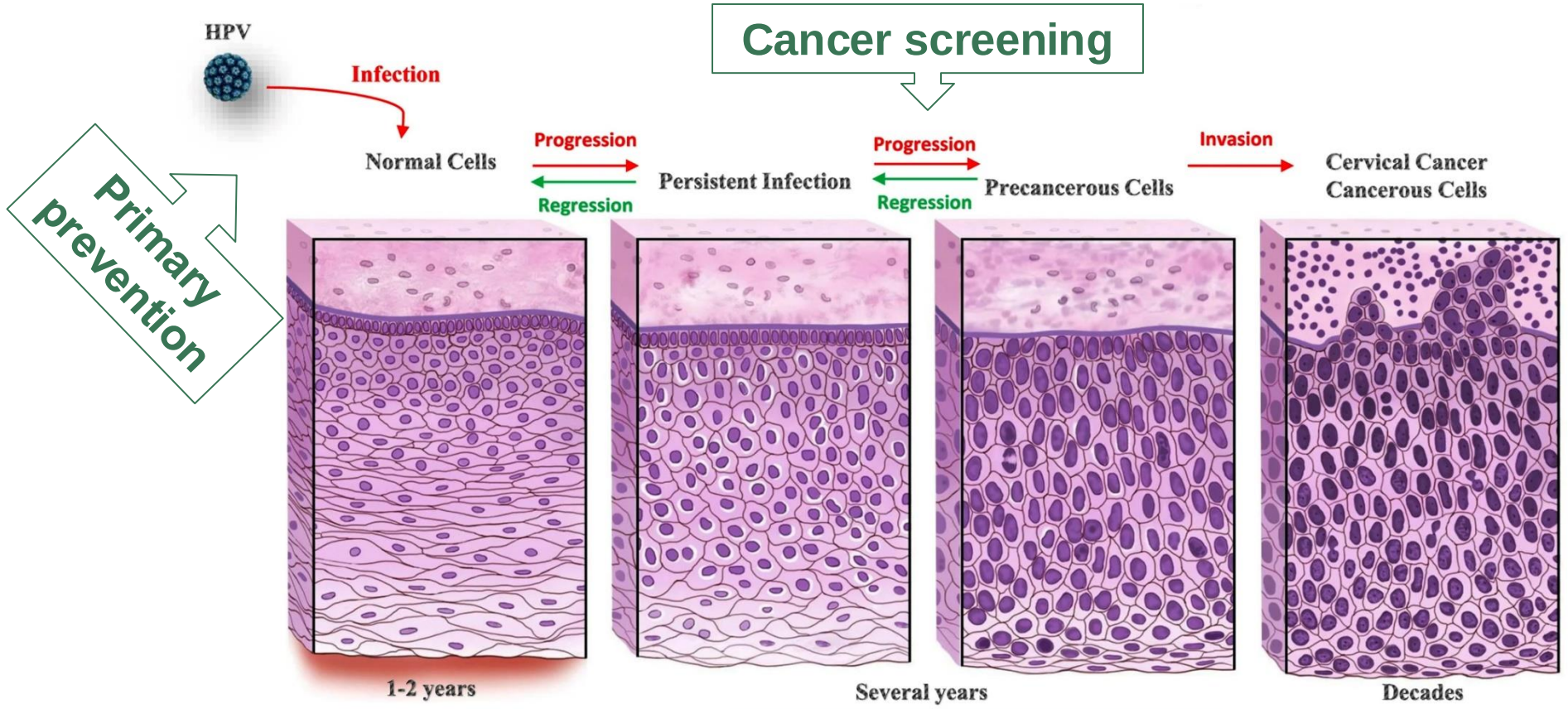
Each year, high risk HPV (HR-HPV) causes

- ~5% of human cancers (>700,000 cases)
- >400,000 deaths

Cervical cancer in 2022

- ~660,000 new cases
- ~350,000 deaths (94% in LMICs)

Prevention is better than cure!



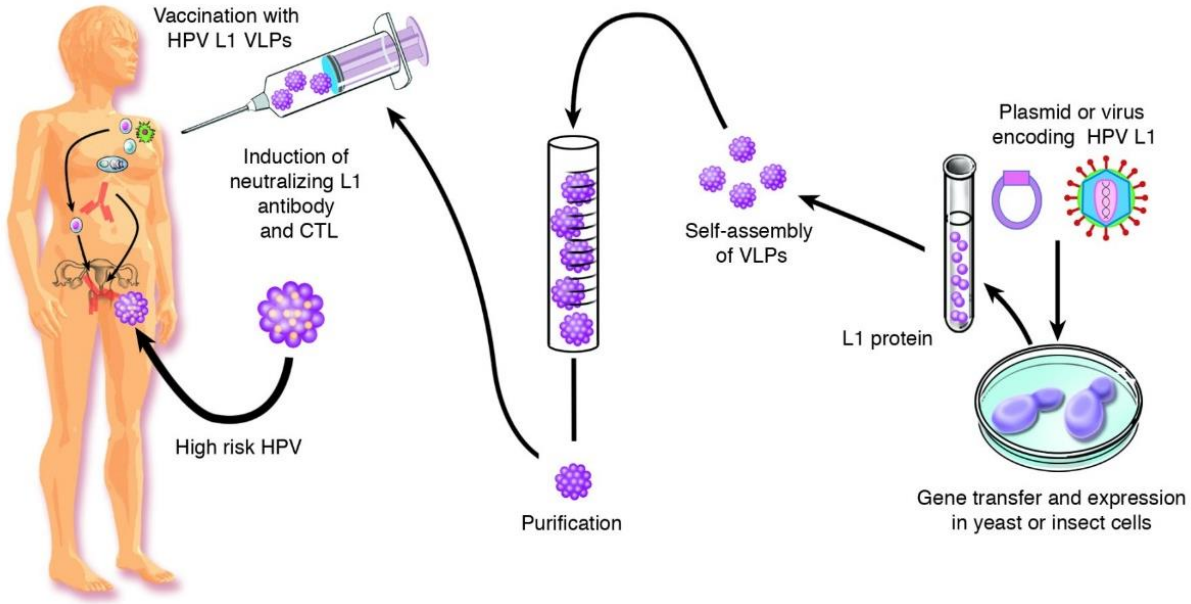
Adapted from: Khairkhah N, et al. *J Mol Med* 2022;100:829-45.

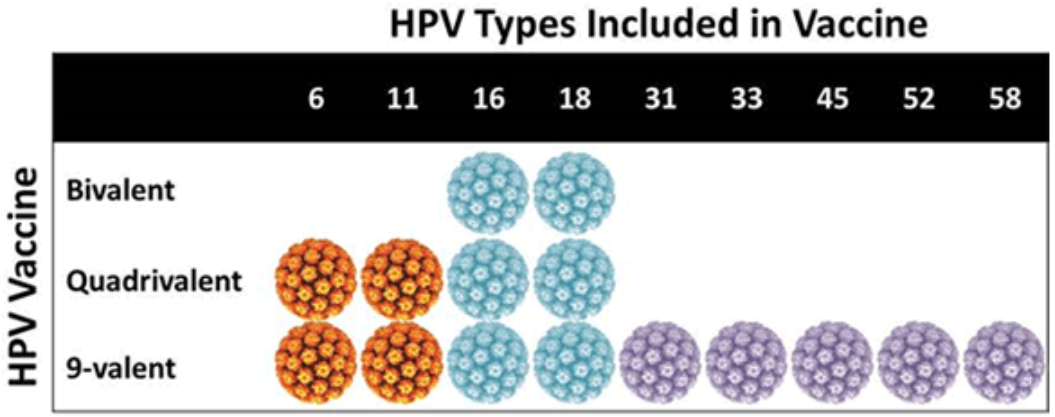
Condoms are effective in preventing most sexually transmitted infections but not HPV infection.

Therefore, HPV vaccines are essential for primary prevention.

Source: *The Naked Gun*.

HPV vaccines





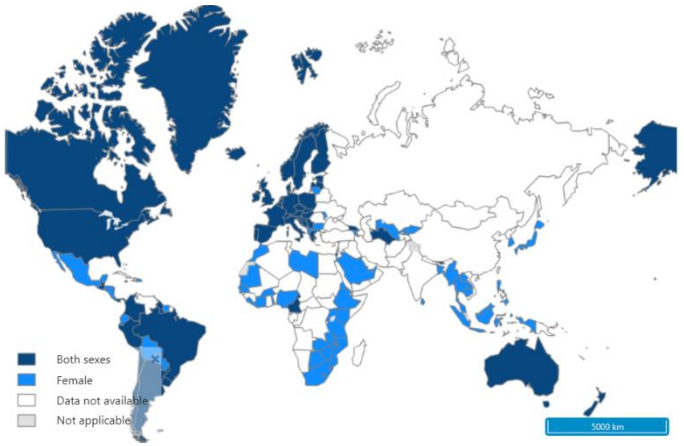
HPV vaccines are produced from virus-like particles made from the L1 protein. There are bivalent, quadrivalent, and 9-valent HPV vaccines available.

HPV vaccines

1st HPV vaccine licensed in 2006

To date (May 2024)

- 141 countries included in the national immunization programme
  - 66 countries for both sexes



Licensed HPV vaccines

- Bivalent
  - *Cervarix*
  - *Cecolin*
  - *Walrinvax*
- Quadrivalent
  - *Gardasil*
  - *Cervavax*
- Nonavalent
  - *Gardasil 9*

WHO. *Wkly Epidemiol Rec* 2022;97:645-72., https://www.who.int/

Safety of HPV vaccines

The Global Advisory Committee on Vaccine Safety (GACVS)

- >270 million doses of HPV vaccines have been distributed
- Anaphylaxis ~1.7 cases per million dose
- Syncope: common stress related reaction to the injection
- No increased risk for Guillain-Barré syndrome, complex regional pain syndrome, postural orthostatic tachycardia syndrome, premature ovarian insufficiency

➔ **Considers HPV vaccines to be extremely safe**

Protection against CIN2+ associated with HPV16/18
Women 15-26 years, who HPV DNA 16/18 negative at baseline

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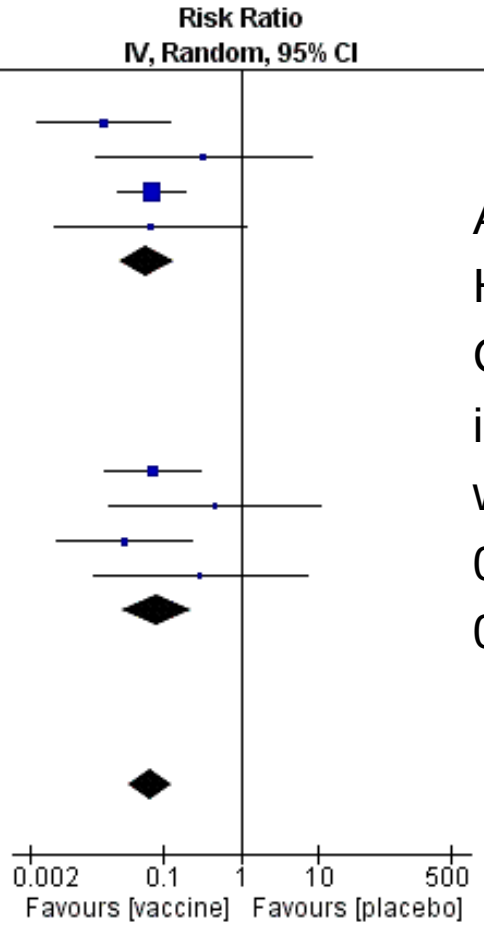
Study or Subgroup	Vaccine Events	Vaccine Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
9.1.1 3 doses						
FUTURE II trial (ph3,4v)	1	5305	58	5260	10.7%	0.02 [0.00, 0.12]
Japanese trial (ph2,2v)	0	408	1	407	4.1%	0.33 [0.01, 8.14]
PATRICIA trial (ph3,2v)	4	7344	56	7312	40.6%	0.07 [0.03, 0.20]
Phase2 trial (v1)	0	114	7	118	5.1%	0.07 [0.00, 1.19]
Subtotal (95% CI)		**13171**		**13097**	**60.6%**	**0.06 [0.03, 0.14]**
Total events	5		122			
Heterogeneity: Tau² = 0.00; Chi² = 2.77, df = 3 (P = 0.43); I² = 0%						
Test for overall effect: Z = 6.59 (P < 0.00001)						
9.1.2 1 or 2 doses						
FUTURE II trial (ph3,4v)	2	560	29	603	20.5%	0.07 [0.02, 0.31]
Japanese trial (ph2,2v)	0	14	1	20	4.3%	0.47 [0.02, 10.69]
PATRICIA trial (ph3,2v)	1	696	35	768	10.6%	0.03 [0.00, 0.23]
Phase2 trial (v1)	0	105	1	94	4.1%	0.30 [0.01, 7.25]
Subtotal (95% CI)		**1375**		**1485**	**39.4%**	**0.08 [0.03, 0.23]**
Total events	3		66			
Heterogeneity: Tau² = 0.00; Chi² = 2.72, df = 3 (P = 0.44); I² = 0%						
Test for overall effect: Z = 4.74 (P < 0.00001)						
Total (95% CI)		**14546**		**14582**	**100.0%**	**0.07 [0.04, 0.13]**
Total events	8		188			
Heterogeneity: Tau² = 0.00; Chi² = 5.70, df = 7 (P = 0.58); I² = 0%						
Test for overall effect: Z = 8.11 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.65), I² = 0%						

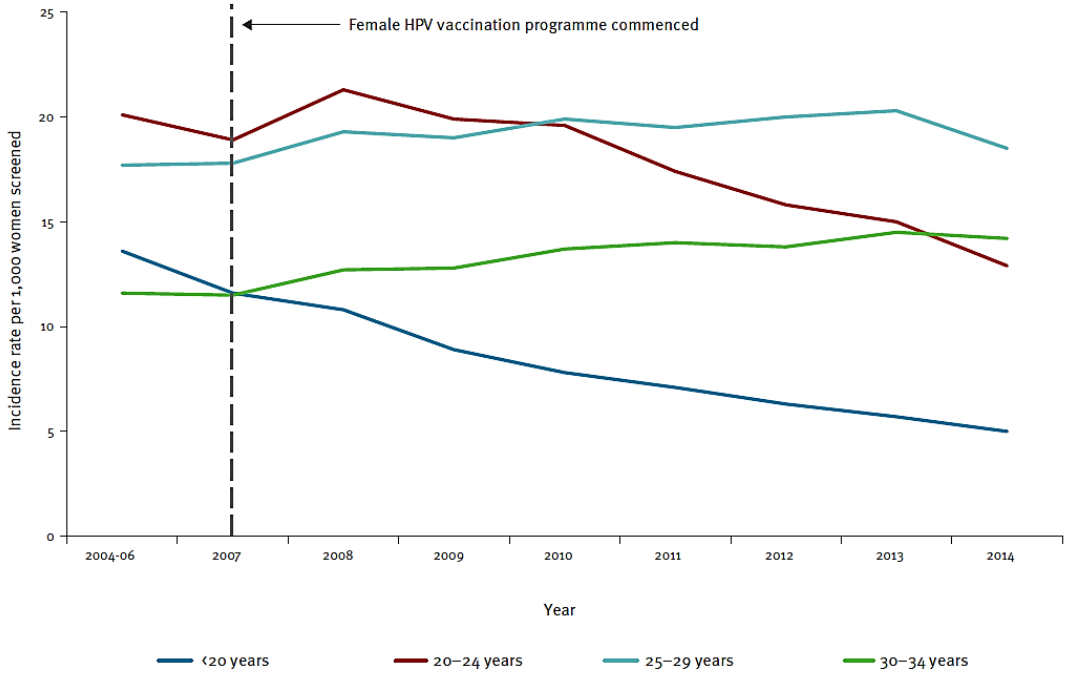


A meta-analysis showed that HPV vaccines could prevent CIN2+ associated with HPV16/18 in initially HPV DNA negative women, with an OR of
0.06 for those completing 3 doses, and
0.08 for those receiving 1 or 2 doses.

Real-world effectiveness of HPV vaccination

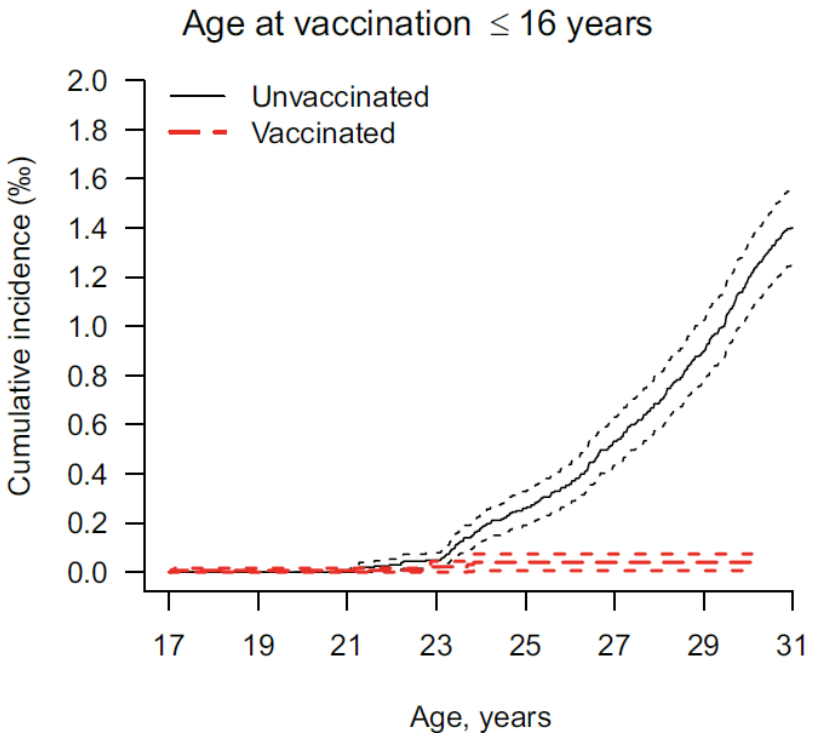
Australia, 2004-2014

High-grade cervical lesions



Denmark, 2006-2019

Cervical cancer



Ten-year follow-up data from the Indian HPV vaccine study group showed that the vaccine efficacy against HPV16/18 infection was similar in participants aged 10-18 years receiving one, two or three doses at 95%, 93% and 93%, respectively.

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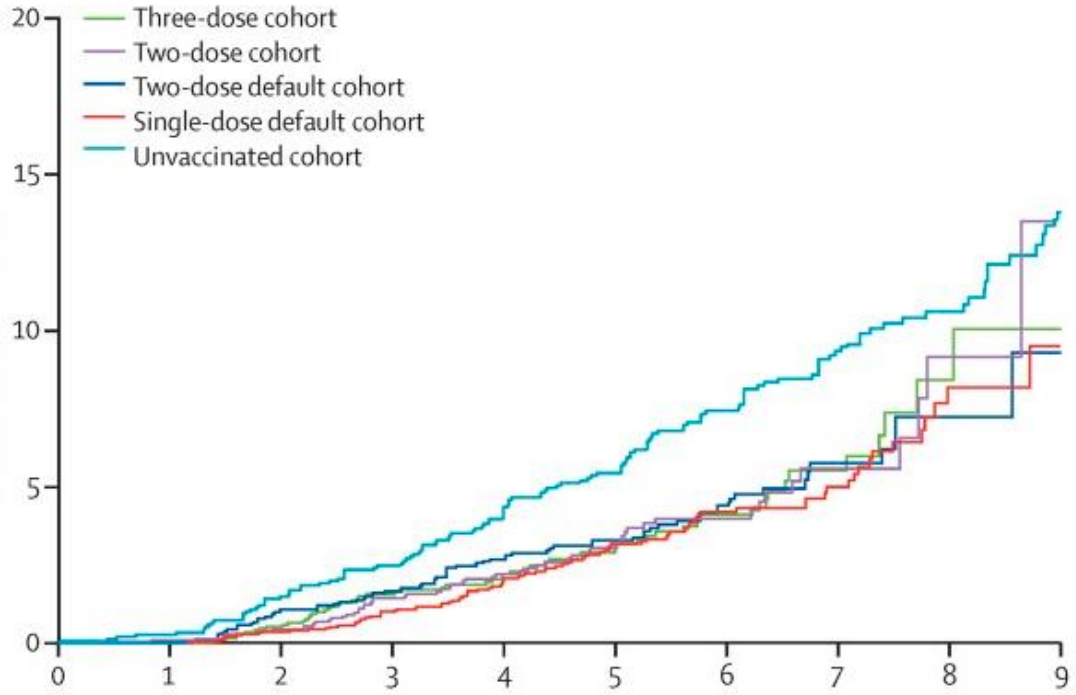
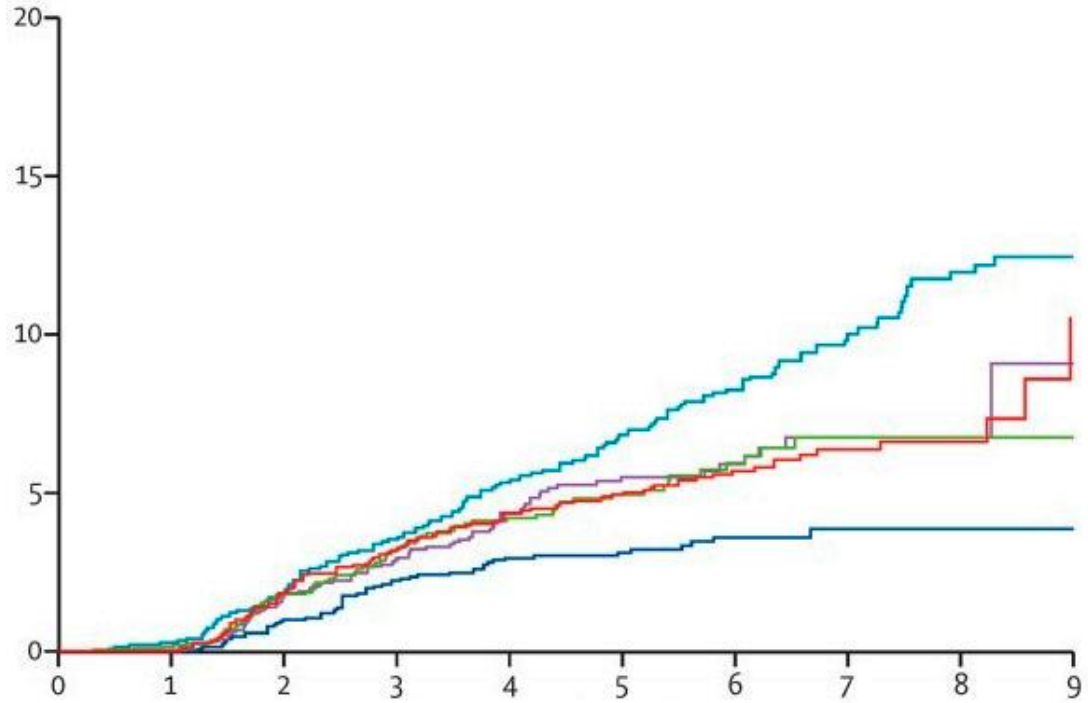
HPV16 & HPV18



HPV31, HPV33 & HPV45



Illah O, et al. *Diagnostics (Basel)* 2023;13:243., Sankaranarayanan R, et al. *Vaccine* 2018;36:4783-4791.

Cervical Cancer Elimination Initiative

- May 2018, the World Health Organization (WHO) Director-General announced a global call for action to eliminate cervical cancer, underscoring renewed political will to make elimination a reality and calling for all stakeholders to unite behind this common goal
- Cervical Cancer Elimination Initiative (https://www.who.int/initiatives/cervical-cancer-elimination-initiative) was established to develop a global strategy for the elimination of cervical cancer
- The Global Strategy for cervical cancer elimination has been adopted by the World Health Assembly in August 2020

WHO Global Strategy to Accelerate the Elimination of Cervical Cancer

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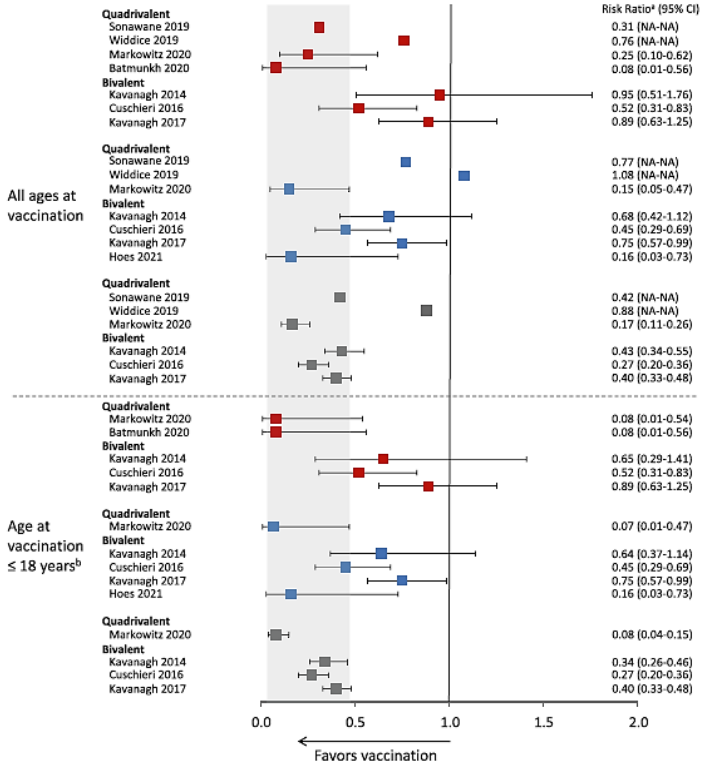
By 2030

- 90% of girls fully vaccinated with HPV vaccine by 15 years of age
- 70% of women screened using a high performance test by 35 years of age and again by 45 years of age
- 90% of women identified with cervical disease are treated

➔ **Prevent 60 million cervical cancer cases and 45 million deaths** over the next 100 years

Most observational studies indicate that three doses of HPV vaccines are most effective, with no statistically significant differences observed based on the number of doses, particularly among those vaccinated at younger ages or when longer buffer periods are used.

Against HPV infection

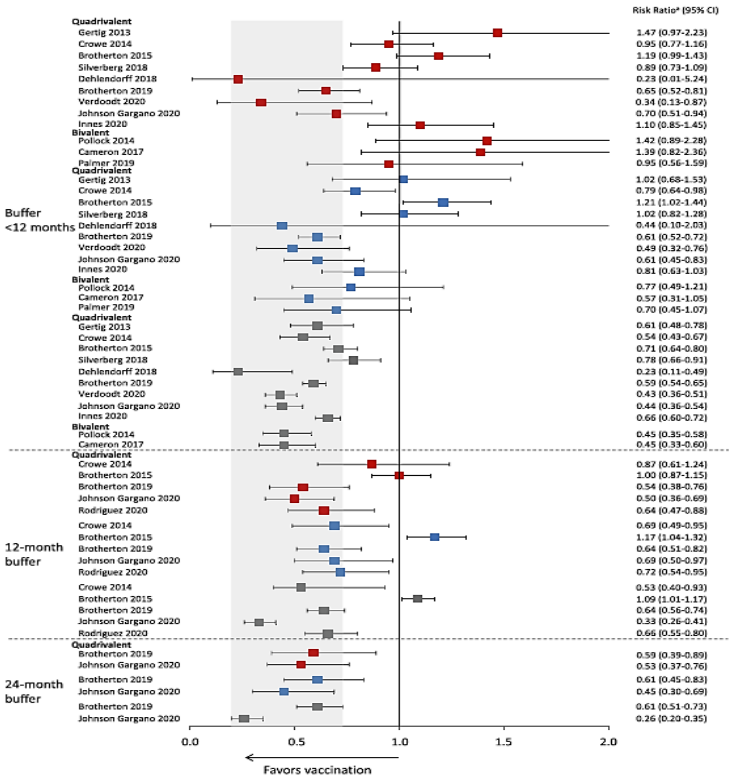


1 dose

2 doses

3 doses

Against CIN2+



An updated systematic review of evidence from clinical trials showed that the incidence or prevalence of HPV16/18 infection was very low among HPV-vaccinated participants, regardless of the number of doses received, with no evidence of a difference between dose groups.

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Incident HPV16/18 infection

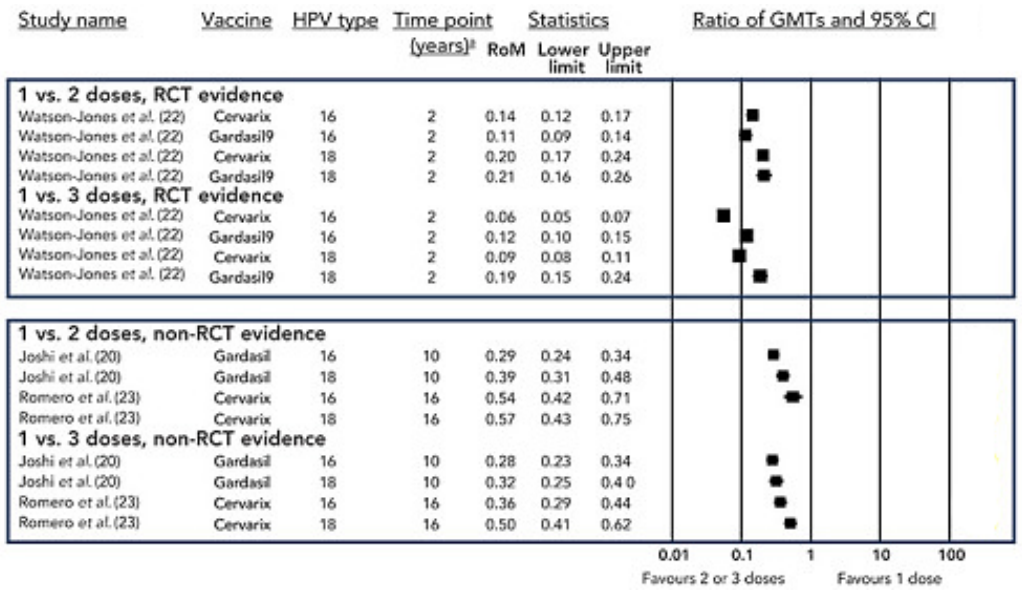
Reference / study	Follow-up duration	Infection outcome	RR or PR (95%CI), *p-value*		
			1 dose/ 3 doses	1 dose/ 2 doses	1 dose/ control
Incident HPV16/18 infection					
Kreimer 2015 / CVT & PATRICIA	Mean: 4.0y SD: 0.7y	One-time incident	0.6 (0.3–1.1) *0.12*	0.8 (0.3–1.7) *0.56*	0.2 (0.1–0.3) *<0.01*
Safaeian 2018 / CVT LTFU	Median: 6.9y IQR: 6.5-7.3y	One-time incident	0.0 (CI NC) *1.0*	. *UTC*[f]	-
		Cumulative incident	0.3 (0.1–1.4) *0.17*	0.4 (0.1–2.3) *0.36*	-
Kreimer 2020 / CVT LTFU	Median: 11.3y IQR: 10.9-11.7y	One-time incident	3.0 (0.7–14.2) *0.17*	1.1 (0.1–12.0) *1.00*	0.5 (0.1–1.9) *0.44*
Tsang 2020 / CVT LTFU	11y[b]	One-time incident	3.0 (0.6-14.0) *0.18*	1.1 (0.1-11.9) *1.00*	0.5 (0.1-1.8) *0.44*
Sankaranarayanan 2016 / IARC India Study	Median: 4.7y IQR: 4.2-5.1y	Cumulative 1st incident	3.1 (0.7–14.0) *0.17*	1.5 (0.5–4.8) *0.06*	-
Sankaranarayanan 2018 / IARC India Study	Up to 7y[f]	Cumulative incident	1.8 (0.9–3.5) *0.11*	1.8 (0.9–3.5) *0.11*	0.3 (0.2–0.4) *<0.01*
Basu 2021 / IARC India Study	Median:9.0y IQR: 8.2-9.6y	One-time incident	1.1 (0.8-1.5) *0.62*	1.2 (0.9-1.6) *0.31*	0.3 (0.3-0.4) *<0.01*

Prevalent or persistent HPV16/18 infection

Reference / study	Follow-up duration	Infection outcome	RR or PR (95%CI), *p-value*		
			1 dose/ 3 doses	1 dose/ 2 doses	1 dose/ control
Prevalent HPV16/18 infection					
Safaeian 2018 / CVT LTFU	Median: 6.9y IQR: 6.5-7.3y	One-time prevalent	0.0 (CI NC) *0.63*	0.0 (CI NC) *0.37*	0.0 (CI NC) *<0.01*
Kreimer 2020 / CVT LTFU	Median: 11.3y IQR: 10.9-11.7y	Y9 or Y11 prevalent	0.9 (0.2–3.7) *1.00*	1.1 (0.1–12.0) *1.00*	0.2 (0.04–0.7) *<0.01*
Tsang 2020 / CVT LTFU	11y	One-time prevalent	1.2 (0.3-5.1) *0.69*	0.9 (0.1-9.3) *1.00*	0.2 (0.0-0.8) *<0.01*
Persistent HPV16/18 infection					
Kreimer 2011 / CVT & PATRICIA	Median: 4.2y	6m persistent	0.0 (CI NC) *0.17*	0.0 (CI NC) *0.18*	0.0 (CI NC) *<0.01*
		12m persistent	0.0 (CI NC) *0.40*	0.0 (CI NC) *0.56*	0.0 (CI NC) *<0.01*
Kreimer 2015 / CVT	Mean: 4.0y SD: 0.7y	6m persistent	0.3 (0.0–2.4) *0.37*	0.5 (0.1–4.7) *1.00*	0.0 (0.0–0.3) *<0.01*
		12m persistent	0.5 (0.1–3.2) *0.72*	0.7 (0.1–6.7) *1.00*	0.1 (0.0–0.4) *<0.01*
Tsang 2020 / CVT LTFU	11y	6m persistent	0.0 (CI NC) *1.00*	. *UTC*[f]	0.0 (CI NC) *0.26*
Barnabas 2022 /KEN-SHE	1.5y	6m persistent	-	-	0.0 (0.0-0.2) *<0.01*
Sankaranarayanan 2018 / IARC India Study	Up to 7y	12m persistent	0.0 (CI NC) *0.39*	. *UTC*	0.0 (CI NC) *<0.01*
Basu 2021 / IARC India Study	Median:9.0y IQR: 8.2-9.6y	10m persistent	0.7 (0.0-10.9) *0.79*	0.7 (0.0-10.9) *0.78*	0.0 (0.0-0.1) *<0.01*
Barnabas 2022 / KEN-SHE	1.5y	6m persistent	-	-	0.0 (0.0-0.2) *<0.01*

Adapted from: Whitworth HS, et al. *Vaccine X* 2024;19:100486.

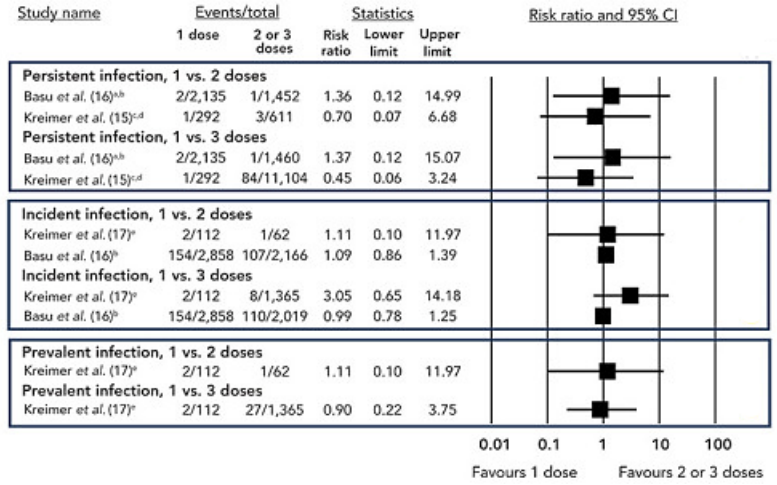
Although antibody levels against HPV vaccine types were statistically significantly lower with a single dose schedule compared to 2 or 3 doses, titers were sustained for up to 16 years. Additionally, 1-, 2-, or 3-dose HPV vaccine schedule may offer similar protection from HPV infection.



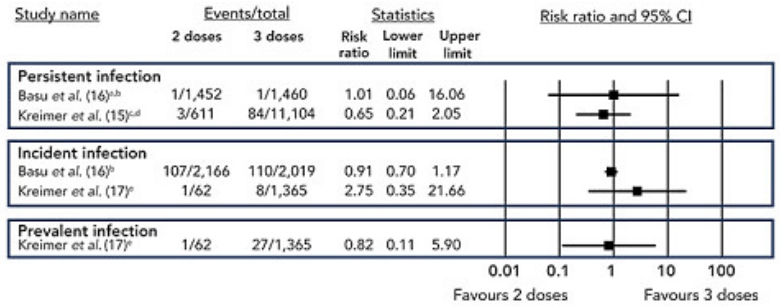
Ratio of geometric mean titers comparing 1 dose to either 2 or 3 doses

Risk ratios for persistent, prevalent and incident HPV infections

1 dose VS. 2 or 3 doses



2 doses VS. 3 doses



HPV vaccines: WHO Recommendation

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Target groups

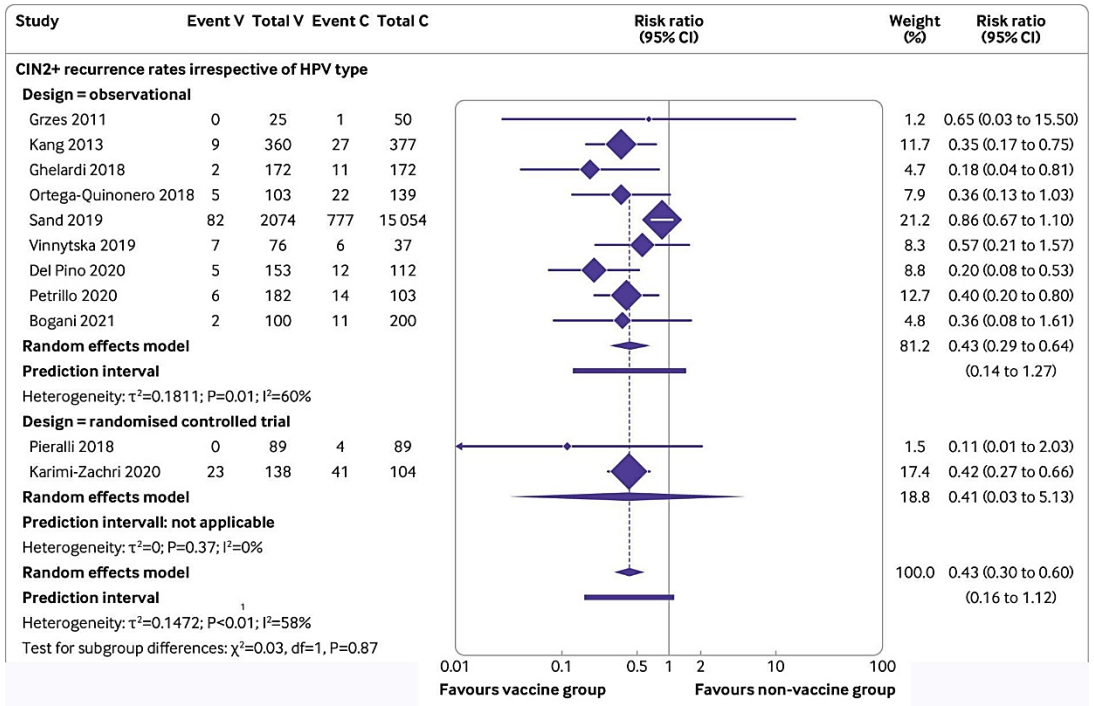
- Primary: girls aged 9-14 years before they become sexually active
- Secondary: women aged ≥15 years, boys, older men or men who have sex with men

Vaccination schedule

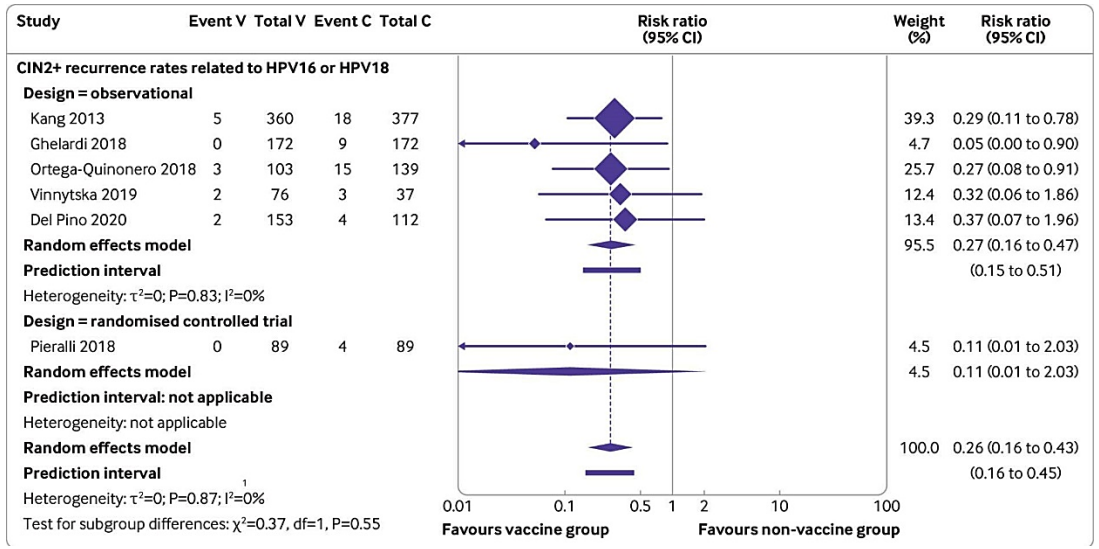
- One or two-dose schedule (6-month interval) for girls and young women aged 9-20 years
- Two doses with a 6-month interval for women aged ≥21 years
- Immunocompromised individuals (including people with HIV): 3 doses if feasible, and if not at least 2 doses

The risk of recurrence of CIN2+ after local surgical treatment was reduced in individuals who were vaccinated compared with those who were not vaccinated (RR 0.43).
The effect was stronger when CIN2+ related to HPV16 or HPV18 (RR 0.26).

Any HPV



HPV16 or HPV18



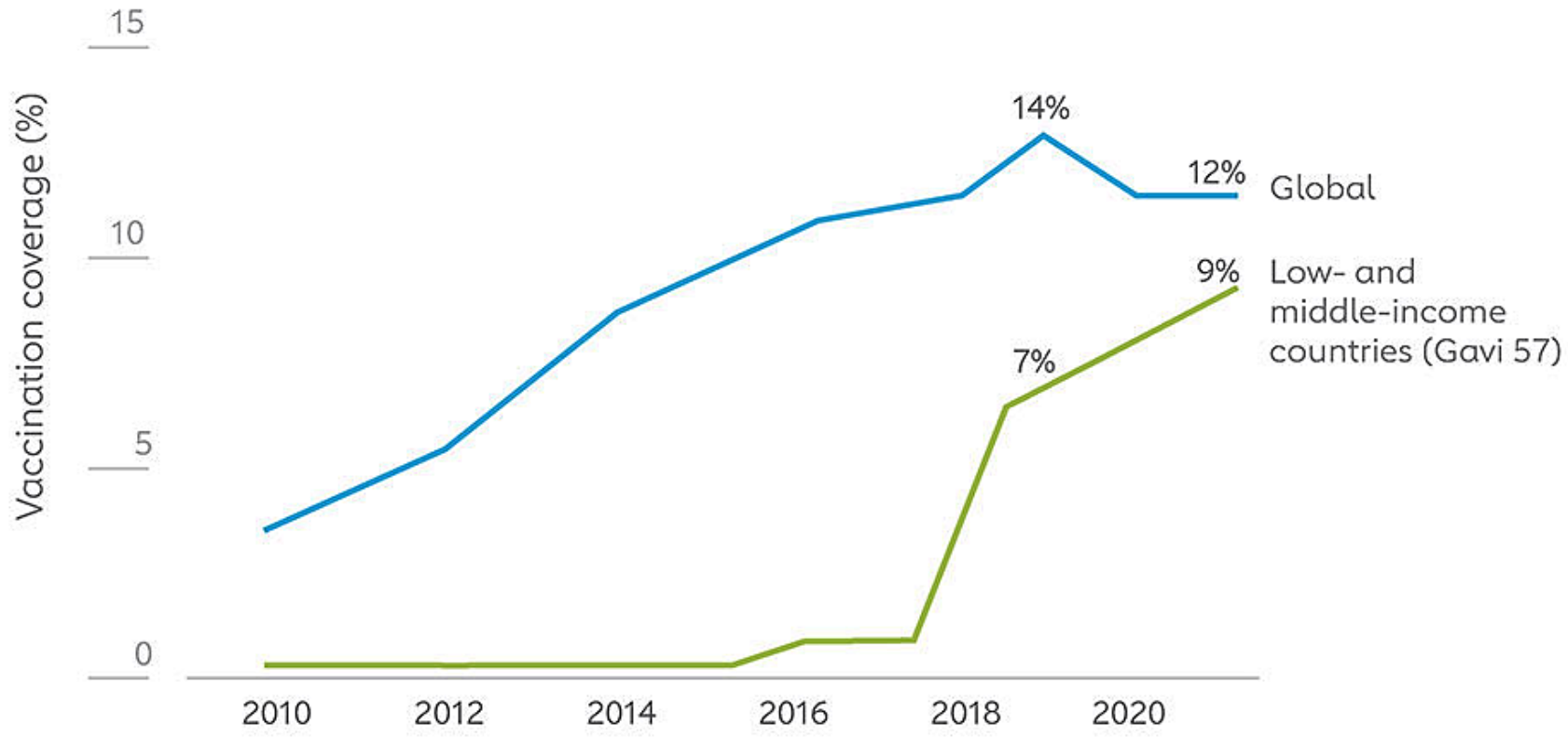
ACOG Practice Advisory, July 2023

Consider adjuvant HPV vaccination for

immunocompetent previously unvaccinated people aged 27-45 years

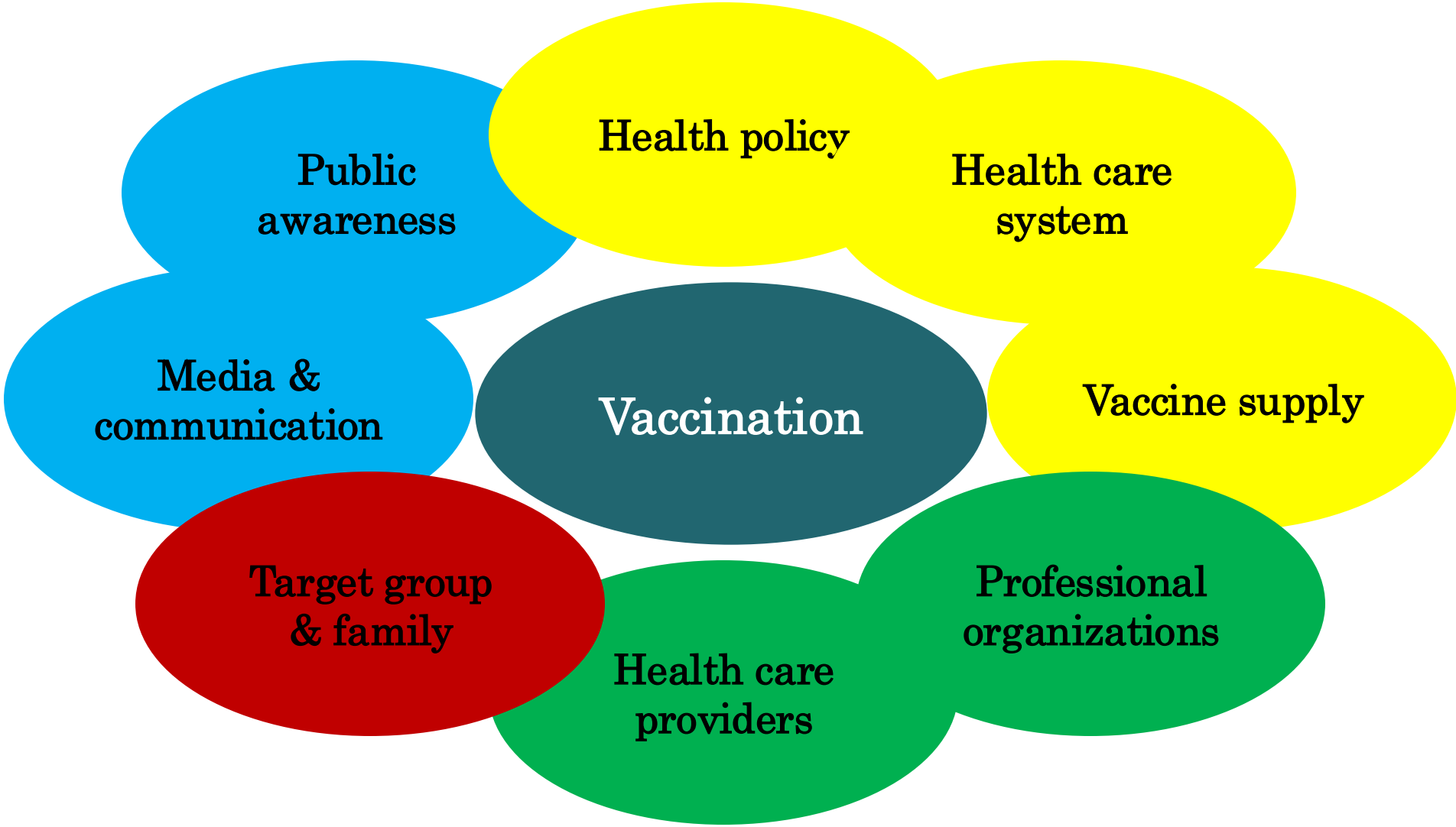
who are undergoing treatment for CIN 2+

HPV vaccination coverage, 2010-2021



https://www.gavi.org/vaccineswork/five-charts-15-years-hpv-vaccine

The implementation of vaccination requires the involvement of multiple stakeholders.



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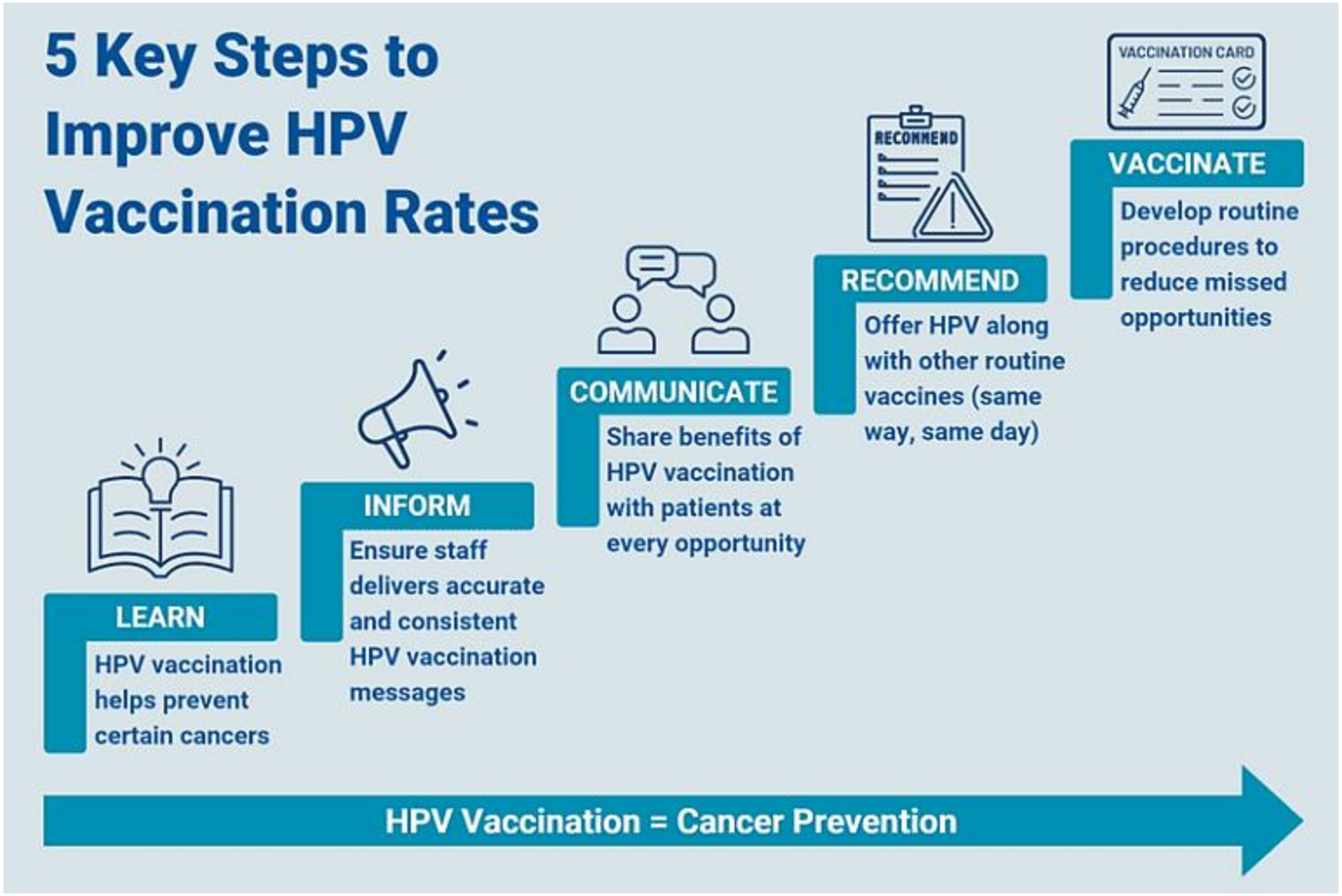

https://www.nfid.org/resource/5-key-steps-to-improve-hpv-vaccination-rates/

FIGO Statement

- FIGO is a partner on the Cervical Cancer Elimination Initiative and endorsed the Statement on Eliminating Cervical Cancer (https://www.figo.org/statement-eliminating-cervical-cancer) in January 2020
- Expert FIGO representatives actively contribute to the WHO's work in accelerating cervical cancer elimination. In addition, FIGO members are embedded on the frontlines of global health, and committed to solving the preventable tragedy of cervical cancer by 2030.

FIGO Resources

- Descamps P, Dixon S, Bosch Jose FX, et al. Turning the tide-Recommendations to increase cervical cancer screening among women who are underscreened. *Int J Gynecology and Obstetrics* 2024;166 Suppl 1:3-21. (https://obgyn.onlinelibrary.wiley.com/doi/10.1002/ijgo.15600)
- Amaral E, Cain JM, Hearing F, et al. FIGO guidance for sustainable implementation of vaccination programs for women: Pregnancy and HPV. *Int J Gynecology and Obstetrics* 2023;162 Suppl 1:3-23. (https://obgyn.onlinelibrary.wiley.com/doi/full/10.1002/ijgo.14894)
- Wilailak S, Kengsakul M, Kehoe S. Worldwide initiatives to eliminate cervical cancer. *Int J Gynecology and Obstetrics* 2021;155 Suppl 1:102-6. (https://obgyn.onlinelibrary.wiley.com/doi/10.1002/ijgo.13879)
- Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri: 2021 update. *Int J Gynecology and Obstetrics* 2021;155 Suppl 1:28-44. (https://obgyn.onlinelibrary.wiley.com/doi/10.1002/ijgo.13865)
- Simelela PN. WHO global strategy to eliminate cervical cancer as a public health problem: An opportunity to make it a disease of the past. *Int J Gynecology and Obstetrics* 2021;152:1-3. (https://obgyn.onlinelibrary.wiley.com/doi/10.1002/ijgo.13484)

Take home message

- HPV vaccines provide robust protection against common high risk HPV, reducing the risk of cervical and other HPV-related cancers
- Extensive research and real-world data continue to affirm the safety and effectiveness of HPV vaccines
- Girls <15 years are the primary target group for HPV vaccination to accelerate the elimination of cervical cancer
- One or two-dose schedule (6-month interval) for girls and young women aged 9-20 years and two-dose schedule for women aged ≥21 years are recommended