From Cervical Cancer to HPV-related Oropharyngeal Cancer: The Expanding Role of HPV Vaccination in Cancer Prevention

Evidence • Clinical counseling • Public health implementation

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HPV-ATTRIBUTABLE CANCER

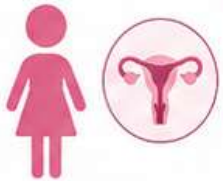
The core thesis

One of the clearest examples of a vaccine as population-level cancer prevention.

From Cervical Cancer Prevention to Broad Cancer Prevention Strategy for All Genders

Elimination requires vaccination plus screening and treatment—not vaccination alone

1. Epidemiologic shift



- Cervical cancer burden has declined with screening and early vaccination programs.
- At the same time, HPV-related oropharyngeal cancer has risen markedly, especially in middle-aged men.

- In the United States, oropharyngeal cancer is now the most common HPV-associated cancer among males.
- HPV—especially type 16—is a major driver of this disease.

Female-only focus → All-gender, multi-site cancer prevention

2. Why vaccination is essential

- Cervical cancer has established screening tools (Pap test and HPV testing).

- Oropharyngeal cancer has no approved, standardized routine screening program.

- Early lesions are often hidden in the tonsils and base of tongue.

- Therefore, vaccination is the key primary prevention strategy.

No reliable screening → prevention must begin before infection.

3. Policy expansion: Gender-neutral vaccination

- Gender-neutral vaccination protects boys directly against HPV-related cancers.

- It also strengthens herd immunity and helps reduce transmission.

- Protection extends beyond cervical cancer to oropharyngeal, anal, penile, vulvar, and vaginal cancers.

- Taiwan expanded publicly funded HPV vaccination to junior-high school boys in September 2025.

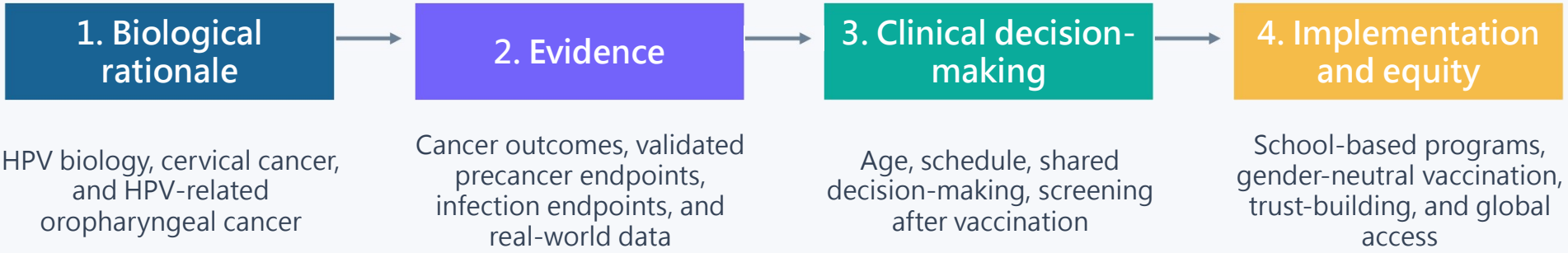
Taiwan example: boys + girls

Sources: WHO cervical cancer fact sheet 2025; CDC United States Cancer Statistics 2025/2026.

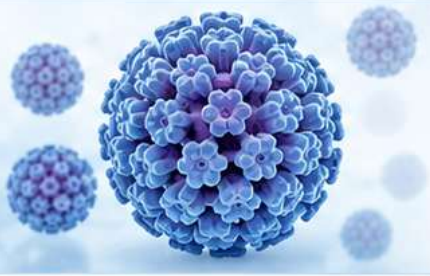
STRUCTURE

The Roadmap

Moving from disease rationale to evidence, clinical decision-making, and implementation



Recommendations should be grounded in cancer outcomes, validated precancer or infection endpoints, and implementation science.



HPV is the most common sexually transmitted infection in the United States.

Most HPV infections are asymptomatic and resolve spontaneously.

Persistent infection can lead to disease.

NATURAL HISTORY AND POTENTIAL OUTCOMES

1 HPV infection → 2 Often asymptomatic / self-limited → 3 Persistent infection → 4

- **Anogenital warts**
- **Precancers**
- **Cancers**
  - Cervical cancer *(emphasized in women)*
  - Anogenital cancers
  - Oropharyngeal cancers

These outcomes can occur in women and men.

Cervical cancer is a key HPV-related cancer in women.

KEY MILESTONES IN HPV DISCOVERY AND PREVENTION

>100 years ago	1960s	Early 1980s	1990s	More recently	2006	2009	2014
Possible link between cervical cancer and sexual behavior suspected	Epidemiologic studies established the association	HPV DNA identified in cervical cancer cells	Consistent epidemiologic evidence linked HPV and cervical cancer	HPV recognized as a cause of other mucosal cancers	Quadrivalent vaccine licensed in the United States	Bivalent vaccine licensed	9-valent vaccine licensed

Source: CDC Chapter 11: Human Papillomavirus.

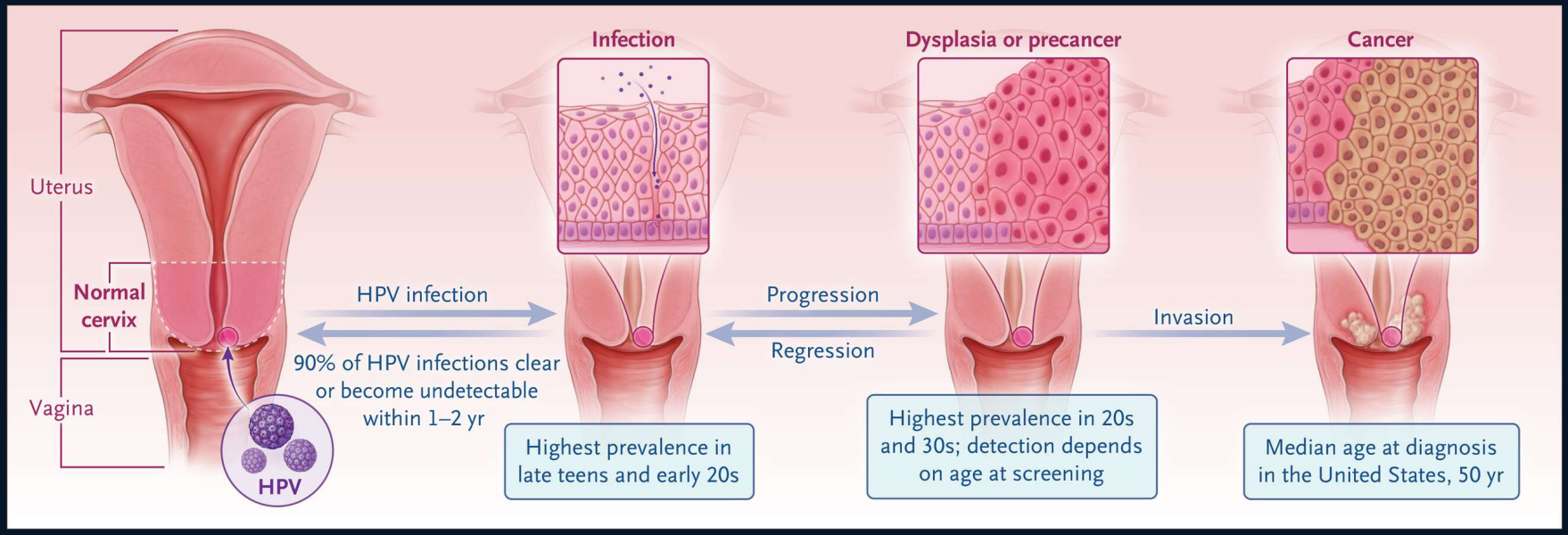
HPV CARCINOGENESIS

The biology: vaccination prevents infection before the carcinogenic cascade begins

Vaccine-induced neutralizing antibodies block HPV entry into basal epithelial cells.

Cervical carcinogenesis typically evolves over 15–20 years; immunocompromise can accelerate progression.

Exposure mucosal HPV → Persistent infection high-risk HPV → Oncoproteins E6/E7 → Precancer CIN2/3 or AIS → Cancer cervical / HPV-related oropharyngeal

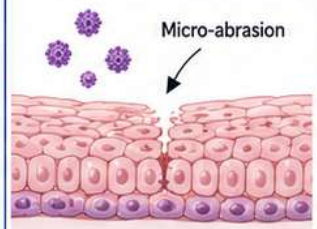


Sources: WHO HPV and cancer fact sheet; CDC HPV vaccination guidance; Schiffman et al., Lancet 2007; NCI cervical cancer prevention. Markowitz LE, Unger ER. Human Papillomavirus Vaccination. N Engl J Med. 2023;388(19):1790-1798. doi:10.1056/NEJMcp2108502

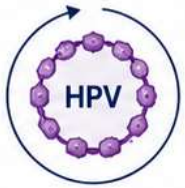
Mechanism of HPV Carcinogenesis and Prevention by Vaccination

HPV CARCINOGENESIS: FROM EXPOSURE TO INVASIVE CANCER

1 HPV exposure at mucosal epithelium

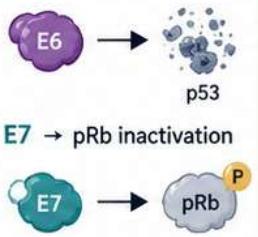


2 Persistent high-risk HPV infection

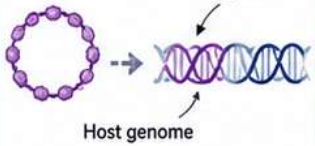


Key gateway to carcinogenesis

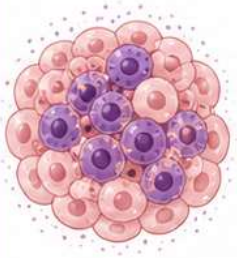
3 Sustained E6/E7 oncogene expression



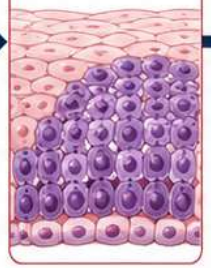
4 Viral DNA integration: frequent and important, especially in cervical cancer, but not obligatory



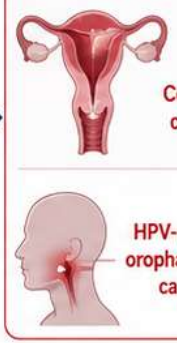
5 Genomic instability and clonal expansion



6 Cervical precancer: CIN2/3 or AIS



7 Invasive cancer



Most infections are transient and clear within 1–2 years

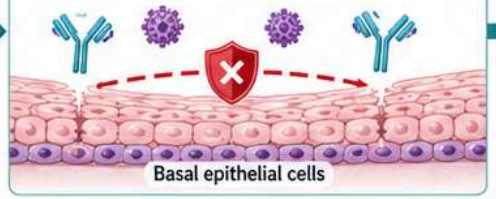
Persistent infection is the critical gateway to oncogene expression, genomic instability, and malignant transformation.

PREVENTION BY VACCINATION: BLOCKING HPV AT THE FIRST STEP

L1 virus-like particle (VLP) vaccine

Induces type-specific neutralizing antibodies

Blocks HPV entry into basal epithelial cells



Prevents establishment of vaccine-type infection and persistent infection

Most effective before HPV exposure

Does not clear established infection or treat existing precancer/cancer

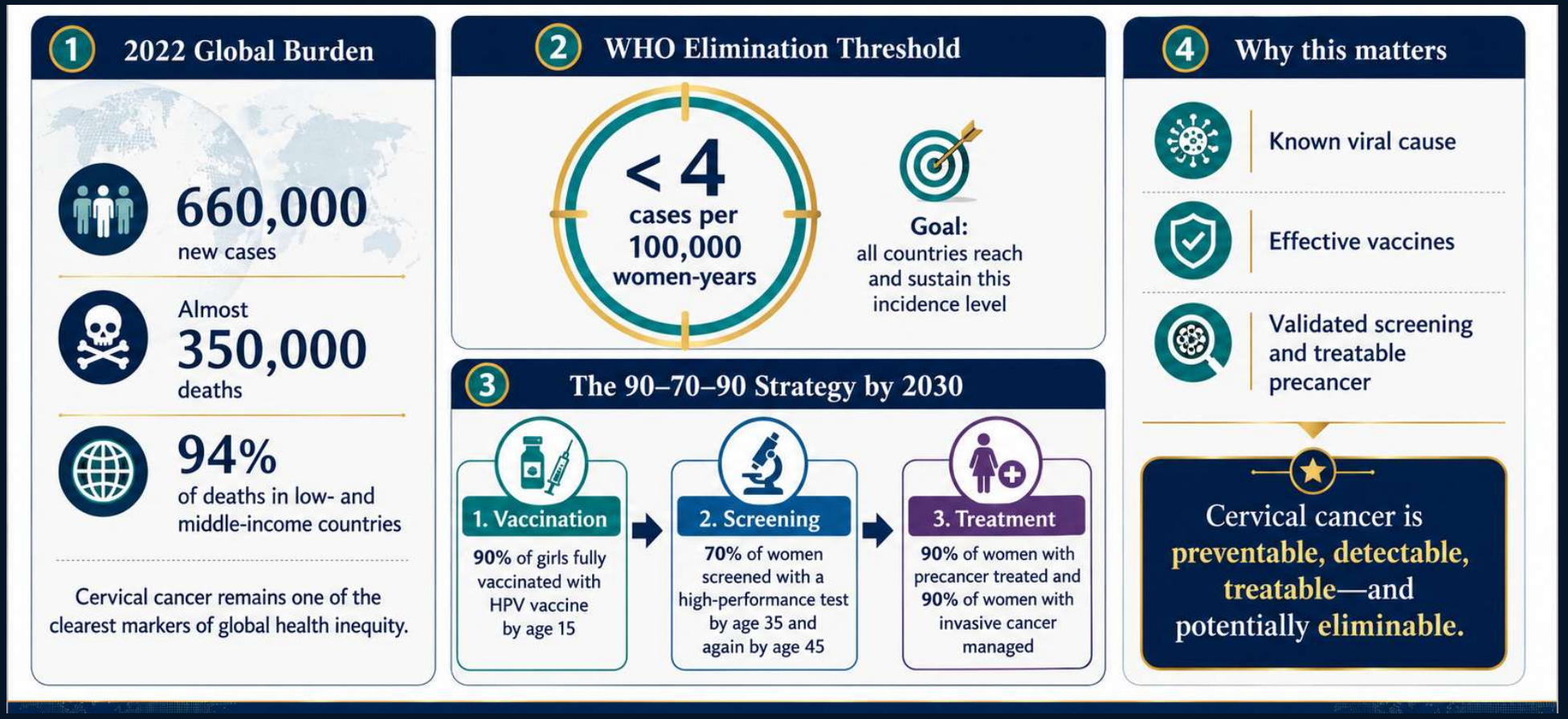
KEY MESSAGE: HPV vaccination acts before persistent infection and malignant transformation.

CAUTION: Integration is common in HPV-driven carcinogenesis, but not universal.

GLOBAL BURDEN

Cervical cancer: a preventable cancer with unacceptable inequity

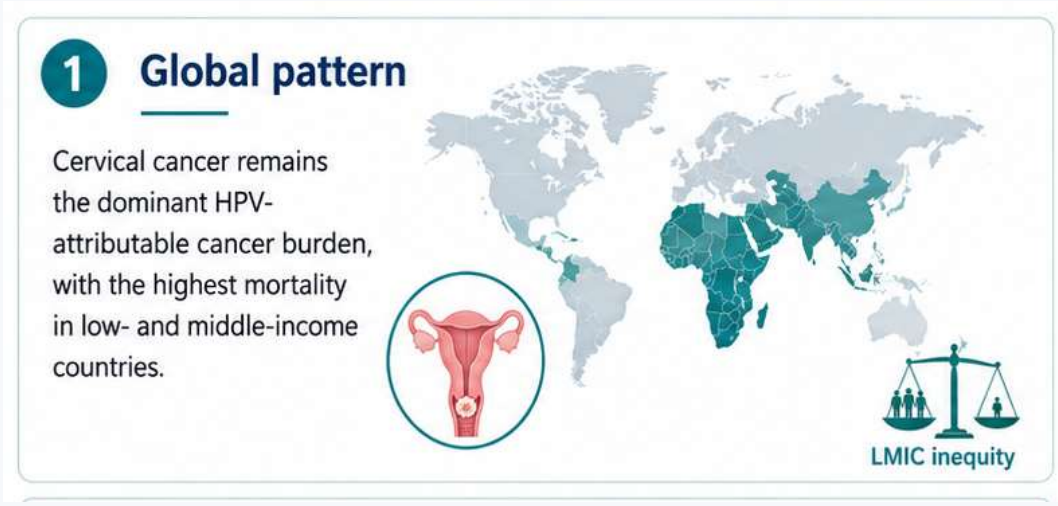
The disease remains common where vaccination, screening, and treatment are least available.



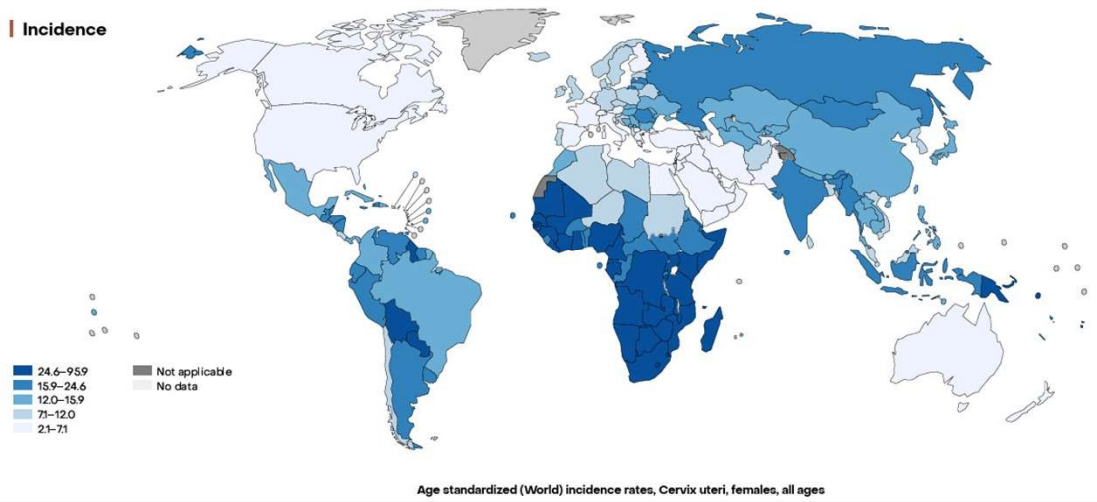
Source: WHO cervical cancer fact sheet, updated Dec 2025.

GLOBAL BURDEN

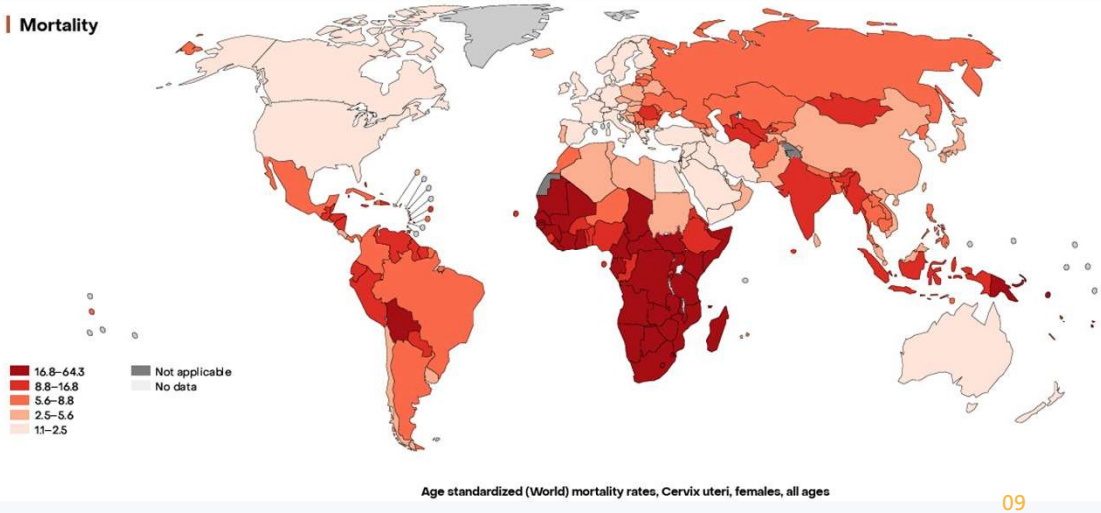
HPV cancer burden



- The HPV cancer burden is not uniform across the world.
- Globally, cervical cancer remains the dominant HPV-attributable cancer and the clearest target for elimination. The burden is concentrated in low- and middle-income countries, where access to vaccination, screening, diagnosis, and treatment remains limited.
- Asia carries a large absolute burden of cervical cancer.



Age standardized (World) incidence rates, Cervix uteri, females, all ages



Age standardized (World) mortality rates, Cervix uteri, females, all ages

GLOBAL BURDEN

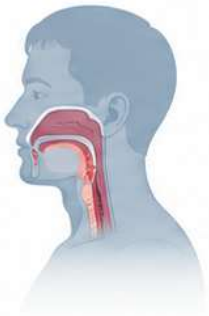
HPV cancer burden

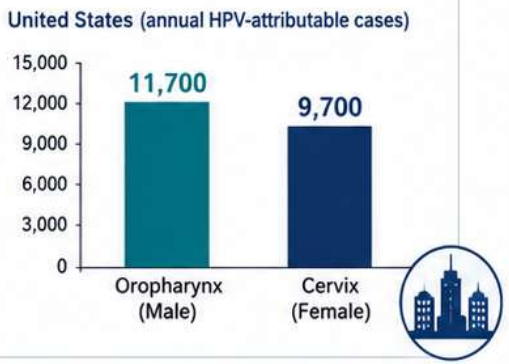
~397k
new cervical cancer cases in 2022

~200k
cervical cancer deaths in 2022

2 High-income country pattern

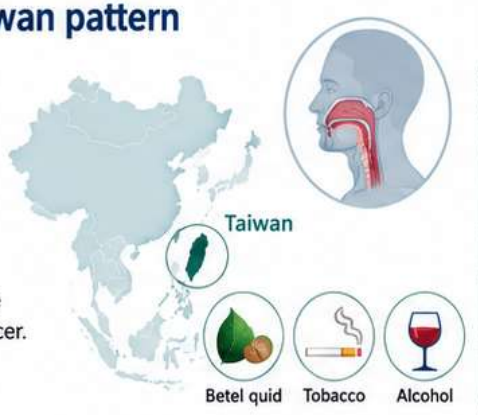
HPV-related oropharyngeal cancer is an emerging male cancer burden and, in the United States, exceeds cervical cancer in estimated HPV-attributable annual cases.





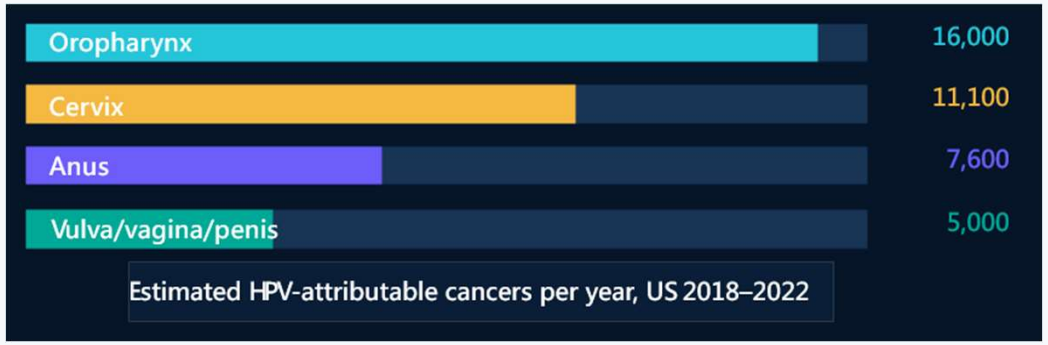
3 Asia and Taiwan pattern

Asia carries a large absolute burden of cervical cancer. In Taiwan, head and neck cancer burden is high, but much of it is driven by betel quid, tobacco, and alcohol; HPV-related OPSCC is increasing but should not be equated with oral cavity cancer.



HPV-related OPSCC is not the same as oral cavity cancer.

- In high-income countries, a different pattern has emerged.
- HPV-related oropharyngeal cancer has become a major male cancer burden, and in the US it now exceeds cervical cancer in estimated HPV-attributable annual case counts.



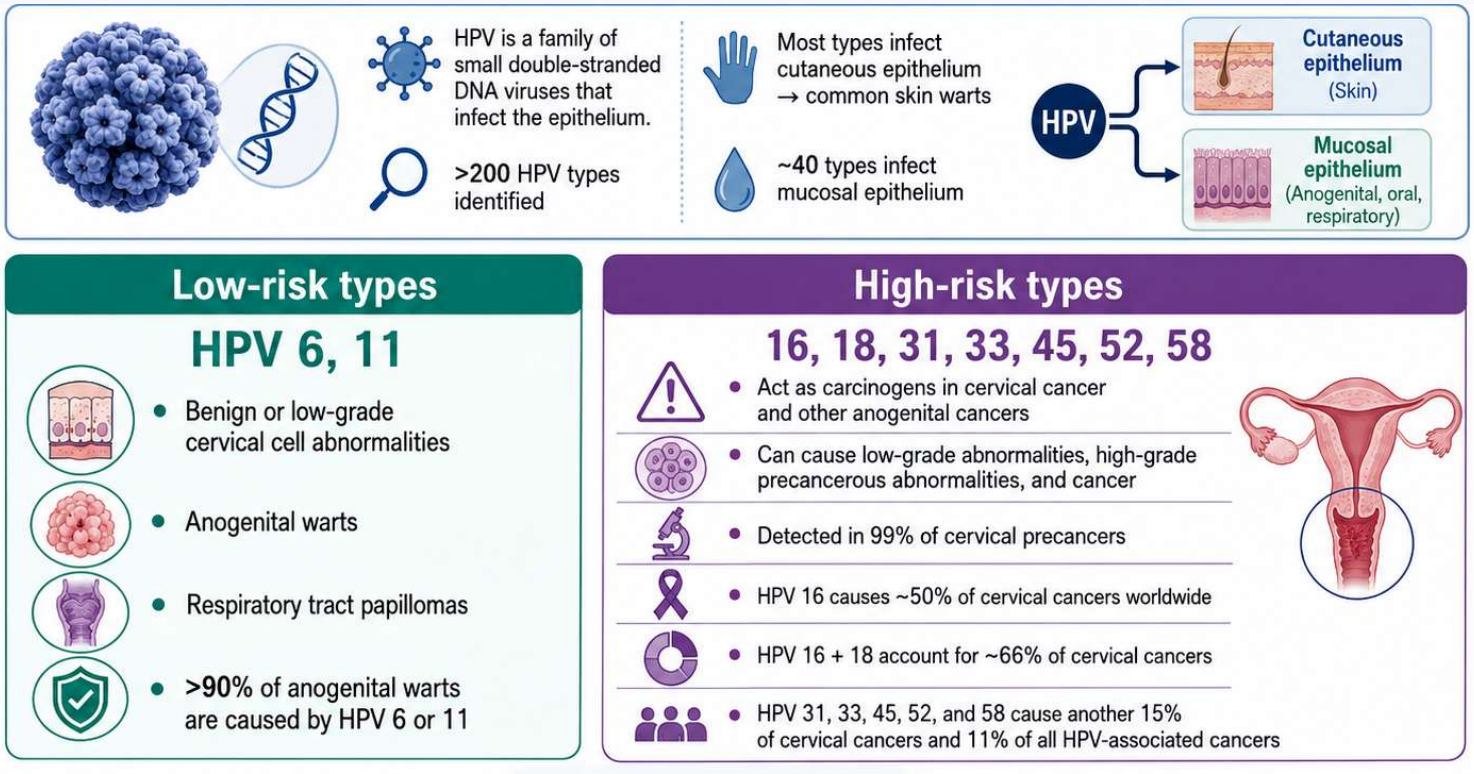
- Asia and Taiwan: **cervical cancer** remains central, while **HPV-related OPSCC** is emerging
- Asia carries a large absolute burden of **cervical cancer**

- **Taiwan: dual-burden pattern.**
  - Cervical cancer remains a measurable prevention target
  - Head-and-neck cancer burden is high, but much is driven by **betel quid, tobacco, and alcohol**.
  - **HPV-positive OPSCC** is rising, and Taiwan has moved toward gender-neutral school-based HPV vaccination.

Source: CDC Cancers Associated with HPV, Apr 2026; CDC Cancers Linked with HPV Each Year, Dec 2025.

VACCINE FORMULATIONS

What the vaccines cover



Bivalent

16, 18

Core cervical cancer types

Quadrivalent

6, 11, 16, 18

+ genital wart types

Nonavalent

6, 11, 16, 18, 31, 33, 45, 52, 58

Source: CDC Chapter 11: Human Papillomavirus.

IMMUNOLOGY

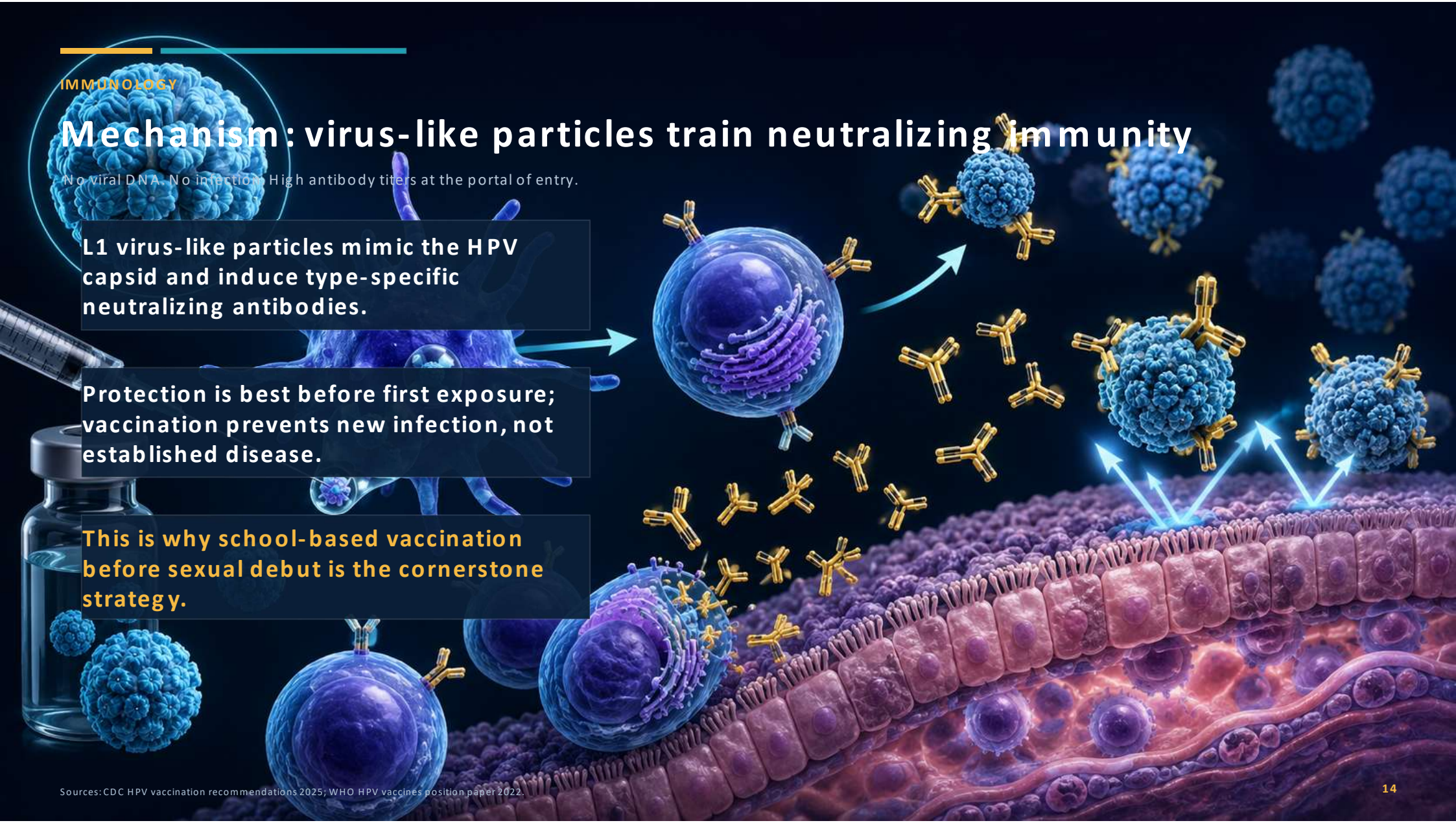
Mechanism: virus-like particles train neutralizing immunity

No viral DNA. No infection. High antibody titers at the portal of entry.

L1 virus-like particles mimic the HPV capsid and induce type-specific neutralizing antibodies.

Protection is best before first exposure; vaccination prevents new infection, not established disease.

This is why school-based vaccination before sexual debut is the cornerstone strategy.

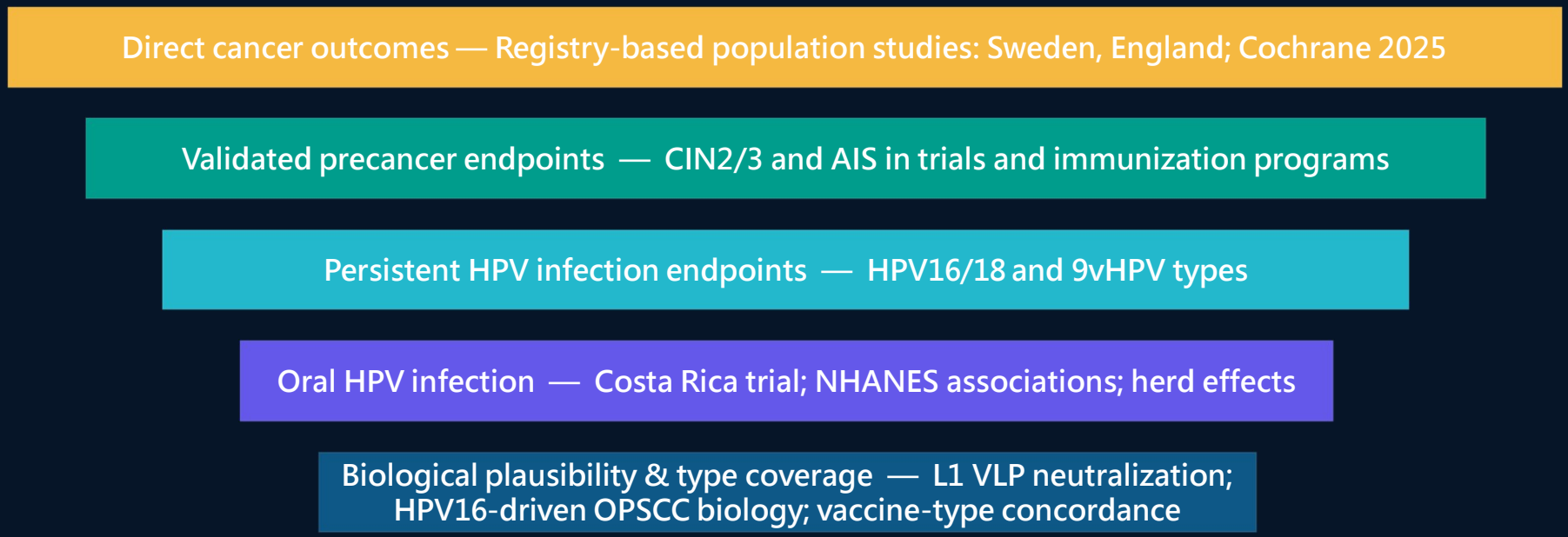


Sources: CDC HPV vaccination recommendations 2025; WHO HPV vaccines position paper 2022.

EVIDENCE HIERARCHY

Evidence map: cervical cancer is the model; oropharynx is the emerging frontier

The question is not whether HPV causes cancer; the question is which endpoint we can observe today.



Cervical cancer prevention has mature cancer and precancer endpoints.

HPV-related OPSCC prevention is biologically coherent and increasingly supported, but cancer-outcome evidence will take longer to mature.

Sources: Lei et al., NEJM 2020; Falcaro et al., Lancet 2021; Herrero et al., PLoS ONE 2013; Chaturvedi et al., JAMA 2018; CDC.

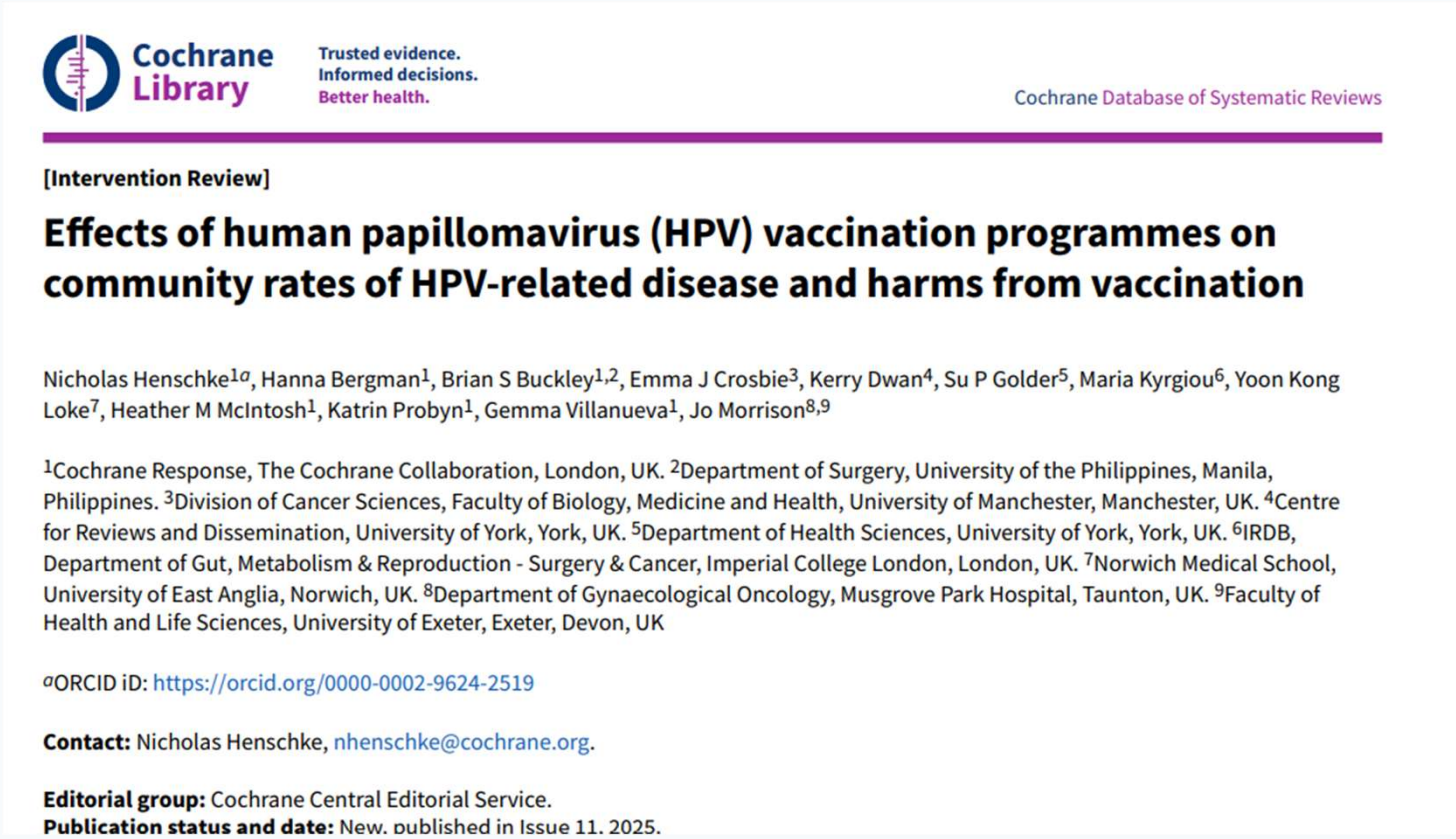
COCHRANE 2025 · POPULATION-LEVEL EVIDENCE

HPV vaccination programmes: Cochrane 2025 evidence summary

GRADE: MODERATE*

KEY AGE ≤16 YEARS

Systematic review of 225 studies including >132 million people; evidence current to September 2024.



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[Intervention Review]

Effects of human papillomavirus (HPV) vaccination programmes on community rates of HPV-related disease and harms from vaccination

Nicholas Henschke[1a], Hanna Bergman[1], Brian S Buckley[1,2], Emma J Crosbie[3], Kerry Dwan[4], Su P Golder[5], Maria Kyrgiou[6], Yoon Kong Loke[7], Heather M McIntosh[1], Katrin Probyn[1], Gemma Villanueva[1], Jo Morrison[8,9]

[1]Cochrane Response, The Cochrane Collaboration, London, UK. [2]Department of Surgery, University of the Philippines, Manila, Philippines. [3]Division of Cancer Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK. [4]Centre for Reviews and Dissemination, University of York, York, UK. [5]Department of Health Sciences, University of York, York, UK. [6]IRDB, Department of Gut, Metabolism & Reproduction - Surgery & Cancer, Imperial College London, London, UK. [7]Norwich Medical School, University of East Anglia, Norwich, UK. [8]Department of Gynaecological Oncology, Musgrove Park Hospital, Taunton, UK. [9]Faculty of Health and Life Sciences, University of Exeter, Exeter, Devon, UK

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Editorial group: Cochrane Central Editorial Service.
Publication status and date: New, published in Issue 11, 2025.

*Moderate-certainty evidence for cervical cancer, CIN3+/CIN2+, anogenital warts, and several specific harms; lower certainty for rare long-latency cancers. Source: Henschke et al., Cochrane Database Syst Rev 2025; CD015363.

COCHRANE 2025 · POPULATION-LEVEL EVIDENCE

HPV vaccination programmes: Cochrane 2025 evidence summary

GRADE: MODERATE*

KEY AGE ≤16 YEARS

Systematic review of 225 studies including >132 million people; evidence current to September 2024. **CD015363**

Review scope

- 225 **studies**
- >132M **people**
- 86 cohort studies
- 69 pre–post studies

Focus of meta-analysis: adjusted estimates, especially vaccination at or **before age 16.**

Cervical cancer

RR 0.20

(95% CI 0.09 to 0.44; I^2 = 69%)

≈80% lower risk among those vaccinated ≤16 years

CIN3+

RR 0.26

(95% CI 0.12 to 0.56; I^2 = 80%)

≈74% lower incidence in long-term cohort evidence

Anogenital warts

RR 0.47

(95% CI 0.36 to 0.61; I^2 = 99%)

≈53% lower long-term incidence in pooled cohort data

- Long-term outcome that consistently report a reduction in the development of **high-grade CIN and cervical cancer** in females vaccinated against HPV in **early adolescence**
- Greater benefit to vaccinating younger adolescents prior to **becoming sexually active**
- There is evidence that HPV vaccination does **not increase the risk** of the most common adverse events reported on social media

Safety signal

No increased risk was found for infertility, POTS, chronic fatigue syndrome/ME, paralysis, complex regional pain syndrome, or premature ovarian failure or infertility.

Interpret carefully

Evidence is lower-certainty for rare, long-latency HPV-related cancers beyond the cervix. No study reported community rates of serious adverse events.

Population-level evidence now supports HPV vaccination as a cancer-prevention intervention, with strongest cancer-outcome evidence for cervical cancer.

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COCHRANE 2025 · POPULATION-LEVEL EVIDENCE

HPV vaccination: a network meta-analysis

KEY AGE ≤16 YEARS

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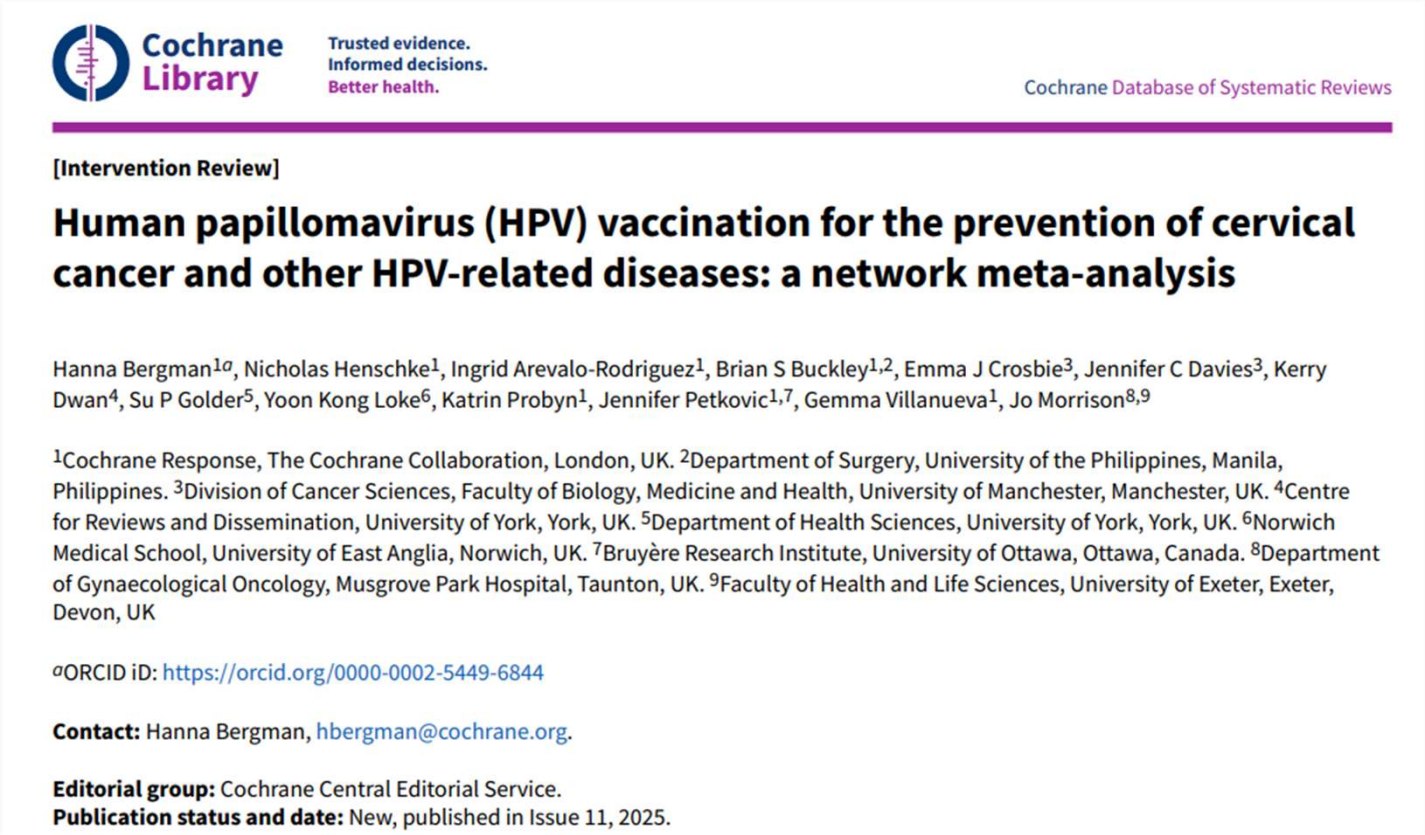

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[Intervention Review]

Human papillomavirus (HPV) vaccination for the prevention of cervical cancer and other HPV-related diseases: a network meta-analysis

Hanna Bergman[1a], Nicholas Henschke[1], Ingrid Arevalo-Rodriguez[1], Brian S Buckley[1,2], Emma J Crosbie[3], Jennifer C Davies[3], Kerry Dwan[4], Su P Golder[5], Yoon Kong Loke[6], Katrin Probyn[1], Jennifer Petkovic[1,7], Gemma Villanueva[1], Jo Morrison[8,9]

[1]Cochrane Response, The Cochrane Collaboration, London, UK. [2]Department of Surgery, University of the Philippines, Manila, Philippines. [3]Division of Cancer Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK. [4]Centre for Reviews and Dissemination, University of York, York, UK. [5]Department of Health Sciences, University of York, York, UK. [6]Norwich Medical School, University of East Anglia, Norwich, UK. [7]Bruyère Research Institute, University of Ottawa, Ottawa, Canada. [8]Department of Gynaecological Oncology, Musgrove Park Hospital, Taunton, UK. [9]Faculty of Health and Life Sciences, University of Exeter, Exeter, Devon, UK

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COCHRANE 2025 · POPULATION-LEVEL EVIDENCE

HPV vaccination: a network meta-analysis

KEY AGE ≤16 YEARS

1 STUDY DESIGN

- 60 randomized controlled trials
- 157,414 participants
- Follow-up: 7 months to 11 years
- WHO-prequalified vaccines: Cervarix, Gardasil, Gardasil-9, Cecolin
- Pairwise meta-analysis + network meta-analysis

2 MAIN EFFICACY FINDINGS (FEMALE 15–25 YEARS)

CIN2+ (all HPV types):
RR 0.70 (95% CI 0.56–0.88)

Vaccine-matched CIN2+:
RR 0.40 (95% CI 0.30–0.54)

Reduced anogenital warts:
RR 0.38 (95% CI 0.32–0.46)

Reduced treatment for HPV-related pre-invasive disease:
RR 0.76 (95% CI 0.65–0.89)

Moderate-certainty for CIN2+ outcomes; high-certainty for anogenital warts.

3 SAFETY

Serious adverse events:
RR 0.99 (95% CI 0.94–1.04)

- No increase in serious adverse events
- High-certainty evidence

4 IMPORTANT LIMITATIONS

- Trials were not long enough to assess cancer incidence
- No cancers detected in the included trials
- Very limited data for <15 years
- No studies in males <15 years or >25 years
- Most studies enrolled participants aged 15 years and older

5 BOTTOM-LINE TAKE-HOME MESSAGE

RCT evidence supports HPV vaccine efficacy against precancerous disease and anogenital warts, with no safety signal for serious adverse events. Direct cancer-outcome evidence requires longer-term population studies.

Source: Bergman et al. *Cochrane Database Syst Rev.* 2025; Issue 11: CD015364. DOI: 10.1002/14651858.CD015364.pub2.

REAL-WORLD CANCER ENDPOINTS

The decisive shift: invasive cervical cancer is reduced

Two landmark registry studies turned a prevention hypothesis into population-level cancer evidence.

Sweden

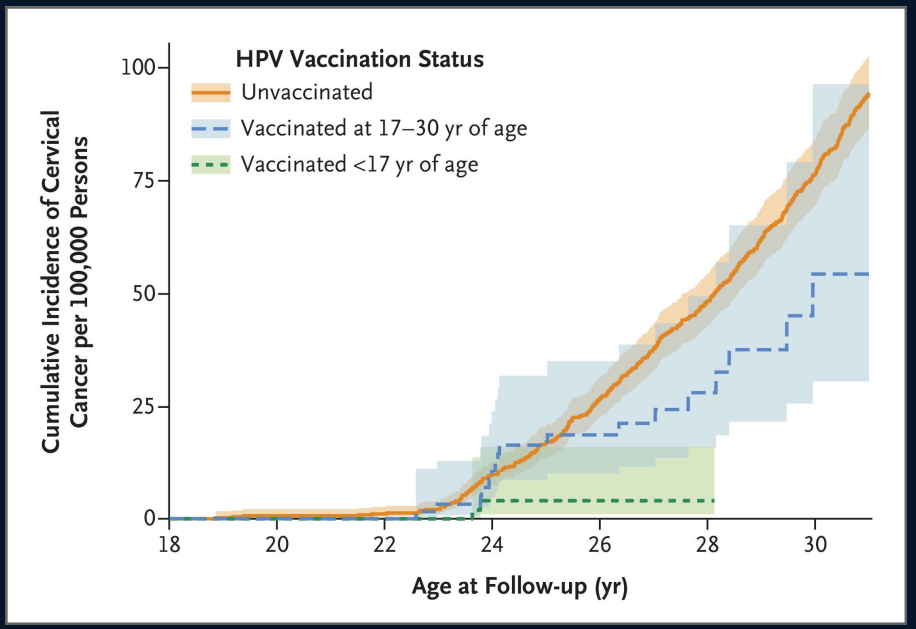
88% lower risk

vaccinated before age 17

Quadrivalent HPV vaccine associated with **lower invasive cervical cancer risk**.

Table 2. HPV Vaccination and Invasive Cervical Cancer.

HPV Vaccination Status	No. of Cases of Cervical Cancer	Crude Incidence Rate per 100,000 Person-Yr (95% CI)	Age-Adjusted Incidence Rate Ratio (95% CI)	Adjusted Incidence Rate Ratio (95% CI)*
Unvaccinated	538	5.27 (4.84–5.73)	Reference	Reference
Vaccinated	19	0.73 (0.47–1.14)	0.51 (0.32–0.82)	0.37 (0.21–0.57)
Status according to age cutoff of 17 yr				
Vaccinated before age 17 yr	2	0.10 (0.02–0.39)	0.19 (0.05–0.75)	0.12 (0.00–0.34)
Vaccinated at age 17–30 yr	17	3.02 (1.88–4.86)	0.64 (0.39–1.04)	0.47 (0.27–0.75)
Status according to age cutoff of 20 yr				
Vaccinated before age 20 yr	12	0.49 (0.28–5.73)	0.52 (0.29–0.94)	0.36 (0.18–0.61)
Vaccinated at age 20–30 yr	7	5.16 (2.46–10.83)	0.50 (0.24–1.06)	0.38 (0.12–0.72)



Sources: Lei et al. N Engl J Med 2020;383:1340–1348. DOI:10.1056/NEJMoa1917338. Wu et al. BMJ 2026;392:e087326. DOI:10.1136/bmj-2025-087326.

Swedish population-based evidence: HPV vaccination and invasive cervical cancer

Two landmark nationwide register-based cohort studies: NEJM 2020 and BMJ 2026

1 NEJM 2020

First major direct evidence of cervical cancer reduction

Population	Period	Cancer cases
1,672,983 girls and women Age 10–30 years	**2006–2017** Nationwide registry cohort	**19 vs 538** Vaccinated vs unvaccinated

Key findings

- Overall adjusted IRR: 0.37 (95% CI 0.21–0.57)
- Vaccinated before age 17: IRR 0.12
- Vaccinated at age 17–30: IRR 0.47
- Cumulative incidence by age 30: 47 vs 94 per 100,000

HPV vaccination was associated with a substantially lower risk of invasive cervical cancer, with the greatest benefit when vaccination started before age 17.

2 BMJ 2026

Extended follow-up showing durable protection

Population	Period	Cancer cases
926,362 girls and women Born 1985–2001	**2006–2023** Up to 18 years follow-up	**97 vs 833** Vaccinated vs unvaccinated

Key findings

- Overall adjusted IRR: 0.44 (95% CI 0.35–0.55)
- Vaccinated at age 10–16: IRR 0.21
- **Protection persisted 13–15 years after vaccination: IRR 0.23**
- **School-based cohort** vs opportunistic cohort: IRR 0.28 (72% ↓ risk)
- No indication of waning protection

Long-term protection remained durable, and organised school-based vaccination showed clear population-level benefit.

Overall synthesis

Together, these Swedish studies provide some of the strongest population-level evidence that HPV vaccination prevents invasive cervical cancer, works best when given early, and delivers sustained long-term benefit without evidence of waning protection.

Sources: Lei et al. N Engl J Med 2020;383:1340–1348. DOI:10.1056/NEJMoa1917338. Wu et al. BMJ 2026;392:e087326. DOI:10.1136/bmj-2025-087326.

REAL-WORLD CANCER ENDPOINTS

The decisive shift: invasive cervical cancer is reduced

Lancet 2021 register-based observational study of the bivalent Cervarix programme in England

1 Study design

- Population-based cancer registry study
- England, 2006–2019
- Outcomes: cervical cancer and CIN3
- Model: age–period–cohort Poisson regression

Vaccination

Routine vaccination: girls aged 12–13 years
Catch-up: females aged 14–18 years (2008–2010)

Coverage (3-dose

Age 12–13	Age 14–16	Age 16–18
80.9–88.0%	70.8–75.7%	38.9–48.1%

The study analysed 13.7 million person-years of follow-up among women aged 20 to younger than 30 years in vaccinated cohorts.

2 Main results

Estimated reduction in incidence vs unvaccinated cohort

Age at vaccine offer	Cervical cancer	CIN3
16–18 years	34% (95% CI 25–41)	39% (95% CI 36–41)
14–16 years	62% (95% CI 52–71)	75% (95% CI 72–77)
12–13 years	87% (95% CI 72–94)	97% (95% CI 96–98)

The strongest impact: routine school-based cohort vaccinated at age 12–13 years.

England

87% lower rate

offered vaccine at age 12–13

High-coverage school-based HPV vaccination can sharply reduce cervical cancer and CIN3 incidence in young women

Source: Falcaro M, Castañon A, Ndlela B, et al. Lancet 2021;398:2084–2092. DOI: 10.1016/S0140-6736(21)02178-4.

England HPV vaccination programme and socioeconomic inequality

BMJ 2024 population-based observational study: sustained effectiveness through mid-2020 and impact across deprivation groups

1 Study design

- England, 2006/01/01–2020/06/30
- Population-based observational study
- Outcomes: invasive cervical cancer and CIN3

Table 5 | Estimated cohort specific numbers of invasive cervical cancers predicted and prevented by mid-2020 among women in the least and most deprived areas

	Predicted No of invasive cervical cancers* (95% CI)			Predicted rates per 100 000 women years			
	Scenario A: counterfactual	Scenario B: factual	Difference: scenarios A-B†	Scenario A: counterfactual	Scenario B: factual	Difference: scenarios A-B	% of cancers prevented: (A-B)/A
Cohort 5 (offered vaccine at age 16-18)							
Index of multiple deprivation (fifths):							
1st (most deprived)	331 (304 to 358)	234 (205 to 263)	97 (58 to 137)	14.8	10.4	4.3	29.4
5th (least deprived)	107 (98 to 116)	80 (63 to 96)	27 (9 to 46)	8.5	6.3	2.2	25.6
Cohort 6 (offered vaccine at age 14-16)							
Index of multiple deprivation (fifths):							
1st (most deprived)	105 (94 to 115)	33 (26 to 40)	71 (59 to 84)	11.0	3.5	7.5	68.3
5th (least deprived)	38 (34 to 42)	13 (9 to 16)	25 (20 to 30)	6.5	2.2	4.3	66.8
Cohort 7 (offered vaccine at age 12-13)							
Index of multiple deprivation (fifths):							
1st (most deprived)	27 (24 to 31)	4 (2 to 7)	23 (19 to 27)	3.0	0.5	2.6	84.6
5th (least deprived)	10 (9 to 12)	2 (1 to 3)	9 (7 to 10)	1.8	0.3	1.5	83.5

Results are reported under two scenarios: one as observed in the dataset (scenario B: factual) and one hypothetical where women had not been offered the HPV vaccination (scenario A: counterfactual).
CI=confidence interval; HPV=human papillomavirus.
*Numbers rounded to nearest integers.
†Difference may not equal scenarios A–B due to rounding.

burden?

2 Main results

Routine vaccination cohort (offered at age 12–13 years)

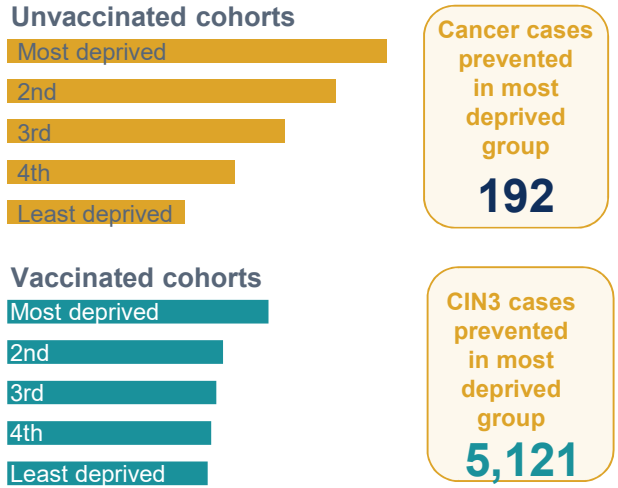
Cervical cancer reduction | CIN3 reduction

12–13 y	**86.0%**	**95.9%**

3 Equity impact

Before vaccination, England had a strong social gradient in cervical cancer incidence, with the highest rates in the most deprived women. HPV vaccination substantially reduced disease in all five deprivation groups.

Cervical cancer incidence gradient



Programme reduced cervical cancer and CIN3 across all socioeconomic groups and helped level the cervical cancer inequality gradient.

Source: Falcaro M, Soldan K, Ndlela B, Sasieni P. BMJ 2024;385:e077341. DOI: 10.1136/bmj-2023-077341.

Single-dose HPV vaccination: durable efficacy and noninferiority evidence

KEN SHE 3-year RCT and ESCUDDO 5-year noninferiority trial support dose simplification for scalable cervical cancer prevention

Evidence question
Can one dose protect?

→ **Clinical endpoint used**
Persistent HPV infection

→ **Policy relevance**
Coverage, supply, equity

→ **Implication: fewer doses may accelerate implementation**

1 KEN SHE trial — Kenya

Single dose versus control; randomized, double-blind, controlled trial

Participants	Follow-up	Trial arms
2,275	**36 mo**	**9v / 2v / control**
women aged 15–20	median 35 months	1:1:1 allocation

Primary endpoint

Incident-persistent vaccine type-specific cervical HPV infection

HPV16/18: nonavalent	HPV16/18: bivalent	9v high-risk types
98.8%	**97.5%**	**95.5%**
95% CI 91.3–99.8	95% CI 90.0–99.4	95% CI 89.0–98.2

No severe adverse events; efficacy remained durable through 3 years.

2 ESCUDDO trial — Costa Rica

One dose versus two doses; randomized, double-blind, noninferiority trial

Participants	Follow-up	Trial groups 1:1:1:1
20,330	**5 yr**	**1-dose or 2-dose**
girls aged 12–16	month 12–60 endpoint	bivalent or nonavalent

Primary endpoint

New HPV16/18 infection persisting ≥6 months from month 12 to month 60

Bivalent 1 vs 2 doses	Nonavalent 1 vs 2 doses	Vaccine Effectiveness, VE
−0.13/100	**0.21/100**	**≥97%**
95% CI −0.45 to 0.15	95% CI −0.09 to 0.51	in each trial group

One dose was noninferior to two doses for both bivalent and nonavalent vaccines

WHO schedule one or two dose for aged 9-14 and 15-20 years.
Immunocompromised people and people living with HIV generally require at least two doses, and often three where feasible

Sources: Barnabas et al. Nature Medicine 2023;29:3224–3232. Kreimer et al. NEJM 2025;393:2421–2433.

DOSE SIMPLIFICATION

Why can a single dose work? The immunology behind durable HPV protection

1. **Virus-like particles create a strong immune signal:**
   HPV vaccines use L1 virus-like particles that mimic the native viral capsid but contain no viral DNA. This ordered structure makes the vaccine highly immunogenic.
2. **Repetitive epitopes trigger potent B-cell activation:**
   The dense, repetitive surface of VLPs promotes B-cell receptor crosslinking, generating a strong neutralizing antibody response even after one dose.
3. **Long-lived plasma cells sustain antibody production:**
   Single-dose vaccination can induce durable antibody responses, with antibody levels stabilizing after the first year and persisting over time.
4. **HPV is highly susceptible to antibody neutralization:**
   HPV infection can be blocked at the mucosal surface by neutralizing antibodies, before persistent infection is established

Sources: Barnabas et al. Nature Medicine 2023;29:3224–3232. Kreimer et al. NEJM 2025;393:2421–2433.

ORAL HPV ENDPOINTS

Oropharyngeal prevention: the direct infection evidence is encouraging

HPV vaccination reduces oral vaccine-type HPV infection

RANDOMIZED TRIAL

Costa Rica Vaccine Trial

Bivalent HPV16/18 vaccine vs hepatitis A control; women aged 18–25 years; oral specimens collected at the **4-year** blinded visit.

Analytic cohort	Oral HPV16/18	Cervical HPV16/18
5,834	**93.3%**	**72.0%**
oral + cervical HPV results	VE; 1 vs 15 infections	VE in same cohort

Interpretation

First randomized evidence showing substantially lower oral HPV16/18 prevalence after vaccination. The finding supports oral vaccine-type HPV infection as a plausible intermediate endpoint for OPSCC prevention.

POPULATION SURVEILLANCE

US NHANES 2011–2014

Nationally representative cross-sectional analysis; adults aged 18–33 years; vaccination defined as ≥1 HPV vaccine dose before age 26.

Study population	Vaccine-type oral HPV	Men: HPV16/18/6/11
2,627	**88.2%**	**0.0% vs 2.13%**
young US adults	adjusted prevalence reduction (0.11% vs 1.61%)	vaccinated vs unvaccinated

Implementation signal

Individual-level association was strong, but low uptake limited population impact: vaccination uptake was 18.3% overall and only 6.9% in men; estimated population-level effect was 17.0% overall and 6.9% in men.

- Direct randomized cancer endpoint data are not yet mature because of long latency.
- The prevention argument rests on causal biology + **oral infection endpoints** + type coverage.

Sources: Herrero et al. PLoS ONE 2013; Chaturvedi et al. J Clin Oncol 2018. Abbreviations: VE, vaccine efficacy; OPSCC, oropharyngeal squamous cell carcinoma.

HPV vaccine safety: reported events are signals, not conclusions

A mature safety discussion starts by naming concerns, then testing causality with appropriate evidence.

REPORTED CONCERNS WORLDWIDE

Acute reactions
Pain, swelling, fever, dizziness, syncope

Neurologic/autonomic symptoms
POTS (Postural Orthostatic Tachycardia Syndrome), CRPS (Complex Regional Pain Syndrome), chronic pain, dizziness, fatigue

Reproductive concerns
POI (Primary Ovarian Insufficiency), infertility, menstrual concerns

Rare neurologic/autoimmune events
Guillain-Barré syndrome, paralysis, autoimmune conditions

Clustered symptoms
School-based clusters and amplified concern

Policy crisis
Japan 2013–2022: safety concerns disrupted trust

→ Every report is a signal to investigate

KEY DISTINCTION

Temporal association ≠ causation
Events that occur after vaccination may represent **background disease**, **reporting bias**, **nocebo effects**, or **true vaccine-related adverse events.**

Signal detection

Case reports and passive surveillance identify patterns that deserve attention.

Causality testing

Controlled studies compare risk against appropriate background rates and unvaccinated groups.

Clinical response

Symptoms deserve care even when causality is not established.

Safety communication goal

Take patient experiences seriously, investigate systematically, and communicate the evidence proportionately.

Sources: WHO GACVS HPV vaccine safety reviews; EMA PRAC review of CRPS/POTS; Haruyama et al., Lancet Oncology 2022 on Japan resumption.

EVIDENCE SYNTHESIS

What did major reviews and surveillance conclude?

Safety claims are strongest when regulatory review, systematic review, and post-licensure monitoring converge.

1 Regulatory review

WHO GACVS

No new adverse events of concern identified from many very large, high-quality studies since HPV vaccine licensure.

EMA PRAC

Evidence does not support a causal link between HPV vaccines and CRPS or POTS; no change in product use recommended.

2 Systematic evidence

SAEs in RCTs
RR 0.99

97,272 participants
39 studies

Cochrane RCT network meta-analysis
Serious adverse events were similar in HPV vaccine and control groups. Evidence certainty: high for serious adverse events.

Cochrane population-level review
No increased risk for POTS, CFS/ME, paralysis, CRPS, premature ovarian failure, infertility, or sexual activity.

3 Post-licensure surveillance

Safety evidence
>160 studies

Monitoring systems
VAERS, VSD, CISA

CDC safety monitoring

Multiple monitoring systems support a favorable safety profile. Passive reports are used to detect signals, not prove causality.

Common events

Injection-site pain or swelling, fever, dizziness, nausea, headache, and syncope precautions. Serious allergic reaction is rare but a contraindication.

Sources: WHO GACVS HPV vaccine safety; EMA PRAC 2015 CRPS/POTS review; CDC HPV Vaccine Safety 2025; Cochrane CD015363 and CD015364, 2025.

CLINICAL INTERPRETATION

How should clinicians interpret and communicate safety?

The goal is not to dismiss symptoms; it is to separate care, reporting, causality, and policy-level inference.

1

Listen and care

Patients with symptoms after vaccination deserve evaluation, support, and appropriate treatment.

→

2

Report and investigate

Serious, unusual, or clustered events should be reported through pharmacovigilance systems.

→

3

Assess causality

Compare timing, background rates, biological plausibility, recurrence patterns, and epidemiologic data.

→

4

Communicate proportionately

Explain what is known, what is uncertain, and why population recommendations follow high-quality evidence.

What to do

- Validate symptoms and explain the evaluation pathway
- Use background rates and controlled data when discussing causality
- Observe for syncope and manage contraindications
- Continue cervical screening where indicated after vaccination

What to avoid

- Dismissing patient experiences as “not real”
- Treating temporal association as proof of causation
- Overstating rare case reports against large epidemiologic evidence
- Framing safety as “nothing can happen”

Listen carefully. Investigate systematically. Communicate proportionately.

Sources: WHO GACVS; EMA PRAC; CDC vaccine safety guidance; Cochrane reviews; general vaccine pharmacovigilance principles.

PRACTICAL RECOMMENDATION

Dosing schedules: global evidence, local implementation

Several countries have moved toward single-dose schedules, while others retain 2- or 3-dose schedules depending on age and immune status.

Country / authority	Primary target group	Routine schedule	Special notes
WHO	Girls and women 9–20 years	1 or 2 doses	> 21 years: 2 doses; immunocompromised or HIV: at least 2, preferably 3
United Kingdom	Routine adolescent programme, Routine age 12–13; Catch-up under 25 years; GBMSM under 25 years	1 dose (Publicly funded: NHS)	< 25 years usually 1 dose; GBMSM 25–45 years usually 2 doses; immunosuppressed/HIV: 3 doses
Australia	Immunocompetent persons 9–25 years	1 dose (National Immunisation Program funded)	≥26 years or immunocompromised: 3 doses
Canada / NACI	Immunocompetent persons 9–20 years	1 dose (publicly funded)	21–26 years: 2 doses; immunocompromised or HIV: 3 doses
United States / CDC	Routine age 11–12; start age 9 allowed, catch-up through 26 years	2 doses if start < 15 years (VFC/Medicaid / ACA/)	3 doses if start ≥15 years or immunocompromised
Singapore	Females 9–26 years under NCIS/NAIS	2 doses if age 9–14; 3 doses if ≥15	Female-only national schedule; subsidised/MediSave-claimable depending on eligibility
Taiwan	Junior-high school students	2-dose (Publicly funded)	Girls since 2018; boys included from Sept 2025

Sources: WHO HPV schedule update 2022; CDC HCP HPV vaccine recommendations 2025; Taiwan HPA/CNA 2025.

PRACTICAL RECOMMENDATION

Dosing schedules: global evidence, local implementation

Several countries have moved toward single-dose schedules, while others retain 2- or 3-dose schedules depending on age and immune status.

Country / authority	Primary target group	Routine schedule	Special notes
Japan	Girls from approximately 6th grade to 10th grade	2 doses if start < 15 years	3 doses if start ≥15 years, proactive recommendation resumed in 2022; male vaccination not yet routine
South Korea	Female adolescents 12–17 years; low-income women 18–26 years; 12-year-old boys from 2026	2 doses — national immunisation programme	National HPV programme began for girls in 2016; expanded to 12-year-old boys born in 2014 from May 2026
Hong Kong	Eligible female Primary 5–6 students	2 doses — free under HKCIP	Female-only routine school programme
New Zealand	All persons 9 to under 27 years	2 or 3 doses depending on age	HPV9 is free for all individuals aged 9–26 regardless of gender; school-based Year 8 programme plus clinic access
India	Girls aged 14 years	1 dose — free national campaign	Nationwide free HPV vaccination launched in 2026
China	13-year-old girls	2 doses bivalent vaccine — national programme	Free two-dose bivalent HPV vaccination began nationally from Nov 2025
Gavi-supported countries	Usually girls aged 9–14 years	Varies by country; many adopting 1 dose	examples include Rwanda, Kenya, Tanzania, Nigeria, Ethiopia, Zambia

Sources: WHO HPV schedule update 2022; CDC HCP HPV vaccine recommendations 2025; Taiwan HPA/CNA 2025.

VACCINATION + SCREENING + TREATMENT

Elimination requires all three: vaccination, screening, and treatment

Vaccination prevents future disease; screening detects precancer; treatment prevents progression and death.

90%

girls fully vaccinated by age 15

Primary prevention

70%

women screened by ages 35 and 45

Early detection

90%

Precancer treated and invasive cancer managed

Treatment and care

Source: WHO cervical cancer elimination strategy and fact sheet 2025.

BOYS, MEN, AND HERD IMMUNITY

Gender-neutral HPV vaccination: direct protection, equity, and programme resilience

Boys and men are not only transmitters; they are direct beneficiaries of HPV cancer prevention.

A stronger programme vaccinates adolescents before exposure—regardless of sex.

1 Direct protection

Protects **boys and men** against vaccine-type HPV infections that can lead to oropharyngeal, anal, and penile cancers.

2 Cancer burden

HPV-related oropharyngeal cancer is the most common HPV-associated cancer among men in the United States.

3 Equity

Girls-only programmes may not fully protect GBMSM, people outside heterosexual herd-effect networks, or populations with unequal vaccine access.

4 Herd protection

Vaccinating all adolescents reduces HPV circulation across sexual networks and strengthens population-level protection.

5 Programme resilience

Universal adolescent vaccination reduces gendered stigma, simplifies communication, and makes the programme less fragile when uptake in one group falls.

Policy message Move from "girls-only cervical cancer prevention" to "all-adolescent HPV cancer prevention."

Taiwan relevance Including boys aligns school-based implementation with broader HPV-related cancer prevention.

Suggested source frame: CDC HPV-associated cancer statistics; WHO HPV vaccine position paper; gender-neutral vaccination policy literature.

FUTURE DIRECTIONS

The questions that remain

A mature field still has consequential unanswered questions.

OPC endpoints

When will vaccinated cohorts show measurable cancer reduction by age, sex, and geography?

Single-dose durability

How durable is protection beyond 5–10 years, especially for males and immunocompromised groups?

Risk-based screening

How should cervical screening evolve as vaccinated cohorts age?

Oral HPV biomarkers

Can we identify high-risk persistent oral HPV infection without causing overdiagnosis?

Therapeutic vaccines

Can immunotherapy treat established HPV-driven lesions or cancers?

Sources: Zhang JAMA Oncology 2021; Barnabas Nature Medicine 2023; Kreimer NEJM 2025; screening guideline literature.

CLOSING FRAMEWORK

HPV vaccination is a cancer-prevention platform

Cervical cancer elimination is the measurable flagship; HPV-related oropharyngeal cancer is the emerging frontier.

1 Cervical cancer prevention is proven at the cancer-outcome level. Vaccination, screening, and treatment create a measurable elimination pathway.

2 HPV-related OPSCC prevention is biologically strong and infection-endpoint supported. Direct cancer-outcome evidence will take longer to mature.

3 Population impact depends on equitable adolescent delivery. High coverage, gender-neutral access, trust, screening, and treatment determine real-world success.

Make cancer prevention routine before infection becomes disease.

Thank you for your attention