



COALITION to STRENGTHEN
the HPV IMMUNIZATION
COMMUNITY



HPV Prevention
and Control Board



THE INCLEN TRUST INTERNATIONAL

Overview of Efficacy and Safety of HPV vaccines & new WHO recommendations on schedules

Paul Bloem, WHO/IVB , HPV vaccine Impact Lead

South Asia Regional Meeting

HPV Prevention and Control Landscape and the way forward.

13th , 14th and 15th - Dec 2022 – New Delhi, India.

Overview

- Background
- Characteristics of HPV Vaccines
- Efficacy and impact of HPV vaccines
- Safety of HPV vaccines and lessons learned
- WHO position on HPV vaccines

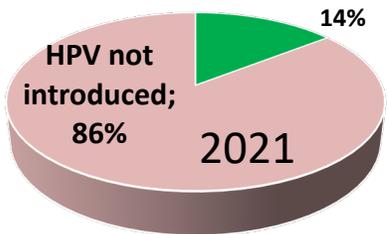
Global Strategy towards the Elimination of Cervical Cancer 2020

VISION: A world without cervical cancer

THRESHOLD: All countries to reach < 4 cases 100,000 women years

2030 CONTROL TARGETS

% SEA region cohort
(Females, 9-14 yr) with
access* to HPV vaccines



90%

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

70%

of women screened
with high precision tests
at 35 and 45 years of
age

90%

of women identified
with cervical disease
receive treatment and
care

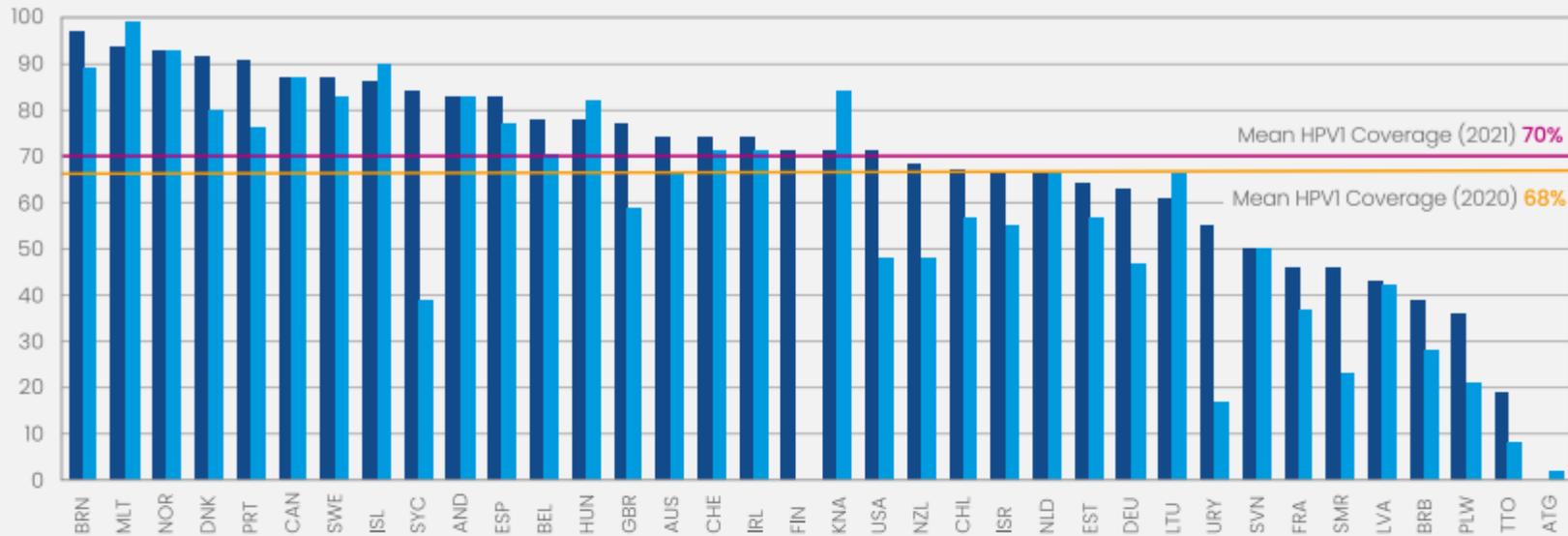
SDG 2030: Target 3.4 – 30% reduction in mortality from cervical cancer

2021 WHO/UNICEF HPV Vaccine coverage estimates by income level

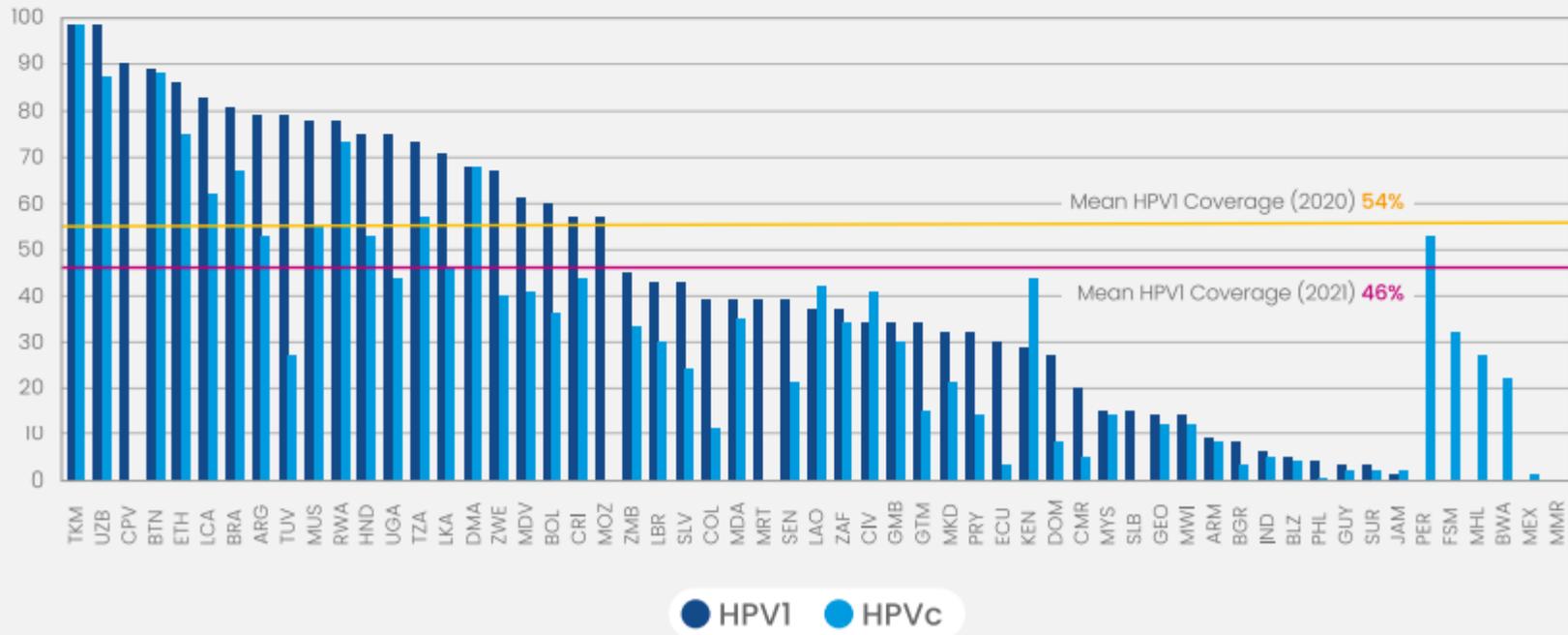
HPV Programme indicator, females

Few countries currently meet the 90% coverage target
Many countries have low to very low coverage

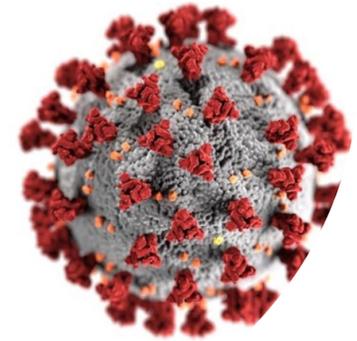
HIC Programme Coverage



L&MIC Programme Coverage



Characteristics of HPV vaccines



Available HPV vaccines in the market

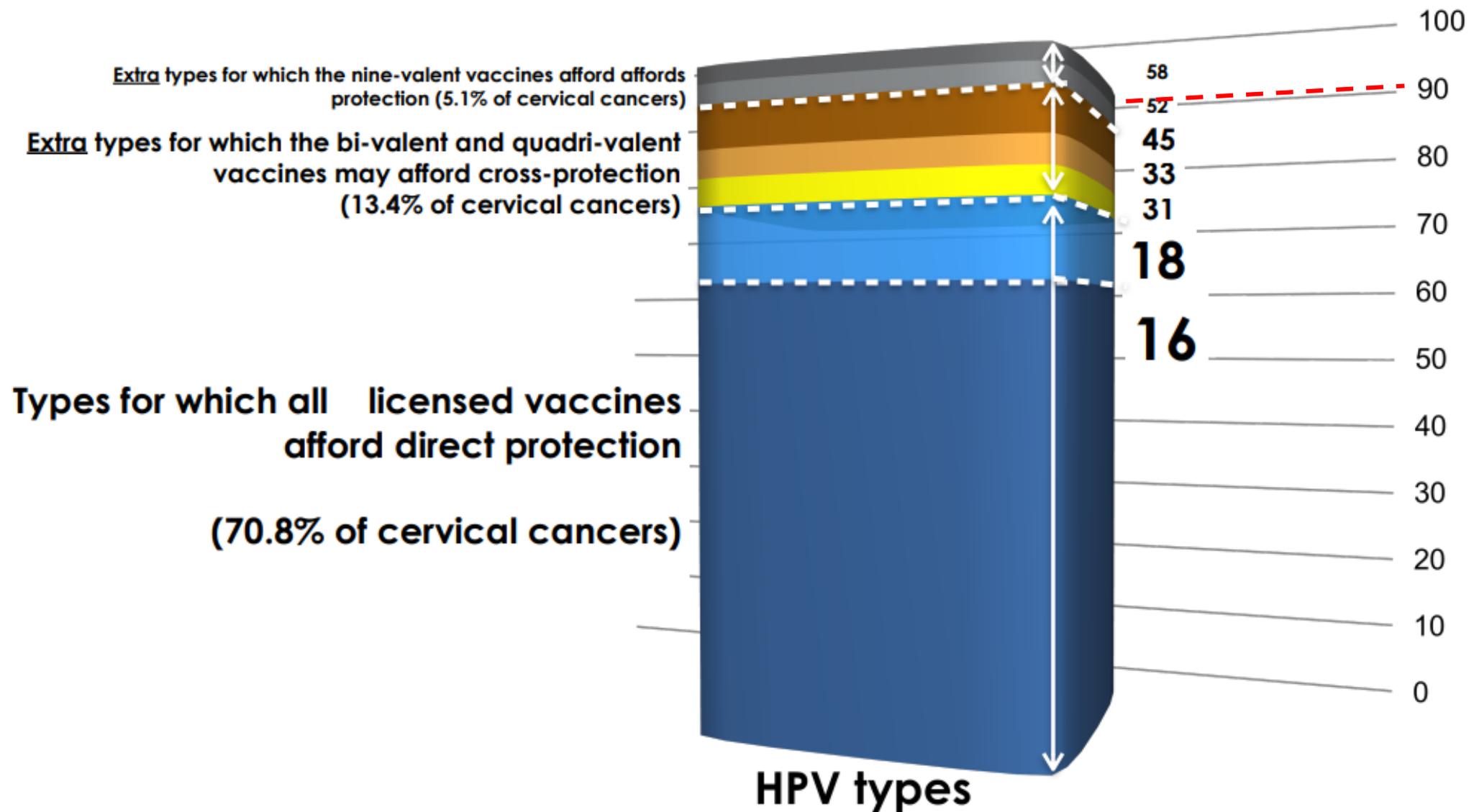
Trade Name	Cervarix™	Gardasil®	Gardasil-9®	Cecolin®	Walrinvax®	Cervavax®
Valency	Bivalent	Quadrivalent	Nonavalent	Bivalent	Bivalent	Quadrivalent
Manufacturer	GlaxoSmithKline Biologicals (GSK) Belgium	Merck/MSD USA	Merck/MSD USA	Xiamen Innovax Biotech Co. Limited (Innovax) China	Walvax Biotechnology Co. Limited China	Serum Institute of India (SII)
HPV types included	16/18	6/11/16/18	6/11/16/18/31/33 /45/52/58	16/18	16/18	6/11/16/18
Presentation	Single dose vial (0.5ml) Two Dose vial (1.0ml)	Single dose vial (0.5ml)	Single dose vial (0.5ml)	Single dose vial (0.5ml)	Single dose vial (0.5ml)	
WHO PQ decision	2009	2009	2018	2021	Under review	To be submitted
Price HIC/UMIC*	\$27 (Median)	\$39 (Median)	\$101 (Median)	---	---	---
Price Gavi/UNICEF	\$5.18	\$4.50	---	\$2.90	---	---
Data on 1-dose efficacy **	Yes	Yes	Yes	Immunobridging Study Ongoing	no information	No information

* WHO MI4A Global HPV market study 2022 ** WHO Position Paper 2022

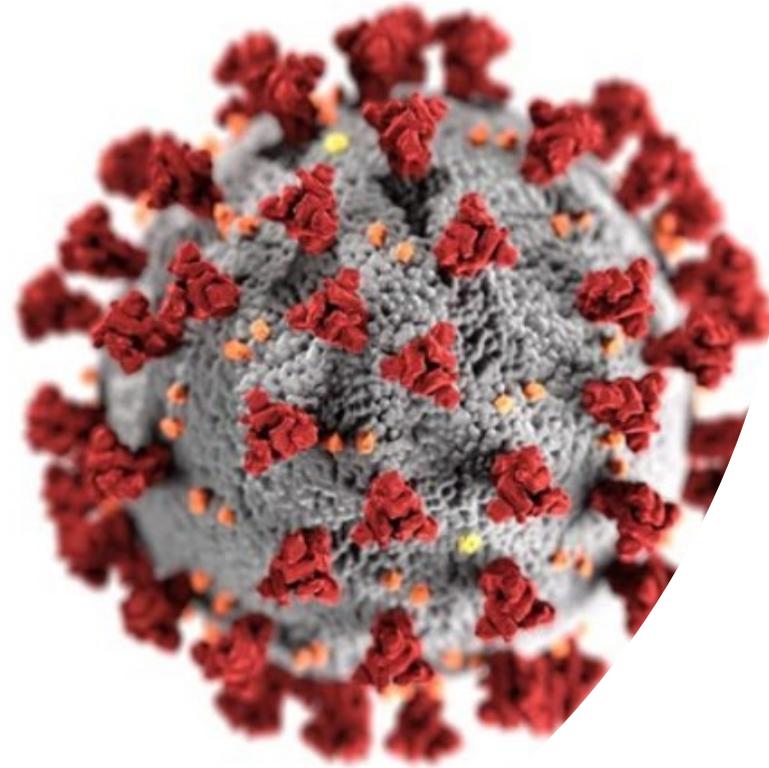
Update on Global HPV supply situation (2022)

Global HPV supply situation improving towards being unconstrained* => countries can plan introductions
Unconstrained situation achieved under condition all available products/volumes are used

HPV types contribution to cervical cancer and protection offered by HPV vaccines



Efficacy, Effectiveness and Impact of HPV vaccines



Efficacy (VE) from original Phase III Clinical trials¹

Among women 15/16 to 26 years for HPV 16/18

	Persistent Infection	CIN2+
• Cervarix VE	94% (92-96%)	98% (88 -100%)
• Gardasil VE	96% (83-100%)	98% (94 -100%)
• Cecolin VE	98% (86 -100%)	100% (56-100%) ²
• Walrinvax VE		79% (23 - 96%) ²

Among women 15/16 to 26 years for HPV 31/33/45/52/58

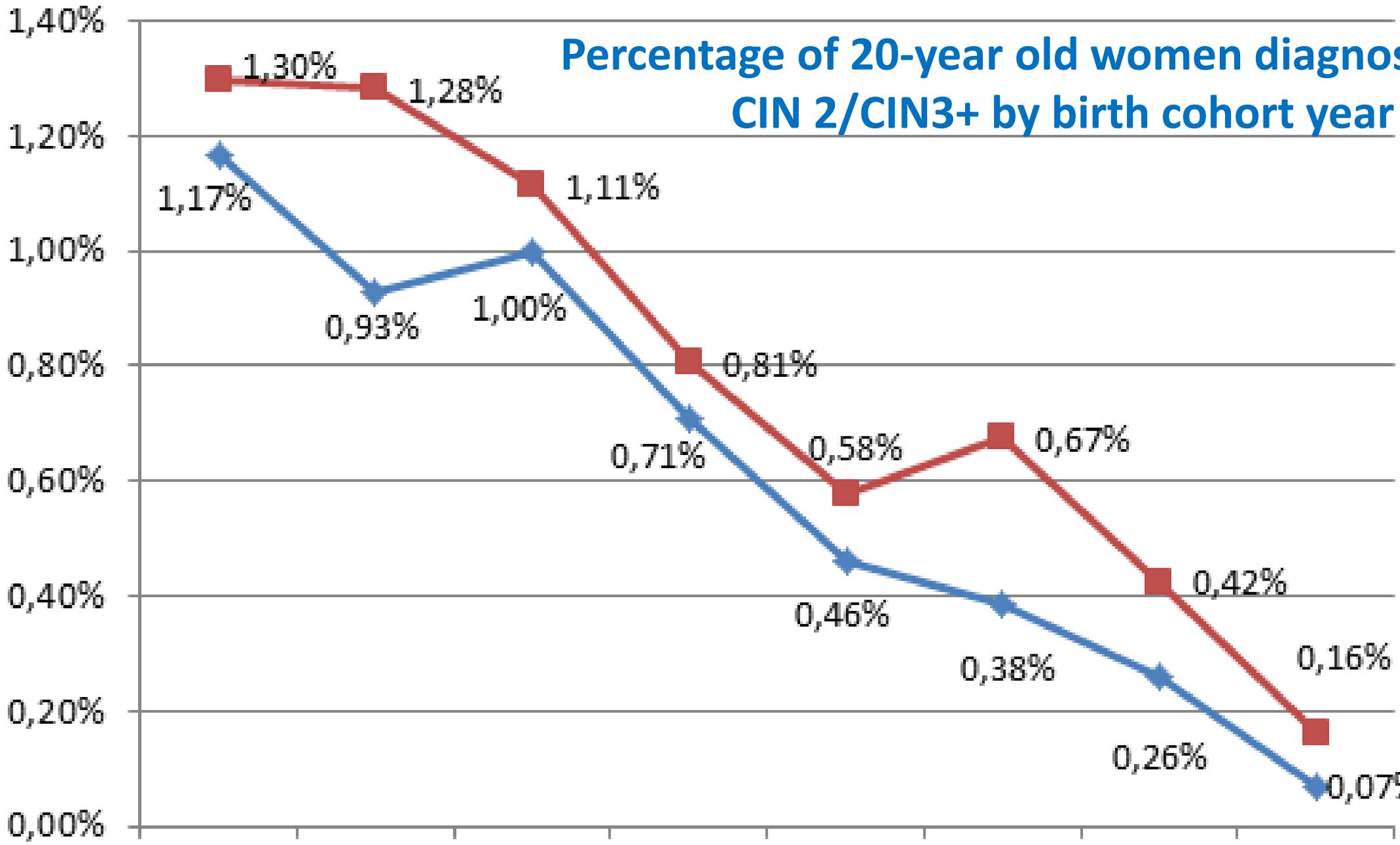
• Nonavalent VE	96% (94-98%)	100% (varying by type)
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¹: Harper, DeMars. HPV Vaccines –a review of the first decade. Gynec. Oncol. 2017.

²: Vaccine Package Insert.

- Immuno-bridging studies to license for 9-14 yr old populations
- Efficacy against persistent HPV infection sufficient for vaccine licensing*

Percentage of 20-year old women diagnosed with CIN 2/CIN3+ by birth cohort year



CIN3+
CIN2

Kavanagh et al.
Lancet 2017

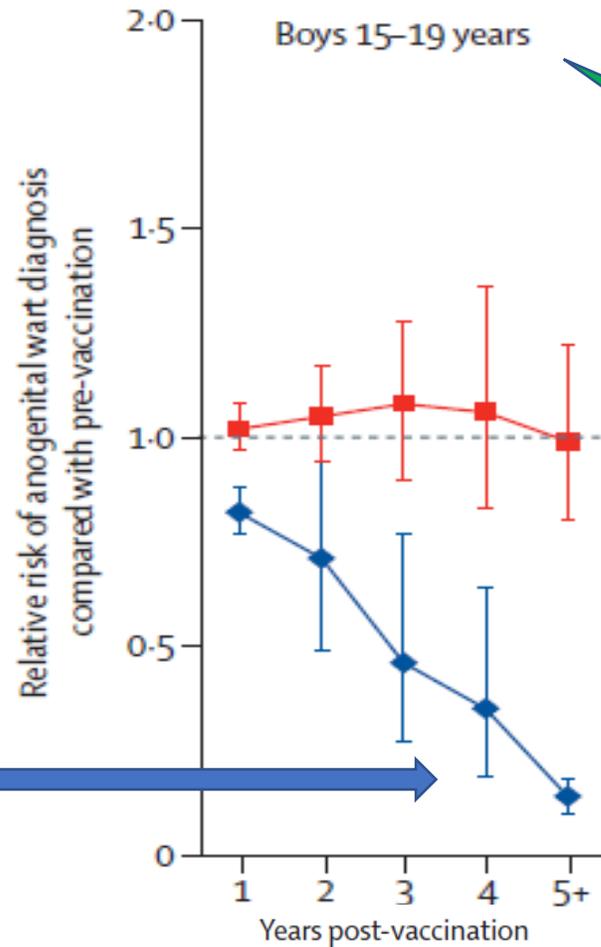
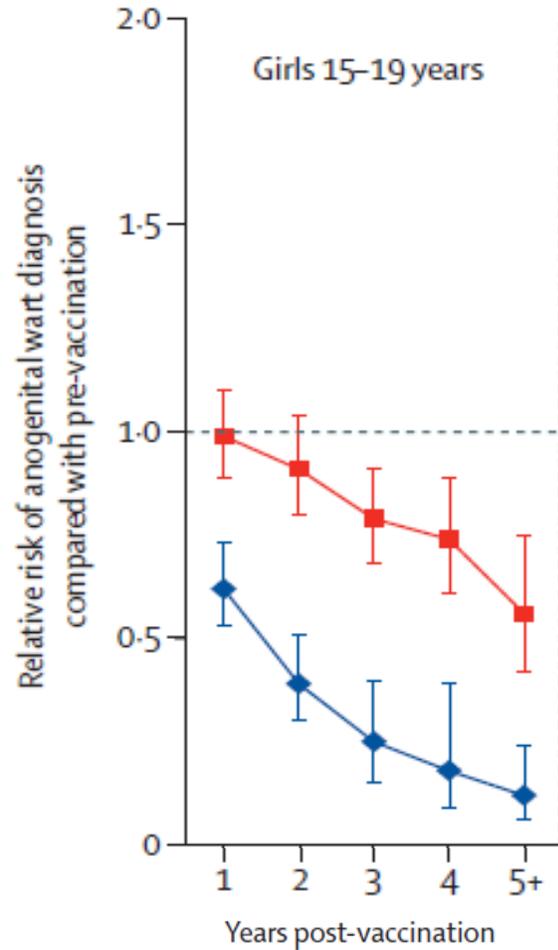
(94% reduction)

Bi-valent vaccine coverage 3-doses (12/13 yr) ←

1988 1989 1990 1991 1992 1993 1994 1995

(1.0) (4.2) (35.6) (65.2) (69.3) (70.1) (86.5)

Impact - High coverage/MAC (Gardasil) results in strong reduction in anogenital warts + herd protection in unvaccinated



Non vaccinated
Herd protection

Source: Drolet et al. Lancet 2019; 394: 497-509
Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis

- Countries with single-cohort vaccination and/or low vaccination coverage (<50%)
- ◆ Countries with multi-cohort vaccination and high vaccination coverage (≥50%)

Impact: HPV vaccination, particularly in young girls strongly reduces invasive cervical cancer

SWEDEN

Time period: 2006 - 2017
Study Cohort: All Females 10-30 years old (1.6M)
Age at Vx: < 17 year: 83%
17 -19 year: 11%
≥ 20 year: 6%
Product: Gardasil 4

Results Compared to non-vaccination:

- HPV vaccination < age 17 resulted in **88% reduction** in invasive cervical cancer
- HPV vaccination in women ≥ age 17 (majority 17-20) was less effective but still a **53% reduction**.
- A Danish study* showed **small/no effect** in 20-30 yr old

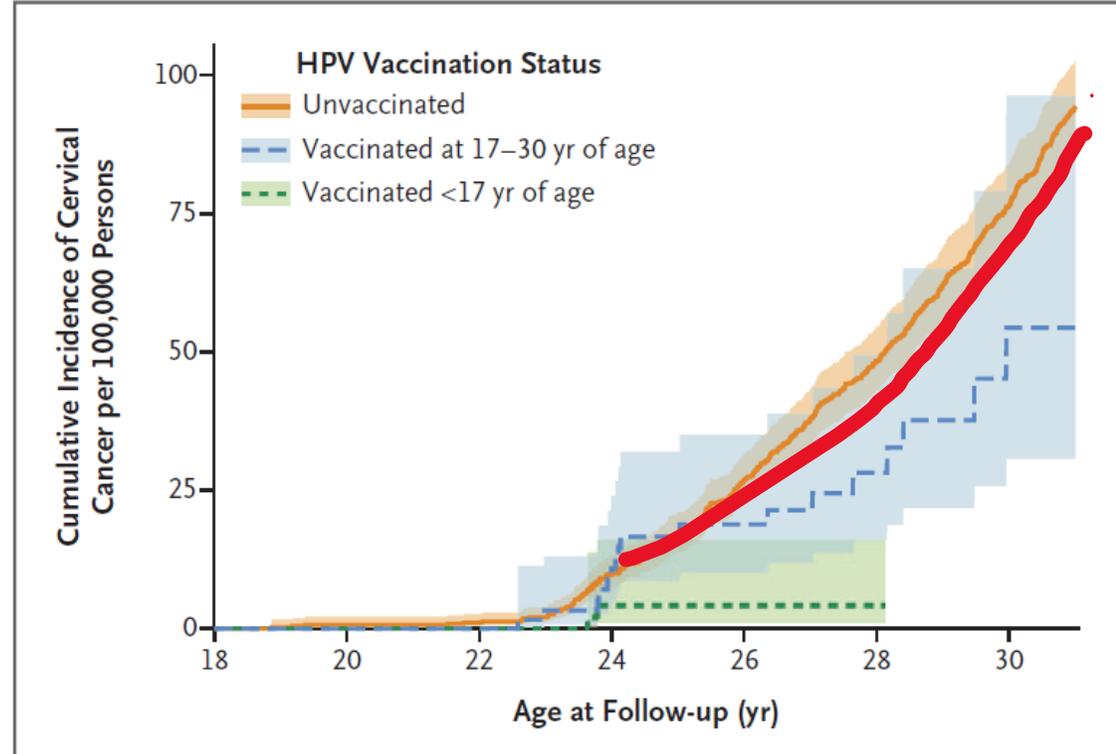


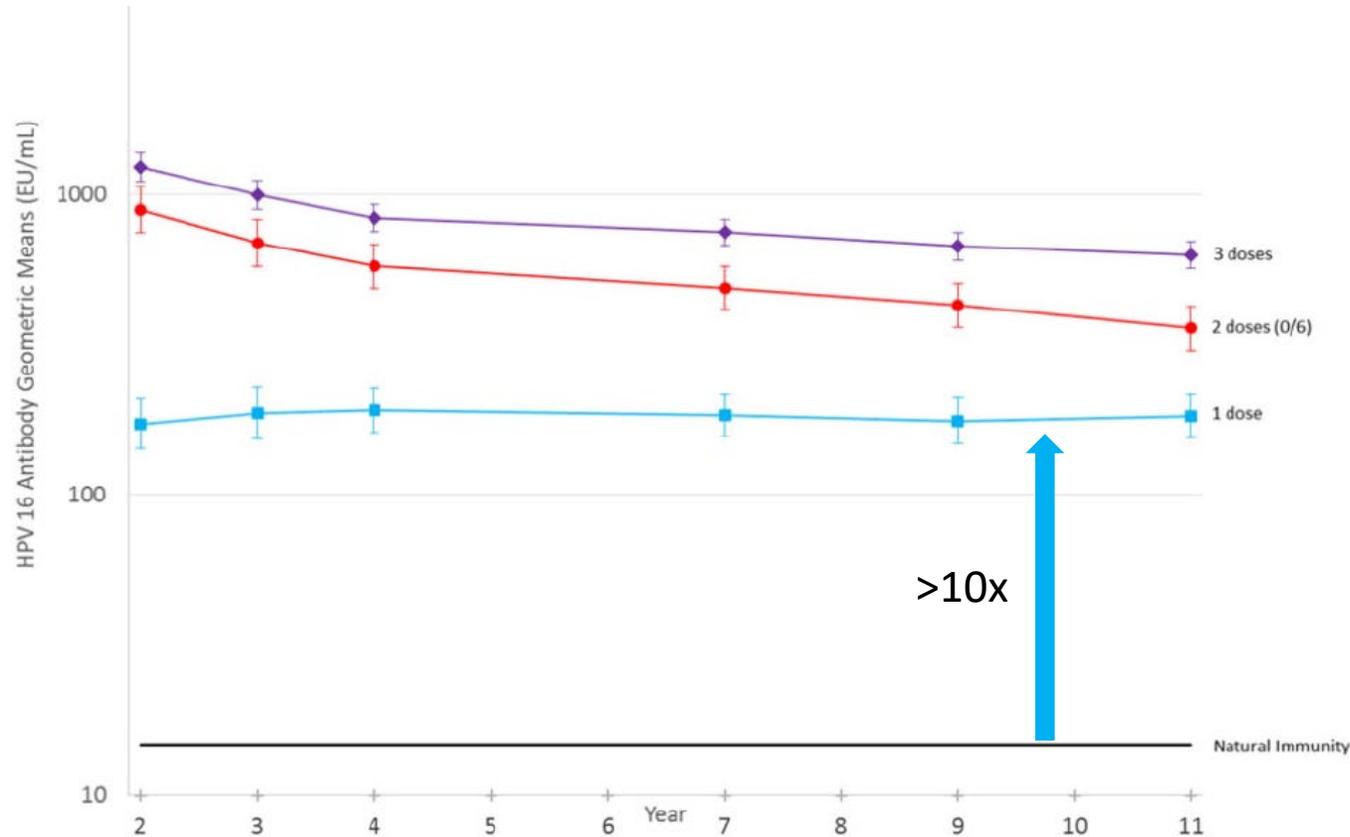
Figure 2. Cumulative Incidence of Invasive Cervical Cancer According to HPV Vaccination Status.

Age at follow-up is truncated in the graph because no cases of cervical cancer were observed in girls younger than 18 years of age.

Source: HPV Vaccination and the Risk of Cervical Cancer. Lei et al. *n engl j med* 383;14. 2020

* Kjaer et al. 2021. doi: 10.1093/jnci/djab080.

HPV 16 antibody* after 1, 2 or 3 doses of 2vHPV through 11 years, Costa Rica Vaccine Trial



Post-hoc analysis of RCT: women vaccinated at age 18–25 years randomized to receive 3 doses of 2vHPV or control but not all completed series

Note: 16 yr data available in 2023

Stable HPV 16 and 18 antibody levels (by ELISA) through 11 years post vaccination with different dosing schedules, at least 10 fold above natural immunity

*By VLP-based ELISA at the NCI HPV Immunology Laboratory
Kreimer A, et al. J Natl Cancer Inst 2020

Protection after 1, 2 or 3 doses of 4vHPV through 10 years, India IARC Trial

Doses	Number	Incident 16/18 HPV % (95% CI)	Persistent 16/18 HPV % (95% CI)	VE against persistent infection % (95% CI)
3 doses	1649	3.0 (2.3–3.8)	0.1 (0.0–0.4)	91.2% (75.3–98.7)
2 doses (0, 6 months)	1685	2.6 (2.0–3.3)	0.1 (0.0–0.4)	94.5% (82.4–99.8)
1 dose	2454	3.1 (2.6–3.8)	0.0 (0.0–0.3)	94.2% (83.7–99.1)
Control	1268	9.7 (8.2–11.3)	2.7 (1.9–3.7)	Reference

Post-hoc analysis; women vaccinated at age 10-18 years, randomized to receive 3 or 2 4vHPV doses

Unvaccinated women age-matched to married vaccinated participants recruited as controls

Persistent infection defined as the same HPV type detected in consecutive samples at least 10 months apart

VE adjusted for background HPV infection frequency, time between date of marriage and first cervical specimen collection, and number of cervical specimens per participant

KEN SHE

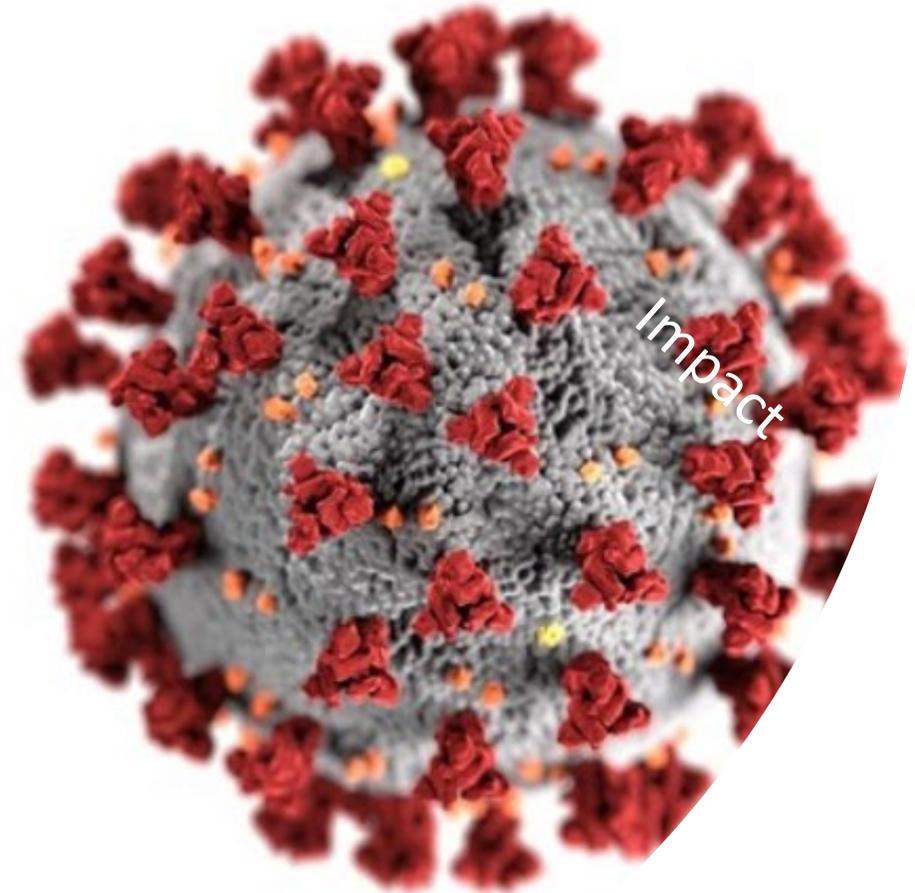
- Randomized trial of 1 dose of 9vHPV or 2vHPV or meningococcal vaccine
 - 2250 Kenyan women aged 15–20 years; 1-5 lifetime partners; HPV and HIV negative
- 1458 girls evaluated for efficacy at month 18 in mITT HPV 16/18 cohort

Study arm	Number	Incident persistent HPV 16/18	Incidence/100 PY	VE % (95% CI)
9vHPV	496	1	0.17	97.5% (81.7–99.7)
2vHPV	489	1	0.17	97.5% (81.6–99.7)
MCV	473	36	6.83	Reference

Enrollment between December 2018 and June 2021

mITT, modified intention to treat: HPV 16/18 HPV DNA negative (external genital and cervical swabs) at enrollment and month 3 (self-collected vaginal swab) and HPV antibody negative at enrollment

Safety of HPV vaccines



>500 M doses used
Globally by 2022

“Excellent Safety profile”

WHO Global Advisory Committee on Vaccine Safety (GACVS) *Statement on the continued safety of HPV vaccination (2017)**

Mild AEFI include local (injection site pain, redness swelling) and systemic reactions (fever, headache, fatigue) that are of transient nature

- Syncope was established as a common anxiety or stress-related reaction to the injection.
- The risk of anaphylaxis has been characterized as approximately 1.7 cases per million doses, and

GACVS Reviewed signals of serious AEFI: Complex regional pain syndrome (CRPS), postural orthostatic tachycardia syndrome (POTS), premature ovarian insufficiency, primary ovarian failure, venous thromboembolism, Guillen-Barré, Infertility. *None were causally related to HPV vaccines.*

"Since licensure of HPV vaccines, GACVS has found no new adverse events of concern based on many very large, high-quality studies." *

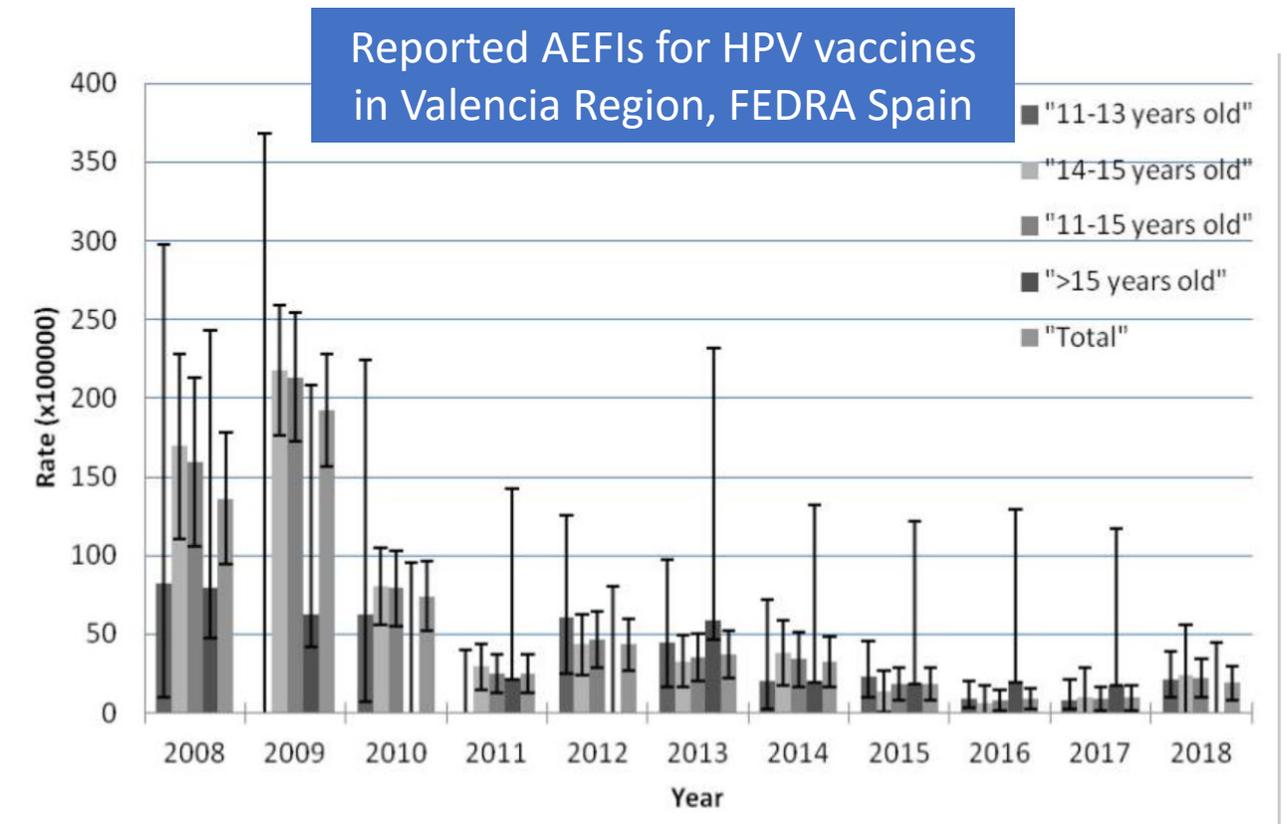
* <https://www.who.int/groups/global-advisory-committee-on-vaccine-safety/topics/human-papillomavirus-vaccines>

AEFI reporting, surveillance and crisis management

- Global surveillance data from around the world such as FEDRA data from Spain are pooled in Vigibase (Uppsala Monitoring Centre) to detect and analyze safety signals

On Valencia data:

- 2 cases in the media (local & intern.) in early 2009 probably behind high reporting
- “Lowering vaccination age from 14 to 12 may have contributed to decrease the AEFI reports that were mainly related to anxiety”
- In long term, rates of AEFI for HPV vaccines low



Source: Egoavil et al . Vaccines 2020, doi: [10.3390/vaccines8010117](https://doi.org/10.3390/vaccines8010117)

Summary of new WHO recommendations on HPV vaccine (2022)

WHO Position Paper on HPV vaccines (16 Dec 2022)

Primary target group

Girls, 9-14 years old

Vaccination Schedule (F = M)

≥ 9 years old => 26/45yr

2 doses, *min interval 6m, 12 recommended, no maximum interval**

9-20 years old

1-dose*

* Off-label recommendation

Immuno-compromised & HIV+ individuals (*any age*)

Min 2 doses, ideally 3 doses

Vaccination prioritization

MAC

- Prioritize multi-age cohort (MAC) vaccination at introduction or catch-up missed girls through 18 years of age
- Offer multiple opportunities to receive at least 1 dose before age 15

HIV+ & Sexually abused individuals

Prioritize vaccination of PLWHIV and children or adolescents who faced sexual abuse, including outside routine eligibility ages

Boys

Introducing the vaccination of boys and older females should be carefully managed until the global supply situation is fully unconstrained.

Older age cohorts

Priority research

- Duration of protection offered by single dose in 9-14 year old girls;
- Immunogenicity and protection of reduced schedules in immunocompromised individuals
- Single dose in boys & older cohorts
- Immunogenicity and protection of reduced schedules <9 year old

Considerations for decision on 1-dose schedule option

- “ The *off-label* single-dose option for routine and MAC catch-up vaccination is recommended from a public health perspective based on comparable levels of individual protection, while being more cost-effective, efficient (fewer doses per cancer case prevented), and providing more programmatic flexibility.”

SAGE April 2022

Considerations for NITAG deliberations to decide on *off label* single-dose use:

- **Performance of ongoing HPV programme:** Coverage high (>80%) or not? Drop-out?
- **Perceived capacity of single dose strategies to boost coverage** – innovative strategies?
- **Extend MAC:** same resources can prevent up to twice as many cases in catch up strategies (introduction MAC or COVID recovery)
- **Funding:** easier to introduce/sustain programme
- **Efficiency of resource allocation within national cervical cancer elimination strategy**
 - Reallocate funds to strengthen screening & treatment may prevent more cervical cancer cases in short term

Countries that have announced HPV schedule optimization /adopted 1-dose

- *July 2022* AFR Cap Verde (introduced in 2021):
 - Routine programme as of 9 yrs in girls 1-dose
 - Eligible group extended from 9 yr old girls to 9-14 yr old girls (catch up)
- *August 2022* EUR UK (introduced in 2008) 1-dose, 9 to 25 yr Girls and Boys
MSM 25+ : 2-doses (from 3)
Netherlands (from 3) -> 2-doses for 15 - 26 year in catch up (F&M)
- *October 2022* WPR Tonga (October 2022) Introduction with 1 dose , extension of catch up age
Solomon Islands (2019) switch to 1 Dose in ongoing programme

NITAGs in several GAVI-eligible countries have recommended GAVI HPV introduction with 1-dose schedule, including Bangladesh (2023/4), Nigeria (2023/4)

Conclusions

- Increasing # of HPV vaccine products are available
- Reaching high coverage important than vaccine used
- HPV vaccines are remarkably effective and have shown they reduce cancer
- HPV vaccines are safe - it is our task to communicate that effectively to build vaccine confidence
- New WHO recommendations allow for more programme flexibility

Thank you



WHO HPV Vaccine introduction Clearing house

Visit each area for related resources:



POLICY & DECISION-MAKING

Informing national decision-making for HPV vaccine introduction



PLANNING

Planning for HPV vaccine introduction



FINANCING

Budgeting and financing for HPV vaccine introduction



VACCINES & SAFETY

Characteristics, presentations and safety profiles of HPV vaccines



COMMUNICATION

Communicating effectively using research-based approaches



IMPLEMENTATION

Delivering HPV vaccination programmes



MONITORING & SURVEILLANCE

Monitoring the coverage and impact of HPV vaccine programmes



HPV PARTNERS

Links to HPV partners and resources

Global HPV vaccine introduction and coverage by country
visit: [HPV Introduction Dashboard](https://www.who.int/immunization/hpv/en/)

Visit: <http://www.who.int/immunization/hpv/en/>