Briefing on single-dose HPV vaccination evidence

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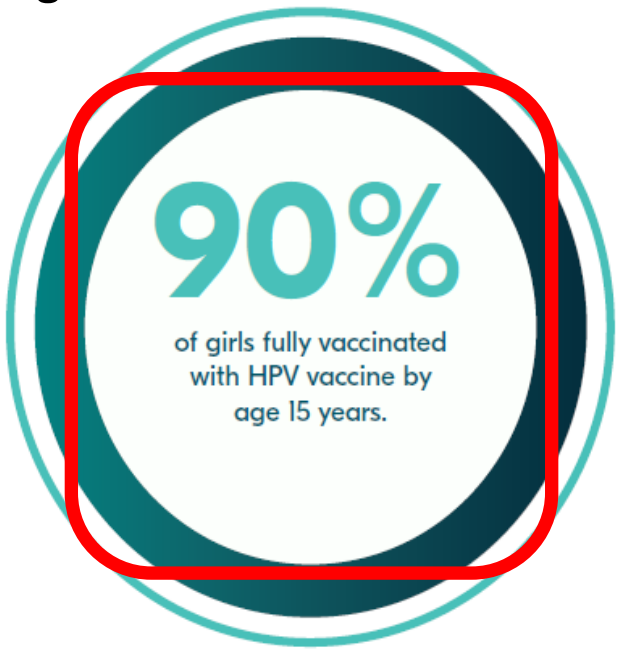
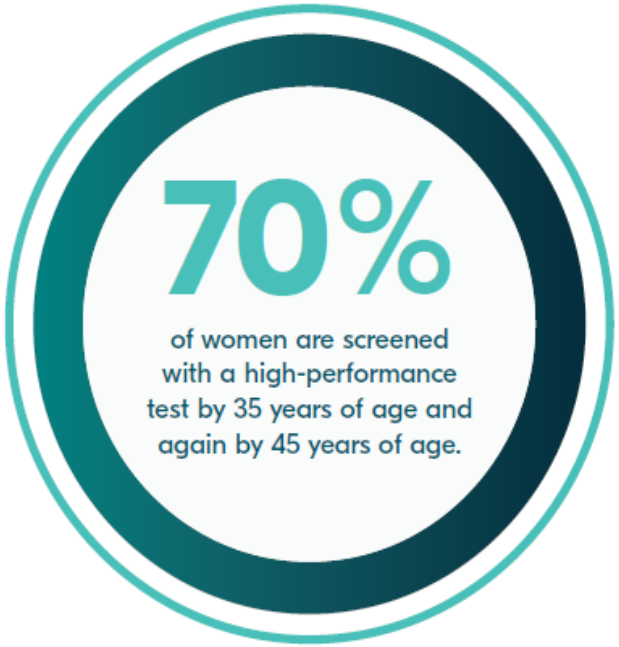
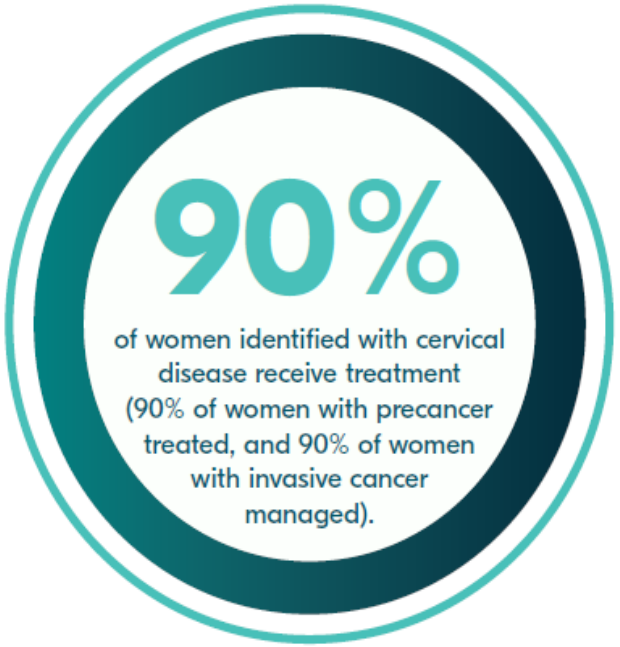
Background

- Cervical cancer is a leading cause of cancer death among women in low- and lower-middle-income countries (LMIC)
- More than 604,000 cases and 341,000 deaths occur annually, with more than 85% of deaths occurring in LMIC
- HPV is present in virtually all cervical cancers and is a necessary cause of cervical cancer
- In November 2020, WHO launched the global strategy to accelerate the elimination of cervical cancer as a public health problem







https://gco.iarc.fr/today/data/factsheets/cancers/23-Cervix-uteri-fact-sheet.pdf

https://www.who.int/publications/i/item/9789240014107

Background

- Current HPV vaccines are prophylactic, i.e., to be administered prior to exposure with HPV, optimally before sexual debut
- HPV vaccines were first introduced in 2006 on a three-dose schedule
- There is accumulating evidence that a single-dose of HPV vaccine may elicit an immune response that can protect against HPV infection
- The HPV vaccination schedule has been reduced before. In 2014, the WHO reduced the schedule from three doses to two, following an evidence review by the Strategic Advisory Group of Experts (SAGE) on Immunization

HPV vaccines and schedule

Currently, WHO recommends:

- 2 doses for girls 9 - 14 yoa, with dosing flexibility for dose 2 as early as 5 months after dose 1
- 3 doses for girls ≥15 yoa and immune-compromised girls (including HIV infected) - original dosage recommendation

Table 1. Summary of available HPV vaccines

	Cervarix™ [a]	GARDASIL® [b]	GARDASIL9® [b]	Cecolin® [c]
Manufacturer	GlaxoSmithKline	Merck & Co., Inc.	Merck & Co., Inc.	Xiamen Innovax Biotech Co. Limited
HPV VLPs included	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58	16, 18
Injection Schedule [d] (2 doses)	0, 6–12 months	0, 6–12 months	0, 6–12 months	0, 6 months
Injection Schedule [d] (3 doses)	0, 1, 6 months	0, 2, 6 months	0, 2, 6 months	0, 1, 6 months

Note: HPV, human papillomavirus; VLP, virus-like particle.

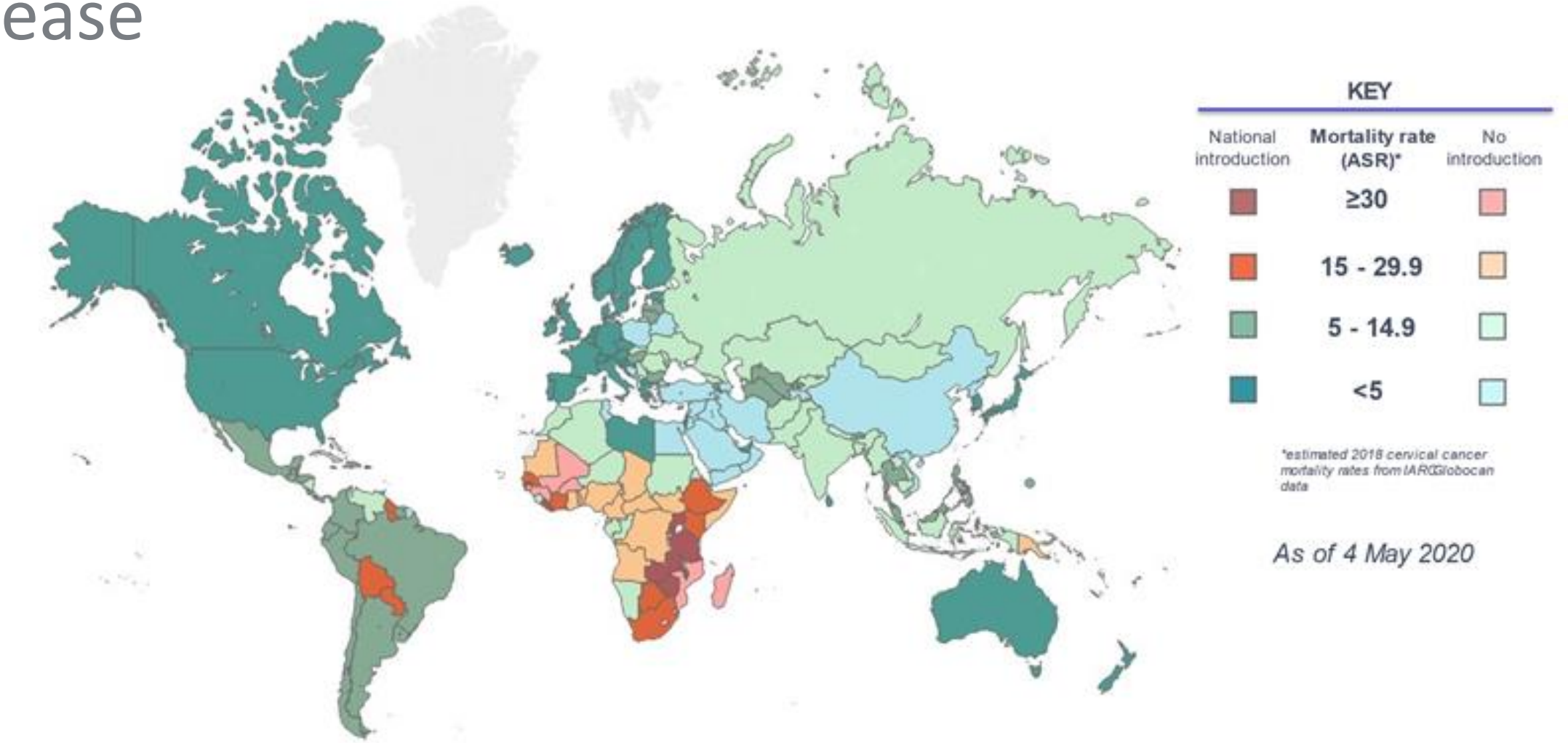
[a] Cervarix is a trademark of GlaxoSmithKline Biologicals, Belgium.

[b] Gardasil and Gardasil-9 are registered trademarks of Merck Sharp & Dohme Corp., United States.

[c] Cecolin is a registered trademark of Xiamen Innovax Biotech Co. Limited, China. Cecolin is licensed and used only in China and is currently under review for WHO prequalification (expected 2021).

[d] In some countries, the vaccines are also licensed and recommended for boys, in the same dosing schedules as for girls.

Global HPV vaccine introductions by burden of disease



Expanding access to HPV vaccines

If demonstrated to be effective, single-dose HPV vaccination could:

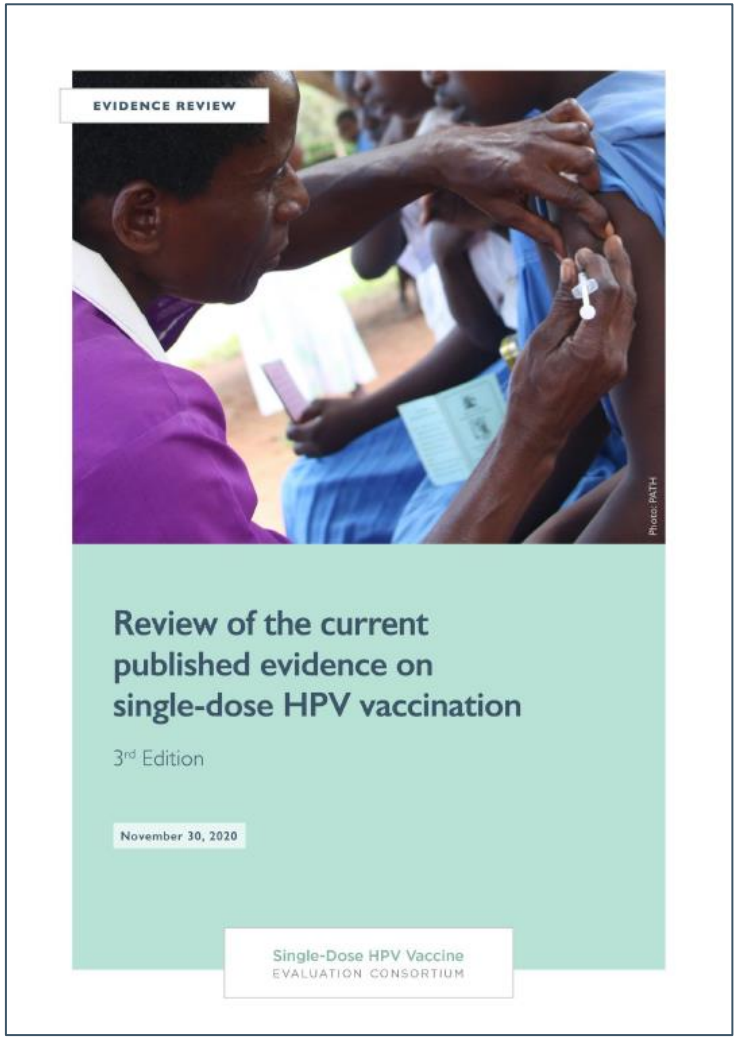
- accelerate introduction for countries that have yet to introduce the vaccine
- facilitate new options for current national programs by simplifying delivery costs and lowering program costs
- reduce the potential for supply shortages and delivery challenges, such as those faced during the COVID-19 pandemic

Single-Dose HPV Vaccine
EVALUATION CONSORTIUM

The Single-Dose HPV Vaccine Evaluation Consortium encompasses eight leading health and research institutions working together to collate and synthesize existing evidence and evaluate new data on the potential for single-dose HPV vaccination

Evidence review

- Summarizes existing evidence from trials, non-trials, and impact and economic modeling work into one paper
- Third edition is now available, and fourth edition will be available in 2022
- Each edition accompanied by a synthesis and summary (available in English, French, and Spanish)



Single-dose HPV vaccination evidence from clinical trials and observational studies

Rationale for Single Dose HPV vaccination strategy

- Current HPV vaccines (multidose regimens) are highly efficacious in preventing persistent infections and cervical lesions associated with vaccine genotypes
  - HPV-16 and 18 account for ~ 70% of cervical cancers worldwide
- Vaccines elicit a strong and durable neutralizing antibody response
  - Stability of antibody responses observed ≥ 10 years after vaccination
  - In healthy young women, seroconversion rates are virtually 100%
- After a single dose of vaccine
  - The durability of the antibody response remains
  - The quantity of neutralizing antibodies is lower, but the quality is similar to multidose vaccination

Schiller J, Lowy D. Explanations for the high potency of HPV prophylactic vaccines. Vaccine. 2018;36(32 Pt A):4768–4773. https://doi.org/10.1016/j.vaccine.2017.12.079.

Clinical trials – Efficacy and immunogenicity

A systematic review was conducted on the efficacy and immunogenicity of a single HPV vaccine dose compared to multidose schedules (or no HPV vaccination)

Seven articles identified (additional 2 published early 2020) reporting on results from four studies***
Except for 1 study, data originated from randomized controlled trials participants having failed to complete their allocated 2 or 3-dose schedule

- HPV 16 and 18 infections were extremely low in all efficacy trial participants who received any HPV vaccine, and significantly lower than in unvaccinated participants or control vaccine recipients
- HPV 16 and 18 efficacy was comparable following 1-dose and 2- or 3-dose in healthy young females up to eleven years post-vaccination
- High proportion of participants seroconverting to HPV 16 and 18 in all HPV vaccine dosing regimens

Two in India [International Agency for Research on Cancer (IARC) India HPV Trial], five in Costa Rica [Costa Rica Vaccine Trial (CVT)], one in the United States of America, and one multinational study [PApilloma TRIal against Cancer In young Adults (PATRICIA)].*

Protection against HPV-16/18 infections after a single dose of 2vHPV - Combined analysis of Costa Rica Vaccine and PATRICIA Trials

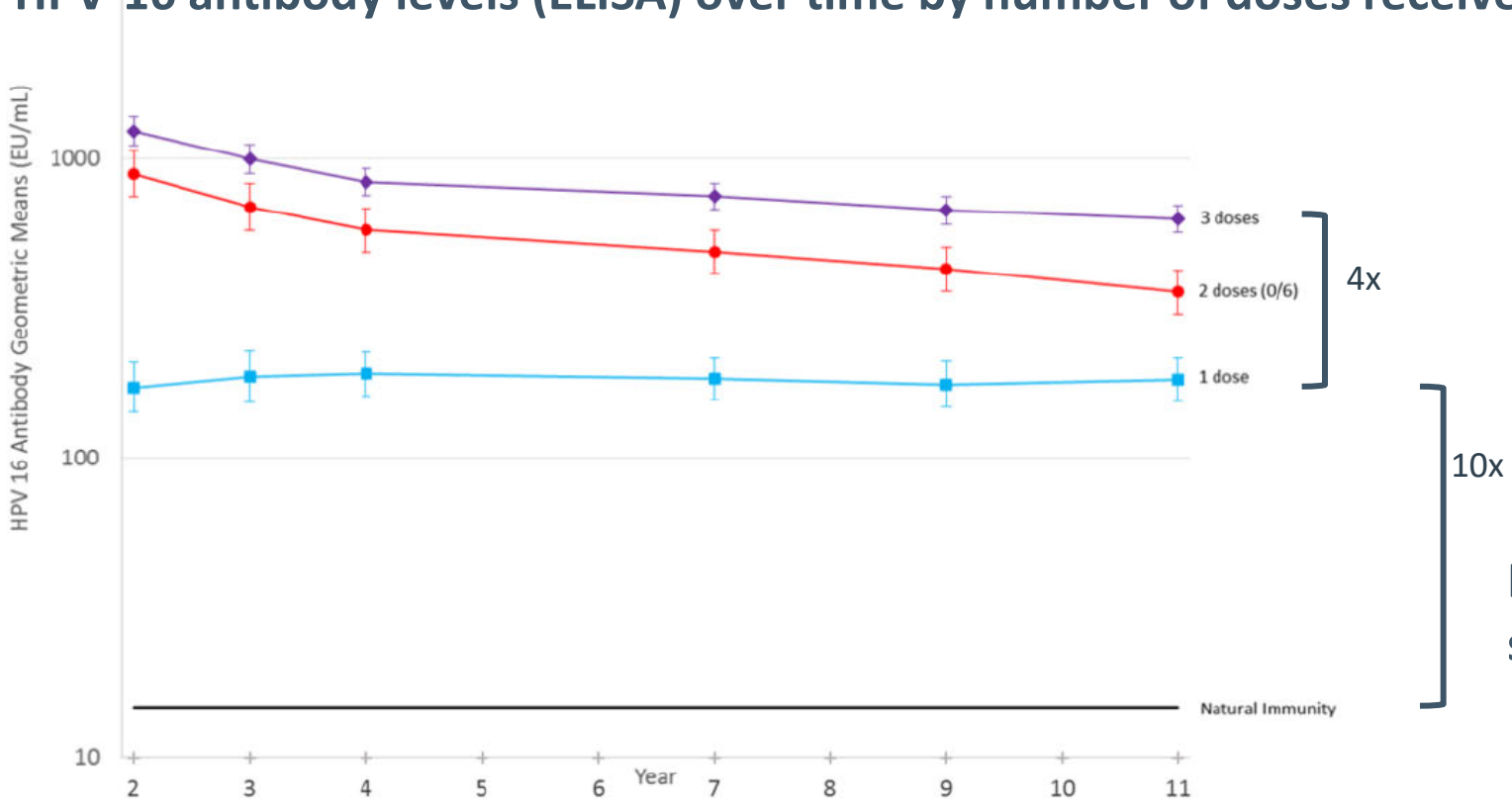
Dose-stratified vaccine efficacy against HPV-16/18 infections

	Number of women	Number of events	Person-years	Rate per 100 person-years (95% CI)	Vaccine efficacy (95% CI)
Incident one-time detection of HPV-16/18					
3 doses (standard regimen)					
HPV	11 110	529	43 140	1·23 (1·12–1·34)	77·0% (74·7–79·1)
Control	11 217	2172	40 682	5·34 (5·12–5·57)	
2 doses					
HPV	611	22	2538	0·87 (0·56–1·29)	76·0% (62·0–85·3)
Control	574	82	2271	3·61 (2·89–4·46)	
1 dose					
HPV	292	8	1220	0·66 (0·30–1·25)	85·7% (70·7–93·7)
Control	251	45	982	4·58 (3·38–6·08)	
Incident detection of HPV-16/18 that persisted for at least 6 months					
3 doses					
HPV	11 104	114	43 706	0·26 (0·22–0·31)	89·1% (86·8–91·0)
Control	11 209	1000	41 913	2·39 (2·24–2·54)	
2 doses					
HPV	611	4	2573	0·16 (0·05–0·38)	89·7% (73·3–96·9)
Control	574	35	2308	1·52 (1·07–2·09)	
1 dose					
HPV	292	1	1234	0·08 (0·00–0·40)	96·6% (81·7–99·8)
Control	250	24	1017	2·36 (1·55–3·46)	

Kreimer A., Lancet Oncol(2015) 16: 775-86

Durability of the immune response after a single dose of 2vHPV Costa Rica Vaccine Trial

HPV-16 antibody levels (ELISA) over time by number of doses received



Results for HPV-18 ELISA show a similar kinetics response

Stable antibody levels for HPV16 and HPV-18 antibodies up to 11 years post vaccination with different dosing schedules of 2vHPV at least 10 fold above natural immunity

Kreimer A., JNCI J Natl Cancer Inst (2020) 112(10): djaa011

Observational studies - Immunogenicity

Eleven articles were identified reporting on immunogenicity with results from 9 studies*:
Participants receiving only one HPV dose resulted from noncompletion of an intended multidose schedule

- A single-dose HPV vaccination results in high rates of seroconversion and sustained seropositivity
  - one study presenting data up to eight years after vaccination
- Antibody titers were lower with 1-dose than with 2- or 3-doses
  - Titers in 1-dose arms remained stable
  - Titers are considerably higher than with natural infection
- Some adolescents demonstrated higher antibody titers after a single-dose than those observed in 3-dose clinical efficacy trials conducted in adult women (using the same laboratory methods)

**one each from Uganda, the Netherlands, and Mongolia; two from the United States; and three each from Canada and Fiji.*

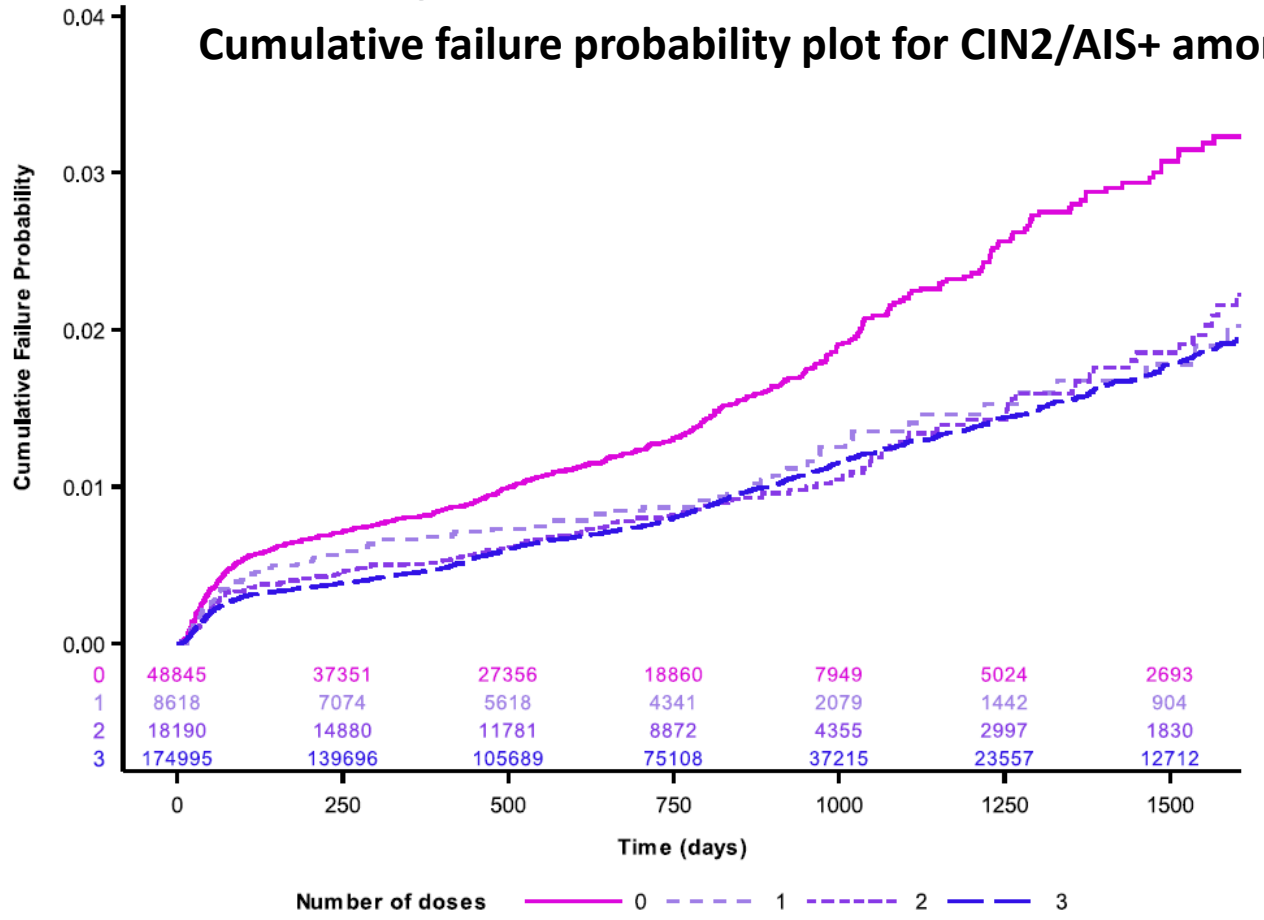
Observational studies - Effectiveness

A systematic review provided evidence of HPV vaccine effectiveness by number of doses.

Results from 32 studies: HPV infections [8]; anogenital warts [9]; cervical abnormalities [15]

- Most of the studies found highest effectiveness with 3 doses, followed by 2 doses, and then 1 dose
- Biases in many studies; most that would result in apparent lower effectiveness with fewer doses
- Half of the studies found significant vaccine effectiveness for single dose HPV vaccination in some or all analyses
- Higher effectiveness estimates was found with younger age at vaccination
- More recent studies with younger vaccine recipients, or with analyses stratified by age at vaccination, have found high effectiveness with one dose or similar effectiveness for one, two, and three doses

Protection against High grade cervical lesions after single dose of 4vHPV National cohort analysis - Australia



Hazard ratio for1 dose compared to 3 doses: 1.01 (95%CI 0.81–1.26)

One dose had comparable effectiveness as two or three doses in preventing high–grade disease in a high coverage setting in women vaccinated ≤ 15 yoa

Brotherton JM, Papillomavirus Res 2019

Global impact and cost-effectiveness of one-dose versus two-dose human papillomavirus vaccination schedules: a comparative modelling analysis

K. Prem, Y. Choi, E. Benard et al, https://doi.org/10.1101/2021.02.08.21251186.

What data do we have to estimate HPV impact and cost-effectiveness globally?

Most countries (150+)	Many countries (20+)	Few countries (<10)
Population size Age structure Cervical cancer incidence and mortality	HPV prevalence HPV type distribution Vaccine delivery costs Age of sexual debut	Prevalence of cervical neoplasia Detailed sexual history

What can we do with these data?

Most countries (~200)	Many countries (20+)	Few countries (<10)
Population size Age structure Cervical cancer incidence and mortality	HPV prevalence HPV type distribution Vaccine delivery costs Age of sexual debut	Prevalence of cervical neoplasia Detailed sexual history

PRIME
Impact and cost-effectiveness in >190 countries
No herd effects, no vaccine waning

HPV-ADVISE, Harvard, PHE
Impact and cost-effectiveness in a few countries
Herd effects, waning, gender-neutral, catch-up etc.

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PRIME
Impact and cost-effectiveness in >190 countries
No herd effects, no vaccine waning

Direct impact with no waning
In all countries
+
Indirect impact with waning
in all countries

HPV-ADVISE, Harvard, PHE
Impact and cost-effectiveness in a few countries
Herd effects, waning, gender-neutral, catch-up etc.

IMPUTATION

Indirect impact with waning

One-dose HPV vaccine schedule

- To assess the extent to which a one-dose HPV vaccine schedule will **provide sufficient protection** and be **cost-effective**, we compared the impact of **three different vaccine strategies**:

1. **no** HPV vaccination;
2. **one-dose** HPV vaccination giving either
   i. 20 years protection, or
   ii. 30 years protection, or
   iii. lifetime protection at 80% vaccine efficacy (VE);
3. **two-dose** HPV vaccination giving lifetime protection.

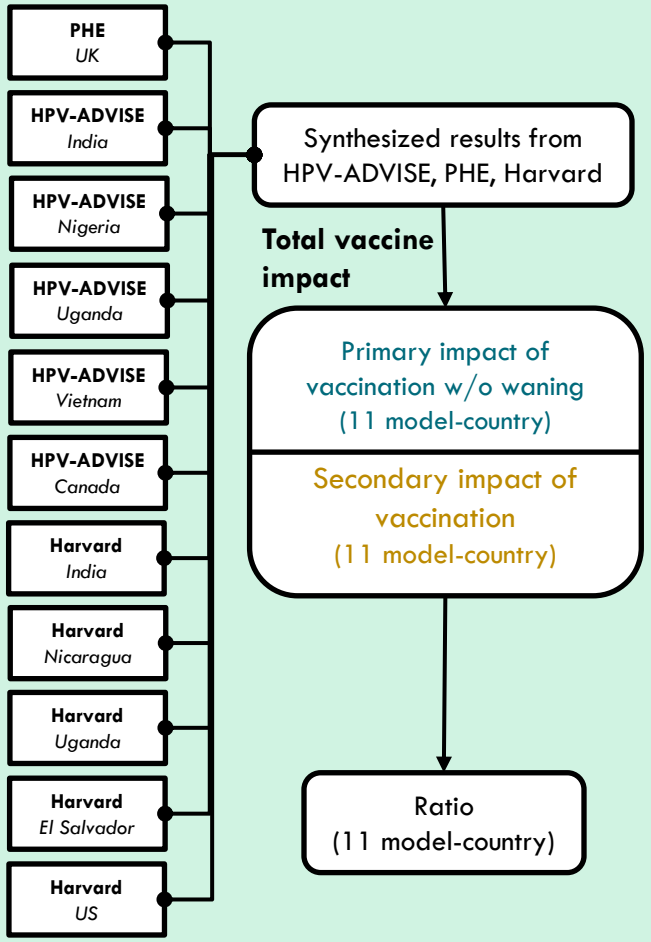
For 1-dose to be cost-effective:
1) **cost effective: 0 → 1 dose**
2) **<u>not</u> cost effective: 1 → 2 doses**

Overview

1. Synthesised the results of 3 published HPV dynamic models—**HPV-ADVISE[1], Public Health England (PHE) model[2], Harvard model[3]**

A HPV DYNAMIC MODELS

Demographics, sexual activity, HPV natural history and disease, HPV transmission



Assumptions

- 80% vaccine coverage against all high-risk HPV types in the 9-valent vaccine (16, 18, 31, 33, 45, 52, 58)
- Routine vaccination at 10y girls + catch-up 11-14y girls (for first year)
- Routine annual vaccination in 2021–2120

Legend

DALYs: disability-adjusted life years
NNV: number (of females) needed to vaccinate

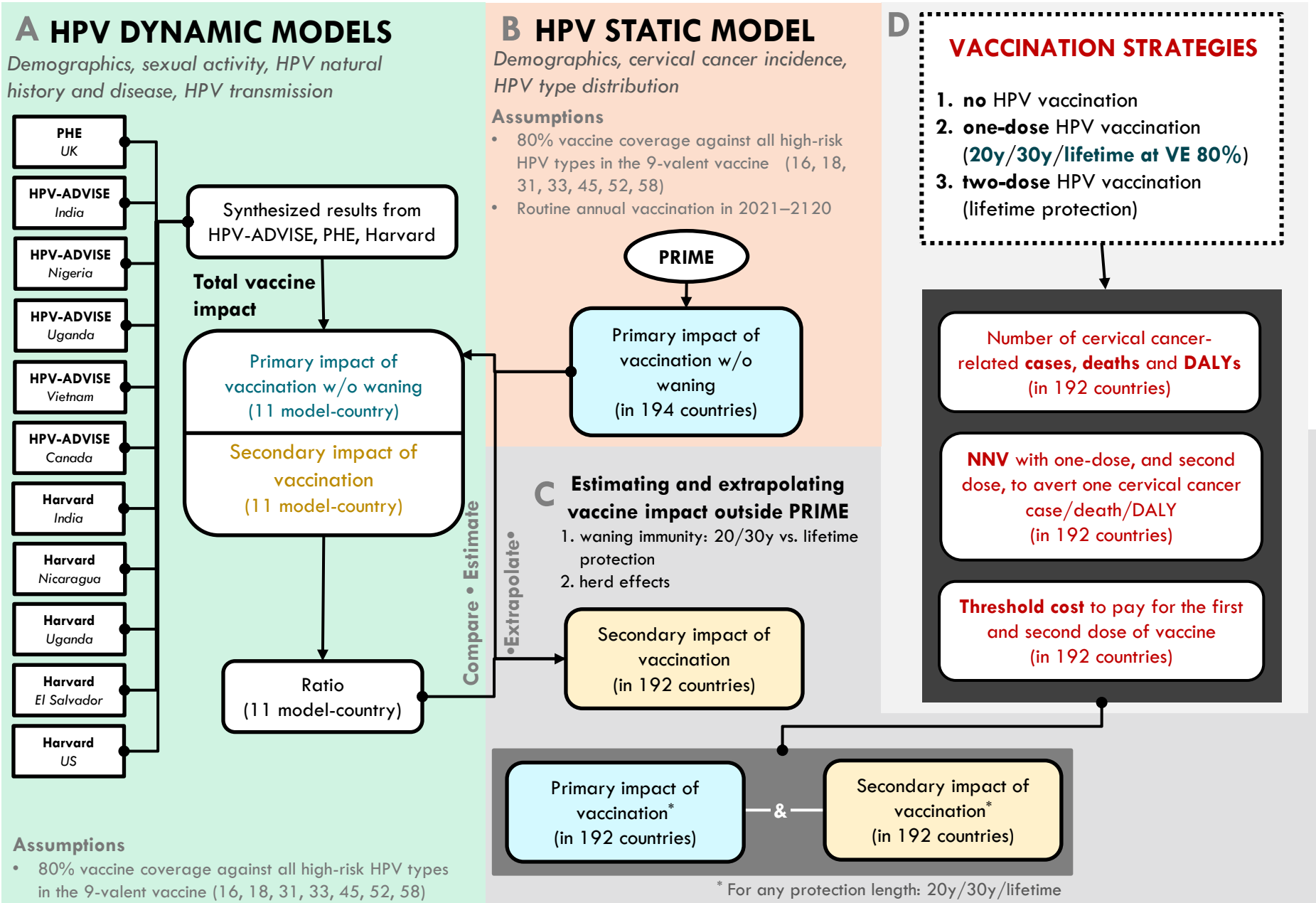
Input
Model
Estimates

[1]Brisson et al., 2016. [2]Choi et al., 2010. [3]Campos et al., 2014. [4]Jit et al., 2014.

Overview

1. Synthesised the results of 3 published HPV dynamic models—**HPV-ADVISE[1], Public Health England (PHE) model[2], Harvard model[3]**

2. Compared the impact and cost-effectiveness of one-dose v two-dose vaccination in 192 countries for the **3 different vaccine strategies using PRIME model[4]**



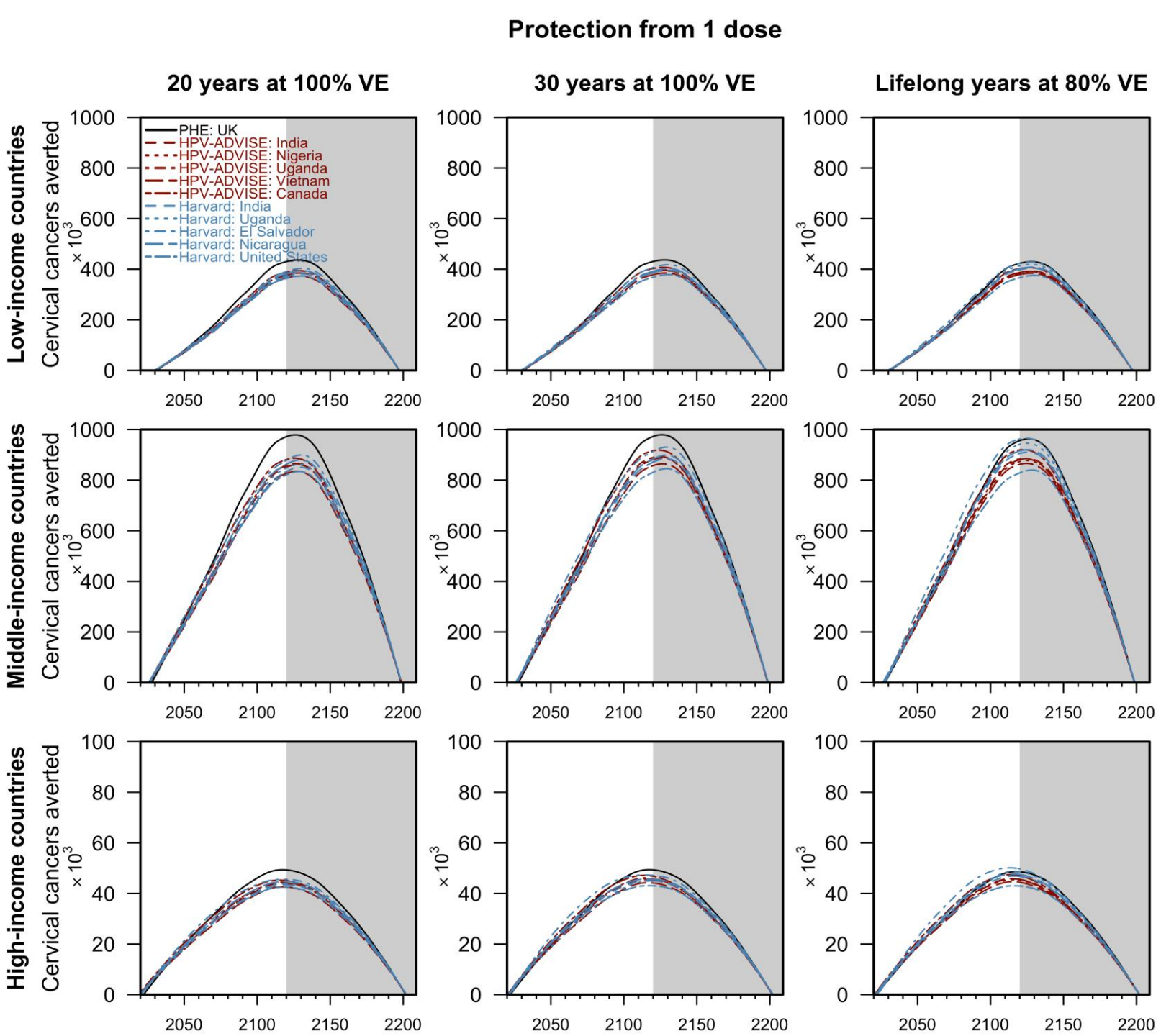
[1]*Brisson et al., 2016.* [2]*Choi et al., 2010.*
[3]*Campos et al., 2014.* [4]*Jit et al., 2014.*

Model assumptions

1. **Future population projection** using UNWPP life tables[a]
2. **Time horizon**
   - Routine annual vaccination to start from **2021** to **2120**
3. **80% coverage**
4. **9-valent vaccine**
5. **Mortality** from cervical cancer by IARC's Globocan 2018
6. **Discounting**
   - 3% on costs (0% as well but not presented)
   - 0% on health outcomes (3% as well but not presented)

[a] *World Population Prospects 2019*

Cervical cancers averted



0% discounting on health outcomes

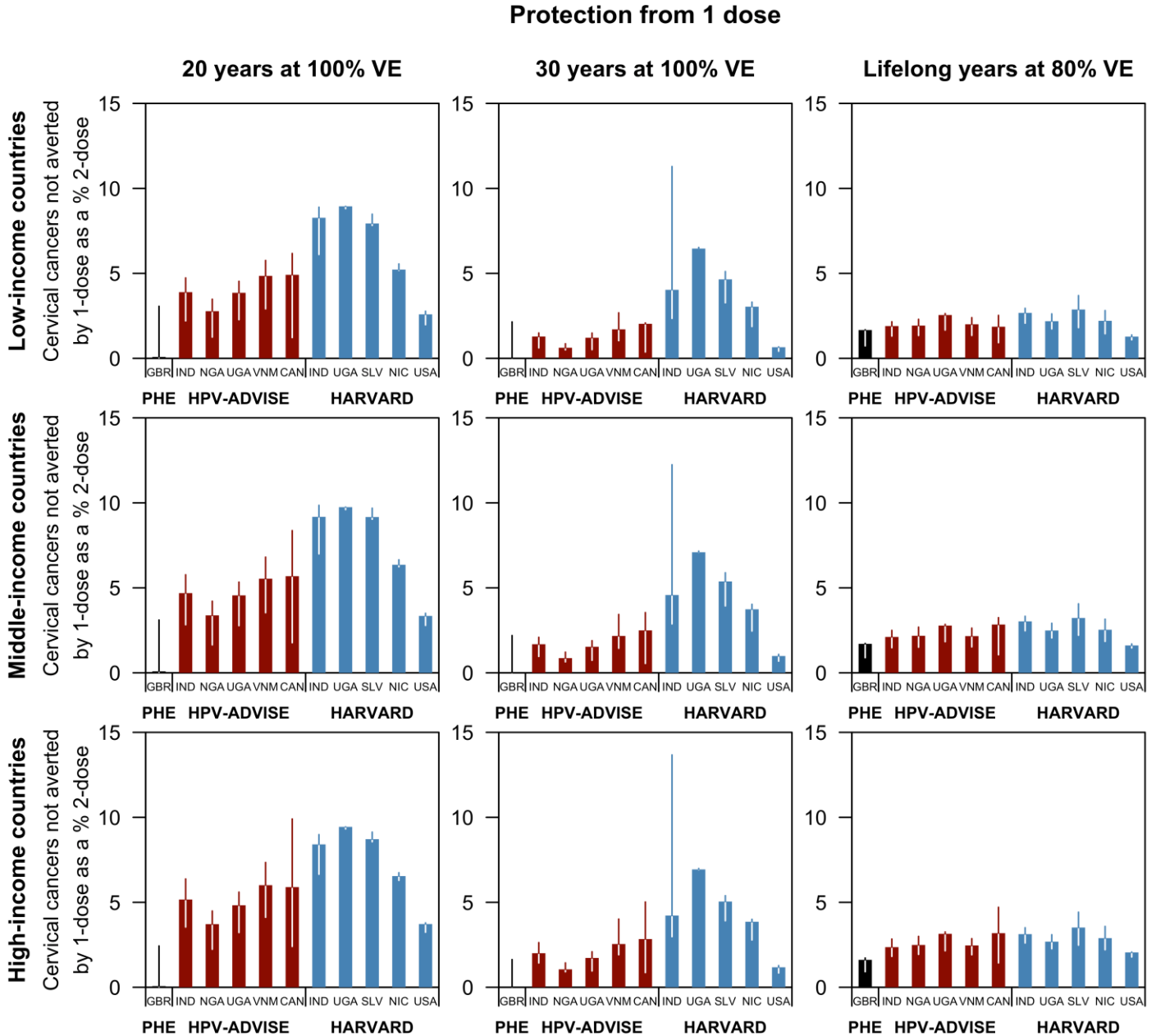
Perfect vaccine vs one-dose scenarios

One-dose schedule with a shorter duration of protection compared to perfect vaccine

- **PHE model** (parameterised with data from the UK): **99.9% (80%UI 97·6–100%)** cases could be averted

- **HPV-ADVISE and Harvard models** (mostly parameterised with data from LMICs): **93.8% (80%UI 92·1–95·0%)** cases could be averted

*y-axis scale of the figure is 0–15%, not 0–100%



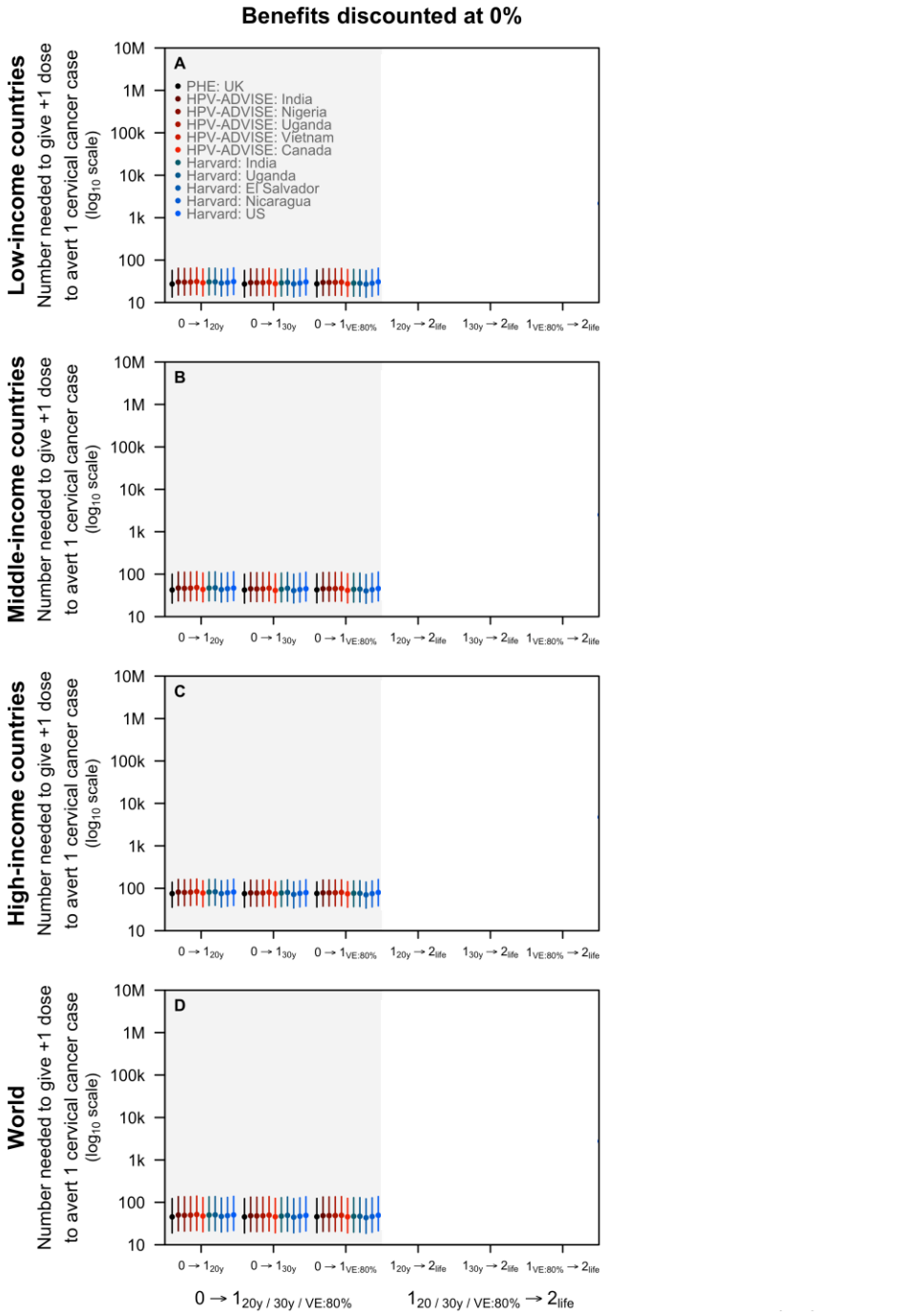
0% discounting on health outcomes

Number needed to “vaccinate”

Number needed to give that extra dose to avert one more cervical cancer case

0 ⟶ 1 dose (20y/30y/VE80% protection)

- **Fewer girls** need to be vaccinated with the **first dose** to prevent one cervical cancer case **in LIC than HIC**
  - If one-dose confers 20 years of protection, LIC: 30 (80%UI 15–64), MIC: 47 (80%UI 23–112), HIC: 81 (80%UI 39–161)



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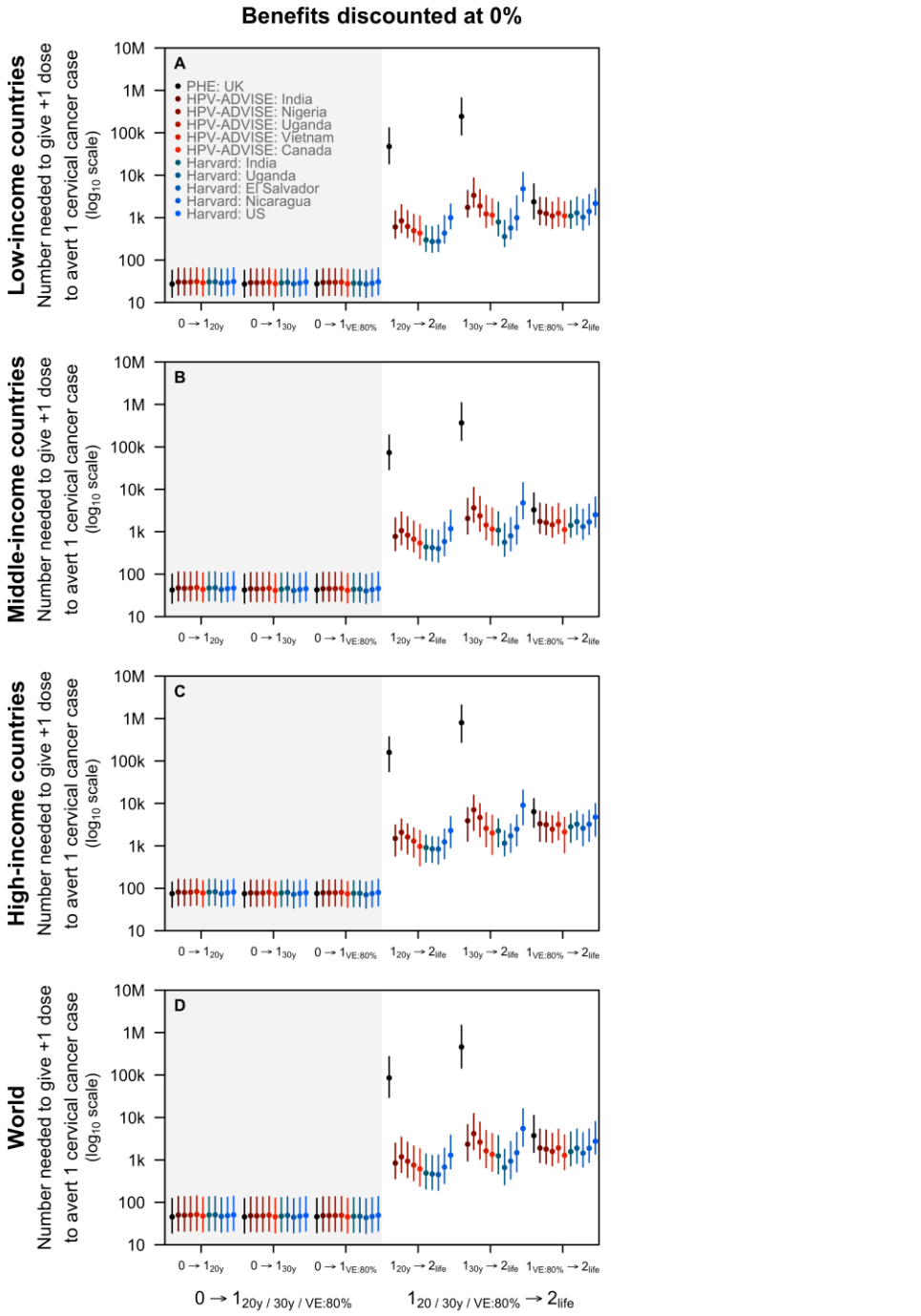
1 dose (20y/30y/VE80% protection) ⟶ 2 doses (lifetime protection)

- **Many more girls** need to be vaccinated with the **second dose**
  - (~330 to 5230 additional, depending on the epidemiological profiles of the country)



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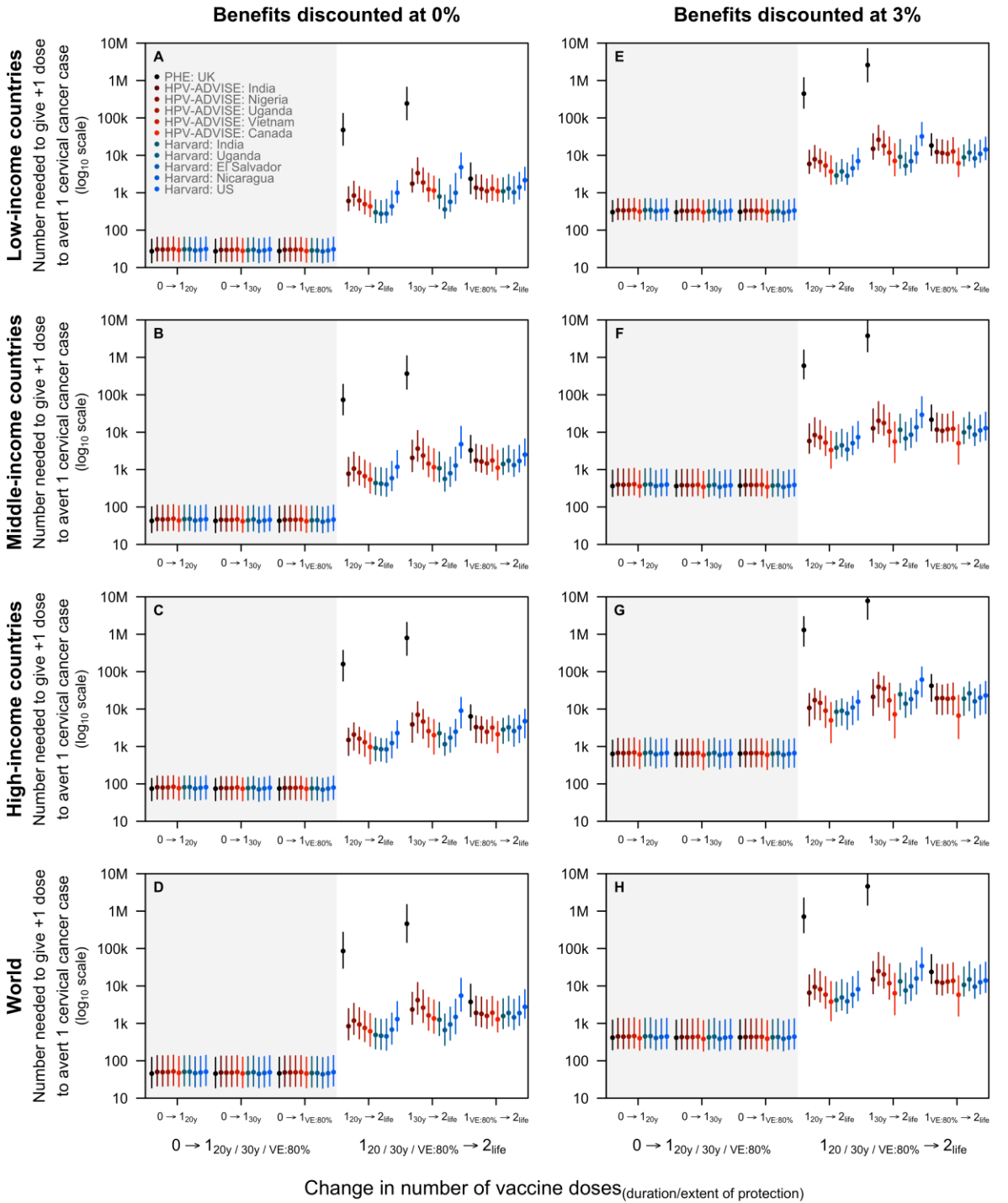


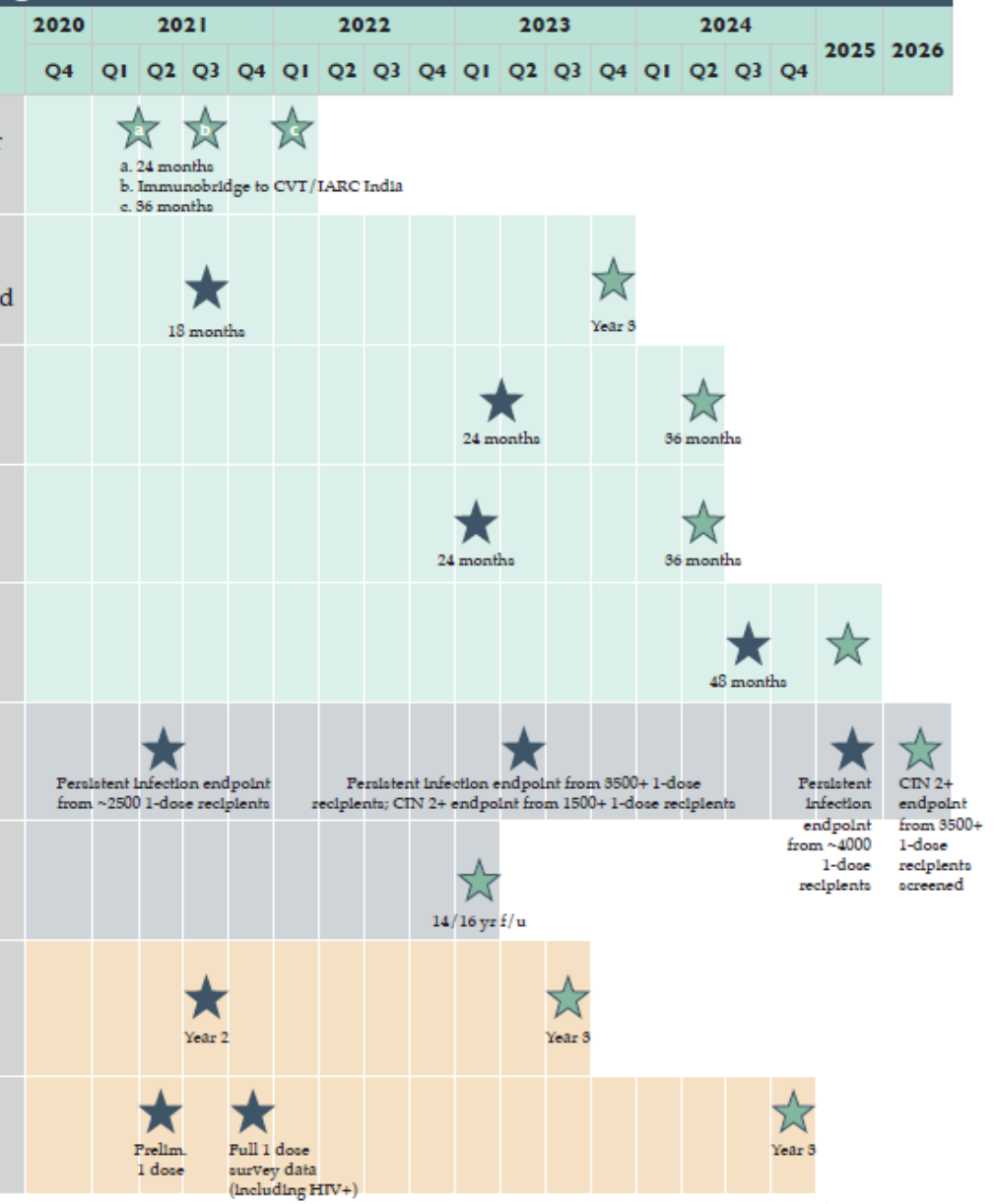
Looking ahead

Gaps, research priorities, and forthcoming evidence

- More evidence on single-dose HPV vaccine is needed. Several clinical studies are underway to address the durability of protection, efficacy, effectiveness, immunogenicity of a single dose, and the standardization of laboratory assays will also be important
- An updated systematic review will include any newly published studies on efficacy and immunogenicity; single-dose effectiveness of HPV vaccination from observational studies; and new quality assessments of the evidence
- Evidence generated by future modeling work will focus on integrating new trial, non-trial, and effectiveness data into existing models, as well as conducting model-based analyses in LMICs with different sexual behavior and epidemiological profiles
- In South Africa and other countries with high prevalence of HIV infection, it will be critical to generate more evidence on the health and economic impacts of reduced-dose HPV vaccination in HIV-positive individuals

Table 3.
Ongoing and forthcoming efficacy, effectiveness, and immunogenicity studies of single-dose HPV vaccination

Study name (country)	Evidence type	Vaccine(s)	Brief description
DoRIS Tanzania	Immuno-genicity	HPV2 and HPV9	Girls 9-14 yo randomized to 1, 2, or 3 doses of HPV2 or HPV 9; n=155 each arm
KEN SHE Kenya	Efficacy *(virological EP)*	HPV2 vs HPV9 vs MenACWY (delay HPV)	Girls 15-20 yo randomized to 1 dose of HPV2, HPV9, or MenACWY; n=750 each arm; delayed dose 2 planned
HANDS The Gambia	Immuno-genicity	HPV9	Girls 4-8 yo and 9-14 yo randomized to 1 or 2 doses; girls 15-26 yo given 3 doses; n=344 each arm
Primavera Costa Rica	Immuno-genicity	HPV2 and HPV4	Girls 10-13 yo 1-dose HPV2 immunobridge to women 18-25 yo 3-doses HPV4; n=520 each
ESCUDDO Costa Rica	Efficacy *(virological EP)*	HPV2 and HPV9	Girls 12-16 yo randomized to 1 or 2 doses of HPV2 or HPV9; n=5000 each arm
India IARC India	Efficacy *(virological and histological EP)*	HPV4	Girls 10-18 yo received 1, 2, 3 doses of HPV4; n=17586, 1-dose n=4980
CVT Costa Rica	Efficacy *till Y11* / Immuno-genicity	HPV2 vs control	Women 18-25 yo received 1, 2, or 3 doses of HPV2; n=3727, 1-dose n=196
Thailand impact study Thailand	Effectiveness *(virological EP)*	HPV2	Girls in grade 8 given 1 or 2 doses; n=~8000 each arm | prevalence surveys of girls grades 10, 12; n=2,400 each grade x 2 provinces
HOPE South Africa	Effectiveness *(virological EP)*	HPV2	Girls 17-18 yo serial prevalence surveys: unvaccinated (17-18 yo), 1-dose catch up (15-16 yo), and 2-dose routine (9 yo) cohorts; n≥3260



Available Resources

- Fact sheet
- Evidence Review
- Technical Synthesis
- General Summary
- Consensus statement
- Website: path.org/singledosehpv
- HPVFlash newsletter: path.org/hpvflash

Questions

For more information

The consortium, coordinated by PATH, includes Harvard University, London School of Hygiene & Tropical Medicine, Université Laval, University of British Columbia, US Centers for Disease Control and Prevention, US National Cancer Institute, and Wits Reproductive Health and HIV Institute.

In addition to the consortium members, representatives from the following institutions serve as advisors: the World Health Organization, International Agency for Research on Cancer; Medical Research Council Unit The Gambia at the London School of Hygiene & Tropical Medicine; Instituto Nacional de Salud Pública de Mexico; Quebec Institut National de Santé Publique; Victorian Cytology Service, Australia; University of Washington, USA; and International Vaccine Institute, South Korea.

Inquiries about this project can be directed to Evan Simpson, esimpson@path.org.