Current and Future Impact of HPV Vaccination

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The HPV Day
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The views expressed are my own and do not necessarily reflect those of NCI/NIH

Disclosures

- National Institutes of Health (NIH) has patents on papillomavirus L1 virus-like particle (VLP) vaccine technology. John and I are inventors.
- NIH has licensed L1 VLP technology to Merck and GlaxoSmithKline, the two companies with FDA-approved versions of the vaccine.
- **I will discuss a potential off-label use of the FDA-approved vaccines: fewer vaccine doses**
- Licensees of other NIH technologies of which we are inventors: GlaxoSmithKline, Sanofi, Shanta Biotech, Cytos Biotech, Aura Biosciences, Etna Biotech, Acambis, PanVax

Today's topics from John and me

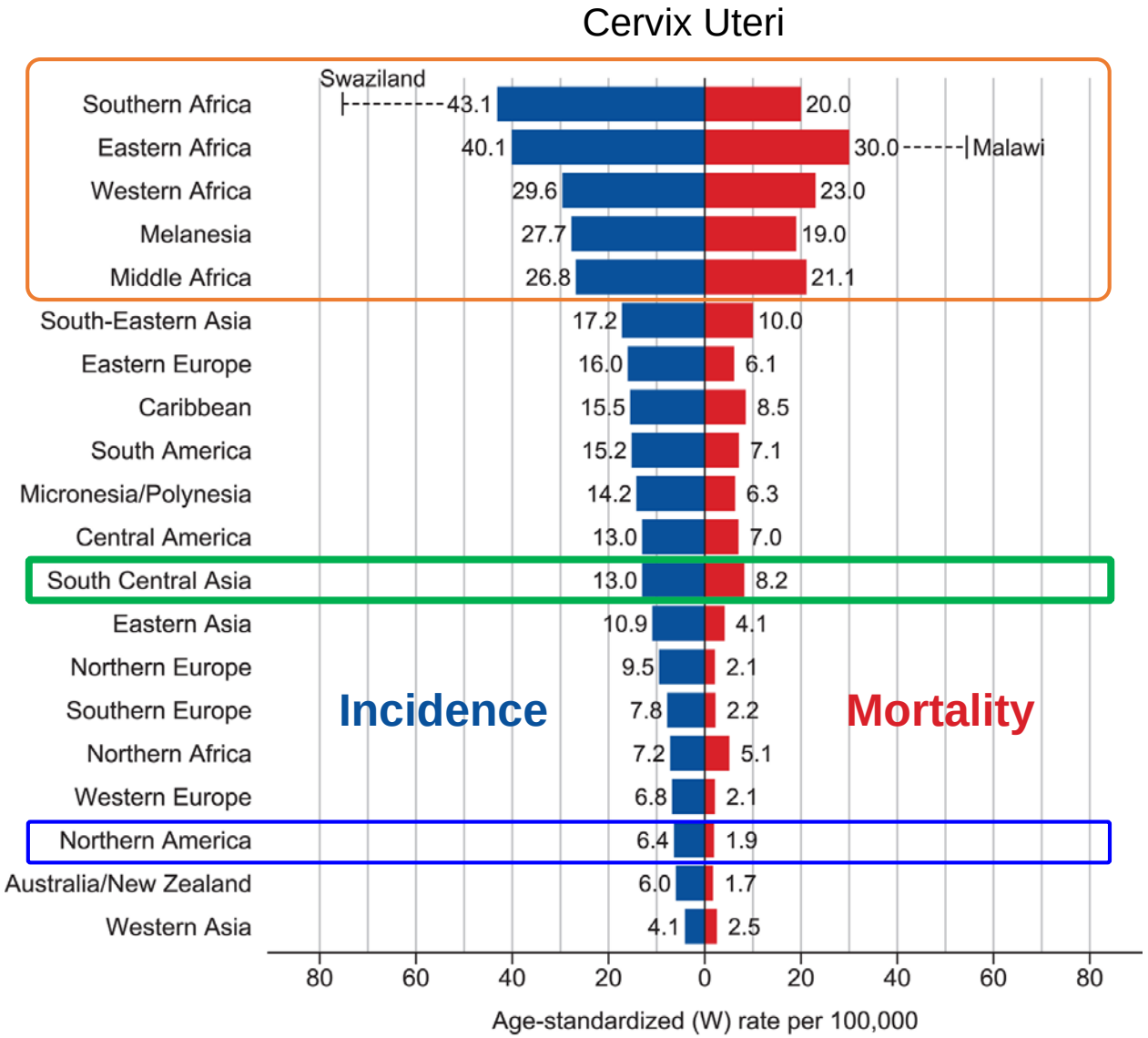
- **Epidemiology of HPV-associated cancer:** mainly cervical cancer in some countries, several forms of cancer in other countries
- **HPV vaccine:** Highly immunogenic, can prevent mild and serious infection and disease, can confer long-term protection even after a single dose
- **John's presentation:** Will discuss mechanistic basis for long-term high efficacy of HPV vaccine

Epidemiology of HPV-associated cancers:

It depends on where you live

Global Disparities in Cervical Cancer Cases & Deaths:

~Compared with USA: ~2-fold higher in Asia, >5-fold higher in Africa



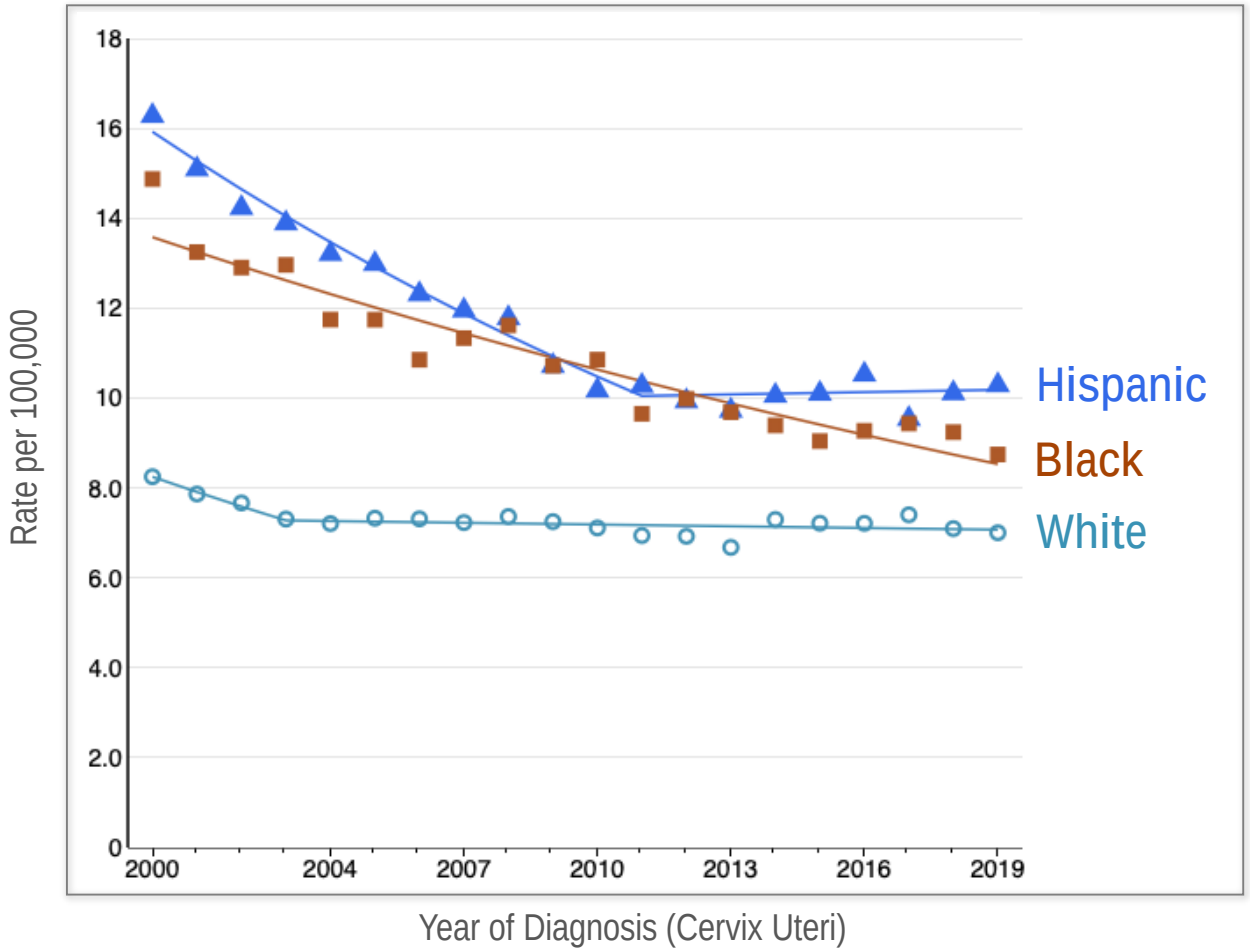
Low- and middle-income countries:

- **90% of cervical cancer cases and deaths** (projected to increase by 2% each year)
- Cervical cancer represents 90% of HPV-associated cancer

Bray et al, Global cancer statistics 2018, Cancer 2018.

USA Cervical Cancer Incidence and Mortality

Age-Adjusted Incidence Rates 2000-2019

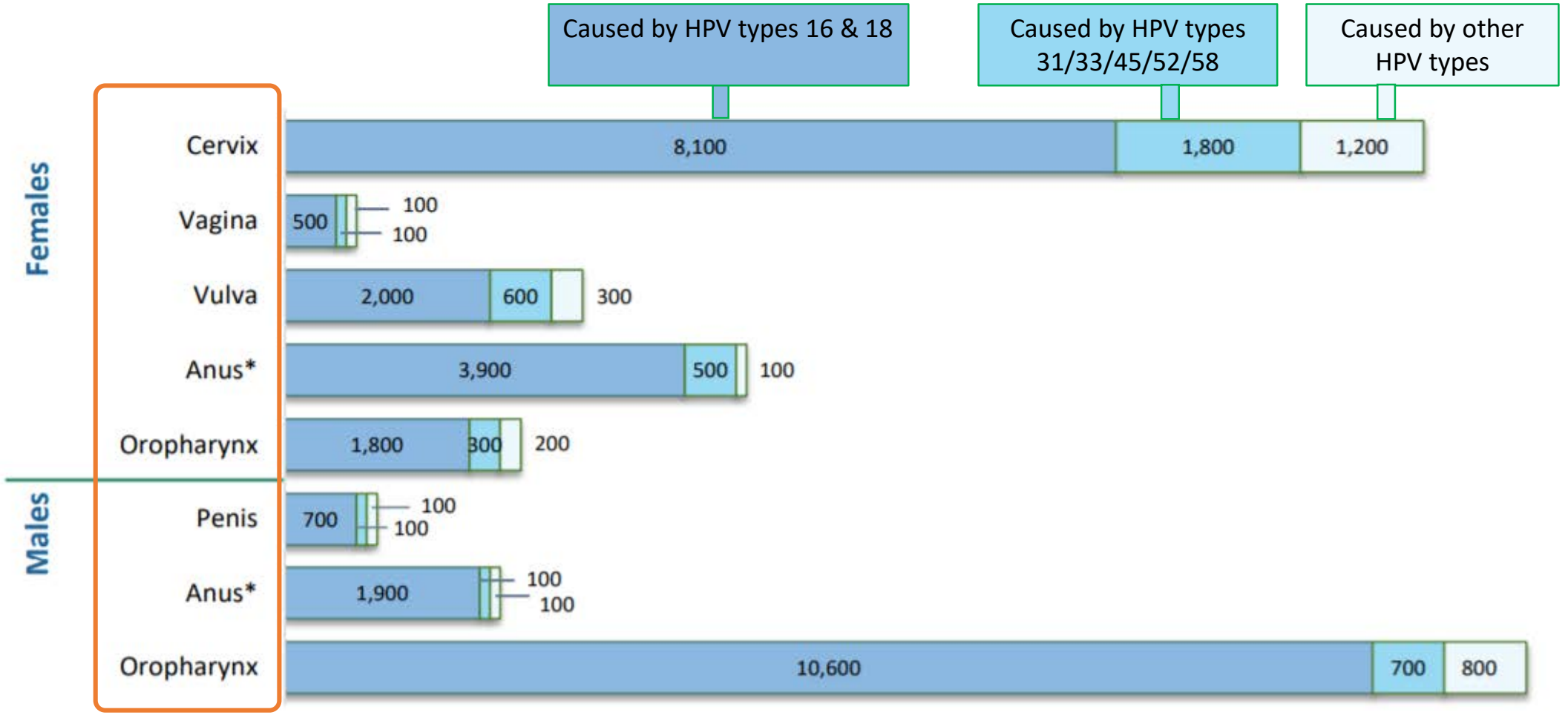


Est. new cases/deaths in 2022:

- New cases: 14,100
- Deaths: 4,280

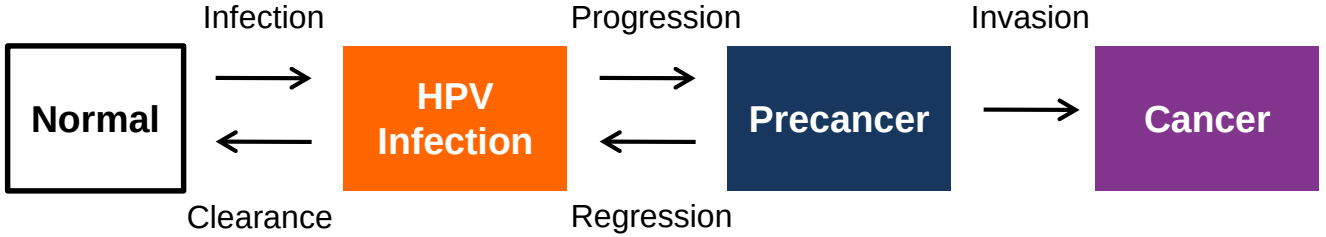
Current Mortality Rates (2020) per 100,000	
Black women	3.2
Hispanic	2.5
White	2.1
American Indian / Alaska Native	2.1
Asian / Pacific Islander	1.7

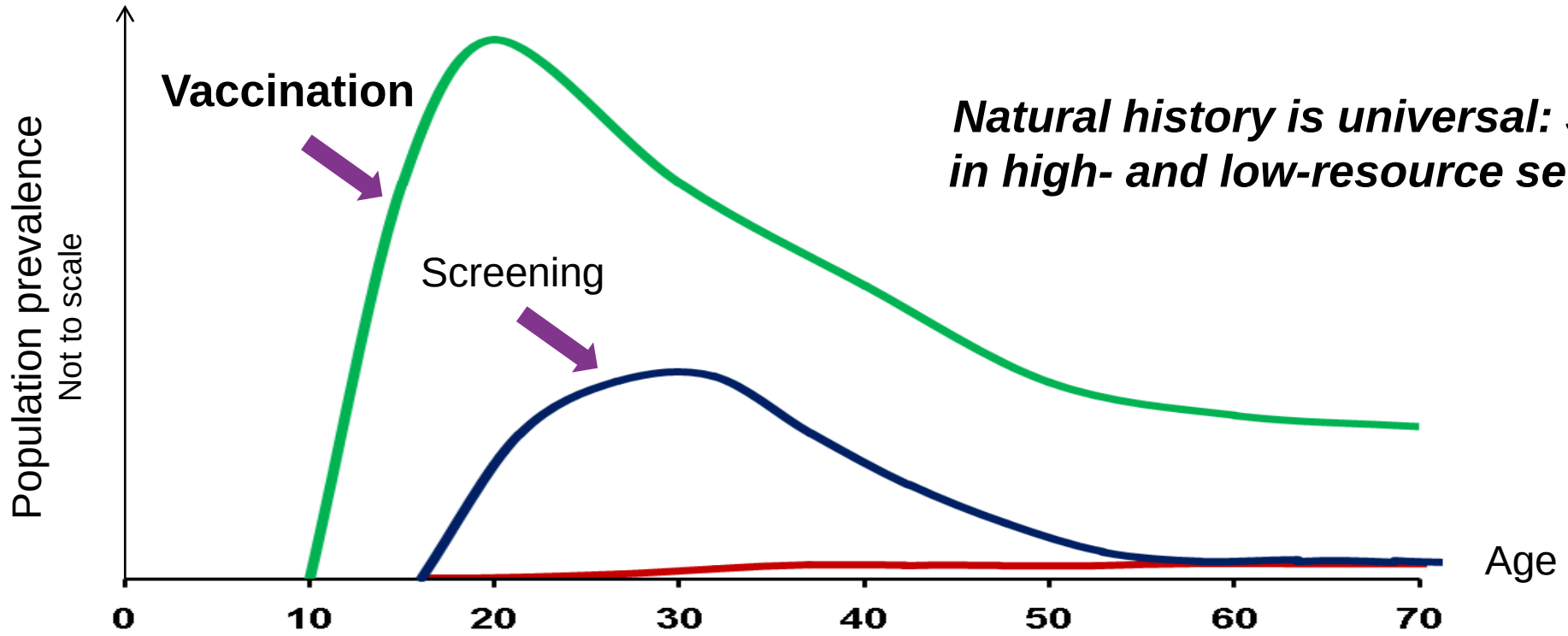
HPV-attributable cancer cases/year in USA = 36,500



Centers for Disease Control and Prevention. Cancers Associated with Human Papillomavirus, United States—2014–2018 USCS Data Brief, no. 26. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services; 2021.

Cervical cancer natural history and prevention: Intervene before cancer develops

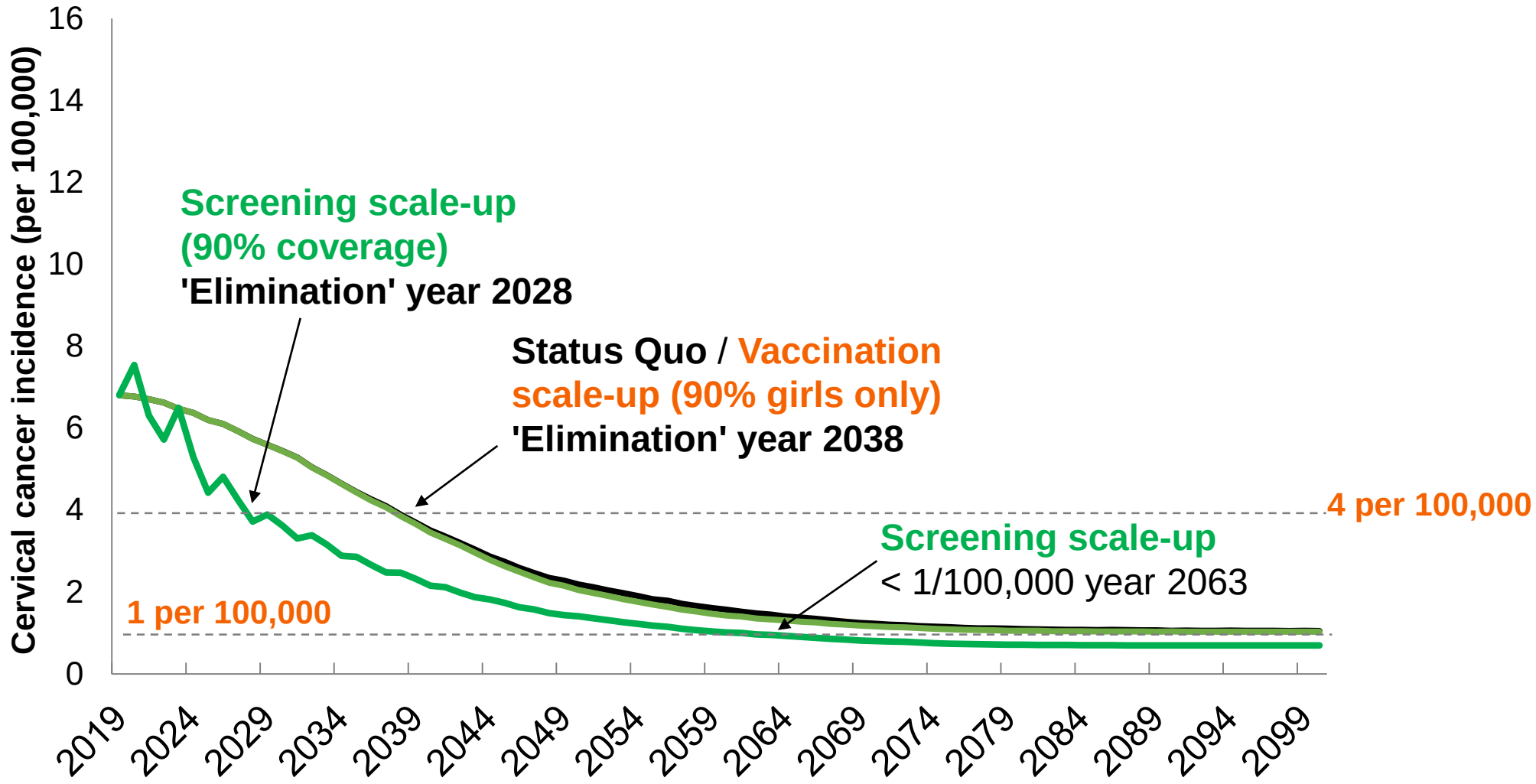




Natural history is universal: Same in high- and low-resource settings

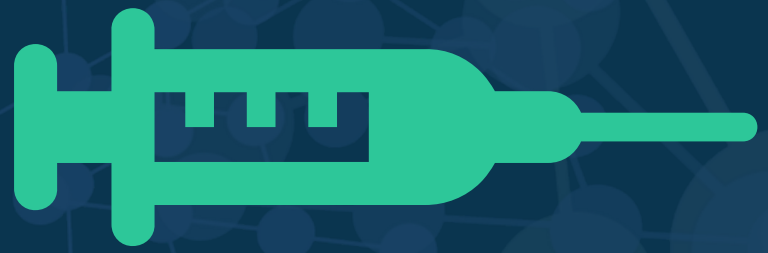
Wentzensen and Schiffman Lancet Public Health 2017

Cervical cancer incidence in USA will decline more rapidly by increasing screening than by increasing HPV vaccination

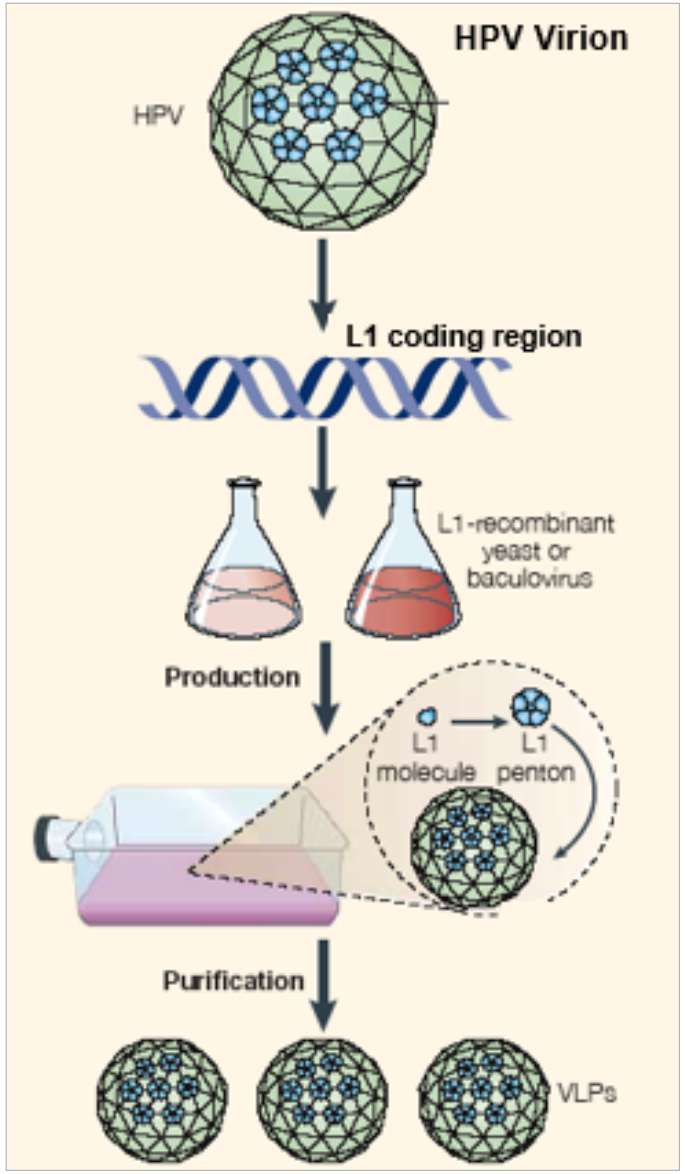


Burger et al, Lancet Public Health 5: e213-e222, 2020

HPV Vaccines

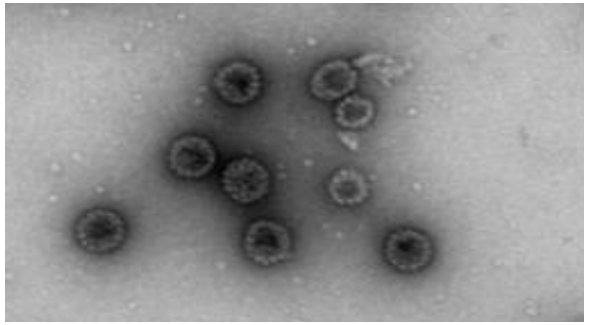


Prophylactic HPV Vaccines Are L1 Virus-Like Particles (VLPs)



Reinhard Kirnbauer et al. PNAS 1992

- Spontaneous assembly of 360 copies of L1 into a VLP
- VLPs induce high titer virion neutralizing antibodies
- VLPs are non-infectious & non-oncogenic



HPV16 L1 VLPs

HPV vaccines: L1 virus-like particles, multivalent

Cervarix (GSK):
(1st generation vaccine)

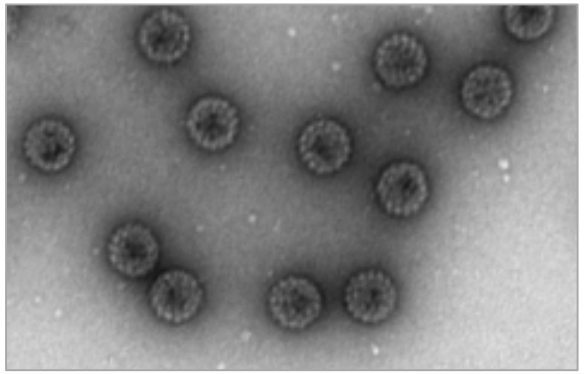
- HPV16/18

Gardasil (Merck):
(1st generation vaccine)

- HPV6/11
- HPV16/18

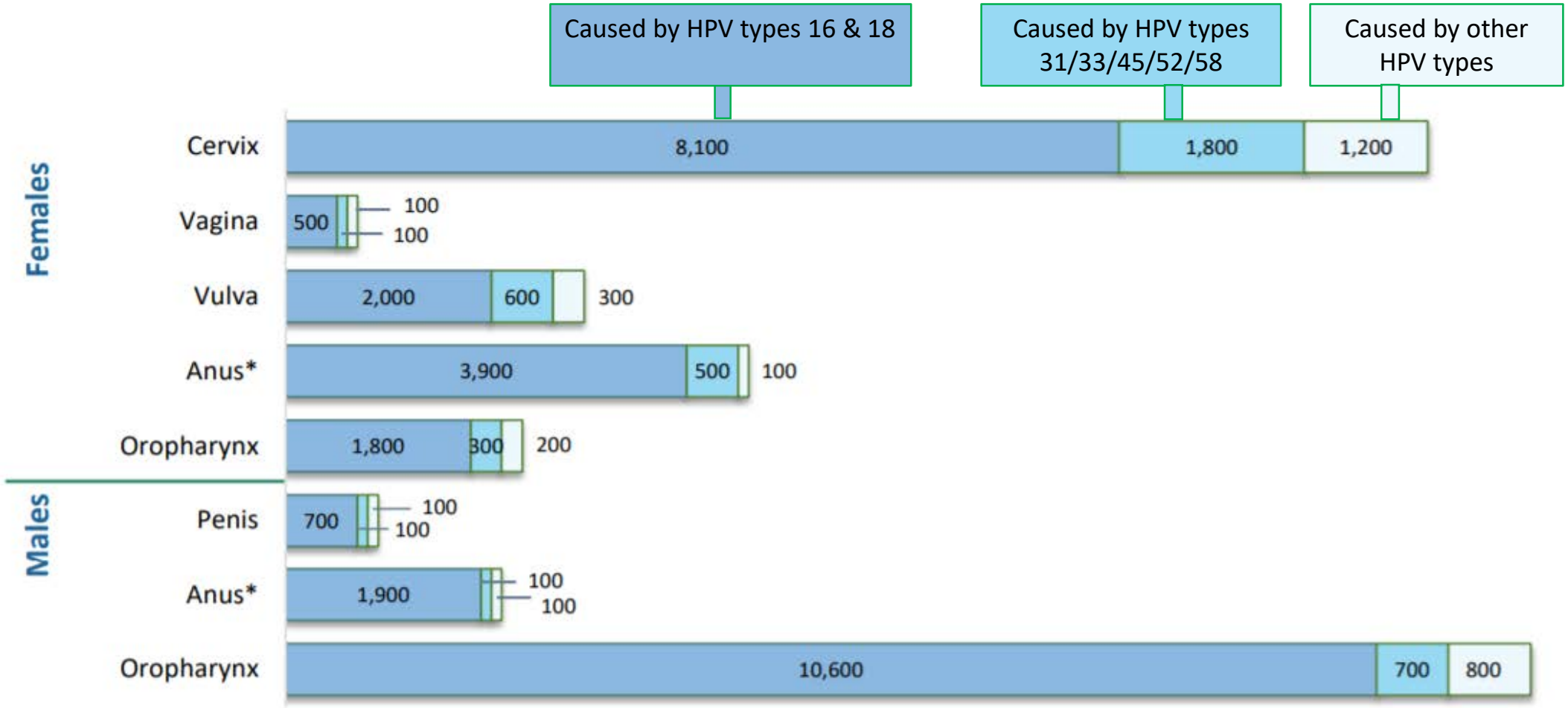
Gardasil-9 (Merck):
(2nd generation vaccine)

- HPV6/11
- HPV16/18
- HPV31/33/45/52/58



HPV16 L1
Virus-like particles

HPV-attributable cancer cases/year in USA = 36,500



Centers for Disease Control and Prevention. Cancers Associated with Human Papillomavirus, United States—2014–2018 USCS Data Brief, no. 26. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services; 2021.

Goals of HPV Vaccination

- Directly reduce risk of infection and disease in vaccinees
- Indirectly reduce risk by reducing prevalence of “HPV vaccine types” in general population (herd protection)

HUMAN VACCINES & IMMUNOTHERAPEUTICS
2016, VOL. 12, NO. 6, 1406–1417
http://dx.doi.org/10.1080/21645515.2016.1168952

Taylor & Francis
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REVIEW

OPEN ACCESS

Quadrivalent HPV vaccine safety review and safety monitoring plans for nine-valent HPV vaccine in the United States

Published 2016

Julianne Gee[a], Cindy Weinbaum[a], Lakshmi Sukumaran[a], and Lauri E. Markowitz[b]

[a]Division of Healthcare and Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA; [b]Division of Viral Diseases, National Center Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA

- *"With the exception of syncope, both pre-licensure and post-licensure 4vHPV safety data have been reassuring with no confirmed safety signals identified."*

HUMAN VACCINES & IMMUNOTHERAPEUTICS
https://doi.org/10.1080/21645515.2022.2159215

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RESEARCH ARTICLE

OPEN ACCESS Check for updates

Extended surveillance to assess safety of 9-valent human papillomavirus vaccine

Published 2022

Maria E. Sundaram[a], Burney A. Kieke[a], Kayla E. Hanson[a], Edward A. Belongia[a], Eric S. Weintraub[b], Matthew F. Daley[c], Rulin C. Hechter[d,e], Nicola P. Klein[f], Edwin M. Lewis[f], Allison L. Naleway[g], Jennifer C. Nelson[h], and James G. Donahue[a]

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- *"During a surveillance period of more than 5 years where more than 1.8 million doses of 9vHPV were administered…our longer term findings support the existing robust literature on 9vHPV vaccine safety."*

Some important clinical results against HPV types targeted by the vaccine

Vaccine has very high efficacy (>95%) & long duration of protection (>10 years)

Vaccine confers sterilizing immunity

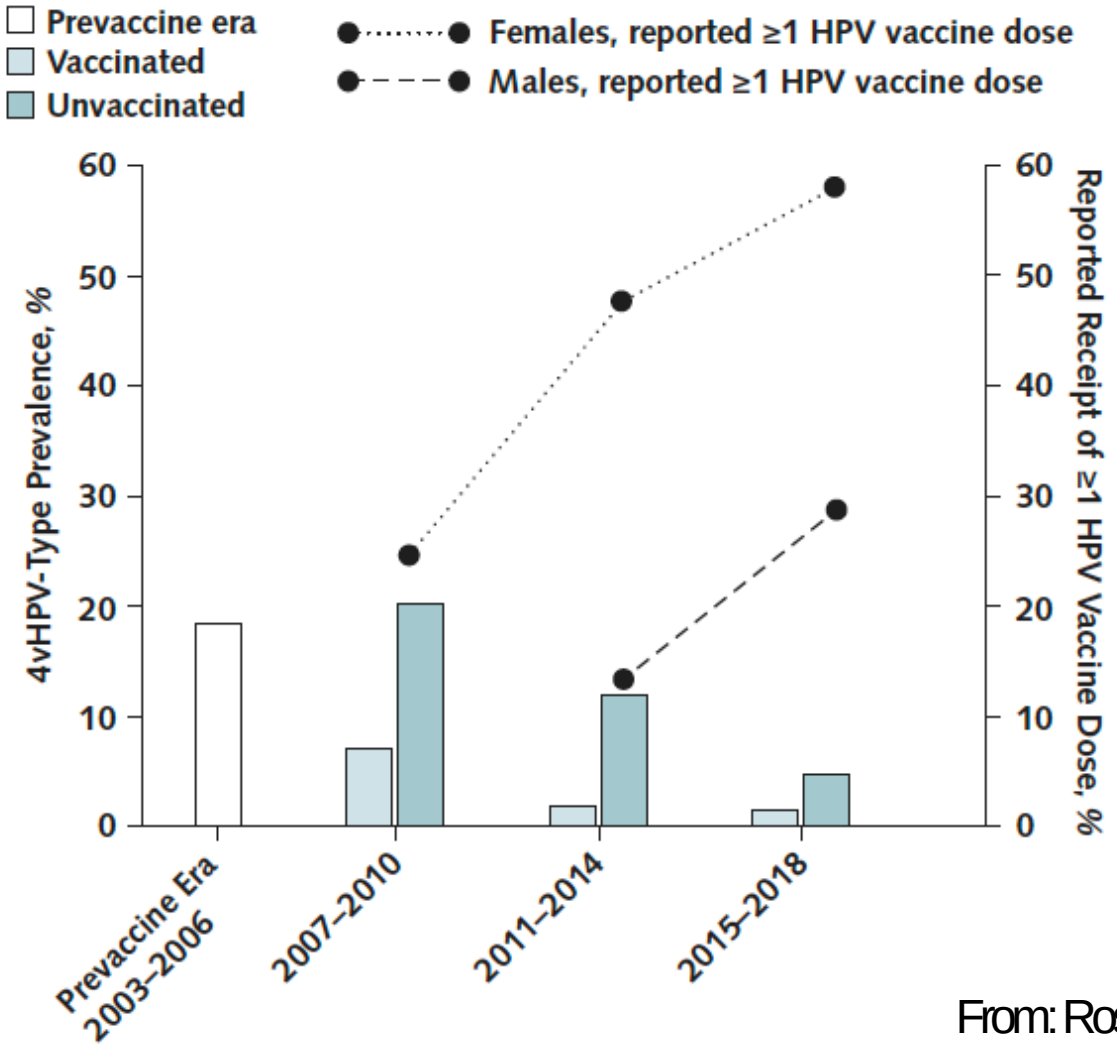
Prevents infection in most vaccinees

Vaccine induces herd immunity even with sub-optimal vaccine uptake

Vaccine does not treat established infection

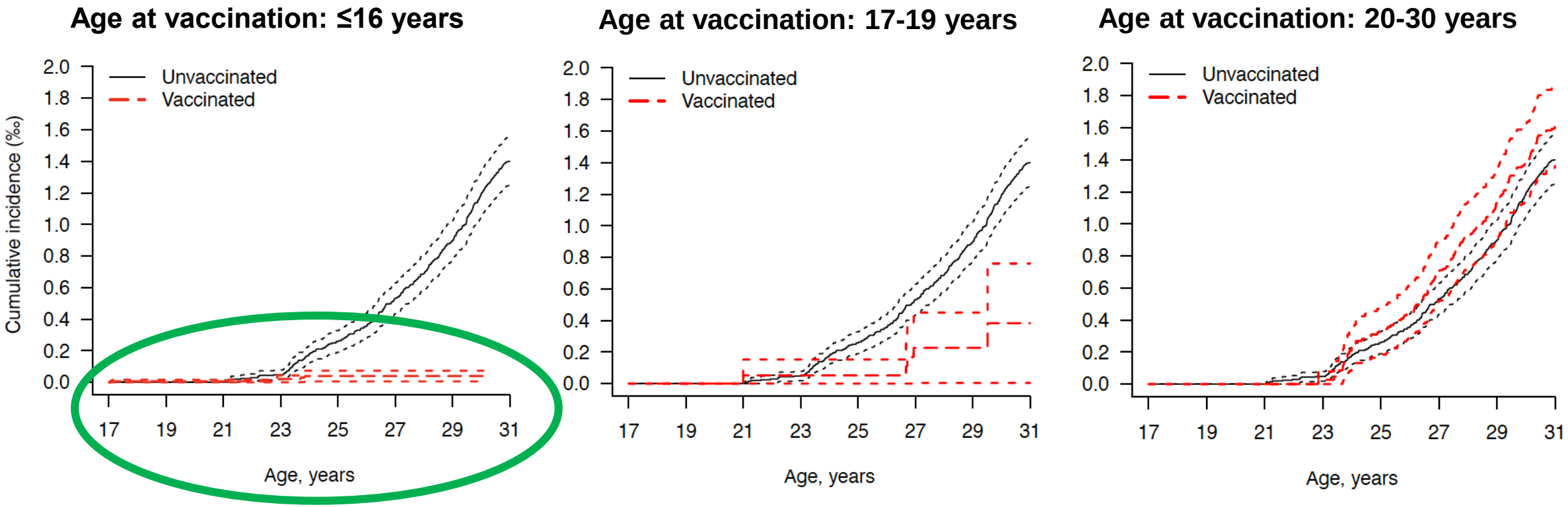
Schiller & Lowy, Vaccine, 2018; *Hildesheim et al, American Journal of Obstetrics and Gynecology, 2016; Rosenblum et al, CDC Morbidity and Mortality Weekly Report (MMWR), 2021*

Herd protection in 14-24 year old women 12 years after HPV vaccine introduction in USA



From: Rosenblum et al, Annals Int. Med. 2022

Cervical cancer incidence decreased ~90% in Danish women vaccinated at 16 years old or younger



Kjaer, et al. Real world effectiveness of human papillomavirus vaccination against cervical cancer. *Journal of the National Cancer Institute*, 2021.

Similar results have been reported in England and Denmark

Some clinical differences between HPV vaccine and SARS-CoV-2 mRNA vaccine (1)

HPV vaccine

- Vaccination prevents even benign infection in most vaccinees
- Vaccination readily induces herd protection

SARS-CoV-2 vaccine

- Many vaccinees remain susceptible to mild infection
- Vaccination not shown to induce herd protection

Some clinical differences between HPV vaccine and SARS-CoV-2 mRNA vaccine (2)

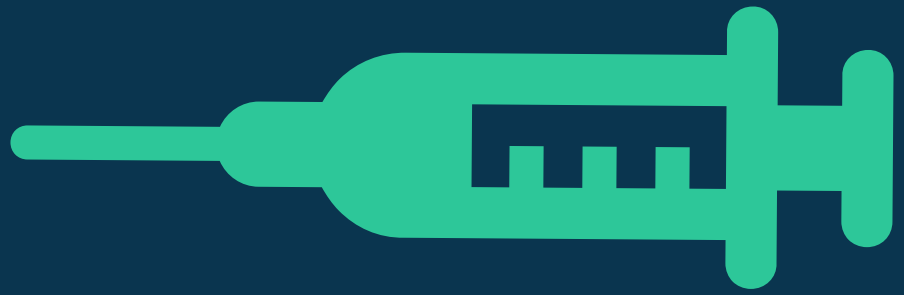
HPV vaccine

- Vaccine confers strong protection against all variants within a given HPV type
- Vaccine induces >10 years of strong protection

SARS-CoV-2 vaccine

- Vaccine may confer reduced protection against some variants
- Two doses provide several months of protection

Might a single HPV vaccine dose confer years of protection?



Worldwide control of cervical cancer requires worldwide female vaccination

The need

- HPV vaccination of >40 million women in each birth cohort is needed
- Most of these women live in LMICs
- Each birth cohort is ~60 million women

Current reality

- ~10% of eligible young women in LMICs get vaccinated each year

A possible solution

Single dose HPV vaccination

- Less expensive and logistically easier than two doses
- **Not yet standard of care**

OXFORD

JNCI J Natl Cancer Inst (2020) 112(10): djaa011

doi: 10.1093/jnci/djaa011
First published online February 10, 2020
Article

Evaluation of Durability of a Single Dose of the Bivalent HPV Vaccine: The CVT Trial

Aimée R. Kreimer, PhD,[1,*,‡] Joshua N. Sampson, PhD,[1,‡] Carolina Porras, MSc,[2] John T. Schiller, PhD,[1] Troy Kemp, PhD,[3] Rolando Herrero, MD, PhD,[2,4] Sarah Wagner, BSc,[1,5] Joseph Boland, PhD,[1,5] John Schussler, BS,[6] Douglas R. Lowy, MD,[1] Stephen Chanock, MD,[1] David Roberson, BS,[1,5] Mónica S. Sierra, PhD,[1] Sabrina H. Tsang, PhD,[1] Mark Schiffman, MD,[1] Ana Cecilia Rodriguez, MD,[7] Bernal Cortes, PharmD,[2] Mitchell H. Gail, MD, PhD,[1] Allan Hildesheim, PhD,[1] Paula Gonzalez, MD,[2,^] Ligia A. Pinto, PhD; [3,^] for the Costa Rica HPV Vaccine Trial (CVT) Group

- 1 vaccine dose prevented HPV16/18 infection as effectively as 2 or 3 doses 11 years after vaccination (post-hoc analysis)
- 100% of women who received 1 vaccine dose remained positive for HPV16/18 antibodies 11 years after vaccination

Current research is evaluating efficacy of a single HPV vaccine dose

- **Post-hoc analyses: >10 years of strong protection (Cervarix or Gardasil):** *Kreimer et al, J Natl Cancer Inst 112:1038-46, 2020; Basu et al, Lancet Oncol 11:1518-29, 2021*
- **Ongoing NCI efficacy trial comparing one-dose vs. two-doses of Cervarix or Gardasil-9:** *Porras et al, Vaccine 40:76-88, 2022*
- **18 month trial >95% efficacy (Cervarix or Gardasil-9):** *Barnabas et al. NEJM Evid. DOI: 10.1056/EVIDoa2100056, 2022*

An April 2022 Landmark Decision by the WHO

A single dose of the HPV vaccine offers solid protection against cervical cancer

WHO SAGE* now recommends:

- One or two doses for girls aged 9-14 (previously only two doses)
- One or two doses for young women aged 15-20 (previously three doses)
- Two doses for women older than 21 (previously three doses)
- Immunocompromised, including HIV+: at least two doses, three if feasible

**SAGE = Strategic Advisory Group of Experts on Immunization*

Summary and Conclusions

- Basic research led to identification of HPV as the cause of several cancers and to development of HPV vaccines
- Virus-like particle display is highly immunogenic; it can induce herd immunity, durable protection, and prevent cervical cancer
- If the HPV vaccine is FDA-approved for a single dose, it will be the first sub-unit vaccine to achieve single-dose approval
- **A global single-dose recommendation could make it feasible to control the worldwide public health problem of HPV-associated cancer**