

Single-dose HPV vaccination

Aimée R. Kreimer, PhD

Senior Investigator
Division of Cancer Epidemiology and Genetics

February 2021

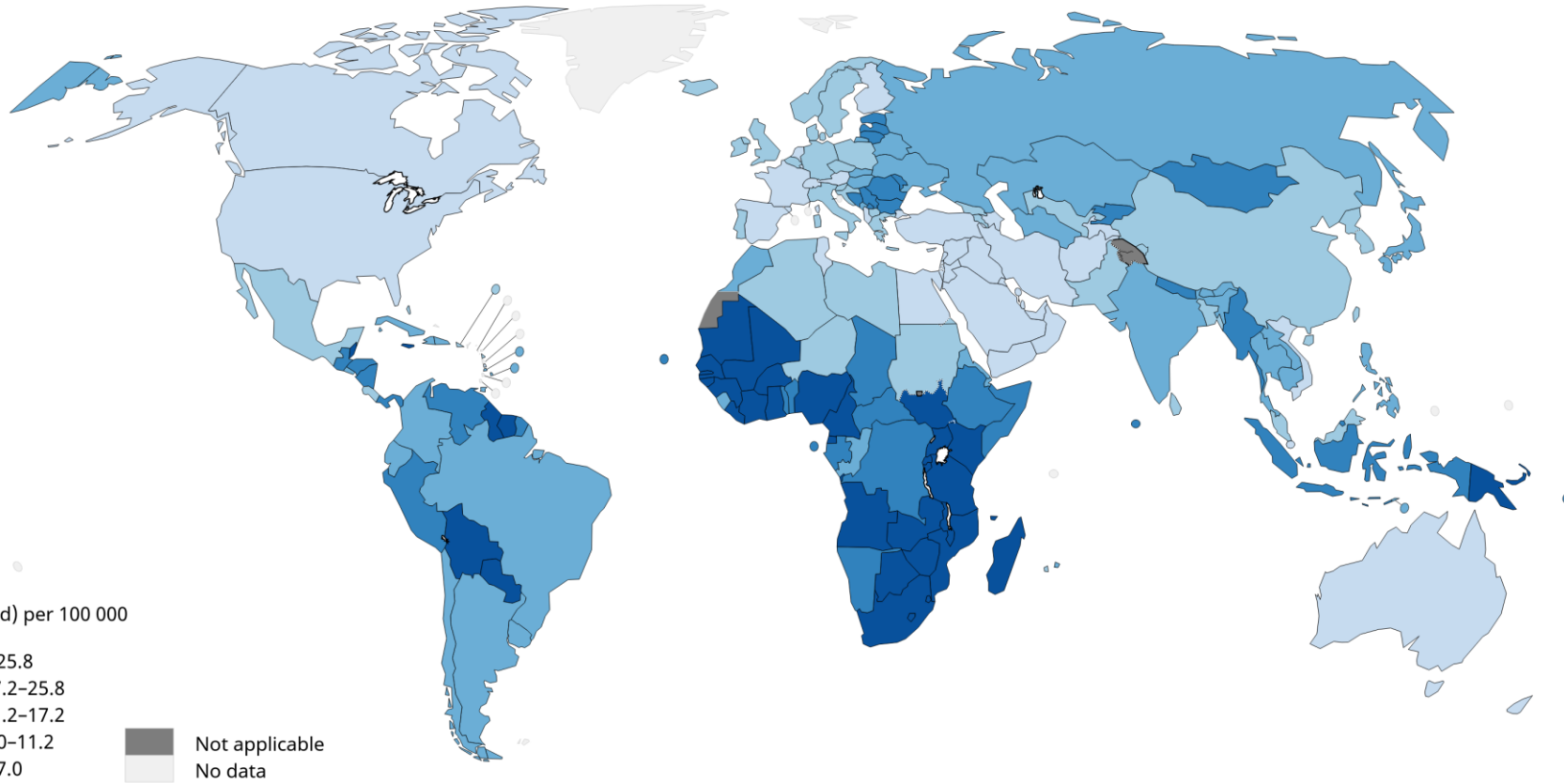
Nothing to disclose



Global Cervical Cancer Incidence

“A Story of Inequality”

Estimated age-standardized incidence rates (World) in 2018, cervix uteri, ages 0-79



HPV Vaccine Introductions by World Bank Category

LIC	7 of 34 have introduced
LMIC	9 of 47 have introduced
UMIC	34 of 58 have introduced
HIC	68 of 86 have introduced

PATH
10A0+//20

Number of cases and deaths expected to increase substantially in the coming decades



“Cervical cancer is one of the most preventable and treatable forms of cancer...”



November 17, 2020

Home / News / A cervical cancer-free future: First-ever global commitment to eliminate a cancer



**A cervical cancer-free future:
First-ever global commitment to
eliminate a cancer**

Share icons: WhatsApp, Email, Facebook, Twitter, Plus

Language buttons: العربية, 中文, Français, Русский, Español

Global strategy, by 2030:

- HPV vaccinate 90% of girls by age 15 years;
- Screen 70% of women at age 35 and 45 years with a high-precision test; and,
- Provide treatment and care to 90% of women identified with cervical disease.



How can we accelerate HPV vaccination?

Presentation outline

1. Post-hoc analyses of RCTs
 - Bivalent HPV Vaccine- Costa Rica HPV Vaccine Trial
 - Quadrivalent HPV Vaccine- India HPV Vaccine Trial
2. Vaccine registry/phase 4 studies
3. Trials that aim to investigate single-dose efficacy



NCI Costa Rica Vaccine Trial (CVT)



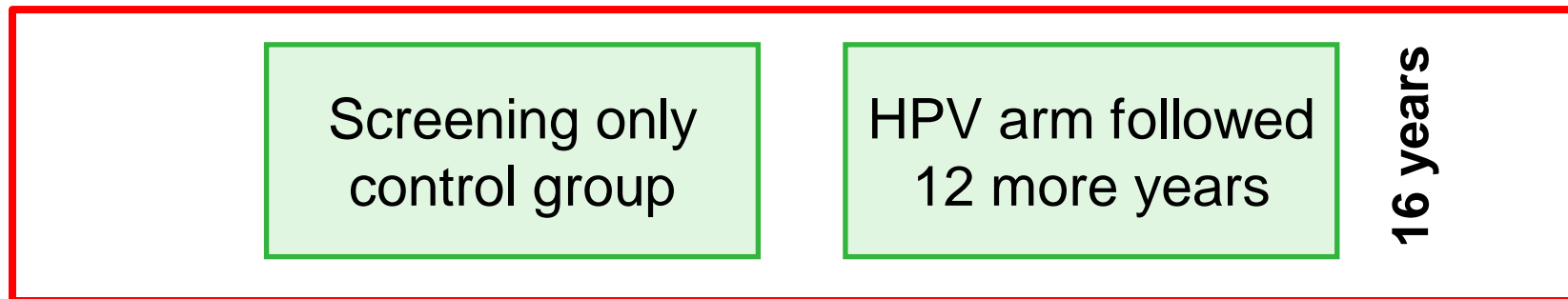
7,466 Women
18-25 years old
2004 - 2005

Annual follow-up for
4 years

Hepatitis A Vaccine
(control)

Cervarix
GSK HPV-16/18

20% received <3 doses

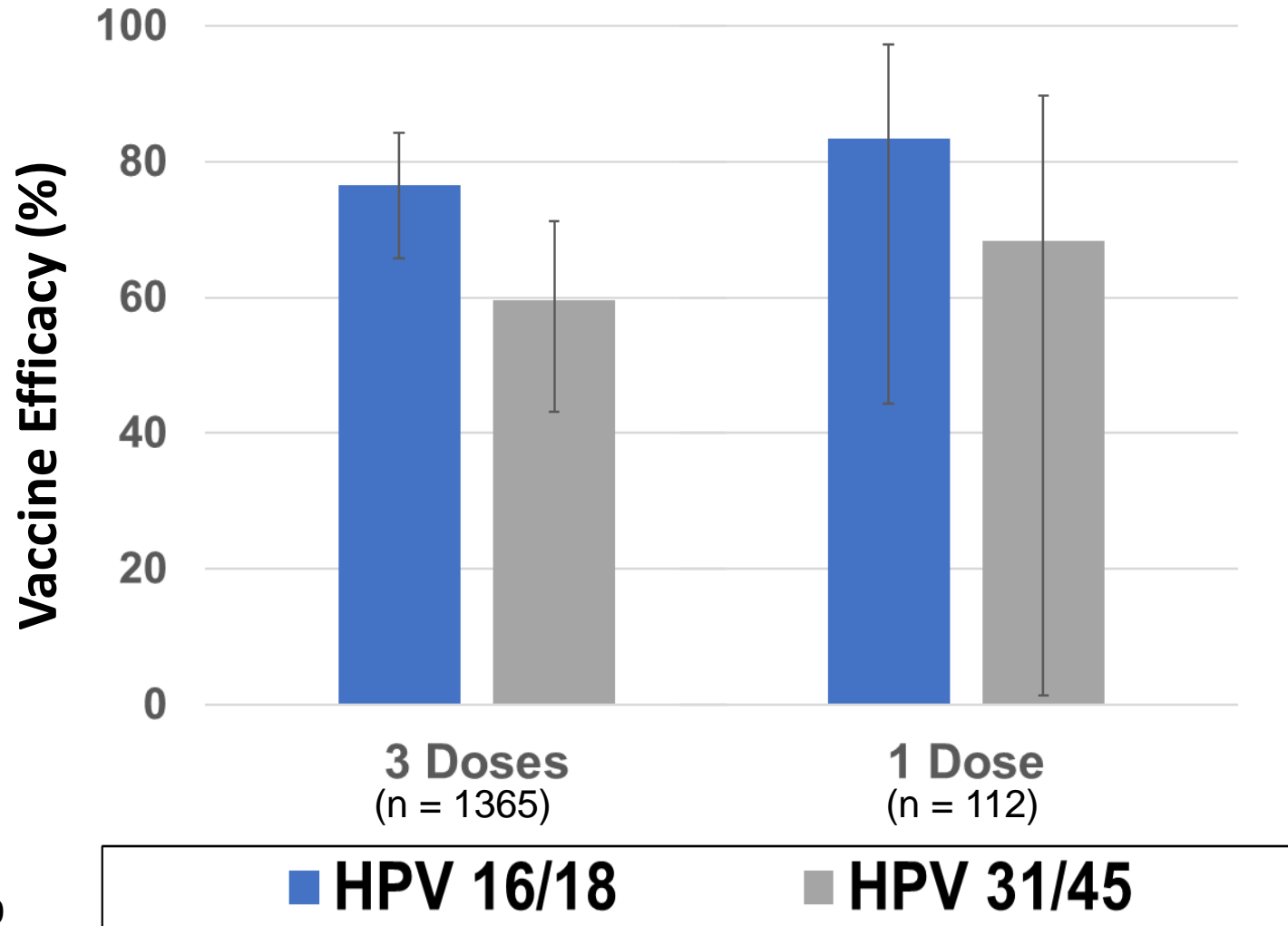


**Research questions shift to DURABILITY of HPV vaccination:
CVT Long-term Follow-up**



CVT: VE 11 years since bivalent HPV vaccine, by dose

Endpoint: Prevalent HPV infection; Cohort: total vaccinated cohort



Kreimer AR et al, JNCI 2020

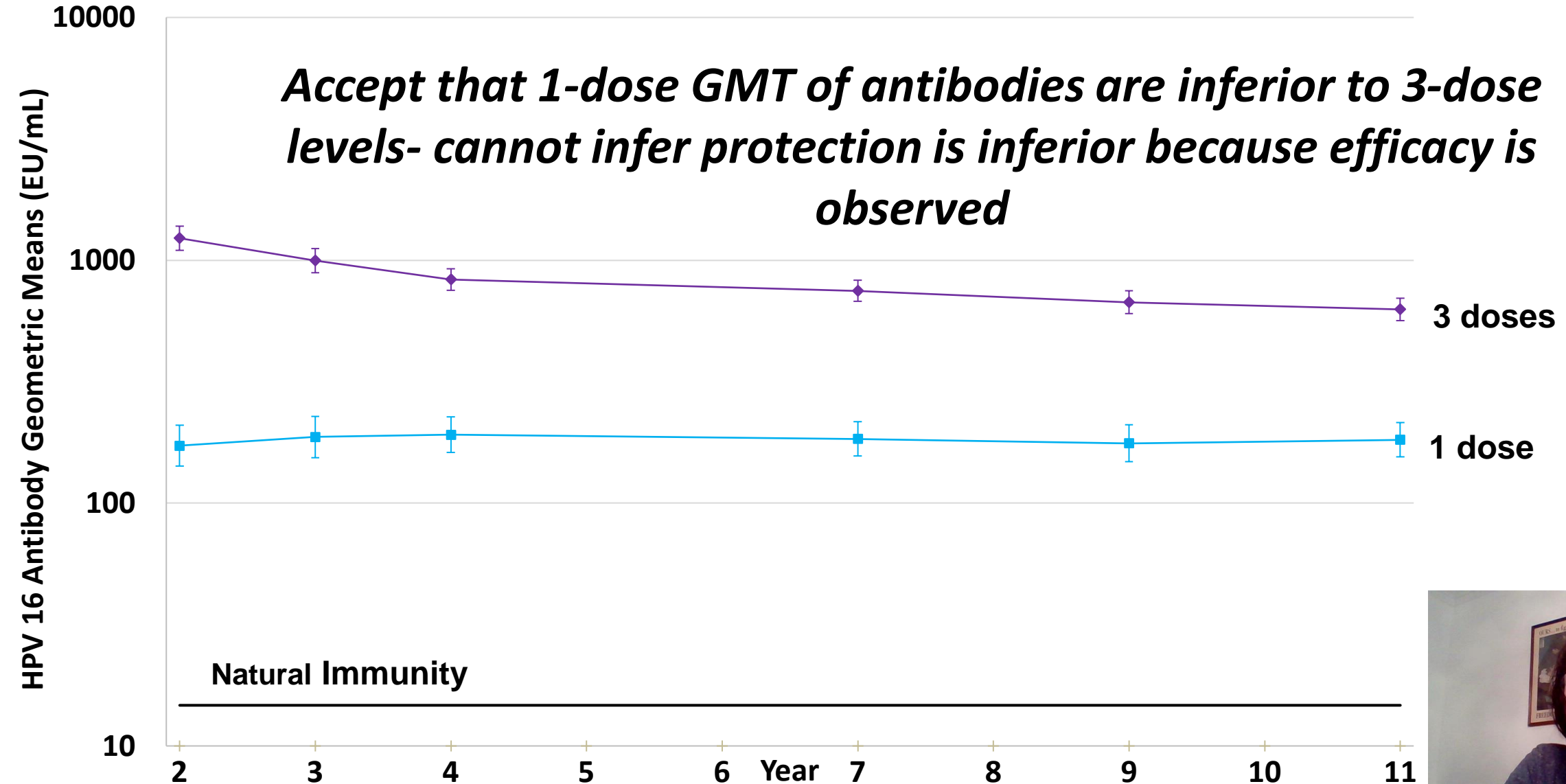
Tsang SH et al, JNCI 2020



CVT: Stable HPV16 serum antibodies for 11 years

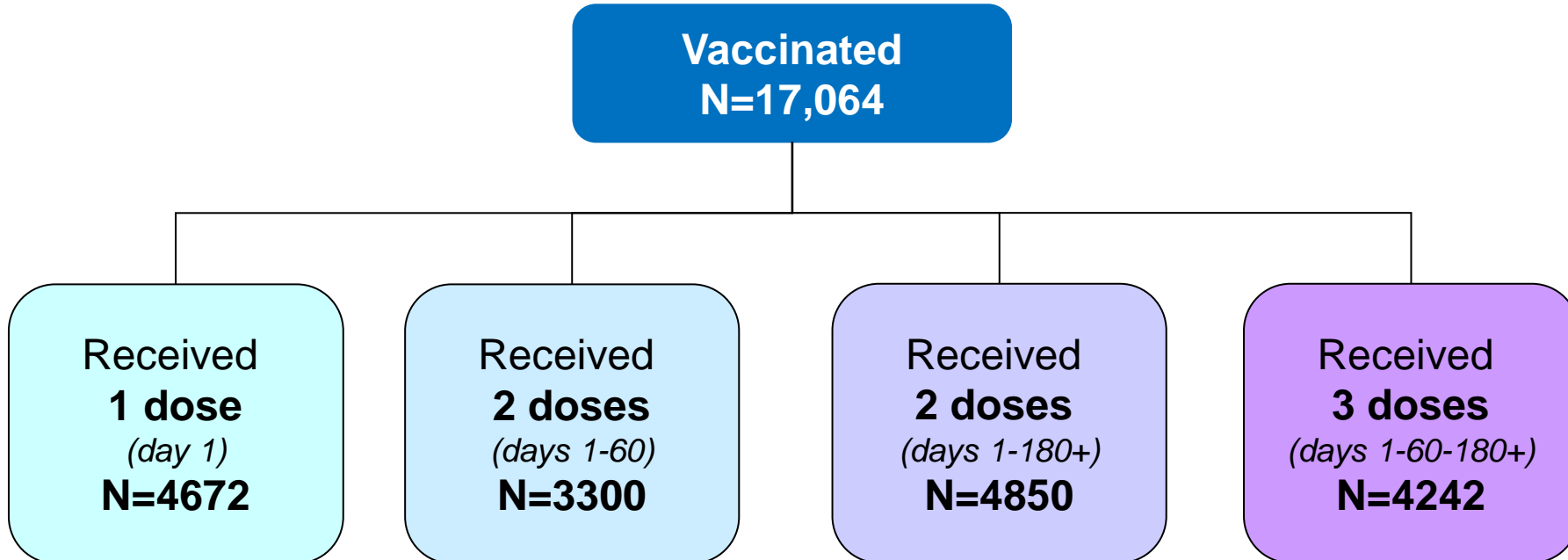
Results similar for HPV18

Accept that 1-dose GMT of antibodies are inferior to 3-dose levels- cannot infer protection is inferior because efficacy is observed



IARC 2- vs 3- dose 4v HPV Vaccine randomized clinical trial

- Recruitment initiated in 2009
- Aimed to recruit 20,000 unmarried girls aged 10-18 years
- 17,729 girls enrolled when recruitment and vaccination phase suspended



Conducted epidemiologic surveys among unvaccinated age-matched women



Table 6
 Persistent* HPV infections in women vaccinated with quadrivalent HPV vaccine over a 7-year follow-up period and in the unvaccinated women.

Group	Persistent HPV 16/18 infection	Persistent HPV 31/33/45 infection	Persistent non-vaccine targeted HPV infection excluding 31, 33, and 45
Three doses (Days 1, 60 and 180+)			
N positive/Total	1/604	1/604	16/604
%	0.2	0.2	2.6
95% CI	(0.0–0.9)	(0.0–0.9)	(1.5–4.3)
One dose (Day 1)			
N positive/Total	0/959	7/959	16/959
%		0.7	1.7
95% CI		(0.3–1.5)	(1.1–2.7)
Unvaccinated			
N positive/Total	14/1141	6/1141	27/1141
%	1.2	0.5	2.3
95% CI	(0.7–2.1)	(0.2–1.1)	(1.5–3.3)

* Persistent infections defined as incident infections that persisted for 12+ months without an HPV negative test (for HPV type in question) between positive tests.

Vaccine 36 (2018) 4783–4791

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine



Can a single dose of human papillomavirus (HPV) vaccine prevent cervical cancer? Early findings from an Indian study

Rengaswamy Sankaranarayanan^{a,*}, Smita Joshi^b, Richard Muwonge^a, Pulikottil Okkuru Esmay^c, Partha Basu^a, Priya Prabhu^d, Neerja Bhatla^e, Bhagwan M. Nene^f, Janmesh Shaw^g, Usha Rani Reddy Poli^h, Yogesh Vermaⁱ, Eric Zomawia^j, Sharmila Pimple^k, Massimo Tommasino^l, Michael Pawlita^m, Tarik Gheit^l, Tim Waterboer^m, Peter Sehrⁿ, Madhavan Radhakrishna Pillai^d, for the Indian HPV vaccine study group¹



Post-hoc analysis of RCTs provides compelling evidence of single-dose protection

1. Reasons for missing doses are known and usually unrelated to randomization and subsequent risk of HPV acquisition
2. Trials have pre-vaccination information (i.e.: HPV status at time of HPV vaccination, important for vax of older girls) and in-depth information on covariates
 - **Robust comparisons between vaccinated and unvaccinated**
3. Data available for both alum- and AS04-adjuvanted vaccines



Dose-specific vaccine effective in phase 4 registry studies

- Registry studies provide important information on programmatic effectiveness
 - Vaccine linkage studies have been used to reduced-dose schedules of HPV vaccines
- Initial studies included women vaccinated outside of routine program (i.e.: catchup vaccination) resulting if differences in characteristics of women by number of doses received
- Older women have more HPV infection at time of vaccination and thus more likely to appear as vaccine failures
- Hypothesized these earlier studies would be biased and suggest 1 dose was less effective than 3 doses



Example of older age at vaccination having lower vaccine effectiveness

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

HPV Vaccination and the Risk of Invasive Cervical Cancer

Jiayao Lei, Ph.D., Alexander Ploner, Ph.D., K. Miriam Elfström, Ph.D.,
Jiangrong Wang, Ph.D., Adam Roth, M.D., Ph.D., Fang Fang, M.D., Ph.D.,
Karin Sundström, M.D., Ph.D., Joakim Dillner, M.D., Ph.D.,
and Pär Sparén, Ph.D.

- Sweden started 3 dose vaccination program with 4vHPV in 2007
- Linked vaccine information to health registries
- Overall adj. IRR = .37 (.21-.57)
 - Vaccinated <17yr IRR = .12 (.00-.34)
 - Vaccinated 17-30 IRR = .47 (.27-.75)

If older women are more likely to receive 1 dose, we will falsely conclude that 1 dose is less effective




2018 systematic review of dose-specific vaccine effectiveness in phase 4 registry studies

- 14 studies included, from many world regions
- Most studies found number of doses impacted effectiveness estimates
 - Greater effectiveness with 3 doses, followed by 2 doses and 1 dose
 - Some effectiveness for 1 dose found in main or sub-analyses in 9 studies
 - More recent studies and studies that stratified by age at vaccination - less difference by dose


Vaccine 36 (2018) 4806–4815

Contents lists available at [ScienceDirect](#)

 **ELSEVIER**

Vaccine


journal homepage: www.elsevier.com/locate/vaccine



Human papillomavirus vaccine effectiveness by number of doses: Systematic review of data from national immunization programs

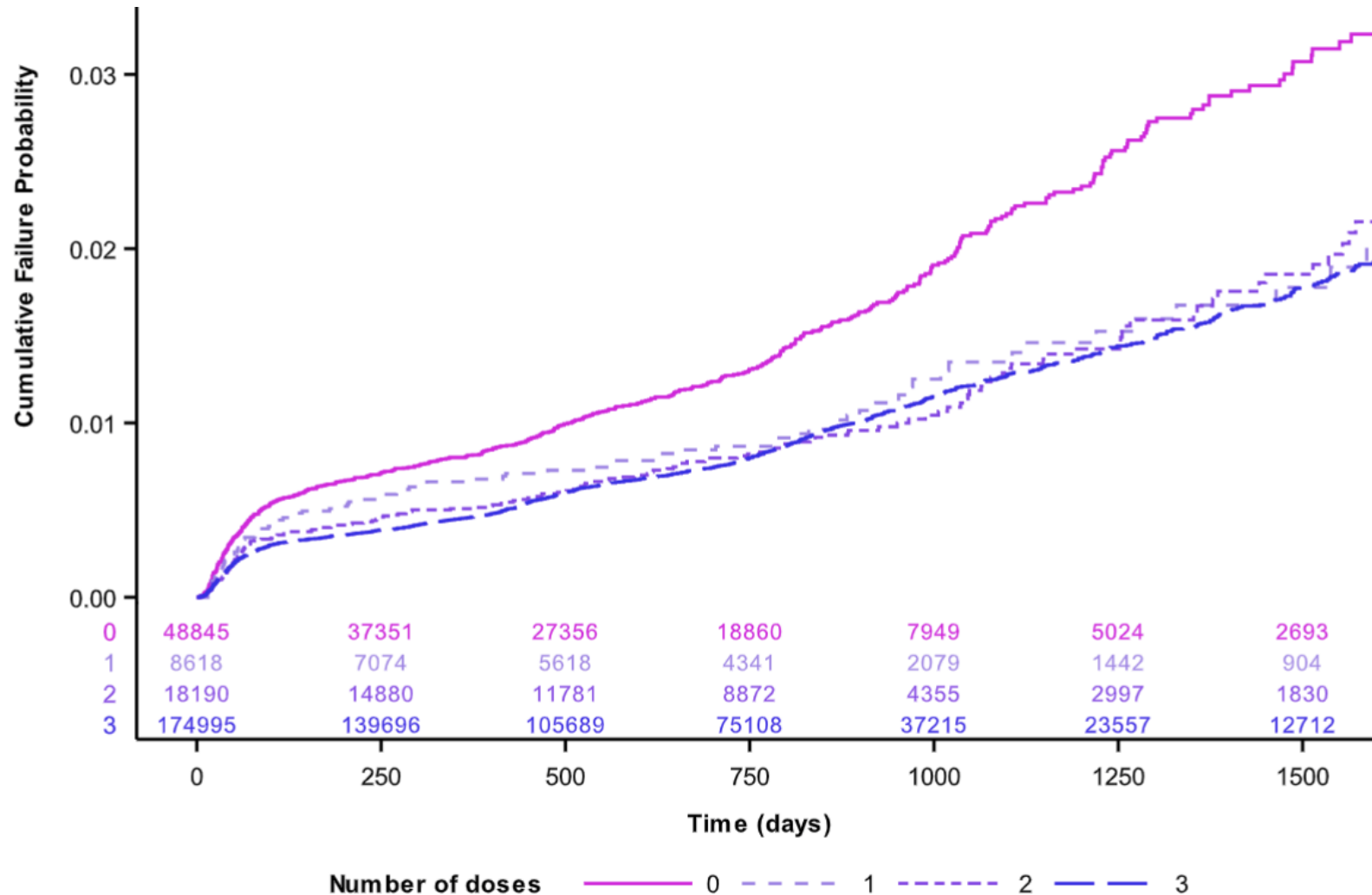
Lauri E. Markowitz^{a,*}, Melanie Drolet^b, Norma Perez^b, Mark Jit^{c,d}, Marc Brisson^{b,e,f}

^aNational Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA
^bCentre de recherche du CHU de Québec – Université Laval, Axe santé des populations et pratiques optimales en santé, Québec, Canada
^cModelling and Economics Unit, Public Health England, London, United Kingdom
^dDepartment of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, United Kingdom
^eDepartment of Infectious Disease Epidemiology, Imperial College, London, United Kingdom
^fDépartement de médecine sociale et préventive, Université Laval, Québec, Canada





A national cohort analysis of dose-specific HPV protection against CIN2/AIS+ in Australia



Ongoing trials and studies investigating single-dose HPV vaccine protection

Study name (if available)	Country	Population	Primary aim	Initial data available*
KenSHE	Kenya	Women, 15 to 20	Efficacy	2021
DoRIS	Tanzania	Girls, 9 to 14	Efficacy through immunobridging	2021
HOPE	South Africa	HIV+ and -women 17 to 18	Effectiveness	2021
Thailand Impact Study	Thailand	Girls, grade 8	Effectiveness	2021
Primavera	Costa Rica	Girls, 9 to 14	Immunobridging	2022/3
HANDS	Gambia	Girls, 4 to 14	Immunobridging	2022
ESCUDDO	Costa Rica	Girls, 12 to 16	1 vs 2 dose non-inferiority trial	

**COVID19 pandemic may impact timelines*



Summary

- Continuing post-hoc analyses of two RCTs suggest that HPV vaccines may generate long-term protection after a single dose
- Vaccine registry studies support the possibility of substantial single-dose protection in national immunization programs, but controlling for potential bias is critical
- A series of ongoing efficacy, immunobridging and demonstration trials will provide increasingly robust data over the next 4 years
 - Several important studies generating data in 2021

Thank you!

