National Cancer Institute

Will a single dose of the prophylactic HPV vaccines provide durable protection against cervical cancer?

Aimée R. Kreimer, Ph.D.

Division of Cancer Epidemiology and Genetics
kreimera@mail.nih.gov

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

RCT to evaluate protection afforded by one and two doses of the HPV vaccines

NCI and Proyecto Epidemiologico Guanacaste (Costa Rica)

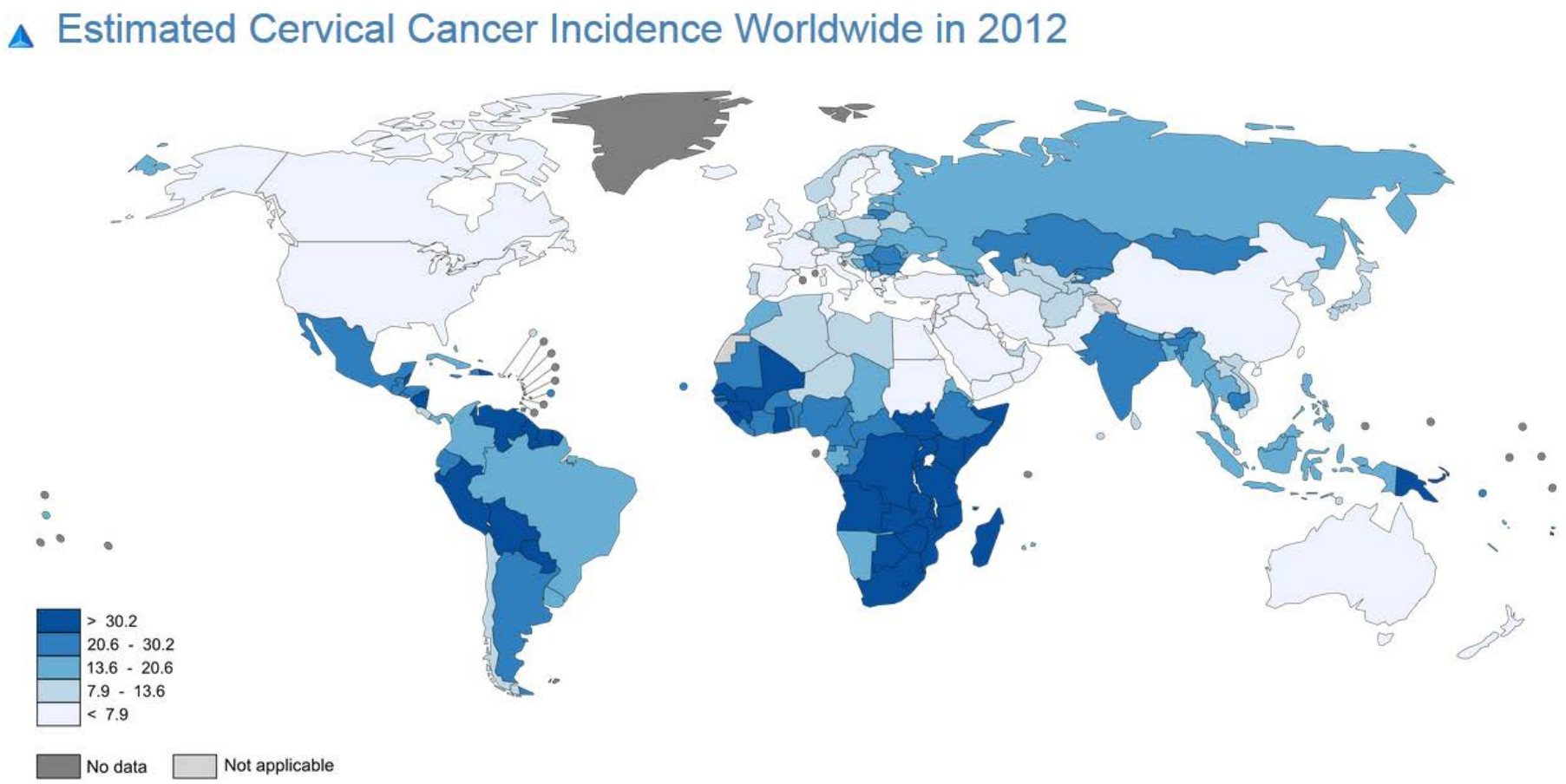
Study goal and components

Main aim: Prove single-dose protection of HPV vaccines in order to change standard of care

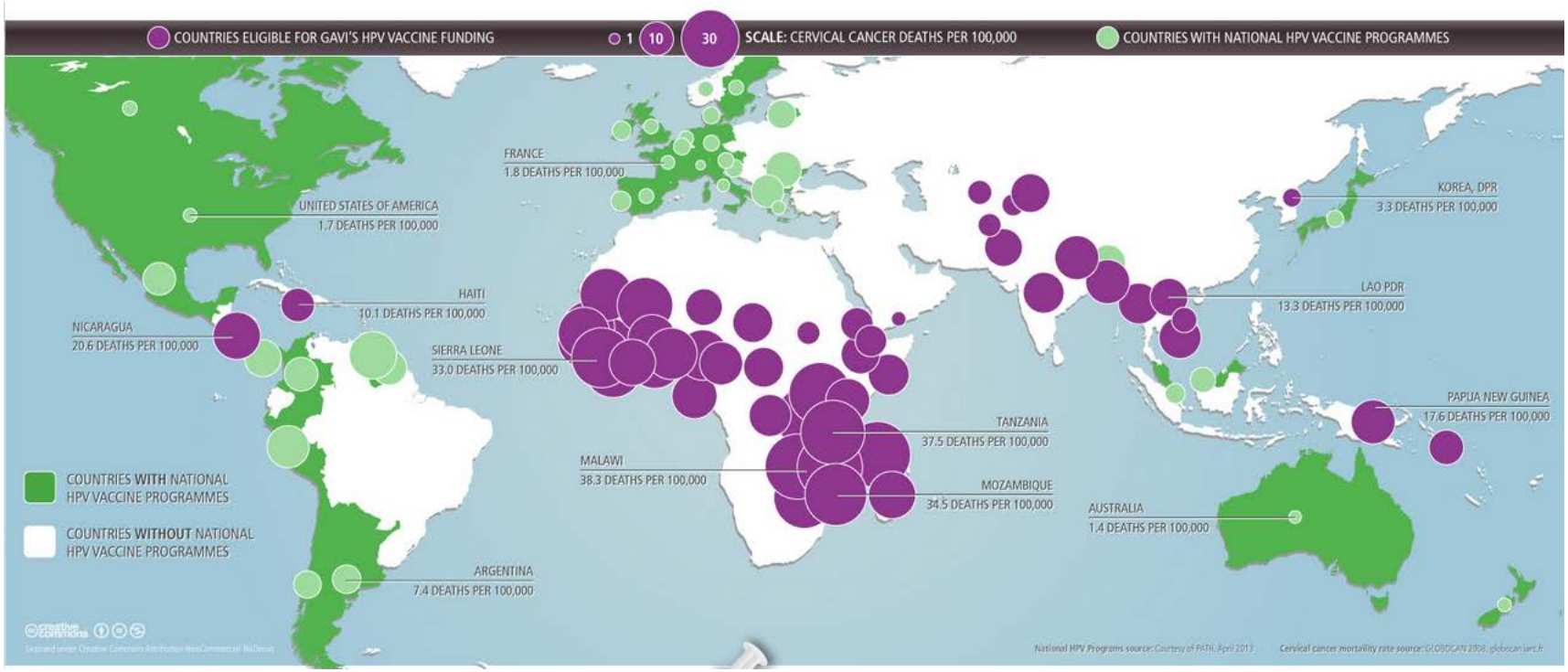
- Four-arm trial: 1 and 2 doses* of GSK (bivalent) and Merck (9-valent) HPV vaccines
- Immunobridging to accelerate implementation in other populations or using other vaccine formulations

*WHO and EMA recommend two doses for adolescents

Global burden of cervical cancer greatest in developing countries



Current global vaccination patterns will only have a marginal reduction on cervical cancer



http://www.gavi.org/uploadedImages/Types_of_support/NVS/HPV/HPV-vaccine-infographic-1600_source.jpg

HPV vaccines and schedules licensed in the US

	Bivalent (Cervarix)	Quadrivalent (Gardasil)	Nonavalent (Gardasil-9)
Company	GlaxoSmithKline	Merck	
HPV types	16, 18	16, 18, 6, 11	16, 18, 6, 11 31, 33, 45, 52, 58
Adjuvant	ASO4	Alum	
Schedule	3 doses (0,1,6 months)	3 doses (0,2,6 months)	
Licensed	Females Aged 9-26*	Females and males Aged 9-26*	

*Vaccinate to eradicate peak of HPV acquisition

Single-dose vaccine efficacy

Post-hoc analysis of bivalent HPV vaccine in Costa Rica HPV Vaccine Trial

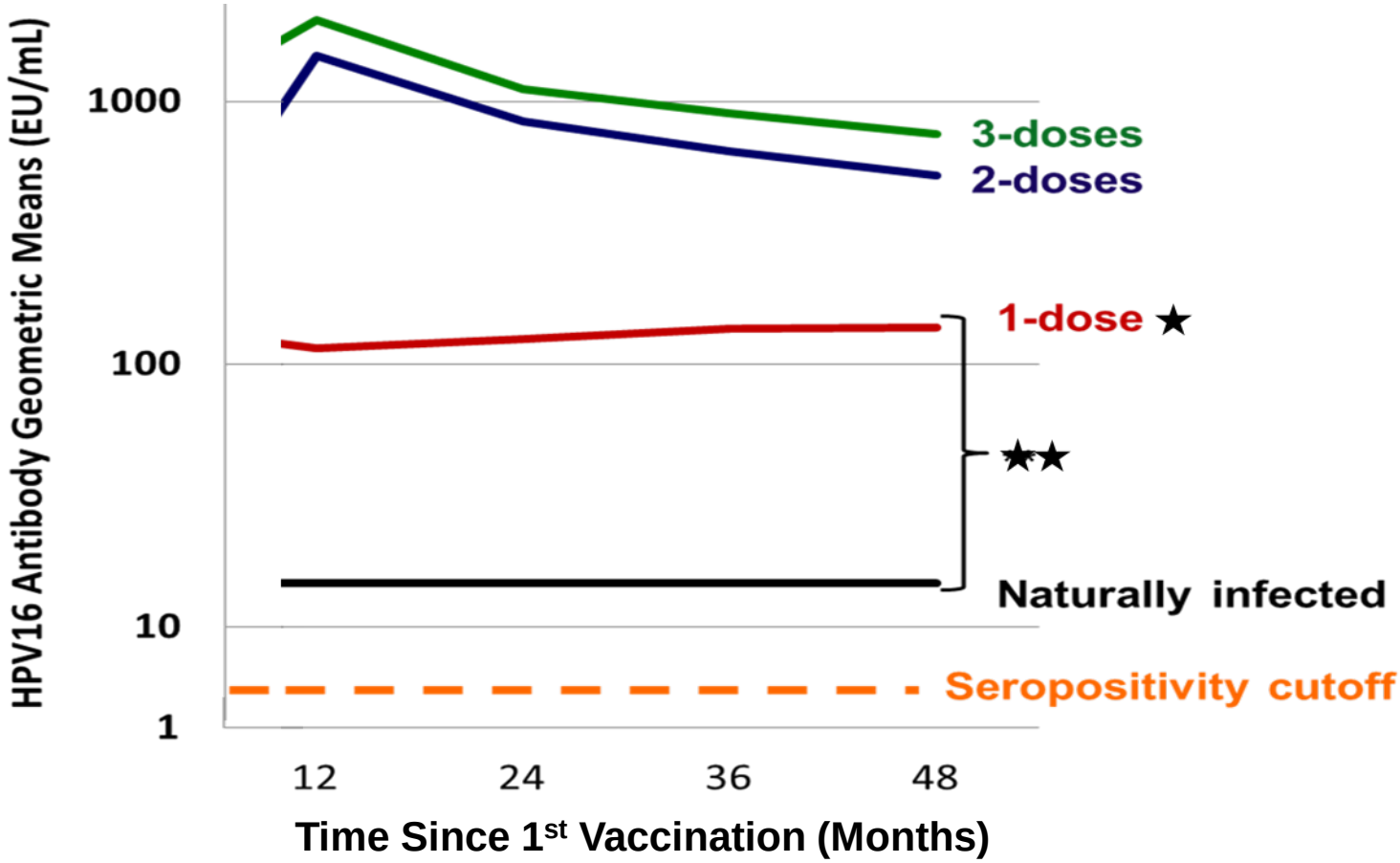
# of Doses	Arm	# Women	HPV16/18 6+ mo Persistence N (%)	HPV16/18 Vaccine Efficacy (95%CI)
3	Control	3010	229 (8%)	84% (77% to 89%)
	HPV	2957	37 (1%)	
2	Control	380	24 (6%)	81% (53% to 94%)
	HPV	422	5 (1%)	
1	Control	188	15 (8%)	100% (79% to 100%)
	HPV	196	0 (0%)	

Kreimer AR, et al. *JNCI* 2011

Single-dose immunogenicity

** 4-fold difference between 1 and 3 dose plateau titers*

*** ~10-fold difference between 1 dose and natural infection plateau titers*



Safaeian M, et al. *Cancer Prev Res* 2013

No precedent for a single dose of a subunit vaccine to confer stable serum antibody levels or long-term protection

- Current CVT Long-term follow-up (LTFU) study - documents protection afforded by one dose (non-randomized) of the bivalent vaccine
  - DCEG planning to further extend follow-up out to 15 years
- GSK-sponsored PATRICIA trial (bivalent vaccine) - independent confirmation of post-hoc single-dose efficacy*
- India Vaccine Study (non-randomized) - quadrivalent HPV vaccine (Merck)
  - Political suspension yielded ~5000 one-dose vaccinees on study with 3 years of follow-up

*Kreimer AR, Struyf F, et al. *Lancet Onc* 2015

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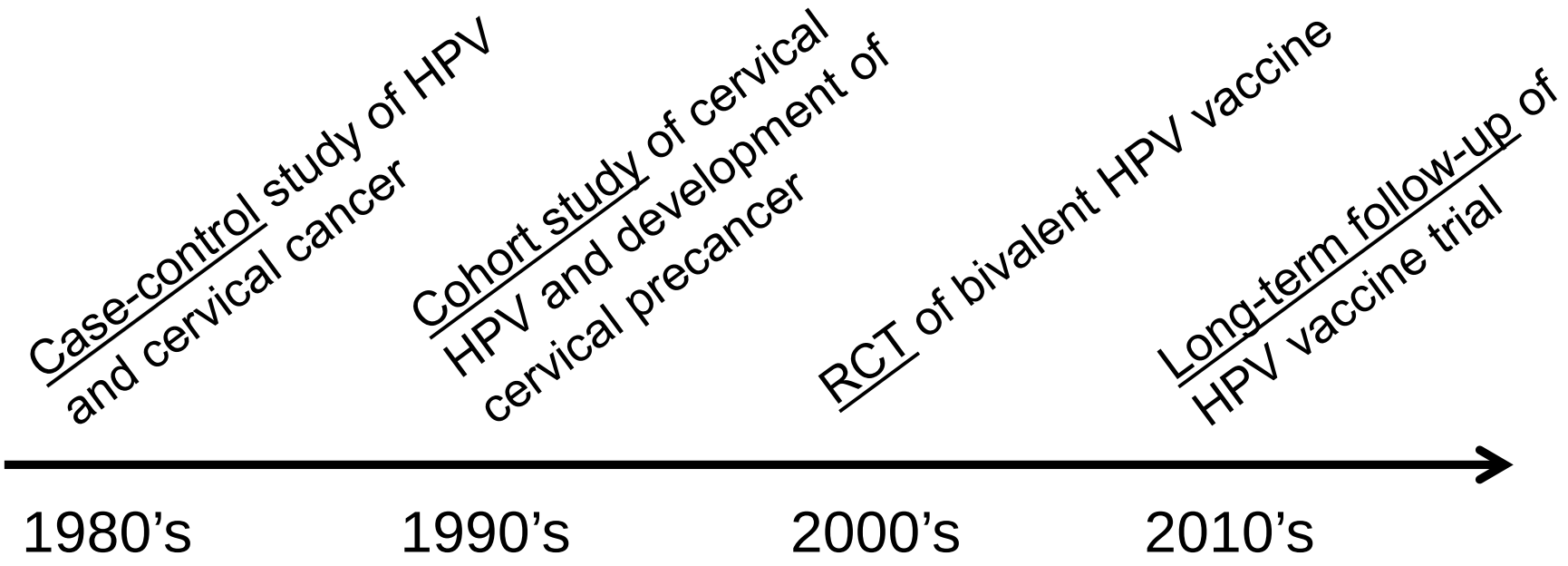
History of NCI/CR collaboration



Contributed substantially to the understanding of cervical cancer natural history and primary and secondary prevention approaches to reduce disease burden

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- Epidemiologic HPV survey: document HPV infection among unvaccinated girls
- Immunobridging to accelerate implementation in other populations or using other vaccine formulations

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Primary objectives

1. Non-inferiority of 1 vs 2 doses in the prevention of new cervical HPV16/18 infections that persist 6+ months

2. Evaluate 1 dose of HPV vaccination compared to 0 vaccination doses

Secondary objective

Compare sustained immune titers via measurement of serum antibodies between girls who received 1 and 2 doses of the HPV vaccines

- Primary focus: HPV16/18
- Additional HPV types in nonavalent HPV vaccine will be investigated

Study design

RCT: Girls only, N=5,000 per arm (20,000 total)

- Trial must be large given the non-inferiority design and the expected high VE among girls in the first 4 years
- Ages 13 to 16 years (chosen based on median age at sexual debut)

Epidemiologic HPV survey

- Goal: document HPV attack rate among unvaccinated girls
- 3 study visits over 1 year
- Collect same samples as in RCT
- Offer HPV vaccination at conclusion of participation

Additional immunologic studies

1. Establish lowest serum antibody level that confers strong protection with a single dose
2. Immunobridging studies to other populations
3. Subsequent trials of biosimilar VLP-based HPV vaccines to be immunobridging trials
4. NCI DCP plans to conduct a companion 1-dose/2-dose immunogenicity trial in the U.S.

Early efforts for the study

Pilot study

- Quantify expected enrolment and retention rates, and acceptability of study procedures

Real-time monitoring of enrolment phase

- Milestones for accrual
- Contingency plans

Summary

- Four years of strong protection in our trial intended to provide the level of evidence needed to change policy
  - Opportunities to evaluate other populations and vaccine formulations
  - VLP-based vaccines should be considered in future vaccine development, to reduce doses needed for protection
- Longer-term follow-up of the proposed trial would be needed to provide confirmation of duration of protection out to 10 years
  - Herd immunity if sustained vaccine uptake was present in a population

Thank you