

World Experience with HPV Vaccination

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“HPV-associated Cancer: Primary Prevention and Screening”

Moscow, Russian Federation, June 2019

Call to Action 2018

- Global partnership
- **HPV vaccination**
- Screening & treatment of pre-cancer
- Treatment of invasive cervical cancer
- Symptom management and palliative care

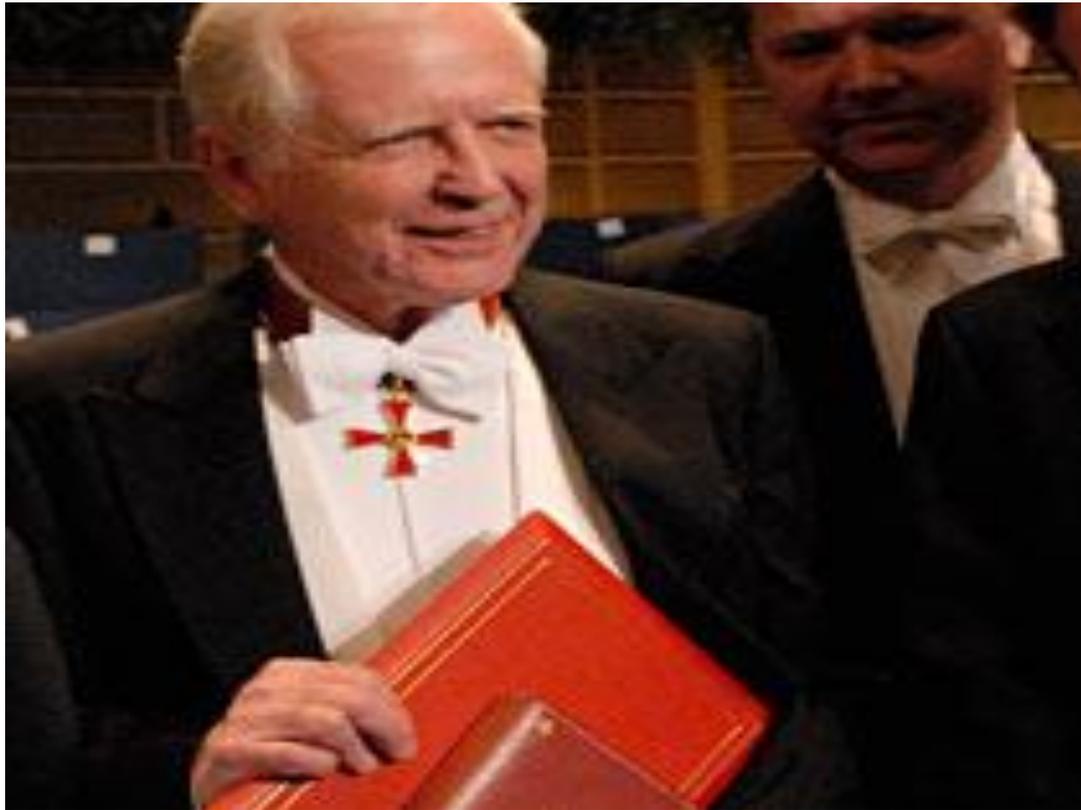


Dr Tedros Adhanom Ghebreyesus

Director-General



HPV and Harald zur Hausen



- 1976: Harald zur Hausen reported finding HPV in warts and cervical cancer
- Family of 120+ papillomaviruses which can infect skin or mucous membranes in mammals
- HPV 6,11: genital warts
- HPV 16,18: most carcinogenic
- E6 protein (p53) & E7 protein (Rb) block normal cellular control mechanisms

Primary prevention

- Development of prophylactic HPV vaccination
 - Four academic laboratories:
 - Georgetown University
 - US National Cancer Institute
 - University of Rochester
 - University of Queensland
- Non-exclusive license to Merck and GSK

Jian Zhou & Ian Frazer, U of Queensland



Jian Zhou and Ian Frazer

Doug Lowy & John Schiller, US NCI



Prophylactic HPV vaccines



- Empty viral capsid (L1)
- Gardasil®: HPV 6,11,16,18
- Gardasil9®: HPV subtypes 6,11,16,18,31,33,45,52, 58
- Cervarix®: 16,18 + adjuvant
- Efficacy of reduction of incident infection: 91.6%
- Efficacy of reduction of persistent infection: 100%
- 2-3 doses over 6 months; strongest protection if given before start of sexual activity

Which regulatory authorities have approved HPV vaccination?

- US Food and Drug Administration (US FDA)
 - US FDA approved quadrivalent HPV vaccine (Gardasil®) in 2006; bivalent vaccine (Cervarix®) in 2009; nonavalent vaccine (Gardasil9®) in 2014
- European Medicines Agency (EMA)
 - EMA approved bivalent vaccine (Cervarix®) in 2007; quadrivalent HPV vaccine (Gardasil®) in 2008; nonavalent vaccine (Gardasil9®) in 2014

Who has endorsed HPV vaccination?

- HPV vaccination recommended for girls and boys in US by American Committee on Immunization Practice (advisory to US CDC)
- HPV vaccination for girls recommended by WHO Strategic Advisory Group on Immunization (WHO SAGE)
- HPV vaccination for girls recommended by Global Alliance for Vaccines and Immunization (GAVI)

How many doses?

- US CDC: all HPV vaccines (Cervarix[®], Gardasil[®], and Gardasil9[®]) 2 doses for girls and boys (aged 9-14 years) 6-12 months apart
- WHO: 2 doses for adolescent girls (aged 9-14 years) (Cervarix[®], Gardasil[®])

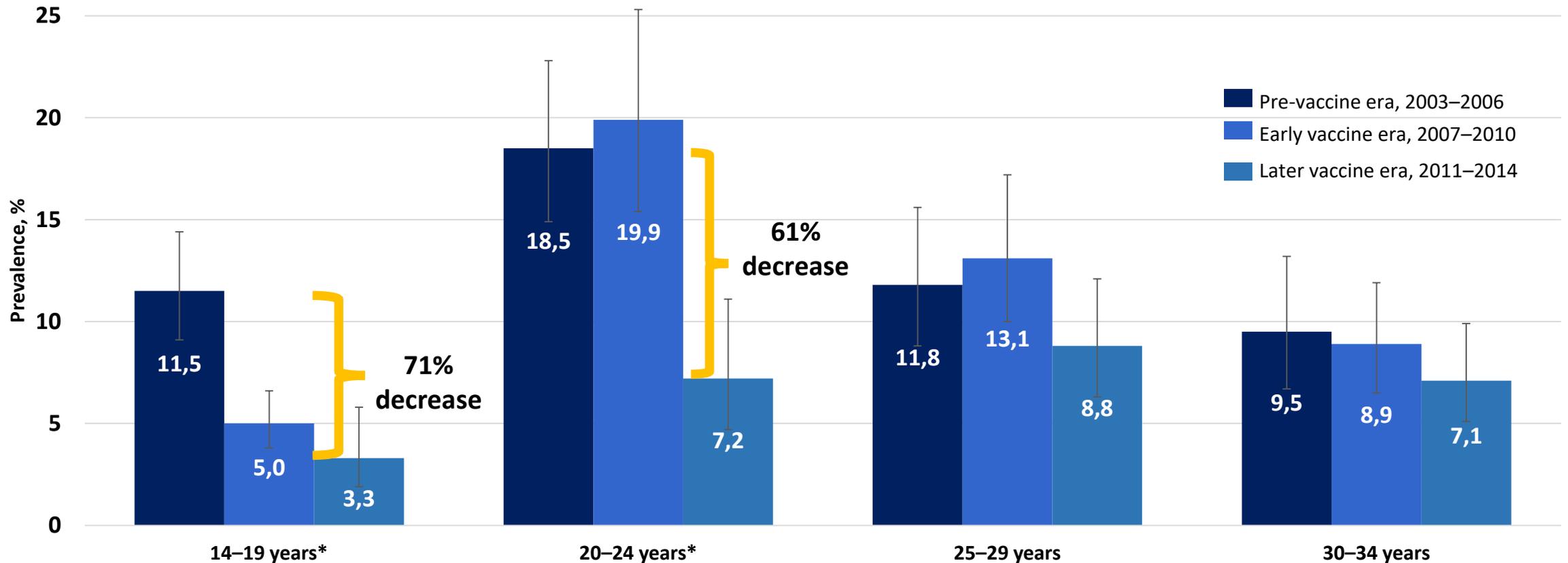
World experience with HPV vaccination

- What is the real-world impact on HPV-associated neoplasia?
- What toxicities have been observed?
- What have we learned about implementation of HPV vaccination?

Real-world impact on HPV-associated neoplasia

- Significantly decreased HPV-vaccine-type prevalence among young women who were vaccinated
- Significantly decreased prevalence of HPV-vaccine-type among young women and young men who were not vaccinated (herd effect)
- Markowitz LE et al, Vaccine 2019, US experience
 - Within 9-10 years of HPV vaccine introduction
 - Women aged 20-24 years: 78% reduction in HPV-vaccine-type prevalence
 - Women aged 25-29 years: 38% reduction in HPV-vaccine-type prevalence

Prevalence of Vaccine-type HPV (HPV 6,11,16,18) in Females, Late and Early Vaccine Era Compared to Pre-vaccine Era



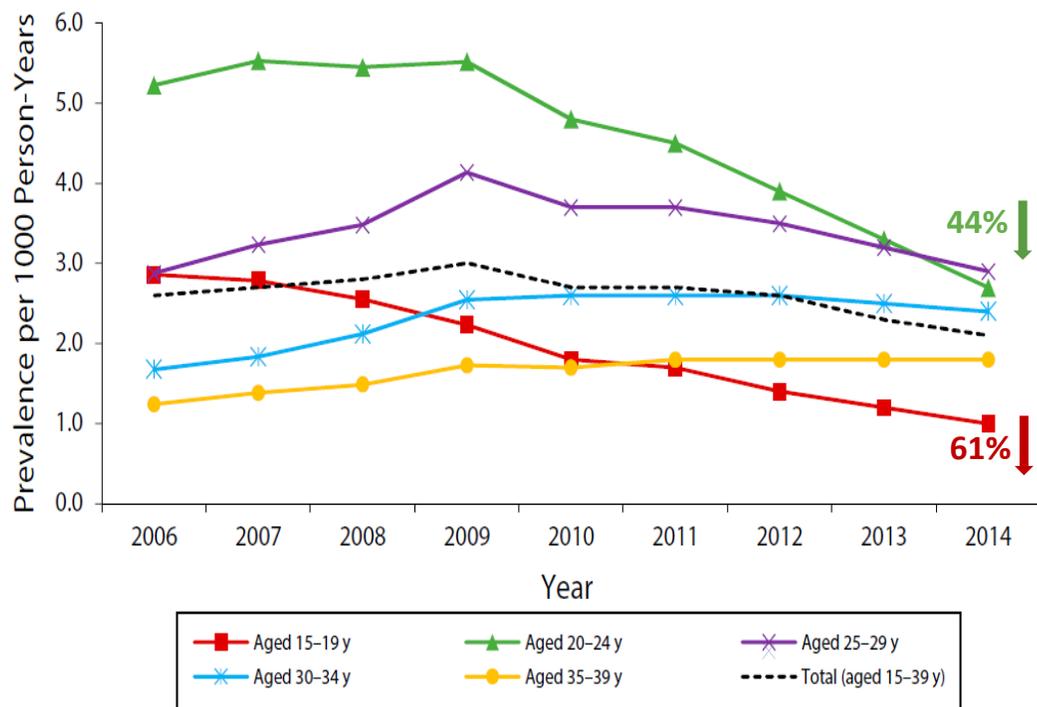
Oliver et al. J Infect Dis 2017

NHANES: National Health and Nutritional Examination Survey

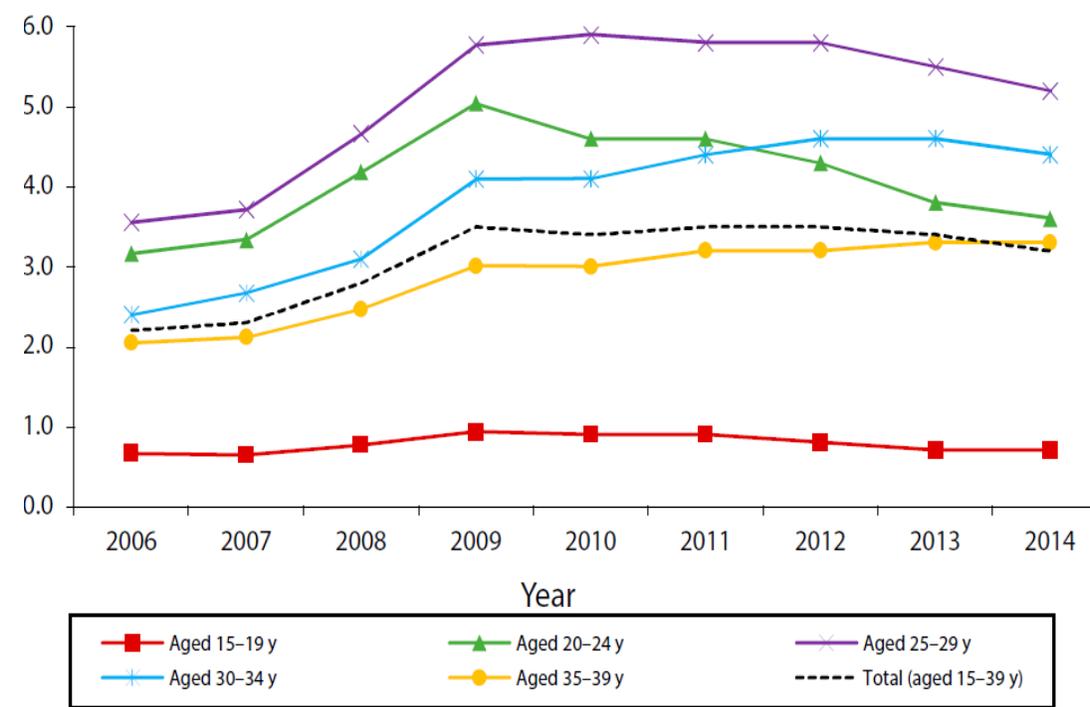
Real-world impact on HPV-associated neoplasia

- Significantly decreased incidence of genital warts in young women and young men
 - Smith MA et al, Journal of Infectious Disease 2015, Australian experience
 - From 2006-2007 to 2010-2011: **90%** reduction in girls aged 12-17 years; **73%** reduction in young women aged 18-26 years; **38%** reduction for young men aged 18-26 years
- Significantly decreased incidence of abnormal PAP smears in young women
 - Garland SM et al; Clinical Infectious Disease 2016, global experience
 - Low-grade abnormalities: 45% reduction; high-grade abnormalities: 85% reduction

Anogenital Wart Prevalence among 15–39 Year-Olds with Private Insurance, United States, 2006–2014



Females

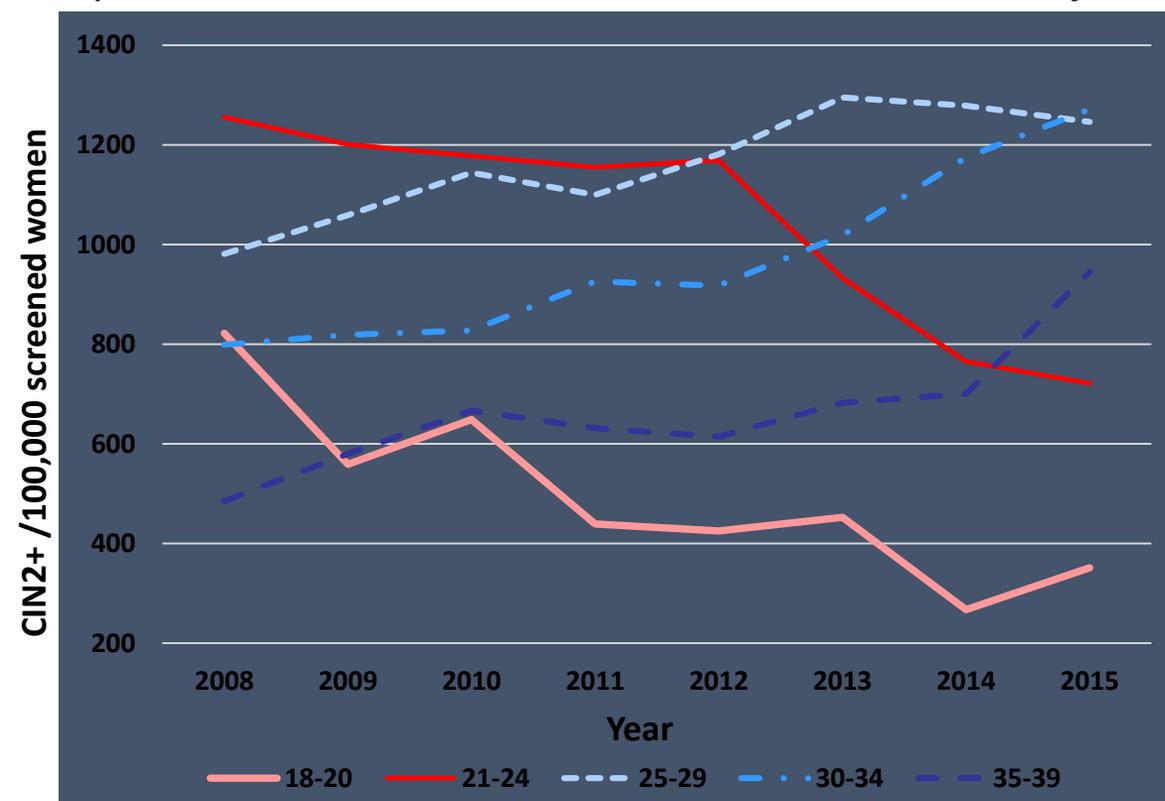


Males

Cervical Precancer Incidence Rates among Screened Women, HPV-IMPACT Project, 2008-2015

- CIN2+ rates decreased significantly in estimated screened women aged 18–20 and 21–24 years
- CIN2+ rates increases in screened women aged 25–29, 30–34, and 35–39 years
- Could be attributable to:
 - Longer screening intervals and/or
 - Increased sensitivity of screening or diagnostic tests

Estimated Cervical Precancer Incidence Rates per 100,000 Screened Women, HPV IMPACT Project



CIN2+: Precancerous lesions called “cervical intraepithelial neoplasia, grade 2 or worse; or adenocarcinoma in situ”

Gargano et al. Clin Infect Dis (in press)

What are the acute side effects?

- Brief soreness at injection site
- Occasional dizziness and syncope: individuals receiving HPV vaccination should remain seated or lying down for 15 minutes after vaccination

Are there medium- and/or long-term toxicities?

- Arnheim-Dahlstrom L et al, BMJ 2013
- Cohort registry study in Sweden and Denmark, 2010-2014
- 1 million girls aged 10-17 years
 - 300,00 girls had received 700,000 doses of quadrivalent HPV vaccine
- No increased risk of autoimmune, neurologic, or thromboembolic adverse events

U.S Vaccine Safety Monitoring Systems

System	Collaboration	Description
Vaccine Adverse Event Reporting System (VAERS)	CDC and FDA	Frontline spontaneous reporting system to detect potential vaccine safety issues
Vaccine Safety Datalink (VSD)	CDC and 9 Integrated Health Care Systems	Large linked database system used for active surveillance and research ~9.4 million members (~3% of US pop.)
Clinical Immunization Safety Assessment (CISA) Project	CDC and 7 Medical Research Centers	Expert collaboration that conducts individual clinical vaccine safety assessments and clinical research
Post-Licensure Rapid Immunization Safety Monitoring Program (PRISM)	FDA and 6 partner organizations	Large distributed database system used for active surveillance and research ~170 million individuals

Post-Licensure Monitoring and Safety Reviews of HPV Vaccines, VAERS

- Updated surveillance review of AE reports following 4vHPV in females and males between 2009-2015
 - No new or unexpected safety concerns or reporting patterns of 4vHPV with clinically important AEs were detected
- Review of AE reports following 2vHPV (Cervarix – no longer available in the United States) reports between 2009-2017 found no new or unexpected safety concerns
- Published reviews on postural orthostatic tachycardia syndrome (POTS) and complex regional pain syndrome (CRPS): no unusual or unexpected patterns

Post-Licensure Safety Monitoring and Research of 4vHPV, Vaccine Safety Datalink (VSD)

- No concerning safety signals detected among pre-specified outcomes in weekly sequential monitoring between 2006-2009 among 9-26 year-old females
- Multiple VSD studies conducted on specific outcomes following 4vHPV with no associations detected
 - Venous thromboembolism (VTE)
 - Guillain-Barré syndrome (GBS)
 - Primary ovarian insufficiency (POI)
 - Diabetes
 - Mortality
- No increase risk of spontaneous abortion or adverse maternal or infant outcomes observed following inadvertent 4vHPV vaccination during pregnancy

Initial Post-Licensure Monitoring of 9vHPV

- **VAERS:** From Dec 2014-Dec 2017, enhanced safety monitoring in VAERS found no unexpected or new safety concerns
 - Approximately 29 million doses distributed in the United States during this time
 - Safety profile consistent with data from 9vHPV pre-licensure clinical trials and similar to post-licensure safety data from 4vHPV monitoring in VAERS
- **VSD:** Between Oct 4, 2015-Oct 3, 2017, VSD conducted weekly sequential monitoring among persons aged 9-26 who received 9vHPV
 - Approximately 900,000 doses administered and no concerning safety signals detected among pre-specified outcome monitored, which included:
 - GBS, appendicitis, injection site reaction, anaphylaxis, stroke, syncope, venous thromboembolism, allergic reaction, chronic inflammatory demyelinating polyneuropathy, pancreatitis, seizures

Closing Gaps in Knowledge of HPV Vaccine Safety: Ongoing Safety Monitoring and Studies

- VAERS: Continue safety surveillance and review reports for unusual or unexpected AEs or changing patterns of AEs following 9vHPV
- VSD – studies of:
 - Risk of autoimmune disease following 4vHPV
 - Descriptive study of postural orthostatic tachycardia syndrome (POTS)
 - Descriptive study of complex regional pain Syndrome (CRPS)
 - Descriptive study of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)
 - Risk of spontaneous abortion following 9vHPV
 - TreeScan data mining to detect unsuspected AEs following 9vHPV
- CISA: Regular consultation with experts, as needed, on clinically complex AEs

US Safety Data on quadrivalent HPV vaccine

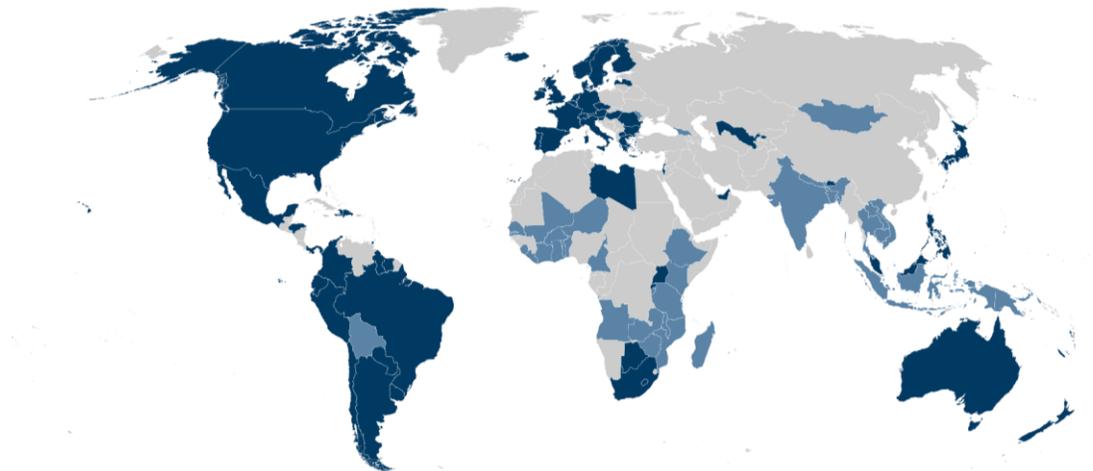
- Arana JE et al. Vaccine 2018
- Vaccine Adverse Event Reporting System: 2009-2015
- 60 million doses
- 19,720 adverse event reports
 - 94% non-serious: predominantly dizziness, syncope, & injection site reaction
 - 6% serious: predominantly headache, fatigue, & nausea
- Conclusion: no new or unexpected safety concerns or reporting patterns; safety profile of quadrivalent vaccine consistent with pre-licensure trials and post-marketing safety data

Other key analyses

- European Medicines Agency Pharmacovigilance Risk Assessment Committee: Report on HPV vaccines, 2015
- Arbyn M et al. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors (review). Cochrane Database of Systematic Reviews 2018. www.cochranelibrary.com

Global Progress in HPV vaccine introduction

September 2016



National programs

American Samoa	Curacao	Lesotho	Portugal
Andorra	Czech Republic	Libya	Romania
Argentina	Denmark	Lichtenstein	Rwanda
Aruba	Dominican Republic	Luxembourg	San Marino
Australia	Ecuador	Macedonia	Seychelles
Austria	Fiji	Malaysia	Singapore
Bahamas	Finland	Malta	Slovenia
Barbados	France	Marshall Islands	South Africa
Belgium	French Polynesia	Mexico	Spain
Belize	Germany	Micronesia	St. Eustatius
Bermuda	Greece	Monaco	Suriname
Bhutan	Guam	Netherlands	Sweden
Bonaire	Guyana	New Caledonia	Switzerland
Botswana	Honduras	New Zealand	Trinidad and Tobago
Brazil	Hungary	Niue	Uganda
Brunei	Iceland	Northern Marianas	United Arab Emirates
Bulgaria	Ireland	Norway	United Kingdom
Canada	Israel	Palau	United States
Cayman Islands	Italy	Panama	Uruguay
Chile	Japan	Paraguay	Uzbekistan
Colombia	Kiribati	Peru	Vanuatu
Cook Islands	Latvia	Philippines	

Pilot programs

Angola	Moldova
Bangladesh	Mongolia
Benin	Mozambique
Bolivia	Nepal
Burkina Faso	Niger
Burundi	Papua New Guinea
Cambodia	Sao Tome
Cameroon	Senegal
Cote d'Ivoire	Sierra Leone
Ethiopia	Solomon Islands
Gambia	Tanzania
Georgia	Thailand
Ghana	Togo
Haiti	Vietnam
India	Zambia
Indonesia	Zimbabwe
Kenya	
Lao PDR	
Liberia	
Madagascar	
Malawi	
Mali	

Lessons learned from national HPV vaccine programs

- <http://www.rho.org/HPVlessons/>
- Between 2014 and 2016 a team from the London School of Hygiene and Tropical Medicine and PATH (www.path.org) reviewed pilot HPV vaccination programs conducted in 46 low- and middle-income countries
- Across 5 areas: preparation, communications, delivery, achievements, and sustainability

Key themes

- HPV vaccines effective and safe
- Cost
- Advance planning
- Health communications
- Supply issues
- Health surveillance

Advance planning

- Extensive health communications with opinion leaders, religious leaders, teachers, parents, health care providers, media about cervical cancer, HPV, and HPV vaccination before start of HPV vaccination
- Social media monitoring
- Prepare for rapid response by medical experts and high-level government representatives to any misinformation
 - Press, TV, radio, websites, and social media

National HPV Vaccination Roundtable: Members



Materials for Clinicians

- CE Activities
- Clinician Factsheets
- Clinician Listicle
- Peer-to-Peer Educational Videos
- Mobile-friendly Web Content
- Webinar Series
- Training Slide Deck
- Posters for Clinics
- Digital and Print Ads
- Clinician Recognition Program

Materials for Parents

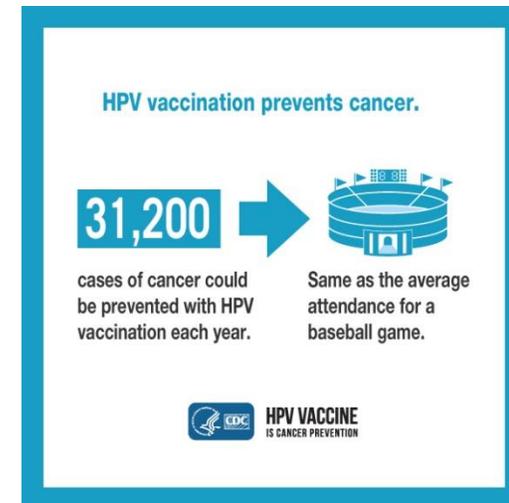
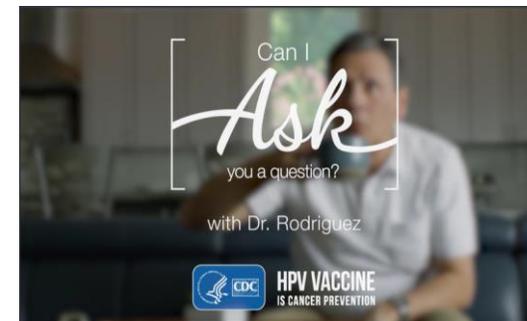
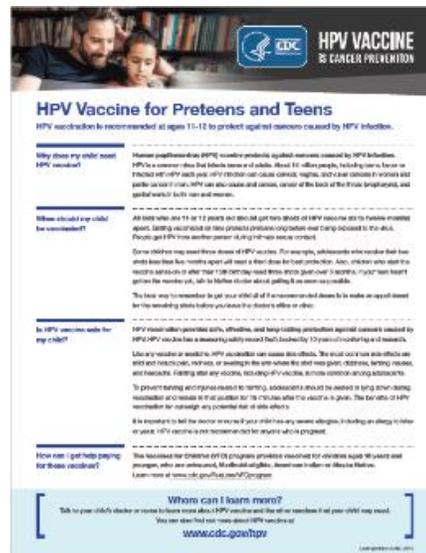
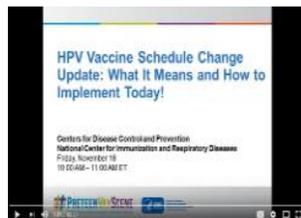
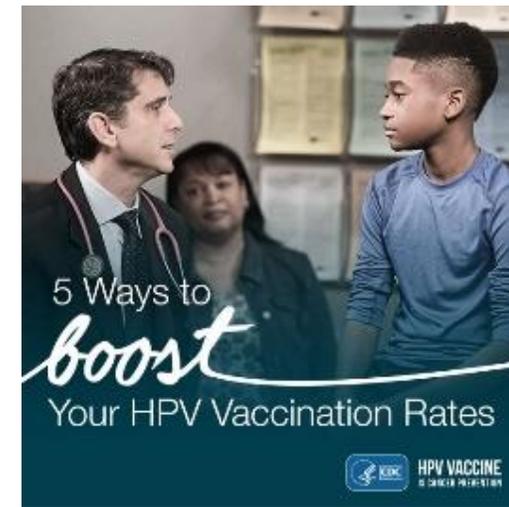
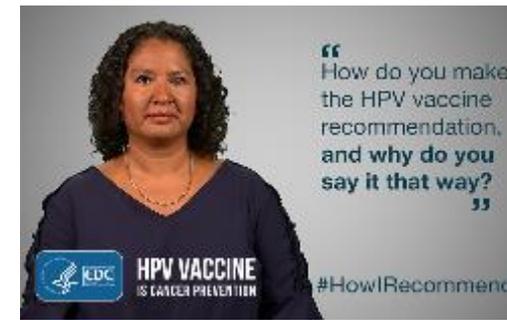
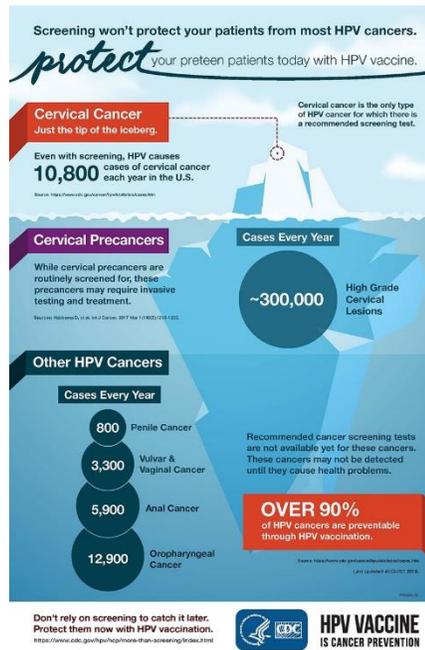
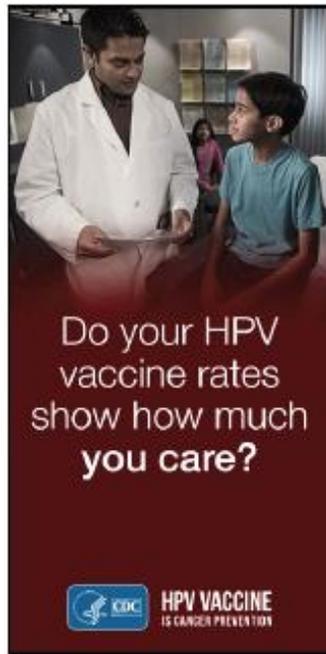
- Parent-friendly Immunization Schedule
- Adolescent Vaccine Factsheets
- Broadcast Quality Videos
- Radio PSAs
- Videos and Graphics for Social Media
- Listicle
- Digital and Print Ads
- Mobile-friendly Web Content
- Spanish-language Materials

Materials for Partners and Programs

- Digital Toolkit of Resources
- Preteen Vaccine Newsletter
- Webinar Series
- Clinician Recognition Program

www.cdc.gov/hpv

www.cdc.gov/vaccines/parents



General observations

- Involve Ministries of Health, Education, and Finance
- Integrate into routine vaccination programs (EPI) for sustainability
- Most effective influencers: health care workers, teachers, and social/ religious leaders
- Develop crisis communications strategy and monitor social media closely
- <http://www.rho.org/HPVlessons/>

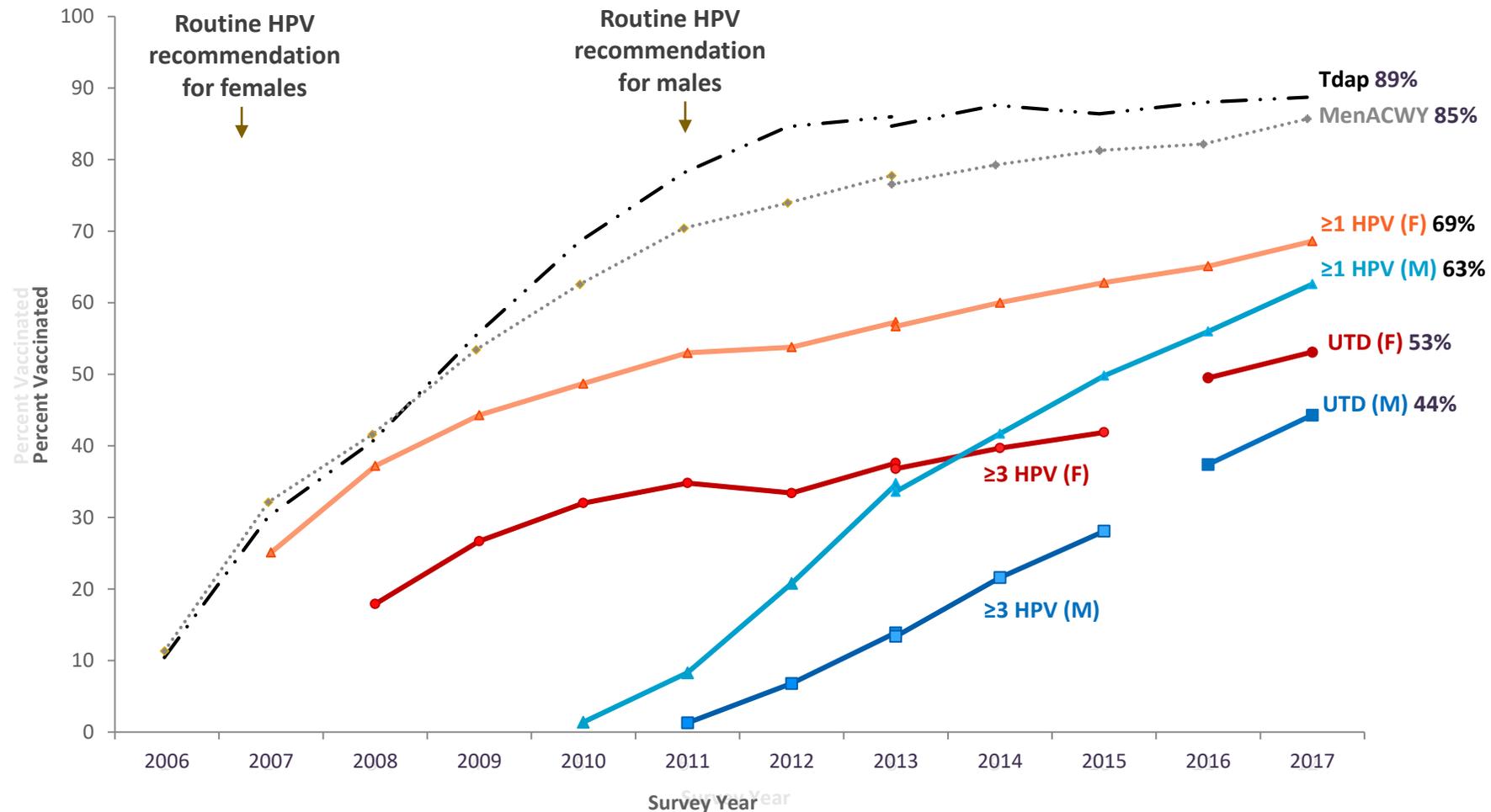
Country-specific observations

- Australia, Canada & USA: vaccinating girls and boys
- Australia, Malaysia, Rwanda & UK: effective school-based vaccinations
- Malaysia & Rwanda: two-year planning and education phase; endorsement by religious leaders; active program to combat misinformation; 85-90% HPV vaccination rates among eligible girls
- Colombia, Denmark, India, Ireland, Japan:
 - Anti-vaccine misinformation has led to poor uptake
 - Late or absent response by government
 - Delayed or absent peer-reviewed scientific evaluations of side-effects reported by media

Vaccination for adolescents in US: 2017

- Tdap (tetanus, diphtheria, pertussis): 88%
- Meningococcal vaccine 1+ dose: 85%
- MMR 2+ (measles, mumps, rubella): 92%
- Hepatitis B 3+ dose: 92%
- Varicella 1+ dose: 96%
- HPV vaccine 1+ dose (girls): 69%
- HPV vaccine 1+ dose (boys): 62%
- Walker TY et al, MMWR 2018

Estimated HPV vaccination coverage among adolescents aged 13–17 years, NIS-Teen, United States, 2006–2017



Adapted from Walker et al. MMWR 2018; NIS-Teen, National Immunization Survey-Teen; UTD, Up-to-date
 Note: revised definition of adequate provider data in 2013

Sustainability for HPV vaccination

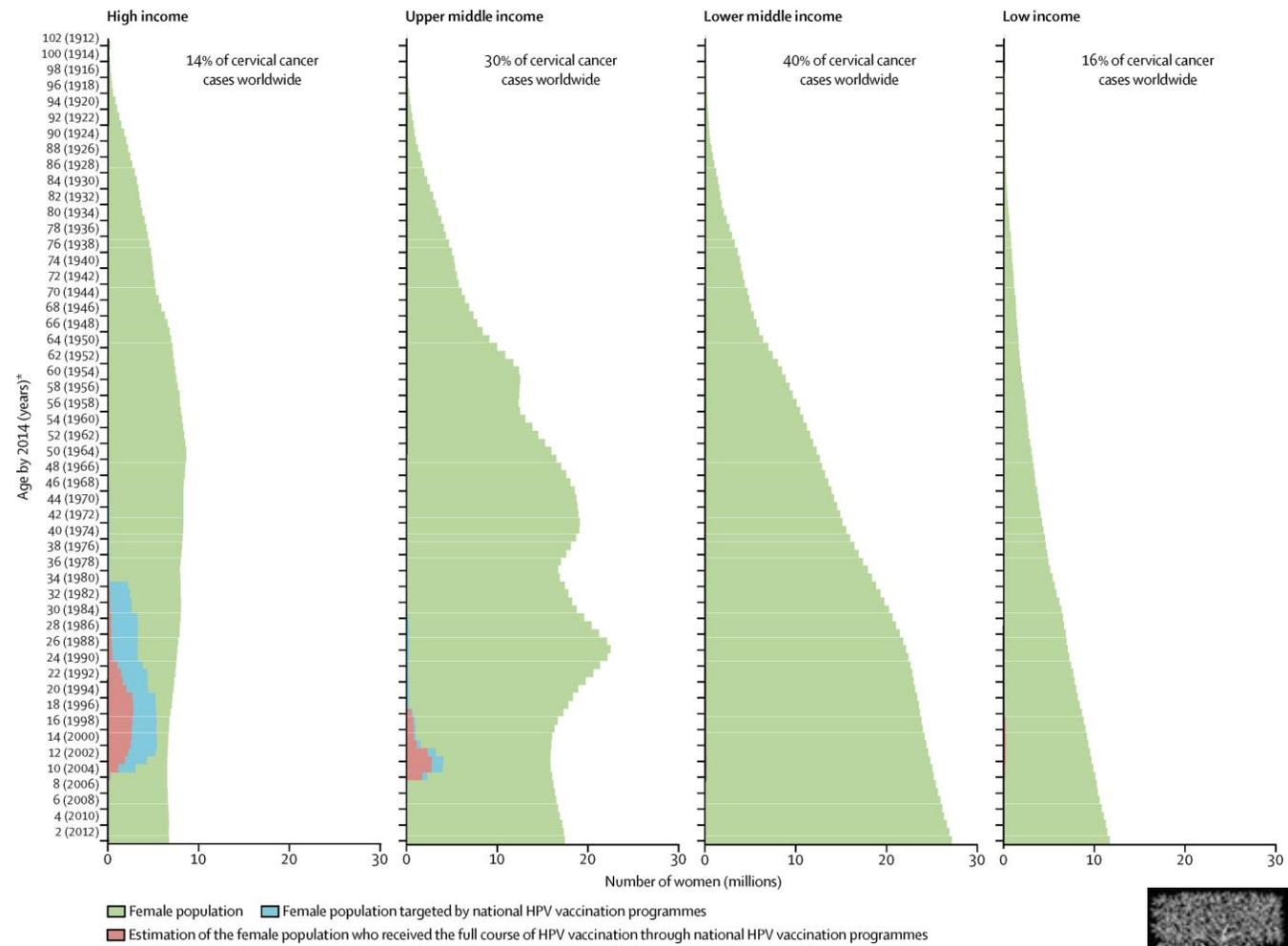
- Integration into national immunization programs
- Development of adolescent health programs and platforms
- Infrastructure for vaccinating adolescents
 - School-based versus clinic-based
 - How to reach girls not in school?

Adolescent health priorities

- Healthy diet
- Exercise
- Normal weight
- Reproductive health
- Prevention of smoking initiation, alcohol, other drugs
- School participation
- Vaccination

Health surveillance relevant to HPV vaccination and cervical cancer

- Unique Personal Identifier Number (UPIN) used in health records
- Vaccine registry
- Vaccine adverse event reporting system
- Screening registry
- Linked cancer and death registries
- Population-based database for disease diagnosis linked to UPIN
- Information on treatment for pre-cancer and cancer linked to UPIN



Next steps in HPV vaccination

- Projected global shortage of vaccine until 2026
- Proposal: give every girl one dose with booster dose if needed when vaccine shortage resolved; 1-dose versus 2-dose trial underway
- Bulk purchasing with price negotiation through UN system or non-governmental organizations
 - USA: \$150/dose for 2-3 doses + administration costs
 - GAVI: \$4/dose
 - PAHO: tender for bulk purchasing: \$14->\$8
- Generic HPV vaccine manufacturing
 - Gates Foundation has supported development of generic HPV vaccines in China and India

US NCI-Bill & Melinda Gate Foundation partnership in one-dose consortium

- Definitive phase III trial:
- 2x2 design
 - Randomization to 1 versus 2 doses
 - Randomization to Gardasil9[®] versus Cervarix[®]
- Clinical sites: Costa Rica and USA
- Multiple randomized phase II studies in other regions using immunogenicity as primary endpoint

Call to Action 2018

- HPV vaccination
- Screening & treatment of pre-cancer
- Treatment of invasive cervical cancer
- Symptom management and palliative care
- Plan and endpoints in draft; to be finalized 2020 World Health Assembly



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Special Thanks



Dr. Sophia Michaelson
Executive Director
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