THE PATH TO THE ELIMINATION OF CERVICAL CANCER

Anna-Lise Williamson

WHO Director-General calls for all countries to take action to help end the suffering caused by cervical cancer

Woman being screened for cervical cancer in a rural clinic, Kenya

Jonathan Torgovnik

19th May 2018: Cervical cancer is one of the most preventable and treatable forms of cancer as long as it is prevented with HPV vaccination, detected early, and managed effectively. Prevention and early treatment are highly cost-effective. Worldwide however, cervical cancer remains one of the gravest threats to women's lives, and globally, one woman dies of cervical cancer every two minutes. This suffering is unacceptable, and cannot continue. In recognition of this, WHO Director-General, Dr Tedros Adhanom Ghebreyesus today made a global call for action towards the elimination of cervical cancer.

Dr Tedros Adhanom Ghebreyesus, WHO Director-General

Call to action by Dr Tedros, Director General of the World Health Organization for

"coordinated action globally to eliminate cervical cancer by making sure that all women and girls, in particular those in low-income countries, have equal access to life-saving prevention technologies and services".

World Health Organization

human reproduction programme hrp research for impact UNDP-UNFPA-UNICEF-WHO-WORLD BANK

(https://www.who.int/reproductivehealth/DG_Call-to-Action.pdf

Elimination by 2060 – Targets for 2030

Vision: A world without cervical cancer

Goal: **below 4 cases of cervical cancer per 100,000 woman-years**

2030 TARGETS

90%	70%	30%
of girls fully vaccinated with HPV vaccine by 15 years of age	of women screened with an HPV test at 35 and 45 years of age and all managed appropriately	reduction in mortality from cervical cancer

The 2030 targets and elimination threshold are subject to revision depending on the outcomes of the modeling

From WHO treatment guidelines update – HPV screening and treatment

Human Papillomavirus (HPV) and Cancer

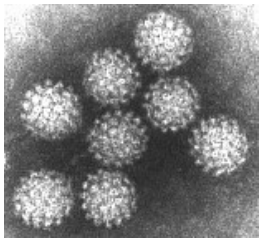
- Globally, one woman dies of cervical cancer every two minutes, which is unacceptable.
- Cervical cancer is largely preventable and treatable, when detected early.
- Nearly 90% of deaths from cervical cancer each year are of women living in low- and middle- income countries
  - Most of these women will not have had access to the key cervical cancer services which could have saved their lives, nor the palliative care to help them manage their symptoms with dignity and respect.
- Women living with HIV are at 4-5 times higher risk of cervical cancer.

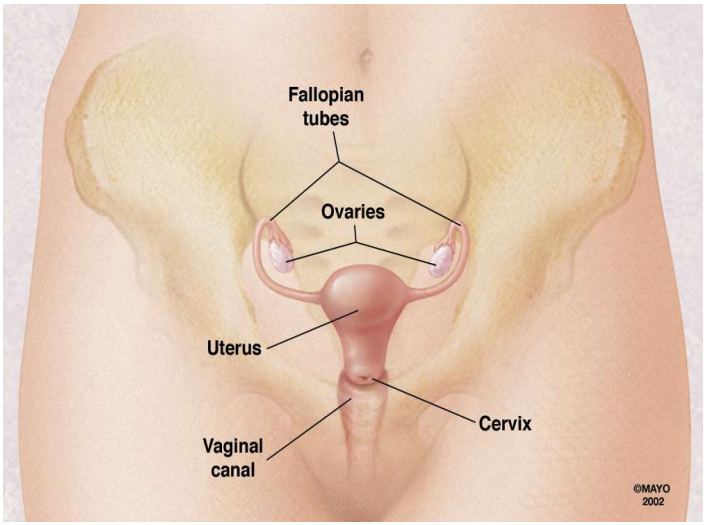
https://www.figo.org/Declaration-Cervical-Cancer2018

SPECIFIC TYPES OF 'HIGH-RISK' HPV ARE CAUSALLY INVOLVED IN CANCER OF THE CERVIX

HIGHEST WORLDWIDE ATTRIBUTABLE FRACTION SO FAR REPORTED FOR A SPECIFIC CAUSE OF ANY MAJOR HUMAN CANCER

Not all women with HPV will get Ca Cervix but almost all cervical cancers have detectable "high-risk" HPV DNA



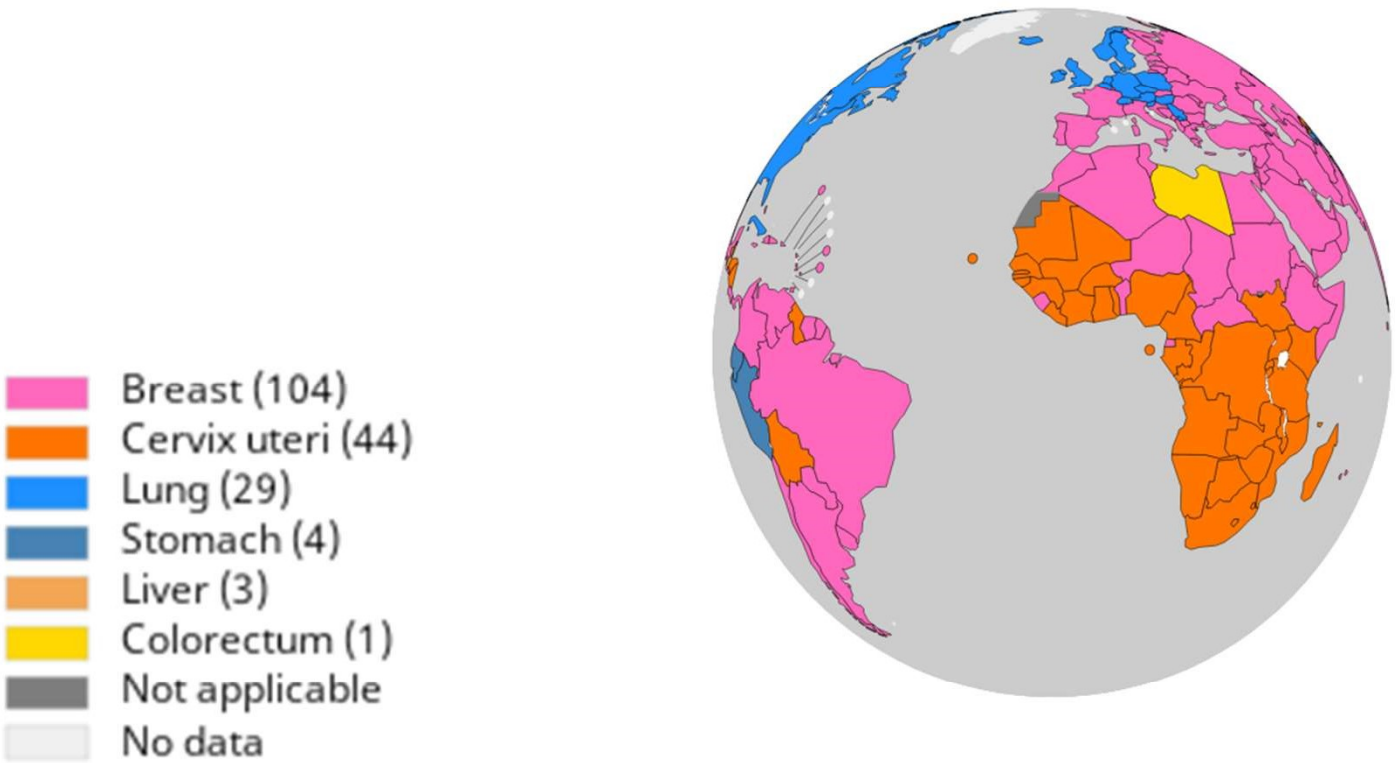


Estimates of Global Burden of HPV Associated Cancer

(Garland et al. (2016) Clinical Infectious Diseases)

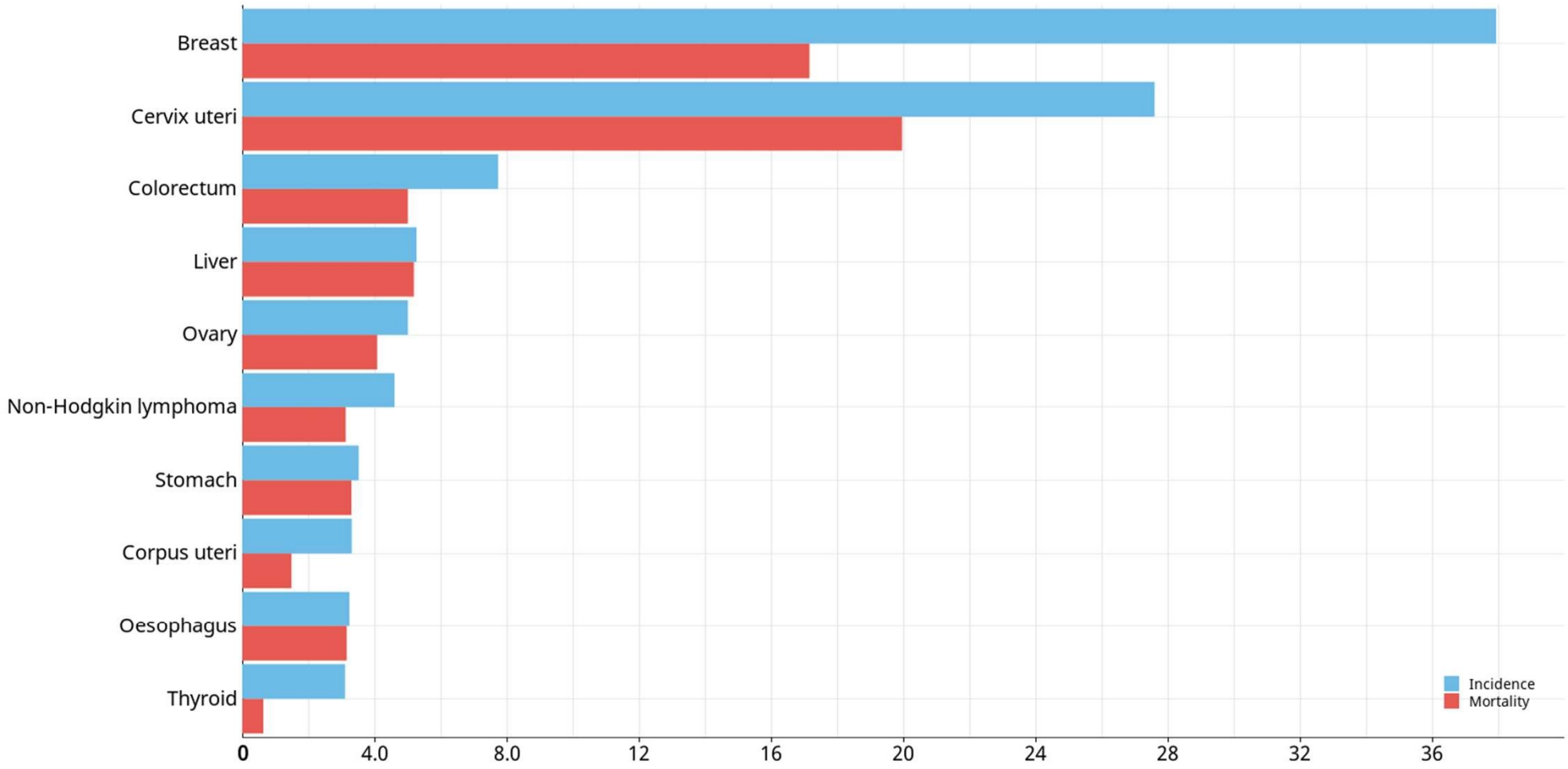
- 100% cervical cancers
- 90% anal cancers
- 40% of cancers of the vulva
- 70% of cancers of the vagina
- 50% of cancers of the penis
- 13-72% of oropharyngeal cancers

Top cancer per country, estimated age-standardized mortality rates (World) in 2018, females, all ages



Data source: GLOBOCAN 2018
Graph production: IARC
(http://gco.iarc.fr/today)
World Health Organization

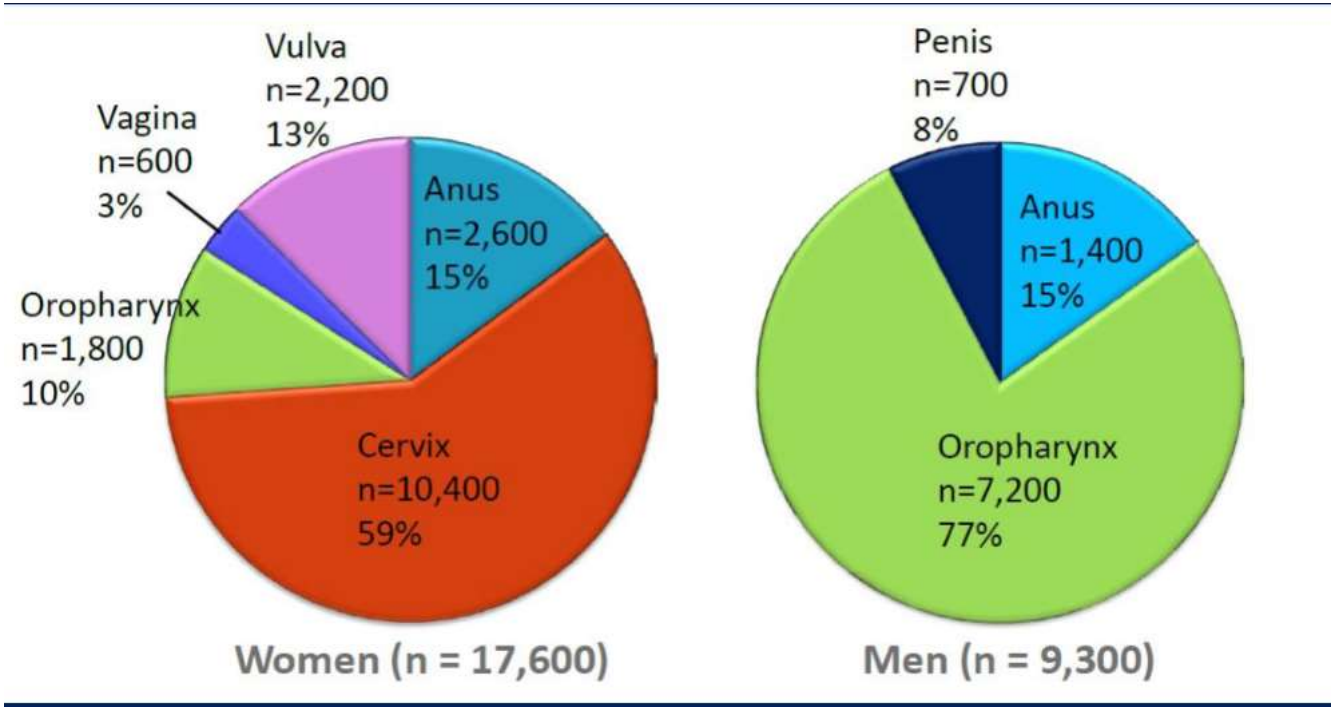
Estimated age-standardized incidence and mortality rates (World) in 2018, Africa, females, all ages



Data source: Globocan 2018
Graph production: Global Cancer Observatory (http://gco.iarc.fr)

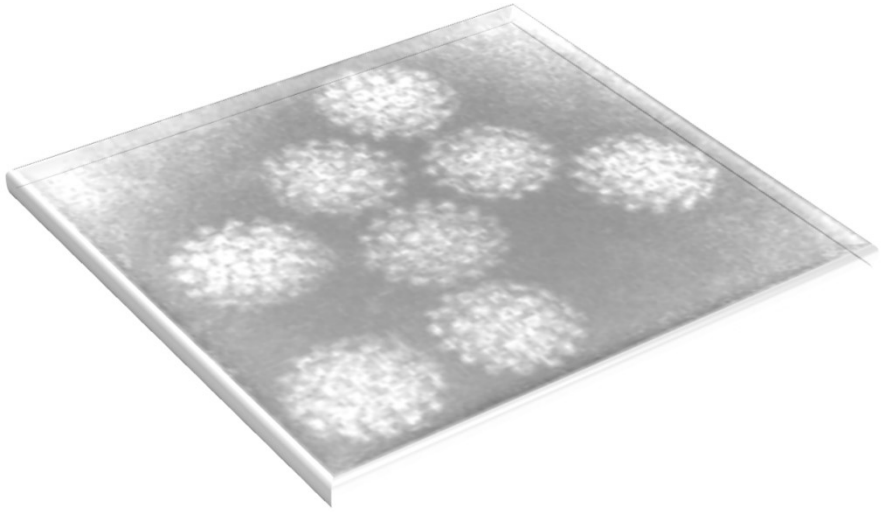
International Agency for Research on Cancer
World Health Organization

New cancers caused by HPV per year, United States, 2006-2010

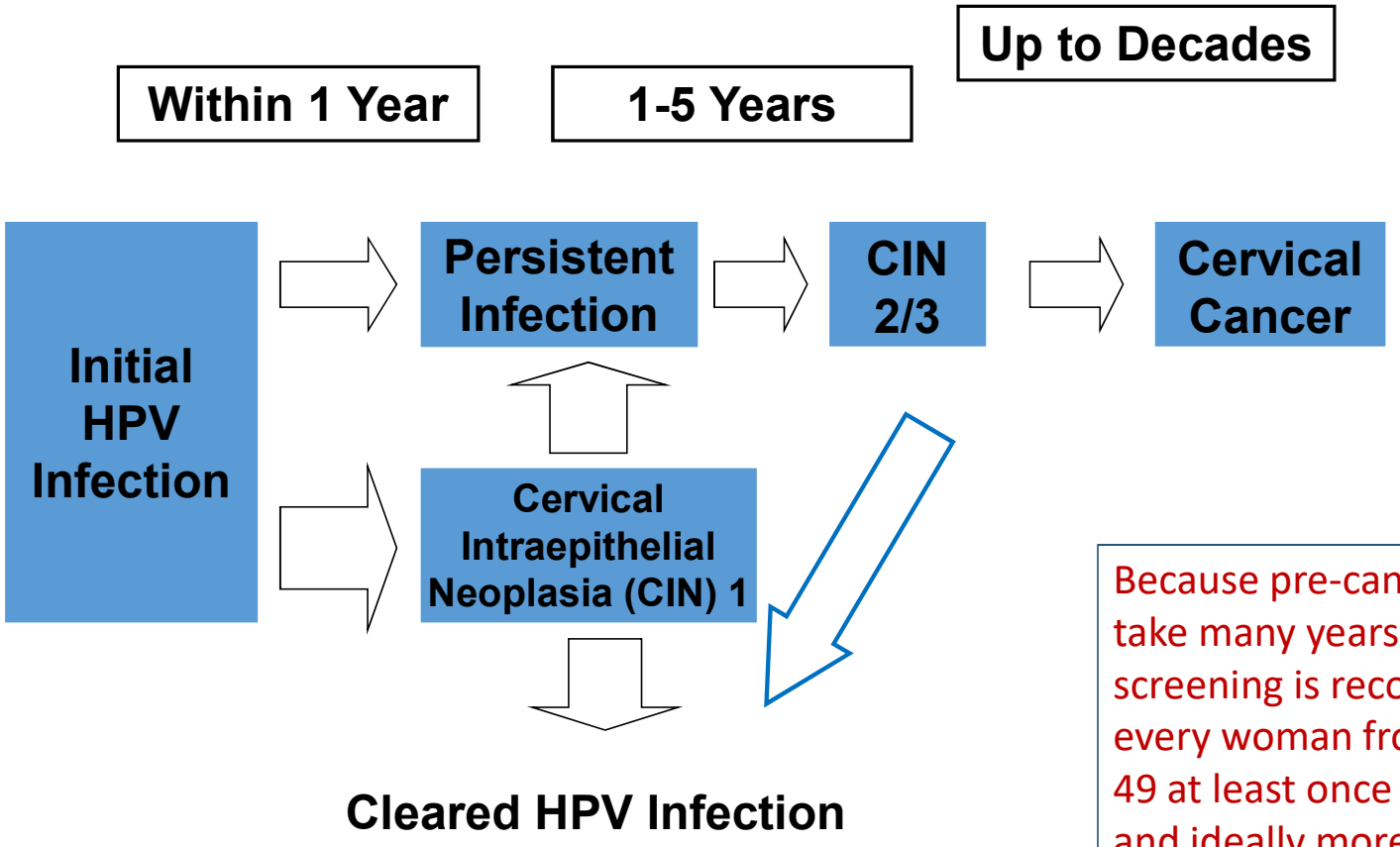


CDC. You Are the Key to HPV Cancer Prevention. PowerPoint Presentation. June 25 th, 2015.
CDC, United States Cancer Statistics (USCS), 2006-2010

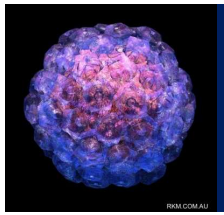
Background on Human Papillomavirus



Natural History of HPV Infection



Because pre-cancerous lesions take many years to develop, screening is recommended for every woman from aged 30 to 49 at least once in a lifetime and ideally more frequently.



HUMAN PAPILLOMAVIRUSES

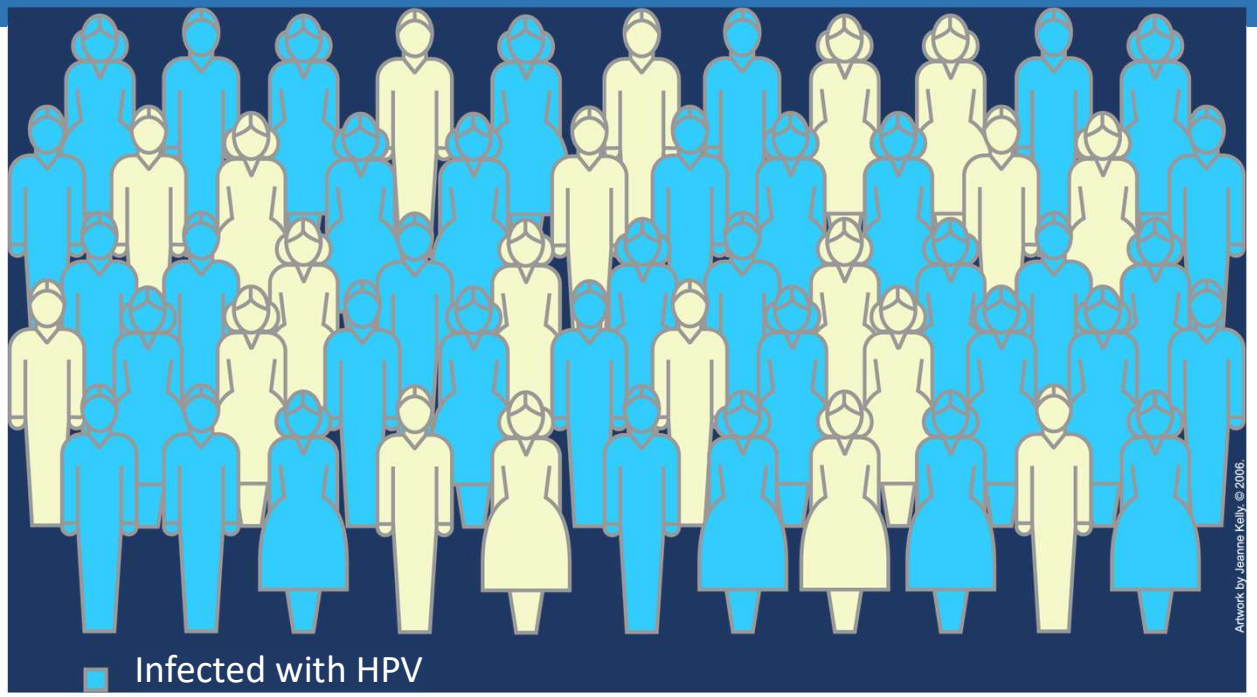
INSTITUTE OF INFECTIOUS DISEASE AND MOLECULAR MEDICINE

TWO MAJOR GROUPS – over 200 HPV Types

1. CUTANEOUS WARTS

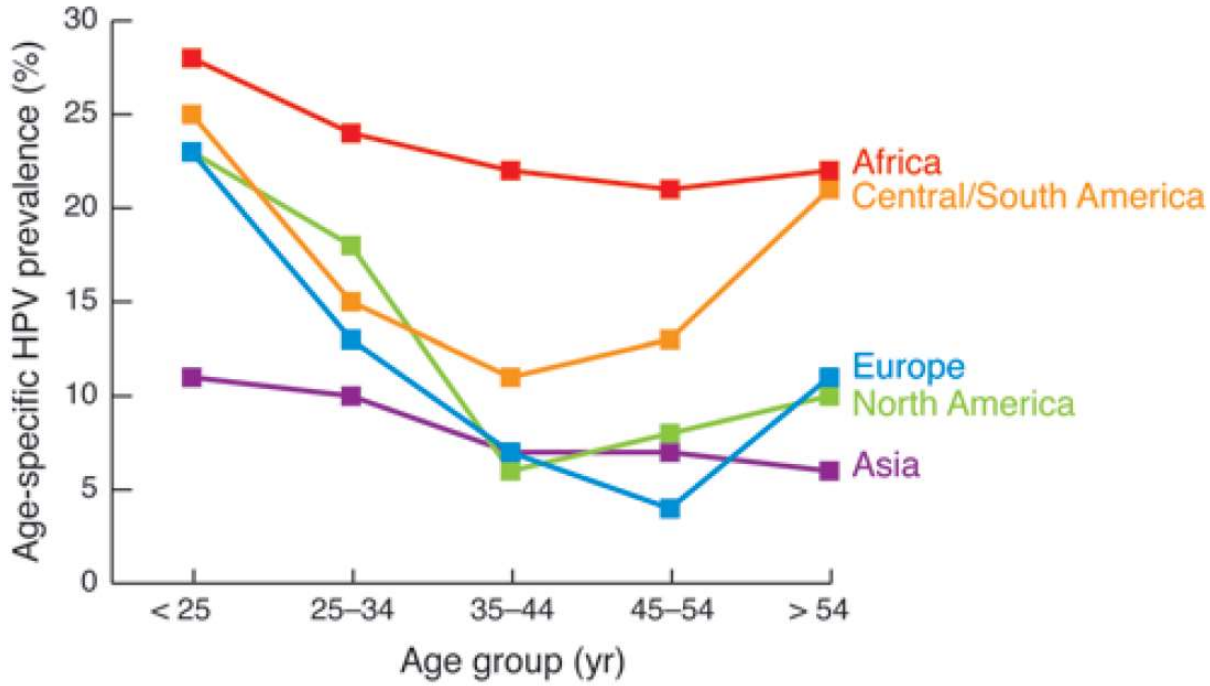
2. MUCOSAL HPVs
   - divided into high and low risk types depending on their association with disease
     - Low-risk HPV types 6 and 11 cause genital warts (different types to cutaneous warts)
     - High-risk HPV types cause cancers

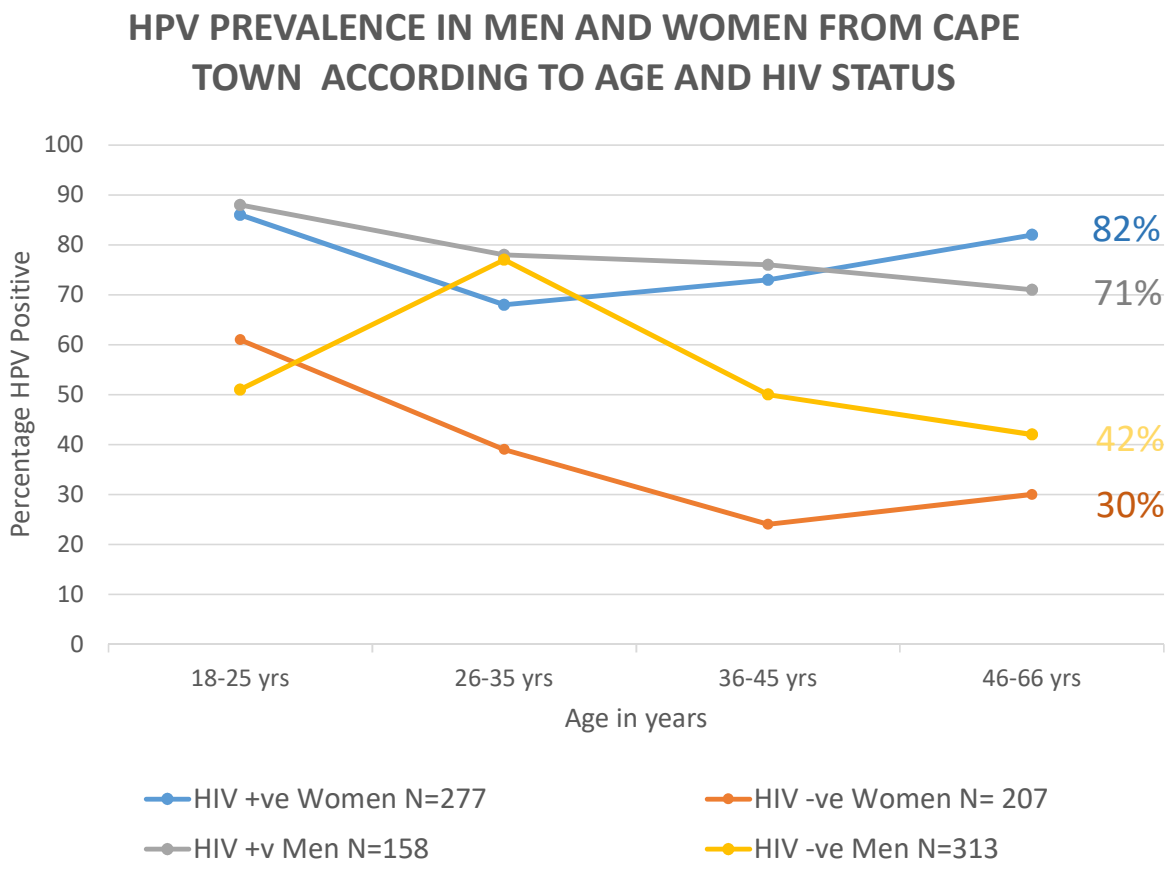
- **HPV is the most common sexually transmitted virus**
- At least 70 percent of sexually active persons will be infected with genital HPV at some time in their lives. HPV infects both men and women.
- **Not all women with HPV will get Ca Cervix but almost all cervical cancers have detectable "high-risk" HPV DNA**



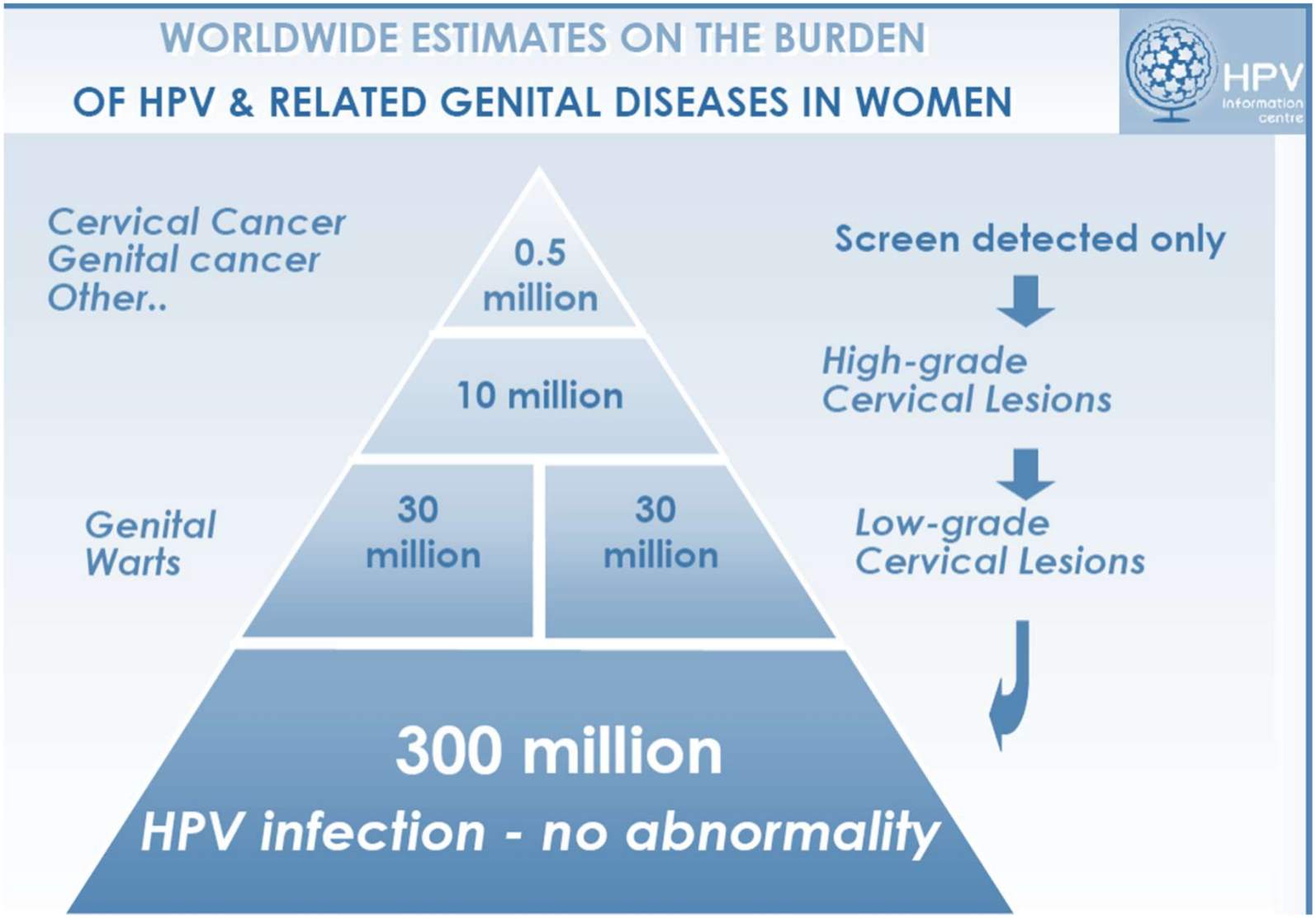
AGE-SPECIFIC HPV PREVALENCE IN WOMEN WITH NORMAL CYTOLOGY FROM FIVE WORLD REGIONS

Bosch FX, et al. *Vaccine.* 2008;26



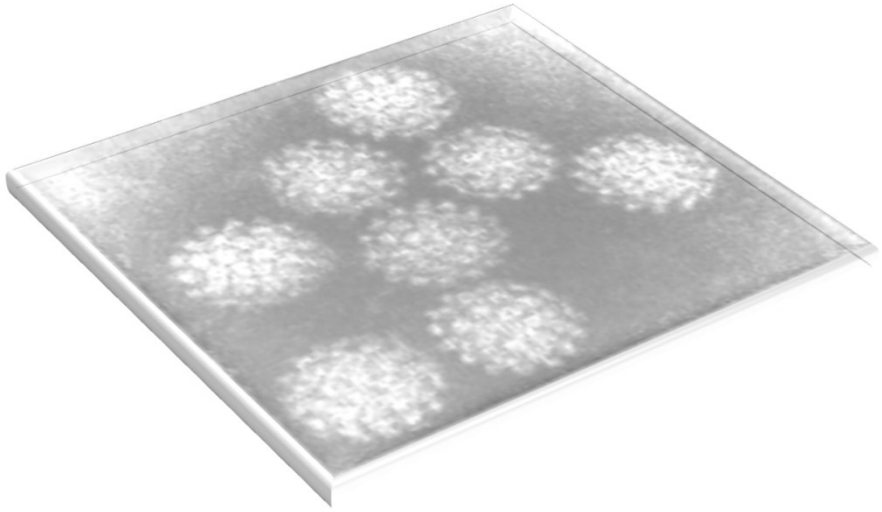


Mbulawa, Coetzee, Williamson (2015) BMC Infectious Diseases



*www.who.int/**hpvcentre***

CERVICAL CANCER SCREENING

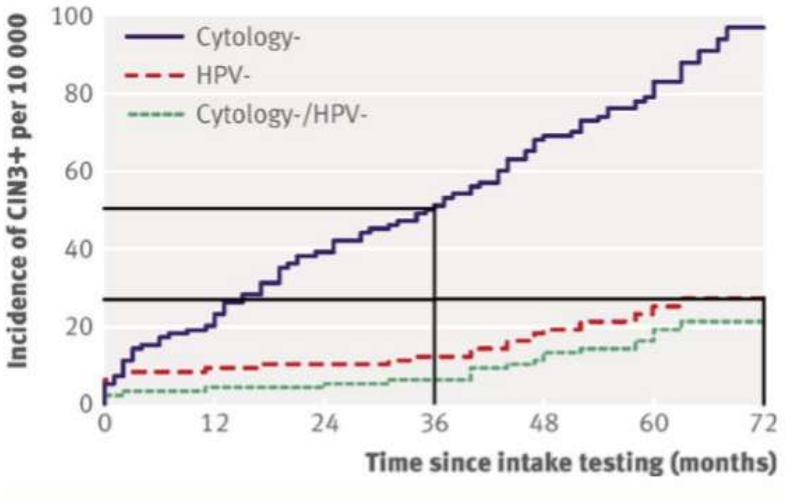


CERVICAL CANCER SCREENING OPTIONS

Platform	Technology	Application	Resources	
Cytology	Cytology/Automation	Screening and Triage	High/Middle	
	P16/Ki67 dual stain / Automation	Triage	High/Middle	
Molecular	HPV testing and Genotyping	Screening and Triage	All settings	
	Methylation	Triage	All settings	Not yet routine
Visual	Colposcopy	Triage	High/Middle	
	VIA/Automation	Screening and Triage	Low Resource	

MODIFIED FROM NICOLAS WENTZENSEN - IPVS PLENARY SESSION 2

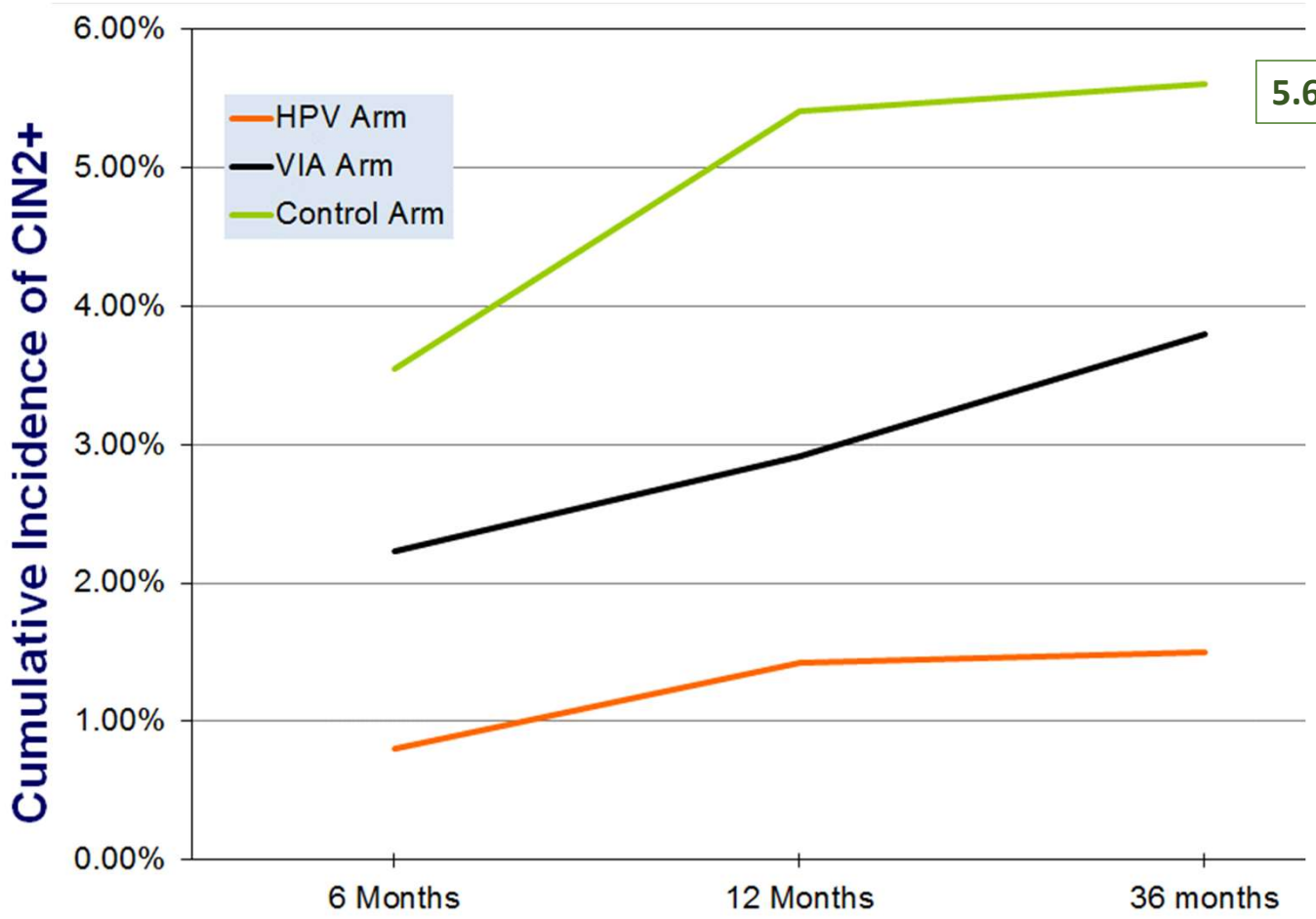
HPV TESTING REPLACING PAP SMEARS IN MANY PARTS OF THE WORLD



- HPV test protects against cancer in situ for more than 6 years whereas cytology protects for 3 years
- No additional benefit of cytology for HPV negative women
- CIN3+ risk for a cytology negative women after 3 years is the same as risk for HPV negative women after 6 years.

Dillner , Molecular Oncology 13 (2019) 591–598

Screen (VIA or HPV) and Treat in South Africa



5.6% CIN2/3 cumul. Inc

32% reduction

73% reduction

Denny *et al.*, JNCI, 2010

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Australia

- Australia has had a comprehensive cervical screening program since 1991 – resulted in halving cervical cancer rates by 2010.

- In 2017 Australia transitioned to 5 year screening interval with validated HPV assays which is expected to reduce cervical cancer by a further 20%

K Canfell, M Hall, K Simms, M Smith, M Saville (2018). Australia on-track to be the first country to achieve cervical cancer elimination.

PROJECTED LONG TERM IMPACT OF SWITCHING TO PRIMARY HPV ON HEALTH OUTCOMES, COSTS AND HEALTH RESOURCES UTILZATION

- Cytology Screening – 2-yearly cytology from 18-20 to 69 years
- HPV: Final guidelines 5-yearly HPV screening 25-74

	CYTOLOGY SCREENING		HPV: FINAL GUIDELINES*	
	If HPV vaccination had not been introduced	Cohort offered vaccination at age 12 year	If HPV vaccination had not been introduced (reduction compared to cytology screening program)	Cohort offered vaccination at 12 years (reduction compared to cytology screening program)
Cervical cancer incidence †	6·92	2·87	4·73 (-31%)	2·17 (-24%)
Cervical cancer mortality †	1·80	0·74	1·15 (-36%)	0·53 (-29%)
Cervical cancer cases (n) ‡	850	353	584 (-265;-31%)	267 (-85;-24%)
Cervical cancer deaths (n) ‡	227	94	145 (-82;-36%)	66 (-28;-29%)
Colposcopies (n) ‡	85795	60995	116889 (31094; 36%)	56479 (-4516;-7%)
Treatments (n) ‡	22661	13899	23963 (1302;6%)	13240 (-659;-5%)
Annual cost‡ of screening programme (AUS$)	$223 million	$192 million	$182 million ($41 million; -19%)	$142 million ($50 million; -26%)

†Age-standardised rate (0–84 years), standardised using the 2001 Australian standard population and represented per 100 000 women. ‡Using the female Australian standard population as predicted for 2017.

K Canfell, M Hall, K Simms, M Smith, M Saville (2018). Australia on-track to be the first country to achieve cervical cancer elimination.

Near Point of Care Test

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Near Point of Care Diagnostic Test – GeneXpert® (Cepheid)

Cepheid has developed and commercialized an HPV assay for detection of hrHPV DNA for its GeneXpert® platform – a fully-automated and integrated system for PCR-based NAAT. TAT of <60 minutes for cervical cancer-related HPVs.

A multiplexed test that targets the E6 and E7 oncogenes of 14 hrHPV types in five fluorescent channels:

- HPV16
- HPV18/45
- HPV31/33/35/52/58; HPV51/59
- HPV39/56/66/68.
- Specimen adequacy control

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Performance of the Xpert HPV assay in women attending for cervical screening

Cuzick et al. PapillomavirusResearch1(2015)32–37

- 3408 cases – general screening population
- HPV Positivity for Xpert was 19.6%, cobas 19.2% and hc2 19.9% with high concordance
- Histology was available for 172 participants.
  - Xpert, cobas and hc2 showed similar sensitivity (98.7%,97.5%,98.7%) for CIN2 (n=79). One case of CIN2 was negative for all assays.
  - All CIN3 (n=47) were positive on Xpert and hc2 and one case negative for cobas.
- Conclusions: The performance of Xpert HPV Assay is comparable to established HPV tests. It offers simplicity of testing, flexibility with non-batching of individual samples and rapid turnaround time.

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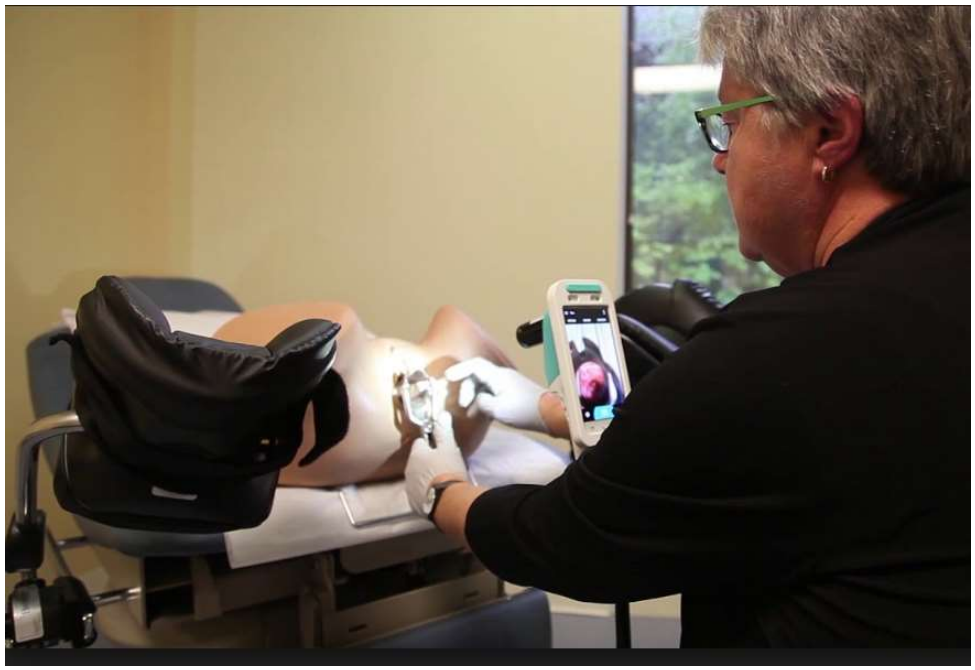
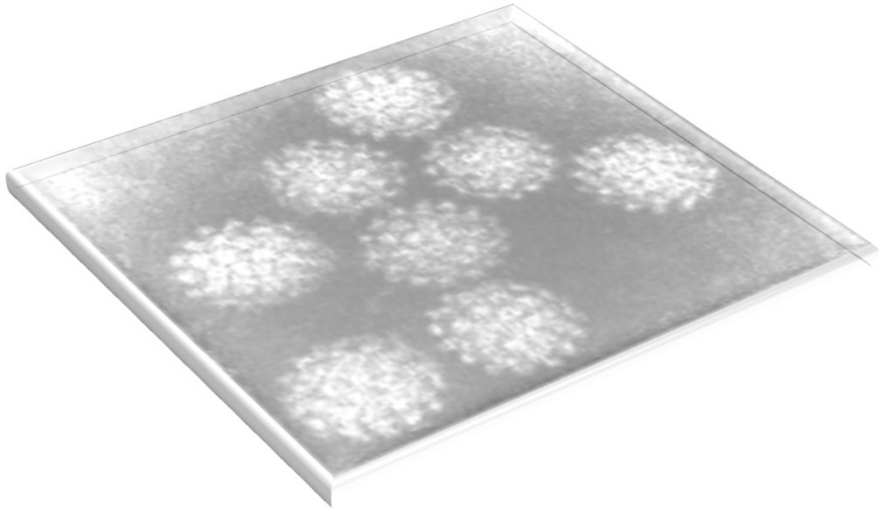
MOBILE ODT - automated visual evaluation of cervical images



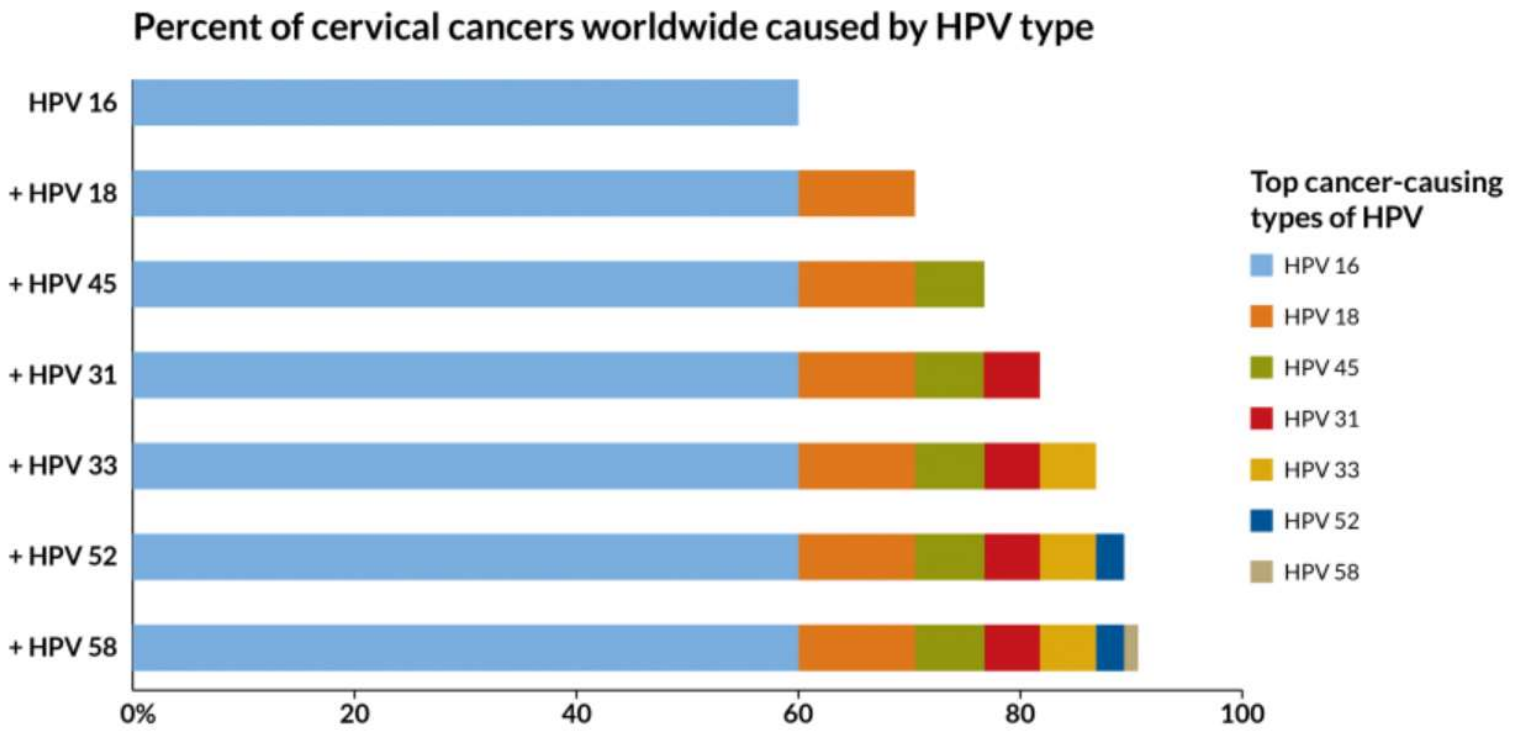
HPV Vaccines



HPV Vaccines

	2vHPV (Cervarix, GSK)	4vHPV (Gardasil, Merck)	9vHPV (Gardasil 9, Merck)
Virus types	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 59
Adjuvant	Yes	Yes	Yes
Licensure	Females 9–25 yrs	Females 9–26 yrs Males 9–26 yrs	Females 9–26 yrs Males 9–26 yrs
Prevents	Cervical cancer and precancerous lesions	Cervical, vulvar, vaginal, and anal cancer and precancerous lesions, genital warts	Cervical, vulvar, vaginal, and anal cancer and precancerous lesions, genital warts

World Health Organization (WHO) **recommended 2 doses of the HPV vaccine for girls below 15 y on the basis of the immune-bridging studies demonstrating non-inferior immune response of 2 doses in the adolescent girls compared to 3 doses** in the young adult women in whom the efficacy against disease is established



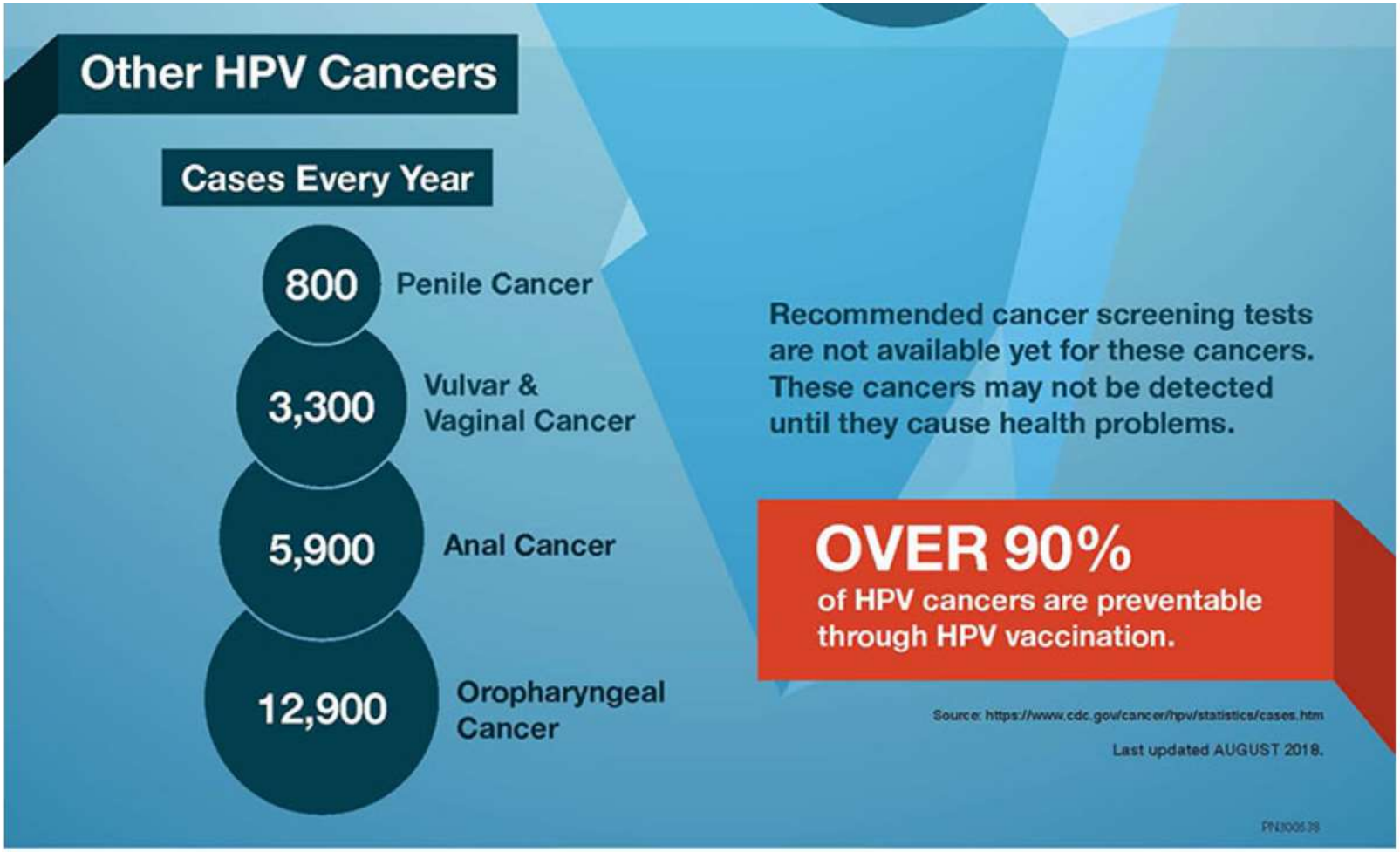
Gardasil 9 : HPV-6, -11, -16, -18, -31, -33, -45, -52, and -58

https://www.sciencenews.org/sites/default/files/styles/article-main-image-large/public/main/articles/ns_HPV_vaccine_graph-01.

Burden of Disease associated with HPV types

	HPV Type	Cervical Cancer	All HPV-Associated Cancers	Anogenital Warts	
Gardasil	6			90%	Gardasil 9
	11				
	16	66%	64%		
	18				
	31	15%	10%		
	33				
	45				
	52				
	58				

Gardasil 9 is approved by FDA for males and females 9 through 26 years of age. Note: Gardasil 9 was originally approved for males through age 15 only, and CDC's recommendations for vaccinating older males were off-label. But on December 14, 2015, FDA approved the vaccine for males through age 26.



Don't rely on screening to catch it later. Protect them now with HPV vaccination.

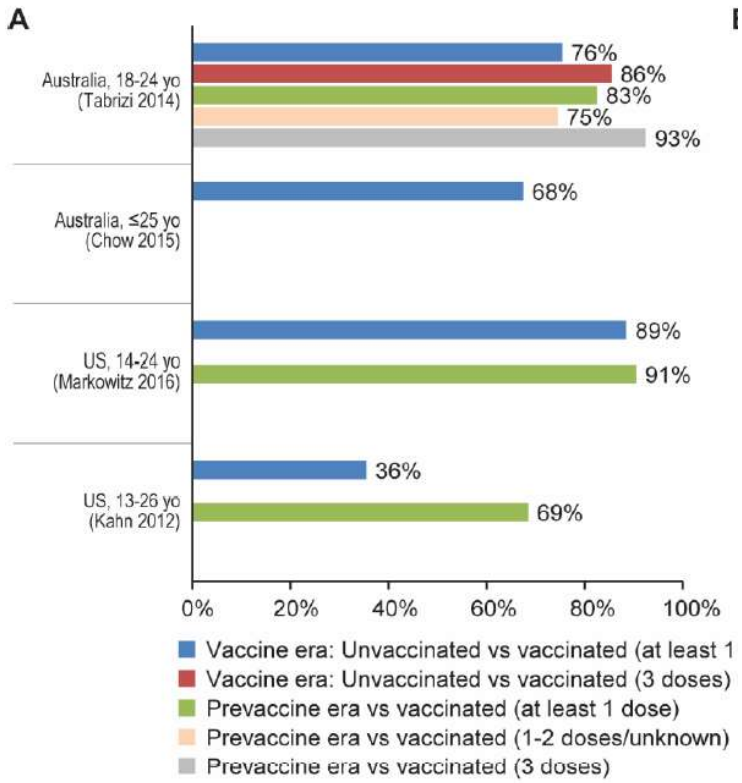
https://www.cdc.gov/hpv/hcp/more-than-screening/index.html

HPV VACCINE
IS CANCER PREVENTION

HPV VACCINES

- Vaccines induce high titres of neutralizing antibody which persist for extended times - duration of protection is unknown.
- Neither vaccine is therapeutic.
- All three vaccines are very effective against HPV 16 and 18 and will have a major impact on cervical cancer prevalence. 9 valent vaccine targets another 5 HPV types protecting against over 80% of cancers
- None of the vaccines protect from all cervical cancers and so cervical screening will need to continue on vaccinees as well as the unvaccinated women.

Percent reduction of prevalent HPV 16/18 infection in vaccine era compared to pre vaccine era or contemporaneous unvaccinated females



Within 6 years, prevalent HPV 6/11/16/18 infections among Australian women 18-24 years old decreased by 86% after 3 doses and by 76% after ≥1 dose, compared to contemporaneous unvaccinated women

In the US, 89% reductions within 6 years in nationally-representative samples of sexually active females aged 14- 24 years who received ≥1 dose, in comparison to unvaccinated females in the vaccine era

Australia and the US reported decreased infection prevalence among unvaccinated females in the vaccine era compared to the prevaccine era, evidence potentially reflecting herd protection (17-49%).

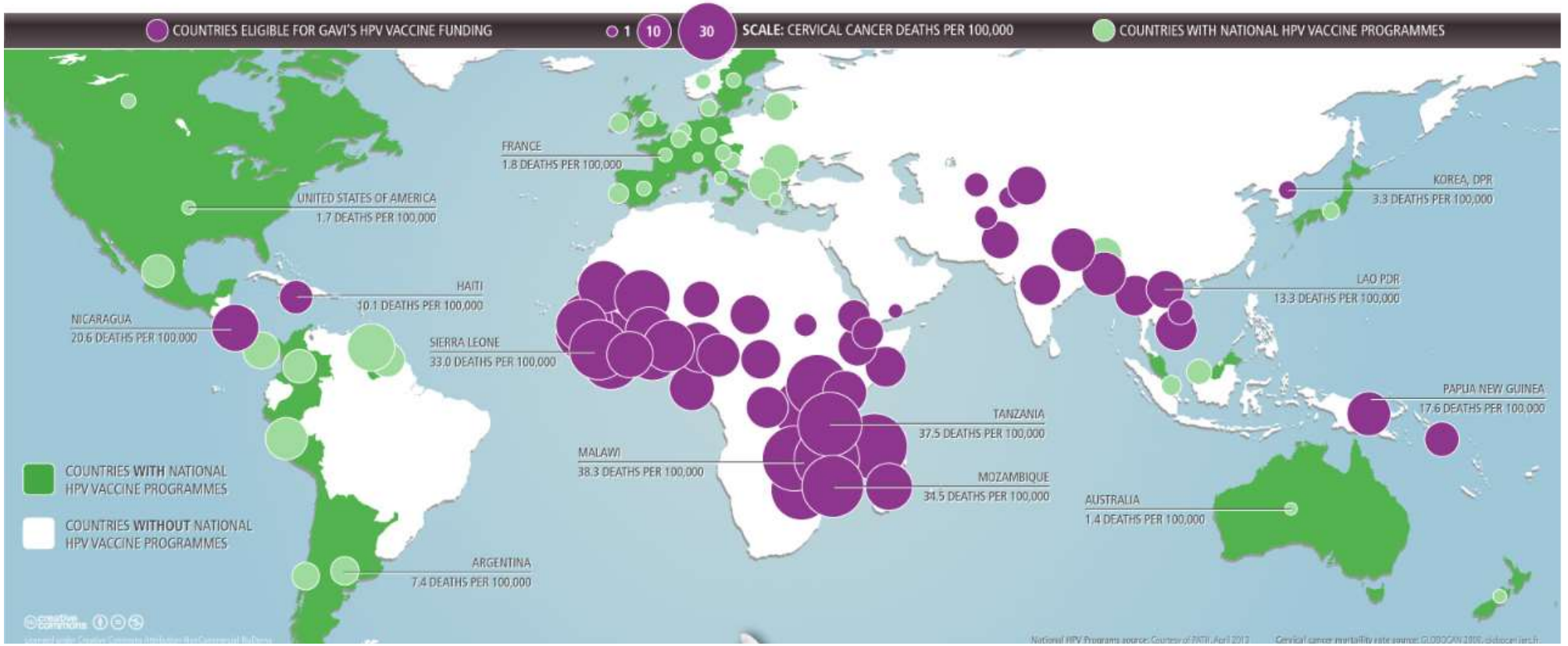
Garland *et al.* (2016) Clinical Infectious Diseases

GAVI ALLIANCE

SAVING LIVES AND PROTECTING HEALTH THROUGH IMMUNISATION IN DEVELOPING COUNTRIES

GAVI ALLIANCE TACKLES CERVICAL CANCER

EVERY YEAR, 275,000 WOMEN DIE OF CERVICAL CANCER. OVER 85% OF THOSE DEATHS ARE IN DEVELOPING COUNTRIES



HPV Vaccination an essential Component of Cervical Cancer Prevention Programmes

- **Primary prevention:** HPV vaccination targets girls aged 9 to 13 years, aiming to reach them before they become sexually active.

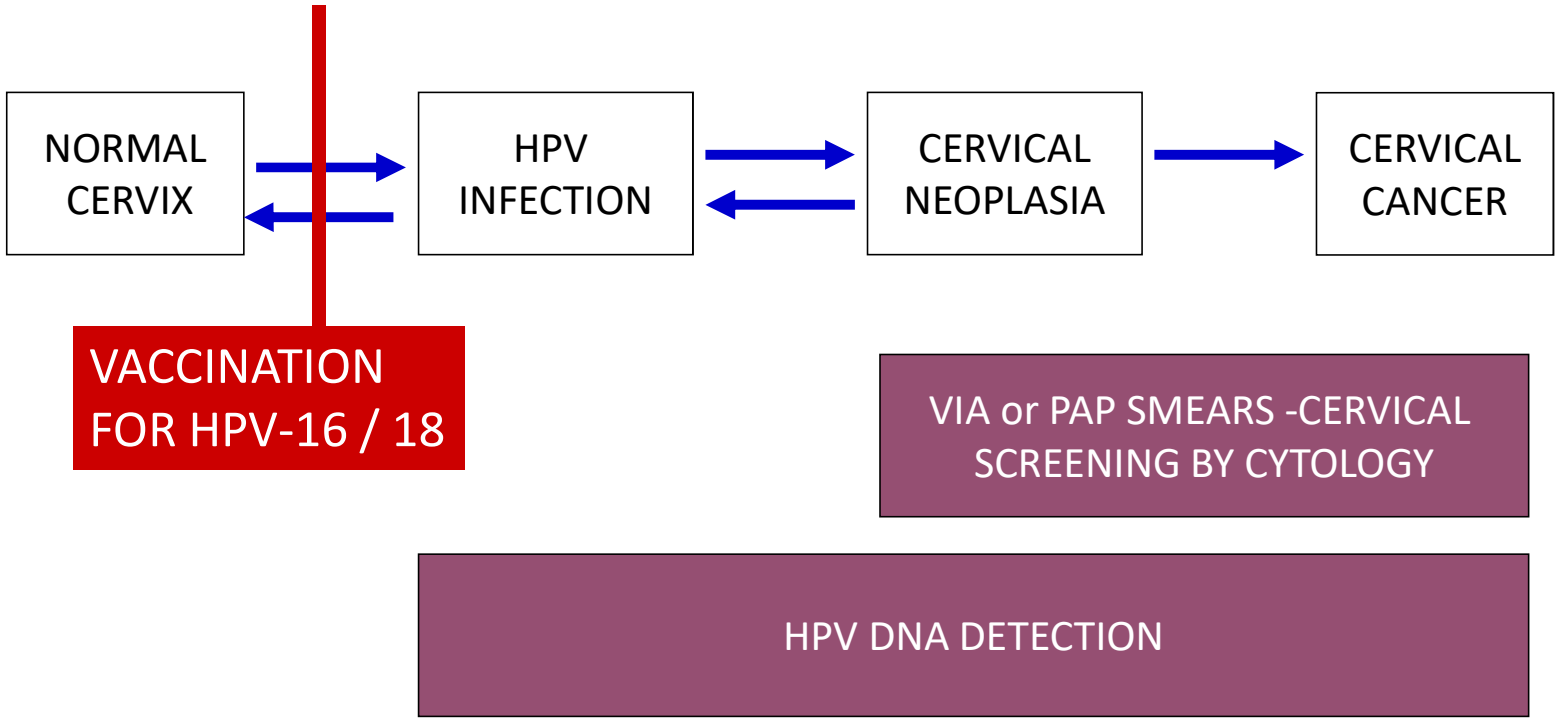
- **Secondary prevention:** access to technology for women over 30 years of age, such as VIA (visual inspection of the cervix with acetic acid) or HPV testing for screening, followed by treatment of detected precancerous lesions, which may develop into cervical cancer.

- **Tertiary prevention:** access to cancer treatment and management for women of any age, including surgery, chemotherapy and radiotherapy.

- When curative treatment is no longer an option, access to **palliative care is crucial**.

http://www.who.int/mediacentre/news/releases/2014/preventing-cervical-cancer/en/

CERVICAL CANCER PREVENTION STRATEGIES NEED TO INTEGRATE VACCINATION AND CERVICAL SCREENING PROGRAMMES




You're not opening the door to sex.
You're closing the door to cancer.
HPV vaccine is cancer prevention.
Talk to your child's doctor about vaccinating your 11-12 year old against HPV.
www.cdc.gov/vaccines/teens
CDC
YOU ARE THE KEY TO HPV CANCER PREVENTION