Natural History of HPV and Cervical Cancer: The Case for Global Cervical Cancer Prevention

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DIALOGUE FOR ACTION™ ON CANCER SCREENING

prevent cancer FOUNDATION

Natural History and Epidemiology of Cervical Cancer: The Case for Global Cervical Cancer Prevention

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GLOBAL COALITION AGAINST CERVICAL CANCER

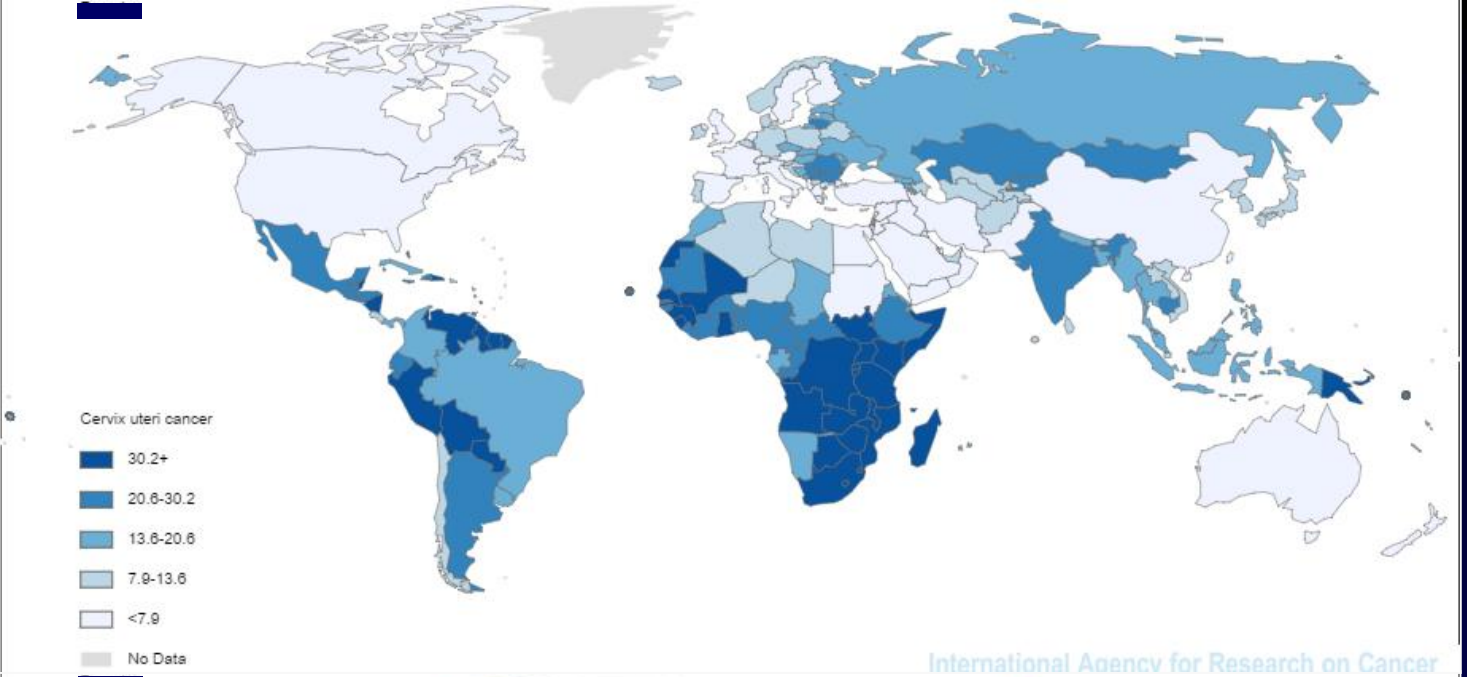
Declarations

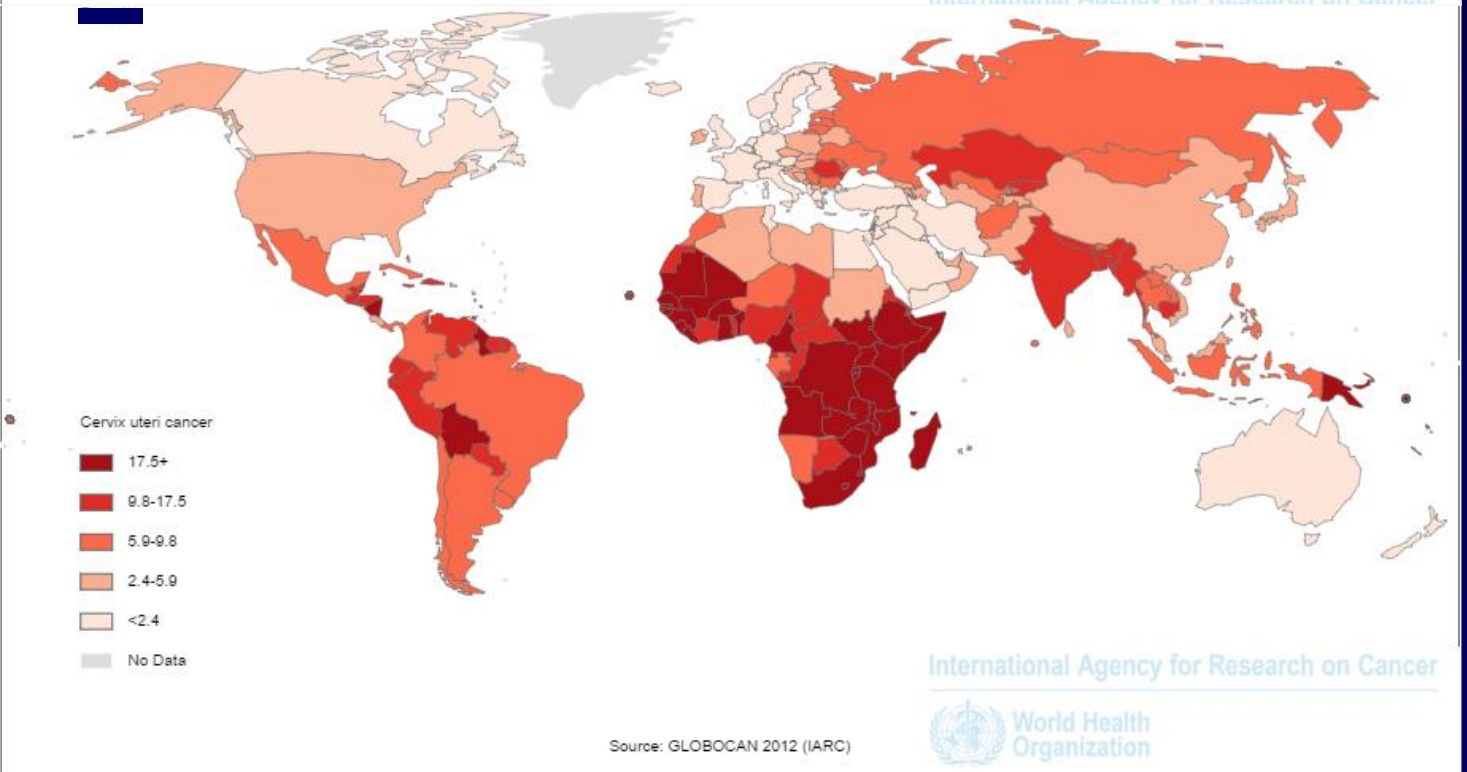
- I have received commercial HPV tests for research at a reduced or no cost from Roche, Qiagen, Norchip, BD, AVC, & mtm.
- I have been compensated as a member of a Merck Data and Safety Monitoring Board for HPV vaccines.
- I have been paid as consultant for BD, Gen-Probe/Hologic, Roche, Cepheid, ClearPath, Guided Therapeutics, Teva Pharmaceuticals, Inovio, & GE Healthcare.

Today's Talk

1. Global Cervical Cancer Burden
2. Natural History Of HPV: The Rational Basis For Cervical Cancer Prevention
3. 1º Prevention: HPV Vaccination
4. 2º Prevention: Screening
5. Global CxCa Prevention And Control: How Do We Make It Available To Everyone?

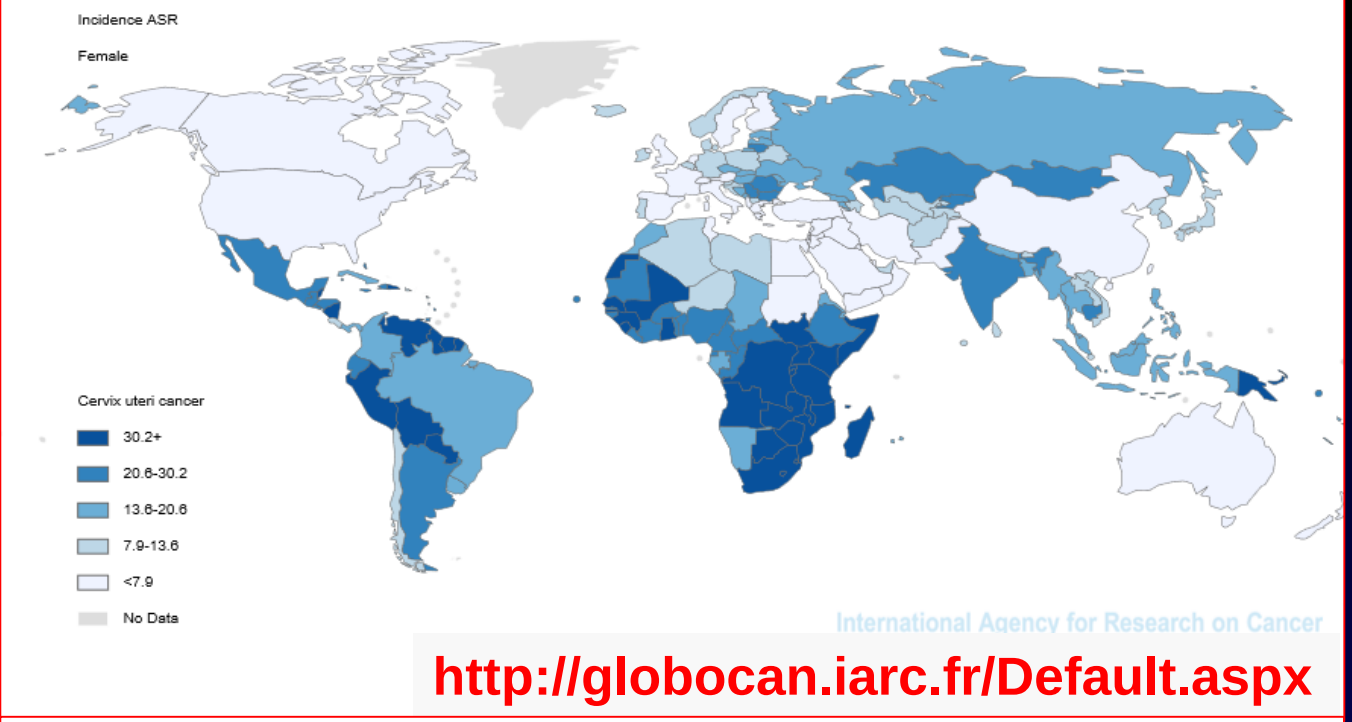
Global Cervical Cancer Burden



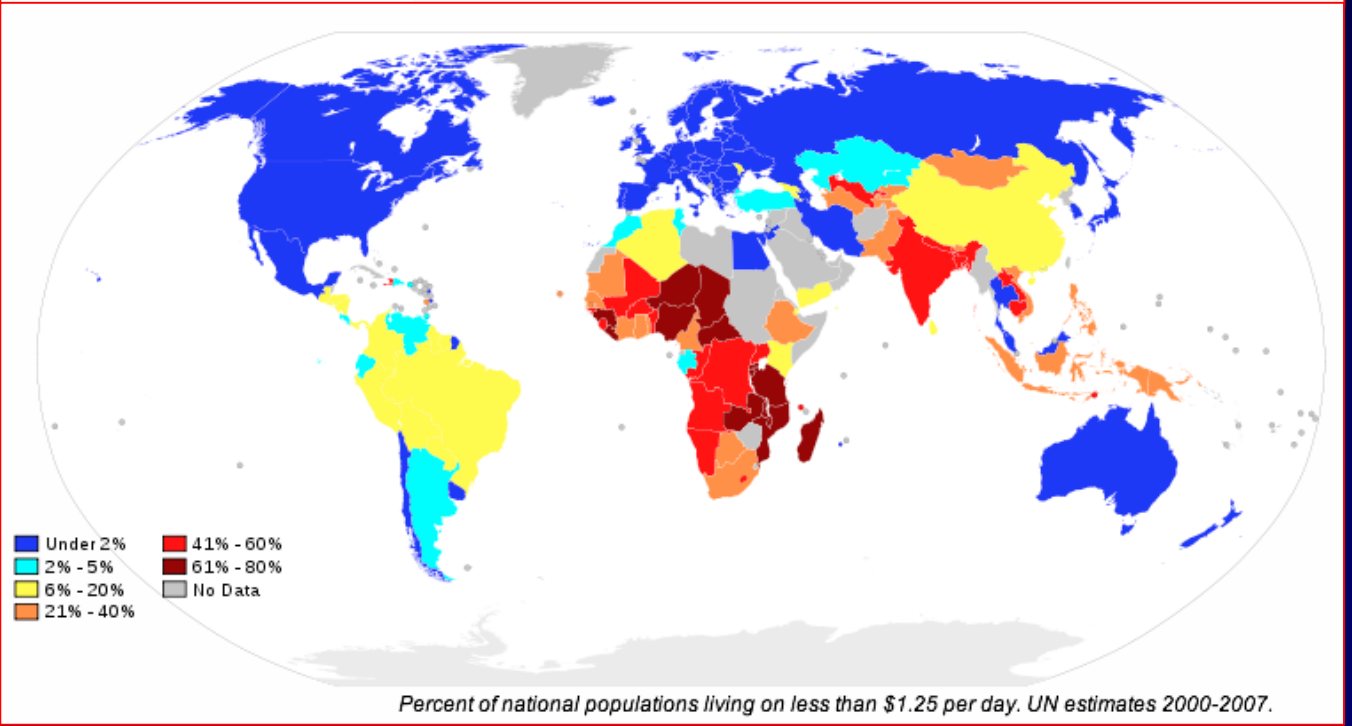


Source: GLOBOCAN 2012 (IARC)

Global Cervical Cancer & Poverty

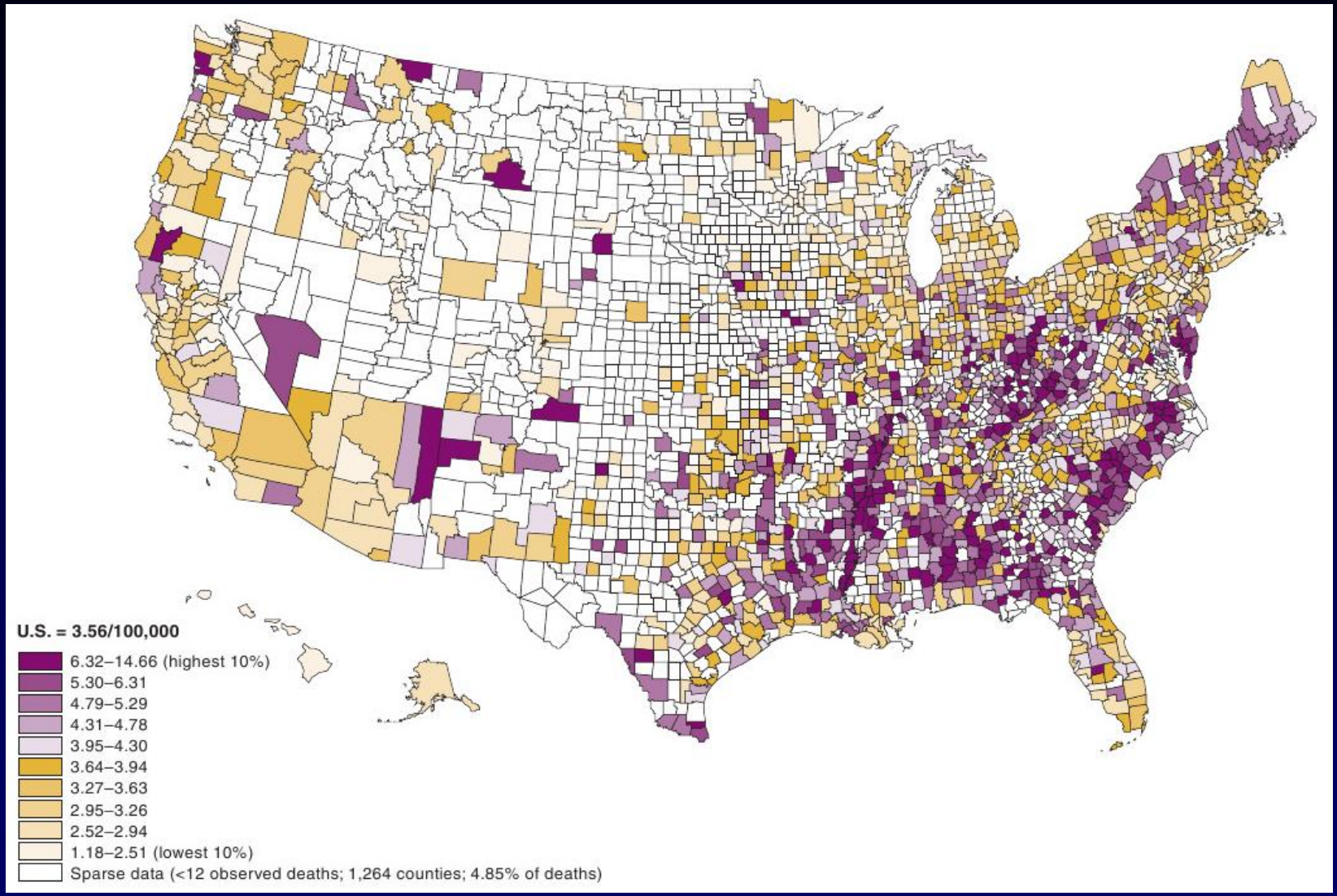


http://globocan.iarc.fr/Default.aspx



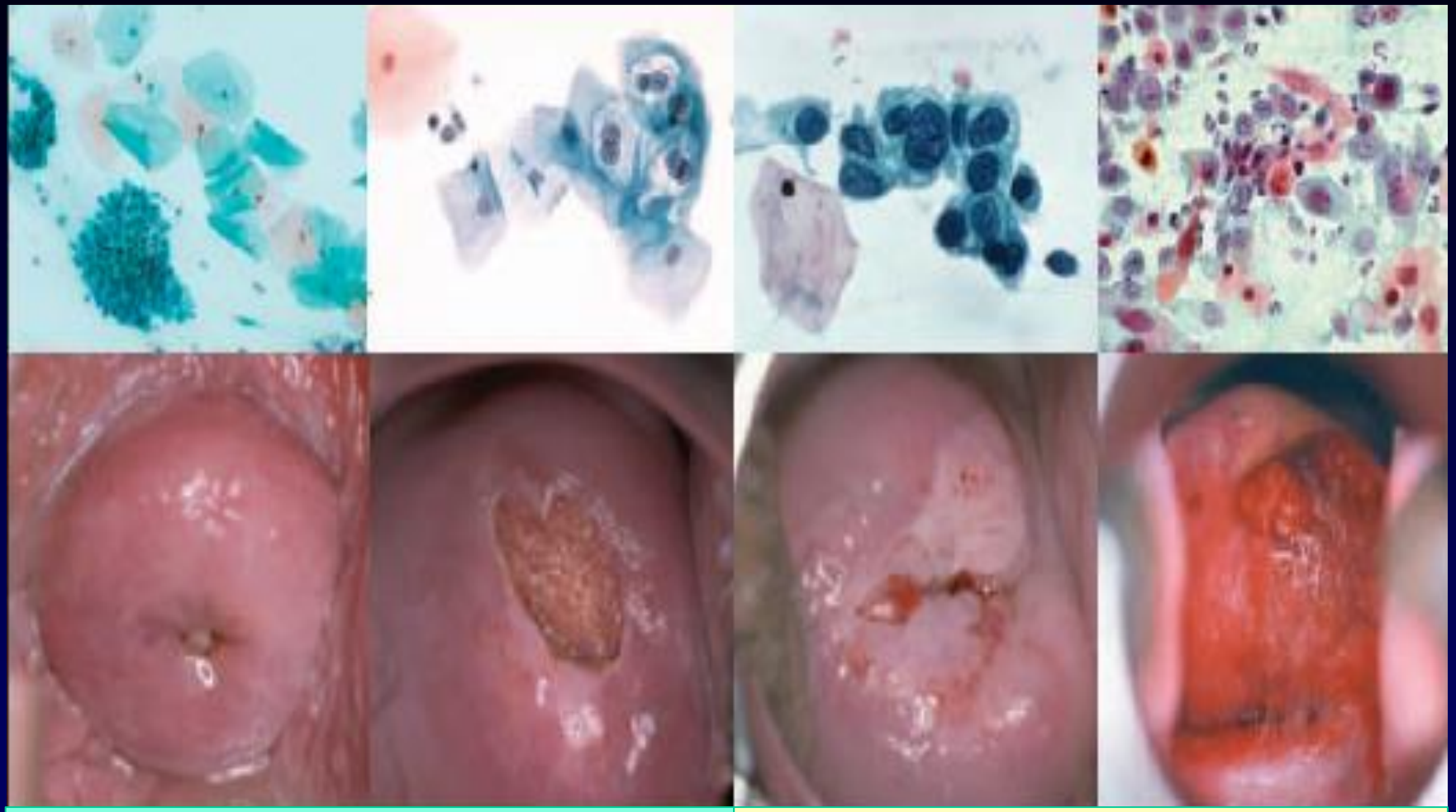
Percent of national populations living on less than $1.25 per day. UN estimates 2000-2007.

U.S. Cervical Cancer Mortality Map



Freeman HP, Wingrove BK. Excess Cervical Cancer Mortality: A Marker for Low Access to Health Care in Poor Communities. Rockville, MD: National Cancer Institute, Center to Reduce Cancer Health Disparities, May 2005. NIH Pub. No.

New Model of Cervical Carcinogenesis

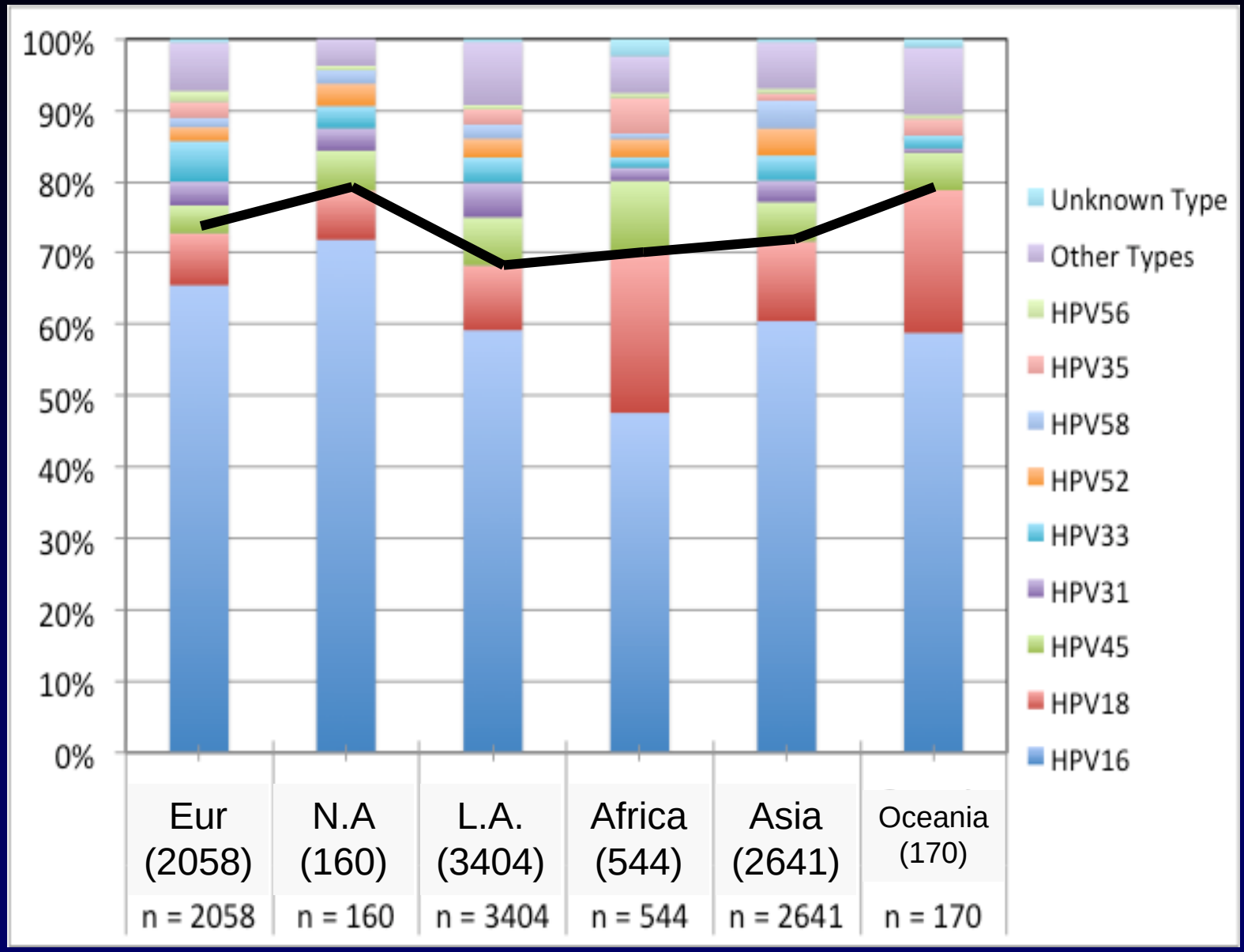


Transient infection | Persistent HPV

Normal cervix → (INFECTION / CLEARANCE) → HPV-infected cervix → (PROGRESSION / REGRESSION ?) → Precancer → (INVASION) → Cancer

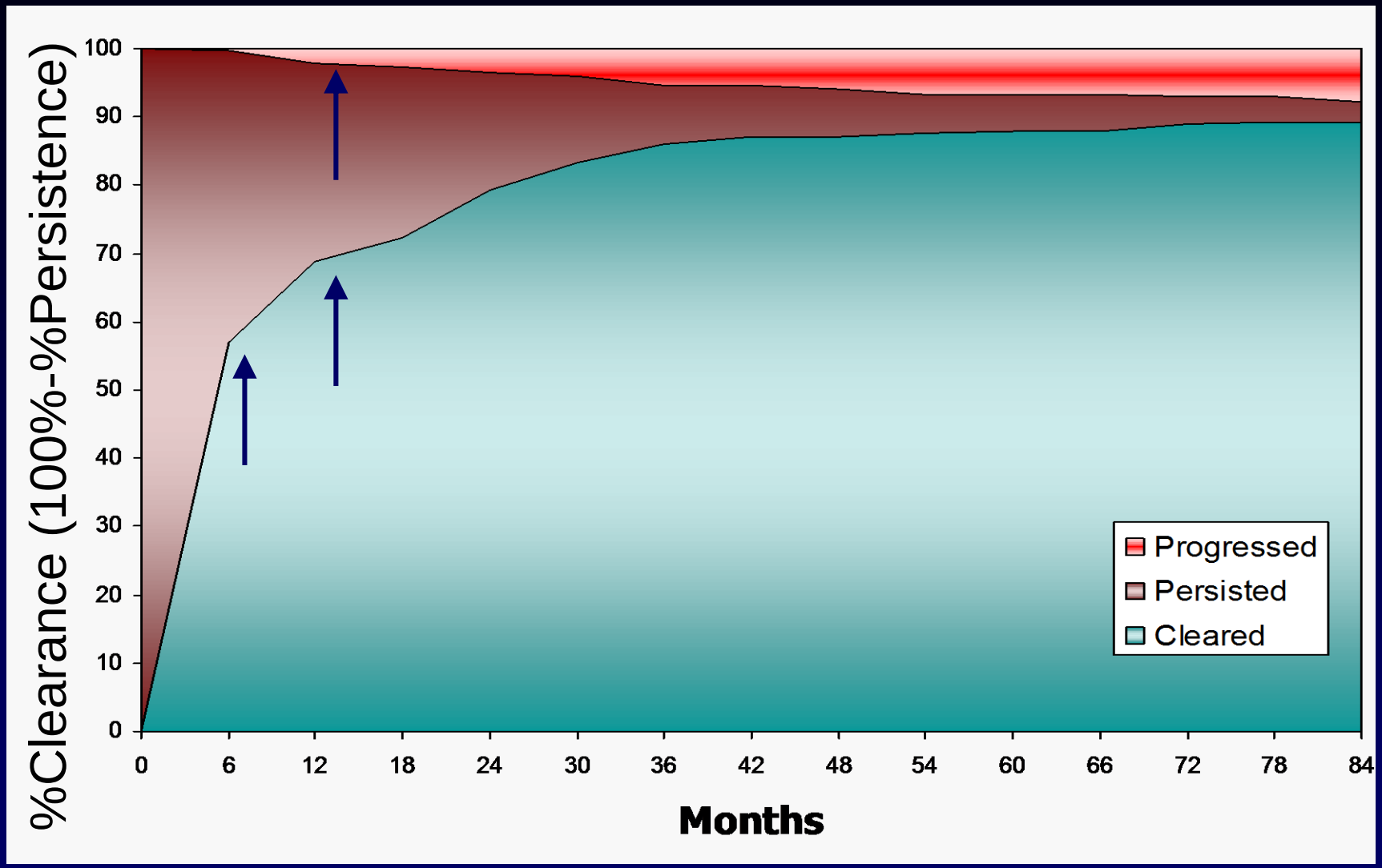
Schiffman et al., Lancet, 2007

Global Variation of HPV Genotypes in CxCa



de Sanjose *et al*., Lancet Oncol, 2010

Natural History Profile of Prevalent HPV

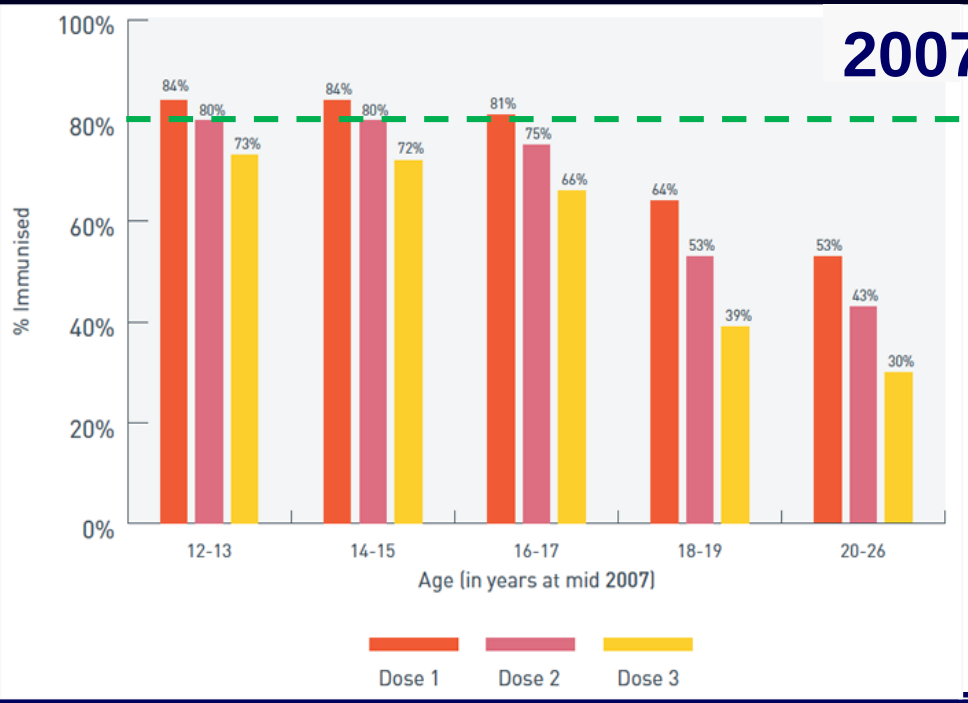


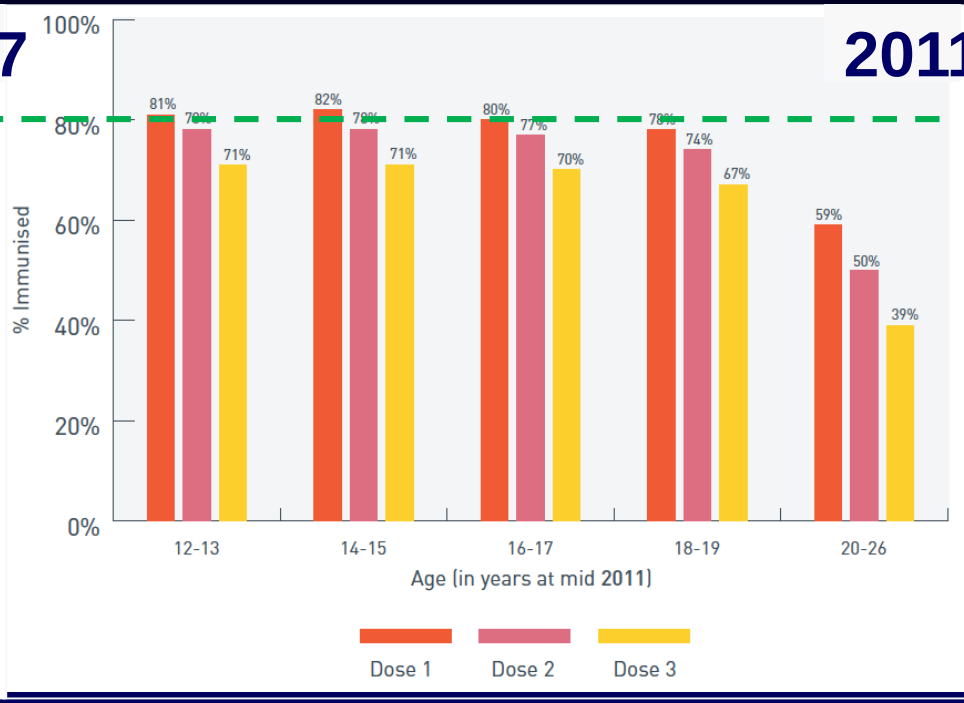
Schiffman *et al*., Lancet, 200

Risk Factors for Cervical Cancer

Risk Factor	Association	Absolute Risk
Having a cervix (SCJ)	**Nearly Infinite**	**Low**
Persistent HPV	**Infinite**	**High**
Lack of Preventive Services	**Infinite**	**Low**
Having Sex/Exposure to HPV	Infinite	Low
HPV16 Detection	500	High
HR-HPV (pooled) Detection	100	Medium
Abnormal Pap	25-50	Medium
AIDS	10-20	Medium
HIV	5-10	Medium
Parity (vs. none)	2-4	Low
Oral Contraceptive Use (vs. none)	2-4	Low
Smoking	2-5	Low
Immunogenetics (e.g., HLA)	2-5	Low

Australian Vaccine Program: Coverage

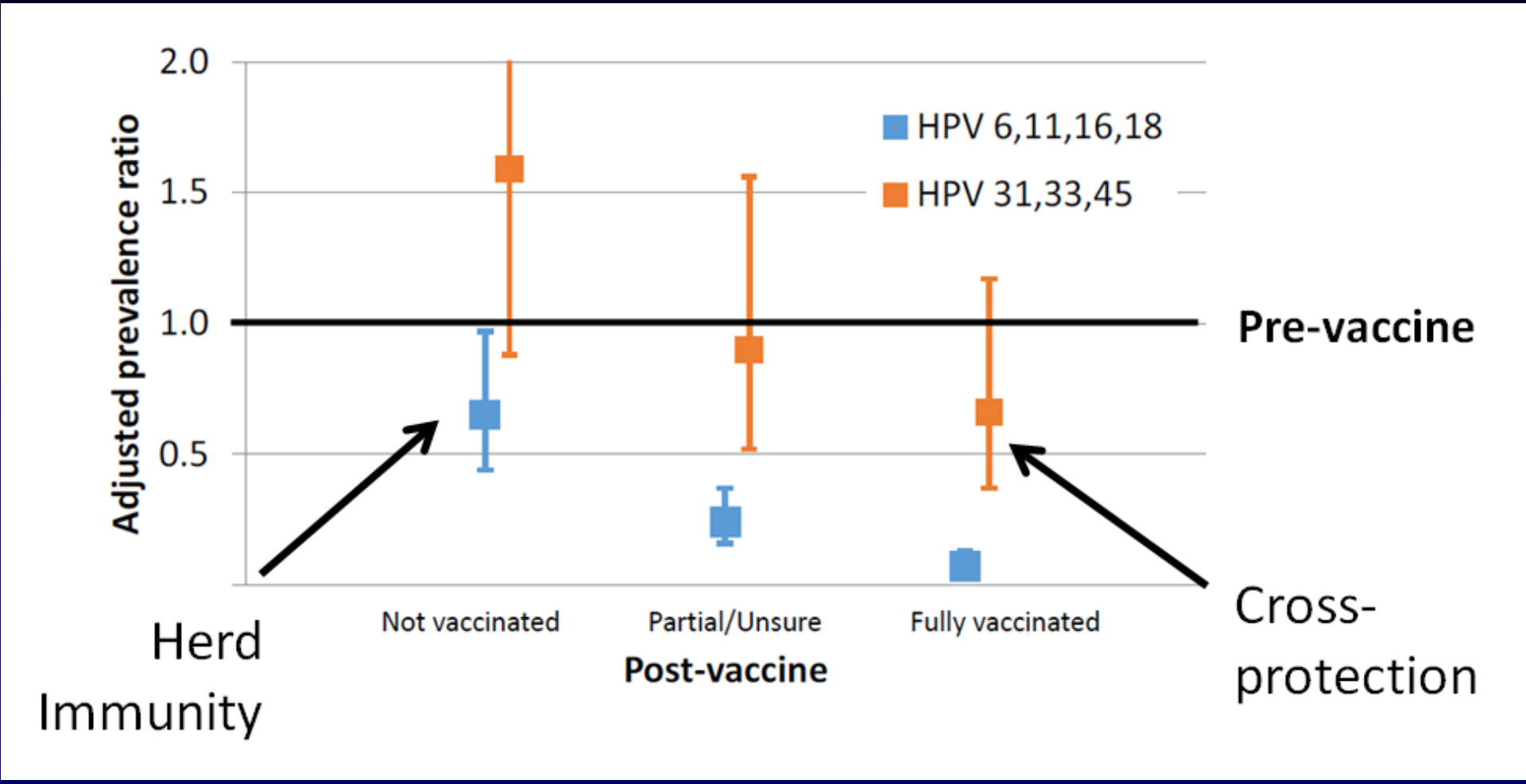




- Reminder: 2006 US FDA Approval
- Mostly Gardasil in Australia

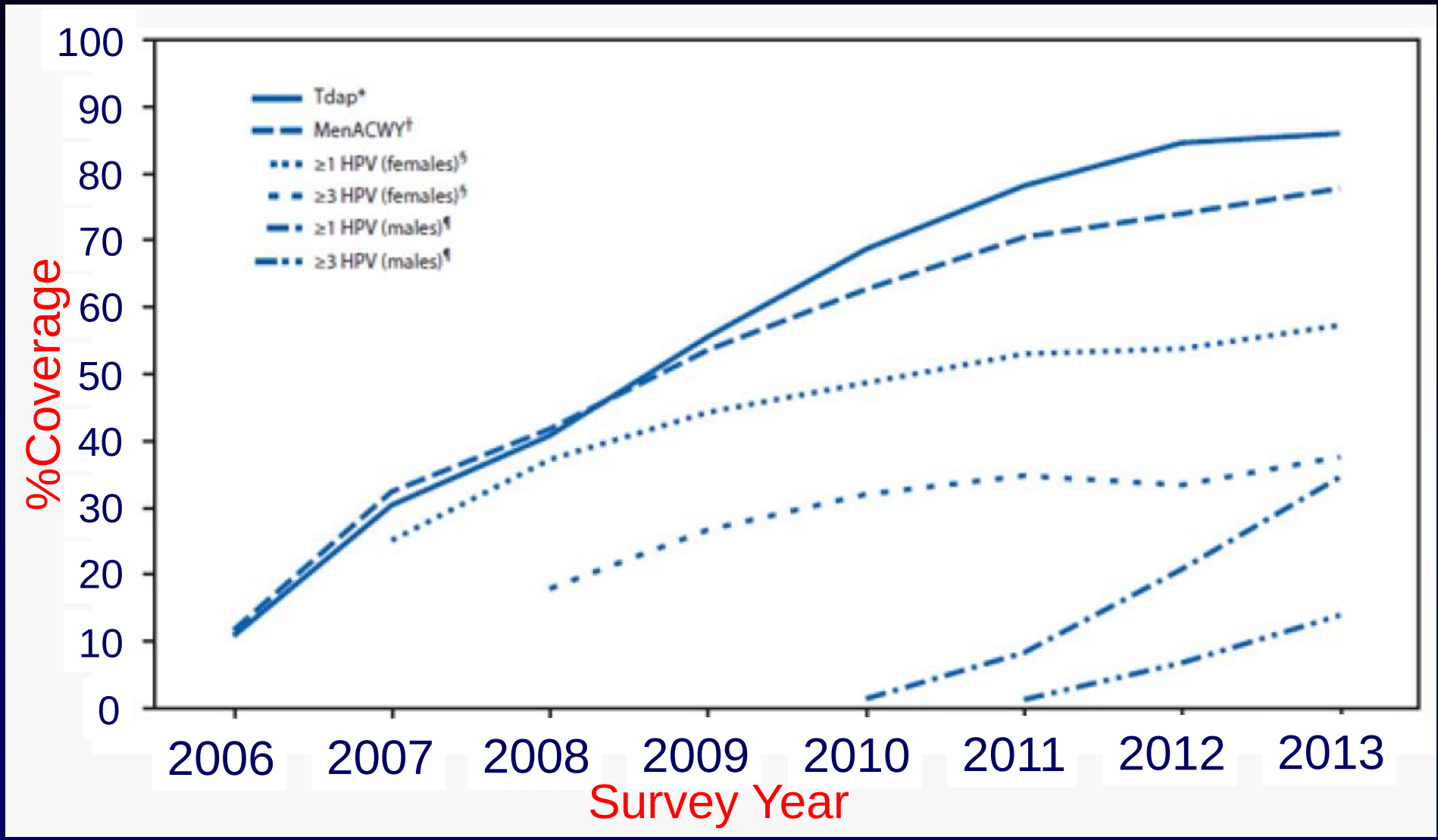
http://www.hpvregister.org.au/research/coverage-data

Australian Vaccine Program: Impact



Tabrizi *et al*., Lancet Infect Dis, 2014

U.S.

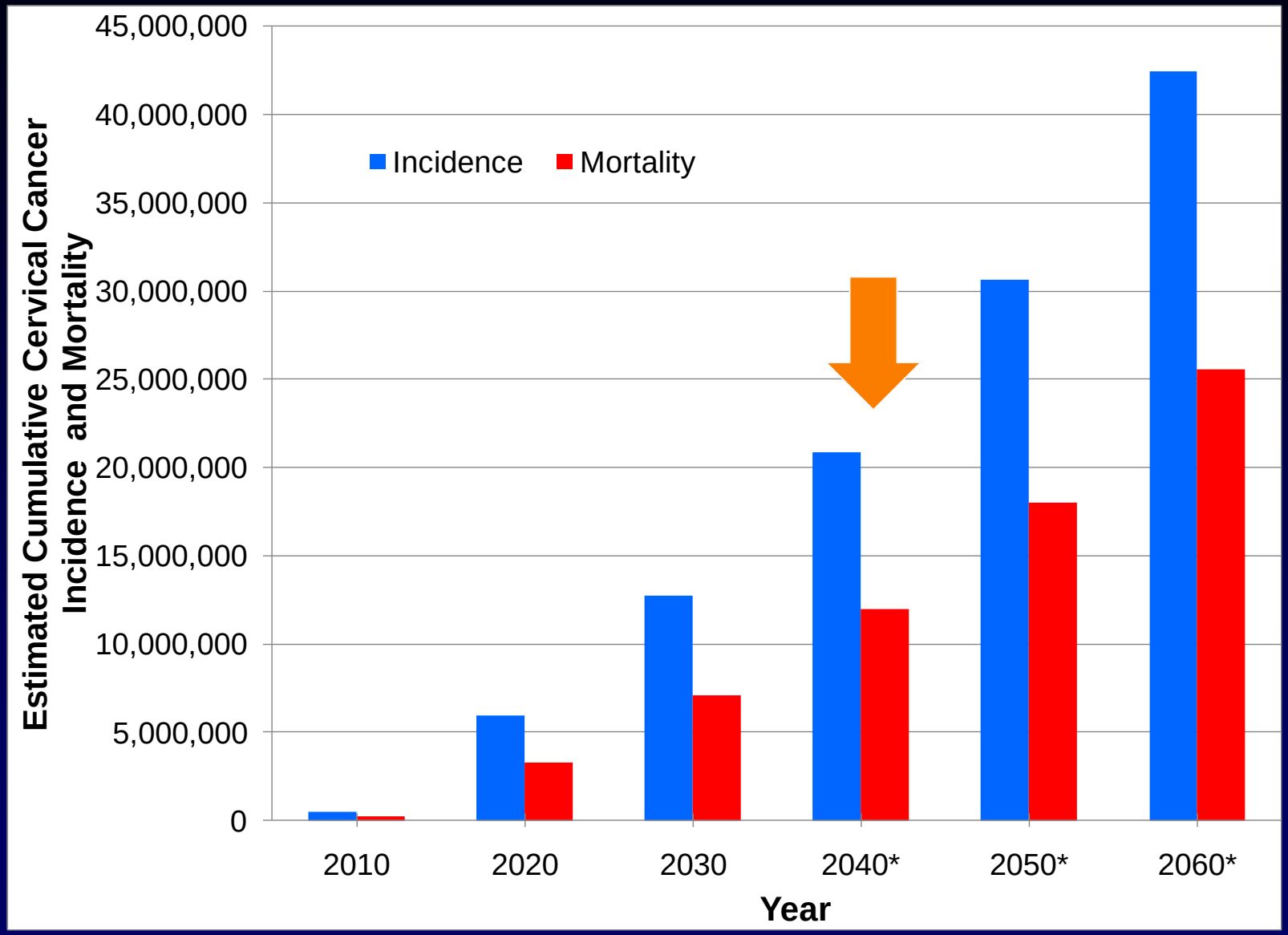


Elam-Evans *et al*., MMWR, 2014

Safety

As stated by the World Health Organization's Global Advisory Committee on Vaccine Safety on March 12, 2014, "We continue to closely monitor the safety of HPV vaccines and, based on a careful examination of the available evidence, continue to affirm that its benefit-risk profile remains favorable. The Committee is concerned, however, by the claims of harm that are being raised on the basis of anecdotal observations and reports in the absence of biological or epidemiological substantiation."

The Forecast Calls For Pain

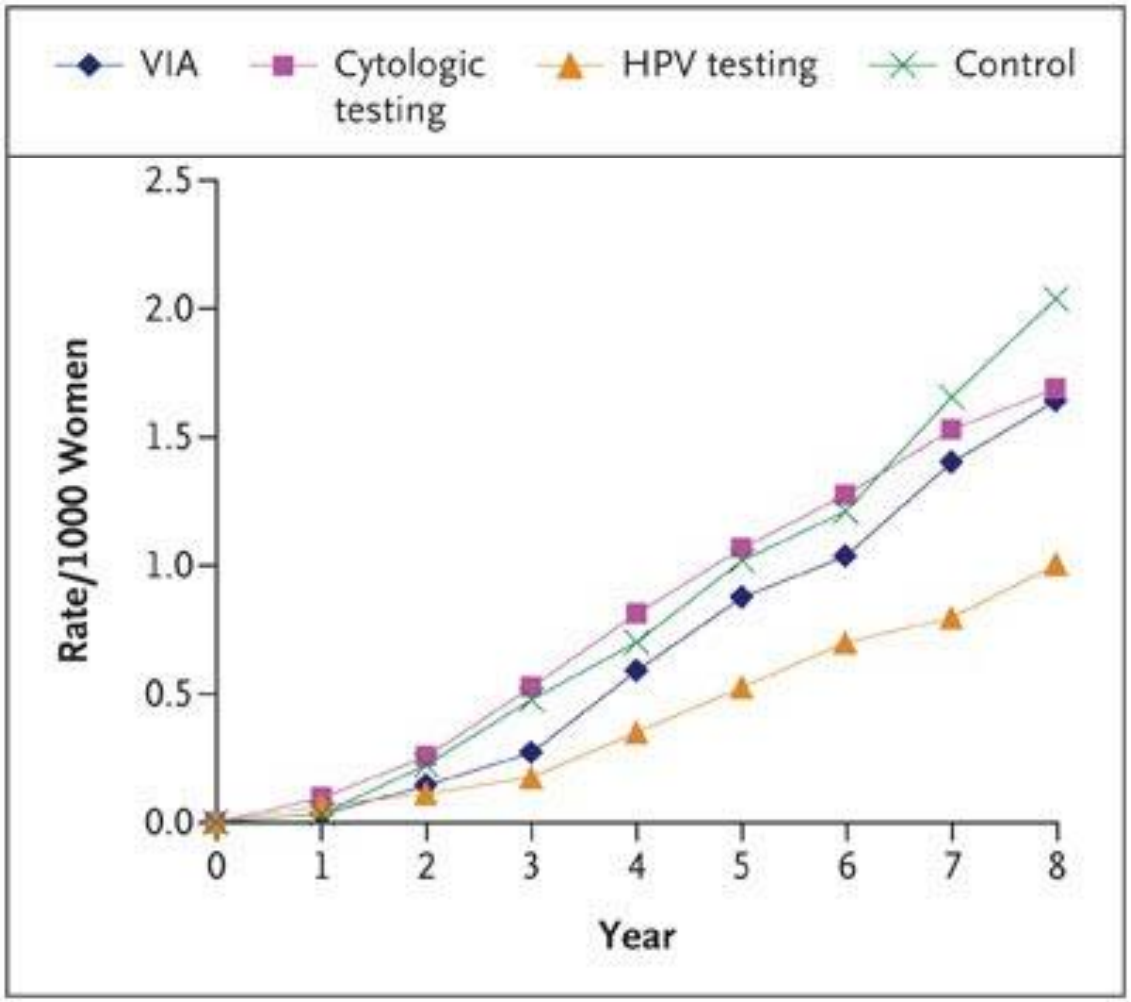


Castle and Gage, JNCI, 2011

The Menu of Options

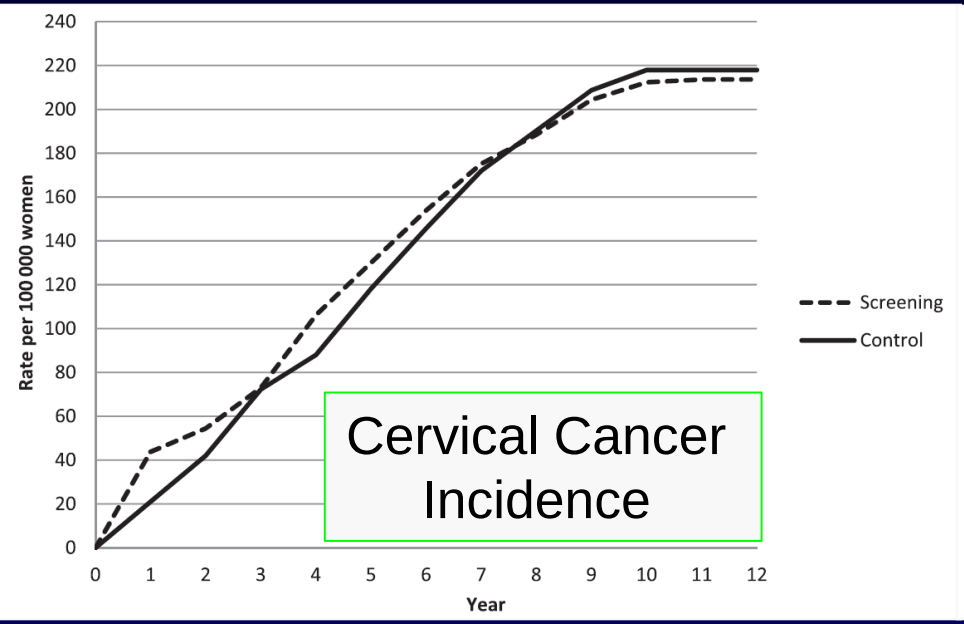
STEPS	OPTIONS	STRENGTHS	ISSUES/LIMITATIONS
Sampling	Clinician	Better Se and SP	Requires most personel, disposables, clinic time and space; transportation
	Self @ home	Logistically easier	Specimen transport & acceptability
	Self @ clinic	Help available (vs. @ home)	Clinic time and space; transportation
Testing	Pap	Well-accepted; considered standard of care	Difficult to establish and maintain; facility; chemicals
	VIA	Lowest cost; well suited to screen&treat strategy	Detects on the most large and obvious lesions; reliability?
	HPV DNA	Best Se; proven with self-collection	More expensive than VIA; laboratory needed; disposables
	Biomarkers (E6; p16)	May provide a good tradeoff of Se and Sp; Triage	Large-scale validation needed; more specific, less long-term impact
Management	Colposcopy	Well-accepted; diagnostic confirmation	Requires trained personnel and equipment: colposcopy misses small precancerous lesions
	Triage to Colposcopy	Reduces colposcopy; more specific	Requires a more Sp test that still has reasonably high Se; losses to follow-up
	Treatment	Limits losses to follow-up	Over-treatment
	Triage to Treatment	Reduces over-treatment	Reduces over-treatment; losses to follow-up in triage-negative women
Treatment	Excision	Most efficacious (90-95%)	Requires trained personnel; Excessive bleeding
	Cryotherapy	Can be implemented by any health worker	Selected population; risk of HIV infection?; acceptability; CO_2?

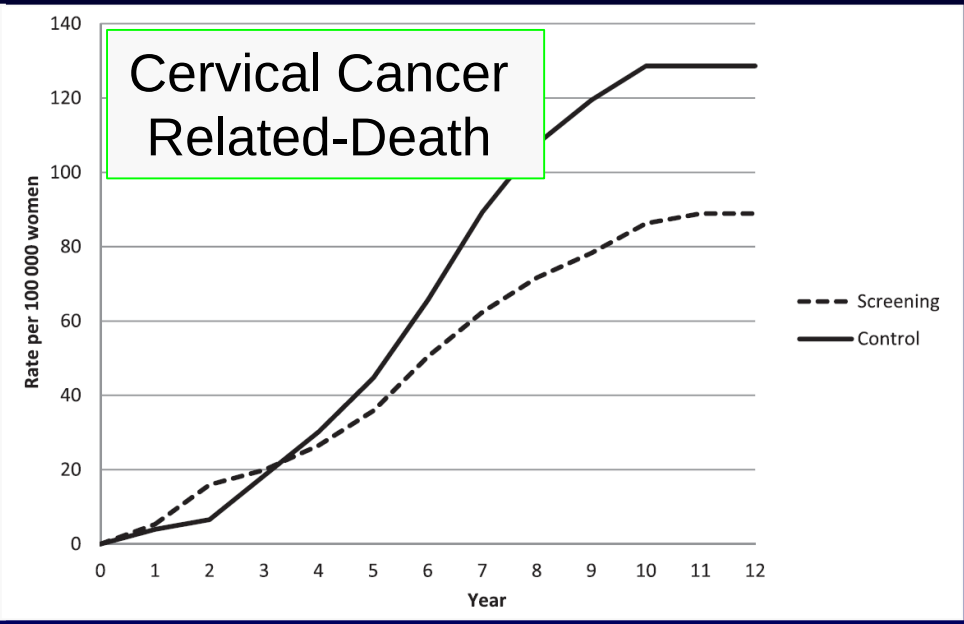
HPV Testing Reduces the Risk of Cervical Cancer Related Death (India)



Sankaranarayanan *et al*., NEJM, 2009

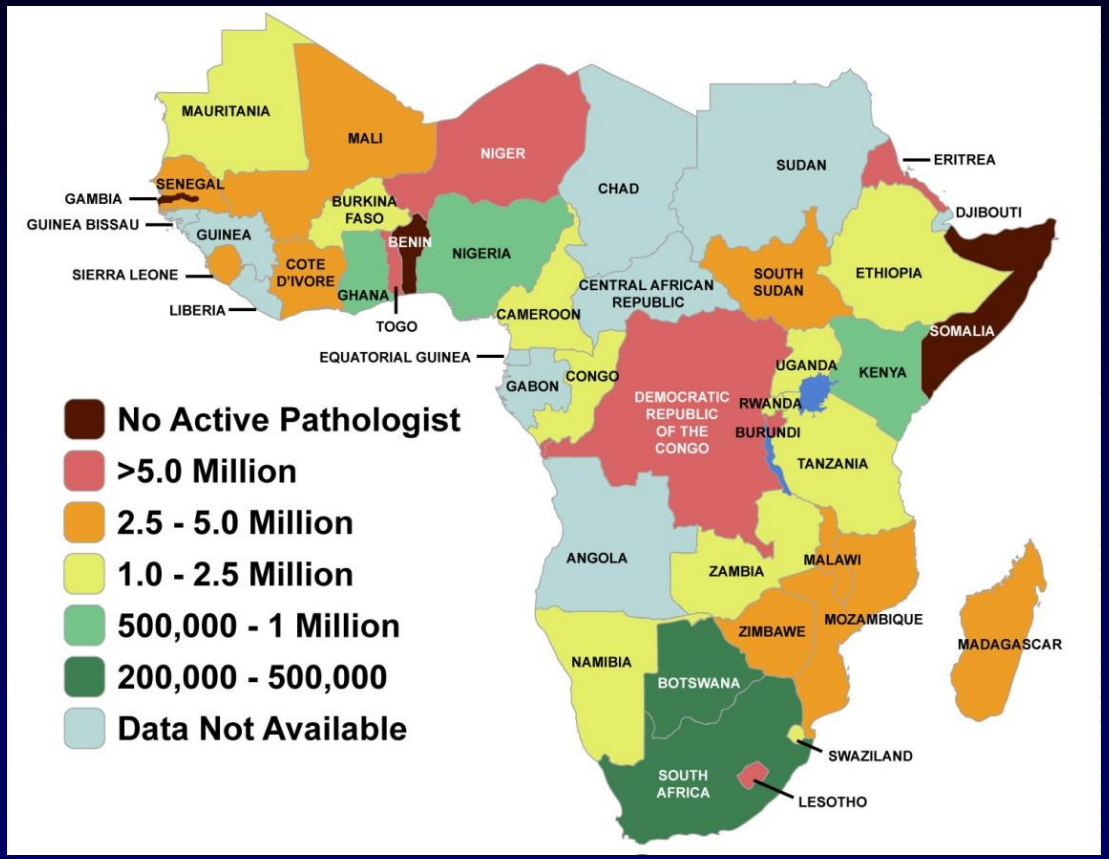
Four Rounds of VIA: Success or Failure?





Shastri *et al*., JNCI, 2014

Availability of Pathologists



Number of people per pathologist:

- UK: 15,108*
- U.S.: 19,232**

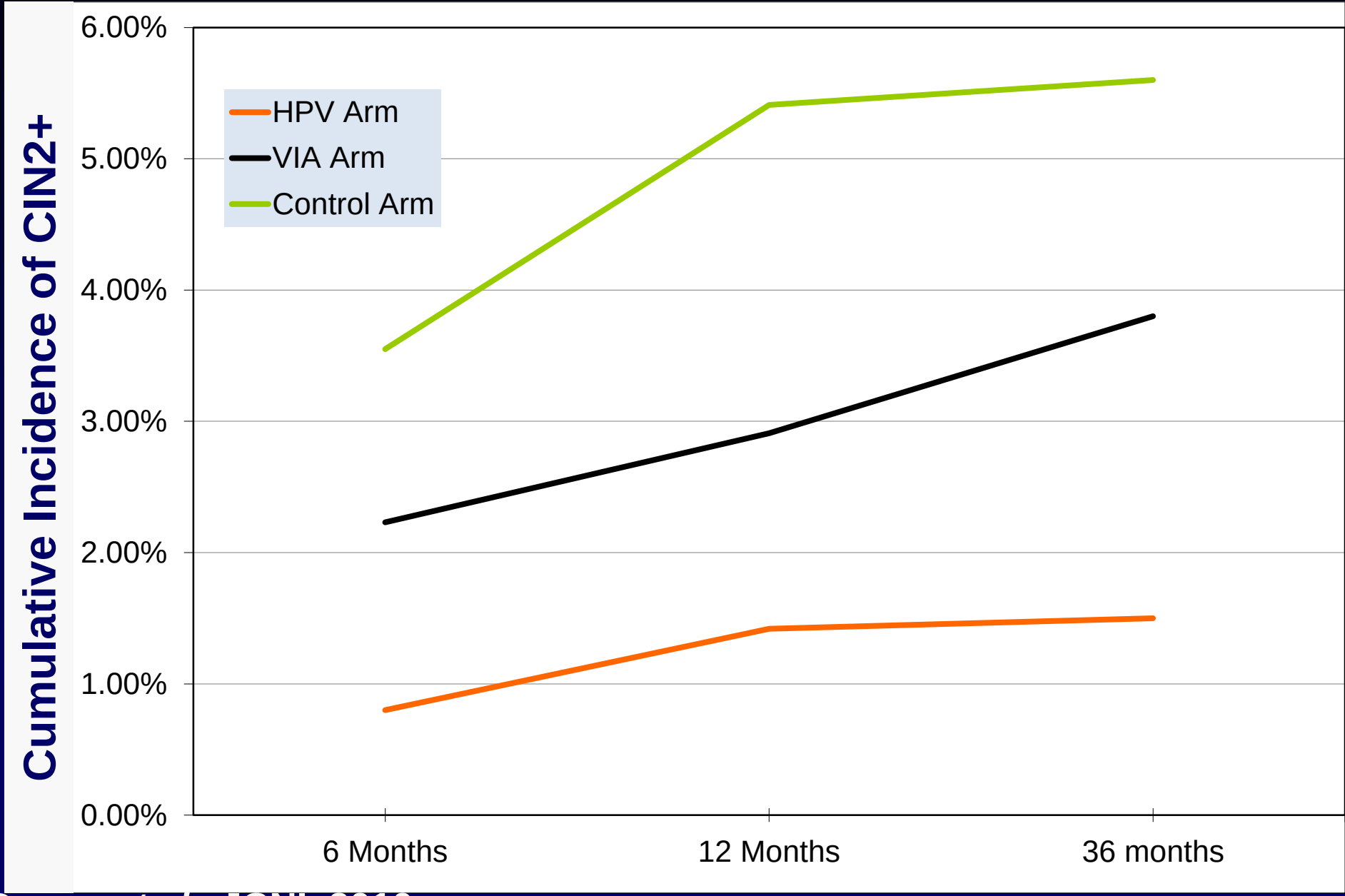
*Royal college of Pathologists, 2012

**Anatomic and Clinical Pathologists, AAMC, 2007

Adesina *et al*., Lancet Oncol, 2013

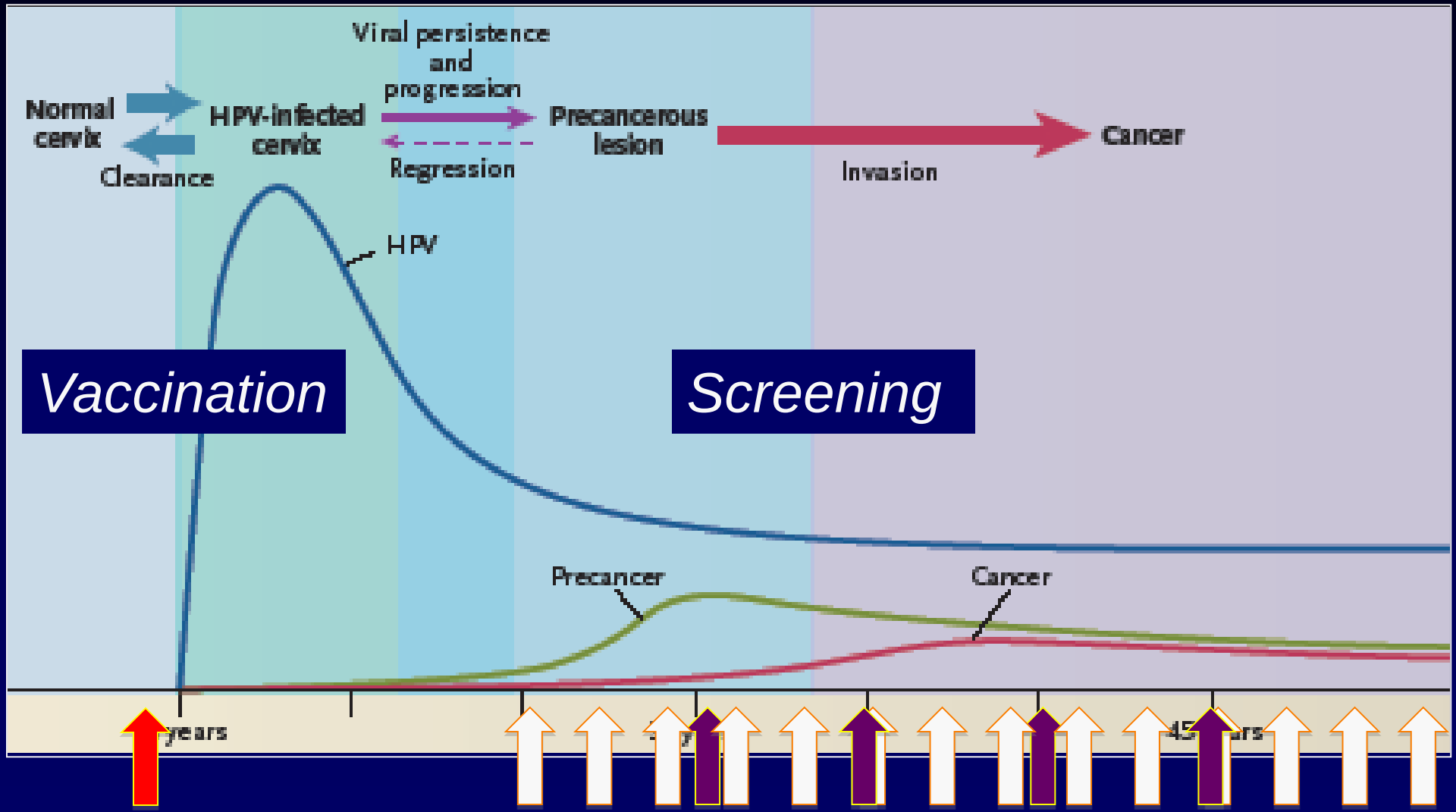
Adesina A et al., Lancet Oncol 2013 14(4):e152

Screen and Treat in South Africa



Denny *et al*., JCNI, 2010

The Promise of Cervical Cancer Prevention



Schiffman & Castle, NEJM, 2005

Reality Check

- **HPV Vaccination:** 300 million girls aged 10-14 y. need vaccination now; another 30 million girls aged 5-9 years will become eligible for HPV vaccination in the next 5 years.
- **Screening:** 500 million need screening, 200 million have been poorly screened; another 200 million aged 25-29 y. will become of screening age.
- **Cancer Management:** 550,000 women will be diagnosed with cervical cancer annually and need cancer care or palliation, 90% of which live in LMICs. By 2020, another 2 million women living in LMICs will be diagnosed with cervical cancer

Executive summary (1/2)

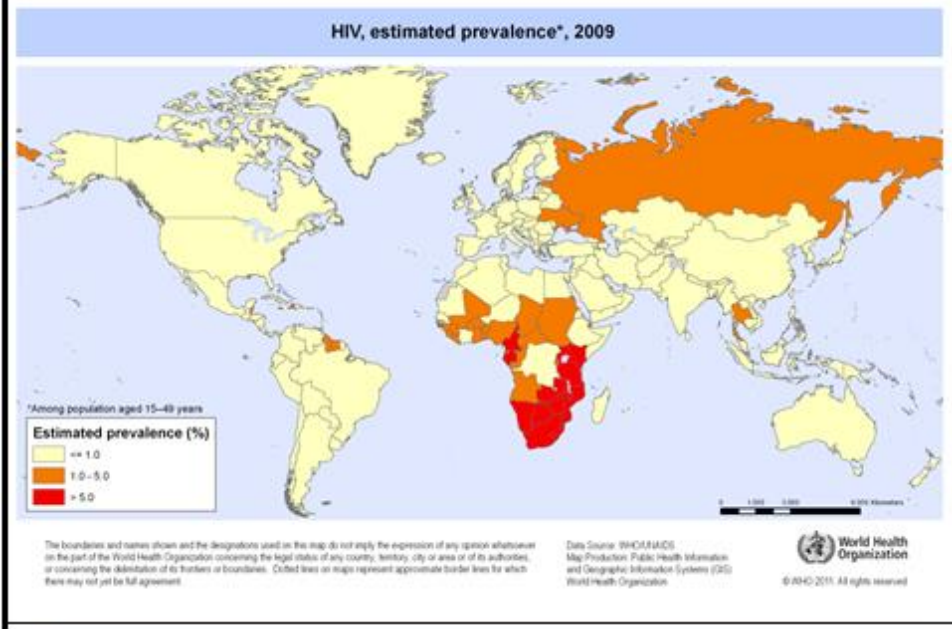
The global burden of cervical cancer

- Prevention of CaCx is one component of a comprehensive approach to women's health, especially **in the developing world, where a woman is at least four times as likely to die from CaCx as in the US and this mortality gap is projected to increase**
- **CaCx spending is low relative to other leading causes of death for women despite the cost-effectiveness of CaCx prevention**; global spending on CaCx was just 2 USD per DALY compared to 91 USD per DALY for maternal conditions in 2010, even though CaCx prevention costs between $15-$50 per DALY while maternal care costs between $77-$255 per DALY

The role of secondary prevention

- **Addressing CaCx mortality requires inter acros life**, including primary prevention through vaccination, secondary prevention with screening & tre &T) and tertia tion for women with invasive cervical cancer
- While the HPV Vx can reduce mortal g-run, **there is a sig in women that will not receive the Vx and are at risk for CaCx**; further, roll-out ma nd S&T is the only opti en who will never be vaccinated
- As a result, **scaling S&T could sav 2 million lives in low- and income countries in the next 40 years**

CaCx spending is low relative to other leading causes of death for women despite the cost-effectiveness of CaCx prevention; global spending on CaCx was just 2 USD per DALY compared to 91 USD per DALY for maternal conditions in 2010, even though CaCx prevention costs between $15-$50 per DALY while maternal care costs between $77-$255 per DALY


HIV, estimated prevalence*, 2009
*Among population aged 15–49 years
Estimated prevalence (%)
<= 1.0
1.0–5.0
> 5.0
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.
Data Source: WHO/UNAIDS
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization
World Health Organization
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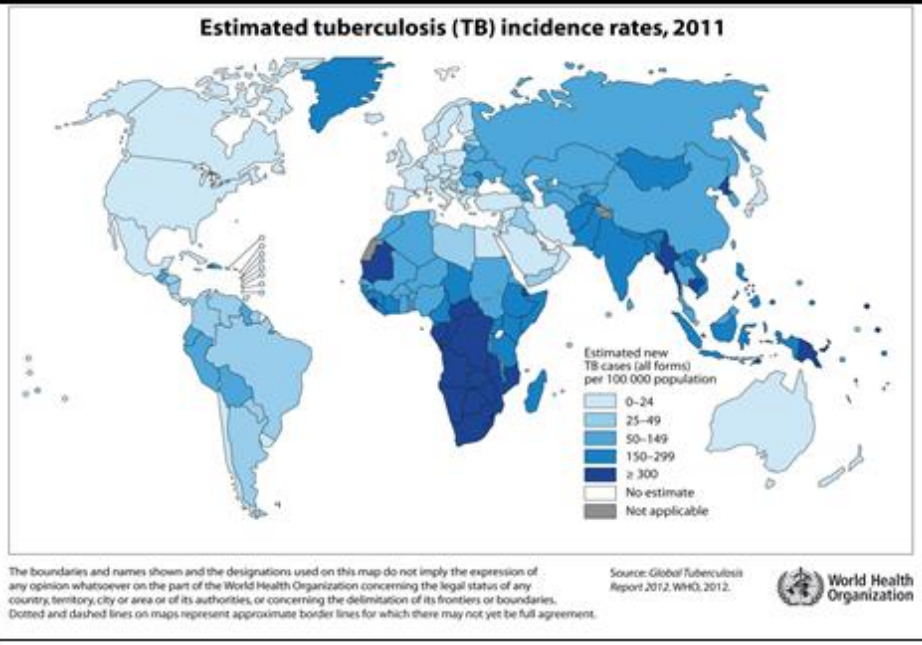
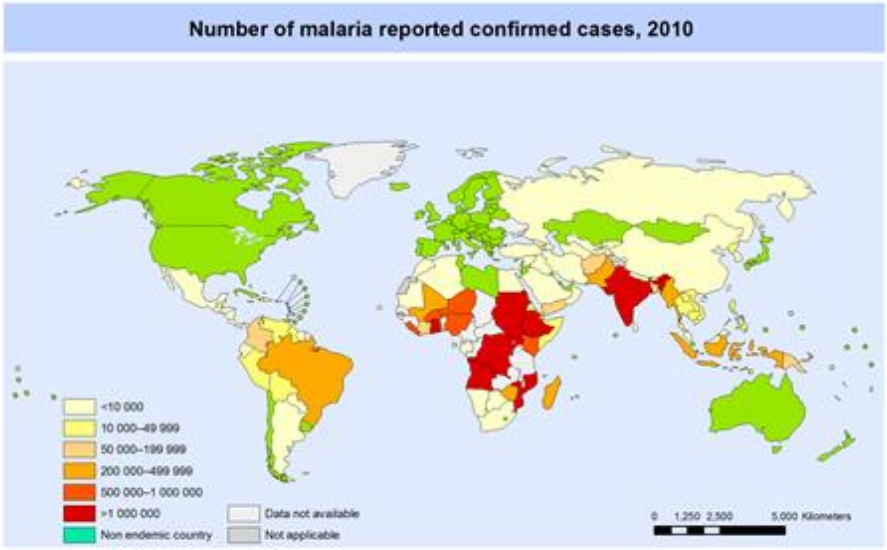

Estimated tuberculosis (TB) incidence rates, 2011
Estimated new TB cases (all forms) per 100 000 population
0–24
25–49
50–149
150–299
≥ 300
No estimate
Not applicable
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.
Source: Global Tuberculosis Report 2012, WHO, 2012.
World Health Organization


Number of malaria reported confirmed cases, 2010
<10 000
10 000–49 999
50 000–199 999
200 000–499 999
500 000–1 000 000
>1 000 000
Non endemic country
Data not available
Not applicable
0 1,250 2,500 5,000 Kilometers
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.
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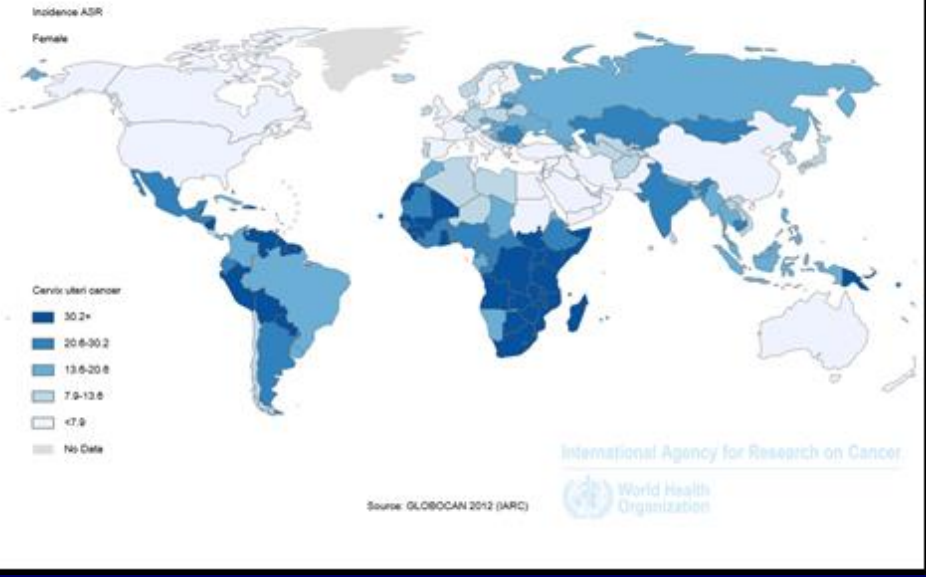
Incidence ASR
Female
Cervix uteri cancer
30.2+
20.6-30.2
13.6-20.6
7.9-13.6
<7.9
No Data
Source: GLOBOCAN 2012 (IARC)
International Agency for Research on Cancer
World Health Organization

Final Comments

1. Prophylactic HPV Vaccination will likely be the ultimate cervical cancer prevention strategy. But there are 2-3 generations of at risk (HPV+) women who will not benefit greatly from and will not be targeted for HPV vaccination. Screening will be needed for the foreseeable future.
2. Screening can reduce the incidence of cervical cancer within a few years and mortality in a few more after that. Investment in screening builds infrastructure for other care.
3. Let's not forget about those who already have cancer. We can help them live and die with dignity and a high quality of life.
4. None of this will happen without significant increases in commitments and investment.