

# Primary prevention of cervical cancer through HPV vaccination – what is the future?

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# Declaration of interests

- Received honoraria in the past for appearing on speaker forums for GlaxoSmithKline, Merck (HPV Vaccination) and Roche (HPV DNA Testing)
- Research grants from all three companies in the past
- No current conflicts of interest

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# Introduction\*

- Childhood vaccination programmes have had a dramatic impact on child morbidity and mortality worldwide
- 1974 WHO established Expanded Program on Immunization (EPI) which included:
  - Diphtheria-Tetanus-Pertussis (DTP)
  - Measles Containing Vaccine (MCV)
  - Polio vaccine (Pol3)
  - BCG
- Later other vaccines added:
  - Haemophilus influenzae type b (Hib 3)
  - Yellow fever (YF)
  - Hepatitis B vaccine (HepB3)
- New vaccines:
  - Rotavirus
  - Pneumococcal conjugate vaccine

\*[www.who.int](http://www.who.int)

# Introduction

- Many health interventions that may stimulate economic growth
- One is the 'demographic dividend'\*
  - The demographic dividend is the **accelerated economic growth** that results from shifts in the population age structure such that the proportion of the *working age population* (defined as 15 – 64 years) is larger than the *non working population* (i.e.  $\leq 14$  and  $\geq 65$ )
  - The greatest demographic opportunity for a country occurs when the working age population has **GOOD HEALTH**, quality education, decent employment and a lower proportion of young dependents
  - Leads to larger investment per child, more freedom for women to enter workforce and more savings for old age
  - National economic payoff may be substantial

\*[www.unfpa.org/demographicdividend](http://www.unfpa.org/demographicdividend)

# Introduction

- Achieving the demographic dividend requires multiple investments that build on people's capabilities to reach their full potential
- Derailing factors, particularly for millions of girls include (among others):
  - Being pushed from school or denied education
  - Subjected to early child marriage
  - Early and unplanned pregnancy
  - POOR ACCESS TO HEALTH CARE (including vaccination)
  - Failure to provide services aimed at prevention of disease and premature death (sexual and reproductive health needs, cervical cancer as two examples among many)
  - Gender-based violence

# Demographic Dividend – the role of Vaccination

- Value of vaccination lies in preventing disease
  - Estimated to save 3 million lives per year and 750 000 from disability
  - Preventative medicine
  - High acceptability in developing countries if made accessible
  - Reduction in cost of health care due to prevention of disease
  - Increased lifetime productivity due to better health
  - Economic improvements due to increased health of working age population and ability to care for the young and elderly

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# Vaccination

- Global immunisation effort emerged following the success of the Smallpox Eradication Program – an unprecedented public health achievement
- By 1990s the global immunization program reached 75% of target population, except in India and SSA where it was less than 65%
- During 1990s the Polio Eradication program reached 90% world's children
- 2000 GAVI Alliance was formed and raised billions of dollars for introduction of new and underutilized vaccines
- In first 10 years GAVI prevented 5 million future deaths
- And an additional 288 million children were immunized in period 2000 - 2010

# HPV Vaccination

- GAVI agreed in principle to support HPV vaccination in 2008 but only had resources for funding in 2011
- Funding was conditional on:
  - Successful negotiations for an affordable vaccine
  - Development of plans to reach pre-adolescent girls
  - Support pilot programs prior to national scale-up
- Negotiated price of \$4.50 per dose with commercial companies
- ***So why is HPV vaccination relevant in developing countries??***

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# Cancer in 2012– global perspective\*

- 14.1 million new incident cases of cancer
- 8.2 million deaths
- 32.6 million living with cancer (within 5 years of diagnosis)
- Of these majority occurred in LMIC
  - 8 million new cancers
  - 5.3 million deaths
  - 15.6 million of the 5 year prevalent cases

\*[www.iarc.fr/globocan](http://www.iarc.fr/globocan)

# Overview of HPV-Associated Cancer - Globocan 2012\*

- Cervical cancer fourth most common cancer in women worldwide, second to breast, lung and colo-rectal cancer
- And 4<sup>th</sup> most common cancer cause of death (275 000) after breast, lung and colorectal
- Cause of 7.8 million years of life lost (YLL), third after breast and lung cancer
- Strong association between cervical cancer incidence and level of development
  - 88% of deaths occur in less developed regions
  - Incidence and mortality at least 4 x higher in poor countries (mostly in sub-Saharan Africa)

\*Forman et al. 2012

# New cases of cancer in 2008 attributable to HPV by anatomic site globally\*

HPV Cancer Site	New cases 2008	Attributable to HPV	Attributable Fraction
Cervix	530 000	530 000	100 %
Vulva	27 000	12 000	43.0 %
Anus	27 000	24 000	88.0 %
Penis	22 000	11 000	50.0 %
Vagina	13 000	9 000	70.0 %
Oropharynx	85 000	22 000	25.6 %
Total	700 000	610 000	86.3 %

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\*Forman et al. 2012

# Key issues on HPV natural history

- Sexually transmitted through skin to skin contact
- Highly transmittable
- Prevalence of HPV is highest among women when initiating sexual activity and decreases with increasing age
- Usually asymptomatic, majority of infections transient and are cleared within 1 – 2 years
- Persistent infection with high risk types, notably HPV 16 and 18 is associated with development of cervical cancer precursors and cervical cancer
- HPV 16/18 associated with 70% of cancers and 50% of HSIL
- HPV 6/11 associated with 90% of genital warts

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# HPV Vaccines

## MSD

### Types 6, 11, 16, 18

- VLP L1 of four HPV types
- Yeast expressed
- Adjuvant aluminum
- First licensed in 2006 to over 100 countries
- Prequalified by WHO 2009
- Age 9 – 26
- **2 (3) doses**
- **Intramuscular injection**
- **Cold chain required**
- Safe, immunogenic and effective

## GSK

### Types 16, 18

- VLP L1 of two HPV types
- Baculovirus expressed in insect cells
- ASO4 adjuvant - Aluminum salts and monophosphoryl lipid A
- First licensed in 2007 in over 90 Countries
- Prequalified 2009
- Age 10 – 26
- **2 (3) doses**
- **Intramuscular injection**
- **Cold chain required**
- Safe, immunogenic and effective

# WHO recommendations on HPV Vaccination\*

- High coverage of target population of girls aged 9 – 14
- Females < 15 years at the time of first dose
  - 2 dose schedule recommended (0 and 6 months)
  - If interval between doses is shorter than 5 months, then a third dose should be given at least 6 months after the first dose
- Females  $\geq$  15 years at the time of first dose
  - 3 dose schedule (0, 1 -2, 6 months) recommended
- If known to be immunosuppressed or HIV positive 3-dose schedule remains necessary
- No WHO recommendations as yet on the nonavalent vaccine, but has been licensed by FDA

\*[www.who.int/immunization/diseases/hpv/en](http://www.who.int/immunization/diseases/hpv/en)

# Rationale for HPV vaccination

- Large international controlled clinical trials have shown both HPV vaccines to be safe, well tolerated, highly efficacious against vaccine-type persistent HPV infection and precancerous lesions in women
- Some degree of cross-protection against three non-vaccine types (31, 33, 45) – the latter being associated with 10 – 15% cervical cancers worldwide
- Cross protection against 31, 33 and 45 greater in bivalent versus quadrivalent vaccine
- Mathematical models consistently predict that the overall burden of HPV – related disease in women will decrease substantially due to vaccination
- And that vaccination of girls against HPV is cost-effective

# Population level impact and herd effects of HPV vaccination\*

- Since 2007, 52 out of 195 countries worldwide have implemented HPV vaccination programmes
- Wide variation on impact depending on:
  - Vaccine used
  - Implementation strategies
  - School-based or non-school based programmes
  - Vaccine coverage
  - Target age group with or without 'catch up' and gender (USA and Australia now vaccinate boys as well as girls)

\*Drolet et al. Lancet Infect Dis 2015;15(5):565 - 580



# Population level impact: systematic review and meta-analysis\*

- 20 reports met inclusion criteria - studies in 9 HICs
- Main results:
  - Girls 13 – 19 years
    - Overall prevalence of HPV types 16 and 18 decreased by 64% in the post vaccine period (RR 0.36 [95% CI 0.25 – 0.53] compared to pre-vaccination period
    - Strong association with high coverage of targeted population
  - Overall prevalence of HPV types 31, 33, 45 decreased by 28%, but reductions not associated with coverage

\*Drolet et al. Lancet Infect Dis 2015;15(5):565 - 580

# Population level impact

- Girls aged 15 – 19 years vaccinated with quadrivalent vaccine:
  - Anogenital warts decreased by 31% in post-vaccination period
  - Strong association with high coverage
- Non-significant decreases in anogenital warts in women 20 – 39 years (11%)
- However in countries with high female vaccine coverage
  - Anogenital warts were significantly reduced (32%) in women aged 20 – 39 years
  - By 34% in boys aged 15 – 19 years (but only 5% in programmes where there was low coverage of women)
- A significant decrease in high-grade precursors was reported only in one study in girls aged 15 – 19 years

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# Caution in interpretation of results

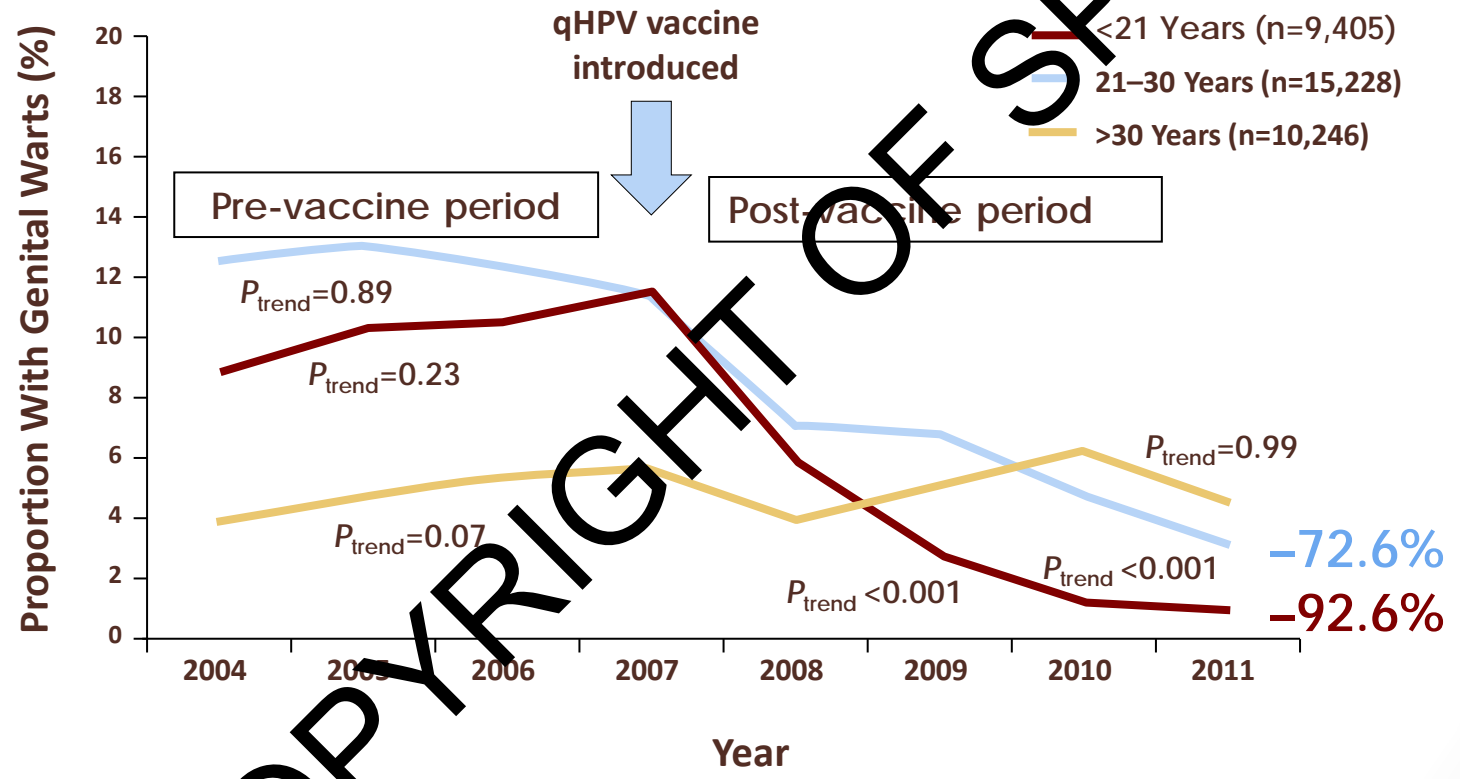
- Short – term population effects (4 years) and the cohort of girls vaccinated have not yet reached the ages with the highest incidence rates of HPV infection, anogenital warts and cervical cancer precursors
- Time horizon too short to examine waning efficacy of the vaccines, although RCTs have shown no waning of vaccine efficacy after 9.5 years
- No direct evidence of the effect of vaccination on HPV-related cancers currently available
- Results may be generalizable to HICs but should be extrapolated to LMICs with caution due to differences in:
  - Sexual behavior
  - HPV epidemiology
  - Co-factors for HPV Infection e.g. HIV prevalence although HPV vaccination has been shown to be safe and immunogenic in HIV-positive individuals

# Genital warts in Australian-born patients in the 5<sup>th</sup> year of qHPV vaccination programme\*

- Patients attending 8 sexual health service centers for the first time between 2004 and 2011 (N=85,770)
- Patients with new genital warts diagnosis (n=7,686) were stratified by age group at the time of presentation to the clinic
  - <21 years (all females eligible for free vaccine)
  - 21 through 30 years (some females eligible for free vaccine)
  - >30 years (none eligible)

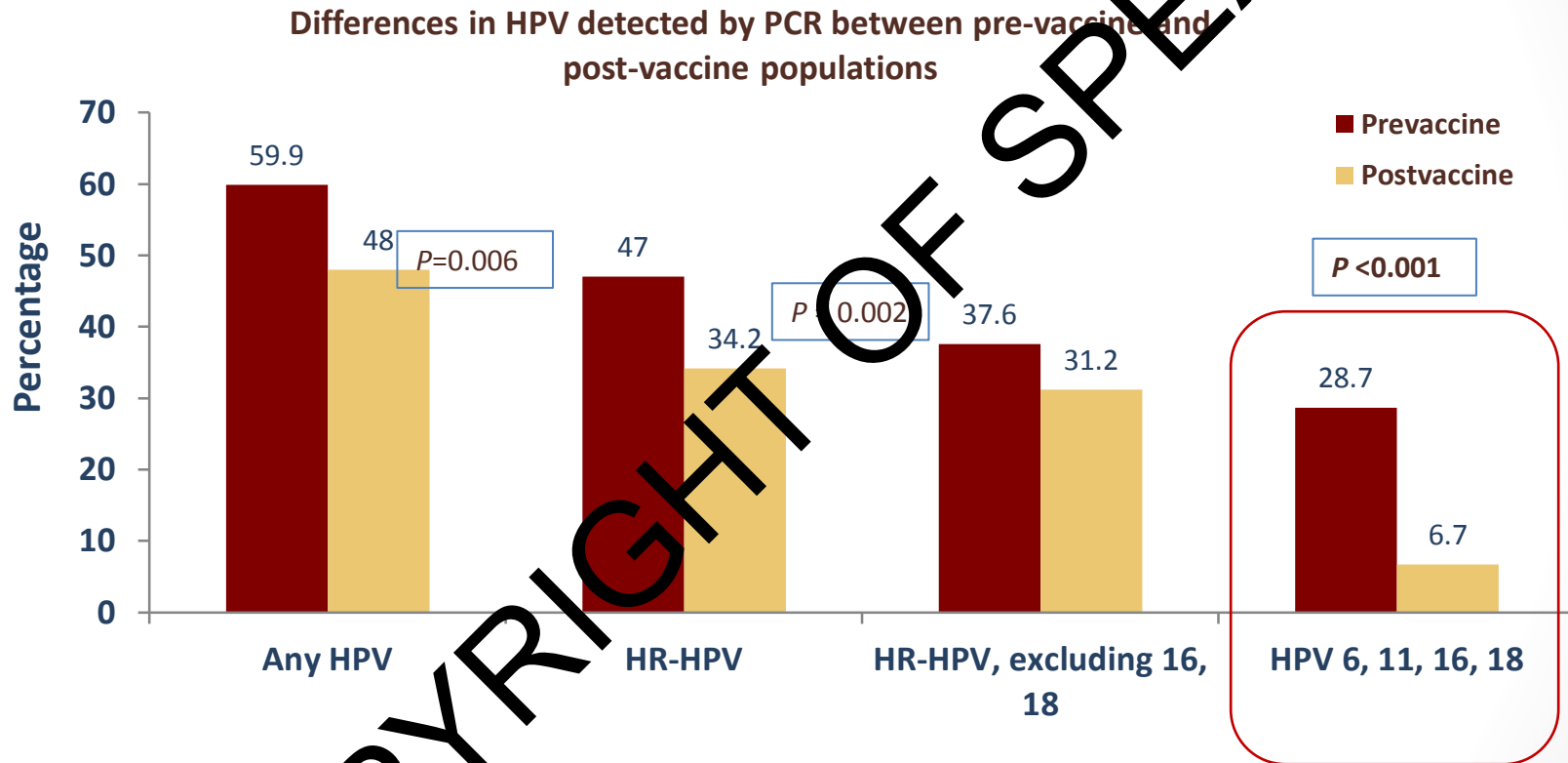
\*Ali H et al. *BMJ* 2013;346:f2032.

# Proportion of Australian-born females with GW by age group, 2004–2011\*



\* Ali H et al. *BMJ* 2013;346:f2032.

# HPV prevalence in Australian females following a National Vaccination Program\*



High risk genotypes included HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, or 68.

\*Tabrizi SN et al. *Infect Dis* 2012;206:1645

# Global estimates of HPV vaccination coverage by region and income level\*

- Bruni et al studied publicly funded coverage of HPV immunization programmes and potential impact on future cervical cancer and deaths
- June 2006 – Oct 2014, 64 countries nationally, 4 countries subnationally and 12 overseas territories had implemented HPV vaccination
- 180 million women targeted but only 1% were from LMICs
- 47 million received full course by 2015 and 59 million at least one dose – 20 countries introduced 2 dose regimen in 2014
- In more developed regions 33.6% of women received full course of vaccine, compared to only 2.7% in less developed regions
- Calculated that about 370 000 cases of cervical cancer and 157 000 deaths by age 75 averted in the 47 million vaccinated women
- Overall, despite accounting for only 14% of annual cervical cancer cases, HICs accounted for almost 70% of vaccinated women worldwide by end of 2014

\*Bruni L et al. Lancet Global Health 2016;4:e453 - 63

# Efficacy and immunogenicity of fewer than three doses

- Proof of principle study in the Costa Rica bivalent vaccine trial, which included women who were HPV negative at baseline and did not get all their doses, reported similar vaccine efficacy as one, two or three doses\*
- Immune responses were significantly higher than in natural infection
- Other studies have reported that the immunogenicity of two doses of both vaccines, particularly in girls aged 9 – 14 years, separated by 6 months, is non-inferior to that of 3 doses in women aged 15 – 26 in whom vaccine efficiency has been proven^

\*Safaeian M et al, Cancer Prev Res (Phila). 2013;6:1242 – 50; ^ Dobson SR et al JAMA 2013;309:1793 802



# Link between HIV and HPV

- 2–22 fold increased risk of cervical cancer among HIV-positive women vs the general population\*
- Meta-analysis of 20 studies: overall prevalence of HPV infection in HIV-positive women:<sup>^</sup>
  - Normal cytology: 36.3%; ASCUS/LSIL: 69.4%; HSIL: 84.1%
- HPV 18 and 45 more common in HIV-positive populations than HIV negative<sup>#,&</sup>
- The safety and immunogenicity of HPV vaccines has been found to be adequate in different HIV-positive populations (children, women, adolescents, adults)
- However, efficacy has not yet been evaluated\*

ASCUS, atypical squamous cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesions; LSIL, low-grade squamous intraepithelial lesions

\* Denny LA, et al. Vaccine 2012; **3(suppl)**: F168–74; <sup>^</sup>Clifford GM, et al. AIDS 2006; **20**: 2337–44; <sup>#,&</sup> Denny LA, et al. Int J Cancer 2014; **134**: 1389–98; 4. Van Aardt MC, et al. Int J Gynecol Cancer 2015; **25**: 919–925

# Vaccine programs in developing countries

- Ladner et al\* evaluated 29 programmes in 23 institutions in 19 LMICs
- Most frequent obstacles to implementation were concerns related to vaccine safety and efficacy
- Reaching and maintaining follow-up with target populations, as well as adequate infrastructure, human resources, financing and the vaccine delivery requirements were significant health system barriers
- In general coupling vaccination of girls increased uptake of cervical cancer screening by mothers
- Almost all programmes had international partners to assist with implementation

\*Ladner et al BMC Health Services Research 2016: 16:575

# Way forward

- Political awareness
- Understanding burden of disease associated with HPV and the possibilities for prevention
- Combat the status of inequity between HIC and LMICs
- Evaluate one versus two versus three dose regimes for efficacy over time
- Use school based platforms - ideal opportunity to develop adolescent health programs
- Integrated implementation with all stakeholders working together
- Community buy-in essential
- Manage adverse events promptly and transparently

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## Way forward

- Worse than doing nothing is doing it badly!
- Careful pre-implementation planning is critical to success
- Phased introduction more likely to be successful than attempting mass roll-out
- Well prepared communities and public health sector key starting point
- Do it, but do it well in order to reap the demographic dividend!

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## Recent announcement in South Africa

- Since 2014
- 1.2 million grade 4 girls have been vaccinated with bivalent vaccine with over 70% return rate for dose 2!

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