HPV update: towards cervical cancer elimination

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Summary

• BOD
• Elimination statements: definitions
  • tools to achieve elimination goal

• predictions & challenges

• modelling
• surveillance
Burden of disease: top 10 cancers, females 2018

- 570,000 new cases cervical cancer and 311,000 deaths in 2018
- HPV causes ~5% of all cancers globally

~84% percent of CC cases occur in less developed regions of the world

low incidence rates of CC in HIC largely attributable to widespread screening programs
Countries with HPV vaccine in National Immunization Program, January 2018

WHO/IVB Database, as of January 2018  79 countries.

- Introduced to date: 79 countries
- Not introduced/no plans: 115 countries
WHO Director-General calls for all countries to take action to help end the suffering caused by cervical cancer

• **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.

A global initiative

  - partner organizations: GAVI, GFATM, Unitaid, the Union for International Cancer Control (UICC), and the Clinton Health Access Initiative (CHAI)

- USA NCI-designated cancer centers endorse goal of eliminating HPV-related cancers

- International PapillomaVirus Society (IPVS)

- HPV Awareness Day March 4th
IPVS Statement: Moving towards Elimination of Cervical Cancer as a Public Health Problem

• IPVS is releasing a *Call to Action* to health authorities to adhere to international standards developed by WHO to develop national, regional and local plans to ultimately achieve the goal of cervical cancer elimination as a public health problem. A markedly reduced incidence of cervical cancer is possible in the near term, with elimination thereafter, if high rates of HPV vaccination and cervical screening are achieved.

The facts

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• Cervical cancer is a cancer caused by human papillomavirus (HPV) infection, which can be effectively prevented as a public health problem by vaccination & screening.
• Highly safe and effective vaccines that can prevent the majority of HPV infections that cause cervical and other HPV-associated cancers are available.
• Tests to screen for, and methods to treat, cervical pre-cancerous lesions are available and are proven to reduce cervical cancer incidence.
The facts

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- Recent modelling suggests that, with the tools available, elimination of cervical cancer in local populations is achievable within our lifetime. To achieve this, these effective and cost-effective prevention methods will need to be expanded, to include those not currently vaccinated or screened.
The facts

• Combining HPV vaccination at high coverage for adolescents and high coverage of cervical screening, with appropriate treatment of all women, can eliminate cervical cancer as a public health problem.

• Recent modelling suggests that, with the tools available, elimination of cervical cancer in local populations is achievable within our lifetime. To achieve this, these effective and cost-effective prevention methods will need to be expanded, to include those not currently vaccinated or screened.

• Broad dissemination of HPV vaccines has been achieved in some low and high resource countries, but needs to be scaled up globally, to reach the majority of age eligible individuals.
• Today we are poised to markedly reduce the incidence of cervical cancer, with the vision of eventually eliminating it as a public health problem, using the combination of sustained high coverage HPV vaccination and sustained high coverage screening with treatment.
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• Please help spread the message that we can markedly reduce cervical cancer. We have the science and the tools. We now urgently need the policy, the resources, political will and the public’s determination to move forward to implement these actions.

Definition of elimination of cervical cancer as a public health problem?

- CC incidence elimination threshold (10, 4 or even 1 case per 100,000 women-years)?
  - WHO SAGE 10,2018

Predictions without action?

- Without immediate, focused action, the burden of cervical cancer is projected to grow over the next 20 years, with about 35% more women being affected by the disease by 2040.  
  - new cases 528,000 2012 to 710,000 2030 current trends incidence, ~50% increase deaths 2040

- This increase will also be inequitable, with low HDI countries having the greatest relative increase in the annual number of cancer cases from 2012 to 2035.

Vaccarella et al, Lancet Oncol 2016

Nearly 50% of cervical cancer cases have probably been prevented by screening in the Nordic Countries, 1956-2010

Global Cancer Observatory’s GLOBOCAN 2012: “Predictions from GLOBOCAN”. HDI = Human Development Index
http://globocan.iarc.fr/Pages/burden_sel.aspx
Tools to achieve elimination?

- **Vaccines**: to young girls +/- boys at high coverage
- **Cervical screening**: high coverage high sensitive assays HPV DNA [1-2 screens lifetime]
- **Treatment**: of screen positive women: fast, appropriate

Each will all need to be ongoing

** 2030 all countries globally
Coverage: vaccines & cervical screening?

- Ideally want all countries to have at least **80% vaccine coverage**
  - only 44% of countries & territories [99] have introduced HPV vaccine into their routine immunization schedule:
  - 94% of LIC [GAVI-eligible] & 86% of LMIC Countries have not yet introduced the vaccine.
  - Of those introducing HPV vaccines, few report 90% coverage of the target groups.

- Ideally want all countries to have at least **70% cervical screening coverage**
  - ~ 60% report having cervical cancer screening programs
  - most are opportunistic rather than organized, limiting their reach.
  - very few countries report screening coverage rates over 70%, the current WHO/IARC target for participation in screening.
Vaccine coverage by delivery status

Fig. 1. Average reported HPV coverage by delivery strategy, 52 countries with coverage data reported in the period 2014–2016. Figure footnote: PHC – Primary-level health centres. Y axis: Full HPV coverage, %.

Vaccination of girls only as single/multiple age-cohorts 9-14 years?

- All 3 currently licensed vaccines offer excellent safety, efficacy, immunogenicity & effectiveness profiles.

- 2-dose schedule with at least 6-month interval between doses induces comparable levels of protection from HPV 16/18 infection as a 3-dose schedule, for girls aged 9-14 years.

- One-dose schedule ALL observational & promising, but need RCT.

- Girls-only vaccination at high coverage has a herd effect on boys/men and women.
What key indicators should be used to monitor programs?

- National HPV vaccine introduction..... AIM by 2030 ALL countries
- Vaccine coverage in countries: AIM coverage vaccine at least 80% final dose, at least one cohort, prioritized to those with >BOD CC
- Reduction in genotype prevalence of HPV 16/18 in young women
- Cervical precancer screening coverage [70/80%]
- Treatment rate of women screened positive [~90%]
- Reduction in rate of CIN3+
- Reduction in cervical cancer incidence & mortality
- Requires surveillance
As an example: Australia’s HPV vaccine program

- Commonwealth Government funded the 4vHPV vaccine GARDASIL®, for girls and women aged 12 to 26 years from 2007

- **2007 (April) school based program**
  - girls 12 - 13 years (ongoing and as a 3 dose regimen) α first year of high school
  - girls 13 - 18 years (catch-up)
  - GP based (July 2007)
    - young women 18 - 26 years (catch-up) December 2009
    - girls 12 - 18 years who missed doses at school

- **2013 gender neutral approach: ongoing school-based HPV program for boys**
  - 12-13 year old boys (ongoing and as a 3 dose regimen)
  - 14-15 -year-olds catch-up to December 2014

- **2018 2 dose, 9 valent [9vHPV] HPV vaccine girls and boys catch-up to 19 years age**
Achieved HIGH coverage

National HPV vaccination program cohorts

4vHPV program start

Switch to 9-valent vaccine

Pre-vaccine cohorts

Catch-up 4vHPV cohorts

School-based 4vHPV cohorts

Courtesy D Machalek
Australian coverage: females at age 15 years by dose

Fig. 3. Trend in coverage at age 15 in Australia. (A) HPV vaccination coverage at age 15 in females by dose number, 2007–2016, Australia (Source: National HPV Vaccination Program Register, data as held on 12 July 2017)
HPV detection among 18–35 year old Australian females before\(^1\) and 9 years after vaccine introduction presenting for cervical screening\(^2\)


2. Machalek Garland et al JID 2018 Very low prevalence of vaccine HPV types among 18–35 year old Australian women, 9 years following implementation of vaccination-
HPV detection among 18-35 year old females by age group

- 18-24 years old: 22.7% in 2005-07 (n=275) vs. 11.8% in 2015 (n=389), p<0.001
- 25-35 years old: 1.5% in 2005-07 (n=275) vs. 1.6% in 2015 (n=389), p<0.001

- 92% relative reduction in 18-24 years old
- 64% relative reduction in 25-35 years old

- 90% received ≥1 dose
- 66% received 3 doses
- 78% received ≥1 dose
- 39% received 3 doses

Relative reduction in 4vHPV type prevalence among 18-35 year old females by study group and vaccination status

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Adjusted rate of HPV prevalence</th>
<th>Relative reduction</th>
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<tbody>
<tr>
<td></td>
<td>Ratio</td>
<td>P-value</td>
</tr>
<tr>
<td>Vaccine-target HPV types 6, 11, 16, 18</td>
<td>1.0 (ref)</td>
<td>--</td>
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<tr>
<td>Prevaccine implementation</td>
<td>0.30 (0.19–0.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postvaccine implementation</td>
<td>0.22 (0.05–0.61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>0.10 (0.02–0.39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Partial or unconfirmed</td>
<td>0.05 (0.01–0.22)</td>
<td>&lt;0.001</td>
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Machalek Garland et al JID 2018 Very low prevalence of vaccine human papillomavirus (HPV) types among 18 to 35 year old Australian women, nine years following implementation of vaccination
Baseline HPV prevalence in unvaccinated heterosexual men: first data **males** benefit from a national female vaccination program: HERD effects

Prevalence of penile HPV genotypes by age group among 511 register-confirmed unvaccinated Australian heterosexual males

Machalek D, Chow E, Garland SM et al, HPV Prevalence in unvaccinated heterosexual men after a National
Goals: HPV vaccination & cervical screening
Proportion of Australian-born females with genital warts, by age group (2004–2011)\textsuperscript{1}

- 2004 2005 2006 2007 2008 2009 2010 2011

- <21 Years (n=9,405)
- 21–30 Years (n=15,228)
- >30 Years (n=10,246)

qHPV vaccine introduced

Genital Wart Diagnosis (%)

- 72.6%
- 92.6%

\textsuperscript{1} Ali H et al. \textit{BMJ}. 2013;346:f2032
Impact on cervical abnormalities to <30 years

Trends in prevalence rates of high-grade histologically confirmed cervical abnormalities* diagnosed in Victorian women, by age group, 2000–2014

- 65% decline <20yrs since 2007
- 40% 20-24yrs since 2010
- 13% 25-29 since 2013

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40% 20-24yrs since 2010
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1. AIHW 2017
First HPV vaccine effect on cervical cancers

- Finnish data¹:
- Scottish data²: "There is also some evidence from evaluations after national introductions; in Scotland, national statistics suggest a decline in cervical cancer in 20-24 year olds, the majority of those being vaccine eligible (ISD, 2018)." K Pollock

• USA data³ Results: The 4-year average annual incidence rates for cervical cancer in 2011-2014 were 29% lower than that in 2003-2006 (6.0 vs 8.4 per 1,000,000 people,


³ Guo et al Am J of Preventative Medicine
CHALLENGES HPV vaccination?

- Relatively new vaccine, long latency
  - education all levels
- HPV common & sexually transmitted
  - HPV vaccination does not to increase promiscuity¹
- Government investment
  - target population
  - infrastructure
  - finances
- Impact on cervical screening
- Perceived safety concerns → vaccine hesitancy
  - forward plan KOL
- Vaccine availability** constrained supply ~ 2024: globally need more equitable distribution

¹ Bednarczyk et al
Modelling: Australia may be first!

Figure 1: The (A) age-standardised annual incidence of invasive cervical cancer and (B) associated mortality. Data are the model predictions for rates from 2015 to 2100, accounting for the transition to primary human papillomavirus screening in 2017 (the renewed NCSP) and the switch to nonavalent vaccine in 2018. NCSP = National Cervical Screening Programme.

Base-case estimate for 4/100,000pa 2028
Conclusions

• Elimination of cervical cancer within our lifetime [Australia next 20 years]
• tools to achieve elimination goals
• modelling predicts findings
• surveillance
• Political will [WHO]
• Maintain high levels of vaccination, screening & Rx
Research requirements: Data on

- Data on single dose vaccination
- Different (extended) regimens 2 doses (>15 years of age)
- HIV(+) and chronic disease
- Effectiveness of non-cervical HPV related cancers