Introduction to Primary Prevention of Cervical Cancer

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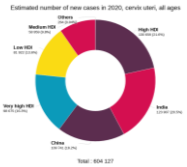
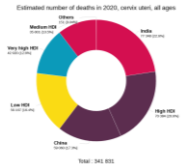
Content

Inequality of cervical cancer burden worldwide

- Cervical cancer is the fourth most common Cancer in women worldwide, as well as the fourth most common cause of cancer death.





New cases of cervical cancer worldwide: 604,127
LMICs: 532,239 (88.1%)

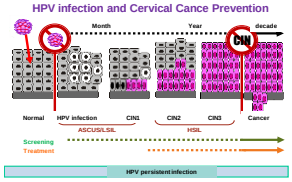
Death cases of cervical cancer worldwide: 341,831
LMICs: 312,373 (91.4%)

Ref: 1. Global Cancer Observatory 2020: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today

Essential Cause of Cervical Cancer: High-risk HPV Persistence

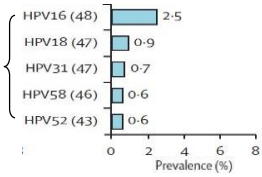
- More than 200 human papillomavirus (HPV) genotypes found, ~40 of them related with anogenital infection and lesions
  - **14 oncogenic types (high-risk):** 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73
  - non-oncogenic types (low-risk): 6, 11; related with benign lesions, e.g geital warts, recurrent respiratory papillomatosis

HPV infection and Cervical Cance Prevention



Type-specific HPV infection in women with normal cervical cytology worldwide

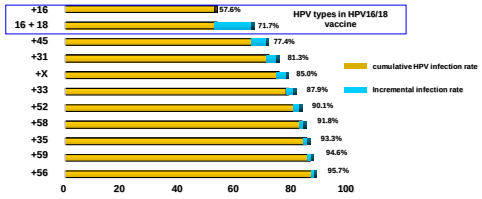
- A systematic review suggested that overall HPV prevalence in 157 879 women with normal cervical cytology was estimated to be 10·4% (95% CI 10·2–10·7).



Top 5 cervical high-risk HPV types worldwide

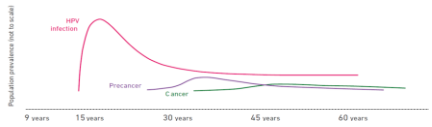
Ref: Lancet Infect Dis 2007; 7: 453–59

Type-specific HPV infection in women with cervical cancer



Ref: Munoz N, et al. N Engl J Med. 2003;348:518-527.

Life-course approach to cervical cancer interventions



Primary Prevention

Girls 9-14 years
- **HPV vaccination**

Girls and boys, as appropriate
- Health information and warnings about tobacco use
- Sexuality education tailored for age and culture
- Condom promotion/Male circumcision

Secondary Prevention

Women >30 years of age
- Screening with a high-performance test equivalent to or better than HPV test
- Followed by immediate treatment or as quickly as possible, of precancerous lesions

Tertiary Prevention

All women, as needed

Treatment of invasive cancer at any age
- Surgery
- Radiotherapy
- Chenotherapy
- Palliative care

WHO Call for Elimination of Cervical Cancer

Targets for Period 2020–2030

- In Nov. 2020, WHO launched the global strategy to accelerate the elimination of cervical cancer as a public health problem with the following 2020 targets.

Vision: A world without cervical cancer

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

2030 TARGETS

90% of girls fully vaccinated with HPV vaccine by 15 years of age

70% of women are screened with a high-performance test by 35 and 45 years of age

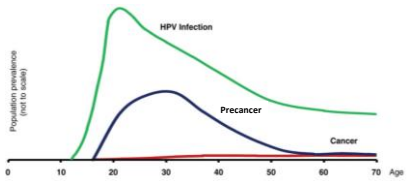
90% of women identified with cervical disease (precancer or cancer) receive treatment and care

SDG 2030 Target 3.4: 30% reduction in mortality from NCDs

https://www.who.int/cancer/cervical-cancer/cervical-cancer-elimination-strategy

Goals of HPV Vaccination

To *directly* reduce the risk of HPV acquisition in vaccinees

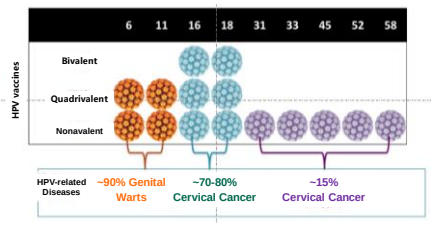


To *indirectly* reduce risk of HPV acquisition by reducing the prevalence of HPV-vaccine types in the general population (**herd immunity**)

Available Prophylactic HPV vaccines in China

				
Manufacturer	Merck (Gardasil)	Merck (Gardasil 9)	GSK (Cervarix)	Innovax (Cecolin)
HPV VLP types	6/11/16/18	6/11/16/18 **/31/33/45/52/58**	16/18	16/18
Expression system	Yeast	Yeast	**Baculovirus**	**E.Coli**
Adjuvant	aluminum	Standard aluminum	AS04	Standard aluminum
Year (FDA approval)	2006	2014	2009	/
Year (CFDA approval)	2017	2018	2016	2019

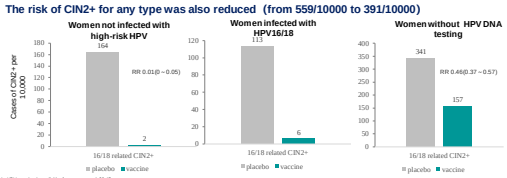
HPV types protected by HPV vaccines



A Cochrane review confirmed the protective efficacy of HPV vaccine

According to a Cochrane systematic review of 26 clinical trials involving 73,428 women *:
* women aged 15-26 years who were not infected with high-risk HPV, women aged 15-26 years who were not infected with HPV16/18, and women aged 15-26 years who were not tested for HPV DNA received at least one dose of 2vHPV or 4vHPV vaccine, followed for 3-9 years. *, *,

- **HPV vaccine significantly reduced the risk of CIN2+ associated with HPV16/18 (from 341/10000 to 157/10000)**
- **The risk of CIN2+ for any type was also reduced (from 559/10000 to 391/10000)**

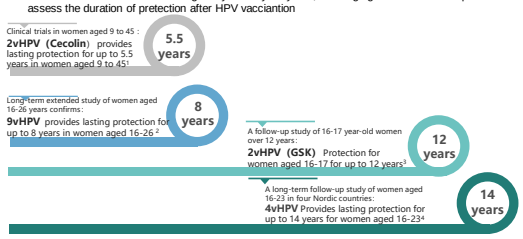


* In China, the 4v HPV vaccine is available for women aged 20-45
a.design: A systematic review of 26 clinical trials involving 73,428 adolescent women and women to assess the protective efficacy of HPV vaccine against precervical cancer and HPV16/18 infection
b.design: A total of 23,676 women aged 15-26 years with negative HPV DNA testing were enrolled in three clinical trials, including 11,815 in the vaccine group and 11,861 in the control. The number of cases of CIN2+ associated with HPV16/18 was observed during 3-6 years of follow-up
c.design: The analysis included 3 clinical trials involving 34862 women aged 15-26 without HPV DNA testing, including 17,404 in the vaccine group and 17,458 in the control, followed for 3.5-6.5 years to observe the incidence of CIN2+ associated with HPV16/18

Arbyn M , Xu L , Simoens C , et al. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors.[J]. Cochrane Database Syst Rev, 2018, May

Duration of protection after HPV vaccination

The HPV vaccine has been used globally for only 15 years, and onging observation is required to assess the duration of pretection after HPV vacciantion



1 Hu YM, et al. Sci China Life Sci. 2019 Jun 21
2 Olsson S E et al. Papillomavirus Research, 2020Kianna Artemchuk, Tiina Eriksson, Mario Poljak, et al.
3 Artemchuk H et al. The Journal of Infectious Diseases, 2019, 219(4): 582–589
4 Kjaer S K et al. EClinicalMedicine, 2020, 22:

After routine vaccination for three doses, there is no need for booster immunization

A systematic review confirms the effectiveness of HPV vaccine immunization programmes in vaccinated population

A review of 65 articles including 60 million vaccinated people in high-income countries :

5-8 years after HPV vaccination:

Infection of HPV16/18:

- **83%** reduction for girls aged 13-19 (RR 0.17,95%CI 0.11-0.25), **66%** reduction for girls aged 20-24 (RR 0·34, 95% CI 0·23–0·49)

Infection of HPV31/33/45:

- **54%** reduction for girls aged 13-19 (RR 0·46, 95% CI 0·33–0·66)

Genital warts:

- **67%** reduction for girls aged 15-19 (RR 0·33, 95% CI 0·24–0·46), **54%** reduction for girls aged 20-24 (RR 0·46, 95% CI 0.36–0.60) , **31%** reduction for girls aged 25-29 (RR 0·69, 95% CI 0·53–0·89)
- **48%** reduction for boys aged 15-19 (RR 0·52, 95% CI 0·37–0·75), **32%** reduction for boys aged 20-24(RR 0·68, 95% CI 0·47–0·98)

5-9 years after HPV vaccination:

Incidence of CIN2+:

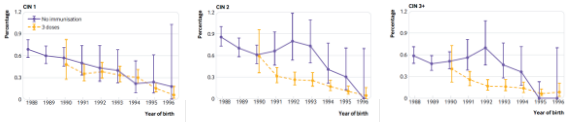
- **51%** reduction for girls aged 15-19 (RR 0·49, 95% CI 0·42–0·58), **31%** reduction for girls aged 20-24 (RR 0·69, 95% CI 0·57–0·84)

Ref: Lancet, 2019

Herd immunity observed in women without HPV vaccination

- A real world study including 138,692 screened women in Scotland showed that after the implementation of bivalent HPV vaccination program, compared with women without vaccination in the 1988-1990 birth cohort, herd immunity was observed in the 1995-1996 birth cohort.

CIN1 reduce 63% (11% to 85%), CIN2 reduce 67%(19% to 86%), CIN3+ reduce 100% (69% to 100%)

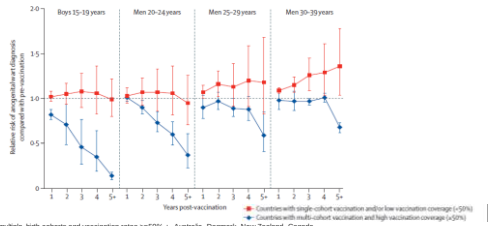


1988-1989: without vaccination; 1990-1994: catch-up; 1995-1996: routine vaccination

BMJ, 2019

Herd immunity observed in men without HPV vaccination

- After 4v HPV vaccination, the incidence of genital warts in male populations was significantly reduced in countries vaccinated with multiple birth cohorts and vaccination rates >=50%



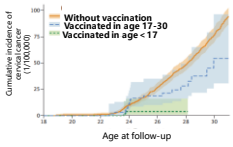
countries with multiple birth cohorts and vaccination rates >=50% : Australia, Denmark, New Zealand, Canada

Lancet, 2019

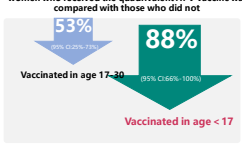
A study in Sweden shows for the first time that HPV vaccine reduces the incidence of invasive cervical cancer

According to a Swedish real-world study that included nearly 1.7 million women in 2020[19,▲]:

- Nearly 1.7 million women aged 10 to 30 years from 2006 to 2017 were tracked. Women who received at least one dose of the 4v HPV vaccine had a significantly lower incidence of invasive cervical cancer than those who did not. Greater protection was identified among women who received the vaccine before age 17, with an 88% reduction in the incidence of invasive cervical cancer



After adjustment, the incidence of invasive cervical cancer in women who received the quadrivalent HPV vaccine was compared with those who did not



4v human papillomavirus vaccine is recommended for women aged 9-45 years to prevent the following diseases due to high-risk HPV16/18: cervical cancer; CIN2/3 and AIS; CIN1: Domestic clinical trials have not confirmed the protective effect of this product on low risk HPV6/11 related diseases.
As any vaccine, there is no guarantee that the 4v HPV will protect all recipients. This product does not prevent all lesions caused by high HPV infection. The product has not been proven to protect against lesions caused by HPV infection other than the vaccine type and non-HPV disease.
Design: A total of 1,672,983 women aged 10-30 years were followed for 11 years from 2006 to 2017 using the Swedish National Demographic and Health Registry. Cervical cancer incidence and HPV vaccination data were collected and controlled for age, year, place of residence, and parental characteristics at the time of follow-up. To assess the relationship between HPV vaccination and the risk of cervical cancer.
[19] Li H, Rosso A, Ehrström KM, et al. HPV Vaccination and the Risk of Invasive Cervical Cancer. N Engl J Med. 2020;383(14):1340-1348.

The safety of vaccines has been demonstrated by a large amount of global surveillance data

- Results of a Cochrane review of 26 clinical trials showed no significant difference in the incidence of serious adverse events between the HPV vaccine and the control group, RR=0.98[95%CI: 0.92, 1.05]
- The WHO Global Advisory Committee on Vaccine Safety (GACVS) systematically reviewed HPV vaccine safety data in 2017 and concluded that the available evidence suggests no safety concerns for the use of HPV vaccine
- The International Federation of Obstetrics and Gynaecology (FIGO) reviewed the available data and supported the continuous use of HPV vaccine in the applicable population

Ref: Vincenzo, et al. Int J Women's Health 2014
Scheller,et al. JAMA 2015
Arbyn M , Xu L, Simoens C, et al. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors.[J]. Cochrane Database Syst Rev. 2018 May

WHO recommends that HPV vaccines being included into national immunization programmes (NIP)

World Health Organization — WHO in 2017 《HPV vaccines：WHO position paper》

- WHO recognizes the importance of cervical cancer and other HPV-related diseases as a global public health issue and reiterates its recommendation of including HPV vaccine into NIP.
- HPV vaccines should be part of a comprehensive strategy to prevent cervical cancer and other diseases caused by HPV.
- All three HPV vaccines on the market have demonstraged good safety and efficacy.

Ref: World Health Organization. Human papillomavirus vaccines: WHO position paper. 2017[J].

WHO Position paper, May 2017 Recommendations

- **Population**
  - Primary target population：girls before first sexual behaviour，aged 9-14 years
  - Secondary target population：female adolescents and young women
  - Male HPV vaccination is not recommended as a priority, especially in areas with limited resources
- **Schedule**
  - girls aged<15：A 2-dose vaccination program with an interval of 6 months (before sexual activity)
  - girls aged>=15：Three doses of vaccination program（0、1/2、6month）
  - booster vaccination has not been confirmed
  - No HPV or HIV testing is required prior to vaccination

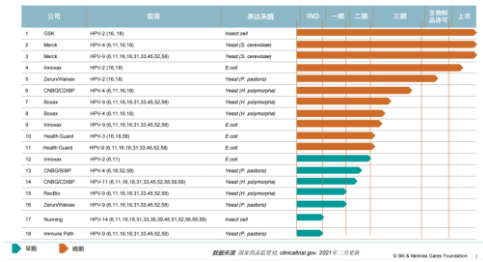
Ref: World Health Organization. Human papillomavirus vaccines: WHO position paper. 2017[J].

Countries with HPV vaccine in the national immunization programme

- Until Oct. 27, 2020, a total of **110 countries** have introduce HPV vaccination into national immunization programme (NIP).

Ref: http://www.who.int/immunization/monitoring_surveillance/VaccineIntroStatus.pptx?ua=1.

China has a rich pipeline of HPV vaccine research and development, supporting global immunization rogrammes



Slide courtesy of Ms. Ann Du from Bill & Melinda Gates Foundation

One dose schedule would improve HPV vaccination coverage

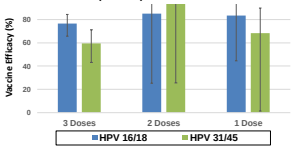
- Reduce Delivery Cost and vaccine price
- Reduce Delivery Complexity in Multi-visit dosing regimen
- Alleviate Supply challenges
- Achieve Higher coverage

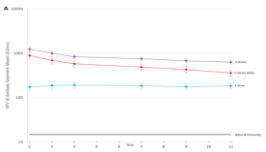
WORLD HEALTH ORGANIZATION / GLOBAL MARKET STUDY, 2018

Evidence for onde dose HPV vaccination

Costa Rica HPV Vaccine Trial (CVT): Bivalent HPV vaccine
(Followed up to 11 years)

- **VE of one dose shedule against HPV16/18 was 82.0% 11 years after the first vaccination.**
- **Comparable efficacy of one dose schedule against HPV31/33/45 was observed (VE=64%).**
- **Stable HPV16 serum antibodies for 11 years after bivalent HPV16/18 vaccine Following different doses.**





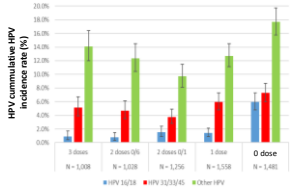
结局：HPV感染率；分析人群：total vaccinated cohort

Ref: 1. Kreimer AR et al, JNCI 2020; 2. Tsang SH et al, JNCI 2020

Evidence for onde dose HPV vaccination

HPV Vaccine Trial in India: Quadrivalent HPV vaccine(Followed up to 7 years)

- **HPV 16/18 cummulative incident rates had no significant differences among one, two and three doses groups during 7 years.**
- **No cross-protection against HPV31/33/45 was shown.**



Ref: Sankaranarayanan R, et al. Vaccine. 2018;36(32 Pt A):4783-91

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Summary of single-dose HPV vaccine studies

Study	Evidence type	Brief description
ESCUDDO Costa Rica	Efficacy/Immuno	Girls 12-16 yo randomized to received 1 or 2 doses of 2v or 9v (n=5000 per arm); survey of 5000 unvax women aged 16 to 20
Primavera Costa Rica	Immunobridging	Girls aged 9 to 14 received 1d of 2v; women aged 18 to 25 received 3 doses of 4v (n=620 per group)
DoRIS Tanzania	Immunogenicity	Girls 9-14 yo randomized to 1, 2, or 3 doses of HPV2 or HPV 9; n=155 per arm
KEN-SHE Kenya	Efficacy	Girls 15-20 yo randomized to 1 dose of HPV2, HPV9, or MenA; n=750 per arm
Thailand Impact Study Thailand	Effectiveness	Girls in grade 8 given 1 or 2 doses; n=~8000 each arm, prevalence surveys of girls grades 10, 12; n=2,400 each grade x 2 provinces
HOPE South Africa	Effectiveness	Girls 15-16 yo catch-up 1-dose, 9 yo routine dose, 17-18 yo unvaccinated (baseline); n≥3260

Summary

- **HPV vaccination** is an effective way against cervical cancer.
- **Vaccine efficacy is better in younger age group than older age groups,** and the higher effectiveness is achieved before sexual exposure, so efforts should be taken to improve the coverage in younger age group.
- **High cost of vaccines & insufficent supply** are important reasons impeding HPV vaccine included into NIP.
  - More vaccine development is expected to alleviate the shortage of vaccine supply.
  - More research evidence, especially from RCT studies, will drive the introduction of single-dose HPV vaccination regimens into WHO and national NIP recommendations.