

Elimination of Cervical Cancer and the Role of HPV Vaccination



Neerja Bhatla

Professor, Department of Obstetrics & Gynaecology,

All India Institute of Medical Sciences, New Delhi, India

Chairperson, FIGO & FOGSI Gyn Oncology Committees, 2015-18

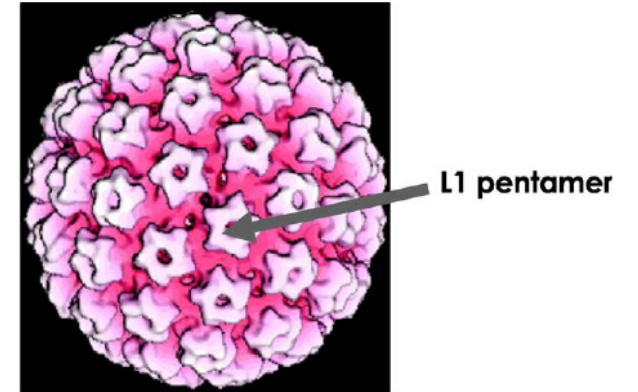
Secretary General, IFCPC

President AOGIN, 2014-16

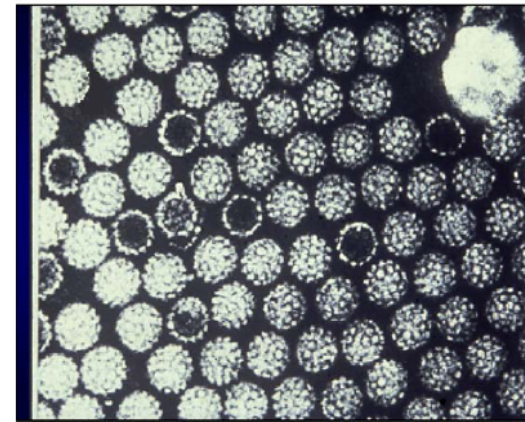
Cervical Cancer and the HPV vaccine

- One of the few cancers that is caused by a virus – Human Papilloma Virus
- One of the few that can be prevented by a vaccine
- First generation (bHPV and qHPV) targeted against high risk types 16 and 18
 - In India, 84% of cervical cancers are caused by HPV 16/18, more than the global average of 70%

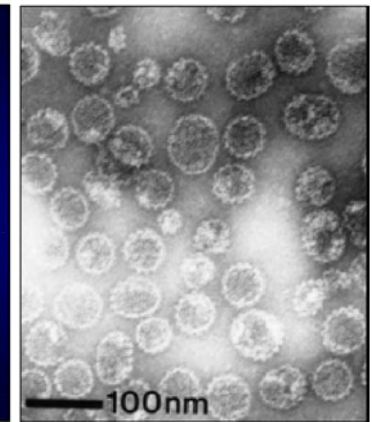
(A) MODEL OF THE VIRUS CAPSID



(B) VIRUS PARTICLES



(C) VIRUS-LIKE PARTICLES

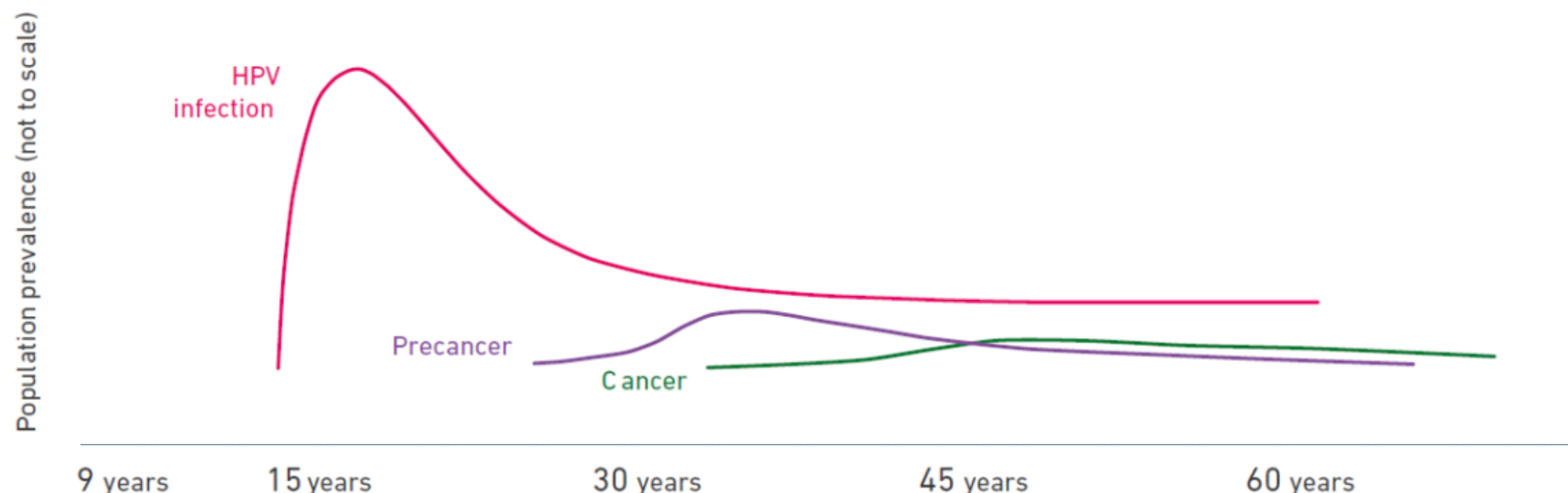


Indian statistics

Burden of cervical HPV infection	
HPV prevalence (%) in the general population (among women with normal cytology)	7.9
Prevalence (%) of HPV 16 and/or HPV 18 among women with:	
Normal cytology	6.0
Low-grade cervical lesions (LSIL/CIN-1)	28.2
High-grade cervical lesions (HSIL//CIN-2/CIN-3/CIS)	56.0
Cervical cancer	84.1

Data sources: Bhatla N, Int J Gynecol Pathol 2006;25:398; Franceschi S, Int J Cancer 2003; Gheit T, Vaccine 2009; Munirajan AK, Gynecol Oncol 1998;69:205; Nagpal JK, Eur J Clin Invest 2002;32:943; Peedicayil A, Int J Gynecol Cancer 2006; Sowjanya AP, MBC Infect Dis 2005; Neyaz MK, Biomarkers 2005; Nambura L, Asian Pacific J Cancer Prev 2009; Basu P, Asian Pacific J Cancer Prev 2009; Peedicayil A, J Low Genit Tract Dis 2009

WHO LIFE COURSE APPROACH TO CERVICAL CANCER CONTROL



Primary Prevention

Girls 9-14 years

- HPV vaccination

Girls and boys, as appropriate

- Health information and warnings about tobacco use
- Sexuality education tailored to age & culture
- Condom promotion/provision for those engaged in sexual activity

Secondary Prevention

Women > 30 years of age

“Screen and treat” – single visit approach

- Point-of-care rapid HPV testing for high risk HPV types
- Followed by immediate treatment
- On site treatment

Tertiary Prevention

All women as needed

Treatment of invasive cancer at any age and palliative care

- Surgery
- Radiotherapy
- Chemotherapy
- *Palliative Care*

MAY 2018: WHO DIRECTOR-GENERAL'S CALL TO ACTION TO ELIMINATE CERVICAL CANCER AS A PUBLIC HEALTH PROBLEM BY 2030

✓ Political will !



International Agency for Research on Cancer



WHO Call for Elimination of cervical cancer



Cervical Cancer Prevention and Control 2018-2030

Vision: A world without cervical cancer

Threshold: All countries to reach ≤ 4 cases per 100,000 woman-years

2030 CONTROL TARGETS

2030 TARGETS

90%

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

70%

of women screened with
an effective test at 35
and 45 years of age

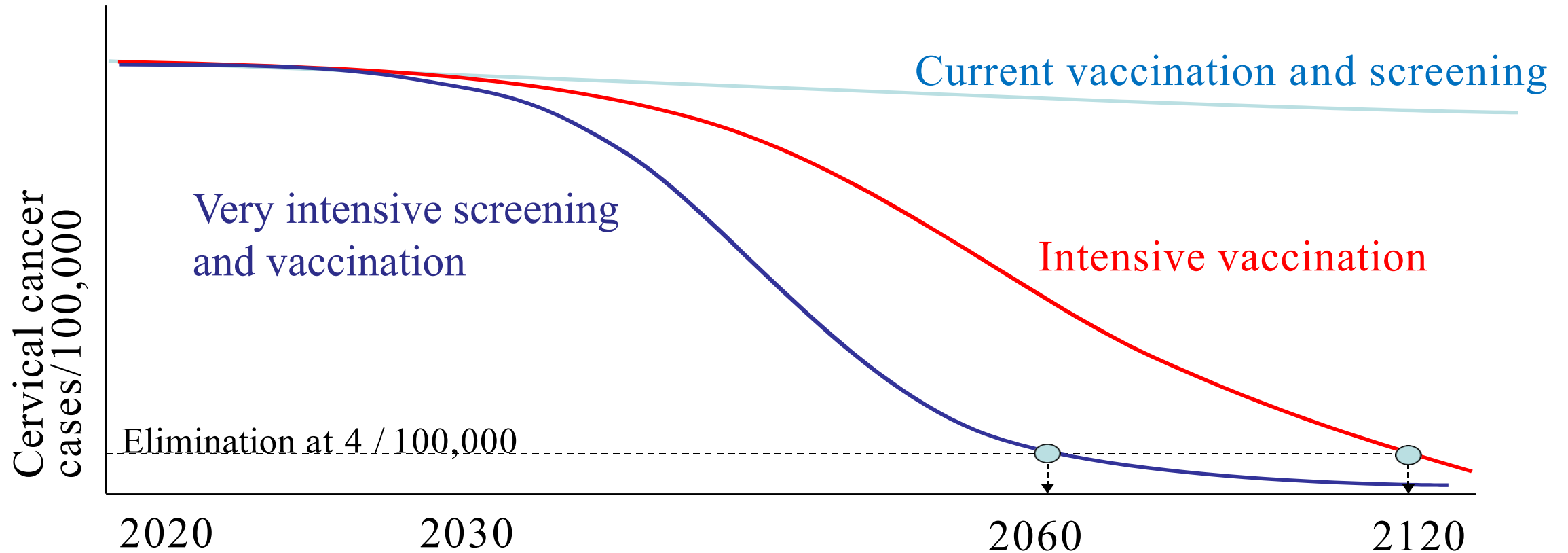
90%

of women identified
with cervical disease
receive treatment and
care

SDG 2030: Target 3.4 – 30% reduction in mortality from cervical cancer

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

Cervical Cancer Elimination: Conceptual Framework



FAQ 1

Is the HPV vaccine safe !

Did it cause deaths among vaccinated girls in Andhra Pradesh and Gujarat?

The HPV vaccine is not related with any serious side effects

- 5 deaths of girls 1-6 months after HPV vaccination in a demonstration project by PATH in Andhra Pradesh and Gujarat in 2008-9
- Causes of death
 - Suicide
 - Drowning in well
 - Viral fever
 - Snake bite
 - Malaria
- Investigated thoroughly by ICMR – **not related to the vaccine**

Immunogenicity and safety of human papillomavirus-16/18 AS04-adjuvanted cervical cancer vaccine in healthy Indian women

Neerja Bhatla¹, Vanita Suri², Partha Basu³, Surendra Shastri⁴, Sanjoy K. Datta⁵, Dan Bi⁵, Dominique J. Descamps⁵, Hans L. Bock⁵ and the Indian HPV Vaccine Study Group*

¹All India Institute of Medical Sciences, New Delhi, ²Postgraduate Institute of Medical Education and Research, Chandigarh, ³Chittaranjan National Cancer Institute, Kolkata, ⁴Tata Memorial Cancer Hospital, Mumbai, India; and ⁵GlaxoSmithKline Biologicals, Rixensart, Belgium

Results: A total of 330 subjects completed the study. One month post-Dose 3, all initially seronegative subjects in the Vaccine group had seroconverted for HPV-16 and HPV-18 antibodies with anti-HPV-16 and anti-HPV-18 geometric mean titer levels of 10226.5 EL.U/ml (95% confidence interval: 8847.1–11821.0) and 3953.0 EL.U/ml (95% confidence interval: 3421.8–4566.8), respectively. Initially seropositive subjects also showed an increase to similar geometric mean titer levels. Six serious adverse events (two in the Vaccine group and four in the Placebo group), all unrelated to vaccination, were reported. Commonly reported solicited local (injection-site pain) and general (fatigue, headache and fever) symptoms were similar in both groups. Compliance to the three-dose vaccination course was >97%.

Conclusions: The AS04-adjuvanted HPV-16/18 cervical cancer vaccine was highly immunogenic and generally well-tolerated making it a potential tool for prevention and control of cervical cancer in India.

Randomised Trial of 2 versus 3 doses of HPV vaccination in India

World Health Organization (WHO)
International Agency for Research on Cancer (IARC)
Lyon, France

In collaboration with

TMH-Mumbai

NDMCH-Barshi

JCDC-Pune

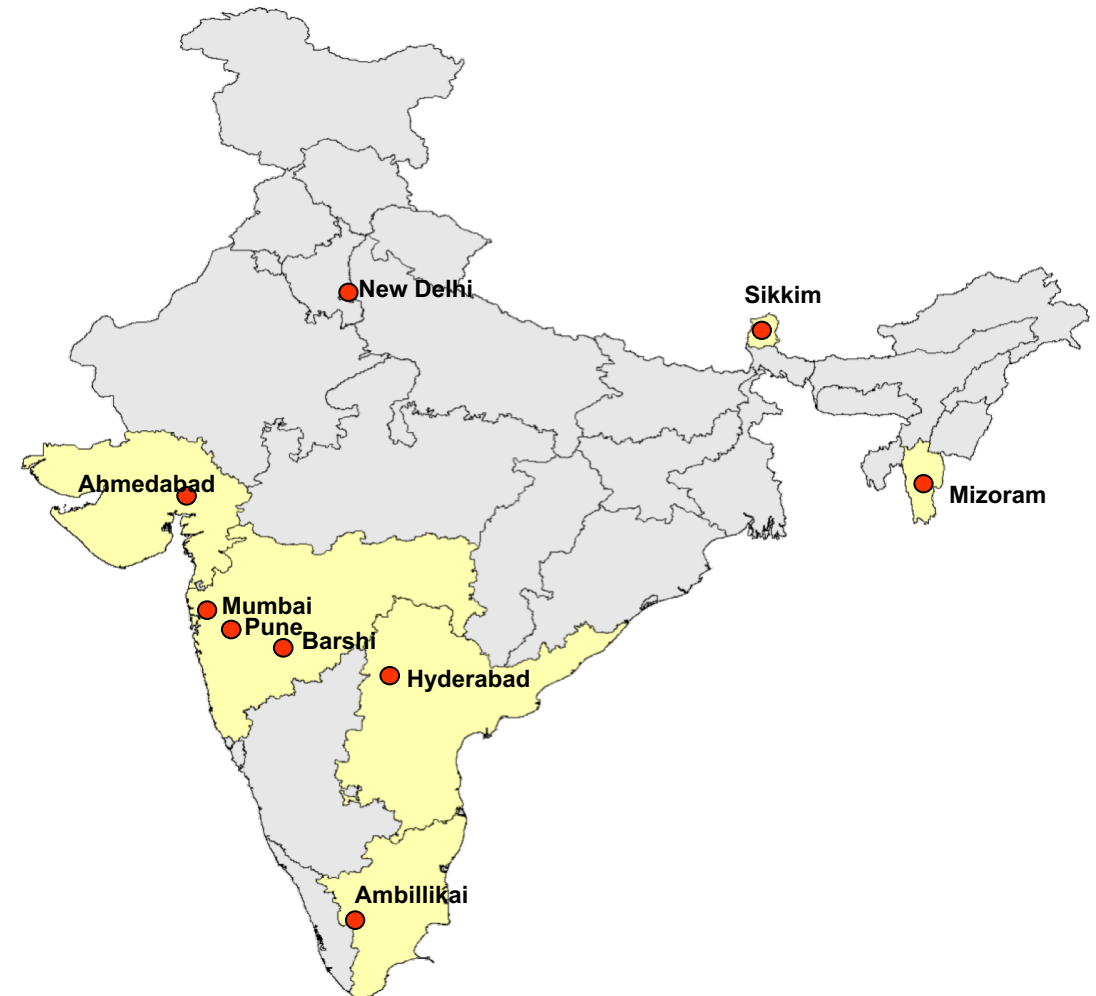
CFCHC-Ambillikai

GCRI-Ahmedabad

AIIMS-New Delhi

MNJ Institute of Oncology and RCC, Hyderabad

Cancer Foundation of India (CFI), Kolkata



Supported by the Bill & Melinda Gates Foundation

Indian trial (Delhi site): AEs within 30 days of vaccination with qHPV vaccine

Adverse Events (N=239)	2-dose Group (N=968)	3-dose Group (N=1406)	Total (%) (N= 2374)
Injection site pain	90	94	184 (7.75%)
Low-grade fever	15	11	26 (1.1%)
Dizziness	5	5	10 (0.42%)
Mild injection site swelling	3	1	4
Skin irritation	0	3	3
Abdominal cramps	3	0	3
Rash	2	0	2
Mild headache	1	1	2
High fever	1	0	1
Mild muscle pain	1	0	1
Pneumonia	1	0	1
Bronchial asthma	1	0	1
Anaemia	1	0	1

Safety of HPV Vaccine

- **Vast majority of suspected AEs are related to**
 - **recognised side effects already listed in product information**
 - **were due to injection process and not vaccine itself (i.e., ‘psychogenic’ in nature)**
 - **were events that occur commonly in the population receiving the vaccine**
- **following substantial usage, no serious new risks have been identified**



**World Health
Organization**

Organisation mondiale de la Santé

Weekly epidemiological record Relevé épidémiologique hebdomadaire

19 JULY 2013, 88th YEAR / 19 JUILLET 2013, 88^e ANNÉE

No. 29, 2013, 88, 301–312

<http://www.who.int/wer>

- > 300 million doses distributed
- Committee continues to be reassured by the safety profile
- Surveillance has not detected any adverse outcomes above the expected rates

**The HPV vaccine is now included in the national program in
over 100 countries**

The vaccine is as safe as the tetanus toxoid !

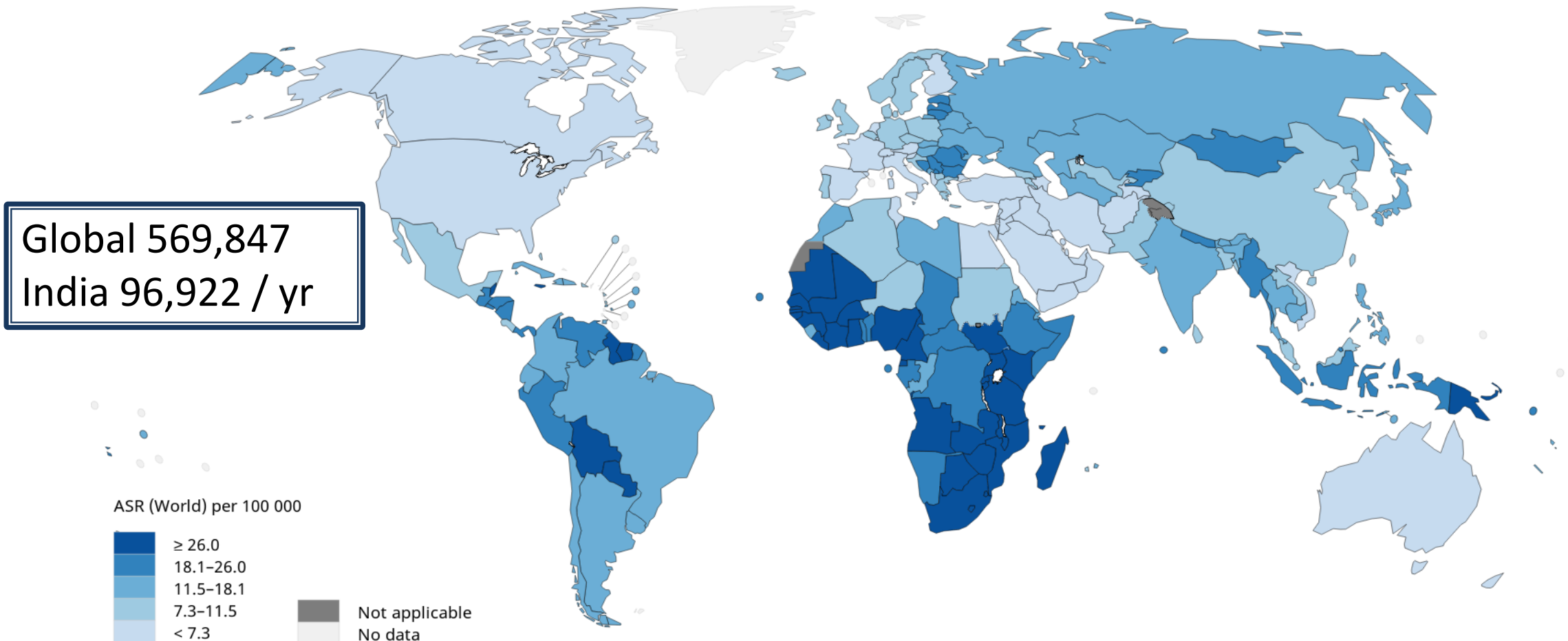
- *CDC, Atlanta*

FAQ 2

Cervical cancer is decreasing – Do we need a cervical cancer vaccine?

Cervical cancer – an avoidable NCD with gross inequities (GLOBOCAN 2018)

Estimated age-standardized incidence rates (World) in 2018, cervix uteri, all ages

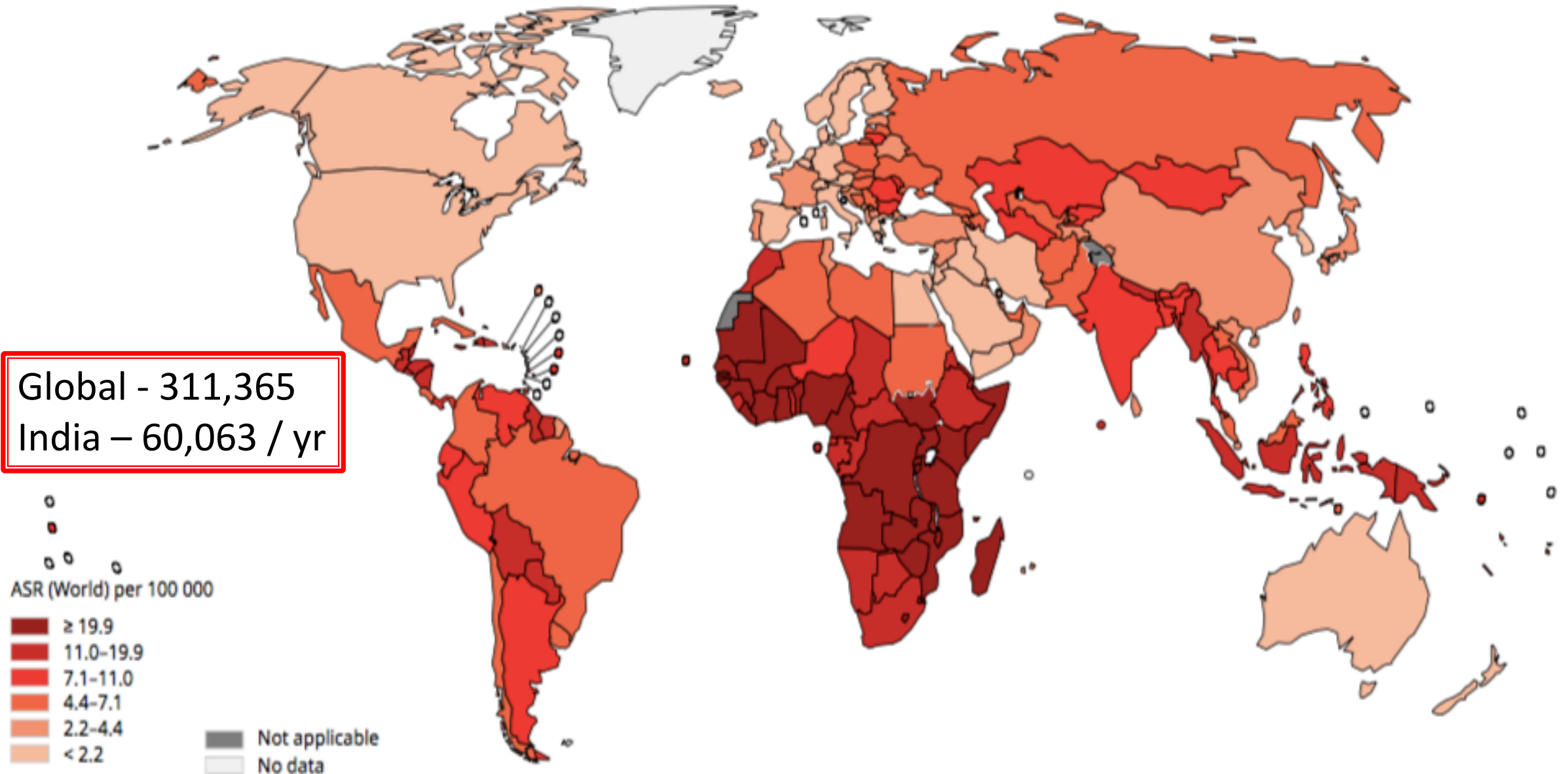


All rights reserved. The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization / International Agency for Research on Cancer concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate borderlines for which there may not yet be full agreement.

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

Age standardized (World) mortality rates, cervix uteri, all ages

Global - 311,365
India – 60,063 / yr

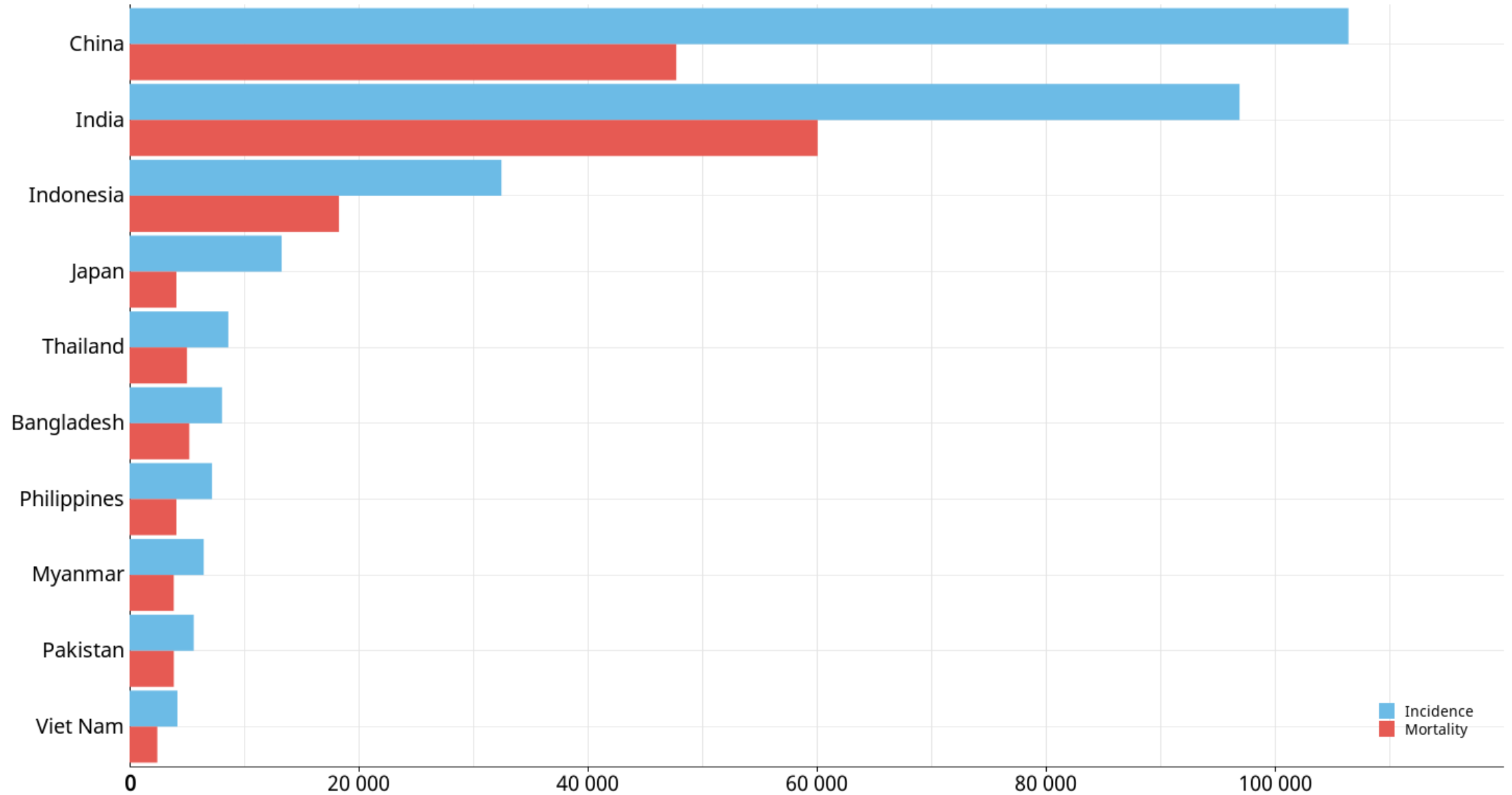


Data source: GLOBOCAN 2018

Graph production: IARC (<http://gco.iarc.fr/today>)

World Health Organization

Estimated number of incident cases and deaths females, all ages



Incidence
Mortality

“TOO OFTEN, women who are now being saved by the reduction in maternal mortality are dying instead from cervical cancer. A preventable disease.”

Professor CN Purandare
President, FIGO

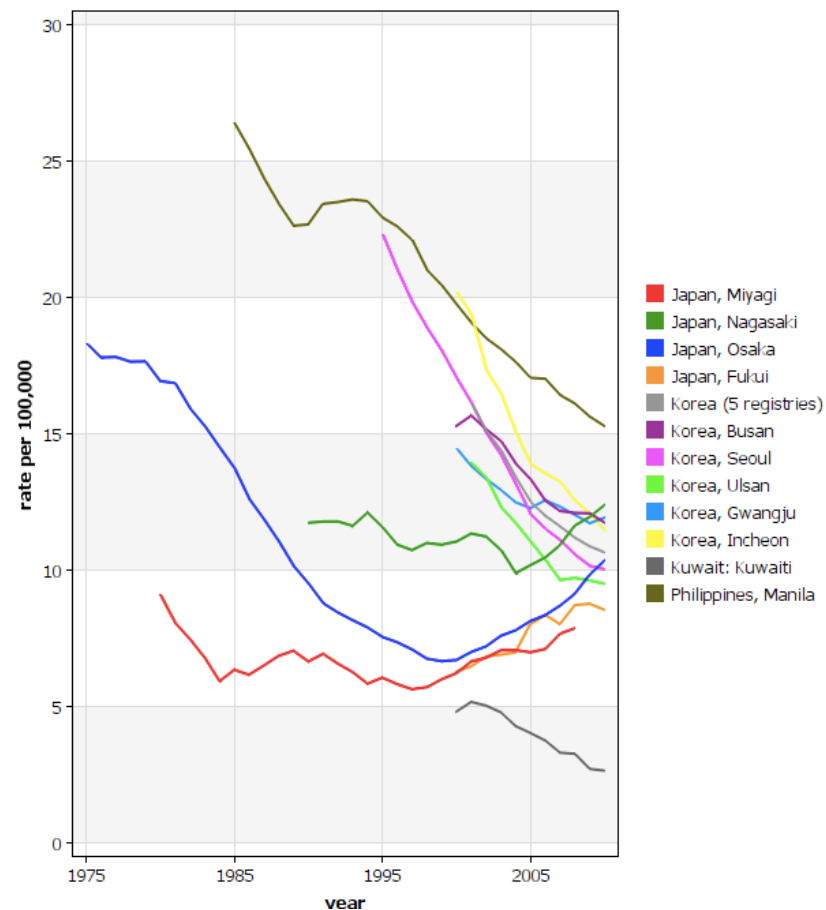
*at FIGO Oncology Side Event,
World Health Assembly,
Geneva, May 2018*



Trends in Cervical Cancer Incidence

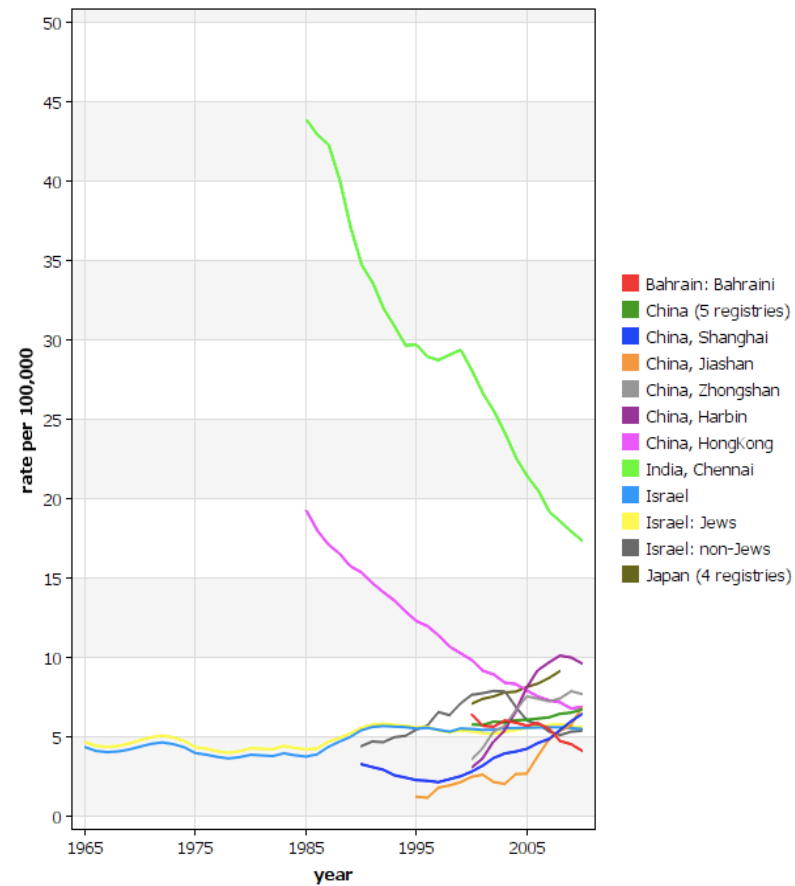
Cervix uteri

Age Standardised Incidence Rate (World), age [0-85+]



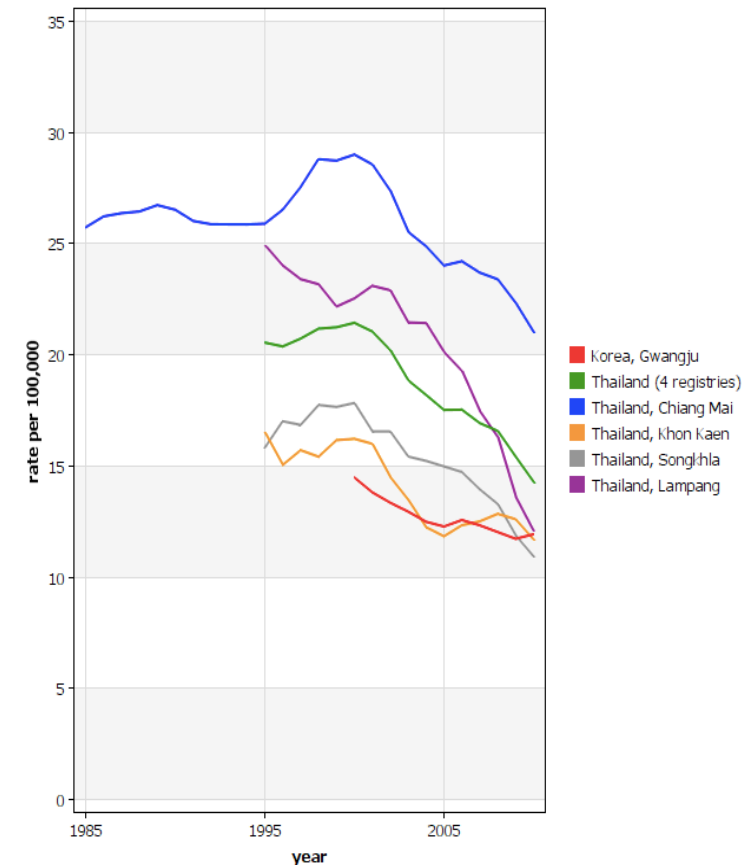
Cervix uteri

Age Standardised Incidence Rate (World), age [0-85+]



Cervix uteri

Age Standardised Incidence Rate (World), age [0-85+]



**We do need a serious prevention effort.
Vaccination is simple, acceptable and easily
implemented**

**If all Indian girls were vaccinated it could translate into
saving nearly 50,000 lives per year**

(A) Accumulation of global HPV vaccine experience, 2007



(B) Accumulation of global HPV vaccine experience, 2010



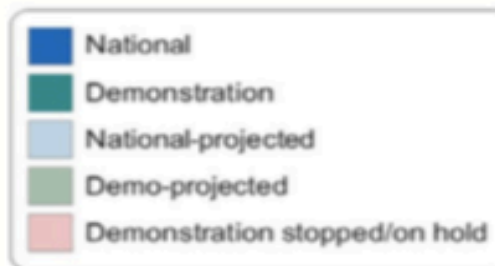
(C) Accumulation of global HPV vaccine experience, 2013



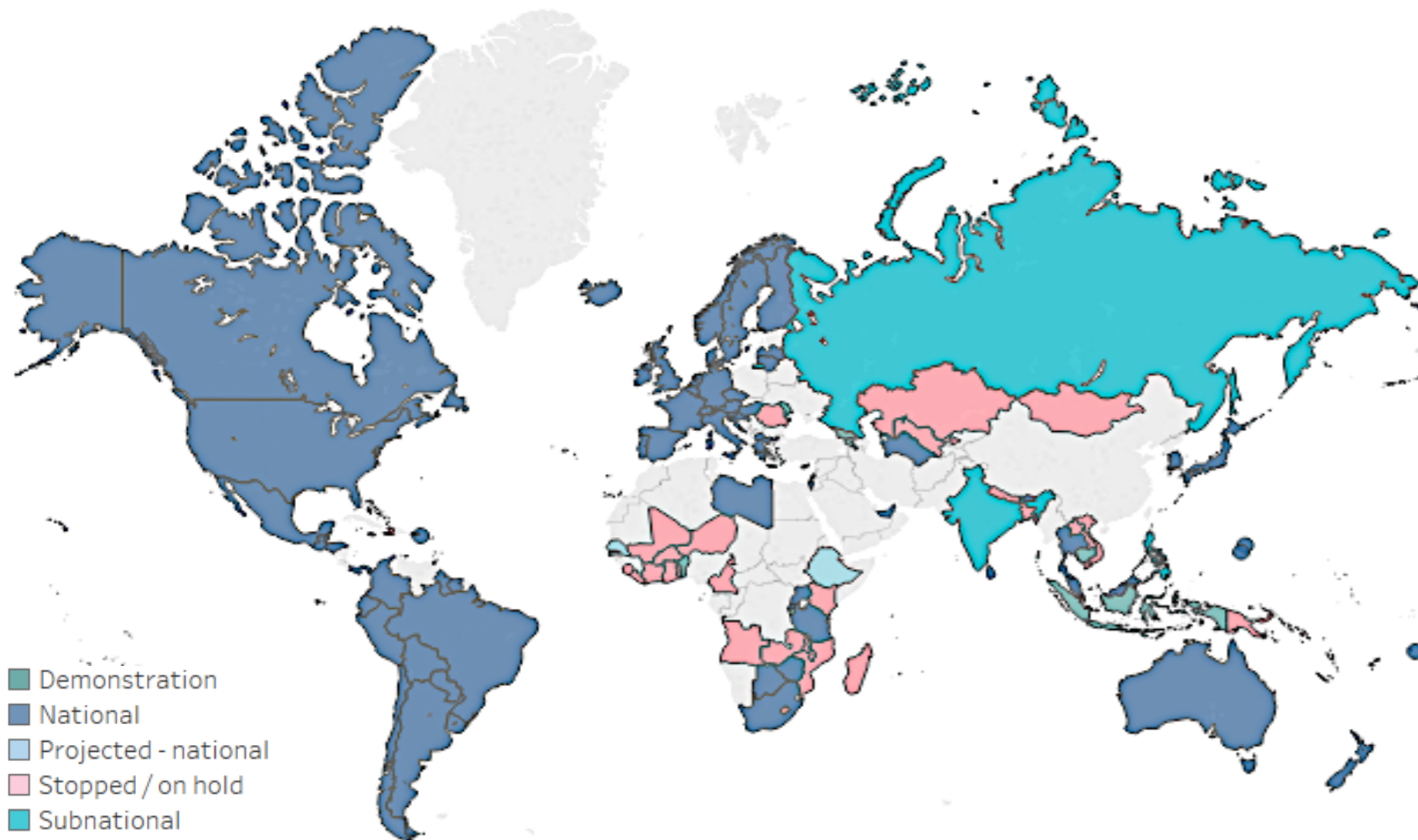
(D) Accumulation of global HPV vaccine experience, October 2016



Progress in HPV vaccination



Global HPV vaccine introduction, 2018



108 countries and territories have HPV vaccine on national schedule.

As of 17 August 2018

FAQ 3

Does giving HPV vaccine encourage promiscuity?

Effect of human papillomavirus (HPV) vaccination on clinical indicators of sexual behaviour among adolescent girls: the Ontario Grade 8 HPV Vaccine Cohort Study

CMAJ, February 3, 2015, 187(2)

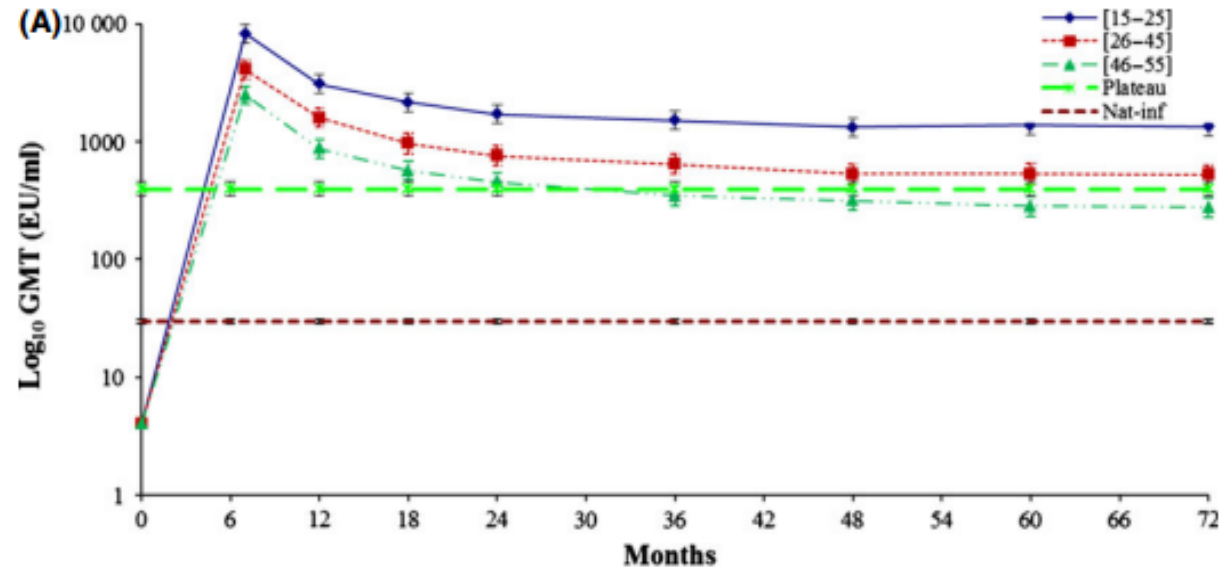
N=260493

- Indicators of sexual behaviour :
 1. **Pregnancy**
 2. **Non-HPV-related sexually transmitted infections** in grades 10–12
- Neither HPV vaccination nor program eligibility increased the risk of pregnancy and non-HPV-related sexually transmitted infections among females aged 14–17 years
- **Concerns over increased promiscuity following HPV vaccination are unwarranted and should not deter from vaccinating at a young age**

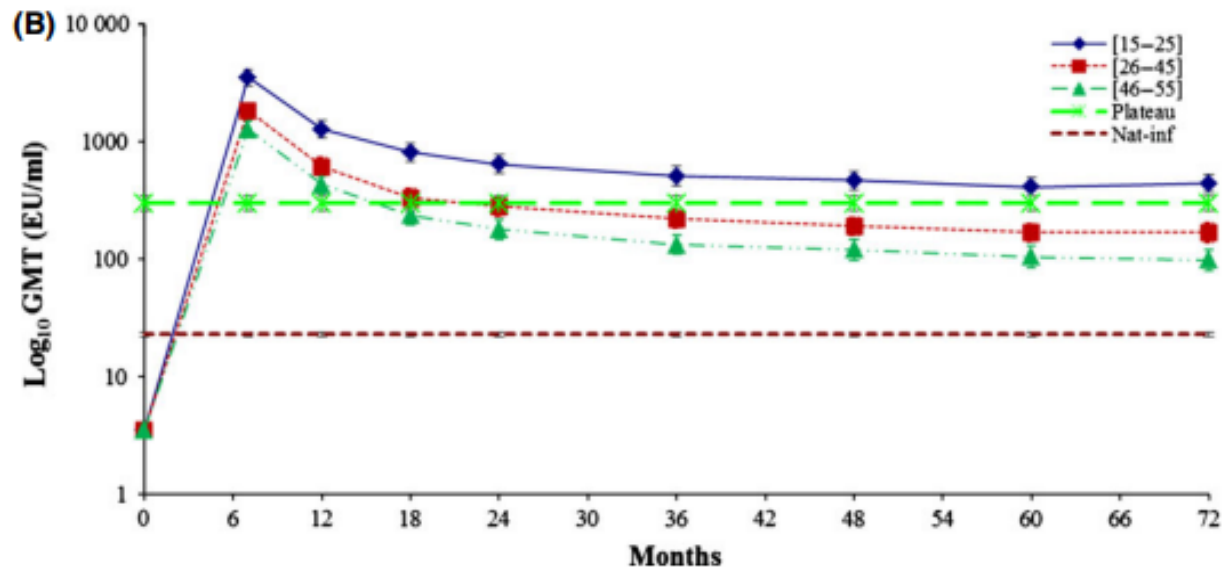
FAQ 4

At 9-14 year, is my daughter too young for vaccination?

Bivalent vaccine: high immunogenicity in Women 15-55 yrs is sustained up to 6 years



- At a younger age group, a brisker immune response results in antibody levels 2-3 times as high as in older women



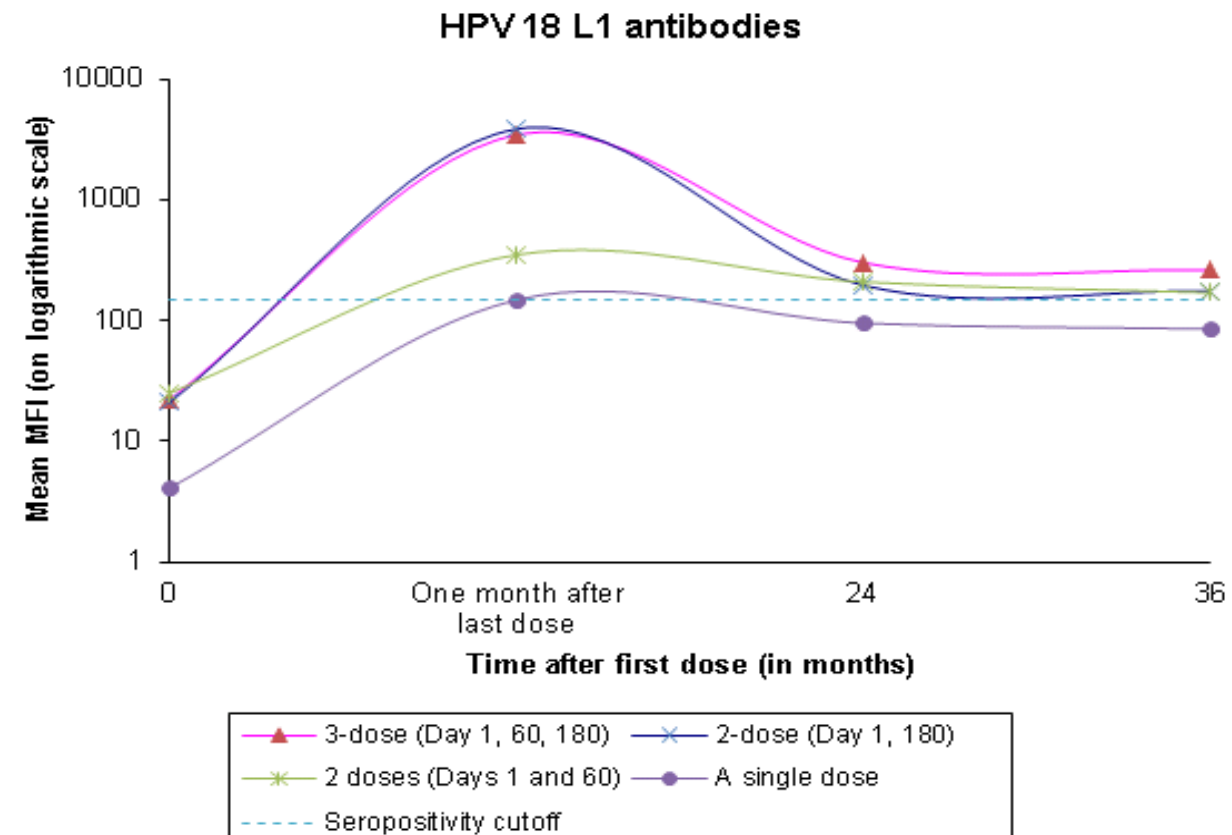
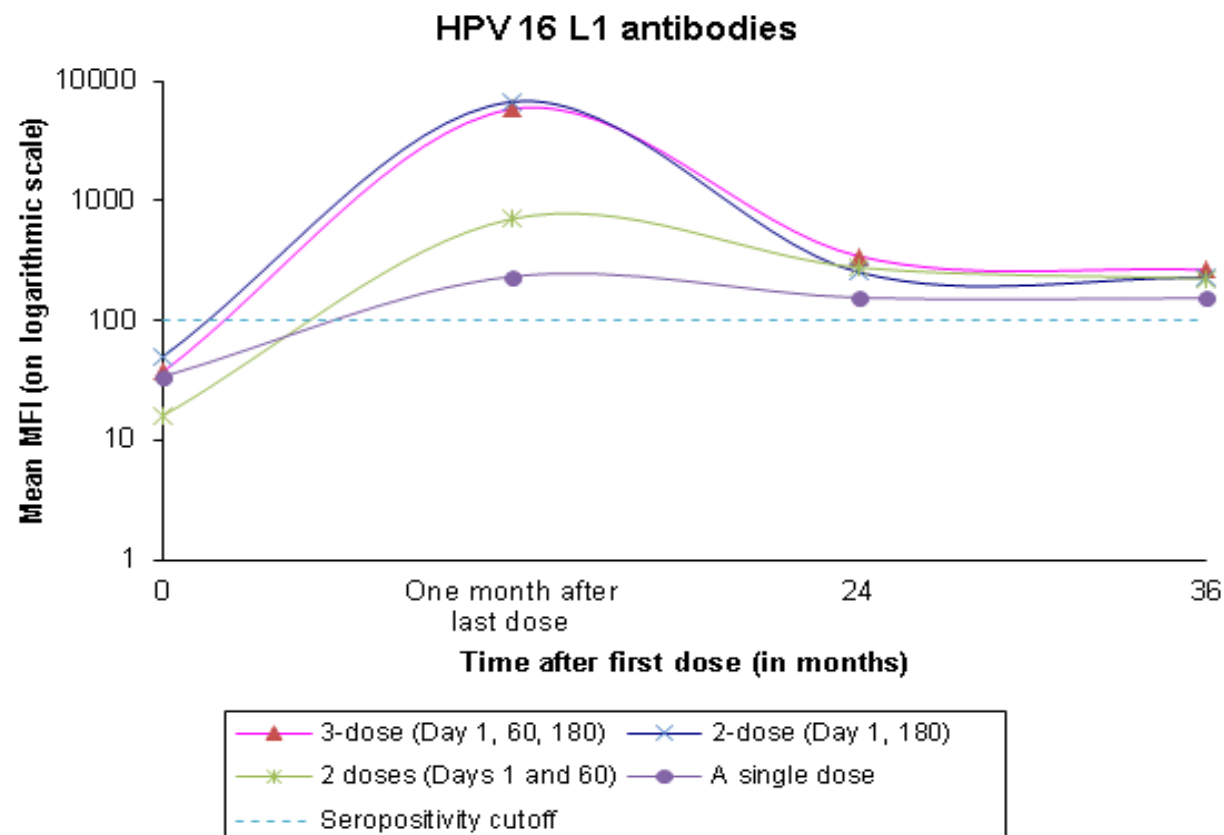
Consensus

- Younger girls mount a brisker immune response and have better antibody titres
- It covers the possibility of an unexpected exposure

Recommended age is **9-14 years**. Most national programs vaccinate age group 11-13 years

Evaluation of less than 3 doses of HPV vaccination in India

Mean MFI values for HPV 16 and 18 L1 antibodies at different time points among girls who completed vaccination per protocol (vaccination at day 1, 60 and 180 (3-dose group) or day 1 and 180 (2-dose group)), and those who did not have their complete vaccine schedules (vaccination at day 1 and 60 or a single dose)



Consensus

- Girls up to 15 years of age at the time of receiving the first dose may receive two doses at 6 months interval but no more than 15 months apart
- Intervals <6 months result in one-tenth of the antibody levels
- Immunocompromised or HPV positive individuals should receive the original three dose regime

Two dose schedules have been approved by WHO for healthy girls aged up to 15 years

Can one dose of HPV vaccine be sufficient?

- Preliminary data suggest that one dose could be sufficient
- WHO's Strategic Advisory Group of Experts (SAGE) has made an off-label recommendation in Nov 2019
- One dose to adolescent girls followed by a delayed second 3-5 years later, while more robust data accumulates

Indian Progress in HPV vaccination

- Approved by NTAGI
- Delhi launched the vaccine program for school girls aged 11 years in 2016
- Punjab launched in Nov 2016
 - CHC based program
 - Class 6 students
 - Allows opt-in approach
- Sikkim statewide program in 2018



Other developments in HPV vaccine

Nonavalent vaccine

- Restricted availability – in India after 2023

Chinese vaccines

- cFDA approval process

Indian HPV vaccine (SIIL)

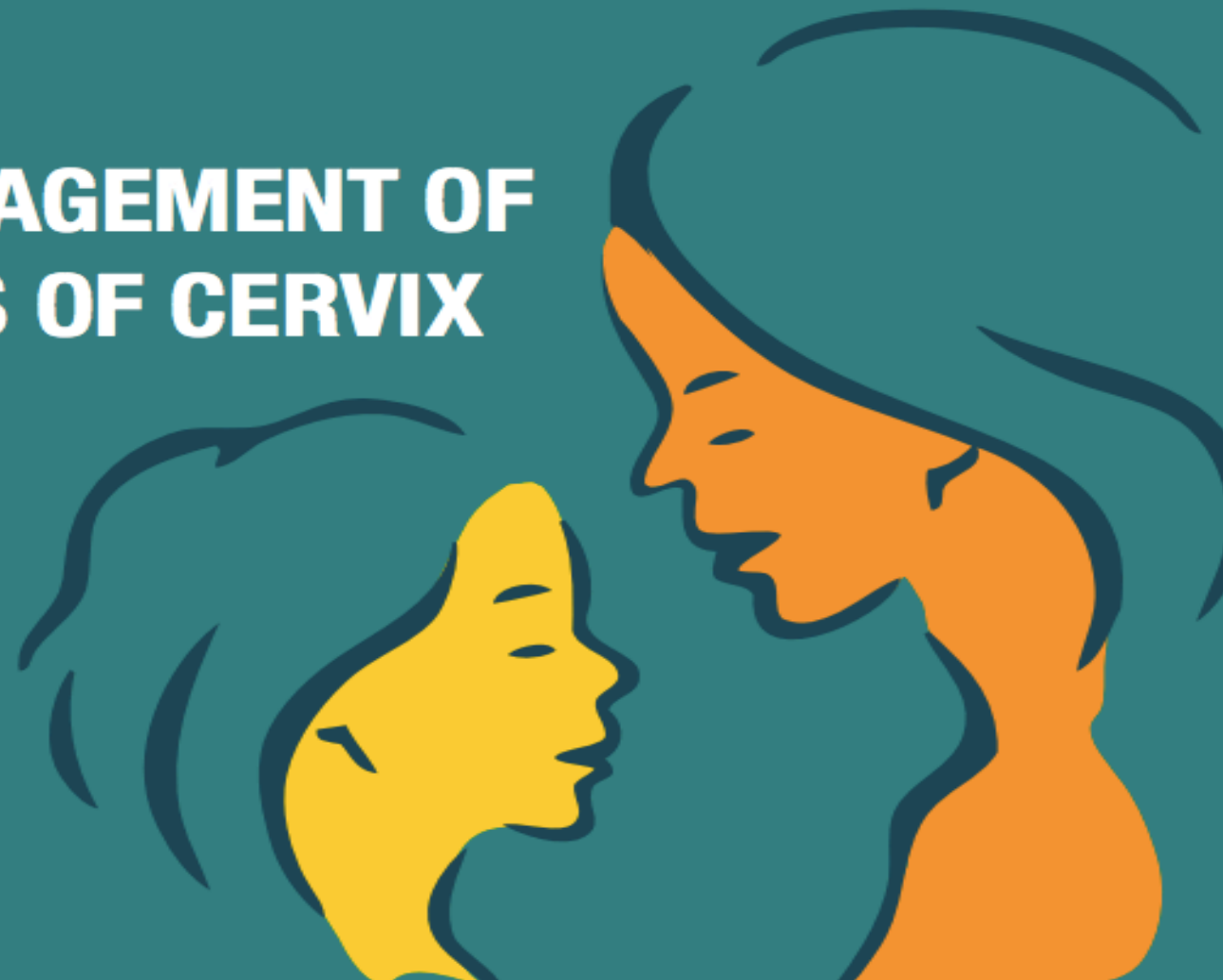
- Multicentric phase II trial is completed – results awaited
- Phase III trial to start soon



FOGSI GCPR

SCREENING AND MANAGEMENT OF PREINVASIVE LESIONS OF CERVIX AND HPV VACCINATION

FOGSI GYNAECOLOGIC ONCOLOGY COMMITTEE
January, 2018



Conclusions

- HPV vaccination is an effective method of cervical cancer prevention
- HPV vaccine is safe and provides long lasting protection
- HPV vaccination is more protective when given to girls between 9 and 14 years
- HPV vaccination requires two doses 6 months apart