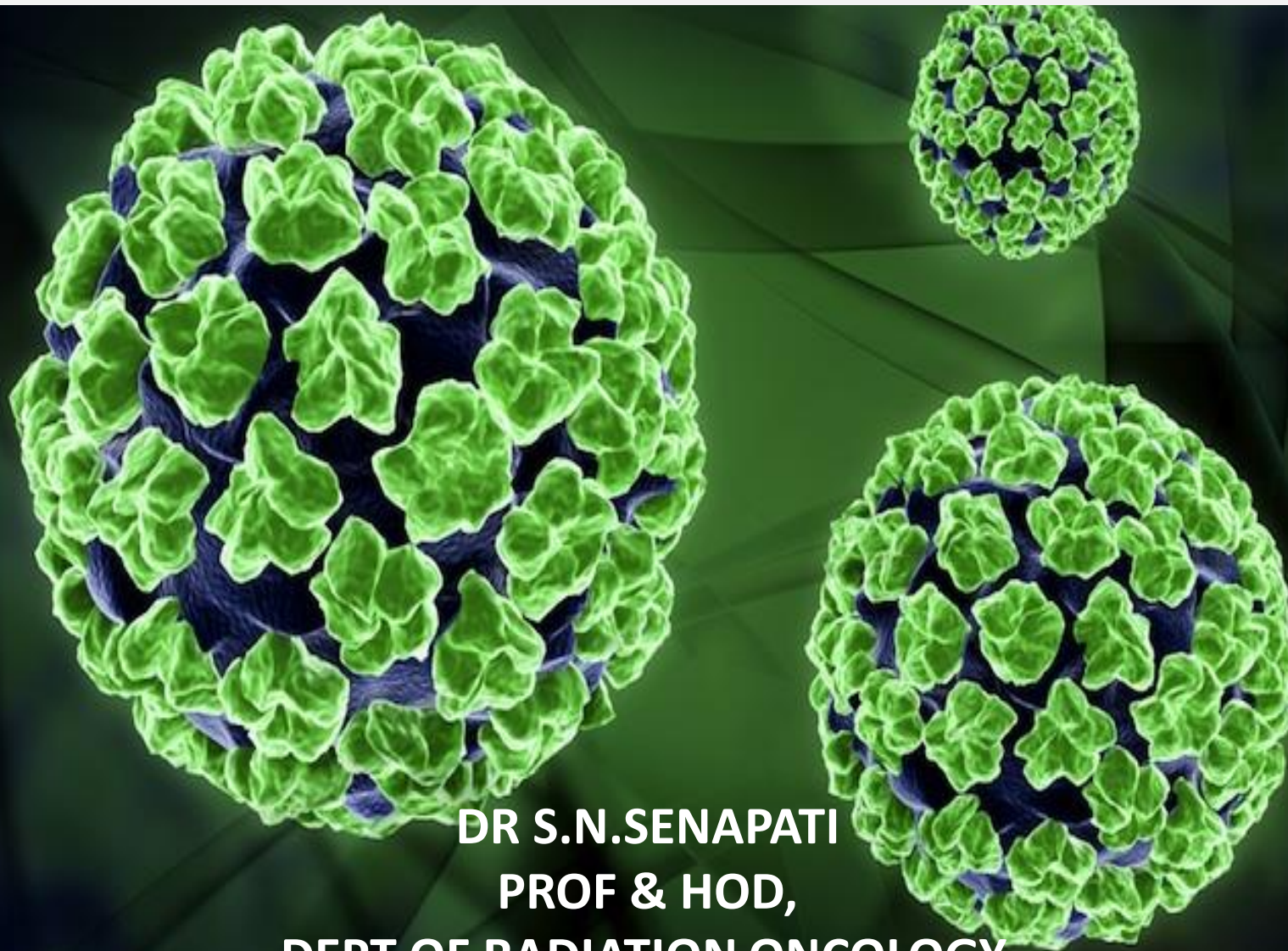


EMERGING DATA ON ROLE OF HPV VACCINE IN CERVICAL CANCER

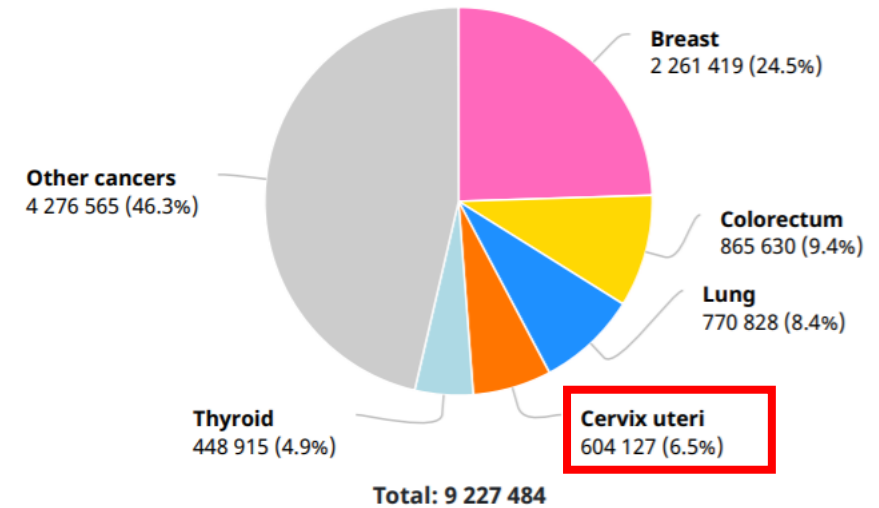


**DR S.N.SENAPATI
PROF & HOD,
DEPT OF RADIATION ONCOLOGY,
AH POST GRADUATE INSTITUTE OF CANCER,
CUTTACK,ODISHA**

CERVICAL CANCER INCIDENCE

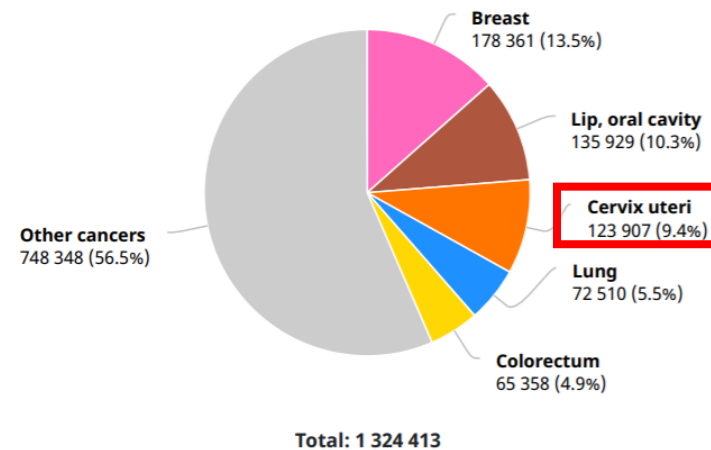
- According to GLOBOCAN 2020
 - Worldwide incidence
 - 4th most common cancer among females and 8th most common cancer overall
 - Accounting for 6.5% (604 127) of all new cases in females and 3.1% of all new cases
 - In India
 - 2nd most common cancer among females and 3rd most common overall
 - Accounting for 18.3% (123 907) of all new cases in females and 9.4% of all new cases

Number of new cases in 2020, females, all ages

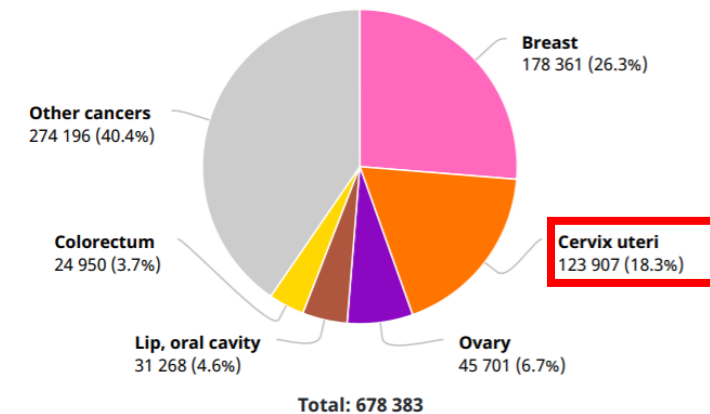


WORLDWIDE

Number of new cases in 2020, both sexes, all ages



Number of new cases in 2020, females, all ages



INDIA

CARCINOMA CERVIX INCIDENCE - GLOBAL Vs INDIAN SCENARIO

Key	Global	India
Women aged 15 years and above who are at risk of developing cervical cancer	2,869 million	483.5 millions
Every year number of women diagnosed with cervical cancer	6,04,127 women	1,23,907 women
Deaths every year due to Cervical cancer	3,41,831 women	77,348 women
Cervical cancer ranks	4 th most frequent cancer among women in the World.	2nd most frequent cancer among women in India

Cervical Cancer Incidence in India 2020

Estimated **1,23,907** new cases per year...with **77,348** deaths...

5,006 deaths per month...

167 deaths per day...

Almost **8** deaths per hour...

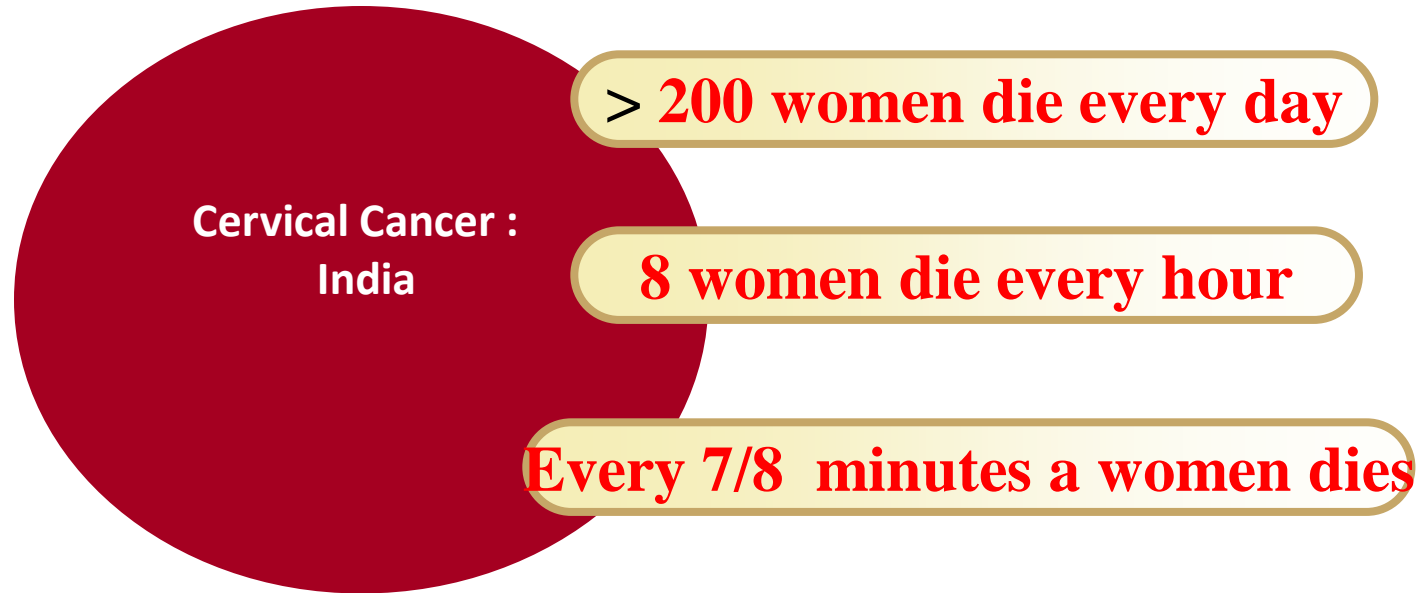
Every 8 Minutes, 1 Woman Dies Of Cervical Cancer In India



Cervical cancer is the 2nd most common cancer among women aged 15 to 44 years in India

Cervical Cancer in India

- The alarming facts



This 'Cause' need to be taken up by multiple stake holders.

Public health issue needs urgent attention and action



1 out of 4

***women who die due to Cervical Cancer in the world is an Indian**

**Human
Suffering**

Due To

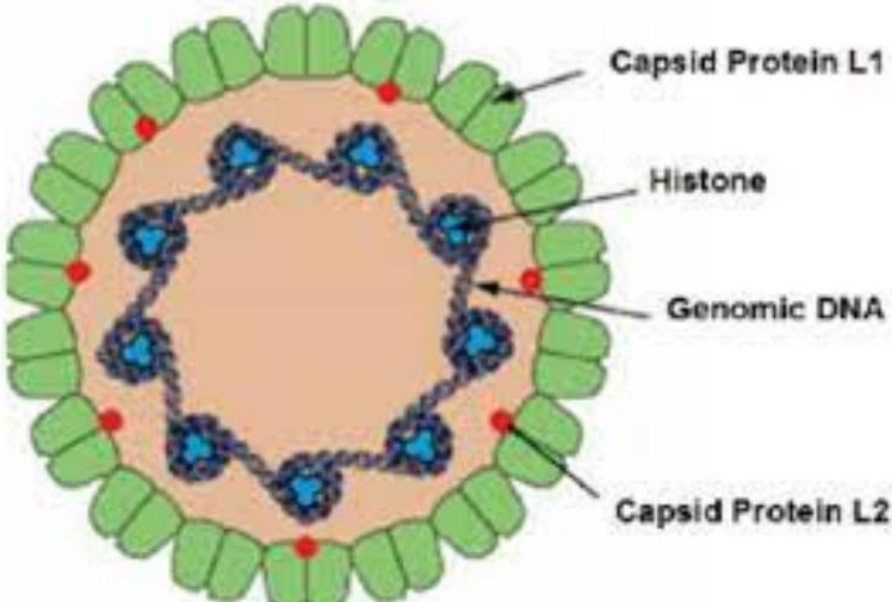
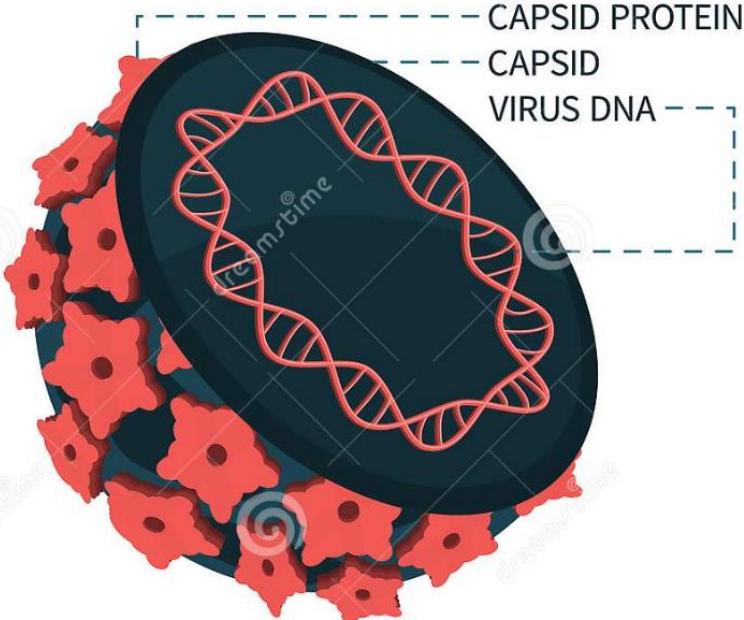
**Cervical
Cancer in India**

Is depressing

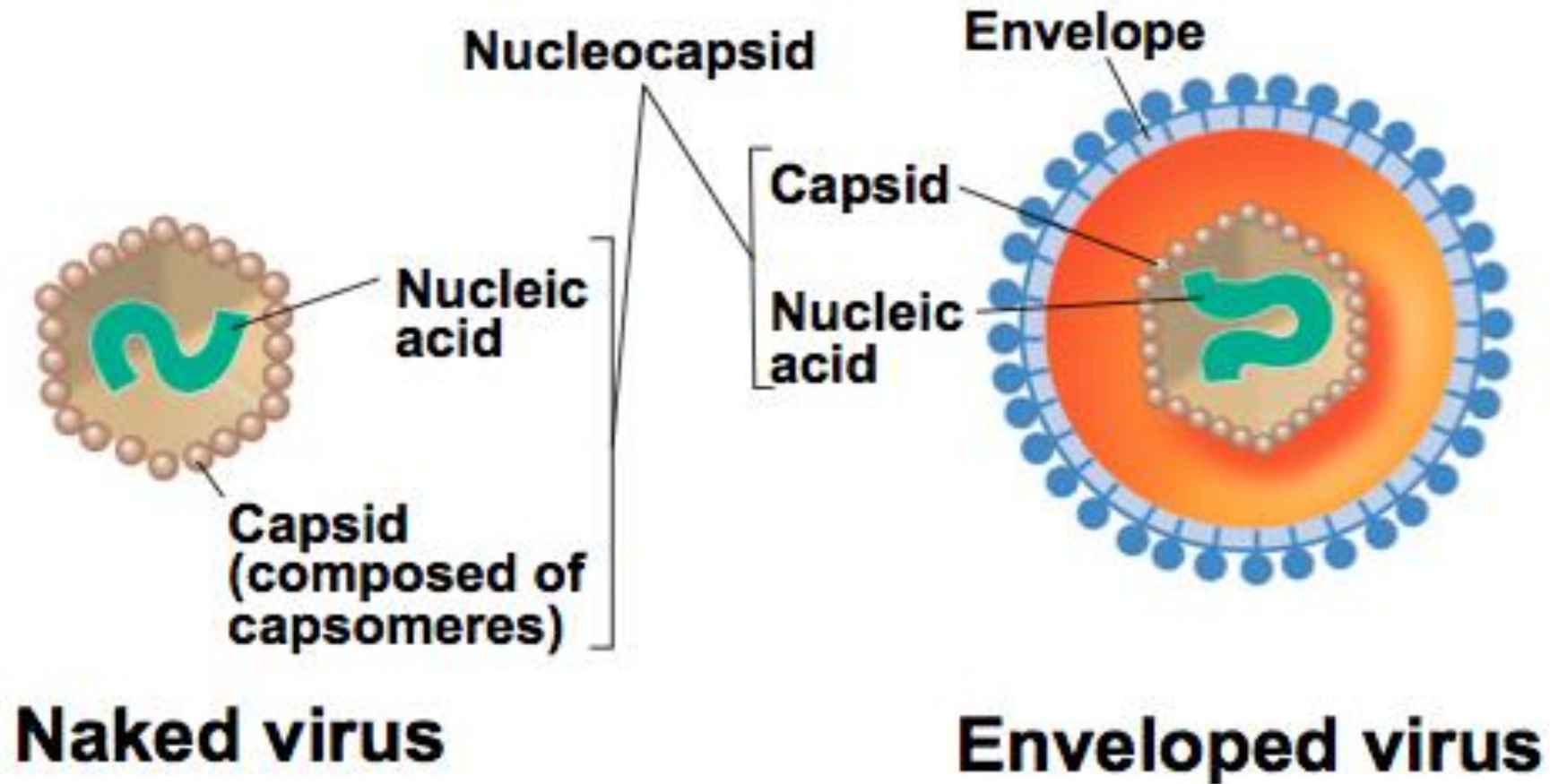
**ONE FOURTH OF WORLD'S CANCER CERVIX IS IN INDIA .
LACK OF EFFECTIVE SCREENING PROGRAMMES.
PERSISTENT INFECTION WITH HR HPV IS A NECESSARY CAUSE**

HPV

HUMAN PAPILOMAVIRUS HPV



STRUCTURE OF A VIRUS



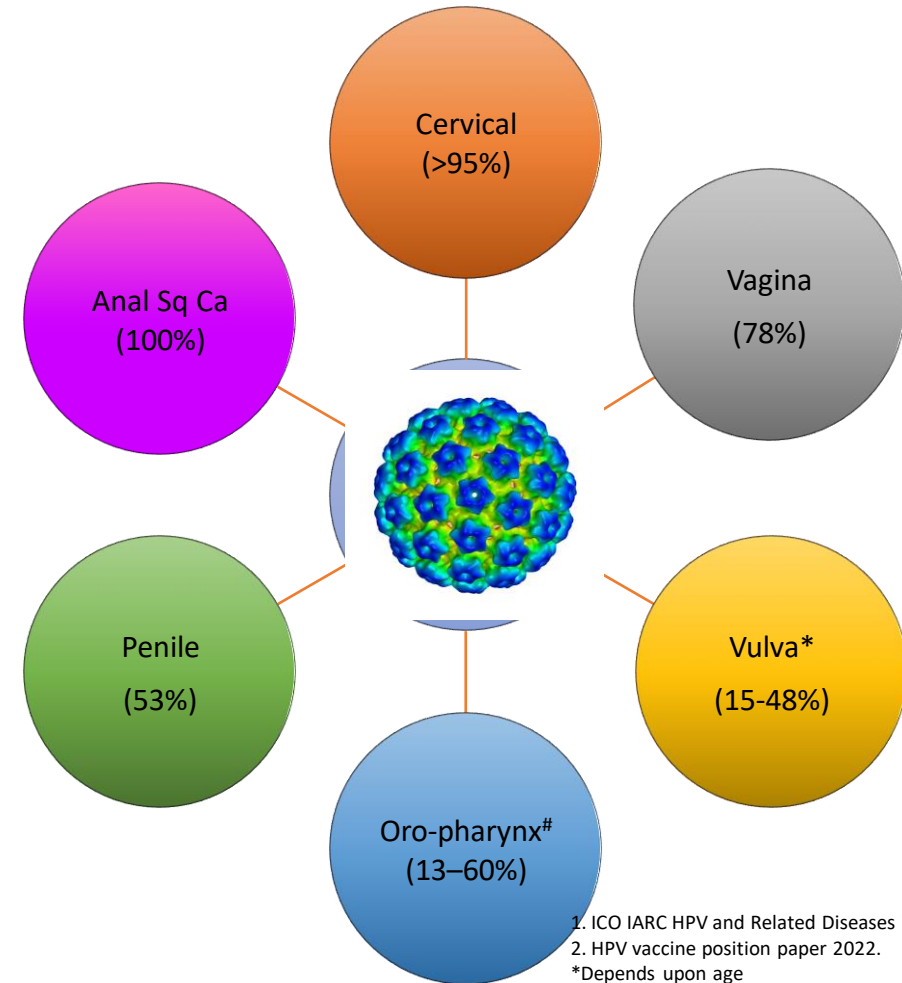
HPV RELATED DISEASES

- ▶ HPV - MOST COMMON VIRAL INFECTION OF REPRODUCTIVE TRACT; CAUSES A RANGE OF CONDITIONS IN MEN & WOMEN, INCLUDING PRECANCEROUS LESIONS THAT MAY PROGRESS TO CANCER.
- ▶ LOW-RISK HPVS (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81)
- ▶ HIGH-RISK (ONCOGENIC) - THERE ARE ABOUT 14 HIGH-RISK HPV TYPES (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, AND 68).
- ▶ HPV16 AND HPV18, ARE RESPONSIBLE FOR MOST HPV-RELATED CANCERS.

BURDEN OF CERVICAL HPV INFECTION IN INDIA¹:

- ▶ PREVALENCE (%) OF HPV 16 AND/OR HPV 18 AMONG WOMEN WITH:
 - LOW-GRADE CERVICAL LESIONS (LSIL/CIN-1) - 28.2%
 - HIGH-GRADE CERVICAL LESIONS (HSIL/CIN-2/CIN-3/CIS) 62.8%
 - CERVICAL CANCER - 83.2%

Percentages of cancers attributable to HPV globally²



1. ICO IARC HPV and Related Diseases in India.2021

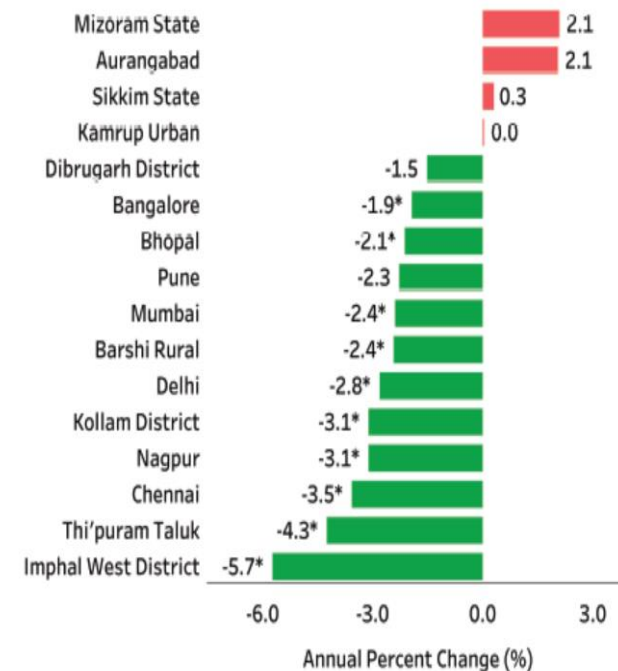
2. HPV vaccine position paper 2022.

*Depends upon age

#Depending upon geographical location

INCIDENCE OF HPV IN INDIA

- Nine out of ten HPV related cancers are cervical cancers in India.
- Papumpare district and Aizawl district in north eastern India reported the highest age adjusted incidence rate (AAR) of 27.7 and 27.4 per 100,000 women and
- Lowest AAR (4.8 per 100,000) in Dibrugarh district, Assam

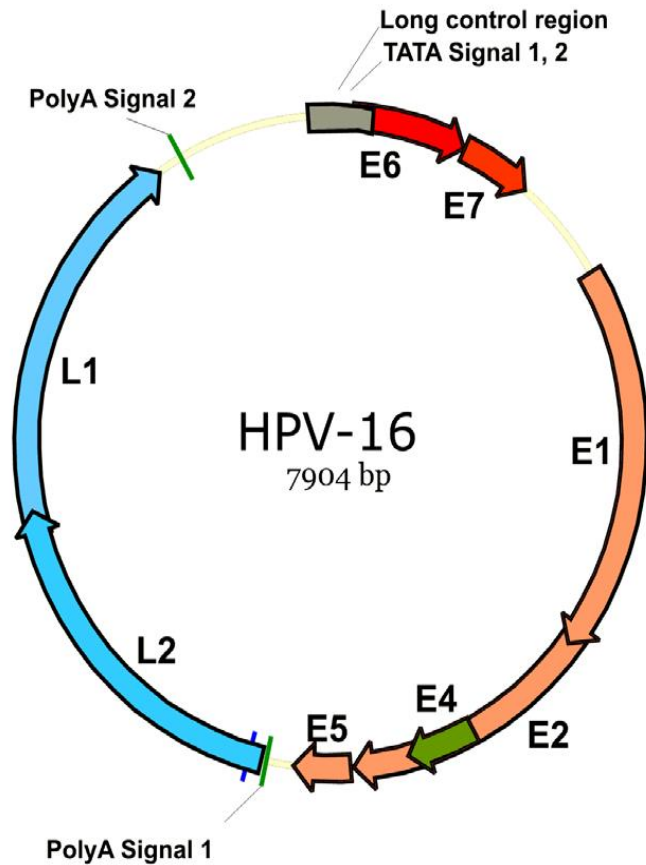


*Increase in APC, Decrease in APC ; *Significant increase or decrease in APC at 95% confidence level*

Figure 2. Annual Percent Change (APC) in age adjusted incidence rates (AARs) over the time period for cervical cancer

Ramamoorthy Thilagavathi, Sathishkumar Krishnan, Das Priyanka, Lakshminarayana Sudarshan Kondalli, Mathur Prashant (2022) **Epidemiology of human papillomavirus related cancers in India: findings from the National Cancer Registry Programme** *ecancer* 16 1444

HPV GENOME



	FUNCTION
E6	DESTRUCTION OF P53 TUMOR SUPPRESSOR PROTEIN
E7	INACTIVATION OF pRB TUMOR SUPRESOR PROTEIN
E1	VIRAL DNA REPLICATION
E2	VIRAL DNA REPLICATION AND REPRESSION OF E6 AND E7
E5	INTERACTION WITH EPIDERMAL GROWTH FACTOR
L1	MAJOR CAPSID PROTEIN
L2	MINOR CAPSID PROTEIN

HPV VS. PREMALIGNANT & MALIGNANT NEOPLASM

summary

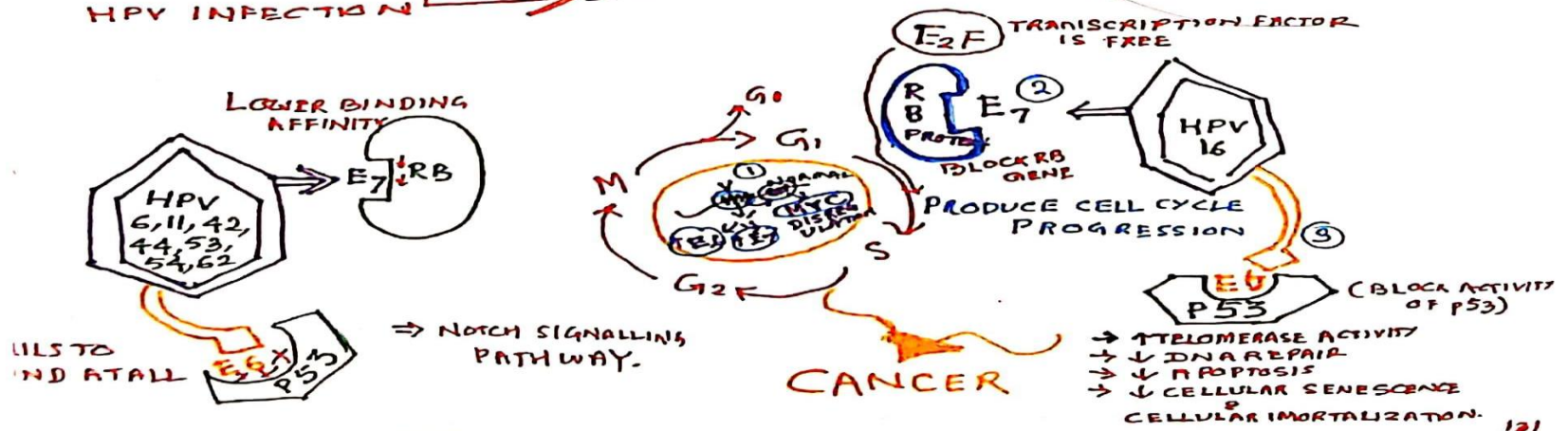
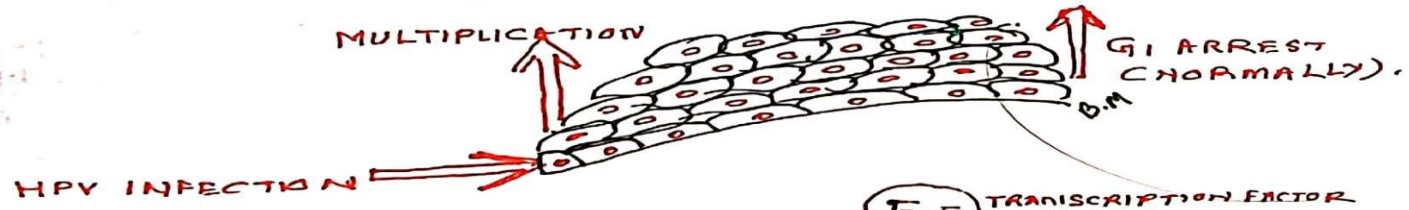


PEER INFECTION AT :- 20-29 YRS
SUBSEQUENTLY ↓ DUE TO
- ACQUISITION OF IMMUNITY
- MONOGAMOUS RELATION.

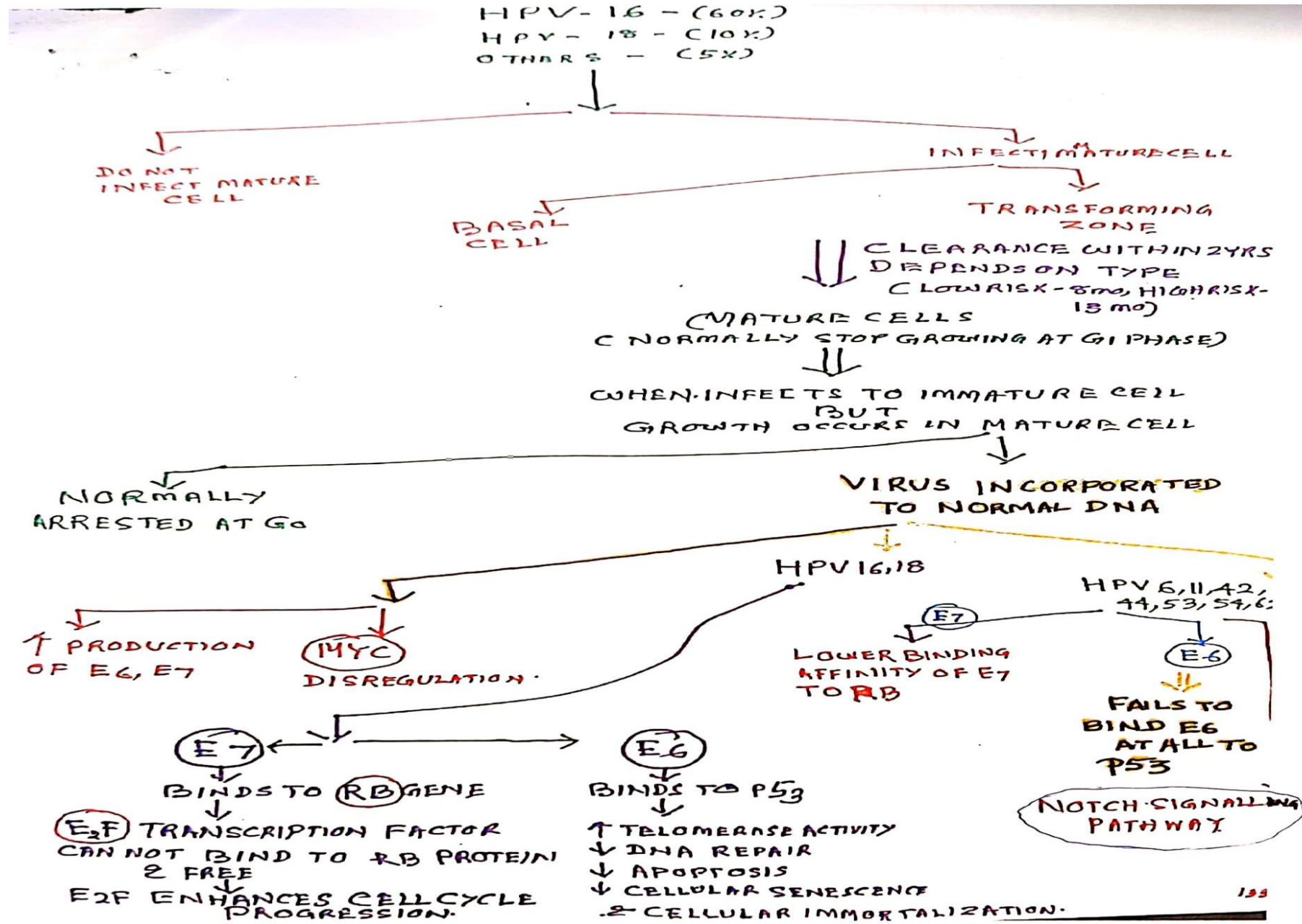
CLEARANCE OF HPV INFECTION
(MOSTLY WITHIN 2 YRS, DEPENDS ON TYPE, LOW RISK - 8 MO, HIGH RISK - 13 MO)
50% CLEARED WITHIN - 8 MO, 90% CLEARED WITHIN - 13 MO.

PERSISTENCE OF INFECTION

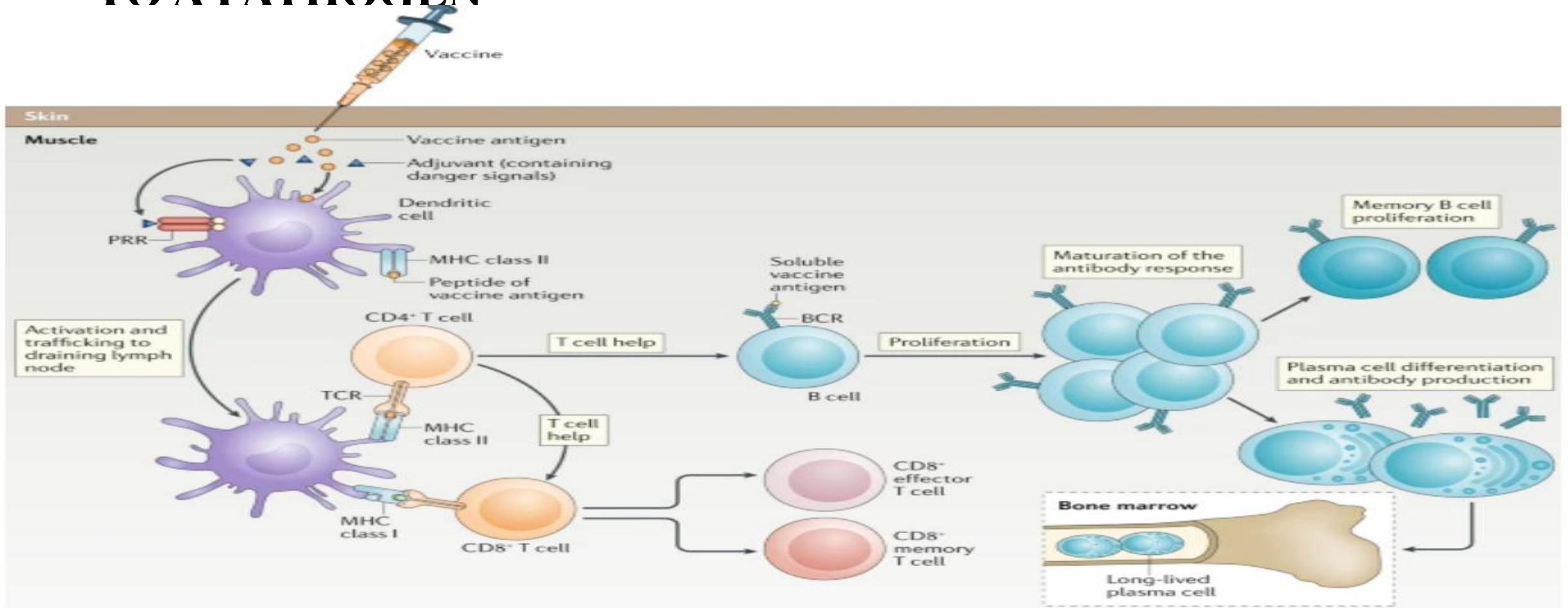
GROWTH OF VIRUS TAKES PLACE IN MATURE CELL.
(NORMALLY MATURE CELL GROWTH ARREST AT G0)



HPV MECHANISM OF ONCOGENESIS



VACCINE:- DEFINITION - A VACCINE IS A BIOLOGICAL PRODUCT THAT CAN BE USED TO SAFELY INDUCE AN IMMUNE RESPONSE THAT CONFERS PROTECTION AGAINST INFECTION AND/OR DISEASE ON SUBSEQUENT EXPOSURE TO A PATHOGEN







The vaccine injected into muscle and

1. The protein **antigen is taken up by dendritic cells**,
 - **Dendritic cells are activated** through pattern recognition receptors (PRRS) by danger signals in the adjuvant, and then **trafficked to the draining lymph node**.
 - Here, the **presentation of peptides of the vaccine protein antigen by MHC molecules (MHC I AND II)** on the dendritic cell **activates T cells through their T cell receptor (TCR)**.
2. MHC II mediated T cell activation activates CD4+ T cells (**activates antibody mediated immunity**)
 - In combination with signalling (by soluble antigen) through the B cell receptor (BCR), the **CD4+ T cells drive B cell development in the lymph node**.
 - Here, the CD4+ T cell-dependent B cell development **results in maturation of the antibody response to increase antibody affinity and induce different antibody isotypes**.
 - The production of **short-lived plasma cells**, which actively secrete antibodies specific for the vaccine protein, **produces a rapid rise in serum antibody levels** over the next 2 weeks.
 - **Memory B cells are also produced, which mediate immune memory**.
 - **Long-lived plasma cells** that can continue to produce antibodies for decades **travel to reside in bone marrow niches**.
3. MHC I mediated T cell activation activates CD 8+ T cells (**activates cell mediated immunity**)
 - **CD8+ memory T cells** can proliferate rapidly when they encounter a pathogen, and
 - **CD8+ effector T cells** are important for the elimination of infected cells.


WHO URGES NATIONS TO PACE UP EFFORTS

May 2018: WHO Director General's Call to Action to Eliminate Cervical Cancer as a Public Health Problem



 World Health Organization (WHO)   
@WHO

WHO Director-General @DrTedros calls for all countries to take action to help end the suffering caused by #CervicalCancer bit.ly/2Izh9vB



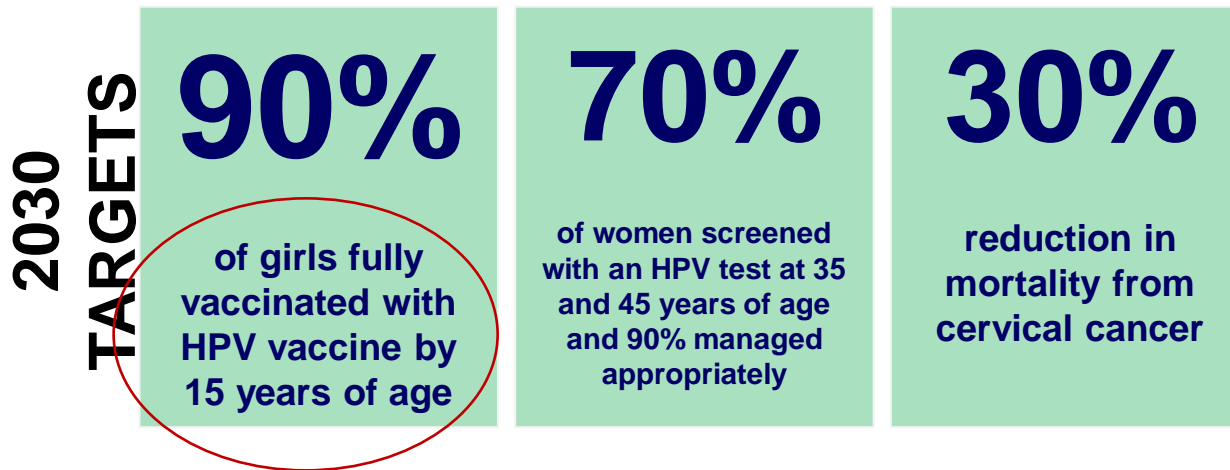
We can eliminate **cervical cancer** as a public health problem through intensified vaccination against HPV, screening and treatment.



2020-2030 Acceleration plan towards elimination

Vision: A world without cervical cancer

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



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

HPV Introduction: Global Status

- **HPV vaccine has been licensed in about 137 countries across the world.**
- **The vaccine so far has been introduced in National Immunization Program of 67 countries or 34.5% of the world.**
- **The primary objectives of HPV vaccines are to prevent cervical and other genital cancers.**
- **HPV vaccine has high efficacy ranging from 90% to 100% and can prevent significant proportion of cases of cervix cancer and deaths associated with HPV 16 and 18.**

Primary prevention

90%

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

71.4 million girls (9-14 years) in India in 2020
90% of that is 64.3 million
Every year 1.14 million entrants to this cohort

Implementation of HPV vaccine program

JCO® Global Oncology
An American Society of Clinical Oncology Journal



Stemming the Wave of Cervical Cancer: Human Papillomavirus Vaccine Introduction in India


 Check for updates

[Ravi Mehrotra](#) , [Roopa Hariprasad](#), [Preetha Rajaraman](#), [Vini Mahajan](#), [Rajesh Grover](#), [Prabhdeep Kaur](#),

THE LANCET
Oncology

Current status of human papillomavirus vaccination in India's cervical cancer prevention efforts

[Rengaswamy Sankaranarayanan, MD](#) • [Partha Basu, MD](#)   • [Prabhdeep Kaur, DNB](#) • [Rajesh Bhaskar, MD](#) • [Gurinder Bir Singh, MD](#) • [Phumzay Denzongpa, MBBS](#) • et al. [Show all authors](#)

Published: November, 2019 • DOI: [https://doi.org/10.1016/S1470-2045\(19\)30531-5](https://doi.org/10.1016/S1470-2045(19)30531-5)  Check for updates

2016- Delhi first state to implement opportunistic HPV vaccination for school girls aged 11–13 years

No severe adverse events

Programme was limited in its reach



Govt. of Punjab- operational guidelines for HPV vaccination (technical inputs of ICMR, WHO, UNICEF)

Campaign mode in two districts: Bathinda and Mansa

November 2016- Phase 1 started, excellent coverage, **98%** (9672/9922) completed two doses

November 2017- Phase 2 completed, first dose received by **94%** (15,140/16,106) and **99%** (14,988 /15,140) received second dose



2018- Sikkim first state to completely vaccinate girls aged 9–14 years

25,284 girls in 1166 schools; first dose received by **97%** girls with a second dose 6 months later

Minor adverse events- headache, dizziness, nausea, pain at injection site

Subsequently followed by inclusion of vaccination of girls at nine years in **routine immunization schedule**

RECOMMENDED TARGET POPULATION

- **Females/girls:**
- **Age: 9-13 years**
- **Before onset of sexual activity**

- **Who should NOT receive HPV vaccination?**
 - **Pregnant women**
 - **Girls younger than 9 years of age**
 - **Persons with Severe febrile illness**
 - **Persons with a life-threatening allergy to any component of the vaccine**

VACCINE SCHEDULE

FDA-approved HPV Vaccines

Vaccine	Coverage (HPV types)	Gender and age range
Cervarix (bivalent HPV vaccine)*	HPV 16 and 18	Females, 9-25 y
Gardasil (quadrivalent HPV vaccine)	HPV 6, 11 (genital warts), 16, and 18	Males and females, 9-26 y
Gardasil 9 (9-valent HPV vaccine)	HPV 6, 11 (genital warts), 16, 18, 31, 33, 45, 52, and 58	Males and females, 9-26 y

*Recently taken off the market in the United States.

Abbreviation: HPV, human papillomavirus.

Sources: Markowitz et al. *MMWR Recomm Rep*. 2014²; ACOG. 2017⁶;

Meites et al. *MMWR Morb Mortal Wkly Rep*. 2016.⁷

Vaccines Available



Bivalent

Cervarix

Licensed 2010

Nonavalent Vaccine

SII, Indigenous



Quadrivalent

Gardasil

Licensed 2009

Recombinant DNA technology, No biological products or viral DNA used



axoSmithKline) and quadrivalent Gardasil (4vHPV, Merck) are the world.



HPV vaccine being distributed in the United States.

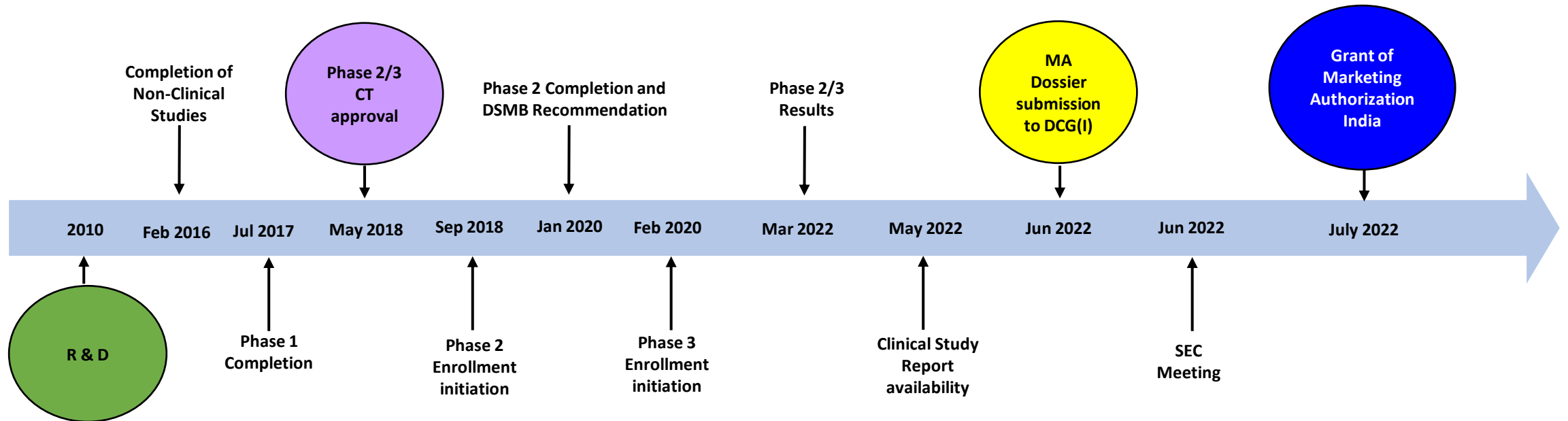
licensed by the Food and Drug Administration in 2014.

) HPV types (16, 18, 31, 33, 45, 52 and 58) and two HPV and 11).

es and males age 9 to 26 years.

Figure 3: Enlisting three commercially available HPV vaccines. The three major commercially available and FDA approved HPV vaccines available commercially are Gardasil, Cervarix and Gardasil9. A comparative analysis of the Phase III clinical trials shows high efficacy for all the three vaccines with Gardasil9 being effective for five more HPV subtypes w.r.t to Gardasil.

CERVAVAC Development Timeline



CT – Clinical Trial
CSR- Clinical Study Report
DCG(I)– Drug Control General of India
MA– Marketing Authorization
SEC– Subject Expert Committee
R & D- Research and Development

CERVAVAC - Product Information

Target Population

CERVAVAC is indicated in 9 through 26 years of age (girls/women and boys/men) for the prevention of the diseases caused by Human Papillomavirus (HPV) types 6,11,16 and 18.

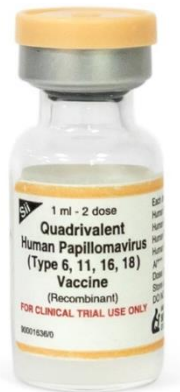
Name of the ingredient	Quantity	Function
Active Ingredients		
Human Papillomavirus type 6 L1 protein	≥ 20 µg	Immunogen
Human Papillomavirus type 11 L1 protein	≥ 40 µg	
Human Papillomavirus type 16 L1 protein	≥ 40 µg	
Human Papillomavirus type 18 L1 protein	≥ 20 µg	
Inactive ingredients		
Aluminium hydroxide (as Al ⁺⁺⁺)	≤ 1.25 mg	Adjuvant

Name of the ingredient	Quantity	Function
Residuals from DS		
L-Histidine	0.78 mg	Stabilizer
Polysorbate 80	50 mcg	Stabilizer
Sodium Chloride	9.56 mg	Tonicity Modifier
Water for Injection (WFI)	q.s.	Vehicle

Note: Tris base and Glacial Acetic acid are used for pH adjustment.

Mode of Administration, Presentation and Storage condition

- The vaccine is administered by an **intramuscular injection**.
- **Presentation:** 1-dose and 2-dose vial (without preservative).
- **Dose:** 0.5 mL
- **Vaccination Schedule :**
 - Aged 9-14 years (2 dose) - 0 and 6 months
 - Aged 15-26 years (3 dose) - 0, 2 and 6 months
- **Store in refrigerator (2° C to 8° C), Do not freeze.**
Once opened, multi-dose vials should be used as soon as practically possible and within 6 hours when kept between +2°C and +8°C.
- **Shelf life : 36 months**



HPV Vaccine Dosing Schedules Based on Age

Age (males and females)	Doses	Schedule
9-14 y*	2-dose series [†]	Dose 1: 0 mo Dose 2: 6-12 mo
15-26 y	3-dose series	Dose 1: 0 mo Dose 2: 1-2 mo Dose 3: 6 mo

*Populations with primary or secondary immunocompromising conditions should receive the 3-dose series regardless of age.

†If a second dose is given earlier than five months after the first dose, a third dose is needed at least four months after the second dose. If the first dose of any type of vaccine is given before age 15 and six months have passed, only a second dose is needed. The 9-valent vaccine can be used to complete the schedule if started with bivalent or quadrivalent vaccine.

Source: Meites et al. *MMWR Morb Mortal Wkly Rep.* 2016.⁷

ADVISORY COMMITTEE ON IMMUNISATION PRACTICES RECOMMENDATION

- **2 DOSES:- BEFORE 15Th BIRTHDAY.**
- **DOSES SHOULD BE SEPARATED BY 6 TO 12 MONTHS.**
- **THE MINIMUM INTERVAL IS 5 CALENDAR MONTHS.**
- **IF LESS A THIRD DOSE IS GIVEN AT LEAST SIX MONTHS AFTER THE FIRST DOSE.**
- **A 3-DOSE RECOMMENDED :- IF VACCINATION STARTS AFTER 15TH BIRTH DAY AND IMMUNOCOMPROMISING CONDITIONS (CANCER, HIV INFECTION, OR TAKING IMMUNOSUPPRESSIVE DRUGS).**
- **TIMING:-SECOND DOSE -1 TO 2 MONTHS AFTER FIRST DOSE**
- **THIRD DOSE 6 MONTHS AFTER THE FIRST DOSE.**
 - **THE MINIMUM INTERVAL BETWEEN THE FIRST AND SECOND DOSES OF VACCINE IS 4 WEEKS.**
 - **THE MINIMUM INTERVAL BETWEEN THE SECOND AND THIRD DOSES OF VACCINE IS 12 WEEKS.**
 - **THE MINIMUM INTERVAL BETWEEN THE FIRST AND THIRD DOSES IS 5 CALENDAR MONTHS.**



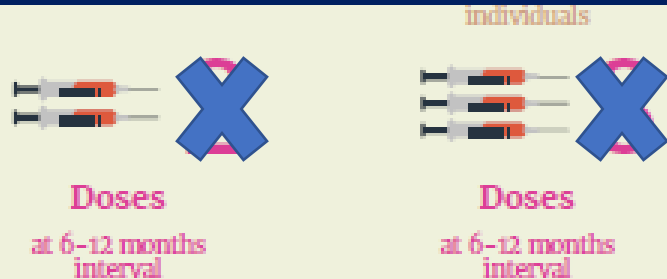
SAGE RECOMMENDATIONS

1 or 2 dose ,9 to 14 years.

1 or 2 dose, 15 to 20 years.

2 doses > 21 years

3 doses in immunocompromised



**2 doses
beyond.**

The single dose
recommendation will take us
faster to our goal.

SINGLE Vs MULTIDOSE HPV VACCINE

SYSTEMATIC REVIEW

HILARY S et al

one HPV vaccine dose may be as effective in preventing HPV infection as multi-dose schedules in healthy young women. However, it also highlights the paucity of available evidence from purpose-designed, prospectively-randomised trials

COSTARICA VACCINE TRIAL

PATRICIA TRIAL

PARTHA BASU et al

SINGLE DOSE OF HPV VACCINE PROVIDES SIMILAR PROTECTION AGAINST PERSISTENT INFECTION FROM HPV-16 AND 18 TO THAT OF TWO OR THREE DOSES

SOME FACTS ABOUT HPV VACCINE

- CATCH UP VACCINATION;-21-26 YRS,2 DOSES
- SEXUAL ABUSE VICTIM:-3 DOSES. **FOGSI GCPR 2018**
- **CERVAVAX RECOMMENDED FOR MALE**
- HPV VACCINE IS RECOMMENDED FOR FEMALES AND MALES REGARDLESS OF THEIR SEXUAL ORIENTATION
- SCREENING STILL NECESSARY FOR WOMEN AFTER HPV VACCINE?RECOMMENDED
- THE VACCINE DOES NOT PROVIDE PROTECTION AGAINST ALL TYPES OF HPV THAT CAUSE CERVICAL CANCER, SO EVEN VACCINATED WOMEN WILL STILL BE AT RISK FOR SOME CANCERS FROM HPV.
- ACIP AND WHO RECOMMEND VACCINATION WITH 3 DOSES OF HPV VACCINE FOR FEMALES AND MALES AGE 9 TO 26 YEARS WITH PRIMARY OR SECONDARY IMMUNOCOMPROMISING CONDITIONS

SOME FACTS ABOUT HPV VACCINE

- **SEXUALLY ACTIVE:-**
 - **HPV VACCINATION IS MOST EFFECTIVE WHEN GIVEN BEFORE SEXUALLY ACTIVE.**
 - **STILL BENEFITED FROM BEING VACCINATED.**
 - **WOMEN WHO HAVE ALREADY BEEN INFECTED ;- STILL BE PROTECTED FROM OTHER HPV TYPES IN THE VACCINE THAT HAVE NOT BEEN ACQUIRED**
- **IF DELAYED A DOSE**
 - **DO NOT START THE ALL THE DOSES.START WHERE LEFT**
- **PREGNANCY:-SHOULD NOT GET THE VACCINE.**
- **BREAST FEEDING:- MAY SAFELY GET THE VACCINE.**
- **ALLERGY:- ANY ONE WHO HAS EVER HAD THESE SHOULD NOT GET THE VACCINE**
- **PEOPLE WITH MODERATE OR SEVERE ILLNESSES :-SHOULD WAIT UNTIL THEY RECOVER**
- **COADMINISTER:-CAN BE SAFELY COADMINISTERED WITH OTHER VACCINES.(DIPHTHERIA,TETANUS,PERTUSIS ,HEPATITIS B)**

SAFETY?

- More than 270 million doses of HPV vaccines have been administered worldwide. Over 10 million doses of Gardasil 9 have been given in the US in the past year.
- The Global Advisory Committee on Vaccine Safety of the World Health Organization has reviewed all published and emerging data about the vaccines in real world use and declared HPV vaccines safe for use seven times so far.
- All people are monitored for 15 minutes after having the vaccine. If an allergic reaction does occur, it can be treated quickly and successfully –
- Every immunisation provider is trained and equipped to deal with such a reaction.

SIDE EFFECTS

- Pain at the injection site (about eight people in 10)
- Redness or swelling at the injection site (about one person in 10)
- Mild fever (100 F) (about one person in 10)
- Itching at the injection site (about one person in 30)
- Moderate allergic reactions (about one person in 65)

All suspected AEFI should be immediately reported to the respective authorities.

- Life-threatening allergic reactions from vaccines are very rare.
- Vaccine Adverse Event Reporting System (VAERS)

Vaccine hesitancy

Sexual
promiscuity

Cost
effective

Side effects



DOUBT
KILLS
MORE
DREAMS
THAN
FAILURE
EVER
WILL

Vaccine Hesitancy

Tell parents that **almost everyone gets HPV** and HPV can cause a variety of cancers in women and men

Remind parents that
HPV vaccine is for cancer prevention

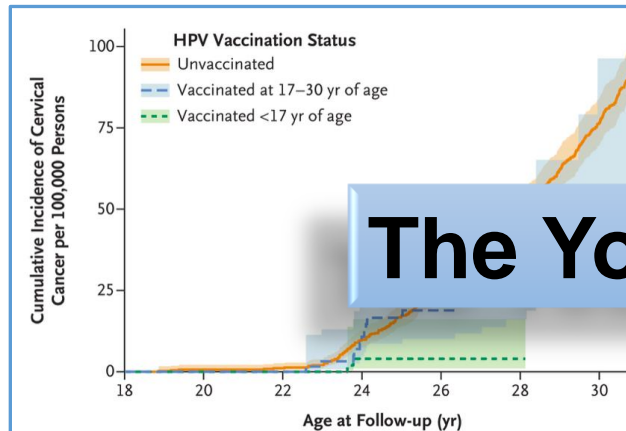
Provide a **strong recommendation for HPV vaccine** when they are 11 or 12 years old

Listen carefully to and **welcome queries** especially about safety

HPV vaccine and Cancer prevention: Real world data

Risk of cervical cancer who were vaccinated before the age of 17 years was 88% lower than among those who un-vaccinated.

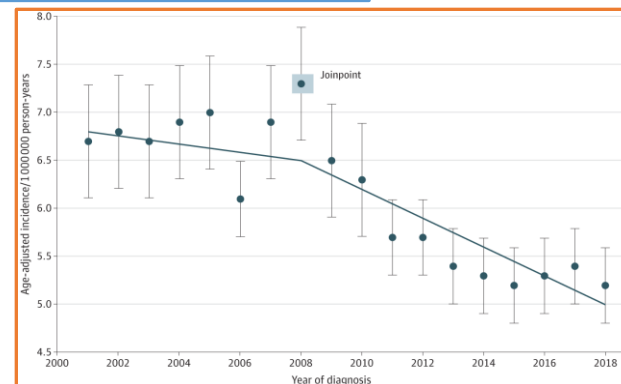
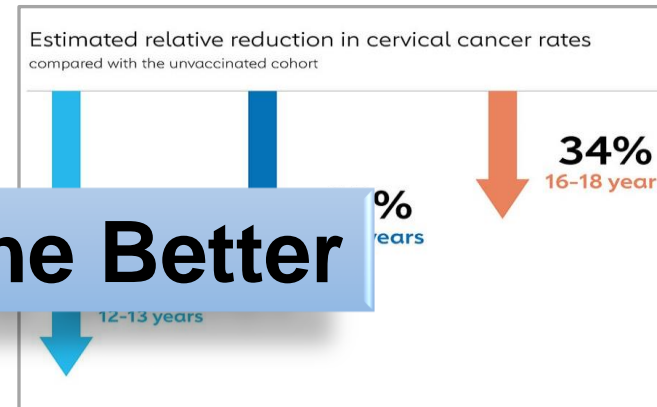
- *N Engl J Med.* 2020 Oct;383(14):1340-1348



The Younger, the Better

87% reduction in cervical cancer for age 12–13 years, compared to unvaccinated cohort

- *Lancet.* 2021 Dec 4;398(10316):2084-2092.



Anal cancer - Relative to 2001 to 2008 period, incidence significantly decreased among aged 20 to 44 years.

- *JAMA Oncol.* 2022 Apr 1;8(4):1-3.

Summary

- HPV vaccine is a safe vaccine and holds promise for cervical cancer elimination.
- The responsibility lies with all practicing physicians.
- With your whole hearted support we will be able to say Good Bye to Cervical Cancer as we did to polio and smallpox.
- Seek the help of all to include HPV vaccination in UIP.

**Thank
You!**