



# CANCER CERVIX AND IT'S RELATION TO HUMAN PAPILLOMA VIRUS & ROLE OF VACCINATION

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**ABSTRACT**

**Burden of disease**

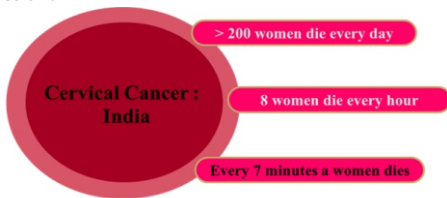
- Globally, each year:

- 500,000 women are diagnosed with Cervical Cancer.
- 270,000 women die due to Cervical cancer<sup>1</sup>.
- In India, each year:
  - 1,34,000 women are diagnosed with Cervical Cancer<sup>1</sup>
  - 72,000 women die due to Cervical Cancer<sup>1</sup>
  - 1 out of 4 women who die of cervical cancer in the world is an Indian<sup>1</sup>

Cervical Cancer is the **No. 1** cause of cancer related death amongst women in India

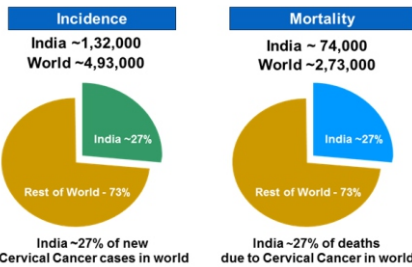
**KEYWORDS :**

**Introduction:**

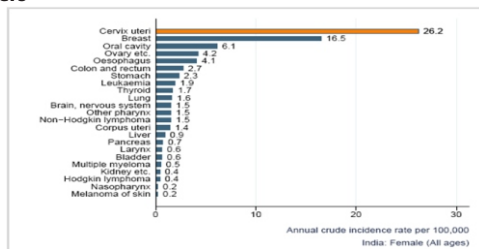


This 'Cause' need to be taken up by multiple stake holders.

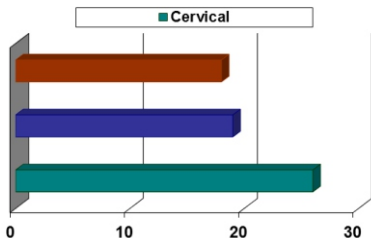
**Cervical Cancer – Disease Burden**



**Incidence ( women or all ages) – Cervical Cancer vs other Cancers**

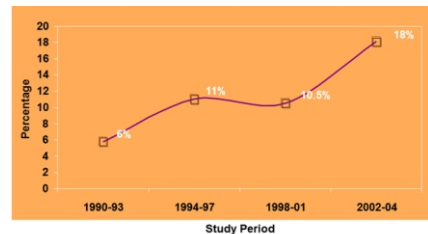


**Years of Life Lost to Cervical Cancer\***



26 Average years of life lost in women with Cervical Cancer

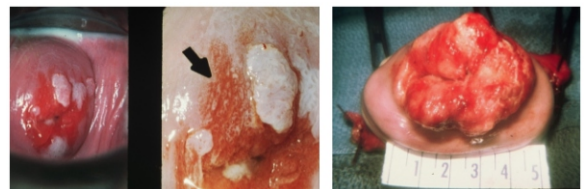
**Genital Warts – Disease Burden: India\*  
Increasing trend of Genital warts in India**



- Treatments can cause discomfort and carry risks of erythema, epithelial erosion, ulceration, depigmentation, and scarring.
- Recurrence rates vary greatly. As low as 5% and as high as 65%

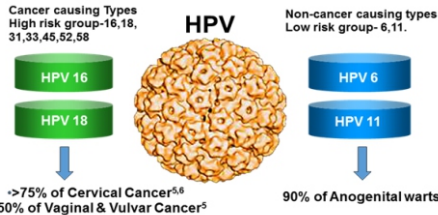
**Genital Warts: Treatment Issues1  
Nobel Prize – 2008**

- The Nobel Prize in medicine in 2008 went to
- Harald zur Hausen for his discovery of "human papilloma viruses causing cervical cancer"**

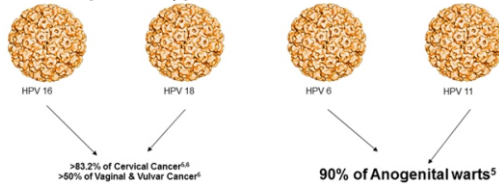


Human Papillomavirus (HPV)

**HPV is a necessary cause of cervical cancer – 99.7%<sup>4</sup>**



**The 4 most important types of HPV**

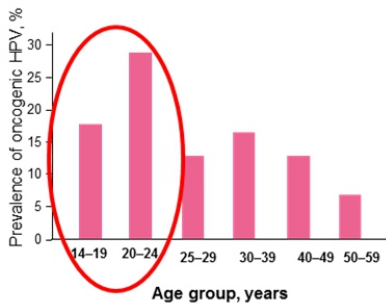


**HPV infections are very common and up to 80% of women will acquire an HPV infection in their lifetime<sup>1-3</sup>**

- The risk of oncogenic HPV infection is high even after first intercourse and **continues throughout** a woman's sexually active lifetime<sup>4,6</sup>
- Although new infections decrease with age, risk of their persistence increases with age<sup>7</sup>
- The cumulative risk of acquiring cervical HPV infection in women with only one sexual partner is **46%** (3 years after first sexual encounter)<sup>8</sup>

**The risk of infection begins in adolescence and continues in to Adulthood**

- **Young women are at a greater risk of HPV infection<sup>1</sup>**
- Women continue to acquire new HPV infections, regardless of prior infection with the same or different HPV type<sup>1-3</sup>
- HPV infections are very common and up to 80% of women will acquire an HPV infection in their lifetime<sup>4,6</sup>

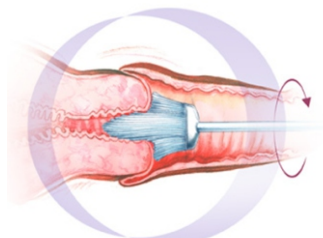


**Cervical Cancer – Classified into 2 types**

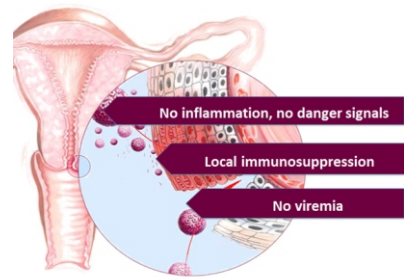
- 1. Squamous Cell Carcinoma<sup>1-2</sup>** – affects the squamous cell (majority cases)
- 2. Adenocarcinoma<sup>1-2</sup>** – affects the columnar cells.

**Adenocarcinoma<sup>3-4</sup>**

- **Increasing in incidence, especially amongst young women**
- Are harder to detect by routine screening methods
- Are more aggressive
- Have a poor prognosis
- Have poor survival rates

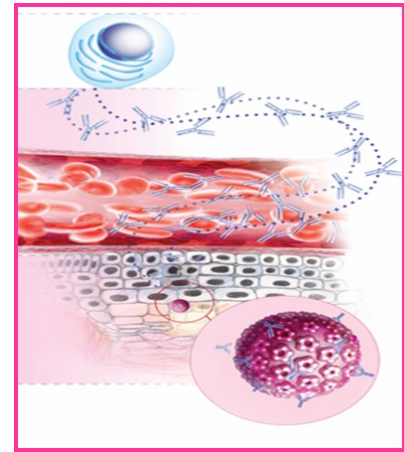


**Natural HPV infection induces a weak immune response<sup>1-4</sup>**

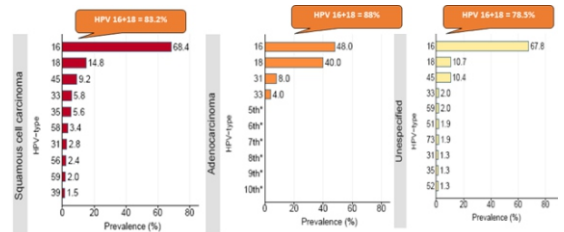


**Vaccination induces higher antibodies in the blood and site of infection**

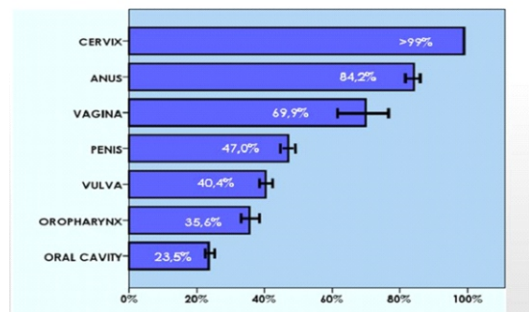
- Vaccine induces higher antibody levels in the blood which means higher antibody levels at the site of infection (the Cervix)<sup>1</sup>
- These Antibodies neutralize the virus & prevent entry into cells<sup>1</sup>



**Ten most frequent HPV types among women with invasive cervical cancer**



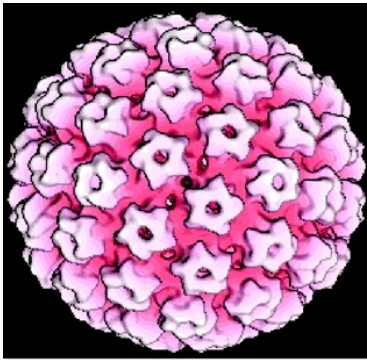
**ESTIMATED HPV CONTRIBUTION IN CANCER**



**What is HPV?**

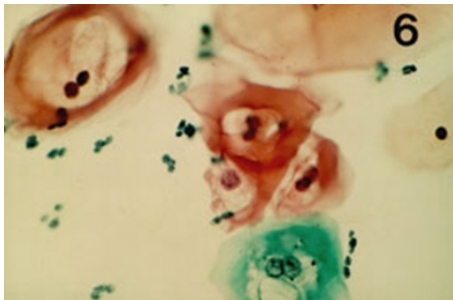
- **Small DNA virus**
- **Family: Papillomaviridae**
- **Only infects squamous epithelia**
- **Common virus with >100 types identified**
- **60-70 types infect the skin- common warts**
- **30-40 infect the genital area of women and men**
- **2 groups**
  - **low risk types causing warts**

- high risk types causing cancer oncogenic types



**HPV DNA Detection**

- Hybrid capture II assay by Digene Diagnostics
  - Only pos. or neg. for Hi Risk HPV: not type specific
- Research techniques
  - In-situ hybridization
  - Polymerase chain reaction
  - Dot blot
  - Filter hybridization
  - Southern transfer hybridization

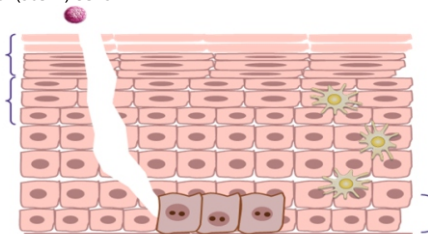


**HPV Lifecycle in the Cervix**

- Shedding of virus-laden epithelial cells
- Viral assembly (L1, L2, E4)
- Viral DNA replication (E6 & E7)
- Episomal viral DNA in cell nucleus (E1 & E2, E6 & E7)
- Infection of basal cells (E1 & E2)

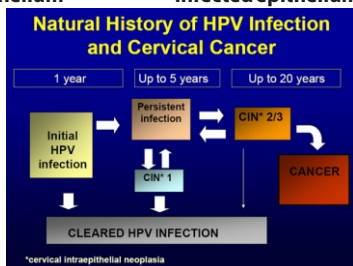
**Cervical canal**

- Mature squamous layer
- Squamous layer
- Parabasal cells
- Basal (stem) cells

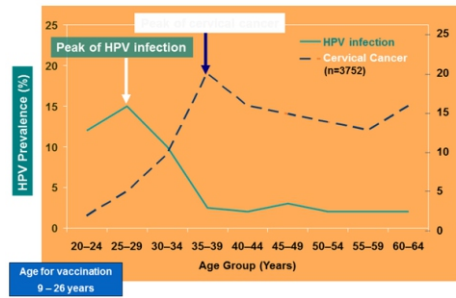


Basement membrane

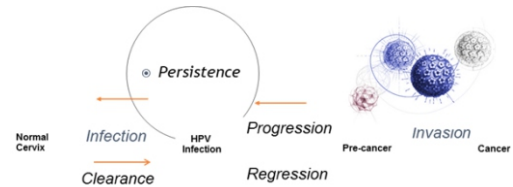
Normal epithelium      Infected epithelium



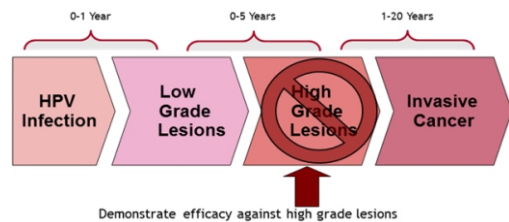
**Age-Specific Rates of HPV Infection & Cancer\***



**Natural History of HPV & Cervical Cancer**

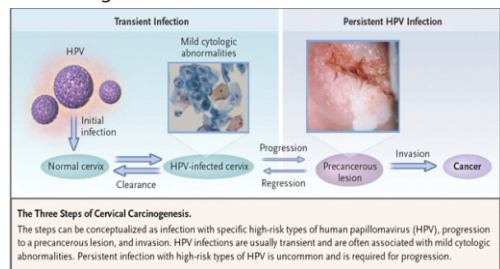


**Natural History of HPV Infection: Surrogate Markers for Cervical Cancer**

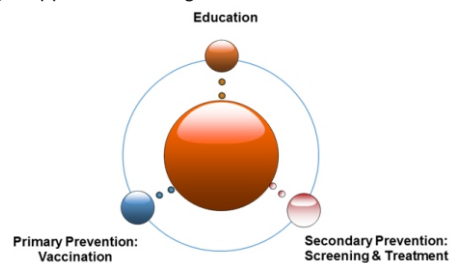


Demonstrate efficacy against high grade lesions  
LSIL (CIN1) or HSIL (CIN2/3), low- or high-grade squamous intraepithelial lesion.  
CIN= Cervical Intraepithelial Neoplasia

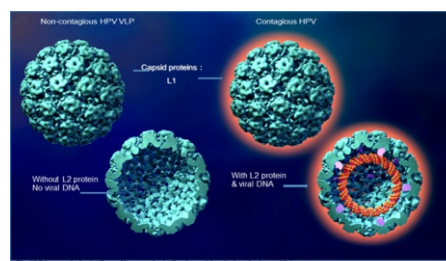
**Cervical Carcinogenesis**



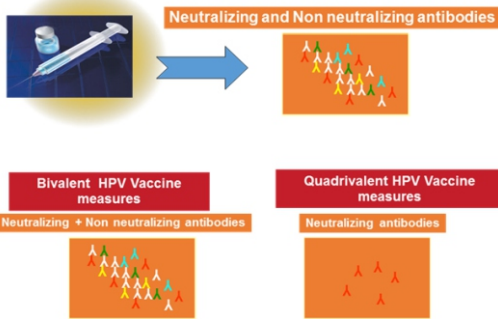
**3 pronged approach to saving the lives of women...**



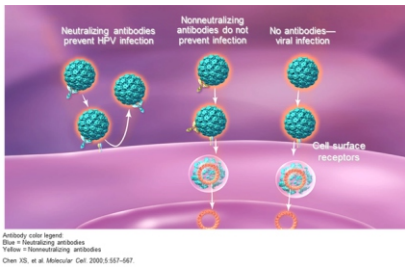
**The chemistry of the protein is such that it assembles into virus like particles-VLP**



**Types of antibodies after HPV vaccination**



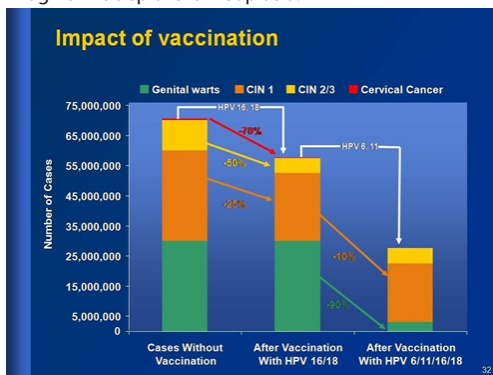
**Neutralizing Antibodies Correlate With Prevention of HPV Infection**



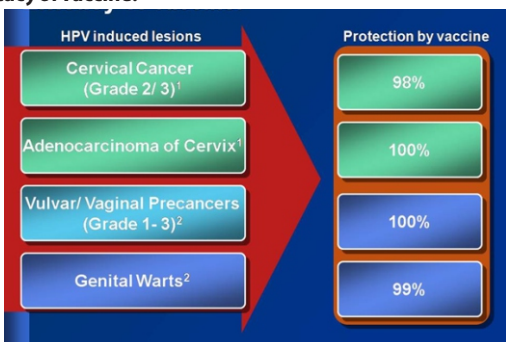
**Targeting a High Disease Burden With Human Papillomavirus Vaccine**

HPV Type	Approximate Disease Burden
<b>16 &amp; 18</b>	<ul style="list-style-type: none"> <li>70% of cervical cancer, AIS, CIN 3, VIN 2/3, and VaIN 2/3 cases</li> <li>50% of CIN 2 cases</li> </ul>
<b>6, 11, 16 &amp; 18</b>	<ul style="list-style-type: none"> <li>35%–50% of all CIN 1, VIN 1, and VaIN 1 cases</li> <li>90% of Genital warts cases</li> </ul>

AIS = adenocarcinoma in situ.  
 CIN = cervical intraepithelial neoplasia.  
 VIN = vulvar intraepithelial neoplasia.  
 VaIN = vaginal intraepithelial neoplasia.



**Efficacy of vaccine:**



**Efficacy: 100% Efficacious Against HPV 6/11/16/18-Related CIN**

**PPE population; subjects were free of HPV 6, 11, 16, 18 infection through 1 month Postdose 3.**

End Point by Lesion Type	Vaccine (n=2,241)	Placebo* (n=2,258)	Vaccine Efficacy	CI
<b>HPV 6/11/16/18 CIN</b>	0	65	100%	94–100
<b>CIN 1</b>	0	49	100%	92–100
<b>CIN 2</b>	0	21	100%	81–100
<b>CIN 3</b>	0	17	100%	76–100
<b>AIS</b>	0	6	100%	15–100

CI = confidence interval.  
 CIN = cervical intraepithelial neoplasia.  
 AIS = adenocarcinoma in situ.

**Efficacy: 100% Efficacious Against HPV 6/11/16/18-Related VIN/VaIN and Genital Warts**

**PPE population; subjects were free of HPV 6, 11, 16, 18 infection through 1 month Postdose 3.**

End Point by Lesion Type	Vaccine (n=2,261)	Placebo* (n=2,279)	Vaccine Efficacy	CI
<b>HPV 6/11/16/18 VIN/VaIN, genital warts</b>	0	60	100%	94–100
<b>Genital warts</b>	0	48	100%	92–100
<b>VIN 1 or VaIN 1</b>	0	9	100%	49–100
<b>VIN 2/3 or VaIN 2/3</b>	0	9	100%	49–100

VIN = vulvar intraepithelial neoplasia.  
 VaIN = vaginal intraepithelial neoplasia.

**FOGSI**

**RECOMMENDATIONS**

**FOGSI Recommendations**

- Cervical cancer causes significant morbidity/ mortality
- HPV vaccine to be offered to all appropriate females who can afford the vaccine
- Vaccine should be preferably given prior to sexual debut

**FOGSI Recommendations – Vaccine Schedule**

- Age for initiation of vaccination is 10- 12 years. Catch up vaccination is permitted up to the age of 45 yrs for both vaccines
- 3 doses at 0, 2 and 6 months with quadrivalent vaccine
- 3 doses 0, 1 and 6 months with bivalent vaccine

**FOGSI Recommendations Need for Booster**

- At present there is no data to support use of boosters
- FOGSI Recommendations: Vaccination of Sexually Active Women
- Sexually active women and women with abnormal cervical cytology can receive the HPV vaccine
- Benefits may be limited to the protection against infection of HPV genotypes with which they have not been infected

**FOGSI Recommendations: Women With Previous CIN**

- The vaccine can be given to patients with previous CIN, but the benefits may be limited to the protection against infection of HPV genotypes (and related CIN) with which they have not been infected
- The HPV vaccine is not therapeutic. It does not treat existing HPV infection or cervical intraepithelial neoplasia (cervical precancers)

**FOGSI Recommendations: Pregnancy & Lactation**

- Not recommended for use in pregnancy
- If patient becomes pregnant - Delay remaining doses till delivery
- If vaccinated during pregnancy - No intervention (MTP) needed
- Lactating women can receive the QHPV vaccine and still continue breastfeeding as it is a vaccine without live viral DNA.

**FOGSI Recommendations: Vaccination & SCREENING**

- Vaccinated women should be screened as per the standard guidelines
- Screen positive women may be vaccinated after counselling
- Screening/HPV test is NOT REQUIRED prior to vaccination