

EVOLVING TRENDS IN HPV VACCINATION IN INDIA AND THE WORLD

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I. INTRODUCTION

Cervical cancer has been a concern of mankind for a long time. Research into the risk factors and aetiology of cervical cancer began as early as the 1840s. However, it took nearly a century before cervical cancer was found to be directly related to increased frequency of intercourse, childbirth, and sexual partners. The earliest pathogen implicated in the development of cervical cancer was the herpes simplex virus. Although some researchers at the time were able to demonstrate the presence of antibodies against the virus in sera from cervical cancer patients, no plausible explanation for this association was found.

In the 1970s, German virologist Harald zur Hausen discovered that the papillomavirus caused genital warts in cattle, some of whom later died of genital cancer. He postulated that papillomavirus infection could also cause genital warts and cancer in humans. A decade later, in 1983, Hausen and Gissmann isolated papillomavirus DNA from HeLa cells. HeLa cells were the first immortal cell lines to be cultivated in vitro. The name HeLa derives from the initials of Henrietta Lacks, an African American who died of cervical cancer in 1951 after providing samples of cervical tissue. Since then, the HeLa cells have been used in the formulation of various chemotherapeutic drugs and vaccines. Hausen showed that the papilloma virus DNA isolated from HeLa cells did not resemble that obtained from genital warts. He named this papilloma strain as the 'Human papilloma virus-16' or 'HPV-16'. Around the same time, another immunologist, Frazer, who was studying HPV infection in immunocompromised patients, had made ties with Hausen. In the years that followed, Frazer demonstrated that certain high-risk HPV (hrHPV) strains are also responsible for causing anorectal dysplasia, a precursor to anorectal cancer.¹

For the ground breaking discovery of the HPV as a cause of cervical cancer, Hausen was later awarded the Nobel Prize in medicine in 2008.

II. THE HUMAN PAPILOMA VIRUS

1. hrHPV and lrHPV Strains: HPV is a double-stranded DNA virus that belongs to the Paillomaviridae family. Today, more than 100 different types of HPV strains are known. The alphavirus HPV strains with high oncogenic potential are referred to as high-risk HPV (hrHPV). Those that cause benign lesions are called low-risk HPV (lrHPV).

About 95% of cervical cancers are caused by the human papillomavirus (HPV). Notably, more than 70% of all cervical cancers, 90% of all anal cancers, and a majority of vulva, vaginal, and penile cancers are caused by hrHPV strains 16 and 18. Another 20% of cervical cancer cases are attributed to the five hrHPV strains, namely 31, 33, 45, 52, and 58. The lrHPV strains are mainly responsible for oroanogenital warts in both sexes.

Table: 1

Table 1: Important hrHPV and lrHPV Strains

	HPV strains	Most common strains
Low risk	6, 11, 42, 43, 44	6 and 11
High risk	16, 18, 33, 35, 45,58	16 followed by 18

III. PATHOGENESIS OF CERVICAL CANCER

The HPV virus is sexually transmitted and infects more than 80% of men and women early in their reproductive lives. However, most (95%) men and women are able to clear the virus within the first two years after infection. Because of this, a decrease in the prevalence rate of HPV infection is observed after the age of 35. Unfortunately, about 10 to 20% of women remain persistently infected with HPV. Such women are at increasing risk of developing invasive cervical cancer within the next 15 to 20 years if they have a competent immune system, and much sooner within 5 to 10 years if their immune systems are compromised.

1. Key Molecular Events in Persistent HPV Infection: The HPV genome contains three important regions: the long control region (LCR), the early (E) region and the late (L) region. The LCR regulates the expression and replication of genes; the protein encoded by the E region is necessary for genetic expression, replication and survival of HPV; The L region encodes HPV structural proteins. The two major hrHPV proteins responsible for persistent infection and tumor progression are the E6 and E7. These alter the host's cell cycle by inactivating the tumor suppressor proteins p53 and pRB, respectively. **Figure.1**

In women with an intact immune system, the Toll-like receptors (TLRs) on the surface of macrophages, Langerhans cells, and natural killer cells play an important role in establishing an innate immune response against HPV infection. Binding of the TLRs to the viral components activates the nuclear factor kappa B transcription factor and interferon response factor-3 (IFR-3).

This leads to increased production of pro-inflammatory cytokines and viral clearance. The TLRs also indirectly activate MHC (major histocompatibility complex) expression on the antigen presenting cells and trigger adaptive immunity. The hrHPV E5

protein inhibits the expression of the MHC class I molecule and decreases the production of antiviral cytokines. The E6 protein also inactivates TLRs and promotes immune evasion.²

It can be seen that the TLR gene expression increases with the severity of the cervical lesion. This is because overexpression of oncoproteins E5 and E7 downregulates TLR-9 expression and impairs the release of antiviral cytokines. The end result is resistance to host immunity and persistent infection.² (**Figure.1**)

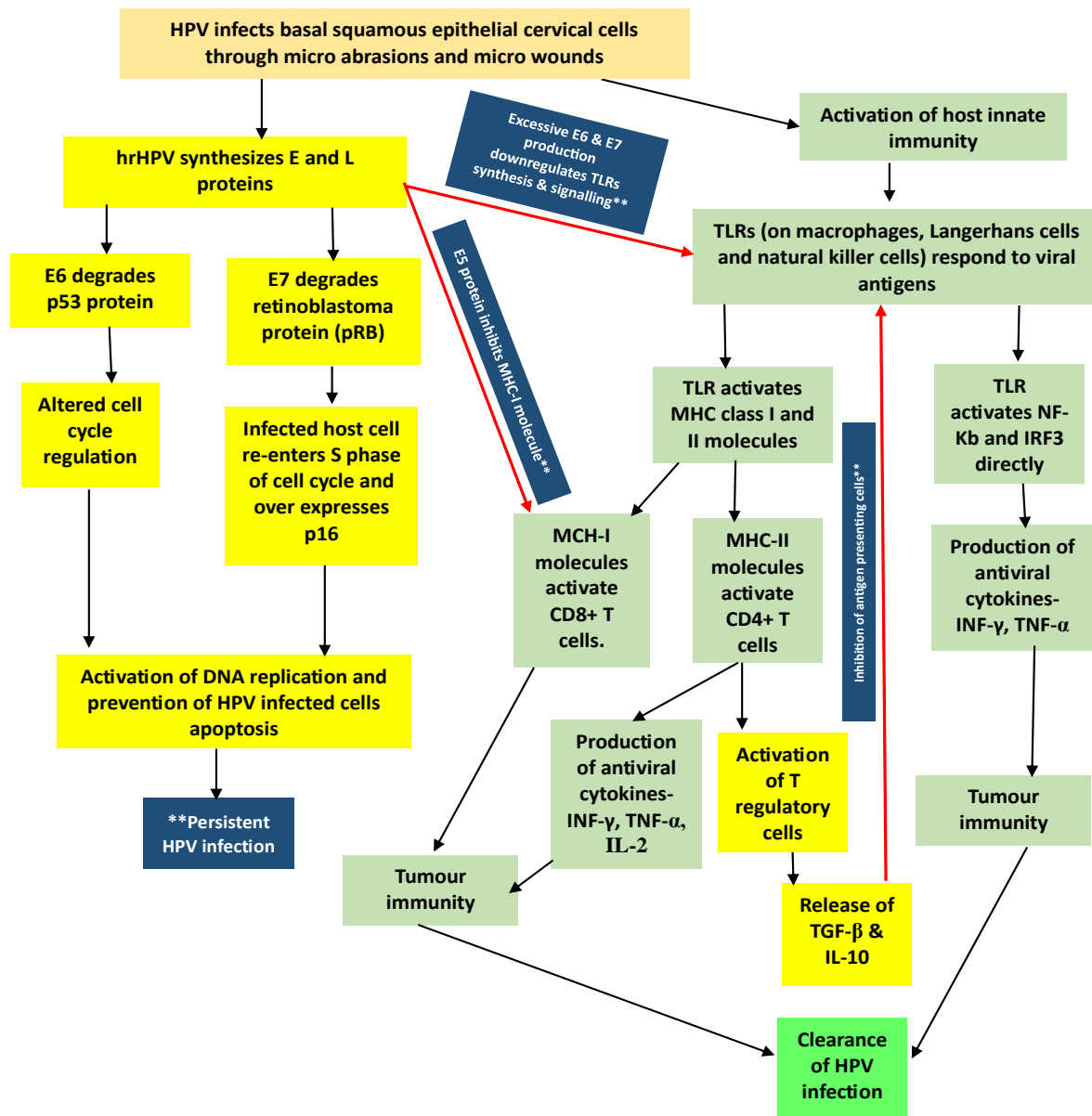


Figure 1: Molecular mechanism of persistent cervical infection with HPV

Pathway leading to persistent HPV infection; INF- γ , interferon-gamma; TGF α/β , Tumor growth factor alpha/beta; IL, interleukin; NF-Kb, Nuclear factor kappa B; TLRs, Toll like receptors; IFR-3, interferon response factor-3; hrHHPV, high risk HPV

IV. WHY A VACCINE?

Cervical cancer is the fourth most common cancer in women worldwide. It is responsible for 600,000 new cancer cases and 300,000 cancer-related deaths each year. Low- and middle-income countries carry the highest (90%) global annual burden of cervical cancer and related mortality.³⁻⁵

Today we know that cervical cancer can be prevented and millions of lives saved. However, the foundation for this must be laid on two main prevention strategies; primary prevention against HPV infection and secondary prevention for early detection of the disease.

V. THE HPV VACCINE

The quest for an HPV vaccine began with a series of murine experiments employing transgenic HPV oncoproteins. However, it was not until 1989 at Cambridge University that Fraser met a Chinese virologist, Dr Jian Zhou, who had a similar interest in HPV. Little was known that this alliance would write a new history. In 1990 Jian and his partner Xiao-Yi Sun moved into Fraser’s laboratory in Brisbane and synthesized a vaccine from viral capsids (or virus-like particles/VLPs). They applied for its patency in 1991, but received it more than a decade later, in 2006.¹

After 2006, most of the development and production of HPV vaccine was taken over by two pharmaceutical giants: Merck and GSK. The first HPV vaccine to receive FDA approval was Merck’s *Gardasil* in 2006. Three years later, in 2009, the FDA approved GSK’s bivalent *Cervarix*. The first nonavalent vaccine, *Gardasil-9*, was approved by the FDA in 2014. All of these vaccines proved to be highly immunogenic and were able to induce long lasting immunity against HPV infection in HPV naïve men (90-100%) and women (80-90%). (Table.2)

Table 2: The Three Major Types of HPV Vaccines

	Bivalent vaccine	Quadrivalent vaccine	Nonavalent vaccine
HPV subtype coverage	16, 18	6, 11, 16,18	6, 11, 16, 18, 31, 33, 45, 52, 58
Immunogenicity in HPV naïve person	Females- 93% -100% Males- 99% -100%		
Brand	<i>Cervarix</i> (GSK) <i>Cecolin</i> (Xiamen Innovax Biotech Co ltd)	<i>Gardasil</i> (Merck) <i>Cervavac</i> (Serum Institute of India)	<i>Gardasil-9</i> (Merck)
Drug approval	<i>Cervarix</i> was approved by the FDA in 2009. Not approved in India by the CDSCO	<i>Gardasil</i> was approved by FDA in 2006. Not approved in India by the CDSCO	<i>Gardasil-9</i> was approved by the FDA in 2014.
Availability	Available in India. Not available in US. China prepares its own bivalent vaccine that is prequalified by the WHO for use in resource-limited	Available in India. Not available in US.	Available in India and US.

	settings under the brand of <i>Cecolin</i> .		
Indication	For the primary prevention of cervical, vaginal, vulval, oropharyngeal, penile and anal cancers.	For the primary prevention of cervical, vaginal, vulval, oropharyngeal, penile and anal cancers. For the prevention of anogenital warts.	For the primary prevention of cervical, vaginal, vulval, oropharyngeal, penile, anal cancers and anogenital dysplastic lesions. For the prevention of anogenital warts.
Price in the Indian market (INR)	<i>Cervarix</i> - INR 2270 for a prefilled dose containing 0.5 mL vaccine suspension.	<i>Gardasil</i> - INR 3927 for a prefilled dose containing 0.5 mL of vaccine suspension. <i>Cervavac</i> - INR 2000 for two doses.	<i>Gardasil-9</i> - INR 10340.75 for a prefilled dose containing 0.5 mL vaccine suspension.

CDSCO, Central Drug Standard Control Organisation; FDA, Food and Drug Administration

1. Is vaccination Required for Boys and Men?

Male immunisation can reduce the rate of anogenital cancers in both sexes through herd immunity.⁶ However, this may not be cost effective, particularly in low resource settings.

2. When to Vaccinate?

- Vaccination should be ideally be initiated prior to first sexual contact.
- HPV vaccination does not treat or increase the clearance rate of the viral infection. Nevertheless, vaccination can prevent infection with other HPV strains in sexually active men and women, although the benefit is far less than in HPV naïve persons.
- The US Advisory Committee on Immunisation Practices (ACIP), along with the American College of Obstetricians and Gynecologists (ACOG), the American Society of Clinical Oncology (ASCO), the Centre for Disease Control (CDC), the American Academy of Paediatrics (AAP), the American Academy of Family Physicians

(**AAFP**), and the **American Cancer Society (ACS)** agree to initiate HPV vaccination as follows:

- 11-12 years of age: Initiate HPV vaccine as routine vaccination; the vaccine can be started as early as 9 years of age.
- 13 to 26 years of age: Initiate vaccine as Catch-Up vaccination for those who have never been vaccinated or who have received an incomplete dose.
- ≥ 27 years and up to 45 years: Initiating a Catch-Up vaccination is not recommended because the benefit and cost-effectiveness of vaccination in preventing cervical cancer decreases with age. However, the AICP states that the decision to vaccinate can be individualised.⁷⁻¹³

3. WHO and ASCO recommendations on HPV vaccination in resource poor settings:

- The ‘primary vaccine targets’ should be girls aged 9-14 years.
- Local public health programs should only recommend vaccinating older females when it is logistically and financially feasible and only when it does not divert resources from the primary target group or cervical cancer screening.^{9,13}
- **The Indian Academy of Paediatrics (IAP) Recommendations On Vaccination Schedule¹⁴:**

	Vaccine dose	Vaccine schedule	
Girls aged 9-14 year- <i>Preferred target vaccination</i>	2 doses	Bivalent/ Quadrivalent/ Nonavalent	Dose 1: 0 month Dose 2: 6 months or between 5 and 15 months of the first dose
Girls aged 15-26 years- <i>Catch-Up vaccination</i>	3 doses	Bivalent	Dose 1: 0 month Dose 2: 1 month Dose 3: 6 months
		Quadrivalent/ Nonavalent	Dose-1: 0 month Dose-2: 2 months Dose-3: 6 months
Older women 27 to 45 years of age	3 doses	Similar to catch-up vaccination	

4. Which is the Best Vaccine?

There is no consensus on the best HPV vaccine. In fact, the nonavalent and quadrivalent vaccines show broader disease coverage in both sexes.

In general, the same vaccine should be used to complete a vaccination series. However, if it is not known which vaccine was administered or if the patient is known to have been vaccinated with a nonavalent vaccine, another vaccine may be used.

5. When not to administer The Vaccine?

Hypersensitivity to the vaccine or its components.

6. Vaccination in Pre-Existing HPV Related Disease

- In women with a positive history of genital warts, positive HPV testing or abnormal cytology results, HPV vaccination should be based on age specific recommendations.
- These women should be advised that the vaccine does not affect the rate of progression of a preexisting cervical dysplastic or neoplastic lesion and hence cannot cure the disease.

7. How to administer the vaccine?

- 0.5 mL of the vaccine suspension is administered intramuscularly in the deltoid muscle of the arm.
- The vaccine may be concurrently administered with tetanus, acellular pertussis, diphtheria, or inactivated polio virus vaccine.

8. What is not required when prescribing an HPV vaccine?

- Pre-vaccination pregnancy testing
- Pre-vaccination HPV DNA testing
- Post-vaccination anti HPV antibody titre estimation.
- Booster vaccination or initiating vaccination after completion of a vaccination series-

There is no evidence that booster vaccination increases protective immunity. This also applies to patients who have completed their vaccination schedule with either a bivalent or quadrivalent vaccine and are considering revaccination with the nonavalent vaccine.

9. What is the Role of Cervical Cancer Screening in women who have already been Vaccinated Against HPV Infection?

HPV vaccination should not alter the frequency and schedule of cervical cancer screening.

10. HPV Vaccination during Pregnancy and Lactation

- For safety reasons, HPV vaccination is not recommended during pregnancy. However, if the vaccine was accidentally administered, this is not an indication of termination of pregnancy. The rest of the vaccine series should be completed after delivery.
- HPV vaccines are safe for breastfeeding women.

11. Vaccination in Health Care Workers Exposed to HPV Infection: Healthcare workers can be exposed to nasal and oropharyngeal HPV infection from fumes generated during the surgical removal or ablation of HPV-related lesions. The American Society of Colposcopy and Cervical Pathology recommends that healthcare workers who are regularly exposed to HPV should be vaccinated.¹⁵

12. What should be Done if a Vaccine Dose is Missed?

If the vaccination series is interrupted, the vaccination can be resumed without restarting the entire vaccination series, regardless of the duration of interruption.

13. What are the Side Effects of HPV Vaccine?

HPV vaccine contains virus like particles that mimic the viral capsid protein. The vaccine contains no HPV genetic material and is considered extremely safe. However, due to the occurrence of syncope attacks after vaccination, patients are advised to lie down for at least 15 minutes after the injection.

VI. GLOBAL STANDS ON HPV VACCINATION

1. **The 90-70-90 Target:** In August 2020, the WHO called for the elimination of cervical cancer by 2030 as part of its "Global Cervical Cancer Elimination Initiative". This would roughly correspond to a reduction in the cervical cancer rate to 4 per 100,000 women. To this end, WHO has set the 90-70-90 target for countries. The goal is to vaccinate 90% of girls by age 15, screen 70% of women for cervical cancer by age 35 and then by age 45, and to treat 90% of women with cervical precancerous or invasive lesions.¹⁶
2. **Taskforce on Cervical Cancer Elimination in the Commonwealth:** The Commonwealth accounts for about 40% of the global incidence rates for cervical cancer and associated mortality. No wonder, India is a major contributor. An international Taskforce on Cervical Cancer Elimination in the Commonwealth was established by the Commonwealth Secretariat and the Union for the International Cancer Control (UICC) in 2021 with the aim of stepping up efforts towards prevention and treatment of cervical cancer in the commonwealth region and achieve cancer elimination goals, put forward by the WHO Global Cervical Cancer Elimination Strategy.
3. **WHO SAGE Committee Opinion on Vaccine Schedule:** In April 2022, the WHO Strategic Advisory Group of Experts (SAGE) on immunization found evidence of similar efficacy of the single-dose HPV vaccine compared to the 2- or 3-dose HPV vaccination schedules. The SAGE concluded that a single-dose HPV vaccine offered solid protection against the virus and viewed it as a game-changer in the fight against cancer.¹⁶ (Table.3)

Table 3: HPV vaccination schedule as proposed by the WHO SAGE committee

	Girls aged 9-14 years	Girls aged 15-20 years	Girls aged over 21 years	Immunocompromised females (including HIV infected)
Number of doses	One or two doses	One or two doses	Two doses, with a minimum of 6-month interval	Minimum of two doses. Preferred- Three doses

- 4. The Big Catch-Up Initiative :** In December 2022, the WHO reiterated its position on the single-dose schedule. This newly recommended schedule promised an expansion in vaccination coverage and a reduction in morbidity and morbidity associated with HPV infection. In April 2023, WHO, in collaboration with UNICEF endorsed the ‘The Big Catch-up’ initiative, which is a targeted global approach to increase vaccination rates in children after a decline in vaccination coverage rates during the COVID-19 pandemic.¹⁷

VII. INDIA’S STAND ON HPV VACCINATION

- 1. India’s Burden of Cervical Cancer :** While African countries lead in cervical cancer incidence rates, India fares no better; the incidence rate and annual cancer-related mortality rate for cervical cancer in India are 6-29% and 9.1%, respectively. In fact, cancer cervix is the second leading cause of cancer-related death in India. The district of Papumpare in the state of Arunachal Pradesh has the highest incidence rate (27.7%) for cervical cancer in all of Asia. Adding to this apathy, immunization coverage and cervical cancer screening rates in India are a meagre <1% and <2%, respectively.¹⁸
- 2. A Tumulous Path to Vaccination :** Countries like United Kingdom, and Denmark have achieved high HPV vaccination coverage (>60%). This is secondary to the inclusion of the vaccine in their national immunisation programme. In January 2023, India rolled out first of the three phases of the nationwide immunisation programme as recommended by the National Technical Advisory Group for Immunisation (NTAGI).¹⁹ This move was urgently needed and far delayed compared to its neighbours, Bhutan, Sri Lanka, Thailand, and the Maldives, which established their national HPV immunisation programmes years ago.

The vaccines *Gardasil* and *Cervarix* were licenced for use in India back in 2008. Soon the international NGO Programme for Global Health Organisation (PATH) in collaboration with the Government of Andhra Pradesh and Gujrat and the Indian Council of Medical Research (ICMR) launched a project entitled, ‘A post-licensure observational study of HPV vaccination: Demonstration Project’ to test their effectiveness and tolerability. This project was part of a larger global project, ‘HPV vaccine: Evidence for Impact’. The vaccines used in the PATH’s project were donated by pharmaceutical companies, GSK and MSD. Unfortunately, the project was halted prematurely due to seven alleged vaccine-related deaths. However, it turned out that the deaths were unrelated to vaccination. Nonetheless, this was a major setback for HPV vaccination efforts in the country.²⁰

In 2016, Delhi became the first Indian state to vaccinate school girls. A year later, the Punjab government launched a vaccination campaign in two districts (Bathinda and Mansa). In 2018, Sikkim became the third state to start an HPV vaccination program with the goal of targeting girls aged 9 to 14 in 1,166 schools. In 2022, the Serum Institute of India, in collaboration with the Department of Biotechnology of the Government of India, launched *Cervavac* after receiving the Drug Controller General of India. *Cervavac* is the first indigenous vaccine and it promises to overcome rural-urban vaccine inequity in the country.

3. The NTAGI Recommendations for Vaccinating School Girls²¹: In 2023, the Government of India National Technical Advisory Group for Immunisation (NTAGI) recommended following:

- The inclusion of the HPV vaccination in the Universal Immunisation Programme (UIP) as a one-time Catch-Up Vaccination for adolescent girls aged 9 to 14 followed by routine vaccination of girls at 9 years of age.
- School going adolescent females will be vaccinated using a Graded-approach i.e. Between 5th and 10th school grades.
- Girls who miss the school health vaccination campaign as well as those who do not go to school, will be vaccinated in health facilities or through community outreach programmes and mobile health campaigns.

In line with the NTAGI Recommendations, the Government of India, has Proposed Following Plan of Action:

- The state governments and union territories will ensure smooth HPV vaccination campaigns in schools.
- The District Educational Officer will assist the District Immunisation Officer in vaccination drives. The District Task Force on Immunisation will oversee the campaign and report directly to District Magistrate.
- One person will be appointed from each school as the nodal person. He/she will coordinate vaccination activities and collate the number of girls in the school.
- The registration, recording and reporting of vaccination data should be done through the U-WIN software application.
- Special parent teacher meet will be organised to spread awareness about cervical cancer and the HPV vaccine.
- UpToDate list of all types of schools (UDISE+) should be created for all blocks for microplanning.
- GIS mapping of the schools should be done to district immunisation officers for developing micro plans so that all schools are covered.
- Vaccination camps should be scheduled on days other than holidays and vacations.

VIII. CONCLUSION

India is lagging behind the goal of eliminating cervical cancer by 2030. The launch of Cervavac and the roll out of a phased HPV vaccination program are the much-needed welcome steps by the government towards a cervical cancer free India. However, much remains to be done. The masses need to be made aware of this preventable and curable cancer. The government needs to address logistical and infrastructural deficiencies that create rural-urban inequities and sponsor a statewide cervical cancer screening programme to identify at risk women.

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