REVIEW ARTICLE

Opportunities for Cervical Cancer Prevention in India

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Introduction:

Cervical cancer is the fourth most common cancer among women in the world. Of the 528,000 new cases detected globally in 2012, developing countries accounted to about 85% of its global burden [1]. This is one of the most well studied cancers, several landmark studies have been completed in the past few decades and cost-effective interventions to prevent cervical cancer are now available. We are in the era with dual prong strategy for cervical cancer prevention with the availability of Human papillomavirus (HPV) vaccines and affordable and effective methods for early detection and treatment of cervical cancer precursor lesions so that cervical cancer can prevented.

India accounted to more than one fifth of the global burden of cervical cancer in 2012 with 123,000 new cases of cervical cancer [1]. This burden is likely to increase to 149,000 new cases by 2020 due to demographic effect of population growth and increased life expectancy [1]. Although breast cancer incidence was higher than cervical cancer incidence in India in 2012, it is highly probable that cervical cancer incidence rates are an underestimate for India possibly due to under-diagnosis of cervical cancer cases in rural areas and among most impoverished women as well as due to non-inclusion of sub-clinical cervical cancers in routine hysterectomy specimens not subjected to histopathology, which is a common practice in many regions of India. In spite of the high burden and available effective interventions, there are very few and sporadic initiatives for cervical cancer prevention in India. We summarize the evidence for effective interventions and recent WHO guidelines for cervical cancer prevention to catalyse prevention efforts.

Primary prevention of cervical cancer by HPV vaccination:

HPV vaccination of girls prior to initiation of sexual activity is an important intervention for primary prevention of cervical cancer. Extensive epidemiological studies have concluded that certain high-risk HPV types are causally related to development of cervical cancer [2-4]. The knowledge that persistent HPV infection is necessary for the development of cervical cancer has led to the discovery of vaccines to prevent HPV infection. The process of vaccine development and rigorous evaluation took nearly 25 years [5]. Two HPV vaccines; a quadrivalent vaccine and a bivalent vaccine are now licensed in over 150 countries in the world and about 65 countries have included them in the national programme [6, 7]. The characteristics of two HPV vaccines and their WHO recommended schedule of vaccination is presented in (Table 1). These vaccines primarily prevent infection of HPV 16 and 18 types which are responsible for 70% of cervical cancers and in addition provide partial cross protection against other phylogenetically related high-risk HPV types which are HPV 31, 45 and 52. In addition to prevention of HPV 16 and 18 infections, the quadrivalent vaccine provides

protection against HPV 6 and 11 which are low-risk types of HPV responsible for 90% genital warts.

The WHO has recommended the target age group of 9 to 13 years old girls with catch up vaccination of 14 to 18 years old girls for national immunization programs [8]. A 2-dose schedule with an interval of at least 6 months between doses for girls aged ≤15 years (0 and 6 months) and a 3 dose schedule (0, 1-2, 6 months) for girls >15 years of age and for immunocompromised individuals is recommended by the WHO [9]. WHO recommends HPV vaccination prior to initiation of sexual activity. The utility of these vaccines in adult sexually active women is yet to be fully established. Vaccinated girls will need screening in their adult life after 30 years preferably with an HPV test.

The U.S.FDA has recently approved a 9-valent HPV vaccine (V-503) which provides protection against five additional high-risk HPV types 31, 33, 45, 52 and 58 which cause approximately 20 percent of cervical cancers (in addition to protection against HPV 16, 18, 6 and 11) [10].

Majority of the high-income countries which already had cervical cancer screening programs in place have included HPV vaccination in their National Immunization Programs (NIP) and Australia, United States, Canada and UK were among the first high-income countries to introduce HPV vaccination in their NIPs. Some lower- and lower-middle income countries that have included HPV vaccination in their national programs are from Latin America (Argentina, Brazil, Chile, Colombia, Equador, Panama, Paraguay, Mexico, Peru, Uruguay, Guyana and Suriname), Asia (Malaysia, Bhutan, Fiji, Uzbekistan) and Africa (Uganda, Rwanda, Seychelles, Zambia, Kenya, Ghana, Lesotho and South Africa) [7]. More than 175 million doses of HPV vaccine have been given worldwide [11]. and these vaccines are safe and effective in reducing incidence of cervical cancer precursor lesions [12].

Secondary prevention of cervical cancer:

The progression of HPV infection to cervical cancer is characterized by a series of histological abnormalities of the cervical epithelium, which are regarded as potential precursors of cervical cancer [13]. Secondary prevention aims at early detection of cervical cancer precursor lesions called as cervical intra-epithelial neoplasia (CIN). The precursor lesions of squamous cell carcinoma are three grades of cervical intraepithelial neoplasia (CIN 1-3). In CIN 1, abnormal cells occupy the lowest third of the cervical squamous epithelium; in CIN 2, the abnormal cells occupy the lower two-thirds and in CIN 3, abnormal cells occupy the full thickness or nearly the full thickness of the cervical squamous epithelium. Adenocarcinoma *in-situ (*AIS) is the precursor lesion for cervical adenocarcinoma which arises from the columnar epithelium of the endocervix. Correlation between CIN, dysplasia and the Bethesda terminology is presented in (Table 2).

The objective of cervical cancer screening is to detect women with CIN and treat them for prevention of cervical cancer. Cervical cancer screening can be done by different methods and there are advantages and disadvantages of these methods in different settings. A decision making tool regarding the test to be included in the programme is presented in flow chart I (Fig. 1).

Different methods of cervical cancer screening

Conventional cytology screening (Pap smear screening):

In India, majority of the health care providers are aware of only cytology screening (Pap smears). In fact cytology has been effective in reducing cervical cancer incidence rates only in the

Table 1: Characteristics of HPV vaccines

Attributes	**Quadrivalent**	**Bivalent**
Commercial name (manufacturer)	Gardasil® (Merck)	Cervarix® (GlaxoSmithKline)
HPV types in vaccine	6, 11, 16, 18	16, 18
Disease protection	Cervical cancer, genital warts	Cervical cancer
Number of doses (for girls aged 9 to ≤15)	2 doses, the second dose 6 months after the first dose	2 doses, the second dose 6 months after the first dose
Duration of protection	No decrease in protection noted during the period of observation	No decrease in protection noted during the period of observation
Presentation	1 dose vial	1- and 2- dose vials
Method of administration	Intramuscular injection: 0.5 ml of liquid suspension	Intramuscular injection: 0.5 ml of liquid suspension
Contraindications	• severe allergic reaction to any vaccine component or after receiving the vaccine • severe febrile illness • not recommended during pregnancy	• severe allergic reaction to any vaccine component or after receiving the vaccine • severe febrile illness • not recommended during pregnancy
Co-administration with other adolescent vaccines studied and found to be effective	Hepatitis B diphtheria/tetanus/pertussis poliomyelitis	Diphtheria/tetanus/pertussis poliomyelitis
Shelf life	36 months at 2-8°C	1-dose vial: 48 months at 2-8°C 2-dose vial: 36 months at 2-8°C

(Source: Comprehensive Cervical Cancer Control: A guide to essential practice, Second edition, WHO 2014)

Table 2: Correlation between CIN, Dysplasia and the Bethesda Terminology

CIN 1	**CIN 2**	**CIN 3**
Mild dysplasia	Moderate dysplasia	Severe dysplasia / Carcinoma *in situ*
Low-grade squamous intraepithelial lesion (LSIL)	High-grade squamous intraepithelial lesion (HSIL)	High-grade squamous intraepithelial lesion (HSIL)

(Source: Sankaranarayanan R, Wesley R. A practical manual on visual screening for cervical neoplasia. IARC Technical Publication, No. 41. Lyon, France7 IARC Press; 2003)

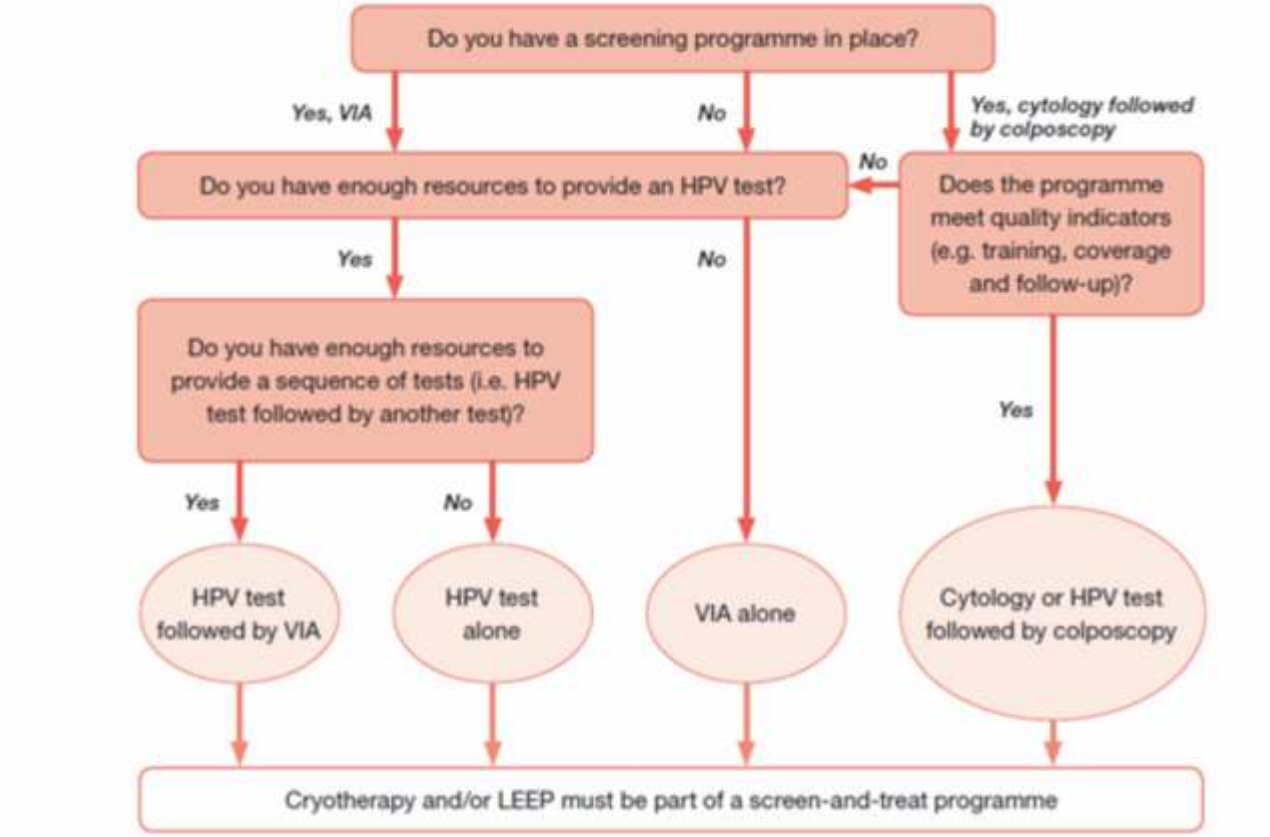

Fig. 1: Decision Making for Screening Strategy

(Source: WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention, 2013)

developed regions with complex health care infrastructure, adequate screening coverage (>70% eligible women) and good internal as well as external quality control. Such significant downward trend in cervical cancer incidence following introduction of large cytology screening was not seen in some lower-resourced settings [14, 15]. In addition, cytology has highly varying sensitivity to detect CIN 2-3 lesions in different settings. A meta-analysis of studies conducted in the developed countries such as UK, France, Germany, Netherlands, US, Canada involving more than 60,000 women aged 30-60 showed that clinical sensitivity of cytology was 53% which indicates that there is a 47% chance of missing an abnormality with each smear [16]. But this low sensitivity is balanced by frequent rounds of screening in these countries. Developed countries screen women at least 15 times in their lifetime with about 70 to 80% coverage of eligible women and such frequent rounds of quality assured cytology screening at repeated intervals of 3-5 years are not feasible in most developing countries including India [17, 18].

Visual inspection of the cervix using acetic acid (VIA):

Alternative low-cost, more sensitive method for cervical cancer screening is visual inspection with acetic acid (VIA). VIA involves application of 3-5% dilute acetic acid using a cotton swab or a spray on the cervix and then naked eye inspection of the cervix under bright light after 1 minute and

looking for the appearance of acetowhite areas in the transformation zone abutting the squamocolumnar junction (SCJ). Test performance of VIA has been evaluated in several cross-sectional studies and in these studies, the sensitivity varied from 67% to 79% and the specificity ranged from 49% to 86% [19].

VIA does not require complex infrastructure and the results are available immediately after the test. VIA is recommended for women aged 30 to 50 when the transformation zone is visible. In older women generally over 50 years of age, the transformation zone recedes inside the endocervical canal and is not properly visible.

Immediate availability of test results with VIA offers an opportunity to treat screen positive women in a single visit 'screen and treat' approach thus overcoming the logistics of recalling screen positive women for further investigations and or treatment and issues associated with lost to follow-up. Cryotherapy is an ablative treatment and it is a simple, less expensive, out-patient treatment modality for the treatment of CIN. Eligibility criteria for the treatment with cryotherapy include full visibility of the squamo-columnar junction, ectocervical lesion, lesion not covering more than 3/4th of the transformation zone, lesion not suspicious of an invasive cancer and lesion not extending into the fornix or vagina. If CIN is detected during pregnancy, treatment may be deferred to 3 months after delivery unless indicative of an invasive cancer.

A single visit 'screen and treat' approach with screening with VIA and treatment with cryotherapy or loop electro-excision procedure (LEEP) is presented in flow chart II (Fig. 2). Women who have been treated for CIN should be followed after a year and offered an HPV test if possible or repeat VIA or cytology. Hysterectomy is rarely needed for the treatment of CIN. Any grade of CIN in fact can be treated with cryotherapy or LEEP which are less invasive procedures whereas hysterectomy is associated with more short-term as well as long-term complications.

A meta-analysis involving 77 papers, including 28,827 cases of treated CIN showed that cryotherapy achieved cure rates of 94.0%, 92.0%, and 85.0% for CIN 1, 2 and 3 respectively; use of the double-freeze method and absence of endocervical involvement significantly increased cure rates [20]. Excisional treatment with LEEP is needed for less than 10% of the women with CIN.

A single round of screening using VIA in a randomized trial in rural South India was associated with a 25% reduction in cervical-cancer incidence and a 35% reduction in mortality [21]. Another study in western Maharashtra showed feasibility of VIA screening at the community level and 31% reduction in cervical cancer mortality with four rounds of screening with the potential to reduce 22,000 deaths per year in India [22].

HPV testing:

The knowledge that HPV infection is necessary for development of cervical cancer has led to the evaluation of HPV test as a primary screening test for detecting high-grade cervical cancer precursors. An HPV test can correctly identify women who have CIN 2-3 lesions or who could be at risk in the next 5-10 years. At least 10 randomised trials have shown that HPV testing is superior to cytology for detecting CIN 2-3 lesions. A single round of screening using HPV testing in the rural India involving 130,000 women was associated with 53% reduction in cervical cancer incidence and 48% reduction in mortality [23] with immediate and global implications [24] for re-structuring cervical cancer screening practices across the world. Among women who tested HPV negative, there were no cervical cancer deaths in the 8-10 year period suggesting that at least once

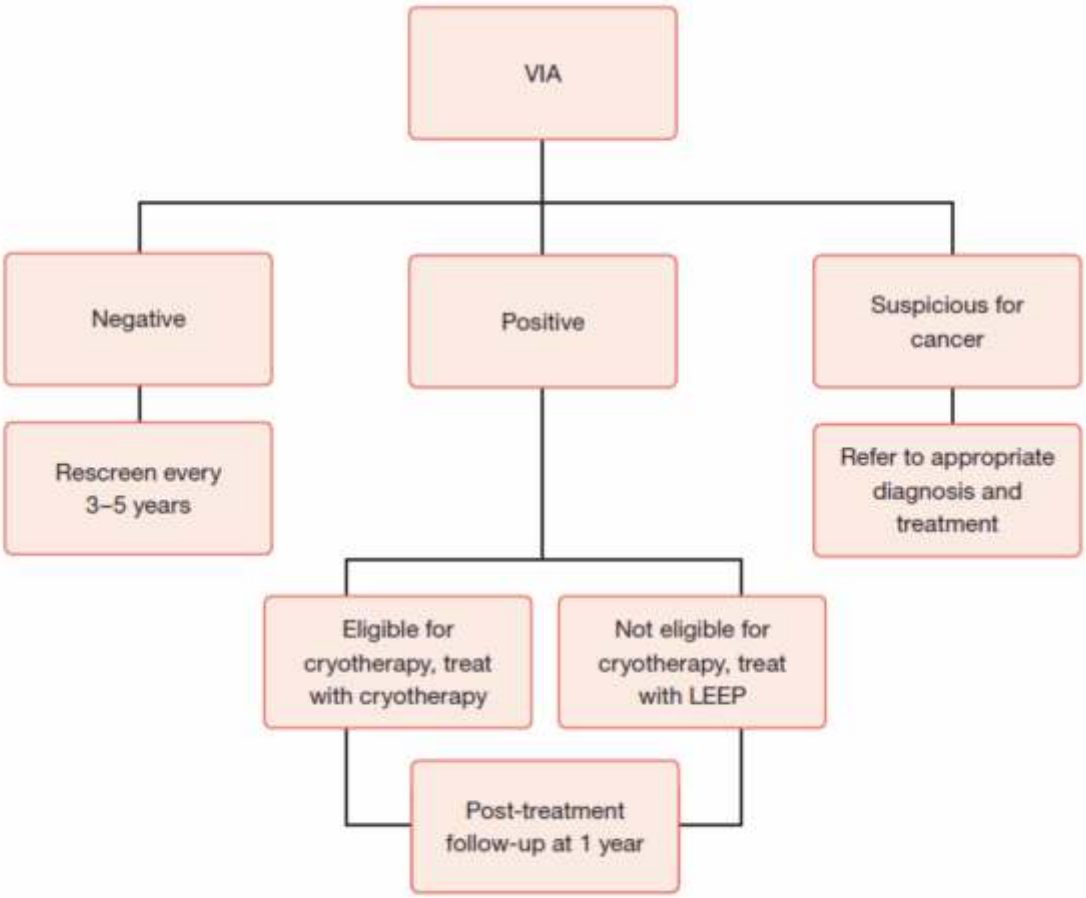

Fig. 2: Screen with VIA and Treat with Cryotherapy or LEEP when Not Eligible for Cryotherapy

(Source: WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention, 2013)

in a life time screening can prevent substantial number of cancer deaths. About 6 countries have included primary screening using an HPV test for women over 30 years in their national program [7].

HPV DNA test is currently expensive and a low cost HPV test, the *care*HPV test has good sensitivity and specificity for the detection of HPV infection and is a promising primary screening method for cervical cancer in low-resource regions [25]. This test is specially developed for the low-resource setting and does not require running water or electricity and results are available within 2.5 hours. However it is still not as cheap as VIA and till the time its cost comes down for widespread use, VIA screening and treatment of CIN with cryotherapy is a viable and well documented option. Implementation of VIA screening can develop health infrastructure for integrating low-cost HPV test in the future.

An algorithm when HPV test is used as a primary screening test and VIA is provided as a second screening test to determine whether or not treatment is offered, is presented in flow chart III (Fig. 3). When HPV test is used as a primary screening test and colposcopy with or without biopsy is offered for histological confirmation of disease followed by treatment with cryotherapy or LEEP (as indicated) is presented in flow chart IV (Fig. 4). Women who are less than 30 years of age

should not be screened with an HPV test because transient HPV infections are common in young women. HPV testing of women over 30 years can exclude women with transient infections that are likely to get resolved with the natural immune response and can avoid unnecessary interventions. Whenever there is a facility for colposcopy and directed biopsy, it can be included for those who screen positive by either VIA or by an HPV test.

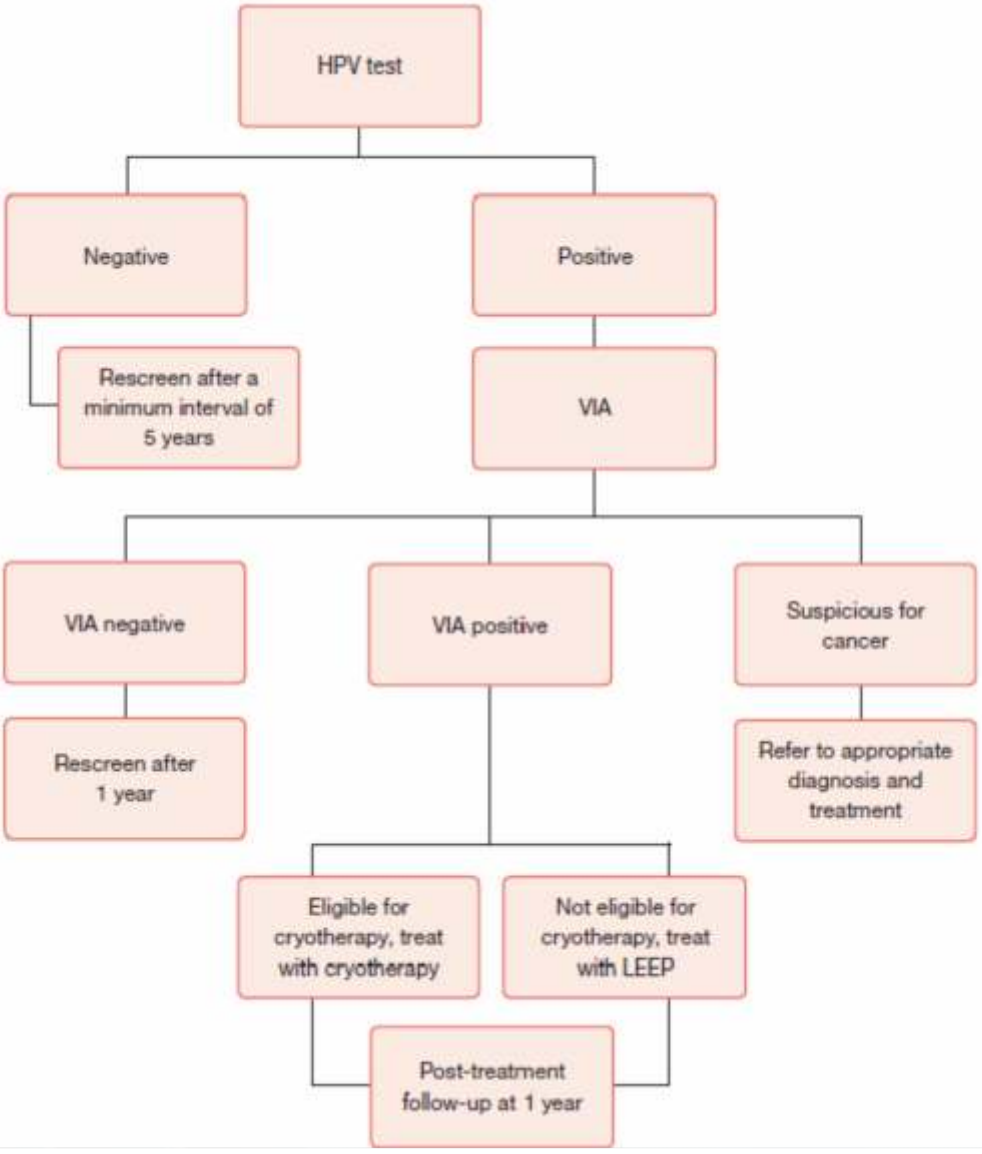

Fig. 3: HPV Test as the Primary Screening Test and VIA as a Second Screening Test and then Treat with Cryotherapy or LEEP

(Source: WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention, 2013)

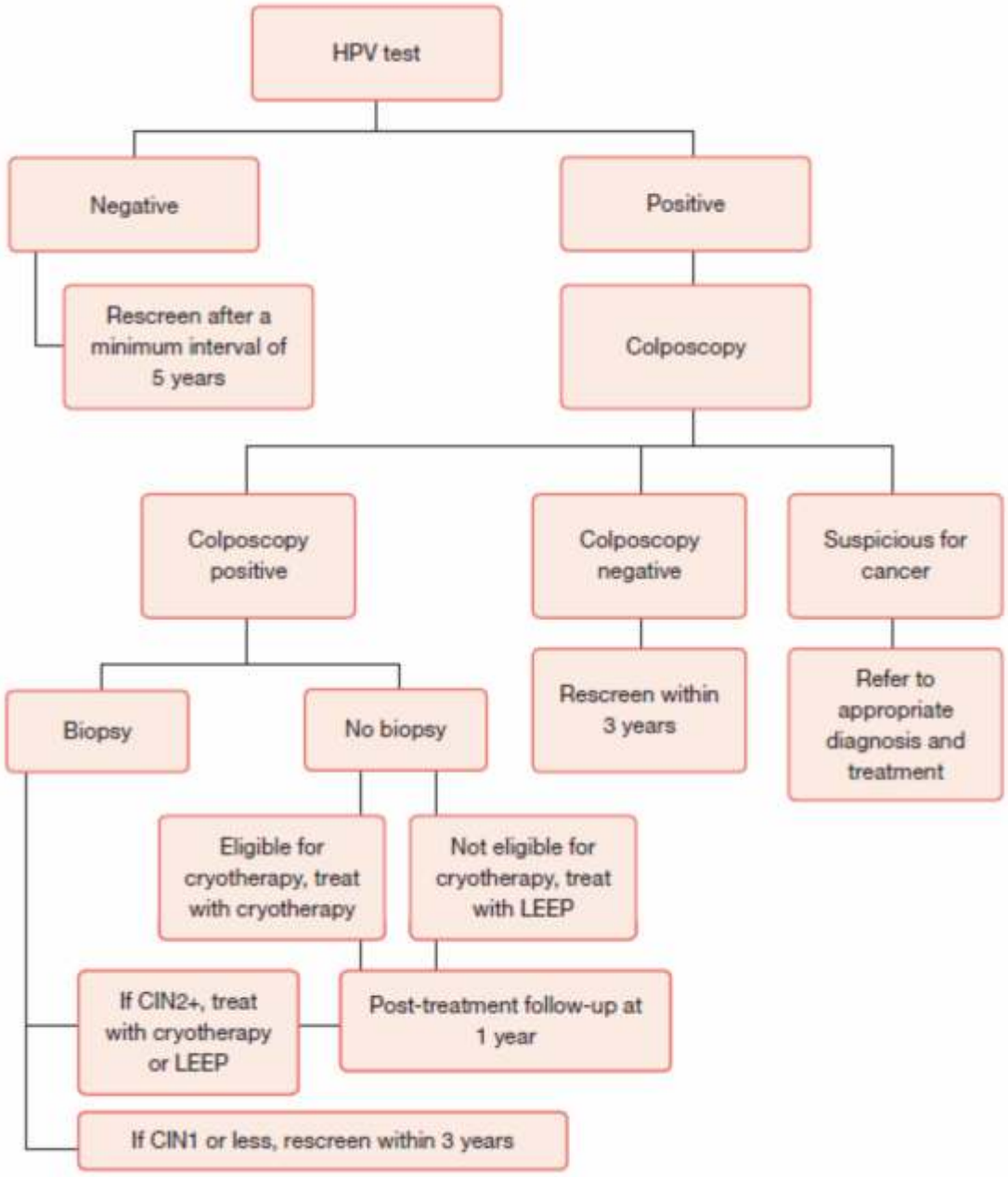

Fig. 4: Primary Screening with an HPV Test followed by Colposcopy (with or without biopsy) and Treatment

(Source: WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention, 2013)

Scope for India to prevent cervical cancer deaths:

Following recommendations of the WHO, about 25 countries have included VIA screening in their national programme. Some of the countries in Asia that have implemented VIA screening in the public health programme are China, Thailand (some provinces implement VIA and some provinces implement cytology) and Bangladesh [7, 26] whereas only two Indian states (Tamil Nadu and

Sikkim) have implemented VIA screening in their public health programme.

Public as well as private health care providers/ obstetricians/gynecologists in India have refrained from introducing VIA screening and treatment with cryotherapy in their practice without realizing that the guidelines incorporating cytology screening developed in the western countries are not always applicable to the developing regions. Majority of the Medical Colleges in India continue to include only cytology screening in the medical curriculum/ public hospitals and therefore new generation of doctors remains unaware of VIA screening and its benefits. According to an estimate in year 2000, 80 percent of outpatient visits in India are to private clinics [27]. With this background, an initiative by the Population Services International-India to screen about 300,000 women from 3 districts in Uttar Pradesh using VIA and treatment using cryotherapy through a network of about 100 private providers which was launched in mid 2014 is noteworthy [28].

Cervical cancer burden can be reduced in India and other developing countries if recent advances in primary as well as secondary prevention of cervical cancer prevention are considered and a comprehensive strategy is planned and implemented. India is a home to 115 million adolescent girls aged 10-19 years [29]. Considering half of them to be in 10-15 age groups, about 57.5 million girls are immediately eligible to receive 2 doses of HPV vaccine. Primary prevention with vaccination will prevent next generation women from developing cervical cancer about 20 years later.

There are inequalities in the screening coverage in Indian women and effective screening coverage is less than 10% [30]. Majority of the women in India are unaware of the benefits and necessity for screening for themselves and vaccination of their daughters. If high rates of cervical cancer vaccination as well screening uptake have to be achieved, we need large scale mass awareness programmes and community education with a well designed communication strategy with innovation and advocacy by cancer survivors and celebrities. Cervical cancer prevention efforts should be integrated with the national programmes. Cervical cancer screening tests have evolved in the last 40 years and there is a need for integrating evidenced based cervical cancer screening and treatment into medical education as well as private practice.

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