Introduction

The burden of cervical cancer in India is enormous accounting for about 20 per cent of all cancer related deaths in women and is the number one cause of death in middle aged Indian women. It is paradoxical that so many deaths are occurring in spite of cervical cancer being a preventable disease. Organized population based screening linked to treatment of the detected neoplasias can lead to more than 70 per cent reduction of disease related mortality. Unfortunately, cervical cancer control is not yet among the top ten National health priorities in India. As a result, a comprehensive National Health Strategy for cervical cancer prevention is still lacking. Until recently, cervical cancer screening was dependent on Pap smear cytology that has certain inherent problems, especially in resource-poor settings. The test needs laboratory based infrastructure not available in the primary health care centres in India.

The training requirement is intensive and trained cytopathologists are largely unavailable. The cost of the test is high and is unaffordable for a nationwide program. Certain logistic issues like transporting the smears from the screening center to the laboratory, delivering the reports and recalling the test-positive women for further management are hard to implement. The sensitivity of Pap smear when objectively evaluated by a multi-centric trial in different institutions in India was found to be moderate to poor. The quality control needs for a cytology based screening program are very stringent and difficult to put into practice in our country.

Significant research developments over the last few years have the potential to change the paradigm of cervical cancer prevention and control. These are: the validation of VIA as the alternative, low cost screening test; resurgence of cryotherapy as a simple yet effective...
technology to treat cervical precancers; identification of simpler logistics like ‘single visit approach’ and most crucially, the availability of two very efficacious vaccines against human papilloma virus (HPV). A comprehensive national strategy based on the appropriate and judicious use of the above-mentioned approaches can make cervical cancer control a reality in India.

Current status of cervical cancer screening activities in India

In absence of the organized screening program, routine screening of asymptomatic women is almost non-existent in India. In the public sector, the facilities for Pap smears are mostly limited to the tertiary care centers where the test is usually offered to women with symptoms of reproductive tract infections or advanced cervical cancer. Most of the institutions performing Pap smears do not have facilities for colposcopy or treatment of cervical precancer. Management of abnormal Pap smear is either follow up or hysterectomy. So the low intensity, opportunistic screening without any linkage with diagnostic/treatment services and without any quality control mechanism is totally ineffectual. The awareness about cervical cancer and its prevention, among educated as well as illiterate population, is extremely poor. As a result there is no demand to provide cervical cancer screening service from the potential beneficiaries. The public health authorities and the health policy-makers are not adequately sensitized to the need and are not aware of the recent developments.

The National Cancer Control Program (NCCP) formulated and funded by the Ministry of Health, Government of India has stressed upon the implementation of community based cervical screening program at least in select districts of each state. A national guideline for cervical screening was prepared by the expert committee of the Ministry that included representatives from the Regional Cancer Centres, Federation of Obstetrics and Gynaecologists of India, Indian Academy of Cytologists, World Health Organization and International Agency for Research in Cancer, France. The NCCP has made provision for fund to be given to all the states to implement the cancer control program that includes cervical cancer screening activities. Unfortunately, very few states have initiated the program due to competing priorities of the state health services, lack of dedicated leadership and under-developed facilities for service delivery.

Implementation of organized screening programme

For such a diverse country as India it is difficult to advocate a uniform implementation strategy. The new program should ideally be integrated into the existing health services and should have components as well-defined target population, linkage between detection and treatment and appropriate quality control. A key determinant of success of cervical cancer screening program is the coverage of the target population. At least 60 per cent of the women belonging to the designated age group have to be screened to attain an appreciable reduction in mortality. To achieve a high coverage, the screening facilities should be made accessible to the rural population who comprise nearly 70 per cent of our total population. The primary health centers and the district hospitals are the ideal places to set up the screening facilities. As recommended by the National Guidelines for Cervical Cancer Screening, women between 30-60 yr of age are to be screened by VIA, at least once in a lifetime to begin with. Nurses and female health workers need to be trained to perform the test. The VIA positive cases should be referred to the colposcopy clinics that should be set up at the district headquarters to perform colposcopy as well as treatment of precancers. Cryotherapy has been proved to be a safe, low cost and effective method of treatment for selected cases of all grades of cervical intra-epithelial neoplasia (CIN). Cure rates after cryotherapy for CIN are between 86 and 95 per cent, comparable to Loop Electrosurgical Excision Procedure (LEEP). All CIN cases should be evaluated for the feasibility of cryotherapy during colposcopy. If appropriate, cryotherapy should be done at the same sitting as colposcopy after obtaining a punch biopsy without waiting for the biopsy report. Such ‘see and treat’ approach can reduce the number of non-compliance to treatment and improve the efficiency of the program. At the district hospitals with both screening and colposcopy facilities, VIA, colposcopy and treatment can be completed in a ‘single visit approach’. Cervical precancers not suitable for cryotherapy need to be treated by LEEP either at the district hospitals or at higher centers. Single or two visit screening and treatment of every woman with VIA, once in her lifetime at age 35-40, would lead to a 22-32 per cent reduction in cervical cancer incidence for less than US $50 per year of life saved.

Health care delivery in India is multifaceted, consisting of varied practitioners and institutions and have mixed ownership patterns. The logistics of
implementation of cervical screening program, like any other program, will be different in different states and regions. The local state health authorities have to work out the mechanisms of utilization of the existing health infrastructure, programme management and supervision, quality assurance and involvement of other stakeholders like non-governmental voluntary organizations. The public awareness and education campaign have to be designed to meet the local needs and should be culturally appropriate. All the components of service delivery should be in place before the awareness campaign is launched. Structured, competency-based training and periodic refresher courses for all levels of service providers have to be organized.

Cervical cancer control programme in the context of HPV vaccines

The facts that HPV infection (oncogenic types) is necessary for the development of cervical cancer and that more than 70 per cent of the cervical cancers are attributed to types 16/18 led to the development of the HPV vaccines directed to HPV 16/18. Both the vaccines ready for licensing in India (Cervarix™ by GlaxoSmithKline and Gardasil™ by Merck & Co.) have been found to be very effective in preventing persistent infection with HPV 16/18 and high grade CIN attributed to these two subtypes11. This is likely to be translated into high protection against cervical cancer in the vaccinated population. One mathematical model suggested that a vaccine with 98 per cent efficacy against 16 and 18 could, within 40 to 50 years, reduce cervical cancer incidence by 51 per cent, if all adolescent girls were vaccinated before sexual debut12.

Both the vaccines are likely to get regulatory approval for marketing in India within a short time. The vaccines should be administered to girls and young adults before they become sexually active. The HPV vaccines are a major breakthrough in the control of cervical cancer for countries like India with high disease load and without any organized screening program.

Introduction of HPV vaccine in a country with existing cytology-based screening programme is likely to reduce substantially the number of abnormal Pap smears, number of follow ups due to low grade abnormalities on cytology or histology and number of treatments for cervical precancers. This will not only reduce the logistics and fiscal burden on the programme but will also spare large number of women from unnecessary anxiety related to abnormal screening test results.

In India, it can always be debated whether introduction of cervical cancer screening programme at this juncture is at all practicable or we should straightaway settle for a HPV vaccine based primary prevention strategy. In addition to the huge logistics and fiscal implications of launching a new screening program, the following shortcomings of cervical cancer screening program should be considered.

- No screening test is 100 per cent accurate. As a result there is bound to be false positive or false negative results leading to unnecessary investigations or screening failures.
- Since all the CIN cases are not likely to progress to invasive disease, a certain amount of over-treatment is inevitable in any screening program.
- A number of women are likely to suffer from treatment complications.
- The psychological consequences of getting a positive screening test are enormous as many of the women mistake the positive test result as diagnosis of cancer.
- The morbid fear of getting a cancer diagnosis will always keep a group of women away from the screening programme13.

In spite of all the drawbacks we need to have a screening program in India. A vaccine-based programme is not going to be 100 per cent protective as cervical cancer can still be caused by HPV types not prevented by the vaccines. Girls and women who are already infected by the HPV types 16 and/or 18 are not likely to be benefited by the vaccines. The cost of vaccine is still prohibitively high to consider its introduction in a broad based national program. Even after introduction the impact of vaccination on the disease burden in the population is going to take 15-20 years to be evident. During this intervening period cervical cancer screening is the only feasible option to reduce cervical cancer deaths in India. To increase the uptake of the cervical cancer screening program public education campaign is essential. The improved awareness about cervical cancer will set the stage for the introduction of the new vaccine in the near future.

Efficacy & safety of HPV vaccines

In randomized double blind studies, the bivalent vaccine (Cervarix™) was found to have 87.5 per
cent efficacy in preventing persistent infection due to HPV 16/18 and 92.9 per cent efficacy in preventing HPV 16/18 associated cytological abnormalities on intention-to-treat analysis\textsuperscript{14}. Intention-to-treat analysis of the efficacy of the quadrivalent vaccine (Gardasil\textsuperscript{138}) observed that the vaccine was 88 per cent effective at preventing persistent infection and 100 per cent effective in preventing histologically proved cervical disease associated with HPV 6/11/16/18\textsuperscript{14}. As the intention-to-treat cohorts represent the more ‘real world’ situation, both the vaccines have high potential of reducing HPV 16/18 associated cervical neoplasias. Both the vaccines were found to be safe with mild and transient adverse effects.

The results from the trials evaluating the safety and immunogenicity of both the vaccines among Indian women are likely to be published soon. Further information can be obtained from the demonstration projects planned after the licensing of the vaccines. The vaccines are likely to offer substantial protection against cervical cancers to Indian women since a recent meta-analysis observed that HPV 16/18 were responsible for 78.9 per cent of all the invasive cervical cancers in India\textsuperscript{15}.

A national program based on vaccinating a target population appears to be logistically simpler than the screening based approach in India. The infrastructure and trained personnel for vaccination are already in place at all levels of health service delivery. There is a reasonable degree of awareness and acceptance of vaccines in general in the community. The results of the latest 2005-06 National Family Health Survey (NFHS 3) of India revealed that 95 per cent children aged 12-23 months received at least some of the recommended vaccines\textsuperscript{16}. However, the HPV vaccine has certain potential problems that may interfere with its widespread acceptance in the general population.

**Potential barriers to HPV vaccine**

The HPV vaccine is going to pose certain socio-cultural obstacles due to the facts that the vaccine is against a sexually transmitted infection (STI). It is advocated only for women, at least to begin with, and the target age group is adolescent girls.

A vaccine targeting an STI has the potential to be stigmatized. The parents may not give consent and the young adult women may not be willing to go for such a vaccine. The health care providers may also be reluctant to recommend the vaccine to general population due to their personal beliefs (that girls from good families do not require such protection) and anxieties about the parental reactions. Some parents may get concerned that if they give consent for administering HPV vaccine to their daughters that may convey a ‘no objection to sex’ message to them. A recent survey on the acceptability of HPV vaccine among the educated, high income, urban parents in Kolkata (eastern India) observed that only 11 per cent of the parents agreed to this statement (unpublished data).

The issues related to the sexual transmissibility of HPV and girls requiring protection before being sexually active may have to be discussed with the young girls that neither the parents nor the health care providers may feel very comfortable about. A proposed solution to this problem has often been that the vaccine should be popularized as an anti-cancer vaccine and not an anti-STI vaccine. It is too early to comment on the accuracy of this hypothesis.

A gender-specific public health approach always runs the risk of causing misconceptions about future fertility and child bearing in certain segments of the community. These issues require sensitive handling with appropriate public education and peer group support.

The adolescent girls who are the primary targets of HPV vaccine do not receive any vaccine under the expanded program on immunization (EPI) except for the booster dose of Diphtheria-Tetanus around 10 yr of age. They visit the health facilities infrequently. In India the schools generally do not actively participate in vaccination program. So the target age group for the vaccine may be hard to reach. The current recommendation is that the vaccine should be administered in three doses. The experience with other vaccines requiring three doses (DPT, Polio) shows that there is a high rate of dropouts between first and third doses in our country\textsuperscript{16}. To be effective the vaccination program has to achieve high coverage as well as high compliance to the recommended dosage schedule. The service delivery model of packaging the new vaccine into the existing vaccination program has to be worked out and may not be uniform all over the country.

**Cost of the vaccine and financing options**

The HPV vaccines will be much more expensive than the traditional EPI vaccines even after substantial subsidization promised for the developing countries. The entry price for the Merck vaccine in US was...
US $120 per dose. The highest UNICEF Weighted Average Price per dose for any of the EPI vaccines is US $0.177 for DTPw vaccine. In comparison even a US $2 price-tag for HPV vaccine appears to be unaffordable from public health point of view. Several other important vaccines are already in the market or will be available soon and are going to compete for limited resources. In addition to the HPV vaccine costs, other expenses incurred due to vaccine wastage, freight, maintaining the cold chain, transport cost need to be financed.

Both GlaxoSmithKline and Merck have pledged to offer lowered prices to developing countries for their HPV vaccines and are likely to use multi-level pricing to ensure availability of the vaccines in the resource-poor countries. They have also committed to provide free vaccines to conduct the demonstration program by Government of India in collaboration with Programme on Appropriate Technology in Health (PATH). In the long run the prices are going to come down with entry of more suppliers in the market and with a stable and high volume demand. Till that happens the vaccine will remain too expensive to be supported by the government agencies and will be opportunistically used by those who can pay from their own pocket.

Global Alliance for Vaccines & Immunization (GAVI) is going to be a major source of external assistance for the HPV vaccine as they have already included HPV vaccine in their Advanced Market Commitment (AMC) plan. The policy makers at the Ministries of Health and Finance need to be convinced that the new strategy is cost-effective and sustainable before approaching international agencies for funding. The impact of HPV vaccination of preadolescent girls in India was calculated assuming 70 per cent coverage of the target population. Vaccination alone was observed to reduce lifetime risk of cervical cancer incidence by 44 per cent (range, 28-57%). The authors also found that a combined approach of pre-adolescent vaccination and screening three times per lifetime after age 30 using single visit VIA, both at 70 per cent coverage, is expected to prevent more than 1.25 million cervical cancer deaths over the lifetimes of 10 consecutive birth cohorts. At a cost per vaccinated child of 2005 international $ 10 (per dose cost $ 2) pre-adolescent vaccination followed by screening three times per lifetime using VIA would be considered cost-effective using the country’s per capita gross domestic product ($ 3452) as a threshold.

Summary

In India Cervical Cancer Control Program is not yet implemented in spite of the formulation of national guidelines and availability of fund from the National Cancer Control Programme. The state health administrations have to be sensitized to launch the program using service delivery models most suitable to them. Launching community based low intensity cervical screening in combination with awareness campaign and monitoring system should be the priority of the cervical cancer control program. The HPV vaccine is a safe and effective option for cervical cancer prevention. The cost is prohibitive to consider it for a national program in India at this juncture. Experience gathered in terms of vaccine effectiveness, safety, acceptability, service delivery logistics and cost-effectiveness from demonstration programs will be useful to plan future vaccination strategies. Such demonstration programs with 100 per cent financing options for the vaccine should be the priority. The national consensus guidelines for vaccine administration in India should be formulated.

References


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