Original Article

Does India need an indigenous HPV vaccine and why?

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Abstract Cervical cancer is the most common form of cancer in Indian women, causing high morbidity and mortality. Two effective and safe vaccines exist, but these remain out of reach of most people due to their high cost. It is imperative that an Human Papillomavirus (HPV) vaccine be affordable and cheap so that the target population can be vaccinated, to make a real impact in reducing the disease burden. We argue that in the long run India needs to develop and manufacture its own HPV vaccine in order to bridge this price gap. We also explore other strategies that can be adopted to increase the accessibility and affordability of this life-saving vaccine during the interim period.
Journal of Public Health Policy (2013) **34,** 272–287. doi:10.1057/jphp.2013.4; published online 28 February 2013

Keywords: India; HPV vaccine; health policy

Cervical Cancer (CaCx) – An Important Cause of Mortality in Indian Women

CaCx is the most prevalent form of cancer in Indian women, having an annual incidence of 134 420 that accounts for 25.9 per cent of all cancers affecting women. Data generated by the National Cancer Registry Programme (NCRP) of the Indian Council of Medical Research, which has a number of population-based cancer registries (PBCRs) under its purview, indicate that cancer of the cervix and breast are the leading sites of cancer in Indian women. Under the NCRP, the PBCR at Barshi is the only cancer registry that is currently representative of India's rural population. The Chennai PBCR has the highest age-adjusted incidence

rate of CaCx, which could be the *tip of the iceberg*, as many cases go unreported and undiagnosed, with approximately 70 per cent of the Indian population residing in rural areas. Therefore, CaCx is an important cause of mortality in Indian women associated with much suffering and disruption of family life that has societal implications.

Human Papillomavirus (HPV) – The Etiologic Agent of CaCx

HPV are epitheliotropic, non-enveloped DNA viruses classified under the family *Papovaviridae*. At least 30 HPV types infect the genital mucosa and are sexually transmitted. Genital HPV can be low-risk, causing genital warts, or high-risk, causing CaCx. The most common low-risk HPV types that cause up to 90 per cent of all genital warts are HPV-6 and HPV-11, whereas the most common high-risk HPV types that account for ~70 per cent of CaCx are HPV-16 and HPV-18. The most prevalent high-risk HPV types present in Indian women with CaCx are HPV-16 and HPV-18, with HPV-16 being the most prevalent type. The order of the other high-risk types following HPV-18 is not constant and varies from study to study. A recent comprehensive study, representing 4 regions of India and involving 667 histopathologically confirmed cases of squamous cell carcinoma, found that HPV types 45, 73, 31, 56 as well as others could play a more important role in the Indian context than previously thought.[1]

Approximately 80 per cent of sexually active women become infected with HPV at some point in their lives.[2] Most infections are transient and asymptomatic, but persistent infection can lead to CaCx.

CaCx Versus Other Diseases: Priority Setting – A Difficult Balancing Act!

Although CaCx is a major cause of mortality in Indian women, other diseases also deserve equal attention, including childhood killers such as diarrheal diseases and pneumonia. Despite safe and effective vaccines for many diseases, programmatic hurdles, including cost and logistics, hinder vaccination. Implementation of second-dose measles vaccine is hindered by space constraints in the cold chain, as polio eradication is still ongoing. Human resources are another hindrance in vaccination drives.

Setting priorities is difficult in countries like India, often becoming a juggling act, with need for carefully weighing the *pros and cons* before taking any concrete decisions. The process resembles triage decision making commonly undertaken in hospitals, but on a much larger scale.

HPV Vaccines – Issues, Challenges, and Opportunities

Two safe and effective licensed HPV vaccines, Gardasil® (Merck) and Cervarix® (GSK), are available internationally and offer previously unthinkable opportunities for promoting women's health (Table 1).

In the vaccine development process, the technology platform used can affect the product's price. The virus like particle (VLP) technology used in HPV vaccine development is made up of particles mimicking the structure of a natural virus but lacking its genetic material required for replication or infection. Hence, these non-infectious particles have the ability to trigger strong immune responses capable of protecting against viral infection. The HPV–VLP platform was originally developed at the United States (US) National Cancer Institute (NCI), National Institutes of Health.

Table 1: Comparison of Gardasil® and Cervarix®[a]

	Gardasil®	*Cervarix®*
Manufacturer	Merck & Co., Inc.	GlaxoSmithKline Biologicals
Vaccine	L1 VLP vaccine based on recombinant yeast (*Saccharomyces cerevisiae*) technology	L1 VLP vaccine based on recombinant baculovirus technology
Valency; HPV types covered; Protection conferred	Quadrivalent; Covers Types 6, 11, 16, 18; Protects against CaCx and genital warts	Bivalent; Covers Types 16, 18; Protects against CaCx
Adjuvant	Alum (aluminum salt)	AS04 (alum plus proprietary adjuvant MPL)
Dosage and schedule	0.5 ml IM. Three injections at months 0, 2, 6	0.5 ml IM. Three injections at months 0, 1, 6
Target audience	Adolescent girls and boys	Adolescent girls
Cold chain	✔	✔
Safety	✔	✔
Immunogenicity	✔	✔
Efficacy	✔	✔
Price	Highly expensive	Highly expensive

MPL: 3-deacylated monophosphoryl lipid A; VLP: virus like particle; IM: intramuscular; ✔: yes.
[a]After PATH (2006). Current and future HPV vaccines: Promise and challenges.

Originally, both the major (L1) and the minor (L2) capsid proteins of HPV were employed to generate VLPs, although currently only L1 is used. The gene encoding L1 is cloned into an expression vector and expressed either in the yeast *Saccharomyces cerevisiae* (Gardasil®) or in baculovirus system (Cervarix®). The other low-cost, low-technology platform for production of VLPs, although of smaller size, is the *E. coli* platform, originally developed at the University of Colorado, Boulder, USA. The *Pichia pastoris* platform is also currently being explored for generating a less costly version of the VLP-based HPV vaccine. The immunogenicity of VLP-based vaccines depends on the VLP size and structure that mimic the natural configuration of the virus, ideally exhibiting a $T=7$ geometry. From this standpoint, yeast systems are superior to the bacterial system.

VLP platform choice depends on factors such as the capacity of the vector to carry foreign DNA, the yield of the VLPs, as well as process development issues such as scalability, purification, formulation, and analytical methods. Properly standardized and validated assays are required for pre-clinical development as well as for clinical trials for assessment of safety, immunogenicity (type and magnitude), as well as for determination of end-points and establishment of surrogates of protection.

Intellectual Property (IP) issues are important because they affect decision-making about the availability of expression system(s) to Indian manufacturers for developing a second-generation HPV vaccine. Collaborative efforts seem likely to yield better results in overcoming IP challenges. Important collaborations already in progress include those between NCI (Bethesda, USA) and Johns Hopkins University (Baltimore, USA) working with Shantha (Hyderabad, India); and between University of Lausanne (Lausanne, Switzerland) and Indian Immunologicals (Hyderabad, India).[3]

Technicalities and complexities involved in vaccine development have a direct bearing on pricing of the end product. The simpler the method, the less expensive the vaccine. The current first-generation HPV vaccines – Gardasil® and Cervarix® – both employ expensive expression systems and complicated methods that add to the cost of the final product. In addition to the direct costs of the vaccine manufacturing process, others are added during the delivery process: Costs to maintain supplies, involving labor, transportation, communication, training, and storage space. The polio elimination drive is far from over in India, as even in today's polio-free situation maintenance continues. Therefore, any new vaccine will be jostling for space in the cold chain. These ground-level

realities need to be incorporated during early stages of planning. Wastage due to power failures, human errors, and expiry due to underutilization can all increase delivery costs.

HPV vaccine raises special issues pertaining to adolescent health. HPV will be the first adolescent vaccine in India, where the concept of adolescent health is still in its infancy. Deciding on the ideal age of vaccination remains unresolved. How to place the vaccine in advocacy campaigns is also a major issue. Should it be an anti-cancer vaccine or a vaccine against sexually transmitted infections (STIs)? Resolution of some societal and moral issues will be India-specific. Adequate data are unavailable on whether the vaccine is likely to promote promiscuity among adolescents. Thus, societal norms prevailing in Indian society pertaining to ethical and moral value systems regarding sexuality need to be investigated.

Vaccine Cost

Currently available first-generation HPV vaccines are the most expensive vaccines in the US Centers for Disease Control and Prevention Pediatric/Vaccines for Children (CDC Pediatric/VFC) vaccine price list (updated on 2 November 2011).[4] A major factor contributing to the high cost of these vaccines is that the manufacturers are trying to recover rapidly their financial investment in R&D, making cost the major limiting factor for access to these vaccines.

Although the Indian Academy of Pediatrics Committee on Immunization recommends the HPV vaccine,[5] access will, for the present, be restricted to those who can afford the vaccine from the private sector, and who ironically require the vaccine least of all. Most Indian households cannot bear the costs of the current HPV vaccines out of pocket (Figure 1).[22]

Are there ways to expedite access to this life-saving vaccine for those people who need it most? Yes, and these must be explored. With vaccine price the major impediment to access, our goal should be to bring down the cost. We discuss strategies to lower the price of the existing HPV vaccines in the short-term, while simultaneously exploring the possibility of developing an indigenous HPV vaccine as a possible long-term solution. We highlight below lessons from the Hepatitis B vaccine development and implementation era that may help planning the introduction of HPV vaccine in India. The Hepatitis B and HPV vaccines share common attributes. Both are anti-cancer vaccines. Both diseases can be spread by sexual contact, HPV more commonly.

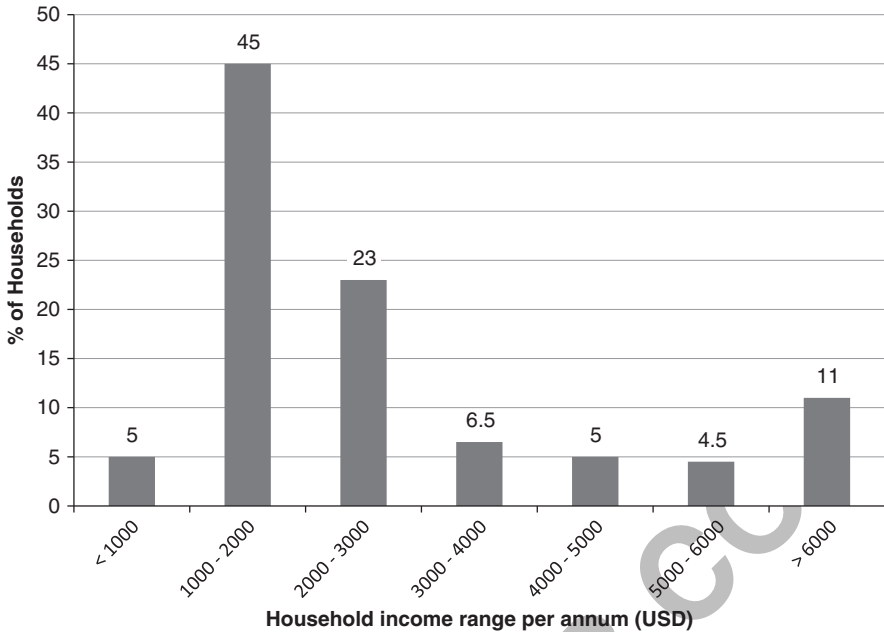

Figure 1: Distribution pattern of income of Indian households.
Note: On the basis of data obtained from the World Resources Institute.[22]

The Hepatitis B Vaccine Development Era – What Lessons Have We Learnt?

India has been historically slow to introduce new vaccines (Table 2).

For Hepatitis B vaccine, it has taken approximately 17 years for India to initiate a process for adding it to the national program. Following pilot projects, the Government of India expanded Hepatitis B vaccination through the routine immunization program in all districts of the 10 best-performing states, and is planning further expansion.[6]

The contribution of a number of Korean companies toward price reduction of the Hepatitis B vaccine provides a useful lesson. Three Korean companies, namely, Cheil Co (then a subsidiary of Samsung Corp.), LG Chem Korea, and Korea Green Cross contributed most. (LG Life Sciences is a LG affiliate spun-off from LG Chem in 2002.) These companies produced the initial plasma-derived Hepatitis B vaccine and later a recombinant DNA Hepatitis B vaccine.[7]

Table 2: Comparison of the timeline for the introduction of major vaccines in India and in other countries of the world

Diseases	*Type of vaccine*	*Year of introduction*		*Time lag (in years)*
		India	*Other countries*	
Smallpox	Glycerinated vaccine lymph	1898	1890s	8
	Live-attenuated freeze-dried vaccine	1965	1941	24
Cholera	Killed whole cell (WC) *Vibrio cholerae* with rBS vaccine (Dukoral®)	Not introduced	1991	21 years and counting …
Tetanus	Tetanus Toxoid (TT): Purified toxoid adsorbed to aluminum phosphate	1972	1963	9
Tetanus, Diphtheria, Pertussis, Childhood TB	TT, DPT, BCG: Purified toxoids adsorbed to aluminium hydroxide	1978	1963	15
Polio	Inactivated vaccine	1984	1955	29
Hepatitis B	Recombinant Hepatitis B Surface Antigen (HBsAg)	1997	1980s	17

TB: Tuberculosis; DPT: Diphtheria, Pertussis, Tetanus; BCG: Bacillus Calmette-Guérin.

A global effort involving Global Alliance for Vaccines and Immunization (GAVI), WHO, and UNICEF, among others, promoted the introduction of Hepatitis B vaccine into national programs, but commitment from developing-country companies made lower-cost vaccines available to national programs. In addition to the three Korean companies, other contributors from developing countries include Bio Farma (Indonesia) and Shantha (India). When companies become involved in producing less-expensive vaccines, it is important that they have assurances of vaccine uptake so that they can invest in vaccine development.

Satisfying India's HPV Vaccine Needs – Short-Term and Long-Term Strategies

An affordable HPV vaccine is still a long way off. Recent Indian efforts in both the private and public sectors are very encouraging, but will likely require up to a decade to bear fruit. Any vaccine development endeavor requires time, effort, and money.

Every 5 years of delay in introduction of a HPV vaccine is likely to result in ~2 million more deaths arising from HPV infections.[8] Importantly, >80 per cent of women dying from CaCx are from developing countries, and projections indicate that by 2020 this figure could well increase to ~90 per cent.[9] Modeling studies suggest that the current HPV vaccines (Gardasil®/Cervarix®), if used judiciously along with screening strategies in developing countries, have the potential to reduce the lifetime risk of CaCx by as much as 60 per cent.[8] Unfortunately, the major hindrance remains the high price. Therefore, there is an urgent need to explore strategies from which not only India but potentially the entire South East Asia Region (SEAR) can benefit.

Two strategies may be needed to expedite the delivery of HPV vaccine to the people who urgently need it. *Short-term* and *long-term* strategies are discussed below.

Short-Term Strategies

The short-term strategies aim to make the current HPV vaccines available at lower cost to ensure easier uptake by national programs. Thus, uninfected adolescent girls can be immunized early and catch-up vaccination can be given to those considered at lower risk. Cost-reduction strategies are discussed below.

Evolving an 'ideal' bulk-purchasing mechanism

Can a fund be created along the lines of the Revolving Fund (RF) of the Pan American Health Organization (PAHO) that would specifically cater to the vaccine procurement needs of the countries of the SEAR? The PAHO–RF was authorized in 1977[10] and has operated for over three decades. Organizing joint procurement of vaccines and allied supplies for its participating member states, it dramatically increased vaccine access in Latin America and Caribbean countries, particularly for *Haemophilus influenzae* Type B (Hib) and Hepatitis B vaccines as components of the pentavalent conjugate vaccine. Between 1999 and 2007, the uptake of the pentavalent conjugate vaccine increased from 3.9 million doses to 10.5 million doses, with participating member countries increasing from 4 to 31.[11] To establish a RF in the SEAR, along the lines of the PAHO–RF, a major prerequisite is that each member state allocates funds for the purchase of vaccines and allied supplies, distinct

from their national health budgets. This will be the first step toward sustainability of long-term vaccination programs and require us to generate greater political will.

A somewhat similar bulk-purchasing strategy was established in the Middle East in 1978. This initially involved six Gulf countries, namely, Bahrain, Kuwait, Oman, Saudi Arabia, and UAE, followed later by Yemen. This bulk-purchasing mechanism is controlled by the Gulf Cooperation Council, and the purchasing model is popularly known as the 'Gulf Cooperation Model'. Unlike the PAHO–RF, this purchasing mechanism uses what is called 'group contracting' with a centralized tender and bidding mechanism, overseen by a designated committee that scrutinizes the process and awards the tenders. The committee is thereafter dissolved and a fresh committee is constituted annually. The Gulf Model, unlike the PAHO–RF, purchases in bulk not only vaccines and allied supplies but also a wide range of other medical products.[12]

Neither model can be followed blindly. A plan must be tailored to the specific needs of the SEAR after careful evaluation of the various bulk-purchasing mechanisms and their utility for this region. A model that has been successful elsewhere might not be so in the SEAR. Therefore, careful consultation and dialogue among the stakeholders, across the countries of the SEAR, is a prerequisite for design and continuing evolution of an 'ideal' bulk-purchasing mechanism for the region.

Advance market commitments (AMCs): The pros and cons

The collective strength of the vaccine manufacturers of the SEAR is formidable. The Developing Countries Vaccine Manufacturers Network (DCVMN)[13] (www.dcvmn.org) testifies to this strength and aims to ensure a consistent and sustainable supply of quality vaccines at affordable prices to developing countries for their National Immunization Programs (NIPs). To combat infectious diseases specific to the developing world, through its 25 companies it encourages and supports R&D efforts, as well as strengthens the capacity of vaccine producers in developing countries. It tries to improve the access of DCVMN members to technologies needed to improve the quality of their products.

Serum Institute of India, Biological E, and Bharat Biotech are Indian companies in DCVMN who are also WHO prequalified. A few other Indian companies also supply WHO-prequalified vaccines.

Non-members of the DCVMN include Shantha, Haffkine, Chiron Behring, and Zydus Cadila.[14] With these resources, India and other South-East Asian countries possess the infrastructure and capacity to develop world-class vaccines.

DCVMN is a step in the right direction and the network's vaccine manufacturers should be encouraged to make AMCs to manufacture and supply HPV vaccines. AMCs typically aim to cover both 'push' and 'pull' mechanisms. 'Push' accelerates vaccine development, whereas 'pull' mechanisms ensure vaccine uptake. In a country like India, the development push is satisfied, as India has adequate infrastructure, R&D facilities, and workforce to accelerate vaccine discovery and development, in both public and private sectors. India still lacks adequate 'demand' that is needed to give manufacturers sufficient confidence to enter and comply with the terms and conditions of the AMCs.[15] Without accurate demand forecasts, it will be difficult for companies to 'take the plunge'. Demand generation is a 'must' to sustain long-term vaccination programs, notably for HPV vaccines, where decades may pass before any impact on disease burden becomes apparent.

Demand generation can occur by first raising awareness of the health benefits of vaccines. Advocacy will help to raise awareness, whereas operational research will shed light on areas where we have failed.

Sustaining financing versus financing sustainability

Both are needed to sustain vaccination programs. India needs informed policy decisions based on solid, scientific, country-specific data with reference to health interventions such as vaccines. India's National Vaccine Policy (NVP 2011) is a step toward that goal.[16] Importantly, the NVP highlights the role of the National Technical Advisory Group on Immunization in generating country-specific 'situation analysis' for expediting vaccine introduction.

The creation of the NVP is only the first step. Creation of a 'Vaccine Fund' within the framework of the National '5-year plans' would aid sustainable financing. A stable vaccine supply chain based on 'pull' mechanisms could create demand so that vaccine companies are not hesitant to make AMCs for developing a HPV vaccine, thereby increasing public confidence in the NIP.

Long-Term Strategy – Development of Indigenous HPV Vaccine

Reduction of HPV disease burden requires the judicious application of vaccines as well as screening. As this is a long-term process, spanning decades, indigenous vaccines can eventually sustain the program at minimal cost.

Justification for an indigenous HPV vaccine

Cost is only one variable affecting the introduction of HPV vaccine into the public health system in a country like India. External funding, from public–private partnerships like the GAVI Alliance, is an essential prerequisite. Currently, 57 countries are eligible for GAVI support, based on Gross National Income (GNI) per capita. Countries having a GNI per capita below or equal to US$1520 (as per the latest World Bank data) are eligible.[17] India belongs to the category of low middle-income countries, with a GNI per capita (Atlas Method) of $1340.[18] Despite a slowing growth rate (Gross Domestic Product (GDP) growth rate 6.9 per cent as of 30 November 2011),[19] India is likely to become ineligible for GAVI Alliance support as early as 2013 (Figure 2). Therefore, long-term sustenance of HPV vaccine introduction in the public health system will not be possible without internal capacity development within India. This is a major justification why a HPV vaccine needs to be manufactured indigenously.

Calculations based on the last Indian Census (2001)[20] suggest that there were approximately 62.4 million girls aged 10–14 years (assuming 1:1 sex ratio), about 6 per cent of the population – the approximate target age group for HPV vaccinations in India. With gradual increase in this number through 2015, there is a need to develop capacity to make HPV vaccines indigenously.

Looking Ahead – Forging a Way Forward

The need to manufacture HPV vaccines indigenously is urgent. India has already taken initiatives in this direction in the private and public sectors (Table 3).

Can developmental costs be lowered to keep the cost of the final product lower? Perhaps, more collaborative efforts are required to

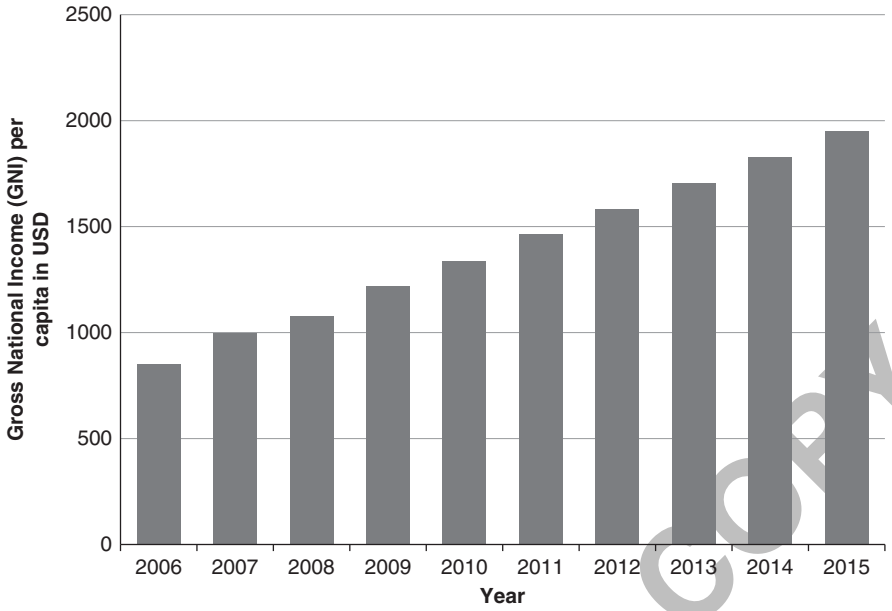

Figure 2: India's projected GNI per capita in USD over the next 3 years.

overcome the IP barrier based on more transparency, both nationally and internationally.

Historically, although India has had a low vaccine-coverage rate, the polio elimination effort is commendable. India has been polio-free for over two years, illustrating that India has the capacity to deliver life-saving vaccines. Vaccine coverage can be increased by careful planning and judicious use of human resources, like *Anganwadi* (Rural Health) workers, who form the backbone of the National Rural Health Mission.

India's Health Budget is comparatively meager. The Union Budget 2012 projects a GDP growth rate for 2012–2013 of 7.6 per cent, higher than that for 2011–2012 (6.9 per cent). Health spending as a percentage of GDP will have risen from 2.15 per cent (2011–2012) to 2.31 per cent (2012–2013).[21] Thus, India will soon be ineligible for GAVI Alliance support, which is based on a 'Tiered Pricing Model'. India must put a 'bulk-purchasing mechanism' in place quickly. We suggest that a percentage of the GDP should be set aside for a

Table 3: HPV vaccine development initiatives in India

Organization	*Collaboration/Support/Funding*	*Comments*
Private sector		
Indian Immunologicals Ltd., Hyderabad	Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland	Oral vaccine; Attenuated *Salmonella enterica* strains expressing HPV-16 and 18 L1 antigens
Shantha Biotechnics Ltd. (wholly owned subsidiary of Sanofi), Hyderabad	NCI, NIH, Bethesda, USA; Johns Hopkins University, Baltimore, Maryland, USA	L2 VLP-based vaccine; *E. coli* expression platform
Bharat Biotech International Ltd., Hyderabad	NCI, NIH, Bethesda, USA	L1 VLP-based vaccine; Chimeric VLP-based vaccine (L2-HPV VLP co-expressing L2-HBV small surface antigen as a fusion protein); *Pichia pastoris* expression platform
Serum Institute of India Ltd., Pune	NCI, NIH, Bethesda, USA; Rhein Biotech (subsidiary of Dynavax Technologies Corp.), Düsseldorf, Germany	L1 VLP-based vaccine; *Hansenula polymorpha* expression platform
Gennova Biopharmaceuticals Ltd., Pune	BIPP, DBT, Government of India	Recombinant vaccine
Virchow Biotech Pvt. Ltd. Hyderabad	BIPP, DBT, Government of India	Mucosal vaccine
Public sector		
Translational Health Science and Technology Institute, Gurgaon, Haryana	DBT, Government of India	VLP-based vaccine
Institute of Cytology and Preventive Oncology, Noida, Uttar Pradesh	DBT, Government of India	DNA vaccine

BIPP: Biotechnology Industry Partnership Programme; DBT: Department of Biotechnology; NCI: National Cancer Institute; NIH: National Institutes of Health.

'Vaccine Fund' – specifically for procuring vaccines and allied supplies. As the benefits of HPV vaccines will come slowly, a dedicated amount needs to be kept aside, as mid-phase disruption will waste both time and money, and limit results. We need greater political will and commitment that will be generated only with greater demand for

vaccines, thus the need for more advocacy and Information, Education, and Communication activities. Print and electronic media could play an immense role – the media being encouraged to highlight positive aspects pertaining to the 'value of vaccines' – often understated, underestimated, and under-appreciated. They can highlight the positive health impacts that vaccines bring about, and link them to a Nation's economic growth. This may convince policymakers, and thereby bring about changes in health policy.

Acknowledgement

The authors wish to thank the Department of Biotechnology, Government of India for its continued support.

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