Human Papillomavirus (HPV) is the most common sexually transmitted disease which can infect different parts of the body. More than 100 HPV types have been characterized molecularly and about 40 types are able to infect the genital tract. Some of these HPV types can cause cervical, penile and anal cancers. Other types of HPV can also cause certain cancers of the head and neck. Cervical cancer is the second most common cancer among women worldwide. In 2008, Zur Hausen received the Nobel Prize in "Medicine or Physiology" for proving the causative link between HPV and cervical cancer research. The HPV-related disease appears to be increasing but treatment is limited, difficult and insufficient with high relapse rate. This growth in disease burden had made the development of two an effective prophylactic Human Papillomavirus vaccines namely Gardasil®- quadrivalent (Merck) and Cervarix®- bivalent (GlyaxoSmithKline). These vaccines are widely marketed internationally. The different steps and challenges faced during development these vaccines, from exploratory stage to commercialization of vaccines, have been reviewed.

Keywords: Human Papillomavirus, Cervical Cancer, Bivalent Human Papillomavirus Vaccine, Quadrivalent Human Papillomavirus Vaccine, Virus Like Particle (VLP) Technology.

INTRODUCTION

Human Papillomavirus (HPV) is the most common sexually transmitted disease which can infect different parts of the body. More than 100 HPV types have been characterized molecularly and about 40 types are able to infect the genital tract. Some of these HPV types can cause cervical, penile and anal cancers. Other types of HPV can also cause certain cancers of the head and neck. Cervical cancer is the second most common cancer among women worldwide with an estimated 5,29,409 new cases and 2,74,883 deaths in 2008. About 86% of the cases occur in developing countries and may constitute up to 25% of all female cancers. Worldwide, mortality rates of cervical cancer are substantially lower than its incidence with a ratio of mortality to incidence being 52%. According to WHO: Human Papillomavirus and Related Cancers Summary Report (2010), in India, cervical cancer is reported to be responsible for almost 20% of all female deaths and takes the lives of 8 women in India every hour. India recorded 1,32,000 new cases out of these cases 74,000 cases lost their lives. The HPV-related disease appears to be increasing but treatment is limited, difficult and insufficient with high relapse rate. This growth in disease burden had made the development of an effective prophylactic Human Papillomavirus vaccine in international health policy.

THE ASSOCIATION BETWEEN HUMAN PAPILLOMAVIRUS AND CERVICAL CANCER

More than 2000 years ago a famous Greek doctor Hippocrates in 450 BC wrote the first description about the cervical cancer. He referred it as cancer of the uterus. ‘The Medieval Women’s guide to Health’ in the early 15th century recorded a certain "cancer and festering of the wombs resulting from old injuries that have not healed well". In 1793, Mathew Bailie observed that cervical cancer causes continuous ulceration of the uterus due to which, whole organ is destroyed. John Clark, in 1812 noted the cervical tumour grew like peculiar cauliflower. Rigoni-Stern, an Italian physician in 1842, analyzed the death records of the city of Verona for the years of 1760 to 1839. After analyzing research data he concluded that cancer of the cervix was high among married ladies and widows and low among the Jewish women, rare in the unmarried ladies and absent in Italian nuns. That time he concluded that the development of this type of cancer should be related to sexual contacts. Samuel Ashley, in 1844 noted that the patients with cervical cancer were often of dark complexion. Another published study in 1872 stated that deaths due to cervical cancer in South America (USA) were much higher in black women which tried to link the socio-economic status as one of the risk factors.

In the 1930s, the papillomavirus was first glimpsed as a disease by Dr. Richard Shope of Rockefeller University. Dr. Shope experimented by taking samples of the warts, grinding them up and injecting them into healthy rabbits. The healthy rabbits soon developed the same warts. During 1970, doctors noticed that women with cervical cancer also tended to have genital herpes so by the 1970s, they assumed that some kind of sexually transmitted infection like Herpes was causing cervical cancer. Initially a number of confirmatory data have been published for showing causative relationship between Herpes and cervical cancer. However, a large scale prospective study performed in former Czechoslovakia failed to confirm the association.

In 1974, German virologist Harald zur Hausen conducted a pilot study which showed that there are different types of papilloma viruses. In 1976, Harald zur Hausen...
proposed that HPV is the cause of cervical cancer. In 1979, his co-researchers Lutz Gissmann and Ethel-Michele de Villiers were successful in cloning the first DNA from a genital wart, HPV-6. After HPV-6, they discovered HPV-11. During discovery of HPV 6 and 11, unknown faint bands became visible. The unknown bands were cloned and in 1983 and 1984, they isolated HPV-16 and HPV-18 respectively. In 1985, they demonstrated the presence of HPV DNA in cervical cancer cells. In 2008, he received the Nobel Prize in “Medicine or Physiology” for proving the causative link between HPV and cervical cancer research.14,11

Construction and overall development strategy: from preclinical to Clinical development

The development of any new vaccine is highly challenging, complex and an expensive process. Each vaccine is different however; they need to go through the defined research and development processes stages. The development of Virus-like particle (VLP) vaccine is the most challenging of all. This HPV VLP vaccines development is the result of fortunate molecular biological and epidemiological evidence that HPV infection is the central cause of cervical cancer and the development of molecular technologies for production of the L1 virus-like particles (VLPs) vaccines and serological assays to measure their immunogenicity.10 In 1990, the actual considerable activity aimed toward developing HPV vaccines was initiated. After that the group of scientists worked for more than 14 years and conducted more than 10 years of clinical studies HPV VLP vaccines become recent addition to our vaccine arsenal. A total of more than 30,000 patients and 33 counties have been involved in the clinical trials.15 The Virus-like particle (VLP) nature of these vaccine necessitated extensive preclinical and clinical characterization, from the early stage of research to large scale phase III clinical development, industrialization, and vaccine introduction.

PRE-CLINICAL EVALUATION

Identify HPV types responsible for infection of cervical cancer

It was important at that time to identify which HPV types are responsible for the majority of cases of infection and cancer. After Dr. Harald zur Hausen established the link between genital human papillomavirus (HPV) infections and cervical cancer several molecular and epidemiological studies demonstrated a strong correlation between HPV type infection and cervical cancer. Finally the great attention of scientists has been focused on at least 4 types of the virus that cause the most cases of HPV-related diseases in women. HPV Types 16 and 18 cause 70% of cervical cancer cases; HPV Types 6 and 11 causes 90% of genital warts cases.15

Vaccine design

Timely ahead few groups of laboratory-based researches were already on the track to work on development of prophylactic HPV vaccines before the prospective epidemiology studies came to conclusion that there is a link between HPV and cervical cancer.16 From initial days, vaccine developers were not keen on developing HPV vaccines based on a live attenuated HPV strains for two reasons because first, HPVs could not be propagated in replicating cells in culture for virus production and second, HPV contain E5, E6 and E7 oncogenes. The delivery of these via a vaccine was not considered safe for general use.10 Therefore, to make these HPV vaccines most effective, subunit vaccine strategies are needed to implement because it was known previously that most effective viral vaccines functioned primarily through the induction of neutralizing antibodies. As a result, attention was mainly focused on subunit vaccine strategies that might induce neutralizing antibodies to the papillomavirus virion proteins.17

Since 1980, researchers had sound knowledge about the self-assembly of the viral S protein into lipid bilayer-containing VLPs which is required during the commercial hepatitis B vaccine. In addition to that, they were also aware that E. coli-derived VP1 of several polyomaviruses were structurally similar to papillomaviruses and they proved that VLP self-assemble into morphologically correct VLPs from capsomeric subunits in vitro reactions.18,19 Thus, in 1990 it was reasonable to consider a VLP-based vaccine displaying conformationally correct L1, or L1 and L2, as a potential candidate for an HPV vaccine.

In-vitro Immunogenicity

After designing vaccine candidate, it was necessary to develop in vitro neutralization assays that could critically evaluate the antibody responses. Till 1990, there were only two assays were present for measuring neutralizing antibodies induced by papillomavirus vaccine. In 1970, Schiller and Dowdy developed the first assay to monitor in vitro infectious events of bovine papillomavirus (BPV) types 1 and 2 by the induction of transformed foci in NIH3T3 and C127 mouse cell lines. In this assay neutralizing antibody titers were determined from the reduction in the number of foci induced by a standard stock of wart-derived virions. This assay study formed the basis for studying morphologic transformation by BPV.20

In 1987, Kreider et al., in the journal of virology published a study title “Laboratory production in vivo of infectious human papillomavirus type 11”. According to this study, wart-derived virions from BPV1, CRPV, HPV1 and HPV11 could be used to infect mucosal or cutaneous epithelial chips if these chips were placed under the renal capsule of athymic mice. Later on infection was monitored by hyperproliferative changes in the transplanted chips and infection inhibition by type-specific antibodies could be semi-quantitatively evaluated for inhibition of in vitro infection by cumbersome xenograft assay.10

Virus-Like Particle (VLP) technology

Virus-Like particles (VLPs) are comprised of recombinant HPV capsid proteins. These proteins can attain the exact
capsid conformation of viable HPV virions but these virions are not infectious as they do not contain genetic material within VLPs. However, due to the foreign protein presentation, VLPs are capable of eliciting an antibody-mediated immune response upon injection.21

The group of researcher that led to the development of the HPV vaccine began in the 1980s at the University of Rochester, Georgetown University, the University of Queensland, and the US National Cancer Institute.15 Zhou et al. (1991) reported the co-expression of HPV16 L1 and L2 in monkey CV-1 cells via a vaccinia virus vector which resulted in the generation of "virus-like" particles that could be concentrated by sucrose gradient centrifugation.22 For this novel idea Dr. Ian Frazer’s group at the University of Queensland in Australia received a patent for this technology in 1994.23,24 The VLP research was supported by Australia’s largest biotechnology company-Commonwealth Serum Laboratories (CSL). In 1995, CSL licensed the technology from the University of Queensland. At same year, a license agreement was reached between CSL and Merck and Co. to use the technology in the development of a vaccine to prevent against cervical cancer and genital warts. Under this agreement, Merck obtained worldwide rights to the vaccine outside of Australia and New Zealand, and CSL retained the rights in these two countries.23

The involvement of vaccine development of Dr. John Schiller and Dr. Doug Lowy, National Cancer Institute, USA began in early 1991 when after Reinhard Kirnbauer, a dermatologist from the University of Vienna, arrived to begin a postdoctoral fellowship. In 1993, Dr. John Schiller showed that the L1 major capsid protein alone could induce immune response however; the L2 protein is required to envelop genomic DNA.25 As a result, at the end of 1993, there was considerable evidence that the ability to self-assembly into VLPs is a general property of wild type papillomavirus L1 proteins. These findings were demonstrated in many subsequent studies, which involve the L1s of other human and animal papillomavirus types.10

Richard Schelgel and colleagues at the German Cancer Institute in Heidelberg, Georgetown University and the University of Rochester in 1993 made their own contributions to the development of VLP technology. This group validated this VLP technology using canine model.21,22 After demonstrating proof of principle study in a small, Phase 1 trial in humans involving HPV 11 strain, this technology was licensed to MedImmune. Then MedImmune initiated clinical evaluation with HPV-16/18 VLPs in humans. In 1997, MedImmune and GSK entered into a research and development (R&D) license agreement for the development of a cervical cancer vaccine. According to their agreement, MedImmune was responsible for conducting Phase 1 and Phase 2 trials of the cancer vaccine, whereas GSK was responsible for the final development, regulatory, manufacturing and marketing activities which were related to the vaccine’s production. In exchange for exclusive worldwide rights to MedImmune’s HPV technology, GSK agreed to provide MedImmune with an upfront payment, research funding, equity investment as well as potential developmental and sales milestones and royalties on any product sales.27,21

After commercialization of the vaccine, controversy involving intellectual property arose between the various groups that played a role in developing the vaccine. At that time, this intellectual property right issue was so complex that US Patent Office eventually declared a "four-party interference" whereby the patent applications from each of the groups would be examined for their distinct content and dates of invention. However, after a 10-years “interference” to adjudicate the overlapping claims, Georgetown won the dominant patent for its contribution to the “background science”.16,25

**Vaccine expression system**

After Schiller et al., (2011) reviewed potential production systems, Schiller and his team decided to express L1 in insect cells via recombinant baculovirus vectors for the following reasons. First, they were known to produce exceptionally high levels of recombinant protein and a L1 capsid protein concentration might be needed to drive the VLP assembly reaction. First, they were known to produce exceptionally high levels of recombinant protein and a critical capsid protein concentration might be needed to drive the VLP assembly reaction. Second, researchers had a reason to expect that their preclinical vaccine studies can produce encouraging results because FDA had already approved clinical trials of other proteins produced in this system. Third, they had a stock of cow wart-derived infectious BPV virions in the laboratory and expertise in the in vitro focal transformation assay which they used to evaluate neutralizing antibodies elicited by any vaccine candidate. Schiller team was able to generate the L1 recombinant baculovirus, infect insect cells and demonstrate robust L1 expression in the infected cells. The above results proved that BPV L1 without any other viral proteins had the intrinsic capacity to assemble into VLPs that were able to induce high titers of neutralizing antibodies.10,28

The MedImmune and the NCI (National Cancer Institute) under the contract to Novavax chose to continue producing their VLPs in recombinant baculovirus infected insect cells. During developing the expression system, MedImmune encountered one particularly vexing issue related to the production of HPV-16 VLPs which is a critical component of their vaccine composition. The VLPs produced using a L1 gene sequence obtained from a clinical isolate (GU-2) provided by the Georgetown University group proved to be much less immunogenic than VLPs prepared from a C-generated truncated form of a different version of the gene (114 K) generated originally by a group at the Deutsches Krebsforschungszentrum (DKFZ). Later on the detailed molecular analysis traced out that the effect is due to a single amino acid difference between the two sequences.
at position 50. The L1 gene from a further clinical isolate obtained from the Georgetown group (GU-1) turned out to lack one of the antibody neutralization sites that had been identified by monoclonal antibody mapping. For this reason, the MedImmune program was ultimately based on the 114K HPV-16 reference sequence which contained all HPV-16 neutralization sites identified at the time.16 However, Merck decided to manufacture their vaccine in Saccharomyces cerevisiae, presumably because they had extensive experience in yeast production of their HBV vaccine.10

Scientific evidence of animal studies

The most crucial factor in stimulating HPV vaccine development was the scientific evidence that protection against infection caused by papillomaviruses could be accomplished successfully. Both vaccines development programmes set in motion on the basis of the discovery by several academic groups that the L1 coat protein of papillomaviruses can assemble into a virus-like particle (VLP) when expressed as a recombinant protein in a heterologous eukaryotic system.16 Collaborative studies with a several academic groups proved that immunization with L1 VLP structures could protect against viral challenges like cottontail rabbit papillomavirus (CRPV), bovine papillomavirus (BPV) and canine oral papillomavirus (COPV).10

Merck Gardasil® HPV vaccine program was influenced by CRPV studies. In 1995, Jansen et al., vaccinated New Zealand white female rabbits with varying amount of yeast-expressed cottontail rabbit papillomavirus (CRPV) virus-like particles. This experiment showed that it protects the rabbits from CRPV-induced wart formation. Sera of immunized rabbits were shown to contain high-titered serum antibodies to CRPV L1 VLP and to neutralize CRPV in vitro policy.7 MedImmune Cervarix™ HPV vaccine program was influenced by COPV studies. In 1995, Suzich et al. employed a canine model to develop a systemic vaccine that completely protects against experimentally-induced oral mucosal papillomas. In his experiment, he injected L1 COPV into the foot pad of beagles. Vaccinated animals developed circulating antibodies against COPV and became completely resistant to experimental challenge with COPV even at extremely low doses. Successful immunization was strictly dependent upon native L1 protein conformation and Li type. Serum immunoglobulins passively transferred from COPV L1-immunized beagles to naive beagles conferred protection could be generated by passive transfer of antibody.20

Overall, the findings from the animal models served to convince both pharmaceutical groups that native L1 VLPs were immunogenic.

Adjuvant selection in vaccine design

After successful completion of animal studies it was proven that a vigorous antibody response to the L1 protein of HPV would be required for a successful vaccine and sustained detectable levels of antibody at the site of primary infection would be necessary for continued protection. However, the major concern of that time during vaccine design was how to generate such a response in humans and whether it was likely to be sufficient to block the development of malignant genital disease? At that time, there was a substantial body of literature which was pointing to the importance of T-cell responses in clearing HPV infection. Therefore an effective T-cell response could be added to the efficacy of a prophylactic vaccine by "mopping up" any infected cells which will be resulting from the virus breaking through antibody defenses.31 Additional viral proteins (e.g. E6 and E7) could have been included in the vaccine composition as specific targets for T-cells, but the additional development hurdles would have been very significant. Nevertheless, the possibility of developing a vaccine formulation that could result in T-cell responses from the antigens already included was an important consideration.16

The careful selection of antigens and the addition of adjuvants to amplify the immune response is one of the most used approaches in vaccine design today. The addition of adjuvants in that context proofs useful in ensuring a good immune response along with an acceptable reactogenicity and safety profile. Adjuvants are substances with immunostimulatory properties.32 The VLPs alone might trigger T-cell responses on the basis of their efficient uptake into antigen presenting cells but an additional option was taken to seek an adjuvant formulation that would boost T-cell responses specifically.16 By considering this crucial factor in their vaccine development programme MedImmune/GSK decided to formulate the VLP vaccine using a novel adjuvant. The bivalent HPV vaccine adjuvant (AS04) is composed of monophosphoryl-lipid A, which enhances cellular and humoral immune response, adsorbed to aluminium hydroxide.33,34 Although the selection of a novel adjuvant can always present a risk, promising safety data had already been generated with this adjuvant and the hepatitis B surface antigen. This choice was based on a desire to promote sustained protection through induction of high and persistent antibody titers while also inducing cell-mediated immunity.35,36

On the other hand, Merck decided to proceed with a traditional aluminium-based adjuvant. Aluminium salts were the first to be registered for use in humans and are still the most widely used adjuvants in vaccines in all age populations.37,38 At present aluminium-containing adjuvants are found in the several childhood vaccines like DTP (Diphtheria–Tetanus–Pertussis combination), Pediarix (DTP–HBV–Polioc combination), Pentacel (DTP–Haemophilus influenza B (HIB)–Polioc combination), Hepatitis A, HBV, HIB and pneumococcal vaccines. It is important to note that aluminium salts not only serve as an adjuvant in vaccine preparations. Since they absorb proteins well, aluminium salts also stabilize vaccines by preventing the proteins in the vaccine from precipitating
or sticking to the walls of the container during storage. It offers a satisfactory compromise between tolerability and performance.\textsuperscript{39}

L1 VLPs causes very limited cross-neutralization against other genotypes and therefore multiple vaccine components would be needed to provide good coverage against diseases caused by more than one virus type. Merck and MedImmune each made a strategic decision early on to develop a multivalent vaccine composed of L1 VLPs corresponding to HPV types 6, 11, 16 and 18 in order to prevent both genital warts and the majority of cervical cancers. Following their development alliance later in the programme, MedImmune/GSK elected to concentrate specifically on prevention of cervical cancer, focusing on the two most common oncogenic HPV types found in tumours, 16 and 18.\textsuperscript{15}

**VLP HPV VACCINE PRODUCT DEVELOPMENT**

**Gardasil**

**Genetic Development**

The Plasmids or phage libraries used during genetic development were obtained from human clinical specimens or cell lines which are positive for HPV types 6, 11, 16 and 18. The L1 genes for HPV 6, 16 and 18 were derived by a direct cloning protocol. However, HPV 11 L1 gene coding sequences were synthetically reconstructed on the basis of HPV6 L1 nucleotide sequences. After sub-cloning either the whole or parts of HPV genomes into standard cloning vectors, polymerase chain reaction (PCR) was used to subclone the L1 genes into the yeast expression vector pGAL110, which contains the divergent yeast GAL1-GAL10 promoter and the yeast ADH1 terminator (ADH1t). This pGAL110 yeast expression vector was used during the expression of all four HPVL1 proteins.\textsuperscript{40}

A clone for each HPV type was selected to establish the two Master Cell bank (MCB). All cGMP master seed stocks were prepared using a two-stage expansion. Later these master seed vial stocks are used to inoculate the HPV Shakeflask Medium. For future use, these work seeds are prepared using the same process steps and equipment which are used for the original working seed. Following freezing, these seed are stored at -60°C.

**Fermentation and Harvesting**

During fermentation process, a recombinant yeast expression system uses a galactose inducible promoter (GAL1) to express HPV capsid proteins of high cell densities before the L1 protein is expressed. The raw material used during the fermentation culture medium is D-galactose. This D-galactose is obtained from bovine milk sourced from healthy animals and no other ruminant material used in its production. To initiate, harvesting process galactose needs to reach at designated level. Due to this process, the L1 protein makes up approximately 15% of the total soluble protein. Then freezing process takes place.\textsuperscript{16}

**Cell Thaw / Disruption**

After thawing, benzonase is added to the cells to weaken the cell membrane and the cell slurry is passed twice through a homogenizer, which achieves a cellular disruption of greater than 95%. The mixture is incubated at 48°C for 12–20 h to complete the lysis.\textsuperscript{41}

**Microfiltration, Capture Chromatography and Polishing Chromatography**

The lysate is then clarified by cross-flow microfiltration in diafiltration mode and followed by two CEX (Cation Exchange) fractionation steps; the first pass captures the VLPs and the second pass serves as a polishing step. Using this process, the purified VLPs are 98% homogeneous (purity) and overall purification yield is 10%.\textsuperscript{41,16}

**Sterile Filtration and aseptic filling**

The final step in the purification process is the sterile filtration process. In this sterile filtration, all four types buffer exchange occurs to produce the final aqueous product (FAP). The FAP for each type is then adsorbed onto amorphous aluminium hydroxyphosphate sulfate to produce the MBAP (Monovalent Bulk Adsorbed Products). Then this MBAP for each type is filled into bulk storage containers and stored at 2-8°C. The final product "Quadrivalent Bulk Adsorbed Product" (QBAP) is prepared from six sterile ingredients: histidine buffer, adjuvant diluent, and the four MBAPs. The portable formulation tank is maintained under positive pressure before it is transferred to the appropriate fill line for subsequent filling.

Before filling QBAP, the homogeneity is ensured by mixing by agitation and recirculation. Then aseptically filling process initiates. The final product filled into vials or syringes such that each vial or syringe contains a minimum recoverable volume of 0.5 ml. After each vial or syringe is filled, it sent for quality control like in vitro relative potency (IVRP), sterility, pH, endotoxin, aluminium, package defects and recoverable volume are taken during the fill. After inspection, the vials are placed into trays and stored at 2-8°C until they are labelled and packaged proteins.\textsuperscript{40}

![Figure 1: Gardasil® manufacturing process.](image-url)
Cervarix™

Cell and Seed Banking

The two-step process step in Bivalent HPV vaccine manufacturing process is cell banking and seed banking. Cervarix™ is made up of two monovalent HPV 16 and 18 antigens bulks which contain recombinant C-terminally truncated versions of the HPV 16 and 18 major capsid L1 proteins in two separate bioreactors. Both the manufacturing of the HPV-16 L1 VLP and HPV-18 L1 VLP takes place with the help of an established two tiered cell bank system of the Trichoplusia ni Hi-5 Rix4446 insect cells line and two-tiered baculovirus Seed Lot system of the HPV-16 L1 and HPV-18 L1 gene-encoding recombinant baculoviruses. The L1 proteins of HPV 16 and 18 types are obtained through same manufacturing process except HPV-18 baculovirus Seed is used instead of HPV-16 baculovirus Seed as the inoculum. The infection of the Hi-5 Rix4446 cell line with the recombinant Baculoviruses are followed by extensive purification.16,42

Figure 2: Cervarix™ manufacturing process.

Extraction and Purification of L1

Following replication of the L1 encoding recombinant Baculovirus in Trichoplusia ni an insect cell line, cell suspension is centrifuged, the infected cell retrieved from the bioreactor and re-suspended in the buffer so that the L1 proteins start to accumulate in the cytoplasm of the cells. The L1 proteins are released from the cell after osmotic shock. Then the cell disruption process is purified by a series of chromatographic and filtration methods like anion exchange chromatography, affinity chromatography, nano filtration process, nano filtration process and sterilization filtration process. The major objective of each process is to remove impurities such as DNA, protein, viruses and adjustment of pH and electroconductivity.16,42

Formulation, filling and packaging

During formulation, the HPV-16 L1 VLP and HPV-18 L1 VLP as well as the liquid MPL (3-O-desacyl-4.-monophosphoryl lipid A) are first individually adsorbed to Al(OH)₃ to generate adsorbed bulks. The final bulk vaccine is then produced by mixing defined amounts of adsorbed bulks and adding buffer solutions and Al(OH)₃ to reach the intended final formulation.16 The final product is then tested for sterility, identity, general safety, in vitro relative potency, pH, volume, protein content, aluminium content, MPL content and completeness of adsorption for MPL, HPV-16 L1 VLP and HPV-18 L1 VLP proteins. The final vaccine is filled as a monodose in either sterile syringes (type 1 glass) or sterilised type I glass vials. Both container types are closed with grey butyl rubber stoppers. After inspection, the vials are placed into trays and stored at 2-8°C until they are labelled and packaged.42

CONCLUSION

HPV-related diseases are associated with significant morbidity and mortality. The development of any human vaccine is mammoth task. However, two highly promising human papillomavirus (HPV) vaccines have been licensed in many countries and are now available in the market and. It appears that the quadrivalent and bivalent HPV vaccines have significantly reduced the HPV-related disease burden throughout the world.

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