HPV, cervical cancer and vaccination

Marwan Albuhtori

In December 2025, the World Health Organization (WHO) reported that cervical cancer is the fourth most common cancer in women worldwide and the leading cause of death due to cancer in women. Virologist Marwan Albuhtori explains the relationship between human papillomavirus (HPV) and cervical cancer, and why many choose vaccination

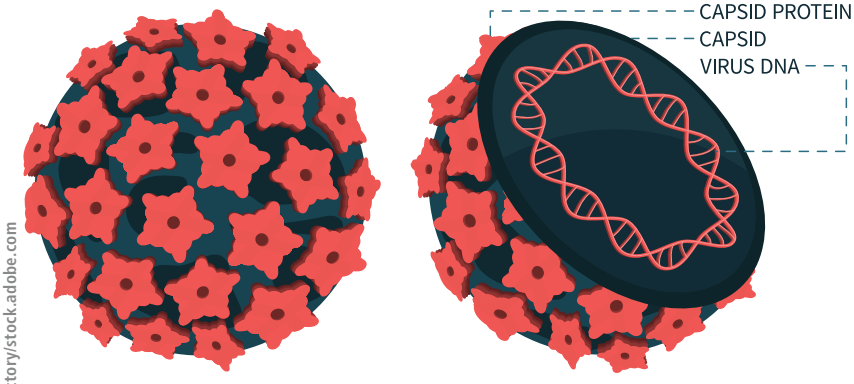
In the UK, a school-based human papillomavirus (HPV) vaccination programme is routinely offered to children aged 12–13 years. HPV is a small, **non-enveloped** DNA virus with a diameter of approximately 52–55 nanometres. The HPV DNA genome is circular and is surrounded by a protein capsid with **icosahedral symmetry**, typical of many viruses (see Figure 1).

HPV enters cells using two receptors. First, the virus binds to carbohydrate molecules on the cell surface, leading to a conformational change. This allows the virus to interact with a secondary plasma membrane receptor protein, followed by the entry of the virus into the cell before its DNA is delivered to the nucleus.

The genome of HPV contains a total of nine genes (see Figure 2). When it enters the nucleus, these genes are tightly controlled, determining the order of transcription and mRNA translation. The first genes expressed, the 'early genes', *E1*, *E2*, *E4* and *E5*, encode proteins involved in viral replication and transcription. *E6* and *E7* encode proteins that interact with cellular proteins. Certain variants of these are important in the development of cancer. *E3* genes are found in some animal papillomaviruses, but not in HPV genomes. The 'late genes', *L1* and *L2*, encode structural proteins that make up the protein capsid of the virus particles.

High-risk versus low-risk HPVs

There are more than 200 genotypes of HPV, broadly divided into high-risk and low-risk HPVs based on their potential to cause cancer. Low-risk HPV (LR-HPV) infections typically cause benign lesions, genital warts and skin warts on the face, feet and hands. Indeed, genital warts are a common sexually transmitted condition. Estimates from the WHO report that around one in three sexually active males has some form of LR-HPV infection. Common genotypes



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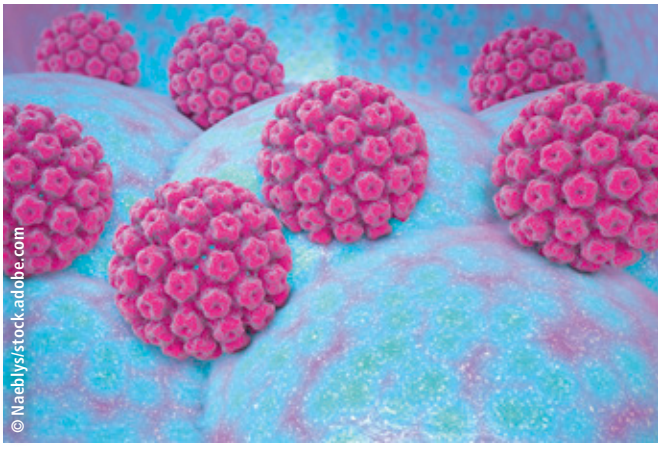

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Figure 1 Structure of HPV with its icosahedral capsid

TERMS EXPLAINED

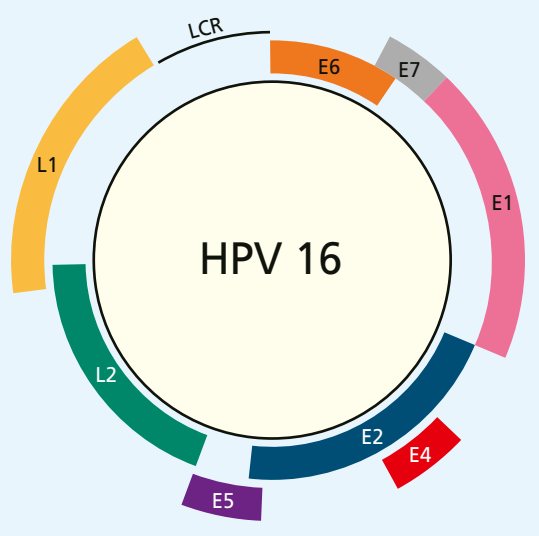
Apoptosis Programmed cell death in which cells self-destruct when they are no longer needed or are damaged.

Herd immunity The indirect protection from infectious diseases that occurs when a large portion of a population becomes immune (due to vaccination), making the spread of disease from person to person unlikely.

Icosahedral symmetry A three-dimensional geometric shape (polyhedron) with 20 identical triangular faces, 12 vertices and 30 edges.

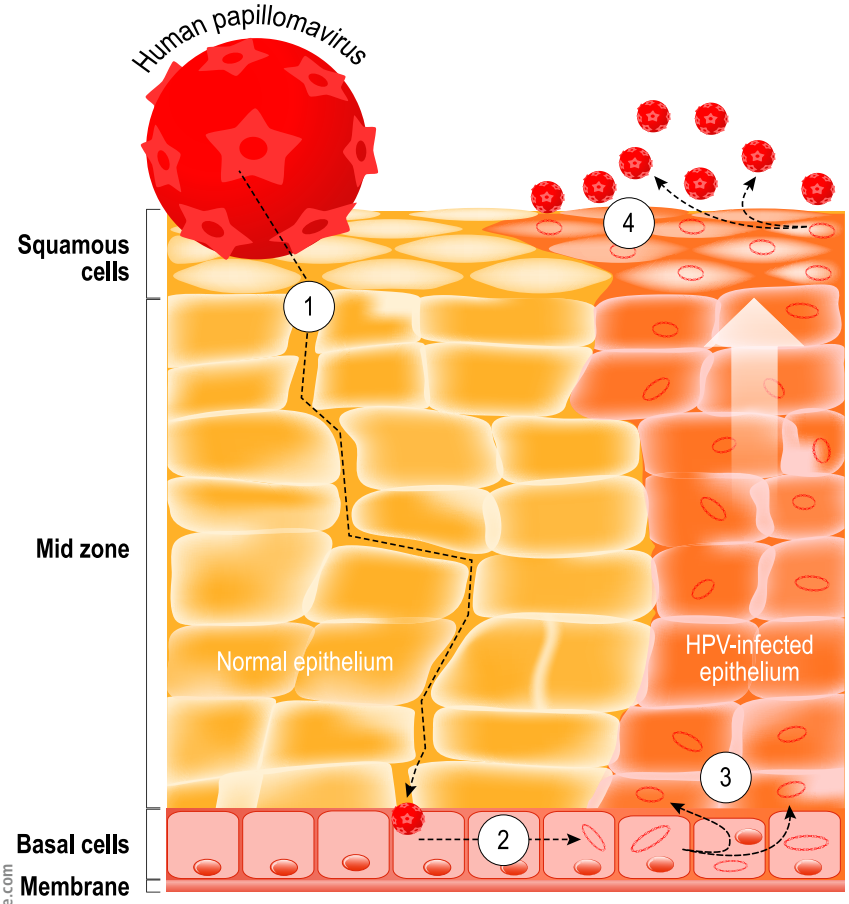
Mucosa A specialised tissue lining many internal surfaces of the body that are exposed to the external environment.

Non-enveloped Indicates that a virus lacks a lipid envelope surrounding its protein capsid.



Source: Sausen, D.G., *et al.* (2023) 'Herpes simplex virus, human papillomavirus, and cervical cancer: overview, relationship, and treatment implications', *Cancers*, 15, 3692, https://creativecommons.org/licenses/by/4.0/

Figure 2 HPV's DNA genome is approximately 8000 bp, containing 8 genes encoding proteins and a non-coding gene (LCR). The two structural proteins are encoded by L1 and L2, while the six non-structural protein genes – E1, E2, E4, E5, E6 and E7 – encode proteins controlling its cellular interactions



1. The virus invades epithelial layers
2. Infected basal cell
3. HPV in epithelial cells
4. Viral replication

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Figure 3 Life cycle of an HPV infection. Viral entry infects basal stem cells of the epidermis. Genome integration occurs and viral gene expression is regulated as the stratified epidermal cells divide

associated with genital warts are HPV 6 and HPV 11. High-risk HPV (HR-HPV) infections are termed 'oncogenic' as they can sometimes lead to precancerous and cancerous changes. Common genotypes include HPV 16 and HPV 18, responsible for around 70% of cervical cancers.

Types of HPV infection

HPVs infect epithelial cells of the skin, especially the face, hands and feet, and those of the **mucosa** of the mouth, throat, cervix, anus and genitals. HPV infections in these areas lead to proliferation or overgrowth of cells, forming a papilloma, commonly called a wart.

Symptoms of HPV infections vary by HPV type and target. Infections of the skin can cause skin warts, termed cutaneous warts, including common warts (hands/nails) and plantar warts (feet). These are usually painless unless subjected to friction. Oral infections can be seen as small white papilloma (see Figure 3) on the lips, tongue, cheek or throat. They can often be quite painful, even obstructive. Genital infections, seen as skin-coloured warts, can cause itching, bleeding and urinary discomfort.

While around 90% of infections with HPV are cleared naturally by the immune system, some high-risk genotypes can persist in the body and cause abnormal cell changes, most commonly in the cervix. If these changes go undetected and untreated, they can progress to cancer.

HPV transmission and life cycle

HPV is primarily transmitted through direct skin-to-skin contact, including sexual transmission – the most common route. Indeed, HPV causes the most common sexually transmitted infection (STI) worldwide, affecting people across all demographics and regions. The WHO estimates that around 80% of sexually active individuals will be infected with HPV at some point in their lives.

The virus typically gains entry through abrasions or cuts in the skin or mucosa that occur during physical contact, including sexual activity or minor trauma. The epithelia cells are typically stratified (see Figure 3) and HPV will only cause infection if it gets to the basal stem cells. These cells are capable of self-renewal and long-term replication, allowing the viral genome to persist and propagate over time.

As HPV is transmitted through contact with infected skin/mucosal surfaces, the virus is easily able to move between hosts. This makes HPV highly contagious. However, practicing safe sex, such as using condoms during sexual activity, can significantly reduce exposure to infected areas and lower the risk of HPV infection.

A cellular disruptor

The WHO reports that there are 660 000 new cases of cervical cancer globally each year, commonly among women aged 30–50 years. Cervical cancer is closely linked to persistent infection with high-risk types of HPV, particularly types 16 and 18.

The ability of HR-HPV types to cause cancer is primarily due to the actions of two viral proteins, E6 and E7. The different genetic sequences of these in HR-HPV genomes, compared with those of LR-HPVs, results in the HR-HPV protein versions being oncoproteins. Their altered properties have the potential to interfere with several normal host cell regulatory functions, promoting uncontrolled cell growth and leading to cancer (see Figure 4).

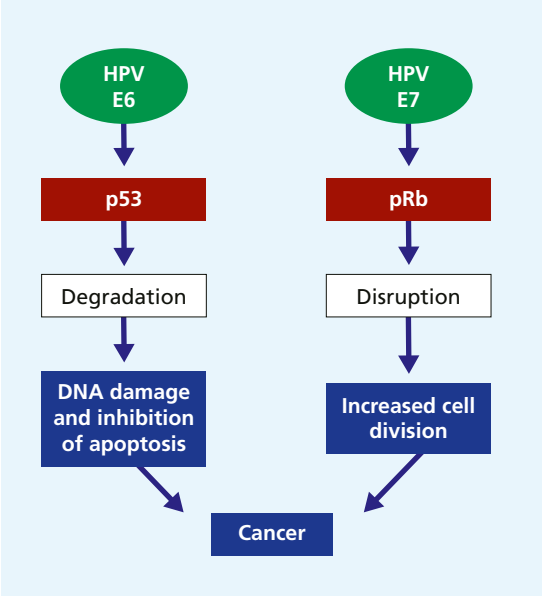

Figure 4 The mechanism of action of HPV E6 and E7 proteins in the development of cancer

The E6 protein of HR-HPVs targets a host protein known as p53. Normally, p53 protein detects DNA damage and either repairs it or destroys cells with damaged DNA via **apoptosis**, preventing their proliferation. Often termed 'the guardian of the genome', when p53 is bound to HR-HPV's E6 protein it is degraded. As a result, damaged cells are allowed to survive and proliferate.

The E7 protein of HR-HPV types primarily targets another host protein known as retinoblastoma protein (pRb). Under normal conditions, pRb binds to and inhibits the function of proteins necessary for progression from the G1 to the S phase of the mitotic cell cycle. When E7 binds to pRb, it 'inhibits the inhibitor' by releasing a protein regulator bound to pRb. Subsequently, pRb can no longer regulate the cell cycle, leading to increased cellular proliferation. This deregulation of the mitotic cell cycle contributes to the transformation of normal cells into cancerous cells (see Figure 4).

HPV vaccines

Persistent infection with high-risk HPV types, particularly HPV 16 and 18, has been strongly linked to the development of cervical, anal and genital cancers. This strong association led to the development of vaccines that target these oncogenic types. The development of HPV vaccines has revolutionised the prevention of these diseases, offering a safe and effective method to block infection. This achievement came with the development of virus-like particles (VLPs) composed mainly of the L1 capsid protein.

Major health organisations worldwide, including the NHS, the United States Centre for Disease Control and the WHO, state that the HPV vaccines are safe and effective, with most side effects being mild. While there have been case study reports of some serious side effects following HPV vaccination, large-scale studies and reviews have found no causal link between the vaccine and these chronic conditions. These conditions occur with similar frequency in both vaccinated and unvaccinated populations.

How the vaccines work

HPV VLPs are made of synthetic L1 protein, the major capsid protein of HPV, produced using

recombinant DNA technology. VLPs mimic the capsid of the virus but do not contain viral DNA. They are non-infectious and non-oncogenic, so while they can trigger a strong immune response, they pose no risk of causing infection or cancer.

This form of HPV vaccine is given by intramuscular injection, usually in the upper arm. Once inside the body, these VLPs are recognised as foreign, stimulating the immune system to produce a strong response against the virus, including the production of high-affinity antibodies that remain in circulation and are ready to neutralise the virus upon future exposure. If the individual later encounters HPV, these antibodies bind to the virus and prevent it from attaching to and entering basal epithelial cells – effectively blocking infection at its earliest stage.

Approved HPV vaccines

Currently, there are three main HPV vaccines approved for use:

- Cervarix (bivalent), a first-generation HPV vaccine, targets the two most common HR-HPV types (16 and 18).
- Gardasil (quadrivalent), a first-generation HPV vaccine, targets HPV-16 and HPV-18 in addition to the two most common LR-HPV types (6 and 11).
- Gardasil 9 (nonavalent), a second-generation HPV vaccine, targets nine HPV types – 6, 11, 16, 18, 31, 33, 45, 52, and 58 – providing broader protection.

HPV vaccines are prophylactic, meaning they are designed to prevent infection, not to treat existing disease. They are most effective when given before any sexual activity begins, which is why they are routinely offered to children aged 12 to 13, where it is given as one dose. Gardasil 9 is currently the most widely used vaccine worldwide and is the only HPV vaccine used in the UK.

Gardasil administration

The number of vaccine doses required depends on the age and immune system status of the recipient. People under the age of 25 usually require a single dose, while adults aged 25–45 typically receive two doses, spaced between 6 months and 2 years apart. This is because younger individuals tend to have a stronger immune response to the HPV vaccine and their immune system can produce sufficient protective antibodies with fewer doses. As people get older, the immune response is generally less robust, so additional doses are needed to ensure long-term protection. It is recommended that people with weakened immune systems have three doses, administered over a 12-month period.

HPV vaccines are not approved or recommended for pregnant people because of ethical concerns and the lack of data. However, no serious side effects have been reported as a result of accidental administration to women unaware of their pregnancy.

HPV vaccination in men

In the UK, HPV vaccination programmes started in 2008 and were initially aimed at girls in year 8 (aged 12–13). Since September 2023, the vaccine has been extended to boys in year 8 as well. Catch-up doses are currently available for males up to the age of 25.

In 2024, a US study reported that a cohort of 3.5 million vaccine recipients had significant reductions in reported cancers, including anal, penile, oral, head and throat cancers. Vaccination protects sexual partners and contributes to broader **herd immunity**.

While the uptake of a vaccine is always a personal choice, the success of the HPV vaccination programme is likely to be one of the most significant public health achievements in cancer. This is especially the case in the context of cervical cancer, which can now be thought of as largely preventable.

RESOURCES

UK schools vaccination information:
www.schoolvaccination.uk/hpv-vaccine

US press release on the study on 3.5 million vaccinated individuals:
https://tinyurl.com/HPV-immunization

NHS vaccination information:
www.nhs.uk/vaccinations/hpv-vaccine/

KEY POINTS

- HPV infection is the most common sexually transmitted infection in the world.
- Persistent infection with high-risk HPV types (mainly HPV-16 and HPV-18) is strongly associated with cervical cancer, as well as other cancers.
- HPV vaccination is a major strategy in cervical cancer prevention.

Dr. Marwan Albuhtori is an assistant professor at the School of Life Sciences, University of Warwick. He is interested in exploring the association between HPV and cervical cancer and identifying strategies for prevention and early detection.