

Vaccination to Prevent Cancer

Dennis Clements

Vaccines stimulate the immune system, mimicking infectious attacks and thereby promoting the development of protective antibodies and/or cellular immunity so that the body is immune to infection when live native infections attack. Some of these infections are associated with cancer-causing changes in the body; thus some vaccines may help prevent cancer.

Chronic inflammation caused by persistent infection—often resulting in cancer—is seen in at least 4 infections: hepatitis B virus (HBV), causing hepatoma; human papillomavirus (HPV), causing cervical cancer; Epstein-Barr virus, causing nasopharyngeal carcinoma and other cancers [1]; and *Helicobacter pylori*, causing gastric cancer. The first 2 diseases have available vaccines that have been shown to prevent cancer by preventing persistent infection and subsequent cancer. Development of vaccines to prevent infection from the latter 2 microbes is underway.

Hepatitis B vaccination began in 1981 and has decreased the incidence of new HBV infections from about 20,000 per year to 5,000 per year. HPV vaccination began in 2006, and there has been a remarkable drop in prevalence rates of HPV in cervical cultures. Epstein-Barr virus—which is associated with Burkitt's lymphoma in Uganda, nasopharyngeal carcinoma in China, and several other cancers—has no vaccine at present. *H. pylori* was first described by 2 Australians as a bacteria that lived in the stomach. They received much ridicule until their findings were confirmed, and the bacterium has since been linked to gastric cancer. At present no vaccine is available for *H. pylori*.

Hepatitis B Vaccine

The first evidence of cancer prevention by vaccination in humans was provided by HBV vaccination of infants. Chronic HBV infection results in approximately 60%–90% of adults developing hepatocellular carcinoma, and this rate reaches almost 100% among children in parts of the world where HBV infection is endemic. Hepatocellular carcinoma is the 6th most common human tumor, afflicting mostly people in the Asia-Pacific region and sub-Saharan Africa, where 750,000 new cases occur each year. The first universal HBV vaccination program began in July 1984 in Taiwan, where children were given 3 or 4 doses of HBV vaccine; children of mothers positive for hepatitis B surface antigen were

also given hepatitis B immune globulin within 24 hours after birth. Twenty years after the launch of the HBV vaccination program in Taiwan, chronic HBV infection rates in vaccinated populations plunged from 10%–17% before the vaccination program to 0.7%–1.7% after the program, and cancer rates have decreased 70%. This suggests that, with time, HBV-induced cancer may be virtually eliminated in Taiwan [2]. Figure 1 shows results from surveillance conducted by the Centers for Disease Control and Prevention (CDC) in the United States from 1980 through 2013.

Regrettably, other parts of the world, such as the western Amazon, have not experienced the same level of success due to the cost of the vaccine or the lack of delivery systems required to get the vaccine to those in need in a timely fashion [4]. In the United States, those most at risk of acquiring infection are babies born to mothers who are hepatitis B carriers, intravenous drug users, and men who have sex with men.

HBV was first described in 1965 and was originally called “Australian antigen” hepatitis, because the virus was isolated from an Australian aboriginal. In 1971, a test to detect hepatitis B surface antigen was first used in blood banks, and a heat-treated HBV vaccine was developed in 1975. Ten years later, a plasma-derived inactivated vaccine was approved by the US Food and Drug Administration (FDA). It was discontinued in 1990, 4 years after a genetically engineered DNA recombinant vaccine was produced. Today there are 5 hepatitis B vaccines available: 2 vaccines for HBV alone (Engerix-B, Recombivax HB), one vaccine for HBV combined with hepatitis A (Twinrix), and 2 vaccines for HBV combined with other childhood vaccines (Comvax and Pediarix).

The use of the HBV vaccine at birth followed by 2 or 3 additional doses, with the second dose administered at age 1–2 months and the final dose no earlier than age 24 weeks, has meant that for the last 10 years the majority of infants born in the United States have been immunized and should never experience chronic HBV-related hepatitis or hepatocellular carcinoma. Children born to mothers who are

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positive for hepatitis B surface antigen should also receive hepatitis B immune globulin, which further diminishes their risk of chronic infection.

The CDC has reported that some individuals who have been exposed to HBV infection after vaccination have had transient liver enzyme elevations but no chronic infection, indicating an aborted acute infection. Additionally, some individuals fail to mount a humoral antibody response following vaccination. Although routine testing for HBV vaccine response is not cost effective, testing is recommended in certain high-exposure situations, such as infants born to mothers who are positive for hepatitis B surface antigen and health care workers at high risk of percutaneous exposure. For vaccine nonresponders, repeat vaccination is recommended by the CDC but not by the World Health Organization [5].

The history of HBV vaccination highlights the benefits of public health. It is the first vaccine given in infancy to eliminate disease in adults.

Human Papillomavirus Vaccine

Recent US population-based studies by the CDC document that 66% of cervical cancers, 55% of vaginal cancers, 79% of anal cancers, and 62% of oropharyngeal cancers are caused by HPV types 16 or 18. Of the 26,000 total annual HPV cancers documented in the United States, 17,000 occur in women and 9,000 occur in men [6].

Three HPV vaccines are available in the United States at present: Gardasil, Gardasil 9, and Cevaxix. All are approved by the FDA to prevent diseases caused by the HPV types included in the vaccines. All 3 vaccines prevent diseases caused by HPV types 16 and 18, which cause nearly 70% of cervical cancers. Gardasil and Gardasil 9 also prevent disease due to HPV types 6 and 11, which cause nearly 90% of genital warts. These vaccines are given in a series of 3 injections

over a period of 6 months. In 2015 Gardasil expanded from a 4-component vaccine to a 9-component vaccine, adding 5 additional HPV strains. These new strains cover an additional 10% of HPV-associated cancers and an additional 15% of cervical cancers.

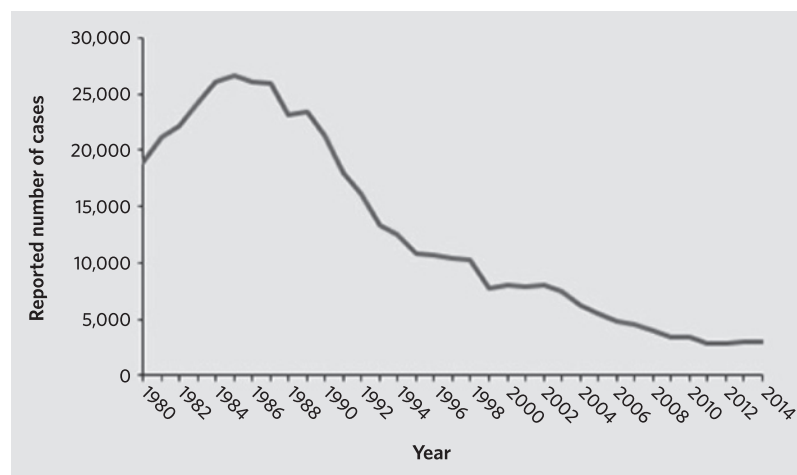
Gardasil (types 6, 11, 16, and 18) and Gardasil 9 (6, 11, 16, 18, 31, 33, 45, 52, and 58) are approved for people aged 9–26 years to prevent all of the cancers previously mentioned (except oropharyngeal cancer). Cevaxix (types 16 and 18 only) is approved for the prevention of cervical cancer in girls and young women aged 10–25 years. None of the vaccines are currently approved to prevent oropharyngeal cancers, but it would not be surprising if future data prove that these cancers would be prevented also.

Gardasil 9, the newest vaccine, has been shown in trials to prevent 97% of cancers caused by the new strains of HPV (types 31, 33, 45, 52, and 58). The original Gardasil (which protected against 4 strains) prevented almost 100% of vaginal, cervical, and vulvar cancers caused by HPV types 16 and 18. With the addition of HPV types 6 and 11, virtually 100% of genital warts are also prevented [7]. Results from many clinical trials are displayed in Table 1.

Antibody levels are extremely high following receipt of the HPV vaccine and are higher in the youngest patients. The excellent antibody response and higher levels in younger children suggest that vaccination before exposure to HPV infection (ie, prior to sexual debut) is the best time to initiate the vaccine series. This information, combined with the fact that acquisition of HPV infection at a younger age (<15 years) is up to 6 times more likely than acquisition of infection at an older age (>18 years) to have a cancerous conclusion 20 years later, makes vaccination of both male and female children a high priority [9].

A few countries and provinces—including the United Kingdom, Switzerland, Mexico, and Quebec—have embarked

FIGURE 1.
Incidence of Acute Hepatitis B, by Year, United States, 1980–2014



Source: Centers for Disease Control and Prevention [3].

TABLE 1.
Results of Selected Clinical Trials on HPV Vaccine Efficacy Against HPV Vaccine-Type Precancers and Anogenital Warts^a

Outcome	Vaccine	Sex	Vaccine efficacy
Cervical precancer	Bivalent and quadrivalent	Females	>93%
Vaginal/vulvar precancer	Quadrivalent	Females	100%
Anal precancer	Quadrivalent	Males	75%
Anogenital warts	Quadrivalent	Females	99%
		Males	89%

^aPopulation includes the per-protocol and according-to-protocol population. Subjects received all 3 doses, and cases were counted 1 month after dose 3. Note. HPV, human papillomavirus. Source: Adapted from Dunne EF, et al [8].

on a 2-dose schedule for HPV vaccination. At least 2 articles recently suggested that antibody persists after just 1 dose of vaccine, so trials may begin to see if 1 dose is sufficient. Julia Brotherton, an epidemiologist from Australia, hypothesized that 1 dose of vaccine may be sufficient to prevent cancer resulting from HPV types 16 or 18 but that multiple doses may be required to get cross-protection from other subtypes [10].

Cancer Vaccines

In addition to vaccines that protect against infection and subsequent cancers, vaccines have also been developed to treat cancer. These cancer treatment vaccines are also called therapeutic vaccines. These vaccines are used only in patients who already have cancer. The vaccines may be used to prevent a cancer from coming back after other treatment has begun, to destroy residual cancer cells in the body after other treatment, or to prevent a tumor from growing or spreading to another part of the body.

All vaccines present foreign antigens to the body so that it can make antibodies and create T-cells that would identify the foreign antigens if they were to present themselves again. The body gains a heightened sense of awareness of these antigens, and if they were to appear, the immune system can elicit a response without delay. This memory of foreign antigens is the goal of all immunization programs.

It is important to understand that sometimes antigens alone are not enough of an immune stimulus, so antigens are frequently combined with adjuvants, which enhance the body's ability to respond to the antigens in all vaccinations. These adjuvants (various oils and aluminum salts are common) are chemicals or sometimes configuration changes that accelerate, prolong, or enhance antigen-specific immune responses. This increase in the body's ability to recognize and respond to the foreign antigens is a welcome trait.

Cancer treatment vaccines boost the immune system's ability to recognize and destroy antigens. Cancer-specific antigens on the surface of cancer cells (which are different than on native cells) are given to an individual as a vaccine;

these surface markers stimulate the immune system to recognize and destroy cancer cells that have these antigens on their surface. At present, most cancer treatment vaccines are only available to volunteers through clinical trials. However, the FDA approved Provenge [11] for men with metastatic prostate cancer in 2010. The vaccine is customized for each patient through a series of steps. Some of the patient's white blood cells are removed, modified to recognize prostate cancer cells, and then returned to the patient. This is the future of personalized anti-cancer therapy.

Public Health Impact

While HBV and HPV are spread primarily through sex or drug abuse, it is still possible for prepubescent children to be exposed to these viruses either at birth or on another occasion. Fortunately, herd immunity can be an effective deterrent to disease spread [12]. When a significant percentage of the population is immunized, then the disease is much less likely to spread. Even those who are not vaccinated are protected, because there is less virus available to cause infection. Once sufficient numbers of individuals are immunized, then the spread can literally drop to zero. This is particularly useful for protecting those who cannot be vaccinated, such as immunocompromised individuals undergoing transplantation, people who are on immunosuppressive therapy, children whose parents refuse to allow them to be vaccinated, and individuals in hard-to-reach geographic locations.

The proportion of the population that must be immunized to achieve herd immunity varies, but the underlying idea is that when enough people are vaccinated and successfully immunized, they protect other members of their community by reducing the spread of the disease. However, often this decrease in disease rates, even among unimmunized individuals, leads to complacency and a false sense of security. As immunization rates subsequently fall, an increase in disease prevalence and subsequent sequelae may be seen. This has occurred on multiple occasions and in many countries. No country is immune to this emotional issue. Once the disease decreases, people argue that they do not need to submit themselves or their children to a vaccine and its possible side effects. Hopefully, appropriate education can enhance vaccine acceptance and increase herd immunity. **NCMJ**

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