

Commentary

Commentary on Fitzgerald et al., p. 34

Preventing Cancer with Vaccines: Progress in the Global Control of Cancer

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Abstract

The cancer control community is largely unaware of great advances in the control of major human cancers with vaccines, including the dramatic control of hepatocellular (liver) cancer with hepatitis B virus (HBV) vaccine, now used routinely in more than 90% of countries. The biotechnology revolution has given us a new generation of highly effective vaccines against major global killers, global funding for immunization is orders of magnitude higher than ever before, and the vaccine delivery infrastructure has improved very significantly even in the poorest countries. Liver cancer is the greatest cause of cancer deaths in men of sub-Saharan Africa and much of Asia. Even in highly endemic countries such as China, the prevalence of HB surface antigen carriers has fallen from 10% to 1%–2% in immunized cohorts of children, and liver cancer has already fallen dramatically in Taiwanese children. The Global Alliance for Vaccines and Immunization (now called the GAVI Alliance) has greatly expedited this success by providing HBV vaccine free for five years in most of the world's 72 poorest countries. HBV vaccination can serve as a model for the global control of human papillomavirus (HPV)–related cervical and other cancers with HPV vaccines. Cervical cancer is the greatest cause of cancer death in women in many developing countries; HPV vaccines are highly effective in preventing HPV infection and precancerous lesions in women, and the quadrivalent vaccine also prevents genital warts in men and women and precancerous anal lesions in men. HPV is causing a growing proportion of oropharyngeal cancers, and HPV-related noncervical cancers (penile, anal, and oropharyngeal) may exceed the incidence of cervical cancer within a decade in industrial countries, where cervical screening is effective, causing reevaluation of male HPV immunization. In developing countries, few women are screened for cervical precancerous lesions, making immunization even more important. Currently, 26 primarily industrial countries routinely immunize girls with HPV vaccine, and GAVI will begin to accept applications in 2012 to fund vaccine in developing countries that can deliver the vaccine and if GAVI can negotiate an acceptable price (one manufacturer has already offered a price of \$5 per dose). *Cancer Prev Res*; 5(1); 24–29. ©2012 AACR.

As populations around the world benefit from declines of infectious disease mortality and of maternal and infant deaths, many more people will live to the age in which chronic diseases and cancer become increasingly important. Focusing on smoking prevention, safe food and water, radiation, screening, and environmental and occupational exposures, the cancer control and prevention community has largely been unaware of the increasing role that vaccines play in the prevention of cancer. Vaccines probably have had the largest role of medical and public health approaches in controlling infectious diseases (Table 1). The first great success in the area of cancer control is the control

of chronic hepatitis B (HB) infection with HB vaccine and its impact on hepatocellular cancer (HCC). As of 2009, 177 (92%) of the world's countries had introduced routine HB vaccine for infants in their national immunization programs (1). The second success is the availability of human papillomavirus (HPV) vaccine to prevent cervical and other HPV-related cancers, which is now included in the national immunization programs of most industrial countries and will be used, it is hoped, in developing countries within the next few years (2). High global coverage of these 2 vaccines will prevent more than 1 million cancer deaths per year (3). The tools to prevent these major human cancers are here, so political will and infrastructural and financial constraints now define how successful they will be. Although there is much work still to do, there has been a quiet revolution in global immunization since the turn of the century. The biotechnology revolution has given us a new generation of highly effective vaccines against major global killers; global funding for immunization is

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doi: 10.1158/1940-6207.CAPR-11-0533

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Table 1. Impact of vaccines: comparing annual disease morbidity in the 20th century with current morbidity in the United States^a (41)

Disease	20th Century annual morbidity (42)	2010 Reported cases (43)	% Decrease
Smallpox	29,005	0	100
Diphtheria	21,053	0	100
Pertussis	200,752	21,291	89
Tetanus	580	8	99
Polio (paralytic)	16,316	0	100
Measles	530,217	61	>99
Mumps	162,344	2,528	98
Rubella	47,745	6	>99
CRS	152	0	100
<i>Haemophilus influenzae</i> (<5 years of age)	20,000 (est.)	270 (16 serotype b and 254 unknown serotype)	99

^aTable modified from CDC Ref. 41.

orders of magnitude higher than ever before; and improvements in delivery infrastructure in even the poorest countries is very significant.

Before HB vaccine, HB virus infected most children in the developing world either perinatally (at birth from carrier mothers) or through horizontal transmission from child to child, unsafe injections and other medical procedures, or other parenteral or sexual exposures. Infection at birth or during early childhood often leads to the development of the chronic carrier state, and the 350 million chronic carriers in the world are at a high risk of death from liver cancer and cirrhosis. HCC is the number one or two cause of cancer death in males in most of sub-Saharan Africa and Eastern and Southeast Asia, and a significant cause of cancer death in women. Beasley and colleagues showed that the relative risk of a carrier developing HCC is more than 100 times greater than that of a noncarrier, which is 10 times that of smokers versus nonsmokers for developing lung cancer (4). There were an estimated 694,000 deaths worldwide from liver cancer in 2008 (477,000 men and 217,000 women), and because of its high fatality (0.93 overall ratio of mortality to incidence), liver cancer is the third most common cause of death from cancer worldwide (5). Most liver cancers develop in chronic HB carriers and are preventable with infant HB immunization. In China alone, 257,000 men and 101,000 women are estimated to die from liver cancer (6), most in chronic HB carriers. Early delivery of HB vaccine is more than 90% effective in preventing development of the carrier state in infants of carrier mothers and more than 95% effective in preventing HB infection in children of noncarrier mothers. The impact of this vaccine on cohorts of immunized children is dramatic: carrier rates fall from highly endemic levels of 8%–15% to 1%–2% (7). Because these young carriers are highly infectious and older carriers become less infectious with age, infection pressure in the population is reduced and rates of acute HB fall dramatically. In Taiwan, a country where infection was so

prevalent that childhood HCC was frequent, HB vaccination has already produced a dramatic decline in HCC in children (8). In low-endemicity areas such as the United States, the incidence of new cases of acute HB has declined by 82% since universal infant immunization began in 1991, and transmission is uncommon except in groups such as IV-drug users and people with high numbers of sexual partners. Occupational Safety and Health Administration–mandated immunization of health care workers in the United States has reduced HB infection in this group to very low levels (9).

The global uptake of HB vaccine has been highly successful, with more than 90% of countries including the HB vaccine as a routine vaccine for children in their national immunization programs. The success of this program and the lessons learned from it provide a useful model for the introduction of HPV and other new vaccines on a global scale (10). However, introduction of HB vaccine to the poorest developing countries took decades. The vaccine first became available in 1982 in the United States and other industrial countries, and it was recommended primarily for adults in "high risk" groups (health care workers, gay men, IV-drug users, "promiscuous" heterosexuals, immigrants from highly endemic areas, people with certain medical conditions, and infants of carrier mothers). With the exception of health care workers and infants of carrier mothers, few of the "high risk" groups got vaccinated and so this high-risk immunization strategy failed to have the desired impact on rates of HB in the community (11). It certainly had no impact on global rates of liver cancer. By the early 1990s it became clear to the public health community that only universal immunization of children would have an impact on community rates of HB and that global immunization of all children was the proper strategy to control liver cancer.

In terms of delivery infrastructure, by 1990 the global rate of routine infant immunization with the vaccines recommended at that time was about 75%. However, rates in

sub-Saharan African countries were usually in the range of 50% to 70%. The real problem was economic: the cost of HB vaccine was high and funds available for new vaccine introduction from global funders were low. In 1990, the vaccine cost to fully immunize a child against tuberculosis (Bacillus Calmette-Guérin vaccine), polio, DTP (diphtheria, tetanus, and pertussis), and measles was about \$1 (12). Three adult doses of HB vaccine cost more than \$100 in the United States, and immunization in the developing world was not feasible at that price. However, producers in South Korea began making vaccine and offered it to public sector programs for about \$1 per dose (13). This price made use in developing countries feasible, and western producers soon dropped prices dramatically for the developing world. The current price for public sector programs in the developing world is approximately \$0.20 per pediatric dose (14).

The breakthrough that made it possible for the poorest countries in the developing world to get new vaccines occurred with the creation of the Global Alliance for Vaccines and Immunization (now called the GAVI Alliance) and the Bill and Melinda Gates Foundation establishment of the Global Fund for Children's Vaccines (later called the GAVI Fund), which financed GAVI's activities; these efforts were soon joined by a number of government bilateral donor agencies. GAVI has raised more than U.S. \$7 billion in support of immunization in the world's poorest countries (15) and has supplied free HB vaccine for 5 years and single-use syringes for 3 years to most of the 75 poorest developing countries. GAVI also supplied *Haemophilus influenzae* type b (Hib) and yellow fever (YF) vaccines to many countries, along with infrastructural support. Results were dramatic as most of the poorest developing countries could now supply HB vaccine to their children. From the point of view of global cancer control, the most significant impact will be in China, where HB coverage is over 90% and where the HB-carrier prevalence in immunized cohorts of children has fallen from 10% to 1% (16).

The global success of the introduction of HB vaccine provides a model for the introduction of HPV vaccine and other new vaccines in the future. The discovery and development of HPV vaccine certainly is a major achievement in medicine, but the delivery of this vaccine to the poorest countries, where the burden of disease is highest, will be a major challenge. HCC is the number one or two cause of cancer death in males in much of the developing world (17), and cervical cancer shares this dubious distinction for females. Chronic HPV infection is believed to be the sole cause of cervical cancer, which is responsible for more than 275,000 deaths (estimated) per year, of which 240,000 occur in the developing world (18).

Although the developed world manages to have significantly lower rates of cervical cancer by screening women and treating precancerous lesions and early cancer, it does so at a considerable cost. Unfortunately, the developing world has had much less success with screening, with few developing countries screening more than 10% of women. The cost, lack of screening personnel including cytologists,

lack of infrastructure and laboratories, and, in some parts of the world, cultural barriers to screening women are all impediments to successful screening programs. Furthermore, many developing countries lack effective treatment, including palliative care, when cancer is diagnosed (19). Cervical screening is not on the list of global health priorities for most global health agencies, and unlike immunization, which has received billions of dollars over the past decade, no large-scale investment in screening has occurred at the global level. Alternatives to Pap testing that have been developed include visual inspection with acetic acid, low-cost colposcopes, and low-cost HPV tests, which could function as primary screening (20). Although comprehensive programs of immunization, screening, and treatment are the goal for every country, immunization is even more important in countries with poor screening programs because even the poorest developing countries generally do well at immunizing children. Immunizing adolescents will be more of a challenge (versus immunizing younger children), but one that should be possible in most developing countries, especially if they can do school-based immunization. Human immunodeficiency virus (HIV) infection greatly potentiates cervical cancer risk (21), making the control of cervical cancer in developing countries with a high prevalence of both HIV and HPV infection especially important. Very recent work in Haiti (reported in this issue of the journal) indicates that HIV infection increases cervical (and systemic) markers of inflammation and suggests a mechanism for the increased cervical cancer risk of coinfection with HIV and HPV (22). Twenty-six primarily industrial countries have introduced HPV vaccine in routine, government-funded programs targeting 9- to 14-year-old girls as a primary strategy (23), but countries vary considerably in how they handle "catchup" in vaccinating young women, with programs varying from no catchup to free immunization for all women below the age of 26. In the United States, HPV vaccine is recommended for all girls between 9 and 14 years of age and the Vaccines for Children program will pay for vaccine for all girls who are 17 and younger, who do not have health insurance (24). In general, countries with school-based immunization programs achieve higher coverage than do those that require each child to visit a health provider. The United States does not have school-based programs, and the vaccine is not required for school entry except in Virginia and the District of Columbia. Coverage in 9- to 14-year-old girls is in the range of 40% to 50%, which is not atypical for nonrequired vaccines. However, there is significant use of the vaccine in girls who are 15 to 18 years old (25). Some parents feel that 9- to 14-year-old girls are "too young" but accept immunization of their daughters when they become older. Anti-vaccine groups and messages also affect coverage in many countries.

The critical event that will make HPV vaccine available to children in the poorest countries, where the burden of cervical cancer is highest, will be the inclusion of HPV vaccine in the portfolio of vaccines offered by GAVI to these countries. As well as supporting vaccines such as

DTP-Hib-HB (pentavalent) and YF vaccines, GAVI is currently making pneumococcal conjugate, rotavirus, meningococcal conjugate A, and second-dose measles vaccines available to the poorest countries. In November 2011, the GAVI Alliance Board announced that GAVI will begin to accept applications in 2012 from developing countries to fund HPV vaccine if the countries can show the ability to deliver the vaccine and if GAVI can negotiate an acceptable price with manufacturers (26). One manufacturer has offered GAVI a price of US \$5.00 per dose (27). GAVI will also help to fund demonstration projects in countries to help them develop the ability to deliver the vaccine. According to GAVI estimates, 30 countries will apply by 2015. These lower prices will require economic modelers to revisit their analysis of the cost effectiveness of HPV vaccine introduction in the developing world, as well as that of male immunization.

Countries with a per capita gross national product of more than \$1500 are not eligible for GAVI support and must issue a tender and bid to get HPV vaccine. In principle, vaccine manufacturers have agreed to provide vaccine to these countries at a "tiered price," but this process is not precisely defined. In practice, countries must decide if they want a particular vaccine (in which case they must negotiate with only one producer) or if they are willing to use the vaccine that gives them an acceptable price following a tender and bid procedure. The prices of HPV vaccines have been significantly lower for developing than for industrial countries, but there is no consistent pattern to these prices.

Inclusion of HPV vaccine in national immunization programs is not just a financial issue but will require changes in vaccine delivery infrastructure. While most countries, including most of the poorest countries, deliver vaccines effectively and at relatively high coverage to children younger than 24 months, reaching preadolescents is not routinely done except in vaccine campaign settings. Routine use of 3 doses of HPV vaccine in preadolescents will present a challenge to these systems (28). Some countries have experience delivering vaccine in school-based programs, and experience in countries such as Australia (29) and the United Kingdom (30) shows that school-based delivery is the most effective way to deliver this vaccine and achieve high coverage (31). Fortunately, there has been great improvement in school enrollment globally, including girl enrollment (32), so school-based programs have the potential to achieve relatively high coverage.

Two important emerging issues will affect HPV policy and use in the future. First, an increasing proportion of head and neck cancers are caused by HPV infection (33). Virtually all HPV-related cancer in the head and neck occurs in the oropharynx (tonsils and base of tongue), and at least 25% of all head and neck cancers are believed to be HPV-related oropharyngeal cancer; this proportion is increasing to epidemic dimensions in the industrial world, but it is not known whether dramatic increases in this incidence are also occurring in the developing world. In the United States, HPV-related oropharyngeal cancer is primarily a disease of white men, although recent trends

indicate that it is increasing in both white and black men (34). Thus, the proportion of head and neck squamous cell cancers (e.g., oral cancer) due to alcohol and tobacco use is declining whereas that due to HPV infection is increasing. Unlike cervical lesions which can be detected and treated while precancerous, procedures to screen the head and neck and treat precancers have not been adopted. Furthermore, "Pap-test equivalent" screening for HPV-related oropharyngeal cancer has not been effective (35). Prevention seems the obvious best strategy to prevent these cancers.

The second emerging issue of great importance to future HPV policy and use is male immunization. Although cervical cancer is the most prevalent single cancer that is preventable with HPV vaccine, the Centers for Disease Control and Prevention estimates that approximately 7,500 cases of HPV-related cancer, primarily head and neck and anal cancer, occur in men each year in the United States alone (36). Actually, more cases of anal cancer are reported in women than men, but rates of anal cancer in men who have sex with men are extremely high, and rates in HIV-positive men are astronomical (37, 38). On the basis of recent data directly establishing the efficacy of HPV vaccine in preventing anal precancerous lesions in males, the Food and Drug Administration licensed the quadrivalent HPV vaccine for this indication in males. In October 2011, the CDC Advisory Committee on Immunization Practices (ACIP) recommended routine immunization of boys who are 11 to 12 years old with the quadrivalent vaccine to help prevent anal cancer caused by HPV types 16 and 18, anal dysplasia and precancerous lesions caused by HPV types 6, 11, 16, and 18, and genital warts caused by HPV types 6 and 11. ACIP also recommended the quadrivalent vaccine for males who are 13 to 21 years of age who have not previously been vaccinated. However, the Strategic Advisory Group of Experts of the World Health Organization (WHO) have not yet changed their recommendations, which are to immunize only females (39), and most countries who have licensed the vaccine have not yet changed their policy on male immunization.

Although cervical cancer is clearly the predominant HPV-related cancer in the developing world, where screening is uncommon and treatment is often unavailable, Gillison and colleagues (40) point out that noncervical HPV-related cancers may surpass the incidence of cervical cancer within a decade in the United States and other industrial countries with effective screening. This prospect should cause us to reframe the issue of HPV immunization, broadening it from primarily a cervical cancer-prevention effort in women to an effort to control HPV-related cancers and genital lesions in both women and men.

Conclusion

The great success of HB immunization worldwide will have a major impact on rates of HCC and cirrhosis in the future. More than 90% of countries now use HB vaccine as a routine part of their national immunization

programs, producing a dramatic fall in the prevalence of HBsAg carriers in immunized cohorts of children. HB vaccine for controlling HCC provides a model for the control of cervical cancer and other HPV-related cancers with HPV vaccine. In November 2011, the Board of the GAVI Alliance, the global mechanism for funding new vaccines in the poorest countries, announced that GAVI will begin accepting applications to fund HPV vaccine for eligible countries if they can show the ability to deliver the vaccine and if GAVI can negotiate an acceptable price with manufacturers. New data on HPV's role in head and neck cancers and the efficacy of HPV vaccine in preventing

precancerous anal lesions in males, as well as a dramatic fall in the price of the vaccine in the poorest countries, call for revisiting the economic analysis and our global strategy for HPV control.

Disclosure of Potential Conflicts of Interest

Dr. Kane is a member of the Merck Advisory Board for HPV vaccine and has received consulting fees, honoraria and travel support from Merck.

Received October 19, 2011; revised November 5, 2011; accepted November 22, 2011; published OnlineFirst January 4, 2012.

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