ARTICLE TITLE: The Importance of Immunization in Cancer Prevention, Treatment, and Survivorship

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After reading the article “The Importance of Immunization in Cancer Prevention, Treatment, and Survivorship,” the learner should be able to:
1. Summarize the relevance of human papillomavirus and hepatitis B virus infection and vaccination to cancer prevention.
2. Highlight the importance of individual-level and population-level adherence to vaccination against preventable infections (such as measles, influenza, Streptococcus pneumoniae, and varicella-zoster virus) to preventable mortality and morbidity among cancer survivors and individuals undergoing immunosuppressive cancer treatment.
3. Describe barriers and facilitators to achieving high levels of adherence to vaccination recommendations and clinical and public health strategies for overcoming these factors.

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The Importance of Immunization in Cancer Prevention, Treatment, and Survivorship

Elizabeth M. Ward, PhD; Christopher R. Flowers, MD, MS; Ted Gansler, MD, MBA, MPH; Saad B. Omer, MBBS, MPH, PhD; Robert A. Bednarczyk, PhD

Abstract: A measles outbreak originating in California during 2014 and 2015 called attention to the potential for infectious disease outbreaks related to underimmunized populations in the United States and the potential risk to pediatric patients with cancer attending school when such outbreaks occur. Compliance with vaccine recommendations is important for the prevention of hepatitis B-related and human papillomavirus-related cancers and for protecting immunocompromised patients with cancer, and these points are often overlooked, resulting in the continued occurrence of vaccine-preventable neoplastic and infectious diseases and complications. This article provides an overview of the importance of vaccines in the context of cancer and encourages clinician, health system, and public policy efforts to promote adherence to immunization recommendations in the United States. CA Cancer J Clin 2017;67:398-410. © 2017 American Cancer Society.

Keywords: hepatitis B, herpes zoster, human papillomavirus, immunization, influenza, neoplasms, Streptococcus pneumoniae

Introduction

On January 5, 2015, the California Department of Public Health received reports of 7 suspected measles cases, all of which were linked to visits to 1 of 2 adjacent Disney theme parks in Orange County, California, between December 17 and 20, 2014. By February 11, 125 measles cases had been confirmed in US residents connected with this outbreak, 110 of them among California residents. Among the 110 California patients, 49 (45%) were unvaccinated, including 12 infants who were too young to be vaccinated. This outbreak raised to national attention the potential for widespread transmission of vaccine-preventable diseases when populations are not protected by a high rate of immunization (herd immunity). Although the measles outbreak was the most widely publicized outbreak in recent history, resurgence of other infectious diseases preventable by childhood immunization,
including pertussis and mumps, has also occurred in the United States.\textsuperscript{2} Such outbreaks pose a special hazard for vulnerable populations, including children too young to be vaccinated, children and adults receiving chemotherapy or other immunosuppressive therapies, and other immunocompromised patients.

The importance of immunization in the context of cancer goes beyond the protection of immunocompromised patients through herd immunity. Currently, vaccines for 2 carcinogenic viruses—oncogenic human papillomavirus (HPV) types and hepatitis B—are recommended specifically because they are protective against cancer.\textsuperscript{3,4} Several other vaccines recommended for the general population are particularly important for patients with cancer as well as cancer survivors, because they reduce the probability of complications during and after treatment. This article reviews information on several aspects of the relationship between immunizations and cancer. Although we describe vaccine recommendations for the general population, individuals with cancer, and/or other immunocompromised patients, the article is not intended to serve as a primary reference for vaccine recommendations or clinical guidance for vaccination in patients with cancer or others with immunocompromising conditions but, rather, to call attention to the important relationships between vaccination and cancer across the cancer-control continuum. We address this topic by reviewing outbreaks, guidelines, guideline adherence, and infection incidence in the United States. The extent of international differences in health care and public health systems precludes a broader scope, although we include some international information that raises unique points relevant to the United States. Nonetheless, it is important to recognize that much of this information applies to many other countries and that other nations’ successes and challenges are relevant to the United States.

**Why Did the Recent Measles Outbreak Generate So Much Concern?**

The 2014 to 2015 measles epidemic attracted national attention in part because of its origin at a national tourist attraction, the size of the epidemic and the high rate of transmission, and the potential severity of measles infection and its complications. Measles is a highly transmissible disease; the likelihood of a susceptible person developing measles after face-to-face contact with an infected person is approximately 90\%.\textsuperscript{5} Approximately 20 million cases occur globally each year, with highest incidence in countries with developing economies. These infections result in approximately 164,000 deaths, with the highest case fatality rates among children aged younger than 5 years.\textsuperscript{6} In the United States, about 28\% of young children with measles are hospitalized, and about 3 in 1000 die from it.\textsuperscript{7} Serious complications include pneumonia, neurologic involvement (eg, 1 in 1000 cases develop acute encephalitis, 6-7 in 1000 cases develop seizures, and approximately 1.5 in 1000 cases develop subacute sclerosing panencephalitis), and hearing loss.\textsuperscript{8,9}

Pediatric patients with cancer are recognized as being particularly vulnerable to measles infection, although infection among adult recipients of bone marrow transplants has also been reported.\textsuperscript{10} Even children who were fully immunized before their diagnosis may lose immunity because of immunosuppressive chemotherapy drugs and are at high risk of severe complications and death should they develop measles. Although data on measles in immunosuppressed children with cancer are very limited, a case series report in 1992 found a case fatality rate of 55\% among 40 pediatric patients with cancer, 32 of whom had acute lymphoblastic leukemia. Twenty-three (58\%) patients developed pneumonitis, 8 (20\%) developed encephalitis, and 3 (8\%) had both.\textsuperscript{11} A more recent report suggests that prior measles immunization mitigates the severity of illness, that early ribavirin therapy prevents complications, and that postexposure prophylaxis with ribavirin prevented the development of measles among pediatric patients who were close contacts of cases.\textsuperscript{12} Vaccination of pediatric patients with cancer during measles outbreaks is not recommended, because it is a live vaccine.\textsuperscript{13}

The first live (attenuated) vaccine against measles was licensed for use in the United States in 1963; measles vaccine is now available combined with vaccines against mumps and rubella (MMR) or combined with mumps, rubella, and varicella vaccines as MMRV (ProQuad; Merck & Company Inc, West Point, Pennsylvania). Before 1963, epidemic cycles occurred every 2 to 3 years. Although approximately 500,000 measles cases and 500 related deaths were reported annually in the United States, the actual number of cases was estimated at 3 to 4 million annually.\textsuperscript{5} The highest incidence was among children ages 5 to 9 years, who generally comprised more than one-half of reported cases. In the years after licensure of the vaccine, the incidence of measles fell by 95\%, and 2-year to 3-year epidemic cycles no longer occurred.\textsuperscript{5} Although high immunization coverage eliminated endemic measles (interruption of year-round endemic transmission) from the United States in 2000, continuing importations of measles cases from endemic regions led to secondary measles cases and outbreaks in the United States, primarily among individuals who had not been vaccinated.\textsuperscript{14} The incidence of measles in the United States rebounded, with a recent record number of cases—668 cases from 27 states—reported to the National Center for Immunization and Respiratory Diseases of the Centers for Disease Control and Prevention (CDC) during 2014, including 1 large outbreak of 383 cases, occurring primarily among unvaccinated Amish communities in Ohio.\textsuperscript{15} Many of the cases reported in the United States during 2014 were associated with cases imported from the Philippines, which experienced a large
measles outbreak. Low rates of vaccine coverage in communities in the United States contribute to the transmission and spread of measles from imported cases. A recent study estimated that 8.7 million US children and adolescents ages 17 years and younger are susceptible to measles and cautioned that there is a potential for large measles outbreaks even in the context of generally high vaccination coverage.

Measles is not the only vaccine-preventable disease undergoing a resurgence in the United States. Unlike measles, pertussis remains endemic in the United States, with an estimated 20,762 reported cases in 2015. A recent article summarized studies that examined the relationship between vaccine delay, refusal, or exemption and the risk of outbreak-related measles or pertussis in the United States. Several studies have estimated the relative risk of outbreak-related infection for vaccinated versus unvaccinated children, but only a few have examined associations between rates of illness and rates of vaccine exemption at the population level. A study in Colorado found an association between county-level frequency of vaccine exemptions and measles and pertussis incidence rates among vaccinated children. Another study, which used national measles surveillance data and state immunization reports, used statistical models to estimate that, if the number of exemptions doubled, then the incidence of measles infection in nonexempt individuals would increase by 5.5%, 18.6%, and 30.8% for intergroup population mixing ratios of 20%, 40%, and 60%, respectively (a higher percentage reflects greater likelihood of contact between exempt and nonexempt individuals). Another study, which evaluated spatial clustering of nonmedical vaccine exemptions in children and geographic overlap between exemption clusters and clusters of reported pertussis cases in Michigan, found that census tracts in exemptions clusters were about 3 times more likely to be in pertussis clusters. Although it does not appear that recent outbreaks of vaccine-preventable diseases in the United States have affected patients with cancer or health care facilities, should these outbreaks become more frequent, the potential will increase for patients with cancer to be exposed to infectious cases in the community and health care settings. It is worth noting that the first measles death in the United States in 12 years was reported by Washington state health officials in 2015; the woman who died had several health conditions, was taking immunosuppressive drugs, and lived in a county where a measles outbreak had occurred.

**Immunization Requirements and Parental Concerns**

Parental concerns about childhood vaccinations are common. Many concerns have centered on a potential association between vaccines and autism, sparked by an article published in 1998 in *The Lancet* and speculation by its author that the measles component of the MMR vaccine was associated with increased incidence of autism. That article was retracted by *The Lancet* in 2010 based on conclusions that that several elements of the paper were incorrect. Concerns about the paper included its claim to have investigated a “consecutive series” of 12 children, whereas further investigation revealed that the patients had been carefully selected and that attorneys acting for parents who were involved in lawsuits against vaccine manufacturers had provided some of the funding for this research. Several well-designed epidemiologic studies have found no evidence for an association between MMR vaccination and autism, and a recent systematic review of the safety of vaccines concluded that there is strong evidence that the MMR vaccine is not associated with autism. Public concerns about childhood immunizations and neurodevelopmental defects have also focused on thimerosal, an ethylmercury-containing preservative that has been used in very low concentrations in some vaccines since the 1930s. Because of theoretical concerns about the potential toxicity from ethylmercury, in 1999, the American Academy of Pediatrics and the US Public Health Service issued a joint statement calling for the removal of thimerosal from vaccines. The Institute of Medicine supported this recommendation as “a prudent measure in support of the public health goal to reduce mercury exposure of infants and children as much as possible.” Since 2001, with the exception of inactivated influenza vaccine, all vaccines manufactured for the US market and routinely recommended for children ages 6 years and younger have contained no thimerosal or only trace amounts (≤1 μg of mercury per dose) remaining from the manufacturing process. Removal of thimerosal has generally resulted in the distribution of vaccines in single-dose rather than multidose vials, which is feasible in high-income countries but not in low-resource countries, where thimerosal remains an important vaccine preservative. Studies from around the world have not found evidence of significant harm from thimerosal-containing vaccines.

Potential associations between childhood immunizations and childhood cancer do not appear to be a significant public concern; however, it is reassuring to note that high-quality epidemiologic studies have investigated the potential relationship between vaccinations and childhood leukemia, and none found a positive association. In fact, one study found that that several vaccines may have a protective effect against acute lymphoblastic leukemia, and another study found a protective effect of complete immunization schedules for rhabdomyosarcoma.

A comprehensive review of the safety of vaccines used for routine immunization of children in the United States, published in 2014, found evidence for adverse reactions associated with specific vaccines but noted that severe adverse
reactions are rare and must be weighed against the substan-
tial protective benefits provided by these vaccines.26 Informa-
tion about the frequency of adverse reactions associated
with specific vaccines is available on the CDC Web site
(cdc.gov/vaccines/vac-gen/side-effects.htm). For example, the
Web site states that studies have demonstrated a very
slightly increased risk (approximately 1 in 3000 to 4000) of
febrile seizures among children younger than 7 years occur-
ing approximately 6 to 14 days after MMR vaccination.
The risk of immune thrombocytopenic purpura is elevated
during the 6 weeks after an MMR vaccination, with 1 study
estimating 1 case per 40,000 vaccinated children.

Despite reassurance about the safety and efficacy of vac-
cines and the public health and medical importance of vacci-
nation, a significant proportion of parents have questions
and concerns about the decision to vaccinate.22 Disclosures
about potential adverse reactions, even those that are
uncommon, understandably provoke anxiety for parents.
Environmental and social factors that may contribute to
vaccine hesitancy include lack of parental experience with
the serious nature of the diseases being prevented and an
increase in the number of vaccines recommended for chil-
dren, which raises parental concerns about associated dis-
comfort. Some parents may delay vaccination because they
fear that multiple vaccinations may have adverse conse-
quences for very young children.35 These factors and others
have resulted in more frequent use of exemptions to avoid
or delay childhood vaccinations and have increased public
policy debate about vaccine mandates.35

Vaccine mandates are promulgated through state law;
approval by the US Food and Drug Administration (FDA)
and recommendation by the Advisory Committee on
Immunization Practices (ACIP) of the CDC are the foun-
dation for state mandates.35 State vaccine mandates across
the country vary substantially with regard to reasons for
allowable exemptions and procedures for granting these
exemptions.36 All US states permit medical exemptions for
immunocompromised individuals, persons with allergies to
the vaccine or its components, or those with other relevant
medical contraindications. Participation of a licensed health
care provider is typically required to approve medical
exceptions under state immunization laws. In contrast, reli-
gious or philosophical or personal belief exemptions are typ-
ically based on parental preference. In total, 47 states plus
the District of Columbia allow religious exemptions, and 19
states allow personal belief or philosophical exemptions.37
Less than 0.5% of children in the United States were
granted medical exceptions to 1 or more immunizations
required for school attendance during 2004 through 2011,
with state medical exemption rates ranging from 0.26% to
0.41% of enrolled children.38 During 2004 through 2011,
US rates of nonmedical exemptions increased from 1.48%
to 2.2%, with striking geographical variability; for example,
in the state of Washington, the state-level nonmedical
exemption rate was 4.2%, but rates among counties varied
from <1% to 26%.39 In California, the percentage of kin-
dergarten children with nonmedical exemptions doubled
from 1.56% to 3.06% between 2007 and 2013 and, during
the 2013 to 2014 school year, greater than 25% of kinder-
gartens in California had immunization rates below the
92% to 94% recommended to maintain herd immunity.40
Several states with high nonmedical exemption rates,
including California, Oregon, and Washington, increased
the stringency of their philosophical exemption procedures
during 2011 through 2013 by requiring parents to docu-
ment that they received information from a health care pro-
vider about the benefits and risks of vaccination.35 The
recent measles epidemic and public and media attention to
the high rates of nonmedical exemptions in some areas in
California stimulated further changes in state vaccine legis-
lation. On June 30, 2015, California Governor Jerry Brown
signed a bill that eliminated vaccine exemptions based on
philosophical and religious beliefs, making California the
largest state to enact such strict vaccine requirements. The
law went into effect on July 1, 2016.

In addition to strengthening state mandates, there have
been efforts to reduce financial barriers to vaccination and
reinforce the role of health care providers in promoting
adherence to childhood immunization. In the United States,
financial barriers to childhood immunization have been
reduced by the Vaccines for Children (VFC) program,
which was created by the Omnibus Budget Reconciliation
Act of 1993 and implemented in 1994. This goal of this
program is to ensure that eligible children do not contract
vaccine-preventable diseases because of an inability to pay.
Approximately 50% of children aged <19 years are eligible
to receive vaccines through the VFC, including those who
are Medicaid-eligible, uninsured, American Indian/Alaska
Native, or, for underinsured children (ie, whose health
insurance does not fully cover immunizations), when they
are receiving services at a federally qualified health center
or rural health clinic.41 Furthermore, the Patient Protection
and Affordable Care Act of 2010 eliminated cost sharing in
the form of copays, coinsurance, or deductibles for vaccines
recommended by the ACIP.42 In addition to reducing
financial barriers, studies have been done to better under-
stand parental concerns about childhood immunizations and
reasons for vaccine hesitancy, resulting in guidance for health
care providers to enhance parental communication.43,44

Childhood Immunizations and Pediatric Patients With Cancer

Depending on their age at cancer diagnosis, the recom-
manded childhood immunization schedule for pediatric
patients with cancer is delayed or interrupted during chemotherapy treatment. Most chemotherapy drugs depress humoral and cellular immunity, which limits the patient’s capacity to maintain previously acquired immunity against vaccine antigens or mount a primary immune response to new vaccine stimulation. Studies suggest that a substantial proportion of children who were vaccinated before their cancer diagnosis have lower antibody titers than those considered protective after treatment. In addition, immunocompromised patients are at increased risk of adverse events with live attenuated vaccines and thus cannot receive vaccines such as MMR or varicella during their treatment.46

Patients who were too young to have received recommended childhood immunizations before treatment can generally be vaccinated with inactivated or recombinant vaccines 3 months after completion of chemotherapy and with live attenuated vaccines (MMR and varicella) 3 to 6 months after completion of chemotherapy.13,45-47 Children who completed their vaccination schedule before cancer treatment often have declines in immunity to vaccine antigens and may receive a booster dose of all vaccines, including Haemophilus influenzae type B vaccine and pneumococcal vaccine, at 3 months postchemotherapy for inactivated or recombinant vaccines and 6 months for live attenuated vaccines. Alternatively, patients can receive serologic testing for protection against vaccine-preventable diseases with a recognized serologic correlate of protection and vaccination for those with inadequate serum antibody concentrations.46 The optimal approach for children who had received some but not all doses of a specific vaccine at the time of diagnosis is not clear; it may be recommended that they receive all of the doses usually needed to confer protection.45

A 35-year longitudinal study found elevated incidence rates of infections and infectious complications among 12,360 five-year survivors of childhood cancer compared with their siblings.48 Childhood cancer survivors also had an increased risk of death from infectious complications compared with the US population (standardized mortality ratio, 4.2; 95% confidence interval [95% CI], 3.2-5.4). Among the 65 deaths attributed to infections, 25% were due to pneumonia, 17% were due to septicemia, 12% were due to human immunodeficiency virus-associated infections, 9% were due to bacterial endocarditis, and 37% were due to miscellaneous other causes (eg, gastrointestinal infections, encephalitis, etc). Patients with exposure to total body irradiation had the highest mortality (standardized mortality ratio, 7.8; 95% CI, 1.8-33.0). Although additional research is needed to understand the immunologic factors that may explain elevated morbidity and mortality from infectious diseases among cancer survivors, receipt of appropriate immunizations and prompt care for suspected infections are recommended to mitigate these risks.48

Vaccines for Cancer Prevention

Hepatitis B

Chronic infection with hepatitis B, a double-stranded DNA virus, is an important cause of hepatocellular carcinoma in the United States and globally. Chronic infection is most common in those who are infected at a young age; occurring in as many as 90% of infants who acquire hepatitis B infection at birth, in 30% to 50% of children infected at ages 1 through 5 years, and in 5% of otherwise healthy individuals who are infected as adults.49 An estimated 800,000 to 1.4 million persons in the United States live with chronic hepatitis B infection, many of whom are not aware of it. The hepatitis B vaccine was first approved for use in the United States in 1981 and, in 1982, the ACIP recommended hepatitis B vaccination for adults at increased risk for hepatitis B infection. In 1991, recognizing the challenges of vaccinating adults at increased risk and the substantial burden of chronic hepatitis B infections acquired in childhood, the ACIP recommended that children receive a hepatitis B vaccine series starting in infancy. In 1995, the ACIP recommended routine vaccination for all previously unvaccinated adolescents ages 11 to 12 years and, in 1999, the recommendations for vaccination were expanded to all previously unvaccinated children and adolescents ages birth to 18 years. Ensuring that children and adolescents receive full hepatitis B virus immunization has become a high priority in the United States, with many states modifying school immunization laws to reflect hepatitis B recommendations.49 As of 2015, 91.1% of adolescents ages 13 to 17 years had received 3 or more doses of hepatitis B vaccine.50

Recommendations for hepatitis B vaccination also apply to selected adult populations, including those who have multiple sexual partners, household or sexual partners with chronic infection, and individuals whose occupations involve contact with blood and body fluids. Hepatitis B vaccination is recommended for people who travel to parts of the world where hepatitis B infection is common. In December 2011, the ACIP added the recommendation that all previously unvaccinated adults ages 19 to 59 years with type 1 or 2 diabetes be vaccinated against hepatitis B as soon as possible after the diagnosis is made because of the higher incidence and prevalence of hepatitis B associated with contact of glucose-monitoring equipment with infected blood.51 As of 2014, hepatitis B vaccination coverage was 32.2% among adults ages 19 to 49 years and 15.7% among adults age 50 years and older.52

The role of chronic hepatitis B infection in hepatocellular carcinogenesis is well documented, and the efficacy of hepatitis B vaccination programs for liver cancer prevention has been clearly shown in studies of populations for whom this infection comprises a large portion of the attributable risk for hepatocellular carcinoma.53,54 In addition to the
prevention of hepatocellular carcinoma, individuals and birth cohorts who receive hepatitis B vaccination early in life will be protected against primary infection and thus do not face the risk of reactivation of hepatitis infection during receipt of immunosuppressive therapy. Because reactivation is a significant risk for those who receive high-dose chemotherapy for stem cell/bone marrow transplantation or treatments that lower the number of B lymphocytes, such as anti-CD20 therapy, the American Society of Clinical Oncology and other clinical guidelines recommend that patients for whom such therapy is planned and those in groups at high risk for hepatitis B infection be screened for prior hepatitis B infection. Those who are positive for hepatitis B surface antigen are recommended to start antiviral prophylaxis before systemic therapy, and those who are hepatitis B surface antigen-negative/anti-hepatitis B core antibody-positive are considered for antiviral prophylaxis or are monitored closely and can start antiviral therapy if hepatitis B virus reactivation occurs.

**Human Papillomavirus**

HPV is a necessary agent in the pathogenesis of cervical cancer and is associated with a significant proportion of cancers of the anus (88%), vulva (43%), penis (50%), vagina (70%), and oropharynx (13%-56%). HPV is a double-stranded, encapsulated DNA virus of which there are more than 100 types; at least 40 are known to infect the human genital tract, and 15 are potentially oncogenic. Ninety percent of cervical cancers worldwide are caused by 9 HPV types, with types 16 and 18 responsible for two-thirds to three-quarters of cases. In 2006, the FDA approved the quadrivalent HPV vaccine (Gardasil; Merck & Company Inc) to prevent cervical, vulvar, vaginal, and anal lesions associated with HPV types 6, 11, 16, and 18 for females and males ages 9 to 26 years and, in 2009, the FDA approved the bivalent HPV vaccine (Cervarix; GlaxoSmithKline Biologicals, Rixensart, Belgium) for administration to females ages 9 to 25 years for the prevention of cervical cancer caused by oncogenic HPV genotypes 16 and 18. A third vaccine, Gardasil 9, was approved by the FDA in December 2014; this vaccine protects against the 4 HPV types in Gardasil and 5 additional oncogenic types (HPV types 31, 33, 45, 52, and 58). Gardasil 9 was recommended by the ACIP at its February 2015 meeting. It is recommended that HPV vaccination occur at age 11 to 12 years, before sexual intercourse begins. HPV vaccination is recommended as a 2-dose schedule (at least 6 months apart) for children who initiate vaccination between the ages of 9 through 14 years, whereas 3 doses (at baseline, 1 to 2 months, and 6 months later) are recommended for immunocompromised persons and for individuals who initiate the vaccination series at ages 15 through 26 years.

Eight years after HPV vaccines were first recommended in the United States, coverage remains well below the Healthy People 2020 target of 80%. According to the National Immunization Survey-Teen, in 2015, coverage with 3 doses of HPV vaccine by age 13 to 17 years was 41.9% among girls and 28.1% among boys. Most states do not require HPV vaccination for school attendance, and such mandates have been controversial and met with limited success. A recent study of state vaccination mandates found that, as of March 2015, only Virginia and the District of Columbia required HPV vaccination, and both included broad, vaccine-specific exemption procedures; a similar requirement took effect in Rhode Island in August 2015. HPV immunization rates are substantially lower than rates of other childhood and adolescent immunizations. In addition to cost and parental concerns about vaccine safety, barriers to HPV vaccine uptake among adolescents and young adults include the misperceptions among some parents that HPV immunization is not needed for children who are not sexually active and that the receipt of the vaccine might increase promiscuity. Strategies to increase HPV vaccination include reminder/recall systems; practice-focused interventions targeting staff, clinicians, and parents; assessment and feedback activities; and school-based HPV vaccination programs.

HPV vaccination is important for pediatric, adolescent, and young adult cancer survivors because of the increased incidence of subsequent HPV-associated malignancies among long-term survivors. Survivors with a history of hematopoietic stem cell transplantation, treatment with pelvic irradiation, and other cancer treatments resulting in sustained immunosuppression are at the greatest increased risk for HPV persistence and complications. Analyses of Surveillance, Epidemiology, and End Results data from 1973 to 2010 demonstrated that female pediatric and young adult cancer survivors had a 40% relative excess of HPV-associated malignancies overall compared with females in the general US population. The relative excess of HPV-associated malignancies among male pediatric and young adult cancer survivors was even greater—150%.

Two studies have examined HPV vaccine uptake among childhood cancer survivors. A survey of parents of female cancer survivors 5 or more years after their diagnosis and 2 or more years after therapy (age range, 11-18 years) at Texas Children’s Hospital found that that 32% of cancer survivors had initiated the 3-dose series. A study conducted among patients and maternal caregivers attending a survivor clinic at St. Jude Children’s Research Hospital found that 32.6% (75 of 230) of cancer survivors initiated and 17.9% completed the 3-dose vaccine series, whereas 34.3% (24 of 70) of healthy controls initiated and 20.0% completed the HPV vaccine series. Although these studies suggest that HPV
vaccination rates among survivor populations are similar to those in the general population, the prevalence of HPV vaccination in this vulnerable population should be higher.\textsuperscript{65}

Most children who are undergoing cancer treatment at the age when HPV vaccination is recommended can be vaccinated, because current guidelines recommend administration of nonliving vaccine administration on schedule, even during chemotherapy, if the patient is not severely neutropenic.\textsuperscript{65} Additional research is needed to assess the need for boosters in patients who receive vaccinations during periods of immunological compromise. It is important that health care providers encourage childhood and adolescent cancer survivors who have not completed their HPV vaccination series to do so.

**Selected Vaccines Important for Patients With Cancer and Survivors**

**Influenza**

Routine annual influenza vaccination is recommended for all persons aged 6 months or older for whom vaccination is not medically contraindicated.\textsuperscript{70} Ideally, vaccination should occur before the onset of influenza activity in the community. Clinicians are encouraged to vaccinate patients by October, if possible, and to continue to offer the flu vaccine for as long as influenza viruses are circulating. Children ages 6 months through 8 years who require 2 doses should receive their first dose as soon as possible after the vaccine for that year becomes available and should receive the second dose >4 weeks later. To avoid missed opportunities for vaccination, vaccination should be offered to unvaccinated persons aged >6 months during routine health care encounters and hospitalizations when vaccine is available.\textsuperscript{70} Some patients and health care providers may be concerned about an increased risk of Guillain-Barre syndrome after influenza vaccination. An increased incidence of Guillain-Barre syndrome was observed in 1976 after receipt of the swine flu vaccine, with an estimated frequency of 1 additional case per 100,000 vaccinated persons.\textsuperscript{71} However, in studies of patients receiving influenza vaccines in subsequent years, those that found any increased risk of Guillain-Barre syndrome estimated an additional risk of 1 or 2 additional cases per million people vaccinated. Studies have also shown an increased risk of Guillain-Barre syndrome after influenza infection of higher magnitude than the risk observed after vaccination.\textsuperscript{71}

The receipt of inactivated influenza vaccine is generally encouraged for patients with hematologic or solid tumor malignancies aged 6 months and older, with the exception of those receiving intensive chemotherapy, such as consolidation or induction therapy for acute leukemia, and those treated with B-cell antibodies whose B-cell depletion renders a response unlikely.\textsuperscript{47} Although patients with cancer may have a suboptimal response to the vaccine, it is safe to administer to immunocompromised patients and has the potential to decrease their risk of severe infection and complications and to reduce the risk of transmission among high-risk patients. Immunocompromised patients should not receive the live attenuated influenza vaccine. (The live attenuated influenza vaccine is not recommended for any population during the 2016-2017 flu season because of lack of effectiveness in recent flu seasons.) The effectiveness of influenza vaccination is likely to be lower in patients at the highest risk for severe disease; thus, influenza vaccination for family members and health care providers is strongly encouraged. Caregivers for persons who require a protective environment because of severe immunosuppression should not receive live attenuated influenza vaccine. Because of the theoretical risk for transmission of the live attenuated vaccine virus to close contacts, these caregivers should also avoid contact with persons who received the live attenuated influenza vaccine within the past 7 days.\textsuperscript{70}

Patients receiving systemic chemotherapy as treatment for any form of cancer are considered at high risk of influenza-related complications. Information about influenza frequency and severity among adults receiving chemotherapy is limited, although a 2009 review article cited several studies reporting case fatality rates greater than 10%\textsuperscript{72} A recent multicenter study of 115 patients with solid tumors who were infected with influenza A (H1N1) in 2009 found high rates of hospitalization (50%), pneumonia (23%), and death (9.5%).\textsuperscript{73} Up to two-thirds of children receiving cancer therapy who contract influenza are hospitalized, for 2 to 7 days on average, with respiratory complications such as pneumonia, respiratory failure, and a need for ventilator support in 10% to 20% of patients.\textsuperscript{74} In addition to influenza-related morbidity, influenza infection in children can result in treatment delays averaging 3 weeks, potentially affecting long-term prognosis.\textsuperscript{74} Vaccination of pediatric patients with cancer and family members is an important prevention strategy.\textsuperscript{74} In addition, vaccination of health care workers is critical to prevent nosocomial transmission of influenza to patients with cancer. A recent multiyear intervention to increase influenza vaccination rates among health care workers in a large comprehensive cancer center found that an increased health care worker vaccination rates was associated with a decreased proportion of nosocomial influenza infections in patients with cancer.\textsuperscript{75} Recommendations and strategies to increase influenza vaccination rates among health care providers have been published.\textsuperscript{76}

**Streptococcus pneumoniae**

*Streptococcus pneumoniae* bacteria (also called pneumococcus) cause acute bacterial infections, including pneumonia,
bacteremia, and meningitis. Approximately 400,000 persons in the United States are hospitalized each year because of pneumococcal pneumonia.77 This bacterium is responsible for approximately one-third of cases of community-acquired pneumonia. The case-fatality rate for pneumococcal pneumonia is 5% to 7% and may be even higher for elderly patients. Although the most common presentation of pneumococcal infection among adults is pneumonia, typical presentations in young children include acute otitis media and bacteremia without a known site of infection.77

There are 2 types of pneumococcus vaccines in current use in the United States: pneumococcal polysaccharide vaccine (PPSV23) (Pneumovax [Merck & Company Inc] or Pnu-Immune [Wyeth Pharmaceuticals Inc/Pfizer Inc, New York, New York]) and pneumococcal conjugate vaccine (PCV13) (Prevnar 13; Wyeth Pharmaceuticals Inc/Pfizer Inc). The former consists of capsular material from 23 pneumococcal serotypes. PPSV23 has been recommended for adults older than 65 years since 198378 but is not used in infants or toddlers younger than age 2 years, for whom unconjugated polysaccharide antigens are poorly immunogenic. PCV13 consists of capsular polysaccharides from the 13 most common pathogenic pneumococcal serotypes covalently linked to a nontoxic recombinant protein that is nearly identical to diphtheria toxin. PCV13 is recommended for infants and toddlers because of its excellent immunogenicity in this age group.77 PCV13 also has been shown to stimulate good antibody responses in adults and, since 2011, has been approved by the FDA for use in adults ages 50 years and older.77 In 2014, the ACIP began recommending sequential administration of both PCV13 and PPSV23 for all adults at least 65 years of age who have not previously received a pneumococcal vaccine.79 The recommended intervals between administration of the 2 vaccines vary, depending on factors such as patient age, risk group, and which vaccine is given first.80 In 2012, the ACIP began recommending sequential administration of PCV13 and PPSV23 for individuals at least 19 years of age who have immunocompromising conditions and, in 2013, recommended sequential administration of PCV13 and PPSV23 for children ages 6 to 18 years with immunocompromising conditions.81,82 In 2013, the Infectious Disease Society of America issued guidelines for vaccination of the immunocompromised host stating that PCV13 should be administered to adults and children newly diagnosed with hematologic or solid malignancies and that PPSV23 should be administered to children 2 years and older and to adults at least 8 weeks after the indicated doses of PCV13.46 The sequence of administration of PCV13 and PPSV23 is recommended based on studies documenting a better response to serotypes common to both vaccines when PCV was given first.80 The interval between administration of PCV13 and PPSV23 is shorter for patients with cancer and those with other medical conditions than for immunocompetent persons to minimize the risk window for invasive pneumococcal disease caused by serotypes unique to PPSV23 in these highly vulnerable groups.80

Introduction of the PCV7 vaccine for children younger than 5 years in 2000 (before the introduction of PCV13) resulted in a rapid decline in the incidence of invasive pneumococcal disease (IPD), not only among children targeted for vaccination but also among unvaccinated children and adults, demonstrating strong direct and indirect protective effects. A study of overall, age group-specific, and serotype-specific IPD incidence from 1998 through 2007 found that dramatic reductions in overall and serotype-specific incidence had persisted in all age groups, including older adults. Even greater declines occurred for PCV7 subtypes accompanied by increases in non-PCV7 subtypes of much smaller magnitude.83 A subsequent study examined trends in IPD incidence rates after the introduction of PCV13 in 2010 and reported that incidence rates of IPD with serotypes included in PCV13, but not in PCV7, declined by 58% to 72%, which is comparable to declines reported after the introduction of PCV7, leading to overall reductions in IPD of 12% to 32%.84

Immunocompromised individuals, including those with hematologic cancers and those receiving immunosuppressive therapies, are at increased risk for IPD. A national study of IPD rates in adults with specific chronic conditions was conducted using 1999 and 2000 data from the Active Bacterial Core Surveillance and the National Health Interview Survey. The rates of IPD in individuals at least 18 years old with chronic conditions were compared with rates in healthy adults, controlling for age, race, and the other chronic illnesses. Overall incidence rates, expressed as IPD cases per 100,000 persons, were 8.8 in healthy adults, 300.4 in adults with solid cancer (adjusted relative risk, 22.9; 95% CI, 11.9-44.3), and 501.3 in adults with hematologic cancer (adjusted relative risk, 38.3; 95% CI, 15.9-92.2).85 In both the numerator and the denominator of these rates, the definition of patients with cancer would likely include patients under treatment as well as posttreatment survivors.85 An analysis of trends in IPD incidence rates from 1998 to 2009 in adults of all ages showed declines for healthy individuals and those with high-risk conditions, although incidence rates in 2009 remained substantially higher for those with high-risk conditions (34.9 vs 8.8 IPD cases per 100,000).86

The most recent available data from the National Health Interview Survey (2014) found that reported pneumococcal vaccine coverage (PPSV23 and PCV13) among adults ages 19 to 64 years with high-risk conditions was 21.3% overall, similar to the estimate from 2013. Coverage among whites was higher (21.1%) than coverage among Hispanics (16.4%) and Asians (14.6%), but coverage was not significantly different for blacks (20.2%) or persons of other races (25.3%).
TABLE 1. Vaccine Resources

| Recommended Immunization Schedule for Children and Adolescents Aged 18 Years or Younger, United States, 2017 | cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf |
| Recommended Immunization Schedule for Adults Aged 19 Years or Older, United States, 2017 | cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf |
| ACIP disease-specific recommendations | cdc.gov/vaccines/hcp/acip-recs/index.html |
| 2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host | idsociety.org/Templates/Content.aspx?id=32212256011 |

Abbreviations: ACIP, Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention; IDSA, Infectious Diseases Society of America.

Among adults aged at least 65 years, coverage was 61.3% overall, similar to the estimate for 2013. Coverage among whites (64.7%) was higher than among blacks (49.8%), Hispanics (45.2%), and Asians (47.7%).

Herpes Zoster

Varicella-zoster virus (VZV) is a neurotropic member of the herpes virus family. Primary infection with VZV causes varicella (chickenpox). After clinical resolution of the primary infection, VZV can remain latent in the dorsal root ganglia. Latent VZV can reactivate years later, resulting in productive viral infection that causes a painful, maculopapular rash known as herpes zoster or shingles. Varicella vaccination in children to prevent chickenpox, which began in the United States in 1995, does not prevent herpes zoster, because it contains live attenuated VZV, which causes latent infection that can reactivate. Children vaccinated against varicella appear to have a lower risk of herpes zoster than people infected with the virus, but it is unclear whether the decreased risk will persist at older ages. The CDC estimates that the lifetime cumulative incidence for developing herpes zoster is almost 1 in 3 people in the United States. The incidence of herpes zoster increases with age, particularly after age 50 years, as does the severity of associated symptoms, such as postherpetic neuralgia, the incidence of nonpain complications, the need for hospitalizations, and interference with activities of daily living.

A live attenuated herpes zoster vaccine (Zostavax; Merck & Company Inc) was recommended by the ACIP in 2008 for prevention of herpes zoster among adults aged at least 60 years. Although the FDA approved the use of Zostavax in 2011 for adults ages 50 through 59 years, the ACIP reviewed evidence relevant to vaccination in this age group but has not broadened its recommendation for routine vaccination beyond the initial one for adults aged at least 60 years. In 2014, 27.9% of adults aged at least 60 years reported receiving a herpes zoster vaccination. There are substantial racial disparities in vaccine coverage. Among persons aged 60 years or older, vaccination coverage was 32.0% among whites, 11.6% among blacks, 14.6% for Hispanics, 20.7% for Asians, and 19.6% among those identifying their race as “other.”

Patients with cancer, especially those with leukemia and lymphoma, have an increased risk for herpes zoster, as do individuals with other immunosuppressive medical conditions or treatments. A study of elderly patients with cancer diagnosed during 1991 through 2007 using Surveillance, Epidemiology, and End Results-Medicare–linked records found that the incidence rate of herpes zoster was 31 per 1000 person-years for patients who had hematologic cancers and 14.9 per 1000 person-years for patients who had solid cancers, with adjusted risk ratios compared with patients who did not have cancer of 2.36 (95% CI, 2.30–2.42) and 1.19 (95% CI, 1.17–1.21), respectively. Another study using records from Kaiser Permanente Northern California found similar incidence rates of 31 per 1000 person-years for patients with hematologic cancers and 12 per 1000 person-years for patients with solid malignancies diagnosed during 2001 through 2005. A more recent study conducted among Kaiser Permanente Southern California members aged 60 years and older who received chemotherapy for cancer found that those who previously were vaccinated against herpes zoster had a lower cumulative incidence rate than unvaccinated patients (3.28% in vaccinated patients and 5.34% in the unvaccinated group; adjusted hazard rate, 0.58 [95% CI, 0.46–0.73]).

Conclusions

The development of vaccines and resulting declines in infection-related morbidity and mortality during the 20th century was a remarkable medical and public health achievement that saved countless lives. In the United States, parental resistance to childhood immunizations, the reemergence of measles and other infectious diseases preventable by childhood immunizations, low rates of HPV vaccination for adolescents, and suboptimal uptake of vaccines recommended for high-risk and older adults cause unnecessary suffering, deaths, and increased costs for the health care system. High rates of immunization and herd immunity are critically important to protect immunosuppressed patients.
with cancer from exposure to vaccine-preventable diseases when their own immunity is weakened. The trend for decreasing receipt of oncology care as inpatients in specialized cancer centers and increasing care in outpatient and community hospital settings could increase patient exposure to infected individuals and heightens the importance of herd immunity. Clinicians play an important role in encouraging parents to vaccinate children and adolescents and in identifying and providing vaccines to high-risk and age-eligible adults. Table 1 provides links to up-to-date resources for more comprehensive vaccine recommendations. Clinicians caring for patients with cancer and survivors should be aware of their heightened susceptibility to vaccine-preventable diseases and ensure that patients receive revaccination after treatment if necessary.

Barriers to the receipt of vaccines in adults include lack of an adult vaccine delivery system; lack of current, easily accessed immunization records; and insufficient knowledge and awareness, as well as problems related to patient cost and vaccine storage. The National Vaccine Advisory Committee recently evaluated the barriers to adult immunization and made recommendations related to general infrastructure, expanded access, and provider- and based health system-based interventions. It has been estimated that only 31% of family physicians and 20% of internists stock all vaccines routinely recommended for adults. Offering vaccines at retail pharmacies and clinics can expand opportunities for adult immunization. Systematic and concerted efforts to improve vaccination adherence in the United States is important for the prevention of cervical and hepatocellular cancer as well as the protection of vulnerable patients with cancer and survivors from vaccine-preventable infectious diseases (including, but not limited to, those described in this review) and should be a priority for cancer control and advocacy.

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