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Use of Licensed Vaccines for Active Immunization of the Immunocompromised Host

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INTRODUCTION

The prevention of infection in patients with impaired immunity is paramount for the success of therapies for malignancy, autoimmune diseases, and AIDS. Vaccination is an attractive means to realize this end, but infections in patients with impaired immunity present a formidable challenge. The course of infections in these individuals can be more aggressive than in normal hosts; e.g., varicella infection, a benign disease of childhood, has a mortality rate of up to 10% in children with leukemia. Also, antimicrobial therapy can be less effective in individuals with impaired immunity, because the contribution of underlying host defense mechanisms is absent. Many infections in patients with impaired immunity are incurable despite the administration of microbicidal therapy; e.g., infections with the fungi *Cryptococcus neoformans*, *Coccidiodes immitis*, and *Histoplasma capsulatum* are difficult to cure in patients with AIDS. They can be suppressed with powerful antifungal drugs, but lifelong suppressive therapy is required to prevent relapses. Some infections in hosts with impaired immunity, e.g., those caused by *Streptococcus pneumoniae*, may be of similar severity to those with normal immunity, but they may be recurrent and necessitate frequent courses of antibiotic therapy. In this regard, the extensive use of antibiotics for treatment and pro-

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phylaxis in patients with impaired immunity may be playing a role in the emergence of drug-resistant organisms.

Many vaccines now under development target specific pathogens that cause infections in patients with impaired immunity. For example, a conjugate vaccine has been made against *C. neoformans* (73, 74), which is a pathogen almost exclusively in patients with impaired immunity. However, nearly all of the licensed vaccines in use today were developed for administration to individuals with normal immunity, and assessment of their immunogenicity was carried out exclusively in normal hosts. Therefore, there are many unresolved questions about the feasibility of using existing vaccines to prevent infectious diseases in patients with impaired immunity. This review summarizes the experience with licensed vaccines in various populations with underlying immune defects. Our goal was to assess the immunogenicity of commonly used vaccines in those with impaired immunity and to illustrate important issues, problems, and potential solutions related to the use of these agents in this patient population.

TERMINOLOGY

Impaired Immunity

Although human populations have probably always included some individuals with immune disorders, the concept that patients with impaired immunity represent a specific group did not evolve until the late 20th century. Advances in the therapy of neoplastic diseases and the use of corticosteroids have led to the emergence of specific patient populations with chronically depressed immune function who are at high risk for both opportunistic and nonopportunistic infections. The human immunodeficiency virus (HIV) pandemic, which was recognized in 1981, has resulted in unprecedented numbers of patients who have developed severely impaired immune function. Armstrong has eloquently described the origins of various terms used to describe patients with impaired immunity, including compromised host, immunodeficiency, and immunocompromised host (17). We have chosen to use the phrase "individual with impaired immunity" because it encompasses a broad range of individuals who are at risk for infections as a result of immunological dysfunction.

"Impaired immunity" refers to any condition that decreases immune system function. The immune response is extraordinarily complex, and many aspects of immune system function remain poorly understood despite a century of intense study. In general, the immune system can be divided into two main arms: specific and nonspecific immunity. Specific immunity refers to the ability of the host to mount an immune response to discrete antigenic determinants of particular pathogens and/or vaccines. For example, an episode of mumps or vaccination with the mumps vaccine will elicit specific immunity to mumps that will not protect against other microbes. The immune system components responsible for specific immunity are B and T lymphocytes. Nonspecific immunity refers to complex humoral and cellular mechanisms by which the host can protect against microbial pathogens without the requirement for recognition of specific antigenic determinants. Some infections may be cleared by macrophages and neutrophils with the help of complement-derived opsonins without eliciting a measurable antibody or T-cell response. Nonspecific humoral mechanisms include complement and serum iron-binding proteins, and nonspecific antimicrobial effector cells include macrophages, neutrophils, NK cells, eosinophils, and platelets.

A problem in defining and understanding the host with impaired immunity is that the human population is outbred and genetically diverse. The genetic diversity of the human population contributes to variability in immune responses to pathogens and vaccines. In some instances, impaired responses to certain antigens result from genetic factors. In this regard, the affected individuals manifest impaired immunity to a specific pathogen or vaccine but are otherwise normal. For example, a subset of the human population will not respond to hepatitis B immunization despite having no apparent immune system defect that would predispose them to more severe infections, possibly because of their genetic background (see below). These individuals are not immunodeficient in the common use of this term but do have impaired immunity to hepatitis B surface antigen. The inability of certain individuals to respond to particular antigens and infections is a price of genetic diversity which provides survival insurance for the species. For the purposes of this review, the term "impaired immunity" will be used only to refer to conditions that predispose an individual to an increased risk of infection.

Vaccines

The term "vaccine" refers to a preparation of live (usually attenuated) or inactivated organisms or their antigenic constituents which have been formulated to stimulate specific immunity.

Toxoid

A toxoid is a modified preparation of a bacterial toxin such that it is no longer toxic but retains its antigenic properties and can elicit neutralizing responses against the native toxin.

Vaccination and Immunization

Although the terms "vaccination" and "immunization" are often used interchangeably, their meanings are not identical. The terms "vaccine" and "vaccination" are derived from vaccinia, a virus used to prevent smallpox. Immunization has its roots in the Latin word immune, which originally referred to an exception to taxation. Vaccination is the act of administering a vaccine. Immunization is the process by which immunity to a pathogen is elicited or transferred. Vaccination does not necessarily mean that immunization has occurred, because the individual may not make an immune response to the vaccine. The term "immunization" encompasses the act of vaccination and the acquisition of protective immunity by the administration of a vaccine or immune components (immunoglobulin, cytokine, T-cell transfer, etc.). Active and passive immunization usually refer to vaccine and immunoglobulin administration, respectively.

LICENSED VACCINES

This review is concerned primarily with vaccines that are licensed for use in the United States. The decision to limit the scope as such was based on the fact that because the licensing process requires extensive studies, a significant amount of information on the efficacy and safety of each vaccine is available. Table 1 lists the currently licensed vaccines with their type and recommended route of administration.

VACCINE RISK VERSUS BENEFIT IN PATIENTS WITH IMPAIRED IMMUNITY

All therapy including vaccine administration involves a risk-benefit decision. For most vaccines, the benefit greatly outweighs the risk, but these parameters are usually defined in the

TABLE 1. Vaccines licensed in the United States by type

Type	Vaccine	Route of administration
Live virus	Adenovirus	Oral
	Measles	Subcutaneous
	MMR	Subcutaneous
	Mumps	Subcutaneous
	Poliovirus	Oral
	Rubella	Subcutaneous
	Varicella	Subcutaneous
	Yellow fever	Subcutaneous
Live bacterium	BCG	Intradermal/ percutaneous
	Typhoid	Oral
Inactivated virus	Japanese encephalitis	Subcutaneous
	Poliovirus	Subcutaneous
Inactivated viral antigen	Hepatitis B	Intramuscular
	Influenza	Intramuscular
Inactivated bacterium	Anthrax	Subcutaneous
	Cholera	Subcutaneous or intradermal
	Pertussis (whole cell preparation)	Intramuscular
	Acellular pertussis	Intramuscular
	Plague	Intramuscular
	Typhoid	Subcutaneous
Toxoid	Diphtheria	Intramuscular
	Tetanus	Intramuscular
Polysaccharide	Meningococcal	Subcutaneous
	Pneumococcal	Subcutaneous or intramuscular
	Vi (typhoid)	Intramuscular
Conjugate of polysaccharide and protein	Hib	Intramuscular

context of a normal host. Patients with impaired immunity are usually at greater risk from both infection and vaccination. For example, chickenpox is usually a benign disease of childhood caused by varicella virus, but it caused significant mortality in children with lymphoproliferative malignancies before antiviral therapy was available. The varicella vaccine is highly effective in normal children. In children with impaired immunity who are at great risk for severe varicella infections, the vaccine is less effective and has more severe side effects, but it is nevertheless still useful because it can reduce the morbidity and mortality associated with wild-type virus infection. Hence, vaccine efficacy in the patient with impaired immunity involves a risk-benefit assessment that is different from that for healthy populations. In general, pathogen inactivated, toxoid, and subunit vaccines pose little or no risk to individuals with impaired immunity, and the benefits of such vaccines far outweigh their risk. Conversely, most live vaccines are contraindicated in patients with impaired immunity. One notable exception is that the varicella vaccine is recommended for children with acute lymphocytic leukemia but not HIV infection or other malignancies (64).

The risk-benefit algorithm for vaccine use in patients with impaired immunity is dependent on the prevalence and severity of infection with the particular pathogen, the nature of the underlying host immune defect, and the efficacy and safety of the vaccine. For example, the worldwide eradication of smallpox indicates no benefit to continued use of vaccinia virus. For most vaccines, the risk-benefit algorithm is complex and involves choices between acceptable risk and expected benefits.

ADJUVANTS

Many patients at high risk for vaccine-preventable infections are poor responders to immunization because of their underlying immune defect and/or the weak immunogenicity of some vaccines. An option for enhancing the immune response to some vaccines is to use adjuvants which can augment the immune response to an antigen. Vaccine adjuvants are a widely diverse group of reagents that include aluminum compounds, oil emulsions, plant products, bacterial products, biopolymers, and natural immunomodulators such as cytokines (for reviews, see references 117 and 201). A persistent problem in adjuvant development has been uncertainty as to their safety.

The only adjuvants currently approved for human use are aluminum compounds. The aluminum adjuvant, often referred to as Alum, is a complex mixture of aluminum compounds including aluminum phosphate and aluminum hydroxide (117). Aluminum compounds are effective in increasing antibody responses to some antigens but have little or no effect on cell-mediated immune responses (117). The mechanism of action of aluminum adjuvants appears to involve a combination of enhanced immunogenicity by serving as antigen depots (in particular for the toxoids) and effects on antigen-presenting cells (117). At present, other adjuvants, such as Quil (72), monophosphoryl lipid (124), and others (24, 117), are being investigated for human use.

In recent years, there has been considerable interest in the potential of cytokines to function as vaccine adjuvants (201). The use of cytokines is attractive because these peptides are natural products of the immune system that have the potential to modulate specific immune functions. The ability of cytokines to shift an immune response toward a cell-mediated or humoral response suggests their potential to enhance specific areas of immunity. Cytokines could be particularly useful adjuvants in patients with impaired immunity who have defects in activation of antigen-specific cells. At present, the use of cytokine adjuvants for vaccine efficacy is a research tool, and a considerable amount of basic and clinical research remains to be done before the efficacy of cytokines or other immunomodulators as vaccine adjuvants is established.

The potential of the adrenal hormone dihydroepiandrosterone sulfate (DHEAS) to function as an adjuvant in the elderly is being explored (15, 96). Available data suggest that DHEAS can augment the primary antibody responses of elderly mice (15, 96). Clinical information that is available from humans who were immunized with DHEAS and the 1994 to 1995 trivalent influenza vaccine suggest that the number of individuals who can generate primary antibody responses to new antigens is increased by DHEAS (15). A study of elderly mice demonstrated that DHEAS administration enhanced the immunogenicity of a polyvalent pneumococcal polysaccharide vaccine (96). Although the elderly manifest decreased antibody responses to many vaccines (172), we have not included this population in this review because their defects in antibody formation are heterogeneous, poorly understood, and a function of immunosenescence rather than primary or exogenously induced immune system dysfunction.

Although there is considerable interest in developing new adjuvants, the efficacy of these compounds in patients with impaired immunity is unknown. Since immune responses in

normal and immunocompromised individuals may be qualitatively and quantitatively different, it is not certain that adjuvants developed for routine immunization of healthy populations will be effective in patients with impaired immunity. Hence, vaccine adjuvant development for the immunocompromised host may require different strategies from those used in healthy hosts.

VACCINE EFFICACY DATA

Studies of vaccine efficacy often report efficacy in terms of a measurable immune parameter such as the amount of antibody elicited or the development of delayed-type hypersensitivity response. The adequacy of measurable immune system parameters as markers for vaccine efficacy has been established primarily in patients with normal immune function. However, for most vaccines, it is not known whether the same parameters should be used in patients with impaired immunity as a measure of vaccine efficacy. In evaluating the meaning of the term "efficacy," it is important to consider that there are few or no data on the ability of most vaccines to actually prevent infection (or complications of infection) in patients with impaired immunity. Such information has been difficult to obtain because the incidence of vaccine-preventable infections is often low and, overall, there are relatively few patients with impaired immunity who have been vaccinated and studied. A notable exception to this generalization is the case for the varicella vaccine, which has been shown to be effective in children with lymphoproliferative malignancies (see above and below).

The amount of antibody elicited by vaccine administration can be determined by enzyme-linked immunosorbent assays (ELISA), agglutination, complement fixation, and viral neutralization. Determinations of antibody binding to antigen are influenced by a complex set of variables including antibody amount, affinity, avidity, and functional efficacy. Hence, sera could have comparable antibody measurements but differ significantly in antibody composition.

Patients with impaired immunity may have qualitatively different antibody responses from normal hosts. One should not assume that a given antibody level has the same protective efficacy in patients with and without normal immunity. Antibody responses can differ in the amount, isotype, and affinity of the antibody generated in response to immunization. Another variable in the efficacy of antibody function is the status of cellular immunity. In mice infected with the fungus *C. neoformans*, $CD4^+$ helper T cells are required for antibody-mediated protection (292). Similarly, cutaneous delayed-type hypersensitivity to an antigen may or may not correlate with a protective immune response to vaccination. Hence, an important caveat of vaccine use in patients with impaired immunity is a lack of efficacy data that document their ability to actually prevent disease.

PRINCIPLES OF VACCINATION WITH LIVE VACCINES

Live-agent vaccines are licensed in the United States for the prevention of several viral and bacterial diseases. Currently available live-virus vaccines include those for the prevention of adenovirus, measles, mumps, rubella, polio, varicella zoster, and yellow fever infections. A live attenuated *Salmonella typhi* vaccine is available for the prevention of typhoid fever. Vaccinia virus was used for almost two centuries for the prevention of smallpox, but its use has been discontinued with the eradication of smallpox.

Live-agent vaccines use attenuated pathogenic strains that produce a mild infection and elicit a strong immune response without the symptoms that accompany infection with the wild-type infectious agent. Live-agent vaccines generally induce stronger and longer-lasting immunity than either killed-agent or subunit vaccines. In general, most live-attenuated-agent vaccines require only one immunization dose to elicit long-lasting immunity. The greater immunogenicity of live vaccines reflects the fact that the organism replicates in vivo before being checked by an immune response, perhaps representing differences in class I (live-agent) and class II (killed-organism) antigen presentation. In contrast, killed-agent or subunit vaccines tend to require multiple doses for an adequate response and regular booster doses for the maintenance of immunity.

The risk-benefit equation for the use of most live attenuated vaccines in immunocompromised patients is complex because this population is at very high risk for severe infection with the wild-type pathogen. Live-agent vaccines used in immunocompromised hosts include the measles-mumps-rubella vaccine in children with HIV infection. It is noteworthy that a primary impetus for the development of the varicella vaccine was prevention of chickenpox in children with lymphoproliferative disorders, but it is not yet licensed for this indication.

LIVE VACCINES

Adenovirus Vaccine

Oral vaccines containing live, nonattenuated virions are used for prevention of adenovirus type 4 and type 7 infections in military recruits (97). Adenovirus infection has been associated with self-limited acute respiratory disease in healthy hosts. However, several epidemics of adenovirus infection, resulting in significant morbidity, have occurred among military recruits during their time of basic training (97). Adenovirus-related respiratory illnesses in military recruits due to type 4 and 7 viruses have been controlled by the use of a live, enteric-coated vaccine (97). Release of the virus in the gastrointestinal tract results in local proliferation of the virus and elicits immunity which protects against subsequent respiratory infection. In healthy men, the adenovirus vaccines are safe and immunogenic (77, 260, 263, 264). Their efficacy and safety in individuals with impaired immunity is unknown since experience with these vaccines is limited largely to healthy individuals in military service. Adenovirus vaccine use is contraindicated in individuals who have impaired immunity or are pregnant. Routine adenovirus vaccine use is not recommended in civilian populations because a clear need for immunization has not been established (97).

Measles Vaccine

Measles is an RNA virus that causes a syndrome of cough, fever, and rash in children. Although measles is usually a self-limited infection, a significant number of patients can develop severe complications including pneumonia and encephalitis. A live attenuated vaccine has been available in the United States since 1963. Initially, the vaccine was administered at 15 months of age to avoid interference by residual maternal antibodies to measles virus. However, current recommendations are to administer the vaccine (as MMR [see below]) at 12 to 15 months, sometimes earlier, and prior to school entry.

The efficacy of the measles vaccine in many types of immunocompromised patients depends on the type of underlying disorder. A small study of attenuated measles virus vaccine administration to eight children with acute leukemia in remission revealed that seven (87%) produced antibody to measles virus with titers ranging from 2 to 128 by hemagglutination

inhibition (265). Neutralizing antibody was measured in six of the eight children, and no cases of measles were reported in this small group (265). Among 20 recipients of allogeneic bone marrow transplant, the seroconversion rate following immunization with measles virus was 77% (171).

Malnutrition could contribute to poor measles vaccine responses in children in developing countries. Nevertheless, the measles vaccine can be immunogenic in the setting of malnutrition: 70 and 90% of vaccinated children with protein-calorie malnutrition had protective antibodies within 21 and 42 days, respectively, of vaccination with the live measles vaccine (281). Measles vaccination may have higher side effects in malnourished children and could have predisposed to fatal pneumonia in one child (281).

Measles vaccination is contraindicated in patients with disorders of cell-mediated immunity and in pregnant women. This recommendation dates to 1962 and is based on observations of abnormal antibody responses to vaccination in such persons and the possibility of disseminated infection from the attenuated measles virus strain (187). Several cases of disseminated infection following measles vaccination in children with impaired immunity have been described (33, 187, 190). However, these individuals are also at high risk for severe measles as a result of natural infection (40, 153). The risk-benefit assessment for the risk of vaccination versus the benefit of protection against natural infection in immunocompromised patients is unknown. The mortality rate from measles infection in children with HIV infection or cancer is 40 and 70%, respectively (143). The live attenuated measles vaccine appears to be significantly less immunogenic in children with HIV infection. A retrospective study of 18 New York City children with HIV infection who received the measles vaccine revealed serum antibody in only 3 (17%) (153). When eight children were vaccinated prospectively, antibody to measles was detected in only two (25%) (153). Recently, a review of cases of measles infection in HIV-infected patients suggested that those who were vaccinated had lower mortality rates, and the authors recommended a reassessment of the existing practice of avoiding vaccination in patients with impaired immunity (143). Two small studies suggest that measles vaccination is safe in children with leukemia in remission after chemotherapy (265) or in children who received bone marrow transplants at least 2 years earlier, had no graft-versus-host disease, and were not being treated with immunosuppressive drugs (171).

The measles vaccine (in the form of the MMR vaccine) is recommended for all asymptomatic patients with HIV infection (51). For symptomatic children with HIV infection, measles vaccination should be considered (51), recognizing that measles infection has been reported in children with HIV infection (53). Measles vaccination with MMR has been well tolerated by children with HIV infection (91, 185), but cases of measles have been reported after vaccination (153). Children with HIV infection on regular immune globulin therapy may not respond to the MMR vaccine because of passive transfer of virus-specific antibodies (51).

A concern specific to the use of the measles virus vaccine in immunocompromised patients is the potential for a worsening of immune function. Measles virus infection has been classically associated with susceptibility to other viral and bacterial infections as a result of a transient state of immunosuppression following infection. Immune suppression may follow vaccination with live attenuated measles vaccines. Skin test responses to antigens are depressed in children receiving live attenuated virus vaccine (86). The mechanism for the transient depression of immunity which can accompany measles vaccination is not well understood (125). The immunosuppressive effect of measles virus vaccine requires live virus, since immunization with killed measles virus had no measurable effect on host immunity (86). The measles vaccine produces significant leukopenia in many patients 7 to 13 days after vaccine administration, causing reductions in the numbers of lymphocytes, monocytes, neutrophils, and eosinophils (38). Interestingly, the vaccine has the most severe effect on eosinophil counts, which fall to zero at approximately 10 days postvaccination (38). Lymphocytes from children who received measles vaccine have depressed lymphocyte proliferative responses to many common antigens in vitro (86). This may account for the reduction in lymphocyte proliferative responses among healthy children receiving the MMR vaccine (194). Administration of measles vaccine to individuals who are seropositive for measles can suppress chemotactic factor production in response to a variety of antigens (125). Hence, live attenuated measles vaccine administration is associated with a series of abnormal immunological tests that measure cell-mediated immunity and probably reflect a period of transient immunosuppression.

The experience with high-titer measles vaccines in developing countries indicates problems that may have implications for measles vaccine use in immunocompromised hosts (1, 95, 127, 167). High-titer measles vaccines are designed to elicit high-titer responses in infants. The high-titer vaccines protected children against measles but were associated with a higher mortality from other infectious diseases (1, 95, 127, 167). The increase in mortality occurred in girls and not boys (1, 127). Its cause remains unknown (167, 236).

Mumps Vaccine

Mumps is a generalized viral illness of childhood which is usually characterized by parotitis. Mumps can be prevented by vaccination with an attenuated mumps strain, and such a vaccine has been available in the United States since 1967. Few studies have evaluated the efficacy of the live attenuated mumps vaccine in individuals with impaired immunity, but the available evidence suggests that this vaccine is often immunogenic in this population. In an early study, four Japanese children with acute leukemia in remission were immunized, and all produced a neutralizing-antibody response (265). Vaccination of six children on continuous ambulatory peritoneal dialysis with mumps vaccine revealed that all mounted immunoglobulin G (IgG) responses in serum, albeit lower than those in controls (126). However, another study in children on continuous ambulatory peritoneal dialysis revealed only a 50% response when the antibody level in serum was measured by ELISA (244). Other immunosuppressed states may result in lower vaccine response: of 10 children with HIV infection immunized with the MMR vaccine, only 4 had serum antibody detected by indirect immunofluorescence (91). In recipients of allogeneic bone marrow transplants (BMT), the efficacy of the mumps vaccine was 64% (171). Vaccination of HIV-infected children against mumps with the MMR vaccine has revealed no significant adverse effects, and vaccine use is recommended in this population (91, 185). Similarly, no adverse effects were noted among BMT recipients (171).

Rubella Vaccine

Rubella virus causes rubella or German measles, which is a self-limited viral infection of childhood characterized by fever, rash, and lymphadenopathy. Rubella infection in pregnancy can be devastating to the fetus, resulting in birth defects. A live attenuated strain of rubella virus has been licensed for vaccination against rubella in the United States since 1969. In BMT recipients vaccinated with rubella vaccine, the prevalence of

seroconversion was 75% (171). Rubella vaccination can result in viremia and persistent infection in some individuals without apparent immune system defects. In 1981, the isolation of rubella virus 2 years after rubella vaccination in an apparently healthy woman was described (56). A follow-up study documented persistent rubella infection in six women with rubella vaccine-associated arthritis (57). An advisory panel concluded that there was a causal association between rubella vaccination with the RA27/3 strain and the occurrence of chronic arthritis in women (128). Whether individuals at risk for this unusual complication of rubella vaccine have a specific immune system defect or genetic predisposition is unknown. Vaccination with rubella virus is generally contraindicated in patients with impaired immunity. Erroneous administration of rubella vaccine to a boy with leukemia in remission resulted in a persistent infection accompanied by acute arthritis and arthralgia (98). However, vaccination with rubella virus had no adverse effects in 10 children with symptomatic HIV infection who were vaccinated with the MMR vaccine (91). Similarly, no adverse effects of rubella vaccination were observed among 20 patients recovering from BMT (171).

Polio Vaccine

For the prevention of poliomyelitis there are two vaccines available: a live attenuated oral polio vaccine (OPV) and an inactivated polio vaccine (IPV). Both are highly effective. OPV produces a gastrointestinal infection that induces long-lasting immunity and has the added advantage of immunizing individuals in close contact with the vaccine recipient. IPV is administered by intramuscular injection and induces systemic immunity. OPV has, on rare occasions, been associated with paralytic episodes, and the frequency of such events is higher in adults and individuals with impaired immunity. Furthermore, the only cases of polio in the United States at present are vaccine associated. IPV is now recommended for primary immunization of those with impaired immunity, and OPV is only recommended for booster vaccinations (64).

Both OPV and IPV can elicit neutralizing antibody responses in children with HIV infection (26). The magnitudes of serum titers to poliovirus in HIV-positive and -negative children appear to be comparable (26). Children with AIDS can produce weaker responses to IPV vaccination than normal children do (25). A review of 138 cases of vaccine-associated paralytic poliomyelitis identified 13 cases in patients with impaired immunity (200). These patients all had either congenital immunodeficiency or acquired hypogammaglobulinemia, but none had been diagnosed with impaired immunity prior to vaccine administration (200). The risk of vaccine-associated poliomyelitis appears to be 10,000 times greater in patients with hypogammaglobulinemia than in normal individuals (291). Many well-documented cases of vaccine-related progressive poliomyelitis have been described in patients with immunodeficiencies (68, 82, 200, 239, 291). For some patients, immune system deficiencies have been diagnosed only when paralytic poliomyelitis developed as a consequence of vaccination. Feigin et al. in 1971 described a 7-year-old child who developed fatal paralytic poliomyelitis after immunization with OPV without a history of recurrent infections or adverse reactions to previously administered live viral vaccines (82). Vaccine-related poliomyelitis was described in a girl with cartilage-hair hypoplasia, a congenital cause of dwarfism, leading to the suggestion that live viral vaccines be avoided in children with dwarfism until an immunologic evaluation has been completed (239).

Several studies suggest that the OPV is well tolerated by patients with HIV infection. No adverse reactions were reported in eight Italian children with prenatal HIV infection to whom OPV was given (26). A retrospective study of 221 children with perinatal HIV infection in New York City who received OPV revealed no cases of paralytic disease or other adverse effects (185). Nevertheless, IPV is recommended for vaccination against poliomyelitis in all individuals with impaired immunity, including patients with HIV infection (51). IPV use eliminates any theoretical risk to the vaccinee and to close contacts who may also have impaired immunity. IPV appears to be well tolerated in HIV-infected children (26). Another study in which an enhanced IPV vaccine was given to children born to HIV-positive mothers revealed no significant side effects (25). The effect of IPV administration in adults with advanced HIV infection has been studied in a small number of patients who had preexisting antibody (182). Poliovirus antibody titers decreased in adult patients vaccinated with IPV, a finding that was attributed to a desensitization phenomenon analogous to that observed in the treatment of allergy by antigen immunization (182).

Varicella-Zoster Vaccine

Chickenpox is usually a mild disease of childhood, which can be complicated by encephalitis, pneumonia, and superinfection of skin lesions. In patients with impaired immunity, chickenpox can produce severe infections with high mortality. A live attenuated strain of varicella virus (the Oka strain) is licensed for use in patients older than 1 year with no history of chickenpox (154). The Oka strain was isolated in Japan from a healthy child with chickenpox and attenuated by passage through a variety of human and animal cell lines (262). The vaccine underwent a tortuous development process in part because of the need to demonstrate efficacy and safety in the immunocompromised individuals who would benefit most from immunization (180). The Oka varicella virus strain was tested extensively in children with malignancies because this population is at high risk for severe chickenpox infections. A small early study suggested that administration of varicella vaccine to hospitalized children with a variety of illnesses was effective in preventing an outbreak of infection (19). Several large studies have shown that the vaccine is effective in individuals with and without impaired immunity. Among 86 healthy adults, the seroconversion rate after one dose was 58% and the rate after more than one dose was 92% (100). Administration of varicella vaccine to 437 children with leukemia in remission resulted in a seroconversion rate of 89% after one dose and 98% after two doses (99). After 5 years, 30% of children were seronegative and chickenpox was documented in 8% of vaccinated children (99). In children with acute lymphoblastic leukemia, the seroconversion rate after vaccine administration did not differ regardless of whether chemotherapy was being administered (16). Follow-up studies of leukemic children without breakthrough varicella revealed that more than 90% had antibodies in serum 8 to 10 years after vaccination. In children on chronic dialysis and with renal transplants, the antibody response was 76%, but for many children the appearance of antibody was delayed relative to the timing in normal hosts (293). Hence, the varicella vaccine is effective in individuals with and without malignancies, and immunity lasts for at least a decade.

Some authorities have suggested that use of the varicella vaccine be limited to immunocompromised patients at high risk for chickenpox (231). Safety issues with the varicella vaccine include communicability to household contacts, the development of chickenpox-like rashes in immunized individuals, and the possibility of long-term reactivation as shingles. The

incidence of a chickenpox-like maculopapular rash after vaccination was 6 and 42% in children receiving and not receiving chemotherapy, respectively (100). The Oka strain can reactivate in immunocompromised hosts, but the rate of reactivation with zoster appears to be similar to that which follows natural infection (154). Hence, the varicella vaccine appears to be relatively safe in children with leukemia who are in remission. Vaccination of susceptible children with leukemia undergoing induction chemotherapy or experiencing a relapse is not recommended (100). A small study suggests that vaccination prior to chemotherapy may be safe and effective (59). The efficacy and safety of the varicella vaccine in children with HIV infection are being studied. Similarly, there is little information on safety in individuals with impaired immunity not related to malignancy or its treatment.

Yellow Fever Vaccine

Yellow fever is caused by a flavivirus and can be prevented by vaccination with the live attenuated virus strain 17D (256a). The 17D vaccine was generated by serial passage of yellow fever virus in cell culture (256a). This vaccine has been used primarily in Africa and South America and is considered safe and effective (260). The vaccine elicits long-lasting immunity in the majority of recipients but should not be given before the age of 6 months because of the risk of vaccine-related encephalitis. There is little or no information on the efficacy or safety of the 17D vaccine in individuals with impaired immunity. Protein malnutrition has been associated with impaired antibody responses to the yellow fever virus vaccine (44). The response to 17D immunization has been reported to be enhanced by simultaneous administration of the Vi polysaccharide vaccine for typhoid fever (6). Despite the scarcity of literature reports indicating adverse effects in individuals with impaired immunity, administration of 17D to patients with immunodeficiency is contraindicated on hypothetical grounds (208). The safety of the 17D vaccine in pregnant women is also uncertain. A retrospective study of inadvertent vaccination in pregnancy revealed a case of congenital infection without apparent adverse effects to the fetus (266).

Smallpox Vaccine

Vaccinia virus was used for the prevention of smallpox but was discontinued when worldwide eradication of the virus was declared. It remains a viable vaccine against smallpox and may conceivably find employment for the expression of microbial and tumor antigens (193). If live vaccinia virus derivatives are used as carriers of microbial or vaccine antigens, caution should be exercised in their use in immunocompromised patients. Vaccinia necrosum was a severe complication of vaccinia virus administration in patients with immunologic deficiencies; it was characterized by a progressive virus-induced tissue necrosis originating at the site of inoculation (78, 205). Vaccinia gangrenosum was frequently associated with agammaglobulinemia (78). Recently, a case of disseminated vaccinia infection was reported in a military recruit with unrecognized HIV infection who was vaccinated with vaccinia virus (220).

Typhoid Vaccine

Typhoid fever is caused by *S. typhi*. Typhoid fever is endemic in most areas of the world, but in the United States most cases occur among international travellers (289). A live attenuated vaccine made from *S. typhi* Ty21a was licensed in 1989 (289). This vaccine is administered orally in four doses over 7 days. The concept behind the development of an oral live attenuated vaccine for typhoid fever was a large body of direct and circumstantial evidence that ingestion of live bacilli conferred immunity (290). In addition to Ty21a, a killed parenteral vaccine against *S. typhi* is available, but it appears to be less effective and has more side effects (289). Large-scale trials of the Ty21a vaccine in children in Chile and Egypt have shown 67 to 95% efficacy (276, 289, 290). The efficacy of this vaccine in patients with impaired immunity is unknown. The Ty21a attenuated strain was generated by chemical mutagenesis, and one of the mutants accumulates galactose precursors, which kill the bacteria in vivo. The inability of Ty21a to persist in vivo prevents stool shedding among individuals receiving a normal vaccine dose (289). These characteristics suggest a high safety profile, and there are no reports of disseminated or progressive infection among patients receiving this vaccine in large field trials. Ty21a, like all live attenuated agent vaccines, is contraindicated in individuals with impaired immunity (289). In a situation analogous to that of poliomyelitis, for which both live and killed vaccines are available, typhoid fever immunization with the killed parenteral vaccine may be preferable in patients with impaired immunity on theoretical grounds (289). The Vi polysaccharide vaccine, which is now licensed to prevent typhoid fever, is preferable for those with impaired immunity.

Bacillus Calmette-Guérin Vaccine

The bacillus Calmette-Guérin (BCG) vaccine is derived from an attenuated strain of *Mycobacterium bovis* and is used for the prevention of tuberculosis. The efficacy of BCG vaccine in populations at risk for *M. tuberculosis* infections is variable, and BCG vaccination is not currently recommended for routine use in the United States because of the low prevalence of tuberculosis in this country (52). Considering the difficulties encountered in establishing vaccine efficacy in normal populations, it is not surprising that there is no conclusive information for the efficacy of BCG vaccine in patients with impaired immunity. There is evidence that tuberculin skin tests after BCG vaccination in patients with HIV infection are weaker than in normal hosts, suggesting a lower vaccine efficacy in this population (52). BCG administration is contraindicated in patients with impaired immunity. The most serious complication of BCG administration is disseminated infection, which occurs at a rate of 0.06 to 1.56 cases per million doses of vaccine administered (52). Most deaths due to disseminated BCG infection have occurred in patients with impaired immunity. Several cases of disseminated BCG infection have been reported in patients with HIV infection (293). A comparison of the outcome of BCG vaccination in children from HIV-positive and -negative mothers in Haiti revealed a higher complication rate in children of HIV-positive mothers, but the reactions were usually mild and not life-threatening (203). BCG vaccination is not recommended for HIV-infected patients in the United States, but the World Health Organization does recommend vaccination of asymptomatic HIV-infected children who live in countries with a high prevalence of tuberculosis (52).

Use as adjunctive immunotherapy in patients with bladder cancer. Brief mention should be made of the use of the BCG vaccine for the therapy of bladder cancer (121, 250). Immunotherapy with live BCG vaccine delays the progression of superficial bladder cancer and reduces the mortality rate (121, 250). The mechanism of action of the vaccine is poorly understood, but it is generally believed that the antineoplastic effect is a result of an immune response to BCG (250). Complications of BCG therapy in these patients include fever, cystitis, and extravesical dissemination (250). Intravesical administration of BCG for bladder cancer is an effective immunotherapy

TABLE 2. Response rates to live vaccine agents by individuals with impaired immunity

Vaccine	Group	Response rate (%)[a]	Reference(s)
Varicella	Renal disease	100	19
	ALL (acute)[b]	88–91	16, 265
	ALL (remission)	88–98	99, 100
	Cancer	77	59
	Elderly	67	261
	Collagen vascular disease	66	261
Typhoid	Healthy Egyptian children	95	276
Measles	Malnutrition	83–86	281
	Bone marrow transplant	77	171
	HIV infection	25–77	153
Rubella and mumps	Bone marrow transplant	75	153
	Bone marrow transplant	64	153
	ALL	100	265
Polio	HIV infection	>80 (IPV or OPV) 61–88 (IPV)	26 25, 157

[a] This number denotes the percentage of patients who manifested an immunologic response (i.e., measured by serum antibody or skin testing), and this response does not necessarily imply protection against infection.
[b] ALL, acute lymphoblastic leukemia.

involving the use of a live pathogen vaccine in an unconventional role.

USE AND FUTURE OF LIVE VACCINES IN HOSTS WITH IMPAIRED IMMUNITY

Assessing the risks versus the benefits of live-pathogen vaccination in persons with impaired immunity results in a complex calculation, and there are often inadequate data for rigorous and objective problem solving. Table 2 summarizes the response rates of various groups of patients with impaired immunity to some live agents. The use of live-pathogen vaccines in patients with impaired immunity implies, to a certain extent, a contradiction in vaccine design and expected efficacy. Attenuated live-pathogen vaccines replicate in the host until an immune response develops that inhibits replication and prevents the disease associated with infection by wild-type pathogens. Unfortunately, the immune response necessary for checking the proliferation of an attenuated strain may not be adequate in patients with impaired immunity. Therefore, live-pathogen vaccines which elicit protective immunity in normal hosts are likely to always carry some risk in immunocompromised hosts. Furthermore, the immune system deficit of the host will determine the magnitude of the risk associated with a particular live vaccine, e.g., the attenuated live measles vaccine may pose little risk to HIV-infected children but a significant risk to children with lymphoproliferative disorders. A complicating factor is that the patients who are at the greatest risk for the negative sequelae of live-pathogen vaccines often experience the most severe courses of natural infection. The possibility that a live attenuated pathogen vaccine will reduce the baseline immune system function is another important consideration in patients with impaired immunity. Theoretically, the administration of a live vaccine could either enhance or decrease preexisting immunity (e.g., measles vaccination, as detailed above).

In malnourished populations, live-pathogen vaccines carry the parallel concerns that the immunologic response will be suboptimal because of malnutrition and that some vaccines could exacerbate the malnourished state. Kwashiorkor is associated with weak responses to immunization. However, immunization with live virus vaccines can also precipitate a negative nitrogen balance in nutrition. In 1961, Gandra and Scrimshaw reported a negative nitrogen balance in children who were given the live attenuated 17D yellow fever vaccine (93). The effect appeared to be the result of increased catabolism or tissue destruction associated with a subclinical infection by the attenuated yellow fever virus (93). In 1977, Kielmann demonstrated statistically significant reductions in weight in children younger than 6 months old who were given live-pathogen vaccines (BCG, smallpox, and polio) relative to matched nonimmunized controls (148). The weight loss was attributed to increased catabolism from vaccine-induced infection and was not observed with killed or toxoid vaccines such as diphtheria-pertussis-tetanus (148). These observations raise the concern that live-agent vaccination in malnourished children could result in a clinically significant deterioration of the nutritional state (148).

Live attenuated pathogen vaccines are always likely to carry some risks for hosts with impaired immunity, despite their efficacy. The experience with the varicella vaccine shows that it is possible to develop a relatively safe and effective live-agent vaccine for use primarily in patients with impaired immunity. However, the lengthy development and licensing process of the varicella vaccine (due in part to concerns about safety) also illustrates the difficulty that can be encountered in the development of live attenuated pathogen vaccines. For vaccines to be widely accepted in industrialized countries with low mortality rates due to infectious diseases, the risk of vaccination must be zero or close to zero. In the future, it is likely that some of the live vaccines presently in use will be replaced by subunit vaccines that do not carry the risk of infection in patients with impaired immunity.

SUBUNIT VACCINE

Hepatitis B Vaccine

Hepatitis B virus (HBV) causes acute and chronic infections of the liver. Chronic HBV infection has been associated with a high risk for cirrhosis and primary hepatocellular carcinoma. HBV infection is transmitted through exposure to infected body fluids, and the modes of transmission include sexual contact, intravenous drug use, perinatal contact, and blood product transfusions. The first vaccines for prevention of HBV infection contained surface antigen (HBsAg) made by purifying noninfectious 22-nm viral protein particles from the plasma of individuals with chronic infection. In 1981, a plasma-derived vaccine was licensed in the United States. This vaccine was used throughout the 1980s but was replaced in 1989 with a vaccine composed of HBsAg made by expression in the yeast *Saccharomyces cerevisiae* (recombinant DNA vaccine). The antigen produced in yeast has the same amino acid sequence as the viral protein but is not glycosylated. Hence, the recombinant DNA vaccine is not identical to the plasma-derived product. Several comparative studies of the plasma-derived and recombinant HBsAg have shown that the plasma-derived vaccine was more immunogenic, especially in homosexual men at risk for HIV infection (206) and in patients with renal failure (247). In healthy medical students, the recombinant vaccine elicited antibody titers that were only one-fourth those elicited by the plasma-derived vaccine, and there was a higher propor-

tion of nonresponders (162). The change in vaccine formulation introduces some uncertainty in comparing results from the early studies that used plasma-derived vaccine to those obtained with the presently available recombinant DNA vaccine.

A major impetus for the replacement of the plasma-derived vaccine was a theoretical concern that unrecognized infectious agents may exist in the human plasma preparation. The AIDS epidemic was recognized in the same year that the plasma-derived HBV vaccine was licensed, and the increased awareness of blood-borne pathogens heightened concern about the possibility of infectious-agent transmission by the use of plasma-derived products. Despite strong evidence that the plasma-derived vaccine was safe, this vaccine was phased out in favor of a theoretically safer but less immunogenic recombinant DNA vaccine.

The development of the HBV vaccine introduced several novelties in antiviral vaccine design. For the first time, a viral illness was prevented in humans by immunization with a viral protein subunit preparation. Since a major complication of hepatitis B infection is chronic hepatitis leading to cirrhosis and hepatocellular carcinoma, the HBV vaccine was also an anticancer vaccine. The early vaccine was made from the plasma of patients with chronic infection—a fact that hindered widespread acceptance and provided a source of theoretical fears about the possibility of contagion with other infectious diseases. The HBV vaccine was developed in the midst of the molecular biology revolution, which permitted its rapid replacement by a recombinant formulation. The design of the HBV vaccine relied on basic science knowledge gathered by studying the HBV and the course of infection and avoided the empiricism of attenuated live virus vaccines.

The HBV vaccine has been extensively studied for more than three decades, and the response to vaccination is dependent on many variables including the site of injection, host genetic background, concomitant diseases, and immune status of the host. Intramuscular injection is more likely to elicit antibody responses than is subcutaneous injection (267). Obesity has been associated with poor response to buttock injection with a short needle, presumably because of antigen deposition in the subcutaneous space (282). Poor responses have also been associated with advanced age (69, 282), leading to the recommendation that vaccination should be performed at an early age if possible (179). The mental state of the vaccine recipient is also a variable in efficacy of vaccination with HBV. A study of medical students showed that probability of mounting an antibody response to the first injection of HBV given on the third day of a 3-day examination series was inversely proportional to the level of anxiety and stress (107). Furthermore, the students with better social infrastructures demonstrated stronger immune responses by the time they received the third vaccine dose (107). Another study correlated the antibody titer at 7 months with psychological stress and reported that stress, coping styles, and loneliness had a negative impact on the antibody response (132). The effect of anxiety and psychological stress on vaccine response may be important in patients with impaired immunity, who are often chronically ill.

Despite optimal vaccination schedules, approximately 5 to 10% of healthy adults fail to make a high-level antibody response to HBV. A considerable body of evidence indicates that antibody responsiveness to HBV is under genetic control. A study in Taiwan demonstrated differences that appear to have a genetic basis between Han Chinese and people in aboriginal villages in immune response to HBV (129). Children of Han Chinese parents had significantly higher immune responses to HBV than did children of aboriginal parents, and those of mixed parentage had intermediate responses (129). Analysis of nonresponders to HBV has shown that genetic factors are important in determining the likelihood of mounting an antibody response after vaccination. In a small study of nonresponders among health care workers, there was a higher frequency of the HLA haplotypes DR7 and DR3 (66). Patients who are homozygotes for the HLA haplotypes B8-SC01-DR3 have been shown to mount lower responses to HBV in a small prospective study (5). In Japanese vaccinees who are nonresponders to HBV, other HLA haplotypes have been associated with suboptimal antibody responses (119). The response to HBV follows a dominant inheritance pattern in families (159). The mechanism by which nonresponders fail to make an antibody response is not well understood, but the defect does not appear to be an inability to present peptide in major histocompatibility complex class II molecules (71). Analysis of lymphocytes from nonresponders has shown depressed reactivity to pokeweed mitogen, which has been interpreted to suggest that the lack of response to HBV may reflect a larger number of suppressor T cells in these individuals (202). Many individuals who are nonresponders will respond to a second complete course of vaccination (179).

TABLE 3. Response rates of individuals with impaired immunity to hepatitis B vaccine

Group	Response rate[a] (%)	Reference(s)
Alcoholism	43–82	198
End-stage liver disease	44–54	270
End-stage kidney failure on hemodialysis	50–88	67, 70, 232, 247, 257
HIV infection	24–43	45, 63, 147
Children with cancer on chemotherapy	67	16
Adults with cancer on chemotherapy	73	280
Advanced age	46	69

[a]Percentage of patients who manifested on antibody response. This response does not neccessarily imply protection against infection.

The immune response to HBV is greatly dependent on the immune status of the host and on the presence of concurrent medical conditions. Table 3 lists HBV vaccine efficacy in a variety of patient groups. Many conditions that affect the immune system are associated with significantly reduced antibody responses to the HBV vaccine (Table 3). However, not all patients with impaired immunity manifest the same type of response to the HBV vaccine. Chronic hemodialysis patients given HBV vaccine have consistently shown high rates of seroconversion to multiple-dose vaccine schedules, and the antibody response in this population has been associated with protection against infection (67, 70, 257). HIV-infected individuals consistently show weaker responses to HBV vaccine (147). Furthermore, HIV infection may be associated with a loss of previously acquired antibody responses to HBV vaccine administration (37). Therefore, larger doses are recommended in immunosuppressed adults and those on dialysis (64). However, at this time, few data support this practice.

The HBV vaccine consists of purified viral protein expressed in yeast. This vaccine carries no risk for viral infection and can be safely used in immunocompromised patients.

INACTIVATED VACCINES

Toxoids

Toxoids are inactivated bacterial products that elicit strong immune responses. Two of the toxoids in current use, diphthe-

ria and tetanus, are inactivated toxins. The third toxoid is an inactivated preparation of *Bordetella pertussis*. The discovery by von Behring that inactivated diphtheria toxin could produce protective immunity against diphtheria provided the basis for modern immunology and for the development of effective vaccines from inactivated agents or their components (192). These toxoids are strong immunogens that have been used extensively since their development in the early 20th century. At present, the diphtheria-pertussis-tetanus (DPT) vaccine is universally recommended in all patient groups (50). However, an acellular preparation of the pertussis component (aP) was introduced in 1992 for booster vaccinations. As of December 1996, the acellular pertussis vaccine is also recommended for primary vaccination (64). However, this vaccine has not been extensively evaluated in patients with impaired immunity (64).

In HIV-infected individuals, antibody responses to tetanus toxoid have been decreased in comparison to control subjects (156, 157, 207). The magnitude of the IgG response to tetanus in HIV-infected patients correlates with the $CD4^+$ cell count (207). Although vaccination of HIV-infected individuals with tetanus toxoid has been reported to result in a transient increase in HIV-1 plasma viremia that did not correlate with $CD4^+$ cell counts (254), another group reported that booster vaccination had no effect on plasma viremia (79). The significance of this phenomenon and its potential impact on the long-term prognosis in HIV-infected individuals is unknown. However, some conjugate vaccines, including one of the *H. influenzae* type b conjugates that is administered to HIV-infected infants and children, use tetanus toxoid as their carrier protein (see below). Tetanus toxoid is generally considered safe, but the relationship between vaccination with this agent and immune system activation in HIV-infected individuals suggests a need for caution and further study.

Diphtheria and tetanus toxoid vaccines are immunogenic in BMT recipients when they are administered 12 and 24 months after transplantation (172). Increased antibody responses of vaccinated recipients have been demonstrated when the bone marrow donors were also vaccinated (284). Children with malignancies generally respond to DPT vaccination (8, 161). Toxoids are adequately immunogenic in a variety of patients with impaired immunity, and DTaP is recommended in all children according to the guidelines of routine childhood immunization.

Whole and Subunit Influenza Vaccines

Human influenza infection is caused by influenza A and B viruses, which are single-stranded RNA viruses. The pathogenicity of the viruses is linked to their capacity to undergo antigenic variation. Influenza A viruses regularly undergo two kinds of antigenic mutation, which occur only rarely in influenza B viruses. Antigenic variation occurs as the result of antigenic drift, which is due to point mutations in the hemagglutinin (HA), or antigenic shift, which leads to the emergence of a new HA subtype. These processes establish new, antigenically distinct viral strains, which are less well recognized by preexisting antibodies. The consequence of this phenomenon for the host is that existing antibodies are less effective. Also, the new strains can stimulate heterologous (to the original strain) rather than homotypic antibodies, a phenomenon that is referred to as "original antigenic sin" (41, 88). The human antibody response to both of the major influenza virus antigens, HA and neuraminidase (NA), is predominantly IgG1 and IgG3 (218).

Serum antibody protects against influenza virus infection and facilitates recovery after infection (155, 217). The role of cell-mediated immunity in host defense against influenza viruses remains unclear. In one animal model of influenza infection, transfer of immune spleen cells to a susceptible recipient did not provide protection in the absence of antibody (274), but others have demonstrated that cytotoxic T cells are necessary and sufficient for recovery from influenza in nude mice (34). Passive antibody administration can protect normal or immunosuppressed animals from influenza virus infections (34, 273, 274), but IgA antibodies may prevent only pneumonia, not tracheobronchitis (34). Despite the proven role of antibody immunity in animal models, influenza virus infection is generally thought to be confined to the respiratory tract and viremia is usually not demonstrated (149). Passive antibody has been cited as ineffective in altering disease pathogenesis (149), but strain-specific antibodies with known biological function have not been studied in this capacity. Serum antibody provides primarily strain-specific protection against influenza viruses, but heterologous antibodies can protect against variants of the same subtype (antigenic drift) (186). The presence of secretory as well as serum antibody is optimal for protection, but the evaluation of vaccine immunogenicity is generally based upon measurements of antibody in serum. The amount of antibody that is needed for protection is unknown, but hemagglutination inhibition titers of greater than 40 are associated with protection (149). Hemagglutination inhibition titers of less than 20 are associated with less protection, and the elderly may require titers of greater than 40 for protection (35).

Influenza has plagued humanity for at least 500 years. The scientific progress that led to the introduction of inactivated influenza vaccines in the 1940s included the first isolation of the virus from humans in the 1930s and the cultivation of the virus in embryonated hen eggs in 1940 (35). These developments, in combination with the discovery of hemagglutination, provided the scientific and serologic basis for the production of influenza vaccines. The influenza vaccines currently manufactured in the United States are trivalent, consisting of two currently circulating influenza A subtypes and one influenza B strain. Viral preparations are inactivated with formalin, and split-virus preparations are then prepared by ether or detergent disruption. The vaccines are contaminated with egg products, and influenza vaccine is contraindicated in those with egg hypersensitivity. The major target groups for influenza vaccination are adults or children with underlying pulmonary or cardiac disease, nursing home residents, health care personnel, and other high-risk patients. Influenza vaccines must be administered yearly so that antibody responses can be elicited by preparations that contain prevalent subtypes. The problem of determining the long-term duration of vaccine-elicited protection in immunosuppressed individuals is not an issue for the presently available inactivated influenza vaccines, but antibody levels must be maintained throughout the influenza season to afford protection. Table 4 lists the response rates of various groups with impaired immunity to influenza vaccines.

The importance of influenza vaccination for patients with cancer may exceed that of other vaccines which prevent less common infections, because of the worldwide prevalence of influenza. Viral infections are associated with increased morbidity and mortality in patients with cancer (75), which makes this group a major target for influenza vaccination. Studies of influenza vaccination of patients with different cancers have generally reported decreased antibody responses in comparison to normal controls (81, 94, 113, 115, 173, 209, 240). The administration of whole bivalent influenza vaccine to patients with solid tumors and lymphoreticular neoplasms either at the time of administration of chemotherapy or at the nadir of blood counts resulted in a 71% seroconversion rate, in contrast

TABLE 4. Response rates of individuals with impaired immunity to influenza vaccination

Group	Response rate[a] (%)	Reference(s)
Renal disease: chronic renal failure	66	92, 123
Renal disease: hemodialysis	25–100	36, 92, 123, 271
Renal disease: transplant	18–93	92, 112, 160, 258, 272
SLE	Normal, decreased if on immunosuppression	42, 122, 177, 222, 283
Cancer	24–71	81, 94, 113, 115, 173, 240
BMT	18–60	183
HIV infection	15–80	54, 130, 131, 133, 156, 199

[a] Percentage of patients who manifested an antibody response. This response does not necessarily imply protection against infection.

to a 94% rate in normal controls (209). Those who were vaccinated at the time of chemotherapy had lower antibody titers, lower responses to antigens in the absence of preexisting immunity, and a fourfold increase in antibody titer 50% of the time (209). Those who were vaccinated at the nadir of their blood counts had equal antibody responses regardless of preexisting immunity, higher postvaccination antibody titers, and a 93% response rate (209). The poor response rates during antineoplastic therapy have been documented in a large number of patients (115). Additional factors that have been implicated in poor antibody responses to influenza vaccine in some groups are low initial antibody levels in patients with hematologic cancers (81, 113, 209), and low IgG levels in serum in patients with chronic lymphocytic leukemia (113). A major review of the studies that evaluated influenza vaccination in patients with cancer concluded that the overall response rate was 24 to 71% and that antineoplastic therapy was a major determinant of decreased antibody responses (115). The response of patients with solid tumors to influenza vaccine has been reported to be greater than the response of those with hematologic cancers (259). The antibody response of adults with lymphoma who were vaccinated during chemotherapy increased from 42 to 71% after a second dose of influenza vaccine (173). A similar booster regimen increased antibody responses in the elderly (38). Booster vaccinations are rational because the initial antibody responses can decline by 60 days after immunization (113).

Influenza vaccination of renal transplant recipients is safe (112, 123). The proportion of renal transplant patients who manifested a fourfold increase in antibody titer for each of three influenza antigens was 42, 58, and 48% 1 month after vaccination and 88, 100, and 93% 2 months after vaccination (112). Pediatric renal transplant recipients responded to the 1993 to 1994 trivalent influenza vaccine similarly to normal controls (92). However, decreased response rates were reported for transplant recipients in the 1970s (160, 258). Poor antibody responses in patients on cyclosporine therapy did not increase with booster vaccination (272), suggesting that immunosuppressive therapy itself can impair antibody responses to influenza vaccine irrespective of the underlying process (see above). An uncontrolled study of influenza vaccine safety in cardiac transplant recipients reported that there were no episodes of graft rejection and that 33 and 67% of the vaccinees responded with a twofold increase in titer to the influenza B and A antigens, respectively (151).

Administration of influenza vaccine to dialysis patients results in lower antibody levels than in normal individuals (123). Differences have been demonstrated in the production of antibodies against the individual components of a trivalent vaccine preparation, which resulted in protection against only one of three antigens (36). In this study, response rates to two of the antigens were only 25 and 27% and a significant booster effect was not observed upon administration of a second dose of vaccine. This phenomenon was interpreted to indicate a defect in primary rather than secondary immunity in the population of hemodialysis patients who were studied. However, others have suggested a role for booster vaccination in hemodialysis patients who manifest poor antibody responses (271). A cohort of 10 pediatric hemodialysis patients had response rates to the influenza A and B antigens that were similar to those of control subjects (92). In this study, the patients with chronic renal failure had lower antibody responses against influenza A antigens, but the differences were not statistically different.

Influenza vaccination of patients with systemic lupus erythematosus (SLE) has resulted in normal (42, 122) and impaired (222, 283) antibody responses. Decreased antibody responses to some influenza A virus antigens among subjects with SLE have correlated with corticosteroid administration (122), which suggests that administration of immunosuppressive therapy to patients with SLE can impair normal antibody responses to influenza virus antigens. Influenza vaccination of patients with stable SLE has not been associated with the precipitation of accelerated disease (42, 177, 222, 283).

Individuals who are infected with HIV, particularly children who have a high incidence of underlying cardiac and respiratory dysfunction, are at risk for the complications of viral respiratory infections. Influenza vaccination has been recommended in HIV-infected patients, but there has been concern about immune system activation of HIV-infected $CD4^+$ cells by influenza vaccine. Several groups have reported increases in plasma viremia that follow the kinetics of the antibody response in influenza vaccine-vaccinated HIV-infected individuals (204, 255). Following influenza vaccination with a trivalent split-virus preparation, threefold or greater increases in plasma viremia were documented in 90% of HIV-infected individuals with more than 500 $CD4^+$ cells (255). Although 30 to 90% of all subjects in this study manifested threefold or greater increases in plasma viremia following vaccination, only those with more than 500 $CD4^+$ cells had a return to baseline viremia after 4 weeks. These individuals also had the greatest serologic response to vaccination, although the overall responses of the HIV-infected individuals in the study were lower than those of normal controls (255). Increases in HIV-1 plasma viremia following tetanus toxoid booster and pneumococcal polysaccharide administration have been reported by some (137, 254), but not others (79, 158). The effect of this phenomenon on disease progression and whether it is inhibited by antiretroviral therapy is unknown.

HIV-infected men who were vaccinated with influenza vaccine had a response rate of 73% to at least one influenza antigen, whereas the response rate of normal subjects was 93% (131). Protective titers of 40 or greater to all of the antigens postvaccination were manifested by fewer of the HIV-infected persons than by the normal subjects, but the difference was not statistically significant (131). The antibody response did not correlate with the $CD4^+$ count in the HIV-infected subjects in this study, but others have shown an association between the $CD4^+$ count and antibody responses to influenza vaccination (54, 156). Antibody titers to each antigen in a tetravalent split-virus vaccine were markedly decreased in HIV-infected subjects; those with fewer than 100 $CD4^+$ cells did not respond,

but those with higher $CD4^+$ cell counts did manifest antibody responses (156). Furthermore, a booster dose did not increase antibody titers in this study (156). In HIV-infected children, antibody responses to a standard trivalent vaccine were correlated with $CD4^+$ cell counts (54). Pre- and postimmunization titers were lower for the HIV-infected children than for the controls, but protective responses were observed for both influenza A virus strains, although children older than 9 years did not respond to H3N2 antigens (54). Higher antibody responses were observed in vaccine-naive children who received a two-dose regimen, suggesting that booster doses can increase the influenza virus antibody titers of these children (54). Immunization of HIV-infected children with a split-virus preparation resulted in a fourfold increase in antibody titers in 18.9% to A/Texas, in 26.4% to A/Shangdong, and in 26.4% to B/Panama (133). Immunization did not result in plasma viremia, but a low prevaccination $CD4^+/CD8^+$ ratio was associated with decreased antibody responses (133). Taking into consideration the impaired antibody responses of HIV-infected individuals to influenza vaccination and the possibility that vaccine-elicited immune activation will activate HIV-infected $CD4^+$ cells and increase viral production, caution should be exercised regarding influenza vaccination in this population. Some have suggested that amantadine prophylaxis rather than vaccination should be considered (255), and others have recommended vaccination of close contacts to decrease the risk of influenza infection in HIV-infected people. However, it should be noted that the impact of potent antiretroviral therapy upon vaccine-elicited enhancement of viral load and the long term consequences of this phenomenon are presently unknown.

POLYSACCHARIDE VACCINES

Overview

Several polysaccharide vaccines are available for the prevention of infections by encapsulated pathogens. The development and improvement of the existing capsular polysaccharide vaccines have paralleled our understanding of human antibody responses to T-independent antigens. T-independent antigens are categorized as type 1 or type 2 (191). The bacterium *Brucella abortus* and lipopolysaccharide are type 1 antigens; they stimulate B cells in the complete absence of T cells (191). Capsular polysaccharides of microorganisms are type 2 antigens; they can stimulate B cells without T-helper cells, although T cells do amplify and/or suppress host immune responses to these antigens (23, 191). In adult humans, T-cell-independent type 2 antibody responses are restricted largely to the IgG2 subclass and perhaps to specific idiotypes (2, 3, 215, 216, 246). T-cell-independent antigens do not elicit memory B cells, and T-cell-independent antibody responses cannot be boosted to produce secondary responses (191), although antibody responses may be long-lived (120). Neonatal B-cell unresponsiveness to bacterial polysaccharides is well known (114), but adults with normal immunologic function develop protective anti-polysaccharide antibodies to both natural infection with capsular pathogens and vaccination with bacterial polysaccharides.

Encapsulated microorganisms are surrounded by antiphagocytic polysaccharide capsules, which are key virulence factors. Infants, young children, the elderly, and those with impaired B-cell function are at increased risk for infections with encapsulated bacterial pathogens. For infants, this is the result of a normal physiologic delay in the capacity of the human immune system to respond to bacterial polysaccharides (114). Neonates become susceptible to infection when transplacentally acquired maternal immunity wanes 3 to 6 months after birth (225). Susceptibility persists throughout early childhood until the development of naturally occurring immunity. The latter is derived from antibodies against cross-reactive, commensal, and colonizing organisms (225) and from maturation of the immunoglobulin repertoire. A report in the 1980s that patients who manifest decreased levels of IgG2 antibodies had poor antibody responses to polysaccharide vaccines (252) suggested that IgG2 is needed for protection against encapsulated pathogens. Patients with deficient antibody-mediated immunity due to primary immunodeficiencies or chemotherapy-induced defects have markedly increased susceptibility to encapsulated pathogens and poor antibody responses to immunization with bacterial polysaccharides. In addition, patients who manifest impaired complement-mediated opsonization can be highly susceptible to capsular pathogens (123).

One approach to increasing the immunogenicity of bacterial polysaccharides has been to conjugate the polysaccharide antigen(s) to immunogenic proteins such as diphtheria-tetanus toxoid and the outer membrane protein of *Neisseria meningitidis* (31). Such polysaccharide-protein antigens elicit T-cell-dependent antibody responses that are characterized by their ability to elicit secondary responses and the generation of memory B cells. The primary advantage of conjugate vaccines is that they can confer immunity to infants and young children, who are unable to respond adequately to purified bacterial polysaccharide vaccines. Vaccination with bacterial polysaccharide-protein conjugates has successfully prevented *H. influenzae* type b disease in children younger than 2 years (224). A variety of other conjugate vaccines are under development, and pneumococcal polysaccharide conjugate vaccines have begun to be tested in various populations including the elderly and those with impaired immunity.

The licensed polysaccharide vaccines that have been administered to immunocompromised individuals are (i) polyvalent pneumococcal polysaccharide vaccines for the prevention of infections with *S. pneumoniae* (Pnuimmune and Pneumovax), (ii) polyribitol phosphate conjugates for the prevention of *H. influenzae* type b infections (HibTITER, ProHIBiT, ActHIB), and (iii) tetravalent meningococcal polysaccharide vaccines for the prevention of infections with *N. meningitidis* (Connaught Laboratories, Stillwater, Pa., serogroups A, C, Y, and W135). A safe and immunogenic *S. typhi* O-antigen polysaccharide vaccine has undergone successful testing in field trials (276) and is now licensed. *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* capsular polysaccharide conjugate vaccines have been developed, and a few have also been evaluated in clinical trials.

The evaluation of responses to bacterial polysaccharide vaccines in immunosuppressed hosts is generally based upon measurement of pre- and postvaccination antibody levels and comparison of the levels obtained to those in normal vaccinated individuals. "Minimal protective levels" of antibody have been defined as 2,000 ng/ml for meningococcus A and C (213), 300 ng of antibody nitrogen/ml for pneumococcus (163), and 150 ng/ml (223) (or 1 μg/ml for "long-term" protection) for *H. influenzae* (146). Historically, these levels have been accepted as serologic standards to assess the immunogenicity of polysaccharide vaccines. However, the assay for pneumococcal antibodies noted above was contaminated with cell wall polysaccharide (CWPS); therefore, it did not discriminate between protective polysaccharide-specific antibodies and nonprotective cell wall polysaccharide-specific antibodies. There are no data that correlate serologically documented immunogenicity with vaccine efficacy in immunosuppressed individuals or that

TABLE 5. Response rates of individuals with impaired immunity to PRP polysaccharide conjugate and purified pneumococcal polysaccharide vaccine[a]

Vaccine	Group	Response rate[b]	Comments[c]	References
Hib conjugates[d]	Sickle cell anemia	74–100	Response increases with age	104, 105, 144, 238
	Asplenia	100	Postsplenectomy response is normal before antineoplastic therapy	8, 123
	Hodgkin's disease	50–99	Response is almost normal before therapy	8, 144, 188
	BMT	55–97	Timing of immunization posttransplant is determinant of response	28, 116, 188, 189
	Cancer	50–86	Leukemia and solid tumors; some studies show correlation of antineoplastic therapy and poor responses	83, 106, 165, 221, 278
	HIV infection	33–97	Not all responses correlate with CD4 count; symptomatic children had very poor responses, and recent seroconverters responded like controls	214, 256, 279
Polyvalent pneumococcal polysaccharide vaccines	Sickle cell anemia	10–70	Age dependence: <2 years do not respond, serotype-specific antibodies exceeded protective levels for under 20% of subjects for 4–10 serotypes	142, 219, 238
	Asplenia	Normal-reduced	Antibody response is decreased after antineoplastic therapy; antibody titers are 70% of postimmunization 2 years postsplenectomy	12, 76, 102, 163, 251
	Renal disease	43–90	Renal failure: poorest responses; transplant recipients: good responses; hemodialysis patients: excellent responses (similar to normal subjects); children with nephrosis: poor if steroid unresponsive, excellent if steroid responsive; splenectomized: 50–80%	18, 65, 102, 169
	Hodgkin's disease	Normal-reduced	Response is decreased after therapy and can correlate with IgG2 levels; maximal responses can be significantly lower than in normal subjects	8, 12, 55, 251, 252
	Myeloma	33–59	Fold increases in antibody reported rather than specific levels	166, 242
	BMT	Reduced-poor	Better responses 12 months posttransplantation; low serotype-specific IgG2; response to 23-valent vaccine greater than response to 7-valent conjugate; infection in 5/39 (116)	103, 116, 176, 286
	HIV infection	Reduced-poor	17% had no response, 83% had titers greater than preimmune titers; methods to evaluate response vary and are not comparable	Normal: 130, 156; decreased: 4, 101, 181, 207, 227, 228, 268, 269

[a] The meningococcal polysaccharide vaccine is not included in this table because meningococcal disease in the United States is caused predominantly by serotype B (14), and this serotype is not included in available meningococcal vaccines.

[b] Response rate is defined as the proportion (shown as a percentage) of individuals who attained levels of antibody that have been defined as protective: 1 μg/ml of anti-Hib antibody and 300 ng nitrogen antibody/ml of antipneumococcal antibody (146, 163, 213). In the instances when multiple studies did not present data in this fashion, immunogenicity is reported in qualitative terms. The efficacy of polysaccharide vaccines in immunocompromised individuals in terms of disease prevention has not been documented. The reader should bear in mind that the magnitude of the antibody response of nearly all immunocompromised hosts after polyvalent pneumococcal vaccination is smaller than that of normal controls, although the antibody level attained might exceed the amount thought to be necessary for protection.

[c] The data summarized in this column refer to immediate postimmunization antibody levels. Few studies in immunocompromised hosts have evaluated long-term immunity, especially for the Hib conjugates.

[d] Many of the studies summarized in this table used different conjugates.

can confirm that hosts with impaired immunity require the same levels of protective antibody as normal subjects.

Principles of Vaccination of Impaired Hosts

Mechanisms of antibody-mediated protection against encapsulated pathogens include nonspecific immune mechanisms, such as complement activation by capsular polysaccharides, and specific mechanisms, such as antibody-dependent opsonization, phagocytosis and killing of opsonized organisms by effector cells, and cell-mediated mechanisms. Immunosuppressed patients with asplenia and a variety of primary and chemotherapy-induced defects in humoral immunity have a markedly increased risk of infection with encapsulated bacteria, although for most individuals an increased susceptibility to encapsulated bacteria is associated with impaired antibody responses to capsular polysaccharides. Indications for the administration of polysaccharide and polysaccharide-protein conjugate vaccines differ, and they are not all recommended in all individuals. A major problem that is associated with the vaccination of hosts with impaired immunity against encapsulated pathogens is that the mechanisms which prevent the development of natural immunity also prevent the development of vaccine-elicited immunity. The duration of protection following polysaccharide vaccination is unknown. Therefore, revaccination of immunosuppressed hosts is recommended at 2- to 6-year intervals after the primary vaccination (8, 50). Table 5 lists the response rates of various groups with impaired immunity to commonly used polysaccharide and conjugate vaccines.

Meningococcal Vaccines

Classic studies by Goldschneider et al. demonstrated that serotype-specific antibodies acquired during the carrier state with *Neisseria meningitidis* could protect against infection (109). Natural antibodies against meningococci are acquired from nasopharyngeal carriage of meningococcal organisms and exposure to cross-reactive antigens (225). Purified meningococcal polysaccharides of groups A, C, Y, and W135 are licensed for the prevention of epidemic meningococcal menin-

gitis. The vaccine is used primarily in populations at high risk for meningococcal infections, such as military recruits. The incidence of serotype A and C meningococcal infections has been drastically reduced since 1971, when routine vaccination of recruits with a bivalent serotype AC meningococcal polysaccharide vaccine began. At present, the primary serotype of sporadic meningococcal disease in the United States is serotype B, which is not among the serotypes included in the tetravalent vaccine (168). Age is a major determinant of meningococcal vaccine immunogenicity. The antibody responses of 2-year-old children are 10% of those of adult vaccinees (168). The meningococcal polysaccharide vaccines elicit protective antibody responses in more than 90% of vaccinated immunocompetent individuals who are older than 2 years. Candidate meningococcal polysaccharide conjugate vaccines have not yet been tested in immunocompromised patients.

Asplenic patients are at high risk for developing overwhelming infections with encapsulated bacteria including *N. meningitidis*. For individuals splenectomized because of trauma or with nonlymphoid tumors, vaccination with the bivalent group A and C meningococcal polysaccharide vaccine resulted in seroconversion rates similar to these in normal controls (233). Splenectomized subjects who had prior chemotherapy and/or radiotherapy had poor seroconversion rates, and the IgM responses were poor among patients with lymphoid tumors: IgM seroconversion was one of eight patients for group C and zero of eight patients for group A (233). The specific role of IgM in protection against meningococcal infections is unknown, although it may serve as an opsonin (43). Antimeningococcal IgM may be generated in the spleen, and in splenectomized patients with lymphoid tumors the antibody levels of all isotypes to group A were significantly lower than in normal controls 1 year after vaccination, whereas in those with nonlymphoid tumors, only IgG antibody levels were lower (233).

Hodgkin's disease patients treated with radiation, chemotherapy, or bimodal therapy and asplenic controls manifested decreases in their preimmune anti-group A antibodies, poor antibody responses to group C meningococcal polysaccharide vaccine, and significant declines in the numbers of vaccine-elicited antibodies (251). The rate of antimeningococcal antibody decline in asplenic subjects was slightly lower than that in controls, but subjects with Hodgkin's disease had marked declines after completion of either chemotherapy or bimodal therapy with radiation (251). After therapy, Hodgkin's disease patients did not manifest spontaneous recovery of antibodies, nor did they mount antibody responses to booster vaccination, although normal individuals may also fail to respond to booster polysaccharide vaccination (13). In view of their increased risk of infection, it is recommended that Hodgkin's disease patients receive the tetravalent meningococcal vaccine before the beginning of therapy (50, 251). The timing of vaccine administration is critical, and vaccination should take place at least 7 days before therapy is begun. For patients who had not received chemotherapy or radiotherapy, the timing of splenectomy had no effect on meningococcal vaccine responses (253). Revaccination at 3- to 5-year intervals after the completion of therapy for Hodgkin's disease and then every 6 years is recommended (8).

There is little published experience with meningococcal polysaccharide vaccines in other immunocompromised patient groups. The response rate of 15 recent HIV seroconverters (mean $CD4^+$ cell count, 523) to meningococcus group C polysaccharide vaccine was only 71%, compared to 100% in normal controls, although those who manifested fourfold increases in titer postvaccination had bactericidal activity equivalent to those of the controls (279). The tetravalent vaccine may be considered in BMT recipients at both 12 and 24 months after either allogenic or autologous transplantation and in patients with leukemia (8). Routine immunization with the tetravalent vaccine is also recommended for patients with terminal complement deficiencies and asplenia (50, 123). Vaccine efficacy has not been evaluated in any of the aforementioned patient groups.

H. influenzae Type b Vaccines

In 1933, Fothergill and Wright established that the age-related risk of *H. influenzae* meningitis resulted from an absence of serum bactericidal antibodies (87). It then took many decades to establish that the protective efficacy of bactericidal serum was attributable to antibodies that bind the type b polyribosyl-ribitol-phosphate (PRP) capsular polysaccharide determinant of type b *H. influenzae* (Hib) (243). The recognition that PRP was poorly immunogenic in young children and infants led to the concept of PRP-protein conjugate vaccines. The landmark work of Goebel and Avery with bacterial conjugates early in the 20th century (108) provided the scientific underpinnings for the development of PRP conjugates. These vaccines elicit T-dependent antibody responses and are immunogenic in infants as young as 2 months of age (62, 224). The first PRP conjugate, PRP-D (PRP conjugated to diphtheria toxoid), was licensed in December 1987. In the decade since its introduction, this and other PRP conjugates have steadily eliminated Hib infections from the pediatric population (27, 224). This constitutes proof that in addition to being immunogenic, the vaccines elicit protective antibodies that prevent infection. Available PRP conjugates include PRP-OMPC, for which the protein determinant is the outer membrane protein of *N. meningitidis* (PedvaxHIB; Merck Sharp and Dohme); PRP-T, for which the protein determinant is tetanus toxoid (ActHIB; Pasteur Merieux); and HbOC, for which a short oligosaccharide of PRP is conjugated to a nontoxic derivative of diphtheria toxin (HibTITER; Praxis Biologics). An earlier generation PRP-diphtheria toxoid conjugate was used in some of the studies reviewed below (ProHIBIT; Connaught Laboratories). HbOC and PRP-T elicit antibodies with higher avidity than does PRP-OMPC (241), but the impact of antibody avidity differences on antibody function is unknown.

Children with sickle cell disease have impaired splenic function, which has been hypothesized to contribute to their increased susceptibility to encapsulated pathogens including Hib. PRP-TT conjugate vaccination was as immunogenic in a group of children with sickle cell anemia as it was in normal children of similar ages (144). Since conjugate vaccines are T-dependent antigens, they should elicit antibody responses that are longer lived than polysaccharide-elicited antibodies. Seven months after vaccination, children with sickle cell disease who were vaccinated with a HIB-TT conjugate manifested antibody levels that were 40-fold greater than their preimmune antibody levels (238). Different PRP conjugates have different immunogenicities in infants (111, 241). A single injection of a Hb-OC conjugate (HibTITER) was more immunogenic that a PRP-D conjugate (ProHIBiT) in children with sickle cell disease: children who received HibTITER had a geometric mean PRP antibody level of 51.4 μg/ml 6 months after vaccination, and those who received ProHIBiT had 2.29 μg/ml (235), although both levels exceeded the protective level of antibody for long-term protection (146). Persistence of Hib antibody in children with sickle cell disease who were 2 to 6 months of age at the time of vaccination required three doses of a Hb-OC conjugate (105), whereas two doses of a PRP-D conjugate were needed in children who were 3 to 17 months of age (178).

PRP-protein conjugates are immunogenic in children with sickle cell disease, but children with anatomic or functional asplenia may require higher levels of Hib antibody in serum for protection against encapsulated *H. influenzae* infections (234). The necessity for revaccination of asplenic children will have to be critically evaluated as those who were vaccinated in infancy and early childhood reach young adulthood.

Vaccination with a PRP conjugate vaccine is recommended for asplenic patients (50). Antibody responses to the PRP-D conjugate vaccine (ProHIBIT) were evaluated in 13 children who underwent splenectomy (7 for Hodgkin's disease, 2 for hereditary spherocytosis, and 4 for idiopathic thrombocytopenia) (7). These children responded with higher mean anti-Hib antibody concentrations than did healthy control children who received a purified polysaccharide vaccine instead of the conjugate. The antibody response of asplenic controls and subjects with Hodgkin's disease to purified PRP was equivalent to healthy controls 3 to 4 weeks after vaccination, although the patients with Hodgkin's disease had markedly decreased responses after the completion of lymphocytic therapy (83). The timing of vaccine administration should take into account the fact that polysaccharide vaccine antibody responses of patients with lymphoid cancers are markedly decreased after the initiation of antineoplastic therapy but nearly normal before therapy. In patients with Hodgkin's disease or leukemia, posttreatment vaccination with either purified polysaccharide (PRP) or a conjugate vaccine (ProHIBiT) resulted in markedly decreased anti-Hib antibody levels (83, 251). One dose of HibTITER was immunogenic in adults who had completed therapy for Hodgkin's disease at least 2 years prior to vaccination (188). It has been suggested that levels of anti-Hib antibodies should be used to determine the necessity for revaccination of children undergoing splenectomy who have received prior Hib vaccination (7).

The postvaccination Hib antibody titers in 80 to 100% of children with leukemia and solid tumors have exceeded the levels thought to confer protection (165, 221, 278). However, the antibody levels in children with cancer are lower than those in normal children (83, 165, 278), and one study found protective antibody levels in only 50% of children with leukemia after 6 months (165). Children older than 2 years with acute lymphoblastic leukemia who were treated with chemotherapy for less than 12 months responded like normal controls, but only 18% who received more than 12 months of treatment responded to Hib conjugate vaccine (83). The latter children had mean antibody concentrations that were one-half to one-third lower than those in normal children, which declined significantly after 12 months (83). The geometric mean antibody titer in children with cancer on maintenance therapy (13 of 18 had leukemia) who were vaccinated with PRP-T was 1.4 μg/ml, but only 50% had antibody levels greater than 1 μg/ml 1 to 2 months postimmunization (144). Older children (mean age, 7.3 years) with acute lymphoblastic leukemia who were vaccinated with a HbOC conjugate that was administered 28 days after diphtheria-tetanus toxoid vaccination had an 84% response rate (221), and the antibody responses were inversely correlated with the intensity, but not the duration, of the chemotherapeutic regimen. The success of this vaccination protocol supports the concept of carrier priming to achieve higher polysaccharide-conjugate antibody responses.

An increased risk of infection with encapsulated pathogens occurs in adult BMT recipients during the late posttransplantation period (8). These infections are the result of waning natural immunity and impaired de novo antibody responses. The most significant correlate of decreased antibody responses in BMT recipients appears to be T-cell depletion. Neither intravenous immunoglobulin therapy nor graft-versus-host disease has been consistently shown to have an effect on Hib conjugate-induced antibody responses (116, 189). Vaccination with a Hib conjugate vaccine has been suggested at 12 and 24 months after either autologous or allogeneic transplantation (8). Vaccination of 35 BMT recipients with Hb-OC (HibTITER) resulted in a protective level of antibody (above 1.0 μg/ml) in 56% of the subjects immunized 24 months posttransplantation, but 80% of those who were immunized at both 12 and 24 months attained significantly higher levels of antibody (116). In comparison to controls, all vaccinees had significantly lower IgG2 concentrations in serum (the IgG subclasses of anti-Hib antibodies were not reported) and the magnitude of their anti-Hib antibody responses was markedly lower (116). Although their antibody responses were decreased compared to normal subjects, 85% of allogeneic BMT recipients responded to two doses of a PRP-T (HIB-T; Pasteur Merieux) conjugate with antibody levels greater than 1 μg/ml (28). Donor and recipient vaccination with Hb-OC before allogeneic BMT followed by recipient vaccination 3, 6, 12, and 24 months after transplantation resulted in higher anti-Hib antibody levels in donor-immunized versus donor-unimmunized recipients (189). This supports other studies suggesting that donor immunization primes recipients for early antibody responses to protein-polysaccharide conjugates (285), and may explain why others failed to demonstrate an effect of donor vaccination when recipients were vaccinated 1 year after transplantation (176). It has been suggested that donor immunization with T-independent purified polysaccharide antigens does not prime the recipient to respond to polysaccharide vaccination (176, 189).

An increased risk of Hib infections has been reported in HIV-seropositive individuals (48). The susceptibility of HIV-infected individuals to encapsulated pathogens has been attributed to HIV-induced B-cell defects (11, 134, 164). In comparison to HIV-uninfected individuals, the immunogenicity of both Hib and Hib conjugates is decreased in HIV-infected individuals (140, 214, 256). However, recent seroconverters who were infected for a mean of 7.4 months had normal responses to Hb-OC (HibTITER) vaccination compared to HIV-uninfected controls (279). The immunogenicity of Hb-OC (HibTITER) correlates with $CD4^+$ T-cell counts in HIV-infected adults (256) and infants (140). HIV-infected infants who achieved anti-Hib antibody levels of greater than 1.0 μg/ml had mean $CD4^+$ T-cell counts of 2,842 cells/mm^3 before the third dose of Hb-OC, whereas those who failed to produce this amount of antibody had mean $CD4^+$ T-cell counts of 1,655 cells/mm^3 (140). In HIV-seropositive children older than 15 to 18 months old, PRP-TT conjugate (ActHIB) vaccination produced Hib antibody levels that were significantly lower than those in seronegative children, but the antibody levels did not correlate with the $CD4^+$ T-cell counts (101). Only 7 of 19 children older than 15 months who received one dose of either ProHIBiT or HibTITER manifested Hib antibody concentrations higher than 0.15 μg/ml 22 to 65 months after vaccination, and the antibody levels did not correlate with the $CD4^+$ T-cell count (214). Explanations for the differences in adult and infant responses to different PRP conjugates and the relationship between the immunogenicity of a given agent and the $CD4^+$ T-cell count are likely to be multifactorial. In patients with AIDS, in comparison to seropositive patients without AIDS, the immunogenicity of unconjugated PRP was independent of the $CD4^+$ T-cell count and greater than that of the Hb-OC conjugate (256). Similarly, the immunogenicity of a purified polyvalent pneumococcal polysaccharide vaccine was greater than that of a pneumococcal polysaccharide-protein conjugate

vaccine in individuals with decreased preimmune serotype-specific antibodies (4, 188) (see below).

Polyvalent Pneumococcal Polysaccharide Vaccines

The history of the development of pneumococcal polysaccharide vaccines has paralleled the thinking in the field of infectious diseases in the 20th century. After the first isolation of *S. pneumoniae* at the end of the 19th century, the etiologic role of the organism in the pathogenesis of pneumonia was rapidly recognized. The scientific focus of the first half of the 20th century was largely on the biology of the pneumococcus. Pioneering studies of pneumococcal transformation ultimately gave birth to the modern scientific disciplines of molecular biology and microbiology and immunology and the clinical discipline of infectious diseases (21, 195). Although the protective effect of antiserum was first demonstrated before the turn of the century (21, 49), the inaugural hexavalent pneumococcal vaccine was soon withdrawn after its introduction in 1946, despite the success of clinical trials with the vaccine (21). The introduction of penicillin diminished interest in pneumococcal vaccination, and nearly two decades passed before the need for pneumococcal vaccines was accepted and led to a new initiative to develop pneumococcal polysaccharide vaccines in the late 1960s (22, 80). As we approach the 21st century, we are again faced with a crisis in therapy of pneumococcal infections because of the rise of antibiotic resistance of *S. pneumoniae* (229, 245, 275) and the emergence of hosts with impaired immunity.

There are two 23-valent pneumococcal polysaccharide vaccines licensed for use in the United States, Pneumovax (Merck, Sharp and Dohme) and Pnu-Immune (Lederle Laboratories). The 23-valent preparations, which were licensed in 1983, were preceded by 14-valent preparations first licensed in 1977 (80). Two large reviews of pneumococcal vaccine efficacy in the 1990s reported that efficacy in immunocompetent individuals who had an indication for vaccination was 61 to 75% (46, 249) but that efficacy was either not demonstrated (46) or 21% responded (249) in those with severe immunosuppression. Efficacy in the elderly did not decline over 9 years (46).

The most important immune correlate of protection against infections with *S. pneumoniae* is the presence of opsonic anticapsular antibodies (80, 85, 225, 226). Therefore, the goal of pneumococcal polysaccharide vaccination is to elicit anti-capsular antibodies. Adult IgG to pneumococcal capsular polysaccharides is restricted largely to IgG2, including opsonic antibodies (90, 152, 175, 215, 237, 294). As a risk factor for infection with encapsulated organisms, the role of IgG2 deficiency remains controversial. However, the increased susceptibility of numerous patient groups with decreased IgG2 levels to pneumococcal disease lends support to the hypothesis that pneumococcal polysaccharide IgG2 is protective (90, 252). Infants and young children (84), HIV-seropositive individuals (20, 230), and BMT recipients (116, 176), have reduced levels of IgG2. Individuals who express the G2m(n) IgG2 subclass allotype have been reported to have greater antibody responses to some purified capsular polysaccharides (9, 248) but not to polysaccharide conjugates (110).

The evaluation of pneumococcal vaccine efficacy has been fraught with controversy. First, the vaccine is indicated in individuals at high risk for infection. Second, it is difficult to compare the results of many studies, because the methods used to determine immunogenicity often measure different parameters. The radioimmunoassay that was used to evaluate the 8-valent and 14-valent and some of the 23-valent vaccines was contaminated by CWPS and did not identify individual immunoglobulin isotypes. The determination that 300 ng of antibody nitrogen/ml was associated with protection against *S. pneumoniae* was based upon radioimmunoassay measurements of antibody (80, 163). More recent studies have used ELISA techniques for the measurement of antibody levels (80, 197). One advantage of antigen-based ELISAs is that they permit identification of the isotype of specific antibodies. This has led to an understanding that decreased levels of serotype-specific IgG2 are often found in patients with poor responses to pneumococcal vaccines (141, 175, 176). Preabsorption of sera with CWPS has revealed that before the use of this procedure, anti-CWPS antibodies were often measured, which produced erroneous serotype-specific antibody determinations (196, 197). The assessment of vaccine efficacy has been investigated by determinations of serum opsonic activity. Some studies have shown an association between vaccine-elicited antibody levels and enhancement of opsonic activity against several serotypes, including serotypes 7, 6A, 14, 19F, and 23 (39, 60, 61, 175).

Historically, individuals with anatomic and functional asplenia were among the first target groups for pneumococcal vaccination. Splenectomized children and adults without underlying cancer manifest antibody responses similar to those of normal controls (80). The immunogenicity of pneumococcal vaccination in children with sickle cell disease was evaluated extensively in the 1980s (29, 30, 60, 61, 139, 211, 219, 287, 288). The success of pneumococcal vaccination in this population has been assessed by measurements of serotype-specific antibody concentrations and serum opsonic activity and by attempts to discern vaccine efficacy based on predicted rates of pneumococcal infection (287). An early study indicated that 2 years after immunization, an octavalent pneumococcal polysaccharide vaccine protected a cohort of 77 individuals with sickle cell disease ranging in age from 2 to 25 years (10). No infections occurred in the immunized individuals, whereas eight infections with *S. pneumoniae* occurred in 106 unimmunized controls with sickle cell disease (10). Postvaccination serum opsonization of *S. pneumoniae* was increased in children with sickle cell disease who were older than 2 years (61). In this study, the children with sickle cell disease had serum opsonic activity equivalent to those in normal (adult) controls, although they manifested significantly lower serotype-specific antibody concentrations (61). This and other studies (60) suggest that opsonic defects in sickle cell disease can be overcome with type-specific antibodies.

Pneumococcal vaccine-elicited protection is mediated by serotype-specific antibodies (210, 287). Postvaccination antibody levels are influenced by preimmunization antibody levels (211). Preimmune serotype-specific antibody concentrations are significantly lower in children with sickle cell disease who are younger than 2 years, and these children manifest lower pre- and postvaccination antibody levels and serum opsonic activity (61, 210), although polyvalent pneumococcal polysaccharide vaccines are poorly immunogenic in all children younger than 2 years (61, 287). Serospecific vaccine failures have been reported with poorly immunogenic serotypes, such as serotype 6, and with vaccine serotypes 6b, 14, 18, 19F, and 23F in children with sickle cell disease (39, 139, 287).

Antibody levels frequently decline in children with sickle cell disease; revaccination increases antibody levels (219, 277), but rarely above primary postvaccination levels (277). The major risk of pneumococcal infection in children with sickle cell disease begins at the age of 4 months and continues until the age of 4 to 5 years (80). Therefore, the current recommendations for prophylaxis against *S. pneumoniae* in these children are to institute oral penicillin prophylaxis at the age of 4 months and to vaccinate with a polyvalent pneumococcal polysaccharide

vaccine beginning at the age of 2 years (64). One investigational pneumococcal polysaccharide conjugate vaccine was reported to elicit protective levels of antibody in 2- to 5-year-old children with sickle cell disease (238), suggesting that conjugate vaccination might be able to elicit protective antibody levels in infants with sickle cell disease. Studies of pneumococcal conjugates are under way. No efficacy studies are available, but several different conjugates appear to be immunogenic in young children (145).

Patients with multiple myeloma, chronic lymphocytic leukemia, or Hodgkin's disease are at increased risk for infections with *S. pneumoniae*, and the lack of specific antibody is a critical factor in susceptibility to these infections (8, 58). Comparisons between cohorts of patients with multiple myeloma and normal subjects revealed that 21 of 37 (242) and 4 of 13 (166) myeloma patients had twofold increases in serotype-specific antibody levels against 6 of the vaccine serotypes in the 23-valent pneumococcal polysaccharide vaccine. In some cohorts of patients with multiple myeloma, reduced antibody responses have been associated with low levels of prevaccination antipneumococcal antibodies and the administration of multiagent chemotherapy (166, 242).

Patients with Hodgkin's disease generally respond to pneumococcal polysaccharide vaccines prior to the initiation of antineoplastic therapy, but afterwards they have markedly decreased and short-lived responses (12, 89, 251, 253). Poor responses to polyvalent pneumococcal polysaccharide vaccination have been documented for as long as 7 years after treatment for Hodgkin's disease (89). Children with Hodgkin's disease who were vaccinated before undergoing splenectomy responded to 67% of the pneumococcal antigens tested, but those immunized after undergoing splenectomy responded only to 40% of the antigens (76). Decreased levels of IgG2 in serum have been proposed to correlate with poor antibody responses to pneumococcal and other polysaccharide antigens (252). For those who have received intensive therapy for Hodgkin's disease, the preimmune IgG2 concentration in serum correlated with the ability to respond to pneumococcal polysaccharides and with the postvaccination antibody levels 6 months after vaccination (252).

An investigational heptavalent pneumococcal conjugate vaccine that links serotypes 4, 9V, 14, 18, 19F, 23F, and 6b to the outer membrane protein of *N. meningitidis* (Merck) was administered to treated patients with Hodgkin's disease who had not relapsed or developed a second cancer (188). In this cohort, a single dose of the pneumococcal conjugate was less immunogenic than a 23-valent polysaccharide vaccine. Postvaccination antibody determinations of each individual serotype and for total antipneumococcal IgG levels were lower for conjugate vaccinees than for both 23-valent polysaccharide vaccinees with Hodgkin's disease and normal conjugate-vaccinated subjects (188). Nonetheless, the conjugate vaccine recipients were successfully primed to respond to the 23-valent polysaccharide vaccine 1 year later: the unprimed group had lower geometric mean antipneumococcal antibody levels for serotypes 4, 6b, and 19F and lower, but not significantly different, antibody levels for serotypes 9V and 14 (55). Successful priming of antipneumococcal antibody responses by a polysaccharide conjugate vaccine indicates that T-dependent antigens can prime later T-independent antibody responses, suggesting that the same antibody-forming cells are activated by both the glycoconjugate and unconjugated polysaccharide. For those who have the necessary B-cell precursors, conjugate vaccination may succeed in increasing antibody responses to pneumococcal polysaccharide antigens. However, it appears that larger and repeated doses of pneumococcal protein conjugate vaccines may be required to achieve the same immunogenicity as that provided by existing polyvalent pneumococcal polysaccharide vaccines (145).

Patients who have undergone BMT are susceptible to infection with *S. pneumoniae* during the late posttransplantation period (8). This phenomenon results from waning pretransplantation antipneumococcal antibody levels and delayed maturation of polysaccharide antibody responses by donor lymphocytes (8). Only 19% of allogeneic and autologous BMT recipients vaccinated with Pneumovax had at least to 300 ng of antibody nitrogen/ml against pneumococcal serotypes 1, 3, 6A, 7F, 8, and 9, and none of 14 autologous BMT recipients had protective levels for all six vaccine serotypes tested (116). Allogeneic BMT recipients who were vaccinated with a 14-valent polyvalent pneumococcal polysaccharide vaccine had prevaccination antibody levels that were 2- to 12-fold lower and postvaccination antibody levels that were significantly lower than those in normal controls (286). Pneumococcal infection developed in 12.8% (5 of 39 patients) of the patients who were vaccinated within 6 months of transplantation. For the instances in which a vaccine serotype was identified as the infecting organism (two of three cases), preinfection antibody levels were lower than the protective level (286).

Low IgG2 levels in serum 12 and 24 months posttransplantation in both allogeneic and autologous BMT recipients did not correlate with polysaccharide antibody responses (116), but serotype-specific IgG2 levels were not examined. Studies that have evaluated serotype-specific IgG2 levels have reported low serotype-specific antipneumococcal IgG2 levels and severely impaired antibody responses (118, 176). Graft-versus-host disease has been reported to contribute to the failure of pneumococcal vaccination in BMT recipients by some authorities (118, 286) but not others (116). All eight allogeneic transplant patients in one study lost their pretransplantation IgG2 antibodies against *S. pneumoniae*, and six of the eight did not respond to pneumococcal vaccination at all (118). Children who were vaccinated with Pneumovax 1 year after receiving a BMT had reduced antibody levels compared to normal controls (176). In this study, the recipients who received bone marrow from Pneumovax-immunized donors did not have better antibody responses, but the recipients were vaccinated 1 year after donor vaccination. The success of recipient immunization with a Hib conjugate soon after donor vaccination (189) suggests that earlier recipient vaccination might elicit higher antibody levels.

The immunogenicity of polyvalent pneumococcal polysaccharide vaccine in patients with SLE has been examined. The mean antibody levels were lower at both 1 month and 1 year postvaccination in 38 patients with SLE than in normal controls (138). A study that examined the persistence of antipneumococcal polysaccharide antibodies in vaccinated SLE patients demonstrated significantly lower mean antibody levels 1 year after vaccination and lower but statistically nonsignificant levels 2 and 3 years after vaccination (184). In this study, almost 50% (8 of 19) of the patients had antibody levels considered to be protective after 3 years, but 1 developed pneumococcal pneumonia. In a study of 77 SLE patients who received the 14-valent vaccine, those on and not on immunosuppressive therapy (prednisone with cyclophosphamide and/or azathioprine) manifested significantly higher postimmunization antibody levels than did placebo-vaccinated subjects 1 and 6 months after vaccination (170). Vaccination of SLE patients with polyvalent pneumococcal polysaccharide vaccines has not been associated with alterations in underlying disease activity (150).

Vaccination of renal transplant and hemodialysis patients

with polyvalent pneumococcal polysaccharide vaccines has resulted in antibody levels in the range that is considered to be protective (65, 102, 169). In a study that compared postvaccination antibody levels in different patient populations with renal disease, 90% of normal controls manifested a twofold increase and the patients undergoing hemodialysis responded like these normal subjects, but only 43% of those with chronic renal failure and 80% with renal allografts responded (102). Pneumococcal vaccination is recommended while patients are on dialysis prior to renal transplantation, because dialysis patients have higher pre- and postvaccination antibody levels (169). Both splenectomized and nonsplenectomized renal allograft recipients had decreased antibody responses to polyvalent pneumococcal vaccination (102). Functional opsonic antibodies were elicited in 59% (for serotype 12) and 76% (for serotype 14) of nonimmune renal transplant patients on maintenance immunosuppression with prednisone and azathioprine (21). In this study, splenectomized and nonsplenectomized patients had similar antibody responses, although both had lower preimmunization antibody determinations than did normal controls. Among children with nephrotic syndrome, five of five with steroid-resistant disease had markedly decreased geometric mean antibody levels of anti-pneumococcal polysaccharide antibodies before vaccination and only one achieved a postvaccination level of greater than 200 ng/ml, but 26 children with steroid-responsive disease (14 taking steroids and 12 not taking steroids) had normal postvaccination antibody levels (102). This suggests that polyvalent pneumococcal vaccines are not immunogenic in children with steroid-unresponsive nephrotic syndrome.

HIV-infected individuals are at high risk for infection with *S. pneumoniae* (134), and penicillin-resistant strains are on the rise in this group (32, 212, 229). Pneumococcal carriage rates were comparable in HIV-infected and HIV-uninfected subjects in the early 1990s (136), but recent studies have reported an increased frequency of penicillin-resistant strains and invasive disease due to these organisms in HIV-infected individuals (32, 212, 229). One recent study documented that 25 of 34 isolates from HIV-infected individuals were penicillin resistant and 19 were resistant to more than three antimicrobial agents (229). Vaccination with either a 23-valent pneumococcal polysaccharide vaccine or a 5-valent pneumococcal polysaccharide conjugate vaccine containing serotypes 6B, 14, 18, 19F, and 23F reduced vaccine strain carriage in HIV-uninfected people, but HIV-infected subjects continued to manifest persistent carriage of vaccine strains (229). Only 8 of 14 HIV-infected persistent carriers had twofold increases in postvaccination IgG titers for two or more pneumococcal vaccine serotypes (229). This study examined a relatively small cohort, but it is of great importance because it suggests that available vaccines cannot prevent persistent carriage of *S. pneumoniae* vaccine serotypes in HIV-infected subjects.

A majority of studies have reported that HIV-infected individuals have decreased antibody responses to polyvalent pneumococcal vaccines (4, 47, 101, 135, 174, 181, 207, 228, 268), although some have found similar responses in HIV-infected and uninfected individuals (130, 156, 279). In the early years of the AIDS epidemic, subjects were stratified by clinical designations such as asymptomatic, symptomatic, persistent generalized lymphadenopathy, and AIDS. In the 1990s, most investigators began to stratify HIV-infected individuals by $CD4^+$ T-cell count. IgG responses to pneumococcal polysaccharide after vaccination in HIV-infected subjects have been reported to be independent of the $CD4^+$ T cell count in some studies (156, 268, 269), but a trend and/or statistically higher antibody responses in those with more than 500 $CD4^+$ T cells has been observed by others (135, 228). HIV-infected seroconverters who have been infected for a mean of 7.4 months manifest normal antibody responses to the 23-valent polysaccharide vaccine (279). Impaired synthesis of isotype-specific antipneumococcal antibodies has been implicated in some studies as a $CD4^+$ T-cell-independent factor that is responsible for decreased postvaccination antibody responses of HIV-infected individuals (268). Antipneumococcal IgG2 levels at least 50% higher than prevaccination levels were found in only 50% of HIV-infected individuals and 100% of normal, HIV-uninfected subjects (268). The numbers of circulating antipneumococcal IgM-secreting cells have also been reported to be markedly decreased in HIV-infected individuals (47, 181). This may be significant for the generation of antipneumococcal antibodies by isotype switching. Studies that have examined the use of pneumococcal conjugate vaccines in HIV-infected individuals have failed to demonstrate superior immunogenicity of these preparations (4, 229). This is similar to findings for in a cohort of Hodgkin's disease patients, who did not mount increased antibody responses to one dose of a conjugate vaccine (188). However, newer conjugates may prove to be more immunogenic.

In conclusion, the immunogenicity of polyvalent pneumococcal polysaccharide vaccines is significantly decreased in those who have received immunosuppressive therapy such as BMT recipients, patients with Hodgkin's disease, and those with immature or dysregulated B-cell function such as neonates, young children with sickle cell anemia, and individuals with AIDS. Individuals on steroids (with the exception of children with steroid-unresponsive nephrotic syndrome) who are postsplenectomy without immunosuppressive therapy and who have chronic rheumatologic diseases or renal failure have only modestly impaired responses to pneumococcal polysaccharide vaccination.

CONCLUSIONS

Several themes have emerged from our review of the vaccine literature in individuals with immunologic impairment: (i) the magnitude of the immune response is decreased in patients with a broad spectrum of immunologic impairments relative to normal hosts; (ii) the timing of vaccination is a critical determinant of the magnitude of antibody responses in individuals who are receiving antineoplastic therapy (radiotherapy and/or chemotherapy), and vaccine immunogenicity is greatest before the initiation of such therapy; (iii) the vaccines in current use are well tolerated in individuals with impaired immunity, although isolated cases of disseminated infection have occurred with live vaccines; and (iv) with the exception of the varicella and hepatitis B vaccines, the antibody levels that are required for protection and the ability of vaccination to prevent the targeted infection in individuals with impaired immunity are largely unknown. Table 6 summarizes the safety, response rates, and recommendations for the use of several common vaccines.

Efficacy is defined as the ability of a vaccine to prevent infection or its complications. In this article, we have attempted to evaluate the efficacy and safety of licensed vaccines in patients with impaired immunity by reviewing the literature. In retrospect, this approach was problematic, because for most vaccines we asked a question that available studies on vaccine efficacy cannot answer. With the exception of the varicella and hepatitis B vaccines, efficacy studies prior to vaccine licensing were performed in normal hosts, not in patients with impaired immunity. Studies of administration of vaccines to individuals with impaired immunity that have been performed after licen-

TABLE 6. Summary of recommendations for active vaccination of immunocompromised hosts with HIV infection or severe and mild immunosuppression[a]

Vaccine	Safety in patients with:			Response rate[b] in patients with:			Recommendation[c] for patients with:		
	HIV	Immunosuppression		HIV	Immunosuppression		HIV	Immunosuppression:	
		Severe	Mild		Severe	Mild		Severe	Mild
MMR	Risk	Risk	Safe	Poor	Decreased	Good	Recommend[d]	Contraindicated	Recommend
Varicella	?	Safe	Safe	?	Moderate	Moderate	?	Recommend	Recommend
Hepatitis B	Safe	Safe	Safe	Decreased	Moderate	Good	Recommend	Recommend	Recommend[e]
Influenza	Safe[f]	Safe	Safe	Very poor	Decreased	Moderate	Recommend[g]	Recommend	Recommend
Toxoids	Safe[f]	Safe	Safe	Decreased	Decreased	Good	Recommend[g]	Recommend	Recommend
Hib conjugates	Safe	Safe	Safe	Decreased	Decreased	Good	Recommend[h]	Recommend	Recommend
Pneumococcal	Safe	Safe	Safe	Very poor	Very poor	Poor	Recommend[i]	Recommend	Recommend

[a] In this table patients are stratified according to HIV status, or, for HIV-uninfected individuals, immunosuppression is characterized as "severe," which includes patients with cancer on antineoplastic therapy, BMT recipients receiving immunosuppressive therapy, and patients receiving high-dose corticosteroids, and "mild," which includes patients with rheumatologic disorders, those receiving lower-dose corticosteroids, those with renal diseases, and those with asplenia in the absence of intercurrent antineoplastic therapy. These categories are derived from the Committee on Immunization Practices, Centers for Disease Control and Prevention (50).

[b] The levels of antibody that are required to protect individuals with impaired immunity are unknown and may exceed the concentrations that are thought to protect immunocompetent individuals. Individuals with impaired immunity generally respond to vaccines with lower antibody concentrations than do normal individuals.

[c] The recommendations in this table apply to both adults and children. All routine infant and childhood vaccinations should be given to HIV-infected and other immunosuppressed children with the exception of the MMR vaccine, which should be administered only to children with HIV (50). Polio vaccines are not listed in this table because the live preparations are contraindicated in all immunosuppressed individuals (50) and their household contacts, and inactivated polio preparations should be used in these individuals.

[d] Vaccinated and unvaccinated symptomatic HIV-infected individuals and unvaccinated immunocompromised patients should receive immunoglobulin following a measles exposure (50).

[e] Vaccination with HBV should be considered in patients with renal disease whose titers have fallen. Similarly, health care personnel should receive vaccination when indicated.

[f] Influenza and toxoid vaccination can increase plasma viremia in HIV-infected individuals; the long-term prognostic consequences of this phenomenon are unknown (204, 254, 255). The acellular pertussis vaccine has not been tested in immunocompromised groups (64).

[g] Influenza and toxoid vaccination are recommended in HIV-infected individuals, although plasma viremia has been noted following vaccination as noted in footnote *f*. Amantadine prophylaxis is an appropriate alternative to vaccination for influenza and should be considered during influenza epidemics or in the case of exposure of a severely immunocompromised individual.

[h] Hib conjugates are safe in HIV-infected individuals, but a minimum of studies on the immunogenicity of these vaccines in this group have been published to date.

[i] The 23-valent pneumococcal polysaccharide vaccine is the vaccine of choice in HIV-infected individuals. Studies published to date indicate that pneumococcal conjugates are less immunogenic than the purified polysaccharide vaccines in both HIV-infected and severely immunocompromised individuals (4).

sure have relied exclusively on surrogate markers of the immune response which were determined in normal hosts, and the relevance of these parameters to the immunocompromised host are undefined. Unfortunately, one cannot conclude that immune system responses associated with protection in normal hosts will be protective in individuals with impaired immunity, even if the assays do not reveal quantitative or qualitative differences between the immune system responses of normal and impaired hosts. Antibody responses are usually a measure of the immunogenicity of the vaccine preparation, and the presence of serum antibody does not necessarily imply immunity. For instance, impaired effector cell function and nonspecific immune system mechanisms such as complement activation may lead to ineffective antibody-mediated immunity. Hence, efficacy data that are relevant for vaccine utilization in patients with impaired immunity are not available for most licensed vaccines.

The evaluation of true vaccine efficacy in patients with impaired immunity remains a major challenge, because these individuals represent a heterogeneous population and the prevalence of most vaccine-preventable infections is too low to rapidly assess efficacy in relatively small populations. The mechanisms of protective immunity are not completely defined for many infectious diseases, and protective immune responses in patients with impaired immunity may be qualitatively different than those in normal hosts. Immunocompromised hosts are now a major challenge in the control of infectious diseases. When possible, such individuals should be included in future studies of vaccine efficacy.

What should physicians do when confronting the issue of vaccinating patients with impaired immunity? First, they should consult the most recent recommendations on vaccine use that are issued by the Centers for Disease Control and Prevention (Atlanta, Ga.) from the Advisory Committee on Immunization Practices (see, e.g., reference 50). Second, they should avoid live-agent vaccines when possible, unless these vaccines have been shown to be safe in the group being vaccinated. Third, they should consider that efficacy data are lacking for most vaccines in patients with impaired immunity and that the decision to vaccinate must be based on individual risk-benefit calculations for each patient. Vaccination may be beneficial to some patients and not others. The adage of "do no harm" should always guide clinical decision making. Patients with impaired immunity, like all other individuals who are vaccinated, should be advised that protection against infection is never ensured by vaccine administration. Although unsatisfactory from the viewpoint of certainty, these suggestions reflect our current state of knowledge regarding the subject of vaccinating patients with impaired immunity.

After developing strategies to control most infectious-disease killers of normal hosts through a combination of vaccination, improved sanitation, and antimicrobial drug discovery, the major challenges in the developed nations are (i) to reduce mortality from infectious disease in patients with impaired immunity, (ii) to contain the spread of drug-resistant microbes, and (iii) to develop better therapies for emerging pathogens. These are interrelated problems, because the failure of underlying host immune mechanisms in patients with impaired immunity compounds the challenge of prudent antibiotic use in this population. Increasing rates of antimicrobial drug resistance have paralleled increasing rates of antibiotic usage in

patients with immunologic impairments. These individuals are also vulnerable to a variety of emerging pathogens.

Experience with the varicella vaccine in leukemic children and the hepatitis B vaccine in chronic dialysis patients has demonstrated that vaccines that do prevent infection in patients with impaired immunity can be developed. Success with these agents provides hope that vaccination can reduce mortality in immunocompromised hosts. This should serve as an impetus for increased research efforts. A better understanding of the two arms (cell mediated and antibody mediated) of the immune system may reveal strategies to overcome defects in one arm by eliciting enhanced responses in the other. Success in this endeavor will require a multidisciplinary effort that involves basic science, clinical, and epidemiological researchers.

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