CLINICAL AND VACCINE IMMUNOLOGY, July 2010, p. 1055–1065 Vol. 17, No. 7
1556-6811/10/$12.00 doi:10.1128/CVI.00131-10

MINIREVIEW

Correlates of Protection Induced by Vaccination[▽]

Stanley A. Plotkin*

University of Pennsylvania and Vaxconsult, 4650 Wismer Road, Doylestown, Pennsylvania 18902

This paper attempts to summarize current knowledge about immune responses to vaccines that correlate with protection. Although the immune system is redundant, almost all current vaccines work through antibodies in serum or on mucosa that block infection or bacteremia/viremia and thus provide a correlate of protection. The functional characteristics of antibodies, as well as quantity, are important. Antibody may be highly correlated with protection or synergistic with other functions. Immune memory is a critical correlate: effector memory for short-incubation diseases and central memory for long-incubation diseases. Cellular immunity acts to kill or suppress intracellular pathogens and may also synergize with antibody. For some vaccines, we have no true correlates, but only useful surrogates, for an unknown protective response.

The correlates of vaccine-induced immunity are a subject of continued interest for both theoretical and practical reasons. The latter include the need to evaluate the consistency of vaccine production; the susceptibilities of individuals and populations after vaccination; the validation of vaccines for which efficacy trials are not ethical, as when a prior-generation vaccine is already licensed; and the licensure of combination vaccines (38). I have twice previously reviewed knowledge in this area, first in a general overview (138) and second to define the notions of correlates and surrogates of protection (139). This article attempts to survey all examples known to me of immune responses to licensed vaccines that correlate with protection and is an update of the overview published in 2001, including excerpts used by permission of the original journal, *Pediatric Infectious Diseases*. The reader is also referred to one of the preceding articles for conceptual discussion (139).

For clarity, Table 1 gives definitions of correlates and surrogates that are used in this article. Although the distinctions may be semantic, the literature is confusing, because some authors use the words correlate and surrogate interchangeably, whereas precision in language is preferable. In essence, I define an immune function that is responsible for protection as a correlate, while an immune response that is simply an easy measurement but not functional in protection is a surrogate.

GENERAL PRINCIPLES

There are at least six general principles that should be understood before taking up specific examples. They are as follows. (i) Large challenge doses may overwhelm vaccine-induced immunity and confuse the identification of correlates (117, 142). However, the relationship between the dose and failure of protection may not be linear, as demonstrated recently for hepatitis B infection of chimpanzees (7). (ii) The mechanism of protection is not necessarily the mechanism of recovery from infection. The latter are often cellular immune functions, which may be irrelevant to vaccine-induced prevention of infection (124, 133, 134). (iii) Indeed, most vaccines available today act through antibodies, on condition that they are functional (137), as is evident from the frequent efficacy of passive antibodies and transplacental antibodies (203). However, as will be repeatedly emphasized in this article, the immune system has evolved to be redundant, and vaccines, like prior natural infection, may protect through multiple mechanisms. (iv) Memory induced by vaccination may be crucial to protection, particularly in long-incubation diseases, such as hepatitis B (86, 185). Although loss of antibody after vaccination may render vaccinees again susceptible to some infections (90), central memory established by vaccination is sufficient under certain circumstances to confer protection (20). (v) Correlates may vary according to individual characteristics, such as age, gender, and major histocompatibility complex (MHC) group (see the discussion of influenza below). (vi) It is important to define protection against what. Correlates may differ quantitatively and qualitatively, depending on whether the objective is to prevent systemic infection, mucosal infection, disease, or severe disease.

ENCAPSULATED BACTERIA

Where protection is based on anticapsular antibody or antitoxin antibody, it has been relatively easy to define correlates. For bacteria that do not have capsules to prevent phagocytosis or toxins that are pathogenic, the situation becomes more complex.

For the three main bacterial pathogens that cause bacteremic disease—*Haemophilus influenzae* type b (Hib), pneumococci, and meningococci—the correlates are opsonophagocytic or bactericidal antibodies, although binding antibodies are useful as surrogates. In the case of *H. influenzae*, binding antibodies are routinely used to define protection, as indicated in Table 2. A correlate of immunity is best known for the Hib polysaccharide, which was formerly used as a vaccine (74). In Finland, before the use of the vaccine, the age-specific incidence of Hib disease declined significantly at the age when most of the population showed antibody concentrations of 0.15

* Corresponding author. Mailing address: Vaxconsult, 4650 Wismer Road, Doylestown, PA 18902. Phone: (215) 297-9321. Fax: (215) 297-9323. E-mail: stanley.plotkin@vaxconsult.com.

▽ Published ahead of print on 12 May 2010.

TABLE 1. Definitions of terms used in this article

Term	Definition
Correlate	An immune response that is responsible for and statistically interrelated with protection
Absolute correlate	A specific level of response highly correlated with protection; a threshold
Relative correlate	A level of response variably correlated with protection
Cocorrelate	One of two or more factors that correlate with protection in alternative, additive, or synergistic ways
Surrogate	An immune response that substitutes for the true immunologic correlate of protection, which may be unknown or not easily measurable

μg/ml or more, and in the efficacy study of the polysaccharide (94), age-specific vaccine efficacy was correlated with the induction of 1.0 μg/ml of antibody postvaccination. Consequently, an antibody level of 0.15 μg/ml is probably protective against bacteremia and is likely to remain present for some period in vaccinees who respond initially with 1 μg/ml of antibody.

Even more direct information is available from studies of gamma globulin prophylaxis and of the decline of maternal antibodies in relation to disease incidence (94, 151, 159). These studies support the idea that concentrations between 0.03 and 0.1 μg/ml are protective, and thus, the commonly accepted 0.15-μg/ml cutoff seems reasonable (73). However, more recently, three important points have emerged with regard to protection against Hib: (i) that anamnestic responses are insufficient and that the antibody must be present at the time of exposure (6, 90, 147, 184), (ii) that the antibodies must be of high avidity in order to protect (82), and (iii) that with the T-cell-dependent response reduced by protein conjugates, a 1ower concentration may be protective (73).

Prevention of nasopharyngeal carriage is achieved through diffusion of *H. influenzae* antibodies from serum and is correlated with postimmunization levels of >5 μg/ml (44).

Pneumococcal antibodies are also often measured by enzyme-linked immunosorbent assay (ELISA), but in the very young and in elderly adults, these antibodies tend not to be opsonophagocytic, which accounts for the relatively poor efficacy of unconjugated polysaccharides that elicit only binding antibodies in the aged (153). The protective level of antibody as measured by ELISA has been variously calculated, but there is a reasonable consensus that it lies between 0.18 and 0.35 μg/ml (68, 81, 127, 167). The critical issue is the relationship between ELISA values and functional opsonophagocytic antibodies, which may vary with serotype (81). Goldblatt et al. found that at 0.2 μg/ml antibody by ELISA, most vaccinees were positive for opsonophagocytic antibodies (54). A bactericidal titer of 1/8 for those antibodies may correlate with protection (42). However, a recent analysis of a study done in Africa, where the efficacy of the vaccine was lower, showed a correlate of 2.3 μg/ml (156). The more compressed vaccine schedule used in Africa or a higher challenge dose of pneumococci may account for this difference. Thus, the protective concentration appears to vary, depending on the population, the serotype, and the clinical end point.

TABLE 2. Quantitative correlates and surrogates of protection after vaccination

Vaccine	Test	Level required	Reference(s)[a]
Anthrax	Toxin neutralization	1,000 IU/ml	87, 136, 149, 170, 191
Diphtheria	Toxin neutralization	0.01–0.1 IU/ml	14, 92
Hepatitis A	ELISA	10 mIU/ml	45, 110
Hepatitis B	ELISA	10 mIU/ml	66
Hib polysaccharides	ELISA	1 μg/ml	74
Hib conjugate	ELISA	0.15 μg/ml	73
Human papillomavirus	ELISA	ND[b]	140
Influenza	HAI	1/40 dilution	50, 171
Japanese encephalitis	Neutralization	1/10 dilution	63
Lyme disease	ELISA	1,100 EIA U/ml	128
Measles	Microneutralization	120 mIU/ml	24, 120, 158
Meningococcal	Bactericidal	1/4 (human complement)	96
Mumps	Neutralization?	ND	189
Pertussis	ELISA (toxin)	5 units	25, 173, 180.
Pneumococcus	ELISA; opsonophagocytosis	0.20–0.35 μg/ml (for children); 1/8 dilution	68, 81, 167
Polio	Neutralization	1/4–1/8 dilution	41, 95, 139
Rabies	Neutralization	0.5 IU/ml	196,
Rotavirus	Serum IgA	ND	49, 67, 104, 199, 200
Rubella	Immunoprecipitation	10–15 mIU/ml	2, 27, 53, 99, 141, 169
Tetanus	Toxin neutralization	0.1 IU/ml	13, 37,
Smallpox	Neutralization	1/20	89, 93, 139, 160
Tick-borne encephalitis	ELISA	125 IU/ml	77
Tuberculosis	Interferon	ND	46
Varicella	FAMA gp ELISA	≥1/64 dilution; ≥5 IU/ml	195
Yellow fever	Neutralization	1/5	79, 97
Zoster	$CD4^+$ cell; lymphoproliferation	ND	190

[a] Also see the text.
[b] ND, not defined.

Prevention of nasopharyngeal carriage of pneumococci is important to individual and herd immunity. Diffusion of IgG antibodies from serum is thought to correlate with protection against carriage (31). However, the situation may be more complex, as there is evidence in mice that prevention of pneumococcal carriage correlates with a Th17 cellular response (202). Moreover, antibody response to the PspA surface protein of pneumococci may also correlate with prevention of carriage (101).

Humoral responses to meningococci also may be measured by ELISA, but only bactericidal tests correlate with protection, as is demonstrable in children, who develop the former but not the latter after unconjugated polysaccharide immunization. The level of bactericidal antibody necessary for protection depends on the complement used in the test, but with human serum, a level of >1/8 or even >1/4 is usually considered sufficient for all serogroups, including outer membrane vesicle vaccines against group B (17). In adults, this correlates with an ELISA antibody measurement of 2 μg/ml (96, 132).

TOXIN-PRODUCING BACTERIA

Correlates of protection are particularly clear for the class of toxin-producing bacteria (Table 2). Tetanus and diphtheria have been well studied, and the levels of antitoxin after vaccination that correspond to protection were established years ago. For both pathogens, a level of 0.01 μg/ml provides considerable protection, whereas a level of 0.1 μg/ml corresponds to virtually complete protection against the respective diseases (56, 65, 89, 100, 113), although more antibody may be required for diphtheria (92). Exceptional cases of diphtheria and tetanus occur despite high concentrations of antibodies, perhaps because of poor diffusion into sites of toxin production, but the illnesses are usually mild (13, 14, 34, 37, 65). Measurement of antitoxin in animals is preferable to *in vitro* methods, as the latter may also detect nonneutralizing antibodies (36).

Bacillus anthracis acts through toxin production, although its capsule is also a virulence factor. For obvious reasons, there are no data on human challenge, but two methods are generally used to measure resistance against an aerosol challenge in animals: an ELISA binding the "protective-antigen" (PA) part of the toxin, and toxin neutralization (TN). It appears that PA antibodies at more than 100 units and TN antibodies at more than 1/1,000 correspond to good protection (87, 136, 149, 170, 191).

The case of pertussis is more complex, as in addition to the pertussis toxin, the vaccines usually contain one or more attachment factors, which also may be protective. Therefore, protection correlates with antibodies not only against pertussis toxin (PT), but also against pertactin and fimbrial hemagglutinins. The exact level of each of these antibodies that is protective is controversial, and in any case, there is no absolute threshold, but 5 to 10 units of ELISA antibodies to PT have been proposed as an important benchmark (25, 173, 174, 180).

BACTERIA INTRODUCED DIRECTLY INTO THE BLOODSTREAM

The only bacterial infection that is transmitted by insects for which a vaccine has been developed is Lyme borreliosis. Although no longer licensed, the vaccine acted by inducing antibodies against the outer surface protein A of the organism, which neutralized *Borrelia burgdorferi* in the intestine of the tick vector at the time of the blood meal. Retrospective analysis of the efficacy trial allowed the determination of a protective level of antibodies equivalent to 1,100 enzyme immunoassay (EIA) units/ml after immunization and 400 EIA units/ml at the time of the tick bite (128).

BACTERIA THAT REPLICATE INTRACELLULARLY

The causative agent of tularemia is partially susceptible to the action of passive antibody. However, induction of cellular immunity in addition to antibody is necessary for maximum protection (161, 165).

On the other hand, protection against the plague bacillus appears to be mediated by antibodies, particularly those directed against the LcrV virulence antigen, but also those directed against the F1 capsular antigen. The ability to neutralize *in vitro* more than 20% of cytotoxicity by the organism in macrophages correlates with protection (197, 201).

It is generally believed that cellular immunity induced by *Mycobacterium bovis* BCG is the protective function against tuberculosis, although this is largely, though not exclusively, an extrapolation from animal studies of infection (59, 179). Immunity correlates best with $CD4^+$ cells that produce cytokines, particularly interleukin 23 (IL-23), which stimulates IL-17-producing $CD4^+$ cells, which in turn stimulate gamma interferon at the time of challenge, and it is the presence of the last in the lungs that is protective (46, 75, 106). However, $CD8^+$ cells contribute to protection (119), and it has been argued that antibodies play a role in enhancing uptake of mycobacteria by macrophages (1). No firm conclusion can yet be drawn.

VIRUSES TRANSMITTED BY ARTHROPODS

Vaccines against viruses injected into the bloodstream appear to be a straightforward case for antibodies, but as we shall see, the situation is more complex.

To be sure, it was established many years ago that neutralizing antibodies induced by yellow fever vaccine correlate well with protection (97), although early after immunization, innate immune responses play an important role (146, 166). However, in general, a level of 0.7 neutralization units, equivalent to a 1/5 titer, is considered protective (97).

Japanese encephalitis vaccines are also based on induction of antibodies, and a neutralization titer of 1/10 is considered protective (55, 63). Although no licensed vaccine yet exists for West Nile virus, it is interesting that, whereas antibodies are protective in mice, once infection of the brain takes place, $CD4^+$ cells are required for clearance from the central nervous system (168).

The case for tick-borne encephalitis seems reasonably clear: antibodies are protective, and a level of 125 ELISA units is considered sufficient (77).

Dengue vaccines are in advanced clinical trials, and therefore, the definition of a correlate of protection has become important. Whereas neutralizing antibody clearly protects against a homologous serotype (157, 175), controversy has centered on what function gives heterologous serotype protec-

tion in the face of the enhanced disease that occurs in the presence of antibody-dependent enhancement (ADE) (57). It appears from studies in a mouse model that heterotypic neutralizing antibodies do give heterotypic protection if they are present in concentrations sufficient to protect but insufficient to cause ADE (8, 78, 186).

VIRUSES THAT INFECT THE MUCOSAE AND THEN CAUSE VIREMIA

The largest category of agents for which we have vaccines is viruses that infect the mucosae and then cause viremia, which includes viruses that initially replicate in the nasopharynx and intestine. The classical example is smallpox, the disease for which the first vaccine was developed. The situation for smallpox is clear: antibody provides the best correlate of immunity to infection after vaccination, but cellular responses, particularly $CD8^+$ cells, influence the severity of disease if infection occurs despite antibodies. The evidence for this comes from animal experiments and also from human data showing persistence of antibodies and protection against death virtually forever after vaccination but susceptibility to mild disease once $CD8^+$-mediated cytotoxic T lymphocytes (CTL) have faded away (5, 58, 125, 126). The protective titer of neutralizing antibody appears to be about 1/20 (93, 160) and may be directed against one or several smallpox proteins with neutralizing epitopes (12).

Interestingly, whereas the above is the case for smallpox acquired naturally, cellular immunity plays a more important role in the prevention of poxvirus growth in the skin after an initial introduction by scarification, illustrating the importance of organ-specific factors (88).

The two vaccines against poliomyelitis, inactivated (IPV) and oral (OPV), work in both parallel and different ways. Each vaccine elicits serum antibodies that prevent viremia, and neutralization at titers of 1/8 (or even 1/4) is protective (143, 193).

Live, attenuated polio vaccines are well known to give local immunity to subsequent superinfection (176), although this immunity may be abrogated if the challenge is sufficiently large. IPV has been reputed not to provide the same immunity, but as previously reviewed (41, 109), poliovirus replication in the nasopharynx is reduced after both IPV and OPV vaccination (95), However, the resistance induced by IPV in the intestines, although substantial, is clearly less than that afforded by live vaccine (95, 117), Intestinal resistance is proportional to the serum antibody titer (95), which suggests that passage of IgG into the lumen of the intestine is partly responsible for the local immunity. On the other hand, Ogra and Karzon (115) found that intestinal resistance after OPV was induced only where the vaccine virus had previously replicated and induced a secretory-antibody response. Interestingly, elderly people who had received OPV many years previously and who still had serum and salivary IgA antibodies were resistant to reinfection with OPV, whereas those who lacked those antibodies could be reinfected (19).

With regard to the four live vaccines commonly given in infancy, measles, mumps, rubella, and varicella, antibodies are certainly relevant to protection, but there are important qualifications to take into account. The role of antibodies in protection against measles is indisputable. Gamma globulin has been effective in preventing infection and disease, and maternal antibodies are well demonstrated to protect. The plaque neutralization test shows good correlation with protection (3, 24, 118). Microneutralization titers of $\geq$120 mIU/ml give protection against disease, whereas titers of $\geq$1,000 mIU protect against both infection and disease. Cases of secondary vaccine failure may be related to loss of antibodies (98).

However, measles vaccine also induces cellular responses (10, 52), and the importance of cellular immunity is evident when immunosuppressed subjects are vaccinated, for they develop transient protection (76, 155). On the other hand, suppression of cellular responses does not seem to render subjects again susceptible as long as they maintain antibodies (2, 204). Immunosuppression may lead to severe measles in unvaccinated subjects, but that is related to poor control of established replication.

An interesting study was conducted in rural Senegal in which antibodies were measured early after exposure to measles (158). Both unvaccinated and vaccinated children with plaque neutralization titers of $<$40 mIU/ml were highly susceptible to clinical measles. Unimmunized children with trace amounts of antibody (40 to 125 mIU/ml) still had a high risk of measles, whereas immunized children with such titers were usually protected. Both immunized and unimmunized children with titers of $>$125 mIU/ml showed a high degree of protection. One interpretation of the results is that unimmunized children were not protected by trace amounts of maternal antibody whereas immunized children had cellular immunity in addition to the trace amounts of antibody (130, 144, 145, 148). Antibodies against the measles virus hemagglutinin are most important, as shown in experiments with DNA-based vaccines (130), but protective neutralizing antibodies against either hemagglutinin or fusion protein can protect (144). However, if infection does take place, T cells must be functional to close off replication, which is why T-cell-deficient children may suffer complications from vaccination (124, 133, 134). The complexity of T-cell action is illustrated by results showing that whereas $CD8^+$ T cells are mainly responsible for viral clearance in the lungs, only $CD4^+$ T cells are necessary for control of virus in the central nervous system (145, 148).

In the case of mumps vaccine, many attenuated strains have been widely used, including Jeryl Lynn, Leningrad, Urabe, and Rubini. Field studies done after vaccination with the Rubini strain showed low efficacy, although the strain appeared to elicit an antibody response. Closer study revealed that whereas the Jeryl Lynn and Rubini strains both induced neutralizing and indirect fluorescent antibodies in the majority of vaccinees, the latter strain induced low titers of ELISA antibodies (22, 164). This surprising result is unexplained but may suggest that antigens other than surface antigens of the virus are important to protection. In this regard, it is interesting that passive immunization against mumps has not been demonstrated to be effective, which again suggests that other factors are important. Differences in neutralizing specificities between vaccine viruses and circulating viruses have been advanced as a reason for vaccine failure, but this remains controversial (33, 62, 71, 114, 154). Titers of 1/2 by neutralization or 1/8 by hemagglutination inhibition (HAI) have been proposed as protective levels (40, 189), but no certain serologic correlate of protection is ac-

cepted. T-cell responses to mumps vaccine have been demonstrated, but their protective effect is unknown. The need to define a correlate of immunity to mumps has become acute owing to the recent outbreaks in previously vaccinated young adults who had apparently lost prior immunity (9).

During the early development of rubella vaccine, several live, attenuated strains were proposed and tested clinically. Eventually, the RA 27/3 strain was widely accepted as the standard vaccine strain. Among the reasons for this choice was the fact that, although hemagglutination-inhibiting antibodies were induced by both the RA 27/3 and HPV-77 vaccine strains and by natural infection, only natural infection and RA 27/3 vaccine induced high levels of neutralizing antibodies, which apparently correlated better with protection (141). Other advantages of RA 27/3 included the elicitation of secretory antibody in the nasopharynx and resistance of vaccinees to challenge with intranasally administered rubella virus (116). In an intranasal challenge study in subjects who had low or absent levels of serum antibodies, seronegative controls were regularly infected and subjects seropositive after natural infection or after RA 27/3 vaccination were resistant, whereas subjects vaccinated with other strains were sometimes infected (121).

In recent years, radioimmunoassay has become the predominant test for immunity to rubella, and 10 IU/ml has been proposed as the correlate of immunity (99, 169). This corresponds to a neutralization titer of 1/8. Although there is a cellular immune response to the vaccine (4), attempts to define a cellular correlate to immunity after rubella vaccination have thus far failed (182).

Clinicians are well aware of the crucial role of intact cellular immune responses in recovery from primary infection by varicella-zoster virus (VZV) (43). In addition, the recurrent disease known as zoster occurs because T-cell immunity flags with age, whereas antibodies persist (60).

Nevertheless, antibodies also play a key role in protection against varicella. Passively administered varicella-zoster immunoglobulin can prevent infection, and there is good correlation between the strength of the antibody response after varicella vaccine and the protection seen after later exposure (27, 69, 195). Titers of >1/64 by fluorescent antibody to membrane antigen (FAMA) give the best indication of protection against disease (79, 80). Healthy vaccinees who do not mount a titer of at least 1/8 do not seem to be protected against infection (107). A VZV glycoprotein (gp) antibody ELISA has also been used as a correlate of protection, and evidence of seroconversion by that assay is related to long-term protection (85), although the gp ELISA can produce false-positive reactions in varicella-susceptible children (107). In one study, $CD4^+$ cell responses were found to be more persistent than antibodies (91).

In contrast, children often resist infection after vaccine-induced antibodies are undetectable, suggesting a protective function for T cells, and agammaglobulinemic children nevertheless become immune after natural infection (53). Thus, antibody measurements correlate with protection against varicella, but it is possible that they are mainly a surrogate for cellular immunity.

HEPATITIS VIRUSES

Gamma globulin from naturally infected subjects has been used for many years to prevent hepatitis A (172). This circumstance permits one to compute a protective correlate from the concentration of antibodies induced by the dose of IgG shown to be protective in clinical studies. That concentration is ~10 mIU/ml if maintained over a 2-month period, although some individuals may be protected at much lower concentrations (29). The inactivated hepatitis A virus vaccines generate an average concentration 1,000-fold higher than the protective concentrations and also induce immunologic memory (29, 45, 110, 163, 172, 192).

Antibody tests often become negative years after hepatitis B vaccination, yet protection appears to be solid and long-lasting, and no booster vaccination is recommended (30, 185, 188, 193). Postvaccination titers of 10 mIU/ml or greater correlate with the induction of the T helper cell responses that mediate the memory of B cells. Thus, when the vaccinee is exposed to hepatitis B virus, there is an anamnestic response that prevents disease, and often infection as well (23, 30, 48, 64, 108, 178, 185, 187). In a study of children vaccinated 5 to 7 years previously, 46% had antibody titers below 10 mIU/ml. Nevertheless when given a booster dose, 90% showed evidence of an anamnestic response (86). The long incubation period of the disease allows the anamnestic response to be highly protective.

VIRUSES REPLICATING ONLY ON MUCOSAE

The literature on correlates of protection against influenza is rich, and there is a consensus that in the case of inactivated vaccine, a serum HAI antibody level of about 1/40 against the hemagglutininogen (HA) is protective. However, that level is protective only at 50 to 70%, which makes it a relative rather than an absolute correlate of protection. Evidence that other influenza virus antigens add to the protection afforded by the HA is scant (112). However, one must distinguish between the young and the old with regard to influenza vaccine. In adults up to about age 50 years, serum IgG antibodies correlate well with protection (32, 39, 183). However, inasmuch as influenza virus infection is not normally invasive, the question arises as to how serum antibodies exert an effect. Diffusion of IgG antibodies into the nasopharynx and lungs, as well as some degree of local IgA generation, offer possible explanations (28).

Nevertheless, the importance of cellular immune responses in protection by influenza vaccine has long been moot, based primarily on studies in mice (181). More recently, compelling evidence in humans has been adduced that in the elderly, CTL responses associated with granzyme B production correlate better with protection than does antibody (55a, 102, 103, 150).

The picture with regard to live, attenuated influenza vaccine is clearer. The intranasal vaccine elicits both serum IgG and secretory IgA antibodies, and each class is protective, with synergy when both are present (11). However, cellular immunity induced by replicating vaccine virus may also contribute to protection against clinical symptoms (47).

Arguably, rotavirus vaccination provides the most complex and controversial puzzle with respect to definition of correlates of immunity in current vaccinology. Neutralizing antibodies, nonneutralizing antibodies, secretory antibodies, and cellular immune responses have all been proposed as correlates, and indeed, it may be that all of these play a role, depending on the situation. Differences between data obtained in mice, pigs, or humans contribute to the confusion. The subject has been well

reviewed by Franco et al. (49). The bases of neutralizing antibodies are epitopes on two surface proteins of the virus, vp4 and vp7. Soon after initial vaccination, these antibodies, of both the IgG and IgA classes, can be detected by neutralization or by ELISA, and titers of 1/200 or 1/800, respectively, offered protection against rotavirus gastroenteritis (120). Moreover, parenteral immunization with rotavirus virus-like particles (67a, 120) and passive administration to monkeys of IgG can protect (67, 194), clearly implicating antibodies produced in the intestine or diffused into the intestine as effectors. Experiments in mice and pigs suggested that intestinal antibody was more important to protection than serum antibody (16, 104, 129, 198, 199). To add to the confusion, an efficacy study of the pentavalent vaccine showed a correlation between neutralizing antibody against serotype G1, but not against other serotypes, and protection, and in that study, fecal and serum IgA did not correlate with efficacy (26).

On the other hand, the vp6 internal protein of rotaviruses induces a $CD4^+$-mediated lymphocyte proliferation response with production of gamma interferon that correlates with long-term protection after vaccination of mice and pigs (15, 72, 105, 200). Thus, the interim conclusions seem to be that neutralizing antibodies diffused into the intestine or locally produced there are responsible for homotypic short-term protection but that broadening of either antibody or cellular responses in the intestine mediates heterotypic and long-term protection. Despite this complex situation, measurement of serum IgA responses after oral vaccination provides a surrogate for stimulation of intestinal immune responses, and thus protection (49).

Vaccines against human papillomaviruses are based on virus-like particles of the L1 protein that stimulate both type-specific antibodies and cellular responses (135). However, in animal models of vaccination, passive antibody is sufficient for protection (18, 50, 171, 177), and the high level of vaccine efficacy against infection in humans suggests that antibody is the effector mechanism (51, 123). Antibody to papillomavirus can be measured by a pseudovirus-based neutralization assay, as well as by ELISA (131). Serum antibody does transudate into the cervix (111), and as papillomaviruses infect through minor abrasions in the skin and mucosa, it is likely that antibody prevents cell entry at those sites. Efficacy has been maintained for 6 to 7 years postvaccination (152), but although the level of antibody needed for protection and the role of B-cell memory if antibody wanes have not been established (70), studies in animals suggest that very low levels are protective (171).

RABIES

Rabies is a viral agent introduced into subcutaneous tissue that is transported to the brain and spinal cord after attachment to peripheral nerve axons. However, the virus has a phase of slow replication and persistence in subcutaneous tissues during which prevention of attachment to neurons by antibody is possible (35). Both preexposure and postexposure vaccinations seek to elicit the presence of antibody to the rabies glycoprotein, which is responsible for viral attachment to cellular receptors. The correlate of immunity has been redundantly established as 0.5 IU/ml (a neutralization titer of about 1/5) in experimental animals and verified by absence of failures in humans possessing that level (196).

ZOSTER

Zoster consists of a reactivation of varicella virus from latency in dorsal route ganglia owing to loss of cellular immunity due to age or immunosuppression. The vaccine, although composed of live varicella virus, acts through restimulation of flagging cellular responses (84, 122). Accordingly, it is not surprising that $CD4^+$ proliferative responses correlate with protection, although no specific protective value has been established (190). Nevertheless, vaccinees have had reduced incidence of zoster over a period of at least 7 years (162), during which, on average, they have maintained their renewed $CD4^+$ responses to varicella antigen.

CONCLUSIONS

This review has shown that after the administration of nearly all vaccines, with the exceptions of BCG and zoster, prevention of infection correlates with the induction of specific antibodies. However, the situation is far from simple: antibodies must be present at the site of replication on the mucosae or in specific organs and must have sufficient breadth to affect heterologous serotypes, if they exist. Moreover, $CD4^+$ responses, key to B-cell help and cytokine production, are sometimes better correlates of protection than antibody titers. Although I have sought to identify single correlates, for many of the vaccines considered above, multiple immune responses interact to protect. B-cell memory is crucial to prolonged protection after vaccination and is dependent on the magnitude of the innate immune response that enhances adaptive cellular responses (21). Nevertheless, the generalization holds that antibodies prevent infection whereas cellular responses control infection once replication has been established. It is likely that vaccines of the future, such as those for HIV, will obey the same paradigm (61, 83, 140).

ACKNOWLEDGMENTS

I thank the following colleagues who reviewed parts of this paper: Ann Gershon, Diane Griffin, Scott Halstead, Keith Klugman, Paul Offit, and Mark Slifka.

REFERENCES

1. **Abebe, F., and G. Bjune.** 2009. The protective role of antibody responses during Mycobacterium tuberculosis infection. Clin. Exp. Immunol. **157:** 235–243.
2. **al-Attar, I., J. Reisman, M. Muehlmann, and K. McIntosh.** 1995. Decline of measles antibody titers after immunization in human immunodeficiency virus-infected children. Pediatr. Infect. Dis. J. **14:**149–151.
3. **Albrecht, P., K. Herrmann, and G. R. Burns.** 1981. Role of virus strain in conventional and enhanced measles plaque neutralization test. J. Virol. Methods **3:**251–260.
4. **Allmendinger, J., F. Paradies, M. Kamprad, T. Richter, B. Pustowoit, and U. G. Liebert.** 2010. Determination of rubella virus-specific cell-mediated immunity using IFN gamma-ELISpot. J. Med. Virol. **82:**335–340.
5. **Amanna, I. J., M. K. Slifka, and S. Crotty.** 2006. Immunity and immunological memory following smallpox vaccination. Immunol. Rev. **211:**320–337.
6. **Anderson, P., D. L. Ingram, M. E. Pichichero, and G. Peter.** 2000. A high degree of natural immunologic priming to the capsular polysaccharide may not prevent Haemophilus influenzae type b meningitis. Pediatr. Infect. Dis. J. **19:**589–591.
7. **Asabe, S., S. F. Wieland, P. K. Chattopadhyay, M. Roederer, R. E. Engle, R. H. Purcell, and F. V. Chisari.** 2009. The size of the viral inoculum

contributes to the outcome of hepatitis B virus infection. J. Virol. **83:**9652–9662.
8. **Balsitis, S. J., K. L. Williams, R. Lachica, D. Flores, J. L. Kyle, E. Mehlhop, S. Johnson, M. S. Diamond, P. R. Beatty, and E. Harris.** 2010. Lethal antibody enhancement of dengue disease in mice is prevented by Fc modification. PLoS Pathog. **6:**e1000790.
9. **Barskey, A. E., J. W. Glasser, and C. W. LeBaron.** 2009. Mumps resurgences in the United States: a historical perspective on unexpected elements. Vaccine **27:**6186–6195.
10. **Bellanti, J. A., R. L. Sanga, B. Klutinis, B. Brandt, and M. S. Artenstein.** 1969. Antibody responses in serum and nasal secretions of children immunized with inactivated and attenuated measles-virus vaccines. N. Engl. J. Med. **280:**628–633.
11. **Belshe, R. B., W. C. Gruber, P. M. Mendelman, H. B. Mehta, K. Mahmood, K. Reisinger, J. Treanor, K. Zangwill, F. G. Hayden, D. I. Bernstein, K. Kotloff, J. King, P. A. Piedra, S. L. Block, L. Yan, and M. Wolff.** 2000. Correlates of immune protection induced by live, attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine. J. Infect. Dis. **181:**1133–1137.
12. **Benhnia, M. R., M. M. McCausland, H. P. Su, K. Singh, J. Hoffmann, D. H. Davies, P. L. Felgner, S. Head, A. Sette, D. N. Garboczi, and S. Crotty.** 2008. Redundancy and plasticity of neutralizing antibody responses are cornerstone attributes of the human immune response to the smallpox vaccine. J. Virol. **82:**3751–3768.
13. **Bizzini, B.** 1984. Tetanus, p. 37–68. *In* R. Germanier (ed.), Bacterial vaccines. Harcourt Brace Jovanovich, New York, NY.
14. **Björkholm, B., M. Bottiger, B. Christenson, and L. Hagberg.** 1986. Antitoxin antibody levels and the outcome of illness during an outbreak of diphtheria among alcoholics. Scand. J. Infect. Dis. **18:**235–239.
15. **Blutt, S. E., K. L. Warfield, M. K. Estes, and M. E. Conner.** 2008. Differential requirements for T cells in viruslike particle- and rotavirus-induced protective immunity. J. Virol. **82:**3135–3138.
16. **Blutt, S. E., K. L. Warfield, C. M. O'Neal, M. K. Estes, and M. E. Conner.** 2006. Host, viral, and vaccine factors that determine protective efficacy induced by rotavirus and virus-like particles (VLPs). Vaccine **24:**1170–1179.
17. **Borrow, R., P. Balmer, and E. Miller.** 2005. Meningococcal surrogates of protection—serum bactericidal antibody activity. Vaccine **23:**2222–2227.
18. **Breitburd, F., R. Kirnbauer, N. L. Hubbert, B. Nonnenmacher, C. Trin-Dinh-Desmarquet, G. Orth, J. T. Schiller, and D. R. Lowy.** 1995. Immunization with viruslike particles from cottontail rabbit papillomavirus (CRPV) can protect against experimental CRPV infection. J. Virol. **69:**3959–3963.
19. **Buisman, A. M., F. Abbink, R. M. Schepp, J. A. Sonsma, T. Herremans, and T. G. Kimman.** 2008. Preexisting poliovirus-specific IgA in the circulation correlates with protection against virus excretion in the elderly. J. Infect. Dis. **197:**698–706.
20. **Buisman, A. M., C. G. de Rond, K. Ozturk, H. I. Ten Hulscher, and R. S. van Binnendijk.** 2009. Long-term presence of memory B-cells specific for different vaccine components. Vaccine **28:**179–186.
21. **Castellino, F., G. Galli, G. G. Del, and R. Rappuoli.** 2009. Generating memory with vaccination. Eur. J. Immunol. **39:**2100–2105.
22. **Chamot, E., L. Toscani, P. Egger, D. Germann, and C. Bourquin.** 1998. Estimation of the efficacy of three strains of mumps vaccines during an epidemic of mumps in the Geneva canton (Switzerland). Rev. Epidemiol. Sante Publique **46:**100–107.
23. **Chan, W., M. Petric, E. Wang, G. Koren, S. Read, and V. Blanchette.** 1990. Response to hepatitis B immunization in children with hemophilia: relationship to infection with human immunodeficiency virus type 1. J. Pediatr. **117:**427–430.
24. **Chen, R. T., L. E. Markowitz, P. Albrecht, J. A. Stewart, L. M. Mofenson, S. R. Preblud, and W. A. Orenstein.** 1990. Measles antibody: reevaluation of protective titers. J. Infect. Dis. **162:**1036–1042.
25. **Cherry, J. D., J. Gornbein, U. Heininger, and K. Stehr.** 1998. A search for serologic correlates of immunity to Bordetella pertussis cough illnesses. Vaccine **16:**1901–1906.
26. **Ciarlet, M., and F. Schodel.** 2009. Development of a rotavirus vaccine: clinical safety, immunogenicity, and efficacy of the pentavalent rotavirus vaccine, RotaTeq. Vaccine **27**(Suppl. 6)**:**G72–G81.
27. **Clements, D. A., C. B. Armstrong, A. M. Ursano, M. M. Moggio, E. B. Walter, and C. M. Wilfert.** 1995. Over five-year follow-up of Oka/Merck varicella vaccine recipients in 465 infants and adolescents. Pediatr. Infect. Dis. J. **14:**874–879.
28. **Clements, M. L., and B. R. Murphy.** 1986. Development and persistence of local and systemic antibody responses in adults given live attenuated or inactivated influenza A virus vaccine. J. Clin. Microbiol. **23:**66–72.
29. **Conrad, M. E., and S. M. Lemon.** 1987. Prevention of endemic icteric viral hepatitis by administration of immune serum gamma globulin. J. Infect. Dis. **156:**56–63.
30. **Coursaget, P., D. Leboulleux, M. Soumare, P. le Cann, B. Yvonnet, J. P. Chiron, A. M. Coll-Seck, and I. Diop-Mar.** 1994. Twelve-year follow-up study of hepatitis B immunization of Senegalese infants. J. Hepatol. **21:**250–254.
31. **Dagan, R., N. Givon-Lavi, D. Fraser, M. Lipsitch, G. R. Siber, and R. Kohberger.** 2005. Serum serotype-specific pneumococcal anticapsular immunoglobulin G concentrations after immunization with a 9-valent conjugate pneumococcal vaccine correlate with nasopharyngeal acquisition of pneumococcus. J. Infect. Dis. **192:**367–376.
32. **Davies, J. R., and E. A. Grilli.** 1989. Natural or vaccine-induced antibody as a predictor of immunity in the face of natural challenge with influenza viruses. Epidemiol. Infect. **102:**325–333.
33. **Dayan, G. H., and S. Rubin.** 2008. Mumps outbreaks in vaccinated populations: are available mumps vaccines effective enough to prevent outbreaks? Clin. Infect. Dis. **47:**1458–1467.
34. **de Moraes-Pinto, M. I., R. S. Oruamabo, F. P. Igbagiri, M. C. Chan, S. M. Prado, M. D. Vancetto, P. M. Johnson, and C. A. Hart.** 1995. Neonatal tetanus despite immunization and protective antitoxin antibody. J. Infect. Dis. **171:**1076–1077.
35. **Dietzschold, B., M. Schnell, and H. Koprowski.** 2005. Pathogenesis of rabies. Curr. Top. Microbiol. Immunol. 2005 **292:**45–56.
36. **Dokmetjian, J., C. D. Valle, V. Lavigne, P. V. Eriksson, and M. A. Manghi.** 1998. Relationship between structure and neutralizing activity of rabbit tetanus antibodies elicited by acellular and whole-cell pertussis DTP vaccines. Vaccine **16:**672–677.
37. **Edsall, G.** 1959. Specific prophylaxis of tetanus. J. Am. Med. Assoc. **171:**417–427.
38. **Edwards, K. M.** 2001. Development, acceptance, and use of immunologic correlates of protection in monitoring the effectiveness of combination vaccines. Clin. Infect. Dis. **33**(Suppl. 4)**:**S274–S277.
39. **Eichelberger, M., H. Golding, M. Hess, J. Weir, K. Subbarao, C. J. Luke, M. Friede, and D. Wood.** 2008. FDA/NIH/WHO public workshop on immune correlates of protection against influenza A viruses in support of pandemic vaccine development, Bethesda, Maryland, US, December 10–11, 2007. Vaccine **26:**4299–4303.
40. **Ennis, F. A.** 1969. Immunity to mumps in an institutional epidemic. Correlation of insusceptibility to mumps with serum plaque neutralizing and hemagglutination-inhibiting antibodies. J. Infect. Dis. **119:**654–657.
41. **Faden, H., J. F. Modlin, M. L. Thoms, A. M. McBean, M. B. Ferdon, and P. L. Ogra.** 1990. Comparative evaluation of immunization with live attenuated and enhanced-potency inactivated trivalent poliovirus vaccines in childhood: systemic and local immune responses. J. Infect. Dis. **162:**1291–1297.
42. **Feavers, I., I. Knezevic, M. Powell, and E. Griffiths.** 2009. Challenges in the evaluation and licensing of new pneumococcal vaccines, 7–8 July 2008, Ottawa, Canada. Vaccine. **27:**3681–3688.
43. **Feldman, S., W. T. Hughes, and C. B. Daniel.** 1975. Varicella in children with cancer: Seventy-seven cases. Pediatrics **56:**388–397.
44. **Fernandez, J., O. S. Levine, J. Sanchez, S. Balter, L. LaClaire, J. Feris, and S. Romero-Steiner.** 2000. Prevention of Haemophilus influenzae type b colonization by vaccination: correlation with serum anti-capsular IgG concentration. J. Infect. Dis. **182:**1553–1556.
45. **Fiore, A. E., S. M. Finestone, and B. P. Bell.** 2008. Hepatitis A vaccine, p. 177–203. *In* S. A. Plotkin, W. A. Orenstein, and P. A. Offit (ed.) (ed.), Vaccines, 5th ed. Elsevier-Saunders, Philadelphia, PA.
46. **Fletcher, H. A.** 2007. Correlates of immune protection from tuberculosis. Curr. Mol. Med. **7:**319–325.
47. **Forrest, B. D., M. W. Pride, A. J. Dunning, M. R. Capeding, T. Chotpitayasunondh, J. S. Tam, R. Rappaport, J. H. Eldridge, and W. C. Gruber.** 2008. Correlation of cellular immune responses with protection against culture-confirmed influenza virus in young children. Clin. Vaccine Immunol. **15:**1042–1053.
48. **Francis, D. P., S. C. Hadler, S. E. Thompson, J. E. Maynard, D. G. Ostrow, N. Altman, E. H. Braff, P. O'Malley, D. Hawkins, F. N. Judson, K. Penley, T. Nylund, G. Christie, F. Meyers, J. N. Moore, Jr., A. Gardner, I. L. Doto, J. H. Miller, G. H. Reynolds, B. L. Murphy, C. A. Schable, B. T. Clark, J. W. Curran, and A. G. Redeker.** 1982. The prevention of hepatitis B with vaccine. Report of the Centers for Disease Control multi-center efficacy trial among homosexual men. Ann. Intern. Med. **97:**362–366.
49. **Franco, M. A., J. Angel, and H. B. Greenberg.** 2006. Immunity and correlates of protection for rotavirus vaccines. Vaccine **24:**2718–2731.
50. **Frazer, I.** 2007. Correlating immunity with protection for HPV infection. Int. J. Infect. Dis. **11**(Suppl. 2)**:**S10–S16.
51. **Future Study Group.** 2007. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N. Engl. J. Med. **356:**1915–1927.
52. **Gallagher, M. R., R. Welliver, T. Yamanaka, B. Eisenberg, M. Sun, and P. L. Ogra.** 1981. Cell-mediated immune responsiveness to measles. Its occurrence as a result of naturally acquired or vaccine-induced infection and in infants of immune mothers. Am. J. Dis. Child. **135:**48–51.
53. **Gershon, A. A., and S. P. Steinberg.** 1989. Persistence of immunity to varicella in children with leukemia immunized with live attenuated varicella vaccine. N. Engl. J. Med. **320:**892–897.
54. **Goldblatt, D., J. Southern, L. Ashton, et al.** 2010. Immunogenicity of a reduced schedule of pneumococcal conjugate vaccine in healthy infants and correlates of protection of serotype 6B in the United Kingdom. Pediatr. Infect. Dis. J. **29:**401–405.
55. **Goncalvez, A. P., C. H. Chien, K. Tubthong, I. Gorshkova, C. Roll, O.**

Donau, P. Schuck, S. Yoksan, S. D. Wang, R. H. Purcell, and C. J. Lai. 2008. Humanized monoclonal antibodies derived from chimpanzee Fabs protect against Japanese encephalitis virus in vitro and in vivo. J. Virol. **82:**7009–7021.

55a. **Goronzy, J. J., J. W. Fulbright, C. S. Crowson, G. A. Poland, W. M. O'Fallon, and C. M. Weyand.** 2001. Value of immunological markers in predicting responsiveness to influenza vaccination in elderly individuals. J. Virol. **75:**12182–12187.

56. **Goulon, M., O. Girard, S. Grosbuis, J. P. Desormeau, and M. F. Capponi.** 1972. Antitetanus antibodies. Assay before anatoxinotherapy in 64 tetanus patients. Nouv. Presse Med. **1:**3049–3050.

57. **Halstead, S. B.** 1988. Pathogenesis of dengue: challenges to molecular biology. Science **239:**476–481.

58. **Hammarlund, E., M. W. Lewis, S. G. Hansen, L. I. Strelow, J. A. Nelson, G. J. Sexton, J. M. Hanifin, and M. K. Slifka.** 2003. Duration of antiviral immunity after smallpox vaccination. Nat. Med. **9:**1131–1137.

59. **Hanekom, W. A.** 2005. The immune response to BCG vaccination of newborns. Ann. N. Y. Acad. Sci. **1062:**69–78.

60. **Hayward, A. R., and M. Herberger.** 1987. Lymphocyte responses to varicella zoster virus in the elderly. J. Clin. Immunol. **7:**174–178.

61. **Heeney, J. L., and S. A. Plotkin.** 2006. Immunological correlates of protection from HIV infection and disease. Nat. Immunol. **7:**1281–1284.

62. **Heininger, U., and J. Bonhoeffer.** 2008. Interstrain antigenic variability of mumps viruses. Clin. Infect. Dis. **46:**150–151.

63. **Hombach, J., T. Solomon, I. Kurane, J. Jacobson, and D. Wood.** 2005. Report on a WHO consultation on immunological endpoints for evaluation of new Japanese encephalitis vaccines, WHO, Geneva, 2–3 September, 2004. Vaccine **23:**5205–5211.

64. **Horowitz, M. M., W. B. Ershler, W. P. McKinney, and R. J. Battiola.** 1988. Duration of immunity after hepatitis B vaccination: efficacy of low-dose booster vaccine. Ann. Intern. Med. **108:**185–189.

65. **Ipsen, J.** 1946. Circulating antitoxin at the onset of diphtheria in 425 patients. J. Immunol. **54:**325–347.

66. **Jack, A. D., A. J. Hall, N. Maine, M. Mendy, and H. C. Whittle.** 1999. What level of hepatitis B antibody is protective? J. Infect. Dis. **179:**489–492.

67. **Jiang, B., J. R. Gentsch, and R. I. Glass.** 2002. The role of serum antibodies in the protection against rotavirus disease: an overview. Clin. Infect. Dis. **34:**1351–1361.

67a. **Jiang, B., J. R. Gentsch, and R. I. Glass.** 2008. Inactivated rotavirus vaccines: a priority for accelerated vaccine development. Vaccine **26:**6754–6758.

68. **Jódar, L., J. Butler, G. Carlone, R. Dagan, D. Goldblatt, H. Kayhty, K. Klugman, B. Plikaytis, G. Siber, R. Kohberger, I. Chang, and T. Cherian.** 2003. Serological criteria for evaluation and licensure of new pneumococcal conjugate vaccine formulations for use in infants. Vaccine **21:**3265–3272.

69. **Johnson, C. E., T. Stancin, D. Fattlar, L. P. Rome, and M. L. Kumar.** 1997. A long-term prospective study of varicella vaccine in healthy children. Pediatrics **100:**761–766.

70. **Joura, E. A., S. K. Kjaer, C. M. Wheeler, K. Sigurdsson, O. E. Iversen, M. Hernandez-Avila, G. Perez, D. R. Brown, L. A. Koutsky, E. H. Tay, P. Garcia, K. A. Ault, S. M. Garland, S. Leodolter, S. E. Olsson, G. W. Tang, D. G. Ferris, J. Paavonen, M. Lehtinen, M. Steben, X. Bosch, J. Dillner, R. J. Kurman, S. Majewski, N. Munoz, E. R. Myers, L. L. Villa, F. J. Taddeo, C. Roberts, A. Tadesse, J. Bryan, L. C. Lupinacci, K. E. Giacoletti, S. Lu, S. Vuocolo, T. M. Hesley, R. M. Haupt, and E. Barr.** 2008. HPV antibody levels and clinical efficacy following administration of a prophylactic quadrivalent HPV vaccine. Vaccine **26:**6844–6851.

71. **Kaaijk, P., B. van der Zeijst, M. Boog, and C. Hoitink.** 2008. Increased mumps incidence in the Netherlands: review on the possible role of vaccine strain and genotype. Euro. Surveill. **13:**18914.

72. **Kaufhold, R. M., J. A. Field, M. J. Caulfield, S. Wang, H. Joseph, M. A. Wooters, T. Green, H. F. Clark, D. Krah, and J. G. Smith.** 2005. Memory T-cell response to rotavirus detected with a gamma interferon enzyme-linked immunospot assay. J. Virol. **79:**5684–5694.

73. **Käyhty, H.** 1994. Difficulties in establishing a serological correlate of protection after immunization with Haemophilus influenzae conjugate vaccines. Biologicals **22:**397–402. doi:S1045-1056(84)71062-1.

74. **Kayhty, H., H. Peltola, V. Karanko, and P. H. Makela.** 1983. The protective level of serum antibodies to the capsular polysaccharide of Haemophilus influenzae type b. J. Infect. Dis. **147:**1100.

75. **Khader, S. A., G. K. Bell, J. E. Pearl, J. J. Fountain, J. Rangel-Moreno, G. E. Cilley, F. Shen, S. M. Eaton, S. L. Gaffen, S. L. Swain, R. M. Locksley, L. Haynes, T. D. Randall, and A. M. Cooper.** 2007. IL-23 and IL-17 in the establishment of protective pulmonary CD4+ T cell responses after vaccination and during Mycobacterium tuberculosis challenge. Nat. Immunol. **8:**369–377.

76. **Krasinski, K., and W. Borkowsky.** 1989. Measles and measles immunity in children infected with human immunodeficiency virus. JAMA **261:**2512–2516.

77. **Kreil, T. R., I. Burger, M. Bachmann, S. Fraiss, and M. M. Eibl.** 1997. Antibodies protect mice against challenge with tick-borne encephalitis virus (TBEV)-infected macrophages. Clin. Exp. Immunol. **110:**358–361.

78. **Kyle, J. L., S. J. Balsitis, L. Zhang, P. R. Beatty, and E. Harris.** 2008. Antibodies play a greater role than immune cells in heterologous protection against secondary dengue virus infection in a mouse model. Virology **380:**296–303.

79. **LaRussa, P., S. P. Steinberg, E. Shapiro, et al.** 2000. Letter. Nat. Med. **6:**1299.

80. **LaRussa, P., S. P. Steinberg, E. Shapiro, M. Vazquez, and A. A. Gershon.** 2000. Varicella vaccine revisited. Nat. Med. **6:**1299–1300.

81. **Lee, L. H., C. E. Frasch, L. A. Falk, D. L. Klein, and C. D. Deal.** 2003. Correlates of immunity for pneumococcal conjugate vaccines. Vaccine **21:**2190–2196.

82. **Lee, Y. C., D. F. Kelly, L. M. Yu, M. P. Slack, R. Booy, P. T. Heath, C. A. Siegrist, R. E. Moxon, and A. J. Pollard.** 2008. Haemophilus influenzae type b vaccine failure in children is associated with inadequate production of high-quality antibody. Clin. Infect. Dis. **46:**186–192.

83. **Letvin, N. L.** 2007. Correlates of immune protection and the development of a human immunodeficiency virus vaccine. Immunity. **27:**366–369.

84. **Levin, M. J., M. N. Oxman, J. H. Zhang, G. R. Johnson, H. Stanley, A. R. Hayward, M. J. Caulfield, M. R. Irwin, J. G. Smith, J. Clair, I. S. Chan, H. Williams, R. Harbecke, R. Marchese, S. E. Straus, A. Gershon, and A. Weinberg.** 2008. Varicella-zoster virus-specific immune responses in elderly recipients of a herpes zoster vaccine. J. Infect. Dis. **197:**825–835.

85. **Li, S., I. S. Chan, H. Matthews, J. F. Heyse, C. Y. Chan, B. J. Kuter, K. M. Kaplan, S. J. Vessey, and J. C. Sadoff.** 2002. Inverse relationship between six week postvaccination varicella antibody response to vaccine and likelihood of long term breakthrough infection. Pediatr. Infect. Dis. J. **21:**337–342.

86. **Liao, S. S., R. C. Li, H. Li, J. Y. Yang, X. J. Zeng, J. Gong, S. S. Wang, Y. P. Li, and K. L. Zhang.** 1999. Long-term efficacy of plasma-derived hepatitis B vaccine: a 15-year follow-up study among Chinese children. Vaccine **17:**2661–2666.

87. **Little, S. F., B. E. Ivins, P. F. Fellows, M. L. Pitt, S. L. Norris, and G. P. Andrews.** 2004. Defining a serological correlate of protection in rabbits for a recombinant anthrax vaccine. Vaccine **22:**422–430.

88. **Liu, L., Q. Zhong, T. Tian, K. Dubin, S. K. Athale, and T. S. Kupper.** 2010. Epidermal injury and infection during poxvirus immunization is crucial for the generation of highly protective T cell-mediated immunity. Nat. Med. **16:**224–227.

89. **Livorsi, D. J., M. Eaton, and J. Glass.** 2010. Generalized tetanus despite prior vaccination and a protective level of anti-tetanus antibodies. Am. J. Med. Sci. **339:**200–201.

90. **Lucas, A. H., and D. M. Granoff.** 2001. Imperfect memory and the development of Haemophilus influenzae type B disease. Pediatr. Infect. Dis. J. **20:**235–239.

91. **Ludwig, B., F. B. Kraus, R. Allwinn, S. Keim, H. W. Doerr, and S. Buxbaum.** 2006. Loss of varicella zoster virus antibodies despite detectable cell mediated immunity after vaccination. Infection **34:**222–226.

92. **Lumio, J. T., R. Olander, O. Melnick, et al.** 2003. What is a protective level of diphtheria antitoxin antibodies?, abstr. G-1660. Abstr. 43rd Intersci. Conf. Antimicrob. Agents Chemother.

93. **Mack, T. M., J. Noble, Jr., and D. B. Thomas.** 1972. A prospective study of serum antibody and protection against smallpox. Am. J. Trop. Med. Hyg. **21:**214–218.

94. **Mäkelä, P. H., H. Peltola, H. Kayhty, H. Jousimies, O. Pettay, E. Ruoslahti, A. Sivonen, and O. V. Renkonen.** 1977. Polysaccharide vaccines of group A Neisseria meningtitidis and Haemophilus influenzae type b: a field trial in Finland. J. Infect. Dis. **136**(Suppl.)**:**S43–S50.

95. **Marine, W. M., T. D. Chin, and C. R. Gravelle.** 1962. Limitation of fecal and pharyngeal poliovirus excretion in Salk-vaccinated children. A family study during a type 1 poliomyelitis epidemic. Am. J. Hyg. **76:**173–195.

96. **Maslanka, S. E., J. W. Tappero, B. D. Plikaytis, R. S. Brumberg, J. K. Dykes, L. L. Gheesling, K. B. Donaldson, A. Schuchat, J. Pullman, M. Jones, J. Bushmaker, and G. M. Carlone.** 1998. Age-dependent Neisseria meningitidis serogroup C class-specific antibody concentrations and bactericidal titers in sera from young children from Montana immunized with a licensed polysaccharide vaccine. Infect. Immun. **66:**2453–2459.

97. **Mason, R. A., N. M. Tauraso, R. O. Spertzel, and R. K. Ginn.** 1973. Yellow fever vaccine: direct challenge of monkeys given graded doses of 17D vaccine. Appl. Microbiol. **25:**539–544.

98. **Mathias, R. G., W. G. Meekison, T. A. Arcand, and M. T. Schechter.** 1989. The role of secondary vaccine failures in measles outbreaks. Am. J. Public Health **79:**475–478.

99. **Matter, L., K. Kogelschatz, and D. Germann.** 1997. Serum levels of rubella virus antibodies indicating immunity: response to vaccination of subjects with low or undetectable antibody concentrations. J. Infect. Dis. **175:**749–755.

100. **McComb, J. A.** 1964. The prophylactic dose of homologous tetanus antitoxin. N. Engl. J. Med. **270:**175–178.

101. **McCool, T. L., T. R. Cate, G. Moy, and J. N. Weiser.** 2002. The immune response to pneumococcal proteins during experimental human carriage. J. Exp. Med. **195:**359–365.

102. **McElhaney, J. E., C. Ewen, X. Zhou, K. P. Kane, D. Xie, W. D. Hager, M. B.**

Barry, A. Kleppinger, Y. Wang, and R. C. Bleackley. 2009. Granzyme B: correlates with protection and enhanced CTL response to influenza vaccination in older adults. Vaccine **27:**2418–2425. doi:S0264-410X(09)00319-3.
103. **McElhaney, J. E., D. Xie, W. D. Hager, M. B. Barry, Y. Wang, A. Kleppinger, C. Ewen, K. P. Kane, and R. C. Bleackley.** 2006. T cell responses are better correlates of vaccine protection in the elderly. J. Immunol. **176:**6333–6339. doi:176/10/6333.
104. **McNeal, M. M., R. L. Broome, and R. L. Ward.** 1994. Active immunity against rotavirus infection in mice is correlated with viral replication and titers of serum rotavirus IgA following vaccination. Virology **204:**642–650. doi:S0042-6822(84)71579-0.
105. **McNeal, M. M., S. C. Stone, M. Basu, J. D. Clements, A. H. Choi, and R. L. Ward.** 2007. IFN-gamma is the only anti-rotavirus cytokine found after in vitro stimulation of memory CD4+ T cells from mice immunized with a chimeric VP6 protein. Viral Immunol. **20:**571–584. doi:10.1089/vim.2007.0055.
106. **McShane, H.** 2004. Developing an improved vaccine against tuberculosis. Exp. Rev. Vaccines **3:**299–306.
107. **Michalik, D. E., S. P. Steinberg, P. S. Larussa, K. M. Edwards, P. F. Wright, A. M. Arvin, H. A. Gans, and A. A. Gershon.** 2008. Primary vaccine failure after 1 dose of varicella vaccine in healthy children. J. Infect. Dis. **197:**944–949. doi:10.1086/529043.
108. **Milne, A., and J. Waldon.** 1992. Recombinant DNA hepatitis B vaccination in teenagers: effect of a booster at 5 1/2 years. J. Infect. Dis. **166:**942.
109. **Murdin, A. D., L. Barreto, and S. Plotkin.** 1996. Inactivated poliovirus vaccine: past and present experience. Vaccine **14:**735–746.
110. **Nalin, D. R., B. J. Kuter, L. Brown, C. Patterson, G. B. Calandra, A. Werzberger, D. Shouval, E. Ellerbeck, S. L. Block, and R. Bishop.** 1993. Worldwide experience with the CR326F-derived inactivated hepatitis A virus vaccine in pediatric and adult populations: an overview. J. Hepatol. **18**(Suppl. 2)**:**S51–S55.
111. **Nardelli-Haefliger, D., D. Wirthner, J. T. Schiller, D. R. Lowy, A. Hildesheim, F. Ponci, and G. P. De.** 2003. Specific antibody levels at the cervix during the menstrual cycle of women vaccinated with human papillomavirus 16 virus-like particles. J. Natl. Cancer Inst. **95:**1128–1137.
112. **Nayak, B., S. Kumar, J. M. DiNapoli, A. Paldurai, D. R. Perez, P. L. Collins, and S. K. Samal.** 2010. Contributions of the avian influenza virus HA, NA, and M2 surface proteins to the induction of neutralizing antibodies and protective immunity. J. Virol. **84:**2408–2420.
113. **Newell, K. W., D. R. Leblanc, G. Edsall, L. Levine, H. Christensen, M. H. Montouri, and N. Ramirez.** 1971. The serological assessment of a tetanus toxoid field trial. Bull. World Health Organ. **45:**773–785.
114. **Nöjd, J., T. Tecle, A. Samuelsson, and C. Orvell.** 2001. Mumps virus neutralizing antibodies do not protect against reinfection with a heterologous mumps virus genotype. Vaccine **19:**1727–1731.
115. **Ogra, P. L., and D. T. Karzon.** 1969. Distribution of poliovirus antibody in serum, nasopharynx and alimentary tract following segmental immunization of lower alimentary tract with poliovaccine. J. Immunol. **102:**1423–1430.
116. **Ogra, P. L., D. Kerr-Grant, G. Umana, J. Dzierba, and D. Weintraub.** 1971. Antibody response in serum and nasopharynx after naturally acquired and vaccine-induced infection with rubella virus. N. Engl. J. Med. **285:**1333–1339.
117. **Onorato, I. M., J. F. Modlin, A. M. McBean, M. L. Thoms, G. A. Losonski, and R. H. Bernier.** 1991. Mucosal immunity induced by enhanced-potency inactivated and oral polio vaccines. J. Infect. Dis. **163:**1–6.
118. **Orenstein, W. A., P. Albrecht, K. L. Herrmann, R. Bernier, K. J. Bart, and E. Z. Rovira.** 1987. The plaque-neutralization test as a measure of prior exposure to measles virus. J. Infect. Dis. **155:**146–149.
119. **Orme, I. M.** 1993. The role of CD8+ T cells in immunity to tuberculosis infection. Trends Microbiol. **1:**77–78.
120. **O'Ryan, M. L., D. O. Matson, M. K. Estes, and L. K. Pickering.** 1994. Anti-rotavirus G type-specific and isotype-specific antibodies in children with natural rotavirus infections. J. Infect. Dis. **169:**504–511.
121. **O'Shea, S., J. M. Best, and J. E. Banatvala.** 1983. Viremia, virus excretion, and antibody responses after challenge in volunteers with low levels of antibody to rubella virus. J. Infect. Dis. **148:**639–647.
122. **Oxman, M. N., M. J. Levin, G. R. Johnson, K. E. Schmader, S. E. Straus, L. D. Gelb, R. D. Arbeit, M. S. Simberkoff, A. A. Gershon, L. E. Davis, A. Weinberg, K. D. Boardman, H. M. Williams, J. H. Zhang, P. N. Peduzzi, C. E. Beisel, V. A. Morrison, J. C. Guatelli, P. A. Brooks, C. A. Kauffman, C. T. Pachucki, K. M. Neuzil, R. F. Betts, P. F. Wright, M. R. Griffin, P. Brunell, N. E. Soto, A. R. Marques, S. K. Keay, R. P. Goodman, D. J. Cotton, J. W. Gnann, Jr., J. Loutit, M. Holodniy, W. A. Keitel, G. E. Crawford, S. S. Yeh, Z. Lobo, J. F. Toney, R. N. Greenberg, P. M. Keller, R. Harbecke, A. R. Hayward, M. R. Irwin, T. C. Kyriakides, C. Y. Chan, I. S. Chan, W. W. Wang, P. W. Annunziato, and J. L. Silber.** 2005. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N. Engl. J. Med. **352:**2271–2284.
123. **Paavonen, J., P. Naud, J. Salmeron, C. M. Wheeler, S. N. Chow, D. Apter, H. Kitchener, X. Castellsague, J. C. Teixeira, S. R. Skinner, J. Hedrick, U. Jaisamrarn, G. Limson, S. Garland, A. Szarewski, B. Romanowski, F. Y. Aoki, T. F. Schwarz, W. A. Poppe, F. X. Bosch, D. Jenkins, K. Hardt, T. Zahaf, D. Descamps, F. Struyf, M. Lehtinen, G. Dubin, and M. Greenacre.** 2009. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet **374:**301–314.
124. **Pan, C. H., A. Valsamakis, T. Colella, N. Nair, R. J. Adams, F. P. Polack, C. E. Greer, S. Perri, J. M. Polo, and D. E. Griffin.** 2005. Inaugural article: modulation of disease, T cell responses, and measles virus clearance in monkeys vaccinated with H-encoding alphavirus replicon particles. Proc. Natl. Acad. Sci. U. S. A. **102:**11581–11588.
125. **Panchanathan, V., G. Chaudhri, and G. Karupiah.** 2006. Protective immunity against secondary poxvirus infection is dependent on antibody but not on CD4 or CD8 T-cell function. J. Virol. **80:**6333–6338.
126. **Panchanathan, V., G. Chaudhri, and G. Karupiah.** 2008. Correlates of protective immunity in poxvirus infection: where does antibody stand? Immunol. Cell Biol. **86:**80–86.
127. **Paradiso, P.** 2009. Essential criteria for evaluation of pneumococcal conjugate vaccine candidates. Vaccine **27**(Suppl 3)**:**C15–C18.
128. **Parenti, D. L., M. Gillet, E. Sennewald, et al.** 2007. Correlate of protection for Lyme disease (LD) using lYMErix recombinant adjuvant *Borrelia burgdorferi* outer surface lipoprotein A (L-OspA) vaccine, abstr. 704. Abstr. Infect. Dis. Soc. Am. (IDSA) 36th Annu. Meet., Denver, CO.
129. **Parez, N., C. Fourgeux, A. Mohamed, C. Dubuquoy, M. Pillot, A. Dehee, A. Charpilienne, D. Poncet, I. Schwartz-Cornil, and A. Garbarg-Chenon.** 2006. Rectal immunization with rotavirus virus-like particles induces systemic and mucosal humoral immune responses and protects mice against rotavirus infection. J. Virol. **80:**1752–1761.
130. **Pasetti, M. F., K. Ramirez, A. Resendiz-Albor, J. Ulmer, E. M. Barry, and M. M. Levine.** 2009. Sindbis virus-based measles DNA vaccines protect cotton rats against respiratory measles: relevance of antibodies, mucosal and systemic antibody-secreting cells, memory B cells, and Th1-type cytokines as correlates of immunity. J. Virol. **83:**2789–2794.
131. **Pastrana, D. V., C. B. Buck, Y. Y. Pang, C. D. Thompson, P. E. Castle, P. C. FitzGerald, K. S. Kruger, D. R. Lowy, and J. T. Schiller.** 2004. Reactivity of human sera in a sensitive, high-throughput pseudovirus-based papillomavirus neutralization assay for HPV16 and HPV18. Virology **321:**205–216.
132. **Peltola, H., H. Makela, H. Kayhty, H. Jousimies, E. Herva, K. Hallstrom, A. Sivonen, O. V. Renkonen, O. Pettay, V. Karanko, P. Ahvonen, and S. Sarna.** 1977. Clinical efficacy of meningococcus group A capsular polysaccharide vaccine in children three months to five years of age. N. Engl. J. Med. **297:**686–691.
133. **Permar, S. R., S. A. Klumpp, K. G. Mansfield, A. A. Carville, D. A. Gorgone, M. A. Lifton, J. E. Schmitz, K. A. Reimann, F. P. Polack, D. E. Griffin, and N. L. Letvin.** 2004. Limited contribution of humoral immunity to the clearance of measles viremia in rhesus monkeys. J. Infect. Dis. **190:**998–1005.
134. **Permar, S. R., S. A. Klumpp, K. G. Mansfield, W. K. Kim, D. A. Gorgone, M. A. Lifton, K. C. Williams, J. E. Schmitz, K. A. Reimann, M. K. Axthelm, F. P. Polack, D. E. Griffin, and N. L. Letvin.** 2003. Role of CD8(+) lymphocytes in control and clearance of measles virus infection of rhesus monkeys. J. Virol. **77:**4396–4400.
135. **Pinto, L. A., J. Edwards, P. E. Castle, C. D. Harro, D. R. Lowy, J. T. Schiller, D. Wallace, W. Kopp, J. W. Adelsberger, M. W. Baseler, J. A. Berzofsky, and A. Hildesheim.** 2003. Cellular immune responses to human papillomavirus (HPV)-16 L1 in healthy volunteers immunized with recombinant HPV-16 L1 virus-like particles. J. Infect. Dis. **188:**327–338.
136. **Pitt, M. L., S. F. Little, B. E. Ivins, P. Fellows, J. Barth, J. Hewetson, P. Gibbs, M. Dertzbaugh, and A. M. Friedlander.** 2001. In vitro correlate of immunity in a rabbit model of inhalational anthrax. Vaccine **19:**4768–4773.
137. **Plotkin, S. A.** 1999. Vaccination against the major infectious diseases. C.R. Acad. Sci. III **322:**943–951.
138. **Plotkin, S. A.** 2001. Immunologic correlates of protection induced by vaccination. Pediatr. Infect. Dis. J. **20:**63–75.
139. **Plotkin, S. A.** 2008. Vaccines: correlates of vaccine-induced immunity. Clin. Infect. Dis. **47:**401–409.
140. **Plotkin, S. A.** 2009. Sang froid in a time of trouble: is a vaccine against HIV possible? J. Int. AIDS Soc. **12:**2.
141. **Plotkin, S. A., and S. E. Reef.** 2008. Rubella vaccines, p. 735–771. *In* S. A. Plotkin, W. A. Orenstein, and P. A. Offit (ed.), Vaccines, 5th ed. Elsevier-Saunders, Philadelphia, PA.
142. **Plotkin, S. A., S. E. Starr, H. M. Friedman, et al.** 1989. Protective effects of Towne cytomegalovirus vaccine against low-passage cytomegalovirus administered as a challenge. J. Infect. Dis. **159:**860–865.
143. **Plotkin, S. A., and E. Vidor.** 2008. Poliovirus vaccine—inactivated, p. 605–630. *In* S. A. Plotkin, W. A. Orenstein, and P. A. Offit (ed.), Vaccines, 5th ed. Elsevier-Saunders, Philadelphia, PA.
144. **Polack, F. P., S. H. Lee, S. Permar, E. Manyara, H. G. Nousari, Y. Jeng, F. Mustafa, A. Valsamakis, R. J. Adams, H. L. Robinson, and D. E. Griffin.** 2000. Successful DNA immunization against measles: neutralizing antibody against either the hemagglutinin or fusion glycoprotein protects rhesus macaques without evidence of atypical measles. Nat. Med. **6:**776–781.

145. **Pueschel, K., A. Tietz, M. Carsillo, M. Steward, and S. Niewiesk.** 2007. Measles virus-specific CD4 T-cell activity does not correlate with protection against lung infection or viral clearance. J. Virol. **81:**8571–8578.
146. **Querec, T., S. Bennouna, S. Alkan, Y. Laouar, K. Gorden, R. Flavell, S. Akira, R. Ahmed, and B. Pulendran.** 2006. Yellow fever vaccine YF-17D activates multiple dendritic cell subsets via TLR2, 7, 8, and 9 to stimulate polyvalent immunity. J. Exp. Med. **203:**413–424.
147. **Ramsay, M. E., J. McVernon, N. J. Andrews, P. T. Heath, and M. P. Slack.** 2003. Estimating Haemophilus influenzae type b vaccine effectiveness in England and Wales by use of the screening method. J. Infect. Dis. **188:**481–485.
148. **Reich, A., O. Erlwein, S. Niewiesk, V. ter Meulen, and U. G. Liebert.** 1992. CD4+ T cells control measles virus infection of the central nervous system. Immunology **76:**185–191.
149. **Reuveny, S., M. D. White, Y. Y. Adar, Y. Kafri, Z. Altboum, Y. Gozes, D. Kobiler, A. Shafferman, and B. Velan.** 2001. Search for correlates of protective immunity conferred by anthrax vaccine. Infect. Immun. **69:**2888–2893.
150. **Rimmelzwaan, G. F., and J. E. McElhaney.** 2008. Correlates of protection: novel generations of influenza vaccines. Vaccine **26**(Suppl. 4)**:**D41–D44.
151. **Robbins, J. B., J. C. Parke, R. Schneerson, and J. K. Whisnant.** 1973. Quantitative measurement of "natural" and immunization-induced Haemophilus influenzae type b capsular polysaccharide antibodies. Pediatr. Res. **7:**103–110.
152. **Romanowski, B., P. C. de Borba, P. S. Naud, C. M. Roteli-Martins, N. S. De Carvalho, J. C. Teixeira, F. Aoki, B. Ramjattan, R. M. Shier, R. Somani, S. Barbier, M. M. Blatter, C. Chambers, D. Ferris, S. A. Gall, F. A. Guerra, D. M. Harper, J. A. Hedrick, D. C. Henry, A. P. Korn, R. Kroll, A. B. Moscicki, W. D. Rosenfeld, B. J. Sullivan, C. S. Thoming, S. K. Tyring, C. M. Wheeler, G. Dubin, A. Schuind, T. Zahaf, M. Greenacre, and A. Sgriobhadair.** 2009. Sustained efficacy and immunogenicity of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine: analysis of a randomised placebo-controlled trial up to 6.4 years. Lancet **374:**1975–1985.
153. **Romero-Steiner, S., D. M. Musher, M. S. Cetron, L. B. Pais, J. E. Groover, A. E. Fiore, B. D. Plikaytis, and G. M. Carlone.** 1999. Reduction in functional antibody activity against Streptococcus pneumoniae in vaccinated elderly individuals highly correlates with decreased IgG antibody avidity. Clin. Infect. Dis. **29:**281–288. doi:10.1086/520200.
154. **Rubin, S. A., L. Qi, S. A. Audet, B. Sullivan, K. M. Carbone, W. J. Bellini, P. A. Rota, L. Sirota, and J. Beeler.** 2008. Antibody induced by immunization with the Jeryl Lynn mumps vaccine strain effectively neutralizes a heterologous wild-type mumps virus associated with a large outbreak. J. Infect. Dis. **198:**508–515.
155. **Rudy, B. J., R. M. Rutstein, and J. Pinto-Martin.** 1994. Responses to measles immunization in children infected with human immunodeficiency virus. J. Pediatr. **125:**72–74.
156. **Saaka, M., B. J. Okoko, R. C. Kohberger, S. Jaffar, G. Enwere, E. E. Biney, C. Oluwalana, A. Vaughan, S. M. Zaman, L. Asthon, D. Goldblatt, B. M. Greenwood, F. T. Cutts, and R. A. Adegbola.** 2008. Immunogenicity and serotype-specific efficacy of a 9-valent pneumococcal conjugate vaccine (PCV-9) determined during an efficacy trial in The Gambia. Vaccine **26:** 3719–3726.
157. **Sabin, A. B.** 1952. Research on dengue during World War II. Am. J. Trop. Med. Hyg. **1:**30–50.
158. **Samb, B., P. Aaby, H. C. Whittle, A. M. Seck, S. Rahman, J. Bennett, L. Markowitz, and F. Simondon.** 1995. Serologic status and measles attack rates among vaccinated and unvaccinated children in rural Senegal. Pediatr. Infect. Dis. J. **14:**203–209.
159. **Santosham, M., R. Reid, D. M. Ambrosino, M. C. Wolff, J. Almeido-Hill, C. Priehs, K. M. Aspery, S. Garrett, L. Croll, S. Foster, G. Burge, P. Page, B. Zacher, R. Moxon, B. Chir, and G. R. Siber.** 1987. Prevention of *Haemophilus influenzae* type B infections in high-risk infants treated with bacterial polysaccharide immune globulin. N. Engl. J. Med. **317:**923–929.
160. **Sarkar, J. K., A. C. Mitra, and M. K. Mukherjee.** 1975. The minimum protective level of antibodies in smallpox. Bull. World Health Organ. **52:** 307–311.
161. **Savitt, A. G., P. Mena-Taboada, G. Monsalve, and J. L. Benach.** 2009. Francisella tularensis infection-derived monoclonal antibodies provide detection, protection, and therapy. Clin. Vaccine Immunol. **16:**414–422.
162. **Schmader, K. E., M. N. Oxman, R. F. Betts, et al.** 2008. Persistence of zoster vaccine efficacy, abstr. G-409. Abstr. 48th Intersci. Conf. Antimicrob. Agents Chemother.
163. **Schmidtke, P., P. Habermehl, M. Knuf, C. U. Meyer, R. Sanger, and F. Zepp.** 2005. Cell mediated and antibody immune response to inactivated hepatitis A vaccine. Vaccine **23:**5127–5132.
164. **Schwarzer, S., S. Reibel, A. B. Lang, M. M. Struck, B. Finkel, E. Gerike, A. Tischer, M. Gassner, R. Gluck, B. Stuck, and S. J. Cryz, Jr.** 1998. Safety and characterization of the immune response engendered by two combined measles, mumps and rubella vaccines. Vaccine **16:**298–304.
165. **Sebastian, S., J. T. Pinkham, J. G. Lynch, R. A. Ross, B. Reinap, L. T. Blalock, J. W. Conlan, and D. L. Kasper.** 2009. Cellular and humoral immunity are synergistic in protection against types A and B Francisella tularensis. Vaccine **27:**597–605.
166. **Shresta, S., J. L. Kyle, B. P. Robert, and E. Harris.** 2004. Early activation of natural killer and B cells in response to primary dengue virus infection in A/J mice. Virology **319:**262–273.
167. **Siber, G. R., I. Chang, S. Baker, P. Fernsten, K. L. O'Brien, M. Santosham, K. P. Klugman, S. A. Madhi, P. Paradiso, and R. Kohberger.** 2007. Estimating the protective concentration of anti-pneumococcal capsular polysaccharide antibodies. Vaccine **25:**3816–3826.
168. **Sitati, E. M., and M. S. Diamond.** 2006. CD4+ T-cell responses are required for clearance of West Nile virus from the central nervous system. J. Virol. **80:**12060–12069.
169. **Skendzel, L. P.** 1996. Rubella immunity. Defining the level of protective antibody. Am. J. Clin. Pathol. **106:**170–174.
170. **Staats, H. F., S. M. Alam, R. M. Scearce, S. M. Kirwan, J. X. Zhang, W. M. Gwinn, and B. F. Haynes.** 2007. In vitro and in vivo characterization of anthrax anti-protective antigen and anti-lethal factor monoclonal antibodies after passive transfer in a mouse lethal toxin challenge model to define correlates of immunity. Infect. Immun. **75:**5443–5452.
171. **Stanley, M., D. R. Lowy, and I. Frazer.** 2006. Prophylactic HPV vaccines: underlying mechanisms. Vaccine **24**(Suppl. 3)**:**S3–106–S3-113.
172. **Stapleton, J. T.** 1992. Passive immunization against hepatitis A. Vaccine **10**(Suppl. 1)**:**S45–S47.
173. **Storsaeter, J., H. O. Hallander, L. Gustafsson, and P. Olin.** 1998. Levels of anti-pertussis antibodies related to protection after household exposure to Bordetella pertussis. Vaccine **16:**1907–1916.
174. **Storsaeter, J., H. O. Hallander, L. Gustafsson, and P. Olin.** 2003. Low levels of antipertussis antibodies plus lack of history of pertussis correlate with susceptibility after household exposure to Bordetella pertussis. Vaccine **21:**3542–3549.
175. **Sun, W., A. Nisalak, M. Gettayacamin, K. H. Eckels, J. R. Putnak, D. W. Vaughn, B. L. Innis, S. J. Thomas, and T. P. Endy.** 2006. Protection of rhesus monkeys against dengue virus challenge after tetravalent live attenuated dengue virus vaccination. J. Infect. Dis. **193:**1658–1665.
176. **Sutter, R. W., and S. L. Cochi.** 2008. Live attenuated poliovirus vaccine, p. 631–686. *In* S. A. Plotkin, W. A. Orenstein, and P. A. Offit (ed.), Vaccines, 5th ed. Elsevier-Saunders, Phildalphia, PA.
177. **Suzich, J. A., S. J. Ghim, F. J. Palmer-Hill, W. I. White, J. K. Tamura, J. A. Bell, J. A. Newsome, A. B. Jenson, and R. Schlegel.** 1995. Systemic immunization with papillomavirus L1 protein completely prevents the development of viral mucosal papillomas. Proc. Natl. Acad. Sci. U. S. A. **92:**11553–11557.
178. **Szmuness, W., C. E. Stevens, E. A. Zang, E. J. Harley, and A. Kellner.** 1981. A controlled clinical trial of the efficacy of the hepatitis B vaccine (Heptavax B): a final report. Hepatology **1:**377–385.
179. **Tang, C., H. Yamada, K. Shibata, N. Maeda, S. Yoshida, W. Wajjwalku, N. Ohara, T. Yamada, T. Kinoshita, and Y. Yoshikai.** 2008. Efficacy of recombinant bacille Calmette-Guerin vaccine secreting interleukin-15/antigen 85B fusion protein in providing protection against Mycobacterium tuberculosis. J. Infect. Dis. **197:**1263–1274.
180. **Taranger, J., B. Trollfors, T. Lagergard, V. Sundh, D. A. Bryla, R. Schneerson, and J. B. Robbins.** 2000. Correlation between pertussis toxin IgG antibodies in postvaccination sera and subsequent protection against pertussis. J. Infect. Dis. **181:**1010–1013.
181. **Thomas, P. G., R. Keating, D. J. Hulse-Post, and P. C. Doherty.** 2006. Cell-mediated protection in influenza infection. Emerg. Infect. Dis. **12:** 48–54.
182. **Tosh, P. K., R. B. Kennedy, R. A. Vierkant, R. M. Jacobson, and G. A. Poland.** 2009. Correlation between rubella antibody levels and cytokine measures of cell-mediated immunity. Viral Immunol. **22:**451–456.
183. **Treanor, J., and P. F. Wright.** 2003. Immune correlates of protection against influenza in the human challenge model. Dev. Biol. (Basel) **115:**97–104.
184. **Trotter, C. L., M. E. Ramsay, and M. P. Slack.** 2003. Rising incidence of Haemophilus influenzae type b disease in England and Wales indicates a need for a second catch-up vaccination campaign. Commun. Dis. Public Health **6:**55–58.
185. **Tuaillon, E., Y. A. Tabaa, G. Petitjean, M. F. Huguet, G. Pajeaux, J. M. Fondere, B. Ponseille, J. Ducos, P. Blanc, and J. P. Vendrell.** 2006. Detection of memory B lymphocytes specific to hepatitis B virus (HBV) surface antigen (HBsAg) from HBsAg-vaccinated or HBV-immunized subjects by ELISPOT assay. J. Immunol. Methods **315:**144–152.
186. **Ubol, S., W. Phuklia, S. Kalayanarooj, and N. Modhiran.** 2010. Mechanisms of immune evasion induced by a complex of dengue virus and preexisting enhancing antibodies. J. Infect. Dis. **201:**923–935.
187. **Van Hattum, J., T. Maikoe, J. Poel, et al.** 1991. *In vitro* anti-HBs production by individual B cells of responders in hepatitis B vaccine who subsequently lost antibody, p. 775–776. *In* F. B. Hollinger, S. M. Lemon, and H. S. Margolis (ed.), Viral hepatitis and liver disease. Williams & Wilkins, Baltimore, MD.
188. **Wainwright, R. B., B. J. McMahon, L. R. Bulkow, A. J. Parkinson, and A. P.**

Harpster. 1991. Protection provided by hepatitis B vaccine in a Yupik Eskimo population. Seven-year results. Arch. Intern. Med. **151:**1634–1636.
189. **Weibel, R. E., E. B. Buynak, A. A. McLean, and M. R. Hilleman.** 1975. Long-term follow-up for immunity after monovalent or combined live measles, mumps, and rubella virus vaccines. Pediatrics **56:**380–387.
190. **Weinberg, A., J. H. Zhang, M. N. Oxman, G. R. Johnson, A. R. Hayward, M. J. Caulfield, M. R. Irwin, J. Clair, J. G. Smith, H. Stanley, R. D. Marchese, R. Harbecke, H. M. Williams, I. S. Chan, R. D. Arbeit, A. A. Gershon, F. Schodel, V. A. Morrison, C. A. Kauffman, S. E. Straus, K. E. Schmader, L. E. Davis, and M. J. Levin.** 2009. Varicella-zoster virus-specific immune responses to herpes zoster in elderly participants in a trial of a clinically effective zoster vaccine. J. Infect. Dis. **200:**1068–1077.
191. **Weiss, S., D. Kobiler, H. Levy, H. Marcus, A. Pass, N. Rothschild, and Z. Altboum.** 2006. Immunological correlates for protection against intranasal challenge of Bacillus anthracis spores conferred by a protective antigen-based vaccine in rabbits. Infect. Immun. **74:**394–398.
192. **Werzberger, A., B. Kuter, and D. Nalin.** 1998. Six years' follow-up after hepatitis A vaccination. N. Engl. J. Med. **338:**1160.
193. **West, D. J., and G. B. Calandra.** 1996. Vaccine induced immunologic memory for hepatitis B surface antigen: implications for policy on booster vaccination. Vaccine **14:**1019–1027.
194. **Westerman, L. E., H. M. McClure, B. Jiang, J. W. Almond, and R. I. Glass.** 2005. Serum IgG mediates mucosal immunity against rotavirus infection. Proc. Natl. Acad. Sci. U. S. A. **102:**7268–7273.
195. **White, C. J., B. J. Kuter, A. Ngai, C. S. Hildebrand, K. J. Isganitis, C. M. Patterson, A. Capra, R. W. Ellis, and G. B. Calandra.** 1992. Modified cases of chickenpox after varicella vaccination: correlation of protection with antibody response. Pediatr. Infect. Dis. J. **11:**19–23.
196. **WHO.** 2007. Rabies vaccines. Wkly. Epidemiol. Rec. **82:**425–435.
197. **Williamson, E. D., H. C. Flick-Smith, E. Waters, J. Miller, I. Hodgson, C. S. Le Butt, and J. Hill.** 2007. Immunogenicity of the rF1+rV vaccine for plague with identification of potential immune correlates. Microb. Pathog. **42:**11–21.
198. **Yuan, L., A. Geyer, and L. J. Saif.** 2001. Short-term immunoglobulin A B-cell memory resides in intestinal lymphoid tissues but not in bone marrow of gnotobiotic pigs inoculated with Wa human rotavirus. Immunology **103:**188–198.
199. **Yuan, L., L. A. Ward, B. I. Rosen, T. L. To, and L. J. Saif.** 1996. Systematic and intestinal antibody-secreting cell responses and correlates of protective immunity to human rotavirus in a gnotobiotic pig model of disease. J. Virol. **70:**3075–3083.
200. **Yuan, L., K. Wen, M. S. Azevedo, A. M. Gonzalez, W. Zhang, and L. J. Saif.** 2008. Virus-specific intestinal IFN-gamma producing T cell responses induced by human rotavirus infection and vaccines are correlated with protection against rotavirus diarrhea in gnotobiotic pigs. Vaccine **26:**3322–3331.
201. **Zauberman, A., S. Cohen, Y. Levy, G. Halperin, S. Lazar, B. Velan, A. Shafferman, Y. Flashner, and E. Mamroud.** 2008. Neutralization of Yersinia pestis-mediated macrophage cytotoxicity by anti-LcrV antibodies and its correlation with protective immunity in a mouse model of bubonic plague. Vaccine **26:**1616–1625.
202. **Zhang, Z., T. B. Clarke, and J. N. Weiser.** 2009. Cellular effectors mediating Th17-dependent clearance of pneumococcal colonization in mice. J. Clin. Invest. **119:**1899–1909.
203. **Zinkernagel, R. M., and H. Hengartner.** 2004. On immunity against infections and vaccines: credo 2004. Scand. J. Immunol. **60:**9–13.
204. **Zolopa, A. R., C. A. Kemper, S. Shiboski, J. R. Hamilton, A. R. Moss, and S. C. Deresinski.** 1994. Progressive immunodeficiency due to infection with human immunodeficiency virus does not lead to waning immunity to measles in a cohort of homosexual men. Clin. Infect. Dis. **18:**636–638.