

Correlates of Vaccine-Induced Immunity

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The immune system is redundant, and B and T cells collaborate. However, almost all current vaccines work through induction of antibodies in serum or on mucosa that block infection or interfere with microbial invasion of the bloodstream. To protect, antibodies must be functional in the sense of neutralization or opsonophagocytosis. Correlates of protection after vaccination are sometimes absolute quantities but often are relative, such that most infections are prevented at a particular level of response but some will occur above that level because of a large challenge dose or deficient host factors. There may be >1 correlate of protection for a disease, which we term “cocorrelates.” Either effector or central memory may correlate with protection. Cell-mediated immunity also may operate as a correlate or cocorrelate of protection against disease, rather than against infection. In situations where the true correlate of protection is unknown or difficult to measure, surrogate tests (usually antibody measurements) must suffice as predictors of protection by vaccines. Examples of each circumstance are given.

The ascertainment of correlates of immunity is one of the most controversial areas of infectious diseases. Aside from its basic scientific interest, determination of a correlate is often the first step in the development of strategies of vaccination against a disease, it provides an objective criterion for protection of individual vaccinees, and even more practically, it permits the licensure of a vaccine without demonstration of field efficacy in situations where clinical trials are dangerous or when new combinations of existing vaccines are tested. Although the literature is rich in attempts to define correlates for particular vaccines, few synthetic analyses have been published. In 2001, I attempted a descriptive summary [1], and more recently, Qin et al. [2] reviewed the subject of correlates from a statistical viewpoint. They grouped correlates into 4 categories, several of which were labeled “surrogates.” The dictionary definition of a correlate is “something that is closely and mutually related,” whereas a surrogate is defined as a

“substitute.” It appears that Qin et al. [2] use the term “surrogate” to mean a substitute for clinical protection, rather than a substitute for a protective immune function.

The definitions used in this article are shown in table 1, including 4 categories of immune functions that relate to protection: absolute correlates, relative correlates, cocorrelates, and surrogates, with a surrogate being an immune function that is measured when the true correlate is unknown or difficult to measure.

PRELIMINARY GENERAL POINTS

There are many adaptive immune responses that potentially correlate with protection, listed in table 2. In addition, it should be understood that each correlate must be qualified as to the end point. Is it a correlate of protection against infection, disease, hospitalization, or death? These may be very different for the same vaccine. For example, smallpox vaccine protects against infection by antibody but against disseminated disease by both antibody and responses mediated by CD4⁺ and CD8⁺ T cells [3].

Another important point is that the challenge dose influences the quality and quantity of a correlate. Several examples can be given: a study done on inactivated polio vaccine showed that intestinal excretion of an attenuated poliovirus challenge was blocked in 80% of

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Table 1. Definitions employed in this article.

Term	Definition
Correlate	A specific immune response to a vaccine that is closely related to protection against infection, disease, or other defined end point
Absolute correlate	A quantity of a specific immune response to a vaccine that always provides near 100% protection
Relative correlate	A quantity of a specific immune response to a vaccine that usually (but not always) provides protection
Cocorrelate	A quantity of a specific immune response to a vaccine that is 1 of ≥ 2 correlates of protection and that may be synergistic with other correlates
Surrogate	A quantified specific immune response to a vaccine that is not in itself protective but that substitutes for the true (perhaps unknown) correlate

vaccinees after low-dose challenge but in only 30% after high-dose challenge, a study in which unattenuated cytomegalovirus was injected in graded doses and in which protection against low-dose challenge was equal for both natural and vaccine-induced immunity [4] but in which high doses overcame the latter [5], and the observation that higher amounts of pertussis toxin antibody are necessary to protect vaccinees against household exposure than against nonhousehold exposure [6].

Lastly, it is crucial to understand that the correlate of protection induced by vaccination is not necessarily the same correlate that operates to close off infection. An excellent example of this principle is measles vaccine. Titers ≥ 200 mIU/mL of antibody after vaccination are protective against infection, whereas titers between 120 and 200 mIU/mL protect against clinical signs of disease but not against infection. Titers < 120 mIU/mL are not protective at all [7]. Nevertheless, the importance of cellular immunity to measles in recovery from disease and in terminating replication of the attenuated vaccine virus is well established. In fact, B cell-deficient humans do recover from measles, whereas T cell deficiency leads to serious and fatal disease. Studies in monkeys confirm that antibodies usually protect against infection, but if infection occurs, CD8⁺ cells are needed to control viremia and consequent infection of organs [8–11].

ANTIBODIES AS CORRELATES OF PROTECTION

Most vaccines protect through induction of antibodies, because many pathogens reach their target organs by passage through

the bloodstream in an extracellular state (table 3) [12]. Other pathogens exert their action through toxin production that can be neutralized by antitoxin, still others replicate on mucosal surfaces where locally produced antibodies or antibodies diffused from the serum can protect, and in the special case of rabies, there is a period before the virus enters the neuronal axons when it is extracellular and susceptible to the action of antibodies.

An important means of showing that antibodies are the correlate of protection is to passively administer them by injection or to observe a protective effect of maternal antibodies in the newborn [13]. Many diseases for which vaccines are effective are in this category, including smallpox, diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b (Hib) infection, pneumococcus infection, hepatitis A, hepatitis B, varicella, measles, rubella, polio, and rabies. Table 4 lists antibody quantities that correlate with protection against selected diseases [14–29].

However, it should be understood that a correlate of protection may be either absolute or relative. Examples of absolute correlates (situations in which a certain level of response almost guarantees protection) include diphtheria, tetanus, measles, and rubella. In addition, the protective effect of immune globulin on hepatitis A virus is well known. A level of 10 mIU/mL in the serum is almost always protective against disease. Hepatitis A vaccines induce average levels in the thousands of mIU/mL, with excellent persistence, thereby providing high efficacy [30].

Another interesting example is the Lyme disease vaccine that was briefly marketed in the late 1990s. The mechanism of pro-

Table 2. Potential protective adaptive immune responses induced by vaccination.

Type of antibody	CD4 ⁺ T cells	CD8 ⁺ T cells
Serum antibody		
Neutralizing	B cell help	
Nonneutralizing	T cell help	
Functionality (opsonophagocytosis, cytotoxicity, etc.)	Cytokines	
Avidity	Lysis	
Mucosal antibody		
IgA locally produced		Lysis
IgG diffused from serum		Avidity, cytokines

Table 3. Major licensed viral and bacterial vaccines for humans, according to the mechanism of disease prevented by the vaccine.

Type of vaccine, mechanism prevented	Licensed vaccine(s)
Viral	
Viremia	Smallpox, yellow fever, measles, mumps, rubella, polio, varicella, hepatitis A, hepatitis B, Japanese encephalitis, tickborne encephalitis
Mucosal replication	Influenza, rotavirus
Mucosal and skin invasion	Papillomavirus
Neuronal invasion	Rabies
Reactivation in neurons	Zoster
Bacterial	
Bacteremia	<i>Haemophilus influenzae</i> type b meningococcal, pneumococcal, typhoid (Vi)
Mucosal replication	Pertussis, typhoid (Ty21a)
Toxin production	Diphtheria, tetanus, pertussis, cholera, anthrax
Macrophage replication	Tuberculosis

tection was induction of antibodies against the OspA surface protein that neutralize *Borrelia burgdorferi* in infected ticks taking blood meals from vaccinees and thus prevent regurgitation of the spirochete. During one of the efficacy trials, it was established that infected vaccinees (vaccine failure) always had antibodies significantly less than 1100 EIA U/mL, which was the average titer in vaccinated non-case patients [20]. Therefore, 1100 EIA U/mL was an absolute correlate of protection.

Although an absolute correlate of protection is highly desired, unfortunately, many correlates are relative—that is, protection is usually achieved at a certain level of response, but breakthroughs occur even at nominally protective levels. In animal models testing anthrax vaccines based on the protective antigen component of the toxic complex, an antitoxin level of 1/1000 gave complete protection, whereas titers of 1/500–1/800 gave only partial protection [31–33]. An example more relevant to routine human vaccination is provided by a recent analysis of protection after influenza vaccination (L. Coudeville, F. Bail-

leux, F. Megas, and P. André, personal communication). One of the criteria often used to judge the acceptability of an influenza vaccine is a hemagglutination-inhibition antibody titer of 1/40 [34]. As shown in a model based on published efficacy data, at that titer, 70% of subjects were indeed protected, but protection increased gradually to 90% with higher titers (figure 1). The model suggests that the relationship of titer to protection is described by a curve, rather than by a threshold.

ALL ANTIBODIES ARE NOT EQUAL

Assays for antibodies are often based on binding of antigen, formulated in ELISA tests for convenience and rapidity. However, binding antibodies do not necessarily have functions, such as opsonophagocytosis for bacteria and neutralization for viruses. The subclass of IgG may also be important for protection [35].

Meningococcal polysaccharide vaccines give notoriously

Table 4. Some quantitative correlates of protection after vaccination.

Vaccine	Test	Correlate of protection	Reference(s)
Diphtheria	Toxin neutralization	0.01–0.1 IU/mL	[14]
Hepatitis A	ELISA	10 mIU/mL	[15]
Hepatitis B	ELISA	10 mIU/mL	[16]
Hib polysaccharides	ELISA	1 mcg/mL	[17]
Hib conjugate	ELISA	0.15 mcg/mL	[18]
Influenza	HAI	1/40 dilution	[19]
Lyme	ELISA	1100 EIA U/mL	[20]
Measles	Microneutralization	120 mIU/mL	[7]
Pneumococcus	ELISA; opsonophagocytosis	0.20–0.35 mcg/mL (for children); 1/8 dilution	[21, 22]
Polio	SN	1/4–1/8 dilution	[23]
Rabies	SN	0.5 IU/mL	[24]
Rubella	Immunoprecipitation	10–15 mIU/mL	[25, 26]
Tetanus	Toxin neutralization	0.1 IU/mL	[27]
Varicella	SN; gpELISA	≥1/64 dilution; ≥5 IU/mL	[28, 29]

NOTE. gp, glycoprotein; HAI, hemagglutination inhibition; Hib, *Haemophilus influenzae* type b; SN, serum neutralization.

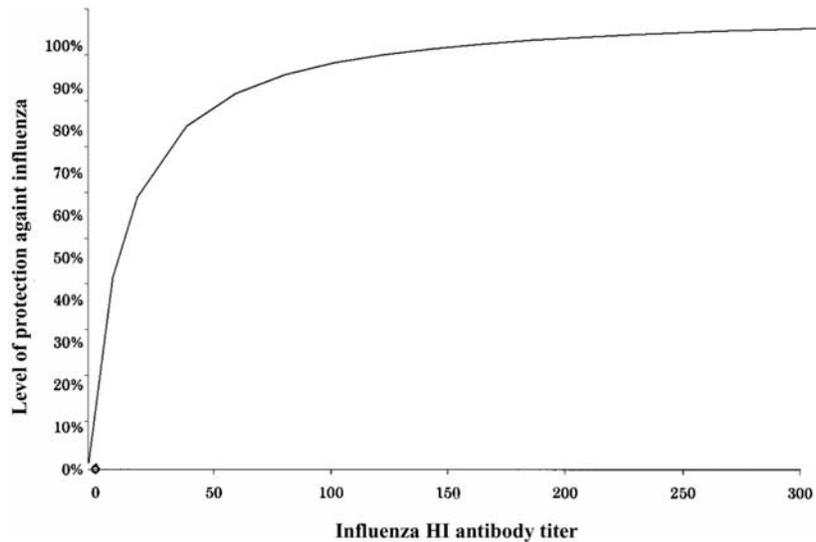


Figure 1. Relationship between hemagglutination-inhibiting (HI) antibodies and protection of a population against influenza, illustrating that the correlation is relative and not absolute (L. Coudeville, F. Bailleux, F. Megas, and P. André, personal communication).

poor protection in young children, although children do have significant ELISA antibody responses. In contrast, bactericidal assays show low responses in children, gradually improving with age and correlating with increased protection [36]. The decreased efficacy of Hib vaccine that has been observed in combination with acellular pertussis vaccine may be the result of lower avidity maturation [18]. Another striking example is that of the pneumococcal polysaccharide vaccine. Although shown to be highly effective in young adults, attempts to prove efficacy in elderly persons have yielded conflicting and often

negative estimates. An explanation of this disparity is found in studies of opsonophagocytic antibodies, which reveal that adults aged <46 years respond much better than older adults (figure 2) [37].

An example from virology is taken from a comparative study of rubella vaccine strains. Although both the HPV-77 and RA 27/3 strains induced hemagglutinin antibodies, titers of neutralizing antibodies were considerably higher after vaccination with the latter strain, which corresponded with greater protection against superinfection by wild rubella virus [38, 39].

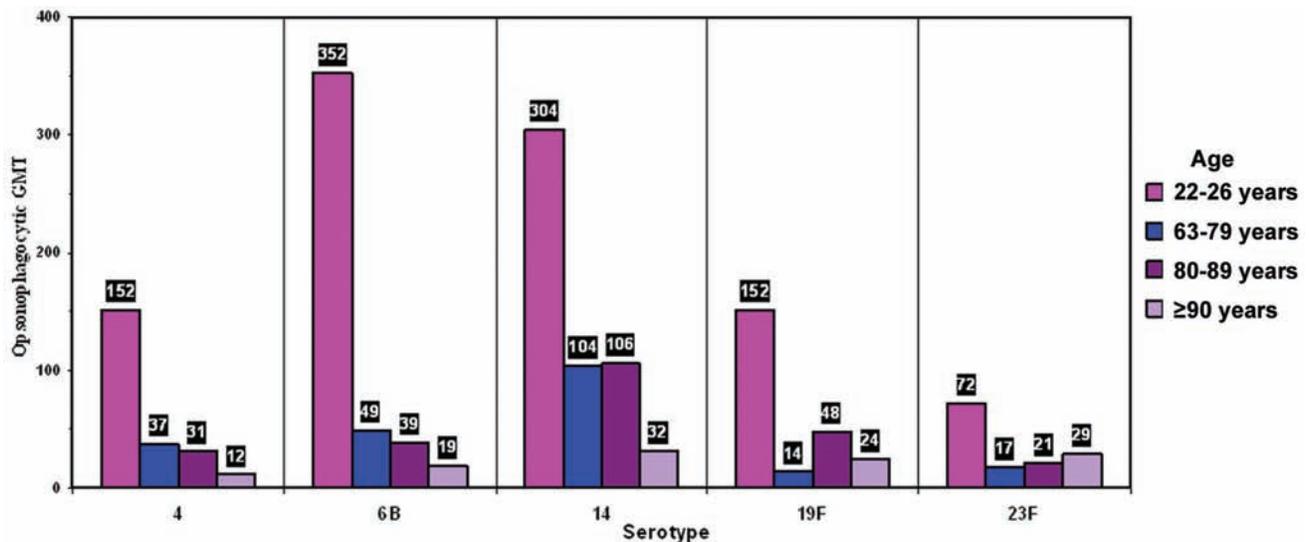


Figure 2. Opsonophagocytic antibodies against 5 pneumococcal serotypes measured in subjects of varying ages who were vaccinated with pneumococcal polysaccharide [37]. Only the youngest age group makes high levels of opsonophagocytic antibodies, with corresponding high protection against invasive pneumococcal disease. GMT, geometric mean titer.

Table 5. Correlates of immune protection after live influenza vaccine under conditions of artificial challenge in children.

Serum HAI antibody	Nasal IgA	Shedding, %
-	-	63
-	+	19
+	-	15
+	+	3

NOTE. HAI, hemagglutination-inhibiting. Data are from [40].

MUCOSAL ANTIBODIES AS COCORRELATES

Antibodies on the mucosal surfaces, either locally secreted IgA or transcytosed IgG, may protect against organisms that exert pathology on those surfaces and against organisms that colonize the mucosa before invading systemically. Examples of the former organisms include respiratory viruses, whereas examples of the latter include the encapsulated bacterial pathogens that frequently cause bacteremia in children.

A clear demonstration of mucosal antibodies as cocorrelates of protection was made during the development of intranasally administered live influenza vaccine [40]. Children who had been previously vaccinated and placebo control individuals were challenged intranasally with the live vaccine under circumstances in which some children lacked both serum and nasal antibody, some had one but not the other, and some had both antibodies (table 5) [40]. The doubly antibody-negative control children shed virus 63% of the time, in contrast to the doubly antibody-positive vaccinated children, of whom only 3% shed virus. Those with serum IgG antibody alone shed virus 15% of the time and those with nasal IgA antibody alone shed virus 19% of the time. Thus, there were 2 correlates of protection against infection, which were synergistic.

Protection against encapsulated bacterial pathogens consists of either prevention of bacteremia or prevention of colonization. The latter does not refer to prevention of colonization through herd immunity, which has been strikingly demonstrated in adults whose child contacts have received pneumococcal conjugate vaccine [41], but rather to direct effects on colonization. Figure 3 [42] shows the cumulative curves of serum antibody against Hib in colonized and uncolonized vaccinees. Almost all the vaccinees have sufficient antibody to be protected against invasion (>0.15 mcg/mL) (table 4), but the uncolonized vaccinees have serum antibody levels >5 mcg/mL, indicating that higher levels are needed to diffuse into the pharynx and to prevent carriage of Hib [42]. The same principle also appears to be true for at least some pneumococcal serotypes [43].

A remark in passing: it has become cliché to say that vaccines prevent only disease, not infection. Although that may be often the case, it is not a general truth. If the presence of antibodies

is sufficient to prevent colonization of mucosal surfaces, vaccines can produce “sterile” immunity. Vaccines against polio, measles, rubella, Hib, pneumococcus, meningococcus, and probably human papillomavirus are all capable of preventing infection as well as disease.

ORGAN-SPECIFIC CORRELATES

An emerging area of research concerns correlates of protection that are organ specific. From experimental studies, it appears that CD4⁺ cells are key to the prevention of brain pathology after measles [44] and in helping CD8⁺ cells to close off West Nile virus CNS infection [45]. Although vaccination will normally prevent microbes from reaching target organs, more work is needed to define correlates that are organ specific.

ANTIBODIES AS SURROGATES

To repeat, surrogates are immunological measurements that are feasible to make but that are only indirectly related to the true correlate of protection. A recent example of the use of a surrogate concerns rotavirus vaccine. The generally accepted surrogates of protection from rotavirus disease are serum IgA or total neutralizing antibodies against each G or P serotype, corresponding to the vp7 and vp4 surface proteins, respectively [46]. However, although rotavirus vaccines are efficient in protecting against disease, they do not always prevent intestinal infection with wild virus (although they may reduce the quantity shed). Antibodies to vp7 are more able to protect against infection and disease, whereas antibodies to vp4 modify disease but not infection [47]. In addition, antibodies against at least one protein without neutralizing epitopes (vp6) protect mice, and both helper T cell and CD8⁺ cell functions at the intestinal level have been proposed as effectors of immunity [47–49]. Thus, in the absence of an agreed correlate, serum IgA antibody is a useful surrogate.

Varicella vaccine provides another example of antibody surrogate. During the development of the vaccine, a test was developed to measure binding antibodies to varicella glycoproteins, the so-called gpELISA. Seroconversion to the vaccine was $>90\%$ by this technique, and there was a relative correlation with protection and with a neutralization test [28]. The putative protective titer was >5 gpELISA units [29]. However, another test, the fluorescent antimembrane antigens test, although more labor intensive to perform, shows better correlation with the protection observed after 1 dose ($\sim 75\%$) [50]. Moreover, several studies reported that antibodies to varicella fade after vaccination and that CD4⁺ cell responses to varicella antigens were closer correlates of protection [51, 52], although the presence of varicella-specific CD4⁺ cells may simply reflect the ability to respond with antibodies when exposed to the virus. Nevertheless, these ideas remain to be confirmed, and antibodies and

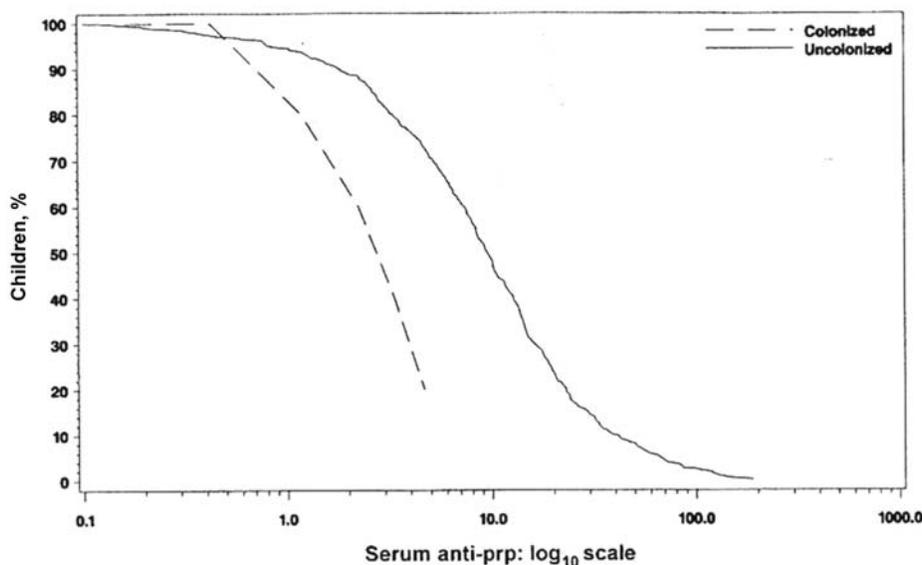


Figure 3. Levels of ELISA antibodies to *Haemophilus influenzae* type b polysaccharide (prp) in the sera of children whose nasopharynges are colonized or not colonized by the organism [42]. The level necessary to prevent colonization is higher than that necessary to prevent systemic infection.

cell-mediated immunity both may be important to protection against infection.

Lastly, there is the vexing question of correlates of protection against pertussis, in which *Bordetella pertussis* causes a mucosal infection and a toxic disease due to pertussis toxin. Much ink has been spilled about which components of pertussis vaccines are protective and whether antibodies against them are sufficient correlates. In my opinion, the problem is not lack of correlates but its opposite; there appear to be multiple responses that reduce the risk of disease. Antibodies to pertussis toxin, pertactin, and agglutinogens, as well as cellular responses, have all been proposed as correlates on the basis of evidence from trials in humans and in animals [6, 53, 54]. Whether they are surrogates or cocorrelates is difficult to judge, but antibodies to several different components have been associated with protection by vaccines, probably because protection can be mediated both by antitoxin to pertussis toxin and by antibody to attachment factors. In any case, the example of pertussis shows that correlates of protection may act synergistically.

ANAMNESIS AS A SURROGATE

Immunological memory, either effector or central, is necessary for long-term protection against infection [55, 56] unless exposure to a microbe is frequent enough to maintain the presence of antibodies [57]. The utility of passive antibodies against hepatitis B virus is proof of the importance of antibodies in hepatitis B, as well as the observation that antibody levels >10 mIU/mL after vaccination are protective [16]. Nevertheless, antibodies decline rapidly, and half of vaccinees may be seronegative at 5 years after vaccination [58]. Despite the loss of

antibodies, B cell central memory is prolonged and protective efficacy is maintained at a high level [59, 60]. B cell memory to hepatitis B virus acts as a surrogate of protection, which is actually mediated through the antibodies evoked by antigenic stimulation of memory cells. Revaccination induces anamnestic antibody responses in most subjects. It is probable that infection can also induce an anamnestic response and that the long incubation period of hepatitis B virus allows antibodies to close off or modify the course of infection to protect the liver.

The opposite case was seen in the United Kingdom when Hib vaccine was introduced using a vaccine schedule of 3 doses at age <1 year, without a booster [61]. Anamnestic responses to Hib polysaccharide were demonstrable in vaccinees who had lost effector memory and thus circulating antibodies [62, 63], but the extremely high effectiveness of the vaccine in countries that use a booster was reproduced in the United Kingdom only during the period when catch-up vaccination of older children was also employed. In the absence of herd immunity from catch up, infants who were not boosted became susceptible to disease. The rapid invasion of vaccinees by the organism moved faster than the antibody recall, which also appears to be true after natural Hib infection [64].

CELLULAR RESPONSES AS CORRELATES OR COCORRELATES

In recent years, immunologists have devoted much of their attention to cellular responses, but it is obvious from the above discussion that, in the case of vaccines, antibodies in sufficient quantity are the predominant protective correlate. Nevertheless, it is also obvious that cell-mediated immune functions are crit-

ical in protection against intracellular infections, and in almost all diseases, CD4⁺ cells are necessary to help B cell development.

The best case for the importance of cellular immunity is the bacille Calmette-Guérin (BCG) vaccine against tuberculosis. Production of IFN- γ by CD4⁺ cells is necessary to prevent disease after exposure but apparently is not an adequate correlate of BCG vaccine-induced protection [65]. CD8⁺ cells maintain the tubercle bacilli in a latent state [66]. Almost all current attempts to develop better protection against tuberculosis are based on improving cellular responses to BCG vaccine, but at the moment, no true correlate is known [67]. Zoster vaccine induces both antibody and cellular immune responses, but no quantitative correlate of protection emerged from the efficacy trial [68]. However, because the duration of cellular responses, rather than that of antibody responses, paralleled clinical efficacy and because the waning of cellular immunity with age is responsible for herpes zoster, it appears likely that it is the boost in cellular response that correlates with protection [69].

As mentioned above, antibodies that are present in the serum and on mucosal surfaces are good correlates of immunity to influenza, but this may be true only for children and young adults. McElhaney et al. [70] found that cytokine production and proliferation of T cells in the presence of influenza antigen correlated with protection of elderly adults. Thus, whereas antibody production is critical in the young to prevent primary influenza infection, CD4⁺ cells may be more important in immunologically experienced individuals undergoing heterosubtypic infection.

The interplay between antibody- and cell-mediated immunity is well exemplified by the case of cytomegalovirus. Protection by vaccination has been demonstrated with both live-attenuated and glycoprotein vaccines, and passive antibodies also have been shown to protect [71]. Nevertheless, once latent infection has been established, good T cell function is necessary to control reactivation and disease. Thus, one could say that antibodies are a correlate of protection against infection, whereas T cell immunity is a correlate of protection against disease [1, 72].

Another apposite example is protection against poxviruses, such as smallpox and monkeypox. For monkeypox, it has been demonstrated that antibodies are necessary for prevention of infection and that CD4⁺ cells must be present to help antibodies to develop, but that once antibodies are present no cellular functions are necessary [73–75]. Immunity against smallpox due to vaccinia induces lifelong persistence of antibodies, and although infection and even disease may nevertheless occur many years after vaccination, the patient is likely to have modified disease and to survive [3, 76]. This resistance to clinically typical smallpox depends on T cell memory, which declines with time. Thus, antibody alone prevents infection and severe

disease, but the combination of antibody and cellular immunity is required for infection to be asymptomatic [77].

CONCLUDING REMARKS

For the most part, it is the production of antibodies by B cells that protect vaccinees exposed to the pathogen concerned, whereas aside from their help to B cells, cellular immune responses are more important in the control of established infection. This paradigm is not strict, but rather a relative and statistical truth, subject to variation from one infection to another.

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