

Booster Vaccinations: Can Immunologic Memory Outpace Disease Pathogenesis?

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KEY WORDS

vaccines, immunologic memory, pathogenesis, *Neisseria meningitidis*, *Haemophilus influenzae* type b, human papilloma virus

ABBREVIATIONS

TLR—Toll-like receptor

Hib—*Haemophilus influenzae* type b

DTaP—diphtheria-tetanus-acellular pertussis

HPV—human papilloma virus

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abstract

Almost all current vaccines work by the induction of antibodies in serum or on the mucosa to block adherence of pathogens to epithelial cells or interfere with microbial invasion of the bloodstream. However, antibody levels usually decline after vaccination to undetectable amounts if further vaccination does not occur. Persistence of vaccine-induced antibodies usually goes well beyond the time when they should have decayed to undetectable levels because of ongoing “natural” boosting or other immunologic mechanisms. The production of memory B and T cells is of clear importance, but the likelihood that a memory response will be fast enough in the absence of a protective circulating antibody level likely depends on the pace of pathogenesis of a specific organism. This concept is discussed with regard to *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and *Neisseria meningitidis*; hepatitis A and B; diphtheria, tetanus, and pertussis; polio, measles, mumps, rubella, and varicella; rotavirus; and human papilloma virus. With infectious diseases for which the pace of pathogenesis is less rapid, some individuals will contract infection before the memory response is fully activated and implemented. With infectious diseases for which the pace of pathogenesis is slow, immune memory should be sufficient to prevent disease. *Pediatrics* 2009;124:1633–1641

With the introduction of so many new vaccines over the past decade and many more on the horizon, clinicians are often asked, or wonder themselves, whether boosters for all these vaccines will be necessary down the road. Sentinel study populations have been established by vaccine companies as phase 4 postlicensure evaluations to forewarn public health authorities and practitioners if such boosters will be needed. In this review I will present information on what is known about B-cell and T-cell immune memory and innate immunity and the pace of pathogenesis for the diseases we are currently preventing with vaccination, and I will examine the dynamic nature of the situation as changes in natural boosting occur.

IMPORTANCE OF ANTIBODIES

As observed by Robbins et al¹ and Plotkin,² almost all current vaccines work by the induction of antibodies in serum or on the mucosa (by local production or transudation from serum) to block adherence of pathogens to epithelial cells or interfere with microbial invasion of the bloodstream. To protect, the induced antibodies must either be functional against the relevant pathogen or aid the immune system as an opsonin, or, if the organism exerts its pathogenic effect by elaborating a toxin, then the antibodies must neutralize that toxin.² The importance of antibodies in vaccine-induced protection is undeniable, as supported by studies in which passive administration prevents or ameliorates disease and the observation of a protective effect in the newborn by maternal antibody.³ All maternal protection of the fetus and newborn occurs as a result of antibodies, because maternal B cells and T cells do not cross the placenta.

Specific levels of antibody have been correlated with protection against

TABLE 1 Quantitative Correlates of Protection After Vaccination

Vaccine	Test	Correlate of Protection
Hib conjugate	ELISA	0.15 $\mu\text{g}/\text{mL}$
Pneumococcus	ELISA; opsonophagocytosis	0.20–0.35 $\mu\text{g}/\text{mL}$ (for children); 1/8 dilution
Meningococcus	Bactericidal	1:8 human complement 1:16 rabbit complement
Diphtheria	Toxin neutralization	0.01–0.10 IU/mL
Tetanus	Toxin neutralization	0.01 IU/mL
Acellular pertussis	ELISA	Unknown
Polio	Microneutralization	1/4–1/8 dilution
Measles	Microneutralization	120 mIU/mL
Mumps	ELISA	2 ELU/mL
Rubella	Immunoprecipitation	10–15 mIU/mL
Varicella	SN; gpELISA	$\geq 1/64$ dilution; ≥ 5 IU/mL
Hepatitis B	ELISA	10 mIU/mL
Hepatitis A	ELISA	10 mIU/mL
Rotavirus	ELISA IgA; microneutralization	Unknown
HPV	ELISA; microneutralization	Unknown

ELISA indicates enzyme-linked immunosorbent assay; ELU, ELISA Units; SN, serum neutralization; gpELISA, glyco protein ELISA enzyme-linked immunosorbent assay; Ig, immunoglobulin.

Adapted from Plotkin SA. *Clin Infect Dis*. 2008;47(3):401–408.

many diseases (Table 1). The levels of antibody that correlate with protection are generally derived from population studies wherein observations have been made that individuals with a certain level of antibody are always or nearly always protected from disease. However, a specific level of antibody is not an absolute correlate of protection for every person, because it is not only the quantity of antibody that is important but also the functionality of the antibody. Also, there is genetic variation in susceptibility to disease, differences in virulence among pathogen strains, differences in innate immune responses among individuals, and variation in the inoculum of the pathogen, and there may be an impact from concurrent illness or coinfection. Therefore, a specified protective level of antibody should be considered as a close estimate applicable in the majority of hosts as a relative correlate of protection.

Antibody levels usually decline to undetectable amounts over time if further antigen stimulation does not occur, because antibodies have a half-life of ~ 30 days. However, persistence of vaccine-induced antibodies usually goes well beyond the time when the

antibodies should have disappeared according to the mathematics of their half-life. This may be a result of ongoing “natural” boosting or other immunologic mechanisms discussed below.

Natural boosting can occur by asymptomatic colonization by the pathogen or by a nonpathogen expressing a cross-reactive antigen. Natural boosting can decrease over time as a pathogen circulates less widely in a population because of increasing use of a vaccine and/or the establishment of herd immunity. This is an ongoing issue relative to several vaccines, because the absence of natural boosting among vaccine recipients may lead to a return to disease susceptibility.

Other explanations have been proposed for the persistence of low levels of circulating antibodies long after antigen exposure has occurred. One hypothesis is that small amounts of antigen are retained and persist inside peripheral lymph nodes and spleen. The small amount of antigen is enough to keep the immune response ongoing.⁴ A second hypothesis suggests that some memory B cells become sequestered in the bone marrow sanctuary, where they periodically divide, ma-

ture to plasma cells, and produce small amounts of antibody in serum.⁵ A third hypothesis is that nonspecific polyclonal B-cell activators maintain a continuous, small memory B-cell pool. The hypothesized nonspecific B-cell activators include several microbial products that stimulate Toll-like receptors (TLRs) (discussed later) and may also occur through bystander T-cell help.^{6,7}

ROLE OF MEMORY B CELLS

The production of memory B cells is a complex developmental process that occurs in lymph node and spleen germinal centers. During the generation of memory B cells a selection process occurs called affinity maturation.⁸ As antigen becomes less and less available after vaccination, random mutations of immunoglobulin genes occur and the B cells expressing antibodies on their surface with the highest affinity for the diminishing vaccine antigen win out and persist as memory B cells. There is a strong correlation between highly functional antibody and antibody with high affinity for a vaccine antigen. The features of vaccine-induced B-cell-mediated immune memory are (1) a rapid production of antibody, (2) predominately immunoglobulin G antibody, (3) a higher antibody level than occurred after primary exposure, and (4) production of antibody of higher affinity (and an antibody population of higher avidity) for the antigen as a result of a process known as affinity maturation.

To assess the duration of immune memory, vaccinated subjects provide serum and lymphoid cells for *in vitro* analysis at time intervals after vaccination. Persistence of antibody levels, B memory cells, and T memory cells can then be measured. The best tool for assessing immune memory is to perform challenge experiments

whereby a one-fifth to one-tenth standard antigen dose is given to the test subjects, and then the immune response is evaluated. This simulation is not perfect, because (1) we do not know the actual pathogen-specific antigen dose, (2) delivery of the antigen by the parenteral route is clearly not the same as the reality in nature, where nearly all exposures occur via the skin, respiratory, gastrointestinal, or genitourinary tracts, and (3) the context of the simulation is not during a concurrent illness (eg, a viral upper respiratory infection, as often occurs in nature).

T-CELL MEMORY

T-cell immunity plays a role in terminating disease or maintaining protection against disease over time. Indeed, T-cell-dependent and antibody-independent mechanisms of protection against infections were recently described in mice^{9–11} and in man.¹² Cell immunity is a term often used synonymously with T-cell immunity.

Two memory T-cell populations are now known to exist. Effector memory T cells reside in peripheral tissues, whereas another pool, termed central memory T cells, reside in lymphoid organs.¹³ Both memory T-cell populations express surface proteins that make them distinguishable from naive T cells.¹⁴ The continuous circulation of effector memory T cells into tissue is a key feature of the immune system that ensures that memory T cells of particular specificities are disseminated throughout the body.

It is well established that memory CD4⁺ T cells respond more quickly and with a wider array of cytokines and that memory CD8⁺ T cells respond with the release of a greater quantity of cytotoxic molecules (perforin and granzyme B) than occurs during a primary response.¹² Also, memory CD4⁺ T cells are more effective at helping B cells compared with naive CD4 T cells.^{15,16}

A faster and broader memory T-cell response has the potential to control infection quickly after reexposure to pathogens.^{17–19} In both CD4 and CD8 *in vitro* models the generation of T-cell effector functions (cell-mediated immunity) can be evident ~2 to 7 days after antigen stimulation.^{20–23} The maintenance of T-cell memory varies according to the antigen. T-cell memory after vaccination with small protein fragments is much shorter than that achieved after vaccination with an attenuated but replicating virus.^{24–27}

INNATE IMMUNITY

In addition to adaptive immunity, the pace of pathogenesis can be slowed by the innate immune response.²⁸ New information over the past decade has revealed that the innate immune system has developed a strategy to recognize conserved structures of microbes that are not present on mammalian cells: so-called pathogen-associated molecular patterns.²⁹ Also, a recognition and signaling system called TLRs has been described, which initiates a cascade of immunologic events in human host cells to contain infection, giving the adaptive immune response time to respond.^{30,31} TLR2 is a receptor for lipoteichoic acid of Gram-positive bacteria, bacterial lipoproteins, and zymosan (yeasts); TLR3 is a receptor for viral double-stranded DNA; TLR4 is a receptor for lipopolysaccharides of Gram-negative bacteria; and TLR9 is a receptor for bacterial DNA.^{32,33} Once the TLRs are stimulated by the pathogen-associated molecular patterns, immunologic effector cells do not need to proliferate or mature; they can immediately respond by releasing multiple proinflammatory and antiinflammatory mediators and cytokines. Because it takes 2 to 7 days for sufficient amounts of antibodies and effector T cells to be produced, the host relies on the innate immune system to hold the infection in check tempo-

rarily. If the innate response is not adequate, then infection may occur despite immune memory.

OUTPACING INFECTION WITH AN IMMUNE RESPONSE

The likelihood that a B-cell or T-cell memory response will be fast enough in the absence of a protective circulating antibody level likely depends in large part on the pace of pathogenesis of the infection caused by a specific organism (Table 2). Several examples are described below to illustrate this point.

Haemophilus influenzae Type b, *Streptococcus pneumoniae*, and *Neisseria meningitidis*

The pace of pathogenesis for encapsulated respiratory bacteria such as *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae*, and *Neisseria meningitidis* is very rapid. In a matter of hours bacteria can adhere to the nasopharynx, gain entry to the bloodstream, replicate, and begin to seed the meninges. Infection by these encapsulated bacteria is prevented by the presence of functional antibody directed to the polysaccharide capsule.

The speed of production of measurable antibody responses after memory B-cell stimulation has been measured

for Hib and meningococcus.^{34–37} In both cases a detectable response was observed no sooner than 2 to 7 days after antigen exposure. It takes some time from antigen exposure to antibody production, because the antigen must be taken up and processed by antigen-presenting cells (eg, dendritic cells and macrophages); then, the antigen-presenting cells must interact with B cells and helper T cells, the B cells must proliferate and mature to plasma cells, and, finally, the plasma cells release antibody into the circulation.

After introduction of the Hib conjugate vaccines, a debate emerged on the protective role of immune memory in the absence of detectable antibody.³⁸ This occurred with the introduction of diphtheria-tetanus-acellular pertussis (DTaP) vaccines combined with Hib conjugate vaccines, because several DTaP-Hib combination vaccines did not produce as high of an antibody level as administration of the 2 separate vaccines.^{39,40} The debate ended when Hib disease began to occur in England and Wales, where DTaP-Hib combinations were licensed and researchers showed that a circulating level of functional antibody was necessary for long-term protection for some children.^{41–43} This same scenario was repeated again in

the United Kingdom after the introduction of meningococcal conjugate vaccines. A decrease in antibody despite persistence of immunologic memory was associated with a decline in vaccine effectiveness.^{44–46} As a result of the breakthrough cases of disease, the United Kingdom revised its vaccination program to require booster doses of Hib and meningococcal conjugate vaccines so as to maintain protective antibody levels in the blood.

After the primary vaccination series in infancy is completed for Hib conjugates, only 1 booster is needed in the second year of life to afford protection until ~5 years of age. This is because during the third through the fifth year of life children develop “natural” immunity to Hib induced by colonization of their gastrointestinal tract by a species of *Escherichia coli* that expresses a polysaccharide capsule (K1 capsule) nearly identical to the Hib polysaccharide capsule⁴⁷ (Fig 1). Natural antibody also is produced to meningococci and pneumococci, but it is currently unknown whether the frequency of development of such natural antibody will be sufficient to supplement vaccine-induced immunity. The sporadic occurrence of meningococcal and pneumococcal disease throughout life speaks to the likelihood for the need for boosters.

Hepatitis B and A

The pace for pathogenesis of hepatitis B and hepatitis A pathogenesis is slow. Clinically, before hepatitis B and hepatitis A vaccines became available, the administration of passive antibody in the form of intramuscular γ globulin could be done 2 weeks after exposure and still be effective. Immunity to hepatitis B and A is lifelong after natural infection.

Hepatitis B vaccine-induced antibody levels wane over time such that by 10 years after vaccination only approxi-

TABLE 2 Pace of Pathogenesis, Memory Mechanism, and Need for Boosters

Disease	Pace of Pathogenesis	Live (Attenuated) vs Inert	Booster Needed
Diphtheria	Fast	Inert	Yes
Tetanus	Slow	Inert	Yes ^a
Pertussis	Fast	Inert	Yes
Polio	Slow	Inert	No
Measles	Slow	Live (attenuated)	No
Mumps	Slow	Live (attenuated)	No
Rubella	Slow	Live (attenuated)	No
Hib	Fast	Inert	Yes
Hepatitis B	Slow	Inert	No
Varicella	Slow	Live (attenuated)	?
Pneumococcal	Fast	Inert	Yes
Meningococcal	Fast	Inert	Yes
Hepatitis A	Slow	Inert	No
Rotavirus	Fast	Live (reassortant)	No
HPV	Unknown	Inert	?

^a The booster can be given after exposure, because the pace of pathogenesis is slow.

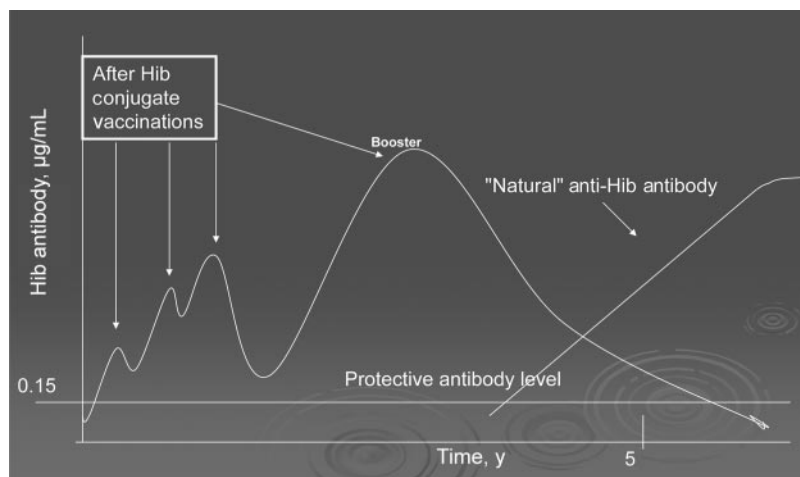


FIGURE 1

Vaccine raises serum antibody levels to Hib, and then serum antibody levels wane. However, “natural” serum antibody to the capsular polysaccharide of Hib is produced by colonization of the gastrointestinal tract by a strain of *E coli* that expresses a polysaccharide capsule that is virtually identical to the Hib capsule, thereby maintaining protection without the need for further boosters. Hib conjugate indicates Hib polysaccharide conjugated to a protein carrier vaccine.

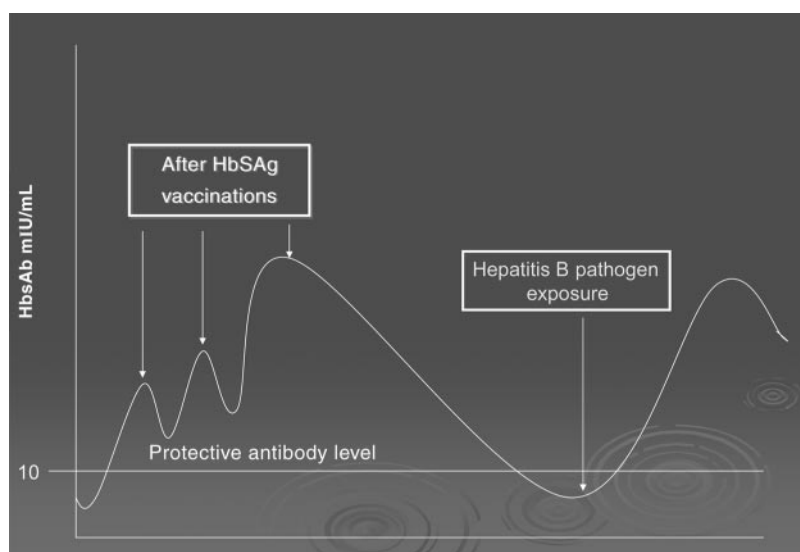


FIGURE 2

Vaccination raises serum antibody level to hepatitis B surface antigen, and then serum antibody levels wane. After exposure to hepatitis B, a memory antibody response occurs over 2 to 14 days. Because the pace of pathogenesis is slow for hepatitis B, the memory response occurs in time to prevent infection. HbsAg indicates hepatitis B surface antigen; HbsAb, hepatitis B surface antibody.

mately one third of vaccine recipients still have detectable antibody levels.⁴⁸ Nevertheless, up to now there has been no breakthrough disease. This success has been attributed to memory antibody responses that occur in sufficient time to afford protection after exposure (Fig 2). However, a recent

report of the persistence of immunologic memory 15 to 18 years after hepatitis B vaccination raises concerns.⁴⁹ Less information is available about persistence of immunity and immune memory after hepatitis A vaccination, because it was introduced more recently.

Diphtheria, Tetanus, and Pertussis

Diphtheria, tetanus, and pertussis are diseases caused by release of toxins; there is no bacteremia. The pace of pathogenesis is several days (diphtheria and tetanus) to several weeks (pertussis) between infection and the elaboration of sufficient toxin to manifest as disease. Natural infection does not confer lifelong protection from any of these 3 diseases. Memory responses to tetanus have been shown to occur after a time lag of several days to 2 weeks.⁵⁰

Breakthrough cases of diphtheria in the former Soviet Union produced an epidemic in the 1980s that included many vaccinated individuals.⁵¹ Breakthrough cases of tetanus are well known to occur among vaccine recipients, thus leading to the recommended every-10-year booster.⁵² Waning immunity has been demonstrated to occur after use of whole-cell pertussis vaccines,^{53–56} leading to adolescent and adult cases among vaccinated individuals^{57–59} and likely will occur in the future after acellular pertussis vaccines if boosters are not given. In terms of pathogenesis one might predict that the prolonged prodrome of pertussis, generally 1 to 3 weeks of upper respiratory–like symptoms before cough illness begins, should be sufficient in length to allow immune memory to outpace disease. However, this does not occur most likely because replication of the organism is only on the mucosal surface (not in the bloodstream) and the organism itself does not elicit a vigorous inflammatory/immunologic response when it is present in the tracheobronchial tree. Perhaps only with the elaboration of sufficient pertussis toxin does the immune system become stimulated.

Polio, Measles, Mumps, Rubella, and Varicella

Polio, measles, mumps, rubella, and varicella are characterized by 2 viremic phases during pathogenesis. A first vire-

mia occurs 2 to 4 days after exposure, and then there is a 1- to 3-day hiatus followed by a second and larger viremic stage during which wider dissemination of the virus occurs. Thereafter, the onset of prodrome symptoms occurs, followed by the classical manifestations of disease. Permanent immunity is acquired after natural infection.

For polio, measles, mumps, rubella, and varicella, the pace of pathogenesis may be sufficiently slow to allow immune memory responses to intervene and prevent the important, disease-causing second viremic phase in most individuals. Booster doses of polio, measles, mumps, rubella, and varicella vaccines are not currently recommended, but waning immunity has been raised as a concern.^{60–64} Additional doses of these vaccines have been suggested to produce immunity among a relatively small cohort of individuals who fail to respond to primary vaccination.^{65,66} Live, attenuated strains as opposed to killed viral vaccines more closely mimic natural infection where immunity is known to be lifelong. It is possible that reactivation of latent vaccine virus induces boosts in antibody levels. The duration of immunity from enhanced inactivated polio vaccine is under prospective study.⁶⁷

Rotavirus

Natural rotavirus infections are not fully protective, although reinfections are uniformly milder in severity than primary infections.⁶⁸ The 2 currently available rotavirus vaccines are live attenuated reassortant vaccines. The pace of pathogenesis of rotavirus involves several days from infection to disease. Although immunity may be incomplete after infection and may wane after vaccination, it is unlikely that boosters will be recommended in later

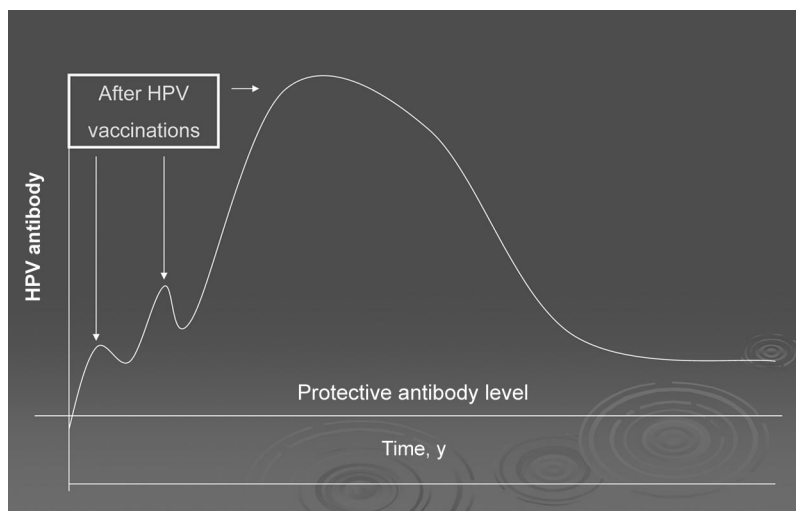


FIGURE 3

Vaccination raises antibody levels in serum to HPV (that have the potential to transudate onto the mucosa), and then serum antibody levels wane. Persistence of serum antibody above protective levels may occur from natural exposure to HPV (ie, natural boosting or other immunologic mechanisms).

childhood, because the infection rate is much lower in older children.

Human Papilloma Virus

The mechanism of protection after human papilloma virus (HPV) vaccination seems to be the production of neutralizing antibody.^{69–72} The pace of pathogenesis for HPV in humans is not known. In animal models it takes 30 minutes to 24 hours^{73–77} for the virus to gain entry to the basal epithelial cells (and infect the cell); thereafter, the virus becomes largely inaccessible to antibody. Therefore, it would seem that a minimum level of antibody would need to be present in mucus (whether locally produced or as a result of transudation from serum) at the time of exposure to prevent infection (Fig 3). After HPV vaccination, it is currently uncertain whether “natural” cervical HPV infection would be sufficient to stimulate a protective antibody response (natural boosting).^{78–83} Although the role of immune memory remains uncertain, high and sustained neutralizing antibody titers are considered to be the

best surrogate marker for protection from HPV infection after vaccination.⁸⁴

CONCLUSIONS

It generally requires ~2 to 5 days for B memory cells and T memory cells (cell-mediated immunity) to expand and give rise to mature immune effector cells after a host experiences exposure to a potential pathogen. The innate immune system and preexisting circulating antibody levels must prevent progression of disease until memory responses occur. With infectious diseases for which the pace of pathogenesis is rapid, some individuals will contract infection before the memory response is fully activated and implemented. With infectious diseases for which the pace of pathogenesis is slow, immune memory should be sufficient to prevent disease. For some newer vaccines there is uncertainty whether breakthrough infections will occur. This is an area of active research that will provide answers to this important question in the future.

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Rating, Ratings: *The increasing public availability of rankings and ratings of physicians and hospitals is gaining attention in the social media. According to a recent article (Maney K. The Atlantic. July/August, 2009, p. 38), 47% of internet users now search online for information about doctors, which can include ratings of such measures as waiting times or medical/surgical errors. As a result, about 2000 physicians have thus far sought assistance from a company called Medical Justice that provides advice on the legal rights of physicians who want to stop some of the ratings being made available to the public. Despite these concerns, public information on physician ratings—if it is valid and reliable—may be just what the doctor ordered when it comes to improving the overall quality of our medical care.*

Noted by JFL, MD